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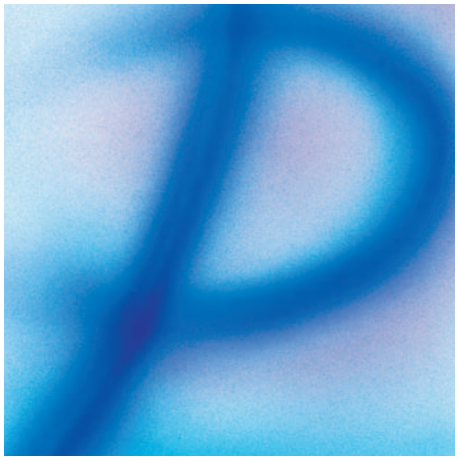

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AIMS AND SCOPE

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

The aim of *Phlebolymphology* is to provide doctors with updated information on phlebology and lymphology written by well-known international specialists.

Phlebolymphology is scientifically supported by a prestigious editorial board.

Phlebolymphology has been published four times per year since 1994, and, thanks to its high scientific level, is included in several databases.

Phlebolymphology comprises an editorial, articles on phlebology and lymphology, reviews, news, and a congress calendar.

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Phlebolymphology

Preface

To be effective, any work must be announced, disclosed, explained, and clarified. In the words of Pericles, "having knowledge but lacking the power to express it clearly is no better than never having any ideas at all." As a company, Servier also has this approach to medical information and to communication in its fields of interest. As a leading company in most of its markets, Servier considers it a duty to help young doctors to communicate their work.

In line with this approach is the Medical Reporters' Academy (MRA) to which we belong. We, as members of the MRA, are an international group of young specialists with a core interest in venous disease drawn from various fields, including dermatology and internal medicine in addition to the more directly related areas of angiology and vascular surgery. Each year, we are invited to report on an international congress of interest to venous disease specialists. This year, we attended the **19th European Chapter Meeting of the International Union of Angiology, September 24-26, 2010 in Paris, France. Our reports form the core of part I of this issue**. Through such meetings, we are trained in identifying potential breakthrough presentations among those on offer, and in honing our critical skills by reporting them succinctly and objectively to our colleagues.

We also thank Prof Boisseau for reporting from the 9th World Congress for Microcirculation held in Paris in conjunction with the 19th EUROCHAP (Part II).

Servier's educational program also includes training programs aimed at facilitating the writing up or presentation of studies.
One such was the recent **training course entitled 'Introduction to Effective Medical Writing" held on September 23rd 2010**, under the chairmanship of Professor Andrew Nicolaides. Nineteen participants from 15 different countries attended this meeting, showing that, at least in the field of venous research, the need for and expectations of such courses are high. Servier made available its wealth of expertise and know-how by providing in-house speakers whose technical knowledge in editing, publication design and communication (electronic or other) together with their human qualities were greatly appreciated. Part III of the current issue is devoted to brief reports from this course.

None of these projects could have been run without the authoritative experience of Professor Nicolaides. We thank him for his continuous help and efforts in improving medical education and communication, which are recognized and appreciated by the international medical community.

Happy reading.

The MRA members

Medical Report

Part I of the current issue comprises reports from the 19th European Chapter Meeting of the International Union of Angiology, September 24-26, 2010 in Paris, France. Reports were prepared by the following members of the Medical Reporters' Academy:

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I

Report from the 19th European Chapter Meeting (EUROCHAP)

of the International Union of Angiology,

September 24-26, 2010,

Paris, France.

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Fundamentals

New insights into calf muscle pump function

Chairmen: P Carpentier (Grenoble, France), and A Nicolaides (Nicosia, Cyprus)

Pathophysiology of the calf muscle pump

A Nicolaides (Nicosia, Cyprus)

The important role of muscle contraction in the lower extremities is to support the venous return at three consecutive levels: foot, calf, and thigh. The function is dependent on the competency of venous valves and may be impaired because of reflux in the superficial venous system at various locations (great saphenous vein, small saphenous vein, perforating veins). A proportion of the expelled blood returns down, resulting in an increased ambulatory venous pressure.

The efficacy of the muscle pump can be assessed by measuring blood volume changes during walking. One of the useful methods is air-plethysmography, which measures reflux in mL per second. To evaluate the reflux, venographic studies with a contrast agent were used in the past while today a precise measurement of its presence is possible noninvasively with duplex ultrasound.

The degree of reflux in mL per second correlates with the grade of venous insufficiency, with swelling and ulcer development, respectively. The other underlying cause of impaired muscle pump function and venous insufficiency is venous obstruction. The function may be improved by several measures, eg, elastic compression, intermittent pneumatic compression or electrical stimulation of calf muscles.

Functional imaging of the calf muscle pump

JF Uhl and C Gillot (Paris, France)

3D imaging tools (anatomical dissection after latex injection of venous network, CT venography, MRI) have been used to demonstrate the complex anatomy of the muscular veins of the lower extremities. These veins work as a component of the muscle venous pump. Venous return from the lower extremities is performed by contraction of the muscles, propelling the blood in the veins from the foot to the thigh. The system includes: lateral plantar veins in the foot pump; soleus muscle (the lateral part being more important than medial) with its veins; popliteal pump consisting of gastrocnemial muscles (the medial being more important) and the respective veins; thigh pump represented by semimembranosus muscle with the venous arcades inside it. The most important component is the gastrocnemius pump. The four parts of this system unit produce a synchronous chain of events, thus working as a functional unit.

Electrical stimulation of the calf muscle pump

A Jawien (Bydgoszcz, Poland)

Failure of the muscle venous pump may have severe consequences, resulting even in skin damage. The possible causes of impaired function are valvular incompetence, perforator incompetence, deep vein thrombosis, and also paralysis and lack of mobility. Possibilities to improve the function of a muscle pump include compression, exercise, and electrical stimulation of the muscles. Ankle joint mobility is inversely related to the clinical stage of chronic venous insufficiency. Several publications have provided evidence of a role of structured exercise in improving ankle mobility, resulting in positive changes in the functional parameters of the muscle pump (increased ejection fraction and decreased residual volume fraction). An electrical stimulator of calf muscles is an option for activation of the physiological pump, leading to reduction of stasis and to significant improvement of venous return. The device can be used in twenty-minute sessions and may be of special interest in patients with reduced mobility or during long periods of sitting or standing (working, traveling, etc.). The search for efficacy and possible indications is ongoing.

Clinical microcirculation

Chairmen: M Vayssairat (Paris, France), P Carpentier (Grenoble, France)
Experts: C Allegra (Rome, Italy), AT Guillaumon (Brazil), J C Wautrecht (Brussels, Belgium)

This session was based on the interactivity between the audience and an international panel of experts, discussing decision making about 5 clinical cases with the help of script concordance tests and PowerVote.

Case report 1: A 30-year-old male from a small mountain village consulted his family doctor for itching, almost burning pain of the first left toe, which he discovered when waking up. He had a history of Raynaud's phenomenon of mild intensity and both feet were involved with erythema, papula, and blistering of the left second toe. Chilblains were diagnosed. The diagnostic workup and the differential diagnoses were discussed. The need for Doppler investigation and positive antinuclear antibody determination was emphasized in order to differentiate from other vascular or systemic disorders (lupus). Chilblain lesions mainly involve the foot (87.6%) and blistering is present in 17.7% of the cases according to a former study.

Case report 2: A 27-year-old woman sought medical advice because of highly itching small papular lesions of both hands, which had bothered her a lot for the two last winters in spite of several local treatments she had tried. She had Raynaud's attacks and a history of chronic urticaria accompanied by some arthralgia and swelling of the fingers. The diagnosis was chilblain lupus. In this clinical entity the elementary lesions are clinically quite similar to primary chilblains. It is classically associated with discoid lupus, but association with systemic lupus erythematosus can also be found. When associated with systemic lupus, chilblains are almost never inaugural; associated lupus manifestations are mostly cutaneous and rheumatic. Positive antinuclear antibody determination and skin biopsy (lupus

band) help the diagnosis. The blue phase of Raynaud's phenomenon is often secondary. There was intense discussion about when and how to treat this kind of patient. According to some experts, antimalarial drugs could be beneficial, but systemic treatment is not always needed, argued others.

Case report 3: A 48-year-old theater actress, nulliparous with no significant medical history, consulted her doctor because of toe pain that hampered her performances in winter. She described her pain as throbbing and worsened by a warm environment. She had scars on her right toe and permanent livedo reticularis not only on the legs but in the shape of irregular broken circles on the trunk also (called livedo racemosa). Her diagnosis was antiphospholipid syndrome. The 2006 Sydney criteria of diagnosis were discussed.

Case report 4: A 59-year-old butcher with a history of sarcoidosis was referred by his attending physician for a diffuse form of disabling chilblain-like lesions of the hands that worsened gradually for several years. This year the summer remission was restricted to July and August (patient's vacation period) and in September he already had swollen and itching fingers, with a slight improvement every weekend, which made him think it was due to working in his cold room. His final diagnosis was occupational protein contact dermatitis. This was first described by Hjorth ad Roed-Petersen in 1976. It is a chronic and recurrent dermatitis caused by contact with proteinaceous material first observed in sandwich makers. Hand erythema, scaling and fissures with immediate urticaria after protein exposure can be observed. It is mainly induced by food proteins (meat, fish, milk, eggs), but also some flowers. The mechanism is unknown. The diagnosis is based on immediate reading skin tests.

Case report 5: The last case presented was that of a 21-year-old who had sold fish in a fish market for 18 months, and who was worrying about having to stop this job. Mornings at the market had become unbearable because of pain in the hands, the appearance of which, in addition, was off-putting for customers. He had tried wearing rubber gloves, but this did not avoid the occurrence of new deep cracks, which, on several occasions, became secondarily infected. His diagnosis was an analogue of "trench foot" called "immersion hand". Trench foot or immersion foot was first described in the First World War, and appears as painful cyanotic edema with frequent complications (cellulitis, gangrene, nerve lesions) after prolonged exposure of a previously healthy foot to cold humidity >0 C (water, mud and so on) because of altered thermoregulation of the skin. It is not the same as frostbite. Its civilian forms are seen in homeless people. The above mentioned patient recovered completely after changing his job.

At the end of this very useful interactive session participants gained a broader understanding of the needs of patients seeking medical help for vascular acrosyndromes.

Venous Thromboembolic Diseases

Venous thromboembolic diseases: evolving concepts and practices

Chairmen: I Quéré (Montpellier, France), A Comerota (Michigan, USA)

Medical significance of asymptomatic venous and pulmonary embolism

G Pernod (Grenoble, France)

Pulmonary embolism (PE) is a common disorder with an estimated annual incidence of approximately 300 000 cases in Europe and a mortality estimated to vary from 7% to 11%. The speaker reported that there have been an increasing number of diagnoses of incidental, asymptomatic PE detected in patients undergoing chest computer tomography for reasons other than studies on suspected PE. However, information on the prevalence and natural history of unsuspected silent PE is extremely limited. Furthermore, the optimal therapeutic strategies when asymptomatic PE is incidentally diagnosed are uncertain, but it is currently recommended to prescribe the same initial and long-term anticoagulation as for comparable patients with symptomatic PE.

New anticoagulants: their impact in the management of venous thromboembolic disease

E Kalodiki (London, UK)

The development of orally bioavailable anticoagulant drugs (anti-Xa and IIa agents), which are alternatives to oral anticoagulants, was reviewed. Both anti-factor Xa (rivaroxiban and apixiban) and antithrombin (dabigatran) agents have been developed for oral use and have resulted in impressive clinical outcomes in randomized controlled trials for the postoperative prophylaxis of venous thrombosis. However, safety concerns related to liver enzyme elevations have been reported. The speaker considered that these newer parenteral and oral antithrombin and anti-Xa agents may be useful in the short- and long-term management of heparin-compromised patients, in particular those who develop thrombocytopenia. However, because of their lower molecular weight, they may pass through the placenta and also through the blood-brain barrier and cannot be used in pregnant women and patients with central nervous system disorders. The relative therapeutic value of the newer anticoagulants will remain unknown until additional clinical data become available. The generic versions of heparin and low-molecular-weight heparin along with other anticoagulants will become available, but their safety and efficacy have to be closely monitored and confirmed. The speaker concluded that heparins, warfarin, and aspirin will continue to play a major role in the management of thrombosis and related vascular disorders beyond 2010.

Superficial thrombophlebitis, a significant subset of venous thromboembolic disease

I Quéré (Montpellier, France)

Superficial venous thrombosis is very frequent according to the recent important advances in the epidemiological field. In the large prospective multicenter observational POST (Prospective Observational Superficial Thrombophlebitis) French study, one out of four patients with superficial venous thrombosis had concurrent deep venous thromboembolism (DVT, PE) and 10% of patients with isolated superficial venous thrombosis, ie, without concurrent deep venous thromboembolism at presentation, experienced a venous thromboembolism complication at three months.

The concept of early thrombus removal for iliofemoral deep venous thrombosis

A Comerota (Michigan, USA)

Patients with iliofemoral deep vein thrombosis have increased postthrombotic morbidity and suffer significantly higher recurrence rates than patients with infrainguinal deep vein thrombosis. Studies of the natural history of iliofemoral deep vein thrombosis treated with anticoagulation alone reveal that the overwhelming majority of patients have a poor quality of life, 15% will develop ulceration within 5 years, and at least 40% will have venous claudication. Randomized trials of venous thrombectomy versus anticoagulation alone have demonstrated that patients receiving thrombectomy have significantly better outcomes at 6 months, 5 years, and 10 years. It has recently been observed that the amount of thrombus removed is directly proportional to improved quality of life and reduced postthrombotic morbidity. The speaker concluded that based upon available data, a strategy of thrombus removal for patients with iliofemoral deep vein thrombosis appears superior to anticoagulation alone and should be recommended to all who are active and ambulatory.

Free communications on venous thromboembolic diseases

Comparison of the clinical history of symptomatic isolated muscular calf vein thrombosis versus deep calf vein thrombosis

J Galanaud, MA Sevestre, C Geny, J P Laroche, V Zyzka, I Quéré, J L Bosson (Montpellier, Amiens, Grenoble, Fort de France, France)

Distal deep vein thrombosis (DVT) represents about 50% of DVT in the legs and can occur in the calf axial deep veins or in muscular veins. Though the reported incidence of proximal extension is higher in the case of deep calf venous thrombosis (DCVT), the guidelines for the treatment of DCVT and muscular calf vein thrombosis (MCVT) do not differ.

OPTIMEV is a French national, multicenter, prospective, observational study of patients with venous thromboembolism. The data from this study were used to compare risk factors, clinical presentation, and outcome in 268 patients with symptomatic isolated DCVT and 457 with symptomatic isolated MCVT. DCVT manifested more often with swelling and MCVT with localized pain; otherwise

there were no significant differences in clinical presentation, or in the risk factors. Of both groups, 222 patients with DCVT and 390 with MCVT were followed up for 3 months. Only 3% in both groups were not anticoagulated. The duration of treatment of DCVT was slightly longer. Venous thromboembolism recurrence was comparable in the two groups (1.4% in DCVT and 1.5% in MCVT). There were 29 cases of bilateral MCVT and this subgroup had a very high mortality (17.4%).

MCVT and DCVT differ in clinical presentation but have the same clinical profile and comparable outcome. However, the prognosis of bilateral MCVT seems to be poor.

Bleeding complications in patients with cancer receiving anticoagulant therapy for venous thromboembolism. Findings from the RIETE registry

A Visona, P Di Micco, JA Nieto, J Truijllo Santos, R Quintavalla, P Prandoni, M Monreal (Castelfranco Veneto, Naples, Parma, Padova, Italy – Cuenca, Cartagena, Badalona, Spain)

RIETE is an ongoing, multicenter, international registry of consecutive patients with acute venous thromboembolism.

Cancer is a known risk factor for venous thromboembolism and its recurrence, as well as for anticoagulation-related major bleeding. Moreover, cancer patients have a higher risk of fatal pulmonary embolism and of fatal bleeding. The reported risk factors of fatal bleeding are weight, recent bleeding, renal insufficiency, immobility, metastatic cancer.

Data from the RIETE registry were used to define the risk factors of major bleeding in deep venous thrombosis patients with active cancer during the first 3 months of anticoagulant therapy. Of 4709 patients, 200 (4.4%) developed major bleeding (fatal in 36% of them). The most common characteristics of the patients with major bleeding were anemia, immobility for more than 4 days, metastatic cancer, and the most common locations were gastrointestinal, genitourinary tract, or the brain. The risk of bleeding persisted throughout the 3 months of follow-up.

Fatal bleeding in patients receiving anticoagulant therapy for venous thromboembolism. Findings from the RIETE registry

A Visona, P Di Micco, A Niglio, M Amitrano, M Cimmaichella, P Prandoni, M Monreal, JA Nieto (Castelfranco Veneto, Naples, Avellino, Rome, Padova, Italy – Cuenca, Badalona, Spain)

Data from RIETE were used to assess the incidence of fatal bleeding in venous thromboembolism patients during the first three months of anticoagulant therapy and to identify the risk factors associated with fatal bleeding. Of 24 395 patients, 135 (0.55%) developed fatal bleeding. The independent risk factors for fatal bleeding were age above 75 years, recent major bleeding, metastatic cancer, immobility for more than 4 days, platelet count below $100x10^9$/L, abnormal prothrombin time. In contrast, distal deep venous thrombosis location was a protective factor.

A clinical prediction model was derived from these parameters, stratifying the risk of fatal bleeding.

Venous thromboembolism in the elderly: epidemiological data overview based on the prospective OPTIMEV cohort

G Pernod, MA Sevestre, C Genty, J Labarere, P Couturier, JL Bosson (Grenoble, Amiens, France)

It is well known that age is one of the strongest risk factors of venous thromboembolism (VTE). OPTIMEV is a French national, multicenter, prospective, observational study of VTE patients. The data from OPTIMEV were used to evaluate clinical characteristics of VTE patients older than 75 years. The diagnosis was confirmed in 655 of 2149 subjects with suspected VTE.

Proximal deep venous thrombosis with or without pulmonary embolism was found in 69%; distal in 31%. Compared with a control group, without VTE and aged less than 75 years, the following risk factors were found: bed rest, acute cancer, history of previous VTE, cardiac or respiratory failure and travel.

Logistic regression was used to test the possible interaction between age and risk factors. The results revealed that male gender, recent surgery, and lower limb immobilization were significantly more associated with VTE in younger patients (less than 75 years old).

It seems that there are few VTE risk factors specific to older patients.

Thrombosis of atypical location, Mayo series: profile of local causes in organ vein thrombosis

W Wysokinski, R McBane (Rochester, USA)

Atypical locations of venous thrombosis include retinal veins, cerebral venous sinuses, renal, ovarian and splanchnic veins (portal, superior mesenteric, inferior mesenteric, hepatic). These cases are usually considered as a result of a general prothrombotic state. However, local causes may also be important risk factors.

In the Rochester Epidemiologic Project, the following numbers of patients with atypical venous thromboses were included – 154 patients with thrombosis in cerebral, 218 in renal, 35 in ovarian, 329 in portal, 76 in mesenteric, 62 in splenic, and 45 in hepatic veins.

In cerebral vein thrombosis, the identified risk factors were female gender, pregnancy, estrogen therapy, brain cancer, and neurosurgery. Renal vein thrombosis occurred more often on the left side, in men, in patients with cancer (especially renal cancer) and with nephrotic syndrome. Ovarian vein thromboses were distributed equally bilaterally, the patients were young or middle-aged and the risk factors were cancer (predominantly pelvic cancer), infection (mainly ovarian), estrogen therapy and surgery (mainly pelvic). In splanchnic veins, the associated factors were hepatobiliary or gastrointestinal cancer, cirrhosis, inflammatory bowel disease, pancreatitis, myeloproliferative disease, surgery (especially abdominal), and infection (mainly abdominal).

Taken together, with the exception of cerebral sinus thromboses, most of the atypical venous thromboses were associated with local causes.

Evaluation of a pneumatic device to prevent venous disorders in air travel

F Fernandez, I Chirosa, M Martinez, JJ Sanchez-Cruz, E Ros (Granada, Spain)

Limited mobility and resulting venous stasis in the legs is one of the risk factors of travel-related venous thromboembolism. A special pneumatic device was developed to improve venous stasis by device-mediated exercise. In a randomized controlled trial, the efficacy of this device was evaluated in 60 healthy volunteers, in conditions simulating air travel (hypoxia-hypobaric altitude at 2400 meters, space and condition similar to those of a commercial flight). The anthropometric parameters were obtained, ultrasound of the leg and venous occlusion plethysmography were performed, and a quality of life questionnaire was administered before and after exposure and with and without induced exercise. Significant differences were found in the following parameters: decreased edema (decrease in dermis-fascial distance, measured by ultrasound) and improved venous return (outflow and capacitance, measured by plethysmography). Exercise simulation by pneumatic compression may be useful in prevention of venous stasis during long-haul flights.

Venous thromboembolic diseases –Thrombophilia

Chairmen: G Pernod (Grenoble, France), P Nguyen (Reims, France)

Experts: A Visona (Padova, Italy), ME Reno de Castro Santos (Brazil), M Sprynger (Belgium)

An interactive session with case report presentations and discussions with the expert

Case report 1: A 17-year-old girl was hospitalized with deep vein thrombosis on the left side (ileofemoral with vena cava inclusion) and bilateral pulmonary embolism. The only identified risk factor was the use of contraceptive pills. Therapy with low-molecular-weight heparin was started but, later on, a neural deficit developed. Catheter-directed thrombolysis was performed. The next day, a recurrence of the thrombosis occurred. After inferior vena cava filter implantation, catheter-directed thrombolysis was continued, with thrombus aspiration and subsequent balloon angioplasty and stenting of iliac vein (because of stenosis of the iliac vein, evaluated as May-Thurner syndrome).

Later on, the girl developed fever and shock. CT scan revealed a changed position of the inferior vena cava filter – the head of the filter was in the renal vein, one branch in the vertebra and one branch in the duodenum, thus causing septicemia with digestive bacteria.

The filter was removed; the anticoagulation therapy (low-molecular-weight heparin with transition to warfarin) was restarted. One year later, the patient was in a good condition, without any sequelae.

Despite complete thrombophilia screening, no hypercoagulable state was found. The cause of the venous thromboembolic event was probably the combination of contraception pills and local conditions (May-Thurner syndrome).

Case report 2: A 35-year-old man presented in 2001 with distal deep venous thrombosis. He reported a history of bone marrow transplantation at the age of 19 (because of acute leukemia; his brother was a donor). He was treated with anticoagulants for 3 months. Shortly after treatment discontinuation he developed superficial thrombophlebitis in the great saphenous vein (the vein was not varicose).

Because of these two episodes (not very serious but unprovoked) and because of a family history of venous thromboembolism, thrombophilia screening was performed. Resistance to activated protein C was confirmed. However, factor V Leiden was negative.

An unusual explanation was found. In fact, the patient was a carrier of factor V Leiden but the cells tested in genetic assays were his blood cells. Blood cells are produced by the bone marrow. He underwent bone marrow transplantation many years ago and the donor – his brother- was factor V Leiden negative. Thus, the patient was an example of a genetic chimera.

Case report 3: A young patient (25 years old) suffering from abdominal pain for 2 weeks was diagnosed with splanchnic vein thrombosis (upper mesenteric, portal, pancreaticoduadenal vein). Treatment with unfractionated heparin was started, and later switched to low-molecular-weight heparin and warfarin.

Though the guidelines are not consistent regarding the recommendation for thrombophilia screening in cases of abdominal vein thrombosis, in this patient testing was done because of the absence of any local factor. However, no thrombophilia was revealed, only a slight decrease of antithrombin. The basal level was normal, indicating aacquired antithrombin deficiency.

More detailed testing was performed, taking into consideration the other possible underlying causes – paroxysmal nocturnal hematuria and myeloproliferative disease (in spite of a normal blood count and differential count). The patient tested positive for JAK-2 kinase mutation (V617F mutation, respectively). This mutation is associated with myeloproliferation and therefore the patient should be followed up by a hematologist because of the possibility of developing myeloproliferative disease.

Vascular Diseases

Abdominal aortic aneurysm: an update

Chairmen: P Gloviczki (Rochester, USA), A Jawien (Bydgoszcz, Poland)

Pathogenesis of the abdominal aortic aneurysm

E Allaire (Créteil, France)

Abdominal aortic aneurysms form and rupture because of the destruction of aortic extracellular matrix digested by an excess of proteinases and some of these proteinases are activated by the plasmin pathway. Inflammatory cells infiltrating the aortic wall are important sources of proteinases, and other cells like endothelial or vascular smooth muscle cells can be other putative sources. The speaker explained that an important observation is the disappearance of vascular smooth muscle cells in the media layer of abdominal aortic aneurysms, which may impair adequate wall repair. He also emphasized that vascular smooth muscle cells produce TGF-beta1 and inhibitors of proteinases, thereby protecting the aortic wall against inflammation and proteolysis. Consequently, lack of vascular smooth muscle cells may turn the aortic wall into a structure vulnerable to inflammation-driven proteolysis. Another striking feature is that patients with abdominal aortic aneurysms associated with atherosclerosis have generalized "atrophy" of vessels distant to the main lesion, and that other tissues of these patients heal poorly. Recent data from his own laboratory suggest that mechanisms of healing of tissues under strain are altered in these patients and this observation may help identify new molecular and genetic factors linked to this deadly aortic disease.

Screening for abdominal aortic aneurysm

J S Lindholt (Viborg, Denmark)

Abdominal aortic aneurysm includes an asymptomatic phase with a relatively low-risk treatment, compared with the symptomatic phase, which is a good argument to consider screening. Ultrasonographic screening is a valid, suitable, and acceptable method of screening as sensitivity and specificity are estimated to be 98% and 99%, respectively, fulfilling the criteria formulated by the Council of Europe. The speaker emphasized that the benefits of screening must outweigh the costs and all four existing randomized trials reported benefit of screening of men aged 65 and above. The pooled mid-term and long-term relative risk reduction is both around 50% with 2% reduction in overall mortality. Cost effectiveness has proven attractive in the large MASS trial, and recently the Viborg Study reported after 14 years that the number needed to screen to save one life was just 135 and the frequency of emergency operations due to rupture was significantly reduced by 56%. The speaker concluded that the cost per life year gained has been calculated as 157€ and the cost per QALY as 178€ based upon all-cause mortality. This is less than 1/10 of the cost in well-known implemented cancer programs.

The long-term results of the EVAR-1 trial

JT Powell (London, UK)

The 3 published randomized trials (EVAR-1, DREAM and OVER) comparing elective endovascular versus open repair for abdominal aortic aneurysms have been remarkably consistent in showing a 3-fold 30-day operative survival benefit of endovascular aneurysm repair (EVAR). The EVAR 1 trial randomized patients with large aneurysms (at least 5.5 cm in diameter, anatomically suitable for EVAR) to either endovascular repair or open repair and after 8 years of follow-up EVAR was not associated with a long-term survival benefit. In fact, 54% remained alive, but exactly the same proportion in those randomized to EVAR as in those randomized to open repair. According to the speaker, the reporting of new endograft-related complications was highest within the first 6 months of aneurysm repair (22.9 new complications per 100 patient years of follow-up), reducing to 3.4 new complications per 100 patient years of follow-up between 6 months and 4 years, with weak evidence that rates might start to increase again after 4 years. There is evidence that EVAR might not be as durable as open repair because there were 25 secondary ruptures after EVAR, the majority (72%) of which proved to be fatal. In contrast, there were no secondary ruptures reported after open repair. The speaker concluded that these endograft ruptures appear to explain the erosion of the statistically significant 3% aneurysm-related survival benefit for EVAR versus open repair, observed during the first 4 years of follow-up, and these long-term results question the durability of EVAR.

Medical approach to the patient with an abdominal aortic aneurysm

F Becker (Geneva, Switzerland)

Rupture of an abdominal aortic aneurysm (AAA) is not the main cause of patient death and may even be the least important. Operative mortality in scheduled surgery for AAA is largely due to pre-existing co-morbidities. Even if we have no evidence-based drug to slow the progression of AAA, actions against some reducible factors (like smoking and sedentary lifestyle) are likely to slow the AAA progression rate. Faced with a patient who has just been found to have an AAA <50 mm, we must monitor not only the progression of AAA by scheduled ultrasound examinations, but also cardiovascular risk factors and comorbidities able to increase surgical risk. The speaker concluded that smoking cessation, improvement of respiratory function, regular exercise, and pharmacological treatment of cardiovascular risk factors are probably as important as repeated ultrasound scans.

Carotid stenosis: evolving concepts and practices

Chairmen: E Bastounis (Athens, Greece), F Becker (Geneva, Switzerland)

Surgical treatment of carotid stenosis: new information from recent trials and what is required for future studies

J Fernandes e Fernandes (Lisbon, Portugal)

Carotid endarterectomy (CEA) has been shown to reduce stroke risk in stenosis >70% for symptomatic and asymptomatic patients (ECST; NASCET, ACAS and ACST) and became the established procedure for the treatment of severe carotid bifurcation disease, because there was less combined mortality and neurological morbidity than with the best medical treatment. The speaker showed that recently published randomized clinical trials (EVA-3S, SPACE, ICSS and CREST) comparing CEA and carotid angioplasty and stenting (CAS) in symptomatic >70% stenosis have provided evidence that CAS is associated with higher incidence of ipsilateral stroke, and increased incidence of silent brain infarcts as assessed by DW NMR (ICSS), and concluded that CEA should continue as the procedure of choice for symptomatic patients. The speaker considered that asymptomatic carotid stenosis is a relatively benign disease with a stroke risk of 3%/year as suggested in natural history studies and is a marker of cardiovascular disease. He emphasized that increased stroke risk in asymptomatic stenosis must be associated with plaque vulnerability as assessed by its echogenicity, plaque structure analysis, and evidence of progressing stenosis on repeated duplex examinations. He also reported that noninvasive evaluation of plaque activity provided by the Activity Index identifies asymptomatic stenosis with higher risk of developing neurological events, thus improving selection of patients who will benefit from carotid interventions to prevent stroke. He concluded that a study in asymptomatic patients at high risk of stroke is required to compare interventional procedures (CEA and CAS) with a subgroup of patients receiving the best well-established contemporary medical treatment.

Carotid stenosis: place of carotid stenting

J L Mas (Paris, France)

Randomized clinical trials in patients with symptomatic carotid disease show inferior results of carotid angioplasty and stenting (CAS) compared with carotid endarterectomy (CEA) with regard to the risk of stroke or death within 30 days of treatment. These two methods of treatment seem to have similar efficacy at preventing medium-/long-term ipsilateral stroke after the perioperative period, but with wide confidence intervals, despite a higher incidence of restenosis in patients treated with stenting. The speaker considered that to improve the risk-benefit profile of stenting, it is crucial to establish which factors among patient characteristics (age, gender, anatomical features) and the procedure itself (material, cerebral protection, operator experience) are associated with a high risk of stroke after CAS. A recent meta-analysis showed a striking age-related difference, with equivalent risks of stroke or death after stenting and surgery below the age of 70 and a two-fold increase in risk of stenting over endarterectomy above this age.

The speaker pointed out that randomized clinical trials in patients with asymptomatic stenosis have shown that the absolute benefit of endarterectomy versus medical treatment alone is small, especially in women. In addition, there is growing evidence that the risk of ipsilateral stroke without surgery has been decreased to <1% per year, thanks to more effective medical therapy. If CAS is associated with an excess procedural risk of stroke (as it probably is), this excess risk will probably erode or nullify the small benefit of revascularization versus medical treatment alone. The speaker concluded that in asymptomatic patients the right question may be whether CEA/CAS further reduces stroke risk in patients who receive best medical therapy and, if revascularization is deemed necessary, whether CEA is a safer option and CAS can be an alternative only if there is a contraindication to CEA.

Stroke and thrombolytic therapy: an update

V Larrue (Toulouse, France)

Fifteen years after demonstration of its efficacy, intravenous thrombolytic therapy with alteplase remains the only validated treatment of acute ischemic stroke. According to the author, the efficacy of treatment is strongly time-dependent: better results have been demonstrated up to 4.5 h after stroke onset and efficacy rapidly decreases after this. He showed that the safety of intravenous thrombolysis for stroke in clinical practice has been confirmed by large phase IV studies, but that implementation of this treatment is still a challenge in many hospitals because it requires expertise in both clinical neurology and brain imaging interpretation. In addition, the efficacy of intravenous thrombolysis remains uncertain in important subgroups such as patients over 80 years and intravenous thrombolysis with alteplase is poorly effective in patients with large vessel occlusion. He concluded by saying that additional or alternative therapies are currently being evaluated in these patients, including thrombolysis acceleration with transcranial ultrasound, intra-arterial administration of fibrinolytics, and embolectomy with mechanical devices.

Asymptomatic carotid stenosis and risk stratification

A Nicolaides (Nicosia, Cyprus)

Best evidence indicates that the annual risk of ipsilateral cerebral stroke in patients with moderate-severe asymptomatic internal carotid stenosis (ACS) receiving optimal medical intervention alone has fallen to approximately 1% per year, making routine carotid endarterectomy unjustified. However, while patient subgroups with sufficiently higher average risk, despite current optimal medical intervention, can be reliably identified, then carotid surgery may still be justified. The ACSRS study performed under the auspices of the IUA was a prospective, multicenter, cohort study of patients undergoing medical intervention for vascular disease, and has answered this question. Severity of stenosis, history of contralateral TIAs or stroke, GSM, plaque area and presence of discrete white areas without acoustic shadowing (DWA) were independent predictors of ipsilateral stroke. The speaker concluded that modern medical intervention is highly effective and that cerebrovascular risk stratification is possible using a combination of clinical and

ultrasonic plaque features, but we need further studies to validate these results in patients receiving current optimal medical therapy.

Early detection of the high vascular risk subjects

Chairmen: J Belch (Dundee, UK), S Novo (Palermo, Italy)

Screening for peripheral arterial diseases in the general population

V Aboyans (Limoges, France)

The usefulness of screening for a disease in the general population depends on three conditions: a poor prognosis and consistent prevalence of the disease; availability of an efficient screening test; and the chance to improve the prognosis with management. Peripheral artery disease has a pooor prognosis and its prevalence increases consistently with age; it can be easily detected by ankle-brachial index (ABI) measurements. This technique was first published 40 years ago, is easily accessible, relatively easy and cheap, but still underused in practice. The abnormal ABI values (ie, outside the range 1.1-1.4) correlate well with cardiovascular mortality and add value to the traditional cardiovascular risk factors. However, some unresolved issues remain, such as insufficient standardization of ABI measurement and lack of evidence concerning the benefit of the management of asymptomatic subjects with abnormal ABI.

Role of asymptomatic carotid lesions and inflammation in predicting future cardiovascular events

S Novo (Palermo, Italy)

Screening asymptomatic subjects for subclinical atherosclerosis provides an opportunity to improve the prevention of cardiovascular diseases. Abnormal ultrasound findings in the carotid arteries (increased intima-media thickness, ie, above 0.9 mm, with or without an atherosclerotic plaque) are some of the indicators of asymptomatic atherosclerosis. Some laboratory tests can be used in cardiovascular risk assessment. Inflammatory markers especially are correlated with increased cardiovascular risk (circulating TGF-beta, soluble sCD40L, IL-6, fibrinogen, high-sensitivity CRP). Markers of subclinical organ damage can further improve the risk evaluation. There is a possible interaction between various risk factors. Using a combination of factors improves risk prediction. Some subjects considered to be at low risk may subsequently be reclassified to a higher risk category.

Early markers of hypertension: many are of vascular origin

DL Clément (Ghent, Belgium)

According to the recent guidelines, patients with arterial hypertension should be evaluated for total cardiovascular risk. Various tests and techniques may be used (ECG, echocardiography, intima-media thickness, carotid-femoral pulse wave velocity, creatinine or glomerular filtration rate, ankle-brachial index, microalbuminuria, and fundoscopy). The usefulness of these tests in daily practice

differs because of variable accessibility, financial cost, and predictive value for cardiovascular events. Microalbuminuria is easily performed, cheap, and correlates very well with cardiovascular risk, but is still underused by clinicians. Abnormal ankle-brachial index also has a high prognostic value (below as well as above normal range) and is very easy to determine. Intima-media thickness of carotid arteries, measured by ultrasound, correlates very well with total cardiovascular risk. Fundoscopy has a moderate prognostic value, but nowadays it can be digitized and provide quantifiable information.

These relatively easy and not too expensive tests may detect the signs of subclinical organ damage and thus enable earlier prevention.

Atherosclerosis and venous thrombosis: the same disease entity with two different faces

P Poredos (Ljubljana, Slovenia)

Arterial and venous thromboses have long been considered as different entities, but they have common features revealed by some recent findings (etiology, autopsy findings, risk factors, clinical manifestations). A new study was presented, focusing on the preclinical markers of atherosclerosis in 49 patients with idiopathic deep venous thrombosis. The patients, as well as 48 age- and sex-matched controls, underwent ultrasound of carotid and femoral arteries and endothelial dysfunction testing (flow-mediated dilation, nitroglycerin-mediated dilation in the brachial artery and laboratory assays - von Willebrand factor, P-selectin, VCAM-1, TNF-alpha). In the patient group, there was significantly increased intima-media thickness, number of atherosclerotic plaques, total plaque thickness, impaired endothelium-dependent and independent dilating capacity and increased levels of laboratory markers of endothelial dysfunction.

Arterial and venous thromboses are probably closely interrelated, having an important common pathogenetic mechanism – chronic inflammation.

Physical exercise and vascular medicine

Chairmen: PL Antignani (Rome, Italy), GM Andreozzi (Padova, Italy), P Abraham (Angers, France)

Effects of physical exercise on the cardiovascular system

P Abraham (Angers, France)

A normal vascular function is essential for exercise. The energy substrate ATP required for the biochemical processes leading to movement, as well as the oxygen used to oxidize this substrate, are both provided to the exercising muscle by blood. Muscle blood flow must increase with exercise to fit the oxygen and metabolic requirements of the active muscle. As a result, the increase in workload is linearly associated with an increase in blood flow to the exercising muscles. As is well known, cardiac output increases to fit the increase in muscle blood flow and a redistribution of the total flow to the different vascular beds (splanchnic, renal, cutaneous, etc.) also occurs during exercise. The fraction of the cardiac output

distributed to each vascular bed is variable and depends on the intensity and duration of exercise, environmental conditions and training status. Among the physiological mechanisms involved in blood flow regulation in peripheral vessels during exercise there are local (mechanical, neurogenic, NO, adenosine, myogenic, etc.) regional (flow-mediated vasodilatation, retrograde vasodilatation) and systemic (posture/baroreflex, renin-angiotensin-aldosterone system, chemoreceptors, epinephrine, thermoregulation, splanchnic sympathetic activity, etc.) factors also. The underlying mechanism of short-term and long-term vascular changes induced by exercise are still subject to debate.

Could the balance or imbalance of atherosclerosis risk factors compromise the results of physical training in claudicants?
G M Andreozzi (Padova, Italy)

The goals of conservative treatment in intermittent claudication are prevention of fatal and nonfatal cardiovascular events, prevention of disease progression, and improvement of walking ability. These goals can be achieved by interventional/surgical procedures, physical training, and drugs. The correction of atherosclerotic risk factors is essential to maximize the effectiveness and duration of the results of any pharmacological and surgical intervention. There is clear evidence that supervised physical training can improve walking ability and quality of life in claudicants.

The speaker presented a study whose aim was to verify if the presence/absence of risk factors and the degree of their correction could compromise the responsiveness of claudicant patients to supervised physical training. Initial (ICD), absolute (ACD) claudication distance, and recovery time (RT) were measured by maximal treadmill exercise (speed 3.2 km/h, slope 12-15%) in 74 claudicants, according to a published protocol (Int Angiol 2008). These measurements were repeated after 18 days of supervised physical training (3 days/week for 6 weeks) consisting of a daily walking with a distance target of 1-2 km or a time target of at least 30 min (exercise-rest-exercise pattern). The working load of each single training session was tailored to 60-70% of the ACD measured by a sub-maximal treadmill exercise (speed 1.5 km/h, slope 6±2%) according to the same protocol. At day 10 a new assessment of walking ability was performed. Before entering the study the patients had undergone clinical and duplex arterial examination and cardiac evaluation. The risks/benefits of alternative therapeutic options (pharmacologic, percutaneous and surgical intervention) were also discussed. The patient cohort was stratified in seven groups and eighteen subgroups according to their atherosclerotic risk factors and concomitant cardiovascular diseases (age, BMI, smoking, diabetes, hypercholesterolemia, arterial hypertension, endothelial dysfunction, previous myocardial infarction and TIA or stroke). Half of the population of this study showed inadequate control of the risk factors, which is not an occasional feature and is attributable to the low adherence to guideline recommendations in clinical practice. At the same time the results confirmed the effectiveness of supervised physical training in increasing the walking capacity of claudicants. Moreover, there weren't any significant differences between the groups, indicating that risk factors did not influence the result of physical training. This is a very important statement, because it highlights that physical training is

the only therapeutic tool which is independent of the results of risk factor treatment. Therefore, GPs and vascular specialists should propose physical training in claudicants even if the correction of risk factors is inadequate.

Interval training in patients with intermittent arterial claudication

B Villemur (Grenoble, France)

The 2008 Cochrane Database Review of 22 trials with 1200 patients shows improvements in maximum walking time, pain-free distance (or initial claudication distance), and maximum walking distance (or absolute claudication distance). The exercise did not affect ankle-brachial pressure index. The improvements were seen for up to 2 years, but the results were inconclusive on mortality, amputation rate, and peak exercise calf blood flow. There are limited studies on exercises compared with surgical intervention, angioplasty, pneumatic foot and calf compression, or drug therapy. Therefore, vascular rehabilitation is a first intention treatment if not contraindicated. It is more efficient and superior to simple walking. In the case of failure after 3 months of vascular rehabilitation and medication, revascularization should be considered. Vascular rehabilitation has positive effects on muscle metabolism, muscle microcirculation, and cardiovascular risk factor control. Vascular rehabilitation for arterial claudication consists of upper (arm ergometer) and lower extremity exercises, intermittent pressotherapy, gymnastics, education, and risk factor control. There are two types of treadmill training. The first uses constant intensity and moderate velocity during a given period of time (McDermott MM et al, JAMA 2009) or higher intensity with walking periods until exercise has to be stopped because of claudication (Bronas et al, Vasc Med 2009, Gardner et al J Vasc Surg 2002, Milani et al, Vas Med 2007). The second is interval training with submaximal training periods and an active recovery period which was never used before for peripheral artery disease and was mainly used in the training of athletes. This interval training was recently used in rehabilitation of heart failure, metabolic syndrome, and after coronary artery by-pass and has been recommended for cardiac rehabilitation since 2001.

The objective of the study presented was to determine the effects and the adverse events of treadmill interval training with active recovery in a prospective design. Eleven patients at the second stage of peripheral arterial disease took part in a rehabilitation program 5 days a week for 2 weeks. Each day they had to practice global physical activity, upper and lower extremity exercises, intermittent pressotherapy and a program of treadmill walking. Maximum walking distance was measured on days 0, 15 and 30. The interval training program consisted of treadmill exercise for 30 minutes each morning and evening with increased intensity: for the first week speed was increased, for the second the slope. Each session of interval training consisted of 5 successive 6-minute cycles. Each cycle consisted of 3 minutes of work followed by 3 minutes of active recovery. At the end of the 2 weeks, every patient had significantly increased their walking distance (from an average of 610 m to 1252 m). No adverse event was noted. Patients' motivation was excellent. This study shows that interval training with active recovery is efficient and safe for arterial claudicant patients. More studies are needed to confirm these results, concluded the author.

Physical exercise in elderly arterial disease patients

M Prior (Verona, Italy)

The beneficial effects of exercise response in peripheral arterial disease patients include improvements in leg blood flow and oxygen delivery due to increased muscle capillary density and nitric oxide release, improved skeletal muscle metabolism, and blood viscosity. Moreover, exercise reduces local and systemic inflammation, and in addition improved biomechanics of walking may contribute to increased walking ability. An elevation of pain perception threshold, possibly induced by an increase in endorphine release, could also be considered. The best results are obtained when a supervised treadmill walking program is used. More than 100% increases in treadmill exercise performance, together with significant improvements in peak oxygen consumption and quality of life are described. These effects of exercise do not seem to be age-related. Older PAD patients benefit from exercise training too, provided that comorbidity does not limit their involvement in the training session. Once the main exercise response determinants are considered, age is not per se significantly correlated with a reduced increase in claudication distance upon completion of the treadmill walking program. Moreover, the lower the initial fitness, the greater the fitness increase at the same training load. It is particularly important that elderly arterial disease patients take part in specific supervised exercise training programs, given they are usually more compromised than younger ones in functional capabilities and quality of life.

The author's rehabilitation program includes treadmill training sessions with gymnastics based on physical exercises specifically aimed to enhance proprioceptive ability, joint flexibility, muscle mass and strength, and walking mechanics. Such a program led to improvement not only in walking distance, but also in quality of life scores measured with questionnaires. A short supervised training program may be as effective as longer ones in increasing walking ability, while reducing training costs. A simple and clear definition of the work load may help produce better results and avoid the risk of activating inflammation. Although treadmill training is probably the best to increase claudication distance, other types of exercise can be taken into account to further improve quality of life, concluded the speaker.

Patient education and treatment

Varicose vein treatment in the future

Chairmen: M de Castro-Silva (Brazil), P Nicolini (Lyon, France)

Clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum on the care of patients with varicose veins

P Gloviczki (Rochester, USA)

The guidelines provided by the Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) for treatment of patients with varicose veins (CEAP Class 2) were presented together with recommendations for treatment of superficial and perforator vein incompetence in patients with more advanced (CEAP Class 3-6) venous disease. The recommendations were divided into grade 1 (for strong recommendation) and grade 2 (for weak recommendation), and the level of available evidence was marked as A (for high level of evidence), B (for medium level of evidence), or C (for low level of evidence). The following recommendations were proposed:

- in patients with varicose veins a complete history and detailed physical examination must be complemented by duplex scanning of the deep and superficial veins (Grade 1A);
- the CEAP classification must be used for patients with varicose veins and the revised Venous Clinical Severity Score to assess treatment outcome (both Grade 1B);
- compression therapy for patients with symptomatic varicose veins (Grade 2C);
- compression therapy as the primary treatment to aid healing of venous ulceration and as an adjuvant treatment to prevent ulcer recurrence (Grade 1B);
- ablation of the incompetent superficial veins in addition to compression therapy to decrease recurrence of venous ulcers (Grade 1A);
- for treatment of the incompetent great saphenous vein (GSV) the committee recommended endovenous thermal ablation (radiofrequency or laser) over high ligation with inversion stripping of the saphenous vein to the level of the knee (Grade 1 B);
- the committee also recommended phlebectomy or sclerotherapy to treat varicose tributaries (Grade 1B) and suggested foam sclerotherapy as an option for treatment of the incompetent saphenous vein (Grade 2C);
- the committee advised against selective treatment of perforator vein incompetence in patients with simple varicose veins (CEAP Class 2, Grade 1B), and suggested treatment of pathologic perforators (outward flow of > 500 ms duration, vein diameter of >3.5 mm) located underneath healed or active ulcers (CEAP Class 5-6, Grade 2B);
- the committee also recommended treatment of pelvic congestion syndrome and pelvic varices with coil embolization, plugs or transcatheter sclerotherapy, used alone or in combination (Grade 2B).

Future techniques for varicose vein ablation

P Nicolini (Lyon, France)

During the last 10 years, crossectomy and stripping of the saphenous veins associated with stab avulsions have been gradually replaced by endovenous thermal ablation (radiofrequency or laser). According to the speaker a new technique of thermal destruction with steam is in the course of evaluation. The technique consists of warm sterile water that is sent under pressure (600 bars) in the form of vapor (temperature from 100 to 150 °C) into the trunk of the saphenous vein by a percutaneous approach. The results of a prospective multicenter study in 80 patients begun in November 2008 showed no differences compared with radiofrequency and laser. The speaker concluded that this technique is promising, cheaper than other endovenous thermal techniques, and also allows treatment of collateral varicose veins without phlebectomy. These results must be confirmed by other prospective studies.

We need to know more about the natural history of venous hemodynamics in patients with varicose veins

P Carpentier (Grenoble, France)

The natural history of venous hemodynamics in patients with varicose veins is far from understood. The speaker stated that the classic model favoring the reflux hypothesis and describing chronic vein disease progressing downwards under the effect of venous hypertension lacks objective scientific evidence and is currently challenged by the theory of a primary parietal disease of the venous wall. According to the speaker several observational studies using duplex ultrasound have produced evidence in favor of the ascending hypothesis of varicose disease progression. It has been demonstrated that primary venous reflux can occur in any superficial or deep veins of the lower limbs, suggesting that reflux appears to be a local or multifocal process and that the type of reflux correlates with the age of patients as well as with the CEAP clinical class. On the other hand, some data suggest that reflux progression does not affect all patients and thus competent valves will not necessarily deteriorate over time. The speaker concluded that prospective studies of the natural history of superficial vein disease are needed with standardized evaluation of postoperative outcomes after different varicose vein treatment modalities. These studies should help to optimize therapeutic strategy.

Molecular mechanisms for microvascular endothelial apoptosis under pressure elevation and therapeutic targets

G Schmid-Schonbein (San Diego, USA)

Chronic venous hypertension is associated with elevated markers of microvascular inflammation, tissue remodeling, and apoptosis, but the cellular and molecular mechanisms underlying these processes remain uncertain. The speaker presented a study which tested the hypothesis that acutely elevated venous pressure together with reduction of shear stress can induce elevated enzymatic activity in venules. Using a rodent model for venous hypertension by repeated venular occlusions of 15-min duration, microzymographic techniques for enzyme activity detection in vivo, and immunohistochemistry for receptor labeling, they found increased

activity of matrix metalloproteases (MMP-1, -8 and -9). In this short time they also observed that elevated pressure causes in some venules causes reduced labeling density with an antibody against the extracellular domain of the vascular endothelial growth factor receptor 2 (VEGFR2), while in other venules they observed increased VEGFR2 expression compared with the levels before venous pressure elevation. He concluded that short-term pressure elevation increases enzymatic activity in venules, which may contribute to the endothelial dysfunction associated with this disease.

Efficient compression therapy to treat venous disease: scientific, medical and practical key factors

Chairmen: P Carpentier (Grenoble, France), P Kern (Vevey, Switzerland)

Compression therapy in chronic venous disorders: a bright future requiring much effort

P Carpentier (Grenoble, France)

The speaker emphasized that although compression therapy is increasingly acknowledged as the cornerstone of treatment in chronic venous disorders, its use in everyday practice is far from satisfactory. Despite the well-known beneficial effects of compression therapy, compliance with treatment is very low. Therefore considerable effort is required from vascular scientists, manufacturers, attending physicians, and patients to maximize the benefits of this major therapeutic tool. Manufacturers are nowadays able to make highly sophisticated elastic textiles with better physical properties and acceptability (esthetics, comfort, ease of handling). However, a lot remains to be done. Testing pressure, working pressure, hysteresis and, the massage effect of medical compression stockings are all important physical properties which have to be taken into consideration in order to improve the effectiveness and quality of medical compression stockings. From the medical point of view vascular scientists need a single worldwide classification of compression categories to be able to speak a common language in phlebology. There is a need to better characterize the compression device (not just ankle pressure) and to conduct phase II and phase III trials. Attending physicians have to play their part in therapeutic education programs (like "Veinothermes" presented by the author) and are key to building motivation, to insuring the device is appropriate to the patient's vascular status, and to customizing it to the patient's personal needs. Of course, education of physicians is also necessary. Patients wish to have more personalized products, have to use and look after medical compression stockings, and need to adapt their lifestyle to the treatment. All these objectives require knowledge, skills, and motivation, which points to the need for specific therapeutic education programs. All these efforts and their coordination are necessary to make compression therapy more effective in real life.

New strategies to improve compliance to compression therapy

D Rastele (Grenoble, France)

Compression therapy is part of or key to treatment of severe venous disorders. Postthrombotic syndrome is the main example of this: at least 30 mm Hg at the ankle is required over a 2-year period of wearing. Nevertheless, compliance to compression therapy is poor. A survey in France conducted by JJ Guex shows that 24% of patients are not compliant for French class 3 (20-36 mm Hg) medical compression stockings. The greatest difficulty reported was the putting on of compression stockings (70% of patients). New research strategies have been followed to improve compliance by identifying patient morphology, resistance, skin parameters, difficulties, by innovations in the manufacture of stocking textiles, by educating patients and family, improving posture, and so on. One of the key points for compliance is the putting on compression hosiery, where the main parameter is fabric friction at the instep and ankle. The objective of the strategy was to reduce friction, by studying the skin-stocking interface, coefficient of friction, secondary skin parameters, hydration, microstructure, water loss, and elasticity. A biomechanical approach has been used to optimize the ergonomic description of the patient's body movement when putting stockings on and taking them off. Muscle activities were investigated using surface electromyography measurements. The speaker concluded that muscle activity of the thumb is mainly involved in putting on medical compression stockings, and muscle groups of the shoulder in removing them. To facilitate the putting on process (slipperiness), improvements (yarn selection) and innovations (dynamic elasticity) were implemented in the design of medical compression stockings. The putting on process was improved in 79% of patients, 93% of whom felt more comfortable with these new stockings.

These attempts to improve compliance in a poorly documented field constitute progress, but we still need more data on skin parameters (the heel, for example), morphology, and improvements in posture and textile[5].

Compression after sclerotherapy

P Kern

The aim of applying compression after sclerotherapy is to reduce the size of the endoluminal thrombus, to decrease inflammation, enhance endofibrosis, reduce the risk of recanalization, lower the rate of pigmentation, and decrease the risk of thrombophlebitis. There are many differences regarding the use of compression therapy after sclerotherapy in different countries. As recommended in the guidelines of the German Society of Phlebology, most specialists apply compression after sclerotherapy of saphenous varicose veins and tributaries. Applying extrinsic selective compression combined with compression bandaging after sclerotherapy of the great saphenous vein significantly enhances results at 2 years. In contrast, short-term results (less than 6 weeks) and the incidence of side effects are not influenced by compression. Trials are too scarce to permit any definite conclusion. But as Ferrara showed, compression could have an effect on long-term results and recanalization rate, particularly using selective eccentric compression under medical

elastic stockings to compress the saphenous veins. However, formal proof of this is required. Interestingly, in the setting of telangiectasias, several earlier studies demonstrated a beneficial effect of wearing medical compression stockings after sclerotherapy. Recently, this benefit was confirmed by a prospective study conducted by the author of this presentation. Therefore, after the sclerotherapy of telangiectasias we now have strong evidence that wearing medical compression stockings significantly enhances the esthetic results of treatment (better clinical vessel disappearance, avoiding treatment failures, reducing pigmentation). The mechanisms underpinning this beneficial effect are unclear. Compression of the reticular feeder veins could play a role. The utility of wearing medical compression stockings after sclerotherapy of saphenous veins seems obvious, but its efficacy is less well documented in this indication than after sclerotherapy of telangiectasias.

The effects of medical compression stockings on venous anatomy

J F Uhl

Thanks to imaging techniques it is now possible to evaluate in vivo the biophysical impact of compression of veins. The speaker presented 3 different tools for studying the effects of medical compression stockings on both the superficial and deep veins of the lower limbs. Duplex ultrasonography through a stocking with a transparent window is a simple way to assess the anatomical and hemodynamic effects of medical compression stockings on the venous system. Spiral computed tomography with 3D reconstruction of the lower limbs with or without injection is an accurate method to assess the 3D shape of the leg and the diameter of the superficial/deep veins. It is possible to obtain a realistic 3D model of the leg and its anatomical structures for use in evaluating interface pressure and effects due to compression stockings. T2-weighted magnetic resonance imaging in the standing position is a more informative protocol. It is also possible to do 3D modeling of calf anatomy in the standing position and to quantify venous volume before and during compression.

These studies show that the Laplace law and interface pressure measurement work well regarding the superficial veins. A compression of about 25 mm Hg is necessary to obtain a significant flattening in the lying position, and 50 mm Hg to occlude the vein. In reality, however, the problem is much more complex regarding the effect of medical compression stockings on the deep veins: during muscle contraction they act like an “extra aponeurosis” and seem to play an important role even for a lower pressure interface, concluded the speaker.

Therapeutic education of the vascular patient

Therapeutic education of the patient with peripheral arterial disease

PH Carpentier

Patients with peripheral arterial disease can be treated mainly by concentrating on underlying arterial modifications (called the “lesion-centered approach” by

the author). This could be effective in the short term, but fails in the long term because of inadequate risk factor reduction and lifestyle modification. In a disease-centered approach, patients are expected to control their risk factors, to be compliant with nonsymptomatic long-term treatment, and to be able to detect any warning signs of complications. This cannot be achieved only by the usual information delivered by the physician during a classic medical consultation. The patient-centered approach, beyond pharmacological intervention, includes a lifestyle modification program plus help with stopping cigarette smoking, supervised exercise training 3 times a week, weight reduction dietetic guidance, and a multidisciplinary therapeutic education program including psychological help and involvement of patients' spouses. The aim of this approach is to modify behavior and help the patient cope with the disabilities related to the disease or its treatment and to make him or her an active partner in the management of the disease. Of course, these three approaches should be combined in daily practice and are not mutually exclusive.

A program called "Let's walk" was developed by the vascular medicine teams of Grenoble and Montpellier with the collaboration of a group of patients with arterial claudication. This educational course consists of three educational consultations and five workshops where small groups of patients were interactively informed about the risk factors, natural history, and treatment modalities of peripheral arterial disease and atherothrombosis, and are motivated to exercise more, implement dietary changes, and implement other needed lifestyle changes. Only two-thirds of the patients completed the whole educational course, but this group experienced a significant increase in knowledge, motivation, self-perceived health status, and physical activity. This program is currently available in 12 other French centers.

In conclusion, the speaker emphasized that therapeutic education of the patient is an important cultural change in medical practice. It increases the effectiveness of the usual medical care, greatly changes the patient-physician relationship, and makes our highly technical medical practice more humane.

Therapeutic education of the patient with venous thromboembolic disease

P Léger (Toulouse, France)

Therapeutic education of patients with thromboembolic disease is mainly focused on anticoagulation treatment. The objectives are to avoid hemorrhagic and thrombotic events, to train the patient on how to manage treatment with vitamin K antagonists through a comprehensive patient-centered approach by sharing knowledge and expertise with caregivers. The aim is to integrate the treatment and disease in the patient's daily life and allow him or her to achieve an acceptable quality of life. For this purpose a multidisciplinary team is needed. Education is based on the achievement of educational diagnosis for each patient and the setting up of a therapeutic agreement with patient followed by an action plan and evaluation. The speaker referred to the minimum knowledge required for the patient as a "safety agreement". The education program should be done in the doctor's office, pharmacy, hospital, specialized center, and also at home.

Recent studies confirm the importance and efficiency of therapeutic patient education, especially in self-monitoring of oral anticoagulation. Education reduces bleeding and thrombosis complications and therefore saves lives.

Therapeutic education of the patient with chronic venous disorders

B Satger (La Léchère, France)

The speaker pointed out that chronic venous disease has no effective curative therapy and needs long-term care management. Patients have to manage their disease for a long time, so high motivation and good compliance to compression therapy are required, along with important lifestyle changes and venous hygiene. In order to address these needs, several educational programs for voluntary patients were developed in French spa resorts, some improvement being made over the years. The first one called "The Vein School" started 15 years ago in the spa resort of La Léchère, with topics approached during interactive work groups, as follows: anatomy and physiology of the circulatory system, venous diseases, and practical aspects of life with compression stockings. A series of patients showed improved knowledge and compliance to compression therapy. The "Veinothermes" program developed by a multidisciplinary group with the help of referred patients combines three educational workshops and an individual education consultation aimed at defining goals that the patients must achieve within three months. A systematic evaluation of the first 94 patients showed significant behavioral changes, including improved compliance to compression therapy and quality of life. A third program was used for people with a recent history of proximal deep vein thrombosis, with a six-day training course combining four educational workshops and a specific rehabilitation program using spa therapy and 3 months of telephone follow-up.

In conclusion, the speaker stressed the great interest of patients in such programs. The programs provide short-term improvement of knowledge, long-term beneficial effects on compliance to compression therapy, and significant behavioral changes among patients with venous disorders.

II

Report from the 9th World Congress for Microcirculation

Paris, France, September 26-28, 2010.

Contents

Ninth World Congress for Microcirculation

Content Overview and Comments

Prof Michel René Boisseau - Department of Pharmacology - University of Bordeaux 2

This high-level scientific meeting, chaired by Prof Eric Vicaut, included 164 oral presentations, 277 posters, and 1360 authors. Emphasis was laid on the considerable progress made in the technologies used: capillaroscopy performed not only on the fingernail bed, the forearm, in animal mesentery models, and hamster cheek pouch, but also in vivo in the pia mater, or in organs. Furthermore, data collected by capillaroscopy or Doppler laser are now digital and are used in mathematical and physical models. Many animal models allow an *in situ* approach and, in particular, a genetic approach by a chromosome-mediated or gene transfer method. In addition, the use of animals with a single deficiency (*knockout animal)* enables a molecular approach to pathways of activation of cell function. The spectacular progress achieved in understanding microcirculatory processes is linked to their now recognized role in major organic dysfunction. In light of the large number of communications, the present review only reports results that the author considers novel and important.

New aspects in the physiology of the microcirculation

Adhesion and migration of blood cells in the microcirculation

Leukocyte adhesion takes place mainly in post-capillary venules under conditions of low *shear rate* flow (300 sec^{-1}). Under such conditions, the platelets do not adhere (their adhesion requires higher shear stress conditions). Aggregation of red blood cells promotes the formation of a *cell-free layer* where leukocytes roll and adhere and from which platelets are rejected. Conversely, when there are fewer and more rigid red blood cells, platelet adhesion is promoted (***G Nash, Birmingham***).

Glucose-based polymers form bridges between the endothelium and leukocytes are organized into microvilli 16 µm in length, *tethers* forming a net whose mesh retains white blood cells. It should be noted that such microvilli have been described previously by morphologists. On the molecular level, the primary role in formation of these microvilli is attributed to the chemokine CXCL5, ITAM *immunoreceptor tyrosine-based activation motif* and tyrosine kinase SK. As soon as leukocyte adhesion is triggered, other chemokines are activated, oxygenated molecules are produced and endothelial permeability occurs (***K Ley, La Jolla***). Many other pathways contribute to such adhesion, in particular in diseased areas such as the area surrounding plaque and in ischemia-reperfusion. Thus, uPA increases adhesion while PAI decreases it (it is abolished in the PAI-/- mouse) (***C Reichel Munich***). The newly described function of *strengthening* is related to the protein kinase theta (***A Bertram, Hanover***).

Microvessel permeability, role of the glycocalyx

The glycocalyx, the superficial layer of endothelial cells, decreases leukocyte migration: syndecam -/- mice, thus deprived of a heparan sulfate in the glycocalyx, have higher migration (***O Kehoe, Oswestry***). Generally, the glycocalyx has to undergo shedding for migration to occur. This is due to activation of MMPs (matrix metalloproteinases) (***H Lipowski, Penn State*).** In fact, the glycocalyx has many functions including a role in permeability: made thin by hyaluronidase, its permeability increases (***L Gao, Penn State***); conversely, citrulline injected into an animal model thickens it (***K Wijnands, Maastricht***).

From a structural standpoint, permeability is related to junctional proteins: thus PAF increases it by s-nitrosylation of these proteins (***F Sanchez, Valdivia***), for example, connexin-43 associated with NOS (***A Straub, Charlottesville***). During apoptosis (*BAK-related*) permeability increases as the result of cleavage of endothelial β-catenin. In the cochlea, occludin can be hyper-phosphorylated by an Na+K+ ATPase leading to rupture of the labyrinth barrier (***X Shi, Portland***). On the molecular level and among pathways, the key regulators are forms of VEGF (vascular endothelial growth factor) which insert into signaling complexes. Thus, a signalplex consists of activation of the VEGF-R2 receptor, calcium channels, γ phospholipase, and then downstream activation of eNOS, rho-rac and lastly of junctional proteins such as cadherin bound to actin in the cytoskeleton. This entire structure becomes spatially organized (***D O Bates, Bristol***). Furthermore, caveolae, in some places, play a part in permeability: this is the case in the fenestrated endothelium of the liver which depends on a balance between the constructive component caveolin and deconstructive aquaporin; the latter is implicated in portal hypertension (***M Oda, Tokyo***).

Conductance

Propagation of the wave of depolarization along the endothelium of microvessels governs vasomotricity, two related factors. Propagation depends on junctional proteins: thus connexin 40 -/- mice respond less, comparatively, to electrical stimulation (***C Sorensen, Copenhagen***). The role of EDHF (*endothelium-derived hyperpolarizing factor*) is emphasized, associated with opening of calcium and potassium channels, but regulated by the TRP (*transient receptor channel*), which is over-activated in TRP -/- mice (***H Schmidt, Lübeck***).

The link between vasomotricity and conductance occurs by release of NO, but many other pathways exist. Thus hypoxia has a vasodilator effect via the potassium channels and hyperoxia has a vasoconstrictor role by production of HETE (hydroxyeicosatetraenoic acid) (***A Ngo, Copenhagen***). Electrical stimulation can lead to the production of PGI2 according to the pathway: COX-1, PGI-2 synthase, IP-receptor with a relaxant function (***S Gohin, Lyon***). Lastly, organ specificity exists. Thus, for pulmonary microvessels, vasomotricity related to entry of Ca2+ via the vanilloid channels is stopped by inhibition of MLCK (*myosin light chain kinase*) described in this congress as a new system of protection (***J Parker, Mobile***).

Hemorheology and the microcirculation

Contrary to firmly entrenched older concepts, moderate hyperviscosity, as observed in vascular disorders, is far from being injurious because red blood cells provide NO via a non-enzymatic mechanism, with eNOS being activated by *shear stress* (***O Baskurt, Istanbul***). Therefore, a higher quantity of red blood cells in the microcirculation makes more NO available, but this in a pulsatile vascular system constantly subjected to endothelial mediators (***S Forconi, Siena***). In rats, a 10% increase in the hematocrit lowers blood pressure, an event related to NO. NO acts in contact with the endothelium in the *cell-free layer* made thinner by high shear stress, which in turn allows hemoglobin to destroy it (Intaglietta concept) (**M Intaglietta, La Jolla**).

V*asomotion*, a periodic rhythm independent of the capillaries, measurable by the Doppler laser method, has a function in the delivery of O_2 to tissues, because low oxygen saturation enhances it (***C Thorn, Exeter***).

Aggregation of red blood cells (RBCs) is related to fibrinogen with a specific relation to phosphorylation of band 3. Fibrinogen decreases efflux of NO from RBCs by promoting nitrite derivative species, nitrates and s-nitroso-glutathione derivatives (***C Saldanha, Lisbon***).

In malaria (P. falciparum), proteins of the parasite are exported to the surface of RBCs, ie, kinases called FIKKs, and make the RBCs adhere to the endothelium, an essential pathological event (***LM Kats, Melbourne***).

Microvessel angiogenesis

Researchers consider that the *Zebra fish* is an ideal model to observe the formation of blood vessels, along with transgenic cell lines.

Hemostatic factors have a pro-angiogenic action: activated protein C stimulates the Ang/tyrosine-kinase-R2 receptor (***N Minhas, Sydney***). TXA2-R -/- mice have defective angiogenesis in a paw ischemia protocol; this is related to a defect in platelet and P-selectin activation resulting in a defect in recruiting the hemangiocytes CXCR4+VEGF1+ from the bone marrow (***H Amano, Kanagawa***). Lastly, thrombin participates in activation of PAR-4 (*G protein-coupled activated receptor*) responsible for *sprouting* of endothelial cells (***E Garonna, London***).

Adhesion proteins play a part in angiogenesis: the transmembrane part of ICAM (*ICAM-1 tail*) produces superoxide generation (*ROS pathway*), the basis of the process of angiogenesis (***C Pattillo, Shreveport***).

Hypoxia produces an angiogenic reaction in fibroblasts that express HIF (*hypoxia inducible factor*) 1a and 2a isoforms that participate in the regulation of VEGF and ANGPL-4 (angiopoietin-like 4) (***B Muz, London***).

During angiogenesis, new blood vessels organize spatially. Thus a fragment of rat arteriole placed in a collagen gel and re-implanted spatially reconstitutes a vascular tree with venules and capillaries (depending on plasticity) (***S Nunes, Louisville***). Using vital microscopy, it is observed that the implanted blood vessels connect by surrounding the host cells (depending on *wrapping and tapping*) (***L Munn, Boston***). An important finding is the need in all these processes for the provision of bone marrow stem cells activating the *homing receptors*. Lastly, many pathways regulate neoangiogenesis: thus, physical exercise is angiogenic, but muscles produce vasohibin-1 (VASH-1) which in turn inhibits the process. VASH-1 is increased in muscle in diabetic rats, thus contributing to capillary regression in diabetes (***M Kishlyansky, Montreal***).

The pulmonary microcirculation

The study of microvessels in the lung is an example of a particular aspect in that specific events can be identified in it. Thus, TXA2 contracts arterioles but not venules in the lung (***K E Watson, Madison***). Cells in lung capillaries can be identified by the fact that they bind a lectin from *Griffonia simplicifolia*. This can be seen even though they have an actin-strengthened border (*actin cortical rim*) associated with RhoA (protein GTPase regulating the cytoskeleton) (***T Stevens, Alabama***). Subjected to high tension by strong ventilation in mice, this rim is protected and strengthened by PGI2 (iloprost). This disappears in *siRNA-based Rap1 knockdown mice*. Another particular aspect: in pulmonary hypoxia, the red blood cells produce H_2O_2 via a pathway involving cdb3 (*protein cytoplasmic domain of band 3*) (***A Huertas, New York***).

The lymphatic microvessels

The propagation of lymphatic fluid is related to a constriction-dilatation rhythmic cycle and to lymphatic pumping reacting to stretch of the lymphatic wall and to changes in transmural pressure. Regarding this cycle, which is similar to that of a pacemaker, lymphatic muscle cells (LMCs) react to the release of Ca2+ by the IP3 receptor, and then to temporary opening of the Ca2+ Cl- channels and lastly to depolarization associated with the Ca2+ L channels. *Lymphatic pumping* seems not to follow this series (***M Imtiaz, Calgary***). It is inhibited by VIP (*vasoactive intestinal peptide*), a neuro-immunomodulator produced by peptidergic nerves and the inflammatory cells. Its sites of action include the VPAC2 receptor (demonstrated by use of an antagonist), protein kinase A, and the ATP-sensitive K channels, but there is no interference with the metabolites of NO and COX (***P Von der Weid, Calgary***). A study with cannulation of lymphatics in the diaphragm in rats, on the surface of the pleura, demonstrated the existence of two types of channels, those on the surface, compliant, and others located deeper associated with pressure and stretching of cardiac and diaphragmatic movements (***D Negrini, Milan***). There are two types of muscle cells in the lymphatics (guinea pig mesentery): circular and elongated (fewer in number). The study of their functioning and the resulting mathematical model make it possible to understand that longitudinal cells synchronize movements in the channel by modulating the movement of Ca2+ (***M***

Imtiaz, Calgary*).** Contractility of the thoracic duct is related to *shear stress* and is dependent on NO. A study of a segment of the rat thoracic duct made it possible to understand that the response to *shear stress* of eNOS is due to a Ca-independent pathway and that contractility, responding to flow, is controlled by the *cGMP/PKG regulatory pathway* (protein kinase controlled by cGMP involved in relaxation of LMCs) (O Gasheva, Temple***).

Rats with metabolic syndrome have smaller diameter mesenteric lymphatics, with an accelerated cycle but decreased amplitude and an exaggerated response to substance P (***M Muthuchamy, College Station***). In old rats, the lymphatics have a reduced flow rate, related to the reduction of LMCs (***A A Gashev, Temple*).** In mice with apolipoprotein E deficiency (apoE -/-), hypercholesterolemia is associated with a deficiency of lymphatic transport and of dendritic cells. Wider lymphatics are observed and there is a decrease in LMCs.

Microcirculatory damage in clinical practice

Metabolic syndrome, obesity and diabetes

Anatomical and in particular functional alterations of the microcirculation in subjects with metabolic syndrome, obesity and arterial hypertension are far from being an epiphenomenon. They are related to the pathogenesis of disorders even before they are clinically manifest and then when they worsen. Animal cell lines (*obese Zucker rats*) reproduce this same process. If we analyze cutaneous blood flow using a Doppler laser technique with a sophisticated low frequency method (*wavelet transform*), the former are decreased in their endothelial components. In an obese subject, peripheral vascular resistance is inversely correlated with the vasodilator effect of insulin and not with reactivity to acetylcholine (***J Hornstra, Amsterdam***).

The occurrence of these dysfunctions can be followed in the rat receiving fructose supplementation (***E Bouskela, Rio de Janeiro***) and similarly in the hamster subjected to a high-fat diet where the occurrence of insulin resistance is also noted (***R R S Costa, Rio de Janeiro***); but these alterations are partially improved by aerobic exercise (***B S C Boa, Rio de Janeiro***). A study of the function of microvessels by fingernail bed capillaroscopy in obese young women without a patent metabolic disorder showed a functional and thus predictive alteration and higher adiponectin and leptin levels (**LG Kremer &** ***N R Villela, Rio de Janeiro***).

Perivascular fat has a modulator effect on arterioles via the action of mediators in conjunction with NO-dependent and -independent vasomotor modulation of the endothelium. It appears that such fat, or its effects, are decreased in an obese subject (***A S Greenstein, Manchester***). This is to be compared with the decrease in adiponectin in the perivascular fat of db/db mice resulting in a loss of vasodilation related to insulin (***R I Meijer, Amsterdam***). In rats subjected to such diets, in vivo capillaroscopy reveals capillary rarefaction in striated muscle (***M V Machado, Rio de Janeiro***). The mother's nutritional status during pregnancy has an influence on the outcome of obesity and arterial hypertension (***L Poston, London***). In eclampsia in diabetic women, pathways of defense are altered: anti-oxidant

Nrf2/ARE and anti-hypertensive EPHX2 (***G E Mann, London***)(***M P Koeners, Utrecht***). In populations of male subjects, correspondence between a fatty diet and functional disorders was demonstrated with video-capillaroscopy (***C Buss, Rio de Janeiro***), in particular in the Amsterdam longitudinal study (***N J Wijnstok, Amsterdam***).

In diabetes, the accumulation of advanced glycation end (AGE) products acts on the microvessels: thus the arteries of rats subjected to AGE products lose their endothelium-dependent reactivity (***M Azzawi, Manchester***).

In monkeys subjected to experimental diabetes, vasomotion progressively decreases (***X Tigno, Tempa***).

Microvessels and arterial hypertension

In spontaneously hypertensive rats, insulin resistance is attributed to cleavage of the extracellular domain of the insulin receptor by proteases, above all MMPs, which also cleave the 2 adrenergic receptor, thus accounting for blood pressure elevation (***F A Delano, La Jolla***). In spontaneously hypertensive mice, injection of angiotensin II produces cerebral bleeding associated with oxidative stress and activation of MMPs. These two activities are related. In addition, superoxide dismutase diminishes the effects of Ang II (worsening in SOD -/- mice). This effect of Ang II, which involves remodeling, is more dangerous that that of norepinephrine (***D D Heistad, Iowa City***).

In humans, different types of microcirculatory disorders occur: decreased capillary density, tortuous blood vessels, sacculation, slow speed of red blood cells, and an increase in myogenic tone (***Y Guo, Beijing***). A decrease in endothelium-dependent vasodilatation is also observed (***I Tikhomirova, Yaroslavl***). The red blood cells acclimate to hypertension: their deformability increases depending on arterial stiffness, as measured in the carotid artery (***M Fornal, Krakow***). In a cohort of hypertensive men with hypercholesterolemia, the increase in blood flow associated with hyperemia (Doppler method) is inversely correlated with levels of von Willebrand factor (***C Serban, Timisoara***).

Microvessels and atherogenesis

During atherogenesis, recruitment of monocytes is essential, but neutrophils are associated with it. A study of aortic recruitment in mice with a chemoreceptor deficiency has made it possible to confirm that monocytes use CCR1 and CCR5 receptors; neutrophils use CCR2 and CXCR2 receptors (***O Soehlein, Aachen***). In addition, neutrophils recruit early, at the start of plaque formation with the chemoattractant CCL5 (***M Dreschler, Aachen***). The role of MIF, a ligand of CXCR, has been clarified: in association with the CD74 gene, it inhibit the migration of macrophages and thus growth of the plaque (***N Tuchscheerer, Aachen***). Development of the vasa vasorum is accompanied by development of the atherosclerotic plaque.

Serum homocysteine

Homocysteine increases the risk of vasospasm associated with atherosclerotic plaque. In mice heterozygous for serum homocysteine, a coronary artery is highly reactive to acetylcholine and has less NO due to a decrease in eNOS activity, which is corrected by folic acid (***N Qipshidze, Louisville***). Under the same conditions, excessive production of TXA2 derived from COX2, ROS and a PGI2 deficiency have been demonstrated, all of which indicate a major deficiency of vasomotor regulation in small arterioles (***A Koller, New York & Pecs***). Permeability of the pia mater, increased by perfusion of fibrinogen in normal mice, is enhanced in mice heterozygous for hyperhomocysteinemia (cystathionine β-synthase knockout -/+ mice) (***D Lominadze, Louisville***). Low vitamin B concentrations and elevated homocysteine levels are risk factors for Alzheimer's disease. A correlation appears between P-tau protein in the CSF and plasma homocysteine and conversely for levels of folates. A diet resulting in elevated levels of homocysteine in rats is accompanied by an increase in P-tau protein in the CSF (***W Herrmann, Hamburg***). In the setting of the *Amsterdam Growth and Health Longitudinal Study,* 259 subjects were examined by fingernail bed capillaroscopy: disorders, such as capillary rarefaction, were correlated with plasma homocysteine (***J Hornstra, Amsterdam***).

Shock, sepsis and acute inflammatory conditions

Sepsis

The authors do not hesitate to state that sepsis is a disorder of the microcirculation and this is true in all models and clinical cases. Capillary "*stop flow*" involves tissue anoxia, but also inflammatory disorders, disorders of hemostasis, endothelial functioning with oxidative stress and leukocyte activation (***D De Backer, Brussels***). In a mouse model of sepsis, the formation of microthrombi in microvessels was related to iNOS (abolished in iNOS -/- mice), and NADPH oxidase (abolished in gp91phox-/- mice). In a mouse model of pulmonary sepsis, ANP (*atrial natriuretic peptide*) protected the thin alveolar endothelial barrier against the accumulation of leukocytes and from enhanced permeability to Evans blue. In fact, this protection disappeared in the ANP -/- mouse (***A Birukova, Chicago***). Experimental endotoxinemia (LPS) in mice produces multiple organ dysfunction and sepsis. This condition is conserved by the immunomodulator DEHA associated with SOV (sodium orthovanadate) a phosphatase inhibitor (***D Pavlovic, Greifswald***).

Inflammation

In experimental colitis in mice, microvascular thromboses were related to IL6 (no effect in the IL6 -/- mouse). In the same model, thromboses associated with Ang II were related to lymphocyte activation. These experimental findings demonstrate the links between inflammation and thrombosis (***K Tyml, London***). In a mouse model of intestinal inflammation, activation of PARs (*protease-activated receptors*) produced the recruitment of leukocytes in a microvenule. Yet PARs are activated by many products, such as thrombin, trypsin, factors Xa and VIIa. In this model, the injection of protease inhibitors into the colon (elafin, *secretory leukocyte response*

inhibitor) reduced leukocyte recruitment (***M Majima, Sagamihara***). Lipoxins and eicosanoids produced in the cell are anti-inflammatory. Thus LXA4 binds to the G-coupled receptor Fpr2/ALX of the macrophages, and then the complex is internalized (PKC-dependent) by inducing phagocytosis of neutrophils undergoing apoptosis. This function is absent in Fpr2 -/- mice. Synthetic compounds analogous to some lipoxins may be used in therapeutic practice (***C Godson, Dublin***). Endothelial protection is also dependent on Notch 4. Under the effect of TNF, it is under-regulated, while Notch2 is over-regulated. This imbalance produces apoptosis of endothelial cells by the effect of survivin. Notch 2 *knockdown* mice escape this effect and have high levels of survivin (***B Charreau, Nantes***). Cultures of human endothelial cells subjected to LPS in the presence of CORM-3, a compound that delivers CO, were protected by CO with respect to oxygenated species, while CO produced a decrease in the expression of metalloprotein SOD-3 (membrane superoxide dismutase) (***S Mizuguchi, London***). In mice subjected to sepsis of the colon by dextran, the intestinal flora exacerbated the lesions, partly by high recruitment of leukocytes on the wall of intestinal microvessels, which does not occur in *germ-free* mice (***J Alexander, Shreveport***). The same authors observed in the same mouse model of colitis that inflammation worsened because of intense angiogenesis of microvessels, in particular related to high expression of VEGF-A. Introduction into the mouse of a VEGF-A inhibitor (adenovirus encoding rVEGF164b) significantly reduced this event.

The injection of LPS in mice produced leukocyte adhesion in glomeruli of the kidney, but also the release of angiopoietin II endothelial cell Weibel-Palade bodies, the basis of protection of renal function (absent in Ang II -/- mice) (***N F Kurniati, Groningen***).

Shock

In hemorrhagic shock, multiple organ failure occurs and is related to dissemination of pancreatic enzymes into the blood. These enzymes cleave the extracellular domain from the insulin receptor in the microvessels, thus creating insulin-resistance and hyperglycemia. This auto-digestion can be moderated by administration of protease inhibitors (***F Delano, La Jolla***). The role of auto-digestion was also found in a rat model where permeability of the intestinal mucosa was increased: the dissemination of pancreatic enzymes produced shock (***E Kistler, La Jolla***). After occlusion of the rat splanchnic artery, shock developed related to dissemination of chymotrypsin, elastase and trypsin through the endothelium by digestion of mucin and the extracellular domain of E-cadherin within a few minutes. These processes can be reduced by anti-enzymes (***M Chang, La Jolla***).

Ischemia-reperfusion

In the mouse intestine ischemia-reperfusion (I/R) model, leukocyte adhesion to the endothelium is the primary event. Adhesion occurs solely in post-capillary venules, but is promoted by failure of NO upstream, ie, in the arterioles. Once they are in the interstitium, the leukocytes promote migration and then degranulation of mast cells, which are responsible for generation of Ang II, which itself promotes

activity of NADPH oxidase, inactivating NO (and tests using ACh). Thus, I/R associates leukocyte migration and vasomotor dysfunction upstream (***R J Korthuis, Columbia***). In the mouse intestine I/R model, hematopoietic stem cells are recruited by microvessels of the mucosa under the influence of SDF-1 (***A Yemm, Birmingham***). The same process occurs in I/R n the mouse kidney: stem cells obey *homing factors* (including the hematopoietic markers CD18 and CD44) and accumulate in ischemic areas (***R White, Birmingham***).

In the mouse intestine I/R model, microthrombi form in villi, due to activated, adherent platelets (decrease in P-sel -/- mice). Platelet inhibition and administration of anti-P-selectin decrease leukocyte adhesion (***I Holyer, Birmingham***).

Therapeutic aspects were emphasized. I/R by occlusion of a coronary artery in the rat was moderated after administration of a Chinese traditional medicine preparation: the size of an infarction was decreased, and there was less action of MMPs and TGF and of CD68 macrophages (***X Wei, Beijing***). Other Chinese authors specify the use of a polyphenol, total salvianolic acid. In I/R of the rat mesenteric arteries, this product reduced the generation of oxygenated species and neutrophil activation (***Y Liu, Beijing***). The effects of I/R in the dog heart by ligation of the coronary artery were attenuated by the infusion of fructose-1-6 diphosphate, increasing the energy of glycolysis and decreasing free radical and cytokine production (***A Markov, Jackson***).

Neuronal lesions associated with I/R in the rat hippocampus were attenuated by a period of *preconditioning*, which acts by overregulation of UCP2 (*uncoupling protein*) a mitochondrial anti-oxidant or ghrelin, an activator of UCP2, which acts on eNOS (***Y Liu, Beijjing***). For the same anti-oxidative reasons, UCP2 reduces the accumulation of leukocytes in the microvenules of the rat cremaster muscle in I/R (***A Bougle, Paris***). The same authors showed that preconditioning prevents stress in the endoplasmic reticulum of myocardial cells in culture by inhibiting the CHOP pathway of apoptosis including the Bax/Bcl-2 ratio. Similarly, in I/R induced in the rat paw, preconditioning attenuated lesions and in particular apoptosis of muscle cells by expression of calreticulin, an endoplasmic reticulum protein that binds calcium.

Cancers, tumors and microvessels

Cell proliferation and apoptosis are major processes in oncology. Melatonin increases apoptosis of human umbilical cells in culture. It binds to MT1 and MT2 (*melatonin G-coupled receptors*) and to nuclear receptors producing activity of PKC-α, which in turn under-regulates the receptors (***P Cui, Beijing***).

Histology of hepatic metastases from colon cancer shows an increase in density of the microvessels, and therefore increased angiogenic activity. The localization of genes by qRT-PCR shows the presence in tissue adjacent to metastases of CD31 (PECAM) and HIF1 , which are members of the VEGF family (which have in common the HRE sequence (*hypoxia-responsive element*). Elevated levels of the RNA of Tie2 and a high Ang-2/Ang-1 ratio are noted. Therefore, the liver offers

metastases a "permissive" angiogenic environment, thus promoting their development (***G Van Der Wahl, Groningen***).

Endocan (or *ESM-1: endothelium-specific molecule*) appears to be an important new marker in oncology. It is expressed in excess in glioblastoma, lung cancer, angiosarcoma and liposarcoma. It is related to VEGF activity and can be assayed in the plasma by ELISA (***M Delehedde, Lille***).

Remodeling

Remodeling includes all changes in the arterial wall leading to plaque formation and weakening. It is based on differentiation and migration of LMC. Epoxy eicosatetraeonic acids (ETAs) moderate this process but are converted into less protective products by SEH (*soluble epoxide hydrolase*), which can be inhibited pharmacologically (***J D Imig, Milwaukee***). Diabetic pregnant female rats present defective remodeling of uterine arteries. This is due to a signaling defect in EDHF, which is improved by activation of IKCa channels (***N Gonika, Burlington***). In obese diabetic rats, with high amounts of AGEs, an increase in blood flow produces hypertrophy of arterial wall resistance related to oxidative stress and COX2 activity (***L Loufrani, Angers***). In experimental colitis in mice, the processes of angiogenesis are the basis for remodeling of microvessels of the colon mucosa, resulting in serious symptoms. In fact, this is due in large part to VEGF-A. Mice treated with an adenovirus coding for VEGF164b, the isoform that inhibits VEGF-A, present very attenuated symptoms of colitis produced by trinitrobenzene (TNBS) (***W Cromer, Shreveport*).**

Contrary to remodeling such as increased plaque size, remodeling of small arteries subjected to hypertension and/or reduction of blood flow consists of a reduction in their diameter. A mechanism of action is ROS-dependent activation of MMPs by the combined effect of norepinephrine and Ang II (***L A Martinez-Lemuz, Columbia***). This also depends on translocation in the membrane of LMCs of transglutaminase activity (***J Van Den Akker, Amsterdam***). Remodeling of uterine arteries can be triggered by intra-uterine stress: the injection of silicone (***G Osol, Burlington*)**. In the pulmonary circulation, the vasoactive peptide urotensin-II presides over remodeling through the F-box protein pathway: Fox 03 over-regulating MMP2. This function disappears in the Fox03a -/- mouse (***I Diebold, Munich***).

Remodeling of microvessels involves several steps and, in particular, reconstitution of their muscle wall. This function is due to PDGF BB supplied by bone marrow cells and not by the local endothelium, as demonstrated in irradiated mice and PDGF -/- (***L Glaw, Charlottesville***).

Microparticles and microvessels

Vesicles

Microparticles are membrane vesicles which detach from groups of cells and are able to enter the microcirculation because they are small. Those most investigated are from platelets and have a prothrombotic action. They are not uniform or uniformly distributed. Thus, the microparticles CD42b+ with hematopoietic value are found in diabetes and CD62P and CD63+ in coronary artery disease (***S Nomura, Osaka***). In human cerebral malaria and in experimental malaria in mice, levels of microparticles are elevated and their number is correlated with severity. In sepsis, microparticles are formed from monocytes that are carriers of signals of inflammation and activate the kinases ERK 1 and 2 in situ (***V Combes, Sydney***). In cerebral malaria, not only do the microparticles adhere to and activate the endothelium of cerebral microvessels, they also adhere to red blood cells infected by the parasite and to which they provide the platelet antigen CD41 (GP Iib IIIa), with the resultant increased adhesion of red blood cells to blood vessels (***G Grau, Camperdown***). In arterial hypertension, and in coronary artery disease, the microparticles produce various effects: coagulating by their phosphatidyl-serine content, a pro-apoptotic effect, but they participate in vascular renovation, an ambivalent effect (***C M Boulanger, Paris***). This was demonstrated in athymic mice (*athymic nude mice*) undergoing arterial occlusion: endothelial regeneration after elimination of ischemia was related to provision of *blood outgrowth endothelial cells* but accelerated by the addition of platelet microparticles (***S Mause, Aachen***).

Particles

Microparticles also come from inhaled airborne pollutants. Rats subjected to particles from diesel fuel by tracheal intubation present not only with local but also systemic disorders that are detectable in isolated muscle: arteriolar vasodilation, an increase in *shear stress*, and vasoconstriction upstream (***K Porter, Morgantown***). Under the same conditions, the same authors demonstrated in the rat that inhalation of TIO2 nanoparticles, derived from titanium and used in industrial applications, reduced the bioavailability of NO in microvessels in an isolated muscle and an increase in sensitivity of α-adrenergic receptors (***T Knuckles, Morgantown***). Nanoparticles (200 nm) can also be beneficial: biodegradable, they are captured by endothelial cells in culture (diabetic rat) and increase cofactor BH4 of eNOS (***C Meininger, Temple***).

Lifestyle, exercise and training

Intense physical exercise is harmful insofar as, under the effect of oxidative shock, the recruitment of capillaries does not occur. Nevertheless, it involves preconditioning that is protective for subsequent exercise (***T Gori, Siena***). In obese rats, where capillary muscle recruitment is lacking, exercise is beneficial and diminishes the expression in skeletal muscle of anti-angiogenic factors such as thrombospondin TSP-1 and increases the expression of VEGF-A (***P Forn, Toronto***).

Rehabilitation in the elderly in a specialized institution involves rheological improvement. Measurements recorded with a LORCA viscosimeter show improvement in deformability of red blood cells and a decrease in their tendency to aggregate (***K Filar-Mierzwa, Cracow***). In elderly rats, the observation of blood vessels in the brain (by confocal microscopy combined with laser application) shows the rarefaction of capillaries. This anomaly is correlated with an insufficient antioxidant potential (increased MDA). Subject to a program of swimming, these animals improved (***S Viboolvorakul, Bangkok***). In coronary arteries of old rats, a decrease was observed in AMP protein kinase, resulting in a decrease in contractile activity. This anomaly markedly improved with exercise (***J Muller-Delp, Gainesville***). All these events are found in elderly subjects: rarefaction of capillaries, alteration of cutaneous blood flow, and a poor response to hyperemia (***F G Lopez, Rio de Janeiro***). In the elderly, a decrease in cutaneous blood flow is observed in response to hyperthermia, which is due, independently of other vasomotor factors, to a decrease in the number of C sensory fibers in the skin (effect utilized in topically applied anesthetic creams). This process is attenuated by physical training (***J M Saxton, Sheffield***). In the same type of concept, compression of the sciatic nerve in rats altered the vasodilator effect of pressure on the corresponding limb (laser Doppler method), which can be attributed to lesions of C fibers (***J Pelletier, Lyon***).

In trained cyclists, vasomotor reactivity is high, as measured with the laser Doppler method. Such reactivity is attributed to the intervention of NO and PGI2, but also to independent events that persist after neutralization of these products (***H Lenasi, Ljubljana***).

CONCLUSION

This congress presented an update on novel findings obtained in sophisticated scientific experiments and models. Many therapeutic targets were mentioned, but are not described in detail in this report. Let us mention the effects of antioxidants, some of which are obtained from Chinese plants, the effect of irbesartan, which inhibits angiotensin II, of DEHA, of synthetic prostacyclins, and of sildenafil, which acts by iontophoresis in Raynaud's syndrome, and also acupuncture, which can act on eNOS associated with microvessels.

III

Shortcuts from the training session: "Introduction to effective medical writing"

September 23, 2010, Paris, France

Contents

Selecting a target journal

Françoise Pitsch
Servier International, Suresnes, France

There are many journals in the field of phlebology. Some are aimed primarily at vascular surgeons treating patients with arterial, venous, and lymphatic diseases; others deal more with basic research or focus on specific areas (thromboembolic diseases, investigations in venous diseases, etc.). Depending on the type of manuscript you intend to submit, select the journal carefully. Before submission, read the instructions for authors. Complete information for authors and editorial policies are available on journal web sites. Below is a non-exhaustive list of journals indicating their subject matter, impact factors, and Web site addresses.

Good luck with your submission.

Journal	Impact Factor 2009*	No. of issues /year	CATEGORY				
			General topics on venous diseases	Surgery oriented	Thrombo-embolic diseases	Basic sciences	Other
European Journal of Vascular and Endovascular Surgery **http://www.ejves.com**	2.919	12	+++	+++	+		Arterial & lymphatic disease
Journal of Vascular Surgery **www.jvascsurg.org**	3.517	12	+	+++			
Phlebology **http://phleb.rsmjournals.com**	1.548	4	+++				
International Angiology **http://www.minervamedica.it/en/journals/international-angiology/index.php**	1.155	6	++		++		
Thrombosis Research **www.thrombosisresearch.com**	2.406	12			+++	+	Hemostasis *Optional online-only publication*
Annals of Vascular Surgery **www.annalsofvascularsurgery.com**	1.169	8		++		++	
Journal of Thrombosis & Haemostasis **www.journalth.com**	6.069	12			+++	+	Bleeding disorders
Angiology **http://ang.sagepub.com**	1.097	6		+		++	Peripheral & cardiovascular disease
British Journal of Surgery **www.bjs.co.uk**	4.077	12		+++			Cardiovascular disease
Circulation **http://circ.ahajournals.org**	14.816	50				++	Peripheral & cardiovascular disease - Hematology
Circulation Research **http://circres.ahajournals.org/misc/stats.shtml**	9.214	24				++	Peripheral & cardiovascular disease - Hematology
Journal of the American Academy of Dermatology **http://www.eblue.org**	4.105	12					Dermatology
Journal des Maladies Vasculaires (French)	0.439	6	+		+	+	
Journal of Endovascular Therapy **http://jevtonline.org/**	2.902	6		+++			Peripheral endovascular intervention

Understanding impact factors

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The journal impact factor is widely used as a means to assess the impact of scientific journals, and is often interpreted as an index of quality. But how should it really be interpreted?

Journal impact factors are produced by the Journal Citation Reports from data published by the Science Citation Index (part of the ISI Web of Science®). The Science Citation Index includes more than 6500 journals, with 19 000 new articles added every week. It covers disciplines throughout the physical and life sciences. There are over 150 categories within medicine alone, including general medicine, peripheral vascular disease, and surgery. For each article in the database, the Science Citation Index produces citation data, ie, counts of the number of times the article subsequently appeared in the reference lists of other articles.

How is the impact factor calculated?

A journal's impact factor is the ratio of the total number of citations of articles published by the journal in the two previous years to the number of articles published in the same two years (**Figure 1**). The 2009 impact factors appeared in the summer of 2010. The highest impact factors in medicine are found for the general journals, such as the *New England Journal of Medicine*, *The Lancet*, and *JAMA* (**Table 1**).

Figure 1. Formula for the calculation of the 2009 impact factor (IF) of a journal.

$$\text{2009 IF} = \frac{\text{No. of 2009 citations of articles published in 2007 \& 2008}}{\text{No. of articles published in the journal in 2007 \& 2008}}$$

To simplify, the impact factor for 2009 could be regarded as the average number of citations an article published in the journal in 2007 or 2008 could expect to have in 2009. This means that an article with 15 citations or more per year in *Circulation* could be considered to have had a positive effect on the impact factor of the journal. This should be weighed against the observation that about 80% of the impact factor is determined by around a fifth of the articles in the journal.

Table 1. Selected impact factors from the Science Citation Index 2009.

2009 impact factors			
General medicine		**Peripheral vascular disease**	
New Engl J Med	47.05	*Circulation*	14.82
The Lancet	30.76	*J Thromb Haemos*	6.07
JAMA	28.90	*J Vasc Surg*	3.52
BMJ	13.66	*Eur J Vasc Endovasc Surg*	2.92
PLoS Med	13.05	*Thromb Res*	2.41
Annu Rev Med	9.94	*Phlebology (UK)*	1.55
		Ann Vasc Surg	1.17
		Int Angiol	1.16
		Angiology	1.10
		Phlebologie (Ger)	0.83

What affects the impact factor?

There are a number of features of journals that can affect impact factors, above and beyond the quality of the articles it contains (**Table 2**). Journals in the field of peripheral vascular disease are lower than in general medicine (**Table 1**), simply because the domain is smaller, and therefore there are fewer articles with fewer citations. Field is therefore fundamental to the magnitude of the impact factor: the larger the field, the higher the impact factor. A striking example of this is that a typical impact factor in fundamental life science is between 3 or 4, while in mathematics it is 0.4.[1] Clearly, this does not imply that the quality of research in fundamental life science is eight times better than that in mathematics. The difference is simply a question of the size of the field.

Similarly, journals publishing a large number of review articles have higher impact factors, since such articles are more frequently cited. On the other hand, journals that publish abstracts of presentations at conferences or proceedings, which are less well cited, can expect to have lower impact factors. Other factors that may affect journal impact factors include self-citation, which is unethical if it is done with the sole of aim of increasing the impact factor. Any major change in the journal, for example, a change in the journal title, an increase in the number of pages, articles, or issues, or publication of a special issue, may have a detrimental effect on the impact factor.

Perusal of the impact factors also highlights just how important it is to publish international studies in English. English-language journals systematically have higher impact factors. This is not to discourage publication in local or national society journals. Indexation in the Science Citation Index should be regarded as a positive feature of a local journal and it is vital to support such institutions. Publishing in the author's mother tongue can also improve information and continuing medical education in his or her country. On the other hand, results

from international trials or other international projects should always be published in English in international journals for wider dissemination of research.

Table 2. What affects the impact factors?

What increases the impact factor?	What decreases the impact factor?
• Quality of journal articles	• Field (eg, general medicine versus peripheral vascular disease)
• Authoritative review articles	• Brief reports, abstract books
• Self-citation (but unethical)	• Change in title of journal
	• Increasing the number of pages, number of issues, or number of articles
	• Supplements and special issues
	• Language

Who uses the impact factors?

Impact factors are used by authors to help select a journal for publications. They help publishers assess and market their journals, and also libraries manage acquisitions. Another potential application is the assessment of individual researchers, for instance, by counting the number of articles in high impact factor journals. This has been the source of considerable debate, and has led specialists in bibliometrics to design new indices to measure performance.

Is there an impact factor for people?

The Hirsch (h) index is a new index that can be calculated within the Science Citation Index. The h index is becoming a reference in the assessment of quality of individual scientists and researchers, much like the impact factor for journals. The h index considers the distribution of the number of citations of articles by a researcher. The general definition is as follows: the Hirsch index will be h if h of the researcher's papers had at least h citations each.[2] This can be understood through a couple of examples. First, consider a researcher with 10 articles published over 15 years and count the number of citations for each article (see example in **Figure 2**). If we then sort the list of articles according to the number of citations, then we see that 6 of the articles in our example have been cited 6 times or more. The h index of this fictitious researcher is therefore 6. On the other hand, if we consider a much more active researcher with 200 articles published over the last 15 years. If 50 of these 200 articles were cited 50 times or more, then this particular author would have an h index of 50.

Figure 2. The h index explained: if a researcher has 10 articles published over 15 years (left), and 6 of them have been cited 6 times or more (right), then his or her h index would be 6.

List sorted according to publication data	
	Number of cites
Paper 1	20
Paper 2	1
Paper 3	2
Paper 4	100
Paper 5	8
Paper 6	4
Paper 7	1
Paper 8	8
Paper 9	6
Paper 10	7

List sorted according to publication data	
	Number of cites
Paper 4	100
Paper 1	20
Paper 5	8
Paper 8	8
Paper 10	7
Paper 9	6
Paper 6	4
Paper 3	2
Paper 2	1
Paper 7	1

The advantage of the h index is that it is not affected by one paper with many citations, and thus constitutes a better measure of influence than simply counting citations or number of papers. Like the impact factors, h is field-specific, and will be affected by self-citation, authoritative review articles, and multiple author papers. It may deemphasize authors who have had one or two very influential articles, for instance, the researcher in **Figure 2** had one very highly cited article (100 citations) but a relatively low h index. Finally, a single number cannot give more than a rough estimate of an individual's profile, and the h index should always be interpreted alongside other knowledge of the individual.

Conclusion

The journal impact factors and the h index are widely regarded as good measures of quality in scientific research—they are certainly the only ones we have. However, they are undoubtedly influenced by a variety of factors beyond the quality of the research published in the scientific literature. This had led to much debate in recent years,[3] and to increasing efforts to find new complementary methods of evaluating journals and researchers. One option is the use of other databases, such as Google Scholar® or Scopus®, both of which provide the opportunity to count citations or the impact of an article. Bibliometric studies comparing the three databases indicated qualitatively and quantitatively different number of citations from the three databases.[4] For the time being, the impact factors should be used alongside knowledge of the journal, in terms of the studies it publishes and the quality of the editorial board, for the best selection of target journals for submission of manuscripts in science.

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3. The impact factor game. It is time to find a better way to assess the scientific literature. *PLoS Med*. 2006;3:707-708.
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Illustration matters

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Why use figures?

In a page of text the eye is drawn to those things that stand out—first to the titles in bold text, and then to the illustrations, which make the page more interesting, and therefore easier to read. They serve a useful purpose in presenting data in a way that is easily understandable, and in giving information an importance that would be lost in the body of the text.

Before you start to create your illustration you need to decide why? What information do you want to present? Do you need a table or a figure? What shape will it fill in the article—a portrait shape in one column or a landscape format over two or more columns? You need to think about this before submission, as afterwards it will be too late—the editor will have full control.

What tools should you use? Of course this depends on what you have available and what you feel at ease with—PowerPoint is good for drawing shapes, Excel is a good choice for data, Word is a clumsy tool for illustration. There are also professional software packages such as CorelDraw and Illustrator. All these programs can be used to cut, resize, and post illustrations into Word (embedded such that they cannot be edited by someone else).

When creating your illustration, try to avoid common mistakes concerning the following subjects:

Typeface choice

Among four basic different typefaces, there exist sans serif types such as Arial or Helvetica (a clear no-nonsense font good for titles and captions); serif typefaces such as Times or Century (classic typefaces that are easy to read and good for body copy, and also numerals, as there is less likelihood of a number one being mistaken for a lower-case "l").
Typewriter faces and scripts are not good choices as they are inappropriate and look unprofessional.
Use only one typeface and use different weights and styles (bold and italic) for emphasis.

Letter sizing

Often too small or too big—test the size of your text by simply resizing it to the final format and printing it out to see how it reads. Keep your letter sizing consistent from figure to figure. For example, use 10-point text for the titles, 8-point for the body text. Use the variations in weight and style logically, important information in bold type, but don't go wild.

Scale

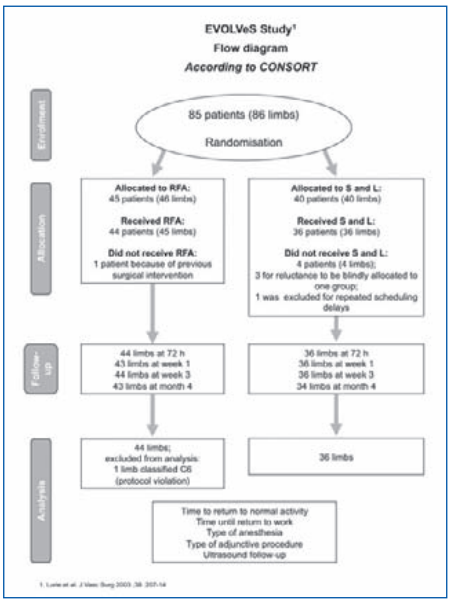
Try and create all your figures the same size, so that when they are resized for print there will be no unpleasant surprises. Ensure that the text is readable and that there are no glaring variations in type size.

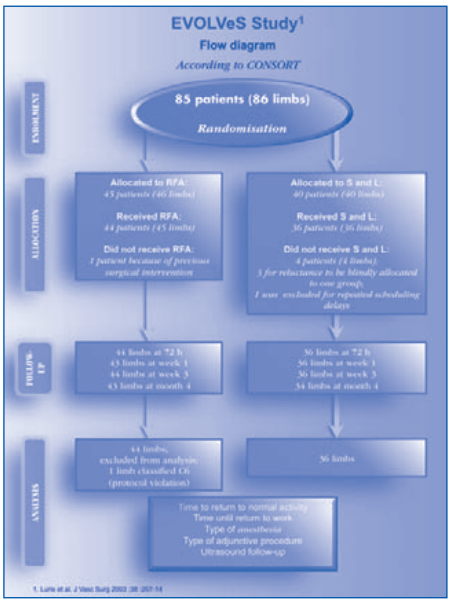
Color

Think twice before you use color—you need first of all to know if the journal for which your article is intended accepts color (it might simply print in black and white) and if it does will it charge you for the extra costs incurred? When using color photos, will they reproduce in monochrome?

Where possible, use shades of gray and the contrast of black and white to make your illustrations both interesting and easy to reproduce. Another point to consider is that if you create your illustrations in color (or use color photos) the journal might simply print them in black and white, and you will have no control over the final result.

Does the journal for which your article is intended simply print in black and white? Or does it accept color? And if it does will it charge you for the extra costs incurred?

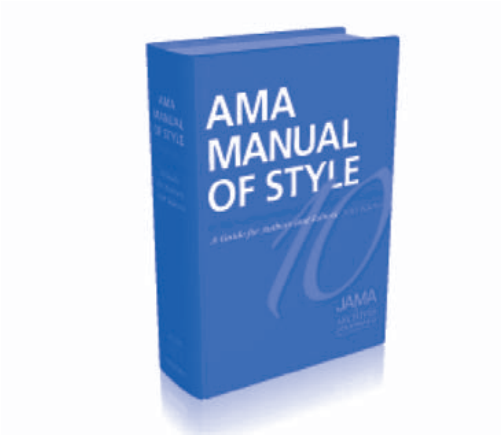




Spelling

Use the spell-checker. It helps you to correct mistakes as they happen, and to check the final result—nothing is so unprofessional as a spelling mistake.

Finally, whatever your choices, keep everything uniform. Create your figures in the same style, using the same typefaces in the same styles and weights, at the same size, so that they can all be resized by the same amount. Ensure that the axes on your graphs are always in the same position; ensure continuity with your figures by, for example, using "X" for drug and "P" for placebo in each figure.

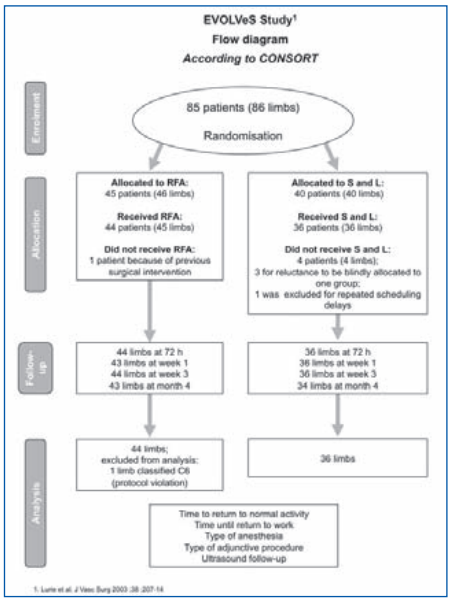


If in doubt, refer to the American Medical Association Manual of Style for the best way to create graphs, flowcharts, and tables.

Illustrations work better when in each case the information has been clearly structured with the eye being drawn through from the start to the end in a logical flow; black and white and gray provide both contrast and emphasis where needed and are easy to reproduce; type sizes, styles, and weights are kept to the minimum consistent with ease of understanding.

Illustration matters because the figures you use in your articles are the key to the presentation of your results. They should be one of the first choices you make when you start your article as the results you choose to illustrate have an effect on the structure of your article.

Which figure works best? The left one or the right one?



In short, good figures mean clearer presentation of key results which means a better chance of article acceptance.

Hell is other people

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We've all felt this from time to time. Some of you may even be thinking it right now. But why, you may wonder, in an article on editing, have I used this quote (from the play "No Exit" by Jean-Paul Sartre)? Because it allows us to segue smoothly into the arcane world of the editor. Yes, that nameless individual empowered to fashion a readable article from your decent/passable/imperfect/abysmal (delete as applicable) prose. Why, you may be wondering, should you care about this faceless person behind a desk along some dimly lit corridor? Two reasons. First, because the editor is to be respected and looked up to. Stephen King said it best: "To write is human, to edit is divine." Second, and here we revert to the commonplace concerns of everyday life, because the editor has the power to send you scurrying back to your computer to rewrite your manuscript. Again. And again.

So you would be well advised to put yourself in the editor's shoes, to try to understand the work of editing a manuscript. What is the editor thinking over that first coffee of the day, as your manuscript arrives on the desk? I would suggest it may be something along the lines of "Hell is other people's prose."

The moral then of this story is: Don't make the editor's life hell. That way you increase your chances of publication. So, how can you make the editor happy? The answer, surprisingly, has been around for 2500 years, albeit in a different guise: the Buddha's Noble Eightfold Path to Enlightenment. Or at least to a better manuscript.

What is the first step on this eightfold path? Avoid wordiness. An editor's life is too short to wade through pages of turgid prose. Be concise. After all, as Shakespeare wrote (Hamlet, Act 2, Scene 2), "Brevity is the soul of wit." Here's an example. An inspiration in fact—Victor Hugo. It may seem perverse to turn to this 19th century French writer as a model of brevity. After all, didn't he rack up 500 pages in *Notre-Dame de Paris* (*The Hunchback of Notre-Dame*) and a staggering 1200 in *Les Misérables*? So how can we speak of conciseness and Victor Hugo in the same breath? Bear with me. It all comes down to sales (doesn't everything?). Book sales, that is. When *Les Misérables* came out in 1862, Hugo was fretting about his readership and telegraphed the publishers. What did he write? Perhaps it was, "I was wondering how the book sales are going" (albeit in French, of course). Or, "Are my readers doing me proud and buying up all available copies of *Les Misérables*?" Neither actually—too wordy. Instead he graced his telegram with "?". Yes, that's right, "?". His publishers promptly telegraphed back "!". Their meaning was clear.

The second step on the noble eightfold path is: Avoid laziness. But, I hear you protest, *Cessare humanum est* (To idle is human). That may well be, but don't try the editor's patience. Here's a common example: "Uncontrolled hypertensive

patients." What, in fact, does this mean? Does "uncontrolled" apply to hypertension or to the patients? Normally the editor will change this to "Patients with uncontrolled hypertension." On a bad day, though, the editor may well be tempted to write "Psychotics."

Step three on the noble eightfold path is: Avoid redundancy. Less is more. The minimalist's maxim. Or to paraphrase the engineer and inventor Buckminster Fuller (he of the geodesic dome): "Do more with less." Here's an example. "An early effect was soon observed after 2-3 weeks." I think we can agree that "early" and "soon" add nothing.

Avoid bias. Step four on the noble eightfold path. Naturally you wish to convince skeptics that your work is not only publishable, but worthy, important even. Egged on by a little voice in your head urging you to put everything into it, you may be tempted to use tendentious words and phrases to put an unjustified slant on what is written. Such as "The vast majority of" (All? Almost all? More than half?); "It is generally believed" (By whom?); "Interestingly" (Who says so?)… You get the idea.

The fifth step on the noble eightfold path is: Avoid imprecision. A common example will illustrate the problem: "The physical examination was abnormal." An examination is not in itself abnormal or normal (or positive or negative). What is actually meant is: "The examination findings were abnormal."

We are nearing enlightenment now, as we come to step six: Avoid abbreviations. Minimize them. They reduce readability. And if they (or acronyms) are necessary, expand them on first use, and don't make up your own. Remember too that it's pointless to define an abbreviation and then use it only two or three times in a 15-page article.

Step seven on the noble eightfold path is: Avoid inconsistency. This is self-explanatory. Decide which spelling—British or American—is appropriate, and, if the journal doesn't specify, choose one and stick with it. Use standard medical terms and don't vary them in vain pursuit of some sort of literary "style." Keep it simple, Stupid!

And here we are, finally, at enlightenment. At the eighth and last step on the noble eightfold path to a better manuscript. Avoid anarchy. Organize your manuscript. Format in the journal's style. Do they want a structured abstract or not? What's their policy on abbreviations? Do they use the Vancouver style for references? And if you feel yourself above such trivia, prepare for disappointment. And the return of your manuscript.

Have your manuscript checked by a native English speaker (preferably one with medical or scientific training). And if despite your best efforts the manuscript is rejected, don't despair. You are in good company. Here's a nonexhaustive list of scientists whose papers were initially turned down: Enrico Fermi (beta decay) 1938 Nobel Prize in Physics; Hans Krebs (Krebs cycle) 1953 Nobel Prize in Physiology or Medicine; Pavel Cherenkov (Cherenkov radiation) 1958 Nobel

Prize in Physics; Arthur Kornberg (DNA synthesis) 1959 Nobel Prize in Physiology or Medicine; Rosalind Yalow (radioimmunoassay) 1977 Nobel Prize in Physiology or Medicine; Sidney Altman (catalytic properties of RNA) 1989 Nobel Prize in Chemistry. They didn't give up—they sent their work to other journals. In one survey, 85% of manuscripts rejected by *Journal of Clinical Investigation* were subsequently published elsewhere.

What then is the take-home message? It's this: Write, rewrite, revise, all the while using what Ernest Hemingway considered the most valuable of writing aids—"a built-in, shock-proof shit detector." Do you have one?

Disclosure of potential conflicts of interest & transfer of copyright

Brigitte Oget-Chevret
Servier International, Suresnes, France

When you submit a manuscript , you will be asked to do two things that interest us here. One, give the publisher a list of your relationships with industry, thereby disclosing potential sources of conflict of interest relevant to the article submitted, and, two, once your article is accepted for publication, sign an agreement transferring copyright to the publisher.

Disclosure of potential conflict of interest

This is all about transparency and ethics. It has become common practice and, for years now, has been part of good publishing practices applied by all biomedical journals.

The ICMJE (International Committee of Medical Journal Editors) gives the following definition: "*a conflict of interest exists when an author (or author's institution), reviewer, or editor has financial or personal relationships that inappropriately influence (bias) his or her actions…*".[1]

All manuscripts are subject to disclosure of potential conflict of interest: *editorials, letters, clinical cases, research or study manuscripts, review articles, articles in supplements*, etc, and every signatory to the article has to provide to the publisher his/her own conflict of interest disclosure. Most journals will require it as part of the submission package.

What kind of information should be disclosed?

Financial ties are the most easily identifiable form of potential conflict of interest, and most journals will focus on this aspect of any relationships the authors may have with commercial entities. Clearly then all direct financial support from a commercial entity for the writing of the manuscript or for the study or for both will have to be disclosed in the manuscript. The reference period of time is the lifespan of the work/study reported. All indirect financial support, over the 3 years preceding submission, such as *stock ownership, consultancies, paid travel expenses, board membership, honoraria*, etc, as well as all financial support to the author's institution should also be listed. In brief, authors are expected to disclose all relationships with commercial entities that may have a direct or indirect interest in the submitted work.

You may also want to disclose any personal relationships, particular ideology, or other information relevant to the article submitted that you think might be of interest to the Editor-in-Chief, peer reviewers, or, the readers, to help them understand the environment in which you wrote your article.

And if you are unsure whether or not you should declare something, err on the safe side and do so. You may think that something is not worth disclosing, but the Editor-in-Chief or peer reviewers or readers may think differently. Ultimately, the Editor-in-Chief will decide which of your disclosures to publish.

How should the disclosure be made?

Refer to the "authors" section of the journal's Web site and follow the instructions. Each journal has its own policy when it comes to disclosing potential conflict of interest. Nevertheless, there are basically two options: either include a conflict of interest notification page in the manuscript itself, or use the standardized disclosure form which you can download from the ICMJE Web site,[2] save on your computer and easily update for each new submission.

What happens if you forget to declare something?

It depends on when it happens, who realizes, and the degree of importance of the oversight. Before publication, there is always time to add the missing information. After publication, it may be a bit more complicated. A simple addendum in the next issue may suffice, but the publisher may decide to remove your article from its databases and even to go public. There are many well-publicized examples of undisclosed potential or real conflicts of interest revealed after publication of an article. Such situations can discredit you as an author, your work, the journal, and science itself.

Not only authors are concerned by conflict of interest disclosure. Editors-in-Chief and peer reviewers too are expected to make their own conflict of interest disclosures if, when receiving a manuscript or being asked to be a reviewer, they find themselves in a potential conflict of interest situation and therefore should not be involved in the assessment or review of the manuscript.

We all know that industry funding is very important in helping you advance medical knowledge and research. To maximize the impact of your work and publications, clear disclosure of potential conflicts of interest is vital. Transparency will prevent ambiguity and give increased validity and weight to your ideas and discoveries.

Copyright

With copyright, we are on legal ground. There are rules and regulations.

When it comes to copyright for literary and artistic works (writing an article for a biomedical journal falls into this category), the reference is the Berne Convention,[3] dated 1886 and signed so far by 164 countries. This convention was designed to ensure international protection for creations for at least 50 years after the author's death, and is automatic as soon as the creation exists in a physical medium.

The moral right and exploitation rights

The moral and exploitation rights are the two aspects of copyright. They offer recognition and economic reward to the author. When it comes to publishing, it is common practice for the author to transfer the exploitation rights (*the right to represent, reproduce, distribute, translate, and create derivative works from the work*) to the publisher, by signing a transfer of copyright agreement. Once you sign this document, the article no longer belongs to you but rather to the publisher, who becomes the "original publisher".

Standard copyright agreements

Most print journals use copyright agreements that generally limit the author's re-use of his/her work (in full or in part), without the publisher's permission, to mainly *personal or educational use, classroom use, posting of a Word-processed version of the article on the author's personal or institutional Web site*.

But things are changing and more and more print journals use **licenses** *(the author no longer transfers copyright to the publisher, but retains ownership of copyright and grants an exclusive license to the publisher to exploit the work and to represent him/her in consultation with third parties)*. Creative Commons *Attribution* Licenses, already used for years by many online and open-access journals, are more flexible and offer more possibilities to the author to re-use his/her work.
In this matter too, each publisher/journal has its own copyright policy,[4] and you have to comply with it. Carefully read the document you sign to know what you can and cannot do.

Should you wish to use someone else's published work, some on-line open-access journals like those published by BioMed Central[5] and PLoS (Public Library of Science)[6] provide, under license and certain conditions, free use of the articles. But in most cases you will have to seek written permission from the original publisher to re-use published material.

In all cases, keep in mind that you should always respect the integrity of the work, give proper credit to the author(s) and to the original publisher, otherwise you risk committing plagiarism or even self-plagiarism. The best way to avoid that is to cite the work fully *(author(s), title, journal, full publication references, publisher)*.

What about the Internet?

When it comes to using material you find on the Internet (text, graph, figure, table, picture, drawing, etc) that is "just exactly what you need", remember that every single thing posted on the Web belongs to someone, somewhere, so, unless otherwise clearly specified in a disclaimer or a "permission" or "copyright" section on the Web site, you must seek permission to use it from the owner of the material.

Last but not least, let's get back to two elementary rules before submission: make sure that you have the authorization to submit from your co-authors and full authority to submit, and that your article is original and was not the object of a previous transfer of copyright.

References

1. www.icmje.org.Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest, www.icmje.org/ethical_4conflicts.html
2. Download this form from www.icmje.org/coi_disclosure.pdf
3. The Berne Convention is administered by the World Intellectual Property Organization. www.wipo.int, www.wipo.int/treaties/en/ip/berne/trtdocs_wo001.html
4. Check www.sherpa.ac.uk/romeo/ This Web site provides a summary of permissions that are normally given as part of each publisher's copyright transfer agreement. Go to the "Browse" section and select "all publishers".
5. www.biomedcentral.com/info/authors/license
6. www.plos.org/journals/, www.plos.org/oa/index.php, www.plos.org/oa/definition.php

Optimize your use of Google and PubMed

Sébastien Cros
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Finding relevant data is a key step before starting to write any scientific article. The Internet can be an incredibly rich source of information if you know how to refine your queries in search engines such as Google for general information and PubMed for scientific publications.

Google: tips and tricks

In France, nine out of ten people seeking information on the Internet use Google as a search engine. More than a minimalist search field and two main buttons, Google offers a large range of useful services that most users are unaware of.
For instance, Google can be used as a powerful calculator (enter the calculation in the search box and click on the search button). Google can also be used to convert different units of measurement, such as height, weight, and volume: see http://www.google.com/help/features.html.The language tools available on the Google homepage can help you to translate any text into more than 130 different languages. The "Translate a web page" function helps you to translate a full Web site into your own language, so that you can browse it without losing its initial layout. Go to http://www.google.com/language_tools?hl=en to read more about these features.
You can also use Google to search within a specific Web site you are interested in. Type "site:www.yourwebsite.com" in the search window to look for information within this Web site only. Or you can also use Google to search for terms used in a specific file type. For instance, if you are looking for a PowerPoint® presentation on venous disease, simply type in "filetype:ppt venous disease". This trick works with the main file types, such as .doc, .txt, .xls, .jpg, and .ods.
Google News is a computer-generated news site that aggregates headlines from the main news sources worldwide. You can sort the news by date, relevance, or topic: visit Google News and search for "venous insufficiency" to find the most recent news about this subject. To receive regular automatic updates from Google News on this topic, you can create an e-mail alert by using the Google Alerts service, available at the following address: http://www.google.com/alerts

Use PubMed to find relevant publications

PubMed is a service of the US National Library of Medicine which includes more than 20 million scientific publications. You can use PubMed as a traditional search engine to find references of interest: complex queries can be made by using the Boolean operators AND, OR, NOT, brackets, and parentheses in order to refine your search and select relevant publications in the Medline database.
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daflon® 500mg

Micronized purified flavonoid fraction

A unique action at the core of chronic venous disease

No.1

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Grade A Recommendation[1,2]

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

Les Laboratoires Servier - France. - Correspondent: **Servier International** - 35, rue de Verdun - 92284 Suresnes Cedex - France. Website: www.servier.com

Daflon 500 mg (MPFF) is also registered under various trade names, including: Detralex, Arvenum 500, Elatec, Alvenor, Ardium, Capiven, Variton

1 - Ramelet AA, *Clin Hemorheol Microcir.* 2005;33:309-319. **2** - Nicolaides A, *Int Ang.* 2008;27:1-60.

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