Treatment of Superficial Vein Thrombosis: A Systematic Review and Meta-Analysis

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Abstract

Background The optimal first line treatment for patients with isolated superficial venous thrombosis (SVT) of the lower extremity is unknown.

Objective This article reports estimates of the rate of venous thromboembolic complications among patients with SVT according to treatment.

Materials and Methods A systematic review and meta-analysis was performed using unrestricted searches of electronic databases. Reported events were transformed to event per 100 patient-years of follow-up and a random effects model was used to calculate pooled rates according to pre-specified treatment categories. The primary outcome was the occurrence of deep vein thrombosis (DVT) or pulmonary embolism (PE) during the study follow-up period.

Results Seventeen articles, including 6,862 patients, were included in the meta-analysis. Fondaparinux had the lowest event rate with 1.4 events per 100 patient-years of follow-up (95% confidence interval [CI], 0.5–2.8, $I^2 = 18\%$). Pooled event rates for DVT or PE ranged from 9.3 to 16.6 events per 100 patient-years across other treatment categories, and the pooled event rate for no treatment/placebo was 10.5 events per 100 patient-years (95% CI, 3.0–22.0). Major bleeding was low and similar across all treatment categories. Heterogeneity was moderate to high for most pooled estimates.

Conclusion While pooled event rates suggest that fondaparinux achieves the lowest rate of DVT or PE, low-quality evidence for other treatments prevents firm conclusions about the optimal treatment for SVT.

Keywords
- superficial vein thrombosis
- thrombophlebitis
- systematic review
- anticoagulants
- anti-inflammatory agents

Introduction

Superficial venous thrombosis (SVT), also referred to as superficial thrombophlebitis, is a common inflammatory and thrombotic pathology within a superficial vein.[1–3] Patients may present clinically with localized pain, tenderness, redness, oedema and/or a firm palpable cord[1,2,4,5] with diagnosis typically being confirmed via compression ultrasound (US).[4,6–9] Similar to other venous conditions, risk factors for SVT include immobilization, recent surgery, active cancer, pregnancy/puerperium, use of oestrogen therapy, obesity, advanced age, history of prior venous thrombosis or SVT, inherited thrombophilia, autoimmune disease, varicose veins, chronic venous insufficiency and sclerotherapy.[1,2,4,7,8,10]

Various interventions have been studied for the treatment of SVT, including observation, elastic compression stocking, topical heparins, topical non-steroidal anti-inflammatory drugs (NSAIDs), oral NSAIDs, anticoagulant medications (unfractionated heparin [UFH], low molecular weight heparin [LMWH], fondaparinux, vitamin K antagonists

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[VKAs] and direct oral anticoagulants [DOACs]) at various dose intensities (low/prophylactic, intermediate or high/therapeutic dose) as well as surgical procedures (ligation or venous stripping).[1,10] The largest trial to date is the 'Comparison of Arixtra in Lower Limb Superficial Vein Thrombosis with Placebo' (CALISTO), which randomized 3,002 patients with SVT of at least 5 cm in length to receive prophylactic dose fondaparinux or placebo for 45 days.[11] The primary outcome was a composite of symptomatic pulmonary embolism (PE), symptomatic deep vein thrombosis (DVT), extension to the saphenofemoral junction (SFJ), recurrence of SVT or death at day 47, which occurred in 0.9% of the fondaparinux group compared with 5.9% of the placebo group ($p < 0.001$). Each component of the composite outcome, except for death, was also statistically significantly reduced.[11] Although this trial is considered practice changing,[1,10] since the control arm in this trial was placebo, the patients were prohibited from taking oral NSAIDs which limits the clinical relevance. Additionally, the composite outcome used includes outcomes of unequal clinical significance. The number of patients needed to treat with fondaparinux to prevent the most serious outcome, PE, is 300 and a cost-effectiveness analysis did not support this treatment strategy.[12] The 'Superficial Phlebitis Treated for Forty-five Days with Rivaroxaban versus Fondaparinux' (SURPRISE) trial randomized patients with acute SVT and one or more high-risk factors to treatment with either rivaroxaban or fondaparinux, both in low/prophylactic dose.[13] The primary outcome of this non-inferiority trial was a similar composite outcome as the CALISTO trial of either DVT, PE, progression or recurrent SVT or death. The SURPRISE trial concluded that rivaroxaban was non-inferior to fondaparinux. NSAIDs have historically, and in many clinical settings, remained to be an inexpensive, safe and readily available treatment for SVT. However, the efficacy of fondaparinux or rivaroxaban has never been compared with oral NSAIDs in a randomized control trial (RCT). Ultimately, the role of NSAIDs as the optimal first line management strategy for patients with SVT remains unclear. To further investigate this, we conducted a systematic review to estimate venous thromboembolic (VTE) complication rates in patients with acute lower extremity SVT who receive various treatments.

Materials and Methods

The primary objective of our systematic review was to estimate the rate of development of symptomatic VTE disease during follow-up in patients with acute lower extremity SVT treated with: (1) NSAIDs, (2) anticoagulant therapies, (3) surgical therapies or (4) observation/placebo. Treatment strategy categories are defined as follows: (1) NSAIDs (including aspirin at a dose higher than 100 mg per day), (2) anticoagulant therapies: any oral or parenteral anticoagulation at any dose (classified as low/prophylactic or intermediate/high/therapeutic), (3) surgical therapies: any acute surgical intervention (e.g. venous ligation or surgical removal/stripping of the affected superficial vein) and (4) observation/placebo (also including patients receiving aspirin at a dose of 100 mg per day or less or elastic compression).

The systematic review protocol, including all planned analysis, was registered a priori through PROSPERO, an international database of prospectively registered systematic reviews in health and social care.[14]

Search Strategy

An electronic search of the following databases was performed: MEDLINE (1948–July 27, 2018), EMBASE (1947–July 30, 2018) and the Cochrane Central Register of Controlled Trials (CENTRAL) (July 30, 2018). The electronic search strategy used was designed following consultation with a health science librarian with experience in systematic reviews of medical literature. A peer review of the electronic search strategy was performed by an independent librarian using the Peer Review of Electronic Search Strategies (PRESS) guidelines.[15] The final systematic search strategy using Medical Subject Indexing is shown in ►**Table 1**. Scientific meeting abstract publications for the American Society of Hematology and International Society on Thrombosis and Haemostasis (ISTH) conferences within 7 years were manually and/or electronically searched. There was no restriction on search language, and results included non-English studies that had been translated. Reference and abstracts were imported into the Reference Manager Version 12.0.1 software and duplicates were removed manually. Study title and abstract of identified publications were first screened by two independent investigators (L.D. and M.C.) for potential eligibility using a standardized form. Discrepancies during level 1 screening were resolved by including all discrepant articles for full-text screening. Full-text articles were chosen for inclusion in the final review if the article: (1) reported on unselected patients in either a cohort study or RCT, (2) only included patients with objectively proven acute lower extremity SVT by US and (3) reported one or more of the primary outcomes of interest (DVT and PE) according to treatment category. Studies were excluded if they did not report information about any one of the following treatments: (1) NSAIDs, (2) anticoagulant therapies, (3) surgical therapies, (4) no therapy/placebo, (5) did not objectively confirm the diagnosis of SVT with compression US or (6) did not provide the proportion of patient with the primary outcome of DVT or PE within a minimum of 30 days of follow-up. Any disagreements were resolved by discussion, consultation with a third party and/or requesting additional information from the study authors. The results of the systematic review are reported according to the Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA) (for systematic review of RCTs)[16] and Meta-analysis Of Observational Studies in Epidemiology (for systematic review of non-randomized trials)[17] guidelines (►**Supplementary Appendices A** and **B**, available in the online version).

Outcome Measures

The primary outcome measure was defined as symptomatic DVT and/or PE during the follow-up period. The follow-up period was defined as either within 90 days of diagnosis of

Table 1 Electronic search terms for MEDLINE and EMBASE databases

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>	EMBASE Classic + EMBASE <1947 to Present>
1 Thrombophlebitis/	1 superficial thrombophlebitis/
2 (superficial adj3 (thrombo$ or phlebitis)).tw.	2 (superficial adj3 (thrombo$ or phlebitis)).tw.
3 (saphenous adj3 (thrombo$ or phlebitis)).tw.	3 (saphenous adj3 (thrombo$ or phlebitis)).tw.
4 or/1–3	4 or/1–3
5 exp Anti-Inflammatory Agents, Non-Steroidal/	5 *thrombophlebitis/
6 (nsaid$ or non steroid$ anti inflammat$ or nonsteroid$ anti infllammat$).tw.	6 4 or 5
7 exp Anticoagulants/	7 exp nonsteroid antiinflammatory agent/
8 anticoagulant$.tw.	8 (nsaid$ or non steroid$ anti inflammat$ or nonsteroid$ anti inflammat$).tw.
9 (heparin or warfarin or lmwh or Apixaban or Ximelagatran or dabigatran or rivaroxaban or aspirin or Pradax$ or xarelto or eliquis or coumadin or edoxaban or fondaparinux).tw,rn.	9 exp anticoagulant agent/
10 Direct thrombin inhibit$.tw.	10 anticoagulant$.tw.
11 ligation/ and (saphenous vein/ or femoral vein/)	11 (heparin or warfarin or lmwh or Apixaban or Ximelagatran or dabigatran or rivaroxaban or aspirin or Pradax$ or xarelto or eliquis or coumadin or edoxaban or fondaparinux).tw.
12 Saphenous Vein/su	12 antithrombin/
13 Femoral Vein/su	13 exp thrombin inhibitor/
14 (surg$ adj3 (vein or venous or saphen$)).tw.	14 vein ligation/
15 (strip$ adj3 (vein or venous or saphen$)).tw.	15 (ligation or vein excision).tw.
16 Fibrinolytic Agents/	16 surg$.tw.
17 or/5–16	17 fibrinolytic agent/
18 4 and 17	18 or/7–17
	19 6 and 18

Abbreviations: EMBASE, Excerpta Medica database; MEDLINE, Medical Literature Analysis and Retrieval System Online.

the initial SVT event, or the closest follow-up period to 90 days, with a minimum follow-up of 30 days. DVT was defined as a non-compressible venous segment on compression ultrasonography, an intra-luminal filling defect on venography or as per individual study definition. Proximal DVT was defined as involving the popliteal or a more proximal vein. Distal DVT was defined as thrombus that was confined to the deep veins caudal to the popliteal vein. PE was defined as an intra-luminal filling defect on computed tomography pulmonary angiography (CTPA), a high-probability perfusion defect resulting on ventilation/perfusion lung scintigraphy, an inconclusive CTPA or a lung scintigraphy with demonstration of DVT in the lower extremities.

Secondary outcomes were: (1) recurrent or progression of SVT, (2) symptomatic improvement of SVT, (3) bleeding and (4) death from any cause during the same period of follow-up. Progression or recurrence of SVT was defined as either: a new non-compressible segment of a superficial vein, a new intra-luminal filling defect on venography or a substantial increase (2 cm or more) in the size of the initial SVT on US or venography, or as per individual study definition.[11] Symptomatic improvement of SVT was defined as resolution of patient-reported symptoms related to SVT (pain, swelling, tenderness, erythema or as defined in individual study). Bleeding was classified as either major (according to the ISTH standardized criteria[18]) or fatal. The ISTH definition of major bleeding is: fatal bleeding, and/or symptomatic bleeding in a critical area or organ (such as intracranial, intraspinal, intra-ocular, retroperitoneal, intra-articular or pericardial or intramuscular with compartment syndrome), and/or bleeding causing a fall in haemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells.[18]

Planned sub-group analysis included comparison of outcomes (primary and secondary as previously listed) according to the following patient characteristics: (1) with or without varicose veins, (2) with or without cancer, (3) different anatomical locations of the SVT (SFJ, great saphenous vein $\leq$ 5 cm of the SFJ, great saphenous vein above the knee but $>$ 5 cm from the SFJ, below knee great saphenous vein, small saphenous vein $\leq$ 5 cm of the saphenopopliteal junction, small saphenous vein $>$ 5 cm of the saphenopopliteal junction).

Assessment of Study Quality

The quality of RCTs was evaluated using the Cochrane Risk of Bias assessment tool.[19] The quality of observational studies was evaluated using the Newcastle–Ottawa Assessment scale for case–control and cohort studies.[20] A funnel plot analysis was performed to assess for publication bias.

Strategy for Data Synthesis

Individual study events were converted to rates per patient-year of follow-up by estimating the total observation period as the number of patients multiplied by the mean (or median) duration of follow-up. Converting all events to per 100 patient-year rates permitted better comparison of outcomes in studies with different follow-up durations. Event rates were pooled using a pooled proportion meta-analysis with a random effects model. The random effects model was chosen to reduce the influence of inter-study heterogeneity and to account for unknown differences in study characteristics. The random effects model assumes that the variability between studies (known and unknown) follows a normal distribution and the single proportion estimate extracted from individual studies are random samples from this distribution.[19] The random effects model assigns a smaller weight to studies with smaller sample sizes.[19] The pooled event rates are presented as weighted mean proportions with 95% confidence intervals (CIs). All analyses were performed using StatsDirect statistical software (StatsDirect Ltd, England, 2013).

Data were analysed as intention-to-treat regardless of the original study protocol and published analyses. The I^2 statistic was used to estimate variation that was accounted for by differences across studies. An I^2 of $< 25\%$ was considered as low-level, 25 to 50% as moderate-level and higher than 50% as high-level heterogeneity.[19] Exploration of heterogeneity was planned using pre-specified sub-group analysis and meta-regression that assessed differences in study inclusion/exclusion criteria (pre-specified explanatory variables: cancer patients, varicose vein patients, SVT ≤ 5 cm of SFJ and concurrent NSAID use allowed). However, insufficient reporting of these variables in the included studies prevented such exploration analysis from being completed.

Results

Search Results

The initial electronic search strategy identified 13,094 records, with 5 additional records identified through hand searching of reference lists and scientific meeting abstracts. The total number of records after removing duplicates was 10,525, of which 10,107 were excluded after screening of title and abstract, leaving 418 records for the level 2 review of full text for eligibility (see ►**Fig. 1**). Of these 418 records, 17 articles met our systematic review eligibility criteria.[11,13,21–35] Reasons for study exclusions are outlined in ►**Fig. 2** and include: not original research ($n = 95$), primary outcome not reported ($n = 144$), did not meet inclusion criteria ($n = 73$), case reports ($n = 15$), duplicate publication of same patients ($n = 31$) and could not obtain full text ($n = 43$).

From the 17 studies that met our inclusion criteria, a total of 6,862 adult patients were included in the final analysis. ►**Table 2** summarizes these studies; 11 were RCTs and 6 were cohort studies (3 prospective and 3 retrospective). Duration of pharmacological treatments ranged from 6 to 45 days and length of follow-up from the start of therapy was 42 days to 6 months. Mean age of included patients was 59.4 years, 58.9% were female, 65.5% had varicose veins and the mean duration of symptoms prior to study treatment was 5.3 days.

Assessment of Quality

►**Tables 3** and **4** summarize the assessment of study quality for RCTs and cohort studies, respectively. Of the 11 RCTs included, 7 adequately reported how the randomization sequence was generated and 6 reported that there was both allocation concealment and blinding of participants and physicians. Four studies had incomplete outcome reporting as assessed by having patients lost to follow-up. Of the six cohort studies included, all had appropriate election of patient participants (representativeness, ascertainment of exposure and demonstration that the primary outcome was not present at the start of the study). Three out of the six cohort studies were deemed to have inadequate assessment of outcome because of patients lost to follow-up.

Assessment of Publication Bias

Funnel plots were generated by plotting the individual study reported event rate (proportion, *x*-axis) against the standard error (*y*-axis) for all pooled estimates obtained from four or more studies. These graphs were visually inspected for symmetry around the pooled proportion estimate and no suggestion of publication bias was identified (see ►**Fig. 3** and ►**Supplementary Appendix C**, available in the online version).

Primary and Secondary Outcomes

►**Table 5** and ►**Fig. 1** show the pooled event rates for the primary outcome of DVT or PE by treatment category. Fondaparinux (3 included studies) appears to have the lowest event rate of 1.4 events per 100 patient-years of follow-up (95% CI, 0.5–2.8), with an I^2 score of 18% (low heterogeneity[19]). Event rates for DVT or PE ranged from 9.6 to 16.6 events per 100 patient-years for treatment categories other than fondaparinux, including a placebo/observation event rate of 10.5 events per 100 patient-years (95% CI, 3.0–22.0). Heterogeneity was moderate to high for most pooled estimates. The trend of fondaparinux having the lowest event rates was also seen across secondary outcomes, including PE alone (0.10 events per 100 patient-years, 95% CI, 0.00–0.58), DVT alone (1.44 events per 100 patient-years, 95% CI, 0.53–2.79) and extension or recurrent SVT (7.71 events per 100 patient-years, 95% CI, 1.86–17.05) (►**Table 6**). Major bleeding occurrence was low and similar across all treatment categories (►**Table 6**), with UFH having the highest rate of 1.59 events per 100-patient years (95% CI, 0.25–8.87). The duration of treatment across anticoagulant treatments varied, with duration of treatment shorter and more heterogeneous

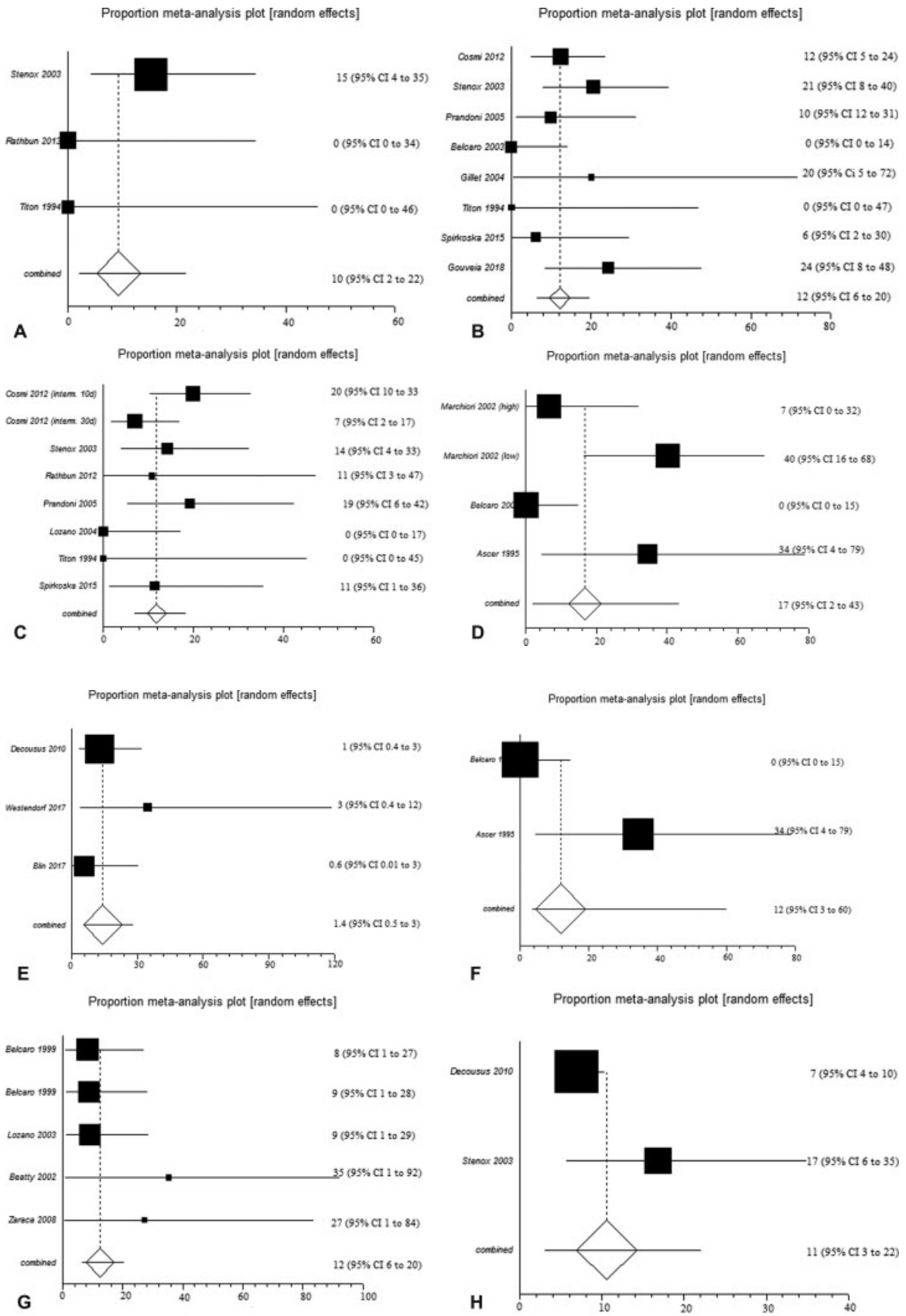

Fig. 1 Forest plot for meta-analysis of study primary outcome (occurrence of deep vein thrombosis [DVT] or pulmonary embolism [PE]) according to treatment category. (**A**) Non-steroidal anti-inflammatory drugs (NSAIDS), (**B**) low molecular weight heparin (LMWH) low/ prophylactic dose, (**C**) LMWH intermediate/full dose, (**D**) unfractionated heparin (UFH) any dose, (**E**) fondaparinux, (**F**) warfarin, (**G**) surgery and (**H**) no therapy.

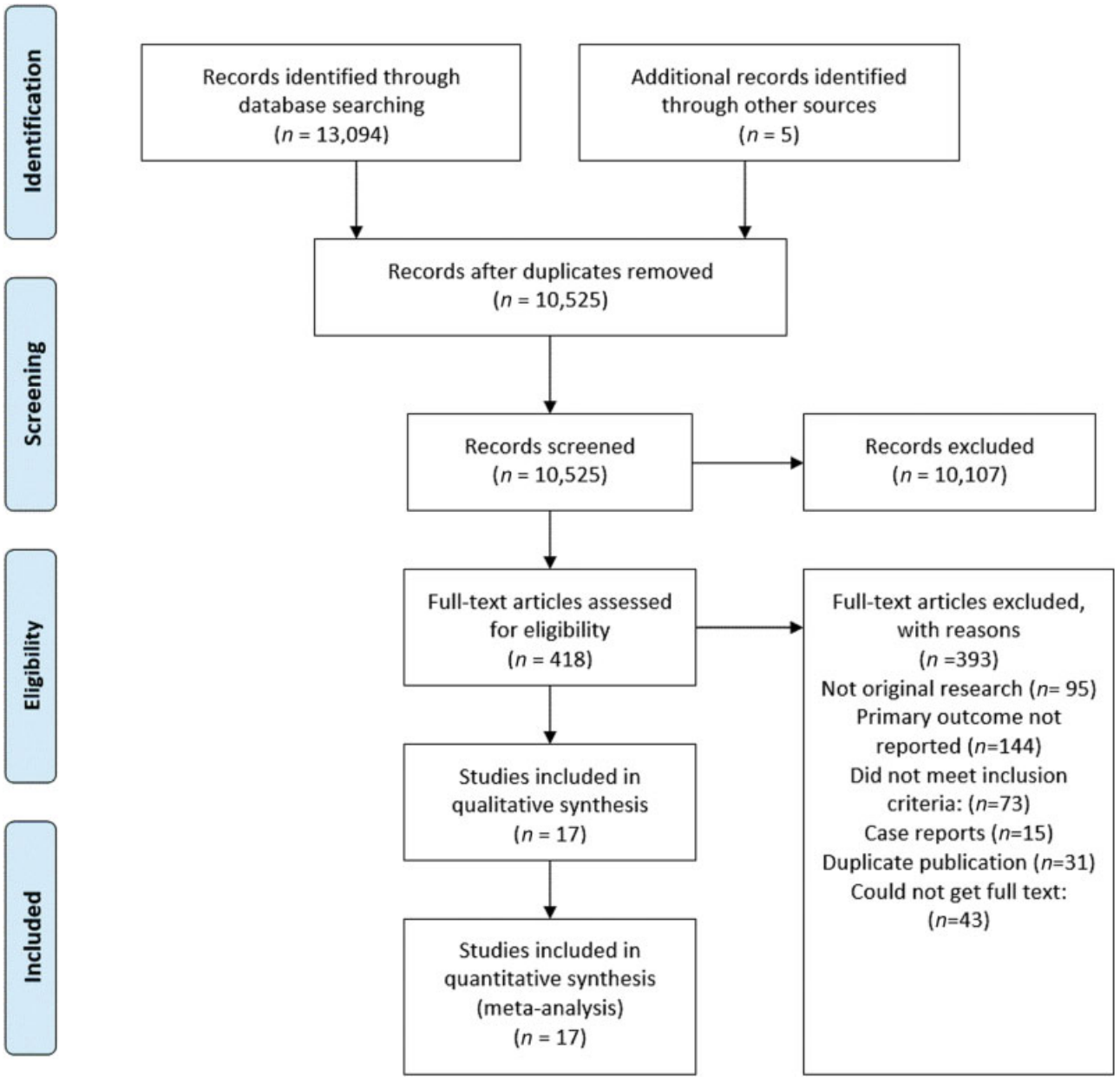

Fig. 2 Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram.

across studies for LMWH. The median duration of treatment was: fondaparinux 43.6 days (range, 34–45 days), low/prophylactic LWMH 30 days (range, 6–42 days) and rivaroxaban 45 days (one study). For LMWH, sub-group analysis based on duration of treatment showed primary outcome event rates of 10.0 events per 100 patient-years (95% CI, 5.3–16.1) for patient treated for 30 to 42 days, compared with 18.3 events per 100 patient-years (95% CI, 8.3–31.1) for patients treated for less than 30 days (not significant).

Discussion

Our systematic review and meta-analysis of 6,862 patients with isolated SVT demonstrates that there is insufficient data to determine the optimal treatment option. Pooled event rates suggest that fondaparinux, when administered at a low/prophylactic dose of 2.5 mg subcutaneous once a day for 45 days, has the lowest occurrence of the primary outcome of DVT or PE at 1.4 events per 100 patient-years of follow-up (95% CI, 0.5–2.8). This is based on weight pooled proportions of 3 RCTs and included a combined 2,473 patients. The heterogeneity associated with this pooled proportion was low with an I^2 of 18% and likely reflects presence of different inclusion criteria in the three studies. The study by Decousus et al[11] included any patient with a lower limb SVT of greater than or equal to 5 cm long provided that it did not extend to within 3 cm of the SFJ, the study by Blin et al[21] included any symptomatic isolated SVT, whereas the study by Beyer-Westendorf et al[13] required patients to have at least one 'high-risk factor' (older than 65 years, male sex, previous VTE, cancer, autoimmune disease or thrombosis of a non-varicose vein). The discrepancy in the event rates between

Table 2 Summary of included studies

Study, Year (Reference)	Study design	Total number of patients	Study description	Treatment duration (d)	Follow-up (d)
Cosmi et al, 2012[23]	RCT	664	Randomization to one of following LMWH (parnaparin) treatments: intermediate dose for 10 days, intermediate dose for 30 days, low (prophylactic) dose for 30 days	10 or 30	93
Marchiori et al, 2002[24]	RCT	60	Randomization to one of following UFH treatments: intermediate/high dose subcut UHF or low (prophylactic) dose subcut UFH for 4 weeks	28	182.5
Decousus et al, 2010[11]	RCT	3,002	Randomization to either low dose fondaparinux (prophylactic) or placebo for 45 days	45	77
Stenox, 2003[22]	RCT	427	Randomization to either: low dose LMWH (enoxaparin); high dose LMWH; oral NSAID (tenoxicam) or placebo for 8–12 days	8–12	97
Rathbun et al, 2012[25]	RCT	72	Randomization to either intermediate/high LMWH (dalteparin) or oral NSAID (ibuprofen) for 7 days	7	91.2
Prandoni et al, 2005[26]	RCT	164	Randomization to either intermediate/high dose LMWH (nadroparin) or low dose LMWH for 30 days	30	91.2
Belcaro et al, 1999[27]	RCT	562	Randomization to elastic compression stockings (ECS); ECS and saphenous vein flush ligation; ECS and complete saphenous vein stripping with perforation vein ligation; ECS and low dose subcut UFH; ESC and low (prophylactic) LMWH, ECS and warfarin	n/a	91.2
Lozano and Almazan, 2003[28]	RCT	84	Randomization to saphenous vein ligation or intermediate/high dose LMWH (enoxaparin) for 4 weeks	28	182.6
Beatty et al, 2002[29]	Prospective cohort	17	All patients treated with saphenous vein ligation	n/a	60.8
Ascer et al, 1995[30]	Prospective cohort	14	All patients treated with IV UFH then warfarin	n/a	152
Gillet et al, 2004[31]	Retrospective cohort	20	All patients treated with low (prophylactic) LMWH for 15–21 days	15–21	91.2
Titon et al, 1994[32]	RCT	117	Randomization to low dose LMWH (nadroparin); intermediate/high dose LMWH; or oral NSAID (naproxen) for 6 days	6	56
Zaraca and Ebner, 2008[34]	Retrospective cohort	32	All patients treated with saphenous vein ligation	n/a	42
Spirkoska et al, 2015[33]	RCT	68	Randomization to intermediate/high LMWH (dalteparin) or low LMWH for 6 weeks	42	182.5
Beyer-Westendorf et al, 2017[13]	RCT	472	Randomization to low dose fondaparinux (prophylactic) or low dose rivaroxaban (prophylactic) for 45 days	45	90
Blin et al, 2017[21]	Prospective cohort	735	Patients treated with either fondaparinux 2.5 mg (prophylactic) (78.1%), or $\geq$5.0 mg at treating physician's discretion	34	90
Gouveia et al, 2018[35]	Retrospective cohort	60	Patients treated with either low dose LMWH (enoxaparin 40 mg) or modified low dose for obesity (enoxaparin 80 mg) at treating physician's discretion	42	126

Abbreviations: ECS, elastic compression stockings; IV, intravenous; LMWH, low molecular weight heparin; n/a, not available; NSAID, non-steroidal anti-inflammatory drug; RCT, randomized control trial; subcut, subcutaneous; UFH, unfractionated heparin.
Note: Not reported by authors or treatment was a surgical intervention and treatment duration not applicable.[35]

Table 3 Risk of bias summary for randomized control trials

Author, Year	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data addressed	Free of selective outcome reporting	Free of other sources of bias
Cosmi et al, 2012[23]	Y	Y	Y	Y	Y	Y
Marchiori et al, 2002[24]	Y	N	N	Y	Y	Y
Decousus et al, 2010[11]	Y	Y	Y	Y	Y	Y
Stenox, 2003[22]	Y	Y	Y	Y	Y	Y
Rathbun et al, 2012[25]	Y	Y	Y	Y	Y	Y
Prandoni et al, 2005[26]	Y	Y	Y	Y	Y	Y
Lozano and Almazan, 2003[28]	U	U	N	N	Y	Y
Belcaro et al, 1999[27]	U	U	N	N	Y	Y
Titon et al, 1994[32]	U	U	N	N	Y	Y
Spirkoska et al, 2015[33]	Y	Y	Y	Y	Y	Y
Beyer-Westendorf et al, 2017[13]	n/a	n/a	N	N	Y	Y

Abbreviations: N, no; n/a, not available; U, unclear; Y, yes.

Table 4 Risk of bias Newcastle–Ottawa for cohort studies

Reference	Summary: Selection (max. four stars)	Summary: Comparability (max. two stars)	Summary: Outcome (max. three stars)
Beatty et al, 2002[29]	☆☆	.	☆
Ascer et al, 1995[30]	☆☆☆	.	☆☆
Gillet et al, 2004[31]	☆☆☆	.	☆☆
Zaraca and Ebner, 2008[34]	☆☆	.	.
Blin et al, 2017[21]	☆☆	.	☆
Gouveia et al, 2018[35]	☆☆	.	☆

Note: ☆, one score; ., no score.

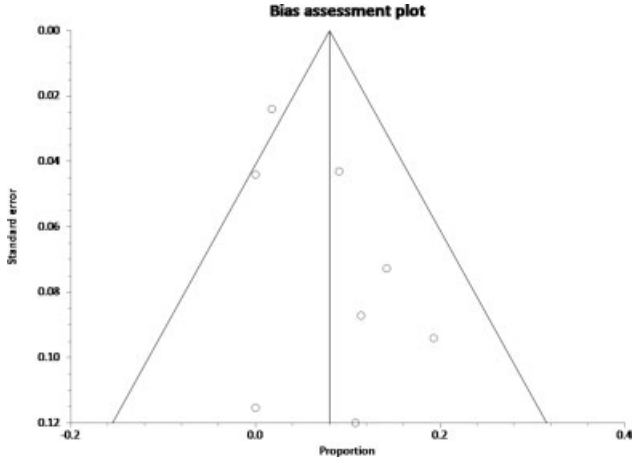

Fig. 3 Sample funnel plot for meta-analysis of occurrence of deep vein thrombosis (DVT) or pulmonary embolism (PE) (primary outcome) after treatment with low molecular weight heparin (LMWH) at intermediate/full dose.

Table 5 Meta-analysis results for study primary outcome (occurrence of DVT or PE) according to treatment category

Treatment	Events per 100 patient-years (95% confidence interval)	I^2
NSAIDs	9.6 (2.1–21.8)	14%
LMWH low/prophylactic dose	12.1 (6.2–19.6)	45%
LMWH intermediate/ full dose	11.9 (6.8–18.2)	38%
UFH any dose	16.6 (1.6–43.0)	80%
Fondaparinux	1.4 (0.5–2.8)	18%
Warfarin	11.7 (3.3–59.5)	83%
Rivaroxaban low/ prophylactic dose	11.0 (4.3–20.2)	–
Surgery	12.1 (5.9–20.2)	0%
No therapy	10.5 (3.0–22.0)	67%

Abbreviations: DVT, deep vein thrombosis; LWMH, low molecular weight heparin; NSAIDs, non-steroidal anti-inflammatory drugs; PE, pulmonary embolism; UFH, unfractionated heparin.

Table 6 Meta-analysis results for secondary outcomes, events expressed as events per 100 patient-years (95% confidence interval)

Treatment	PE	DVT	Extension or recurrent SVT	Bleeding	Death
NSAIDs	4.43 (0.38–12.57)	8.47 (2.09–18.58)	48.62 (28.81–68.66)	1.57 (0.06–7.43)	n/a
LMWH low/ prophylactic dose	2.9 (0.97–5.8)	10.4 (5.3–16.9)	26.5 (12.5–43.5)	0.1 (0.01–2.9)	0.1 (0.01–2.9)
LMWH intermediate/ full dose	2.37 (0.79–4.78)	10.72 (6.07–16.19)	33.59 (17.04–52.55)	0.81 (0.06–2.44)	0.64 (0.01–2.32)
UFH any dose	2.88 (0.20–8.53)	15.17 (1.67–38.61)	35.23 (9.17–67.41)	1.59 (0.25–8.87)	1.59 (0.25–8.87)
Fondaparinux	0.10 (0.00–0.58)	1.44 (0.53–2.79)	7.71 (1.86–17.05)	0.33 (0.03–0.98)	0.48 (0.08–1.22)
Warfarin	1.48 (0.32–8.78)	11.68 (3.34–59.54)	14.78 (1.35–38.84)	n/a	n/a
Rivaroxaban low/ prophylactic dose	0.00 (0.00–3.68)	10.97 (4.33–20.16)	17.74 (9.12–28.46)	0.42 (0.39–3.68)	0.42 (0.39–3.68)
Surgery	4.66 (0.50–12.73)	7.42 (1.98–15.92)	11.40 (0.04–38.55)	n/a	n/a
No therapy	1.92 (0.74–3.62)	10.09 (2.10–23.08)	62.98 (2.22–197.25)	0.49 (0.03–1.49)	0.49 (0.03–1.49)

Abbreviations: DVT, deep vein thrombosis; LWMH, low molecular weight heparin; n/a, not available; NSAIDs, non-steroidal anti-inflammatory drugs; PE, pulmonary embolism; UFH, unfractionated heparin.

the two studies is likely due to this difference in patient characteristics.

When anticoagulation is prescribed for the treatment of SVT, LMWH (low/prophylactic dose) is commonly prescribed interchangeably with fondaparinux (low/prophylactic dose).[10] However, our pooled primary outcome event rate (DVT or PE) was higher for prophylactic dose LMWH than for fondaparinux (12.1 vs. 1.4 events per 100 patient-years of follow-up) (►**Table 5**). This was based on pooled results from 8 studies and 661 patients and moderate heterogeneity was observed ($I^2 = 45\%$). Sub-group analysis suggests that some of the differences across anticoagulants could be because of duration of treatment and notably the duration of therapy for LMWH was on average shorter. Nonetheless, events rates observed with fondaparinux remain lowest even when duration of therapy is accounted for. NSAIDs are alternatively a common treatment for SVT because of favourable safety and cost profile. Among patients treated with NSAIDs, our pooled primary event rate (of DVT or PE) was closely comparable to that of LMWH at 9.6 events per 100 patient-years ($I^2 = 14\%$). However, it can be noted that these pooled estimates were generated using data from studies in which patients were not randomized to NSAIDs and LMWH, and in which there were different patient populations (i.e. eligibility criteria), durations of treatment and follow-up periods. Consequently, these estimates and indirect comparisons need to be interpreted with caution—direct randomized comparisons of anticoagulant therapies and NSAIDs are required for valid results.

A recently published Cochrane systematic review highlighted uncertainties about the optimal management of lower extremity SVT,[1] which is in agreement with our data. Their systematic review included 26 randomized trials that assessed an intervention's ability to treat symptoms or prevent complications of SVT. Similar to our analysis, there were few data from direct comparisons of NSAIDS and LMWH. The authors concluded that LMWH and NSAIDs, when compared with placebo, appeared to reduce extension and recurrence of SVT, but recommended further research to identify whether treatment should be adjusted based on SVT location or cause, an optimal agent, dose, duration and effect of combination therapy. They observed similar efficacy for LMWH and NSAIDs for the outcomes of SVT extension and development of VTE but includes methodological flaws. One should caution against drawing firm conclusions based on their analysis. Their review did not include any studies using DOACs (such as oral direct Xa inhibitors or oral direct thrombin inhibitors).[1] Given the limited number of direct comparison of treatments for management of SVT, we decided to estimate events rates with the different management strategies, which is a helpful information for planning future clinical trials.

The pooled event rates observed in our systematic review are consistent with other reports. A French prospective multi-centre observational study (Prospective Observational Superficial Thrombophlebitis), observed that in their cohort, 90% of which were treated with some form of anticoagulation, 8.3% had a symptomatic thrombosis event (1.2% proximal DVT, 1.4% distal DVT, 0.5% PE, 1.9% recurrent SVT, 3.3% extension of SVT) during 3 months of follow-up.[36] Male sex, prior venous thrombosis, previous cancer and SVT not associated with varicose veins were associated with increased risk of thrombotic complications.[36] Similarly, in an analysis of the OPTIMEV study, a large French observational study of patients with isolated SVT who were followed for 3 months, 3% had a thrombotic complication (0.6% DVT, 0.6% PE, 1.8% recurrent SVT).[37]

Comparison of treatment options for SVT must also consider the bleeding complications with each therapy. While our systematic review protocol attempted to capture

standardized bleeding using the ISTH criteria,[18] most studies included did not report bleeding in a standardized way. Nonetheless, bleeding events were infrequent with all treatments.

Strengths of our review include that we have performed a thorough systematic review with no limitations on publication date or language. The systematic review was designed and reported following the PRISMA statement[38] and electronic search strategies were peer reviewed following the PRESS guidelines.[15] We also reported outcomes based on an intention-to-treat analysis.

Our review does have several limitations worthy of consideration. Despite aggressive searching, some abstracts ($n = 43$) could not be obtained in full text. These were predominately older publications and unlikely to significantly bias our results since we observed that older publications did not use US to confirm the diagnosis of SVT, which was required for inclusion in our systematic review. The pooled proportions we report are based on study level data rather than individual patient level. Patient-years of follow-up were estimated based on median (or mean) follow-up rather than actual patient level follow-up before censoring for outcome event. This estimate is only valid if we assume that the event rate would remain consistent over the entire follow-up period. Studies with very short follow-up (less than 30 days) were therefore excluded from our analysis as event rate observed during the acute period of SVT diagnosis and treatment would not be expected to meet this assumption. We also chose a follow-up period as close to 90 days as possible from included studies. Event occurring in the follow-up period include both on and off treatment events and the relative lengths of these two treatment periods differed across studies. Additionally, the pooled estimates calculated in our meta-analysis were generated by indirect comparisons of non-randomized treatment groups. While a meta-analysis which maintained study randomization with direct comparisons of proportional differences would have been preferred, such an analysis has previously been attempted but was unsuccessful owing to a lack of trials with the same treatments and/or outcomes.[1] Finally, most analyses were associated with moderate heterogeneity, as measured using the I^2 statistic. Rates of venous thrombotic complications following SVT treatment are known to depend on several patient factors such as age, gender, prior VTE history, presence of thrombus within varicose veins, cancer and proximity to the SFJ.[10,36] A range of differences between patients included in studies may therefore have contributed to heterogeneity among studies. As these patient factors were not consistently reported, we were unable to do sub-group analysis based on their presence or absence.

The results of our systematic review demonstrate that there is uncertainty about the optimal treatment of SVT. Our review suggests that fondaparinux is associated with the lowest VTE event rate during follow-up; however, this is strongly influenced by a single large publication.[11] Obstacles that may prevent the widespread adoption of this treatment in clinical practice include the drug cost[12] and route of administration by subcutaneous injections. Rivaroxaban, on the other hand, has an oral route of administration, is less expensive and has been demonstrated to be non-inferior to fondaparinux in a 'high-risk' sub-population of patients.[13] Additionally, the role of NSAIDs alone for the treatment of SVT has not been adequately studied. Future randomized trials directly comparing such treatment options are required. Until such future studies are complete, the authors are reassured by the overall low absolute event rates observed across all treatment options for the most clinically significant outcomes (DVT and PE). Treatment should be individualized, incorporate patient preference and weigh the burden of follow-up visits and imaging, as well as cost and convenience between oral or parenteral anticoagulants. Conservative treatment approach with NSAIDs and close follow-up with close serial clinical assessment and US versus initiation of a 6-week course of low/prophylactic dose of anticoagulant remain acceptable options.

What is known about this topic?

- Superficial vein thrombosis (SVT) is a common condition.
- Various medical and surgical treatments for SVT have been proposed.
- Clinical practice guidelines offer weak recommendations only for the treatment of SVT.

What does this paper add?

- Systematic review presenting current knowledge for treatment of SVT.
- Assessment of quality of research to date in this field.
- Hypothesis generating information for the design of a future clinical trial.

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Conflict of Interest
None declared.

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