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CRITICAL/NARRATIVE REVIEW

Treatment of Superficial Venous Thrombosis: critical review of the literature, current management Strategies, and future perspectives

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ABSTRACT

Treatment of the majority of superficial venous thrombosis is based on the results of the excellent CALISTO trial: Treatment with fondaparinux 2.5 mg once daily for 45 days is recommended.

However, some patients require **therapeutic-dose anticoagulation**, including:

- concomitant deep vein thrombosis (DVT) occurring with SVT,
- extension of the thrombus to the saphenofemoral junction or to a perforating vein,
- extensive SVT despite prophylactic-dose anticoagulation.
- An SVT longer than 5 cm in a **patient with cancer** may also justify therapeutic-dose anticoagulation.

Surgery has no role as an emergency treatment (except in rare cases where anticoagulation is contraindicated).

For other patients, the question of extending anticoagulant therapy arises.

There are **risk factors for thromboembolic events within 3 months**.

These factors should be known:

- Hospitalized patients
- Male sex
- History of cancer or active cancer
- Involvement of the saphenofemoral or saphenopopliteal junction
- Prior history of DVT or PE
- Severe chronic venous insufficiency
- Extensive superficial venous thrombosis under treatment
- Prior SVT
- Thrombus length

A carefully selected population of patients presenting with several of these risk factors may benefit from **extending fondaparinux 2.5 mg once-daily therapy to 3 months**.

A **rigorous diagnostic and therapeutic approach** is therefore essential to ensure that each patient receives the treatment that most appropriately optimizes the **benefit–risk balance** of anticoagulant therapy.

Keywords: Superficial venous thrombosis, Fondaparinux, CALISTO, Doses of anticoagulant therapy, Duration of anticoagulant therapy.

Introduction

Superficial venous thrombosis (SVT) remains a challenging topic because few studies have been conducted, and those available are often of limited quality, including retrospective designs and small patient samples. This explains why relatively few recommendations exist regarding the management of SVT.

Nevertheless, SVT is a common condition. The annual prevalence of SVT is 0.64 per 1,000 individuals.

Superficial venous thrombosis has long been mistakenly considered a benign disease. However, 25% of SVT cases are associated with deep vein thrombosis (DVT) at the time of SVT diagnosis.

Fifty percent of SVT recurrences are in fact DVT[1]. The risk of developing DVT or pulmonary embolism (PE) remains 3- to 6-fold higher at 5 years in patients with isolated SVT. This excess risk of DVT and PE persists for up to three decades following an isolated SVT[2].

Finally, SVT may also, although in a small number of cases, lead to the diagnosis of an underlying malignancy.

For all these reasons, SVT must be managed as appropriately as possible, particularly from a therapeutic perspective.

The aim of this work is to develop a therapeutic algorithm adapted to each clinical situation, consistent with the current results of the most rigorous studies on the subject.

The most rigorous study is the CALISTO trial[3], a large prospective study with high statistical power and no significant methodological bias. Since this study, the treatment of SVT longer than 5 cm and located more than 3 cm from the saphenofemoral junction has been based on fondaparinux 2.5 mg administered once daily for 45 days.

However, we will see that, despite its high quality, this study cannot be applied to all clinical situations.

Some cases of superficial venous thrombosis require therapeutic-dose anticoagulation. In other situations, the question of extending the duration of anticoagulant therapy legitimately arises.

The purpose of this article is to propose, for each clinical scenario, the most reasonable therapeutic approach based on the current literature.

Initial Treatment of superficial venous thrombosis

The clinical diagnosis of SVT is most often straightforward: pain, redness, and induration along the course of a superficial vein (Fig.1).

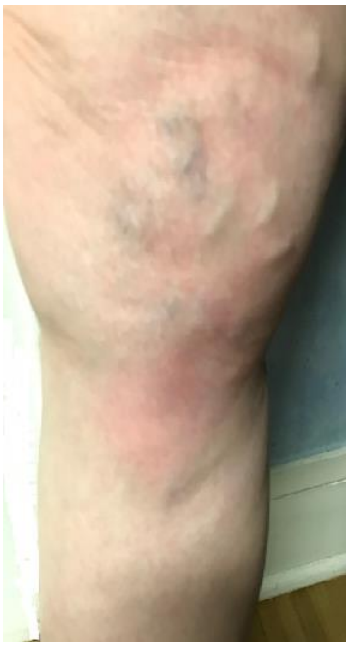

Fig 1: Svt of the great saphenous vein

However, clinical diagnosis alone is insufficient, as it cannot determine three essential points[4]:

- The length of the thrombus is not always correlated with the length of erythema.

- The distance between the upper end of the thrombus and the saphenofemoral or saphenopopliteal junction is often clinically underestimated, with the thrombus frequently extending beyond the area of visible redness (Fig.2).

The presence of associated deep vein thrombosis. An associated deep vein thrombosis is found in 25–30% of patients with SVT (OPTIMEV[5], POST[6], and STEPH[7] studies). These associated DVTs may be located in the ipsilateral or contralateral limb, making bilateral lower-limb exploration absolutely mandatory. A venous Doppler ultrasound of the lower limbs is therefore essential.

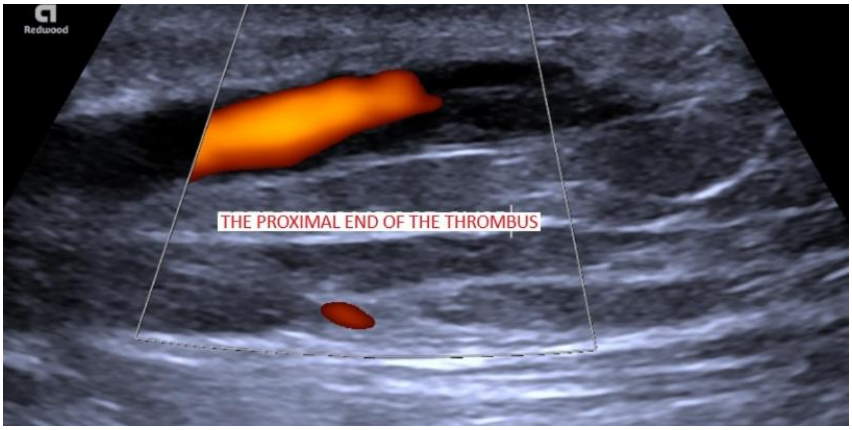

Fig 2: The proximal end of the thrombus

Given the frequency of associated DVT, the general practitioner should initiate full-dose anticoagulation while awaiting Doppler ultrasound results, in the absence of contraindications.

Which superficial venous thromboses do Not Require Anticoagulant Therapy?

Some SVTs are considered benign and do not require anticoagulant treatment.

A thrombus length < 5 cm was arbitrarily chosen in the STENOX study (2003) to define benign SVTs[8]. Only patients with SVT longer than 5 cm were included. Subsequent studies (POST[6], CALISTO[3], SURPRISE[9]) adopted the same 5 cm threshold, except for STEFLUX (10), which included SVTs ≥ 4 cm. Only OPTIMEV (5) included all SVT patients regardless of thrombus length.

Interestingly, the rate of DVT and PE at 3 months was lower in OPTIMEV than in other studies. In OPTIMEV, 6 patients (1.2%) out of 499 developed thromboembolic events over 3 months: 3 DVTs and 3 pulmonary embolisms (PE). Higher rates were observed in other studies: 2.8% DVT and 0.5% PE in POST[6] at 3 months, and 4.6% DVT/PE in a post hoc analysis of STENOX[11].

Although comparison between studies is difficult due to differences in anticoagulant dosing and duration, a trend toward increased thromboembolic complications in SVTs longer than 5 cm appears clearly.

Therefore, an SVT shorter than 5 cm does not require anticoagulant therapy except in four situations[12]:

- Thrombosis close to a saphenous junction (saphenofemoral or saphenopopliteal)
- Thrombosis close to a perforating vein
- Multisegmental or bilateral superficial thrombosis
- Thrombosis in a patient with cancer

Patients with SVT longer than 5 cm should receive anticoagulant therapy after exclusion of contraindications and assessment of bleeding risk.

Contraindications to Anticoagulant Therapy and Bleeding Risk

The issue of contraindications mainly concerns patients requiring full-dose anticoagulation.

There is no validated bleeding risk score specific to SVT. Four factors are consistently found in bleeding risk scores: age, anemia or bleeding, renal failure, and cancer. Vascular physicians commonly use the RIETE score, validated in venous thromboembolism (VTE). In the absence of a specific score, it may be applied to SVT despite its limitations.

Chengelis showed that untreated great saphenous vein thrombosis extends into the common femoral vein between day 2 and day 10 in 11% of cases. Since mortality from proximal venous thrombosis is approximately 5%, the risk of death from untreated great saphenous vein thrombosis is estimated at 0.55%[13].

Under full-dose anticoagulation (warfarin), the risk of major bleeding is 4.9% with a RIETE score of 4.5, and mortality from major bleeding is 11.3%. The mortality risk is the same (0.55%). If the RIETE score exceeds 4.5, bleeding risk outweighs the risk of death from untreated great saphenous vein thrombosis.

Patients with venous thromboembolism fortunately have fewer comorbidities than patients with atrial fibrillation, and a marked increase in the RIETE score is rare.

Contraindications to prophylactic anticoagulation include active bleeding, severe thrombocytopenia, and hemorrhagic coagulation disorders.

In such cases, treatment with compression therapy and ambulation will be initiated, together with monitoring by Doppler ultrasound.

In the event of thrombus extension, a surgical procedure (ligation of the saphenofemoral junction or stripping of the great saphenous vein) will be considered. However, we will see that this emergency surgical intervention is not without drawbacks.

Treatment of Isolated superficial venous thrombosis > 5 cm Located More Than 3 cm from the Saphenofemoral or Saphenopopliteal Junction

This is the most commonly encountered situation.

The 3 cm threshold has an anatomical basis. A thrombus extending more than 3 cm from the saphenofemoral junction must cross the preterminal and terminal valves of the great saphenous vein to extend into the common femoral vein. A thrombus extending to within 3 cm of the saphenofemoral junction has already crossed the preterminal valve and only needs to cross the terminal valve to extend into the deep venous system[14].

Treatment of this type of SVT is based on the results of the CALISTO study (3), a remarkable prospective, randomized, high-power trial. In this study, 3002 patients were randomized into two groups: One group received fondaparinux at a daily dose of 2.5 mg, while the other group received a placebo.

However, several points should be noted. A proportion of patients treated for SVT develop thromboembolic complications at 3 months, including SVT recurrence, SVT extension, and recurrence in the form of DVT or pulmonary embolism.

Risk factors for the development of these thromboembolic complications within 3 months should be identified[15]:

- Hospitalized patients
- Male sex
- History of cancer or active cancer
- Involvement of the saphenofemoral or saphenopopliteal junction
- Previous history of DVT or PE
- Severe chronic venous insufficiency
- Extensive superficial venous thrombosis progressing despite treatment (whether or not the extension reaches the saphenofemoral junction)

These factors therefore predispose patients to recurrence in the form of deep vein thrombosis or pulmonary embolism within 3 months after the diagnosis and treatment of superficial vein thrombosis.

In the CALISTO study[3], as one out of two patients received placebo, it was not ethical to include patients at high thromboembolic risk. Patients with a recent history (within 6 months) of DVT or PE, those treated for cancer within the previous 6 months, and those with a thrombus extending to within less than 3 cm of the saphenofemoral or saphenopopliteal junction were excluded.

Similarly, patients at high bleeding risk (severe renal failure, liver failure) were excluded from the study. Treating a patient at high bleeding risk with placebo would have exposed them to the risk of thrombus extension to the saphenofemoral junction under placebo, thereby necessitating the initiation of full-dose anticoagulant therapy.

This study confirms that SVT is not a benign disease, as 5.9% of events (death from any cause, symptomatic recurrence of SVT, symptomatic extension to the saphenofemoral junction, symptomatic DVT or symptomatic pulmonary embolism) occurred by day 47 in the placebo group.

Fondaparinux was effective in this selected patient population, with an 85% reduction in events observed in the fondaparinux 2.5 mg group compared with the placebo group, including an 85% reduction in the combined endpoint of DVT and PE.

What sets this study apart is that treatment was continued for 45 days, while in previous studies anticoagulant therapy was limited to a maximum of one month. Importantly, the beneficial effect of fondaparinux persisted after discontinuation of anticoagulant therapy, as at day 77 (i.e., 32 days after treatment cessation) there was an 81% reduction in thromboembolic events in the fondaparinux group compared with the placebo group.

There is no rebound effect, whereas such a rebound effect has been observed in studies in which the treatment duration was shorter.

The treatment of the vast majority of SVTs (i.e., SVTs longer than 5 cm extending more than 3 cm from the saphenofemoral junction) is therefore now well established, at least in a selected population

of patients without a history of cancer, DVT, or PE: fondaparinux 2.5 mg, one injection daily for 45 days.

Some SVTs require an increased anticoagulant dose, and the question of extending the duration of treatment arises for others.

Superficial venous thromboses Requiring Full-Dose Anticoagulant Therapy

Five indications for full-dose anticoagulant therapy may be considered in SVT[15]:

- Deep vein thrombosis associated with Superficial venous thrombosis
- Extension of the thrombus to within less than 3 cm of the saphenofemoral or saphenopopliteal junction
- Extension of the thrombus into a perforating vein
- Superficial venous thrombosis longer than 5 cm in a patient with cancer
- Extensive superficial venous thrombosis progressing despite prophylactic-dose anticoagulant therapy

Management of Superficial Venous Thrombosis Presenting Initially With Deep Vein Thrombosis

We have seen that 25% of SVTs are associated with DVT at the time of diagnosis. Full-dose anticoagulant therapy is required in cases of DVT for a duration of 3 months.

If the DVT is located at a distance from the SVT (particularly if it is located in the contralateral lower limb), the presence of an underlying hypercoagulable state should be considered and malignancy should be investigated. The diagnosis of cancer would have a significant impact on the duration of anticoagulant therapy.

Management of Thrombosis of the Saphenofemoral or Saphenopopliteal Junction

Thromboses involving the saphenofemoral or saphenopopliteal junctions should be regarded as proximal venous thromboses occurring in the setting of a major provoking factor (typically severe chronic venous insufficiency).

As with proximal vein thromboses, there is a risk of thrombus extension to the external iliac vein, with a consequent risk of pulmonary embolism.

JP Galanaud observed, albeit in small patient cohorts, that patients with thrombosis of the saphenofemoral or saphenopopliteal junction always experience recurrence in the form of proximal DVT or PE[1].

The recurrence rate is similar at 3 years whether non-cancer patients present with saphenofemoral junction thrombosis (5,2% per patient-year) or proximal venous thrombosis (6,5% per patient-year).

For all these reasons, full-dose anticoagulant therapy should be initiated for a duration of 3 months.

Surgical treatment of the thrombosed great saphenous vein should be performed at the end of the 3 months to prevent recurrence.

Emergency surgical treatment of saphenofemoral junction thrombosis is not recommended because it is associated with complications[16]:

- Emergency stripping of the great saphenous vein is associated with a 10% rate of thromboembolic complications[13].
- Simple crossectomy of the great saphenous vein is associated with a 7% rate of thromboembolic complications[13].

A review of five prospective and retrospective studies and one randomized trial[17] showed that emergency surgical treatment of the great saphenous vein is associated with a 2% rate of PE and a 3.4% rate of DVT. These figures are significantly higher than those observed in patients treated with anticoagulants.

In the STEFLUX study, only one patient in group B (parnaparin 8,500 IU/day for 10 days followed by 6,400 IU/day for 20 days) out of 223 developed DVT, and no patient developed PE.

Although these results were obtained after only 1 month of anticoagulant therapy, it is well known that the majority of thromboembolic complications occur within the first month following the onset of DVT.

Extension of the Thrombus Into a Perforating Vein

There are no specific studies addressing this complication, but by analogy with thrombus extension to within less than 3 cm of the saphenofemoral junction, full-dose anticoagulant therapy is advisable. A thrombus that is no longer separated from the deep venous system except by a valve, or that has crossed this valve, can easily extend into the deep venous trunks.

Superficial venous thrombosis and Cancer

Studies show that SVT, like DVT, is a marker of aggressive cancer. Patients with superficial vein

thrombosis and cancer recur as deep vein thrombosis or pulmonary embolism, in proportions similar to those observed in patients with deep vein thrombosis and cancer.

Therefore, a patient presenting with SVT and cancer should receive anticoagulant therapy.

There are no specific studies defining the optimal dosage in these situations; a pragmatic approach may be proposed pending further evidence[15].

In cases of so-called "benign" SVT extending less than 5 cm, prophylactic-dose anticoagulant therapy may be proposed. Full-dose anticoagulant therapy may be prescribed if SVT extends over a length greater than 5 cm.

A rigorous study will be necessary to support this approach, which currently can only be considered as a suggestion.

The Issue of superficial venous thrombosis Extension

Extension of a thrombus in a patient with an initially benign, non-anticoagulated SVT requires the initiation of prophylactic-dose anticoagulant therapy.

Such extensions necessitate close surveillance.

In the CALISTO study (7), 54 out of 1,500 patients treated with placebo developed extension of great saphenous vein (GSV) thrombosis to within less than 3 cm of the saphenofemoral junction (SFJ). Given the severity of this complication, these patients were excluded from the study. Forty-eight patients received either full-dose anticoagulant therapy or ligation of the saphenofemoral junction. Despite these treatments, 5 patients developed DVT or PE.

Fifty-six placebo-treated patients developed thrombus extension to more than 3 cm from the saphenofemoral junction. These patients were treated with full-dose anticoagulation and saphenofemoral junction ligation in proportions similar to those who developed extension to within less than 3 cm of the SFJ. Despite these treatments, 5 patients developed DVT or PE, representing the same proportion in both groups[7].

Therefore, thrombus extension in non-anticoagulated patients must be monitored very carefully, and follow-up duplex ultrasound should be scheduled if a decision is made not to initiate anticoagulant therapy.

In the event of thrombus extension, the minimum intervention is to initiate prophylactic-dose anticoagulant therapy under duplex ultrasound surveillance.

In the CALISTO study, despite selecting a population at low risk of thromboembolic events at 3 months, thrombus extension occurred in 54 + 56 = 110 out of 1,500 placebo-treated patients (7.3%).

In cases of SVT extension despite prophylactic-dose anticoagulant therapy, escalation to full-dose anticoagulation is required.

In patients already receiving anticoagulant therapy, the occurrence of venous thrombosis extension requires an etiological assessment (This represents the classic migratory thrombophlebitis).

Extension of venous thrombosis under prophylactic-dose anticoagulation is a warning sign that mandates verification that cancer screening recommendations for the general population are being correctly applied (biennial mammography in women over 50 years of age, PSA testing in men, fecal occult blood testing). Depending on the findings from the medical history and clinical examination, further etiological investigations may be required.

Full-dose anticoagulant therapy should be continued for a duration of 3 months.

Superficial venous thromboses Requiring Prolongation of Anticoagulant Therapy

The issue of thromboembolic recurrence at 3 months. As previously discussed, all studies report a percentage of recurrences in the form of DVT or PE after discontinuation of anticoagulant therapy. Rates range from 1.2% in OPTIMEV (5) to 4.6% in STENOX (11) at 3 months.

Risk factors for thromboembolic complications at 3 months have been identified. These factors should be known and deserve to be reiterated:

- Hospitalized patients
- Male sex
- History of cancer or active cancer
- Involvement of the saphenofemoral or saphenopopliteal junction
- Prior history of DVT or PE
- Severe chronic venous insufficiency
- Extensive superficial venous thrombosis under treatment

More recently, the INSIGHT study[18] identified additional risk factors for thromboembolic events at 3 months: prior SVT and thrombus length.

To reduce the risk of thromboembolic complications at 3 months, strategies involving either increased anticoagulant dosing or prolongation of anticoagulant therapy have been evaluated.

There is very limited evidence in the literature supporting dose escalation:

The STENOX study[8] compared enoxaparin 40 mg versus enoxaparin 1.5 mg/kg/day administered for 8–12 days. No significant difference was observed at day 12 or day 97 between the two groups regarding DVT, PE, SVT extension, or SVT recurrence.

The VESALIO study[19] compared prophylactic-dose nadroparin for 1 month versus therapeutic-dose weight-adjusted nadroparin for 10 days followed by half-dose treatment for 20 days. More extensions of superficial vein thrombosis occurred during treatment in the prophylactic anticoagulation group, although the difference was not statistically significant.

Deep vein thromboses occurred after discontinuation of anticoagulation: 2 DVTs in the prophylactic group and 3 DVTs in the higher-dose group, with no significant difference.

Only the STEFLUX study[10] demonstrated a significant difference at day 33 between parnaparin 4,250 IU/day for 30 days and parnaparin 8,500 IU/day for 10 days followed by 6,400 IU/day for 20 days.

However, three important remarks must be made regarding STEFLUX:

- A significant difference was observed only when SVT extensions and recurrences were included; no significant difference was found for the isolated endpoint of DVT and PE.
- Although a significant difference was observed for overall thromboembolic events at day 33, this difference was no longer significant at day 93.
- Patients with a prior history of DVT were not excluded from STEFLUX.

It should be noted that in these studies, anticoagulant therapy was administered for only 1 month, and many thromboembolic recurrences occurred after treatment discontinuation.

In the SURPRISE study (9), which included patients at high thromboembolic risk, treatment was extended to 45 days, yet many recurrences still occurred after anticoagulant discontinuation, whether with fondaparinux or rivaroxaban.

High rates of thromboembolic recurrence after discontinuation of anticoagulant therapy are consistently observed in studies including patients with risk factors for thromboembolic events at 3 months (STENOX, STEFLUX, SURPRISE).

There are therefore arguments in favor of extending fondaparinux 2.5 mg once-daily therapy to 3 months in a highly selected population of patients with multiple risk factors for thromboembolic events at 3 months, such as men with a history of DVT or SVT, or women with a history of cancer and a long thrombus in a superficial vein complicating severe chronic venous insufficiency for example.

In the non-randomized study by Nikolopoulos (20), no thromboembolic events were observed at day 120 in the group treated with tinzaparin 131 IU/kg (75% of the therapeutic dose) for 3 months. A 1 year, recurrent thromboembolic events occured less frequently in the group treated with Tinzaparin 131 UI/kg for 3 months (4,1% of patients) compared with 18,4% of events in the group receiving variable-dose tinzaparin for up to 60 days.

Only randomized studies will be able to confirm these findings, which currently cannot form the basis for formal recommendations. At a minimum, if anticoagulant therapy is discontinued after 45 days, compression therapy and duplex ultrasound surveillance should be instituted after treatment cessation in this small subset of patients at risk of thromboembolic events at 3 months.

Role of Direct Oral Anticoagulants (DOACs) in the Treatment of superficial venous thrombosis

If a study demonstrates that DOACs are non-inferior to fondaparinux in the treatment of SVT, they would likely be preferred because of their simpler administration (no injections) and lower cost (eliminating the need for a nurse visit).

Only one non-inferiority study has been published: the SURPRISE study[9]. Unlike CALISTO, SURPRISE included patients at high thromboembolic risk : SVT longer than 5 cm above the knee in patients with at least one risk factor for thromboembolic

events, including age over 65 years, male sex, prior VTE, active or prior cancer, or autoimmune disease (Behçet's disease).

The SURPRISE study concluded that rivaroxaban 10 mg was non-inferior to fondaparinux 2.5 mg.

However, some figures reported by the authors raise concerns: the hazard ratio in the rivaroxaban group was 1.9. If 10 patients experienced a thromboembolic event in the fondaparinux group (DVT, PE, SVT extension or SVT recurrence), 19 patients would experience a thromboembolic event in the fondaparinux group, representing a 90% increase. The upper limit of the confidence interval for the relative risk was 6.4.

This study is therefore not fully convincing and leaves doubt regarding the non-inferiority of DOACs versus fondaparinux in the treatment of SVT.

Even if DOACs were shown to be non-inferior to fondaparinux in terms of efficacy, they would still need to demonstrate that this non-inferiority is not associated with an increased bleeding risk.

It is noteworthy that in the SURPRISE study, at the end of the 45-day treatment period, there were six times more non-major bleeding events in the rivaroxaban 10 mg group than in the fondaparinux 2.5 mg group at day 45 (6 vs. 1). The SURPRISE study did not show a statistically significant difference in bleeding risk; however, this was a low-power study including only 435 patients. In a higher-powered study, statistically significant differences might emerge to the detriment of rivaroxaban, with a higher rate of bleeding complications.

The study by Kearon, conducted after the SURPRISE study, starts from first principles by aiming to demonstrate that rivaroxaban 10 mg administered for 45 days is superior to placebo (21). Unfortunately, this study had to be prematurely terminated due to recruitment difficulties, with only 85 patients enrolled out of the 600 initially planned. The results favored DOACs, although differences were not statistically significant because of the small sample size.

In cases where deep vein thrombosis is present at the time of SVT diagnosis, full-dose anticoagulant therapy is required. DOACs have been shown to be non-inferior to vitamin K antagonists and to be associated with fewer bleeding events, and should therefore be preferred. DOACs may also be prescribed at full dose in patients with thrombosis of the saphenofemoral or saphenopopliteal junction.

Management of Idiopathic superficial venous thrombosis

Idiopathic SVT is defined as SVT occurring in the absence of any identifiable cause or provoking factor.

The vast majority of SVTs occur in varicose veins. The more dilated a vein is, the greater the venous stasis. A smaller proportion of SVTs occur in non-dilated veins. The concept of "SVT in a normal vein" is a clinical one.

Regardless of whether reflux is present on duplex ultrasound, idiopathic thrombosis occurs in small-caliber veins, with or without reflux. These veins are classified as C0 or C1 in the CEAP classification. In such small-caliber veins, venous stasis is minimal or absent in the absence of reflux.

The occurrence of superficial venous thrombosis in this context is therefore surprising. According to Virchow's triad, in the absence of stasis and endothelial injury, hypercoagulability should be suspected.

In the vast majority of cases, this hypercoagulability is related either to cancer or to an underlying thrombophilia.

Cancer screening is desirable in patients presenting with idiopathic SVT, as the detection of malignancy would significantly alter therapeutic management.

Many patients with SVT carry a thrombophilic disorder. However, systematic thrombophilia testing is not recommended in SVT because its detection would not modify management, with two exceptions: antithrombin deficiency and antiphospholipid syndrome[16].

These two thrombophilias are rare, and the diagnostic yield of systematic thrombophilia screening would therefore be very low. Testing for antithrombin deficiency should be considered in cases of failure of anticoagulant therapy. Antiphospholipid syndrome should be suspected in cases of skin necrosis or a history of recurrent spontaneous miscarriages.

In the absence of an identified etiology, there is no evidence in the literature to justify increasing the dose or duration of anticoagulant therapy in patients with idiopathic superficial vein thrombosis.

The frequency and type of recurrences observed in idiopathic SVT do not differ from those seen in other forms of SVT[1]. Treatment therefore relies on standard therapy with fondaparinux 2.5 mg, administered once daily for 45 days.

In which patients treated for superficial vein thrombosis should follow-up Doppler ultrasound be performed ?

The purpose of systematic duplex ultrasound follow-up is to detect asymptomatic SVT extension. Such events are uncommon.

In the POST study (6), systematic duplex ultrasound performed at day 10 detected asymptomatic events in only 2.1% of patients. In STEFLUX, asymptomatic events occurred in 3.3% of patients in group C treated with prophylactic-dose anticoagulation.

A follow-up duplex ultrasound at day 10 may be proposed in the following situations[15]:

- Patients treated for SVT who have cancer. It is known that there is a risk of DVT extension in cancer patients even when treated at full dose. There is no reason to believe that this risk does not also apply to SVT, particularly when prophylactic-dose anticoagulation has been initiated.
- Patients with a prior history of DVT. The STEFLUX study (10), which included patients with a history of DVT, showed a significant difference at day 33 between parnaparin 4,250 IU/day for 30 days and parnaparin 8,500 IU/day for 10 days followed by 6,400 IU/day for 20 days. Caution is therefore warranted in patients with a history of DVT treated at prophylactic dose.
- Thrombosis close to the saphenofemoral or saphenopopliteal junction. When the pre-terminal valve of the great saphenous vein is crossed despite prophylactic anticoagulation, anticoagulant therapy at a therapeutic dose is indicated.
- A superficial vein thrombosis close to a perforating vein also requires monitoring, as thrombus extension into the perforating vein would alter the therapeutic approach.

Follow-up duplex ultrasound after discontinuation of anticoagulant therapy is advisable in patients with risk factors for thromboembolic events at 3 months[15]. In the absence of these risk factors, routine systematic duplex ultrasound follow-up is more debatable. It should be noted that in the CALISTO study, which is the reference trial for patients not at high risk of thromboembolic recurrence, no follow-up duplex ultrasound was performed.

Superficial venous thrombosis and Pregnancy

As in the general population, prophylactic-dose anticoagulant therapy should be prescribed for 45 days for SVTs longer than 5 cm extending more than 3 cm from the saphenofemoral junction.

Fondaparinux is contraindicated during pregnancy.

Anticoagulant therapy should be prolonged in cases of[12]:

- Bilateral SVT
- Highly symptomatic SVT
- SVT close to the deep venous system

These SVTs frequently occur late in pregnancy. The increased thromboembolic risk in the postpartum period must be taken into account[12]. In the absence of contraindications, anticoagulant therapy should be continued for 6 weeks after delivery.

Superficial venous thrombosis and Renal Impairment

Prophylactic-dose anticoagulation:

- Fondaparinux 2.5 mg should **not** be prescribed if the glomerular filtration rate (GFR) is below 50 mL/min.
- According to the Vidal (France), the dose of fondaparinux should be reduced to 1.5 mg/day if GFR is between 20 and 50 mL/min.
- If fondaparinux 1.5 mg is unavailable and the GFR is between 20 and 50 mL/min, tinzaparin 0.45 mL at a prophylactic dose (4500 IU anti-Xa) should be prescribed under anti-Xa activity monitoring.

Therapeutic-dose anticoagulation:

- Tinzaparin is contraindicated if GFR < 20 mL/min.
- If GFR is between 15 and 30 mL/min, enoxaparin can be administered once daily at 1 mg/kg for therapeutic anticoagulation.
- If GFR is below 20 mL/min and therapeutic anticoagulation is required, vitamin K antagonists (VKAs) can be used under strict INR monitoring.

Conclusion:

The CALISTO study helped define the treatment of the vast majority of patients presenting with SVT

longer than 5 cm and located more than 3 cm from the saphenofemoral junction or the saphenopopliteal junction.

However, due to its design (50% of patients receiving placebo), this study included patients at low risk of thromboembolic events at 3 months and at low risk of bleeding.

A review of the most reliable studies in the literature suggests that some patients require therapeutic-dose anticoagulation, particularly in cases of concomitant DVT at the time of SVT diagnosis, thrombus extension to the saphenofemoral junction or to a perforating vein, or extensive SVT occurring despite prophylactic-dose anticoagulation.

SVT longer than 5 cm in patients with cancer may also require therapeutic-dose anticoagulation. No studies have specifically addressed this issue. A rigorous study will be necessary to support this approach, which currently can only be considered as a suggestion.

Several risk factors for thromboembolic events at 3 months have been identified. A carefully selected population of patients presenting with multiple such risk factors may benefit from extending fondaparinux 2.5 mg therapy to 3 months.

The CALISTO study successfully extended treatment duration from 1 month to 45 days in patients at moderate risk of thromboembolic events at 3 months.

The present proposal consists of extending fondaparinux 2.5 mg treatment to 3 months in a population at higher risk of thromboembolic recurrence.

There are many arguments supporting the relevance of this proposal; however, a large, randomized prospective study is necessary to fully validate this approach.

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None.

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