ISOLATED DISTAL DEEP VEIN THROMBOSIS IN SYMPTOMATIC AMBULATORY PATIENTS: A PROSPECTIVE DATA ANALYSIS AND THERAPEUTIC FEASIBILITY STUDY

A thesis submitted to the University of Manchester for the degree of Doctor of Medicine in the Faculty of Medical and Human Sciences

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Abstract

The University of Manchester

Abstract of thesis submitted by Daniel Edward Horner for the degree of Doctor of Medicine and entitled "Isolated distal deep vein thrombosis in symptomatic ambulatory patients: a prospective data analysis and therapeutic feasibility study". January 2013.

Isolated distal deep vein thrombosis (IDDVT) is a condition recently suggested to be a different entity to that of proximal disease. There is currently little evidence defining the clinical importance of detection and treatment. International guidelines vary regarding management advice.

An observational cohort study, prospective service evaluation and pilot randomised controlled trial were performed within a United Kingdom ambulatory thrombosis service. This project aimed to describe the burden of disease and explore three poorly researched aspects of IDDVT assessment and management: whole-leg compression ultrasound (CUS) performed by non-physicians within an ambulatory framework as a principal diagnostic modality; clinical presentation data and risk profile in comparison to that of proximal disease; the feasibility of further interventional randomised research and the risk/benefit profile of therapeutic anticoagulation.

Within this ambulatory cohort, IDDVT accounted for 49.7% of acute thrombosis and differed significantly to proximal disease regarding provocation and symptomatology at clinical presentation. A negative whole-leg CUS excluded deep vein thrombosis with an adverse event rate (diagnosis of symptomatic venous thromboembolism during the 3 month follow up period) of 0.47% (95% CI 0.08 to 2.62). Future interventional research was proved feasible within an ambulatory setting.
The randomised controlled trial conducted within this project is the largest to date comparing therapeutic anticoagulation against conservative strategy for the management of acute IDDVT. Patients allocated to therapeutic anticoagulation had significantly less overall propagation of thrombus (Absolute risk reduction [ARR] 25.7%, 95% Confidence interval 5.9 to 44.3 p<0.01), less short-term symptomatic progression (ARR 16.7%, 95% CI 2.6 to 32.1 p=0.05) and a result trending towards significance for reduction in serious thromboembolic complications (ARR 11.4%, 95% CI -1.5 to 26.7 p=0.11).
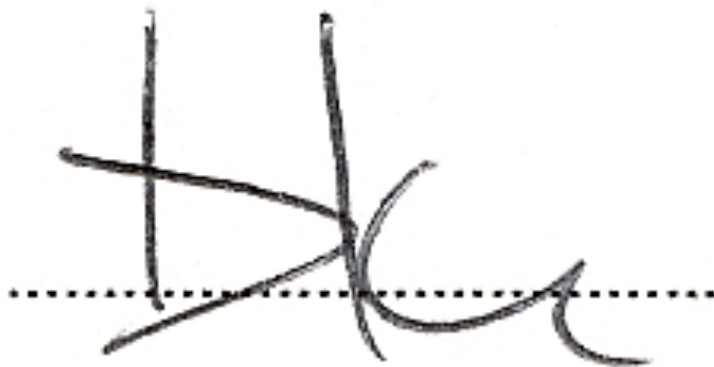
IDDVT is a condition of equal prevalence to proximal venous thrombosis, which varies significantly regarding risk profile and clinical presentation. Using a single whole leg CUS reported by a non-physician within an emergency department pathway is associated with a low adverse event rate. This contemporary data also suggests that therapeutic anticoagulation is beneficial for reduction of short-term complications in IDDVT. The risk of false positive diagnosis and excess anticoagulation remains.

This data can inform and direct future design of adequately powered randomised studies, in order to attempt external validation of these findings.

Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning

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List of Abbreviations

IDDVT	Isolated Distal Deep Vein Thrombosis
DVT	Deep Vein Thrombosis
VTE	Venous Thromboembolism
CUS	Compression Ultrasound
ED	Emergency Department
NHS	National Health Service
UK	United Kingdom
NICE	National Institute of Health and Clinical Excellence
ACCP	American College of Chest Physicians
ICMVT	Isolated Calf Muscle Vein Thrombosis
DCVT	Deep Calf Vein Thrombosis
HTA	Health Technology Assessment
95% CI	95% Confidence Interval
ELISA	Enzyme Linked ImmunoSorbant Assay
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
MOOSE	Meta-Analysis of Observational Studies in Epidemiology
BCSH	British Committee for Standards in Haematology
DOH	Department of Health
GCP	Good Clinical Practice
RCT	Randomised Controlled Trial
NOAC	New Oral Anti Coagulant
TSC	Trust Steering Committee
DSMB	Data Safety and Monitoring Board
ACT	Anticoagulation of Calf Thrombosis
ISTH	International Society for Thrombosis and Haemostasis

The Author

The author graduated in 2003 from University College London with MBBS and distinction in clinical medicine, in addition to an intercalated BA from the University of Manchester obtained in 2000 with first class honours.

Since registration, the author has always held a keen interest in Emergency Medicine and is currently towards the latter stages of registrar training in the North West Deanery. He is currently dual accrediting with higher specialist training in Intensive Care Medicine following competitive application.

Although the author has had previous input to original research projects and several publications as first author preceding the MD, this is the first project conceived, designed, conducted, analysed and written up independently.

During the time as MD student, the author has become heavily involved in on-going research within the department acting as co-investigator for multiple additional studies, drafting guidelines for national dissemination and acting as one of two lead clinicians within the innovative emergency medicine and intensive care (EMERGING) regional research group.

Acknowledgments

Rationale for submission of the Thesis in Alternative Format

The Anticoagulation of Calf Thrombosis project is a multi-faceted assessment of disease burden, disease characteristics, investigative strategy and feasibility of further interventional study regarding isolated distal deep vein thrombosis (IDDVT). As such, the project lends itself well to direct segregation of these components in the format of papers suitable for submission to peer-reviewed journals.

In addition, submission in alternative format is likely to improve both the publication trail and the potential for future research progression. Collaboration is necessary for validation of these study findings and also to continue towards a definitive international management strategy in IDDVT. The MD student has already visited the Ottawa Thrombosis Centre in Canada after successfully obtaining a scholarship bursary through regional competitive application, in order to present the preliminary findings of the project and generate peer interest. It is vital that this is followed by publication of the results as scientific manuscript, in order to generate debate within the readership and stimulate interest from potential centres willing to involve themselves in future collaboration. Presentation in the alternative format encourages and supports this rapid dissemination.

Furthermore, there is a distinct lack of prospective randomized, methodologically robust research conducted on this topic that is available in the public arena to guide clinical practice. It is hoped that once published, some of this research will enable clinicians to make more informed and evidence based decisions when considering management strategies for IDDVT.

Introduction

Venous thromboembolic (VTE) disease is a topical and costly global healthcare burden. Incidence rates are virtually equivalent to that of stroke within the western hemisphere [1] and rise sharply in later life [2]. It remains the third most common cause of vascular death after myocardial infarction and cerebrovascular insult [3].

Previous studies addressing outcome provide a stark reminder of prognostic severity. Large international registries quote 17% mortality 3 months post diagnosis for VTE involving the pulmonary vascular tract [4]. Thrombosis confined to the lower limbs has equal implications, with reported short term mortality rates between 7 and 15% [5]. There are longer-term consequences of disease also. Kaplan-Meier curves from extended observational studies show a steadily decreasing survival over 8 years following first episode of symptomatic deep vein thrombosis [6].

Clinical research demonstrating poor outcome has led to a national focus on early diagnosis and active prevention. Both a Health Technology Assessment (HTA) and a National Institute of Clinical Excellence (NICE) guideline have been produced within the last decade [7, 8]. The condition retains enough prominence to feature in recent Prime Ministerial questions and is currently described as the "UK's number one hospital killer" [9]. There is no doubt that VTE disease remains at the forefront of clinical medicine and the national political healthcare agenda.

Despite the large body of work, controversy still remains regarding many aspects of clinical practice. One such area is that of isolated distal deep vein thrombosis (IDDVT), a condition previously thought by many to be benign [10]. Current international guidance on investigation and treatment is conflicting, highlighting the lack of robust evidence [11-13]. Limited data exists on prevalence, aetiology and clinical presentation. Most important is the lack of evidence to guide therapeutic intervention. Contemporary papers continue to urgently call for prospective randomised clinical trial data, to aid bedside decision-making [13-22].

The Emergency Department has recently been formally tasked with the duty of ambulatory investigation and initial management in venous thromboembolic disease [23]. As well as the caveats in the evidence noted above, limited data exists on VTE management validated in an emergency department setting.

This controversial area and unexplored terrain constitute the basis for the following thesis and research project.

Key definitions

Isolated Calf Muscle Vein Thrombosis (ICMVT) refers to any isolated thrombi within the muscular calf veins (soleal and/or gastrocnemial veins).

Deep Calf Vein Thrombosis (DCVT) refers to any isolated thrombi within the axial deep veins of the lower leg (posterior tibial, anterior tibial and peroneal veins).

Isolated Distal Deep Vein Thrombosis (IDDVT) is a composite term to include any/all of the above thrombi occurring in isolation or combination, in the absence of proximal thrombosis or pulmonary thromboembolic disease.

Venous Thromboembolic (VTE) disease refers to a composite of any extremity deep vein thrombosis, pulmonary embolism, unusual site thrombosis, central vein thrombosis or other venous thromboembolic disease state.

A schematic representation is presented overleaf, reproduced from the Journal of Thrombosis and Haemostasis [18].

The Emergency Department (ED) will be abbreviated for the remainder of the thesis.

Figure 1: Anatomical considerations in the diagnosis of IDDVT.
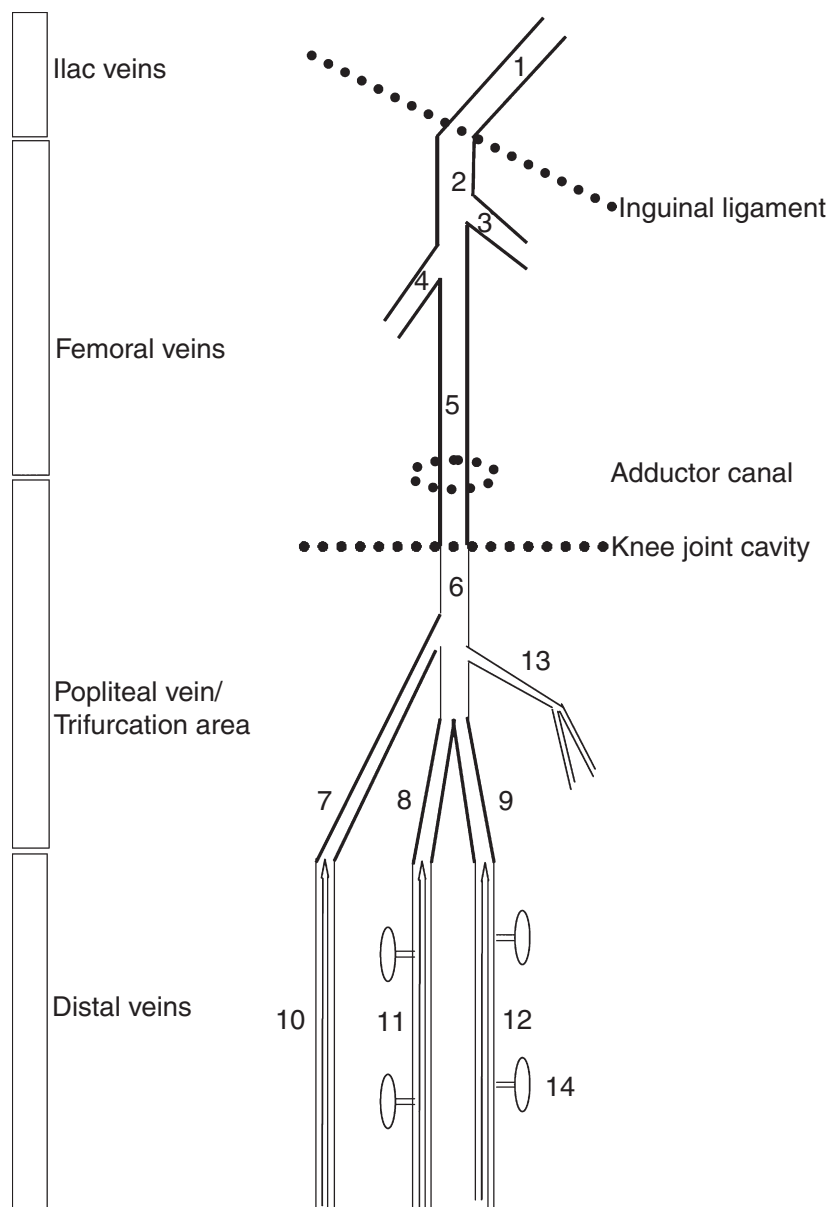
Fig. 1. Schematic representation of leg veins as discussed in this review: 1, external iliac vein; 2, common femoral vein; 3, greater saphenous vein; 4, profound femoral vein; 5, (superficial) femoral vein; 6, popliteal vein; 7, anterior tibial confluent segment; 8, posterior tibial confluent segment; 9, peroneal confluent segment; 10, anterior tibial veins; 11, posterior tibial veins; 12, peroneal veins; 13, gastrocnemius muscle veins (medial head); 14, soleus muscle veins.

Context of the Research Project

Epidemiology of Deep Vein Thrombosis stratified by anatomical location

Estimates of population incidence

The true incidence of deep vein thrombosis (DVT) confined to the extremities varies depending on geographical location and diagnostic criteria. However, large cohort studies conducted throughout Europe and North America provide data enabling age and sex adjusted quantification of disease burden, with population based annual estimates ranging from 48 episodes/ 100,000 to 155/100,000 [1, 24]. Based on this data, United Kingdom (UK) national guidance supports the oft-proposed incidence of 1/1000 as a reasonable estimate [25]. To ascertain an idea of healthcare burden, this figure can be set within the context of all suspected DVT cases. Using gold standard objective testing and excluding patients with previous limb thrombosis, the actual prevalence of DVT in those investigated with *suspected* disease has been estimated at 25.5%, roughly 1 in 4 [26]. As such, four times as many people will present with suspected disease as are eventually diagnosed with acute DVT. The population incidence of *suspected* DVT can thus be approximated at 4/1000, or 1/250. Given that this figure is derived from attendance at specialist vascular or thrombosis centres, attendance with suspected disease in an unselected ED population is likely to be even higher.

Western studies assessing epidemiological trends from the last 30 years report a fairly consistent annual incidence for DVT in males, with slight fluctuation in female patients dependent on age [1]. Eastern studies replicate this trend, with incidence rates remaining static over consecutive years [27]. On-going relevance and the continuing need for vigilance in diagnostics are reiterated. No clear reduction in disease burden has yet been observed, despite the modern focus on preventative therapy and established national guidance for thromboprophylaxis [8].

Demographics

Recent ambulatory outpatient prospective cohort studies estimate the male to female ratio as evenly balanced, at 54/46% [28]. Further research including both inpatients and outpatients has reported a slight female preponderance, often suggested to result from a heightened obstetric risk [1]. This discrepancy has been replicated in large collaborative observational cohorts [29]. Although DVT is seen throughout all ages, with documented cases ranging from childhood to early nineties, there is a clear trend towards increased frequency of presentation in advancing age [1]. Some cohort studies suggest >70% patients diagnosed with confirmed DVT will be over 50 years of age [28].

Several articles have recently focussed on ethnicity in VTE [30, 31]. This is a complex issue. Previous American studies have evaluated comprehensive hospital discharge datasets and found a significantly higher incidence in black patients compared to Caucasian (141 vs. 104 /100,000 adults/yr respectively, $p<0.001$) [32]. The same authors suggest a significantly lower rate in Hispanic patients by comparison (55/100,000 adults/yr, $p<0.001$). These differences are more pronounced when looking directly at provoked, or secondary thrombosis and show no discrimination by age. Not only are incidence rates higher, but also mortality seems to vary by ethnicity [1, 33]. There are multiple potential known and unknown confounders when attempting to account for these differences. The contribution of genetic, physiological and clinical differences to this variation has been assessed but as yet remains undefined. Sickle cell trait, high factor VIII levels and increased prevalence of chronic associated medical co morbidities have all been suggested as potential causes for increased VTE rates in afro-Caribbean patients [34-37]. As yet, these concerns have not been addressed in a clinical study.

There is some observational evidence to suggest that distal disease differs from proximal regarding demographics. Two recent registries have prospectively evaluated a combination of 12,500 patients with acute DVT and performed multivariate analysis to compare the presenting features of proximal to distal disease [38, 39]. Both studies suggest distal disease to be less likely in elderly and male patients, with respective odds ratios of 0.56 (95% CI 0.50 to 0.64) and 0.89 (95% CI 0.80 to 0.99) in the largest sample [38]. Although the work is multi-centre, it is limited to two European

countries and as such in need of further external validation.

The proportional contribution of distal disease

Many leading authors would suggest that distal thrombi contribute to approximately half the disease burden of DVT [22, 40]. This figure is robustly supported by multiple cohort studies investigating the role of distal ultrasound [41-44]. However, this data needs further clarification regarding patient cohort. Studies predominately assessing inpatients with suspected DVT produce lower proportional rates of distal disease in positive cases and thus downplay topical relevance [45]. Alternatively, in ambulatory cases the importance of distal thrombi and contribution to symptomatic presentation is well recognised. European studies from the beginning of the last decade note distal disease contributing 48% of the annual DVT incidence rate (1.24/1000) [46]. Surgical research conducted around the same time supports this data, with a 10 year retrospective analysis from Detroit noting IDDVT to account for 35% of all DVT patients, diagnosed from over 2700 venograms in patients with suspected disease [47]. Contemporary research lends support to these findings. The OPTIMEV collaborators recently followed a two-year multi-centre French cohort of over 1600 objectively confirmed, symptomatic, DVT patients [39]. Distal disease accounted for 56.8% of their patients.

Further studies investigating DVT in *asymptomatic* patients would suggest the proportional contribution of distal disease to be even higher. The TADEUS project recently utilised compression ultrasonography to screen all medical patients referred from outpatient clinic to an internal medicine unit for hospitalization [48]. Only patients asymptomatic and not currently receiving anticoagulation of any kind were included. Over a ten-day serial ultrasound period, 14% of the 122 recruited patients were found to have asymptomatic DVT. More than 80% of these thromboses were confined to the calf. Similar results have been produced recently by Ciuti *et al* [49]. The authors here enrolled 154 patients consecutively hospitalised for acute medical illness, in whom VTE was not the admission diagnosis, and performed bilateral whole leg CUS on all. Asymptomatic IDDVT were noted in 16.2% (25/154) of the cohort and accounted for 78% of all detected thrombotic disease.

Identifying the proportion of DVT within the ambulatory population directly attributable to distal disease is of particular interest to those working in emergency care. With international consensus recommendations supporting the use of d-dimer testing and clinical risk assessment in suspected DVT, the ED has become the first port of call for initial assessment and investigation in the majority of ambulatory patients [7, 13, 23, 50]. Recent publications suggest individual capital city departments in the developed world will already see over 1300 patients annually with suspected VTE [51]. Over 40% of these attendances will be self-referred, demonstrating a steadily rising public awareness. These figures are likely to increase further with developing health promotion, charity campaigns and political pressure. An increasing index of suspicion is already leading to a corresponding decrease in prevalence within some countries [52].

More complex diagnostic services are also moving to the front door of the hospital, in order to prevent costly unnecessary admissions. Indeed many authors have gone on to explore and promote evidence supporting focused vascular ultrasound performed at the bedside by emergency physicians. This type of research demonstrates a potential to encompass the diagnostic process within a single hospital visit, within a single department [53, 54]. If IDDVT constitute >50% of the objectively diagnosed ambulatory caseload for lower extremity thrombosis (as previously suggested), it is vital that emergency services have a clear understanding of the therapeutic evidence base. It is also important that further study and contribution to the literature is directly relevant to this environment and patient cohort.

Anatomical Location

If IDDVT do indeed account for 50% of objectively diagnosed deep vein thrombosis, then it is worth briefly considering the anatomical distribution between cases. Previous authors have attempted to segregate IDDVT into thrombi within the axial deep veins of the calf (peroneal and paired anterior/posterior tibial veins) and the muscular calf veins (soleal and gastrocnemial). Separation has been thought to help delineate treatment strategy and indeed there is some weak evidence that certain types of untreated IDDVT have a lower propagation risk than others [20, 55]. However, modern authors encourage the use of IDDVT as an undifferentiated term for both

clinical and research purposes [18].

Anatomical location has been considered in epidemiological and observational cohort studies. Ouriel *et al* collated data on a decade of venography for suspected DVT and surmised that the peroneal vein is the commonest affected segment, involved in 67% of acute disease in their cohort [47]. However, it is unclear from their paper exactly how much of this was in IDDVT alone, with calf thrombi commonly involved in disease extending proximally. Labrapoulus *et al* support these general findings in their retrospective analysis of 282 acute IDDVT cases: peroneal veins were the commonest involved site (41%) for disease followed by soleal (39%) posterior tibial (37%) and gastrocnemial veins (29%) [56]. Mattos *et al* echo the relative dominance of peroneal and posterior tibial thrombi in their retrospective review including 110 calf vein thrombi, in comparison to thrombi at other locations within the calf (p<0.001) [57]. Lastly, Singh *et al* concur in their recent prospective observational study of 180 consecutive IDDVT cases [58]. They again note the peroneal (30.6%), soleal (50.0%) and posterior tibial veins (23.9%) as common sites for thrombi. Gastrocnemial disease was seen in 16.7% cases. All the above papers provide clear evidence that the anterior tibial vein is a particularly rare site for acute thrombi.

Few papers appear to have directly compared the incidence of isolated calf muscle vein thrombi (ICMVT) to that of deep calf vein thrombi (DCVT) in patients presenting with distal disease. However, the OPTIMEV registry has been evaluated to this purpose, with the conclusion that ICMVT and DCVT are essentially equivalent in incidence [59]. The authors also note the two conditions as a fairly homogenous entity, with identical risk profile, co morbidity and clinical prognosis regarding recurrence. The only notable differences on multivariate analysis came with symptomatology, in that ICMVT was significantly more likely to be painful (p = 0.02) and less likely to result in leg swelling (p<0.001). Data such as this provides further argument for the collation of DCVT and ICMVT as IDDVT in further research studies.

Aetiology

Introduction

Many single factors that contribute to the formation of DVT are already well recognised, with others being continuously discovered. All associate with the pathological process of thrombogenesis previously described by Virchow in 1860 [60]. He proposed three related factors contributing to clot development: alteration in blood flow, damage to the endothelial vessel wall and hypercoaguability. These three factors are commonly known as Virchow's triad. A basic understanding of individual risk areas allows separation of contributory factors and a brief review of the evidence regarding thrombogenesis.

Altered blood flow

The majority of venous thrombi originally form in regions of slow or disturbed flow and consist primarily of fibrin and erythrocytes, in contrast to the platelet clumping of arterial thrombi [61]. Turbulent flow through a vessel, although relevant, is of less direct importance than venous stasis. With stagnancy and blood pooling secondary to periods of immobilisation/decreased muscle contraction, blood will collect in the large venous sinuses of the calf or valve cusp pockets of the deep calf/thigh veins [62]. Small fibrin deposits develop. The initial fibrin nidus grows by apposition, thus occluding sequential distal venous segments eventually leading to symptomatology and clinical signs. This reminds us of the stark importance of understanding distal DVT as an entity, given it is often suggested to be the precursor to proximal and embolic disease.

Many studies have quantified the clinical risk of altered flow occurring through immobility. Observational research in spinal cord injury patients has demonstrated a 100% prevalence of DVT in a cohort of paralysed, immobilised patients compared to a 0% prevalence in those with injury but without paralysis [63]. Long-haul air travel has been extensively investigated for its role in thrombogenesis, with a landmark paper in 2001 demonstrating asymptomatic DVT in 10% travellers on return from an international flight [64]. Randomised compression stocking prophylaxis reduced the

incidence to 0%. Recent geriatric research using univariate analysis to predict DVT occurrence in a cohort of over 800 elderly patients, highlights immobilisation of >30 days and inability to perform a 'timed get up and go' test as significantly predictive of clot development [65]. Odds ratios of 1.83 and 3.09 are quoted respectively. Other important risk factors regarding immobilisation and consequent venous stagnation are extensively described within the literature, such as postoperative bed rest [66], plaster cast application in the context of bony injury [67] and pregnancy [68]. Of interest, the latter point has been analysed prospectively to suggest that uterine compression causing altered flow is a predominant reason for the high number of left sided thrombi seen in pregnant patients. So much so that a decision rule incorporating this facet has been recently suggested [69]. All of these issues significantly contribute to thrombogenesis to the extent that prophylactic anticoagulation is recommended by national, regional and multidisciplinary guidance in the majority of circumstances [8, 70, 71].

Endothelial Vessel Wall damage

Far less is understood regarding the contributory role of endothelial damage. Microscopic vessel wall injury has been detected in the context of thrombosis following hip and knee surgery [72]. However, postoperative immobility as a confounding factor makes it difficult to prove isolated aetiological effect. No evidence has been gathered in relation to invisible metabolic change to the vascular wall, although it has been suggested that alteration of receptors in the endothelial lining may interfere with an inherent anticoagulatory effect [61]. The suggestion that venous distension may lead to endothelial damage links two distinct elements of Virchow's triad and thus again reduces the ability to prove isolated causation.

Traumatic injury has been directly associated with increasing thrombotic risk. A prospective study in 1994 identified DVT by ascending venography in 58% (201 of 349) of all trauma patients with an Injury Severity Score >9, despite limited clinical suspicion [73]. Focusing on patients with lower limb trauma, the incidence of thrombosis rises even higher. Thrombi were objectively identified in 69% of lower extremity orthopaedic injuries overall, found in 80% of patients with femoral limb fractures and 77% of those with tibial fractures. Using multivariate analysis, the

authors noted lower extremity trauma as an independent risk factor for development of DVT, with an odds ratio of 4.82 (95% CI 2.79 to 8.33). Extrapolation would suggest a direct link between disruption of vascular integrity/endothelial wall injury and DVT. However, venous stasis and immobility in trauma patients often confounds the direct relevance again, as do studies which suggest post-injury hypercoaguability [74]. Thrombotic disease in trauma patients, especially those receiving critical care, remains a pressing issue. Debate continues on the value of screening in those deemed at particularly high risk. In a recent cohort of 106 level 1 trauma patients, Thorson *et al* report a significant VTE incidence of 28% in high risk patients receiving weekly doppler assessment, despite adequate provision of prophylaxis [75]. Scanning was also limited to the proximal veins, implying a far greater percentage with the addition of distal vein assessment.

Interestingly, some research on trauma patients using duplex ultrasonography rather than venography and sub grouping high-risk individuals, has looked to specifically identify below knee thrombosis rates and assess propagation or embolism. These authors report a lower frequency of IDDVT, only 14% in over 600 patients considered high risk [76]. Following diagnosis these patients received only prophylactic anticoagulation in this study, rather than therapeutic. Propagation occurred but was extremely limited, in 4.7% cases (4 of 85) with a resulting change in management. Only one patient (1.2%) developed a pulmonary embolus.

Hypercoaguability

Any major imbalance in the physiologic equilibrium between clot formation and fibrinolysis has the potential to promote either a bleeding, or thrombotic tendency. The main areas of research with regard to thrombosis lie in explanation of hypercoaguability, or inhibited fibrinolysis. There are numerous examples of increased clotting tendency and association with DVT found in the literature. A recent observational study assessing patients with known VTE for evidence of procoagulant states, noted detection of thrombophilia in 42% on routine screening, with the majority involving a genetic cause [77]. This is often thought to account for the importance of family history as an independent risk factor for VTE, quoted as present

in 14% of ambulatory cases in one study [78]. The authors note the presence of Factor V Leiden as the most common occurrence, followed by diseases causing natural anticoagulant dysfunction (protein C and S deficiency). This high prevalence of inherited thrombophilia in patients with confirmed VTE is supported by earlier work and remains a key issue in disease management [79, 80]. Other disease states such as the paradoxical lupus anticoagulant and antithrombin III deficiency are well recognised to contribute to development of VTE, although the direct mechanism often remains poorly understood. Acquired procoagulant disease states such as cancer have been cited as strong independent risk factors for VTE, one epidemiological study noting an odds ratio of 4.05 (95% CI 1.93 to 8.52) for females with cancer compared to females without [81]. The relationship to malignancy has been further explored, through assessment of subsequent cancer diagnosis in patients diagnosed with VTE. A recent *Lancet* publication evaluated a Swedish registry of patients admitted to hospital between 1965 and 1983 for venous thromboembolic disease [82]. The authors noted a standardized incidence ratio for new cancer diagnosis of 3.2 (95% CI 3.1 to 3.4) within the first year of follow up. The conclusion was either premalignant change provoking thrombotic disease, or shared risk factors between cancer and thrombosis.

Superficial venous thrombosis (SVT), previously thought to be a relatively benign condition, is another physical disease with clear evidence suggesting progression to VTE in a high proportion of patients. Epidemiological studies demonstrate a 24.9% prevalence of symptomatic VTE in patients with superficial thrombophlebitis and a 10.2% incidence of new VTE during short term follow up, often despite anticoagulation [80]. These findings are supported by prospective randomized trial data from the recent CALISTO study, noting a 5.9% progression to symptomatic VTE in a cohort of SVT patients randomised to placebo at diagnosis [83].

There is less definitive data to suggest inhibition of fibrinolysis as a contributory cause for VTE development, but several scientific papers attempt to explain rationale. Decreased fibrinolytic activity has been observed within the postoperative period and impaired t-PA release demonstrated in a high proportion of patients with recurrent idiopathic VTE [84, 85]. It unfortunately remains unclear as to whether these and other changes are seen as a precursor to, or a direct consequence of deep vein thrombosis.

Additional evaluated risk factors

Additional risk factors are best described based on epidemiological study rather than pathophysiological understanding. In a retrospective cohort review of 232 UK patients with confirmed lower limb DVT, Syed and Beeching cite smoking as the most prevalent risk factor for both community and hospital acquired thrombosis [78]. Other quantifiable risk factors noted in this study include oral contraceptive use, intravenous drug abuse, focal leg inflammation and alcoholism. No attempt at multivariate analysis or predictive odds ratios were made in this paper and multiple sources of confounding exist in the presentation of their results.

There is also fascinating community work on the quantification of risk factors for thrombosis development. Recently, a prediction model has been derived and validated within a primary care population database of over 3.5 million patients [86]. Independent predictors included some usual suspects (age, body mass index, smoking status, cancer, varicose veins, hospital admission in past six months) but also several medical co morbidities (congestive cardiac failure, chronic renal disease, chronic obstructive pulmonary disease, inflammatory bowel disease) and antipsychotic drug prescription. Hormone therapy was also included within the model for female patients, including HRT, oral contraception and Tamoxifen. There has been much debate about oestrogen therapy and venous thromboembolism over the last decade: it would appear that current evidence suggests both oral [87] and non-oral [88] hormonal medication carry a significantly increased relative risk for thrombosis [89].

Infection and inflammatory states have also been assessed for aetiological contribution recently, via systematic review. Tichelaar *et al* quote a relative risk of venous thrombosis in generic infection of 1.7 to 2.5, but highlight increased risk specifically with pneumonia, urinary tract infections and inflammatory bowel disease [90]. There is significant chance of confounding and publication bias in this work as the authors acknowledge. Despite this an accompanying editorial questions whether the data should trigger a revised definition of 'unprovoked' DVT [91].

Many authors have also subdivided risk based on transience, separating permanent and temporary risk factors in order to determine prognosis and manage treatment strategy [92]. Other authors collate these individual risks to produce a binary definition of provocation, with according variation in therapy [93]. There is some evidence to suggest such categorisation is an asset to management, particularly with

regard to duration of therapy [94, 95]. However, there are currently no validated scoring systems that assess risk factors in the context of disease and prospectively advise on management strategy.

The concept of Provocation

The association of transient risk at presentation appears to be linked with an increased likelihood of distal (rather than proximal) disease and a decreased likelihood of short-term recurrence. As such, it is suggested that 'provoked' disease has a better prognosis and may therefore need less aggressive management. Thus, it becomes useful to segregate disease in this manner, to dictate therapy. Several authors have looked at this in detail and demonstrate low rates of recurrence following withheld anticoagulation after a provoked VTE [95]. There is also compelling evidence that patients with unprovoked disease are more likely to suffer recurrence [96-99]. Indeed, recent national guidance documents utilize the idea of provocation to delineate management strategy [100]. However, a strict definition of provocation fails to exist.

The OPTIMEV and RIETE registries utilize different definitions of transient risk [38, 39]; for example, the RIETE paper considers both hormone replacement therapy or use of the contraceptive pill to be a transient risk factor for VTE, whereas OPTIMEV lists this in the chronic section. A recent patient level meta-analysis records hormone use within unprovoked [101], whereas national UK guidance clearly defines oestrogen use as a provoking risk factor [13]. OPTIMEV also lists acute infection and congestive cardiac failure/respiratory insufficiency within its list of transient provoking factors; these elements are conspicuously absent from the RIETE data.

There is also the issue of timing of risk. The RIETE registry is fairly clear about transient risk defined as antecedent within the last 2 months, in order to be considered provocation. OPTIMEV uses variable timings, including surgery within 45 days, 'recent' travel or plaster immobilisation and 6 weeks post partum. Contemporary UK guidance refers to a 3-month window of antecedent exposure [13]. Until standardization occurs these caveats must be noted.

There is further additional confusion regarding the role of infectious disease on the provocation of VTE. A recent systematic review has provided compelling evidence to support the association of transient acute infective/inflammatory disease with an increased incidence of VTE [90]. Currently many of these diseases are collated in the

unprovoked/chronic risk factor group. However, there is recent suggestion that VTE in association with transient infection does not have the same rate of recurrence needing secondary prevention as other unprovoked cases, and as such should be reclassified [91]. The authors here suggest further research and clarification.

Recent guidance from the National Institute for Clinical Excellence (NICE) within the UK [13] describes a clear, but unreferenced definition of provocation to include the following: antecedent (within three months) and transient exposure to a major risk factor for VTE including surgery, trauma, significant immobility, pregnancy, puerperium or hormone therapy of any kind. This is more homogenous as a time period but slightly open to subjective interpretation. There is no consensus definition on the idea of provocation and no international guidelines resolving this debate. Until then, all published work describing a difference between IDDVT and proximal disease with regard to provocation and antecedent risk must be carefully scrutinized to define what is considered transient/permanent risk and the temporal associations used.

Aetiology of Distal vs. Proximal Disease

Having already alluded to the differing risk profile between IDDVT and proximal thrombosis, we must consider this in detail. Several recent papers attempting to separate the two disease entities have addressed this question directly, in order to provide further insight into the lack of consensus regarding management. Small prospective studies such as that by Masuda *et al* have been the first to provide an assertion that IDDVT patients have a high incidence of exposure to temporary provocation [102]. The authors describe a simple retrospective cohort of 58 IDDVT cases and noted antecedent major transient risk factors in greater than 50% cases. Utilising an on-going, international, multi-centre prospective cohort of consecutive patients presenting with confirmed symptomatic VTE, Galanaud *et al* published observational data in 2009 addressing trends in aetiology and clinical history in over 11,000 patients with symptomatic thrombosis [38]. Seventeen percent of their cohort exhibited IDDVT. The authors note several independent risk factors predictive of IDDVT when compared to proximal disease on multivariate analysis, which they

cohort under the term 'transient risks'. The individual factors and associated odds ratios include hospitalisation (OR 1.47, 95% CI 1.31-1.64), recent surgery (OR 1.38, 95% CI 1.18-1.61) and a recent travel history of greater than 6 hours duration within the last 3 weeks (OR 1.62, 95% CI 1.20-2.20). They also include leg varicosities as an independent predictor of IDDVT (OR 1.35, CI 1.19-1.52), perhaps again highlighting the importance of superficial thrombophlebitis and potential propagation to deep vein thrombosis discussed previously. In stark contrast, independent predictors of proximal DVT on multivariate analysis were deemed mostly permanent risk factors, such as age >75, active cancer or personal history of VTE.

Further research provides external validation of these findings. The OPTIMEV study published the same year generated a cohort of 6000 DVT patients, 1643 with proven isolated lower extremity DVT [39]. A multivariate analysis comparing risk factors for distal vs. proximal disease again demonstrates 'transient' risk factors to be predictive of IDDVT. The strongest individual associations included recent plaster immobilisation (OR 2.2, 95% CI 1.3-3.8), recent travel (OR 1.7, 95% CI 1.0-2.8) and recent surgery <45 days before presentation (OR 1.8, 95% CI 1.3-2.5). Again, statistical analysis surmised proximal DVT to be more likely in the presence of chronic/permanent risk factors, including age >75, long term cardio-respiratory disease and active cancer. These authors cite no discernible difference in risk profile association between inpatients and outpatients. Both studies are collated and summarized in an additional review article [94]. There is further discussion here regarding comparison of risk in disease to 'controls', a group derived from data collection and investigation for suspected DVT with negative imaging. The authors mention the similarity of risk profile for both IDDVT and proximal disease when compared to controls, but highlight the magnitude of difference in certain risk characteristics.

In addition to OPTIMEV and RIETE, the Worcester VTE group have recently published a 4 year retrospective analysis of isolated lower extremity thrombi, examining prevalence and comparing clinical characteristics stratified by thrombus location [103]. The authors analysed data from 1497 cases of objectively confirmed DVT and note recent surgery (p<0.006) and recent fracture (p<0.001) to be associated with significantly increased risk of distal, rather than proximal thrombi. Conversely, a history of severe infection (p<0.001), prior VTE (p<0.0002) and lack of provocation (p=0.01) are all associated with significantly increased likelihood of proximal disease.

Although derived from retrospective medical record review, these findings go some way towards validating the ideas put forward by the OPTIMEV/RIETE data and encourage further prospective research.

All the above studies also support previous observational data, taking first steps towards segregation of distal and proximal DVT as distinct disease entities [104]. Modern research provides a strong suggestion that although aetiology will overlap, variation in risk profile warrants an altered approach to management stratified by thrombus location. Indeed, some authors have gone further to examine differences in epidemiological data based on sub-stratification of IDDVT alone. A comparison of 457 muscular calf vein thromboses against 256 deep calf vein thromboses published in late 2010 addressed this issue directly [59]. However, the authors noted minimal significant differences between groups at presentation, failing to support the need for further segregation of lower extremity thrombosis based on anatomical location within the lower leg.

Data supporting a transient risk profile as predictive for distal disease also highlights the issue regarding duration of anticoagulation. A prolonged course of at least three months treatment is often recommended in the context of IDDVT by national bodies, despite a lack of high-level evidence [12, 93]. These recommendations are often extrapolated from research on proximal VTE. Consequently, many clinicians choose not to follow this guidance regarding distal disease. It naturally follows that specific therapeutic studies on IDDVT have been suggested in order to determine an "optimal and consensual treatment", given regional and national fluctuation in practice [38].

Clinical Presentation

Introduction

The atraumatic, acutely swollen lower limb has many differential diagnoses other than DVT. Indeed, an alternative organic diagnosis is established in roughly half of all ambulatory patients presenting with suspected thrombosis [105]. Given the recognised risks of untreated VTE, the exclusion of thrombotic disease often takes precedence in assessment. Until this has been ruled out, ambulatory patients will often receive therapeutic anticoagulation to minimise risk.

The approach to excluding deep vein thrombosis is not a simple one. A thorough history and examination, in order to establish type and urgency of clinical presentation, should always come first. However, despite its fundamental importance clinical assessment alone has proven unreliable in isolation. Early comparative work has recorded an overall diagnostic accuracy of only 60% for 'vascular specialists' [106] and 58% for 'consultants from various specialities' [107] for clinical identification of DVT in patients with suspected disease. Awareness of the limitations in clinical assessment has led to research evaluating sensitivity of examination findings, both in isolation and combination.

Diagnostic utility of Individual clinical signs and symptoms in suspected DVT

Classic clinical symptoms associated with deep venous thrombosis include swelling, pain, erythema and warmth [108]. Corresponding documented signs have previously included oedema, tenderness, palpable phlebitis, warmth, erythema, superficial dilatation and a number of eponymous provocation tests. However, it was recognized as early as the 1960s that clinical findings are a poor discriminator for the presence of acute disease. In a prospective evaluation of 72 patients, Haeger and Sjukhuset noted that only 46% of patients on treatment with classical clinical findings tested positive on contrast venography [106]. They concluded that clinical signs "cannot be trusted" to diagnose DVT. Conversely, 50% patients with confirmed objective disease by imaging were shown to lack symptomatology by Mclachlin *et al* [109]. Kahn summarises the remaining work in the 20th century on this topic eloquently in a

review article [108] and draws particular attention to the *Lancet* paper by Sandler *et al* [107]. The authors here compared standardized clinical assessment to a gold standard of contrast venography reported by two independent and blinded radiologists, with consensus. This paper also utilised the Kappa index to measure the likelihood of interobserver agreement. No clinical feature had either a sensitivity >80% or a specificity >25% following adjustment and the accuracy of clinical features overall was noted to be "barely more than expected by chance". Again, the authors conclude that objective diagnostic testing is necessary in suspected disease. Some later work suggests that collation of signs and symptoms allows high sensitivity when compared to formal diagnostic ultrasound [110]. As such, a physical examination with NO clinical signs of DVT may have a high negative predictive value. This research is flawed by the retrospective design, non-standardised assessment and focuses only on the need for ultrasound prior to lung imaging in pulmonary embolism.

A modern meta-analysis has essentially confirmed the limited value of individual clinical features for diagnosis, in patients with suspected disease. Goodacre *et al* extracted data from 54 cohort studies to produce pooled likelihood ratios for the presence and absence of predefined clinical features [111]. No single clinical sign or symptom generated a positive likelihood ratio >2 or <0.5 in isolation, though it is notable that several *historical* features performed well. The presence of cancer generated a LR+ of 2.71 (95% CI 2.16 to 3.39, p<0.007) and a previous history of thrombosis a LR+ of 2.25 (95% CI 1.57 to 3.23, p<0.001) and as such may be of some use in adjusting physician gestalt. No single feature was associated with a sufficiently negative likelihood ratio to be of practical use in guiding imaging decisions in suspected DVT. The authors conclude individual clinical features in isolation to have "limited value" in diagnosis of thrombotic disease.

Combining clinical features to form predictive indices: the creation of clinical probability models

Many experts have focused on the generation of pre-test probability estimation through structured or unstructured clinical assessment prior to definitive testing. This allows stratification of patients into differing at-risk groups for disease, based on a combination of clinical signs, symptoms and intuition. This process can be performed by empiric judgment or standardised decision rule.

There is some evidence that unstructured clinical gestalt is a worthwhile tool in the approach to suspected DVT. Several articles from the turn of the century have formally evaluated this by assessing implicit clinical suspicion against a reference standard diagnosis for DVT. Perhaps the two most relevant are from Chan & Reilly (2000) and Blattler *et al* (2004) [105, 110], both performed using dichotomized implicit clinical assessment within a symptomatic ambulatory population. Chan & Reilly report a sensitivity of 95% (95% CI 92 to 98) for their dichotomized clinical assessment in comparison to ultrasound, but a perhaps expected disappointing specificity of 31% (95% CI 24 to 38). Blattler *et al* fare slightly better overall, with a lower sensitivity of 81% (95% CI 69 to 89) but a much-improved specificity at 85% (95% CI 79 to 90). Both authors conclude a potential role for overt clinical judgment based on the high negative predictive values seen (95% and 92% respectively) and the potential to reduce unnecessary imaging when used in tandem with laboratory resources.

Several other authors have presented explicit clinical decision rules, usually derived from preceding multivariate analysis. The use of objective reproducible scoring systems attempts to standardize and allows more robust evaluation of both reliability in assessment and generalisability of research. External validation is straightforward and easily achieved. Kahn *et al* (1999), Oudega *et al* (2001) and Constans *et al* (2001) have all produced categorical scoring systems, stratifying patients into variable levels of risk based on a variety of clinical parameters [108, 112, 113]. Derivation cohorts have all performed appropriately, with prevalence matching apportioned risk, yet none have been externally validated. As such, assessment of pooled likelihood ratios has thus far been omitted from previously described meta-analysis [111].

The most well known clinical prediction model regarding DVT is that derived by Wells *et al* in 1995, combining clinical assessment with non-invasive ultrasound testing [26]. They concluded that low clinical risk in combination with a negative non-invasive test could obviate the need for serial or invasive testing. This clinical model was refined in 1997 and prospectively validated in 593 patients to show a DVT prevalence of 3%, 17% and 75% in low, moderate and high risk groups respectively based on assignation of clinical risk score [114]. The authors demonstrate a reduction in both serial ultrasound use and false negative studies with application of the model and highlight its safety and feasibility when combined with ultrasound of the proximal veins. They go on to modify the algorithm further with addition of

laboratory testing and demonstrate excellent diagnostic utility in landmark journal articles 5 years later [115].

There have been several attempts at validation of clinical scoring systems and subsequent comparative literature has also been produced. Goodacre *et al* assess the original Wells score in their recent meta-analysis and conclude that clinical probability templates outperform individual clinical characteristics [111]. There is little doubt that either an implicit or explicit formal assessment of probability carries more diagnostic weight than individual signs and symptoms. In a systematic review, Tamariz *et al* also concur that the Wells score is likely to significantly aid diagnosis and outperforms others to date [116]. However, there is still debate about the ideal clinical prediction model. As yet, multiple comparative studies have failed to show any particular advantage to use of previously or newly derived scoring systems over the modified Wells criteria [117-119].

The role of fibrin D–dimer testing in suspected lower limb thrombosis

Activation of the coagulation system in vivo results in production of fibrin, the main component of an eventual thrombus. Fibrin production is followed by activation of the fibrinolytic system, with a natural balance between the opposing processes of coagulation and fibrinolysis in the normal physiological state. Dissolution of fibrin leads to specific degradation products including the D-dimer. This product can be quantified in whole blood and plasma using monoclonal antibody techniques, which bind to epitopes on D-dimer fragments and can serve as a reflection of overall clot formation/lysis [120].

The use of D-dimer testing as a diagnostic aid in suspected deep vein thrombosis was first proposed over 24 years ago [121]. Plasma levels have been shown to increase 8-fold with venous thrombosis, in comparison with controls [122]. Initial research focused on labour intensive use of enzyme-linked immunosorbant assays (ELISA) as the gold standard [123]. Improving laboratory techniques have resulted in development of several rapid, quantitative and automated tests. Additional semiquantitative point of care tests are available, to be performed on whole blood at the patients bedside. However, common caveats remain with all d-dimer assays. The plasma half-life of D-dimer fragments is approximately 8 hours with clearance occurring via the kidney and reticulo-endothelial system. Levels have thus been

shown to fall in parallel with symptom duration and treatment [124]. Systemic values are also raised in a variety of additional conditions [125-127] and with advancing age [128]. As such, careful interpretation of data is needed in tandem with clinical presentation and context.

As a result of generally low specificity, a clear role has emerged for d-dimer testing to facilitate the exclusion of venous thromboembolic disease. Given the large number of conditions leading to elevated serum values, clinicians have found most benefit in the reassurance of negative testing. With a low D-dimer level, the likelihood of active thrombotic turnover is purported to be minimal. However, sensitivity is the key test characteristic of interest here, and this value is dependent on the assay used. Although previous gold standard ELISA tests have demonstrated a sensitivity of between 97-100% for exclusion of proximal DVT [121, 122], a recent systematic review of diagnostic accuracy would suggest limitations [129]. In appraisal of 217 test evaluations for suspected DVT, the authors note highest pooled sensitivity rates to be between 93 and 96% with immunofluoresence, ELISA, and latex quantitative assay testing. These strategies all had correspondingly low specificities. There is also on-going debate regarding sensitivity to detect IDDVT, purported to be weaker in general [130] albeit with some recent studies demonstrating 100% sensitivity using a reference standard of whole leg ultrasound [131]. As a result of these concerns, D-dimer use is often combined with clinical probability stratification as described previously. This combination in clinical practice will be addressed in a future section of the thesis.

Due to the variety of different assays in use, standardization also remains an issue with D-dimer testing. Study results have limited generalisability to other populations where alternative assays are used. Fluctuation in unit reporting is also problematic, with many centres reporting results in Fibrinogen Equivalent Units (FEU) rather than ng/mL. This can lead to confusion regarding interpretation of result. Harmonisation and standardization have been promoted as concepts recently and various methods have been suggested and published to this end [132, 133]. Review articles in high impact journals continue to call for standardization, both from a research and clinical care perspective [134, 135]. Until an international consensus is declared, clinicians must be certain of the assay used in their institution with units and range, and cautious of extrapolating results using different assays to their population.

Variation in clinical presentation between distal and proximal lower limb thrombi

If the aetiological profile of IDDVT differs significantly from proximal disease then it could also be reasoned that the clinical presentation may differ. This is an important point to explore. Differing symptomatology could add weight to the theory of distal and proximal disease as separate entities, while also allowing further stratification of investigation in patients with suspected disease. As yet, this is an area of limited clinical research. The majority of studies assessing the value of signs and symptoms in diagnosis of acute DVT have compared against a reference standard which often fails to comprehensively assess for IDDVT. As such, limited datasets exist. Wells *et al* for example have limited ultrasound confirmation of DVT to the proximal veins when assessing their clinical prediction model in practice [26, 114]. This omission was purposeful, with intention to demonstrate the safety of using a clinical prediction model in routine practice. However, the use of this technique as reference standard will undoubtedly miss some distal disease, whether clinically relevant or otherwise. Thus their derivation of clinical factors suggestive of acute thrombosis may not be accurate for IDDVT. In their meta-analysis, Goodacre *et al* report only 6 studies that stratify reference standard outcome between proximal and distal disease, out of a total of 51 articles retrieved after systematic review [111]. The presentation of likelihood ratios derived from individual clinical signs and symptoms appears to use a composite of proximal and distal DVT, detected at venography and/or ultrasound as reference standard. The only described data specific to IDDVT as a dependent variable is the categorization and performance of the Wells score. Interestingly, they conclude that the Wells score does not accurately categorise distal DVT and raise questions about repeated sonography following clinical assessment. This again suggests key differences between distal and proximal disease. It is a finding also supported by recent studies directly comparing clinical decision rules and stratifying by location of thrombus [118]. Despite this, in combination with modern D-dimer testing the Wells and other clinical prediction scores have been shown to demonstrate high sensitivity for the exclusion of IDDVT [131]. Indeed, despite the caveats, a combination of low pre-test clinical probability and negative D-dimer has been recently shown to provide a negative predictive value of > 95% [136]. However, differing performance in prediction of pre-test probability must be understood when utilised within a service

actively looking for and treating IDDVT. More importantly, very few studies have directly compared aspects of the clinical presentation in both proximal and distal disease cohorts from the same population. There is therefore limited understanding about the difference in clinical profile at presentation.

A handful of studies have focused on specific aspects of clinical presentation and location/extent of disease. Labruto *et al* have recently assessed duration of symptomatology between distal and proximal thrombi via a retrospective case series analysis of 100 patients [137]. They report no significant difference (6.3 vs. 6.2 days respectively, p=0.67) in mean duration. This is supported by previous natural history work noting a median of 7 days to presentation in isolated calf muscle vein thrombosis [55] and the work by Wells *et al* (mean duration of symptoms 6.6 days in those diagnosed with VTE) on clinical probability scoring [114].

Regarding clinical signs and symptoms at presentation, Mclafferty *et al* report calf pain in 46%, leg swelling in 18.9% and a combination in 18.9% of IDDVT patients at diagnosis [138]. However this was a small cohort of patients and no clarification was made regarding severity of symptoms, or comparison attempted with proximal disease. Additional prospective natural history studies with larger cohorts have quoted similar rates of poorly described symptoms. Macdonald *et al* note a prevalence of pain in 35.1% of their 185 ICMVT patients and swelling in 20.5% at presentation [55]. Again there is no comparison made within the study, but the implication is one of variation in both signs and symptoms when compared to proximal disease (78 and 82% in some studies) [139].

Contemporary data has lent direct support to this theory. In 2012, Luxembourg *et al* recruited 243 patients to a prospective study comparing various d-dimer assays, with a diagnosis of proximal/isolated distal in 38/31 patients respectively [131]. They note a reduced incidence of entire leg swelling (55 vs. 13%), calf swelling >3cm (37 vs. 13%), pitting oedema in the symptomatic leg (63 vs. 19%) and collateral distended veins (11 vs. 3%). Also, they note increased presentation with pain along palpation of the deep venous system in IDDVT (11 vs. 32%) and replicate Goodacre *et al's* findings that patients with IDDVT are more likely to score intermediate probability on summation of the Wells score [111]. This data is small in sample size and had no statistical assessment for significance, but the raw numbers create a further impression that in addition to an altered risk profile, IDDVT may actually present in a

different clinical manner. This adds weight to the theory of IDDVT as a distinct entity and supports segregation throughout further trials.

Finally there is the issue of laboratory assessment and comparison between distal and proximal disease. Allowing for issues of standardization and variability in presentation, there is good evidence to suggest that D-dimer levels correlate with thrombus burden in VTE [129, 134]. This is a concept that has face validity and has been demonstrated in diagnostic studies, with many assays underperforming (regarding sensitivity) for the detection of IDDVT or isolated subsegmental PE [140, 141]. Yet few studies have directly compared assays or results stratified by location of thrombus, reporting mostly isolated sensitivity data.

Luxembourg *et al* address this in their recent paper assessing the performance of 5 separate assays for the detection of IDDVT [131]. They conclude that several modern assays, when combined with a low pre-test probability Wells score, have a negative predictive value for IDDVT of 100%. This ratifies use in modern practice and provides much sought after data for those championing early detection/exclusion of IDDVT. Interestingly however, they also note a significant difference between the median d-dimer value for cases of proximal and distal disease across all 5 assays (p <0.001). This paper is one of the few to directly quantify the difference between values in acute proximal and distal disease and provides further information to suggest that multiple aspects of presentation can be used to gauge likelihood of VTE location.

Diagnostic algorithms and objective imaging in suspected deep vein thrombosis

Introduction

Ambulatory symptomatic patients with suspected DVT need access to expert assessment, diagnostic imaging and parenteral drug therapy. This can be provided by either rapid access specialist outpatient vascular clinics, or via hospital services. Across much of Europe and North America, specialist vascular clinics appear to provide default management [42, 104, 142]. In the UK, hospital assessment is increasingly falling to the ED as the only arena with 24-hour open access, expertise in diagnostics and the ability to safely and rapidly deliver therapeutic anticoagulation. Indeed, the recently published quality indicators for judging excellence in unscheduled emergency care contain the management of ambulatory DVT patients as a specific target [23]. Thus, governmental focus rewards those trusts that effectively facilitate ambulatory assessment.

Ruling out Deep Vein Thrombosis in patients with a low pre-test probability

It has already been established within this review that modern d-dimer techniques have a high sensitivity for the detection of acute venous thrombosis. Indeed, Bounameaux *et al* collated several studies utilising the rapid ELISA d-dimer assay to provide an estimated sensitivity of 98% (95% CI 94-100%) for detection of DVT in suspected cases, with a corresponding specificity of 54% (95% CI 47-62%) [143]. Thus, the test becomes a SnOUT, in that the high sensitivity allows use of the test as a rule out/exclusion tool [144]. This diagnostic method can be strengthened by inclusion of clinical probability assessment prior to testing. Wells *et al* have prospectively evaluated this theory and demonstrated a significant reduction in the use of diagnostic imaging, with a low subsequent VTE event rate over three month follow up [115]. To expand briefly, a score of less than or equal to 2 using modified criteria generates a pre-test probability/ estimated prevalence of <22% [145]. Thus, with a negative quantitative ELISA d-dimer assay in addition, the post-test probability becomes <2%. This is considered sufficient to exclude the diagnosis without further

diagnostic imaging. As such, this policy has been advocated by the British Society of Haematology [25], suggested as the most cost effective by a Health Technology Assessment within the last decade [7] and endorsed by leading VTE experts [146]. A meta-analysis of 11 studies including over 6800 patients, subsequently confirmed the safety of withholding anticoagulants based on a low clinical probability with a negative d-dimer result, giving a overall VTE rate of 0.44% (95% CI 0.2-0.83%) [147] at three month follow up. This approach to diagnostics has been internationally accepted and recommended in several contemporary guidance documents [13, 148].

The decline of venography and ultrasound as an emerging reference standard: ruling in DVT

When a patient is deemed to have a high pre-test probability using an established prediction rule or has a positive d-dimer in the context of suspected DVT, further investigation and objective tests are mandatory. This is principally as a result of the poor specificity seen with modern d-dimer assays: treatment of all positive cases would result in unnecessary anticoagulation and potential maleficence. Previously this used to mean ascending contrast venography, a technique still described as 'the gold standard diagnostic test' by some experts [25]. However, this technique carries multiple restrictions as a result of its invasive nature, use of iodinated contrast and both time/resource implications. The test also has documented practical failure rates of up to 14% with the need to cannulate pedal vessels in swollen limbs, high levels of disagreement with regard to key findings and common inadequate visualisation of specific vascular segments [149-151]. It has also been shown to cause DVT with recurrent examination in up to 7% cases [152]. It is a poor choice for patient comfort, diagnostic accuracy and serial monitoring.

After early studies utilising compression ultrasonography as a non-invasive diagnostic tool demonstrated comparable sensitivity data [153], frank editorials questioned the 'gold standard' label of venography as early as the 1980s [154]. Further clinical research cast sharp focus on technical failure rates of contrast venography in practice and reiterated the high sensitivity seen using compression ultrasonography [155]. This led to adoption of ultrasound as a non-invasive test and consequent widespread reduction in use of contrast venography. At the turn of the century, a diagnostic meta-

analysis was performed demonstrating a 97% (95% CI 96-98%) sensitivity for proximal DVT detection [156]. However, a vital distinction here is made between the sensitivity of compression ultrasound (CUS) for detection of proximal and *distal* DVT. Results published in the above meta-analysis quoted sensitivity rates for IDDVT detection as low as 73% with CUS, rendering the test unable to confidently exclude the condition. However, this was not quite the setback expected. Many authors cited the low propagation and embolic rates for distal DVT in defence of CUS, arguing that sensitivity below the knee was of minimal importance. The suggestion was made to repeat the scan in a week's time, in order to detect the minimal number of calf thromboses that would propagate early and potentially embolise. Thus serial CUS emerged as a diagnostic technique of choice, defined as ultrasound examination of proximal lower leg vessels at presentation and one week.

Additional imaging modalities

Further imaging strategies in suspected DVT other than CUS have been trialled with limited success. CT venography was thought to be a potentially more reliable and robust alternative to ultrasound, with pooled sensitivity rates of 96% (95% CI 93-98) at recent meta-analysis [157]. However, most of the studies included within this review used CUS as a reference standard for comparison, raising concerns regarding under or overestimation of accuracy dependent on local CUS performance. Additionally, the authors note only two studies assessing CT venography for the presence of distal DVT, mostly within the context of suspected PE and comprising only 117 patients [158, 159]. Although sensitivity was reported between 93-100%, all misclassifications occurred below the level of the popliteal vein. This would suggest insufficient research to promote routine use due to cost, increased radiation exposure for limited gain and remaining concerns about accurate detection of IDDVT.

Magnetic resonance imaging has been a worse disappointment, with a pooled sensitivity rate of 91.5% (95% CI 92.6 to 96.5) and a vastly reduced sensitivity for detection of distal disease (62.1%). The meta-analysis providing these test characteristics used contrast venography as a reference standard and reports significant heterogeneity between published studies [160].

Lastly, several methods of plethysmography and rheography have been assessed as

stand alone diagnostic techniques for the investigation of deep vein thrombosis and compared against reference standards of venography/sonography. These techniques work on the premise of either non-invasive detection of alterations in venous capacitance and outflow in the presence of deep vein thrombus, or alterations in venous volume within the lower limb. Nearly all of these techniques have been shown to have a sensitivity of < 90% on meta-analysis and are subject to concerns regarding false positive results [161]. All have a limited role in VTE diagnostics within a modern diagnostic framework.

Current diagnostic strategy: serial proximal vs. whole-leg compression ultrasonography

As use of contrast venography began to decline, the published diagnostic accuracy of distal CUS examination began to improve in comparison to previous results [162]. An expectation arose that technological advancement and increasing experience in the distal limb may advance to acceptable levels. As a consequence, many experts refined and incorporated distal assessment into their CUS imaging strategy. This concept became known as whole-leg CUS, a popular strategy for its multiple advantages over serial examination.

Firstly, whole-leg CUS has the ability to potentially exclude DVT at the first visit, with no need for repeat attendance or sonographic examination. This is potentially more cost effective than serial assessment, although no studies have formally evaluated this and further research has been called for [13]. Whole-leg CUS is also of particular benefit to those clinicians with a mobile population or those of low socio-economic status. Many of these patients will neglect to return for follow up appointment and thus compromise diagnostic strategy with serial CUS [163]. Even if patients do return at 5-7 days for repeat imaging, the diagnostic yield is reported to be <5%, highlighting the large resource use for limited return [163, 164]. Whole-leg CUS also provides a clear window to institute treatment immediately after diagnosis. This is relevant both for symptomatic and propagating IDDVT, but also in poorly compliant cohorts such as intravenous drug users [165]. Sonography of the calf also provides comprehensive imaging to evaluate for common mimics of DVT. Acute confirmed diagnosis of calf haematoma or ruptured Baker's cyst can be useful regarding patient satisfaction and withholding anticoagulation: many patients

awaiting serial ultrasound are treated in the interim week with the potential for complications.

Most importantly however, whole-leg ultrasound makes a thorough assessment for the presence of IDDVT. Although therapeutic management is controversial in this area, diagnosis at least provides both the patient and clinician with as much information as possible on which to base clinical decision-making. It can also play a valuable role in accurate diagnosis of recurrent disease, quantification of post thrombotic risk and tailored therapy.

There are multiple cited caveats to whole-leg CUS. Several authors raise concerns about the lower sensitivity seen on systematic review, with Goodacre *et al* quoting a pooled sensitivity of 75.2% (95% CI 67 to 81) with triplex ultrasonography compared to 96.4% (95% CI 94.4 to 97.1) for detection of proximal disease [166]. Experts argue that if objective imaging is likely to miss 25% cases, it cannot be relied upon as a single test [19]. There are issues with this argument: the above meta-analysis collates studies performed over a 30 year period and as such exposes pooled sensitivity to significant dilution from earlier underperformance. Improving technology and clinical skill has naturally led to a reported higher sensitivity (92-100%) in modern clinical practice [162, 167, 168]. In addition, most studies compare whole-leg CUS to a gold standard of contrast venography. There is evidence to suggest formation of thrombi and false positive results with this standard [152], both of which are more likely in the smaller veins of the calf. Thus sensitivity can be falsely reduced due to over performance of the reference standard. Indeed, some papers have suggested CUS to even *outperform* contrast venography for the diagnosis of calf muscle vein thrombosis [169].

Perhaps a more valid caveat is the concern regarding overtreatment. Diagnostic randomized controlled trials comparing serial to whole-leg CUS suggest a far greater proportion of patients will receive anticoagulation in the latter group, with minimal difference in outcome [164, 170]. This has been confirmed by additional outcome studies assessing clinical sequelae at three months in light of initial blinded distal CUS findings [171]. Although the specificity of whole-leg CUS is reported as high concerns are raised about the proportion of patients that will be 'unnecessarily' anticoagulated with a concomitant haemorrhagic risk [19]. This argument assumes that there are no merits to treating IDDVT that has not propagated within one week, which remains an area of on-going debate: short-term treatment may well reduce

symptomatology and prevent post-thrombotic syndrome at a later stage. In addition, cases of IDDVT have been shown to propagate after 1 week [172]. These studies were also performed at a time when local international guidance clearly suggested at least three months full therapeutic anticoagulation for IDDVT [92, 173, 174]. The new American College of Chest Physicians (ACCP) guidance is more conservative, suggesting serial evaluation in the majority of cases [11]. As such, the burden of anticoagulation within the context of similar studies may well be reduced.

Lastly, variability in reporting is a suggested concern along with additional training, cost and time needed for whole-leg examination. However, several studies have examined inter-rater reliability with distal CUS and report Kappa values of 0.6, 0.9 and 0.75 [167, 175, 176]. Whole-leg CUS can also be performed in at most a third of the time it takes to perform contrast venography, modern data quoting a 10-15 minute examination time for bilateral limb assessment [42]. Cost effectiveness, as alluded to earlier, is an area in need of further study and clarification as confirmed by a recent national call [13, 177].

Both whole-leg and serial proximal CUS have received further attention and developed in tandem as diagnostic reference standards over the last decade. The modern use of two distinct investigative strategies for investigation of such a common problem captures the academic uncertainty regarding IDDVT and reinforces the need for further research. In the North West of England, separate diagnostic strategies are utilised in hospitals no more than 6 miles apart. Shared trainees remain confused about best practice and patients suffer from uncertainty in clinical decision-making.

Current diagnostic strategy: safety and clinical utility of modern ultrasound techniques

Modern work investigating serial CUS focuses primarily on safety. In 2009 Gibson *et al* published a prospective management study randomising consecutive patients with suspected DVT following risk assessment/d-dimer testing to either serial CUS or complete CUS [164]. Five hundred and twenty two patients underwent ultrasound scanning and 3-month follow up. The subsequent incidence of VTE following a negative scan during the review period, was 2% (95% CI 0.6% to 5.1%) in the serial CUS group and 1.2% (95% CI 0.2% to 4.3%) in the complete CUS group, an absolute

difference of 0.8% (95% CI -1.8% to 3.4%) with p=0.69. This figure is in keeping with a previous large diagnostic equivalence trial from 2008 quoting an observed difference between US techniques of 0.3% (95% CI -1.4% to 0.8%), regard development of symptomatic VTE [170].

There is also compelling evidence that serial CUS will lead to a reduction in anticoagulation without a corresponding decline in outcome. Gibson *et al* in the above study note an incidence of venous thrombosis in 23% (95% CI 18 to 28%) of patients undergoing serial CUS, compared to 38% (95% CI 32 to 43%) after complete CUS (p<0.001) within the same prospective patient cohort. 38 of the 99 thromboses detected in the latter were naturally confined to the distal veins. Thus, an extra 38 patients in the complete CUS group received anticoagulation including all inherent risks, with no obvious benefit to three-month outcome. This point is replicated in the recent blinded cohort study by Palareti *et al* [171]. Sixty five cases of IDDVT were diagnosed (15.3% of all patients negative at serial CUS). The majority of these distal thromboses remained quiescent, with only 3 patients achieving the primary outcome who were not diagnosed on initial serial CUS. Serial CUS is rapid, reproducible and widely available round the clock once the relevant staff are trained [178]. This can be achieved in less than 2 hours according to some authors [179]. The technique thus acquires an immediate advantage of availability and accessibility.

There are several drawbacks to serial CUS. The organisational, practical and cost implications of patients returning for a second scan one week later are not without concern, especially with the limited diagnostic yield seen at return visit [164, 170]. The technique is considered by many to carry a large onus on resource for minimal diagnostic return. Fatal VTE events have also been reported during the seven days while patients await serial scan and other studies confirm the potential concern that patients may decline to return for a secondary imaging [163, 180]. Although these are rare occurrences, they are potentially avoidable events.

Serial CUS also completely ignores the potential pathology of non-propagating calf thrombosis. This is an area with limited definitive research, therefore open to diverse opinion based on small studies. The largest trials assessing safety of serial CUS follow patients for 3 months post scan and look for confirmed incidence of VTE events only [164, 170]. This ignores the potential influence of IDDVT on acute symptomatology, recurrence, later VTE events and perhaps most importantly the long

term consequence of venous obstruction, post thrombotic syndrome (PTS). Saarinen *et al* followed 50 patients with phlebographically confirmed calf DVT for a mean of 8.4 years after the acute event, reporting their findings in 2002 [181]. They noted recurrence in 14%, deep popliteal reflux in 40% and using the CEAP classification noted skin changes suggestive of veno-occlusive disease in 34% patients. They conclude that IDDVT may lead to significant post-thrombotic disease, a finding supported by earlier studies [182]. Contemporary studies corroborate this association [183]. Further conclusive proof of causation is needed. However, no measures can be taken against this potential outcome unless diagnostic strategy includes initial visualisation of the calf veins.

Advocates of the above continue to cite the argument that complete CUS will lead to overzealous anticoagulation. However, this view is not shared international consensus. The more work that is done, the more consensus bodies appear to recognise the value of treatment; if not to reduce short term events, then to improve long term outcome. A more relevant argument against complete CUS could be the poor sensitivity shown in earlier studies and lack of modern definitive data. Many authors remain unconvinced of its applicability to the distal lower limb and diagnostic accuracy has been questioned, with articles citing variation in sensitivity from 50% to 95% in studies conducted only three years apart [184]. Other authors also highlight the increased need for superior technology and higher levels of experience training to perform complete CUS, often resulting in limited availability out of hours and a high rate of technical failure [185]. As noted previously, serial CUS has been demonstrated as reliable in the hands of emergency physicians after minimal formal training. Indeed, when using formal radiologist performed ultrasound as a reference standard, a recent diagnostic study has confirmed a sensitivity and specificity of 100% and 99% respectively in a cohort of 199 prospective ED patients [186]. It remains to be seen whether complete CUS will ever reach this degree of accessibility and transferability. Contemporary studies remain positive however, quoting ever-decreasing failure rates to less than 1% and improved sensitivity and specificity with specialist equipment [42]. The concept of single complete CUS allowing rapid and conclusive diagnosis, while also specifically identifying IDDVT in the acute stage to allow informed treatment decisions, is one supported and championed by many leading authors [22].

The most modern and conclusive work advocating complete CUS concentrates again

on safety. Given the difficulty in conducting accurate diagnostic trials due to multiple problems with the reference standard of venography, recent large prospective trials have focussed on the clinical impact of withholding anticoagulation following a negative complete CUS. In a landmark issue of a 2003 journal, both Elias and Schellong published multi-centre prospective cohort studies addressing this directly [41, 42]. Both authors combined followed over 1400 patients for three months after complete CUS to determine symptomatic VTE incidence data and concluded event rates <1% (0.3% (95% CI 0.1% to 0.8%) and 0.5% (95% CI, 0.1% to 0.8%) respectively). A further systematic review and meta-analysis performed by Johnson *et al* in 2010 confirms the safety of withholding anticoagulation following a negative whole-leg CUS, with a combined VTE event rate at 3 months of 0.57% (95% CI, 0.25% to 0.89%) [177]. This followed a meta-analysis of data for over 4700 patients, the only caveat being the low proportion of patients deemed to be at intermediate - high risk after pre-probability assessment. This is a further area of research interest, as noted by the authors.

Conclusion

The fact that both serial CUS and complete CUS remain in modern diagnostic practice highlights the sustained academic uncertainty regarding IDDVT. A cohort of physicians reiterate the concept that non propagating IDDVT is not worth looking for, while others cite the sequelae of untreated disease and the need to identify thrombus acutely. The British Committee for Standards in Haematology (BCSH) clearly advocate treatment for IDDVT but also endorse a diagnostic algorithm ignoring the importance of it. This equipoise within the literature is reflected in the diversity of contemporary management strategies.

Clinical Management of IDDVT: Review of Primary Research

Introduction

IDDVT differs from proximal disease not just in epidemiology, aetiology and clinical presentation. The natural history seen with distal thrombi is variable and often quite different to that of proximal DVT. With less direct morbidity and mortality consequences, many authors argue that the potential benefits of aggressive investigation and treatment are outweighed by the quantifiable complications [16, 19]. This issue creates a divide in expert opinion, leading to contradictory advice and variable practice.

The main risks of proximal DVT have been well established in the literature as acute symptomatic progression, propagation, embolisation and chronic post-thrombotic syndrome [187-189]. There is full agreement between international experts and national advisory panels that in the event of proximal DVT, the perceived benefit from treatment with anticoagulation outweighs potential risk in the majority of cases [11, 12, 173]. This balance of risk against benefit is far more even in IDDVT, leading to clinical equipoise. In order to highlight the importance of each key issue it is appropriate to consider the impact of disease on the individual patient, the magnitude of each potentially serious risk and the supporting evidence in turn.

The evidence regarding symptomatic progression of IDDVT in the absence of anticoagulation

As noted previously, IDDVT can present with acute symptoms. Indeed, some studies suggest >50% of symptomatic acute disease will be confined to the distal veins in an outpatient setting [39]. Pain, swelling and superficial venous distension are all well documented [190]. Disregarding the inherent risk of thrombus progression/embolisation, clinicians facing patients with any DVT are naturally keen to ameliorate symptoms and suffering. Experts often comment on the prominent role of anticoagulant therapy for acute relief in this aspect of management [191].

However, there is little evidence to evaluate the benefit of therapy in this aspect of disease management.

Some natural history studies have reported long term clinical follow up of IDDVT. McLafferty *et al* followed 25% of patients diagnosed at their institution for a median of 3.4 years (IQR 2.2 to 5.8) [138]. They report 62% of patients to be asymptomatic at review, with only 3 patients demonstrating either on-going oedema or ulceration using a clinical scoring system. Their study results are hampered by the fact that 51% of patients received therapeutic anticoagulation, but there is no attempt to discriminate symptomatology between those treated and conservatively managed. They offer no short-term data on outcome. No correlation was noted between symptomatology and repeat vascular imaging.

Meissner *et al* offer similar natural history data, with identical confounding [182]. The authors recruited 50 extremities with IDDVT confirmed by duplex CUS and followed up by clinical review at 2 weeks and 12 months. They note a sustained decrease in the prevalence of symptoms (oedema and/or pain) from 70% at diagnosis, to 33% at 2 weeks and 23% at 1 year. Multiple patients were lost to follow up during this time. Also, over 70% patients were treated with some form of anticoagulation. Thus, although the authors quote a significant difference in prevalence of symptoms compared to either normal limbs or proximal disease, this study offers no information as to whether therapeutic treatment aids early resolution of acute symptoms.

A more recent retrospective study examined the proportion of symptom resolution at 7-month follow up, in patients initially presenting with IDDVT [192]. Subjects were managed by attending clinician with either conservative care, a short course of LMWH or 3 months phased warfarinisation. No statistically significant difference was reported between groups regarding symptom resolution, with 85.7% of conservatively managed patients purporting to be symptom free at final follow up.

Lastly, Lagerstedt *et al* report vague data on clinical progression scores in a small cohort of patients with IDDVT, randomly managed by therapeutic anticoagulation or conservative follow up [172]. They report that the pain score utilized (a non-validated 4 point scale [193]) "fell in the same way between the two groups", with 56% patients overall symptom free at 14 days and 93% at 90 day follow up. There is no attempt at statistical comparison or presentation of raw data. All patients also received a 5-day therapeutic course of intravenous heparin prior to discharge, which many would consider a form of acute treatment. Of note, they report significantly higher pain

scores in conservatively managed patients who went on to have propagation or recurrence, compared to those who did not (p<0.05). Although there are many flaws with this data, it provides some face validity to the concept of worsening symptoms correlating with the acute inflammatory component of the disease.

This is clearly an area devoid of pragmatic research. Quality of life outcomes and short-term clinical features with or without anticoagulation, are particularly absent from the literature. Recent discussion articles highlight the need for contemporary data and note that clinically relevant end points for further DVT trials "might reasonably include *the relief of acute symptoms*, in addition to the prevention of proximal extension, embolisation, and recurrence" [194].

The evidence regarding propagation of IDDVT in the absence of anticoagulation

Much of the literature has considered extension of IDDVT only relevant if it reaches the level of the popliteal trifurcation, or proximal veins. This is not necessarily the only clinical endpoint of interest with disease. Local extension/increased thrombus burden within the calf can acutely worsen symptoms and potentially exacerbate long-term complications [183]. As such, the most recent American guidance documents promote full treatment if any local extension is seen [148]. Although the risks with local and proximal propagation differ, it is worthwhile to consider the evidence regarding both in the context of untreated IDDVT.

Local propagation confined to the calf veins

Both observational and prospective randomized trials have assessed the extension rate of IDDVT within local calf veins. Some studies have utilized novel short-term treatment protocols in attempt to validate the theory that calf thrombi require limited intervention. In addition, several authors have assessed the rate of extension utilizing prophylactic anticoagulation only. In the TICT study for example, Parisi *et al* restricted IDDVT patients to a reducing regimen of LMWH for only four weeks [195]. They describe a 1.7% and 4.1% rate of local and overall extension respectively. Singh *et al* have followed this recently, with a prospective evaluation of 180 limbs with IDDVT treated with prophylactic dose heparin [58]. Patients were followed with

sequential duplex exam for at least three months. Propagation was seen in only 11/180 (6.1%) limbs. Other subsets within larger trials, looking specifically at the rate of extension within IDDVT patients receiving prophylactic dose heparin report even lower rates of propagation (3.0%) [196]. These trials are often subject to selection, measurement and assessor bias.

Of more interest are patients receiving no anticoagulation for treatment of IDDVT and their subsequent rates of extension. The rate of propagation here and the consequent reduction with therapeutic anticoagulation is poorly defined. Publications in the literature demonstrate variable data, likely as a result of extensive heterogeneity in sample population, methodology and follow up regimen. A summary of studies within the last 20 years including local and total (local and/or proximal) propagation rates is provided in Table 1 overleaf.

A trend is noted of higher local propagation rates in the earlier studies. Lohr *et al* collated symptomatic inpatient and outpatients in both 1991 and 1995, demonstrating a 17.3% and 16.7% risk of local propagation with conservative management [197, 198]. Schwarz *et al* noted a local extension rate of 25% (95% CI 11.5 to 43.4) for ICMVT in 32 patients treated with only compression therapy in 2001 [199]. Over 15% of these patients had active cancer and the cohort was essentially observational. Macdonald *et al* followed this in 2003 with a natural history study assessing ICMVT by duplex follow up and recording local extension in 13.3% patients without anticoagulation [55].

Later studies are more conservative in their description of event rates. Lautz *et al* describe only 5.2% local propagation in their 2009 retrospective review [200], although this is likely to be falsely low due to bias in treatment decisions (as per clinician) and lack of rigorous follow up for the cohort of interest. Both Schwarz and Palareti *et al* report rates less than 2% in their 2010 prospective cohorts [171, 201]. Whether this decline is attributable to methodological changes, exclusion of inpatients or failure to quantify local venous changes accurately is uncertain. The possibility of selection bias must also be considered. Up until very recently, international guidance has clearly recommended 3 months anticoagulation for IDDVT [92, 174]. Trials

Table 1: Studies assessing local and total propagation in untreated IDDVT patients

CUS refers to compression ultrasound. Data is 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 commenced on therapeutic LMWH on diagnosis of extension to the deep calf veins. This may explain the notably low rate of proximal extension.

Author/Year	Population	Sample Size	Diagnostic method	Duration of follow up for primary endpoint	Local propagation rate	Total propagation rate
Lohr et al 1991[194]	Symptomatic medical and surgical inpatients	75	CUS	3 months	13/75 (17.3%)	24/75 (32.0%)
Lohr et al 1995 [193]	Mostly symptomatic surgical and medical inpatients (59.4%)	192	CUS	4 weeks	32/192 (16.7%)	53/192 (28%)
Schwarz et al 2001 [195]	Symptomatic outpatients with isolated calf muscle vein thrombosis	32	CUS	3 months	8/32 (25%)	8/32 (25%) *
Macdonald et al 2003 [54]	Mostly symptomatic surgical and medical inpatients (68.6%) with isolated calf muscle vein thrombus	135	CUS	3 months	18/135 (13.3%)	22/135 (16.3%)
Lautz et al 2009 [196]	Retrospective cohort of in 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 [197]	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 [167]	Symptomatic outpatients	65	CUS	3 months	1/64 (1.6%)	4/64 (6.3%)

conducted prior to recent developments may have found it increasingly difficult to recruit subjects with acute symptomatic disease, focusing only on those with inconclusive results or minimal symptoms.

One of the key problems with this data is that of objective definition for local recurrence/extension. Several papers base their results on subjective interpretation of ultrasound, performed by unblinded clinicians who have knowledge of treatment regimen, symptomatology and risk profile. There is reasonable evidence to suggest that increases in thrombus length less than 9cm can be within the bounds of measurement error [202]. Minor incidental changes may thus falsely be classed as local propagation, especially in the context of open label therapy creating subconscious and conscious bias in the ultrasonographer. Several IDDVT studies seem to abandon the idea of measuring extension within the calf, possibly for these reasons [163, 194]. This is less likely when local propagation is classed by additional segment involvement. More recent study of blinded modern ultrasound techniques performed by independent technicians would suggest the interobserver reliability to be vastly improved. Tan *et al* have recently reported detection of residual thrombus presence, length and occlusion to be very good (Kappa 0.92), good and fair respectively [203]. Several scoring systems have been proposed to quantify thrombus load and location, in an attempt to provide a more objective estimate of changing disease burden during follow up [204]. The Marder and the Tibial Thrombosis Score appear to be in most common use. Modern studies must consider objective criteria essential.

There is no high level evidence that anticoagulation reduces local propagation at present. Schwarz *et al* in 2001 noted a reduction in calf extension/propagation from 25% to 0% with therapeutic nadroparin, but refuted that data with a subsequent randomized controlled trial [199, 201]. All the other papers quoted fail to randomise treatment and essentially perform observational follow-up studies in groups of patients treated by clinician discretion.

Proximal propagation to the level of the popliteal trifurcation and above

The popliteal trifurcation has been labelled as the diagnostic cut-point for proximal propagation. Thrombus at this level or above has been associated with a rising

increase in embolism, recurrence and post thrombotic syndrome if left untreated. These are the principal reasons for the use of proximal propagation as a surrogate marker for morbidity in clinical trials.

Recent observational studies assessing proximal propagation in untreated IDDVT patients are numerous and summarized in table 2 overleaf [102, 205-207]. Perhaps the most well-known, is that conducted by Lagerstedt *et al* in 1985, the only prospective randomized trial comparing standard phased oral anticoagulation to conservative treatment in the management of acute IDDVT [172]. The authors describe a proximal propagation rate of 17.9% in the conservative group, reduced to 0% with three months full therapeutic anticoagulation. Multiple concerns have been raised about this study, including the high prevalence of prior thrombosis in the conservative group, the use of radio labelled technetium scan for diagnosis and small sample size. However, it remains often cited by proponents of anticoagulation whenever the debate is raised as the highest level of applicable evidence.

Contemporary research includes the recent study published in 2010 by Palareti *et al.* The authors managed 431 subjects with suspected DVT via normal protocols and serial above knee ultrasound scan, but also performed calf ultrasound via operators blinded to the results of above knee imaging [171]. Treatment decisions were based on above knee scan outcome only. The distal CUS results were only disclosed to clinicians and patients after 3 months follow up. 65 of the 431 patients had distal DVT for which they were not treated. One patient was lost to follow up. Of the remaining 64, only 3 patients developed symptomatic proximal propagation confirmed by ultrasound (4.7%, 95% CI 1-13). At three month follow up 59 of 64 were free from thrombotic complications and symptoms had markedly improved in the majority, despite receiving no specific treatment other than elastic compression stockings and non-steroidal anti-inflammatory drugs.

Following this, Schwarz *et al* published an open label controlled trial, prospectively randomising sonographically proven acute isolated calf muscle vein thrombosis to treatment with 10 days of LMWH anticoagulation at therapeutic dosage and compression stockings, or compression stockings alone [201]. Although their cohort excluded DVT in the deep calf veins, they report similarly low rates of propagation to proximal DVT, only 1.9% in untreated patients. They also report thrombus recannalisation in 66% of the cohort receiving heparin and 60% in the group without anticoagulation. These modern studies are a far cry from the predicted propagation

rates of 29-44% quoted previously and perhaps reflect an increasingly low risk presenting population, given the escalating attention on VTE as a disease entity.

Table 2: Studies assessing proximal propagation in untreated IDDVT patients

CUS refers to compression ultrasound. Data is presented as Mean (SD), Median (IQR) or n/N (percentage) as seen. Proximal propagation rate refers to any propagation of thrombus above the popliteal trifurcation.

Author/Year	Population	Sample Size	Diagnostic method	Duration of follow up	Proximal propagation rate
Lagerstedt et al 1985 [168]	Symptomatic medical patients	28	Isotope uptake then phlebography	90 days	5/28 (17.9%)
Lohr et al 1991 [194]	Symptomatic medical and surgical inpatients	75	CUS	3 months	11/75 (14.7%)
Solis et al 1992 [207]	Inpatient combination of postoperative hip and knee arthroplasty patients. Physician led follow up.	28	Ascending Venography with follow up CUS	Unclarified	2/25 (8.0%)
Oishi et al 1994 [206]	Asymptomatic postoperative THR/TKR patients	41	CUS	12 months	7/41 (17.1%)
Lohr et al 1995 [193]	Mostly symptomatic surgical and medical inpatients (59.4%)	192	CUS	4 weeks	21/192 (11.3%)
Masuda et al 1998 [102]	Retrospective outpatient cohort managed by attending physician	26	CUS	6 months	2/26 (7.7%)
Kazmers et al 1999 [205]	Symptomatic outpatients undergoing at least one follow up scan	35	CUS	Unclarified	2/35 (5.7%)
Macdonald et al 2003 [54]	Mostly symptomatic surgical and medical inpatients (68.6%) with isolated calf muscle vein thrombus	135	CUS	3 months	4/135 (3.0%)
Lautz et al 2009 [196]	Retrospective cohort of in and outpatients with ICMVT who received at least 1 follow up CUS	406	CUS	7.5 (11) months	45/406 (11.1%)
Schwarz et al 2010 [197]	Low risk ambulatory patients with isolated calf muscle thrombus	53	CUS	3 months	1/53 (1.9%)
Palareti et al 2010 [167]	Symptomatic outpatients	65	CUS	3 months	3/64 (4.7%)
Labropoulus et al [247]	Symptomatic medical and surgical inpatients and outpatients	29	CUS	5-11 months	5/29 (17.2%)

The evidence regarding embolisation of IDDVT in the absence of anticoagulation

Introduction

There are two separate issues with regards to embolisation risk and IDDVT. First is the issue of asymptomatic disease. Silent pulmonary embolisation has been demonstrated as early as the 1970s, albeit in trials with low sample size and poor methodological quality [208, 209]. Later data performing ventilation/perfusion lung imaging in patients with venographically confirmed lower extremity thrombosis, documents a 33% prevalence of associated pulmonary embolism [210]. This data has been replicated in patients with distal disease, one study again confirming the prevalence of silent PE in 33% of patients with recently venographically confirmed calf vein thrombus [211]. A recent systematic review confirms the risk, albeit significantly less than that associated with the detection of proximal disease (13 vs. 36% respectively, p<0.0001) [212]. Interestingly, the authors here state that recurrent pulmonary emboli are statistically more likely to occur in DVT patients with previous silent PE, compared to those with no silent PE. Further trials are not likely to be forthcoming given the ethical complexity of further radiation exposure via screening for asymptomatic disease.

Second and perhaps more important, is the issue of subsequent and symptomatic embolisation in the context of IDDVT. This is an issue of far greater clinical relevance and one of particular interest to clinicians undecided about therapeutic management of distal disease. The evidence regarding this topic is explored below.

Symptomatic embolisation following diagnosis of IDDVT

That a risk of symptomatic embolisation exists with IDDVT is not currently debated. Some authors cite this risk of embolisation as an sole indication for full therapeutic anticoagulation in all patients [213]. However, it is perhaps more appropriate to focus on the quantification of this risk, the possibility of predicting embolisation and the numerical and qualitative balance associated with the dangers and social burden of anticoagulation. If the rate of IDDVT propagating to proximal is low then can it be construed that the embolic potential will be negated in a similar manner?

Although hard data are scarce, many authors would suggest is the case. In 1992 Monreal *et al* attempted to determine the influence of multiple disease factors on the presence of pulmonary embolism in patients with DVT, by performing baseline lung scintigraphy in 434 patients with confirmed DVT regardless of respiratory symptoms [214]. Indeterminate lung scan findings excluded 76 patients leaving a cohort of 364 in total. Five key variables were examined by logistic regression analysis to determine embolic potential in known DVT cases. Scintigraphic evidence of PE *without clinical symptoms* was found in a higher proportion of proximal DVT patients compared to distal (31% vs. 9% respectively, p=0.005). Some authors cite this data as proof that IDDVT have a lower embolic potential [21]. However this assumption is certainly not based on conclusive data. Looking at the total burden of pulmonary VTE (silent and clinically apparent) in both groups revealed no significant difference between proximal and distal location, with an odds ratio of 1.0 (95% CI 0.38-1.73). In fact the true incidence of PE in the context of DVT was quoted as 44.4% and 45.2% for distal and proximal disease respectively. This study also based diagnosis of DVT on ascending venography and diagnosis of pulmonary VTE on isolated lung scintigraphy, a process with worryingly low sensitivity when used independently, as noted in earlier studies [215]. Further research provides evidence that IDDVT has the potential to embolise, but lacks prospective data collection and follow up. Ohgi *et al* demonstrated pulmonary VTE at presentation in 21.4% patients with confirmed IDDVT (via venography) in 1998 but neglected to follow up those without PE [216]. Kazmers *et al* took this a step further and recorded retrospective data looking at confirmed IDDVT patients who underwent V/Q scanning over a two year period, reporting a subsequent diagnosis of PE in 8.5% patients [205]. Lack of standardised treatment, follow up and criteria for investigation of pulmonary VTE renders these results ungeneralisable to a modern cohort. Other investigators have assessed PE risk post operatively in treated and untreated IDDVT patients [217, 218]. However, although it is established that IDDVT can present in tandem with pulmonary VTE, the key question remains to what degree untreated distal disease renders the patient at risk of developing *symptomatic* PE. A summary of studies exploring this element of prognosis is presented in Table 3 overleaf.

Table 3: Studies assessing pulmonary embolism rates in untreated IDDVT patients

CUS refers to compression ultrasound. Data is presented as Mean (SD), Median (IQR) or n/N (percentage) as seen. Total propagation rate refers to any propagation of thrombus above or below the popliteal trifurcation.

Author/Year	Population	Sample Size	Diagnostic method	Duration of follow up for primary endpoint	Pulmonary embolism rate
Lagerstedt et al 1985 [168]	Symptomatic medical patients	28	Isotopic uptake confirmed by ascending phlebography	90 days	1/28 (3.6%)
Solis et al 1992 [203]	Inpatient combination of postoperative hip and knee arthroplasty patients. Physician led follow up.	28	Ascending Venography with follow up CUS	Unclarified	0/28 (0%)
Pelligrini et al 1993 [213]	Post operative Hip athroplasty patients nested within prophylaxis RCT	24	Blinded contrast venogram	33 days (22 to 52)	4/24 (16.7%)
Oishi et al 1994 [202]	Asymptomatic postoperative THR/TKR patients	41	CUS	6 months	0/41 (0%)
Masuda et al 1998 [101]	Retrospective outpatient cohort managed by attending physician	26	CUS	6 months	0/26 (0%)
Schwarz et al 2001 [195]	Low risk ambulatory patients with isolated calf muscle thrombus	32	CUS	3 months	0/32 (0%)
Dorr et al 2007 [214]	Post operative Hip and knee athroplasty patients nested within prophylaxis RCT	25	Single CUS at 24 hours post op	6 months	0/25 (0%)
Lautz et al 2009 [196]	Retrospective cohort of in and outpatients with ICMVT who received at least one follow up CUS	406	CUS	7.5 (11) months	7/119 (5.9%)
Schwarz et al 2010 [197]	Low risk ambulatory patients with isolated calf muscle thrombus	53	CUS	3 months	0/53 (0%)
Palareti et al 2010 [167]	Symptomatic outpatients with confirmed IDDVT	65	CUS	3 months	1/64 (1.6%)
Labropoulus et al [247]	Symptomatic medical and surgical inpatients and outpatients	29	CUS	5-11 months	1/29 (3.4%)

The only previous randomised trial comparing standard oral anticoagulation with conservative treatment in 51 patients with distal thrombosis confirmed by venography, reported a single PE (via scintigraphy) in the conservative group [172]. The patient refused confirmation by pulmonary angiography. At 90 day follow up however, abnormal lung scans were noted in 8.7% and 10.7% anticoagulated and conservatively treated patients respectively. The authors do not comment on whether these perfusion defects were further investigated or to what degree they were symptomatic, but the implication is clearly one of limited difference between the groups.

Recent papers have attempted to provide further insight. In the TICT study, Parisi *et al* assigned consecutive isolated calf thrombosis to a four week reducing dose course of low molecular weight heparin (rather than the standard three months anticoagulation) and followed all patients clinically for three months [195]. They quote no clinical presentation of symptomatic PE in 171 patients over three months, despite proximal propagation in 2.9% patients. Similar results with six-week treatment regimens have further emphasised the lower embolic potential of IDDVT [219]. However, prospective data is still needed on untreated patients to convince clinicians. Macdonald *et al* performed a natural history study on patients with untreated isolated gastrocnemius and soleal vein thrombosis in 2003, reporting no episodes of PE over a three month follow up period [55]. Following this, Lautz *et al* performed a retrospective review of 406 patients with isolated DDVT in 2009, with a mean follow up of 7.5+/-11 months [200]. They report a 5.9% incidence of PE in untreated calf muscle vein DVT, compared to a minimally lower incidence of 3.7% in fully anticoagulated patients (p=0.67). Schwarz *et al* slightly dispute these findings with their previously noted prospective randomised trial in 2010, using clinical pulmonary embolism (with objective confirmation) as part of the composite primary outcome [201]. None of their 53 untreated patients with confirmed isolated calf muscle vein thrombosis developed PE during three months of follow up.

Can these results suggesting decreased embolic potential with calf *muscle* vein thrombosis be extrapolated to all of the distal leg veins? The only contemporary paper attempting to prospectively investigate is that of Palareti *et al,* alluded to previously [171]. Of 64 untreated IDDVT patients achieving review, only one developed symptomatic pulmonary embolism (1.6%). Again, this is a particularly noteworthy result when one considers the risk of major bleeding with anticoagulation. If national

UK guidelines are to be followed, 64 patients in the above cohort would be warfarinised for three months at a major bleeding risk of 2.4% patients/year [220] in order to avoid development of 1 symptomatic pulmonary embolism. This is a balance of risk that does not sit well with the utilitarian philosophy adopted by many practising and pragmatic acute clinicians [221].

The evidence regarding IDDVT and development of post-thrombotic syndrome

Research into the development of post-thrombotic syndrome (PTS) has been hampered for many years by lack of a clear definition and inadequate long term follow up. This naturally affects the understanding of the role played by IDDVT in the disease. Although the pathophysiology lacks complete clarity, the condition is attributed mainly to deep venous obstruction, calf muscle dysfunction and venous reflux post thrombosis [222]. Clinical PTS is a constellation of non-specific clinical signs including aching pain, dependent oedema and lipodermatosclerotic skin changes, often leading to venous ulceration in the context of minor trauma. According to the most recent studies, the majority of patients become symptomatic within two years of the acute thrombotic event [223]. As other clinical conditions may mimic PTS in the absence of precipitant thrombus, such as increased body mass index and superficial venous insufficiency, the issue can become further clouded [224]. Previous vague definitions, lack of standardisation and premature termination of follow up has led to both under and over reporting in the literature, with rates fluctuating from 20% [225] to 100% [226] in earlier published studies. There are considerable socio-economical implications with diagnosis [226, 227].

Accepted modern definitions of PTS have gone some way to rendering further research more applicable to clinical practice. Of particular note, the Villalta scale has been recently recommended as the standard definition of PTS by the Scientific and Standardisation committee of the International Society on Thrombosis and Haemostasis [228]. This is based primarily on its high level of inter-observer agreement and ability to discriminate cases of true PTS amongst patients with venous disease [229].

Randomised controlled trials have described a significant reduction in incidence of

PTS with the use of graduated compression stockings. One study generated a hazard ratio of 0.49 for PTS with use of compression stockings compared to control (95% CI 0.29 to 0.84, p=0.011) [225]. Stockings were worn for two years and patients were followed for 5 years, using the Villalta scale to assess PTS prevalence at regular intervals. A Cochrane review followed in 2008 directly supportive of compression therapy for acute DVT [230]. Although there is minimal trial data it is also postulated that anticoagulation may reduce incidence, following evidence suggesting an increased risk of PTS with an insufficient quality of therapeutic anticoagulation [231]. This data concentrates solely on patients with proximal DVT.

PTS has been shown to develop after asymptomatic DVT [232]. There has also been a systematic review looking directly at the comparative incidence of PTS in postoperative patients with asymptomatic DVT and those without [233]. The relative risk for development of PTS was found to be 1.58 (95% CI 1.24 to 2.02) in those with disease. Although the review is not specific about thrombus location, many experts have assumed the majority of thrombi here to be IDDVT in view of asymptomatic presentation [18]. There is also retrospective data alleging an association with distal thrombotic disease [181], which goes against earlier reports suggesting the presence of proximal vein / popliteal reflux to be crucial for the development of PTS [222]. This latter suggestion has since been discounted, with studies looking directly at popliteal valve incompetence alone as a predictor for development of PTS and demonstrating a relative risk of 1.0 (95% CI 0.5 to 2.2) in patients with proximal DVT [234]. Recent research highlights the importance of failed recannalisation at six months [235] and lists specific clinical risks such as obesity (RR 1.5, 95% CI 1.2-1.9), proximal thrombosis (RR 1.3, 95% CI 1.1 to 1.6) and associated varicosities (RR 1.5, (95% CI 1.2 to 1.8) as independent predictors of increased risk [236].

Further research has unequivocally cited the association of proximal disease with a higher risk of developing PTS [189, 237]. Some authors have even gone on to demonstrate minimal significant clinical symptoms in IDDVT patients at long term (2.2-5.8 years) follow up, further negating the association [138]. This latter study does suffer from lack of standardisation for PTS, a small sample size and heterogenous cohort. However, its general assertions are supported by later prospective work noting a proportionately low incidence of PTS defined by criterion standard in focal calf

DVT, or disease confined to a single involved distal vein [183]. These authors use the CEAP classification of venous disease, internationally utilised since its description in 1994, which comprises the four contributory elements of clinical signs (C), Aetiology (E), Anatomical location (A) and pathophysiological change (P) [238]. They note a class of 0 (no evidence of venous disease) in >50% of all IDDVT patients at mean follow up of 3.4 years and describe all focal calf thrombosis patients as asymptomatic at this stage. The authors also describe a clear association between thrombotic burden (multiple affected venous segments proximal and distal) and PTS, regarding prevalence and severity.

Attempting to further quantify the actual burden of PTS in *untreated* IDDVT is problematic, given the paucity of literature addressing the question. Some authors estimate a PTS incidence of 20% to 25% based on studies in proximal DVT. With compression hosiery, further extrapolation could see this reduced to 12.5%. However, the majority of current research is based on studies of anticoagulated patients. Given the association of PTS with residual thrombosis [181], the argument can be convincingly made that failure to anticoagulate may lead to a higher incidence of PTS. Limited data exist to prove this. Only one study currently cites insufficient anticoagulation as associated with development of PTS [231], but recruited only patients suffering from proximal thrombotic disease. No prospective data exists following patients with untreated IDDVT to assess for the long-term risks. However, low level evidence such as the retrospective study by Mclafferty *et al* describes a low incidence of venous valvular insufficiency and clinical symptoms at 3-4 years post IDDVT, despite only 51% patients receiving anticoagulation [138]. In fact, when the authors of this paper assessed valve closure time as a surrogate marker of venous insufficiency, only the anticoagulated patients demonstrated abnormalities on duplex assessment. Therefore the threat of PTS as an indication for exposure to the inherent risks of anticoagulation is not validated in available evidence. Contemporary reviews describe the association between distal thrombosis and the post thrombotic syndrome as 'far from established' [21]. Further research is clearly warranted, especially with the increasingly positive results seen with use of compression therapy and modern trials of exercise programs designed to treat PTS [239]. As matters stand, there is only very limited low level evidence of poor methodological quality to support the use of anticoagulation for three months as recommended, to reduce the risk of PTS.

The evidence regarding IDDVT and recurrence of thrombotic disease

Finally, we must examine the risk of recurrence in IDDVT. This is a difficult area for research, given the limitations of univariate analysis and broad definitions of recurrence. Firstly, practical timing between initial thrombosis and recurrence appears arbitrary in the context of prospective research. Previous studies consider a thrombotic event within three months of the original to be defined as recurrence [172]. Some modern papers adhere to this convention without further explanation [92], while others go on to explore the long term risks of recurrent thromboses at 5 - 10 years off treatment [78]. It is suggested that early recurrence is of the highest interest, given the implication that anticoagulation may negate this at minimal risk. It remains to be seen whether the benefits of therapeutic intervention outweigh the risks of later recurrence without inherently increasing morbidity and mortality through risks of treatment. Secondly, as any VTE is independently associated with a heightened risk of further events [240], it remains hard to segregate the impact of IDDVT on the risk of recurrent thromboses. Any measure of recurrence is subject to multiple confounders. Limited research has been achieved to identify univariate predictors of recurrence while adjusting for these potential confounders within baseline characteristics.

The impact of proximal disease in this area is well researched, based on studies comparing duration of anticoagulation for prevention of recurrence. A prospective randomised controlled trial and meta-analysis performed in 2004 confirmed the value of prolonged anticoagulation for at least three months in patients with VTE, to prevent recurrent disease [241]. The authors, collating their recent prospective data and that from the last 20 years, calculate an odds ratio of 2.9 (95% CI 1.2-6.9) in favour of recurrence at 1 year for patients receiving only four to six weeks of treatment, compared to three to six months. The majority of VTE patients within the current study had symptomatic proximal DVT at presentation (48%), the remainder split between either acute PE or distal DVT. This leads to the assumption that limited anticoagulation in this cohort would further increase the risk of recurrence. However, only 27% patients within this study had symptomatic IDDVT. This limits the applicability of the results to all cohorts. Also, the bulk of data for the meta-analysis comes from the 1995 study performed by Schulman *et al*, who included 897 patients with VTE randomised to 6 weeks or 6 months of anticoagulation [242]. Conventional

ascending venography was used as a diagnostic standard for DVT, rather than ultrasound. Only 32% of patients in this study had IDDVT as their initial presentation, the majority being a combination of proximal disease and pulmonary VTE. A sub-analysis is presented of IDDVT patients, suggesting a recurrence rate of 11.4% and 5.8% in the six week and six month anticoagulation cohort respectively, with an odds ratio of 2.1 (95% CI 0.9 to 4.5, p=0.10). Both the lack of statistical significance and the risk associated with an increased duration of anticoagulation in the control group, are noteworthy.

In patients receiving standard three months anticoagulation, recurrence rates have been shown to differ between proximal and distal disease. The three-month outcomes for large cohorts of IDDVT patients were assessed by the aforementioned OPTIMEV and RIETE investigators [38, 39]. The respective recurrence rates at three months were found to be 2.2% and 2.0%. The latter investigators also suggested a trend towards reduced incidence of recurrence in distal compared to proximal disease, albeit without statistical significance, calculating an odds ratio of 0.72 (95% CI 0.51 to 1.02, p=0.07). Recent studies assessing long-term risk of recurrence have echoed this finding of reduced recurrent events with IDDVT. Labrapoulous *et al* followed 153 consecutive patients with a first episode of acute thrombosis for 5 years, noting a recurrence rate of 24.5% in proximal DVT patients, compared to 19.6% in distal disease [243]. They failed to demonstrate statistical significance here, but their findings continue to hint at lower than expected recurrence rates with IDDVT. Lastly and perhaps most conclusively, is the patient level meta-analysis by Baglin *et al* in 2010 [101]. The authors here assessed the cumulative 5-year VTE recurrence rate in over 2500 patients diagnosed with DVT and treated with phased oral anticoagulation for at least 12 weeks. Patients were followed for a median of 22.3 months (IQR 0.2 to 117.3). They subsequently segregated this cohort by initial anatomical thrombus location, into proximal or distal disease. In patients presenting with proximal disease (independent of pulmonary embolism), the chances of recurrence were four times greater than that seen with distal disease (HR, 4.76 (95% CI, 2.06–10.98). The authors also comment on specific recurrence rates for 171 patients presenting with IDDVT, of which PE recurrence was seen in 1.2% and DVT in 6.4%. These figures compare favourably against those seen with isolated proximal presentation, at 3.8% and 22.8% respectively.

While this is of interest, the real clinical concern is the issue of recurrence in *untreated* IDDVT patients. Few studies exist which have followed patients for the necessary duration to provide evidence here. The only randomised controlled trial conducted into anticoagulation of calf thrombosis produced highly significant findings in this area, citing a three-month recurrence rate of 28% in patients treated without anticoagulation, compared to 0% in those treated for three months (p<0.01) [172]. No further follow up data was provided. However, this study has been heavily criticised for its diagnostic methods, disparity of baseline characteristics between groups and limited sample size [19]. For instance, 50% of the patients experiencing recurrence had previous thromboembolic events. These patients were subsequently at high risk of recurrence regardless of treatment allocation.

Contemporary studies dispute the findings of this previous research. In their separate work, both Schwarz and Palareti [171, 201] note three-month recurrence rates of 0% using compression bandaging and symptomatic treatment only. Both these studies have yet to report on long-term follow up. As such there is limited evidence overall to suggest that transient therapeutic anticoagulation in IDDVT will limit the risk of recurrent disease.

Although recurrence is a pertinent issue after VTE, it is clear that a vast number of factors influence the rate and severity of future disease. It therefore seems unwise to generalise lengthy anticoagulation decisions based on unreliable data, isolated thrombotic location and past experience. A recently proposed approach to prediction would constitute an individual risk assessment for each patient, looking to identify key predictors of likely recurrence and bleeding, thus stratifying treatment decisions. In this context, benefit can be titrated directly against risk. Recent papers identifying clinical and laboratory characteristics predictive of recurrence have attempted collation and estimation of cumulative probability models for recurrence [240]. These models need external validation, but provide an interesting alternative to the default stance of therapeutic anticoagulation for all.

Clinical Management of IDDVT: Secondary Research

Introduction

There have been at least four attempts at systematic review and meta-analysis regarding therapeutic anticoagulation of IDDVT within the last decade. Conclusions are variable and no consensus recommendations have been reached. All individual articles have called for further research.

Narrative reviews

The natural history of both treated and untreated IDDVT has been explored systematically by multiple previous authors, albeit with significant heterogeneity amongst the included studies. In 1988 Philbrick and Becker were the first to draw attention to the variability in literature data on this topic, reporting rates of extension to the proximal veins ranging from 0%-29% in collated patients [244]. They specifically comment on the lack of "methodologically sound research" existing for analysis and highlighted the need for further study. Giannoukas *et al* followed this in 1995 with similar conclusions following their narrative review of the literature [245]. Modern data from contemporary research offers little in the way of further clarification, but provides supporting evidence of limited propagation rates with IDDVT. Narrative reviews draw attention to the concept that many isolated DDVT will become 'abortive' without anticoagulation [20]. This is supported by earlier natural history studies quoting an 88% rate of complete lysis in all IDDVT patients after receipt of anticoagulation therapy in only 50% of the cohort [102]. Clinical outcome studies also reinforce the concept that withholding anticoagulation following negative serial proximal CUS carries a low risk of VTE over the following 3 months, further indicating a low risk of propagation for IDDVT [164, 170].

Rhigini *et al* attempted to collate data in 2006 after a narrative literature review, providing pooled separate estimates of propagation for IDDVT in both untreated and treated patients [21]. They included data from 11 studies prospectively recruiting patients with IDDVT and using conservative management strategies. Although this

cohort included over 600 patients followed clinically for at least 3 months, the inclusion of post-operative, ambulatory, asymptomatic and hospitalised patients rendered the findings subject to multiple sources of confounding. Inherent bias was also present from non-randomisation of treatment decisions. The included studies quote complication rates (mainly proximal extension) in untreated patients ranging between 0% [199] and 29% [172] though it must be noted that variable methodology regarding diagnostic strategy, follow up and assessment for extension raises concern when collating data. The authors pool the propagation rates throughout to estimate a mean complication rate of 10% (95% CI 7 to 12%) for untreated IDDVT, while acknowledging the limitations of their methodology. This is more than double the pooled propagation rate of the 13 studies assessing extension in patients treated with some form of anticoagulation, identified within the review as 4% (95% CI 3 to 6%). Interestingly, variation in propagation rates was wider in the therapeutic cohort, ranging from 0% to as high as 44% [246] in one study using IV heparin followed by warfarinisation. The lack of standardisation between studies, variation in design and target population detract from the significance of these results and suggest cautious interpretation. Many of the included studies also utilise venography for both initial diagnosis and repeat imaging, a process recognised to carry a small risk of venous thrombosis in itself, increasing with multiple examinations [152]. The review also fails to quantify the on-going risk of PE, PTS and recurrence associated with randomly untreated IDDVT. Although this literature review does not therefore provide a definitive answer, it certainly highlights the fact that untreated IDDVT carries far lower rates of serious complication than would be expected with untreated proximal disease.

Systematic reviews and meta-analyses

The first contemporary attempt at systematic review on the subject of IDDVT was published recently by Masuda *et al* in the Journal of Vascular Surgery [17]. The authors reviewed over 1500 citations and included 31 for full analysis, providing methodological assessment using a previously published modified rating system [244]. Their inclusion criteria stretched to any natural history study of IDDVT using any form of therapy. As such, the majority of studies were observational cohorts looking at progression/complication rates with a variety of therapeutic regimens,

which may lead to sampling error. In fact, while they identify 6 randomised controlled trials with the review, only 2 of these compare therapeutic anticoagulation to conservative management [172, 201]. The other 4 all compare duration of full dose anticoagulation (usually 6 vs. 12 weeks) and so fail to address the key question at hand.

The authors collate data from 6 studies rated high or moderate methodology with at least three months prospective follow up to provide gross estimates of propagation, quoting 8% for local, 4% for proximal and 3% for femoral propagation. They summate this as a 15% overall risk of any propagation in the absence of full therapeutic anticoagulation. This is interesting data. However, it is likely to under represent true propagation rates. The 6 studies in question include several prospective datasets that failed to perform routine follow up whole-leg CUS. Palareti *et al* performed only a single examination of the calf at baseline for example [171]: Labrapolous *et al* performed a single follow up after 10 days [247]. They also refer to descending propagation (local extension) but remain unclear about whether or not these patients received non-randomised anticoagulation. This data is thus excluded from the final conclusion. Lastly, Masuda *et al* (in their incorporated natural history study) comment only on proximal propagation with non-standardised CUS follow up [102]. It remains to be seen how many patients may have extended locally if rigorous follow up and formal reporting had been obtained in all patients. Including these studies in collated assessment of thrombotic extension reduces the internal validity of their results – the low percentages presented could simply be a result of missed disease.

The authors subsequently examine the role of anticoagulation in reducing propagation rates, but are only able to comment on the two studies of moderate quality performed by Lagerstedt and Schwarz. Although the suggestion is of reduction in events, the methodological issues previously mentioned and the lack of robust data mean no firm conclusions are drawn.

There are several other potential issues to be noted. The proposed system of methodological assessment is not validated or supported by the Cochrane collaboration. No attempt at formal meta-analysis has been made, although the authors suggest this is due to a 'lack of sufficient well designed comparative trials'. Collated trials are small in sample size and heterogenous, although no attempt at quantification of heterogeneity was performed. Lastly, no assessment of symptomatic

pulmonary embolism incidence in conservatively managed patients was performed, despite this being a key management issue in the decision to recommend anticoagulation with IDDVT. The authors conclude "no study of strong methodology could be found to resolve the controversy of optimal treatment for IDDVT". They suggest either duplex surveillance or anticoagulation as current acceptable standards for management.

This systematic review was interestingly followed by later publication of an attempted meta-analysis, in the same journal, the same year [14]. De Martino *et al* used methodological techniques outlined in the Cochrane database and reported to standards set by PRISMA and MOOSE guidelines [248, 249], in order to try and provide a contemporary estimate of treatment effect. They compared rates for development of pulmonary embolism, post thrombotic syndrome, proximal propagation and mortality between IDDVT patients receiving either anticoagulation (therapeutic dosing for at least 1 month) or control (nothing, prophylactic dose anticoagulation, antiplatelet agents or serial compression devices). The authors suggest a potential benefit for anticoagulation in reducing the incidence of PE (OR 0.12, 95% CI 0.02 to 0.77) and proximal propagation (OR 0.29, 95% CI 0.14 to 0.62), but no reduction in mortality (OR 0.57, 95% CI 0.06 to 5.66). Only one study assessed the incidence of PTS and as such the data was not suitable for meta-analysis. Although these results are interesting the authors again note the heterogeneity between studies, low collated sample sizes/event rates and poor methodological quality of studies, concluding their findings to be "not robust". There are several key issues to be noted with their methodology.

Overall, the findings are subject to a high risk of bias. More than 50% of control patients assessed for PE risk are postoperative patients from within larger arthroplasty trials and have no formal clinical review, relying on retrospective identification of disease from case note review. Indeed, these cases make up for 80% of the thrombotic events in this forest plot. There are several issues with this approach. Firstly, such a method is likely to identify provoked cases of IDDVT only – there is a suggestion that these cases are slightly lower risk for clinical deterioration/recurrence when compared to unprovoked disease and thus it would be flawed to draw conclusions about IDDVT in general from this data. Secondly, the majority of these patients were all undergoing some form of prophylaxis following their surgery, whether this be compression

devices or pharmacological. This renders the data difficult to generalize to a modern ambulatory population presenting spontaneously. Thirdly, these patients are exposed to a particular cohort of on-going additional risk – hospitalization, immobility and recent surgery are all well recognized risk factors for acute thrombosis [35, 36]. It follows again that the patient cohort under assessment may not be reflective of the general ambulatory population with IDDVT. Lastly, many of these surgical patients were assessed within trials comparing conservative methods of surgical thromboprophylaxis. There is good evidence to suggest pharmacological thromboprophylaxis reduces event rates and this is now standard care within the UK for arthroplasty patients [8]. As such, it can be argued that many of the included trials did not conform to routine contemporary care and as such their results are compromised.

The variability between intervention and control patients is also notable. The authors allowed any patient receiving greater than 4 weeks therapeutic anticoagulation with IDDVT to act as intervention and any receiving less than therapeutic anticoagulation to act as a control within the meta-analysis. Thus, the anticoagulated cohort (of variable duration) is compared to a composite of patients receiving prophylactic dose anticoagulation, long-term antiplatelet therapy and serial compression devices. This is not quite the question under scrutiny with regard to IDDVT: most clinicians are keen to know the difference in event rates when standardised anticoagulation is compared to placebo, or non-steroidal anti-inflammatory medications alone. For example, the authors include the trial by Sachdev *et al* in their forest plot for thrombus propagation [196]. In this study, patients in a long-term rehabilitation centre were screened for asymptomatic IDDVT and after diagnosis, provided with regular pharmacological prophylaxis. On following these 65 non-randomised patients, it transpired that 2 propagated over an indeterminate follow up period (3.0%). The study by Dorr *et al* is another that identifies asymptomatic post-operative IDDVT, allows non-randomized management at clinician discretion and provides no standardized follow up other than chart review to acknowledge later diagnosis of PE [218]. Thus, high-risk patients are likely to be anticoagulated and then compared to low risk, already receiving some form of prophylaxis. It is little wonder few events are seen in either group. As such the findings are again difficult to generalize.

Inclusion criteria and definition of events also raise issues. The authors included all studies with a minimum of 30 days follow up, although this is far shorter than the

standard 3 months follow up applied to the majority of thromboembolic disease trials. They also initially allowed for diagnosis of PE by clinical criteria. Both these factors may encourage under or over reporting of events respectively.

There is acknowledgement of these limitations in the discussion section and clarification of the key issues. The authors draw attention to the low event rates, inadequate duration of follow up, high loss to follow up and overall low methodological quality of included studies. Heterogeneity is established between datasets and reported for studies assessing thrombus propagation, with an $I^2 = 38\%$. The point is also made that few studies reported adverse outcomes, such as bleeding. They conclude that it remains unknown whether the harms of anticoagulation outweigh the benefits in IDDVT management. Again, they issue a call for further rigorous, randomized controlled trials.

Clinical Management of IDDVT: Equipoise reflected in Clinical Practice

Introduction

International variation in management of suspected IDDVT is recognised through conflicting guidance, peer debate and modern epidemiological research. UK guidance documents published in leading haematology journals support the safety of serial CUS and endorse withholding therapeutic anticoagulation with negative above knee scan [25]. Guidance published in the same journal one year later endorses anticoagulation for three months in all cases of calf thrombosis [92]. Prior American guidance is slightly less contradictory, but acknowledges the recommendation of three months immediate anticoagulation for IDDVT as grade 2B, a weak recommendation based on moderate quality evidence only [174]. This has recently changed to suggestion of serial sonographic follow up for the majority of IDDVT patients in the most recent American College of Chest Physicians (ACCP) guidance, despite limited addition to the evidence base [93]. It is clear that clinical equipoise remains.

Vernacular debate

Multiple debates have been published in the last three years on this topical issue [15, 16, 19, 22]. Leading authors agree on relevance and the pressing need for further research, but remain committed to variable approach in investigation and management. This diversity is reflected in recent epidemiological studies. In 2008, Palareti *et al* examined prospective data from a large thromboembolism cohort (over 1500 patients) recruited from 25 Italian centres in order to identify the burden of distal disease. Their results note variable prevalence between centres, with IDDVT contributing anything from 0% to 24% of the acute disease burden [104]. Interestingly, they go on to highlight the fact that diagnosis of IDDVT was often delayed and frequently resulted in short term LMWH only, when compared to proximal disease (p<0.001 for both). This data leads to the conclusion that "diagnostic strategy for suspected leg DVT differs greatly among Italian centres". They discuss this further in a later commentary, focusing in particular on how the variety in practice highlights the important and clinically unresolved dilemma of managing

IDDVT [250]. This is reiterated by recent US survey research highlighting the variable practice and differing opinions between practicing vascular surgeons regarding calf vein thrombosis [142].

International guidance

International recommendations offer no easy solution to the on-going controversy of IDDVT management. Opinion has fluctuated over the last decade, despite limited addition to the evidence base and no robust, large randomized trials on the topic. This perhaps goes some way to accounting for the difficulty faced in clinical practice.

At the turn of the millennium, several national and international consensus guideline groups supported the idea of full therapeutic anticoagulation in IDDVT, for a duration of 3 months. Australasian, British and American guidance all seemed to concur [92, 173, 251], albeit with a variable level of specific interest in distal disease. This was later endorsed in 2008 guidance from the ACCP [174] and 2011 guidance from the British Committee for Standards in Haematology (BCSH) [12]. The latter authors addressed the evidence level as 1A for treatment, reducing the recommended regimen to 6 weeks based primarily on the DOTAVAK study by Pinede *et al* [219]. However, they also began to show signs of compromise by qualifying recommendations with the caveat that strategies utilizing serial proximal CUS leaving IDDVT undiagnosed and untreated were "as safe as those in which isolated calf vein DVT is diagnosed and treated".

The most recent guidelines have deviated from these recommendations. NICE have produced contemporary guidance on investigation and diagnosis of all DVT, specifically recommending serial proximal CUS over whole leg CUS as a principal diagnostic strategy [13]. This will of course fail to diagnose or treat any IDDVT that do not extend to the level of the popliteal vein within a single week. Within the guidance, there is a call for further research on the clinical and cost effectiveness of whole leg CUS compared to serial proximal CUS. This acknowledges the on-going controversy.

In addition, the most up to date guidance from the ACCP have also recently altered their stance on management of IDDVT [11]. Although they acknowledge that either whole-leg CUS or serial proximal serve as viable first line imaging strategies for the

exclusion of distal disease, they are clear that "if isolated distal DVT is detected on whole leg US, we suggest serial testing to rule out proximal extension over treatment." This is qualified by a further paragraph to explain where situations may dictate advantage to treatment over surveillance, such as high-risk patients or those who place a high value on avoiding the inconvenience of re-attendance. The recommendation is graded as 2C.

Differing recommendations, presented levels of evidence and failure to address the question head on has led to emergence of various therapeutic regimes for IDDVT across the developed world. Two main approaches currently exist in modern practice. That of early detection and therapeutic anticoagulation, versus above knee serial CUS and duplex surveillance for propagating clot.

Proponents of Anticoagulation

Most modern authors believe 90% of all proximal DVT to be of the ascending type: that is, the majority of proximal thrombi will originate in the calf and propagate upwards [22]. This follows natural history studies reporting an association of proximal with distal DVT in 99% patients [28]. It thus follows that almost all proximal DVT and the majority of clinical PE will originate from initial IDDVT. Proximal disease comes with a clearly demarcated morbidity and mortality burden [187-189]. To reduce the risk of proximal and/or pulmonary disease, many argue that IDDVT must be systematically screened for and treated in symptomatic patients.

Routine anticoagulation in IDDVT has the potential to reduce risk in multiple areas. In the first instance, research exists demonstrating a reduction in propagation to proximal DVT with treatment. It is also postulated that the more serious risk of pulmonary embolism can be negated by therapeutic anticoagulation. Secondly, with a reduced rate of proximal disease comes a further reduction in development of post thrombotic syndrome. There is even suggestion that IDDVT alone can lead to PTS without treatment. Lastly, formal anticoagulation has the potential to reduce thrombotic recurrence.

There is evidence to support these claims. The only randomised controlled trial regarding full anticoagulation of calf thrombosis, conducted in 1985, was strongly suggestive of benefit with therapy [172]. The authors noted a 29% recurrence rate

within 90 days in the conservative group (95% CI 13 to 49%), compared to a 0% recurrence rate in the anticoagulated arm (p<0.01). Five patients had proximal extension, one developed pulmonary embolism and two had further non-specific thrombotic events. This trial is often cited as the highest level of evidence regarding therapeutic decision-making in IDDVT. It is supported by further collated observational research, previously quoting an increased rate of thromboembolic complication in approximately 20% of untreated patients [244]. This research and later modern studies have been combined recently by Rhigini *et al* to produce a cohort of over 1000 patients. They note a mean reduction in overall proximal propagation from 10% (95% CI 7 % to 12%) to 4% (95% CI 3% to 6%) with anticoagulation [21]. The more compelling issue of pulmonary embolism lends further support to those championing anticoagulation in IDDVT. Routine lung scanning in calf DVT patients has previously demonstrated asymptomatic PE in up to 33% patients [210]. Even if asymptomatic PE does not force anticoagulation as standard, a valid concern remains about the potential of this disease to cause irreversible harm if left untreated. Indeed, some authors have reported a rate of fatal PE with post-operative asymptomatic calf DVT as high as 13-15% [252]. A clear association has been suggested over the last three decades between IDDVT and fatal PE from autopsy studies [252-254]. The clear fact remains that some preventable deaths may occur as a direct result of untreated IDDVT. Many believe these unfortunate events ethically justify the potential harms of broad therapeutic anticoagulation. This point is also relevant when considering the main alternative to detection and anticoagulation, that of serial ultrasound to detect propagation. Again, fatal PE has been shown to occur while awaiting second look at 7 days, adding weight to the argument for rapid detection and early anticoagulation [163]. This certainly appeared until recently to be the majority view of expert consensus. As well as convincing academic argument in recent publications supporting therapeutic anticoagulation in IDDVT, European guidance appears to have taken a clear stance.

Clinical practice studies would suggest this guidance is being acknowledged, with a recent registry noting use of warfarin in over 60% patients diagnosed with IDDVT [104]. There is clearly a well-respected international body of opinion that would support the suggestion of IDDVT as the previously described 'wolf in sheep's clothing' [244]. This body would propose that the benefits of anticoagulation outweigh the potential risks.

Proponents of proximal CUS and duplex surveillance

That IDDVT has the potential to propagate with resultant pulmonary embolism, post thrombotic syndrome and recurrence is not debated. However, the burden of morbidity resulting from untreated disease is highly contentious. Proponents of conservative therapy draw attention to poor methodology, lack of randomised controlled trial data and inconsistencies within the current literature. The only randomised controlled trial examining the benefits of anticoagulation in IDDVT [172] is subjected to heavy criticism, including the use of serial isotopic testing to evaluate propagation (later abandoned due to insufficient performance) and an imbalanced prothrombotic tendency at baseline between groups. It is also now over 25 years old, thus failing to meet current standards in diagnostics, methodology and reporting technique.

Natural history studies regarding IDDVT report highly variable rates of propagation (0-44%) and significant heterogeneity precludes an accurate pooled estimation of risk [21]. Although rare occurrence of pulmonary embolism remains a concern, modern prospective cohort studies suggest a much lower three-month incidence than previously suspected, of 0% to 5.9% using 4-6 weeks anticoagulation or conservative treatment only [55, 195, 200, 219]. It should also be noted that full anticoagulation in one of these studies only reduced the incidence of PE from 5.9% to 3.7% (p=0.69), a minimal benefit [200]. Contemporary research also suggests a much lower rate of propagation in untreated patients than previously described, quoting a three month incidence between 1.9% and 4.7% [171, 201]. The link with post thrombotic syndrome and IDDVT remains far from established. This data in combination suggests caution with blanket anticoagulation, based on analysis of both risks and benefits.

The most convincing argument made by those opposing routine anticoagulation, is based on safety results when utilising techniques *directly avoiding* detection of IDDVT. Modern outcome studies utilising two point above knee serial CUS in suspected DVT clearly demonstrate a low incidence of thromboembolic events following two negative scans, a pooled estimate of nearly 6000 patients recently suggesting a three month VTE rate of only 0.6% (95% CI 0.4 to 0.9%) [245]. This

estimate was followed by work from the ERASMUS investigators, who randomised over 2000 suspected DVT patients to either full leg (complete) CUS or serial 2 point CUS [170]. Over 750 patients in each group subsequently suitable for 3 month follow up, with matching baseline characteristics. The three-month VTE event rates for the 2-point CUS and complete CUS were 0.9% (95% CI 0.3 to 1.8%) and 1.2% (95% CI 0.5 to 2.2%) respectively. This 0.3% difference was within the chosen equivalence limit. Even earlier studies performing only a single 2 point CUS (rather than serial) appear relatively safe, noting three month VTE rates of only 2.6% (95% CI, 0.2 to 4.5%) [255].

If the clinical safety of imaging limited to the proximal veins is equivalent to that imaging the whole leg in suspected DVT, then a convincing case can be made against anticoagulation of all IDDVT. This is especially relevant when one considers the potential increase in treatment burden arising from the use of complete CUS. In his defence of a conservative approach to IDDVT, Rhigini pools the performance and safety from six studies of complete CUS, incorporating over 3000 patients [19]. Six hundred and fifty three of these patients were found to have DVT, of which 329 (50%) were located distally. The majority of IDDVT patients within these studies received full therapeutic anticoagulation. The collated 3-month thromboembolic risk following a negative scan was 0.3% (95% CI 0.1 to 0.6%). When we compare this to the collated three month thromboembolic risk following above knee serial CUS at 0.6% (95% CI 0.4 to 0.9%) the difference is clearly minimal. However, use of serial proximal CUS in the latter group only, implies that any IDDVT failing to propagate within a week goes undetected within this diagnostic cohort, and therefore untreated. Thus although the 3 month VTE risk increases slightly with use of proximal CUS, a substantially lower number of patients are exposed to the risks of therapeutic anticoagulation. These figures raise the question of need for detection of IDDVT given the potential harms of treatment.

Adverse events with therapeutic anticoagulation using heparin initially and subsequent warfarinisation, are well documented. Drug interactions, poor compliance and inter-current illness can lead to nuisance, major and life threatening bleeding events. A meta-analysis performed in 2003 confirms the morbidity and mortality burden of treatment and provides interesting data regarding therapeutic risk [256]. The authors here collate data from 33 studies involving 4374 patient years of oral anticoagulant therapy. During the initial three months of anticoagulation, cumulative

rates for major and intracranial bleeding were 2.06% (95% CI 2.04 to 2.08%) and 1.48% (95% CI 1.40 to 1.56%) respectively. The case fatality rate for major bleeding was calculated at 9.3% (95% CI 3.1 to 20.3%). This risk continues with prolonged anticoagulation, estimated at 2.74/100 patient-years for major bleeding and 0.65/100 patient-years for intracranial bleeding. These findings are supported by results from the RIETE registry, comprising data from 19,274 patients with acute VTE treated with anticoagulation as per standardised protocols [220]. The authors here recorded major bleeding rates of 2.4% during the first three months of anticoagulation therapy, with 105 fatalities directly attributed to therapy. Thus, they propose an even higher case fatality rate of 33.4% for major bleeding. They do not record minor or nuisance bleeding events, although these are undoubtedly more prevalent than major bleeding and impact negatively on a patient's quality of life. Contemporary research also continues to highlight anticoagulation risks other than spontaneous bleeding tendency. A recent trauma registry analysed data from over 1.2 million patients in an attempt to define the relationship between pre-injury warfarin use and mortality [257]. The authors calculate an odds ratio of 2.02 (95% CI 1.95 to 2.10, p<0.001), with double the mortality in warfarinised patients. This ratio persists even after adjustment for baseline covariates. They conclude warfarin use as a significant predictor of adverse outcome, noting a definitive association with increased mortality in trauma patients. This data raises real concerns, especially when one considers the increasing prevalence of warfarin use in the community. The authors of this paper note warfarin use in 12.8% of patients >65 years old in 2006 within their cohort, a significant increase from the prevalence of 7.3% in 2002 (p<0.001). There is good reason to believe this will increase, as a result of evidence supporting aggressive prophylaxis for cerebrovascular and cardiac disease.

The risks of therapy, combined with the plethora of data suggesting serial CUS is safe and effective provides a robust platform for those who refute IDDVT as an indication for three months full anticoagulation. With modern studies also suggesting greatly reduced rates of propagation, pulmonary embolus and post thrombotic syndrome development compared to those expected [171, 201] it is no surprise that leading authors continue to defend this stance. Both camps agree on the need for further randomised controlled trials, [19, 22] but proponents of serial CUS argue that until this is available the documented risks of anticoagulation are not warranted for the treatment of IDDVT.

Is there a role for initial complete CUS with stratified decision making?

Proponents of serial CUS do acknowledge the benefits of complete leg scanning, regarding detection of other pathology manifesting with similar symptoms to DVT [16, 19]. A final strategy to guide management in IDDVT involves the use of whole leg CUS initially followed by an evidence-based consideration of propagation risk, prior to treatment. This is a proposal suggested and endorsed by multiple leading authors, having recently found its way into international guidance [19, 20, 22, 148]. Benefits include patient and physician confidence in an exact diagnosis, avoidance of repeat diagnostic testing, the ability to provide detailed counselling and informed decision making for all regarding analysis of the risks and benefits. Although there is progress in this area, more data is needed regarding progression rates in varying populations. Schwarz *et al* have recently shown propagation rates for muscle vein thrombosis in the calf to range from 2% to 25%, depending on the prevalence of associated specific risk factors [199, 201]. However, larger studies are needed in well-defined cohorts, culminating with a randomised controlled trial. Prediction indices for major bleeding with anticoagulation have already received much attention [258, 259] and easy to use models have recently been validated in large appropriate populations [220]. Once the data is available predicting outcome in untreated IDDVT, concerns regarding a conservative approach to care can be balanced directly against therapeutic risk. This process could allow fully informed decision-making and maximise beneficence alongside non-maleficence.

Research currently planned/in progress

Due to the on-going call for further prospective trial data, several projects are in active recruitment or grant application stage. Perhaps the most well-known of these is the CACTUS study, with a leading expert as principal investigator [260]. This trial has been highlighted in several recent reviews on the subject of IDDVT and is due to finish in September 2013 [14, 261]. The study aims to compare 6 weeks of therapeutic dose subcutaneous Nadroparin against placebo in the management of acute symptomatic IDDVT, as defined by robust sonographic criteria. The trial design is essentially sound, as a double blind, randomized, prospective controlled trial with

standardized follow up, blinded assessment and centrally adjudicated outcomes. A few concerns limit validity and generalisability however: choice of 6 weeks therapy is currently outside of international guidance and based on limited evidence [219]: lack of anti-inflammatory medication within the control group perhaps renders this cohort more likely to symptomatically return and receive further investigations as a result: there appears to be no assessment planned for symptom progression, local extension or the evolution of post thrombotic syndrome within the clinical follow up: six weeks of subcutaneous injections is not standard therapy within the UK and likely to compromise participation, firstly with a high refusal rate and secondly with uptake only by those patients likely to comply, introducing selection bias: lastly, the primary outcome (and as such the power calculation/sample size) is based entirely on proximal propagation data. There are real concerns regarding the place of pulmonary embolism as a secondary endpoint and many previous authors have seen fit to collate venous thromboembolic events as a composite.

Another planned research project already recruiting is TWISTER, an Australasian open label study evaluating a single cohort receiving 2 weeks of therapeutic enoxaparin for treatment of IDDVT [262]. This study offers no evaluation of propagation rates or disease without treatment and seeks to simply assess a short-term therapeutic regimen.

Finally, there is also current discussion regarding a multicentre American trial to assess efficacy, safety, cost effectiveness and long-term outcome of anticoagulation treatment vs. duplex surveillance for a first episode of acute symptomatic IDDVT [263]. As yet, this trial appears to be in the design stage with no clarified funding and no registration on any recognized international trial database.

Summary and Relevance of the Project to the Research Area

Deep vein thrombosis is an expensive, time consuming and increasing burden on the National Health Service. The current strategy of investigation at Manchester Royal Infirmary costs £97,538 per 1000 patients, with additional costs of treatment/complications at £180,936, bringing the total to an estimated £278,473 [7]. The condition comprises two thirds of the 1:1000 total incidence of venous thromboembolism. Roughly half of these patients will initially present with distal disease. Despite this frequency of presentation there is a dearth of high-level research into IDDVT, which can support evidence based clinical decision-making. Few studies have reported on incidence in unselected acute ED attendances. The majority of work on aetiological factors in distal disease has come from specialist vascular centres [38, 39]. Only one randomised trial has ever compared the current national anticoagulant recommendations to conservative therapy [172]. This study is over 25 years old and has been heavily criticised by current leading experts.

There is a pressing need to quantify disease burden, identify causation and rigorously evaluate therapeutic options for this controversial aspect of venous thromboembolic disease. An urgent call for prospective randomized controlled trial data has been placed across the literature, in national guidance documents and general, vascular, respiratory and haematology journals alike [13-22]. The proposed project aims to address these issues and add novel insight to existing research.

Methodology

Hypotheses arising from controversy

The need for further robust research on the management of IDDVT is clear following review of the recent literature. There is also a parallel need to validate previous findings within an ED setting, given the transfer of diagnostic services with modern ambulatory protocols.

The preceding chapters draw attention to multiple aspects of epidemiology and investigative strategy in need of further work. Firstly, the use of whole-leg CUS within an ED management protocol has yet to be robustly assessed regarding IDDVT incidence rates, technical failure and VTE complication rates. Within their recent diagnostic meta-analysis, Johnson *et al* pool the results of 7 studies [177], with only one recruiting patients through the emergency department [44]. In this study, all scans were interpreted by vascular radiology consultants, thus raising queries regarding the generalisability of their findings within a sonographer reported pragmatic ED system. The remaining 6 studies all assess whole-leg CUS in the context of specialist vascular clinics or inpatient cohorts, with sonography often performed by non-blinded clinicians or reported by vascular surgeons. As previously mentioned, there are also few patients within the analysis with high pre-test probability and this cohort requires further study. Thus the first null hypothesis arising for this research project is the following:

"In ambulatory patients presenting to the ED with suspected deep vein thrombosis and proceeding to sonographic evaluation, it is unsafe to withhold anticoagulation in the event of a routinely reported negative whole-leg CUS."

Secondly, while the aetiological differences between proximal and distal thrombotic lower limb disease have been explored, there has been little attempt at assessment of differing clinical presentation. The limited applicable work has all been performed within specialist vascular clinic settings and as such requires further validation before it can be generalized to ambulatory ED care. A further null hypothesis follows as

such:

"In ambulatory patients attending the ED and receiving a diagnosis of acute DVT, there is no difference in clinical presentation or risk factor profile between those diagnosed with isolated distal, or those with proximal disease."

Although the above issues are of academic interest, there is a particular question with overwhelming clinical need of prospective study: whether the combined benefits of prolonged (>6/52) anticoagulation in IDDVT outweigh the risks and inconvenience of therapy. Several direct hypotheses arise from this query, such as the individual risks of local extension, symptomatic progression, proximal propagation, pulmonary embolism, recurrence and even late onset PTS with conservative treatment. The bulk of these issues can be collated to form a principal null hypothesis, which is proposed for analysis within this project timeframe:

"In patients with IDDVT and no overt additional indication for anticoagulation (such as cancer or thrombophilia), there is no significant difference in short term rates of symptomatic deterioration, propagation, PE or recurrence between patients receiving either full anticoagulation for three months or conservative treatment alone."

Given the inherent risks of treatment noted previously, the study must further consider the impact of therapeutic anticoagulation and the potential harms. Thus an additional null hypothesis is proposed:

"In patients with IDDVT and no overt additional indication for anticoagulation (such as cancer or thrombophilia), there will be no difference in nuisance, major or fatal bleeding events between those patients treated with full therapeutic anticoagulation for three months and those managed conservatively."

Aims of the project

The overall aim of the project is to explore the role of whole leg CUS in the evaluation of suspected DVT.

Introduction

To address the previous hypotheses with sound methodology, a primary research study is required with six distinct aims:

1. To design a study enabling assessment of the feasibility of future head to head randomized controlled trials regarding therapeutics in IDDVT.

2. To compare serious VTE complication rates in a prospective, randomized population of IDDVT patients treated with either prolonged therapeutic anticoagulation or conservative treatment only.

3. To compare clinical outcomes and markers of symptomatic progression in a prospective, randomized population of IDDVT patients treated with either prolonged therapeutic anticoagulation or conservative treatment only.

4. To assess the clinical safety and technical failure rate of an ED based protocol utilising single whole leg CUS as a diagnostic test in ambulatory patients with suspected DVT

5. To compare this data to that of proximal disease, in order to evaluate differences in presentation and provocation between IDDVT and proximal DVT.

6. To determine incidence, causation and presentation data regarding IDDVT in an acute, unselected, ambulatory ED cohort presenting with suspected lower limb thrombosis.

Available research approach techniques and the specific choice for this project

Secondary research techniques are of limited use with regard to the proposed null hypotheses. Previously attempted systematic reviews have acknowledged the heterogeneity between trial cohorts and the constriction of variable methodology and diagnostic technique on collation of data [14, 17, 21]. No additional primary research has been published since last review. Further attempt at meta-analysis would therefore likely offer little to change current thinking. The paucity of current data available from ambulatory ED cohorts would also fail to achieve validation of previous studies.

Thus, primary research techniques were considered. Given the importance of treatment outcome in the first null hypothesis, questionnaire, survey and interview based techniques were concluded to be inappropriate. An observational study was considered, but deemed unable to answer the hypothesis directly given that national guidance on treatment would most likely preclude the study of untreated IDDVT in the vast majority of patients. Lastly, a multi-centre prospective audit of data was considered to determine outcome in untreated patients and compare to those treated. There were several methodological issues with this approach. Firstly, with no randomisation regarding treatment, there would likely be multiple confounding reasons for omission of treatment in the conservatively managed IDDVT cohort. This would no doubt lead to biased outcome data. Secondly, few centres in the North West employ the routine use of full leg ultrasound. Thus, patients in these hospitals would never achieve the diagnosis of IDDVT; rather, they would have an initial negative CUS above the knee with persistent clinical suspicion of distal disease. These patients could never provide data on propagation of IDDVT, due to inaccurate catalogue of baseline disease.

Thus a prospective randomised controlled trial was proposed, in order to address the principal null hypotheses. This trial will need to randomly assign patients with IDDVT to standard therapeutic anticoagulation or conservative treatment alone. All patients will be followed clinically and radiologically for a predefined period of three months, with all necessary short term outcomes considered and sequentially evaluated. Longer-term outcomes will be considered within the cohort, but data will

be incomplete prior to submission of the project thesis. As such, these outcomes will not form part of the composite primary or secondary endpoint for the research project.

The other aims of the research project will be addressed by conducting of a prospective, single site, observational cohort study, taking place within the screening log for the randomized controlled trial. All ambulatory patients attending the ED and referred for ultrasonography to exclude VTE, will have basic data collected on potential causation, pre-test probability assessment, clinical features and eventual diagnosis. This cohort will be formed from a continuous, pragmatic sample of patients attending the ED and referred for ultrasonography by non-research clinician to exclude DVT. The cohort data will provide an estimation of population prevalence within low, moderate and high pre-test probability groups and the incidence of actual DVT within these groups, to compare to earlier work. It will also allow prospective quantification of the disease burden attributable to IDDVT seen in emergency medicine, along with basic epidemiology and comparison of aetiological factors with proximal disease.

Patients with a negative or inconclusive scan will be prospectively followed within a further observational study for a period of three months, in order to determine subsequent VTE event rate. This will allow a pragmatic estimation of safety for a single complete compression ultrasound within an emergency department setting. Data from an ED setting will add to the current body of published research on complete CUS for exclusion of DVT [177] and hopefully offer new insights into safety within high-risk populations.

These studies will be conducted in tandem, as a prospective service evaluation, observational cohort study and subsequent recruitment to a pilot feasibility randomized controlled trial within the same continuous patient sample.

Methods and ethics

Core Study Design

The proposed randomized controlled trial (RCT) was designed to assess therapeutic efficacy and address the priority aim of quantifying the risk/benefit profile of anticoagulation in IDDVT. Given the national recommendations championing anticoagulation and the promotion of prophylaxis against VTE, the ease of potential recruitment, follow up and maintenance of allocation were all noted as potential issues. As such, a feasibility pilot trial was considered the most appropriate methodological design, to clarify both the achievability of further research on this topic and an accurate contemporary estimation of treatment effect. Collection of additional observational data to address non-principal study aims was built in to the RCT design via the screening log, in order to address the additional hypotheses within a continuous real time sample of patients.

Consultation and Contribution

The trial was primarily designed by the MD student, in collaboration with local senior Emergency Department clinicians, several academics from the University of Manchester with an interest in VTE, the lead Haematology clinician for Haemostasis & Thrombosis at the participating NHS trust and senior vascular laboratory ultrasound staff.

All research findings presented in this thesis were derived from original research led by the MD student following registration with the University of Manchester for the doctorate. All results are presented in the format of academic papers for publication in peer-reviewed journals. The MD student drafted each of these papers independently and consequently received internal peer review from listed contributing authors.

Prior to initiation of the study, all medical and nursing staff were introduced to the protocol and encouraged to notify the research team regarding any potential concerns. Contact numbers were provided for all clinicians listed as able to consent on the delegation of duties log. A research team member was available on site at the trust at all times when diagnostic ultrasound was being undertaken throughout the study

period.

Funding

The study was initially funded by the College of Emergency Medicine, a national charity and supervisory body. The study was subsequently adopted by the National Institute for Health Research (NIHR) onto the Injuries and Emergencies network portfolio, allowing access to further research support and infrastructure through the comprehensive local research network (CLRN).

Ethical Approval

Following study design and protocol approval by all collaborators, an application was made and approval granted from the Central Manchester Research and Ethics Committee. As a controlled trial of an investigative medicinal product, application was also made to the Medicines and Healthcare products Regulatory Authority (MHRA) and approval granted. The trial was registered with an international public access service to allow transparency and visibility of the aims, protocol and targets within the study [264]. This also provided a point of contact for the study for all international queries and a recognizable trial identifier (ISRCTN75175695).

Setting

This project was conducted within the ED of the Manchester Royal Infirmary (MRI), part of the Central Manchester University Hospitals NHS Foundation Trust. This department serves a resident population of approximately 464,200 within the city and metropolitan borough [265]. The city centre population is heavily influenced by migrating urban / student groups and has been shown to fluctuate by between 0.5 to 0.75 million people on certain days of the year [266]. The conurbation of Greater Manchester exceeds 2.7 million persons. Ethnicity is predominately white at 75.8% with the remainder comprised of South Asian, Black, East Asian/other and mixed race constituents. The department has annual adult attendance figures approximating 100,000.

Patient Flow, Recruitment and Eligibility

Patients were screened within an ambulatory thrombosis service operating within the ED. This service is managed by non-research clinicians and comprises several local protocols and a clinical decision support guideline. In brief, the protocol requires data completion regarding symptomatology, risk profile, clinical findings and formal estimation of pre-test probability using the modified Wells score. An evidence based diagnostic process is then encouraged, with d-dimer as appropriate for exclusion in low risk patients and progression to whole-leg CUS for all others. All pregnant patients, intravenous drug users and those with a history of prior confirmed thrombosis proceed straight to ultrasound. Imaging occurs the same day if available, otherwise patients are treated with daily full dose therapeutic dalteparin and discharged for outpatient return the next day. Outpatient scanning is performed by a dedicated vascular lab of vocationally trained technicians, accredited to standards set by the Society for Vascular Technology of Great Britain and Ireland.

Following sonography, patients immediately return to the department for senior clinical review and are managed as appropriate by a doctor of ST4 grade or above. Specialist thrombosis advice is available at all times as required, provided by local Haematologists with interest in thrombosis and haemostasis.

Regarding the prospective service evaluation, clinical data recorded by non-research clinicians and all investigation results were collated and analysed with source data verification and retrospective validation. For the observational cohort study, patients receiving a negative or inconclusive scan result were directly approached by the research team and invited to participate. For the feasibility RCT, patients receiving a diagnosis of IDDVT were directly approached by the research team and invited to participate. All patients were recruited by a Good Clinical Practice (GCP) trained member of the research team, following scan result and formal diagnosis by an independent clinician. Research team members were monitored throughout the study by the trust Research and Development department regarding training, standards and on-going productivity. All patients deemed eligible for recruitment to the RCT arm of the study were assessed and consented by a senior Emergency Physician with not less

than seven years clinical experience post qualification. This was a mandatory part of the consent process due to controlled medicinal product use within the trial.

Results in the format of papers presented for publication in a peer reviewed journal

Paper 1: The Anticoagulation of Calf Thrombosis (ACT) Project: study protocol for a randomized controlled trial

Paper Overview

Study protocol paper explaining the design of a prospective external pilot randomized controlled feasibility trial, regarding the management of IDDVT

Contribution to the thesis and novelty

This paper addresses the principal and first aim of the thesis, the design of a feasibility trial to examine whether further contemporary research on the management of IDDVT is achievable within a modern cohort. This is the only protocol published on the topic with specific feasibility objectives.

Contribution of candidate

Study design, ethical and trust approval, trial steering committee organization, statistical input and amendments post external peer review. The MD student also wrote and managed all drafts of the manuscript, incorporating suggestions from co-authors.

Publication strategy/status

Published April 2012 in Trials (Impact factor 2.5)

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TRIALS

STUDY PROTOCOL   **Open Access**

The Anticoagulation of Calf Thrombosis (ACT) project: study protocol for a randomized controlled trial

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Abstract

Background: Half of all lower limb deep vein thrombi (DVT) in symptomatic ambulatory patients are located in the distal (calf) veins. While proximal disease warrants therapeutic anticoagulation to reduce the associated risks, distal DVT often goes untreated. However, a proportion of untreated distal disease will undoubtedly propagate or embolize. Concern also exists that untreated disease could lead to long-term post thrombotic changes. Currently, it is not possible to predict which distal thrombi will develop such complications. Whether these potential risks outweigh those associated with unrestricted anticoagulation remains unclear. The Anticoagulation of Calf Thrombosis (ACT) trial aims to compare therapeutic anticoagulation against conservative management for patients with acute symptomatic distal deep vein thrombosis.

Methods: ACT is a pragmatic, open-label, randomized controlled trial. Adult patients diagnosed with acute distal DVT will be allocated to either therapeutic anticoagulation or conservative management. All patients will undergo 3 months of clinical and assessor blinded sonographic follow-up, followed by 2-year final review. The project will commence initially as an external pilot study, recruiting over a 16-month period at a single center to assess feasibility measures and clinical event rates. Primary outcome measures will assess feasibility endpoints. Secondary clinical outcomes will be collected to gather accurate data for the design of a definitive clinical trial and will include: (1) a composite endpoint combining thrombus propagation to the popliteal vein or above, development of symptomatic pulmonary embolism or sudden death attributable to venous thromboembolic disease; (2) the incidence of major and minor bleeding episodes; (3) the incidence of post-thrombotic leg syndrome at 2 years using a validated screening tool; and (4) the incidence of venous thromboembolism (VTE) recurrence at 2 years.

Discussion: The ACT trial will explore the feasibility of comparing therapeutic anticoagulation to conservative management in acute distal DVT, within a modern cohort. We also aim to provide contemporary data on clot propagation, bleeding rates and long-term outcomes within both groups. These results will inform the conduct of a definitive study if feasibility is established.

Trial registration: Current Controlled Trials ISRCTN75175695

Keywords: Anticoagulants, embolism, lower extremity, venous thrombosis

Background

Venous thromboembolic (VTE) disease is an international, topical and costly healthcare burden. Incidence rates are equivalent to that of stroke within the western hemisphere [1] and disease consequences can be as severe. Recent studies addressing prognosis provide a stark reminder of continuing poor outcome, quoting a 15% mortality rate at 3 months post diagnosis for VTE involving the pulmonary vascular tract [2]. Outcome from VTE confined to the lower extremities fares little better, with a reported short-term all-cause mortality between 7% and 15% [3]. Observational data suggests reduced survival compared to control subjects after first episode of symptomatic deep vein thrombosis. This

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trend has been shown to persist for up to 8 years post diagnosis [4]. Clinical research demonstrating poor outcome has led to a national focus on early diagnosis and active prevention, with the creation of guidelines from both the UK Health Technology Assessment (HTA) group and the National Institute of Clinical Excellence (NICE) within the last decade [5,6].

Despite the large body of research on VTE, controversy still remains regarding many aspects of therapeutic clinical practice. One such area is that of distal deep vein thrombosis (DVT), a condition previously thought to be of limited clinical significance. There are multiple epidemiological studies suggesting distal thrombi constitute approximately 50% of objectively diagnosed lower limb disease in symptomatic ambulatory patients [7-9]. This proportion may be even higher in asymptomatic disease or hospitalized patients [10]. However, the benefits of intervention in distal disease remain poorly researched, with conflicting international guidance on investigation and treatment.

Some authors question the ability of ultrasound to diagnose distal DVT. Indeed, recent meta-analyses have consistently failed to show a pooled sensitivity for detection of distal thrombosis by ultrasound any higher than 75% [11,12]. This failing could well be related to the potential pitfalls of the current gold standard: contrast venography has been noted as a potential cause of DVT and has many additional caveats, including extravasation reactions, technical limitations and variable interobserver reliability [13,14]. Despite these failings, many clinicians cite the poor sensitivity data and choose to base their management strategies on serial compression ultrasound of the thigh, avoiding the distal veins altogether. In the absence of sonographic progression to proximal veins after 7 days, the presence of distal disease is presumed to be clinically irrelevant. Recent well conducted studies report a non-significant difference in 3-month VTE event rates between patients randomized to be investigated by serial or complete leg ultrasound in suspected DVT [15,16]. The British Society of Haematology endorse this approach to suspected lower limb VTE in a national guidance document [17]. Thus, many clinicians withhold anticoagulation after serially negative proximal ultrasound.

Conversely, it is also well recognized that a proportion of untreated distal disease will propagate, embolize and/or lead to chronic venous pathology. Current estimates of proximal propagation in untreated patients range between 0% and 29%, with some untreated patients developing pulmonary emboli during short-term follow-up [18]. The most relevant studies assessing complication rates in untreated patients can be seen in Table 1 [19-25]. There have also been previous reports of fatal pulmonary embolism occurring within the 7 days after

initial negative proximal ultrasound in suspected disease [26]. The potential to cause post-thrombotic syndrome (PTS) is valid but as yet unquantified [27,28]. These sequelae prompt some clinicians to advocate standard therapeutic anticoagulation for all. Several international organizations endorse this approach when diagnosis is clarified [29-31].

It remains unclear whether the benefits of treatment outweigh the potential harms. The only randomized trial comparing conservative management to standardized oral anticoagulation in distal DVT was performed by Lagerstedt et al. in 1985 [19]. A total of 51 participants were included. The authors demonstrated a 29% 3-month recurrence rate and a 32% 1-year recurrence rate for conservatively managed patients with distal DVT. The incidence of recurrence in warfarinized patients was significantly lower, 0% at 3 months and 4% at 1 year. The results from this trial have been much debated, with many authors highlighting the small sample size, composite diagnostic standards and unequal baseline characteristics between groups [32].

Recent studies using ultrasonography to detect recurrence or propagation have failed to replicate Lagerstedt et al.'s data. Using a limited treatment regimen of reduced dose heparin for 4 weeks only, Parisi et al. demonstrated a 2.9% propagation rate at 3-month follow-up [33]. The blind, prospective CALTHRO study has recently reported low rates of venous thromboembolism/recurrence in untreated patients at 3 months, noting an event rate of 7.8% (95% CI 3% to 17%) [23]. Schwarz et al. have demonstrated further reduced event rates when selecting out low-risk distal DVT for conservative treatment, with propagation in only 3.7% of untreated patients [24]. However, no study has attempted to definitively answer the question by performing an adequately powered prospective randomized controlled trial (RCT). This is highlighted by a recent meta-analysis that notes the heterogeneity of trial data and fails to provide a robust conclusion, despite analyzing data from over 450 patients [34]. Equipoise remains, perhaps best highlighted by recent European research noting the profound and continuing regional variability in diagnostic and therapeutic approach to distal DVT [35]. Recent articles have highlighted the need for robust evidence and called urgently for further prospective RCT data to inform clinical decision making [32,36,37].

We designed a trial to examine the feasibility of testing the applicable null hypothesis: that therapeutic anticoagulation for 3 months confers no significant clinical benefit in the management of acute symptomatic distal DVT, when compared to conservative treatment alone.

Table 1 Prospective studies assessing complication rates in untreated distal deep vein thrombosis (DVT) patients

Author/year	Population	Sample size	Diagnostic method	Duration of follow-up for primary endpoint	VTE complication rate
Schwarz et al. 2010 [22]	Low-risk ambulatory patients with isolated calf muscle thrombus	53	CUS	3 months	2/53 = 3.77%
Palareti et al. 2010 [21]	Symptomatic outpatients	65	CUS	3 months	5/64 = 7.8%
Macdonald et al. 2003 [19]	Mostly symptomatic surgical and medical inpatients (68.6%) with isolated calf muscle vein thrombus	135	CUS	3 months	4/135 = 3%
Schwarz et al. 2001 [23]	Symptomatic outpatients with isolated calf muscle vein thrombosis	32	CUS	3 months	8/32 = 25%
Lohr et al. 1995 [18]	Mostly symptomatic surgical and medical inpatients (59.4%)	192	CUS	4 weeks	21/169 = 12.4%
Oishi et al. 1994 [20]	Asymptomatic postoperative total hip replacement/ total knee replacement patients	41	CUS	12 months	7/41 = 17.1%
Lagerstedt et al. 1985 [17]	Symptomatic medical patients	28	Isotopic uptake confirmed by ascending phlebography	90 days	8/28 = 29%

CUS = compression ultrasound; VTE = venous thromboembolic complication rate: this refers to ascending proximal extension of the thrombus to the popliteal vein or development of symptomatic pulmonary embolism, except for the study by Schwarz et al. [23]. In this trial, patients were commenced on therapeutic anticoagulation if the distal thrombus propagated to any of the deep calf veins. Many cases were therefore treated prior to potential popliteal extension.

Methods

Study aims

The Anticoagulation of Calf Thrombosis (ACT) trial aims to compare the incidence of venous thromboembolic complications in patients with distal deep vein thrombosis treated with either standard therapeutic anticoagulation or conservative management.

Study design and setting

The study will be initially conducted as a prospective, randomized, open-label, pragmatic, controlled trial within the Emergency Department (ED) at Central Manchester University Hospitals NHS Foundation Trust. The ED has an average annual attendance figure of 110,000. The trial will begin as an external pilot project, recruiting distal DVT patients over a 16-month period at a single center to assess feasibility and gather accurate clinical outcome data. A study process flow chart is given in Figure 1.

Ethical considerations

Ethical approval for this study has been obtained from the North West Greater Manchester Central Research Ethics Committee (ref: 10/H1008/97) as a Controlled Trial of an Investigative Medicinal Product (CTIMP). The Medicines and Healthcare products Regulatory Agency (MHRA) have granted clinical trial authorization. A Data Safety and Monitoring Board (DSMB) including a leading expert in thrombosis/hemostasis will be convened to evaluate data and comment on safety within the trial. A Trust Steering committee will oversee local trial conduct and governance. The study is subject to all ongoing NHS Research and Development governance checks regarding CTIMP projects.

Study interventions

Patients randomized to trial group A will receive immediate therapeutic anticoagulation with initial daily administration of subcutaneous low molecular weight heparin (LMWH), followed by 3 months oral standard NHS anticoagulant pharmacotherapy. Pending UK adoption of novel agents, oral anticoagulation will be achieved with warfarin targeted to an international normalized ratio (INR) of 2.5 (range 2.0 to 3.0). Patients will be monitored by a dedicated anticoagulant clinic at the study site and seen at regular intervals for INR testing. Methods for adjusting warfarin dose and maintaining target INR will be at the discretion of the anticoagulant clinic service. Compliance will be evaluated within treatment groups. Group A patients will also receive grade 2 compression hosiery fitted externally through the orthotics department.

Group B trial patients will receive symptomatic treatment only, in the form of simple analgesia and fitted grade 2 compression hosiery.

Identification of eligible patients

All ambulatory patients with suspected DVT attending the ED will undergo risk stratification, blood investigation and subsequent complete lower limb duplex compression ultrasound (CUS), in line with standard practice. Prior to ultrasonography, all patients with suspected DVT will be provided with a patient information sheet outlining the trial protocol.
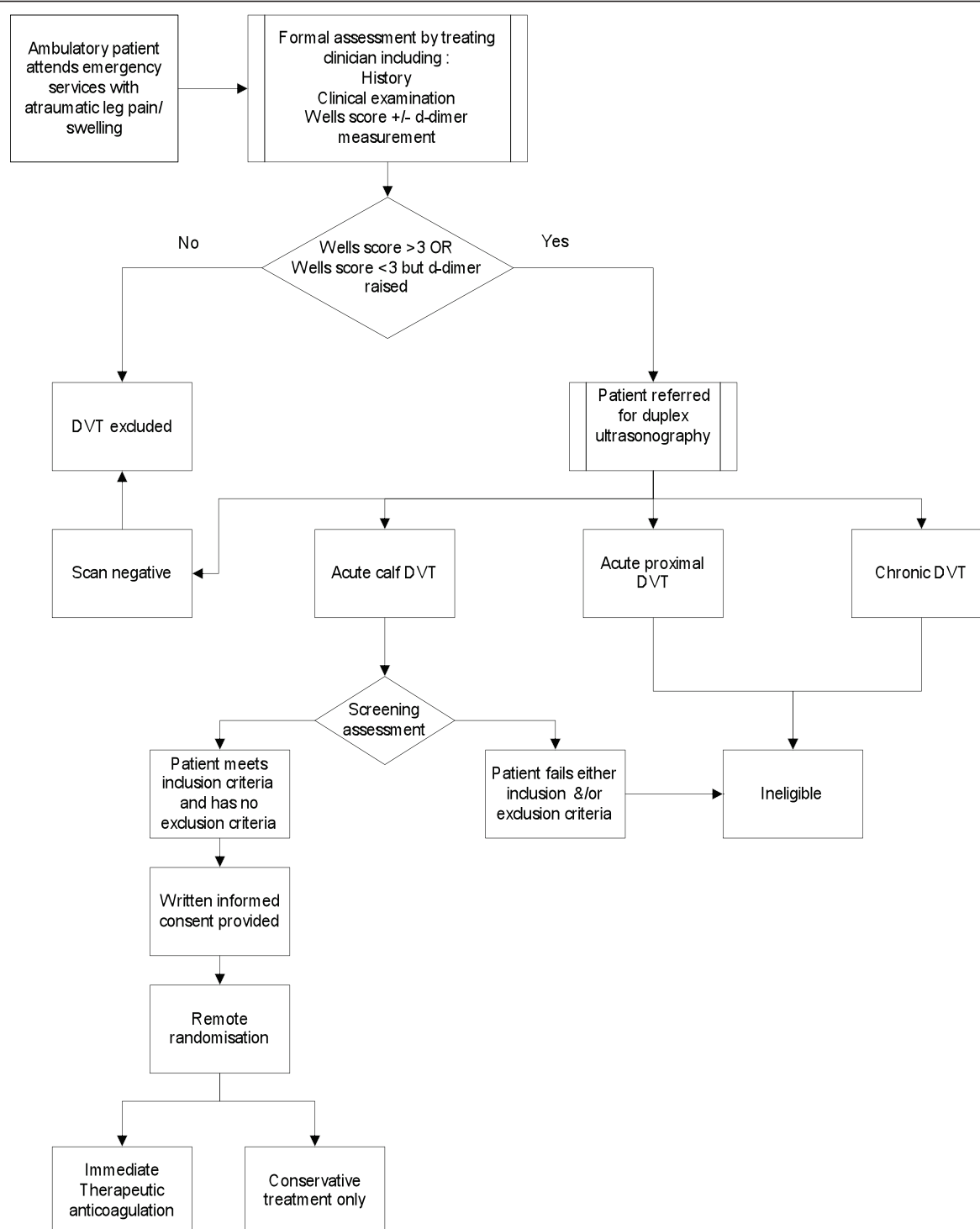
Figure 1 Summary of trial design/patient flow. Proximal DVT relates to acute thrombotic disease above the level of the trifurcation of the popliteal vein. Chronic DVT relates to any reported thrombosis detected on prior documented ultrasound, previously treated, or with chronic appearance on contemporary ultrasound exam. DVT = deep vein thrombosis.

Patients will be managed in an ED thrombosis clinic the same day, where they will be further counseled regarding diagnosis and treatment options. The presence of isolated thrombus in any of the peroneal, soleal, gastrocemial, or tibial veins on duplex CUS detected by an accredited vascular technician, will constitute the

diagnosis of distal DVT. Patients with confirmed distal disease will be screened for eligibility by a trained researcher. Inclusion/exclusion criteria are documented below. Only patients able to provide written informed consent will be approached for inclusion. Demographic data will be collected on case report forms, including risk factors (permanent and temporary), provocation, baseline blood tests and examination findings.

Inclusion criteria

- Aged 16 or above
- Symptomatic attendance to the Emergency Department with atraumatic leg pain and/or swelling as the principal complaint
- Objective diagnosis of distal deep vein thrombosis by duplex vascular ultrasound

Exclusion criteria

- Hospitalised patients (all inpatients)
- Long term therapeutic anticoagulation
- Associated confirmed venous thromboembolic disease (Proximal leg DVT, PE or central vein thrombosis)
- Contraindication to anticoagulation (presence of active bleeding, recent haemorrhagic stroke or upper gastrointestinal bleed)
- Active cancer
- Any other indication for anticoagulation according to national/local guidance: prior confirmed and treated above knee DVT/PE, antiphospholipid syndrome or symptomatic inherited thrombophilia.
- Pregnancy
- Chronic non propagating thrombus
- Previous enrollment to the ACT trial

Randomization technique

Randomization will occur after patient consent has been taken. Participating patients will be assigned to one of two groups by a remote, computerized, web-based randomization sequence, constructed with variable permuted block size. Group A will be allocated to receive therapeutic anticoagulation with standard pharmacotherapy, group B to receive conservative management. All patients will be briefed in person and writing regarding the clinical signs of extending DVT/PE and advised to contact the trial team or return to the ED with any concerns.

Blinding

This is an open-label study. Although previous trials have used 'sham' anticoagulant clinics we feel use of placebo and frequent hospital visits to maintain blinding would be potentially unethical and deleterious to recruitment. Complications in the context of warfarinization also need urgent treatment and an unblinding protocol would naturally delay this.

All ultrasonographers will be blinded to allocation for repeat scans. Clinical outcome measures are primarily objective, which should minimize the risk of measurement bias.

Patient follow-up procedures

Patients will return at 7 and 21 days for follow-up duplex CUS and clinical review. Vascular radiology technicians will be blinded to treatment allocation for all scans. Propagation of DVT to the level of the popliteal vein (above the trifurcation) at any point post randomization will be considered as proximal extension and result in immediate therapeutic anticoagulation. Patients will be clinically reviewed and outcome data collected when they attend for repeat CUS. Worsening symptoms in the context of non-propagation above the trifurcation will be assessed carefully and further investigations will be dictated by clinical need.

At the end of the 3-month treatment period all subjects will be followed up via medical record review and structured telephone interview. An ED appointment will be arranged if any queries or clinical concerns persist. All patients will be encouraged to continue wearing compression stockings daily for 2 years, as per current evidence [38]. Suspicion of pulmonary VTE at any stage will be investigated as per current practice and confirmed by Prospective Investigation Of Pulmonary Embolism Diagnosis (PIOPED) reported V/Q scan or computed tomography (CT)-pulmonary angiography [39]. Any patient diagnosed with pulmonary VTE will receive immediate therapeutic anticoagulation as per current practice. Out of normal working hours, patients will be advised to attend the ED with any concerns, where a protocol for investigation of suspected pulmonary embolism in ambulatory patients is already standard practice.

Final clinical review and data collection will occur at 2 years post inclusion, regarding the incidence and severity of post thrombotic syndrome and the incidence of DVT recurrence in all patients. The diagnosis and severity of PTS will be assessed using the standardized scoring system validated by Villalta et al. [40].

Patient outcome measures

As an external pilot study, the primary endpoints for the trial will constitute measures of feasibility only. A successful pilot RCT seeks to collect data regarding process, resources, management and scientific data [41]. Feasibility outcomes have been designed to reflect this. Clinical measures of treatment effect and safety will be recorded

as secondary outcomes, in order to inform further sample size calculations and data inference for potential future multicenter research.

Primary feasibility outcomes are: incidence of the index condition, the proportion of eligible patients within the screening cohort, recruitment rate for those deemed eligible, allocation crossover and short-term compliance with the study protocol.

Secondary outcomes are: combined incidence of thrombus propagation to the popliteal vein, DVT recurrence, development of pulmonary embolism or VTE related sudden death during the 3-month intervention period; incidence of major and minor bleeding episodes during the 3-month treatment period; incidence of post-thrombotic leg syndrome at 2 years; and incidence of VTE recurrence at 2 years.

Outcome measures will be defined using the following tools: DVT recurrence or development of pulmonary embolism will be confirmed by objective diagnostic criteria, either via repeat CUS in the presence of worsening symptoms or PIOPED reported ventilation-perfusion scan or CT pulmonary angiogram in the presence of new chest symptoms [39]. Any cases of sudden death during the interventional phase of the trial will be assessed by a panel of experts blinded to treatment allocation, including a Professor of Emergency Medicine, Consultant Hematologist and Consultant Respiratory Physician. A consensus decision will be required regarding VTE as the principal cause of death.

Major bleeding episodes will be defined as standardized in 2005 by Schulman et al.: clinically overt and associated with a fall in hemoglobin of 20 g/l, resulting in the need for transfusion of two or more units of red cells, involving a critical site, or fatal [42]. Minor bleeding episodes will be subcategorized as per Schulman et al. in 2009 into clinically relevant, or nuisance bleeding [43].

Post-thrombotic syndrome will be diagnosed and numerically graded using the validated and internationally adopted Villalta scale [40].

Withdrawal, allocation crossover and protocol violation
Participants withdrawing from the study voluntarily will be included in the intention to treat analysis. Allocation crossover will be deemed to occur if patients allocated to conservative treatment are prescribed full dose therapeutic anticoagulation for > 5 days at any stage during 3-month follow-up, or patients allocated to anticoagulation have therapy withheld for > 5 days.

Data safety and monitoring board (DSMB)
The DSMB will be independent and composed of three principal members: a leading expert in thrombosis/hemostasis, an independent statistician and an expert in clinical trials (chair). All pharmacovigilance reports including serious adverse events, adverse events, protocol violations and allocation crossovers will be reported to the DSMB along with all clinical endpoint data collected. The group will be convened after recruitment of 50 patients. No criteria exist for early termination of the pilot study; judgment of the DSMB will be acknowledged and followed.

The board comprises: Professor Henry Kitchener (Chair), honorary consultant gynecological oncologist and chair of the National Cancer Research Institute's Gynaecological Clinical Studies Group; Dr Trevor Baglin, consultant hematologist and President of the British Society for Haemostasis and Thrombosis; and Dr Steve Roberts, medical statistician and senior lecturer at the University of Manchester.

Sample size considerations
The most recent prospective evidence estimates the 3-month composite risk of VTE in untreated patients with undifferentiated distal DVT to be approximately 5% [23]. Data from separate research cites the above risk to be 1% in patients receiving anticoagulation [16]. To achieve this expected difference between groups, 489 patients per group would provide statistical power of 80% with a two-sided α of 0.05. For a definitive study, the required sample size is thus currently estimated at approximately 1,000 patients.

For the primary feasibility study we will recruit over a 16-month period initially, aiming to achieve roughly 10% of the current sample size estimate at 100 patients. An updated power calculation will be derived from the primary feasibility data along with refinements to trial design for use in the definitive RCT.

Statistical analysis
As a feasibility study, principal analysis will focus on the incidence of distal DVT as the index condition within the screening cohort and the proportion of eligible patients willing to participate in the trial. Protocol violations and allocation crossover rate will also be assessed within the two groups to determine the feasibility of maintaining treatment allocation within each cohort for the duration of the study period. Binomial confidence intervals will be estimated for all proportions using the Wilson score exact method.

The predefined criteria for assessing success of feasibility will constitute the following: (1) index disease incidence > 5% within the screening cohort, (2) > 70% recruitment rate within eligible participants and (3) < 25% protocol violation rate.

The secondary analysis will be a comparison of anticoagulation versus conservative treatment for prevention of the secondary clinical endpoint following the 'intention to treat' principle. A further 'per protocol' analysis

of all clinical endpoints will take place excluding all withdrawals, allocation crossovers and protocol violations. Proportions will be compared for statistical significance using Fisher's exact test and a further descriptive analysis made of the individual components forming the composite primary outcome. An estimate will be made with 95% confidence interval of absolute risk reduction. Together with the primary feasibility outcomes, this data will allow estimation of the number of sites, duration of recruitment and resources needed to conduct the definitive multicenter study.

Further intention to treat analyses of secondary and tertiary endpoints occurring within the two groups will be compared using Fisher's exact test. All significance tests will be two sided.

Discussion

Management of isolated distal DVT is controversial throughout the developed world. Investigation and treatment strategies continue to vary locally and internationally. National management guidance continues to change based on emerging evidence [44,45]. These guidelines acknowledge the deficit in the literature and modern papers continue to call for prospective clinical trials [18,32,36,46]. There is a pressing and documented need to clarify the benefits of any treatment and the risks involved.

The ACT study has begun as a feasibility project, recruiting over a 16-month period. The main clinical outcomes assessed will incorporate both VTE-related and anticoagulant-related complications. Analysis of feasibility data will support future sample size calculations, allow refinement of methodology and inform the conduct and coordination of an adequately powered multicenter RCT.

Selection of the most appropriate primary outcome for the definitive trial is scientifically challenging. We propose a composite primary outcome of VTE-related death, DVT propagation, pulmonary embolism or major bleeding occurring within 3 months. This outcome combines the most relevant considerations for clinicians facing the decision of whether to prescribe anticoagulation for a patient with isolated distal DVT. Acknowledging the current equipoise, this composite outcome focuses on net benefit, balancing the risks of withholding anticoagulation against the risks of prescribing anticoagulation.

Each component of this composite outcome is directly relevant to our research question. While death is arguably the most important outcome, it is not the only consideration in the decision to anticoagulate. Proximal propagation is a proxy marker for aggressive disease and, due to the potential for death and pulmonary embolism, it would be unethical to continue to withhold anticoagulation in its presence. Major hemorrhage is the main concern with therapeutic anticoagulation and largely responsible for our situation of equipoise.

The use of composite outcomes within controlled trials is supported by international bodies [47]. Advantages include the engagement of multiplicity and derivation of a clinically important result from a smaller sample, with consequent reduction in costs and timely introduction of appropriate treatments. Modern interventional trials in venous thromboembolic disease continue to rely on a composite of endpoints as the primary outcome [43,48]. Disadvantages include dilution of treatment effect, the detrimental impact of subjective outcomes and the equal weighting that is given to factors of varying importance to patients and clinicians [49,50]. We aim to address these concerns as follows: (1) our composite outcome includes primarily objective measures, (2) the composite outcome includes only those factors that would directly influence the decision to anticoagulate and are therefore crucial to definitively answer our research question, and (3) all individual features of the composite endpoint will be separately identified within the secondary clinical outcomes to allow direct and transparent statistical comparison between groups.

In tandem with the use of a composite outcome we will also involve a health economist within the definitive trial design/analysis, to assess economic merits and overall health utility of the research question.

Other bleeding events, VTE recurrence and the development of post-thrombotic syndrome will constitute additional secondary outcomes. With a large dataset, analysis can also extend to search for individual factors significantly associated with propagation within the conservatively treated cohort. This can be achieved using regression techniques to examine elements within the history, examination and workup that can subsequently be classed as predictive of adverse outcome. If significant predictors exist, consideration can be given to development of a decision tool aimed at helping clinicians to decide which distal thrombi to anticoagulate. This research is essential in developing an ideal model of risk stratification and individualized treatment [36]. Therapeutic anticoagulation should be tailored to those at risk.

A definitive answer to the management questions surrounding investigation and treatment of distal DVT has huge implications for both patients and clinicians. If a real and significant reduction in risk of complications is seen with therapeutic anticoagulation, diagnostic strategy and clinical guidance can become focused and coherent both nationally and internationally. All patients can subsequently receive evidence-based therapy aiming to prevent both short and long-term complications of disease. If the absolute risk reduction seen is deemed

non-significant, or benefit limited by bleeding risks, then clinicians can pursue conservative management with confidence. Anticoagulation can be restricted in the majority of cases, resulting in reduced healthcare costs and bleeding complications. Either way, the ACT study aims to benefit both patients and clinicians by providing modern evidence to assist decision making for this challenging and relatively common clinical scenario.

Trial status

The ACT trial was conceived and designed in 2009, with successful application for peer reviewed funding through the College of Emergency Medicine (UK) in 2010 and National Institute for Health Research (NIHR) portfolio adoption in 2011. Recruitment to the trial began in January 2011. As of 15 January 2012, 62 patients have been successfully recruited within a 12-month period. Steering committee review has occurred with governance oversight and full approval for continued recruitment to the end of the feasibility window. Recruitment is planned to continue until the end of April 2012. Following protocol completion and subsequent analysis, preliminary results will be available towards the end of the year.

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Authors' contributions

KH, KM-J and DH were responsible for identifying the research question and contributing to drafting of the initial protocol. RB and MJN both contributed to the development of the protocol and study design, as members of the research group. DH was responsible for the drafting of this paper, although all authors provided comments on the drafts and read and approved the final version.

Competing interests

The authors declare that they have no competing interests.

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Paper 2: The Anticoagulation of Calf Thrombosis (ACT) Project: a randomized controlled external pilot trial.

Paper Overview

A prospective RCT comparing therapeutic anticoagulation to conservative management in the treatment of ambulatory IDDVT. Predefined markers of feasibility and clinical outcomes were assessed.

Contribution to the thesis and novelty

This paper addresses the principal hypothesis further, alongside the first and second aims of the thesis, by providing contemporary data on the feasibility of further prospective randomized controlled trials regarding IDDVT management. The trial also provides clinical point estimates for use in further study design. This is the largest conducted trial to date comparing variable strategies in IDDVT management and adhering to modern standards and ethical codes.

Contribution of candidate

Study design, patient recruitment and follow up, data management, monitoring response, MHRA liaison, conduct of the analysis and co-ordination of the independent adjudication committee. The MD student also wrote and managed all drafts of the manuscript, incorporating suggestions from co-authors.

Publication strategy/status

For submission to the following journals in order of preference:

1. The Lancet   38.28
2. Annals of Internal Medicine   16.73
3. British Medical Journal   14.09

Title:

The Anticoagulation of Calf Thrombosis (ACT) Project: a randomized controlled external pilot trial

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Abstract

Objectives

There is currently little evidence defining the clinical importance of detecting and treating isolated distal deep vein thrombosis (IDDVT). Contemporary international guidelines vary regarding diagnostic and therapeutic advice. The potential benefits of anticoagulation remain poorly defined.
We sought to evaluate the feasibility of a randomized controlled trial within a modern cohort, to determine whether patients with IDDVT benefit from therapeutic anticoagulation.

Methods

A pragmatic, open label, external pilot randomized controlled trial. Consecutive symptomatic IDDVT patients were approached for inclusion, within an ambulatory thrombosis service. Participants were randomized to receive either phased therapeutic anticoagulation or conservative management. All patients underwent colour duplex imaging after 7 and 21 days, and follow up at three months. Principal feasibility outcomes were recruitment rate and attrition, including loss to follow-up and allocation crossover. The primary clinical outcome was a composite of proximal propagation, pulmonary embolism, death attributable to venous thromboembolic disease or major bleeding. Analysis was by intention to treat.

Results

In total, 93 patients with IDDVT were screened and 70 (88.6%) of those eligible were recruited. All patients but 1 were followed up by direct contact after 90 days. A single patient (1.4%) was personally uncontactable: follow up occurred through medical record review and discussion with the primary care practitioner. Allocation crossover occurred in 15 (21.4%) patients.
The primary clinical outcome occurred in 4/35 (11.4%) controls and 0/35 in the intervention group (Absolute Risk Reduction 11.4%, 95% CI -1.5 to 26.7, p=0.11, number needed to treat of 9). There was no major bleeding in either group. Minor bleeding occurred in 3/35 (8.6%) controls and 7/35 (20.0%) anticoagulated patients (p=0.31).

Conclusion

We have established feasibility for a definitive trial on the value of therapeutic anticoagulation for IDDVT. Our study is the largest prospective randomized trial conducted on this topic and demonstrates a non-significant trend towards benefit with anticoagulation. This highlights the importance of further evaluation with an appropriately powered design.

Trial Registration

ISCTRN 75175695

Background

Venous Thromboembolic (VTE) disease is a topical and costly healthcare burden. Diagnosis is associated with significant morbidity and mortality despite modern advances in care [1-4]. Unfortunately, standard therapeutic dose anticoagulation also carries a quantifiable and significant risk [5-7]. There are many grey areas where the benefits of aggressive treatment are counterbalanced by potential harm.

Isolated distal deep vein thrombosis (IDDVT) is one such area. A composite of calf muscle and deep calf vein thrombosis, isolated disease restricted below the popliteal trifurcation continues to divide clinical opinion [8]. This is perhaps best exemplified by the ongoing international variation in practice and recent vernacular debate [9-16].

Only one prospective randomized controlled trial (RCT) has ever compared phased oral anticoagulation against conservative management in IDDVT [17]. This was conducted over 25 years ago on a sample of 51 patients, demonstrating a significant recurrence rate in those patients treated conservatively (Absolute Risk Reduction (ARR) 29%, p<0.01). The article was followed by multiple additional case series highlighting the dangers of conservative management [18-28]. Subsequent international guidance was produced supporting therapeutic anticoagulation for IDDVT [29-31].

Further trials have suggested a lower risk in more conservatively managed IDDVT. Parisi *et al* showed only a 2.9% proximal propagation rate with four weeks of low dose anticoagulation [32]. Singh *et al* quote a 7% rate of popliteal extension with prophylactic dose anticoagulation [33]. In 2010, Schwarz *et al* showed no difference in propagation of calf *muscle* thrombosis with 10 days full anticoagulation versus no anticoagulation [34]. The CALTHRO study recorded a 7.8% rate of proximal extension or pulmonary embolism in patients with conservatively managed IDDVT [35]. The American College of Chest Physicians have consequently adjusted recommendations in current guidance to principally support surveillance rather than anticoagulation in low risk patients [36]. It is clear that experts remain uncertain about the ideal management strategy for IDDVT.

No systematic review or meta-analysis has been able to provide clear recommendations due to the paucity of publication and heterogeneity of available results [37-40]. Recent literature continues to highlight the need for specifically designed and adequately powered clinical studies. There is a widespread call for prospective randomised trial data on the treatment of IDDVT [8, 10, 11, 13, 15, 33, 35, 37-41].

Uncertain quantification of risk reduction with therapeutic anticoagulation currently poses a major issue for the conduct of adequately powered multicentre research. Therefore we initially sought to establish the feasibility of a definitive trial. Specific objectives of this project were to define the incidence of IDDVT in ambulatory patients and to evaluate recruitment and compliance to trial protocol. We also sought to assess complication rates in patients randomly treated with and without therapeutic anticoagulation.

Methods

All subsequent data presented conform to CONSORT 2010 guidelines [42]. We have also adhered to published templates incorporating the CONSORT format into the reporting of pilot investigations [43].

Design, setting and participants
The trial protocol has previously been published and gives a detailed account of the background, methods and oversight, including details of the Trial Steering Committee [44]. Briefly, we undertook a pilot randomised controlled trial set in the Emergency Department (ED) at a university-affiliated teaching hospital with approximately 100,000 ED attendances per annum. Patients presenting with symptoms compatible with deep vein thrombosis (DVT) underwent standardised investigation in accordance with an evidence-based pathway, in line with current international guidance [45, 46]. Patients aged >16 years who were diagnosed with acute IDDVT following colour duplex ultrasound scanning were eligible for inclusion. We excluded inpatients, pregnant women, patients with active cancer, a contraindication to anticoagulation or

prior proximal deep vein thrombosis, and patients already taking anticoagulants at the time of the initial presentation. Transient and permanent risk factors were documented at inclusion, prior to randomisation. We defined provocation using the recent criteria proposed by the National Institute for Health and Clinical Excellence (NICE) within the UK [47].

The trial was approved by the Greater Manchester Central Research Ethics Committee (ref: 10/H1008/97) and the Medicines and Healthcare products Regulatory Agency (ref: 2010-021813-22). The trial is registered with an international open access database [48]. All participants provided written informed consent.

Randomisation, intervention and follow up

Using a web-based platform with an externally generated randomization sequence in variable permuted blocks, we randomized patients to receive either therapeutic anticoagulation (intervention group) or conservative treatment (control group) in a 1:1 allocation ratio. Patients in the intervention group were initially given subcutaneous therapeutic dose dalteparin with phased transition to an oral vitamin K antagonist (warfarin or acenocoumarol) for a total of three months. All patients were followed up in a dedicated anticoagulant clinic for international normalised ratio (INR) monitoring. The target INR was 2.5 (range 2.0 to 3.0), with overall quality of anticoagulation assessed by proportional time in therapeutic range (TTR), as a standard measure of compliance [49]. Patients in the control group received no anticoagulation. As this pragmatic trial had an open label design, these patients did not receive placebo control. All patients, regardless of treatment allocation, received analgesia (including anti-inflammatory medication) to use as required and grade 2 compression stockings. Patients were followed up in clinic on days 7 and 21 for clinical review and repeat colour duplex scanning by accredited vascular sonographers blinded to treatment allocation, and by telephone on day 90. Proximal propagation or development of pulmonary embolism following randomisation mandated therapeutic anticoagulation as per trial protocol. Local propagation was managed expectantly without protocol, to allow and record the clinical decisions made by treating physicians.

Imaging and Laboratory Protocols

Initial diagnosis and follow up imaging was performed by colour duplex

ultrasonography in a dedicated environment external to the ED. Technicians within the vascular lab are vocationally trained to postgraduate level in Vascular Science and accredited to standards set by the Society for Vascular Technology of Great Britain and Ireland.

Patients were scanned using a 9-4MHz linear and 5-2MHz curvilinear transducer to a standard proforma. This includes documented assessment of all proximal, muscular calf and deep calf veins using B mode, colour Doppler and spectral Doppler including compression, augmentation and Valsalva manoeuvre. Clot burden at recruitment was assessed and recorded using the Marder scoring system [50].

All d-dimer measurements were conducted using a rapid and quantitative immunoturbidometric assay (STA Liatest (Diagnostica Stago)) and reported in ng/mL. This assay has been validated as highly sensitive for the exclusion of VTE in multiple previous studies [51-53].

Outcomes

Primary feasibility outcomes were: (a) incidence of the target condition within the ambulatory population of interest, (b) recruitment rate and (c) attrition (including loss to follow up and protocol violations including allocation crossover). The main secondary clinical outcome was the proposed primary outcome for the full future trial: that of serious thromboembolic complications. This composite outcome was defined as the occurrence of either proximal propagation to the level of the popliteal trifurcation or above (recorded objectively at blinded ultrasound) with or without symptoms, development of symptomatic pulmonary embolism, VTE related sudden death or major bleeding. Additional secondary outcomes included major, minor and nuisance bleeding episodes. Pharmacovigilance (including all sudden adverse events and adverse events) was recorded to recommended standards [54] and monitored by the sponsor. Bleeding events were defined and categorised as per the harmonised definition produced by the standardisation committee of the International Society for Thrombosis and Haemostasis (ISTH) [55]. Diagnosis of pulmonary embolism was objectively confirmed by PIOPED reported V/Q scan or CTPA imaging [56, 57].

Criteria for establishing feasibility were defined *a priori* and include: 1) index disease incidence >5% within the screening cohort, 2) >70% recruitment rate within the eligible population 3) >50% protocol completion rate and 4) <25% protocol violation

rate with regard to allocation crossover.

Statistical analysis

Categorical data are described as percentages and compared using Fisher's exact test. Continuous data were tested for normality using the Kolmogorov-Smirnov test and parametric data summarized by the mean (standard deviation). Non-parametric data were summarized by the median (interquartile range) and compared using the Mann-Whitney U test. We calculated 95% confidence intervals with the Wilson method. All p values reported are two tailed, with a value of <0.05 considered statistically significant. Analysis of clinical outcomes was by intention to treat. All analyses were performed using SPSS version 20.0 (IBM) and were checked and verified by an independent statistician.

Results

During the recruitment phase, 951 patients underwent ambulatory assessment for suspected DVT. Proximal disease was confirmed in 104 cases. A total of 93 patients were diagnosed with IDDVT, of whom 79 were deemed eligible for the trial. 70 patients provided consent and were included in the study (Figure 1). Prior proximal venous thrombosis, declined consent or missed cases due to investigator unavailability were the principal barriers to participation. Baseline characteristics of recruited and missed participants are shown in Table 1. Clinical features at presentation are described in Table 2. The proportional difference in provocation between groups at baseline was not significant (p=0.33).

One (1.4%) participant was uncontactable by telephone at 90 days. For this patient, follow up data was obtained by review of electronic medical records and discussion with the primary care practitioner.

Feasibility outcomes

The incidence of IDDVT within the screening cohort was 93/951 patients at 9.8% (95% CI 8.1 to 11.8%). Seventy-nine (84.9%) of these patients with confirmed IDDVT were eligible for participation. Therefore, 75.3% (95% CI 65.5 – 82.9%) of all patients with IDDVT and 88.6% (95% CI 79.7 – 93.9%) of eligible patients during

Figure 1: Flow diagram of patient assessment, recruitment and follow up

Assessed for eligibility (n= 93)

Excluded (n= 23)

- ♦ Not meeting inclusion criteria (n= 1) associated pulmonary embolism
- ♦ Declined to participate (n= 5)
- ♦ Previous proximal VTE (n= 4)
- ♦ Missed cases (n= 4)
- ♦ Already on anticoagulation (n= 3)
- ♦ Requiring hospitalisation (n= 3)
- ♦ Other (n= 3)

Enrollment

Randomized (n= 70)

Allocation

Allocated to therapeutic anticoagulation (n=35)
- ♦ Received allocated intervention (n=35)
- ♦ Did not receive allocated intervention (n= 0)

Allocated to conservative management (n= 35)
- ♦ Received allocated intervention (n=35)
- ♦ Did not receive allocated intervention (n=0)

D7 Follow-Up

Lost to follow-up (n= 0)
Receiving allocated intervention (n=30)
Discontinued intervention (n=5)
- ♦ Patient omission (n=3)
- ♦ Bleeding complications (n=1)
- ♦ Hospitalisation and alteration (n=1)

Lost to follow-up (n= 0)
Receiving allocated intervention (n=33)
Discontinued intervention (n=2)
- ♦ Composite endpoint achieved (n=1)
- ♦ Hospitalisation (n=1)

D21 Follow-Up

Lost to follow-up (give reasons) (n=0)
Receiving allocated intervention (n=33)
Discontinued intervention (n=2)
- ♦ Patient omission (n=2)

Lost to follow-up (n= 0)
Receiving allocated intervention (n=26)
Discontinued intervention (n=9)
- ♦ Composite endpoint achieved (n=3)
- ♦ Allocation changed by other clinician (n=3)
- ♦ Hospitalisation (n=3)

D90 Analysis

Lost to follow-up (n= 0)
Analysed (n=35)

Receiving allocated intervention (n=31)
Discontinued intervention (n=2)
- ♦ Patient omission (n=1)
- ♦ Hospitalisation and alteration (n=1)

Lost to follow-up (n= 0)
Analysed (n=35)

Receiving allocated intervention (n=20)
Discontinued intervention (n=13)
- ♦ Composite endpoint achieved (n=4)
- ♦ Allocation changed by other clinician (n=6)
- ♦ Hospitalisation (n=3)

Table 1: Demographic and provocation data for all randomised patients and excluded cases. Age is presented as mean (SD). All other data is presented as numerator with proportion (n/N).

		Therapeutic Anticoagulation N=35	Conservative Management N=35		Excluded IDDVT cases N=23
Demographics					
Age		60.9 (17.8)	59.8 (17.9)		53.8 (18.3)
Female Sex		26 (74.3)	20 (57.1)		12 (57.1)
Left sided DVT		14 (40)	19 (54.3)		10 (47.6)
Ethnicity	White Black Asian Hispanic Other	29 (82.9) 4 (11.4) 2 (5.8) 0 0	27 (77.1) 5 (14.3) 1 (2.9) 0 2 (5.7)		17 (81.0) 1 (4.8) 0 (0) 1 (4.8) 2 (9.5)
Provoked		**24/35 (68.6)**	**19/35 (54.3)**		**13/23 (56.5)**
Plaster application		6 (17.1)	3 (8.6)		1 (4.8)
Recent Hospital admission		11 (31.4)	8 (22.9)		6 (28.6)
Recent Surgery		12 (34.3)	5 (14.3)		2 (9.5)
Recent Air Travel		4 (11.4)	4 (11.4)		3 (14.3)
Immobilisation		9 (25.7)	9 (26)		7 (33.3)
Oestrogen intake		2 (5.7)	3 (8.6)		4 (19.0)
Pregnancy/puerperium		0 (0)	0 (0)		0 (0)
Unprovoked		**11/35 (31.4)**	**16/35 (45.7)**		**10/23 (43.5)**
Lower limb trauma		7 (20)	6 (17.1)		3 (14.3)
Acute infection		2 (5.7)	1 (2.9)		4 (19.0)
Family history VTE		5 (14.3)	7 (20)		5 (23.8)
Past history VTE		5 (14.3)	6 (17.1)		9 (42.9)
Thrombophilia		2 (5.7)	0 (0)		1 (4.8)
Previous cancer		4 (11.4)	1 (2.9)		0 (0)
Varicosities		9 (25.7)	13 (37.1)		4 (19.0)
Obesity		11 (31.4)	8 (22.9)		4 (19.0)
Smoker		11 (31.4)	13 (37.1)		10 (47.6)
Intravenous drug use		0 (0)	0 (0)		1 (4.8)

Table 2: Baseline clinical data, presenting features and laboratory values for patients randomised to therapeutic anticoagulation, conservative therapy and excluded cases. eGFR = estimated glomerular filtration rate. Age is presented as mean (SD) or median (IQR). All other data is presented as proportions by n (n/N).

	Therapeutic Anticoagulation N=35	Conservative Management N=35		Excluded IDDVT cases N=23
Duration of symptoms	7 (4-14)	7 (3 - 10)		6 (3.25 - 13)
Days of treatment prior to allocation	1 (1-1)	1 (1 - 2)		1 (1 - 1)
Verbal analogue pain score	4.34 (2.1)	4.6 (1.9)		3.84 (1.6)
Pulse rate	79.9 (9.8)	82.9 (18.2)		85.9 (14.8)
Early Warning Score (total)	0 (0-1)	0 (0 - 1)		0 (0 - 1)
High risk Wells score	17 (48.6)	13 (37.1)		10 (47.6)
Marder score	2 (2 - 3)	2 (2 - 3)		3 (2 - 5)
Active cancer	0 (0)	0 (0)		1 (4.8)
Calf swelling	12 (34.3)	6 (17.1)		6 (28.6)
Varicosities	4 (11.4)	13 (37.1)		2 (9.5)
Pitting oedema	19 (54.3)	17 (48.6)		5 (23.8)
Swelling of entire leg	5 (14.3)	4 (11.4)		3 (14.3)
Local pain	24 (68.6)	25 (71.4)		16 (76.2)
Immobilisation	10 (28.6)	6 (17.1)		3 (14.3)
Bedridden	7 (20.0)	5 (14.3)		4 (19.0)
PMH DVT	3 (8.6)	4 (11.4)		6 (28.6)
Alternative diagnosis	1 (2.9)	6 (17.1)		0 (0)
D-dimer (ng/mL)	690 (405 - 1290)	650 (325 - 1260)		612.5 (471 - 813)
C-reactive protein (mg/L)	6 (3 - 13)	9 (3 - 19)		13 (5 - 37)
White cell count (*10^9/L)	6.9 (5.3 - 10.3)	7.5 (5.6 - 9.5)		7.9 (6.1 - 10.9)
Platelet count (*10^9/L)	266.4 (79.4)	275.0 (79.6)		303.2 (123.5)
eGFR	81 (65.75 - 90)	80 (67.75 - 87.75)		85 (70 - 90)

the study period were successfully recruited.

65/70 (92.9%) and 60/70 (85.7%) patients attended for follow up at days 7 and 21 respectively. All patients were alive at day 90 and only 1 could not be contacted directly. Therefore, 59/70 (84.3%, 95% CI 74.0 – 91.0%) patients completed the full protocol. 9 of the 10 patients who did not attend follow up at day 21 had been allocated to the intervention group.

Allocation crossover had occurred in 15 (21.4%, 95% CI 13.4 – 32.4%) patients by day 90, including 13/35 (37.1%) of the control group and 2/35 (5.7%) of the intervention group. Crossover was significantly more likely to occur in the patients allocated to conservative management (p = 0.003). In this cohort, 4 patients achieved the primary outcome (thus mandating anticoagulation); 1 withdrew from the trial following discussion with her GP and requested anticoagulation; 6 patients were admitted to hospital for other reasons and subsequently commenced on either prophylactic or therapeutic dose anticoagulation; and the remaining 2 patients were commenced on anticoagulation in the community by their primary care practitioner or after medical outpatient review.

At follow up on day 90, 35/35 (100.0%) of the control group stated that they had received grade 2 compression stockings and 27/35 (77.1%) had been compliant. 32/35 (91.4%) of the intervention group had received compression stockings and 25/35 (71.4%) had been compliant. The difference in compliance was not statistically significant (p=0.78).

Secondary clinical outcomes

Table 3 shows the proportion of patients with each clinical outcome, stratified by treatment allocation. 4 patients (11.4%) in the intervention group and 0 in the control group reached the composite clinical outcome of serious thromboembolic complications (p=0.11). Although non-significant, the absolute risk reduction is estimated at 11.4% (95% CI -1.5 to 26.7).

The rate of adverse (AE) and sudden adverse events (SAE) were also recorded as described previously and are collated for each group in Table 3. SAEs were most often related to unplanned hospital admission in both groups, for reasons unrelated to VTE. AEs were chiefly characterised by repeat attendance to the ED or complaints of

TABLE 3: Incidence of the primary composite and all clinical secondary endpoints, stratified by intervention. All p-values are calculated using Fisher's exact test. All numerical values are listed as n (n/N). Serious adverse events were recorded as predefined within clinical trial literature. Adverse events were recorded in the event of any new or acute deterioration in symptomatology, regardless of causation.

	Conservative Management N=35	Therapeutic Anticoagulation N=35	Absolute Risk Reduction (ARR)	p value
Composite outcome	**4 (11.4)**	**0 (0)**	**11.4% (95% CI -1.5 to 26.7)**	**P = 0.11**
Popliteal Propagation	3 (8.6)	0 (0)	8.6% (95% -3.5 to 23.1)	NS
PE	1 (2.9)	0 (0)	2.9% (95% -7.5 to 15.0)	NS
VTE related death	0 (0)	0 (0)	-	NS
Major Bleeding	0 (0)	0 (0)	-	NS
Minor Bleeding	3 (8.6)	7 (20.0)	-11.4% (95% -29.7 to 7.1)	NS
Nuisance Bleeding	9 (25.7)	9 (25.7)	0% (95% CI -11.9 to 11.9)	NS
Investigated for suspected PE	4 (11.4)	0 (0)	11.4% (95% CI -1.5 to 26.7)	NS
Sudden Adverse Event Rate	7 (20.0)	8 (22.9)	-2.9% (95% -18.12 to 23.69)	NS
Adverse Event Rate	17 (48.6)	9 (25.7)	22.9% (95% -1.66 to 44.78)	NS

increased pain and/or swelling in the control group.

Clot propagation to the popliteal vein occurred in 3 patients (2 patients at day 7; 1 patient at day 21) and 1 patient developed symptomatic pulmonary embolism (on day 3; confirmed by both high probability V/Q scan and diagnostic CTPA). Specific patient details, progression and provocation are provided in Figure 2.

No patient in either group developed major bleeding. Minor bleeding episodes occurred in 7/35 (20%) anticoagulated patients and 3/35 (8.6%) conservatively treated patients (p=0.31). The incidence of nuisance bleeding was equal in both groups (9/35; 25.7%).

Quality of anticoagulation

The median time from diagnosis to anticoagulant clinic review was 6 (4 to 11) days. In the interim, patients were prescribed a daily therapeutic weight and eGFR (estimated glomerular filtration rate) adjusted dose of subcutaneous dalteparin by ED staff. This was administered by the patient or community nursing team as needed. Patients requiring 5 or more doses were instructed to attend the ED for platelet monitoring and clinical review. Following registration with the anticoagulant clinic, an average of 9 (7 to 10) visits were needed per patient for INR testing during the treatment period. Patients were treated for a median of 14 (12 to 14) weeks. The average proportion of time spent within the therapeutic range (TTR) for patients in the intervention group was 56.0% (41.7 to 73.5%). The proportion of time in or *above* the target INR range was 68% (48.2 to 87.7%).

Discussion

Statement of Principal Findings

Although these are pilot data, to our knowledge this trial is already the largest to date comparing phased oral anticoagulation to conservative therapy in the management of IDDVT. There are two key findings from this work.

First, we have established feasibility for conduct of a definitive randomized controlled

trial. Our findings will enable protocol modifications including revision of the proposed sample size, to maximize the scientific value of that work. Second, we have established an accurate point estimate of clinically relevant complication rates in conservatively managed ambulatory IDDVT patients (11.4%). This data can help to inform clinical decision-making and discussions of perceived risk and benefit with therapeutic anticoagulation, pending further evidence. Our work also highlights the urgent need for that further evidence to definitively evaluate early intervention in IDDVT.

Strengths

The key strengths of this study are reproducible methodology and robust internal validity. We were able to approach a consecutive sample of patients for participation and manage them to a strict, standardised protocol. This trial was designed to be replicated by other centres after publication of pilot results; we have seen no reason why this could not be the case. Our follow up and surveillance rates were excellent due to the relatively modest participant numbers and strong research presence on site. Our chosen follow up method and secondary endpoints were also clinically relevant. Serial sonography is widely considered the gold standard for patients with IDDVT treated conservatively throughout the developed world [8, 36]. Assessor blinding within our protocol limited potential bias and ensured objective interpretation of results. The inclusion of symptomatic PE within the composite outcome also specified that only patients returning with symptoms would be assessed and diagnosed with complications. The potential of silent proximal propagation and new symptomatic pulmonary embolism are the key issues upon which clinicians are likely to make treatment decisions. Our methodology was designed to reflect that.

Perhaps the biggest strength of our study is that of pragmatism and real world evaluation. Our open label design and protocol purposefully allowed clinicians encountering recruited patients to manage any complications as they saw fit, in order to assess the outcome of conservatively managed patients within the context of current National Health Service practice. Thus many patients in the conservative group received additional investigations, reviews and over a third were anticoagulated at some stage during the three month follow up. Despite this, we were still able to show a sizeable ARR between treatment groups.

Limitations

We chose to use an open label methodology *a priori*. This perhaps contributed to the high rate of allocation crossover. The relative merits of this design included pragmatic assessment (as mentioned above), protocol simplification, avoidance of harm within the trial context (no sham blood tests, immediate knowledge of anticoagulation status in the event of complications), reduction in onerous follow up (potentially increasing recruitment) and transparent participation. The relative limitations include potential observer bias arising from subjective interpretation of clinical, laboratory and imaging results and protocol violation by attending clinicians with preconceptions regarding IDDVT. We attempted to minimize limitations by assessor blinding and objective standardization whenever possible with regard to outcomes and adverse events. With the introduction of equally efficacious, novel oral anticoagulant agents requiring less onerous management [58], a blinded trial design is a potential protocol modification worthy of further discussion.

There were subtle differences between the two groups at baseline, including a higher prevalence of provocation within the anticoagulated cohort. These differences, as a result of the small sample size, may have contributed to the increased complication rate seen with conservative treatment. Unprovoked disease is recognised to present a higher risk for recurrence and complication. An additional protocol amendment using stratified randomisation would address this in a subsequent trial, although it is likely that with a larger sample size these factors would be neutralized. We believe our sample is reflective of a standard UK population. A larger study would address this issue further.

The median TTR in our warfarinised patients was notably lower than in other previous exploratory studies. Indeed, this has already been a criticism of several novel oral anticoagulant trials [59]. However, this is reflective of our pragmatic trial design and makes the results more generalisable. In addition, no patient achieved the composite endpoint in the intervention group despite the proportion of sub therapeutic TTR. It may well be the case that any degree of anticoagulation is beneficial in preventing propagation and complication from calf thrombosis. Several studies have already suggested this [32, 33].

Comparison to previous research

Our data has several notable strengths in comparison to other studies. Firstly, we chose to compare conservative management to current international recommendations of phased oral anticoagulation. Many recent studies on IDDVT have compared serial follow up with short, intermediate and prophylactic dose courses of LMWH [32-34]. This is not current practice in the UK/US/North America [60, 61]. In our experience, patients can often be reluctant to use subcutaneous injections for a prolonged period. As such, compliance issues arise and the generalisability of results comes into question.

Secondly, we chose to investigate only an ambulatory cohort specifically, with extensive exclusion criteria. This reflects the patient cohort of interest; previous studies including hospitalized patients and those with previous disease can be criticized for including high-risk participants [17, 21]. Our methodology attempted to include only patients for which there is genuine equipoise about the need for any anticoagulation.

Thirdly, all IDDVT patients, regardless of location, were invited to participate. Subdivision of IDDVT into isolated calf muscle vein thrombi has been attempted in previous trials with the suggestion of lower event rates [34, 62]. We believe that further separation of IDDVT into different forms will only allow increasing confusion and uncertainty about which patients stand to benefit from treatment. This study was designed to directly assist clinicians on the shop floor with emergency decision-making. As such, the applicable cohort has to be simple to define, reproducible and homogenous.

A final discussion point for our work is the classification of proximal propagation within 7 days as 'treatment failure', evidenced by inclusion within the composite outcome. Many clinicians would not consider this as 'failure' per se, in lieu of expected propagation in a proportion of patients and easy commencement of anticoagulation in those cases. This is an interesting point for debate. We included popliteal propagation within the composite outcome for several reasons; Firstly, serial ultrasound is often difficult to facilitate in the UK and thus clinicians often make decisions based on results of initial imaging. There is also a potential cost

effectiveness argument, to suggest the price of short course anticoagulation may actually be less than serial duplex assessment, with inherent travel and time costs. Secondly, although treatment can be rapidly instigated with propagation, we are still none the wiser about long-term outcome in these patients. We know that post-thrombotic syndrome and recurrence rates are higher with proximal DVT than with IDDVT [24, 63-65]. Will this consequently be the case if calf thrombi are left to extend? It is essential that we understand exact timing and burden of propagation, before we decide whether measures should be taken to limit extension whenever possible.

Meaning of the study

The results of our trial carry several key messages. Firstly, further research is achievable in this population and may offer definitive answers. Secondly, IDDVT is not a benign phenomenon. 1 in 10 of our conservatively treated participants suffered serious consequences and local extension rates were significantly increased to more than 1 in 4. Although some propagation is to be expected, our study highlights the degree and severity of complications. Adherence to latest guidelines in our cohort (suggesting therapeutic anticoagulation with any evidence of local propagation, complications or severe symptomatology [36]) would have resulted in eventual treatment of 17/35 patients, 48.6% (95% CI 33.0 to 64.4%) within the three-month study period. The implication of this data is a limited cost effectiveness to serial ultrasonography, especially with a potential reduction in treatment duration and avoidance of routine monitoring with novel agents.

Lastly, the potentially severe consequences of conservatively treated IDDVT are reiterated. Early pulmonary embolism and delayed popliteal propagation were seen in our small cohort of patients treated without anticoagulation. Given our patients were a low risk group (ambulatory, outpatient, no active cancer or prior proximal VTE), these risks must be considered in other patient populations when making treatment decisions.

The direction of future research

First and foremost, our pilot results need to be validated in an adequately powered large prospective multicentre cohort. Several further interventional trials are already

underway or at funding application stage [66-68]. However, protocols and methodology vary extensively. Protocol adjustments will be made following this project and a large RCT is in preparation, using pilot data to guide a contemporary and accurate sample size calculation.

Even if a statistically significant and definitive benefit can be eventually shown from therapeutic anticoagulation, discussions will follow regarding cost effectiveness. There has already been a recent call from the UK National Institute of Clinical Excellence for research on this subject [47]. Further large randomized diagnostic trials comparing serial proximal compression ultrasound against whole-leg are indeed warranted and may well constitute "the final frontier", as recently described [69]. These trials must include the relief of acute symptoms and prevention of post thrombotic syndrome if they are to truly assess the effectiveness of early intervention, as well as the prevention of propagation, embolisation and recurrence [70].

Conclusions

Our pilot data suggests that a definitive trial to assess the benefits of therapeutic anticoagulation in the management of IDDVT is both acceptable to patients and feasible in a modern healthcare environment. Preliminary clinical results suggest that greater than 1 in 10 patients treated conservatively will go on to suffer a potentially serious VTE related complication. A definitive trial is urgently needed, to provide a concise and generalisable estimate of both benefits and cost effectiveness seen with therapeutic anticoagulation.

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Paper 3: Symptomatic progression and local sonographic progression in Isolated Distal Deep Vein Thrombosis randomly treated with therapeutic anticoagulation or conservative management

Paper Overview

A subgroup comparative analysis of symptomatic progression and local sonographic progression in IDDVT patients treated randomly with either therapeutic anticoagulation or conservative management.

Contribution to the thesis and novelty

This paper addresses the third aim of the thesis, by providing contemporary data on progression in conservatively treated IDDVT patients. This is the largest randomized trial conducted to compare these outcomes in undifferentiated IDDVT and the only trial to prospectively assess symptom progression between anticoagulated patients and those managed expectantly.

Contribution of candidate

Study design, patient recruitment and follow up, data management, monitoring response, MHRA liaison, conduct of the analysis and co-ordination of the independent adjudication committee. The MD student also wrote and managed all drafts of the manuscript, incorporating suggestions from co-authors.

Publication strategy/status

For submission to the following journals in order of preference:

1. Journal of Vascular Surgery   3.210
2. Thrombosis Research   2.440
3. International Angiology   1.652

Title:

Symptomatic and sonographic progression in isolated calf vein thrombosis randomly managed by therapeutic anticoagulation or conservative strategy

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Abstract

Objective

An ideal management strategy for symptomatic calf vein thrombi remains elusive. Although propagation rates and symptom progression are key to clinical decision making, few controlled studies have prospectively compared benefit between recommended therapeutic regimes.

We sought to assess patterns of propagation, symptom progression and risk factors for extension in symptomatic patients with isolated calf thrombi, randomly managed by therapeutic anticoagulation or conservative strategy.

Study Design

An additional analysis conducted using the Anticoagulation of Calf Thrombosis (ACT) project dataset. This was a prospective, open label, assessor blinded randomized controlled trial (ISCTRN 718875).

Setting

Symptomatic patients seen by an ambulatory thrombosis service at a university affiliated hospital in England, during January 2011 to May 2012.

Subjects

A consecutive sample of patients with objectively diagnosed isolated calf vein thrombosis on whole leg vascular ultrasound were approached. 70 patients in total were recruited and followed for 90 days, with clinical review/repeat sonography at day 7 and 21. All patients but 1 completed the full follow-up protocol.

Interventions

Patients were randomized to receive phased therapeutic anticoagulation for a period of three months or conservative management. All patients were referred for grade 2 compression stockings and prescribed anti-inflammatory medication for symptomatic relief.

Main outcome measure(s)

The primary outcome was a comparison between overall propagation rates including local calf and/or proximal extension.

Secondary outcomes included serial pain scoring to assess symptomatic progression, initial thrombus distribution, propagation patterns and assessment for factors predictive of propagation.

Results

Propagation to any site occurred in 11/35 (31.4%) of conservatively treated patients compared with 2/35 (5.7%) of those randomized to anticoagulation (Absolute Risk Reduction 25.7%, 95% Confidence Interval 5.9 to 44.3%, P = 0.001).

Pain scores at day 7 rose from baseline in a significantly higher number of patients treated conservatively, compared to patients treated by therapeutic anticoagulation (6/35 vs. 0/35, p=0.03).

No factors other than lack of anticoagulation were significantly associated with an increased likelihood of propagation, although pain, oestrogen use, obesity and prior history of thrombosis all demonstrated a non-significant trend.

Conclusions

Three months of full dose therapeutic oral anticoagulation significantly reduced the risk of overall propagation in patients with isolated calf thrombi by >25%, albeit with a wide confidence interval. In this non-blinded trial, symptomatic progression was also significantly reduced in patients receiving anticoagulation.

Funding

Background

Isolated calf vein thrombosis is a common and under researched condition [1]. Significant equipoise remains concerning the risks and benefits of therapeutic anticoagulation [2, 3]. There is ongoing international variation in practice [4-6] and significant variability in contemporary national recommendations [7-9].

Limited evidence exists to direct practitioners towards a particular therapeutic regimen. At least three systematic reviews and one meta-analysis have been published on this topic comparing anticoagulation with expectant management within the last 6 years [10-12]. However, the heterogeneity of applicable trials and limited prospective data available has rendered a definitive conclusion impossible. Experts continue to call for further prospective research and debate the merits of current strategy [1-3, 13-15].

There are several key factors in the decision to anticoagulate calf thrombi. Of paramount importance is the prevention of immediate and serious morbidity, such as popliteal propagation and development of symptomatic pulmonary embolism. Many clinicians choose some form of anticoagulation for these specific reasons, even if short-term risk may be negligible with certain types of disease [16]. However, reduced local propagation within the calf veins and consequent symptomatic relief are additional and valid reasons to consider therapy. Although the literature is variable and heterogenous, natural history studies assessing local propagation quote rates as high as 27% with conservative management [17-19]. These figures are consistent over the last decade. There is potential for these locally propagating patients to suffer increased symptoms and later morbidity [20]. As a result, the most contemporary guidance on calf thrombi supports treatment in the face of local extension or worsening symptomatology [9].

Few of the natural history studies described are prospective, randomized or blinded. There is profound heterogeneity within the dataset with the inclusion of inpatients, those with active cancer, postoperative cases and patients with ongoing high clinical risk. The applicability of previous data to a modern ambulatory cohort is limited. This is highlighted in recent topic reviews and the call for further prospective study [1].

We analysed the dataset from the recently conducted Anticoagulation of Calf Thrombosis (ACT) project [21], in order to provide prospective, randomized controlled data on symptomatic, ambulatory patients.

Our aim was to delineate the pattern of sonographic propagation and symptomatic progression within a prospective cohort of isolated calf thrombosis patients, treated randomly with either full dose therapeutic anticoagulation or conservative management.

Methods

All subsequent data presented conform to CONSORT 2010 guidelines with appropriate extensions and recommended structure [22-24].

Design, setting and participants

The ACT project is a prospective, open label, assessor blinded single centre randomized controlled trial. The trial protocol has been previously published and gives a detailed account of the background and methods [21, 25].

Briefly, we undertook a pilot randomised controlled trial set in the Emergency Department (ED) at a university-affiliated teaching hospital with approximately 100,000 ED attendances per annum. Patients presenting with symptoms compatible with deep vein thrombosis (DVT) underwent standardised investigation in accordance with an evidence-based pathway, in line with current international guidance [26, 27]. Patients aged >16 years who were diagnosed with isolated acute calf thrombosis following colour duplex ultrasound scanning by accredited vascular sonographers were eligible for inclusion. We excluded inpatients; pregnant women; patients with active cancer, a contraindication to anticoagulation or prior proximal deep vein thrombosis; and patients already taking anticoagulants at the time of the initial presentation. Transient and permanent risk factors were documented at inclusion, prior to randomisation.

The trial was approved by the Greater Manchester Central Research Ethics Committee (ref: 10/H1008/97) and the Medicines and Healthcare products Regulatory Agency (ref: 2010-021813-22). The trial is registered with an international open access database [25]. All participants provided written informed consent.

Randomisation, intervention and follow up

Using a web-based platform with an externally generated randomization sequence in variable permuted blocks, we randomized patients to receive either therapeutic anticoagulation (intervention group) or conservative treatment (control group) in a 1:1 allocation ratio. Patients in the intervention group were initially given subcutaneous therapeutic dose dalteparin with phased transition to an oral vitamin K antagonist for a total of three months. All patients were followed up in a dedicated anticoagulant clinic for international normalised ratio (INR) monitoring. The target INR was 2.5 with overall quality of anticoagulation assessed by proportional time in therapeutic range (TTR), as a standard measure of compliance [28]. Patients in the control group received no anticoagulation. As this pragmatic trial had an open label design, these patients did not receive placebo control. All patients, regardless of treatment allocation, received analgesia (including anti-inflammatory medication) to use as required and were referred for fitted grade 2 compression stockings. Patients were followed up in clinic on days 7 and 21 for clinical review and repeat colour duplex scanning by accredited vascular sonographers blinded to treatment allocation, and by telephone on day 90. Clinical review at day 7 and 21 was performed prior to divulging ultrasonography results.

Clinical, Imaging and Laboratory Protocols

Initial diagnosis and follow up imaging was performed by colour duplex ultrasonography in a dedicated environment external to the ED. Technicians within the vascular lab are vocationally trained to postgraduate level in Vascular Science and accredited to standards set by the Society for Vascular Technology of Great Britain and Ireland.

Patients were scanned using a 9-4MHz linear and 5-2MHz curvilinear transducer to a standard proforma. This includes documented assessment of all proximal, muscular calf and deep calf veins using B mode, colour Doppler and spectral Doppler including compression, augmentation and valsalva manoeuvre. Clot burden and location at recruitment was assessed and quantified using the Marder scoring system [29].

All D-dimer measurements were conducted using a rapid and quantitative immunoturbidometric assay (STA Liatest (Diagnostica Stago)) and reported in

ng/ml.

Provocation was retrospectively defined using the recent criteria proposed by the National Institute for Health and Clinical Excellence (NICE) within the UK [30]. These criteria were subsequently applied to the prospective dataset.

Outcomes

The primary outcome for this analysis was the presence of *any* thrombus propagation, including infrapoliteal and proximal extension, defined by increase in the Marder score at repeat compression ultrasound during any stage of follow up.

Secondary outcomes included assessment of serial pain score and rise from baseline, descriptive analysis of initial thrombus distribution, adverse event reporting rates and a comparison of clinical characteristics between propagators / non-propagators with univariate analysis to determine factors predictive of disease extension.

Symptomatology was chiefly characterized by a four point ordinal scale, utilized in previous trials comparing oral anticoagulation against conservative management for calf thrombosis [31] and validated previously [32]. We chose this scale for clinical relevance and ease of analysis. The scale ranges from 1 to 4, with 1 representing no pain, 2 pain on palpation only, 3 pain on palpation and walking, 4 pain at rest.

Adverse events and serious adverse events were recorded in accordance with MHRA regulations and reported to the trial sponsor. A previous definition to guide adverse event reporting has been documented in the literature [33].

Sample Size Calculation

As this is a further analysis performed on a trial sample predefined for a feasibility study, no prospective sample size calculation was performed.

Statistical analysis

All categorical variables are reported as percentages and compared using Fisher's exact test. All continuous variables were assessed for normality of distribution using the Kolmogorov-Smirnov test and reported as medians with interquartile range or

means with standard deviation as appropriate. Missing data were coded and excluded within the database. Confidence intervals were calculated to 95% using the Wilson method.

Comparison of variables was made using the Mann-Whitney U test for non-parametric data and Chi squared, or Fishers exact test where appropriate, for parametric data. Analysis of participants was by intention to treat for all clinically relevant outcomes.

All calculations and statistical tests were checked and verified by an independent statistician employed by the University of Manchester, external to the research team. All p values quoted are two tailed, with a value of <0.05 considered statistically significant. All analyses were performed using SPSS version 20 (IBM).

Results

Patient Flow

A consecutive sample of 93 ambulatory patients were approached for inclusion between Jan 2011 and May 2012. Seventy patients in total were recruited to the ACT project. Recruitment and flow is shown in Figure 1. All patients were followed up by ultrasound and clinical review for a period of three months.

Only a single patient was uncontactable by telephone at three months. Data on this participant was ascertained from computerized medical records and a discussion with the primary care practitioner.

Baseline data

Demographics, baseline risk profile and clinical presentation data for all participants are summarized in Table 1. Missed cases have been included in this table to provide

CONSORT 2010 FLOW DIAGRAM

Assessed for eligibility (n= 93)

Excluded (n= 23)
- ♦ Not meeting inclusion criteria (n= 1 [associated pulmonary embolism)
- ♦ Declined to participate (n= 5)
- ♦ Previous proximal VTE (n= 4)
- ♦ Missed cases (n= 4)
- ♦ Already on anticoagulation (n= 3)
- ♦ Requiring hospitalisation (n= 3)
- ♦ Other (n= 3)

Enrollment

Randomized (n= 70)

Allocation

Allocated to therapeutic anticoagulation (n=35)
- ♦ Received allocated intervention (n=35)
- ♦ Did not receive allocated intervention (n= 0)

Allocated to conservative management (n= 35)
- ♦ Received allocated intervention (n=35)
- ♦ Did not receive allocated intervention (n=0)

D7 Follow-Up

Lost to follow-up (n= 0)
Receiving allocated intervention (n=30)
Discontinued intervention (n=5)
- ♦ Patient omission (n=3)
- ♦ Bleeding complications (n=1)
- ♦ Hospitalisation and alteration (n=1)

Lost to follow-up (n= 0)
Receiving allocated intervention (n=33)
Discontinued intervention (n=2)
- ♦ Composite endpoint achieved (n=1)
- ♦ Hospitalisation (n=1)

D21 Follow-Up

Lost to follow-up (give reasons) (n=0)
Receiving allocated intervention (n=33)
Discontinued intervention (n=2)
- ♦ Patient omission (n=2)

Lost to follow-up (n= 0)
Receiving allocated intervention (n=26)
Discontinued intervention (n=9)
- ♦ Composite endpoint achieved (n=3)
- ♦ Allocation changed by other clinician (n=3)
- ♦ Hospitalisation (n=3)

D90 Analysis

Lost to follow-up (n= 0)
Analysed (n=35)

Receiving allocated intervention (n=31)
Discontinued intervention (n=2)
- ♦ Patient omission (n=1)
- ♦ Hospitalisation and alteration (n=1)

Lost to follow-up (n= 0)
Analysed (n=35)

Receiving allocated intervention (n=20)
Discontinued intervention (n=13)
- ♦ Composite endpoint achieved (n=4)
- ♦ Allocation changed by other clinician (n=6)
- ♦ Hospitalisation (n=3)

Table 1: Demographic, provocation and clinical presentation data for all randomised patients and excluded cases. All data is presented as mean (SD), median (IQR) or numerator with proportion (n/ N).

	All cases N=70	Therapeutic Anticoagulation N=35	Conservative Management N=35		Missed cases N=23
Demographics					
Age	60.3 (17.7)	60.9 (17.8)	59.8 (17.9)		53.8 (18.3)
Female Sex	46 (65.7)	26 (74.3)	20 (57.1)		12 (57.1)
Left sided DVT	33 (47.1)	14 (40)	19 (54.3)		10 (47.6)
Provocation					
Provoked	43 (61.4)	24/35 (68.6)	19/35 (54.3)		13/23 (56.5)
Unprovoked	27 (38.6)	11/35 (31.4)	16/35 (45.7)		10/23 (43.5)
Ongoing risk factors					
Immobilisation	18 (25.7)	9 (25.7)	9 (26)		7 (33.3)
Plaster application	9 (12.9)	6 (17.1)	3 (8.6)		1 (4.8)
Acute infection	3 (4.3)	2 (5.7)	1 (2.9)		4 (19.0)
Family history of VTE	12 (17.1)	5 (14.3)	7 (20)		5 (23.8)
Prior history of VTE	11 (15.7)	5 (14.3)	6 (17.1)		9 (42.9)
Thrombophilia	2 (2.9)	2 (5.7)	0 (0)		1 (4.8)
Obesity	19 (27.1)	11 (31.4)	8 (22.9)		4 (19.0)
Smoker	24 (34.3)	11 (31.4)	13 (37.1)		10 (47.6)
Oestrogen intake	5 (7.1)	2 (5.7)	3 (8.6)		4 (19.0)
Clinical Presentation					
Early warning score	0 (0 to 1)	0 (0 to 1)	0 (0 to 1)		0 (0 to 1)
High Wells score	30 (42.9)	17 (48.6)	13 (37.1)		10 (47.6)
Marder	2 (2 to 3)	2 (2 to 3)	2 (2 to 3)		3 (2 to 5)
D-dimer	677 (341 to 1268)	690 (405 to 1290)	650 (325 to 1260)		612.5 (471 to 813)
CRP	6 (3 to 16)	6 (3 to 13)	9 (3 to 19)		13 (5 to 37)
Symptom duration	7 (4 to 14)	7 (4 to 14)	7 (3 to 10)		6 (3.25 to 13)

evidence of even recruitment strategy. The median Marder score at baseline was equivocal between groups (2 (IQR 2-3), implying evenly distributed initial thrombus burden. Clinical assessment is presented as the proportion of patients with an overall high clinical pretest probability risk score using the modified Wells criteria [34] and comparison of the independent variables.

Primary outcome

Ninety-day evaluation for resolution versus propagation was assessed in both groups. Any increase in Marder score from baseline during follow up, suggesting a degree of propagation, was seen in 11/35 (31.4%, 95% CI 18.6 to 48.0) conservatively treated patients and 2/35 (5.7% 95% CI 1.6 to 18.6) of those receiving therapeutic anticoagulation (p=0.01). Absolute risk reduction (ARR) was therefore 25.7%, with a number needed to treat (NNT) of 4. Of the 11 patients propagating in the conservative group, 3 extended to the level of the popliteal vein. An additional patient in the conservative group was diagnosed with pulmonary embolism at day 3. There was no evidence of propagation on day 7 scan in this individual. No other patients were diagnosed with pulmonary emboli during follow up.

No patients extended to the popliteal vein in the anticoagulated cohort. A boxplot of sequential Marder scores displaying variation during follow up is shown in Figure 2 for conservatively treated and anticoagulated patients. Individual patterns of propagation in patients with an increasing Marder score is shown in Table 2.

Conversely, a decrease from baseline in Marder score (suggesting a degree of resolution) was seen in 8/35 (22.9%, 95% CI 12.1 to 39.0) conservatively treated and 13/35 (37.1%, 95% CI 23.2 to 53.7) anticoagulated patients (p = 0.30). No change in Marder score during the initial 21-day review was seen in 16/35 (45.7%, 95% CI 30.5 to 61.8) and 20/35 (57.1%, 95% CI 40.9 to 72.0) respectively.

Secondary outcomes

Pain scores at day 7 rose from baseline in a significantly higher number of patients treated conservatively than in patients treated by therapeutic anticoagulation (6/35 vs. 0/35, p=0.03). By day 21, the difference in rise from baseline had become non significant, likely as a result of allocation crossover in over a quarter of conservatively treated patients. As expected, propagation was significantly associated with an increased rise from baseline in pain score at day 7 follow up (p=0.009), and

Figure 2: A boxplot comparison of sequential Marder scores in both the anticoaglated and conservatively managed cohorts.
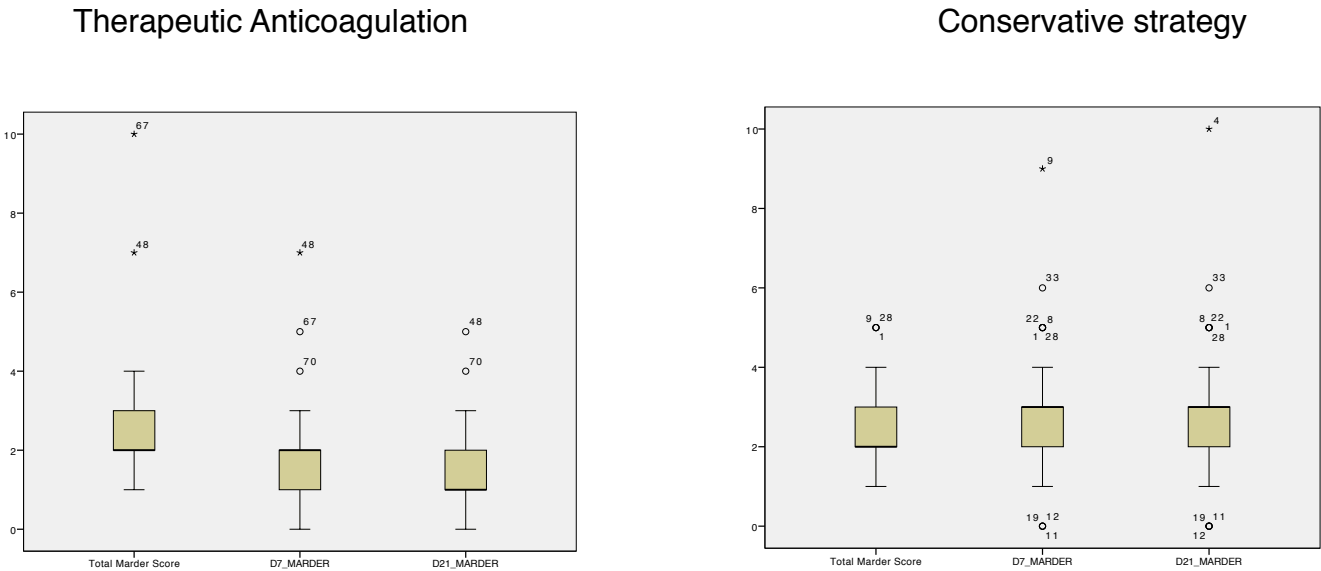
TABLE 2: Patterns of propagation in those patients with an increasing Marder score during 90 day follow up

Age	Original Thrombus	Intervention arm	Day 7 whole leg CUS result	Day 21 whole leg CUS result
64M	DCVT limited to posterior tibial vein	Conservative	Similar	Additional thrombus in peroneal veins
43F	DCVT limited to posterior tibial vein	Conservative	Additional thrombus in peroneal veins	Extension to popliteal vein
60F	DCVT limited to peroneal vein	Conservative	Similar	Local extension within peroneal vein
57M	DCVT in both posterior tibial and peroneal veins	Conservative	Local extension within peroneal vein	Similar to Day 7
33M	ICMVT in both soleus and gastrocnemial veins	Conservative	Additional thrombus in posterior tibial vein and extension to popliteal vein	Resoloution of all thrombi other than soleal (changed to therapeutic anticoagulation after D7 result)
62F	DCVT limited to peroneal vein	Conservative	DNA	Local extension within peroneal vein
86M	DCVT limited to peroneal vein	Conservative	Similar	Additional thrombus in posterior tibial vein
81F	DCVT limited to peroneal vein	Conservative	Additional thrombus in posterior tibial vein	Local extension within posterior tibial vein
59F	DCVT in both posterior tibial and peroneal veins	Conservative	DNA	Local extension within posterior tibial vein
47F	DCVT limited to peroneal vein	Conservative	Additional thrombus in posterior tibial vein	Similar to Day 7
38F	DCVT in both posterior tibial and peroneal veins	Conservative	Extension to popliteal vein	Similar to Day 7
81F	DCVT in both posterior tibial and peroneal veins	Anticoagulation	Local extension within both peroneal and posterior tibial veins	DNA
48M	DCVT limited to peroneal vein	Anticoagulation	Local extension within peroneal vein	DNA

an increase in symptom prevalence (ordinal pain score 2 or above) at day 21 review (p=0.018) compared to non-propagators.

Anatomical distribution of disease is summarized in Table 3. There were no significant differences in the distribution of thrombi between intervention groups. However, propagating patients were significantly more likely to have thrombus originating from the peroneal/posterior tibial system as deep calf vein disease, rather than isolated calf muscle vein thrombosis (12/13 (92.3%) vs. 1/13 (7.7%) respectively (p < .0001).

Adverse events were seen in the 17/35 (48.6%) and 9/35 (25.7%) of conservatively managed and anticoagulated patients respectively. The majority of these events in the conservative cohort were complaints of increasing/worsening symptoms or re-attendance to the ED. Comparison of proportions did not reach statistical significance (P=0.08). Serious adverse events were recorded in 8/35 anticoagulated patients and 7/35 of those conservatively managed. There were no episodes of fatal or major haemorrhage in either group.

Patients with propagating disease had similar baseline demographics to non-propagators including age, sex preponderance and ethnicity. Thrombus burden at baseline was also equivocal (Marder score 2 (2-4)). Clinical and risk factor characteristics between propagators and non-propagators are displayed in Table 4 along with univariate analysis. Use of therapeutic anticoagulation was the only clear factor to significantly affect the likelihood of propagation (OR 0.14 95% CI 0.03-.70, p=0.016). A non-significant trend towards increasing likelihood of propagation was seen with unprovoked calf thrombi, higher pain score at baseline, past history of venous thromboembolism, oestrogen use, obesity or involvement of the deep axial veins of the calf. Of interest, increasing VA pain score at triage was associated with borderline statistical significance for increasing the odds of propagation. This concept has face validity and is supported by recent recommendations to treat isolated calf thrombi with severe symptomatology [9].

Table 3: Distribution of initial thrombus, segregation between ICMVT and DCVT and spread between randomised groups.

All figures are given as n/N (%age)

	Therapeutic Anticoagulation N=35	Conservative Management N=35		All cases N=70
Isolated Calf Muscle Vein Thrombi	6/35 (17.1)	5/35 (14.3)		11/70 (15.7)
Gastrocnemial Vein	3	2		5
Soleal Vein	1	3		4
Gastrocnemial and Soleal Vein	2	0		2
Deep Calf Vein Thrombi	25/35 (71.4)	28/35 (80)		53 (75.7)
Peroneal Vein	12	16		28
Posterior Tibial Vein	4	2		6
Anterior Tibial Vein	0	0		0
Peroneal and Posterior Tibial Vein	9	10		19
Combined Calf Vein Thrombi	4/35 (11.4)	2/35 (5.7)		6/70 (8.6)
Peroneal and Soleal Veins	1	0		1
Posterior Tibial, peroneal and gastrocnemial Veins	0	1		1
Peroneal and Gastrocnemial Veins	2	0		2
Posterior Tibial and Gastrocnemial Veins	0	1		1
Posterior Tibial, Gastrocnemial and Soleal Veins	1	0		1

TABLE 4: Comparison of individual clinical risk score components between propagating and non-propagating patients and subsequent univariate analysis. Exposure was considered a risk factor if occurring in the last 3 months. NS = non significant. Values are given as n/N (%age), mean (SD) or median (IQR) where applicable. *p=0.051 **p=0.082 ***axial calf vein involvement refers to thrombus within the posterior/anterior tibial or peroneal veins.

	Propagating patients (N=13)	Non propagating patients (N=57)	Odds ratio for propagation vs. non-propagation	Significance Testing
Anticoagulation	2 (15.4%)	31 (54.4%)	0.14 (95% CI 0.03 to 0.70)	p=0.016
Wells score	2 (1 to 3)	2 (2 to 3)	0.91 (95% CI 0.60 to 1.37)	NS
Unprovoked	6 (46.2)	21 (36.8)	1.50 (95% CI 0.44 to 5.09)	NS
VA Pain scale	5 (4 to 8)	4 (3 to 6)	1.38 (95% CI 0.99 to 1.90)	NS*
Family history of VTE	1 (7.7)	9 (15.8)	0.43 (95% CI 0.50 to 3.70)	NS
Past history of VTE	3 (23.1)	8 (14.0)	1.76 (95% CI 0.40 to 7.84)	NS
Recent Surgery	1 (7.7)	16 (28.1)	0.20 (95% CI 0.24 to 1.70)	NS
Immobilisation	3 (23.1)	14 (24.6)	0.88 (95% CI 0.21 to 3.66)	NS
Plaster of paris	1 (7.7)	7 (12.3)	0.57 (95% CI 0.06 to 5.10)	NS
Hospital Admission	1 (7.7)	18 (31.6)	0.17 (95% CI 0.02 to 1.42)	NS
Axial calf vein involvement***	12 (93.3)	47 (82.5)	2.67 (95% CI 0.31 to 22.9)	NS
Oestrogen use	1 (7.7)	4 (7.0)	2.21 (95% CI 0.19 to 26.40)	NS
Smoking	4 (30.8)	20 (35.1)	0.78 (95% CI 0.21 to 2.85)	NS
Obesity	6 (46.2)	12 (21.1)	3.07 (95% CI 0.87 to 10.88)	NS**
Varicosities	3 (23.1)	19 (33.3)	0.54 (95% CI 0.13 to 2.19)	NS

Discussion

To our knowledge, this prospective randomized trial is the largest conducted comparing phased oral anticoagulation to conservative therapy in undifferentiated ambulatory calf thrombosis. In our cohort, conservative treatment of acute calf thrombi was associated with a significant increase in the rate of overall propagation and short-term symptomatic deterioration.

Additionally, our data suggest a non-significant trend towards increased likelihood of propagation in patients with axial (rather than isolated calf muscle) thrombi, unprovoked disease, obesity, oestrogen use or past history of thromboembolism. These findings require external validation and further assessment, but suggest the potential approach of risk stratification and selective anticoagulation to reduce therapeutic risk may be possible.

This trial is one of few prospective randomized studies following patients with calf thrombi and delineating patterns of propagation by compression ultrasound. We are confident that our trial design is suitable to the hypothesis and provides multiple methodological advantages over natural history studies. We feel that randomisation at the point of inclusion has maintained allocation concealment within our study and as such, selection bias is minimized. This should lead to our results being internally valid.

Likewise, we attempted to reduce measurement bias by the use of assessor blinded follow up performed by vascular technicians external to the research team. Technicians are non-physicians, had no idea of symptom progression and were blinded to treatment allocation. As such, subconscious bias should be minimized on repeat ultrasound and results obtained are essentially objective. This is in stark contrast to many previous studies, where follow up ultrasound is performed by vascular physicians with full knowledge of clinical history, blood markers, therapeutic intervention and symptomatic progression [35-38]. These factors no doubt influence the result of subjective sonographic follow up.

Our trial is the largest prospective randomised dataset of undifferentiated calf

thrombus patients. Although Schwarz *et al* have studied a larger sample set previously [16], they focused only on isolated calf muscle vein thrombosis (ICMVT). Our data allows additional comparison of propagation patterns between ICMVT and axial calf vein thrombosis.

We followed up patients clinically as well as sonographically. This allowed us to compare not just radiological extension but also to document worsening symptomatology. These results are equally important: clinicians often base their decision-making on a composite of factors rather than pure sonographic extension or resolution. A locally propagating calf thrombus may only receive therapeutic anticoagulation with an accompanying increase in symptoms, for example. Many natural history studies focus only on sonographic progression or duplex assessment of venous insufficiency [36]. We feel our study is more pragmatic for inclusion of clinical data.

Lastly, the conduct of this study within the context of a clinical drug trial (the ACT project) offered several benefits. Rigorous assessment of adverse events as part of pharmacovigiliance monitoring ensured any uncategorized element of symptomatic deterioration could be quantified. Also, follow up was robust within a research framework rather than a routine vascular clinic and oversight was provided in the form of quality assurance and a Trust Steering committee throughout the project. As such we are confident that we have captured all key events of interest and again that our data is internally valid.

Limitations

We chose to use the Marder score as a sequential marker of thrombus propagation for ease of use, objectivity and reproducibility. There are real issues with any quantifiable scoring system that relies heavily on subjective estimate by the vascular specialist. Interobserver reliability studies of these scoring systems are few and far between [39]. This raises the issue of whether we can be confident in the internal validity of the scoring system. Our defence here would be twofold: assessor blinding of all ultrasonographers should ensure that no element of unconscious bias influenced the scan report. Secondly, our vascular reports provide an objective description of involved venous segments and the extent of thrombus as standard. We have merely

quantified this for ease of analysis using an available and published tool. The majority of our propagating patients developed thrombi in additional ipsilateral calf veins, rather than direct extension. Thus, concerns regarding the potential for error with estimated direct extension are minimal.

Another potential criticism of our study could be the lack of predetermined power calculation or sample size. This is a natural result of our post-hoc analysis within the cohort derived from the ACT feasibility population. We feel this is a negligible drawback given our primary outcome shows a statistically significant difference.

The open label design of our study has several limitations. When assessing subjective complications and ongoing symptomatology, it is easy to see how patients not receiving therapeutic anticoagulation could perceive their symptoms to be worse, given they have been potentially 'denied' a treatment. This was unavoidable within the context of this study. Reasons for the open label nature of trial design have been discussed at length within the previous published ACT protocol. We would suggest however, that with the prearranged assessor blinding this methodological factor should have at least limited influence over the sonographic outcomes.

Our use of an ordinal pain scale could be called into question, given that previous research within an ED setting usually favours the verbally administered numerical rating scale [40]. We would argue that an ordinal scale specifically focusing on the symptomatology within the limb and the impact on mobilization offers a clearer view of disease effect.

Finally, it must be noted that following randomization further treatment was at the discretion of any additional treating physician. Thus, several of the propagating patients were changed over to therapeutic anticoagulation as a result of representation to other sites/physicians with worsening symptoms. Indeed, propagation to the level of the popliteal vein mandated therapeutic anticoagulation within the ACT study protocol. This is quantified in the Figure 1 regarding maintenance of allocation. Although this could interfere with some study results (lack of significant difference in pain scores at day 21 follow up), it should have no effect on the positive outcomes. Indeed, positive outcomes in the context of an intention to treat analysis such as this

only strengthen the associations seen.

Comparison to previous research

Our overall propagation rate in conservatively treated patients, either to adjacent calf veins or the level of the popliteal vein, compares favourably to previous research [10]. The reduction seen with therapeutic anticoagulation is also reproduced. Several studies have reported fairly consistent composite extension rates of between 27-32% [41-43]. Lower rates have been reported in natural history studies, but this is most likely a result of selection bias and conservative treatment in only those subjectively deemed to be low risk [17].

Our results are compatible with recent literature, noting a high incidence of disease involving the peroneal veins and negligible volume of disease within the anterior peroneal compartment [17, 19, 36]. Of interest, 15.7% of our population presented with isolated calf muscle vein thrombosis confined to the soleus or gastrocnemial veins. This was spread evenly between groups and showed no significant difference on statistical testing. In addition, there was negligible propagation within ICMVT patients treated conservatively. This is in keeping with recent randomized research [16].

Very few studies have attempted to address the issue of predictive factors associated with propagation. In a natural history study, Lohr *et al* demonstrated an increasing prevalence of oestrogen use, malignancy, varicosities and immobilization within propagating patients [42]. Patients were managed at physician discretion (10% treated with heparin) and no attempt at regression analysis was made. Schwarz *et al* have touched on the subject in two prospective studies (the latter randomized), analysing patients with ICMVT treated by short-term anticoagulation or conservative management [16, 18]. In their first interventional cohort study, they note active malignancy to be associated with symptomatic progression but fail to quantify this. In their later randomized trial, they display several ongoing risk factors in the handful of patients who suffered propagation, including oral contraception, malignancy, immobilization and previous thromboembolic disease. Our study places the prevalence of these risk factors in context of propagation and is a step towards the strategy of 'risk adopted therapy' suggested recently by leading experts [3].

Meaning of the study

Our findings suggest that short-term anticoagulation of acute calf thrombi in ambulatory patients reduces the overall risk of propagation and symptomatic progression. Although the former point may be intuitive, our data is the only modern study to provide estimates of absolute risk reduction with robust methodology. Recent international guidance has suggested that patients with calf thrombi are more likely to benefit from anticoagulation in the presence of 'severe symptoms or risk factors for extension', or 'if the thrombus extends but remains confined to the distal veins' [26, 44]. Our data suggest that the former will be present in approximately 25% patients and the latter will occur in over 30% without treatment. Thus, the potential cost effectiveness of serial proximal compression ultrasound must be carefully considered.

The direction of future research

These findings need to be externally validated in additional populations. However, such trials must be randomized, controlled and methodologically robust. Outcomes must also be clearly established and quantified. As well as sonographic progression, clinical symptoms and development of postthrombotic syndrome must be prospectively assessed. Within such a trial context, further evaluation of risk factors associated with propagation could lead to derivation of a decision rule aiming to risk stratify patients at diagnosis and maximize therapeutic effectiveness.

There is also a further role for diagnostic randomized trials assessing the cost effectiveness, clinical safety and patient satisfaction with serial proximal compression ultrasound and whole leg imaging. Such trials have been recently called for and may help to clarify international guidance [9, 30]. Outcomes would need to include those mentioned previously, as well as the most clinically relevant sequelae of missed thromboemoblic disease (symptomatic pulmonary embolism and death).

Conclusions

Therapeutic phased oral anticoagulation in isolated calf thrombosis significantly reduces overall propagation rates, with a number needed to treat of 4. There was also an additional short-term reduction in symptomatology with anticoagulation. Although

we could find no risk factors significantly predictive of propagation on univariate analysis, several factors with face validity suggested a trend towards increased likelihood of propagation. This aspect of the study requires further prospective research within a large dataset.

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Paper 4: The safety and utility of single whole-leg compression ultrasound for exclusion of deep vein thrombosis in ambulatory emergency department patients

Paper Overview

A prospective observational cohort study of withheld anticoagulation in patients with suspected DVT following negative whole leg CUS

Contribution to the thesis and novelty

This paper addresses the fourth aim of the thesis, by providing contemporary data on VTE event rates following withheld anticoagulation in a modern cohort of ED patients with suspected DVT and negative imaging. This study provides the largest group of high pre-test clinical probability patients for assessment in this setting and is also one of the first to address potential predictors of technical failure in whole leg CUS.

Contribution of candidate

Study design, patient recruitment, data management, conduct of the analysis and co-ordination of the independent adjudication committee. The MD student also wrote and managed all drafts of the manuscript, incorporating suggestions from co-authors.

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Single whole-leg compression ultrasound for exclusion of deep vein thrombosis in symptomatic ambulatory patients: a prospective observational cohort study

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Abstract

Objectives

International guidance has recently recommended serial proximal compression ultrasound (CUS) as first line imaging for suspected deep vein thrombosis (DVT). Single whole-leg CUS is a routine alternative diagnostic strategy that can reduce repeat attendance and identify alternative pathology.

We sought to assess the performance characteristics of an established emergency department ambulatory protocol incorporating whole-leg CUS by non-physicians for exclusion of DVT.

Methods

A prospective observational cohort study. Consecutive, ambulatory, adult patients with suspected DVT and negative or inconclusive whole-leg CUS had anticoagulation initially withheld and were followed up after three months.

The primary outcome was a predefined clinically relevant adverse event rate: a subsequent diagnosis of symptomatic venous thromboembolism (VTE) or VTE related death during three month follow up. Secondary outcomes included alternative diagnoses, technical failure rate and characteristics associated with failure.

Results

212 patients agreed to participate and were followed for three months. One patient was subsequently diagnosed with a calf DVT. The adverse event rate was thus 1/212, 0.47% (95% confidence interval 0.08 to 2.62%).

150/212 patients were provided with a clear documented alternative diagnosis. CUS directly contributed to or confirmed the alternate diagnosis in 55/150 patients. Technical imaging failure occurred in 11.3% of cases (95% CI 7.7 to 16.3). Several potential predictors of an inconclusive result were identified on multivariate analysis.

Conclusion

Patients who have anticoagulation withheld following a negative or inconclusive whole leg CUS for suspected DVT have a low rate of adverse events at 3 months. Technical failure remains an issue: several factors were significantly associated with inconclusive results in our cohort and may warrant an alternative diagnostic approach.

Background

Deep vein thrombosis (DVT) is an increasingly topical issue in modern healthcare. Clinical signs and symptoms are of limited use in diagnosis [1]. Physicians suspecting disease rely heavily on objective testing.

There is ongoing debate regarding the optimal diagnostic approach. Use of contrast venography is in worldwide decline due to limitations in reliability, technical adequacy and associated potential hazards, including thrombogenesis and extravasation [2-5]. Duplex compression ultrasound (CUS) has become the initial investigative modality of choice, primarily based on safety, availability and cost [6, 7]. CUS is often limited to serial imaging of the proximal veins, with tests a week apart. This technique was recently endorsed as first line by the National Institute for Health and Clinical Excellence (NICE) and the American College of Chest Physicians (ACCP) [8, 9]. However, serial proximal CUS necessitates repeat attendance after index visit, which can be both time consuming and costly for patient and clinician. The rationale in support of the second (7 day) scan is also based on low level evidence with a demonstrably low diagnostic yield: between 0 and 2% on recent assessment of 5 studies and >2,500 patients with repeat imaging performed [HTA] [10]. Other limitations include an expected attrition rate approximating 10%, lack of assessment for alternative pathology and continuing uncertainty for the patient. It is also impossible to diagnose and individually stratify management for isolated distal DVT (IDDVT) using this technique [11].

Whole-leg CUS evaluates both proximal and distal veins within the leg and with experience, appears to be reliable [12], increasingly sensitive [13] and safe [14]. The technique addresses the majority of concerns with serial proximal imaging and saves time for both patient and clinician, as well as providing additional clinical information on which to base management decisions.

The external validity of previous research assessing the safety of whole-leg CUS is limited. Many studies focus on sonography performed by vascular physicians in specialist referral centres within the context of clinical review [15-17]. Others incorporate inpatient assessments [16, 18, 19], or include few patients with a high pre-

test probability for disease [17, 19]. Only one of seven studies in a recent meta-analysis included patients recruited through the Emergency Department (ED) [14]. Nearly all the other studies based the decision to withhold anticoagulation on the decision of the attending vascular specialist, with access to personally interpreted clinical and sonographic data. There is no guarantee that this safety data is generalizable to non specialist ED services utilising external sonography.

There is also limited work assessing technical failure rates (and associated patient characteristics) with whole leg CUS performed by non-clinicians. Data on utility regarding re-attendance, repeat imaging and therapeutic intervention are consequently lacking. Several authors have called for further work to clarify the safety of withheld anticoagulation in high-risk patients and evaluate the efficacy of modern ambulatory protocols incorporating whole leg CUS [13, 14]. With publication of the recent ACCP recommendations, it is both urgent and important that this data is made readily available while it remains routine practice, prior to international uptake of serial proximal CUS.

Our institution has been operating an ambulatory pathway for suspected DVT using whole-leg CUS for the last decade. In this study, we aimed to provide modern data on adverse event rates using this protocol. We primarily sought to assess short term clinical outcomes in patients with a single negative scan who had anticoagulation withheld. We also sought to make a pragmatic assessment of utility through quantifying alternate diagnoses, technical failure rate, patient characteristics associated with failure and subsequent resource utilisation.

Methods

Study design, setting and population
We undertook a prospective observational cohort study, conducted within the screening pool of the Anticoagulation of Calf Thrombosis (ACT) project. Protocol and registration data for the ACT study have been previously published and are publicly available [20, 21]. We approached a consecutive sample of ambulatory patients with suspected DVT who tested either negative or inconclusive on whole leg colour duplex ultrasound and had anticoagulation withheld after index visit.

The study was conducted in the ED of a large tertiary academic teaching hospital, located within the city centre of Manchester. The urban population is approximately 0.5 million, with a large additional migrating student population and a conurbation of 2.7 million [22]. The segregated adult ED has an annual attendance of approximately 100,000. A dedicated research team conducted the study, enrolling patients over a 10-month period between July 2011 and April 2012.

Study protocol

All ambulatory patients attending the ED with suspected DVT, who were subsequently referred for CUS imaging were screened for inclusion. All clinical management decisions, including referral for CUS, were made by non-research emergency physicians using a local ambulatory protocol. This protocol included clinical pretest probability scoring, associated d-dimer testing in low risk patients, daily administration of therapeutic dose dalteparin prior to definitive imaging and expert thrombosis advice as required. All patients deemed at high clinical risk or with a positive d-dimer measurement were referred for whole leg CUS. Patients subsequently testing negative or inconclusive on whole leg CUS and having anticoagulation withheld were highlighted by vascular laboratory and clinical staff. They were consequently approached by the research team for participation. Patients testing positive for acute or chronic disease, those requiring inpatient admission, with confirmed PE, superficial thrombophlebitis, unable to provide informed consent, unable to perform follow up (non UK resident), previously enrolled or on any form of ongoing formal prophylactic or therapeutic anticoagulation (warfarin, heparin, low molecular weight heparin, dabigatran, rivaroxaban) were excluded. All participants provided full and informed written consent. Demographic, risk factor and clinical data were collected at index assessment.

Follow up was performed at three months in line with previous research [14, 23]. Patient records, regional imaging databases and referral data were comprehensively reviewed. All patients were additionally contacted by telephone to complete a short standardised questionnaire. For those patients not responding to telephone contact after multiple attempts, the research team contacted the primary care provider or next of kin to complete the questionnaire and obtain any relevant further information.

Clinical, Imaging and Laboratory Protocols

Imaging was performed by sonographers based outside the ED, using whole-leg colour duplex CUS. All sonographers within the vascular laboratory are vocationally trained in Vascular Sciences to postgraduate level and accredited to standards set by the Society for Vascular Technology of Great Britain and Ireland. Patients were scanned using a 9-4MHz linear and 5-2MHz curvilinear transducer to a standard proforma. This includes documented assessment of all proximal, muscular calf and deep calf veins using B mode, colour Doppler and spectral Doppler including compression, augmentation and Valsalva manoeuvre. Results are descriptive and also categorized into 5 typical findings: Acute proximal DVT, Acute distal/calf DVT, Chronic DVT, inconclusive scan (negative above knee, unable to exclude calf thrombus) and negative scan. Scan appointments last 20 minutes, but performance of the actual scan takes approximately 10 to 15 minutes per patient. No formal policy is in place regarding the management of patients with an inconclusive scan result. Sonographers had access to the clinical request data, d-dimer result and pre-test probability score as standard.

All d-dimer measurements were conducted using a rapid and quantitative immunoturbidometric assay (STA Liatest (Diagnostica Stago)).

Key outcome measures

The primary safety outcome was a composite of subsequent venous thromboembolic events and/or death related to VTE, during the three-month follow up period. Events were objectively defined by previously reported criteria using repeat duplex examination [23, 24], PIOPED reported ventilation/perfusion imaging [25] or CT Pulmonary Angiogram [26]. Clinical outcomes were considered by a central adjudication committee with full access to medical records, comprising a consultant haematologist, intensivist and emergency physician. Disagreements were resolved by consensus discussion. Deaths during the follow up period were classed within an ordinal scale of 1: likely related to VTE, 2: potentially related to VTE and 3: Unrelated to VTE. Outcomes 1 or 2 were both classed as positive primary endpoints in line with previous studies [17].

Secondary outcomes included alternate diagnoses attributable to CUS, technical failure rate (calculated as the total number of initial scans reported as inconclusive / total number of scans performed), all cause mortality and several estimates of ongoing

resource use: re-attendance, repeat vascular imaging and therapeutic intervention with anticoagulation, stratified by CUS result. Both primary and secondary outcomes were also evaluated within subgroups of *a priori* moderate or high pre-test clinical probability, using the original Wells score [27]. Lastly, we attempted to compare categorical variables using multivariate analysis to assess characteristics predicting technical failure of whole-leg CUS, as determined by inconclusive scan result.

Sample Size Calculation

Based on previous research, we estimated the prevalence of the primary safety outcome to be approximately 0.5% within our cohort [14, 17]. In line with previous authors, we considered a failure rate (subsequent VTE) of more than 3% (upper boundary of 95% CI) to be unsafe [28]. Thus, in a sample of 200 patients receiving no anticoagulation following a negative/inconclusive whole leg ultrasound scan, we would expect to see 1 VTE event. This would provide an upper limit 95% confidence interval of 2.8% for any VTE occurring within a three-month period.

Data analysis

Continuous variables were assessed for normality of distribution using the Kolmogorov-Smirnov test. Categorical data were summarised by percentage and compared using Fishers exact test. Non-parametric data were summarised by the median (interquartile range) and compared using the Mann-Whitney U test. Missing data were coded and excluded within the database. Multivariate analysis was performed using binary logistic regression. Confidence intervals were calculated to 95% using the Wilson method. All p values reported are two tailed, with <0.05 considered statistically significant. All analyses were performed using SPSS version 20 (IBM) and were checked and verified by an independent statistician.

All data presented conform to the STROBE recommendations on reporting of observational cohort data [29] .

Ethical review

The study was approved by the North West Greater Manchester Central Research Ethics Committee (ref: 10/H1008/97) and the institutional Research and Innovation department.

Results

Patient Flow and Demographics

During the recruitment period, 610 ambulatory patients attended the ED with suspected DVT and were referred for diagnostic imaging. The median delay to duplex ultrasound was 1 day (IQR 1-2). At least one dose of therapeutic dalteparin prior to scan was received by 91.2% (95% CI 86.4 to 94.3) patients, with a median of 1 dose administered (IQR 1-2).

Of 432 patients with negative or inconclusive ultrasound imaging, 214 eligible subjects agreed to participate in the study. Two patients were subsequently withdrawn, leaving 212 suitable for analysis. Reasons for exclusion prior to and post recruitment are listed in the patient flow chart (Figure 1).

Twenty-four (11.3%, 95% CI 7.7 to 16.3) of the 212 participants had an inconclusive index scan. Follow up was completed for all patients, principally by direct telephone contact with the subject (N=188, 88.7%). Those uncontactable after multiple attempts were followed up through their primary care practitioner/next of kin (N=16). If this proved unsuccessful a regional database and medical record search was conducted for evidence of further attendance/investigation (N=8). Participant demographics and baseline characteristics are shown in Table 1, with stratification by CUS result. The results are in keeping with previous synthesised research [14].

Primary outcome

During the follow up period, only one patient received a subsequent objective diagnosis of VTE. This patient was a 95 year-old female with an initial negative ultrasound, who had an unplanned re-attendance with ongoing symptoms at 2 weeks post recruitment. She underwent repeat duplex exam, which recorded the presence of

Figure 1: A recruitment flow chart delineating the number of screened, excluded and recruited participants. Also shown are cumulative positive results over the study period and methods of follow up, with proportions.

610 patients undergoing complete limb ultrasonogrpahy for exclusion of DVT

Acute Distal DVT
N=45

Acute proximal DVT
N=66

Negative Scan
N=362

Inconclusive Scan
N=70

Chronic Thrombus
N=67

432 potentially eligible for inclusion

130 patients excluded after review

Declined — 25
Long term anticoagulation — 18
Unable to provide informed consent — 15
Superficial thrombophlebitis — 10
Requiring hospital admission — 20
Receiving thromboprophylaxis — 5
Upper limb scanning — 8
Non UK resident — 6
Previously enrolled to study — 23

88 patients missed

214 recuited

2 patients withdrawn post consent:

Warfarinised at time of recruitment — 1
Chronic calf DVT on USS — 1

212 analysed

Follow up by medical record review only
N = 8 (3.8%)

Follow up by direct patient contact
N = 188 (88.7%)

Follow up by contact with GP /Relative
N = 16 (7.5%)

Table 1: Demographic and clinical presentation data, with stratification by result. Age is presented as mean (SD). All other data is presented as categorical (%). Valid percentages are given in the context of missing data. Obesity was defined as Body Mass Index >30. Recent surgery was defined as operative intervention within the last 3 months. NRS = Numerical Rating Scale. Data on Wells scoring is recorded as valid percentages only (163 patients total).

	All patients N=212	Inconclusive ultrasound N= 24	Negative ultrasound N= 188	Univariate analysis (p value)	Multivariate analysis (OR and p value)
Demographics					
Age	56.7 (18.8)	59.5 (19.6)	56.4 (18.7)	0.84	-
Female	137 (64.2)	20 (83.3)	117 (62.3)	0.04	OR 6.9 (0.5-90.3), p=0.13
Left Sided Right Sided Bilateral	107 (50.5) 79 (37.3) 26 (12.3)	11 (45.8) 9 (37.5) 4 (16.7)	96 (51.1) 70 (37.2) 22 (11.7)	0.66	-
White Afro-Caribbean Asian Other	169 (79.7) 24 (11.2) 12 (5.6) 7 (3.4)	19 (79.2) 3 (12.5) 1 (4.2) 1 (4.2)	150 (79.8) 21 (11.2) 11 (5.9) 6 (3.2)	0.99	-
Risk factors					
Family history VTE	36 (17.0)	4 (16.7)	32 (17.0)	0.57	-
Past history VTE	35 (16.5)	4 (16.7)	31 (16.5)	0.47	-
Thrombophilia	8 (3.8)	0(0)	8 (4.3)	1.00	-
Obesity	43 (20.3)	12 (50)	31 (16.6)	<0.01	OR 4.15 (95% CI 1.5-11.2) p < 0.01
Smoker	63 (29.7)	6 (25.0)	57 (30.5)	0.59	-
Acute infection	49 (23.1)	10 (43.5)	39 (20.7)	0.02	OR 2.9 (95% CI 1.1-8.0) p = 0.04
Immobilisation	20 (9.4)	6 (25.0)	14 (7.4)	0.02	OR 4.9 (95% CI 1.5-16.2) p = 0.01
Active cancer	9 (4.2)	3 (12.5)	6 (3.2)	0.05	OR 7.9 (95% CI 1.5-41.7, P = 0.01
Oestrogen use	14 (6.6)	1 (4.2)	13 (6.9)	0.94	-
Recent surgery	30 (14.2)	3 (12.5)	27 (14.4)	0.74	-
Clinical Presentation					
Wells High	47 (28.8)	9 (41.0)	38 (27.0)	0.66	-
Wells Moderate	73 (44.8)	7 (31.8)	66 (46.8)	0.64	-
Wells Low	43 (26.4))	6 (27.2)	37 (26.2)	0.84	-
Symptom duration	7 (3 to 14)	7 (3 to 21)	7 (3 to 14)	0.07	-
NRS Pain Score	3 (2 to 5)	4 (2.75 to 5.25)	3 (2 to 5)	NS	-

isolated distal deep vein thrombosis (IDDVT) within a single posterior tibial vein. The clot was chronic in appearance. No anticoagulation was prescribed by the attending clinician and the patient was alive and well at three month follow up. We also noted 1 death during the study period. This patient had known renal carcinoma and was diagnosed with metastatic disease 10 days after presentation to the ED and recruitment to the trial. She was later transferred to a hospice for palliation. Cause of death was recorded by the coroner as disseminated metastatic cancer. This event was ruled as unrelated to VTE by the central adjudication committee.

The subsequent incidence of the composite primary outcome in our population following withheld anticoagulation after single whole-leg CUS was 1/212 = 0.47% (95% CI 0.08 to 2.62%).

Secondary Outcomes

Technical failure occurred within 11.3% (95% CI 7.7 to 16.3) of our study population. This rate was replicated within the original screening cohort (70/610 - 11.5%, 95% CI 9.1 to 14.3) – Figure 1. Obesity, acute infection, immobilisation and active cancer were all significantly associated with technical failure on multivariate analysis (Table 1). All cause mortality within three months was 0.47% (95% CI 0.08 to 0.26), due to the single death noted above.

Re-attendance to the Emergency Department occurred in 43 (20.3%) cases during follow up. Only 17 (8.0%) of these attendances were directly related to suspected VTE, with a significant increase in the proportion attending following an initially inconclusive (10/24 [41.7%]) vs. negative (7/188 [3.7%]) whole leg CUS (p < 0.001). Further imaging related to VTE was performed in 22 cases (10.4%) during the follow up period. Repeat vascular imaging was significantly more frequent in patients with an initially inconclusive CUS scan, with a 50% chance of repeat imaging in this group (12/24) as compared to a 5% (10/188) chance in the negative scan group (p < 0.001).

Six patients were commenced on temporary anticoagulation during the study period, all with less than a week of therapeutic LMWH. Anticoagulation was prescribed by non-research clinicians following representation. Again, this was significantly more likely to occur within the context of an inconclusive scan (3/24 [12.5%] vs. a negative scan 3/188 [1.6%] respectively, P = 0.02).

All patients with completed Wells score data were subsequently analysed as a pre-

specified subgroup for both primary and secondary outcomes. One hundred and sixty three patients had complete data suitable for analysis (76.9%). In the remaining 23.1% patients the Wells score had not been adequately documented by the attending clinician, prior to referral for ultrasonography. No significant differences were found on direct comparison between patients deemed at high risk or otherwise. Stratification is shown in Table 2. The composite primary outcome for those patients with a high pre-test probability was achieved in 2.1% (95% CI 0.4 to 11.1).

An alternative diagnosis was provided by the attending clinician in 150/212 cases. Clinicians providing diagnostic labels operated outside the research team and were of registrar (resident) or consultant (attending) grade. The alternate diagnosis was felt to be directly identified or confirmed by CUS in 55 of these cases, such that 25.9% (95% CI 20.0 to 31.8) of the original cohort were provided with a conclusive diagnosis and appropriate management as a result of whole leg CUS. A list of alternate diagnoses stratified by CUS is given in table 3.

Discussion

These findings support previously published low adverse event rates after withholding anticoagulation following a single negative whole-leg CUS examination in suspected DVT. Our data validates this approach within an ambulatory ED setting, basing clinical decision making on imaging performed by qualified non-physicians, rather than after clinical assessment and imaging performed by vascular specialists.

We also highlight several new points regarding process measures: the technical failure rate of whole leg CUS was 11.3% (95% CI 7.7 to 16.3) in our study population. Obesity, acute infection (any site), active cancer and immobilization were all potentially associated with technical failure on multivariate analysis. As expected, patients with suspected DVT and an inconclusive CUS result subsequently had higher rates of re-attendance, repeat imaging and therapeutic intervention.

Additionally we provide new data on subsequent event rates in patients with high pre-test probability. To our knowledge, this is the largest cohort of high-risk patients prospectively studied following withheld anticoagulation after initial

Table 2: Primary outcome data stratified by clinical pretest probability scoring. All data is recorded as n/N (%). Data on Wells scoring was available for 163 patients.

	High risk N=47	Moderate risk N = 73	Low risk N = 43	Non High (<3) N = 116	Comparison High vs non high
Primary outcome					
VTE event	1 (2.1)	0 (0)	0 (0)	0 (0)	NS
VTE related death	0 (0)	0 (0)	0 (0)	0 (0)	NS
Secondary outcome					
All cause mortality	1 (2.1)	0 (0)	0 (0)	0 (0)	NS
Reattendance	13 (27.7)	11 (15.1)	8 (18.6)	19 (16.4)	NS
VTE related reattendance	6 (12.8)	6 (8.2)	3 (7.0)	9 (7.8)	NS
Therapeutic intervention	2 (4.3)	1 (1.4)	3 (7.0)	4 (3.4)	NS
Repeat imaging	7 (14.9)	7 (9.6)	6 (14.0)	13 (11.2)	NS
Scan Result					
Negative	38 (80.9)	69 (94.5)	37 (86.0)	106 (91.4)	NS
Inconclusive	9 (19.1)	4 (5.5)	6 (14.0)	10 (8.6)	NS

Table 3: Alternative diagnoses provided to patients during the study, stratified by the contribution of whole leg CUS.

	Patients with negative or inconclusive whole leg CUS N=212
Alternate diagnosis provided	**150/212 (70.8%)**
Yes	150
No (idiopathic / unknown)	38
Inconclusive scan recorded - no diagnosis offered	24
Diagnosis directly attributable to or confirmed by whole leg CUS	**55/150 (36.7%)**
Severe arterial vascular disease	1 (0.7%)
Bakers cyst	13 (8.7%)
Musculoskeletal (including calf haematoma, tendonitis and muscle rupture)	32 (21.3%)
Superficial thrombophlebitis	4 (2.7%)
Post thrombotic syndrome / venous incompetence	5 (3.3%)
Diagnosis unassisted by whole leg CUS	**95/150 (63.3%)**
Crystal Arthropathy	2 (1.3%)
Dependent oedema (Cardiac / pregnancy / liver failure)	27 (18.0%)
Diabetic neuropathy	1 (0.7%)
Infective Process	43 (28.7%)
Meralgia parasthetica	2 (1.3%)
Post operative swelling	13 (8.7%)
Arthritic disease	5 (3.3%)
Lymphoedma	1 (0.7%)
Bony injury	2 (1.3%)
Venous eczema / lipodermatosclerosis	2 (1.3%)
Sciatica	2 (1.3%)

negative/inconclusive full leg ultrasound [14, 17, 19]. We have also recorded a list of alternate diagnoses provided following negative whole leg CUS examination for suspected DVT, and the proportional influence of CUS in confirming these diagnoses.

This study has a number of strengths. Our cohort was similar at baseline to previous ambulatory populations. A 29% pre-test probability of disease is also in keeping with other sample estimates, ranging from 13.7 to 32.7% at recent systematic review [14]. This study was pragmatic and used existing healthcare resources. This should ensure that our findings can be generalised to other centres performing whole-leg CUS.

We made a deliberate *a priori* decision to include patients with an inconclusive scan result, as we deemed it vital to evaluating the pathway. Technical failure is a real concern with whole-leg CUS, with previous studies quoting a wide variation in failure rates between 9.3-82.7% [13]. As such, our study is one of the few to provide an open assessment of the caveats with whole-leg CUS and the characteristics associated with technical failure. We had no formal protocol for management of an inconclusive scan result. As such, our rates of repeat imaging and intervention are reflective of real-time decisions made by practicing emergency physicians.

Finally, we attempted to standardise all interventions and outcomes in an objective manner. Protocolised scanning allows reproduction of whole leg ultrasound within external research environments and thus renders our intervention transparent and reproducible. Also, use of an independent central adjudication committee promotes unbiased dialogue regarding potentially subjective endpoints [30]. This is essential for a study with few expected positive outcomes.

The potential benefits of whole-leg CUS are well known and often cited in VTE research. Principally, they include a purported reduction in re-attendance/repeat imaging with substantial cost and time savings; thorough assessment of the deep calf veins to allow risk stratification and fully informed discussion in the event of IDDVT; detection of additional pathology in the lower limb such as calf haematoma, Bakers cyst or thrombophlebitis; and the opportunity to clarify diagnosis at initial visit. This last point is especially important for a mobile emergency department population, who will often have even higher rates of non-return than seen with vascular outpatients

[23].

The 0.47% (95% CI 0.08 to 2.62) composite primary outcome that we report is similar to that published in a recent meta-analysis of 7 studies and over 4700 patients. Johnson *et al* report a VTE event rate following negative whole-leg CUS of 0.57% (95% CI 0.25 to 0.89), in patients with suspected DVT after three month follow up [14]. This data includes inpatient studies and several cohorts managed exclusively by vascular specialists. Our results thus externally validate these findings within an emergency protocol using ultrasound performed by qualified non-physicians.

Two studies have previously analysed outcomes in patients with high pre-test probability and documented higher VTE event rates of 2.63% (95% CI 0.07 to 13.81) and 2.38% (95% CI 0.06 to 12.57) [17, 19] over 3 month follow up. Our data support this increased risk, albeit with similarly broad confidence intervals due to the modest sample size. The reproducibility shown here argues for further robust study within a larger cohort of patients. If higher VTE event rates are proven, this may suggest a benefit to further clinical review or serial imaging after negative whole-leg CUS in patients with high pre-test probability. This is currently not recommended practice [31].

We saw a higher rate of technical failure than perhaps expected with whole-leg CUS. However, rates have been shown to vary significantly throughout the literature, the most recent assessments ranging from 0 to 5% [15, 28, 30]. It is notable that these three studies assess technical failure in the hands of non-blinded accredited vascular physicians: all examinations within our study were performed by dedicated non-medical ultrasonographers. Our findings are therefore less likely to be influenced by conscious or subconscious bias as a result and as such, this is not a limitation in our study per se. Most emergency departments utilize external imaging services for confirmation of venous disease: modern protocols must be assessed in light of this.

Our study does not assess the cost effectiveness of an ambulatory pathway utilizing single whole-leg CUS assessment. This is an area in pressing need of further research, yet limited by the equipoise regarding therapeutic approach to IDDVT. Proponents of serial proximal CUS cite data regarding efficacy of the protocol but also increased

safety due to reduction in anticoagulation [32]: this assumes that all IDDVT failing to propagate after 7 days do not benefit from treatment. Concerns remain regarding withheld anticoagulation in high risk, symptomatic and recurrent IDDVT patients. All IDDVT cases do not necessarily warrant treatment, but whole leg ultrasound at least provides an estimation of clot burden and location to allow risk stratification and tailored therapy [11].

Several limitations of this study must be acknowledged. Although we strived for a consecutive sample, the research team did not screen 15% of patients: the majority of these patients underwent imaging late on in the day, and then attended the ED outside of normal working hours with their result. In addition, we restricted recruitment to those patients we believed would be able to provide robust follow up data (exclusion of non-UK residents). As such, generalisability may be limited. Vascular ultrasonography was also performed and reported by non-physicians. A decade of whole leg scanning implies our vascular laboratory is both practiced and experienced, again raising concerns about the generalisability of our results to other centres. This is particularly pertinent with regard to our technical failure rates – these rates may well be higher in centres with limited experience. However, we do not consider this a limitation as such: whole-leg CUS is used internationally and modern protocols have shown good inter-rater reliability. We attempted to standardise results using accepted and previously described protocolised assessment. As such, our results should be reflective of any institution using whole-leg CUS with adequate governance and oversight.

Only 50% of our patients with inconclusive imaging received repeat scans. As this was a non protocolised, pragmatic assessment within an ambulatory service, this is likely reflective of several issues – failure to reattend, clinician preference and improving symptomatology. However, it must be acknowledged that enforcing a 100% repeat scan rate in this potentially high risk cohort could well have resulted in further adverse events. Indeed, 37.5% of inconclusive cases were deemed high risk by Wells score.

Only symptomatic individuals who re-attended the department were assessed for further disease. This could potentially lead to verification bias in our results.

However, we would suggest that an alternative approach would fail to accurately test the study hypothesis: screening for incidental disease and detection of future spontaneous DVT may lead to unwarranted concern with whole leg CUS. We were interested in a pragmatic assessment looking chiefly for symptomatic returns, as we would be in clinical practice. Screening and treatment for asymptomatic DVT remains controversial, even in at risk groups [33].

Lastly, it must be acknowledged that our multivariate analysis was not adequately powered to provide definitive evidence of characteristics associated with technical failure. This was always a secondary outcome and aimed to be hypothesis generating, rather than conclusive.

The future direction of research in this area needs to focus on several key issues. Firstly, the ongoing management of patients with technical failure of whole-leg CUS is an area in which limited robust evidence exists to guide decision-making. Given the higher rates of resource use and subsequent events, an argument can be made for serial follow up. This would be likely to suffer from a similarly low diagnostic yield as an initial approach with serial proximal CUS. Secondly, further study of outcome in patients with high pre-test probability and a negative whole-leg CUS result is needed, to reassure physicians regarding the current recommendations to avoid serial follow up or further imaging.

Finally, an assessment of cost effectiveness comparing whole leg to serial above knee ultrasound is urgently needed and has recently been the subject of a national research call [34]. Such a trial would need to provide standardised care for IDDVT patients and focus not just on short term outcomes, but also those relevant to conservative treatment of non propagating IDDVT, such as post thrombotic syndrome, symptomatology, representation and recurrence. Standardisation remains difficult while therapeutic equipoise continues to exist regarding treatment of IDDVT and international guidelines offer conflicting recommendations [35, 36].

Conclusion

In conclusion, patients who have anticoagulation withheld following a negative or

inconclusive whole leg CUS for suspected DVT, within the context of an ambulatory ED service, have a low rate of adverse events at 3 months. In addition, whole leg CUS can offer or confirm an alternative diagnosis in roughly 1 out of every 4 patients. Several factors are potentially associated with technical failure, including obesity, immobilization, active cancer and acute infection. Further comparative study is warranted to confirm these findings and determine whether such patients could benefit from alternative diagnostic strategy.

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Paper 5: Clinical presentation of isolated distal deep vein thrombosis differs significantly from proximal disease states

Paper Overview

A prospective service evaluation exploring the incidence, burden and unique disease characteristics of IDDVT within an ambulatory population.

Contribution to the thesis and novelty

This paper addresses the fifth and sixth aims of the thesis, by prospectively evaluating an ambulatory thrombosis service over the course of a year. Data is provided on IDDVT incidence rates and disease burden in comparison to proximal thrombi. A univariate analysis is performed to identify clinical and aetiological differences in disease stratified by thrombus location. This study is the largest work to date on the topic and to our knowledge the only one directly comparing clinical presentation features stratified by location as a primary outcome.

Contribution of Candidate

Study design, data management and conduct of the analysis. The MD student also wrote and managed all drafts of the manuscript, incorporating suggestions from co-authors.

Publication strategy

For submission to the following journals in order of preference:

4. Journal of Thrombosis and Haemostasis   5.731
5. Thrombosis and Haemostasis   4.701
6. Clinical and Applied Thrombosis / Haemostasis   1.332

Title:

Clinical presentation of isolated distal deep vein thrombosis differs significantly from proximal disease states

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Abstract

Objectives

There is ongoing lack of consensus on the management of isolated distal deep vein thrombosis (IDDVT). While some clinicians treat as they would for proximal disease, other experts manage the condition as a distinct entity. Limited comparative literature exists on risk profile and presenting clinical features in direct support of this assertion. We sought to determine the clinical and aetiological presentation of IDDVT and compare it to that of proximal disease.

Methods

An observational, ambulatory prospective cohort study. Consecutive patients attending an established outpatient thrombosis service during the year 2011 were included. Historical, aetiological and clinical data were collected routinely by attending physicians on a standardized proforma during the initial clinical encounter. This data was anonymised and stratified by outcome at vascular ultrasound. Descriptive and regression analyses were performed to identify and quantify predictors of distal versus proximal thrombotic disease.

Results

1,888 patients attended the service with suspected deep vein thrombosis, with a retrospective pre-test probability of 8.3% for acute thrombotic disease. Distribution of acute disease was shared evenly between distal (78 cases [49.7%]) and proximal (79 cases [50.3%]) thrombi.

Distal cases were significantly more likely to be provoked (p=0.025), right sided (p=0.039) and to present with localised pain (p=0.003). Distal cases were less likely to present with entire leg swelling or calf swelling >3cm (both p<0.01). Laboratory markers of clot burden and inflammation were all significantly reduced in the IDDVT group compared to proximal cases.

Conclusion

Patients with IDDVT are significantly different to those with proximal disease, regarding clinical presentation and risk profile. Our results concur with previous

evidence supporting the idea of IDDVT as a distinct disease entity. Diagnostic algorithms which place clinical importance on accurate diagnosis of IDDVT could potentially use these findings to guide investigative strategy.

Background

Isolated distal deep vein thrombosis (IDDVT) is a condition yet to be accurately quantified and understood. A composite of calf muscle and deep calf vein thrombosis, IDDVT continues to cause controversy regarding diagnosis, prognosis and optimal therapeutic approach [1-5]. Recent review articles highlight limitations in the evidence regarding symptomatology and presenting clinical features [6].

Several authors have already suggested that IDDVT is a distinct disease entity from proximal venous thrombosis. This assertion is based mainly on differences in risk profile stratified by thrombus location [7]. Several prospective European thromboembolism registries have recently provided support to this theory [8, 9]. However, these findings require further external validation given the heterogenous patient group included and variable definitions of provocation.

Little research has been conducted on the difference in *clinical presentation* stratified by thrombus location. Several previous articles have included brief descriptions of symptomatology in presentation of IDDVT but few have drawn direct comparison against proximal disease [10-12]. A single retrospective review has recently assessed duration of symptoms in 100 patients with phlebographically confirmed deep vein thrombosis (DVT) and found no significant difference between distal or proximal thrombi [13]. Another contemporary article has prospectively explored individual clinical characteristics within the Wells prediction model and variation by proximity [14]. This variation has been examined previously in a diagnostic meta-analysis with similar results [15]. However, no study has attempted to prospectively address the question as a primary hypothesis.

The equipoise regarding diagnostic strategy and therapeutic intervention is central to the need for further study in this area [1, 2]. If distal disease can be predicted by clinical characteristics at presentation then the potential exists to individually tailor management, a strategy previously endorsed as the ideal approach to IDDVT [2]. Patients with a negative proximal compression ultrasound (CUS) and clinical predictors strongly suggestive of IDDVT may warrant extended whole leg CUS for example. In addition, clinical characteristics and risk profile may be of use in guiding

the decision to treat IDDVT: patients with confirmed distal disease but clinical predictors usually associated with proximal thrombi, may benefit from a more aggressive strategy.

The objective of this study was to evaluate the assertion that IDDVT differs significantly to proximal disease at point of assessment. We sought to prospectively compare demographic data, risk factors, laboratory investigations and clinical assessment variables between patients receiving an eventual diagnosis of either isolated distal or proximal deep vein thrombosis, using a reference standard of whole leg CUS.

Methods

Study design

A prospective, ambulatory, observational cohort study conducted within the screening pool of the Anticoagulation of Calf Thrombosis (ACT) project. Protocol and registration data for the ACT study have been previously published and are publicly available [16, 17]. During screening and recruitment to the ACT study, we utilized a predesigned ambulatory care pathway to evaluate historical, clinical and aetiological data on a consecutive sample of patients attending the department with suspected deep vein thrombosis. Subsequent reference standard outcomes were recorded and cases uploaded to an anonymised database.

Study setting and population

The study was conducted at a large city centre, tertiary referral, academic teaching hospital serving an ethnically diverse population. The adult Emergency Department (ED) has an annual attendance of approximately 97,000 – 110,000 and sees 4000 ambulatory patients with suspected VTE each year. Patients were actively enrolled by emergency department and thrombosis staff throughout the entire year 2011.

Study protocol

All consecutive, adult, ambulatory patients attending the ED with suspected DVT were included in the study. Hospital inpatients, patients with confirmed pulmonary

embolism, or those undergoing duplex ultrasonography as a proxy diagnostic marker for suspected pulmonary VTE, were excluded.

All patients were clinically managed by non-research physicians, using local protocols and a clinical decision support guideline (CDSG). This document requires data entry regarding symptomatology, risk factors for VTE and clinical findings. An evidence based diagnostic process is then utilised including formal documented pre-test probability assessment via modified Wells score [18], D-dimer measurement and whole-leg CUS [19]. The CDSG has been in use within the department for 8 years and is subject to ongoing appraisal and review.

Patients proceeding to duplex ultrasonography were scanned by a dedicated vascular service independent of the research team. Outpatient sonography was performed during 9-5pm Monday to Friday excluding bank holidays. Presentation out of hours resulted in once daily outpatient administration of therapeutic dose dalteparin pending imaging, in accordance with national guidelines [20]. Following ultrasound results, patients were immediately seen within the ED and managed by a senior tier of emergency physicians.

Imaging and Laboratory Protocols

Diagnostic imaging was performed by colour duplex whole-leg CUS. Technicians within the vascular lab are vocationally trained to postgraduate level in Vascular Science and accredited to standards set by the Society for Vascular Technology of Great Britain and Ireland.

Patients were scanned using a 9-4MHz linear and 5-2MHz curvilinear transducer to a standard proforma. This includes documented assessment of all proximal, muscular calf and deep calf veins using B mode, colour doppler and spectral doppler including compression, augmentation and valsalva manoeuvre. Results are descriptive and categorized into 5 typical findings: Acute proximal DVT, Acute distal/calf DVT, Chronic DVT, inconclusive scan and negative scan. Distal disease was further subdivided into thrombus within the muscular veins of the calf, or the deep axial system. Vascular technicians have access to the clinical request data and pre-test probability score as standard.

D-dimer measurements were obtained using a previously validated, rapid and quantitative immunoturbidometric assay (STA Liatest [Diagnostica Stago]) and are reported in ng/mL [21, 22]. In line with current opinion, we considered a result

<250ng/mL (equivalent to <500 Fibrinogen equivalent units (FEU)) to be a negative result [23].

Key outcome measures

Our primary outcome was to explore clinical characteristics at presentation in patients diagnosed with acute deep vein thrombosis, stratified by thrombus location. Secondary outcomes included the analysis of risk factor characteristics and variation in aetiology between distal and proximal disease.

We defined provocation as any known transient risk factor occurring within the 3-month antecedent period, in keeping with recent United Kingdom (UK) National Institute of Clinical Excellence (NICE) definitions [24]. Pain at presentation was assessed using a previously validated, verbally administered numerical rating scale (NRS) [25] and additionally via the 4 point functional scale utilised by Lagerstedt *et al* in their previous landmark randomised controlled trial [26].

Data analysis

All categorical variables are reported as percentages. All continuous variables were assessed for normality of distribution using the Kolmogorov-Smirnov test and reported as medians with interquartile range or mean with standard deviation as appropriate. Missing data were coded as such within the database. Confidence intervals were calculated to 95% using the Wilson method.

Comparison of variables was made using the Mann-Whitney U test for non-parametric data and Chi squared, or Fishers exact test where appropriate, for parametric data or proportions.

Univariate analysis to assess for differences in clinical presentation and risk profile was performed using binary logistic regression.

All calculations and statistical tests were checked and verified by an independent statistician employed by the University of Manchester, external to the research team. All P values were 2 tailed and <0.05 was considered statistically significant. All analyses were performed using SPSS version 20 (IBM).

Funding organizations, sponsors and their role

This analysis was performed within the remit of a study funded by the College of

Emergency Medicine, a registered charity within the UK. The college had no input in design, oversight, the decision to publish or drafting of the manuscript. The hospital Research and Innovation department performed local governance checks and general oversight, including approval of submission.

STROBE statement

As a prospective evaluation, all data presented conform to the STROBE recommendations on reporting of observational cohort data [27].

Ethical review

Enquires were made to the National Research Ethics Service regarding approval of study conduct (www.nres.npsa.nhs.uk/applications/apply) and need for formal ethical review. A study protocol was also submitted through the institutional Research & Innovation department, ED directorate management team and the trust information governance officer. The requirement for formal ethical review was waived by all parties, due to the lack of intervention or additional procedures and evaluation of data within the context of routine service provision.

Results

Patient Flow

Over the study period, 1888 ambulatory patients attended the ED with a suspected diagnosis of DVT. Roughly two thirds of this cohort (63.1%, 95% CI 60.9 to 65.2) had a low clinical prediction risk score in tandem with a negative D-dimer and were discharged without further diagnostic testing. All remaining patients were referred for whole leg CUS. Two hundred and fourty two (34.8%, 95% CI 31.3 to 38.5) had a modified Wells score greater than/equal to 3. Four hundred and fifty four (65.2%, 95% CI 61.5 to 68.8) patients scored low risk, but had a laboratory D-dimer value above the predefined cut point. All patients underwent reference standard whole leg CUS. The median delay to duplex ultrasound was 1 day (IQR 1-2) with >85% patients undergoing sonography <48hours after presentation. A flow diagram is shown in Figure 1.

In patients referred for sonographic evaluation, the diagnosis of acute DVT was confirmed in 157 patients. This represents an incidence of 8.3% (95% CI 7.2 - 9.6)

Figure 1: Flow chart of patient attendance and data collection throughout 2011. This includes all patients attending the Emergency Department thrombosis service with a chief complaint of atraumatic lower limb swelling. 'Low risk' denotes a modified 3 level Wells score <3.
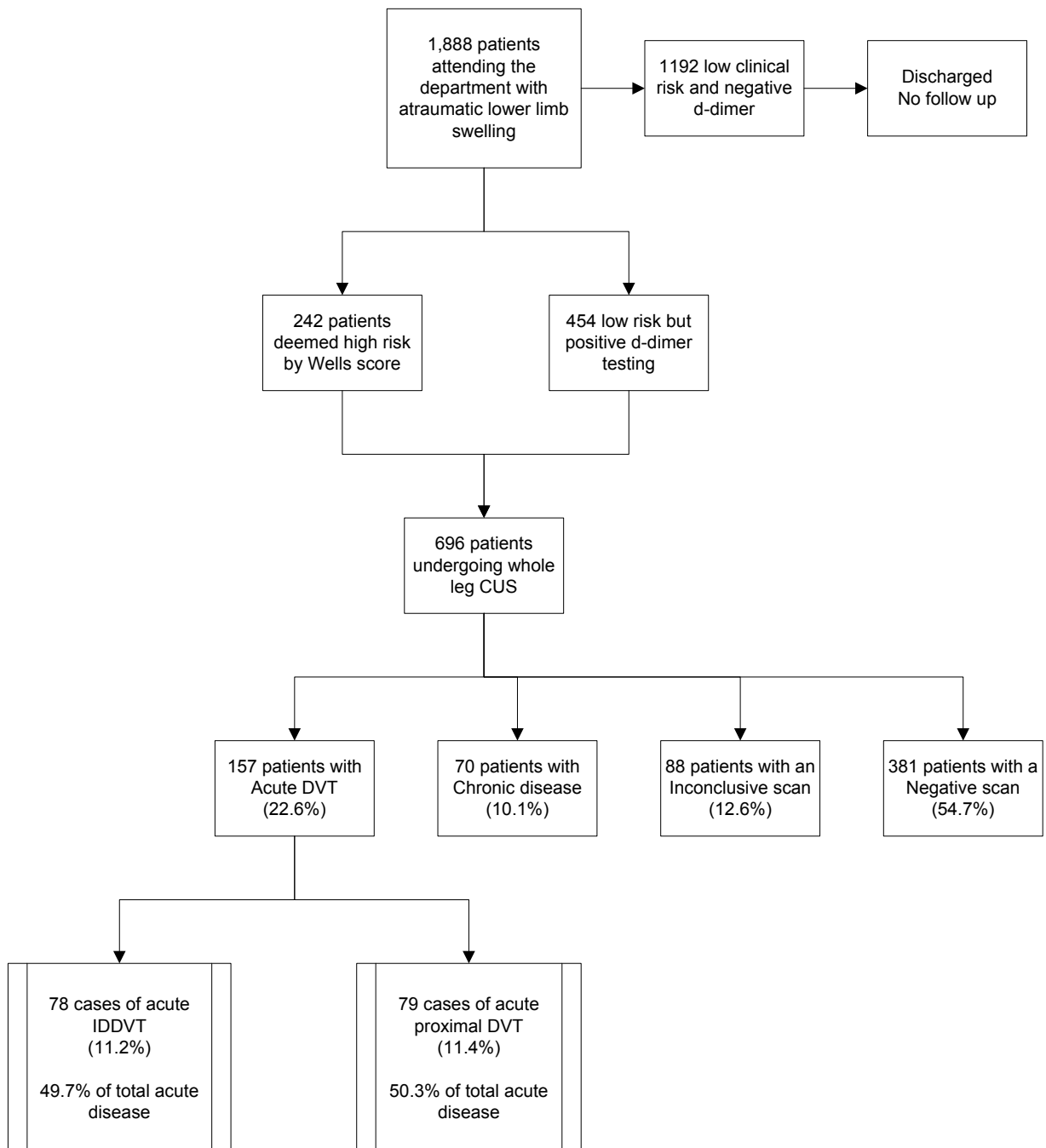
within the original presenting cohort, and 22.6% (95% CI 19.6 – 25.8) in those referred for imaging. Acute disease cases were distributed evenly between proximal and distal thrombosis.

Demographics

Data is reported subsequently only for patients who underwent the reference standard test of duplex ultrasonography. A control group was formed from those patients with a negative whole-leg CUS result (n=381). Patients with an inconclusive scan report and those with chronic disease were omitted from the control group.

The ambulatory population referred for ultrasonography had a mean age of 57.5 (SD 18.4), a female preponderance (60.9%, 95% CI 57.2 to 64.5) and an ethnicity in keeping with regional figures (79.0% white Caucasian, 95% CI 75.8 to 81.9). Suspected laterality (side of investigation) was overall evenly distributed with 45.8% left, 44.7% right and 9.5% scans ordered bilaterally. Eleven percent of all patients with acute disease were aged 35 or under. A significant association with right-sided disease was seen in IDDVT compared to proximal. The findings are presented in Table 1.

Presenting Features

Clinical and laboratory features at initial presentation were assessed and compared between all DVT patients vs. controls, and IDDVT vs. proximal disease. Data is presented in Table 2. No significant differences were seen between presenting duration of symptoms, pain scores or observational data.

Overall clinical risk score was significantly higher in the PDVT group compared to the IDDVT group. The majority of our patients with IDDVT had an intermediate, rather than high Wells score. Ranked and median d-dimer values were significantly different between groups, as were inflammatory markers such as the C-reactive protein and baseline white cell count.

Completed clinical risk prediction scores were available for 95.6% of IDDVT patients and 87.8% of PDVT patients. There were several notable differences between individual risk components regarding proximal and distal disease in clinical presentation. IDDVT patients presented with significantly less calf swelling and entire leg swelling (p=0.006 and <0.001 respectively). IDDVT patients also had a significantly increased incidence of localized tenderness and recent immobilisation

TABLE 1: Demographic comparison between patients with IDDVT, proximal disease and controls. Comparison between distal and proximal disease is made using univariate analysis and presented as odds ratios with 95% confidence Intervals.

*Given the paucity of samples, ethnicity was recoded for univariate analysis as binary categories of 'white' or 'other'. The ratio presented here denotes the odds of being white rather than other in patients with confirmed IDDVT.

**The single case of bilateral IDDVT was excluded from this comparison. The ratio presented here denotes the odds of having left sided disease in patients with IDDVT, compared to PDVT

		All Patients (n=696)	Control (n=382)	IDDVT (n=78)	PDVT (n=79)	Comparison of IDDVT vs. PDVT	Significance testing
Age Mean (SD)		57.5 (18.4)	55.7 (18.9)	59.7 (17.7)	57.1 (17.9)	1.008 (95% CI 0.99 - 1.03)	NS
Female Sex N (%)		424 (60.9)	234 (61.3)	51 (65.4)	46 (58.2)	1.355 (95% CI 0.71 - 2.59)	NS
Ethnicity N (%)	White Asian Black Hispanic Other	550 (79.0) 71 (10.2) 58 (8.3) 5 (0.7) 12 (1.7)	295 (77.2) 52 (13.6) 27 (7.0) 2 (0.5) 6 (1.6)	61 (78.2) 3 (3.9) 10 (12.8) 1 (1.3) 3 (3.8)	65 (82.3) 4 (5.1) 7 (8.9) 2 (2.5) 1 (1.3)	0.773* (95% CI 0.35 - 1.70)	NS
Side of symptoms/ disease N (%)	Left Right Bilateral	318 (45.7) 311 (44.7) 67 (9.6)	166 (43.5) 170 (44.5) 46 (12.0)	36 (46.2) 41 (52.6) 1 (1.3)	50 (63.3) 29 (36.7) 0 (0)	0.509** (95% CI 0.27 - 0.97)	P = 0.039

TABLE 2: Comparison of presenting features between all patients with acute DVT, IDDVT, PDVT and controls. All data are described in mean (SD), median (IQR) or proportions (%age) dependent on distribution and type. NS = non significant. D-dimer measurements are reported in ng/mL. 3 IDDVT, 9 IDDVT and 43 control patients had no Wells score recorded and valid percentages are given. * = 2 tailed significance testing using Mann-whitney U

	Control (n=382)	IDDVT (n=78)	PDVT (n=79)	All DVT (n=157)	Odds ratio for IDDVT vs. PDVT	Significance Testing
Symptom duration in days	6 (3 to 14)	7 (4 to 14)	7 (4 to 12)	7 (4 to 14)	1.00 (95% CI 0.98 - 1.03)	NS
Categorical pain score	2 (1 to 2)	2 (2 to 3)	2 (2 to 3)	2 (2 to 3)	0.73 (95% CI 0.46 - 1.12)	NS
VA Pain score	3.8 (2.1)	4.4 (2.0)	4.2 (1.9)	4.3 (2.0)	1.003 (95% CI 0.98 - 1.03)	NS
EWS score	0 (0 to 1)	0 (0 to 1)	0 (0 to 1)	0 (0 to 1)	1.07 (95% CI 0.68 - 1.68)	NS
Total wells score	2 (0 to 3)	2 (2 to 3)	3 (2 to 4)	3 (2 to 3)	0.70 (95% CI 0.53 - 0.91)	P = 0.008*
High (>/3)	106 (31.4)	34 (45.3)	43 (61.4)	77 (53.1)	n/a	NS
Intermediate (1-2)	132 (39.0)	36 (48.0)	24 (34.3)	60 (41.4)	n/a	P = 0.049
Low (</0)	100 (29.6)	5 (6.7)	3 (4.3)	8 (5.5)	n/a	NS
D-dimer	455 (300 to 780)	660 (338 to 1210)	1880 (1212 to 3235)	1172.5 (527.5 to 1980)	n/a	P < 0.001*
CRP	7 (3 to 21)	7 (3 to 19)	20 (7.5 to 57.5)	11.5 (4.3 to 28.8)	0.97 (95% CI 0.96 - 0.99)	P = 0.001*
WCC	7.8 (2.4)	7.6 (2.8)	8.7 (2.7)	8.2 (2.8)	0.86 (95% CI 0.76 - 0.97)	P = 0.016

compared to proximal (p=0.003 and 0.012 respectively). This data is presented with odds ratios demonstrating strength of association in Table 3.

Analysis of Risk Factors

Data is presented comparing gross frequencies across IDDVT vs. PDVT patients with univariate analysis to assess significance. Results are presented in Table 4. Additional potential risk factors with no clear or accepted association to permanent or chronic risk are presented separately in Table 5.

Using the predefined NICE criteria for provocation, distal thrombi were significantly more likely to be provoked than proximal in our population (p = 0.025). Over half of all IDDVT cases had a least one major antecedent risk factor within the last 3 months. We could find no significant association between individual temporal risk factors and proximity of deep vein thrombosis, other than plaster of Paris immobilization and IDDVT (p=0.003). Although we failed to reach statistical significance for other individual risk factors, our results were in line with previous registries: active cancer, smoking and prior thromboembolic disease were all more likely to be seen in proximal cases than distal. Conversely, the majority of accepted transient risk factors were more likely to be present in IDDVT cases. Intravenous drug use was the only additional risk factor that predicted thrombus location: the presence of drug use was significantly associated with proximal disease.

Of interest, the frequency of obesity, varicosities and known thrombophilia were all higher in the control rather than either DVT group. This likely represents modern awareness of DVT in patients with known risk factors and symptoms from venous incompetence in obese patients, or those with varicosities.

Discussion

Our principal findings are two fold. Firstly, we report new data to suggest significant differences between the clinical presentation of distal and proximal DVT. Secondly, our results support the hypothesis that IDDVT is a disease more likely to be associated with transient risk and direct antecedent provocation. These principal findings bolster the assertion that distal thrombi differ significantly from proximal DVT states, and constitute a separate disease entity.

TABLE 3: Comparison of individual clinical risk score components between IDDVT and PDVT patients. Complete data on Wells score was available for 75 patients in the IDDVT group and 69 in the PDVT group. Valid percentages are utilised. NS = non significant.

	IDDVT (N=78)		PDVT (N=79)		Odds ratio for IDDVT vs. PDVT	Significance Testing
Active Cancer	2	2.7%	7	10.1%	0.243 (95% CI 0.05 - 1.21)	NS
Calf Swelling>3cm	22	29.3%	36	52.2%	0.381 (95% CI 0.19 - 0.76)	P = 0.006
Varicosities	15	20.0%	14	20.3%	0.982 (95% CI 0.44 - 2.22)	NS
Pitting oedema	33	44.0%	41	59.4%	0.537 (95% CI 0.28 - 1.04)	NS
Swelling of entire leg	9	12.0%	30	43.5%	0.177 (95% CI 0.08 - 0.41)	P < 0.001
Localised pain	56	74.7%	35	50.7%	2.863 (95% CI 1.42 - 5.78)	P = 0.003
Immobilisation	16	21.3%	4	5.8%	4.407 (95% CI 1.39 - 13.93)	P = 0.012
Bedridden	13	17.3%	12	17.4%	0.996 (95% CI 0.42 - 2.36)	NS
PMH DVT	12	16.0%	18	26.1%	0.540 (95% CI 0.24 - 1.22)	NS
Alternative diagnosis	5	6.7%	1	1.4%	4.857 (95% CI 0.55 - 42.66)	NS

TABLE 4: Comparison of temporal risk factors between all patients with IDDVT, PDVT and controls. Data are described as n/N proportions and percentages. Univariate analysis is used to compare and provide OR. Zero values are unassessable by odds ratio.

	Control (n=382)		IDDVT (n=78)		PDVT (n=79)		Odds ratio for IDDVT vs. PDVT (95% CI)	Significance Testing
Provoked			**49/78 (62.8%)**		**35/79 (44.3%)**			p = 0.025
Plaster	4/381	1.0%	9/78	11.5%	0/78	0.0%	-	p = 0.003
Immobilisation	29/381	7.6%	21/78	26.9%	16/78	20.5%	1.428 (95% CI 0.68 - 3.00)	NS
Surgery	48/381	12.6%	14/78	17.9%	7/78	9.0%	2.219 (95% CI 0.84 - 5.84)	NS
Travel	44/381	11.5%	10/78	12.8%	9/78	11.5%	1.127 (95% CI 0.43 - 2.95)	NS
Hospital admission	64/381	16.8%	20/78	25.6%	15/78	19.2%	1.448 (95% CI 0.68 - 3.09)	NS
Pregnancy	29/381	7.6%	1/78	1.3%	1/78	1.3%	1.000 (95% CI 0.06 - 16.28)	NS
Oral contraception	8/381	2.1%	4/78	5.1%	4/78	5.1%	1.000 (95% CI 0.24 - 4.15)	NS
Hormone replacement therapy	3/381	0.8%	4/78	5.1%	2/78	2.6%	2.054 (95% CI 0.37 - 11.56)	NS
Unprovoked			**29/78 (37.2%)**		**44/79 (55.7%)**			p = 0.025
Varicosities	127/379	33.5%	21/77	27.6%	16/77	20.8%	1.456 (95% CI 0.69 - 3.07)	NS
Obesity	90/380	23.7%	21/78	26.9%	13/78	16.7%	1.842 (95% CI 0.85 - 4.01)	NS
Family history VTE	35/380	9.2%	13/78	16.7%	11/78	14.1%	1.218 (95% CI 0.51 - 2.91)	NS
Past medical history VTE	74/381	19.4%	18/78	23.1%	29/78	37.2%	0.507 (95% CI 0.25 - 1.02)	NS
Thrombophilia	14/380	3.7%	2/78	2.6%	0/78	0.0%	-	NS
Active cancer	11/381	2.9%	3/78	3.8%	7/78	9.0%	0.406 (95% CI 0.10 - 1.63)	NS
Smoking	135/379	35.6%	29/77	37.7%	36/78	46.2%	0.371 (95% CI 0.37 - 1.33)	NS

TABLE 5: Comparison of additional risk factors between all patients with IDDVT, PDVT and controls. Data are described as n/N proportions and percentages. Univariate analysis is used to compare and provide OR. NS = non significant

	Control (n=382)		IDDVT (n=78)		PDVT (n=79)		Odds ratio for IDDVT vs. PDVT	Significance Testing
Intravenous drug use	8/381	2.1%	1/78	1.3%	8/78	10.3%	0.114 (95% CI 0.01 - 0.93)	P = 0.043
Alcohol dependance	28/379	7.4%	4/77	5.2%	11/78	14.1%	0.334 (95% CI 0.10 - 1.10)	NS
Diabetes	53/380	13.5%	10/78	12.8%	9/78	11.5%	1.127 (95% CI 0.43 - 2.95)	NS
Liver disease	12/386	3.1%	5/78	6.4%	3/78	3.8%	1.712 (95% CI 0.40 - 7.42)	NS
Cardiac disease	69/381	18.1%	7/77	9.1%	14/79	17.7%	0.929 (95% CI 0.40 - 2.13)	NS
Respiratory disease	32/381	8.4%	9/78	11.5%	5/78	6.4%	1.904 (95% CI 0.61 - 5.96)	NS
Renal failure	25/290	8.6%	9/74	12.2%	8/64	12.5%	0.969 (95% CI 0.35 - 2.68)	NS
Acute infection	59/380	15.5%	7/78	9.0%	8/78	10.3%	0.863 (95% CI 0.30 - 2.50)	NS
Lower limb trauma	33/381	8.7%	14/78	20.6%	9/78	11.5%	1.825 (95% CI 0.75 - 4.46)	NS
Cerebrovascular disease	27/379	7.1%	7/67	10.4%	8/78	10.3%	0.875 (95% CI 0.30 - 2.54)	NS
Hypertension	180/280	47.4%	40/78	51.3%	28/81	34.6%	1.880 (95% CI 0.99 - 3.57)	NS
Previous Cancer	23/381	6.0%	4/78	5.1%	5/78	6.4%	0.789 (95% CI 0.20 - 3.05)	NS

The key strengths of this study focus on pragmatism and generalisability. Our chosen methodology allowed real world evaluation of an ambulatory DVT service in a busy UK ED. All historical, clinical and aetiological data were collected by non-research practicing emergency physicians, utilising a clinical guideline to aid decision making on a daily basis. Laboratory tests were ordered by clinicians only when deemed to be directly relevant and appropriate. Vascular ultrasound scans were performed and interpreted by technicians external to the research team, with appropriate clinical data. Results were given in real time and for clinical use rather than research interest. As a result this study is a genuine reflection of UK practice. Measurement bias was also minimized within data collection, by limiting researcher contact with patients: any results analysed arose from direct service provision and thus could not be manipulated or altered as a result of subconscious bias to support a specific hypothesis.

In addition, we chose to define *acute* venous thromboembolic disease as that reported by protocolised whole leg duplex CUS as reference standard. This decision was based on evidence citing the increasing utilisation of complete leg CUS and the pitfalls of contrast venography as a validating gold standard [28-31]. We deliberately chose this option to increase the generalisability of our findings: contrast venography is a test in decline and one rarely utilised during the UK diagnostic process.

Comparison with previous research raises several interesting points for discussion. Firstly, the pre-test probability of DVT in our ambulatory cohort was 8.3% on initial clinical encounter. This figure is much lower than the often cited 20% [32]. Indeed, Wells *et al*, Galanaud *et al* and Gibson *et al* have reported pre-test probabilities of 16%, 27% and 38% within their respective study cohorts within the last 15 years [9, 18, 33]. These figures naturally vary to an extent dependent on scanning protocol and confirmatory testing, but remain between 2 – 5 times that of our population. This perhaps reflects both methodological issues and contemporary change in practice. We deliberately classified patients with chronic disease into a separate category at analysis and subsequently excluded these patients from comparative analysis. The exclusion of all inpatients reduces our pre-test probability even further. Inpatients are a high-risk group with associated increased prevalence of disease.

However, the drop in our pre-test probability may also reflect changes in practice. A national UK political agenda on venous thromboembolism and an increasing body of

literature has combined over the last decade to raise awareness, both in patients and clinicians. This may well be leading to a reduction in incidence due to increased rates of presentation and early definitive investigation. This concept has been recently discussed in the literature [34].

A second comparison to published work follows naturally with the data presented by established registries [9, 35]. Our findings support the previously described general association between transient risk and IDDVT, but also go one step further to demonstrate a significant association with provocation. This is an important concept as it may well impact on management decisions when faced with an individual IDDVT patient and therapeutic uncertainty.

Interestingly, our data also supports that seen previously suggesting an association between varicosities in the presence of suspected DVT and an eventual diagnosis of distal, rather than proximal deep system disease.

Our findings have several potentially important meanings. For thrombosis clinicians operating ambulatory DVT pathways, our data firstly establishes that IDDVT is a prevalent and ongoing problem, with an equivalent incidence to proximal disease. Analysis of risk factor and clinical presentation data also supports the theory that distal disease differs significantly to proximal: patients with IDDVT seem to present in a different clinical manner and with a different provocation profile. Although this may be intuitive, our data is the first clear publication to demonstrate both clinical and aetiological differences.

While diagnosis and treatment of IDDVT remains controversial, our findings have several implications for the future direction of research. Firstly, with regard to diagnostics, we have demonstrated several clinical variables strongly suggestive of IDDVT at presentation. This data could be used to immediately assess the merits of progression to whole-leg CUS or withheld repeat imaging, following a negative initial proximal CUS. Such a strategy may afford the benefits of early IDDVT detection, whilst minimising the cost and inconvenience of a diagnostic pathway reliant on serial imaging. Further diagnostic study is practice dependent. Those centres currently omitting anticoagulation in IDDVT may find use in a modified clinical decision rule aiming only to identify proximal disease. Those centres currently anticoagulating may

benefit from evaluation of different D-dimer and other laboratory value cut points, given the lower levels seen with distal disease in our cohort.

Secondly, is the issue of intervention. Recent guidance has reintroduced the concept of stratified decision-making in confirmed IDDVT [36]. Anticoagulant therapy is recommended only for those at risk or acutely symptomatic. Our results suggest that IDDVT is commonly provoked, with limited clinical signs (other than pain) and minimal inflammatory response. This data has the potential to be incorporated into clinical decision making regarding therapeutic management: patients with unprovoked IDDVT, severe symptomatology or those with laboratory values in keeping with proximal disease may benefit from immediate anticoagulation, based on supposition of high risk. Prospective study of this theory is required.

Our study does not address the diagnostic accuracy, therapeutic efficacy or cost effectiveness of a pathway that incorporates full leg compression ultrasound and treatment of IDDVT. Although recent systematic reviews have addressed several of these issues [37] there are still many questions left unanswered, as demonstrated by the ongoing variability in practice. It is essential that further rigorous trials are conducted and service provision evaluated, in order that care can be standardized both nationally and internationally. Until further evidence is available, we echo the call for continual robust service evaluation as the best means of capturing accurate data on the incidence, nature and pathology of IDDVT [2].

Limitations

Our main limitations stem from the choice of methodology for this project. The decision to perform a prospective service evaluation resulted in no opportunity to consent patients for follow up, a potentially increased proportion of missing data and a fixed sample size. Thus the study was not adequately powered to detect any estimated difference in specific characteristics between groups. Despite the worldwide use of whole leg ultrasound, concerns regarding limited sensitivity in comparison to contrast venography also remain. Therefore despite a consecutive sample, our IDDVT cohort may not include all cases. We would argue that it includes all cases of interest: those patients testing positive for IDDVT using an internationally agreed protocol including pre-test probability scoring, d-dimer assay and duplex

ultrasound performed by an expert vascular scientist.

Although our data is generalisable and gives a contemporary insight into the burden of suspected disease in the average UK ambulatory DVT diagnostic service, restriction of data to one year may possibly have limited the analysis. This may be an explanation for failure to reproduce the strength of association seen in previous studies.

A consensus definition of provocation in VTE unfortunately fails to exist. There are numerous alternatives used throughout the literature and ongoing discussion as to whether previous definitions should be reconsidered [38]. We chose the criteria provided by the recent NICE guidance [20] as contemporary, relevant, reproducible and appropriate. Until other criteria are published and agreed by leading authors, we would suggest any criteria with face validity is reasonable providing it is defended, explained and reproducible with ease.

The lack of follow up hindered our ability to examine differences in outcome for patients with both acute disease and negative ultrasound. Three month review, such as that performed by the OPTIMEV / RIETE investigators would have allowed useful comparison of symptomatology, prognosis and the occurrence of missed disease. Our primary data provides strong argument for development of a UK registry with prospective inclusion and consent, to allow ongoing quantification and research on this expanding cohort of patients.

Finally, as a consequence of limited event numbers we were only able to perform univariate exploratory analysis. Although this highlighted interesting features supporting previous assertions, firm conclusions cannot be drawn from our data. Further case collection and analysis will allow multivariate regression and more robust assessment of clinical variables with the associated outcomes of both proximal and distal DVT.

Conclusions

In our ambulatory cohort with acute lower limb thrombosis, patients with IDDVT accounted for half the disease burden and varied significantly from those with proximal disease regarding provocation and clinical presentation. These findings support the premise of IDDVT as a disease occurring in a different group of patients and with different clinical features, compared to proximal. Further observational and

therapeutic research data is needed, in order to delineate prognosis within this group and to tailor management decisions.

Acknowledgements

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Discussion

Introduction

On commencement of this research project, a series of aims were set out with regard to increasing the understanding of IDDVT and investigating the benefit of differing therapeutic options. A series of five papers have been produced which directly address these aims and furthermore highlight the relative frequency of presentation. These papers represent a key step towards further understanding the nature, clinical presentation and clinical sequelae of IDDVT.

The discussion below is a reflection on the overall results, strengths and limitations within the project as a whole. In order to avoid repetition of those discussion points raised within each individual paper, this synopsis will focus on generic themes within the work and updated aspects since conclusion and closure of the trial.

Statement of Principal Findings

This project proposed six direct aims at outset and four associated null hypotheses. All of these have been addressed with prospective research. In addition, prospective data collection has afforded transparent and pragmatic evaluation of the disease burden with IDDVT and the demands on a modern NHS emergency service. Principal findings can be summarized as follows:

Withholding anticoagulation in patients with suspected DVT following negative whole-leg CUS reported by a vascular sonography service appears to be safe, with a negligible incidence of venous thromboembolic events at three months. As such, the first null hypothesis can be rejected. Technical failure rates with this approach are approximately 1 in 10 and several patient characteristics suggest an increased likelihood of technical failure (obesity, acute infection, immobilization).

IDDVT is a persistent problem and accounts for approximately half the disease burden of acute DVT in ambulatory patients.

Clinical presentation differs significantly from that of proximal disease regarding provocation, pain, leg swelling and laboratory markers of inflammation. As such the second null hypothesis can be rejected.

Further interventional research on IDDVT appears feasible, with a reasonable recruitment rate and protocol compliance seen within our prospective randomised cohort.

Preliminary modern randomized controlled trial data suggests that symptomatic deterioration and local propagation are significantly reduced by therapeutic anticoagulation. Further study in the same patient group suggests that rates of proximal extension and/or pulmonary embolism trend towards reduction. Given the sample size and lack of statistical significance achieved in the latter comparative aspect, the third null hypothesis cannot be rejected.

Lastly, no significant difference was seen between rates of major, minor or nuisance bleeding between IDDVT patients treated with therapeutic anticoagulation or conservatively managed. As expected, there was a trend towards increased minor bleeding rates in the anticoagulated cohort. This was a secondary outcome within the therapeutic trial and as such these findings are underpowered and at risk of type 2 error. As such, the fourth null hypothesis cannot be rejected.

Strengths of the research

Introduction

The key strengths of this project are highlighted through discussion of several specific methodological aspects. All aspects of each study were designed to ensure that results would be valid, generalisable and easily reproducible in other centres. Also, we aimed to provide novel data on the topic through sample sizes superior to those within the previous literature and assessment of hitherto unexplored topics. These themes carry through each individual paper. As such, they will be considered in turn.

Internal Validity

Of utmost importance to a project of this nature is the definition of disease. This is especially relevant when the sensitivity of a diagnostic technique is questionable and a subjective element exists to reporting of imaging. We chose to rely on diagnosis through whole-leg CUS reported by a dedicated vascular service for all aspects of the project. This could be criticized for several reasons. The most contemporary diagnostic meta-analyses quote a sensitivity of whole-leg CUS for IDDVT between 73 and 75.2% [156, 166]: the potential for false negative results is therefore an issue and could lead to potentially inaccurate quantification of burden. Likewise, specificity for modern triplex techniques has been estimated at 94.3% (95% CI 92.5 to 95.8) [166]. This renders the technique susceptible to false positive diagnoses for every 1 in 20 patients without the disease, which could lead to falsely reassuring rates of complication in prospectively evaluated patients. This is also an important point raised by those supporting serial proximal CUS - with a high false positive diagnostic rate, the risks of anticoagulation in IDDVT are starkly apparent [19].

However, we believe the use of whole-leg CUS as a pragmatic reference standard is a particular strength to our study. Contrast venography has not been performed at the authors institution for over 20 years, and its status as reference standard has been called into question since the late 1980s [154]. Throughout this thesis attention has been drawn to the multiple caveats, including technical failure, inability to cannulate pedal vessels, interobserver variability, thrombotic complications, patient discomfort

and high level of resource use. As such, contemporary clinicians are making decisions based directly on compression ultrasound results with very few centres resorting to confirmatory phlebography. This approach is ratified in recent international guidance [11]. Thus, our diagnostic technique mimics that performed around the world. We chose to prospectively evaluate patients based on the whole-leg CUS results obtained in routine practice and as such have studied epidemiology, aetiology and complication rates within this group. We have consequently measured that which we set out to measure: the burden of disease and the complication rates seen with IDDVT in symptomatic ambulatory patients as diagnosed by a pragmatic, internationally adopted standard performed within a routine clinical service.

In fact, the concerns regarding sensitivity and specificity of whole leg CUS for IDDVT diagnosis only serve to make the majority of our findings more robust. Should we have had a significant number of false negative diagnoses in the ambulatory observational cohort study for example, we would expect complications within a percentage of these patients. In fact we saw very little in the way of VTE sequelae, in keeping with previous literature. Likewise, in the prospective RCT a significant number of false positive diagnoses would render a reduction in overall propagation/embolisation, as patients *without* disease would be receiving serial follow up and dilute the overall complication rates in both groups. In fact, we saw a significant increase in overall propagation and symptomatic progression with conservative management and a serious complication rate (albeit non significant) in keeping with prior estimates. Thus our findings are actually more relevant in light of internal validity concerns. They also not only assess the scientific hypotheses at hand, but their assessment within a standard modern framework.

External Validity / Generalisability

It also follows from the above that our findings are directly applicable to front line services. There are several key reasons for this. Firstly, this project is one of the few to utilize an external dedicated vascular laboratory within a routine clinical service and base decision-making on objective reporting by non-clinicians. This was not a tightly controlled exploratory study on many levels and thus serves to provide a pragmatic representation of ambulatory DVT. Not only did this make our findings

more generalisable regarding technical failure, access delay and disease burden, but in addition served to minimize both measurement and assessor bias. The result is a series of data that is hopefully representative of any ambulatory population utilising sonographer performed whole-leg CUS for management of suspected DVT. The most recent systematic review of whole-leg CUS for diagnosis of acute DVT included seven studies deemed suitable for meta-analysis [177]: of these, only one of the seven used sonographer performed results to guide clinical decision making [43]. These images were all consequently reviewed and reported by a vascular radiologist prior to clinical management. Another study utilised radiology trainees (residents) to perform whole-leg imaging, with subsequent reporting via vascular radiology consultant staff [44]. The remaining 5 studies all based management decisions on whole-leg CUS performed and interpreted by dedicated vascular physicians, following clinical assessment. Specialist training and experience in sonography ranged from 3 months to 8 years [41, 42, 170, 267, 268]. This methodology presents major issues with generalisability and the clinical process under evaluation differs to that performed in the majority of the UK. All physicians in the above studies performed sonographic examination within the context of clinical assessment. They had access to past history, laboratory data and a recent clinical encounter. This could easily allow subconscious or conscious bias to influence the result of the scan. There is consequent strong potential for bias within the reported results. In addition, the studies utilising sonographic images interpreted by a vascular radiologist raise important concerns regarding delay to diagnosis within a UK system. Urgent consultant reporting is often unachievable within a pressurized NHS framework. Our study renders these concerns negligible by providing objective sonographic reports via technicians with no formal clinical training and little access to patient data. All clinical management decisions were also based on immediate results. Thus our findings are essentially more generalisable than previous, more pragmatic and potentially easier to reproduce outside of a trial setting.

Secondly, the project was conducted with a pragmatic approach rather than through a tightly controlled exploratory study. Thus all data was collected within the context of routine clinical assessment by non-research clinicians and outcomes were based on sonographic evaluation within a routine protocol. Multiple NHS services were engaged within the context of the project including orthotics, anticoagulation clinic,

pharmacy, and district nurse support. Although many were aware of the RCT aspect to the project, none had any direct stakeholder involvement in the research or responsibility within the project. As such these results should be a pragmatic assessment of ambulatory care within a standard NHS framework and further increase generalisability. For example, there was a reasonable delay within the study context to receive both an anticoagulation clinic appointment or to be fitted with grade two compression stockings. Within a tightly controlled protocol, this delay may have been negligible but would result in limited generalisability to current practice.

This is reflected in many other aspects of the project results. The average time in therapeutic range (TTR), compression hosiery compliance, missing data and loss to follow up are all reflective of a standard ambulatory population managed routinely within the North West of England. The decision to make generalisability robust at the expense of some internal validity was taken a priori. There is good evidence to demonstrate the value of compression stockings, sensitivity of sonography and the benefits of a high TTR in the context of venous thromboembolism [166, 225, 269]. This project was not looking to further assess these measures: rather it was looking to evaluate an established service and compare management strategies within the confines and restrictions of standard NHS care.

Thirdly, the project tried to focus only on outcomes of direct clinical relevance. Symptomatic re-attendance, songraphic propagation and prospective venous thromboembolic complication rates are all issues that directly affect clinical decision-making. Although it could be possible to perform baseline/serial pulmonary imaging for silent PE this is an outcome unlikely to ever be used in practice and questionable regarding influence on therapeutic management. The same could be said for sonographic assessment of venous reflux/stasis seen with previous natural history studies [138], or potential surrogate outcomes for later development of post thrombotic syndrome. The protocol within this project allows 2-year follow up of recruited patients using a validated scale for assessment of PTS: we saw no reason to attempt prior assessment. The results of the project should thus be more generalisable to practising physicians.

Finally, the open label design of the project in tandem with the intention to treat analysis can be considered strengths, regarding generalisability of results. One of the key clinical issues potentially encountered over the next 5 years will no doubt be the variation in practice regarding IDDVT. Several observational studies have already demonstrated heterogeneity in management of this relatively common problem [104, 142]. With recent guidance suggesting serial sonographic follow up as first line management for IDDVT [148], a change in practice may arise for many clinicians. This is especially pertinent given the on-going recommendations from other national guidelines in favour of anticoagulating IDDVT [12].

This project not only evaluated the evolution of IDDVT in patients randomized to conservative management, but also the influence of other clinicians over their treatment within the following three months. Rather than manage patients to a strict protocol, we chose to observe therapeutic changes enforced by other practitioners in order to provide an assessment of how conservative management of IDDVT may work in practice. This naturally resulted in a degree of allocation crossover. However, despite this our absolute risk reduction remained significant for overall propagation and sizeable for the composite outcome of serious complications. These findings imply that the benefits of anticoagulation may be even larger than reported and also promote the generalisability of the work.

Reproducibility

Another key strength to this project is that of reproducibility. All studies were conducted within the context of a standard NHS ambulatory framework. A minimal grant was obtained in order to perform additional ultrasound scans in recruited patients. The comprehensive local research network was utilized in order to provide research nurse support for trial logistics. As such, minimal assistance would be required to attempt validation of these findings.

As a feasibility work, the randomised interventional trial was designed to be replicated and conducted at other sites with proof of pilot data. We have seen no reasons why this could not be achieved. Any service using whole-leg CUS within the UK is likely to have results reported by sonographers or radiology staff. Providing

reporting delays can be minimized and limited clinical information is available to the service, assessor bias remains negligible with either strategy and both are inherently reproducible. Indeed, any service which utilized whole-leg CUS should already be actively monitoring, auditing, studying and reporting their findings as recommended in recent literature [22]. It is a small step from here to approaching patients for participation in either observational or interventional research.

In addition, all of the research performed was conducted within the confines of standard NHS care. No acute specialist thrombosis service or dedicated vascular physicians were involved within the project, other than in an advisory role. Simple objective outcomes were used, which are of direct clinical relevance to practising clinicians and should be fairly simple to ascertain in any other setting. Indeed, any service providing whole-leg CUS or treating IDDVT should ideally be monitoring all patients for a period to observe complications of treatment and/or recurrent disease.

The real reproducibility of this project however, stems from an essential lack of intervention within the RCT aspect. Even if randomized to therapeutic anticoagulation, patients should only ever receive standardized anticoagulation within a normal NHS setting. The open label nature of the trial and licensed pharmacology renders the resources needed for administration, follow up and pharmacovigiliance minimal. The only onerous aspect of the trial is that required for screening, given the increasingly low pre-test probability encountered with modern practice. This is a simple staffing concern and should in no way affect reproducibility.

Sample size and Novelty

A further strength to the project is that of size and novelty. Much of the work is new to the field and several aspects of the project constitute larger samples than any published study to date. This work is the first to directly address clinical presentation of IDDVT and compare it to proximal as a primary outcome. As such we also have the largest dataset for comparison of multiple key clinical presenting features.

Although the pool within the observational cohort study is smaller than many previously conducted, our group of patients with a high clinical pre-test probability

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represents the largest sample prospectively followed to date. This addresses the call for further research [177] and adds significantly to the previous literature.

The randomized controlled trial conducted on IDDVT management is to date the largest comparing undifferentiated disease. The only previous study recruited 51 patients and is subject to multiple methodological concerns. Although further research in this area is on-going, all other projects are still in recruitment phase at the time of thesis completion.

Comparison to other published work

The IDDVT disease burden, population demographic and risk profile within this project compare favourably to previous published research [14, 17, 21]. A single notable difference is the inclusion of inpatients within previous reviews, who were excluded from the project due to the confounding element of regular administration of thromboprophylaxis.

The event rate following withheld anticoagulation in patients with negative imaging in our cohort was very similar to that defined at previous meta-analysis [177]. The demographic and risk profile of the same patients were also near identical to cohorts within previous published research [41, 43, 44, 170, 268]. As such, the internal validity of the project is highlighted. These findings support the previous assertion that withholding anticoagulation based on a single whole-leg CUS is safe and carries a low rate of failure. This may result from the natural history of disease: missed cases are likely to be small thrombi with minimal clinical sequelae. Either these thrombi will spontaneously abort as has been reported or persist with minimal symptomatology. It indeed appears rare that missed thrombi are large enough to propagate or develop worsening clinical symptoms.

The rate of technical failure reported within our prospective cohort is slightly higher than noted previously. Schellong [42], Elias [41] and Gibson [164] report technical failure rates of 1, 1.4 and 5% respectively in their prospectively studied cohorts. These lower rates are most likely a result of scanning within the remit of clinical assessment by a vascular physician. With preceding history, clinical examination and

laboratory work, subconscious bias could easily influence the scan result in borderline cases. This project utilized a sonographer reported protocol with the aim of making the reference standard as objective as possible. Although this provides a greater degree of external validity, it is not necessarily surprising to see it come with a higher rate of technical failure.

The prospective service evaluation findings again compare well with both epidemiological studies and the scant previous literature regarding clinical presentation. The findings of no difference in symptom duration between proximal and distal disease have been reported previously in a small retrospective cohort [137]. In addition, subgroup analyses from smaller studies have already highlighted the variation in d-dimer result stratified by location [131] and more robust research the reduced performance of the original Wells score for prediction of IDDVT [111, 118, 131]. Our data adds further external validation to these findings in addition to novel comparison of pain scores, laboratory data, provocation and limb swelling at presentation.

Although data from this aspect of the project trended towards association of transient risk profile with IDDVT, we failed to reproduce the strength of association seen in previous research [38, 39]. However with transient risk collated as provocation using predefined criteria, the difference between proximal and distal disease reached statistical significance. This is a step forward in the analysis and understanding of risk profile stratified by location in DVT. It also adds further weight to the assertion that IDDVT is a distinct disease entity to proximal and should be managed as such.

The composite event rate in the randomized trial aspect of the project compares favourably with prior narrative reviews [21]. In addition to providing contemporary data within an ambulatory population, these findings also serve to remind us of the inherent risks of conservatively treated IDDVT: symptomatic progression, early pulmonary embolism and delayed proximal propagation were all seen within the context of the trial. Of note, half the composite events in our cohort would have been essentially missed using a serial proximal CUS strategy (One PE at day 3, one delayed propagation at day 21). This is potentially important when considering the cost effectiveness of a strategy mandating return appointment, assessment and

ultrasound. It should also be noted that our event rate in the anticoagulated cohort was lower than previously reported [21]. This may be a reflection of the small sample size (major bleeding rates are currently estimated at between 1-2.5%) or potentially the open label design resulting in less re-attendance/further imaging. Clinicians may well have been reluctant to image respiratory symptoms for a patient already on warfarin for example. However, low complication rates with anticoagulation are increasingly seen within the modern literature. Recent publications suggest that any degree of anticoagulation may be effective in IDDVT, reporting low rates of propagation with reducing doses, prophylactic doses and short courses of LMWH [58, 195, 219].

Whilst discussing the contemporary literature, it is worth considering potential reasons for the higher complication rate seen within this project, compared to recent studies. In their blind, prospective evolution study Palareti *et al* record a composite event rate for conservatively managed IDDVT of 7.8% (95% CI 3 to 17) [171]. Although this is lower than the proportional composite endpoint seen in ACT, it is notable that our result lies within their 95% confidence interval. Also, if anything the rate of complications in Palareti's cohort is likely to be an underestimate. These patients received no clinical follow up other than a repeat proximal scan at day 5 to 7. It follows that more propagations may have been apparent with additional imaging or standardized clinical review. No assessment was made for calf vein extension or worsening symptomatology. Schwarz *et al* also document a lower rate of complications, noting asymptomatic propagation at day 8 and 31 in two patients within their conservatively managed cohort of ICMVT [201]. They record a complication rate of only 3.8% with no confidence intervals. However, the limitation here to ICMVT (omitting study of axial calf vein thrombosis) immediately renders the population at low risk of progression [18, 55]. This is notably supported by the ACT project data, with a statistically significant difference seen in the rate of propagation stratified by initial thrombus location. Additionally, the population in the Schwarz study was acknowledged as representing a "rather low risk population for thrombosis" regarding baseline and on-going risk for progression. For both of these reasons, the low rates of complication compared to results from the ACT study are understandable.

Lastly, some consideration should be given to why rates of overall propagation and pulmonary embolism in this project were lower than that seen in the single previous randomized controlled trial on the topic, by Lagerstedt *et al* [172]. In this study, despite an initial 5-day course of IV heparin, 5/28 patients had proximal extension and one suffered pulmonary embolism confirmed by V/Q scan. This gives an acute complication rate of 21.4% (no confidence intervals provided, but subsequent estimates using the Wilson method can be calculated at 95% CI 8.3 to 39.4). An additional 2 patients propagated locally within the calf, for a total 29% recurrence rate within 90 days. Whilst the overall propagation rates from the ACT data are similar to these estimates, the rate of proximal propagation is almost half. There are several potential reasons for this difference. Firstly, the evidence base in support of grade two compression stockings or anti-inflammatory medication for conservative treatment had not been established at the time of the Lagerstedt trial: as such patients randomized to no warfarin received no additional care. Secondly, patients randomized to conservative treatment had twice the prevalence of previous thrombotic disease. Thirdly, multiple additional scans were performed, including a final phlebogram at day 90, which increases the chances of detecting asymptomatic propagation. Lastly, inpatients with on-going risk were included within the study. All of these factors are likely to increase the complication rate, as well as the use of prothrombotic phlebography over 4 times in 90 days.

Of note, our rate of complications almost mirrors that suggested by Lohr *et al* in 1995 [197], following their natural history study of 192 patients with isolated calf vein thrombi. Propagation to the popliteal vein or above was seen in 10.9% patients in this research, despite heparinisation of over 23 participants at some stage during follow up.

Limitations

Individual limitations to the project have been discussed within relevant papers and will not be repeated. Several limitation themes run through the project and are worthy of further expansion.

Firstly, all studies within this project were conducted at a single centre. Thus the population characteristics and demographic may limit the generalisability of the results. In addition, we used a dedicated vascular laboratory with over 10 years of whole-leg CUS scanning experience. Although this provided objective data, it may well be the case that such a service would take time, investment and effort to establish elsewhere. Indeed, this is a cited caveat with whole-leg CUS noted by several authors previously [16, 19]. In attempt to render our assessment process transparent and reproducible, we utilised a standardised protocol performed by sonographers trained to specific accreditation standards through a national body. Standard imaging machines were used and scans take approximately 20 minutes to complete and report. As such, there is no reason other NHS trusts and potentially international institutions could not replicate the training programme, protocolised imaging and eventual service provision.

Within this project the decision was taken early not to confirm suspected IDDVT by venography, for the reasons previously stated. Although there were multiple advantages to this decision, this may have compromised internal validity to a degree. Recruitment, data entry and follow up were principally completed by the MD student within the project timeframe. As such a potential for selection and assessor bias is inevitable within the project. This was minimized through consecutive recruitment, the use of assessor blinded ultrasound, pharmacovigilance and trial monitoring throughout the study, use of independently adjudicated outcomes and oversight of the RCT by a trial steering committee. The project was also designed to assess objective outcomes as far as possible within the study context. Outside the trial protocol, further vascular or pulmonary imaging was requested, performed and interpreted by non-research clinicians within the context of standard practice. In addition, source data verification was performed by the Research and Innovation department several times prior to trial termination, through the clinical governance lead. A trial database was subsequently created and locked prior to statistical evaluation. This ensured quality and accuracy of the dataset.

This project did not set out to evaluate cost effectiveness of whole-leg CUS or a direct comparison of serial proximal against whole-leg CUS for the evaluation of suspected DVT. Although this is not a limitation per se, it is a potential concern with the project.

Many authors consider that only a diagnostic randomised controlled trial will provide the necessary answers to overall effectiveness, patient satisfaction and clinical benefit of the ideal IDDVT management strategy [18, 194]. However, there is a reasonable argument that to undertake such trials without accurate estimates of IDDVT complication rates would be unfair to patients. This issue is further discussed within the future work section.

This work focuses only on ambulatory patients with suspected disease and their management through an emergency medicine service. By default, our work may be limited in its applicability to international vascular centres or specialist thrombosis departments that manage VTE independently. This project design was chosen in order to externally validate previous findings in ambulatory thrombosis patients managed within the ED and to conduct new research within a contemporary VTE management framework. The ED is fast becoming the front door of the hospital VTE service. As such, contemporary research must be applicable, valid and generalisable to that specific setting in order to allow clinicians to practice evidence based medicine with confidence.

Lastly, this project has used phased warfarinisation as gold standard management of acute disease throughout the study period. The advent of New Oral Anticoagulant (NOAC) medications and prospective evaluation with robust trial data has led to their increasing use in clinical care. If recommended treatment algorithms change to use these drugs our findings may be considered out-dated. However, during the ACT trial design and conduct, these drugs were unlicensed for acute VTE. The recent NICE appraisal and recommended cost effectiveness in acute VTE creates further opportunities for research, as will be discussed in a later section of the thesis [270].

Meaning of the Study

This project set out to explore several aspects of IDDVT epidemiology, diagnostics and therapeutics. The findings have several potentially important meanings.

Firstly, and perhaps most importantly, we sought to assess whether IDDVT is a real problem within acute ambulatory diagnostic DVT care. The prospective service evaluation has established that it is, with IDDVT constituting half of the disease burden - a figure replicated throughout international literature. Thus the project establishes the need for further understanding of the condition and the diagnostic / therapeutic options available, given its relative prevalence.

Secondly, the observational cohort study has externally validated previous safety literature, within an ambulatory ED based service utilising sonographer reported whole-leg CUS. This is the first study to report outcomes following the decision to withhold anticoagulation, taken by an emergency physician and based solely on a single sonographer reported CUS. These findings confirm the safety of whole-leg CUS, while accentuating the caveat of a higher event rate in patients deemed to be at high clinical risk prior to imaging. We have also explored technical failure and the potential causes. Put together, these two findings have interesting implications for an adjusted management strategy. Serial proximal CUS may be the imaging modality of choice in those with an increased pre-test likelihood of technical failure and/or those with high pre-test probability. This could be easily achieved within a whole-leg CUS pathway and would perhaps reduce unnecessary delays and returns, while maximizing safety.

Third, prospective study has added to the literature supporting segregation of IDDVT and proximal disease as separate entities. This is important for several distinct reasons. These findings reinforce the case against extrapolation of proximal DVT study results and suggest an on-going need for further randomized controlled trials looking specifically at IDDVT. In addition, such data raises further questions about long term IDDVT management, including duration of therapy, need for clinical review and risk assessment to delineate prognosis.

Fourth, we have established the feasibility for further prospective randomised controlled trial data. Patients in our screening cohort were happy overall to participate, with allocation crossover rates below the predefined feasibility criteria during follow up. This establishes the potential for further clinical trials to occur and

provides accurate contemporary data for sample size calculations and future trial design.

Lastly, our randomized trial results highlight the short-term risks of conservatively managed IDDVT. These findings are in contrast to other observational and interventional studies published recently on the natural history of IDDVT and perhaps reiterate the potential consequences of propagation in a clearer light. The findings also demonstrate a low rate of anticoagulant related complications within our cohort. This trial can be used as the highest level of evidence to date regarding risks and benefits of anticoagulation in ambulatory IDDVT for clinical decision making. The findings can also be used to delineate the need for further trial data and adequate powering of future trials.

Summary of Future Work

Whilst this project has established the need for segregation of therapeutic IDDVT trials, there is still on-going debate regarding ideal diagnostic strategy in this area. Thus several key themes emerge for future study.

Further observational research

While our work has suggested several factors that trend towards an increased likelihood for propagation in conservatively managed IDDVT, we have been unable to offer any definitive conclusions. The potential use of a 'risk adopted' strategy is endorsed and recommended [19, 22, 93], but no authors have been able to provide a reliable predictive approach.

Further work is warranted here, to record risk profile at baseline and on-going clinical features associated with propagation. Any authors including IDDVT patients within *randomized prospective* trials should be able to provide further data, providing adequate data is collected at baseline and through clinical follow up. There is also a potential for pooling of data and meta-analysis to produce likelihood ratios for individual characteristics and eventual derivation of a decision rule. This is a potential area to explore with publication of the impending CACTUS data [260], in combination with that from the ACT study.

Further therapeutic randomized controlled trials

Further external validation of our work is urgently needed to confirm complication rates in conservatively managed disease and ratify the argument for/against anticoagulation. Such additional trials should also be powered to detect significant complications such as major bleeding. Although there are several methodological approaches here, we believe our composite outcome (which includes major bleeding) is perhaps the most pragmatic approach: in a large study clinicians would be able to directly see which group benefits regarding overall reduction of composite serious events with untreated IDDVT. This data could then be used to inform management decisions for individual patients.

Additional work must also focus on duration and strength of treatment. Limited data have suggested reduced anticoagulant regimes to be equally efficacious to 3 months duration [219]. Further trials have suggested low rates of propagation with reducing regimes and even prophylactic dose anticoagulation [58, 195]. If anticoagulation can be limited in duration or cost with continuing effectiveness in prevention of IDDVT complications, the risk/benefit balance will begin to swing in favour of treatment through reduction of complications. In patients without cancer, the majority of bleeding complications related to anticoagulation have been shown to occur during the first three months of treatment [271]. If both the period and strength of anticoagulation could be reduced in the early stage, it follows that adverse events may decline significantly.

There is also a pressing need to evaluate the NOAC drugs in the management of IDDVT. Although reasonable contemporary data has been published regarding their efficacy [272] and effectiveness [273, 274], all clinical trials to date have excluded IDDVT. There is real merit in the theory that short term NOAC treatment in IDDVT may offer equally reduced thrombotic complication rates to warfarinisation, but without the short term major bleeding risk seen with loading of phased oral anticoagulation. Their use would also negate the onerous monitoring and re-attendance program. Reduction in hospital appointment times, transport costs, serial medical review and time off work for patients may render the increased outlay cost effective. This needs prospective study and robust evaluation, with eventual direct comparison against other therapeutic options.

Diagnostic randomised controlled trials

Once an ideal management strategy for IDDVT has been derived, additional work will need to focus on comparison of diagnostic process. This would evaluate the overall advantage of diagnosing and treating IDDVT against a method that omits examination of the calf veins. Diagnostic randomized controlled trials have recently been proposed as the 'final frontier' [275] and provide valuable data on the effectiveness and safety of interventions. The enigma of IDDVT is a perfect scenario

for such trials and two have previously been attempted [164, 170]. However, these prior studies have failed to evaluate all necessary patient outcomes.

In order to ascertain the effectiveness of a diagnostic protocol that searches for and treats IDDVT, certain methodological concerns must be addressed. Firstly, management of IDDVT must be standardized: whether this should include serial sonographic follow up for selected low risk patients is debatable. Secondly, outcomes must include clinical as well as radiological progression: quality of life surveys, serial pain scoring, mobilization and late development of post thrombotic syndrome must all be robustly assessed in all patients. Lastly, a health economic analysis conducted alongside clinical review is mandatory: this would address the on-going uncertainty regarding the overt and covert risks of treating IDDVT and balance this against the prevention of harm. Such an analysis would also answer the recent call from NICE regarding further assessment of cost effectiveness for whole-leg CUS in the management of suspected DVT [13].

Conclusion

In conclusion, IDDVT is a prevalent issue within ambulatory management of suspected DVT and differs significantly to proximal disease. Further interventional research on the topic is feasible, ethical and urgently needed in order to provide an evidence based management strategy.

Throughout this thesis I have attempted to delineate the extent of the problem, visit the aetiology, assess diagnostic strategy and obtain contemporary complication rates with variable therapeutic regimens. The ACT project has provided contemporary and methodologically robust data to advance understanding of all these areas and further inform the design of future trials. The need and potential strategy for future research has been explored and a prospective research plan drafted to facilitate on-going exploration of this issue.

This thesis has subsequently provided novel data on the topical matter of IDDVT and addressed all aims within the study project.

Appendix 1: Study documentation for the Anticoagulation of Calf Thrombosis (ACT) Project

1.1   **Patient Information Sheet for the ACT Project: part one**

1.2   **Patient Information Sheet for the ACT Project: part two**

1.3   **Case Report Form for the ACT Project**

1.4   **GP letter at patient recruitment for the ACT Project**

<u>Patient information Sheet</u>   Rec Ref: 10/H1008/97

The **A**nticoagulation of **C**alf **T**hrombosis (ACT) Study

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Part One

What is the purpose of the study?

A calf thrombosis is a blood clot in the leg, below the level of the knee. At the moment, we do not have enough research to be sure on the best way of treating this. Some hospitals in Greater Manchester will treat the clot with blood thinning drugs. These drugs carry their own risks. Other centres will treat with stocking supports and reassess the leg in 7 days time, treating only if the clot gets larger.

In the studies so far, both of these methods have roughly the same rate of complications. Nobody has performed a trial large enough to tell if one method is better than the other. Our research is aiming to try and find out which method of treatment is best. We are also trying to make sure that we are diagnosing all calf blood clots correctly.

Why have I been chosen?

You are being investigated for suspected deep vein thrombosis (DVT). There is a chance that you may be diagnosed with a calf DVT when you have your ultrasound scan. There is also a chance that your scan may be negative or inconclusive. If any of the above apply to you, we will approach you to participate in the study.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are free to withdraw at any time. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care that you receive.

What will happen to me if I take part?

If your ultrasound test is negative, you will simply be contacted at three months to ensure you have had no further problems. If we have any problems contacting you directly, we will liaise with your GP. We will also look at your hospital records to ensure you have not returned with problems over the study period. No further appointments will be issued as standard, but we will be happy to see you if you would like.

If you have a calf thrombosis on ultrasound, the trial involves different treatments. Before you enter the trial, a researcher will ask you some questions to make sure you are suitable. After this you will be allocated to one of two treatment groups. The allocation is random, in order to allow us to fairly compare the two types of treatment for this condition. You will either receive blood thinning drugs and stocking supports for three months, or receive stocking supports on their own. Either way you will have a repeat leg scan in 7 days and 21 days time, and see a doctor after each scan. Treatment lasts for 3

months, after which we would like to examine you one last time. We would also like to contact you after 2 years. This is to look at the long term effects of the two different treatments and see if they differ.

Some of the above scans and assessment would be extra to what we normally do. For example, the scan at day 21 is in addition to normal care in the region. The study is performing extra scans and examinations in order to ensure that we pick up any progression of your symptoms as early as possible. We will be able to provide some support towards your travel expenses.

How many scans will I have?

In the trial arm (if you have a calf thrombosis) you will have 3 ultrasound scans of your leg in total, including the one you have had today. Ultrasound scanning has no known side effects or potential to harm.

What do I have to do?

There are no restrictions on you if you take part in this study. If you have a calf thrombosis and are allocated to receive blood thinning drugs, you will need to attend the anticoagulant clinic to receive your medications and intermittently have your blood tested.

What are the possible disadvantages of taking part in this trial?

Those who are treated with blood thinning medication have an increased risk of bleeding. The risk of a serious bleed is approximately 1 patient in every 50. Those patients who are treated with compression stockings only will be less likely to bleed, but they may have a risk that the leg clot could get worse. We don't know for sure, but we think the chance of this might be 2-5 patients in every 50. If your clot worsens during the trial we will treat it accordingly.

We have made this a safe study by ensuring that everyone sees a doctor and has a repeat scan after 1 and 3 weeks. We will also have a clinic service available Monday to Friday between 12 and 5pm in the emergency department, and would be happy to see you should you have any problems during the trial.

Whether you have a negative scan or a calf thrombosis, you will also be contacted by a researcher after three months. This may take up some of your own time. We are grateful for your consideration.

What are the possible advantages of taking part in this trial?

You will receive more intensive follow up than normal and as such we will be able to provide help and advice when necessary. In addition, your results may help patients like you in the future.

What if something goes wrong?

There are no new treatments involved in this study and we do not anticipate that any harm will come to people who take part in the study.

Will my taking part in this study be kept confidential?

Yes. All data is kept securely and anonymously.

This completes part 1. If the information in part one has interested you and you are considering participation, please read the additional information in part two before making any final decision.

The **A**nticoagulation of **C**alf **T**hrombosis (ACT) Study

Thank you for getting this far. This sheet contains more detailed information about the conduct of the study and also gives the contact details for the research team members. Again, please feel free to ask any questions or point out anything that is not clear.

Part two

What will happen when the research study stops?

At the end of the three month treatment period we will contact you by phone to make sure you are recovering well. If there are any ongoing problems at this stage then we can easily organise an appointment to see you direct, or ongoing NHS care with a specialist.

What if relevant new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study he may ask you to sign an agreement outlining the discussion.

What will happen if I don't want to carry on with the study?

If you decide not to proceed in the trial, you will be referred to a separate specialist and enter a period of standard care. Any further appointments for scans of your leg would be cancelled.

If you allow it, we would still like to keep in contact with you in order to follow your progression.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the research team via the contact details provided at the end of this information sheet or the Research and Development Department of Manchester Royal Infirmary 01612763565. If you remain unhappy and wish to complain formally, you can do this via the Patient Advice and Liaison Service (PALS) on 01612768686.

Given that both treatment options for calf thrombosis and discharge after negative scans are standard practice within the NHS, compensation will not be available through the hospital for any non-negligent harm caused during the trial period.

What are the side effects of any treatment received when taking part?

Some patients will receive blood thinning drugs. The well known side effect is bleeding. We would stress that this is not a new therapy and is simply the treatment you would be offered if you were not partaking in the trial. The team at anticoagulant clinic will have a dedicated time period to discuss the risks and benefits of anticoagulation with you, along with side effects and potential drug interactions. Some blood thinning drugs can harm the unborn child. Therefore if you are pregnant, we will not invite you to participate. If you become pregnant during the trial, your medication can be specially changed.

Will my taking part in this study be kept confidential?

All data pertaining to the study will be kept on dedicated anonymised case report forms, a copy of which will be left in your main hospital notes and another copy kept in a locked filing cabinet in a dedicated research office.

Involvement of the General Practitioner / Family Doctor

We would like to write to your GP and inform them of your participation within the trial. They will also be notified if you withdraw from the trial prematurely. Only the nature of the trial and your allocation group will be noted.

What will happen to any samples I give?

Blood samples taken during the trial will not be stored and will be subject to normal trust safeguards.

What will happen to the results of the research study

You will be informed of all personal scan and examination results at the time they are done.

When all trial data have been collected and analysed, the results will be presented at local and national meetings and published in peer reviewed journals.

Copies of the final report will be available from the research team in the emergency department should you wish to obtain one.

Who is organising and funding the research?

The research has been funded by the College of Emergency Medicine, a registered charity.

Who has reviewed the study?

This study has been peer reviewed by the College of Emergency Medicine. It has been given favourable opinion by Central Manchester Research Ethics Committee. It has also been reviewed and approved by Central Manchester University Hospitals Foundation Trust Research and Development offices.

Further information and contact details

If you wish to speak to someone independent who is not involved in the trial prior to taking part, we would recommend discussing the issues with your general practitioner.

Many thanks for your help. If you need to get in touch with us again please use the contact details below. If you have any more questions now, ask the doctor treating you.

For further information about the study please contact:

Dr Daniel Horner

Department of Emergency Medicine

Manchester Royal Infirmary

Phone: 0161 276 6784
Email: daniel.horner@cmft.nhs.uk

ACT STUDY 2010: Case Report Form   DATE:

Please use protocol deviation sheet at end of document if necessary

Patient Identification Number: _ _ _
Age: _ _
Ethnicity: W   AC   I   H   O   Other
SEX: Male / Female
Side of DVT   Left   /   Right / Bilateral

ULTRASOUND RESULT = POSITIVE / NEGATIVE / INCONCLUSIVE

**If negative, omit page 1, complete pages 2/3 and record alternative diagnosis.
If positive, proceed below to consider for inclusion in ACT**

INCLUSION CRITERIA (ANY NO - DO NOT ENTER PATIENT INTO TRIAL	
Confirmed diagnosis of infrapopliteal DVT by vascular ultrasound	Y/N
Copy of PIS given and explained	Y/N
Able to provide informed consent	Y/N
EXCLUSION CRITERIA (ANY YES - DO NOT ENTER PATIENT INTO TRIAL)	
Hospitalised patient	Y/N
Patient on long term anticoagulation	Y/N
Associated proximal DVT or confirmed PE	Y/N
Contraindication to anticoagulation (active bleeding, recent haemorrhagic CVA or upper GI bleed)	Y/N
Other indication for immediate warfarinisation as per BSH guidelines: Prior confirmed and treated above knee DVT/PE, antiphospholipid syndrome, symptomatic inherited thrombophilia	Y/N
Pregnancy	Y/N
Chronic non propagating thrombus seen on prior USS	Y/N
Previous enrollment to the ACT study and achievement of the primary outcome	Y/N
SCREENING LOG	
Patient meets criteria for inclusion	Y/N
Patient agreement to participate in trial	Y/N
Informed consent obtained and consent form signed	Y/N
Consent affirmed by telephone at 24 hours if appropriate	Y/N

Treatment Allocation: **A / B**
Name and signature of researcher:

DAY ONE - BASELINE DATA COLLECTION
ANY SUGGESTION OF CONTRALATERAL OR PULMONARY VTE SHOULD BE INVESTIGATED AS APPROPRIATE

COMMON IDENTIFIABLE RISK FACTORS	YES / NO
Family history VTE	Y/N
Personal history of VTE (If yes please specify number and location: PE DVT CENTRAL)	Y/N
Known thrombophilia (name:_____)	Y/N
Active cancer receiving chemotherapy/radiotherapy/surgery within last 6/52 OR palliative	Y/N
Surgery requiring GA within last 6/52 (date and nature_____)	Y/N
Immobilisation within last 6/52 (Date and nature:_____)	Y/N
Air travel within last 6/52 (Length of flight_____) (destination_____)	Y/N
Post Partum (If yes - Date of delivery: ____/____/____) (gravida_____)	Y/N
Lower limb trauma within last 6/52 (date and nature_____)	Y/N
Pregnant (Gestation_____)	Y/N
Plaster of Paris application to lower limbs within last 6/52	Y/N
Hospital admission and type/length (Type_____ LOS_____)	Y/N
Previous history of cancer now in remission	Y/N
Current acute infectious disease	Y/N
Oral contraception	Y/N
Varicose Veins	Y/N
Hormone Replacement Therapy	Y/N

PAST MEDICAL DETAILS AND FURTHER INFORMATION			
Injecting drug use with last 5 years	Y/N	COPD on treatment	Y/N
Smoking history (>5 pack years)	Y/N	Cardiac Disease (include AF/CCF/MI)	Y/N
BMI > 30 (KG/M2)	Y/N	Vascular Surgery	Y/N
Liver disease	Y/N	CVA of any severity	Y/N
Diabetic on medication (Type 1 or 2)	Y/N	Hypertensive on medication	Y/N
ETOH history (>20 units/week for over 5y)	Y/N	Hypercholesterolaemia on medication	Y/N

Total duration of symptoms before hospital attendance: _____days

Duration of time on LMWH prior to scan: _____days

Severity of pain on VA scale: _____/10

Alternative diagnosis if scan negative: _____

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Page 2

BLOOD RESULTS TABLE, BJORGELL AND WELLS SCORE

TEST	D1	D7	D21	3/12	VEIN SEGMENT	D1	D7	D21	3/12
Sodium					Inf. caval vein				
Potassium					Com. Iliac vein				
Urea					Ext. iliac vein				
Creatinine					Int Iliac vein				
ALP					Com femoral vein				
Albumin					Deep femoral Vein				
ALT					Sup. femoral vein				
HB					Popliteal vein				
WCC					Ant. tibial vein				
Platelets					Post tibial vein				
APTT					Fibular veins				
PT					Soleus				
D Dimer					Gastrocnemius				
CRP					Planta pedis				
eGFR					Total / 42				

WELLS SCORE	D1	PAIN SCORE	D1	D7	D21	3/12
Active Cancer	1	(1 - 4)				
Calf swelling >3cm compared to contralateral	1	**OBSERVATIONS**	D1	D7	D21	3/12
Collateral superficial veins	1	Temp				
Pitting oedema in symptomatic leg	1	Pulse				
Swelling of entire leg	1	Resp				
Localised pain	1	BP				
Paralysis/paresis or recent cast immobilisation	1	MAP				
Recently bedridden >3 days	1	Sats				
Previous documented DVT	1	EWS				
Alternative diagnosis at least as likely	-2	Was the Wells Score completed by the ED Dr?	Y/N			
Total		Has an ambulatory care pathway been properly completed?	Y/N			

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DAY SEVEN - INITIAL FOLLOW UP   DATE:

Has treatment allocation been maintained	Y/N
Has the patient achieved either the primary or the secondary outcome for the study at this stage?	
Propagation on USS	Y/N
Confirmed Pulmonary VTE	Y/N
Investigated for suspected pulmonary VTE (including today)	Y/N
Recurrence of ipsilateral or contralateral leg thrombus	Y/N
Major bleeding episode	Y/N
Minor bleeding episode	Y/N
Nuisance bleeding episode	Y/N
Adverse events note (If present complete AE form, record in AE log via investigator file and document in clinical notes. Remember, bleeding is an adverse event)	
Any OTHER adverse events noted by patient or hospital notes?	Y/N
If yes, describe:	

DAY TWENTY ONE - FURTHER FOLLOW UP   DATE:

Has treatment allocation been maintained	Y/N
Has the patient achieved either the primary or the secondary outcome for the study at this stage?	
Propagation on USS	Y/N
Confirmed Pulmonary VTE	Y/N
Investigated for suspected pulmonary VTE (including today)	Y/N
Recurrence of ipsilateral or contralateral leg thrombus	Y/N
Major bleeding episode	Y/N
Minor bleeding episode	Y/N
Nuisance bleeding episode	Y/N
Adverse events note (If present complete AE form, record in AE log via investigator file and document in clinical notes. Remember, bleeding is an adverse event)	
Any OTHER adverse events noted by patient or hospital notes?	Y/N
If yes, describe:	

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THREE MONTH END OF TREATMENT FOLLOW UP   DATE:

ACT (use below)

Has treatment allocation been maintained	Y/N
Has the patient achieved either the primary or the secondary outcome for the study at this stage?	
Propagation on USS	Y/N
Confirmed Pulmonary VTE	Y/N
Investigated for suspected pulmonary VTE (including today)	Y/N
Recurrence of ipsilateral or contralateral leg thrombus	Y/N
Major bleeding episode	Y/N
Minor bleeding episode	Y/N
Nuisance bleeding episode	Y/N
Adverse events note (If present complete AE form, record in AE log via investigator file and document in clinical notes. Remember, bleeding is an adverse event)	
Any OTHER adverse events noted by patient or hospital notes?	Y/N
If yes, describe:	

Negative / Inconclusive Scan (Use below)

Is the patient alive	Y/N
If no chase case notes and determine cause of death / suspected cause of death / no post mortem:	
Has the patient been subsequently diagnosed with any kind of VTE (DVT or PE over the three months post negative scan?	Y/N
If yes, what type, where at and the outcome:	
Has the patient been further Investigated for suspected VTE (DVT or PE investigation at any other hospital)?	Y/N
If yes, what was the outcome:	
Has the patient been commenced on any type of long term anticoagulation (Heparin/Warfarin/aspirin)	Y/N
If yes, what type, when and for how long	
Any other significant events of note over the three month follow up period:	

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Page 5

Is the patient suitable for discharge from hospital follow up?   Yes / No
If not, why not:

If not what further follow up has been arranged:

1. No follow up
2. Hospital admission
3. GP Follow up appointment
4. Hospital hematology outpatient appointment
5. Emergency Department Clinic follow up appointment
6. Respiratory follow up appointment
7. Other follow up appointment

ADDITIONAL TO / DEVIATION FROM PROTOCOL

DATE	DEVIATION

SCORING SYSTEMS AND DEFINITIONS WITHIN THE CRF

PAIN SCORE:

Referenced from Lagerstedt et al. (Lancet 1985) and includes the following categories 4 categories:
1 = no pain, 2 = pain on palpation, 3 = pain on walking and palpation, 4 = pain at rest.

BJORGELL SCORE:

Score DVT's depending on degree of occlusion within each segment i.e each segment is scored out of 3 (1=<1/3, 2=1/3<2/3, 3=>2/3) and collated to give a total/42

WELLS SCORE:

Score based on addition of clinical parameters as documented and combine to give a single numerical score.

MAJOR BLEEDING:

Clinically overt and associated with a fall in haemoglobin of 20g/L, resulting in the need for transfusion of two or more units of red cells, involving a critical site, or fatal.

MINOR (clinically relevant) BLEEDING:

Spontaneous skin haematoma at least 25cm sq; Spontaneous epsitaxis >5mins duration; macroscopic haematuria lasting >24h; spontaneous rectal bleeding; gingival bleeding for more than 5 mins; bleeding requiring hospitalization and/or surgical treatment; bleeding leading to a transfusion of <2 units; any other bleeding event considered clinically relevant by the investigator.

MINOR (nuisance) BLEEDING:
Any other bleeding episodes.

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The **A**nticoagulation of **C**alf **T**hrombosis (**ACT**) Study: Initial Recruitment Phase

Dear Dr………………..

RE:

The above patient, listed at your surgery, has been registered recently in the ACT study. He/she has been investigated for DVT by vascular USS and recruited to the following arm of the study:

Group 1 –   Negative USS: For three month telephone follow up only.

Group 2 –   Calf DVT: For three months standard oral anticoagulation.

Group 3 –   Calf DVT: For three months TED stockings and analgaesia.

Confirmed DVT patients will be followed up by repeat vascular USS at 7 and 21 days. All Patients will be followed clinically for three months. Any patient developing propagation to above knee DVT or pulmonary embolism will be removed from the trial and started on therapeutic anticoagulation, as per national guidance.

If you have any queries, please do not hesitate to contact me at the above address.

Best wishes,

Dr Daniel Horner
Principal Investigator – ACT study

Emergency Medicine / Critical Care
Research fellow

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