PANEL DISCUSSION

Putting Recent DVT Trial Data Into Context and Practice

Experts discuss the main takeaways of key trials in deep venous thrombosis therapy, nuances in their designs and data, whether the results have affected referrals, and more.

WITH RIYAZ BASHIR, MD, FACC, RVT; RABIH CHAER, MD, MSc; RICK DE GRAAF, MD, PhD; MITCHELL J. SILVER, DO, FACC, FSVM; AND BROOKE SPENCER, MD, FSIR

Riyaz Bashir, MD, FACC, RVT
Professor of Medicine
Lewis Katz School of Medicine
Temple University
Director, Vascular and Endovascular Medicine
Temple University Hospital
Philadelphia, Pennsylvania
riyaz.bashir@tuhs.temple.edu
Disclosures: Equity interest in Thrombolex, Inc.

Rabih Chaer, MD, MSc
Professor of Surgery
Division of Vascular Surgery
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania
chaerra@upmc.edu
Disclosures: None.

Rick de Graaf, MD, PhD
Interventional Radiologist
Department of Radiology
Maastricht University Medical Center
Maastricht, the Netherlands
r.de.graaf@mumc.nl
Disclosures: None.

Mitchell J. Silver, DO, FACC, FSVM
OhioHealth Heart & Vascular
Columbus, Ohio
mitch.silver@ohiohealth.com
Disclosures: Consultant to Boston Scientific Corporation, Inari Medical, Cook Medical; board member for/equity in Contego Medical; speaker's bureau for Bristol-Myers Squibb, Pfizer.

Brooke Spencer, MD, FSIR
Medical Director and CEO
Minimally Invasive Procedure Specialists
Highlands Ranch, Colorado
bspencer@mipscenter.com
Disclosures: Consultant for Boston Scientific Corporation, Philips, Gore & Associates; speaker for Boston Scientific Corporation, Philips, Bristol-Myers Squibb.

What are your main take-home points from recent trials such as ATTRACT and CAVA?[1,2]

Dr. Bashir: The take-home message from the ATTRACT trial has been that pharmacomechanical catheter-directed therapy (PCDT) is not effective in reducing postthrombotic syndrome (PTS) in femoropopliteal deep vein thrombosis (DVT); however, there was a consistent reduction in frequency and severity of moderate to severe PTS and

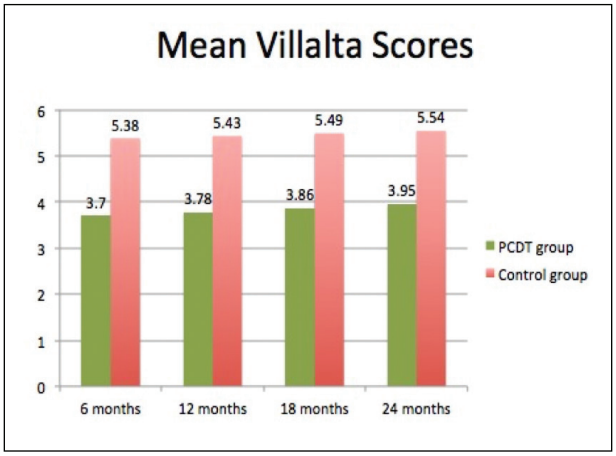

Figure 1. Mean Villalta scores in the ATTRACT study. Moderate or severe PTS: 18% versus 28%; risk ratio, 0.65; 95% confidence interval, 0.45 to 0.94; *P* = .021.

improvement in venous disease–specific quality of life (QOL) in patients with iliofemoral DVT (Figure 1).

Both trials have shown that moderate to severe PTS rates are significantly reduced with catheter-based thrombus removal, particularly when accomplished successfully.

The ATTRACT trial is truly a landmark study, which I believe will lead to better patient and endpoint selection for future trials evaluating the role of PCDT in iliofemoral DVT. I also believe that intravascular ultrasound (IVUS)–guided evaluation of the outflow veins, along with the availability of dedicated venous stents and effective thrombolysis catheters, will further improve the outcomes of PCDT. It has become apparent that optimizing the venous outflow after PCDT is crucial for durable improvement in symptoms and signs of PTS.

Dr. Chaer: The ATTRACT and CAVA trials were essentially negative trials. Across the board, they failed to show a benefit for thrombolysis to prevent PTS in patients with acute iliofemoral DVT. They concluded that adding PCDT to anticoagulation among patients with acute proximal DVT did not result in a lower risk of PTS but did result in a higher risk of major bleeding.

Dr. de Graaf: I can't gather any worthwhile take-home messages from the headlines to be honest. Outdated protocols (ATTRACT was conceived in the early 2000s) and protocol violations (in CAVA, a significant number of patients fell outside the 14-day treatment window) make the primary outcomes hard to digest. We have to look beyond this to find information we can actually benefit from. Next to the obvious—don't treat isolated femoral DVT and stent the underlying cause of the DVT—for me, the most important message is that successful (endovascular) treatment determines clinical success. Regrettably, there are indications in both studies that a relevant number of patients were treated suboptimally. The "open vein hypothesis" has not been falsified, simply because we have no idea if the veins were actually open when treatment was ceased.

Dr. Silver: We must recognize that the field of venous intervention has gained considerable procedural experience and improvements in technology since the start of ATTRACT in 2009 and CAVA in 2010. Importantly, as a vascular community we cannot stand idle and accept the very high rate of PTS in patients with acute proximal DVT from these earlier trials.

Great advances have been made in acute proximal DVT thrombectomy devices that have allowed for more efficient treatment times and minimized the use of adjunctive thrombolytics. In addition, we now know it is essential to incorporate the guidance of IVUS during venous intervention for proximal DVT after the findings of the VIDIO trial.

Both the ATTRACT and CAVA investigators should be praised for the important bodies of work and clinical data these trials have provided and for paving the way for more contemporary trials of venous intervention.

Dr. Spencer: The key takeaway is that treating iliofemoral DVT in young and active patients significantly reduces moderate to severe PTS. These patients are often preselected to us because they are admitted and significantly symptomatic. There is a statistically significant improvement in QOL in the first 30 days.

There was not much hope to show improvement in the femoropopliteal DVTs because posterior tibial access was not required and these patients cannot be successfully treated from the popliteal vein. The jury is still out on this for me. In ATTRACT, 44% of patients with femoropopliteal DVT developed PTS, so this should not be ignored. I perform several chronic femoropopliteal DVT recanalizations weekly and see very symptomatic patients who score low on CEAP (clinical, etiology, anatomy, pathophysiology) classification, Venous Clinical Severity Score (VCSS), and Villalta score. Many of these patients are on chronic narcotics and disability from pain. I think they are not captured in these studies, and many develop worsening symptoms years after the original thrombotic event. We still have a lot to learn about this population, and a patent popliteal vein may be more important than we have previously understood.

I am concerned about reading too much into the data; only 30% of patients were stented, and IVUS was not used much, if at all. Patients with extensive DVT have a high rate of central stenoses that were likely underdiagnosed

and undertreated in this study because it was performed before routine use of IVUS. In addition, by placing patients on anticoagulation for 5 days before intervening, some patients may progress to subacute DVT, which is extremely difficult to treat.

Have these trials changed your approach to iliofemoral DVT management?

Dr. de Graaf: Not really. The only thing I can think of is to use IVUS more, principally in every case. In both studies, residual thrombus load was poorly evaluated. There is absolutely no better way to determine full lumen patency than with IVUS. We know that even small amounts of thrombus may enhance the inflammatory reaction and thereby cause recurrent DVT and/or PTS.

Dr. Silver: Neither the ATTRACT nor CAVA trial findings have changed my venous intervention practice. In general, with sophisticated preprocedural imaging such as CT venography (CTV), the information gained by IVUS during venous intervention, dedicated venous stents, and the safety profile of direct oral anticoagulants, the field of venous intervention has truly evolved since both of these trials. Most importantly, devices are now available that can perform venous thrombectomy without any adjunctive thrombolytic drug, which is truly a real paradigm shift. The long-term results of these pure thrombectomy devices certainly need to be investigated, but for now, the ability to perform proximal DVT intervention without a thrombolytic drug is perhaps a game changer. Of course, we must all be clinicians first and foremost and always take into account the patient's functional status, presence of a reasonable life expectancy, bleeding risk, and available local expertise.

Dr. Spencer: No, I do not treat DVT using these algorithms. I use far less lytic, tenecteplase at 0.25 mg/hour, posterior tibial access, and IVUS, none of which were used in these trials. So, it is hard to extrapolate the treatment approaches used in ATTRACT to my patients.

Dr. Bashir: These results have not changed my approach to iliofemoral DVT, but they have reinforced my belief that we must confirm the patency of outflow veins with IVUS if we do not stent them post-PCDT. Both the ATTRACT and CAVA trials had relatively low rates of iliac vein stenting, presumably because IVUS was used infrequently in these patients.

Both trials have highlighted that we need to improve the efficacy of thrombus removal therapies, which could include the use of better thrombolysis and thrombectomy devices or better thrombolytics. Additionally, we have started to do more PCDT cases via a tibial approach with the aim of restoring patency of the popliteal vein. The majority of PCDT procedures in these trials were performed via a popliteal approach. Unfortunately, this approach leaves a large burden of residual occlusive thrombus in the popliteal vein, thereby leading to below-the-knee signs and symptoms of PTS.

Dr. Chaer: The trials have not changed my approach to iliofemoral DVT management. The design of the ATTRACT trial included patients with acute DVT in the femoropopliteal segments alone as well as those with more proximal iliac thrombosis, in part to ensure completion of patient enrollment in a reasonable amount of time. As a result, the study was powered only to answer the question statistically of whether the entire group, iliofemoral and more distal femoropopliteal DVT combined, experienced significantly improved outcomes with PCDT as compared with anticoagulation alone. This may have diluted and skewed the study in favor of anticoagulation.

Inclusion of femoropopliteal DVTs may have given us the answer that femoropopliteal DVTs should not be lysed, but this had been part of our standard practice. Looking at a subgroup analysis, the data suggest that PCDT may benefit patients with the most proximal DVT involvement, including the iliac vein, given that fewer patients developed moderate to severe PTS. Those are the patients I typically treat in my practice.

What factors help you determine which patients with iliofemoral DVT may benefit most from early thrombus removal strategies?

Dr. Chaer: We typically combine the clinical presentation with the anatomic distribution of the clot and decide on the need for intervention based on the patient's functional status and bleeding risk profile. Healthy patients with good life expectancy and a low risk of bleeding with lytic therapy benefit the most if they have symptomatic iliofemoral DVT. I offer early thrombus removal strategies for those patients but inform them that it is not endorsed by societal guidelines as the standard of care.

Dr. Spencer: If there is an underlying anatomic obstruction, correction is important to reduce recurrence and persistent symptoms. This requires intervention or CTV for diagnosis, although CTV may underdiagnose these lesions. Young patients with unprovoked DVT are especially important to treat because DVT often recurs and symptoms worsen with each subsequent thrombotic event.

Dr. de Graaf: Location and thrombus age. Location is obvious; we agree that only iliofemoral DVT should

be treated. Thrombus age is a little more difficult. Clinical evaluation and the duration of symptoms are not accurate. In my experience, symptoms may have lasted a couple of days, and still the thrombus constitution tells me it is evidently older. Full thrombus removal is hampered by older thrombus. Magnetic resonance techniques are very accurate to identify the different stages of thrombus aging and may predict treatment success.

Dr. Silver: Certainly, as both ATTRACT and CAVA demonstrated, patients with more severe symptoms at presentation seem to have the most relative benefit. However, it is very difficult to treat this population of patients in a "one-size-fits-all" fashion. It is important to look at each patient's individual situation, which would include thrombus burden, age, both acute and long-term bleeding risk, medical comorbidities, and functional capacity. If the initial venous duplex ultrasound demonstrates a large thrombus burden involving both the common and external iliac vein that is "obstructive to flow," recanalization typically will not occur with standard anticoagulation. Some previous treatment algorithms that considered factors such as the duration of symptoms prior to presentation are now changing as the technology changes. After all of these considerations, I have a balanced discussion with the patient and family, reviewing what I perceive to be that individual's risk/benefit equation, and we make a collective decision together.

Dr. Bashir: Patients with the most severe symptoms of pain and thigh swelling despite anticoagulation are most likely to benefit from early thrombus removal. Unfortunately, in randomized trials such as ATTRACT and CAVA, operators hesitated to enroll such patients, thereby biasing the results in favor of anticoagulation alone. Another group of patients that we believe benefit greatly are those who have an occlusive rather than a nonocclusive thrombus.

We need to perform PCDT as soon as possible after the onset of symptoms, because it is significantly more effective when the thrombus is fresh rather than subacute. Therefore, we need to educate the general public about the need to seek prompt medical attention if they notice any symptoms of DVT or pulmonary embolism.

Based on your conversations with patients, which outcomes are the most important in successfully treating their DVT?

Dr. Spencer: Young patients with unprovoked DVT are very likely to have recurrent DVTs and worsening symptoms over time. I suspect that they have the highest degree of anatomic obstruction as well. I think it is critical to perform venography and IVUS on young patients.

Many patients, especially young patients, cannot afford nor do they prefer to have prolonged pain and swelling with activity for a month or more, and when given the option, they almost invariably prefer early symptom resolution even if it requires a procedure. Believe it or not, swelling alone can limit the ability to wear clothes—patients may have to buy two different shoe sizes, and these simple things are the issues patients raise the most (after pain).

Dr. Bashir: The most important outcome from a patient's perspective is the absence of venous claudication and ulcerations. Patients are not able to exercise or play sports because of these symptoms, and they markedly impair their QOL. This leads to weight gain and a sedentary lifestyle. Many patients are also concerned about leg swelling and skin changes such as hyperkeratosis and ulcerations. Another concern is the cosmetic disfigurement related to the development of varicose or reticulate veins. An outcome that is very important for younger populations is recurrent DVT, which can lead to loss of work days. We have seen many patients lose their jobs because of recurrent DVT and PTS.

Dr. de Graaf: In general, patients have no idea about PTS and what it may mean to them in the future. Rapid symptom relief is the most important outcome—no pain, no swelling, and the ability to walk normally again. It's very difficult to convince a patient that we are doing the right thing after 4 hours on the table or 2 days in the intensive care unit, just to prevent pain or ulceration they may develop in 5 to 10 years or perhaps never. That's why smoking cessation, although the smart thing to do, is still so challenging.

Dr. Chaer: The most important outcome in my opinion is symptom relief and improvement in QOL. The ability for patients to regain their functional status, even with incomplete clot resolution, has a tremendous impact on their QOL.

Dr. Silver: Assuming the individualized risk of the procedure is accepted by the patient, most patients desire rapid resolution of pain and swelling, which are typically the most common reasons they present, and a long-term good functional outcome. However, an essential part of treating the patient with a DVT is education on both the short- and long-term implications of their new "disease state." For the short term, this would include the importance of medication compliance, drug-to-drug interactions, need for surveillance with venous duplex ultrasound, and bleeding risk while on anticoagulation. For the long term, patients have to understand family planning if a woman is of child-bearing age, implications of future surgeries, pros/cons of compression therapy, and the importance of continued communication as medical issues may arise.

How has the ATTRACT trial influenced referral volumes in your center?

Dr. Silver: The referral volumes have not been influenced by the ATTRACT trial at our center. We have tried to educate our hospitalists and referring physicians about some of the limitations of the ATTRACT trial design as it contrasts to modern-day venous intervention. In fact, our volumes have increased since release of the ATTRACT trial, because we offer both acute and chronic disease state management (acute DVT, chronic Iliac vein, and inferior vena cava reconstruction).

Dr. Chaer: Although this is difficult to measure, my sense is that the trial did not have a significant impact on the referral volumes in our center. What is unfortunate is the fact that early referral is still not always initiated, and I continue to see patients referred for symptomatic iliofemoral DVT well outside the preferred window for lytic therapy.

Dr. Bashir: The ATTRACT trial results have not significantly changed our referral volumes because most referred patients have severe symptoms from iliofemoral DVT despite anticoagulation. We believe that our referral base has seen the positive results of PCDT and become believers in the percutaneous treatment of iliofemoral DVT.

Dr. de Graaf: I get more referrals than ever before. You might say bad press is better than no press; however, I think something else is going on. Awareness is way more important than difficult-to-interpret outcomes from one or two studies. They aren't visible to the lay public. We have to realize that we are working in a patient-oriented health care system. Patients want us to alleviate their symptoms and give them back their QOL.

Dr. Spencer: It has not; however, I am aware that it may have in other institutions. With low-dose thrombolytics and an ankle access approach, bleeding complications can be markedly reduced, although this remains to be published.

We have a policy that patients with extensive DVT should have a consult with an endovascular specialist to best determine the risk/benefit ratio of intervention.

When speaking to referral sources, are there specific subtleties of the data that you address individually? Have you been successful in explaining the data and how they apply to your everyday cases?

Dr. Spencer: Yes, specifically:

- If you test an open vein hypothesis, the vein needs to be fully opened. The low stenting rates, moderate residual thrombus burden, and popliteal access site all leave a question in my mind as to whether this hypothesis was truly tested. We perform lysis from the ankle, so these data don't really apply to patients treated with more advanced techniques. There was significant variability on treatment techniques in the study.
- The lack of imaging follow-up does not allow us to know who rethrombosed. The number of patients lost to follow-up was also greater than expected.
- The study did show more rapid resolution of symptoms and benefit in young active patients.
- We discuss the limitations of the current "validated" scales in identifying patients with pain as the primary issue and the issue of lost days of work and revenue for patients. If the VCSS was used, results of the ATTRACT trial would have been positive. The Villalta score has been shown to overestimate mild PTS, and a Villalta score of > 5 may not have been a great endpoint to use.

Dr. de Graaf: Again, successful thrombus removal, treating the right patients, and stenting the underlying cause of DVT are the main aspects I focus on and most understand. Also, I communicate the results from the patients that the referral source or their close colleagues sent to me. This usually is quite convincing.

Dr. Silver: Some of the limitations of the ATTRACT trial that we review with our referral sources would include[3]:

- The ATTRACT results do not apply to patients we see every day. Only 1 out of 50 patients screened were randomized, which means the results are not generalizable.
- There was no true clinical equipoise demonstrated in enrollment among the investigators. With 56 sites, it took 5 years to complete the trial (2009–2014).
- The primary endpoint was flawed—the Villalta score was applied in a binary fashion (PTS, yes or no). The lack of clinical benefit should not be defined simply by the presence of a Villalta score > 5.
- ATTRACT was underpowered to evaluate the group with the highest risk of PTS, as only 57% of patients had iliofemoral DVT.
- Only 68% of patients in the control arm completed the full 24-month follow-up, which likely underestimated the benefit of venous intervention.
- Venography was used as the endpoint to define the use of stenting; however, IVUS has been shown to be superior to venography to make clinical decisions.[4]
- Only 28% of patients with iliofemoral DVT underwent venous stenting. Research has shown that the majority of patients with an iliofemoral DVT have an underlying anatomic etiology (ie, extrinsic iliac vein compression).[5]
- The median duration of thrombolysis was 21 hours. With modern-day thrombectomy, thrombolysis time this long is rarely needed. Thrombolysis time drives bleeding risk. There are now devices that require no adjunctive thrombolytic.

Dr. Chaer: Referral sources do not often scrutinize the subtleties of the data, but I do stress the fact that patients with symptomatic proximal DVT seem to benefit from early thrombus removal in terms of preventing postthrombotic complications as well as acute symptom relief. On the other hand, this may not apply to patients with isolated femoropopliteal DVT. This had been our standard approach well before the trial results became available, and referral sources seem to be on board with this rationale and patient selection strategy.

Dr. Bashir: We believe the major subtlety that needs to be appreciated is the difference in PTS outcomes when using a dichotomous variable of PTS (yes or no) versus a continuous variable such as Villalta score or VCSS. We also emphasize the following points:

- The difference in the recanalization rates of femoropopliteal DVT versus iliofemoral DVT (80% vs 20%) with anticoagulation alone. Therefore, the inclusion of the former group in the ATTRACT trial diluted the benefits observed with PCDT, making the results of anticoagulation alone appear more acceptable.
- It is well established that outflow patency is associated with lower PTS rates and stenting of the outflow veins is associated with better long-term patency. Therefore, we believe that assessment of the patency of iliofemoral veins should be based on IVUS rather than venograms alone, especially if you are not planning to stent.
- We also discuss the improvements noted in the PCDT group in venous disease–specific QOL.

- Finally, the most important takeaway from the CAVA study is that the PTS rates were low in patients who underwent successful PCDT. Therefore, the overall efficacy of this procedure is critically dependent on the effectiveness of thrombus removal.

How does the availability of single-stage thrombus removal technologies and dedicated venous stents affect your decision-making for iliofemoral DVT management?

Dr. Bashir: The availability of dedicated venous stents is long overdue and will be very helpful. Single-stage thrombus removal technologies could be a catalyst for the wider adoption of this treatment modality, provided that they do not damage the venous valves. If they do, this may lead to long-term venous incompetence with the attendant sequelae.

Dr. Spencer: The more I know, the more I believe thrombolytics are important in treating acute DVT. Many of the currently available single-setting devices are helpful, and some patients can complete therapy in a single session. However, my practice has migrated back to placing an infusion catheter from posterior tibial with fentanyl and a local anesthetic, and thus the patient is not required to be NPO. This often means the length of the hospital stay is not as long because you don't have to wait a day to keep the patient NPO for sedation for single-setting treatment. I use single-setting devices mostly as an adjunct to thrombolytics the next day if needed or up front to debulk in inferior vena cava and large-volume iliac DVT.

I was involved in several of the stent trials. I have yet to be convinced that all of the problems are resolved with the current-generation stent or even that they will prove to be markedly better, but I do believe that ease of placement and accuracy will improve outcomes, and better strength at the compression point will help as well. There is added protection in having a venous-indicated stent, but we have been placing stents in veins for over 20 years, so I don't see it changing much other than hopefully better outcomes.

Anyone placing stents needs to understand flow dynamics and be aware of Murray's law. The inflow and outflow of the iliac venous system needs to be addressed and considered when placing and sizing stents. Oversized stents and undersized stents are both proving to be a problem. The stent should match the vein size and inflow must be addressed. We have been blaming stent design for many of our failures when the culprit is more often inaccurate or inappropriately sized stents and/or stenting into distal obstructions. The new stents will not fix this issue. Treating venous disease is complex, requires appropriate training, and should not be engaged in after a weekend venous course.

Dr. Chaer: The ongoing evolution of technologies available to treat iliofemoral DVT supports the interventional management approach, because they can potentially improve the safety profile and durability of the interventions. The improved efficacy of single-stage removal technologies could obviate some of the bleeding complications associated with lytic therapy and allow for more cost-effective delivery of care by eliminating intensive care unit and hospital lengths of stay.

Dedicated venous stents can also increase the durability of such interventions and thus long-term outcomes. As such, with improved devices and technologies, providers and referring physicians may be more likely to offer early thrombus removal strategies to patients with proximal DVT.

Dr. de Graaf: In my opinion, stents are only indicated to treat the underlying cause of DVT, most notably May-Thurner compression, not residual thrombus. This lesion is usually short and uncomplicated to treat. Previously, virtually all stents perform well, so the availability of (more) dedicated venous stents does not directly affect my decision-making. Thrombus removal technology does have strong potential. I have used literally every serious thrombus removal device on the market; however, none is perfect. Sometimes, I even have had to revert to the large-bore sheaths, with better results than the devices available to me. Nevertheless, new devices with optimal clot removal capability will enter the market in the next years, and we will definitely benefit from that.

Dr. Silver: The newer technology that was not available during the ATTRACT trial (including thrombectomy devices that offer single-stage procedures), devices that do not require adjunctive thrombolysis, and dedicated venous stents, have expanded our patient population. The best example would be the patient who has an absolute contraindication to thrombolysis due to recent surgery, who can now be treated with a pure catheter thrombectomy system that does not require adjunctive thrombolysis. ■

1. Vedantham S, Goldhaber SZ, Julian JA, et al; for the ATTRACT trial investigators. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. N Engl J Med. 2017;377:2240-2252.
2. Wittens C. CAVA trial. Presented at: American Venous Forum Annual Meeting; February 21, 2019; Rancho Mirage, CA.
3. Silver MJ, Jolly M. Acute DVT: are we overtreating or undertreating? Endovasc Today. 2018;17:84-87.
4. Gagne P, Gasparis A, Black S, et al. Analysis of threshold stenosis by multiplanar venogram and intravascular ultrasound examination for predicting clinical improvement after iliofemoral vein stenting in the VIDIO trial. J Vasc Surg Venous Lymphat Disord. 2018;6:48-56.e1.
5. Chung JW, Yoon CJ, Jung SI, et al. Acute iliofemoral deep vein thrombosis: evaluation of underlying anatomic abnormalities by spiral CT venography. J Vasc Interv Radiol. 2004;15:249-256.