Superficial vein thrombosis: a current approach to management

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Summary

Superficial vein thrombosis (SVT) was considered to be a benign and self-limiting condition. However, it is now appreciated that a significant proportion of those presenting with SVT will have concomitant deep vein thrombosis or pulmonary embolism, or are at significant risk of developing deep venous thromboembolism. Potential therapeutic options include topical preparations, compression therapy (stockings, bandages), medication such as non-steroidal anti-inflammatory drugs (NSAIDs) or anticoagulants (therapeutic or prophylactic doses) and surgery, ligation or stripping, of superficial veins. The treatment of choice is therapeutic/intermediate dose low molecular weight heparin or prophylactic dose fondaparinux administered for 4–6 weeks. The cost-effectiveness of treatment is a concern and more targeted therapy is required.

Keywords: superficial vein thrombosis, thrombophlebitis, anticoagulation.

Introduction

Superficial vein thrombosis (SVT) has traditionally been considered to be a benign and self-limiting condition, often receiving little attention both clinically and in medical research. However, there is increasing recognition that a significant proportion of those presenting with SVT will have concomitant deep vein thrombosis (DVT) or pulmonary embolism (PE), or are at significant risk of developing venous thromboembolism (VTE). In fact, patients with a clinical history of previous SVT have a four- to six-fold increased risk of developing PE or DVT, respectively, in the future (van Langevelde *et al*, 2011).

The term superficial vein thrombosis (SVT), also referred to as superficial thrombophlebitis, is used to describe venous thrombosis in the superficial veins and must not be confused with thrombosis of the superficial femoral vein, which is a DVT. The most commonly affected superficial veins are the long (great) and short saphenous veins of the leg. However, superficial veins on other areas of the body, for example, the abdominal wall, breasts or arms can also be affected. We will review the increasing awareness of the importance of SVT as a disease entity, along with a discussion of current management strategies, with a focus on lower limb SVT.

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Epidemiology

Venous thromboembolism has an incidence of approximately 1 in 1000 of the adult population (White, 2003). The Incidence of Superficial Vein Thrombosis (STEPH) study examined a community of 265 687 people in France and found a yearly incidence rate of 0·64% (Frappé *et al*, 2014), a six-fold higher incidence than that of VTE.

The most robust evidence for the potential sequelae of SVT has come from a recent large prospective epidemiological cohort study - The Prospective Observational Superficial Thrombophlebitis (POST) study undertaken in France (Decousus *et al*, 2010a). It examined 844 consecutive patients presenting with SVT. For inclusion into the study the thrombus was required to be least 5 cm in length and confirmed by compression ultrasonography (CUS). During initial assessment, 210 patients (~25%) were found to have an associated VTE at diagnosis. Of these, 198 had a DVT and 33 were found to have a symptomatic PE. Among 600 patients with isolated SVT, who were followed up for 3 months, 56 (10·6%) developed a further thrombotic complication, including PE (n = 2, 0·4%), DVT (n = 15, 2·8%) SVT extension (n = 17, 3·1%) and SVT recurrence (n = 10, 1·9%) despite 90·5% having received some form of anticoagulation. Of these, 62·9% received therapeutic dose low molecular weight heparin (LMWH) for a median duration of 11 days, with 16·8% receiving a vitamin K antagonist for a median of 81 days. Other treatments received were topical non-steroidal anti-inflammatory drugs (NSAIDs) (47·2%), oral NSAIDs (8·2%), compression stockings (97·7%) and venous surgery (10·2%). Risk factors associated with complications were male gender, previous history of DVT or previous cancer and absence of varicose veins.

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Similar VTE complication rates were found in the STEPH study. Of the 171 patients with SVT, a concomitant DVT was found in 24·6%, with a PE rate of 4·7% (Frappé *et al*, 2014). The DVT was not contiguous with the SVT in 45·2% patients.

There are also a number of earlier studies that examined and demonstrated an association between SVT and VTE, with reported rates varying between 2·7% and 33%. (Lutter *et al*, 1991; Jorgensen *et al*, 1993; Chengelis *et al*, 1996; Bounameaux & Reber-Wasem, 1997; Blumenberg *et al*, 1998; Verlato *et al*, 1999; Unno *et al*, 2002; Quenet *et al*, 2003; van Weert *et al*, 2006). The reasons for this variability probably lie in the heterogeneous design of the studies. Most were retrospective in nature and have only small numbers of patients.

In addition, it has been found that risk factors predisposing to VTE, which include malignancy, the post-operative period, increasing age, obesity, trauma, varicose veins, immobility, pregnancy and the post-partum period, use of HRT or the combined oral contraceptive pill are also risk factors for the development of SVT (Bergqvist & Jaroszewski, 1986; de Moerloose *et al*, 1998); (Chengelis *et al*, 1996); (Lutter *et al*, 1991); (Martinelli *et al*, 1999); (Samlaska & James, 1990).

The relationship between unprovoked VTE and undiagnosed cancer is well recognized (Baron *et al*, 1998), with current National Institute for Health and Care Excellence (NICE) guidelines recommending investigating for cancer in patients with apparently unprovoked VTE over the age of 40 years (Howard & Hughes, 2013). Whilst an increased incidence of SVT is seen in patients with cancer, there have been no robust studies investigating the incidence of undiagnosed cancer in patients with SVT. However with evidence of shared risk factors with VTE, it would seem appropriate to consider the possibility of an undiagnosed cancer in patients presenting with SVT.

There are a few specific situations where there is a proven association between SVT and malignancy. Recurrent superficial thrombosis in different sites (migratory thrombophlebitis) is a well documented paraneoplastic phenomenon, particularly associated with pancreatic cancer (Trousseau, 1865). Mondor disease is where there is superficial thrombosis affecting the superficial veins in the breasts. In 1992 a case series examined 63 patients presenting with this condition found 12·7% had an associated breast cancer (Catania *et al*, 1992). This led the authors to recommend that patients with this condition should be evaluated with mammography. There have been no further robust studies undertaken, and this association has been disputed due to the probable over-representation of patients being investigated for other breast lesions (Shetty & Watson, 2001).

The role of inherited thrombophilia in SVT is not clearly defined. An observational study of 615 patients after discontinuation of secondary thromboprophylaxis for a first spontaneous VTE was undertaken (Schönauer *et al*, 2003). The authors point to the significant incidence of SVT (7·3%) in this population with high factor VIII levels (>234 iu/dl) as an independent risk factor for SVT development (relative risk 2·0). In addition, predictors of SVT development also included age and weight (body mass index >25 kg/m^2). The presence of *F5* R506Q (Factor V Leiden), *F2* G20210A (prothrombin G20210A) and hyperhomocysteinaemia did not reach statistical significance.

The validity of the incidence rate of SVT in this study is unclear as radiological investigation (CUS or venography) was only undertaken when recurrent DVT was suspected based on a high clinical probability. The diagnosis of SVT relied on clinical symptoms and signs alone.

Clinical features and diagnosis

The presenting clinical features are varied but commonly include a tender cord with pain, itching and erythema along the course of the affected vein. There is often accompanying oedema of the surrounding tissues (Gloviczki, 2009). There is a paucity of information in the literature describing the clinical features of superficial thrombosis, with no real data examining the clinical features that make a diagnosis of SVT more likely. There are no recognized clinical scoring systems for superficial thrombosis currently available (cf. The Wells' score for DVT). There have been several studies examining the utility of the D-dimer test in SVT. A study undertaken in 2001 performed rapid semi-quantitative D-dimer tests on 414 patients who presented with symptoms of deep or superficial thrombosis (Siragusa *et al*, 2001). The diagnosis was then confirmed or refuted with CUS. The sensitivity and specificity of the test for isolated superficial thrombosis of the great saphenous vein was 48% and 90·6%, respectively. The high false negative rate greatly impairs the clinical utility of the test. Other studies have also examined the use of D-dimer in SVT, producing varying estimates of sensitivity and specificity (Aguilar & del Villar, 2005; Gillet *et al*, 2007). However, the conclusion from all studies has been similar; the D-dimer has not been found to be useful for the diagnosis of isolated SVT. The diagnosis of SVT has historically been on clinical grounds alone. However with the significant risk of concurrent DVT being increasingly recognized, the utilization of CUS has increased, both to aid the distinction of SVT from other causes of leg swelling and inflammation, such as cellulitis, and for the assessment of the deep veins. The basis of diagnosis of SVT by CUS is the same as that for DVT, i.e., the observation of a lack of compressibility of the affected vein and a corresponding reduction of blood flow through the segment. An analysis of data from the POST study (Decousus *et al*, 2010a) confirmed the value of this radiological technique (Quéré *et al*, 2012). All patients within the study had a CUS exploratory screening of the whole of the venous system of the affected limb, with the striking finding that 23·5% of patients had a concomitant DVT. Over half of the DVTs were found not to be contiguous with the SVT and 17% were found to have a DVT

affecting the contralateral lower limb. However an isolated contralateral DVT was only found in 1% of cases. These findings address the importance of ultrasonographic evaluation of the deep veins, as management is obviously different. In contrast, the routine investigation of PE in the absence of clinical features cannot be recommended. The POST study established a 4% PE rate in all patients with SVT, however only patients with symptoms were investigated (Decousus *et al*, 2010a). The asymptomatic PE rate has not been established.

The study also attempted to examine which ultrasonagraphic risk factors make a DVT more likely. The involvement of the perforating veins or an SVT <3 cm from the sapheno-femoral junction (SFJ) was found to increase the risk significantly. The odds ratios for concomitant DVT were 8·1 and 3·3 respectively. Indeed, the proximity of SVT to the SFJ has long been accepted as a risk factor for developing complications. In patients with SVT <3 cm from the SFJ, consensus groups have recommended full-dose anticoagulant therapy and surgical ligation of the SFJ or thrombectomy is commonly performed in some centres (Hill *et al*, 2008; Tait *et al*, 2012).

Management

The approach to the management of SVT has evolved as greater understanding of the thrombotic complications and associations has been established. Therapeutic options that have been tried include topical preparations, compression therapy (stockings, bandages), medication, such as NSAIDs or anticoagulants (therapeutic or prophylactic dose), and surgery, ligation or stripping of superficial veins.

Topical treatments with heparin spray gel or diclofenac gel appear to provide a non-significant reduction in localized symptoms, but there is no evidence that they prevent SVT extension or new VTE (De Sanctis *et al*, 2001; Incandela *et al*, 2001). Similarly, there is little in the published literature to support the sole use of compression therapy (Di Nisio *et al*, 2012).

The recognition of the potential thrombotic complications of SVT as well as the acknowledgement that there are shared risk factors between DVT and SVT has resulted in significant interest in the potential role for anticoagulation using LMWH, unfractionated heparin (UFH) or fondaparinux.

In the Vesalio study, patients were randomized to receive a treatment dose of weight-adjusted nadroparin for 10 days followed by half-dose for 20 days or a prophylactic low dose of nadroparin daily for 30 days (Prandoni *et al*, 2005). At the end of treatment two patients (2·4%) in the treatment group developed SVT progression or VTE compared to five patients (6·2%) in the low dose group. During 3-month follow-up the advantage of therapeutic LMWH was not maintained, with a total of six (7·2%) patients in the treatment group and seven (8·6%) in the prophylactic group having either SVT progression or new VTE. The rate of improvement in symptoms and signs was similar in both groups (Prandoni *et al*, 2005).

In a subsequent study of nadroparin, patients received a daily therapeutic subcutaneous dose (190 anti-Xa iu/kg) for 10 days ± the addition of the NSAID, acemetacine, 60 mg orally twice daily. The combination of LMWH and anti-inflammatory agent appeared to be superior to LMWH alone in terms of symptomatic improvement; however the authors did not measure SVT extension or VTE occurrence (Uncu, 2009).

Three studies have investigated the effects of LMWH versus NSAIDs (Titon *et al*, 1994; Decousus *et al*, 2003; Rathbun *et al*, 2012). A fixed dose of nadroparin (6150 anti-Xa iu) or dose-adjusted for body weight (31·5 anti-Xa iu/kg) were compared with naproxen 500 mg/day for 6 days. There was a significant improvement in both symptoms and signs of SVT at the end of treatment (day 7) in the 2 groups receiving nadroparin compared to naproxen. The persistence of symptoms and signs was also less frequent in the nadroparin groups at 8 weeks. There was no difference in efficacy between the nadroparin groups (Titon *et al*, 1994).

The Superficial Thrombophlebitis Treated by Enoxaparin (Stenox) Study Group randomized patients with acute SVT into one of four arms, to receive enoxaparin, either as a prophylactic dose of 40 mg/day or a therapeutic dose of 1·5 mg/kg once daily, or tenoxicam 20 mg/day or placebo for 8 to 12 days. During treatment, four patients (4%) in the placebo group and one patient (1%) in both of the enoxaparin groups suffered a DVT. There were two VTEs (2%) in the tenoxicam group; one PE and one DVT. During 3 months follow-up the trend in favour of the active treatment groups was no longer present, with approximately 5% of patients suffering a VTE event (DVT and/or PE). There was however, a significant reduction in symptomatic SVT recurrence and/or extension in favour of the active treatment groups that was maintained at follow-up, with no significant difference between the therapies (Decousus *et al*, 2003).

In the most recent study to compare LMWH with NSAIDs, patients were randomized to dalteparin (200 units/kg first dose, then 10 000 units/day for 6 additional days) versus ibuprofen 800 mg three times daily for 7 days. If the symptoms had not resolved by day 7–9, in the absence of thrombus extension, a further 7 days of treatment was administered. Both treatment groups showed a significant reduction in symptoms, but there was no difference between the treatment modalities. Four patients (11%) receiving ibuprofen experienced extension of their SVT during the 2-week treatment period. Two additional patients had thrombus progression during the 3-month follow-up period (17% in total). There were no on-treatment thrombotic events in the dalteparin group, but four patients (11%) had thrombus progression, including one PE, during the 3-month follow up. The results suggested that dalteparin treatment is superior to ibuprofen, but, similar to the Stenox group study,

that a 2-week duration of treatment with LMWH is too short (Rathbun *et al*, 2012).

The Superficial Thromboembolism Fluxum (STEFLUX) study was undertaken in an attempt to answer the question regarding optimal dose and duration of LMWH for SVT treatment. Patients were randomized to receive parnaparin 8500 units/day for 10 days followed by placebo for 20 days (Group A), parnaparin 8500 units/day for 10 days followed by a dose reduction to 6400 units/day for 20 days (Group B) or parnaparin 4250 units/day for 30 days (Group C). Patients in Group B had the lowest rate of the combined outcome of SVT extension, DVT or PE. All three groups showed an increase in events after stopping treatment with a difference remaining between the three groups, indicating a subset of patients may benefit from longer treatment. These results support the earlier studies which suggested that a longer treatment period would be superior to a shorter one and that an intermediate dose of LMWH is superior to a prophylactic dose (Cosmi *et al*, 2012).

The largest of the anticoagulant studies is the Comparison of Arixtra (fondaparinux) in lower Limb Superficial vein Thrombosis with placebo (CALISTO) study, which reported in 2010. This trial randomized 3002 patients to receive either fondaparinux 2·5 mg for 45 days or placebo, with follow up for a month after. The primary end-point was a composite of death, symptomatic PE or DVT, symptomatic extension or recurrence of SVT (Decousus *et al*, 2010b).

The overall incidence of thrombotic complications was 0·9% in the treatment group and 5·9% in the placebo group, with no increased risk of bleeding. The incidence of each

Table I. Summary of anticoagulation studies in the management of superficial vein thrombosis.

Study	Design	*n*	Follow-up	Primary outcome	Treatment groups (duration)	% events (n) of primary outcome
Cosmi *et al* (2012)	Randomized, placebo controlled	663	93 days	DVT (symptomatic and asymptomatic), PE (symptomatic), asymptomatic SVT recurrence in the first 33 days	Parnaparin 8500 iu/day for 10 days then placebo for 20 days Parnaparin 8500 iu/day for 10 days then 6400 iu/day for 20 days Parnaparin 4250 IU/d for 30 days	15·6 (33/212) 1·8 (4/219) 7·3 (16/217)
Rathbun *et al* (2012)	Randomized, placebo controlled	72	3 months	Thrombus extension or new symptomatic VTE during the 14-day and 3-month follow-up period	Daltaparin 200 iu/kg for 1 day then 10000 iu for 6 days Ibuprofen 800 mg/8 h for 7 days	0 (0/37) 11·4 (4/35)
Decousus *et al* (2010b)	Randomized, placebo controlled	3002	47 days	Death, symptomatic PE or DVT, symptomatic extension to SFJ, symptomatic recurrence of SVT (confirmed by CUS) within 47 days	Fondaprinux 2·5 mg/day for 45 days Placebo	0·9 (13/1502) 5·9 (88/1500)
Prandoni *et al* (2005)	Randomized controlled	164	3 months	Asymptomatic/symptomatic extension of SVT and/or VTE	Nadroparin 2850 anti-Xa iu for 30 days Nadroparin 31·5 anti-Xa iu/kg for 10 days then half dose for 20 days	8·6 (7/81) 7·2 (6/83)
Decousus *et al* (2003)	Randomized, placebo controlled	416	3 months	DVT (symptomatic and asymptomatic), symptomatic PE, SVT recurrence and/or extension toward the SFJ (symptomatic and asymptomatic)	Enoxaparin 40 mg/day for 2 weeks Enoxaparin 1·5 mg/kg/day for 2 weeks Tenoxicam 20 mg/day for 8–12 days Placebo for 8–12 days	22·7 (25/110) 19·8 (21/106) 20·2 (20/99) 38·4 (43/112)
Lozano & Almazan (2003)	Randomized controlled	60	6 months	SVT recurrence, symptomatic DVT, symptomatic PE	Sapheno-femoral disconnection Enoxaparin 1 mg/kg/12 h for 1 week then daily for 3 weeks	10 (3/30) 10 (3/30)
Titon *et al* (1994)	Randomized controlled	117	8 weeks	VTE	Naproxen 500 mg/day for 6 days Nadroparin 6150 anti-Xa iu for 6 days Nadroparin 31·5 anti-Xa iu/kg for 6 days	0 0 0

DVT-deep vein thrombosis, SFJ-sapheno-femoral junction, SVT-superficial vein thrombosis, LMWH-low molecular weight heparin, PE-pulmonary embolus, VTE-venous thrombosis, UFH-unfractionated heparin, CUS-compression ultrasonography, h-hour.

individual component of the composite end-point was significantly reduced. Importantly the rate of PE or DVT was reduced by 85% in patients treated with fondaparinux (0·2%, 3/1502 patients) compared to placebo (1·3%, 20/1500 patients). The longer treatment period also appeared to avoid the 'catch-up' phenomenon seen with shorter courses of LMWH with the benefit persisting through until day 77 (Decousus *et al*, 2010b).

However, a recent cost-effectiveness analysis of the CALISTO study has implied that the use of Fondaparinux 2·5 mg to treat isolated SVT is not cost- effective. It estimates that although fondaparinux would prevent 123 VTEs and two deaths per 10 000 patients treated, this translates into an incremental cost-effectiveness ratio of $500 000 per quality-adjusted life year (Blondon *et al*, 2012).

Although the American College of Chest Physicians (ACCP) (Kearon *et al*, 2012), the British Committee for Standards in Haematology (BCSH) (Tait *et al*, 2012) and the International Union of Angiology (IUA)/Phlebology (IUP), and Central European Vascular Forum (CEVP) (Kalodiki *et al*, 2012) recommend medical treatment in the form of anticoagulation, in preference to surgical treatment for the acute management of SVT, there does appear to be a body of consensus opinion, particularly amongst vascular surgeons (Gloviczki *et al*, 2011) that promotes the role of surgical procedures, such as vein stripping or ligation for patients with chronic venous insufficiency. Advocates of surgical management claim that it treats both the cause as well as the complications of SVT (Kalodiki *et al*, 2012). Further study is required to support or refute these claims.

The wide variation in study methodologies, especially the definition of primary and secondary outcomes in clinical trials examining the management of SVT (Table I), limits the conclusions that can be made when undertaking a cross-study analysis. Many SVT studies have recruited only small patient numbers. The importance of asymptomatic events, especially SVT extension, has not been clearly defined.

Use of extended prophylactic dose LMWH and exact dose of LMWH are additional areas of contention. Only one study (Decousus *et al*, 2003) directly examined the first issue where no significant difference between the incidence of symptomatic VTE and asymptomatic DVT was found when comparing prophylactic and therapeutic enoxaparin (5·7%, 6/110 vs. 3·9%, 4/106). Data from the STEFLUX Study (Cosmi *et al*, 2012), however, suggested a clear advantage of intermediate dose parnaparin (8500 iu/day for 10 days followed by 6400 iu/day for 20 days) over a limited therapeutic course of treatment (8500 iu/day for 10 days) and an extended prophylactic course (4250 iu/day for 30 days). The current evidence in support of fondaparinux is of higher quality than the evidence in support of LMWH (Kearon *et al*, 2012). There are no studies that directly compare fondaparinux and LMWH and we can only assume both anticoagulants are comparable in their antithrombotic efficacy in SVT.

These issues highlight the difficulty of having a truly evidence-based approach to the management of SVT. The UK-based NICE currently recommends that patients with SVT and an increased risk of DVT should consider discussion with a haematologist to discuss the use of LMWH or fondaparinux (NICE, 2014). Particularly high-risk groups are

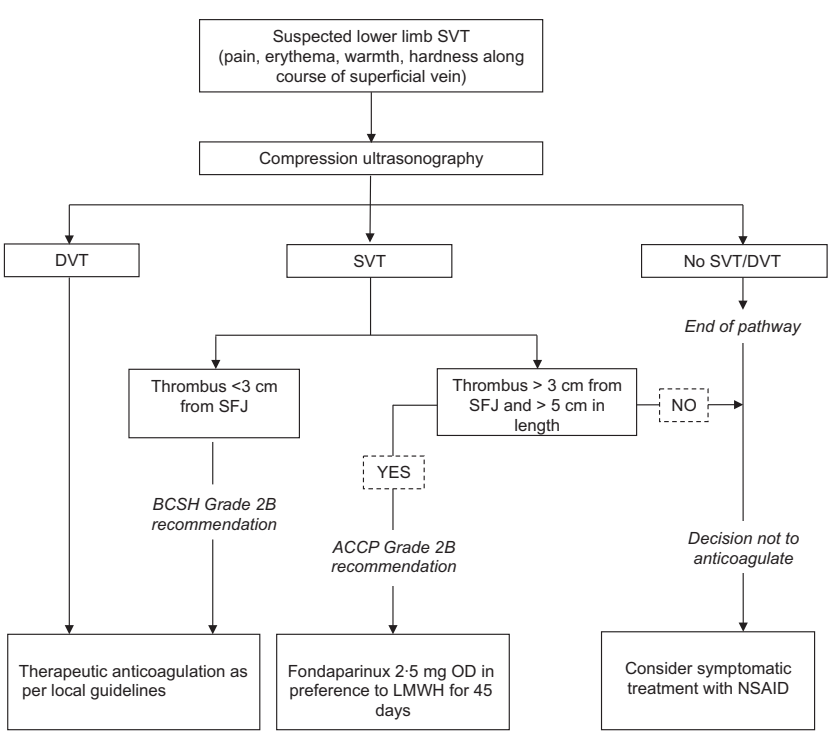

Fig 1. Management of patient with suspected superficial vein thrombosis, adapted from ACCP guidelines *(The antithrombotic therapy and prevention of thrombosis,* 9th *Ed.)* and BCSH guidelines *(Management of venous thrombosis at unusual sites)*. ACCP-American college of chest physicians; BCSH-British committee for standards in haematology; d-day; DVT-deep vein thrombosis; LMWH-low molecular weight heparin; NSAID-non-steroidal anti-inflammatory drug; OD-once daily; SFJ-sapheno-femoral junction; SVT-superficial vein thrombosis.

where SVT is in close proximity SFJ, reduced mobility and SVT is not associated with varicose veins and previous DVT or PE. Symptomatic relief with oral NSAID/paracetamol or topical NSAID for mild or limited SVT are also recommended. Swelling should be managed with British standard class 2 compression stockings in the absence of lower limb arterial insufficiency.

The ACCP consensus guidelines are more specific in their advice (Kearon *et al*, 2012). They recommend prophylactic dose fondaparinux or LMWH for 45 days over no anticoagulation in patients with SVT of the lower limb of at least 5 cm in length. Other risk factors that should be considered to influence the decision to start anticoagulation are: extensive SVT; involvement above the knee, particularly if close to the SFJ: severe symptoms; involvement of the greater saphenous vein; history of VTE or SVT; active cancer and recent surgery. Fondaparinux 2·5 mg/day is recommended over prophylactic LMWH in light of the higher quality evidence for the former.

Our current management of patients diagnosed with superficial thrombophlebitis (Fig 1) utilizes a pragmatic approach which incorporates evidence from the literature along with recommendations from current British and International guidelines. It should be appreciated that although NSAIDs are useful adjuncts in SVT therapy, their use is for symptomatic relief only and do not play a role in the treatment of the underlying thrombosis.

Conclusion

The myth that SVT is a benign, self-limiting condition should be dispelled. Treatment should no longer be focussed solely on local symptomatic relief, but emphasis should be placed on preventing DVT complications. The annual incidence rate of SVT is six-fold higher than DVT and, with up to 25% of SVT cases potentially suffering a DVT event, the burden of disease is large. Although the diagnosis of SVT can be made clinically, the importance of identifying the position and size of the thrombus as well as excluding associated DVT compels mandatory Duplex ultrasound imaging of all symptomatic patients. Randomized controlled studies have demonstrated the efficacy and safety of systemic anticoagulation with therapeutic/intermediate doses of LMWH or prophylactic doses of fondaparinux administered for 4–6 weeks most effective. Fondaparinux 2·5 mg/day is currently the only anticoagulant with a license for the treatment of SVT. However, there are concerns regarding drug cost and cost-effectiveness and therefore future studies will need to identify those patients who will benefit most from treatment (Leizorovicz *et al*, 2013).

The novel oral anticoagulants will perhaps play a future role in the treatment of this condition and there is currently a phase 3 study underway comparing fondaparinux 2·5 mg with rivaroxaban 10 mg/day for 45 days (ClinicalTrials.gov identifier NCT01499953). This study began recruitment in 2012 and is expected to be completed in December 2015.

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None of the authors have any competing financial or conflict of interest associated with the topic of this review.

Author contributions

GS, AJM and RA co-authored this manuscript.

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