INVITED REVIEW

Spontaneous acute superficial vein thrombosis of the legs: do we really need to treat?

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Summary. Spontaneous acute superficial vein thrombosis (SVT) of the leg is now generally recognized as an integral component of venous thromboembolic disease with potentially severe consequences. However, the relatively low grades of some current international recommendations and uncertainty regarding the cost-effectiveness of available therapies may prompt questioning of the real need to treat patients with SVT and explain the persisting heterogeneity of their management in practise. Yet several studies have consistently shown high rates of thromboembolic complications associated with SVT, whether at first presentation or during follow-up. The CALISTO trial established for the first time the clinical benefit of a well-defined anticoagulant regimen for the prevention of serious thromboembolic complications in SVT patients, and we believe that patients such as those included in this trial should receive this regimen as tested. However, several areas of uncertainty remain for categories of SVT patients not evaluated in CALISTO.

Keywords: anticoagulants; saphenous vein; thrombosis; treatment; venous thromboembolism.

Introduction

Due to considerable efforts in clinical research during the past decade, the perception of superficial vein thrombosis (SVT) has progressed from a benign, localized inflammation of a superficial vein (as reflected by the previous, probably misleading, terminology 'superficial thrombophlebitis') to a recognized integral component of venous thromboembolic disease with potentially severe consequences. Several consensus groups have now issued recommendations for more aggressive therapy, mainly with

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anticoagulants (Table 1) [1–5]. However, the relatively low grades of some of these recommendations and uncertainty regarding the cost-effectiveness of available therapies [6] may prompt questioning of the real need to treat patients with SVT. Considerable variations in the management of these patients still exist, including underuse of anticoagulant therapy [7,8]. In the present review, SVT will refer exclusively to acute, spontaneous SVT of the lower limbs.

What is SVT?

Superficial vein thrombosis is a thrombus developing in a superficial vein. It has long been estimated to be more frequent than deep vein thrombosis (DVT) and pulmonary embolism (PE) [9]. In the recently published, and so far only, community-based study evaluating the incidence of SVT in a well-defined area of France, we found that this incidence was 0.64 per 1000 person-years, was higher in women, and increased with advancing age irrespective of gender [10]. This incidence is half that of DVT and close to that of PE, when compared to data obtained in another French community-based study using similar methodology [11]. These data nevertheless indicate that SVT is a frequent disease.

Superficial vein thrombosis is most often seen in outpatients, typically women, with a mean age of 60 years, high body weight and/or a history of varicose veins [10,12,13]. Clinical signs and symptoms include the presence of a visible warm, red, tender, swollen area along the course of a superficial vein, often palpable as a cord [14,15]. In 60–80% of cases, the SVT is located in the great saphenous vein (GSV), in 10–20% in the short saphenous vein (SSV) and in 10–20% in other leg veins, occurring bilaterally in 5–10% of patients [10,12,16]. As signs and symptoms are sometimes not specific, and extension of SVT is often underestimated clinically, duplex ultrasonography is necessary for the confirmation of diagnosis and extent of thrombosis [14,15].

Considering the inflammatory component of SVT, often associated with pain and impaired mobility,

Table 1 Main recent recommendations for the treatment of SVT

Kearon *et al.* [1]	In patients with 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)
	In patients with SVT who are treated with anticoagulation, we suggest fondaparinux 2.5 mg daily over a prophylactic dose of LMWH (Grade 2C)
Kalodiki *et al.* [2]	All patients with SVT should be treated with compression therapy
	Immediate mobilization with elastic compression is mandatory. Patients should not be confined to bed
	Patients with SVT, with an inflamed and thrombosed superficial vein longer than 5 cm on duplex ultrasound should have LMWH at intermediate or therapeutic dose for 4 weeks. The dosage and duration of anticoagulation depends on concomitant diseases and other risk factors for VTE
	In patients with extended SVT (> 10 cm) with additional risk factors for VTE, subcutaneous fondaparinux in prophylactic doses should be considered for 6 weeks
	Routine surgical ligation of the sapheno-femoral or sapheno-popliteal junction to prevent SVT extension into the deep veins is not advised. However, following SVT treatment, as SVT on varicose veins could recur and it is a sign of advanced chronic venous insufficiency, appropriate treatment of varicose veins could prevent further problems
Tait *et al.* [3]	Patients with confirmed SVT within 3 cm of the sapheno-femoral junction should be considered for therapeutic anticoagulation (2B)
	Patients with SVT and risk factors for extension, recurrence or progression should be offered treatment with prophylactic doses of LMWH for 30 days (currently an unlicensed indication) or fondaparinux for 30–45 days (1B)
	Other patients with SVT should be offered 8–12 days NSAIDs unless contraindicated (1A).
Di Nisio *et al.* [4]	Given the available evidence, prophylactic dose fondaparinux appears to be a valid treatment option in patients with SVT. Fondaparinux should be given at a dose of 2.5 mg s.c. Once daily for 45 days
	Final recommendations cannot be drawn for LMWH, UFH, or NSAIDs
	Data are still too preliminary to draw firm conclusions on the role of surgery and the topical, oral, and parenteral treatments evaluated this far
Nicolaides *et al.* [5]	The LMWH in intermediate doses for at least 1 month is recommended (level of evidence: moderate)
	Fondaparinux 2.5 mg daily for at least 4 weeks is an effective treatment (level of evidence: high). Surgery is not better than LMWHs (level of evidence: low)

Table 1 (Continued)

	When thrombus is close to sapheno-femoral or sapheno-popliteal junctions, LMWHs in therapeutic doses or surgery (ligation) are both acceptable options depending on the patient's characteristics and the treating physician's preference (level of evidence: low)
	For isolated SVT at the below knee segment confined to varicosities, local application of heparinoids, NSAIDs, and elastic stockings are acceptable treatment options (level of evidence: low)

treatment should first aim to relieve local symptoms. This may be achieved with analgesics, topical or oral nonsteroidal anti-inflammatory drugs (NSAIDs), and topical formulations of heparin, in combination with compression stockings, and thrombectomy in patients suffering from intense pain [4,14,15]. However, such symptomatic treatment is likely to be insufficient in many SVT patients.

What is beyond superficiality at first presentation?

There are evident links between SVT and DVT/PE. The risk factors are shared [14,16]. SVT is itself a risk factor for DVT or PE: the lifetime risk of DVT or PE is increased four- to sixfold in patients with a history of SVT [17–19]. However, venous insufficiency is much more common in the context of SVT (> 80% of cases) [10,12,13]. In the absence of varicose veins, other possible causes of SVT include autoimmune disease, malignant disease, and thrombophilia, as for DVT [14]. Another difference is that the 3-month mortality of patients with SVT is less than 1% as opposed to ~5% in patients DVT or PE, probably because SVT patients are younger and have fewer comorbidities [14,15]. Two mechanisms conceivably underlie the association between SVT and DVT or PE, namely: (i) migration of the SVT toward the deep venous system *via* the sapheno-femoral junction (SFJ), the sapheno-popliteal junction or a perforating vein, and (ii) a state of hypercoagulability that may explain the non-contiguous coexistence of the two types of thrombosis. Several historical studies raised the alert that SVT may be indicative of more widespread concomitant thrombosis. In these studies, systematic ultrasonography revealed a concomitant DVT in 6–36% of SVT patients [20–25], a concomitant PE was clinically suspected in 2–13% [21,26–28], while systematic lung scanning resulted in the detection of asymptomatic PE in up to 33% [29].

These early studies were criticized due to their predominantly retrospective nature, the small number of patients included and the fact that patients were selected in the vascular units to which they had been referred. However, their results were consistently confirmed in larger prospective epidemiological studies, whether conducted in the secondary/tertiary or primary care settings: about 25–30% of patients with SVT exhibit a concomitant DVT or

symptomatic PE at first presentation, around 5% having PE (Table 2) [10,12,16]. SVT in non-varicose veins, age > 75 years, inpatient status and active cancer were found to be independently associated with the presence of concomitant DVT at presentation [16]. Interestingly, these studies showed that about 40–50% of concomitant DVT were proximal DVT, more prone to embolization, and about 40–45% were not contiguous to the SVT [10,12,16]. These findings emphasize that duplex ultrasonography should be mandatory in all SVT patients at first presentation not only to confirm diagnosis but also to exclude concomitant DVT. The examination should be bilateral as contralateral DVT is sometimes observed [2,5]. Careful search for symptoms or signs suggestive of PE is also of major importance. Clearly, SVT patients identified as having associated DVT or PE at presentation require treatment with therapeutic doses of an anticoagulant agent administered according to guidelines [1].

What is the risk of subsequent thromboembolic complications in patients with isolated SVT at first presentation?

Patients with acute isolated SVT (i.e. with no DVT or PE at presentation) are at risk of subsequent thromboembolic complications, including DVT or PE, as well as SVT recurrence or extension (Table 3). The main independent risk factors for such complications reported to date include male gender, severe venous insufficiency, SVT in a non-varicose vein, a history of DVT or PE, and a history of cancer [12,30–32]. Most studies, whether randomized or prospective observational, showed that the risk of symptomatic DVT or PE at 3 months from the index isolated SVT event was between 3.0% and 3.5%, even though most patients received some form of active anticoagulant treatment [12,33–35]. These data suggest either that the risk of symptomatic venous thromboembolic complications observed in these studies was underestimated or that the treatments administered were poorly effective. In two retrospective cohort studies of patients with isolated SVT not routinely treated with anticoagulants, the rate of symptomatic DVT or PE was still consistently found to be 3.2% at 6 months [36] and 3.4% at 3 months [19] in a real-life setting. The CALISTO study was a randomized, double-blind, placebo-controlled study evaluating the benefit–risk ratio of a 45-day course of an anticoagulant (fondaparinux) in patients with isolated SVT at inclusion [13]. Its placebo group therefore provided a unique opportunity to evaluate the rate of symptomatic thromboembolic complications in such patients when untreated [13,37]. However, in this study, the rate of symptomatic DVT or PE at day 77 after the SVT index event was only 1.5%. This apparently low rate of DVT or PE can likely be explained by the exclusion of patients at particularly high risk of such complications (such as those with active cancer and recent venous thromboembolism) from CALISTO to avoid their possible exposure to placebo. In such high-risk patients, the 3-month risk of DVT or PE was estimated to be 4.7% in prospective observational studies, even though 84% of patients received various anticoagulant treatments [32]. In addition, the close clinical monitoring of patients in the context of a trial including placebo-treated patients (probably more intensive than that in a real-life setting) may have elicited early discovery of SVT extensions, that is, before their propagation into the deep venous system. In favor of the latter explanation, the rate of confirmed symptomatic extensions found in CALISTO (7.3%) [37] was twice that found in the prospective observational POST study of patients with isolated SVT (3.3%) [12], while the rate of DVT or PE in POST (3.3%) was twice that in CALISTO (Table 3), POST having included unselected patients monitored as *per* routine practise. Moreover, in CALISTO, the management of venous thromboembolic events occurring during follow-up was left to the investigator's discretion. The placebo group of CALISTO therefore allowed interesting observations regarding the clinical management and outcome of symptomatic SVT extensions in patients with isolated SVT at presentation [13,37].

The primary efficacy endpoint of CALISTO was a composite of symptomatic outcomes including DVT, PE, SVT recurrences, and SVT extensions [13]. The SVT extensions considered in this endpoint were those spreading to within ≤ 3 cm from the SFJ. Patients with such extensions at

Table 2 Concomitant DVT or PE in patients with SVT at first presentation

Study	POST [12]	OPTIMEV [16]	STEPH [10]
Setting	Secondary/ tertiary	Secondary/ tertiary	Primary
No. of patients with SVT, no. (%)	844	788	171
Concomitant DVT or PE, no. (%)*	210 (24.9)	232 (29.4)	45 (26.3)
Concomitant DVT, no. (%)†	198 (23.5)	227 (28.8)	42 (24.6)
Proximal	82	–	20
Distal	114	128 (16.2)	23
Not contiguous to the SVT	83	–	19
Concomitant symptomatic PE, no. (%)	33 (3.9)	54 (6.8)‡	8 (4.7)

*Patients could have had more than one concomitant event. All events were confirmed by objective tests. †DVT location was missing for two patients in POST and 12 in OPTIMEV. The number of patients with proximal DVT is not reported in the OPTIMEV publication and cannot be calculated due to the missing data on location. ‡In five patients, no concomitant DVT was identified.

Table 3 Subsequent symptomatic thromboembolic complications in patients with isolated SVT at first presentation in the main studies addressing this issue*

Study/setting	Treatment received	Symptomatic thromboembolic complications
STENOX [33] Randomized trial, $N = 427$	LMWH low dose: 25.9% LMWH high dose: 24.8% NSAID: 23.2% Placebo: 26.2% For 8–12 days	DVT or PE at 3 months: 3.3% DVT: 2.8%; PE: 0.7%
VESALIO [34] Randomized trial, $N = 164$	LMWH low dose: 49.4% LMWH high dose: 50.6% For 30 days	DVT or PE at 3 months: 3.1% DVT: 2.4%; PE: 0.6%
POST [12] Prospective observational study, $N = 600$	One or more anticoagulant: 90.5% LMWH high (62.9%) of low (36.7%) dose for a median of 11 days VKA: 16.8% for a median of 81 days Oral NSAID (8.2%) and surgery (10.2%)	Thromboembolic complications at 3 months: 8.3% DVT or PE: 3.3% DVT: 2.8% (half being proximal); PE: 0.5% SVT extension: 3.3% (irrespective of distance to the SFJ) SVT recurrence: 1.9%
OPTIMEV [16] Prospective observational study, $N = 499$	Anticoagulants: 76.4% (for > 45 days: 24.6%) LMWH only: 53.5% LMWH + VKA: 29.9%	DVT: 0.6%; PE: 0.6% SVT recurrence: 1.8%
CALISTO [13,37] Randomized trial (placebo group), $N = 1500$	Placebo	Thromboembolic complications at 77 days: 9.4% DVT: 1.3%; PE: 0.4% DVT or PE: 1.5% SVT extension: 7.3% (≤ 3 cm from the SFJ: 3.6%; > 3 cm from the SFJ: 3.7%) SVT recurrence: 1.7%
STEFLUX [35] Randomized trial, $N = 648$	LMWH intermediate dose for 10 days: 32.7% LMWH intermediate dose for 30 days: 33.8% LMWH low dose for 30 days: 33.5%	DVT or PE at 3 months: 3.4% DVT: 3.1%; PE: 0.3%
van Weert [36] Retrospective cohort study, $N = 185$	NSAID: 8%; Acenocoumarol: 1% No treatment registered: 83%	DVT or PE at 6 months: 3.2% DVT: 2.7%; PE: 0.5%
Danish National Patient Registry [19] Retrospective nationwide cohort study, $N = 10\,973$	No routine anticoagulant treatment	DVT or PE at 3 months: 3.4% DVT: 2.5%; PE: 0.9%

*The main independent risk factors for such complications reported to date include male gender, severe venous insufficiency, SVT in a non-varicose vein, a history of DVT or PE, and a history of cancer [12,30–32].

screening were excluded from the trial, as most authors and consensus groups emphasize that extensions involving the SFJ: (i) are associated with an increased risk of thrombus propagation into the deep venous system, (ii) can be considered as serious as a proximal DVT, and (iii) should be treated with full-dose anticoagulant or surgically by ligation of the SFJ or thrombectomy [3,5,38–42]. In accordance with these recommendations, most (48 of 54) placebo-treated patients with a SVT extension involving the SFJ received these treatments [37]. Moreover, such extensions were associated with other significant medical resource consumption, including additional face-to-face visits, ultrasonography examinations and hospitalizations [37]. Nevertheless, 5 of these 54 patients (9.3%) subsequently developed DVT or PE, confirming the severity of extensions involving the SFJ.

What was less expected was the outcome of placebo-treated patients experiencing symptomatic SVT extension not reaching the SFJ (i.e. extensions to > 3 cm from the SFJ) [37]. These extensions were not part of the primary outcome of CALISTO but could be analyzed *post hoc* as they were prospectively recorded and confirmed by ultra-

sonography and central blind adjudication. First, these extensions occurred as frequently as those involving the SFJ (3.7% vs. 3.6%). Second, patients with such extensions received anticoagulant therapy just as often, were treated surgically almost as often, and had a medical resource consumption similar to that of patients with an extension involving the SFJ. Importantly, as in the latter patients, this care did not prevent these patients from subsequently experiencing DVT or PE, which occurred in 5 (8.9%) of the 56 placebo-treated patients having such extensions. Overall, these findings suggest that patients with an extension to > 3 cm and to ≤ 3 cm, respectively, from the SFJ are similar, the only difference being that the former were seen at an earlier disease stage. Thus, it appears that SVT extension *per se* is indicative of severity, regardless of the distance from the SFJ. In CALISTO, ultrasonography was permitted only to confirm symptomatic events, systematic ultrasound examinations being discouraged. It could therefore be reasoned that monitoring of asymptomatic SVT patients using serial ultrasonography may have been of value for early detection of extensions. However, data from POST indicated that

systematically planned compression ultrasonography was neither efficient nor cost-effective [43]. Taking into account SVT extensions not reaching the SFJ, the overall rate of serious symptomatic thromboembolic complications observed at day 77 in the placebo group of CALISTO was 9.4% [37].

What evidence supports anticoagulant treatment for patients with acute isolated SVT?

Considering the above data, the therapeutic approach for SVT should aim not only to resolve or relieve local symptoms, but more importantly to prevent the possible extension of SVT into the deep venous system. Several small studies investigated the ability of surgery or oral NSAIDs to prevent thromboembolic complications, but data are too limited to draw conclusions about their overall clinical benefit, if any [4]. A few other studies evaluated anticoagulants for secondary prevention in patients with isolated SVT.

Early studies evaluated prophylactic, intermediate or therapeutic doses of unfractionated heparin (UFH) or low molecular weight heparin (LMWH), but were small and had various methodological limitations [33,34,44–47]. None provided clear conclusions on anticoagulant strategies for the effective prevention of symptomatic thromboembolic complications of SVT, leading at that time to weak and/or varying recommendations regarding the use of anticoagulant therapy in patients with isolated SVT (ranging from 'watchful waiting' to anticoagulant treatment for 6–12 weeks) [14,40–42], and consequently to heterogeneous therapeutic strategies in clinical practise. For instance, in the POST study, 90.5% patients with acute isolated SVT received one or more anticoagulant drugs, mostly LMWH (Table 3) [12]. Elastic compression stockings were prescribed for 97.7% of patients, topical NSAIDs and oral NSAIDs being prescribed for 47.2% and 8.2% of patients, respectively. Specific surgery (e.g. stripping or ligation) was planned in 10.2% of patients. In contrast, in a retrospective cohort study conducted in the Dutch primary care setting, only 17% of patients with SVT were treated, receiving mainly NSAIDs and compression stockings [36].

Despite their limitations, these early studies provided useful information, which served as foundation for subsequent investigations. First, they showed encouraging results in favor of anticoagulation over first-line surgery or oral NSAIDs [33,34,44–47]. Second, they provided hints on what could be the optimal anticoagulant regimen for patients with SVT. The four-arm STENOX study comparing a low (prophylactic)- and high (therapeutic)-dose regimen of LMWH to oral NSAIDs and placebo for 12 days suggested that the high-dose LMWH regimen did not provide any additional benefit compared with the low-dose regimen [33]. Importantly, the initial benefit seen with LMWH was lost at 3-month follow-up, indicating that the duration of treatment of 12 days was too short.

The two-arm VESALIO study comparing a low-dose LMWH treatment to an intermediate-dose LMWH treatment for 30 days showed that the early apparent benefit observed with the intermediate dose was lost after treatment had been stopped, suggesting that even 30 days of LMWH treatment was insufficient [34]. It is striking that these findings were consistently confirmed in more recently published studies [35,48], which showed that treatment with an intermediate dose of LMWH for either 14 [48] or 30 days [35] was insufficient.

It was thus in a context of uncertainty regarding the clinical benefit of LMWH in preventing thromboembolic complications in patients with acute isolated SVT and the optimal dose and duration of LMWH treatment to be used, that European investigators involved in the field designed the CALISTO randomized trial, including 3002 patients with a SVT longer than 5 cm [13]. The study had to be placebo-controlled in order to demonstrate that patients with acute isolated SVT were indeed at increased risk of serious thromboembolic complications, and because no treatment had previously shown clinically relevant benefit. Only symptomatic events were considered in the primary efficacy outcome, including the most serious events, namely DVT, PE and SVT extension reaching the SFJ. A prophylactic dose of fondaparinux (2.5 mg) was chosen, based on the STENOX results. The duration of treatment had to be more than 30 days to avoid any rebound phenomenon, as was seen in VESALIO, and was empirically set at 45 days. CALISTO met its primary objective, demonstrating that fondaparinux significantly reduced at day 49 (end of treatment) the risk of the composite of death and symptomatic thromboembolic events (primary efficacy) by 85%, symptomatic DVT or PE by 85%, symptomatic SVT extension by 92%, and symptomatic SVT recurrence by 79%. These benefits were achieved without increase in the risk of bleeding and were maintained at 1-month follow-up after treatment cessation (day 77). Interestingly, fondaparinux reduced by the same magnitude the risk of extension to ≤ 3 cm and to > 3 cm from the SFJ, from 3.6% to 0.3% and from 3.7% to 0.8%, respectively, at day 77 [37]. This was associated with reduced use of medical resources, particularly in terms of anticoagulant treatment at therapeutic dosage (0% vs. 2.4%), surgery to treat SVT (0.5% vs. 3.6%), and need for additional ultrasonography examinations (0.5% vs. 3.2%), face-to-face visits (0.5% vs. 3.9%) and hospitalizations (0.5% to 3.7%) [37]. Importantly, none of the fondaparinux-treated patients presenting symptomatic SVT extension, whether or not involving the SFJ, subsequently experienced DVT or PE, emphasizing that serial ultrasonographic monitoring is not necessary when effective treatment is applied [37]. Overall, in CALISTO, fondaparinux reduced by 79% the rate of any symptomatic thromboembolic complication up to day 77, from 9.4% (141/1500) with placebo to 1.9% (29/1502; $P < 0.001$; number needed to treat: 13) [37].

Do we really need to provide anticoagulant treatment to patients with acute isolated SVT?

CALISTO was a large randomized, double-blind study conducted in a well-defined patient population. Considering the 9.4% risk of serious events at day 77 observed in the placebo group of CALISTO, all patients with a spontaneous acute isolated SVT of the leg at least 5 cm long, but not reaching the SFJ, should in our view receive fondaparinux [1,4]. LMWH may represent an alternative in such patients [1]. However, even though some studies suggested that intermediate dose LMWH might be effective [34,35], this has to be confirmed, as does the optimal duration of LMWH treatment. Considering the 45-day treatment duration, and despite the feasibility of self-injection (performed by over 90% of patients in CALISTO), new oral anticoagulant agents seem attractive alternatives to subcutaneous injections. However, their benefit–risk ratio in this context remains to be established (ClinicalTrials.gov identifiers of ongoing trials: NCT01499953 and NCT02123524).

In Europe, fondaparinux is the only anticoagulant approved for the treatment of adults with acute symptomatic spontaneous SVT of the leg without concomitant DVT. Yet the fondaparinux Summary of Product Characteristics recommends that treatment should be continued for a minimum of 30 days and up to a maximum of 45 days in patients at high risk of thromboembolic complications, a reduced 30-day treatment duration being suggested for some patients [6,49]. Although there is some evidence allowing identification of patients at high risk of thromboembolic complications that should receive a 45-day treatment, patients at lower risk who could receive a shorter 30-day course of fondaparinux (a treatment duration never tested in a clinical trial) are less easy to identify. As previously mentioned, male gender, severe venous insufficiency, SVT in a non-varicose veins, a history of DVT or PE, and a history of cancer have been reported to be independent risk factors for subsequent thromboembolic complications in patients with isolated SVT at presentation [12,30–32]. Although no multivariate analysis was performed on CALISTO data, subgroup analyses on the primary outcome (day 49) showed, not surprisingly, numerically higher rates of events in patients aged over 75 years, those weighing over 100 kg, and those with a creatinine clearance below 50 mL min^{-1}, a history of DVT, PE or SVT or multiple SVT (even though these events were not recent in CALISTO), a qualifying SVT located above the knee, involving the GSV, or with its head < 10 cm from the SFJ (up to 14% of events at day 49) [13]. Interestingly, in the fondaparinux group, whatever the subgroup risk profile, the thromboembolic complication rate was low, close to 1%. As among placebo-treated patients in CALISTO, the rate of primary efficacy events at day 49 was still 4.1% in those with no evident risk factors [49], identifying

patients at lower risk who could benefit from a reduced 30-day course of treatment without any rebound phenomenon remains a challenge. Although the cost-effectiveness of a 45-day treatment has been challenged [6], such economic evaluations should now include recent data regarding the actual cost of SVT extensions observed in a real-life setting [26]. Moreover, as it appears ethically difficult to leave untreated any patients resembling those included in CALISTO, the cost of managing such patients without using fondaparinux, including use of inadequately evaluated treatments and repeated ultrasonographic examinations as practiced in some countries [12,16], should be considered. All these costs, including the direct cost of fondaparinux, vary widely between countries. In contrast, the 45-day fondaparinux regimen is a well-defined (in terms of dose and duration), effective, and safe treatment, not requiring any additional monitoring tests [4,13].

Conclusion and areas of uncertainties remaining

Available clinical evidence indicates that patients such as those included in the CALISTO study should receive a 45-day course of once-daily subcutaneous fondaparinux 2.5 mg, ideally by self-injection. Further analyses are needed to establish whether this strategy is cost-effective. The benefit–risk ratio of using shorter treatment durations or other anticoagulant agents remains speculative, and in our view such strategies cannot be recommended. It is acknowledged that various patient groups were not included in CALISTO, and thus, several questions remain unanswered. For instance, should we increase the dose and/or duration of anticoagulant treatment in patients with a recent history of venous thromboembolism or active cancer? Would the recommendation of anticoagulant use at therapeutic dose or surgery in patients with SVT involving the SFJ be confirmed in a dedicated trial? Should we decrease the dose and/or duration of anticoagulation in patients with a high bleeding risk? Do patients with a SVT measuring less than 5 cm really need anticoagulant treatment and if so, at what dose and for what duration? Which anticoagulant should we use (and with what dosage regimen) in pregnant women with SVT, as fondaparinux is not recommended during pregnancy? Would a combination of anticoagulants and NSAIDs provide any additional benefit in some patients, considering the increased bleeding risk of such combination therapy? Finally, should we modify our strategy for thromboprophylaxis in patients with a history of SVT exposed to additional risk factors in a later life, as suggested by the results of a recent study [50,51]? All these areas of uncertainty deserve further investigations as such situations are frequently encountered in clinical practise and can currently only be managed on a case-by-case basis according to the treating physician's judgement.

Disclosure of Conflict of Interests

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