Are isolated distal deep-vein thromboses clinically significant?

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The authors consider isolated distal deep-vein thrombosis (DVT) to be significant and recommend treating isolated symptomatic distal DVT in the same way as proximal lower-limb DVT. There is no guidance for the treatment of asymptomatic isolated distal DVT; however, certain triggers could be used to guide therapy. Our policy is as follows: all patients with distal DVT (asymptomatic and symptomatic) are given graduated compression stockings and early ambulation. We use anticoagulant therapy to treat asymptomatic distal DVT greater than 10 cm in length, or more proximal ones that are near the confluence of the venous trifurcation that forms the popliteal vein. Those patients with asymptomatic thrombi of 5–10 cm and with ongoing risk factors for propagation, for example immobilization or malignancy, generally receive treatment. We generally do not anticoagulate asymptomatic soleal vein and other small isolated distal DVT. We empirically watch untreated patients more closely, with repeat compression ultrasound scanning, and even continue anticoagulant thromboprophylaxis for varying lengths of time.

There are some subjects that divide the medical, surgical and thrombosis specialists to a great degree and the clinical significance and management of isolated distal deep-vein thrombosis (DVT) is definitely one of them. To cast some light on this controversy, we undertook a search of PubMed and Medline for articles dealing with 'distal', 'calf vein', 'deep vein thrombosis' and 'DVT' and then hand-searched the references for relevant articles that were cited.

Before we even consider the debate about treatment, we must consider the natural history, epidemiology and decision to commence investigations that would diagnose isolated distal DVT. There is great debate over the degree of extensiveness of an ultrasound examination of the lower limb. Most centers offer only proximal vein compression ultrasound scanning (CUS). Some experts advocate that only proximal examination is necessary and is sufficient, and others recommend examining both proximal and distal veins.

On the subject of treatment, one camp says it is unnecessary to treat such patients, while the other says the failure to treat puts patients at risk of life-threatening complications, and not treating isolated distal DVT is like playing 'Russian roulette' with your patients.

Some say only symptomatic distal DVT need treatment, and others say both symptomatic and asymptomatic distal DVT should be treated. Another view is that the clot size and patient characteristics are important. As usual, the correct approach is probably somewhere in between all these opinions.

Epidemiological (observational) studies examining the natural history of isolated distal DVT may be useful for determining the prognosis, and therefore help us plan therapeutic intervention studies in settings where they are most needed. However, epidemiological studies on their own can only give an indication for the necessity for treatment, and they cannot guide the type of therapy or whether it would be effective. Epidemiological studies combined with data from clinical trials provide much more information on likely outcomes and treatment effects. We have used both to give our opinion on this matter. The distinction between the epidemiology and treatment of symptomatic and asymptomatic venous thromboembolic disease is important, as the natural histories, although linked, are different. Therefore, we have considered symptomatic and asymptomatic isolated distal DVT separately.

Epidemiology of distal deep-vein thrombosis

Little is known about the natural history and long-term sequelae of isolated distal thrombosis, such as thrombus propagation, post-thrombotic syndrome, pulmonary embolism (PE) and resultant mortality. Distal thrombosis is usually non-obstructive and causes very little in the way of venous or perivenous inflammation and, therefore, the majority of cases remain asymptomatic [1].

Distal DVT is a very common complication, particularly after joint arthroplasty, and can occur in 41% of non-anticoagulated patients after total

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knee replacement (TKR) based on venography [2]. However, in this setting, the prevalence of DVT varies depending on the diagnostic method, as shown in a recent study [3]. It compared venography and ultrasound post-TKR and detected frequencies of 58 and 42%, respectively. In the postoperative setting, spontaneous lysis of calf thrombi occurs within 3 months in 72–88% of patients [4,5]. Another study of 48 patients post-TKR showed that DVT in the calf disappear spontaneously with time. None of these 48 patients developed a recurrent DVT, proximal propagation or embolization [6]. Based on natural history studies, distal DVT of less than 5 cm rarely propagate [7]. Propagation occurs in approximately 16% (8–23%) of untreated patients [7–9], with an overall recurrence rate of 10.3% in 2 years [10]. However, mortality rates after isolated distal DVT are thought to be low, and are quoted as between 0.1 and 0.2% [11,12]. Post-thrombotic syndrome and recurrences can occur in a considerable proportion of patients, approximately 30 and 13%, respectively; however, those complications are underestimated and undervalued in clinical practice [13,14]. The post-thrombotic sequelae of distal DVT has been described following the diagnosis in obstetric–gynecological, general surgical and medical clinics [15].

Etiology

Idiopathic and secondary isolated distal DVT occur in the community and following medical and surgical admissions [16–19]. Most DVT start in the calf, as evidenced by postoperative leg scanning [7]. A large proportion (perhaps half) of DVT associated with surgery start intraoperatively; many resolve spontaneously, approximately half within 72 h [7,8,20]. The risk of progression of postoperative venous thromboembolism (VTE) is greater when there are continuing risk factors for thrombosis (e.g., immobilization) and when the initial thrombus is large [7,20]. The risk of VTE differs with type of surgery: major orthopedic surgery is associated with approximately twice the risk of VTE associated with major general surgery [17,21]. Isolated calf DVT rarely cause leg symptoms (80% of symptomatic DVT involve the proximal veins) and rarely cause clinically important PE [7,22].

Proximal and distal DVT are found in association with all the well-recognized risk factors. However, a number of studies have shown that the relative frequency of risk factors for distal DVT is different to those for proximal DVT. Distal DVT have been associated with immobilization, recent surgery (depending on type, but particularly orthopedic and abdominal surgery) and trauma. Distal DVT most commonly follow TKR. Factor V Leiden is associated with more distal location of DVT of the leg [23]. Bilateral distal DVT have been associated with cancer [24]. Proximal DVT have been associated with cancer, a previous history of VTE and estrogen use [25].

Bilateral distal deep-vein thrombosis

The epidemiology of DVT diagnosed by routine bilateral proximal and distal ultrasonography has shown a prognostic impact of bilateral distal DVT over 2 years. One study found that bilateral distal DVT have worse prognosis than unilateral distal DVT [24]. An interesting finding of this study was that bilateral distal disease had a worse prognosis (for thrombosis recurrence, cancer and death) than unilateral distal disease, and that the bilateral distal disease group had a similar poor prognosis to proximal disease.

From a clinical perspective, this makes good sense. Bilateral disease makes a systemic etiology more likely, and both inherited and acquired thrombophilia may be associated with higher recurrence rates, cancer and underlying medical conditions, all of which are associated with increased mortality. In this study, cancer rates (26 vs 17%), age and underlying medical disorders (11.6 vs 6.1%) and recent immobility (40 vs 31%) were higher and more common in those with bilateral distal disease than those with unilateral distal disease. The association with cancer and bilateral thromboses has been described in other studies. The findings of increased mortality and recurrence rates make sense in view of the disease associations. Furthermore, the probability that calf DVT will extend to involve the proximal veins and subsequently cause PE increases with the severity of the initiating prothrombotic stimulus [12].

Association between isolated distal deep-vein thrombosis & pulmonary embolism

A number of epidemiological studies have shown that distal DVT infrequently cause clinically important PE [7,22]. This could be for a number of reasons apart from a lack of association. Epidemiological studies of PE are notoriously inaccurate due to the misdiagnosis of this condition. Many studies have shown that over 60% of all PE cases are misdiagnosed prior to death [26].

A recent large observational study using computed tomography pulmonary angiography (CTPA) for PE diagnosis in patients presenting

with symptoms of PE, combined with computed tomography (CT) venography, showed that distal DVT are common, with nearly half the patients (48%, 125/259) with DVT having distal thrombi. Isolated distal DVT without evidence of PE on CTPA occurred in 12% (38/329) of patients presenting with symptoms of PE who had VTE [25]. This is of significance when one considers epidemiological studies that fail to show an association between distal DVT and PE.

Diagnosis of isolated distal deep-vein thrombosis

Firstly, there is debate as to whether to undertake diagnostic testing for distal DVT. Before the use of CUS, venography was used as the standard diagnostic tool. Venography routinely examined distal and proximal veins at the same time, unlike CUS. A recent letter that reviewed this subject has argued against examining the distal veins [27]. The arguments for and against investigating only the proximal veins of the lower limb with CUS, and those arguments for undertaking 'complete' CUS of the proximal and distal veins, are delineated below.

CUS investigation of only the proximal veins of the lower limb

Experts continue to argue about the correct extent of a lower-limb CUS. The question centers around whether or not to include distal (calf) veins in the diagnostic procedure. Management studies show that in the 3 months following a negative CUS of the proximal veins, the frequency of diagnosed VTE is approximately 1% in series using serial CUS (CUS repeated after 1 week in patients with an initially negative CUS) [28–31] and approximately 2% in the study that examined a single CUS [32]. This is similar to the 3-month thromboembolic risk in patients with clinically suspected DVT who had a negative venogram, which was found to be as high as 1.9% (95% CI: 0.4–5.4%) [33]. Some argue that this low rate of clinical recurrence (1–2%) is acceptable and, therefore, we do not need to look any further; that is to say, further examination involving the distal veins is unnecessary. However, this view does not take into account undiagnosed and misdiagnosed disease and its associated morbidity and mortality [26].

CUS investigation of both proximal & distal veins of the lower limb

Other experts feel that further improvement is worthwhile and support more extensive investigation. Three large studies [34–36] concluded that complete CUS of the lower-limb deep-vein system without any follow-up CUS was safe and effective in managing patients with clinically suspected DVT. In the 3 months following a negative CUS of the proximal and distal veins, the frequency of diagnosed VTE is around 0.5%. This reduction of approximately 1.5% is impressive in relative terms (a 75% relative risk reduction). Following the diagnosis of any symptomatic isolated distal DVT, treatment similar to that used for proximal DVT is recommended by the American College of Chest Physicians (ACCP). The protagonists for 'complete' CUS argue that the main advantage of undertaking a complete study is that it diagnoses these distal DVT that require treatment. The other advantage relates to the fact that 75% of patients presenting with DVT have other diagnoses, such as cellulitis, post-thrombotic syndrome, ruptured Baker's cyst, superficial thrombophlebitis, varicose veins, trauma including muscle strain/tear and hematoma, gout, congestive cardiac failure and lymphangitis. More detailed and distal ultrasound will help diagnose the first six of these nine common differential diagnoses.

However, the advantages of diagnosis and treatment of these extra distal DVT must be weighed against a number of factors. One randomized study did not show an advantage for complete scanning when compared with proximal scanning [37]. The absolute clinical advantage of reducing the 3-month thromboembolic risk is small, because the risk of 2% is already low. There is a risk of a false-positive finding and subsequent unnecessary anticoagulant treatment, particularly as 31–56% of the DVTs diagnosed in recent series using complete examination of the lower-limb veins were distal. In addition, the examination protocols that include a study of the distal veins are quite cumbersome and require more specialized skills. Finally, the cost of investigation and time consumption need to be considered.

Bilateral CUS investigation of both proximal & distal veins

In a few centers, routine bilateral complete CUS is performed in patients presenting with symptomatic DVT and in some cases of symptomatic PE. This practice is not established, and there is no evidence of improved outcomes or related safety data. The risk of false-positive examinations and the potential cost benefit are unknown. However, the thorough application of complete bilateral lower-limb ultrasonography

may help us in a number of areas [24]. Firstly, knowing the prognosis of unilateral and bilateral thrombotic disease allows us to make more informed decisions in our empirical practice. Bilateral distal disease should be taken more seriously than unilateral disease, and the recognition of this helps add to the available evidence and support future empirical decisions, such as the length of secondary prophylaxis. Secondly, bilateral disease should help us consider the contribution of associated risks, such as cancer and medical disorders, to VTE and lead to further investigation. Thirdly, in an environment of resource rationing, the choice of appropriate patients to investigate with costly tests for underlying causes of VTE, such as cancer, can be guided not just by age, but also by the topography of the venous disease [38].

Symptomatic isolated distal deep-vein thrombosis

Natural history

Symptomatic isolated distal DVT are those with symptoms of pain, swelling and discoloration and signs of erythema, tenderness, swelling, pitting edema, superficial vein dilation and temperature change. What do the natural history and clinical trials tell us if we do not treat symptomatic distal DVT? To answer this, we have to extrapolate and interpolate from a number of studies.

The natural history shows that the risk of proximal extension is 21–36% [39,40]. Proximal vein thrombosis results in embolization (PE) in 50% of patients (8–18% of all distal DVT) [41,42]. Half of these PE cases will be symptomatic PE (i.e., 4–9% of all distal DVT will result in symptomatic PE) [12,43]. If left untreated, 26% (1.5% of the total distal DVT) will have symptomatic non-fatal PE recurrence and 26% (1.5% of the total) will be fatal PE [44]. In other words, if you follow 100 untreated symptomatic distal DVT cases, the natural history indicates that 1.5 will have a nonfatal symptomatic recurrence and 1.5 will have a fatal PE.

Treatment

The management of symptomatic distal venous thrombosis has been clearly defined by the ACCP recommendations on Antithrombotic Therapy for Venous Thromboembolic Disease. These recommendations apply equally to patients with proximal vein thrombosis, and to patients with symptomatic DVT confined to the calf veins [45]. Patients with objectively confirmed DVT should have initial short-term treatment with subcutaneous (sc.) low-molecular-weight heparin (LMWH) or intravenous (i.v.) unfractionated heparin (UFH) or sc. UFH. For secondary prophylaxis, patients with acute proximal or distal calf DVT require long-term anticoagulant treatment to prevent a high frequency (15–50%) of symptomatic extension of thrombosis and/or recurrent venous thromboembolic events [39,43,46]. The treatment dosages and length of treatment recommended for symptomatic distal DVT are the same as those for proximal DVT.

Asymptomatic isolated distal deep-vein thrombosis

The management of asymptomatic DVT is far from clear, is usually based on empirical therapy and remains controversial. None of us could ignore an asymptomatic proximal thrombosis diagnosed incidentally or following investigation in a clinical trial that involved screening. However, how should a small or even large asymptomatic distal DVT be managed? Do we need to follow these patients closely or offer treatment? Does the epidemiology of VTE allow us to make more informed decisions about empirical management?

The natural history shows that asymptomatic isolated calf vein thrombosis can occur in up to 30% of hospitalized patients, as demonstrated by radioactive-labeled fibrinogen scanning and by venography [7,17]. The risk of proximal extension is 16–23% [7,8]. Proximal vein thrombosis results in embolization (PE) in 50% of patients (8–11% of all distal DVT) [7,41]. Half of these PE will be symptomatic PE (i.e., 4–5% of all distal DVT will result in symptomatic PE) [7]. If left untreated, 26% (1.0% of the total distal DVT) will have symptomatic non-fatal PE recurrence and 26% (1.0% of the total) will be fatal PE [44]. In other words, if you follow 100 untreated asymptomatic distal DVT cases, the natural history indicates that one will have a non-fatal symptomatic recurrence and one will have a fatal PE.

A conservative aspect of this calculation is that it does not take into account the morbidity and mortality from asymptomatic proximal disease or asymptomatic PE, both of which have been implicated as a major cause of morbidity [47] and resultant mortality from undiagnosed or sudden death [26].

A recent study of 359 consecutive patients undergoing TKR found 160 cases of distal DVT at routine venography 5–7 days postoperatively [48]. Of the 160, 38 patients had isolated muscular DVT, including gastrocnemius and soleus DVT. The outcome of those with isolated distal muscular vein DVT was compared to those with other

DVT, and comparable rates of clinical symptoms, late DVT, thrombus propagation and PE were found. The authors concluded that the clinical significance of isolated muscular DVT is comparable with that of the major leg veins and other distal DVT. Isolated muscular DVT in the calf is considered a significant clinical entity and should be treated accordingly.

The probability of a thrombus to propagate involving proximal veins is increased in patients with bilateral distal DVT, and with the severity of the initiating prothrombotic stimulus [49].

Treatment

The management of asymptomatic DVT is an area where data are lacking. There has been no guidance from the ACCP recommendations on Antithrombotic Therapy for Venous Thromboembolic Disease. Management options range from no therapy and no monitoring, to monitoring for extension, to therapies such as ambulation, graduated compression stockings, continuation of thromboprophylaxis, short courses (approximately 3–6 weeks) of therapeutic LMWH, and even a full course of anticoagulation.

Points in favor of treating calf vein thrombosis

The following are points that favor the treatment of calf vein thrombosis:

- Pulmonary emboli from isolated distal DVT have been considered to be small and nonfatal. Nevertheless, in necropsy studies, calf DVT have been found to be the source of fatal pulmonary emboli in 13–25% of cases;
- Proximal extension of untreated isolated distal DVT occurs in 8–23% of patients, usually within 10–20 days of symptom onset;
- In untreated patients, distal DVT will recur in 30% within 1 year;
- Approximately 30% of patients with symptomatic distal DVT develop chronic venous insufficiency. It is unknown whether anticoagulant treatment of distal DVT will prevent this complication;
- Extrapolation of data indicates that potentially 1.5% of symptomatic and 1% of asymptomatic distal DVT may have non-fatal PE and a similar proportion have fatal PE.

Points in favor of not treating calf vein thrombosis

The following are points that do not favor the treatment of calf vein thrombosis:

- Most isolated distal DVT are asymptomatic and will often undergo spontaneous lysis;
- Isolated distal DVT have been shown to propagate proximally during heparin treatment. No controlled trials for propagation rate have been carried out;
- Only 0–10% of asymptomatic (silent) distal DVT have been found to cause lung emboli;
- Only approximately 50% of pulmonary emboli are symptomatic, and prospective studies have shown that the incidence of fatal pulmonary emboli with distal DVT is very low;
- Chronic venous insufficiency seldom occurs in patients with 'silent calf' DVT.

Triggers to treat isolated distal DVT

- Symptomatic disease
- Bilateral disease
- Multiple thrombi (more than a single clot)
- Extensive thrombi, more likely to propagate (more than 5 cm in length)
- More proximal distal thrombi (near to the trifurcation)
- Associated with an inherited or acquired thrombophilia
- Associated with a medical condition that increases the risk of thrombosis (e.g., immobility, cancer and chronic medical conditions)
- Past history of symptomatic VTE
- High clinical probability of VTE (Wells or Geneva score)
- Low risk of bleeding

Conclusion

In summary, those who advocate therapy say that distal DVT are like a 'wolf in sheep's clothing', and not treating them is negligent. Those who advocate not treating claim there is not enough evidence to do so, and that treatment may not confer any major benefit and has risks related to anticoagulation.

Based on the above findings, the authors would recommend treating isolated symptomatic distal DVT the same way as proximal lower-limb DVT. There is no guidance for the treatment of asymptomatic isolated distal DVT; however, the triggers above could be used to guide therapy. We feel that a reasonably low threshold should be used to treat asymptomatic isolated distal DVT, as it is likely that their impact is grossly underestimated for four main reasons. Firstly, these DVT are usually not recognized outside of clinical trials, and hence their

consequences are not attributed. Secondly, asymptomatic disease often precedes nonfatal and fatal PE. Thirdly, treated disease has relatively low death rates. Finally, the majority of fatal PE are not diagnosed (except at autopsy, which is very infrequent now), and hence any relationship to the common related finding of distal DVT at autopsy is not recognized.

However, in all situations, common sense and experience must prevail. Our policy is as follows, but we are not sure where this lies in relation to common sense and experience prevailing. All patients with distal DVT (asymptomatic and symptomatic) are given graduated compression stockings and early ambulation. We use anticoagulant therapy to treat symptomatic distal DVT, and asymptomatic distal DVT greater than 10 cm in length, or more proximal ones that are near the confluence of the venous trifurcation that forms the popliteal vein. Those patients with asymptomatic thrombi of 5–10 cm and with triggers such as ongoing risk factors for propagation (e.g., immobilization or malignancy) generally receive treatment. We generally do not anticoagulate asymptomatic soleal vein and other small isolated distal DVT. We are guilty of using a number of other therapies with no evidence base, including following untreated patients more closely, with repeat CUS, and even continuing anticoagulant thromboprophylaxis for varying lengths of time. In the end it comes down to the clinical situation, the liberal interpretation of the literature, and common sense.

Future perspective

It is likely that diagnosis will improve with the availability of magnetic resonance venography, and treatments will become safer with the introduction of factor-specific coagulation inhibitors. We will then be better able to follow patients who do not receive therapy and will have a lower threshold to treat patients with safe and effective oral therapies that will not require monitoring.

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• **Natural history of PE leading to pulmonary hypertension.**

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