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"Non-standard" superficial venous thrombosis management. Should we consider a tailored approach? A critical review and discussion

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Abstract

Thrombophlebitis is an inflammatory process of the superficial veins with coexistent venous thrombosis, usually occurring in patients with specific preconditions (trauma, surgery or inactivity, signs of venous insufficiency, malignancies). The concept of thrombophlebitis has evolved over time and also the definition has changed from "Thrombophlebitis" to "Superficial venous thrombosis" (SVT). SVT course is usually benign if an appropriate and prompt treatment is undertaken. Pharmacological treatment includes anticoagulation with low molecular weight heparin (LWMH), fondaparinux and, more recently, rivaroxaban. In selected cases the course of thrombophlebitis is not self-limited and the management definitely appears challenging for clinicians and not homogeneous among different Centres. SVT complications include deep venous thrombosis (DVT) and Pulmonary Embolism (PE)

and thrombosis recurrence. In this review we define "*non standard"* SVT those cases presenting with one or more of the following features: SVT involving healthy veins; recurrent, migrant or significantly extended SVT; SVT involving deep vein confluence; SVT not associated to recognized risk factors, especially if occurring in young subjects). In such "*non standard*" cases, SVT may also represent the epiphenomenon of a more complex systemic condition. Therefore investigation may require more attention and resources. This series of clinical cases focuses on uncertainties in the management of "*non standard*" SVT, from diagnosis to treatment, and it underlines on the one side the need of a multidisciplinary approach to investigation and care and on the other side the opportunity of a systematic data collection and analysis to provide more reliable recommendations in this setting.

Key words

angiopathies, management of disease, tailored medicine, venous thrombosis,

Definition

Thrombophlebitis, more modernly called superficial venous thrombosis (SVT), is an inflammatory process of the superficial veins with coexistent venous thrombosis [1-2] occurring usually but not exclusively in the lower limbs. Varicose veins represent the main risk factor for lower-limb SVT (80–90%) [3]. Moreover, patients may have a history of antecedent trauma, surgery or inactivity, intravenous cannulation or infusion of irritants [2]. A number of local and systemic risk factors is recognized for SVT, both non modifiable and acquired (largely modifiable), some of these with a still controversial role. A list of recognized risk factor for SVT development is included in Table 1**.** The discussion of these latter is outside the scope of this review.

Despite currently underestimated, the prevalence of SVT is higher than deep venous thrombosis (DVT) and Pulmonary Embolism (PE), ranging from 3% to 11 % [4-6].

If appropriate treatment is promptly undertaken SVT prognosis is generally more favorable than in DVT [7].

In some cases, this relatively common process is less benign and self-limited than previously supposed. Superficial venous thrombosis can be associated with DVT in 6 to 40% of patients at diagnosis [8-11] and can also be linked to more serious complications, such as asymptomatic PE, in 20 to 33% of cases, and symptomatic PE, in 2 to 13% of cases [12-14]. In the POST (Prospective Observational Superficial Thrombophlebitis) Study cases of DVT confirmed by Ultra Sound Doppler (USD) and symptomatic PE were reported in 24.9% and 3.9 % of all 844 patients with SVT respectively [15]. A meta-analysis by Di Minno et al. reported a weighted mean prevalence of 18.2% for DVT, and 8.2% for PE among patients with SVT [16].

A residual risk for recurrence is not negligible. In particular individuals with previous SVT seem to have an increased risk of venous thrombosis successively, compared with individuals without previous SVT (a 5.5-fold increased risk in a large case-control study with over 10 000 participants). A similar recurrence rate has been reported in patients with isolated SVT in comparison with patients with proximal DVT (5.4% vs 6.5% per patient/year) actually, the former recurring more often as SVT than as DVT [7]. The risk of recurrence was further increased in individuals with an acquired mild thrombotic risk factor (smoking or overweight) in addition to previous SVT, with different impact on risk of SVT recurrence according to the type of risk factor (31.4-fold increased risk in patients with a strong thrombotic risk factor ie. surgery, hospitalization, plaster cast immobilization, or malignancy and 34.9-fold increased risk in women with a reproductive risk factor among hormonal therapy, pregnancy and puerperium) [17].

In contrast with DVT, reliable scores allowing the identification of SVT cases at high risk of DVT and recurrence are lacking; the promising ICARO SCORE, a clinical score predicting

the risk of DVT in patients with SVT, was not so successful [18]. Nevertheless, specific features are commonly used to identify an episode of SVT considered as "high risk" of VTE: proximal SVT, involvement of non-varicose vein, the presence of autoimmune disease, age > 65 years old, previous VTE, diagnosis of cancer [19]. Concerning recurrence, in the POST study, risk factors for recurrence were identified as SVT involving an apparently healthy vein, cancer, male sex and previous DVT [19]. Recurrence rate as DVT and as SVT is similar [7]. In those we define "*non standard"* SVT (SVT involving healthy veins; recurrent, migrant or significantly extended SVT; SVT involving deep vein confluence; SVT not associated to recognized risk factors, especially if occurring in young subjects) SVT may represent the epiphenomenon of a more complex, often systemic, condition.

Background of current treatments and perspectives

In general, anticoagulant treatment of SVT appears to be the most appropriate choice as up to a quarter of untreated cases was associated with extension to deep venous system or recurrence, while this did not occur in anticoagulated patients [20-21].

In case of SVT ≥3 cm away from the deep venous system and ≥5 cm in length a 45-day regimen of anticoagulation is recommended (Class I B). Guidelines recommend treatment of SVT with fondaparinux at the dose of 2.5 mg (Class I B) or with low-molecular-weight heparins (LMWH) at intermediate doses (Class IIa B) [22].

An overview of the main randomized trials exploring anticoagulant treatment of SVT is included in Table 2.

STEFLUX trial compared parnaparin 8500 IU OD for 10 days followed by placebo for 20 days (group A) with parnaparin 8500 IU OD for 10 days followed by 6400 IU OD for 20 days (group B) and parnaparin 4250 IU OD for 30 days (group C) in the treatment of SVT ≥ 4 cm in length. In this study intermediate dose of parnaparin for 30 days

was more efficacious than a 30-day prophylactic dose or a 10-day intermediate dose for reduction of DVT, PE and SVT recurrence after lower limb SVT [23].

In the CALISTO multicenter, double blind, placebo-controlled trial Fondaparinux 2.5 mg once daily given for 45 days subcutaneously in approximately 3000 patients was effective and safe as compared to placebo in acute SVT of the legs (symptoms onset less than 3 weeks before randomization). In this study the risk of DVT and PE was significantly reduced in fondaparinux arm vs placebo (p: 0.001 and p: 0.02 by day 77 respectively), as well as other efficacy outcomes [24].

In comparison with the setting of patients with DVT / EP less robust data support direct oral anticoagulants (DOACs) for SVT treatment. In the prospective, randomized SURPRISE trial rivaroxaban 10 mg OD for 45 days was safe and non-inferior as compared to fondaparinux in preventing thromboembolism in the setting of high- risk SVT [25]. In real world clinical practice due to a lack of power of the non-inferiority study SURPRISE, rivaroxaban is still not considered in guidelines [22] and for approval by Regulatory Agencies.

Studies testing the possible application of direct oral anticoagulant agents for SVT treatment are still not available at the moment.

However, with a view to hypothetical or off-label (at the moment) use of DOACs in this setting, selection of patients remains challenging, requiring a "*case by case*" discussion and the patient's personal involvement.

In our opinion these agents have to be considered for very selected cases actually; in particularly extended proximal SVT (meaning SVT significantly >5 cm), especially those located along the thigh) or SVT located very close to the junctions with deep veins (<3 cm) direct oral anticoagulants may represent a more convenient choice than parenteral anticoagulation for a full-dose 3 months-course DVT-like treatment, as already suggested by Potere and Ageno for distal DVT treatment (26).

Obviously DOACs could be also an option for patients with SVT who deliberately refuse the parenteral administration of drugs and when reduced compliance to parenteral administration may severely compromise the results of treatment.

Role of NSAIDs alone is still not adequately studied [21]. In any case NSAIDs are not taken into consideration by the guidelines to date.

No study to date is available showing increased rate of thrombosis recanalization with increased dose of anticoagulation. Nevertheless, it has been postulated that risk stratification systems could be useful at baseline as patients at high risk of SVT complications may benefit from a more aggressive treatment; on the opposite low risk patients with SVT may not need anticoagulation at all (asymptomatic, less than 5 cm length) [27], thus improving the cost-effectiveness ratio of therapy in this setting actually.

Despite no strong data support long-lasting anticoagulant treatment, in a recently published metanalysis on 24 studies prolonged anticoagulant courses was associated with reduction of DVT risk in patients with lower extremities isolated SVT; on the opposite the highest rates of DVT and PE was associated with particularly short term (≤14 days) treatment courses [28].

The decision about a long- term anticoagulant course requires a case-by-case evaluation, taking into account all risk factors for SVT complications and frequency of SVT relapses.

In our view DOACs prophylaxis dose (ex Rivaroxaban 10 mg OD, SURPRISE trial like) could be an option not only in the acute treatment (45 days) but also in the following long-lasting prophylaxis in case of SVT at high risk of recurrence, for instance those associated with persistent risk factors as malignancies and autoimmune diseases (not associated with high risk of bleeding).

In case of recurrent SVT (n ≥3) the possibility of a prolonged treatment requires discussion with the patient, particularly with regard to patient's own bleeding risk and personal preferences [27].

Investigation

Limited consensus exists about the need and modality of investigation of SVT actually, thus making further studies on this topic advisable in our opinion, as available data are not only scarce but also only retrospective.

We defined "*non standard SVT*" cases of SVT presenting with one or more of the following features: not adequately explained SVT, not involving varicose vein, recurrent, migrant or particularly extended proximal SVT, SVT with deep vein confluence involvement, etc.

In "non standard SVT", thrombophlebitis may conceal several clinical settings absolutely deserving of specific attention because of high risk of complications or in case of SVT concealing more complex, systemic conditions.

Informations about the association between oncologic diseases and SVT is relatively scarce compared to DVT (in some studies in SVT patients cancer was an exclusion criterion, in other studies the prevalence of cancer is not mentioned).

Anyway cancer may represent the strongest determinant of SVT complications, according to results of specific studies. In particular in a single center study on n 276 consecutive SVT cases, a cancer diagnosis was present in a significantly higher percentage of SVT with concurrent DVT / PE (18.8 vs 8.7% of those in the SVT-only group, P <0.001) [29].

The prospective trial INSIGHT SVT, including patients with isolated SVT, showed that 6.7% of patients in study received diagnosis of cancer before SVT or within one year after SVT and that the diagnosis of malignancy increased the risk of VTE vs non cancer patients (13% vs. 5.4% after three months), opening to the possibility of an extended anticoagulation in this setting [30].

Beyond cancer, SVT may represent the event filtering many other more complex conditions (chronic autoimmune diseases, thrombophilia, etc.), not necessarily known at SVT diagnosis, probably acting as local or systemic triggering factors.

Here we report a series of clinical cases of patients with “non standard” SVT history opening to the possibility of a tailored management of SVT (diagnosis and treatment) in specifical settings.

Case 1

A 55 years old female patient of normal weight and without cardiovascular risk factors is referred to our observation for her first episode of SVT of right leg occurred spontaneously, in absence of signs of venous insufficiency at USD examination; her family and previous personal history were both negative for arterial and / or venous thrombosis She had 2 pregnancies, without obstetric complications.

2 years later recurrency of SVT became particularly frequent (n 3 episodes/year) in different sites and in both legs; deep venous system was never involved.

Each episode was treated with a standard prophylaxis dose of LMWH for a total of 6 weeks, with only temporary complete resolution of thrombosis. Congenital and acquired thrombophilia testing resulted negative as well as abdomen US, chest-X rays and mammography. The patient reported abdominal pain and diarrhea in the last months.

A diagnosis of ulcerative rectocolitis was performed 18 months after the first recurrence of SVT and treatment with anti TNF-alfa was undertaken and is still carried out regularly. Alongside a long-term anticoagulant treatment with Rivaroxaban 10 mg OD was started in order to reduce relapses. This latter still represents an off-label use of a direct oral anticoagulant, as Authorithies do not allow the use of Rivaroxaban for SVT treatment and Secondary Prophylaxis in all Countries.

The link between autoimmune diseases and SVT has been showed (1.3% of SVT patients in POST Study and 0.9% in CALISTO Study) [31] and it appears widely variable and therefore unpredictable, depending on the specific underlying condition [32].

Despite mechanisms explaining the increased risk of thrombosis in autoimmune disease are not all known, systemic inflammation is largely recognized as the first contributor to endothelial dysfunction and platelet hyperactivation leading to hypercoagulability in this setting [33].

Patients with inflammatory bowel disease (IBD) are at an increased risk for venous thrombosis, significantly affecting morbidity and mortality [34]. More often thrombosis in this setting is represented by DVT of the lower limbs and PE [35]. The prevalence rate of VTE among patients with IBD ranges from 5.6% to 7.6% [36], independently from male or female sex [37], accounting for a 2,3-fold greater risk of VTE events versus general population, particularly in ulcerative colitis and Crohn's disease [38-40]. Moreover the risk of thrombosis recurrence is higher in patients with previous unprovoked VTE [41].

A pro-thrombotic state represents the possibile result of qualitative and quantitative abnormalities in hemostatic balance in this setting, especially (but not exclusively) shown in acute inflammatory phase, particularly: 1) the increase in coagulation factors, also acting as acute-phase reactants (fibrinogen, FII, FV, FVII, FVIII, FX, FXI and FXII); 2) natural anticoagulant proteins downregulation (AT, TFPI, PC and PS); 3) impairment of fibrinolytic system consisting in fibrinolysis activators reduction (tPA) and inhibitors increase (PAI-1 and TAFI); 4) more reactive and sensitive platelets to agonists (increased platelet activation markers reported: P-selectin, GP53 and beta-thromboglobulin, CD40L in surface and serum; increased platelet microparticles circulation); 5) high rates of antiphospholipid positivity (anticardiolipin, antibeta2 GPI) [42-44].

Clinical factors that increase the likelihood of thrombosis among IBD patients include older age, pregnancy, active disease, more extensive disease, hospitalization [34].

Medications such corticosteroids and more specific drugs like tofacitinib (jak inhibitor) and surgeries can further increase the risk of thrombosis in this setting [44]. On the other side anti TNF alfa agents resulted in a 5-fold decreased risk of venous thrombosis vs steroids [45].

Published data about SVT and IBD are scarce (a few anecdotal cases available) actually. In our view the phenomenon is underestimated in literature, as lower limb SVT usually shares common risk factors with DVT and, as a matter of fact, SVT in this setting is common in everyday angiologists' and gastroenterologists' practice, with or without co-existence of other local or systemic risk factors.

At least a basic investigation for a possible IBD diagnosis is advisable in patients referred to our Centers for recurrent SVT when one or more gastrointestinal symptoms coexist, especially if SVT involved healthy superficial veins.

In this regard, particularly in acute inflammatory phases of disease, IBD is considered a sort of acquired thrombophilia condition, requiring attention about the need of thromboprophylaxis in course of hospitalization.

A reliable risk stratification system in this setting is desirable to identify those patients who may benefit the most from prophylaxis in case of hospitalization but also in post-discharge, surgery, in case of therapy increasing the risk of thrombosis or when cardiovascular risk factors coexist.

Thromboprophylaxis should be given to patients with IBD during hospitalization (6-fold higher risk vs non-hospitalized patients) [40] of any cause and at least considered in ambulatory patients with active IBD [39]. The current debate is about the opportunity of thromboprophylaxis in patients with inactive disease; in general control of disease activity seems to reduce the risk of venous (and arterial) thrombotic events in patients with IBD [40].

The optimal anticoagulation treatment strategy is not clear in many cases. Data supporting DOACs use for SVT in this specifical setting are still lacking. The possible use of direct oral

anticoagulants (DOACs) in IBD is even more challenging because of the local high bleeding risk of these patients. Apixaban appears as the most appropriate at the moment for its lower impact on gastrointestinal bleeding in IBD setting, despite the only agent tested in SVT is Rivaroxaban, actually [24].

Case 2

A Female patient aged 45 years old, of normal weight with previous personal history negative for arterial and / or deep venous thrombosis, reported 2 episodes of SVT in her past history. Her father had myocardial infarction at the age of 49 years, in absence of cardiovascular risk factors.

After a reddened, warm, tender area and a palpable cord became evident on her left limb she underwent a doppler USD examination, showing the presence of great saphenous vein thrombosis, not involving deep venous system; promptly a treatment with fondaparinux 2.5 mg sc/die was started. Coagulation tests previously performed on the advice of her gynecologist, because of multiple abortions, showed free protein S reduced levels (42%); normal values are included in the range 60-100%. Hereditary anticoagulant protein S deficiency was confirmed in patient's father and sister.

On the one side SVT is not included among conditions strictly requiring genetic thrombophilia testing according to current recommendations [46]. On the other side thrombophilia was reported in 19.8% of all SVT cases in a study on 100 patients [46] and De Moerlose showed a statistically higher incidence of a mild thrombophilia, FV Leiden (but not G20210A prothrombin variant) among 112 consecutive patients with SVT diagnosis than in controls (14.3% vs 6.1%) [48].

It should be noted that in this regard specific data about different populations of patients with or without varicose veins are still not available.

In Authors' view genetic testing could be appropriate certainly not routinely but in very selected cases of recurrent SVT, for example occurring on healthy veins, in young patients with personal or family history strongly positive for thrombotic diathesis (previous DVT / EP, significant obstetrical complications).

Moreover it is a matter of fact that thrombophilia testing is widely performed even in unselected patients, as clinicians worldwide do not always adequately select patients for investigation [49] or simply these tests are available for a single patient even before SVT has occurred. Therefore the meaning of data previously acquired about thrombophilia, especially not mild thrombophilia, in the management of SVT episodes is not well established.

Genetic thrombophilias only minimally increase the risk of VTE in patients with a history of SVT [50]. There are no clear data suggesting thrombophilia changes rates of SVT recurrence or progression [51-52].

Otherwise, no significant differences were found concerning SVT symptom duration, family or personal history of DVT / PE, personal history of SVT between the thrombophilia carrier and not [29].

There are many uncertainties about SVT management at least in case of non-mild thrombophilia, potentially modifying treatment strategy. If SVT is considered just a local and non-systemic condition, the information about thrombophilia should not have an influence on the choice about type and duration of anticoagulation.

On the opposite, at least in some cases of SVT (SVT involving confluence with deep venous system, SVT diagnosed in subjects with previous DVT history) being carrier of a non-mild thrombophilia could be more likely associated with higher risk of complications and therefore a long- term anticoagulation strategy appears as the most appropriate choice, as in DVT.

No study to date explored treatment of SVT in this setting. At the moment no data support administration of higher doses or longer treatment in SVT in general.

Case 3

This is the case of a female, normal weight patient, aged 60 years old with hypercholesterolemia; her thrombotic family history is negative; her personal history include 3 pregnancies without obstetric complications; a previous SVT of the right leg occurred many years ago, after surgery and was treated with LMWH prophylaxis doses for nearly 40 days. 2 months ago, after acute pain of the left limb appeared, a doppler ultrasound was carried out, showing the presence of thrombosis of left great saphenous vein with extent up to 2.0 cm from the confluence in the femoral vein, in absence of clear signs of venous insufficiency. We performed a "SVT / DVT" diagnosis, thus requiring a therapeutic approach similar to the one reserved to DVT, according to current guidelines [53-54].

Acquired thrombophilia testing including antiphospholipid antibodies, homocysteine levels and tumor markers resulted negative as well as abdomen US, chest-X rays and bilateral mammography.

A treatment with edoxaban 60 mg/die was started and is still ongoing. The estimated treatment time is 3 months overall, according to current guidelines treatment for DVT [55]. *At the end of this period the patient will be assessed for the eventual need of extended anticoagulant therapy.*

Despite current guidelines recommend full dose anticoagulation in case of SVT extending to deep veins or in case of distance from the junction with deep circulation is < 3 cm [56], randomized clinical trials specifically exploring the usefulness of therapeutic versus preventive anticoagulation in the setting of SVT closer to the junction are not yet available; the presence of thrombus head within 3 cm from the superficial-deep venous system junction often made the patients ineligible for recruitment in studies addressing the treatment of SVT; the same phenomenon occurred usually in studies addressing the treatment of DVT [56].

As reported in different studies these patients have an higher risk of severe complications described in this setting [11] and thus they are considered in need of more aggressive management (usually anticoagulant treatment for at least 3-6 months [57].

In the RIETE trial less thromboembolic events were observed in patients treated with anticoagulants at therapeutic doses (1.3% vs. 2.7%), despite more significant bleeding complications (1.3% vs. 0.7%) after 3 months follow-up, thus exploring patient's own bleeding risk is crucial especially in case of controversial anticoagulant treatment as SVT / DVT [56]. In a recent retrospective study, n 192 patients of 316 total patients (60.8%) had an SVT >3 cm from the SFJ / SPJ at presentation and underwent a 90 days follow-up. Of 192 patients n 59 (30.7%) started an anticoagulation treatment and n 125 (65.1%) received conservative management. Complications occurred in 46.4% of patients managed conservatively and in 17.5% of those on any dose anticoagulation; DVT / PE occurred in 8% of patients treated with conservative strategy vs 0% in those on full anticoagulation [58].

Despite SVT diagnosis could be theoretically based on the clinical presentation, US is the most used diagnostic method as it is cheap, accurate for diagnosis and safe for patients [59].

Considering the number of patients with SVT symptoms having also DVT at diagnosis, it seems advisable to perform a venous USD in all patients with SVT suspicion [15].

Beyond confirming or excluding DVT, USD scanning at diagnosis is useful for evaluation of SVT extension, definition of the distance to the deep circulation, and in order to identify the presence of varicose veins [60].

USD reports are still not homogeneous and they do not always include all parameters considered essential for diagnosis and management of SVT. The exact distance of thrombus from saphenous-femoral or saphenous-popliteal junction as well as the SVT extension are not always specified in clinical practice, actually.

As a consequence clinicians will not consider the eventual DVT involvement in many cases of SVT. In this regard a recent survey among Italian angiologists and vascular physicians showed a definitely heterogeneous therapeutic approach to SVT involving the Sapheno-Femoral Junction [54].

Conclusions

In conclusion a few evidence is available about investigation and treatment of SVT, actually. A small number of trials focusing on treatment of lower limb SVT is available (Table 2); as a result, in spite of recommendations available, therapy is often managed at treating physician's discretion, ranging from conservative treatment (including NSAIDs and close USD follow-up) to *standard* anticoagulation, mostly with fondaparinux and low-molecular-weight heparin, in various dosing schemes. There is also variability among different Centers about duration of anticoagulation, usually 45 days (however ranging between 4 and 8 weeks) [1,21,29,61].

We strongly support the hypothesis that the best approach to treatment should be tailored and take into account the specific clinical setting and pathogenesis of SVT, although always in respect of current guidelines.

This series of clinical cases of patients with "*non standard*" SVT history opens to the possibility of a personalized management of SVT considering comorbidities, site and extent of the thrombosis, features eventually predisposing to DVT and PE and finally evaluating interprofessional team strategies to improve coordination of investigation and care [62].

In our view initial diagnosis in patients older than 40 years, SVT involving healthy veins, in subjects without specific risk factors or migratory thrombophlebitis should prompt consideration of possible underlying conditions.

Trials are needed pursuing the following aims 1) to describe interprofessional team strategies to improve coordination of care, thus allowing a more precise diagnosis, and to investigate underlying causes, thereby improving outcomes; 2) to underline the importance of identifying

different etiology of superficial thrombophlebitis in order to promptly begin the most appropriate treatment according to the site and extent of the thrombosis; 3) to individuate critical elements in the evaluation of patients that predispose to deep vein thrombosis and pulmonary embolism; 4) to outline the management options available identifying those cases in need of a possible more aggressive management. Our proposal consists in a multidisciplinary approach to "*non standard SVT*", mainly based on age, thrombotic family and personal history and SVT extension in order to establish a proper complete diagnostic algorithm including blood tests, acquired thrombophilia, instrumental examinations and congenital thrombophilia tests, variously combined (Figure 1).

Such an approach has multiple goals. 1) First of all in this way we will be sure to collect data for a local registry of all "*non standard"* SVT for a complete data analysis, providing further informations about the origin of the phenomenon; 2) the need of collecting data for local registry will make more homogeneous the approach to SVT; 3) as a direct consequence of data collection more complete informations will be available about the most effective treatment according to the specific clinical setting; 4) SVT may become a potential "filter" to investigate more complex clinical setting like cancer or autoimmune diseases that we could not diagnose limiting our investigation to the sole USD examination.

More validated and reliable suggestions and / or recommendations about management in this setting will be available after systematic data collection and analysis (Figure 2).

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Table 1 Recognized risk factors for superficial vein thrombosis development	
Non modifiable	**Acquired**
Age >65 years	Obesity
Personal history of SVT / DVT / PE	Cancer
Family history of SVT / DVT	Surgery / Vascular Surgery
Chronic Vein Insufficiency	Hospitalization / Immobilization
Lower Limb Varicose Veins	Prolonged Travel
Thrombophilias	Pregnancy
	Hormonal Therapy
	Autoimmune Diseases
	Drugs (steroids, janus kinase inhibitors, chemotherapy, parenteral nutrition)
Abbreviations: DVT, deep venous thrombosis; OD, once daily; PE, pulmonary embolism; SVT, superficial vein thrombosis	

Table 2 Main results of available randomized controlled trials about superficial vein thrombosis treatment

Trial	**Inclusion criteria**	**Agent vs Comparator**	**Efficacy Outcomes**	**Safety**
STENOX [21]	SVT ≥5 cm length on ultrasound	Enoxaparin therapeutic or prophylactic for 12 days	Risk of recurrence and / or proximal extension 5.7% in therapeutic dose vs 8.2% in prophylactic dose vs 29.5% in placebo	No death or major hemorrhage
STEFLUX [23]	SVT ≥4 cm in length	Parnaparin 8500 IU OD for 10 days followed by placebo for 20 days (group A) vs 8500 IU OD for 10 days followed by 6400 IU OD for 20 days (group B) vs 4250 IU OD for 30 days (group C)	Composite outcome (DVT, PE, and SVT recurrence) in 15.6% (group A) vs 1.8% (group B) vs 7.3% (group C)	No major hemorrhages

CALISTO [24]	SVT ≥5 cm in length, located 3 cm away from the junction with the deep veins	Subcutaneous fondaparinux 2.5 mg OD or placebo for 45 days	Death or symptomatic VTE events (PE, DVT, SVT extension to junction, and SVT recurrence in 0.9% in the fondaparinux group and 5.9% in the placebo group (*P* <0.001)	Not increased bleeding risk
SURPRISE [25]	Symptomatic SVT, location above the knee, ≥5 cm, and at least one additional risk factor	10 mg oral rivaroxaban or 2.5 mg subcutaneous fondaparinux OD for 45 day	Symptomatic DVT, PE, progression or recurrence of SVT, and all cause mortality in 3% in the rivaroxaban group vs 2% in fondaparinux group (p: 0.003).	No major bleeds in either group
Abbreviations: see Table 1				

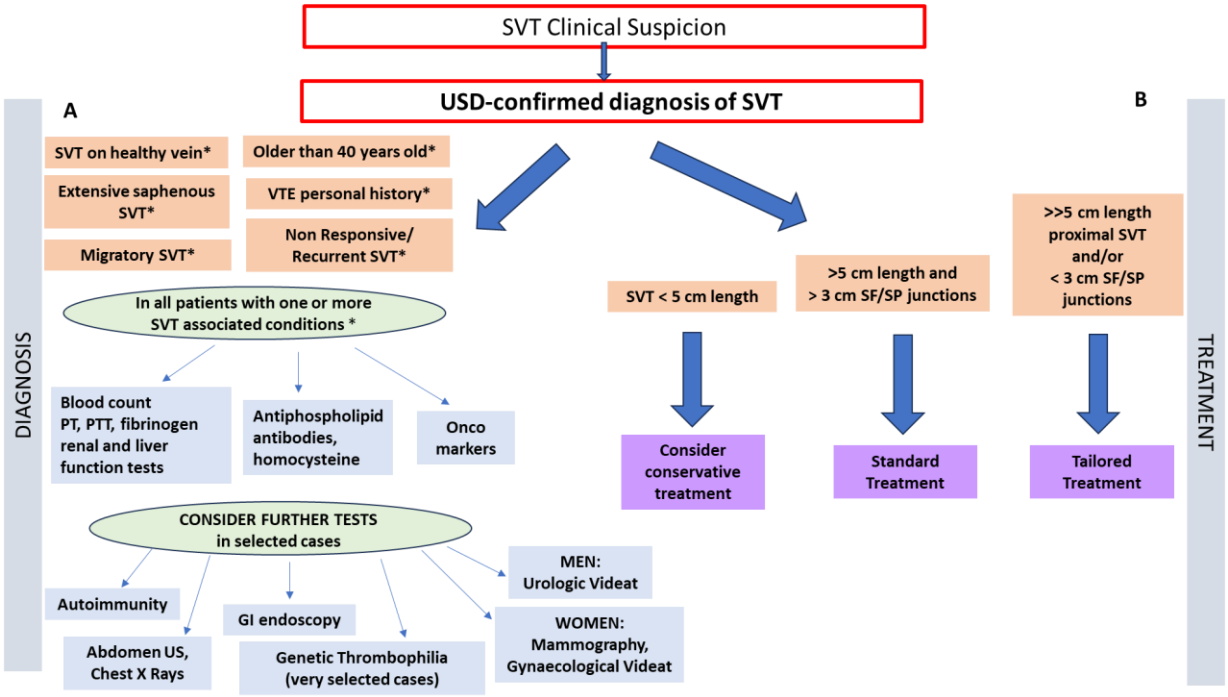

Figure 1 Proposal for a systematic algorythm for diagnosis and therapy in *"non standard"* superficial vein thrombosis; A – diagnostic algorythm; B – the choice of treatment

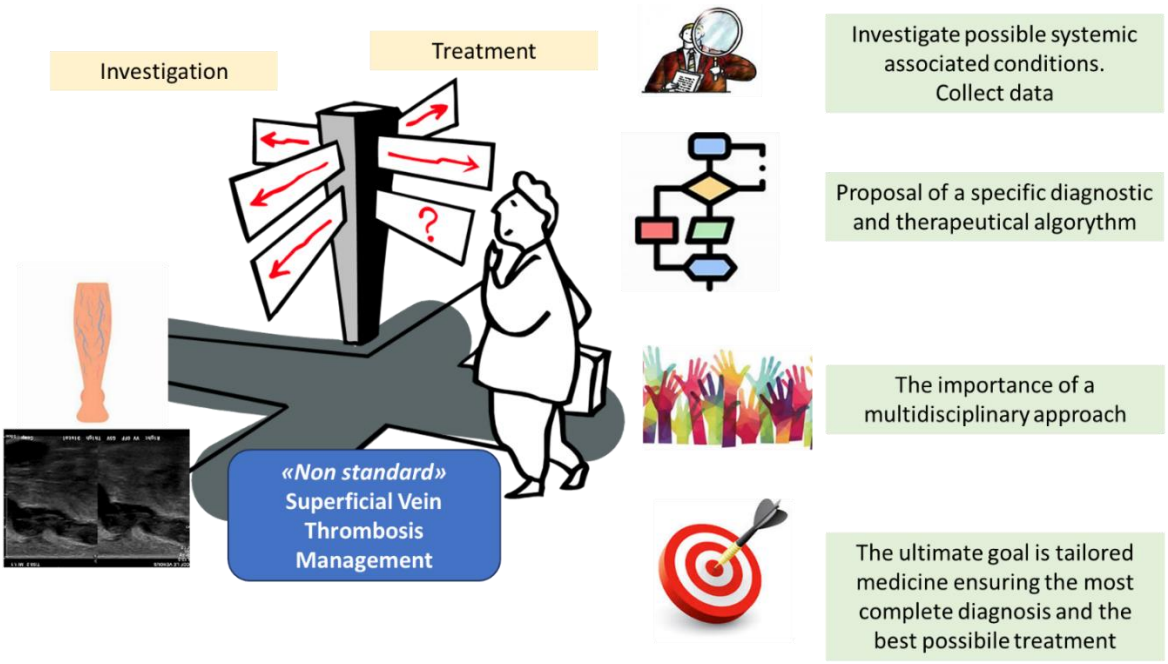

Figure 2 Proposal for a more standardized and exhaustive approach to "non standard" superficial vein thrombosis