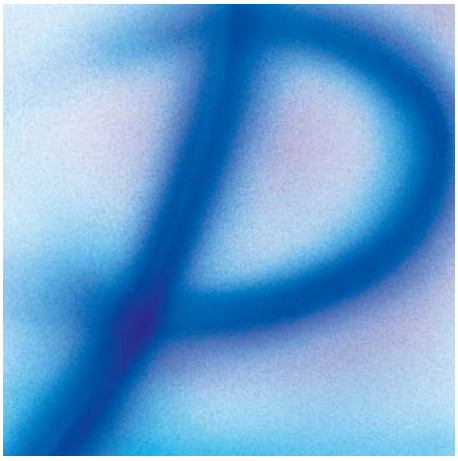
PHLEBOLYMPHOLOGY

ISSN 1286-0107



Vol 16 • No.1 • 2009 • p161-234

Special congress issue

XXIII
World Congress of
the International Union on Angiology
Athens - Greece
21-25 June 2008

AIMS AND SCOPE

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

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

Phlebolymphology is scientifically supported by a prestigious editorial board.

Phlebolymphology has been published four times per year since 1994, and, thanks to its high scientific level, was included in the EMBASE and Elsevier BIOBASE databases.

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

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Indexed in EMBASE, PASCAL and Scopus

ISSN 1286-0107

Phlebolymphology

Preface

By the members of the Medical Reporters' Academy

This report from the XXIIIrd World Congress of the International Union of Angiology (IUA), which was held in Athens, Greece, from June 21 to 25, 2008, has been prepared by our Medical Reporters' Academy (MRA) group. We are an international group of young specialists with a core interest in venous disease. We work in various fields including dermatology and internal medicine in addition to the more directly related areas of angiology and vascular surgery, not to mention phlebology itself. We all have hospital practices and come from countries around the world (Czech Republic, France, Greece, Italy, Portugal, Spain, Romania, and Russia). Each year, we are invited to report from an international congress of interest to venous disease specialists. International congresses such as the last IUA congress in Athens are annual events, each spread over 4 to 5 days, comprising hundreds of presentations, not to mention plenary lectures, round tables, satellite events, and meet the specialist sessions. The tight schedule can only be completed if events run in parallel, often up to seven at a time. No matter how carefully delegates sift through the telephone directory-sized program—which will not contain the latest data gathered in the weeks since the abstracts were submitted—they will inevitably miss a number of key presentations. The solution is a team of peer reporters as we are, collecting and selecting the best information on the many presentations, under the supervision of our chairman, Professor Andrew Nicolaides. We have organized the information in different chapters: cerebrovascular diseases, cardiovascular diseases, peripheral arterial disease, venous thromboembolic diseases and chronic venous and lymphatic disease. We hope this report will be useful, not only for those who were present at the Congress, but also for those who were unable to attend.

We wish you an enjoyable read.

Medical Reporters' Academy (MRA)

The reports from the XXIII World Congress of Angiology were prepared by the following members of the MRA team:

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Presidential lecture

"Prometheus Fire: Challenges for Vascular Science and the Role of IUA"

J. Fernandes e Fernandes (Portugal)

J. Fernandes e Fernandes gave a brief report of important historical landmarks in the field of angiology and vascular surgery such as arteriography, phlebography, lymphography, endarterectomy, bypass, and the new endovascular revolution.

He emphasized the importance of the guidelines in the creation of vascular centers, especially the new vision of the vascular specialist and how to establish competence in vascular treatment by education, training programs, and experience.

In his opinion the IUA can play a very important role in creating strong bridges between specialists in different fields.

I
Investigation

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1 - Investigation

Vascular Centers in 2008: team approach to medicine, surgery and endovascular intervention

Chairman: R Simkin (Argentina)
Lecture by P Gloviczki (USA)

In the spirit of the words of Dr. William P. Mayo—"No one is big enough to be independent of others"—P Gloviczki described the new model of multidisciplinary teams in the treatment of vascular patients. With this aim, P Gloviczki and the Mayo Clinic created the Mayo Clinic Gonda Vascular Center in 1991. At the center patients with vascular diseases receive high-quality medical, endovascular, and open surgical treatment by appropriate experts working as a coordinated team. The principal advantages are that the attention is disease- and patient-centered and the needs of the patients come first in a multidisciplinary, integrated approach to the patient care, education, and research. This is an integrated program with participation of all disciplines involved in vascular care.

A major project developed by the Mayo Clinic Gonda Vascular Center was the Integrated Endovascular Program. Specialists from interventional cardiology, vascular and interventional radiology, vascular medicine, and vascular surgery participated in this exciting project. The aim was to build a premier endovascular program designed to provide every patient with the best care every day through integrated clinical practice, education, and research. The success of this strategic plan depends entirely on the full support, expertise, and collaboration of each participant .

Reference

Gloviczki P. Vascular and endovascular surgeons: the vascular specialist for the 21sth century and beyond. J Vasc Surg 2006;43:412-21.

Investigations for carotid endarterectomy and carotid angioplasty stenting

Moderators: F Benedetti Valentini (Italy), PL Antignani (Italy)
Participants: PL Antignani (Italy), C Liapis (Greece), B Gossetti (Italy), O Martinelli (Italy), E Hussein (Egypt), C Setacci (Italy), F Benedetti Valentini (Italy).

This session consisted of a number of presentations from several countries dealing with the value of different diagnostic methods in the fields of carotid endarterectomy (CEA) and carotid angioplasty stenting (CAS). **PL Antignani** emphasized that the cost of a general screening for carotid disease is high, the absolute risk of stroke in asymptomatic stenosis is low, and that CEA performed with surgical morbidity and mortality <3% would prevent one stroke in five years.

High-risk patients have to be identified by evaluating risk factor, i.e., ageing, cervical bruits, peripheral arterial disease. Carotid ultrasonography and magnetic resonance are similar, but cost, availability, and local experience are important in choosing the best test. Duplex screening can result in many false positives. Screening

for bypass surgery is recommended among patients who are 65 years or older and have other significant risk factors, symptomatic peripheral vascular disease, a history of abdominal aortic aneurysm in a setting of cerebrovascular disease, restenosis, restenosis following carotid stenting, patients who receive radiation therapy for head and neck cancer, patients with a history of retinal ischemic events.

B Gossetti discussed plaque morphology and emphasized the role of color flow duplex imaging and its efficacy in establishing the degree of stenosis, echogenicity, surface contour.

The introduction of computer-assisted objective grading solved the problem of inter and intra-observer agreement on plaque echogenicity which was high in few comparative studies. In patients with high-grade carotid stenosis, ultrasound study using contrast enhancement is a sensitive method of detecting pseudo-occlusion of the internal carotid. Radiological imaging obtained by computed tomography or magnetic resonance imaging allows complete evaluation of the aortic arch, of the origin of carotid arteries and of intra-cranial vessels, avoiding the use of angiography. Microembolic events and strokes are the major drawback of CEA and CAS and may be investigated by transcranial Doppler, which allows good monitoring of blood flow changes and of microembolic signals in the middle cerebral artery. **O Martinelli** reported her personal experience in transcranial Doppler monitoring on 1326 CAS and 157 CEA. In CAS, the rate of microembolic events was 54.2% during cannulation + filter positioning (2.7% neurological events), 64.3% during peripheral transluminal angioplasty (PTA) and/or stenting and ballooning (1.2% neurological events). In CEA, microembolic events were detected in 74% of cases and the highest incidence during dissection and 30' after declamping. Microembolic events were symptomatic in 18% cases of CEA and 3.9% cases of CAS. For **C Setacci** the accuracy of carotid ultrasound has not been well established in predicting intrastent restenosis (ISR) after carotid stenting (CAS). The aim of this study was to determine different degrees of ISR using ultrasound velocity criteria compared with angiography. After CAS, each patient underwent angiography to measure ISR (NASCET method) which was compared with peak systolic velocity (PSV) end-diastolic velocity (EDV), and the ratio between PSV values of the internal carotid artery and common carotid artery (ICA/CCA). This was done within 48 hours, thus creating a baseline value. An ultrasound examination was performed at 30 days, 3, 6, 9, and 12 months. Patients with a more than 3-fold increase in PSV above baseline or with PSV $\geq$200 cm/s underwent angiography. RESULTS: 814 CAS procedures, 6427 ultrasound examinations and 1123 angiographies were performed. ISR $\geq$70% and ISR $\geq$50% were detected, respectively, in 22 and 73 patients. We defined velocity criteria for grading carotid ISR: PSV $\leq$104 cm/s with <30% stenosis; PSV:105 to 174 cm/s with 30% to 50% stenosis; PSV:175 to 299 cm/s with 50% to 70% stenosis; PSV $\geq$300 cm/s, EDV $\geq$140 cm/s, and ICA/CCA $\geq$3.8 with $\geq$70% stenosis. Receiver operator characteristic (ROC) curves for ISR >or=70% were, respectively, for PSV, EDV, and ICA/CCA: 0.99, 0.98, and 0.99. Conclusions: ultrasound grading of carotid ISR can guarantee a correct follow-up after CAS if new customized velocity criteria are validated by skilled operators using a specific follow-up protocol in a certified laboratory. **F Benedetti Valentini** summarized the cases when the use of color-coded duplex

sonography (CD) is not sufficient: unclear color-coded duplex sonography in the presence of heavy calcifications or discrepancy of symptoms versus color-coded duplex sonography. Pseudocclusion with the patency of distal internal carotid also suggests the use of transcranial Doppler. Finally in occlusion of the distal internal carotid with ocular/cerebral symptoms, external carotid stenosis, anomalies/lesions of supraortic trunks, intracranial aneurysm >7 mm, associated nonvascular disease of the neck, the use of angio computed tomography (aCT) and nuclear magnetic resonance (MR) is recommended.

II
Cerebrovascular diseases and disease of the thoracic aorta

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2 - Cerebrovascular diseases and disease of the thoracic aorta

Cerebrovascular diseases

Beyond endarterectomy, is there a better option for management of carotid disease?
Lecture by J Fernandes e Fernandes (Portugal)

In the first part of his lecture, Professor Fernandes presented the results of several trials analyzing medical treatment versus open surgery in the treatment of carotid artery stenosis. He listed the indications for open surgery in symptomatic and asymptomatic patients, and recommended the use of carotid ultrasound as a test of choice. If ultrasound does not produce a clear-cut result, the preoperative study should be completed by angio computed tomography (aCT) and nuclear magnetic resonance (MR) and, only in selected cases, by digital arteriography.

Professor Fernandes e Fernandes emphasized the importance of disabling strokes in previously asymptomatic patients with carotid stenosis. The stability of the carotid plaque will be one of the most important criteria in deciding on the best treatment in the near future. There is evidence that, in asymptomatic carotid disease, the risk of stroke is 2% per year, and these patients also have increased cardiovascular risk and mortality. Plaque structure and activity index, measured by high-definition ultrasonography with power Doppler and computer-assisted analysis, will establish new indications in the treatment of carotid stenosis. Higher activity index reflects and unstable plaque which can produce symptoms proximally. Plaque echolucency, measured by grey scale median (GSM) values, indicates plaque stability. The author presented the ACSRS study where 112 carotid plaques were studied by a double-blind analysis to determine the activity index in asymptomatic patients. The absolute risk of cerebrovascular events was 2.9% per year. A high activity index (more than 65) is very frequent when plaque is unstable, and surgery in 5 such patients is needed to prevent one event in four years.

In the second part of his lecture, Professor Fernandes e Fernandes analyzed the choice between carotid artery stenting (CAS) and carotid endarterectomy (CEA). He performed a review of published trials and emphasized the importance of microembolization during CAS determined by transcranial Doppler. Microembolization is more frequent during CAS in the presence of echolucent plaques. Some issues concerning CAS must be resolved before it can be selected as a first-choice therapeutic option. There is a need for studies with adequate analysis of patients, patient registries, standardization of CAS procedures and analyses of plaque structure (pre-procedural, quantification of heparin-induced thrombocytopenia, brain imaging pre- and post-procedure and cognitive function analysis). Surgery is highly effective in the treatment of carotid stenosis. It is non-selective, low-risk, has a low restenosis rate, and is cost effective.

Professor Fernandes e Fernandes concluded that there is no balanced decision between CAS and CEA. Current evidence does not support a shift away from CEA as standard treatment of carotid stenosis. CAS is an attractive treatment and potentially useful in selected patients (neck radiation, restenosis after CEA, very high-risk patients and ostial disease in supra-aortic trunks). For these reasons, CEA continues to be the first option in the treatment of carotid stenosis. We need properly designed randomized trials to define the indications of CAS.

Endoluminal interventions for occlusive arterial disease. What is the new scientific evidence?

Moderators: J Fernandes e Fernandes (Portugal), M Lazaridis (Greece)
Participants: Sir P Bell (UK), J Fernandes e Fernandes (Portugal), C Liapis (Greece), D Palumbo (Italy)

Carotid stenting – what went wrong? The procedure or the trials?

Sir P. Bell (UK)

The author started his presentation by commenting on the low scientific quality of the majority of studies designed to evaluate carotid artery stenting (CAS). Most studies are nonrandomized or series without follow-up. Sir P Bell outlined the principal problems with the majority of trials, such as failure to include sufficient patients in both arms, exclusion of females or elderly patients, exclusion of difficult cases, protocol violations, industry funding and involvement in the trials, use of biased end points, poor training of operators, crossover of patients, etc.

In the majority of trials, carotid stenting gave worse results than open surgery. CAS is probably indicated only in very specific cases (neck radiation, restenosis)and so Professor Bell avoids recommending CAS to most of his patients.

There are several unresolved questions in the field of carotid stenosis, such as the best timing of treatment of symptomatic patients with unstable plaque, with recent studies demonstrating the benefit of very early surgery. Another question is the use of statins and antiplatelet drugs in the acute phase to stabilize the plaque before surgery after one non-disabling stroke.

In conclusion, Sir P Bell highlighted the importance of analyzing plaque characteristics and of correct medical therapy, and the need to wait for new well-designed trials.

Controversies in carotid artery disease

Moderators: Sir P Bell (UK), C Klonaris (Greece)
Participants: E Bastounis (Greece), B Van Bellen (Brazil), G Torsello (Germany), G Biasi (Italy), MF Giannoni (Italy)

Carotid endarterectomy: is it still the gold standard?

E Bastounis (Greece)

The results of a personal series including 1271 carotid endarterectomy (CEA) were presented. The study was performed in 1083 patients (260 females, 130 high-risk patients, 120 older than 80 years, 89 redo operations, 127 with high cervical lesions, 59% symptomatic). All underwent conventional endarterectomy, with shunt and vein patch. The speaker reported a rate of major morbidity and mortality of 1.02%. He considered that high-risk patients may be as well served by CEA as low-risk patients, but should be referred in specialized centers with skilled personnel in order to lower the risk of stroke.

Neurological dysfunction following carotid artery stenting: is it predictable?

B Van Bellen (Brazil)

The possible important risk factors involved in poor outcome following carotid artery stenting (CAS) was discussed. According to the speaker, the more symptomatic the patient, the higher the risk of the procedure (x7 with stroke and x6 with transient ischemic attack), as in carotid endarterectomy (CEA). CAS did not increase risk in females, although sex is a known risk factor in CEA. Age, on the other hand, was an important risk factor, but it is possible that the cause of complications is only indirectly related to age since aortic arch calcification and ulcerated plaques, which have a higher prevalence in elderly patients, are closely related to a higher incidence of new ischemic cerebral lesions. Diabetes was not considered to be a risk factor for CAS, and so for contralateral carotid occlusion. A possible explanation for this is the fact that carotid occlusion time during angioplasty is very short, and so there is little ischemia of the brain during the procedure. A significant increase in periprocedural complications was observed in patients with long lesions (>15 mm) and ostial lesions. Considering >85% stenosis as an increased risk for CAS is still controversial. Plaque calcification was also unrelated to periprocedural complications, but hypercholesterolemia can be considered as an additional risk factor. The observation that statins diminish the incidence of intraprocedural complications can possibly be related to the instability of symptomatic plaques, which result in a higher incidence of stroke during CAS. The speaker concluded that the answers to the majority of these issues may be provided by the ongoing trials.

Cerebral protection: myth or reality?

G Torsello (Germany)

Embolization during carotid stenting (CAS) may occur at predilation, stenting, or

postdilation, due to the manipulation of sheaths/guiding catheters, carotid plaque, or aortic arch. Proximal protection systems may be limited by the need for larger femoral sheaths and intolerance of clamping, limitations of filter devices with increased embolic events, internal carotid spasm, technical mishaps in attempts to retrieve the filters after stent deployment, and by filter pore size (100-150 µm). According to the results of a meta-analysis by Kastrup, the CAS registry in Germany, and a recently published randomized trial (Barbato et al, JVS 2008), the use of filters during CAS does not demonstrably reduce microemboli, and also filters cannot prevent embolic events in the aortic arch. He concluded that there is no level-1 evidence that cerebral protection improves outcomes. Filter-type devices may increase microemboli but can also trap macroemboli and because of this we should routinely use cerebral protection to prevent one major stroke by the capture of a large macroembolus.

Carotid plaque echostructure: its predictive role in future neurological events

G Biasi (Italy)

The ICAROS study pointed out the importance of echolucent carotid plaques with low gray-scale median (GSM) values as an increased risk factor for stroke during carotid artery stenting (CAS). The speaker considered that the analysis of carotid plaque morphology also has the potential to indicate the best brain protection device (echolucent plaques with proximal device and hyperechoic plaques with distal filter). He also noted that change in GSM scores can be a marker of the efficacy of statins and can predict future coronary events in patients with clinically stable coronary artery disease (OR 7.0, $p<0.001$). The speaker also presented the results of his personal experience (1996-2007) including 1151 cases of carotid endarterectomy (CEA) and 193 of CAS, with a rate of major morbidity and mortality of 2% in both groups, assuming that CEA is always the first choice and CAS only for high-risk patients.

Carotid artery stenting under protection. Limitations and new developments

M F Giannoni (Italy)

The new concept of silent cerebral ischemia detected with diffusion-weighted imaging in patients treated with protected and unprotected carotid artery stenting (CAS) was presented. This was done through a review of the characteristics and criteria for choice of different embolic protection devices (EPDs). This showed that embolism can occur during each step of the procedure, although most emboli do not produce clinical sequelae. The conclusion was that there is no ideal EPD (or stent), that CAS planning with EPD is mandatory, and also that skilled operators can make a difference because CAS is not an easy procedure.

Disease of the thoracic aorta

Thoracic aortic disease

Moderators: W. Sandman (Germani)-D. Kiskinis (Greece)
Participants: J. Brunkwall (Germany), E. Verhoeven (The Netherlands), K. Papazoglou (Greece)

Thoracoabdominal aortic aneurysm (TAAA) is one of the most severe conditions in vascular surgery. There are two basic surgical treatments of TAAA: thoracic open aneurysm repair (TOAR) and thoracic endovascular aneurysm repair (TEVAR). Each of these methods has advantages and disadvantages. TOAR has a clinical history of 50 years and can be applicable in most cases. However, TOAR is a long time surgical procedure (6-8 hours) accompanied by serious operational trauma, blood loss, frequent paraplegia (3-15%), renal insufficiency (5-10%), and high mortality rate (15-30%). Paraplegia is bound to damage the spinal cord arteries dissected during TAAA preparation. Artificial circulation, cardioplegia, and intraoperation perfusion are useful for protection of the brain, kidneys, and intestine. For these purposes, Sadmann et al used temporary ilio-subclavian or ilio-bi-subclavian shunting. Also, the authors have applied constant monitoring of the spinal cord conduction during surgery. Sadmann et al underline that restoration of the spinal cord blood circulation is possible during TOAR only. TEVAR has proven to be a useful alternative to TOAR in selected cases. There are fenestrated and branched endovascular techniques. The Achilles' heel of the fenestrated technique is stability and durability of the seal between the nitinol ring and the covered stent. So, high-accuracy positioning of the fenestrated stent is necessary. Branched grafts are a better choice for most cases of TAAA. Branches are easier to position and to fix for the bridging stent-graft. Disadvantages include the required cranial approach to catheterize the branches and target vessels (E. Verhoeven et al.). Great variability in the anatomy of TAAA often requires a combination of both fenestrations and branches. The serious limitation of TEVAR is its very high cost and long-term manufacturing of the stent-graft. TEVAR is characterized by low mortality (20%) and paraplegia rates (5%). K. Papazoglou et al used TEVAR for treatment of a chronic dissection of the TAAA. The common contraindications to TEVAR are extreme tortuosity, narrow diameter, and calcification of the access vessels. The hybrid technique is a compromise between TOAR and TEVAR. Open visceral debranching is done before implantation of a thoracoaortic stent-graft. According to J. Brunkwall, hybrid operations use the advantages of TEVAR and decrease the disadvantages of TOAR. At the end of the discussion all participants agreed that randomized clinical studies are necessary to define the indications for and contraindications to open or endovascular repair of TAAA.

III
Cardiovascular diseases

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3 - Cardiovascular diseases

Cardiovascular diseases and prevention

Metabolic syndrome-managing the patient at cardiometabolic risk

Moderators: E Diamantopoulos (Greece), S Novo (Italy)

Participants: E Diamantopoulos (Greece), A Nicolaides (Cyprus), A Trichopoulou (Greece), S Novo (Italy), U Pagotto (Italy)

E Diamantopoulos presented an introduction to various definitions of metabolic syndrome. Despite sometimes confusing criteria, every definition has the same core components: abdominal obesity, impaired fasting glucose tolerance, dyslipidemia and arterial hypertension. The prevalence of metabolic syndrome is almost the same in all countries: around 20-25%. From the pathophysiological point of view, visceral fat accumulation and consequent insulin resistance seems to have pivotal roles. It was also highlighted that, according to the studies, abdominal obesity and insulin resistance increase the risk of CV morbidity and mortality. The metabolic syndrome is also a predictor of coronary heart disease, of type 2 diabetes mellitus, and increases CV and overall mortality. Finally, the speaker pointed out that metabolic syndrome is a cluster of cardio-metabolic risk factors with a central role for abdominal obesity, needing appropriate non-pharmacological and pharmacological management strategies. Metabolic syndrome should be used for the identification of individuals at increased risk for future CV disease and can complement Framingham scoring.

A Nicolaides presenting the Cyprus Study demonstrated that plaque morphology assessed by high-resolution ultrasound is a better predictor of CV risk than intima-media thickness. In the Cyprus Study it was found that in the presence of metabolic syndrome there was a higher prevalence of CV disease. Also in the presence of the metabolic syndrome, intima-media thickness (IMT), total (two common carotid and two common femoral arteries assessed) plaque thickness (TPT), the black (echo lucent) plaque burden (according to the Widder 1-5 classification) and the rate of plaque growth were higher. A Nicolaides concluded that unstable plaque develops earlier in the presence of the metabolic syndrome. Finally, he stressed that future interventional studies in individuals with metabolic syndrome should measure TPT and black plaque burden in addition to IMT.

A Trichopoulou from Athens talked about the challenge of lifestyle and dietary intervention in cardiometabolic care. According to several well-designed studies, adhesion to the Mediterranean diet with its 9 components significantly reduced not only cardiovascular mortality, but also cancer mortality and overall mortality. The result was the same in USA as in Mediterranean and European countries. This dietary approach reduced the incidence of type 2 diabetes mellitus, was not associated with obesity and lowered the systolic and diastolic blood pressure. Mediterranean diet reduces inflammation, has antiatherogenic properties, and is inversely correlated with metabolic syndrome and the associated cardiovascular risk.

S Novo from Italy presented multifactorial drug treatment modalities in patients with metabolic syndrome. In his introduction he highlighted the role of early diagnosis. Individuals with metabolic syndrome commonly manifest insulin resistance, prothrombotic and pro-inflammatory state, and endothelial dysfunction. All guidelines recommend that first-line therapy should be based on lifestyle modification, consisting of the Mediterranean diet and moderate physical activity. When this approach is inadequate, it is recommended that drug treatment is used to reduce the overall impact on cardiovascular disease and type 2 diabetes mellitus risk. Metformin, thiazolidinediones, and acarbose are antihyperglycemic drugs, but they also reduce the incidence of type 2 diabetes mellitus and insulin resistance, and decrease or stabilize visceral adipose tissue mass. Also, angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors reduce the incidence of type 2 diabetes mellitus and insulin resistance. Telmisartan has been considered particularly useful in the treatment of hypertension associated with cardiometabolic risk factors due to its PPR-gamma receptor agonism and improvement of insulin sensitivity. Beta-blockers and thiazide diuretics should be avoided because they can reduce insulin sensitivity, impair lipid profile, and increase type 2 diabetes mellitus incidence. This is not the case of carvedilol, indapamide, or spironolactone. Orlistat and sibutramine are used with a reduced calorie diet plus exercise program to help people who want to lose weight, but the former causes gastrointestinal malabsorbtion syndrome, and the latter may cause hypertension. Statins, fibrates and omega-3 fatty acids normalize dyslipidemia. Statins have additional therapeutic benefits in reducing inflammatory activity. Fibrates effectively reduce triglycerides and increase HDL, and have also shown some anti-inflammatory activity. Low-dose aspirin is also recommended for patients with a prothrombotic state. Rimonabant, the first cannabinoid receptor (CBI) antagonist studied in obesity, modulates cardiometabolic risk factors, through its impact on visceral fat and through direct pathways not related to weight loss. In this issue the lecture of **U Pagotto** was particularly useful in reminding everyone about the physiologic and pathophysiologic role of cannabinoid receptors, named CB1 and CB2. The ability of the endocannabinoid system to control appetite, food intake, and energy balance has recently received great attention. This system modulates rewarding properties of food by acting at specific mesolimbic areas in the brain. Interestingly, the endocannabinoid system was recently shown to control several metabolic functions by acting on peripheral tissues, such as adipocytes, hepatocytes, the gastrointestinal tract, skeletal muscle, and the pancreas. Visceral obesity seems to involve overactivation of the endocannabinoid system, so drugs that interfere with this overactivation by blocking CB1 receptors are considered valuable candidates for the treatment of obesity and related cardiometabolic risk factors. Recent pharmacological studies with rimonabant in obese patients with and without comorbidities are promising. Rimonabant should not be used, however, in the presence of serious uncontrolled psychiatric problems, because it can cause depression, irritability, and anxiety .

Primary prevention of cardiovascular diseases

Moderators: D Mikhailidis (UK), A Jawien (Poland)

Participants: DB Panagiotakos (Greece), E Liberopoulos (Greece), V Athyros (Greece), G Kolovou (Greece)

The first lecture of this session by **DB Panagiotakos** dealt with the role of smoking, alcohol intake, and Mediterranean diet in cardiovascular disease risk. As is well known, active smoking is one of the most important risk factors for cardiovascular and peripheral arterial disease. Moreover, exposure of nonsmokers to environmental tobacco smoke has been associated with a substantial increase in the risk of coronary heart disease and perhaps of peripheral atherosclerosis also. According to the lecturer the effect of passive smoking (occasional and regular) is still controversial because of difficulties in objective measurement and quantification of tobacco-smoke exposure. Some studies use self-reported questionnaires, others biochemical indices (C-reactive protein, white blood count, homocysteine level, LDL cholesterol, etc.) in order to establish exposure and quantify the degree of passive smoking. Nevertheless, a meta-analysis of 18 cohort and case-control studies conducted by Jiang provides clear evidence of an increase in the overall relative risk (24-26%) of cardiovascular mortality and morbidity associated with passive smoking. The same results were also found in the ATTICA and GREECS studies. The latter shows that passive smokers have 61% higher risk of recurrent CV event or death after acute myocardial infarction compared with the non-exposed population. In the "Seven Country Study" conducted in 1970s, 10-year follow-up assessing the relationship between dietary habits and cardiovascular events of seven countries showed zero mortality in the Corfu group. The main explanation for this is the Mediterranean diet (diet rich in fruits, vegetables, whole grains, olive oil, fish, nuts, small-moderate amount of alcohol) and the supposed effect of the Mediterranean "way of life". Since this first study, a large number of trials have shown that the Mediterranean diet significantly reduces (8-32%) CV morbidity and mortality. Dietary factors exert their influence largely through their effects on body weight, blood pressure, plasma lipids, blood coagulation, and inflammatory markers. The author concluded that smoking and passive smoking account for a large proportion of cardiovascular risk and that the Mediterranean diet seems to be an effective means of primary and secondary prevention of cardiovascular disease which can be easily applied in other cultures also.

In the second lecture of this round table **E Liberopoulos** talked about a two-way strategy of preventing type 2 diabetes mellitus, today's dangerous with an attendant huge increase in CV complications. The first modality of prevention is lifestyle intervention. Studies conducted in this field, especially the Diabetes Prevention Program (DPP) and the Finnish Diabetes Prevention Study (FDPS), showed that lifestyle changes (including weight loss of about 4 kg, Mediterranean diet, physical activity) significantly reduced the incidence of type 2 diabetes mellitus in prediabetic patients. This effect seems to be evident on a long-term basis also. The major problem is that radical lifestyle modifications are difficult to implement in everyday clinical practice, especially in the long term. Therefore preventive pharmacological interventional modalities were also discussed. The results of trials using metformin, orlistat, acarbose, glitazones, statins, or fibrates are either encouraging or require more extensive evaluation. In addition, studies

with antihypertensive drugs (mainly ACE inhibitors and angiotensin II receptor antagonists) showed that these drugs could also reduce progression to type 2 diabetes mellitus in high-risk individuals. Attention is needed in the selection of antihypertensive drugs since beta-blockers and thiazide diuretics increase the risk of new-onset type 2 diabetes mellitus, which during hypertension treatment is very dangerous with an increased risk of stroke. Finally, the speaker stressed the importance of intensive lifestyle interventions for type 2 diabetes mellitus prevention in individuals at high risk. These are, unfortunately, difficult to achieve and sustain in daily practice. Among drugs metformin may be of value especially in younger obese patients with prediabetes, and the glitazones are the most promising pharmacologic agents.

V Athyros used compelling scientific evidence to show that the presence of metabolic syndrome as a clinical entity with cumulative risk of CV events and CV death is a fact and not a fiction. The controversy of this issue is mainly due to the several confusing definitions. Despite the fact that abdominal obesity, glucose metabolism disturbances, hypertension, and dyslipidemia are the main components of this syndrome, there are significant differences in quantifying these variables in different definitions. The WHO definition of 1999 was abandoned because of lack in daily practice applicability. The ATP III\NCEP definition of 2001 has been widely used (3 or more components are present, including abdominal obesity >102 cm men and, >88 cm women, triglycerides>150 mg/dL, HDL<40 mg/dL men, <50 women, blood pressure <130/85 mm Hg and fasting glucose >110 mg/dL), but in 2005 the IDF-EASD-EAS reduced the limit of abdominal obesity to >94 cm in men and >80 cm in women and also the limit of fasting glucose level>100 mg/dL (abdominal obesity plus 2 or more components). In the same year the AHA/NLHBI definition returned to ATP III abdominal obesity values, but the fasting glucose level remained above 100 mg/dL. The prevalence of metabolic syndrome is almost the same in USA and in Europe: about 1 in 4 people in the general population. Of course, the prevalence in different studies depends on the definition used, as stressed by the speaker. As the metabolic syndrome increases by 3.55 the risk of CV mortality, it needs a multifactorial approach, including lifestyle modification and drug treatment as well.

In her exciting lecture, **G Kolovou** told us about the well known and scientifically proved CV risk of elevated Lp(a), plasma fasting triglycerides and low HDL levels. However, there is less evidence regarding whether or not the proatherogenic role of high postprandial level of plasma triglycerides is an independent risk factor for premature CV disease or not. As postprandial hypertriglyceridemia is associated with fasting lipoproteins, gender, age, body mass index, glucose metabolism, blood pressure, genetic and lifestyle factors, it is not yet entirely clear whether postprandial hyperlipemia is an independent risk factor. The magnitude of the postprandial response appears to play a role in the etiology and progression of CHD. The mechanisms involved in postprandial elevated triglyceride levels are not fully understood, but could involve the malfunction of LP-lipase due to increased cholesterol synthesis in the liver after a reduction of cholesterol absorption from the intestine. The postprandial peak is after 3-4 hours and values above 220 mg/dL seem to be pathological. Many studies show that in the hypertriglyceridemic state the secreted VLDL particles are large and result in formation of small dense LDL

particles, which are particularly atherogenic. The main limitation in assessing postprandial lipemia is the lack of an established standard method. Such a method should be easily and widely applicable and reproducible as well.

Statins: a role in protection against cardiac and cerebrovascular events

Moderators: F Fedele (Italy), S Novo (Italy)

Target of LDL-Cholesterol in High-Risk Patients and in Secondary Prevention according to Guidelines

S Novo (Italy)

It is crucial to define a high6risk patient. Individuals with established cardiovascular (CV) disease who have both diabetes mellitus and metabolic syndrome have the highest risk.

There are several disease entities that confer a CV risk similar to that of coronary artery disease (CAD). These CAD "equivalents" are periphery artery disease (PAD), abdominal aortic aneurysm, symptomatic carotid disease, asymptomatic carotid disease, diabetes mellitus, metabolic syndrome, and chronic renal insufficiency. Patients with a very high risk are either those with established CV disease and multiple risk factors or those with established CV disease and only several but poorly controlled risk factors.

Trials concerning primary as well as secondary prevention of CV events have proved the importance of lowering total and especially LDL-cholesterol. The greater the reduction in LDL-cholesterol, the greater the observed reduction in CV events. Statins have shown their efficacy in the reduction of all events and this effect was independent not only of age, gender, hypertension, and diabetes mellitus, but also of the baseline levels of total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides. Persistent therapy leads to progressive risk reduction so adherence to the treatment is the key issue. According to the risk profile of an individual patient, the target LDL-cholesterol for the high-risk population should be 100mg/dL or better 70mg/dL. The concept "the lower the better" is valid.

Prevention of Coronary Events

G Novo (Italy)

Many trials have proved that statins effectively prevent major coronary events. The benefit of statin therapy is seen irrespective of baseline LDL-levels (Heart Protection Study). Standard statin doses are able to reduce LDL-cholesterol levels by about 30%. Higher than standard doses decrease LDL-cholesterol levels more, and this is also associated with more significant reduction of CV events (PROVE-IT study). Higher doses of statins are well tolerated and the changes in liver and muscle enzymes are not significant. Based on the study results, statin therapy can also be recommended in patients with acute coronary syndrome.

The reduction in coronary events seen with statins is not explained only by lowering of total and LDL-cholesterol, but also by reduction in atherosclerosis progression (decrease in atheroma volume and of percentage of obstruction proved in REVERSAL study) and by stabilization of coronary plaque (anti-inflammatory effect – decreasing C-reactive protein proved in REVERSAL study).

Statins are the cornerstone treatment in coronary prevention. There is no LDL-cholesterol level beyond which there are no additional benefits from statin therapy.

Prevention of Cerebrovascular Events

E Diamantopoulos (Greece)

For many years cholesterol was not considered a risk factor for stroke. However, the association was later clearly proved for ischemic stroke. The effect of LDL-cholesterol reduction on reduction in stroke incidence has been proved as well (a meta-analysis of statin trials, published in 2005, showed a 21% reduction in stroke without any increase in hemorrhagic stroke). The effect of statins is pleiotropic and comprises not only LDL-cholesterol reduction but also atheromatous plaque stabilization, anti-inflammatory properties, improving endothelial functions, decreasing oxidative stress, enhancing angiogenesis, and reducing ischemic/reperfusion injury. Aggressive statin treatment (atorvastatin 80 mg daily in SPARCLE study) demonstrated a higher efficacy in reducing the incidence of fatal and nonfatal strokes as well as major coronary events and the benefit was significant despite a very slight increase in the incidence of hemorrhagic stroke, compared with the placebo group. The recent AHA guidelines have been updated with a recommendation for statin treatment for all patients with ischemic stroke or transient ischemic attack, even without known coronary artery disease.

Prevention of Events in Patients with Peripheral Arterial Disease

A Balbarini (Italy)

Atherosclerosis is a generalized disease. The presence of peripheral arterial disease (PAD) is a powerful predictor of coronary artery disease (CAD), and both increase with age and have similar risk factors. A 15% prevalence of PAD was found in asymptomatic individuals over 70 years of age. However, asymptomatic persons with lower limb arterial disease have the same risk as patients with intermittent claudication.

The prognosis of patients with PAD is poor; 55% of them die from CAD.

Ankle brachial index is an important predictor of CV events and death. There is a strong correlation between the severity of PAD and survival.

Prevention of CV events in patients with PAD should comprise smoking cessation, lifestyle changes, physical activity, weight loss, lipid lowering, glycemic control, and long-term antiplatelet therapy. Like patients with all clinical forms of

atherosclerosis, PAD patients also benefit from statin therapy. The target LDL-cholesterol level should be at least 100 mg/dL (2.59 mmol/L).

In PAD patients, it is strongly recommended to assess the global CV risk (ie, to examine the carotid and coronary arteries as well) and to reduce aggressively all modifiable risk factors.

Past, present, and future of antiplatelet therapy for angiologic disorders

Moderators: G Rao (USA), A Halaris (USA)
Participants: D Clement (Belgium), J Fareed (USA), G Rao (USA), A Halaris (USA)

A survey of newer antiplatelet agents

J. Fareed (USA)

Aspirin, clopidogrel, and GP IIb/IIIa inhibitors are the most commonly used antiplatelet drugs. Aspirin activity causes irreversible inhibition of COX-I and is proven to prevent vascular death and to reduce the incidence of nonfatal vascular events. However, the optimal dose and aspirin resistance are still unclear.

Clopidogrel, is an active metabolite of thienopyridines and causes irreversible alteration of the platelet P2Y12 receptor and selective inhibition of ADP-induced platelet aggregation. Clopidogrel is commonly used in patients who undergoing percutaneous coronary intervention. Clopidogrel activity has an inter-individual variability and the optimal timing and size of the dose to achieve an acute antiplatelet effect are not yet well established.

Among novel thienopyridines, prasugrel seems to have more rapid onset of action and more platelet inhibition than clopidogrel. Cangrelor and AZ06140 do not require metabolic activation and their action has a rapid onset and offset.

GPIIb/IIIa inhibitors include monoclonal antibodies against the receptor and RGD mimetics and are commonly used to prevent ischemic complications with percutaneous coronary intervention. Their risk-benefit ratio in patients with acute coronary syndrome not undergoing early revascularization is less certain. Efforts to develop oral GPIIb/IIIa antagonists have been unsuccessful.

Proteases as SCH-530348 and E 5555, which block thrombin-mediated activation of platelets, are in various phases of clinical trials. An active thromboxane receptor inhibitor (S 18886) is undergoing phase II evaluation for secondary prevention of stroke.

Despite these developments it should be emphasized that most of the newer antiplatelet drugs are administered with aspirin with which they show variable degrees of interaction.

Aspirin resistance: need for a point-of-care assay.
G. Rao (USA)

The author highlighted the efficacy of aspirin in preventing heart attacks and stroke, but emphasized the fact that several studies have shown that a significant percentage of patients (from 4% to 50%) are nonresponders to the action of this drug. Furthermore, monitoring of aspirin sensitivity, using arachidonic acid-induced platelet aggregation, have not identified a specific diagnostic method.

The author proposed a new reliable instrument to measure coagulation (platelet reactivity POC instrument -PRT) to test aspirin sensitivity alone without agonist. This instrument has a microcapillary with a coil of stainless steel inside and this coil is the site of clot formation. In his personal experience using 325 mg of aspirin in normal subjects and measuring clotting time, aspirin inhibited platelet activation in 30% of subjects. This percentage was not very high and depended on clotting time increase. In conclusion, there is a need to develop a point-of-care assay to monitoring global hemostasis.

Serotonin reuptake inhibitors as antiplatelet drugs: what is the evidence?
A Halaris (USA)

Selective serotonin reuptake inhibitor (SSRI) antidepressants exert their effect by inhibiting the reuptake of serotonin by the presynaptic nerve terminals. They have the same effect on platelets. As demonstrated in several studies, SSRIs reduce the incidence of recurrent MI in post-MI patients who develop depression.

The possible mechanisms of the antithrombotic action of SSRIs are: inhibition of 5-HT reuptake by platelets, formation of weaker platelet aggregates, decreased release of antiplasmins, promotion of fibrinolysis. Platelet inhibition by SSRIs may represent an independent avenue of pharmacological effects responsible for the ultimate success of these drugs in patients, not only with depression, but with coronary artery disease and ischemic stroke. Future strategies in patients after vascular events must consider safe approaches to protect platelets from extensive activation

Cardiovascular diseases and aneurysms

Selection criteria of endovascular aortic aneurysm repair
Lecture by R Greenhalgh

The endovascular aortic aneurysm repair (EVAR) trial 1 showed that although there was an early operative mortality benefit with endovascular repair, by 4 years there was no difference in survival between patients receiving open or endovascular abdominal aortic aneurysm repair. The EVAR 2 trial remains regrettably unique and randomized patients considered unfit for open repair to either endovascular repair or no intervention. In this trial of unfit patients, the 30-day mortality in

the group randomized to endovascular repair was 9% and by 4 years there was no difference in overall survival between those randomized to endovascular repair or no intervention. Moreover, by the 4-year time point about two-thirds of the patients had died. The results of the EVAR trial were the subject of a commentary suggesting that the younger, fitter patient, with a large abdominal aortic aneurysm, would still benefit from having open repair of the aneurysm. This hypothesis was tested using data from EVAR trial 1. There is some evidence to suggest that the fittest patients may benefit the most under a policy of EVAR rather than open repair and this is contrary to the above hypothesis. The publications have highlighted the importance of fitness in patient selection for aneurysm intervention and optimization of patients in terms of fitness and medical therapy should be prioritized as well as consideration of their aneurysm size.

From the start, the EVAR trial participants realized that the fitness of the patient was a key issue with respect to endovascular aneurysm repair. However, it was recognized that endovascular aneurysm repair could be performed in two separate populations of patients and the EVAR scientists recommended keeping these populations separate. The first indication was in patients who were fit for open repair and these patients were recruited to EVAR trial 2. The EVAR trialists tried very hard to get the anesthetists to agree to a precise protocol for entry into EVAR 1 or EVAR 2, but the anesthetists, along with the 41 trial centers, had their own criteria in selecting for endovascular or open repair. Consequently, we made suggestions in terms of renal function, respiratory function, and cardiac function which were pointers to encourage the anesthetists in the way in which they categorized the patients. This was adopted very well and in no small part, contributed to the very low operative mortality achieved across the board in 41 centers in EVAR 1, patients who were otherwise fit for open repair, a remarkable EVAR mortality of 1.7% at 30 days.

Unanswered issues regarding endovascular aortic aneurysm repair (EVAR)

Moderators: R Greenhalgh (UK), D Papadimitriou (Greece)
Participants: P Glovicszki (USA), P Cao (Italy), R Greenhalgh (UK), D Kiskinis (Greece), JB Ricco (France), G Deriu (Italy)

Repair of Abdominal Aortic and Iliac Artery Aneurysms: The Changing Concept of Management at the Mayo Clinic

P Gloviczki (USA)

Since the introduction of endovascular aortic aneurysm repair (EVAR) in the early 1990s, robust data have accumulated from thousands of patients who underwent EVAR with a low early morbidity and mortality. However, the durability and indications for EVAR are questioned by the need for continuous surveillance using expensive imaging studies and the nephrotoxicity of contrast agents, the high cost of the device, complications, late ruptures, and the lack of evidence of improved late mortality and a better quality of life vs. open repair. The risk of late endoleaks at 5 years in a recent report by Greenberg et al was 12% to 15% , representing the primary indication for secondary interventions which occur in 20% of standard patients and 25% of high-risk patients through 5 years.

The proportion of EVAR vs open repair (OR) in the last 5 years has been constant at 47% (512/572).

Results of open repair of abdominal aortic aneurysm (AAA) have continuously improved during the past 5 decades. This can be attributed to progress in evaluation and imaging modalities as well as improved selection of patient at high risk for EVAR. Early mortality in a series of 2452 AAA repairs reported in 1993 at the Mayo Clinic was 2.9%. West and Duncan recently reported a 2.5% 30-day mortality of 247 pararenal aneurysms in patients operated between 1993 and 2003. Knott and Kalra analyzed results of open repair of juxtarenal AAAs and found a 30-day mortality of 0.8% (1/126), with 5 cases of temporary dialysis, but no permanent dialysis, and the same low mortality and complication rate as EVAR. Both elective and emergency open repairs have been durable. At 5 years after open surgery Hallett found graft-related complications in 7% of the patients operated on at the Mayo Clinic.

EVAR has emerged during the last decade as an excellent alternative, but less risky treatment for AAAs. Recently published 5-year results of the FDA approved endografts in the United States showed a decreased early mortality and morbidity compared with open surgical repair with a low rate of late complications. The EVAR 1 trial failed to confirm long-term survival advantage of patients who underwent EVAR. In addition, EVAR was more expensive, and associated with a greater number of complications and reinterventions. The issue, however, remains unanswered since in the EVAR 1 study there was a 3% better aneurysm-related survival. The EVAR 2 study failed to show any benefit of EVAR in those high-risk patients who were unfit for surgery. The US Veterans Administration Hospital data support offering EVAR to high-risk patients and this has been our observation as well: high-risk patients benefit from the low early complications of EVAR. In 555 consecutive patients who underwent elective EVAR for aortic or iliac aneurysm at the Mayo Clinic during the last decade, early mortality was 1.26% (7/555). In open surgery mortality was 7.4% for symptomatic, non-ruptured aneurysms (2/27) and was 11.8% for ruptured aneurysms (2/17). In a comparison of the results in 355 consecutive Mayo Clinic patients with infrarenal AAA (261 had OR, and 94 had EVAR), there was no difference in 30-day mortality (1.1%, 3/261 for OR and 0% for EVAR). There were more high-risk patients in the EVAR group, but cardiac and pulmonary complications were less frequent after EVAR than OR (11% vs. 22%, P=0.02, and 3% vs. 16% , P=0.0001, respectively). Graft-related complications were less frequent after OR (4% vs. 13%, P=0.002).

Indications for AAA repair.

Based on data of prospective, randomized, multicenter studies, surgical treatment is recommended for males who harbor an abdominal aortic aneurysm of >5.0 cm. The United States Preventive Services Task Force also found evidence that surgical repair of AAAs 5.5 cm or larger in men aged 65 to 75 years who have ever smoked leads to decreased AAA-specific mortality. At the Mayo Clinic, open repair remains an excellent treatment of AAAs and open surgery (transabdominal, retroperitoneal, or mini-laparotomy) is offered as the first option to many high-risk patients less than 70 years of age. At the Mayo Clinic, EVAR are offered to

most high-risk patients with suitable anatomy for endograft repair and to selected patients with symptomatic and ruptured AAAs. With introduction of fenestrated and branched graft technology and with the judicious use of abdominal aortic debranching and retrograde visceral artery revascularization, an increasing number of patients with juxtarenal and paravisceral abdominal aortic aneurysms will undergo endovascular repair in the future.

Gloviczki et al in a recent review of 715 common iliac artery aneurysm (CIAA) repairs, performed in 438 patients between 1986 and 2005, found 396 patients (9%) had elective repair and 42 (10%) had emergency repair. OR was performed in 394 patients (90%). Thirty -day mortality was not different among the groups. Complications were more frequent and hospitalization was longer after OR than EVAR ($P<0.05$). Freedom from reintervention was similar after OR and EVAR (83% vs. 69%, P=NS), as were survival rates (76% vs. 77%, P=NS).
Gloviczki et al currently recommend elective repair for asymptomatic patients with CIAA >3.5 cm. Although buttock claudication after EVAR remains a concern, results at 3 years support EVAR as first-line treatment in most anatomically suitable patients who require repair of a CIAA. Patients with compressive symptoms or those with iliocaval fistula should be preferentially treated with OR.

Is endovascular aortic aneurysm repair going to become the gold standard for ruptured abdominal aortic aneurysms?
D. Kiskinis (Greece)

The following topics were discussed regarding endovascular aortic aneurysm repair (EVAR) and ruptured abdominal aortic aneurysms (AAAs):

- Preoperative imaging: CT is necessary for diagnosis of rupture, and other organ pathology, eg, aortocaval fistula, morphology of aneurysm and iliac arteries. Other options for graft sizing are: intravascular ultrasound (not available in every department) and intra-operative angiography and use of a marker catheter.
- Anesthetic management
  Hypotensive hemostasis: blood pressure ≤100 mm Hg is sufficient for vital organ perfusion and decreases the tearing force on the aortic wall. With local anesthesia, which is feasible, hemodynamic instability during induction of general anesthesia is avoided.
- Type of endograft (aorto, uni-iliac or bifurcated)
- Postoperative management (compartment syndrome)

The compartment syndrome increases mortality 5-fold. It is monitored through urinary bladder pressure, which is mandatory in every patient after EVAR for ruptured AAA. Decompression laparotomy is performed when bladder pressure is greater than 25 mm Hg

- Evidence from the literature
  There are no completed randomized controlled trials comparing EVAR with conventional open surgical repair for the treatment of rAAA. There are only case reports.

Conclusions

There is no high-quality evidence to support the use of EVAR in the treatment of RAAA. EVAR is feasible in selected cases. Repair in selected patients may be associated with a trend to reductions in blood loss, in duration of intensive care treatment, and in mortality.

Follow-up strategies after endovascular aortic aneurysm repair

JB Ricco (France)

Although endovascular aortic aneurysm repair (EVAR) offers immediate advantages over open aneurysm repair, it carries the need for lifelong surveillance to monitor aneurysm size and/or potential complications including endoleak, change in aneurysm size, graft migration, structural failure, and limb outflow impairment. Current modalities for EVAR surveillance include computed tomography (CT) scan and color-flow duplex ultrasound scanning (US). The most important downside of repetitive CT imaging includes renal dysfunction due to intravenous contrast and problems related to radiation exposure. Recent reports have suggested that US is as effective as and even better than CT. Dr Ricco compared both CT and US as modalities of surveillance for endoleak detection and change in aneurysm size after EVAR. He found a small size difference (<5 mm) in abdominal aortic aneurysm (AAA) measurement by CT and US. However, in his practice and in many other studies, US has a low sensitivity and a low predictive value limiting its use. Technical factors can be very important in the diagnostic value of US and they could not duplicate the excellent results of other centers. Recently, noninvasive sac pressure monitoring using implantable sensors has been shown to have the potential to provide a reliable alternative for post-EVAR surveillance.

Finally, recent studies have shown that follow-up surveillance after EVAR is less intense in practice environments outside clinical trials and that these patients with incomplete follow-up have higher fatal complication rates than patients with regular follow-up.

These data expose a potential under-appreciated limitation of EVAR which is dependent on compliance with a monitoring program. Duplex ultrasound "only" surveillance post-EVAR is safe in patients with stable or shrinking AAA after one year of CT follow-up. It seems possible that half of the patients treated with EVAR will be eligible at 3 years for this follow-up modality. This policy should result in cost savings and should avoid the complications associated with CT.

Unfavorable abdominal aortic aneurysm anatomy. Should we challenge endovascular aortic aneurysm repair or proceed with open repair?

G. Deriu (Italy)

The following recommendations were put forward:

- abdominal aortic aneurysm (AAA) with unfavorable anatomy in low-risk patents: conventional surgery

- AAA with unfavorable anatomy in high-risk patients:
  a) Iliac problems: EVAR
  b) Neck problems: pararenal and suprarenal aneurysms: fenestrated or branched grafts

Neck problems: juxtarenal aneurysms with short (<2 cm) or very short (0.7-1 cm) neck, neck calcifications, thrombotic appositions, pyramidal shape, angulations >60%. EVAR is justified considering secondary results since the neck problem, and iliac artery problems are predictive factors for more frequent complications, either periprocedural or during the follow-up.

Duplex guided balloon angioplasty and stenting for infrainguinal occlusive and aneurysmal disease.
Lecture by E Ascher (USA)

The conventional balloon angioplasty of infrainguinal arteries requires the use of fluoroscopy and injection of contrast material. The author reported his personal experience of 303 balloon angioplasties of the superficial femoral and/or popliteal arteries under duplex guidance in 352 patients to avoid the nephrotoxic effect of contrast and to minimize radiation exposure. Critical ischemia was the indication in 37% of cases and severe claudication in 63%. Infrapopliteal angioplasties in 15% of all cases were performed in order to improve the run-off (as well as) after completion of femoral-popliteal angioplasties. For femoral-popliteal segments, overall technical success was 95% (stenosis 99.6%, occlusions 85%). For infrapopliteal arteries, technical success was achieved in 62 of 65 cases, with an overall success rate of 95% (stenosis 96%, occlusions 91%). The overall 30-day survival rate was 100%. Overall limb salvage rates were 94% and 90% at 6 and 12 months, respectively. Twelve-month patency rates for TASC class A, B, C, and D lesions were 90%, 59%, 52%, and 46%, respectively. Duplex-guided balloon angioplasty and stent placement appears to be a safe and effective technique for the treatment of femoral-popliteal and infrapopliteal arterial occlusive disease.

IV
Peripheral arterial disease

XXIII World Congress
of the
International Union on Angiology
Athens - Greece
21-25 June 2008

4 - Peripheral arterial disease

Atherothrombotic risk associated with peripheral arterial disease

New developments in the management of atherothrombotic risk associated with peripheral arterial disease

Moderators: J Belch (Scotland), D Clement (Belgium)
Participants: J Belch (Scotland), P Cacoub (France), D Clement (Belgium), E Wahlberg (Sweden)

Peripheral arterial disease today: what do the registries tell us?
P Cacoub (France)

The author emphasized the importance of data from registries and epidemiological studies to understand the prevalence of, and risk associated with, peripheral arterial disease (PAD) in different populations. The target population is large: in the IPSILON study, which included 5679 patients (aged ≥55 years) treated in the French primary care system, PAD (defined as an ankle brachial index [ABI] <0.9) was present in 38% of patients with documented atherothrombotic disease and only 10.4% of those with cardiovascular (CV) risk factors. In the getABI study in 6880 patients treated in primary care in Germany, the prevalence of PAD was 19.8% in men and 16.8% in women. The IPSILON study suggests risk factors that may identify patients who may benefit from screening for PAD. These include age, smoking, diabetes, hypertension, intermittent claudication, and atherothrombotic events.

PAD is associated with a high risk of CV events and death. This is clear in data from the REACH registry, which includes 68 000 patients with established atherothrombotic disease or ≥3 CV risk factors. Over the subsequent 2 years among 8581 patients with PAD, 10.09% had a myocardial infarction (MI), stroke or CV death. These event rates remained high even in asymptomatic PAD patients (9.30%). In the getABI study, the risk of all-cause mortality after 5 years was almost equal in patients with or without manifest PAD symptoms. In the registry data PAD frequently occurs with other manifestations of atherothrombotic disease. In the REACH registry at 2 years, 44% of PAD patients had diabetes, 24% were smokers and 66% had hypercholesterolemia. The use of risk-modifying therapies was high, in contrast with the ATTEST study in which only 13% of PAD patients were receiving a combination of ACE inhibitors, statins, and antiplatelet agents, suggesting that clinicians were underestimating CV risk.

These data encourage early detection of PAD and indicate the need to establish optimal risk reduction strategies to reduce the morbidity and mortality due to this prevalent and underestimated condition.

Adherence to guidelines: myth or reality?

D Clement (Belgium)

The Transatlantic Inter-Society Consensus Document for the Management of Peripheral Arterial Disease (TASC II) has provided new information on optimal treatment. In the TASC guidelines, treatment and therapy options are similar in symptomatic and asymptomatic patients. In the TASC guidelines, the low-density lipoprotein (LDL) target for PAD patients is <2.59 mmol/L. For patients with PAD and history of acute coronary syndrome the target is <1.8 mmol/L. The blood pressure target with hypertension should be <140/90 mm Hg or <130/80mm Hg in patients also with diabetes or renal insufficiency. In diabetic patients, the HbA_{1c} target is <7.0%. TASC II recommends for all PAD patients the use of an antiplatelet agent (aspirin or clopidogrel monotherapy).

In reality, in registry data risk factors remain prevalent among PAD patients. In the EUROASPIRE registry, the control of hypertension among patients with PAD is poor and has not changed over 12 years. Primary care practitioners are often unaware of PAD. In the REACH registry, the number of risk factors is associated with improved clinical outcome in PAD. On the basis of these data, the first step should be to inform both patients and their families of the risk associated with PAD and the possible options available for controlling and preventing complications linked with the disease.

Antiplatelet therapy in peripheral arterial disease. How to improve the management of atherothrombotic risk.

E Wahlberg (Sweden)

Peripheral arterial disease (PAD) is associated with a similar risk of cardiovascular (CV) events to coronary artery disease and reduction of CV risk is a priority in the treatment of PAD patients.

Risk modification has three major aspects: lipid-lowering, antiplatelet therapy, and ACE inhibitor therapy. Patients with diabetes should also receive therapy for glucose control.

Some data have demonstrated the efficacy of aspirin in PAD. The Antithrombotic Trialists' Collaboration showed that antiplatelet therapy is associated with a 23% relative risk reduction for vascular events vs placebo. CLIPS, a randomized placebo-controlled trial of aspirin in 366 PAD patients with critical limb ischemia, showed a 64% reduction in vascular events, but the confidence interval was wide. When CLIPS data were included in another meta-analysis, antiplatelet therapy was associated with 26% relative risk reduction in vascular events vs placebo.

In the CAPRIE registry, clopidogrel, compared with aspirin, was associated with an 8.7% relative risk reduction for the primary end point of myocardial infarction, ischemic stroke, and vascular death. In subgroup analyses, compared with aspirin, clopidogrel was associated with a 23.8% relative risk reduction in the primary end point. As the CAPRIE trial was not powered to evaluate efficacy of individual

subgroups, it is unclear whether the differences in relative risk reduction across qualifying condition are real or a result of chance.

Current data support the use of antiplatelet therapy for the reduction of CV risk in PAD and either aspirin or clopidogrel monotherapy is recommended by TASC II in all patients with PAD. However, there is a need to establish the treatment in different patient populations (such as obese patients or those with diabetes) and whether particular treatment combinations are beneficial in PAD.

Renal interventions and peripheral arterial disease

Renal and mesenteric interventions

Moderators: M. Jacobs (The Netherlands), J. Moros (Greece)
Participants: G Geroulakos (UK), M Henry (France), C Klonaris (Greece), A Von Ristow (Brazil)

Renal revascularization: when is it indicated?

G. Geroulakos (UK)

The results of a systemic review of all prospective studies of renal artery revascularization or medical treatment of patients with atherosclerotic renal artery stenosis (RAS), reported mortality rates, kidney function, blood pressure, cardiovascular events, or adverse events at 6 months or later. Overall there was weak evidence suggesting no large difference in mortality rates or cardiovascular events between medical and revascularization treatments; similar kidney-related outcomes, but better blood pressure outcomes with angioplasty, particularly in patients with bilateral disease; and finally that the available evidence does not clearly support one treatment approach over another for atherosclerotic renal artery stenosis.

In order to determine which patients, if any, with atherosclerotic RAS would benefit from angioplasty and stenting (percutaneous transluminal renal angioplasty [PTRA]) as opposed to aggressive medical treatment, two large, randomized, multicenter studies are currently being conducted: the CORAL study in the USA and the ASTRAL trial in the UK.

According to the recommendations of the ACC/AHA/SVS/Society for Vascular Medicine and Biology on the indications for renal revascularization published in Circulation in 2006, PTRA is reasonable for patients with RAS and accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with an unexplained small kidney, and hypertension with intolerance to medication. In addition, PTRA seems reasonable for patients with RAS and progressive chronic kidney disease with bilateral RAS or RAS to a solitary functioning kidney.

Protection during renal intervention: is it worthwhile?

M Henry (France)

Despite good immediate and long-term results, postprocedural deterioration of renal function may occur after percutaneous transluminal renal angioplasty (PTRA) in 20-40% of patients, which limits the immediate benefits of the technique, and atherothrombosis seems to play an important role.

Dr Henry presented his own results of 141 PTRAs performed using a distal protection device to reduce the risk of intraprocedural atheroembolism. He reported an immediate technical success rate of 100% with 112/141 lesions stented directly, debris removed in 80% of cases, one acute renal function deterioration, and a mean follow-up of 29.6 ± 14 months. At 2 years (84 patients included), he observed that 60 were stabilized, 20 improved, and only 4 (5%) had renal function deterioration. He concluded that these results demonstrate the feasibility and safety of distal protection during renal interventions which seem to avoid renal function deterioration after the procedure and in the long term. The beneficial effects of this technique should be evaluated by large, multicenter, randomized studies.

Primary stenting in the solitary functioning kidney, under distal embolic protection

C Klonaris (Greece)

Significant renal artery stenosis (RAS) in a solitary functioning kidney represents one of the most acceptable indications for renal revascularization. According to some reports from the literature, percutaneous transluminal renal angioplasty (PTRA) is increasingly used as first-line treatment for renal revascularization, and is associated with renal improvement or stabilization in the majority of patients with solitary kidneys, but also with deterioration in up to 38% of cases. Based on the hypothesis that this phenomenon may be partly or totally due to distal atheroembolization during the procedure, the use of distal embolic protection was investigated in patients undergoing primary stenting of the renal artery for solitary kidney salvage. The authors treated 14 patients with uncontrollable hypertension, stenosis (range 70%-100%) located at the ostium, all of them with primary stenting and an immediate technical success rate of 100%. They observed macroscopic visible debris collected in the filter in 9 cases and microscopic particles detected in 11 of 14 filters. No deterioration was noted in any patient at 6 months of follow-up, and additionally there was a statistically significant reduction in the mean serum creatinine level, in both systolic and diastolic BP and in the number of antihypertensive drugs. Despite the inherent limitations of this small nonrandomized study, the authors concluded that filter protection devices should probably be used routinely in this patient population with significant RAS and a solitary functioning kidney.

Arteriopathy and diabetes

Diabetic arteriopathy

Moderators: C Allegra (Italy), E Diamantopoulos (Greece)
Participants: C Allegra (Italy), PL Antignani (Italy), E Diamantopoulos (Greece), A Stella (Italy), GM Andreozzi (Italy)

This session consisted of a number of presentations which addressed the diagnosis and treatment of diabetic arteriopathy.

PL Antignani suggested the optimal vascular diagnostic protocol in patients with diabetes.

Once a year objective vascular examination (pulses, bruits, claudication) and ankle brachial index (ABI) measurement in patients with insulin-dependent diabetes mellitus and >35 years, noninsulin-dependent diabetes mellitus and >40 years, diabetes >20 years. ABI measurement has to be repeated every 2 years with a negative screening, every year with arteriopathy, every six months with moderate arteriopathy (ABI <0.6 on ultrasound). An ABI of more than 1.2 should be considered indicative of medial calcification. The most definitive evidence is provided by X-ray of the forefoot in which the medial calcification is visualized as a "tramline finding". In these cases, a toe systolic blood pressure (TSBP) measurement should be performed. A TSBP index 0.6-1 is normal, an absolute TSBP <50 mm Hg is a cut-off for the diagnosis of critical ischemia, and absolute TSBP >30 mm Hg is a cut-off for a possible healing of trophic lesions. If ultrasound does not produce a clear-cut result on the morphological features of occlusions, angio computed tomography (aCT) and nuclear magnetic resonance (MR) should be used when considering revascularization options.

Diabetic foot: the primary task in assessing diabetic foot lesions is the differentiation of neuropathic and (neuro-) ischemic findings. The underlying differences between the two forms is the existence (or absence) of foot pulses. The most important basic diagnostic measure is therefore the palpation of foot pulses. Doppler examination of the peripheral arteries using ABI and, where necessary, a toe pressure measurement are noninvasive examinations. The diagnostic structure in diabetic foot: underlying disease, localization, extent of injury, wound healing stage, infection.

Microcirculatory disorders: the significance of microcirculatory disorders at the capillary level is still a matter of debate. The presence of lumen-occluding processes in the microcirculation of diabetics was used before as justification for early and extensive limb amputation. Today, the presence of occlusive disease can be measured and hence excluded. However, functional abnormalities of the microcirculation with deterioration of hemodynamic, endothelial, and cell function as a consequence of poor blood glucose control must be considered definite. These conditions impair healing. Therefore, the presence of gangrene with palpable foot pulses in patients with diabetic foot syndrome should no longer be considered a consequence of occlusive microangiography but much more as evidence of a neuropathic infected foot. At present, capillary microscopy, laser flow measurement,

and transcutaneous oxygen tension measurement are standard procedures used in the investigation of microcirculatory problems.

E Diamantopoulos discussed medical treatment of diabetic foot. The most common precursor of amputation is diabetic foot ulceration. The therapeutic objectives include debridement, pressure relief, appropriate wound management, infection control, revascularization, and medical management of comorbidities. In neuro-ischemic foot the preferred method is frequent sharp debridement. The ischemic foot should be revascularized and the digital necrosis removed surgically but, if revascularization is not possible, necrotic amputation may be allowed . Indications for surgical debridement: presence of necrotic tissue, localized fluctuance and drainage of pus or crepitus with gas in the soft tissue. Occlusive dressings may lower the risk of infection.

Diabetic foot infections may be classified as non-limb-threatening or limb-threatening. Initial antibiotic treatment is based on the most commonly involved bacteria. Diabetic foot infections that are non-limb-threatening can usually be treated with minor surgical debridement, whereas those that are limb-threatening are often polymicrobial, and require hospitalization and prolonged intravenous treatment with broad-spectrum antibiotics.

The pharmacological treatment to improve perfusion has not been well established. The only drug that has showed a positive influence on the outcome of ischemic diabetic foot ulceration is prostacyclin. The majority of studies have found that the parenteral administration of iloprost reduces ischemic pain, ulcer size, and amputation rate. Wound healing and neutrophil function is impaired by hyperglycemia. Glycemic control is essential. An antiplatelet drug with aspirin or clopidogrel is indicated in all diabetic patients. Hyperlipidemia and hypertension should be treated.

A Stella reported his personal experience of peripheral angioplasty (percutaneous transluminal angioplasty [PTA]) in 993 diabetic patients with critical limb ischemia followed between 1999-2003. PTA criteria for inclusion: single or multiple stenosis >50%, calcified or noncalcified occlusion. Results: restenosis with symptoms 2.2 per year, 5-year limb salvage 88%, death rate/year 6.7%. Angioplasty was the treatment of choice in diabetic patients with critical limb ischemia. In another study from Jan 2005 to Aug 2007, 87 limbs were treated with tibial angioplasty. Inclusion criteria: single or multiple stenosis and/or occlusion <4 cm long. Primary patency at 12 months 37.9%. Negative prognostic factors for primary patency: infected gangrene, smoking, PTA of posterior tibial artery. The rate of assisted patency at 12 months was 71.2%.

From Jan 2005 to Dec 2007, 38 diabetic patients with critical limb ischemia (inclusion criteria: complete occlusion of tibial arteries, patency of peroneal without perforating branches, poor run-off, TUC III D gangrene) were treated for ankle and pedal by-pass. Follow-up at 6 months: primary patency 62%, limb salvage 75%, wound healing 65% (100% at 12 months), survival at 12 months 88.2%.

GM Andreozzi emphasized the role of the physical training to improve walking

ability in claudicants and reported his personal experience. Initial and absolute claudication distances, recovery time (RT) and ankle brachial index were measured by maximal treadmill exercise in 74 patients at day 0 and repeated after 18 days of supervised physical training (daily walk with a distance goal 1-2 km or a time goal of at least 30 min). The patients were divided into three groups: 33 nondiabetics, 20 with HbA_{1c} <7% (balanced diabetics), 21 with HbA_{1c} >7% (unbalanced diabetics). After the training period, absolute claudication distance increased from 106.12 m to 195.97 in nondiabetics, from 92.50 m to 173.85 in balanced diabetics, and from 114.62 to 214.0 in unbalanced diabetics.

Ankle brachial index increased from 0.66 to 0.71 in nondiabetics, from 0.65 to 0.69 in balanced diabetics, and from 0.65 to 0.69 in unbalanced diabetics.

In conclusion, physical training was effective for treatment of claudicant patients. In the improvement of walking ability there was no difference between patients without diabetes, balanced diabetics, and unbalanced diabetics. The persistence of unbalanced metabolic status is predictive of mediocre results. Ankle brachial index changes, which were statistically significant but clinically irrelevant, were likely due to improvement in endothelial function after physical training, with a higher arteriolar vasodilation and reduction in peripheral resistance.

Myopathy and peripheral arterial disease

Peripheral Arterial Disease

Moderators: G Torsello (Germany), J Iliopoulos (Greece)
Participants: H Pipinos (USA), S Merreilles (Brazil), F Moll (The Netherlands), I Vanhandenhove (Belgium)

Myopathy of Peripheral Arterial Disease

H. Pipinos (USA)

In the first part of the presentation, the author described the anatomical changes observed in the muscles of patients with peripheral arterial disease (PAD). In these patients one can observe myopathy with advanced atrophy of muscle fibers, muscle fiber vacularization, target lesions, perimysial thickening and fibrosis, and fibrofatty infiltration of the muscle. The author remarked that PAD pathophysiology is much more than a simple imbalance between blood supply and demand. The mitochondria of the muscles are directly affected by PAD, and have an abnormal ultrastructure, altered enzymatic activities, and altered carnitine metabolism.

In the second part of the presentation, the author considered different questions and their answers.

Question - Are these mitochondrial abnormalities in structure and biochemical composition associated with defective energy production? To answer this question the author designed an in vivo study to compare the gastrocnemius muscle of PAD patients with that of a control group, by determining the spectra of phosphorus

(^{31}P), which represents the ATP, ADP, PCr and Pi levels as mitochondrial function markers. The study demonstrated that PCr recovery and ADP recovery are lower in the PAD patients.

Question.- Is mitochondriopathy initiated by PAD or the associated comorbid conditions (chronic heart failure, diabetes mellitus, kidney failure, dyslipidemia, etc)? The author recruited patients with unilateral PAD and compared the muscle bioenergetics in ischemic versus normal legs. PCr recovery and ADP recovery were lower in the symptomatic leg than in the asymptomatic leg.

The conclusion arising from these questions is that PAD, rather than comorbid conditions, is the primary association with this mitochondriopathy.

Question.- Where in the mitochondria is the problem underlying the observed defective bioenergetics? The hypothesis was that a deficiency in the respiratory chain causes PAD mitochondriopathy. The study designed to answer the question was to measure mitochondrial respiration in PAD patients and in normal controls. Respiration was measured in vitro after stimulation with substrates and ADP. After stimulation, the mitochondrial respiration increases in the normal population but not in the PAD patients. The conclusion is that a deficiency in the respiratory chain seems to be the underlying cause of PAD mitochondriopathy.

In the third part of his presentation, the author discussed the inflammatory changes produced in the muscles during exercise in the PAD patients. During exercise, patients with ischemic claudication develop leg muscle pain, which forces them to rest. When rested, perfusion returns to normal levels. These cycles of ischemia and reperfusion launch a cascade of inflammatory changes and induce the production of reactive oxygen species (ROS). The next question was whether there is any evidence of oxidative stress/damage in PAD skeletal muscle. The authors designed one study to evaluate PAD patients and normal controls for evidence of oxidative stress and damage and for alteration in the activities of the antioxidant defense enzymes. The multiple daily ischemia-reperfusion events produce morphological and ultrastructural changes in the contractile elements of the muscle and its mitochondria. Dysfunctional mitochondria then further lower the already decreased (by compromised blood supply) energy levels in the pathologic muscle, and become sources of ever increasing levels of ROS, and possibly induce apoptosis. This vicious cycle impairs mitochondrial function and escalates ROS production, which results in damage to every structure in the myocytes. Apoptosis leads to severe myopathy that significantly affects the function and performance of PAD limbs.

There is increasing evidence that the injury route expands to damage nerves, skin, and subcutaneous tissues, ultimately leading to the characteristically atrophic legs of patients with advanced PAD.

New stents and stentgrafts in the treatment of superficial femoral occlusions: will they provide long term patency?

I Vanhandenhove and J Bleyn (Belgium)

Neo-intimal hyperplasia has limited the success of several techniques in the treatment of the long (more than 7 cm) superficial femoral artery occlusions. The authors reported follow-up from 1997 to 2008 of 65 patients with superficial femoral occlusions treated with subintimal recanalization and implantation of a polytetrafluoroethylene-covered nitinol stentgraft (Hemobahn® WL Gore). Polytetrafluoroethylene acts as a barrier to growth of tissue through the stent struts and eliminates the deleterious effects of neo-intimal hyperplasia.

At 10 years the primary patency rate was 55.5% and every occlusion was treated by thrombolysis with urokinase. Secondary patency was 83.8% at 10 years.

This was a retrospective study with good results. Prospective randomized studies are needed to demonstrate to superiority of covered stent grafts over other techniques in the treatment of superficial femoral occlusions.

Angiology

Moderators: A. Mansilha (Portugal), J. Aggelakas (Greece), N. Tentolouris (Greece)
Participants: M. Mooschou (Greece), A. Bairaktari (Greece), FA Allaert (France)

Is graft type related to perigraft fluid collection after aortobifemoral bypass?

M. Mooschou (Greece)

Perigraft reaction and groin fluid accumulation following aortobifemoral bypass were seen in all three reported cases, along with negative ultrasound examinations for false aneurysms, and negative cultures, all managed conservatively with groin aspiration, daily wound changes, blood examinations, and prophylactic antibiotics. She reminded the audience that noninfectious inflammation is a rare complication following vascular synthetic graft abdominal implantation, which can mimic microbial infection, and such a complication must be taken into consideration before making the decision to remove the hypothetically infected graft.

Efficacy of pregabalin for painful diabetic neuropathy

A. Bairaktari (Greece)

Results of a small, open, non-controlled study to evaluate the efficacy of pregabalin in painful diabetic neuropathy were reported. Thirteen patients (64-75 years) with VAS>6 were given pregabalin at total doses of 450-600 mg per day. Improvements in pain (VAS<5) and sleep in 9 patients after two weeks of treatment were maintained 12 weeks later, with common side effects including dizziness, somnolence, headache, and dry mouth.

Effect of body mass index on antihypertensive treatment: meta-analysis of 41 625 observations

F. Allaert (France)

A meta-analysis of 41 625 patients (age 63±11 years; 55% male) studied the effect of body mass index (normal <25, overweight 25 to 30, obese >30) on the rate of blood pressure control (≤140 mm Hg and ≤90 mm Hg) by antihypertensives. The normalization rate did not vary as a function of gender but decreased significantly with body mass index: 63.7% in patients with normal weight, 61.1% in overweight patients, and 56.7% in obese patients. These results remained statistically significant after adjusting for weight and gender using logistic regression analysis. In conclusion, body mass index, which is a recognized risk factor for hypertension, also appears statistically to limit the effect of antihypertensive treatment.

V
Venous thromboembolic diseases

XXIII World Congress
of the
International Union on Angiology
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21-25 June 2008

5 - Venous thromboembolic diseases

Venous thromboembolism and guidelines

Prophylaxis and treatment of venous thromboembolism (VTE)

Moderators: MM Samama (France), A Katsamouris (Greece)
Participants: MM Samama (France),W Leong (Canada), J Walenga (USA), J Fareed (USA)

Regarding prophylaxis and treatment of venous thromboembolism (VTE) in special populations, **MM Samama** in his presentation focused on pregnant women with confirmed VTE or at risk of VTE. It is well known that pulmonary embolism is a major cause of maternal mortality. Moreover in pregnancy the risk of VTE is 5- to 10-fold higher than in the non-pregnant population, the risk being much higher after delivery. Therefore, there is a need for clinical vigilance when there is a suspicion of VTE in pregnant women. There are no randomized clinical trial data on this subject, and the recommendations from the American College of Chest Physicians (ACCP) are scarce. The new ACCP 2008 guidelines recommend the following:

- For women receiving anticoagulation for the management of VTE who become pregnant, vitamin K antagonists have to be replaced by unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) (grade 1A)
- For lactating women using warfarin or UFH who wish to breastfeed it is recommended to continue these medications (Grade 1A).
- For pregnant women it is suggested LMWH over UFH for the prevention and treatment of VTE (grade 2C), but a switch to UFH 4 weeks before delivery is required, as noted by MM Samama. For prevention, the prophylactic and intermediate dose (the prophylactic dose given twice daily) should be used, depending on the patient's risk level. In acute VTE, the body weight-adjusted therapeutic dose (full dose) of LMWH or adjusted iv or sc dose of UFH (with activated partial thromboplastin time within therapeutic range) should be used for at least 5 days (Grade 1A). After the initial therapy, sc LMWH or UFH should be continued throughout pregnancy (Grade 1B) or at least 3 months.. The question when to reduce the full dose of LMWH if VTE occurs in the 2^{nd} or 3^{rd} month of pregnancy remains unanswered. Anticoagulation should be continued for at least 6 weeks postpartum (for a minimum total duration of therapy of 6 months) (Grade 2C).
- Regarding prevention it is crucial to find out whether the patient had prior episodes of VTE (0,1, =,>2) or not, and if so whether it was provoked or unprovoked, whether the patient has primary or secondary thrombophilia or other risk factors such immobilization, obesity, older age, twin pregnancy, cesarean section, etc. Even the thrombophilic states do not have the same risk: AT deficiency, homozygous thrombophilias and combined thrombophilias are considered high risk, heterozygous PC deficiency is deemed intermediate risk, and PS deficiency, heterozygous FII G20210A status, and heterozygous FV Leiden status are low risk. ACCP 2008 guidelines suggest that a thrombosis risk assessment be carried out in all women

undergoing cesarean section to determine to need for prophylaxis (Grade 2C). In patients without other risk factors undergoing Cesarean section, only early mobilization is recommended (Grade 1B). In the presence of at least one risk factor in addition to pregnancy and cesarean section, pharmacologic (UFH or LMWH) or mechanical (graduated compression stockings or intermittent pneumatic compression) prophylaxis is recommended while in hospital following delivery (Grade 2C). In patient with high risk and cesarean section it is suggested to combine the pharmacologic prophylaxis with the use of graduated compression stockings or intermittent pneumatic compression or both, which can be extended following discharge from the hospital (Grade 2C). The other recommendations for prevention vary regarding the presence of one or more episodes of prior VTE, transient or permanent risk factors, and the presence of thrombophilic states at different risk levels. In women with lower risk, antepartum prophylactic or intermediate dose of LMWH/UFH or clinical surveillance is recommended throughout pregnancy, plus postpartum anticoagulation. For higher risk patients, antepartum prophylactic or intermediate dose LMWH/UFH (Grade 2C) is recommended in addition to postpartum prophylaxis. For pregnant women with very high risk, the recommendation is for antepartum prophylactic, intermediate or adjusted dose LMWH/UFH followed by postpartum anticoagulation (Grade 2C). For pregnant women receiving long-term anticoagulants for prior VTE, the recommendation is for either adjusted-dose LMWH or UFH, 75% of adjusted dose LMWH or intermediate dose LMWH throughout pregnancy followed by resumption of long-term anticoagulants postpartum (Grade 1C). For all pregnant women with previous deep vein thrombosis (DVT), the use of graduated compression stockings is suggested both antepartum and postpartum (Grade 2C). For pregnant patients with thrombophilia but no prior VTE, physicians are advised not to use routine pharmacologic antepartum prophylaxis (but in antithrombin deficiency antepartum and postpartum prophylaxis is recommended), but postpartum prophylactic anticoagulants are recommended.

In conclusion, **MM Samama** said that treatment of pregnant women with confirmed VTE is well documented, although appropriate dose regimens and the optimal duration of treatment is still disputed. Individual decisions and clinical judgment are also necessary.

W Leong from Canada talked about outpatient management of deep vein thrombosis. She presented a functional model of outpatient treatment based on the activities of an anticoagulation clinic, a medical day-car clinic, and an emergency department. About 40% of their patients are treated as outpatients. She presented the indications and contraindications and stressed the usefulness of the guide-book given to the patients. The number of outpatient treatments is continuously increasing with increasing use of LMWH in daily practice. Clinical follow-up is crucial. Treatment failure in generally is due to LMWH underdosage, administration for less than 5 days, subtherapeutic international normalized ratio, noncompliance, and inappropriate follow-up.

Finally, **J Fareed** presented two lectures about the role of new anticoagulants in the management and prophylaxis of venous thromboembolism. The main question he posed was: will they replace heparins and oral anticoagulants? Despite progress in the science, he said, none of these new drugs (oral dabigatran, an anti-IIa, and fondaparinux, an anti-Xa, and oral apixaban and rivaroxaban) will ever match the various pharmacological effects of heparins. There is a major thrust in the development of orally bioavailable anti-Xa and anti-IIa agents, which are slated to replace oral anticoagulants. Both anti factor-Xa and anti-IIa agents have been developed for oral use and have given impressive clinical results. However, safety concerns related to liver enzyme elevations and thrombosis rebound have been reported with their use. For these reasons the FDA in USA did not approve oral Ximelagatran for several indications. Fondaparinux (a synthetic pentasaccharide) also produced major bleeding problems at minimal dosages. Fondaparinux represents only one of the multiple pharmacologic effects of heparins. Thus, its therapeutic index will be proportionately narrower.

IUA guidelines on venous thromboembolism and beyond - Part A

Moderators: VV Kakkar (UK), A Comerota (USA)
Participants: A Nicolaides (Cyprus), S Kakkos (UK), M Samama (France), J Fletcher (Australia), H Gibbs (Australia)

In the first lecture **A Nicolaides** presented interesting evidence on venous thromboembolism (VTE) prevention. The cross-sectional international study **ENDORSE** evaluated VTE prophylaxis (according to the ACCP 2004 guidelines) in hospitalized patients in 32 countries. The results showed a great variance between countries in application of prophylactic measures and proved that quite a high proportion of hospitalized patients at risk for VTE do not receive prophylaxis (59% of surgical and 40% of medical patients at risk). Implementation of prophylaxis in every day practice is necessary. Every admitted patient should be assessed for the VTE risk. It is also important to educate the public about VTE risk and prevention.

In 2006 the IUA released the last VTE prophylaxis guidelines (updated every 4 years). According to the risk stratification (low, moderate, and high), the appropriate prophylaxis is recommended and the strength of recommendation is graded based on the level of existing evidence. Duration of VTE prophylaxis is an unresolved issue but the recent **EXCLAIM** study has produced the evidence of substantial risk reduction (44%) with extended prophylaxis (with enoxaparin) in medical patients.

S Kakkos summarized the results of a review assessing the efficacy of combined modalities in venous thromboembolism (VTE) prophylaxis. He performed the database search of randomized controlled trials, controlled clinical studies and other studies, comprising 9998 patients in a variety of specialties. Pharmacological intervention (heparin, low-molecular-weight heparin [LMWH] or warfarin) and a mechanical method (intermittent pneumatic leg compression used together were more efficient in preventing deep vein thrombosis (DVT) as well as symptomatic pulmonary embolism (PE). These results support the use of combined

prophylactic modalities in a subgroup of high-risk patients, based on thorough individual risk assessment. However, this topic deserves further research, including cost-effectiveness studies.

M Samama concentrated on prophylaxis in two special patient populations – patients with cancer and with myeloproliferative disease (MPD). Cancer patients have a 4-fold higher VTE risk, but the mechanism of this association is still not fully understood. VTE prophylaxis in cancer is strongly recommended, especially in immobilized patients and in patients undergoing surgery. In the treatment of VTE, the benefit of long-term dalteparin has been proved in the CLOT study. Cancer patients are a very heterogeneous group and the risk assessment should take into account age and comorbidities, additional risk factors (chemotherapy, radiotherapy, some inherited thrombophilic disorders), primary site of the cancer, and its stage.

MPD represents 4 entities – chronic myeloid leukemia, polycythemia vera, essential thrombocythemia , and primary myelofibrosis. In the last three diseases, and especially in polycythemia vera, a recently discovered the JAK2 mutation plays a substantial role. MPD represents a hypercoagulable state and is frequently associated with splanchnic vein thrombosis. Therefore, every patient with splanchnic vein thrombosis should be tested for the JAK2 mutation, which may uncover occult MPD. Whether the JAK2 mutation modifies VTE risk and prognosis in MPD is not known and research is ongoing.

In patients with essential thrombocythemia, aspirin is efficient in VTE prophylaxis. **J Fletcher** presented the Australian and New Zealand VTE prophylaxis guidelines (created by the Australian and New Zealand Thrombosis Working Party and based on the IUA and ACCP guidelines) and how the aim is to improve their application in clinical practice. The recommendations are summarized and distributed them as booklets, seminars and workshops are organized, and medical record alerts are implemented, etc. The initiative is intended to increase awareness of VTE and its prophylaxis among government officials, healthcare professionals, medical organizations, as well as the public. An analysis of VTE cases in Australia in 2008 revealed the substantial cost burden of the disease (not only health expenditure but also lost productivity, lost wellbeing, and other factors were taken into account). It is necessary to achieve mandatory VTE risk assessment in hospital-admitted patients as well as to check adherence to the evidence-based guidelines.

H Gibbs reported on venous thromboembolism (VTE) prevention in medical patients. VTE treatment is not always fully successful and the consequences could be serious or even fatal. However, the efficacy of VTE prophylaxis is very well documented (according to three recent meta-analyses with heparin and LMWH) and so it is crucial to optimize prophylaxis, especially in hospitals. It is reasonable to use heparin, LMWH, or fondaparinux in medical patients. There is a lack of data about the efficacy of mechanical methods (graduated compression stockings) in medical patients (the only evidence is for patients with an ischemic stroke), so they can only be recommended for patients with a contraindication to anticoagulant therapy. The risk assessment and choice of appropriate prophylaxis is necessary. Prophylaxis is usually continued until discharge or until the resolution of the

acute condition. However, the recent EXCLAIM study has provided evidence of the benefit of extended VTE prophylaxis in some groups of medical patients. Prolonged duration of VTE prophylaxis should be considered, especially in patients with marked immobility, advanced age, cancer, or a history of VTE. Though effective prophylaxis reduces VTE incidence by 50% to 90%, it is still underused in practice (as shown in the recent ENDORSE study). Multiple strategies should be applied to improve implementation of prophylaxis guidelines (education, reminders, audit, and feedback).

IUA guidelines on venous thromboembolism and beyond - Part B

Moderators: J Fletcher (Australia), M de Castro Silva (Brazil)
Participants: A Comerota (USA), E Ascher (USA), VV Kakkar (UK), R Hull (Canada), J Fareed (USA)

In his very interesting presentation about aggressive management of ilio-femoral deep vein thrombosis (DVT), **A Comerota** highlighted that the 2004 ACCP guidelines do not explicitly recommend clot removal in proximal DVT, but this will change in the 2008 ACCP recommendations, which will be published this month. Recent studies show a clear benefit of clot removal in ilio-femoral DVT, in which efficient anticoagulation and elastic stockings are frequently not sufficient to prevent recurrence and sequelae or to improve quality of life. In the new guidelines, two strategies of venous thrombus removal in acute proximal DVT will be implemented. The first one is catheter-directed thrombolysis with many newer facilities and devices (modern catheters, ultrasound accelerated devices, ultrasound-guided venous access, aspiration, etc.). The case control and cohort studies available in this field since 2001 show relatively low bleeding complication (<5%, with much lower intracranial bleeding). The method has a significantly higher patency rate and valve function preservation than anticoagulation and elastic compression alone. The second strategy includes venous thrombectomy with creation of an arteriovenous fistula, especially in patients who have contraindications for thrombolysis. Studies have also shown a better patency rate, lower incidence of post-thrombotic syndrome, and better valvular function preservation. The importance of routine chest, abdominal, and pelvic CT scan in ilio-femoral DVT patients because of high rate of subsequent malignancy was also stressed.

E Ascher dealt with the controversial issue of superficial thrombophlebitis (SVT). He posed several questions: Is there a correlation between SVT and deep vein thrombosis (DVT)? Does SVT correlate with hypercoagulable states? Does SVT correlate with pulmonary embolism (PE)? How should it be treated? His answers showed that the SVT is not as benign a clinical entity as the medical community believes. The SVT patient may have a hypercoagulable state, parallel DVT, or PE, or a combination thereof. According to a recent meta-analysis, the incidence of DVT in SVT patients is 6% to 44%, the incidence of asymptomatic PE is 20% to 33% and of symptomatic PE 2% to 13%. Up to 25% of DVT cases are non-contiguous, suggesting the presence of systemic predisposing factors. The same conclusion is suggested by the incidence of primary thrombophilias in SVT patients, which varies between 38% and 50% in different studies. The incidence of PE in SVT patients varies between 0% and 33%, and is mostly clinically silent. For proximal great saphenous vein thrombosis anticoagulation, elastic stockings and

mobilization are more effective for prevention of DVT and PE, whereas surgery (crossectomy) with or without stripping is only superior in symptomatic relief. The speaker didn't highlight the potential etiologic, prognostic, and therapeutic differences between non-varicose and varicose-superficial vein thrombophlebitis. More studies are needed for clearer recommendations.

VV Kakkar in his partly historical review talked about half a century of challenges in VTE prophylaxis. In the 1960s, the problem was defined: incidence, natural history of VTE, and identification of high-risk group of patients. The low fixed-dose unfractionated-heparin era was in the 1970s. In the 1980s, low-molecular-weight heparin (LMWH) was developed with more clinical trials proving the efficacy and safety of LMWH in both prophylaxis and treatment of DVT and PE. Eventually it became evident that there is a need for prophylaxis in medical patients also. Today's challenges are: why does prophylaxis still fail frequently? Are the available guidelines followed? What would be the ideal guidelines? How can the implementations of guidelines be improved? The answers need more public awareness, well-defined strategies from health authorities, and more well-designed studies, of course.

R Hull raised the main question of when to start and finish thromboprophylaxis. Prevention started perioperatively (shortly before or soon after surgical intervention) seems to be the best choice, the decision depending on the patient's risk-benefit ratio.

J Fareed summarized the newer anticoagulants (anti-Xa and antithrombin inhibitors) pointing out that heparins will remain in the landscape of VTE patient management. Since VTE has a multifactorial etiology, heparins due to their various pharmacologic effects remain the standard therapy. For this reason monotherapy (anti-Xa and anti-IIa inhibitors) at this moment have a reduced but well-defined area of indication, especially in management of heparin-induced thrombocytopenia (parenteral antithrombin agents) or in orthopedic prophylaxis (parenteral pentasaccharides). The oral anti-Xa and anti-IIa are promising agents, but at this moment they are not a replacement for warfarin.

Superficial thrombophlebitis: a significant subset of venous thromboembolic disease

Moderators: I. Quere (France), K. Katsenis (Greece)
Participants: M.A. Sevestre-Pietri, G. Boge, I. Quere, P. Carpentier, G. Pernod (France)

MA Sevestre-Pietri presented the results of the OPTIMEV study. A total of 8253 patients with suspected venous thromboembolism (VTE) were investigated by Duplex scan, computer tomography, and lung scan. The diagnosis was confirmed in 2795 cases (33.9%). Superficial thrombophlebitis (ST) was found in 595 cases, ST and pulmonary embolism (PE) were noted in 32 cases, and ST and deep venous thrombosis (DVT) in 174 cases. Among ST risk factors, the greatest were varicose veins (odds ratio [OR]=5.5; 95% CI) and hormone therapy (OR=2.7; 95% CI).
G. Boge et al presented the results of the POST study, which estimated risk factors for VTE in patients with isolated ST. A total of 810 patients with symptomatic ST were separated into 2 groups. First group included 210 patients with deep vein

thrombosis (DVT) or symptomatic pulmonary embolism (PE) or both. The second group included 600 patients with isolated ST. Analysis of patients with ST and VTE revealed the following risk factors: current hospitalization or bedridden for more 3 days in previous 20 days (odds ratio [OR]=15.1), history of autoimmune disease (OR=6.5), absent of the varicose veins (OR=4.5), age above 75 years (OR=3.1), history of VTE (OR=2.2). Interestingly, there was no significant relation with traditional risk factors of VTE (active cancer, cardiac or respiratory insufficiency, permanently restricted mobility, previous surgery, infection, long-haul travel, pregnancy). Traditional risk factors were found in the group of patients with isolated ST, such as male sex (OR=3.10), history of VTE (OR=2.6), and cardiac or respiratory insufficiency (OR=2.5). Absence of varicose veins and venous insufficiency was a risk factor too (OR=2.2). **I Quere** confirmed the relation between ST and cancer.

Malignant neoplasms were found in 3.8% cases of isolated ST and in 13.4% cases of ST and VTE (POST-study). The OPTIMEV study has demonstrated a relation between cancer and ST in 10.3% cases and between cancer and VTE in 20.7% cases. There is no consensus about optimal treatment of ST (**G Pernod**). Compression stockings and LMWH are most commonly used for treatment ST. Only two randomized, controlled trials have been devoted to efficacy of LMWH. The Stenox (2003) and Vessalio (2005) studies did not find significant differences between prophylactic and therapeutic dosages of LMWH in patients with ST. The international, multicenter, randomized, controlled trial CALISTO started recently and should provide answers to many problems of ST treatment.

Antithrombotic drugs

Generic antithrombotic drug development: what are the guidelines?

Moderators: G Rao (USA), W Raake (Germany)
Participants: J Fareed (USA), W Leong (Canada), W Raake (Germany), J Walenga (USA), R Hull (Canada)

As protection of the intellectual property rights of the companies who developed low-molecular-weight heparins (LMWHs) is expiring, concerns arise regarding generic LMWH products. The classic approach to generic development, in which the generic should be similar to the reference product with respect to active substance, content, pharmaceutical form, and bioequivalence, is not adequate for LMWH. LMWHs are biological products, whose active substance is derived from living organisms by chemical modification of the multicomponent mixture of glycosaminoglycans. These kinds of drugs are more difficult to characterize, due to the wide spectrum of molecules that they contain, and limited knowledge regarding the safety and efficacy of each fraction. That is why the regulatory authorities consider each available LMWH as a distinct drug. **R Hull** reviewed how LMWHs differ, and how these differences might affect patient outcomes. LMWHs are all derived from unfractionated heparin, which allows increased bioavailability, decreased protein and endothelium binding, and thus a more predictable effect, improved safety, and generally increased efficacy. However, because the manufacturing process differs, the molecular weight profile of the different branded

LMWHs varies. This has an impact not only on the anti-Xa over anti-IIa ratio, but also on clearance: the lighter the molecules, the greater the renal clearance. This might have clinical implications, since renal impairment is very common in patients treated with LMWH. The risk of accumulation and hence of bleeding could vary amongst the different LMWHs. Another concern is the possibility of drug reversal in the case of bleeding. The proportion of the effect that is reversible is related to the proportion of anti-Xa activity and to the proportion of drug sulfation. These two parameters again differ amongst LMWHs.

This differentiation of LMWHs becomes crucial as we observe a paradigm shift towards a "first do not harm" perspective, and stresses the need for a thorough safety assessment in the development of generic drugs. Various attempts are being made to develop specific guidelines for biological medicine generics. **W Raake** presented the EMEA's ongoing guideline development. In vitro and in vivo studies will be required, as well as a 4-week toxicity study. Due to possible molecular heterogeneity, pharmacodynamic and pharmacokinetic phase 1 studies will also be mandatory. Safety issues, mainly the risks of bleeding and of heparin-induced thrombocytopenia, will need to be addressed for each generic drug. On the other hand, reproduction, mutagenicity, or carcinogenicity studies will not be necessary. Moreover, demonstration of comparable efficacy and safety for example in surgery patients at risk for VTE may allow extrapolation for the other indications of the reference drug.

J Fareed reminded the audience that several generic versions of LMWHs exist in India and in South America. Some of them have been compared with the reference product and exhibited significant pharmacological differences despite chemical equivalence. **J Walenga** insisted on the need for immunogenic studies in this setting. In fact, the immunogenicity and the proportion of antibody subtypes produced could differ according to the composition of the preparation. A generic product that would have an identical composition, with the same proportion of the different oligosaccharides, should induce a similar quantitative and qualitative immunogenic response profile. Demonstration of this equivalence, however, will require clinical trials. Another concern is that LMWHs are able to bind to other endogenous proteins. This might result in the generation of neoepitopes, whose clinical implications are unknown until now. **J Fareed and J Wallenga** both reminded the audience of recent accidents reported after the use of a contaminant, hypersulfated chondroitin sulfate, in heparin preparation. These nonheparin glycosaminoglycans can also have an immunogenic effect. This further illustrates the need for strict control of the bioequivalence of all the agents used.

To conclude, because of their biological nature, developing generic LMWHs is particularly challenging. To ensure not only chemical similarity, but also comparable efficacy and safety, regulation authorities (EMEA, FDA) are currently developing specific guidelines that will include pharmacokinetic and pharmacodynamic studies, as well as safety and immunogenic studies. These requirements will, however, make the approval of a generic LMWH a very long, complicated and expensive process which could significantly decrease the cost-savings of such an approach.

From low-molecular-weight heparins to specific factor xa inhibitors. Pharmacological and clinical issues

Moderators: G.T.Gerotziafas (France), MM Samama (France)
Participants: G.T. Gerotziafas (France), P Prandoni (Italy), A Kakkar (UK), J Walenga (USA), MM Samama (France)

After a short historical overview concerning discoveries of antithrombotic drugs and their clinical use, **G.T. Gerotziafas** concentrated on the explanation of the different mechanisms of action of some of the current antithrombotic drugs, as well as that of the recently developed agents, on the anti-IIa and anti-Xa effect, respectively. Thrombin (factor IIa) plays multiple roles in many processes beside coagulation, e.g. in the activation of protein C (natural inhibitor of coagulation), in fibrinolysis, inflammation, cell proliferation, and angiogenesis. Factor Xa has a central function in coagulation. In a free form it participates in the initiation phase of coagulation, while the prothrombinase-bound FXa plays an important role in the propagation phase.

In comparison with heparin (which is a mixture of different polysaccharide chains and possesses both anti-IIa and anti-Xa activities), low-molecular-weight heparins (LMWHs) have prevalent anti-Xa activity, with some preserved anti-IIa activity. More LMWHs are in clinical use, with different molecular weights, different anti-Xa/anti-IIa activity ratio, and different impact on thrombin generation. Therefore, they are not interchangeable.

It is also necessary to realize that there are differences between the two groups of new anti-Xa agents. Indirect inhibitors (eg, fondaparinux) inhibit only free FXa, while direct inhibitors (eg, rivaroxaban) inhibit both free and bound FXa. These two groups differ as to the mode of action, the mode of administration, and the impact on prothrombin time (PT) and activated partial thromboplastin time (aPTT).

Whether factor IIa or Xa is a better target remains an open question.

P. Prandoni reviewed evidence on the use of LMWH and pentasaccharides in the prevention and treatment of venous thromboembolism (VTE):

- in the prevention in major orthopedic surgery, LMWH are superior to unfractionated heparin (UFH). Fondaparinux (a synthetic pentasaccharide) is even more effective than LMWH, without increased bleeding. The use of fondaparinux is safe also with the concomitant use of neuroaxial or peripheral anesthesia. Prolonging the prophylaxis with LMWH or fondaparinux further reduces VTE risk without increasing the risk of hemorrhage.
- in general surgery, LMWHs are as effective and safe as UFH; fondaparinux is comparable to LMWH but probably more effective in cancer patients.
- in medical patients the prophylaxis of VTE is underused in spite of the proven risk reduction with LMWH as well as with fondaparinux. In the EXCLAIM study, the postdischarge prolongation of prophylaxis with LMWH (for up to 4 additional weeks) was efficient in VTE reduction, but caused a small but significant increase in bleeding and therefore the extended prophylaxis should be reserved only for high-risk medical patients.

- fondaparinux is as effective and safe as the conventional initial treatment of VTE with UFH or LMWH.
- idraparinux, a new pentasaccharide with once-weekly dosing, was comparable to UFH or LMWH in the initial treatment of deep vein thrombosis with a trend to a better tolerability. However, it was inferior to a conventional initial treatment of primary pulmonary embolism (more symptomatic recurrent VTE observed in Van Gogh PE study). In the extension of the secondary VTE prophylaxis after the conventional 6-month anticoagulation, idraparinux resulted in fewer recurrent events than placebo, but increased rate of major bleeding. A new, potentially safer version of idraparinux (biotinylated idraparinux) is currently being tested.

G.T. Gerotziafas briefly considered oral specific factor Xa inhibitors (rivarobaxan) and stressed the absence of dose-dependent efficacy in all Xa inhibitors. Rivarobaxan binds specifically at an active center of FXa. After repeated administration, no significant accumulation was observed. Rivaroxaban has proven more effective than LMWH in major orthopedic surgery. In vitro, even in a very low concentration, rivaroxaban suppresses thrombin generation.

M. M. Samama added a short comment. While we nowadays already have efficient anticoagulants available for VTE prophylaxis in orthopedic surgery, the main objective for the new drugs in this indication should be the decrease in bleeding risk.

J. Fareed presented the next lecture on behalf of **J. Walenga.** He stressed the polypathologic nature of the thrombotic process and the role of some of the existing as well as newly developed drugs (UFH, LMWH, ultra-LMWH, pentasaccharides, oral anti-Xa and anti-IIa agents, recombinant thrombomodulin and recombinant antithrombin).

- The advantages of LMWH versus direct anti-Xa agents are lasting effect after subcutaneous or intravenous administration, multiple sites of action, and multiple indications.
- The disadvantages of direct anti-IIa agents are their variability, delayed onset, and the suppression of the regulatory functions of thrombin.
- Moreover, in both oral anti-IIa and anti-Xa agents, there are still concerns about potential hepatotoxicity and additional data from phase III clinical studies are needed.
- These agents do not have any known antagonist and their long-term toxicity is not known.
- So, the total conversion from heparin and LMWH to new anticoagulants is highly unlikely. However, the new agents may find their place in some special indications (heparin-induced thrombocytopenia; resistance to the conventional anticoagulant therapy; short-term prophylaxis; and stroke prevention in atrial fibrillation).

M. M. Samama concentrated on the action of anti-Xa agents and the possibility of their laboratory monitoring. It is necessary to distinguish between oral and parenteral, direct and indirect anti-Xa agents. In general, laboratory monitoring

is not necessary. However, it may be useful for some special patient populations and in some special clinical settings. Therefore, appropriate coagulation tests should be available. Such a test should be available in any laboratory, 24 hours a day. He reported the results of his extensive research work in this field (published and unpublished). The possible coagulation tests studied are prothrombin time (PT), dilute PT, activated partial thromboplastin time (aPTT), Heptest, prothrombinase-induced clotting test (PiCT), thrombin generation test, anti-FXa test, and the Russell´s viper venom test (RVVT). Only some of these tests are potentially suitable for anti-Xa agents. A good practical option seems to be modified PT, RVVT for rivaroxaban, and maybe PiCT with some modification. Before the introduction of some of these tests to practice, standardization is needed and the research is ongoing.

Do low-molecular-weight heparins have a future in thrombosis management?

Moderator: A Kakkar (UK)
Participants: A Kakkar (UK), S Haas (Germany), J Arcelus (Spain)

A. Kakkar introduced the session with an interesting historical overview of some key publications from the last 50 years that have influenced the approach to the prevention and treatment of venous thromboembolism (VTE). The first evidence about the efficacy of the prophylaxis with anticoagulation in orthopedic surgery was published in The Lancet in 1959. At that time, the diagnosis of postoperative VTE was based only on clinical symptoms, but later on the imaging method (radiolabeled fibrinogen scanning) demonstrated the high incidence of postoperative VTE (Lancet, 1961). Low-dose unfractionated heparin (UFH) proved to be efficient in the prophylaxis of postoperative VTE in the 1970s.

The advent of low-molecular-weight heparin (LMWH) was in the 1980s. In 1986 the first evidence was published about the efficacy of LMWH (versus placebo) in the prevention of VTE in major orthopedic surgery.

Later on, a meta-analysis clearly demonstrated that prophylaxis with heparins is efficient in reducing postoperative pulmonary embolism (PE) including fatal PE, but does not increase fatal bleeding.

In the mid 1990s, LMWH proved at least as effective as heparin in the initial treatment of VTE, with potentially better safety (fewer bleeding complications).

S. Haas summarized current knowledge of LMWHs, which have become the golden standard in a variety of conditions because of the convincing evidence of their efficacy in:

- VTE prevention:
  - in major orthopedic surgery (no increase in bleeding risk was found; better efficacy than UFH was proven; better efficacy of prophylaxis prolonged to 4-5 weeks after surgery)

  - in general surgery (better efficacy of prolonged prophylaxis)
  - in medical patients (similar efficacy as UFH, but less major hemorrhage)
  - in patients with ischemic stroke (better efficacy than UFH; the large body of evidence proved consistent benefit across multiple comorbidities)
- the initial treatment of VTE (LMWHs are at least as good as UFH and cause fewer bleeding complications; there is evidence of their efficacy even in proximal DVT and in PE which facilitates the outpatient management of VTE)
- the treatment of VTE in cancer patients (better efficacy in long-term secondary prevention of VTE was shown in the CLOT study; a potential favorable effect on survival was shown in CLOT and also some other studies, probably due to the pleiotropic effect of LMWH)
- the treatment of acute coronary syndrome (the meta-analysis significantly favors LMWH over UFH)

In the patients with renal impairment, LMWHs should be used cautiously respecting the recommendations about dose reduction according to creatinine clearance.
For obese patients, LMWH in prophylactic indications should be given without any special dose adjustment (the exception may be bariatric surgery for which there is evidence of the benefit of a doubled prophylactic dose).

Taking into account the unresolved issues regarding new antithrombotic drugs and the above mentioned evidence, LMWHs will definitively survive for many more years, at least in acute indications.

J.I. Arcelus concentrated on the new oral antithrombotic agents. In spite of having quite safe and effective antithrombotic drugs available, there is still a need to develop new and better ones. The new oral agents may have potential advantages but are still far from being ideal anticoagulants. They target only one coagulation factor – either factor Xa or thrombin (factor IIa). Dabigatran, an oral anti-IIa agent, has low bioavailability, interacts with pantoprazol, and is of limited use in renal insufficiency. Rivaroxaban, a direct anti-Xa agent (inhibits both free and clot-bound factor Xa), has high bioavailability, interacts with food and drugs, and its excretion is both urinary (66%) and biliary (30%). Both drugs have been tested in phase III clinical trials (in VTE prophylaxis in patients with total hip replacement (THR) and total knee replacement (TKR), compared with enoxaparin) and the results can be summarized as follows:

- dabigatran is as effective as enoxaparin, without significantly increased bleeding risk
- rivaroxaban is more effective, but there is a tendency to more bleeding complications

So the conclusion is that the new oral anticoagulants are at least as effective as enoxaparin in prophylaxis after THR and TKR and could be promising due to greater convenience (oral administration is better accepted by patients), but before a definitive conclusion is drawn more experience is needed, ie, broader population of treated patients.

Will heparins and oral anticoagulant drugs survive? Newer developments in anticoagulation

Chairman: D Hoppensteadt (USA)
Lecture by J. Fareed (USA)

Many new anticoagulant drugs are being developed with a view to potentially replacing the two old agents, heparin and warfarin. These two anticoagulants have their limitations, but both have been used for many years and are of proven efficacy and relative safety in the treatment and prevention of thrombosis. As thrombosis involves a variety of pathologic processes, it requires multidrug therapy. The new anticoagulant drugs have various mechanisms of action: they inhibit thrombin (factor IIa) or factor Xa or tissue factor or influence thrombin generation. There are 22 oral anti-Xa agents under development, the most advanced being rivaroxaban (recent application to the EMEA for approval in deep vein thrombosis (DVT) prophylaxis after orthopedic surgery) and apixaban.

The parenteral anti-Xa agents are pentasaccharides: fondaparinux (already approved for several indications) and idraparinux, a new generation drug, with a very long half-life.

Of anti-IIa inhibitors, development is most advanced in dabigatran, an oral direct anti-IIa inhibitor (already approved by EMEA for DVT prophylaxis after orthopedic surgery), but many other anti-IIa inhibitors are under development. The previously introduced ximelagatran is no longer used because of several cases of severe hepatotoxicity.

There are also parenteral anti-IIa inhibitors—hirudin, hirulog, and argatroban—approved by the FDA exclusively for cases of heparin-induced thrombocytopenia. The new anticoagulants are currently being evaluated in a number of clinical trials, in the indication of DVT (with or without pulmonary embolism) therapy, DVT prophylaxis, and stroke prevention in atrial fibrillation. They differ in their pharmacokinetic properties.

In spite of some possible advantages, there are several reasons why these new agents are unlikely to totally replace heparin, low-molecular-weight heparin (LMWH), and warfarin in a near future.

- All the oral agents cross the placental barrier.
- None of the new drugs have multiple therapeutic effects and none induces the release of endogenous mediators, such as tissue factor pathway inhibitor (TFPI), which is induced by heparin and LMWH. That is why the therapeutic spectrum of the new drugs is much narrower than that of the older ones.

- There are great concerns with both anti-IIa and oral anti-Xa agents regarding hepatotoxicity and rebound effect and additional data may be needed to demonstrate their safety in this sense in phase III trials.
- The other problem is the lack of any potential antagonist.
- There is also no knowledge of the long-term toxicity of the new anticoagulants.

The possible perspective is the continuing use of heparin and related drugs, probably in an expanded range of indications, and introducing new anticoagulants just for special indications, while paying further attention to safety issues.

Thrombocytopenia, bleeding

Heparin-induced thrombocytopenia (HIT) - When to suspect the paradoxical hypercoagulable state?

Moderators: J Fareed (USA), R Hull (Canada)
Participants: J Fareed (USA), J Walenga (USA), I Elalamy (France), H Gibbs (Australia)

Update on the detection, prevention and management of patients with heparin-induced thrombocytopenia

Chairman: J Fareed (USA)
Lecture by J Walenga (USA)

Heparin-induced thrombocytopenia (HIT) is a rare but severe adverse effect of heparins (both unfractionated and low-molecular-weight). **J Walenga** reminded the audience that HIT is an immune-mediated response to heparin, often but not always resulting in thrombocytopenia. The pathophysiology is complex and involves antibodies directed against the complex formed between heparin and platelet factor 4 (PF4). She emphasized that HIT gives much more than a "just-platelet" response. It also has important pro-inflammatory effects, and induces activation of leukocytes, endothelial cells, platelets, and the formation of cellular micro particles. The result is the most important procoagulable state known, with an increase thrombin generation. The risk of thrombosis is very high (more than 50% if untreated), often leading to severe arterial as well as venous thrombosis, amputation, and death. As stressed by **I Elalamy**, a sudden decrease in platelet count in patients treated with heparin, either at prophylactic or therapeutic dose, should prompt the suspicion of HIT. The threshold over which a HIT should be suspected varies according to the clinical setting: a 30% to 50% decrease in platelet count. The timing is also important, as thrombocytopenia develops after day 5 of treatment. It may be observed earlier, during the first hours of treatment, in the case of exposure to heparin in previous weeks. Some cases of delayed onset, even two weeks after heparin is stopped, have also been described. In surgical patients, transient thrombocytopenia is often seen in the immediate postoperative period. In this particular setting, from a low level the platelet count increases again after 3 or 4 days. A discontinuation in the platelet increase curve should prompt the suspicion of HIT. Finally, some patients can even have no thrombocytopenia. In fact, some antibodies have a procoagulant effect without a decrease in the platelet count. That's why HIT should be suspected in patients developing thrombosis during heparin treatment.

All panelists confirmed that all types of heparins should immediately be withdrawn as soon as the diagnosis is suspected. Moreover, **H Gibbs** stressed that stopping heparin is not enough, and that it is mandatory to start the patient on an alternative anticoagulant (the risk of major thrombotic events in patients not started on an

alternative anticoagulant is higher than 50% over the following weeks). Physicians should not await diagnostic confirmation to make this substitution. **J Walenga** went over the different therapeutic options. Danaparoid is a nonheparin antithrombotic with multiple sites of action and an anti-inflammatory effect. It has a good safety profile, with a risk of bleeding lower than that observed with direct thrombin inhibitors. Other advantages are the subcutaneous route of administration and that there is no need for monitoring. A cross-reaction with anti heparin-PF4 antibodies is rare but possible, and should be suspected in the case of worsening thrombosis, or if platelet count does not recover after a few days, although **I Elalamy** reported that in this case, use of a subtherapeutic dose should be suspected and is more likely than a cross-reaction. Its renal clearance is also a limitation in patients with renal failure. Two direct thrombin inhibitors, argatroban and lepirudin, are also available. Argatroban has the advantage of its rapid reversibility in the case of bleeding. Dose should be adjusted in patients with liver dysfunction. Lepirudin is eliminated by the kidneys, and dose adjustment is required in renal failure patients. Another specific issue is the high rate of antibodies generated that may lead to an anaphylactic response in patients previously exposed to lepirudin. New anticoagulant drugs have been used in case reports or series, mainly fondaparinux and bivalirudin, but not enough evidence is yet available to support their use in this setting.

Unfortunately, because of the heterogeneity of the antibodies produced, there is no simple diagnostic test. **J Walenga** reminded the audience of the importance of not missing a patient with HIT because of the severe complications. Also, the diagnosis must be confirmed, given the specific risks associated with anticoagulant management and the consequences for further medical management. **I Elalamy** presented the current diagnostic strategies for HIT. The clinical probability can be assessed using the 4Ts model, which is based on criteria related to the **T**hrombocytopenia, the **T**iming of events, the presence of a **T**hrombosis, and of a possible o**T**her explanation for the thrombocytopenia. If the clinical probability is low, the diagnosis can be ruled out, and the heparin treatment resumed if a sensitive test (ELISA or ID-PaGIA test) is negative. If the result is positive, or if the clinical probability is high, a more specific test will confirm the diagnosis. However, because of antibody heterogeneity, a cautious interpretation of the results is required. It may be interesting to perform different tests, and to repeat them over time. In fact, some of them are based on the detection of IgG antibodies, which may appear only after several days. The panelists also recommended a multi-disciplinary approach to diagnosis, in order to "build a likelihood" of HIT. Future research will focus on the role and prognosis of nonfunctional antibodies, on new diagnostic tests, and on the evaluation of the new anticoagulant drugs in this clinical setting.

Current approach in the management of bleeding

Moderators: D Hoppensteadt (USA), MM Samama (France)
Participants: D Hoppensteadt (USA), MM Samama (France), J Caprini (USA), G Rao (USA), J Fareed (USA), J Fletcher (Australia)

This session focused on the management of bleeding, either in patients on antithrombotics or during the postoperative period. **J Fareed** stated in the

introduction that the ideal hemostatic agent should work within minutes, stop the inappropriate hemorrhage without clotting working vessels, have no side effects, and be inexpensive. Unfortunately, such an agent is not available. Bovine thrombin, recombinant thrombin, and human thrombin are, however, widely used, in more than 5% of all surgical procedures in the USA. Other options include recombinant activated factor VII, which was primarily developed for the treatment of patients with anti-factor VIII antibodies, aprotinin, recombinant tissue factor pathway inhibitor (TFPI), and desmopressin (DDAVP), whose effect is to release von Willebrand factor.

MM Samama focused on the management of bleeding related to antithrombotic drugs. He reminded the audience that not all bleeding in this setting is related to an overdose, and that half of the bleeding episodes occur in patients with an international normalized ratio within target. For patients on vitamin K antagonist, the recently published 8th ACCP guidelines recommend for bleeding associated with an elevated international normalized ratio intravenous vitamin K (10 mg), and either fresh frozen plasma, prothrombin complex, or recombinant factor VIIa. For heparins, if protamine sulfate is able to fully reverse their anti-IIa activity, only about one half of their anti-Xa activity is antagonized. This means that not all bleeding episodes on LMWHs (whose anti-Xa activity is stronger than that of UFH) may be controlled by protamine sulfate. This is a limitation of the use of LMWH. However, **MM Samama** stressed that the absence of an antidote is a common characteristic of all the so-called "new anticoagulants" (apixaban, bivalirudin, dabigatran, fondaparinux, hirudin, rivaroxaban). He cited the exception of idraparinux, a pentasaccharide administered subcutaneously once weekly. The development of this drug has been hampered by an increased risk of intracerebral hemorrhage observed in phase 3 trials. This, along with its long half-life, was a major concern. A biotin component has been successfully added to the molecule, without modifying its pharmacologic properties, but allowing its rapid reversal by the use of avidine.

In terms of the management of surgical bleeding, beyond the technical causes and their management (inadequate vessel repair, occult or unrecognized unrepaired injury to the vascular system either remote or in the operative field), **J Caprini** stressed the importance of pre-operative assessment of bleeding risk. A thorough history taking and physical examination should be performed, including familial and personal history of bleeding or easy bruising, with a focus on previous surgery, childhood trauma, and gynecological bleeding in women. Patients' current medications are of primary importance, including over-the-counter medications (NSAIDs and anti-histamine, in particular). The comorbidities also play a role: malignancy, sepsis, chronic medical disorders, and collagen vascular disease. After surgery is performed, any bright red blood at any site should prompt a basic clinical and laboratory assessment: body temperature, complete blood count, platelet count, prothrombin time, partial thromboplastin time. **J Caprini** and other panelists and attendees also voiced their interest in the bleeding time in such a context. If all these tests are normal, an urgent surgical re-exploration should be considered. One of the frequent causes of bleeding after surgery is disseminated intravascular coagulation, whose management mainly relies on cause eradication (tumor, infection, abrupt placenta removal), and sometimes on the use of low doses of heparin.

G Rao reviewed the different topical hemostatic agents, such as oxidized cellulose, gelatin sponge, microfibrillar collagen, bovine thrombin, fibrin sealants (whose structure is similar to that of fibrin strands in a plasma clot), biological glue and nonbiological glue. **G Rao** also went over the different hemostatic agents currently used in battle fields by the US army and marines. Uncontrolled hemorrhage is the leading cause of death in this context. Two new approaches have been developed: the use of a granular mineral zeolite, and of a mix of powdered human fibrinogen, thrombin, and factor XIII. Although promising, these have never been formally tested in trauma or surgical patients, nor are they approved for this indication.
Finally, **J Fareed** summarized the evidence on two recent controversies. The first one was following the report of anti-factor V antibody development in patients treated with bovine thrombin. The manufacturing process has been improved since, and this has been shown to decrease the level of detectable factor V. He then addressed the controversy on the off-label use of recombinant activated factor VII. He reminded the audience that outcome studies have shown no improvement in prognosis when this drug is used for the treatment of hemorrhagic stroke. There are also concerns about its strong procoagulant effect, which could lead to an increased risk of undesirable thrombotic events, highlighting the risks of its off-label prescription.

Among future perspectives, the management of bleeding on new anticoagulant drugs needs to be addressed. Further studies should also focus on the estimation of bleeding risk, and on the off-label use and efficacy monitoring of recombinant activated factor VII.

VI
Chronic venous disease and lymphatics

XXIII World Congress
of the
International Union on Angiology
Athens - Greece
21-25 June 2008

6 - Chronic venous disease and lymphatics

Veins and their impact on the cardiovascular system

Chairman: A.T. Guillaumon (Brazil)
Lecture by D. Clement (Belgium)

The venous system returns blood from various organs and tissues to the heart. The venous circulation is regulated at two levels. Local control is achieved by neurohormones (noradrenaline, histamine, serotonin, etc.), physical factors (temperature change), and the mechanical properties of the venous wall (valves, flexibility, deformability). A number of these mechanisms have genetic determinants. Central regulation of the venous circulation is carried out by the reflex arcs including peripheral baroreceptors and muscle receptors. For example, rhythmic muscle contraction activates muscle receptors, thus causing generalized venoconstriction in turn. As a result, blood return to the heart is increased. Cardiac output is also increased, as required for maintenance of adequate circulation during muscular contractions. Peripheral and central regulation of the venous circulation change venous tonus and venous pressure. Lasting increase in venous pressure can lead to disturbances of the microcirculation and development of varicosities. Disturbances of venous tone lead to specific clinical signs, such as orthostatic hypotension, edema, venous stasis. Venous stasis can activate inflammation, the coagulation cascade, and thrombus formation. Many drugs used for treatment of cardiac diseases (nitrates, digitalis, diuretics etc.) have a negative effect on venous tonus, and their long-term use can provoke venous disturbances. There is an association between atherosclerosis and spontaneous venous thrombosis (Prandoni et al., 2003). Also, Poredos and Jezonik (2007) found a relation between arterial and venous thromboembolism. Lastly, the author emphasized that venous disease is very important socioeconomically, and this must be considered when formulating insurance policy in public health services.

Life with chronic venous insufficiency

Participants: JJ Guex (France), E Bouskela (Brazil), A Nicolaides (Cyprus)

In the first lecture of this satellite symposium, **JJ Guex** dealt with the role of **quality of life** (QoL) score and **patient-reported outcome** (PRO) in evaluation and global assessment of chronic venous disease patients before and after any type of treatment in everyday life. A global assessment is possible through PRO measures. In relation to the evaluation of treatment results, self-report questionnaires and visual analogue scales provide data independent of the physician's appraisal. Dr Guex recently conducted a study (QUALITY) with a combination of *Ruscus aculeatus*, hesperidin, and ascorbic acid and, using both a generic QoL scale (SF 12) and a specific QoL scale (CIVIQ1), demonstrated that QoL scales correlate with CEAP grades and also that this phlebotropic drug improved QoL. However, the CIVIQ1 score was also correlated with body mass index and age, which could result in confusion. Therefore it has been considered

that an improved PRO would be necessary for the less severe cases, assuming that a satisfactory PRO should be used alone, and that this approach would simplify the assessment. A group of specialists from the French Society of Phlebology, American College of Phlebology, and American Venous Forum devised a questionnaire which took into account all relevant questions. Comprising 46 items in 5 dimensions, the **S**pecific **Q**uality **O**f life and outcome **R**esponse-**V**enous (SQORE-V) has been developed, field-tested and validated in French and Spanish, and is freely available for translation into any other languages. Its sensitivity is less affected by age and body mass index.

E Bouskela presented the usefulness of microcirculatory evaluation in the assessment of chronic venous disease (CVD), by studying the effect of severity of CVD on capillary network. She and her team used a newly developed noninvasive technique—orthogonal polarization spectral (OPS) imaging—to identify capillary morphology, capillary and dermal papilla diameter as important morphological parameters in detecting early stages of microangiopathy. Using OPS and duplex ultrasound, they evaluated the changes in cutaneous microangiopathy in chronic venous disease (C2-C3s) after the use of *Ruscus aculeatus*, elastic stockings, or no treatment for 4 weeks and found in the group treated with *Ruscus aculeatus* a decrease on capillary diameter for both limbs and an improvement in capillary morphology in the left limb. The results confirmed the role of capillary diameter in microcirculatory dysfunction observed in CVD and the usefulness of this new noninvasive method in capillary evaluation in CVD.

A Nicolaides in his short overview presented highlights from the **2008 Guidelines on Management of Chronic Venous Disorders of Lower Limbs**, recently published in International Angiology 2008L,27:1-59. The document was drawn up under the auspices of the world's leading venous societies. It has 20 sections, levels of evidence I, II, III,, and more than 800 references. Part I deals with pathophysiology, symptoms, and investigations, and stresses that 30% of deep venous reflux is due to primary valvular incompetence, spontaneous lysis of deep veins after deep vein thrombosis occurs in 50% to 70% of cases, and early recanalization preserves valve function after deep vein thrombosis. Part II presents evidence for the efficacy of the therapeutic method. Part III deals with management of symptomatic individuals, and also with prevention of postthrombotic syndrome. The last section consists of key questions that need to be answered. This presentation stimulated interest in the auditorium and a desire to read and "digest" in detail the written consensus.

Varicose veins. Is there any evolution?

Moderators: C. Allegra (Italy)-A. Giannoukas (Greece)
Participants: E. Kalodiki (UK), P. Gloviczki (USA), M. Vasquez (USA), D. Kontothanassis (Italy), R. Simkin (Argentina)

Three reports of a strictly practical nature were presented during this session. Kalodiki presented the detailed description of foam sclerotherapy. She used the Tessari technique and mixed 1.2 mL of 1% or 3% sodium tetradecyl sulfate solution with 4.8 mL of air. Six mL of the sclerosing foam was produced after 20 pump movements. Sclerosing foam was injected into varicose vein after previous

ultrasound mapping. The patient was in the upright position during injection. Second class compression stockings were applied just after injection. Compression was prescribed for 5 weeks (day and night - 2 weeks; day- 3 weeks). Kontothanassis reported experience in endovenous laser therapy of the 104 small saphenous veins. There were low postoperative complications. Vasquez presented a series of 402 patients (602 limbs) who underwent radiofrequency ablation and convincingly showed that the venous clinical severity score (VCSS) can be used to estimate early and long-term results after radiofrequency ablation. The average VCSS was 8.3 before procedure and significantly decreased to 4.9 during 3-4 weeks of follow-up. The author underlined that VCSS does not consider cosmetic complaints. Simkin et al presented 487 cases of combination treatment with endoluminal laser and ambulatory phlebectomy. All operations were performed under tumescent anesthesia. There were low postoperative complications. The author concluded that combination treatment is appropriate for all cases.

Gloviczki recalled that incompetent perforating veins (IPVs) play an important role in chronic venous disease (CVD). There is a correlation between the number of IPVs and severity of CVD. There are three basic methods for IPV dissection. The most widely performed is subfascial endoscopic perforator vein surgery (SEPS). The primary benefits of this technique have been reported to include more rapid ulcer healing, fewer perioperative complications, and lower recurrence rate. In the Mayo Clinic's experience, 80% of ulcers had healed 90 days after SEPS. Median time to ulcer healing was 35 days. A meta-analysis confirmed that SEPS in class 5-6 patients (CEAP classification) has recurrence rate of 10% to 20% over 3-5 years. Duplex-guided hook interruption of IPV is under consideration. The healing rate after this procedure is 100%, with a 20% recurrence rate during five-year follow-up. Percutaneous ablation of perforators is an innovative technique, which includes ultrasound-guided sclerotherapy, and radiofrequency and laser ablation.

Deep venous disease. New concepts.

Moderators: F.H.A. Maffei (Brazil)-S. Vasdekis (Greece)

Participants: A. Nicolaides (Cyprus), M. De Castro Silva (Brazil), D. Christopoulos (Greece), N. Angelides (Cyprus), Z.G. Wang (China)

A Nicolaides presented convincing data confirming a key role of leukocytes in damage to the venous wall. Leukocyte activation, adhesion, and migration through the endothelium as a result of altered shear stress contribute to the inflammation and subsequent remodeling of the venous wall and valves. Entrapment of leukocytes in the microcirculation reduces local capillary perfusion. All these reactions have a clinical manifestation. **M de Castro Silva** presented several Brazilian epidemiological studies that show a high prevalence of varicose veins in females (84.3%), 72.2% in pregnant women. Open ulcers were noted in 3.2% of respondents (male-2.3%; female- 4.1%). **D Christopoulos** described various diagnostic procedures in at patients with chronic venous disease (CVD). There are three levels of investigation of patients with CVD: *Level I*: Clinical examination, Doppler or a color flow duplex. *Level II*: Duplex color flow scanning, with or without plethysmography. *Level III*: Phlebography, varicography, venous pressure measurements, CT scan, venous helical scan, magnetic resonance imaging, and

intravascular ultrasound. The choice of the diagnostic level depends on clinical class according to the CEAP classification.

ZG Wang reported a very aggressive treatment strategy in patients with proximal DVT. The author prefers open surgical thrombectomy after preliminary implantation of the removable cava-filter.

Venous and lymphatic diseases of the lower limbs

Moderators: J Fernandes e Fernandes (Portugal), JL Nascimento Silva (Brazil)
Participants: AT Guillaumon , I Merlo, IMMER Castro Santos, SP Marques, C Belczak, H Guedes (Brazil)

Gene Therapy in Vascular Ulcer

A.T. Guillaumon (Brazil)

Gene therapy may have a role to play in possible intervention on target tissues. Gene therapy takes three forms: proliferation and transcription of an active unit to one cell or tissue, amplification of the local or systemic expression of one protein, and inhibition or regulation of endogenous gene expression in the cells and tissues.

In venous stasis ulcers, cell proliferation therapy is used using various factors such as vascular endothelial growth factor [VEGF], fibroblast growth factor, human growth factor, hypoxia-inducible factor.

The therapeutic vascular growth of new vessels is based on the use of angiogenic factors or stem cells or their combination to promote neovascularization. New vessel formation is an important aspect of tissue recovery because it supplies oxygen, nutrients, humoral growth factors, and enzymes to cells. VEGF as a key regulator of the amplification of local or systemic expression of one protein, and the inhibition or regulation of endogenous gene expression in the cells or tissues. VEGF/VEGF-R is a complex of various ligands which has an important relationship with angiogenesis.

Surgical Treatment of the Varicose Veins with Endolaser

I. Merlo (Brazil)

This author reported the experience of the Brazilian working group on laser ablation in great and small saphenous veins. Laser ablation is indicated in patients with saphenofemoral and saphenopopliteal pathologic reflux, vein diameter <11 mm, and in patients without previous sclerotherapy of the saphenous vein.

The technique was described as follows: pulsed mode, energy applied 3 J/mm of diameter (80-100 J/cm^2), after the injection of tumescent cold saline solution around the saphenous vein, Laser Diode 810/980 (if necessary), Introducer 5Fr (if necessary), fiber 600 Ìm diameter, and frequent duplex monitoring. All varicose tributary veins were removed through stab incisions under local or regional blockage anesthesia.

The results Merlo's personal experience—early occlusion 100%, late occlusion 99.6%—were identical to those of the Brazilian working group. Their experience with endovenous laser treatment of incompetent small and great saphenous veins proved that this is a safe, efficient surgical technique and at the same time a good alternative to traditional surgery.

Thrombophilia States and Venous Disease in the Woman

I.M.E.R. Castro Santos (Brazil)

Venous thromboembolic disease is the most prevalent vascular disease in young women, with an incidence of 2 to 5 per 100 000 women-years between the ages of 20 and 49 years.

The higher venous thromboembolism frequency in the female gender is explained by the exposure to known risk factors such as oral contraceptives, hormone replacement therapy, selective estrogen receptor modulator, pregnancy, and postpartum period.

The prothrombotic effects observed with the use of oral contraceptives and hormone replacement therapy are mainly due to the estrogens present in their composition.

The risk of thromboembolic events in users of oral contraceptives remains high even with the use of low-estrogen preparations. The first episode of thromboembolism occurs in 3 to 4 women per 10 000 users of oral contraceptives versus 5 to 10 in 100 000 women during the reproductive age.

Thromboembolic events are up to 30 times more frequent in thrombophilic women who use of oral contraceptives, especially associated with protein C, protein S, or antithrombin deficiency. A 20-fold greater risk is observed in users with the prothrombin gene mutation.

Hormone replacement therapy with low estrogen dose, combined or not with progestin, has been increasingly indicated for healthy women during and after the menopause. However, it has been proved that the risks exceed the benefits, with increased incidence of deep venous thrombosis and pulmonary embolism, in addition to the elevated incidence of acute myocardial infarction, cerebral ischemia, and breast cancer.

There is a 3- to 4-fold higher risk of venous thrombosis with the use of tamoxifen for treatment of breast cancer, and the increase in risk may be as much as 10-fold in advanced breast cancer and chemotherapy.

Pregnancy is an independent risk factor for deep venous thrombosis and pulmonary embolism. The risk is 6-fold higher when compared with women of the same age. The association with other risk factors elevated their incidence even further. Half of the thromboembolic events in pregnancy occur in thrombophilic patients.

The presence of a thrombophilic disorder confers on women a higher risk of venous thromboembolic disease at different periods of life. Large prospective studies are still needed to define the risks and establish the associations of thrombophilia with venous thromboembolic disease among groups with different thrombophilic defects. The real value of routine thrombophilia screening still needs to be determined.

Lymphoscintigraphic Visualization of the Thoracic Duct Confluence in patients with Lymphedema of the Lower Limbs

S.R. Marques (Brazil)

Lymphoscintigraphic Visualization (LSG) of the Thoracic Duct Confluence was used in 38 patients with lymphedema of the lower limbs are presented (26 unilateral and 12 bilateral). Females (46.2%) had a mean age of 41 years and males (53.8%) a mean age of 39 years.

Technique

Subcutaneous injection in the first space between the first and the second toe in each foot of 1.0 mL of a solution of dextran-500 labeled with TC-99m. The first gamma-camera image of the thoracic duct was obtained within 5 minutes after the injection. The images obtained were uploaded and stored using a software program.

Results

The thoracic duct was not visualized in 9 patients (34.2%), but was observed in 11 patients (91.7%) with bilateral lymphedema and in 18 (69.23%). with unilateral lymphedema.

Conclusions

LSG allows adequate analysis of the thoracic duct and the results are comparable with those of classic anatomic studies. LSG of the thoracic duct and its confluence reveals that lymph arrives at the venous confluence even when lymphodynamics are substantially compromised. These findings suggest that poor absorption could have a more important role than previously believed.

Compression Therapy in Lymphedema

C. Belczak (Brazil)

Among all conservative measures, ie, manual lymph drainage, compression, myolymphokinetic exercises and skin care, elastocompression is the most important since it is also effective when applied alone. Compression therapy reduces limb volume, restores limb shape, improves skin quality, enhances limb mobility, improves muscle pump activity, controls lymph formation, inhibits the development of fibrosclerotic tissue, and stimulates lymphatic transport. Compression therapy is not indicated in acute infection, acute contact eczema, acute thrombosis, peripheral arterial disease, neoplasia *in situ*, and cardiac insufficiency.

During lymphedema treatment, two phases are distinct: the first one, the so-called attack phase, reduces the edema quickly. The second phase starts immediately

after the point where no more reduction can be achieved. During the first phase, firm bandages with short-stretching textile elastic material are usually applied. This must be always performed by highly qualified staff. For the maintenance phase in order to consolidate the results obtained during the first phase, medical elastic stockings are prescribed.

For severe grade IV lymphedema patients (elephantiasis), there is a useful inexpensive new kind of multilayer bandage that is applied in the first phase of lymphedema treatment with convincing results.

Compression therapy is the important and effective basic therapy for lymphedema. It acts on the effect, not on the cause of the disease, as it does not heal lymphedema but avoids the symptoms and progression of the disease.

VII
Compression therapy

XXIII World Congress
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7 - Compression therapy

Elastic compression and intermittent pneumatic compression

Moderators: G Geroulakos (UK), J Caprini (USA)
Participants: J Caprini (USA), G Geroulakos (UK), S Kakkos (UK), H Partsch (Austria)

This very instructive session about the role of compression therapy in prevention and treatment of different vascular disorders started with **J Caprini**'s presentation, which dealt with intermittent pneumatic compression for the prevention of venous thromboembolism (VTE). He first emphasized the importance of history taking and physical examination for every patient in order to assess individual risk using validated scoring systems. It is also mandatory to have a checklist of bleeding risk in these patients including the platelet count, renal function, and use of concomitant medications that might increase bleeding. Precautions for the use of intermittent pneumatic compression (IPC) include severe peripheral arterial disease, active leg deep vein thrombosis (DVT), the presence of chronic skin conditions, open ulcerations, and severe eczema. The results of clinical trials from 1983 show a clear benefit of IPC regarding the reduction in incidence of VTE in general surgery patients. There is also a strong history regarding the use of combining IPC with pharmacologic prophylaxis in high-risk patients. A thrombosis rate of <2% has been seen in patients receiving combined therapy following stroke, cardiac, general, or orthopedic surgery using venographic end points. The use of graduated compression stockings has also been associated with a reduced VTE incidence compared with control populations, but their effects are much less robust and well studied than IPC devices. One recent study shows in patients with intracerebral bleeding the addition of IPC to graduated stockings reduces the ultrasonic DVT rate by 50%. In the final analysis, the choice of prophylaxis should be based on the patients' level of risk and those at lower risk may need only IPC whereas those with a very high risk may benefit from combined prophylaxis.

G Geroulakos from the UK afterwards three smallish but consistent studies supporting the benefit of IPC treatment in stable peripheral arterial occlusive disease. Three different research groups (Kakkos et al, Dellis et al, and Ramaswami et al) each published in 2005 data on the efficiency of intermittent pneumatic compression (IPC) devices in stable peripheral arterial occlusive disease patients compared with unsupervised and supervised exercise programs, in terms of initial claudication distance, absolute claudication distance, ankle brachial index, air plethysmography measurements, and QoL improvement. All three studies show a significant improvement in initial claudication distance, absolute claudication distance, and quality of life in IPC-treated stable claudicants compared with unsupervised or supervised exercise programs alone. Although supervised exercise programs showed some benefit in these terms, this benefit was significantly weaker than in the case of exercise and IPC therapy together. The unsupervised exercise program, which is unfortunately the most frequent daily practice, shows no benefit at all in peripheral arterial occlusive disease patients. Larger well-designed studies are needed to confirm this beneficial effect of IPC therapy in stable intermittent claudication.

S Kakkos from the USA talked about the effect of elastic compression on the prevention of venous thromboembolism (VTE) alone and in combination with other modalities. It has been known since 1971 that full-length stockings can significantly reduce the incidence of deep vein thrombosis (DVT). Their mechanisms are complex: reducing the cross-sectional diameter of the veins and shunting the venous flow from the superficial to the deep system increases the blood flow velocity, prevents operative venodilatation, reduces leg swelling, and activates the tissue factor pathway inhibitor . Graduated elastic stockings (with 18 mm Hg pressure at the ankle and 8 mm Hg pressure at the thigh) are more efficient than uniform compression stockings. One can use preventive and therapeutic compression grades also. Correct sizing of the stocking is very important. The effectiveness of graduated elastic stockings alone or in combination in VTE prevention is supported by 14 nonorthopedic randomized clinical trials. The major advantage of the method is the absence of bleeding. Among disadvantages are inapplicability to peripheral arterial occlusive disease patients in the case of ulcers, diabetic foot, or pressure sores, and they are difficult to get on and off. Full compression (thigh) is better than calf compression (Howard, 2003). In low-risk patients, elastic compression can be used as alone or combined with ambulation and hydration. In high-risk patients, elastic compression should be combined with heparins, with or without intermittent pneumatic compression (IPC) therapy. In bleeding risk patients or in case of active bleeding, elastic compression should be combined with IPC devices only. Finally, Dr Kakkos underlined that despite these clear recommendations in the real world this simple and cost-effective preventive method is clearly underused.

At the end of this session **H Partsch** from Vienna summarized the hemodynamic effects of different compression therapeutic modalities in chronic venous diseases. According to basic biophysics, he stressed the large difference between venous pressure values in different positions of the human body. If external compression is applied it is efficient when it exceeds the intravenous pressure. In the supine position, venous pressure at the ankle is about 10-20 mm Hg. That is why the preventive methods using elastic stockings are highly efficient only in this body position. In the upright position the ankle venous pressure rise to 90 mm Hg and the thigh pressure to 30-60 mm Hg. In sitting position there is a need for at least 50 mm Hg external pressure to temporarily occlude the calf veins, as Professor Partsch demonstrated in his various magnetic resonance imaging and ultrasound studies. During the exercise, when the calf muscle contracts only in the case of short-stretch, non-elastic bandages, with high work pressure, raise the external pressure to 90 mm Hg. This is not the case with graduated elastic stockings with higher resting pressure but low work pressure. The application of short stretching bandages during walking produces pressure peaks of 80-90 mm Hg, which cause intermittent venous occlusion, which is beneficial in treatment of severe chronic venous insufficiency. This effect is mainly due to intermittent venous occlusion and not to adaptation of the valves, as the benefit of non-elastic bandages can be seen in avalvular patients also. Finally, Professor Partsch highlighted that in daily practice the applied external pressure has to be adapted to the severity of ambulatory venous hypertension.

More information on Venous or Lymphatic Diseases ?

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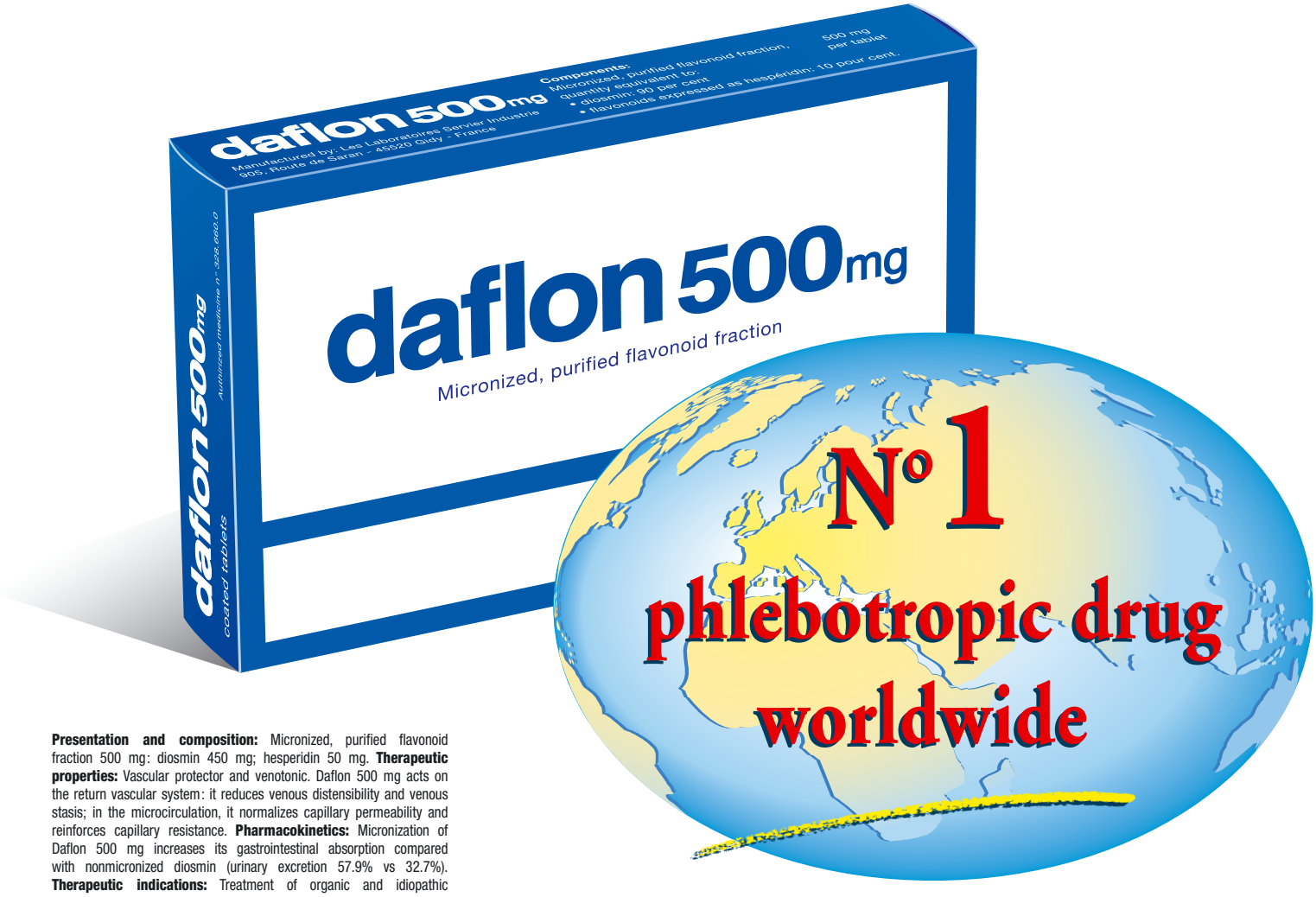

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