CONTENTS

PHLEBOLYMPHOLOGY

EDITORIAL

Dear Readers,

An interesting mixture of practically important and basic science articles can be found in this issue of Phlebolymphology.

The management of venous thromboembolism during and after pregnancy is still widely based on experience because randomized controlled trials in this field are lacking for obvious reasons.

***Christine Biron-Andreani** of the Hematology Unit of the University Hospital in Montpellier gives us a survey of practically very useful, updated recommendations, concerning both prevention and treatment of venous thromboembolic disease, in accordance with the recent ACCP guidelines and supported by numerous references.*

The choice of a proper wound dressing in venous leg ulcers has become an art.

*The article by **Patricia Senet**, Hôpital Tenon, Paris, offers a remarkable overview of local wound dressings on the market, including biological therapy, debridement, skin grafting, and topical negative pressure (VAC). The value of compression as a basic management modality is clearly underlined. In addition to these measures, reflux abolition of incompetent superficial veins by chemical or physical means can be very effective and has been proven to reduce the rate of recurrence.*

*Our current understanding of the molecular regulation of lymphangiogenesis and its relevance to metastasis and survival of cancer patients is reviewed in a basic research article containing a very impressive list of references by **Jonathan P. Sleeman**, Medical University of Mannheim-Heidelberg. The therapeutic consequences of targeting tumor-associated lymphatic vessels are discussed.*

*During recent years the subject of "patient-related outcomes" has gained considerable attention in the medical literature. **Michael A. Vasquez** and **Carolyn E. Munschauer** of Buffalo, NY, have supplied us with a nicely illustrated extended abstract of their original article published in Phlebology 2008 on "Venous Clinical Severity Score and Quality-of-Life Assessment Tools: Application to Vein Practice". Besides generic instruments, like the SF-36 and the Nottingham Health Profile, disease-specific instruments (CIVIQ, VEINES, Aberdeen Venous Vein Questionnaire, and Charing Cross Venous Ulceration Questionnaire) are explained. A revision of the present Venous Clinical Severity Score (VCSS) is recommended.*

The issue ends with an informative book review written by Michel Perrin, Lyon, on vascular aneurysms. This book, dating back some years, was edited by Athanasios Giannoukas form Larissa, Greece, but is still very relevant to current practice.

Happy reading,

Hugo Partsch, MD

Venous thromboembolic disease and pregnancy: prevention and treatment

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ABSTRACT

The management of venous thromboembolism (VTE) during pregnancy is challenging for several reasons. In this article, we address the following questions: in pregnant women, how do we (i) treat VTE once a diagnosis is confirmed? (ii) assess the risk of VTE, and (iii) manage women with a high risk of VTE? When anticoagulants are required in pregnancy and the puerperium, low-molecular-weight heparin (LMWH) is now the preferred drug, but optimal dosage and monitoring remain unresolved issues. In addition, there is a paucity of reliable information about the risk of VTE in women with thrombophilia (asymptomatic or with a previous deep venous thrombosis or pulmonary embolism). Recommendations and limitations of the literature are highlighted.

INTRODUCTION

Pulmonary embolism (PE) is the leading cause of maternal mortality in Western countries.[1-4] The incidence of pregnancy-related venous thromboembolism (VTE) is not known precisely, and depending on the study varies from 0.13 to 2.3 episodes per 1000 deliveries.[5-7] Although these absolute rates are low, the risk of VTE is threefold to tenfold higher than in nonpregnant woman of similar age.[6] A meta-analysis showed that two-thirds of cases of deep vein thrombosis (DVT) occur antepartum, distributed equally throughout all three trimesters.[8] In contrast, 43% to 60% of pregnancy-related PEs occur 4 to 6 weeks postpartum.[9]

I - WHICH ANTICOAGULANT CAN BE USED DURING PREGNANCY?

Is there any place for vitamin K antagonists?

Warfarin readily crosses the placenta and has been associated with congenital malformation (exposure from 6 to 12 weeks) and fetal and neonatal

Keywords:
pregnancy, venous thromboembolism, treatment, prophylaxis, low-molecular-weight heparin

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bleeding.[10] It should therefore be avoided in the management of VTE during pregnancy, preference being given to unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH), which do not cross the placenta and have no teratogenic effects. Warfarin can, however, be considered during pregnancy in women with high-risk valves.

Management of women receiving long-term vitamin K antagonists

In such women who want to become pregnant, repeat pregnancy tests should be proposed and warfarin should be replaced by full-dose LMWH when pregnancy is confirmed.[11]

Low-molecular-weight heparin or unfractionated heparin?

LMWH is now the most commonly used anticoagulant for prophylaxis and treatment of VTE in pregnancy and the puerperium.[12] LMWH is preferred to UFH for several reasons. At least outside pregnancy, LMWHs are as effective as UFH for prevention or treatment of DVT and PE.[13-15] It has a better safety profile both for the fetus and the mother[16] and there is no evidence of teratogenicity or risk of fetal bleeding or that LMWH crosses the placenta.[17] One of the advantages of LMWH is the potentially reduced risk of bleeding. This is of particular relevance in obstetric practice where postpartum bleeding remains the most frequent cause of severe obstetric morbidity. LMWHs are not associated with an increased risk of severe peripartum bleeding. In one systematic review, the frequencies of antenatal bleeding, postnatal bleeding, and wound hematoma were 0.43%, 0.94%, and 0.61%, respectively leading to an overall frequency of 1.98% (95% confidence interval [CI], 1.5-2.57).[18] The observed rate of major bleeding compares favorably with the rate of massive bleeding (0.7%) from one prospective study without the use of LMWH.[19] In their review of 277 pregnancies in which LMWH was used, Greer and Nelson-Piercy noted no case of heparin-induced thrombocytopenia.[18] The reliable pharmacokinetics of LMWHs and their long half-life, which means injections can be less frequent, make them attractive for practical use during several months of pregnancy. Significantly lower bone density in patients receiving UFH than in those receiving LMWHs, and no statistically significant difference between patients receiving LMWHs and untreated patients, suggest that bone loss associated with LMWHs is not different from physiologic bone loss during pregnancy.[17,18]

Is it possible to use danaparoid in pregnant women?

A review of 51 pregnancies in 49 danaparoid-treated patients between 1981 and 2004,[20] showed that all patients developed heparin intolerance (32 due to heparin-induced thrombocytopenia, 19 mainly due to heparin-induced rash) and had current or past VTE complications or both. The median duration of danaparoid use was 10 weeks. Danaparoid was used until delivery of a healthy infant in 37 pregnancies. In the remaining 14 pregnancies it was stopped earlier (anticoagulant treatment no longer required n=3; adverse event leading to treatment discontinuation n=11). Four maternal bleeding events were recorded during pregnancy, delivery or postpartum, two of which were fatal due to placental problems. Three fetal deaths associated with maternal complications antedating danaparoid use were recorded. Anti-Xa activity transfer was not observed in any of five fetal cord blood and three maternal breast milk samples. The authors concluded that danaparoid can be used as an alternative antithrombotic agent in pregnant women with high thrombotic risk and intolerance to heparins.

Is it possible to use pentasaccharide in pregnant women?

Although there have been some reports of the successful use of pentasaccharide in pregnant women, the quality of available evidence is very low. Therefore, the American College of Chest Physicians states that clinicians should avoid the use of fondaparinux and should only discuss its use for those with heparin-induced thrombocytopenia or a history of heparin-induced thrombocytopenia who cannot receive danaparoid.[11]

New anticoagulants

There are insufficient data to evaluate the safety of direct thrombins or anti-Xa inhibitors in pregnant women.

Which anticoagulant can be used in nursing women?

For most anticoagulants, data are limited. There were two early convincing reports about the absence of detection in breast milk and anticoagulant effect of warfarin in breastfed infants.[21,22] Because of its high molecular weight and strong negative charge, UFH does not pass into breast milk. In a study of 15 patients, small amounts of LMWH were found in breast milk.[23] However, due to the low bioavailability of orally ingested LMWH, a clinically relevant effect on the nursing infant is unlikely.[11]

II - HOW WE CAN TREAT VTE DURING PREGNANCY?

The absence of randomized trials in pregnancy complicates the VTE treatment recommendations in pregnancy. It is therefore important to emphasize the need for coordination of physicians, including the hematologist, to establish clear local guidelines for VTE treatment during pregnancy (*Table I*).

1. LMWH is the preferred drug
2. Warfarin should be avoided
3. Twice or once daily regimens should be used
4. A weight-based regimen should be used
5. Monitoring of anti-Xa is not routinely required
6. After a full-dose treatment for at least 1 month, in the absence of additional thrombotic risk factors, an intermediate regimen can be considered
7. At least 3 months of anticoagulant are required. 6 months or longer should be proposed for idiopathic DVT/EP. Anticoagulant should be maintained throughout the pregnancy and 6 weeks postpartum

Table I : Treatment of acute VTE (DVT and/or PE) during pregnancy

Initial anticoagulant treatment

According to the last American College of Chest Physicians (ACCP) recommendations, LMWH is the preferred drug for the treatment of VTE during pregnancy (grade 1A), with a weight-adjusted dosing regimen (as per the manufacturer's recommendations) (*Table II*).

Weight-adjusted dose of LMWH	• Enoxaparin 1 mg/kg every 12 h or 1.5 mg/kg once daily • Dalteparin 100 U/kg every 12 h or 200 U/kg once daily • Tinzaparin 175 U/kg once daily

Table II : LMWH full-dosing regimens

Once or twice daily dosing regimen?

During pregnancy, physiologic changes affect the pharmacokinetics of LMWH:[24] 60% expansion of intravascular plasma volume, 50% increase in glomerular filtration rate. Are these changes significant enough to modify the dosing regimen during pregnancy? A 2004 study in a relatively small number of women has suggested that once daily administration of tinzaparin may be appropriate in the treatment of VTE in pregnancy, despite some criticisms concerning the anti-Xa level.[25] However, the United Kingdom Royal College of Obstetricians and Gynaecologists (RCOG) in 2001 and 2007 and the ACCP in 2004 have suggested a twice daily regimen. In 2008 the ACCP stated that a once daily regimen is acceptable for the treatment of VTE,[11] on the basis of data published by Voke et al[26] who surveyed antenatal VTE practice in the UK and Ireland, and Knight et al,[27] who reported a population-based national case-control study evaluating the incidence and management of obstetric PE in the UK.

Is anti-Xa monitoring necessary during treatment of VTE in pregnancy?

The dose adjustments over the course of pregnancy remain controversial: some authors suggest that dose should be increased in proportion to change in weight; others suggest adjustment using the assay of anti-Xa levels 4 to 6 after the injection (0.5 to 1.2 anti-Xa/ml for a twice daily regimen or 1 to 2 anti-Xa/ml for a once daily regimen).[28] The ACCP considers that definitive advice cannot be provided.[11] The experience of the RCOG indicates that using a weight-based regimen is satisfactory and that anti-Xa monitoring is not routinely required in women with therapeutic doses of LMWH, particularly as there are concerns over the accuracy of anti-Xa monitoring.[29] A study from the UK National External Quality Assessment Scheme (NEQAS) has demonstrated extremely wide coefficients of variation.[30]

In France, routine platelet count monitoring (every 2-3 days up to day 21 and then every 2 weeks) is required in all patients receiving UFH or LMWH, including pregnant women. In the UK, RCOG guidelines advise against routine platelet count monitoring in pregnant women who have received only LMWH as there have been no cases of heparin-induced thrombocytopenia in pregnancies managed with LMWH.

Massive life-threatening VTE

Intravenous UFH is the preferred treatment in massive VTE with cardiovascular compromise.[29] There is also a case for considering thrombolytic

therapy, as anticoagulant treatment will not reduce obstruction of the pulmonary circulation. Data on thrombolytic therapy in pregnancy are limited, with concerns about maternal bleeding and adverse fetal effects.

Vena cava filter

Removable vena cava filters are a reasonable approach to women who have a transient contraindication to anticoagulants, such as the development of a VTE near the time (within 1 to 2 weeks) of delivery.[31]

After the initial period, is it possible to reduce the dose?

There is no clear consensus. Many experts continue with the full treatment dose while others switch to an intermediate regimen. The rationale of the former option is based on the safety of LMWHs during pregnancy and the continuing risk of VTE during pregnancy.[5,16] In contrast, the other option is based on successful intermediate regimens used in patients with contraindications to warfarin or with underlying malignancy.[32,33] In these two studies, patients received dalteparin once daily, which corresponds to 50% (10 000 U/24 h) of full-dose treatment in the first study and 75% (150 U/kg/24 h) in the second. Rodger et al (Canada) treat acute VTE in pregnancy with full-dose LMWH for 3 weeks and then halve the dose throughout the rest of the pregnancy and at least throughout the post-partum period.[34] They argue that the efficacy and safety of the prophylactic dose of LMWH (which is not exactly half the full dose) are comparable to those of warfarin (INR 2-3) for acute DVT.[35] Greer et al (UK) suggest a full dose for a minimum of one month before reducing to an intermediate dose of LMWH in the absence of additional risk factors such as underlying thrombophilia, immobility, and obesity.[12] The ACCP recommends intermediate-dose LMWH: dalteparin 5000 U/12 h or enoxaparin 1 mg/kg/24 h. Intermediate regimens therefore range from 50% to 75% of the full treatment dose.

Finally, these modified regimens could be of interest in women at increased risk of bleeding and perhaps of osteoporosis.

What is the maintenance treatment of VTE in pregnancy?

It is currently admitted that treatment should be employed during the remainder of the pregnancy and for at least 6 weeks postnatally. The rationale for this position is based on the continuing risk of recurrent VTE during pregnancy and the postpartum period since pregnancy is itself a risk factor for VTE. Published recommendations usually advise at least 3 months; a minimum of 3 months of anticoagulation can be proposed for secondary VTE and longer anticoagulation, 6 months, should be considered for idiopathic VTE. The last ACCP guidelines, published in 2008, emphasize that there are no appropriately designed trials to define the duration of anticoagulation for women with VTE during pregnancy and suggest that at least 6 months is a "reasonable duration".[11]

Additional therapy

To our knowledge, there is no study in pregnant women, but in a randomized, controlled trial in nonpregnant patients the incidence of postthrombotic syndrome after a first proximal DVT was reduced from 23% to 11%.[36] Therefore, mobilization with graduated elastic stockings (at least class II) should be encouraged to reduce pain and swelling and also to reduce the risk of postthrombotic syndrome for 2 years after the occurrence of VTE.

Management of anticoagulant therapy at the time of delivery

Women requiring therapeutic doses of LMWH should be counseled before delivery, which should be planned with a team of specialists (obstetrician, hematologist, anesthesiologist, cardiologist).

Spontaneous or planned delivery? Cesarean section?

Delivery by cesarean section should only be decided on the basis of obstetric indications. It should be emphasized that induction of labor in a patient with an unfavorable cervix may increase the risk of cesarean delivery, which should be avoided because of the risk of VTE.[37] Therefore, spontaneous vaginal delivery is preferable.

Time off anticoagulation

To avoid unwanted anticoagulant effects during delivery in women receiving therapeutic doses of LMWH, LMWH should be discontinued before elective induction of labor or cesarean section. A woman taking LMWH should be advised that once she thinks that she is in labor, she should not inject any further LMWH. According to the recommendations of the various societies, it is recommended to stop for 24 hours. The latest ACCP recommendations advise stopping 24 to 36 hours

before elective induction of labor or cesarean section.[11] The approach taken if spontaneous labor occurs in women receiving therapeutic doses of LMWH depends on the proximity of the last dose to the expected time of delivery and, if available, the anti-Xa level.[38]

Is it possible to stop anticoagulation for 24 hours in all women? This depends on the characteristics of the VTE. If the patient is considered to be at *high risk* (ie, VTE within 4 weeks), it is important to minimize the time off anticoagulation. Several approaches can be discussed. It has been proposed to replace LMWH by intravenous UFH, due to a shorter half-life, and to discontinue treatment 4 to 6 hours prior to the expected time of delivery.[39] If spontaneous labor occurs, careful monitoring with aPTT is required and protamine sulfate may be needed to reduce the risk of bleeding.[40] Full anticoagulation with LMWH has been maintained during labor and delivery in women with recent (within 4 weeks) VTE.[41] Dulitzki et al reported no increased risk of major bleeding during cesarean delivery in 41 patients treated with LMWH.[42] Epidural analgesia should be avoided.

If the patient is *not considered to be at high risk* (VTE during the last 3 months and fully anticoagulated), some experts propose switching to prophylactic doses of LMWH at 36 weeks of gestation.[43] In this case, it is usually recommended that LMWH should be stopped as soon as a woman is (or thinks she is) in labor. No increased bleeding is expected with this approach.[39]

Regional anesthesia

There are several recommendations that have been devised to help anesthesiologists reduce the risk of spinal hematoma.[44] However, although the consensus statements are based on evaluation of the available information, data are scarce, especially considering the obstetric population.[37] Two studies showed no complications when using the following recommendations.[42,45] Generally the consensus statements suggest that epidural analgesia should be avoided for at least 24 hours after the last dose of *therapeutic* LMWH or UFH.[37,46] According to the RCOG, LMWH should not be given for at least 4 hours after the epidural catheter has been removed, and the cannula should not be removed within 12 hours of the most recent injection.[29] Epidural analgesia should be avoided for at least 12 hours after the last dose of *prophylactic* LMWH.[37]

Immediate postnatal anticoagulation

There is a paucity of data that can be used to guide postnatal anticoagulation. Bates and Ginsberg consider that LMWH should be restarted as soon as it is safe to do so, usually within 12 hours of delivery, and warfarin can be started at the same time.[38] The ACCP does not address this issue.[11] The RCOG considers that "if the woman chooses warfarin postpartum, this should be avoided until at least the third postnatal day". A thromboprophylactic dose of LMWH should be given by 3 hours postoperatively (more than 4 hours after removal of the epidural catheter, if appropriate).[29] The Obstetric Medicine Group of Australasia suggests that prophylactic doses can be recommenced within 2-6 hours of both vaginal and cesarean deliveries, and therapeutic doses at least 24 hours after surgical delivery.[37]

III - HOW WE CAN ASSESS THE RISK OF VTE DURING PREGNANCY?

Despite decreased mortality over the last 70 years, PE continues to be one of the most common causes of maternal death in developing countries. The age-adjusted incidence of VTE ranges from 5 to 50 times higher in pregnant versus nonpregnant women. The clinician dealing with the risk of VTE and prophylaxis in pregnancy and postpartum faces several questions: Are women who are at greatest risk identifiable? Is pregnancy-related VTE preventable? When is the best time to start prophylaxis? Unfortunately, there has been no large clinical study of the benefit of thromboprophylaxis during pregnancy.[47,48] However, in 2002, Rodger et al found that most Canadian clinicians favor intervening with thromboprophylaxis rather than observing without prophylaxis in pregnant women, asymptomatic or with previous VTE, with thrombophilia.[49] Hence, in the absence of evidence, the default recommendation becomes intervention. But do all women need thromboprophylaxis?

Which prophylaxis for which patients?

It is essential when assessing thrombotic risk associated with pregnancy to take into account acquired factors, as well as genetic predisposition (*Table III*).

Pregnant women with previous VTE

The limitations of historical data hamper reliable estimation of the risk of recurrence during pregnancy

Pre-existing	Transient
Previous VTE	Surgical procedure in pregnancy or postpartum
Thrombophilia	Hyperemesis
Age over 35 years	Dehydration
Obesity, BMI > 30 kg/m^2	Ovarian hyperstimulation syndrome
Parity > 4	Severe infection, eg, pyelonephritis
Gross varicose veins	Immobility (> 4 days of bed rest)
Paraplegia	Pre-eclampsia
Sickle cell disease	Excessive blood loss
Inflammatory disorders, eg, inflammatory bowel disease	Long-haul travel
Some medical disorders, eg, nephrotic syndrome, some cardiac diseases	Prolonged labor
Myeloproliferative disorders, eg, essential thrombocytopenia, polycythemia vera	Immobility after delivery

Table III : Risk factors for VTE in pregnancy and postpartum period

and puerperium in women with previous VTE. In 2000, Brill-Edwards et al conducted a multicenter prospective study of 125 pregnant women with a previous single VTE.[50] Women had antenatal prophylaxis withheld but were given prophylaxis in the postpartum period. Overall, 3 of the women with either abnormal thrombophilia screening or idiopathic previous VTE had an antepartum recurrence (5.9%; 95% CI, 1.2-16.2%). In contrast, there were no recurrences among the 44 women without thrombophilia or a previous VTE with a transient risk factor (relative risk 0, 95% CI, 0-8%). More recently, in 2007, a prospective observational study in the UK and a large Italian cohort study demonstrated a significantly increased risk of recurrence if the previous VTE was unprovoked, related to pregnancy or oral contraceptives, while thrombophilia screening was of limited benefit except in identifying antithrombin (AT) deficiency.[26,51] It is clear that women with thrombophilia have an increased risk of VTE in pregnancy, but this risk varies depending upon the specific thrombophilia (*Table IV*). Current evidence and existing guidelines recommend that women with previous VTE and thrombophilia should receive antenatal thromboprophylaxis with LMWH continued for 6 weeks postpartum.

Risk factor	Prevalence	Odds ratio
Factor V Leiden mutation heterozygote	2-7	9
Factor V Leiden mutation homozygote	0.2-0.5	34
Prothrombin G20210A polymorphism heterozygote	2	7
Prothrombin G20210A polymorphism homozygote	rare	26
Antithrombin deficiency	<0.1-0.6	5
Protein C deficiency	0.2-0.3	5
Protein S deficiency	<0.1-0.1	3

Table IV : Estimated prevalence of congenital thrombophilia and the associated risk of thromboembolism during pregnancy in a European population[58]

Whether thromboprophylaxis is warranted in these women identifiable as at high risk remains to be determined. Several nonrandomized studies have reported low VTE rates with the use of prophylactic doses.[45] Only 2 randomized studies evaluating the efficacy and safety of prophylaxis, with major limitations, have been reported.[52,53] Gates et al performed the only randomized, controlled trial comparing antenatal LMWH with placebo.[52] Unfortunately, its sample size was too small to draw any definitive conclusion. Poor recruitment in this study indicates that large-scale trials using such a design would be difficult to run. In a prospective, nonrandomized study, Bauersachs et al recently showed that risk-stratified heparin prophylaxis is associated with a low incidence of VTE during pregnancy.[54] An alternative way to assess the value of prophylaxis is to examine the balance of risks and benefits using a Markov model to compare prophylactic LMWH with expectant management.[55] In this study, for high-risk women, antepartum prophylaxis is a cost-effective strategy, while for low-risk women expectant management leads to better outcomes than use of LMWH. However, the definition of low- and high-risk women in this study is questionable.

The 8th ACCP recommendations concerning the prevention of VTE in pregnant women with previous VTE are detailed in *Table V*. I feel they are of limited interest for the clinician since several approaches (from clinical surveillance to intermediate-dose) are proposed for each group of patients, as mentioned in the table.

Pregnant women without previous VTE

It is increasingly common for pregnant women to present with known thrombophilia, usually detected because of screening following identification of inherited thrombophilia in a family member. As previously mentioned, the risk of VTE varies greatly depending upon the specific thrombophilia, but the

For pregnant women with a single episode of VTE associated with a transient risk factor that was no longer present and no thrombophilia, we recommend clinical surveillance antepartum and anticoagulant prophylaxis postpartum	Grade 1C
If the transient risk factor associated with a previous VTE is pregnancy- or estrogen-related, we suggest antepartum clinical surveillance or prophylaxis plus postpartum prophylaxis, rather than routine care	Grade 2C
For pregnant women with a single idiopathic episode of VTE but without thrombophilia and who are not receiving long-term anticoagulants, we recommend one of the following, rather than routine care: prophylactic LMWH/UFH or intermediate LMWH/UFH or clinical surveillance throughout pregnancy plus postpartum anticoagulants	Grade 1C
For pregnant women with thrombophilia who have a single prior episode of VTE and who are not receiving long-term anticoagulants, we recommend one of the following, rather than routine care: prophylactic LMWH/UFH or intermediate LMWH/UFH or clinical surveillance throughout pregnancy plus postpartum anticoagulants	Grade 1C
For women with "higher risk" thrombophilias (antithrombin deficiency, persistent positivity for the presence of antiphospholipid antibodies, compound heterozygosity for G20210A variant, and factor V Leiden or homozygosity for these conditions) who have a single prior episode of VTE and who are not receiving long-term anticoagulants, we suggest, in addition to postpartum prophylaxis, antepartum prophylactic or intermediate-dose LMWH/UFH, rather than clinical surveillance	Grade 2C
For women with multiple episodes of VTE not receiving long-term anticoagulants, we suggest antepartum prophylactic, intermediate-, or adjusted-dose LMWH/UFH, followed by postpartum anticoagulants, rather than clinical surveillance.	Grade 2C
For women receiving long-term anticoagulants, we recommend LMWH or UFH throughout pregnancy (either adjusted-dose, 75%, or intermediate-dose LMWH) followed by resumption of long-term anticoagulants postpartum	Grade 1C
For all pregnant women with previous deep vein thrombosis, we suggest the use of graduated elastic compression stockings both antepartum and postpartum	Grade 2C

Table V : The 8th ACCP Recommendations: Prevention of VTE in pregnant women with prior VTE[11]

absolute risk remains low. As an example, the results from cohorts, which are likely to be more reliable, show a pooled odds ratio of 4.46 (95% CI, 1.82-10.94; 7879 pooled women), with no evidence of statistical heterogeneity (p = 0.36), for the risk of a first VTE during pregnancy or the postpartum period associated with the factor V Leiden heterozygous mutation. Case-control studies revealed a higher risk (odds ratio 8.6, 95% CI, 5.85-12.63; 1,433 [corrected] pooled women) with significant heterogeneity ($P< 0.005$). Since the risk of VTE is lower in women with no history of VTE, antenatal thromboprophylaxis does not always seem necessary, even if the women are receiving postpartum thromboprophylaxis for 4 to 6 weeks. In existing guidelines (ACCP, RCOG), women with AT deficiency, those with combined defects, and those homozygous for defects should receive antepartum and postpartum thromboprophylaxis. However, this approach needs further clinical investigation. As an example, in a cohort of 96 women homozygous for the factor V Leiden mutation, the risk of a first symptomatic pregnancy-related VTE was found to be 12.1% per pregnancy (95% CI: 6.3-22.1), 9.1% (95% CI: 4.2-18.4) in the postpartum period and 3.0% (95% CI: 0.8-10.4) during pregnancy.[56] Thrombosis occurred principally in the postnatal period, as already published, whether or not thrombophilia was present. This result reinforces the widely accepted fact that anticoagulants have to be given during the postpartum period for 4 to 6 weeks. On the other hand, there is room for debate regarding antepartum anticoagulant prophylaxis, even if the incidence of pregnancy-related VTE in factor V Leiden homozygotes seems higher than the best estimated incidence observed in an overall population of pregnant women (3% in the present study vs 0.06%; relative risk 10.7;95% CI 9.7-11.7).[7] Studies measuring the effectiveness of prophylactic interventions are lacking.[48] It remains to be established whether intervention with LMWH is of benefit in women at "high" risk.

The relatively equal distribution of VTE throughout all 3 trimesters suggests that when antepartum prophylaxis is used, it should be started early in the first trimester.[8,57]

CONCLUSION

The use of anticoagulant therapy during pregnancy is challenging. LMWHs are now the most commonly used anticoagulant for prophylaxis and treatment of VTE. However, the optimal strategy remains unclear due to the limitations of the available data.

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Local treatment of venous leg ulcers

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ABSTRACT

The current standard of care for chronic venous ulcers involves the use of compression bandages. Dressings are applied beneath the compression and are used to control the exudates and to maintain the wound in a moist environment. Modern dressings are occlusive or semi-occlusive, classified according to their physical composition. Published systematic reviews of the value of different types of dressings in the management of chronic wounds provide only weak levels of evidence of their clinical efficacy, in terms of healing rate. Nevertheless, the indications for modern dressings were recently determined according to a systematic review of the literature and to a formal consensus process. Despite the lack of appropriate studies, modern dressings remain a part of the standard of care and are widely used according to the experience of the clinicians, in larger indications than what may be recommended by evidence-based medicine.

Skin grafting should be considered for large or refractory ulcers, when the venous hypertension is well controlled and when the ulcer bed is clean with healthy granulation tissue.

Topical negative pressure seems to prepare chronic wounds more rapidly for secondary closure surgery, but its clinical value in venous leg ulcers is still debated. More recently, local alternative treatments such as biological dressings and tissue-engineered products have been developed. These products may have the property of interacting directly with the wound, in order to speed the healing process and decrease the time to complete healing. But there is not yet any clear evidence for the efficacy of most of them.

INTRODUCTION

Venous ulcers are characterized by a cyclical pattern of healing and recurrence. The current standard of care for chronic venous ulcers involves the use of compression bandages as a means to reduce ambulatory venous pressure, control edema, and improve venous return. Dressings are applied beneath the compression and are used to control the exudates and to maintain the wound in a moist environment. Since the 1960s it has been accepted that wound healing is optimal when the wound is kept in a moist environment rather than air dried.[1] Modern dressings are occlusive or semi-occlusive, classified according to their physical composition. They have been developed to reduce pain and healing time, absorb blood and exudates and to be painless on application and removal. Current clinical practice guidelines

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on the treatment of leg ulcers have not established a consensual local care strategy, as published systematic reviews of the value of different types of dressings in the management of chronic wounds provide only weak levels of evidence of their clinical efficacy.[2-4] Thus, the choice of the dressing is mainly based on clinical experience and on their absorbent capacity, hydrating ability, adhesive components, and debridement capacity. In fact, except for hydrocolloids, no significant difference has been demonstrated versus the reference treatment, which consists in ensuring a moist environment for the wound through the use of gauze soaked in physiological saline.[2-6] Modern dressings optimize the natural healing process, without accelerating it. They mainly improve the comfort and quality of life of patients and reduce the cost of care by allowing reduced frequency of dressing changes.

More recently, local alternative treatments such as topical growth factors, biological dressings, and tissue-engineered products have been developed. These products may have the property of interacting directly with the wound, in order to speed the healing process and decrease the time to complete healing. Most of these treatments are expensive, which may limit their widespread use, and there is not yet any clear evidence for the efficacy of most of them.

PRINCIPLES OF WOUND CARE

Moisture and occlusion

In the 1960s, Winter demonstrated that acute wounds covered with moisture-retentive occlusive dressings healed twice as rapidly as similar wounds left exposed to air. In contrast, excessively dry wound healing environments caused further tissue death. Thus, modern wound dressings have evolved from the older concept of leaving the wound dry and covered by a protective dressing to the new concept of protection of the wound environment.[7] Semi-occlusive or occlusive wound dressings prevent evaporative water loss from the wound and retain warmth, which improves wound healing. These dressings may also induce relative hypoxia at the wound surface, promoting keratinocyte motility and angiogenesis.[8]

Because leg ulcers are invariably colonized by bacteria, infectious complications seem likely to be more prevalent with the use of occlusive dressings. In fact, infection rates are lower with occlusive dressings than with nonocclusive dressings, probably because they have the ability to maintain a more effective barrier against external contamination.[9,10] Nevertheless, when the wound is clinically infected, with increased erythema, warmth, pain and exudates, absorbent dressings such as alginates are used rather than occlusive dressings such as hydrocolloids.

Antiseptics and antibiotics

It has been suggested recently that bacterial density is associated with the probability of nonhealing in leg ulcers when infection is detected using swabs or tissue biopsies, and that chronic wound healing may also be influenced by the diversity of microorganisms present and their interactions with one another.[11] On the other hand, antiseptics and antibiotics fail to promote the healing process and to reduce the bacterial density of the wound.[12,13] A recent Cochrane review confirms this, as there is actually no evidence to support the routine use of systemic antibiotics to promote healing in venous leg ulcers and the available evidence of topical antibiotic and antiseptic efficacy is not strong.[14] In fact, the cytotoxic effects of antiseptics on pivotal cell types of the healing process have been well documented. Moreover, topical antibiotics and antiseptics are responsible for a great proportion of contact dermatitis in patients with leg ulcers,[15-17] and the use of topical antibiotics may induce the emergence of organisms resistant to the entire class of the antibiotic used topically. In conclusion, antiseptic solutions for cleansing the wound are now avoided in routine care of chronic wounds and leg ulcers.[7,18] Leg ulcers are cleaned using gentle soap and water. Therefore, guidelines recommend that systemic antibiotics should be reserved only for clinically infected ulcers and not for bacterial colonization.[7]

Debridement

Removal of necrotic tissue and slough is thought to allow formation of good granulation tissue and to promote epithelialization. Therefore, any necrotic material should be cleared from the wound bed to allow wound healing to proceed correctly. Wound bed preparation is now recognized as crucial to facilitating ordered restoration and regeneration of damaged tissue. However, there is a clear lack of good clinical evidence to support available wound debridement options, particularly for chronic ulcers of the lower extremities.

Mechanical debridement may be accomplished with a curette, scissors or a scalpel, or with hydrosurgery such as Versajet™, a new technology that simultaneously cuts and aspirates soft tissue. Mechanical debridement is a rapid and selective method, as nonviable tissue is removed until well vascularized tissue appears. However, the procedure may be painful, although Emla® cream has been shown to provide effective pain relief when applied 30 minutes before the procedure.[19] Autolytic debridement is the progressive separation of slough and necrotic tissue from the wound bed, obtained by dressings that keep the wound in a moist environment. It may take several weeks but is painless and often used in association with mechanical debridement. Chemical debridement is obtained by using enzyme-debriding agents. Several topical enzymatic preparations are available in different countries, including collagenase, papain, and trypsin. A double-blind, randomized study showed that Elase™, the only enzymatic agent available in France, was ineffective in debriding venous ulcers.[20]

Maggot debridement is generally a safe therapy that removes sloughy necrotic tissue from ulcers and may eliminate methicillin-resistant *Staphylococcus aureus* from infected or colonized wounds.[21,22] Bagged larval therapy seems to be well tolerated by patients, but is currently available in only a few hospitals in France.

DRESSINGS

Indications for the dressings

Although topical treatment is an important aspect of wound care, it should always be considered secondary to the choice of a compression strategy. Generally, the choice of dressing is guided by the ulcer characteristics (for example, wound drainage absorption), patient requirements (ease of application, comfort), and expense. According to recent systematic reviews, there is little evidence to indicate which dressings are the most effective in chronic wound care,[2,4,5,23] because of the poor methodological quality of most studies of wound dressings. The *Haute Autorité de Santé* in France has determined the indications for modern dressings, according to a systematic review of the literature and to a formal consensus process[2,24] (see *Table I*). Despite a lack of appropriate studies, modern dressings remain part of standard care and are widely used according to the experience of the clinicians, in more indications (*Table II*) than recommended by the *Haute Autorité de Santé*.

Different types of dressings (*Table II*)

HYDROCOLLOIDS

The inner layer of all hydrocolloids is composed of carboxymethyl cellulose, enclosed in an elastic adhesive mass. Hydrocolloids are available in thick and thin versions, as paste to fill cavity wounds, and in a variety of pre-cut shapes aimed at different anatomical sites (heels, sacrum, elbows). The rate of dressing changes is between a few days and a week, depending on the amount of exudate. As it interacts with the exudate, the dressing forms a yellow gel with a characteristic foul smell that can be mistaken for purulent discharge from the wound. An erythematous eruption around the wound is usually a nonallergic irritant reaction, related to excessively frequent dressing changes. They can be used at all stages of healing. The film covering the sheet protects the wound from the outside and allows patients to take a shower.[6]

HYDROGELS

Hydrogels are insoluble cross-linked hydrophilic polymers, containing more than 80% water. They are available in an amorphous gel, packaged in tubes, or in

Healing stage	Dressing
All stages	Hydrocolloids
Debridement	Alginates Hydrogels Silver-coated dressings: Cellosorb Ag, Urgotul Ag (sequential treatments)
Granulation	Impregnated or coated meshes Foam dressings
Epithelialization	Impregnated or coated meshes Foam dressings
Specific cases	
Fragile skin	Impregnated or coated meshes
Prevention of the infection	-
Infected wound	-
Hemorrhagic wound	Alginates
Foul-smelling wound	Charcoal dressings

Table I: Indications of the dressings for chronic wounds, according to the Haute Autorité de Santé *in France*[2,24]

Type of dressing	Trademark	Features	Indications
Hydrocolloids	Comfeel Plus, Duoderm E, Algoplaque HP, Askina Biofilm Suprasorb H, Hydrocoll standard	Thick adhesive 1 application / 2 -7 d without secondary dressing	Mildly exuding ulcer
	Comfeel Plus Transparent, Comfeel Plus Brûlures, Comfeel Ovale, Duoderm Extramince, Duoderm Extramince Ovale, Algoplaque Film, Hydrocoll thin	Thin adhesive 1 application / 2 -7 d without secondary dressing	
Foam dressings Granulation and epidermization stages, exudative ulcers	Allevyn Adhésive, Biatain adhésif, Cellosorb adhésif, Combiderm, Mépilex Border, Permafoam Comfort, Suprasorb P Adhésif Tielle	Thick adhesive 1 application / 2 -7 d without secondary dressing	Heavily exuding ulcer, granulating ulcer, altered peripheral wound skin (nonadhesive form)
	Allevyn Lite Cellosorb Lite Mépilex Border em	Thin adhesive 1 application / 2 -7 d without secondary dressing	
	Allevyn Non Adhésive Biatain non adhésif, Cellosorb Combiderm N, Mepilex Transfer, Suprasorb P Non adhésif Tielle S,	Nonadhesive 1 application / 2 -7 d with a secondary dressing	
	Allevyn Gentle Biatain Contact, Mepilex, Mépilex em,	Microadherent 1 application / 2 -7 d with a secondary dressing	
	Biatain Ibu, Biatain Ibu Contact		Painful ulcer
Alginates	Algostéril, Melgisorb Seasorb Soft pansement, Sorbalgon Plus, Urgosorb	1 application /1 to 2 d with a secondary dressing	Infected ulcer, hemorrhagic ulcer, heavily exuding ulcer (debridement stage)
Hydrogels	Duoderm Hydrogel, Hydrosorb gel or plaque, Hypergel, IntraSite Gel or Conformable, Normlgel, Purilon Gel, Urgo Hydrogel,	1 application /2 d with a secondary dressing	Necrotic ulcer, dry ulcer
Hydrofibers	Aquacel	1 application /1 to 2 d with a secondary dressing	Infected ulcer, heavily exuding ulcer (debridement stage)
Impregnated or coated meshes (= interface dressings or low-adherence dressings)	Adaptic (paraffin) Urgotul (lipido-colloid) Physiotulle (petroleum + hydrocolloid) Mépitel (silicone)	1 application / 1 to 7 d with a secondary dressing	Mildly exuding ulcer, altered peripheral wound skin
Hyaluronic acid–based dressing	Hyalgin (AH film), Hyalofill Hyalogran (AH + alginate) Jaloskin (AH film) Ialuset cream or impregnated gauze, Effidia	1 application / 1 to 7 d with a secondary dressing	Mildly exuding ulcer
Charcoal dressings	Carbonet Actisorb Ag+ (containing Ag) Carboflex (containing hydrofiber)	1 application / 1 to 7 d with a secondary dressing	Foul-smelling ulcer
Silver dressings	Acticoat Actisorb Ag+ Urgotul S Ag	1 application / 1 to 3 d with a secondary dressing	Infected ulcer, foul-smelling ulcer
	Biatain Ag non adhésive, adhésive (foam + Ag) Cellosorb Ag nonadhesive (foam + Ag)	1 application / 1 to 7 d	Infected ulcer, foul-smelling ulcer
	Aquacel Ag (hydrofiber + Ag) Ialuset Plus (hyaluronic acid + Ag)	1application/d with a secondary dressing	Exuding ulcers
Protease-modulating dressings	Promogran (collagen-based dressing) Cellostart (foam dressing)	1application/2 to 7 d with a secondary dressing	Hard-to-heal ulcer
Paraffin or petroleum gauzes	Grassolind neutral, Jelonet, Vaselitulle, Tulle gras Solvay	1application/2 d with a secondary dressing	

Table II : Different types of dressings and their common indications

sheet form. The gel form appears to be the most effective in releasing moisture into wounds. A secondary dressing is necessary, such as a hydrocolloid or a polyurethane film. The dressing is changed every 3 or 4 days. Hydrogels are indicated for dry wounds, at the debridement stage. They are amongst the most efficient products in softening a necrotic plaque. Hydrogels may induce an allergic reaction around the wound, related to the presence of propylene glycol in some products,[16-18] justifying the temporary use of them, at the debridement stage of the leg ulcer.

POLYURETHANE FILMS

Transparent film dressings are made of a polyurethane membrane coated on one side with an adhesive. They are permeable to gases and moisture vapor, but impermeable to water and bacteria. They have no absorbent capacity.

Films are indicated in superficial poorly exudating wounds such as skin tears, low-grade pressure ulcers, and at the epidermization stage of a wound, but are mostly used as a secondary dressing to hold another dressing in place.

ALGINATES

These polymers are mainly composed of fibers of calcium alginate derived from seaweed. They are sometimes mixed with carboxymethylcellulose, in varying percentages. They are commercially available in the form of sheets or ropes for cavities. They need to be covered with a secondary dressing (such as a polyurethane film, or gauze). They have a high absorbent capacity, and a mild bacteriostatic and hemostatic effect. They are indicated for heavily exuding wounds, and infected or hemorrhagic wounds, mainly at the debridement stage.[25] The dressing is changed daily during the cleansing phase, every two or three days during granulation.

HYDROFIBERS

This dressing is made of carboxymethylcellulose fibers and presented in the form of sheets or ropes. The absorbent capacity is almost 2 or 3 times that of alginates. It can be used like an alginate, on heavily exuding wounds, and has to be covered with a secondary dressing. Under a hydrocolloid sheet, it can usually be changed every 3 or 5 days. On the surface of a wound, it interacts with exudate to form a cohesive gel, so hydrofiber dressings do not adhere to the wound. Hydrofibers are proposed at the wound debridement stage.

FOAM DRESSINGS

Foam dressings are usually made of a hydrophilic layer (microporous polyurethane) combined with a film as outer layer. They are available in adhesive and nonadhesive forms as well as in thick or extra-thin versions. Hydroabsorbent or superabsorbent dressings are similar to foam dressings, and come from the diaper industry. Foam dressings are highly absorbent and do not disintegrate in the wound, thus preventing the odors that may be experienced with hydrocolloids. In their nonadhesive form, they can be used even if the skin around the wound is irritated or macerated. The rate of dressing changes ranges from 3 to 8 days. They are indicated particularly from the granulation stage to complete closure for exuding chronic wounds. One of them (Biatain Ibu™) is impregnated with ibuprofen in order to provide local pain relief.[26]

CHARCOAL DRESSINGS

These dressings contain a layer of charcoal, combined with an absorbent dressing. Active charcoal absorbs odors from the wound, which are infected or colonized by anaerobic or Gram-negative bacteria. These dressings can be moistened with physiological saline. They need to be covered with a secondary dressing. They are indicated as a primary or secondary dressing for infected wounds and for cancerous wounds.[27] Some of them contain silver salts that are supposed to have an anti-inflammatory effect or to decrease the bacterial load of the wound.

SILVER-COATED DRESSINGS

Silver acts as a broad-spectrum antibacterial agent. Silver dressings are widely employed for the treatment of infected wounds or chronic wounds with a high risk of infection as recent clinical studies suggest that the probability of chronic wounds healing properly is limited when the bacterial load is high.[11] Unlike acute wounds and burns, the clinical benefit of a reduction in wound bacterial colonization is not established in chronic wounds. Most of the products also contain other components such as hydrocolloid, hyaluronic acid, alginate, or foam. A recent meta-analysis indicates that there is insufficient evidence to recommend the use of silver-containing dressings.[28] Since this meta-analysis, a randomized controlled trial has shown that a 4-week treatment with a silver-releasing lipido-colloid contact layer increases significantly at 4 and 8 weeks the mean area reduction of venous leg ulcers with inflammatory signs that suggest a high bacterial load.[29]

IMPREGNATED OR COATED MESHES (also called "low-adherence dressings" or "interface dressings")
Impregnated or coated meshes, which are less adherent and have a tighter mesh, thereby avoiding traumatic and hemorrhagic removal of the dressing, have now mainly replaced classic paraffin or petroleum gauzes. More recently designed impregnated or coated meshes are impregnated with hypoallergenic, neutral substances such as petroleum, paraffin, silicone, carboxy-methylcellulose, or lipido-colloid particles. These interface dressings do not adhere to the wound and need to be covered with a secondary, absorbent dressing. They are changed between once a day and twice a week. They are indicated for slightly exuding wounds, or chronic wounds, whatever the stage of the wound, especially when the peripheral wound skin is altered.

HYALURONIC ACID–BASED DRESSINGS

The rationale for the use of hyaluronic acid or collagen is to promote healing because they are present at a very high level in the dermis. Cream, impregnated tulles or dressings containing hyaluronic acid, sometimes in combination with alginates, are available. They have to be changed daily and this may be costly. They are used for mildly exuding chronic wounds at the stage of granulation, but may induce a burning sensation.

PROTEASE MODULATING DRESSINGS

Two such dressings are commercially available: Promogran™, which is composed of collagen and oxidized regenerated cellulose, and Cellostart™, which is a foam dressing where a nano-oligosaccharide factor is incorporated.
These dressings are supposed to reduce the protease activity of the fluids and to protect host growth factors against degradation. They are used on hard-to-heal wounds but are ineffective for infected wounds or unhealthy wound beds. Only Cellostart™ is reimbursed in France. A recent comparative study of these 2 products showed a significant reduction of the mean wound area in the Cellostart™ group compared with the Promogran group at 12 weeks of treatment.[30]

SKIN GRAFTS AND EMERGING BIOLOGICAL TREATMENTS

Whilst compression therapy treats the underlying pathology, ulcers remain open in some cases for months or years, or heal very slowly. Additional treatments such as skin grafts or tissue-engineered skin may be used to hasten the healing process.

Skin grafts used for venous leg ulcers are most commonly pinch grafts, but split-thickness skin meshed grafts may also be performed on larger wounds. There are no specific indications for when skin grafting for venous leg ulcers should be used, but grafting should be considered for large or refractory ulcers, when the venous hypertension is well controlled and when the ulcer bed is clean with healthy granulation tissue.[7,15] Despite the common use of skin grafts in venous leg ulcers, no valuable study is available to assess and quantify the effect of grafting on the healing of venous ulcers[31] and to compare this strategy of treatment with other strategies, such as standard wound care.

Apligraf™ is a living bi-layered bioengineered skin substitute. It is composed of a type I collagen matrix in which human foreskin–derived neonatal fibroblasts are grown, and over which human foreskin–derived neonatal keratinocytes are then cultured and allowed to stratify. It was approved by the FDA in 1998 for the treatment of leg ulcers of greater than one-month duration that have not adequately responded to conventional therapy. Used with compression, Apligraf™ heals venous leg ulcers more effectively than simple dressings and compression, from 49% of complete closure to 63% at 6 months.[31,32] Therefore, Apligraf™ is expensive, which limits its use, and is still not available in Europe.

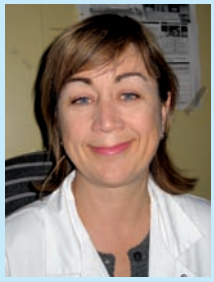
An autologous keratinocyte suspension in a fibrin sealant matrix was recently compared with standard care in the healing of recalcitrant venous leg ulcers in a randomized controlled study. The group treated by cell therapy achieved complete healing in 38.3% of cases compared with 22.4% in the control group, and time to complete healing was significantly reduced by the cell therapy.[33]
Oasis™ is a biomaterial obtained from porcine small-intestine submucosa. It consists primarily of a collagen-based extracellular matrix that contains glycoaminoglycans, proteoglycans, fibronectin, and growth factors. In a recent randomized clinical trial, after 12 weeks of treatment, 55% of the Oasis™-treated leg ulcers were healed, compared with 34% in the standard-care group.[34]

At this time, the efficacy of other emerging treatments such as topical recombinant growth factors or other

products of tissue engineering is not sufficiently evident. Randomized controlled studies are lacking for many biological products.[35]

TOPICAL NEGATIVE PRESSURE

Topical negative pressure is used to promote healing of surgical wounds by using suction to drain excess fluid from wounds and to promote the formation of granulation tissue. Therapy involves first placing a foam or open-pored gauze dressing on a wound. A tube attached to a canister at one end and a suction device at the other is then inserted into the dressing and the area is sealed with a sticky film. The device delivers a controlled negative pressure of -50 to -125 mm Hg which can be applied constantly or intermittently.[36] The first and best known variant is the Vacuum-Assisted Closure (VAC™). The treatment may speed up healing in patients with venous ulcers, given bed rest in hospital,[37] but few such patients are likely to be treated in this way, because of cost. A recent Cochrane review[38] indicates that published trials are insufficient to conclude that topical negative pressure significantly increases the healing rates of chronic wounds. Chronic wounds treated with topical negative pressure appear to be ready for secondary closure surgery (mainly grafts) between 1 and 10 days earlier than controls.[36] As these chronic wounds takes months to heal, the clinical relevance of this difference is debated.



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Results from detection surveys on chronic venous disease in Eastern Europe

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INTRODUCTION

Chronic venous disease (CVD) is common among general populations.[1] Both general practitioners and specialist doctors have to deal with this pathology, which is often mild in presentation but potentially progressive. Despite this, it is acknowledged that CVD is usually overlooked both by doctors who underdiagnose the condition and by patients themselves who rarely consult spontaneously for venous leg problems except in the advanced stages.[2] As a consequence, CVD is undertreated, particularly in the early stages. CVD may be associated with a wide range of lower limb symptoms, which may be present from the outset even before any visible signs of CVD have been identified. Therefore, patients' queries about leg symptoms and their variability with position might be the best way to detect CVD and the first step of a more in-depth investigation.[2]

Recent population-based surveys using the clinical, etiological, anatomical, pathophysiological (CEAP) classification report prevalence rates of CVD of 49% in Poland,[3] 71% in the US,[4] 77% in Italy,[5] 85% in Scotland,[6] and 90% in Germany.[7] Most epidemiological surveys had until recently been conducted in Western industrialized countries and few in the Eastern part of Europe. The aim of the present review was to collect data from this part of the world, ie, from Bulgaria,[2] Poland,[3] and Slovakia.[8]

METHOD

All 3 surveys were multicenter, cross-sectional surveys conducted in primary care centers in which consecutive patients seeking medical help, regardless of cause, were enrolled. They were performed in 2006 in Bulgaria, 2002 in Poland, and 2008 in Slovakia. A total of 26 785, 40 068 and 2009 subjects, respectively, in Bulgaria, Poland, and Slovakia were queried about possible venous leg problems. Clinical interviews were performed according to a questionnaire especially designed for this purpose which reported patients' demographic data, complaints suggestive of CVD and when they were more

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chronic venous disease, epidemiology

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likely to occur, and the presence of visible signs like telangiectasias, varicose veins, edema, skin changes, and healed or active venous leg ulcer. In Slovakia, patients with skin changes and ulcers were not retained in the analysis. Physicians were required to assign patients to one of the CEAP classes by taking into account the highest descriptor.[9]

The Slovak questionnaire included a monitoring part since patients considered as suffering from CVD and requiring pharmacological treatment were treated with Daflon 500 mg, 2 tablets per day for 3 months. Reduction of symptoms after a 3-month Daflon 500 mg treatment was assessed and expressed in the percentage of patients without the symptom, whether or not patients were previously treated with another venoactive drug.

RESULTS

Tables I and II summarize the results in the 3 countries. Results in Slovakia were biased since patients with CVD complications (from C4 to C6) were not included.

Prevalence of C1 to C6 patients was 58% in Bulgaria and 49% in Poland. Prevalence of varicose veins was slightly higher than that of telangiectasias whatever the country (*Table I*), but the percentage of patients with edema varied greatly according to country, pointing to the difficulty of diagnosing this condition.

CEAP class	Bulgaria	Poland	Slovakia
	N (%)	N (%)	N (%)
C0	11 223 (42%)	20 453 (51%)	133 (7%)
C1	4811 (18%)	6611 (16%)	442 (22%)
C2	5421 (20%)	8724 (22%)	928 (46%)
C3	3385 (13%)	1809 (4%)	506 (25%)
C4	1535 (6%)	1840 (5%)	-
C5	306 (1%)	412 (1%)	-
C6	104 (-)	219 (-)	-
Total	26 785 (100%)	40 068 (100%)	2009 (100%)

Table I: Distribution of patients by CEAP class in Bulgaria, Poland, and Slovakia (adapted from ref 2, 3, and 8)

The symptoms most often encountered were 'heavy legs' and 'pain in the legs', while 'night cramps' are less reported (*Table II*).

Symptom related to CVD	Bulgaria N (%)	Poland N (%)	Slovakia N (%)
Heavy legs	9259 (35%)	19 228 (48%)	870 (43%)
Pain in the legs	8050 (30%)	20 479 (51%)	654 (32%)
Sensation of swelling	7528 (28%)	13 722 (34%)	755 (38%)
Night cramps	4626 (17%)	15 375 (38%)	517 (26%)
Mean number of symptoms / patient	1.4	1.7	1.4

Table II: Presence of CVD-related symptoms in Bulgarian, Polish, and Slovak surveys. Each subject could present with one or more symptoms (adapted from ref 2, 3, and 8)

In Slovakia, where patients with CVD were given Daflon 500 mg treatment, a significant improvement was found after 3 months for all symptoms (*Figure 1*). In the sub-groups of patients previously treated with another venoactive drug, a greater improvement in the most reported symptom in Slovakia, ie, 'heavy legs', was noted when patients were switched to the Daflon 500 mg treatment (*Figure 2*).

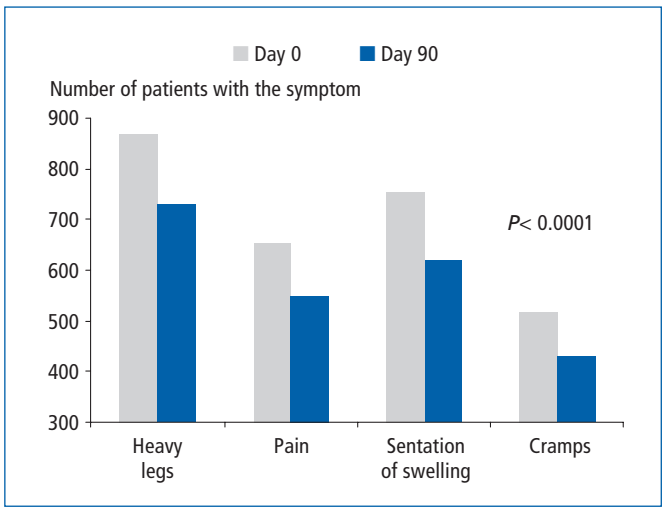

Figure 1. Symptom reduction after 3-month treatment with Daflon 500 mg (adapted from ref 8)

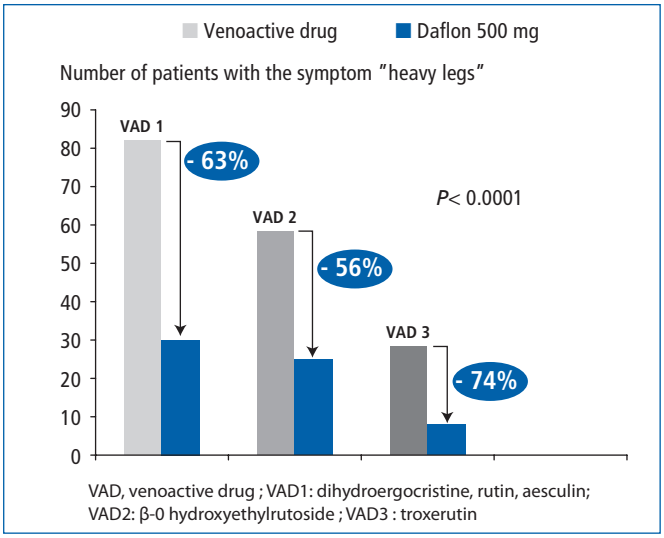

Figure 2. Reduction of 'heavy legs' after 3-month treatment with Daflon 500 mg in the sub-groups of patients previously treated with other drugs (adapted from ref 8)

DISCUSSION

In the Bulgarian survey[2] the prevalence of CVD (58% of subjects had CVD) was close to that of the Polish survey[3] (49%), which had the same design, but far less than in former surveys,[4-7] the design of which was based on voluntary participation (*Table III*). In these last studies, subjects with the disease were therefore more likely to participate. This was most probably the case also in the Slovakian survey, for which patients were given a drug treatment in addition to the interview.

CONCLUSION

This review provides further confirmation that detection programs like the Bulgarian and Polish ones are very useful in heightening awareness of the need for early identification of CVD patients. It might be that due to their mode of recruitment, these types of survey reflect reality better than previous studies.[4-7]

A 3-month Daflon 500 mg treatment relieved symptoms in a substantial proportion of patients, and to a greater extent than did other drugs of different composition (β-0 hydroxyethylrutoside; dihydroergocristine or troxerutin).

Author, year, (country)	Mode of recruitment	Number	Prevalence of C1 to C6 subjects
Rabe, 2003, (Germany)	Spontaneous and voluntary basis	3072	90
Chiesa, 2005, (Italy)		4288	77
McLafferty, 2008, (USA)		2234	71
Evans, 1999, (Scotland)		1566	85
Jawien, 2003, (Poland)	Consecutive outpatients seeking health care	40 068	49
Zahariev, 2009, (Bulgaria)		26 785	58
Stvtinova, 2009, Slovakia)		2009	-

Table III : Presence of C1 to C6 patients in the epidemiological surveys that have used the CEAP clinical classification

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Understanding the mechanisms of lymphangiogenesis: a hope for cancer therapy?

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ABSTRACT

The last fifteen years have witnessed a rapid deepening of our understanding of both the molecular biology of lymphatic vessels and the formation of new lymphatic vessels during lymphangiogenesis. Following the discovery that VEGFR-3, a transmembrane receptor tyrosine kinase, localizes to lymphatic vessels and can orchestrate lymphangiogenesis, the list of molecular regulators of lymphangiogenesis has continued to grow, and includes growth factors, cell surface proteins, and transcription factors. In addition, molecules have been identified that are specifically expressed on lymphatic endothelial cells and therefore allow lymphangiogenesis to be monitored. These findings have in turn allowed lymphangiogenesis to be studied in a variety of diseases, most intensively in the context of cancer and metastasis. In this article I survey our current understanding of the molecular regulation of lymphangiogenesis and its relevance to metastasis and cancer patient survival. I then assess the likely efficacy of cancer therapies that target tumor-associated lymphatic vessels.

INTRODUCTION

Lymphangiogenesis describes the growth of new lymphatic vessels, usually from pre-existing lymphatic vessels in a process that is thought to be similar to angiogenesis. During this process, lymphatic endothelial cells (LECs) sprout, migrate, and proliferate in order to generate new capillaries. In addition, lymphangiogenesis includes vessel enlargement, a process that is probably driven by proliferation of LECs in the absence of sprouting and migration.

The lymphatic vasculature arises mid-gestation following establishment of the cardiovascular system (reviewed in[1]). Endothelial cells from the anterior cardiac vein commit to the lymphatic lineage and sprout and migrate to form the primary lymph sacs in the jugular region. Centrifugal sprouting lymphangiogenesis from these and further lymph sacs that form near other

major veins, followed by merging, remodeling, and maturation of these separate lymphatic capillary networks, populates the developing embryo with its lymphatic vasculature. Mesenchymal progenitor cells may also contribute to this process.[2] In the adult, lymphangiogenesis is only thought to be activated during wound healing and tissue regeneration.[3-5] Pathologically, lymphangiogenesis can also be induced in chronic inflammatory lesions[6,7] and in the context of tumors (see below).

A major breakthrough that has permitted lymphangiogenesis to be studied has been the discovery of proteins that are relatively specifically expressed in LECs, allowing these proteins to be used as markers of lymphatic vessels. The most important of these are the transmembrane receptor tyrosine kinase VEGFR-3, the mucin-type transmembrane glycoprotein podoplanin, the CD44-related cell surface hyaluronan receptor LYVE-1, and the homeobox transcription factor Prox-1.[8] Although these markers have been very useful, it is important to note that none of them is exclusively or homogeneously expressed on all lymphatic vessels, and therefore the detection of a combination of these markers is recommended for the reliable identification of lymphatic vessels.[9]

Newly formed lymphatic vessels are built from proliferating LECs. However, there is increasing evidence that bone marrow–derived and other progenitor cells may also contribute, although their relative contribution to lymphangiogenesis remains to be established. Endothelial progenitor cells, for example, have been shown to insert into existing lymphatic endothelium. Cells expressing CD34+ CD133+ VEGFR-3+ can differentiate into cells expressing vascular and lymphatic endothelial cell–specific markers.[10] Consistently, bone marrow–derived cells can incorporate into the lymphatic endothelium and express lymphatic markers.[11] CD11b+ LYVE-1+ macrophages have also been reported to contribute to lymphatic vessels through vascular mimicry or transdifferentiation.[12,13] Furthermore, mesenchymal stem cells are able to differentiate into lymphatic endothelial cells in response to VEGF-C.[14]

Molecular regulation of lymphangiogenesis: from the cell surface…

The process of lymphangiogenesis is typically activated by extracellular signals such as growth factors that bind to their cognate receptor on the cell surface. As a consequence, intracellular signal transduction pathways are in turn activated that terminate in the nucleus and regulate the expression of genes responsible for orchestrating lymphangiogenesis. The archetypal molecular regulator of lymphangiogenesis on the surface of LECs is the vascular endothelial growth factor receptor family member VEGFR-3. VEGFR-3 is activated by VEGF-C and VEGF-D, members of the vascular endothelial growth factor family.[15] Dimers of VEGFR-3 bind to these ligands and as a consequence tyrosine residues in the cytoplasmic portion of the dimerized receptor are trans-phosphorylated by the intracellular kinase domains of the VEGFR-3 protein. This ligand-induced autophosphorylation of VEGFR-3 activates a variety of signal transduction pathways (see below) that regulate expression of a variety of genes.[16] VEGFR-3 is prominently expressed on the tip cells of sprouting lymphatic capillaries.[17] These tip cells are crucial for the outgrowth of new lymphatic vessels.

VEGFR-2, another member of the vascular endothelial growth factor receptor family expressed on LECs, is also implicated in the regulation of lymphangiogenesis.[18-20] The classical VEGFR-2 ligand VEGF-A can induce lymphatic hyperplasia.[21,22] In addition, proteolytic cleavage of VEGF-C and VEGF-D allows these ligands to activate VEGFR-2. Activation of VEGFR-2 and VEGFR-3 on LECs has different effects: VEGFR-2 activation leads to vessel enlargement, while VEGFR-3 activation leads to sprouting lymphangiogenesis.[17] Furthermore, VEGF-D induces the formation of heterodimers between VEGFR-2 and VEGFR-3, which may lead to differences in the signal transduction pathways that are subsequently activated.[23,24] Our current understanding is that VEGFR-2 and VEGFR-3 cooperate to regulate LEC migration and proliferation[25] and that VEGFR-2 activation may be a modifier but not necessarily an initiator of lymphangiogenesis.[17]

A number of other cell surface molecules on LECs regulate VEGFR-2 and VEGFR-3 activity through binding to their ligands, including α9β1 integrin[26] and the semaphorin co-receptor neuropilin-2.[27] The α9β1 integrin binds to VEGF-A, -C and -D, while neuropilin binds to VEGF-C and -D. The lymphangiogenesis-stimulating activity of VEGF-C and -D has been shown to be dependent on α9β1 integrin.[26] Neuropilin-2 is co-internalized with VEGFR-3 upon ligand binding and is thought to regulate VEGFR-3 activation.[27]

In addition to VEGFR-2 and -3, a number of other cell surface growth factor and cytokine receptors can induce lymphangiogenesis in response to their cognate ligands. These include the receptor tyrosine kinases Tie-1 and Tie-2 and their ligands angiopoietin-1 (Ang-1) and Ang-2,[28] the hepatocyte growth factor receptor c-Met,[29] EphrinB2,[30] and receptors for platelet-derived growth factor,[31] lymphotoxin beta,[32] insulin-like growth factors 1 and 2 and members of the fibroblast growth factor family.[33-35] Not all of these receptor-ligand interactions act directly to induce lymphangiogenesis. Some induce expression of pro-lymphangiogenic factors that in turn induce lymphangiogenesis, while others upregulate the expression of the receptors for these factors. Recently TGF-β signaling has been shown to act as a negative regulator of lymphangiogenesis.[36]

… to the nucleus

The intracellular signal transduction pathways and transcription factors that ultimately coordinate the complex cellular processes of proliferation, migration, invasion, and tubule formation that are required for the formation of new lymphatic vessels are still being unraveled. Activation of VEGFR-3 by its ligands VEGF-C or VEGF-D results in protein kinase C–dependent activation of the MAPK signaling cascade (ERK, JNK) and induction of Akt phosphorylation.[24,37] Specifically, ligand-induced phosphorylation of VEGFR-3 tyrosine residue 1063 on the cytoplasmic tail of the receptor recruits CRKI/II which in turn induces expression of the transcription factor c-jun via JNK1/2. In addition, phosphorylation of tyrosine residues 1230/1231 on the cytoplasmic portion of VEGFR-3 recruits GRB2, activating in turn ERK1/2 and AKT. Lymphangiogenic signaling by FGF-2 also activates the Akt/mTOR/p70S6 kinase pathway,[38] indicating the importance of this pathway in the orchestration of lymphangiogenesis. Consistently, a specific inhibitor of mTOR called rapamycin is able to inhibit tumor-induced lymphangiogenesis and lymphatic metastasis.[39] Furthermore, members of the sprouty/spred family of proteins can inhibit pro-lymphangiogenic VEGF-C signaling by suppressing VEGFR-3–mediated ERK and Akt activation.[40]

The cytoplasmic enzyme cyclooxygenase (COX)-2 is responsible for the synthesis of prostanoids. Recently it was reported to induce expression of VEGF-C by macrophages, and thereby to contribute to lymphangiogenesis.[41] How this works at the molecular level remains to be elucidated.

One of the end points of pro-lymphangiogenic signal transduction pathways is transcriptional activation. A number of transcription factors have been implicated in determining LEC identity, including Foxc-2, Elk3 (Net), Prox1, and Sox18.[15] Sox18 regulates the transcription of Prox-1,[42] a homeobox transcription factor that plays a central role in determining LEC morphology and behavior[43] through regulating the transcription of a battery of genes including the α9 integrin subunit.[44] How these transcriptional regulators are wired into the regulatory pathways that orchestrate lymphangiogenesis largely remains unclear. In addition, the way in which transduction pathways regulate cytoskeleton dynamics and cell adhesion properties that must be central to the process of lymphangiogenesis remains to be identified. A recent insight comes from the discovery of EMS1, a secreted glycoprotein that is specifically expressed in LECs, transcriptionally upregulated by VEGF-A and -C in these cells, and which potentiates the proliferation and migration.[45]

Lymphangiogenesis, metastasis, and the survival of cancer patients.

More than two-thirds of all papers published about lymphangiogenesis concern cancer, making this the most intensively studied aspect of this process. Correlative studies using human tumor samples as well as functional studies in animal models provide strong evidence that tumors can induce lymphangiogenesis. It has been postulated that because of the high internal interstitial fluid pressure within tumors,[46] tumor-induced lymphangiogenesis may reflect a need for increased lymphatic vessel density by tumors to drain this interstitial fluid away, although there is currently no direct evidence to support this notion. Alternatively, tumor-induced lymphangiogenesis may reflect the fact that tumors are similar to wounds that do not heal:[47] mechanisms may therefore be operative in tumors that are similar to those in chronic inflammatory lesions where lymphangiogenesis is induced. Indeed, stromal cells such as tumor-associated macrophages have been implicated in the induction of tumor-induced lymphangiogenesis (see below). The idea has emerged that if tumors develop the ability to induce lymphangiogenesis, then the resulting increase in lymphatic vessel numbers in the vicinity of the tumor may consequently increase the number of tumor cells that invade the lymphatics, in turn stimulating the formation of lymph node metastases. Consistent with the fact that lymph node metastasis is a strong prognostic

indicator for most carcinomas, tumor-induced lymphangiogenesis then also often correlates with poor prognosis.

The number of papers published on lymphangiogenesis and cancer has increased progressively since the year 2000, with more than 160 papers projected for 2009 (*Figure 1*). A detailed review of all 700 or more papers is beyond the scope of this article. I therefore summarize here the main outcomes of these studies as this research area has been reviewed in detail[9,48,49] and critically evaluate the evidence that tumor-induced lymphangiogenesis contributes to lymph node metastasis and poor patient survival.

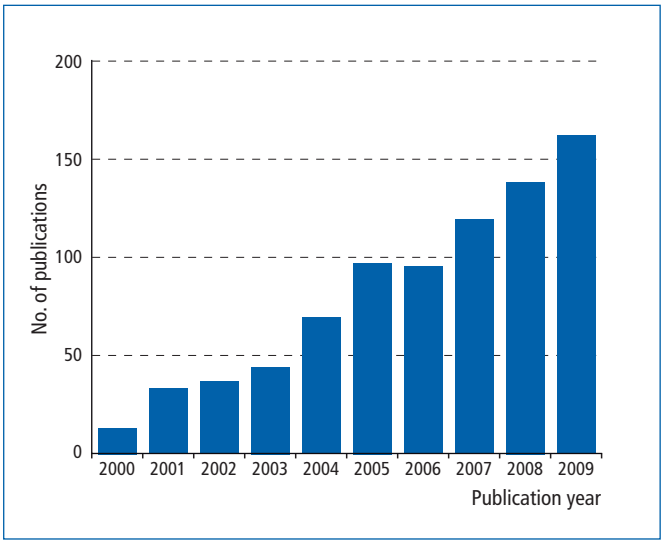

Figure 1. Graph showing the rise in publications that address lymphangiogenesis and cancer since the year 2000. Values are based on papers included in PubMed (www.pubmed.gov). The value for 2009 is projected on the basis of the number of papers published in the first quarter of 2009.

Specific markers of LECs have been used to study the location and density of lymphatic vessels in the context of tumors for a wide variety of different types of cancer. Increased numbers of lymphatic vessels have been reported peripherally within the stroma that surrounds the tumor, as well as within the tumor itself. For some but not all types of cancer, lymphatic vessel density (LVD) peritumorally and/or intratumorally has been correlated with clinical parameters such as lymph node metastasis and poor prognosis. Conflicting data have been published in the case of certain types of cancer such as breast and colorectal carcinomas, as some studies have reported a correlation, while others have not.[49]

In principle, tumor-associated lymphatic vessels could represent pre-existing vessels that have been co-opted by tumors, or could arise through tumor-induced lymphangiogenesis. There is evidence that both mechanisms are operative. Lymphangiogenesis would be typified by proliferation of LECs, and several studies have sought to examine the presence of proliferating LECs within tumor-associated lymphatic vessels. While some of these studies report proliferating LECs or a higher number of proliferating LECs in the tumor-associated lymphatic vessels than in lymphatic vessels from non-transformed tissue, other studies do not.[49] Analysis of these data is complicated by the fact that bone marrow–derived endothelial precursor cells and CD11b+ macrophages have been reported to contribute to the lymphatic vasculature in tumors,[11,50,51] although this contribution may not always be significant.[52] The fact that lymphangiogenesis, vessel cooption, incorporation of progenitor cells and vascular mimicry can all contribute in principle to the lymphatic vasculature of tumors probably accounts for the lack of a tight correlation between lymphangiogenesis, LVD, lymph node metastasis, and poor prognosis. For example, if the tumor is located in an area with a high lymphatic vessel density, cooption of these vessels may obviate any need for lymphangiogenesis.

Studies of many different types of human cancers show that the expression of lymphangiogenic factors increases in more advanced malignant stages of the disease. These factors may be produced by the tumor cells themselves, or by stromal fibroblasts or tumor-associated macrophages within the tumors. The most intensively studied lymphangiogenic factors in the context of cancer are VEGF-C and -D. Many but not all such studies report a correlation between the expression of these molecules and tumor-associated LVD, lymph node metastasis, and poor prognosis.[9]

Tumors have been found to induce lymphangiogenesis not only locally but also distally in draining lymph nodes. In human breast tumors, lymphangiogenesis was observed in 25% of uninvolved axillary lymph nodes.[53] As tumor-induced sentinel lymph node lymphangiogenesis substantially increases lymph flow to the lymph node,[54] it has been postulated that lymph node metastasis may be promoted as a consequence of

increased lymphatic fluid flow that brings disseminating tumor cells to tumor-draining lymph nodes.

Animal models have provided strong experimental evidence for a role for tumor-induced lymphangiogenesis in promoting metastasis. Specifically VEGF-A, VEGF-C, VEGF-D, COX-2, and PDGF-BB can contribute to tumor-induced lymphangiogenesis, as inhibition of the activity of these factors in vivo has been shown to suppress tumor-induced lymphangiogenesis (eg, [31,41,55-57]). COX-2 is likely to act indirectly by inducing expression of VEGF-C.[41] The majority of these studies using animal tumor models have focused on VEGF-C and VEGF-D. Ectopic or transgenic overexpression of VEGF-C or VEGF-D in tumor cells has been shown to promote lymphangiogenesis in a variety of tumor models, as evidenced by enhanced proliferation rates in tumor-associated lymphatic vessels and increased LVD and/or lymphatic vessel diameter (reviewed in [48]). Ectopic expression of these factors also concomitantly promotes metastasis in regional lymph nodes, and in many studies also in vital organs such as the lung.[55,58-63] Conversely, inhibition of ligand-induced activation of VEGFR-3 in several different animal tumor models suppressed tumor-induced lymphangiogenesis but had no effect on pre-existing vessels. Importantly, this inhibition also reduced the onset or incidence of lymph node metastases, and in many cases also inhibited the formation of metastases in other organs such as the lung.[55,61,64-67] These findings are consistent with the notion that VEGFR-3 activation on LECs promotes lymphangiogenesis in the tumor vicinity, thereby increasing the likelihood that invasive tumor cells will enter the lymphatic vasculature and traffic to regional lymph nodes and beyond.

Animal models also demonstrate that tumors can induce lymphangiogenesis in tumor-draining lymph nodes. Both VEGF-A and VEGF-C produced in primary tumors have been reported to do this.[22,68] In some animal models, tumor-induced lymph node lymphangiogenesis has been reported in the absence of lymphangiogenesis in the vicinity of the primary tumor.[54,69]

In summary, there is substantial evidence that tumor-induced lymphangiogenesis does occur and is associated with metastasis, particularly within regional lymph nodes, but also in other organs. However, tumor-induced lymphangiogenesis is not an obligatory feature of tumor progression, and metastasis can occur in its absence. This reflects complex relationships between tumors and lymphatic vessels that are different not only for different types of cancer, but also for each individual tumor depending on its precise location and genetic constitution.

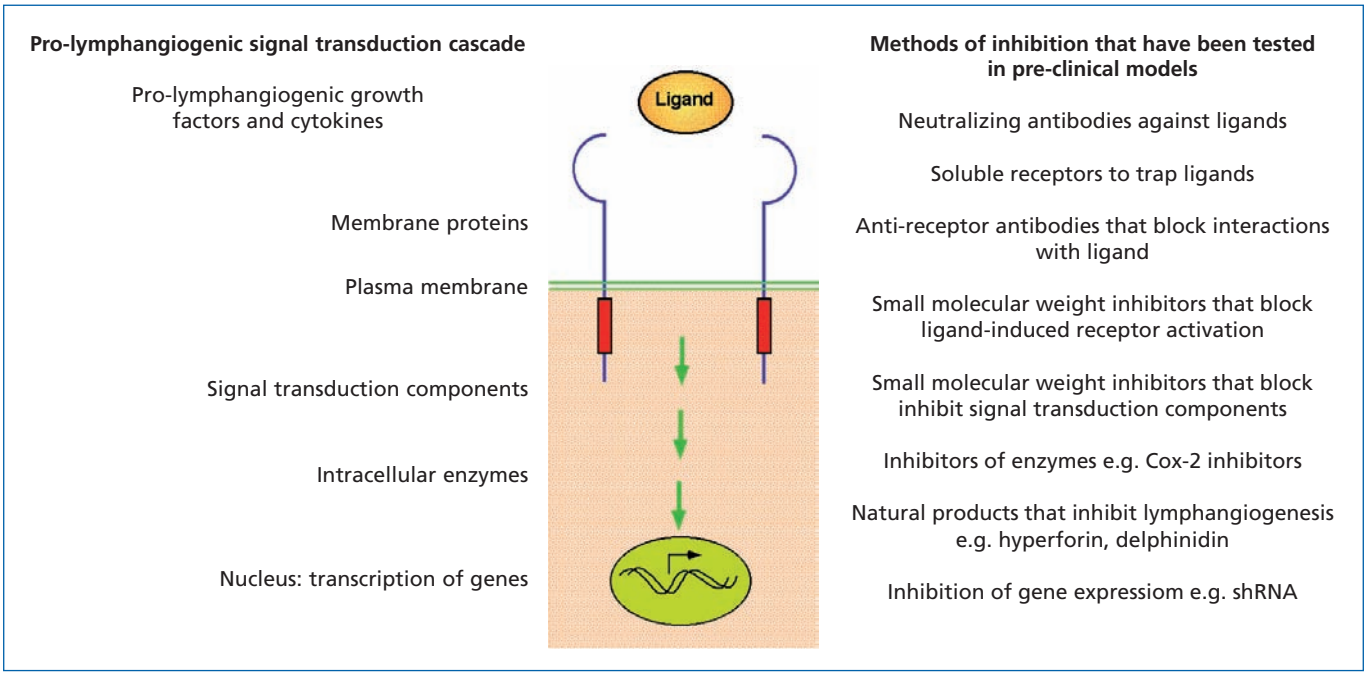

Figure 2. Signal transduction mechanisms that regulate lymphangiogenesis. Listed on the right hand side of the figure are methods for inhibiting lymphangiogenesis that target different levels of pro-lymphangiogenic signal transduction cascades.

Tumor lymphatics: targets for therapy?

The observation in animal models that inhibition of tumor-induced lymphangiogenesis is sufficient to reduce the incidence of metastasis, together with correlative studies on a variety of human cancers that connect lymphangiogenesis with poor prognosis, has raised interest in tumor lymphatics as a possible therapeutic target. For example, following the diagnosis of cancer and during subsequent therapy and remission, chronic inhibition of tumor-induced lymphangiogenesis could potentially reduce the incidence of metastasis. Another potential therapeutic setting might be in cases where patients have relatively slow-growing benign cancers, but where surgical intervention is judged to outweigh the benefit to the patient. In these cases, the tumor is often left in situ. However, a proportion of patients will progress and develop metastases (eg, [70]), and thus chronic suppression of tumor-induced lymphangiogenesis may be beneficial for survival. A variety of pre-clinical models have demonstrated that lymphangiogenesis can be blocked at various levels of pro-lymphangiogenic signaling cascades, including through the use of blocking antibodies, soluble receptors, synthetic chemical inhibitors, natural substances, and shRNA (see *Figure 2*; reviewed in [9]).

There are a number of issues to resolve regarding the therapeutic targeting of tumor-associated lymphatic vessels. As multiple factors probably contribute to tumor-induced lymphangiogenesis, blocking only one of these factors may not effectively suppress tumor-induced lymphangiogenesis. This has recently been elegantly demonstrated in animal models of pancreatic beta cell carcinoma in which tumor-induced lymphangiogenesis is driven by transgenic VEGF-C or -D expression. In these models a broad spectrum inhibitor of the VEGFR family had no effect on tumor-induced lymph-angiogenesis.[71] Furthermore, as outlined above it is clear from studies on human cancers that tumor-induced lymphangiogenesis does not always contribute to the LVD in the vicinity of tumors. Inhibition of lymphangiogenesis does not seem to affect pre-existing vessels, and vessels induced in the context of chronic inflammation do not regress after withdrawal of the original pro-lymphangiogenic stimulus.[7] Thus, if tumors have already induced lymphangiogenesis, or for those tumors where vessel cooption is the major source of tumor-associated lymphatics, inhibition of lymph-angiogenesis is unlikely to be effective. Possible unwanted side effects of targeting tumor-associated lymphatic vessels also have to be considered. Lymphangiogenesis is induced after wounding[3] and so inhibition of lymphangiogenesis might interfere with wound healing and tissue regeneration. Other potential side effects will be dependent on the molecular pathway that is targeted.

Lymph node metastases themselves are rarely life-threatening, despite their strong prognostic relevance.[72] To have an effect on patient survival, inhibition of tumor-induced lymphangiogenesis should therefore suppress the formation not only of lymph node metastases but also metastases in vital organs. The most important question regarding the potential efficacy of targeting tumor-induced lymphangiogenesis therefore concerns the role of lymph node metastases in determining whether metastases form in other organs. As outlined above, manipulation of tumor-induced lymphangiogenesis can influence the formation of both lymph nodes metastases and metastases in vital organs such as the lung. An obvious conclusion would therefore be that lymph node metastases govern the development of metastases in other organs. This would predict that therapeutic removal of lymph nodes should have positive effects on patient survival. However, studies with large series of breast cancer and melanoma patients with follow-up often over several decades do not support this notion. In these studies, surgical removal or non-removal of regional lymph nodes did not correlate with patient survival.[73-76] Nevertheless, the development of lymph node metastases in those patients in whom regional lymph nodes were left in situ was indicative of poor prognosis. From these clinical studies, lymph node metastasis would thus seem to be an indicator but not a regulator of metastasis in vital organs.

The observation that tumor-induced lymphangiogenesis is functionally associated with metastasis in vital organs and poor prognosis needs to be reconciled with these conclusions from clinical studies. One possibility might be that pro-lymphangiogenic factors produced by tumors stimulate not only lymphangiogenesis locally, but may also have other as yet undefined systemic effects that promote metastasis. As we have seen above, pro-lymphangiogenic factors such as VEGF-A and -C can act systemically to induce lymphangiogenesis in regional lymph nodes. VEGF-A is also able to act systemically to induce mobilization of bone marrow–derived cells,[77] which have been suggested to contribute to an organ microenvironment that is conducive to the outgrowth

of disseminated tumor cells.[78] In this scenario, both tumor-induced lymphangiogenesis and lymph node metastasis would serve as indicators that factors have been produced by tumors that can act systemically to promote metastasis in vital organs. However, this scenario remains a speculation.

CONCLUSIONS

The last fifteen years have witnessed the dramatic unraveling of the molecular regulation of lymphangiogenesis. In turn, this has stimulated research into the role of lymphangiogenesis in metastasis and cancer prognosis. Tumor-induced lymphangiogenesis has emerged as a mechanism that appears to contribute to metastasis and poor prognosis for cancer patients. Preclinical studies indicate that by targeting tumor-induced lymphangiogenesis it may be possible to at least partially control metastasis. However, there remain a variety of fundamental questions that need to be answered before translation of these findings into clinical applications is appropriate.

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Venous Clinical Severity Score and quality-of-life assessment tools: application to vein practice

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However beautiful the strategy,
you should occasionally look at the results.
Sir Winston Churchill

Outcome assessment is a term that dominates the global landscape of vascular interventions and has become a catchphrase for determination of the acceptable standard. Its tools allow us to stratify disease and therapy. In his 1996 presidential address to the Society of Vascular Surgery, Rutherford stated: "The results of therapy for vascular diseases have little meaning if presented in isolation, no matter how uniform and valid the criteria used for reporting them. They are intended to be compared with something."[1] For vascular specialists who strive to find something better for their patients and are willing to change based on what they find, outcomes must be analyzed and presented in such a way as to be shared and compared.[2]

With increasing clinical, scientific, and third-party attention being paid to outcome reporting, instruments for measuring standards have become common in the medical literature.

Definition of an outcome and assessment of its efficacy require both an understanding of the disease process and a therapeutic goal that can be objectively measured. The primary treatment goal in venous disease is palliative and varies among physicians and patients. To measure and report only the clinical outcome of therapy through morbidity and mortality statistics omits many collateral effects and potentially serious implications. To fully assess an outcome, the effects on the physician, patient, and community should be reported.[3] This notion is at the heart of quality of care that considers quality-of-life.

There are many definitions of quality-of-life and as many ways to measure it, including instruments completed by the patient or physician. For a quality-of-life instrument to be a valuable measure of what is intended, it must be reliable and valid. For it to gain popularity among researchers and clinicians, it must also be practical.[4] Reliability evaluates the consistency of patient

Keywords:
venous outcomes, venous severity score, venous quality-of-life

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responses. Validity evaluates the ability of a question to measure the object variable and examines the consistency of responses to questions over time.[5] Practicality is a function of the study at hand and the information that can be collected to provide the necessary data.

Quality-of-life instruments include both generic and disease-specific surveys. Generic surveys assess global states of well-being and provide a subjective measure of treatment efficacy. They have high comparative value for unrelated diseases and are generalizable between studies.[4] These help establish the relative priority of a procedure, especially when determining cost-effectiveness in an era of limited resources.

Disease-specific surveys focus on elements associated with particular disease processes and treatment effects. This increases the sensitivity to trends and outcomes of the condition being studied.[4] The survey questions are geared toward expected trends in the study of a particular condition and are more focused in their scope than generic instruments. They have become much more popular in venous disease reporting.

In the study of quality-of-life issues related to chronic venous disease and its treatment, the use of a combination of generic and disease-specific instruments has been advocated.[6]

GENERIC INSTRUMENTS

36-Item Short Form Health Survey (SF-36)

A widely used and well-validated instrument is the SF-36, developed over time with questions in physical health (the patient's level of functioning) and mental health (a measure of well-being). These 2 categories have been broken down into 8 domains that include physical and social functioning, role limitations due to physical or emotional problems, mental health, pain, vitality and health perception. The survey generates a score ranging from 0 to 100, with higher scores indicating better general health perception.[4] The SF-36 has proven to be a good fit for generic quality-of-life assessment in chronic venous disease patients.

Nottingham Health Profile (NHP)

The NHP was devised to be applicable to many conditions. It is a short assessment of emotional, social, and physical health problems from the patient's perspective in various disease states and severities.[7]
In a 2003 study, Wann-Hansson et al[8] compared the SF-36 with the NHP in patients with varying degrees of chronic limb ischemia. Ninety patients were evaluated with each survey following revascularization for lower extremity disease ranging from claudication to severe ischemia. The investigations showed validity in the postoperative period, with good correlation of information. Although the SF-36 demonstrated more internal consistency among patients with claudication and milder ischemic symptoms, the NHP had greater sensitivity to change among patients with more severe ischemia.[8]

DISEASE-SPECIFIC INSTRUMENTS

Chronic Venous Insufficiency Questionnaire (CIVIQ)

The CIVIQ comprises 20 questions in four quality-of-life domains: physical, psychological, social, and pain. The first version of the CIVIQ instrument, the CIVIQ 1, was validated in a sample of 2001 patients, 50% of whom had been diagnosed with venous insufficiency and the remainder of whom presented to a general practitioner for other reasons. A revised version of the instrument, equally weighed the categories across the questions to provide a global score.[3] In 3956 patients, CIVIQ-20 showed good internal consistency and reliability (above 0.80) through test-retest correlations. The discriminating power of items was good in known groups of patients. Factor analysis identified physical, psychological, and pain factors as important, but revealed instability of the social factor. CIVIQ-20 was highly sensitive to changes in the quality-of-life of patients clinically improved after drug treatment.[9] Both versions of the CIVIQ have been used in studies[3,9,10] and proven to be valid quality-of-life measurements.

Venous Insufficiency Epidemiological and Economic Study (VEINES)

The VEINES instrument consists of 35 items in 2 categories that generate 2 summary scores. A quality-of-life questionnaire (VEINES-QOL) comprises 25 items that quantify disease effect on quality-of-life, and a symptom questionnaire (VEINES-Sym) with 10 items that measure physical symptoms. Responses are made on a 2- to 7-point scale that rates intensity, frequency, and agreement. Higher scores are associated with better quality-of-life.[4] The focus of VEINES is on physical

symptoms as opposed to psychological or social aspects. This, coupled with the division of summary scores into symptom and disease effect, makes VEINES beneficial in comparing studies that use different therapies for cardiovascular disease.[11]

Aberdeen Varicose Vein Questionnaire (AVVQ)

The AVVQ is a 13-question survey addressing multiple elements of varicose vein disease. Physical symptoms and social issues, including pain, ankle edema, ulcers, compression therapy use, and limitations on daily activities are examined, as well as the cosmetic effect of varicose veins. The questionnaire is scored from 0 (no effect) to 100 (severe effect).[4]

In a 1993 article, Garratt and colleagues[12] evaluated 373 patients seeking treatment for varicose veins along with 900 persons from the community. The AVVQ was sent with an SF-36 questionnaire to all participants. After scoring, a high correlation was found between the AVVQ and the SF-36 for both groups of patients, with health perception lower in patients with varicose veins than in the general population.

Charing Cross Venous Ulceration Questionnaire (CXVUQ)

The CXVUQ was developed to provide a valid quality-of-life measure for patients with venous ulcers. Although it can be intuitively assessed that venous stasis ulcers negatively affect patient quality-of-life, there was no reliable instrument to evaluate the effects of venous ulcer therapies. Smith et al[13] developed an ulcer-specific questionnaire for use in conjunction with the SF-36 in patients with venous ulcers. The new questionnaire and the SF-36 were tested among a cohort of 98 patients meeting criteria for ulcer size and duration. The questionnaire showed correlation with the 8 domains of the SF-36, and the responses to questions in the disease-specific test questionnaire matched well with the SF-36, and provided a consistent measure of patient-reported quality-of-life in venous ulcers regardless of the treatment option selected. Combining it with a generic measure such as the SF-36 may provide valuable information on the progression of ulcers and their treatment.[13]

Guex et al[14] designed a survey to address this gap in quality-of-life instruments and to be used in clinical practice. Their Specific Quality-of-Life and Outcome Response–Venous survey considers the primary complaint of the patient and the relevance to venous disease. They refer to this as a 'patient-reported outcome' in that it is a completely patient-driven self-report questionnaire designed following a review of existing questionnaires. This tool is unique in its consideration of symptoms, impairment of activities, appearance of the legs, and health-risk concerns. Consideration is given to account more completely for the main concerns of patients, including those in the CEAP C0 to C3 categories. Validated in a test (n ¼ 202) and retest (n ¼ 152) of a European patient cohort, the survey is undergoing English-language validation and additional studies to determine its ability to assess the effect of treatment across the spectrum of venous disease.

Patient-related quality-of-life surveys are not without inherent problems. They may require significant time to complete, and the results can be cumbersome to follow and analyze in daily practice applications. The responses may be overly subjective and vary due to time elapsed since the onset of symptoms. The sheer number of surveys and the design and specificity of each can prove confounding to researchers trying to select one best suited to the problem at hand.

A 2007 chapter by Meissner et al[15] recommended that outcome assessment in vein disorders be objectively measured and based on pretreatment and posttreatment status. Patient-reported quality-of-life assessments are identified as valuable adjuncts to both clinical observations and physician-generated assessments. The 4 disease-specific assessment tools (the CIVIQ, VEINES, AVVQ, and CXVUQ) were noted to be generally acceptable, but inapplicable to the wider spectrum of venous disease. CIVIQ was thought to be consistent and stable but insufficient in addressing more severe venous disease and determination of end points. VEINES is noted to have been validated within a select research group, but in need of additional study outside the original cohort. AVVQ and CXVUQ have been widely validated, but both primarily address specific elements of venous disease and not the wider spectrum of issues surrounding disease course and treatment. The recommendation was made that definitive action be taken to find the best combination of attributes in a questionnaire that will allow the most insight into quality-of-life issues across the spectrum of venous disease.[15]

PHYSICIAN-GENERATED MEASUREMENT TOOLS

Although patient-reported quality-of-life surveys have become important evaluative instruments, the physician-generated survey provides another level of outcome assessment. Several of these tools are in use to evaluate and classify the condition, treatment, and consequences of venous disease.

Clinical, Etiologic, Anatomic, Pathophysiologic (CEAP) Classification

The CEAP classification was developed as a common descriptive platform for the reporting of diagnostic information in chronic venous disease, as well as a tool for regular patient documentation and management.[16] The *clinical* component indicates disease severity, ranging from none (0 points) to active ulcers (6 points). The *etiologic* component denotes the venous disease as congenital, primary, or secondary in nature. The *anatomic* classification pinpoints the veins involved as superficial, deep, or perforating. The *pathophysiologic* classification identifies the presence of reflux in the superficial, communicating, or deep systems, as well as the existence of outflow obstruction.[17] The primary drawback in using the CEAP classification as a stand-alone assessment is its responsiveness, especially in clinical C4 and C5 disease. The static nature of these measurements makes it difficult for a physician to track changes over time in response to therapy.[18]

Venous Severity Scoring (VSS) System

The American Venous Forum in 2000 derived the Venous Severity Scoring (VSS) system from elements of the CEAP classification.[19] The VSS system is an evaluative instrument designed to supplement the CEAP to allow for serial assessment. It has been proven to weather intraobserver and interobserver variability.[20] The basic components of the system are easy to learn and apply. The features of the VSS are critically needed for longitudinal follow-up of a patient's clinical condition during and following an intervention.[2] There are 3 components of this new scoring system.

Venous Disability Score (VDS). The VDS evaluates the effect of venous disease by quantifying the level of work-based disability. It is scored on a scale of 0 to 3, based on the ability to work an 8-hour day with or without provisions for external support. The total score represents the degree of disability attributable to venous disease.

Venous Segmental Disease Score (VSDS). The VSDS uses the anatomic and pathophysiologic classifications in the CEAP system to generate a score based on venous reflux or obstruction. The score is obtained by imaging vein segments with duplex Doppler or phlebography.

Venous Clinical Severity Score (VCSS). The VCSS includes 9 hallmarks of venous disease, each scored on a severity scale from 0 to 3. In order to generate a dynamic score, VCSS categories are scored individually, which adds emphasis to the most severe sequelae of venous disease that are likely to show the greatest response to therapy. These include skin changes and pigmentation, inflammation and induration, and ulcers (including number, size, and duration).[19] The current version of the VCSS contains a category for compression, with higher scores representing greater compliance.

The VCSS has been discussed extensively in studies.[20-28] Ease of use makes it attractive as a stand-alone scoring instrument for longitudinal surveillance of venous disease. The clarity of the CEAP scale is represented in a flexible manner with adjustment capability for physician and patient throughout treatment.[20]

In our study,[20] we evaluated VCSS in patients undergoing saphenous vein radiofrequency ablation (RFA). Four hundred ninety-nine patients (682 limbs) were scored by CEAP clinical class and VCSS before and after the procedure. The preprocedure CEAP clinical classifications included 93% C3 and higher; the mean VCSS was 8.8. Patients were followed up with duplex Doppler and VCSS post-procedure at 4 days, 4 weeks, 4 months, and 12 months. All VCSS components

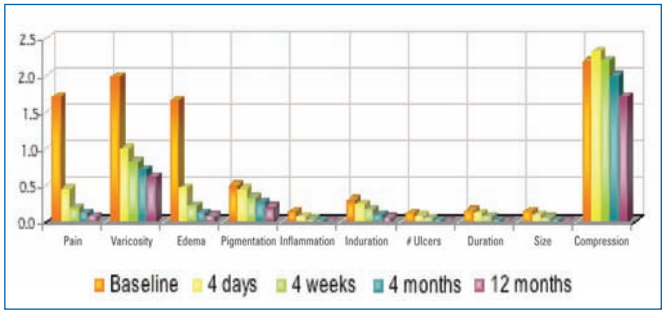
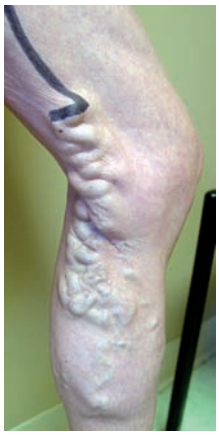
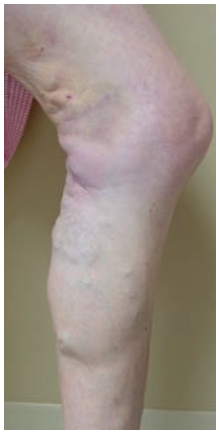


Figure 1. Scores for each VCSS component showed significant improvement at each time interval over the course of follow up.



Attribute	Absent (0)	Mild (1)	Moderate (2)	Severe (3)
Pain	None	Occasional	**Daily**	Daily w/meds
Varicose Veins	None	Few	**Multiple**	Extensive
Venous Edema	None	Evening only	**Afternoon**	Morning
Skin Pigmentation	None	Limited, old	Diffuse, more recent	Wider, recent
Inflammation	None	Mild cellulitis	Mod cellulitis	Severe
Induration	None	Focal <5 cm	<1/3 gaiter	> 1/3 gaiter
No. Active Ulcers	None	1	2	>2
Active Ulcer Size	None	<2 cm	2-6 cm	>6 cm
Ulcer Duration	None	<3 mo	3-12 mo	>1 yr
Compression Therapy	None	Intermittent	**Most days**	Fully comply

Pain=2, VV=2, Edema=2, Pigmentation=0, Inflammation=0, Induration=0, Active ulcers, size, duration=0, Compression therapy=2. **Total VCSS=8**



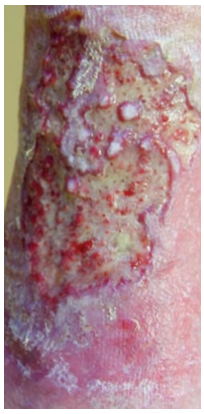
Attribute	Absent (0)	Mild (1)	Moderate (2)	Severe (3)
Pain	**None**	Occasional	Daily	Daily w/meds
Varicose Veins	None	**Few**	Multiple	Extensive
Venous Edema	None	**Evening only**	Afternoon	Morning
Skin Pigmentation	None	Limited, old	Diffuse, more recent	Wider, recent
Inflammation	None	Mild cellulitis	Mod cellulitis	Severe
Induration	None	Focal <5 cm	<1/3 gaiter	>1/3 gaiter
No. Active Ulcers	None	1	2	>2
Active Ulcer Size	None	<2 cm	2-6 cm	>6 cm
Ulcer Duration	None	<3 mo	3-12 mo	>1 yr
Compression	None	Intermittent	**Most days**	Fully comply

Pain=0, VV=1, Edema=1, Pigmentation=0, Inflammation=0, Induration=0, Active ulcers, size, duration=0, Compression therapy=2. **Total VCSS=4**

Figure 2. The "visual language" of VCSS. Consistency in physician scoring and reporting allows a common language of venous disease to emerge. Basic Clinical CEAP 3, VCSS 8 (pre) - CEAP 3, VCSS 4 (post).

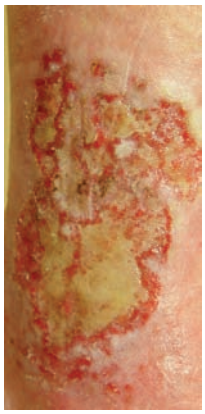
demonstrated significant improvement at each postprocedure visit (*P*<.001 for all), except compression, which varied throughout the follow-up period. At the initial postprocedure visit, the greatest improvement was noted in pain, varicosity, edema, and inflammation components (*Figure 1*). The overall mean VCSS for all components decreased to 5.2 at the first follow-up visit. VCSS components reached a significant mean of 3.3 at the 4-month visit (*P*<.001). The ulcer component of the VCSS demonstrated 86% of ulcers healed by the 4-month follow-up. The VCSS showed usefulness as a stand-alone instrument to track changes in symptoms and clinical status over time following RFA.[20]

The strength of the VCSS lies in its ability to identify subtle intrasubject changes after intervention over time.[20] The components of the VCSS provide outcome analysis on many levels, including technical, patient-reported, and clinical. In this sense, the VCSS is unique among clinical outcome assessments and quality-of-life



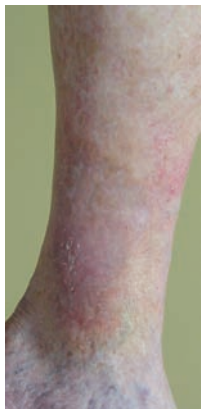
Pain=3
VV=3
Edema=2
Pigment=3
Inflam=3
Indur=3
Ulcers=1
Size=3
Duration=3
Comp=3

CEAP=6
VCSS = 27



Pain=2
VV=2
Edema=1
Pigment=2
Inflam=1
Indur=1
Ulcers=1
Size=3
Duration=3
Comp=3

CEAP=6
VCSS =19



Pain=0
VV=1
Edema=0
Pigment=1
Inflam=0
Indur=1
Ulcers=0
Size=0
Duration=0
Comp=2

CEAP=5
VCSS = 5

Figure 3. The physician-generated "universal language" of VCSS and CEAP scoring CVD. The same patient changes from C6 - V27 to C6 - V19 and lastly C5 - V5.

instruments. Although it is administered by a physician, components are scored based on patient responses to subjective questions. In contrast to more focused instruments such as the AVVQ and the CXVUQ, the VCSS considers most of the salient features of vein disease through clear evaluative parameters for each of its components.

As our experience using CEAP and VCSS has increased, we have become comfortable using them to evaluate changes in patients of all CEAP clinical classes. Although the usefulness of the VCSS has been previously recognized in patients with moderate to severe (C4-C6) disease,[24] patients with even minor symptoms improve after superficial vein ablation.[2,20,21,27] Having a single tool to evaluate patients of all CEAP clinical classes allows assessment of outcomes throughout the spectrum of chronic venous disease. *Figures 2* and *3* give examples of the ease of application of each component of the VSS system. The VCSS has proven to be a useful assessment tool that is easy to administer. However, there has been critical review, mostly of its validation.[29-31] The study by Perrin et al[24] of VSS evaluation among French angiologists also identified some areas of recommended change in the VCSS. Although they noted that the VCSS is easy to score and is relevant in patients with chronic venous disease, there were areas that require clarification. Most notably, the question arose as to the precision of the VCSS in evaluating skin changes that were not necessarily classic pigmentation changes, including dermatitis and hypodermic inflammation.[24]

OUTCOMES REVISION PROJECT

In 2007, through the American Venous Forum, an international ad hoc working group was created to revise the VCSS. The intention was to update the terminology, simplify the application, and clarify ambiguities. The additional objective was to protect the strengths of the VCSS, while acknowledging the limitations. Revisions to each of the clinical descriptors were made using, where applicable, quality-of-life language. The pain component now contains common patient symptoms (aching, heaviness, fatigue, soreness, and burning) that establish a venous origin. The effect on different types of daily activities is clarified. The varicose vein component has been modified to maintain consistency with the revised CEAP: the vein size criterion is greater than 3 mm. Telangiectasias and reticular veins remain without a score; however, corona phlebectatica (ankle flare) has been added to the mild category. The edema component presumes a venous origin and now reflects anatomic distribution and extent. Skin pigmentation has guideline criteria for anatomic distribution and extent and excludes non-venous causes. Inflammation has been expanded to include more than just recent pigmentation changes or underlying infection. Erythema, cellulitis, venous eczema, and dermatitis have been incorporated, as well as anatomic distribution and extent. Induration has been modified to reflect more severe venous disease. Chronic edema with fibrosis, hypodermitis, white atrophy and lipodermatosclerosis have been added. The ulcer categories have been refined to include size and duration to reflect the largest and longest active ulcers.

The compressive therapy category led to the most discussion; and has now eliminated leg elevation to reflect that the category comprises only the wearing of compression garments. This revised VCSS is currently undergoing validation testing internationally.

We believe fully in the usefulness and easy applicability of the VCSS for all venous practitioners. Those who treat patients who suffer want to follow up their clinical outcomes because these practitioners know that they are making a difference. They want a system that they can rely on and that they can use to compare outcomes with others elsewhere. The obvious truth is that quality-of-life and the VCSS are complementary tools. Quality-of-life language is descriptive, comprehensive, and patient-centered. That is why quality-of-life is widely appreciated by so many practitioners and payors. We believe that descriptive quality-of-life language should be added to the VCSS to clarify and improve it. Because the VCSS is physician-driven, this seems to be the natural conclusion. If we can find a way to marry the 2 tools, we can have something truly powerful to use clinically.

UNIVERSAL CONSENSUS

Will there be a universal consensus as to which outcome tool should be used? It is incumbent on the responsible practitioner to do so. Quality-of-life instruments are valuable indicators of patient perspective, are proven to be reliable, and are appreciated by practitioners and payors, but the number of surveys is overwhelming. The VCSS is physician-driven and practical, but needs refinement. The obvious truth is that quality-of-life and VCSS are complementary tools. Quality-of-life language is descriptive, comprehensive, and patient-centered. To blend the patient's language of quality-of-life with the physician's evaluation of the VCSS seems too obvious a solution to ignore. What powerful simplicity!

Our opinion is this: for physicians who want to follow their results and learn from them, a revised VCSS can accomplish this. As the progeny of the clinical CEAP classification, a revised VCSS has a precedent in the revised CEAP and provides common physician-driven clinical language. A revised VCSS that incorporates the language of quality-of-life can become a useful tool from which we will benefit.[32]

In his presidential address to the American Venous Forum, Meissner asserted: "As physicians, we also have obligations to our individual patients and to society. All of us should commit to evidence-based practice, understanding that this does not require submitting to 'a tyranny of the evidence', but integrating our own clinical expertise with the patient's values and preferences… we need to individually participate in both scientifically questioning the existing evidence and generating new evidence."[33]

With the goal set to provide high-quality comprehensive care in the treatment of venous disease, we believe that the international venous community needs to arrive at a consensus as to how outcomes will be assessed and reported.

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Review by Michel Perrin

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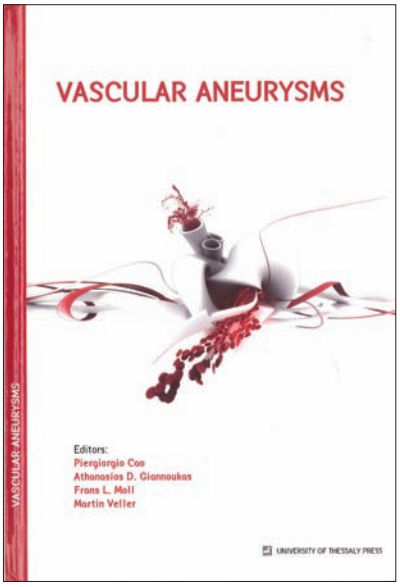

The LARISSA INTERNATIONAL VASCULAR ENDOVASCULAR SYMPOSIUM (LIVES) held every year in June in Greece and organized by Professor Athanasios D. Giannoukas has become a "must". This year the meeting was devoted to vascular aneurysms, and the book published in 2009 by the organizer in collaboration with Frans L. Moll, Piergiorgio Ciao, and Martin Veller deserves both mention and analysis.

The 400-page hardback book in glazed paper contains contributions by 84 authors and is divided into 6 richly illustrated and referenced chapters.

As stated in the preface, vascular aneurysms, including arterial and venous, are multifaceted in their pathophysiology, manifestations, diagnosis, and treatment, and in most cases may remain undiagnosed.

The first chapter deals with the pathogenesis and natural history of vascular aneurysms. After a historical review, many subjects are broached, including the role played by homocysteine in arterial aneurysm and the risk factors for rupture. The second part is devoted to advances and controversies in the management of thoracic aortic aneurysms, and the third part considers abdominal aortic aneurysms, including the lessons learnt from the EVAR trials.

The fourth chapter on issues of concern in endovascular practice is original and contains two articles. The first is an analysis of the importance of the inflammatory response triggered by endovascular procedures, and the second considers the burden of radiation caused by the same procedure.

The fifth chapter is devoted to the management of peripheral arterial aneurysms that are, in fact, not aortic, including traumatic aneurysm and pseudoaneurysms.

The last chapter deals with venous aneurysms—popliteal, saphenous, visceral—and those located in the upper limbs secondary to vascular access. As the book describes the latest significant advances in the study and treatment of vascular aneurysms, we heartily recommend its addition to any vascular library worthy of the name.

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Instructions for authors

AIM AND SCOPE

Phlebolymphology is a quarterly peer-reviewed publication that aims to provide clinicians with updated information on every aspect of the venous and lymphatic disorders: epidemiology, pathophysiology, diagnosis, management, and basic science. Articles are usually in the form of review articles on timely topics with a broad update of recent developments and their clinical applications.

GENERAL INSTRUCTIONS

Articles should discuss a topic of current interest, outline current knowledge of the subject treated, give personal views and also analyze the different opinions regarding the topic discussed, and be up to date on the latest literature data.

The text should be 3000-5000 words, not including references, tables, figures. Illustrations are strongly encouraged. All texts should be submitted in English.

Submission: Manuscripts may be submitted by e-mail[1], double-spaced, 8 to 16 typed. All pages should be numbered. All corresponding authors should supply a portrait photograph for inclusion at the end of the article. This may be sent by e-mail, provided the resolution of the file is at least 300 dpi.

Title page: The title page should include a title, the full names of all the authors, the highest academic degrees of all authors (in country-of-origin language), affiliations (names of department[s] and institution[s] at the time the work was done), a short running title (no more than 50 letters and spaces), 5 to 10 keywords, the corresponding author's complete mailing address, telephone, fax, and e-mail., and acknowledgments.

Abstract: A 150-word abstract should be provided for all articles. The editorial department will edit abstracts that are too short or too long.

Text:. Abbreviations should be used sparingly and expanded at first mention. The style of titles and subtitles should be consistent throughout the text. The editorial department reserves the right to add, modify, or delete headings if necessary. *Phlebolymphology* uses SI units and generic names of drugs.

REFERENCES

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Examples of style for references

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Article in a supplement: Sansilvestri-Morel P, Rupin A, Badier-Commander C, et al. Chronic venous insufficiency: dysregulation of collagen synthesis. *Angiology.* 2003;(suppl 1):S13-S18.

Chapter in a book: Coleridge Smith PD. The drug treatment of chronic venous insufficiency and venous ulceration. In: Gloviczki P, Yao JST, eds. *Handbook of Venous Disorders: Guidelines of the American Venous Forum.* 2nd ed. London, UK: Arnold; 2001:309-321.

Web-based material: Nicolaides AN. Investigation of chronic venous insufficiency: a consensus statement. American Heart Association, 2000. Available at: http://www.circulationaha.org. Accessed October 17, 2005.

Presentation at a conference: Jantet G. Epidemiological results of the RELIEF study across different continents. Paper presented at: 15th World Congress of the Union Internationale de Phlébologie; October 2-7, 2005; Rio de Janeiro, Brazil.

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22-24 April 2010	IV INTERNATIONAL CONGRESS OF POLISH VASCULAR SOCIETIES	Poland	Ossa
27-30 May 2010	7th INTERNATIONAL CONGRESS OF CENTRAL EUROPEAN VASCULAR FORUM	Romania	Timisoara
4-5 June 2010	9th NATIONAL CONGRESS OF THE ROMANIAN SOCIETY OF ANGIOLOGY AND VASCULAR SURGERY	Romania	Cluj - Napoca
10-12 June 2010	56th CONGRESS OF THE SPANISH SOCIETY OF ANGIOLOGY AND VASCULAR SURGEON	Spain	Madrid
24-26 June 2010	11th ANNUEL MEETING OF THE EUROPEAN VENOUS FORUM Joint meeting with the 7th North Sea Meeting on Venous Diseases: 'Long-term follow-up after varicose veins treatment'	Belgium	Antwerp
14-17 July 2010	XVIII CONGRESO COLOMBIANO DE ANGIOLOGÍA Y CIRUGÍA VASCULAR	Colombia	Barranquilla

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7-10 October 2010	5th INTERNATIONAL COURSE / ULTRASOUND GUIDED ENDOVENOUS LASER / RF TREATMENT OF VARICOSE VEINS, SEMINAR AND HANDS-ON COURSE	Slovenia	Otočec
13-16 October 2010	2010 ENDOVASCOLOGY	China	Shanghai
21-24 October 2010	VASCULAR SOCIETY OF INDIA	India	Chennai
10-13 November 2010	52nd ANNUAL MEETING GERMAN SOCIETY OF PHLEBOLOGY	Germany	Aachen
mid of January 2011	VENOUS ASSOCIATION OF INDIA 4th ANNUAL CONFERENCE	India	Rajkot
2-5 June 2011	X ANNUAL CONGRESS OF THE PORTUGUESE SOCIETY OF ANGIOLOGY AND VASCULAR SURGERY	Portugal	Oporto
15-17 September 2011	INTERNATIONAL CONGRESS OF THE UNION INTERNATIONALE DE PHLEBOLOGIE (IUP) EUROPEAN CHAPTER MEETING	Czech Republic	Prague

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