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CORRESPONDENCE

Phlebolymphology

CONTENTS

EDITORIAL

*D*ear Readers,

*This issue of Phlebolymphology contains several highlights. **Anthony Comerota**, Director of the Jobst Vascular Center of the University of Michigan, Toledo, Ohio, USA, gives a very comprehensive overview of the current status of thrombolysis for acute deep vein thrombosis. Due to the development of various forms of special catheter techniques, the rate of successful procedures can be increased and the previous risks connected with systemic fibrinolysis seem to be diminished. Long-term studies will be needed in order to prove that the rate of postthrombotic syndrome can be diminished in comparison with conservative therapy with adequate anticoagulation, mobilization, and compression.*

***Athanasios Giannoukas** of the University of Thessaly, Greece, presents a meta-analysis, which is based on four randomized, controlled studies demonstrating that the incidence of postthrombotic syndrome can be approximately halved if the patients wear medical compression stockings after proximal deep vein thrombosis. Early ambulation and compression together with low-molecular-weight heparin offer symptomatic relief in the acute phase of DVT, without an increased risk of recurrent thromboembolism.*

*One of the problems with compression therapy is poor patient compliance. **Seshadri Raju** and coworkers at the University of Mississippi Medical Center, Jackson, USA, demonstrate in a retrospective analysis that of 3144 chronic venous disease patients who had been under the prior care of primary care physicians or specialists, only 21% reported using the stockings on a daily basis, and 63% did not use them. These data correspond very well to findings from the recently published Bonn vein study showing that of 450 patients to whom compression stockings had been prescribed in the past, 69% did not wear them at the time of the survey (Pannier F, et al. Phlebologie. 2007;36:245-249). It can only be hoped that patients who would benefit from compression stockings, after deep vein thrombosis, for instance, do really wear them. Practitioners would certainly welcome recommendations concerning clear indications for compression stockings based on evidence and not just on convention.*

***Nicolas Danziger** of the Pain Center at the Medical Faculty Pitié-Salpêtrière, Paris, discusses the pathophysiology of pain in venous disease and presents interesting experimental findings suggesting an activation of venous and perivenous nociceptors accounting for the occurrence of pain starting at the early stages of venous disease. The decreasing pain with more advanced stages of venous disease may be related to peripheral sensory neuropathy induced by venous microangiopathy.*

*Results from the TRIANGLE screening program initiated by Servier are presented by **Prof Viera Štvrtinová**, Medical Faculty of Comenius University, Bratislava. TRIANGLE is an international, observational research program concentrating on the triad of clinical signs, symptoms, and quality of life in patients with chronic venous disorders. The results from*

3134 patients who were seen by 99 general practitioners in the Slovak Republic are reported. Patients with subjective symptoms or objective signs of chronic venous disease or both were enrolled and assigned to the clinical classes of the CEAP classification. Heaviness and pain in the lower limbs were present in 77% of patients, more frequently in higher than in lower CEAP classes. Leg swelling in the evening was reported by 20% of patients and edema during the daytime by 13%. Because of the selection criteria, the percentage of patients of CEAP class C1 was lower and of C6 higher than in epidemiological studies, like in the Bonn vein study in which a large, randomly selected population was examined clinically and by duplex scanning (Rabe E, et al. Phlebologie. 2003;32:1-14).

Enjoy reading!

Hugo Partsch, MD

Current status of thrombolysis for acute deep venous thrombosis

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ABSTRACT

An important question involving the management of patients with acute deep venous thrombosis (DVT) is whether thrombus removal improves outcome, either by reducing postthrombotic morbidity or reducing recurrence rates. Eliminating thrombus is intuitively appealing since persistent thrombus causes venous obstruction and destroys valve function, leading to ambulatory venous hypertension and, ultimately, symptoms of the postthrombotic syndrome. Natural history studies of acute DVT have demonstrated that when spontaneous lysis of thrombus occurs, valve function is preserved, especially when lysis occurs within 1-2 months of diagnosis. Early in the course of the development of thrombolytic agents, investigators evaluated the use of systemic thrombolysis for management of patients with acute DVT. While observations were made that postthrombotic morbidity was reduced, failure rates remained high and bleeding complications increased. Intrathrombus delivery of plasminogen activators facilitated thrombus resolution and reduced bleeding complications. This manuscript reviews the evolution of thrombolytic therapy for patients with acute DVT and addresses the integration of pharmacomechanical techniques and the development of new pharmacologic agents.

The standard recommendation for treatment of patients with acute DVT is antithrombotic therapy, beginning with heparin (intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin), followed by oral anticoagulation with warfarin.[1] Therapeutic anticoagulation prevents thrombus extension, pulmonary embolism (PE), and death from PE, and reduces the risk of recurrent venous thrombosis. Elastic compression stockings are recommended to reduce the risk of postthrombotic syndrome. The majority of patients with symptomatic DVT have involvement of the popliteal vein, the femoral vein, or more proximal veins.[2] Approximately

50% of patients with proximal DVT develop symptoms of the postthrombotic syndrome, and in 25% of patients with proximal DVT, the chronic postthrombotic complications are severe.[3] Two well-designed randomized trials have demonstrated that wearing 30-40 mm Hg compression stockings reduces the risk of postthrombotic morbidity by approximately 50%.[3,4]

Postthrombotic complications of acute DVT are the result of persistent venous obstruction and destruction of vein valve function.[5,6] Natural history studies of acute DVT have demonstrated that when spontaneous lysis of thrombus occurs, valve function is preserved, especially when lysis occurs within 1 to 2 months of diagnosis.[7] It seems intuitive that adopting a strategy that eliminates acute thrombus in patients presenting with acute DVT would significantly reduce postthrombotic morbidity.

Early in the course of the development of thrombolytic agents, investigators evaluated the use of systemic thrombolysis for management of patients with acute DVT. While observations were made that postthrombotic morbidity was reduced, failure rates remained high and patients paid the price of significantly increased bleeding.[8] Iliofemoral DVT is associated with the most severe postthrombotic morbidity. The percentage of iliofemoral DVT patients suffering postthrombotic complications and the severity of those complications substantially exceed the postthrombotic complications occurring in patients with infrainguinal DVT. These individuals represent a valid subset of patients with acute DVT who can justifiably be approached with a strategy of thrombus removal. The evolution of management of these patients has demonstrated the value of intrathrombus delivery of plasminogen activators to speed thrombus resolution and reduce bleeding complications.

This manuscript will review the development of thrombolytic therapy for patients with acute DVT and follow its evolution to catheter-directed thrombolysis and the integration of pharmacomechanical techniques. In addition, we will briefly address the development of new pharmacologic agents.

MECHANISM OF THROMBOLYSIS

Clot dissolution occurs as a result of plasminogen being activated by one of a number of plasminogen activators to form plasmin, which is the active enzyme. Plasminogen circulates as an inactive zymogen. In the systemic circulation, free plasminogen circulates as GLU-plasminogen. When thrombosis occurs, plasminogen binds to fibrin and is altered, forming LYS-plasminogen, which is more susceptible to activation by a plasminogen activator. Alkjaersig and colleagues[9] demonstrated that the basic mechanism of clot lysis by plasminogen activators is the activation of fibrin-bound plasminogen within thrombus to form plasmin, which then actively dissolves the clot. When plasmin escapes into the systemic circulation, it is instantaneously neutralized by α2-antiplasmin. Low doses of plasminogen activators are neutralized in the systemic circulation by plasminogen activator inhibitors. Pharmacologic doses of plasminogen activators persist in the circulation since they super-saturate the plasminogen activator inhibitors.

Since a relatively small percentage of systemically-infused plasminogen activators will come in contact with thrombus to activate fibrin-bound plasminogen, it is understandable that systemic therapy will be less effective than techniques that directly deliver plasminogen activator into the thrombus, thereby maximally activating fibrin-bound plasminogen.

Systemic thrombolytic therapy for acute DVT

The initial thrombolytic treatment of acute DVT was performed systemically, with plasminogen activators infused intravenously. Between 1968 and 1990, 13 studies of systemic thrombolysis versus anticoagulation for acute DVT were reported. These studies used ascending phlebography for initial diagnosis and to evaluate lytic success following lysis (*Table I*).[10-25]

An overall analysis of these studies demonstrates that 45% of thrombolysis patients had significant or complete clearing of their thrombus compared with 4% of those treated with anticoagulation alone.[8] Furthermore, the majority (82%) of anticoagulated patients had no clearing or actually worsened.

Elliot et al[20] and Arnesen et al[26] conducted trials of systemic thrombolysis in 78 patients, using the lytic agent streptokinase in similar protocols, and followed them up long term (1.6 and 6.5 years, respectively). Analysis of their outcomes demonstrates that postthrombotic symptoms occurred most frequently and with the greatest severity in patients treated with anticoagulation alone.

Author, year	Investigation type/total no. of patients	Treatment groups	Results			Complications				
			Significant/ complete resolution (%)	Partial resolution (%)	No. resolution/ Propagation (%)	Bleeding		PE	Death due to Rx (%)	
						Minor (%)	Major (%)			
Browse et al,[10] 1968	PR/10	SK/5 Hep/5	3 (60) 0 (0)	1 (20) 0 (0)	1 (20) 5 (100)	0 (0) 0 (0)	0 (0) 0 (0)	None None	None None	
Robertson et al,[11] 1968	PRB/16	SK/8 Hep/8	5 (63) 1 (12)	2 (25) 2 (25)	1 (12) 5 (63)	2 (25) 1 (12)	2 (25) 1 (12)b	NA NA	None 1 (12)b	
Kakkar et al,[12] 1969	PR/18	SK/9 Hep/9	6 (67) 2 (22)	1 (11) 2 (22)	2 (22) 5 (56)	0 (0) 0 (0)	3 (33) 2 (22)	None None	None 1 (11)	
Tsapogas et al,[13] 1973	PR/34	SK/19 Hep/15	10 (53) 0 (0)	0 (0) 1 (7)	9 (47) 14 (93)	0 (0) NA	4 (21) NA	NA NA	None None	
Duckert et al,[14] 1975	PNRB/134	SK/92 Hep/42	39 (42) 0 (0)	23 (25) 4 (10)	30 (33) 38 (90)	24 (26) 4 (10)	58 (62) 2 (5)	7 5	None None	
Porter et al,[15] 1975, e		SK/22	9 (40)	1 (5)	12 (55)	4 (17)	6 (25) b	1	1 (4)b	
Seaman et al,[16] 1976, e	PR/48	Hep/26	2 (8)	5 (19)	19 (73)	1 (0.4)	7 (27)	None	None	
Rosch et al,[17] 1976, e										
Marder et al,[18] 1977	PR/24	SK/12 Hep/12	5 (42) 0 (0)	2 (16) 3 (25)	5 (42) 9 (75)	NA NA	NA NA	NA NA	1 (8) b None	
Arnesen et al,[19] 1978	PR/42	SK/21 Hep/21	11 (52) 2 (10)	4 (19) 2 (14)	6 (29) 16 (76)	1 (5) 1 (5)	2 (10) 2 (10)	1 c None	None None	
Elliot et al,[20] 1979	PR/51	SK/26 Hep/25	17 (65) 0 (0)	1 (4) 0 (0)	8 (31) 25 (100)	1 (4) 0 (0)	2 (8) 0 (0)	None 2d	None None	
Watz et al,[21] 1979	PR/35	SK/18 Hep/17	8 (44) 1 (6)	4 (22) 5 (29)	6 (34) 11 (65)	3 (12) 2 (12)	0 (0) 0 (0)	1 1	None None	
Jeffery et al,[22] 1989	PR/40	SK/20 Hep/20	11 (55) 1 (5)	0 (0) 0 (0)	9 (45) 19 (95)	NA NA	NA NA	NA NA	None None	
Turpie et al,[23] 1990	PRB/82	rt-PA/40 Hep/42	13 (33) 2 (5)	9 (22) 7 (17)	18 (45) 33 (78)	3 (8) 1 (2)	2 (5) 1 (2)	NA NA	None None	
Goldhaber et al,[24] 1990	PRB/67	rt-PA/45 Hep/12	15 (33) 0 (0)	14 (31) 2 (17)	16 (36) 10 (83)	11 (24) 0 (0)	1 (2) b 0 (0)	NA NA	None None	

Table 1. Review of anticoagulation versus systemic lytic therapy for deep vein thrombosis (Reprinted with permission from Elsevier)[25]

A meta-analysis of systemic thrombolytic therapy for acute DVT reported improved clot dissolution at an increased risk for bleeding.[8] Subsequently, a Cochrane analysis of randomized trials of thrombolysis for acute DVT vs anticoagulation reported that complete clot lysis occurred significantly more often in patients treated with thrombolysis when examined at both early and late follow-up.[27] Significantly less postthrombotic morbidity was reported in lytic patients. Although venous ulcers were reduced and valve function improved, the numbers of patients evaluated for these end points were small, and so differences did not reach significance. Bleeding complications occurred more frequently in the thrombolytic group.

Although systemic thrombolysis is associated with better outcomes than anticoagulation alone, failures rates are still high. A likely cause of poor outcome in these studies is the failure of contact of the plasminogen activator with fibrin-bound plasminogen within the thrombus. A technique designed to ensure maximal exposure of fibrin-bound plasminogen to the plasminogen activator will be associated with improved outcomes.

Catheter-directed thrombolysis

The rationale for catheter-directed thrombolysis (CDT), which was initially used in patients with acute arterial occlusion,[28] is that rapid lysis is achieved with lower doses of thrombolytic therapy, resulting in fewer serious bleeding complications. Furthermore, positioning the catheter directly into the thrombus (intrathrombus delivery) takes advantage of the basic mechanism of thrombolysis, which is activation of fibrin-bound plasminogen.[9]

Numerous studies have reported good outcomes from catheter-directed thrombolysis for acute DVT (*Table II*).[29-47] Their outcomes have been summarized and published previously.[25] Three larger reports in particular showed a success rate of approximately 80%.[32,33,48]

Quality of life (QOL) is improved in patients with iliofemoral DVT treated with CDT. This was shown in a study evaluating iliofemoral DVT patients treated with CDT and compared with a contemporaneous group of iliofemoral DVT patients treated with anticoagulation alone.[49] The improved QOL directly correlated with successful lysis. Patients failing lytic therapy had the same QOL as patients treated with heparin.

Correction of underlying venous lesions or residual stenoses following successful thrombolysis was shown to contribute to long-term success. In the National Venous Registry, 74% of limbs treated with stent placement following lysis remained patent at 1 year, compared with 53% of limbs without stent placement ($P<0.001$). This observation most likely underscores the importance of correcting an underlying iliac vein stenosis (May-Thurner). Significant bleeding complications were reported in 9.9% of patients, with the majority being related to the catheter puncture site. Intracranial hemorrhage was reported in 2 patients (0.25%). Reports published during the past five years have shown a bleeding complication rate less than half (4.1%) that in earlier reports. This is likely due to more appropriate patient selection and experience with the technique. The reporting of pulmonary embolism (PE) was limited to symptomatic PE, which occurred in 4 patients (0.5%) and was fatal in one.

Unfortunately, there are few data from randomized trials of catheter-directed thrombolysis versus standard anticoagulation alone. Elshawary et al[39] performed a small study randomizing 35 patients with iliofemoral DVT to a pulse-spray catheter-directed thrombolysis with streptokinase versus anticoagulation alone. A six-month follow-up demonstrated significantly better patency and significantly less valvular reflux in patients receiving catheter-directed thrombolysis ($P<0.001$, $P=0.04$, respectively). Enden et al[50] reported an ongoing trial of 200 patients being randomized to CDT with tissue plasminogen activator (tPA) versus routine anticoagulation with low-molecular-weight heparin and coumadin in Norway. Approximately half of the 200 patients have been randomized to date. The primary outcome is patency of the iliofemoral venous segment at 6 months and the incidence of postthrombotic syndrome at 2 years. Other objectives will evaluate bleeding, health-related QOL, cost-effectiveness of therapy, procedural success, patency at 2 years, and postthrombotic syndrome at 6 months and 5 years.

A much larger 1000-patient trial is currently being evaluated for funding by the United States National Institutes of Health. This study will incorporate patients with proximal infrainguinal DVT as well as iliofemoral DVT randomized to CDT incorporating pharmacomechanical techniques plus anticoagulation versus anticoagulation alone. The results of these randomized trials are anxiously awaited and will most

Author, year	Total no. of patients (limbs)	Intervention	Significant/complete resolution (%)	Partial resolution (%)	No resolution (%)	Bleeding Minor (%)	Bleeding Major (%)	PE	Death due to Rx (%)
Semba et al,[29] 1994	21 (27)	CDT with UK, angioplasty/stenting for residual stenosis	18 (72)	5 (25)	2 (8)	1 (4)	0 (0)	None	None
Semba et al,[30] 1996	32 (41)	CDT with UK, angioplasty/stenting for residual stenosis	21 (32)	9 (28)	2 (6)	0 (0)	0 (0)	None	None
Verhaeghe et al,[31] 1997	24	CDT with rt-PA, stenting for residual stenosis	19 (79)	5 (21)	0 (0))	0 (0)	6 (25)	None	None
Bjarnason et al,[32] 1997	77 (87)	CDT with UK, angioplasty, stenting, thrombectomy, bypass for residual stenosis	69 (793)	0 (0)	18 (21)	11 (14)	5 (6)	1	None
Mewissen et al,[33] 1999	287 (312)	CDT with UK, stenting for residual stenosis systemic lysis (n=6)	96 (31)	162 (52)	54 (17)	15 (28)	54 (11)	6	2 (<1)
Comerota et al,[34] 2000	54	CDT with UK or rt-PA, thrombectomy for residual stenosis	14 (26)	28 (52)	6 (11)	8 (15)	4 (7)	1	None
Horne et al,[35] 2000	10	CDT with rt-PA	9 (90)	1 (10)	0 (0)	3 (30)	None	2 (20)	None
Kasirajan et al,[36] 2001	9	CDT with UK, rt-PA, or rPA	7 (78)	1 (11)	1 (11)	NA	NA	NA	NA
AbuRahma et al,[37] 2001	51	CDT w/ UK or rt-PA, stents/18 Hep/33	15 (83) / 1 (3)	NR / NR	NR / NR	3 (17) / 3 (9)	2 (11) / 2 (6)	None / 2 (6)	None / None
Vedantham et al,[38] 2002	20 (28)	CDT with UK, rt-PA, or rPA, thrombectomy, stenting	23 (82)	NR	NR	None	3 (14)	None	None
Elsharawy et al,[39] 2002	35	CDT w/ SK, angio, stent/18 Hep/17	13 (72) / 2 (12)	5 (28) / 8 (47)	0 (0) / 7 (41)	None / None	None / None	None / None	None / None
Castaneda et al,[40] 2002	15	CDT with rPA	15 (100)	NR	NR	None	None	None	None
Grunwald et al,[41] 2004	74 (82)	CDT with UK, tPA, or rPA, angioplasty, stenting	54 (73)	26 (32)	NR	6 (8)	4 (5)	None	None
Laiho et al,[42] 2004	32	CDT with rt-PA/16 Systemic lysis with rt-PA/16	8 (50) / 5 (31)	5 (31) / 8 (50)	NR / NR	4 (25) / 6 (38)	2 (13) / 1 (6)	2 (13) / 5 (31)	None / None
Sillesen et al,[43] 2005	45	CDT with rt-PA, angioplasty, stenting	42 (93)	NR	NR	4 (8)	None	1 (2)	None
Jackson et al,[44] 2005	28	CDT with UK or rPA, stenting	5 (18)	20 (72)	NR	2 (7)	None	None	None
Ogawa et al,[45] 2005	24	CDT with UK/10 CDT with UK + IPC/14	0 (0) / 5 (36)	10 (100) / 9 (64)	None / None	None / None	None / None	None / None	None / None
Kim et al,[46] 2006	37 (45)	CDT with UK/23 CDT + PMT/14	21 (81) / 16 (84)	3 (11) / 3 (16)	2 (8) / None	1 (4) / None	2 (7) / 1 (5)	1 (4) / 1 (5)	None / None
Lin et al,[47] 2006	93 (98)	CDT with rPA, rt-PA, or UK, angioplasty, stenting/46 PMT with rPA, rt-PA, or UK, angioplasty, stenting/52	32 (70) / 39 (75)	14 (30) / 13 (25)	5 (11) / 4 (8)	2 (4) / 2 (4)	1 (2) / None	None / None	None / None

Table II. Review of catheter-directed thrombolysis for acute deep vein thrombosis (Reprinted with permission from Elsevier)[25]

certainly guide future care of these patients with extensive venous thrombosis.

When successful, catheter-directed thrombolysis can relieve obstruction, maintain valve function, and preserve QOL.[42,43,49] However, the technique has been associated with prolonged infusion times, large doses of plasminogen activators, and the potential for bleeding complications. In the National Venous Registry, average urokinase dose was 7.8 million units with a mean infusion time of 53.4 hours. To address these concerns, adjunctive techniques designed to facilitate thrombolysis have been developed in recent years. These include percutaneous mechanical and pharmacomechanical devices that macerate and/or aspirate thrombus particles from the venous system.

Percutaneous mechanical thrombectomy and pharmacomechanical thrombolysis

Percutaneous mechanical venous thrombectomy was put into proper perspective by Vedantham et al[38] in their analysis of patients with acute DVT managed with mechanical thrombectomy in addition to other techniques, including CDT and balloon dilation and stenting. Percutaneous thrombectomy is unlikely to be effective as the only management option for patients with acute lower extremity DVT. Only 26% of the thrombus calculated by quantitative venography was removed, as analyzed in a retrospective study. The addition of catheter-infused plasminogen activator significantly improved results.[38] Overall success was that which could have been anticipated with CDT alone. The investigators thought the overall treatment time with the pharmacomechanical technique was shortened, although both on-table procedure time and the cost of the procedure increased. Others have noted similar observations that mechanical thrombectomy alone has unsatisfactory results that can be substantially improved with the addition of a plasminogen activator.[36] Pharmacomechanical thrombolysis combined with catheter-directed thrombolysis was the technique used with good results and no major complications in the randomized trial comparing CDT with anticoagulation.[39]

Pulmonary emboli have been observed with percutaneous mechanical thrombectomy. In a small series of 18 patients treated with a rotational thrombectomy device for iliocaval DVT following placement of a vena caval filter, all patients experienced oxygen desaturation and hypoxemia during the procedure, and 5 were found to have thrombus trapped within the caval filter. There was one procedure-related death (6%).[51]

Pulse-spray pharmacomechanical thrombolysis of clotted hemodialysis grafts demonstrated an 18% incidence of PE in patients treated with a plasminogen activator pulse-spray solution compared with a 64% incidence of PE in patients treated with a heparinized saline pulse-spray solution ($P<0.04$).[52] Because hemodialysis grafts are in direct communication with the venous circulation, embolic complications in these patients should be similar to those with proximal acute DVT. However, embolic complications with mechanical devices alone might be magnified when treating thrombus in much larger veins such as the iliofemoral venous system.

Segmental pharmacomechanical thrombolysis is an increasingly popular method in patients with acute DVT. One of the more promising pharmacomechanical catheter systems is the Trellis® catheter (Bacchus Vascular, Santa Clara, CA). This double-balloon catheter allows segmental infusion of a relatively high concentration of plasminogen activator per unit time and volume of thrombus treated. Thrombus is segmentally treated between two balloons. The proximal and distal balloons restrict the plasminogen activator to the segment of thrombus being treated. The intervening catheter assumes a spiral configuration and, when activated, spins at 1500 rpm. After a 15-20 minute treatment cycle, the liquefied and particulate debris is aspirated. Repeat phlebograms evaluate lytic success and whether treatment should be repeated or whether additional vein segments should be treated (*Figure 1*). Preliminary observations demonstrate rapid resolution of the thrombus treated with minimal exposure of the systemic circulation to the thrombolytic agent.

Ultrasound-accelerated thrombolysis is another interesting adjunctive technique for catheter-directed thrombolysis. The LYSUS catheter system (EKOS Corp, Bothell, WA) integrates a lytic infusion catheter with multiple ultrasound-emitting foci along the length of the catheter. The ultrasound waves distort and fragment fibrin, increasing its surface area and improving the rapidity of activation of fibrin-bound plasminogen, which increases the speed of lysis. Preliminary observations on both the arterial and venous sides of the circulation suggest that this unique method of
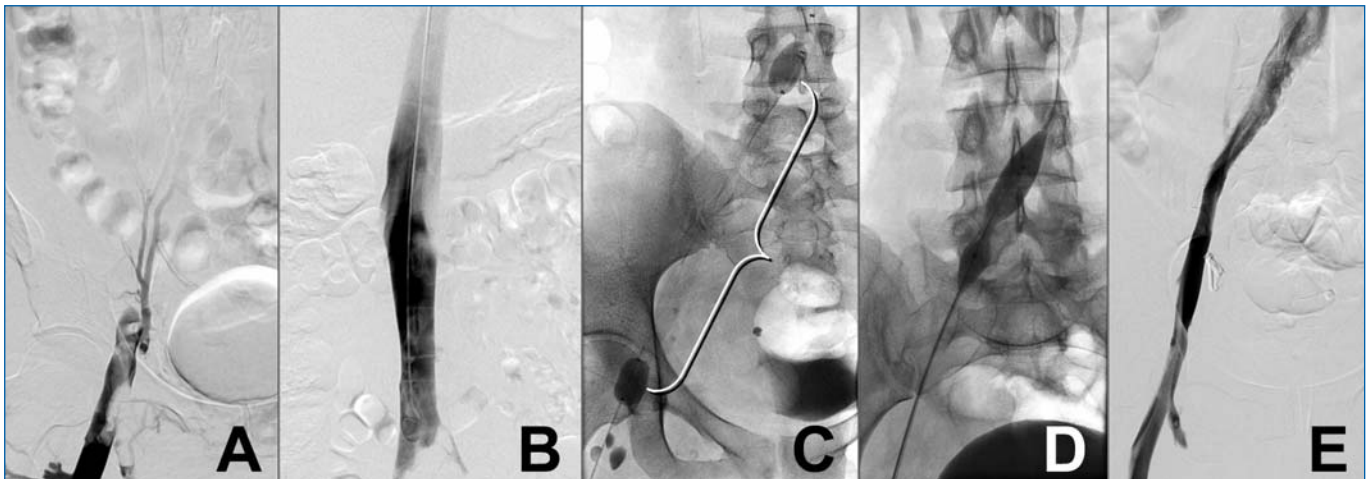
Figure 1. A 26-year-old woman presents with a two-day history of severe left lower extremity pain and edema extending from the toes to the upper thigh. A venous duplex exam suggested iliac vein thrombosis. (A) The ascending phlebogram (prone position) demonstrates left common femoral, external iliac, and common iliac vein thrombosis. (B) The vena cava was patent. Isolated segmental pharmacomechanical thrombolysis with a double-balloon catheter (Trellis®) was used. (C) The proximal and distal balloons are visualized. Three mg of tissue plasminogen activator was injected in a volume of 6 cc of fluid. A single 20-minute run of the intervening catheter rotating at 1500 rpm resolved the thrombus and revealed a residual common iliac vein stenosis. (D) A balloon angioplasty was performed and the stenotic "waist" is visualized (arrow). A stent resolved the stenosis. (E) A completion phlebogram demonstrates complete thrombus resolution and unobstructed venous drainage into the vena cava. The patient was discharged and has been symptom-free.

pharmacomechanical thrombolysis reduces treatment times, thereby reducing potential complications.

New pharmacologic agents

In addition to new developments in the mechanical delivery of plasminogen activators to thrombus and the mechanical management of thrombus itself, a new class of pharmacologic agents that directly lyse clots without requiring a plasminogen activator is being developed. These agents appear to act more rapidly than traditional plasminogen activators and are immediately neutralized upon entering the systemic circulation.

Alfimeprase and plasmin are two such agents. They are direct fibrinolytic agents that are not plasminogen-dependent and are not inactivated by plasminogen activator inhibitor-1.

Alfimeprase is a direct-acting lytic agent which is a fibrinolytic zinc metalloproteinase, which is a truncated form of fibrolase. It is derived from southern copperhead snake venom and is produced by recombinant techniques in *Pichia pastoris*. Alfimeprase is instantly neutralized in the systemic circulation by α2-macroglobulin. Although no studies have been performed in patients with acute DVT, intrathrombus infusion has been studied in patients with acute arterial occlusion. Phase 1 and phase 2 studies demonstrated safety, but phase 3 trials demonstrated no benefit of catheter-directed alfimeprase versus placebo in patients with acute arterial and graft occlusion.

Plasmin is also a direct-acting fibrinolytic agent. It is produced from pooled plasma. It is instantly neutralized by α2-antiplasmin when it escapes into the systemic circulation. Animal studies have demonstrated improved efficacy compared with recombinant tPA (rtPA) in models of acute aortic occlusion.[53-55] Reduced distant bleeding compared with rtPA has also been observed. The explanation for improved safety of plasmin is that antiplasmins rapidly neutralize plasmin that escapes into the circulation, whereas rtPA circulates, binds to hemostatic plugs at sites of vascular injury, degrades fibrin, and thereby induces new hemorrhage. Plasmin is currently in phase 1/2 trials for acute arterial and graft occlusion, with plans for study in patients with acute DVT.

CONCLUSION

Available evidence supports the use of CDT in patients with extensive, symptomatic acute DVT. Bleeding complications have been reduced, especially during the past five years. The improvement in technology allowing the incorporation of mechanical and pharmacologic techniques has improved the speed of lysis, reduced treatment times, and reduced doses of plasminogen activators.

The development of a new class of thrombolytic agents that act directly on thrombus without the need for a plasminogen activator and are rapidly neutralized upon entry into the systemic circulation holds promise of further improving outcomes and reducing risks of bleeding complications.

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The role of compression in the prevention of postthrombotic syndrome

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ABSTRACT

The role of compression with or without early ambulation in patients with deep venous thrombosis (DVT) in the prevention of postthrombotic syndrome (PTS) has not been widely accepted in clinical practice. This article investigates the existing evidence regarding the effects of compression in the prevention of PTS, with or without early ambulation after proximal DVT.

Electronic and hand searching of the relevant literature was undertaken. Two systematic reviews and four randomized studies were identified. In these four studies there was lack of uniformity in reporting standards. In all but one study a clear benefit (48% risk reduction in the development of PTS) was shown by the use of compression with or without early ambulation, without any difference in respect of recurrent thromboembolic complications (DVT or pulmonary embolism). In one study the early symptomatic outcome was better with a combination of early ambulation plus compression.

Despite the lack of uniformity in reporting standards in the literature, compression with or without early ambulation appears to be associated with a decreased rate of PTS.

INTRODUCTION

Subcutaneous low-molecular-weight heparin (LMWH) has revolutionized the treatment of deep venous thrombosis (DVT), because it is at least as effective and safe as conventional unfractionated heparin,[1-5] allowing outpatient treatment without the need for laboratory monitoring.[3,5-7]

There is lack of consensus regarding the definition of postthrombotic syndrome (PTS), and several scoring systems have been proposed to aid diagnosis.[8-10] Venous hypertension secondary to outflow obstruction or vein valve incompetence or both, and the condition of the calf muscle pump

function, play an important role in the development of PTS.[11-15].

Removable elastic bandages, inelastic adherent bandages, graduated compression elastic stockings, and intermittent compression pneumatic devices have all been used to reduce swelling by promoting acceleration of venous return and improving muscle pump function.[16-20]

This article investigates the evidence regarding the effects of compression on the prevention of PTS, with or without early ambulation after proximal DVT.

MATERIAL AND METHODS

A literature search was undertaken in MEDLINE from 1966 and EMBASE from 1980 using the terms DVT, elastic compression, compression, and PTS. Handsearching of the journals Phlebology (1990-2007), Journal of Thrombosis and Haemostasis (2003-2007), and the abstract books of the Annual Meetings of the European Venous Forum (2000-2007) and American Venous Forum (1989-2007) was undertaken. The references of relevant papers were also consulted.

Only systematic reviews and studies that had a randomized controlled design in the evaluation of any kind of compression treatment in patients with a proven proximal thrombosis (extended at least up to the popliteal vein) were considered.

RESULTS

Four studies[21-24] that met the inclusion criteria and two systematic reviews[25,26] were identified. In all but one study[22] compression was associated with beneficial effects in the prevention of PTS. The benefit conferred in each study separately and when all four studies were considered together was analyzed in a systematic review (*Table I*).[26] This analysis showed that PTS developed in 24% (61/254) of patients in the compression group and in 46% (110/239) in the control group (x^2= 25.36, *P*=0.0001; odds ratio, 0.37; 95% confidence interval [CI], 0.25-0.54; relative risk [RR], 0.52; 95% CI: 0.40-0.67; RR reduction,: 0.48; 95% CI, 0.33-0.60), with a 48% risk reduction because of the use of compression.

DISCUSSION

The diversity in standards of reporting PTS remains unresolved. The pain and swelling that patients experience during the acute phase of proximal DVT usually subside within two to twelve weeks as a result of various factors, including the lytic process of the thrombus, how fast the recanalization occurs, as well as the timing of the development of collateral flow.[14,15] However symptoms similar to those of PTS, such as leg pain, aching, and swelling on standing, may persist despite the good compensation of the thrombotic process. Additionally, it should be acknowledged that not all patients develop PTS after proximal DVT.[22] The devel-

Study or sub-category	Treatment n/N	Control n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
Brandjes et al	19/96	46/98		42.29	0.28 (0.15, 0.53)
Ginsberg et al	11/42	11/40		9.63	0.94 (0.35, 2.49)
Prandoni et al	23/90	44/90		37.94	0.36 (0.19, 0.67)
Rartsh et al	8/26	9/11		10.14	0.10 (0.02, 0.56)
Total (95% CI)	254	239		100.00	0.35 (0.24, 0.52)

Total events: 61 (Treatment), 110 (Control)
Test for heterogenety: Chi² = 6.39, df = 3 (P = 0.09), I² = 53.1%
Test for overall effect: Z = 5.22 (*P* < 0.00001)

0.2 0.5 1 2 5 10

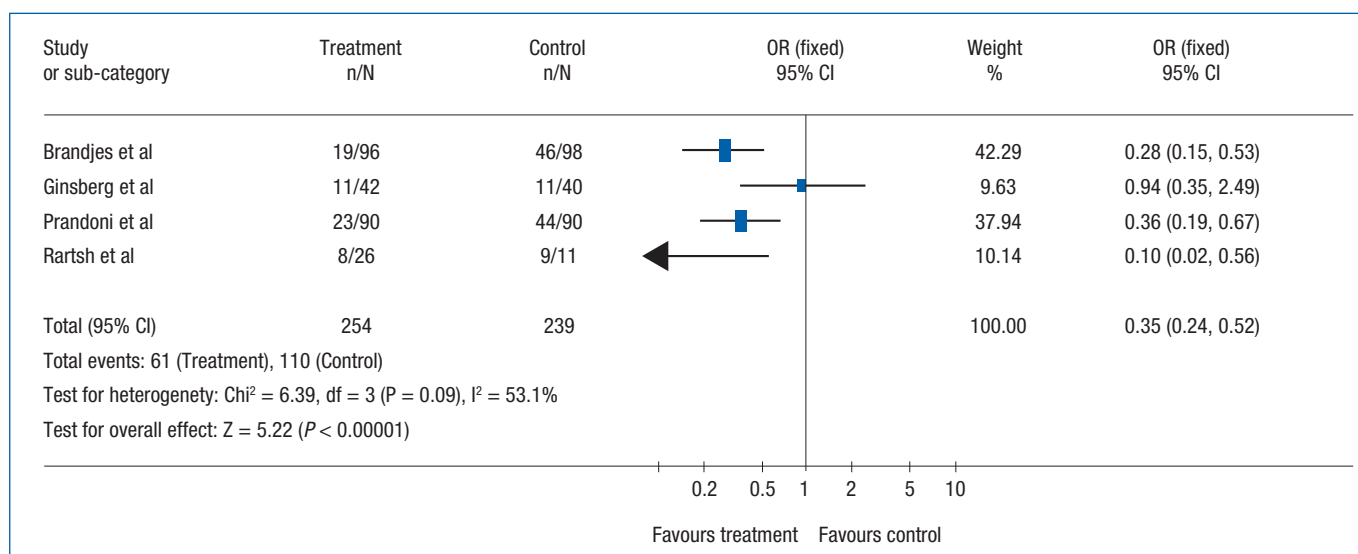Favours treatment   Favours control

Table I. Benefit provided by compression when all four studies were considered together.[26]

opment of true PTS is a consequence of venous hypertension secondary to venous valvular incompetence or occasionally to residual venous obstruction or to both.[27-29] The adoption of the most recent CEAP classification[10] in future studies may help overcome the problems in reporting PTS.

Another diversity found in the literature[21-24] was in the type of compression and the timing of its application after the onset of DVT. The latter varied from immediately after the index event to three weeks. In one study[22] the control group was also given elastic stockings one to two sizes too large, which still can exert some compression. Furthermore, the treatment group in this study[22] was given elastic stockings that exerted a pressure of 20-30 mm Hg at the ankle. In two of the other studies,[21,23] compression at the ankle was 30 to 40 mm Hg, and in the remaining study[24] compression was offered either by combination of a firm inelastic bandage with Unna's boot and a firm adhesive bandage or by thigh length compression stockings.

Nevertheless, all but one study[22] demonstrated that compression offers significant benefit, with 48% risk reduction in PTS development. Additionally, early ambulation even at the acute phase of DVT combined with compression offered a more favorable symptomatic outcome compared with bed rest.[30,31] This adds further to the perceived benefits of the treatment of DVT with LMWH by offering early symptomatic relief and improved well-being.

In conclusion, compression with or without early ambulation appears to be associated with a decreased rate of PTS without any increased risk of recurrent thromboembolism. However, because of the methodological defects in the relevant literature, a large, randomized, controlled trial is needed to prove these effects conclusively. Alternatively, if such study is questionable on ethical grounds a large observational study could be done instead.

Finally, future studies should address issues such as the optimal timing of elastic compression, the minimum duration that stockings must be worn after the episode of DVT, and the pressure required to optimize the beneficial effects.

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Chronic venous disease in general practice in the Slovak Republic: the TRIANGLE Survey

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RATIONALE OF THE TRIANGLE SURVEY IN THE SLOVAK REPUBLIC

The TRIple Assessment in chronic venous disease linkiNg siGns, symptoms and quaLity of lifE (TRIANGLE) Survey is a screening program initiated by Servier. TRIANGLE is an international observational research program designed to provide information on the prevalence of chronic venous disease (CVD) and to help achieve better understanding of the triangular relationship between symptoms, signs, and the quality of life in patients suffering from CVD.

The Slovakian TRIANGLE program, which is reported in this paper, was professionally endorsed by the Slovakian Medical Association for Angiology. The program was focused mostly on the prevalence of symptoms and signs of CVD in Slovakia, with some data reported on the quality of life. No validated quality of life questionnaire was used, but a simple six-item questionnaire was to be filled in by patients. Part of these recent surveys used the basic Clinical, Etiologic, Anatomic, Pathophysiologic (CEAP) classification,[1] in which the single highest descriptor is used for clinical class. The aim of the program was not only to diagnose patients with CVD in a primary care setting, but also to broaden knowledge of the incidence on well-being of particular clinical stages of CVD as well as of associated symptoms.

INTRODUCTION

CVD of the lower limbs is often characterized by symptoms and signs as a result of structural or functional abnormalities of the veins.[2] Symptoms include aching, heaviness, leg tiredness, cramps, itching, burning sensations, swelling, and restless legs syndrome. Signs include telangiectasias, reticular and varicose veins, edema, and skin changes such as pigmentation, lipodermatosclerosis, dermatitis, and ultimately venous leg ulceration.[2]

CVD signs are described in the CEAP classification[1,3] which comprises four components, ie, the clinical (C), etiologic (E), anatomic (A), and pathophysiologic (P) aspects of such signs. Basic CEAP should include *all four*

Keywords:
chronic venous disease in Slovak Republic - epidemiology - symptoms, signs, quality of life

components, but the majority of general practitioners do not have a duplex scan that provides data on E, A, and P. The highest descriptor is used for clinical class in the basic CEAP (*Table I*).

C0	no visible or palpable signs of venous disease
C1	telangiectasias or reticular veins
C2	varicose veins
C3	edema
C4	skin changes C4a: pigmentation and/or eczema C4b: lipodermatosclerosis and/or atrophie blanche
C5	healed venous ulcer
C6	active venous ulcer
S	symptoms including ache, pain, tightness, skin irritation, heaviness, muscle cramps, as well as other complaints attributable to venous dysfunction
A	asymptomatic

Table I: Clinical classification of chronic venous disease according to the revised CEAP[1]

Symptoms are not specific to CVD and to be attributed to CVD should meet at least two of the following criteria:[4] exacerbated after prolonged standing, but diminished after rest, or improve or disappear on walking,

exacerbated at the end of the day, but disappear in the morning, after night rest, exacerbated by warmth (summertime, hot baths, floor-based heating systems, hot waxing to remove body hair), but are less intense in winter and at low temperatures, and for women, exacerbated before menstruation or occur with hormonal therapy, but disappear with discontinuation of such treatment, or after the menstruation.

The aim of the Slovakian TRIANGLE survey was to provide updated figures on the prevalence of symptoms and signs of CVD, using clear and globally accepted clinical definitions for venous disease, based on the CEAP classification.[1]

MATERIAL AND METHODS

Investigators could include consecutive patients within a period of 20 continuous days. These were adults (> 18 years) consulting for general health care, whether for cardiology, diabetology, or infectious diseases. To be enrolled in the survey, patients had to present with subjective symptoms and/or objective signs of CVD. Investigators had to examine patients' lower limbs and assign them a class according to the C of the CEAP classification (*Table I*). Patients willing to cooperate were requested to fill out a questionnaire consisting of six simple questions dealing with the incidence of subjective symptoms on their daily lives (*Table II*).

1/ Was the main reason for visiting a physician pain in your legs, leg cramps, feelings of tension in your leg, or leg swelling?			
✍ no	✍ yes		
2/ Have you felt heaviness or even pain in your legs during the past 4 weeks?			
✍ no	✍ slight	✍ moderate	✍ severe
3/ Do you have cramps in your lower limbs?			
✍ no	✍ occasionally	✍ often	✍ daily
4/ Do you have swelling of the lower limbs?			
✍ no	✍ occasionally in the evening	✍ every evening	✍ even during the day
5/ Do some of the above mentioned symptoms reduce your daily activities or tasks, eg, longer standing, traveling, fast walking, kneeling and bending down, housework, sports, entertainment?			
✍ no	✍ slightly	✍ considerably	✍ greatly
6/ Do you have problems exposing your legs (e.g. in a swimming pool)?			
✍ no	✍ slightly	✍ considerably	✍ greatly

Table II: Questionnaire to be filled in by patients

RESULTS

A total of 99 GPs from all parts of Slovakia were involved in the TRIANGLE study (*Figure 1*). They enrolled 3134 patients who met the inclusion criteria defined above.
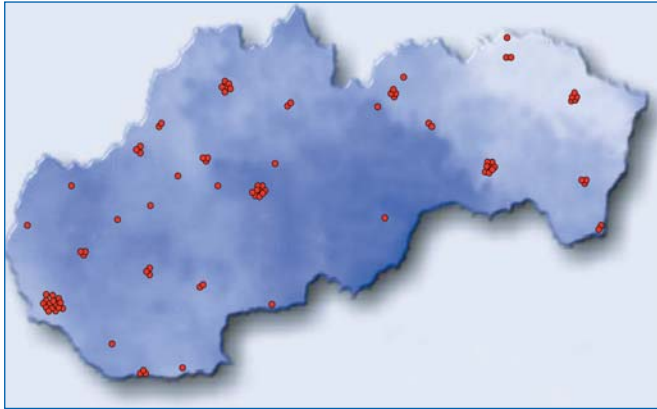

Figure 1. Participating centers in Slovakia

Signs of CVD

Figure 2 shows the results of medical examinations of the lower limbs of the 3134 examined individuals using the CEAP classification. The largest proportion of patients—35%—was assigned class 2 (trunk varicose veins) of the CEAP, 20% had edema (C3), and 19% had skin changes (C4). Telangiectasias and reticular veins were present in 15% of examined patients. A quite high proportion of patients had active (2%) or healed (4%) venous leg ulcers.
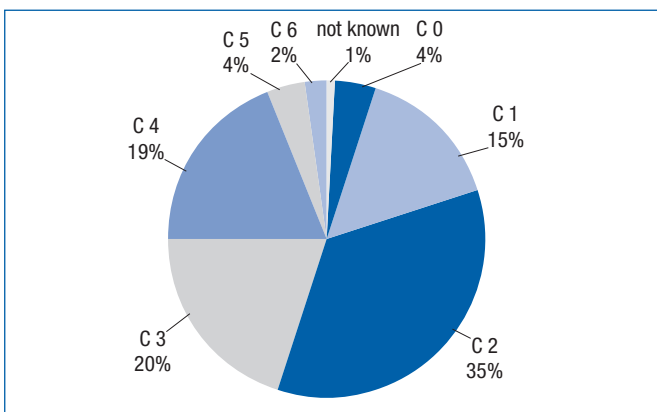

Figure 2. Distribution of patients according to the CEAP classification

Symptoms of CVD

Four per cent (4%) of patients suffered from subjective symptoms of CVD (heaviness, aching, edema, cramps)

without associated objective signs of the disease. Such patients can be classified as C0s according to the C of the CEAP. A duplex scan could have told us whether they had reflux or not.

Symptoms like leg heaviness and pain in the lower limbs were present in 77% of patients, 13% of whom complained of severe pain (*Figure 3*). With progression of the clinical stages of the disease, the percentage of patients with moderate to severe pain increased (*Figure 4*), since 42% patients with healed varicose ulcer (C 5) and 70% of those suffering from active varicose ulcer (C 6) had severe pain. Intermittent edema of the lower limbs was reported by 36% of patients (*Figure 5*). In 20% of patients, the edema appeared every evening, and 13% of patients noticed the edema occurring already during the daytime. With disease progression, the percentage of those with edema every day increased (*Figure 6*). Similarly, the frequency of cramps increased with clinical stage (not shown).
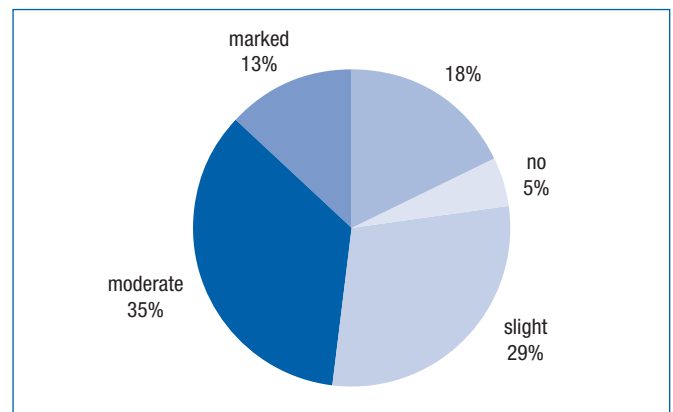

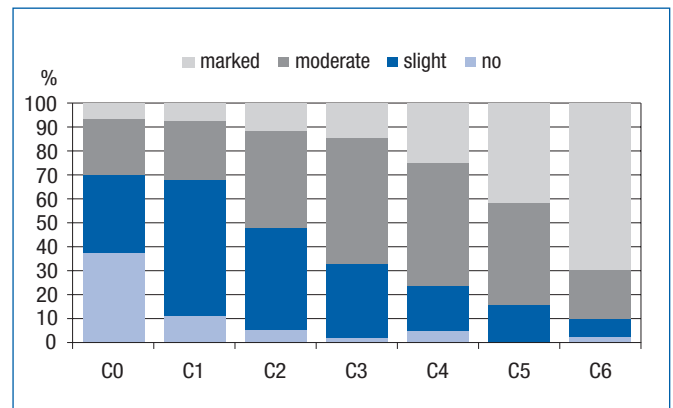*Figure 3. Severity of pain and/or leg heaviness in patients with CVD*

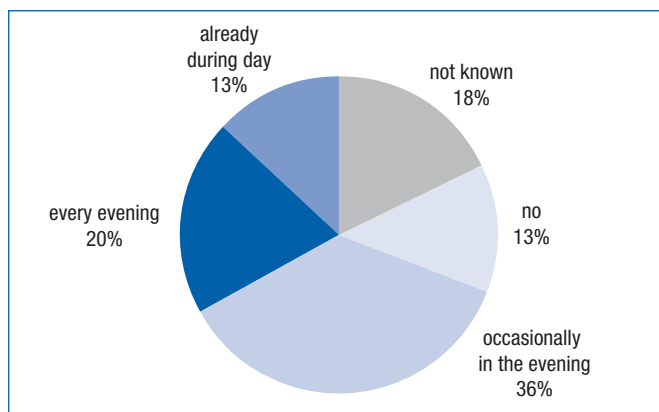*Figure 4. Severity of pain and/or leg heaviness according to CEAP class*

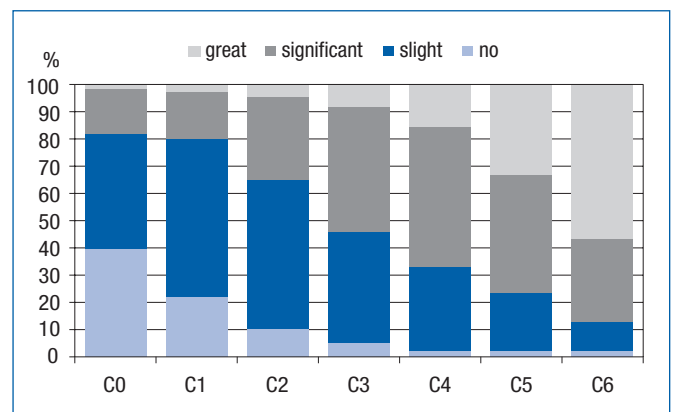Figure 5. Frequency of edema in patients with CVD

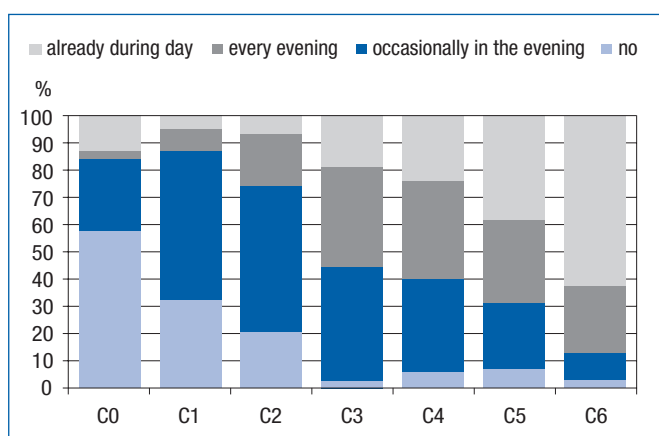Figure 8. Reduction of daily activities in patients with CVD

Figure 6. Frequency of edema according to CEAP class

Quality of life

Data from the self-administered questionnaires (*see Table II*) indicated that the quality of life of patients suffering from venous disease was decreased compared with that of the healthy population (*Figure 7*). More than half (56%) of
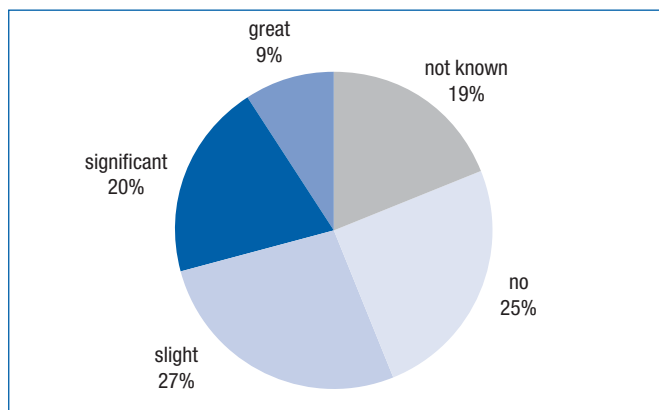
patients were embarrassed to show their legs because of visible signs of CVD. As a consequence, these patients avoided going to the swimming pool and, for women, wearing skirts. A third had very serious or substantial social problems. The number of individuals who were prevented from doing certain daily activities or tasks increased with disease severity (*Figure 8*).

DISCUSSION

A recent survey in the USA[5] reported visible signs like telangiectasias, varicose veins, and trophic changes in 67% of men and 89% of women with CVD. Telangiectasias and reticular veins are the most widespread signs of CVD in the countries of Europe,[4] accounting for 50% in men and 65% in women.[6] Little epidemiologic research has been conducted in Eastern Europe.[6,7] In a cross-sectional survey among 40 095 individuals of the adult population in Poland, a prevalence of CVD signs similar to that observed in Western countries was reported. A high prevalence of varicose veins was found in the Slovak Republic in a previous survey among 696 female employees in a department store: telangiectasias in 30.7%, reticular varicose veins in 15.4%, and trunk varicose veins in 14.4%, which means 60.5% of women with visible varices.[7] In the present TRIANGLE survey, the proportion of patients with varicose veins is slightly higher (35%) and with telangiectasias and reticular veins less (15%) than in our previous trial[7] and in the medical literature.[4-6] This may be the result of a discrepancy in the evaluation of "visible" signs by GPs (as in the present survey) compared with specialists, who investigate patients in most epidemiological publications. Active and healed ulcers were more prevalent in the TRIANGLE

Figure 7. Distribution of patients according to the cosmetic embarrassment they feel due to leg problems

survey (respectively, 2% and 4%) than in other reports, in which its prevalence does not exceed 0.5% to 1%.

We found a correlation between the severity of CVD according to the CEAP C classes and the prevalence of venous symptoms, in agreement with previous trials.[4,5,8,9] In Edinburgh, Ruckley et al[8] found a significant correlation between the severity grades of CVD (assessed according to the Widmer classification) and the prevalence of heaviness/tension, feeling of swelling, aching, and itching. Criqui et al in San Diego[5] found an increased prevalence of symptoms with increasing severity of signs, in agreement with the findings of Kahn[9] and Carpentier.[4]

In spite of the high incidence of the disease-related signs as mentioned above and of their considerable social and economic burden for society, there is still only a partial understanding of the pathogenesis of such chronic disorders. This probably explains the insufficient management of patients with CVD. Not uncommonly, unsatisfactory treatment outcomes in CVD are the result of negligence of health care providers themselves, not to mention insufficient clinical and instrumental examination of patients, as well as improper therapeutic methods.[10] As Professor John Bergan points out,[11] it is an unfortunate fact that research interest and funding attracted by CVD has been in inverse proportion to its prevalence and socioeconomic burden and this state of affairs is unwarranted, not simply for humanitarian reasons, but also in terms of fundamental research. Furthermore, varicose veins of the lower limbs are often considered a merely cosmetic defect. However, the "trivial" varicose veins of the lower limbs usually presage the development of a full spectrum of pathologic conditions ranging from mild signs of CVD to ulcer of the lower limbs, with possible fatal pulmonary embolism. Early treatments including lifestyle changes, mechanical devices, and oral drugs may prevent or slow the development and recurrence of troublesome outward manifestations.

CONCLUSION

The TRIANGLE program has confirmed the high prevalence in Slovakia of CVD, which can cause considerable subjective symptoms and frequent social problems for sufferers. The survey findings show that CVD treatment must be both timely and complete.

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Compliance with Compression Stockings in Chronic Venous Disease*

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ABSTRACT

Data regarding past and present stocking use was collected from 3144 chronic venous disease (CVD) patients who had been under the prior care of primary care physicians or specialists. Only 21% of patients reported using the stockings on a daily basis, 12% used them most days, and 4% used them less often. The remaining 63% did not use the stockings at all or abandoned them after a trial period in the past. Compressive stockings were inapplicable in about a quarter of patients due to the condition of the limb or the general health of the patient. They were ineffective despite wear in about a third of CVD patients. In the remainder, noncompliance with prescribed compressive stockings is an apparent major cause of treatment failure. Nonuse and noncompliance with compressive stockings is very high in patients with CVD regardless of age, sex, etiology of CVD, duration of symptoms, or disease severity. Reasons for nonuse of stockings can be broadly divided into three categories: (1) inapplicability (2) inefficacy, and (3) noncompliance. The reasons for noncompliance can be grouped into two interdependent major categories: (1) wear-comfort factors, and (2) intangible sense of restriction imposed by the stockings.

INTRODUCTION

Compression is effective when used as intended in treating the various symptoms of chronic venous disease (CVD).[1] Some patients, however, will not use compression stockings on a regular basis or at all, leading to persistence or recurrence of symptoms. This problem of noncompliance is well known to treating phlebologists and has been the subject of debate as to how compliance with compression stockings could be improved.[2] Available data to delineate the extent of noncompliance in CVD has been limited to small series of patients with stasis ulceration.[3,4] The degree of noncompliance in other symptom subsets is as it undefined.

PATIENTS AND METHODS

A total of 3144 CVD patients were referred to our clinic over an 8-year period from 1998-2006 for evaluation and treatment. As a tertiary referral center for CVD, patients had been under the care of other physicians for a variable time prior to referral. A compression history detailing prior use was part of the initial evaluation. Data was entered into an electronic medical record and later analyzed. Nonparametric Wilcoxon's signed-rank test for unpaired data and chi-square tests were used as appropriate in statistical analysis.

RESULTS

The median age was 58, with a male to female ratio of 1:2. Clinical class (CEAP) was as follows: C 0-2, 67%; C 3, 22%; C 4, 4%; C 5, 4%; C 6, 3%.

Only 37% of the patients reported using compression; 21% on a daily basis and 16% less often (*Figure 1*). Sixty-three percent did not use stockings, or had abandoned their use after trying them for a period of time in the past. The reasons for nonuse are shown in Table I. Use of stockings was poor and similar in both men and women (39% vs 38%, p=ns). There was no difference among the various decile age groups in the use of compression stockings (*Figure 2*). Severity of symptoms did not encourage greater stocking use; nonuse was similar in all symptom groups (*Figure 3*) and only a minority used stockings. There was no difference between the various CEAP classes in the low stocking usage (*Figure 4*). Patients who had a history of deep venous thrombosis tended to
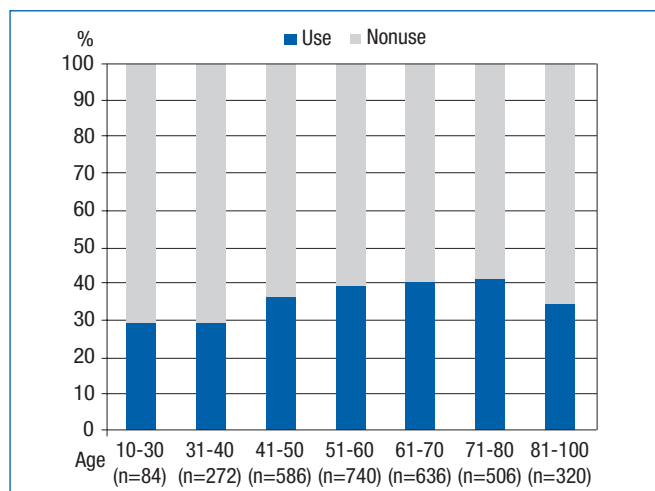
Figure 2. Stocking use among decile groups. Stocking use was low and similar (P=ns) in all age groups.
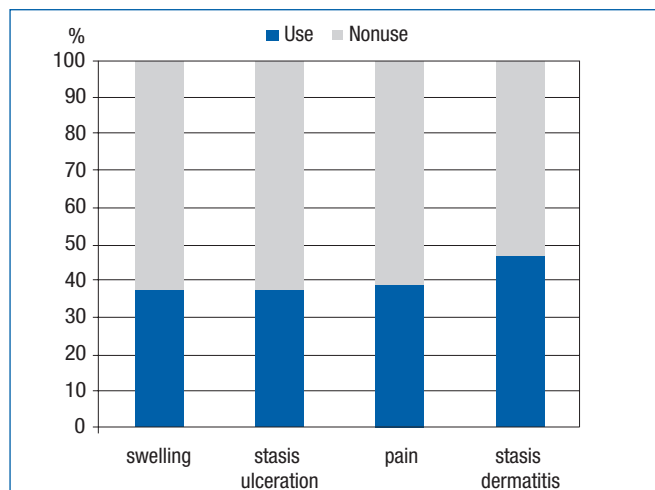
Figure 3. Stocking use was poor in spite of significant symptoms. There was no difference in stocking use among the various subsets (P=ns).

Figure 1. Use of stockings among 3144 patients with chronic venous disease. Nearly two-thirds of patients did not use stockings. Only 21% were using them on a daily basis.

Figure 4. Stocking use in CEAP clinical classes. Use was low and similar (P=ns) regardless of the clinical class.

Figure 5. Use of stockings related to prior history of deep vein thrombosis. Patients with a history tended to use stockings somewhat more than others (P<0.0001), though half (50%) were still not using stockings.

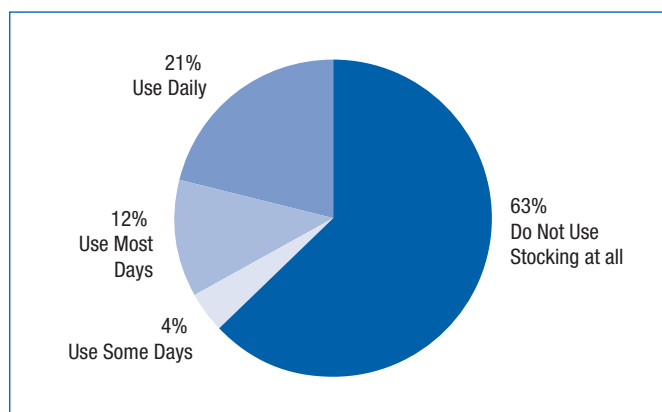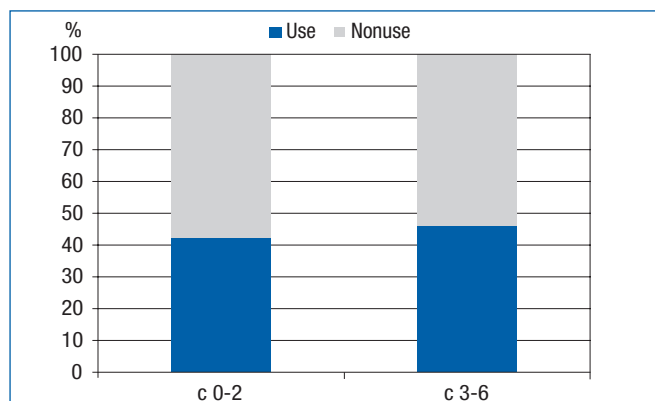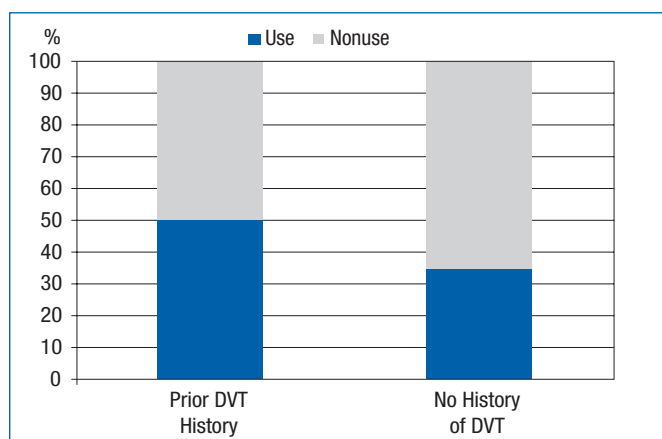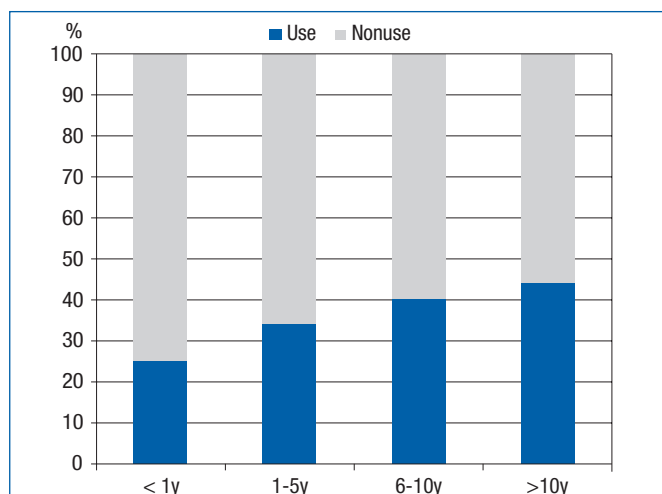*Figure 6. Compliance with stockings related to duration of symptoms. Compliance was significantly better with longer duration of symptoms (P<0.003). However, noncompliance was still high and the majority of patients were not using stockings even after ten years of symptoms.*

use stockings relatively more (50% vs 35%, *P<0.0001*) than patients without such history, yet half the patients in the former group were still not using stockings (*Figure 5*). Longer duration of symptoms also seemed to result in slightly increased use (*Figure 6*), within the context of overall very low usage.

DISCUSSION

Compression has been used since antiquity to control CVI symptoms. Despite its acknowledged efficacy, its use among patients remains poor. Only a minority of CVI patients use it. Nonuse is widespread, among both sexes, all age groups, and symptom subsets and CEAP classes. Longer duration of symptoms and a history of deep venous thrombosis tend to increase stocking usage somewhat, yet half or even more of these subsets were still not utilizing compression stockings. Examining the reasons for such low usage, three broad categories emerge: (1) those who are not candidates for compression, (2) those in whom it is ineffective, and (3) others who were unwilling to use compression stockings. The last group can be termed as noncompliant patients. Noncompliance was either due to (a) complaints related to the physical properties of the stockings, such as fit and wear, or (b) because of attitudinal reasons that were often unstated.

The primary physician had not recommended or prescribed stockings in 25% of patients in this series (*Table I*). In most such cases, the reasons for not prescribing stockings appeared valid: the local condition of the limb (fragile skin, blisters, massive edema, soreness of the limb on touch, contact dermatitis, irregular limb shape from obesity folds etc.) or the general condition of the patient (old age, frailty, massive obesity, arthritis of the hand, etc) precluded effective usage. Not all patients are candidates for compression therapy.

Reasons for nonuse of stocking	%
Could not state a specific reason	30
Not recommended by doctor	25
Ineffective, did not help	15
Binding, cuts off circulation, poor fit	13
Too hot	7
Soreness	2
Needs application assistance	2
Cosmetic, poor appearance	2
Aggravating, itching, dermatitis	2
Made symptoms worse	1
Lack of self-discipline	0.5
Cost considerations	0.4
Work-related	0.2

Table I: Reasons stated by patients for nonuse of compression stockings. n=3144

Stockings are not effective in some patients; 37% of patients in this series were compliant (21% used them daily), yet were referred to our clinic because of persistent symptoms. Sixteen percent in this series abandoned stockings after trial because they did not help or made their symptoms worse.

Others *can* use compression stockings but are noncompliant with prescribed compression for a variety of reasons. Seven percent of patients in this series blamed the hot weather for nonusage. This is probably a minor factor worldwide as overall noncompliance is similarly high in hot as well as cold climates.[5,6] Noncompliance was due to physical reasons related to the stockings (tightness, binding, "cutting off circulation", etc) in 24% of patients in this series. Another 30% of the patients in this series could not state a specific physical reason for noncompliance. These patients are unwilling to tolerate the intangible sense of restriction imposed by daily stocking wear. There is probably considerable overlap between these two groups. In either case, the central factor behind noncompliance appears to be to the pressure exerted by the compression stockings themselves— precisely the property that underpins efficacy in controlling symptoms. The high degree of noncompliance even in high CEAP classes and symptomatic subsets suggests that many patients consider compression stockings a quality of life issue in and of itself and are willing to forego its use at the cost of persistent symptoms. In a randomized trial comparing two brands of support stockings, in ulcer patients, similar statistics of nonuse as in current study were reported: 11% were not candidates for compression stockings,[7] it was ineffective in 26% with ulcer recurrence, 30% to 41% had difficulty using stockings related to wear and use, and 16-19% were noncompliant. Noncompliance ranged between 22% and 67% in other studies.[3,5,8]

Noncompliance is a serious issue as it is a major cause of recurrence in CVI.[7,8] Some authorities have suggested that poor patient education and inadequate doctor-patient communication may lie at the heart of the high noncompliance rate. However, noncompliance is high among closely monitored patients even under direct physician supervision[3,5,8] for advanced manifestations of CVD. And patients continue to be noncompliant despite severity of symptoms, as shown in the current study. This suggests that some patients will continue to be noncompliant regardless, because of physical or "lifestyle" restriction imposed by the required daily regimen of compression wear. Further patient education is unlikely to be of benefit in this subset.

The high degree of nonuse and noncompliance also affects data reporting in significant ways. Stocking results are typically reported only in those who use the device and become compliant; noncompliant patients are seldom included in the reported results distorting the "intent to treat" standard currently required in reporting treatment results and outcome comparisons.

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Pathophysiology of pain in venous disease

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SUMMARY

Pain is the chief complaint that leads to the diagnosis of venous disease and it has a significant impact on patients' quality of life. But for the clinician as well as the researcher, pain in venous disease is difficult to assess, both because of its multifaceted nature and due to the absence of a close relationship between pain as a symptom and the severity of venous disease. Current hypotheses on the mechanisms of pain in venous disease emphasize a local inflammatory origin. However, although indicators suggesting an inflammatory reaction in varicose veins have accumulated dramatically over the last five years, the precise mechanisms governing the interaction between the mediators of inflammation and venous nociceptors, which may account for the variability of pain in venous disease, remain difficult to explain, both clinically and experimentally.

Pain, the chief complaint that leads to the diagnosis of venous disease[1,2] has a significant impact on patients' quality of life.[3,4] But for the clinician as well as the researcher, pain in venous disease is difficult to assess. First, pain of venous origin is often multifaceted and is frequently associated with other unpleasant sensations, often difficult to describe, which do not belong to the range of symptoms of nociception, ie, a sensation of heaviness, cramps, and tension in the legs, or pruritus.[1] Second, pain intensity in venous disease can vary considerably, both from one patient to another or in the same patient over the course of time, as venous disease continues to progress. Lastly, although the neurophysiological mechanisms of pain of venous origin are better understood,[5] and although some biochemical and cellular processes involved in varicose vein remodeling have been elucidated by recent studies,[6-8] the causal relationship between venous disease and pain of venous origin remains difficult to explain, both clinically and experimentally, in particular due to the absence of a close correlation between pain and the severity of venous disease.

ANATOMY OF VENOUS INNERVATION AND PHYSIOLOGICAL PROPERTIES OF VENOUS AND PERIVENOUS NOCICEPTORS

Data obtained by electron microscopy show that veins are innervated by sensory nerve fibers whose cell body is located in the dorsal root ganglia of the spinal cord.[5] These sensory fibers are located along the venous wall and are subdivided into collaterals, which have two possible destinations. Some collaterals cross the tunica adventitia and end in the venous wall between endothelial cells and smooth muscle cells of the tunica media. Other collaterals reach the connective tissue of the perivenous space where they branch into unmyelinated free nerve endings, in close contact with the microcirculation. These subendothelial and perivascular nerve endings are nociceptors: they are the sole source for transmission of nociceptive afferent signals generated both in the venous wall itself and also in the perivenous connective tissue. The properties of venous and perivenous nociceptors account for the type of stimuli that can generate a painful sensation of venous origin. Clinical experience has shown that pain of venous origin can be induced by mechanical stimuli such as venipuncture and traction exerted on a vein or the existence of an indwelling catheter, as well as nonphysiological chemical stimuli such as the injection

Figure 1. Experimental set-up to study painful sensations evoked by stimulation of an isolated venous segment in man (5). A venous segment in the back of the hand located between two Teflon canulas is isolated from the rest of the circulation by two occlusive pneumatic cuffs. Local anesthesia of the skin around the isolated venous segment ensures that sensations induced are specifically related to activation of venous afferent fibers, without the participation of cutaneous sensory fibers.

of hyperosmolar saline or a glucose solution, the injection of a frankly acidic (pH < 4), or alkaline (pH > 11) solution, or the injection of isotonic saline at low (<20°C) temperature.[9] Furthermore, superficial venous inflammation or deep vein thrombosis is a source of acute pain of venous origin frequently observed in clinical practice. Experimentally, the properties of venous nociceptors have been studied in humans by applying different types of stimuli (mechanical, thermal, chemical) in an isolated venous segment and by asking the subject to qualify and grade the intensity of the sensation induced by these stimuli (*Figure 1*). Concomitantly, electrophysiological tracings of nerve fibers that innervate the venous wall recorded in anesthetized animals have shown that two types of small-diameter afferent fibers can transmit nociceptive information of venous origin: type Aδ myelinated afferent nerve fibers and type C unmyelinated afferent nerve fibers.[10]

The human venous pain model has made it possible to demonstrate that different types of nonphysiological endovenous stimuli, such as balloon dilation of the vein, the application of cold or heat, an electrical stimulus, and infusion of hyperosmolar saline produce a painful sensation, starting at a certain threshold, whose quality is the same whatever the method of stimulation used, and whose intensity increases exponentially with the intensity of the stimulus, and which totally disappears after injection of a local anesthetic in the isolated venous segment.[5] Remarkably, the stimulus-sensation curve (intensity of the painful sensation according to the intensity of the applied stimulus) is superimposable from one stimulus to another. These results suggest that the different stimuli used activate the same venous nociceptors, which means that the vast majority of nociceptors located in the venous wall are polymodal nociceptors. These experiments show that mechanical venous balloon dilation starts to be experienced as painful only from the moment that the diameter of the vein reaches a value three times that of normal. If we add to this observation the fact that venous dilation generally is not perceived as painful when induced by pharmacological methods such as the local application of adenosine,[11] it appears that venous dilation, even major, is not by itself a significant source of pain in normal subjects. Moreover, the painlessness of an arteriovenous fistula created for the purpose of hemodialysis is evidence in support of this hypothesis.
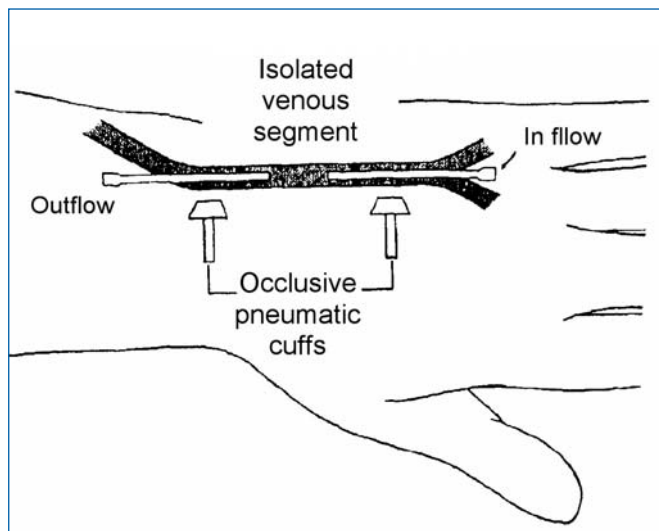
DISCREPANCY BETWEEN PAIN SYMPTOMS AND CLINICAL SEVERITY OF VENOUS DISEASE

In light of recent clinical studies designed to identify the subpopulation of patients with chronic venous disease most likely to undergo surgical therapy, the first observation that should be made is that there is no close correlation between pain and the severity of venous disease. Quantitative assessment of the stage of chronic venous disease is based on the CEAP clinical classification,[12] a system for classification of severity of clinical signs in seven classes (C0 to C6) (*Table I*). Several epidemiological studies have shown that the existence or intensity or both of lower limb symptoms that can be associated with chronic venous disease are not correlated with the severity of clinically evaluated venous disease. In a population study of over 1500 subjects 18 to 64 years of age (Edinburgh Vein Study), Bradbury et al demonstrated a correlation between truncular varices seen in a clinical examination and three lower limb symptoms in women: pain, sensation of heaviness or tension, and pruritus.[1] Although statistically significant, the correlations observed between each of these symptoms and truncular varices were too low to determine a causal relationship with the discomfort or pain associated with confirmed venous disease. In fact, in this study about 40% of asymptomatic women presented with varicose veins in the clinical examination while 45% of patients who complained of lower limb pain compatible with chronic venous disease did not have varicose veins. Furthermore, in male subjects, no significant correlation was found between pain and the existence of truncular varices. Lastly, none of the symptoms studied appeared to vary according to severity of the varicose veins, whatever the patient's gender.

Many studies of patients with advanced chronic venous disease (classes C4 to C6) have demonstrated a relation between the degree of venous reflux identified with Doppler scanning and the severity of clinical signs and symptoms of venous origin. However, the search for such a correlation in the setting of the Edinburgh Vein Study, which focused primarily on patients presenting with early-stage venous disease, proved disappointing.[13] In fact, only a low correlation was observed between pathologic superficial venous reflux (duration greater than or equal to 0.5 seconds) and sensation of swelling, heaviness, or tension. In addition, this correlation was limited either solely to men (sensation of swelling) or solely to women (sensation of heaviness or tension). No significant correlation was observed between superficial venous reflux and pain strictly speaking. Furthermore, there was no correlation between the studied symptoms and deep venous reflux (popliteal vein), whatever the

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The essential aim of this classification is to assess quantitatively the stage of chronic venous disease

The acronym "CEAP" stands for	C	**C**linical severity
	E	**E**tiology or cause
	A	**A**natomy
	P	**P**athophysiology

The clinical classification is the one most widely used and consists of the following classes:

C0	no visible or palpable clinical sign of venous disease
C1	telangiectases or reticular veins
C2	varicose veins
C3	edema
C4	venous-related skin changes (pigmented dermatitis , hypodermatits, white scar tissue)
C5	skin changes as defined in C4 with healed ulceration
C6	skin changes as defined in C4 with active ulceration

A: Asymptomatic
B: Symptomatic

Table I: The CEAP classification[12]

patient's gender. Similarly, in a study of over 120 patients presenting with mild to moderate venous disease,[14] no correlation was observed between pain intensity and clinical severity of venous disease based on the CEAP classification. Lastly, in a cohort study of 132 patients, Howlader and Smith reported no statistical relation between pain score or heaviness score, evaluated on a 10-point visual analogue scale, and the clinical severity of venous disease.[15] Thus, for example, the median pain score was 2.8 in the group of patients with class C2 venous disease, 4.5 in class C3, only 0.5 in class C4 and 0 in patients with class C5 venous disease. In addition, no difference was observed in pain scores between patients presenting with a superficial venous reflux and those presenting with deep venous reflux. These results totally confirm the observations made in the setting of a survey conducted in France focused on the frequency of clinical symptoms according to duration of venous disease.[2] In fact, this survey demonstrated a very significant decrease in the frequency of functional signs of venous disease, in particular pain, over time. Thus, the frequency of the painful heaviness sensation declined from 71% in the group with symptoms of less than 5 years' duration to only 50% in the group whose symptoms were of 30 years duration or longer. These results are in agreement with findings of an epidemiological study conducted in Switzerland, showing that the prevalence of varicose veins increases with age, while pain decreases with age.[16]

PAIN MECHANISMS IN VENOUS DISEASE: INFLAMMATORY MARKERS

Current hypotheses on pain mechanisms in venous disease are focused on a local inflammatory origin, related to venous stasis. Interestingly, the same processes assumed to generate pain in venous disease also seem to be involved in the longer term in the process of varicose vein remodeling, defined as all of the qualitative and quantitative alterations in the cellular and matrix components of the venous wall.[17] The starting point for these mechanisms probably is local hypoxia associated with capillary stasis. A significant fall in the partial pressure of oxygen after 30 minutes in the standing position has been demonstrated in lower limb veins in venous disease[8] and several studies have demonstrated that hypoxia induced by capillary stasis has the effect of activating endothelial cells.[7] Such activation is manifest by elevation of calcium concentrations in the cytoplasm

of endothelial cells,[18] which itself is responsible for an increase in phospholipase A2 activity.[19] Activation of phospholipase A2, in turn, leads to the synthesis and local release of proinflammatory mediators such as bradykinin, prostaglandins E2 and D2, platelet-activating factor (PAF), and leukotriene B4.[20,21] PAF seems to play a pivotal role: first, it enhances local release of serotonin and histamine, and, second, it produces abnormal adherence of neutrophils to the venous endothelium, prior to their infiltration of the venous wall itself, and stimulates the synthesis of leukotriene B4 by activated neutrophils. Evidence for such an inflammatory reaction in patients with varicose veins has accumulated dramatically over the last five years,[22] and the biochemical changes identified suggest that endothelial cells and neutrophils are the source of this local inflammation (*Figure 2*).[8,23-26] The presence of neutrophils, monocytes, and activated T lymphocytes, the accumulation of macrophages and mast cells, the expression of adhesion molecules on the surface of leukocytes and endothelial cells (LFA-1, VLA-4, ELAM-1, ICAM-1, VCAM-1), the synthesis of cytokines (IL-1 beta, IL-6, TNF alpha) and prothrombotic factors (von Willebrand factor) are all indicators of inflammation in venous disease.[12,27]
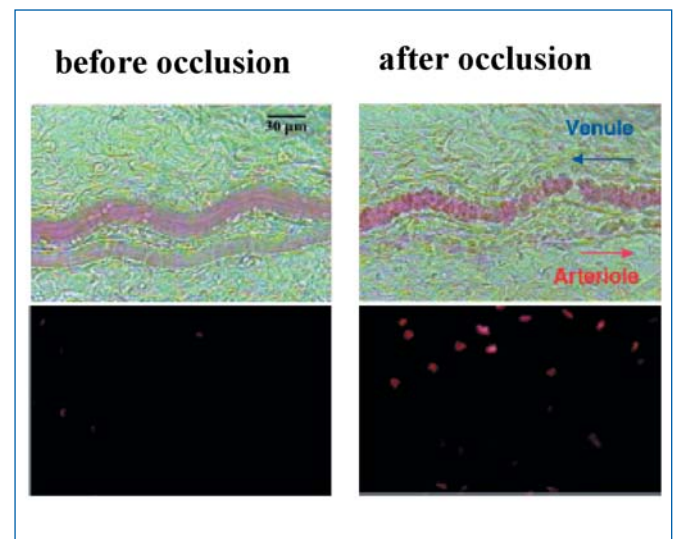
Figure 2. Inflammatory reaction observed in the microcirculation after one hour of venous hypertension induced by acute occlusion of a venule in the rat. The tissue adjacent to the venule shows signs of extensive cell apoptosis identified by fluorescent marking of parenchymal cell nuclei with propidium iodide (lower right), representing an advanced stage of inflammation.
Figure taken from Takase S, Lerond L, Bergan JJ, Schmid-Schönbein GW. The inflammatory reaction in venous hypertension in the rat. Microcirculation. 2000;7:1-11.

Some proinflammatory mediators released locally as the result of hypoxia can activate nociceptors located in the venous wall (between endothelial cells and smooth muscle cells of the media) and in the connective tissue that forms the perivenous space, in close contact with the microcirculation. Therefore, the study of the painful sensation evoked in healthy subjects by the intravenous or perivenous application of bradykinin unambiguously demonstrates the role of this neuromediator in venous pain.[28] Moreover, several studies suggest that the algogenic action of bradykinin in and around the vein depends on the release of nitric oxide (NO) by endothelial cells or by smooth muscle cells in the wall of the vein or by both,[29] and the subsequent activation of cyclic GMP synthesis.[30] This algogenic action of bradykinin is potentiated by the local administration of prostaglandin E2.[31] Prostaglandin E2, whose application is by itself painless, thus has a sensitizing effect on venous nociceptors. Based on these data, the hypothesis can be formulated that such a cascade of reactions, by an auto-amplification process, can lead to the local release of a true "inflammatory mixture", which can activate venous and perivenous nociceptors, as well as extravasation of plasma with transmural and tissue edema. As time passes, this process also results in varicose vein remodeling characterized by cellular and matrix alterations that lead to the loss of structural integrity of the venous wall and of its elastic properties.[17] In agreement with this hypothesis, Howlader and Smith have previously demonstrated that nitric oxide concentrations measured in blood collected in the saphenous vein or in a vein in the dorsal aspect of the foot were significantly higher in patients with the most severe stage of venous disease.[32] Similarly, some studies have reported a higher levels of markers of endothelial activation in experimental venous hypertension in the most advanced stages of venous disease.[33]

Considering the key role played by these inflammatory processes, both in pain as well as in varicose vein remodeling, it would have been expected that levels of some inflammatory markers are correlated with the intensity of pain in venous disease. But, following the example of clinical estimation and evaluation by venous Doppler scanning, this search proved negative.[15] In fact, no significant correlation was found between levels of the twelve inflammatory markers (measured in a vein on the dorsal aspect of the foot) and pain intensity score on a visual analogue scale in a population of 132 patients with chronic venous disease ranging from class C2 to C5.

In spite of the solid physiological basis explained in the above, the assumed relationship between the inflammatory processes generated in the venous wall and pain associated with venous disease thus seems difficult to demonstrate formally.

POSSIBLE HYPOTHESES TO EXPLAIN DISCREPANCIES BETWEEN THE PAIN SYMPTOM AND OBJECTIVE MARKERS OF VENOUS DISEASE

Pain, clinical severity, and inflammatory markers

The intensity of pain of venous origin is not correlated with the extent of truncular varices observed in clinical examination, the severity of reflux measured with Doppler scan, or levels of inflammatory markers measured in a lower limb vein. Therefore, if hypoxia is indeed the major factor that triggers pain of venous origin, it is entirely possible that many painful hypoxia-related conditions can occur transiently in a given patient, for example, solely at the end of the day, after standing for a prolonged period, or during certain periods of the menstrual cycle. In other words, the cascade of chemical reactions that activate venous and perivenous nociceptors can occur before any significant remodeling of large venous vessels arises. This could explain the frequency of functional signs such as pain or heaviness in the legs in patients who do not have varicose veins in the clinical examination and no abnormal reflux seen in a Doppler scan, as was observed in the Edinburgh Vein Study. In this regard, it is obvious that if pain and varicose vein remodeling involve biochemical and cellular processes to a similar extent, essentially inflammatory, the time line of these pathological mechanisms is basically different. In fact, pain occurs as the short-term consequence of venous hypoxia, while varicose vein remodeling only participates at a much later stage of venous disease.

The fact that pain is not closely correlated with objective parameters of varicose vein remodeling, incompetent venous valves, and inflammation suggests that the primary activation site of venous and/or perivenous nociceptors may not be in the large venous vessels. In this regard, the hypothesis of local activation of nociceptors in the microcirculation, where contact between nerve endings, the arteriole, the vein, and the capillary is probably much closer than on the macrovascular level, seems entirely plausible.

Consequently, several studies recently have focused on the search for microcirculatory parameters of venous disease.[34,35] Furthermore, several recent studies using an experimental model of acute venous occlusion in the rat have shown the specific role of the increase in microvascular pressure in triggering an inflammatory reaction characterized by infiltration of neutrophils in the endothelium and adjacent tissues.[24] The alteration of friction forces on the endothelium (shear stress) produced by blood flow is another essential factor that can promote local inflammation of the venous wall.[22] In fact, several experimental studies have shown that shear stress, through integrins anchored in the endothelial cell membrane, can influence many intracellular biochemical processes, such as protein G phosphorylation, activation of tyrosine kinases, free radical production, and the synthesis of different nuclear transcription factors.[36-38] In the light of available data, it seems that a physiologically normal shear stress produces a potent, local inflammatory effect, while a reduction or an increase in this force below or above a given physiological threshold can lead to overexpression of proinflammatory genes.[22,27]

How to explain the diminution of pain in the most advanced stages of venous disease?

The main hypothesis that can explain a significant decrease in the frequency and intensity of pain in the most advanced stages of venous disease is based on alteration of innervation of the venous wall and the perivenous tissue. This alteration of nerve fibers may reflect sensory peripheral neuropathy, possibly related to ischemia secondary to venous microangiopathy, and an increase in endoneural pressure.[39] Consequently, several studies have demonstrated a significant elevation of the threshold of tactile, vibrational, and thermal sensation in the extremities in patients with chronic venous disease, suggesting the loss of sensory axons.[39-41] Interestingly, sensory threshold elevation was significantly more pronounced in class C5 than in class C2 disease.[41] It can be seen that such a reduction in the number of venous and perivenous nociceptors can account for a diminution of pain in the most advanced stages of venous disease.

Other factors that may explain inter-individual variability of pain in venous disease

The complexity and diversity of mechanisms that can be activated in the pathogenesis of pain in venous disease are a considerable source of interindividual variability.

Such variability involves both the reactivity of the cellular components involved (endothelial cells, neutrophils, venous, and perivenous nociceptors) and the mechanisms of integration of nociceptive stimuli in the brain. On the cellular level, for example, experimental studies of human umbilical cord venous endothelial cells have demonstrated that the quantity of different prostaglandins released as a result of the effect of hypoxia can vary by a factor of 10 depending on the donor.[7] Similarly, neutrophil reactivity varies with age and previous sensitization ("priming") to other inflammatory signals. Furthermore, the density of venous and perivenous innervation as well as the density of nociceptors' ion channels, which allow conversion of the chemical message into a nerve impulse coding for nociceptive information, can also vary considerably from one subject to another. Lastly, at the other end of the chain of these algogenic processes, the intensity of brain modulation of nociceptive sensation resulting from the effect of endogenous opioids, whose variations from one subject to another are partly due to genetic factors, is also likely to partly determine pain sensitivity in a given subject with respect to venous nociceptive stimuli. As an example, recently it was demonstrated that the genotype of the enzyme catechol-O-methyl-transferase, on which depends the quantity of endogenous opioids released during a pain stimulus, significantly affects pain sensitivity in healthy subjects.[42] But all these variable factors are only relative obstacles to the elucidation of the pain mechanisms in venous disease. In the absence of a correlation between the condition of the large venous vessels and the degree of pain reported by patients, the essential point perhaps consists of lessons learned by questioning not necessarily the validity of this complaint, but rather the primary site of interaction between the mediators of inflammation and venous nociceptors, with a view to developing a method to test the nociceptive function of the microcirculation in venous disease.

CONCLUSION

- Epidemiological studies demonstrate a discrepancy between pain severity in venous disease based on clinical findings and the degree of pain reported by patients.
- Such a discrepancy complicates the objective evaluation of analgesic therapies in venous disease.
- The neurophysiological mechanisms involved in

venous pain are now better understood, but the causal relationship between venous disease and pain remains difficult to explain by experimental methods.

- The localized release of proinflammatory mediators seems to play a decisive role in the activation of venous and perivenous nociceptors and may account for the occurrence of pain starting at the early stages of venous disease.

- Diminution of pain in the advanced stages of venous disease may be related to peripheral sensory neuropathy induced by venous microangiopathy.

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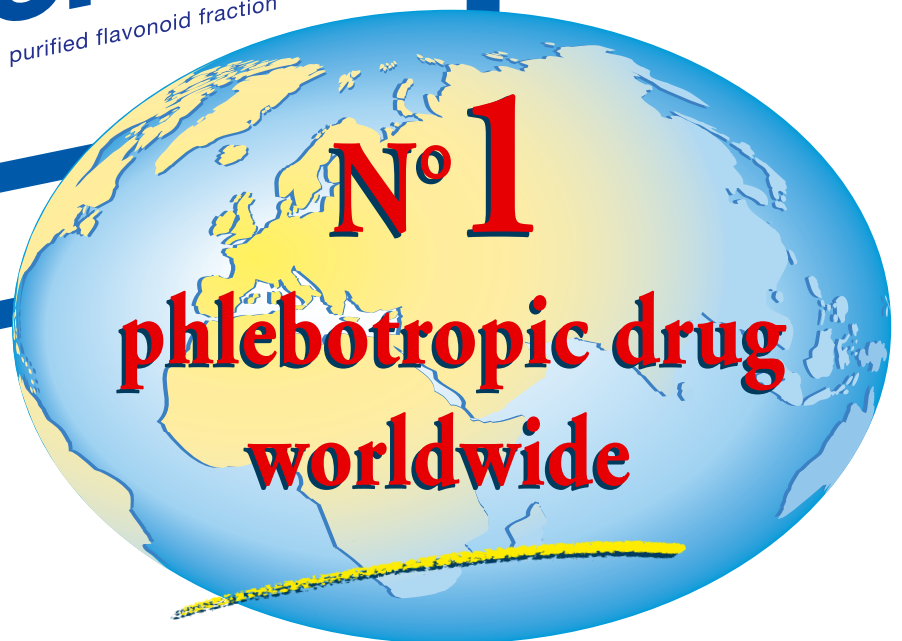
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