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Phlebology

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Aims and Scope

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

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

Phlebology is scientifically supported by a prestigious editorial board.

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

Phlebology comprises an editorial, articles on phlebology and lymphology, reviews, and news.

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Medical Reporters' Academy

The report from the *Union Internationale de Phlébologie* chapter meeting
was prepared by the following members of the Medical Reporters' Academy:

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Foreword

The Medical Reporter's Academy is comprised of an international group of young specialists in dermatology, vascular surgery, angiology, and/or phlebology who all have a keen interest in venous disease. Each year, Servier invites the Medical Reporter's Academy to cover one of the most important international congresses for venous disease specialists. This year, the IUA-SMV congress, which was held in Lyon, France, was selected because the congress involved renowned international and national experts and young health care professionals. Therefore, this congress was a unique opportunity for interactions and discussions. Together, with Andrew Nicolaides, the chairman of the group, they explored the program of the congress, selected the most interesting sessions to attend, and wrote short reports after each session. These reports are provided in this issue of *Phlebology*.

We hope that this issue will be beneficial for those who did not attend the congress.

This issue has been possible due to the commitment and hard work of the Medical Reporter's Academy throughout the congress to provide the chairman with reports of excellent quality.

We would like to thank Andrew Nicolaides for his work and each member of the Medical Reporter's Academy: José Daniel Brandao, Daciana Branisteanu, José Benhur Parente, Roman Bredikhin, Daniela Mastroiacovo, Mustafa Sirlak, Stanislava Tzaneva, Robert Vlachovsky.

The Daflon International Team



I Arterial Diseases



IUA-SFMV Lyon, October 5-8, 2016

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Awareness, Investigation, Management, and Prevention

Keynote lecture

Renal revascularization: a lost art? When is it imperative and which technique?

José Fernandes e Fernandes (Portugal)

Secondary renal arterial hypertension is mostly due to atherosclerosis (80%), which is often found in men >50 years. Most of the atherosclerotic lesions occur in the ostia or the proximal segment of the renal artery, where 20% have renal atrophy. A minority of renal arterial hypertension is caused Takayasu's disease, spontaneous dissections, aneurysms, and fibromuscular dysplasia (10%). Fibromuscular dysplasia is found in women, where the lesions are centered in the distal two-thirds of the artery, where 90% of the lesions are caused by medial fibromuscular dysplasia. The renal artery, and induces arterial hypertension and ischemic nephropathy due to a reduction in blood flow and atheroembolization.

Several questions and controversies remain concerning the pathophysiology and the indications for intervention for secondary renal arterial hypertension. In fact, should it be considered a "benign disease?" Are there any hemodynamic or biological markers that can act as prognostic factors? What is the role of ischemic nephropathy, considering the evidence of areas of renal infarction areas detected by MRI and the progressive renal dysfunction? What is the real morbidity and mortality of revascularization? Additionally, there has been a reduction in patient referrals due to insufficient knowledge regarding the cause of renal artery stenosis, inadequate methods to assess its hemodynamic effects, lack of routine imaging to identify renal infarcts and determine the plaque structure, new advances in medical treatment, and, perhaps, most importantly, the negative outcomes of the two most recent randomized trials (ie, the ASTRAL and CORAL trials). The negative results of these trials could be due to several weaknesses in the trial design, such as the high number of patients included who did not have a severe stenosis (>70%) and the high rates of complications associated with renal artery stenting. Patient selection needs to be improved for future trials and in the clinical setting, eg, for patients with severe bilateral disease; a single or transplanted kidney; a hemodynamic assessment of the lesions (consider focal increased velocities and low resistive index); a rapid decline in the renal function (without proteinuria); accelerated, malignant, and resistant hypertension (>4 drugs); or flush pulmonary edema.

For endovascular techniques for renal revascularization, Fernandes e Fernandes argued that low profile systems and stents reduce the risk of complications (dissection, distal embolization), reduce the combined morbidity and mortality rates to <3%, increase long-term efficacy on blood pressure control, and preserves or improves renal function. Low-profile systems and stents should be the first-line treatment for atherosclerotic renal artery stenosis. Open revascularization has restricted, but clear, indications, and it should be kept as an alternative for the treatment of specific renal

artery issues (mainly, aortic occlusion or abdominal aortic aneurysm with surgical indication and symptomatic renal artery stenosis).

What do we need for a better perspective in the vascular field?

Data on the worldwide epidemiology of peripheral arterial disease

Gerry Fowkes (UK)

Peripheral arterial disease is a worldwide problem, but data on its prevalence are not available in many countries. Ankle brachial index data are the most appropriate tool for the global comparison of peripheral arterial disease. The estimated prevalence of peripheral arterial disease in Europe is 17% to 20%. More data is required for age, sex disparities, and risk factors in low and middle-income countries. The burden of peripheral arterial disease is projected to increase (aging of the population, trends in cardiovascular risk factors, and survival from acute myocardial infarction and stroke); therefore, data are needed regarding treatment planning and prevention services.

Peripheral arterial disease prevalence and characteristics: data from the ERV study

Katalin Farkas (Hungary)

The objectives of the ERV study were to evaluate the prevalence of clinical and preclinical peripheral arterial disease in hypertensive patients and make a risk assessment comparison using the traditional risk factors from the SCORE model (Systematic COronary Risk Evaluation) and ankle brachial index in a hypertensive population during a 5-year prospective phase. The prevalence of low ankle brachial index increases in hypertensive patients and the presence of peripheral arterial disease doubles the 5-year cumulative mortality in the same patients. An ankle brachial index <0.9 was a stronger predictor of death than was the presence of diabetes. In the different risk groups of the SCORE model, the presence of an ankle brachial index <0.9 doubled the mortality during the observational period. In hypertensive patients with an ankle brachial index <0.9, the mortality risk increases with a systolic blood pressure <120 mm Hg in both sexes and with a diastolic blood pressure <70 mm Hg in men, regardless of a previous acute myocardial infarction or stroke.

SVS iPG: easy access to evidence-based guidelines to aid appropriate care of the vascular patients

Peter Gloviczki (USA)

Peter Gloviczki presented the interactive practical guidelines (iPG), a free application created by the Society for Vascular Surgery. Currently, the application contains 11 guidelines that cover most vascular fields (eg, diabetic foot, peripheral arterial disease, venous leg ulcers, threatened lower limb, acute deep vein thrombosis, carotid disease, varicose veins and chronic venous disease, thoracic aortic trauma, subclavian artery and thoracic endovascular aortic repair, abdominal aortic aneurysm, and hemodialysis access); other topics are under development.

Ultrasound-guided vascular procedures

Guidance for endovascular procedures: current place and ultrasound perspectives

Antoine Diard (France)

There are three important steps to consider before conducting endovascular procedures. First, before puncture, information about the patient's clinical condition,

choice of the puncture site, and the appropriate material is needed. Second, during the procedure, it is necessary to have adequate guidewire progression, repair, and positioning in the lesion to be treated, and be able to adapt the strategy. Third, after the procedure, efficacy control measures need to be taken, and the ability to treat occasional complications is needed. Ultrasound guidance results in fewer complications, uses no irradiation, and is cheaper. The echo-guidance contributes to medical information by visualizing the anatomic repair (less legal medical implications). Avoiding radiation exposure and the risk of leukemia, lung cancer, thyroid cancer, gonadal cancer, etc, especially in endovascular procedures, for the entire surgical team (surgeon, nurses) justifies moving from radiation to echography in endovascular procedures when possible. In conclusion, the benefits are significant for the patients who avoid contrast for renal protection and for the surgeons and surgical team who avoid radiation exposure; therefore, it is recommended to use ultrasound guidance as much as possible during endovascular procedures.

Ultrasound guidance for endovenous treatments

Olivier Pichot (France)

Duplex ultrasound, which is complementary to clinical examinations, helps analyze and precisely describe superficial venous insufficiency (ie, the anatomic extent of reflux or obstruction). It is essential for defining the management strategy (medical or interventional treatment), type of ablation, and technical modalities because it provides information on the reflux origin, extension, and drainage. In endovenous procedures, ultrasound guidance has a grade 1C recommendation for vein access, grade 2C for catheterization, grade 1B for catheter positioning, and grade 1B for tumescent anesthesia. In conclusion, duplex scanning is mandatory before endovenous therapy to select patients, techniques, and decide upon the strategy; during endovenous therapy to guide the procedure safely and effectively; and after endogenous therapy to evaluate the results.

Ultrasound guidance angioplasty for vascular access during hemodialysis

Fabrice Abbadie (France)

The first communication about using ultrasound guidance during angioplasty for vascular access in hemodialysis was in 2007. Abbadie discussed a current study on 78 ultrasound-guided angioplasties in 50 patients between January 2015 and January 2016. Patients were excluded when there was a recanalization of occluded segments, salvage angioplasty (volume flow <100 mL/min), and angioplasty of the arterial site only. Four types of arteriovenous fistula were identified, including radio-cephalic (54%), ulnar-basilica (4%), brachial-cephalic (26%), and brachial-basilica (10%). The stenoses were crossed in 100% of the cases, and all procedures were managed with ultrasound guidance. The complications included wall hematoma (50%) without hemodynamic repercussions, full vein thrombosis (2.6%), rupture (1.3%), arterial spasm (2.6%), radial artery thrombosis (1.3%), surgically repaired pseudoaneurysm (1.3%), and a puncture hematoma site (2.6%). Despite the small patient numbers, all published series have the same conclusion: duplex ultrasound-guided angioplasty for arteriovenous fistula is safe. Anatomical limits include clavicle calcified radial artery, some cephalic arcs, and small caliber cephalic veins. More data, good quality criteria, and long-term results are needed.

Peripheral arterial angioplasties: place of ultrasound guidance

Enrico Ascher (USA)

The main advantages of ultrasound-guided vascular interventions include no radiation exposure, no nephrotoxic contrast, multiplanar magnification, and arterial wall visualization. Other advantages include the selection and placement of the balloon and stent, treatment of complications, and technical adequacy (anatomical and hemodynamic). During 2005 to 2015, Ascher performed 1533 cases of ultrasound-guided balloon angioplasty using the following access points: arteriovenous (n=741 cases), femoral-popliteal (n=514), infrapopliteal (n=86), infrainguinal bypass (n=66), carotid artery (n=62), popliteal aneurysm (n=38), and others (n=26). The popliteal arterial volume flow measured by ultrasound is a good predictor of patency. Technical success was observed in 95% of cases (stenoses 99.6% and occlusions 87%). Ascher recommends using ultrasound-guided angioplasty for peripheral arterial disease.

Ultrasound guidance angioplasties: a medical and surgical collaborative model

Carmine Sessa (France)

Sessa emphasized the importance of a hybrid treatment of ultrasound-guided angioplasty with collaboration between vascular surgeons and angiologists. The presence of an angiologist who has vascular ultrasound knowledge provides better surgical results for the patients. The standardization of ultrasound guidance procedures will benefit new generations of vascular surgeons.

Is endovascular management the first option in the treatment of popliteal aneurysms? Why not?

José Fernandes e Fernandes (Portugal)

Open repair remains the reference treatment for a majority of surgical centers, but the use of an endovascular approach has been increasingly reported with favorable outcomes. The availability of the great saphenous vein appears to be the determinant in the decision for open repair (3-year patency, 88% for veins vs 57% for prosthetic grafts). Treatment is indicated for aneurysms over 2 cm in the presence of an intravascular thrombus and/or symptoms. Open surgery is still the first choice for patients with acute ischemia, distal embolization, and concomitant occlusion of crural vessels and the presence of an adequate vein conduit.

Guidelines Sessions

Guidelines of the European Society for Vascular Medicine

Peripheral arterial diseases guidelines

Sigrid Nikol (Germany)

Nikol presented the peripheral arterial disease guidelines from the European Society for Vascular Medicine. The mission of this work was to homogenize the management of this group of patients who are at a high risk for cardiovascular events, to improve their management, and to introduce new and rational diagnostic and therapeutic options with proven efficacy. The existing guidelines were written by cardiologists, interventional radiologists, and vascular surgeons; however, the European Society for Vascular Medicine wants to create guidelines prepared by angiologists. The provision of care for vascular patients is nonhomogenous, and the guidelines should cover all of the different facilities and knowledge from different countries. Currently, the S3 guidelines for the management of peripheral arterial occlusive disease (PAOD), which was prepared by the German Society of Angiology, are being translated from German to English. The document will then be sent to national societies of vascular medicine (members of European Society for Vascular Medicine) for endorsement and review by the guidelines committee in November 2016; the publication is planned for *Vasa*. The European Society for Vascular Medicine plans to improve the treatment of PAOD include a European Society for Vascular Medicine training program for peripheral interventions and European Society for Vascular Medicine Position paper and campaign: awareness for PAOD.

Raynaud's guidelines

Patrick Carpentier (France)

Carpentier presented Raynaud's guidelines for primary care with 13 recommendations covering the definition and nomenclature, history and examination, associated conditions of primary and secondary Raynaud's phenomenon, investigations, such as blood tests, referral to secondary care, and management (lifestyle, drugs, and surgery). The definition of Raynaud's phenomenon is cold-induced ischemic attacks of the extremities that are manifested by transient reversible digital color changes; the terms primary and secondary Raynaud's phenomenon should be used in place of the terms disease and syndrome. As for the management of Raynaud's phenomenon, lifestyle modification is an effective way to control attacks, and it is necessary to avoid triggers, such as the cold, and to wear warm clothes and stop smoking. If lifestyle modifications alone fail, then nifedipine is the recommended first-line treatment. More than half of the recommendations are level C; therefore, the evidence base needs to increase.

Guidelines of the American College of Rheumatology

American College of Rheumatology's criteria for Takayasu's disease

Ahmed Hatri and Rachida Guermaz (Algeria)

Takayasu's disease is a vasculitis of large and medium vessels with an unknown etiology. The disease has two phases: a systemic inflammatory phase and a scleral phase, which is the phase responsible for ischemic events. The two phases can occur successively or together. The Ishikawa criteria proposed in 1988 are too restrictive because they exclude patients older than 40 at the time of disease onset and patients with an involvement of the abdominal aorta and iliac arteries (occurring in 11% to 30% of cases). Despite improvements to these criteria, the American College of Rheumatology's criteria for Takayasu's disease are still questionable. Takayasu's disease can be confused with other stenotic diseases of the subclavian artery, and arteriography is the only recommended reference method for diagnosis. A duplex ultrasound examination, a noninvasive, highly sensitive, and specific examination for the vascular lesions of the supra-aortic trunk and abdominal aorta, can help establish the diagnosis of Takayasu's disease. The advantage of an ultrasound examination is that the circumferential thickening observed in the systemic inflammatory state is often undetected by angiography. This presentation advocated for the systematic use of duplex ultrasound investigation to identify inflammatory thickening of the vessel wall, especially in children and young adults.

Carotid Stenosis

Multifocal atherosclerosis and cardiovascular outcomes

Preclinical atherosclerosis of carotid arteries and future cardiovascular events

Pavel Poredos (Slovenia)

An increase in intima-media thickness, the earliest structural marker of vascular damage, is associated with the extent and severity of atherosclerosis in different arterial beds, and it can predict cardiovascular events. The increase in intima-media thickness is related to vascular risk factors, the adequate treatment of which may prevent its progression or even induce its regression. Consequently, intima-media thickness can be very useful clinically to assess the harmful effects of vascular risk factors on the vessel wall, determine the risk for cardiovascular events, and identify high-risk individuals for cardiovascular incidents. An increase in intima-media thickness clearly constitutes an independent risk factor for cardiovascular events.

The connection between carotid and coronary arteries

Salvatore Novo (Italy)

Patients with an acute myocardial infarction and patients with acute or chronic coronary heart disease have a very high frequency of asymptomatic atherosclerosis in carotid and peripheral territories and an enhanced atherosclerosis progression. In addition, multifocal atherosclerosis worsens the outcomes for these patients. Consequently, a strong secondary prevention and intensive follow-up are mandatory for these patients.

Ankle brachial index and the prediction of future events

Denis Clement (Belgium)

Ankle brachial index has been used as a numerical value to define peripheral arterial disease. Meanwhile, ankle brachial index measurements have several problems and limitations; in fact, according to the peripheral arterial disease guidelines from the ESC, ankle brachial index has a specificity of 96%, but a sensitivity of only 79%. Diabetic patients have increased arterial wall stiffness, which leads to an above-normal ankle brachial index, resulting in misleading normal ankle brachial index values and underestimating peripheral arterial disease. Therefore, in these situations, toe brachial index, which assesses skin perfusion, should be used. Additionally, ankle brachial index is operator dependent and has additional questions to be answered (ie, what decrease in ankle brachial index should be considered clinically relevant, is the risk for future events clearly graded, or what is its relevance in the long term). Furthermore, in addition to its more common use to predict long-term prognosis (local and systemic cardiovascular morbidity and mortality), it can be used to evaluate the functional status, and it is related to specific genetic characteristics. In fact, there is a relationship between ankle brachial index and functional impairment (cross-sectional), and ankle brachial index predicts the evolution of functional impairment over time (longitudinal).

Asymptomatic aortic abdominal aneurysm and future cardiovascular events

Philippe Lacroix (France)

Patients with an abdominal aortic aneurysm are multivascular patients, and the rate of myocardial infarction and stroke before and after surgery is greater for these patients than in an age- and sex-matched general population. Antiplatelet therapy is recommended not only for patients with an abdominal aortic aneurysm who have a preexisting cardiovascular disease (or who are at high risk), but rather for all patients with an abdominal aortic aneurysm. Statin therapy should be initiated in all patients with an abdominal aortic aneurysm and maintained for life after that. In addition, in the presence of hypertension, ACE inhibitors should be considered. Finally, these patients have higher rates of cancer-related mortality.

Progress in the interventional therapy of carotid and peripheral arterial disease

José Fernandes e Fernandes (Portugal)

Remarkable developments have been made in carotid stenting with low-profile devices (eg, guidewires, balloons), better stent designs (closed vs open cells), safer cerebral protection devices, flow-reversal systems, and a cervical approach (vs the standard femoral access). However, the results of carotid stenting are still associated with early neurological deficits in symptomatic patients and worse results during early interventions. The early results of carotid stenting in asymptomatic patients, even in high-volume centers, are not superior to carotid endarterectomy. However, long-term durability and stroke-free survival rates appear comparable with carotid endarterectomy in both symptomatic and asymptomatic patients. In addition, the selective use of carotid stenting is advised for carotid bifurcation disease, and carotid endarterectomy should be reserved for restenosis (early), radiation arteritis, hostile necks, and high surgical risk patients.

Critical Limb Ischemia

Extreme revascularizations

Criteria for critical ischemia in 2016

Joël Constans (France)

It is fundamental to confirm critical limb ischemia using objective criteria because the typical classifications of critical limb ischemia are mostly based on absolute ankle pressure, which is associated with an important number of false negatives, thus excluding a relevant number of critical limb ischemia patients. Today, toe pressure (or the TcPo₂) is a noninvasive first-choice technique to confirm critical limb ischemia objectively. As the definition of critical limb ischemia varies, caution should be used when regarding the clinical trial data. Clear and conclusive standardized definitions are needed.

Interest in angiosome revascularization for the healing of arterial trophic problems in patients with femoral-peroneal bypass

Jean-Baptiste Ricco (France)

Ricco presented a retrospective review study that compared direct revascularization with indirect revascularization according to foot angiosomes and the runoff score of the peroneal branches (anterior perforating and lateral calcaneal branches) using a propensity score analysis. Overall limb salvage at 2 years was 69%, amputation-free survival was 56%, limb salvage at 3 years in patients with direct revascularization was 70.6±5% compared with 68.5±6% in patients with indirect revascularization, no significant difference in wound healing ($P=0.42$), and limb salvage at 3 years in patients with two peroneal branches open was 80±5% compared with 60.8±5% in patients with one open branch and a significant difference in wound healing ($P=0.001$). In a multivariate analysis with matched propensity scores, patency of both peroneal branches was a significant predictor for wound healing (OR, 2.7; 95% CI, 1.7-8.9), as was pedal arch patency, Wlfi classification (wound infections and foot infection classification), diabetes, and renal failure, but not direct angiosome revascularization. There are many limitations to the angiosome concept, and the results suggest that patency of both peroneal branches provides better wound healing, irrespective of the primary wound angiosome. Direct revascularization of wound angiosomes using a peroneal bypass was possible in only half of the patients with tissue loss, and it did not seem to improve wound healing significantly (*J Vasc Surg.* 2015;61[6 suppl 1]:37S).

Extreme bypasses

Sébastien Deglise (France)

Even if endovascular techniques are currently considered the first-line therapeutic modality for patients with critical limb ischemia, a distal bypass is still relevant. Several issues should be considered for a successful open surgery, with the conduit as a key point. Deglise stressed the relevance of a correct preoperative mapping of the available veins (ie, the diameter [>3 mm], lumen, wall, and path) and a very gentle surgical technique to adequately preserve the harvested vein(s). As there is no adequate great saphenous vein in 20% to 45% of the cases, arm veins (even spliced) can be used safely, with good results. Anticoagulation, lymphatic drainage,

and frequent clinical and imaging follow-up visits after the surgery are important. In conclusion, a good selection of patients is obligatory (arterial and venous mapping; comorbidities); distal bypasses still have a place as they are complementary to endovascular techniques; and vascular surgery plans have to take these specific surgical procedures into account.

Therapeutic angiogenesis and other therapeutic progress

Marie-Antoinette Sevestre-Pietri (France)

Therapeutic angiogenesis is a process that aims to induce the formation of new vessels in order to increase the amount of blood in the tissues. There are two types of therapeutic angiogenesis—cellular therapy and gene therapy. Cellular therapy uses endothelial stem cells from bone marrow, blood, or mesenchymal stem cells. These stem cells are placed in the ischemic tissues to induce the formation of new vessels. Gene therapy delivers a proangiogenic factor to ischemic tissues as either recombinant proteins or viruses with the replication sequence replaced by the gene of interest. In the initial experimental and nonrandomized clinical studies on peripheral arterial disease, therapeutic angiogenesis produced promising results. However, the first randomized clinical trials performed in claudicant patients failed to demonstrate a clear benefit of this alternative therapy, pointing to the complexity of the angiogenic process. Retrospectively, since angiogenesis occurs mainly in ischemic tissues, it is quite comprehensible that, in claudicant patients, it could not work per se as the tissues do not have ischemia at rest. The Talisman study (*Mol Ther.* 2008;16(5):972-978; *Lancet.* 2011;377:1929-1937), the first randomized controlled trial on critical limb ischemia for no-option patients, showed no difference regarding amputation rates. Sevestre-Pietri concluded that, due to the complex mechanisms involved in angiogenesis, there is still a lot to learn before achieving an effective and stable therapeutic angiogenesis.

Infragenicular PAOD in the Southern Mediterranean: towards an optimal endovascular strategy

Emad Hussein (Egypt)

Hussein presented options for an optimal endovascular strategy in infragenicular peripheral arterial occlusive disease, especially in patients with critical limb ischemia. This pattern of disease is more prevalent than proximal disease, and it is often associated with diabetes. The possible treatment options include transluminal/subintimal percutaneous angioplasty; cutting and drug-coated balloons; bare-metal, drug-eluting, and bioabsorbable stents. New devices have a role in heavy calcifications, lesions lengths >10 cm, and ulcerated plaques. Patients with critical limb ischemia always need a multidisciplinary approach, but, in most cases, Hussein prefers the “endo first approach.” For patients with critical limb ischemia, open surgery has been partially replaced by endovascular procedures, but if endovascular attempts fail or are not indicated, open surgery may follow.

Peripheral Arterial Diseases

Peripheral arterial diseases

Peripheral arterial disease in Europe

Dan Olinic (Romania)

Peripheral arterial disease begins as an asymptomatic disease, which is often associated with a high risk of cardiovascular disease. Of the 17 million people diagnosed with peripheral arterial disease in the European Union, the estimated prevalence in people ≥ 65 years is 17.1%. In a study that analyzed 460 patients with known peripheral arterial disease, atypical pain symptoms occurred in 60% of the patients (*JAMA*. 2001;206:1599-1606). These symptoms include (i) pain that is different from typical exertional claudication pain; (ii) pain not requiring cessation of physical activity; (iii) pain lasting longer than 10 min after cessation of physical activity; and (iv) pain that occurs both at rest and upon exertion. The prevalence of peripheral arterial disease is higher in men aged 50 to 59 (3.1% to 2.7%) and aged 70 to 79 (11.6% to 11.5%) than in women, and its distribution across ethnic origins is as follows: non-Hispanic whites (43.5%), African-Americans (20%), Hispanics (20.7%), and Chinese-Americans (15.6%). Peripheral arterial disease risk factors include behavioral factors (eg, tobacco use, physical inactivity, harmful use of alcohol, and a diet rich in salt, fat, and calories), metabolic factors (eg, hypertension, diabetes, high cholesterol levels, and obesity), and other factors (eg, poverty, low education status, advancing age, sex, genetic disposition, stress, and depression). In European populations, there are 500 to 1000 cases of critical limb ischemia every year per million, with a prevalence of 1% to 3% in patients with peripheral arterial disease and 1% to 2% in patients with critical limb ischemia requiring lower limb amputation. Future trends are difficult to predict, especially with the changing risks in the population (eg, tobacco smoking and diabetes) and the limited evidence on trends during the past few decades that have suggested a decline in the incidence of intermittent claudication. Active screening/ankle brachial index vs a "passive" symptomatic diagnosis needs to be conducted to decrease the impact of peripheral arterial disease.

Cost of peripheral arterial disease and trends in complications

Mariella Catalano (Italy)

The frequency of peripheral arterial disease is expected to increase by about 35% by the year 2030, considering that there is the marked increase in peripheral arterial disease burden with advancing age. From 2005 to 2009, total peripheral arterial disease cases increased by 20.7%, critical limb ischemia by 2.9%, major amputations decreased by 1.1%, and minor amputations slightly increased by 0.13%. The crude overall in-hospital mortality remained unchanged in patients with a limp (2.2%), while it decreased by 1.4% in patients with critical limb ischemia; however, the mortality rate increased significantly in patients with a limp ($P < 0.001$). Total endovascular revascularizations increased by 46%, thromboembolectomy by 67%, endarterectomy by 42%, and patch plastic by 21%, whereas, peripheral bypasses decreased by 2%. The total reimbursement costs for peripheral arterial disease for inpatient care increased by 21%, with an average per-case reimbursement cost in 2009 of 4506 euros for patients with a limp and 6791 euros for patients with critical

limb ischemia. The focus should be turned to prevention, early diagnosis, cooperation and networking, patient endorsement, awareness education, and specific target populations to reduce the impact of peripheral arterial disease on health care costs and outcomes.

The concept of prevention

Jean-Claude Wautrecht (Belgium)

What are the differences between prevention and health promotion? Health promotion refers to a set of strategies and methods implemented at different social levels in an attempt to increase people's health resources and potentials. Health promotion interventions are often designed and conducted by public health specialists, without a specific problem, risk factor, or disease in mind; they usually promote general health. Prevention, unlike health promotion, involves activities aimed at avoiding and reducing the likelihood of or delaying harm to a person's health. Prevention activities can take place on three levels (primary, secondary, and tertiary) depending on the time, objective, and target of preventive intervention. Preventive interventions are performed by medical experts to fight specific diseases (eg, cardiovascular diseases). Specifically, health promotion is resource oriented, nonspecific, related to health science, requires an active participation from patients/citizens, and focuses on health; whereas, prevention is burden oriented, specific, related to medicine, requires passive participation from patients/citizens, and focused on disease. Prevention has many faces; therefore, it needs more than one approach because the results depend on how early the interventions are planned. In the future, simple and inexpensive interventions will produce significant results. Education, at all levels (specialists, family doctors, health professionals, patients, and the whole population), is the key to success.

European biobanks

Bahare Fazeli (Iran)

According to *Time Magazine*, the creation of biobanks is one of ten ideas that are changing the world. A biobank is a safe house for biological samples that could be used to research new treatments for diseases. A biobank contains biological material, and it is connected to information and legal issues, such as consent and patient data safety and protection. Biobanks enable a shift from "one-size-fits-all" to more targeted therapies with respect to age, sex, demography, and relevant costs (personalized medicine). Biobanks promote a personalized genetic study with genome information (demographic, social, and environmental data) to help predict and identify risk factors for the development of better prevention methods. One limitation for vascular disease researchers is low sample sizes. In light of the large sample size of biological specimens and clinical data on vascular diseases, personalized medicine can be developed with the main goal being to avoid amputation. The VAS Biobank is a biorepository that accepts, processes, and stores biospecimens and associated data for use in research and clinical care on peripheral diseases. It is possible to contact VAS Biobank at vas@unimi.it.

Best papers of the ESVM 2016 meeting

Residual cardiovascular risk in peripheral artery disease: exploring the role of albumin-creatinine excretion rate (ACR) in a prospective study

Sandra Mastroianno (Italy)

This study assessed whether a marker of microvascular dysfunction, such as the albumin-creatinine excretion rate (ACR), might be useful for evaluating residual cardiovascular risk in patients affected by advanced peripheral arterial disease. A total of 264 patients with a diagnosis of advanced peripheral arterial disease were followed for approximately 33 ± 11 months. According to the overall median ACR value, the investigators divided their population into lower and higher ACR groups. Of the 64 major cardiovascular events, defined as myocardial infarction, cerebral ischemia, myocardial and/or peripheral revascularization, or death, observed, 23 occurred in the lower ACR group and 41 in the higher ACR group. Thus, in this prospective study, high ACR levels were predictive of cardiovascular events in patients affected by advanced peripheral arterial disease.

Effects of supervised exercise on reticulated reactive platelets and erythrocyte fragments in patients with peripheral atherosclerosis

Sergio De Marchi (Italy)

Platelet activation plays an important role in atherosclerosis progression. The immature platelet fraction reflects the degree of reticulated platelets, which are highly reactive young platelets associated with cardiovascular complications. Furthermore, the presence of a wide red blood cell distribution, mostly due to fragmented red blood cells, is considered a negative prognostic factor for coronary artery disease. The effects of a 15-day aerobic training period on the immature platelet fraction and fragmented red blood cells were evaluated at rest and after a maximal walking exercise in 12 patients with intermittent claudication (stage II of Leriche-Fontaine classification). Exercise training can reduce the immature platelet fraction and the fragmented red cells in patients with peripheral arterial disease. The immature platelet fraction increases after maximal exercise testing, which is attenuated during the training period. Marchi hypothesized that training, which probably improves oxidation, inflammation, and endothelial function, is effective in reducing both the platelet activation (immature platelet fraction) and fragmented red blood cell count.

Undernutrition, a novel marker of peripheral arterial disease: the EPIDEMCA study

Ileana Desormais (France)

There is an ongoing debate regarding the association between obesity and peripheral arterial disease. However, the association between undernutrition and prevalent peripheral arterial disease has been poorly assessed. This study evaluated the association between undernutrition and peripheral arterial disease in elderly patients in an African population. Patients ≥ 65 years from two urban and two rural areas of the Republic of Congo and the Central Africa Republic ($n=1815$) were enrolled in the study. The existence of peripheral arterial disease was defined by an ankle-brachial index value < 0.90 . The patients were categorized into four groups according to the World Health Organization criteria and their BMI: (i) undernutrition (< 18.5 kg/m²); (ii) normal (18.5 to 24.9 kg/m²); and (iii) overweight (25 to 29.9 kg/m²); and (iv) obese (≥ 30 kg/m²). The prevalence of undernutrition was higher in patients with peripheral arterial disease than in those without the disease (37.1% vs 33.5%, $P=0.0333$). Undernutrition remained significantly associated with

peripheral arterial disease after adjustment for all potential confounding factors, such as the general population (OR, 2.09; $P=0.0009$) and sex (males: OR, 2.82; $P=0.0038$ and females: OR, 1.75; $P=0.0492$). In the multivariate analysis, there was no association between the overweight (OR, 1.10; 95% CI, 0.62-1.96) or obesity (OR, 1.55; 95% CI, 0.74-3.23) groups and peripheral arterial disease in the overall cohort and per country. Therefore, undernutrition seems to be associated with peripheral arterial disease in elderly communities in central Africa. Pending further confirmation, this potentially novel risk factor should be taken into account as a target to improve global cardiovascular health.

Symptomatic lower-limb giant-cell arteritis: characteristics, management and long-term outcomes

Claire Le Hello (France)

The characteristics, evolution, and long-term outcomes of symptomatic lower-limb giant-cell arteritis are rarely reported. In a retrospective analysis of 8 patients (6 women; mean age 63.6 ± 10.9 years; follow-up, 137.3 ± 57.3 months), the classic signs of giant-cell arteritis, such as headaches, polymyalgia rheumatic, and inflammatory syndrome, were less frequently observed. Conversely, a bilateral and rapidly progressive lower limb claudication was documented in all patients, which appeared as the first sign in 5 patients. Inflammatory lesions were localized more frequently in the superficial femoral and popliteal arteries. All patients received corticosteroids for 132 ± 76.2 months; 2 subjects were treated with an immunosuppressive agent. Only 3 patients required a revascularization. In this group, thromboendarterectomy and endovascular procedures were not effective, whereas bypasses were successful. Lower limb claudication regressed slower than cephalic signs in 7 patients (10.5 ± 12.1 months) and disappeared in 5 (16.8 ± 9.8 months). Every patient had one relapse (23.9 ± 26.7 months; mean corticosteroid dose, 0.28 ± 0.30 mg/kg/day). Lower-limb giant-cell arteritis caused only one of the 4 deaths observed during the follow-up. In conclusion, long-term mortality that is attributable to symptomatic lower-limb giant-cell arteritis seems low despite frequent relapses and corticosteroid dependence.

Vascular diseases: particularities for women

Peripheral arterial diseases

Alessandra Bura-Riviere (France)

Little is known about sex-specific differences in peripheral arterial disease. Although the age-dependent prevalence of peripheral arterial disease in adult women is lower than that for men, the total population burden of peripheral arterial disease appears to be higher in women. The women included in most of the studies were older, were less frequently smokers, and presented at more advanced stages of the disease. Although women were less likely than men to undergo lower extremity revascularization (eg, fewer bypasses in the COPART registry), procedural complications and stent or bypass occlusion are more frequent, and the long-term mortality is higher (72% vs 54% at 3 years). In conclusion, the prevalence of peripheral arterial disease is high in women, the symptoms are often absent or underestimated, and the diagnosis is often made at more advanced stages.

Aortic and peripheral arterial vascular surgery

Nellie Della Schiava and Antoine Millon (France)

Estrogens often protect women from aortic aneurysms. Although the screening and indications are the same between women and men, there are many controversies about earlier surgery because of smaller body sizes. In comparison with men, the evolution of aortic aneurysms is more aggressive with faster growth, higher rupture rates (4 times), higher mortality in case of rupture (3 times), and lower repair rates in women with the same comorbidities. For elective or emergency surgery, female sex is an independent risk factor. In the long term after an operation or endovascular aneurysm repair, women have lower survival rates, which may be due to older age and the advanced disease state at the time of repair due to the delay in diagnosis and hormonal differences. Compared with men, women have an anatomy that is often less suitable for endovascular aneurysm repair due to a shorter neck length, increased neck angulation, and smaller iliac vessel diameters. For carotid stenosis, women have poorer short-term outcomes after surgery compared with men, which may be due to older age at the time of the surgery, smaller vessel diameter, hormonal differences, lower sensitivity to antiplatelet therapy, different plaque morphology, higher occurrence of microembolic signals, and higher stenosis rates. Compared with men, women with lower extremity arterial occlusive disease are older, with a more advanced disease at presentation, smaller vessel diameters, and have poorer outcomes, including higher bypass failure and amputation rates. The small aorta syndrome especially affects young women, and it is associated with coronary artery disease (88%) and diabetes (42%). Endovascular treatment is feasible for this group of patients. In conclusion, earlier screening and better medical management of cardiovascular risk factors are important for women. Biomedical research will help solve these issues. Specific recommendations with better scientific evidence from studies including only women are necessary.

Vascular acrosyndromes

Pavel Poredos (Slovenia)

Acrosyndromes are acral circulatory disorders caused by vasomotor deterioration or occlusion of distal arteries that involve the distal part of the toes or fingers.

- Primary Raynaud's phenomenon predominantly affects young women, where the treatment consists of lifestyle modifications and, in advanced cases, vasodilating drugs. The secondary form has the symptoms and signs of an underlying disease, such as systemic lupus erythematosus.
- Acrosyanosis is a symmetric, painless, and bluish discoloration of distal parts of the body, where the diagnosis is based on the clinical description. Constriction of venules and capillaries of unknown causes are responsible for the disease. The secondary form is associated with hypoxemia, neoplasms, hematological diseases, and toxicities.
- Chilblains are caused by an abnormal skin reaction to cold, and the symptoms fade with warmer temperatures.
- Paroxysmal finger hematomas occur spontaneously with recurring episodes, and they are characterized by ecchymosis on the volar side of the proximal phalanx, with an associated risk of brain and gastrointestinal bleeding. Treatment only involves treating the symptoms.
- Blue-toe syndrome is caused by the release of cholesterol crystals from atheromatous plaques.

- Acral necrosis is frequently accompanied by renal failure. Treatment involves treating the symptoms with antiplatelet drugs.
- Cryoglobulinemia is a medical condition in which the blood contains large amount of cryoglobulins that become insoluble at low temperatures.
- Cryoglobulinemia can be associated with multiple myeloma, hepatitis C, and systemic lupus erythematosus.
- Primary antiphospholipid antibody syndrome is related to antibodies (anticardiolipins), but there is no clinical manifestation of systemic lupus erythematosus or Sjögren's syndrome.
- Primary systemic vasculitis is caused by inflammation and the destruction of blood vessel walls. Treatment consists of cytostatic drugs and corticosteroids.

In conclusion, the primary forms of these diseases are usually benign, periodic, and provoked by a cold environment; however, the secondary forms are related to other systemic diseases. Clinical symptoms are constant, more serious, and often accompanied by necrosis and ulcers. Diagnosis is based on clinical presentation of the tips of the fingers and toes. These conditions are more frequent in women than in men. Treatment of primary (benign) acrosyndromes consists of treating the symptoms and making lifestyle modifications. For secondary acrosyndromes, treatment of the underlying disease and the symptoms with drugs is necessary.

Vascular diseases in the Middle East

Study of clinical course and natural history of thromboangitis obliterans (Buerger's disease)

Hadi Modaghegh (Iran)

Thromboangitis obliterans (Buerger's disease), a nonatherosclerotic, segmental, occlusive, inflammatory condition of small- and medium-sized arteries (affecting adjacent veins and nerves), is characterized by highly cellular vessels (continued by recanalization or fibrosis) in young smokers. Thromboangitis obliterans is a common vascular disease in South and Southeast Asia, the Middle East, Far East, and Eastern European countries. In Iran, the prevalence rate is 3.3 per 100 000 people. The etiology is unknown with many hypotheses: autoimmune, genetic, hypercoagulable state, oral infection (poor oral hygiene), and inflammatory. Smoking (even passive) is the most important risk factor for the pathogenesis, initiation, and progression of thromboangitis obliterans. In Iran, patients with thromboangitis obliterans are usually addicted to opium in addition to tobacco. In Modaghegh's clinical experience, there is a 46% amputation rate. Among the therapeutic options, only prostaglandin IV and sympathectomy shorten the exacerbation episode. In some cases, prostaglandin therapy induces prolonged remission.

Middle East vascular entities, what is special?

Louy Altarazi (Syria)

Altarazi emphasized the high prevalence of inflammatory vascular diseases in the Middle East. In Syria, more than 56% of males and 18% of females are smokers. Teenagers start smoking around age 16 (1 Nargleh = 20 to 50 cigarettes), and the high prevalence of smoking causes early atherosclerosis and Buerger's disease. About 15% to 35% of the population is diabetic with a high amputation rate due to a lack of a consensus for the management of the diabetic foot. Therefore, proper prevention and management of vascular diseases are crucial public health concerns in the Middle East.



II

Venous Diseases



IUA-SFMV Lyon, October 5-8, 2016

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Diagnosis, Investigations, Management, and Progression

Keynote lectures

Clinical implications and diagnostic applications of hemodynamic measurements in chronic venous disease

Andrew Nicolaides (Cyprus)

Venous hemodynamic concepts are useful in understanding the pathophysiology of venous disorders, the significance of investigation results, the hemodynamic changes associated with symptoms, and the hemodynamic changes associated with treatment. Hemodynamic measurements of pressure, volume, pressure/volume relationship, velocity, flow, resistance, compliance/elasticity, function of the calf muscle pump, and changes in the microcirculation are very important. Unfortunately, only velocity and flow can be measured by duplex ultrasound. Four main phases are observed in the progression of chronic venous disease: valve damage (reflux), vein wall remodeling (varicose veins), capillary leakage (edema), and capillary damage (skin changes). Venous hypertension is the underlying hemodynamic change associated with the increased prevalence of skin changes and ulceration. However, there are protective mechanisms, such as lymphatic drainage and fibrinolytic activity. Lymphatic drainage can increase 5 to 10 times in some individuals, but only 2 times in others and 0 in patients with lymphedema. In the presence of moderate venous hypertension, if the fibrinolytic activity is low, 90% develop skin changes and 70% develop ulcers; however, if the fibrinolytic activity is normal or high, only 16% develop ulcers. For quantitative measurements of reflux in individual veins, volume flow can be measured using duplex ultrasound (time average velocity x vessel cross-sectional area = rate of volume reflux in mL/min). For whole leg measurements, air-plethysmography can be used. In patients with venous obstruction, the degree to which a venous stenosis is critical is not known because outflow resistance depends not only on the degree of stenosis, but also on the degree to which the collateral circulation is developed. Resistance can be measured from simultaneously obtained outflow curves of pressure and volume ($R=P/Q$). When reflux and resistance are measured, there is a high correlation between these combined measurements and the venous clinical severity score. Therefore, the statement that "there is a poor correlation between hemodynamic measurements and the clinical severity of chronic venous disease" should be modified to "there is a poor correlation between duplex measurements and the clinical severity of chronic venous disease." Duplex measurements provide information on the presence or absence and anatomic extent of reflux or obstruction. If quantitative information is needed for how much reflux or obstruction exists for clinical decisions, duplex measurements should be complimented with plethysmography.

Changing concept on venous hemodynamics: contemporary interpretation!

Byung-Boong Lee (USA)

Lee addressed the contemporary interpretation of Cockett's blow-out syndrome. Despite the many excellent guidelines for clinicians on the management of venous disorders, the hemodynamic background of venous disorders has rarely been

reviewed seriously as an independent issue. Therefore, the hemodynamics of the venous system is largely unexplored, not at all understood, and the available models have been shown to be inadequate. Indeed, the hemodynamic concepts involved have remained unchallenged through recent decades mainly due to their complicated nature. However, the development of duplex scanning and other imaging techniques with outstanding resolutions that can provide information on the anatomic extent of reflux and obstruction have become a mainstay for the diagnosis and clinical decisions without an in-depth understanding of the background hemodynamic processes involving flow, pressure, compliance, and resistance. Based on tremendous improvements in the diagnostic technology, physicians can understand many difficult conditions/phenomena better.

The term “competent calf perforator” is misleading; the division into “competent” and “incompetent” calf perforators is arbitrary, freely contrived, and unjustified (*Rozhl Chir.* 1973;52:142). Lower leg perforators do not function in healthy people as a competent, one-way system. Pressure recordings in the posterior tibial veins and great saphenous veins show both unhindered pressure transmission in either direction within the calf perforators and prompt systolic and diastolic pressure equalization both in patients with varicose vein and large “incompetent” perforators and healthy people with “normal” perforators. Therefore, deep and superficial veins of the lower leg form conjoined vessels to maintain a “physiological” bidirectional flow. The outward flow in calf perforators is not reflux; the reflux is a diastolic, centrifugal, pathological flow within the calf perforators with inward-oriented flow into deep lower leg veins inducing ambulatory venous hypertension. The outward flow is a systolic, centripetal flow that is propelled by the calf pump via the great saphenous vein in the physiological direction of the heart. The calf pump has a double-barreled outflow, with the main flow being through the popliteal-femoral axis and the second flow through the great saphenous vein. Simultaneous pressure recordings in the posterior tibial veins and the great saphenous vein showed that calf perforators provide free pressure transmission between deep and superficial veins of the leg, resulting in quick pressure equalization. These findings indicate that deep and superficial veins of the lower leg form conjoined vessels to meet physiologic needs.

Innovations in the treatment of varicose veins

The new Latin American therapeutical guidelines in the treatment of chronic venous insufficiency

Roberto Simkin (Argentina)

Dr Simkin presented an overview of the recently published Latin American guidelines on the management of chronic venous insufficiency. For grading of the recommendations and quality of evidence, the grading scheme GRADE, which was formulated by the American College of Chest Physicians (ACCP) and published in *Chest* in 2006, was used. This grading scheme classifies recommendations as strong (grade 1) or weak (grade 2), according to the balance of and the degree of confidence in the benefits, risks, burdens, and possibly cost. The system classifies the quality of evidence as high (grade A), moderate (grade B), or low (grade C) according to factors that include the study design, consistency of the results, and directness of the evidence. The Latin American guidelines were adapted to the socioeconomic reality of Latin America countries. The following tables show the results for treating the great saphenous vein (*Table I*), the small saphenous vein (*Table II*), insufficient perforator veins (*Table III and*

Table IV), telangiectasias and reticular veins (Table V), symptomatic relapsed varicose veins (Table VI), and venous ulcers (Table VII). Simkin pointed out that these guidelines do not intend to be a dogma and they should be used with the experience of the treating specialists and the preferences of the patients.

Table I. Grading recommendations for treating the great saphenous vein.

Guideline	Grade of recommendation	Grade of evidence
Major saphenectomy	1	B
Laser ablation	1	A
Radiofrequency ablation	1	A
Sclerotherapy	2	B
Cyanoacrylate	2	C
Clarivein/water steam technique	2	C

Table II. Grading recommendations for treating the small saphenous vein.

Guideline	Grade of recommendation	Grade of evidence
Saphenectomy	1	C
Recurrences saphenectomy	1	C
Laser ablation	1	B
Radiofrequency ablation	1	B
Sclerosant treatment	2	A
Sclerosant treatment of dependent varicose relapses	2	A

Table III. Grading recommendations for the general treatment of insufficient perforator veins.

Guideline	Grade of recommendation	Grade of evidence
Treatment is not recommended in patients with simple varicose veins (CEAP class C ₂)	1	B
Treatment of pathological perforator veins located in the affected area (CEAP class C ₅)	2	B
Subfascial endoscopic perforating vein surgery, echo-guided sclerotherapy, or thermoablation	2	A
Selective treatment in the thigh or popliteal fossa	1	B
Selective treatment of isolated insufficient perforator veins that produce secondary varicose veins	1	B
Techniques, such as Linton, Cockett, or Felder, are not recommended	1	A

Table IV. Grading recommendations for treating insufficient perforator veins.

Guideline	Grade of recommendation	Grade of evidence
Laser ablation	1	C
Laser ablation with relapse of insufficient perforator veins	1	C
Radiofrequency ablation	1	C
Sclerosant treatment	2	B

Table V. Grading recommendations for treating telangiectasia and reticular veins.

Guideline	Grade of recommendation	Grade of evidence
Sclerotherapy with liquid sclerosants	1	A
Laser treatment with Nd: YAG (1064 nm)	1	C
Laser treatment + complementary sclerotherapy	1	C

Table VI. Grading recommendations for treating symptomatic relapsed varicose veins.

Guideline	Grade of recommendation	Grade of evidence
Surgery, endovascular treatment	2	C
Sclerotherapy	2	C

Table VII. Grading recommendations for treatment of venous ulcers

Guideline	Level of evidence
Pentoxifylline or MPFF in combination with compression to speed up healing	B
Compression as primary therapy for healing	B
Compression as adjuvant treatment to avoid relapse	A
Ablation of the insufficient superficial venous system plus compression to reduce relapse	A
Treating the insufficient perforator veins around open or closed ulcers (CEAP classes C ₅ or C ₆)	B
Using subfascial endoscopic perforating vein surgery, sclerotherapy, or thermoablation for ligation of insufficient perforator veins	C

Compression therapy during EVLA of the GSV

Ruben Velletaz (Argentina)

In a randomized controlled study that evaluated the effect of compression therapy after endovenous laser ablation of the great saphenous vein showed that neither graduated compression stockings nor concentric compression bandages could achieve adequate compression of the thigh while standing. In the clinical guidelines for the diagnosis and management of varicose veins from the National Institute of Clinical Excellence, no clear recommendations about the type and duration of compression therapy after endovenous laser ablation have been determined. The primary objective of this study was to establish a compression therapy protocol. The patients were randomized into two parallel groups: (i) group 1 (n=98) received conventional compression therapy with high extension bandages 0 to 7 days postprocedure; and (ii) group 2 (n=76) received eccentric compression 0 to 2 days postprocedure. After day 7 or 2, respectively, both groups received graduated compression stockings (20 to 30 mm Hg) until day 14. The following outcomes were assessed: clinical scores (CEAP, VCSS), quality of life (CIVIQ 20), adherence to compression therapy, pain (VAS), tolerability, and safety parameters. The patients in group 2 had a lower pain intensity, lower analgesic intake, lower rates of side effects (ecchymosis, induration, and pigmentation), a lower rate of progression of endothermal heat-induced thrombosis, and a higher quality of life score than did the patients in group 1. In conclusion, in terms of pain intensity, tolerability parameters, and quality of life, eccentric compression for the first 2 days after endovenous laser ablation of the great saphenous vein followed by graduated compression stockings for 14 days is superior to compression therapy with high extension bandages for 7 days followed by graduated compression stockings for 14 days.

Telangiectasia: etiological classification and combined synergic treatment

Carlos Simkin (Argentina)

According to the consensus statement from the Latin American Venous Forum, telangiectasias are classified as primary or secondary on an etiologic point of view. Telangiectasias was further subdivided into those with a high response, a good to moderate response, and a low to poor response depending on their behavior in front of the light impact and therapeutic effect obtained. In his daily practice, Simkin combines transdermal cryolaser (Nd:YAG [1064 nm]) with cryosclerotherapy (0.5% liquid polidocanol and a 50% glucose hypertonic solution mixed with 0.33% sodium tetradecyl sulfate) to treat telangiectasia and reticular veins. This combination treatment should result in a synergistic effect between the chemical effect of sclerosis, the physical effect of the laser, and the anesthetic and local anti-inflammatory effect of the cryotherapy. In Simkin's opinion, transdermal cryolaser is indicated when conventional sclerotherapy is not effective, in patients with a needle phobia, when patients would like a new treatment, in the case of an allergy to the sclerosant agents, when the patient is taking anticoagulants, and when the patient is breastfeeding. Contraindications for cryolaser include Raynaud phenomenon, autoimmune diseases, peripheral occlusive arterial disease, laser phobia, and certain skin diseases (pemphigus, psoriasis).

Simkin reported on his 10 years of clinical experience. Of the 7964 patients treated with cryolaser and cryosclerotherapy between 2001 and 2012, 20% received cryosclerotherapy, 22% cryolaser, 41% cryolaser plus cryosclerotherapy, and 17% cryolaser plus cryosclerotherapy plus microsurgery. Complications after cryolaser

treatment included skin burns (0.26%), hyper/hypopigmentation (0.7%), hematoma and ecchymosis (6%), and localized intravascular coagulation (11%). Therefore, Simkin concluded that the combination treatment with cryolaser and cryosclerotherapy was more effective and faster acting than monotherapy. In trained hands, the combination of transdermal cryolaser associated with cryosclerotherapy is a good technique with excellent esthetic and clinical results, high patient satisfaction, and a low rate of complications.

Klippel-Trenaunay syndrome: treatment with endovenous laser. Long term results with the regional segmentary skeletonization technique

Roberto Simkin and Carlos Simkin (Argentina)

Klippel-Trenaunay syndrome presents with atypical varicose veins, diffuse angiomas, arteriovenous fistulas, pigmentary nevus of variable sizes and length on the extremities. There are three types of surgical management for this disease, including vein resection, regional segmentary skeletonization (named the Simkin technique), and endoluminal laser. Eight cases were treated with a hybrid technique, which consisted of treating the junction and the saphenous veins with the endoluminal laser technique (980 nm), and treating collateral veins, perforator veins, and vulvar veins by resection, cryolaser (540 nm), or foam sclerotherapy. In conclusion, regional segmentary skeletonization is a good technique for reducing the abnormal growth of the affected extremities, and the endoluminal laser technique is a good choice for treating recurrent varicose veins in patients with Klippel-Trenaunay syndrome.

Evaluation of CVD patients: from CEAP to symptoms

Introduction

Lowell S. Kabnick (USA)

Kabnick thanked the International Union of Angiology for bringing the American Venous Forum and the European Venous Forum together to discuss the session's topics. He expressed his expectations on controversy and disagreement. He also posed several questions to think about, such as "how reliable are symptoms in predicting venous disease and severity" and "what are the benefits and the issues of the CEAP classification," and "do we really need to revise." Finally, Kabnick congratulated the authors of the SYM Vein Consensus statement that was developed under the auspices of the European Venous Forum.

Do venous symptoms tell all?

Michel Perrin (France)

Perrin explained why venous symptoms provide few or even false information on patients status. One reason is that leg symptoms are not pathognomonic of venous disease (except venous claudication), and venous disease can be asymptomatic, and there is a weak correlation between symptom intensity and severity of the venous disease. However, secondary symptoms, such as disquiet, malaise, insomnia, ill-being, etc, may be related to a venous disease, but this relationship might be difficult to establish. There is also a weak correlation between symptom intensity and the information drawn from the instrumental investigation; some patients obtain symptom relief with any treatment (ie, the placebo effect). Another factor is that the perception of symptoms is individual, and consequently, the patients' self-reported information

on symptoms is not valuable in the assessment of symptom severity. While venous symptoms provide physicians with important information, the symptoms do not reflect the pathophysiologic disorders that affect the venous system: reflux, obstruction, or both.

From June 2014 to June 2016, 23 participants from 14 countries agreed to work together to clarify some of the problems raised by the issue of venous symptoms. Five groups were formed to deal with five major topics: description and definition of venous symptoms; attributing leg symptoms to venous disorders; pathophysiology of venous symptoms; venous symptom scoring, clinical examination, and instrumental investigations. The results of this work were published as the SYM Vein Consensus statement (*Int Angiol.* 2016;35:374-398). Perrin concluded that this consensus document helps with many issues, but many points remain to be clarified.

Venous symptoms: what are they and how can we be certain?

André van Rij (New Zealand)

Venous symptoms are related to different venous problems, such as thrombosis, reflux, obstruction, perforator dysfunction, phlebitis, varicose veins, skin manifestations, recurrence, and ulcers. There is the dilemma regarding the lack of specificity, frequency, overlap, variety in intensity, and lack of correlation between these symptoms and pathology, and as a result, there could be a high treatment bias. van Rij suggested how to attribute symptoms to venous disease: (i) the human factor should be understood, which consists of many psychosocial and individual factors; (ii) the symptom story has to be interrogated and established; (iii) the probability of association needs to be known, other causes should be excluded, and symptoms should be related to signs/investigations; and, finally, (iv) the response to conservative therapy has to be evaluated.

History of CEAP: past and present

Bo Eklof (Sweden)

A classification of chronic venous disease is needed because it is fundamental to the understanding of the clinical disease processes and communication between institutions. There have been many published classifications of chronic venous disease; the first classification was published by Widmer in 1978, and it distinguished between stage I (edema and dilated subcutaneous veins with corona phlebectatica), stage II (trophic lesions of the skin with hyperpigmented or depigmented areas), and stage III (healed or active venous ulcers). The problem with the old classification systems is that, because venous disease is complex, the clinical diagnosis is not enough, as it provides no information about the etiology, anatomy, and physiology of the disease. In 1993, the need for a better classification was discussed at the American Venous Forum, and as a result, an ad Hoc Committee of the American Venous Forum developed a new "Classification and Grading of Chronic Venous Disease in the Lower Limbs." This "CEAP" classification was based on 4 points: (i) what: Clinical manifestation; (ii) why: Etiologic basis; (iii) where: Anatomic distribution; and (iv) how: Pathophysiology. This classification was distributed over 5 continents with 26 publications and 11 language translations.

Further improvements to the CEAP classification concerning the definition of C were made at the International Union of Phlebology meeting in 2001. The suggested definitions and refinements of C in CEAP were published in the *Journal of Vascular*

Surgery in 2003. By 2004, an ad hoc committee to review the CEAP classification and make recommendations for change was established. The main points of the revision included a refinement in the definitions used to describe chronic venous disease, a refinement of the C classes, and the addition of the descriptor n. The revision also defined levels of investigation: (i) Level I: office visit with history and clinical examination; (ii) Level II: noninvasive vascular lab; and (iii) Level III: invasive investigations or complex imaging studies. Besides the revision, Eklof introduced basic CEAP with the use of the single highest descriptor for the C class vs the advanced CEAP where the use of all of the components is encouraged. The revision of the CEAP classification was published in the *Journal of Vascular Surgery* in 2004, and now a new revision is planned in collaboration between the American Venous Forum and the international phlebology community.

What are the benefits of CEAP?

Ruth Bush (USA)

Bush discussed the CEAP classification from different points of view. For the practicing physician, CEAP can be an instrument to diagnose the disease correctly, guide the treatment, and assess the prognosis. For reporting standards and researchers, CEAP should be a descriptive instrument to categorize patients into different groups of chronic venous disease severity. Bush pointed out that a proper diagnosis and accurate classification of the underlying venous problem is the cornerstone for the management of chronic venous disease; however, there is heterogeneity in the reporting standards concerning demographics and outcomes.

In a medical database search, which was conducted by Thakur et al and published in *Eur J Vasc Endovasc Surg* in 2010, randomized clinical trials published between 1968 and 2009 that evaluated endovenous interventions for varicose veins were included, and the trial details were compared with the recommended reporting standards published by the American Venous Forum in 2007. From 2384 identified abstracts, only 28 randomized trials fulfilled the inclusion criteria, and there were wide variations in both the reporting and the assessed outcome measures. Meaningful comparisons were difficult due to variations in the study design, the lack of quality of life data, and the lack of comparison to published reporting standards. The only good news was that demographic reporting improved after 2007. The CEAP revision includes more detail on severity, pathology, and anatomy; the CEAP classification is not a static classification and revision is an ongoing process. CEAP represents the clinical and functional situation of the patient, but not disease severity. In a trial published by Kahn et al in 2004, the clinical category, based on CEAP classification, predicted patients reported quality of life and symptom severity in chronic venous disease.

Some of the advantages of the CEAP classification include assisting in the evaluation of various treatment modalities, allowing results from multiple institutions to be compared, enhancing the understanding of the potential etiologic factors and the pathogenesis of the disease, and improving the scientific standards of the published literature. A standardized approach for assessing the outcomes helps minimize the number of expensive and lengthy prospective randomized trials, improves practice audits, and assists in registry data acquisition. Finally, Bush introduced the Varicose Vein Registry (VQI) that was launched in January 2015. To date, 13 countries have reported data on 826 patients and 844 limbs from the first 6 months. In conclusion,

considerable variation exists in study populations and outcome measures; therefore, randomized trials should adhere to reporting guidelines and agreed upon standards, which will allow for greater objectivity when assessing new technologies. Bush marked CEAP as very beneficial, and she recommends using the basic CEAP for daily practice and the full CEAP for scientific use.

What are the issues with CEAP?

Pier-Luigi Antignani (Italy)

CEAP remains the gold-standard classification for chronic venous disease, which was confirmed in a recent review article where the authors conducted a Medline analysis that retrieved 266 publications using CEAP. The CEAP classification has limits because it is not a severity classification and the classes C_0 to C_3 are controversial. The C_{0s} patient condition was the true problem in clinical practice because the majority of people classified as C_0 (20% of general population) were symptomatic (C_{0s}). Antignani stressed that venous disorders are individual-based pathologies and patient satisfaction becomes a hallmark of effective treatment. Then Antignani pointed out that the CEAP classification and venous clinical severity score (VCSS) are different tools that do not measure the same items equally. For example, C_2 uses a definition of >3 mm for a varicose vein, whereas the VCSS uses a cut-off point of 4 mm. In Antignani's opinion, the major handicap of CEAP is its complexity, which makes it difficult to use in everyday practice. Other limitations include the lack of general information provided (ie, patient history), the lack of reversibility of language (eg, C_4 means, at the same time, one or several skin changes), the lack of a varicose vein score, the fact that C_2 summarizes all kinds of varicose veins, separating venous and other cause of edema in the C_3 class may be difficult, and corona phlebectatica of the foot is not taken into account, which is classified as a strong clinical predictor of chronic venous disease and the subsequent occurrence of skin changes. Corona phlebectatica has been identified as a highly significant clinical sign indicating chronic venous insufficiency. It has prognostic value for the progression of chronic venous disease, and it should be evaluated in every patient with chronic venous disease. Antignani proposed that corona phlebectatica be considered for inclusion in existing or future classifications/scoring of chronic venous disease.

The future of disease classifications and the impact of classification change

Fedor Lurie (USA)

Lurie explained the three different types of classifications: clinical classification, research classification, and demographic/descriptive health statistics classification. They differ radically due to different goals, development, basis, reliability/repeatability, responsiveness, and convenience/practicality. For example, demographic/descriptive classifications, such as CEAP, have a goal of defining distinct diseases and conditions, they are on a phenotype basis after empiric development, and they have high reliability/repeatability; however, responsiveness is not important, and convenience/practicality is low. The big challenge in working out classifications is disease heterogeneity. One possible solution includes merging clinical and research classifications, but this requires knowledge of the pathologic mechanism or molecular etiology. Another solution includes increasing the discriminatory precision of clinical classification, which requires knowledge of the phenotypic variations of mechanism-based subtypes.

Lurie also showed some effects of changing descriptive classifications; for example, after introducing the new classification on the analysis of respiratory mortality trends in England and Wales, the number of deaths assigned to the respiratory disease decreased by 22%. In a publication comparing two scoring systems for injury mortality, it was shown that changing classifications could affect the ranking of the causes of injury mortality, with consequences for public health policy. A study was presented dealing with human disease classification in the postgenomic era and with a proposed complex systems approach to human pathobiology, published in *Molecular Systems Biology* in 2007, where the authors stated that the contemporary classification of human disease has significant shortcomings as there is a lack of sensitivity in identifying preclinical disease and a lack of specificity in defining disease unequivocally. Lurie classified CEAP as a descriptive classification, where there is insufficient knowledge for a true clinical or research classification, and revisions will result in an additional time delay for evidence synthesis. Improvements in a descriptive classification do not serve the general trend toward a mechanistic classification of diseases.

Chronic venous insufficiency: different viewpoints?

Unusual etiology of recurrent varicose leg ulcer

Georges Tabet (Lebanon)

Six clinical cases of patients with posttraumatic arteriovenous fistula presenting with recurrent leg ulcers simulating varicose leg ulcers were discussed. Most of the patients had a delayed correct diagnosis and treatment, sometimes even for decades. Chronic leg ulcers may be the only symptom of a large posttraumatic arteriovenous fistula in young adults, but varicose leg ulcers are more frequent in the elderly. Other symptoms of an arteriovenous fistula could be congestive heart failure, varicose veins due to venous hypertension, skin pigmentation with or without eczema, and distal ischemia. The femoral artery is most often affected. Patients with an arteriovenous fistula are usually asymptomatic on presentation, and 30% to 70% had a delayed diagnosis. The late complications include arterial and venous dilatation, distal ischemia, venous congestion, and congestive heart failure. In the discussion, the surgical treatment of arteriovenous fistula involving control of arteries and veins above and below the fistula was mentioned, and a distinction was made between endovascular techniques by use of stent-graft coverage with embolization and open repair of the fistula. In conclusion, an accurate history, including any history of trauma in addition to standard examinations (clinical presentation, duplex investigation), should be carried out in patients with leg ulcers. Rare causes for leg ulcers should also be kept in mind to avoid disadvantages for the patients.

Which evaluation criteria for recurrent superficial venous insufficiency?

José Maria Escribano (Spain)

Varicose vein recurrence could reach 80% at the 10-year follow-up. These recurrences may be caused by surgical techniques (20% to 30%), a progression of the underlying disease, or neovascularization. The possible mechanisms involved in the development of recurrences include (i) "in situ" junction (12%), which was often due to a faulty surgical technique; (ii) neojunction (6%); (iii) cavernoma with stump (31%); (iv) cavernoma without stump (20%); cavernoma of the fossa poplitea (8%); and (v) telangiectasia after surgery (72%). Classification of recurrences was presented

related to surgical inaccuracies: (i) class A: default closing of the escape point; (ii) class B: drainage failure; and (iii) class C: the emergence of a new leak point. In conclusion, the majority of recurrences follow a defect in the closure of the escape point, which is linked to a technical error, but some recurrences, such as pelvic shunts, are technically difficult to prevent.

Minimally invasive procedure for pelvic leak points in women

Roberto Delfrate (Italy) and Claudine Hamel-Desnos (France)

Between January 2003 and August 2016, the incidence of inguinal and perineal leak point treatment in women was as high as 9.2% of all surgical treatments in Delfrate's department. The diagnosis in all patients was performed by duplex scan according to the anatomic, functional findings and systematization published by Claude Franceschi. Minimally invasive surgery was used on an outpatient basis under local anesthesia. A total of 250 surgical procedures with at least a 1-year follow-up were performed. Among all of the controlled pelvic leak points, no reflux redo was detected in 98% of the procedures, and no major complications occurred. Taking into separate consideration each pelvic leak point, the recurrence rate was 1.8% for the perineal point, 1.13% for the inguinal point, and 25% for the clitoridian point. These results show that a minimally invasive surgery for reflux with pelvic origin is possible. While the recurrences are low for the inguinal point and perineal point treatment, they are high for the clitoridian point. Therefore, accurate ultrasound assessment of each specific pelvic leak and a specific surgical technique are the keys for satisfactory outcomes.

For Hamel-Desnos, she treats perineal and vulvar varices by first conducting a pretreatment assessment that includes a clinical assessment and a duplex ultrasound of the iliac veins, lower leg veins, and perineal and vulvar varices. If there is no pelvic congestion syndrome and suspected pelvic or suprapelvic obstruction, sclerotherapy of varicose veins is done. Hamel-Desnos recommended using foam sclerotherapy, stretching the skin, and gently puncturing the vein, but she did not recommend using alcoholic solutions for vulvar aseptis. In conclusion, if there is no obstruction or pelvic congestion syndrome, she recommended sclerotherapy for pudendal and vulvar varices. In the case of a doubtful pelvic congestion syndrome, obstruction, or very large varices, further investigation and eventually embolization should be performed.

Complex chronic limb edema: a practical approach

The concept of complex chronic limb edema

Christine Moffatt (UK)

Moffatt explored the different types of patients suffering from chronic edema, discussed the difficulties in establishing the size and impact of the problem worldwide, introduced emerging evidence that chronic edema is a major public health problem, described an international response to the lack of epidemiology (LIMPRINT), and explored the results of the LYMPHORAC study that examined the cost of care to patients. Chronic edema is predicted to increase substantially due to demographic changes, such as an increasing elderly population, increasing obesity, decreased mobility, and the association with cancer and long-term conditions. Approximately 140 to 250 million people worldwide and about 3% of the western population

are affected with chronic edema. Chronic edema has a major financial impact in Europe. If chronic edema is treated early and properly, the health care costs could be reduced from 36.3 to 16.5 million euros annually, which is especially important when treating elderly patients (>80 years old) where the costs are 3 times greater than patients aged 65 to 74.

Edema is defined as the presence of abnormally large amounts of fluid in the intercellular tissue spaces of the body. Chronic edema is defined as chronic swelling lasting longer than 3 months that is not resolved by elevation or diuretics. Lymphedema is defined as a chronic, permanent swelling of a whole or part of a limb due, at least in part, to interstitial fluid accumulation and related damage to the lymphatic system and it can be subdivided as either primary or secondary. Moffatt stressed the importance of determining the correct diagnosis and reported that 70% of UK patients have no diagnosis or an incorrect diagnosis. The difficulties are due to the lack of an internationally validated method of classification. In primary care, different types of patients are seen, eg, patients with lymphovenous leg ulcers, obesity, immobility, chronic heart failure, complex chronic illness, and palliative patients. In a prevalence study conducted by Moffatt et al in southwest London in 2003, 833 patients had chronic edema in a population of 619 100. In a prevalence study in Derby City in 2013, 984 patients with chronic edema were identified in a population of 246 900. The difference in prevalence between these two studies in England was statistically significant, which can probably be explained by the different age/sex structures and identification through different specialists; however, a real difference in prevalence cannot be excluded. In the trial in Derby, 17% of the patients had primary chronic edema, 82% had secondary chronic edema, 31% had cancer, 67% had no cancer, and 2% had chronic edema and cancer, and 69% were obese or morbidly obese.

Subsequently, the LIMPRINT study, an ongoing international epidemiology study designed to define the size and impact of patients with chronic edema internationally, was introduced. The data collected from this study will be the largest epidemiology dataset on chronic edema. The study is assessing the prevalence of chronic edema and wounds in each country, the international profile of prevalence, and the impact of chronic edema on patients, the health care system, and society. The results of this study will contribute to a greater understanding of the deficits in health care delivery and provide information on reimbursements. The core tool of the trial that will be used for all patients and in all settings was validated through an international consensus and translated into different languages, and it included five modules: (i) demographics and disability; (ii) quality of life; (iii) details of swelling; (iv) wounds; and (v) cancer. Nine countries—Australia, Canada, Denmark, France, Ireland, Italy, Japan, Turkey, and the UK—are involved in the study.

Complex chronic limb edema: clinical implications and medico-economic consequences

Isabelle Quere (France) and Christine Moffatt (UK)

Quere presented the preliminary results of the LIMPRINT studies from the UK, Denmark, and France in hospitals. The study included 726 patients, and the prevalence results were as follows: in France, 48% had no chronic edema, 22% had wounds, 19% had chronic edema, and 11% had chronic edema and wounds; in the UK, 50% had no chronic edema, 21% had wounds, 17% had chronic edema, and 12%

had chronic edema and wounds; and in Denmark, 40% had chronic edema in the Bispebjerg Hospital and 35% had chronic edema in the Frederiksberg Hospital. Quere also reported the results of a study conducted between 2014 and 2015 that aimed to quantify and analyze the out-of-pocket expenses related to the treatment of lymphedema in France. The initial demographic, clinical, and socioeconomic data was collected from LIMPRINT. Of the expenditures, 33% were due to transport, 26% to medical devices, 13% to nursing, physiotherapy, and drugs, 9% to thermal therapy, and 26% to other expenses; 23% forgo medical care because of the costs. Total expenditures over 6 months were 1346±1320€, and the total out-of-pocket payments were 506±588€. In summary, the significant out-of-pocket expenses related to lymphedema treatment in France are mainly due to compression therapy devices and transport. Two ways to see change is by advocating for improved pricing and reimbursement policies and in improving the geographic distribution of reference centers.

Which varicose veins lead to venous ulcers (C₆)?

The epidemiological analysis

Eberhard Rabe (Germany)

Patients with varicose veins who have an elevated risk for venous leg ulcers should be selected for early varicose vein ablation. Patients who are at risk include C₂ patients with corona periphlebectatica, C₄ patients with eczema, lipodermatosclerosis, and white atrophy, and patients with popliteal reflux, obesity, and an ineffective calf muscle pump. Obesity and prolonged sitting must be avoided, and compression therapy is mandatory in patients at risk for a venous leg ulcer.

Importance of venous symptoms

Michel Perrin (France)

Perrin discussed the role of venous symptoms in the identification of patients at risk for developing a venous ulcer. No publication shows that venous symptoms, at any severity or intensity, can identify the patients with this risk. In addition, the international SymVein consensus document on venous symptoms was published in *International Angiology* in 2016. The aim of the consensus document was to describe and define venous symptoms, specify how these symptoms can be attributed to a venous cause, determine the pathology of the symptoms, establish a score dedicated to the symptoms, and determine which clinical examinations and investigations are useful to link symptoms to a venous cause.

The haemodynamic approach

André van Rij (New Zealand)

van Rij stated that, in severe clinical disease, the measurements of reflux and pressure are frequently abnormal, but the specificity is poor.

Duplex ultrasound: characteristics of disease severity, beyond "reflux"

Marianne De Maeseneer (Netherlands)

De Maeseneer focused on hemodynamic measurements (presence of reflux and its duration, peak reflux velocity, and recirculation index) and venous morphology investigations. Duplex ultrasound offers more possibilities than just looking at the

presence or absence of reflux, for instance, it can be used to quantify reflux or visualize the venous anatomy and morphology. The relationship with disease severity should be further investigated to increase our understanding of chronic venous disease, and to refine the selection criteria for treatment, targeting those with the largest risk for chronic venous disease deterioration.

Other anatomical factors: microvenules and perforators

André van Rij (New Zealand)

van Rij presented a study describing the presence of microvalves in the very small veins of the skin, which may be critical to whether skin changes occur with venous insufficiency. The concept may explain why some people with long-standing varicose veins do not develop venous ulcers. In addition, degenerative changes in the network of very small veins in the skin of the leg may be related to the appearance of reticular veins, corona phlebectatica, and venous flares. These degenerative changes occur without varicose veins, but are much worse when they occur together. Valvular incompetence could occur independently in small superficial veins in the absence of reflux within the great saphenous vein, small saphenous vein, and the major tributaries. He has shown that, once there is incompetence in third generation "boundary" microvalves, reflux can extend into the microvenous networks in the skin. These effects are markedly worse in the presence of great saphenous vein or small saphenous vein incompetence. It is possible that degenerative changes with valve incompetency are required in larger proximal vessels and small superficial veins, particularly at the "boundary" valves, for the severe skin changes in venous insufficiency to occur.

What can we learn from ultrasound of the skin?

Alberto Caggiati (Italy)

Currently, ultrasonography is used only to designate the location and pattern of venous lesions; however, modern ultrasound devices provide an excellent morphological evaluation of the cutaneous and subcutaneous layers. Ultrasonography refines the visual evaluation of skin changes in legs with venous disorders, and it may reveal changes that are not highlighted by clinical examination. Some of these changes could require further investigation because they have not yet been explained or described. Accordingly, skin sonography may contribute to a better grading of venous disease severity. In particular, in C₂ legs, ultrasound evidence of skin changes should be considered to identify those legs in which varicose veins are more than just a cosmetic problem.

How to detect early skin changes?

Patrick Carpentier (France)

Early clinical detection of skin changes would be a major step forward in the evaluation of patients with chronic venous disease because ulcers occur in the altered skin of the lower limbs, which are preceded by induration, pigmentation, and even corona phlebectatica. Early detection remains an unmet challenge due to the problems with specificity, the variability of measurements, and the difficulty in establishing diagnostic thresholds. Carpentier proposed ankle capillaroscopy as a good and feasible tool for the early detection of microvascular skin changes.

Multifactorial approach for treating leg ulcers

New trends in the epidemiology of leg ulcers

Patricia Senet (France)

The available information on the epidemiology of leg ulcers is insufficient, and the existing data is of variable quality and comes from social, economic, and epidemiologic studies published in the USA and some Northern European countries (Sweden, Germany, and the UK). According to the data, the prevalence of all leg ulcers (not just venous ulcers) is estimated to vary between 0.045% and 0.7%, without a real decreasing trend, although older studies had reported a prevalence of 1%. This prevalence increases with age, reaching 2% to 4% in people over 65 years old. A German study (2010-2012) showed that there was a decrease in venous leg ulcers, but an increase in arterial or mixed leg ulcers, which is similar to data from a Swedish registry. There is a female predominance for leg ulcers (60% to 75%), the average age increased to 70-75 years, and the duration of venous leg ulcers and their relapse rates remain high. According to studies conducted in Germany, Italy, the UK, and the USA, the presence of ulcers over 1 year is registered in 24% to 54% of cases; however, in one-third of patients, the leg ulcer is present for over 2 years. The average size of ulcerations is large (35 to 45 cm²).

Patients with leg ulcers have significant comorbidities because 29% to 45% are obese with a BMI >30 (particularly patients with venous leg ulcers), 60% to 80% have high blood pressure, and 30% to 40% have diabetes. A UK study showed that patients frequently come from modest socioeconomic backgrounds, and leg ulcer etiology is constantly changing. The studies on >30 000 German patients and >1000 Italian patients showed a decreasing trend of venous leg ulcers (45.5% to 55% vs the 60% to 80% observed previously), concomitant with an increase in arterial leg ulcers (15%) and mixed leg ulcers (17.5% to 25%). Mixed ulcers or rare etiology leg ulcers represent 10% to 20% of all ulcers. The changing etiology may reflect a real evolution in the etiology or it may be due to a more accurate diagnosis of the leg ulcer etiology. There are no recent studies published regarding the etiology of venous leg ulcers. The data published in 2010 in the *Journal of Vascular Surgery* showed a network of deep vein involvement in 47% to 60% of venous leg ulcers (one-third of patients had no known history of deep vein thrombosis) and superficial venous insufficiency in 40% to 50% of cases. The life expectancy of patients with venous leg ulcers is identical to that of the general population.

According to data from large clinical trials and Cochrane reviews, the prognosis for venous leg ulcers is a median healing rate of 100 days; 60% to 80% of venous leg ulcers close after 6 months and 65% to 80% in 1 year; 12% to 50% of venous leg ulcers recur at 12 months; in 80% of cases, the venous leg ulcers are small (area <10 to 15 cm²). Data from real life (Germany, Sweden, and France) show an average healing duration (not median) of 210 days in France and 139 days in Sweden (the country that has a proactive policy for screening, prevention, and treatment of venous leg ulcers). Complete healing of the venous leg ulcers is 66% at 2 years.

The costs related to the care of patients with leg ulcers are large and growing, representing about 1% to 2% of the annual health care budget in developed countries. In Germany, the costs related to leg ulcers are, on average, 9570 euros/patient/year, which is higher if the patient is hospitalized. In Sweden, the median

reduction in healing from 160 days to 100 days resulted in a significant decrease in the treatment cost from 4000 euros/patient in 2009 to 2134 euros/patient in 2012. New cell therapies for leg ulcers may seem expensive initially, but later they reduce the healing period, which leads to costs that are comparable with standard therapies.

Quality of life is impaired in patients with leg ulcers. A recent UK study showed that the psychosocial impact of leg ulcers is very high: 24.3% had depression, 17.5% anxiety, and 8.4% suicidal ideas. Leg ulcers are a frequent, severe, and costly pathology that can be improved by a correct and early diagnosis, reducing the time of healing, and preventing complications, especially infections.

Major etiological factors: from scientific data to clinical practice

Philippe Leger (France)

There are many causes of skin trophic disorders (erosions or ulcers) in the lower limbs; the most common leg ulcers are venous leg ulcers, arterial leg ulcers, and mixed leg ulcers. Necrotic angiodermatitis is a rare vascular leg ulcer that has well-defined clinical and pathophysiological features; however, it should not be confused with the rarer nonvascular ulcers, leading to genuine problems for diagnosis and treatment. These ulcers can occur in the following pathologies: pyoderma gangrenosum, skin cancers, pressure sores, skin infections (eg, tuberculosis, streptococcal ulcers, ecthyma, and skin leishmaniasis), drug rashes, some immunological diseases (eg, disseminated lupus erythematosus, scleroderma, and periarteritis nodosa), hemopathies, or pathomimias. In these cases, a skin biopsy is mandatory. Many factors influence the rate of healing of these leg ulcers, including malnutrition, some medications, additional local infections, diabetes, etc. The same patient may have a venous leg ulcer, diabetes, malnutrition, and a dysimmune disease; therefore, it is important to look at, identify, and treat leg ulcers starting from the existing algorithms for diagnosis and treatment, and the specifics of each patient. In conclusion, Leger proposed a set of seven questions that clinicians should answer when confronted with a new leg ulcer case: (i) is there a contributing low arterial pressure?; (ii) is there venous hypertension?; (iii) is there a problem of local pressure on the skin?; (iv) is there a secondary or superinfection?; (v) are there any associated factors (diabetes, drugs, etc)?; (vi) are there any nutritional problems?; and (vii) is there an atypical aspect of ulceration (pyoderma gangrenosum, skin cancer, angiodermas, pathomimias)?

Leg ulcer patient pathway: wound healing center

Damien Barcat (France)

Chronic ulcers are a public health problem due to their increased prevalence and incidence and the high costs. In some countries, even France, there are wound healing centers, where patients with chronic vascular ulcers are being cared for and monitored. In France, there are still controversies regarding the internal organization and functional procedures in these centers, the center's financial support, and the assessment of the results. Due to the increasing number of patients with chronic ulcers and the long and difficult journey of patients from one doctor to another, the number of these wound healing centers should increase in the future, and the different specialists should work as a coordinated team. The results must be quantified and published to obtain an accurate and realistic picture regarding the diagnosis, treatment, prognosis, monitoring, and costs for patients with chronic ulcers. These medical structures must be organized, validated, and financed according to the real needs of each country.

Leg ulcer patient pathway: the wound expert nurse

Patricia Bocquet (France)

The care of chronic ulcers, including leg ulcers, means the intervention of experienced or expert nurses in the field. Expert nurses have a special theoretical and practical education, and they work under the direct coordination of a complex medical team (dermatologist, vascular physician, vascular surgeon, diabetologist, etc). Following a first examination by the doctor, the nurses have an active role in the global evaluation of the healing process (ulcer etiology, factors delaying healing, prognosis), implement the therapeutic plan issued by the medical team, and monitor the patients. They offer support to the different medical teams in the hospitals, for ambulatory patients, or at patients' homes. They are involved in telemedicine, and they make sure that patients with chronic ulcers have good hygiene. They are also involved in the correct application of topical treatments and use of medical devices for ulcer healing according to the indications. In the future, the role of these expert nurses will increase, leading to a better management and a decrease in the costs of caring for patients with chronic ulcers.

Place of the vascular physician in the management of patients with leg ulcers

Christine Jurus (France)

Vascular physicians who are managing patients with chronic wounds, including those with leg ulcers, belong at the center of a complex medical team, preferably in wound healing centers. The reasons for this are that 90% of chronic leg ulcers have a vascular cause and the physician can establish the etiology of these ulcers by complete functional explorations, both on the arterial and the superficial and deep venous hemodynamics. Following these investigations, the vascular physician will issue a therapeutic strategy adapted to each patient. Nevertheless, the vascular physician must work in collaboration with a multidisciplinary team to improve therapeutic results because the incidence of chronic ulcers of other etiologies (infectious, inflammatory dermatological diseases, neoplasia, etc) is increasing.

Chronic venous disease: varicose veins

Results of the prospective noncomparative study of endovenous laser ablation of the saphenous vein more than 2 cm in diameter

Alexey A. Fokin and Denis A. Borsuk (Russia)

This study aimed to determine if veins larger than 20 mm could be ablated. The authors investigated both anatomic and hemodynamic results. They treated 91 patients with saphenous veins that had a mean diameter of 28 ± 4.5 mm using a 1470 nm laser. In the midterm follow-up (total follow-up time, 157 ± 47 days), there was a 98.9% occlusion rate. For this procedure to be successful, it is important to place the fiber in the center of the vein lumen.

Surgical procedure for incompetent perforators: VANST technique

Valerian Ciubotaru (Romania)

The VANST technique (Varices' Ambulatory Non-stripping Surgical Therapy) relies on the assumption that excluding the failing perforators would eliminate the need for ablating the saphenous vein. The procedure necessitates the mapping and ligation of the failing perforators. A 5-year follow-up of 1279 cases revealed that

recurrence occurred only in 89 of the cases. This approach can be applied to a great spectrum of cases, such as axial insufficiency of the great saphenous vein and the small saphenous vein, CEAP classes with more than 4 varicose veins, and recurrent varicose veins. It also obviates the need for postoperative compression, provides minimal invasiveness, and it has ambulatory advantages.

Intraoperative sonography in open venous surgery

Simon Julinek (Czech Republic), Ivan Maly, and Daniela Klein

Intraoperative sonography facilitates the location of optimal puncture sites, determines the diameter of the saphenous vein, assists in the application of a tumescent solution during endovenous surgery, and helps find the tip of the stripper during high ligation of the saphenous vein with local anesthesia. It also protects the surgeon from accidentally treating the sufficient great saphenous vein instead of an incompetent accessory saphenous vein.

Vascular gel model for central venous catheterization

Pongpol Sriphan (Thailand), Piyanut Pootracool, Wiwat Tirapanich, Sapon Jirasiritum, Surasak Leela-Udomlipi, Suthas Horsirimanont, and Nutsiri Kittitiratong

The aim of the study was to develop a homemade vascular gel model for an ultrasound-guided puncture that would be comparable to the standard phantom model to lower costs. The first phase of the study was to develop a homemade gel model. The second phase of the study was to compare the gel model with the standard phantom model used for trainees. The images obtained using the homemade gel models were of high-reliance quality and similar to the standard phantom model, and the gel model is cheaper due to the easy preparation using readily available materials.

An investigation of the relationship between exercise, range of ankle joint movement (ROM) and venous leg ulcer (VLU) healing

Omar Mutlak (UK), Mohammed Aslam, and Nigel Standfield

Mutlak reported the results on the relationship between exercise, the range of ankle joint movement, and venous leg ulcer healing. Two groups of patients were compared: group 1 (n=20) performed exercise only at home and group 2 (n=20) performed exercise at home in combination with compression therapy (short-stretch bandages). The range of ankle joint movement and ulcer size were assessed at baseline and after 3 months of regularly conducted exercises (10 dorsiflexions per hour). At the end of the study, the range of ankle joint movement increased significantly in both groups to the same extent compared with baseline, and ulcer size decreased to a greater extent in the compression group. In conclusion, exercising regularly at home increased the range of ankle joint movement, and it may play a positive role in ulcer healing in patients with venous leg ulcers.

A body weight transfer manoeuvre with minimal ankle movement significantly outperforms the tip-toe manoeuvre in assessing calf muscle pump function

Christopher R. Lattimer (UK), Evi Kalodiki, Claude Franceschi, and Fausto Passariello

This prospective study analyzed the body weight-transfer maneuver with minimal ankle movement vs the tiptoe maneuver on calf muscle-pump function. Three different pumping performances were tested with air-plethysmography: 3 tiptoe movements, 3 ankle dorsiflexion, and 3 body weight-transfer maneuvers. The results showed higher pump efficiency after weight transfer (60%) compared with tiptoe (43%) and dorsiflexion (38%). The isometric weight transfer maneuvers have a better pumping action than ankle maneuvers. Walking exercises should be recommended for patients with chronic venous disease rather than just ankle movements.

Utilising gravitational manoeuvres with a tilt-table to assess a gravitational disease

Christopher R. Lattimer (UK) and Erika Mendoza

In this presentation, the results of a study on gravitational maneuvers on the tilt-table for assessing the effect of gravity on chronic venous disease were reported. The study aimed to quantify gravitational venous drainage in three Trendelenburg positions (standing, reclining, and head down) in 3 groups of 11 patients (healthy, patients with venous obstruction, and patients with venous reflux). Air-plethysmography calf volume changes were continuously recorded. The results showed that gravitational maneuvers on a tilt-table and venous drainage index could be used as noninvasive screening for obstruction, selection for stenting, and stent monitoring.

Correlation between reflux volume of the great saphenous vein and severity of chronic venous disease in patients with primary varicosities

Kirill Lobastov (Russia), A. Vorontsova, A. Bargandzhiya, Victor Barinov, Leonid Laberko, Valeriy Boyarintsev, and Grigoriy Rodoman

Lobastov presented the results of a study correlating reflux volume of the great saphenous vein and severity of chronic venous disease in patients with primary varicosities. In this observational cross-sectional study, 80 patients underwent duplex ultrasound investigations where reflux volume was measured, and both clinical and quality of life parameters were assessed. There was a significant weak correlation between reflux volume and clinical, etiology, anatomy, pathophysiology (CEAP) class, venous clinical severity score (VCSS), and quality of life scores (CIVIQ, VEINESS). The reflux volume was significantly higher in the most severe classes.

Results of endovenous radiofrequency thermal ablation with and without high ligation in comparison with high ligation and stripping in for treatment of great saphenous varicose veins

NS Abushov (Azerbaijan), EJ Zakirjaye, MM Karimov, ZM Aliyev, FE Abbasov, and GN Abushova

In this nonrandomized, observational study, 166 patients were divided into 3 groups and evaluated (75 to high ligation and stripping; 61 to endovenous radiofrequency thermal ablation without high ligation, and 30 to endovenous radiofrequency thermal ablation with high ligation). The patients receiving endovenous radiofrequency thermal ablation with or without high ligation could return to habitual activities earlier, and they had a painless postprocedure period and a better cosmetic effect compared

with patients receiving high ligation and stripping. High ligation and stripping should only be used in selected patients with a large great saphenous vein diameter, a proximal aneurysm, and/or superficial thrombophlebitis.

Early patency and feasibility of cutting balloon treating central vein stenosis in hemodialysis patients

Jakchai Boonyavanich (Thailand), Wiwat Tirapanich, Wiwat Tirapanich, Sapon Jirasiritum, Surasak Leela-Udomlipi, Piyanut Pootracoool, and Suthas Horsirimanont

Central vein stenosis in hemodialysis patients can be treated with angioplasty together with stenting, although there is a high incidence of restenosis. This study compared cutting to noncutting balloon angioplasty on the success rate (primary outcome) and the restenosis rate (secondary outcome). The hypothesis was that the low pressure used in the cutting balloon technique would result in less strain on the vessel wall, which would reduce any intimal proliferation and lower the restenosis rate. Successful treatment was defined as a residual stenosis less than 30%, resolution of upper extremity symptoms, and an improvement in elevated venous pressures during dialysis. The cutting balloon technique necessitated a lower inflation time. The between-group success rates were similar ($P=0.132$) and the restenosis rates were not statistically different ($P>0.05$). In conclusion, although cutting balloon angioplasty seemed safe, the results did not reach statistical significance compared with noncutting balloon angioplasty.

Shared decisions in vascular medicine

Shared decision making: concept, evidence and development in France

Nora Mounjid (France)

Although shared decision-making is an important aspect in empowering patients in France, it is not as developed as either patient information, which is a regulatory requirement, or therapeutic education. Shared decision-making is a process where the health care professional and the patient exchange information to achieve an agreement regarding a specific decision. Consequently, the exchange of information has to be bilateral and the decision should result from an interactive deliberation. There are several stages in the process: (i) define the situation; (ii) verbalize that there is a decision to make; (iii) present the options; (iv) discuss the potential pros and cons; (v) identify the patient's preferences; (vi) be sure to have the correct understanding of the patient; (vii) make a decision and be capable of anticipating the next steps. Studies have shown that a practice based on shared decision-making in prevention, primary care, or chronic disease management improves the safety and quality of care, the agreement and communication between health care professionals and patients, and the rights and knowledge of the patients, and it may reduce costs in certain situations. Some of the challenges for the future include: (i) making sure that everyone is talking about the same concept when discussing shared decision-making between professionals and patients; (ii) be able to develop multidisciplinary projects for intervention and implementation; (iii) determine how to mobilize health care professionals, decision-makers, and public funders.

The patient's perspective

Eliane Rosay (France)

Eliane Rosay described her expectations when being treated for a disease. She detailed the problems she had when she developed primary lymphedema during her pregnancy, 30 years ago. She emphasized that she had wanted to be treated as a person with a disease instead of a disease. As such, she said she felt abandoned, and therefore, she did not comply with the recommended treatments. Finally, she discovered the multidisciplinary team in Paris at the Hôpital Cognacq-Jay, where everybody was keen on explaining all available techniques in each context and understanding each patient's particularities. She concluded by stating that the fundamental aspect of making decisions is that health care professionals should look at the patients as humans and not just as a disease.

Best papers of the ESVM 2016 meeting

Hedgehog signaling in human brain arteriovenous malformations

Roberto Pola and Paulo Tondi (Italy)

Hedgehog proteins are morphogens that play an important role in angiogenesis and vascular development. Recent findings suggest a role for hedgehog signaling in the pathogenesis of brain arteriovenous malformations. This study evaluated the hypothesis that an angiogenic growth with the characteristic features of arteriovenous malformations may be obtained by activating the hedgehog-signaling pathway and investigating the expression levels of the various components of the hedgehog-signaling pathway in humans with arteriovenous malformations. Among the various components of the hedgehog pathway, the hedgehog inhibitory protein was significantly and constantly downregulated in all human brain arteriovenous malformation specimens compared with controls. When pellets containing Sonic hedgehog were implanted into the cornea of ephrinB2-lacZ mice, the resulting angiogenic process was characterized by the growth of both arterial and venous vessels that were interconnected with a complex set of arteriovenous shunts without an interposed capillary bed, as has been seen with arteriovenous malformations in humans. These findings show that the hedgehog inhibitory protein is downregulated consistently and significantly in brain arteriovenous malformations. Moreover, the activation of the hedgehog signaling pathway results in a robust angiogenic process that is characterized by the growth of both arteries and veins, with several arteriovenous shunts, which mimic the angle of abnormal vessels observed in human arteriovenous malformations. Taken together, these data strengthen the hypothesis that the hedgehog pathway might play a role in the pathogenesis of arteriovenous malformations, with potentially important clinical implications.

Vascular remodeling in hypertensive patients with well controlled BP values

Massimo Puato and Giacomo Buso (Italy)

This study evaluated the impact of well-controlled blood pressure levels on structural and functional properties of arteries in hypertensive subjects. The authors studied 80 patients who had either been kept on pharmacological treatment (n=55) or lifestyle modification (n=25) for at least 12 months to maintain their target blood pressure. The mean carotid intima-media thickness and the maximum intima-media thickness were assessed in several carotid artery segments bilaterally using a B-mode ultrasound

evaluation. Moreover, endothelial function was evaluated using postocclusion flow-mediated dilation of the brachial artery and arterial elastic properties were evaluated by assessing carotid distensibility and carotid compliance. A total of 40 normotensive subjects, who were paired for age and sex, served as controls. In well-controlled hypertensive patients, proatherogenic remodeling was still present in normotensive controls. Structural impairment (intima-media thickness) was mainly dependent upon age, whereas functional impairment (flow-mediated dilation) was related to cholesterol levels. Moreover, carotid elasticity was impaired in hypertensive subjects. Therefore, the "pseudo-normalization" of the blood pressure levels does not seem to be sufficient to eliminate the hypertensive status that contributes to functional and structural impairment.

Thromboembolic diseases

Endovascular treatment of venous thromboembolic disease: state of the art

Endovascular treatment of acute DVT

Anthony Comerota (USA)

The results of anticoagulation therapy for deep vein thrombosis are still unsatisfactory. After 5 years, there is a high level of valvular dysfunction (95%), venous hypertension (95%), obstructive iliac vein lesions (70%), calf muscle dysfunction (50%), and, finally, venous claudication and ulcers (30%). Direct venous thrombectomy can significantly improve the result of deep vein thrombosis treatment. It is characterized by significantly improved patency, lower venous pressure, less leg swelling, and fewer postthrombotic symptoms compared with anticoagulation (Level I data). The level of intramuscular pressures (a surrogate for venous pressure) decreased from 38 mm Hg to 12 mm Hg after direct venous thrombectomy. Therefore, if we have the contraindication to thrombolysis, we perform thrombectomy.

Another method that improved the treatment results is catheter thrombolysis, which improved health-related quality of life (71.4 vs 55.8; $P<0.006$) in patients with iliofemoral thrombosis. According to the results of randomized trial by Elsharawy et al (*Eur J Vasc Endovasc Surg.* 2002;24:209-214), the rate of patency was high after catheter thrombolysis vs anticoagulation (72% vs 12%; $P<0.0001$) and the rate of normal valve function was 89% vs 59% ($P=0.041$). According to the CaVenT study (*Lancet.* 2012;379:31-38), the development of postthrombotic syndrome with catheter thrombolysis was significantly better than anticoagulation therapy (iliofemoral thrombosis patency, 66% vs 47%; postthrombotic syndrome rate after 24 months, 41% vs 56%). Compared with catheter thrombolysis, pharmacomechanical thrombolysis can improve the result of treatment because this technology provides a higher rate of thrombolysis (92.3% vs 84.3%), requires less recombinant tissue plasminogen activator (33.5 vs 59.3), reduces the treatment time (24.2 vs 55.4), and results in more competent valves (57% vs 43%). The rate of residual thrombus is a significant predictor of deep vein thrombosis recurrence after all types of thrombolysis. So, in the group with a residual thrombus <50% the recurrent rate was 5%; it was 50% for the group with a residual thrombus rate >50%. In conclusion, the strategy of early thrombus removal is a validated and evidence-based method for treating acute deep vein thrombosis.

Endovascular treatment of obstructive DVT sequelae

Frederic Thony and Caroline Menez (France)

Endovascular treatment is the first-line treatment for postthrombotic syndrome. The fibroblastic invasion period occurs between 7 days and 1 month, and the period of recanalization, fibrosis, and retraction of thrombus occurs between 1 month and 6 months. The goals of treating an iliofemoral obstruction are to improve or heal the postthrombotic syndrome, to lower the risk of deep vein thrombosis recurrence, and to restore venous patency. In recent guidelines (AHA 2015, ESVS 2015) for severely symptomatic patients (or relevant postthrombotic syndrome) with iliac vein or vena cava occlusion, surgery or percutaneous endovascular recanalization may

be considered (class IIb, level C) for every patient who suffers from clinical symptoms related to venous sequelae and who would like improved or restored venous access.

Before treatment, clinical disability needs to be measured and a venous duplex examination needs to be performed with an estimation of the type of lesion (obstruction/synechia/compression), the extent of obstruction (popliteal-femoral evaluation), concurrent reflux, and cartography for treatment planning (venous access/landing zone). After a CT scan, Thony uses the grading of venous sequelae upstream of the common femoral vein. The three main veins of the thigh are graded from 0 to 2 (0, the vein is totally occluded; 2, large normal vein). According to this scale, he uses the three values to quantify venous sequelae as grade 0 (6 points; normal vein), grade 1 (4 to 5 points; minor sequelae), grade 2 (2 to 3 points; severe sequelae), and grade 3 (0 to 1 point; major sequelae). For the procedure, Thony prefers using the jugular vein access (80%), a 0.035 hydrophilic guidewire, and nitinol stents (with a high radial force for the common iliac vein and inferior vena cava and with high flexibility in the femoral vein). The patients receive aspirin (75 mg) for 1 month and anticoagulation treatment for 6 months. Thony also prefers using an intermittent pneumatic compression for the first night and compression stockings for 6 months.

A review of the literature shows a technical success rate of 97%, a major complication rate of 0% to 8.7%, a primary patency rate of 32% to 99%, a secondary patency of 66% to 96%. The treatment appears promising and safe; therefore, it should be considered as a treatment option while the evidence base is improved. According to the Thoney's experience, the patency rate was high depending on values of venous sequelae. After a 24-month follow-up, the primary and secondary patency rates for the different grades of sequelae were as follows: grade 0, 87% to 100%; grade 1, 82% to 100%; grade 2, 58% to 90%; and grade 3, 8% to 63%. The author concluded that treating a deep vein thrombosis sequelae with an endovascular treatment is a highly efficient and long-lasting treatment. Patency correlated with the severity of the sequelae upstream of the common femoral vein, and concurrent deep or superficial venous insufficiency and extensive sequelae worsen the clinical results. The indication for endovenous treatment should be extended to every patient suffering from symptoms related to postthrombotic venous sequelae.

Vena cava filters

Patrick Mismetti (France)

According to the US Nationwide Inpatient Sample, between 1999 and 2010 in the US, there were 556 658 patients with a pulmonary embolism and vena cava filters were inserted in 17% of these patients. According to the Prospective European Registry from 2001 to 2012, among the 40 142 patients with a pulmonary embolism, only 1% received vena cava filters. According to the US National Register, there were no differences in the in-hospital mortality between patients with or without vena cava filters (mortality rate, 7.2% vs 7.9%). The use of vena cava filters in patients with a venous thromboembolism and no contraindications to anticoagulants increases the mortality rate (4.5% vs 3.5%) and significantly elevates deep vein thrombosis recurrence after 1 year (5.4% vs 3.7%). However, among the group of patients with unstable pulmonary embolism receiving fibrinolytic therapy, the mortality rate was lower after vena cava filter placement (7.6% vs 18%; $P < 0.001$).

The PREPIC 1 study (*N Engl J Med.* 1998;338:409-415) demonstrated the negative effect of permanent vena cava filters for pulmonary embolism incidence (15.1% with vs 6.2% with no vena cava filter; HR, 0.37; 95% CI, 0.17-0.79) and for recurrent deep vein thrombosis (35.7% vs 27.5%; HR, 1.52; 95% CI, 1.02-2.27). The PREPIC 2 trial on the effects of retrievable vena cava filters showed that pulmonary embolisms at 3 months, pulmonary embolisms at 6 months, and death at 6 months were high, but not significant, in the group receiving vena cava filters. The conclusion was that there was no apparent benefit with the use of vena cava filters in stable pulmonary embolism patients without any contraindication to anticoagulants. However, the use of vena cava filters in venous thromboembolism patients with active bleeding (temporary or permanent contraindications to anticoagulants) significantly decreased mortality (9.5% vs 11.5%; $P < 0.003$; HR, 0.68; 95% CI, 0.52-0.88).

In conclusion, vena cava filters are contraindicated in stable pulmonary embolism patients. For patients with an unstable pulmonary embolism, we can use vena cava filters with uncertain benefit; however, there is a clear benefit in the cases of recurrent venous thromboembolism despite adequate anticoagulation therapy and patients with bleeding and contraindications to anticoagulants. However, if the contraindications to anticoagulants are due to surgery, then vena cava filters are not beneficial. The use of retrievable vena cava filters needs an experienced multidisciplinary team to manage indications and retrieval.

Treatment of post-PE pulmonary hypertension

Helene Bouvaist (France)

Surgical pulmonary endarterectomy is the preferred treatment for chronic thromboembolic pulmonary hypertension, according to the 2015 ESC/ERS guidelines. However, 40% to 50% of such patients are inoperable due to distal lesions or comorbidities. In addition, surgical mortality is $> 10\%$ if pulmonary vascular resistance is > 15 WU, and residual chronic thromboembolic pulmonary hypertension occurs in 25% of patients. Balloon pulmonary angioplasty is a good method to treat chronic thromboembolic pulmonary hypertension. It is characterized by a decrease in mean pulmonary arterial pressure from 45.4 mm Hg to 24.0 mm Hg and a decrease in pulmonary vascular resistance from 942 to 327 dyne-sec/cm². Bouvaist performs angioplasty under local anesthesia using a femoral access, an international normalized ratio of 2 to 3, and a bolus injection of unfractionated heparin 1000-2000 UI, and she uses a 0.014 hydrophilic wire and coronary/renal angioplasty balloon and 2 to 8 sessions for each patient with duration of 1.5 to 2 hours per session. The preliminary results (33 patients at 12 months) were good: the pulmonary vascular resistance decreased from 9 to 4.94 WU, mPAP decreased from 45 mm Hg to 34 mm Hg, and, out of 147 procedures, there were 6 minor hemoptysis and 2 pulmonary injuries. These results show that interventional balloon pulmonary angioplasty may be considered in patients who are technically inoperable or carry an unfavorable risk-benefit ratio for pulmonary endarterectomy (IIB, C). The ongoing RACE French multicenter (23 centers) study that is comparing the effects of riociguat balloon pulmonary angioplasty on pulmonary vascular resistance after 6 months for inoperable chronic thromboembolic pulmonary hypertension). The results of this trial will clarify the long-term prognostic effect of balloon pulmonary angioplasty.

Cancer-associated thrombosis: realities, actualities, and perspectives

Cancer and thrombosis: an intimate and dynamic relation

Anna Falanga (Italy)

The strong association between cancer and thrombosis was recognized for the first time in Paris by Armand Trousseau in 1865. Today, we know that approximately 20% of all venous thromboembolism cases occur in the population affected by cancer. Cancer increases the risk of thrombosis, and vice versa, thrombosis or hypercoagulation can affect cancer progression. Cancer-associated thrombosis has unique and multifactorial pathogenic mechanisms. Cancer tissues can activate blood clotting using three main routes: (i) expressing procoagulant factors in tumor cells, including tumor factor, tumor factor bearing microparticles, and heparinases; (ii) expressing adhesion receptors, which platelets and leucocytes can use to adhere to the endothelium; and (iii) releasing soluble mediators, such as inflammatory cytokines (IL-1 β , TNF- α , VEGF) and proangiogenic factors (*Best Pract Res Clin Haematol.* 2009;22:49-60). Different tumor cell lines can activate coagulation by preferentially using one or more of these routes.

Tumors also differ in their capacity to express procoagulant activities (*Haematologica.* 2012;97:1173-1180). An important step in the last 15 years has been the recognition that tumor genetic programs drive the activation of clotting proteins so that oncogenes can upregulate the expression of procoagulant proteins in tumor cells. For example, patients with acute promyelocytic leukemia have a strong activation of blood coagulation with very dramatic thrombotic and bleeding manifestations. The mortality rate of this disease is mainly due to coagulopathy more than to leukemia per se, and it is recognized as one of the most curable forms of leukemia. In acute promyelocytic leukemia, the typical PML/RAR α genetic lesion is associated with overexpression of anticoagulant activity (ie, tumor factor) and the occurrence of coagulopathy. During differentiation therapy with all-trans-retinoic acid (ATRA), which targets the molecular lesion, the bone marrow cell procoagulant activity expression decreases and the coagulopathy is simultaneously resolved (*Semin Thromb Hemost.* 2008;34:204-210).

Some coagulant activities are important for tumor biology and tumor growth and dissemination. Indeed tumor cells can attach to the endothelium by receptors and attract leucocytes and platelets, but they can also release cytokines, thus activating the endothelium and causing localized clot activation, microthrombi formation, and fibrin deposition. All of these mechanisms can help tumor cells extravasate to form a distant metastasis (*Lancet Oncol.* 2005;6:401-410). Tissue factor (TF) and TF-bearing microparticles are the links between the blood coagulation cascade and cancer. The transmembrane glycoprotein, expressed by extravascular cells, is the main physiological activator of coagulation. TF is an important risk factor for venous thromboembolism in cancer patients, and its cellular properties play a pivotal role in primary tumor growth and metastasis in a broad set of cancer types (*Semin Thromb Hemost.* 2015;41:747-755). In addition, malignant cells produce microparticles (*Blood.* 2005;105:1734-1741) that can activate coagulation, and therefore, supports in vivo thrombosis (*J Thromb Haemost.* 2008;6:1517-1524; *Am J Haematol.* 2014;89:68-73).

The hypercoagulable state in cancer patients is a subclinical condition characterized by an alteration in thrombotic markers, without overt thrombosis. Clotting abnormalities increase at the start of chemotherapy and with tumor progression.

Measuring biological markers of thrombosis can have important clinical utility in predicting the occurrence of thrombosis, cancer survival, and cancer diagnosis. The occurrence of a venous thromboembolism in cancer patients may have important clinical implications, including an increase in treatment failure rates and quality of life deterioration in long-term cancer survivors. Therefore, identifying the risk factors for venous thromboembolism and establishing an effective preventive strategy are necessary to avoid life-threatening complications among cancer patients. The venous thromboembolism predictive value of circulating thrombotic biomarkers in cancer patients is under active investigation. Prospective studies are warranted to evaluate their clinical utility in identifying cancer patients who are at a high risk of thrombosis and who can benefit from thromboprophylaxis (*Blood*. 2013;122:2011-2018). A novel and promising approach for the stratification of patients according to their thrombosis risk include risk assessment models that have both clinical parameters and biomarkers.

Clinical prediction rules are appealing because they offer several potential benefits for practitioners, patients, and the health care system, such as a reduction in clinical uncertainty at the bedside and an improvement in the quality of life for patients. The most validated model is the Korana score, but scientists are trying to improve the quality of this score by adding biomarkers to clinical and standard laboratory parameters (*Blood*. 2010;116:5377-5382). For instance, adding D-dimer and soluble platelet selectin improves the score, which allows five levels of risk to be identified, thus distinguishing the intermediate risk patients better. The addition of ADAMTS-13 activity and F1+2 levels to Khorana or cancer-associated thrombosis scores considerably increases the predictive value of venous thromboembolism (*Thromb Haemost*. 2016;14:306-315). Therefore, the ASCO guidelines recommend that cancer patients be assessed for venous thromboembolism risk at the time of chemotherapy initiation and periodically after that. Individual risk factors, such as biomarkers or the cancer site, do not reliably identify cancer patients at high risk of venous thromboembolism. Risk assessment should be conducted based on a validated risk assessment tool, especially in the outpatient setting.

Prevention of CAT: a challenge for the personalized medicine

Grigorios Gerotziapas (France)

The major determinants of the risk of cancer-associated thrombosis include the type of cancer, the time from the diagnosis, the treatment, and the stage of the disease. In addition, venous thromboembolism risk factors not related to cancer, such as underlying comorbidities, hospitalization, and genetic variability polymorphisms, have to be considered in these patients. The incidence of symptomatic cancer-associated thrombosis differs in different cancer types and different stages of the disease. For instance, breast cancer, which is considered a cancer with a low-risk of venous thromboembolism, has almost the same level of risk as pancreatic cancer, which, in the metastatic stage of the disease, is known as a high-risk cancer. In addition to the increased risk according to the metastatic stage, the time from the cancer diagnosis is another important factor to be considered because the greatest number of the venous thromboembolism events occur in the first 3 to 6 months after diagnosis. A similar "critical interval" can be observed in lung cancer, which can also be stratified according to histological type, with adenocarcinoma being the most thrombogenic form and squamous cell carcinoma the least (*Clin Oncol*. 2009;21:425-426; *J Thromb Haemost*. 2008;6:601-608). When a venous thromboembolism event occurs,

independently of both the type of cancer and the stage of the disease, it represents a bad prognostic factor for patient survival, which can be explained considering the type of cancer, which provokes venous thromboembolisms more aggressively, but also other factors are to be taken into account. Indeed, anticoagulation, the risk of bleeding, and the change in the general status of the patient can compromise the best chemotherapeutic or anticancer treatments.

Gerotziapas emphasized that the Khorana risk assessment model was constructed by a retrospective analysis of preexisting databases to evaluate only chemotherapy-associated thrombosis, it was restricted to ambulatory patients with specific cancer types, including stomach, pancreas, lung, gynecological, and testicular cancer, or lymphoma. It is not applicable to patients with breast cancer, the most frequent cancer in the community, and it can only be used before the initiation of chemotherapy (*Blood*. 2008;111:4902-4907; *Cancer*. 2007;110:1149-1161). In real life, the frequency of thromboprophylaxis in cancer patients is very low, and this lack of prophylaxis probably happens because oncologists are unaware of the risk of venous thromboembolism in their patients. The results of the COMPASS-CAT study, a prospective trial conducted to generate a new tool capable of detecting cancer and not just chemotherapy-associated thrombosis, were presented. Approximately 1300 patients with the most common cancers, such as breast, lung, colon, and ovarian, in different stages of disease, were included. Most of the patients were on treatment when they were assessed. Initially, data regarding comorbidities and risk factors for venous thromboembolism not related to cancer, such as family history of venous thromboembolism, underlying cardiovascular or lung diseases, and hospitalization, were introduced in the analysis. The number of events observed in this study was around 8%. This holistic approach allowed for the stratification of patients at a high level of risk (rate of venous thromboembolism during follow-up, 13.3%) or a moderate level of risk (rate of venous thromboembolism, 1.7%) and the selection of patients suitable for anticoagulant treatment.

Regarding biomarkers for hypercoagulability, it is almost impossible to find the best, single biomarker able to predict venous thromboembolism, and their dosage can only give a snapshot without any kinetic profile. In spite of these limitations, the weighted incorporation of several biomarkers in proposed risk assessment models for venous thromboembolism seems to improve their capacity to identify patients eligible for pharmacological thromboprophylaxis. In breast cancer patients, the levels and procoagulant activity of platelet-derived microparticles are interconnected with biological activity and the overall burden of cancer. Thrombin generation reflects the procoagulant properties of breast cancer and chemotherapy in the initial period of cancer diagnosis (*BMC Cancer*. 2014;14:991). In the ROADMAP study, an ongoing trial involving patients with lung adenocarcinoma, showed that hospitalization and time from cancer diagnosis were the most important clinical risk factors for cancer-associated thrombosis in patients with metastatic disease. In addition, baseline values of thrombin generation, heparinases, procoagulant phospholipids, and D-dimers were related to mortality and thrombosis. Therefore, when biomarkers are combined with clinical risk factors, they significantly improve the predictive value of the risk assessment models (*Thromb Res*. 2016;140[suppl 1]:S196).

In conclusion, a contextualized approach to improve prophylaxis and treatment of venous thromboembolism needs to be elaborated by checking the patient's profile,

optimizing the patient management (especially in the critical intervals of increased risk), applying multidisciplinary approaches, and, finally, guaranteeing the quality of life, if not the life expectancy, of the patient.

EuroG20 on CAT, Bergamo 2016: challenges in the treatment of VTE

Ismail Elalamy (France)

Elalamy discussed the expert workshop on cancer-associated thrombosis, which was held in Bergamo, Italy. The aim of the meeting was to discuss unmet needs requiring clarification and produce Pragmatic and Practical Proposals for Patient care Promotion (5 Ps) and a European guideline for practices in complex cancer-associated thrombosis situations, for example, the limits and advantages of the Khorana score. The addition of biomarkers (eg, D-dimers and sP-selectin) to clinical and standard laboratory parameters can help predict the prediction of venous thromboembolisms and identify cancer patients at high or low risk for venous thromboembolisms (*Blood*. 2010;116:5377-5382). The Khorana and the Vienna scores need further validation to develop a more practical and specific score.

The meeting also discussed treatment strategy (dose and duration) in patients with tumors at a high bleeding risk, such as glioblastoma and/or cerebral metastasis. Glioblastomas are rare tumors that have a very high risk of thrombosis, and they are linked to a high risk of major bleeding (*Thromb Res*. 2015;136:1199-1203). Patients with glioblastomas receive slightly lower doses of anti-thrombotic medication than those with other cancers. Currently, there is no indication for thromboprophylaxis after the postoperative period in patients with brain tumors (*Neuro Oncol*. 2012;14[suppl 4]:iv73-iv80). The challenge now is to be able to propose thromboprophylaxis over a long period and to determine the right dose and duration. The optimization of prophylaxis in patients with brain tumors can probably be done by designing a double-blind, randomized controlled trial for the pharmacological prophylaxis of venous thromboembolism, identifying specific risk factors for bleeding and elaborating risk assessment models for bleeding.

Two further discussion points were to determine the occurrence of recurrent venous thromboembolism under low-molecular-weight heparin and define the risk of increasing dose and treatment by using a once or twice daily scheme. Indeed, despite effective treatment, a high risk of recurrence in cancer patients under anticoagulation has been observed in several studies (from 5% to 20%) (*J Thromb Haemost*. 2015;13:1010-1018). Once-daily treatment with low-molecular-weight heparin is as effective and safe as is twice-daily treatment with low-molecular-weight heparin in patients with no cancer (*Cochrane Database Syst Rev*. 2013;7:CD003074). Conversely, in cancer patients, the twice-daily scheme appears more effective without increasing the bleeding risk (*J Oncol Pharm Pract*. 2011;18:264-270). Currently, guidelines suggest shifting to a therapeutic dose of low-molecular-weight heparin if the recurrence occurs during treatment with direct oral anticoagulants or vitamin K antagonists for at least 1 month, increasing the dose by 25% if recurrence occurs during optimal treatment with low-molecular-weight heparin, and avoiding inferior vena cava filters, except for those with absolute contraindications to anticoagulation (*J Thromb Thrombolysis*. 2016;41:81-91).

For the antifactor Xa (anti-Xa) determination, the optimal therapeutic range at peak and trough has only been established for noncancer patients. The clinical relevance

of monitoring seems to be low because there is no correlation between the level of anti-Xa and clinical efficacy or safety. The experts proposed that monitoring should be based on clinical context and reserved for special subgroups of cancer patients, such as patients with a low body weight, renal impairment, thrombotic recurrence, obese with a high glomerular filtration rate, high risk of bleeding, and fear of accumulation. Finally, regarding prophylaxis in myeloma patients, according to the International Myeloma Working group recommendations, aspirin still has a place in prophylaxis, but only for patients with ≤ 1 risk factor. However, low-molecular-weight heparin should be preferred depending on the type of myeloma treatment even in these patients. Patients with ≥ 1 risk factors should receive prophylactic low-molecular-weight heparin.

Is there any place for DOAC in the prevention and treatment of CAT?

Isabelle Mahe (France)

The incidence of cancer and cancer-associated thrombosis is increasing; however, due to the progress in cancer-associated thrombosis treatments and supportive cares, a longer survival of patients with cancer-associated thrombosis has been observed. Direct oral anticoagulants—breakthrough molecules with a quick onset of action, a short half-life, few food and drug interactions, a broad therapeutic window at fixed doses, and no need for anticoagulant monitoring—have undoubtedly opened new scenarios for the management of venous thromboembolism, providing the opportunity to overcome vitamin K antagonist restrictions. However, to date, no specific clinical trial in cancer is available. We only have some data from registries and post hoc analyses of phase 3 clinical trials, which cannot be translated into a real-life setting. Furthermore, in the phase 3 trials, direct oral anticoagulants were compared with vitamin K antagonists and not with low-molecular-weight heparin, the gold-standard treatment for cancer-associated thrombosis, and few patients with low-risk cancer were included (5%), the definition of “active cancer” was heterogeneous among the studies, and little information on cancer characteristics and potential drug interference were provided (*Thromb Res.* 2015;136:582-589). Consequently, the guidelines do not recommend using direct oral anticoagulants as the first-choice therapy for the acute treatment of cancer-associated thrombosis.

Regarding extensive treatment, beyond the first 3 to 6 months, the comparator of the extended phase 3 trial assessing direct oral anticoagulants was variable because it was either vitamin K antagonists or placebo, and the subset of patients with active cancer was very small. The duration of treatment in cancer-associated thrombosis is still an open and debatable question. The DALTECAN study showed that the highest risk of major bleeding complications or cancer-associated thrombosis recurrence occurs in the first month of therapy. Despite this information, both recurrences and major bleeding persist over time with a similar rate, which is estimated to be around 10% at 1 year (*J Thromb Haemost.* 2015;13:1028-1035). For the management of cancer-associated thrombosis beyond the first 6 months of therapy, the guidelines suggest a more intensive treatment with low-molecular-weight heparin as the preferable option for higher risk patients and oral treatment discontinuation, and, for lower risk patients, oral anticoagulants (vitamin K antagonists or direct oral anticoagulants). For the prevention of cancer-associated thrombosis, there is currently no place for direct oral anticoagulants.

Direct oral anticoagulants seem to be an attractive option for patients with cancer-associated thrombosis, but at this time, we have no data from studies focusing on patients with cancer-associated thrombosis. The ongoing trials comparing direct oral anticoagulants with low-molecular-weight heparin, such as the Hokusai-VTE cancer study and the Casta Diva study, should be able to answer these questions and determine if direct oral anticoagulants could represent a more convenient oral alternative that is at least as safe and effective as low-molecular-weight heparin, even in cancer patients.

Heparin centennial symposium

Heparin centennial: a century of clinical and scientific progress

Jawed Fareed (USA)

The year 2016 marked 100 years since the discovery of heparin. Heparin has had a very interesting life that has been full of difficulties. In 1916, heparin was placed in clinical trials, and regulatory bodies were put in place to regulate and develop guidelines for its use. In 1938, the Food and Drug Cosmetic Act for the Safety of Drug products was introduced; however, it was not until 1962 that the US Congress passed an amendment requiring premarketing proof of the effectiveness of drugs. Then, in 1966, there was another act put in place to regulate drug efficacy. Only in the 1970s was heparin labeling devised. The next 20 years was difficult for heparin due to its adverse effects, which led to it being withdrawn from the market. Today, the FDA has decided to reintroduce natural heparin, which is primarily due to the heparin contaminant crisis, which ultimately led to improvements. Guidelines are needed concerning natural, synthetic, and biotechnical heparin for multiple reasons, such as sourcing, required political controls, and other things, such as bovine issues. One study showed that the efficacy of heparin is the same regardless of its species of origin, especially for open-heart surgeries. Also, both bovine- and ovine-derived heparins have a higher level of activity when ingested. Today, heparin treatment is manageable, and, due to regulatory requirements, the risk of contaminants is no longer a concern. Dosing errors can now be minimized through a color-coding system and training; bleeding can now be easily reduced with an adequate dosage and monitoring; bovine spongiform encephalopathy (BSE) is no longer an issue because only BSE-free heparin is used and tested; and osteoporosis can now be avoided by using low-molecular-weight heparins. Thus, heparin is the only pleiotropic drug with multiple targets and broad applications. Furthermore, there are many innovations on the horizon, such as anticancer effects, neuromodulatory actions, and fertility and reproductive biology. The future success of heparin is dependent on increased awareness from the public and regulatory levels. Throughout its history, heparin has passed the test of the "survival of the fittest," and it came out on top.

The pleiotropic effects of heparins: clinical relevance

Ludovic Drouet (France)

Glycosaminoglycans are long, nonbranching, negatively charged polysaccharide chains. Heparin is a highly sulfated glycosaminoglycan of natural origin. Only 20% of heparin chains are pentasaccharide sequences, which are responsible for its anticoagulant activity. Chains with pentasaccharide sequences lead to antifactor Xa activity, and, if the chains are long enough, they can additionally lead to antifactor II activity. At least 18 saccharide units are required to inactivate factor IIa; therefore,

the antifactor IIa/antifactor Xa activity ratio only depends on the length of the molecule. The half-life of different molecules of heparin is inversely correlated with the length of the chains. Other than anticoagulant properties, including the chains with no anticoagulant activity, part of the complexity of the pharmacokinetics and pharmacodynamics of heparin can be explained by the interaction with the endothelial glycocalyx. Indeed, it has been demonstrated that heparin also has a broad anti-inflammatory activity. Using the low-dose anticoagulant 2-O,3-O-desulfated heparin (ODSH), it was shown that most of the anti-inflammatory pharmacology of heparin was unrelated to its anticoagulant activity. In mice, ODSH was more effective than heparin in reducing selectin-mediated lung metastasis from melanoma, and it inhibited the airway inflammation mediated by the receptor for advanced glycation end product from the intratracheal high mobility group box protein-1 (*Am J Physiol Cell Physiol.* 2010;299:C97-C110).

Furthermore, inflammatory conditions provoke the generation of extracellular DNA traps, which are recently discovered large DNA fibers produced by neutrophils (neutrophil extracellular traps [NETs]). The recently described mechanism, called NETosis, implies that leukocytes can release a meshwork of chromosomal DNA, which includes histones and granular antimicrobial proteins, such as myeloperoxidase or neutrophil elastase, to trap and kill microorganisms. Extracellular DNA traps have been linked to several diseases, including sepsis and venous thrombosis. Unfractionated and low-molecular-weight heparins can block the DNA–von Willebrand factor (vWF) interaction, which contributes to thrombus initiation and progression (*Arterioscler Thromb Vasc Biol.* 2014;34:1382-1389). Such mechanisms, independently of the anticoagulant properties of heparin, have a great clinical relevance because they may contribute to the observed beneficial effects of heparin in the treatment of sepsis patients. It has been shown that nonanticoagulant heparin, purified from clinical grade heparin, binds histones, prevents histone-mediated cytotoxicity in vitro, and reduces mortality from sterile inflammation and sepsis in mouse models without increasing the risk of bleeding (*Blood.* 2014;123:1098-1101). In cancer patients, thrombosis is also related to the NETosis system. It has been demonstrated that neutrophils isolated from patients with gastric cancer presented a significantly enhanced NET formation compared with those in healthy controls, which can be prevented by heparin (*Int J Clin Exp Pathol.* 2015;8:14075-14086; *Thromb Res.* 2016;139:56-64). In conclusion, all the pleiotropic activities of heparin are extremely important and can have great clinical implications.

From unfractionated heparins to low molecular weight heparins and the evolution of synthetic heparins

Jeanine Walenga (USA)

In terms of anticoagulants, only 20% of heparin chains are now familiar and in use today, which leads to an enormous potential for these drugs. Throughout the history of heparin, many important discoveries have been made. In the 1930s, with the first-generation heparins, unfractionated heparin originated from bovine and porcine sources. From the 1970s to 2000, the second-generation heparins—low-molecular-weight heparin and ultra-low-molecular-weight heparin—were being used clinically. From 2000 to 2015, the third-generation heparins—pentasaccharides, the first synthetic heparin—started being used. Currently, these pentasaccharides are now being made using different bioengineering processes, such as chemo-enzymatic synthesis, to make the production more cost-effective, and it allows the other 80% of chains (the nonanticoagulant components of heparin) to be studied for additional

clinical uses. Unfractionated heparin is still used, and it will continue to be used for a variety of clinical situations; however, low-molecular-weight heparin led to important changes in the scope of how we treat thrombosis.

Heparin fractionation has resulted in the isolation of high-, medium-, and low-molecular-weight components that have defined biological activities. Low-molecular-weight heparin was the focus of drug development, and, to this day, low-molecular-weight heparins continue to be the standard of care for prophylaxis and treatment of venous thrombotic disorders. Additional fractionation methods for heparin, including ion exchange chromatography and affinity chromatography, have also provided components with differential pharmacologic profiles. With the advent of the generic low-molecular-weight heparin enoxaparin, it became important to determine how the low-molecular-weight heparins compare to each other, and to determine if they have some differences in molecular weight, structural chains, and chemistry.

Since the discovery of the antithrombin effect of the heparin-binding protein in the 1970s, structural activity studies have been ongoing. This work then led to the isolation of the high antithrombin affinity heparin fractions. The most active fractions were found to contain a unique region containing antithrombin binding consensus sequences. In the late 1970s, the Choay group (Paris) isolated octasaccharides and hexasaccharides with a high affinity for antithrombin from the lower-molecular-weight fractions of heparin, and then they discovered the pentasaccharides. In 1968, the heparin cofactor antithrombin was discovered, then, in the late 1970s, data was ascertained about heparin binding to antithrombin; thereby, inhibiting factor Xa, which inhibits thrombin activity within the coagulation cascade; therefore, inhibiting thrombin production. Later, it was shown that pure antifactor Xa activity had antithrombotic activities. Throughout the 1980s, studies carried out with pentasaccharides led to it becoming a clinical drug. Due to the success of these pentasaccharides, there is more interest today in synthetic heparins to reduce the heparin-induced side effects while maintaining the antifactor Xa activity. Heparins are polytherapeutic, and they can be used for a wide range of situations beyond their conventional use as anticoagulants. Synthetic- and biotechnology-based heparin-related agents will emerge for certain clinical indications and new therapeutic targets, but natural source heparins will remain the agents of choice for broad clinical use.

Heparins: from pharmacokinetic properties to clinical practice

Patrick Mismetti (France)

The pharmacokinetic properties of low-molecular-weight heparin allowed us to move beyond the limits of unfractionated heparin and consider these drugs as an option in several clinical conditions. Indeed, the higher specificity and reduced variability, which is due to low binding to plasma and matrix proteins, resulted in fixed-dose usage without monitoring. Furthermore, the longer elimination half-life, which is due to an almost exclusive renal excretion, resulted in once-daily doses and long-term treatments. Meta-analyses have shown that low-molecular-weight heparin is more effective than is unfractionated heparin, which significantly reduces the occurrence of major bleeding during the initial treatment of venous thromboembolisms (*Cochrane Database Syst Rev.* 2004;18:CD001100). In addition, low-molecular-weight heparin appears significantly superior to vitamin K antagonists regarding the risk reduction in recurrent venous thromboembolism in cancer patients, with comparable safety to vitamin K antagonists (*Thromb Res.* 2015;136:582-589). Population

pharmacokinetic studies, using antifactor Xa activity measurements, have shown that patient characteristics may influence the residual pharmacokinetic variability of low-molecular-weight heparin, with age, body weight, and renal function being significant covariates (*Br J Clin Pharmacol.* 2003;56:96-103; *Clin Pharmacol Ther.* 2005;77:542-552). Interestingly, maintaining the same doses of low-molecular-weight heparin throughout pregnancy resulted in a progressive reduction in mean and peak antifactor Xa activities. Therefore, the administration of doses normalized for body weight variations to counteract pharmacokinetic changes during different stages of pregnancy is recommended. However, the use of a standard dosing regimen in patients with moderate or severe renal impairment resulted in elevated levels of antifactor Xa and reduced low-molecular-weight heparin clearance (*Ann Intern Med.* 2006;144:673-684). Thus, dose adjustment or laboratory monitoring of low-molecular-weight heparin is commonly recommended in these patients to reduce the risk of major bleeding. In conclusion, the benefit-risk ratio of these molecules can be improved by consistently taking into consideration their pharmacokinetic properties.

Glycosaminoglycans and beyond

Job Harenberg (Germany)

As of September 2016, 181 clinical studies on low-molecular-weight heparin were registered on clinicaltrials.gov, with particular reference to rare localization of thrombosis, acute gastrointestinal bleeding, renal failure and hemodialysis, infectious diseases (pancreatitis), intraocular-infusion cataract operation in children, cardiac indications (coronary artery bypass surgery, aspirin discontinuation, bridging), superficial vein thrombosis (dose finding), and other specific indications (in vitro fertilization). In the future, other than improving the current use of heparin as a therapy for traditional circumstances and more specific indications, the nonanticoagulant activities should be considered just as important. Most probably, following the present scenario, attention should be focused on the pleiotropic effects of glycosaminoglycans (antitumor, anti-inflammatory, antiproliferative, anti-Parkinson) on the inhibitors of heparinases and heparin-derived polysaccharides without anti-thrombin binding sites, which are currently under development for the treatment of nonthrombotic diseases (*Graefes Arch Clin Exp Ophthalmol.* 2015;253:829-837; *PLoS One.* 2015;10:e0118798)

The development of low molecular weight heparins and their impact on VTE

Sylvia Haas (Germany)

Heparin is one of the oldest drugs still in widespread use. Heparin and vitamin K antagonists have been the main anticoagulant drugs for more than 70 years. Although heparin was first discovered a century ago, many years passed before it was mass-produced and used as an anticoagulant. Today, the main challenges of venous thromboembolism treatment remain almost the same—to prevent acute pulmonary embolism, thrombus extension, venous thromboembolism recurrence, and long-term sequelae and facilitate thrombus regression. Low-molecular-weight heparins have been the cornerstone of venous thromboembolism treatment for several decades. Despite the development of a monotherapy treatment with two oral factor Xa inhibitors, low-molecular-weight heparins will remain a key element in venous thromboembolism treatment. Low-molecular-weight heparins cannot be replaced in the near future in pregnant patients and other patient subgroups.

VTE prevention with heparin and other glycosaminoglycans in major orthopedic surgery: a personal journey

Graham Turpie (Canada)

Since 1962, venous thromboembolism was recognized as an important factor in orthopedics and a major cause of death in the wards, particularly in young individuals. Six years later, when the first hip replacement was done, Sir John Charnley recognized that "thromboembolic complications are the commonest of post-operative complications following hip surgery and the single largest cause of death." These findings highlighted the relevance of venous thromboembolism in orthopedics, and therefore, the importance of prevention. Orthopedic surgery involving patients who are at risk for thrombosis and bleeding is a perfect setting to study new anticoagulants. The first randomized controlled trial using enoxaparin to prevent deep-vein thrombosis in patients undergoing elective hip surgery spawned the developments of new anticoagulant prophylaxis with low-molecular-weight heparin (*N Engl J Med.* 1986;315:925-929). In double-blind trials using the factor X inhibitor in major orthopedic surgery, fondaparinux showed a major benefit over enoxaparin, achieving an overall venous thromboembolism risk reduction >50% without increasing the risk of clinically relevant bleeding. These studies revealed that fractionation of heparin resulted in greater advantages for the patients (*Arch Intern Med.* 2002;162:1833-1840). Finally, in 2011, the initial evaluation of direct oral anticoagulant drugs through four randomized controlled trials looking at rivaroxaban compared with enoxaparin in an orthopedic setting showed an approximate 50% reduction in the risk of venous thromboembolism with an oral agent compared with enoxaparin, and it did not increase the risk of major bleeding complications (*Thromb Haemost.* 2011;105:444-453). However, phase 3 clinical trials are not the final word, meaning that real-world evidence, particularly from phase 4 noninterventional studies, is needed to evaluate the safety and effectiveness of new treatments further in clinical care settings. In this regard, the XAMOS study, which enrolled 17 701 unselected patients from 252 centers in 37 countries, confirmed the favorable benefit-risk profile of rivaroxaban that was seen in the RECORD program and routine clinical practice (*Thromb Haemost.* 2014;111:94-102). Thus, in 2016, the journey continues with direct oral anticoagulants.

Stepwise evolution of heparins and pentasaccharide: the French logic

Pierre Willaime (France)

At the end of the 1950s, heparin was thought to be a lifesaving drug to be used with caution because of the pathogenic effects. At the same time, open-heart surgery became almost standard. In addition, this combination led to the necessary and continuous research on this drug. Initially, Choay became interested in the drug because of the necessity of using heparin prophylactically, to administer small volumes using an easy to inject system, and to find a way to keep it sterile. These requirements led to multicenter studies. Facing two very different approaches, in the late 1970s, two studies were undertaken: the first to try to fractionate heparin and isolate the antithrombin factor, and the second, once fractionated, to produce it synthetically. In 1985, the second study resulted in a hexasaccharide becoming the first low-molecular-weight heparin on the international market. Studies on hexasaccharide continued until the late 1990s when Sanofi decided to put the project on hold as the synthesis process was becoming too costly; therefore, making the product commercially nonviable. Two years later, the process was shortcut, and it was once again commercially feasible; the product was launched on the market as a pentasaccharide. The world market

for heparin is worth 8 billion dollars, 85% of which is due to low-molecular-weight heparin, it has a growth rate of about 6%, and the number of studies today on heparin is in the hundreds; therefore, heparin can be compared to a “distinguished, attractive old lady who maintains and offers appealing features.”

The role of heparins and other glycosaminoglycans in VTE management: recent international guidelines

Andrew Nicolaides (Cyprus)

Nicolaides discussed the recent international guidelines produced by the International Faculty, which meets every 4 to 5 years to revise and update the document. The aim of these guidelines is to provide a clear and concise account of the evidence regarding efficacy or harm for various methods available to prevent and manage venous thromboembolisms. The evidence is presented for several outcomes, such as symptomatic deep vein thrombosis or pulmonary embolism, fatal pulmonary embolism, mortality, postthrombotic syndrome, and, interestingly, even for asymptomatic deep vein thrombosis. The decision to use asymptomatic deep vein thrombosis as well as symptomatic deep vein thrombosis and pulmonary embolism was based on several reasons:

- There is a relationship between symptomatic and asymptomatic venous thromboembolism, and a reduction in the incidence of asymptomatic deep vein thrombosis has been correlated with a reduction in symptomatic deep vein thrombosis and pulmonary embolisms.
- Reducing silent deep vein thrombosis is related to a reduction in clinical deep vein thrombosis, clinical pulmonary embolisms, and fatal pulmonary embolisms.
- Regulatory authorities have recognized asymptomatic proximal deep vein thrombosis as a valid end point for clinical trials in drug evaluation.
- Relatively few pulmonary embolisms occur in patients with symptomatic deep vein thrombosis, the majority of pulmonary embolisms and fatal pulmonary embolisms occur in patients with asymptomatic deep vein thrombosis.

Therefore, it has been argued that asymptomatic deep vein thrombosis is an important stage of venous thromboembolism that has not yet manifested itself and it cannot be ignored. Several clinical trials have compared unfractionated heparin or low-molecular-weight heparin first with placebo and later, for ethical concerns, with active treatment.

The level of evidence for low-molecular-weight heparin and intermittent pneumatic compression has to be considered high for both moderate- and high-risk patients undergoing general or orthopedic surgery. Low-molecular-weight heparin is considered the method of choice for general surgery. Fondaparinux has a moderate level of evidence for general surgery and a high level for elective orthopedic surgery, showing it to be the most effective treatment available in elective orthopedic surgery. In addition, if low-molecular-weight heparin is used, it is recommended to start the treatment before or after surgery. Conversely, if fondaparinux is used, the prophylaxis should begin at least 6 hours after surgery to minimize the bleeding risk. Regarding treatment duration, extended prophylaxis (4 to 6 weeks) is recommended for total hip replacement patients (based on the Hull study results), for cancer surgery (based on the Enoxacan study), and for major abdominal surgery (Rasmussen study). In addition, the Exclaim multicenter trial, in spite of a great reduction in the incidence of venous thromboembolism, showed that, in medical patients, the price to be paid is an increased risk of bleeding.

VTE treatment with heparin and other glycosaminoglycans

Russell Hull (Canada)

The Achilles heel of unfractionated heparin was monitoring and dosage. These concerns led pharmaceutical and medical research to make an effort to tweak the drug to overcome these limitations. Low-molecular-weight heparins turned out to be more effective, safer, with a lower risk of thrombocytopenia, and, ultimately, had enormous benefits for patients, shifting venous thromboembolism treatment from the hospital setting to home care. Currently, low-molecular-weight heparins remain the gold-standard therapy for cancer-associated thrombosis in both acute and long-term phases of therapy. In addition to being superior to unfractionated heparin, low-molecular-weight heparin produces a better recanalization than standard treatment with vitamin K antagonists.

The rationale for the management of VTE in cancer with heparins: current and future perspectives

Lord Professor Ajay Kumar Kakkar (UK)

Kakkar covered four areas: (i) the challenge of managing venous thromboembolism in cancer patients; (ii) the rationale for using low-molecular-weight heparin as the gold-standard treatment for cancer-associated thrombosis; (iii) the duration of secondary prevention; and (iv) the value of these strategies. Cancer patients, despite long-term anticoagulation, have a three-fold higher risk of recurrent venous thromboembolism and a two-fold higher risk of major bleeding complications when compared with noncancer patients (*Blood*. 2002;100:3484-3488). In this population, strategies that can optimize the treatment by reducing the risk of recurrence and bleeding to improve the quality of life are indispensable.

Findings from several randomized controlled trials showed that low-molecular-weight heparins are more effective and safer than oral anticoagulant therapy in preventing recurrent thromboembolism in patients with cancer-associated thrombosis. In the CLOT study, 676 patients with cancer-associated thrombosis were randomly assigned to receive dalteparin once daily for 5 to 7 days and a coumarin derivative for 6 months or dalteparin alone. During the 6-month study period, 27 of the 336 patients in the dalteparin group had recurrent venous thromboembolism vs 53 of 336 patients in the oral anticoagulant group (hazard ratio, 0.48; $P=0.002$). No significant difference between the dalteparin group and the oral anticoagulant group was detected in the rate of major bleeding (*N Engl J Med*. 2003;349:e23). Similar results were observed in the CATCH trial with the use of tinzaparin (*JAMA*. 2015;314:677-686). Furthermore, the guidelines recommend low-molecular-weight heparin for at least 3 to 6 months and possibly indefinitely for patients with an active malignancy.

However, there is little data supporting treatment with low-molecular-weight heparin beyond 6 months. The DALTECAN study was conducted to determine the safety of dalteparin between 6 and 12 months for cancer-associated venous thromboembolism. Of the 334 patients enrolled, 185 and 109 completed 6 and 12 months of therapy, respectively; 49.1% had deep vein thrombosis; 38.9% had pulmonary embolism; and 12.0% had both on presentation. The overall frequency of major bleeding was 10.2%. Major bleeding occurred in 3.6% of the patients in the first month, and 1.1% and 0.7% per patient-month during months 2 to 6 and 7 to 12, respectively. Recurrent venous thromboembolism occurred in 11.1%; the incidence rate was 5.7% for month 1, 3.4% during months 2 to 6, and 4.1% during months 7 to 12. Thus, major bleeding

was less frequent during dalteparin therapy beyond 6 months. The risk of developing major bleeding complications or venous thromboembolism recurrence was greatest in the first month of therapy and lower over the subsequent 11 months (*J Thromb Haemost.* 2015;13:1028-1035).

There are still a number of outstanding clinical questions to address. How do we determine those patients who should have extended low-molecular-weight heparin therapy? How does the natural history of venous thromboembolism affect that of cancer? How will changes in cancer therapy affect the burden of venous thromboembolism? More research is certainly required in those areas. Moreover, the challenge of contemporary health care should be to demonstrate the value of aggressive strategies to prevent recurrent venous thromboembolism and improve outcomes because venous thromboembolisms have a terrible impact on cancer outcomes.

Current consensus on the management of VTE: a focus on heparin

Samuel Goldhaber (USA)

The 2016 American Heart Association statistics show that pulmonary embolism is still the third cause of cardiovascular death in the US, and the prevalence of venous thromboembolisms is increasing. Anticoagulation is the foundation of venous thromboembolism treatment. Parenteral anticoagulants for the initial management of venous thromboembolism include unfractionated heparin, low-molecular-weight heparin, fondaparinux, and direct thrombin inhibitors (eg, argatroban and bivalirudin). At this time, unfractionated heparin is used with advanced therapy, such as thrombolysis, embolectomy, or inferior vena cava filters. Low-molecular-weight heparin or fondaparinux are reserved for patients who only require anticoagulation, or they are used for 5 days before switching to dabigatran or edoxaban. Direct thrombin inhibitors are the choice treatment for confirmed or suspected heparin-induced thrombocytopenia. The guidelines from the American College of Chest Physicians (ACCP) for venous thromboembolism treatment, which are based on less bleeding with direct oral anticoagulants and greater convenience for patients and health care providers, now suggest that a direct oral anticoagulant should be used in preference to a vitamin K antagonist for the initial and long-term treatment of venous thromboembolism in patients without cancer (*Chest.* 2016;149:315-352).

Currently, three anticoagulation strategies are available: (i) classic strategy, which involves the overlap of low-molecular-weight heparin and unfractionated heparin with warfarin; (ii) switching strategy, which uses primarily low-molecular-weight heparin for the first 5 days and then switches to dabigatran or edoxaban; and (iii) an oral monotherapy regimen strategy, which uses rivaroxaban or apixaban as a single-drug approach (*Lancet.* 2012;379:1835-1846). Rivaroxaban, apixaban, and edoxaban work directly against factor Xa, and they are similar to the oral fondaparinux. Conversely, dabigatran is a direct thrombin inhibitor that is similar to argatroban or bivalirudin. For cancer patients, the updated ACCP guidelines suggest beginning treatment with 3 months of low-molecular-weight heparin as a monotherapy, and then either continuing low-molecular-weight heparin or switching to a different anticoagulant as long as the cancer remains active.

We are currently awaiting the results of ongoing trials comparing direct oral anticoagulants with low-molecular-weight heparin. The biggest change in recent

years concerns the concept of managing venous thromboembolism mostly as a chronic inflammatory illness, not a “one-shot” event that is “cured” with 3 to 6 months of anticoagulation. Indeed, an extended duration of anticoagulation is often needed, and, as soon as the extended duration of anticoagulation is discontinued, the rate of new pulmonary embolisms or a new deep vein thrombosis is likely to increase (*Haematologica*. 2007;92:199-205). The anti-inflammatory effects of heparins and glycosaminoglycans can help to prevent recurrent venous thromboembolism.

Superficial venous thrombosis

Introduction

Claudio Allegra (Italy)

Many questions remain in the treatment of superficial vein thrombosis, including the role of direct oral anticoagulants on superficial vein thrombosis; the real activity of these non-vitamin K antagonist oral anticoagulants on the recanalization of the venous thrombosis; the fibrinolytic action of rivaroxaban; the influence of rivaroxaban on the rate of recanalization; and the role of heparin in these processes?

Epidemiology and the clinical picture

Marie-Antoinette Sevestre-Pietri (France)

Between 1998 and 2003, the frequency of deep vein thrombosis decreased from 1.83 to 1.57 per 1000 and the incidence of pulmonary embolisms increased from 0.6 to 0.81 per 1000; however, there is no direct data on superficial vein thrombosis (*Thromb Haemost.* 2016;116(5):967-974). The STEPH community-based study, which was conducted on 265 687 inhabitants of Saint Etienne, France, showed that the annual diagnosis rate of superficial vein thrombosis (0.64%) was lower than the rate of deep vein thrombosis (1.24%) and similar to that of pulmonary embolisms (0.6%) (*J Thromb Haemost.* 2014;12(6):831-838). The risk factors for superficial venous thrombosis include varicose veins, hormone replacement therapy, thrombophilia, cardiac-respiratory failure, compression therapy, and a history of pulmonary embolism and deep vein thrombosis. According to the OPTIMEV study, the risk factors for deep vein thrombosis/pulmonary embolism in the case of superficial vein thrombosis are age >75, active cancer, inpatient status, superficial vein thrombosis on a non-varicose vein (*Thromb Haemost.* 2011;105:31-39). Superficial venous thrombosis affects the great saphenous trunk in 53% to 68% (33% above the knee and 15% to the saphenofemoral junction), the small saphenous trunk in 13% to 15% (saphenopopliteal junction 33%), and other veins in 59% to 63% of cases. In 4% to 12% of cases, the thrombus extends to the perforating vein. Superficial vein thrombosis has clear clinical signs, but clinical examinations cannot diagnose associated deep vein thrombosis; therefore, an ultrasound analysis is necessary because the combination of deep vein thrombosis and superficial vein thrombosis is a frequent occurrence (up to 25%).

Instrumental evaluation

Pier-Luigi Antignani (Italy)

Superficial vein thrombosis on a healthy vein may be associated with a systemic disease, and there may be another reason for the thrombosis, such as a malignancy elsewhere, an autoimmune disease, Berger's disease, or an inherited blood clotting disorder. Migratory thrombophlebitis requires a more detailed evaluation of the patient to find the malignant lesion (eg, CT scans, mammography, colonoscopy, serum

carcinoembryonic antigen, and prostate-specific antigen). The duplex ultrasound is still the diagnostic method of choice for finding a vein thrombosis, and, during the examination, it is important to verify whether the clot is adherent to the vein wall, evaluate the deep venous system, and consider the thrombosis as a deep vein thrombosis if the thrombus is located 2 cm from saphenofemoral junction or the saphenopopliteal junction. Venography is rarely required to diagnose a superficial vein thrombosis. If information on the pelvic veins or iliac vein outflow tract is required, CT venography, if available, is the preferred method. The consensus document for the evaluation of superficial vein thrombosis was published in 2012 (*Int Angiol.* 2012;31(3):203-216).

What we learned from clinical trials

Isabella Quere (France)

An analysis of the STEPH, POST, and OPTIMEV epidemiological studies showed that the frequency of deep vein thrombosis and pulmonary embolism is 18.1% and 6.9%, respectively. The predictors of symptomatic vein thromboembolism (deep vein thrombosis/pulmonary embolism) and extension/recurrence of symptomatic pulmonary embolism include male sex, previous deep vein thrombosis or pulmonary embolism, cancer, and a superficial vein thrombosis in a non-varicose vein. Symptomatic extensions are common complications of superficial vein thrombosis, and they are associated with a significant risk of venous thromboembolic complications, irrespective of whether or not they reach the saphenofemoral junction. The STENOX and STAFLEX trials showed that 12 days or 30 days of heparin treatment (intermediate dose of low-molecular-weight heparin or unfractionated heparin), respectively, is not long enough, and there is a rebound effect. The CALISTO trial showed that patients with superficial vein thrombosis who were treated with fondaparinux had a significant reduction in symptomatic venous thromboembolism, superficial vein thrombosis extension, and superficial vein thrombosis recurrence, and there was no rebound effect. The 2012 American College of Chest Physicians guidelines recommend using a prophylactic dose of fondaparinux or low-molecular-weight heparin for 45 days in patients with a superficial vein thrombosis at least 5 cm in length (2B), and it is recommended to use fondaparinux 2.5 mg daily over a prophylactic dose of low-molecular-weight heparin.

Heparin: when and why?

Eva Kalodiki (UK)

Heparin is a pleiotropic drug that has anticoagulant and anti-inflammatory effects. According to the 2012 Cochrane review, low-molecular-weight heparin appears to reduce the extension or recurrence of superficial venous thrombosis or both vs placebo, whereas the available data did not show any significant effect on venous thromboembolism. The new classification for the management of superficial vein thrombosis—the SEAP classification (S [I, isolated; M, multifocal; D, deep vein thrombosis]; E [N, non-varicose vein, V, varicose vein, R, reticular]; A [A, above knee; B, below knee; S, saphenous; J, junctional]; and P [S, spontaneous; M, malignancy; I, inflammatory; T, trauma; H, hematological])—was presented. A registry that is based on the SEAP classification is needed for the management of superficial vein thrombosis that may identify the categories that would benefit from heparin or other treatment.

Is there a place for NOACs?

Jawed Fareed (USA) and Eduardo Ramacciotti

Although direct oral inhibition is likely efficacious and safe, no studies have been completed on its use for patients with superficial venous thrombosis; therefore, the efficacy, safety, appropriate dose regimens, and treatment duration are not known. The SURPRISE trial, an ongoing, prospective, randomized, open-label, blinded, adjudication trial, is evaluating the efficacy and safety of rivaroxaban 10 mg once daily vs fondaparinux 2.5 mg once daily for the treatment of superficial venous thrombosis in high-risk patients over a period of 45 days. The aim of SURPRISE is to demonstrate noninferiority of rivaroxaban vs fondaparinux in the prevention of the combined efficacy end point of thrombus progression, superficial venous thrombosis recurrence, deep vein thrombosis, pulmonary embolism, and death. In addition to the SURPRISE trial, the multicenter randomized controlled trial RASET is evaluating the effects of rivaroxaban vs placebo in patients with superficial venous thrombosis.

Venous thromboembolic diseases

Marie-Antoinette Sevestre-Pietri (France)

The risk of venous thromboembolism is lower in men than in women; however, in women, venous thromboembolisms are related to hormonal conditions, such as pregnancy, contraception, ovulation-inducing hormones, and hormone replacement therapy. In addition, thrombophilia is often identified during pregnancy, and 40% to 50% of women who have a venous thromboembolism during pregnancy have thrombophilia. Different combined oral contraceptives have different impacts on the risk of venous thromboembolism in women; topical contraceptives seem to have the lowest risk. In predictive models, sex is factored into the evaluation of venous thromboembolism recurrence. The HERDOO2 rule is the only validated rule to help predict the risk for a venous thromboembolism in both sexes. The HERDOO2 rule is named for the following four risk factors used to determine the risk for a venous thromboembolism recurrence: (i) hyperpigmentation, edema, or redness in either leg (1 point); (ii) D-dimer >250 µg/L (1 point); (iii) obesity, BMI ≥30 (1 point); (iv) older age ≥65 (1 point). Women with ≥2 HERDOO points should continue anticoagulants to prevent recurrence where women with ≤1 HERDOO point can discontinue their anticoagulant treatment. In conclusion, women with a first unprovoked venous thromboembolism and a HERDOO score of 0 to 1 have a low risk of recurrent venous thromboembolism, and they can safely discontinue anticoagulants after completing a short-term treatment.

Venous thromboembolism in Behçet's disease: from guidelines to everyday practice

Zoubida Tazi (Morocco)

Behçet's disease is a systemic disease that is characterized by a large clinical polymorphism with a high frequency of dermatological manifestations; in addition, there are ocular, rheumatologic, vascular, and neurological manifestations. Vascular involvement was reported in 1946 by Adamantiades, and it is often called vascular Behçet's disease. It is observed in 20% to 35% of the patients, and it has specific epidemiological and clinical aspects. Indeed, it is mostly observed in young men without thrombotic risk factors or cardiovascular diseases. All vessels, regardless of type (arterial or venous), size, or location may be affected. These attacks are readily associated multifocal vascular manifestations, and they may be accompanied by a

fever and an inflammatory biological syndrome. The venous involvement covers 80% to 90% of the vascular attacks, and it is observed in approximately one-third of patients. Deep vein thrombosis of the lower limbs remains the most frequent manifestation, and it represents 60% to 70% of the venous locations of the disease. However, the involvement of large venous trunks is classic and particularly serious (cava veins, hepatic veins, cerebral sinuses, etc). Arterial involvement is rare (2% to 7% of cases), resulting in a bleak prognosis because arterial lesions are often multifocal, they can affect all territories, and they may manifest with stenosis, aneurysm, or arterial thrombosis. Vascular involvement is the main life-threatening condition that requires a specific, rapid, and aggressive treatment. While the treatment options are under debate, initiation with an anti-inflammatory drug along with an anticoagulant is often considered necessary. Further data is required to determine the best treatment course.

CACTUS study: how to treat the distal deep venous thrombosis?

Isabelle Quere (France)

Currently, it is unknown what place anticoagulants have in the treatment of distal deep venous thrombosis, but the rationale for using anticoagulant is to prevent a lethal pulmonary embolism or a postthrombotic syndrome occurring after a deep vein thrombosis. There are only three clinical studies published about distal deep vein thrombosis, which only involved a small number of patients (n=228). The first study showed that deep vein thrombosis must be treated over 3 months with anticoagulants (warfarin). The second study showed that, after 6 weeks of oral anticoagulant treatment, the risk of a recurrent thromboembolism event is identical to that of patients receiving no anticoagulants, and, after 12 weeks of treatment, the risk of bleeding is higher in the patients treated with oral anticoagulants for a proximal deep vein thrombosis. The third study demonstrated that, in patients with deep muscle venous thrombosis, therapeutic nadroparine and compression therapy did not lead to additional benefits compared with compression therapy alone.

The CACTUS study, a multicenter, double-blind, randomized, placebo-controlled study, was designed to determine the effectiveness of a 6-week course of a therapeutic dose of low-molecular-weight heparin (nadroparine) injections vs placebo (compression stocking) in patients with a first symptomatic isolated distal deep vein thrombosis. The study aims include determining the rates of proximal deep vein thrombosis and symptomatic pulmonary embolisms after the 6 weeks, determining whether the 6-week treatment decreased the frequency of postthrombotic syndrome at 1 year, and monitoring serious or clinically significant bleedings after 6 weeks of treatment and the patients' quality of life. The rate of proximal thromboembolic events in the case of distal deep vein thrombosis was less frequent than initially believed. In addition, anticoagulant therapy was not superior to simple compression. There were no serious events (pulmonary embolism) in the placebo group, but the risk of bleeding was significantly higher in patients receiving anticoagulants, which is why it is recommended to use only echo-doppler control in patients with symptomatic distal deep vein thrombosis, without any associated anticoagulant therapy. New studies are necessary to assess the utility of prophylactic or intermediary anticoagulant doses in distal deep vein thrombosis patients.

Post-pulmonary embolism dyspnea: from physiopathology to clinical management:

Olivier Sanchez (France)

The 2014 ESC guidelines recommend that systematic screening for detecting chronic thromboembolic pulmonary hypertension be compulsory in patients with severe dyspnea following a pulmonary embolism. Dyspnea typically occurs 12 months after a pulmonary embolism, and it is more severe and frequent due to scintigraphic sequelae of pulmonary embolisms. In addition, effort dyspnea is common during a pulmonary embolism (20% to 40%). The pathophysiological mechanisms are not well known, but it is likely that the persistence perfusion and ventilation inequalities, as well as increasing physiological dead space, play an important role. Effort dyspnea in a pulmonary embolism requires systematic investigations to identify an underlying cardiovascular disease or chronic thromboembolic pulmonary hypertension. When chronic thromboembolic pulmonary hypertension is suspected, echocardiography and pulmonary scintigraphy are recommended, and confirmation can be obtained using right heart catheterization, pulmonary angiography, and an angioscanner. The 2014 ESC guidelines recommend using echocardiography as a first-line noninvasive investigation for diagnosis in case of suspected pulmonary hypertension with effort dyspnea. Right cardiac catheterization is recommended by the 2015 ESC-ERS guidelines for patients with an echocardiographic probability of intermediate or high pulmonary hypertension. Clinical trials have demonstrated that ventilation-perfusion scintigraphy is more sensitive than multidetector angioscanner (CTPA) for detecting chronic thromboembolic pulmonary hypertension. A clinical prediction score has been proposed for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism, but this model requires external validation before being applied in practice. Risk factors for chronic thromboembolic pulmonary hypertension within an acute pulmonary embolism include a personal history of pulmonary embolism, proximal pulmonary embolism, unprovoked pulmonary embolism, and an increase in systolic pulmonary artery pressure >60 mm Hg.

III Digital



IUA-SFMV Lyon, October 5-8, 2016

Digital revolution and e-vascular health

Introduction

François Becker (France)

New information technologies and nanotechnologies are expected to change the medical world deeply. Soon, telemedicine will be organized for vascular physicians, and image transfer will become common. These changes will affect the consultation regimens (acrosyndromes, ulcers, trophic disorders, limb edema, superficial venous thrombosis, etc), the management of vascular risk factors, the prevention of primary and secondary disease, the follow-up of chronic diseases, and the monitoring of patient compliance. The diagnosis and management of claudicant patients will evolve with sports applications, which will become peripheral arterial disease applications. Not only will blood pressure measurements become (already are) automated, but the screening and follow-up tests for asymptomatic patients will also become automated. Delays regarding the clinical visits and the overall costs will diminish. The author concluded by stating that whether we agree or not, a revolution is happening. Thus, the question is not if vascular physicians approve it or not, but whether they will become involved in the digital revolution.

Connected objects and e-health: what are we talking about?

Antoine Poignant (France)

Currently, 15 billion devices are connected worldwide, but it is estimated that this number will reach 80 to 100 billion by 2018. In France, three million patients were already using ambulatory monitoring devices in 2013, and it is estimated that this number will reach 19 million in 2018. Thus, connected health is becoming the new paradigm in medicine. Today, there are portable EKGs or automated retinopathy diagnostic devices that can detect and send relevant information to physicians. A very promising innovative device for vascular physicians is the Instent[®]. By providing instantaneous and noninvasive identification of the composition of tissues in contact with the stent (either myoepithelial cells from hyperplasia and restenosis or thrombus), Instent[®] sensor technology can overcome the limitations of vascular imaging techniques that are used in both interventions and patient follow-up, and it can alert the physician if any critical problem occurs. The combination between the life sciences and technology is now considered the third coevolution, making the victory of the transhumanism inevitable.

Place of the physician in this time of big data

Mehdi Benchoufi (France)

Big data in health care refers to the digital collection of health data that is so large or complex that conventional database management tools are insufficient to deal with the data. Three basic paradigms have been associated with the internet: connectivity, collectivity, and calculability. The possibility of putting together all existing data regarding a particular disease or a patient (medical notes, imaging, laboratory testing, sensor data, or even social applications (eg, Twitter, Tinder, blogs) will probably help save lives and money. In fact, finding associations or recognizing patterns and trends within the available data can be effective for these purposes. For instance, Spotify can track the first symptoms of depression, and Twitter has been used to keep up with HIV infections. The current issue concerning big data in medicine is to clearly understand how to predict, how to conceive, and how to know.

IV

Multidisciplinary Management



IUA-SFMV Lyon, October 5-8, 2016

Multidisciplinary vascular centers

The concept and its implementation

Fabrizio Benedetti-Valentini (Italy)

and The vascular medicine perspective

Adriana Visona (Italy)

Both speakers discussed two parts of the same subject. They introduced the problem of using a multidisciplinary treatment approach for vascular patients. According to the definition, a vascular center is a “dedicated center where patients with vascular disease can receive high-quality medical, endovascular, and open surgical treatment by appropriate experts working as a coordinated team.” A key component of a vascular center is the collaboration between vascular medicine, endovascular treatment, and vascular surgery; however, the center also provides training in vascular medicine, vascular surgery, and endovascular therapy and participates in vascular research. The idea for creating vascular centers was presented in 2003, and, in 2009, it was published in the guidelines (*Int Angiol.* 2009;28:347-352).

The majority of patients referred to a vascular center do not require surgical treatment. Vascular centers should have a minimum number of inpatients for conservative treatment: peripheral arterial occlusive disease >100; diabetic foot >80; deep vein thrombosis >100; chronic venous insufficiency >70; others ≈20. Patients should be cared for by a team who understands their condition completely and who can organize appropriate investigations and treatment. The minimum number of endovascular and open surgical procedures per year for vascular centers are as follows: carotid >50; abdominal aortic aneurysm >50; occlusive disease >100; combined procedures >20; trauma ≈20; varicose veins >100. For accreditation, vascular centers should have an endovascular unit, vascular surgical theater, C-arm radiolucent table, and a cell-saver that are all available 24 hours a day for emergencies and a hybrid radiosurgical unit, if possible. Therefore, only large articulated hospitals can host a vascular center.

The Commission for Accreditation of Vascular Centers was created in Buenos Aires, Argentina on April 21, 2010. After completing all requirements for visiting commissioners, any vascular center around the world can obtain the Diploma of Accreditation. Accreditation means that patients will know where to find the best vascular care and they can find these accredited vascular centers via the internet, even in an emergency. In addition, valuable supranational accreditation is crucial when dealing with the health authorities for funding and personnel equipment. Additional information can be obtained by sending an email to secretariat@angiology.org.

The vascular surgery perspective

Stephan Acosta (Sweden)

Acosta shared his experience working in the vascular center at the Skåne University Hospital (Malmö, Sweden). The center includes vascular surgeons, vascular physicians, and radiologists, and it focuses on transient ischemic attacks, ischemic stroke, angina pectoris, angina abdominals, pulmonary artery disease, and critical limb ischemia. Acosta is focused on the impact of preoperative evaluation by vascular physicians on mortality in patients undergoing surgical or endovascular procedures.

The best care to the vascular patient, every day: the benefit of a multidisciplinary vascular center

Peter Gloviczki (USA)

Peter Gloviczki from the Mayo Clinic (USA) started by quoting Dr William W. Mayo "No one is big enough to be independent of others," which is now a principle of the Mayo clinic. The Mayo Clinic's Gonda Vascular Center was founded in 1991. The center treats more than 30 000 people annually. The structure of the center includes units, such as peripheral vascular laboratories, an interventional radiology clinic, a thrombophilia clinic, a vascular surgery clinic, ultrasound laboratories, a wound care center, a vascular medical clinic, an early atherosclerosis and vascular rehabilitation clinic, a vein clinic, a vascular access clinic, a vascular malformation clinic, a lymphedema clinic, and an aortic center. Now, many multidisciplinary vascular forums are available, such as the Vascular Annual Meeting (VAM) of the Society for Vascular Surgery (SVS), the VEITH symposium, VIVA meetings, the American Venous Forum, European Venous Forum, Latin American Venous Forum, and Central European Vascular Forum, and the International Union of Angiology congress. The objective of these multidisciplinary forums and vascular clinics is to unite forces and include large-scale medicine, surgery, and endovascular interventions to treat vascular diseases at an international level.

Other experiences in Europe?

Karel Roztocil (Czech Republic)

The Czech Republic has created an original two-level system to care for vascular patients. In the first level, vascular care is performed in an outpatient vascular center, where the number of centers is expected to be around 2 to 3 per 100 000 inhabitants. The primary settings include essential diagnosis, outpatient therapeutic and prophylactic care for vascular patients with arterial, venous, lymphatic, and microvascular disorders, and the centers should have one or more physicians and one or more vascular nurses. First-level centers usually have the equipment to noninvasively evaluate pulmonary artery disease, diagnose venous thrombosis, evaluate chronic venous disease, lymphatic disorders, and vascular functional disturbances, and collaborate with the vascular centers. The vascular centers (angiology and vascular medicine centers) have highly specialized facilities that should provide all traditional and newer innovative approved surgical, nonsurgical, interventional, and medical treatment. The vascular center philosophy involves a multidisciplinary cooperation of vascular medicine with vascular surgery, cardiovascular surgery, cardiology, noninterventional and interventional radiology, podiatry, diabetology, wound care, hematology, etc. Per year, each vascular center must have a minimum number of patients, including 1000 noncoronary diagnostic or interventional cases; 100 open vascular surgeries; 25 stent grafts, and they must have accreditation for angiology. Today, the density of vascular centers is 1.8 centers per million inhabitants. Highly specialized care for selected vascular cases is available by intermediacy of vascular centers covering the territory of the country. Patients are benefiting from a comprehensive approach, concentrated technologies, devices, and treatment strategies provided by a multidisciplinary team. As a result, according to the registry data on open vascular surgery and endovascular interventions in the Czech Republic, there are around 250 per 100 000 inhabitants (one-quarter are open surgery and three-quarters are endovascular interventions).

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