PANEL DISCUSSION

Perspectives on Acute Deep Vein Thrombosis in 2021

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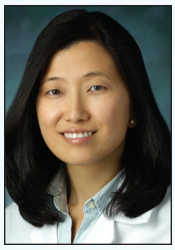

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Key developments in deep vein thrombosis (DVT) in recent years include the publications of the landmark ATTRACT trial and the CAVENT trial. In addition, several dedicated venous stents have been approved, two of which were recently recalled by their manufacturers. This expert panel seeks to explore the practical ramifications of recent trial data and changes in the technology landscape.

Patients with acute DVT may not be offered endovascular intervention initially, but often present 7 to 14 days after their initial event with continued pain and swelling seeking relief. In addition, patients who are candidates for intervention rarely present with an isolated iliac-common femoral vein and more often have involvement of the femoral and popliteal veins. Given the results of these recent trials with a primary outcome of prevention of postthrombotic syndrome (PTS), which patients are ideally suited for endovascular intervention?

Dr. Vedantham: The routine use of endovascular thrombolysis for proximal DVT does not exert a large effect in preventing PTS. It does increase major bleeding (1.4% absolute increase in ATTRACT) and it is not cost-effective (in ATTRACT, $220,041 per quality-adjusted life-year gained). Therefore, it should not be routinely used for "all comers" with proximal DVT.

However, patients presenting with acute iliofemoral DVT appear likely to benefit. The definition of "iliofemoral DVT" used in ATTRACT was the one endorsed by the Society of Interventional Radiology and the American Heart Association—DVT involvement of the iliac and/or common femoral vein with or without additional (eg, femoral, popliteal) veins. Using that definition, ATTRACT found that the use of pharmacomechanical catheter-directed thrombolysis (PCDT) in iliofemoral DVT resulted in greater resolution of leg pain and swelling within 30 days, a reduction in the point prevalence of PTS at 6 months (but not later), and a reduction in PTS severity during 2 years, compared with no PCDT. PCDT led to a sizable quality of life (QOL) benefit for the first 6 months; beyond that, the QOL benefit was smaller.

In the overall trial, patients aged > 65 years experienced reduced efficacy (ie, more PTS) with PCDT and worse safety in nearly all of the observed major bleeds.

Therefore, select younger, highly symptomatic patients with acute iliofemoral DVT and low expected bleeding risk can be reasonably considered for endovascular thrombolysis in addition to anticoagulation. This consensus is now supported by medical (2020 American Society of Hematology) and surgical (2021 European Society for Vascular Surgery) society guidelines.[1,2]

Dr. Razavi: Patient selection for catheter-based therapies in the setting of acute DVT (thrombectomy, thrombolysis, recanalization/stent placement, etc) should be based on patient symptoms. Although proximal clot location (such as iliofemoral) is a strong determinant of the risk of PTS, we do offer intervention in patients with isolated femoropopliteal DVT who are severely symptomatic. In general, ambulatory patients with symptomatic acute iliofemoral DVT who have a reasonable life expectancy are the best candidates for catheter-based therapies. The decision to intervene in symptomatic patients with significant frailty or with limited life expectancy is a complex one. The risks of intervention, degree of symptoms, and symptom improvement on anticoagulation alone are the main decision-making drivers in such patients in our practice.

Dr. Kiguchi: PTS is often underrecognized, and intervention at the time of diagnosis can reduce the risk of PTS or decrease its severity in select patients, as shown in the CAVENT and ATTRACT trials, respectively. Our department strives to offer same-day office and vascular lab appointments to ensure timely initiation of treatment, whether medical or surgical, to our patients to ensure an optimal outcome. In our patient population, any patient with adequate life expectancy with acute iliofemoral DVT is offered intervention to decrease clot burden, and thus, the severity of PTS.

What is the ideal timing of these interventions to assess the effectiveness of anticoagulation therapy alone and subacute presentation of many of these patients?

Dr. Kiguchi: Early intervention is important, as true thrombus age is often difficult to determine from clinical history alone. If a patient is newly diagnosed with an iliofemoral DVT and is an appropriate patient for intervention to decrease clot burden (appropriate life expectancy, low bleeding risk, benefit from decreased severity of PTS, etc), intervention is offered in addition to anticoagulation. Lytic-based therapeutic interventions are often most effective within the first 2 to 3 weeks of DVT occurrence. Mechanical thrombectomy can be more effective for older, newly diagnosed DVT.

Dr. Razavi: Ideally, the sooner the intervention, the better the results. Although not examined for statistical significance, patients within 7 days of symptom onset appeared to do better in the ATTRACT trial as compared to those with 7 to 14 days of symptoms. In our practice, we tend not to wait for symptom improvement in patients with iliofemoral involvement but do so in those with isolated femoropopliteal DVT. Although 14 days is a reasonable cutoff for the definition of acute clot, in practice the efficacy of clot removal versus time of symptom onset likely follows a logarithmic curve. Hence, we do offer catheter-based therapy to symptomatic patients with iliofemoral DVT beyond 2 weeks.

It is important to note that there are no data to show that thrombectomy alone is effective in "subacute" or

chronic thrombosis. Although in the ACCESS-PTS registry there was a signal for symptom reduction, their observations should be considered preliminary since it was a single-arm study with a small number of patients. ACCESS-PTS was a multicenter, single-arm, prospective study of venoplasty and ultrasound-accelerated thrombolysis in patients with chronic DVT and PTS (Villalta score ≥ 8).

Dr. Lichtenberg: Many patients are referred for treatment at a late stage, on average 7 to 10 days after the first symptoms of DVT. Typical reasons for this are misdiagnosis and ignorance of the fact that iliofemoral DVTs can be treated safely. Patients are usually quite compromised in this "subacute" phase. In these scenarios, the interventionalist is confronted with a large quantity of thrombotic material adherent to the wall. This has an impact on technical and procedural success rates; not every existing technique is able to remove organized thrombotic material. Therefore, I always recommend treatment at a very early stage. Enhancing awareness is crucial for this purpose.

Please comment on the necessity and placement of an inferior vena cava (IVC) filter prior to CDT.

Dr. Kiguchi: IVC filter use as an adjunct to CDT remains controversial and selective. Filters should not be used routinely, as CDT and pharmacomechanical and mechanical thrombectomy haven not been shown to increase the rate of pulmonary embolism (PE). Filters may be used in patients with established large symptomatic PE and/or evidence of right heart strain if there is significant concern for a "second hit" intolerance. Filters are important in cases of high-risk thrombus such as visualized mobile or tethered proximal thrombus. If an IVC filter is used, there should be clear clinical pathway for removal.

Dr. Lichtenberg: The placement of an IVC filter is no longer advisable. As we now have efficient and safe mechanical thrombectomy systems, CDT is not performed at my institution. Mechanical thrombectomy devices usually do not need a filter protection because they permit very efficient thrombus extraction. If a protective device is needed in specific circumstances (IVC, floating thrombus), we use a retrievable IVC filter.

Many interventionalists still prefer to perform thrombolysis/thrombectomy and venoplasty without placement of a venous stent during initial treatment and reassess for stent placement later. What do recent studies and experience indicate about the timing of venous stent placement?

Dr. Vedantham: There are no comparative studies with which to inform decisions on venous stent placement. Observational studies, shared anecdotes, and personal

experience have convinced me that residual stenosis on venography after CDT is associated with a high risk of early rethrombosis. When I have reintervened on patients with acute rethrombosis, often I have discovered residual obstructive lesions (ie, lesions not stented, or incomplete coverage of lesions with stents), so I use a relatively low threshold to place iliac vein stents in that situation.

Dr. Lichtenberg: An iliofemoral DVT usually has an underlying cause outside the vein (such as tumor compression or May-Thurner syndrome) or within the iliofemoral venous system itself. Thrombectomy or thrombolysis relieves the immediate symptoms. Patients feel better directly after effective thrombus removal. However, the treatment is incomplete without final venous stenting because the underlying cause is not remedied. During the procedure, the interventionalist needs to decide whether inflow is stable and sufficient after thrombectomy, as this is a prerequisite for final stenting. Stenting should be performed from one healthy vein to another. In the absence of sufficient inflow, stenting should be postponed to a later time during follow-up. I refer to this staged procedure as "stenting when possible."

Do intravascular ultrasound (IVUS) findings affect this decision?

Dr. Lichtenberg: To define sufficient inflow, I usually employ IVUS and Doppler to assess morphology and flow. Based on our recent analysis, our threshold for stenting is at least a 30 cm/second Doppler flow from the deep femoral or femoral vein into the common femoral vein.

Dr. Kiguchi: IVUS is imperative in every venography procedure.[3] Venograms alone may be falsely misleading in predicting residual clot burden, and thus, any residual clot seen on IVUS should be retreated with pharmacomechanical thrombectomy or additional days of lysis. Residual stenosis > 50% should be retreated with stent at the time of initial treatment to ensure no rethrombosis.[4]

Dr. Razavi: IVUS facilitates many aspects of venous stenting and interventions, but its role in the decision to stage the procedures has not been rigorously investigated. Anecdotal experience from our center and others suggest that beyond the delineation of stenoses, IVUS may identify diseased venous segments better than single view venography.

Are there any nuances in women of childbearing age?

Dr. Kiguchi: Limited evidence suggests pregnancy affects the outcomes of iliocaval stents placed after lysis or DVT or May-Thurner syndrome, according to a few published studies, and thus, stenting is not contraindicated in women of reproductive age, but I suggest close clinical and ultrasound follow-up during and after pregnancy.[5,6]

Dr. Vedantham: The literature suggests that pregnancy-associated stent fractures are infrequent and often asymptomatic, with consequences usually limited to stent stenosis or rethrombosis. Hence, childbearing capacity does not generally deter me from placing stents to manage venous obstruction when it is present. For patients undergoing CDT, the potential for stent placement and the potential risks (known and unknown) should be discussed with the patient beforehand.

Dr. Razavi: The evidence is weak so far but suggests a protective role for the use of stents to relieve venous obstructions. We do advise all our patients as such and do not hesitate to use stents in pelvic veins when necessary.

With the recent recall of two venous stents for migration and placement issues (Vici [Boston Scientific Corporation] and Venovo [BD Interventional], respectively), please comment on potential changes to the approval and postmarketing device surveillance process?

Dr. Vedantham: The FDA continues to review the information available on these devices. In general, I believe that long-term data collection should be mandated during the early years after approval of permanent (and many nonpermanent) device implants. However, FDA mandates are only one part of the solution here. Far more importantly, it is crucial for the culture among endovascular physicians to evolve to where we report every device malfunction into the MAUDE database quickly, so that we become aware of such issues as soon as possible and act to mitigate risk to our patients. We should be objective in assessing possible device causality, and we should not "pull punches" in transparently sharing device-related problems we encounter with each other.

Dr. Razavi: It should be clarified that both venous stent recalls were completely voluntary by the manufacturers and not FDA mandated. Such recalls and needs for improvements are not rare and are an important reason why postapproval studies are necessary. To my knowledge, neither platform had any issues during their pivotal studies. Problems were identified when a larger number of stents were deployed by a wider group of practitioners. This confirms the need for continued postmarket surveillance.

Dr. Lichtenberg: At this stage, our knowledge about the recent recall is incomplete. We have no official statements that would permit definitive conclusions that may have an impact on the approval process and the device surveillance process. Venous recanalization has been a safe and effective treatment for millions of patients with acute DVT and PTS. Any hasty conclusion may compromise trust in this therapy, which would be undesirable. The industry, as well as regulatory authorities and physicians, are called upon to achieve complete clarification. With the new medical device regulation in Europe, I believe we now have a very efficient and strong approval system.

Postprocedure care including prescription of anticoagulation and antiplatelet agents as well as venous stent patency surveillance often falls to the vascular medicine specialist. It is my clinical observation that immediately postprocedure, patients often have significant recurrent thrombosis in treated veins prior to or just after the sheath being pulled. Can you comment on the timing on the first dose of anticoagulation postprocedure?

Dr. Razavi: Recurrent thrombosis in the immediate postprocedural period is becoming more common. There are several reasons for this trend as outlined below.

1. With the more widespread use of PMT devices that need large-bore access (≥ 10 F) in the popliteal vein, postprocedural rethrombosis should be expected, especially in the popliteal and femoropopliteal veins. Venous punctures usually heal by a process of layered thrombosis, and when the ratio of venous puncture size to its diameter exceeds a certain limit, total access site thrombosis occurs at a higher frequency. Furthermore, it is unknown whether an aggressive scraping of vessel walls in the already inflamed veins has an additive effect in promoting rethrombosis.
2. To reduce the risk of bleeding after placement of a large-bore access, many practitioners delay the onset of anticoagulation. This increases the risk of rethrombosis in freshly thrombectomized and inflamed venous segments.
3. Finally, pharmacomechanical thrombectomy devices do not effectively reestablish inflow if the access site (popliteal vein) is thrombosed. Poor popliteal inflow in turn increases the risk of femoropopliteal rethrombosis.

Given the above, I use the following guidelines in my practice: (1) minimize venous access sheath size to the extent possible; (2) use adjunctive CDT or thrombolytics (if not contraindicated) in patients with access site thrombosis; (3) resume full therapeutic anticoagulation after the procedure, usually within 30 minutes—my preference is to use heparin or heparinoids in the immediate postprocedure period; and (4) apply sequential compression devices to the ipsilateral calf immediately after the sheath is pulled. It may be discontinued as soon as the patient is ambulatory.

Dr. Vedantham: For patients on low-molecular-weight heparin (LMWH), we simply continue it before, during, and after the CDT/PCDT procedure, without interruption. For patients on unfractionated heparin, we will sometimes briefly stop the infusion to enable the sheath to be pulled, but we restart anticoagulation within 1 hour after hemostasis. We do not allow a prolonged "off" period because postintervened patients are prone to reclot.

What is the current recommendation for anticoagulation and antiplatelet treatment after intervention ± venous stenting, dose and duration?

Dr. Razavi: After interventions for acute DVT, we prefer therapeutic LMWH for 3 to 4 weeks before switching to oral anticoagulants. Duration of anticoagulation is per American Society of Hematology guidelines for the management of patients with DVT.[1]

After venous stent placement, we use the same protocol as was used in the VIRTUS trial. In patients with nonthrombotic obstruction, we prescribe antiplatelets only unless there are risk factors for DVT such as history of malignancy. For patients with chronic postthrombotic obstruction or history of DVT, we use therapeutic anticoagulation for a minimum of 3 to 6 months. It is then discontinued if the stented segment is patent and there is no history of thrombophilia. Anticoagulation may be extended if there is coexistent femoropopliteal disease with suboptimal inflow.

We have observed asymptomatic partial stent thrombosis shortly after discontinuation of anticoagulation in a few patients. Resumption of anticoagulation for an additional 3 months has been sufficient so far in such patients.

Dr. Vedantham: In general, patients who undergo CDT or who receive stents during the management of acute DVT (ie, after lysis) or chronic DVT (treatment of established PTS) should receive anticoagulant therapy for at least 3 to 6 months. Stent recipients may also receive an antiplatelet drug. Patients stented for symptomatic nonthrombotic iliac vein lesions (ie, no DVT history) seem to have very high stent patencies and can usually receive antiplatelet therapy without anticoagulation.

However, current recommendations are not based on rigorous studies in endovascular therapy recipients but are extrapolated from medical DVT treatment guidelines in nonintervened patients. This is problematic, because patients selected/referred for endovascular therapy may represent a highly prothrombotic subgroup of patients, and catheter manipulations can contribute to venous injury that increases the predilection to rethrombose.

Taking stock of ATTRACT, although PCDT was statistically significantly associated with more bleeding, the absolute increase in major bleeds (1.4%) was smaller than expected, and there were no PCDT-related fatal or intracranial bleeds. However, the efficacy of PCDT was worse than expected—no effect on PTS prevention—and has been linked to the reformation of thrombus. Specifically, despite venograms showing good thrombus removal, a substantial share of PCDT-treated vein segments were noncompressible at 1 month, and noncompressibility of the common femoral vein correlated with more PTS, more moderate-or-severe PTS, and worse venous QOL. Hence, I believe more aggressive antithrombotic regimens are needed and that close attention must be paid to ensuring adequate anticoagulation during the initial postintervention weeks. We also need comparative studies to assess which regimens work best. In our practice, we have evolved towards routinely using LMWH for at least 1 to 3 weeks postintervention prior to transition to oral therapy, but the feasibility of doing so depends on patient-specific factors.

Dr. Lichtenberg: Anticoagulation therapy started prior to the intervention is continued after the intervention, usually for 3 months in nonthrombotic cases, and 6 to 12 months in acute DVT and PTS cases. Over the last few years, I recommend even more prolonged anticoagulation because this seems to have a positive impact on the prevention of restenosis and rethrombosis. When using vitamin K antagonists for anticoagulation, the clinician should aim to achieve a target international normalized ratio of 2.5 to 3.5. When the value drops below minimum, it would be advisable to additionally administer LMWH in a therapeutic dose. New oral anticoagulants are being used to an increasing extent, but we still lack sufficient experience with these agents.

What is the recommended timing of postprocedure vascular ultrasound surveillance to identify restenosis and what degree of stenosis warrants reintervention?

Dr. Vedantham: In our clinical practice, we do not perform routine surveillance ultrasound because we would not be likely to reintervene unless the patient was symptomatic. If this is to be done, then I suggest it should be done 7 to 10 days after the intervention, to enable lysis of recurrent/residual thrombi. Unlike the arterial system, even small degrees of stenosis (eg, 30%-40% narrowing) can limit flow and increase peripheral venous pressure. However, the problem with reintervening for stenosis is that to be beneficial, the improvement in luminal caliber that one gains (which is hard to predict with venous angioplasty) must be large enough to outweigh the prothrombotic effects of angioplasty-mediated endothelial injury. However, if a patient has residual or recurrent symptoms, repeat ultrasound is very helpful in distinguishing the etiology—either by identifying residual/recurrent obstruction, superficial venous reflux, or other causes.

Dr. Lichtenberg: We believe intensive postprocedure surveillance is a significant factor in preventing restenosis and rethrombosis. At our institution, we perform duplex ultrasound investigations at 2 to 4 weeks, 3 to 6 months, and 12 months after the procedure, followed by an annual examination. I believe that a 50% restenosis is associated with a high risk of rethrombosis. If the patient is completely free of symptoms, I usually schedule another analysis after 4 to 6 weeks. If the restenosis has progressed at this time, I recommend urgent reintervention. The same applies to patients with 50% restenosis plus symptoms such as new venous claudication and/or swelling.

Dr. Kiguchi: We perform duplex ultrasound surveillance should be continued at regular intervals (4 weeks, 3 months, 6 months, and then annually). I encourage all patients to present urgently if clinical conditions suddenly worsen. Any patient with > 50% stenosis and/or residual unresolved symptoms should be considered for reintervention. ■

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