

For Adults with Chronic Venous Thrombosis and Venous Obstruction, is There Sufficient Evidence for an Intervention?

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Question 2

For adults with chronic venous thrombosis and venous obstruction (including individuals with post-thrombotic syndrome), how confident are you that there is sufficient evidence for an intervention that improves:

- a. Immediate/near term health outcomes in patients presenting with symptoms? In patients presenting without symptoms but with signs?
- b. Long-term health outcomes in patients presenting with symptoms? In patients without symptoms but with signs?

Treatment of Chronic Venous Insufficiency

- **Sustained Compression**
- **Intermittent Pneumatic Compression**
- **Certain Medications and Nutrition**
- **Active Exercise**
- **Balneotherapy**
- **Correction of Superficial Reflux**
- **Correction of Venous Obstruction**
- **Venous Reconstructive Surgery**

Prevention of Chronic Venous Insufficiency

- **Ambulation/Stockings**
- **LMWH**
- **Aggressive Therapies**

Sustained Compression

Compression will increase venous leg ulcer healing (1A) and decrease the risk of ulcer recurrence (2B). Our guidelines suggest the use of multicomponent bandaging over single-component bandaging.

Mauck KF et al, J Vasc Surg 60:73S-92S, 2014

O'Meara, et al, Cochrane Database Syst Rev 11:CD000265, 2012

Vandongen YK and Stacey MC, Phlebology 15:33-37, 2000;

Nelson EA, Bell-Syer SE, Cochrane Database Syst Rev 9:CD002303, 2012

Barwell JR et al, Lancet 363:1854-1859, 2004

O'Donnell et al, J Vasc Surg 60: 3S-59S, 2014

Intermittent Pneumatic Compression

When other compression options are not available or have failed, intermittent pneumatic compression has been found to useful (2C).

Nelson EA et al, Cochrane Database Syst Rev 5:CD001899, 2014

Cohen JM et al, Chest 141:308-320, 2012

The treatment of C2 disease with compression alone remains debated. Although third party payers often require compression prior to authorizing a surgical procedure, this is unsupported in the literature.

[Gloviczki P et al, J Vasc Surg 53:2S-48S, 2011](#)

The REACTIV trial randomized C2 to compression hosiery and lifestyle modification or surgery (high ligation, stripping, and phlebectomy). This trial demonstrated more symptomatic relief, improvements in QOL, and more cost-effectiveness with surgery. The SVS/AVF recommend (1B) against compression therapy prior to surgery.

[Michaels JA et al, Br J Surg 93:175-181, 2006](#)

[Gloviczki P et al, J Vasc Surg 53:2S-48S, 2011](#)

Certain Medications and Nutrition

Nutrition assessment should be performed, especially if the patient has malnutrition and nutritional supplementation should be provided (best practice)

Pentoxifylline or micronized purified flavonoid fraction used in combination with compression has been found useful to heal venous ulceration (1B).

[Jull A et al, Cochrane Database Syst Rev 3:CD001733, 2007](#)

Active Exercise

Active exercise will improve calf muscle pump function and reduce pain and edema in patients with active leg ulcers (2B).

[Brown A. J Wound Care 21:342-350, 2012](#)

Balneotherapy

Limited data suggests that this therapy can improve skin trophic changes and quality of life in those with advanced venous disease (2B).

[Carpentier PH et al, J Vasc Surg 59:447-454, 2014](#)

Correction of Superficial Reflux

Ulcer healing (C6) is improved with ablation of the incompetent superficial veins of the leg combined with compressive therapies (2C), while ulcer recurrence (C5) is significantly reduced with ablation of incompetent superficial veins (1B-C).

[Barwell JR et al, Lancet 363:1854-1859, 2004](#)

For patients with significant skin changes and no ulcer yet (C4b), superficial venous ablation is also recommended (2C).

[Mauck KF et al, J Vasc Surg 60:60S-72S, 2014](#)

For patients with venous ulcers (C6) and incompetent perforating veins (outward flow >500 ms, diameter >3.5mm located beneath or associated with the ulcer bed), or with a healed ulcer (C5), ablation of both superficial veins and the perforators is recommended plus standard compression therapy (2C). Perforator ablation can occur simultaneously or staged.

For patients with advanced venous disease but no ulceration yet (C4b), superficial ablation +/- perforator interruption is warranted (2C), either at the same time or staged. Perforators are now treated with percutaneous techniques (1C).

[Tenbrook JA Jr et al, J Vasc Surg 39:583-593, 2004](#)

Correction of Venous Obstruction

In a patient with infrainguinal deep venous obstruction and skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), autogenous venous bypass or endophlebectomy in addition to standard compression therapy aids in venous ulcer healing and to prevent recurrence (2C). Deep vein ligation of the femoral or popliteal veins as a routine treatment is not recommended (2C).

In a patient with inferior vena cava or iliac vein chronic total occlusion or severe stenosis, with or without lower extremity deep venous reflux disease, that is associated with skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), venous angioplasty and stent recanalization in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence is recommended (1C).

O'Donnell et al, J Vasc Surg 60: 3S-59S, 2014

Table XIII. Evidence summary for endovascular ilio caval stents placed for total venous occlusive disease

	<i>Year</i>	<i>No. of limbs/limbs with ulcers</i>	<i>Follow-up, years</i>	<i>Cumulative patency</i>	<i>% Ulcers healed</i>
Venous stenosis					
Hartung et al ⁴¹³	2009	89/6	7	93%	83%
Meng et al ⁴¹⁴	2011	272/78	5	94%	85%
Raju and Neglen ¹⁷³	2006	99/19 (inferior vena cava only)	4	82%	62%
Neglen et al ⁴¹⁵	2007	982/167	6	Nonthrombotic: 100% Thrombotic: 86%	58%
Ye et al ⁴¹⁶	2012	224/63	4		99%
Chronic total occlusions					
Raju and Neglen ⁴¹⁷	2009	139/32	4	66%	58%
Rosales et al ⁴¹⁸	2010	34/7	7	90%	57%

Venous Reconstructive Surgery

In a patient with infrainguinal deep venous reflux and skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), **individual valve repair** for those who have axial reflux with structurally preserved deep venous valves in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence (2C), **valve transposition or transplantation** for those with absence of structurally preserved axial deep venous valves when competent outflow venous pathways are anatomically appropriate for surgical anastomosis in addition to standard compression therapy (2C), or **autogenous valve substitutes** by surgeons experienced in these techniques (2C) is recommended.

O'Donnell et al, J Vasc Surg 60: 3S-59S, 2014

Table XII. Evidence summary for venous valve transplantation

	<i>Year</i>	<i>No. of limbs</i>	<i>Follow-up, range (average), months</i>	<i>Valve competent</i>	<i>Symptom resolved/healed</i>
Taheri et al ³⁶⁵	1986	46	8-36	91.7%	89.1%
Nash ³⁶⁶	1988	25	12-18	80%	92.0%
Iafrati and O'Donnell ⁴⁰⁵	1997	15	(64)	92%	82%
Perrin ³⁶³	1997	30	12-120 (58)	30%	60%
Sottiurai ³⁶⁸	1997	33	8-169 (89)	38.7%	45.1%
Raju et al ⁴⁰⁶	1999	83	12-180	83%	60%
Tripathi et al ³⁷⁷	2004 ^a	38	(24)	47.5%	55.3%

^aImproved results with multiple valves repaired.

Table X. Evidence summary for internal valvuloplasty

	<i>Year</i>	<i>No. of limbs</i>	<i>Follow up, range (average), months</i>	<i>Valve Competent</i>	<i>Symptom resolved/healed</i>
Ferris and Kistner ³⁹¹	1982	32	12-156 (72)	72.7%	81.2%
Ericksson ³⁹²	1990	19	44	68.4%	73.7%
Cheate and Perrin ³⁹³	1994	52	3-54	85.2%	86.3%
Masuda et al ³⁷⁶	1994	32	48-252 (127)	77.5%	71.9%
Raju et al ³⁷⁸	1996	81	12-144	42.3%	76.5%
Sottiurai ³⁶⁸	1997	143	9-168	75%	75%
Perrin ³⁹⁵	2000	85	12-96 (58)	61.5%	71.4%
Tripathi and Ktenidis ³⁹⁶	2001	25	1-12 (6)	85.4%	84.0%
Tripathi et al ³⁷⁷	2004	90	(24)	79.9%	67.7%

Table XI. Evidence summary for venous valve transposition

	<i>Year</i>	<i>No. of limbs</i>	<i>Follow-up, months</i>	<i>Valve competence</i>	<i>Ulcer recurrence</i>
Johnson et al ⁴⁰⁰	1981	12	18	—	33%
Masuda et al ³⁷⁶	1992	14	120	40%	—
Sottiurai ⁴⁰¹	1996	20	9-149	40%	56%
Cardon et al ⁴⁰²	1999	16	24-120	75%	44%
Perrin ³⁹⁵	2000	17	12-168	53%	25%
Lehtola et al ⁴⁰³	2008	14	24-78	43%	—

O'Donnell et al, J Vasc Surg 60: 3S-59S, 2014

Prevention of Chronic Venous Insufficiency

Ambulation/Stockings

Rate and Severity of Post thrombotic Syndrome after Proximal DVT
can be cut by 50% by the use of Compression Stockings

Brandjes DP et al, Lancet 349:759-762, 1997

Prandoni P et al, Ann Int Med 141:249-56, 2004

Walking with Good Compression does not Increase the Risk of PE,
while significantly Decreasing the Incidence and Severity of the Post
thrombotic Syndrome

Schellong SM et al, Thromb Haemost 82(Suppl 1):127-129, 1999

Aschwanden M et al, Thromb Haemost 85:42-46, 2001

Partsch H et al, Sem Vasc Surg 18:148-152, 2005

Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial

Susan R Kahn, Stan Shapiro, Philip S Wells, Marc A Rodger, Michael J Kovacs, David R Anderson, Vicky Tagalakakis, Adrielle H Houweling, Thierry Ducruet, Christina Holcroft, Mira Johri, Susan Solymoss, Marie-José Miron, Erik Yeo, Reginald Smith, Sam Schulman, Jeannine Kassis, Clive Kearon, Isabelle Chagnon, Turnly Wong, Christine Demers, Rajendar Hanmiah, Scott Kaatz, Rita Selby, Suman Rathbun, Sylvie Desmarais, Lucie Opatrny, Thomas L Ortel, Jeffrey S Ginsberg, for the SOX trial investigators

Summary

Background Post-thrombotic syndrome (PTS) is a common and burdensome complication of deep venous thrombosis (DVT). Previous trials suggesting benefit of elastic compression stockings (ECS) to prevent PTS were small, single-centre studies without placebo control. We aimed to assess the efficacy of ECS, compared with placebo stockings, for the prevention of PTS.

Methods We did a multicentre randomised placebo-controlled trial of active versus placebo ECS used for 2 years to prevent PTS after a first proximal DVT in centres in Canada and the USA. Patients were randomly assigned to study groups with a web-based randomisation system. Patients presenting with a first symptomatic, proximal DVT were potentially eligible to participate. They were excluded if the use of compression stockings was contraindicated, they had an expected lifespan of less than 6 months, geographical inaccessibility precluded return for follow-up visits, they were unable to apply stockings, or they received thrombolytic therapy for the initial treatment of acute DVT. The primary outcome was PTS diagnosed at 6 months or later using Ginsberg's criteria (leg pain and swelling of ≥ 1 month duration). We used a modified intention to treat Cox regression analysis, supplemented by a prespecified per-protocol analysis of patients who reported frequent use of their allocated treatment. This study is registered with ClinicalTrials.gov, number NCT00143598, and Current Controlled Trials, number ISRCTN71334751.

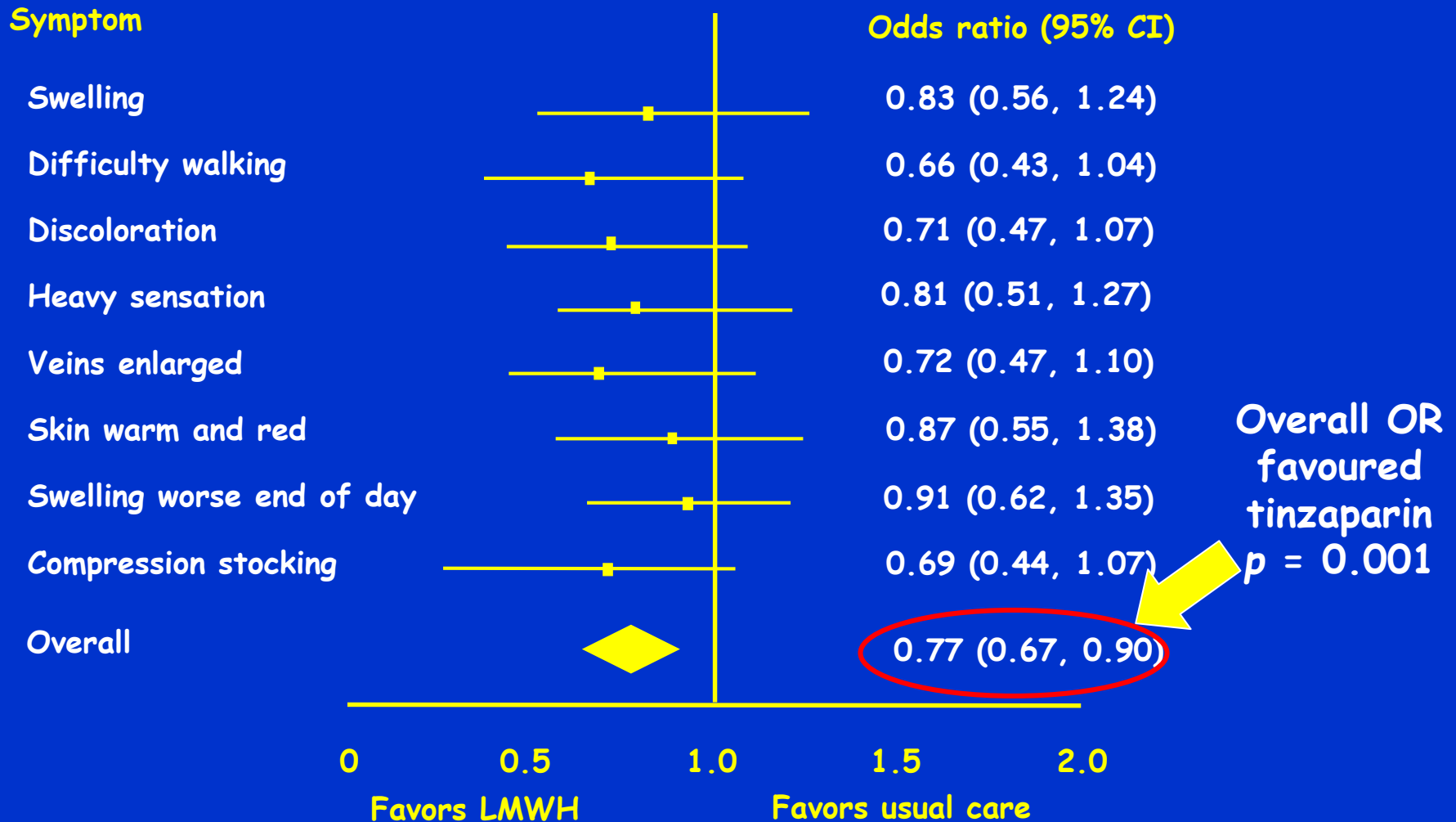
Findings From 2004 to 2010, 410 patients were randomly assigned to receive active ECS and 396 placebo ECS. The cumulative incidence of PTS was 14·2% in active ECS versus 12·7% in placebo ECS (hazard ratio adjusted for centre 1·13, 95% CI 0·73–1·76; $p=0·58$). Results were similar in a prespecified per-protocol analysis of patients who reported frequent use of stockings.

Interpretation ECS did not prevent PTS after a first proximal DVT, hence our findings do not support routine wearing of ECS after DVT.

Funding Canadian Institutes of Health Research.

Symptoms and signs of PTS following 12 weeks of therapy in Home-LITE

Tinzaparin (n240) vs. Tinzaparin + Warfarin (n240)



Aggressive Therapies

Goals of Therapy for Venous Thromboembolism (VTE)

- 1. Prevent Extension or Recurrence of Deep Venous Thrombosis (DVT)**
- 2. Prevent Pulmonary Embolism (PE)**
- 3. Minimize Early and Late Squeal of the Thrombosis**

Anticoagulants Accomplish #1, #2

Anticoagulants in General do not Accomplish #3

Randomized Thrombolysis vs Anticoagulation

35 patients with Iliofemoral DVT
18 Thrombolysis, 17 Anticoagulation

6 Month Patency 72% vs. 12% (Lysis)
6 Month Venous Reflux 11% vs. 41% (Lysis)

Table 3. Patency of the iliofemoral vein after 1 week and 6 months of the treatment.			
	Anticoagulant	Thrombolysis	<i>p</i> -value
Complete lysis			
1 week	0	11 (61%)	<0.001
6 months	2 (12%)	13 (72%)	<0.001
Incomplete lysis			
1 week	0	7 (39%)	0.004
6 months	8 (47%)	5 (28%)	0.238
No lysis			
1 week	17 (100%)	0	<0.001
6 months	7 (41%)	0	<0.001

Elsharawy M & Elzayat E, Eur J Vasc Endovasc Surg 24:209-214, 2002

Catheter-directed Thrombolysis vs. AC

Ca VenT Study

Open, Multicenter Randomized Controlled Trial

Patients with Iliofemoral DVT within 21 days from Symptom onset

90 : CDT + Conventional Therapy

99 : Conventional Therapy (6 months INR 2-3)

***All wore knee-high ECS Class II for 24 mo (*63% vs.52%)**

**Complete Lysis 43/90; Partial 37/90; 5 Major Bleed
6 Months, Iliofemoral Patency, 66% vs. 47%, $p=0.012$
PTS (6 mo), 30% vs. 32%, NS**

**PTS (24 mo), 41% vs. 56%, $p=0.047$
PTS (24 mo) for Patent Iliofemoral Segments vs.
Non-Patent Segments, 37% vs. 61%, $p=0.001$**

Enden T et al, Lancet 379:31-38, 2012

Long-Term Results with CDT - Iliofemoral DVT

**101 Patients (103 Limbs) with Iliofemoral DVT treated
with CDT**

**12 Months Anticoagulation and Stockings
Mean Age 29, 78 Women, 79 Left Sided**

Stents in 57

FU median 50 months

**82% Patency at 6 years with Competent Valves and No
Evidence of Skin Changes or Venous Claudication**

Baekgaard N et al, EJVES 39:112-117, 2010

Post thrombotic Morbidity Correlates with Residual Thrombus s/p CDT for Iliofemoral DVT

**71 Patients with Iliofemoral DVT treated with CDT
Pre and Post treatment Venograms Assessed for Quantity of Residual Thrombus**

**PTS assessed with CEAP and Villalta scores
Residual Thrombus $\leq 50\%$ (Gp 1) or $>50\%$ (Gp 2)**

CEAP: 1 vs. 4, $p=0.25$

Villalta : 2.21 vs. 7.13, $p=0.011$

Correlation CEAP and Residual Thrombus $R^2=0.74$

Correlation Villalta and Residual Thrombus $R^2=0.61$

Comerota AJ et al, J Vasc Surg 55:768-773, 2012

Early Removal of Thrombus Conveys Significant Benefits

The Earlier the Removal, the Better the Outcome

However, the Therapy is Complicated with Bleeding risk and the Value of such Therapy is Not Defined

Attract Trial (Acute Venous Thrombosis: Thrombus

Removal with Adjunctive Catheter-Directed Thrombolysis)

NIH NHLBI Funded, 10 Million, Phase III, Multicenter, Randomized, Open-label, Assessor-blinded, Parallel two-arm, controlled clinical trial with 30-50 US centers

692 Symptomatic Acute Proximal DVT, 1:1 PCDT +AC/ECS vs. AC/ECS

PTS, QOL, Symptom Relief, Safety, Cost, etc

Management of venous leg ulcers: Clinical practice guidelines of the Society for Vascular Surgery® and the American Venous Forum

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The care of patients with varicose veins and associated chronic venous diseases: Clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum

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The Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) have developed clinical practice guidelines for the care of patients with varicose veins of the lower limbs and pelvis. The document also includes recommendations on the management of superficial and perforating vein incompetence in patients with associated, more advanced chronic venous diseases (CVDs), including edema, skin changes, or venous ulcers. Recommendations of the Venous Guideline Committee are based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system as strong (GRADE 1) if the benefits clearly outweigh the risks, burden, and costs. The suggestions are weak (GRADE 2) if the benefits are closely balanced with risks and burden. The level of available evidence to support the evaluation or treatment can be of high (A), medium (B), or low or very low (C) quality. The key recommendations of these guidelines are: We recommend that in patients with varicose veins or more severe CVD, a complete history and detailed physical examination are complemented by duplex ultrasound scanning of the deep and superficial veins (GRADE 1A). We recommend that the CEAP classification is used for patients with CVD (GRADE 1A) and that the revised Venous Clinical Severity Score is used to assess treatment outcome (GRADE 1B). We suggest compression therapy for patients with symptomatic varicose veins (GRADE 2C) but recommend against compression therapy as the primary treatment if the patient is a candidate for saphenous vein ablation (GRADE 1B). We recommend compression therapy as the primary treatment to aid healing of venous ulceration (GRADE 1B). To decrease the recurrence of venous ulcers, we recommend ablation of the incompetent superficial veins in addition to compression therapy (GRADE 1A). For treatment of the incompetent great saphenous vein (GSV), we recommend endovenous thermal ablation (radiofrequency or laser) rather than high ligation and inversion stripping of the saphenous vein to the level of the knee (GRADE 1B). We recommend phlebectomy or sclerotherapy to treat varicose tributaries (GRADE 1B) and suggest foam sclerotherapy as an option for the treatment of the incompetent saphenous vein (GRADE 2C). We recommend against selective treatment of perforating vein incompetence in patients with simple varicose veins (CEAP class C₂; GRADE 1B), but we suggest treatment of pathologic perforating veins (outward flow duration ≥ 500 ms, vein diameter ≥ 3.5 mm) located underneath healed or active ulcers (CEAP class C₅-C₆; GRADE 2B). We suggest treatment of pelvic congestion syndrome and pelvic varices with coil embolization, plugs, or transcatheter sclerotherapy, used alone or together (GRADE 2B). (J Vasc Surg 2011;53:2S-48S.)