

# A volumetric index for the quantification of deep venous thrombosis

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**Purpose:** The evaluation of treatment strategies for deep venous thrombosis (DVT) is assessed through the use of a reliable method of quantifying the extent of the thrombotic process. Previous indices of thrombus burden have suffered from various limitations, including lack of clinical relevance, poor correlation with actual thrombus mass, and failure to include important venous segments in the methodology. The use of a novel scheme of quantifying venous thrombus was evaluated as an alternative method that would avoid some of the drawbacks of existing indices.

**Methods:** The volumes of 14 venous segments (infrarenal inferior vena cava, common iliac, hypogastric, external iliac, common femoral, profunda, superficial femoral, and popliteal and six tibial veins) were calculated from computed tomography (pelvic vein diameter), duplex ultrasound scan (infrainguinal vein diameter), and contrast venography (length of all segments) measurements. A venous volumetric index (VVI) was assigned with the normalization of the values to the volume of a single calf vein. The VVI was validated with the assessment of the ability to discriminate between asymptomatic and symptomatic DVT and between those DVT that were associated with pulmonary emboli and those that were not.

**Results:** With the imaging data, the VVI ranged from 1 for a single calf vein thrombus to 26 for the infrarenal inferior vena cava. Each VVI unit represented 2.3 mL of thrombus, with a maximum possible score of 63 representing a thrombus burden of 145 mL for a single extremity, including the infrarenal inferior vena cava. In 885 patients with DVT, the VVI ranged from 1 to 56, averaging  $3.9 \pm 0.2$  in patients who were asymptomatic and  $8.7 \pm 0.3$  in patients who were symptomatic ( $P < .001$ ). The VVI was similar in the patients with pulmonary emboli as compared with those without ( $9.6 \pm 1.2$  vs  $7.7 \pm 0.2$ , respectively). In comparison with the three existing methods of quantifying venous thrombus burden, the receiver operating characteristic curve analysis results suggested that the VVI and the Venous Registry index were better than the other two indices in the discrimination of patients with symptomatic and asymptomatic DVT ( $P < .001$ ).

**Conclusion:** A novel index of venous thrombus burden, on the basis of actual venous volume measurements, was more accurate than present indices in the differentiation between clinical categories of patients with DVT. As such, it offers an acceptable alternative to current scoring systems. (*J Vasc Surg* 1999;30:1060-6.)

The treatment of venous thromboembolic disease, whether it comprises anticoagulation therapy alone, pharmacologic thrombolysis, or mechanical thrombectomy, can be objectively assessed with the quantification of the extent of thrombus at

baseline and after treatment. The Marder score was the first such index to be described and was originally used as a method for gauging the success of intravenous streptokinase for deep venous thrombosis (DVT).<sup>1</sup> Despite the widespread use of this measure, an objective basis for the methodology was not included in the original report and the validity of the index has never been proved. An ad hoc committee of the Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery (SVS/ISCVS) devised a simpler index for quantifying venous thrombus, originally described in a 1988 publication<sup>2</sup> and modified in a revised version in 1995.<sup>3</sup> The SVS/ISCVS index was developed in an attempt to standardize the reporting

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criteria of venous thromboembolic studies. Like the Marder score, the SVS/ISCVS index represented an arbitrary method of assigning an arithmetic score to gauge thrombus burden. Similar to the Marder score, the SVS/ISCVS index was never validated in a population of patients with DVT. In response to a need for a method of quantifying DVT before and after venous thrombolysis, a third paradigm was developed for use with the American Venous Registry.<sup>4</sup> The Registry index was a modification of the SVS/ISCVS index. The index was validated in the initial report of the Registry when a 1-year clinical outcome was associated with the change in the index after urokinase thrombolysis. Despite this finding, the Registry index was not based on a quantitative estimate of thrombus mass—an important attribute of a valid index of venous thrombus. Further, calf vein thrombi were not included in the methodology, which accounted for an underestimation of the extent of the thrombotic process in many patients.

Because of the perceived shortcomings of the existing indices to gauge the extent of venous thrombosis, a new method was developed on the basis of actual volumetric calculations made from imaging studies of patients with DVT. This new index was validated through an assessment of its ability to discriminate patients with symptomatic versus asymptomatic DVT and patients with pulmonary embolism versus patients without.

## METHODS

The pelvic venous measurements were made from computerized tomographic imaging study results from 13 patients, with the tabulation of the diameters of the external iliac, hypogastric, and common iliac veins and of the infrarenal inferior vena cava. Pelvic venographic results were evaluated in a separate group of 10 patients to calculate the length of the same venous segments. The infrainguinal venous measurements were obtained from the results of duplex ultrasound scans (diameter determinations) that were performed in 12 patients and from the results of venograms (length determinations) that were performed in 10 patients. The common femoral, profunda femoris, superficial femoral, popliteal, and calf vein segments were evaluated. The volume of each segment was calculated as the product of  $\pi$ , length, and the square of the radius. In this manner, an estimate of the actual volume of venous thrombus was assigned to each of four abdominopelvic venous and 10 lower extremity segments. A point value was assigned to

each of the segments with the normalization of the volume of each segment to the volume of a calf vein and the rounding to the nearest integer, such that the score for a single calf vein was 1. For technical reasons, the soleal and gastrocnemius veins were excluded from the methodology. These segments were inconsistently visualized on the imaging study results.

A venous volumetric index (VVI) was calculated for each patient with the summation of the representative scores for each thrombus-containing venous segment. The partially occlusive thrombi were assigned a score equal to one half of the point value for that particular segment. The VVI was not corrected for the thrombotic involvement of one of two paired proximal veins (eg, double popliteal or duplicated superficial femoral veins), but the index did account for the involvement of one versus both paired calf veins.

During a 10-year period, a total of 2534 lower extremity venographic procedures were performed and were of sufficient quality for review. Of these, 885 cases (34.9%) had evidence of acute DVT, and this subset of all positive venographic results represented the clinical database used to validate the VVI. Validation was accomplished through an assessment of the index in the subgroups of patients with asymptomatic versus symptomatic DVT and in those patients with DVT and pulmonary embolism documented with radionuclide scanning, pulmonary angiography, or dynamic computed tomography. Similar statistical calculations were made for the Marder score and the SVS/ISCVS and Registry indices. The comparative validity of the different indices of thrombus burden were compared with the determination of the ability of each measure to differentiate between the following three clinical categories: patients who were asymptomatic, patients who were symptomatic, and patients with pulmonary embolism. In this manner, the most valid index would be associated with the greatest degree of discrimination between these categories, assessed through receiver operating characteristic (ROC) curve analysis. ROC curves were generated for each index and graphed the relationship between the true-positive rate and the false-positive rate. The performance of each index was displayed as it related to the discrimination between: (1) those patients who were asymptomatic versus those patients who were symptomatic, and (2) those patients with pulmonary emboli versus those patients without. A *P* value was generated for the comparisons between the two ROC curves with the method of Metz.<sup>5</sup>

**Table I.** Methodology used to calculate the venous volumetric index

Segment	Length (cm)	Diameter (cm)	Volume (mL)	Ratio	Score
Inferior vena cava	14.0	2.34	60.21	26.22	26
Common iliac	6.0	1.39	9.10	3.97	4
Hypogastric	7.0	0.91	4.55	1.98	2
External iliac	13.0	1.40	20.01	8.72	9
Common femoral	6.0	1.41	9.37	4.08	4
Superficial femoral	20.0	0.96	14.60	6.36	6
Profunda femoral	12.0	0.85	6.81	2.97	3
Popliteal	15.0	0.82	7.86	3.42	3
Each calf vein	18.0	0.40	2.30	1.00	1

**Table II.** Volume and relative contribution by anatomic system

Region	Volume (mL)	Percent
Iliac	32.1	41
Femoropopliteal	34.2	43
Calf	12.8	16
Total	79.18	100

## RESULTS

**Calculation of the venous volumetric index scores by anatomic segment.** With the measurements from the computed tomographic images, venograms, and duplex scans, the volumetric scores for the various venous segments ranged from 1 for a single calf vein to 26 for the infrarenal inferior vena cava (Table I) and corresponded to a ratio of 2.30 mL of thrombus per unit VVI. The maximum possible VVI was 63 for one leg, which represented the sum of the scores for all nine segments. With the conversion factor of 2.30 mL/U, there was a maximum thrombus burden of 145 mL within the deep venous segments of one leg, including the infrarenal inferior vena cava, and 85 mL exclusive of the cava. When grouped by anatomic system, the calf veins accounted for 16% of the total (excluding caval) thrombus burden of each leg, versus 43% for the femoropopliteal system and 41% for the iliac system (Table II).

**Venous volumetric index determinations in patients with deep venous thrombosis and pulmonary embolism.** The VVI ranged from 1 to 56 in the 885 patients with DVT. The VVI was significantly lower in the patients with asymptomatic versus symptomatic DVT ( $3.9 \pm 0.2$  vs  $8.7 \pm 0.3$ , respectively;  $P < .001$ ; Table III). An apparently lower mean VVI in the patients without clinically significant pulmonary emboli was not statistically

different from the VVI in patients with such a history ( $7.7 \pm 0.2$  vs  $9.6 \pm 1.2$ , respectively; Table IV). Although the patients with pulmonary emboli had a mean residual lower extremity thrombus burden of  $21 \pm 0.5$  mL, pulmonary emboli were observed in patients with as little as a 6-mL residual thrombus.

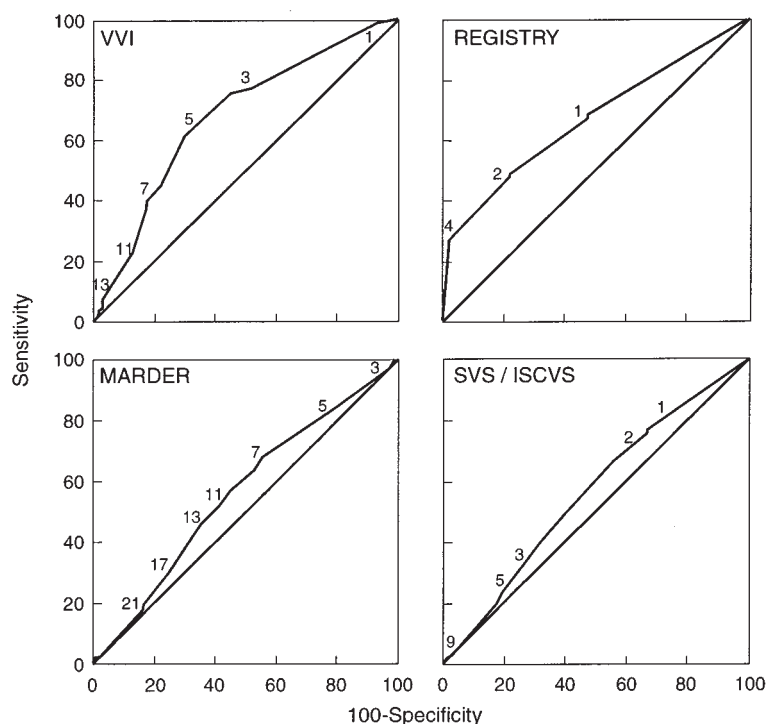
**Comparison of different indices of thrombus burden.** The comparative validity of the four indices of thrombus burden was assessed with the tabulation of the number of asymptomatic patients whose scores were above the threshold (95% confidence interval for the symptomatic group) and of the number of symptomatic patients whose scores were beneath the threshold (95% confidence interval for the asymptomatic group). The VVI and the Registry index appeared to be the most valid measures, with the lowest rates of improperly categorized patients (Table V). There was a trade-off between the false identification of asymptomatic versus symptomatic patients, however. The Registry index was best for the correct identification of patients with asymptomatic DVT, and the SVS/ISCVS index was best for the discrimination of patients with symptomatic DVT.

With ROC curve analysis (Fig 1), the VVI and the Registry index offered improved discrimination between asymptomatic and symptomatic DVT when compared with either the Marder score ( $P < .001$ , vs VVI;  $P < .001$ , vs the Registry index) or the SVS/ISCVS index ( $P < .001$ , vs VVI;  $P < .001$ , vs the Registry index). There were no statistically significant differences noted between the discriminatory value of the VVI versus the Registry index ( $P = .838$ ) or of the Marder score versus the SVS/ISCVS indices ( $P = .863$ ). When the indices were evaluated with respect to the discrimination of those thrombi that were associated with pulmonary emboli versus those that were not, the VVI and the Registry index also appeared better than the other two measures, but the small numbers of patients with pulmonary emboli precluded a meaningful statistical analysis.

## DISCUSSION

The advent of therapies directed at clearing thrombi from the venous system has appropriately prompted the performance of trials designed to assess the benefits of such treatments in an objective fashion.<sup>6-10</sup> The availability of a valid index with which to gauge the extent of DVT is crucial to the conduct of these investigations, both to assess the success of thrombolytic and other treatment methods and to compare the baseline status of different groups of patients.

At least three scoring systems for venous throm-



**Fig 1.** Receiver operating characteristic curves for differentiation of asymptomatic and symptomatic deep venous thrombosis. Numbers along lines indicate criterion thresholds points along receiver operating characteristic curves.

**Table III.** The venous volumetric index in symptomatic and asymptomatic deep venous thrombosis, contrasted with the Marder score, the Society for Vascular Surgery/North American Chapter of the International Society for Cardiovascular Surgery index, and the Registry index

	VVI	Marder score	SVS/ISCVS	Registry
<b>Asymptomatic DVT</b>				
No. of patients	169	169	169	169
Mean	3.9	9.4	2.3	0.5
SD	2.7	5.7	1.9	1.0
SEM	0.2	0.4	0.1	0.1
95% CI	3.5 - 4.3	8.5 - 10.3	2.0 - 2.6	0.3 - 0.6
Median	2.0	6.0	1.0	0.0
Range	1.0 - 13.0	2.0 - 24.0	0.5 - 9.0	0.0 - 4.0
1st quartile	2.0	6.0	1.0	0.0
3rd quartile	6.0	16.0	3.0	0.0
<b>Symptomatic DVT</b>				
No. of patients	716	716	716	716
Mean	8.7	14.2	5.0	2.4
SD	7.6	8.0	3.5	2.5
SEM	0.3	0.3	0.1	0.1
95% CI	8.1 - 9.3	13.6 - 14.8	4.8 - 5.3	2.2 - 2.6
Median	6.0	14.0	4.0	2.0
Range	1.0 - 56.0	0.0 - 34.0	0.5 - 17.0	0.0 - 12.0
1st quartile	4.0	6.0	2.0	0.0
3rd quartile	13.0	20.0	8.0	4.0

VVI, Venous volumetric index; SVS/ISCVS, Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery; DVT, deep venous thrombosis; SEM, standard error of the mean; CI, confidence interval.

**Table IV.** The venous volumetric index in patients with and without clinically significant pulmonary emboli, contrasted with the Marder score, the Society for Vascular Surgery/North American Chapter of the International Society for Cardiovascular Surgery index, and the Registry index

	VVI	Marder	SVS/ISCVS	Registry
<b>No PE</b>				
No. of patients	853	853	853	853
Mean	7.7	13.1	4.4	2.0
SD	7.2	7.9	3.4	2.4
SE	0.2	0.3	0.1	0.1
Confidence	0.5	0.5	0.2	0.2
95% CI	7.2 - 8.2	12.6 - 13.7	4.2 - 4.7	1.8 - 2.2
Median	6.0	12.0	3.0	2.0
Range	1.0 - 56.0	0.0 - 34.0	0.5 - 17.0	0.0 - 12.0
1st quartile	2.0	6.0	1.0	0.0
3rd quartile	11.0	20.0	7.0	4.0
<b>PE</b>				
No. of patients	32	32	32	32
Mean	9.6	17.1	5.9	2.7
SD	6.9	7.4	3.2	2.7
SEM	1.2	1.3	0.6	0.5
Confidence	2.4	2.6	1.1	0.9
95% CI	7.2 - 12.0	14.6 - 19.7	4.8 - 7.0	1.8 - 3.6
Median	8.0	17.0	5.8	2.0
Range	3.0 - 30.0	4.0 - 34.0	2.0 - 14.0	0.0 - 10.0
1st quartile	6.0	12.0	3.0	1.8

VVI, Venous volumetric index; SVS/ISCVS, Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery; PE, pulmonary embolism; SEM, standard error of the mean; CI, confidence interval.

**Table V.** Discriminatory abilities of the indices

	VVI	Marder	SVS/ISCVS	Registry
1. Asymptomatic, > threshold*	9.5%	28.4%	13.0%	4.7%
2. Symptomatic, < threshold†	34.1%	40.9%	26.8%	36.2%

VVI, Venous volumetric index; SVS/ISCVS, Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery. 1. Percentage of asymptomatic patients with index incorrectly more than threshold. 2. Percentage of symptomatic patients with index incorrectly less than threshold.

\*Threshold defined by the lower limit of the 95% confidence interval for the symptomatic patients.

†Threshold defined by the upper limit of the 95% confidence interval for the asymptomatic patients.

basis have been used. The first of these to be described, the Marder score, is the only index that was based on the volume of venous thrombus within each anatomic segment.<sup>1</sup> The Marder score is, however, somewhat arbitrary. The data on which the scores were based did not appear in the publication, although each score was said to reflect the calculated volume of the corresponding segment. The Marder score also failed to separate the relative contributions of thrombus within the three iliac veins, and the contributions of the profunda femoral vein and the inferior vena cava were excluded from the

scoring system. Calf DVT appears to be over represented in the Marder score, accounting for fully 40% of the total lower extremity score and an amount greater than that assigned to either of the more proximal femoropopliteal or iliac regions.

The SVS/ISCVS<sup>3</sup> and Registry indices<sup>4</sup> are not, per se, based on the volume of thrombus. These methods assign arbitrary values to each of the venous segments. Whereas the SVS/ISCVS methodology includes scores for the soleal and gastrocnemius veins, the Registry index ignores thrombus below the popliteal level. Despite the arbitrary nature of these measures, they are remarkable in their ability to discriminate asymptomatic and symptomatic DVT. Although the Registry index performed well in the present analysis, the failure to include calf vein thrombi makes it less useful for the quantification of the total thrombus burden in patients with DVT.

The VVI appears to offer an acceptable alternative to the current scoring methods. Unlike other methods, it is strictly based on venous volume measurements and therefore provides a more accurate assessment of thrombus mass. Normalization to the volume of a single calf vein and rounding to the nearest integer makes the VVI easy to use. It better discriminated symptomatic from asymptomatic thrombi when compared with both the Marder score and the SVS/ISCVS index and was as accurate



as the Registry index in this regard. The inclusion of calf vein thrombi in the VVI scoring methodology may render this index more attractive than the Registry index. For these reasons, the VVI appears to be a useful scoring paradigm for the assessment of venous thrombus burden and of the changes in thrombus after intervention. Nevertheless, the validity of the index remains to be proven with regard to its association with the long-term sequelae of DVT. A valid index would be one that would be closely linked to post-thrombotic complications. This feature can only be assessed with the comparison of the VVI to other scoring systems in longitudinal studies of patients with DVT, a feature that must be critically assessed before the VVI can replace the available indices as the methodology of choice in venous thromboembolic studies.

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#### DISCUSSION

**Dr Enrico Ascher** (Brooklyn, NY). I would like to start by thanking the Program Committee for asking me to discuss this interesting and well-presented paper. I consider this both a duty and an honor.

It is not unexpected that Dr Ouriel, Dr Greenberg, and colleagues have attempted to develop new indices to better assess the results of venous thrombolysis. Their contributions to this field of vascular intervention have been recognized by the most stringent editorial boards.

Approximately 23 years ago, Victor Marder and his associates at Temple University developed a quantitative venographic assessment of acute deep vein thrombosis whereby a scoring system was developed according to the location and extent of the thrombotic process. With this scoring system, they prospectively demonstrated in patients that the rate of clot resolution was significantly higher for streptokinase when compared with heparin.

Today Dr Greenberg has introduced a more refined method in which not only the site and the extent of the clot are taken into consideration but also the volume. Clearly, the new scoring system is less arbitrary than the one described by Marder. Of course, if volume of clot were the only criterion for the prediction of success or failure of any treatment protocol, I would congratulate Drs Greenberg and Ouriel, pack, and go home.

However, deep vein thrombosis is a dynamic process that is constantly changing and that is subject to a myriad of processes related to thrombogenic and thrombolytic

stimuli. Even anatomically, the response to exogenous thrombolytic agents may vary according to the length or diameter of the vein and not necessarily the volume. It seems logical to me that six completely occluded infrapopliteal veins would take longer to lyse than one external iliac vein segment. Yet, the venous volumetric index for the latter is much higher than for the infrapopliteal veins: 9 versus only 6. Dr Greenberg, could you please comment on this assumption?

Also, I wonder why you used a different number of patients when you calculated the length and diameter of the vein segments? Was there any attempt made to include the superficial venous system into this scoring? This may potentially influence the long-term results of venous insufficiency and its sequelae.

In the same breath that the authors are proposing the preferential use of venous volumetric index scoring, they conclude that the Registry index was best at correctly identifying patients with asymptomatic deep venous thrombosis and that the index of the Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery was best at discriminating those patients with symptomatic deep venous thrombosis. Of course, in my practice, if I want to find out about symptoms, I simply ask the patient.

Furthermore, none of the indices presented today reliably predicted pulmonary embolism. In our experience, the best criterion has been the demonstration of clot

extension despite adequate systemic anticoagulation therapy. Could you comment on the potential benefits of repeat venous volumetric index scores?

Also, did you by any chance divide the 885 patients with proven deep venous thrombosis into those patients with suprainguinal extension versus those patients with deep venous thrombosis limited to the infrainguinal location? How would the venous volumetric index fare as a predictor of pulmonary embolism in both groups? You may have been surprised to find that perhaps the proximal extension has a higher rate of pulmonary embolism.

As the authors correctly pointed out on their well-written manuscript, longitudinal studies of patients with deep venous thrombosis are critical to validate the proposed scoring system. In the meanwhile, I want to congratulate Dr Ouriel, Dr Greenberg, and colleagues for their continued efforts to improve on standard methodologies. Perhaps they should consider a multi-institutional project to definitively validate the venous volumetric index scoring system.

Once again, I would like to thank the Society for this assignment and the authors for allowing me to review their well-organized manuscript. Thank you.

**Dr Roy K. Greenberg.** Thank you, Dr Ascher, for your comments and eloquent discussion.

With respect to your first question about the calculation of calf vein thrombosis versus a single external iliac thrombosis, our scoring system is really not designed to assess the time it takes to complete lysis or the success of lysis. What we really want to do is determine, prospectively, whether or not these patients are going to get better, become symptomatic, or benefit from lysis. Perhaps, if a patient had a high score and we were able to lower that score with lysis, we may improve their symptoms.

Because this is a comprehensive index designed to assess all lower extremity deep venous thrombosis, there will be unusual situations in which the scores may not accurately reflect the clinical scenario. If this were not the case, we would be 100% sensitive and specific.

We consciously elected not to include the superficial venous system in the venous volumetric index because we are not aware of any studies that define its relationship to the deep venous system in the setting of deep venous thrombosis. To include that within the venous volumetric index would require a great deal of speculation. We have to remember that the purpose of this is to evaluate the need of benefit of treatment for venous thrombosis.

The system is designed to allow clinicians to obtain sequential scores. The first score is assessed before any treatment, and the second score is assessed at each follow-up venographic evaluation during the treatment. We are looking for a change in the score and trying to correlate that with a change in the symptoms or the presence of reflux.

We did not segregate the patients into those with infrainguinal or suprainguinal disease by looking for clini-

cal sequelae on the basis of those anatomic discrepancies. That may be something that is worthwhile in the future.

I think that addressed your questions.

**Dr Herbert Dardik** (Englewood, NJ). This sounds labor intensive to me. How long does it take to do a calculation per patient?

**Dr Greenberg.** Well, it is actually quite simple once you are familiar with it. But you are right, it is somewhat labor intensive. However, venous thrombosis is not a simple problem. We have been thwarted for many years when attempting to develop longitudinal studies that compare patients. A complex scoring system may be a price we have to pay.

**Dr Peter J. Pappas** (Newark, NJ). That was a great presentation. I have always been intrigued by the concept of the amount of clot in a vein and whether or not we could somehow use that to predict a successful thrombolytic event. As a matter of fact, at the American Venous Forum meeting, when Dr Mewissen presented the data from the registry before it was published, I was intrigued by the fact that the iliac segments had a higher rate of thrombolysis and success and that the femoropopliteal segments had an abysmal response. I have always wondered why this is so. Recently, I spoke with Tom Wakefield and I saw some of his data on vein wall inflammation. I wondered whether there was a differential response in vein wall inflammation in the femoropopliteal segment as opposed to the iliac segment.

I bring this up because I have always been intrigued by Dr Nicolaides' plaque morphology work, and I wonder why we cannot translate that into the deep venous system to do some kind of clot morphology work or maybe vein wall morphology work. It seems to me that the system that you have used with your computed tomographic scanning and your duplex scanning might be able to be applied in that way. So, I wonder whether you intend to do any of that clot morphology or vein morphology work and whether or not it may help you determine a successful thrombolytic event.

**Dr Greenberg.** I completely agree with you, especially with your comments about the femoropopliteal segment. Given the frequency of thrombosis of this segment, it is the most underserved, primarily because we have not been able to document good results with treatment. Perhaps that is because of the clot morphology, perhaps it is because of the number of valves or the fibrotic nature of the valves or vessel wall, or perhaps it is a different biologic entity than iliac vein thrombosis. One of the concerning things that comes to mind is that most patients with iliac clot also have femoral clot and frequently popliteal clot. These patients are a difficult population to treat, and they are the patients who have the highest scores in these indices and probably the worst prognoses in terms of long-term consequences. Any further definition in this area would be beneficial. However, we have not embarked on this pathway yet.