

Two Weeks of Low Molecular Weight Heparin for Isolated Symptomatic Distal Vein Thrombosis (TWISTER study)

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Title Page:**Two Weeks of Low Molecular Weight Heparin for Isolated Symptomatic Distal Vein Thrombosis (TWISTER Study)****Short Version: TWISTER Study for Isolated Symptomatic Distal DVT**

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Abstract

Background: Treatment of low-risk patients with isolated symptomatic distal deep vein thrombi (IDDVT) is uncertain. **Objective:** assess whether two weeks of therapeutic anticoagulation is efficacious/tolerable for IDDVT. **Primary outcome:** symptomatic three-month venous thromboembolism (VTE) incidence in the two-week anticoagulation group. **Secondary outcomes** included post-thrombotic syndrome(PTS) and bleeding.

Methods: Prospective multicentre cohort study. Consecutive low-risk IDDVT patients enrolled within 72 hours of diagnosis and treated with therapeutic dose enoxaparin or rivaroxaban. At two weeks, patients had repeat complete whole leg compression ultrasound(CUS)/clinical review. If resolution of leg symptoms AND no radiological evidence of thrombus extension, anticoagulation was stopped. If ongoing symptoms and/or radiographic extension within distal veins, anticoagulation was continued for four more weeks. Patients with extension into the popliteal vein on two-week ultrasound were treated off-study. Patients were reviewed at three and six months.

Findings/Interpretation: 241 eligible patients received ≥ 2 weeks anticoagulation. 167/241(69%) were assigned to the 2-week anticoagulation group; 71/241(30%) to the six-week anticoagulation group); 3/241 patients(1%) had extension into the popliteal vein on two-week CUS.

Two patients in the two-week anticoagulation group had symptomatic IDDVT recurrence in ≤ 3 months; VTE recurrence 2/156; 1.3%(95% CI 0.05-4.85%). 69% of patients had complete resolution of symptoms within two weeks. Six-month PTS rates were 8/184, 4.4%(95% CI

2.1-8.5%). No major bleeding was reported.

Our findings suggest it's safe/efficacious to stop therapeutic anticoagulation at two weeks in low-risk IDDVT patients with resolution of symptoms/no extension on ultrasound.

This could replace 6-12 weeks of anticoagulation for ambulatory, low-risk IDDVT patients.

Highlights:

- The optimal treatment for isolated distal deep vein thrombosis (IDDVT) is uncertain.
- This was a multicentre prospective cohort study enrolling consecutive patients with IDDVT.
- Two weeks of anticoagulation achieved symptomatic relief in the majority of patients with low-risk IDDVT (69%).
- Two weeks of anticoagulation was associated with a low risk of recurrent venous thromboembolism (VTE); 1.3% (95% CI 0.05-4.85%).

Keywords: Anticoagulants; calf vein thrombosis; distal deep vein thrombosis; pulmonary embolism; venous thromboembolism.

Trial Registration: ClinicalTrials.gov NCT01252420

Introduction

The standard of care for DVT diagnosis in Australia and New Zealand is whole leg compression ultrasound (CUS). Consequently, calf vein thrombi (distal DVT) are routinely diagnosed, accounting for 50% of patients diagnosed with symptomatic DVT (1). When left untreated, the proportion of distal DVT that propagate to proximal veins, increasing the risk of PE, is unknown but likely low (0.9-6%)(2, 3). Therefore the management of isolated symptomatic distal deep vein thrombi (IDDVT) is uncertain. Treatment strategies range from withholding anticoagulation and repeating the ultrasound in seven to ten days (and anticoagulating if thrombi have propagated into proximal veins), through to three months of full dose anticoagulation. Overall the preference in Australasia has been to treat with therapeutic dose anticoagulation for at least six weeks, and even out to three months.

A recent Cochrane review (4) found a benefit (i.e. reduced VTE recurrence) for patients with distal DVT treated with anticoagulation therapy in the form of vitamin K antagonists (VKA), with little or no difference in major bleeding events, but an increase in clinically relevant non-major bleeding (CRNMB) compared to placebo. However the CACTUS study (3), a randomised controlled trial investigating six weeks of therapeutic dose nadroparin versus placebo, showed no difference in the risk of proximal DVT extension or VTE, with an increased risk of bleeding. In accordance with this, a systematic review including fifteen studies on management of calf vein DVT (including five randomised controlled trials and ten cohort studies) concluded that the literature on calf DVT was heterogeneous, with infrequent adverse outcomes and no evidence that anticoagulant therapy reduced the rate of adverse outcomes (5). The impact of anticoagulation on initial patient symptoms and the subsequent risk of post-thrombotic syndrome (PTS) are also less clear than for proximal DVT. The largest group studied to date, the IDDVT population in the post-hoc CACTUS-PTS study (6) (n=178), reported rates of 29% and 32% in the nadroparin and placebo groups, respectively (p=0.06). A second post-hoc analysis of the same study showed that there were no differences in mean pain score reduction between patients in the therapeutic nadroparin and placebo groups(7).

We now report the results of the TWISTER (Two Weeks of Low Molecular Weight Heparin for Isolated Distal Deep Vein Thrombosis) study, where the outcome of two weeks of therapeutic anticoagulation for IDDVT was prospectively assessed. The hypothesis was that this would lead to complete resolution of symptoms and a low rate of recurrent VTE during three months follow-up.

2. Methods

2.1 Design and Study Population

This multicentre prospective cohort study was performed at twelve centres in Australia and New Zealand. We enrolled consecutive adult patients (referred via the hospital wards/outpatient clinics or from primary care practices) with a first, acute (within 72 hours), symptomatic, objectively confirmed IDDVT. The diagnosis of DVT was established with whole-leg compression ultrasonography (CUS). The criterion for IDDVT was the presence of non-compressible thrombus on ultrasound in infrapopliteal veins based on the local radiologist's report i.e. involving one or more of posterior tibial, anterior tibial, peroneal, or muscular (gastrocnemius and/or soleal) calf veins. Patients with bilateral IDDVT were not eligible. Other exclusion criteria included: concomitant superficial vein thrombosis, pregnant or within six weeks post-partum, duration of symptoms for more than two weeks, DVT involving trifurcation or more proximal leg veins on imaging, prior DVT, active malignancy (present at time of diagnosis, or on treatment, or treatment completed within three months), ongoing risk factors for propagation e.g. ongoing immobility ($> 50\%$ of the day in bed or ≥ 72 hours), plaster cast or non-weight bearing, other indication for therapeutic anticoagulation (e.g. AF), active gastro-oesophageal ulceration or bleeding, other high risk for bleeding (e.g. recent neurosurgery, vascular retinopathy, coagulopathy), platelet count $< 80 \times 10^9/L$ and severe renal impairment (CrCl < 30 ml/min). Compression stockings were used at the investigator's discretion. The protocol was amended in 2012 to allow the use of treatment dose rivaroxaban, once this became licensed for VTE treatment first in Australia and then in New Zealand.

The study was approved by the ethics committees of the participating centres. All participants gave written informed consent. A steering committee was responsible for the design, conduct and reporting of the study. The trial was registered with ClinicalTrials.gov, number NTC0125240.

2.2 Procedures

Within 72 hours of diagnosis, patients were commenced on either full dose enoxaparin (1 mg/kg BD or 1.5 mg/kg once daily) or rivaroxaban (15 mg BD) for two weeks.

Investigators recorded basic demographics, risk factors, signs and symptoms using a standardised case report form. Subjects were asked to record symptoms daily, using Visual Analogue Scale (VAS) pain scores and a functional assessment using a modified Veines-sym scale (Appendix). A Villalta assessment was not performed at baseline.

At two weeks, patients had repeat whole leg CUS and clinical review. If patients were assessed to have resolution of DVT symptoms with no radiological evidence of thrombus extension, anticoagulation was stopped (2-week anticoagulation group). If patients had ongoing DVT symptoms and/or extension within distal veins on CUS, anticoagulation was continued for another four weeks (six-week anticoagulation group). If the two-week CUS showed proximal extension, patients were treated with a minimum of three months anticoagulation.

Patients in the two-week and six-week anticoagulation cohorts were reviewed at the study centre at three and six months for VTE recurrence and PTS, usually face-to-face but occasionally by telephone. Patients were educated on signs/symptoms of recurrent VTE and instructed to contact the study centre if they had any concerns. For those unable to be contacted at each time point, repeated attempts were made to contact patients via telephone, in writing and via search of local hospital records.

2.3 Outcomes

The primary outcome was the symptomatic recurrence of VTE (proximal or distal DVT, non-fatal and fatal PE) within three months in the group receiving two weeks of anticoagulation. Secondary outcomes reported for all groups included asymptomatic proximal thrombus

extension at two weeks, time to complete symptom resolution and proportion of patients with complete resolution at two weeks, all-cause mortality, post-thrombotic syndrome at six months, and predictors of recurrent or progressive DVT/PE, including D-dimers. The safety outcomes were bleeding and adverse effects of any study interventions leading to cessation of therapy. Major bleeding was defined using the International Society on Thrombosis and Haemostasis (ISTH) criteria (8). The presence of post-thrombotic syndrome was assessed at 3 and 6 months using the Villalta PTS scale ((9); appendix). CUS were performed by experienced ultrasonographers or radiologists. Events were adjudicated centrally by three independent observers (who were blinded to ultrasound reports and length of anticoagulation) for all reported extensions and VTE recurrences within three months of enrolment on the study, with differences resolved by consensus. Extension of distal DVT within distal veins was defined as lengthening of total length of non-compressible vein as evidenced by the actual images or the sonography worksheet.

2.4 Sample Size & Statistical Analysis

We assumed a 1% incidence of recurrence in two-week anticoagulation group after stopping anticoagulation. To be confident that the true VTE recurrence rate in this group would be <4% (upper limit of 95% CI <4%), we calculated that 215 patients would be needed in this group, based on the following assumptions: for patients presenting with confirmed calf vein thrombosis and who had received two weeks of anticoagulation, (1) we estimated that 65% of patients would be asymptomatic at this time point with no evidence of extension on the 2-week CUS (2-week anticoagulation group); (2) 15% of patients would have radiological extension of the thrombus into the popliteal vein (proximal extension group) and therefore would be treated off-study, and, at the same time point (3) 20% of participants would have ongoing symptoms or radiological extension (confined to the distal veins), allowing the treating clinician to complete 6 weeks of anticoagulation (six-week anticoagulation group). In order to recruit 215 subjects into the two-week anticoagulation arm, we aimed to recruit 330 patients with confirmed distal DVT. However by June 2018, after eight years and with declining recruitment, the steering committee decided that the last patient would be recruited up to 31st December 2018.

Statistical analyses were performed using GraphPad Prism v9.09 (GraphPad Software Inc., San Diego, USA) or SPSS v22. The primary outcome was calculated as the proportion of patients in the 2-week anticoagulation group who developed VTE within three months (+/- 95% confidence interval; CI; calculated using modified Wald method). The secondary outcomes were also calculated as proportions (+/- 95% CI). Baseline variables were compared between patients with either VTE recurrence or any radiological extension and those patients without either event. Continuous variables are expressed as mean \pm standard deviation (SD) for normally distributed data and median (interquartile range, IQR) for non-normally distributed data. Categorical data were compared using χ^2 tests or Fisher's exact test as appropriate. Comparisons between continuous variables were performed using paired or unpaired t tests and Wilcoxon or Mann-Whitney U tests as appropriate for normally and non-normally distributed data with Benjamini correction for multiple comparisons. The results of prespecified interim analyses were reviewed by a data safety monitoring board after enrolment of 100 and 200 patients, contingent on stopping rules which deemed that the study should stop if the lower 99% confidence limit of the composite primary outcome (symptomatic proximal extension or symptomatic recurrent vein thrombosis) was > 2%. This was not so, and therefore it was deemed safe to continue after each interim analysis.

3. Results

3.1 Study Participants/Demographics

247 patients were enrolled between November 8, 2010 and December 31, 2018 (figure 1). Three were found to be ineligible for study and were excluded from the analysis. One was

found retrospectively to have PE symptoms at IDVT diagnosis but PE was not objectively confirmed until day three. Of the 243 patients, one was lost to follow-up before the two week visit, and one was withdrawn on day five due to CRNMB consisting of an 18cm haematoma involving a ruptured plantaris tendon.

Two hundred and forty-one patients completed two weeks of therapeutic anticoagulation, progress ultrasonography and clinical review. Baseline demographics and clinical characteristics are outlined in table 1. Of these, 48% were men, median age of 52 years. A provoking factor was identified in 61% of cases; 46% of cases involved the muscular (soleal +/- gastrocnemius) veins only.

Figure 1: Study Flow & Outcomes

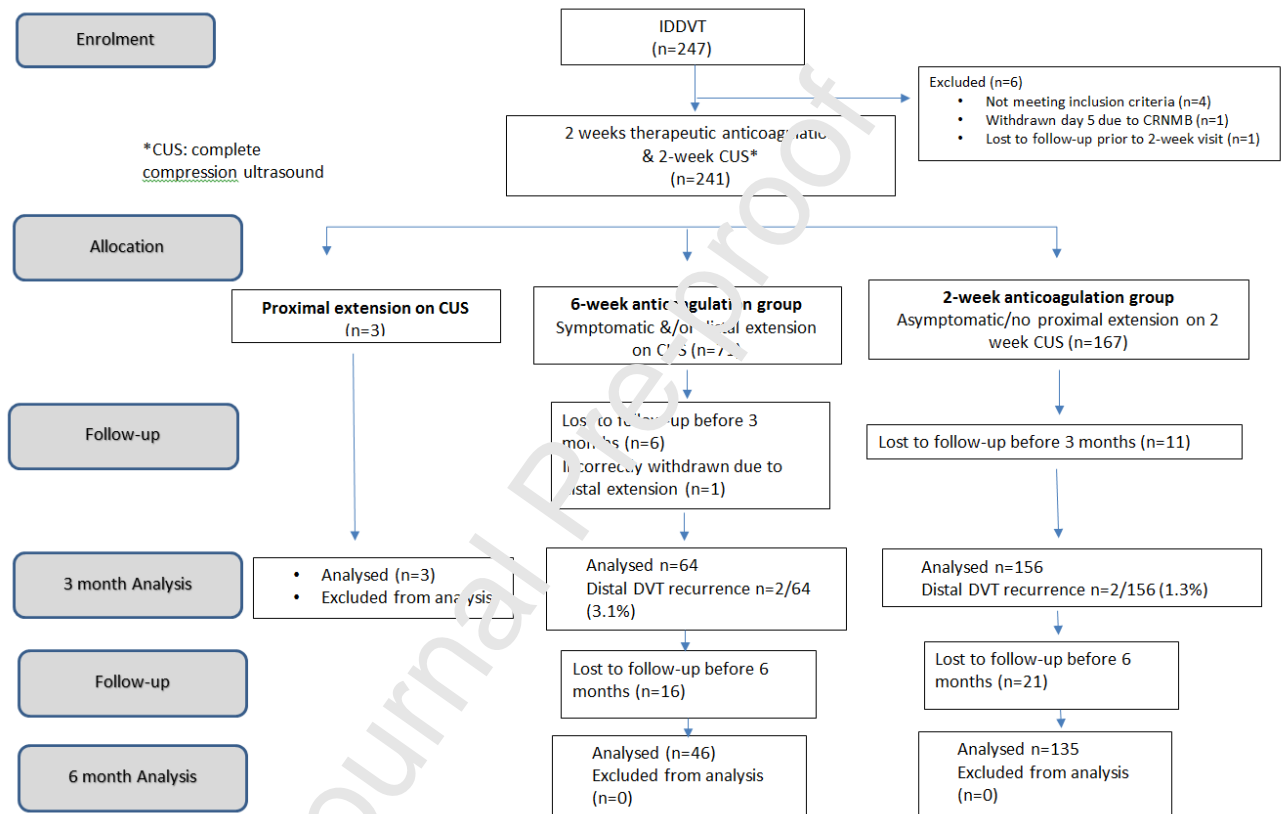


Table 1: Baseline Demographics/Clinical Characteristics

	Total (n=243)	6 Weeks Anticoagulation (n=71)	2 Weeks Anticoagulation (n=167)	P*
Men	116 (48%)	31 (44%)	83 (50%)	0.4
Age (yrs); median (IQR)	52 (40-68)	54 (42-68)	52 (38-67)	0.37
BMI (kg/m ²); median (IQR)	28.6 (24.7-32.5)	28.6 (24.5-33.4)	28.3 (24.8-32.0)	0.38
Ethnicity				
White	203 (83.5%)			
Asian	13 (5.3%)			
Black	1 (0.4%)			
Maori	4 (1.6%)			
Pacific Island	2 (0.8%)			
Other	10 (4.1%)			
Not stated/recorded	10 (4.1%)			

Unprovoked	95 (39%)	26 (39%)	61 (37%)	0.89
Risk Factors				
Family history VTE	26 (12%)			
Systemic oestrogen	29 (12%)			
Surgery/Trauma	88 (36%)			
Immobilisation	51 (21%)			
Travel >4 hours	59 (25%)			
Venous incompetence	34 (14%)			
Left leg	125 (51%)			
Bilateral	2 (1%)			
Veins involved				
Muscular vein only	112 (46%)	28 (42%)	78 (48%)	0.47
Gastrocnemius	73 (30%)			
Soleal	33 (14%)			
Gastrocnemius&soleal	6 (2%)			
Axial +/- muscular vein	131 (53.6%)			
Unknown	1 (0.4%)			
Signs/Symptoms				
Swelling	149 (61%)			
Pain	195 (84%)			
Erythema	48 (20%)			
Treatment				
Rivaroxaban	97 (40%)	29 (44%)	58 (35%)	0.23
LMWH	144 (59%)			
LMWH/warfarin	2 (1%)			
Concomitant aspirin	21 (9%)			

*Group A excluded from comparisons as only 3 patients in this group

3.2 Study Flow (figure 1)

At the two-week clinical review 167 patients (69%) were asymptomatic with stable ultrasonography and received anticoagulation (asymptomatic, two-week anticoagulation group); 71 patients (30%) continued anticoagulation for a further 4 weeks (symptomatic and/or thrombus extension within distal veins), and three patients (1%) had ultrasound extension into the popliteal vein (proximal extension) and were treated at the investigator's discretion. One was incorrectly withdrawn at the two-week time point, due to thrombosis extension within distal veins.

Eighteen patients were lost to follow-up before three months, including 11 and 7 in the two-week and six-week anticoagulation groups, respectively. Sixty-four patients received six weeks anticoagulation. Three patients (1%) received at least three months anticoagulation due to proximal extension on the two-week ultrasound.

3.3 VTE recurrence

The primary outcome (symptomatic recurrence of VTE, i.e. DVT, non-fatal and fatal PE) occurred in two patients in the two-week anticoagulation arm, $2/156 = 1.3\%$ (95% CI 0.05-4.85%) (Table 2). Both were distal DVT; one ipsilateral (involving different veins from the index IDDVT) and one contralateral to the original IDDVT. There were no symptomatic proximal DVT or PE recurrences (0/156, 95% CI 0.00-2.89%). One patient in the two-week anticoagulation group had an asymptomatic proximal DVT detected on an unscheduled

ultrasound at ten weeks, whilst off anticoagulation. This patient remained asymptomatic, remained off anticoagulation over six-month follow-up and was not included in the primary outcome. There were also two episodes of VTE recurrence in the six-week anticoagulation arm, both distal DVT, $2/64 = 3.1\%$ (95% CI 0.23 – 11.3%).

Table 2: VTE Recurrences and Extensions Within Three Months

	Total N=241	2 Weeks N=156	6 Weeks N=64	Proximal Extension N=3
VTE recurrence total	4	2	2	-
Distal DVT Recurrence	4	2	2 [@]	-
Proximal DVT Recurrence	0	0	0	-
Proximal Vein Extension on 2-Week CUS	3	0	0	3
Distal Vein Extension	15	5*	10 [#]	0
PE	0	0	0	0

@ One diagnosed at 4 weeks while on therapeutic enoxaparin; one diagnosed 5 weeks after stopping 6 week course of rivaroxaban

*One on day 2; remainder on 2-week CUS (placed in two-week anticoagulation group at investigator's discretion)

#One associated with concomitant superficial vein thrombophlebitis

3.4 Mortality

No deaths were reported during the six-month follow-up period.

3.5 Bleeding

There were no episodes of major bleeding. Twenty-five patients (25/242=10.3%) developed bleeding during the course of the study. Of these (22; 88%) occurred within the first two weeks. Five were CRNMB (2.1% of patients overall); table 3. The remainder were minor bleeds.

Table 3: Clinically Relevant Non-Major Bleeds

Index DVT	Location	Time	Anticoagulant	Management
Gastrocnemius + soleal	10cm bruise chest traumatic	Week 1	Enoxaparin	Enoxaparin reduced to 50% day 5
Gastrocnemius	25cm haematoma LMWH Injection site	Week 1	Enoxaparin	Enoxaparin stopped day 7
Soleal	Menorrhagia	First 2 weeks	Rivaroxaban	Iron infusion
Gastrocnemius	Haematoma complicating muscle tear	First 2 weeks	Rivaroxaban	Rivaroxaban stopped week 2
Posterior tibial	18cm haematoma at site of plantaris tendon rupture	Week 1	Enoxaparin	Enoxaparin stopped day 5

3.6 Predictors of recurrent/progressive VTE

Given there were very few VTE recurrences and extensions (proximal/distal), we did not have sufficient power to undertake this analysis.

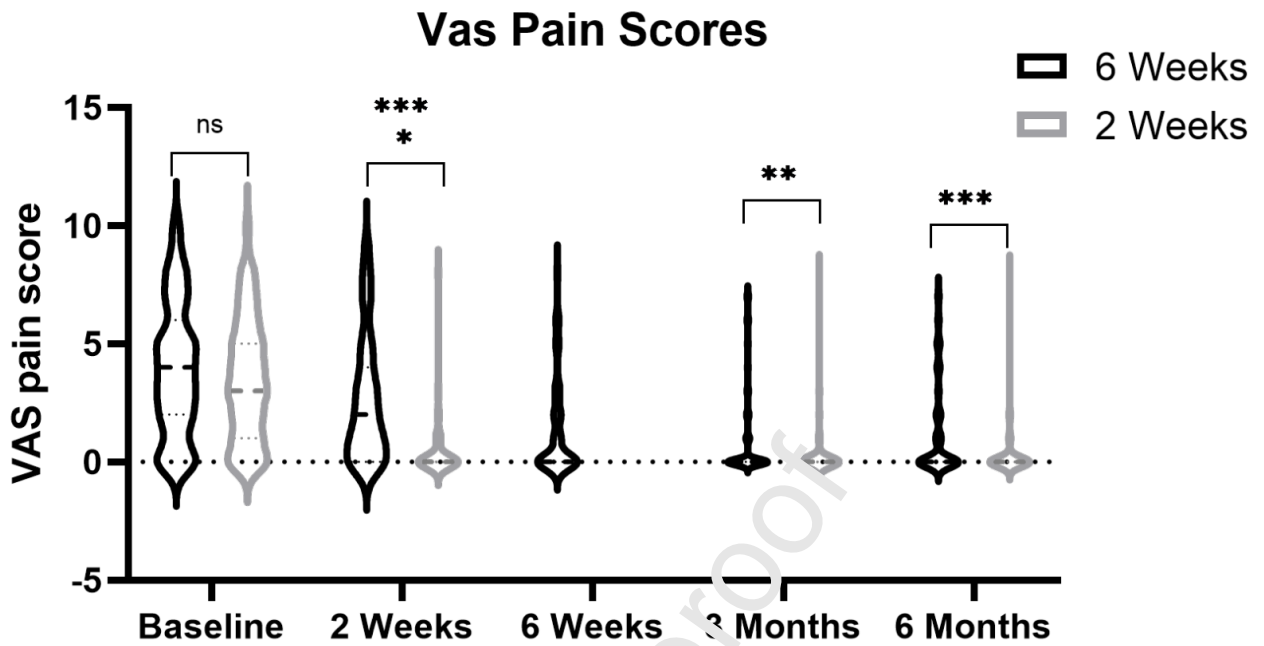
3.7 Symptom Resolution

At two weeks, 69% (n=167) of patients had complete resolution of symptoms and were

allocated to the two-week anticoagulation group. 29% (n=71) had persistent symptoms and were allocated to the six-week anticoagulation group; 10% (n=7) of patients were also allocated to six weeks of anticoagulation due to extension within the distal veins on 2-week CUS despite complete symptom resolution, and five patients were allocated to the 2-week anticoagulation group despite distal extension on the 2-week CUS at the investigator's discretion (as they were asymptomatic at that time point). Two of the three patients with proximal extension on the 2-week CUS reported complete resolution of symptoms, with no symptom data recorded for the third patient. Baseline demographics were no different between patients allocated to two versus six weeks anticoagulation (Table 1). Median Vas pain scores were not significantly different at baseline while median Veines-sym scores were significantly lower in the six-week group (10; [8;13] versus the two-week group (12; [10; 15]; $p < 0.05$). As symptoms were the basis of allocation, distributions of Vas Pain and Veines-sym scores were statistically significantly different at two weeks between the two and six week groups as expected, Vas score median 2 [0;4] versus 0 [0;0], $p < 0.0001$ and Veines-sym scores of 12 [8;16] versus 16 [12;20]; $p < 0.0001$. These statistical differences in distribution persisted at three and six months (figure 2).

Regardless of group or initial severity, both groups showed improvement over time, with a minority of patients experiencing persistent symptoms beyond two weeks (Fig 2). There was no increase in symptom score in the two-week cohort after cessation of anticoagulation at two weeks. Patient recording of VAS and Veines-sym scores was incomplete, therefore a Kaplan-Meier analysis for time dependent symptom resolution was not performed.

(a)



(b)

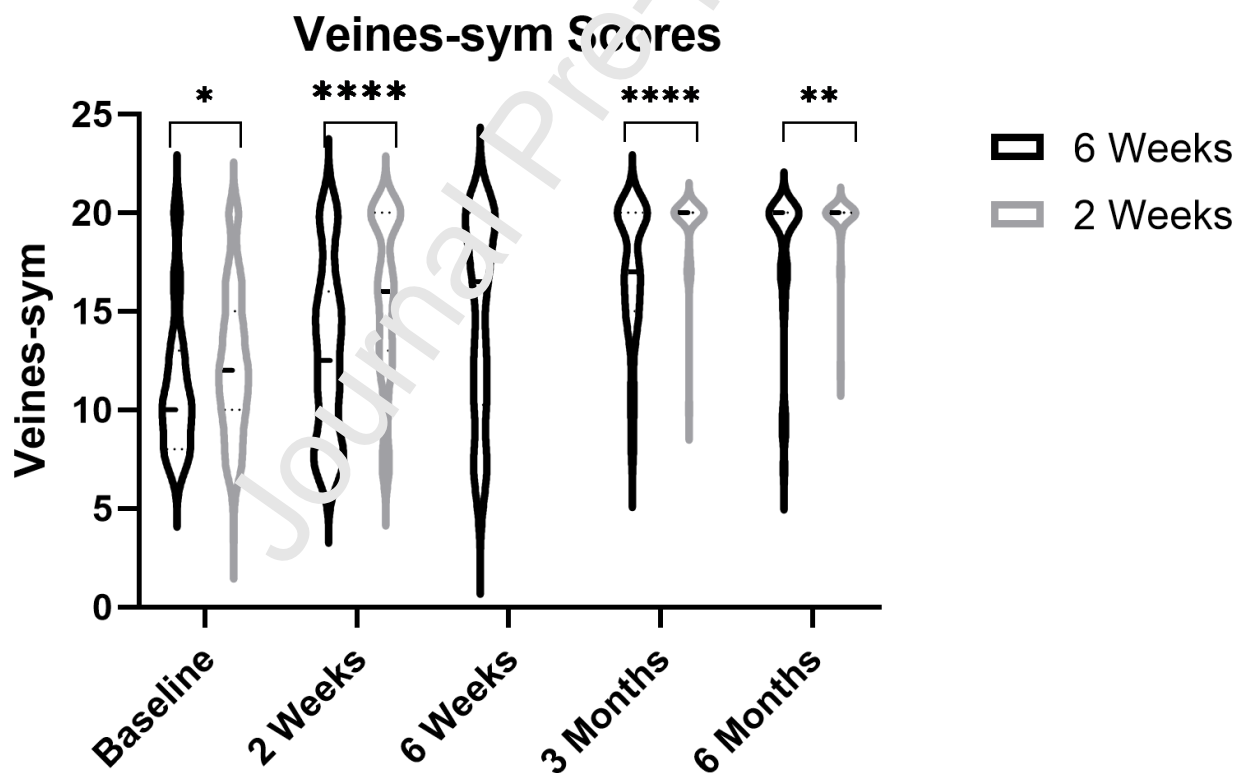


Figure 2: Vas Pain and VEINES-SYM-scores improve over time with no recurrence in symptom scores at 3 or 6 months in group C patients. (A) Vas Pain Scores are not significantly different between 2-week anticoagulation (n=161) and 6-week anticoagulation (n=66) groups prior to allocation; both groups improve over time with 6-week group having significantly higher pain scores at 3 and 6 months (mixed effect analysis, ** p<0.01, *** p<0.001, ****p<0.0001). (B) Veines-sym scores are significantly different between 2-week (n=129) and 6-week (n=50) anticoagulation groups prior to allocation, both groups improve

over time, however 6-week group has significantly higher symptoms score at 2 weeks, and 3 and 6 months (mixed effect analysis, * $p < 0.05$, ** $p < 0.01$, **** $p < 0.0001$). Medians (---) and IQR (···) shown. 6-week data not collected in 2-week anticoagulation group as per protocol. Mann Whitney between group analysis with Benjamini correction for multiple comparisons.

3.8 PTS

The development of PTS was assessed by Villalta scale at three (n=218) and six months (n=181). Three patients in the two-week anticoagulation group (n=156 evaluated at this time point) were recorded as having signs/symptoms compatible with PTS at three months; 3/156; 1.92% (95% CI 1.17-7.48%), increasing to five patients at six months (n=135 evaluated at this time point); 5/135; 3.7% (95% CI 1.36-8.60%). All were mild (median score of 6, IQR 5-6) with no ulcers present. These proportions were higher in the six-week anticoagulation group, with PTS rates of 6.4% (95% CI 2.08-15.9) and 6.5% (95% CI 1.59-18.15) at three and six months, respectively; again, all scored as mild on the Villalta scale at six months (median 6; IQR 5.5-6.5), and the differences between groups were not statistically significant. The six-month PTS rate for the study cohort as a whole was 4.4% (95% CI 2.1-8.6%).

Two of the patients with symptoms compatible with PTS at three months had resolution of symptoms by six months; one was lost to follow-up. No baseline characteristic predicted for the development of PTS.

3.9 D-dimers

Eight centres participated in the D-dimer sub-study, with 134 subjects having D-dimers measured at baseline. Baseline D-dimers were higher in the proximal extension group, with a mean of 2410 $\mu\text{g/L}$ (median 2410 $\mu\text{g/L}$; SD 2242.6; IQR 820-4000 $\mu\text{g/L}$), compared with a mean of 847.91 $\mu\text{g/L}$ in the six-week anticoagulation group (median 905 $\mu\text{g/L}$; SD 839.92; IQR 285-1190 $\mu\text{g/L}$) and a mean of 1175 $\mu\text{g/L}$ (median 1043 $\mu\text{g/L}$; SD 1292.51; IQR 365-1408 $\mu\text{g/L}$) two-week anticoagulation group. However we excluded the proximal extension group from further D-dimer analysis due to low numbers in the proximal extension group (n=3). D-dimers were not found to be predictive for treatment group allocation, VTE recurrence/extension or any other outcomes measured in this study.

Discussion

The optimal treatment for IDDDVT patients remains uncertain, with recommendations ranging from no anticoagulation to long term therapeutic dose anticoagulation in unprovoked IDDDVT (3, 10-12). In this prospective cohort study, we have demonstrated that the majority (69%) of low-risk IDDDVT patients can be treated with two weeks of anticoagulation with resultant symptom resolution, no proximal DVT/PE and a low rate of VTE recurrence (2/156 or 1.3%; 95% CI 0.05-4.85%). No major bleeding or mortality was observed over 3 month follow-up. In this study, one of the largest prospective cohort of six month IDDDVT PTS data (n=181) reported in the literature to date, rates of PTS at six months were low at 3.7% (95% CI 1.36-8.60%) in the 2-week anticoagulation group and 4.4% (95% CI 2.1-8.6%) overall; all were graded as mild (median score 6).

A recent Cochrane review (4) of distal DVT (eight RCTs reporting on 1239 participants) concluded that anticoagulation with a VKA reduced the risk of any recurrent VTE during follow-up compared with participants receiving no anticoagulation (RR 0.34, 95% CI 0.15-0.77), but with an increase in CRNMB in the group treated with anticoagulants (RR 3.34, 95% CI 1.07-10.46). In contrast, the largest management study evaluating IDDDVT to date, the CACTUS study (3), a randomised, double-blind placebo-controlled trial comparing six weeks of therapeutic dose nadroparin with six weeks of placebo injections, concluded that nadroparin was not superior to placebo in reducing the risk of proximal extension or VTE in low-risk outpatients with symptomatic IDDDVT. However, nadroparin was associated with an

increased bleeding risk (risk difference 4.1, 95% CI 0.4-9.2; $p=0.0255$).

Similarly, a smaller RCT randomised patients with IDDVT to either ten days of treatment dose nadroparin, along with three months of compression therapy, versus three months of compression therapy alone(13). Progression to proximal deep vein thrombosis was not significantly different in the two groups, at 2/54 (3.7%; 95% CI 0.3 – 13.2%) versus 2/53; (3.7%; 95% CI 0.3 – 13.5%), however this may have been underpowered to show a significant difference.

Finally, a study using a shortened duration of anticoagulation, the TICT (Treatment of Isolated Calf Vein Thrombosis) study(14), used twice daily treatment dose LMWH for one week followed by a half dose of LMWH once daily for three weeks. Only 2.9% (95% CI 1.1 – 6.9%) of patients showed progression of thrombosis to proximal deep veins.

Recurrence rates for IDDVT are lower than for proximal DVT, with studies reporting recurrence rates that range from 0 – 3.5% at 1 year (15-17)with the long-term risk of recurrence reported to be two-fold higher for unprovoked events in one study(15). We did not find a difference in VTE recurrences between those with provoked and unprovoked IDDVT in our cohort, however the amount of VTE recurrences in our study were very small and we acknowledge that it is possible that our study was underpowered to detect such a difference. The protocol for the TWISTER trial was developed in 2010 when anticoagulation for six to twelve weeks was the standard practice for IDDVT in Australia and New Zealand. CACTUS had not yet reported and many treating clinicians were reluctant to consider a trial design where IDDVT patients were not offered any anticoagulation. However, they were willing to evaluate shorter duration of anticoagulation which might have resulted in reduced bleeding risk. Therefore, a cohort study design powered to allow a precise estimate of the recurrence risk was favoured as the most feasible study. CACTUS had similar inclusion/exclusion criteria to TWISTER. Similarly, the target sample size for CACTUS (286 patients) was not reached by the trial conclusion but final numbers were similar between these two trials (TWISTER $n=247$, CACTUS $n=259$). Rates of recurrent VTE were similar between the anticoagulation arms of the two trials with 3% on nadroparin in CACTUS versus 1.3% in TWISTER. Bleeding (major or CPNEM) occurred in 4% of patients on nadroparin, and 2.1% in TWISTER. Our results suggest that, conservatively, patients with IDDVT who have resolution of symptoms and a non-progressive CUS at two weeks can safely have their anticoagulation discontinued.

As the CUS has low sensitivity and high inter-observer variability for IDDVT, the two-week CUS to detect recurrence or extension confined to the calf veins may be of limited value. However two out of three proximal extensions at two weeks were clearly asymptomatic and had these patients ceased treatment along with the third patient (unclear/equivocal symptoms), and assuming all three subsequently “recurred”, our rate of recurrent VTE could have been recorded as 5/156 (1-7.32%) similar to the CACTUS placebo arm (5%). Finally, the index IDDVT diagnoses were based on the local radiologist’s report, without a second reading or adjudication.

A strength of this study was that the PTS data was collected prospectively using the Villalta scale, and was a pre-specified secondary outcome. Our observed rates of PTS, with a median score of six, are lower than historically reported for IDDVT at 4-30%, and are substantially lower than rates following proximal DVT (20-50%) (12). In a post-hoc CACTUS study analysis, PTS was assessed as present in 30% of 178 patients at six years. The difference in primary chronic venous insufficiency may explain some of the difference in PTS rates between the two studies; being present at baseline in 21% and 14% of the CACTUS PTS and baseline TWISTER cohorts, respectively. In accordance with this, there was a higher incidence of PTS in patients with versus without primary chronic venous insufficiency on CACTUS (24% vs 9%, $p=0.04$). However we acknowledge that the presence of primary

chronic venous insufficiency in TWISTER was not strictly defined and the assessment of its presence or absence was left to the discretion of the investigator.

Study Strengths/Limitations:

We have enrolled one of the largest cohorts of patients with symptomatic IDDVT in the literature. The multicentre pragmatic design of our study is widely generalisable, especially to health systems where whole leg CUS for suspected DVT is the standard of care. Our PTS data is strong and reproducible, and represents one of the largest prospectively collected group to date.

There are a number of limitations to our study. Firstly, the upper 95% CI estimate of the primary outcome is just over 4% and therefore we did not fulfil our prespecified primary objective. In July 2018 we decided to halt recruitment after 31 December 2018 due to poor recruitment, and therefore did not reach our estimated sample size. Based on a point estimate of 1.3% recurrence we estimate that a final sample size of 280 patients (i.e. an additional 30-40 patients) could have achieved the required precision. Therefore we have confidence in our primary outcome, which is comparable to other prospective literature, and have demonstrated no proximal recurrent DVT/PE.

Secondly, eighteen (7%) of patients were lost to follow-up before the three-month assessment, eleven of whom were in the experimental group. It is perhaps not surprising that the majority of those lost to follow-up were in the two-week treatment arm, as this cohort were by definition asymptomatic at two weeks, were no longer on anticoagulation, and therefore less likely to feel the need to be reassessed at the three-month time point. All patients were instructed to re-present or contact the study team if any worrying symptoms recurred after stopping anticoagulation. Every effort was made to contact these patients to complete follow-up and to search for further admissions via hospital records and databases. It therefore seems unlikely that these patients would have experienced an undocumented VTE recurrence, and the loss to follow-up in the experimental arm, at 6.6%, is in keeping with the average loss to follow-up in the LOST-TT trial(18), a systematic review examining the effect of loss to follow-up in randomised controlled trials. However, with this in mind, we have chosen to present the results using as a denominator the subjects who have completed three-month follow-up.

Conclusion

We suggest that may be safe and efficacious to stop therapeutic anticoagulation at two weeks in patients with low-risk IDDVT who have resolution of symptoms and no extension on ultrasound, with very low rates of recurrent VTE and no proximal DVT/PE recurrence. This could replace six to twelve weeks of anticoagulation for ambulatory, low-risk IDDVT patients.

Addendum

Author roles in study: E. Merriman: lead investigator, protocol design/amendments, enrolled subjects, study monitoring, data analysis, write-up of paper for publication. H. A. Tran, S. Chunilal, T. Brighton: protocol design/amendments, enrolled patients, assisted with data analysis and write-up for publication; Huyen Tran/Sanjeev Chunilal were also primary and co-supervisor, respectively, for this project for E. Merriman's PhD. S. McRae: protocol design/approval of protocol amendments, assisted with data analysis and write-up for publication. V. Chen: assisted with statistical analysis and write-up for publication, enrolled patients onto study. P. Ockelford, J. Curnow, G. Royle, H. Crowther, A. Slocombe, H. Tran, B. Chong: enrolled patients, assisted with data interpretation/write-up for publication.

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Data Access, Responsibility & Analysis: Eileen Merriman has had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

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Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Eileen Merriman: \$60,000 grant from Sanofi-Aventis to fund statistical analysis/investigator steering group meeting; previous honorarium from Bayer for educational meeting; previous funding from Sanofi –Aventis for accommodation at ISTH meetings

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