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How I treat superficial venous thrombosis

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Thrombosis of superficial veins has long been regarded as a benign disorder. If patients with a clinical diagnosis of superficial venous thrombosis (SVT) are thoroughly evaluated, the degree and extent of thrombosis in patients with SVT are characteristically underestimated (~ 75% of the time) and such patients have coexistence (~ 25% of the time) of, and/or rapid progression (~ 10% of the time) to, systemic venous thromboembolism (VTE). Pulmonary embolism (PE; ~ 25% of the time) and death (~ 1% of the time) occur. Contributory risk factors for SVT are the same for VTE. Treatment of patients' SVT with parenteral anticoagulants appears to be both efficacious and certainly safe. I regard most patients with a clinical diagnosis of SVT the same as those with VTEs. Systemic anticoagulant therapy of patients with a clinical diagnosis of SVT obviates extensive imaging and laboratory workup and may be cost effective while encompassing treatment of any unknown concomitant thromboses with only low risk for hemorrhage. This decision is especially clear in those patients with known hypercoagulability. Patients without clinical risk factors are at lower risk to develop VTE complications and might be those who can be simply observed. (*Blood*. 2011;117(1): 39-44)

Introduction

The term venous thromboembolism (VTE) has been used since the 1970s in an inclusive manner representing unification of those pathophysiologic processes that lead to either venous thrombosis and/or pulmonary embolism. As such, VTE includes not only deep vein thrombosis (DVT) of the legs and pulmonary embolism (PE), but also thromboses occurring in less typical veins, such as the cerebral, hepatic, renal, splenic, portal, mesenteric, and ovarian veins. The term VTE is also used to include thrombosis of the deeper veins of the upper extremities. Focusing on causes of hypercoagulability (such as genetic hypercoagulability [thrombophilia], obesity, immobility, prolonged travel, inflammation, impaired blood flow, pregnancy, malignancy, trauma, surgery, and others) emphasizes the prime role played by blood within the vessels rather than any major role played by anatomic location of the vessels. Thus, causation and its major serious outcome (fatal PE) should be at the forefront in consideration for initiation of systemic anticoagulant therapy. As treatment of VTE, regardless of cause or location, is both highly effective and safe, if one considers superficial venous thrombosis (SVT) as a type of VTE, invoking a diagnosis of SVT justifies therapeutic action. I regard SVT comparable with VTE and herein present the supporting logic.

Curiously, to date, the term VTE has not included SVT. The explanation may be historically based. Before modern biochemical explanations of hypercoagulability as well as the availability of modern imaging to diagnose even the deepest or most occult of venous thromboses, it was held that thrombosis of the superficial veins (with particular reference to the great saphenous vein [GSV]) was so easily identifiable that the diagnosis of SVT was held separate and apart from the more occult and subtle DVT. The medical literature of the latter part of the 19th and first half of the 20th centuries supported that, although SVT was easy to diagnose (requiring neither "blood tests" nor imaging studies), its potential consequences, namely, PE and death, were not directly predictable by the extent of the disease seen at the bedside.[1] A leading medical treatise of 1885 stated thus regarding venous thrombosis: "Except in the cases of superficial veins, in which the vessel may be felt as a hard cord, the affliction cannot be recognized during life."[2] Ease of clinical diagnosis of SVT somehow was translated into its being safer than its more occult and dangerous cousin DVT.

Extensive earlier medical literature subdivided SVT into primary inflammation of the venous wall leading to thrombosis versus primary thrombosis leading to inflammation of the vessel wall, namely, phlebothrombosis versus thrombophlebitis, terms of which the meanings now are vague, hold little merit, and should be discarded.

Hematologists and internists did not participate in diagnosis and management of venous thrombosis to any extent until the second half of the last century; such was the purview of surgeons. Linkage of venous thrombosis to surgical procedures was clear, and the surgical techniques of thrombectomy and ligation of the thrombosed superficial vessels they diagnosed were considered state of the art. Although therapy with either heparin or oral vitamin K antagonists was in the developmental stage, there were no established or agreed-on guidelines for indications, dosage, intensity, monitoring, or duration for use of either anticoagulant. Underanticoagulation with its resultant failure to control thrombosis or overanticoagulation with hemorrhagic complications were commonplace and indirectly served to impede their usage to their present place. This degree of disorganization persisted until the initiation of modern studies of dosage and duration of anticoagulant therapy along with the concept of evidence-based medicine, which essentially began with the seminal 1960 report of heparin's efficacy in treatment of PE by Barritt and Jordan[3] and continues with the efforts initiated by Hirsh et al.[4] As the usage of anticoagulant therapy has became both safer and of proven efficacy, the use in patients with SVT needs to be reconsidered.

Submitted May 21, 2010; accepted October 18, 2010. Prepublished online as *Blood* First Edition paper, October 27, 2010; DOI 10.1182/blood-2010-05-286690.

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The experiential approach to SVT being limited only to what one saw and felt at the bedside is no longer appropriate or sustainable. Why clinicians continue to segregate SVT from all other venous thromboses is not readily explainable, particularly now that the experimental approach has become dominant and prophylaxis and therapy are so effective. If thromboses of the visceral, cerebral, renal, and pelvic veins fit well into our modern thinking of VTE, the time seems right to abandon anatomic location of a venous thrombosis as a special sanctuary having its own diagnostic niche, therapy, and separate clinical approach. I argue that, because the epidemiology, causation, natural history, complications, and increasingly, therapy of SVT are more similar than not to those of VTE, the approach to SVT should be more akin to that of DVT.

What exactly is and is not SVT?

What is regarded as "superficial" has been obscure if not controversial. This confusion has obfuscated review of the literature. There are at least 4 different usages of the term "SVT," and most publications do not exactly define which clinical situation is being discussed. The preponderance of reports and data on SVT involve thrombosis of the long saphenous vein, the longer proximal part of which is the GSV (the now-preferred term) and the smaller, more distal part, the lesser saphenous vein.[5]

The second use of the term SVT, whether intentional or not, includes the extremely inappropriate use of the term "superficial" when discussing that segment of the femoral vein proximal to the popliteal vein yet distal to the common femoral vein; this has been called the "potential fatal misnomer" for good reason.[6] Because the majority of physicians have been taught that "SVT" does not need to be treated, imaging studies reporting thrombosis of the "superficial femoral vein" may be incorrectly regarded as a true typical SVT and therefore anticoagulant therapy might not be even considered, occasionally with disastrous consequences. Several anatomic, radiologic, and vascular surgical societies have agreed that the term "superficial femoral vein" should be completely eliminated from our lexicon.[5-7] That portion of the femoral vein that had previously been regarded as superficial femoral vein should also be termed "femoral vein" as it is neither superficial nor free from embolism, to include fatal pulmonary embolism. The time has come to eliminate this nomenclature; no reason to support retention of this misleading term has been advocated by any professional organization.

Third, superficial veins also include the veins that occur anywhere superficially on the body whether they are on the abdominal wall, thoracic wall, or arms. These painful thromboses may be collaterals of deeper occluded veins, such as the inferior vena cava or deep veins of the arm.[8] These thromboses may also be manifestations of Trousseau syndrome.[9]

Lastly, small cannulated veins of the hands and arms may thrombose up to 25% of the time after infusion of medications and, in and of themselves, require no anticoagulant therapy. Neither infusional thromboses nor septic thrombophlebitis[10-14] will be further discussed in this article.

How I regard SVT

That all these terminologies, incorrect usages of anatomic terms, and incomplete studies are confusing issues was deduced by the 2007 Cochrane Collaboration systemic review of SVT by DiNisio et al.[15] Their review expressed frustration in the definition of SVT. They noted that, although SVT had long been regarded as a fairly benign disease, that stance has been increasingly called into question.[15-19] They were unable to construct evidence-based therapeutic recommendations because of a lack of data and concluded that more studies to include randomized clinical trials are desperately needed. The lack of clinical trials combined with the frequency that clinicians encounter SVT has resulted in this paper of how I perceive, approach, and treat SVT in clinical practice.

The few available studies are heterogeneous and descriptive in nature, and follow-up of patients is so limited that meaningful recommendations cannot be gleaned from the existing literature. These studies probably significantly underestimate the occurrence of concomitant comorbidities of SVT, namely, DVT and PE, because appropriate stratification for coexisting DVT and PE was not used; thus, inclusion into clinical studies is restricted to clinical diagnosis of SVT. Because most reports specifically excluded patients having known concomitant DVT and PE, excluded patients with prior DVTs and PEs, excluded those with family histories positive for DVT, and excluded those who had ever been treated with anticoagulant therapy, generalization of these data to one's own SVT patients may be flawed in that those results might be too benign as these real risk factors had been eliminated in the study group. When treatment with systemic anticoagulation was offered, most studies used anticoagulant therapy at doses either subtherapeutic or prophylactic and/or administration was brief compared with current consensus reports.[14] One study[20] treated patients with low-molecular-weight heparin for only 10 days with follow-up as brief as a few weeks. These approaches are not compatible with our current view that VTE is best regarded as systemic, chronic, and often familial rather than isolated, acute, and random.

When a clinical diagnosis of SVT is made, that patient may either harbor a concomitant DVT or PE or within days subsequently develop a DVT or PE. Using modern imaging techniques prospectively at the time of a clinical diagnosis, Chengelis et al[21] studied the progression of thrombosis between day 2 and day 10 (average, 6.5 days) without anticoagulant therapy. They found that 11% of their patients with proven GSV-only thrombosis developed progression of their thrombosis into the femoral vein system. In 1995, Ascer et al,[22] using ultrasonography, proved that, of their cases deemed to have only isolated GSV thrombosis, 25% concomitantly had contralateral DVT, an observation that greatly negated the then-held theory that SVT progressed in a strict, contiguous, ipsilateral, anatomic pattern and was more consistent with the notion that thrombosis is a systemic hematologic process. Similarly, in 1997, again using duplex ultrasonography, Marković et al[16] sought evidence for the extent of GSV thrombosis made at the bedside and found that in 77% of their cases the disease was significantly more extensive than estimated by clinical examination alone. At that same time, they found that 28% of patients, if studied, had concomitant DVT and/or PE. In their review of 37 reports of SVT in the literature, Leon et al,[23] while noticing the extreme heterogeneity of diagnostic criteria and duration of follow-up, found that the coexistence of DVT at the time of SVT diagnosis ranged from 6% to 53%, whereas the reported coexistence of pulmonary embolus using various diagnostic methodologies ranged from 0% to 33% and subsequent development of DVT ranged from 3% to 15%.

Recently, in a 2010 cross-sectional prospective cohort study, Decousus et al[24] prospectively described such data among 844 SVT

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Table 1. Reasons to incorporate SVT into the VTE family

Risk/history	Reasons	Comments (references)
Risk factors	1. Not an entirely benign disease	DVT, PE, and fatality not rare (15-19, 23, 24, 26)
	2. Both SVT and VTE associated with similar clinical hypercoagulability (eg, trauma, surgery, pregnancy, immobility, obesity, advancing age, malignancy)	23, 25
	3. Incidence of thrombophilia enriched in both SVT and VTE patients	18, 23-26
Natural history	1. Coexistence of VTE at time of diagnosis of VTE	Averages ~ 25% (17, 22-24)
	2. Progression of SVT to VTE	Averages ~ 10%-20% per year
	3. Prior VTE a risk factor for future SVT	21, 23, 24
	4. Prior SVT a risk factor for future VTE	15, 23
	5. No current plausible putative theory that justifies segregation of (local) SVT apart, different, and unique from (systemic) VTE	27, 28

patients. They determined that at initial evaluation 25% of such patients had concomitant DVT and/or PE and also that, of those 600 patients initially without VTE, 10% developed VTE within a follow-up period of only 3 months despite most having received some anticoagulant therapy. By multivariate analysis, risk factors favoring development of VTE were male sex, prior DVT or PE, and a diagnosis of cancer.

Multiple studies written in the last decade have demonstrated enrichment of thrombophilia among patients diagnosed with SVT. In 2005, Leon et al[23] reviewed SVT and concluded that many risk factors for the development of SVT were the same as those for routine DVT. Among their strongest risk factors were the hypercoagulable states to include thrombophilia as well as malignancy. Martinelli et al[25] reported that 16% of their patients harbored the factor V Leiden mutation, 10% had the prothrombin 20210 mutation, and 10% had deficiency of antithrombin III, protein C, or protein S. Wichers et al[18] in 2008 discovered that 79% of their patients had some type of putative underlying hypercoagulability. Mouton et al[26] in 2009 showed that 13% of their patients had a concomitant malignancy at or soon after their diagnosis of SVT. Other risk factors included aging and impaired blood flow from obesity, pregnancy, or even prolonged air travel. Heit et al[27] were the first to note that a prior history of SVT served as an independent risk factor for the future development of DVT, again linking etiology. Their observation was confirmed by Schönauer et al.[28]

Thus, I regard SVT as simply the superficial venous manifestation of a systemic process that is associated with what is more commonly called VTE. These observations, recorded in Table 1, support that concomitant VTE is common and progressive and that relapses of VTE in patients initially without DVT or PE is considerable.

How I treat SVT

If, as outlined in Table 1, the epidemiology, risk factors, and natural history of SVT are extremely similar to DVT, the central issue in the rationale behind selecting therapy for SVT depends on one's perception of the likelihood of coexistence of and/or progression of any thrombosis into more VTE, and the likelihood of untoward outcomes without therapeutic intervention.

There is no therapy for SVT that is agreed on and, given the wide variety of options and the lack of randomized clinical trials, one may deduce that a clear and effective evidence-based therapy is not currently available[14] (Table 2).

Clinical observation coupled with strict bed rest with complete immobility was recommended in the past as therapy for SVT by many authorities. Such passive therapy may have seemed effective in part because relief of pain and swelling generated by SVT was

Table 2. Therapeutic considerations for patients with SVT

Therapy	Considerations	Comments (references)
Passive therapy	1. Observation, bed rest, and immobility	Not always effective; fatalities occur (1)
	2. Serial US surveillance	Passive therapy marginally effective at best (15)
Active nonanticoagulant therapy	1. Look for coexisting VTE or progression to VTE	These findings might justify systemic therapy (29)
	2. Screen for hypercoagulability/thrombophilia	May impact therapeutic decision (23, 25)
	3. NSAIDs/antibiotics	Not thought to be effective (15, 23, 29)
	4. Topical anticoagulants and/or antiplatelet agents	Not thought to be effective (15, 29)
	5. Surgery	May actually exacerbate VTE (27); 7%-10% complication rate (30, 31); not recommended (14)
Active anticoagulant therapy	1. Systemic administration of anticoagulants	In studies to date, seems useful yet too little administered over too brief a time (15, 23); appears safer and more economical than surgery (31)
	2. Extant case series are few and use very brief therapy and typically at low intensity, yet heparin-based therapy seems to be rational, efficacious, and safe; economic considerations are currently not established	14, 15, 20, 32, 32
	3. The only RCT (CALISTO) demonstrates that prophylactic doses of fondaparinux compared with placebo is efficacious, safe, and durable	34

US indicates ultrasound; and NSAIDs, nonsteroidal anti-inflammatory drugs.

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the predominant endpoint. Once serial measuring for either regression or progression of the SVT became available, first by venography and then by plethysmography and now by ultrasound, it was rational to observe patients for evidence of progression, treating with heparin only those who demonstrated progression. A frequently quoted value was that 10% to 20% of patients with SVT would experience progressive thrombosis, whereas the remaining 80% would regress. The question remains whether the risk/benefit ratio of any active therapy netly negates the risk. There are still some patients for whom observation and serial ultrasounds every 5 to 7 days may be appropriate, but these appear to be the minority of patients. These might include those patients in whom anticoagulant therapy might be effective yet pose excessive risk (such as patients with severe thrombocytopenia or concomitant ongoing hemorrhage) or patients perceived to be at lower risk for further thrombosis (such as patients with no prior personal or family history of thrombosis and those having no other clinical hypercoagulability risk factors, such as malignancy, immobilization, or concurrent inflammatory disease).

Several reports have advocated that ultrasonographic imaging be routinely made for evidence of thrombosis more extensive than just the observable SVT. Such logic hinges on the belief that any thrombosis discovered above and beyond the SVT should be systemically treated, whereas those cases of SVT existing alone should not be systemically treated. That many patients' limited SVT might soon progress also implies that one must periodically reimage to observe for evidence of progression. Many publications have also suggested that laboratory searches for thrombophilia should be carried out, the logic of which is based solely on the concept that such findings would alone and critically change one's therapeutic intent. Were one rather to deduce that the SVT itself, whether alone or coexisting with other VTE, warranted anticoagulant therapy, complete initial imaging, serial imaging, and laboratory testing could be abrogated, thus limiting expense. Any known or unknown coexisting thrombosis would be treated by incorporation if one selects to use systemic anticoagulant therapy of their SVT patients.

Nonsteroidal anti-inflammatory drugs have traditionally been used either orally or topically. This approach seems to be in doubt because, even if inflammatory manifestations of SVT markedly respond to either time, the administration of nonsteroidal anti-inflammatory drugs, or the combination, such symptomatic improvement does not necessarily indicate that clot progression has been mitigated.[15]

Some physicians frequently apply topical anticoagulants in the form of heparin gels.[33] Even should there be a reduction in typical inflammation, several have opined that, if the basic disease process has not been modified, these gels should no longer be used as the primary treatment modality.[15] Antibiotic therapy is no longer routinely advocated for SVT treatment.[23,29]

For a century, surgical procedures have been used to treat thrombosis of the GSV. The basis of this approach was that, if the proximal end of the clot approaches within a few centimeters of, let alone passes into, the junction of the GSV with the femoral vein, the risk of possible embolism became serious enough to warrant surgical intervention. Surgical approaches involved a variety of procedures, ranging from ligation of the GSV, surgical removal of thrombus in the GSV, surgical excision of the entire GSV, and multiple diverse surgical procedures. To the extent that one thinks systemically (especially with regard to causation), one sees this surgical approach has limited credibility. Surgery itself serves an enormous impetus[27] for additional thrombosis. Blättler et al,[30] as recently as 2008, reported that surgical "stripping" of the saphenous venous system carries a 10% complication rate, whereas Lozano and Almazan[31] reported a 7% complication rate resulting from saphenofemoral disconnection, values that must be compared with complications of systemic anticoagulant therapy. Medical treatment is now recommended over surgical treatment.[14]

Several groups have proposed heparin-based therapy, to include unfractionated heparin or low molecular weight heparins, and most recently pentasaccharide. These reports used lower-than-therapeutic doses rather than commitment to full therapeutic dosage.[15] In addition, the duration of treatment in most such reports was truncated.[15,23] The STENOX[20] study limited treatment of patients with SVT to enoxaparin for less than 2 weeks, yet those so treated had an extension or relapse rate of less than half that of those SVT patients receiving only placebo therapy.

With those 2 limitations (too low intensity for too brief a period), it remains surprising that any benefit was observed. The Cochrane Collaborative reviewers concluded that any treatment with any anticoagulant over any period of time not only seemed logical but resulted in trends toward efficacy.[15] Noting that what appeared to be early efficacy may be lost within several months after brief therapy, the Cochrane Collaborative reviewers concluded that duration of therapy was too brief for long-term efficacy to be significantly demonstrable. Importantly, the Cochrane Collaborative reviewers documented negligible bleeding complications with anticoagulant therapy.[15]

A recent retrospective cohort study of 185 patients cited no increase in stroke or myocardial infarction, yet a 10-fold increase in DVT among patients with spontaneous SVT suggested anticoagulant therapy be withheld.[32]

Lozano et al[31] compared surgical and medical treatment of a group of patients with SVT. The medical group received 4 weeks of moderately intensive enoxaparin therapy, whereas the surgical group underwent saphenofemoral surgical disconnection. Not only did the enoxaparin group appear to have better outcomes (fewer progressions to DVT and/or PE), the treatment costs were substantially less than in those undergoing the surgical approach.

Recently, clinicians of the CALISTO study group[34] performed the first randomized controlled trial regarding a large group of patients with SVT followed prospectively. Their selection process excluded many patients who one sees in actual clinical practice, such as those patients with probable or known hypercoagulability, patients with known prior DVT and PE, patients with malignancy, and patients with renal failure. Patients were randomized between a prophylactic dose of fondaparinux 2.5 mg once a day versus placebo. Patients were treated for 45 days (the longest treatment group studied thus far) and then followed for the subsequent 30 days off treatment. The study showed that, at 45 days, the treatment group had developed the primary endpoint of progression of thrombosis at a rate of 0.9%, whereas in those in the placebo group such events occurred at 5.9%. The fondaparinux group, compared with the placebo group, experienced a significant decrease in PEs, DVTs, and SVT extension as well as recurrence of the incident SVT by day 75. The CALISTO investigators also noticed the extremely low rate reported bleeding and concluded that such therapy was rational, flexible, effective, and durable after cessation of the fondaparinux therapy.[34]

If one elects not to offer therapeutic anticoagulant therapy, consideration must include risks of coexistence of VTE, progression of VTE, development and advancement of postphlebitic syndrome, and ultimately fatal PE. One must be mindful that many

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of at-risk patients with a clinical diagnosis of SVT in their practice may be the ones excluded from most reports, implying that, in one's clinic, results might actually be significantly better yet sparing the expenses of laboratory testing or serial ultrasound examination in most SVT patients.

One can now logically argue to preemptively treat patients, even if one perceives thrombosis is limited to the SVT stage. VTE risks are higher for an untoward event in untreated patients, especially if their history suggests a significant personal or family VTE history, the presence or likelihood of underlying malignancy, or limited cardiovascular and respiratory reserve to such an extent that even a modest-sized PE may prove fatal.

We can risk-stratify our patients using current risk factors and knowledge of SVT as herein reviewed to determine whether systemic anticoagulant therapy is warranted. Admittedly, with the exception of the Decousus et al report,[34] there are no high-grade evidence-based data currently available. Clinical considerations include the size of the thrombosed vessel, whether there was provocation, history of recurrence, history of prior treatment with anticoagulant therapy for VTE, family history, known thrombophilia, and overall perceived risk of a PE to this patient. The *gestalt* of the situation will typically allow one to decide for or against systemic anticoagulant therapy.

Consider a patient who had dental work and peripheral intravenous lines inserted into the veins of the back of his hand resulting in a thrombosis extending into his veins of the upper arm. If he were known to have had a prior DVT and administration of anticoagulants for a year after a PE related to a broken leg 10 years ago, I would consider anticoagulant therapy for him for the next 3 months, based on my perception that he is hypercoagulable and this small untreated thrombus could provoke a VTE elsewhere in such a patient.

In a second scenario, an obese 55-year-old woman with active inflammatory bowel disease develops a 15-cm, palpable, tender, warm cord in her left GSV as her initial experience with thrombosis after several weeks of near total bed rest. I would prescribe 6 months of anticoagulant therapy or even longer should her inflammatory bowel disease remain active.

In conclusion, I treat the majority of patients with a clinical diagnosis of SVT on an equal footing as patients with other VTE. In the routine treatment of patients with DVT lacking symptoms of PE, imaging studies to document the presence of PE are generally not held as necessary as the decision to treat with systemic anticoagulant therapy is sufficient with DVT alone. Accordingly, I do not routinely repeatedly and serially and exhaustively image patients with SVT as I hold that those patients have reason enough to be treated with systemic anticoagulation, saving a significant amount of time and expense. Such an approach can be modified if symptoms so suggest. Similarly, I would perform laboratory testing for thrombophilia only in situations that I thought might change the type of therapy, the duration of the therapy, or if such would have any clinical impact on the patient or especially his family members. One anxiously awaits randomized controlled trials to document the validity of these suggestions, but until that time it seems efficacious and safe to regard the majority of SVTs, particularly those of the long saphenous vein, as being of potential danger and worthy of anticoagulant therapy.

Authorship

Contribution: C.S.K. wrote the paper.

Conflict-of-interest disclosure: C.S.K. is on the speakers' bureau for GlaxoSmithKline.

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