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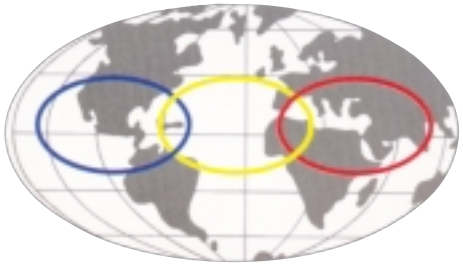

21st World Congress of the International Union of Angiology

May 22-26, 2004 - Rome, Italy

AIMS AND SCOPE

Phlebolymphology is an international scientific journal entirely devoted to venous disease.

The aim of *Phlebolymphology* is to provide doctors with updated and interesting information on phlebology and lymphology written by well-known specialists from different countries worldwide.

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, was included in the EMBASE database in 1998.

Phlebolymphology is made up of several sections: editorial, articles on phlebology and lymphology, news, review, and congress calendar.

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EDITORIAL

The 21st World Congress of the International Union of Angiology was held in Rome, from May 21 to 26, 2004. This Congress is always a major opportunity for an overview of current scientific progress in this field. The international participation featured over 200 world experts in the fields of vascular medicine and biology, interventional radiology, cardiology, vascular, and endovascular surgery.

During daily lectures, world-renowned invited speakers, who are recognized for their significant contribution to research or clinical investigations in the field of venous diseases, reflected on their work and its repercussions. Talks by these renowned specialists alternated with plenary sessions, which covered the many facets of arterial, venous, and lymphatic diseases.

In order to promote the work of a wide range of speakers and young scientists, the best abstracts on each topic were selected for free communications or poster sessions. In addition, several prizes were granted for oral presentations and articles (eg, the IASACO Prize and the IUA Prize).

Unfortunately, it was only possible for the participants to attend a small number of the presentations. Therefore, the Medical Reporters Academy, a team of medical reporters organized by Servier International and chaired by Prof Nicolaides, has collected as much information as possible on the many presentations, not only for those who were present at the Congress in Rome, but also for those who were unable to attend. These articles are presented in this issue, and we hope that you will enjoy reading them.

The Medical Reporter'Academy team

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BENEDICTVS XIV

Part 1

PREVENTION OF VASCULAR DISEASES

EXPANDING ROLE OF THROMBOPROPHYLAXIS: BENEFITING THE MEDICAL PATIENT

Chairpersons: A. K. KAKKAR (UK), S. NOVO (Italy)

Venous thromboembolism in medical patients: burden of the disease

W. AGENO (Italy)

The incidence of venous thromboembolism (VTE) in the USA is 117/100000. There are 107 000 new cases of deep venous thrombosis per year. More than 70% of pulmonary emboli are diagnosed at autopsy, and approximately 80% of DVT cases are clinically asymptomatic. Epidemiological data have shown that the risk of VTE in medical patients is comparable to the risk in surgical patients. The incidence of VTE in patients with ischemic stroke is 11% to 75%, in patients with myocardial infarction 17% to 34%, and in the intensive care 25% to 42%. The risk factors for the development of deep venous thrombosis are determined both by the patients' characteristics and by the clinical settings, and also by the fact that there is still a low rate of patients receiving prophylaxis. According to Aujesky and Rahim, the rates amount to 22% to 33%. The reasons for underuse of thromboprophylaxis are: lack of awareness of the guidelines, lack of outcome expectancy, concern about bleeding, and difficulty in defining medical patients at risk. To improve patient selection, individual risk assessment and clinical decision support tools should be used. The Medenox study has shown that the most important risk factors for venous thromboembolism are: chronic respiratory failure, age over 75 years, chronic heart failure, obesity, varicose veins, cancer, history of VTE, and hormone therapy.

The authors concluded that the medical inpatients can be at substantial risk for venous thromboembolism, and they should be assessed for risk of venous thromboembolism based on the acute clinical condition and on the concomitant presence of predisposing risk factors.

State-of-the-art thromboprophylaxis in medical patients

D. IMBERTI (Italy)

Venous thromboembolism is a common, potentially life-threatening complication in acutely ill medical patients. In the absence of thromboprophylaxis, the risk of deep venous thromboembolism ranges from 5% to 26%. The risk of DVT in patients with spinal cord injury range from 5% to 100%. A recent survey (Baglin et al 1997) reported that without prophylaxis, up to 1 in 20 hospitalized medical patients with multiple clinical problems develops fatal pulmonary embolism. There are several methods of DVT prophylaxis in medical patients: unfractionated heparin, low-molecular-weight heparins, new antithrombotics, oral anticoagulants, antiplatelet therapy, mechanical compression, and early ambulation. Several trials and meta-analyses have clearly demonstrated the prophylactic beneficial role of UFH and LMWHs with a significant 50% reduction of VTE. Two important double-blind randomized placebo-controlled clinical trials validated the use of LMWHs in the medical patients. In the Medenox Study prophylaxis with enoxiparine 40 mg once daily for 6 to 14 days reduced the risk of VTE by 63%. This was achieved without a significant increase in adverse events such as hemorrhage or thrombocytopenia. Patients immobilized with severe cardiopulmonary, infectious, or rheumatic disease are at significant risk of VTE. In the Prevent Study (still unpublished) the administration of dalteparin 5000 UI daily subcutaneously was associated with a risk reduction of VTE of 45% in acutely ill patients with a low risk of bleeding.

The authors mentioned new antithrombotics: ximelagatran, an oral direct thrombin inhibitor but currently not evaluated in medical patients, and fondaparinux, an indirect (AT III-dependent) anti-factor Xa inhibitor that is in one trial being used in medical patients (Artemis study).

Optimizing management of the medical patient in the future

C. CIMMINIELLO (Italy)

In venous thromboembolism (VTE) prophylaxis in medical patients there are still unresolved issues:

1. Patient selection: identifying those who benefit most from thromboprophylaxis
2. Dosing of heparins
3. Duration of treatment

It is still difficult for clinicians to assess which medical patients should be given thromboprophylaxis. The risk assessment model (RAM) does not exist for medical patients. Data from the Medenox study has enabled us to identify patients at a very high risk of VTE who benefit most from thromboprophylaxis, such as elderly people or patients suffering from congestive heart failure in the worst functional class.

Also, as mentioned above, the dosing of heparins is a matter of controversy. The Prevent and Artemis Studies have demonstrated that high prophylactic doses of dalteparin or fondaparinux reduced the burden of VTE risk but there are still topical issues:

- do we have to use high prophylactic doses (eg, dalteparin 5000UI and fondaparinux 2.5 mg) also in the common practice for the low-risk patients?
- are lower dosages possibly ineffective?

The optimal duration of thromboprophylaxis in medical patients remains an unresolved issue. Several studies underline the fact that the risk of VTE of medical patients is likely to be sustained as in high-risk surgery where a prolonged prophylaxis with low-molecular weight heparins has proven to be benefit. The ongoing Exclaim study (Extended Clinical Prophylaxis with Enoxaparin in Acutely Ill Medical Patients) with 5800 medical patients at 450 sites worldwide may determine whether a 4-week course of 40 mg enoxaparin would be better than the current practice of 1 week to 10 days of enoxaparin administration.

UPDATE ON THE PREVENTION OF VENOUS THROMBOEMBOLISM

Chairpersons: J. FAREED (USA) A. NICOLAIDES (Cyprus)

Pentasaccharides and melagatran

D. BERGQVIST (Sweden)

Heparin is effective in reducing the incidence of deep vein thromboses (DVT) in elective hip surgery and many other situations.

If we have to propose a new drug to take the place of heparin, it should be better, safer, cost-effective, and if possible oral.

Since the clinical use of unfractionated heparin (UH), many new drugs have been synthesized, with more specific action. Many low-molecular-weight heparins (LMWH) that are more effective than UH in some situations are now in use, and they show no clinically relevant differences.

Among the new synthesized pentasaccharides, fondaparinux, melagatran, and, ximelagatran are now in clinical use. They have been compared in various settings with placebo, LMWH, and oral anticoagulants. In general they have proved themselves to be at least as effective as LMWH.

Venous thromboembolism in patients with cancer

A. K. KAKKAR (UK)

It is a well-known fact that venous thromboembolism (VTE) is much more frequent in cancer patients. Cancer patients who are surgical candidates may benefit from prophylactic therapy. Randomized, well-conducted studies have shown that low doses of unfractioned heparin and LMWH give very similar results, stand shoulder to shoulder, and can both be used for prophylaxis.

Prolonging prophylaxis for 4 weeks after operation offers a significant reduction of VTE when compared with 1-week therapy. A different subgroup of patients is acutely ill patients that are not surgical candidates, and in this group of high-risk patients LMWH seems to be the best option, and greatly reduces the frequency of DVT. One study has shown that low-dose warfarin can reduce the number of VTE episodes in cancer patients on palliative therapy.

The use of central venous catheters (CVC) is widespread in cancer patients, and these devices have been shown to be associated with in situ thrombosis in a high number of cases. Warfarin or LMWH can reduce the number of these episodes.

However, quite recently the improvement of the CVC material and construction, together with better catheter care, has much reduced the number of thromboses, and at the moment we are not sure if prophylactic therapy is warranted in cancer patients with CVC, and if so, what type of treatment should be used. There have been some reports that therapy with LMWH can improve the overall mortality of cancer patients, as well as reduce the number of VTE. To assess this survival benefit, a number of studies such as CLOT, SCLC, and MALT have been conducted.

Although there is a benefit for the general population, this is maximal mainly in the patients with a better prognosis.

Extended prophylaxis

O. DAHL (Norway)

That patients undergoing major orthopaedic surgery are at an increased risk of developing deep vein thrombosis (DVT) is a well-known fact, and prophylaxis is commonly used, but it is less clear for how long these patients have an increased risk of developing thrombosis.

In total hip replacement (THR) giving prophylaxis for 1 to 2 weeks and then continuing prophylaxis for 3 to 4 weeks reduced DVT by half, when compared with a group of patients treated with placebo during the second period.

A metanalysis showed that in such an approach the number needed to treat (NNT) is 45, which means that we have to treat 45 patients to avoid one DVT, with a number needed to harm (NNH) of 862, which means that we will have one bleeding in 862 patients treated, with a gain times 40, which is a really good result.

On the contrary, data on total knee replacement (TKR) has failed to show a similar gain for extended prophylaxis for this subgroup of patients.

Hip fracture, an increasingly frequent disease with the growing elderly population, impairs venous function for a very long period of time, up to 6 weeks or more, and so benefits from long-term prophylaxis.

Treatment at home

H. PARTSCH (Austria)

Home treatment of venous thromboembolism (VTE) has been made possible by the introduction of low-molecular-weight heparins (LMWHs), which are safe and effective like unfractionated heparins (UH) but much simpler to use and without the need for specific laboratory monitoring.

This treatment can be offered to about 80% of deep vein thrombosis (DVT) patients, while about 20% still need to be hospitalized for medical or social reasons.

Of course the patients must be investigated for the presence of occult cancer, which can be found in up to 7% of patients with proximal DVT.

Patient with suspected recurrent DVT or pulmonary embolism (PE) should stay in the hospital.

Even hospitalized patients should be mobilized as soon as possible.

One of the advantages of home therapy is the fact that at home the patient is much more free to move around, which actually helps clot lysis and prevent thrombus extension.

Duration of anticoagulant therapy

R. HULL (Canada)

On anticoagulant therapy for deep vein thrombosis (DVT) one issue has been resolved: the INR in these patients must be maintained between 2.0 and 3.0, to give the best benefits. This regimen must be maintained for at least 3 months in patients with transient risk factors, like accidents

In cancer patients with DVT, LMWH should be administered for 3 to 6 months.

Patients with thrombophilic states should be treated 6 to 12 months, or indefinitely, like the patients with idiopathic VTE, also, if there are recurrent episodes, patients should be treated for life with an annual review.

It is most important to listen to the patient, to talk to him or her, and to involve him or her in therapeutic decisions, to the degree that he feels is right for him or her.

ASA IN THE PREVENTION OF CARDIOVASCULAR DISEASES

The rationale for using aspirin in metabolic syndromes

G. DAVI. A. FALCO (Italy)

The biosynthesis of thromboxane A_2 is associated with several cardiovascular risk factors. Thromboxane-dependent platelet activity represents the mechanism that amplifies the consequences of vascular acute occlusions and other longstanding metabolic disturbances. Aspirin reduces the level of thromboxane A_2 diminishing the risk of metabolic disorders. The authors have demonstrated the reduction of thromboxane levels in patients with type 2 diabetic mellitus who take aspirin. The authors have demonstrated the reduction of thromboxane-dependent platelet activation in patients with hypercholesterolemia who are having the same treatment. The AHA has recommended the prescription of aspirin in several metabolic syndromes such as abdominal obesity, atherogenic dyslipemia, elevated blood pressure, insulin resistance, and glucose intolerance. The authors support the recommendation for aspirin in healthy women with android obesity, and suggest that low-dose aspirin may be an option in subjects who fail to lose weight. In conclusion, low-dose aspirin represents the best primary and secondary prevention strategy in metabolic syndromes characterized by high cardiovascular risk.

Meta-analysis of randomized trials of aspirin versus control in low-risk populations

C. BAIGENT (UK)

The authors presented a meta-analysis of primary and secondary prevention trials of aspirin versus control for vascular events. This meta-analysis included 55 580 patients. The principal results of this work are the primary prevention is effective for vascular events and principally for cardiac events. Secondary prevention is not effective for the prevention of ischemic stroke and vascular death.

The authors recommend primary prevention with low doses of aspirin for patients at high risk of vascular events. In this group of patients thedecrease in vascular events is 10 times greater than in the patients with no preventative treatment. If the patients have a moderate risk of CHD events it is necessary to evaluate the risk of hemorrhagic bleeding. If the risk of bleeding is low, they must take long-term aspirin therapy. The patients with moderate cardiovascular risk and high risk of bleeding and the patients with low cardiovascular risk for ischemic events do not need primary prevention with aspirin.

Aspirin resistance

C. PATRONO (Italy)

The doses normally used in all international guidelines represents a 3- to 10- fold excess over the minimum amount of the drug necessary and sufficient to fully inactivate platelet COX-1. There exists an aspirin resistance whose origin is not clear but whose incidence is very low. The European Society of Cardiology Task Force on Antiplatelet Agents and The American College of Chest Physicians Consensus Conference on Antithrombotic Therapy recommend that no test of platelet function be performed to assess the antiplatelet effect of aspirin in the individual patient. Like the other treatments to prevent artherothrombosis, antithrombotic, lipid-lowering, or antihypertensive agents, failure can occur with aspirin, but there is no scientific basis to change therapy in the case of a treatment failure. The author maintains that there is no controlled evidence that changing therapy is a more effective strategy than maintaining an evidence-based therapy. The real incidence and the importance of aspirin resistance must be evaluated with new studies. This studies must include a sufficient number of patients to correctly evaluate the sensitivity and specificity of aspirin resistance, which until now no published studies have done.

Determinants of the risk of upper gastrointestinal bleeding complications

L. A. GARCIA RODRIGUEZ (Spain)

The author describes the incidence of upper gastrointestinal bleeding complications in patients with treatment with nonaspirin, nonsteroidal antinflamatory drugs (NA-NSAIDs) and in patients in treatment with aspirin. In general, the risk of bleeding increase with age, and higher in patients with previous hemorrhagic episodies. The risk of bleeding of patients with NA-NSAIDs is fourfold compared with nonusers, and this risk increases with dose. Once treatment is stopped the risk quickly returns to baseline. There are several differences with aspirin. The risk of bleeding with aspirin is only twofold with respect to nonusers. Another difference is that the risk does not increase with the dose, and there are no differences between doses of 75, 150, and 300 mg a day. The risk is higher during the first month of treatment, and after this remains constant. It seems that the new cyclo-oxygenase-2 selective NA-NSAIDs (coxibs) would be half of that observed among NA-NSAIDs users and the same is true for the aspirin risk.

Carotid and femoral artery intimal-medial thickness as an early predictor of arterial occlusive disease in patients with diabetes

A. MOZAINI, M. ASLAM, K. HUMPHRIES, N. J. STANFIELD (UK)

The aim of this study was to evaluate the influence of risk factors of atherosclerosis by measuring the intima-media thickness (IMT) in the common carotid artery (CCA) and in the common femoral artery (CFA).
The greatest increase in IMT was observed in diabetes patients, and then in patients with peripheral arterial disease. There are no differences between insulin and non-insulin-dependent diabetes.
This is a useful method to detect patients with arterial asymptomatic pathology, and it could be used to follow the progression of subclinical atheroclerosis.

Endothelium-dependent vasodilatation predicts restenosis after coronary stenting

R. MELFI, G. PATTI, C. GOFFREDO, A. D'AMBROSIO, L. LASSANDRO PEPE, G. P. CARBONI, M. CHELLO, G. DI SCIASCIO (Italy)

This is a small-group study on the relationship between endothelium-dependent vasodilatation and restenosis after coronary stenting. The authors demonstrate statistical differences in the index of vasodilatation measured in the brachial artery during hyperemia in patients after coronary stenting. The patients with a lower index of vasodilatation have a higher risk of coronary postangioplasty restenosis. There are no differences if the index of vasodilatation is calculated after administration sublingual nitrates.
Probably the in-stent restenosis is mainly due to intimal hyperplasia, but endothelial dysfunction may have a role in predisposing the mechanisms to intimal proliferation after coronary stenting.

Does peripheral vasomotion reflect coronary vasomotion?

A. PEPE, M. LOMBARDI, I. TAKACS, V. POSITANOC, E. HOFFMANN, G. PANZARELLA, E. PICANO (Italy)

The authors wished to demonstrate the relationship of endothelial-independent vasomotor function to nitrate, measured in the brachial artery with ultrasounds, and in the coronary artery measured with magnetic resonance angiography (MRA).
This study demonstrates that there are differences in the index of vasodilatation between the coronary and the brachial artery. This lack of correlation could express the impossibility of comparing the coronary bed with the peripheral bed. In any case the small group of patients in this study does not allow the authors to establish definitive conclusions.


BENEDICTVS XIV

Part 2

INVESTIGATIONS IN VASCULAR DISEASES

Chairpersons: P. L. ANTIGNANI (Italy), K. JAEGER (Switzerland)

Treatment of postcatheterization femoral false aneurysms: usefulness of color Doppler

J. P. LAROCHE (France)

The incidence of iatrogenic femoral false aneurysms has risen dramatically in recent years, and is estimated at 0.5% for diagnostic and 9% for therapeutic procedures. This increased incidence related to the increased number of arterial punctures for diagnostic and therapeutic purposes and their major complexity and duration. Risk factors for development of iatrogenic false aneurysms include operator experience, age greater than 60 years, female gender, catheter size greater than 8F, atheromatic plaque presence, and concurrent anticoagulation. Prevention of false aneurysms is based upon an atraumatic arterial puncture, good compression therapy after the procedure, and use of precutaneous arterial closure devices. Contrary to the arterial lesions following severe injuries, the natural evolution of false aneurysms is quite benign, with spontaneous occlusion in the majority of cases. Therefore a mandatory surgical approach is no longer advocated, and alternative therapeutic options have been proposed. These include sonographic surveillance, compression ultrasonography, precutaneous thrombin, or coil embolization. Surgery is clearly indicated in the presence of local nervous or venous compression, associated homolateral lower limb ischemia, large size of aneurysm (>3 cm) and unsuccessful noninvasive treatment. Echographic surveillance has been shown to be safe in hospitalized or ambulatory patients. However, fear of aneurysm rupture and cost of repeated ultrasonographic exams preclude wide utilization. Compression echography is safe, and effectiveness varies between 70% and 100% according to studies. Thrombin injection seems particularly effective, is painless, and has a low rate of complications in expert hands. Severe anaphylactic reactions and severe coagulopathy in reexposed patients have been described, and represent a clear contraindication to thrombin injection. Coil embolization of false aneurysms is as effective as a thrombin injection, and has been reported in a limited number of patients. There is no formal consensus about treatment of the vast majority of nonsurgical false aneurysms. If compression therapy fails, precutaneous injection of thrombin or coil embolization are effective, and associated with a low complication rate. However, these techniques are less widely available, and necessitate an experienced operator.

CRURAL ARTERIAL, INTRAOPERATIVE, AND VENOUS DUPLEX SCANNING

Chairpersons: H. VAN DAMME (Belgium),
D. UBBINK (The Netherlands)

This interesting workshop started with the presentation by M. Koelemay from Amsterdam, on how to study lower leg and foot arteries. He recommended the use of a linear transducer at a frequency of 5 MHz for the proximal track from the knee arch to the calf and a high-frequency transducer (7.5-10 MHz) for the distal part, due to the superficial location of vessels. In cases of superficial, severely calcified vessels, he suggested the use of lower frequencies. A venous preset was used considering the expected low flow in the lower leg arteries and the "Power-Doppler" function; also, the zoom option could facilitate visualization of very-low-flow and small vessels. He stressed the importance of ensuring that the leg is relaxed and not overstretched during the exam. He recommended the use of a good seat with mobile back, and arm and elbow rests in order to protect one's back. Moreover, he presented a critical appraisal of the literature concerning crural duplex scanning (CDS). Some 29 studies between 1989 and March 2004 were identified, with an overall moderate methodological quality. Evidence from this literature suggests that CDS can safely be used as the sole pre-treatment imaging modality in patients with severe limb ischemia.

Afterwards, Professor Albäck from Helsinki presented his experience on intraoperative scanning of infrainguinal autologous vein grafts. The detection and possible correction of these abnormalities early during the primary procedure would be of great importance. The exam should include vessel imaging, velocity spectra analysis, grading of stenotic lesions, and graft hemodynamics. He recommended the study of the whole length of the reconstruction, giving special attention to common sites of defects. Next, he defined the findings and actions recommended: when there are moderate defects (PSV 125-180cm/s or a velocity ratio between 2 and 3) the exam should be repeated under the effects of papaverine, and then repair performed if a severe hemodynamic defect is confirmed. When there is a detection of severe stenosis (PSV>180 cm/s, velocity ratio>3 and spectral broadening) it should always be repaired if possible. Another problem is when no stenosis is detected but there is a low graft flow with PSV< 45 cm/s or EDV< 8 cm/s these could be sings of graft failure, an angiogram should then be performed.

Professor Schellong from Dresden presented his protocol for detecting DVT, based on a complete compression ultrasound from the femoral to the crural veins, and the hands,-on session started in which everybody could see the application of duplex scan on studying crural vessels.

Real-time ultrasound evaluation in PTA stenting

A. AMATO (Italy)

Precutanous transluminal angioplasty (PTA) has been used for several years to treat arterial stenosis in short obstructions. The vessels most frequently treated are the iliofemoral arteries, renal arteries, and subclavian arteries. The assessment for endovascular treatment should be not only morphological but clinical and functional, since PTA is not a technique without risks. In the last few years it has become possible, and in some cases recommended, to place endoluminal stents during the angioplasty to favor the maintenance of the dilatation. The PTA-stenting technique has been extended to other vessels such as carotid arteries. The follow-up is based on the color Doppler ultrasonography as the most suitable noninvasive method for early and late evaluation of the stent. It is possible to investigate stent position, relationship with the endoluminal surface, and eventually residual plaque. Besides, it can detect the flow quality, early complications such as thrombosis, or late complications such as restenosis. Compared with angiography the sensitivity and specificity was about 96% to 97%.

Utility of D-dimer in diagnosis of deep vein thrombosis in hospitalized patients at high risk of venous thromboembolism

F. VERLATO, A. BERTAGNIN, G. CAMPORESE, M. NARDI, G. M. ANDREOZZI (Italy)

The authors of this work aimed to evaluate the utility of D-dimer as a screening tool in populations at high risk of DVT, optimizing the use of noninvasive imaging with ultrasound. They studied a population of patients who had been operated on for neurosurgical pathology. They studied, using ultrasound, 103 patients with high levels of D-dimer, but only 31 patients had DVT. There is not a clear level which indicates patients at greater risk of a DVT. One way of increasing the positive and negative predictive value is to use a two-step screening process involving an initial D-dimer estimation to improve the utility of D-dimer in DVT diagnosis.

The appropriate use of the duplex scan in carotid artery disease

T. MEHTA, I. CHETTER, A. VENKATASUBRAMA, K. MYLANKAL, B. RAY, P. McCOLLUM (UK)

The authors examinded carotid ultrasound studies of patients with specific and nonspecific symptoms, from several medical specialties, over 25 months. The higher incidence detection of a significant internal carotid artery (ICA) stenosis (higher than 70%) was in patients from the vascular surgery ward (25.4% of scans) and the lowest was from the neurology service (5.9% scans). The authors recommenderedefined protocols for carotid duplex requests to increase efficiency and improve the pick-up rate of significant ICA lesions. It is necessary to develop good protocols, but these protocols must include both symptomatic and asymptomatic patients.

Duplex sonography in obstructive aortoiliac disease: the diagnostic value of flow reversal in the inferior epigastric artery

M. HAUMER, R. A. BUCEK, M. SCHILLINGER, A. HAUMER, M. REITER, J. LAMMER, E. MINAR (Austria)

The authors obtained spectral Doppler curves by duplex sonography in the inferior epigastric arteries of 78 patients with aortoiliac arterial pathology. They compared the results with those of conventional angiography. They describe several spectral Doppler curves to define the severity of aortoiliac pathology.

This test could be another tool to study arterial pathology with noninvasive methods, but is probably more useful for studying the spectral curves measured in the common femoral artery. Moreover, it is necessary to consider the influence of superficial femoral artery pathology in the curves registered in the common femoral artery or in the epigastric artery.

Noninvasive foot blood volume measurement in the assessment of limb ischemia

T. KANETAKA, T. KOMIYAMA, A. ONOZUKA, T. MIYATA, H. SHIGEMATSU (Japan)

The authors have developed a new air chamber to measure blood volume in the foot by an air plethysmography technique.

The results of this work demonstrate that the fee of patients with critical ischemia contain more blood than those of patients with claudication or healthy people, and this might be due to the vasodilation compensating for the decrease of inflow.

The method could be problematic in patients with ischemic lesions, but could be a useful tool in diabetic patients, in whom arterial calcification does not permit the use of cuff pressure.


BENEDICTVS XIV

Part 3

THERAPY OF VASCULAR DISEASES

A PHARMACOTHERAPY

Selective factor Xa inhibition: role in acute coronary syndromes

A. G. G. TURPIE (Canada)

Fondaparinux (Arixtra®) is a synthetic antithrombotic agent with specific anti-factor Xa activity. Its pharmacokinetic properties allow for a single daily injection without the need for monitoring. It was recently compared with enoxaparin for the prevention of venous thromboembolism (VTE) in major orthopedic surgery in 4 randomized double-blind studies. The metanalysis of these studies showed a major benefit of fondaparinux over enoxaparin achieving an overall risk reduction of VTE of 55.2% without increasing the risk of clinically relevant bleeding [AGG Turpie et al. *Arch Intern Med*. 2002;162:18333-1840.

Aspirin (ASA), clopidogrel, and low-molecular-weight heparins (LMWH) are indicated for the treatment of acute coronary syndromes (ACS). In non-ST-elevation ischemia (NSTEMI) or in unstable angina pectoris, guidelines now suggest in using ASA in addition to anti-ischemic therapy and LMWH. Clopidogrel is added, except in patients who are potential candidates for urgent coronary artery bypass grafting. For patients undergoing percutaneous coronary intervention, glycoprotein IIb/IIIA inhibitors are added. After invasive treatment, or if no invasive treatment is required, the combination of aspirin (ASA) and clopidogrel is recommended for long-term treatment of non-STEMI patients. Patients with acute ST-segment elevation ischemia (STEMI), should receive thrombolysis if primary angioplasty is not indicated or available.

Fondaparinux was evaluated for treatment of acute non-STEMI patients in phase II PENTUA study. This study included 1147 patients who received either enoxaparin 1 mg/kg twice daily or fondaparinux once daily at the dosage of 12, 8, 4 or 2.5 mg for 9 days. Fondaparinux was found to be as effective for reducing thrombotic events and as safe for major bleeding events as enoxaparin. In the PENTALYSE study, 326 STEMI patients were included. They received ASA and thrombolysis by rtPA, in combination either with fondaparinux or UFH. Similar coronary patency rates were demonstrated in all groups at 90 minutes, but there was a strong trend in decreasing reocclusion in the fondaparinux group.

Two phase III trials are actually ongoing (OASIS 5 and 6), and are planned to include 16 000 non STEMI patients and 10 000 STEMI patients to evaluate fondaparinux as an alternative treatment to LMWH or UFH for ACS.

Heparins, oral anticoagulants, and ASA: survival of the fittest

J. FAREED (USA)

The current management of thrombotic and cardiovascular disorders is largely dependent on the use of classic anticoagulants and antiplatelet agents such as heparin, warfarin, and aspirin. Although the cumulative usage of these drugs extends beyond 200 years for several indications, the mechanism of their actions and therapeutic spectrum is not fully explored. Several of the consensus groups have continued to endorse these drugs for the thrombotic and vascular indications. The last decade has also witnessed the development of several newer anticoagulants and antiplatelet drugs with claimed superiority over conventional drugs. Parenteral antithrombin agents such as hirudin, angiomax, and argatroban have been used with specific indications such as heparin-induced thrombocytopenia. Oral antithrombin agents such as ximelagratran were developed with claimed superiority over oral anticoagulant drugs for broad indications. Heparinomimetic agents, namely arixtra, which represents an indirect parenteral anti-Xa agent, have been used mainly for postorthopedic surgical indications. Synthetic parenteral anti-Xa agents have also been developed without clinical success. Oral anti-Xa agents are currently developed for several clinical indications, including extended management of thrombotic and cardiovascular disorders. While these drugs are useful in heparin and oral anticoagulant-compromised patients, almost all have a narrow therapeutic index and are monotherapeutic. Furthermore, their pharmacology is not completely understood. The development of glycoprotein IIb/IIIa inhibitors added a new dimension in parenteral antiplatelet therapy with profound impact on interventional cardiology. However, these drugs were not promising as oral agents. Furthermore, they have very narrow safety-efficacy windows. The ADP-receptor inhibitors such as ticlopidine and clopidogrel, represent drugs with antiplatelet effects which are different from aspirin. However, the efficacy of these agents is dependent on the simultinaeous use of aspirin. Moreover, ticlopidine exhibits serious adverse effects by suppressing PMM production. Long-term toxicity data is not available. Thrombosis is a polypathologic process requiring drugs with polypharmacologic actions. The newly developed drugs can only mimic the effects of conventional drugs in multiple therapeutic forms. Thus heparin, oral anticoagulants, and aspirin will further expand in optimized forms. The newer agents may be useful in heparin-compromised patients and targeted therapeutic approaches.

Response to variations in antiplatelet drugs: clinical manifestations

H. K. BREDDIN (Germany)

Currently three types of antiplatelet drugs (APD) are in use:
- aspirin
- ADP-receptor antagonists and thienopyridines (ticlopidine and clopidogrel)
- glycoprotein IIb/IIIa receptor antagonists as Abciximab, eptifibatide, and integrilin.

Aspirin reduces stroke and coronary events by about 25% with the safe dose range being from 75 to 325 mg per day. however, in many cases low doses of aspirin, such 100 mg per day, may not be enough with 10% of nonresponders. Resistance to aspirin is currently discussed but still ill-defined. The inhibition of platelet function in different test systems shows large variations. Whether patients who do not respond to aspirin in this test have less clinical benefit has been thought likely, but by no means proven. A better standardization of tests is urgently needed before they are used in prospective studies.

Ticlopidine and clopidogrel are widely used, especially in patients with coronary heart disease. They effectively prevent acute reocclusions in patients undergoing PCI. These drugs can be monitored using platelet aggregation induced by APD. Also here non-responders have been described. How much inhibition of APD-inducted aggregation is needed to provide clinical efficacy? Due to poor standardization of the aggregation tests this can not be answered today. Does clopidogrel inhibit progression of peripherial arterial occlusive disease? This is not known because it has not yet been studied. Rules for such studies are urgently needed.

Glicoproteins IIb/IIIa inhibitors (GP IIb/IIIa inhibitors) are potent drugs. Nowadays there are three groups of these drugs:
- humanized monoclonal antibodies (abciximab, YM 337)
- IV effective synthetic peptides and peptidomimetics (integrilin, tirafiban, lamifiban, DMP728)
- orally effective peptidomimetics (mainly “double prodrugs” – xemilofiban, sibrafiban, fradafiban)

It is very likely that for their clinical effects a strong inhibition of the GP IIb/IIIa receptors is needed, possibly more than 95%. There is, however only one study with insufficient data on this important question. GP IIb/IIIa inhibitors are not mentored in clinical practice. It is that their clinical efficacy could be improved by simple monitoring tests. Orally available GP IIa/IIIb receptor antagonists have failed to show any clinical benefit. The reason for this is much discussed but virtually unknown.

Three practical conclusions:
- platelet function inhibitors should be used in combinations
- aspirin + clopidogrel is a promising combination, today mainly used in PCI
- aspirin + clopidrogrel are also promising for new studies in PAOD.

Chairpersons: S. A. MOUSA (USA), M. R. LARSEN (Denmark)

Serum transaminases do not increase after a 4-week administration of fondaparinux. No episodes of thrombocytopenia are seen after 4 weeks of fondaparinux in major orthopedic surgery

M. R. LARSEN (Denmark)

Fondaparinux is a synthetic selective factor Xa inhibitor with a favorable profile:
- absolute bioavailability 100%
- linear dose-dependent pharmacokinetics
- long elimination half-life ~ 17 hours allowing once-daily injection
- low interindividual variability allowing fixed dose and no monitoring
- distribution volume close to blood volume
- excreted unchanged in the urine
- no metabolism
- selective binding to ATIII

Turpie et al proved the superior efficacy of fondaparinux after major orthopedic surgery in their comparative study (2002 - fondaparinux versus enoxiparin) with a similar safety profile. Increase in serum transaminases is known as an adverse event with a number of antithrombotic compounds. The variations in serum transaminases observed after major orthopedic surgery may be related to surgical context or to study drugs. HIT is a severe complication of heparin therapy mediated by antibodies to PF4 complex. The safety of prolonged administration of fondaparinux on liver enzymes, on blood platelet count, and the evolution of serum transaminases in the double-blind randomized PENTHIFRA-PLUS trial in which fondaparinux was administered up to 4 weeks after hip fracture surgery were studied. Serum transaminases (AlT, AST) were measured at randomization (7 days after surgery) and at the end of the study (4 weeks). Variation in serum transaminases during the study period were comparable between the two groups. Increase in serum transaminases was rare in the 1-week as well as 4-week fonadaparinux groups. Penthifra-Plus demonstrated that extending fondaparinux prophylaxis from 1 week to 4 weeks after hip fracture surgery reduced significantly by around 90% all venous thromboembolism events and symptomatic deep vein thrombosis and pulmonary embolism. Extended administration of 2.5 mg fondaparinux from 1 to 4 weeks did not increase clinically relevant bleeding or significant changes in liver enzymes in comparison with placebo. Increase in serum transaminases observed in the short-term trials was more likely related to surgical context rather than to fondaparinux therapy. There were no cases of heparin-induced thrombocytopenia with prolonged administration of 2.5 mg fondaparinux.

Inhibition of thrombin activatable fibrinolytic inhibitor by heparin and defibritide

M. FLORIAN (USA)

Thrombin activatable fibrinolitic inhibitor (TAFI) is a carboxypeptidase capable of modulating fibrin, rendering it resistant to the action of plasmin. Polyelectrolytes such as heparins produce varying degrees of inhibition of the functional activity of TAFI, presumably due to their effects on thrombin-thrombomodulin complex. The authors assessed the molecular weight dependence on the inhibition of TAFI by heparin and defibrotide.

In the summary the authors stated that heparins and LMWHs are capable of inhibiting the activation of TAFI. The degree of inhibitions depends on the molecular weight of the heparin fractions. Higher molecular weight fractions inhibit TAFI more effectively. Defibrotide and aptamers isolated from defibrotide are capable of inhibiting TAFI activation. Molecular weight of defibrotide fractions also influences the inhibition of TAFI. Heparin and LMWHs inhibit TAFI more effectively than does defibrotide.

These studies clearly demonstrate that both MW and MW composition of heparins and defibrotide contribute to the differential inhibition of TAFI which in turn may contribute to their therapeutic actions. The profibrinolytic effects of heparin may be a result of its ability to inhibit TAFI. Bleeding is a commonly seen adverse effect of heparins. Since the primary hemostatic plug is composed of platelets and fibrin strands, a molecularly transformed fibrin resistant to localized lysis may be more important in restoring hemostasis than the native fibrin molecules. TAFI is implicated in maintaining primary hemostatic plug at the site of vascular insult, where a residual amount of this enzyme is important. It is important to consider that an indiscriminant inhibition of TAFI functionality may lead to bleeding, whereas a balanced inhibition may add to the therapeutic efficacy and profibrinolytic actions of these agents.

Thrombin activatable fibrinolytic inhibitor (TAFI) modulation by heparin: influence of endogenous variables

M. FLORIAN (USA)

The primary objective of this research was to determine the effect of various heparins on the functionality of TAFI as measured by using a specific synthetic substrate. Additionally, the relevance of the observed inhibition of TAFI with the antithrombin potency was also addressed.

The study design was as follows:

- to validate a newly developed chromogenic substrate method for the functional evaluation of TAFIa
- to determine the effect of various anticoagulants on the functional TAFI levels at expected clinical concentration
- to demonstrate the relevance of thrombin inhibitory actions and TAFI functionality
- to demonstrate any potential direct inhibitory actions by anticoagulant drugs on TAFIa.

Citrated plasma samples from 289 healthy persons and patients treated with heparin, antithrombin, and oral anticoagulants were collected. A chromogenic substrate-based method (Pefakit® TAFI, Pentapharm Ltd, Switzerland) was used to determine TAFI levels. Pefakit® TAFI (Pentapharm Ltd, Switzerland) utilizes a specific substrate which measures the generated TAFIa. In the current assay configuration, the effect of anticoagulant drugs on TAFI and TAFIa is measured. Various anticoagulant drugs produce different degrees of TAFI inhibition which is not proportional to their relative antithrombin actions. Hirudin, which is the strongest inhibitor of thrombin, produces relatively weaker effects on TAFI. Also anti Xa drugs have a relatively weak effect on TAFI. Molecular weight dependence is observed with heparin and LMWHs. The level of heparinization is directly proportional to the inhibition of TAFI activity, as observed at the prophylactic, therapeutic, and interventional levels. Oral anticoagulants in the therapeutic range (INR 2.0-2.5) did not have any effect on TAFIa. In conclusion the authors stated that using a chromogenic substrate-based method for TAFI functionality, the differential inhibitory effects of various anticoagulant drugs can be readily assessed. The differences in the inhibitory profile of TAFI may also contribute to the observed variations in heparinization responses among patients. Finally the authors presented the clinical implications:

- anticoagulant drugs such as heparins and antithrombin agents can produce varying degrees of modulation of the fibrinolytic process by downregulating TAFI functionality. This modulation of TAFI functionality by anticoagulant drugs may directly impact on their safety and efficacy. While an inefficient inhibition of TAFI mat result in a hypercoagulable state, excessive inhibition of TAFI can lead to bleeding.

Generic versions of commercially available low-molecular-weight heparin (LMWHs): product individuality in therapeutic implications

J. MADDINENI (USA))

Enoxaparin represents one of the most widely prescribed LMWHs, with approval for several applications. This drug is made by using benzylation followed by alkaline depolymerization of porcine mucosal heparin. One of the patents covering this drug has already expired, whereas the second patent will expire in December 2004. Therefore, this LMWH will be without patent coverage after this time. Being aware of this, several manufactures of LMWHs have produced generic versions of enoxiparin with claimed equivalence in accordance with the available specifications. Though the generic products may have a similar molecular weight and anti-Xa potency, their biochemical and pharmacologic behavior may not be the same, and may require further characterization. For the approval of generic versions of enoxaparin, four different products have been submitted. To utilize standardized analytical and biochemical methods which have been employed to demonstrate differences among LMWHs and to validate the generic equivalence or nonequivalence in various available generic versions the authors compared three generic versions of enoxaparin: two from India and one from Brazil, with the commercial form from the US. The comparison of the molecular profile of the three generic versions and the commercial product did not show any significant differences in terms of MWs but had different oligosaccharide distributions. The heparinase-I digestion profile of two Indian products and the commercial product were identical; however, the Brazilian product showed a strong resistance to the depolymerization effects by heparinase -1. The commercial product and the Indian generic version were digested to deca- and dodecasaccharides. The USP anticoagulant activities of each of these agents were comparable. Similarly, the anticoagulant activities as measured by PT, aPTT, Heptest, and TT were comparable in all these agents except for the Brazilian product. The anti-Xa and IIa actions of different products were similar; however, the Brazilian product was somewhat weaker. However, the calculated anti-Xa/IIa ratio of the Brazilian product was comparable to that of the other products. These studies clearly suggest that the molecular and biological activities of the generic versions can be adjusted to mimic the branded product. However, these adjustments may not be sufficient for bioequivalence. The authors concluded that some generic versions of enoxaparin have been introduced in many countries around the world. These products exhibit similar molecular and anti-Xa/IIa activities. These agents have not been evaluated for the specific attributions, which are unique for enoxaparin. This has clinical implications:

1. Enoxaparin represents a low-molecular-weight heparin with wide clinical indications, including arterial, venous, and cardiovascular use.
2. The dosage range varies widely, and this drug is administered with other anticoagulant and antithrombotic agents.
3. The generic version of enoxaparin must exhibit all physiochemical and biological attributes to mimic the clinical performance of the branded product.

NEW EVIDENCE ON CARDIOVASCULAR EFFECTS OF STATINS

Chairpersons: S. NOVO (Italy), R. PAOLETTI (Italy)

New evidences on CV event reduction with statins in type 2 diabetic patients

H. COLHOUN (Ireland)

The risk of CV death remains high in diabetic patients compared with nondiabetic patients with the same cholesterol levels. Several studies (CARE, 4 S, Heart Protection Study) have demonstrated that adding statins to existing treatments reduces the risk of cardiovascular events by about 22% to 25% in secondary prevention for a wide range of high-risk patients, irrespective of their initial cholesterol concentrations. The place of lipid-lowering for primary prevention of CV events is, however, more controversial. The ASCOTT-Lipid Lowering Arm study included 10 305 hypertensive patients with nonfasting total cholesterol concentrations of 6.5 mmol/L or less, with at least three cardiovascular risk factors. They were given atorvastatin 10 mg or placebo. Nonfatal and fatal coronary heart disease risk was reduced by 36% in the atorvastatin group compared with the placebo group. The statistical analysis of the subgroup of diabetic patients was lacking power. The Heart Protection Study documented the beneficial effect of simvastatin in reducing all-cause mortality among 5963 diabetic patients but there is still a paucity of large prospective randomized outcome trials designed only for diabetic patients. However, some guidelines (Europe) now routinely recommend lipid-lowering treatment for all type 2 diabetic patients while others recommend treating only patients with an increased LDL-c concentrations and an increased risk of coronary heart disease. The Collaborative Atorvastatin Diabetes Study (CARDS) is still ongoing. This study will evaluate the effectiveness of atorvastatin in type II diabetic patients for primary prevention of cardiovascular events. A total of 2838 patients have been included and randomely assigned to receive either atorvastatin 10 mg daily or placebo. They all have at inclusion LDL-c < 4.14 mmol/L and hypertension (79% of the patients), retinopathy (30%), microalbuminuria (11%), or current smoking (23%). None of the patients have a history of cardiovascular disease, coronary heart disease, or peripheral arteriopathy. The results of this study and the results of other ongoing studies such as Fenofibrate Intervention and Event Lowering in Diabetics will define the place and the safety of lipid-lowering strategy in primary prevention of cardiovascular events in diabetic patients.

The antiatherothrombotic effects of statins: the ATROCAP study results

M. CORTELLARO (Italy)

Thrombogenicity of the atherosclerotic plaque is dependent on the imbalance between tissue factor (TF) and tissue factor pathway inhibitor (TFPI). Statins are able to inhibit the expression of TF, but their effects on plaque thrombogenicity have never been reported in humans. Patients (n=59) eligible for bilateral carotid endarterectomy (CEA) were included in the study. After the first CEA, they were randomly assigned to atorvastatin 20 mg daily or placebo till the second CEA, 4 to 6 months later. Histological and immunohistochemical analyses of the endarterectomy specimens were performed with particular reference to the distribution of TF and TFPI. TF, TFPI antigens and TF activity and compared between the two endarterectomy specimens. Plaques removed at the second CEA in the atorvastatin group had a lower inflammatory cell infiltrate and a reduction in TF activity, TF and TFPI antigens compared with plaques of the placebo group. These results indicate that atovarstatin decreases the inflammatory activity of the atheromatic plaque and may reduce the risk of plaque thrombogenicity.

Cortellaro M, Cofrancesco E, Arbustini E, et al. Atorvastatin and thrombogenicity of the carotid atherosclerotic plaque: the ATROCAP study. *Thromb Haemost*. 2002;88:41-47.

Lipid-lowering and non-lipid-lowering effects of statins in cerebrovascular diseases prevention

P. RUBBA (Italy)

Clinical trials on secondary prevention of coronary heart disease showed a reduction in cerebrovascular events among patients undergoing long-term treatment by statins. While it is generally accepted that the clinical beneficial effect associated with statin treatment is due to the lipid-lowering effect, the possibility that statins have additional protective effects on the arterial system cannot be excluded;

- Carotid plaque stabilization:

Carotid plaque stabilization can be evaluated by high-resolution B mode ultrasound which assesses intima-media thicknesss (IMT) of the common carotid artery and of the carotid bifurcation. First, maximum IMT (measured at baseline) evaluates the lesion severity and the mean maximum IMT (measured during the follow-up) evaluates the lesion extension. Pravastatin has been shown to decrease the mean maximum IMT while the first maximum IMT remained unchanged, suggesting that pravastatin is able to inhibit the formation of new lesions in asymptomatic moderately hypercholesterolemic patients.[1] Moreover, marked LDL reduction (<100 mg/dL) with a high potent statin treatment provides superior efficacy for atherosclerosis regression, measured by carotid IMT, at 1 year.[2]

- Enlargement of carotid lumen:

Maintained lipid-lowering therapy with simvastatin has also been demonstrated to be associated with significant regression of established atherosclerotic lesions. Lesions were assessed by high-resolution noninvasive magnetic resonance imaging.[3] Vessel wall thickness and vessel wall area decreased during lipid-lowering therapy while lumen area increased slightly.

- Reduction of stroke, transient ischemic attacks, and vascular bruits:

The Prospective Pravastatin Pooling Project pooled three large placebo-controlled randomized trials and included 19 768 patients with 102 559 person-years of follow-up. Pravastatin 40 mg daily, in secondary prevention, reduced stroke rates (fatal and non fatal) by 20%. The benefit was observed mostly for ischemic strokes as there was no statistical difference for hemorrhagic or strokes of unknown cause.[4] The Heart Protection Study also provided evidence of stroke prevention through simvastatin treatment in individuals at high risk of atherosclerotic cardiovascular disease, independently of the presence of coronary disease.[5] The MIRACL study determined that intensive cholesterol lowering with atorvastatin over 16 weeks in patients with acute coronary syndromes reduced the overall stroke rate by half and did not cause hemorrhagic stroke.[6] More recently, the ASCOT-LLA study showed that stroke rate can be reduced in hypertensive normolipidemic patients, without any evidence of coronary heart disease. Patients of the study received atorvastatin 10 mg/d or placebo. A 27% reduction of stroke incidence was observed during the 3 year-follow-up period.[7]

In conclusion, statins have a protective effect on the arterial system at different levels: carotid plaque stabilization, enlargement of carotid lumen, fewer vascular bruits and TIAs, and prevention of stroke in high-risk patients.

1- Mercuri M, Bond MG, Sirtori CR, et al. Pravastatin reduces carotid intima-media thicknes progression in asymptomatic hypercholesterolemic mediterranean population: the Carotid Atherosclerosis Italian Ultrasound Study.
Am J Med. 1996;101:627-634.

2- Taylor AJ, Kent SM, Flaherty PJ, Coyle LC, Markwood TT, Vernalis MN. ARBITER: Arterial Biology for the Investigation of the treament effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness.
Circulation. 2002;106:2055-2060.

3- Corti R, Fuster V, Fayad ZA, et al. Lipid lowering by simvastatin induces regression of human atherosclerotic lesions: two years follow up by high resolution non invasive magnetic resonance imaging. *Circulation*. 2002;106:2884-2887.

4- Byington RP, Davis BR, Plehn JF, et al. Reduction of stroke events with pravastatin: the Prospective Pravastatin Pooling (PPP) Project. *Circulation*. 2001;103:387-392.

5- Heart protection study collaborative group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7-22.

6- Waters DD, Schwartz GG, Olsson AG, et al. Effects of atorvastatin on stroke in patients with unstable angina or non-Q-wave myocardial infarction: a Myocardial Ischemia Reduction with Agressive Cholesterol Lowering (MIRACL) substudy. *Circulation*. 2002;106:1690-1695.

7- Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOTT-LLA): a multicentre randomised controlled study.
Lancet. 2003;361:1149-1158.

Is it possible to stop the progression of atherosclerosis? The REVERSAL Trial

G. DE FERRARI (Italy)

Glagov's remodeling hypothesis of atherosclerosis indicated that the arterial lumen is reduced at the end stage of the process. At earlier stages, there is a production of atheroma on one part of the vassel, then extension occurs until eventually it becomes circumferential with a reduced arterial lumen. Intravascular ultrasound (IVUS) provides a complete evaluation of the vessel circumference, the vessel wall, and the lumen area. Atheroma area and total atheroma volume can be calculated on a target vessel. IVUS can visualize atheroma in cases of diffuse symmetrical disease with nonsignificant stenosis on arteries, which is one of the limitations of angiography. In the REVERSAL trial, 654 patients requiring coronary angiography were included. They were randomly assigned to receive atorvastatin 80 mg/d (agressive treatment) or pravastatin 40 mg/d (moderate treatment) during 18 months of follow up. Atorvastatin significantly decreased total cholesterol, LDL-C, and triglycerides more than pravastatin. Total atheroma volume decreased in the atorvastatin group while it increased in the pravastatin group. It was possible to calculate that a 50% reduction of LDL-C was associated with an absence of atherosclerosis progression, measured by IVUS. This was correlated with a significant reduction of major cardiovascular events after 30 months of follow-up in the atorvastatin group compared with the pravastatine group (Relative risk=16).

Microcirculation reactivity ischemia and pharmacological reperfusion

C. ALLEGRA (Italy)

Microcirculation is a terminal part of the systemic circulation and connecting system between arteries, venous macrovessels, and tissues. It is called “exchange circulation” since it is the site of hemo-tissue exchanges. The microcirculatory unit consists of a terminal arteriola, a meta-arteriola, the capillary network, the initial venula, arterovenous anastomoses, lymphatic capillaries, and nervous fibers, all held in matrix of connective tissue. The local blood perfusion is regulated through two main ways: 1) the metabolic pathway, conditioned by changes in tissue PO_2 and PCO_2 which uses endothelium-derived relaxing factor (EDRF) or nitrous oxide (NO) and adenosine as vasoactive mediators; 2) the myogenic pathway, conditioned by changes in pressure of flow. A third mechanism invoked is arteriolar vasomotion. It consists of rhythmic arteriolar dilatations and constrictions at frequently of 1 to 20 to 30 cycles per minute, inversely proportional to the diameter of the terminal arteriole. The cyclical changes in arteriolar diameter are accounted for by a presence of a sphincter-type endarterial thickening, acting as a pacemaker. Vasomotion is thought to be responsible for: 1) redistribution of the blood flow in the capillary network; 2) changes in capillary blood viscosity, in the oncotic-hydrostatic pressure ratio. In turn the variations of frequency of arteriolar vasoconstriction and vasodilatation seem to be determined by changes in interstitial pressure and PO_2, through adenosine-balanced feedback between EDRF and endothelin. Capillary hemodynamics result from arteriolar vasomotion and rheological changes according to stochastic laws. Capillary endothelium lies on the basement membrane and lacks underlying muscle cells. It sets up a continuous barrier which allows diffusion of fluids and muscles though direct and indirect mechanisms of selective transport. Most capillaries have oxygen pressure in the range 20 to 30 mm Hg – it should be apparent that this is not the primary mechanism for tissue oxygenation. The large O_2 consumption of the arteriolar wall and primary the endothelium is due to biological activity of these cells and the synthesis and secretion of rennin, prostaglandins, prostacyclins, interleukins, clearance of proteins, lipids, and lipoproteins and mechanical work in contracting against blood pressure. So vessels wall oxygen gradients – and therefore microvessel wall metabolism – increase with vasoconstriction. When oxygen availability has run out, the endothelial damage is not reversible, and consequently thrombosis, decrease in capillary perfusion and density, with tissue damage, occur.

Short and repeated ischemia results in resistance to serious ischemia, increasing ATP and adenosine release by the tissue. Both ATP and adenosine stop white cell activation, and RBC aggregation, they improve fibrinolysis, vessel dilatation, and protect capillaries from reperfusion injury. The restoration of normal vasomotion is requested by greater supply of ATP and decreasing consumption of O_2 by arteriolar endothelial cells. Consequently much more O_2 is available for ischemic tissues. In practice ischemic preconditioning is interesting to explain:

- the improvement of walking distance after repeated exercise
- the action of some vasoactive drugs
- the target of antiischemiac therapy in the exchange vessels.

Autologous skin grafting in treatment of lower-leg cutaneous lesions

R. BRAMBILLA, P. MAGGIONI, S. SORDO, G. CIUFFO, S. MANGIAROTTI, E. STELLINO (Italy)

The authors describes a series of 127 patients with lower-leg cutaneous ulcers. There are arterial, venous, and other ulcers whose origins are not clear. After preparing the lesion correctly the treatment was performed with autologous skin grafting obtained with non-woven scaffold (Hyalograft) or with a microperforated lamina of HYAFF (Laserskin). The results are excellent with healing of the ulcer in 110 patients. The patients still have the ulcer close 6 months after complete clinical closure. The authors do not explain whether they have performed any special treatment depending of the origin of the ulcers. This could prove to be another useful treatment for this difficult pathology.

B COMPRESSION THERAPY

Compression therapy: a powerful but underestimated treatment modality

H. PARTSCH (Austria)

Clear proof of effectiveness of different compression devices endorsed by evidence-based medicine (EBM) will be a prerequisite for reimbursement by health budgets in the near future. Unfortunately, until now randomized controlled trials (RCT) of compression which have demonstrated clinical effects in different setting are very rare or non-existant. Based on the initiative of the UIP, the available RCTs and systematic reviews reporting outcomes after compression therapy in the different settings of phlebology and lymphology were evaluated by an international group of experts (San Diego, August, 2003). Recommendations were graded A, B or C according to the scientific levels of evidence (*Table I*).

Table I. Scientific level and grade of recommendation.

Level	Grade	Publication
I	A	Large, homogenous RCTs Meta-analyses (systematic reviews)
II	B	RCTs in smaller populations, one RCT only
III	C	Cohort studies, cas- control studies, observation studies

Positive effects of compression therapy endorsed by EBM criteria (grade A) were found only in two settings: venous ulcers (bandages, not stockings); prevention of thrombosis and postthrombotic syndrome (stocking, not bandages). Grade B recommendations were based on studies of subjective symptoms in small and large varicose veins, postoperative or postsclerotherapy care of varicose veins, acute DVT, and lymphedema. There were no data about compression treatment for patients with CEAP class C4a (stasis dermatitis and pigmentation) and with superficial phlebitis. The most impressive effect of compression reduction of edema (CEAP C3) has not yet been investigated adequately. Future investigations devoted to the efficiency of compression therapy are necessary for planning in conformity with the following demands:

- A priori calculation of sample size, large population (multicenter)
- Objective outcome parameters, eg, ulcers healing
- Pairs of baseline-characteristics (stratification)
- Objective definition of compression pressure and material
- Blinded assessment of outcome
- Publication also of studies with negative results.

THE ROLE OF COMPRESSION THERAPY IN THE EVOLUTION OF DVT

Chairpersons: C. ALLEGRA (Italy), P. GLOVICZKI (USA)
With the participation of C. MOFFAT (UK), E. RABE (Germany), P. L. ANTIGNANI (Italy), H. PARTSCH (Austria), C. ALLEGRA (Italy), P. GLOVICZKI (USA)

State of the art in elastic compression

C. MOFFAT (UK)

Two main types of the compression therapy for venous ulcers were presented. Passive compression, is produced by inelastic bandages which counteract the increase in muscle volume resulting from muscle contraction. Active compression is provided by elastic materials. It is independent of muscle activity. There are three types of this material: short-stretch (extension < 70%), medium-stretch (extension 70% to 140%) and long stretch (extension >140%). The treatment of venous ulcers includes:

1. Compression
- Multilayer (elastic or nonelastic)
- Reduced compression
- Medical stocking
- Intermittent pneumatic compression (IPC)

2. Medical and surgical treatment
3. Appropriate dressing
4. Education of the patients.

The treatment options are different for mobile and immobile (fixed ankle) patients. The first line of the therapy for mobile patients includes multilayer compression (elastic or nonelastic) and then medical stockings as a second line. For immobile patients, first-line therapy includes elastic multilayer compression bandage and combination multilayer elastic bandages with IPC as a second line. Industrial multi-layer bandages including elastic and nonelastic properties (eg, Profore®) have obviously advantages.

Compression therapy in CVD - epidemiological data from the Bonn Vein Study

E. RABE (Germany)

A total of 3072 respondents from the general population of the Bonn and rural townships were included in an epidemiological study (October 2000 to March 2002). The aims of the study were:
1. Estimation of the prevalence of CVI in urban and rural population
2. Investigation of the complaints and type of therapy
3. Identification of risk factors for chronic venous diseases.

A special questionnaire, clinical examination, and duplex scanning were used. Distribution of the respondents according to CEAP classification is presented in *Figure 1*.

Most responders had a previous history of venous or lymphatic disorders. Signs of deep venous thrombosis and pulmonary embolism were found in 2.9% and 0.9% cases. 1.1% of the patients had leg ulcers. Reflux in the superficial or deep venous system was discovered in 28% of cases. In 0.9% male and 1,2% of females, there were clinical and ultrasound signs of the postthrombotic syndrome. Different types of treatment were used. Compression stockings were used by 14.6% of the responders.

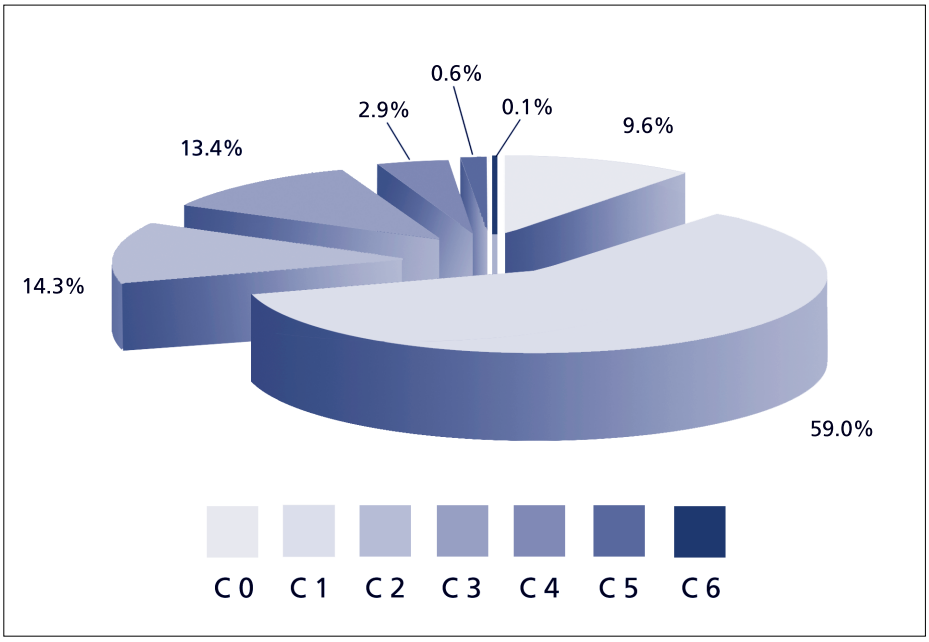

Figure 1. Distribution of the Bonn study respondents according CEAP classification (N=3072)

Monitoring in DVT evaluation

P. ANTIGNANI (Italy)

One thousand two hundred and thirty-eight patients with suspected DVT were investigated with color-flow duplex scan. DVT was found in 354 cases (28,5%). Localization of the thrombosis and its relation with pulmonary embolism is shown in *Table I*.

Table I. Localization of the thrombosis and pulmonary embolism (n=354).

Venous segment	DVT (cases)	Pulmonary embolism (cases)	Frequency of pulmonary embolism (%)
Iiac vein+ IVC	35	19	54,2
Femoral vein +external iliac vein	144	52	36,1
Popliteal vein + femoral vein	107	66	61,6
Popliteal vein	18	6	33,3
Gastrocnemius vein	34	4	11,7
Long saphenous vein	16	5	31,2

Free-floating thrombi were found in 40 cases (11.2%). Twenty-five patients (60.2%) of this group had pulmonary embolism. Very often calf DVT will extend to involve proximal veins and subsequently cause pulmonary embolism and severe post-thrombotic syndrome. Proximal DVTs resolved very slowly in spite of anticoagulant and compression therapy. Ten percent of patients with symptomatic DVT developed severe post-thrombotic syndrome within 5 years. Also, they have a high risk of recurrent DVT. Superficial femoral vein remained occluded in 15% to 20% cases after DVT. Good collaterals protect from severe venous insufficiency. Seventy-five percent of venous segments which were occluded initially were restored during the subsequent 8 to 12 years. Complete resolution of the thrombus is very rare, and can be found only in 30% of cases. Complete and fast lysis of the thrombus during the first 90 days can restore the lumen of the vein without valve damage and prevent CVI in the future.

Compression therapy reduces symptoms and signs of acute deep vein thrombosis and post-thrombotic syndrome

H. PARTSCH (Austria)

Fifty three patients with proximal DVT were randomized into 3 groups:
A. Inelastic compression bandages and walking (18 cases)
B. Thigh-length compression stockings (Sigvaris 503) and walking (18 cases)
C. Bed rest for 9 days without compression (17 cases).
All patients received low-molecular-weight heparin (Dalteparin sc, 200 IU/kg/24 h). Disease-orientated parameters (recurrence, pulmonary embolism, bleeding, death, post-thrombotic syndrome) and patient-oriented parameters (QOL, walking ability, pain, edema) were estimated.

In the acute stage of DVT pain and swelling were significantly improved in the groups A and B vs group C. There was no significant difference in cases of pulmonary embolism between the mobile and bedrest groups. CVI symptoms in A and B groups were significantly lower in comparison with group C during 2 years' follow-up. Thus, immediate ambulation of patients with DVT with good compression on low-molecular-weight heparin provides faster reduction of the symptoms of DVT without serious risk of pulmonary embolism, and reduces the severity of the post-thrombotic syndrome.

C SURGERY

Innovation and challenges. The vascular surgeon at the crossroads

J. FERNANDES E FERNANDES (Portugal)

Innovation has certain requirements (comparison with established technique which is the gold standard, placebo effect, risk versus benefit, cost-effectiveness), limitations (adequate information for patient and relatives; pressure from industry and public; individual needs) and regulations (informed consent).

The introduction of endovascular therapy created a hybrid vascular specialist with surgical and interventional skills, working in a vascular center instead of a surgical unit.

Several vascular problems can be resolved with either surgery or less invasive endovascular interventions:

- treatment of carotid lesions
- treatment of lower-limb ischemia
- treatment of abdominal aortic aneurysm

Decisions will depend on the results of properly designed randomized trials.

In the meantime, we have to invest in well-organized training in vascular science (competence in vascular surgery and medicine).

Minimally invasive treatment of varicose veins

J. BERGAN (USA)

Elimination of reflux in the long saphenous vein (LSV) and perforators with removal of the varicose veins are the basic principles of modern treatment of primary varicoses. Inversion stripping of the LSV provides good long-term results. Unfortunately, crossectomy produces a high risk of neovascularization in the groin region. The neovascularization rate can be as high as 50% during the 5-year follow-up. Radiofrequency coagulation (RFC) and endovenous laser treatment (EVLT) are the new methods of eliminating reflux without crossectomy. RFC provides abolition of reflux and varicose veins in 95.7% of cases during 2 years' follow-up versus 87% after stripping and 58% after crossectomy. EVLT has a similar rating. The LSV was closed in 94% to 100% of cases during a 3-year follow-up. Blood flow through the superficial epigastric vein and circumflex iliac vein protect the stump of the LSV against thrombosis. Obesity (BMI> 30), anti-coagulation treatment, and unsatisfactory technique are the principal causes of a recurrence of reflux and varicoses after RFC and EVLT. Foam sclerotherapy is the method of a choice in the treatment of varicose veins. The foam technique has serious advantages in comparison with liquid sclerotherapy. These are: low concentration, low volume, and high efficacy. The main indications for foam sclerotherapy are saphenous trunk varices, severe CVI, venous angiomas, arteriovenous malformation, and neovascularization after operation. Careful ultrasonic investigation with mapping of all sites of reflux and varicose veins is necessary for the achievement of good results.

Is carotid intervention before coronary bypass grafting necessary?

N. ANGELIDES (Cyprus)

The incidence of neurological vascular events after coronary bypass grafting is from 0.6% to 15%. There are different etiologies of these vascular events but the carotid lesion seems to be the principal etiology. There is no doubt that carotid endarterectomy for symptomatic carotid stenosis must be performed before coronary bypass surgery in patients with stable angina or simultaneously in patients with unstable angina. However there is a lack of evidence, in terms of controlled trials, in patients who need coronary revascularization and present asymptomatic carotid disease. The ACST recommends carotid endarterectomy in healthy men and women under 75 years. The 5-year reduction of neurological vascular events of this group is 6%. The author of this lecture presents one study whose aim is to determine the prevalence of carotid stenosis in coronary surgery patients and determine the timing of carotid and coronary surgery. They review 1250 consecutive carotid duplex studies in asymptomatic patients before coronary surgery. The overall incidence of severe carotid stenosis was 7.36% with this distribution:

- Unilateral stenosis (≥ 70%) 4.32% cases
- Unilateral stenosis (≥ 70%) and contralateral occlusion 0.64%
- Bilateral stenosis (≥ 80% in both sides) 2.4%.

This incidence increases with age and is not different between patients with stable and stable angina. The author states three possibilities in relation to timing for treating these patients:

- Staged surgery, carotid surgery before coronary surgery, in 74 patients
- Simultaneous surgery in 5 patients
- Reverse surgery, coronary surgery prior to carotid surgery, in 13 patients.

The overall neurological morbidity was 6.2%. The final conclusion was not to recommend reverse surgery, and to wait for more results of the carotid stenting before deciding on his indications in this group of patients.

The timing of carotid and coronary surgery in asymptomatic patients continues to provoke an interesting discussion. In the study the small number of patients presented and the distribution do not allow us to make definitive conclusions. For the majority of authors in the literature the mortality and morbidity in the reverse surgery do not favour this option. Nowadays, the principal discussion is the choice between simultaneous or staged surgery. Probably the best solution, until the appearance of specific trials with a sufficient number of patients, it is decided on the timing of surgery depending of the cardiac state. Patients with stable angina must be operated on in stages and patients with unstable angina simultaneously.

FROM ANGIOPLASTY TO STENT AND ELUTING STENTS: ADVANCES AND CONTROVERSIES IN INTERVENTIONAL THERAPY

Chairmen: B. GORENEK (Turkey), Y. HASIN (Israel)

Carotid artery stenting with wallstents: stent inhealing, and arterial remodeling

H. EHRINGER (Austria)

Duplex ultrasonographic information on inhealing of carotid stents is limited.

This prospective study followed the inhealing of 121 carotid Wallstents (112 patients) by colour duplex sonography at day 1 and at 1, 3, 6, 12, and 24 months.

The layer between stent and perfused lumen (SPL) was evaluated in respect of thickness (mm) and echogenicity. The stent diameter was measured in the proximal, middle, and distal stent area. The ratio PSV ICA/PSV CCA served as a hemodynamic index of the degree of the stenosis.

Inhealing of stent was characterized by three phases:

(1) acute unstable phase: at day 1 the inner stent surface was covered by a thick echolucent layer interpreted as a fibrin layer (median 0.70 mm). This layer disappeared at 1 month and rarely resulted in stent occlusion.

(2) moderately unstable phase: from 1 to 6 months the SPL layer is characterized by an increasing echogenecity and a median thickening of 1.00 mm at 12 months. The substrate is an ingrowing neointima (negative remodeling). This phase results in restenosis in 3% to 4% of cases (especially diabetic patients). The diameter of the self-expandable stent is increasing up to 2 years (positive remodeling) and results in a balance of remodeling from 6 to 12 months.

(3) stable phase: from the second year on without further changes in the SPL layer.

Carotid stenting: indications and patient selection

G. BIASI (Italy)

The choice of performing a carotid endarterectomy or a carotid stenting should be based on evidence-based medicine (surgery). Several ongoing trials have been designed for this. We should rather speak of MBIE (medicine based on interpretation of evidence) because we have to deal with potential biases (selection of amplitude of samples, period of observation, type and number of centers included, years before data are available).

The decision of treating a stenotic lesion with carotid stenting depends on the preoperative ultrasound evaluation of the plaque: presence of ulceration, the site of intraplaque hemorrhage, the site and extension of the plaque and especially the GSM (ICAROS study: GSM > 25: 3.09% complications; GSM < 25: 12.90% complications).

According to the author's experience, the key points for performing carotid stenting are:

- local anesthesia
- intervention in the operation theater
- puncturing the groin
- no predilatation
- always use brain protection devices
- poststent deployment dilatation
- completion intracerebral angiography.

PTA/stent is the first option for proximal aortoiliac stenosing disease

J. FERNANDES E FERNANDES (Portugal)

In the treatment of aorto-iliac stenosing disease there has been a trend toward replacing the endarterectomy by grafting, and now there is a tendency towards endovascular procedures.
Several studies have demonstrated the benefit of stenting over PTA with improvement in technical success and long-term patency rates. Indications depend on anatomical location, extension, and degree of the lesion.
In his lecture the author presented his own experience in a group of 114 procedures (claudicants: 73%; critical limb ischemia 27%) with a median abkle-brachial index (ABI) of 0.43. Angiography shows single-level disease in 26% and multilevel disease in 74% of cases.
The author performed 6 PTAs without and 108 PTAs with stenting, the technical success rate being 94.8%.
Cumulative 5-year results show a primary patency of 90%, a restenosis rate of 12%, and an occlusion rate of 7.9%.
In selected cases an endovascular approach must be the first option, with routine stenting being mandatory in order to have similar results to conventional surgery.

Developments in drug eluting coronary stenting: is it the final step?

V. AYTEKIN (Turkey)

After the first surgical revascularization procedure in 1968, intracoronary balloon angioplasty was reported in 1977 and the second important step, stent implantation, started in 1993. The third important step is the introduction of drug eluting stents (2000) for the problem of restenosis. Restenosis is caused by elastic recoil (mechanical phase), thrombosis (thrombogenic phase), neointimal proliferation (smooth muscle cells in media and intima) and negative remodeling (remodeling phase). Treatment of the restenotic lesions with PTA, atherectomy, laser, cutting balloons, etc are not succesfull, but initial results with drug eluting stents are very promising. Drug eluting stents have other specific characteristics: larger surface area and minimal gaps between strudges when you compare them with the classic stents. Different categories of drugs have been tested: anti-inflammatory drugs (corticosteroids, gene therapy with supression of monocytes), immunosupressants (sirolimus, everolimus, taccolimus, ABT-578), antiproliferating drugs (paclitaxel, angiopeptin, 17-β-estradiol), antithrombotic agents and pro-healing agents (EPC captine coating). Future directions show that biodegradable polymers and biodegradable stents may provide additional benefit. Multilayered polymers and stents with laser-cut holes may combine the effects of different kind of drugs on the same stent.

UPDATE ON SURGICAL AND ENDOVASCULAR TREATMENT FOR CAROTID DISEASE

INTERNATIONAL UNION OF ANGIOLOGY AND ITALIAN SOCIETY OF VASCULAR AND ENDOVASCULAR SURGERY
President: G. R. PISTOLESE (Italy)
Chairpersons: D. PALOMBO (Italy), C. PRATESI (Italy)

This session offered an in-depth review of carotid disease focusing on indications, preoperative studies, surgery (CEA), and endovascular (CAS) treatment.

Professor Bertoglio, from Imperia, has summarized the established indications based on the ECST and NASCET trials for symptomatic patients, and the ACAS and recently published ACST results for the asymptomatic patients. Subsequently, he reviewed controversial aspects in different areas: preoperative imaging studies, type of anesthesia, surgical technique, and monitoring use during surgery. The introduction of developments in carotid stenting adds a challenge to the decision-making process but as he said, his personal experience on 221 CEA with a mortality and major stroke rate of 2.7% and 48 CAS with a mortality and major stroke rate of 10% makes him prefer the surgerical procedure.

The tendency to operate on the majority of patients (92%) by using duplex scanning and avoid angiographic preoperative studies in carotid disease was presented by professor Gossetti from Rome. He has described the use of a combination of B-Mode ultrasound and duplex scan to determine the degree of stenosis. He has pointed out the necessity to explore the value of transcranial Doppler studies to asses the intracranial circulation and imaging of cerebral tissue by means of CT scan or MR.

Professor Settembrini from Milan, presented a summary of early and late results of CEA advocating the need for intraoperative quality control in order to minimize postoperative restenosis. This control could be done by means of angiography or preferably colour Doppler. The echo color Doppler allows one to differentiate between normal, moderate (residual plaque of less than 50% or peak systolic velocity (PSV) between 125 and 180 m/s) and severe (flaps, residual stenosis of more than 50% or PSV>180 m/s) which require surgical revision.

Before presenting the indications of carotid stenting, professor Cao pointed out that the main goal of any treatment was to prevent stroke disability. He presented his experience from 2001 to 2003 on 673 CEA and 254 CAS, in which he used different type of filters and stents (Carotid Wallstent ® 89%, Aculink ® 1.5%, and Precise ® 7.5%). The complications in terms of mortality and stroke are 3.7% in CAS and 0.9% in CEA. After the introduction he divided CAS indications on anatomic grounds, such as recurrent stenosis, distal carotid lesions, or postradiation lesions, and medical indications such as severe cardiac or pulmonary disease. In order to avoid CAS complications correct patient selection is crucial, taking into consideration the presence of soft plaque, calcification, tortuosity, aortic arch disease, or advanced age in asymptomatic patients. Regarding the eternal controversy about who performs the endovascular treatment, he remarked on the need for surgical availability in case of needing to convert to open repair, which in his experience, has occurred in 10 patients.

UPDATE ON TREATMENT OF AORTIC ANEURYSMS

Chairpersons: G. DERIU (Italy), and P. GLOVICZKI (USA)

This interesting session was introduced by Professor Norgren, who gave an overview of the different causes which have been related to aneurysm formation such as atherosclerosis, degeneration of arterial wall, inflammatory process, infectious process, and genetics. His personal belief is that there is a genetic base in which different factors take part. For this reason he feels that in the not-too-distant future the treatment of AAA could be done on a genetic basis.

Prof Gloviczki presented the experience at the Mayo Clinic where repair of AAAs represents 15% of the vascular surgical practice, with an average of 250 cases repaired each year. Endovascular (EVAR) treatment is performed with increasing frequency (41% in 2003 and 51% in 2004 January to March). Minilaparotomy and laparoscopic approaches are performed in selected patients. A recent comparative analysis of 355 elective infrarenal AAA (Open repair (OR)=261 and EVAR=94) revealed that 30-day mortality was not different (OR=1.2%, EVAR=0%). Cardiac and pulmonary complications were less frequent after EVAR, although there were more high-risk patients in this group. Graft-related complications were significantly more frequent after EVAR (13% vs 4%) and primary and secondary patency rates at 1 year were lower following EVAR. According to current guidelines at Mayo Clinic, OR is recommended to all good-risk patients with nonruptured AAA, and for all unstable patients who have ruptured AAAs. EVAR is offered to high-risk patients with suitable anatomy for stent grafts. He pointed out that the need for rigorous follow-up with imaging studies, late device-related failure, late reinterventions, aneurysm rupture, and high costs of the device remain legitimate concerns of EVAR procedures. Laparoscopic and robotic techniques for AAA repair and repair using mini-laparotomy deserve further evaluation.

Prof Gerard from France presented his experience on the follow-up of abdominal aorta endoprosthesis with echocolor Doppler. The latter is a good tool to determine and analyse the type of endoleak and to determine the aortic diameter. CT scan could be used in large AAA follow-up and when an increase in aortic diameter is detected it is further investigated by duplex.

The session concluded with the presentation by Prof Riambau from Barcelona, who presented his personal experience on the endovascular treatment of thoracic aneurysms. He pointed out its feasibility, safety and efficacy, offering clear advantages compared with open surgery. Current limitations on the endograft technology should be solved with future technical developments.

Small abdominal aortic aneurysm repair: should availability of endografts influence our decision?

P. KALMAN (USA)

Optimal management of a small abdominal aortic aneurysm (AAA) is controversial: early surgery or surveillance? The definition of a small aortic aneurysm has changed. Szilagy et al (1966) stated that an increased risk of rupture starts at 6 cm. The only tools available at that time were physical examination, plain X-ray, and autopsy. Darling et al (1977) performed 24 000 autopsies and found 473 aneurysms with a rupture degree of 24%. They concluded that even small aneurysms <4 cm can rupture, and should be repaired. In the 1980s and 1990s, retrospective studies showed that the risk of rupture for aneurysms <5 cm in diameter was small.

Prospective, randomized trials were available in 1998 (UK small aneurysm trial) and 2002 (ADAM study) and the conclusion of both studies was that late survival for patients with AAA <5.5 cm was the same whether patients underwent early surgery or continued surveillance.

Selection of patients for AAA repair depends on:

(1) risk of rupture (size of AAA, documented expansion, tenderness, comorbidities such as hypertension, pulmonary disease, smoking, familial predisposition)

(2) elective operative risk: operative mortality rates are falling (impact of hospital volume, surgeon volume and training)

(3) life expectancy: repair is justified if the predicted survival is good

(4) follow-up: if a patient cannot be followed, then an operation is allowed

(5) patient references: Open repair remains the gold standard, and seems highly effective in preventing rupture. The remaining questions of EVAR are: durability, reason for high reintervention rate (20% to 40%), and length of follow-up.

There is no available clinical study, but using a Markov decision analysis model, it was demonstrated that endovascular surgery does not significantly change the size threshold for elective AAA repair.

Surveillance after carotid surgery: it is worthwhile?

R. PULLI (Italy)

Carotid endarterectomy has been demonstrated to be effective in stroke prevention, both in moderate and severe symptomatic carotid artery stenoses and in severe asymptomatic ones. The level of benefit of CEA in stroke prevention lies both in maintaining low perioperative mortality / neurological morbidity rates and in achieving satisfactory long-term results with a low incidence of carotid-related stroke and of significant restenosis/ occlusion. For these reasons, and also considering that contralateral carotid artery atherosclerotic involvement is a common finding in patients undergoing CEA, a postoperative surveillance program of both operated and contralateral internal carotid artery with duplex scanning has been proposed to be mandatory. However, there is no consensus regarding the real cost-effectiveness of such a surveillance program, due to the poor knowledge on incidence, causes, and natural history of carotid restenosis and of disease in the contralateral carotid artery; moreover, even if carotid duplex ultrasound is universally accepted as the method of choice in postoperative surveillance, the ideal frequency and duration of postoperative controls are still controversial. The rate of asymptomatic stent restenosis ranges between 1% and 8% in published series, with a significative correlation between severe restenosis and ipsilateral neurological events during follow-up and a risk of restenosis progression from a lower value to severe degree approaching 20% 5 years after intervention. Atherosclerotic involvement of the contralateral internal carotid artery is common – nearly one third of operated patients suffer from contralateral significative ICA stenosis. The risk of contralateral stroke is higher in the presence of stenosis increase - the annual rate of stenosis progression is reported to be up to 10% for patients with >50% stenosis and 4% for those with >75% ones.

Carotid angioplasty and stenting under cerebral protection: the dark side

M. HENRY, I. HENRY, A. POLYDOROU, A.D. POLYDOROU, E. LE BORGNE, M. HUGEL (France)

Carotid artery stenting (CAS) is a technique which is being increasingly used. The author indicated the high incidence of embolic phenomenon during CAS, the majority of them being asymptomatic. Today there is a consensus about the routine use of protection devices when CAS is performed. However, there are not, in the authors' opinion, any protective devices which offer absolute protection. Some are difficult to use, others do not close the distal internal carotid artery correctly or complicate the procedure.

In the authors' opinion it is necessary to know the different protection devices which are on the market. All of them have advantages and disadvantages. Depending on the case, it would be preferable to use one or another. Probably, reverse flow, described by Parodi will help reduce the ischemic events during CAS.

Renal angioplasty and stenting under distal protection: the way for the future?

M. HENRY, I. HENRY, A. POLYDOROU, A.D. POLYDOROU, E. LE BORGNE, M. HUGEL (France)

The incidence of renal embolism after renal artery angioplasty and stenting (RAAS) is difficult to determine. In many series, renal function deteriorated after RAAS in 20% to 40% of cases. This limits the immediate benefits of this technique.
The author presented his results in 69 cases of RAAS using occlusion balloon or filters to protect renal mass. The results were very good with this technique. The renal function did not deteriorate after the procedure in any case. During the follow-up only two patients deteriorated.
It seems logical to think that if it is necessary to use a protection device during carotid angioplasty it will be necessary use some protection device during RAAS also to preserve renal mass. The question is: which is the best protection device?

Endolaser multidiode 980 treatment of varicose saphenous veins: personal experience on 50 cases

G. DOMPÈ, V. PELLICCIARI, A. CHIERICHINI (Italy)

This is a descriptive study of a group of patients with varicose saphenous veins which have been treated with endolaser. The author compares his results with a group of patients who has been treated with conventional surgery, open crossectomy, and stripping. Although the author compares both groups they are not comparable for several reasons. For example, in the group with surgical treatment the saphenous vein size is bigger than in the nonsurgical group.
The results in the nonsurgical group are better than in the surgical group, but they could be better if the surgical group was operated on with a technique less aggressive than the stripping technique, such as the CHIVA technique.

Endovenous laser treatment of varicose veins compared with traditional surgery

S. KASPAR, K. HAVLICEK (Czech Republic)

In this work the authors compare two groups of patients with varicose saphenous veins, treated with endolaser therapy alone and endolaser with open crossectomy. The results in both groups related to saphenous reflux are similar, but the authors recommend endolaser therapy to avoid the complications of conventional surgery. However, to obtain good results it is necessary to do an appropiate preoperative duplex ultrasound scan and meticulous endolaser management.

Part 4

NEW INSIGHTS IN VASCULAR DISEASE

A CHRONIC VENOUS AND LYMPHATIC DISEASES

The management of chronic venous disease of the legs in 2004: challenges and opportunities

P. GLOVICZKI (USA)

The lecture was an update on the treatment of chronic venous disease, based on the experience of the speaker and his colleagues at the Mayo Clinic.
Venous disease is widespread in the industrialized world, and it ranges from cosmetic problems to the worst complications of the post-thrombotic syndrome.
Ninety percent of venous problems are caused by reflux, and less that 10% is caused by venous obstruction.
Even in 2004, high ligation and stripping of the saphenous vein is the most effective treatment and the gold standard for decreasing venous reflux, against which all other methods must be compared.
Most of the venous operations performed at the Mayo Clinic are of this kind, 1547 high ligation and stripping, compared with 171 SEPS (subfascial endoscopic perforator surgery) for interruption of perforating veins.
Recent data from Dwerryhouse (1999) has shown that performing stripping after ligation decreases the recurrence rate from about 25% to a fourth of this number.
Even if the results are quite good, the recurrence rate appears to be anywhere between 6% and 26%, and the operation is an invasive procedure.
So new methods have been developed, based on endoscopic surgical procedures that aim to obliterate the saphenous vein using radiofrequency and endovascular laser.
Radiofrequency ablation cannot be used in subcutaneous, tortuous, or very large vessels. Results at 4 years appear to be very good, with absence of reflux in 86% of the patients, and no varicose veins in 79%. Randomized clinical trials (EVOLVeS) are on their way, to compare this technique with stripping.
Very good results for laser endovascular therapy (EVLT) were reported by Dr Min and his group, with 98% immediate and 93.4% 2-year success, and with no deep vein thrombosis complications.
Expansion of this experience has of course given slightly different results, and probably these results, including the appearance of a few cases of deep vein thrombosis, which are more representative of the real world.
The possibility of thrombus extension to the femoral vein is a concern with both endovascular techniques.
In the author's experience, heparin prophylaxis, early ambulation, and infiltrating the tissues with tumescence solution appear to be important prerequisites for a successful laser intervention.
Recently, EVLT is representing an increasing part of the intervention performed at the Mayo clinic.
Power phlebectomy and foam sclerotherapy still need to be validated in this setting.
The SEPS procedure has led to rapid healing of the venous ulcers that prompted the operation, but the recurrence rate is still high: 15% at 4 years.
Foam sclerotherapy of the perforators still needs to be compared with the SEPS procedure, and to be validated.
Occlusive disease of the deep veins can still be treated with traditional options like the Palma crossover graft, or with open surgery, but in most cases the primary option is endovascular, and deep vein stenting has positively changed the approach to venous outflow obstruction.
Deep vein reconstruction, both open surgery or endovenous, appears to be limited to a relatively small number of patients, but in the author's opinion its future is bright.

THE PRESENT AND FUTURE OF THE CEAP CLASSIFICATION

President: C. ALLEGRA (Italy)
Chairpersons: P. L. ANTIGNANI (Italy), B. EKLOF (USA)

The revision of the CEAP classification

B. EKLOF (USA)

The CEAP classification is the internationally accepted classification of chronic venous disease based on Clinical manifestations, Etiologic factors, Anatomy, and Pathophysiologic findings. It is 10 years old, and has been published in at least eight languages. Important contributions have been made at several meetings in the last few years, and in 2004 the results of the work of an ad hoc committee of the American Venous Forum will be published.
Some of the problems that will be addressed are a more refined description of the C, differentiating reticular veins from varices at a diameter of 3 mm, the role of the corona phlebectatica, adding to the P a Pn grade, meaning "No identifiable venous pathophysiology."
The date of the examination will be added, and also the level of investigation. The first level is the office visit; the second level is a noninvasive examination, such as Color Doppler and plethysmography, and a third level will be a complex or invasive exploration.
The present structure will be maintained, but it will be made more precise, and at the same time there will exist a basic CEAP for clinical use, and a more complete one, intended mainly as a research tool.
Many issues remain unresolved, but the CEAP has proved to be a tool that helps us all to talk the same language world wide, and its future will be bright.

Epidemiology of CVI and CEAP

A. JAWIEN (Poland)

There are many epidemiological studies on chronic venous insufficiency, but the lack of a uniform classification has made it impossible to get comparable results.
The author presented his study, based on the CEAP classification, and his findings on a population study of more than 40 000 people, taken from patients 18 years and older, studied initially by general practitioners.
A subgroup of 351 patients was studied with Duplex, for a total of 702 legs.
One of the key messages from this study is that among the CEAP parameters, the disability score is the one that correlates less with the clinical classes (C), but more work must be done.

Prognostic value of the corona phlebectatica and CEAP classification

P. CARPENTIER, M.T. WIDMER (France)

Corona phlebectatica is defined as fan-shaped intradermal telangectases on the medial or lateral aspect of the foot, and although it is part of the C1 (CEAP) class definition, there is controversy on the importance of this finding as a prognostic tool.
To assess this problem, the authors used the data of the Basel study, which in 1971 enrolled 4502 workers from the chemical industries of Basel.
In 1982 1441 subjects were selected, with a bias towards people with venous problems, and a complete clinical and photographic assessment was kept for each patient, which allowed the authors to reclassify the subjects according to the CEAP classification.
There were only nine patients who presented with venous ulceration at the end of the study, but considering the presence of skin trophic changes, the presence of corona phlebectatica was one of the strongest clinical predictors of further occurrence of skin trophic changes. The authors propose including it in a revised CEAP classification, despite comments from others indicating that this finding is widespread, and are questioning its utility in the CEAP classification.

CEAP and instrumental evaluation

C. ALLEGRA (Italy)

Professor Allegra stressed the concept that the CEAP classification is an evaluation criterion that offers an objective and synthetic picture of chronic venous disease (CVD), and not some sort of computerized medical record.
Simplicity and usability must be the keynotes of this classification.
One of the most useful investigations in most situations appears to be the duplex scanner–color Doppler, with phlebography reserved for the study of congenital disease, and water volumetry used for the objective assessment of edema.
Newer techniques, such as nuclear magnetic resonance or computerized tomography, have to prove their work.
Older techniques, such as Doppler tensiometry by Bartolo, could find new applications.
Clinical findings always have a pivotal role.

Computer venous registry: how to make CEAP more useful in your practice

J. F. UHL (France)

A. Cornu-Thenard (France) was unable to attend the meeting, so his place was taken by Dr Uhl, who described and then made a live presentation of the CVR software, used to give a real-time CEAP assessment of venous disease in our patients, following simple instructions on the screen.
The program is freely distributed, and available on a CD.

Proposal for the future

J.F. UHL (France)

CEAP has always been seen as a dynamic tool that must be modified, without compromising its stability.
It is still being modified, but there is the need for more solid epidemiological data for a better understanding of chronic venous disease.
The CEAP will be divided into a simple CEAP for routine clinical practice, and an advanced CEAP, mainly used for research.
To the CEAP classification, a Pn will be added to the P part, meaning normal findings, and the date of observation and level of investigation will be added.
There is the need to better assess the C2 group, into which most of the patients appear to be classified.
An interesting concept is that of the venous imputability score, used to assess which symptoms are attributable to varicose veins, and which are not.
A lot of work remains to be done, but the CEAP classification is an extremely useful standard, and it is here to stay.

CEAP: a never-ending "Tower of Babel"

H. PARTSCH (Austria)

The author showed a series of clinical cases where acrodermatitis chronica atrophicans, muscle hernia, Kaposi sarcoma, erysipelas, lymphoma, and other diseases could be easily confused with venous disease. His recommendation is that the CEAP classification system should include a clear differentiation from nonvenous diseases.

CHRONIC VENOUS INSUFFICIENCY - Part 1

Chairpersons: R. SIMKIN (Argentina), J. ULLOA (Colombia)
With the participation of J. H. ULLOA, J. ULLOA (Colombia),
I. PIZARRO, F. IBANEZ, C. SALAS, A. CAM, J.A. PARRA,
V. BIANCHI (Chile), R. SIMKIN, R. BULLOJ, C. SIMKIN (Argentina),
M.E. RENNO DE CASTRO SANTOS (Brazil)

Ulloa reported about new agent for sclerotherapy-lapidium chloride (LC.) It is more effective and safer in comparison with ethanolamine oleate (EO) and polidocanol. Important advantages of LC were the high degree of adhesion of a venous wall and the long period it remained in a microfoam state. Also, there was a smaller range of complications, such as thrombosis, hyperpigmentation, and hemolysis. Pizzarro presented follow-up results (from 3 months to 3 years) of surgical treatment of 16 limbs (14 patients) with deep venous insufficiency (reflux, obstruction, or combination reflux and obstruction) and venous ulcers. Different operations were performed. There were combinations of Palma and Husni operations, transposition of the superficial femoral vein below the competent valves of the deep femoral vein or internal saphenous vein; and transfer of the axillary vein into superficial femoral vein position. The authors drew the conclusion that individually picked up volume of operation allows correction of chronic deep venous insufficiency and achievement of healing of ulcers in 75% of cases. R. Simkin reported on combination surgical treatment of primary varicose veins. Combination of ambulatory phlebectomy, endovenous laser treatment, and subfascial endoscopic perforator surgery was used. The inversion technique or partial resection were the methods for the removal of the incompetent long saphenous vein. Short saphenous vein incompetence was treated with stripping or endoluminal laser coagulation. The authors concluded that such a surgical technique allows minimization of postoperative complications and achievement of good follow-up results. Renno de Castro Santos noted that recurrent varicose veins occur in 7% to 80% of cases. The author emphasized that it is necessary to differentiate true recurrent varicose and residual veins. True recurrent varicose veins are absent in the early postoperative period, while residual veins can be demonstrated immediately after operation. It is necessary to use various diagnostic tests (clinical examination, handheld Doppler, duplex scanning or phlebography, and quality of life questionnaires) reveal the reasons for recurrent varicose veins.

CHRONIC VENOUS INSUFFICIENCY - Part 2

Chairpersons: J. ULLOA (Colombia), R. SIMKIN (Argentina)
With the participation of A. SCUDERI (Brazil), P. KOMLOS (Brazil), H. GUEDES (Brazil)

Scuderi emphasized that badly applied bandages after surgical treatment of varicose veins can cause serious complications. That is why, for the last 20 years, the author has preferred to use a sterile compression stocking which is placed on the leg at the end of the operation. This has allowed him to lower considerably the frequency of edemas and hematomas in the postoperative period, and also to provide the patient with the necessary comfort. Komlos reported his experience with 1780 operations concerning primary varicose veins. He used epidural (85% of cases) or local (15% of cases) anesthesia. The author performs a small vertical incision above the inguinal fold for crossectomy. Long or short saphenous veins were removed by stripping. Small varicose branches were eliminated with crochet hooks and sclerotherapy. The author achieved good long-term results in all cases with a minimum number of minor complications. Guedes reported the summaries of the 1st Latin American Consensus of Lymphedema (March, 21-23, 2003). Thirty-two leading experts from Latin-American countries took part. It was pointed out that lymphedema is characterized by two basic parameters: liquid and protein accumulation in the intercellular space; and internal or external manifestation of the insufficient lymphatic system. It was decided to distinguish between primary lymphedema connected with dysplasia of the lymphatic vessels and secondary to trauma or an infection. It was proposed that history, clinical sympoms (including Stemmer's sign), results of lymphoscintigraphy, and capillaroscopy should be used for diagnostic of lymphedema. The basis of treatment of lymphedema is compounded by complex physical therapy which includes manual drainage and an intermittent pneumatic compression. Also, it is necessary to use a combination diosmin/hesperidin, 5,6 alfa benzopyrones for oral or topical administration, and sometimes diuretics. Antiparasitic drugs are necessary for elimination of Filaria. Indications for surgical treatment are the following: penoscrotal lymphedema, morbid obesity, and giant forms. Microsurgery can be effective at the early stages of lymphedema. The author concluded that combination and permanent treatment of lymphedema protects against infection complications, fibrosis, and lymphosarcoma.

VARICES AND VARICOPHLEBITIS

Chairpersons: N. ALLAF (UK), R. MARTINEZ (Italy)

Tumescent liposuction anesthesia for varicose vein surgery

M. SIMKA, M. PULTORAK (Poland)

Operation for varicose veins can be performed under:
- general anesthesia
- spinal anesthesia
- or local anesthesia.

Each of these methods has advantages and disadvantages.

General and spinal anesthesia are widely used, mainly in hospitals. They make it easy for the surgeon to operate. However, general anesthesia requires a hospital stay, is expensive, and may be associated with toxic reaction. Spinal anesthesia can be associated with increased intraoperative and postoperative bleeding.

Local anesthesia is believed to be the best choice for the majority of patients. The main problems associated with local anesthesia in varicose vein surgery are: the presence of intraoperative pain and the toxic reaction to the anesthetics, which is usually due to overdose.

The authors presented the method based on the tumescent liposuction fluid developed by Geoffrey Klein, which seems to be very well tolerated and safe.

No toxic reactions were reported, even with a dose of lidocaine up to 50 mg/body kg – which for an average patient is equivalent to 3.5 liters of anesthetic fluid. Components for 1 liter:
- physiologic saline (0.9% NaCl) 1000 mL
- lidocaine 1000 mg – (0.1% solution)
- sodium bicarbonate – 10 m Eq
- epinephrine – 1 mg
- triamcinolane – 10 mg

The authors emphasized that it is very important to warm it up to about 40°C, to avoid stimulation of pain receptors that are very sensitive to cold and to introduce the anesthetic fluid slowly, thus avoiding unpleasant sensations. When stripping of the saphenous vein is planed, it is better to use a more concentrated solution.

The advantages of this method are:
- the anesthesia is safe
- the injection of anesthetic fluid is nearly painless, as it is warm and neutral
- lidocaine acts mainly locally
- there is minimal bleeding because with the use of epinephrine the blood vessels are contracted.

The authors compared 20 patients who were anesthetized with Klein's solution with those who received classic local anesthesia. It was found that Klein's anesthesia was associated with less pain, less bleeding, and postoperative hematomas were smaller.

New posterior video-assisted approach to subfascial perforating vein surgery (VASPS)

C. CAMPISI, F. BOCCARDO (Italy)

The subfascial endoscopic ligation of perforating veins allows for accurate treatment of their incompetence. Over the last few years this procedure has been using the medial approach. According to the authors, poor results with lateral subfascial endoscopic perforatory vein surgery seem to be related to misinterpreted perforator anatomy. For this reason the authors proposed a new posterior video-assisted surgical approach. Over a period of 2 - years, video-assisted subfascial perforating vein surgery on both medial and lateral site of the leg in 7 patients were performed. Two 5 - to - 7 cm incisions, the first one in the middle 1/3 of the posterior aspect of the leg and the second one in the lower 1/3, again on the posterior aspect, were made. Diagnosis was performed by means of phlebography and duplex scanning. Postoperative duplex scans showed the absence of incompetent perforating veins in 5 patients. Despite the small number of patients involved in the examination, video-assisted subfascial perforator vein surgery proved to be a safe and an effective procedure in the treatment of severe chronic venous insufficiency caused by incompetent perforating veins in the calf.

THERAPY ACTIVE ON THE HEART AND PERIPHERAL CIRCULATION

Honorary Chairpersons: M. FÖLDI (Germany) A. LEDUC (Belgium), M. OHKUMA (Japan)
Chairpersons: E. AROSIO (Italy), C. CASSAR (UK)

Inflammatory reaction in venous valves induced by venous hypertension is reduced by MPFF

S. TAKASE, L. PASCARELLA, M. E. PUEYO, J. J. BERGAN, G. W. SCHMID-SCHÖNBEIN (USA and France)

In the USA, chronic venous disease (CVD) is a burden for society. CVD is ranked third in the USA by the Vascular Disease Foundation, after lower-limb arteriopathy and aortic aneurysm. Prevalence of CVD in the USA is 27% in the adult population, while it is 13% in France. Early management of CVD is believed to be the best way to avoid the costs of this disease. Researchers from the Whitaker Institute for Biomedical Engineering of California University in San Diego set up an animal model that mimics venous hypertension in human beings. The objective of their study was, in the first instance, to investigate the mechanism of valve destruction in the saphenous veins. In the second instance, the effect of micronized purified flavonoid fraction (MPFF) on the mechanism of valve destruction was evaluated. Chronic venous hypertension was induced by the creation of an arteriovenous fistula (AVF) in Wistar rats. The subsequent venous hypertension was associated with an inflammatory reaction in the venous valves. Animals were divided into 3 groups: 1 control, 1 treated with MPFF 500 mg/kg/day and 1 treated by MPFF 100 mg/kg/day. After 3 weeks during which animals were submitted to venous hypertension, the morphology of the saphenous valves was examined and the inflammatory markers assessed.

The MPFF treatment reduced the shortening of leaflets. In parallel, the reflux flow was inhibited by MPFF in a dependent manner. Also, the number of adherent leukocytes and their migration across the postcapillary venules was reduced by MPFF.

These results suggest that MPFF reduces the inflammatory reaction associated with venous hypertension. In CVD, MPFF might protect venous valves from destruction.

LYMPHOLOGY IN EUROPE AND IN THE WORLD

Honorary Chairpersons: M. FÖLDI (Germany), A. LEDUC (Belgium), M. OHKUMA (Japan)
Chairpersons: P. BOURGEOIS (Belgium), C. CAMPISI (Italy)

The symposium offered an overview of the various methods used, and the main research topics with which doctors from all over the world are involved.

Intermittent compression therapy: to use or not to use? A review of the literature

J. P. BELGRADO (Belgium)

Intermittent compression therapy is the application of force on an edema, to evacuate its components as much as possible.

Many methods are used to reach this goal, ranging from mercury baths to pneumatic devices, but the latter are the only ones used on a large scale. Unfortunately, not only are there few well-conducted studies on this topic, but also they vary extremely in all aspects.

The machines can be mono-or multichambered; now only the multichambered ones are used, as they give better results, but the number of chambers can vary from 3 to 24, and there are no studies that tell us whether there is any difference between them.

The sleeves can be rigid, made of PVC, and tend not to conform to the leg contour, or are made of Hypalon, which is soft and gives better results and comfort for the patients.

Most studies rely on the pressure that is shown by the machine manometer, but it is often more than indicated, and can be even higher if measured directly on the skin - even twice the theoretical value.

The pressures exerted by manual drainage are usually about 8 millimetres of mercury, while the target pressure can be anywhere from 30 to 80 millimetres.

The cycles can vary from 5 to 25 seconds' inflating time, and 20 to 30 seconds' deflating time.

The sessions can last from 1 to 8 hours, and in some studies intermittent pneumatic compression is used by itself, while sometime it follows manual drainage or compression therapy.

Even the outcomes are measured in different ways, and it is almost impossible to compare different studies. Obviously some form of standardization and more extensive studies are needed.

Prevention of secondary arm lymphedema: diagnostic and therapeutic strategies

F. BOCCARDO (Italy)

The authors reported their experience in a small group of selected patients who underwent conservative surgery for breast cancer.
If preoperative lymphoscintigraphy showed impaired circulation in the arm to be treated, microsurgery was performed at the time of lymph node dissection, to restore drainage, and the results were good in the few treated patients.

Complete decongestive treatment in lymphedema

E. FÖLDI (Germany)

The author reported on her experience in a 140-bed clinic for lymphatic disorders, where patients are treated in an integrated way with manual drainage, additional massage, compression bandage, skin care, individually fitted compression garments, and so on.
Two thirds of the patients have other diseases, such as congestive heart failure, and so a medical check-up is very important, as well as the collaboration of trained and motivated physiotherapists.
Patient education, for skin wound prevention, body weight regulation, and increased physical activity is of paramount importance, and increases with patient compliance.
Using this approach, the results are good and are maintained for up to 4 years.

Complications of pelvic lymphadenectomy

E. IKER (USA)

The author presented a series of 25 patients with various degrees of lymphatic problems in the legs and groin after different kinds of surgical intervention for cancer.
It is important that such symptoms are identified early, and surgeons pay more attention to the preservation of lymphatic pathways when operating on this kind of patients, as is now practised in breast cancer patients.

Rehabilitation protocol in upper-limb lymphedema

O. LEDUC (Belgium)

Even with intensive treatment, sometimes patients retain a volume difference between the affected upper limb and the normal limb.
Using MRI the author has shown that in some cases fat accumulation, intermixed with fluid accumulation, is responsible for this durable volume increase.

Management of primary and secondary lymphedema

S. MICHELINI (Italy)

The author showed the results obtained in his lymphedema clinic, using a complex approach to these patients, that includes several specialists, considers psychological aspects, and teaches self-treatment, to maintain a volume reduction of the limb of up to one third after 2 years.

Effectiveness of long-term penicillin in dermatolymphangioadenitis

W. OLSZEWSKI (Poland)

Filarial lymphedema is a widespread disease in the third world, and the disease affects millions of people.
In rural India there is widespread use of locally produced penicillin, Penidur, for long periods of time, to avoid the main complication of lymphedema, that is, recurrent episodes of dermatolymphadenitis (DLA).
The author studied a group of 40 patients who underwent a treatment with intramuscular injection of 1 200 000 units of Penidur every 3 weeks, for 1 year or more, after one or more episodes of DLA, and compared them with another group of 34 patients who for several reasons were unable to receive the same treatment.
In the treated group there were recurrences in 5.6% of the patients, while in the nontreated group recurrences were as high as 76.4%.
There were fewer bacteria isolated in the lymph, tissue fluids, and subcutis of the treated group, but more in the lymph nodes.
No appreciable change in sensitivity to most antibiotics was found in the treated patients.
These data support the use of penicillin for long periods of time in filarial lymphedema to avoid DLA complication.

Prevention of lymphedema. Hazard or fatality?

A. PISSAS (France)

Activity of the Lymphology Centre of the University Hospital of Nancy, Eastern France

G. THIBAUT (France)

Both authors reported their experience in their respective clinics, stressing the importance of prevention, and the role that scars have in disrupting lymphatic flow after surgical interventions.

Genetics of lymphedema – angiodysplasia syndromes: past, present, and future

M. WITTE (USA)

Molecular biology methods can be used to study the numerous (more than 40) familial syndromes that involve lymphedema – angiodysplasia.
These syndromes have been known for many years, but only recently gene mutations and chromosomal anomalies have been linked to these diseases.
Mutant mice and other sophisticated techniques were used to identify such anomalies, but there is the possibility that in the future, gene therapy and other novel techniques could control such conditions.

Lymphorrhea

M. OHKUMA (Japan)

Lymphorrhea is a complication that affects about 3% of patients with lymphedema, involves the exudate of lymph, and can be divided into oozing and vesicles.
The author obtained good results in these cases using a machine that involves magnetic field, vibration, and compression.

B OBSTRUCTIVE VASCULAR DISEASES

Follow-up and natural history after venous thrombosis: the interaction between reflux, lysis, and recanalization

A. MARKEL (Israel)

Deep venous thrombosis (DVT) is a very important medical problem. Pulmonary embolism and postthrombotic syndrome are common complications of DVT. Clinical pulmonary embolism occurs in 26% to 67% of the cases with a mortality rate of 11% to 23%. Anticoagulant therapy begun on time reduces the hazard of pulmonary embolism up to 5% and mortality rate decrease less than 1%. A frequent outcome after DVT is recanalization with restoration of the venous lumen. The basic mechanisms producing recanalization are clot retraction and thrombolysis. Rapid spontaneous or stimulated thrombolysis provides a better prognosis for preservation of valvular function with decreased incidence of reflux. Clot retraction and organization is the basic mechanism of valve cusp injury. The incidence of reflux increases in the months following DVT through the first year. Reflux occurs in about two thirds of limbs after an episode of DVT. Chronic venous insufficiency (CVI) can develop irrespective of localization of the reflux in the deep or superficial venous system. The high risk of CVI increases in patients with reflux in several venous segments. Ulcers occur more frequently with distal thrombosis. Superficial reflux contributes to the development of the postthrombotic syndrome. A combination of deep and superficial reflux, especially in distal veins, plays a critical role in the pathogenesis of the postthrombotic syndrome and ulceration.

VENOUS THROMBOSIS AND POST-THROMBOTIC SYNDROME

Chairpersons: J. FLETCHER (Australia), E. MARCHITELLI (Italy)

Venous thromboembolism and spinal surgery

J. FLETCHER (Australia)

Combined DVT prevention in acute spinal cord-injured patients

A. PIERI, S. AITO, F. MARCELLI, M. D'ANDREA, M. SANTINI, M. GATTI, A. CARNEMOLLA (Italy)

There are a few well-known risk factors for developing deep vein thrombosis following spinal surgery:
- duration of operative procedure
- prolonged postoperative recumbence
- vessel manipulation during anterior surgical approaches
- compression of the femoral venous system depending on positioning of patients.

The effectiveness of venous thromboembolism (VTE) prophylaxis in orthopedic surgery is well documented. A. Pieri et al demonstrated that combined primary DVT prevention (mechanical plus pharmacological) seems to be a valuable method in acute spinal cord injury patients. Due to the possibility of development of spinal hematoma, surgeons are reluctant to use heparin as a VTE prophylaxis.

To assess the incidence of VTE in patients undergoing spinal surgery 170 consecutive patients between January 2000 and December 2003 were examined. Bilateral lower-extremity venous duplex scan was performed preoperatively, within 1 week and 4 to 6 weeks after operation. Mechanical prophylaxis (graduated compression stockings, intermittent pneumatic compression, and early postoperative ambulation) were used in all patients. Heparin was used in 60.5% of patients:
- commenced preoperatively in 16.3%
- commenced postoperatively in 44.2%

The author's findings showed that following elective spinal surgery where mechanical prophylaxis was applied with selective use of heparin, the incidence of DVT was relatively low at 3.6 %; 1.2% occurred after hospital discharge. There was a surprisingly high incidence of preoperative abnormality in 36.3% of patients (33.3 % superficial thrombophlebitis, 3% developed DVT). These abnormalities may possibly reflect patient immobility prior to spinal surgery. There is a need for caution when interpreting findings of DVT; these should be interpreted with great caution if only postoperative scanning is utilized.

Deep venous thrombosis: polymorphonuclear leukocyte integrin profile

G. CAIMI, M.G. TOZZI, C. CAROLLO, B. CANINO, M. MONTANA, F. FERRARA, R. Lo PRESTI (Italy)

During deep venous thrombosis (DVT) thrombogenesis is accompanied by an inflammatory response, and both processes require an interaction between circulating cells and endothelium. The initial reversible interaction between leukocytes and endothelium is mediated by selectins, while firm adhesion of polymorphonuclear leukocytes (PMN) and their subsequent transendothelial migration need the expression of B2 integrins on PMNs. B2 integrins interact with their corresponding endothelial counterligands, especially intercellular adhesion molecule-1 (ICAM-1) and allow PMN to attach and to go across the endothelium. The expression of B2 integrins increases after activation, stimulated during thrombogenesis by thrombin and local production of proinflammatory cytokines. Up to now there have only been a few data regarding PMN integrin pattern in chronic venous disease and no data in DVT. The aim of the study was to examine, in subjects with acute leg DVT, the PMN B2 integrin pattern (CD11a, CD11b, CD11c, CD18). 19 patients with unilateral lower-limb thrombosis were studied.

The decrease in the basal expression of CD11b, which has a key role in the interaction between PMNs and endothelium, has been also observed as a result of short-term venous hypertension in subjects with chronic venous disease. The increase in the basal expression of CD11c may be related to the spontaneous PMN activation, the latter is confirmed, in these subjects, by the increase in PMN cytosolic Ca 2+ content. In DVT subjects after PMN activation the authors observed an increase in all the integrins with the exception of CD11. These data can add some new information to an aspect of DVT which may have therapeutic implications. Up to now the anti-integrin treatment has been investigated in arterial vascular diseases with controversial results. Considering the availability of well-tolerated molecules, DVT may be a new target, especially with the aim of preventing the post-thrombotic syndrome.

Superficial thrombophlebitis as a clinical sign underlying a systemic condition

E. MARCHITELLI, R. PEPE, R. GLORIA, D. MONETTI (Italy)

Superficial thrombophlebitis is a common condition often observed in patients with varicose veins. It is generally considered as a benign, self-limiting disease, despite numerous reports of prolongation of clot into the deep vein system and the development of pulmonary embolism. The authors of the paper consider that in the presence of idiopathic superficial thormbophlebitis, an extended diagnostic investigation should be performed. In 16 patients with varicose veins and in 18 with normal veins superficial thrombophlebitis was observed. In 18 patients without varices, apparently idiopathic, positivity for immunological diseases (6 patients), tumors (5 patients), as well as abnormal coagulation profile (4 patients) were found.

The authors concluded that the real incidence of STV and its thromboembolic complications is still undefined. Duplex Doppler scanning must be performed in all cases, in order to assess the real extension of thrombus in the superficial and deep venous systems. The underlying conditions must be investigated in cases of idiopathic and/or recurrent superficial thrombophlebitis with or without varicose veins.

Ambulatory treatment of DVT of lower limbs

E. DI NARDO, M.R. VILLANI, N. FEDERICI (Italy)

Deep vein thrombosis is the third most common cardiovascular disorder in the western countries. Twenty to 40% of proximal DVTs are complicated by pulmonary embolism. The standard treatment of DVT includes: hospital admission, bedrest, infusion of unfractioned heparin with subsequent compression and walking. The authors proved that ambulatory treatment is effective and is not associated with an increased danger of pulmonary embolism. Forty - four patients suffering from DVT in one or more segments of deep leg veins were examined. Proximal extension of thrombus:

- 9 patients-femoro-iliac segment
- 21 patients-popliteal femoral segment
- 14 patients-below popliteal segment

All patients received LMWH for 1 month and then 6 months' oral anticoagulation therapy with compression stockings.

A follow-up was performed with duplex at 1.3, and 6 months' and CT-scanner at 6 months. No patients had pulmonary embolism episodes. Three patients required hospitalization for caval filter implantation. Thirty patients with complete follow-up had no other symptoms or complications. In the discussion it was underlined that patients with DVT and suspicion of pulmonary embolism need to be hospitalized.

Residual vein thrombosis establishes the optimal duration of oral anticoagulants for the treatment of DVT

S. SIRAGUSA (Italy)

The optimal duration of anticoagulant therapy (OAT) after a first episode of deep-vein thrombosis (DVT) is still uncertain. Agnelli et al reported that long-term anticoagulation therapy is effective in preventing recurrences, but its benefit is lost after its discontinuation. It would be important to identify the individual risk for recurrences for establishing the appropriate therapy. Residual venous thrombosis (RVT), defined as clot persistence over time detected by venous ultrasonography, has been shown to be an independent risk factor for recurrent VTE. RVT is indicative for an underlying hypercoagulable state since recurrences may occur in the controlateral leg as well. This conclusion applies to patients with both idiopathic and provoked DVT.

The advantage of adjusting the duration of oral anticoagulant therapy according to the presence or absence of residual vein thrombosis is still uncertain. The authors performed a randomized controlled trial for evaluating whether the presence/absence of RVT can help establish the optimal duration of OAT in consecutive patients with a first episode of idiopathic or provoked DVT.

Inclusion criteria were the presence of a first episode of proximal DVT (idiopathic or provoked) of the lower limbs, detected by compression ultrasonography. Death and bleeding were the criteria for assessing safety outcomes. Major bleeding was a criterion if clinical, overt, and associated with either a decrease in the hemoglobin level of at least 2 g/L or the need for the transfusion (>2 units) retroperitoneal, or intracranial. Minor bleeding in other circumstances was included. The authors performed an interim analysis on 261 patients who completed a 2-year follow-up.

Characteristics of VTE events

Type of event	Group A1(n=93)	Group A2(n=91)	Group B(n=77)
	RVT present		RVT absent
Total DVT	9(10.2%)	16(17.6%)	1(1.3%)
Ipsilateral	7	12	1
Contralateral	2(21%)	4(25%)	0
Bilateral	0	0	0
Nonfatal PE	0	1 (1.1%)	0

In patients with persistent RVT, 3 months of OAT was associated with a high risk of recurrences (17%). However, the advantage of prolonging OAT is unclear since 1 year of anticoagulation simply delayed the risk of recurrent VTE.

In patients without RVT, OAT can be safely withheld after 3 months because of the low risk of recurrence (<2%). The low rate of events remains for up to 21 months and applies to patients with idiopathic or provoked DVT.

This study, according to the authors, has a clinical impact:

- identifies RVT as a marker for assessing patient's risk of recurrent VTE
- can be applied in patients with either idiopathic or provoked DVT
- in idiopathic DVT, absence of RVT allows withholding of OAT (after 3 months) in almost 30% of patients
- in provoked DVT, presence of RVT identifies high risk patients who may need prolonged OAT.

MICROEMBOLIC EVENTS

Chairpersons: P. L. ANTIGNANI, S. NOVO (Italy)

Cardiac causes of systemic embolism, including aortic arch embolism

D. L. CLEMENT (Belgium)

At least 75% of emboli come from the heart, and atrial fibrillation is the cause in 75% of the cases. The risk of stroke in AF is 3% to 8% per year.
Therapy with 325 mg of aspirin in the absence of any risk factors and anticoagulation therapy for all other cases is mandatory.
Most of these heart emboli are macroemboli, while many microemboli arise from the aortic arch, and can be dislodged by manipulation following angiography, stenting, or surgery.
Some cases are spontaneous, or follow aggressive medical therapy.
Transoesophageal echocardiography can help assess this disease and show plaques that can be more than 4 mm thick, but most of these patients are old, with disseminated atherosclerotic disease and fragile, making them difficult to treat. Statins can have a role in plaque stabilization in these patients.

Carotid ulcers as a cause for embolism

C. LIAPIS (Greece)

Of all strokes, 25% can be attributed to carotid plaques.
The unstable plaque is the one where the fibrous cap is thin and inflammation is more common. The disruption of the fibrous cap can lead to symptoms. Data from the NASCET and ECST studies indicate that ulcerated plaques double the risk of stroke, and that the irregular plaque is a predictor of adverse effects.
Most of these diagnoses are made from angiograms, but an ultrasound assessment would of course be preferable.
Randomized studies are on their way, but up to now it seems that echolucent plaques, the ones that look darker and are difficult to distinguish from blood, are the most dangerous ones.

Microembolic events during carotid surgery or endovascular treatment

B. GOSSETTI, O. MARTINELLI, R. STUMPO, F. FACCENA, R. GABRIELLI, M. MARINO, L. IRACE, F. BENEDETTI-VALENTINI (Italy)

The author reported his experience with transcranial Doppler (TCD) monitoring in almost 1000 patients undergoing carotid endoarterectomy, and 45 patients who underwent PTA of the carotid arteries.

While microembolic signals are quite common during carotid endoarterectomy, most of them are gaseous in nature, and appear as a shower of bubbles on TCD monitoring.

Particulate emboli are much rarer, and in more than 1000 procedures, the clinical complications were 7 strokes, 7 TIAs, and 3 ocular deficits.

Most particulate emboli appeared during carotid dissection.

TCD showed no emboli in 1 hour of preintervention monitoring, but during PTA emboli were present in all patients without cerebral protection, and were distributed in all phases of the procedure.

There was one TIA during angiography, and the use of a protective device, Epifilter, reduced the number of emboli.

Blue toe syndrome

P. POREDOS (Slovenia)

The blue toe syndrome is a localized necrosis of a toe, caused by occlusion of digital arteries by cholesterol crystals and other thrombotic material, in patients that often have palpable pedal pulses.

In 97.5% of the cases, the source is widespread atherosclerosis in the aortoiliac and femoral system, often in combination, it is only 2% from aneurysms. The patients are usually elderly, but the ankle brachial index is abnormal in only 37% of the patients, even if the toe pressure is almost always decreased.

Different clinical presentations are livedo reticularis, and “trash foot”, where there is major foot damage, while the most dangerous form is the involvement of internal organs, and if the kidneys are affected, mortality can be as high as 70%.

The presence of pedal pulses must not lead us astray, and this situation must not be confused with acro syndromes or trauma.

Therapy can be difficult in these fragile patients, and the prognosis is usually poor.

Degree of anticoagulation and microembolic signals in patients with prosthetic valves

D. RIGHI (Italy)

The author reported on a small series of 47 patients treated with a mechanical prosthetic valve, where the highest number of embolic signals were present in inadequately anticoagulated subjects, supporting the idea that microembolic signals in prosthetic valve patients could be more clinically relevant than previously thought.

Microembolic events during peripheral catheterization and surgery

J. FERNANDES E FERNANDES (Portugal)

The final speaker summarized the data that emerged from the session, and stressed the point that in this kind of condition “prevention is the Holy Grail,” our main objective.

C PERIPHERAL OBSTRUCTIVE ARTERIAL DISEASE

Conservative treatment in patients with PAOD: what is evidence-based?

H. RIEGER (Germany)

The high prevalence and incidence of intermittent claudication have a high medical and socioeconomical importance. The author reviews the nonsurgical treatment of this pathology and evaluates evidence-based medicine in the treatment of intermittent claudication with supervised exercise, drugs, and interventional therapy. The evaluation of the results was done in three fields:

- walking distance improvement
- quality of life
- cardiac and neurological evolution related to intermittent claudication

The evaluation-based medicine, through several meta-analyses, has demonstrated the efficacy of supervised training exercise in improving walking distance (evidence-based medicine 1a).

In relation to drugs, only naftidrofuryl, the prostanoids, and cilostazol have demonstrated efficacy in intermittent claudication (evidence-based medicine 1a) but their use is only allowed in a few countries. Naftidrofuryl is accepted almost all countries, cilostazol is only accepted in the USA, UK, Japan and Ireland, and PGE1 is not accepted for to treat intermittent claudication in the majority of countries.

Finally, the author recommends the use of endovascular therapy in the iliac and femoropopliteal sector for patients with intermittent claudication. But this recommendation must be revised. Endovascular treatment, based on TASC recommendations, is a good treatment in moderated iliac like type A and B lesions. Probably the most severe lesions, TASC type C and D, could be treated effectively in the future with the development of more suitable balloons and stents. In the femoropopliteal sector endovascular therapy remains controversial. Probably in patients with type A lesions who have controlled risk factors and have not improved after supervised exercise training, endovascular therapy could be indicated. In cases of type B, C, and D lesions there are not clear results and there is not enough evidence to recommend endovascular treatment. There is a lack of evidence regarding long-term results in the treatment of femoropopliteal lesions with endovascular therapy. Several prospective randomized trials have demonstrated improvement of walking distance after 1 year's follow-up, but not after 2-year follow-up with chronic femoropopliteal lesions which had been treated with angioplasty compared with walking exercise alone. Several meta-analyses, performed in recent years, have demonstrated that endovascular therapy has a definitive role in the femoropopliteal segment, but the exact indication must be defined, since then we must evaluate every case individually before recommending the general use of endovascular therapy in the femoropopliteal sector in patients with intermittent claudication.

THE ESSENTIAL TASC

Chairpersons: L. NORGREN (Sweden), S. NOVO (Italy)

As Prof Dormandy explained, the TASC document is a consensus which was published in 2000 with the aim of improving care of individual patients suffering from peripheral arterial disease (PAD). It was created by a working group where twelve international associations were represented, including vascular medicine, vascular surgery, and radiology. Methodologically they discussed and included existing acknowledged guidelines and tried to reach a consensus in an evidence-based medicine format. The potential health benefits, risks, and costs incurred from the recommendations were assessed. At the present time, in 2004, there is a need of updated data and possible extension of, or changes to, the original issue. This has been noted by the TASC representatives and they are working on The Essential TASC. Prof Belch pointed out the major achievement of the TASC document, which has been used by trainees as a textbook and has permitted a raised profile of PAD, taking into account the CAD risk of this population and the main importance of claudication symptoms.

The different areas where TASC needed to be updated were risk factors, treatment of symptoms, perioperative care, and recommendations. Apart from the general risk factors we generally modify, TASC should consider a more aggressive treatment for hypercholesterolemia and inflammation markers such as fibrinogen. When considering treatment of symptoms, naftidrofuryl and cilostazol should be included for treatment of pain in the legs, and pentoxifiline should be reevaluated because more recent studies are challenging its believed efficacy. Besides, new drugs must be taken into account in the new TASC consensus such as statins, recombinant growth factors, and carnitine. Prof Belch recommended an inclusion of quality of life terms in the new consensus. Perioperative care of this group of patients must be completed with CAD assessment, DVT prophylaxis in all patients, and β-blockers as disoprolol in order to improve surgical outcome. Finally she pointed out the need of avoiding conflicts with other pre-existing guidelines from the different societies using evidence-based medicine form when writing the new consensus.

Prof Norgren explained The Essential TASC project. He differentiated two possibilities: rewriting or publishing an addendum. The plan is to produce an abbreviated document (no more than 100 pages), easily available to general practitioners and primary health care individuals, disseminated through National Societies and interesting to countries outside Europe and North America. In summary, the contents will be: epidemiology and risk factors, management of risk factors and coexisting diseases (including CoCaLis project), intermittent claudication, critical limb ischemia, acute limb ischemia, and a technical section on open and endovascular procedures.

Finally, Prof Clement presented the CoCaLis project as a clinical approach to the management of the patient with limb ischemia who presents with coronary, carotid, or renal disease. This is a document published in *International Angiology* in 2000 and updated in 2003, presented as different algorithms showing how to deal with the different situations the PAD patient could encounter.

TransAtlantic interSociety Consensus (TASC): what's new?

D. L. CLEMENT (Belgium)

The Transatlantic Consensus document aims to set up guidelines that can be used by vascular physicians and surgeons on both sites of the Atlantic. In the present paper, the document published in 2000 will largely be used as a baseline. After proper diagnosis of the disorder, treatment should be focused on controlling the total risk carried by the disease. Intermittent claudication is indeed a major risk factor for developing coronary and carotid artery disease. Checking out risk factors and controlling them is therefore essential in this condition. In this respect the role of antiplatelet drugs such as aspirin or clopidogrel will be highlighted. Stopping nicotine and performing regular exercises, preferably in a supervised class, are very essential approaches to the symptoms – according to recommendations 28 and 29 of the TASC.

The new problem is what to prescribe first: low doses of aspirin or clopidogrel? Results of the CAPRIE study suggest that for uncomplicated PAD and high-risk patients, clopidogrel is better than aspirin and should be prescribed first.

Many drugs have been developed in the past. Due to recommendation 30 of TASC pentoxifylline, buflomedil, naftidrofuryl, and more recently cilostazol have been shown to objectively improve walking distance, but the improvement for most of them is rather small. Recent studies have also shown that naftidrofuryl is also capable of significantly improving quality of life – NIQOL European Study Program.

The role of other drugs such us statins and ACE inhibitors has not been defined. The ASCOT study using atrovastatin has shown a reduction in cardiovascular events from 22% to 14% for statins. Further studies are needed.

Clinical approach in the second and third stages of peripheral obstructive arterial disease

R. MARTINI G. M. ANDREOZZI (Italy)

Fontaine's second and third stages represent two completely different levels of peripherial arterial disease. The second stage should be assessed keeping in mind that patients are at greater risk of dying from the complications of the atherosclerosis. Claudication needs treatment planned to modify factors responsible for the progression of atherosclerosis and development of atherothrombotic complications such as smoking, diabetes, obesity, hyperlipidemia, hypertension, and raised homocysteine. Long-term and low-dose aspirin and regular supervised walking exercise are likely to be beneficial for legs and general disease. Drugs such as pentoxifylline, naftidrofuryl, or cilostazol improve claudication. Propionyl-l-carnitine has been shown to improve claudication, also improving ischemic muscle metabolism. Ankle brachial pressure index, and a walking test, as well as screening for carotid artery disease or cardiovascular disease should be performed. Diabetic elderly patients walking rarely may not have typical claudication - in these patients a microcirculatory test such as toe pressure or $TcpO_2$ should be performed to predict the onset of chronic limb ischemia. The Second "b" of Fontaine or the severe caludication stage of Rutherford shows a microcirculatory pattern more similar to chronic limb ischemia than to claudication. So in this case clinical decisions about the type of treatment should be based on imaging and/or microcirculatory tests as well patients' lifestyle on one hand and on estimation of the risk of treatment and predictable period of improvement on the other.

The third stage of Fontaine, or rest pain stage, is the onset of chronic limb ischemia. So patients should be assessed keeping in mind that chronic limb ischemia has a poor prognosis for patient limb survival. It is well known that about 60% of patients with PAOD have carotid artery disease or cardiovascular disease, and 40% of patients with cardiovascular disease present with PAOD symptoms. Presentation of leg ulceration at this stage is a less predictable factor for leg amputation than local low blood pressure. So imaging of the arterial tree to rapidly perform revascularization if possible is needed.

MEDICAL THERAPY POSITION IN POAD AT THE SECOND AND THIRD STAGE

Chairpersons: C. ALLEGRA, M. DI SALVO (Italy)

Epidemiology of PAOD and risk factors

E. HUSSEIN (Egypt)

Peripheral arterial occlusive disease (POAD) is caused in the vast majority of patients by atherosclerosis. The prevalence may vary in different parts of the world. However, outcomes of large studies such as the Framingham and Basle studies indicate an incidence of 1% below the age of 50 years, which rises sharply to around 5% above that age with a much higher male preponderance over females. There are a great number of factors which can increase atherosclerotic prevalence. All of these can be divided into two groups – genetic and metabolic. Genetic factors such as gene polymorphism or congenital hyperlipidemia can improve atherosclerotic changes without any symptoms and signs of disease, even at a young age. Metabolic factors are divided into two groups:

- the most important are: arterial hypertension, hypercholesterolemia, diabetes mellitus, and obesity, and the second factors related to lifestyle such as stress and lack of exercise.

Each of the risk factors has an independent influence on plaque formation contributing to proliferation, apoptosis, and thrombotic changes inside the plaque and on its surface. Thus, plaque structure varies due to different intensity of influence of specific factors on one hand, and of apoptosis, proliferation, calcification, and inflammatory changes on the other. In addition to the factors which influence plaque progression and internal structure there are a great number of other so-called aggravating risk factors such as hyperviscosity syndrome, polycythemia, leukemia, thrombophilia, lupus erythematosus, anticoagulants, dysfibrinogenemia and arteritis. These are related to thrombotic complications in the macro- and micro circulation. The main presentation of atherosclerotic changes is claudication, and progress to critical limb ischemia in only in the minority of these, especially in diabetic patients. Complicated plaque with thrombosis is an end-stage PAD related to rest pain, ulcers, and gangrene.

NEW HORIZONS IN THE MANAGEMENT OF ATHEROTROMBOSIS: WHAT ARE THE CRITICAL ISSUES?

Chairperson: J. J. BELCH (UK)

Introduction: a call to action

J. J. BELCH (UK)

Peripheral arterial disease is a distinct atherothrombotic syndrome that is associated with an elevated risk of cardiovascular and cerebrovascular events.

The severity and high prevalence of this disease is underestimated, and multilevel pathologies (coronary, and extracranial vessels, upper-and lower-this limb arteries) are underdiagnosed and this results in undertreatment.

In 2003, the Prevention of Atherothrombotic Disease Network, an international, multidisciplinary group, published a "Call-To-Action" paper with the goal of increasing awareness, detection, and treatment of PAD.

The key action points were:

- increase awareness of PAD and its consequences
- improve the identification of patients with symptomatic PAD
- initiate screening protocols to increase early detection rates in patients at high risk for PAD
- improve treatment rates among patients diagnosed with symptomatic PAD.

Challenging underdiagnosis and undertreatment in PAD: what must we do?

G. AGNELLI (Italy)

Peripheral arterial disease is a major health risk worldwide. The prevalence is high, the risk of myocardial infarction is up to four times higher, and the risk of stroke two to three times higher than in the general population. The relative 5-year mortality for PAD patients is 44%, while over 10 years, 55% of PAD patients die of coronary artery disease and a further 10% of cerebrovascular disease.

Underdiagnosis of PAD is a significant problem, since 41% are symptomatic (33% typical claudication, >50% leg pain on exercise, <5% to 10% critical leg ischemia) and 59% asymptomatic.

Diagnosis of PAD is of high clinical importance since only 25% of PAD patients are undergoing effective treatment.

The PATHOS project studied the frequency of PAD in 1772 patients (screening ABI) admitted to hospital for myocardial infarction, angina pectoris, stroke, or TIA. The study revealed that 30% of these patients had concomitant PAD.

The objectives of therapy for PAD patients are:

- prevent death and disability
- increase quality of life and walking distance
- save limbs.

Preventing atherothrombotic events with clopidogrel: what we know

W. HIATT (USA)

Atherothrombosis represents the unifying pathophysiology of a broad range of cardiovascular diseases. The Antithrombotic Trialists Collaboration meta-analysis provides ongoing recommendations for the use of low-dose aspirin (ASA) in the secondary prevention of cardiovascular events. However, there are additional medications available to optimize treatment for specific groups within the overall cardiovascular population.
Clopidogrel is one of these medications that has been studied in four completed trials.

- CAPRIE: 19185 patients. The study demonstrated that in patients with PAD, clopidogrel was superior to aspirin, providing an overall 24% risk reduction for preventing subsequent cardiovascular events.

- CURE (PCI-CURE): patients with an acute coronary syndrome with unstable angina received a double-blind treatment with aspirin and placebo or with aspirin and clopidogrel. There was a relative risk reduction of 31% provided by the aspirin-clopidogrel combination.

A higher bleeding risk was noticed and required a lowering of the aspirin dose.

- CREDO: PCI patients were treated for 3 to 24 hours before intervention with aspirin + placebo or clopidogrel + aspirin. The combination of clopidogrel-aspirin was superior in preventing cardiovascular events.

- MATCH: aspirin did not show additional clinical value in high risk cerebrovascular patients when added to clopidogrel (there was a non-significant relative risk reduction of 6.4%).

New horizons in the management of atherothrombosis: where are we heading?

I. BAUMGARTNER (Switzerland)

Atherothrombosis poses a significant public health risk and is responsible for over 28% of deaths worldwide.
Publication of results from clinical trials (CAPRIE, CURE, PCI-CURE, CREDO) confirms the potential role of clopidogrel in reducing cardiovascular events.
Ongoing clinical trials help to advance our understanding of atherothrombosis and help to develop future treatment strategies.

- CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation, Management and Avoidance): a large, phase III, multicenter, randomized, parallel-group, double-blind trial of clopidogrel versus placebo on top of background therapy including low-dose ASA in patients at high risk of atherothrombotic events.

- CAMPER (Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularization): evaluates whether clopidogrel versus placebo, on top of standard therapy including ASA, will lead to an increase in the combined rate of primary patency or survival in subjects following PTA +/- stenting.

- CASPAR (Clopidogrel and ASA in Bypass Surgery for Peripheral ARterial disease): double-blind, randomized study of clopidogrel versus placebo, on a background of ASA in patients receiving a unilateral below-knee bypass graft.

SKELETAL MUSCLE METABOLISM AND VASCULAR ENDOTHELIUM. A NEW HORIZON IN THE TREATMENT OF PERIPHERAL ARTERY DISEASE

Chairpersons: W. HIATT (USA), S. NOVO (Italy)

LECTURE

Endothelial dysfunction and atherosclerosis: clinical relevance

P. POREDOS (Slovenia)

Healthy endothelium plays a central role in cardiovascular control. Therefore endothelial cell dysfunction (ED) may have a particularly significant role in the pathogenesis of atherosclerosis. ED is a consequence of the harmful effects of risk factors of atherosclerosis on the vessel wall and is closely related to the number of risk factors, to their intensity and their duration. ED has been demonstrated in subjects with hypercholesterolemia, diabetes, hypertension, smoking, and in patients with atherosclerotic disease (coronary or peripheral). The involvement of risk factors in ED is also supported by results of intervention studies that showed regression of ED with treatment of risk factors. Improvement of ED may be achieved by elimination of risk factors, by substitution of natural protective endothelial substances, inhibitors of endothelium-derived contracting factors (ACE inhibitors), cytoprotective agents (free radical scavengers such as superoxide dismutase), lipid-lowering drugs (statins) or diet and physical exercise. All these data show that ED is reversible and by treatment of risk factors it is possible to restore vascular function. ED promotes progression of atherosclerosis and probably plays an important role in the development of thrombotic complications in the late stages of the disease. There are two groups of markers of ED:

1) disturbances of vessel-wall function
   - ↓ dilatation capability
2) circulating markers of ED:
   - ↓ NO availability, ↑ endothelin
   - ↑ Von Willebrand factor
   - ↓ T-PA, ↑ PAI
   - ↓ Prostacyclins, ↑ TXA_2
   - ↑ Adhesion molecules (VCAM-1, ICAM-1, P-selectin)

Using markers of ED it is possible to follow dose-response or harmful effects of risk factors and the effects of preventive procedures on vessel wall function. Determination of ED also has important clinical implications. It was shown that ED is significantly and directly correlated to the occurrence of cardiac events increased as ED worsens.

Propionyl carnitine: not only a metabolic drug

G. BREVETTI (Italy)

Carnitine is a natural amino acid that plays a key role in the metabolism of skeletal muscle. It permits long-chain fatty acid oxidation and reduces the intracellular buildup of noxious metabolites. The latter function is particularly important under ischemic conditions when acyl CoA accumulates within the mitochondria and inhibits many enzymatic activities.

In 1980 it was published that carnitine supplements improve cardiomyopathy due to carnitine deficiency, and the link to peripheral arterial disease was made by correlating the plasma levels of short-chain acetylcarnitine and walking capacity. Propionylcarnitine (PCL) is a carnitine derivative that provides additional substrates for energy production (in comparison with carnitine) and so supplements are more effective in improving exercise tolerance, walking capacity, and quality of life in patients with intermittent claudication.

PCL is not only a metabolic drug; the pleiotropic effects of PCL are:

- Endothelium-mediated vasodilatation
- free radical scavenging
- anti-inflammatory action (inhibits the synthesis of platelet activator factor from neutrophils)
- endothelium-protective properties.

In summary, PCL is an endothelium-dependent vasodilatator which inhibits PAF synthesis, reduces oxidative damage, reduces peroxidation, improves endothelial function, attenuates intimal hyperplasia following vascular injury, and reduces atherosclerotic lesions.

INFECTIONS, INFLAMMATION, AND ENDOTHELIAL DYSFUNCTION: FROM BENCH TO BEDSIDE

Infectious serology and PAD: how burdensome is the risk?

S. NOVO, I. MURATORI (Italy)

Peripherial arterial occlusive disease (PAOD) is recognized as a symptom of systemic atherosclerosis. Patients with PAOD, even in the absence of a history of myocardial infarction or ischemic stroke, have approximately the same relative risk of death from cardiovascular causes as do patients with history of coronary or cerebrovascular disease. The age-adjusted prevalence of PAOD is approximately 12 percent, and the disorder affects men and women equally. In many papers it was shown that persistent infections can promote proinflammatory, procoagulant, and proatherogenic environment and induce autoimmunity against vascular cells, so leading to an atherogenic process. There are many molecular mechanisms which lead to inflammatory changes, but the most visible for investigators are the increased concentration of different types of antibodies. In the end of the 20th century a correlation was shown between *Chlamydia pneumoaniae* infection and the occurrence of abdominal aortic aneurysm. Many of these patients presented a high concentration of IgG and IgM antibodies. Further observations shown that *Herpes simplex* virus and *Chlamydia pneumoniae* are able to initiate and accelerate the atheromathous process - this was demonstrated both in animals and humans. In hypersensitive patients with high concentration of SIgA and IgG against HSV and *Chlamydia* there was an 8.5-fold increased risk of stroke and 2.7-fold increased risk of cardiovascular events.

All changes caused by micro-organisms can be divided into two groups: local and systemic.

Local changes are related especially to dysfunction or endothelium injury and can be revealed as:

- proliferation and migration of smooth muscles
- local release of cytokines
- inflammation
- modulation and/or inhibition of prostaglandins
- reduction in nitric oxide
- expression and/or modulation of nuclear factor kB
- modulation of apoptosis
- increase in TNF alpha and metalloproteinases

Systemic mechanisms are more complicated and manifest themselves as:

- inflammation and increased blood levels of inflammatory cytokines
- leukocytosis
- induction of C-reactive protein and fibrinogen
- alteration of hemostatic factor levels
- hyperviscosity and hypercoagulability
- autoimmunity (heat shock protein expression)
- genetic polymorphism of CD 14 receptor

There are very interesting results of a multicenter study of PAOD and *Chlamydia pneumoniae*, *Helicobacter pylori*, and *Cytomegalovirus* infections in young women with a several-fold increased CRP level. It was shown that increased level of IgA blood concentration is related to a twofold increased risk of PAOD for women with *Chlamydia pneumoniae* infections and 1.6 times for both *Helicobacter pylori*, and *Cytomegalovirus* infection. Finally it is still undetermined as to whether elevation of these inflammatory markers reflects the degree of underlying atherosclerosis or plaque vulnerability or rather results from some other environmental of infectious stimulus, or even has direct effects on platelet aggregation and coagulation. Ongoing future investigation will clarify the specific pathophysiologic relationships through which these markers correlate with adverse prognosies.

Peripheral arterial disease, inflammation and cardiovascular risk: does endothelial dysfunction provide a link?

G. BREVETTI, A. SILVESTRO (Italy)

Peripheral arterial disease (PAD) is associated with increased cardiovascular risk which, however, appears to be independent of classic risk factors and only partly explained by the expected association of PAD with coronary and carotid artery disease. Conversely, poor long-term prognosis of these patients is strongly related to severity of PAD and has been recently found to be associated with elevated plasma levels of inflammatory markers. A possible mechanism linking severity of circulatory failure in the affected limb and acute phase of proteins to cardiovascular risk could be endothelial dysfunction. Actually, when affected by inflammation and other injurious stimuli, endothelium may adopt a phenotype that, by predisposing to vasoconstriction, thrombosis, leukocyte adhesion, and smooth muscle proliferation, facilitates the formation and progression of atherosclerotic lesions. It is very interesting that acute maximal exercises amplified systemic endothelial dysfunction.

PAD patients have a marked impairment in endothelial function, that in addition to classic risk factors is related to severity of the circulatory failure in the affected limb and with increased plasma levels of several inflammatory markers. Changes are observed not only in affected limbs. This suggests that endothelium, being a target that integrates the damaging effects of traditional and novel risk factors, may be a barometer for cardiovascular risk. Indeed in PAD patients, brachial artery flow-mediated dilatation (FMD), a marker of endothelial function, is an independent predictor of future cardiovascular events. Even more importantly, FMD improves the predictive value of ankle/brachial index which is currently the most powerful prognostic indicator in PAD. What is missing is the demonstration that interventions specifically aimed at improving endothelial function protect against cardiovascular risk.

Role of oxidative stress and white blood cells in peripheral arterial disease

S. SIGNORELLI (Italy)

Many cellular reactions can originate from ischemia, and this cellular damage has been called "oxidative stress" (OS). OS has a crucial role as it is able to affect cell and vascular damage. Different authors have found: reduction of redox ability of cells, increase in release of free radicals from O_2 increase of lipid peroxides, increase in neutrophil pooling, and endothelial cell damage. In peripherial arterial disease there was a higher level of direct and nondirect markers of oxidative stress, such as melonildhyaldehide and oxidized low density lipoproteins in comparison with controls. On the other hand in PAD patients lower levels of glutathione peroxidase enzyme were found. The imbalance between oxidative and redox status was stressed in PAD patients in a treadmill exercise. In fact there was a relationship between OS and cell damage, and this has been demonstrated by high release of cytokines as interleukin 1, 1B, and IL6, both with high levels of intercellular adhesion molecule 1 (ICAM-1). Moreover, there were higher levels of selectins (L,E,PS). More studies have been addressed at studying antagonism of the OS as a crucial key to ischemia and pathophysiology of PAD patients. Interesting results have been reached both in clinical events (ie, intermittent claudication, absolute free walking distance, skin condition and integrity, outcome of disease) and in endothelial markers (ie, reactive post ischemia / hyperemia markers of the OS, cell damage markers).
Some metabolic drugs such as L-carnitine, increase the clinical performance of PAD patients and also cytokine and integrin release – this can be considered as an interesting therapeutic approach to antagonizing OS.

Inflammation in peripheral arterial disease: a predictor of disease progression?

J. J. BELCH (UK)

The atherosclerosis is a more complicated process which receives major contributions from inflammatory mechanisms. The main role in this process is played by white blood cells count (WBC) which is recognized as a predictor of the disease even in the normal range. Physical rolling of WBC in PAD is related to their adhesion and aggregation to the vessel wall – this is observed in patients with claudication and predestined to progressing of critical ischemia. The products released from WBC such as free radicals and proteases intensify oxidative stress and improve endothelial dysfunction. Insufficiency in nitric oxide production by endothelial cells leads to smooth muscle proliferation and degenerative changes. The physical obstructive effects of WBCs combined with oxidative stress generated by these cells and other mechanisms such a reperfusion have a potential deleterious effect in patients with peripherial arterial disease. All these result in poor vasorelaxants function and progression to critical limb ischemia. It was clearly documented that coexistence of inflammatory diseases improves oxidative stress and intensifies atheromatic changes. On the other hand, coexistence of rheumatoid disease with PAD can improve the mortality ratio, for instance 3 fold for rheumatoid arthritis or 4.5 fold for systemic lupus erythematosus. So there is a necessity to focus future studies on this area, and for new therapies not only focused on inflammatory disease but on prevention of atheromatic systemic changes.

Outcome of conservative therapy in patients with severe intermittent claudication

J. AMIGHI, S. SABETI, O. SCHLAGER, M. FRANCESCONI, R. AHMADI, E. MINAR, M. SCHILLINGER (Austria)

This was a retrospective cohort study which aimed to asses the intermediate-term outcome of conservatively treated claudicants, and determine predictors for clinical improvement.
The majority of patients remained clinically and hemodynamically stable. In 20% of the patients who improved clinically, hemodynamic changes were also present. Only a few patients worsened. The worst results were observed in female patients, diabetic patients, and in patients with initial ABI under 0.44.
This study presents several limitations. It is not randomized, it is retrospective, and the patients did not do the exercise under supervision. However, it would be interesting to know which patients will not improve with conservative treatment.

Disease-specific quality of life analysis in intermittent claudication: is it really necessary?

T. MEHTA, I. CHETTER, A. VENKATASUBRAMA, K. MYLANKAL, B. RAY, P. McCOLLUM (UK)

The authors compared three disease-specific quality of life instruments (QOL) in a group of 67 patients with intermittent claudication which were Claudicant Scale (Claus), Kings College Vascular Quality of Life (VASCUQOL) and Sickness Impact Profile: Claudication Specific (SIPIC) and the general QOL scales like SF36 and EUROQOL.
The correlation between disease-specific QOL measures and walking distance is high in the three specific tests. The CLAUS offers no advantage, but the VASCUQOL and the SIPIC are more useful than the generic tests to evaluate quality of life in patients with claudication.

Combination of high homocysteine levels and low ankle-brachial index predicts mortality

C. DIEHM, S. LANGE, H. DARIUS, R. HABERL, D. PITTROW, B.V. STRIZKY, J. R. ALLENBERG, G. TEPOHL, J. J. TRAMPISCH (Germany)

This is a study based in the German Epidemiological Trial on Ankle Brachial Index (GET ABI). It is an observational prospective 3-year study in 6880 unselected patients aged ≥ 65 years. This study was created to determine the real incidence of peripheral arterial disease in the German population. The principal results of this study are no different from other epidemiological studies developed in other European countries. The incidence of peri - pheral arterial disease measured by the ankle brachial index was 18%. The incidence of PAD increases with the age, current smoking or past smoking, the presence of diabetes, or high homocysteine levels. Finally the author points out the premature mortality of patients with low ABI and high homocysteine level.

Noninvasive assessment of collateral circulation and capillary filtration

H. K. DEOL, L. SINGH, M. ASLAM, N. J. STANDFIELD (UK)

The authors describe a new noninvasive method to evaluate collateral circulations and capillary filtration in a group of patients with peripheral arterial disease (PAD) and diabetes mellitus (DM). They measured blood flow in the popliteal artery by ultrasound and total limb blood flow and capillary filtrations by optoelectronic plethysmography. In the patients with PAD there was an increase in total blood flow and in popliteal blood flow which can be attributed to the development of their collateral circulation. This increase was not observed in diabetic patients. Probably the alteration of the microcirculation which exits in diabetic patients is the reason for the lack of increase in blood flow. This method could help study microcirculation in PAD, but is not very useful in the clinical practice.

Treating claudication: angioplasty and exercise, not angioplasty or exercise

T. MEHTA, I. CHETTER, A. VENKATASUBRAMA, K. MYLANKAL, B. RAY, P. McCOLLUM (UK)

The authors compare two groups of patients with intermittent claudication due to angioplastiable femoropopliteal lesions. One group was treated with angioplasty (PTA) alone and the other was treated with angioplasty and a supervised exercise program (PTA+SEP). All the patients were evaluated 3 months later. In both groups there were improvements in the maximum walking distance, quality of life measured by SF36 test, and in the ankle-brachial index, but the increase was superior in the PTA+SEP group.

Probably the first option for treating patients with intermittent claudication due to femoropopliteal lesions is exercise, reserving open surgery or endovascular treatments for some special cases. Obviously supervised exercise will improve the results. In any case, it is important to recommend exercise after any kind of vascular treatment.

The activation of the hemostatic system in PAD

P. GIOLINO (Italy)

There are no clear definitions of atherothrombosis. It may be defined as:

- thrombus formation on an existing atherosclerotic plaque
- or generalized progressive disease of large and middle-sized arteries that affects multiple vascular beds, including cerebral, coronary, and peripheral arteries.

The classical view of thrombosis presents in two ways: platelet activation and coagulation cascade. However, contemporary observations show that the process is more complicated. Thrombosis is initiated by tissue factor. Thrombin triggers platelet activation. Platelet surface plays a central role in coagulation factor assembly and burst of thrombin generation.

So the present observations distinguish three phases of coagulation:

- initiation
- priming
- propagation.

Analysis of the data from the Framingham Heart Study showed that atherothrombosis reduces life expectancy by around 8 to 12 years in patients aged over 60 years. In many other papers relationships were shown between intensification of PAD and high concentration of different products of thrombogenesis. It is important that all these disturbances are related to endothelial cell damage or dysfunction. So PAD should not be considered as a local disease, but rather as a clinical manifestation of atherothrombosis. These observations should prompt us to extend prescription of antithrombotic drugs.

D MISCELLANEOUS

Vascular disease in diabetes: epidemiology, pathophysiology, and treatment

M. A. CREAGER (USA)

The number of diabetic patients is increasing enormously, especially in developing countries. Atherosclerosis is the major cause (80%) of diabetic mortality (75% coronary, 25% CVA or PAD).

Potential mediators of vascular disease (atherosclerosis) in patients with diabetes mellitus are:

1. abnormalities in endothelium, vascular smooth muscle, and platelet function
2. metabolic abnormalities:
   - hyperglycemia
   - increased free fatty acids
   - insulin resistance

These mediators have their effect on the endothelial layer and cause vasoconstriction, inflammation, and thrombosis. These abnormalities contribute to the cellular events that cause atherosclerosis and subsequently increase the risk of adverse cardiovascular events.

Agressive medical treatment that optimizes glucose control (insulin, metformin), achieves normal blood pressure (ACE inhibitors, β-blockers), corrects dyslipidemia (statins, fibrates) and prevents thrombosis (platelet function inhibitors) is necessary.

NEW INSIGHTS INTO RARE VASCULAR DISEASES

Chairpersons: L. BOON (Belgium), I. QUÉRÉ (France)

From homocysteinuria vascular phenotype to mild homocysteinemia

I. QUÉRÉ (France)

Homocysteinemia is a rare constitutive metabolic disease but is treatable. It is defined by a plasma homocysteine concentration above 100 µmol/L, combined with a urinary excretion of large amounts of homocysteine. Homocysteinemia is the result of an enzymatic defect in one of the methionine metabolism pathways. The most common cause is a cystathionine β synthase (CBS) deficiency in the transulfuration pathway. It is characterized by high methionine and low cysteine levels and chronic intoxication disease. An impaired remethylation pathway may also occur, due to defects in methionine synthetase, in methylenetetrahydrofolate reductase (MTHFR), or in enzymes involved in the metabolism or transport of cobalamin. It is characterized by low methionine levels and an acute disturbance in stressful situations.

Histologic vascular abnormalities in patients with homocysteinuria are at the level of large and medium-sized arteries, with focal intimal and medial fibrosis and proliferation of perivascular connective tissues surrounding small arteries. The intima/media thickness measured by echography is much higher than in controls.

Hyperhomocysteinuria, whatever the type of enzymatic deficit, leads to an increased risk of venous and arterial thrombosis. In a cohort of 629 patients with CBS homocystinuria, 25% had thrombosis before the age of 30 years, (49% arterial thrombotic events and 51% venous thrombotic events), In all the published cohorts, venous risk of thrombosis is high, even in patients without other risks of VTE, mutation of factor V for example.

Treatment of homocysteinuria by vitamin B6 (pyridoxine) reduces the risk of thrombosis. In a cohort of 158 patients, 50% of them were responders to treatment with vitamin B6, and 50% were not. Only 17 thrombotic events were observed during follow-up instead of 112 expected without treatment. Despite effective treatment with vitamin B6, the thrombotic risk remains 5 fold superior to the risk observed in the general population.

The prevalence of homocystinuria is underestimated and is probably closer to 1/30 000 live born babies than the previous expected prevalence of 1/ 300 000. This may be due to mild phenotype with predominant vascular thrombotic phenotype diagnosed in the adulthood.

Genetics and mechanisms of aortic aneuryms: from Marfan to isolated familial aneuryms

C. BOILEAU (France)

Thoracic aortic aneuryms may have a mendelian inheritance in Marfan (MFS) and Marfan-like syndromes (MFLS). MFS is diagnosed only by a clinical approach, screening for eye, skeletal, cardiovascular, pulmonary, skin, and integument abnormalities. MFS is associated with mutations of the FBN1 gene located on chromosome 15 and coding for fibrillin 1. More than 600 mutations have been identified in complete and incomplete forms of MFS, each family having its own mutation. Fibrillin 1 mutations have also been identified in various overlapping disorders, among which are isolated forms of aortic aneuryms. Fibrillin-1 is the major protein component of microfibrils, that are closely associated with elastin fibers in elastic tissues such as the aortic media. Pathogenic steps of the formation of aortic aneuryms have been identified in the mouse model with fibrillin 1 mutations and a Marfan phenotype.

Probands (n=81) presenting with isolated thoracic aortic aneuryms were investigated and 16 of them were familial cases. Among these, 10 were undiagnosed complete or incomplete Marfan syndromes but 6 were a pure familial form of aortic aneuryms (FAA). FAA is an autosomal dominant disease with incomplete penetrance. Three different genes were mapped. The identification of these genes will provide further information about the pathogenic mechanisms of aortic aneuryms.

Genetics of lymphedema

L. BOON (Belgium)

Isolated primary lymphedema is associated with a family history in 35% of cases. It may be either congenital, with a puberty onset or with a later onset. Several mutations have been identified in the vascular endothelial growth factor receptor 3 gene (VEGF-R3) in primary congenital lymphoedema families. These mutations are responsible for an nonfunctional receptor, unable to bind its ligands (VEGF-C and VEGF-D). VEGF-R3 is a membranous receptor, specific to lymphatic vessels. Mutations in the gene FOXC-2 are responsible for lymphedema distichiasis phenotype. FOXC-2 is a transcription factor implicated in the signalling pathway of VEGF-R3. Lymphedema hypotrichosis-telangiectasia is characterized by lymphedema often located in a leg, beginning between 0 and 15 years, telangiectasia mostly on the palms and the soles and hypotrichosis of the scalp, and sometimes of the eyebrows and of the eyelashes. Mutations in the SOX 18 gene have been identified in the 3 families who were investigated. These mutations can be both recessive or dominant. SOX 18 is encoding for a transcription factor, which has an established role in hair and blood vessel development in mice. It is also necessary for the development and/or maintenance of lymphatic vessels, probably by an interaction with the VEGF-R3 signalling pathway.

SUPRAORTIC TRUNKS DISEASE

Chairpersons: C. SETACCI (Italy), A. WILLFORT (Austria)

Enoxaparin for cerebral artery dissection

M. MARIETTA, S. VALLONE, M. COBELLI, L. FACCHINI, S. POZZI, M. BERTESI, L. MAVILLA, G. TORELLI (Italy)

Cerebral artery dissection is a rare entity, and its treatment is still a matter of debate because of the lack of trials directly comparing either anticoagulants with antiplatelet agents or any treatment with placebo. The author presented his experience in 9 cases treated with enoxaparin at therapeutic doses for 3 weeks and at prophylactic doses for 3 more weeks. A magnetic resonance angiogram was then performed showing complete recanalization in 6 patients and partial recanalization in 3. As very few literature data are available at the moment the author suggests enoxaparin as a possible treatment, being a safe and useful therapy for thrombosis accompanying cerebral artery dissection.

Arterial remodeling and hemodynamics in carotid stents

A. WILLFORT, R.A. AHMADI, D. GRUBER, M. E. GSCHWANDTNER, A. HAUMER, M. HAUMER, H. EHRINGER (Austria)

After the experience on coronary stents showing positive remodeling (due to stent expansion) and negative remodelling (due to in-stent intimal hyperplasia), the author designed this study for carotid stents.

A total of 121 stented carotid arteries were included in the study. Duplex ultrasound was performed before the procedure (plaques were assigned to three different groups: soft, fibrous and calcified), the day after and at 3, 6, 12, and 24 months. They measured the stent diameters (proximal, distal and medium), the maximal neointimal thickness and hemodynamic parameters. They observed stent expansion over the 2 years, most marked on the middle stent area and related to the type of preinterventional plaque (maximal for soft and minimal for calcified plaques). Neointimal thickness had a marked increase during the first year and a minimal increase thereafter. These interactions resulted in a dominance of negative remodeling with an increased flow ratio during the first year, followed by a tendency to decrease due to stent expansion thereafter. This might contribute to the good midterm outcome of carotid stenting, especially in noncalcified plaques.

Influence of HbA_{1c} on healing of carotid stents

A. WILLFORT, R. A. AHMADI, A. GESSI, M. E. GSCHWANDTNER, A. HAUMER, W. LANG, E. MINAR, S. ZEHETMAYER, H. EHRINGER (Austria)

A total of 112 patients were followed prospectively after carotid artery stenting (CAS) over a period of 24 months. They were assigned to three groups according to their diabetic condition: group A non-diabetic subjects and group B diabetic subjects, who were subdivided into B1 ($HbA_1c<6.5\%$) and B2 ($HbA_1>6.5\%$). The groups were homogenous concerning risk factors and residual stenosis on angiograms. The maximal thickness of the layer between the stent and the lumen was measured at duplex follow-up and analyzed. Patients in group B2 differed significantly compared with B1 and A in respect to the maximal thickness of neointima and the time of its ingrowth. Initial hyperglycemia seems to be a predictor of more pronounced neointimal proliferation after CAS; therefore, a strict optimization of the hyperglycemic state should be aimed for in this kind of patient.

Carotid endarterectomy in Sapphire-eligible high-risk patients

G. MOZES, T. M. SULLIVAN, D. R. TORRES-RUSSOTTO, T. C. BOWER, T. L. HOSKIN, S. SAMPAIO, P. GLOVICZKI, J. M. PANNETON, A. A. NOEL, K. J. CHERRY (USA)

This group from the Mayo Clinic presented a retrospective analysis of carotid endarterectomy (CEA) in high-risk patients, who could be included in the Sapphire trial. With an analysis of 776 CEA, 323 (42%) in high-risk patients, there was no statistical different in the stroke (1.4%) and mortality (0.3%) rates when comparing high-and low-risk patients. The authors conclude that high-risk patients, as defined in CAS trials, can undergo operation with very low stroke and death rates.

ARTERIAL STIFFNESS: FROM BASIC SCIENCE TO CLINICAL EVIDENCE

Chairpersons: D. L. CLEMENT (Belgium), P. RIZZON (Italy)

Arterial stiffness: how to evaluate it

V. VLACHOPOULUS C. STEFANADIS (Greece)

Several theoretical models are available to evaluate arterial stiffness; two models are the most popular. While the Windkessel model is the simplest way to assess the cushioning function of arteries, the most realistic model of the arterial system is a simple tube with one end representing the peripheral resistance and with the other end receiving blood in spurts from the heart.

The methods can assess arterial stiffness on three levels:

1. local determination:
   - ➤ invasive
     - aortic catheter: pressure and diameter measured at the same site
     - transbrachial ultrasound
     - transthoracic echocardiography
   - ➤ noninvasive
     - transesophageal echocardiography
     - Wall Track system
     - Tissue Doppler imaging
2. regional determination
   - ➤ invasive
     - pulse wave-velocity measurement by simultaneous intra-arterial recording
   - ➤ noninvasive
     - Complior
     - Sphygmocor
     - Wall tracking system
     - Simultaneous ultrasound recording
     - Cine MRI
     - Timing of Korotkoff sounds (QKD interval)
3. systemic determination
   - ➤ noninvasive -
     - Sphygmocor-applanation tonometry
     - Diastolic pulse contour analysis
     - Photoplethysmography

Devices and methods are based on measurement of pulse transit time, analysis of the arterial pressure pulse, or on direct stiffness calculation using measurements of dimensions and pressure. The most widely used of these methods are accurate and reproducible enough to allow understanding of arterial mechanics and their impact on cardiovascular function.

Modification of arterial stiffness: is it feasible?

C. VLACHOPOULUS (Greece)

Arterial stiffness has been identified as an independent predictor of cardiovascular risk.

Modification of arterial stiffness is an important target for prevention and therapy.

Determinants of arterial stiffness are genetics, age, height, blood pressure, and heart rate.

Alterations in last two determinants are possible in a pharmocological and nonpharmacological way.

- Pharmacological modifications:
- Antihypertensive drugs: ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, nitrates and NO donors, β-blockers
- Oral antidiabetic drugs
- Hypolipidemic drugs
- Others: ALT-711
- Nonpharmacologic modifications:
- Reduction in obesity: weight reduction results in a reduction of arterial stiffness independent of the type of diet
- Quitting a sedentary lifestyle and starting regular exercise: the more one trains, the less stiff the arterial wall, especially with aerobic training (walking) rather than muscular strength training which causes endothelial damage
- Cessation of smoking (cigarettes and cigars): causes endothelial dysfunction with an acute effect after 1 minute; the chronic effect is unknown
- Nutrition: diminish salt intake, higher intake of foods with antioxidant properties (flavonoids, garlic, vitamin C, chocolate, fruits, tea), reduction of caffeine.

CHRONIC CRITICAL LEG ISCHEMIA

Chairpersons: R. MARTINI (Italy), T. OTHA (Japan)

Intermittent compression pump for nonhealing wounds in patients with limb ischemia

V. M. MONTORI, S. J. KAVROS, E. E. WALSH, T. W. ROOKE (USA)

The Aircast Arterial Flow® system provides intermittent pneumatic compression of the calf in order to help prevent and reduce the complications of poor circulation. Compression is rapid, graduated, and sequential. The rapid inflation produces shear stress within the vasculature and may induce a biologically mediated vasodiatory effect. The graduated sequential compression accelerates venous velocity. This system may represent a rescue treatment for patients unwilling or unable to undergo a limb amputation, but little is known about its safety and its efficacy in ischemic wounds. This retrospective single-center study included 101 patients with wounds in the lower extremity with ulceration, from various etiologies (multifactorial 52%, arterial 36%, small vessel disease 7%). Sixty-four percent of the patients were diabetic, and 25% had a history of amputation. $TcPO_2$ was below 20 mm Hg in 60% of the cases. Complete wound healing was achieved in 40% of patients with a $TcPO_2 < 20$ mm Hg and in 47% of the patients with a $TcPO_2$ between 20 and 30 mm Hg. Seven patients discontinued the treatment by the Aircast Arterial Flow® system because of pain. Wounds healed with a median time of 14 weeks of treatment. These results have to be confirmed in a prospective randomized study.


BENEDICTVS XIV

Part 5

IASACO and IUA PRIZES

IASACO PRIZE

Chairpersons: P. BALAS (Greece), D. L. CLEMENT (Belgium), A. SCHIRGER (USA), A. STRANO (Italy)

Winners: Circulatory changes in CVI patients after different treatments: evaluation with noninvasive methods

C. L. L. PORTO, A. N. N. MILHOMENS, S. AMARAL, F. F. A. FERNANDES, C. E. PIRES, S. X. SALLES, D. A. BOTTINO, E. BOUSKELA (Brazil)

Changes in venous diameters (by duplex scanner), microcirculation (by the orthogonal polarized system Cystoscan®) and calf volume were evaluated in 52 women, before and after 28 days of Cirkan® (Ruscus aculeatus hesperidine methilcalcone + vitamin C), or elastic compression (Venosan®, 30 to 40 mm Hg) without any medication. They were 25 to 65 years old, C2S or C 3S in the CEAP, and healthy except for CVI. Improvement on the venous score (C3 to C2) was significant in the stocking group. Popliteal diameter improved significantly in the Cirkan® group compared with controls. Great saphenous vein diameter improved significantly in both groups compared with controls. Leg diameters improved only in the stocking groups compared with Cirkan® or control groups. Cytoscan® showed a reduction in edema and an increase in the capillary density in both groups. Although stockings are considered to be the most effective medical treatment for CVI, Cirkan® showed an improvement on CVI symptoms in terms of popliteal and GVS diameters or CEAP classification.

Noninvasive evaluation of endothelial function in patients with Anderson-Fabry disease

D. PUCCIO, E. CORRADO, G. COPPOLA, I. MURATORI, G. PISTONE, M. ARICO, S. NOVO (Italy)

Fabry disease is an X-linked recessive disease with a deficit in α-galactosidase A, implicated in the glycosphingolipid metabolism. Cardiovascular involvement of Fabry disease (myocardial hypertrophy, prolapse or thickening of the valves, conduction system involvement, etc) is one of the main causes of death in the 6th decade with renal failure. Endothelial function was studied in 6 cases of Fabry disease and 12 controls. Using high-resolution ultrasound, the brachial vasodilatator responses were assessed, after reactive hyperemia by flow-mediated vasodilatation (FMD; endothelium dependent) and sublingual nitroglycerin (endothelium-independent). No difference was observed between the two groups at baseline for clinical or laboratory markers, homocysteine concentration, and brachial artery diameter. Only inflammatory factors were significantly increased in the Fabry group. After nitroglycerin administration, no significant difference was observed between the groups. After reactive hyperemia, FMD change was significantly higher in the Fabry group, These results suggest an endothelial dysfunction in Fabry disease patients, which may be responsible for the cardiovascular involvement of the disease.

Anti-inflammatory effects of defibrotide as measured in various pathologic states

J. FAREED, D. A. HOPPENSTEADT, M. LASEEN, J. MADDINENI, O. IQBAL (USA)

Defibrotide is a polydeoxyribonucleotide-derived drug known to release fibrinolytic mediators, tissue factor pathway inhibitor (TFPI) and inhibit the platelet activation process. Patients with peripheral arterial disease, post bone marrow transplantation, veno-occlusive disease, and post orthopedic surgery prophylaxis for thrombosis showed an upregulation of inflammatory markers: C-reactive protein, soluble CD 40 ligand, monocyte chemotactic protein (MCP-1), soluble thrombomodulin, and plasminogen activator inhibitor PAI-1. Upon defibrotide treatment time, dependent decrease was seen in all groups of patients, mostly in CD 40-L and PAI-1, with high dosages of IV defibrotide.

IUA PRIZE

Chairpersons: J. FERNANDES E FERNANDES (Portugal),
P. GLOVICZKI (USA), A. N. NICOLAIDES (Cyprus), H. RIEGER (Germany)

High wall shear stress measured by magnetic resonance is a predictor of restenosis in the femoral artery after balloon angioplasty

B. AMANN-VESTI, S. KOZERKE, E. KRIEGER, P. BOESIGER, R. KOPPENSTEINER (Switzerland)

Wall shear stress (WSS) has been implied in the pathogenesis of restenosis. This project presents a possible way to determine WSS in superficial femoral artery from MRI and duplex ultrasonography in healthy controls and in patients after superficial femoral artery PTA. WSS was assessed by calculating the slope of velocity profiles at the vessel wall from data obtained with velocity-encoded cine MR and with duplex using the formula: WSS=4x blood viscosity x peak blood velocity /internal diameter. They studied 17 patients the day after superficial femoral artery PTA to determine WSS, and 6 months later to determine restenosis rate. They observed that patients who developed restenosis were those with higher WSS determined the day after PTA. They suggest that this is a good way to determine WSS in a vessel and use it as a predictive factor after PTA.

Arterial wall remodeling mathematically described by standardized intima-media thickness frequency distribution curves

E. DE GROOT, A. ZWINDERMAN, A. WIEGMAN, A. SMIT, J. KASTELEIN (The Netherlands)

The intima-media thickness (IMT) in different populations exposed to different extents of cardiovascular risk was determined by means of B-mode ultrasound. Then IMT frequency dirtribution curves were created for all populations: control adolescents, control adults, control seniors, young adolescents with familial hypercholesterolemia, patients with coronary artery disease, and adults with familial hypercholesterolemia. IMT curves that deviated from the IMT normal distribution curve were defined as lesions. They observed local differences in increase in wall thickness and increase of lesion formation with age and cardiovascular risk.

Effects of dobutamine on left ventriculoarterial coupling and mechanical efficiency in acutely ischemic pigs

P. KOLH, B. LAMBERMONT, A. GHUYSEN, V. TCHANA-SATO, P. GERARD, J. DOGNE, V. D'ORIO, L. PIERARD, R. LIMET (Belgium)

Although dobutamine is a drug which is widely used, it is not yet clear what its effects are on left ventriculoarterial coupling and mechanical efficiency in the ischemic heart. The author performed the experiment in 12 pigs in which coronary occlusion was produced; vascular properties were estimated with a windkessel model. They observed that in ischemic pigs dobutamine restored ventriculoarterial coupling through an increase in left ventricular contractility and decrease in arterial elastance, due to peripheral vasodilatation. However, myocardial oxygen consumption was increased and efficiency impaired.


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At the forefront of research and education in phlebology

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