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AIMS AND SCOPE

Phlebolymphology is an international scientific journal entirely devoted to venous and lymphatic diseases.

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PHLEBOLYMPHOLOGY

EDITORIAL

Hospital staff have a high risk of developing venous leg problems, particularly in connection with long periods of standing. This is the main message from an interesting study by ***Dr Ziegler*** *from Vienna. The highest prevalence of chronic venous disorders was found in general hospital staff and cleaners. It may be assumed that the number of surgeons in this study was too low to put them into the same risk group of predominantly standing occupations.*

Dr Fischer *from Göttingen discusses in his paper the difficulties for a general practitioner in handling patients with symptoms suspicious of deep vein thrombosis (DVT). Deep vein thrombosis could be diagnosed only in 10% of all patients referred to specialized centers. It remains to be determined how many patients who had not been sent for a detailed examination had a DVT.*

The results from a Bulgarian survey in more than 3000 patients are presented by ***Prof Zahariev*** *and coworkers. A considerable number of the patients with subjective leg symptoms were assigned to the group of CEAP class C0 showing no clinical signs of venous disease. Is this "functional phlebopathy" or may it be caused by another, unrecognized pathology?*

Dr Neglen*, working with Professor Raju in Mississippi, advocates an early invasive approach in patients with post-thrombotic syndrome. Based on his extensive experience and on a comprehensive literature survey, he convincingly demonstrates that beneficial clinical results may be obtained, even when the hemodynamic situation can only be partially improved but not normalized. He refers to leg compression and local wound care as "old-fashioned and counterproductive, which may deny patients modern treatment." Up to now only a minority of colleagues involved in venous surgery seems to share this opinion, most of them preferring to operate on "clean" varicose veins and defending classical stripping operation from several less invasive procedures, for obvious reasons.*

Vascular surgery also plays an important role in the management of venous aneurysms. This is demonstrated in an article by ***Dr Perrin*** *from France, reflecting the state of the art in this field. The authors postulate that usiform popliteal aneurysms with a diameter larger than 20 mm should be resected as a preventive measure, even when no previous thrombotic complication has occurred.*

Again, several fascinating issues and stimulating ideas can be found in this issue of Phlebolymphology.

Enjoy!

Hugo Partsch, MD

Suspicion of deep vein thrombosis – diagnostic strategy at the interface of general practice and specialist care

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SUMMARY

Aim: We describe the characteristics of patients with suspected deep vein thrombosis (DVT) referred to specialists by their general practitioner (GP) and the further management by the specialist.

Patients and method: From August 2001 to April 2003, 114 patients (age 15 to 91, 72 women) with suspected symptoms of DVT were prospectively recruited from a specialist practice for vascular surgery/phlebology. Symptoms and clinical findings were documented by a standard procedure.

Results: Forty percent of the patients received compression therapy and 18% anticoagulation with heparin by their GP. Pain (88%) and swelling (71%) were the leading patient complaints. Physical examination revealed calf pressure pain (40%) and differences in calf circumference (56%) as the dominant results. The clinical signs themselves were not specific enough to exclude DVT. DVT was diagnosed in 12 patients (10.5%). Varicosis (30%) and (pseudo-) radicular pain (20%) were the most frequent differential diagnoses.

Conclusion: The proportion of diagnosed DVT in patients referred by their GPs was low. Clinical examination alone was unsuitable to detect DVT. Therefore, GPs are not able to exclude the diagnosis of DVT without technical diagnostics. The use of D-Dimer tests in connection with clinical signs could be an alternative for GPs to reduce referrals, although this concept has not yet been evaluated in a primary-care setting.

INTRODUCTION

Improvements in the diagnosis and treatment of deep venous thrombosis (DVT) in the past decade have induced a shift from inpatient to outpatient treatment. This development attaches great importance to cooperation between general practitioners (GPs) and specialists.[1] Nevertheless, until now, GP's procedures for treating patients with a suspicion of DVT have been poorly investigated, which might be a consequence of the relatively low incidence of thromboembolic events in the primary care setting.[2]

The leading problem for GPs in diagnosing DVT is that a physical examination can rarely exclude the possibility of a DVT. This problem is very serious in view of the potentially lethal course of the disease.[3-6] Imaging diagnostics are

Keywords:
deep vein thrombosis, diagnostic strategy, primary care treatment.

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predominantly the domain of specialists. Therefore, in the case of clinical suspicion of DVT, a referral is presently the only opportunity to confirm or rule out the diagnosis.

Because of the small incidence of DVTs in the primary care setting, it requires great effort to include a sufficient number of patients from general practices to analyze patient characteristics. Therefore, we acquired patients with a suspicion of DVT referred by their GPs to a specialist (phlebologist) which allowed us to gather a higher number of patients in a shorter period. We characterized these patients with regard to symptoms, complaints, and previous therapy. The aim of the study was to verify the significance of physical examination results in diagnosing DVT compared with specialists' diagnoses based on imaging diagnostics. Furthermore, we analyzed the frequency of the differential diagnoses and whether there were typical patterns of complaints and symptoms, allowing for a differentiation between these diagnoses.

METHODS

From August 2001 to April 2003, all 114 patients (age 15 to 91, 72 women) with suspected symptoms of DVT who had been referred from a GP to a specialist practice for vascular surgery/phlebology were prospectively recruited for this study. Only patients with a tentative diagnosis made by their GPs were included. The completeness of patient inclusion was controlled by a comparison with electronic medical data. Symptoms and clinical findings were documented by a standard procedure. The interval between a GP's referral and the specialist visit in our center was no more than 1 day.

The further diagnostic process was not specified by a study protocol. Phlebologists were free in their decision-making. Thus, all patients were examined using (duplex-) ultrasound of the venous system of the legs (in accordance with the actual guidelines of the German association for phlebology).[7] In divergence from the guidelines, phlebography was added in all patients with a suspicion of DVT in the ultrasound or proven thrombosis. In case of an uncertain ultrasound (eg, in adiposity, massive edema), the further procedure depended on clinical probability of DVT in accordance to Wells et al.[8] In patients with a low clinical probability, a D-Dimer test was added (SimpliRED(r) D-Dimer, Hämochrom Diagnostica GmbH, Essen). In case of medium or high probability, phlebography was added routinely. The diagnostic process is presented in *Figure 1*.

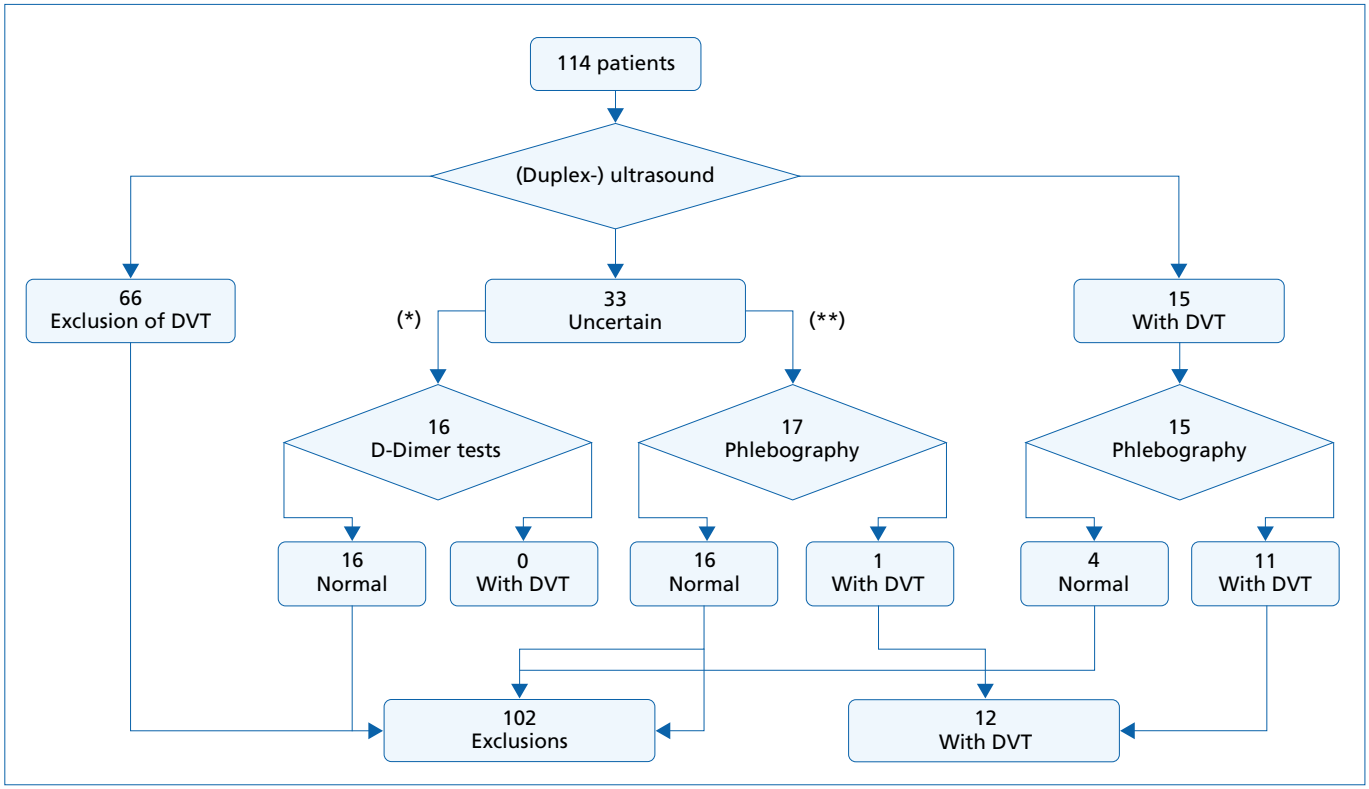

Figure 1. Diagnostic proceeding in 114 patients referred by their general practitioner with suspicion of deep venous thrombosis (= low clinical probability of DVT, ** = medium or high probability).*

Characteristics	All patients (%)	Without DVT (%)	With DVT (%)	Odds ratio [95%-CI]
Demography				
Age (y)				
Median	59	59	61	ns
Range	15-91	15-84	27-91	
Sex				
Female	72 (63.2)	66 (64.7)	6 (50.0)	ns
Male	42 (36.8)	36 (35.3)	6 (50.0)	ns
Anamnesis				
Beginning of complaints (d)				
Median	5	6	4	ns
Range	1-90	1-90	1-90	
Trigger event	22 (19.3)	18 (17.7)	4 (33.3)	ns
Journey	8 (7.0)	7 (6.9)	1 (8.3)	
Trauma	6 (5.3)	5 (4.9)	1 (8.3)	
Immobilization	6 (5.3)	4 (3.9)	2 (16.7)	
Operation	2 (1.8)	2 (2.0)	0	
Risk factors (*)	48 (42.1)	41 (40.2)	7 (58.3)	ns
Chronic venous insufficiency	26 (22.8)	22 (21.6)	4 (33.3)	
Positive family history	17 (14.9)	17 (16.7)	0	
Relapse of thrombosis	16 (14.0)	14 (13.7)	2 (16.7)	
Obesity	8 (7.0)	7 (6.9)	1 (8.3)	
Pregnancy	2 (1.8)	2 (2.0)	0	
Thrombophilia	0	0	0	
Symptoms				
Pain	100 (87.7)	88 (86.3)	12 (100.0)	ns
Swelling	81 (71.1)	70 (68.6)	11 (91.7)	ns
Redness	22 (19.3)	17 (16.7)	5 (41.7)	3.57 [1.01-12.59]
Pretreatment by general practitioners				
Compression bandage	28 (24.6)	21 (20.6)	7 (58.3)	5.4 [1.55-18.73]
Elastic stockings	18 (15.8)	16 (15.7)	2 (16.7)	ns
Anticoagulation	20 (17.5)	14 (13.7)	6 (50.0)	6.29 [1.78-22.26]
Physical examination findings				
Calf pressure pain	45 (39.5)	34 (33.3)	11 (91.7)	22.0 [2.72-177.53]
Difference in circumference (>1 cm)	72 (63.2)	61 (59.8)	11 (91.7)	ns
Ankle area	47 (41.2)	39 (38.2)	8 (66.7)	ns
Calf area	60 (52.6)	49 (48.0)	11 (91.7)	11.90 [1.48-95.58]
Hyperthermia	26 (22.8)	19 (18.6)	7 (58.3)	6.12 [1.75-21.37]
Discoloration (lividity)	16 (14.0)	14 (13.7)	2 (16.7)	ns
Homan's sign positive	8 (7.0)	3 (2.9)	5 (41.7)	23.57 [4.65-119.55]
Payrs' sign positive	8 (7.0)	2 (2.0)	6 (50.0)	50.0 [8.27-302.45]

(DVT = deep venous thrombosis, (*) = multiple nominations possible, ns = not significant)

Table I. Characteristics of 114 patients referred by their general practitioner with suspicion of deep venous thrombosis (given are total number and percentage, odds ratio with 95% - interval of confidence).

Data were processed using SAS 8.1.[9] Multiple logistic regression models were used to test for associations between patient characteristics, symptoms, and diagnoses ($\alpha = 0.05$). The degree of effect is reported as odds ratios (OR) with 95% confidence intervals (CI). Due to the limited number of patients included, the following data analysis is only explorative.

RESULTS

Patients' characteristics were demonstrated in *Table I*. The first symptoms were reported 3 months before the visit in one case, but the majority of patients visited their GPs with recently occurring symptoms. In less than 20% of the patients, a "classical" trigger event of thrombosis (eg, immobilization, trauma) could be detected by anamnesis. In 40% of the patients, compression therapy was started by the GPs, partially by application of an elastic stocking. Anticoagulation with heparin was started by GPs in 17.5% of all cases; 13% of the patients received both compression therapy and an anticoagulation.

The further diagnostic procedures of the specialists are represented diagrammatically in *Figure 1*. Thirty-three patients with an uncertain ultrasound received a supplementary D-Dimer test or phlebography. In one case, the additive phlebography showed calf-vein thrombosis. Sensitivity of the (duplex-) ultrasound was calculated as 0.92 (including the uncertain cases). In 3 patients, the initially pathologic result of the ultrasound could not be confirmed using phlebography. The resulting specificity of the ultrasound was 0.96, the positive predictive value 0.73, and the negative predictive 0.99.

In patients without verifiable thrombosis, varicosis and (pseudo-) radicular pain were the most frequent diagnoses (*Table II*). The classification "other diagnoses" included eg, (nocturnal) calf cramps, and in two cases no certain diagnosis could be made. In patients with the differential diagnosis (pseudo-) radicular pain, the symptoms and complaints differed significantly from those patients with established thrombosis. They showed less typical thrombosis signs, eg, swelling (Odds ratio (OR) 0.08, 95% - Confidence interval (CI) 0.03-0.22]), redness (OR 0.82 [0.75-0.91]), local hyperthermia (OR 0.71 [0.62-0.82], difference in ankle circumference (OR 0.04 [0.01-0.34]) and in calf circumference (OR 0.13 [0.04-0.42]). Patients with the diagnosis "varicosis" complained more frequently of swelling (OR 7.23 [2.04-25.66], but less frequently about pain (OR 0.06 [0.01-0.26]) and redness (OR 0.71 [0.62-0.82]). The classic signs of thrombosis such as calf pressure pain or Homan's sign showed no significant difference between patients with and without established thrombosis, and are therefore inappropriate to exclude DVT from those with (pseudo-) radicular pain or varicosis.

In 73% of the patients, the physical examination showed at least one classical sign of thrombosis. *Table III* shows the discriminatory power of these classical signs. Multiple regression analyses based on physical examination results were performed, but results should be interpreted carefully due the small number of included patients with established DVT. The (max-rescaled) R-square resulted in 0.56. The sensitivity of the model was 0.92, and the specificity 0.87. Corrected for the study prevalence, the positive predictive value resulted in 0.46, the negative in

Diagnoses	Number (%)
Exclusion of DVT	102 (89.5)
Varicosis	38 (33.3)
(Pseudo-) radicular pain	23 (20.2)
Phlebitis	14 (12.3)
Muscular reasons (eg, rupture of a muscle fiber)	11 (9.6)
Post-thrombotic syndrome	4 (3.5)
Lymphangitis erysipelas	4 (3.5)
Gonarthrosis	2 (1.8)
Other	4 (3.5)
Established DVT	12 (10.5)
Distal	7 (6.1)
Proximal	5 (4.4)

(DVT = deep venous thrombosis)

Table II. Differential diagnoses of 114 patients referred by their general practitioner with suspicion of deep venous thrombosis.

Clinical signs	Sensitivity [95%-CI]	Specificity [95%-CI]	Positive predictive value	Negative predictive value
Calf pressure pain	0.92 [0.62-0.99]	0.67 [0.57-0.76]	0.24	0.99
Difference in circumference (>1 cm)				
Ankle area	0.67 [0.35-0.90]	0.62 [0.52-0.71]	0.17	0.94
Calf area	0.92 [0.62-0.99]	0.52 [0.42-0.62]	0.18	0.98
Hyperthermia	0.58 [0.27-0.85]	0.81 [0.72-0.88]	0.27	0.94
Discoloration (lividity)	0.16 [0.03-0.48]	0.86 [0.78-0.92]	0.13	0.90
Homans' sign positive	0.42 [0.15-0.72]	0.97 [0.92-0.99]	0.63	0.93
Payrs' sign positive	0.50 [0.21-0.78]	0.98 [0.93-0.99]	0.75	0.94
(95% - CI = 95% - Interval of confidence)				

Table III. Test criteria of clinical signs in 114 patients referred by their general practitioner with suspicion of deep venous thrombosis.

0.99. The area under the curve (AUC) was 0.90. A cross-validation basing on the same sample detected 11 out of the 12 patients with established DVT correctly.

DISCUSSION

Physical examination and diagnostic procedure

The proportion of patients with an established DVT (11%) seemed to be low compared with international data basing on patients referred by primary care institutions to specialists (16% to 25%).[8,10] This might be influenced by the fact that other investigations studied patients referred to tertiary care institutions, whereas we studied patients with suspicion of DVT in an ambulatory setting.

In all patients, physical examination was followed by an extensive diagnostic procedure. Generally, a (duplex-) ultrasound was performed, a technique which is a very sensitive method (sensitivity varying from 0.62 to 0.97).[3,11] Nevertheless, in 28% of the included patients, the result was classified as "cannot be judged with sufficient accuracy" and additional diagnostics were needed (D-Dimer concentration, phlebography). Other investigations found a relevant proportion of insufficiently classifiable patients too and the significance of the positive predictive value is limited (6.21).[12-14] The noticeable high proportion of phlebographies used here compared with other recent studies comes from the specialists' practical experience with false-positive sonography results.

The explanatory power of the calculated regression model was relatively high (AUC 0.90) but cross-validating the model on the same sample showed that 1 out of the 12 patients with established DVT was not identified (false-negative). Therefore, confirming or ruling out the diagnosis of DVT is not possible based only on clinical signs or patients' symptoms, although the included patients had been prescreened by their GPs. This is in line with other studies reporting the limitations of clinical signs (eg, the high sensitivity of "calf pressure pain" combined with a moderate specificity).[3,4] Richards et al showed the high value of the sensitivity of the "difference in calf circumference," too.[15] The "Homans" sign, which has been termed as appropriate for diagnosing DVT in recent investigations, was of low sensitivity in our study.[3] The shared problem of most studies investigating clinical signs in DVT is the low number of included patients, which affects the significance.[16]

D-Dimer test

In the 1990s, a bedside D-Dimer test became available. It is characterized by a high sensitivity combined with a moderate specificity. This test makes it possible to use D-Dimer testing in an ambulatory setting, and is often used in combination with physical examination results or sonography diagnostics.[5,17,18] The often-cited studies by Perrier et al, Kearon et al, and Wells et al are all based upon preselected patient collectives in hospital outpatient care centers.[10,17,19] Until now, research based upon unselected patients in a primary care setting is lacking. Since important test criteria (eg, the predictive values) are dependent on disease prevalence, the use of D-Dimer tests has not been evaluated in the primary care setting.[20,21] Nevertheless, the prior use of D-Dimer tests in combination with a clinical score (eg, the Wells score) is probably a valuable way to economize health system resources.[22] Therefore, we would seriously recommend a study of the use of bedside D-Dimer tests in the primary care setting.

General practitioners' initial treatment

Less than one fifth of the included patients received anticoagulation therapy before their referral to the specialist. Until now, it has been unclear whether anticoagulation should be started already in patients under suspicion of DVT or whether the definitive diagnosis should be awaited. The risk of a bleeding complication must be balanced with the potential benefits (eg, the prevention of an embolic complication). A systematic study investigating the use of anticoagulants in patients under suspicion of DVT does not exist to the best of our knowledge. Furthermore, there is no explicit information about the incidence of thromboembolic complications in the first 24 hours after the DVT onset (which is the maximum space of time until patients saw a specialist in our investigation). A recent recommendation published in a German journal suggested the early use of anticoagulants based on the low complication rates of heparins.[1] In our study, GPs obviously orientated themselves on the clinical probability of DVT, since those patients with a DVT established by further examination were more likely to receive anticoagulation therapy compared with those patients with excluded DVT (OR 6.3 [1.8-22.3]). In our investigation, no patient developed symptoms of a pulmonary embolism in the space of time before reaching the specialist, but the low number of included patients does not allow these results to be generalized.

Compression therapy is – in addition to symptomatic pain therapy - another pillar of acute therapy in DVT. In this study, about 40% of the patients received a compression therapy. This therapy should inhibit thrombus growth by accelerating the venous flow, and should fix the thrombus locally.[1,23,24] However, these assumptions are based on pathophysiological considerations and experimental studies. Until now, randomized controlled trials investigating the impact of compression therapy under acute conditions are still lacking.

CONCLUSIONS

The prevalence of 10.5% of patients with DVT in our investigated group of patients (already filtered by their GPs) must be considered as low compared with other recent studies. This is again an indicator that GPs work in a field of low incidence, but are confronted here with a potentially lethal disease. Since important test criteria (eg, the predictive values) are dependent on disease prevalence, the transferability of study results established in secondary or tertiary care must be considered as questionable.

Although some clinical signs - like the difference in ankle and in calf circumference and calf pressure pain - showed a high negative predictive value, it was not possible to exclude DVT from the investigated patients with a sufficient certainty. The combination of clinical scores with the D-Dimer test might be a diagnostic alternative to exclude DVT, but has not yet been evaluated in a primary care setting. Deficits in GPs' initial treatment (eg, less than 50% of the patients received compression therapy) clearly show that there is room for improvement in the cooperation between GPs and specialists.

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Chronic venous disease is highly prevalent in hospital employees

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SUMMARY

Chronic venous diseases (CVD) comprise primary/idiopathic abnormalities of the venous system and secondary sequels after deep venous thrombosis. Known risk factors include endogenous and environmental parameters. The aim of the present study was to prove the hypothesis that the development of CVD might also be triggered by occupation-related risk factors. We determined the prevalence and social relationship of CVD in a wide cross-section of a total of 209 hospital employees, including doctors, nurses, medical technicians, secretaries, scientific staff, cleaners, and general staff, all without predocumented CVD. In addition, the restriction in quality of life due to symptoms of CVD was evaluated. CVD was classified according to the CEAP classification and was present in 34% of all employees, predominantly in females. The highest prevalence of CVD was found in general staff and cleaners, and the lowest in medical technicians, secretaries, and scientific workers. Standing at work was a predisposing factor. It can be concluded that within the workforce of a large hospital, females, who are working in a standing position or under hot-humid conditions, are at particular risk for the development of CVD, and should therefore consider to undergo primary prophylactic treatment of CVD.

INTRODUCTION

Chronic venous disease (CVD) of the lower extremities is of multifactorial etiology,[1-4] including primary risk factors, such as genetic predisposition, gender, obesity,[5-10] and secondary possible risk factors, such as dietary habits, use of contraceptives, or hormone replacement therapy, but also workplace conditions of certain professions, such as poor mobility, orthostasis, load-carrying, and/or hot-humid temperatures.[10-17] Every 6th man and every 5th woman are suffering from chronic venous insufficiency. The prevalence of crural ulcers is 0.7%.[18] All reports consistently describe a positive correlation between presence of CVD and increased age.[19] CVD results from venous hypertension caused by venous valve insufficiency, and is characterized by clinical signs or symptoms, such as swelling, skin changes, and ulceration in its most severe form.[20] *Figure 1a-c* shows lower extremities of patients, suffering from various severity degrees of CVD. Patients are subjectively affected in their quality of life due to leg tiredness, heaviness, aching, cramps, itching, and also the

Keywords:
chronic venous disease, hospital employees, occupational risk factors, long periods of standing, hot-humid conditions.

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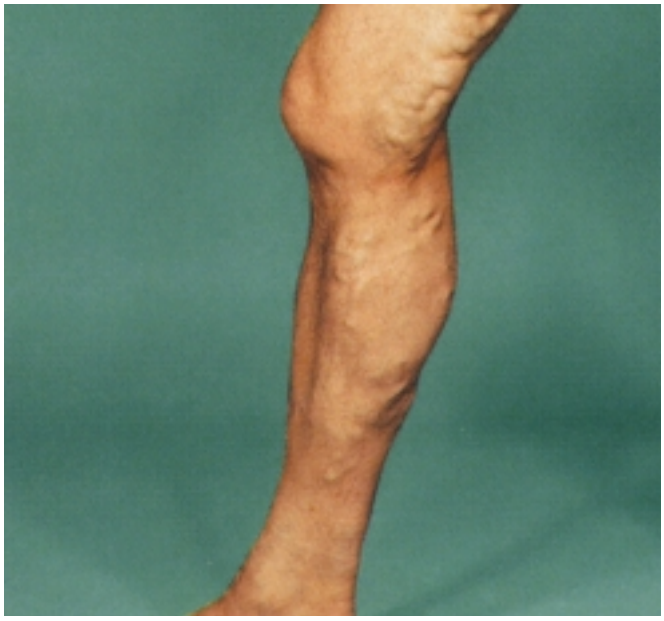

Figure 1a: lower extremity of a patient, suffering from CVD, C2.

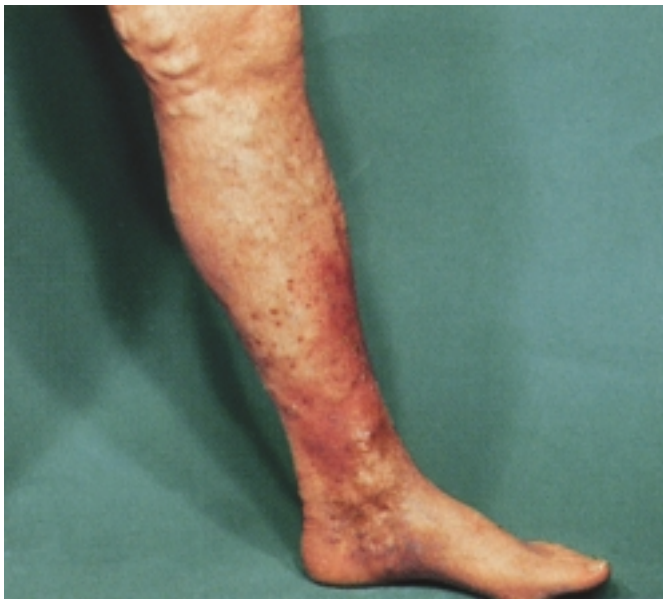

Figure 1c: lower extremity of a patient, suffering from CVD, C4.

Figure 1b: lower extremity of a patient, suffering from CVD, C3.

restless leg syndrome.[4,5] A large step forward in research into CVD was the presentation of the so-called CEAP classification which addresses the clinical (C), etiological (E), anatomic (A) and pathophysiological (P) mechanisms of CVD[21-23] (*Table I*). This accurate classification scheme concerning the pathophysiology and anatomic distribution of the disease is the basis for an optimal treatment, and serves as a basis for scientific studies comparing different treatment regimens.

The aim of the present study was to determine the prevalence of CVD in a cross-section of the workforce population of a hospital, and to investigate possible correlations between endogenous, environmental, and occupational

Absence of symptomatic CVD	**C0**	No visible or palpable signs of CVD
	C1	Telangiectasia or reticular veins (<4 mm in diameter)
Occurrence of symptomatic CVD	**C2**	Varicose veins (>4 mm in diameter)
	C3	Edema as a sequel of varicose veins
	C4	Skin changes ascribed to CVD (pigmentation, venous eczema, lipodermatosclerosis)
	C5	Skin changes with healed ulceration as a sequel of CVD
	C6	Skin changes with active ulceration as a sequel of CVD

Table I. Clinical part of the CEAP classification.

risk factors for CVD and the occurrence of this disease.[24,25] As the field of activity of most hospital employees differs from that of other professions, because of certain conditions, such as long standing periods, working night shifts, or hot-humid workplace temperatures, we tested the hypothesis that these workplace conditions might increase the risk of developing CVD.

SUBJECTS AND METHODS

During 6 months all consecutive subjects who consulted the outpatient department of the Department of Occupational Health Medicine of the Medical University of Vienna for routine medical checkups were asked to participate in the investigation. Twenty people refused to participate; finally 209 employees (49 men and 160 women with a mean age of 38 years) were included. None of the participants had recently seen a doctor because of primary complaints related to venous disorders. Three groups were defined: group 1: doctors and nurses (n = 71; 34%), group 2: medical technicians, secretaries, and scientific staff (n = 68; 33%), and group 3: cleaners and general staff (n = 70; 33%).

Based on physical examination by the same physician, patients were diagnosed as suffering from signs and symptoms of CVD (CEAP classes C2, C3 and C4) or as being free of CVD (CEAP classes C0 and C1).

Endogenous risk factors, ie, family history of venous disease, history of deep venous thrombosis, current oral contraceptive treatment, and exogenous risk factors, ie, frequency of sauna or tanning visits and standing periods in hours per day during work, were surveyed by questionnaire. A body mass index (BMI) >30 was defined as overweight (dietary guidelines for Americans, 2000).

To evaluate the restriction in quality of life, subjects were asked about temporary or permanent occurrence of heavy legs, edema, pruritus, pigment alterations, restless legs, burning legs, paresthesia, and cramps of the lower extremities.

The intensity of these symptoms was graded into four classes (none, mild, moderate, severe). The number of days absent from work in relation to CVD during the last year was documented.

RESULTS

Demographics and venous risk factors of 209 participants are given in *Table II*. 139 subjects presented without CVD (104 subjects with C0, and 35 subjects with C1, who were not taken into consideration for symptomatic CVD). A total of 70 subjects (34%) could be classified as having occurrence of CVD, 17% C2 (n = 36), 12% C3 (n = 24) and 5% C4 (n = 10). No C5 or C6 class could be found. The mean age of subjects with occurrence of CVD was not different from that of subjects without CVD (41 years versus 37 years; $P < 0.77$). Signs and symptoms of CVD were present in 39% of females (n = 63) but only in 15% of males (n = 7), whereby the study population

	Group 1 n = 71	Group 2 n = 68	Group 3 n = 70
Mean age; years ± SD	34.6 ± 8.2	36.4 ± 10.1	42.7 ± 7.8
Mean duration of professional activity; years ± SD	9.2 ± 8.5	11.1 ± 8.6	11.4 ± 8.9
Females n (%)	51 (72)	58 (85)	52 (74)
Males n (%)	20 (28)	10 (15)	18 (26)
Positive family history for CVD; n (%)	32 (45)	32 (47)	14 (20)
Positive history for deep venous thrombosis; n (%)	1 (1)	0	2 (3)
Oral contraceptive therapy; n (%)	11 (16)	21 (31)	13 (19)
Overweight; n (%)	15 (21)	15 (22)	45 (64)
Frequent visit to sauna or artificial tanning centre; n (%)	16 (23)	21 (31)	11 (16)

*Table II. Demographics and risk profile for chronic venous disease for the 3 professional subgroups.**

* Group 1: doctors and nurses (n = 71)
Group 2: medical technicians, secretaries, and scientific staff (n = 68)
Group 3: cleaners and general staff (n = 70)

CEAP classification	Group 1 n = 71	Group 2 n = 68	Group 3 n = 70
C0; n (%)	37 (52)	36 (53)	31 (44)
C1; n (%)	12 (17)	16 (24)	7 (10)
C2; n (%)	14 (20)	10 (15)	12 (17)
C3; n (%)	7 (10)	5 (7)	12 (17)
C4; n (%)	1 (1)	1 (1)	8 (12)

Table III. Correlation of classification of CVD and 3 different professional subgroups ($P < 0.02$).*

* Group 1: doctors and nurses (n = 71)
Group 2: medical technicians, secretaries, and scientific staff (n = 68)
Group 3: cleaners and general staff (n = 70)

consisted of 3 times more females than males. Within the different professional subgroups group 2 had the lowest severity grading of CVD, and group 3 the highest risk profile for the development of severe CVD ($P < 0.02$; *Table III*). Concerning the investigated endogenous risk factors, the only correlation with occurrence of CVD was found for history of deep venous thrombosis. The three subjects who had suffered from earlier deep venous thrombosis were suffering from CVD symptoms, defined as "post-thrombotic syndrome." Neither intensive sauna nor artificial tanning treatment, nor oral contraceptives (n = 45) were found to be associated with higher incidence of CVD. Subjects with occurrence of CVD spent a significantly longer mean standing period at work than subjects without signs and symptoms of CVD (8.3 hours per day versus 5.9 hours per day; $P < 0.02$). Fifty subjects reported feeling restricted in their quality of life due to diverse symptoms of CVD, including cramps, edema, pruritus, and restless legs, whereby 31 subjects (group 1: n = 10; group 2: n = 7; group 3: n = 14) felt temporary restricted, predominantly in the evening; 19 patients (group 1: n = 2; group 2: n = 3; group 3: n = 14) stated that they suffered permanently from these symptoms. None of the 209 subjects had stayed absent from work during the past last year due to complaints of CVD.

DISCUSSION

In the present study we report a prevalence of 34% of CVD in a wide cross-section of hospital employees (n = 209), varying between 22% and 46% among the different subgroups. The major finding was that long-term standing periods during professional activity were a predisposing factor for CVD. Subjects, with signs and symptoms of CVD exposed their venous system to orthostatic burdens 30% more per day compared to asymptomatic subject. This relationship was particular evident in males, though the overall prevalence of CVD was lower in males than in females.

General staff and cleaners were at higher risk for the occurrence of CVD than other professional groups. This elevated risk may result from hot-humid workplace conditions, under which people in this group usually work. Socioeconomic reasons may also be implicated: whereas some studies report a higher prevalence of venous disease in the relatively underprivileged sectors of the population,[26-28] no relationship between the epidemiology of CVD and social class could be found in the Edinburgh Vein Study.[29]

We found the lowest prevalence of CVD in medical technicians, secretaries, and scientific staff. Since the field of activity of such professions is related to the lowest mean periods of working in a standing position, these results correspond well with our hypothesis of working position being a main risk factor for the development of CVD.

Walking improves the efficiency of the calf muscle pump by lowering the capillary pressure and thereby avoiding venous reflux. In addition, we would recommend, especially for subjects who are predisposed to develop venous disorders (ie, those with a history of deep venous thrombosis) the daily wearing of compression stockings, class II, to prevent venous reflux and the subsequent development of CVD. In addition to its prophylactic effect, compression therapy has important impact on preventing deterioration of existing disease. The presence of peripheral artery disease has to be excluded before prescribing compression therapy.

Even if only 5% of subjects were suffering from skin changes ascribed to CVD, class C4, and none suffered from recent or healed trophic lesions due to severe CVD, class C5 or C6, it should be mentioned that this population was very young (mean age 38 years) and the prevalence and severity grade of CVD rises with age.[9]

The unexpected lack of correlation between oral contraceptive therapy and the risk of development of CVD in our investigation can be explained by the fact that only a third of the female study population reported the intake of hormones.

Quality of life is increasingly considered as an important outcome measure in diagnostic and treatment studies. Among the high number of studies on quality of life in correlation with disease, only a few deal with CVD.[18,30] Subjects suffering from CVD did not report time lost from work, most of them stated their quality of life considerably restricted due to discomfort and complaints from part of their venous disorders.

In conclusion, the high prevalence of CVD in selected workforce populations indicates that CVD might be triggered by occupation-related risk factors. Occupation-related risk factors could be even more relevant than endogenous risk factors for CVD. The study underlines the requirement for screening interventions in the workplace such as recommendations for primary prophylactic treatment of CVD, in particular for subjects, spending long periods in a standing position and/or working under hot-humid conditions.

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TRIANGLE (TRIple Assessment linkiNg siGns, symptoms and quaLity of lifE in CVD): a screening program initiated by Servier

RATIONALE OF TRIANGLE SURVEY

TRIANGLE is an international observational research program developed 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.

Chronic venous disease of the lower limb is characterized by symptoms or signs produced by venous hypertension as a result of structural or functional abnormalities of major veins and capillaries. As a result, CVD must be considered to be at stages C0 to C6 of the CEAP classification.[1] From former studies,[2,3] we know that quality of life of patients suffering from CVD is mainly impaired by the presence of symptoms, and that it is poorly influenced by the sex of the patients, the age, the presence of reflux or not, the severity of signs, or the duration of CVD disease.

The primary objective of TRIANGLE was to extend our knowledge regarding prevalence of CVD-related symptoms, and its relationship with the presence of signs, together with the impact both symptoms and signs may have on the quality of life.

Symptoms are not specific to CVD. To be attributed to chronic venous disease, the variability of such symptoms should be seen in at least two of the following situations: 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 (during the summertime season, hot baths, floor-based heating systems, hot waxing to remove body hair), but are less intense in winter and with cold temperatures, and for women, exacerbated before the menstrual period or occur with hormonal therapy, but disappear with discontinuation of such treatment, or after the menstrual period.

The secondary objective was to evaluate the outcome of lifestyle advice or treatment after a 3-month follow-up period.

The Bulgarian TRIANGLE program which is reported on in this paper is focused mostly on the symptoms and signs of CVD, without reporting data on the quality of life. It is part of these recent surveys that used the basic CEAP classification,[4] in which the single highest descriptor is used for clinical class.

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It must be stressed however, that data regarding clinical classification coded as C0-C6 do not provide a full epidemiological background, as recorded information referred only to a single venous pathology, eg, varicose veins, skin changes, or active ulcers, corresponding to the highest clinical category. However, there is a hypothesis for internal consistency in which, in the extremities with a reported higher C category of venous pathologies, were also observed at lower stages of C category in a certain percentage.[5]

Little epidemiologic research has been conducted in non-Western countries; the prevalence of CVD is considered to be low in these areas. It is not known whether the prevalence, clinical expression, and complaints are the same in Eastern European countries as in the Western population. The Bulgarian TRIANGLE survey provided 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.

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The TRIANGLE screening program: Bulgarian results

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ABSTRACT

CVD is a very common condition, which is often overlooked. The epidemiological data for Bulgaria are limited. The TRIANGLE program is an observational study designed to give an initial picture of the demographics and the prevalence of stages, symptoms, and signs of CVD among patients seeing their GPs. Over a period of 5 months, 3047 patients with chronic venous disease were entered in the study and were statistically processed.

The majority of Bulgarian patients with CVD were in classes C0, C1, and C2 (63.8% cumulative incidence of patients with CVD). Female gender prevailed (70.5%). The mean age was 55.4 years. The distribution by age corresponded to the progressive nature of CVD. The most common complaints were fatigue, heaviness in the legs, pain, swelling, and cramps. Nearly half of the patients had not been given prior treatment. In order to improve subjective symptoms, Daflon 500 mg was the treatment of choice in any stage.

INTRODUCTION

Chronic venous disease (CVD) is one of the most common diseases around the world.[1-3] Nevertheless, the problems associated with CVD are overlooked, and often underestimated by medical authorities, physicians, and patients.

CVD is characterized by a broad spectrum of clinical symptoms, including heaviness in the legs, pain, muscle cramps, and a feeling of swelling accompanied or not by clinical signs such as leg edema and trophic skin changes, including venous ulcers. The disease progression is also accompanied by an increased risk of thrombophlebitis, deep vein thrombosis, and pulmonary thromboembolism – conditions that not only worsen patients' quality of life, but may also threaten their lives.[4]

The epidemiological data concerning CVD in Bulgaria are limited, while worldwide the problem of insufficient information has begun to change, especially after the publication of RELIEF,[5] the largest clinical epidemiological study carried out in 23 countries all over the world, which provided data on the prevalence of venous reflux, the impact of CVD on quality of life, and the protective effects of Daflon 500 mg (micronized purified flavonoid fraction).

Thus, the need for deeper knowledge on CVD in our country led us to carry out this study.*

**The TRIANGLE program was carried out with the sponsorship of Les Laboratoires Servier.*

Keywords:
chronic venous insufficiency, risk factor, quality of life.

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AIMS

The primary aims of the TRIANGLE study were:
- To obtain reliable information on the prevalence of the different CEAP stages of CVD among individuals seeing their general practitioners in Bulgaria.
- To obtain reliable information about the most common complaints urging CVD patients to visit a doctor.

STUDY POPULATION AND METHODS

TRIANGLE is an epidemiological observation carried out in 16 of the largest Bulgarian cities (Blagoevgrad, Burgas, Varna, Veliko Tarnovo, Vratza, Dobritch, Kyustendil, Lovetch, Montana, Pazardjik, Pleven, Plovdiv, Russe, Sliven, Sofia, and Stara Zagora) designed to obtain nationally representative data.

Twenty-one surgeons from the BSSAVS (Bulgarian Scientific Society for Angiology and Vascular Surgery) educated 500 general practitioners on the symptoms and signs of CVD; how to diagnose the illness in a patient: through an interview, physical examination, and medical tests, and how to collect the information in the case report form.

Between 1 April and 31 August 2004, the 500 GPs actively looked for patients with CVD, among all their over 16-years old patients, regardless of the visit purpose, excluding patients needing emergency care.

For this period, 3900 CVD patients were enrolled in the observational study. Of these, 3047 met the inclusion criteria and had correctly completed CRFs, and their data were entered and statistically processed.

The first section of the case report forms included anthropometrical data of the patient and data concerning their clinical history and the presence of vascular risk factors (family history, patient's history of vein disease, prior treatment for CVD, prior history of thrombophlebitis, and other risk factors predisposing to CVD). The second section reflected the interviewing physician's evaluation of the severity of disease, classified as C0 to C6 in accordance with the clinical criteria of the CEAP[6] classification (proposed at the Hawaiian meeting of the American Venous Forum in 1995 and nowadays considered to be the most elaborate of all existing classifications), and a description of the symptoms characterizing the disease, such as pain, heaviness in the legs, swelling, cramps, burning sensation, itching, fatigue, and pulsation quantified by a 4-degree verbal scale depending on the severity of the patient's complaints.

STATISTICS

The statistical methods used for data processing and analysis included:

Descriptive methods

- For nonmetrical and group data: tables with absolute and relative distribution rate.
- For metrical parameters: mean values, standard deviation, minimum and maximum values, and median value.

Methods of graphic presentation

- For nonmetrical and group data: column diagrams.
- Methods of statistical processing: in accordance with the nature of data, a chi-square test was applied to test the hypotheses. The real probability for type I errors was calculated using the precise Fisher's criterion. The level of significance when testing an invalid hypothesis was predetermined to be 0.05.

All the calculations were made using the SPSS statistical pack.[7]

RESULTS

Distribution of the CVD patients according to the CEAP classification

The results from this study show that the majority of the observed Bulgarian CVD patients (63.8% cumulative incidence) belonged to classes C0, C1, and C2, according to the CEAP classification (symptoms without signs, telangiectasias, varicose veins), and class C2 signs (varicose veins) prevail – 28.6% relative incidence.

Class C3 (edema) and C4 is common among the study population: 15.9% and 13.2%, respectively. The prevalence of class C5, skin changes with healed ulcerations, and class C6, skin changes with active ulcerations, are lower among the observed CVD patients, respectively 4.5% and 2.4% *(Table I)*.

Demographic distribution of CVD patients seeking medical consultation

Female gender prevails: 70.5% female vs 29.5% male patients. The mean age of the patients included in the study population was 55.41 years. The distribution by age: 43.2% (41 to 60 years) vs 17.4% (19 to 40 years) confirm the progressive nature of chronic venous insufficiency (*Table II*).

Clinical class (CEAP classification)	Prevalence		
	Absolute number	Percentage	Cumulative percentage
C0	486	16.0	16.0
C1	587	19.3	35.2
C2	871	28.6	63.8
C3	484	15.9	79.7
C4	403	13.2	92.9
C5	142	4.7	97.6
C6	74	2.4	
Total	3047	100.0	100.0

Table I. Distribution of patients according to the CEAP classification.

Demographic variable	Absolute number	Percentage
Gender		
Male	899	29.5%
Female	2148	70.5%
Total	3047	100%
Age group		
Under 18 years	3	0.1%
19 - 40 years	529	17.4%
41 - 60 years	1317	43.2%
Over 60 years	1198	39.3%
Total	3047	100.0%
Mean age value	-	55.41
Standard deviation	-	14.66
Minimum	-	17.00
Median	-	56.00
Maximum	-	94.00
Body mass index (BMI) in kg/m^2		
BMI under normal (< 18.5)	33	1.1%
Normal BMI (18.5 - 24.9)	1042	34.2%
Overweight (25.0 - 29.9)	1234	40.5%
Obesity (≥ 30)	738	24.2%
Total	3047	100.0%
Mean BMI value	-	27.15
Standard deviation	-	4.70
Minimum	-	16.41
Median	-	26.57
Maximum	-	45.20

Table II. Demographic distribution.

Prevalence of symptoms

Among Bulgarian CVD patients, the most common complaints that urged them to see their doctors were: fatigue, heaviness in the legs, pain, swelling, and cramps (*Figure 1*).

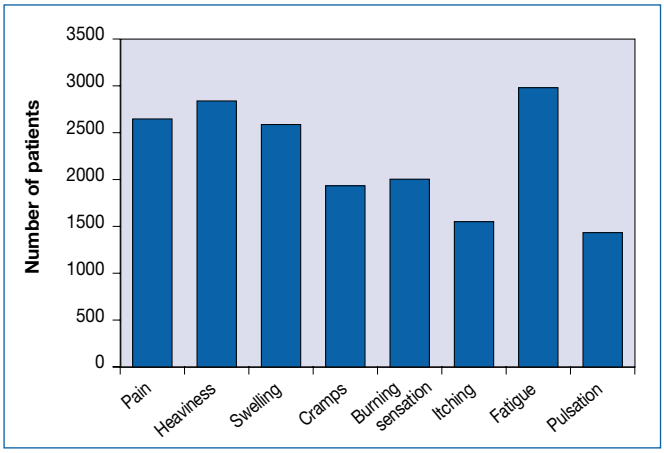

Figure 1. Prevalence of symptoms among chronic venous insufficiency patients.

Distribution according to prior management of CVD patients belonging to different CEAP classes

The distribution of CVD patients belonging to different CEAP classes according to prior management indicates that chronic venous insufficiency is overlooked as nearly half of the patients regardless of the presence of symptoms, varicose veins, and edema did not receive prior treatment (*Figure 2*).

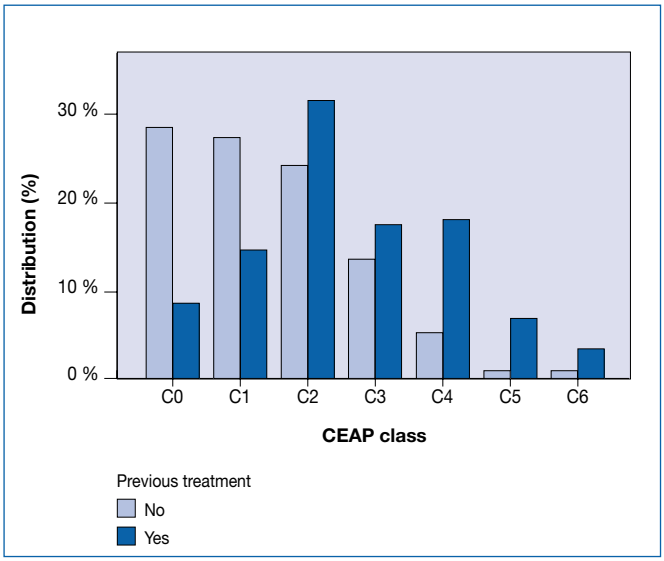

Figure 2. Distribution of patients belonging to different CEAP classes according to prior management of CVD.

CONCLUSIONS

Thanks to countrywide enrolment of 3900 patients, the TRIANGLE program constitutes a large database on the prevailing CVD stages in Bulgaria.

The large number of patients seeking medical help during the study period justifies the conclusion that CVD is a widely prevalent disease among the Bulgarian population.

The study results show that the majority of Bulgarian CVD patients seeking medical help (63.8%) belong to the CEAP classes C0 and C2 (symptoms without signs, telangiectasias, varicose veins), with the latter class (C2, varicose veins) being a majority.

Another important conclusion drawn from the first CVD screening program carried out in Bulgaria is that there was a general lack of prior management within the study population, especially among those at the early stages of disease. This means that, despite its progressive nature, during the initial stages, when complaints are present but signs are trivial or lacking, the disease is often overlooked. However, the early diagnosis and management of CVD is crucial for avoiding severe late complications.

Management should combine changes of lifestyle, phlebotropic agents and, at the advanced stages of the illness, more specific treatments, such as elastic bandages, sclerotherapy, and surgical procedures.

Daflon 500 mg was the phlebotropic agent of choice for participants at any stage of the disease, because it is highly effective in relieving symptoms that sometimes make the life of the patient unbearable, and in preventing the progression of CVD to its complications.

The TRIANGLE program is only the beginning of a wider study of CVD morbidity and its consequences in Bulgaria.

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Invasive treatment of post-thrombotic symptoms

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ABSTRACT

The treatment of symptomatic postthrombotic syndrome is a difficult, evolving, and lifelong undertaking. This chronic disease is not only characterized by the possibility of leg ulcer formation, but more often disabling pain and swelling with minimal skin changes. The prevailing view that intervention, and thus an appropriate workup should only be performed after failure of conservative treatment may deprive patients of early substantial symptom relief. Early investigations of postthrombotic limbs to describe the anatomic distribution of reflux and obstruction are mandatory as the conservative treatment is started. Invasive and conservative treatment may then be continued simultaneously. The decision to intervene is based upon the clinical status of the patient and by the result of adequate investigations. Minimally invasive interventions such as venous stenting and superficial reflux ablation are relatively simple with good efficacy and low risk. When obstruction is associated with reflux, the obstruction should be treated first. Concomitant superficial reflux may be treated in the same sitting, but any associated deep reflux is ignored pending clinical response to these interventions. Deep vein valve repair is considered a second-stage intervention in these limbs when conservative and minimally invasive therapy fail. Deep venous insufficiency with no outflow obstruction appears to be a major determinant for failure after control of superficial saphenous and perforator reflux in postthrombotic limbs. Therefore, it has been suggested that these procedures should be performed concomitantly with deep valve repair.

INTRODUCTION

Symptoms in patients with a previous history of deep venous thrombosis (DVT) may vary from minimal swelling to pain, skin changes, and venous ulcerations. Compression therapy is still considered by many to be the cornerstone of management of not only post-thrombotic symptoms, but of all venous disease. With a history of previous deep venous thrombosis and perceived scarred veins with ruined valves and varying degrees of obstruction, many physicians would assume that leg compression and local wound care is the only remedy. In my opinion, this is an old-fashioned and counterproductive view that may deny patients modern treatment. With new techniques available for the diagnosis and treatment of chronic venous disease, the basis for management should instead be to accurately verify and classify the presence of venous dysfunction. Treatment in symptomatic patients must take

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into account the degree and distribution of valve reflux and outflow obstruction. Invasive treatment should then be considered in combination with conservative measures such as compression therapy, which is certainly one aspect of the treatment.

The complexity of investigations of post-thrombotic disease depends upon the severity of symptoms and the availability of investigatory tools. Three levels have been identified by the CEAP committee of the American Venous Forum:[1] Level 1: Office visit with history, clinical examination, and handheld continuous-wave Doppler; Level 2: Noninvasive vascular laboratory investigations, with mandatory duplex scanning and possibly plethysmography; Level 3: Invasive investigations or more complex imaging studies, including ascending and descending venography, varicography, venous pressure measurements, venous spiral computed tomography (CT), or magnetic resonance venography (MRV). The aim of the investigations is to describe the anatomic distribution of venous disease in the superficial, perforator, and deep systems and the presence of reflux and/or obstruction of these venous segments. In the case of significantly symptomatic post-thrombotic syndrome, level 2 and 3 investigations are usually necessary. It is possible to direct the invasive treatment correctly only with adequate knowledge of the pathophysiologic condition. The final decision to operate is based upon the clinical status of the patient rather than the test data, since the patient's symptoms and signs may not correlate with the laboratory findings.[2]

Conservative or invasive treatment does not necessarily correct the basic cause of the chronic venous disease. Post-thrombotic venous disease appears to be chronic in nature. A progressive functional deterioration is observed long after the initial acute thrombosis, perhaps a result of prolonged inflammatory response, underlying thrombophilia, and subclinical recurrent events of thrombosis. Philosophically, our conceptual approach to invasive treatment of venous disease should perhaps be similar to that of arterial surgery. Like arterial bypass operations, venous surgery ameliorates the symptoms but does not cure the disease. Occlusion of a bypass inserted to treat critical ischemia does not necessarily lead to recurrence of gangrene and loss of the limb. Similarly, it has been observed that late failure of a repaired valve station with reflux does not mandate recurrence of a venous ulcer. Contrarily, recurrence of symptoms of venous and arterial disease, eg, ulcer, is not necessarily failure of treatment, but may instead represent progression of the disease. The aim of invasive treatment is to achieve a compensated state of venous function by correcting one or several factors contributing to the pathophysiology, recognizing that a completely normalized function may be impossible to achieve. For example, it has been shown that a decreased ulcer recurrence rate has been observed in limbs with less reflux as measured by air plethysmography (limbs with venous filling index (VFI) < 4.0 mL/s versus those with > 4.0 mL/s; 28% and 53%, respectively).[3] Similarly it has been reported that the recurrence rate was only 14% if a venous filling time (VFT) of greater than 5s could be maintained as compared with 45% when VFT was less than 5s.[4] The patient appears to show improvement even when the invasive treatments result in only partial correction of the reflux.

Groups of patients have been followed after correction of underlying venous pathology by superficial and deep venous interventions, and most investigators have found a long-term symptomatic improvement in post-thrombotic limbs. Only a few prospective studies have been reported, but they are consistent in reporting, for example, that the ulcer healing rate is shortened and ulcer recurrence rate decreased when intervention is combined with compression therapy and local ulcer treatment in limbs with combined deep and superficial disease.[5] It would appear logical to start with less invasive treatment initially, ie, percutaneous control of great saphenous vein (GSV) reflux or ilio-caval stenting and when minimally invasive therapy fails to proceed to open surgery, ie, valve repair or bypass surgery.

INVASIVE TREATMENT OF VENOUS OBSTRUCTION

Venous outflow obstructions are often observed following acute deep vein thrombosis due to subsequent absent or poor venous recanalization. It is found in combination with reflux in 55% of symptomatic patients, and this combination leads to the higher levels of venous ambulatory pressure and more severe symptoms then when either condition is present alone. The remaining obstruction is the principal cause of symptoms in approximately one third of post-thrombotic limbs.[6,7] It appears that proximal obstruction of the venous outflow, especially the iliac vein, is more symptomatic than is segmental blockage.[8,9] The collateral formation is relatively poor around an iliofemoral obstruction, contrary to the situation when the femoral-popliteal vein is blocked. Following iliofemoral DVT, only 20% to 30% of iliac

veins completely recanalize spontaneously, while the remaining veins recanalize partly and develop varying degrees of collaterals.[10,11] The main purpose of intervention is to relieve proximal obstruction. Most authors agree that when significant obstruction is localized above the inguinal ligament, the obstruction should be treated before any concomitant reflux. The key for the physician is to be aware of the importance and possibility of venous blockage.

Unfortunately, there are no reliable tests to measure a hemodynamically significant stenosis. Although a positive noninvasive or invasive test for obstruction may indicate the need to proceed with further investigations, a negative test should not discourage additional testing. The diagnosis of outflow obstruction is morphologic, and must be made by investigations such as ascending or antegrade transfemoral venography; intravascular ultrasound, which is superior;[12,13] MRV or CT phlebography.[14,15]

FEMORO-ILIO-CAVAL STENTING

The introduction of percutaneous iliac venous balloon dilation and stenting has dramatically changed the treatment of the iliofemoral outflow obstruction. The endovascular technique has emerged as the efficient "method of choice" to relieve at least proximal iliofemoral obstruction. It can be offered to a larger group of patients because it is a safe and relatively simple intervention. Ultrasound-guided percutaneous cannulation is performed distal to the obstruction in the thigh portion of the femoral vein or through the popliteal vein. Partial obstruction of the post-thrombotic iliofemoral vein is usually fairly simple to transverse and treat, but even post-thrombotic limbs with occlusion can more often than not be recanalized and stented (*Figure 1*). Uninterrupted venous outflow and sufficient inflow from below are vital for long-term patency and symptom relief just as in open bypass surgery. It is therefore important to stent the entire diseased area, even if the stent extends below the level of the inguinal ligament. The intraoperative use of intravascular ultrasound is crucial to properly delineate the extent of post-thrombotic disease (*Figure 2*). The results following venous stenting are usually poorly presented. Most studies are case reports and few have a significant number of patients; the follow-up is short-term; patency is not reported in cumulative fashion; stented sites in the upper and lower extremities are mixed; there is no differentiation between etiologies and

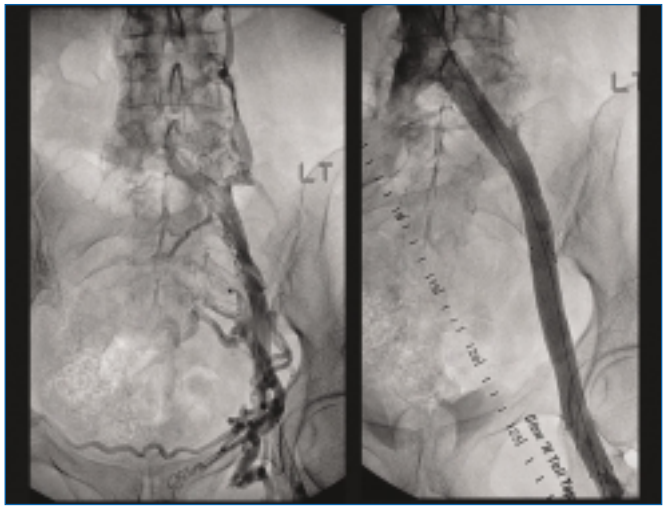

Figure 1. (Left) Left iliofemoral post-thrombotic obstruction with axial and transpelvic collaterals. (Right) Venogram after recanalization and stenting shows no outflow obstruction and disappearance of collaterals.

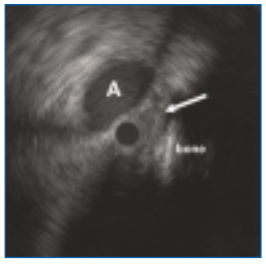

Figure 2. Intravascular ultrasound (IVUS) of the iliac vessel crossing after recanalization but before stenting. The left occluded vein (arrow) is compressed by the right common iliac artery (A) against the bone. The black circle within the vein is the IVUS catheter.

no separation of acute and chronic conditions. Patency rates assessed by duplex ultrasound or venography in successfully stented limbs of mixed groups of patients vary greatly. Primary and secondary patency rates 12 to 52 months after stenting are 50% to 100%, and 75% to 100%, respectively.[16-19]

Patency rates and in-stent recurrence of stenosis appear poorer in stented limbs with post-thrombotic disease as compared with nonthrombotic limbs. Our own experience of iliofemoral stenting has shown cumulative primary, assisted-primary and secondary patency rates at 3 years to be 75%, 92%, and 93%, respectively.[20,21] The stented limbs with thrombotic disease appeared to fare significantly worse than did those with nonthrombotic disease (primary, assisted-primary, and secondary cumulative patency rates of 65%, 85% and 88%, and 89%, 100%, and 100%, respectively, at 36 months). Severe in-stent recurrent stenosis (ISR), ie, >50% diameter decrease on single-plane anterior-posterior venogram, is infrequent overall (only present in 15% present at 42 months).[22] However, cumulative higher rates of severe ISR occurred with treatment of thrombotic as compared

to nonthrombotic limbs (23% and 4%, respectively); in the presence of thrombophilia (18% and 12%, respectively); long stented area (13 to 35 cm; 25%) at 36 months. These results may reflect treatment of a more severe and extensive disease seen in limbs with postthrombotic disease. The above major risk factors for development of ISR are similar to those observed in limbs with late occlusion, although late occlusion is not necessarily preceded by increased in-stent restenosis. Other factors, such as acute recurrent thrombosis with direct occlusion of the stent or deterioration of the venous inflow, may play a major role.

The reports describing patency rates indicate clinical improvement in most patients (>72%).[17,19,23] The incidence of ulcer healing after iliac vein balloon dilation and stent placement in 41 limbs with active ulcer was 68%, and the cumulative ulcer recurrence-free rate at 2 years was 62%.[20] Median swelling and pain severity scores decreased significantly. The frequency of limbs with no swelling increased significantly from 12% to 47%, and limbs with no pain rose from 7% to 71%. The improvement in pain and swelling was significant in both ulcerated and nonulcerated limbs, indicating that the ulcer was not the only cause of pain and swelling. Using a quality-of-life questionnaire, the patients indicated significant improvement in all major categories after venous stenting. The results clearly indicate significant symptom relief in the intermediate term after balloon angioplasty and stent placement in the treatment of iliac venous outflow obstruction.

OPEN BYPASS SURGERY

A crossover bypass can be constructed by using either the contralateral saphenous vein (either by rotation or as a free saphenous graft) or a prosthetic graft. The autogenous cross-femoral venous bypass appears to be less thrombogenetic with better patency than prosthetic grafts, but may afford poor symptom relief owing to its small crosscut area and relatively large resistance to flow.[24] This is why the size of a 10-mm ringed PTFE (PolyTetraFluoroEthylene) graft is generally recommended for bypass as an alternative to the absent or an inadequately sized saphenous vein (< 4 mm).[25,26] The crossover reconstruction has been reported to be durable with good symptom relief with so-called "clinical" and venographic patency ranging from 44% to 100% with a follow-up of 5 years.[26-28]

The anatomic in-line bypass reconstruction can be used in the femoro-ilio-caval axial outflow axis with segmental obstruction in the presence of a sufficient venous in- and outflow of the graft. Patency rates during follow-up from 1 to 150 months range from 29% to 100%.[24,29]

Saphenopopliteal vein bypass of femoropopliteal obstruction is rarely performed, since it requires a patent, nonvaricose great saphenous vein with competent valves and a patent tibial inflow tract. The clinical success and patency rates are poor.[30,31]

The results following open reconstructions have similar shortcomings as for stenting. Most vascular surgeons report a poor experience with open bypasses, with frequent early occlusion despite use of an adjunctive arteriovenous fistulae and meticulous perioperative anticoagulation. The poor patency rate is probably due to low velocity flow of the graft, external compression of the low pressure bypass, inherent thrombogenicity of the nonsaphenous graft material, and poor distal venous inflow due to extensive distal disease. Open bypass surgery, owing to its invasiveness, risky continuous anticoagulation and uncertain long-term result, should, therefore, be reserved to treat limbs after unsuccessful stenting attempts; later stent failure, which can not be adequately disobliterated; and perhaps long total occlusions, which appear to have a poorer result.

CORRECTION OF REFLUX

The only objective means of measuring advanced postthrombotic disease is to estimate the ulcer healing rate and ulcer recurrence rate in the presence of ulcer. It is much more difficult to objectively assess ulcer-free limbs for improvement in swelling, discoloration, pain, and discomfort. Most studies evaluating interventions to correct superficial and deep reflux have therefore been performed in limbs with ulcers. There are many population studies, but few appropriate prospective studies are available to assess the beneficial effect of correction of reflux on leg ulcers.

Interventions and conservative therapy should be instituted simultaneously. In patients with combined superficial and deep venous insufficiency, superficial venous surgery without compression bandaging failed to improve venous hemodynamics and achieve ulcer healing.[32] On the other hand, in a prospective, non-randomized study, McDaniel et al showed a significantly smaller cumulative recurrence rate at 48 months in limbs treat-

ed with a variety of operations vs those treated without surgery (26% and 52%, respectively).[3] They found that patients who were not candidates for surgery or who elected to forego surgery had a 3.4 times higher rate of ulcer recurrence. Another prospective, randomized study allocated ulcer limbs with isolated venous superficial incompetence or mixed superficial and deep venous reflux to either a multilayer compression treatment or a combination of compression and superficial ablative surgery. The overall 24-week healing rates were similar in the two groups, but 12-month ulcer recurrence rates were significantly reduced in the compression and surgery group as compared with the compression alone group (12% and 28%, respectively).[5]

The superficial ablative surgery does not improve an axial (femoropopliteal) deep venous reflux in a post-thrombotic limb. Limbs with ulcer may have axial superficial reflux associated with limited segmental deep reflux. Superficial venous surgery has been shown to abolish deep venous reflux in 50% of these limbs and a 77% ulcer healing rate can be achieved at 12 months.[33] It has also been feared that ablation of the superficial reflux in post-thrombotic limbs would result in worsening of the outflow obstruction by removing potential collateral circulation. Adequate deep axial collaterals, however, are invariably present in the presence of infrainguinal axial venous obstruction, even when not visualized on ascending venography. Superficial ablative surgery can be safely performed in post-thrombotic limbs.[34]

There is increasing support for the beneficial effect of superficial vein surgery on the healing rate and recurrence of venous leg ulcer. The ulcer recurrence rate is, however, markedly increased by the presence of deep reflux even after superficial reflux ablation.[35,36] A cumulative recurrence rate at 4 to 5 years is reported to be 67% to 100%, and 6% to 28% in limbs with and without deep involvement, respectively.[3,35,36] Thus, deep venous insufficiency appears to be a major determinant for ulcer recurrence. Concomitant deep and superficial repair therefore appears logical in limbs with combined deep and superficial axial reflux as an alternative to staged procedures, although this approach has not been assessed prospectively.

ABLATION OF SUPERFICIAL REFLUX

There are several methods for the treatment of truncal and nontruncal superficial reflux. It is generally accepted that liquid compression sclerotherapy is effective in the treatment of venectasias and nontruncal varicosities in the absence of GSV or short saphenous vein (SSV) trunk reflux.[37] In post-thrombotic legs, sclerotherapy is frequently combined with other interventions. Sclerotherapy with foam has been shown to be superior to liquid sclerotherapy in GSV in terms of clinical and hemodynamic outcome.[38,39] Treatment of limbs in clinical class C4-6 is apparently particularly rewarding.[40]

Saphenous vein stripping is still the standard in controlling saphenous trunk reflux. It may be combined with miniphlebectomy. Alternative catheter-based methods of endoluminal obliteration of the GSV have been developed using bipolar energy by radio frequency or laser. Both methods achieve obliteration of the GSV in 85% to 90% after 3 to 4 years.[41,42] Unfortunately, the patency and competency rates were not analyzed cumulatively (Kaplan-Meier method) and are therefore of lesser value because of the substantial dropout of patients in these studies.

Only two randomized controlled trials have been reported, both comparing endovenous GSV ablation by radiofrequency (RF) to open GSV stripping in patients with varicose veins. These studies showed that postoperative pain was reduced; sick leave was shorter; and faster return to normal activities and to work was observed in the RF-treated group, but at 4 months was found to be no different from the conventionally treated group[43,44] A 2-year follow-up has just been published.[45] Owing to the limited number of limbs studied differences do not reach statistical significance (possible type II error). Quality of life score improves to positive values between 1 and 3 weeks after surgery in the stripping group of limbs, but it never reaches the levels observed in the group treated by RF ablation, not even after 2 years. Further randomized long-term studies of more power are currently in progress, and are necessary before endoluminal obliteration can be considered the new standard. Its specific role in patients with post-thrombotic disease has not been assessed. We have successfully combined endovenous stenting with endoluminal obliteration in patients with C4-6 and found that this is a safe and effective one-stage procedure, which is truly minimally invasive. Clinical outcome is apparently no different when radiofrequency or laser is used than in open surgery, but less bleeding results secondary to heparinization during the stenting part of the intervention.

CONTROL OF INCOMPETENT PERFORATORS

The importance of the perforator reflux in the post-thrombotic limb is still debated. Perforating veins can become incompetent as a result of superficial and/or deep venous reflux, but are rarely found in isolation.[46]

The prevalence of IPV, as well as their diameter, volume, and velocity flow, increases linearly with clinical severity of CVI, whether or not there is coexisting deep venous incompetence.[47,48] The importance in the pathophysiology of PTS remains unclear. Opinions among surgeons vary greatly, from totally ignoring incompetent perforators to detailed mapping and specific treatment. In addition, the issue is muddled by the fact that complete eradication of superficial venous reflux will lead most IPVs to be interrupted or regain competence.[49,50]

The incompetent perforators may be controlled specifically by ultrasound-guided sclerotherapy, although long-term results do not exist. Separate multiple oblique incisions over large insufficient perforators are still used. The old Linton operations with large incisions and high wound complication rates have been abandoned for the use of subfascial endoscopic perforator surgery (SEPS). Numerous uncontrolled studies have suggested that SEPS might improve the symptoms of chronic venous disease. Unfortunately, concomitant saphenous surgery was frequently undertaken, rendering it difficult to assess whether the beneficial effect resulted from the SEPS procedure or, more likely, from the saphenous ablation.[51,52] The benefits of SEPS treatment of post-thrombotic syndrome remain especially doubtful. It appears that deep venous reflux (especially if post-thrombotic) might diminish the benefits of SEPS.[52,53] In such patients, the uncontrolled NASEPS registry showed that ulcer healing and ulcer recurrence rates were similar to those expected from compression therapy alone.[35] Until proper prospective randomized studies have been performed and perhaps appropriate subgroups to be treated have been identified, the role of the SEPS procedure in the treatment of post-thrombotic disease remains undefined. The procedure will continue to be used by many investigators, who feel SEPS benefits the patients with post-thrombotic limbs.

DEEP VEIN VALVE REPAIR

An estimated 60% to 85% of patients with deep venous reflux have had a previous deep vein thrombosis. Most commonly the valve station, which is involved in the inflammatory response elicited by the blood clot, is destroyed and cannot be repaired. In a few instances, the valve is minimally affected and can still be directly repaired. Valves above the proximal extent of the deep venous thrombus may be unaffected by the inflammatory process but are still incompetent. In fact, the first open valvuloplasty, performed by Dr Kistner, was performed in a patient with a previous distal DVT.[54] An intact incompetent valve can be repaired by internal valvuloplasty, wrapping,[55] and external transmural[56] or transcommissural[57] valvuloplasty (*Figure 3*). When the valve is completely destroyed the axial reflux can only be controlled by transposition[58] or most commonly axillary vein autotransplantation (*Figure 4*).[59] Other procedures such as silastic gracilis sling procedure, neovalve creation, and insertion of cryopreserved allografts, while initially promising, have now been largely discarded. Much hope is placed in percutaneously placed devices, but these are still experimental and unproven.

Although deep valve repair appears to be beneficial in single-center studies, the proof is circumstantial, since no prospective randomized studies exist. It is unlikely that such a study will ever be performed. Deep valve reconstruction with appropriate long-term follow-up by Masuda and Kistner resulted in a 40% ulcer recurrence

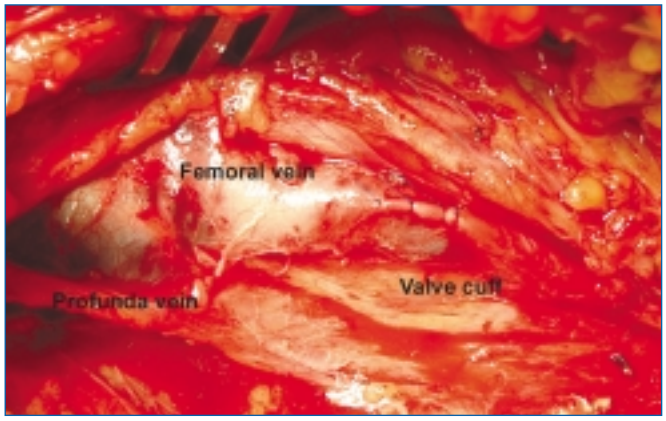

Figure 3. Transcommissural valvuloplasty. The stitches have been placed to narrow the angle between the cuff insertion lines and tightened the valve cuffs on one side. Similar stitching is then performed on the contralateral side.

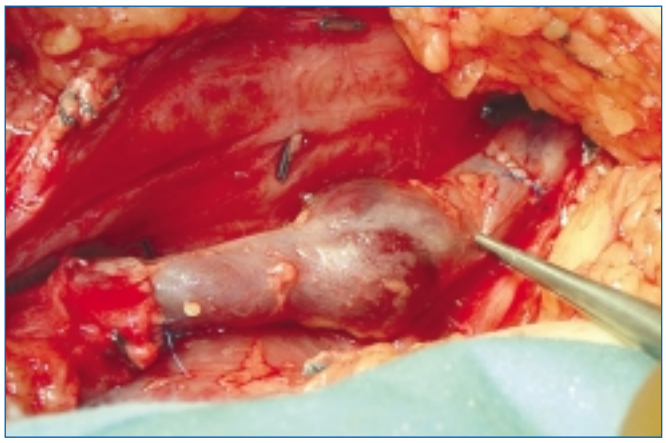

Figure 4. Axillary vein transfer to proximal femoral vein sutured in place. Note the thinner vein wall and the well outlined cuff insertion lines of the transplant.

over a long period and many patients had long ulcer-free periods (5 to 10 years).[58] Results after repair of valves in primary disease has been reported to be superior to post-thrombotic disease.[58,60] Raju et al reported a 6-year cumulative ulcer recurrence rate of approximately 40%, similar in primary and secondary disease after deep reconstruction.[61] The result appears more related to the type of procedure (direct repair versus axillary vein transfer) than to the presence of previous thrombosis. Overall deep venous valve repair in post-thrombotic limbs has a 50% to 60% ulcer recurrence-free rate up to 10 years after the intervention.

PRACTICAL IMPLICATIONS

The treatment of a symptomatic post-thrombotic syndrome is a difficult, dynamic, and lifelong undertaking. Disabling pain and swelling are important symptoms, in addition to leg ulcers. Despite the paucity of prospective, randomized information on efficacy, it may be that open or percutaneous correction of underlying disease is currently underused. The prevailing view that intervention can only be performed after failure of conservative treatment may deprive patients of early substantial symptom relief. Invasive and conservative treatment should be used simultaneously as appropriate, and do not conflict with, but rather are complementary of, each other. The decision to intervene is based upon the clinical status of the patient; the type of intervention is directed by the result of adequate investigations. At least minimally invasive interventions such as venous stenting and superficial reflux ablation may be performed at an early stage. Significant iliofemoral venous obstruction should be treated, whether associated with reflux or not. When obstruction is shown with reflux, the obstruction should be treated first. When concomitant superficial reflux, usually GSV reflux, is present we are now increasingly combining the stenting with percutaneous catheter obliteration with or without miniphlebectomy in the same sitting. Any associated deep reflux is ignored pending clinical response to this intervention. Valve repair of associated deep reflux is considered a second-stage intervention in patients who fail conservative and minimally invasive therapy. Contrarily, as discussed above, deep venous insufficiency appears to be a major determinant for failure after ablation of superficial saphenous and perforator reflux in post-thrombotic limbs. Therefore, it has been suggested that these procedures should be performed concomitantly with deep valve repair.

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Venous aneurysms

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INTRODUCTION

Venous aneurysms are rare vascular disorders which have been described throughout the venous system and can be seen at any age.[1,2] The lower extremities are the most frequently affected, the popliteal vein being the most common site, followed by aneurysms of the head and neck, abdominal veins, and thoracic veins.
The definition of venous aneurysm remains controversial, and there is no precise size criterion in the literature to distinguish between venous dilatation and venous aneurysm. Aneurysms are described as saccular or fusiform, an important distinction not only for anatomical reasons but also in terms of hemodynamic considerations and choice of surgical treatment.

DIFFERENT ANATOMICAL AND CLINICAL FORMS

Venous aneurysms of the neck and face

These aneurysms are rare and usually congenital. The internal jugular vein is the most common site. Most aneurysms of this type have been described in young adults and children. They account for about one third of all aneurysms. A venous aneurysm of the neck presents as a soft, compressible mass that enlarges on Valsalva maneuver or other expiratory effort with the glottis closed. The natural history of these aneurysms is benign, and the indication for surgery is often for cosmetic reasons.

Thoracic venous aneurysms

Some 60 cases have been reported, about two thirds of which involved the superior vena cava or azygos vein.
Although in most cases these aneurysms are large, with an average diameter of 6 to 7 cm, they are often asymptomatic and are found incidentally during imaging studies. A widening aneurysm may produce symptoms such as chest pain and/or dyspnea. Thromboembolic complications and aneurysm rupture are extremely rare events. A literature review by Calligaro[2] identifed 19 aneurysms of the superior vena cava or mediastinal veins. Ten of these patients, with a mean follow-up of 14 years, did not undergo surgical repair and had no complications. Eight patients underwent surgery, including three for aneurysm rupture (with one fatal hemorrhage, one fatal pulmonary embolism).

Abdominal venous aneurysms

While any of the abdominal veins may be affected, the most frequent sites are the portal vein and superior mesenteric vein. Portal vein aneurysms are usually symptomatic, and gastrointestinal bleeding is the presenting symptom.

Keywords:
venous aneurysm; venous surgery, pulmonary embolism, chronic venous disorders.

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These aneurysms can generally be diagnosed by color Doppler imaging, as well as by computed tomography (CT) or magnetic resonance imaging (MRI).

There is still some controversy as to the optimal management of these aneurysms. Nonetheless, surgical repair is recommended for patients with good surgical risk due to the potential for serious complications. Patients with portal or superior mesenteric venous aneurysms and hypertension linked to hepatic damage[2] can be treated with a portocaval shunt when aneurysm resection is difficult. In asymptomatic patients without underlying hepatic lesions or portal hypertension, monitoring is the recommended course of action.

Venous aneurysms of the lower extremities

This is the location most frequently reported in the literature, and there is a wide variety of clinical presentations. The popliteal vein is by far the most common site, followed by the femoral vein and the great saphenous vein. There have been 125 published reports of surgically repaired popliteal vein aneurysms (PVA).[3] The diagnosis is rarely clinical; instead, these aneurysms tend to be discovered incidentally during the workup for thromboembolic disease or on Doppler ultrasound imaging for chronic venous disease (*Table I*).

Most of the published PVA involved the proximal popliteal vein; 75% were saccular and 25% fusiform.

Symptoms and signs	Literature review (n =98)	Authors series[4] (n =27)
Pulmonary embolism	47 (48%)	7 (26%)
Deep venous thrombosis	7 (7%)	6 (22%)
Discovery of a popliteal mass	6 (5%)	0 (0%)
Chronic venous disease		
Pain, edema of lower limb	12 (12%)	3 (10%)
Varices	20 (20%)	14 (52%)
Venous ulcer	2 (2%)	4 (15%)
Angiodysplasia	4 (4%)	0 (0%)

Note: Some patients are listed several times either for symptom or sign.

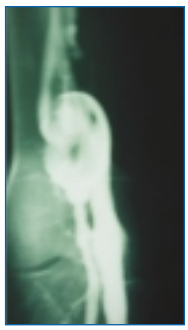
Table I. Clinical characteristics of patients with surgically repaired popliteal venous aneurysm (n =125).

Seven published cases were bilateral. Thrombus was present in the PVA in two thirds of the patients, and although large or saccular aneurysms can potentially lead to pulmonary embolism (PE), there is no clearcut correlation between this complication and the size or type of aneurysm.

Phlebography was the reference examination for these aneurysms, and had the highest diagnostic sensitivity for PVA (*Figures 1 to 5*).

Figure 1. Phlebography. Fusiform aneurysm without thrombus.

Figure 2. Phlebography. Large saccular aneurysm without thrombus.



Figures 3 and 4. Phlebography. Saccular aneurysm with endosaccular thrombus extending to the (superficial) femoral vein.

Figure 5. Phlebography. Saccular aneurysm with thrombus.

Doppler ultrasonography has since become the examination of choice for diagnosis of PVA because it can define aneurysm topography, shape, and diameter as well as the presence and size of any thrombus present therein (*Figure 6*). It is also useful for postoperative control and monitoring.

Figure 6. Ultrasonography. Popliteal venous aneurysm with thrombus in the lumen.

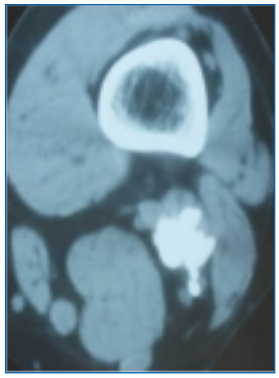
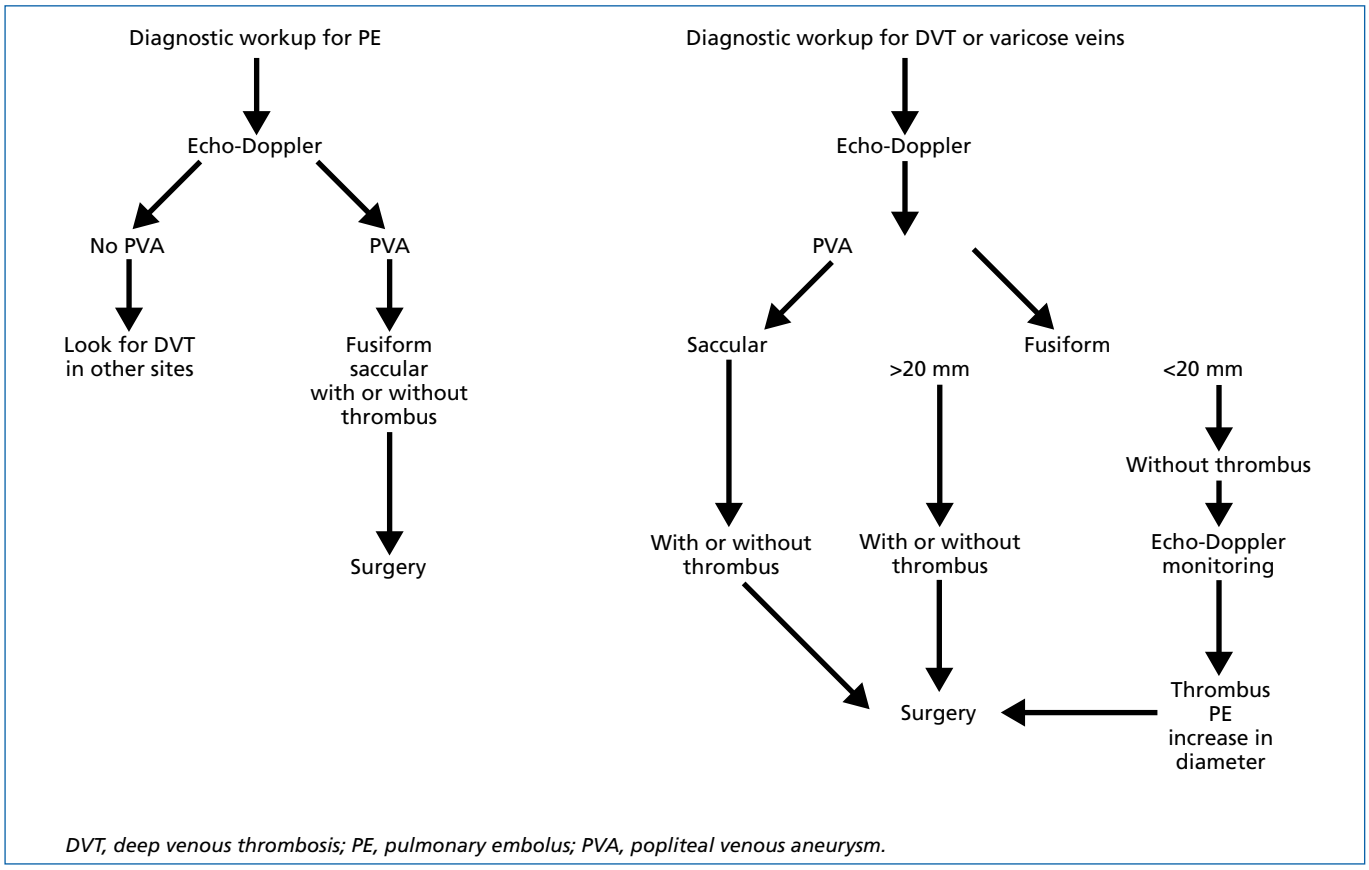


Figure 7. Computed tonography (CT) scan of a saccular popliteal venous aneurysm with thrombus (same patient as in Figure 5).

Figure 8 a and b. Magnetic resonance imaging (MRI) study of a popliteal venous aneurysm without thrombus.

More recently, other techniques including CT (*Figure 7*) and MR angiography (*Figures 8 a, b*) have found a place as diagnostic tools. Nevertheless, phlebography remains useful to anatomically define the lesion prior to surgery in patients with a history of DVT or with venous anatomical variations of the popliteal fossa.

As far as therapeutic indications are concerned (*Figure 9*), surgery is indicated when PVA is diagnosed in a context of PE, regardless of aneurysm size, shape, or presence or absence of thrombus, because of the serious risk of recurrent PE. In fact, when PE is present, an absence of thrombus in the aneurysm at the time of diagnosis does not



DVT, deep venous thrombosis; PE, pulmonary embolus; PVA, popliteal venous aneurysm.

Figure 9. Treatment algorithm according to circumstances under which a popliteal venous aneurysm is diagnosed.

rule out its role in the PE, since the entire thrombus may have embolized.

Anticoagulation alone is ineffective in patients with prior PE, and there is a high risk (80%) of recurrence.[5,6]

The management of asymptomatic aneurysms remains controversial. We believe that surgery (*Figures 10 and 11*)

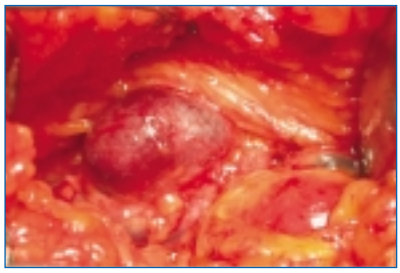


Figure 10. Perioperative view of a saccular aneurysm.

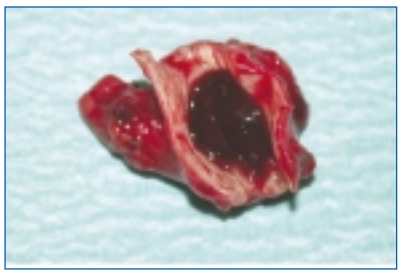


Figure 11. Resected aneurysm with endoluminal thrombus.

is indicated for patients with a saccular PVA, regardless of size, and for those with a fusiform aneurysm > 20 mm, without taking into account the presence or absence of thrombus, due to the unforeseeable risk of thromboembolic complications.

On the other hand, small fusiform aneurysms (< 20 mm) without thrombus pose a lower risk of thromboembolic complications and may simply be monitored by Doppler ultrasonography.[7] Surgery is recommended if thrombus is found in the aneurysm, if the aneurysm enlarges or if the patient presents with thromboembolic episodes.

Different surgical procedures may be used for repair of PVA. While simple ligature and excision of the aneurysm without re-establishing continuity of the vein have been described, we recommend that venous continuity should be preserved whenever possible.

The type of surgical repair depends on aneurysm location and shape and on the presence of thrombus in the wall. The most common procedure is tangential excision with lateral suture as described by Aldridge.[6] This procedure is particularly suited for repair of saccular aneurysms, which account for 75% to 80 % of all PVA.

Aneurysm resection with reestablishment of vein continuity is recommended when tangential excision of a fusiform aneurysm would be unsatisfactory.

There has been no perioperative mortality among the published surgical outcomes for PVA repair, even in patients who developed thrombus postoperatively. No aneurysm recurrence or PE has been identified after surgery. Long-term patency was approximately 75% for the different surgical procedures.[6]

Anticoagulation is prescribed for 3 to 6 months after surgery in most patients. It is known that such treatment does not protect nonoperated patients against the risk of PE.

SUMMARY

Venous aneurysms are rare lesions that have been described throughout the venous system and are seen at any age. The lower extremities are the most frequently involved, with the popliteal vein being the main location. A wide variety of clinical presentations has been reported in the literature and they can be diagnosed as a subcutaneous mass, a widening mediastinal mass, an incidental finding on an imaging study, or during the workup for abdominal pain or chronic venous disease of the lower limb.

Although the natural history of these venous aneurysms is usually benign, depending on their location they have the potential for serious complications and may present initially as an episode of pulmonary embolism, thrombosis, or rupture with bleeding.

The management of venous aneurysms still remains controversial, and the indication for surgery should take into consideration the potential for thromboembolic or bleeding complications. Numerous types of surgical repair have been described, and the most common procedures are tangential excision with lateral suture or excision with interposition grafting. Technical choice is usually dictated by the type of aneurysm and by the anatomical location.

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Congress and conference calendar

IXth INTERNATIONAL MEETING OF COLOPROCTOLOGY

This congress will be held in Turin (Italy) from March 27 to 29, 2006.

• *For further information, please contact:*

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Phlebolymphology. 2006;13:177-179.

VIIth MEETING OG THE EUROPEAN VENOUS FORUM

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XLVIIIth ANNUAL CONGRESS OF THE GERMAN SOCIETY OF PHLEBOLOGY

This congress will be held in the Town hall of Rostock (Germany) from October 4 to 7, 2006.

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LETTER TO THE EDITOR

Letters that raise new or controversial issues of interest to readers, or posing a question or challenge to an article published in Phlebolymphology will be considered for publication. The Editor may send the letter to the authors of the original paper so their comments may be published simultaneously.

Attention has to be called to the erroneous statement printed on issue n° 49, page 392 in the paper of C. Garde entitled: Consensus committee N°2. "Effects of venoactive agents on edema in chronic venous disease", that "a change to positive pressure in the interstitial medium is responsible for …edema" and that negative tissue pressure is a factor which "protects against edema". It is textbook knowledge that
f = CFC [(Pc- P i)- s (p p- p i)], where f = net ultrafiltrate ml/min.
CFC = capillary filtration coefficient
Pc= blood capillary pressure
Pi= interstitial fluid pressure
s = colloid osmotic reflexion coefficient
p p= plasma colloid osmotic pressure
p c= interstitial fluid colloid osmotic pressure
It is evident that CFC (Pc-Pi), the ultrafiltrating pressure increases, if Pi is negative, because in this case one has to write: CFC [(Pc-(-Pi)]
This means, that the ultrafiltrating pressure is CFC (Pc+Pi):

To the contrary of the statement of Garde, the more negative interstitial tissue pressure, the higher the ultrafiltrating pressure, because f increases and this can induce edema! Increasing tissue pressure by compression is the anti-edema treatment par excellence! High tissue pressure is a factor which protects against edema.

The definition of edema is also erroneous.
Excess of interstitial fluid means fluid retention This may only be called "edema" when it causes a demonstrable swelling.
(See: Dorland Medical Dictionary, 29th Edition, p 567: "Edema; the presence of abnormally large amounts of fluid in the intercellular tissue spaces of the body, referring to demonstrable amounts in the subcutaneous tissue.")
Over 2-3 litre fluid has to accumulate in the body before generalized edema appears.

Prof. Dr. med. Michael Földi

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- Letter from a referee supporting the project
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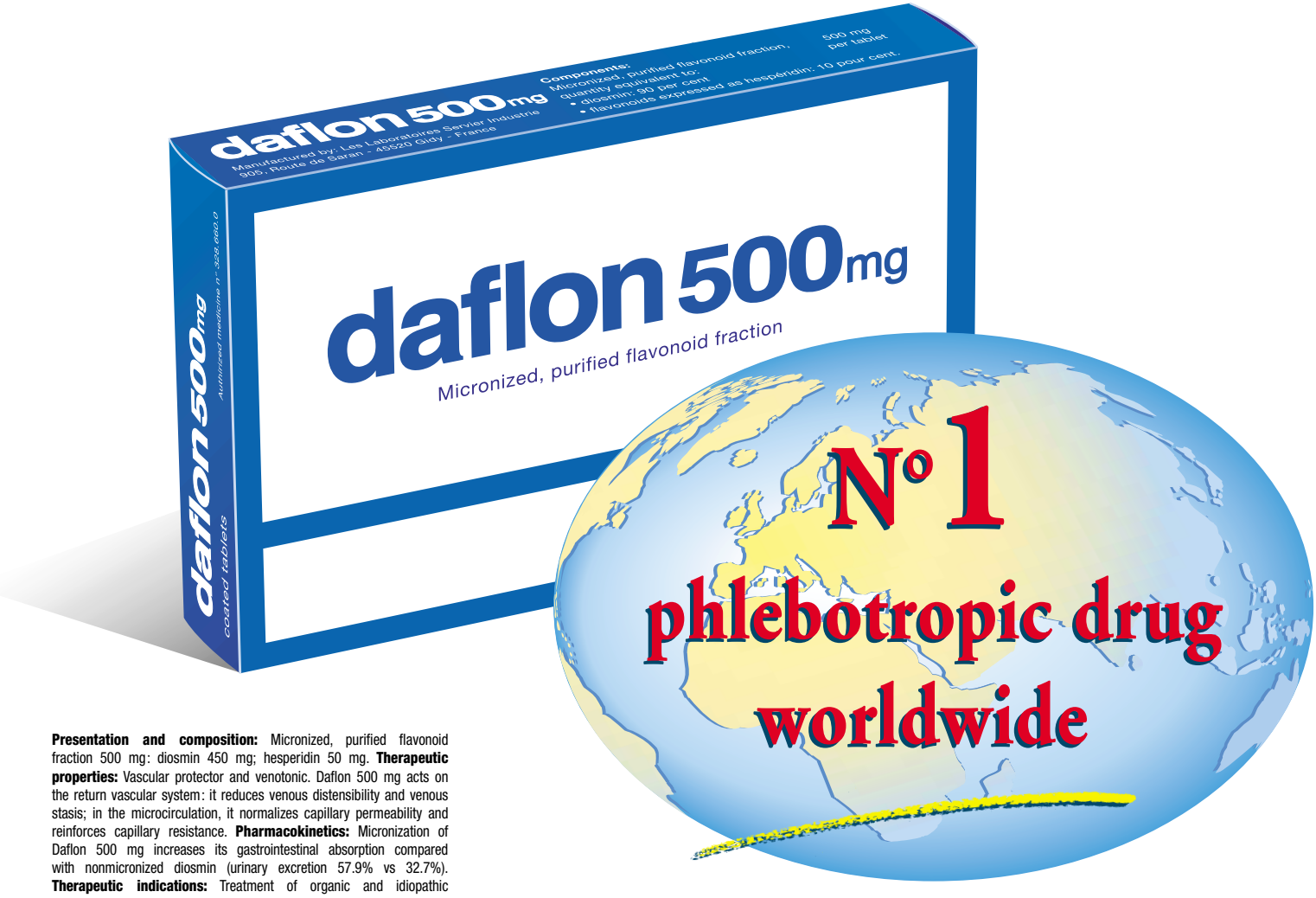

Presentation and composition: Micronized, purified flavonoid fraction 500 mg: diosmin 450 mg; hesperidin 50 mg. **Therapeutic properties:** Vascular protector and venotonic. Daflon 500 mg acts on the return vascular system: it reduces venous distensibility and venous stasis; in the microcirculation, it normalizes capillary permeability and reinforces capillary resistance. **Pharmacokinetics:** Micronization of Daflon 500 mg increases its gastrointestinal absorption compared with nonmicronized diosmin (urinary excretion 57.9% vs 32.7%). **Therapeutic indications:** Treatment of organic and idiopathic chronic venous insufficiency of the lower limbs with the following symptoms: heavy legs; pain; nocturnal cramps. Treatment of hemorrhoids and acute hemorrhoidal attacks. **Side effects:** Some cases of minor gastrointestinal and autonomic disorders have been reported, but these never required cessation of treatment. **Drug interactions:** None. **Precautions:** *Pregnancy:* experimental studies in animals have not demonstrated any teratogenic effects, and no harmful effects have been reported in man to date. *Lactation:* in the absence of data concerning the diffusion into breast milk, breast-feeding is not recommended during treatment. **Contraindications:** None. **Dosage and administration:** *In venous disease:* 2 tablets daily. *In acute hemorrhoidal attacks:* the dosage can be increased to up to 6 tablets daily. *As prescribing information may vary from country to country, please refer to the complete data sheet supplied in your country.*

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