Management of superficial venous thrombosis: A systematic review of literature and survey of Canadian physicians

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Abstract

Superficial venous thrombosis (SVT) is a common inflammatory and thrombotic pathology occurring within a superficial vein. SVT can result in distressing symptoms of redness and pain in the affected area and exposes patients to a risk of developing deep vein thrombosis (DVT) and pulmonary embolism (PE). Various therapeutic options are available to patients including anti-inflammatories, anti-coagulation and surgical procedures, however which of these therapies is the best first line treatment remains unknown. Several randomized controlled trials have been conducted addressing this question, yet methodological and design flaws have limited the translation of their results into a change of clinical practice. The following thesis consists of a multi-step process of reviewing the evidence to date followed by a process of engaging with clinician stakeholders with the goal of designing a randomized control trial that would provide a meaningful answer to patients and their clinicians. In the first step of this process, a systematic review of the literature was performed, including a meta-analysis to estimate pooled risk of developing symptomatic venous thromboembolic (VTE) complications in patients with isolated SVT following various treatments. These results were then presented to expert Canadian clinicians in a series of surveys using a Delphi process to determine the clinical trial design that would have the greatest impact on changing clinical practice. An additional survey of expert clinicians was conducted to determine current practice variation in the diagnosis, management, and follow up of patients with SVT, in order to design a clinical trial that best reflected current standard Canadian clinical practice.

Our systematic review identified 15 articles and including 5775 patients. Quality and assessment of risk of bias was moderate for most included studies. The findings of

our meta-analysis identified that Fondaparinux, at prophylactic dose, to had the lowest event rate of 2.0 events per 100 patient years of follow-up (95% CI 0.4 to 4.7, I^2=33%) for the primary outcome of deep vein thrombosis (DVT) or pulmonary embolism (PE) during follow-up. Pooled event rates ranged from 8.6-16.6 events per 100 patient-years across other treatment categories, including placebo/observation only, with an event rate of 10.5 events per 100-patient years (95% CI 3.0 to 22.0). Heterogeneity was moderate to high for most pooled estimates, limiting the interpretation of these findings.

Our survey of practice variation among expert Canadian clinicians revealed wide practice variation in in diagnosis and therapeutic management including sub-groups (e.g. cancer). There was agreement that clinical equipoise exists for the optimal treatment of SVT (77% of respondents), supporting the need for further research. Two rounds of surveys were performed using Delphi process methods, resulting in consensus for the design of a future randomized control trial (RCT). The agreed on design was for a randomized control trial comparing a direct oral anticoagulant (DOAC) such as Rivaroxaban, to Non-Steroidal Anti-Inflammatories (NSAIDs), using a non-inferiority RCT design with a non-inferiority margin of 3%.

Future direction of this research will be to continue stakeholder engagement by engaging patients in the clinical trial design, followed by development of a pilot RCT protocol and application for peer-reviewed funding.

Chapter 1: INTRODUCTION AND THESIS OUTLINE

Background

Superficial venous thrombosis (SVT), also referred to as superficial thrombophlebitis, is both an inflammatory and thrombotic pathology that can occur anywhere along the anatomical distribution of a superficial vein (1;2). Anatomically, the superficial veins are located superficial to the muscular fascia and drain the cutaneous microcirculation (3). The major veins of the superficial system include the greater saphenous vein (GSV) and the small saphenous vein (SSV). Beginning at the level of the ankle, the GSV transverses the medial leg and connects with the deep venous system in the proximal thigh at the saphenofemoral junction, while the SSV travels along the lateral leg and connects with the deep systems at the saphenopopliteal junction at the level of the knee (3). Both can also communicate with the deep system by perforating veins that penetrate the muscular fascia (3). Symptomatically, patients with SVT may present with localized pain, tenderness, redness, edema or a firm palpable cord along the course of a superficial vein (1;2;4;5). The diagnosis of SVT can be made by clinical examination, although a compression ultrasound is recommended for confirmation as well as an evaluation of the extent of venous involvement and co-existing deep vein thrombosis (4;6-9).

Although estimated to be more common than deep vein thrombosis (DVT) and pulmonary embolism (PE), the exact incidence of SVT has not been accurately determined (1;4;10). In an Italian cross-sectional study of patients in primary care clinics, 4.9% (95% CI 4.2-5.5) of men and 10.8% (95% CI 10.2-11.5) of women self-reported a history of SVT, and recent SVT (< 1 year) was reported in 1.5% of men and 2.5% of women (11). A small US community health survey reported an annual incidence of between 0.4 and 44.6 per 10,000 persons per year, with higher incidence seen in

women and those of older age (12). Risk factors for SVT are similar to other venous thrombotic conditions and include immobilization, recent surgery, active cancer, pregnancy/ puerperium, estrogen 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).

The clinical significance of SVT has been realized on evaluation of recent studies (5;13-15). Once thought to be a benign condition, it is now apparent that SVT is frequently complicated by DVT, either co-existing at the time of diagnosis, or developing shortly after. A French prospective multi-centre observational study (POST), evaluated both the prevalence of co-existing DVT at diagnosis as well as the subsequent development of DVT in patients with an isolated SVT during 3 months of follow up (14). The prevalence of DVT in patients presenting with symptomatic lower extremity SVT was 23.5%: 9.7% proximal DVT (located in popliteal, femoral, or iliac veins) and 13.5% distal DVT (located below the knee within the calf veins). Of the patients with isolated SVT at inclusion, during 3 months of follow up, a total of 10.2% had a thrombotic complication and 8.3% had a symptomatic event (1.2% proximal DVT, 1.4% distal DVT, 0.5% PE, 1.9% recurrent SVT, 3.3% extension of SVT). The overall mortality was 0.4% in this cohort. Most (90.5%) of these patients received one or more anticoagulant drugs during the follow up period. Male sex, prior venous thrombosis, previous cancer and SVT not associated with varicose veins were associated with increased risk of thrombotic complications (14). Similarly, analysis of the OPTIMEV study, a large French observational study, found 28.8% of patients with SVT also had a DVT on the first compression ultrasound (16.2% distal and 12.6% proximal DVT) (15). Of patients with isolated SVT at inclusion, during 3 months of follow up, 3% had a thrombotic complication (0.6% DVT, 0.6% PE, 1.8% recurrent SVT). Among the cohort of patients,

76.4% of patients were treated with one or more anticoagulant drugs during the follow up period. Inpatient status and male gender were associated with increased risk of thrombotic complications. VTE recurrence was not statistically different between patients with SVT involving a varicose vein compared to non-varicose vein in this study (2.8% vs. 3.4%) (15). Other studies have shown that SVT involving the saphenofemoral junction or proximal greater saphenous vein are more likely to progress to deep vein involvement compared to distal saphenous vein involvement; most (90%) by direct extension through the saphenofemoral or saphenopopliteal junction (5).

Current treatment options for SVT

Various interventions have been studied for the treatment of SVT, including conservative (clinical observation only), elastic compression stockings, topical heparins, topical NSAIDs, oral NSAIDs, anticoagulant medications (unfractionated heparin- UFH, low molecular weight heparins-LMWH, Pentasaccharides- Fondaparinux, vitamin K antagonists- Warfarin, direct oral anticoagulants-DOAC) at various dose intensities (low/prophylactic, intermediate or high/therapeutic dose), and surgical procedures (ligation or venous stripping) (1;10). There is wide practice variation, but conservative therapy or oral NSAIDs are commonly used first line and have the advantage of ease of use, availability over the counter, reasonable side effect profile and low cost. Table 1 summarizes the results of the major randomized trials for additional medical therapy interventions.

The largest trial is the Comparison of Arixtra in Lower Limb Superficial Vein Thrombosis with Placebo (CALISTO), which randomized 3002 patients with SVT of at least 5 cm in length to receive prophylactic dose of Fondaparinux or placebo for 45 days (13). The primary outcome was a composite consisting of death from any cause, symptomatic PE,

DVT, extension to the saphenofemoral junction or recurrence of SVT 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 associated with a statistically significant reduction in event rates (13). Although this trial is considered practice changing (2;6;10), the control arm in this trial was placebo, and patients were prohibited from taking oral NSAIDs during the trial. The efficacy of Fondaparinux compared to oral NSAIDs has never been directly compared in a randomized control trial.

Low molecular weight heparins have been compared to NSAIDs alone in two randomized control trials (16;17). The study by Rathbun et al. compared high dose LMWH, Dalteparin, to Ibuprofen (oral NSAID) and found the primary outcome (cumulative proportion of patients with thrombus extension or objectively confirmed DVT on day 14 and 3 months) occurred more frequently in patients receiving oral NSAIDs compared to LMWH ($p=0.05$) on day 14, but no difference was seen between these two groups by the 3 month follow up ($p=0.51$) (16). The Superficial Thrombophlebitis Treated by Enoxaparin Study Group (STENOX) compared two doses of LMWH (Enoxaparin, prophylactic dose and high dose) with Tenoxicam (oral NSAID) or placebo for 8-12 days in a pilot study (17). The primary outcome of this study (DVT or PE) was observed with similar incidences in all four treatment groups ($p>0.05$ compared to placebo). When SVT extension and/or recurrence was included in the pre-specified composite secondary outcome analysis, the event rates were significantly reduced in all active treatment groups (LMWH and NSAIDs) compared to placebo but not compared to each other. This study was discontinued prematurely because of slow recruitment (recruiting 1/3 of the targeted sample size), and as such, did not have statistical power to detect important differences between these groups (17).

Recently the Superficial Phlebitis Treated for Forty-five Days with Rivaroxaban versus Fondaparinux (SURPRISE) trial has been published, which compared Fondaparinux to Rivaroxaban, both at prophylactic doses for 45 days, in patients with SVT and at least one 'high risk factor'(18).(18) This trial concluded that Rivaroxaban 10 mg per day was non-inferior to Fondaparinux for the composite outcome of (DVT, PE, extension or recurrent SVT), as defined by a non-inferiority margin of 4.5%, absolute risk difference for the primary composite outcome of symptomatic DVT, PE, proximal extension of SVT or recurrent VTE within 45 days. This trial did not include a comparison arm of conservative or NSAID therapy.

Di Nisio et al. have published a Cochrane Collaboration systematic review for the treatment of lower extremity SVT (1). This systematic review included 26 randomized control trials that had a comparator arm of an intervention aimed to treat either the symptoms or prevent complications of SVT. They identified only one study of treatment with Fondaparinux, CALISTO, described above. The authors concluded that LMWH and NSAIDs, when compared to placebo, appeared to reduce the extension and recurrence of SVT, but recommended further research for the optimal dose, duration, effect of combination therapy, and adjusting treatment based on SVT location or cause. They observed similar efficacy for LMWH and NSAIDs for the outcomes of extension of SVT and development of VTE, but noted methodological flaws and urged caution drawing conclusions based on their analysis. No studies were identified using novel oral anticoagulation medications (oral direct Xa inhibitors or oral direct thrombin inhibitors). They also note that the quality of most studies included in the review was poor (1).

Table 1: Comparison of major clinical trial for medical therapies for the treatment of SVT

Reference	Comparison	No. patients	Outcome	Results
Titon et al. (1994) (19)	Nadroparin 6150 U (prophylactic LMWH), Nadroparin 31.5 U/kg (high dose LMWH) vs. Naproxen (NSAID) for 6 days	117	Primary: recurrence and/or extension of ST, VTE after treatment and after 2 months	Primary: 0% VTE in either arm, 5.6% extension of SVT in Nadroparin 6150 U arm vs. 0% in remaining arms
Belcaro et al. (1999) (20)	Elastic compression stockings, surgical ligation, surgical vein stripping, low dose subcutaneous heparin, low molecular weight heparin (LMWH), warfarin for 6 months	562	Primary: extension of SVT or new DVT at 3 and 6 months	3 month extension of DVT: 16.7%, 7.7%, 1.4%, 2.8%, 1.3%, 7% (respectfully) 3 month DVT:7.6%, 2.5%, 2.8%, --, --, --, 2.3%
Decousus et al. (2003) STENOX (17)	Enoxaparin 40 mg (prophylactic LMWH), enoxaparin 1.5mg/kg (high dose LMWH), oral tenoxicam (NSAID) or placebo for 8-12 days	427	Primary: new DVT or PE at day 12 Secondary: new DVT, PE or recurrent SVT at day 12	Primary: NS difference between groups, 0.9%, 1.0%, 2.1%, 3.6% (respectfully) Secondary: 8.3%, 6.9%, 14.9%, **30.6%** ($p<0.05$)
Prandoni et al. (2005) VESALIO (21)	Nadroparin 2850 U OD (prophylactic LMWH), Nadroparin (high dose LMWH x 10 days then 50% intermediate dose x 20 days) for 30 days	164	Primary: new DVT, PE or extension of SVT at 3 months Secondary: rate of clinical improvement	Primary: NS difference: 8.6% vs. 7.2% Secondary: NS difference
Uncu (2009) (22)	Nadroparin 190U/kg (high dose LMWH) vs Nadroparin 190U/kg combined with acemetacine (NSAID) for 10 days	50	Primary: visual analogue scale for SVT symptoms (pain, hyperemia, tenderness, palpable cord)	Primary: better VAS pain and tenderness scores for combination treatment ($p<0.05$) but no difference in hyperemia and palpable cord
Decousus et al. (2010)	Fondaparinux 2.5 mg OD (prophylactic dose Pentasaccharide) vs placebo for 45	3002	Primary: death, new DVT, PE, or extension of SVT to the saphenofemoral	Primary: 0.9% vs 5.9% ($P<0.001$) Secondary: incidence of each

CALISTO (13)	days		junction or recurrent SVT at day 47 Secondary: subgroups	component (except death) significantly reduced in Fondaparinux arm
Cosmi et al. (2012) (23)	Parnaparin (intermediate dose LMWH) for 10 days, Parnaparin (intermediate dose) for 30 days, Parnaparin (prophylactic dose) for 30 days	664	Primary: new DVT, PE, or extension of SVT at 30 days	Primary: 16.5%, 1.8%, 7.4% (respectfully)
Rathbun et al. (2012) (16)	Dalteparin 200 U/kg x1 day then 10,000 U OD x 6 days (high dose LMWH), Ibuprofen 800mg TID (NSAID) x 7 days	72	Primary: new DVT or SVT extension at 14 days and 3 months	Primary:14 days: 11.4% vs 0% ($p<0.05$) 3 months: NS difference 17.1% vs. 10.8%
Beyer-Westendorf et al. 2017 (18)	Fondaparinux 2.5 mg subcut x 45 days vs. Rivaroxaban 10 mg PO OD x 45 days	485	Primary: new DVT, PE, extension or recurrent SVT	Primary: 2% vs 3%

Current practice guidelines for treatment of SVT

The American College of Chest Physicians (ACCP) publishes widely used evidenced based clinical practice guidelines for the management of venous thromboembolic disease(10). In the current guidelines, the authors grade the existing evidence for the management of SVT as moderate quality, using the GRADE system (moderate quality is defined as evidence from randomized control trials but with serious risk of bias or inconsistency) (24). They conclude that: "we have interpreted the findings of CALISTO as evidence for anticoagulation in general and assume that prophylactic dose of LMWH and Fondaparinux have similar antithrombotic efficacy and safety (10)".

Their final recommendations state:

> "**In patients with superficial vein thrombosis (SVT) of the lower limb of at least 5 cm in length, we suggest the use of a prophylactic dose of Fondaparinux or LMWH for 45 days over no anticoagulation** (Grade 2B*)**.**
> *Remarks:* Patients who place a high value on avoiding the inconvenience or cost of anticoagulation and a low value on avoiding infrequent symptomatic VTE are likely to decline anticoagulation.
> **In patients with SVT who are treated with anticoagulation, we suggest Fondaparinux 2.5 mg daily over a prophylactic dose of LMWH** (Grade 2C**)**.**
> **(10)"**

*Grade 2B: weak recommendation, moderate quality of evidence with benefits closely balanced with risks and burden.

**Grade 2C: weak recommendation, low or very low quality of evidence with uncertainty in the estimates of benefits, risks and burden may be closely balanced.

Selection of high-risk patient population

The universal adoption of anticoagulation therapy for all patients with SVT has major quality of life and health care cost implications. A cost effectiveness analysis using data from the CALISTO study concluded that the incremental cost-effectiveness ratio (ICER) for treatment of SVT with Fondaparinux for 45 days compared to no treatment was approximately $500,000 per quality-adjusted life year (25). The authors of this analysis suggested that this ICER could be lowered by either treating only a subgroup of patients at a higher risk of VTE complications or decreasing the cost or duration of the treatment (25). In this regard, observational studies have suggested male gender, prior VTE, cancer and SVT not associated with varicose veins as risk factors for important VTE complications (14). Among patients randomized to the placebo arm in the CALISTO trial (described above), VTE complications occurred more often in patients with a prior VTE history, or a SVT either above the knee, within the greater saphenous vein, or within 10 cm of the saphenofemoral junction (13). Age, gender, varicose veins, obesity or cancer did not appear associated with VTE complications (13). Additionally, the ACCP guidelines suggest the following patient subgroups as most favorable for treatment with anticoagulation based on higher VTE complication risk: SVT that is deemed extensive, involving the greater saphenous vein, above knee, close to saphenofemoral junction, severe symptoms, prior SVT or VTE, active cancer or recent surgery (10).

Areas of uncertainty

As outlined above, the current body of evidence does not provide clear guidance for the treatment of patients with SVT. This is reflected in the weak grade recommendation by clinical practice guidelines (10). In particular, the following gaps of knowledge are identified:

1. Role of prophylactic dose of LMWH compared to Fondaparinux
    a. ACCP guidelines are based on an assumption of equivalent antithrombotic efficacy and safety
    b. These two treatments have never been compared directly
2. Role of direct oral anticoagulants in the treatment of SVT
    a. Only one study to date has studied the use of a direct Xa inhibitor (Rivaroxaban) and no study has used oral direct thrombin inhibitors for the treatment of SVT
    b. No studies have compared the use of a direct Xa inhibitor to NSAID, LMWH or placebo.
    c. The reduced cost, ease of administration (oral route), and demonstration of equivalent efficacy for other thrombotic disorders would make these therapies reasonable options
3. What are the clinically important outcomes that therapies should demonstrate reduction?
    a. PE, DVT (proximal or combined proximal and distal)
    b. Symptomatic vs asymptomatic events
    c. Extension of SVT
    d. Patient symptoms or quality of life

Rationale for why research needed

Currently the optimal therapy for acute lower extremity SVT is unclear. The most evidenced based strategy is a 45 day course of prophylactic dose Fondaparinux (13), but this has not been shown to be cost-effective (25). Additionally, methodological issues with this study include the use of a placebo comparator as oppose to oral NSAIDs, the latter being a more common conservative treatment. As outlined in the areas of uncertainty above, there exists a sufficient knowledge gap to justify further randomized control trials.

Identified research questions for thesis

1. What are the venous thromboembolic complication rates after an acute lower extremity superficial venous thrombosis (SVT)?

2. Are there identifiable subgroups of patients with a higher risk for complications and therefore candidates for more aggressive therapeutic interventions?

3. What is the best therapeutic intervention, comparator treatment, and patient population for future clinical trials for prevention of complications of SVT?

Thesis objectives and outline

The following manuscript based thesis will address the following objectives as outlined previously in my thesis proposal:

Objective 1: Conduct a systematic review of literature

   a. Calculation of pooled proportions with 95% CI of VTE rates following acute lower extremity SVT.

   b. Calculation of pooled proportions of VTE rates according to pre-specified treatment subgroups.

   c. Calculation of pooled proportions of VTE rates according to pre-specified patient characteristic subgroups.

Objective 2: Survey of physicians who treat SVT

   a. Summary of current diagnostic process for patients presenting with acute lower extremity SVT in Canada.

b. Summary of current treatment practices for acute lower extremity SVT.

c. Summary of acceptable comparator arms for future clinical trials among clinicians who treat SVT.

d. Determination of clinically relevant and important outcomes of therapy that would need to be demonstrated to lead to a change in clinical practice (eg. symptomatic vs. asymptomatic, PE, proximal DVT, distal DVT, SVT extension, patient reported symptom improvement).

e. Calculation of Minimum clinical important difference (MCID) that would be required from a clinical trial to change practice, using a Delphi process, among clinicians who treat SVT.

f. Evaluation of interest in participation in future clinical trials

These objective will be met through the following 2 manuscripts, which are also being prepared for publication in peer-reviewed medical journals.

Manuscript 1: Treatment of superficial vein thrombosis: a systematic review and meta-analysis

Manuscript 2: Treatment of superficial venous thrombosis: a survey of Canadian physicians and Delphi process for design of future clinical trial

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Chapter 2.

Manuscript 1: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: To report estimates of the rate of venous thromboembolic (VTE) complications among patients with SVT according to treatment.

Methods: A systematic review and meta-analysis was performed using unrestricted searches of MEDLINE, EMBASE, and CENTRAL electronic databases, as well as hand searching of conference abstracts. Reported events were transformed to event per 100 patient years of follow up and a random effects model was used to calculate pooled proportions (with 95% confidence intervals) 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. The systematic review protocol, including all planned analysis, was registered *a priori* through PROSPERO, CRD42013005896.

Results: 15 articles (11 randomized control trials and 4 cohort studies), including 5775 patients, were included in the meta-analysis. Fondaparinux (2 included studies) appeared to have the lowest event rate of 2.0 events per 100 patient years of follow-up (95% CI 0.4 to 4.7, I^2=33%). Pooled event rates for DVT or PE ranged from 8.6-16.6 events per 100 patient-years across other treatment categories, including placebo/ observation only, with an event rate of 10.5 events per 100-patient years (95% CI 3.0 to 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 at low/prophylactic dose, 2.5 mg subcutaneous once a day, for 45 days has the lowest occurrence of the primary outcome of DVT or PE, heterogeneity and lack of quality data of some treatment options prevent firm conclusions for the optimal treatment for SVT. Future randomized control trials are still required to address this question.

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, edema or a firm palpable cord and (1;2;4;5) the diagnosis is typically confirmed with use of compression ultrasound (US) (4;6-9). Risk factors for SVT are similar to other venous thrombotic conditions and include immobilization, recent surgery, active cancer, pregnancy/ puerperium, estrogen 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 conservative (clinical observation only), elastic compression stocking, topical heparins, topical non-steroidal anti-inflammatory drugs (NSAIDs), oral NSAIDs, anticoagulant medications (unfractionated heparin- UFH, low molecular weight heparin- LMWH, Pentasaccharides- Fondaparinux, vitamin K antagonists-VKA 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 3002 patients with SVT of at least 5 cm in length to receive prophylactic dose of Fondaparinux or placebo for 45 days [13]. The primary outcome was a composite consisting of symptomatic pulmonary embolism (PE), 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 associated with a statistically significant

reduction in event rates [13]. Although this trial is considered practice changing [2,6,10], the control arm in this trial was placebo, and patients were prohibited from taking oral NSAIDs during the trial. 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 cost effectiveness analysis did not support this treatment strategy (11). The 'Superficial Phlebitis Treated for Forty-five Days with Rivaroxaban versus Fondaparinux' (SURPRISE) trial randomized patients with acute SVT and one additional high risk factor to treatment with either Rivaroxaban or Fondaparinux, both in low/prophylactic dose (12). The primary outcome of this non-inferiority trial was a similar composite outcome of either DVT, PE, progression or recurrent SVT, or death and found Rivaroxaban statistically non-inferior to Fondaparinux. The efficacy of Fondaparinux or Rivaroxaban, however, has never been directly compared to oral NSAIDs in a randomized control trial. NSAIDs have historically, and in many clinical settings remain, an inexpensive, safe, and readily available treatment for SVT. In the context of these 2 recent clinical trials, the role of NSAIDs remains uncertain and thus the optimal first line management strategy for patients with SVT remains unclear. We therefore conducted a systematic review and pooled analysis to estimate the venous thromboembolic complication rates after an acute lower extremity SVT according to management strategies.

Methods

We conducted a systematic review with the primary objective of estimating the rate of development of symptomatic venous thromboembolic disease (VTE) during follow up among patients with acute lower extremity SVT according to treatment with: (i) NSAIDs, (ii) anticoagulant therapies, (iii) surgical therapies, or (iv) observation/placebo. Treatment strategy categories are defined as follows: (i) NSAIDs: oral or topical non-steroidal anti-inflammatory

medications (including Aspirin, so long as prescribed at a dose higher than 100 mg per day), (ii) anticoagulant therapies: any oral or parenteral anticoagulation at any dose (classified as low/prophylactic or intermediate/high/therapeutic), (iii) surgical therapies: any surgical intervention for the primary treatment of SVT (venous ligation or surgical removal/ stripping of affected superficial vein), and (iv) 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 (13) (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013005896).

Search strategy

An electronic search of the following databases was performed: MEDLINE (1948- July 26, 2016), EMBASE (1947-July 26th, 2016) and the Cochrane Central Register of Controlled Trials (CENTRAL) (July 26, 2016). The electronic search strategy was designed after consultation with a health science librarian experienced in systematic reviews of medical literature and a peer review of the electronic search strategy was performed by an independent librarian using the Peer Review of Electronic Search Strategies (PRESS) guidelines [30,31]. The final systematic search strategy, using Medical Subject Indexing (MeSH) is shown in Table 1. Scientific meeting abstract publications for the America Society of Hematology (ASH) and International Society of Thrombosis and Haemostasis (ISTH) conferences for the past 5 years (2011-2016) were manually and/or electronically searched. There was no restriction on language and included non-English studies were translated. Reference and abstracts were imported into Reference Manager Version 12.0.1 software and duplicates were removed

manually. Study title and abstract of identified records was first screened by two independent investigators (L.D. and M.C.) for potential eligibility, using a standardized form (level 1 screening, see Appendix A: Level 1 title and abstract screening form). Discrepancies during level 1 screening were handled by including all discrepant articles for full text screening. Full text of articles judged potentially eligible during level 1 screening were retrieved and English translation obtained when necessary. Articles were reviewed during level 2 screening by two independent investigators (L.D. and M.C.) and were chosen for inclusion in the final review if they: (i) reported on consecutive patients in either a cohort or randomized control trial study design, (ii) only included patients with objectively proven acute lower extremity SVT by ultrasound, and (iii) reported one or more of the primary outcome of interest (deep vein thrombosis and pulmonary embolism) according to treatment category. Studies were excluded if they did not follow consecutive patients, did not report information about the following treatments: (i) non-steroidal anti-inflammatory medications, (ii) anticoagulant therapies, (iii) surgical therapies, or (iv) no therapy/placebo, did not objectively confirm the diagnosis of superficial vein thrombosis with compression ultrasound, or, did not provide the proportion of patient with the primary outcome of deep vein thrombosis or pulmonary embolism within a minimum of 30 days of follow up. (see Appendix B: Level 2 full text screening form). Any disagreements were resolved by discussion, consulting a third party and/or requesting additional information from the study authors. The results of the systematic review are reported according to the PRISMA (for systematic review of randomized control trials) [32,33] and MOOSE (for systematic review of non-randomized trials) [34] guidelines [Appendix C and D].

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 2013 November 05>**
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

MEDLINE: Medical Literature Analysis and Retrieval System Online; EMBASE: Excerpta

Medica dataBASE

Outcome Measures

The primary outcome measure was defined as DVT and/or PE during the follow-up period. The follow-up period was defined as within 90 days of diagnosis of initial SVT event, or the closest follow-up period provided by study authors to 90 days and at least a minimum of 30 days of follow-up. 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 vein or more proximal to the heart. Distal DVT was defined as caudal to the popliteal vein. Pulmonary embolism was defined as an intra-luminal filling defect demonstrated on CT pulmonary angiography, a perfusion defect resulting in a high-probability ventilation/perfusion lung scintigraphy, an inconclusive CTPA, pulmonary angiography or lung scintigraphy with demonstration of DVT in the lower extremities by compression ultrasound or venography or as per individual study definition.

Planned secondary outcomes were: (i) recurrent or progression of SVT, (ii) symptomatic improvement of SVT, (iii) bleeding, and (iv) death from any cause. Secondary outcomes were measured during a follow-up period defined as within 90 days of diagnosis of initial SVT event, or the closest follow-up period provided by study authors to 90 days and at least a minimum of 30 days of follow-up. Symptomatic progression of SVT was defined as either: a new non-compressible venous segment within an anatomically superficial vein, a substantial increase (2mm or more) in the size of the initial SVT during full compression in a previously abnormal segment on ultrasonography, a new intra luminal filling defect on venography, or as per individual study definition. Recurrent SVT was defined as either: a new non-compressible venous segment on compression ultrasound, a new intra-luminal filling defect on venography within a different superficial vein and not directly continuous with the initial SVT, or as per each individual study definition [13]. 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 major and fatal, according to ISTH standardized criteria [29], or according to individual study definition. The International Society on Thrombosis and Haemostasis (ISTH) definition of major bleeding is: fatal bleeding, and/or symptomatic bleeding in a critical area or organ (such as intracranial, intra-spinal, intra-ocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), and/or bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells [29].

Planned subgroup analysis included: (i) comparison of outcomes (primary and secondary listed above) according to the following patient characteristics: (i) with or without varicose veins, (ii) with or without cancer, (iii) different anatomical locations of the SVT (saphenofemoral junction, great saphenous vein ≤ 5 cm of the saphenofemoral junction, great saphenous vein above the knee but >5 cm from saphenofemoral junction, below knee great saphenous vein, small saphenous vein ≤ 5 cm of the saphenopopliteal junction, small saphenous vein >5 cm of the saphenopopliteal junction).

Assessment of study quality

The quality of randomized control trials (RCTs) was evaluated using the Risk of Bias assessment tool [27]. The quality of observational studies was evaluated using the Newcastle – Ottawa Assessment scale for case-control and cohort studies [35]. A funnel plot analysis was performed to assess whether publication bias is present.

Strategy for data synthesis

The analysis was performed for the total group of patients with lower extremity SVT according to treatments received (pre-specified categories defined above). To estimate the weighted rates and 95% confidence intervals (95% CI) for the systematic review's primary outcomes, individual study estimates were converted to rates of per patient year of follow-up by multiplying the number of patients in the study by the mean (or median) reported follow-up. The conversion of event rates to per 100 patient-years allowed comparison of different follow-up durations across studies. Event rates across studies 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 (14). The random-effects model assigns a smaller weight to studies with smaller sample sizes (14). The pooled event rates for outcomes are presented as weighted mean proportions with a 95% confidence interval for this estimate. All statistical analysis and meta-analysis was performed using StatsDirect Statistical Software (StatsDirect Ltd: England: 2013).

Data was analyzed as intention to treat regardless of original study protocol and published data analysis. The I-squared statistic was used to estimate total variation among the pooled estimates across studies. An I-squared of < 25% was considered as low-level heterogeneity, 25% to 50% as moderate level, and higher than 50% considered as high level [36]. Additional exploration of heterogeneity was planned using pre-specified subgroup analysis as well as meta-regression analysis for variables in study inclusion/exclusion criteria (pre-specified explanatory variables: cancer patients, varicose vein patients, SVT ≤5 cm of

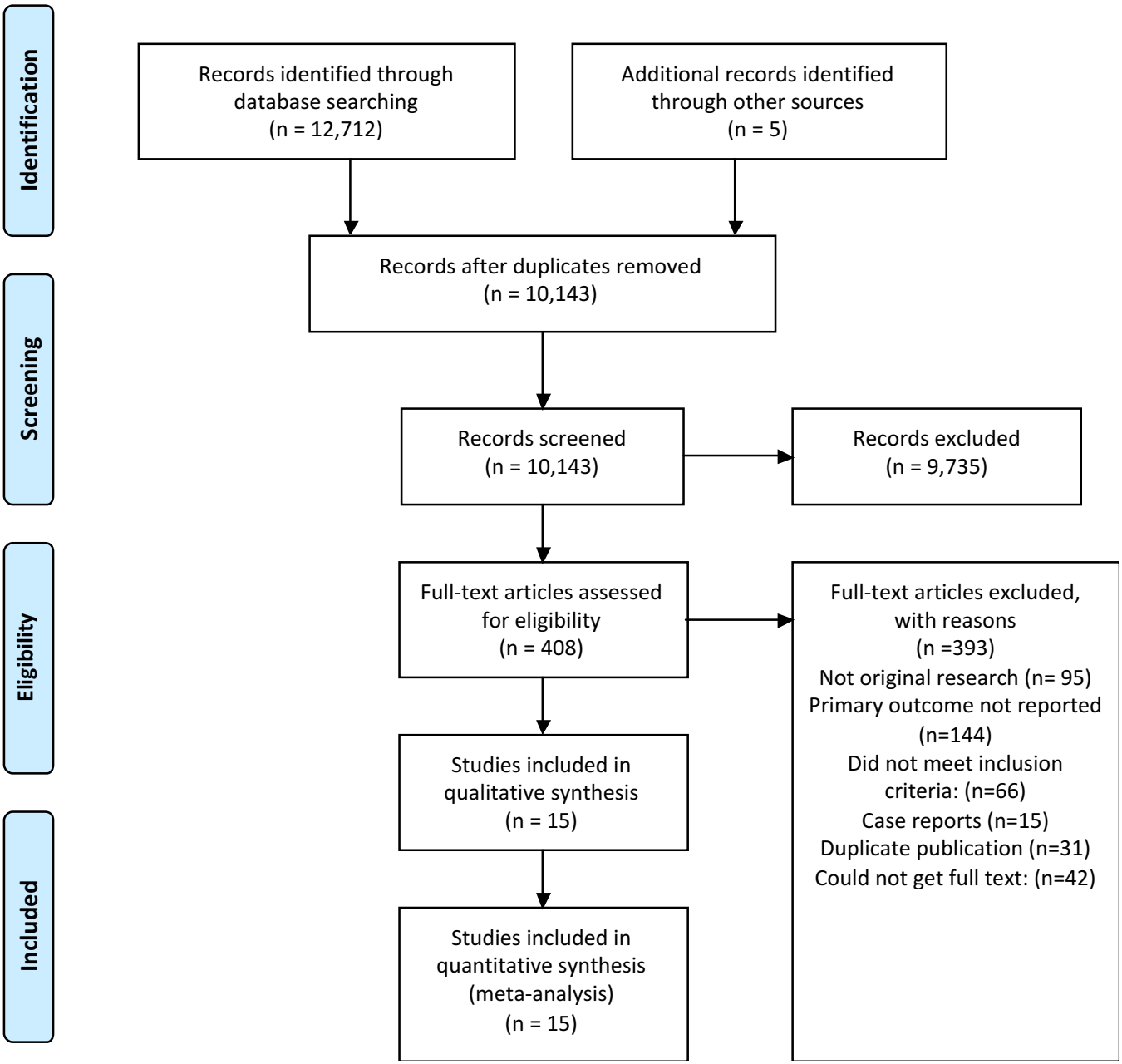
saphenofemoral junction, and concurrent NSAID use allowed), however, insufficient reporting of these variables in the included studies prevented this analysis.

Results

Search results

Initial electronic search strategy identified 12,712 records, with 5 additional records identified through hand searching of reference lists and scientific meeting abstracts. The total number of records after manually removing duplicates was 10,143, of which 9,735 were excluded after level 1 duplicate screening of title and abstract, leaving 408 records for the level 2 review of full text for eligibility (see Figure 3, PRISMA flow diagram). Of these 408 records, 15 articles met our systematic review inclusion criteria (12;15-28). Reasons for study exclusions are outlined in Figure 1 and include: not original research (n=95), primary outcome not reported (n=144), did not meet inclusion criteria: (n=66), case reports (n=15), duplicate publication of same patients (n=31), could not obtain full text: (n=42).

Figure 1: Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA) Flow Diagram



From the 15 included studies, a total of 5775 adult patients were included in the final analysis. Table 2 summarizes these included studies. 11 studies were randomized control trials and 4 were cohort trial design (2 prospective and 2 retrospective). Duration of treatment for 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 59.5 years, 63.8% were female, 85.5% had varicose veins and the mean duration of symptoms prior to study treatment was 5.3 days.

Table 2: Summary of Included Studies

Study, Year (Reference)	Study design	Total number of patients	Study description	Treatment duration (days)	Follow up (days)
Cosmi 2012 (16)	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 2002 (17)	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 2010 (29)	RCT	3002	Randomization to either low dose Fondaparinux (prophylactic) or placebo for 45 days	45	77
Stenox 2003 (15)	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 2012 (19)	RCT	72	Randomization to either intermediate/ high LMWH (dalteparin) or oral NSAID (ibprofen) for 7 days	7	91.2
Prandoni 2005 (20)	RCT	164	Randomization to either intermediate/ high dose LMWH (nadroparin) or low dose LMWH for 30 days	30	91.2
Belcaro 1999 (21)	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 2003 (22)	RCT	84	Randomization to saphenous vein ligation or intermediate/ high dose LMWH (enoxaparin) for 4 weeks	28	182.6
Beatty 2002 (23)	Prospective Cohort	17	All patients treated with saphenous vein ligation	n/a	60.8
Ascer 1995 (24)	Prospective Cohort	14	All patients treated with IV UFH then warfarin	n/a	152
Gillet 2004 (25)	Retrospective Cohort	20	All patients treated with low (prophylactic) LMWH for 15-21 days	15-21	91.2

Titon 1994 (26)	RCT	117	Randomization to low dose LMWH (nadroparin); intermediate/ high dose LMWH; or oral NSAID (naproxsyn) for 6 days	6	56
Zaraca 2008 (28)	Retrospective Cohort	32	All patients treated with saphenous vein ligation	n/a	42
Spirkoska 2015 (27)	RCT	68	Randomization to intermediate/ high LMWH (daltaparin) or low LMWH for 6 weeks	42	182.5
Beyer-Westendorf 2017 (12)	RCT	472	Randomization to low dose Fondaparinux (prophylactic) or low dose Rivaroxaban (prophylactic) for 45 days	45	90

RCT: randomized control trial; LMWH: low molecular weight heparin; UFH: unfractionated heparin; subcut: subcutaneous; ECS: elastic compression stockings; IV: intravenous; n/a: not available, not reported by authors or treatment was a surgical intervention and treatment duration not applicable.

Assessment of quality

Tables 3 and 4 summarize the assessment of study quality for RCTs and cohort studies respectfully. Of the 11 RCTs included, 64% reported adequate sequence generation and 55% reported the presence of both allocation concealment and blinding of both participants and physicians. Thirty-six percent (36%) had incomplete outcome reporting because of missing outcome data on patients lost to follow up. Of the 4 cohort studies included, all studies had adequate selection of patients (representativeness, ascertainment of exposure and demonstration that outcome was not present at the start of the study). None of the cohort studies included a non-exposed cohort or controlled for clinical risk factor of venous thrombosis, therefore no score was allocated for comparability. Three out of the four cohort studies were deemed to have inadequate follow-up and assessment of outcome.

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 2012 (16)	Y	Y	Y	Y	Y	Y
Marchiori 2002 (17)	Y	N	N	Y	Y	Y
Decousus 2010 (18)	Y	Y	Y	Y	Y	Y
Stenox 2003 (15)	Y	Y	Y	Y	Y	Y
Rathbun 2012 (19)	Y	Y	Y	Y	Y	Y
Prandoni 2005 (20)	Y	Y	Y	Y	Y	Y
Lozano 2003 (22)	U	U	N	N	Y	Y
Belcaro 1999 (21)	U	U	N	N	Y	Y
Titon 1994 (26)	U	U	N	N	Y	Y
Spirkoska 2015 (27)	Y	Y	Y	Y	Y	Y
Beyer-Westendorf 2017 (12)	n/a	n/a	N	N	Y	Y

Y= yes; N=no; U= unclear

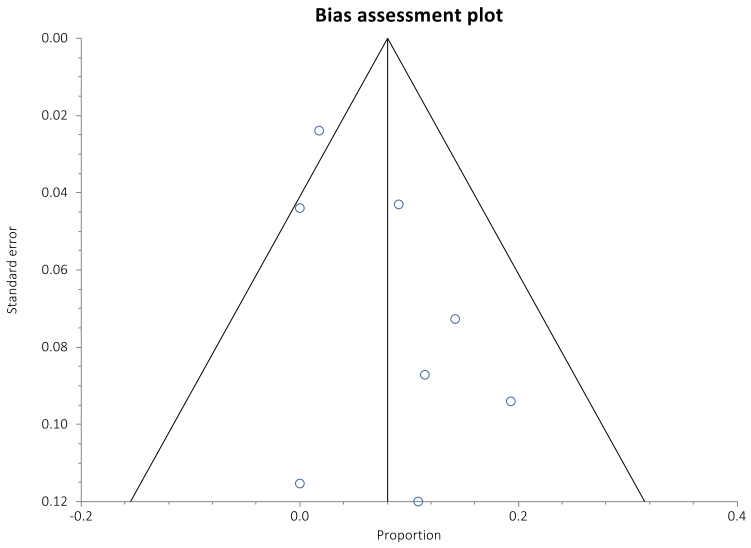
Table 4: Risk of bias Newcastle-Ottawa for cohort studies

Reference	**SUMMARY:** Selection (****)	**SUMMARY:** Comparability (**)	**SUMMARY:** Outcome (***)
Beatty 2002 (23)	**	.	*
Ascer 1995 (24)	***	.	**
Gillet 2004 (25)	***	.	**
Zaraca 2008 (28)	**	.	.

Assessment of publication bias

Funnel plots were generated by plotting the individual study reported event rate (proportion, x-axis) by the standard error (y axis) for all pooled estimate meta-analysis performed with 4 or more studies included. These graphs were visually inspected for symmetry around the pooled proportion estimate and no suggestion of publication bias was identified (see Figure 2: Sample funnel plot and Appendix E: Complete funnel plots for all meta-analysis of the primary outcome).

Figure 2: Sample funnel plot for meta-analysis of occurrence of DVT or PE (primary outcome) after treatment with low molecular weight heparin (LMWH) at intermediate/ full dose



Primary and secondary outcomes

Table 5 and Figure 3 shows the pooled event rates for the primary outcome of DVT or PE by treatment category. Fondaparinux (2 included studies) appears to have the lowest event rate of 2.0 events per 100 patient years of follow-up (95% CI 0.4 to 4.7), I^2=33% (moderate heterogeneity [36]). Pooled event rates for DVT or PE ranged from 8.6-16.6 events per 100 patient-years across other treatment categories, including placebo/ observation event rate of 10.5 events per 100-patient years (95% CI 3.0 to 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 (0.11 events per 100-patient years, 95% CI 0.03 to 0.71), DVT alone (2.10 events per 100-patient years, 95% CI 0.41 to 5.06), and extension or recurrent SVT (11.55 events per 100-patient years, 95% CI 0.39 to 34.82) (Table 6). Major bleeding was low and similar across all treatment categories (Table 6), with unfractionated heparin (UFH) having the highest pooled bleeding event rate of 1.59 events per 100-patient years (95% CI 0.25 to 8.87).

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)	I2
NSAIDs	9.6 (2.1 to 21.8)	14%
LMWH low/prophylactic dose	9.7 (4.5 to 16.5)	35%
LMWH intermediate\/full dose	8.6 (4.1 to 14.5)	42%
UFH any dose	16.6 (1.6 to 43.0)	80%
Fondaparinux	2.0 (0.4 to 4.7)	33%
Warfarin	11.7 (3.3 to 59.5)	83%
Rivaroxaban low/prophylactic dose	11.0 (4.3 to 20.2)	--
Surgery	12.1 (5.9 to 20.2)	0%
No therapy	10.5 (3.0 to 22.0)	67%

DVT: deep vein thrombosis; PE: pulmonary embolism; NSAIDs: non-steroidal anti-inflammatory; LWMH: low molecular weight heparin; 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 to 12.57)	8.47 (2.09 to 18.58)	48.62 (28.81 to 68.66)	1.57 (0.06 to 7.43)	n/a
LMWH low/prophylactic dose	3.13 (1.01 to 6.37)	8.96 (4.57 to 14.63)	37.40 (25.22 to 50.45)	0.84 (0.00 to 3.12)	0.66 (0.02 to 3.06)
LMWH intermediate/full dose	2.35 (0.76 to 4.78)	10.77 (6.31 to 16.23)	33.59 (17.04 to 52.55)	0.81 (0.06 to 2.44)	0.64 (0.01 to 2.32)
UFH any dose	2.88 (0.20 to 8.53)	15.17 (1.67 to 38.61)	35.23 (9.17 to 67.41)	1.59 (0.25to 8.87)	1.59 (0.25 to 8.87)
Fondaparinux	0.11 (0.03 to 0.71)	2.10 (0.41 to 5.06)	11.55 (0.39 to 34.82)	0.45 (0.03 to 1.38)	0.72 (0.12 to 1.82)
Warfarin	1.48 (0.32 to 8.78)	11.68 (3.34 to 59.54)	14.78 (1.35 to 38.84)	n/a	n/a

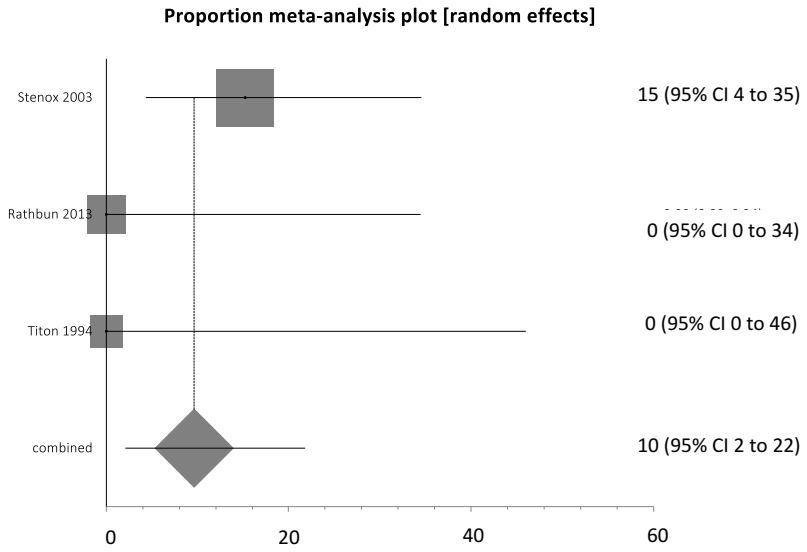
Rivaroxaban low/prophylactic dose	0.00 (0.00 to 3.68)	10.97 (4.33 to 20.16)	17.74 (9.12 to 28.46)	0.42 (0.39 to 3.68)	0.42 (0.39 to 3.68)
Surgery	4.66 (0.50 to 12.73)	7.42 (1.98 to 15.92)	11.40 (0.04 to 38.55)	n/a	n/a
No therapy	1.92 (0.74 to 3.62)	10.09 (2.10 to 23.08)	62.98 (2.22 to 197.25)	0.49 (0.03 to 1.49)	0.49 (0.03 to 1.49)

DVT: deep vein thrombosis; PE: pulmonary embolism; NSAIDs: non-steroidal anti-inflammatory;

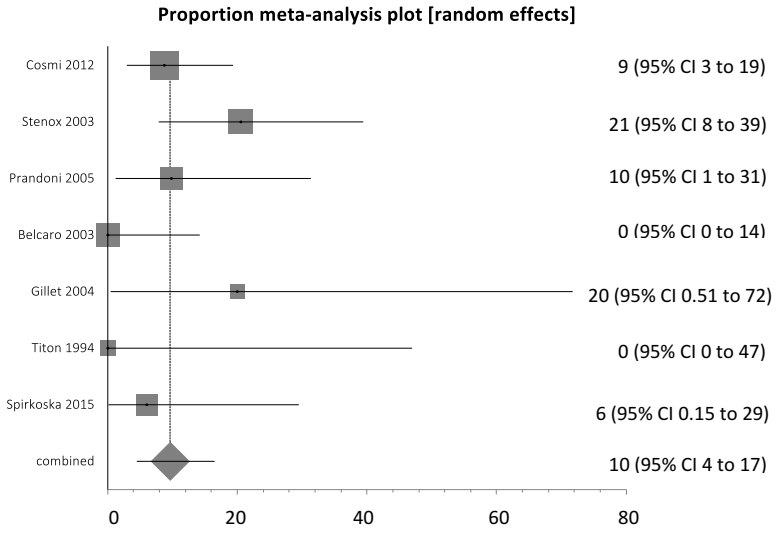
LWMH: low molecular weight heparin; UFH: unfractionated heparin; n/a: not available

Figure 3: Forest plot for meta-analysis of study primary outcome (occurrence of DVT or PE) according to treatment category

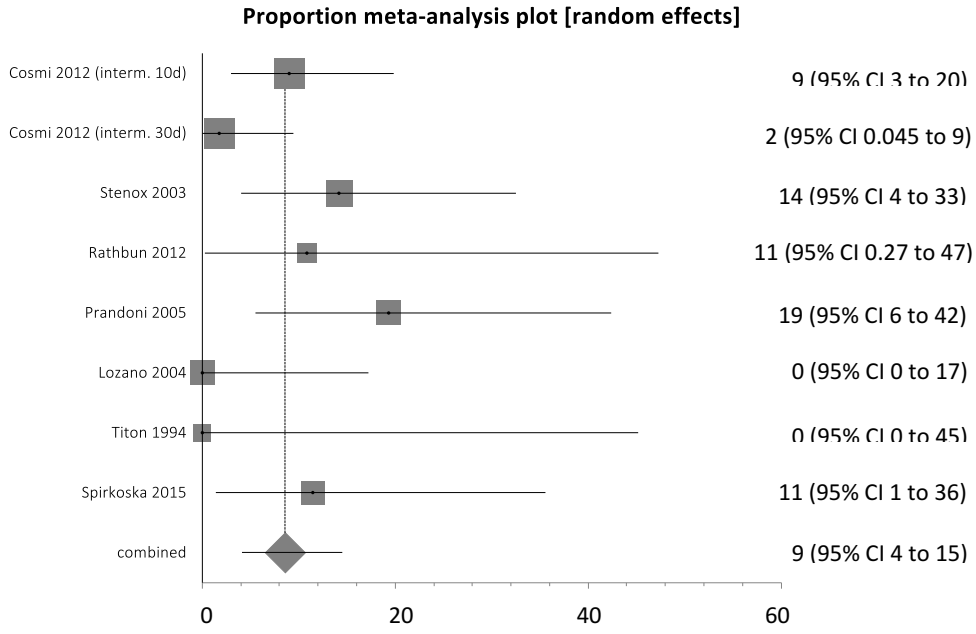
a) NSAIDs



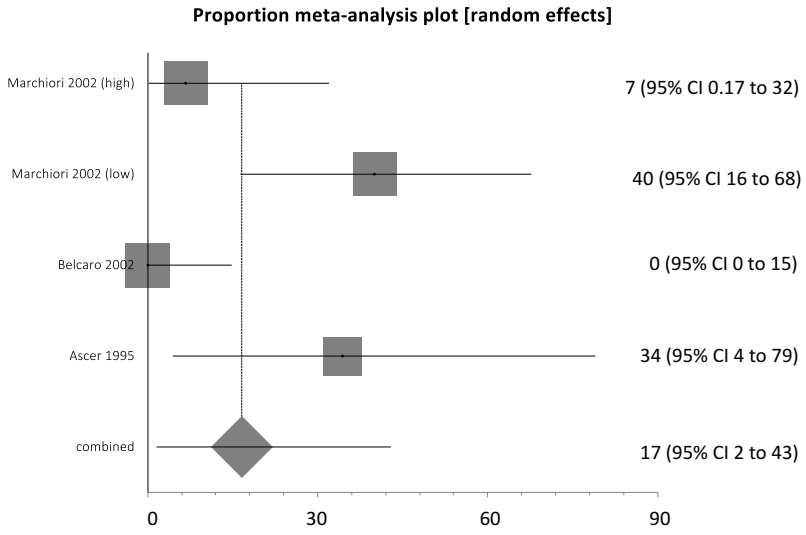
b) LMWH low/ prophylactic dose



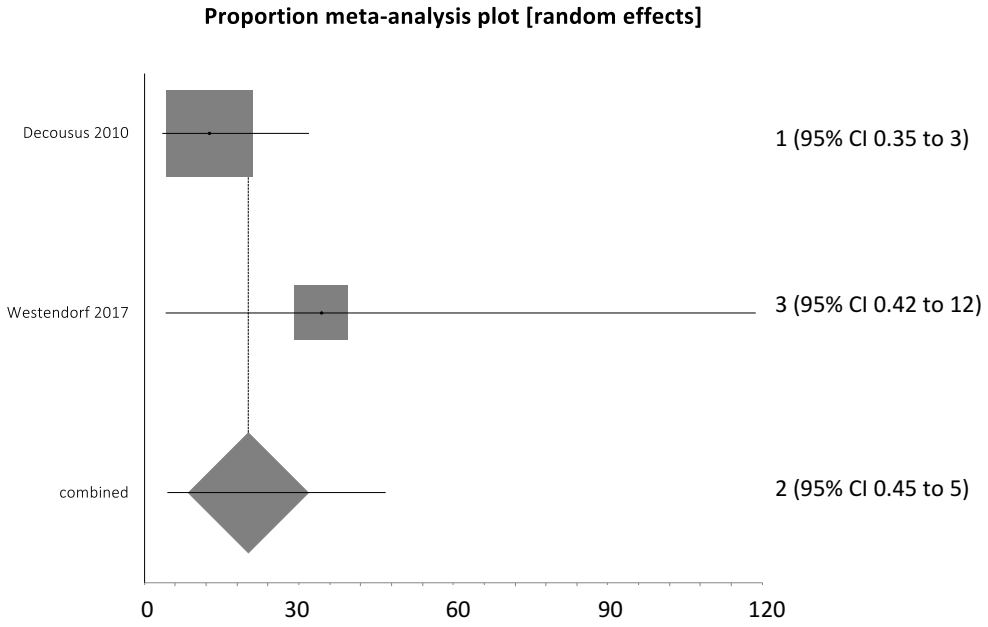
c) LMWH intermediate/ full dose



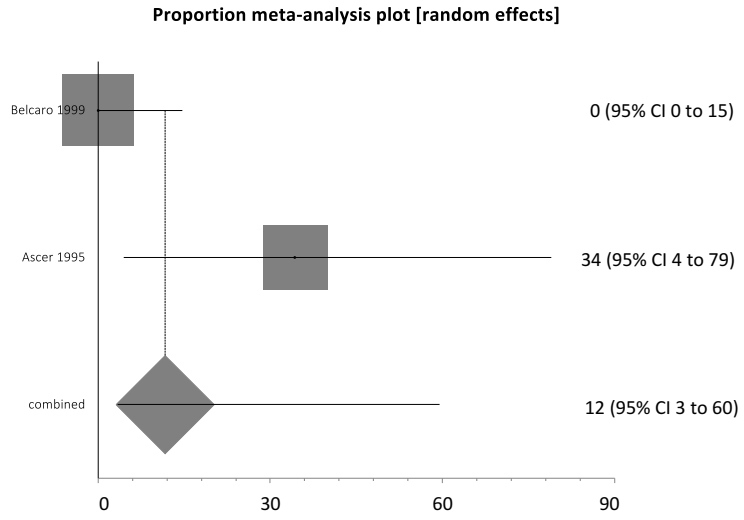
d) UFH any dose



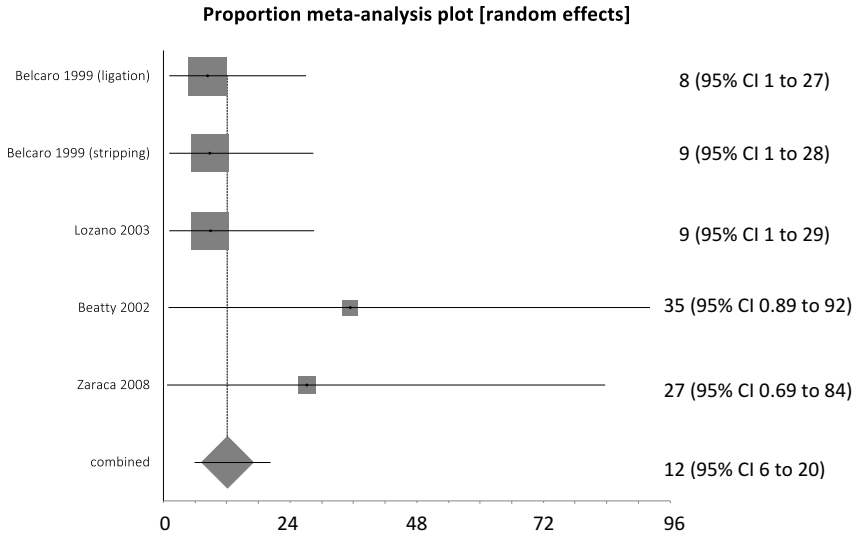
e) Fondaparinux



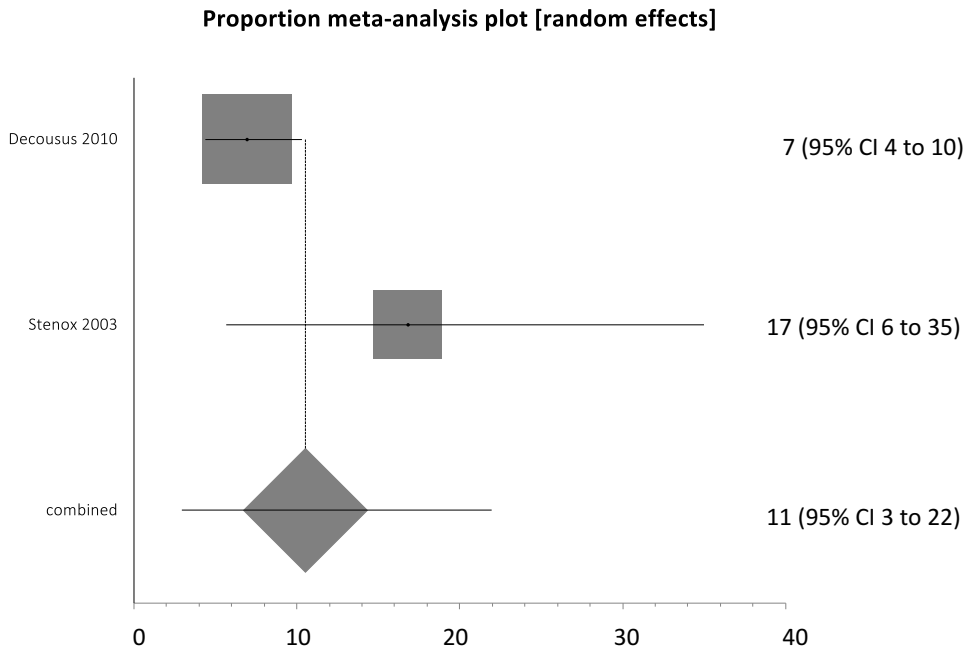
f) Warfarin



h) Surgery


Proportion meta-analysis plot [random effects]
Belcaro 1999 (ligation)
Belcaro 1999 (stripping)
Lozano 2003
Beatty 2002
Zaraca 2008
combined
8 (95% CI 1 to 27)
9 (95% CI 1 to 28)
9 (95% CI 1 to 29)
35 (95% CI 0.89 to 92)
27 (95% CI 0.69 to 84)
12 (95% CI 6 to 20)
0
24
48
72
96

i) No Therapy


Proportion meta-analysis plot [random effects]
Decousus 2010
Stenox 2003
combined
7 (95% CI 4 to 10)
17 (95% CI 6 to 35)
11 (95% CI 3 to 22)
0
10
20
30
40

Planned subgroup analysis for the comparison of outcomes based on: the presence of varicose veins; presence of cancer; and anatomical locations of the SVT were not able to be performed because of insufficient reporting of this information in the included studies.

Discussion

Our systematic review and meta-analysis of 5775 patients with isolated superficial venous thrombosis demonstrates that there is insufficient data to determine the optimal treatment option for SVT. Pooled event rates suggest that Fondaparinux at low/prophylactic dose, 2.5 mg subcutaneous once a day, for 45 days has the lowest occurrence of the primary outcome of DVT or PE at 2.0 events per 100 patient years of follow up (95% CI 0.4 to 4.7). This is based on weight pooled proportions of two RCTs and included a combined 1738 patients. The heterogeneity associated with this pooled proportion was moderate, I^2 of 33%. This likely reflects different inclusion criteria across studies. The study by Decousus et al. (29) included any patient with a lower limb SVT of greater or equal than 5 cm in size so long as SVT did not extend to within 3 cm of the saphenofemoral junction, whereas the publication by Beyer-Westendorf et al. (12) required included 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 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), which is supported by the American College of Chest Physicians (ACCP) clinical practice guides (Grade 2B, weak, moderate quality of evidence), which give only a weak recommendation for Fondaparinux over LMWH (Grade 2C, weak, low or very low quality of evidence) (10).

Compared to Fondaparinux, our pooled primary outcome event rate (DVT or PE) for prophylactic dose LMWH was higher at 9.7 events per 100- patient years of follow up (95% CI 4.5 to 16.5). This was based on pooled results from 7 studies and 601 patients and moderate heterogeneity was observed (I^2=35%). Alternatively, NSAIDs are a common treatment for SVT and have the advantage of being non-anticoagulants as well as favorable safety and cost profile. Among patients treated with NSAIDs, our pooled event rate for DVT or PE was closely comparable to that of LMWH at 9.6 events per 100-patient years (95% CI 2.1 to 21.8). Of note, however, these pooled estimates were generated using non-randomized data and also included trials with different inclusion criteria, durations of treatment and follow up period emphasizing the need to interpreted these estimates and indirect comparisons with caution. Direct comparison of anticoagulant therapies to NSAIDs in randomized control setting is still required before drawing firm conclusions from this data.

A recently published Cochrane systematic review also highlighted uncertainties of the optimal management of lower extremity SVT (1). Their systematic review included 26 randomized control trials that had a comparator arm of an intervention aimed to treat either the symptoms or prevent complications of SVT. The planned analysis of this review attempted to perform direct comparisons but, similar to our finding, there were a lack of trials with the same treatments and/or outcomes compared, and such direct comparisons were not possible. The authors concluded that LMWH and NSAIDs, when compared to placebo, appeared to reduce the extension and recurrence of SVT, but recommended further research for the optimal dose, duration, effect of combination therapy, and adjusting treatment based on SVT location or cause. They observed similar efficacy for LMWH and NSAIDs for the outcomes of extension of SVT and development of VTE, but note methodological flaws and caution drawing conclusions based on this analysis. Their review did not include any studies using DOACs (such as oral

direct Xa inhibitors or oral direct thrombin inhibitors) (1). Given the lack of direct comparison on the management of SVT, we attempted to poolrates in order to provide investigators with estimates of events rates with the different management strategies in order to help planfuture clinical trials.

The pooled event rates observed in our systematic review are consistent with other reports. A French prospective multicenter observational study (POST), 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 (30). Male sex, prior venous thrombosis, previous cancer and SVT not associated with varicose veins were associated with increased risk of thrombotic complications (30). Similarly, analysis of the OPTIMEV study, a large French observational study, of patients with isolated SVT at inclusion, during 3 months of follow up, 3% had a thrombotic complication (0.6% DVT, 0.6% PE, 1.8% recurrent SVT) (31).

Comparison of treatment options to reduce major venous thrombotic events must also consider the bleeding complications observed with each therapy. While our systematic review protocol attempted to capture standardized bleeding using ISTH criteria [29], most studies included did not report bleeding in a standardized way. Overall, however, bleeding events were observed on an infrequent basis through all treatments. Future comparative studies with standardized reporting of bleeding would be required before drawing conclusions regarding bleeding risk between various treatment options.

The strength of our review includes 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 (32) and electronic search strategies were peer reviewed following the PRESS guidelines [30,31]. We also reported outcomes based on an intention to treat analysis regardless of how the individual study results were reported.

Our systematic review does have several limitations worthy of consideration. Despite aggressive searching, some abstracts (n=42) 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 ultrasound to confirm the diagnosis of SVT, which was required for inclusion of in our systematic review. The pooled proportions we report are based on study level results and patient-years of follow-up therefore estimated base on median (or mean) follow-up rather than actual patient level follow-up before censoring for outcome event. This estimate is valid only 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 choose a follow up period as close to 90 days as possible from included 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 unsuccessful owing to a lack of trials with the same treatments and/or outcomes (1). Understanding the limitations of our indirect comparisons, we choose to perform pooled event rates across studies not to determine the best treatment, but in order to guide the planning of a future clinical trial. Finally, most analysis performed was associated with moderate heterogeneity, as measured using the I^2 statistic [36]. Rates of venous thrombotic complications following SVT treatment is known to depend on a number of patient factors such

as age, gender, prior VTE history, presence of thrombus within varicose veins, cancer, and proximity to the saphenofemoral junction (10) (30), and differences between patients included in studies may have contributed to heterogeneity observed. These patient factors were not consistently reported in studies and our planned subgroup analysis based on the presence or absence of these factors was not possible.

The present review is the most comprehensive published in this field, provides a good summary of what is published on the treatment of SVT, and some estimates of pooled event rates to guide future practice and clinical trial development. While Fondaparinux appears to be associated with the lowest VTE event rate during follow-up, this is strongly influenced by a single large publication (29). Obstacles that have prevented the widespread adoption of this treatment include that Fondaparinux is expensive (11) and administered 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' subpopulation of patients (12). Additionally, the role of NSAIDs alone for the treatment of SVT has not been adequately studied.

The results of our systematic review demonstrate that clinical equipoise still exists for the treatment of SVT. Future randomized control studies directly comparing treatment options is required. The next step in this process will be to perform a Delphi process survey (33) of clinicians who regularly treat patient with SVT, presenting our systematic review findings and attempt to find consensus on the design features of a planned randomized clinical trial.

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Chapter 3.

Manuscript 2: TREATMENT OF SUPERFICIAL VENOUS THROMBOSIS: A SURVEY OF CANADIAN PHYSICIANS AND DELPHI PROCESS FOR DESIGN OF FUTURE CLINICAL TRIAL

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Word count: 3067

Abstract

The optimal first line treatment for patients with isolated superficial venous thrombosis (SVT) of the lower extremity is unknown. Clinical practice guidelines offer only weak recommendations to guide clinicians and patients, and, despite several randomized control trials in this area, there remains wide therapeutic practice variation among expert clinicians. Engaging expert clinicians in the design of a future large randomized controlled trial will support and improve trial design, and increase the likelihood of a meaningful impact on clinical practice. A series of surveys of expert clinician members of the Canadian Venous Thromboembolism Clinical Trials and Outcomes Research (CanVECTOR) network was conducted to achieve this goal. We first administered a survey to assess practice variation in the diagnosis and management of SVT among Canadian, self-identified expert clinicians. In addition, a modified Delphi process series of surveys were administered to achieve a consensus among expert clinicians regarding trial design (primary outcome, comparison arms and an acceptable non-inferiority margin to conclude a clinically meaningful difference). The practice variation survey confirmed that there is heterogeneity in the management of patients with SVT in Canada. Clinician experts agreed that clinical equipoise exists for the optimal treatment of SVT (77% of respondents), supporting the need for further research. Through two iterations in our modified Delphi process, consensus was achieved for the design of a future randomized control trial (RCT). The consensus design was a non-inferiority RCT comparing a direct oral anticoagulant (DOAC), such as rivaroxaban, to non-steroidal anti-inflammatories (NSAIDs), with a non-inferiority margin of 3% for the primary outcome of recurrent DVT, PE or death due to venous thromboembolic disease. Next steps will be to continue stakeholder engagement by engaging patients in the clinical trial design, followed by application for peer-reviewed funding of our trial.

Introduction

Despite its common occurrence, the optimal management of superficial vein thrombosis (SVT) is uncertain. SVT most often occurs within either the greater or lesser saphenous veins (GSV or LSV) of the lower extremities and involves both an inflammatory and thrombotic pathology (1-4). Symptomatically, patients present with localized pain, tenderness, redness, edema or a firm palpable cord along the course of a superficial vein (1-4). The diagnosis of SVT is often made by clinical examination alone, although a compression ultrasound can supplement this by confirming the diagnosis, evaluating the size and extent of thrombus, and excluding a co-existing deep vein thrombosis (3;5-8). Treatment options used for SVT may include conservative (clinical observation only), non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulant medications (unfractionated heparin- UFH, low molecular weight heparins- LMWH), pentasaccharides (fondaparinux), vitamin K antagonists (warfarin), direct oral anticoagulants (DOACs), or surgical procedures (ligation or venous stripping) (1;9).

While estimated to be more common than deep venous thrombosis (DVT) and pulmonary embolism (PE) (10), there is a lack of consensus amongst clinicians regarding the diagnosis and management of SVT. The American College of Chest Physicians publishes evidenced based clinical practice guidelines for the management of venous thromboembolic disease (9). In the current guidelines, the authors grade the existing evidence for the management of SVT as moderate quality, using the GRADE system (moderate quality is defined as evidence from randomized control trials but with serious risk of bias or inconsistency) (11). Their final recommendation (GRADE 2B, weak recommendation, moderate quality of evidence with benefits closely balanced with risks and burden) is for the use of prophylactic dose of either fondaparinux or LMWH for 45 days, but include a remark that patients who place a high value on avoiding the inconvenience or cost of anticoagulation and a low value on

avoiding infrequent symptomatic VTE are likely to decline anticoagulation treatment (9). Since the last publication of these guidelines, however, newer studies have been published, including studies evaluating the use of DOACs for the treatment of SVT (12).

Uncertainty in the management of SVT and the many therapeutic options makes designing a future clinical trial challenging. Despite several recent randomized trials in this area (12;13), their results have not fully clarified important questions nor have they had substantial impact on clinical practice guideline recommendations (9). Additionally, there is a lack of consensus on the goal of treatment in patients with SVT (i.e. prevention of DVT or PE, SVT extension, or patient reported symptomatic improvement). The primary outcome of most SVT clinical trials have used a composite outcome which included VTE events of unequal clinical importance with the majority of outcomes observed being extension or recurrence of SVT rather than the more clinically serious outcomes of proximal DVT or PE (12;13). A cost effectiveness analysis of the largest trial using fondaparinux showed that this was not a cost effective intervention, and when evaluated for the most serious complication, PE, the number of patients needed to treat to prevent one PE was 300 (14).

We therefore sought to measure the practice variation and clinical approach to patient with SVT within Canada. We surveyed Canadian physician members of venous thrombosis groups on their current practice for the management of SVT and opinions on the design of a future clinical trial that would have the greatest impact on patient care. We also performed a modified Delphi survey with the same thrombosis experts across Canada. The main objective of both surveys were to gain valuable information to be used in the design of a future clinical trial and to ensure that such future clinical trial addressed clinically meaningful questions and had the greatest impact on patient care.

Methods

A series of self-administered surveys were distributed using Survey Monkey online software software (15) via an email invitation that included a hyperlink to the online survey (Appendix A). A reminder email was sent 7 days after each survey invitation. Physicians were recruited from the mailing list of the Canadian Venous Thromboembolism Clinical Trials and Outcomes Research (CanVECTOR) network. CanVECTOR is an established clinical research network of clinicians involved with diagnosis and treatment of thrombotic vascular disease. This physician sample population represents a wide group of physicians from across Canada and who practice in a variety of clinical settings. The sample population would have sufficient experience and expertise in the treatment of superficial vein thrombosis to provide meaningful feedback concerning study design. They also represent the medical centers that would be potential targets for recruitment of patients in a clinical trial. The invitation to participate in the surveys was sent to 70 members (excluding study authors). Individual email addresses were hidden from viewing by the research team and amongst participants. The survey began with a brief introduction to the research goals and a request for voluntary participation. Consent was implied when participants submitted their responses. The surveys and research protocol was approved by the Ottawa Hospital Research Institute Research Ethics Board. Members of CanVECTOR have agreed to receive such email invitations for research purpose at the time of joining the email list server with the organization. The authors of this paper did not participate in the survey responses. The surveys were administered between March and July 2017.

The initial email request consisted of both a survey of practice variation and round 1 of a modified Delphi survey (16). The objective of the survey of practice variation was to determine the diagnostic approach and therapeutic management among specialized Canadian physicians in the field. The objective of the modified Delphi survey (16;17) was to achieve consensus on

the design of a future clinical trial for the management of SVT. The initial survey included 15 questions, 10 used for the survey of practice variation and 5 (Appendix A, questions 7 to 11) for round 1 of the modified Delphi survey. The later 5 questions were specifically labeled to make participants aware of their use in the subsequent rounds of the Delphi process. A series of iterative rounds of surveys following a modified Delphi process (16) were administered between March and July 2017. The modified Delphi survey was performed by summarizing the results of each previous round using descriptive statistics and redistributing a de-identified summary of responses along with the repeat identical 5 questions (Appendix B). For each round 14 days was allowed before the deadline of responses and one email reminder was sent on day 7. In each subsequent round, participants were asked to review the summarized results from their colleagues and re-submit a response with the goal of achieving a consensus but no pressure or influence provided for an individual participant to conform to the group view. Descriptive statistics were used to summarize survey responses. Agreement for nominal variables was defined as a response having a coefficient of variance of less than or equal to 30% (17;18). The Delphi process was terminated once this level of agreement (coefficient of variance) was achieved or, in the absence of achieving agreement, if it appeared unlikely that further iterations would lead to agreement based on no change in participants' responses between rounds.

Results

The first iteration of the survey (including both the survey of practice variation and round 1 of Delphi process) had 27 respondents (39% response rate). All survey participants identified themselves as practioners treating patients with SVT (one or more patients per year). Baseline characteristics of survey participants are shown in Table 1. The majority of physician surveyed identified their medical specialty as Hematology/Thrombosis or General Internal Medicine, 69% have been practicing medicine for 10 or more years and 58% also had formal training in

research methods. Twenty-two (85%) of respondents of the first survey agreed to participate in subsequent rounds of a Delphi process survey.

Table 1: Baseline characteristics of survey participants.

Medical specialty	
Hematology/ Thrombosis	16 (59%)
General Internal Medicine	9 (34%)
Cardiology or Cardiovascular Medicine	0 (0%)
Respirology	0 (0%)
Emergency Medicine	1 (4%)
Years in practice	
Less than 5	4 (15%)
5 to 10 years	4 (15%)
10 or more years	18 (69%)
Formal training in research methods	
Yes	15 (58%)
No	11 (42%)

Surveyed physicians were asked about their current clinical practice for diagnosis and follow-up of SVT, and in particular the use of compression ultrasound. The majority of respondents reported using compression ultrasound for the initial diagnosis of SVT either routinely in all patients (59%) or occasionally in select patients with diagnostic uncertainty (37%). During the follow-up period of patients with confirmed SVT, however, most respondents did not routinely use serial compression ultrasound (62%) (Table 2).

Table 2: Practice variation: Use of imaging for diagnosis and follow up

Diagnosis:	
Clinical history and examination alone	1 (4%)
Routine use of compression ultrasound in addition to clinical history and examination	16 (59%)
Occasional use of compression ultrasound in select patients with diagnostic uncertainty	10 (37%)
Follow up:	
Clinical history and examination alone	16 (62%)
Serial compression ultrasound	6 (23%)
No follow up	0 (0%)
Combination	4 (15%)

Clinical management of patients with SVT was assessed through two clinical vignettes followed by questions regarding therapeutic management. Both vignettes described a 42 year old female with varicose veins and an isolated SVT of 7 cm in length, confirmed by compression ultrasound, in the greater saphenous vein >5 cm from the saphenofemoral junction (Appendix A). The second vignette differed only in that the patient also had a diagnosis of breast cancer and was on active chemotherapy. The treatment responses are summarized in Figure 1. None of the participants chose surgery or unfractionated heparin for the management of SVT. Conservative, non-anticoagulation therapies were chosen more often in the vignette of SVT alone, compared to the vignette of SVT associated with cancer: clinical observation alone (OR 6.6, 95% C.I. 1.6 to 27.4) and oral NSAIDs (OR 4.3, 95% C.I. 1.3 to 14.0). The only difference between type anticoagulation therapies chosen between the two groups was that prophylactic dose of rivaroxaban was chosen more often in the non-cancer associated vignette (OR 3.9, 95% C.I. 1.2 to 12.8). Seventy-seven percent of surveyed clinicians felt clinical equipoise exists for the optimal treatment of SVT, supporting the need for further research.

Figure 1: Responses for management of SVT

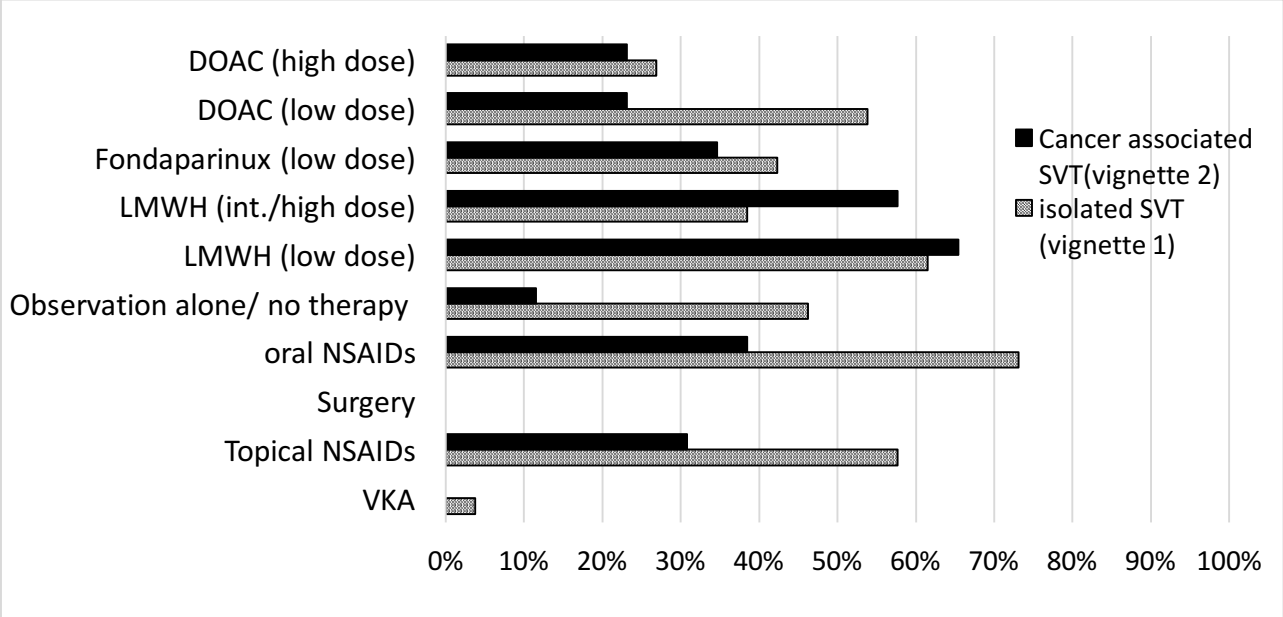
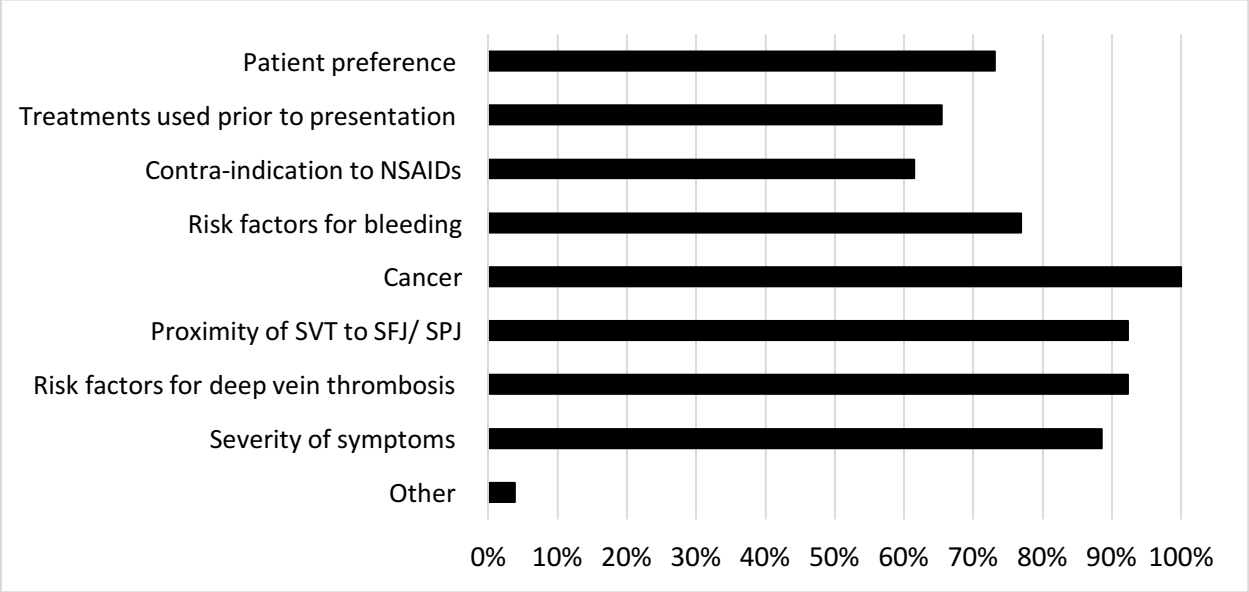


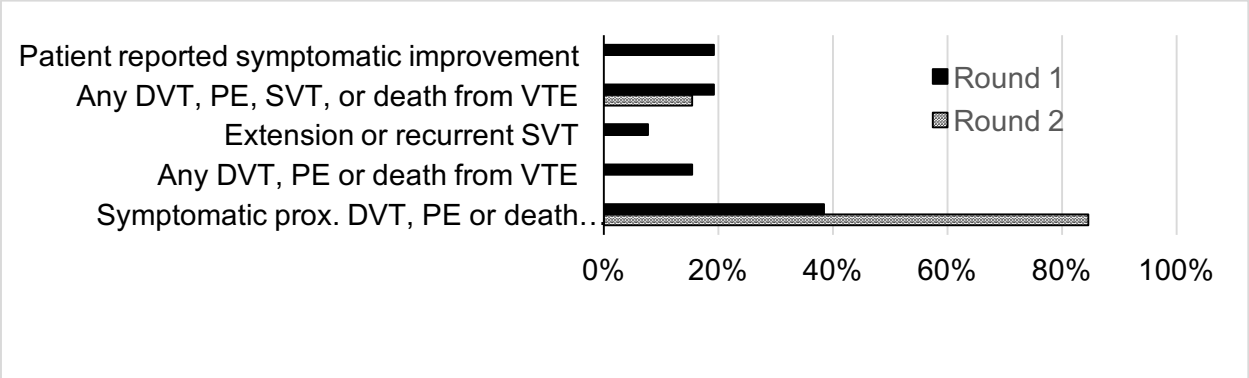
Figure 2: Clinical factors in decision making for SVT treatment



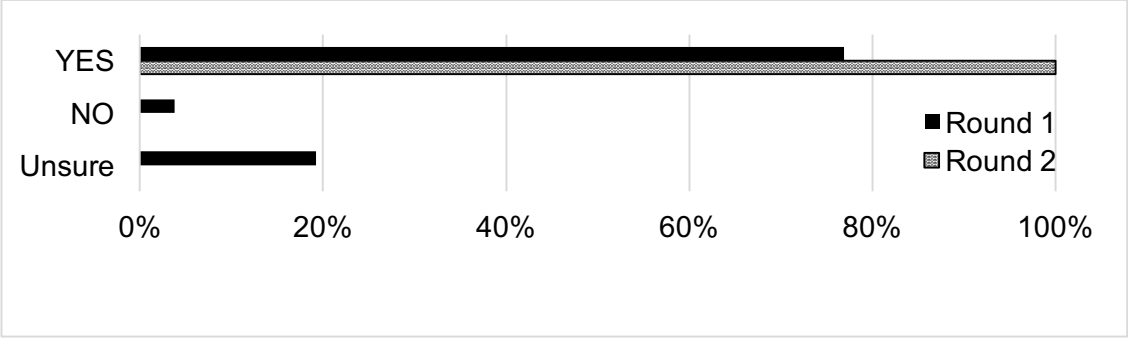
Two iterative survey rounds were performed in the modified Delphi process, at which point the process was terminated as consensus was achieved for the study primary outcome. Twenty-seven physician experts participated in round 1 and 13 in round 2. Response rates were 39% and 68% for round 1 and 2 respectfully. After two iterative rounds, agreement was achieved for all 5 questions (Figure 3). All (100%) of participants agreed that clinical equipoise exists to support a future clinical trial. The consensus design included a primary outcome of symptomatic proximal DVT, PE or death due to VTE (84.6% of respondents). For the future trial comparing DOAC therapy (rivaroxaban), a comparator arm of oral NSAIDs (75% of respondents) was chosen. Consensus on non-inferiority margin was 3% (77% of respondents, coefficient of variance 23%).

Figure 3: Modified Delphi process survey responses

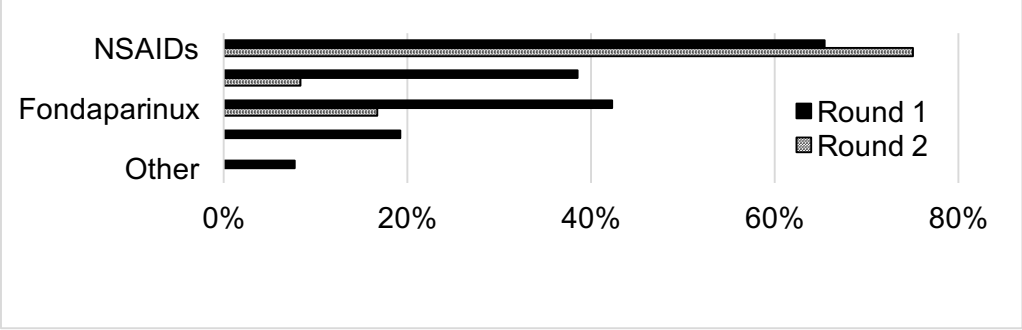
a) If a future randomized clinical trial were to be designed comparing treatments of SVT, what do you feel is the most important clinical outcome to be used as the primary outcome of the trial? Assume equal weighting for each outcome.



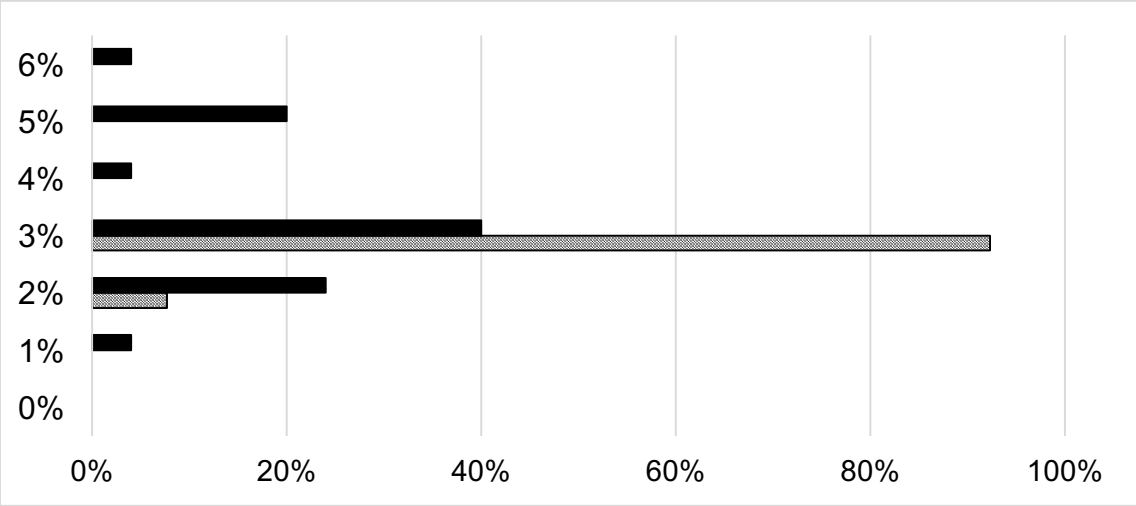
b) Based on these findings, do you feel there is still clinical equipoise on the most appropriate treatment of patients with isolated superficial vein thrombosis to justify a future randomized control trial?



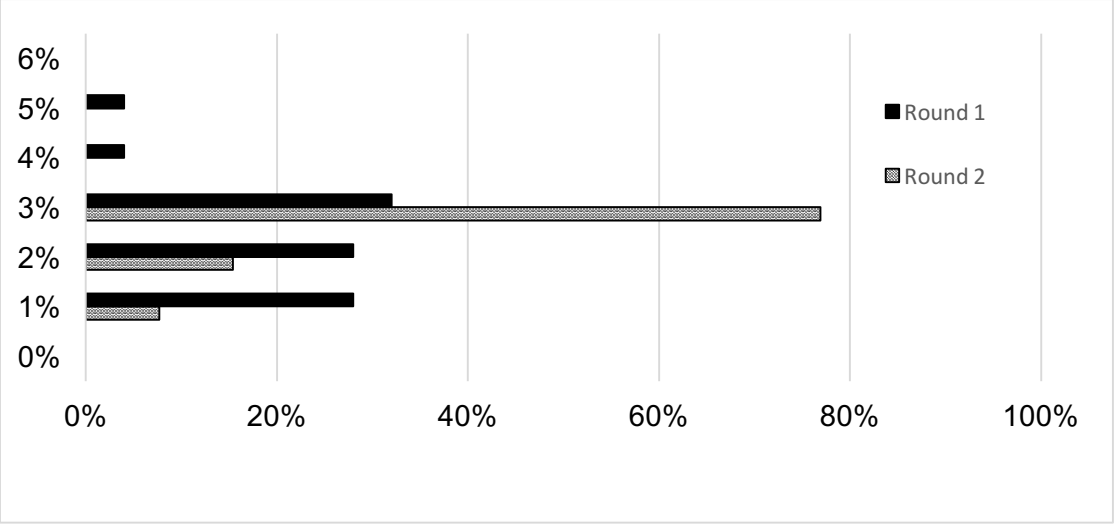
c) Based on these findings, if a future randomized clinical trial were to be designed comparing a direct oral anticoagulant (DOAC) for the treatment of SVT, what do you feel would be the most acceptable comparator arm to represent standard or conventional treatment?



d) If a randomized clinical trial were to be designed to determine if NSAIDs (e.g. twice daily Naprosyn) is non-inferior to a DOAC (rivaroxaban), for the primary outcome of symptomatic DVT, PE, cephalic extension of SVT towards the saphenofemoral junction (but not into common femoral vein), or recurrent SVT, what would be an acceptable non-inferiority margin (or the acceptable upper bound of the 95% Confidence Interval for the absolute risk difference between treatment groups) that you would accept and still conclude that NSAIDs are a 'non-inferior' acceptable treatment option for patients.



e) If the same randomized clinical trial was designed comparing rivaroxaban to NSAIDs, but the primary outcome was changed to symptomatic DVT, PE, or death from any cause within 45 days, what would be an acceptable non-inferiority margin (or the acceptable upper bound of the 95% Confidence Interval for the absolute risk difference between treatment groups) that you would accept and still conclude that NSAIDs are a 'non-inferior' acceptable treatment option for patients.



Discussion

Our series of surveys confirms that there is heterogeneity among Canadian clinicians in the management of SVT. Expert Canadian clinicians agree that evidence to date does not provide sufficient guidance and clinical equipoise exists for the optimal treatment of SVT. Consensus among surveyed clinicians support a future randomized control trial using a non-inferiority trial design, comparing a DOAC (rivaroxaban) to NSAID therapy. The agreed non-inferiority margin for the future study is 3%. Previous research has reported a 45 day event rate of DVT, PE or death in patients treated with rivaroxaban to be 1% (95% CI 0.5-4.1%) (12), therefore a non-inferiority margin of 3% would translate to an outcome rate of up to 4% for patients receiving NSAIDs (upper limits of the 95% confidence interval) and the trial would conclude that NSAIDs are non-inferior to rivaroxaban.

The non-inferiority margin of 3% is lower than that of a recent non-inferiority RCT comparing subcutaneous fondaparinux to oral rivaroxaban, which used a 4.5% non-inferiority margin (12). The non-inferiority margin of the later study was chosen by the study investigators based on estimates of events in a higher risk population. This study also used a broader composite primary outcome which also included recurrent or extension of SVT, which increases the absolute event rate. The acceptance of an estimated 3-fold higher event rate of DVT, PE and death due to VTE by the expert physician in our survey suggests a value placed on the safety and ease of oral NSAIDs compared to rivaroxaban anticoagulation.

The Delphi survey process is a commonly used method for identifying and measuring uncertainty as well as making consensus decisions in health care (16;17;19;20). The advantages of this method is that participants are given time to reflect and respond anonymously without the influence of dominant individuals that can influence opinions in an

open, expert panel situation (16). Self-administered online surveys also allow for greater number of participants from a wider geographic distribution compared to in person expert panel methods. Importantly, the consensus decision formed represents an 'expert opinion' level of evidence and is only as valid as the information on which it is based. Consensus opinions such as ours, however, can guide the development of more rigorous scientific experiments. In our study, we first presented the results of a recently completed and thorough systematic review and meta-analysis to participants to review prior to answering the survey questions. This ensures that responses are made based on the most current evidence. Additionally, our survey was not attempting to obtain a 'correct' answer but rather identify a clinical trial design that would be acceptable and likely to have the greatest impact on patient care.

The overall initial response rate of our survey was low 39%. The objective of our recruitment strategy was not to achieve a large sample size but to have representation from a variety of experts in the field. Respondents were asked at the beginning of the survey to self-identify themselves as experienced clinicians or researchers in the field. It is possible that some physicians who choose not participate may have done so because they self-identified themselves as not having sufficient knowledge to contribute. Still, low response rate may have contributed to a selection bias among those invited clinicians that chose to participate compared to those that declined. There is a potential for further selection bias by surveying only 'self-identified' experts, however, it has been previously shown that physicians participating in expert panels are representative of their colleagues (21).

Our present study confirms that there is clinical equipoise regarding the optimal first line treatment for patients with isolated SVT of the lower extremity, supporting a future randomized clinical trial to address this question. Through a consensus agreement among self-identified

Canadian physician experts, a non-inferiority trial design comparing a DOAC to prescribed NSAIDs with a non-inferiority margin of 3% was established. Next steps will be to continue stakeholder engagement by engaging patients in the clinical trial design, followed by application for peer-reviewed funding of our trial.

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Chapter 4: CONCLUSION AND FUTURE DIRECTION

The work in this manuscript based thesis represents essential research required to address an important knowledge gap in the optimal management of superficial vein thrombosis (SVT). Despite being common and burdensome to patients (1-3), SVT remains an under researched area within venous thromboembolic (VTE) disease (1). While two large randomized controlled trials (RCT) have been completed within the last 10 years (4;5), neither have had a major impact on patient care or guidelines. The lack of translation of the results of these trials into clinical practice change is likely predominately due to their trial designs. Both of these trials used a composite primary outcome consisting of clinical events of varying importance to patients and clinicians and the majority of observed events were the less clinically important outcomes such as extension and recurrent SVT. My work shows that expert clinicians, who are often thought leaders driving practice change, believe only major VTE should be the primary outcome. In the largest trial comparing Fondaparinux to placebo, when analysis is limited to the most serious outcomes, Fondaparinux was not found to be cost effective (6). Additionally, the comparator arm of these trials was either placebo (4) or an alternative anticoagulant medication (5). NSAIDs have historically, and in many clinical settings remain, an inexpensive, safe, and readily available treatment for SVT. In the context of these 2 recent clinical trials, the role of NSAIDs remains uncertain.

Designing and conducting a large clinical trial of patients with acute isolated SVT is challenging. There is considerable practice variation in the diagnostic approach and follow-up of such patients and clinical management may also vary depending on patients' other risk factors. My systematic review, survey of practice variation, and modified Delphi process survey represent a thorough and systematic approach to designing a future RCT. The systematic review provides a summary of all major treatment trials for SVT to date and the involvement of

clinicians in trial design is an important element in ensuring that the results of such a future RCT will have an impact on routine patient care.

The next steps for the research program outlines in this thesis will be to continue stakeholder engagement by engaging patients in the clinical trial design, followed by application for peer-reviewed funding of our trial. Ultimately, we hope that our trial will then define the standard of care for superficial venous thrombosis, a common and potentially serious condition.

Chapter 5: CONTRIBUTIONS OF AUTHORS

Lisa Duffett is the principle investigator of all research presented in this thesis manuscript. Lisa Duffett was responsible for the study conception, design, acquisition of data, analysis and interpretation of data. Lisa Duffett was responsible for the drafting and intellectual content of the written manuscript.

Marc Carrier is the M.Sc. thesis supervisor and provided guidance on the study conception and design as well as acquisition of data for the systematic review as a second reviewer. Marc Carrier participated in the revising and approval of the final written manuscripts.

Clive Kearon is a member of the M.Sc. thesis advisory committee and participated by providing guidance on the study conception, data analysis and revising and approval of the final written manuscript.

Marc Rodger is a member of the M.Sc. thesis advisory committee and participated by providing guidance on the study conception, data analysis and revising and approval of the final written manuscript.

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Appendix A: Level 1 Title and Abstract Screening Form

Included studies must meet all the following criteria:

1. Study design:

- ☐ Randomized control trial, or
- ☐ Retrospective or Prospective cohort or case-control study of consecutive patients

IF STUDY DOES NOT MEET EITHER CRITERIA STOP AND EXCLUDE

2. Includes patients with superficial vein thrombosis

IF STUDY DOES NOT MEET THIS CRITERIA STOP AND EXCLUDE

Reject ☐	**Accept** ☐
Reject but flag for interest ☐ *Reason:*_____ ___ _____ ___	**Uncertain- for discussion** ☐ *Reason:*_____ ___ _____ ___

Appendix B: Level 2 Full Text Screening Form

IF STUDY DOES NOT MEET EITHER CRITERIA STOP AND EXCLUDE

1. Primary outcome (**occurrence of venous thromboembolic disease- proximal or distal DVT and/or PE during follow up**) reported according to <u>at least one</u> of the following treatment groups:
   - o non-steroidal anti-inflammatory medications
   - o anticoagulant therapies
   - o surgical therapies
   - o no therapy/placebo

IF STUDY DOES NOT MEET THIS CRITERIA STOP AND EXCLUDE

2. Review of full text reveals that study does not meet the criteria used in level 1 screening:
   - Study design:
     - ☐ Randomized control trial
     - ☐ Retrospective or Prospective cohort or case-control study of consecutive patients
   - Includes patients with superficial vein thrombosis (must be reported separately)

IF STUDY DOES NOT MEET THIS CRITERIA STOP AND EXCLUDE

3. Study should be excluded based on criteria not mentioned above:
   - o *Specify:* _____

IF STUDY MEETS THIS CRITERIA STOP AND FLAG AS <u>UNCERTAIN</u> FOR DISCUSSION

Reject ☐	**Accept** ☐
Reject but flag for interest ☐ *Reason:*_____ ___ _____ ___	**Uncertain- for discussion** ☐ *Reason:*_____ ___ _____ ___

Appendix C: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias	22	Present results of any assessment of risk of bias across	

across studies		studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

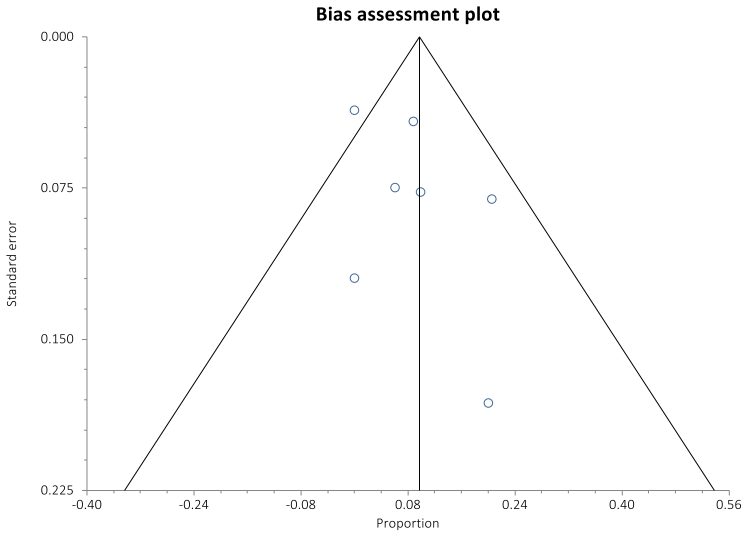
Appendix D: Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Checklist

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	
2	Hypothesis statement	
3	Description of study outcome(s)	
4	Type of exposure or intervention used	
5	Type of study designs used	
6	Study population	
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	
8	Search strategy, including time period included in the synthesis and key words	
9	Effort to include all available studies, including contact with authors	
10	Databases and registries searched	
11	Search software used, name and version, including special features used (eg, explosion)	
12	Use of hand searching (eg, reference lists of obtained articles)	
13	List of citations located and those excluded, including justification	
14	Method of addressing articles published in languages other than English	
15	Method of handling abstracts and unpublished studies	
16	Description of any contact with authors	
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	
22	Assessment of heterogeneity	
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	

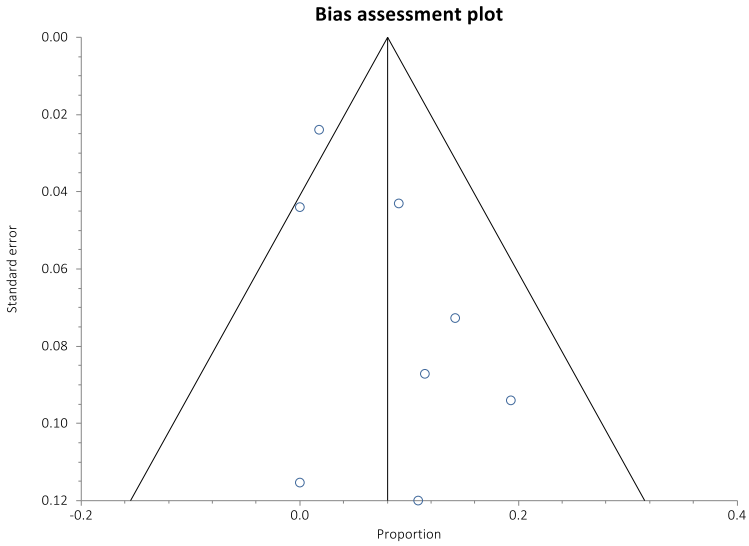
24	Provision of appropriate tables and graphics	
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	
26	Table giving descriptive information for each study included	
27	Results of sensitivity testing (eg, subgroup analysis)	
28	Indication of statistical uncertainty of findings	

Appendix E: Funnel Plots for all meta-analysis of the primary outcome, (DVT or PE) that included 5 or more studies

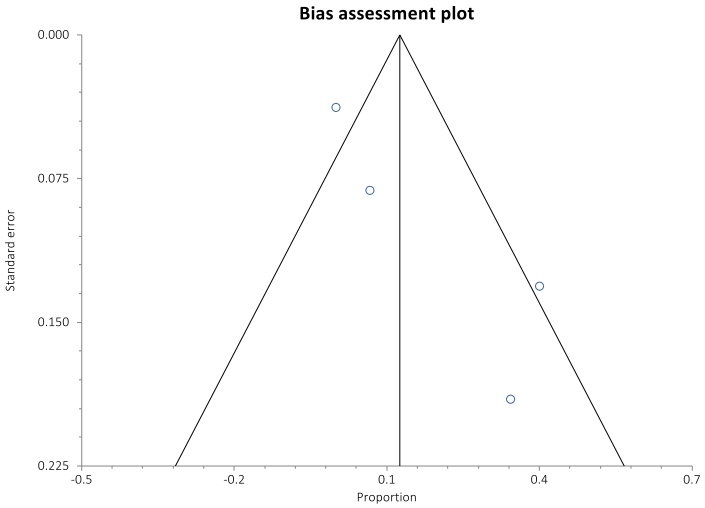
LMWH at low/ prophylactic dose



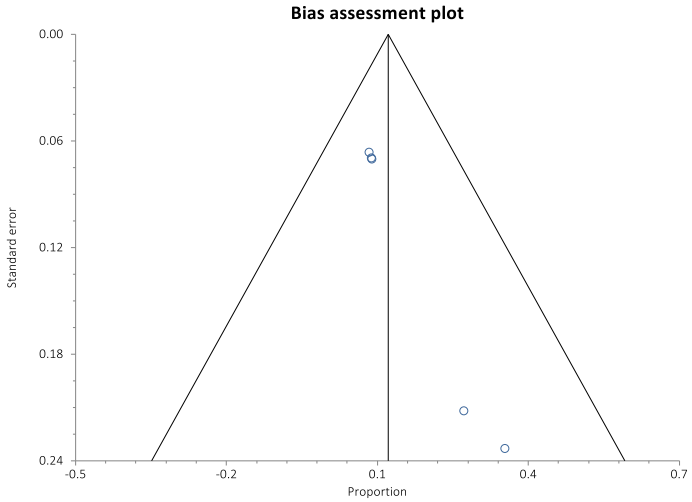
LMWH at intermediate/ full dose



UFH at any dose



Surgery



Appendix F: Initial survey including (i) survey of practice variation and (ii) round 1 of modified Delphi survey