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Evaluating chronic venous disease with a new venous severity scoring system

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Background: **The Venous Clinical Severity Score (VCSS) has been proposed by the American Venous Forum as an objective means to clinically assess venous disease more completely than with the clinical CEAP classification. However, validation of the VCSS against an objective test is lacking. The purpose of this study was to test the VCSS against abnormalities found on venous ultrasound (US) scans.**
Methods: **As part of a screening project in a large kindred population with protein C deficiency, VCSS and venous US scanning were performed in 210 patients (420 limbs). A single examiner scored the VCSS (0-3) clinically for pain, varicose veins, edema, skin pigmentation, inflammation, induration, ulcer duration and size, and compressive therapy. Another experienced examiner, blinded to the subject's medical history, performed a US examination of the deep and superficial venous system, with a hand-carried US system. The relationship between US and VCSS scores was analyzed by calculating an odds ratio (OR) and its 95% confidence interval (CI).**
Results: **Of the 420 limbs screened, VCSS was 0 in 283 limbs, and VCSS was 1 or greater in the following categories: pain, 63 limbs; varicose veins, 70 limbs; edema, 51 limbs; skin pigmentation, 17 limbs; inflammation, 2 limbs; induration, 8 limbs; and compressive therapy, 9 limbs. The highest total score in any limb was 8. A clear association was seen with the VCSS and abnormalities found on US scans. When the score was dichotomized (0 = normal, 1 = any abnormality), it was a strong predictor of US scan abnormalities; limbs with VCSS greater than 0 had a 26-fold greater chance of US scan abnormalities than did limbs with VCSS = 0 (OR, 26.5; 95% CI, 11-64). With ultrasonography as the standard, sensitivity of VCSS compared with US scans was 89.3%, and specificity was 76.1%. Negative predictive value of VCSS = 0 was 97.9%, and positive predictive value for any positive score was 36.5%**
Conclusions: **The results of this study are based on a large kindred population with a higher risk for venous disease than found in the general population. Though the VCSS was devised to quantify the severity of chronic venous disease, this study found it a useful screening tool. The VCSS showed good association with abnormalities on US scans, and when VCSS = 0 there is a high likelihood that the patient does not have venous disease. This simple test may prove valuable in clinical practice. (J Vasc Surg 2003;38:909-15.)**

In an attempt to standardize outcome assessment of venous interventions, an ad hoc committee of the American Venous Forum (AVF) developed a clinical scoring system, the Venous Clinical Severity Score (VCSS),[1] meant to expand and supplement the existing CEAP classification system.[2] In addition, the Venous Segmental Disease Score (VSDS) has been proposed to complement the VCSS, allow scoring with duplex ultrasound (US) scanning, and combine the anatomic and pathophysiologic components of CEAP.[1] Meissner et al[3] determined intraobserver variation with VCSS to be minimal, whereas interobserver variation in three of 10 categories (pain, inflammation, pigmentation) was significant. Interobserver agreement regarding presence or absence of disease (as defined by a score of ≤ 3 or ≥ 8) was good (κ = 0.59 and 0.65).[3] However, the clinical aspects of VCSS have not been validated against an objective test such as venous US scanning. This study was designed to test the association of venous abnormalities detected with US scanning with the VCSS and the "C" (Clinical) component of the CEAP classification.

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METHODS

As part of a population study of a large pedigree of patients who share protein C deficiency as a result of a rare C insertion mutation,[4-6] 210 persons from Vermont and Quebec, Ont, Canada, were studied prospectively between July and November 2002. The propositus for these kindred was a teenager with deep venous thrombosis. The population study included a large homogeneous group of persons with and without protein C deficiency and with or without a history of symptomatic deep vein thrombosis or pulmonary embolism. The University of Vermont Committee on

Table I. Characteristics of CEAP classification

Clinical classification	
Class 0	No visible or palpable signs of venous disease
Class 1	Telangiectasias, reticular veins, malleolar flare
Class 2	Varicose veins
Class 3	Edema without skin changes
Class 4	Skin changes ascribed to venous disease (eg, pigmentation, venous eczema, lipodermatosclerosis)
Class 5	Skin changes with healed ulceration
Class 6	Skin changes with active ulceration
Etiologic classification	
Congenital (E_C)	Cause present since birth
Primary (E_P)	Undetermined cause
Secondary (E_S)	Associated known cause (eg, postthrombotic, posttraumatic, other)
Anatomic classification (may include one, two, or three systems in any combination)	
Superficial (A_S)	Superficial veins
Deep (A_D)	Deep veins
Perforating (A_P)	Perforating veins
Pathophysiologic classification	
Reflux (P_R)	Venous reflux
Obstruction (P_O)	Venous outflow obstruction
Both ($P_{R,O}$)	

Table II. Venous Clinical Severity Score

Attribute	*Absent = 0*	*Mild = 1*	*Moderate = 2*	*Severe = 3*
Pain	None	Occasional, not restricting activity or requiring analgesic agents	Daily moderate activity limitation, occasional analgesic agents	Daily, severe limiting activities or requiring regular use of analgesic agents
Varicose veins (>4 mm diameter)	None	Few, scattered, branch veins	Multiple, greater saphenous veins, confined to calf or thigh	Extensive, thigh ***and*** calf, or greater ***and*** lesser saphenous distribution
Venous edema	None	Evening ankle edema only	Afternoon edema, above ankle	Morning edema above ankle and requiring activity change, elevation
Skin pigmentation	None or focal, low intensity (tan)	Diffuse, but limited in area and old (brown)	Diffuse over most of gaiter distribution (lower 1/3) or recent pigmentation (purple)	Wider distribution (above lower 1/3) plus recent pigmentation
Inflammation	None	Mild cellulitis, limited to marginal area around ulcer	Moderate cellulitis, involves most of gaiter area (lower 1/3)	Severe cellulitis (lower 1/3 and above) or significant venous eczema
Induration	None	Focal, circummalleolar (< 5 cm)	Medial or lateral, less than lower third of leg	Entire lower third of leg or more
Number of active ulcers	0	1	2	>2
Active ulcer duration	None	<3 months	>3 months, <1 year	Not healed >1 year
Active ulcer diameter (cm)	None	<2	2 6	>6
Compression therapy	Not used or patient not compliant	Intermittent use of stockings	Wears elastic stockings most days	Full compliance, stockings + elevation

For complete description see reference 1

Human Research approved the experimental protocol and consent form, and all subjects provided informed consent

Patients were assessed according to clinical signs of the CEAP classification,[2] which combine clinical data (discomfort, swelling, ulceration) and objective data observed at ultrasonography (Table I) In addition, clinical data for each patient was scored by a single investigator (J E) using the VCSS[1] (Table II), which has been validated as reliable [3]

Each abnormality observed on US scans was scored by another investigator according to VSDS criteria (Table III), and each limb was scored according to the Venous Disability Score (VDS) described by Rutherford et al [1] Calf perforating veins or other veins in the calf were not scored, which is allowed in this system [1] Both clinical examination and venous ultrasonography were performed by clinicians blinded to medical history of venous thrombosis and protein C status

Table III. Venous Segmental Disease Score

Score	*Vein*
Reflux*	
½	Lesser saphenous vein
1	Greater saphenous vein
½	Perforator vessels, thigh
1	Perforator vessels, calf
2	Calf veins, multiple (posterior tibial vein alone, 1)
2	Popliteal vein
1	Superficial femoral vein
1	Profunda femoris vein
1	Common femoral vein and above
Obstruction (excision, ligation, traumatic obstruction, thrombosis)*	
1	Greater saphenous vein (only if thromboses from groin to below knee level)
1	Calf veins, multiple
2	Popliteal vein
1	Superficial femoral vein
1	Profunda femoris vein
2	Common femoral vein
1	Iliac vein
1	Inferior vena cava

For complete description, see reference 1
*Maximum score = 10, not all 11 segments can be involved in reflux or obstruction.

Venous US scanning was performed in each patient with a hand-carried ultrasonography system (SonoSite 180PLUS; SonoSite, Bothell, Wash) by a single experienced clinician (J.E.). A solid-state 10-5 MHz 38-mm broadband linear array transducer was used (maximum depth, 7 cm), except in obese patients, in whom a 5-2 MHz 60-mm broadband curved array was used (maximum depth, 22 cm). Patients were examined in the supine position, with the head of the bed elevated 15 to 30 degrees. Transverse compression was performed approximately every 2 cm through the entire length of the vein being examined by applying downward pressure to the transducer until complete cooptation of the anterior and posterior walls of the vein was achieved. Compression began in the common femoral vein just below the inguinal ligament, and proceeded distally through the saphenofemoral junction, the confluence of the profunda femoral vein and the superficial femoral vein, and continued down the limb along the anteromedial thigh through the length of the superficial femoral vein. Next the popliteal vein was imaged from a posterior approach, and compression was performed with the patient sitting. Once the deep veins were completely examined, the greater and lesser saphenous veins were imaged along their length.

Venous Doppler scanning was performed coincident with the patient standing erect with weight on the contralateral leg. Pulsed-wave Doppler scanning of the veins was performed in a longitudinal plane, with the 10.5 MHz transducer, with the cursor parallel to the vein wall, an angle of 60 to 45 degrees, and the sample gate centered in the vein. Spectral display was obtained in all veins previously imaged in the B mode examination. The entire proximal deep venous system, and the greater and lesser saphenous veins were examined for the presence of reflux, with the Valsalva maneuver and distal augmentation. If the patient was unable to stand, Doppler scanning was performed with the patient positioned the same as for the B-mode examination.

Interpretation criteria were defined in advance of patient enrollment. In the standing position, reflux was defined as abnormal valve closure time that produced greater than 0.5- second reversal of venous flow, as described.[7,8] In addition, the normal veins demonstrated the following characteristics: slightly larger diameter than that of the adjacent artery when the limb was dependent; vein enlargement with the Valsalva maneuver or proximal compression; and completely compressible, spontaneous, phasic (with respiration) flow that was augmented with distal compression and with release of Valsalva or proximal compression at Doppler US scanning or color flow scanning. Thrombus was indicated by inability to compress the vein, echogenic material within the vein lumen, dilated vein, absent or decreased spontaneous flow, loss of phasicity, or absent or decreased augmentation. Obstruction, as defined for the VSDS,[1] was defined as greater than 50% luminal narrowing, on the basis of uncompressed residual luminal diameter compared with vein diameter.

Sensitivity and specificity of VCSS in detecting venous disease were estimated with the venous ultrasonography findings as the standard. Positive and negative predictive values in this population of patients were similarly estimated. The association between VCSS greater than 0 and US scan abnormalities was quantified by computing the odds ratio (OR) and its 95% confidence interval (CI). The Fisher exact test was used for statistical analysis.

RESULTS

Venous ultrasonography was performed, and CEAP classification and VCSS were determined in 210 patients (420 limbs). Mean age of patients was 43.8 years (SD, 14.9 years; median, 43.0 years; range, 15-78 years). Fifty-eight percent of patients were female. Thirteen percent had a known history of venous thrombosis, and 46% had protein C deficiency. History of thrombosis was present in 19% of patients with protein C deficiency and 8% of patients without protein C deficiency ($P = .04$). In 22 of 210 patients (10%), edema score was greater than 0 in both legs.

In those patients, US scans demonstrated no anatomic abnormality in 364 limbs (87%), compared with at least one abnormality in the remaining 56 limbs (13%). Clinical CEAP classification in these patients is shown in Table IV. Fifty-two of 364 limbs (14.3%) without anatomic US scan abnormalities had a clinical classification greater than 1, compared with 37 of 56 limbs (66.1%) with US scan abnormalities ($P < .0001$). Significantly more patients with anatomic abnormalities had a score of 3 or greater ($P < .0001$). Thirty-one patients (8.5%) had a score of 3 or greater. When clinical CEAP classification was dichotomized (0 or ≥1 or greater, or <3 and ≥3), it was unable to reliably predict US scan abnormalities (Table V), although

Table IV. Clinical CEAP classification

CEAP class	*Limbs with no anatomic abnormality n (%)*	*Limbs with anatomic abnormality n (%)*	P
0	312 (85 7)	19 (33 9)	< 0001
1	15 (4 1)	3 (5 4)	
2	6 (1 7)	16 (28 6)	
≥3	31 (8 5)	18 (32 1)	

Table V. Dichotomized CEAP clinical classification

*A 0 or ≥1**	*Limbs with no anatomic abnormality*	*Limbs with anatomic abnormality*	*Total*
0	312	19	331
≥1	52	37	89
	364	56	420
B <3 or ≥3†			
<3	333	38	371
≥3	31	18	49
	364	56	420

**P* < 0001, sensitivity, 66 1%, specificity, 85 7%, positive predictive value, 41 6%, negative predictive value, 94 3%
†*P* < 0001, sensitivity, 32 1%, specificity, 91 5%, positive predictive value, 36 7%, negative predictive value, 89 8%

Table VI. Venous Clinical Severity Score

Score	*Limbs with no anatomic abnormality n (%)*	*Limbs with anatomic abnormality n (%)*	P
0	277 (76)	6 (11)	< 0001
1	54 (15)	14 (25)	
2	20 (5)	10 (18)	
3	9 (2)	10 (18)	
4-8	4 (1)	16 (29)	

negative predictive value in either instance remained high (94.3%, 89.8%).

VCSS is shown in Table VI. In this group, only four patients had VCSS greater than 4 without US scan evidence of abnormality. Significantly more patients in the group with anatomic abnormality had VCSS greater than 4 (29%; $P < .0001$). When VCSS was dichotomized (Table VII), patients with VCSS greater than 0 were found to have a 26-fold greater odds of US scan abnormalities than those with VCSS = 0 (OR, 26.5; 95% CI, 11-64). Negative predictive value was high (97.9%). Therefore, if VCSS = zero, the likelihood of finding an abnormality on venous US scans was extremely low (<3%). Conversely, in two thirds of patients with VCSS 3 or greater, an abnormality was observed on venous US scans. For CEAP and VCSS, sensitivity is better for VCSS, specificity is better for CEAP, and predictive values are similar.

Table VII. Dichotomized Venous Clinical Severity Score

*A 0 or ≥1**	*Limbs with no anatomic abnormality*	*Limbs with anatomic abnormality*	*Total*
0	277	6	283
≥1	87	50	137
	364	56	420
B <3 or ≥3†			
<3	351	30	381
≥3	13	26	39
	364	56	

**P* < 0001, sensitivity, 89 3%, specificity, 76 1%, positive predictive value, 36 5%, negative predictive value, 97 9%
†*P* < 0001, sensitivity, 46 4%, specificity, 96 4%, positive predictive value, 66 7%, negative predictive value, 92 1%

Anatomic or functional abnormalities observed included complete obstruction, partial obstruction (eg, evidence of thrombus, thickened vein wall), and reflux. Several patients demonstrated anatomic evidence of obstruction (<50% diameter, not scored) and reflux. Specific abnormalities and VSDS are listed in Table VIII. Of 51 patients with a score greater than zero, average VSDS score was 1.37. VSDS reflux score (only one patient had an obstruction score) was significantly related to VCSS (Table IX; $P < .0001$).

VDS for each limb is listed in Table X. Only 74 patients had a score greater than 1, and in 47 of these patients no anatomic abnormality was observed on US scans. For purposes of analysis, the score was dichotomized as 0 or greater than 1. Surprisingly, 11% of 420 limbs had no US scan abnormality, but had VDS of 1 or greater. When VDS is correlated with VCSS, a high degree of correlation is noted ($r = 0.59$; $P < .0001$; Table XI). If both VCSS and VDS are dichotomized (0 or ≥1), the association is highly significant ($P < .0001$).

For the 44 legs with objective evidence of venous disease (obstruction score >0 [n = 1] or reflux score >0 [n = 43], correlation was determined between VCSS, CEAP, and VDS. These three measures were moderately correlated in the 44 limbs: VCSS and CEAP, correlation coefficient = 0.33, $P = .03$; VCSS and VDS, correlation coefficient = 0.40, $P = .01$; and for CEAP and VDS, correlation coefficient = 0.38, $P = .01$. P values indicate that these correlations are significantly different from zero.

DISCUSSION

In 1994 a consensus committee of the AVF developed the CEAP classification of chronic venous insufficiency[2] as a means to improve simple classification of reporting standards published by vascular societies.[9] Although the CEAP classification could be used to gauge clinical severity of disease at a single point in time, it was not useful for assessing change.[1] Many of its elements are fairly static, for example, presence of subcutaneous fibrosis; others do not

Table VIII. Ultrasound abnormalities and Venous Segmental Disease Score

Ultrasound findings	*Frequency*	*Obstruction score**	*Reflux score*
Complete obstruction, GSV	1	1	0
Complete obstruction, LSV	1	0	0
Partial obstruction, CFV, reflux, GSV	1	0	1
Partial obstruction, CFV, reflux/partial obstruction, POP	1	0	2
Partial obstruction, CFV, reflux, POP	4	0	2
Partial obstruction/reflux, GSV	2	0	1
Partial obstruction, LSV	5	0	0
Partial obstruction, POP	2	0	0
Partial obstruction/reflux, POP	7	0	2
Partial obstruction/reflux, LSV	2	0	0
Reflux, GSV	15	0	1
Reflux, LSV	2	0	0
Reflux/partial obstruction, POP, CFV	1	0	3
Reflux/partial obstruction, POP, partial obstruction, LSV	1	0	2
Partial obstruction/reflux, SFV	1	0	1
Reflux, POP	8	0	2
Reflux, POP, LSV	1	0	2
Reflux, POP, GSV	1	0	3

GSV, Greater saphenous vein, *LSV,* lesser saphenous vein, *CFV,* common femoral vein, *SFV,* superficial femoral vein, *POP,* popliteal vein
*No score assigned for partial obstruction (see text)

Table IX. Venous Segmental Disease Score reflux score versus VCSS

	Reflux score		
VCSS	*0*	*1*	*2 3*
0	282	0	1
1	57	0	11
2	22	6	2
3	10	5	4
≥4	6	8	6

VCSS, Venous Clinical Severity Score
P < 0001

Table X. Dichotomized Venous Disability Score 0 or ≥1

Score	*Limbs with no anatomic abnormality n (%)*	*Limbs with anatomic abnormality n (%)*	*P*
0	317 (87)	29 (52)	< 0001
≥1	47 (13)	27 (48)	

Sensitivity, 48 2%, specificity, 87 1%, positive predictive value, 36 5%, negative predictive value, 91 6%

Table XI. VCSS correlation with Venous Disability Score

	Venous Disability Score	
VCSS	*0*	*1*
0	276	7
1	47	21
2	11	19
3	8	11
4+	4	16

VCSS, Venous Clinical Severity Score
P < 0001

necessarily change significantly even with treatment, for example, presence of telangiectasias) [1] In addition, clinical classification was not reliably reproduced by different observers,[10] although recent efforts have attempted to improve on this [11] Consequently, a subsequent ad hoc committee of the AVF developed the VCSS to supplement and enhance the clinical portion of the CEAP classification [1] The VCSS system includes 10 clinical descriptors (pain, varicose veins, venous edema, skin pigmentation, inflammation, induration, number of active ulcers, duration of active ulceration, size of ulcer, and compressive therapy use), scored from 0 to 3 (total possible score, 30) that may be used to assess changes in response to therapy [1]

Meissner et al[3] attempted to validate the VCSS by assessing its reproducibility with the same and different examiners Three observers classified 64 patients (128 limbs) with chronic venous insufficiency (including asymptomatic limbs) on the same day, and a single observer scored limbs 7 to 28 days apart for determination of intraobserver variation Intraobserver variation was low, with scores differing only by 0 8, resulting in a reliability coefficient of 0 6 Scores for different observers varied by a mean of 0 8 (observers 1 and 3, $P = 03$) or 0 4 (observer 3, $P = 11$), but were not statistically significant overall ($P = 02$), with scores for pain, skin pigmentation, and inflammation differing slightly Agreement was good, with $\kappa = 0\ 59$ for absence of disease and $\kappa = 0\ 65$ for detecting presence of severe disease [3]

In addition, Meissner et al[3] reported that a VCS score of 3 or less was associated with sensitivity of 76% and specificity of 90% for absence of disease, and a score of 8 or

more demonstrated similar sensitivity of 70% and specificity of 96% for presence of disease. Although no subject in this study had VCSS greater than 8, as indicated in Table VII, *B*, a score of 3 or less was sufficiently discriminating for absence of disease to produce a negative predictive value of 92.1%; a score of 3 or greater, however, had a positive predictive value of only 66.7%.

Meant primarily as a mechanism to score treatment outcome for venous disease, VCSS has not been validated against an objective, anatomic assessment tool, such as venous ultrasonography. Indeed, until recently, determination of chronic venous insufficiency has been difficult, indirect, or inaccurate.[7] A variety of tests, including photoplethysmography, air and strain gauge plethysmography, static and dynamic venous pressure, and continuous wave Doppler scanning, can detect presence of reflux, but they cannot identify the specific venous segments involved.[7,8,12] Duplex US scanning has proved accurate for detection of presence of deep and superficial vein thrombosis. Signs of previous deep venous thrombotic episodes include abnormally thickened vein walls, recanalized flow channels, and abnormally small venous segments. With duplex US scanning, deep and superficial venous reflux can be accurately identified with direct anatomic assessment.[8,12] Patient positioning is important when assessing for venous reflux with duplex US scanning. The standing position increases dilation of the venous system, which improves the quality of the US scan, and because reflux is mainly the result of gravity, standing also enhances venous reflux detection.[7,8] Various stimuli, such as manual or pneumatic augmentation of the proximal and distal limb segments or the Valsalva maneuver, can elicit reflux.[7] In the standing position, reflux can be defined as abnormal valve closure time that produces greater than 0.5-second reversal of venous flow.[7,8]

A unique aspect of this study is that all patients were examined with both the clinical VCSS and the anatomic VSDS, something not previously reported in the same patient population. Even though the prevalence of severe disease was low, anatomic score correlated well with clinical score. This adds support for use and reliability of the clinical scoring system, and validates the anatomic system as a useful tool. Because all the veins in the calf were not interrogated in this population, this study underestimated the number of abnormalities, despite the fact that the VCSS enables evaluation of fewer than all 18 venous segments in the score.[1] If asymptomatic calf vein thrombosis were more frequent in this population, abnormalities could have been missed, and would not have been scored. In addition, minor abnormalities on US scans, such as vein wall thickening or minor luminal obstruction, suggested the presence of disease, but not severe enough to tally a score with the VSDS. It may be that this score is insensitive to more minor abnormalities on US scans, particularly with regard to obstruction. Table VIII demonstrates that a variety of abnormal disease patterns do not result in increased VSDS score.

Perhaps the most difficult aspect of the original CEAP classification[2] or its modification[1] is the estimate of disability. Twenty-nine patients with abnormal US scans had VDS of zero, whereas 47 patients with no US scan abnormality had a score of 1 or greater (meaning they were unable to carry out daily activities without wearing compression stockings). Similarly, among those with CEAP clinical class 3 or greater, 31 of 49 limbs (63%) demonstrated no evidence of venous disease on US scans. One must conclude that clinical assessment tools are still extremely insensitive, or that US diagnosis is inaccurate or insensitive in chronic venous disease. Other tests for venous disease, such as air plethysmography or venography, may have demonstrated abnormalities in patients with clinically suspected venous disease. In addition, it cannot be excluded that some patients with normal US scans complained of leg pain or edema, subjective symptoms that can also be due to venous insufficiency.

In this study, venous US scanning enabled detection of abnormalities in this patient population at high risk thought to be asymptomatic, as seen in our preliminary analysis.[6] Presence of superficial venous reflux, the most common abnormality, was similar to that found in a study of healthy patients by van Bemmelen et al.[13] However, equally important was the finding that a negative VCSS was unlikely to be associated with any significant abnormality seen on venous duplex US scans. The study has drawbacks, in that few patients had severe venous disease, and its use in patients with most severe disease may still be in question. While the CEAP classification and VCSS had equally high negative predictive values, the CEAP classification is not intended to respond to changes over time, and thus is not useful as a clinical tool to assess treatment. Correlation between VCSS and VSDS was high, a finding not previously reported. However, it is possible that predictive values would be different in a population with a different prevalence of chronic venous disease. It is likely that negative predictive value would decrease in a population with a higher prevalence of superficial venous insufficiency, whereas positive predictive value might be improved. On the other hand, this study population is at much higher risk for deep vein thrombosis compared with the general population, which argues for use the CEAP clinical classification and VCSS, not only for superficial venous insufficiency, but also for venous insufficiency related to sequelae of deep vein thrombosis. Our results show that both VCSS and VSDS are tools that the vascular specialist can use to objectively assess outcome of treatment of venous disease. Use of these scoring systems is being implemented in the vascular clinics at the authors' institutions. Although not the originally intended use of this scoring system, it may be that VCSS can be used as a screening tool in the clinical setting, though this will require prospective validation.

Such a screening function for VCSS would be of great use in investigation and management of venous thromboembolic disease in the setting of genetically determined thrombophilic families, similar to the subjects of this study. Among members of the kindred with protein C deficiency,

50% were affected by age 50 years, which emphasized the devastating effect of the disease in this population. Investigative efforts would be enhanced by improved definition of clinical disease, especially propensity for chronic venous insufficiency and identification of individuals with subclinical disease. The latter group improves the classification of affected individuals for assessment of genetic risk factors Clinical management would be improved by more effective prediction of chronic sequelae and possibly recurrent disease

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