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Idiopathic upper extremity deep vein thrombosis: A systematic review

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Abstract

Background: Idiopathic upper extremity deep vein thrombosis (UEDVT) management is controversial and ranges from anticoagulation alone to the addition of further interventions such as thrombolysis and decompressive surgery.

Objectives: The objective of this systematic review was to assess the effects of anticoagulation alone compared to anticoagulation with additional interventions such as thrombolysis or decompressive surgery on the incidence of recurrent UEDVT and post-thrombotic syndrome (PTS) in patients with idiopathic UEDVT (including those associated with the oral contraceptive pill).

Patients/Methods: A systematic search was conducted for studies which focused on acute UEDVT treatment defined as therapies starting within 4 weeks of symptom onset. We limited studies to those that recruited 10 or more subjects and involved at least 6 weeks to 12 months anticoagulation alone or together with additional interventions with at least 6-month follow-up. Primary outcomes were symptomatic recurrent radiologically confirmed UEDVT and PTS. Secondary outcomes were symptomatic venous thromboembolism, bleeding and mortality.

Results: We found seven studies which reported recurrent UEDVT rates and five that reported PTS rates. All studies were retrospective or cross-sectional. None compared anticoagulation alone to anticoagulation with additional intervention. Study heterogeneity precluded meta-analysis and risk of bias was moderate to serious. Recurrent UEDVT occurred in 0% to 12% post-anticoagulation alone and 0% to 23% post-additional interventions. PTS rates varied from 4% to 32% without severe PTS. Only limited studies reported on our secondary outcomes.

Conclusion: There is limited evidence behind idiopathic UEDVT management. Prospective comparative studies in this area are essential.

KEYWORDS

anticoagulants, deep vein thrombosis, endovascular procedures, post-thrombotic syndrome, upper extremity deep vein thrombosis, venous thromboembolism

1 | INTRODUCTION

Upper extremity deep vein thrombosis (UEDVT) is commonly due to underlying malignancy, central venous catheters or pacemaker wires. In contrast, idiopathic upper extremity deep vein thrombosis is rare with an estimated annual incidence of 2 per 100 000.[1] We will be focusing on proximal idiopathic UEDVT which we define as proximal to the brachial vein (e.g., internal jugular, axillary, subclavian). For our review, we will include cases associated with the combined oral contraceptive pill given the rarity of idiopathic UEDVT. Idiopathic UEDVT affecting the axillosubclavian veins is speculated to occur in some patients due to venous thoracic outlet syndrome (VTOS) or Paget–Schroetter Syndrome (PSS). VTOS refers to thrombosis due to dynamic axillosubclavian vein compression at the costoclavicular space which lies between the first rib and clavicle. This compression is not usually fixed and is elicited by certain postures or positions such as with overhead throwing[2] or playing bow instruments.[3] It is postulated that compression causes repetitive venous endothelial damage, inflammation and fibrosis.[4] However, the diagnostic criteria for VTOS are not well defined.

VTOS is viewed as a surgically amenable risk factor for thrombosis recurrence and post-thrombotic syndrome (PTS) through acute thrombolysis and surgical decompression such as first rib resection (FRR) and scalenectomy.[5] In some cases, patients also undergo catheter directed thrombolysis (CDT), venous stenting and/or venoplasty. These interventions all aim to restore venous patency and therefore presumably function, reducing ongoing vascular damage and ultimately obviating the need for lifelong anticoagulation. However, these interventions are not without risk; CDT is associated with bleeding whilst surgical decompression is a major 2 to 3 hour operation requiring 3 to 4 days of hospitalisation.[6,7] Up to 4% of patients require re-operations for re-thrombosis[8,9] with 14% readmission.[7] There are considerable risks such as bleeding, vessel injury, pneumothorax in up to 38%,[9] infection and up to 6% risk of neuropathy such as phrenic or brachial plexus injuries.[9,10] All these complications are particularly devastating due to frequent involvement of the dominant arm in young patients who are often in their early 30s.[11] Despite this, conservative management algorithms aiming to avoid potentially unnecessary surgery have been met with considerable criticism and are not widely endorsed.[12,13]

Therefore, the two major areas of clinical equipoise in UEDVT management are whether to employ additional interventions to anticoagulation alone and secondly when, if ever, to cease anticoagulation which is typically considered at 6 months. Therefore, we conducted a systematic review to specifically review the best available evidence on these therapies and the incidence of UEDVT recurrence, PTS risk and quality of life (QoL) outcomes to guide management decisions at both timepoints.

2 | OBJECTIVES

To assess the effects of fixed duration anticoagulation alone (at least 6 weeks to 12 months) compared to anticoagulation together with thrombolysis, endoscopic and/or surgical intervention in patients with idiopathic UEDVT on the post-treatment risk of recurrent UEDVT and PTS (assessed after at least 6-month follow-up).

3 | METHODS

3.1 | Inclusion criteria

Study inclusion was restricted to case series of 10 or more participants with acute and subacute idiopathic, radiologically confirmed, symptomatic UEDVT involving veins proximal to the brachial vein (i.e., axillary, subclavian). We also included UEDVT associated with the oral contraceptive pill which was not otherwise provoked (e.g., by venous catheters, known cancer or pacemaker wires). We defined acute and subacute UEDVT as less than 4 weeks from symptom onset. Studies which otherwise met inclusion criteria but included a mixed population of more than 10% of non-included conditions such as lower limb deep vein thrombosis, provoked UEDVT or solely distal UEDVT were excluded if results were unable to be separated from the target population. No restrictions were placed on study type and thus we included retrospective and cohort studies. We considered conference abstracts if sufficient study details were available for extraction. We accepted studies that included an intervention that was either anticoagulation alone or anticoagulation together with additional intervention such as CDT, venoplasty or surgical decompression. We only accepted studies which assessed anticoagulation of at least 6 weeks to 12 months and followed-up patients for at least 6 months post-anticoagulation cessation. Only studies with outcomes of either symptomatic, radiologically confirmed UEDVT proximal to the brachial vein, recurrent lower limb deep vein thrombosis (LLDVT) or pulmonary embolism (PE), PTS or QoL or disability assessment at least 6 months post-anticoagulation cessation were included. If there were duplicate reports of the same study population or of considerable overlapping populations (>50%), the most recent full-text article was used.

3.2 | Search methods for identification of studies

We conducted a systematic literature search of MEDLINE, EMBASE, APA PsychInfo, Emcare electronic databases (inception to May 2020) restricting citations to adults greater than 18 years of age with no restrictions on language. We also identified ongoing trials by searching trial registries. The search strategies linked filters for unprovoked UEDVT, VTOS and PSS and attempted to exclude papers which focused on venous catheters, cancer and trauma (see Supporting Information Material S1). We examined the reference lists of included studies and relevant reviews for potentially eligible studies. We also attempted to contact authors where information in the publication was insufficient for inclusion or to seek clarification. We thank corresponding authors for their responses.[14–16]

3.3 | Study selection

One reviewer (H.L.A.Y.) scanned titles and abstracts for potentially eligible trials. The full text of these were retrieved and independently reviewed by two reviewers (H.L.A.Y., E.T.) who determined eligibility. They were not blinded to information such as journal names or authors. Disagreements were resolved through consensus by a third reviewer (S.C.).

3.4 | Data extraction

Two authors (H.L.A.Y., E.T.) independently extracted data from included studies using a pre-formed data collection tool. Disagreements were discussed and, where necessary, authors were contacted for clarification. Data extraction was not blinded.

3.5 | Assessment of risk of bias

Two reviewers (H.L.A.Y., E.T.) independently assessed internal validity using the Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I) assessment tool.[17] Overall bias assessment for ROBINS-I is determined by the highest risk assigned in any individual domain and results are displayed visually using the robvis program.[18] Lost to follow-up was assessed through the bias due to missing data variable and was classified as moderate if this was 5%–10% of the included population, serious for 10%–20% and critical for >20%. We included an additional category from the Joanna Briggs Institute Prevalence Critical Appraisal Tool, adequacy of the study subject description and additional criteria for outcome measurement[19] as these were not adequately covered by the ROBINS-I tool. Disagreement was resolved through consensus, attempts to contact authors for clarification and consultation with a third reviewer (S.C.).

3.6 | Outcome measures

The primary outcome measures were the incidence of radiologically confirmed, symptomatic recurrent UEDVT, PTS and QoL assessments at least 6 months post-cessation of anticoagulation. For recurrent UEDVT, both ipsilateral and contralateral events to the index event if involving proximal vessels to the brachial vein were included. For PTS, we accepted studies which utilised a validated tool such as the modified Villalta Scale (MVS) where PTS is deemed present when the score is greater than 4.[20] QoL and disability assessments were accepted if evaluated with a validated tool.

Secondary outcomes included symptomatic LLDVT, proximal and distal or subsegmental or more proximal PE at least six months post-anticoagulation cessation. Other secondary outcomes included bleeding following the International Society of Thrombosis and Haemostasis definitions[21,22] and mortality.

3.7 | Assessment of heterogeneity

Meta-analysis was not carried out due to the clinical and methodological diversity of studies.

4 | RESULTS

4.1 | Results of the search

A total of 1509 citations were retrieved, with the full text of 111 articles assessed (Figure 1). We found no unpublished or ongoing studies. Nine studies met our inclusion criteria with all published in English (Tables 1 and 2). Seven reported the outcome of recurrent UEDVT, four reported PTS and three reported QoL outcomes with a total of 310, 101 and 90 participants respectively.

4.2 | Included studies

Of the nine included studies, five labelled their participants as having VTOS or PSS.[15,26,27,30,31] Criteria for VTOS were not described in three studies[15,26,27] though further information was obtained from the author of one study (A Riera-Mestre, personal communication, 25 September 2020).[15] In one study, the PSS diagnosis was implied by retrospective review limited to patients who had operative intervention.[30] In the only study describing their criteria for VTOS, they defined it as patients with a typical history and examination findings and radiological confirmation of venous impingement or narrowing with dynamic manoeuvres, though neither the degree of impingement nor types of dynamic manoeuvres were specified.[31]

4.2.1 | Included studies reporting on recurrent thrombosis

Seven studies reported the outcome of recurrent UEDVT with two cross-sectional[24,25] and five retrospective studies.[12,15,16,26,27] The index idiopathic UEDVT involved the axillosubclavian vein in most studies however two studies included small numbers of patients with isolated brachial vein thrombosis (3%–6%).[16,24] In the largest retrospective study involving 115 patients, these were restricted to patients who had undergone thrombophilia testing.[16] All patients in our included studies were young with a mean age of 28–41 years.

Four studies assessed anticoagulation alone ($n = 193$)[15,16,24,25] and three studies assessed anticoagulation with other interventions ($n = 117$) such as thrombolysis,[12,26,27] decompressive surgery (first rib resection, scalenectomy)[26,27] and angioplasty.[26,27] No studies (randomised or non-randomised) directly compared anticoagulation alone with anticoagulation and additional interventions with all studies being essentially single-arm cohorts. Anticoagulation comprised mostly therapeutic oral anticoagulation (presumed to be vitamin K antagonists, given the publication era of studies, with no reporting on

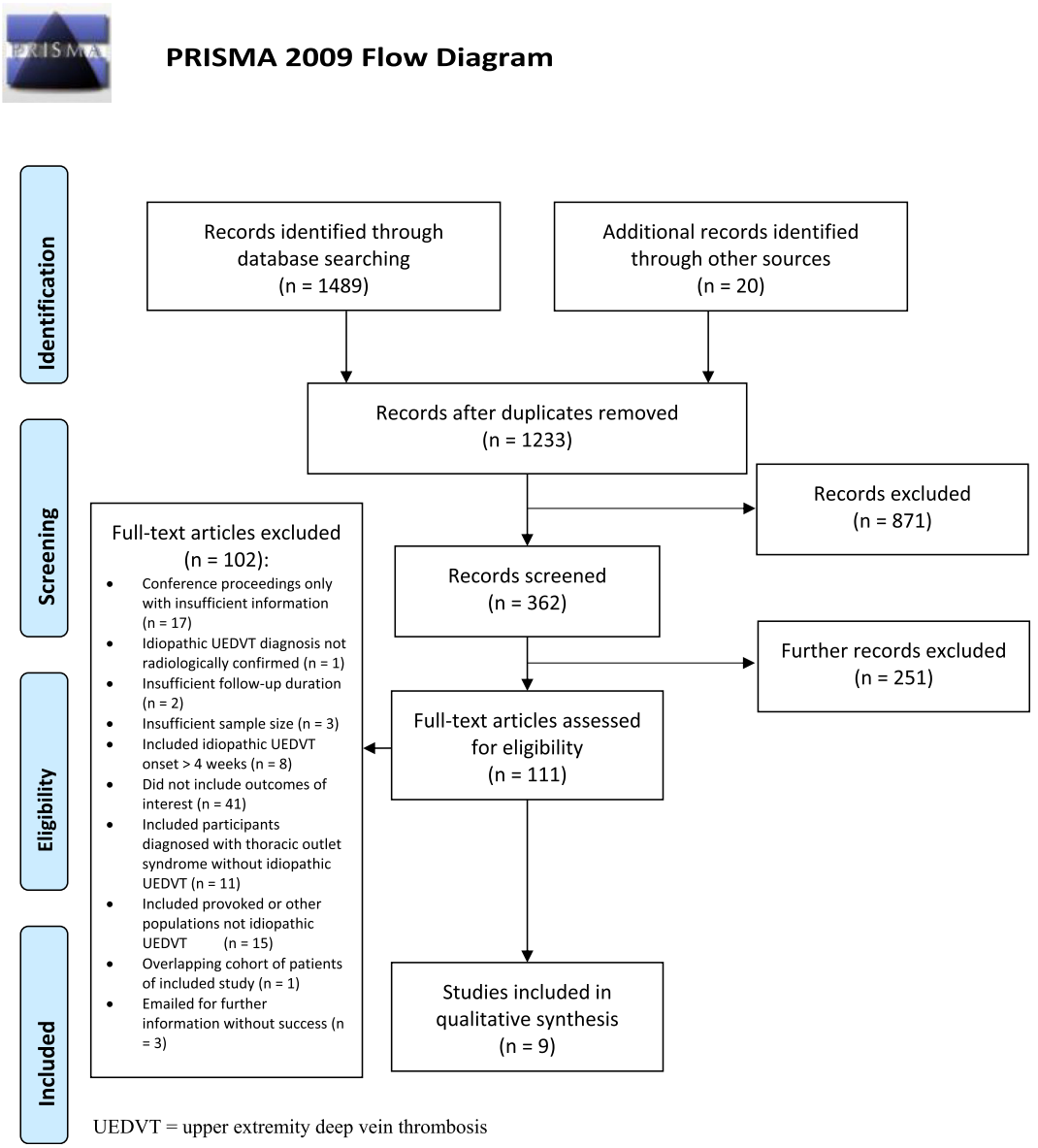

FIGURE 1 PRISMA flow diagram.[23] UEDVT, upper extremity deep vein thrombosis

TABLE 1 Summary of outcomes

Study	Sample size (n)	Intervention	Recurrent UEDVT, % (95% CI)	PTS, % (95% CI)
Martinelli et al.[16]	115	Anticoagulation alone	12 (7–20)	NR
Arnhjort et al.[24]	32	Anticoagulation alone	0 (0–13)	28 (15–46)
Czihal et al.[25]	25	Anticoagulation alone	0 (0–16)	32 (17–52)
Riera-Mestre et al.[15]	21	Anticoagulation alone	5 (0–24)	19 (7–41)
Lee et al.[12]	64	Anticoagulation ± thrombolysis/venoplasty/stenting and FRR	23 (10–40)	NR
Bamford et al.[26]	35	Anticoagulation, CDT and FRR	Delayed FRR: 10 (2–31) Acute FRR: 0 (0–25)	NR
Spivack et al.[27]	18	Anticoagulation, CDT and FRR	11 (2–34)	NR
Elixène et al.[28]	33	Anticoagulation ± thrombolysis/thrombectomy and FRR	NR	NR
Stuck et al.[29]	23	Anticoagulation, CDT ± surgical decompression	NR	4 (0–23)

Abbreviations: CDT, catheter-directed thrombolysis; CI, confidence interval; FRR, first rib resection; NR, not reported; PTS, post-thrombotic syndrome; UEDVT, upper extremity deep vein thrombosis.

TABLE 2 Included studies for recurrent UEDVT

Study	Study design	Population	Sample size	Age (years, median unless otherwise specified, range)	Male (%)	Intervention	Follow-up duration	Outcomes reported	Main limitations and other notes
Martinelli et al.[16]	Retrospective	First primary UEDVT and had thrombophilia testing (included patients regardless of result) 97% axillosubclavian vein involvement	115	32 (14–61)	36	• Oral anticoagulation for median 5 months ($n = 77$) • Subcutaneous heparin ($n = 14$) • Antiplatelet ($n = 7$)	5.1 years (range, 2–12.5 years)	• Recurrent symptomatic UEDVT 12/98 (12% 95% CI 7–20) • Overall, the cumulative probability of recurrence-free survival was 95% at 1 year and 89% at 5 years of follow-up	• Confirmed patients were treated with anticoagulation alone (I. Martinelli, personal communication, 22 June 2020) • Calculation of recurrence excluded patients on ongoing anticoagulation ($n = 8$) and others for reasons not specified ($n = 9$) • Population included isolated brachial vein thromboses (3%) • Outcomes not reported: PTS, subsequent PE, QoL, bleeding
Arnhjort et al.[24]	Cross-sectional study	Primary UEDVT 94% axillosubclavian vein involvement	32	39.5 (17–77)	28	• Anticoagulation alone for 3 to 6 months ($n = 30$) • Thrombolysis and anticoagulation for 3–6 months ($n = 1$) • Long-term anticoagulation ($n = 1$)	5 years (range, 2–9)	• Recurrent symptomatic UEDVT or PE/DVT 0/32 0% (95% CI 0–13) • Residual thrombosis on ultrasound 58% (95% CI 41–74) • PTS present (MVS >4) 9/32 (28% 95% CI 15–46) • No association between PTS and residual thrombosis • DASH scores comparing those with PTS against those without	• 5 eligible patients identified declined participation • No patients had severe PTS • Population included isolated brachial vein thromboses (6%) • Recurrence outcome included 1 patient on long-term anticoagulation • Reported supine static ultrasound findings and plethysmographic assessment of venous emptying • Outcomes not reported: bleeding
Czihal et al.[25]	Cross-sectional study	Primary UEDVT involving axillary, subclavian and/or brachial veins who received anticoagulation only	25	39.3 (mean, NR) at study enrolment, 40.6 months (6–84) since diagnosis	60	• Anticoagulation alone for 3.6 months (range, 3–6 months)	40.6 months (range, 6–84 months)	• Recurrent UEDVT = 0/25 (0 95% CI 0–16) • Mild to moderate PTS based on MVS = 8/25 (32% 95% CI 17–52) • No severe PTS	• Acuity of symptoms to UEDVT diagnosis not reported • 1 patient was excluded due to management of thrombolysis and angioplasty, 9 patients

TABLE 2 (Continued)

Study	Study design	Population	Sample size	Age (years, median unless otherwise specified, range)	Male (%)	Intervention	Follow-up duration	Outcomes reported	Main limitations and other notes
								• Correlated PTS with QoL outcomes (SF-36, VEINES-QoL/SYM, DASH) and compared UEDVT cases with asymptomatic controls	refused or were unable to be contacted • Outcomes not reported: subsequent PE, bleeding
Riera-Mestre et al.[15]	Retrospective	Primary UEDVT (n = 11) and those considered related to VTOS (n = 10)	21	Primary UEDVT 41.4 (mean, NR) VTOS 27.9 (mean, NR)	Primary UEDVT 54 VTOS 40	• Anticoagulation alone for 7.6 ± 3.5 months	46.5 ± 27.5 months following anticoagulation cessation	Overall • Recurrent UEDVT = 1/21 (5 95% CI 0–24) • PTS = 4/21 (19 95% CI 7–41) Primary UEDVT • Recurrent UEDVT = 0/11 (0 95% CI 0–30) • PTS = 2/11 (18 95% CI 4–49) VTOS-related UEDVT • Recurrent UEDVT = 1/10 (10% 95% CI 0–43) • PTS = 2/10 (20% 95% CI 5–52)	• VTOS classified based on MRI/CT findings not described in detail • Confirmed axillosubclavian vein thrombosis in all patients (A Riera-Mestre, personal communication, 25 September 2020) • PTS defined by MVS >4 • Outcomes not reported: subsequent PE, QoL, bleeding
Lee et al.[12]	Retrospective cohort study	Primary axillosubclavian vein thrombosis	64	32 (mean, range for anticoagulation group reported as 16–61)	48	• Anticoagulation ± preceding thrombolysis (83%) or venoplasty (48%) or stenting (6%) (n = 27) with FRR subsequent due to rethrombosis (n = 8) Subsequent surgical intervention • FRR due to recurrent symptoms one month post-thrombolysis (n = 29) • Mean 5 months anticoagulation in all groups	53 months Anticoagulation group 55 months (range, 10–110 months) *FRR upon recurrent thrombosis 51 months (range, 2–103 months)	• Recurrent symptomatic UEDVT = 8/35, 23% (95% CI 10–40) in anticoagulation group with thrombolysis or venoplasty at 13 months (range, 6–33) • Recurrent symptomatic UEDVT after FRR upon recurrent thrombosis = 0/8, 0% (95% CI 0–11)	• Not all information supplied for cohort who received FRR at one month as report focused on those receiving anticoagulation post-thrombolysis • Outcomes not reported: PTS, subsequent PE, QoL, bleeding

(Continues)

TABLE 2 (Continued)

Study	Study design	Population	Sample size	Age (years, median unless otherwise specified, range)	Male (%)	Intervention	Follow-up duration	Outcomes reported	Main limitations and other notes
Bamford et al.[26]	Retrospective	Subclavian or axillary vein thrombosis and underwent endovascular or surgical intervention for suspected VTOS	35	37.9 (mean, 22–67)	58	• CDT ± balloon venoplasty followed by anticoagulation for 3 months before delayed FRR, scalenectomy and postoperative anticoagulation in 45% for 3 months (n = 20) • CDT and acute FRR, scalenectomy and postoperative anticoagulation in 23% for 3 months (n = 13)	44 months (range, 3–85 months)	Delayed FRR • Recurrent UEDVT = 2/20 (10% 95% CI 2–31) Acute FRR • Recurrent UEDVT = 0/13 (0 95% CI 0–25)	• Lost to follow-up = 2 • Follow-up recurrent UEDVT reliant on GP records • 3 patients continued long-term anticoagulation • 42% presented after 7 days of symptoms • Outcomes not reported: PTS (study recorded proportion of patients who were symptom-free at follow-up), subsequent PE, QoL, bleeding
Spivack et al.[27]	Retrospective	Subclavian vein thrombosis felt secondary to VTOS Mean 29 days from symptom onset (range, 0–104) due to patient referral from other institutions	18	35 (mean, 16–60)	61	• CDT followed by FRR ± endovascular or surgical repair or stenting • Anticoagulation with warfarin for 6 months postoperatively	1.6 years (range, 1 month to 13 years)	• Recurrent UEDVT = 2/18 (11% 95% CI 2–34) which occurred within 2 weeks of operation	• Criteria for VTOS and recurrent UEDVT confirmation not described • Inadequate follow-up for some patients who would have still been on anticoagulation • Did not report whether index thrombosis was a first or recurrent event • Outcomes not reported: PTS, subsequent PE, QoL, bleeding

Abbreviations: CI, confidence interval; CDT, catheter-directed thrombolysis; DASH, disabilities of the arm; shoulder and hand; DVT, deep vein thrombosis; FRR, first rib resection; LR, likelihood ratio; MVS, modified Villalta scale; NR, not reported; PE, pulmonary embolism; PSS, Paget–Schroetter Syndrome; PTS, post-thrombotic syndrome; QoL, Quality of Life; SD, standard deviation; SF-36, Short-Form Health Survey-36; UEDVT, upper extremity deep vein thrombosis; VTOS, venous thoracic outlet syndrome.

TABLE 3 Included studies for PTS outcomes not included in Table 2

Study	Study design	Population	Sample size	Age (years, median unless otherwise specified, range)	Male (%)	Intervention	Follow-up duration	Outcomes reported	Main limitations and other notes
Elixène et al.[28]	Retrospective cohort study	Acute (<10 days, $n = 13$) and subacute subclavian vein thrombosis ($n = 20$) considered to be PSS	33	34 (mean, 14–53)	52	Acute thrombosis treated with acute intervention ($n = 13$) • FRR, scanelectomy, resection of costoclavicular ligament and external venolysis ± preceding thrombolysis ($n = 3$), ± thrombectomy ($n = 9$), venoplasty ($n = 1$) followed by 12 weeks anticoagulation Subacute thrombosis treated with starting/continuing anticoagulation followed by late intervention, 30–120 days post-thrombosis ($n = 20$) • FRR, scanelectomy, resection of costoclavicular ligament and external venolysis + anticoagulation (12 weeks)	240 months (1–316)	Acute intervention • Vein patency 85% (95% CI 57–97) • No major bleeding • Quick DASH score 3.5 (95% CI 1.5–5.4) Late intervention • Rethrombosis 15% (95% CI 4–37) • Vein patency 40% (95% CI 22–61) • No major bleeding • Quick DASH score 17.3 (95% CI 8.4–26.2)	• Outcomes not reported: recurrent UEDVT, PTS, subsequent PE
Stuck et al.[29]	Retrospective cohort study	UEDVT due to VTOS based on history, examination and venography with subclavian narrowing or impingement with manoeuvres (not further described) and undergoing CDT	23	39 (mean, NR)	74	• CDT with either pharmacomechanical thrombolysis or ultrasound-assisted thrombolysis • Anticoagulation length post-CDT left to clinician (87% received 3–6 months) • Surgical decompression and venoplasty ($n = 4$) or further CDT ($n = 2$) dependent on subsequent PTS, rethrombosis or restenosis	12 ± 9 months	All groups • Symptomatic rethrombosis 17%, 95% CI 5–39 while on anticoagulation, 2 at 24 hours post-CDT, 2 at 2 and 8 months after thrombolysis • PTS 1/23 (4% 95% CI 0–23) • No bleeding complications	• PTS defined by MVS >4 • Likely inadequate follow-up time post-anticoagulation cessation for some patients • Outcomes not reported: subsequent PE, QoL

Abbreviations: CDT, catheter directed thrombolysis; DASH, disabilities of the arm; shoulder and hand; FRR, first rib resection; NR, not reported; PE, pulmonary embolism; PSS, Paget–Schroetter Syndrome; PTS, post-thrombotic syndrome; QoL, quality of life; UEDVT, upper extremity deep vein thrombosis; VTOS, venous thoracic outlet syndrome.

TABLE 4 Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I) assessment[17] of studies on management of idiopathic upper extremity deep vein thrombosis

Study	Bias due to confounding	Bias in selection of participants into study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Study subject description	Overall risk of bias
Martinelli et al.[16]	Not applicable due to single intervention applied	Serious due to immortal time bias as for calculation of recurrence 'follow-up started after [anticoagulation] discontinuation' and selection based on thrombophilia testing being undertaken, inclusion of 3% isolated brachial vein thrombosis	Low	Low	Serious due to only 98 patients included of 115 in recurrence calculation for unclear reasons	Adequate, provided description of recurrence to be for symptoms and diagnosed 'if a previously compressible venous segment could no longer be compressed or if in the presence of symptoms of recurrence, a previously non-occlusive thrombus had changed into an occlusive one at ultrasound examination'	Moderate due to no clear evidence of pre-registered protocol	Study population description adequate first episode of upper-extremity DVT and had thrombophilia screen, provided information on veins involved and diagnostic study undertaken to diagnose (ultrasound, venography, CT venography)	Serious
Lee et al.[12]	Not applicable due to single intervention arm with subsequent re-treatment on rethrombosis. Outcomes after subsequent surgical intervention upon rethrombosis not included in review as beyond scope of this review	Serious due to inclusion of patients referred from other centres, 12% did not undergo thrombolysis or venography were all from outside institutions where there was a delay of longer than 7 days from diagnosis… or where symptoms had already begun to significantly improve on anticoagulation.	Moderate due to varying interventions prior to therapeutic anticoagulation	Low	No information	Moderate as did not define what constituted recurrence and recurrence reported assumed to be symptomatic as occurred outside of routine ultrasound testing	Moderate due to no clear evidence of pre-registered protocol	Study population description inadequate 'Prospective registry of PSS patients… consecutively treated with an algorithm of selective surgical therapy after thrombolysis and full anticoagulation' Did not define PSS but did mention clinical diagnosis of primary axillosubclavian vein thrombosis was based on history and physical examination. Diagnosis 'confirmed with colour-flow venous duplex ultrasonography' but	Serious

TABLE 4 (Continued)

Study	Bias due to confounding	Bias in selection of participants into study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Study subject description	Overall risk of bias
								did not state criteria for diagnostic confirmation and whether this pertained to PSS or IUEDVT	
Arnhjort et al.[24]	Not applicable as majority (30/32) received anticoagulation alone	Serious due to cross-sectional nature of study, $n = 5/37$ declined participation and included 6% isolated brachial vein thrombosis	Low	Low	No information	Moderate as did not define what constituted recurrent UEDVT in methods	Moderate due to no clear evidence of pre-registered protocol	Adequate 'symptomatic primary UEDVT, diagnosed with colour duplex ultrasound and/or contrast venography' Though did not mention criteria for above	Serious
Bamford et al.[26]	Serious due to time-varying confounding with 'only 19/33 (58%) cases … presented within seven days of onset of symptoms' and from treatment allocation	Serious due to immortal time bias with 'only 19/33 (58%) cases … presented within seven days of onset of symptoms' and selection of patients based on endovascular or surgical intervention for suspected VTOS without description of criteria for VTOS	Insufficient data Likely overlap between two groups as the distinction in groups were based on FRR performed pre-2006 and after rather than acuity of FRR	Low	Moderate due to lost to follow-up of 2/35	Serious as follow-up determined by GP records (assessment of recurrence occurred at 3–85 months post-index UEDVT) Recurrence not radiologically defined in methods—they looked for if 'patient had suffered recurrent symptoms, recurrent thrombosis or had subsequently needed oral anticoagulation for a thrombotic event in the same arm'	Moderate due to no clear evidence of pre-registered protocol	Inadequate, 'subclavian or axillary vein thrombosis… undergoing either endovascular or surgical interventions' and does not include criteria by which these patients were diagnosed as having VTOS apart from the intervention undertaken	Serious
Czihal et al.[25]	Not applicable due to single intervention arm	Serious due to patient inclusion based on treatment received (anticoagulation alone), and cross-sectional nature of study with 9 out of 34 otherwise eligible	Low	Low	Low	Moderate as recurrent UEDVT not defined in methods, assumed to have been history obtained from patients at study visit (cross-sectional)	Moderate due to no clear evidence of pre-registered protocol	Adequate 'first episode of symptomatic primary UEDVT (involving axillary, subclavian and/or brachial veins) that was objectively diagnosed using	Serious

(Continues)

TABLE 4 (Continued)

Study	Bias due to confounding	Bias in selection of participants into study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Study subject description	Overall risk of bias
		patients unable to participate due to 'refusal to participate…or impossibility to contact'						venous ultrasonography at least 6 months prior to the study visit. Only patients who were treated with anticoagulation alone were included' Did not specify criteria for ultrasonographic diagnosis nor acuity from diagnosis of UEDVT to treatment initiation	
Spivack et al.[27]	Not applicable due to single intervention arm	Serious due to immortal time bias in 'majority of patients being referred to after initial treatment elsewhere' and patient selection based on potential VTOS without description of criteria for VTOS	Low	Low	Low	Moderate as did not report criteria applied for recurrent UEDVT	Moderate due to no clear evidence of pre-registered protocol	Inadequate Included all patients 'treated for VTOS' but did not specify criteria applied or whether this was the limited to those with a first event	Serious
Riera-Mestre et al.[15]	Low	Low	Low	Low	Low	Moderate as did not report criteria applied for recurrent UEDVT	Moderate due to no clear evidence of pre-registered protocol	Adequate Included 'all objectively diagnosed primary upper-extremity DVT patients… confirmed in all patients by Doppler'. VTOS assessment was via 'angio-magnetic resonance imaging or angio-computerised tomography with manoeuvres', criteria applied for VTOS not defined in the manuscript but	Moderate

TABLE 4 (Continued)

Study	Bias due to confounding	Bias in selection of participants into study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Study subject description	Overall risk of bias
								confirmed with personal correspondence to be possible reduction of the subclavian vein (and/or artery) diameter between images with the patient at neutral position and images with forced overhead abduction of the arms (Riera-Mestre, personal communication, 25 September 2020)	
Stuck et al.[29]	Not applicable due to single intervention arm with subsequent treatment on rethrombosis or complications	Serious due to patient inclusion based on treatment received (had to have received CDT), also patient selection based on VTOS with some description of criteria applied but unable to be replicated due to absent detail	Low	Low	Low	Low as used MVS for PTS assessment	Moderate due to no clear evidence of pre-registered protocol	Adequate 'UEDVT due to VTOS… diagnosed on basis of typical history and physical examination and subsequently confirmed by digital subtraction venography with subclavian vein narrowing or impingement with provocative manoeuvres after successful thrombolysis… >50% diameter stenosis of the subclavian vein… at the costoclavicular junction'	Serious
Elixène et al.[28]	Not applicable due to single intervention arm eligible for study inclusion (acute intervention component)	Serious due to patient inclusion based on treatment received (FRR for suspected PSS); acuity of presentation	Low	Low	Low	Low as used Quick DASH QoL tool	Moderate due to no clear evidence of pre-registered protocol	Inadequate—did not specify VTOS diagnostic criteria 'consecutive patients who underwent a surgical	Serious

(Continues)

TABLE 4 (Continued)

Study	Bias due to confounding	Bias in selection of participants into study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Study subject description	Overall risk of bias
		dictated acute versus late FRR						decompression of the thoracic outlet procedure… all patients with a confirmed diagnosis of PSS based upon clinical, duplex scan and venographic criteria'	

Abbreviations: CDT, catheter-directed thrombolysis; FRR, first rib resection; PSS, Paget–Schroetter Syndrome; PTS, post-thrombotic syndrome; QoL, quality of life; VTOS, venous thoracic outlet syndrome.

the time within therapeutic range) for 3–7 months with follow-up for study outcomes at 1.6–5 years. One study included small numbers of patients on subcutaneous heparin and antiplatelet agents.[16]

Six of seven studies reporting rate of recurrent UEDVT did not specify the criteria used.[12,15,24–27] One study did not explicitly describe the recurrent UEDVT as symptomatic though this was implied due to lack of routine screening investigations performed post-treatment.[12] One study relied on family practice records to identify recurrent UEDVT.[26]

4.2.2 | Included studies reporting on post-thrombotic syndrome and QoL

Studies reporting PTS and QoL assessments were retrospective[15,28,29] or cross-sectional[24,25] and utilised tools such as the MVS[15,24,25,29] and Quick DASH[28] after anticoagulation alone ($n = 78$),[15,24,25] anticoagulation combined with thrombolysis followed by acute ($n = 13$)[28] or late surgical decompression ($n = 24$)[28,29] (shown in Tables 2 and 3). Surgical decompression was undertaken only if there was PTS, rethrombosis or restenosis in one study.[29] One study reporting on PTS included 6% patients with isolated brachial vein thrombosis.[24] Most studies had adequate follow-up with the exception of one study which conducted PTS assessment between 3 and 21 months from the index event.[29]

4.3 | Risk of bias in included studies

Selection bias and bias in measurement of outcomes were common amongst our studies and resulted in the overall risk of bias using the ROBINS-I tool serious for nearly all studies (Table 4; Figure 2). Selection bias included where patients were referred from other institutions after differing treatments and time between symptom onset to intervention or where patient selection was based on tests performed (e.g., thrombophilia screening[16]) or treatment received (e.g., CDT/FRR[26,28,29] or anticoagulation alone[25]). One study also determined FRR timing based on days from symptom onset (acute presentation treated with acute FRR, subacute or delayed presentation were treated with delayed FRR).[28] Further bias could have been introduced by inclusion of isolated brachial vein thrombosis which likely confers a lower risk of recurrent UEDVT, PTS and PE compared to axillosubclavian vein thrombosis. As mentioned, many studies also did not adequately describe their included population in terms of what constituted VTOS or PSS.

In addition, the cross-sectional studies would have introduced selection bias through potential differences between patients who were willing to participate or had survived their initial event compared to the significant number of patients who refused or were unable to participate.[24,25] Further selection bias would have been conferred in limiting the included population to those who had received a specific treatment or undergone specific diagnostic tests. Two studies also had moderate to serious rates of lost to follow-up.[16,26]

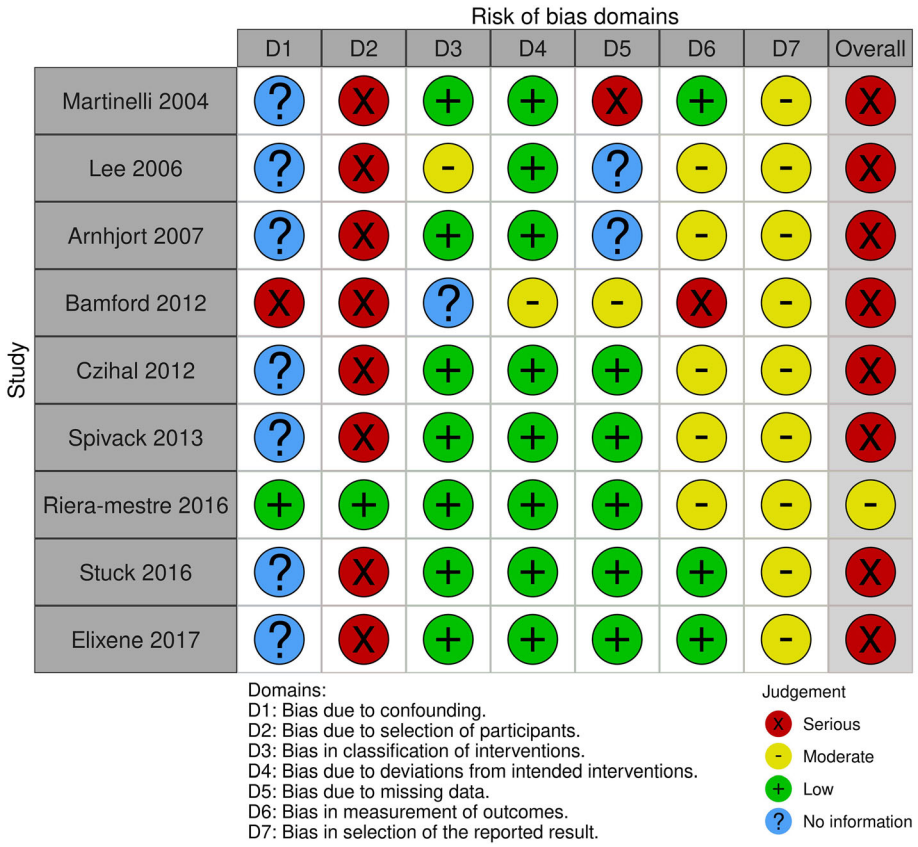

FIGURE 2 ROBINS-I assessment of all included studies, made using robvis[18]

Potential misclassification of recurrent UEDVT was another serious source of bias in nearly all studies. Six of seven studies reporting recurrent UEDVT did not define their criteria for recurrent UEDVT[12,15,24–27] and one study relied on family practice records and therefore, events managed elsewhere would potentially be missed.[26]

4.4 | Effects of treatments on recurrent thrombosis

4.4.1 | Anticoagulation alone

With anticoagulation alone of 3–7 months duration, recurrent UEDVT rates varied from 0 (95% confidence interval [CI] 0–13, 0–16),[24,25] 5% (95% CI 0–24)[15] and 12% (95% CI 7–20)[16] over 3–5 years. The 12% recurrence rate was in the largest study which retrospectively analysed 115 patients who had completed thrombophilia testing, regardless of result.[16] The requirement for complete thrombophilia testing would have led to selection bias as mentioned. In this cohort, 28% had an inherited thrombophilia, mostly consisting of heterozygous factor V Leiden and prothrombin gene mutation in 9% and 10% respectively. All recurrent UEDVT occurred after cessation of anticoagulation with 5% occurring by the 1st-year post-cessation and 20% by 5 years. One other study reported one recurrence, 5% (95% CI 0–24), in their cohort which combined patients with positive and negative imaging findings for VTOS.[15] This recurrence occurred 18 years post-anticoagulation cessation. Therefore, anticoagulation alone is effective with low rates of recurrence which only occurred after cessation of anticoagulation.

4.4.2 | Anticoagulation with additional interventions

Studies which reported outcomes after additional interventions to anticoagulation used therapeutic anticoagulation for 3–5 months and had follow-up of 2–4 years.[12,24,26,27] UEDVT recurred in 23% (95% CI 10–40) after CDT, venoplasty or stenting, occurring 1–28 months post-anticoagulation cessation.[12] After acute FRR, recurrence occurred in 0%–11%[26,27] all occurring within 2 weeks of FRR despite anticoagulation and surprisingly no additional events in long-term follow-up post-anticoagulation cessation.[27] One study compared acute FRR with 3 months of coagulation to 3 months anticoagulation pre- and post-delayed FRR. They reported 0% (95% CI 0–25) recurrent UEDVT in the acute FRR group compared to 10% (95% CI 2–31) recurrent UEDVT in the delayed FRR group, all of which occurred after cessation of anticoagulation.[26] Therefore, UEDVT recurrence rates were numerically higher to those found with anticoagulation alone and occurred either immediately post-acute FRR or after anticoagulation cessation.

Several studies included small numbers of patients who remained on long-term anticoagulation in their recurrent UEDVT calculations.[24,26] This would therefore potentially underestimate the risk of recurrence which presumably would be higher if these patients had

ceased anticoagulation. Such patients were excluded from recurrence data in one study.[16]

4.5 | Effects of treatments on post-thrombotic syndrome, QoL and disability

4.5.1 | Post-thrombotic syndrome

Three studies of 21–32 patients reported PTS incidence of 20% to 32% (using the MVS) at 3–5 years after completing a minimum of 3 months anticoagulation.[15,24,25] Two studies reported on their incidence of severe PTS (MVS ≥ 15) in that they found none (95% CI 0–13 and 0–16).[24,25]

In contrast, one study assessed CDT followed by anticoagulation for 3–6 months and found an incidence of PTS via MVS of 4% (95% CI 0–23) at 3–21 months.[29] However, their assessment of PTS at earlier than 6 months could have led to under or over-estimation of PTS extrapolating from data in LLDVT PTS assessment.[30]

No studies evaluating additional interventions reported severe PTS incidence.[12,24,26,27]

4.5.2 | QoL and disability

Three studies reported QoL or disability scores after anticoagulation alone for 3–6 months[24,25] and after acute and delayed FRR followed by 1–3 months of anticoagulation.[28] With anticoagulation alone, one study correlated MVS to QoL (VEINES-QOL, VEINES-SYM, SF-36) and DASH scores in a cohort of patients with antecedent UEDVT and asymptomatic controls.[25] They found worse scores in the SF-36 physical component, VEINES-QOL, DASH scores in patients with antecedent UEDVT compared to controls. Patients who developed PTS had worse scores across the same components compared to patients without PTS. Similarly, a cross-sectional study found the 28% of patients treated with anticoagulation alone who had PTS (with no severe PTS) had worse DASH scores than those without PTS.[24] Elixène et al.[28] reviewed acute versus late FRR followed by 1–3 months of anticoagulation. Whilst they did not assess for PTS, they found statistically lower Quick DASH scores at median 240 months (range, 1–316) with acute compared to late FRR, suggesting better long-term functional recovery with early intervention.[28]

4.6 | Secondary outcomes

One study reported on symptomatic PE incidence, with no events after fixed duration anticoagulation alone at 5-year follow-up.[24]

Only two studies reported rates of bleeding. No bleeding complications were reported from CDT and delayed intervention[29] and no major bleeding was reported following acute FRR.[28] Neither study used a validated scale for bleeding assessment.

No studies reported specifically on mortality.

5 | DISCUSSION

5.1 | Summary of main results

Overall, the nine included studies were relatively small, retrospective or cross-sectional and nearly all were at serious risk of selection bias. Furthermore, there was considerable variation in included patient characteristics, interventions, follow-up duration and outcome ascertainment and definitions. Though the criteria used for VTOS diagnosis were poorly defined, it is likely that many patients in the included studies would have this condition given their young age at diagnosis. UEDVT recurrence was low post-anticoagulation alone at 0%–12% and occurred after anticoagulation cessation. Recurrence seemed more common after additional intervention at 0%–23% and occurred immediately after acute FRR or after anticoagulation cessation. The numerically higher recurrence rate with additional interventions may reflect a higher risk cohort of patients, variability in local expertise in the additional interventions employed or potentially the prothrombotic nature of surgical or catheter-directed intervention. Therefore, we would caution about making direct comparisons between the two treatment strategies.

These rates of recurrent UEDVT are low when compared to idiopathic PE or LLDVT which confers a recurrence rate of 25% over 5 years.[31] However, our studies included the period on anticoagulation as part of their follow-up duration. Therefore, the follow-up period post-anticoagulation cessation would be less than 5 years for all our included studies. It is, therefore, unclear whether the UEDVT recurrence rates meet the threshold for long-term anticoagulation set by the International Society of Thrombosis and Haemostasis of more than 15% over 5 years post-anticoagulation cessation.[32] The incidence of PTS ranged from 4% to 32% with all being mild to moderate. QoL assessments did not allow for between study comparison due to differences in the tools utilised and underutilisation of norm-referenced scoring tools such as the SF-36 where scores are compared to the general population. However, the findings of these studies are intuitive in that patients with PTS have worse QoL scores and patients with antecedent UEDVT have worse scores than asymptomatic healthy controls.

For secondary outcomes, few included studies reported rates of bleeding or PE. Furthermore, bleeding assessment when undertaken was not graded objectively using validated tools whilst the included studies had insufficient sample sizes to accurately enumerate PE incidence given it is relatively uncommon. No studies reported on mortality and such assessment would have been precluded in cross-sectional studies.

5.2 | Overall completeness and applicability of evidence

5.2.1 | Applicability of findings

Our findings must be interpreted with caution. The quality of included studies was low, with studies being mostly retrospective, at serious risk of selection bias and no randomised studies at all. Furthermore,

the short duration of follow-up in our studies reporting recurrent UEDVT preclude the accurate estimation of recurrence rates at 5 years following anticoagulation cessation.

5.3 | Potential biases in the review process

5.3.1 | Possible limitations

Publication bias is a possibility. However, we attempted to avoid this by including searches in other languages, searching trial registries and employing an extensive search strategy.

5.3.2 | Strengths

This review's strengths lie in its rigorous methodology. We aimed to keep the review transparent by extensively reporting our methods and results and by using validated risk of bias tools. Additionally, article inclusion was not limited by language and we attempted to minimise citation bias through our search of multiple clinical trial databases and reference lists of similar reviews utilising slightly different search strategies.

5.3.3 | Agreements and disagreements with other studies or reviews

A systematic review by Thiyagarajah et al.[33] reported on the effect of various treatments in idiopathic UEDVT on recurrence and PTS risk. Whilst we agree with their conclusion that no recommendation can be made based on evidence to date, their study population included patients with chronic idiopathic UEDVT of more than 4 weeks since symptom onset which may have affected their UEDVT recurrence and PTS risk. Furthermore, they did not differentiate between the outcomes of symptomatic recurrent idiopathic UEDVT and radiological outcomes such as vein outflow obstruction and vein patency. These outcomes are vastly different. Vein patency has not been shown to correlate with recurrence risk or PTS severity and its assessment is affected by the sensitivity and inter-observer variability of the imaging modality utilised and difficulties with detection of chronic residual thromboses. Their meta-analysis was limited by statistical heterogeneity of their included studies and similar to our included studies, their studies did not perform uniform VTOS investigation either.

A recent systematic review on primary and secondary UEDVT found a low risk of recurrent thrombosis (including UEDVT, LLDVT and PE) of 3% (95% CI 2–4) over 13 months' follow-up after a mean of 5 months anticoagulation.[34] However, most included patients had secondary UEDVT related to vascular access devices (60.8%) and cancer (56.1%). Only 7.2% had 'effort-related' UEDVT which was not further defined. Therefore, the results of this systematic review likely reflect the risk of recurrent thrombosis in secondary UEDVT as opposed to idiopathic UEDVT, our target population.

6 | SUMMARY AND IMPLICATIONS FOR RESEARCH

In summary, when faced with patients with idiopathic UEDVT, there is insufficient evidence to support a more aggressive strategy over acute systemic anticoagulation alone to prevent long-term UEDVT recurrence or PTS. Recurrent UEDVT risk seems to be 0%–12% when treated with limited duration anticoagulation alone and 0%–23% with anticoagulation together with surgery or thrombolysis. Furthermore, though the main justification for additional intervention is to prevent PTS or reduce its severity, our studies on anticoagulation alone reported only 20%–32% incidence of PTS with no cases of severe PTS. Therefore, in UEDVT, the adverse events from additional interventions do not seem justified. Furthermore, the not insignificant rate of bleeding of 3%–4% annually with long-term anticoagulation[34] needs to be carefully balanced against recurrence risk. Future prospective studies directly comparing fixed duration anticoagulation alone versus anticoagulation with additional interventions and adequate follow-up of 2–5 years would be ideal. However, given idiopathic UEDVT is an uncommon condition, more realistic research approaches include conducting high-quality single intervention prospective studies with clear inclusion criteria, clear endpoint definition and adequate follow-up or developing well-maintained registries with clear inclusion and outcome measures to enable further research.

In the absence of such research, clinical equipoise remains between anticoagulation alone or more aggressive therapies as well as regarding the duration of anticoagulation to utilise in the management of idiopathic UEDVT.

AUTHOR CONTRIBUTIONS

Hiu Lam Agnes Yuen, Huyen Tran and Sanjeev Chunilal designed and wrote the paper. Ee Tan and Hiu Lam Agnes Yuen reviewed abstracts and undertook data extraction and risk of bias assessment. All authors approved the final version of the manuscript for publication.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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