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Medical Reporters' Academy

The reports from the UIP chapter meeting and Charing cross international symposium

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Foreword

The Medical Reporters' Academy was co-founded in 1994 as a joint initiative by clinical and research venous disease specialists and Servier; with the main objective to develop an international group of young specialists with a core interest in venous disease drawn from various fields including dermatology, vascular surgery, angiology and/or phlebology. Each year the Medical Reporters' Academy members are invited by Servier, to cover one of the most important international congresses for venous disease specialists.

This year, the UIP Chapter Meeting, which was held in Krakow, Poland on August 25th- 27th, 2019 and the Charing Cross International Symposium: Vascular & Endovascular Challenges Update which was held in London, United Kingdom on April 15th - 18th, 2019 were selected because these congresses involved renowned international and national venous experts and young health care professionals providing a great opportunity to exchange ideas, explore strategies for vein care and discuss the latest trends & innovations in the field. Together with Andrew Nicolaides, the chairman of the group, the academy members explored the program of the congress, selected the events and presentations likely to present breakthroughs or new findings to attend, and wrote short reports. These reports are provided in this issue of Phlebolympology.

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 Reporters' Academy throughout the congress.

We would like to thank *Andrew Nicolaides (Cyprus)* and the members of the Medical Reporters' Academy: *Roman Bredikhin (Russia)*, *Kirill Lobastov (Russia)*, *Daniela Mastroiacovo (Italy)*, *Mustafa Sirlak (Turkey)*, *Stanislava Tzaneva (Austria)* for their valuable work in updating venous specialists.

Editorial Manager



I UIP Chapter Meeting



August 25th -27th 2019, Krakow – Poland



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I. UIP: introduction

Presidential Lecture

Nick Morrison (US)

Following a short welcome, the President presented the role of International Union of Phlebology:

1. Strengthen the links between the member societies, either existing or to be created, which have a special interest in the study and therapy of venous and lymphatic disorders.
2. Promulgate recommendations on the teaching of phlebology, as well as the training and continuing medical education of phlebologists.
3. Promote a consensus on all aspects of venous and lymphatic disorders.
4. Encourage clinical and basic research on venous and lymphatic disorders.
5. Promotion of regional, national, and international congresses in order to foster an exchange of information between the phlebology communities.
6. Encourage the creation and activities of national phlebology societies or professional associations.

UIP future: our vision and mission

Kurosh Parsi (Australia)

In 2019, there was a global representation of 74 member societies, including 8 multinational societies from 48 countries.

- International Union of Phlebology strengths
 1. It brings the world of phlebology together.
 2. Multiple consensus guidelines initiated and published under the auspices of the International Union of Phlebology.
- International Union of Phlebology challenges
 1. Juggling language barriers and cultural differences.
 2. It has been criticized for too much "politics."
 3. The International Union of Phlebology is totally dependent on its executive committee.
 4. The regulations are based on out-of-date methods of voting and elections.
 5. No sound financial structure.

The current mandate is for the International Union of Phlebology to represent all member societies equally. Unfortunately, phlebology is present in not more than 100 countries and, when present, it is not represented as a specialty or subspecialty. It is also not understood by the public.

Problems we face as a specialty:

1. Training is limited or nonexistent in many countries.
2. Vascular training programs do not have a strong venous or lymphatic component.
3. In the developing world, doctors need help.
4. Phlebology is a multidisciplinary specialty with several components from vascular surgery, medicine, interventional radiology, and dermatology. Phlebology training needs to bring all disciplines together.

II. Consensus reports

UIP consensus report - contraindications to sclerotherapy

Kurosh Parsi (Australia)

This presentation was a summary of the available literature. Absolute contraindications include previous anaphylaxis to sclerosants and acute deep vein thrombosis. Relative contraindications include deep venous obstruction, peripheral vascular disease, a thrombophilic disorder increasing the risk of deep vein thrombosis, immobility, acute superficial vein thrombosis, pregnancy and breastfeeding, estrogen therapy, hormone-replacement therapy, asthma, migraine, systemic disease associated with skin changes, obesity, advanced age, anticoagulation, pelvic tumors causing varicose veins, foramen ovale, and proposed long-distance travel.

UIP consensus report - pelvic venous insufficiency

Zaza Lazarashvili (Georgia) and Pier Luigi Antignani (Italy)

The main clinical symptom of pelvic congestion syndrome is noncyclical pelvic vein, which can be exacerbated by postural changes, walking, and sexual intercourse; also during menstruation. Other clinical manifestations that may be present include dysmenorrhea, vaginal discharge, dysuria, urinary frequency, nausea, bloating, abdominal cramps, and rectal discomfort. The main clinical sign is the presence of varicose veins on perineal, vulval, gluteal, or posterior thigh areas. Transabdominal ultrasound is the first noninvasive investigation that can exclude intrinsic pelvic conditions, demonstrate pelvic varicosities, and suggest ovarian vein insufficiency. However, transvaginal ultrasound is considered to be the examination of choice since it offers better visualization of pelvic venous plexus. In addition, duplex ultrasonography of the lower extremity veins is a necessary part of the protocol especially in the presence of atypical varicose veins. Catheter-directed retrograde selective venography of ovarian and internal iliac veins is the method of choice for the diagnosis of pelvic venous pathology. Diagnostic criteria for pelvic congestion syndrome include (i) an ovarian vein diameter more than 6 mm with proven reflux, (ii) contrast retention for more than 20 seconds, (iii) congestion of the pelvic venous plexus and/or opacification of the ipsilateral (or contralateral) internal iliac vein, or (iv) filling of vulvovaginal and thigh varicosities. Treatment consists of transcatheter embolization (with mechanical and/or chemical agents) in order to occlude insufficient venous axes as close as possible to the origin of the reflux. Medical therapy for pain relief and micronized purified flavonoid fraction are useful adjuvants. Current challenges consist of (i) adoption of modern terminology and definitions instead of historical nomenclature, (ii) creation of a new classification, (iii) development of a disease-specific patient-reported outcome tool, (iv) introduction of new International statistical classification of diseases and related health problem codes to improve relations with insurance companies, reimbursements, and money for the initiation of large, multicenter clinical trials.

UIP consensus report - venous mapping

Kurosh Parsi (Australia) and Pier Luigi Antignani (Italy)

Currently, inconsistent and variable venous maps are produced by various radiology practices and vascular laboratories. Maps should include the whole system of superficial and deep veins above and below the knee. All veins should be assessed for patency or occlusion. Signs of previous thrombosis (septa, synechia, and wall thickening) should be recorded. Competence and reflux should also be recorded. Additional findings should be recorded, such as duplication, absence or agenesis, popliteal vein or artery compression, Baker's cyst, and vascular anomalies, eg, arteriovenous malformation. Symbols should be used to denote key findings. Proposed symbols in the International Union of Phlebology Consensus on venous mapping should be universally adopted.

UIP consensus report - venous rehabilitation

Alberto Caggiati (Italy)

Currently, prevention and rehabilitation in patients with venous diseases is limited to compression stockings and medications. In contrast to cardiac, arterial, and lymphatic disorders, most guidelines do not mention rehabilitation protocols for venous patients, despite the fact that several studies have demonstrated the efficacy of nonsurgical and nonpharmacological protocols in preventing disease progression and/or recurrence. The aim of venous rehabilitation is to prevent disease progression, prevent complications, reduce symptoms, and improve quality of life. A number of comorbidities influencing venous return should be addressed, such as loss of weight in obese patients, correction of plantar abnormalities, ankle joint flexibility, and muscle strength. Gait analysis has demonstrated that, in venous disease patients, joint flexibility and muscle efficiency are impaired compared with normal age-matched subjects. The goal of gait reeducation is to regain the correct sequence of weight bearing, gait cadence, step length and speed, and to discourage the shuffling gait. Appropriate sports activities should be undertaken. It should be pointed out that the rehabilitative approach is expensive for patients and for the National Health Services; it also time consuming and not remunerative for phlebologists.

Pan-American consensus on ultrasound-guided foam sclerotherapy

Victor Canata (Paraguay) and Sergio Garbarz (Australia)

This presentation was held in the form of questions and answers.

1. Why do you consider ultrasound-guided foam sclerotherapy useful? Ultrasound-guided foam sclerotherapy is useful because it allows a complete view of the superficial intravenous space observing the foam and providing great safety by avoiding the deep venous system.
2. Should the vein be empty prior to the injection? The vein has to be as empty as possible during the injection.
3. Is ultrasound-guided foam sclerotherapy on its own an efficient method of sclerosing venous axes or does it require additional physical procedures? Ultrasound-guided foam sclerotherapy is an efficient method of treatment on its own, but it is not 100% positive.
4. What is the goal of the treatment? The goal of the treatment is the elimination of reflux with eventual occlusion of the vein without residual thrombus.

5. What are the treatment advantages? Ultrasound-guided foam sclerotherapy has the lowest cost with a quick return of the patient to a normal life.
6. How important is the quality of the foam? It is crucial, in terms of density as well as durability. It is important to obtain a strong, dense, and homogenous foam with no visible bubbles.
7. What are the most important ultrasound observations? Vasospasm, parietal edema, needle visualization, direction of the circulation, and foam distribution.
8. What is the liquid:gas ratio? The liquid:gas ratio used in preparation of the foam is 1: 4.
9. What is the needle caliber? The needle caliber used is the same for veins of all sizes.
10. Where should the treatment start? In a patient with great saphenous reflux from groin to ankle, the treatment should start proximally.
11. What is the amount of foam injected? The usual amount of foam is between 1 and 10 mL.
12. What is the maximum amount of foam? The maximum amount of foam is 10 mL for each treatment.
13. Is elastic compression necessary? Elastic compression is used for 7 to 10 days by 55% and 30 days by 40% of phlebologists.

III. Major scientific findings in phlebology in the past 2 years

Major scientific findings in phlebology in the past 2 years

Andrew Bradbury (UK)

- **ATTRACT Trial conclusions**

New Engl J Med. 2017

Among patients with acute proximal deep vein thrombosis, the addition of pharmacomechanical catheter-directed thrombolysis to anticoagulation did not result in a lower risk of the postthrombotic syndrome, but did result in a higher risk of major bleeding.

- **ATTRACT femoropopliteal analysis 2019**

In patients with acute femoropopliteal deep vein thrombosis, pharmacomechanical catheter-directed thrombolysis did not improve short- or long-term efficacy outcomes, but it did increase bleeding.

- **ATTRACT iliofemoral analysis 2019**

In patients with acute iliofemoral deep vein thrombosis, pharmacomechanical catheter-directed thrombolysis did not influence the occurrence of postthrombotic syndrome or recurrent venous thromboembolism. However, pharmacomechanical catheter-directed thrombolysis significantly reduced early leg symptoms and, over 24 months, reduced postthrombotic syndrome severity scores, reduced the proportion of patients who developed moderate-to-severe postthrombotic syndrome, and resulted in a greater improvement in venous disease-specific quality of life. It was pointed out that the proportion of patients benefitting is relatively small and cannot be predicted reliably at baseline. In addition, the clinical benefit is modest for most and the risk of major bleeding has tripled with pharmacomechanical catheter-directed thrombolysis. Now, there is no health economic analysis and the number needed to treated to lead to a clinically meaningful reduction in postthrombotic syndrome severity is not yet known. The primary outcome may yet change with a longer-term analysis.

- **EVRA trial conclusions**

New Engl J Med. 2018

Early endovenous ablation of superficial venous reflux resulted in faster healing of venous leg ulcers and more time free from ulcers than deferred endovenous ablation. However, based on the selection criteria of ulcer duration >6 months and ankle-brachial pressure index <0.8; only 7% of screened patients were eligible. Currently, we do not know if it will be clinically effective and cost effective to refer all leg ulcer patients to secondary care.

- **EVRA cost-effectiveness analysis**

Br J Surg. 2019

Not only is endovenous ablation of superficial venous reflux for venous leg ulcers clinically effective but it is also highly cost-effective (ICER < 5000 Euro per QALY).

IV. Phlebolympiology forum

Functional relationship of the lymphatic and venous systems in clinical aspect

Waldemar L. Olszewski (Poland)

The blood and lymph circulation systems arise simultaneously in the embryo. The lymph sacs are formatted from the venous endothelial cells. Peripheral blood (arteries and veins) and lymphatic vessels originate from the same tissue mesenchymal cells. They differentiate into the hematological (blood vessels) or tissue fluid channel (lymphatic channels) structures. Eventually the lymphatic vessels join veins in the subclavian-jugular angle and hundreds of lymphovenous communications in the limbs and the retroperitoneal space. This order of events indicates that both systems are functionally dependent. This dependence is particularly important in lower limbs, as their skin, subcutaneous tissue, and muscles undergo continuing microtrauma (gait, runs) and penetration of microbes from the foot and perineum (skin microabrasions). Waldemar L. Olszewski raised the question about whether venous insufficiency with incompetent valves and local thrombi affect limb tissue and draining lymphatic vessels. Today, venous ultrasonography and fluorescent indocyanine green lymphography can be performed simultaneously or one immediately after the other to depict sites of venous and lymphatic changes. The obtained pictures give insight into the venous blood and tissue fluid/lymph flow impairment and the clinical consequences as edema, inflammation, dermatoliposclerosis, and ulceration. We can see that both the venous and lymphatic vasculature are simultaneously affected. In conclusion, Waldemar L. Olszewski emphasized that leg venous system insufficiency is followed by changes in the microcirculation (excess capillary filtration), excess fluid/lymph in the tissue, retention of metabolites, cellular debris, and microorganisms. Subsequently damage to lymphatic vessels, fibrosis of skin and fascia, and total depletion of lymphoid tissue from lymph nodes develops. This pathological chain of events shows the functional relationship between the venous and lymphatic systems in case of venous insufficiency.

Contemporary methods of visualization and functional evaluation of lymphatics and veins in limbs-hints for therapy

Marzanna T. Zaleska (Poland)

Impaired venous blood and tissue fluid/lymph flow away from limb tissues causes retention of fluid in the extravascular and extracellular space, which is called edema. The effects are major changes in epidermis, dermis, subcutaneous tissue, fascia, and in muscles (to a lower extent, but it is still present), including hyperkeratosis, dermatofibrosis, subcutaneous and fascia fibrosis, and a dilated muscle vein network. Evidence of fluid accumulation sites and the fluid volume is crucial for effective treatment to prevent development of tissue changes. Marzanna T. Zaleska listed examples of methods used to evaluate limb edema, such as skin water concentration, skin tonometry, tissue fluid pressures during compression, fluid movement measure, bio impedance, effective compression force measurement, and inflated cuff edema fluid movement. She concluded that lymphatic and venous edema is not only an excess of water in the interstitial space, but also an increased mass of cells and ground matrix. Evaluation of the changes in edema requires measurements of fluid volume, pressure, movement through the tissue space, tissue cells, fibers, and blood vessel mechanical structure and resistance to compression force. Massaging out fluid does

not decrease the limb volume to normal values, as the increased cell and matrix mass remains unchanged. Measurements help to understand changes in lymphedematous tissue.

Lymphedema: where we are today?

Tanja Planinsek Rucigaj (Germany)

The incidence of lymphedema after lymphadenectomy for melanoma can be up to 44% after therapeutic groin dissection for palpable disease, but the incidence following sentinel lymph node biopsy is much less. The estimated incidence of breast-cancer related lymphedema ranges from 13% to 50%. The incidence of lower limb lymphedema following radical hysterectomy alone is estimated at 5% to 10%, but can be as high as 49% by 10 years of follow-up in patients who also received adjuvant radiation treatment. The average time from appearance of lymphedema to the start of therapy was 7 years in Slovenia. Only 3 patients received therapy for lymphedema as soon as the edema started. The maximal time from beginning of lymphedema to therapy was 28 years. In Slovenia, secondary lymphedema makes up 74.4% of cases; following cancer therapy it is 56.2% and due to other causes it is 43.8%. Primary lymphedema makes up 25.6% of patients with lymphedema. Tanja P. Rucigaj presented her study in patients with secondary lymphedema in which the edema was quicker, soft, and small in patients where underpadding materials were used in comparison with short-stretch bandages without underpadding. Patients with lymphedema have a poor quality of life and, at a higher stage of lymphedema, the quality is lower. Patients are less mobile and often have associated diseases, such as obesity, degenerative changes in the joint, heart diseases, and carcinomas. It is important to prevent complications and disease progression as soon as possible and as complete a treatment as possible. In a clinical study, two different short-stretch systems were compared from the viewpoint of patients and of staff, showing no differences in slippage, both systems were very comfortable, and patients did not have any problems with mobility and wearing their usual footwear. Compliance was slightly better in the patients with one-layer, adhesive, short-stretch system. The staff said that experience with applying both compression systems is the most important.

Daily practice in diagnosis and therapy of veno-lymphatic disease of limbs

Andrzej Szuba (Poland)

Venolymphatic edema can be caused by chronic venous insufficiency, vein compression/occlusion, and congenital venolymphatic abnormalities. Andrzej Szuba presented the pathophysiology of venolymphatic edema. A venous valve damage/obstruction leads to chronic venous hypertension with the consequences of lymphatic system overload, damaged lymphatic capillaries/vessels, occlusion of lymphatic capillaries, damaged anchoring filaments and lymphatic valves, increased lymphatic capillary permeability, lymph reflux to superficial lymphatic plexus with lymph stasis, and impairment in local immune defense. These consequences cause skin, subcutaneous tissue, and venous wall inflammation, edema, lipodermatosclerosis, and ulcers. In daily clinical practice, medical history, clinical exams, and treatment are the three most important pillars. Medical causes of peripheral edema should be excluded. The general examination includes blood pressure, heart and lung auscultation, jugular vein assessment, and abdominal assessment. A focused examination includes edema, peripheral pulse control, skin

condition, and Stemmer sign. If necessary additional tests can be performed, such as Ratschow, ankle brachial index, venous ultrasound, lymphoscintigraphy, etc. The next step is the selection of optimal therapy, including appropriate skin/wound care, compression therapy (the most important), pharmacotherapy (flavonoids, sulodexide, antibiotics, antifungal, etc). This seminar finished with a discussion on venous obstruction and lymphedema. The clinical course is characterized by sudden onset, rapid worsening, or edema not responding to compression therapy. Signs of venous congestion are delayed emptying of superficial veins, venous collaterals, telangiectasias and, bluish discoloration. As a diagnostic method, color Doppler can be often misleading, MRI venography is promising, and a CT scan is very useful.

Complex lymphedema treatment in the dedicated centre – lesson learned

Franz Josef Schingale (Germany)

Lymphedema treatment can be subdivided in two phases. Phase 1 aims to reduce the edema and consists of manual lymphatic drainage, skin care, bandaging, exercises, self-management. Phase 2 aims for optimization and conservation and consists of manual lymphatic drainage, skin care, made to measure stockings, exercises, and self-management. Franz J. Schingale mentioned additional therapies, such as intermittent pneumatic compression, pulsed magnetic field, CO₂ gas and ozone, Hivamat (electrostatic field, produces deep oscillation), Flowave (hearable sound waves, produce bio resonance to the molecules), infrared cabin, and soft laser.

Contemporary surgical treatment of lymphedema of limbs and other organs-practical hints

Waldemar L. Olszewski (Poland)

Waldemar L. Olszewski elucidated the present state of clinical experience in the surgical treatment of lymphedema. In the early stage I, afferent lymphatic vessels are present on lymphograms. Recommended procedures include lymph node-saphenous vein shunts, lymphatic-saphenous vein branch through vein wall puncture, or end-to-end shunt. In advanced stages II and III, no afferent lymphatics are present on lymphograms. In these stages, the treatment methods are excision of fibrotic lymph nodes and obliterated afferent lymphatic vessels, silicone tubing implant bypassing the sites of lymph flow obstruction. In advanced stage IV, fibrotic skin, subcutaneous tissue, and fascia are present. The treatment of choice for advanced stage IV is debulking by excision of wide skin, subcutaneous tissue, and fascia strips. Compression and long-term penicillin are recommended in all stages.

Professional medical networking in lymphology and phlebology – the patient is the focus

Oliver Gültig (Germany)

Manual lymph drainage is very effective, but only in conjunction with specialized compression bandages, decongestive exercises, professional skin care, and supportive self-management. In 2019, Germany had over 900 curricular-trained physicians in lymphology, 70 000 specialized physiotherapists, a large number of competent garment specialists, more than 90 lymphology-phlebology networks, cooperation with nursing professions, and founding of many lymphology self-help groups. The status quo in

outpatient lymphology is the following: diagnose and treatment quality is under clinical conditions, countrywide seminars for patients about accompanying self-management, the nonprofit organization Lymphologicum German Network association, guides, and magazines for patients. As a result, treatment becomes cheaper, teamwork gives pleasure, and patients have more quality of life.

Translational/integrated medicine and lymphology

Attilio Cavezzi (Italy)

Science is provisional and we are by no means anywhere near the point of knowing all. Science is a constantly changing base of knowledge. We know about 4% of our reality and of science about health and diseases. Translational medicine is an interdisciplinary branch of the biomedical field supported by three main pillars: bench side, bedside, and community. The goal of translational medicine is to combine disciplines, resources, expertise, and techniques within these pillars to promote enhancements in prevention, diagnosis, and therapies. It is a highly interdisciplinary field that wants to join different biomedical cultures to improve the global health care system significantly.

Attilio Cavezzi presented the revised Starling principle, ie, microvascular fluid exchange. In steady state, a slight filtration prevails in most vascular beds. Lymph transport, but not venous capillary reabsorption, is the main process responsible for interstitial fluid balance. Chronic low-grade cellular inflammation is the root of all degenerative chronic diseases and of lymphedema as well. Microvascular tissue derangement in lymphedema includes edema, hypoxia, oxidative stress, inflammation, and fibrosis. Proper nutrition/time-restricted feeding (intermittent fasting) must be included in the holistic treatment of lymphedema to improve anti-inflammatory, antiedema, and antioxidative stress role of the nutrients/fasting, obesity/overweight issue. Excessive carbohydrate intake is the key nutritional factor to generate inflammation. Bad nutrition habits (industrial country nutrition), degeneration of the Mediterranean diet, modern cereals, and industrialized food increase the chronic low-grade proinflammatory cellular processes, which generate and perpetuate edema. Overweight and obesity lead to metabolic syndrome and cardiac/renal edema-generating factors. Fat deposition in the tissues recalls fluids and it is accompanied by liver steatosis, which is related to edema. Antihypertension drugs generate venulodilatation and edema. Hormonal changes, which induce edema, are caused by higher cortisol, insulin, etc. Obesity is also accompanied by dysfunction in the diaphragm and in venolymphatic return. When examining nutrition and dietary interventions for lymphedema, positive effects were found in a systematic review for lymphedema volume reduction. An anti-inflammatory (antiedema) strategy, based on nutrition/nutraceuticals, includes balanced nutrition, integration with omega3, a low carbohydrate diet, and an increase in polyphenol intake.

Hormesis is a biological phenomenon where a beneficial effect (health improvement, improved stress tolerance, longevity) derives from the exposure to (low doses of) a chemical/physical agent that is, conversely, toxic or lethal at higher doses. The main beneficial processes for cell health are autophagy activation, mammalian target of rapamycin (mTOR) blockage, sirtuin activation, interferon gamma 1/leptin decrease, and misfolded protein removal/repair. Intermittent fasting also demonstrated benefits; it improves cardiovascular risk, reduces the risk of cancer, improves immunity, causes weight loss, increases longevity, increases insulin sensitivity, burns fat instead of sugar, reduces

inflammation-inflammaging, improves cognitive function, and improves skin healing process.

Next, Attilio Cavezzi discussed a study with the conclusion that respiratory muscle pressure production is the predominant factor (2- to 3-fold) modulating venous return from the locomotor limb both at rest and during calf contraction even when the veins of the lower limb are distended due to the presence of a physiologic hydrostatic column.

The symposium finished with a review of the anti-inflammatory properties of the vagus nerve. Breathing increases the centripetal lymph drainage as a mechanical action and has an anti-inflammatory action (vagus activation) and a biochemical action.

V. What is new in our understanding of the chronic venous disease?

Our current understanding of the chronic venous obstruction

Christopher Lattimer (UK)

Christopher Lattimer explained the different aspects of obstruction, depending on if it is in a vein (anatomical lesion), on a vein (radiological compression), concerned with venous drainage (hemodynamic), or its clinical definition (symptoms and signs). He elucidated the importance of collaterals on the symptoms and signs and emphasized that symptoms and signs are not specific for postthrombotic syndrome. Radiologically following measurements are possible, including the minor diameter, area, shape, length, tortuosity, aspect ratio. He also introduced the venous filling index (mL/s) and the venous drainage index (mL/s), which can be used to assess the reflux and the obstruction, as well as the difference between waterfall drainage and hydrostatic drainage. Patients with obstructions had a reduced venous drainage index, increased venous drainage time, a hydrostatic curve (not waterfall drainage line), and increased drainage reserve volume. It is important to differentiate leg obstruction from obstruction of a vein. Diameter measurements are unrealistic, but the pathobiology is postthrombotic fibrosis. Christopher Lattimer pointed out that hydrostatic pressure is an obstruction to drainage that patients with suspected obstruction have increased filling and air-plethysmography measurements both in mL/s.

What is new in our understanding of the cerebral venous outflow? – possible link with neurodegeneration

Marian Simka (Poland)

Marian Simka, introduced the term chronic cerebrospinal venous insufficiency (CCSVI). Venous abnormalities in the internal jugular veins can be found not only in patients with multiple sclerosis, but also in patients with other neurological diseases and even in many healthy controls. Three prospective randomized clinical trials (in the US, Canada, and Italy) assessed whether endovascular treatment for CCSVI is effective in patients with multiple sclerosis. The US study concluded that venous angioplasty is not an effective treatment for multiple sclerosis over the short term and may exacerbate underlying disease activity. The data from the Canadian study did not support the continued use of venoplasty of extracranial jugular and/or azygos venous narrowing to improve patient-reported outcomes, chronic multiple sclerosis symptoms, or the disease course of multiple sclerosis. The Italian study summarized that venous percutaneous transluminal angioplasty is a safe, but largely ineffective technique; the treatment cannot be recommended in patients with multiple sclerosis. The Italian study is the only one that used experienced interventionalists. The reasonable conclusion should be that hemodynamically ineffective venous angioplasty, especially if performed by inexperienced interventionalists, is not an effective treatment for multiple sclerosis. However, other studies have shown that only some CCSVI lesions can be successfully managed with balloon angioplasty. In the Brave Dreams study, there were better clinical outcomes (fewer new multiple sclerosis lesions) after successful angioplasty (Zamboni P et al; Brave Dreams Research Group. *JAMA*

Neurol. 2018;75(1):35-43). Endovascular treatment for CCSVI may be effective in some patients, but unfortunately, no new studies have been planned.

Chronic venous thrombosis – does it really exist

Nicos Labropoulos (US)

Nicos Labropoulos opened his talk saying he opposed acute thrombosis to chronic changes. Chronic changes are characterized by decreased vein diameter, wall thickening, rough borders, heterogeneous texture, intraluminal septa, reflux, and increased echogenicity. In addition, secondary chronic venous disease progresses faster than primary.

The diagnosis of recurrent deep vein thrombosis can be difficult; one clue could be if a thrombus in new location is detected in a different vein segment, a different extremity, or it is propagated to a new level. If the thrombus is in a previously affected segment, possible indicators are increments of thrombus thickness >4 mm in proximal veins or >2 mm in calf veins. The problem is that many patients receive anticoagulation and sometimes thrombolysis for the diagnosis of chronic deep vein thrombosis, which is connected to significant costs and puts the patients at risk of bleeding.

Nicos Labropoulos then explained the histological findings. Tissue causing chronic postthrombotic venous obstruction is made up of 80% to 90% type I collagen and 10% to 20% type II collagen, and it shows dystrophic calcification. A prospective clinical study showed that both patients with acute deep vein thrombosis and patients with postthrombotic syndrome had an increase in vein wall thickness localized to the affected segments as compared with controls, demonstrating that the term chronic deep vein thrombosis is erroneous and could be dangerous.

Nicos Labropoulos finished by stating that a new term is needed and he proposed chronic postthrombotic luminal changes, chronic venous or endovenous fibrosis, synechia, or other.

Neck vein obstruction: diagnosis and the role of chronic *Chlamydophila pneumoniae* infection

Paul Thibault (Australia)

Neck vein obstruction associated with chronic diseases is a chronic vascular condition characterized by multiple obstructions of the principal pathways of extracranial venous drainage. Obstruction of venous outflow leads to the development of various collaterals. This condition is usually silent due to the development of collaterals and shunting of the internal jugular vein system to the cerebrospinal system and vice versa. Internal jugular veins are the predominant drainage of the brain in a supine position and the cerebrospinal venous system is the predominant system in an erect position. The cerebrospinal venous system is a unique, large-capacitance, valveless, plexiform venous network in which flow is bidirectional, which plays an important role in the regulation of intracranial pressure; whereas, in a diseased state, it provides a potential route for the spread of infection, emboli, or tumors. *Chlamydophila pneumoniae* was first isolated in 1965 and recognized as a human pathogen in 1985. *C. pneumoniae* is an obligate intracellular bacterium that causes 10% of community-acquired pneumonia, bronchitis, pharyngitis, sinusitis, and otitis media. By the age of 20, 50% of the population have

antibodies, and, by the age of 65, 75% have antibodies. Reinfection is common and is accompanied by a stronger antibody response (IgG and IgA). *C pneumoniae* can survive, multiply, and persist within macrophages and lymphocytes. Infected monocytes transmit *C pneumoniae* to the vascular endothelium. It cannot be eliminated from infected monocytes using standard antichlamydial or antimicrobial agents. Transmission to monocytes can occur via the arterial system or via the lymphatic venous system, and there is evidence of *C pneumoniae* infecting the venous system. Diagnostic markers of chronic persistent *C pneumoniae* infection include *C pneumoniae* serology (sensitivity 60% to 80%), disturbed cholesterol and low-density lipoprotein metabolism, inflammatory markers (C-reactive protein), liver disorders, disturbed iron homeostasis (ferritin, low iron, low transferrin). These five factors and extracranial venous drainage neck veins create an algorithm that can predict the likelihood of a diagnosis of chronic persistent *C pneumoniae* infection in appropriate clinical settings. The diagnostic markers can also be used to monitor treatment effectiveness.

What is new in our understanding of the chronic venous disease pathogenesis at the cell and tissue level

Ferdinando Mannello (Italy)

Although chronic venous disease is among the most frequent diseases worldwide, biomolecular pathophysiology of both chronic venous disease and chronic venous insufficiency is poorly understood. Cytokines, chemokines, and matrix metalloproteinases (MMPs) are implicated in the etiopathogenesis and progression of the disease. A harmful link among hypertension, inflammation, and proteolysis has been proposed, and the five steps in the pathophysiology include: (i) hemodynamic alterations; (ii) endothelial-glycocalyx dysfunction and leucocyte infiltration; (iii) inflammation and proteolysis; (iv) extracellular matrix and vein remodeling; and (v) chronic venous disease/chronic venous insufficiency evolution.

Ferdinando Mannello reported that MMPs are implicated in varicose vein pathology because, experimentally, MMPs cause venous dilatation, meaning they are also implicated in chronic venous insufficiency progression and they may delay healing. Several venoactive drugs improve venous functions. For example, sulodexide improves vein contraction and decreases MMP-2 and MMP-9 levels in veins under prolonged stretch. Sulodexide may be important both in venous leg ulcers and in treating varicose veins and symptoms. Venous hypertension characterizes chronic venous disease/chronic venous insufficiency. Changes in venous hypertension and shear stress lead to a pro-inflammatory state, as well as active proteolytic remodeling. Inflammatory mediators and proteinase MMPs are key regulators in venous leg ulcers and varicose veins conditions. MMP-2 and MMP-9 (gelatinases) and MMP-12 (elastase) play crucial roles in venous dilation during varicose veins and extracellular matrix remodeling during venous leg ulcer formation. Glycosaminoglycan sulodexide restores the vessel glycocalyx, protects the vascular endothelium, presents anti-inflammatory properties, shows antiproteolytic effects inhibiting MMP proteolysis, and promotes venous contraction.

Every valve tells a story! What to do we know from HR ultrasound research on the valve impact on the CVD occurrence and progression – clinical implications

Johann Christof Ragg (Germany)

Healthy valves are so tender they sometimes do not show up on ultrasounds, and B-flow may indicate the outlines. It takes high-resolution ultrasound to visualize valves and valve action. Johann C. Ragg presented The Berlin Vein Valve study performed between 2016 and 2019, where the main objective was early stage evaluation. The participants were children between 4 and 18 years old. The incidence of embryonic valve lesions was 47.8% in children aged 6 to 8 years and 62.2% in children aged 14 to 18 years. There were missing valves in 19%, commissural mismatch in 62%, and single-cusp malformation (fastest progression) in 13% of the participants. In most cases, only 1 valve was initially concerned (74%; children aged 4 to 10 years). The main factors of severity were height of the unseparated diastolic blood column and the vein diameter. The proposed therapy is valve repair with perivenous hyaluronan, which reduces commissural gaps.

Pressure stress, indicated by dilatation, may be focal (valve), segmental (several leaking valves), or general (congestion). Decompensation may be spontaneous or gradual over the years. Primary pressure-related decompensation means the first valve to be concerned in this region. Secondary pressure-related decompensation means that a consecutive valve below the primary leaking valve is involved. Johann C. Ragg divided pressure-related valve decompensation into 3 stages, IR, P1, P2, and P3. P1 is predecompensation with a functional reserve of <20% of the vein diameter at the valvular level, P2 is a diastolic gap and reflux, and P3 is an extending gap, covering >75% of the vein cross section, cusps flipping over, or cusps partially or totally reversed. The proposed therapy for P1 is external or internal compression; for P2, internal compression, (if effective) or external compression; and for P3, internal compression. Stress-related valve degeneration correlates with low flow/stasis and it occurs at the largest distance from the muscle pump. There are three stages of stasis-related valve degeneration: S1a, alteration of sinus hemodynamics; S1b, restriction of cusps function; and S1c, fixation of cusps without reflux. There are three mechanical causes of primary venous insufficiency: embryonic valve lesions, pressure-related valve degeneration, and stasis-related valve degeneration. The data presented in this talk showed a clear demonstration of the physical origins and reasons for progression, meaning that high-resolution ultrasound is the key to understanding venous valve function/dysfunction. The better we understand vein valve function, the better we can learn to stabilize its function.

Venous diameter, clinical severity and quality of life – does the size of incompetent vein matters?

Sarah Onida (UK)

Sarah Onida discussed vein diameter versus reflux, stating that, in a clinical study, a great saphenous vein <5.5 mm in diameter showed an absence of abnormal reflux and a great saphenous vein >7.3 mm in diameter showed critical reflux. She also discussed vein diameter versus CEAP, showing that, in a French study, >50% of the patients had great saphenous vein diameters <6 mm. Great saphenous vein diameter showed a weak association with venous clinical severity scores in two other trials. In a British trial, great saphenous vein diameter was a poor surrogate marker for assessing the effect of varicose veins on a patient's quality of life. Vein diameter is not a parameter on which to rationalize treatment. In a systematic review on the relationship between vein

diameters, clinical severity, and quality of life, it was concluded that there is a weak correlation between truncal vein diameter and clinical severity of disease, but there was no association between vein diameter and health-related quality of life. In addition, there is no mention of vein diameter in treatment strategies. Sarah Onida concluded by stating that vein diameter should not be used as a stand-alone assessment to determine whom to treat. Clinical and quality of life assessments should lead to the decision, whereas, vein diameter is important to determine which treatment modality to use.

Obesity and inflammation in venous and lymphatic diseases

Gabriele Färber (Germany)

Gabriele Färber presented the epidemiological facts about obesity in Germany and discussed how it relates to venous and lymphatic diseases. Normal-weight individuals are a minority. At the end of their working life, 74.2% of men and 56.3% of women are overweight. The proportion of obesity in the population was 12% in 2000, 15% in 2009, and 23.6% in 2015. The proportion of morbid obesity in the population (BMI ≥ 40 kg/m²) increased by 300% (males) and 175% (females) between 1999 and 2013. There is an age-related increase in the prevalence of thromboembolic events, chronic venous insufficiency, and secondary lymphedema. Consequently, the number of patients with these conditions, who are also severely obese, increased. Obesity is not only cause for deterioration, but also often the sole cause. There is a correlation between visceral obesity, chronic inflammation, insulin resistance, and venous thromboembolic events, postthrombotic syndrome, secondary functional venous insufficiency, venous ulcers, obesity-associated secondary lymphedema, and secondary lymphedema in lipedema. There are different explanatory approaches. Mechanical mechanisms that may play a role are increased intra-abdominal pressure and increased intertriginous pressure leading to increased venous pressure in leg vessels. Metabolic, chronic inflammatory, and prothrombotic changes are important factors. Abdominal obesity increases the risk of thrombosis by increasing the activity of the coagulation cascade, decreasing the activity of the fibrinolytic cascade, increasing the inflammatory process, and elevating oxidative stress and endothelial dysfunction. Disorders of lipid metabolism and glucose tolerance, in the context of metabolic syndrome, further affect the proinflammatory effects and enhance endothelial dysfunction. The risk for thromboembolic events is increased by the proinflammatory effects of visceral fat tissue, activation of coagulation, and the decrease in fibrinolysis and endothelial dysfunction. Postthrombotic syndrome occurs earlier and more frequent starting from a BMI of 28 kg/m², and the symptoms are improved by weight loss.

Gabriele Färber introduced the term secondary functional venous insufficiency or "obesity-associated dependency syndrome." The responsible mechanical factor is an increased intertriginous pressure in the groin. Chronic inflammatory changes are mediated by cytokines, interleukins, tumor necrosis factor α , and increased capillary permeability. Of the patients with lymphedema, 76% are overweight. Obesity worsens all forms of lymphedema. Obesity associated lymphedema is the most common form of secondary lymphedema. Obesity causes secondary lymphedema in lipedema, not progression of lipedema. Possible pathomechanisms are compression of lymph vessels, immobility, failure of lymphatic transport mechanisms, and an increase in lymphatic load. Secondary lymphedema is reversible after weight loss. Obesity in phlebological and lymphological diseases consists of at least two different diseases; both must be

treated. Chronic inflammation and insulin resistance are at the core besides treating the respective acute or chronic symptoms with anticoagulation, compression, lymphatic drainage, or wound therapy. Focus on reducing visceral adipose tissue, hyperinsulinemia, and chronic inflammation through dietary and lifestyle changes is mandatory. Weight reduction can improve secondary venous insufficiency, secondary lymphedema, and reduce thrombogenic risk factors.

VI. Innovations in phlebology

Fully percutaneously created or surgically inserted artificial vein valves in CVD treatment – research status and first clinical data

Steve Elias (US)

The Self Valve study analyzed the SailValve, a new self-expanding deep venous valve concept based on a single polytetrafluoroethylene cusp floating up and down in the bloodstream like a sail acting as a flow regulator and allowing minimal reflux to reduce thrombogenicity. Deployment was technically feasible in all 10 iliac veins and all were patent directly after placement. No perioperative or postoperative complications occurred. Ascending phlebograms in the follow-up animals confirmed the patency of all valves after 2 or 4 weeks. Descending phlebograms showed full function in 5 of 8 valves. Limited reflux was seen in 1 valve (4-week group) and the function in the remaining 2 valves (2-week group) was insufficient because of malpositioning. No macroscopic thrombosis was noted on histology. Histology in the follow-up groups revealed a progressive inflammatory reaction to the valves.

The next system for endovascular valve creation is the BlueLeaf Endovenous Valve Formation System, which uses a catheter system, a nitinol dissector, a needle assembly, and performed under intravascular ultrasound guidance. The procedure has 3 main steps: (i) gain subintimal access with a 16 Fr sheath in the common femoral vein after identification of the appropriate valve site with intravascular ultrasound; (ii) perform a hydrodissection; and (iii) create the valve. This method can be used to create monocuspid valves, bicuspid valves, and potentially multilevel valves as well. The trial is currently enrolling outside of the United States, with 15 patients in Australia and New Zealand. The inclusion criteria will be patients who have the most severe disease with C₅ and C₆ disease and significant deep vein reflux.

Another system is the VenoValve. Hancock Jaffe Laboratories has developed a bioprosthetic venous valve, the VenoValve[®], to correct or reduce venous reflux within the deep venous system. The device comprises a biologic valve mounted in a supporting metal frame that will allow for a straightforward surgical insertion of the bioprosthesis into the femoral vein. It is a monocuspid valve with a diameter of 8 to 10 mm. There has been a successful experience of implantation of valves into the external jugular vein in sheep (4 cases) and the common femoral vein in dogs (4 cases). A Columbian surgeon Jorge Ulloa has implanted the valve into 8 patients with C₅/C₆ range into the femoral vein (Elias/Gasparis are the principal investigators). The results of the 90-day observation period are available, showing positive results so far.

Recent development in the dedicated venous stents – lessons learned and future direction

Steven Black (UK)

A meta-analysis conducted in 2016 showed that the patency rates of venous stenting were high (79% to 98%). Now there are eight different stenting systems: Ziver-Vena (Cook), Vici (BSCI), Venovo (BD), Wallstent (BSCI), Sinus-Venous (Optimed), Sinus-Oblicuos (Optimed), Abre (Medtronic), and Blueflow (Plus Medica). The FDA has only approved

the Wallstent, Venonvo, and Vici. Stents are very different in their design and cannot be compared straight away. The VIRTUS exploration data (VICI venous stent in 170 patients) showed an 84% primary patency rate and a 98.8% safety end point rate. The VERNACULAR study (Venovo Venous stent – 170 patients) showed an 88.3% primary patency rate and a 93.5% safety end point rate.

Stents can be implanted with a closed cell, open cell, hybrid cell, and braided cell that will all be very different in terms of the level of crush resistance, flexibility, radial strength, deployment, scaffolding, diameter, and length. A randomized double-blind study comparing medical treatment vs iliac vein stenting in chronic venous disease was conducted in 2018. At the 6-month follow-up, the mean VAS pain score declined from a median of 8 to 2.5 in patients receiving stents and from 8 to 7 in patients receiving only medical treatment ($P<0.001$). The venous clinical severity score decreased from a median of 18.5 to 11 after stenting and from 15 to 14 with medical treatment ($P<0.001$). The 36-item short-form health survey (0-100) improved from a total median score of 53.9 to 85.0 with stenting and 48.3 to 59.8 after medical treatment ($P<0.001$).

Stenting success is dependent on many factors, such as stent choice, placement errors, technical mistakes, level of inflow, and clotting system. Currently, more randomized controlled trials are needed for acute deep vein thrombosis, for chronic venous obstruction comparing different stents, and more data is needed about new stents and systems for stenting.

Hyaluronian injection based treatment in phlebology – why and when?

Johann Chrisof Ragg (Germany)

From a patient's point of view, we should do much more to prevent venous disease or to heal in a vein-preserving way with minimal effort and minimal cost. There are three mechanical causes of primary venous insufficiency: embryonic valve lesions, time/age, and pressure, which induces valve decompensation and stasis and is related to valve degeneration. To prevent and cure valvular lesions of all origins, internal vein compression via injection of hyaluronic acid can be used.

The main ideas of internal compression are to improve the early stages of valve decompensation by eccentric and concentric lumen modification. Hyaluronic acid is a well-established product in esthetic treatments, with the best tissue compatibility of all known synthetic fillers and a simpler and smoother injection than autologous fat. For injections, it is preferably to use a safety cannula to prevent intravenous injection.

Johann C. Ragg discussed eccentric valvuloplasty, which is used to improve valve function in asymmetrical lesions, concentric valvuloplasty, which is used to restore valve function in symmetrical lesions, and hemodynamic venoplasty, which is used to normalize pressure irrespective of valves. Recent results from 2018-2019 showed 42 technically successful cases of concentric valvuloplasty for incompetent valves of the great saphenous vein via injection of monophasic hyaluronic acid (4 to 6.5 mL), and, at the 6-month follow-up, 40 of the 42 cases (95.2%) had orthograde flow. Data from 2018-2019 showed that eccentric valvuloplasty was successful in 17 cases, with hemodynamic success after 3 months in 13 of the 17 cases (76.5%) and after 1 year in 9 of the 13 cases (69.2%).

In addition, other areas for using hyaluronic acid have been demonstrated; for example, using it instead of a saline solution during vein ablation for safety reasons or using it to perform a more precise sclerofoam treatment. All studied variations of internal vein compression by perivenous hyaluronic acid are safe and effective. The different vein-shaping modalities, in particular the vein-preserving ones, open new perspectives to learn about hemodynamics and early stage treatment.

First percutaneous – non invasive – vein ablations using high intensity focused ultrasound (HIFU)

Alfred Obermayer (Austria)

Insufficient veins can be treated in a completely noninvasive manner using high-intensity focused ultrasound (HIFU), as has been demonstrated with the SONOVEIN device. The visualization and treatment unit of the device contains a 3-MHz HIFU transducer for treatment, and embedded 7.5-MHz ultrasound for visualization, and a single-use membrane and liquid for cooling and coupling. Preclinical ex vivo and in vivo animal studies with HIFU showed that the histology results for the veins are identical to those induced by radiofrequency.

A prospective clinical study assessed 50 legs (62% [31/50] were recurrent and 74% (33/50) were classified as C₄-C₆) by treating recurrences, neovascularization at the stump, perforators, great saphenous vein, anterior accessory saphenous veins with no adjunctive methods (sclerotherapy, etc) with a 3-month follow-up period. The procedure was feasible for all patients. Preliminary results showed that the procedure could be performed without anesthesia (only used in a few cases), without sedation or other medications, and there were no significant side effects (skin changes, skin burns), and, for cases of very mild and transient dysesthesia, there was no thrombosis or pulmonary embolism and no need for anticoagulation medication.

The main advantages of HIFU are the it can be used to treat over skin with severe atrophic disorders (ulcers), it has an extreme precision for heat deposition, it does not require a sterile field, it can be performed without anesthesia or sedation, it can treat very tortuous structures, and it is a safe procedure with a high level of patient satisfaction. The main limitations of HIFU include a lack of long-term studies and structures within 5 mm from the skin may need subcutaneous infiltration.

Transcutaneous obliteration of varicose veins by ultrasound: HIFU and Cavitation solutions

Rene Milleret (France)

There are two biological effects of high-intensity focused ultrasound (HIFU): thermal (heating of tissues at temperatures up to 100° C, like laser ablation) and cavitation (in a liquid, microbubbles, which burst and free a lot of energy, like foam sclerotherapy). Rene Milleret demonstrated his model of HIFU, with two different probes for the treatment of telangiectasia and large veins. A successful series of obliterations have been performed on rabbit ears and saphenous veins in sheep with this model. The limitations regarding the thermal effects are that tumescence is often needed, the vein must be compressed, and it is time consuming, and, regarding the cavitation effects, it is less precise, leads to hemolysis, and the reopening rate is not yet known . Indications for use are due to HIFU effects: thermal (valvuloplasty, stumps (recurrences), perforators, malformations)

and cavitation (trunks, building tributaries). Endovenous techniques will be seen as an intermediate stage between aggressive stripping and noninvasive transcutaneous ablation.

Telemetric vein diagnostics: how does technology enable patient compliance?

Willy Chi (US)

Compliance with the use of compression stockings is close to 50%. The SOX trial showed that, during 24 months, only 69.1% of patients reported using compression stocking and only 55.6% used stockings more than 3 days per week. In a report, two devices for telemetric vein diagnostics were described; the purpose of the devices is to improve compliance with compression stockings by monitoring the wearing of compression knitwear.

The Thermotrack® device, which has a cylindrical form (16 mm×6 mm) that is enclosed in stainless steel, started as a sensor in the food industry to measure temperature of food products; it has a 97% accuracy rate with a limitation for the external temperature of >23°C. The temperature curve data from Thermotrack® can be exported in an excel format to local storage. The device has a long battery life of 10 years. Another device, VenoSense® is a plastic disk (41 mm×25 mm) that includes a piezoresistive sensor that measures pressure in mm Hg. When more than 5 mm Hg of pressure is detected, a numerical number 1 generated. If the pressure is less than 5 mm Hg, VenoSense® suggests that a patient is not wearing compression stockings and a 0 is generated. The pressure data from VenoSense® can upload automatically to the cloud in an excel format. The manufacturer is now trying to miniaturize the circuit to 16×4 mm. The battery has a short life of 6 months. All devices are waterproof.

SFALT: Sclerofoam-assisted laser therapy for saphenous refluxes: an innovative tumescence-free technique

Francesco Zini (Italy)

Thermal ablation by endovenous laser treatment of varicose veins with radial fibers is a minimally invasive procedure with good outcomes. However, the literature reports that up to 52% of the procedures are painful and not aesthetic since hematomas or ecchymosis can occur along the treated saphenous area after endovenous laser. There is no correlation between the minimally invasive approach of endovenous laser and the large amount of liquid that is injected with tumescent anesthesia. In addition, the vein is compressed in the groin and, due to liquid from the tumescent anesthesia between the saphenous fascia, the vein is no longer visible and therefore no longer monitored with ultrasound. Tumescent anesthesia is not free from potential complications.

To improve these limitations, Francesco Zini invented SFALT (ScleroFoam-Assister Laser Treatment), an innovative tumescence-free technique. SFALT is a hybrid technique combining foam sclerotherapy and endovenous laser ablation in a tumescence-free approach. It consists of introducing an endovenous laser fiber into the great saphenous vein, shrinking it for a single cm at 200 J/cm. After a shrunk plug is created, keeping the fiber stuck in it, 5 cc of foam sclerotherapy (Tessari method, 1% polidocanol, or 1% sodium tetradecyl sulfate) are injected through the same 6 Fr endovenous laser introducer. The consequent spasm allows a subsequent endovenous laser-mediated

shrinkage by means of a significantly reduced fluence. A clinical and sonographic follow up was done at 1 and 3 weeks.

Francesco Zini described the results after 850 personal cases since October 2014. No major or minor complications were reported. At the mid-thigh, the standing great saphenous vein caliber decreased from a preoperative value by more than 50%. There were no statistical differences between sodium tetradecyl sulfate and polidocanol. At follow-up, there were only 3 complete recanalizations.

The SFALT approach is feasible and safe, with potentially interesting outcomes. This technique offers the chance of a possible tumescence free great saphenous vein treatment, even in case of major calibers vessels.

VII. News in the research on the chronic venous disease – pathophysiology, anatomy and symptoms

How vein disease begins – insufficiency in children and adolescents

Johann Chrisof Ragg (Germany)

Recent studies on the onset of intra and epifascial venous disease show four major components: (i) congenital valve lesions; (ii) stress-induced valve decompensation, as seen in heavy workers or athletes; (iii) stasis-induced inflammatory valve degeneration; and (iv) usually secondary phlebitis. As congenital venous valve damage is the first to occur in life, it should prepare a primary pattern of an individual course of venous disease. Therefore, using high-frequency ultrasound systems (Siemens Juniper, Zonare One Pro, Mindray M9, 16-23 MHz; Vevo MD, 16-32 MHz), Johann C. Ragg examined 102 children and adolescents aged 6 to 18 years (mean, 12.5 years; 59 females, 43 males) who were all asymptomatic. Investigation time was limited to 15 minutes. In case of visible vein changes (protruding, more intense color, increased diameter), ultrasound imaging was started at that site. Otherwise, systematic screening of saphenous veins and typical perforator locations was performed. Overall, 71/102 children (58.8%) and 60/204 legs (34.8%) showed relevant venous pathologies. Lesions were mainly located in the great saphenous vein (60/204 [29.4%]) vs primary saphenous side-branch varices (3.9%), small saphenous vein (3.4%), and perforator veins (1.0%). Lesions in the great saphenous vein in the lower leg occurred in 61.0% of the patients with lesions. In the subgroup of children aged 6 to 8 years, 11/23 (47.8%) already showed a relevant pathology; 42.3% of all cases were related to a single valve failure. Among these, unilateral commissural mismatch was the most frequent pattern (70.0%). In conclusion, the unexpected high incidence of detected valve lesions in children, particularly in the younger ones, could be best explained by congenital disease. The challenge is to understand which patients and at which age might have preventive benefit from early detection and eventually a cost-effective therapy.

Anatomy and 3D modeling of the popliteal fossa perforating veins

Jean Francois Uhl (France)

The aim of this study was to make an anatomical description of the bony venous perforator veins at the knee level, which are frequently missed during investigation of patients with chronic venous disease. Therefore, venous mapping of 25 000 patients and 1200 computed-tomography venographies before surgery for varicose veins were examined. Anatomically, these perforator veins were defined as “perforating veins feeding a varicose

network of the popliteal area not connected to a tributary of small saphenous vein,” with a prevalence of about 4%. Anatomically, they have four main characteristics: (i) always located laterally from the midline; (ii) end in the lateral aspect of the popliteal vein; (iii) located, on average, 2 cm above the saphenofemoral junction; and (iv) no connection to the small saphenous vein. They are very frequently observed in REVAS (recurrent varices after surgery) after ligation of the small saphenous vein, commonly associated with other refluxing perforator veins and to more severe chronic venous disease (the C of CEAP). In all cases, one must look for a systolic reflux of the perforator veins and eliminate a vicarious shunt due to a venous obstruction, in particular a Hunter’s canal stenosis.

Anatomy of the bony perforators veins of the knee

Jean Francois Uhl (France)

The aim of this study was to make an anatomical description of the bony vein perforator veins at the knee level, which are frequently missed during investigation of patients with chronic venous disease. Multiple series of anatomical slices of fresh cadavers injected with green latex and a series of CT venographies as well as Duplex color investigations were used to study their precise location and the connections with the venous network of the knee. Anatomically, these perforator veins are commonly located anteriorly around the patella, and posteriorly in the inter-condylar groove, medially and laterally. Their connections with the popliteal vein are multiple. During Duplex ultrasound assessment, as well as CT venography, they are often ignored due to their small caliber.

The physiological hypothesis is that, at the knee level, the spongy bone of both tibia and femur epiphysis is important for the production of red blood cells. They connect the venous system in the popliteal vein by several tiny perforators. In practice, these tiny perforators are not investigated and are ignored by sonographers. They should be distinguished from the large perforator veins of the tibial diaphysis responsible for varicose veins of the leg.¹ These perforator veins could also be linked to the so-called “phleboarthrosis” that was described recently.²⁻⁴ The bony perforator veins of the knee are commonly responsible for reticular veins or telangiectasias around the knee, but they are underdiagnosed by sonographers. This explains why the injection of these cosmetic lesions around the knee frequently leads to recurrence.

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A systematic review of the relationships between venous diameters, clinical severity and quality of life

Matthew Tan (UK)

Chronic venous disease (CVD) represents a significant impact on patients’ health-related quality of life (HRQOL). To help guide further management, truncal vein diameters

are recorded during duplex ultrasound assessment; these diameters can be used to determine treatment eligibility, for example, by insurance companies. While some studies have shown an association between truncal diameters and both clinical severity and HRQOL scores, this relationship is still poorly characterized. This systematic review aims to synthesize the evidence in the literature pertaining to such relationships to better inform CVD management. Full text studies in English reporting on the relationship between great and/or small saphenous vein diameters and clinical severity and/or HRQOL scores were included. Papers reporting only on truncal vein diameters, clinical severity, or HRQOL scores without describing their relationship and papers focusing on nontruncal veins were excluded. Eleven studies were included in this review, involving a total of 2732 limbs with symptomatic C₀-C₁ disease and C₂-C₆ disease. Relationships between truncal vein diameters and both clinical severity and HRQOL scores were reported in four studies, with the other seven studies reporting on relationships with clinical severity only. Validated classification tools were used to measure both HRQOL (AWQ, CIVIQ, VEINES-QoL/Sym, WSymQ) and clinical severity (CEAP, VCSS).

Truncal vein diameters were related to CEAP stages in seven studies; the majority of studies observed increasing diameters with increasing clinical severity. Four studies reported weak positive correlations between the venous clinical severity score (VCSS) and increasing vein diameters. One study also reported diameters to be correlated with individual VCSS components. However, all studies included in this review failed to show any significant relationship between truncal vein diameters and any HRQOL score. Therefore, current studies suggest that, in CVD, truncal vein diameters exhibit a weak association with clinical severity, but not HRQOL scores, and therefore the patients' perceived impact of CVD. This suggests that truncal vein diameters should not be utilized as a criterion for treatment eligibility.

The Villalta score is a better predictor for pre-existing chronic venous disease than for the development of post thrombotic syndrome

John Fish (US)

Patients with chronic venous disease (CVD) without a history of thrombosis may show some of the same signs and symptoms as those with postthrombotic syndrome. A previous study showed that the contralateral leg of those with a first unprovoked deep venous thrombosis (DVT) also displayed elevated Villalta scores in 40% of patients. The effect of a DVT on the Villalta scores appears to be unpredictable. Although the Villalta scores is a validated tool for classifying postthrombotic syndrome (score >4), misclassification bias may exist. The authors set out to prospectively compare the Villalta scores and venous clinical severity score (VCSS) in patients with and without a history of DVT to determine the degree of misclassification bias as well as any changes in Villalta scores that occurred after the first development of DVT. Patients with chronic venous disease were prospectively enrolled from a single vein center over a period of 12 months. Villalta scores and VCSS were completed for all patients, as well as a bilateral duplex ultrasound. Positive misclassification bias was defined as the percentage of patients identified with postthrombotic syndrome (Villalta scores >4 and a history of DVT), but without reflux or obstruction in the deep veins on venous duplex. Negative bias was defined as the percentage of patients identified as not having postthrombotic syndrome (Villalta scores ≤4 or no history of DVT), but were found with postthrombotic changes in the deep veins.

The studied prospectively enrolled 288 patients with C₂ to C₆ disease, of whom 258 had no history of DVT and a mean Villalta score of 8.12±4.91; 70% of the patients had a score consistent with having postthrombotic syndrome. Villalta scores correlated well with VCSS in this study population. Twelve of these patients subsequently developed DVT during the course of the study, and there were no significant changes in the Villalta scores. The patients with a history of DVT (n=30) had a mean Villalta score of 9.57±5.78. Of these patients, 26 had a Villalta scores ≥4 and would be given the diagnosis of postthrombotic syndrome. Of the 26 patients, 11 (42%) had normal deep veins on ultrasound (including pelvic veins), representing a positive bias. Although the use of the Villalta score is used as a basis for defining postthrombotic syndrome, the score appears to correlate well with VCSS in patients with CVD and does not significantly increase in patients before or after the first episode of DVT. This positive misclassification bias of 42% suggests that the use of the Villalta score may heavily misclassify those with primary CVD as postthrombotic syndrome. The value of the score was also not significantly higher in patients with a history of DVT compared with those with CVD without a history of DVT.

Is the differential diagnosis of lipedema by means of high-resolution ultrasonography possible?

Tobias Hirsch (Germany)

The current German guidelines on treating lipedema recommend the use of flat-knitted compression material and manual lymphatic drainage as well as liposuction. Differentiating lipedema from obesity and asymptomatic lipohypertrophy frequently proves difficult. However, a reproducible and objective differential diagnosis is the foundation of an expedient and cost-effective treatment. Therefore, as part of a multicenter registry study (five centers), ultrasound scans were performed on the legs (n=294) from 147 patients with lipedema (n=136), lymphedema (n=20), lipedema with secondary lymphedema (n=30), lipohypertrophy (n=42), and obesity (n=30), as well as healthy individuals (n=36). Measurements were performed on the thickness of the cutis and subcutis of the lower and upper leg and on their compressibility. An analysis of the sonomorphology was also conducted.

Special sonomorphological properties that allow lipedema to be differentiated from other disease entities and from healthy individuals have yet to be identified consistently and conclusively. The compressibility of the cutis-subcutis complex is completely unspecific and does not allow any conclusions to be drawn concerning lipedema. It has not been possible to detect fluid retention in patients with lipedema. Therefore, to date, the qualitative differentiation of the anatomical and pathomorphological features of lipedema from those of painless lipohypertrophy, obesity, and the skin/subcutaneous tissue from healthy people using sonographic imaging has not been possible to a satisfactory degree. Due to the large individual variation in findings and the likewise considerable differences in ultrasound scanners and their configuration, it is also currently impossible to obtain reproducible results that would enable the individual disease entities to be distinguished clearly. Contrary to expectations, the compressibility of the cutis-subcutis complex is entirely nonspecific. No sonographic correlate for clinical phenomena, such as the mattress phenomenon, could be established. Although ultrasound enables accumulations of interstitial fluid to be demonstrated, it does not provide any indications of edema etiology. As it was not possible to demonstrate fluid accumulations in patients with “painful lipohypertrophy,” the description of this disease as “lipedema” is misleading and should

be reconsidered. Currently, it must be assumed that, in routine care, essentially only the medical history and clinical findings are available for confirmation of the diagnosis of lipedema and its differential diagnosis.

The athlete's vein: venous adaptations of the lower limb in endurance athletes

Kate Thomas (New Zealand)

It is established that arteries in athletes are larger, have thinner wall and have a demonstrated increase in vasodilatation during exercise. The objective of the study was to determine the impact of endurance exercise (20 minutes) on lower-limb venous morphology and function in athletes (n=20) compared with untrained controls (n=20). Prior to exercise, athletes had veins (profunda femoris, medial gastrocnemius, peroneal) with larger diameters and more perforators than normal controls. The venous volume was higher in athletes (160 ± 41 vs 131 ± 40 mL; $P=0.03$). The venous refilling time was also higher (169 ± 42 vs 112 ± 38 seconds; $P<0.01$). The venous filling index, which, in the absence of reflux, indicates arterial inflow, was not significantly different (0.9 vs 1.1 mL/s; $P=0.15$). After 30 minutes of exercise, there was an increased flow in the superficial veins, deep veins, and perforators. The increase was higher in athletes. For example, at 2.5 minutes after exercise, the mean flow in the common femoral vein was approximately 1100 mL/min in the athletes and only 750 mL/min with full recovery to normal resting flows in both groups at 20 minutes. The great saphenous vein was dilated in both groups. After exercise, venous volume decreased in the athletes, but was unchanged in normal controls. The venous filling index increased in both groups 2 to 5 times, indicating increased arterial inflow with a corresponding decrease in refilling time. The unchanged ejection fraction in the presence of an increased venous volume in the athletes suggests an increased ejected volume in this group.

VIII. COs - towards consensus on the diagnostics and therapy

Epidemiology of COs- what do we know about?

Eberhard Rabe (Germany)

Recent CEAP-based studies demonstrated that the prevalence of C₀ and C₁ patients are around 70%, whereas it is 25% for C₂ and C₃ patients and 5% for C₄ and C_{5,6} patients. According to the Bonn Vein study I, age was the main effector in the risk analysis for telangiectases, varicose veins, and chronic venous insufficiency. The Vein Consult Program showed that the epidemiology of chronic venous disease was geographically diverse, but the early stages (C₀, C₁) were predominant (41.6%). The main symptoms were heavy legs (72.4%), leg pain (67.7%), sensation of swelling (52.7%), and nighttime cramps (44.3%). The Bonn Vein study II was realized with the identical population and procedure as in Bonn Vein study I, with a 6.6-year follow-up period. The progression of chronic venous disease in C₀ and C₁ patients was 3.4% per year. Significant risk factors associated with the progression of varicose veins toward venous leg ulcers include skin changes, corona phlebectatica, a higher body mass index, and popliteal vein reflux. Corona phlebectatica was found to be a predictor for the incidence of chronic venous insufficiency (relative risk [severe corona phlebectatica vs no corona phlebectatica], 5.23; 95% CI, 3.68, 7.43). It is important to have a general understanding of how symptoms may be expressed and interpreted, as well as how they might or might not be related to venous disease. The absence of symptoms does not exclude chronic venous disease. To conclude, C_{0s} is frequent in the adult population worldwide. Leg symptoms deserve to be assessed and treated appropriately. Having leg symptoms is not diagnostic of a venous disease. Leg symptoms in C_{0s} may be associated with a venous pathology (eg, deep vein reflux) that is not clinically visible or with other pathology.

The link between hemodynamics and signs as well as symptoms of the chronic venous disease

Andrew Nicolaides (Cyprus)

The aim of this review was to provide a clear understanding of the pathophysiological mechanisms of chronic venous disease at different clinical stages and the possible role of these mechanisms in the development of symptoms in C_{0s} clinical class of the CEAP classification, which consists of symptomatic patients without any visible or palpable signs of venous disease. The prevalence of C_{0s} varies between 13% and 23% of the general population according to several epidemiological studies. Wall remodeling and valve destruction due to white cell endothelial interaction is the main cause of primary varicose veins, while deep vein thrombosis produces secondary changes leading to the postthrombotic syndrome. The underlying mechanism of skin changes and ulceration is venous hypertension, which is transmitted to the skin microcirculation. Over the last 10 years, an improved video capillaroscopic technique, the orthogonal polarization spectral imaging technique demonstrated that quantitative measurements in the skin microcirculation are progressively altered from C₁ to C₆ patients and that certain values in chronic venous disease patients are significantly different from healthy subjects ($P < 0.05$):

(i) capillary diameter increases and capillary morphology worsens from C_2 to C_3 ; (ii) the diameter of the dermal papilla and the capillary bulk increase from C_3 to C_5 ; and (iii) functional capillary density decreases from C_4 to C_5 . In addition, significant changes have been shown between C_{0a} and C_{0s} patients despite the presence of normal conventional duplex scans in the latter, including a decrease in functional capillary density and an increase in the diameter of the dermal papilla.

Functional abnormalities found in C_{0s} patients in recent studies include increased compliance of the venous wall (hypotonic phlebopathy), dilatation of the deep veins in the calf producing an abnormally increased venous volume, reduction in emptying of the venous reservoir, reduction in the venoarteriolar response on standing and blood reflux in small venules despite a normal conventional duplex scan. However, most of the studies are small and their findings need to be confirmed with a larger series. It remains to be seen whether functional changes and microcirculatory changes respond to venoactive medications in parallel to the relief of symptoms.

Symptoms of the chronic venous disease learning through a clinical case. How to assess the symptoms of the chronic venous disease - 2019 update?

Nicos Labropoulos (US)

The SymVein consensus report was produced to describe the venous symptoms, to specify which components enable symptoms to be attributed to a venous cause, to determine their pathology, to establish a score dedicated to symptoms, to determine which clinical examination and investigations are useful for identifying the venous cause of symptoms and to explain the lack of correlation between the persistence of symptoms and a successful procedure. By definition, venous symptoms are related to venous etiology, but, as venous symptoms are rarely specific, this makes their definition difficult. In order to solve this challenge, some points need to be clarified, such as "Are venous symptoms of primary etiology caused by an alteration in the major veins or by venule and capillary anomalies?," "Would major vein alterations be related to reflux in superficial and/or deep veins or to compression of proximal veins?," "Could small venules or capillaries be involved in C_{0s} patients, knowing that both anomalies (major veins and venules) may be combined in C_6 patients?," "Should the absence of clinical venous signs and the absence of reflux on duplex scanning or air plethysmography systematically rule out a venous etiology?," and "Is the presence or the intensity of symptoms, independently of the presence of signs, predictive of chronic venous disease progression?."

The presence and severity of symptoms are subjective. In the Vein Consult Program, more than 80% of the patients presented with symptomatic chronic venous disease. In the Bonn Vein study, more than 50% of the 1800 patients reported chronic venous disease-related symptoms. Limb symptoms are by themselves not diagnostic of venous disease and they deserve to be assessed and treated appropriately. Symptoms are unique and personal experiences. These feelings are variously expressed and with differing intensities, and they may mean many different things to different patients. The story and the clinical context of symptoms are important when conducting an assessment. Distribution and extent of reflux, amount of reflux, distribution and extent of venous obstruction, severity of obstruction, muscle pump efficiency, genetic predisposition, soft tissue cellular responses, rate of chronic venous disease progression, obesity, hormonal factors, and right heart failure are factors contributing in the clinical severity of chronic venous disease.

Chronic venous disease progression- is it unavoidable?

Marc Vuytsteke (Belgium)

Varicose veins are present in 23% of the adult population and chronic venous insufficiency is present in 11% to 17% of the adult population. For chronic venous disease, the progression rate to higher clinical stages reaches 4% per year. Half of the patients with unilateral varicosities develop contralateral chronic venous disease in several years. One-third of patients with varicose veins (C₂) will develop skin changes in 13 years. Untreated patients will develop more signs and symptoms, which has an impact on health-related quality of life for the patients. Persistent venous hypertension, consequences of chronic inflammation within the venous wall and genetics may be independent factors influencing the progression of chronic venous disease. The treatment options are lifestyle changes (weight loss, exercise), compression/leg elevation, medication, and interventional treatments. Risk factors for venous disease include a positive family history of chronic venous disease, pregnancy, obesity, standing/sitting habit, smoking, lack of regular exercise, female sex, and age. Among these risk factors, age, sex, and family history are immutable; however, weight, physical activity, smoking can be modified. The CEAP clinical stage of venous disease is more advanced in obese patients than in nonobese patients, which is a result of increased intra-abdominal pressure. Obesity correlates with symptoms of chronic venous insufficiency, but two-thirds of limbs have no anatomic evidence of venous disease.

Compression improves venous pump function and enhances venous flow velocities. At various stages of chronic venous disease, compression significantly reduces edema, improves symptoms, and has a positive effect on a patient's quality of life. There is insufficient information from randomized controlled trials on preventing chronic venous disease progression with compression; however, the incidence of chronic venous disease progression is higher among patients who are noncompliant with compression stockings. Anti-inflammatory treatment options, such as micronized purified flavonoid fraction (MPFF), reduces the expression of adhesion molecules, reduces the adhesion of leukocytes to the endothelium, decreases capillary permeability, and improves venous tone, suggesting a reduction in the progression of chronic venous disease. In one study, 96 C_{1s} patients were treated with MPFF 1000 mg/daily for 3 months, and 55% of the patients had transient reflux in the great saphenous vein (segmental) on duplex ultrasound. The results showed that the symptoms (leg heaviness, fatigue, pain, nighttime cramps) ceased in 88% of patients and the transient reflux was eliminated in 92% of patients at 3 months with MPFF treatment. There is a need for more randomized, double-blind, controlled clinical trials with long follow-up periods. Sclerotherapy (foam), surgery, endovenous techniques, and other interventional techniques provide clinically significant improvements to patients' quality of life. The recurrence rates for varicose veins are very high: 40% to 50% at 5 years and 70% at 10 years. Of the surgical procedures, 20% are carried out to treat recurrent disease.

In conclusion, several treatment options can be used for treating chronic venous disease, including venoactive drugs. Risk factors have to be assessed carefully. Progression of disease in most patients is not preventable, as the causes of varicose recurrence are multifactorial and only some of them can be prevented.

COs diagnostics-objective evaluation and possibilities of confirmation of the chronic disease presence in COs patients

Patrik Carpentier (France)

C_{0s} does not have a clear prognostic value regarding the subsequent occurrence of varicose veins or venous insufficiency. Although venous symptoms are essentially subjective, they can be objectively evaluated using patient-reported outcome measures: visual analog scale and quality of life scales. C_{0s} symptoms are probably related to subclinical leg edema. Ankle edema measurements can probably be used to assess the pathophysiological substratum of C_{0s} symptoms. Water displacement volumetry, optoelectronic methods, bioimpedance spectroscopy, dermal ultrasonography are some methods to evaluate edema. However, there is a need for future studies to validate new methods of edema assessment using innovative technologies. As C_{0s} symptoms can be found in subjects with any cause of calf muscle pump dysfunction (venous or nonvenous), evaluation of the calf muscle pump is certainly what is most needed in order to further understand this pathology. Ultrasound duplex venous evaluation of C_{0s} patients is recommended. Nevertheless, the potential of high-resolution ultrasound and capillaroscopy for the detection of early chronic venous disease in some C_{0s} patients remains to be determined.

COs treatment possibilities-2019 update

Stavros Kakkos (Greece)

Venoactive drugs, such as micronized purified flavonoid fraction, Ruscus extracts, hydroxyethylrutosides, horse chestnut seed extract, and calcium dobesilate, are widely used as important components of the treatment of chronic venous disease. They constitute a group of heterogeneous agents with different pharmacological properties, including an increase in venous and lymphatic vessel tone, anti-inflammatory actions with inhibition of leukocyte activation, trapping, and migration, leading to a protective effect against leakage of macromolecules and venous edema. Venoactive drugs can be administered alone or when compression is contraindicated (eg, in patients with peripheral vascular occlusive disease) or not tolerated because of patient pruritus or high ambient temperatures. Alternatively, venoactive drugs may be prescribed in combination with elastic compression, since the original trials evaluating venoactive drugs allowed use of compression, which is justified since elastic compression cannot always fully control patient symptoms. Venoactive drugs are effective in improving patient symptoms including pain, heaviness, sensation of edema, cramps, paresthesia, heat or burning sensation and other venous symptoms, but also global symptoms, and objectively assessed leg edema of chronic venous disease. Venoactive drugs are effective across the entire spectrum of chronic venous disease severity, CEAP clinical classes C_{0s} through C_6 . This effectiveness has been evaluated in the original randomized control trials and subsequent observational studies. More recently, systematic reviews, including Cochrane reviews, have confirmed and quantified the favorable effects of the various venoactive drugs on chronic venous disease symptoms and signs. The relative effectiveness of venoactive drugs in chronic venous disease was assessed in the 2018 update of the international guidelines on chronic venous disease (*Table 1*).

| Symptom/sign | MPPF | Ruscus | Oxerutins | HCSE | Calcium dobesilate |
|------------------------------------|--------------------|------------------|-----------------|------------|--------------------|
| Pain (NNT) SMD | A (4.2) -0.25 | A (5) -0.80 | B -1.07 | A (5.1) | B (1.4) |
| Heaviness (NNT) SMD | A (2.9) -0.80 | A (2.4) -1.23 | B (17) -1.00 | | A (1) |
| Feeling of swelling (NNT) SMD | A (3.1) -0.99 | A (4) -2.27 | | | |
| Functional discomfort (NNT) SMD | A (3.0) -0.87 | | | | B (4) |
| Leg fatigue (NNT) SMD | NS | B -1.16 | | | |
| Cramps (NNT) SMD | B (4.8) -0.46 | B/C | B -1.7 | | |
| Paresthesiae (NNT) SMD | B/C (3.5) -0.11 | A (1.8) -0.86 | | | B (2) |
| Burning (NNT) SMD | B/C -0.46 | NS | | | |
| Pruritus/itching (NNT) | | B/C | A (6.1) | | |
| Tightness (NNT) | NS | | | | |
| Restless legs (NNT) | NS | | | | |
| Leg redness (NNT) SMD | B (3.6) -0.32 | | | | |
| Skin changes (NNT) | A (1.6) | | | | |
| Ankle circumference (NNT) SMD | B -0.59 | A -0.74 | NS | A (4) | |
| Foot or leg volume SMD | NS | A -0.61 | NS | A -0.34 | A -11.4 |
| Quality of life SMD | A -0.21 | | | | NS |

Table I. Grade A or B levels of evidence for the effects of the main venoactive drugs on individual symptoms, signs, and quality of life.

IX. Compression treatment solutions in vein and lymphatic diseases

Current indications and guidelines for medical compression stockings

Eberhard Rabe (Germany)

A review article was published in *Phlebology* in 2017 concerning the “indications for medical compression stockings in venous and lymphatic disorders” based on a systematic research from Pubmed, including randomized control trials, observational human studies, and reports of use of compression stockings. The recommendation was grade 1b for use of medical compression stockings to alleviate venous symptoms in chronic venous disease, to improve quality of life and venous severity in chronic venous disease, to prevent leg swelling in chronic venous disease and in healthy individuals at risk of leg swelling and to reduce swelling, whereas, the recommendation was grade 1C for improvement in skin changes. For the improvement in venous leg ulcer healing, the recommendation was grade 1A. For the reduction in pain and swelling in patients with acute deep vein thrombosis, the recommendation was grade 1B, but, for the patients with superficial vein thrombosis, the recommendation was just grade 1C due to study limitations. According to the 2019 German guidelines on compression therapy, which is now available at <http://www.awmf.org>,

The indications for medical compression stockings are summarized as follows with a recommendation of grade 2B:

- Chronic venous disease (for prevention and improvement in venous signs and symptoms, improvement in quality of life, functional venous disease [in obesity or sitting/standing profession])
- Thromboembolic diseases of the extremities (deep vein thrombosis, superficial vein thrombosis)
- Postthrombotic syndrome
- Edema of the extremities

The contraindications for medical compression stockings are as follows:

- Severe peripheral arterial occlusive disease (ankle brachial pressure index <0.5, ankle pressure <60 mm Hg, toe pressure <30 mm Hg or TcPO₂ <20 mm Hg foot level). If inelastic material is used, ankle pressure of 50 to 60 mm Hg can be acceptable.
- Decompensated cardiac insufficiency (NYHA (III) + IV)
- Septic phlebitis
- Phlegmasia coerulea dolens

Elastic and non-elastic compression: how strong should it be to reach the therapeutic goals?

Giovanni Mosti

Intravenous pressure in a standing position is about 70 to 80 mm Hg and physiologically decreases to about 30 mm Hg in normal subjects during movement due to normal muscle-venous valve function. In patients with venous disease, intravenous pressure does not decrease due to valve incompetence and can increase in case of venous obstruction leading to ambulatory venous hypertension (venous reflux, reduced pumping function, etc). Only inelastic multilayer, multicomponent bandages can provide effectiveness and comfort at the same time because they exert a very strong standing pressure and pressure peaks effective in counteracting the arteriovenous hypertension starting from a much lower and comfortable supine pressure. It is not easy to respond to the question “how strong should it be to reach the therapeutic goals?” because there are no specifications in the guidelines, such as the Society of Vascular Surgery/American Venous Forum, International Union of Phlebology, or in Cochrane reviews published in 2009. There are few studies where compression pressure was measured. In addition, it is not easy to apply inelastic compression effectively and to monitor. In one study, ulcer patients were divided into three groups: (i) tubular elastic device (36 mm Hg) were applied; (ii) tubular elastic device (36 mm Hg) plus 1 elastic bandage (54 mm Hg) were applied; or (iv) tubular elastic device (36 mm Hg) plus 2 elastic bandages (74 mm Hg) were applied. There was better healing rate with higher pressure, but the compliance was poor. In another study, using compression greater than 40 mm Hg was effective in achieving faster ulcer healing. In another study, compression pressure >50 mm Hg was effective for ulcer healing. From different studies, the healing rates with elastic kits or stockings in small and recent ulcers were 47% to 96%, with an average of 64%.

In conclusion, compression therapy is very effective in treating venous ulcers. Inelastic bandages or adjustable compression wraps applied with strong pressure are the most effective compression modality. A supine pressure consistently maintained at >40 mm Hg seems to be the most effective for achieving the best healing rate. Due to their pressure loss, inelastic bandages should be applied with an initial pressure >60 mm Hg. Compression devices maintaining the initial pressure (elastic kits and adjustable compression wraps) may be applied with a pressure >40 mm Hg. The pressure must be reduced when moderate arterial disease coexists: the compression pressure at application should not be more than 40 mm Hg. Sustained pressure must be avoided in case of severe arterial disease.

X. Foam sclerotherapy: from the consensus document to the clinical practice

Foam sclerotherapy in C₁ treatment

Neil Khilnani (US)

Neil Khilnani compared liquid and foam sclerotherapy and mentioned that liquid is better for small veins (>4 mm) because it dilutes and reduces the surface area of wall contact, which further dilutes the drug. According to a systematic review of more than 500 patients, the prevalence of visual disturbances is 0.09% to 2%; nearly all cases are associated with foam sclerotherapy. The frequency of visual disturbances increases after 15 mL of foam. Using CO₂ improves the results of foam sclerotherapy, possibly due to the increased stability and half-life of the foam. According to the literature, there is no difference in patient satisfaction, the average amount of injections per one sclerotherapy session, or the number of sessions needed, but the amount of matting and deep vein thrombosis is higher with foam. The European guidelines for sclerotherapy, the American Society for Dermatologic Surgery consensus for sclerotherapy, and the European Society for Vascular Surgery practice guidelines recommend using liquid sclerotherapy as the method of choice for ablation of telangiectasis and reticular varicose veins (C₁, C_{1A}). All guidelines consider foam acceptable and recommend lowering the concentration of foam to avoid side effects.

How sclerotherapy can replace phlebectomy in primary therapeutic attempt or in the recurrent varicose vein treatment?

Claudine Hamel-Desnos (France)

The indications for phlebectomy and sclerotherapy are the same, ie, primary or recurrent nonsaphenous veins (tributaries, accessory saphenous veins, pudendal veins, and reticular veins). The most controversial items are tributaries after thermal ablation of the trunk and the anterior accessory saphenous vein. There are many questions about the management of tributaries after thermal ablation, ie, which technique (phlebectomies or sclerotherapy), what is the timing (concomitant or delayed), and, if concomitant treatment, should it be an exhaustive/extensive treatment of all tributaries or only treatment of the largest tributaries? No study can answer all of these questions. Sometimes the tributaries disappear or shrink spontaneously after trunk ablation occurs, but there is no difference in recurrences between concomitant and delayed treatment and there is an increased number of deep vein thromboses if concomitant phlebectomies are performed. For treating the tributaries, either sclerotherapy or phlebectomies can be performed without preference. Sclerotherapy is possible for large veins that remain dilated at the end of a thermal ablation. For the elderly, the "wait and see" option is preferable and there is a growing tendency to wait 3 to 6 months for most patients. According to the personal

experience of Claudine Hamel-Desnos, after thermal ablation, no phlebectomies and very few or no sclerotherapy sessions have been performed.

Anterior accessory saphenous veins can be treated successfully with sclerotherapy, with a 25% recurrence rate after 1 year and 37.5% after 2 years (2.1% for phlebectomies). For the treatment of pudendal varices, reticular veins, recurrent varicose veins, etc in daily practice, sclerotherapy is more versatile, simpler, and faster than phlebectomies, and easily repeatable if needed. In France, according the French Health Authorities in 2016, 12 million patients were treated with sclerotherapy, a few patients were treated with phlebectomies, and 8 million were treated with thermal ablation, foam, or surgery. In addition, about 1.5 million sclerotherapy procedures and only 12 000 phlebectomy (including those performed concomitantly with thermal ablation) were performed in France in 2016. Sclerotherapy can replace phlebectomies in many cases easily, but phlebectomies can only replace sclerotherapy in a few situations.

Is atrophy blanche irreversible? Effect of foam sclerotherapy

Marianne de Maeseneer (Belgium)

Localized white atrophy, which consists of circular whitish and atrophic skin areas that are surrounded by dilated capillaries, and sometimes hyperpigmentation are the signs of severe chronic venous disease, not to be confused with healed ulcer scars. Scars from healed ulcers may also exhibit atrophic skin with pigment changes, but they are distinguishable by a history of ulceration and the appearance from white atrophy, and are excluded from this definition. At the very base of white atrophy, there are microthromboses of skin capillaries with the following development of micronecroses, microvascular ischemia of avascular skin areas, and white atrophy. In an experiment, the increase in the diffusion speed of Na-fluorescein from 39.2 seconds under normal conditions to 40 minutes in case of white atrophy was mentioned. The slow diffusion of the tracer into the avascular field explains that white atrophy is a predilection site for venous ulcer formation. In addition, in the center, $tcPO_2$ levels were decreased to up to 0 mm Hg in the full absence of capillaries, and, in the border zone, enlarged capillaries, reduced the capillary density and the mean $tcPO_2$ to 24 mm Hg (vs 56 mm Hg under normal conditions). Available information in the literature about whether white atrophy is irreversible is very limited. As an example, two clinical cases on the successful regression of white atrophy were presented where a combined method was used, ie, thermal ablation (radiofrequency ablation of the great saphenous vein) plus phlebectomies of calf varicosities and ultrasound-guided foam sclerotherapy of prominent veins at the medial malleolus. White atrophy may be reversible in certain cases after extensive correction of the underlying venous problem. Ultrasound-guided foam sclerotherapy around the area of white atrophy seems to be useful. Based on preliminary experience, the effect of treatment on white atrophy is clinically obvious at the 1-year follow-up.

Foam sclerotherapy – lessons from physics and chemistry

Johann Chrisof Ragg (Germany)

According to John J. Bergan, sclerotherapy with microfoam eliminates varicose veins in all patients, with no limitations in the size, localization, or morphology of the vessel treated by this method." However, according to Johann C. Ragg, sometimes foam sclerotherapy

is the most versatile modality, but it is also the most underestimated and the most difficult modality. Constant success is dependent on education, skills, and devices more than any other method. There is no perfect sclerosant, ie, one that is complication free and 100% effective. In order to improve the treatment results, the laws of physics and chemistry must be considered. When producing foam, it should be made with a silicone-free syringe to achieve good dispersion of foam and produce small bubbles (<100 µm) for the foam to be stable for more than 1 minute. To create stable foam, it is possible to use CO₂, cold preparation, and high forces. It is important to remember that only 85% of foam is left after 1 minute and only 40% is left after 5 additional minutes.

There are chemical differences between the mechanisms of the two main sclerosants: sodium tetradecyl sulfate and polidocanol. Sodium tetradecyl sulfate consists of smaller molecules with a lower molecular weight, it is anionic, denatures tertiary complexes of proteins, including clotting factors. Polidocanol is nonionic and it has no effect on protein structures. Sodium tetradecyl sulfate and polidocanol have different effects on lipid membranes, target cells, and circulating proteins. Sodium tetradecyl sulfate is more potent than polidocanol by an estimated factor of 1.5 to 3. All sclerosants are deactivated binding to blood cells and blood proteins. Minimization of the target vein diameter improves the treatment results, which depends on patient positioning, manual drainage, aspiration of blood, injection of small foam quantities to obtain a primary spasm, and perivenous injection of tumescence. Decreasing the vein diameter by 50% reduces the consumption of foam by 4 times. Using systems, such as Sclerosafe (foam injection and blood aspiration via different outlets at the same time), helps decrease the contact of the sclerosant. Foam deployment during catheter withdrawal is more precise than injection. Detergents (sodium tetradecyl sulfate, polidocanol) dominate the market of sclerosants due to their excellent benefit-risk ratio, particularly for foams, and they can be used for veins of any size. There are differences between sodium tetradecyl sulfate and polidocanol concerning molecular size, ionic status, and protein attack mode, but the clinical sequelae are not yet well understood. Failures and complications of sclerotherapy are lower due to chemistry, but no physical issues and unqualified use. The "empty vein technique" is mandatory for optimal results, and the best way to obtain an empty vein depends on the anatomic situation. While chemistry acts invisibly, all physical effects can be monitored by ultrasound. Ultrasound monitoring is the first step for quality improvements.

New European guidelines on sclerotherapy – what is new?

Eberhard Rabe (Germany)

Eberhard Rabe reported on the changes that are necessary in the European guidelines on sclerotherapy, which were originally formulated by the Guideline Conference in Mainz, Germany in 2012. The indications remain the same, but additional evidence should be added concerning long-term results, alternative methods in large-diameter veins, patient-reported outcomes, and necessary reinterventions. Regarding contraindications, severe neurological complications due to previous sclerotherapy should be of concern. There are emergency indications for sclerotherapy (eg, variceal bleeding), which may be indicated in immobile patients or patients with other contraindications. Regarding relative contraindications, there are some weak points, such as severe peripheral arterial occlusive disease, which must be defined, poor general health, strong predisposition to allergies, high thromboembolic risk, which needs better clarification and evidence. A chapter on risks should be added. Concerning severe complications, an update of the

frequency from recent studies is needed as well as a discussion on the International Union of Phlebology consensus proposals. Concerning diagnosis, a new discussion on the role of continuous wave Doppler in C₁ veins should be held and eventually an initial duplex investigation should be mandatory. Regarding foam production, a clear statement is needed that “sterile” gas is not mandatory. A reevaluation of concentrations in C₁ varicose veins should be carried out (a lower concentration is possible). Concerning C₁ and C₂ sclerotherapy, a reevaluation of recommendation 2B is needed. Concerning saphenous veins, differences in studies with a shorter (1 to 3 years) and a longer follow-up (5 years) should be evaluated, as well as the high recanalization rate in large-diameter veins. Regarding recommendations, EVRA trial results on ablation of the great saphenous vein in patients with an ulcer in addition to recommendation 32 should be added. Eberhard Rabe recommended adding a chapter on mechanochemical ablation and a chapter on combined treatment of surgery, thermal or nonthermal ablation, and sclerotherapy.

Tips and tricks for maintaining and injecting foam – what we should know

Andrew Bradbury (UK)

Andrew Bradbury discussed the topic of making and maintaining foam and stressed that the Tessari technique probably remains the “industry standard” method of making foam around the world. The optimal ratio is probably 1:4. Only “fresh” foam must be used because foam is rapidly deactivated by blood and nonblood proteins. Small volumes should be injected slowly to maximize both the venous spasm and the foam-endothelial contact and to minimize the foam “fly by” and side effects. Monitoring is also important to know where the foam goes. Short-stretch cohesive bandages (concentric) over wool padding (eccentric) compression for 2 to 3 days is recommended. European grade 2 compression hosiery should be worn for 2 to 3 weeks. It is also recommended to consider aspiration at 7 to 10 days or on “patient demand.” Andrew Bradbury finished by discussing the fact that many patients will develop and seek treatment for further varicose veins, but this need not be viewed as a failure.

Foam sclerotherapy – the safety issue

Lorenzo Tessari (Italy)

Lorenzo Tessari reported on a scintigraphic study about foam and lungs published in 2007. The study results showed that, after a single injection of 5 mL of foam, a very small pulmonary area could become diseased by the sclerosant. However, if repeated injections are performed over years, the authors cannot exclude progressive pulmonary arterial hypertension through sclerosis of a significant area of capillaries. Then Lorenzo Tessari presented his own study that quantitatively and qualitatively assessed the arrival and persistence of the microbubbles within the heart in sclerotherapy, observing that the elevation and immobility of the limb reduced and slowed down the flow of the bubbles toward the right heart. Another new study investigated the possibility of recognizing a pulmonary injury after foam sclerotherapy. The conclusion from this trial was that the sclerosant did not damage the lung. In a laboratory analysis, Lorenzo Tessari investigated the timing and modality of the sclerosant binding to human proteins, concluding that the sclerosant binds to blood proteins in less than 8 seconds. The high production of endothelin 1, histamine, serotonin after foam sclerotherapy might be responsible for neurovascular, respiratory, and visual disturbances. Therefore, Lorenzo Tessari recommends

elevating the limb elevation 20 to 30 cm, immobility for 10 to 15 minutes, and advises against performing the Valsalva maneuver.

Saphenous vein sclerotherapy – does tumescence and blood irrigation make the difference?

Attilio Cavezzi (Italy)

Attilio Cavezzi introduced his method of sclerotherapy using a long catheter with ultrasound-guided tumescence infiltration and saphenous irrigation. He explained that, from a biochemical point of view, the higher the vein diameter and blood flow, the higher the recanalization rate. He discussed the studies by Kurosh Parsis on liquid and foam sclerosants and blood from 2007 to date. In these investigations, albumin significantly inhibited liquid or foamed sclerosants, detergent sclerosants were deactivated and consumed by circulating blood cells, and finally, the chemical action of foam in the great saphenous vein was inversely proportional to the distance from the entrance point. The *in vivo* and *in vitro* results documented that sclerosant activation by blood occurs just after a few seconds. From a mechanical point of view, there are two main negative prognostic factors in sclerotherapy outcomes: vein size and inflow from tributaries, perforators, etc. Tumescence increases transmural pressure with a reduction in vein diameter and in the size of tributary/perforators orifices with decreasing of inflow. Clinical results showed lower blood amounts for a prolonged time, lower thrombus formation, and a higher fibrotic component in the sclerothrombus. As a result, a lower foam amount is needed. By using irrigation (saline solution flushing), saphenous blood, as well as blood from inflowing tributaries/perforators/junctions can be cleared from multiple catheter points. Additionally, the sclerosant dilution can be decreased and the time of sclerosant contact with the vein wall can be increased. Clinical data confirming the “empty vein technique” was then presented. Attilio Cavezzi concluded that ultrasound-guided perisaphenous tumescence infiltration is a safe and inexpensive procedure, which enhances foam sclerotherapy possibilities and allows larger diameters to be treated with good efficacy and safety as well.

XI. Endovenous ablation session

Results of randomized control clinical trial of energy settings in endovenous laser ablation

Denis Borsuk (Russia)

In a previous study, it was demonstrated that, in endovenous laser ablation for chronic venous disease treatment, using the same linear endovenous energy density with a different power setting is associated with significantly different effects on vein wall damage and tissue depth penetration. The aim of this investigation was to analyze three energy settings for clinical effects in terms of vessel recanalization and procedural pain. Patients with chronic venous disease (C₂E_pA_sP₁) were randomized for endovenous laser ablation (n=154) at 5 W (50 patients), 7 W (57 patients), and 10 W (47 patients). All the procedures were performed at 70 J/cm. Pain was evaluated by using a visual analog scale at 1 day, 1 week, and 2 months after endovenous laser ablation. Recanalization was assessed at 6 months. Pain at day 1 was rated as 0 (1 quartile 0; 3 quartile 1) in the 5 W group, 0 (1 quartile 0; 3 quartile 1) in the 7 W group, and 0.5 (1 quartile 0; 3 quartile 2) (P=0.355) in the 10 W group. Administration of painkillers showed no difference between the three groups (X²=0.236; P=0.889). No difference was reported in pain at 1 week and 2 months (1 week, P=0.317; 2 months; P=0.569). No great saphenous vein recanalization was reported at 6 months in all patients. Endovenous laser ablation at different power settings with the same linear endovenous energy density does not present significant differences in terms of pain and recanalization, despite the previously demonstrated difference in vein wall damage.

A randomized clinical study of radiofrequency ablation versus 1470nm laser for great saphenous vein reflux

Christos Karathanos (Greece)

Most studies have compared radiofrequency ablation with a previous generation of laser technology. Our aim was to compare the outcome of radiofrequency ablation and endovenous laser ablation with the new-generation 1470-nm laser for the treatment of great saphenous vein reflux. Consecutive patients with great saphenous vein reflux were randomized to radiofrequency ablation (VNUS ClosureFAST™) or endovenous laser ablation with a 1470-nm fiber (radial [ELVes®] or linear [VenaCure]) at a single academic center. Data on clinical classification (CEAP), 10-cm visual analog scale (VAS) for pain, venous clinical severity score (VCSS), and chronic venous insufficiency quality-of-life questionnaire (CIVIQ) were recorded. Assessment visits were performed at 7 days, 30 days, and 1 year postablation, including clinical examination and duplex scan. The primary outcome was anatomic success, defined as the absence of reflux or recanalization of the great saphenous vein. The secondary outcomes were procedure-related complications (thrombotic complications, ecchymosis, tenderness), postoperative pain using the VAS scale, and improvement in VCSS and CIVIQ scores.

The study randomized 135 patients to radiofrequency ablation (group I; n=45), endovenous laser ablation with a 1470-nm radial fiber (group II; n=45), and endovenous laser ablation with a 1479-nm linear fiber (group III; n=45). Patient demographics, CEAP classification, mean linear endovenous energy density, average vein diameter, and length

of ablated vein were comparable between the three groups. No major complications were observed postoperatively. Endothermal heat-induced thrombosis was observed in 2 patients in group I, 1 patient in group II, and 2 patients in group III (4.4% vs 2.2% vs 4.4%, respectively; $P>0.5$). Minor complications, such as ecchymosis and tenderness, were similar in all groups at all visits. The great saphenous vein occlusion rate at 12 months was 93% in group I, 93% in group II, and 95% in group III ($P>0.5$). During follow-up, all patients showed a significant improvement in all domains compared with the postoperative assessment ($P<0.05$). The VCSS improved more in group II at 1 week ($P=0.02$). The CIVQ pain score improved more at 7 and 30 days after treatment. Endothermal venous ablation using the radiofrequency ablation and 1470-nm radial or linear fiber laser are equally effective and safe modalities for the treatment of great saphenous vein reflux. Endovenous laser ablation with the 1470-nm radial fiber showed better outcomes in terms of early postoperative VCSS and pain CIVQ scores. However, clinical and quality of life improvements were similar after 30 days in all groups during the first postoperative year.

Endovenous laser ablation in patients with venous aneurysms and large diameter of great saphenous vein

Barys Maslianski (Belarus)

Endovenous laser ablation is a commonly used technique to treat patients with varicose veins. The majority of scientific research evaluating the clinical effect of endovenous laser ablation concerns the diameter of the great saphenous vein ≤ 13 mm. There are controversial opinions about the efficacy of endovenous laser ablation in large-diameter great saphenous veins. There are limited data about attempts of endovenous treatment for venous aneurysms in the literature. An aneurysm can be defined as an isolated dilatation of any vessel. Aneurysms may occur in any part of the vascular system. The definition of venous aneurysm remains controversial because there is no precise size criterion. According to different authors, venous aneurysm can be defined as an isolated segment of venous dilatation 1.5- to 2-times the normal size of a contiguous vein or 3-times the size of a normal vein. Venous aneurysms can be isolated or be contained within a segment of varicose vein. Venous aneurysms typically occur in the extremities, either in the superficial or deep venous systems. The incidence of superficial venous system aneurysms is around 0.1%. Types of venous aneurysms include saccular and prejunctional. The most common complications in great saphenous vein aneurysms are deep venous thrombosis, thrombophlebitis, pulmonary embolism, rupture, and focal peripheral neuropathy. This presentation described the experience with using endovenous laser treatment for patients with uncomplicated venous aneurysms and large-diameter great saphenous veins. Great saphenous veins with diameters >14 mm were defined as large. A local 2-fold increase in the diameter of the vein was considered a venous aneurysm. A retrospective review of patients who underwent endovenous laser ablation between January 2016 and December 2018 was conducted. A total of 685 protocols were reviewed.

There were 207 (30%) cases with large great saphenous veins: 64 men (31%) and 143 women (69%), mean age 52.8 years (range, 36.2-72.8 years). Venous aneurysms were diagnosed in 34 (4.9%) patients. Three patients had the saccular type and 31 patients had the prejunctional type. The procedure was performed using a radial laser fiber and a 1470-nm laser under tumescent anesthesia. The follow-up period was 3 to 6 months. The mean great saphenous vein diameter was 16.5 mm before ablation. The

largest diameter was found in patients with saccular aneurysms (28, 31, and 34 mm). The closure rate was 100% in this group. Complications occurred in 8 patients (3.9%). The most common complication was paresthesia, which occurred in 6 (2.9%) cases. In another 2 (1%) cases, thrombophlebitis was diagnosed. There were no major complications. Failure of closure was only seen in 1 (0.48%) case.

Great saphenous vein aneurysms can be associated with a thrombophlebitic process and the risk of a pulmonary embolism. Patients presenting with a great saphenous vein aneurysm containing a thrombus warrant surgical intervention. Endovenous laser ablation should be used as an alternative to surgery in cases of nonthrombosed venous aneurysms to avoid thrombus formation. It is an effective and safe procedure for treating patients with venous aneurysms and large-diameter great saphenous veins. This method has a low risk of serious complications.

Endovenous laser ablation with 1940 nm laser and radial fibers in varicose vein surgery, 2 years follow-up

Uldis Maurins (Latvia)

The study aimed to demonstrate the outcome and side effects after endovenous laser ablation with a 1940-nm diode laser (biolitec) and a 2-ring radial fiber (ELVeS radial 2-ring, biolitec) on refluxing great saphenous veins. Between February 2016 and March 2017, 100 great saphenous veins from 100 consecutive patients were treated by endovenous laser ablation for great saphenous vein incompetence with a 1940-nm laser by using a 2-ring radial fiber, 8 W power, and continuous fiber pullback without using compression therapy after treatment. Mean linear endovenous energy density was 69 J/cm and the endovenous fluence equivalent was 38 J/cm². Endovenous laser ablation was performed under tumescent anesthesia; additional miniphlebectomies were not applied. All patients were examined clinically and with duplex ultrasound prior to intervention and at the follow-up visits at day 10 (D10), day 180 (D180), and after 2 years (D720) for complications, occlusion, flow, and reflux in the treated vein segment. The clinical evaluation included clinical CEAP, venous clinical severity score (VCSS), presence of recurrent varicose veins, and patient satisfaction.

After an average follow-up period of 10 days, 96 treated patients (96 great saphenous veins) were reinvestigated. After 6 months (SD, 5), 96 treated patients (96 great saphenous veins) were reinvestigated, and after 25 months (SD, 5), 92 treated patients (92 great saphenous veins) were reinvestigated. Four patients were lost to follow-up after 6 months and an additional 2 patients after 2 years. At up to 2 years of follow-up, all treated veins remained occluded. After 2 years, 79 patients were very satisfied with the method, 12 were satisfied, and 1 was fairly satisfied. In 1 case, endothermal heat-induced thrombosis II was observed at 10 days of follow-up, but no severe complications, such as deep vein thrombosis, occurred. The average pain score during intervention was 1.8, on the day of the intervention, it was a 1.5, and, during the first 10 days, it was reduced to 0.9. Intake of painkillers during the first 10 days was on average 1 tablet (SD, 2.8).

In this prospective follow-up study with 100 consecutive patients and 100 treated great saphenous veins, a high occlusion rate of 100% could be demonstrated 2 years after treatment. In comparison with other studies using lower wavelengths, postoperative pain was reduced. Taking the very low pain levels and complication rate into account,

posttreatment compression is not necessary if modern treatment devices are used. In conclusion, endovenous laser ablation of great saphenous veins with a 1940-nm diode laser and radial fibers is a minimally invasive, safe, and efficient therapy option with a very high success rate and a very low level of periprocedural pain.

Laser crosssectomy versus infra-epigastric closure – randomized study

Johann Christof Ragg (Germany)

With today's endovenous approaches, the great saphenous vein is ablated with a "safety distance" from the junction, sparing all other branches and thus leading to a considerable number of recurrences, in particular consecutive anterior accessory great saphenous vein (AAGSV) insufficiencies. Consequently, additional treatments are required, potentially more frequently than after a surgical crosssectomy. Should ablation of nonrefluxive AAGSVs be routinely included or are technical modifications required? A prospective, randomized trial was performed to clarify the conditions for distinguished AAGSV strategies. The trial randomized 240 consecutive patients with great saphenous vein insufficiency (C_2 - C_6 ; $d=6.5$ - 17.8), reflux origin from the saphenofemoral junction (destroyed or malfunctioning terminal valve), nonrefluxive AAGSV, and no other refluxive branch of the saphenofemoral junction to endovenous laser ablation (EVLA, 1470 nm, radial, 50-80 J/cm) starting at the femoral vein level ("laser crosssectomy" [group A]) or to endovenous laser ablation starting below the epigastric vein junction (group B). Both procedures were combined with ultrasound-guided coaxial perivenous local anesthesia (CPLA). Ultrasound follow-up was performed after 1 day and after 1, 6, 12, and 24 months.

Great saphenous vein occlusion was obtained in all cases, but with different morphologies. Laser crosssectomy (group A) showed no stumps (88/120 [73.3%]), minor stumps <5 mm (14/120 [11.7%]), or moderate stumps 5 to 17 mm (mean, 11.5 mm; 18/120 [15%] at the 1-month exam); 118/120 (98.3%) entries of AAGSV were covered. In group B, great saphenous vein stumps of 8-31 mm length (mean, 23 mm) were present in 12/120 cases. AAGSV entry was covered in 13/120 cases (10.8%). Within the 2-year follow-up, AAGSV insufficiency was detected in 5/120 cases (4.2%) in group A and 26/120 (21.7%) in group B ($P>0.01$). Just 1/120 (group A) and 6/120 (group B) cases were clinically relevant. Therefore, consideration of AAGSV anatomy is crucial for the right choice of strategy. "Laser crosssectomy," even if attacking just the great saphenous vein, is more effective in preventing secondary AAGSV reflux than techniques leaving stumps. Further studies will have to detect factors of AAGSV vulnerability, such as the diameter or previous phlebitis, to consider primary ablation in selected cases.

Endovenous laser therapy of the GSV: 3-years results of a randomised prospective study comparing 0 and 2 cm ablations distance from the deep vein

Juris Rits (Latvia)

In the last 20 years, endovenous thermal ablation has developed as a gold-standard treatment for insufficient saphenous varicose veins. Nevertheless, the influence of an untreated proximal segment of the target vein on the development of reflux and recurrence after thermal ablation of a refluxing great saphenous vein remains unclear. Between April 2013 and January 2016, 146 legs in 146 consecutive patients were treated by endovenous ablation with a 1470-nm diode laser for great saphenous vein

incompetence by using a 2-ring radial fiber. All patients were randomized into two groups. In group 1, ablation was started from the level of the deep vein and, in group 2, ablation was started 2 cm below the deep vein. Investigations were performed clinically and by duplex ultrasound prior to intervention (screening visit), on the day of intervention (DO), and at follow-up visits on day 14 (D14), 90 (D90), and 900 (D900) after the procedure for side effects, complications, occlusions, reflux, and recurrences. The primary end point of this study was reflux in the saphenofemoral junction (stump left and anterior accessory vein [AASV]) after 3 years. The secondary end points were venous clinical severity score (VCSS), CEAP improvement, pain, and complication rates between the two groups.

At day 900, 35 patients were lost to follow-up: 19 in group 1 and 16 in group 2. There were no statistically significant differences in VCSS and CEAP in improvement between the two groups at any time point of follow-up. Characteristics of pain and necessity to use painkillers did not differ between the groups: 76% of patients did not take any painkillers at any time after the procedure (no between-group differences). There was no difference in the diameter reduction 3 cm below the saphenofemoral junction, but a statistically significant difference was noted according to the greatest diameter of the stump: 0.41 cm in group 1 and 0.60 cm group 2 ($P<0.001$). Reflux in the AASV was observed in 8% in group 1 and 14% in group 2. Reflux in the stump was detected in 4% in group 1 and 19% in group 2 ($P<0.05$). There were no between-group differences according to satisfaction with treatment at any time point. Proximal clinical recurrent varicose veins were observed in 9.6% in group 1 and 15.25% in group 2 ($P<0.05$), which was related to reflux in the stump and/or AASV. There were no between-group differences according to satisfaction with treatment. The improvement in VCSS and CEAP was equal in both groups. In addition, the complication risk was low in both groups. Pain level and usage of painkillers were the same. However, the long stump of the great saphenous vein was associated with higher risk of developing proximal reflux and recurrences in more long-term follow-up.

XII. Thermal tumescent (TT) ablation methods

Wavelengths, fibers or way of procedure performance for successful laser ablation? Lessons learned from 15 years of experience

Uldis Maurins (Latvia)

Laser energy is mainly absorbed by water in the vein wall and water content in the blood. The level of absorption of laser energy with a 1470-nm wavelength laser is 40 times higher than a 980-nm wavelength laser and 40 times lower with the new 1940-nm wavelength laser. The radial fiber, which replaced the bare fiber that heats up to 700°C to 800°C, at a linear endovenous energy density 60 J/cm, heats up to 100±10°C and it is often accompanied with carbonization and loss of effectiveness. The introduction of a 2-ring fiber into practice has improved the procedure due to a reduced and softer sticking potential of reduced side effects. We now have different fibers: (i) radial slim 2-ring fiber (d=1.3 mm), radial Swift 1-ring fiber (d=1.6 mm), and classic radial 2-ring fiber (d=1.9 mm) for different situations for effective closing of different veins of any diameter. Usage of these new fibers with local tumescent anesthesia provided with a pump will help improve treatment results. Today, it is possible to conduct laser ablation without using compression stockings. Integrated use of these principles will help achieve complete resorption of treated great saphenous veins in 96% of cases at the 1-year follow-up (average diameter, 9 mm; linear endovenous energy density, 73 J/cm; endovenous fluence equivalent, 31 J/cm²). The modern trend is a wish to leave the shortest possible great saphenous vein stump in order to decrease the number of relapses.

The future of the endovenous ablation

Lowell Kabnick (US)

Today, endothermal ablation methods with laser and radiofrequency ablation are the gold-standard treatments of varicose veins. The current studies show no differences in efficacy between radiofrequency ablation and laser ablation. All endovenous treatments are safe, with low complication and morbidity rates. Interventions resulted in significant and clinical improvements in symptoms and signs. All interventions result in significant improvements in quality of life. Nonthermal nontumescent methods are a modern alternative to treat varicose veins. Today, the recommended vein diameter should not be bigger than 12 mm (mechanochemical and glue ablation) and 10 mm (foam ablation). Quality of life improvements and an occlusion rate greater than 90% are similar for both nonthermal nontumescent and thermal ablation methods. On the other hand, thermal treatment is associated with discomfort during tumescent infiltration (not the ablation part of procedure itself). Thermal treatment with radiofrequency or endovenous laser ablation is the mainstay of varicose vein treatment at present. All procedures appear to be in clinical equipoise among the ablation procedures because no perfect device is available currently for superficial venous disease.

Thermal ablation of saphenous and non-saphenous varicose veins by steam

Rene Milleret (France)

The first-generation steam machines were available in 2006, with the second-generation being available in 2016. Steam allows even heating of the vein wall, can cross the tortuosities, heat veins close to the skin, does not heat deep veins, and does not induce inflammatory reactions or allergic complications. Steam is efficient and safe for saphenous trunks, even in 10 mm and more. Recurring varicose veins are more tortuous than saphenous trunks and more difficult to catheterize with laser fibers or radiofrequency catheters, but steam will go through the bends and, from one entry point, can treat up to 8 cm of the vein. Perforators are often tortuous, with branches that can be surrounded by sclerotic tissue. Steam is a good option, as, in the deep veins, only droplets of hot water will be released, they are diluted in the fast-flowing blood without risk of deep vein thrombosis. Popliteal perforators are often seen as recurrences after small saphenous vein surgery. Steam can close even large perforators with a small catheter under echo guidance. Steam can heat up to 600 J/cm without damaging tissues; therefore, it can be useful for malformation treatment. Combined with foam for superficial lesions, steam allows less aggressive treatment of these venous malformations. Radiofrequency and laser are the references for thermal endovenous techniques. For teams who perform advanced venous surgery, steam opens up more indications and saves time and trouble.

UGLA – ultrasound guided laser ablation

Peter Dragic (Germany)

Traditionally, the pullback speed of fiber and the amount of energy was based on the calculation of linear endovenous energy density or endovenous fluence equivalent. Ultrasound-guided laser ablation (UGLA) changes this approach. The sense of UGLA is that, based on information obtained from the ultrasound probe about vein wall thickness and the ablation at that place, the pullback speed can be determined to optimize the amount of energy needed for successful ablation. UGLA provides an increased percentage of occlusion and a lower chance of recanalization. The foundation of UGLA is an assumption that vein wall thickness is not always proportional to its diameter and increasing vein diameter is not always followed by increasing its thickness. Sometimes aneurysms of 20 mm or larger have the thinnest wall of the entire vein, but sometimes it is the opposite where a tiny vein has thicker walls than veins with a larger diameter. It is this assumption that can lead to inadequate ablation. Traditionally, a normal vein, a varicose vein, and a vein after postthrombotic syndrome with the same diameter are going to have different thickness. In these cases, UGLA provides an increased percentage of occlusion and a lower chance of recanalization.

Thermal ablation in the extrafascial location – is it safe?

Igor Zolotukhin (Russia)

Endovenous thermal ablation for extrafascial veins is the safest procedure (no pulmonary embolism/deep vein thrombosis), but complications, such as skin injury (burns, retraction), nerve injury, and hyperpigmentation, occur. There are only a limited number of papers about the subject. Igor Zolotukhin reported the data from a pool of members of the Russian Phlebological Association. The questions were sent out to 163 practicing phlebologists,

94 of them participated in the poll (58%), where 87 (53%) practice thermal ablation, of which 17 (20%) do not use thermal ablation for extrafascial veins, 35 (40%) infrequently perform, extrafascial thermal ablation, and 35 (40%) frequently perform extrafascial thermal ablation. Among the 70 doctors who practice thermal ablation for extrafascial veins, 51 (73%) preferred laser, 7 (10%) radiofrequency ablation, and 10 (14%) both methods. Observed adverse events and complications were reported by 57 (71%) doctors. Hyperpigmentation was observed by 46 (66%) doctors and 36 reported that the mean time to resolve the hyperpigmentation was 6 to 12 months, where 3 doctors reported that it took longer than 12 months. The feeling of a tensed cord under the skin was observed by 43 (61%) phlebologists, skin retraction was observed by 16 (23%), phlebitis by 12 (27%), pain by 23 (33%), and the need for pain killers by 10 (14%). Of the 57 extrafascial thermal ablation users, 1 to 5 adverse events were reported by 39 (68%) users, 6 to 10 adverse events by 7 (12%), and ≥ 11 and more adverse events by 6 (11%). The procedure does not lead to life-threatening adverse events, but it does not seem to be free from complications.

Hybrid procedures in varicose vein treatment

Aleksandra Jaworucka-Kaczorowska (Poland)

Some patients seek treatment because of symptoms, fears about future harm, but the majority seeks treatment because of cosmetic appearances. From 14% to 55% of patients have reflux with multiple origins. Endovenous laser therapy alone for the proximal great saphenous vein does not address the multiple sources of clinical reflux. Concomitant treatment can be used effectively in below the knee saphenous veins, tributary varices, and perforating veins. Above the knee great saphenous vein endovenous laser therapy improves the symptoms of chronic venous disease, but persisting below the knee reflux appears to be responsible for residual symptoms; some patients even return with persistent reflux and worsening symptoms. From 30% to 99% of patients, secondary treatment of residual varicosities is required. Advocates of delayed phlebectomy cite "over-treatment" as a primary concern, but "under-treatment" and its sequelae leads to worse outcomes in those patients needing further treatment and in a time of austerity, the additional treatment is not economical, so it is better to do it in a single procedure. Compared with endovenous laser therapy alone, endovenous laser therapy with concomitant sclerotherapy was, on average, 5 minutes longer and endovenous laser therapy with concomitant phlebectomy prolonged the procedure time by 20 minutes. A one-stage treatment reduced the need for secondary procedures, significantly improved quality of life, significantly improved the severity of venous disorders, and reduced the cost.

Aleksandra Jaworucka-Kaczorowska reported on her own experience with endovenous laser therapy and concomitant sclerotherapy. Of 576 patients (508 primary, 40 recurrent, and 28 with previous superficial vein thrombosis of the affected vein), 87 (15%) were multiple origin, 212 (37%) had perforating veins, and 558 (96%) had visible varicosities below the knee. A combined hybrid procedure was used: endovenous laser therapy for the great saphenous vein, small saphenous vein, and accessory saphenous vein (1470 nm, radial fiber) and ultrasound-guided foam sclerotherapy was used for incompetent perforating veins and tributaries. The vein occlusion rate was 100% at the 1-week follow-up, 96.5% at the 6-month follow-up, and 91.8% at the 12-month follow-up. For truncal veins (great saphenous vein and small saphenous vein), the occlusion rate was 99.2% after 1 year, additional sclerotherapy was required in 32 (5.6%) patients, and 184 (31.9%)

patients wanted additional sclerotherapy due to C₁ status. After 1 month, complications and side effects occurred in 22.5% of patients (hyperpigmentation, 13.9%; superficial thrombophlebitis, 4.7%; paresthesia, 1.7%; skin necrosis, 0.7%; visual disturbance, 1.5%), and 98.3% of patients (566/576) said they would have this procedure again. So, a one-stage treatment is not only for patient preference, but it is also valid for many medical indications. A hybrid approach does increase the treatment possibilities and its efficacy with an acceptable increase in procedure risk.

XIII. Non thermal non tumescent (NTNT) ablation methods

Why does the combination of sclerotherapy and mechanical vein injury works better?

Mark Whiteley (UK)

Thermal ablation requires transmural damage of the vein wall for fibrosis and long-term ablation. Unlike thermal ablation, sclerotherapy cannot affect deeply located layers of the venous wall, meaning that the success of great saphenous vein ablation after 1 year is no higher than 75%. The combined usage of sclerotherapy throughout the process of mechanochemical ablation (MOCA) should increase the depth of exposure to the vein wall and lead to transmural fibrosis. To prove this hypothesis, a comparison of sodium tetradecyl sulfate (3%) alone with MOCA on the wall of the extrafascial segment of the great saphenous vein was made by studying the histological and immunohistochemical properties of the vein wall. The exploration showed that MOCA resulted in deep media damage, shear damage from mechanical rotation. Immunohistochemistry revealed the exact location of the deepest injury of the vein wall with MOCA. As such, MOCA enhances sclerotherapy damage to the vein wall in both the endothelium and media layers. The effect in the media appears to be via mechanical shearing of the layers, allowing ingress of sclerosant deeper into the media.

Mechano-chemical saphenous ablation by Flebogrif®

Tomasz Zubilewicz

Given the results of treatment, where 200 procedures were performed in cases of great saphenous vein/small saphenous vein incompetence using the Flebogrif catheter. The clinical success, anatomical success, safety of Flebogrif®, and technical features/advantages were studied. The closure rate was 96% after 3 months, 93% after 6 months, and 92% after 1 and 2 years. There were 15 cases of recanalization (11 for the great saphenous vein and 4 for the small saphenous vein). There was 1 major complication, ie, deep vein thrombosis due to thrombophilia. In 32% of cases, there were minor complications: 1 case of prolongation pain, 35 cases of thrombophlebitis, and 26 cases of discolorations. There were no sclerosant-related side effects (allergic reaction etc). The technical features and advantages of the procedure included no anesthesia, no tumescence, short procedure time, no need to invest in additional medical devices, no hospitalization, catheter available in two lengths (60 and 90 cm), and clearly visible by Doppler.

Infra malleolar access for endovascular treatment of venous insufficiency ulcers

Michael Tal (US)

Michael Tal presented his experience using inframalleolar access to treat venous ulcer patients. Mechanochemical ablation allows treatment below the ulcers because it is characterized by a minimal risk of nerve injury (over 180 000 cases performed worldwide

and no reports of nerve damage). A retrospective enrollment and review of 103 patients (89 with active chronic venous ulcers and 14 with healed ulcer) who were treated with mechanochemical ablation using inframalleolar access using a micropuncture with 16G peripheral surgical catheter and local anesthesia showed that closure was observed in 62 great saphenous veins, 22 small saphenous veins, and 19 great saphenous veins/ small saphenous veins. The average surgery time was 40 minutes; 55 patients received low-molecular weight heparin during the procedures and 47 received antibiotics; 44 patients had debridement during the procedure and 3% had postprocedural phlebitis. A decrease in pain from 4 points to 1 on day 5 postprocedure was observed. A reduction in ulcer size was recorded in 52% of patients after 1 week, in 80% after 1 month, and in 98% after 3 months. Therefore, inframalleolar venous access is feasible and safe, it enables treatment of the underlying vein, and appears to enhance venous ulcer healing. Inframalleolar access should be considered as the preferred access point when treating venous ulcers.

Limitation of the current technology – glue

Nick Morrison (US)

Adhesive ablation has some clinical advantages in the treatment of the below the knee portion of the great saphenous vein and the small saphenous vein, especially in case of cranial extension of the small saphenous vein and perforators. However, the method has some limitations. Strong contraindications are acute deep or superficial vein thrombosis, active skin infection, significant arterial insufficiency (ankle brachial index <0.6), uncontrolled significant medical illness (asthma, malignancy, etc), and lipodermatosclerosis. The weak negative recommendations are the cases of treatment of a very thin patient or a very superficial vein (because a “cord” may be palpable and may irritate the patient), pregnancy, adhesive or chemical sensitivity, autoimmune disease, or compromised immune system. Moderate negative recommendation for use of glue includes patients with very limited mobility, cases of a tortuous saphenous vein, previous great saphenous vein thrombophlebitis, and small diameter vein (<3 mm).

XIV. Complications and failures in phlebological treatment

Underuse, overuse, or misuse of the phlebological treatment? – treatment overuse or insufficiently trained operators

Martin Schul (US)

Martin Schul presented a clinical case and an example treatment overuse. In one patient, an ablation procedure was performed for three veins, but there was no evidence of reflux in any image. We have benchmarks of 1.6 to 1.7 ablations per patient. Overutilization is widespread and involves every specialty. Underutilization is often in patients with leg ulcers. They required on average 0.37 more ablation procedures vs nonulcer patients. On the other hand, early intervention was associated with lower disease progression. Each 30-day delay was associated with a 7% increase in the risk of progression and a 1% increase in the cost of care. In addition, patients receiving sclerotherapy had the lowest rate of new venous leg ulcers. Martin Schul concluded by saying that we have a collective duty to provide appropriate care using established benchmarks and to promote the “limb emergency for venous leg ulcers” in delivering care. Furthermore, we should provide educational venues for a growing field of wound care centers potentially entering the field.

Matting is the issue – how to avoid and treat

Kurosh Parsi (Australia)

Telangiectatic matting is small telangiectasias <0.2 mm that can appear sporadically or in well-defined patches, commonly on the lower limbs. The incidence of telangiectatic matting is up to in 25% of the patients postsclerotherapy, but it can happen after other venous interventions, such as surgery or laser ablation. Telangiectatic matting is commonly found concurrent with phlebitis and pigmentation; however, they can also happen for no reason, with no prior venous treatment. Matting is an enigma. It can be devastating and it can last for years. Some believe it goes away. Traditional risk factors are procedure-related risk factors and patients-related risk factors. Procedure-related risk factors are not treating or incompetently treating the underlying feeding veins, injecting too quickly, using a large volume of injection per site, and using a high concentration of sclerosant. Patient-related risk factors are obesity, estrogen-containing hormones (oral contraceptive pill, hormone-replacement therapy), pregnancy, and a family history of telangiectasias. Inflammation causes endothelial activation and angiogenesis. High-risk areas are the subdermal reticular venous network in the anterior and anterolateral thighs and at the medial knee underlying the great saphenous vein, infragenicular veins, and supragenicular veins. Injection of some of the reticular veins cannot possibly treat and occlude all reticular veins. Ongoing flow from open veins will result in inflammation and matting. Reticular veins are normal vessels and should not be treated.

Matting, pigmentation, and inflammation can happen together. Anecdotal observations reported that patients with telangiectatic matting are more often females, report a

history of easy bleeding and bruising, and have an urticarial reaction at the site of injection. In a retrospective analysis, the patient-related risk factors were female sex, skin types I, II, and III, and a hypersensitivity and bleeding tendency, but not hemostatic abnormalities. In vitro studies have shown that detergent sclerosants at low concentrations activate cells: endothelial cell, keratinocyte, platelets, and leucocytes. In addition, it has been demonstrated that detergent sclerosant can also activate basophils. Activation of basophils and mast cells results in release of granule contents, including histamine. Histamine causes vasodilatation and induces an inflammatory response, which leads to angiogenesis, pigmentation, reactive dilatation of the surrounding vessel, and target vessel nonclosure. We can prevent inflammation and angiogenesis if we avoid treating high-risk areas. The feeders should be treated, as well as higher and more proximal sources of reflux. We should avoid high concentrations and sodium tetradecyl sulfate in subdermal veins. We should use compression. Patients should avoid strenuous exercise afterward because of inflammation. In a current study, Kurosh Parsi is investigating the effect of pretreatment with antihistamines and Cyklokapron (tranexamic acid) in patients predisposed to matting.

Hyperpigmentation after vein treatment. Dermatologists point of view

Eberhard Rabe (Germany)

The incidence of pigmentation is 10% to 30% of patients following sclerotherapy of vessels between 0.1 and 5 mm in diameter. Risk factors are solution strength, vessel fragility, injection pressure, and type of solution used. Histology data suggest that there is no melanocytic alteration. Pigmentation is secondary to extravasation of red blood cells into the dermis following rupture of fragile vessels with resulting deposition of hemosiderin. Therapy has included bleaching agents (hydroquinone), trichloroacetic acid, and phenol peeling agents with variable success. In 80% of cases, pigmentation will clear spontaneously within 6 to 24 months. The remaining patients will have persistence of pigmentation for up to 5 years, with a small number of patients having pigmentation persisting 5 years after therapy. Skin laser treatment has shown different results with 42% to 92% of the lesions lightened after treatment. In a study where deferoxamine mesylate was used, depigmentation was observed in 81% to 100% of cases. In another study, complete regression of hyperpigmentation was reported in 90.48% of the women after using an intense pulse light generator. In a multicenter, randomized trial, microthrombectomy was shown to reduce postsclerotherapy pigmentation. Eberhard Rabe summarized by saying that hemosiderin pigmentation is a common finding after sclerotherapy. Most of the studies are not controlled or they use small patient numbers. The only bigger randomized control trial shows a benefit of early microthrombectomy in small vessels.

Hyperpigmentation after vein treatment. Phlebologist point of view

Neil Khilnani (US)

Residual pigmentation after C₁ sclerotherapy is common (1% to 10% of the population). In the EASI randomized control trial, 0.5% polidocanol liquid was compared with placebo. Pigmentation usually improved over 12 months, but was permanent in 10% of cases. There is only retrospective evidence about pigmentation after C₂ sclerotherapy and the incidence is less precise because it is self-reported by patients. The primary biological

mechanism is by deposition of hemosiderin. Melanin is responsible for postinflammatory hyperpigmentation. Inflammation stimulates increased melanin production with increased melanin leakage from melanocytes. Melanin pigmentation is more common in large-diameter veins with more inflammation. Pigmentation can be related to the technique if the sclerosant is too strong (or even too weak) (thrombosis rather than sclerosis). It is more common with darker skin. Current strategies to minimize pigmentation are to treat the patient in a supine position, which minimizes hemolysis and bleeding, phlebitis, and intravascular coagulum. In terms of compression, there is a weak recommendation with low-quality evidence. Removal of intravascular coagulum is recommended by most. Avoiding sun for 1 week is recommended, but the evidence is limited. Light-based (q-switched laser, intense pulse light/radiofrequency) have been tried. Neil Khilnani summarized by saying that pigmentation is common. The risks are higher with large-diameter veins and darker skin. The evidence in the literature is poor regarding compression, removal of trapped blood, and avoiding the sun. Microphlebectomy is an alternative for C₁ and C₂. There are many opportunities for research in this field, for example, new means of compression, new mechanical means for telangiectasia, and drugs.

Visual and neurological complications of sclerotherapy

Birgit Kahle (Germany)

If performed properly, sclerotherapy is an efficient treatment method with a low incidence of complications. Transient migraine-like symptoms may be observed after any kind of sclerotherapy. They occur more commonly after foam sclerotherapy than after liquid sclerotherapy. It has been suggested that a right-to-left shunt (eg, patent foramen ovale), which is present in approximately 30% of the general population, might be a factor allowing foam bubbles to pass into the arterial circulation. The frequency of occurrence is estimated around 1.5%. Visual disturbance symptoms, flickering lights, spots, lines, or scotoma in one or both eyes, are reversible. They correspond to migraine with aura, but no transient ischemic cerebrovascular events. Visual disturbances can be associated with paresthesia and dysphasic speech disturbance depending on the extension of cortical spreading depression in the cerebral cortex. Cortical spreading depression is a short-lasting depolarization wave that moves across the cortex at a rate of 3 to 5 mm per minute. Cortical spreading depression is the pathophysiological correlate of migraine with aura.

Visual disturbances following sclerotherapy are similar to a migraine with aura after sclerotherapy in patients with a relevant patent foramen ovale. Triggers for cortical spreading depression include the release of endothelin 1 and microembolization with a decrease in cerebral oxygen saturation. Following sclerotherapy, there is a higher amount of endothelin 1 release because of larger volumes of sclerosant or basal augmented release from the endothelium. The presence of a patent foramen ovale with fast passage of endothelin 1-rich blood into the left ventricle could be a causal factor. Other factors are incomplete vein spasm immediately after injection, causing a prolonged release of endothelin 1 from the endothelium, patient variability (migraine patients), and concomitant drugs with an anti-endothelin action.

Strokes related to paradoxical clot venous embolisms usually occur with late-onset symptoms (liquid and foam). Strokes related to paradoxical air embolisms occur with early-onset symptoms, which is a specific complication of foam sclerotherapy. In early-

onset neurological disturbances (“stroke”), no intracerebral clots and no correspondence with thromboembolic pathology have been found. Air bubbles in brain arteries have been reported with (nearly) complete recovery.

Birgit Kahle concluded by saying that sclerotherapy is safe. Documented severe neurological complications (transient ischemic attack, stroke) are very rare – only isolated case reports. Visual disturbances following sclerotherapy are very rare (<0.01%) when liquid sclerosants were used and uncommon (0.1% to <1%) when foamed sclerosants were used. Visual disturbances are reversible. We should take care when treating patients with migraines.

EHIT and ostial thrombotic complications after saphenous ablation – do we need routinely follow up the patients with US?

Lowell Kabnick (US)

There are 4 classes of endothermal heat-induced thrombosis (EHIT): (i) in class 1, there is a thrombus extension up to saphenofemoral and saphenopopliteal junctions; (ii) in class 2, there is a thrombus extension into the deep venous system, with a cross-sectional area <50%; (iii) in class 3, there is a thrombus extension into the deep venous system, with a cross-sectional area >50%; and (iv) in class 4, there is a complete occlusion of the deep vein. The incidence of EHIT is low: total for all classes is 3% to 4% and the total for class 2 is 1% to 2%. The incidence of pulmonary embolism with EHIT is a maximum of 0.03%. In a short series by Lowell Kabnick, 9 patients were followed up with class 2 EHIT and all patients were monitored with serial duplex. Of these patients, 8 were placed on therapeutic low-molecular-weight heparin and all patients obtained resolution of EHIT within 14 days. After resolution of EHIT, chest CTs showed a pulmonary embolism in 2 of the 9 patients, but all patients were asymptomatic. None suffered significant sequelae.

The rate of closure in the immediate postoperative period is around 99%. If we do not look for EHIT, we can save 300 000 duplex scans per year in the US alone (ie, \$100 to \$150 million). With the data and the unclear clinical significance of EHIT, the policy of universal screening after endovenous ablation should be revised in the near future. At most, 30 patients a year will have a clinically significant pulmonary embolism. However, 72 patients will bleed from therapeutic low-molecular-weight heparin. Refraining from mandatory duplex screening would save approximately 150 million US health care dollars. Postoperative morbidity and mortality rates would not change. Duplex screening in the postoperative period is wasteful and not efficacious for the prevention of complications or treatment failure.

Lowell Kabnick finished with the statement that routine postthermal ablation duplex screening is a waste of time, effort, and money.

A multicentric study on the role of heparin prophylaxis of thrombotic complications in foam sclerotherapy (the Prosclep study)

Alessandro Frullini (Italy)

In a retrospective study, assessment of thrombotic adverse events and treatment patterns associated with varicose vein treatment was conducted with health care claims data.

The incidence of deep vein thrombosis was 4.4% after radiofrequency, 3.1% after laser ablation, 2.4% after surgery, and 0.8% after sclerotherapy. The incidence of pulmonary embolism was 0.3% after radiofrequency, 0.3% after laser ablation, 0.3% after surgery, and 0.2% after sclerotherapy. Thrombotic complications after sclerotherapy are the result of two different conditions: progression of the sclerous in the deep venous system and occlusion of a deep vein not in continuity with the sclerous. Progression of the sclerous in the deep venous system is usually a self-limited condition. It is usually asymptomatic and very rarely causes total occlusion. It usually follows with full resolution or resolves after a short treatment with low-molecular-weight heparin. Occlusion of a deep vein not in continuity with the sclerous manifests itself as an occlusion of a muscular vein, with a lower tendency for spontaneous resolution and it is often painful.

Thrombotic complications after sclerotherapy may have no or poor clinical evidence. The Prosclep study, a multicenter prospective study on sclerotherapy, was conducted at 16 vein centers. Sclerotherapy was performed with polidocanol or sodium tetradecyl sulfate (1% to 3% (liquid or foam)). Low-molecular-weight heparin prophylaxis was given in 56.3% of the patients, whereas there was no prophylaxis in 43.7%. Deep vein thrombosis after sclerotherapy of the great saphenous vein was found in 0.31% of the patients with prophylaxis and in 1.91% without prophylaxis (significant results). Deep vein thrombosis after sclerotherapy of the small saphenous vein was found in 2% of the patients with prophylaxis and in 1.88% without prophylaxis (not significant results). No complications were observed after sclerotherapy of the accessory anterior vein, recurrences, and large tributaries.

In conclusion, sclerotherapy carries a very low risk of thrombotic complications. Heparin prophylaxis is advised in sclerotherapy of the great saphenous vein, as it significantly reduces the risk of thrombotic complications. There are not enough data on the role of heparin prophylaxis for the treatment of perforators and small saphenous vein sclerotherapy. There is no need for heparin prophylaxis in sclerotherapy of recurrences, large tributaries, and the accessory anterior vein. The Prosclep study confirms that thrombosis after sclerotherapy is a rare and minor complication that resolves after a short course of anticoagulation.

NTNT ablation complications can happen – how to deal with it?

Frantisek Zemovicky (Germany)

Thermal tumescent operations include lasers with different wavelengths, radiofrequency, and hot steam. They cause complete transmural lesions of the vein wall. Tumescence protects surrounding tissue and requires identification of the saphenous compartment, safety function of the compartment, and compression of the saphenous compartment. Nonthermal nontumescent operations include mechanochemical ablation (Clarivein, Flebogrif), cyanoacrylate glue (Venaseal, Variclose), V-Block (VVT Medical), and duplex-guided foam sclerotherapy (Varithena BTG). Clinical data on these methods showed good outcomes, noninferiority to endovenous thermal ablation, and an improvement in venous clinical severity score and Aberdeen Varicose Vein questionnaire.

VenaSeal procedures may have preferable indications for immobile, hypomobile patients, for patients with unfit anatomy, the Giacomini vein, extremely obese patients, patients with lymphedema, patients with lipedema, patients with severe posttraumatic changes and

mixed leg ulcers. A summary of clinical evidence with VenaSeal system concluded with an acceptable safety profile; side effects were minor and infrequent. One disadvantage is that the system is still not as precise as laser or radiofrequency ablation. Another disadvantage is postoperative redness. Cyanoacrylate glue is a permanent implant with nonequal degradability, with filling of a foreign body, tension during movement, persistent tangible resistance. Glue can cause fast progressing granulomatous reactions.

Frantisek Zemovicky presented a clinical case of a 54-old female, polymorbid with a high risk of bleeding and development of a granulomatous reaction. Immunohistochemical visualization showed a necrobiosis lipoidica-like reaction. It was necessary to perform saphenectomy in this patient. The first symptoms of a granulomatous reaction are an indication for an immediate saphenectomy. The warning signs are painful resistance in the previous position of the vein, hypoechogenic brightening around the treated vein, a moving shadow of the glue, a growing granuloma deforming the saphenous compartment, and negative microbiology.

Granuloma formation following cyanoacrylate glue injection in peripheral veins and arteriovenous malformations

Kurosh Parsi (Australia)

Kurosh Parsi presented the n-butyl cyanoacrylate (n-BCA) products available for the treatment of peripheral veins: VenaSeal, Venablock, Veinoff, and Variclose. The long-term pathological reactions to cyanoacrylate glue are unknown in human veins. A histology study showed that perivascular mast cell degranulation occurred 10 minutes after glue injection, and a recent clinical case report demonstrated suppurative granulomas with extrusion of n-BCA 4 months after bilateral great saphenous vein treatment with VenaSeal.

The aim of a study by Kurosh Parsi was to characterize the late tissue reactions to n-BCA injection and determine whether this process involves a granuloma formation and immune activation. Two patients were included. On ultrasound, the injected glue appeared echogenic and produced a shadow artifact. On histopathology after 1 week, glue was seen in the vein lumen, presenting as a homogeneous eosinophilic material that was crystallized to produce a snowflake-like appearance. Six weeks later, histiocytes, but no granulomas were evident. One year later, fibrosis, cavitated granulomas, extrusion of glue, and lymphocytic infiltrate were present. This study was the first longitudinal histological study in humans following the use of n-BCA in the treatment of peripheral vessels. Tissue response to cyanoacrylate glue is as follows: mast cell degranulation occurs after 10 minutes, followed by acute inflammation, polymorphonuclear cells after 1 to 2 days, foreign body giant cells after 2 to 3 weeks, fibrosis and wall thickening after 8 weeks, and extrusion of n-BCA to the perivascular space, extravascular cavitated foreign body granulomas, lymphoid hyperplasia, and fibrosis of the surrounding tissue after 1 year.

Kurosh Parsi concluded by stating that n-BCA causes delayed extravascular granuloma formation, glue extrusion, and lymphoid hyperplasia in the absence of clinical signs.

XV. Small saphenous and BTK vein treatment

Surgery, thermal or non-thermal treatment in the SSV treatment?

Marc Vuylsteke (Belgium)

Incompetence of the small saphenous vein is observed in 10% to 15% of patients with chronic venous insufficiency and 29% of patients with severe chronic venous insufficiency or truncal vein incompetence. The small saphenous vein is located near the saphenous nerve, with an average distance between them of 3 to 4 mm. There are 5 different types of saphenopopliteal junctions. Surgical treatment of small saphenous vein incompetence is characterized by low anatomical success with a high recurrence rate (30% to 50%) at 1 year and neurological damage (19% paresthesia). The results of ultrasound-guided foam sclerotherapy are characterized by an anatomical success rate in 20% to 96% and a higher occlusion rate in veins with a diameter of <5 mm. Using endovenous laser ablation is characterized by a success rate of 91% to 100%, but the paresthesia/numbness rates of 1.1% to 11%. For radiofrequency occlusion rates of 82% to 100%, the paresthesia rates are 9.7% to 26%. For mechanochemical ablation, the occlusion rate is about 94%; the procedure is safe, feasible, and effective and no paresthesia has been reported. For cyanoacrylate glue ablation, the results are the same, with a closure rate of 97.3% at 6 months and 96.8% at 12 months and no report about saphenous nerve paresthesia. The major flaw of thermal tumescence is saphenous nerve neuritis. To prevent this complication, work near the saphenous nerve should be carried out carefully, which is achievable in 100% of cases. If hydro displacement was done, then the frequency of posttreatment neuritis is reduced to 0.8%. Puncturing the small saphenous vein at the mid-calf may decrease postoperative paresthesia, as the risk point is above mid-calf level in 10% of cases.

Small saphenous vein treatment by thermal and nonthermal ablation methods: focus on popliteal fossa, femoral extension and Giacomini vein atypical

Frantisek Zernovicky (Germany)

The small saphenous vein in the area of saphenopopliteal junction is variable. Treatment results are dependent on the structure of the saphenopopliteal junction. To improve the results of treatment, Frantisek Zernovicky offered the following treatment algorithm. He distinguished three types of saphenopopliteal junction: complete, partial, and absent. A complete (typical) saphenopopliteal junction means that the complete volume of blood is drained to the popliteal vein and it occurs in 50% of cases. This variant of the small saphenous vein is best treated using endothermal ablation methods (out of a rating of 5, endothermal ablation is ranked as 5, and other methods, such as foam, mechanochemical ablation, and glue are ranked as 3). A partial variant of the saphenopopliteal junction means that part of the blood volume is drained to the popliteal vein and part of the volume of blood continues proximally to a thigh-like cranial extension of the small saphenous vein (foam treatment and mechanochemical ablation is ranked at 4 points, endothermal ablation at 3 points, and glue at 2 points). An absent variant

of the saphenopopliteal junction means that none of the blood volume is drained to the popliteal vein and complete volume of blood continues proximally to a thigh-like cranial extension of the small saphenous vein. For this type of junction, mechanochemical ablation is the preferable method (ranked as 5), followed by endothermal ablation (ranked as 3 points), foam and glue (ranked as 2). After determining the saphenopopliteal junction type, it is essential to define the site of connection of the small saphenous vein to the popliteal vein. If the type of connection is lateral/medial, then the best option will be sclerotherapy or mechanochemical ablation. How should we perform small saphenous vein surgery in 2019? It is only perfect, if it fits tangibly with every patient.

How to deal with below the knee saphenous vein incompetence

Steve Elias (US)

The treatment of below the knee saphenous vein is difficult and depends on where the vein is located. The potential problems for treatment would be the nerves (saphenous, sural, tibial, peroneal), skin (veins more superficial and skin can be damaged), and stage of disease (in C_{5,6'} the veins are hard to visualize). According to the basic rules of 2019, we have to treat to the lowest point of incompetence, the more advanced disease (meaning you need to go lower and do more [varicose veins, perforating veins]). A study showed that, in the case of above the knee endovenous laser ablation, 41% of patients with persistent below the knee reflux and 89% required treatment of residual varicose veins. Steve Elias suggested that, in 2019, for primary procedures in C₂ patients, we can treat at least to mid-calf (maybe lower), in C_{4'} at least to mid-calf, and, in C_{5,6'} to the malleolus, under the ulcer. Relying on these principles, nonthermal and nontumescent methods are easier/safer to go to the malleolus. Another indication for below the knee treatment is persistence of symptoms after endovenous laser ablation of above the knee great saphenous vein (occurs in 40% to 50%), incompetent perforating veins in C_{4'} C₅ after great saphenous vein or small saphenous vein ablation.

Current theories on indications and techniques for perforator ablation

Kathleen Gibson (US)

Substantial evidence supports the role of incompetent perforator veins role in chronic venous insufficiency. Approximately two-thirds of limbs with skin changes have incompetent perforator veins as well as superficial or deep reflux. Of the recurrent varicose veins, 63% are associated with incompetent perforator veins. The current guidelines from the Society for Vascular Surgery/American Venous Forum for patients with ulcers suggest ablation of incompetent superficial veins and perforator veins, as well as compressive therapy to aid in ulcer healing and recurrence (2C). For C_{4b} and C₅ patients they suggest that perforator ablation can be performed simultaneously or staged if still incompetent on re-evolution (2C). Currently, the treatments used for incompetent perforator veins are subfascial endoscopic perforator surgery, direct perforator ligation, percutaneous radiofrequency ablation, and laser ablation (recently received FDA approval), foam sclerotherapy, and nonthermal ablation. The closure rates for thermal methods are 71% to 86% and lower than for truncal veins. Nonthermal techniques are promising tools in the treatment of advanced venous disease/ulcers and may offer some advantages over thermal techniques.

Foot vein sclerotherapy

Aleksandra Jaworucka-Kaszorowska (Poland)

Little attention has been devoted to the veins of the foot, which are susceptible to vertical pathologies, including corona phlebectatica, varicose veins, venous ulcers, and deep vein thrombosis. Corona phlebectatica appears due to consequences of the venous stasis of the foot due to venous hypertension and is the best predictor of subsequent occurrence of skin changes. Corona phlebectatica is associated with increasing numbers of incompetent venous segments and a higher rate of venous reflux, preferentially in the saphenous vein and perforator territory. Foot perforating veins constitute the anatomical ground for formation of the corona phlebectatica. Foot varicose veins despite the strongest hydrostatic pressure, usually appear late in the progression of the disease. Foot vein dilatations almost exclusively involve the superficial network (unprotected by the superficial fascia) and spare the saphenous-type veins. Foot venous ulcers are often the result of multiple refluxing foot veins. Nearly 9% of foot ulcers have a venous origin. For diagnosis, an ultrasound examination of the foot segment of the great saphenous vein, small saphenous vein, anterior arch veins extending over the foot dorsum and the superficial venous arch. Foot varicose veins have been grossly overlooked; until recently, the treatment of foot varicose veins was avoided for fear of complications.

Foot varicose veins are a continuation of varicose veins in the leg. Isolated treatment of only the varicosities of the foot is therefore contraindicated. A total workup and systemic treatment from proximal to distal is essential for good results. Treatment of foot varicose veins using phlebectomy is safe and effective, but not without the risk of complications. The treatment of foot varicose veins by sclerotherapy contains some disagreements regarding the use of sclerotherapy to treat the foot veins. Now there is not enough data concerning complications after foot varicose vein sclerotherapy and the incidence of complications is largely derived from publications on sclerotherapy of lower limb varicose veins. Aleksandra Jaworucka-Kaszorowska presented here experience with 682 patients: 483 patients with corona phlebectatica, 180 with foot varicose veins, and 39 with foot ulcers. Hybrid procedures (laser+ultrasound-guided foam sclerotherapy) were performed in 279 cases and isolate ultrasound-guided foam sclerotherapy in 403 cases. A total of 592 (86.8%) patients had an additional sclerotherapy session for foot veins. In case of 146 (21.4%) patients, hyperpigmentation was observed, which disappeared in 74% of cases in 6 months. Foot edema occurred in 26 (3.8%) cases, deep vein thrombosis in 1 case, skin necrosis in 19 (2.8%) patients. A total of 96% of patients were satisfied with the treatment results. The results showed that sclerotherapy is a safe and effective method for treating foot veins.

XVI. Venous leg ulcer forum

Venous leg ulcer treatment – do we really have consensus? Summary of the existing guidelines

Giovanni Mosti (Italy)

Giovanni Mosti started his talk by citing the Evidence-based clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum, an intersocietal document endorsed by the American College of Phlebology and the Union Internationale de Phlébologie. He illustrated all the steps related to the management of venous leg ulcers. Ulcer cleansing is mandatory at each dressing change with a neutral, nonirritating, nontoxic solution. The debridement is mandatory in the initial inflammatory or infected stage. Ulcer dressings may be helpful even though they have not been proven to increase the healing rate of small ulcers. Antiseptics and systemic antibiotics have to be used only in infected ulcers. The periwound area should be maintained clean and hydrated. Compression therapy exerting strong pressure is mandatory. Bones and tendon prominences have to be protected. Compression pressure should be reduced when an arterial involvement coexists and is recommended providing that ankle brachial index is >0.5 and perfusion pressure is >60 mm Hg. In addition, many guidelines addressed the issue of surgery in this context, recommending venous ablation in conjunction with compression to increase the rate of ulcer healing (grade 1A/1B to 2C depending on the guidelines and on the procedure). Concerning the usefulness of venoactive drugs, Giovanni Mosti stated that there is no consensus and evidence that is more consistent is needed (level of evidence usually 2B or 2C; 1B for micronized purified flavonoid fraction in the American Venous Forum and the Latino-American guidelines). Likewise, skin grafting is not a primary procedure and there is not a consensus. According to his personal experience, he suggested performing skin grafting in refractory ulcers when other therapeutical procedures failed after 6 weeks.

Global management of the venous leg ulcer in the pre EVRA era

Sarah Onida (UK)

Sarah Onida discussed the results of a survey aimed at determining the management of leg ulcers worldwide prior to the release of the early venous reflux ablation results. A 26-question format was circulated by various venous and vascular societies worldwide and approximately 15 000 vascular surgeons, phlebologists, and general surgeons were involved. Approximately 800 clinicians, mostly vascular surgeons from Europe and North America, responded to the survey. Among clinicians, 60% performed or arranged an ankle brachial index on the first visit, 84% performed a venous duplex ultrasonography in patients presenting with a leg ulcer, 53% prescribed compression bandaging, and 35% prescribed compression stockings. Almost 80% of the clinicians were confident that treatment of superficial venous reflux benefits ulcer healing and recurrence. Regarding the timing of the intervention, only 60% believed that it should be done prior to ulcer healing. In answering the question “would you change your practice if early venous reflux ablation has positive/negative results?” great uncertainty and divergence in opinions were expressed. In summary, the survey showed a diversity of referral and treatment pathways internationally. Sarah Onida concluded emphasizing that there is a clear need

to develop robust, clear pathways for patients with leg ulcerations, which can be informed by the early venous reflux ablation trial results.

No ulcer treatment without hemodynamic analysis!

Johann Chrisof Ragg (Germany)

According to the Society for Vascular Surgery/American Venous Forum guidelines, a venous ulcer is defined as an “open skin lesion of the leg or foot that occurs in an area affected by venous hypertension.” The elimination of reflux (by an endovenous approach or surgery) is clearly recommended by the guidelines. Therefore, the analysis of venous hemodynamics and vein morphology from heart to foot, the comprehension of the individual history of insufficiency and the determination of reflux considered relevant for the ulcer are crucial aspects in the management of these patients. Indeed, major causes of venous hypertension should be eliminated. Changes in the ulcer area should be checked every 2 to 3 months. If the results seem unsatisfactory, additional reflux elimination should be considered and all supportive modalities (activation, compression, etc) should be applied. Therefore, in the opinion of Johann C. Ragg, the majority of hemodynamic disorders (reflux, hypertension) is treatable successfully. An exact analysis of hemodynamics is crucial for an appropriate treatment strategy and for the improvement in flow. The nearer a venous target is located to an ulcer or to diseased skin, the clearer the decision for endovenous methods should be. Endovenous techniques, in particular those with no heat and no need for tumescence, should be preferred.

Which compression in venous leg ulcer patients? – practical advice

Giovanni Mosti (Italy)

The most effective compression modality for venous leg ulcer patients is also the most efficient in reducing venous hypertension. Therefore, inelastic compression (bandages, Adjustable Velcro® compression device (AVCD) exerting strong/very strong pressure and high-pressure peaks), counteracting ambulatory venous hypertension, is the most effective modality. Indeed, inelastic material, exerting higher working pressure and working peaks to close the vein, is significantly more effective in decreasing venous reflux, in increasing venous pumping function, and in reducing ambulatory venous hypertension when compared with elastic material. Inelastic bandages are very effective, despite significant pressure loss, but they need expert personnel to apply them. AVCD (CircAid) can be safely used in ulcer treatment. Compared with inelastic bandages, it seems to increase the healing rate and shorten the healing time, ensuring cost savings with negligible side effects. AVCD (CircAid) does not require expert personnel for its application. After a brief introduction, it may be self-applied and readjusted to maintain a consistent hemodynamic effectiveness (maintenance of pressure range). Elastic kit exerting a pressure >40 mm Hg could be effective in small and recent-onset ulcers. Compression therapy can be useful even in mixed ulcers when properly applied using a reduced pressure (<40 mm Hg in patients with a perfusion pressure >60 mm Hg and protecting bone and tendon prominences). Indeed, in patients with arterial impairment, compression may increase the arterial inflow due to the reduction in the arterovenous pressure gradient, the myogenic relaxation of the arterial wall and the release of vasoactive substances.

Venous leg ulcer treatment – does pharmacotherapy matter?

Arkadiusz Jawien (Poland)

The 2019 evidence-based guidelines from the Society for Vascular Surgery/American Venous Forum suggest using pentoxifylline or micronized purified flavonoid fraction in combination with compression to accelerate healing of venous ulcers (grade 2B). There are few pharmacologic agents available for the treatment of C₅-C₆ disease, ie, for those with healed or active venous ulcers.

Pentoxifylline is available in the United States and it is an effective adjunct to compression bandages for treating venous ulcers in a Cochrane review of 12 randomized trials involving 864 participants. Pentoxifylline plus compression was more effective than placebo plus compression (risk ratio [RR], 1.56; 95% CI, 1.14-2.13) in terms of complete ulcer healing or a significant improvement. Pentoxifylline in the absence of compression appeared to be more effective than placebo or no treatment (RR, 2.25; 95% CI, 1.49-3.39). In a randomized controlled trial with a 24-week follow-up with blinded allocation to pentoxifylline (1200 mg) or placebo, pentoxifylline increased the healing proportion compared with placebo to the same extent as shown in recent systematic reviews, although this finding was only statistically significant when a secondary adjusted analysis was conducted (RR for healing, 1.4; 95% CI, 1.0-2.0). Randomized trials have similarly shown micronized purified flavonoid fraction, which is not available in the United States, to increase the odds of ulcer healing by 32% in comparison with compression and local wound care alone.

A meta-analysis of 5 randomized prospective studies using Daflon 500 mg as an adjunct to conventional treatment (723 patients with venous ulcers) showed that, at 6 months, the chance of ulcer healing was 32% better in patients treated with adjunctive Daflon 500 mg than in those managed by conventional therapy alone (relative risk reduction [RRR], 32%; 95% CI, 3-70). This translates to a number needed to treat of 7.3 (95% CI, 4.6-17.1). This difference was present from month 2 (RRR, 44%; 95% CI, 7-94) and was associated with a shorter time to healing (16 weeks vs 21 weeks; $P=0.0034$). The benefit of Daflon 500 mg was found in the subgroup of ulcers between 5 and 10 cm² in area (RRR, 40%; 95% CI, 6-87), as well as in patients with ulcers of 6 to 12 months' duration (RRR, 44%; 95% CI, 6-97).

The results of a meta-analysis of four studies involving 482 patients and testing the effect of oral sulodexide plus compression vs placebo or compression alone at 2 months showed that sulodexide may have beneficial effects in ulcer healing in addition to conventional therapy vs placebo (RR, 1.70; 95% CI, 1.33-2.17; absolute risk difference, 0.19; 95% CI, 0.11-0.27).

According to the clinical practice guidelines of the European Society of Vascular Surgery, sulodexide and micronized purified flavonoid fraction should be considered as an adjuvant to compression therapy in patients with venous ulcers (grade IIa; level of evidence A). The latest guidelines on the management of chronic venous disorders developed under the auspices of the European Venous Forum, the International Union of Angiology, the Cardiovascular Disease Educational and Research Trust (UK), and the Union Internationale de Phlébologie suggest pentoxifylline, micronized purified flavonoid fraction, and sulodexide as adjuvants for the healing of venous ulcers as medication with a high level of evidence (grade A). Therefore, the speaker concluded his talk stating

that pharmacotherapy matters because it is able to accelerate the healing of venous ulcers. Until recently, there has been a substantial amount of scientific evidence for pharmacotherapy, but further studies are desirable.

EVRA trial – early invasive reflux ablation brings benefits to the VLU leg ulcer patients

Alun Davies (UK)

The early invasive reflux ablation (EVRA) study provides the first level of evidence for the benefit of early endovenous treatment of superficial venous reflux in venous leg ulcers. Prompt endovenous ablation (within 2 weeks of randomization), in conjunction with compression therapy, accelerated ulcer healing compared with deferred interventions (after ulcer healing or at 6 months). More patients had healed ulcers in the early intervention group, and patients experienced additional ulcer-free time over the 1-year follow-up. Furthermore, early intervention resulted in significant improvements in disease-specific and general health-related quality of life, as well as body pain. Results from EVRA also found that early intervention was highly likely to be cost-effective at UK decision-making thresholds. EVRA provides evidence that early venous reflux ablation benefits leg ulcer patients in terms of ulcer healing and quality of life, and it is cost-effective. The challenge is to implement these results globally, as current pathways of care for patients with leg ulcers, in general, do not include a provision for early assessment and treatment. The current UK guidelines (CG 168) recommend that patients with a venous leg ulcer (defined as a break in the skin below the knee that does not heal within 2 weeks) are referred to a vascular specialist for assessment. However, uptake of the guidelines has been slow and there is limited awareness in the communities where the majority of patients are treated. Although there has been an increase in patients referred with leg ulceration since the release of the guidelines, many are not referred until after they have had an ulcer for many months. Leg ulcer evaluation and treatment pathways are poorly developed across much of the NHS and around the world. Urgent action is required to improve care pathways between primary and secondary care and to ensure patients with a venous leg ulcer receive early diagnosis, referral, and treatment.

The role of the reflux sourcing and ablation in the venous leg ulcer treatment

Alfred Obermayer (Austria)

Venous ulcers are mostly due to local venous hypertension that affects the microcirculation of the skin. Alfred Obermayer showed the main results of a study involving 169 patients with venous leg ulcers. Venous function was assessed with duplex ultrasound. Furthermore, a "sourcing" technique was performed with duplex ultrasound investigation of the ulcer bed and the venous system under manual compression and release of the ulcer. The principle of "sourcing" is to follow venous reflux from the ulcer area to its proximal origin. A total of 20% of patients with ulcers showed no clinically visible varicose veins (CEAP C₂). Reflux in the small saphenous vein occurred in 11% of the medially located ulcers (crossover type) and 14% of patients presenting with lateral ulcers showed great saphenous vein incompetence (crossover type). Identifying the specific route responsible for venous reflux can be crucial for planning a rational treatment of venous reflux ulcers (Obermayer A, Garzon K. *J Vasc Surg.* 2010;52(5):1255-1261). Indeed, a crossover pattern may lead to inaccurate treatment and early recurrence. Finally, Obermayer highlighted that the technique of lateral fasciectomy sparing the superficial peroneal nerve with mesh graft

coverage could be a good treatment of nonhealing lateral leg ulcers of various vascular origin affecting the fascia (Obermayer A et al. *Eur J Vasc Endovasc Surg.* 2016;52(2):225-232.)

Aggressive local venous leg ulcer treatment – does it help?

Dominik Heim (Switzerland)

Venous ulcers are associated with impaired quality of life, reduced mobility, pain, stress, and loss of dignity. The Society for Vascular Surgery/American Venous Forum guidelines do not advise using split-thickness skin grafting for the primary therapy of venous leg ulcers. Local surgical techniques, including fasciectomy, Reverdin pinch grafting, or shaving, are generally indicated in cases of nonhealing ulcers after 3 months of conservative treatment by the German Guidelines of Phlebology. Although few studies assessing the outcomes and the recurrence of ulcers treated with these techniques have been conducted, Heim expressed his confidence in the usefulness of aggressive local surgery in healing recalcitrant ulcers.

Update of the negative wound pressure therapy for the venous leg ulcer

Maciej Zieliński (Poland)

Despite the fact that venous leg ulcers fulfill the criteria of complicated chronic wounds, the majority of international organizations of phlebologists do not recommend negative pressure wound therapy (NPWT) as standard therapy for leg ulcers resulting from venous insufficiency. Nevertheless, there are some reports in the literature reporting a positive impact of topical negative pressure use on the effectiveness of the venous leg ulcer closure, which were summarized in the recommendations issued by international expert panel on NPWT, stating that if compression therapy is not efficacious, NPWT should be used to prepare the wound for surgical closure or to progress to wound closure by secondary intention. Maciej Zieliński presented the status of the application of NPWT and its potential perspective for an efficacy improvement in the different aspects of local treatment of venous leg ulcers.

In the discussion, the influence of hypobaric therapy on wound bed preparation by means of conducting a cleansing mechanism should also be mentioned. The explanation can be found in the active drainage phenomenon that decreases bacterial load and thus helps fight local infection. On the other hand, subatmospheric suction has the potential to generate a proper fluid balance by effectively removing exudate from the venous ulcer and its close vicinity, which also positively affects inflammatory conditions of the surrounding tissue and the degree of edema. The unique structure of foam occlusive dressing facilitates a moist environment, simultaneously providing proper oxygen diffusion through the drape membrane. Additionally, there is strong evidence of a beneficial effect of NPWT on the proliferation phase of chronic wound healing. Hypobaric conditions create local hyperemia and thus improve microcirculation and stimulate neoangiogenesis. It also promotes acceleration of fibroblast mitosis, resulting in faster granulation tissue formation. Lastly, NPWT was proven to have a beneficial effect on skin grafting procedures in different wound types, including venous leg ulcers. Further studies intended to define the real value of NPWT in the treatment of venous leg ulcers have to be encouraged.

Combined and simultaneous reflux ablation and local surgical treatment – lessons learned

Alfred Obermayer (Austria)

Alfred Obermayer reported his experience in the surgical treatment of worst-case scenarios of recalcitrant chronic leg ulcers. In his center, patients presenting with leg swelling underwent “lenient active bed rest” in the hospital to reduce edema before surgery. They performed special exercises in bed at least three times daily to support venous backflow and to reduce leg edema. Many patients underwent ulcer surgery in combination with reflux surgery or thermal ablation in the same session. This “single-shot surgery” appeared a good standard for enabling and accelerating ulcer healing, although it has not been established internationally (Obermayer A et al. *Eur J Vasc Endovasc Surg.* 2016;52(2):225-232).

Venous leg ulcer treatment based on the chronic venous disease pathophysiology – lessons learned

Angelo Scuderi (Brazil)

The Emeritus President of the International Union of Phlebology stated that there are so many ways to treat ulcers that probably no option is good enough. In this regard, we have little scientific evidence, few valid randomized works, and only a group of Good Practice Guidelines, meaning that there is no consensus. He emphasized that venous ulcers or varicose ulcers are wounds following the physiological principles of healing. Therefore, in treating an ulcer, we should aim to obtain physiological rest, ensuring good circulation and venous return; chemical rest, treating the wounds gently without put anything inside them; and mechanical rest with compression therapy or resting in the Tremdelemburg position.

1 year outcomes of VenaSeal glue ablation in diabetics with venous leg ulcer

Sriram Narayanan (Singapore)

Sriram Narayanan presented the results of a study involving 36 diabetic patients with venous ulcers who were treated in his center using a standardized protocol adapted to diabetic patients. VenaSeal glue ablation of venous leg ulcers in diabetic patients seems safe as long as a strict infection control regime is followed. In most cases, it allows for ulcer management without the need for compression therapy. The incidence of phlebitis-like abnormal reactions seems lower than in nondiabetic patients. After a 1-year follow-up, outcomes in diabetic patients were comparable with those obtained in nondiabetic patients or in patients treated with endovenous ablation with additional compression.

Topical sevoflurane as a new treatment modality for painful venous leg ulcers

Manuel Gerónimo-Pardo (Spain)

Sevoflurane was very effective in controlling rest pain in 134 patients, even when a neuropathic component was present. Pain reduction was rapid, intense, and long lasting. Remarkably, sevoflurane was also effective at controlling pain that had been refractory to other conventional systemic analgesic treatments. Sevoflurane was slightly less effective at controlling pain during debridement. Nearly all treated ulcers showed a reduction in both size and depth, and even complete ulcer healing was achieved in some cases. Concerning safety, mild pruritus in the surrounding skin has been the most frequent adverse effect reported so far. Of interest, no patient has experienced any systemic adverse effect.

XVII. Acute deep vein obstruction invasive treatment

Mechanical thrombectomy in acute DVT - lessons learned

Michael Lichtenberg

In the ATTRACT study, after 24 months, patients receiving pharmacomechanical catheter-directed thrombolysis showed an improved result of treatment vs the patients not receiving pharmacomechanical catheter-directed thrombolysis (Vilalta score, 3.95 vs 5.54 [$P=0.03$]; venous clinical severity score, 1.98 vs 2.8 [$P=0.018$]; VEINES score, 28.63 vs 23.02 [$P=0.029$]). Frequency of bleeding complications in the PEARL registry was 4.5% (minor/major), in the CAVENT study 22% (minor/major), and in the Venous registry 16% minor and 11% major. A meta-analysis (review included 19 articles) of catheter-directed thrombolysis or ultrasound catheter-directed thrombolysis and pharmacomechanical thrombectomy with AngioJet, Pneumbra Indigo, or Aspirex devices showed a nonsignificant differences between lysis grade II/III, rates of recurrent deep vein thrombosis, overall postthrombotic rate, moderate/severe postthrombotic syndrome, reflux rate, and adjunctive angioplasty and stenting. Only in cases of frequent major bleeding complications was pharmacomechanical thrombectomy significantly favored. Therefore, pharmacomechanical thrombectomy and catheter-directed thrombolysis are similar in efficacy, but, with pharmacomechanical thrombectomy, the trend moves toward lower overall postthrombotic syndrome and reflux.

The issue of the venous stenting in acute DVT patients

Haraldur Bjarnason (US)

In a registry of lower limb deep vein thrombosis treated with catheter-directed thrombolysis at 63 centers, 99 of 303 treated limbs (32.6%) had stents placed. There were no data about postthrombotic syndrome in the long-term outcomes. In the CAVENT trial (2012), ATTRACT trial (2017) and Avgerinos study, the frequency of stenting and postthrombotic syndrome was 18%/43% (5 years), 28%/47% (2 years), and 100%/14.4% (5 years) accordingly. The mid-term results of CAVENT showed that, in the stenting group ($n=40$), 32 (80%) patients were free of postthrombotic syndrome, but, in the no stenting group ($n=33$), there were only 13 (39%) with postthrombotic syndrome. In conclusion, following successful thrombus removal from the iliac veins, any significant remaining obstruction should be treated with stents.

Who should we treat by local thrombolysis/thrombus removal after ATTRACT trial result publication?

Antonious Gasparis (US)

The results of the ATTRACT trial were published in 2017 and are widely known. The ATTRACT trial previously reported that pharmacomechanical catheter-directed thrombolysis (PCDT) did not prevent postthrombotic syndrome in patients with acute proximal deep vein thrombosis. However, catheter-based strategies of thrombus removal are focused

on patients with iliofemoral deep vein thrombosis (not femoropopliteal); therefore, the results from patients with iliofemoral deep vein thrombosis will be the most meaningful in guiding patient care. In the subanalysis, the effect of PCDT in ATTRACT patients with iliofemoral deep vein thrombosis, a subgroup of 391 patients with acute deep vein thrombosis involving the iliac or common femoral veins were randomized to PCDT with anticoagulation vs anticoagulation alone (no PCDT). The patients were observed for 24 months to compare short-term and long-term outcomes. Between 6 and 24 months, there was no difference in the occurrence of postthrombotic syndrome (Villalta scale ≥ 5 or ulcer, 49% PCDT vs 51% no PCDT; $P=0.59$). PCDT led to a reduction in postthrombotic syndrome severity as shown by lower mean Villalta and venous clinical severity scores ($P<0.01$ for comparisons at 6, 12, 18, and 24 months), and fewer patients with moderate-or-severe postthrombotic syndrome (Villalta scale ≥ 10 or ulcer, 18% vs 28%; $P=0.021$) or severe postthrombotic syndrome (Villalta scale ≥ 15 or ulcer, 8.7% vs 15%; $P=0.048$ and venous clinical severity score ≥ 8 , 6.6% vs 14%; $P=0.013$). From baseline, PCDT led to a greater reduction in leg pain and swelling ($P<0.01$ for comparisons at 10 and 30 days) and a greater improvement in venous disease-specific quality of life (venous insufficiency epidemiological and economic study quality of life unit difference 5.6 through 24 months; $P=0.029$), but no difference in generic quality of life ($P>0.2$ for comparisons of SF-36 mental and physical component summary scores through 24 months). In patients having PCDT vs no PCDT, major bleeding within 10 days occurred in 1.5% vs 0.5% ($P=0.32$), and recurrent venous thromboembolism over 24 months was observed in 13% vs 9.2% ($P=0.21$). In case of patients with acute iliofemoral deep vein thrombosis, PCDT did not influence the occurrence of postthrombotic syndrome or recurrent venous thromboembolism. However, PCDT significantly reduced early leg symptoms and, over 24 months, reduced postthrombotic syndrome severity scores, reduced the proportion of patients who developed moderate-or-severe postthrombotic syndrome, and resulted in a greater improvement in venous disease-specific quality of life. Consequently, we should treat patients with iliofemoral deep vein thrombosis with moderate or severe symptoms with local thrombolysis or thrombus removal and understand that patients with femoropopliteal deep vein thrombosis will not have benefit from PCDT.

XVIII. Chronic deep venous obstruction treatment

Chronic venous obstruction endovascular treatment - lesson learned

Michael Lichtenberg (Germany)

Over the last decade, the number of endovascular interventions has increased significantly, especially as concerns venous stenting, percutaneous venoplasty, and venous thrombus removal. In Germany, approximately two-thirds of such procedures are conducted in specialized venous centers. Such a center should complete more than 100 intravascular ultrasound scans per year, have a hybrid operation room, and have vascular surgeon interventionists. The price of a case with installing one stent is worth 3193 € or 4122 € if two or more stents are installed. In Germany, there are 6 high-volume specialized venous centers. Standards were created for recanalization of chronic venous outflow obstruction. Venous stenting is a safe and efficacious procedure with technical success rates between 94% and 96%. It is very important to consider the fact that it is essential to have different venous stents for different locations. For the inferior vena cava, stents should have a high radial force, for the iliac vein, the stent should have radial force plus flexibility, and for the common femoral vein, the stent should have flexibility, kink resistance, a low fracture rate, but there is no perfect venous stent for the entire venous system. As the last studies showed, stent patency is dependent on the area of the stent lumen, the flow rate, and the pressure gradient. An important factor affecting the success of stenting is the availability of intravascular ultrasound. Advantages of intravascular ultrasound include the possibility of obtaining dynamic measurements of the area and the degree of stenosis, analyzing morphological changes in the vein, dynamically evaluating compression, such as in the presence of the May-Thurner syndrome, not needing contrast, exactly determining the diameter and length of the required vein stent, exactly placing the vein stent, and analyzing the stent after implantation.

Do we need the dedicated venous stents for chronic venous obstruction treatment? Update of the current dedicated venous stents trials

Steve Black (UK)

A meta-analysis conducted in 2016, showed that the patency rates of venous stenting were high (79% to 98%). Now there are 8 different systems: Ziver Vena (Cook), Vici (BSCI), Venovo (BD), Wallstent (BSCI), sinus-Venous (Optimed), sinus-Obliquus (Optimed), Abre (Medtronic), and Blueflow (Plus Medica). The FDA has only approved the Wallstent, Venonvo, and Vici. Today, all explorations in the area of venous stenting are very different in their design and cannot be compared straight away. The VIRTUS exploration data used the VICI venous stent in 170 patients, showing a primary patency of 84%, with a safety end point of 98.8%. The VERNACULAR study used the Venovo venous stent in 170 patients, showing a primary patency of 88.3%, with a safety end point of 93.5%.

Stents can be made as a closed cell, an open cell, a hybrid, or braided and they can be very different in terms of crush resistance, flexibility, radial strength, deployment,

scaffolding, diameter, and length. In 2018, a randomized double-blind study compared medical treatment vs iliac vein stenting in chronic venous disease. At the 6-months follow-up, the mean visual analog scale pain score declined from a median of 8 to 2.5 in patients receiving stents and from 8 to 7 in patients receiving only medical treatment ($P<0.001$). The venous clinical severity score decreased from a median of 18.5 to 11 after stenting and from 15 to 14 with medical treatment ($P<0.001$). The 36-item short-form health survey (0-100) improved from a total median score of 53.9 to 85.0 with stenting and 48.3 to 59.8 after medical treatment ($P<0.001$). Stenting success depends on many factors, such as stent choice, placement errors, technical mistakes, level of inflow, and clotting system. Currently, more randomized control trials are needed for acute deep vein thrombosis, for chronic venous obstruction comparing different stents; in addition, more data is needed about new stents and the systems for stenting, and we need long-term patient outcome data to support their use.

Iliac vein confluence stenting and the contralateral iliac vein coverage consequences

Haraldur Bjarnason (US)

The frequency of contralateral deep vein thrombosis after iliac vein stenting is around 2.6%. The reason for such thromboses is that if, during stenting of the iliac confluence, the stent is installed so that it protrudes into the inferior vena cava, it then overrides the contralateral iliac vein, and, in some cases, the pseudointima is obstructed in the contralateral iliac vein. In a study conducted in 2018, the reasons for 111 rethromboses (10 of which were contralateral) after iliac vein stenting were studied, showing that if the stent is confined in the inferior vena cava, then the frequency of noncontralateral deep vein thrombosis increases. At the same time, if the stent is extended into the inferior vena cava, then the frequency of ipsilateral deep vein thrombosis is much lower, but the frequency of contralateral deep vein thrombosis increases. Therefore, placing overriding stents should be avoided, but current and old stent technology is imperfect; there is no way to avoid these complications and we look forward to future advancement of venous stenting technologies.

Interpretation of venous pathology with IVUS – VIDIO trial results and clinical practice

Antonios Gasparis (US)

The results from the VIDIO trial (Venography versus Intravascular ultrasound for Diagnosing and treating Iliofemoral vein Obstruction) were presented. The study enrolled 100 patients with venous disease of clinical class C_4 to C_6 and suspected iliofemoral vein obstruction; the study was conducted over 14 sites. During the study, the investigators imaged the inferior vena cava, common iliac vein, external iliac vein, and common femoral vein. Venograms were measured for vein diameter; intravascular ultrasound was used to provide diameter and area measurements. Multiplanar venograms included three views: anteroposterior and 30-degree right and left anterior oblique views. A 50% diameter stenosis by venography and a 50% cross-sectional area reduction by intravascular ultrasound were considered significant. Venography identified stenotic lesions in 51 of 100 patients, whereas intravascular ultrasound identified lesions in 81 of 100 patients. Compared with multiplanar venography, intravascular ultrasound was more sensitive for identifying significant venous obstruction, more accurate for determining the degree of stenosis or diameter, and the best guide for stent intervention. Compared with intravascular

ultrasound, the diameter reduction was, on average, 11% lower for venography ($P < 0.001$). The intraclass correlation coefficient was 0.505 for vein diameter stenosis calculated with the two methods. Intravascular ultrasound identified significant lesions not detected with three-view venography in 26.3% of patients. Investigators revised the treatment plan in 57 of 100 cases after intravascular ultrasound, most often because of failure of venography to detect a significant lesion (41/57 [72%]). Intravascular ultrasound led to an increased number of stents in 13 of 57 subjects (23%) and the avoidance of an endovascular procedure in 3 of 57 subjects (5%). Overall, intravascular ultrasound changed the treatment plan in 57 patients; 54 patients had stents placed based on intravascular ultrasound detection of significant iliofemoral vein obstructive lesions not appreciated with venography, whereas 3 patients with significant lesions on venography had no stent placed based on intravascular ultrasound.

Stenting below the inguinal ligament

Michael Lichtenberg (Germany)

Michael Lichtenberg introduced a new system for stenting below the inguinal fold. When comparing patency of stents installed above the ligament with stents installed across the ligament, the rate of primary patency was 77% above the ligament (vs 50% across the ligament), primary-assisted patency was 100% above the ligament (vs 82% across the ligament), and secondary patency was 100% above the ligament (82% across the ligament), showing the advantage of stenting above the ligament. This result is due to a high frequency of stent fracture and stent compression at the ligament area. For the Vici venous stent, the rate of compression/fracture was 8% at 2 years. The common femoral vein places a lot of force on venous stents. Laser-cut nitinol stents seem to have shortcomings below the ligament (fracture, compression). If restenosis occurs, a second stent implantation becomes likely. Avoiding stent fractures means we need to think of different stent designs. A woven nitinol stent design could be an option. To solve these problems, the blueflow Venous Stent was introduced. This stent is a hand-braided meshed stent made of two 0.22 mm electropolished nitinol wires. Using a raiding technique with two wires enabled a closed-loop design. Each wire loops back when it reaches the stent tip, thus creating 14 radial-force stable loops. Two wires are welded together at two points in the center of the stent. The welds are only 5-mm long and placed inside of the mesh to avoid any vessel contact.

The intermediate results of the postmarket clinical follow-up, retrospective and prospective, observational study on the patency rates and clinical outcomes for iliofemoral residual thrombosis, obstruction, or stenosis after implantation blueflow Venous Stent implantation were presented. . Observations were taken at 24 to 72 hours, after 3, 6, and 12 months, and then yearly for up to 5 years. The primary outcome for 20 patients after 12 months was the same: primary patency after 12 months was 19 (95.2%), the primary sustained clinical success rate was 20 (100%), and there were no stent fractures.

Tips and tricks for getting the best IVUS, stent apposition and stent sizing

Stephen Black (UK)

The technical aspects of using intravascular ultrasound were presented. For the first step, the degree of stenosis should be measured (area stenosis [%] and diameter stenosis [%]),

and then intravascular ultrasound should be used to help decide the landing zones. To perform this function better, it is necessary to use the cm marking on the intravascular ultrasound catheter to indicate the extent of stenting and use the intravascular ultrasound head for exact positioning. Next, intravascular ultrasound is used to determine the stent size; it is essential to stent from the centrum to the periphery and to start >5 mm central to the lesion. Another tip is to use intravascular ultrasound to identify the peripheral landing zone. The distal landing zone has priority over extent of overlap; for example, where a 9-cm stent will end if placed with a 5-cm overlap. In conclusion, intravascular ultrasound adds significant diagnostic value, reduces radiation, reduces contrast, is repeatable, improves sensitivity of diagnostic testing, and is an essential part of a complete venous service.

When and how to perform endophlebectomy?

Jan Keşik (Poland)

Stenting distal to the common femoral vein has a higher risk of early failure due to low flow. A hybrid procedure (endophlebectomy+iliocaval stenting±arteriovenous fistulae [AVF]) improves flow into the stent from all major side branches and creates a single lumen-landing zone for the stent. The indication for a hybrid procedure appears if postthrombotic vein-wall fibrosis has a place to be and synechiae are present in at least the common femoral vein, deep femoral vein, and femoral vein. An ipsilateral ultrasound-guided puncture of the mid-thigh femoral vein is performed first, sometimes with the contralateral femoral vein or right jugular vein. After gaining access, a small-caliber (5-Fr) sheath is positioned, and, following a multiplanar venography intravascular ultrasound investigation, there is the passage of the wire. Then, the surgical stage of the procedure (exposure of the femoral veins, endophlebectomy, and creation of an AVF with a side branch of a great saphenous vein) is performed. Depending on vessel diameter, the venotomy is closed primarily or with a venous patch. The last step is the stenting. For postoperative care, intermittent pneumatic compression is started after operation and continued during the hospital stay, low-molecular-weight heparin is started directly after the intervention, and warfarin is started the next day, aiming for an international normalized ratio of 3 to 4. Anticoagulation is continued for at least 6 months. Duplex ultrasound is performed 2 to 3 weeks, 6 to 8 weeks, and 5 to 6 months after surgery. If no stenosis is found in duplex ultrasound, the second hospital admission to close the AVF is performed 2 to 6 months after surgery. If a stenosis in the endophlebectomy segment is identified, a stent extension is performed before the AVF closing. Jan Keşik presented results from de Wolf et al (*Br J Surg.* 2017;104:718-725), showing that, in 70 patients who underwent a hybrid procedure, 16 (23%) had a reocclusion, 32 (46%) had stenosis distal to stent, 2 (3%) had residual stent compression, and 0 had a stent fracture after 1 year. In a comparison of the initial techniques (n=17) with the present contemporary techniques (n=14), a significant improvement was observed for acute thrombosis (0 vs 5 [27%]) and for reintervention for common femoral vein stenosis (0 vs 2 [12%]).

How to deal with the venous stent restenosis?

Antonios Gasparis (US)

Venous in-stent restenosis (ISR) is not the same pathological entity as arterial ISR. The basis of venous ISR is thrombus lining of the stent, which is transformed through inflammation

into collagen and ISR. There are two different “modes” of venous stent ISR: (i) “soft” ISR lesion (fresh thrombus); and (ii) “hard” ISR lesion (organized thrombus). Soft ISR responds to percutaneous transluminal angioplasty, and, to treat hard ISR, it is possible to use high-pressure percutaneous transluminal angioplasty, restenting, and a debulking procedure. Postthrombotic lesions have higher ISR rates over nonthrombotic iliac vein lesions due to long fibrotic lesions and longer stents, and stent extension into the common femoral vein. In addition, postthrombotic patients are more likely to be hypercoagulable and they are more likely to have compromised inflow. The likelihood of thrombus layering is increased due to untreated disease (poor inflow and outflow), undersizing of the stent, and a poor anticoagulation regimen. Preventing ISR is easier than treatment, and for this, it is desirable to use intravascular ultrasound for all steps of stenting, use large balloons pre-dilated to at least a nominal diameter of the stent, use appropriate stent sizes (inferior vena cava [16-18 mm], external iliac vein [12-14 mm], and common femoral vein [10-12 mm]). It is very important to use an adequate anticoagulation (low-molecular-weight heparin twice daily provides predictable treatment, duration of anticoagulation of at least 3 months). Stent surveillance with duplex ultrasound must be done after 1 to 3 months and every 6 and 24 months. If ISR suspected based on symptoms, perform a venogram, look for reasons for the failure, and treat early lesions. If ISR appears, then use a laser atherectomy catheter to debulk the stent-associated organized material to improve the outcome.

What if you have chronic infrainguinal deep vein disease?

Stephen Elias (US)

The prevalence of femoropopliteal deep vein thrombosis in the population is high, with around 950 000 cases of venous thromboembolism per year in the US and 55% of which are femoropopliteal deep vein thrombosis and 30% to 40% of which are due to postthrombotic syndrome (which is around 150 000 to 200 000 annual interventions). Potential options for the management of femoropopliteal obstruction are venous bypass, venous stenting (iliac, nonfemoropopliteal), venous angioplasty, and open endovenectomy. In the ACCESS PTS trial, where balloon dilatation of the segments with occlusive deep vein thrombosis was used, and infusion for ≥ 12 hours with acoustic pulse thrombolysis using the EKOS system showed an improvement in the signs of postthrombotic syndrome in 35% of patients and a reduction in the Vilalta score in 67% of patients.

A retrospective study investigated the use of single-session femoropopliteal venoplasty (SSFPV) with local infusion of tissue plasminogen activator (tPA) using a novel percutaneous transluminal angioplasty balloon with an injection port. All procedures were performed in an office-based laboratory. SSFPV was attempted in 19 patients; 2 patients were classified as C_{4b} and 17 patients were classified as C₆. The average tPA dose was 5 mg, and balloon diameters ranged from 4 to 10 mm. There were no periprocedural complications. Ulcer healing occurred in 11 of 17 patients (65%). Treatment of femoropopliteal obstruction with venoplasty and adjunctive acoustic pulse thrombolysis has been performed, requiring an intensive care unit hospital admission. SSFPV with local tPA infusion can be performed in an outpatient setting and may potentially reduce the signs and symptoms of postthrombotic syndrome. In comparison with ACCESS PTS, treatment with SSFPV takes only 1 to 2 hours and it is characterized by a lower bleeding risk and lower cost. Treatment of femoropopliteal obstruction with venoplasty and adjunctive acoustic pulse thrombolysis has been performed, requiring an intensive care unit hospital admission.

SSFPV with local tPA infusion can be performed in an outpatient setting and potentially may reduce the signs and symptoms of postthrombotic syndrome. These findings may warrant large longitudinal studies to demonstrate the effects of SSFPV.

Iliac vein stenting - is the effort justified? An analysis of published data and single centre real-world register data

Tobias Hirsch (Germany)

The indication for venous stenting in patients classified as C₃-C₆ is caused by deep venous insufficiency or venous claudication. Three groups of patients can be distinguished: (i) nonthrombotic iliac vein lesions without postthrombotic syndrome; (ii) postthrombotic syndrome with inferior vena cava, common iliac vein, and/or external iliac vein; and (iii) group 2 plus femoral vein and bifurcation. At the moment, the expediency of stenting for the nonthrombotic iliac vein lesions (group 1) is not in doubt; however, for group 2 and 3, the benefit of stenting is clear only for patients in group 2. Unfortunately, the frequency of simple iliac vein thrombosis (group 2) is very rare (2% to 7%), so invasive treatment of chronic venous occlusion is only appropriate for a small number of patients. Even for iliac vein obstruction, secondary patency rates (according to a review of 16 studies 2007-2014, 2647 limbs) were 66% to 99%, showing that invasive treatment of chronic iliac vein occlusion has a suboptimal patency rate. Iliac vein stenting can cause complications (bleeding, stent compression, stent stenosis, etc). Therefore, iliac vein stenting warrants meticulous patient selection.

Venous leg ulcer in the patient with the secondary chronic venous disease patients: ablate or stent and which one first?

Joseph Raffetto (US)

According to data from William Marston (*J Vasc Surg.* 2011;53:1303-1308), among patients classified as C₅ and C₆, 50% reported a medical history of deep vein thrombosis. Overall, 37% of imaging studies demonstrated ilio caval venous obstruction of at least 50% and 23% of patients had obstruction >80%. No limb with superficial venous reflux alone was found to have ilio caval venous obstruction >80%. According to Peter Neglén (*J Vasc Surg.* 2007;46(5):979-990), venous ulcers were healed in 58% of patients 5 years after ilio caval venous obstruction stenting. In this study, 99 limbs from 96 patients underwent percutaneous iliofemoral stenting combined with saphenous ablation; 40 limbs had an active ulcer. Seshadri Raju published results (*J Vasc Surg Venous Lymphat Disord.* 2013;1(2):165-172) on treatment of venous ulcers: 189 limbs classified as C₆ were treated (30 with laser ablation, 89 with stenting, and 69 with the both methods). The long-term results were the same for every group and were between 75% and 80% for ulcer healing after 60 months. Therefore, the recommendation was that endovenous saphenous ablation should be the initial procedure of choice if reflux is present in a large saphenous vein (>5 mm). If there is no saphenous reflux, an intravascular ultrasound examination and stenting for stenosis is the procedure of choice. If the refluxing great saphenous vein is small (<5 mm), combined great saphenous vein ablation and iliac vein stenting should be considered.

XIX. Focus on varicose vein recurrence

What do we need: better technology or better strategy? Varicose veins after saphenous ablation and surgery: disease recurrence or disease progression?

Josef Rafetto (US)

Josef Rafetto presented the study showing that nonocclusion and early reopening of the great saphenous vein after endovenous laser treatment is fluence dependent, where fluence is calculated as energy (J) per surface area. Recurrence could occur due to tactical errors, as endovenous laser ablation is not a stand-alone treatment, to technical errors resulting from inadequate tumescence, inadequate injury/energy; however, neovascularization is rarely seen. Josef Rafetto explained the pattern of recurrence: (i) recanalization (10% to 50%); (ii) disease progression from the anterior accessory saphenous vein (15% to 55%); (iii) thigh perforators (18% to 38%); and (iv) neovascularization (radiofrequency ablation [17% to 25%] >>endovenous laser ablation). Opportunities to minimize recurrences include not preparing thermal ablation as a stand-alone treatment, looking at patients vein by vein, and developing a strategy to deliver appropriate energy and educate patients.

In a review article, an update on the currently available nonthermal ablative options in the management of superficial venous disease showed a consistent closure rate >9% at 2 years. If mechanochemical ablation is performed, tactical errors include performing it as a stand-alone treatment or using it for large veins and technical errors include pullback speed and chemical features. Neovascularization was not reported. When using endovenous adhesives, a tactical error is to use glue as stand-alone treatment and technical errors are provider-dependent and related to the volume delivered. Neovascularization was not reported. The same applies for ambulant phlebectomy, which is often not a stand-alone procedure. Technical errors are specific to both patients and operators. If foam sclerotherapy is performed, tactical errors can be due to protocol and the chemical strength of the sclerosant agent. Technical errors are inadequate training and missing provider experience.

In conclusion, recurrences vary by technique (surgical stripping vs thermal). Tactical errors may be minimized by increasing the accuracy of diagnostic testing and a more comprehensive approach. Technical errors may be minimized by training and supervision by an experienced surgeon, the use of a protocol-driven approach, and concern that each patient/leg is unique.

Standard for the investigation of the saphenous terminal and preterminal valve on duplex

Erika Mendoza (Germany)

Erika Mendoza discussed the exploration of the saphenofemoral junction in the context of recurrences. To analyze the cause of recurrences, we have to be sure about the findings prior to treatment. Recurrences depend more on the source of reflux prior to treatment, than on the technique we apply. The saphenofemoral junction consists of a common femoral vein with a valve, the great saphenous vein with valves, groin tributaries, and the common femoral artery. Flow provocation maneuvers are Valsalva/Cremona (folded-straw

maneuver), manual compression calf/release, toe-elevation maneuver (Wunstorf), weight-transfer maneuver (Parana), and dependency maneuver. The standard for saphenofemoral junction exploration includes a standing position and longitudinal and cross sectional morphology. Color duplex exploration should determine the source and path of the reflux and it should be done to document the findings. At least one down-to-top and one top-to-down maneuver should be performed (once Valsalva). After saphenofemoral junction exploration, information will be available on the source of reflux (from where?), the paths of retrograde flow (to where?), and the ways of drainage. Erika Mendoza presented the REVAS classification sheet. Sources of recurrence are listed as no source of reflux, pelvic or abdominal, saphenofemoral junction, thigh perforator(s), saphenopopliteal junction, popliteal perforator, gastrocnemius vein(s), and lower-leg perforator(s). The source of reflux is the saphenofemoral junction in 47% of cases and lower-leg perforator(s) in 43% of cases. There are mainly retrospective studies in the literature about varicose vein recurrence after endovenous thermal ablation. In the REVATA study, recurrent varicose veins in 164 patients after endovenous thermal ablation or radiofrequency ablation (total 2380 patients treated) were documented. Varicose vein recurrence was seen after a median of 3 years. The most common source of reflux was from incompetent perforating veins (64%), recanalization of the great saphenous vein (29%), and new anterior accessory saphenous vein reflux (24%). The recurrence of varicose veins after endovenous thermal ablation in randomized studies was 22%, the same as after high ligation and stripping. There are different mechanisms of recurrence: neovascularization after high ligation and stripping (18%), recanalization after endovenous thermal ablation (32%), and new anterior accessory saphenous vein reflux (19%). Varicose veins increase over time and they are more frequent after endovenous thermal ablation than after high ligation and stripping.

There are possible strategies for preventing saphenofemoral junction and anterior accessory saphenous vein recurrence, but the use of laser crosssectionomy and/or "prophylactic" anterior accessory saphenous vein ablation has been debated. Potential strategies for preventing recurrences due to a large tributary include combining high ligation and stripping with phlebectomies or performing endovenous thermal ablation with concomitant phlebectomies. A prospective study of the fate of venous leg perforators after varicose vein surgery has shown that, in 850 incompetent perforator treatments, 76% of limbs had new incompetent perforators after 3 years.

Erika Mendoza concluded by saying that sources of recurrent reflux are different after endovenous thermal ablation and after high ligation and stripping. Preventing recurrence remains a challenge, but is not possible in all cases.

Alarming high rates of groin recurrence following endovenous laser therapy

Achim Mumme (Germany)

The socioeconomic importance of groin recurrence is growing. Treatment costs per year in Germany accounts for 64 million Euros and 15% is due to varicose vein surgery. The residual stump can be seen as a technical error, but groin recurrence due to neovascularization occurs in spite of a correctly performed crosssectionomy. Residual stump is the main cause of groin recurrences. In the LaVaCro study (n=1090), neovascularization was rare following a correctly performed crosssectionomy. The time between an asymptomatic interval and clinically visible groin recurrence can be 7 to 14 years. Most of the randomized

control trials with 5-year follow-ups showed higher rates (5% to 50%) of groin recurrence compared with high ligation crosssectomy. In conclusion, alarmingly high rates of groin recurrence after endovenous laser ablation were documented in the last years, and an endovenous stump is the problem. A possible solution could be adjunctive crosssectomy or endovenous crosssectomy.

Primary saphenous stump closure – lessons learned from “0 level” saphenous ostial ablation

Juris Riss (Latvia)

Juris Riss discussed the question of whether it is a problem to close at 0 level and which method is the best (crosssectomy, radiofrequency, laser, nonthermal). The distance study is a prospective, randomized single-center study comparing initial, mid-term, and long-term results after endovenous laser ablation for an insufficient great saphenous vein. Patients were randomized to two groups: (i) group 1: the distance for great saphenous vein ablation from the deep vein was 0 cm; and (ii) group 2: the distance for great saphenous vein ablation from the deep vein was 2 cm. There were no severe complications, no deep vein thrombosis, and no pulmonary embolism. However, there was more reflux in the stump and more proximal varicosity and reflux in the anterior accessory saphenous vein in group 2. Patients were equally satisfied with the treatment in both groups. There was a difference according to the venous blood flow at the groin region. Juris Riss suggested obliterating the insufficient vein as close as possible to the deep vein and he emphasized that a longer follow-up is indicated.

Does the choice of the treatment method decrease the recurrence rate?

Marlin Schul (US)

Data on recurrence is difficult due to initial treatment, definition of recurrence, method to define recurrence, and variability in follow-up. The clinical recurrence of varicose veins over 3 to 11 years has been reported to be between 26% and 62%. Pathogenesis of recurrent varicose veins can be due to residual varicose veins, true recurrent varicose veins, or new varicose veins, but the definitions vary between studies. Etiology can be related to inadequate treatment, disease progression, and neovascularization. Treatment of recurrent varicose veins is technically more difficult, as this is a debilitating and costly problem. Patient satisfaction is poorer than after primary intervention. In younger people, reflux progress from segmental to multisegmental is often tributary and nonsaphenous; however, in older people, it is saphenous and more proximal. Of the patients with reflux, 30% have chronic venous disease progression. The 13-year incidence of reflux is 12.7% to 80.9% per year. Today, we know that uncomplicated C₂ progresses to C₃-C₆, and, over 13.4 years, there would be chronic venous disease progression in 57.8% of cases, which is about 4.3% per year. Risk factors for chronic venous disease progression include corona phlebetica, higher BMI, popliteal vein reflux. Of the patients with varicose veins, 31.9% at baseline progressed to chronic venous insufficiency. In an extended 5-year follow-up study of a randomized control study, different treatment methods in 580 limbs were compared. Secondary end points were recurrences and reoperations. There was a 38.6% recurrence after endovenous laser ablation, 18.7% after radiofrequency ablation, 34.6% after surgery, and 31.7% after ultrasound-guided foam sclerotherapy. Marlin Schul concluded that both recurrences and progression occur in chronic venous disease, which is a common problem. Chronic venous disease progression is 4.3% per year

and has an identifiable risk. Secondary disease advances faster than primary disease. Technology is advanced for varicose vein treatment, but long-term follow-up is sparse to see if recurrences can be reduced. Marlin Schul finished with the questions of whether early intervention of disease will reduce recurrences and which biomarkers can predict recurrence and progression.

Reflux sources after surgical treatment and endovenous ablation: does accessory saphenous, big tributaries and perforator closure really work in the varicose vein recurrence prevention?

Marianne de Maeseneer (Belgium)

Marianne de Maeseneer postulated that, if clinically relevant, the superficial venous system should be treated in patients with reflux-type postthrombotic syndrome. Ablation is recommended in case of an incompetent great saphenous vein, small saphenous vein, anterior accessory saphenous veins, posterior accessory saphenous veins, and Giacomini vein, as well as to treat tributaries and use compression treatment for residual deep venous reflux. In obstructive postthrombotic syndrome \pm reflux in the superficial venous system should not be treated; compression treatment is the most important. In patients with (sub)total obstruction of the femoral and/or popliteal vein, collateral circulation through the great saphenous vein is established with a large-caliber great saphenous vein, spontaneous antegrade flow, but no reflux. If there is a combination of collateral circulation and reflux, refluxing tributaries should be treated in addition to compression treatment. In case of partial obstruction of the femoral and/or popliteal vein, collateral function of the great saphenous vein should be assessed with duplex ultrasound and the role of the profunda should be evaluated. There could be ipsilateral or contralateral reflux in the great saphenous vein and varicose tributaries. In these cases, the superficial venous system should be treated by ablating the incompetent great saphenous vein (distally from the collateral circulation), treating the tributaries, and using compression treatment. The take-home message was that, in reflux-type postthrombotic syndrome, the superficial venous system may be treated in case of reflux (symptoms and clinical signs). In obstructive postthrombotic syndrome, the superficial venous system should be evaluated very carefully as well as potential collateral function. In treating obstructive postthrombotic syndrome with reflux, the superficial venous system should be treated "a la carte."

Long term (20 years) results of preventive and venopreserving operations

Evgeny Shaydakov (Russia)

Pathogenesis of primary chronic venous disease is due to activation of the endothelium, release of inflammatory mediators, activation and recruitment of neutrophils, recruitment of T lymphocytes, and vein wall injury. Retrograde blood flow and venous hypertension on the background of congenital anomalies of the vein wall are the main links in the pathogenesis of chronic venous disease. Chronic venous disease is characterized by progressively worsening symptoms, suggesting the necessity of early treatment to prevent severe hemodynamic disturbances and skin changes.

Evgeny Shaydakov presented the results of a study on 106 patients with endothelial dysfunction, especially in C_1 - C_2 patients. A high level of endothelium is an indicator for the early stages of varicose transformation of superficial veins. It may be possible to predict the development of varicose veins, elaborate preventive conservative management,

and perform early preventive and vein-preserving procedures. Today, the prevention of primary chronic venous disease progression consists of surgery on various tributaries, hemodynamic correction, elimination of hemodynamic overload of the deep axial veins, anti-inflammatory therapy, venotonic drugs, and risk factor elimination. Unfavorable sequelae of great saphenous vein elimination are the increased hemodynamic challenge of the deep veins, impairment in the physiologic skin blood outflow, and loss of a conduit for possible vascular interventions.

Evgeny Shaydakov discussed the preventive and vein-sparing procedures in patients with primary chronic venous disease, such as ASVAL (Ambulatory Selective Varices Ablation under Local anesthesia). He presented the types of operations in patients with initial forms of primary chronic venous disease practiced at his center; for example, preventive extravasal correction of great saphenous vein valves and miniphlebectomies in 37% of the patients. The reported outcomes were good, and, as a result, valvular competency was achieved. Mild symptoms of venous disease after long walking or prolonged standing, which were self-limiting, did not significantly affect quality of life and did not require medical management. There were no recurrent varicose veins; ambulatory status and psychological and emotional status were improved. Outcomes were satisfactory in perforator vein incompetence with segmental varicose veins and poor in axial reflux of the great saphenous vein or small saphenous vein, which required a second surgery. Evgeny Shaydakov summarized by stating that chronic disease can be controlled, but cannot be cured. Early detection and timely treatment can reduce serious consequences of the disease. In chronic disease hemodynamic correction, anti-inflammatory therapy and prevention of neoangiogenesis are important.

XX. VTE session

The novel anticoagulants for the initial and long-term treatment of VTE: state of the art

Paolo Prandoni (Italy)

Direct oral anticoagulants are now recognized as the standard of treatment for the majority of patients with venous thromboembolism. Large phase 3 randomized controlled trials showed that direct oral anticoagulants were at least as effective as and safer than vitamin K antagonists. They reduced all major bleeding, particularly intracranial bleeding, which is the most feared complication of anticoagulation.

Apixaban and rivaroxaban can be administered with a single-drug approach, using a loading dose for 1 or 3 weeks, respectively. They have the potential to increase the rate of early discharge or home treatment for selected patients with a low-risk for a pulmonary embolism. Edoxaban and rivaroxaban can be administered once daily, improving patient compliance. All direct oral anticoagulants are contraindicated in patients with severe renal insufficiency, antiphospholipid syndrome, in the presence of prosthetic valves and during pregnancy. Their benefit-risk profile in frail patients is comparable and even better than in nonfrail patients, without the need for decreasing the dose (except for edoxaban). Recent trials have shown that direct oral anticoagulants can be also used for the initial and the long-term treatment of patients with cancer-associated thrombosis. The benefit-risk profile of edoxaban and rivaroxaban was comparable to the benefit-risk profile of low-molecular-weight heparin in trials specifically conducted for patients with cancer-associated thrombosis. However, caution should be used in patients with gastrointestinal cancer, as the potential for major bleeding complications was higher in patients treated with direct oral anticoagulants than in those treated with low-molecular-weight heparin in this subgroup of patients.

A number of recent studies have shown that the use of direct oral anticoagulants leads to an earlier vein recanalization compared with vitamin K antagonists in patients with proximal deep venous thrombosis. Accordingly, they are likely to be associated with a lower risk of postthrombotic syndrome. Finally, according to the most recent trials, we actually know that the long-term administration of low doses of apixaban and rivaroxaban confers a safe protection against the development of recurrent events either in patients with unprovoked venous thromboembolism and in patients with weak risk factors for venous thromboembolism. This evidence opens new scenarios for the long-term treatment of a wide spectrum of patients with venous thromboembolism.

Patient oriented anticoagulation in VTE treatment: efficacy and safety of the new and old therapeutic approach are DOACs the standard of care?

Wojciech Sydor (Poland)

The introduction of direct oral anticoagulants (DOACs), which directly inhibit either thrombin (dabigatran) or factor Xa (apixaban, betrixaban, edoxaban, and rivaroxaban) has been revolutionary for the management of venous thromboembolism. Their oral administration, rapid onset/offset of action, fewer food and drug interactions, and their predictable anticoagulant effects have resolved many of the drawbacks associated with

conventional therapy. DOACs are now endorsed as a first-line treatment in the majority of patients with a venous thromboembolism.

In patients with cancer, the 2016 ESC guidelines suggested low-molecular-weight heparin over vitamin K antagonists (grade 2B) and DOACs (grade 2C). However, with the publication of the results from the Hokusai-VTE Cancer and the Select-D trials, these recommendations are now out of date. The 2019 update of the ASCO guidelines instead recommends low-molecular-weight heparin, edoxaban, or rivaroxaban over vitamin K antagonists for at least 6 months in patients with cancer-associated thrombosis, stating that caution with DOACs is warranted in settings with a high risk of mucosal bleeding (ie, gastrointestinal or genitourinary malignancies). Furthermore, drug-drug interactions should be checked prior to using a DOAC.

The role of DOACs in the management of thrombophilia-associated venous thromboembolism is controversial. A recently published meta-analysis of four studies evaluating rivaroxaban, three evaluating dabigatran, and one evaluating edoxaban highlights that the rates of venous thromboembolism recurrence and bleeding events were both low and comparable in patients with various thrombophilias receiving either treatment, suggesting that DOACs are an appropriate treatment option in this population. However, Wojciech Sydor pointed out that, due to limited data, it is unclear whether these findings apply to specific subgroups, such as high-risk antiphospholipid syndrome, uncommon thrombophilias, or the use of apixaban (Elsebaie MAT, et al. *J Thromb Haemost.* 2019;17(4):645-656). The TRAP trial, involving only high-risk patients who were positive for lupus anticoagulant, anticardiolipin, and anti-b2-glycoprotein I antibodies of the same isotope (triple positivity), was terminated prematurely after the enrollment of 120 patients (59 randomized to rivaroxaban and 61 to warfarin) due to an excess of events among patients in the rivaroxaban arm (Pengo V et al. *Blood.* 2018;132(13):1365-1371). Therefore, efficacy and safety of DOACs seem maintained in low-risk antiphospholipid syndrome subgroups, but their use actually is not recommended in high-risk antiphospholipid syndrome patients due to an increased risk of arterial and bleeding complications.

Conversely, DOACs should be the first choice among currently available anticoagulants in elderly patients (Giustozzi M et al. *J Thromb Thrombolysis.* 2019;48(3):439-453). Indeed, data from the RIETE registry showed that 22% of the 13 011 patients included were aged 80 years or older. Patients ≥ 80 years received long-term treatment with vitamin K antagonists less frequently (66% vs 75%; $P < 0.001$) and with low-molecular-weight heparins more frequently vs patients aged less than 80 years (34% vs 25%; $P < 0.001$). Major bleeding and recurrent venous thromboembolism at 3 months were reported in 3.4% and 2.1% in patients ≥ 80 years and in 2.1% and 2.8% in those younger than 80 years (López-Jiménez L et al; RIETE Investigators. *Haematologica.* 2006;91:1046-1051). Randomized trials on venous thromboembolism patients treated with DOACs or vitamin K antagonists included 13.6% of patients aged 75 years or older. Data from a subgroup analysis of patients aged ≥ 75 years showed a significant reduction in recurrent venous thromboembolisms (risk reduction [RR], 0.56; 95% CI, 0.38-0.82) and major bleedings (RR, 0.49; 95% CI, 0.25-0.96) in patients receiving DOACs vs those receiving vitamin K antagonists (van Es N et al. *Blood.* 2014;124:1968-1975).

Finally, the use of DOACs is not recommended in pregnant and breastfeeding women since they are likely to cross the placenta and the reproductive effects in humans are unknown.

Cancer related DVT – what is new in the prevention and treatment?

Larisa Chernukha (Ukraine)

Patients with cancer are significantly more likely to develop a venous thromboembolism and experience higher rates of thromboembolism recurrence and bleeding complications during thromboembolism treatment than patients without cancer. Comprehensive management of thromboembolism in patients with cancer includes both the identification of patients who are most likely to benefit from pharmacologic prophylaxis as well as the effective treatment to reduce the risk of thromboembolism recurrence and mortality.

Larisa Chernukha summed up the latest recommendations provided by the guidelines in these settings. According to 2019 ASCO guidelines, routine pharmacological thromboprophylaxis should not be offered to all outpatients with cancer. High-risk outpatients with cancer (Khorana score of 2 or higher prior to starting a new systemic chemotherapy regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban, or low-molecular-weight heparin provided there are no significant risk factors for bleeding and no drug interactions. Furthermore, hospitalized patients who have an active malignancy and acute medical illness or reduced mobility should be offered pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications. Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should be offered pharmacologic thromboprophylaxis with either aspirin or low-molecular-weight heparin for lower-risk patients and low-molecular-weight heparin for higher-risk patients. All patients with cancer undergoing major surgical intervention should be offered preoperative pharmacologic thromboprophylaxis with either unfractionated heparin or low-molecular-weight heparin unless contraindicated because of active bleeding, high bleeding risk, or other contraindications. Extended prophylaxis with low-molecular-weight heparin for up to 4 weeks postoperatively is recommended for patients undergoing major open or laparoscopic abdominal or pelvic surgery for cancer who have high-risk features, such as restricted mobility, obesity, history of venous thromboembolism, or with additional risk factors. In lower-risk surgical settings, the decision about the appropriate duration of thromboprophylaxis should be made on a case-by-case basis.

New data on direct oral anticoagulants regarding the primary prevention of cancer-associated thrombosis in surgical patients will become available soon, since these trials are still ongoing. Outcomes of trials with direct oral anticoagulants for the primary prevention in outpatients receiving chemotherapy (CASSINI with rivaroxaban and AVERT with apixaban) suggest a decrease in venous thromboembolism events but have not yet been included in the guidelines. With regard to treatment of cancer-associated thrombosis, low-molecular-weight heparin, edoxaban, or rivaroxaban for at least 6 months are preferred over vitamin K antagonists because of improved efficacy. There is an increase in the risk of major bleeding with direct oral anticoagulants, particularly observed in gastrointestinal and potentially genitourinary malignancies. Anticoagulation with low-molecular-weight heparin, direct oral anticoagulants, or vitamin K antagonists beyond the initial 6 months should be offered to select patients with active cancer, such as

those with metastatic disease or those receiving chemotherapy. Anticoagulation beyond 6 months needs to be assessed on an intermittent basis to ensure a continued favorable risk-benefit profile (Key NS et al. *J Clin Oncol*. 2019 Aug 5. Epub ahead of print). In the near future, the results of trials with apixaban in cancer-associated thrombosis treatment will become available and this drug is likely to be mentioned by the guidelines among the options for the treatment of cancer-associated thrombosis.

Open vein concept in acute DVT treatment – still valid approach or already the past?

Niels Baekgaard (Denmark)

Catheter-directed thrombolysis or other endovenous early thrombus removal methods have to follow strict rules in terms of obtaining as much free lumen as possible. Indeed, residual thrombus is predictive of deep venous thrombosis (DVT) recurrence and of further risk for postthrombotic syndrome (PTS) in patients treated with anticoagulation alone. Niels Baekgaard pointed out that all the procedures should be implemented not only to open the veins, but also to clean the veins and preserve the valves. Studies in this setting have shown a great variation in reducing the rates of PTS. The Copenhagen group demonstrated a rate of any PTS of 17% in 109 patients with iliofemoral DVT treated with catheter-directed thrombolysis after a median follow up of 71 months. The randomized CaVenT trial showed persistent and increased clinical benefit in terms of PTS during a 5-year follow-up in favor of catheter-directed thrombolysis. However, no difference in quality of life was demonstrated.

A recent analysis from the ATTRACT trial, involving a subgroup with iliofemoral DVT alone (196 patients treated with pharmacomechanical catheter-directed thrombolysis and 195 patients in the control group), showed no difference in PTS, assessed as a Villalta score >4, between the thrombus-removal group (49%) and the control group (51%) (risk reduction [RR], 0.95; 95% CI, 0.78-1.15; $P=0.59$). However, a difference was found in patients with moderate-to-severe PTS (Villalta score >9 or ulcer) in favor of pharmacomechanical catheter-directed thrombolysis: 18% vs 28% (RR, 0.65; 95% CI, 0.45-0.94; $P=0.021$) and in patients with severe PTS (Villalta score >14 or ulcer): 8.7% vs 15% (RR, 0.57; 95% CI, 0.32-1.01; $P=0.048$), as in the main study. Furthermore, a positive improvement in the venous clinical severity score was found in pharmacomechanical catheter-directed thrombolysis patients at 2 years.

Many factors may play a role in the success of these procedures. Among these, stenting placement seems to be an important part. Therefore, in the opinion of the author, the open vein theory is valid. However, the recently published papers have shown that the improvement in clot removal techniques might have a more and more important role on cleaning the veins in order to obtain a greater reduction in PTS.

Unmet needs in VTE clinical management

Gualtiero Palareti (Italy)

The first topic illustrated by Gualtiero Palareti was the extension of the anticoagulant treatment beyond the first 6 months of anticoagulation. Indeed, the optimal duration of anticoagulation for venous thromboembolism (VTE) remains uncertain since the benefit of anticoagulation to prevent recurrent VTE must be weighed against the risk of bleeding.

The current guidelines dichotomize VTE as unprovoked or provoked, recommending extended-duration anticoagulation with no scheduled stop date and yearly assessment of the bleeding risk, the risk of recurrence, and the patient's preference for unprovoked events. In contrast, they recommend 3 months of anticoagulation for provoked VTE. However, recent data suggest that dichotomizing VTE into provoked and unprovoked categories to guide decisions about the duration of anticoagulation may not be the best approach. In a Danish nationwide cohort study, patients with cancer and those with unprovoked VTE had the highest risk of recurrence. However, recurrence rates in patients with provoked VTE were not negligible.

The EINSTEIN CHOICE trial randomized patients with prior provoked (59%) or unprovoked (41%) VTE to rivaroxaban (20 mg or 10 mg) or low-dose aspirin after they had received anticoagulation for 6 to 12 months. In the 20-mg rivaroxaban group, 1.4% of the patients with provoked VTE had a recurrence after the first year vs 1.8% of the patients with unprovoked VTE. In the aspirin arm, 3.6% of the patients with provoked VTE had a recurrence vs 5.6% with unprovoked VTE. The risk of recurrent VTE in patients with trauma or major surgery was 0% in both the rivaroxaban and aspirin groups. These results suggest, therefore, that a time-limited anticoagulation for patients with VTE provoked by major surgery or trauma can be correct. For all the other "provoked" events, we probably have to reconsider our approach regarding the duration of anticoagulation.

The second topic addressed by Gualtiero Palareti was related to the secondary prevention of VTE in elderly patients. In fact, the real risk of recurrence in the elderly is still uncertain. However, the risk of bleeding during anticoagulation is higher in the elderly than in young patients. The ACCP guidelines consider all patients aged ≥ 75 years at high risk of bleeding. In the management DULCIS study, 316 patients were aged ≥ 75 years at inclusion (31.3% of all patients); 162 of them (51.3%) resumed anticoagulation based on a positive D-dimer. During subsequent vitamin K antagonist treatment, 8 major bleeds occurred in patients aged ≥ 75 years (4.9%, 3.1% per year; 1 fatal), while only 6 events occurred in the 211 younger patients (< 75 years) (2.8%, 1.7% per year). These data seem to discourage extended anticoagulant treatment using vitamin K antagonists in elderly patients after the first VTE event. Aspirin treatment for secondary VTE prevention has no favorable benefit-risk profile in elderly patients.

The use of low-dose direct oral anticoagulants for extended treatment in elderly patients seems promising, but data on longer periods of therapy are necessary, especially to assess the potentially associated risk of bleeding in the long term. Indeed, the proportion of elderly patients included in these trials was very low and the duration of treatment short (1 year). Moreover, the results for both efficacy and safety were less satisfactory in the older vs younger population. Updated new evidence on the benefit-risk profile of indefinite anticoagulant therapy with direct oral anticoagulants, at different doses, is required, particularly in older patients. Observational prospective registry studies may provide us with real-life data on the advantages and side effects of generalized indefinite treatment with anticoagulants in the next few years. An Italian collaborative trial on extended treatment in elderly VTE patients using oral sulodexide, a drug without an anticoagulant effect and a low risk of bleeding, is currently under way and is planned to start at the end of the current year.

Venous problems in thoracic outlet syndrome: thrombolysis, anticoagulation, rib resection: staged or simultaneous?

Zbigniew Krasiński (Poland)

Primary upper extremity deep venous thrombosis includes idiopathic thrombosis and effort thrombosis. The latter, also called Paget-von Schroetter syndrome, typically occurs in the dominant arm after unusual physical activity. The affected patients are usually young and the male to female ratio is approximately 2 to 1. The major predisposing factor for effort thrombosis is the thoracic outlet syndrome, which is characterized by external compression of the neurovascular bundle at the thoracic outlet. The optimal treatment duration and intensity so far has not been studied in a randomized control trial. Therefore, the management of such patients remains controversial. Based on available data from prospective cohort studies, the current guidelines recommend anticoagulant treatment for at least 3 months. In addition, they suggest that thrombolytic therapy may be considered in selected patients with acute thrombosis of the arm veins and severe symptoms, but low bleeding risk. Catheter-directed thrombolysis is the preferable option due to a lower rate of bleeding complications when compared with systemic thrombolysis. It should be followed by definitive decompression of the anterior part of the thoracic outlet (costoclavicular junction), although proof of effectiveness of such decompression is lacking. Transaxillary first rib resection is the most common method of doing decompression. The major advantage of this method is that it offers excellent exposure of the anterior portion of the first rib. According to Zbigniew Krasiński, “in Paget-Schroetter syndrome, the earlier the diagnosis and treatment, the better the results.”

Optimization of anticoagulation with DOACs: role of proper selection and assessment

Jeanine Walenga (US)

The direct oral anticoagulants (DOACs) are at least as safe and effective as conventional treatment in the majority of patients with venous thromboembolism (VTE). However, many specific subgroups were excluded or underrepresented in these studies and the safety and efficacy of DOACs within these subgroups has yet to be established. The inclusion criteria for the VTE treatment trials included patients aged more than 18 years with an acute symptomatic proximal DVT and/or PE. Patients were excluded if they needed thrombolytic therapy, had a high risk of bleeding, clinically significant liver disease, creatinine clearance (CrCl) <30 mL/min, uncontrolled hypertension, or were breastfeeding or pregnant. The clinical impact of DOACs has not been fully defined for extremes in age or body weight, patients with mechanical heart valves, concomitant use of potent inhibitors or inducers of CYP3A4 or P-glycoprotein, concomitant use of antiplatelets, gastrointestinal malabsorption, thrombophilias with a high prothrombotic state (antiphospholipid syndrome, hypercoagulable state), in case of profound thrombocytopenia, nor in patients with cancer treated with chemotherapy.

The main unresolved issues for the use of DOACs are managing patients with a temporary interruption of therapy and patients with DOAC-induced bleeding, defining a protocol for use with spinal anesthesia or protocol for restarting after brain bleeds, assessing their effect with laboratory test in selected circumstances. Traditional clotting assays, such as prothrombin time, partial thromboplastin time, and thrombin time, are not ideal assays to measure plasma levels of DOACs since they are either too sensitive (thrombin time) or too insensitive (prothrombin time, partial thromboplastin time). International normalized ratio

is not valid for DOACs and it should not be considered. The quantitative chromogenic anti-FXa and anti-FII assays, calibrated to a specific drug, could be more useful to assess DOACs plasma levels. Recently, a product for testing DOACs in urine has been introduced by a German company; it qualitatively detects the presence or absence of these drugs in the urine.

An update on the development of antidotes for NOACs

Jawed Fareed (US)

Jawed Fareed pointed out the clinical problem of bleeding management in patients treated with anticoagulants. Older age, declining kidney function, history of bleeding, anemia, and concomitant medication use (aspirin, other antiplatelet drugs, nonsteroidal anti-inflammatory drugs, etc) are risk factors for bleeding during anticoagulant therapy. A decision pathway, considering the severity of the bleed (major vs nonmajor), acute medical and surgical management, the need for reversal, the appropriateness and time for restarting anticoagulation, and the impact of pertinent comorbidities and concomitant drug therapy should be used as a guide by all clinicians involved in the management of bleeding or in the event of emergency surgery and invasive procedures. Patient-specific factors should be considered at each step in the decision pathway algorithms. Indeed, reversal of anticoagulation is risky in patients with high thrombotic risk, such as patients with CHA₂DS₂-VASc score ≥ 6 , stroke or transient ischemic attack in the past 3 months, VTE in the past 3 months, active cancer or other hypercoagulable state, thrombotic event when anticoagulation was interrupted previously, cardiac thrombus, or left-ventricular assist device. Using advanced molecular approaches, specific antidotes for dabigatran (Praxbind) and for the anti-Xa agents (andexanet alfa) have been developed. Other agents, which have been used for the control of bleeding, include prothrombin complex concentrates (activated and nonactivated) and a universal antidote, ciraparantag (Tomaselli GF et al. *J Am Coll Cardiol.* 2017;70(24):3042-3067).

Praxbind (idarucizumab) is an antidote developed to neutralize the effects of dabigatran. It can be used to stop the anticlotting effect of dabigatran rapidly before emergency surgery or in case of life-threatening bleeding. Praxbind is a monoclonal antibody fragment that works by attaching firmly to dabigatran and forming a complex in the blood. This rapidly stops dabigatran's anticoagulant effects. Praxbind has been investigated in three main studies involving 141 healthy adults who previously received dabigatran. In these studies, volunteers received either Praxbind or placebo after treatment with dabigatran for 3.5 days. Praxbind was able to neutralize dabigatran's anticoagulant effect completely within 5 minutes of administration. An interim analysis of an ongoing trial showed similar results in 123 patients who had uncontrolled bleeding or had required emergency surgery while using dabigatran. Most patients in the study were taking dabigatran to prevent stroke due to atrial fibrillation. These studies showed that Praxbind rapidly and effectively neutralizes the anticoagulant effect of dabigatran, which is sustained for an extended period of time.

Andexanet alfa, the active substance of Ondexxya, the approved commercial name in European countries, is a recombinant protein that acts as a decoy for the direct oral factor Xa inhibitors apixaban and rivaroxaban in the blood. As a result, andexanet alfa neutralizes the anticoagulant effect of these inhibitors. It is projected that andexanet alfa will also neutralize the effects of other factor Xa inhibitors, such as betrixaban and

edoxaban. The effects of treatment with Ondexxya were studied in 352 patients for safety and 167 patients for efficacy. Clinical efficacy is based upon reversal of antifactor Xa activity in healthy volunteers and interim results of a study in patients with life-threatening bleeding. Ondexxya reversed the anticoagulant effects of apixaban and rivaroxaban within 2 minutes of its administration.

Ciraparantag (aripazine) is a synthetic drug that is under investigation as a universal antidote for a number of anticoagulant drugs, including factor Xa inhibitors (apixaban, betrixaban, edoxaban, and rivaroxaban), dabigatran, low-molecular-weight heparins, and unfractionated heparin. According to in vitro studies, this substance binds directly to anticoagulants by forming hydrogen bonds. Clinical studies have shown that Ciraparantag acetate, at doses of 100 mg, produced complete and sustained reversal of steady-state levels of apixaban and rivaroxaban in age-matched healthy volunteers as measured by whole blood clotting time. In previous clinical trials, Ciraparantag produced complete and sustained reversal of the DOAC edoxaban, and the low-molecular-weight heparin enoxaparin following a single intravenous bolus dose, as measured by whole blood clotting time. While the safety profile of Ciraparantag is consistent with previous trials, the most common adverse events observed were transient mild facial flushing and dysgeusia. No procoagulant signals were observed in any clinical trial to date.

Prothrombin complex concentrates, such as Kcentra, and activated prothrombin complex concentrates, such as FEIBA, have been used to neutralize DOACs. FEIBA dosages of 25 to 50 U/kg are effective in reversing the effects of DOACs. Some recent reports have shown that lower dosages can also be effective. Kcentra, a four-factor prothrombin complex concentrate can also be used at a dosage of 50 U/kg. Additionally, recombinant factor VIIa (NovoSeven) has been used to control severe bleeding. These drugs were approved long before the use of newer antidotes, such as Praxbind and Andexxa. Moreover, these plasma-based drugs have a lower cost compared with the newer antidotes.

Although, the antidotes currently available for the management of bleeding with DOACs are useful for managing severe bleeding complications, these antidotes have certain adverse effects that have not been fully explored. Thrombotic complications with the use of both Praxbind and andexanet alfa have been reported. The incidence of thrombotic events within 30 days of reversal is much higher with andexanet alfa (10%) compared with Praxbind (4.8%). Some of these complications have been severe and have resulted in mortality. Andexanet alfa is a decoy protein that retains some of the biologic properties of native factor Xa; it has been shown to interfere with tissue factor pathway inhibitor, AT, and thrombomodulin. Thus, it may create an endogenous thrombotic environment. Praxbind is an antibody that forms complexes endogenously, which may have some adverse effects. Since both of these are proteins, neutralizing antibodies may also be formed. The thrombogenicity of activated prothrombin complex concentrate is also a potential complication that requires close monitoring; similarly, prothrombin complex concentrates have thrombogenic effects, which are relatively mild. Reportedly, ciraparantag may produce allergic or anaphylactoid reactions. The FDA has approved both andexanet alfa and Praxbind in order to provide clinicians with an antidote. However, this approval was based on limited clinical data and an incomplete adverse reaction profile review. The cost of the newer antidotes is rather high.

Superficial vein thrombosis – controversies in superficial venous thrombosis epidemiology and management

Willy Chi (US)

Superficial vein thrombosis (SVT) is a common condition, with an incidence greater than deep vein thrombosis (DVT). It is often associated with concomitant asymptomatic DVT. Recent studies showed that progression or recurrence of SVT is not uncommon and can present as DVT or pulmonary embolism (PE). Known risk factors for SVT include varicose veins, obesity, malignancy, age >60 years, history of thrombosis, pregnancy, infection, or smoking. Thrombophilia may have a role, but testing is not recommended because their results do not influence SVT management. Current guidelines recommend the use of low-molecular-weight heparin or fondaparinux for 45 days.

The large CALISTO trial included 3002 patients with SVT who were treated with 2.5 mg fondaparinux once daily or placebo and were followed for up to 77 days. This trial excluded patients with a very high risk of SVT complications, including individuals presenting with thrombus within 3 cm of the saphenofemoral junction and those with cancer, recent SVT, or DVT/PE. Despite the exclusion of high-risk patients with SVT, the thromboembolic event rates at 45 and 77 days in the placebo arm were 5.9% and 6.3%, respectively. The prospective, randomized SURPRISE trial compared 10 mg rivaroxaban orally vs 2.5 mg fondaparinux subcutaneously over 45 days in selected high-risk patients with above-knee SVT who had additional risk factors for thromboembolic complications, such as male sex, history of DVT/PE, previous or active cancer, systemic inflammatory disease, or SVT in nonvaricose veins. Although this trial demonstrated the noninferiority of 10 mg rivaroxaban once daily compared with 2.5 mg fondaparinux once daily in the treatment of SVT, outcome event rates during treatment were numerically higher in the rivaroxaban arm, as were rates of clinically relevant nonmajor bleeding events. Surgery has been an option for the treatment of SVT. However, according to the results of a low number of studies, surgical treatment seems unable to reduce SVT extension or the occurrence of DVT or PE. Conversely, it could be useful for the reduction in pain. In the Calisto study, patients treated with fondaparinux were less frequently treated with surgery than patients treated with placebo. With regard to compression stockings, some data indicates that it can significantly stimulate a faster thrombus regression in patients with acute SVT when compared with patients receiving nondressing compression stockings. Data regarding the combination of several treatments are lacking.

Anti-DVT prophylaxis in patients undergoing thermal endovenous varicose vein treatment

Isaac K. Nyamekye (UK)

Endovenous thermal procedures may be complicated by venous thromboembolism events. In analyzing adverse events of endovenous laser therapy and radiofrequency ablation that were reported in the Manufacturer and User Facility Device Experience (MAUDE) database from January 2000 to June 2012, 30 (8%) nonfatal PEs and 123 (35%) DVTs were described. Moreover, there were 7 (2%) periprocedural deaths, all from PEs. In absence of clear recommendations by the guidelines, the goal is to identify patients at high risk of developing thrombosis, in order to offer a selective anti-DVT prophylaxis. However, the major risk factors for thrombosis in this setting are not completely understood. A preoperative risk assessment could help clinicians to better identify such patients. The most commonly used scores for this purpose are the Caprini, the Worcester, and the DOH

score. A short-term pharmacological prophylaxis with low-molecular-weight heparin should be offered to intermediate-risk patients. However, a prolonged duration should be considered for patients at high risk of developing thrombosis.

New look at endovenous heat-induced thrombosis risk assessment after endovenous venous thermal procedures

Jaroslav Strejček (Czech Republic)

Endovenous thermal radiofrequency ablation is one of the most effective methods of varicose vein treatment. The term endovenous heat-induced thrombosis (EHIT) is used to describe this situation and includes, in particular, the propagation of the thrombus from the proximal section of the great saphenous vein to the femoral vein. EHIT is a relatively rare complication in technically well-performed endovenous treatment. In addition to the exact position of the endovenous instrument in relation to the saphenofemoral junction, a comprehensive assessment of anamnestic history of the patient seems useful to stratify the risk of thrombosis. A number of significant risk factors, such as male sex, higher Caprini risk scores, thrombophilic states, and obesity have been identified in studies regarding this topic. In clinical practice, different schemes, such as the Caprini score, the Thailand study system, or the Worcester scheme are used to evaluate the risk of developing EHIT, although none of them is validated. Jaroslav Strejček concluded his speech remarking that, in his center from January 2017 to June 2018, 487 endovenous treatments were performed, and due to a preoperative risk assessment, prevention, and careful posttreatment sonography controls, they observed very few EHIT complications.

How to assess the DVT recurrence risk

Paolo Prandoni (Italy)

It is well recognized that patients with acute unprovoked deep venous thrombosis or pulmonary embolism have a higher risk of recurrent venous thromboembolism (VTE) vs patients whose thrombosis is associated with acquired, transient risk factors. However, other clinical parameters can help predict the development of recurrent events. In a prospective study involving 1626 patients followed over a 10-year period after a first VTE event, among patients with secondary VTE, those with medical diseases were more likely to develop recurrent thromboembolism (31.8%) than those with recent trauma or surgery (11.4%) and those in whom the VTE was associated with hormonal therapy, pregnancy, or puerperium (20.3%) (Prandoni P et al. *Haematologica*. 2007;92(2):199-205). In a prospective cohort study, patients with a VTE associated with major surgery have a very low rate of recurrence (Baglin T et al. *Lancet*. 2003;362(9383):523-526).

More recently, a prespecified analysis of data from the EINSTEIN EXTENSION and the EINSTEIN CHOICE trials was performed in order to estimate the risk of recurrence according to the baseline risk factor profiles in patients enrolled in these trials. There were no recurrences in patients with VTE provoked by major transient risk factors. Conversely, recurrence rates in patients with VTE provoked by minor persistent or minor transient risk factors (HR, 0.81; 95% CI, 0.56-1.16) were not significantly lower than in those with unprovoked VTE (HR, 0.68; 95% CI, 0.32-1.30) (Prins MH et al. *Blood Adv*. 2018;2(7):788-796).

In addition, Paolo Prandoni pointed out that there are other considerations when assessing the risk of recurrence. First, the risk of recurrent VTE is two times more frequent in men than in women. Second, the risk of recurrent pulmonary embolism after an episode of pulmonary embolism is 3 to 4 times more frequent than in patients presenting with deep venous thrombosis. In addition, extending anticoagulation for a fixed period simply delays the timing of recurrences. A number of scores, such as Vienna, DASH, DAMOVES, and HERDOO2, were developed with the aim of predicting the risk of recurrence after a first VTE episode. Among them, recently the HERDOO2 score was validated in a study showing that women with a first unprovoked VTE event and none or one of the HERDOO2 criteria have a low risk of recurrent VTE and can safely discontinue anticoagulants after completing short-term treatment (Rodger MA et al. *BMJ*. 2017;356:j1065). Currently, low doses of direct oral anticoagulants are also available for the extended treatment of VTEs. The ongoing Italian APIDULCIS study will assess if patients with a first unprovoked or provoked by minor risk factors VTE and persistent negative D-dimer testing after withdrawal of anticoagulation will safely discontinue treatment.

Paolo Prandoni concluded his talk giving a number of personal suggestions. In the absence of contraindications to anticoagulation, indefinite anticoagulation with therapeutic doses of warfarin or low-molecular-weight heparins or direct oral anticoagulants should be considered in patients with major persistent risk factors. Patients with VTE occurring after surgery or trauma should be treated for 3 months. In patients presenting with life-threatening pulmonary embolism, in those with minor persistent risk factors, and in men with unprovoked VTE, indefinite anticoagulation with low-dose direct oral anticoagulants should be considered. Risk stratification should be done in all other patients and low-dose direct oral anticoagulants should be offered to patients who do not satisfy the criteria for drug discontinuation.

Options for DVT recurrence prevention in cancer and non cancer patients – what to choose? when?

Andrew Nicolaides (Cyprus)

Recurrence of deep venous thrombosis or pulmonary embolism after completion of anticoagulation therapy is high. The most recent randomized control trials have tested various drugs aimed at reducing the risk of VTE recurrence. Aspirin reduced VTE recurrence by approximately 30% (hazard ratio [HR], 0.68; 95% CI, 0.51-0.90) without any increase in bleeding. Dabigatran was effective in reducing VTE (HR, 0.08; 95% CI, 0.02-0.25), but carried a lower risk of major or nonmajor clinically relevant bleeding than warfarin, but a higher risk than placebo (5.3% with dabigatran and 1.8% with placebo [HR, 2.92; 95% CI, 1.52-5.60]). Rivaroxaban was effective in reducing VTE (HR, 0.18; 95% CI, 0.09-0.39), but carried a higher risk of major or nonmajor clinically relevant bleeding than placebo (6.0% with rivaroxaban and 1.2% with placebo [HR, 5.19; 95% CI, 2.3-11.7]). Apixaban at either a treatment dose (5 mg) or a thromboprophylactic dose (2.5 mg) reduced the risk of recurrent VTE (1.7% with apixaban and 8.8% with placebo [relative risk reduction, 81%; $P < 0.001$]) without increasing the rate of major bleeding. Sulodexide reduced the risk of recurrence (HR, 0.49; 95% CI, 0.27-0.92), without any increase in bleeding risk. Furthermore, the risk of VTE recurrence and bleeding are not the same in every patient. Residual thrombus and elevated D-dimer are markers for increased risk of recurrence. Their presence, when combined with other risk factors, allows for the stratification of patients into high, intermediate, or low risk of VTE recurrence. Patients can also be stratified according to their risk of bleeding (high, intermediate, and low risk of bleeding). Based on the

available medications and knowledge of the risk of recurrence versus the risk of bleeding, clinicians can make up a plan or algorithm for extended prophylaxis in patients with a moderate or high risk of DVT. In patients with active cancer, low-molecular weight heparin was more effective than vitamin K antagonists in preventing VTE recurrence without any increase in bleeding. Direct oral anticoagulants are more effective than low-molecular weight heparin in preventing VTE recurrence, but caused more major bleeding (6.5% vs 3.7%). More studies with direct oral anticoagulants are needed.

Long term anticoagulation in VTE recurrence prevention: how to increase the safety of the anticoagulant treatment?

Wojciech Sydor (Poland)

The ACCP guidelines suggest extended anticoagulation in patients with a first unprovoked proximal deep venous thrombosis or pulmonary embolism if the risk of bleeding is low or moderate. However, only 50% of patients with unprovoked VTE are expected to have recurrences within 10 years and proposing an indefinite anticoagulation for all of them may not be correct. Currently, we have many scores that can help us estimate both the risk of recurrence and the risk of bleeding and properly select patient candidates for long-term anticoagulation. Furthermore, we have a number of agents available with reduced dose schemes, which can allow a tailored drug selection. In addition, long-term anticoagulated patients should be well educated about the risk of anticoagulation. A periodic assessment of the risk-benefit balance should be pursued, modifiable bleeding risk factors should be corrected, and drug-drug interactions should always be checked during the follow-up controls. Finally, specific antidotes for direct oral anticoagulants may be useful in the case of emergencies.

DOACS in the cancer related DVT treatment

Larisa Chernukha (ukraine)

Risk of cancer-associated thrombosis may depend on the type and location of cancer, hospitalization, the presence of metastasis, treatments (surgery, chemotherapy), a central venous catheter, and patient-related risk factors. Until recently, the use of direct oral anticoagulants in cancer-associated thrombosis was limited due to a lack of clear evidence. Only data from a subgroup analysis of randomized controlled trials (RE-COVER, RE-COVER II, EINSTEIN-DVT, EINSTEIN-PE, AMPLIFY, Hokusai VTE) were available. In these trials, a small number of patients with active cancer were included. Furthermore, in these trials, the comparator was vitamin K antagonists instead of low-molecular-weight heparin. However, in the CLOT study, vitamin K antagonists appeared to be inferior to low-molecular-weight heparin in terms of cancer-associated thrombosis treatment, risk of recurrence, and bleeding rate. Novel oral anticoagulants have shown a nonsignificant decrease in VTE recurrence and a lower major or clinically relevant bleeding rate compared with vitamin K antagonists. However, cancer patients in these trials were healthier and had lower mortality than patients in the CLOT study. More recently, patients with active cancer were enrolled in the Hokusai VTE-Cancer, Select-D, and ADAM VTE trials.

In the Hokusai VTE-Cancer study, the recurrence rate of VTE was non significantly lower in patients who received a combination of edoxaban with low-molecular-weight heparin

than on dalteparin only. The incidence of major bleeding was significantly higher in the edoxaban group. The mortality rate was not substantially different between groups, and the majority of deaths were caused by cancer. The number of deaths associated with VTE or bleeding was too small to make comparisons between groups.

In the Select-D study, rivaroxaban was associated with a lower rate of VTE recurrence compared with dalteparin at 6 months. The rate of major bleeding was numerically higher in the rivaroxaban arm, but a similar rate of fatal bleeding was found in both the groups. Overall, survival was also similar among treatment arms. In these trials, it was also noticed that patients with gastrointestinal or genitourinary cancer were at high risk of major bleeding when treated with direct oral anticoagulants.

The results of the ADAM VTE trial showed very low bleeding and VTE recurrence rates of apixaban compared with dalteparin, but these data have not yet been included in the guidelines. The 2017 ESC, 2017 ESMO, 2018 NCCN, 2018 ISTH, and 2018 Canadian Expert Consensus recommend low-molecular-weight heparin as the treatment of choice for patients with cancer-associated thrombosis for at least 6 months. Only edoxaban and rivaroxaban are mentioned and suggested for cancer patients with acute VTE, low risk of bleeding, and no drug-drug interactions with current systematic therapy. The choice of treatment should be based on the type and location of the cancer, on the risk of bleeding, concomitant chemotherapy, drug interactions, and patient preferences.

The role of heparin and related glycosaminoglycans in the management of vascular diseases in the era of new oral anticoagulant drugs

Jawed Fareed (US)

Undoubtedly, the introduction of direct oral anticoagulants had a major impact on the management of thrombotic and cardiovascular disorders in the context of oral anticoagulation. However, these drugs are of limited value for parenteral indications. None of these agents can be used for surgical or interventional procedures where heparin is routinely used. Therefore, in the event of a shortage of heparin, direct oral anticoagulants will be of limited value. Parenteral anti-thrombin agents, such as argatroban or bivalirudin, may be an option. However, there is no antidote available for the use of these anti-thrombin agents and the risk of hemorrhagic complications is disconcerting. Among the nonheparin glycosaminoglycan-related drugs, danaparoid, hemoclar (SP54), and sulodexide are currently available for clinical use. In comparison with sulodexide, both of these drugs are relatively weaker anticoagulants when administered parenterally. Sulodexide has a broader therapeutic index vs direct oral anticoagulants and it can be neutralized by protamine sulfate. It might be an option to substitute for heparin in such indications, such as hemodialysis and interventional procedures. Indeed, pharmacodynamics data showed that sulodexide could be used as an alternative to heparin in parenteral indications. However, these indications are not currently approved for sulodexide use. The anticoagulant and anti-thrombotic qualities of heparins and related glycosaminoglycans are also associated with their anti-inflammatory and vasoprotective effects. Up to now, unfractionated heparin remains the anticoagulant of choice for vascular and endovascular procedures and indications. Now that the heparin supply is threatened by several factors, including the increased use of porcine mucosal heparin for the manufacturing of low-molecular-weight heparin, the shortage of heparin due to outbreaks of diseases, such as African swine fever, resourcing and finding alternatives to heparin should be timely

in order to avoid any serious outcomes. The development of bovine and ovine heparin and the use of alternative glycosaminoglycans, such as sulodexide may offer practical approaches to offset the heparin shortage. As a blended glycosaminoglycan, sulodexide is a good candidate for further development as a parenteral anticoagulant drug, which can be optimized for hemodialysis and interventional/surgical indications. In the opinion of Jawed Fareed, both industry and agencies need to work together in order to develop plans and a fast-track review of a number of initiatives to avoid problems that may eventually result in compromised patient care.

Anticoagulation in the arterial thrombotic complications prevention – current evidence

Pier Luigi Antignani (Italy)

The latest guidelines recommend single antiplatelet therapy in symptomatic patients with peripheral artery disease not requiring anticoagulation. More recently, The COMPASS trial showed that low-dose rivaroxaban twice a day plus aspirin once daily reduced major adverse cardiovascular and limb events when compared with aspirin, but increased major bleeding. This combination therapy represents an important advance in the management of patients with peripheral artery disease. Glycosaminoglycans, such as sulodexide, inducing vascular relaxation and increasing the production of nitric oxide, might be an option for the treatment of patients with peripheral artery disease if preliminary data can be confirmed.

First results of the German registry for superficial thrombosis – INSIGHT study

Thomas Noppeney (Germany)

Superficial vein thrombosis (SVT) and venous thromboembolism (VTE) are related entities. In the last few years, a series of observational studies conducted mainly in France may show that “isolated superficial vein thrombosis” (without concomitant deep vein thrombosis and/or pulmonary embolism) is in fact not a benign and spontaneously healing disease, but bears a potential for severe thromboembolic complications once treated inadequately. The INSIGHTS-SVT study aims to collect representative data on the current management and outcomes of superficial vein thrombosis in Germany under real-life conditions. It will document the implementation of the recently issued national superficial vein thrombosis guidelines issued by the Society for Angiology and the Society for Phlebology. It is a prospective, observational cohort study involving approximately 1200 participants followed up for 1 year. Thomas Noppeney presented the preliminary results of the study, showing that 92% of patients were treated with prophylactic doses of anticoagulants, especially fondaparinux (66%). A few patients were treated with surgery at the time of inclusion. Up to now, the incidence of the efficacy and safety end points is quite low (0.9% for death, 1.2% for pulmonary embolism, 2.5% for deep vein thrombosis, 1.6% for bleeding; 11.9% for superficial vein thrombosis persistent or extending). Overall, Thomas Noppeney emphasized that the treatment of this disease in real life seems in accordance with the recommendations of the German guidelines.

XXI. Post-thrombotic syndrome: towards consensus on definition, scoring and effective prevention

What is PTS and how we measure this?

Mark Meissner (US)

The clinical definition of the syndrome is the presence of pain (often described as aching, heaviness, or, in some cases, as venous claudication) with associated swelling and skin changes, which eventually leads to ulceration. In addition, there is evidence of reflux and/or obstruction due to a previous deep vein thrombosis. It has been demonstrated that, after deep vein thrombosis, thrombus organization and recanalization occurs over a period of 6 months with increasing prevalence of reflux reaching 70%. Thus, the measurement of postthrombotic syndrome before 6 months is meaningless. In assessing postthrombotic syndrome, one should first consider the method of treatment of deep vein thrombosis and categorize patients in groups of similar categories according to treatment, extent of thrombosis, etc. In addition, we need a method of evaluating change in response to natural history or intervention. The CEAP classification is considered the gold-standard discriminative instrument that categorizes patients according to different stages of the disease. However, it is based on signs and it ignores symptoms. The Villalta scale is a mixture of patient-reported symptoms and clinician-rated signs. It is overly sensitive to mild postthrombotic syndrome. The venous clinical severity score is clinician-rated because, with the exception of pain, it is based on signs. It is associated with a high interobserver variability. It has been suggested that mild postthrombotic syndrome can be defined by a Villalta score of 5 to 14 with a venous clinical severity score a 4 to 7 and severe postthrombotic syndrome by a Villalta score ≥ 15 or ulcer with venous clinical severity score ≥ 8 . However, in the CaVenT study, where there was a 28% risk reduction in postthrombotic syndrome (Villalta score >4) ($P < 0.001$) in the catheter-directed thrombolysis group, there was no corresponding significant improvement in quality of life. It was concluded that we need better evaluation instruments for postthrombotic syndrome.

Post-thrombotic syndrome: need for a new instrument

Mark Meissner (US)

Although direct oral anticoagulants and extended therapy for unprovoked deep vein thrombosis have been proven very effective in reducing the incidence of recurrent deep vein thrombosis, recent randomized controlled studies have shown that graduated elastic stockings (SOX trial) and thrombolytic therapy for acute deep vein thrombosis (ATTRACT trial) are not effective in reducing the incidence of postthrombotic syndrome. In the SOX trial, which involved 806 patients, the primary outcome was based on the Ginsberg scale and the secondary outcome on the Villalta score. At 2 years, there was no difference between those with 30 to 40 mm Hg graduated elastic stockings and placebo (5 mm Hg

stockings). In the ATTRACT trial, which involved 692 patients with proximal deep vein thrombosis, the primary outcome was also based on the Villalta score. Postthrombotic syndrome was defined as a Villalta score ≥ 5 . At 1 year, there was no difference in the incidence of postthrombotic syndrome between the percutaneous catheter-directed thrombolysis group and the standard care group ($P=0.56$). However, in a subgroup analysis, it was found that, in patients with iliofemoral deep vein thrombosis, the incidence of moderate or severe postthrombotic syndrome (Villalta score >9) was lower in the pharmacomechanical catheter-directed thrombolysis group (17.9% vs 23.7%; $P=0.035$).

Were the failures in the above studies, a result of inappropriate study design or the use of inappropriate primary outcome measures? Postthrombotic syndrome is defined as the presence of chronic pain, edema, skin changes, and ulcerations occurring after an episode of deep vein thrombosis. The Ginsberg scale, which is based on pain and swelling is insensitive to mild postthrombotic syndrome. The Villalta score is based on (i) pain, cramps, heaviness, paresthesia, pruritus (patient-reported symptoms) and (ii) edema, induration, pigmentation, redness, ectasia, and calf tenderness (clinician rated). It is overly sensitive to mild postthrombotic syndrome. In contrast, with the exception of pain, the venous clinical severity score is entirely based on signs (pain, varicose veins, pigmentation, inflammation, induration, ulcer number, size, and duration). These instruments have not been validated for prospective studies and they do not capture typical postthrombotic syndrome complaints or their importance to patients. A direct comparison between the Villalta scale and the venous clinical severity score demonstrated that the Villalta scale overidentifies mild-to-moderate postthrombotic syndrome and underidentifies severe postthrombotic syndrome.

Mark Meissner concluded that recent large, randomized trials addressing the prevention of postthrombotic syndrome have largely been negative. It is possible that these interventions (elastic compression and thrombolysis) are truly ineffective. However, it is more likely that the trials are flawed by inappropriate patient selection, inappropriate interventions, or by using inappropriate outcome measures. What is urgently needed is the development of a validated, patient-important, and widely accepted outcome measure for postthrombotic syndrome. A moratorium on research addressing postthrombotic syndrome prevention should be considered until valid measures can be developed.

Management of the post-thrombotic syndrome - lessons learned

Paolo Prandoni (Italy)

There are four independent predictors of postthrombotic syndrome: excess body weight, residual vein thrombosis with development of popliteal valve incompetence, inadequate anticoagulation therapy, and development of ipsilateral recurrent deep vein thrombosis. A systematic review and meta-analysis of 8 studies involving 1577 patients demonstrated that the development of reflux increased the risk of postthrombotic syndrome by 34%. Three randomized control trials, involving 194, 100, and 518 patients, demonstrated that elastic compression following deep vein thrombosis reduced the development of the postthrombotic syndrome by 35% to 58%. However, a fourth randomized control trial, involving 873 patients, failed to confirm the benefit of elastic stockings. Methodological problems (self-reporting, wearing the stockings only 3 days per week) have brought the validity of the last study into question. More studies are needed. In patients in whom the international normalized ratio is <2 more than 50% of the time during the first 3 months

after deep vein thrombosis, the incidence of deep vein thrombosis and postthrombotic syndrome recurrence is 9 and 3 times higher, respectively, compared with patients with an international normalized ratio <2.0 less than 50% of the time.

PTS predictive factors - what do we know about?

Tomasz Urbanek (Poland)

Risk factors related to the patient's initial state include sex, age, obesity, and preexisting primary chronic venous disease. The latter is associated with a 2-fold increase in postthrombotic syndrome. High rates of postthrombotic syndrome have been reported after surgery, eg, 5.8% following abdominal surgery and 24% to 88% following knee replacement surgery). In a series of 376 patients followed-up after a single deep vein thrombosis episode, there was a strong association between the Villalta score in the leg after deep vein thrombosis leg and the Villalta score in the contralateral leg. Ipsilateral postthrombotic syndrome, defined as a Villalta score >4, developed in 116 (31.6%) patients, and, in 40% of these patients, the Villalta score in the contralateral leg was also >4.

Risk factors related to the initial characteristics of deep vein thrombosis can be symptomatic vs asymptomatic, massive proximal vs distal deep vein thrombosis, poor international normalized ratio control in the treatment phase, residual thrombus, and incomplete resolution of the symptoms at 1 month. The presence of proximal deep vein thrombosis increases the risk of postthrombotic syndrome by 2 to 3 fold. Treatment with low-molecular-weight heparin for 3 to 6 months is associated with a reduced incidence of postthrombotic syndrome compared with vitamin K antagonist therapy.

In conclusion, postthrombotic syndrome is still a challenging condition, a better method of scoring is needed, and it is still difficult to predict its occurrence, despite knowing some of the risk factors.

Does thrombolysis work in PTS prevention? Recent RCT results-ATTRACT trial data

Antonios Gasparis (US)

The CaVenT randomized control trial, which was published in 2012, involved 189 patients with iliofemoral deep vein thrombosis. Of these patients, 99 had anticoagulant therapy only and 90 had catheter-directed thrombolysis plus anticoagulant therapy (combination therapy). At 24 months, postthrombotic syndrome was present in 41% of patients in the combination therapy group and 56% in the anticoagulant therapy group ($P=0.047$). At 5 years, these figures were 43% vs 71% ($P<0.0001$) and the number needed to treat to prevent a postthrombotic syndrome in 1 patient was 4.

The ATTRACT trial, which was published in 2017, involved 691 patients with iliofemoral or femoropopliteal deep vein thrombosis. They were randomized to anticoagulant therapy or catheter-directed thrombolysis plus anticoagulant therapy (combination therapy). The primary outcome was defined as a Villalta score >4 or development of a venous ulcer or for unplanned endovenous procedure to treat symptoms 6 months after randomization. The secondary end points were the changes from baseline to 24 months in leg pain (Likert scale of 7 points), calf circumference, and health-related quality of life (SF36 and VEINES-QOL). At 24 months, the primary outcome was 47% in the combination therapy group and 48% in the anticoagulant therapy group ($P=0.56$).

A subgroup analysis of the 311 patients with iliofemoral deep vein thrombosis in the ATTRACT study showed the presence of postthrombotic syndrome (Villalta score >4) in 49% in the combination therapy group and 51% in the anticoagulant therapy group ($P=0.59$). However, moderate and severe postthrombotic syndrome (Villalta score >9) was present in 18% of patients in the combination therapy group and 28% in the anticoagulant therapy group ($P=0.021$). Severe postthrombotic syndrome (Villalta score >14) was present in 8.7% in the combination therapy group and 15% in the anticoagulant therapy group ($P=0.048$). In these subgroups, the mean Villalta score was 3.82 in the combination therapy group and 5.43 in the anticoagulant therapy group ($P<0.001$). At 30 days posttreatment, the mean reduction in pain score from baseline was -2.36 in the combination therapy group and -1.80 in the anticoagulant therapy group ($P=0.0082$). Mean quality of life scores at 24 months was 21.5 in the combination group and 16.2 in the anticoagulant therapy group ($P=0.043$) (Comerota AJ et al. *Circulation*. In Press)

Although the primary end point was not reached in patients with iliofemoral deep vein thrombosis compared with anticoagulant therapy, combination therapy resulted in: (i) a reduction in postthrombotic syndrome of any severity using the venous clinical severity score; (ii) a reduction in moderate/severe postthrombotic syndrome using the Villalta score; (iii) a reduction in severe postthrombotic syndrome using the Villalta score; (iv) a reduction in pain and swelling; and (v) an improved disease-specific quality of life. Thus, for those offering catheter-directed thrombolysis to patients with moderate/severe symptoms of iliofemoral deep vein thrombosis, the ATTRACT trial confirms the approach. Those who do not offer catheter-directed thrombolysis to their patients with moderate/severe symptoms, they should study the focused results of ATTRACT and seriously consider catheter-based thrombolysis.

Does anticoagulation work in PTS prevention?

Zbigniew Krasinski (Poland)

A recent publication used USA MarketScan claims from 2012 to 2015 to identify adults with the diagnosis of venous thromboembolism who were treated with rivaroxaban or warfarin. A total of 1463 patients treated with rivaroxaban and 26 494 with warfarin were followed for a mean of 16 ± 9 months (range, 4 to 39 months). The duration of anticoagulation was similar between the groups. Rivaroxaban was associated with a 23% (95% CI, 16 to 30) reduced hazard of postthrombotic syndrome compared with warfarin. In addition, rivaroxaban was associated with a significant risk reduction in calf pain and swelling compared with warfarin.

A 5-year follow-up analysis for the development of postthrombotic syndrome was performed in a registry of patients with deep vein thrombosis. Patients were admitted to the registry after completion of an anticoagulation period. A group of 167 patients received standard therapy of elastic compression, a second group of 124 patients received sulodexide, and a third group of 48 received aspirin. The incidence of postthrombotic syndrome was 14.9% at 1 year and 19.5% at 5 years in the standard-therapy group. It was 8.8% at 1 year and 12.2% at 5 years in the sulodexide group. It was 23.5% at 54 months in the aspirin group compared with 12.2% in the sulodexide and 18.2% in the standard therapy groups. Randomized controlled trials are needed to validate these results.

XXII. Diagnostics and treatment of the chronic pelvic vein disease and varicose veins of pelvic origin

Not all pelvic vein disease cases and varicose veins of pelvic origin are related to the same pathology (doubts and difficulties)

Małgorzata Mielnik (Poland)

Transvaginal and abdominal duplex ultrasound scanning can be used in diagnosing pelvic vein disorders, but, in most cases, transvaginal duplex ultrasound scanning is not mandatory to make the diagnosis. So far, we have been strongly focused on transvaginal scanning, but not all patients with abnormal transvaginal duplex ultrasound scanning are symptomatic. Ultrasound examination has many limitations; there are no strict criteria for assessing reflux, some portion of the vessels are invisible on duplex ultrasound scanning and many phenomena are functional (ie, depend on the body's position). Duplex ultrasound scanning still plays an important role assuming that a comprehensive assessment of a venous system is performed.

Transvaginal duplex ultrasound scanning is offered to women whose lower limb duplex results suggest a pelvic venous reflux and/or compression (in cases of pelvic congestion syndrome symptoms, recurrent/atypical varicose veins) or women who are referred by gynecologists with a suspicion of pelvic vein abnormalities with or without concomitant lower extremity varicose veins, symptomatic or asymptomatic. The examination is performed after the patient has been fasting overnight, with the patient in a supine position with the head elevated 45 degrees (semi-upright position), and with the use of a wide bandwidth (transvaginal, valvular L10-5, and convex C9-3).

Perhaps it is evident, but sometimes we forget that the venous vascular bed of the pelvis and abdominal cavity should be treated together as one unit because what we see in the pelvis is very often the result of what happens above the pelvis. During transvaginal duplex ultrasound scanning, we have to search for varicose veins in the uterine area, examine the distal part of the gonadal vein, and examine visible tertiary tributaries. During transabdominal duplex ultrasound scanning, we have to examine the inferior vena cava, search for anatomic and hemodynamic criteria of left renal vein compression, and examine the iliac vessels (flow direction in tertiary tributaries deserves attention).

When performing duplex ultrasound scanning in patients with pelvic congestion syndrome/pelvic congestion incompetence, we are looking for vein pathology, as well as all abdominal and pelvic structure variants/abnormalities contributing to symptoms of the disease. Comprehensive pelvic and abdominal venous vascular bed assessments must be performed because proximal abnormalities have an effect on distal vascular segments. Before the diagnosis of primary pelvic venous insufficiency is established, a careful evaluation of potential compression sources is necessary, including pelvic angle

inclination, abnormalities, and arterial variants (eg, aorta transposition, right renal artery ostial angle and increased diaphragm ligament tension) as sources of potential “venous entrapment.” Assessment of venous compression points is difficult and time consuming due to the temporary and functional nature of signs, often depending on the body's position. Mechanisms responsible for clinical symptoms are probably not due to compression and occlusion of the veins, but due to their functional, temporal compression. The fact that we do not see compression does not mean that it does not exist.

Pelvic vein disease with reflux and/or obstruction? VS diagnostic approach

Nicos Labropoulos (US)

Nicos Labropoulos introduced a standardized diagnostic approach for pelvic congestion syndrome. Pelvic congestion syndrome is one of the many causes of chronic pelvic pain and is often diagnosed based on exclusion of other pathologies. Over the past decades, pelvic congestion syndrome was recognized to be a more common cause of chronic pelvic pain. Multiple diagnostic modalities, including pelvic duplex ultrasonography, transvaginal ultrasonography, computed tomography, and magnetic resonance, were studied. In the current literature, selective ovarian venography, an invasive imaging approach, is believed to be the gold standard for diagnosing pelvic congestion syndrome. The described transabdominal technique takes all potential pathologies that can contribute to pelvic congestion syndrome into account and, in experienced hands, it can consistently identify the ovarian veins, as well as document their diameter and possible reflux. If successful, the patient can potentially avoid other expensive and time-consuming imaging modalities that may require ionizing radiation or intravenous contrast and undergo venography and coil embolization. Other tests, such as computed tomographic venography and magnetic resonance venography, may be useful when there is suboptimal imaging or limited experience with ultrasound.

How to decide when pelvic vein reflux is clinically relevant to the varicose vein and pelvic congestion syndrome occurrence?

Neil Khilnani (US)

Today, there is a need to review the medical nomenclature and use the term pelvic congestion disorder instead of the term pelvic congestion syndrome. It is logical because the term “syndrome” stands for a group of symptoms, when the underlying cause does not figure in, while “disorder” means distinguishing symptoms and signs, with an understood cause. The main indication is to treat the pelvic source: quality of life affecting pelvic pain due to abnormal pelvic venous physiology when alternative diagnoses are unlikely. There are no pathognomonic symptoms for pelvic congestion disorders. The rate of sensitivity/specificity of the most frequent symptoms in patients with chronic venous pain are not high: 71%/32% for increased pain while standing, 84%/26% for dysmenorrhea, 75%/21% for deep dyspareunia, and 79%/41% for postcoital pain. As the causes of pelvic pain are often due to different diseases, multidisciplinary care is important (with gynecology, psychiatry, physical therapy, pain management, urology, and vascular specialists) due to the secondary responses to chronic pain. In particular, conditions, such as depression, occur in 86% of women with pelvic pain and only 38% without it. Central sensitization (maladaptive pain perception secondary to CNS processing issue) often occurs and there may be irreversible pain, even when the cause of the pain is eliminated.

Of the women with pelvic congestion disorders, 51% had lower extremity varicose veins, but only 9% were related to escape point reflux. Therefore, lower extremity veins and symptoms can be successfully treated in most patients without a pelvic vein intervention.

An interventional treatment of the pelvic vein disease - tactics, practical advices, tips and tricks

Antonios Gasparis (US)

Treatment of pelvic vein disease should focus on the patient's clinical symptoms (pelvic pain, heaviness, dyspareunia, dysuria). There are two patterns of disease reflux (reflux in ovarian veins or internal iliac vein reflux due to testicular varices or a nonsaphenous vein) and obstruction. For the treatment of a nonsaphenous varicose vein, microphlebectomy, ultrasound-guided sclerotherapy, and especially fluoroscopy-guided sclerotherapy gives good results. Fluoroscopy-guided sclerotherapy delivers large volumes of sclerosant and reaches the periurethral venous plexus. For the treatment of ovarian vein reflux, Antonios Gasparis prefers a combined procedure. For the first step, he uses embolization of pelvic varicosities with a mixed solution of 3% sodium tetradecyl sulfate and contrast in a 1:1 ratio, sometimes using a 11.5 mm balloon. After that, he performs a coil embolization of the ovarian vein. For the left ovarian vein, he prefers the right common femoral vein access, and, for the right ovarian vein, the right internal jugular veins. He performs the same procedure for the internal iliac vein treatment (selective catheterization, balloon-occlusion sclerotherapy, and coil embolization).

Endovascular treatment: staged or simultaneous reflux ablation?

Radoslaw Pietura (Poland)

Radoslaw Pietura discussed how isolated embolization of the left ovarian vein alone is not enough to treat pelvic congestion syndrome, and, in many cases, 3 to 4 main veins in the pelvis need embolization as well, especially with combined damage to the veins of the pelvis and the lower extremities. He described his own experience where 100 patients were followed up for up to 4 years after embolization of the left ovarian vein (100%), right ovarian vein (91%), left internal iliac vein (98%) and right internal iliac vein (97%). In 39% of the patients, the treatment was done over 1 session and, in 61%, it was done over 2 sessions. The pain score was reduced from 7.2 to 1.2 in 43 patients (93%). Neck hematomas occurred in 4 patients, coil migration occurred in 1 patient, and small neck abscesses occurred in 8 patients. He advocated using a simultaneous approach where doctors try to embolize as much as possible because it is cheaper, faster, and more comfortable for patients than a staged procedure.

Pelvic vein incompetence, unknown aspects & challenging situation and technical difficulties

Louay Altarazi (Syria)

Louay Altarazi presented some complicated cases of pelvic congestion syndrome treatment, including Nutcracker syndrome, anatomy variations and ovarian vein anomalies, dangerous anatomy (close disposition of pelvic varicose veins and magistral trunk, such as the iliac vein), urinary tract compression, reanalyzed sciatic vein, huge veins, ovarian veins thrombosis, male pelvic congestion, and even a case with the worst technical complications.

Sclerotherapy of the pelvic origin varicose veins without embolization of the pelvic vein - does make sense?

Eberhard Rabe (Germany)

Atypical varicose veins without saphenofemoral or saphenopopliteal reflux may develop in the vulvar or pudendal area in women. Reflux in these varices may be connected to insufficient pelvic veins. In the most of the cases, the left ovarian vein or the hypogastric veins are involved. Venous obstruction or a local pathology is another (rare) reason for this condition. Many of the affected women are multiparous and such veins develop during pregnancy and are located only in the genital, pudendal, or proximal thigh area. Only a few case reports and case control series have been published concerning the treatment of vulvar or pudendal atypical varicose veins and no prospective randomized studies comparing different treatment options are available. The benefit of embolization of pelvic veins in patients without pelvic congestion syndrome was not demonstrated in randomized control trials comparing the results with atypical varicose vein treatment by phlebectomy or sclerotherapy alone. Therefore, embolization should only be used in a well-established indication. Embolization should be recommended in pelvic congestion syndrome due to ovarian or pelvic vein reflux with or without vulvar, pudendal, or leg atypical varicose veins. Foam sclerotherapy or phlebectomy without embolization of the ovarian vein shows good results in patients with atypical varicose veins of pelvic origin. Embolization should be considered in symptomatic cases with recurrent varicose veins after treatment even if no pelvic congestion syndrome is present. Randomized comparative studies comparing embolization on incompetent pelvic veins and sclerotherapy of atypical varicose veins with pelvic origin should be performed.

Sclerotherapy can be enough for varicose veins of pelvic origin

Lorenzo Tessari (Italy)

According to Lorenzo Tessari, at least 45% of varicose veins of the great saphenous vein do not originate from the saphenofemoral junction. In spite of a complete saphenofemoral junction and great saphenous vein truncular continence, other kinds of reflux coming from the groin or from the perineal and/or gluteal region can occur. The frequency of pelvic reflux is consistently increased from 5%, 20%, 45%, 65%, and 80% for no pregnancy, 1, 2, 3, and 4+ pregnancies, respectively. According the Franceschi classification, there are 6 points of pelvic reflux: (i) point I (groin) – round ligament vein origin; (ii) suprapubic origin (spontaneous “Palma”); (iii) point P (perineal) – internal pudendal vein origin; (iv) obturator vein origin; (v) ischiatic vein/inferior gluteal vein origin; and (vi) clitoral vein origin. The frequency of reflux is 12% for point I, 1% for suprapubic veins, 13% for obturator veins, 24% for ischiatic vein/inferior gluteal vein, 2% for the clitoral vein, and 48% for point P. It is possible to use foam sclerotherapy to treat each reflux variant (Lorenzo Tessari prefers 2% and 3% sodium tetradecyl sulfate) with good long-term results (88% complete obliteration after 13 years).

XXIII. Keynote lectures

Chronic pelvic vein disease 2019 update: what do we know? what we do not know?

Mark Meissner (US)

Pelvic venous disorders in women can present as chronic pelvic pain, lower extremity and vulvar varicosities, lower extremity swelling and pain, and left-flank pain and hematuria. Multiple evidence gaps exist regarding chronic pelvic disease with the consequence that nonvascular specialists rarely consider the diagnosis. Mark Meissner started his lecture by pointing out that the term “pelvic congestion syndrome” is nonsense and it should be abandoned in favor of “chronic pelvic venous disorders.” Indeed, he highlighted that the term “syndrome” is imprecise, misleading, and could result in inappropriate treatment and poor treatment outcomes. Pelvic venous disorders can include four different clinical presentations: chronic pelvic pain (pain, dyspareunia, dysuria); pelvic varices (gluteal, perineal, vulvar); renal symptoms (flank, pain, hematuria); and leg symptoms (pain, swelling). Two patterns of primary reflux (ovarian and internal iliac reflux) and two patterns of obstruction (iliac vein or left renal vein) can be distinguished. The obstruction patterns can determine, in turn, a secondary reflux either in the internal iliac vein or in the ovarian vein. All of the symptoms seem to be related to distension of the abdominal and pelvic venous reservoir. All reflux and obstruction can occur according to two patterns: uncompensated (no outflow from the distal reservoir) or compensated (collateral outflow from the distal reservoir). However, these mechanisms can all coexist, so patients can manifest similar symptoms with concordant mechanisms or similar symptoms with discordant mechanisms. Therefore, four interconnected systems (left renal vein, ovarian veins, internal iliac veins, and great saphenous veins) and two abdominal-pelvic reservoirs (renal hilum and pelvis) should be considered. Symptoms are usually related to reservoir distension and different patterns of reflux or obstruction can produce identical reservoir distension and symptoms. In uncompensated reflux or obstruction, pressure is transmitted to the distal reservoir. In compensated reflux or obstruction, pressure is decompressed via the collaterals.

Pelvic venous embolization is now recognized as the procedure of choice in the treatment of pelvic venous disorders. However, despite the efficacy of pelvic venous embolization, data from literature¹ suggests that 6% to 31.8% of patients do not get substantial relief from the procedure. Potential explanations for an inadequate response to treatment include patient variability, procedural variability, and inadequate outcome measures. Relevant patient factors may include a differential response of individual symptoms to treatment, underlying psychosocial issues, as coexisting depression or anxiety, and issues related to the processing of chronic pain. Regarding the latter, the role of altered pain processing in pelvic venous disorders is underappreciated and poorly understood. There are at least some data suggesting that substantial differences may occur in central pain processing among patients with chronic pain syndromes.²

Mark Meissner concluded his presentation by mentioning recent scientific efforts related to this topic. Indeed, the Society of Interventional Radiology Foundation funded a Research Consensus Panel in 2018 to prioritize a research agenda to address the gaps related to pelvic venous disorders.³ A panel of experts, representing several societies of physicians involved in the care of pelvic venous disorders, identified, as the most important research topics, the development of a consensus on the clinical and imaging criteria for pelvic

venous disorders, a CEAP-like discriminative tool to categorize patients with pelvic venous disorders, quality of life tools to measure the health burden in women affected by pelvic venous disorders and its change after treatment with disease-specific outcome measures.

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From understanding chronic venous ulceration to effective treatment

Alfred Obermayer (Austria)

Intractable venous leg ulcers are still common, painful, quality of life reducing, expensive and cause amputations despite lots of research, studies, recommendations, and guidelines. Alfred Obermayer asked why all “venous ulcers” without exception are located below the knee. The answer is because of gravity and hydrostatic pressure. Due to gravity, everything on earth is pulled or pushed down. Hydrostatic pressure in healthy skin does not strain the microcirculation of the skin. Contrary, hydrostatic pressure in insufficient veins may strain superficial side branches of the capillaries and interstitium of the skin. The thoracoabdominal pump is central to venous return. Obese people have chronic venous insufficiency despite competent valves. Dependency syndrome can cause “hydrostatic ulcers.” An ulcer is a symptom of gravity and consequently strategies against gravity are required.

Alfred Obermayer presented his study on active bed rest as an accompanying therapy for the successful surgical treatment of venous leg ulcers. A venous ulcer is defined as an open skin lesion of the leg or foot that occurs in an area affected by venous hypertension and shows little or no tendency to spontaneous heal. He compared the results from the ESHAR and EVRA studies with his own results, showing that the ulcers included in his study were bigger, deeper, and more chronic, and patients with ankle-brachial pressure index <0.85 were not excluded.

In addition, Alfred Obermayer discussed his work on lateral fasciectomy sparing the superficial peroneal nerve with a simultaneous mesh graft in nonhealing lateral leg ulcers of diverse vascular origin. Surgery of the ulcer includes debridement, shaving, fasciectomy, and mesh grafts. Data in the literature has shown that “single-shot surgery” is also effective in mixed ulcers. Venous ulcers are complicated by direct causes, such as locoregional venous hypertension, and aggravating risk factors, such as obesity, edema, contact sensitization, diabetes, cerebrovascular insufficiency, chronic peripheral arterial disease. Arterial revascularization in mixed ulcers does not reduce local venous hypertension, but abolition of the responsible incompetent reflux routes does reduce the venous hypertension.

Alfred Obermayer finished his lecture by recommending experienced patient-tailored therapy for chronic venous ulceration.

“Thrombosis” after sclerotherapy: is it the same as a “classical” venous thrombosis?

Kurosh Parsi (Australia)

Kurosh Parsi discussed the question of whether thrombosis after sclerotherapy was the same as a “classic” venous thrombosis. “Thrombi” postsclerotherapy can be divided into four types: (i) sclerothrombus, which is a fibrin thrombus formed as a direct effect of sclerosant on blood; (ii) scleroagulum, a semiliquid material that contains fibrin thrombi, hemolyzed blood, and other sclerosant by-products; (iii) venous thrombosis (true venous thrombosis); and (iv) venous sclerosis, a fibrosis of superficial or deep veins. Sclerothrombi are the only direct effect of sclerosants.

Coagulation studies have shown that low concentration detergent sclerosants activate platelets and induce the release of procoagulant microparticles, soluble P-selectin, and serotonin (sodium tetradecyl sulfate). Detergent sclerosants are biologically active at low, sublytic concentrations. Detergent sclerosants are surfactants that are amphiphilic compounds with a hydrophilic (polar) head and a hydrophobic (nonpolar) hydrocarbon tail. Surfactants have a similar structure to phospholipid molecules. Low-concentration detergent sclerosants activate platelets and consequently coagulation. Activated endothelial cells are responsible for angiogenesis and matting, activated mast cells are responsible for vasodilatation and matting, and activated leucocytes are responsible for inflammation and phlebitis. High sclerosant concentrations (>0.15%) reduce lysed platelets (both sodium tetradecyl sulfate and polidocanol), reduce fibrinogen (sodium tetradecyl sulfate), reduce clotting factors (sodium tetradecyl sulfate), and inhibit clot formation (both sodium tetradecyl sulfate and polidocanol), with a stronger effect with sodium tetradecyl sulfate. Low sclerosant concentrations (0.075% to 0.1%) increase platelet activation and increase clot formation.

Parsi concluded by stating that a low final concentration of sclerosant has procoagulant activity via inflammation and thrombosis with the formation of sclerothrombus (acute closure) and later recanalization or fibrosis (permanent closure). A high final concentration of sclerosant has anticoagulant activity via inflammation, but no thrombosis with nonthrombotic occlusion and formation of scleroagulum or fibrosis (permanent closure).

II

Charing Cross International Symposium

Vascular & Endovascular Challenges Update



April 15th-18th 2019, London – UK



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I. Venous and lymphatic challenges: superficial veins

Foam sclerotherapy can replace phlebectomy for the management of varicosities

Claudine Hamel-Desnos (Caen, France)

A review of the literature on truncal vein ablation showed no difference in terms of recurrences between concomitant and delayed treatment; moreover, Sutton et al¹ showed that deep vein thrombosis occurred more when concomitant phlebectomy is performed. International guidelines are not all in accordance. An important factor for foam sclerotherapy is a relevant choice of access site. Key points before starting are disconnection of the large tributaries and a precise duplex ultrasound examination. Sclerotherapy is possible for large veins remaining dilated at the end of the procedure; however, the doses are decreased because of the inflammation caused by thermal ablation. A “wait and see” option is preferable, especially for the elderly; in fact, Claudine Hamel-Desnos recommends waiting 3 to 6 months for most patients. One of the indications where sclerotherapy can replace phlebectomies is when the subcutaneous part of an anterior accessory saphenous vein is implicated. Some physicians prefer phlebectomies because of the fear of thrombophlebitis. In the management of tributaries, there is no strong evidence supporting the superiority of the options, such as concomitant or delayed sclerotherapy and/or phlebectomies. Hamel-Desnos states that minimal sclerotherapy is a credible option and all extensive treatments of tributaries should be avoided. A new paradigm may be that glue will change habits and make phlebectomies disappear as Dr Kathleen Gibson stressed in her talk.

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The benefit of non-thermal modalities

Steve Elias (Englewood, NJ, US)

Emerging endovenous technologies are divided into either thermal tumescent ablation or nonthermal nontumescent ablation. Thermal tumescent ablation techniques are subdivided into three categories, ie, radiofrequency ablation, laser ablation, and steam ablation, while nonthermal nontumescent ablation techniques are subdivided into mechanochemical (Clariven, Flebogrif), cyanoacrylate, and endovenous foams (polidocanol endovenous microfoam, Varithena) we are waiting for the results on hyaluronic acid (HIFU). When we focus on nonthermal nontumescent ablation, it looks beneficial for patients (less pain, faster, lower risk), for doctors (faster, lower risk), families (faster return to normal activities), and society (faster return to work). Tumescent is the most discomforting aspect of thermal tumescent ablation, the hardest part to learn, and the most time-consuming aspect. As of 2019, the rules for venous ablation can be outlined as follows: treat the lowest point of incompetence, to treat closer to the point of

incompetence, and to increase the implementation of techniques, such as tributary and perforator ablation, for later stages of the disease. The application of these rules can be done while minimizing injury to nerves and skin. Benefits of the technique depend on the size, length, location, the neighboring nerves, surrounding tissues, and veins, disease state, and the patient type. Below the knee is challenging due to (i) the number of nerves (including saphenous, sural, tibial, and peroneal nerves); (ii) the sensory nerve location due to the proximity of the veins to the skin, which is the end organ to be damaged; and (iii) the difficulty in visualizing the veins in patients with clinical class C₅ and C₆. Especially in advanced disease states, tumescence is difficult from the great saphenous vein or small saphenous vein to the ankle and because of the feasibility of retrograde use, nonthermal nontumescent ablation methods should be preferred in the ulcer bed. As no nerve injuries are reported with nonthermal nontumescent ablation in the suprafascial part of the veins, it should be the preferred technique. The future of endovenous ablation is nonthermal nontumescent ablation technologies.

Technique and strategy are as important as modality in the treatment of superficial reflux

Manj Gohel (Cambridge, UK)

Older patients with more advanced disease are more likely to have recurrent veins and deep venous disease. Patient preference, patient variation, and the importance of below-the-knee great saphenous vein reflux must all be taken into consideration before performing a procedure. Better quality of life improvements and lower reintervention rates were obtained with both above- and below-the-knee ablations. Truncal ablation alone may be adequate for some patients, as varicosity treatment is associated with potentially serious complications. However, residual varicosities may be considered a treatment failure by the patient. There may be an argument for prophylactic ablation of a clinically insignificant anterior accessory saphenous vein. Significantly lower procedural pain scores were obtained when using buffered tumescence. Controversial areas can include the following: (i) treatment of perforators; (ii) treatment of superficial venous reflux in patients with a chronic venous disease classification of C₃; (iii) when and how to investigate the obstruction; and (iv) treatment of superficial reflux in patients with a mixed-etiology disease. In conclusion, the enormous choice of endovenous modalities should not distract from important strategic and technical factors. The incompetent below-the-knee segment should be ablated when feasible. These interventions remain more of an art than a science.

VeClose extension study five-year results

Nick Morrison (Scottsdale, AZ, US)

The VenaSeal™ closure system uses an advanced nonthermal nontumescent venous ablation therapy that has no risk of thermal injury, with a rapid return to normal activity, and no need for postprocedural compression stockings. The eSCOPE study, a prospective, multicenter study that included 7 European sites, assessed the safety and efficacy of this system with follow-up visits at day 2 and months 1, 3, 6, 24, and 36. The VeClose trial, a US multicenter, randomized controlled study conducted under investigational device exemption, assessed the safety and efficacy of this system for the treatment of lower extremity truncal reflux compared with radiofrequency ablation. The trial assessed the noninferiority of anatomical closure at 3 months in 242 subjects and 10 sites with follow-

up visits at day 3 and months 1, 3, 6, 12, 24, and 36. The WAVES trial, a postmarket evaluation of the VenaSeal™ closure system conducted in a single center in the US with 5 providers, assessed vein closure, venous clinical severity score, Aberdeen Varicose Vein Questionnaire, pain, and return to normal activities and work in 50 subjects with follow-up visits at week 1 and months 1, 3, and 12.

The VeClose 5-year follow-up extension study was conducted to continue assessing the safety and efficacy of this system for the long-term effect on closure of the great saphenous vein with a follow-up 5 years after the index procedure enrolment in the VeClose study; 89 patients completed the 60-month visit. The primary outcome measure was complete closure and the secondary outcome measures were venous clinical severity score (VCSS), Aberdeen Varicose Vein Questionnaire (AVVQ), EuroQol-5D (EQ-5D), clinical, etiological, anatomical, and pathophysiological (CEAP) classification, satisfaction with treatment, adverse events, and adjunctive procedures. Baseline demographics were similar in both groups. Closure rates were sustained over the long term, with no new failures reported and noninferiority demonstrated through 60 months. Of the patients treated with the VenaSeal closure system, 53 maintained a closure rate of 94.6% at 60 months. Long-term durability in the group randomized to the VenaSeal closure system has been demonstrated with a closure rate of 93.6% at 60 months. The signs and symptoms associated with venous reflux disease (VCSS) improved over time, which was maintained through 60 months. There was a 55% reduction in the signs and symptoms in the VenaSeal closure system group vs 67.5 in the radiofrequency ablation group. Subjects reported a slight improvement in their current health state over time through 60 months with a 22% and 15% increase from baseline in VenaSeal closure system and radiofrequency ablation groups, respectively. Fewer subjects were classified as CEAP C_{3-4b} at 60 months than at baseline in the VenaSeal closure system group. All 47 patients in the VenaSeal closure system were somewhat or very satisfied with treatment at the 60-month follow-up, with 93.6% stating that they would definitely choose the VenaSeal closure system again. No long-term sequelae were reported in this cohort for VenaSeal closure system and radiofrequency ablation between the 36-month and the 60-month follow-up.

Post-procedure care after cyanoacrylate glue closure

Kathleen Gibson (Bellevue, WA, US)

An ideal patient can be defined as young with a healthy lifestyle, active, able to don compression stockings, eager to be back to work at once, and primarily with CEAP C₂ disease. However, today's patients are elderly with limited mobility, have difficulty donning compression stockings, need to maintain mobility and strength by walking right away, and have comorbidities and advanced venous disease. Kathleen Gibson's aftercare for endothermal ablation includes not stopping anticoagulation (except in cases where there is bruising while on anticoagulation), using compression for up to 2 weeks, going back to work the next day, waiting to work out for 48 hours, using nonsteroidal anti-inflammatory drugs for analgesia, and not driving the same day if not taking sedatives. On the contrary, they can start driving the next day. For cyanoacrylate glue closure aftercare, she suggests immediate ambulation, not stopping anticoagulation if the patient is already taking them, usually no compression is needed, going back to work the same day, no restrictions on working out, taking nonsteroidal anti-inflammatory drugs for analgesia, and not driving the same day. She defines her usual follow-up procedure as to stage treatment of the

tributaries/branches and perform a duplex ultrasound at the end of the case. The follow-up visit at 1 to 2 weeks and at 3 months consists of assessing for complications and tributaries and using duplex ultrasound as indicated. Potential common complications can include infection, deep vein thrombosis, phlebitis of a truncal vein, and phlebitis/thrombosis of tributaries. Complications unique to cyanoacrylate glue closure can be systemic allergy, hypersensitivity reaction, and retained foreign body (glue in SQ [ethyl cyanoacrylate adhesive]).

VeClose (VenaSeal saphenous CLOSure system vs radiofrequency ablation for incompetent great saphenous veins) and WAVES (Lake WASHINGTON Vascular VenaSeal Post-Market Evaluation) are the first two trials evaluating cyanoacrylate glue closure. Both trials noted that some patients developed a self-limited cutaneous/dermal reaction within the first several weeks after the procedure, a reaction not typical for the one seen after the endothermal ablation. In the WAVES trial, patients with a reaction did not experience an impact on their return to work, normal activities, or pain scores at 1 month, but higher at 1 week. Kathleen Gibson presented her single-site VeClose trial, WAVES trial, and retrospective chart review from 2016 to 2018. Hypersensitivity was defined as a distinctive dermal reaction with erythema, itching, and variable edema and/or pain, where mild reactions required steroids, and severe and recurring reactions lasting more than 30 days required removal of the vein. No patient had a hypersensitivity reaction after treating the second limb if no reaction was observed after treating the first limb. A severe reaction was one with a recurrent rash and, in this case, the vein was excised with ultrasound guidance via small incisions. In Kathleen Gibson's protocol, important steps to take are screening for an adhesive allergy, waiting a full 30 seconds after the last injection before removing the catheter, resheathing the delivery catheter prior to removal, and testing selective skin patches. Hypersensitivity reactions occurred in 6% of patients treated with cyanoacrylate glue, but the majority of cases were mild and self-limited. Patients classified as CEAP C₄₋₆ showed a decreased reaction. Previous cyanoacrylate treatment was not a predictive factor for a hypersensitivity reaction. The value of screening/skin testing was not proven, but it was used selectively in this cohort.

The evolution of superficial venous management has moved away from thermal techniques

Kursat Bozkurt (Istanbul, Turkey)

Available alternatives to nonthermal nontumescent ablation are foam, mechanochemical ablation, and cyanoacrylate glue. If you take a close look at foam, it has a similar complication profile to that of endovenous laser ablation, radiofrequency ablation, ultrasound-guided foam sclerotherapy, and stripping, but foam has a 25% lower occlusion rate compared with the others. Neurologic events reported make this method less attractive. In other reports, no difference in Aberdeen Varicose Vein Questionnaire (AVVQ), venous clinical severity score (VCSS), EuroQol-5D (EQ-5D), and short form 36 (SF36) were reported. Varithena® may overcome the inconsistency of physician-compounded foam, but its use is limited due to a fixed concentration and cost. Clinical trials have demonstrated equivalent or better efficacy and safety outcomes compared with physician-compounded foam.

Studies analyzing mechanochemical ablation revealed a 92%, 90%, and 87% anatomic success at 1, 2, and 3 years, respectively. Clinical success at 3 years was 83%. The AVVQ and SF36 scores showed improvement, and a significant deterioration was observed in VCSS between 12 and 36 months, which was accompanied by a worsening of disease-

specific and general quality of life. On the contrary, 3-month closure rates for glue were reaching up to 99%, compared with 96% for radiofrequency ablation. Pain scores were mild and similar between treatment groups. At day 3, less ecchymosis in the treated region was present after cyanoacrylate glue adhesion compared with radiofrequency ablation. In the VeClose trial, the complete closure rates at 3 years were 94.4% for VenaSeal and 91.9% for radiofrequency ablation. Studies conducted to show the efficacy of VenaBlock revealed a 99.4% occlusion rate at the 12-month follow-up, and the VCSS and AWQ scores decreased significantly.

In another study conducted for VenaBlock in 573 patients, no adverse events were observed, including deep vein thrombosis, pulmonary embolism, and paresthesia. The clinical recurrence-free rate at 2 years was 99.38% and the VCSS and AWQ scores decreased significantly. An analysis of 7 studies that included 1000 limbs and consisted of 53 cases of small saphenous vein involvement revealed an average procedure duration of 11.7 minutes, an occlusion rate at 12 and 30 months of 96.8% and 94.1%, respectively. Another study with 456 patients compared n-butyl cyanoacrylate, radiofrequency ablation, and endovenous laser treatment showed that, at the 2-year follow-up, n-butyl cyanoacrylate appeared superior with respect to periprocedural pain, time to return to work, and a decreased VCSS. For the small saphenous vein, endovenous laser treatment showed higher pooled anatomic success rates compared with surgery, while neurologic complications were also lower in the endovenous laser treatment group.

Questions regarding nonthermal nontumescent ablation emerged due to a lack of long-term data about the occurrence of phlebitis, granuloma, and long residual stumps. Phlebitis seems to occur less frequently with Turkish glue (4.5%) compared with VenaSeal (14% to 20%), which can be explained by the composition of n-butyl cyanoacrylate, the continuous delivery method, and the fast polymerization that allows getting cyanoacrylate into each cm of the vein to leave no empty space without glue and no residual blood inside the vessel. Kursat Bozkurt stated that they had full reimbursement for glue for over 5 years in Turkey. The overall experience in Turkey and in other countries (>27) is around 8000 cases with no reported granuloma, albeit long-term data is necessary.

3RF trial: randomised trial of three radiofrequency devices for great saphenous vein ablation

Isaac Nyamekye (Worcester, UK)

The 3RF study was conducted to compare the clinical efficacy of Venefit, radiofrequency-induced thermal therapy device (RFiT[®]), and endovenous radiofrequency (EVRF) in a randomized controlled trial. The radiofrequency energy delivery protocol was defined for these three modalities according to the size of the vein to be ablated. Postoperative treatment management was immediate ambulation, discharge after 30 minutes, compression stockings for up to 2 weeks, and recording pain scores for 7 days. The primary outcome was great saphenous vein ablation, and the secondary outcomes were complications, treatment time, 7-day pain scores, health-related quality of life (EuroQol-5D [EQ-5D] and Aberdeen Varicose Vein Questionnaire [AVQ]). Venefit and RFiT resulted in a 100% and 98% ablation, respectively, at 6 months, whereas EVRF resulted in inferior ablation rates (21% failure at 6 months). EQ-5D and AVQ did not differ at 12 months. Existing EVRF users should take special measures for consent and must study and audit their outcomes. One should be more critical before accepting new unproven endovenous technologies into clinical practice.

Current theories on indications and techniques for perforator ablation

Kathleen Gibson (Bellevue, WA, US)

In the US, up to 6 million patients with venous disease per year account for 70% of leg ulcers. The direct costs of leg ulcers reach close to 2.5 billion US dollars per year, while indirect costs include time off work for wound care and disability. Substantial evidence supports a role for incompetent perforator veins in chronic venous insufficiency. Approximately, two-thirds of limbs with skin changes have incompetent perforator veins as well as superficial or deep reflux; 63% of recurrent varicose veins are associated with incompetent perforator veins. A pathologic incompetent perforator vein is described as having an outward flow ≥ 500 msec, a diameter ≥ 3.5 mm, and a location that is beneath a healed or open venous ulceration.

The Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) guidelines suggest ablating incompetent superficial veins and perforator veins, as well as using compression therapy to aid in ulcer healing and prevent recurrence in grade 2C patients with ulcers. In patients at risk for an ulcer (C_{4b}) or a healed ulcer (C₂), the guidelines suggest ablating the incompetent superficial veins to prevent ulcer development or recurrence. Perforator ablation can be performed simultaneously or staged if still incompetent on reevaluation with grade 2C patients. Treatment options are the Linton procedure, subfascial endoscopic perforator surgery, direct perforator ligation, percutaneous radiofrequency ablation, percutaneous laser ablation, foam sclerotherapy, and nonthermal ablation. Radiofrequency ablation for an incompetent perforator vein delivers bipolar radiofrequency energy to the treatment site. Laser ablation for incompetent perforator veins can go directly through a needle or sheath (method supported by data from the SECURE trial [SeCure Endovenous Laser Treatment Study]). Key points to preoperative duplex assessment imaging are positioning the patient in a supine position with reverse Trendelenburg to dilate the perforator veins, performing medial or lateral imaging from the malleolus to the knee (longitudinal orientation shows a path of tortuous perforators and assists with access, alternates between cross-sectional and longitudinal views, often one or several perforators underneath or adjacent to active ulcers), and marking of the incompetent perforator veins on the skin where they penetrate the fascia. Local tumescence is injected to surround the perforator. Drawbacks to endothermal techniques can include nerve injury, arteriovenous fistula, difficulty in positioning once tumescence is in, the need for more tumescence in case of pain, and nonsatisfying closure rates. Possible complications are thrombosis, pulmonary embolism, foot drop/nerve damage, skin burn, phlebitis, hematoma, arteriovenous fistula, and infection. The usefulness of cyanoacrylate and polidocanol endovenous microfoam can be explained by the avoidance of tumescence in damaged skin and avoidance of nerve injury for below the knee procedures. Kathleen Gibson's personal experience includes 30 perforators in patients with advanced disease with 100% technical success at the day of the procedure. The CAPE feasibility study (Cyanoacrylate Adhesive Perforator Embolization) of cyanoacrylate for incompetent perforator veins included 33 perforators, which showed a 76% closure rate; there were 2 infections and no deep vein thromboses. The potential for proprietary foam arises from the truncal ablation with branch treatment, possible direct perforator injection, ulcer bed treatment, and an ongoing clinical trial.

In conclusion, the current guidelines suggest a role for incompetent perforator vein ablation in patients with pathologic perforator veins. Closure rates remain lower for incompetent perforator veins compared with truncal veins. Nonthermal techniques may offer some advantages over thermal techniques.

II. Advanced venous disease session

Role of elevated central venous pressures in chronic venous insufficiency

Raghu Kolluri (Columbus, OH, US)

Marked changes in intrathoracic pressure lead to decreased intrathoracic pressure, resulting in central hypovolemia (from pulmonary vasoconstriction) and an increase in peripheral fluid retention. Intermittent nocturnal right ventricular failure leads to venous pressure within the lower extremities and manifests as edema. Activation of the renin-angiotensin-aldosterone system leads to periodic left ventricular dysfunction during apnea and results in lower extremity edema. Apneic episodes increase systolic blood pressure during sleep, which leads to left ventricular diastolic dysfunction and peripheral edema. The relationship between obesity and edema was analyzed in 20 ambulatory patients with severe chronic venous insufficiency (CVI) and a mean body mass index of 52; 25 limbs had venous ulcers. An ultrasound analysis revealed no evidence of venous insufficiency in 75% of the patients. Elevated central venous pressure by echocardiogram in patients with CVI was evaluated. Every patient underwent a duplex ultrasound to assess reflux and a simultaneous and limited echocardiogram. Demographics revealed body mass index and other important causes that may result in edema and CVI, including obstructive sleep apnea (OSA) documented in the past medical history. Diabetes, older age, and right-sided CVI symptoms may be clues to trigger a work up and treatment of elevated central venous pressure in patients presenting with a diagnosis of CVI. In conclusion, patients with a diagnosis of CVI cannot ignore the 22.7% and 26% prevalence of elevated central venous pressure and OSA, respectively; when summed, 40% have either OSA or a moderate-to-severe risk for underlying OSA.

Chronic venous hypertension: what to do when there is no venous disease to treat

Sergio Giancesini (Ferrara, Italy)

A study about hemodynamic changes in iliofemoral disease revealed higher, but variable pressure values in patients with postthrombotic syndrome compared with the control patients. Raju¹ studied peripheral venous pressure before and after iliac vein stenting and noted that 12 mm Hg iliac pressure gradients were pathological and showed that, before stenting, the pressure did not correlate with the stenosis area, while, after stenting, 55% of patient's pressure improved or normalized. In general, foot venous pressure measurements showed a good correlation with clinical severity and degree of venous reflux. Although dorsal foot venous pressure may be normal, deep venous pressure may decrease or even increase. Ron Eifel² showed that mean walking pressure and walking pressure fall were more reliably associated with anatomic distribution of reflux and the clinic severity of chronic venous insufficiency than the gold-standard ambulatory venous pressure and 90% recover time. Sergio Giancesini's group showed an elevation in the circulating cytokine-chemokine profile in chronic venous disease, while they are downregulated after intervention and elevated again during recurrence. Bergan,³ in his study for venous active drugs, showed that there is no solid evidence for drugs to protect venous hypertension from becoming venous disease. Horner⁴ pointed out the value of graduated compression stockings for deep venous insufficiency as ambulatory venous

pressure was reduced by 20% to 30%. Again, Sergio Giancesini's group showed the beneficial effects of aquatic exercise on reducing chronic lower limb edema.

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III. Deep venous system session: chronic venous outflow/ obstruction/ acute DVT treatment/ deep venous reflux

Optimizing pathways for acute DVT treatment

Prakash Saha (London, UK)

Deep vein thrombosis (DVT) is a common medical condition that occurs in 1 UK resident out of 1000 every year, and the iliofemoral venous segment is involved in 10% to 15% of cases. DVT results in a postthrombotic syndrome in 30% of all cases and costs the National Health Service about 1 billion pounds per year. Improving the outcomes of DVT requires providing appropriate management of these patients in an ambulatory setting with around-the-clock ultrasound imaging and early initiation of anticoagulation, as well as detecting those patients who require an interventional treatment. Three issues are essential to the optimization of acute DVT treatment: identification, management, and surveillance. The most important aspects of identifying DVT involves an appropriate use of the Wells score and D-dimer analysis, providing ultrasound examination within 4 hours if the clinical probability is high, and having access to cross-sectional imaging, such as CT and MR venography (MRV), especially in patients with iliocaaval DVT. Modern MRV with special data processing not only verifies the diagnosis, but also assesses the age of the thrombus, which distinguishes acute and chronic venous obstruction and predicts lysis ability. The most important points of DVT management involves providing adequate information to the patients (including the use of special smartphone applications), conservative management with appropriate limb elevation, elastic compression, and low-molecular-weight heparin, vitamin K antagonists, or direct oral anticoagulants, as well as thrombophilia testing and cancer screening. The interventional options, such as catheter-directed thrombolysis, pharmacomechanical thrombectomy, intravascular ultrasound, venous stenting, and hybrid surgery, should be used in all appropriate patients at the high-volume centers. To choose the right patient for catheter-directed thrombolysis, certain factors should be taken into account, such as bleeding risk (B), life expectancy (L), anatomy (A), severity (S), and timing (T) of DVT (ie, according to the BLAST tool). The venous stenting and robust anticoagulation protocol are crucial after an interventional treatment. Treatment outcome surveillance depends on good hematological management (duration and type of anticoagulation), ultrasound follow-up for vein patency by choosing appropriate criteria for reintervention and long-term clinical outcomes assessment using the Villalta score and patient-reported quality of life scores. Finally, optimal DVT treatment could be carried out by the multidisciplinary team and involve primary care, nursing specialists, ultrasonography specialists, interventional radiologists, hematologists, and vascular surgeons.

Optimal outcomes assessment after acute DVT thrombolysis

Raghu Kolluri (Columbus, OH, US)

The outcomes after deep vein thrombosis (DVT) contain end points and factors that influence the end points. The general requirements for a proper end point include measurability and clinical relevance for physicians as well as for patients. The main efficacy outcomes for acute iliofemoral DVT may include immediate relief of symptoms, absence of long-term sequelae, and recurrences. Immediate symptoms could be measured by leg pain scores, leg circumference, and functional tests, such as a 6-minute walk test or time on the treadmill. The immediate anatomic outcomes may be assessed with a venographic Marder score, intravascular ultrasound of the ilio caval DVT, or by duplex ultrasound and specific obstruction scores (venous segmental disease score) in femoropopliteal DVT. The long-term outcomes may be assessed by patient self-reported questionnaires (generic [eg, short-form 36] or disease-specific [eg, VEINES QOL]), by the CEAP classification or severity scores, such as the venous clinical severity score (VCSS) or the Villalta score. It is important to remember that most of these instruments were developed to assess chronic venous insufficiency in general and were not specified for postthrombotic syndrome. The well-known Villalta score is properly validated for postthrombotic syndrome, but it cannot distinguish between postthrombotic changes and primary venous disease. Among 288 patients with a chronic venous disease without any history of DVT, 70% were classified as having postthrombotic syndrome and 33% as having severe postthrombotic syndrome. In addition, the Villalta score does not mention venous claudication, the very important long-term sequel of iliofemoral DVT. The factors that could affect the end points include the presence of reflux before the index DVT, the fact and type of compression therapy, elevated central venous pressure, and other causes of edema and anticoagulation management.

CAVA trial

Cees Wittens (Maastricht, Netherlands)

The CAVA trial (CAtheter Versus Anticoagulation) is an open-label, assessor-blind, multicenter, randomized controlled trial that is comparing the efficacy and safety of additional ultrasound-accelerated catheter-directed thrombolysis (UACDT with an EKOS® device) versus standard anticoagulation therapy in patients with their first acute iliofemoral deep vein thrombosis (DVT) with complaints for less than 14 days. The primary outcome of the study was the proportion of postthrombotic syndrome measured using the Villalta score at the 1-year follow-up. The secondary end points include the proportion of postthrombotic syndrome by International Society on Thrombosis and Haemostasis (ISTH) criteria, the severity of postthrombotic syndrome, and the health-related and generic quality of life scores. The safety outcome was major bleeding. A total of 184 patients were allocated to either UACDT (n=91) or conventional treatment (n=93). Of those patients allocated to UACDT vs conventional treatment, 74 vs 71, respectively, completed the 12-month follow-up, 77 vs 75, respectively, were analyzed in an intention-to-treat (ITT) modality, and 58 vs 57, respectively, were analyzed per protocol. The baseline characteristics of the patients were similar in both groups. The mean duration of symptoms before UACDT was 11.0 days and the venous stenting rate was 45%. The primary outcome at 12 months was registered in 29.3% of patients after UACDT and in 35.1% of patients after conventional treatment with no statistically significant difference. In addition, there was no difference in secondary outcomes. The subanalysis showed a successful lysis with restored vein patency

of $\geq 90\%$; however, only 53.2% of patients in the UACDT group achieved restored vein patency. Compared with those after unsuccessful lysis, these patients had a significantly higher stenting rate (75.6% vs 11.1%) and better outcomes: less moderate-to-severe postthrombotic syndrome (7.5% vs 25.7%), lower Villata (3.35 ± 3.10 vs 4.72 ± 3.19) and VCSS (3.50 ± 2.57 vs 4.88 ± 2.25) scores, and better quality of life parameters.

Where next after ATTRACT and CAVA?

Mitchell Silver (Columbus, OH, US)

The discouraging results of the ATTRACT trial (Acute venous Thrombosis: Thrombus Removal with Adjunctive Catheter-directed Thrombolysis) may be related to the study limitations (eg, only 1 patient out of 50 screened patients was randomized and the total enrollment in 56 clinical centers took 5 years) and that the study was underpowered to look at the higher-risk population, as only 57% of the patients had iliofemoral deep vein thrombosis (DVT), only 68% of patients in the control group were followed to 24 months, no intravascular ultrasound (IVUS) was used during the intervention, only 20% of patients had a venous duplex ultrasound at 1 year, and the median duration of lysis was 21 hours, which could be reflected with the higher risk of major bleeding. The main limitations of the CAVA trial (CATHeter Versus Anticoagulation) are represented by a long enrollment time (7 years for 184 patients), a low rate of successful lysis (53.2%), an absence of duplex ultrasound follow-up, and the long duration of the lysis procedure (48 hours).

All of these limitations should be overcome by the CLEAR DVT study (Contemporary Endovascular Therapies in Treatment of Acute Iliofemoral DVT). The study will occur over 2 phases. During phase 1, the initial cohort of 65 patients after an endovascular venous intervention will be compared with the propensity-matched medical therapy group of the ATTRACT trial with a primary end point of postthrombotic syndrome, which will be assessed by the Villalta score at 24 months after the intervention. Only iliofemoral DVT with symptom duration of up to 14 days will be included. The thrombolysis will be performed using the AngioJet™ system with mandatory IVUS and venous stenting in all cases where there is a cross-sectional area reduction of $\geq 50\%$. After the intervention, a standardized anticoagulation regimen will be prescribed. The 6-minute walk test will be used as a functional end point, a mandatory duplex ultrasound will be performed at 12 months, and health economics will be calculated. In addition, the study aims to evaluate the prevalence of mechanical abnormalities of the iliac veins, to correlate functional parameters (Villalta and quality of life scores) with posttreatment thrombus burden, recurrent DVT, and vein patency. The results of the phase 1 study will be used for construction of the phase 2 study, ie, the randomized clinical trial.

Complications and disasters during deep venous stenting procedures

Gerard O'Sullivan (Galway, Ireland)

Vein rupture during endovascular iliac vein reconstruction is rare and associated with prior vein surgery, radiotherapy, and vessel catheterization. However, it does not depend on age, sex, the duration, length, or nature of the obstruction, or the presence of cancer. In one example, a 47-year-old woman with endometrial cancer underwent a hysterectomy that was complicated by injury and further repair of pelvic vessels, and

then she developed leg swelling with demonstrated difficulties and dangers of iliac vein endovascular reconstruction. The iliac vein obstruction was verified only by CT venography with a direct injection of the contrast agent into the foot. Attempts at a standard balloon angioplasty led to vein rupture and internal bleeding. The implantation of a bare venous stent in case of a previous dissection is not able to stop bleeding; on the contrary, a stent placed in the zone of inelastic scars can play a role of good conduit and increase blood leakage. Therefore, the woman was transferred to the operating room and the rupture was fixed with an open surgical procedure. To perform an endovascular procedure with a high risk of rupture, it is recommended to have general anesthesia, a urethral catheter, an arterial line, 3-point access, large balloons, and the correct size sheet and stent grafts in the operating room.

An update on stent trials and the role of IVUS

Erin Murphy (Charlotte, NC, US)

The portfolio of venous products is now changing worldwide. There are several ongoing and finished trials aimed at assessing the efficacy and safety of venous stenting with different products: VIRTUS (Evaluation of the VICI™ Venous Stent System in Patients With Chronic Iliofemoral Venous Outflow Obstruction) for the VICI Venous Stent® by Boston Scientific, VIVO (Prospective European Study of the Zilver® Vena™ Venous Stent in the Treatment of Symptomatic Iliofemoral Venous Outflow Obstruction) for the Zilver® Vena™ stent by Cook Medical, VERNACULAR (BARD® The VENOVO™ Venous Stent Study for Treatment of Iliofemoral Occlusive Disease) for the VENOVO™ stent by Bard, and ABRE (Evaluation of the safety and effectiveness of the ABRE™ venous self-expanding stent system) for the ABRE™ stent by Medtronic. All studies have similar aims and designs, with only a few differences. The primary end point is stent patency assessed by venogram, duplex ultrasound, or intravascular ultrasound. Only the ABRE study uses intravascular ultrasound to assess the degree of baseline venous obstruction and vein patency at 12 months, while others use only venogram findings. For all studies, the threshold for venous obstruction at baseline is $\geq 50\%$. VIRTUS and VERNACULAR have already shown good results in terms of efficacy (84.0% and 88.3%, respectively) and safety (98.8% and 93.5%, respectively, of patients without major adverse events for 30 days). Both studies demonstrated a significant decrease in the venous clinical severity score and an improvement in quality of life. The results from VIVO and ABRE should be reported in 2020 and 2012.

The challenge of inflow - how can we assess it and what to look for

Houman Jalaie (Aachen, Germany)

Venous inflow is probably the most important predictor of outcomes after venous recanalization. It could be affected by many factors, such as body position, breathing, state of inflow conduit, outflow possibilities (collaterals), and there are no exact measures because volume flow determination is prone to error. Inflow should be a mandatory assessment prior to vein recanalization with special attention being paid to the anatomical extension of the lesion below the inguinal ligament, the involvement of the main inflow vessels, the degree of lumen reduction in the common femoral, femoral, and deep femoral veins (more than a 50% reduction should be considered as hemodynamically relevant), and collateral veins. For this purpose, duplex ultrasound, CT or direct CT

venography, MR or direct MR venography, phlebography, and IVUS may be used. Duplex ultrasound combines anatomical and hemodynamic data, and it is inexpensive and noninvasive, but it requires a learning curve. CT venography is fast, but holds the patient in the supine position, and it is associated with radiation exposure and does not provide any hemodynamic information. MR venography is more time consuming and expensive compared with CT. According to the literature, air plethysmography is not able to determine patient who will benefit from the treatment and those who will not. Direct CT venography defines the dominant vein inflow. Phlebography may be used to choose the better landing zone with the best inflow, even if it is infrainguinal. However, the most appropriate way to assess venous inflow is duplex ultrasound performed in a supine and upright position compared with the contralateral side, as it reports the postthrombotic changes from the knee up to the inferior vena cava, measures the flow volume at the common femoral vein, and provides a precise venous map. Based on preliminary results, a flow of 200 mL/min measured at the common femoral vein may be a threshold of adequate inflow. Combination of duplex ultrasound and CT/MR venography is the proper way to assess the inflow preoperatively.

What is next when stents fail?

Stephen Black (London, UK)

The patency of a venous stent depends on technical issues (stent choice and position of placing), blood flow (inflow, stenosis), and clotting abnormalities (antiphospholipid antibody syndrome, Bechet disease, vessel wall status, etc). If the stent fails during long-term follow-up, it is important to consider the reason for stenting in the first place, what caused the stent to fail, and what is the aim for further treatment. Only patients with severe symptoms, such as leg ulceration, may be considered for further interventions. Patients with mild and moderate symptoms do not require any additional surgery. The surgical options for failed stents are venous bypass or endophlebectomy with an arteriovenous fistula. It is important to provide good inflow by opening a deep femoral vein. When applying a fistula, arterial inflow should provide enough inflow for the stent, but does not overload the venous system, otherwise, there will be no improvement in terms of venous insufficiency. When applying a venous bypass in patients with a venous ulcer, antibacterial prophylaxis is crucial to prevent graft infection. However, most of the patients with failed stents during the long-term follow-up do not require reintervention.

The challenge of the femoral vein - treating post-thrombotic syndrome with normal iliac outflow

Steve Elias (Englewood, NJ, US)

Among the 950 000 cases of deep vein thrombosis (DVT) per year in the USA, 55% account for a femoropopliteal lesion that reflects with postthrombotic syndrome in 30% to 40% of all cases. Standard care is usually not enough, which is why the intervention should restore flow, decrease venous pressure, and improve the symptoms. The surgical options are venous bypass, venous stenting, and open endophlebectomy. A modern option considers using angioplasty with possible thrombolysis. The efficacy and safety of such a modality were assessed recently in the ACCESS PTS trial (ACCElerrated thrombolySiS for Post Thrombotic Syndrome) that included 78 patients with iliofemoral DVT diagnosed ≥ 6 months ago, a Villalta score of ≥ 8 , and in whom conservative treatment had failed for 3 months. They underwent balloon angioplasty for the occlusive vein segments, EKOS

thrombolysis with an infusion of tissue plasminogen activator (0.5-1.0 mg/hour for ≥ 12 hours) and repeated balloon angioplasty after that. The primary end point, reduction in the Villalta score of ≥ 4 points, was achieved in 67% of patients with a mean decrease in the Villalta score of 34% at 30 days. One major bleeding event occurred within 72 hours after the intervention and one pulmonary embolism event occurred during 30 days of observation. The modification of this technique is called GESSTA (Gasparis/Elias Single Session Thrombolysis/Angioplasty), which suggests sequential segmental tissue plasminogen activator exposure and balloon angioplasty of occluded veins through a specially designed balloon catheter with perforation within one session. The preliminary results showed ulcer healing in 10 of 16 treated patients. The suggested method is more simple, safe, and less expensive than the approach with EKOS, but needs to be studied in randomized clinical trials.

Latest advances with percutaneous deep venous valves

Steven Dubenec (Sydney, Australia)

Chronic deep vein insufficiency may be represented by obstruction, reflux, and the combination of obstruction and reflux. Reflux in deep veins appears due to an absence of valves or to their destruction, resulting in leg ulceration. Standard compression therapy is moderately effective, but ulcer recurrence occurs in 20% of all cases. The option for surgical valve repair included valvuloplasty, external banding, and valve transplantation and transposition. However, endovascular techniques are more attractive, but their efficacy is limited with a small number of animal studies. The novel option is a BlueLeaf technique that constructs neovalves similar to the open technique described by Oscar Malefi. The device is introduced through the large 16 Fr common femoral vein access in the retrograde direction. It provides the construction of subintimal valves by vein wall hydrodissection and nitinol arm separation under intravascular ultrasound visualization. It allows for the creation of monocuspid or bicuspid valves at different levels of the femoral vein. The preliminary results contain data from 11 patients, where 1 to 3 monocuspid valves were created in 10 of these patients. Therefore, technical success was achieved in 91% of the patients. No occlusive deep vein thromboses were registered, but, in 4 patients, mural thrombi were observed, which resolved during the 90 days of observation. Adverse events were represented with one symptomatic arteriovenous fistula, which resolved with compression, and 6 cases with access site complications, where 1 patient required surgical intervention. The patients were followed for 1 to 12 months with a significant reduction in the venous clinical severity score. The device is now undergoing further updates.

Endovascular rescue strategies for in-stent thrombus lining and occlusion

Erin Murphy (Charlotte, NC, US)

In-stent thrombosis (acute or chronic) may be related to physiologic (low inflow, stent mismatch), anticoagulation, or mechanical issues. The intervention is usually indicated in case of recurrence of initially improved symptoms, the persistence of some mechanical issues occluding the stent, or if the stent diameter is less than 3 to 5 mm (threatens the stent). The standard intervention for such cases is a venoplasty, but, in acute cases, catheter-directed thrombolysis or pharmacomechanical thrombectomy may be optional. Chronic stent occlusion may be difficult to resolve even after a few weeks. The main

candidates for intervention are young and symptomatic patients with sufficient inflow and the ability to receive anticoagulation. It is important to consider that the stent may not open or stay open after treatment and that it may require multiple interventions. Laser recanalization may be optional in chronic stent occlusion. The anticoagulation management after reintervention depends on the reason for stent thrombosis. In case of a mechanical issue, the minimal 6-month duration of anticoagulation is indicated with the final decision being based on thrombophilia screening and stent status. In the case of nonmechanical issues, evaluation of compliance, thrombophilia screening, change or escalation of anticoagulation regimen, permanent anticoagulation, and hematologist consultation is indicated.

Meeting the challenges of upper limb venous outflow obstruction

Rick de Graaf (Friedrichshafen, Germany)

Upper extremity venous outflow obstruction may be manifested as Paget-Schroetter syndrome (venous thrombosis on the background of venous thoracic outlet syndrome) or chronic central venous obstruction due to compression or fibrosis. There are no valid instruments to assess the clinical impact of upper limb venous obstruction. The Villalta scale is inadequate for this issue. The incidence of postthrombotic syndrome after upper limb deep vein thrombosis is reported in wide ranges (7% to 46%), but skin ulceration is very rare. The different approach to upper limb interventions compared with lower limb interventions is caused by anatomical differences (bone structures, the significance of inflow veins), etiology of the lesions (structural and anatomical, iatrogenic due to central venous catheters), and physiology of venous return (dependence of flow on exercises). Therefore, the recanalization of upper extremity veins is usually more challenging, and lower extremity knowledge is not transferrable to the upper limbs. For recanalization, hydrophilic wires and catheters, sharp needles, and radiofrequency may be used. Thrombolysis or pharmacomechanical thrombectomy is a good option for acute upper limb deep vein thrombosis. Venous stenting is not well established and there is no good evidence on what kind of stents (dedicated venous or specified upper extremity) should be used. It is important to consider decompressive surgery, such as first rib resection, and additional angioplasty for residual lesions. The main challenge in the treatment of upper limb venous obstruction is selecting the right patients.

Central vein obstruction - stenting in the SVC and IVC

Narayanan Thulasidasan (London, UK)

The obstruction of the superior vena cava may be related to either malignant (bronchogenic, lymphoma) or nonmalignant (central venous catheter, pacemaker, fibrosis) factors. The same factors are present for the inferior vena cava: retroperitoneal metastasis, lymphoma, or thrombosis/postthrombosis, fibrosis, filter-related, or congenital (atresia, agenesis). Recanalization of the superior vena cava depends on the etiology of the obstruction and expectations from the intervention. In the case of postcatheterization obstruction or dialysis fistula, the main aim is to restore dialysis access and avoid stenting unless it is asymptomatic. In the case of an implanted pacemaker, the main reason is to reinsert wires through the stent. Practical advice for superior vena cava recanalization include a careful cross with multiple projections, use of laser or radiofrequency only if sure, predilate stepwise to avoid rupture, avoid aggressive postdilatation, choose a

cephalad stent landing zone carefully to avoid kinking of the brachiocephalic vein, have a cardiothoracic surgeon in the same building and a pericardial drainage kit in the same room.

To cross the occluded or absent inferior vena cava, it is practically important to:

- Identify any residual intraluminal microchannels;
- Use stiff straight hydrophilic wire to “drill” through the occluded vessel;
- Cross in a bidirectional manner through the common femoral and internal jugular veins;
- Use the back end of the guidewire for sharp dissections across short segments; use an arterial chronic total occlusion reentry device or trans-septal needles to bridge between antegrade and retrograde dissection tracts;
- Preserve as much native vein as possible;
- Use heparin after crossing;
- Mandatory use of intravascular ultrasound to confirm successful crossing, assess required proximal and distal landing zones, and choose the proper stent size;
- Make predilation to facilitate deployment of stents to near-nominal length and diameter; use stent constructs that consist of large-bore caval stents with double-barreled iliac stents inside and throughout;
- Ensure sufficient overlap;
- Identify renal drainage and avoid shuttering inflow with multiple layers of overlapping stents if significant drainage into the inferior vena cava is identified;
- Provide postdilation;
- Remove the inferior vena cava filter when possible, but can also leave and stent through; and
- Ensure adequate inflow and provide proper anticoagulation.

Self-expanding nitinol stents are best to deal with repetitive compressive stresses in the inferior vena cava during respiration, trunk flexion, and nearby arterial pulsation. According to the literature, the experience with inferior vena cava reconstruction contains more 400 cases with a patency rate of 57% to 95% and clinical success in 40% to 80% of cases. Therefore, inferior vena cava reconstruction is a feasible and safe procedure that can be technically challenging in patients with advanced postthrombotic syndrome and long-segment occlusions.

Strategies and pitfalls for venous stents for the upper limb

Steven Dubenec (Sidney, Australia)

Upper limb deep vein thrombosis (ULDVT) range from 2% to 4% of all venous thrombi; they are complicated by a pulmonary embolism in approximately 10% of cases. Primary ULDVT develops as Paget-Schroetter syndrome due to physical effort and has no association with disease or trauma. It accounts for about 20% of all cases. Secondary ULDVT appears more frequently in association with malignancy, trauma, thrombophilia, or central venous catheters. Paget-Schroetter syndrome usually occurs in young, active patients around 30 years old and predominantly on the right side on the background of mechanical abnormalities at the thoracic outlet. It is usually provoked by repetitive activity. Initial vein damage leads to a thrombogenic surface and recurrent trauma leads to fibrosis of the vein and development of rib-bypass collaterals. To date, there are no randomized

clinical trials showing the best treatment modality for UL DVT. With anticoagulation alone, about 60% of all patients have recurrent symptoms. Catheter-directed thrombolysis is an alternative option to restore limb function, but without decompressive surgery, it leads to DVT recurrence in 30% of patients at 30 days. The suggested approach contains catheter-directed thrombolysis with possible angioplasty, first rib resection, and venous stenting. The analyzed data contains information on 24 limbs after catheter-directed thrombolysis in 21 patients with a mean age of 40 years; 8 had acute DVT and 3 had a rib resection performed with a mean time after lysis of 64 days. All of the veins were stented. The primary stent patency during the 24-month follow-up was 55%, the primary-assisted patency was 95%, and the secondary patency was 100%. When stenting the upper limb, it is important to: (i) choose an appropriate type and size for the stent, taking into account that not every one of them can accommodate the upper extremity forces; (ii) use dual access for crossing difficult lesions and occlusions; (iii) use high-pressure ultra-noncompliant balloons; (iv) be prepared for balloon rupture; (v) place a stent after rib resection or perform a rib resection as soon as possible after stenting; and (vi) use intravascular ultrasound to identify the diseased segment, to assess the diameter of the vein, to work out the stent length required, and to check appropriate stent deployment. All performed upper limbs stents require ultrasound follow-up. However, restenosis is usually symptomatic.

IV. Venous ulceration session

Novel treatments for intractable leg ulcers

Alfred Obermayer (Vienna, Austria)

Detecting the source of local venous hypertension straining the skin by duplex ultrasound is an important maneuver. Great saphenous vein reflux causes axial-type medial ulcers and small saphenous vein reflux causes axial-type lateral ulcers. On the contrary, small saphenous vein reflux can cause crossover-type medial ulcers. The presence of a swinging blood column is the evidence for the diagnosis of a venous ulcer. A crossover pattern or a small diameter may lead to inaccurate treatment and early recurrence. Sourcing helps to detect the responsible superficial reflux routes that are particularly likely in cases with postthrombotic syndrome and peripheral arterial disease (mixed ulcers). The technique of lateral fasciectomy sparing the superficial peroneal nerve with a simultaneous mesh graft is a procedure to treat nonlateral leg ulcers of diverse vascular origin and includes excising the fascia, taking particular care to protect the thin subfascial perimysium and peritendineum. The nerves are sometimes embedded in inflammatory scar tissue leading to pain. Following subcutaneous fasciotomy, transposition of the peroneal nerve can be performed by fixing two antagonistic muscles by running an absorbable suture followed by a mesh graft implantation. Lateral fasciectomy is a new procedure to treat only hard-to-treat ulcers and it is suitable for different ulcer types. After 3 months, 91% ulcer healing was obtained in 98% of the patients. No local recurrence in follow-up and no major complications were observed.

How to maximize implementation and post-EVRA results

Alun Davies (London, UK)

The global management of venous leg ulceration survey showed a diversity of management pathways internationally and it is clear that it should help inform best practice. Only four of the clinical practice guidelines were deemed to be of good quality with respect to development. Conflicting guidance and no impact on early referral and leg ulcer necessitated a study like EVRA (early vs deferred endovenous ablation in leg ulceration). It showed the potential for even better results if patients are seen and treated within 2 weeks. Studies have also shown promise for the cost effectiveness of an early intervention. The blockages to this policy are education, system failure, adequate facility, and perception of cost. The global pathway is diagnosis, compression, vascular investigation, venous intervention, and long-term compression. Education hurdles are a lack of information for patients, a lack of interest in the disease from politicians, and the lack of health care staff referral and championing. System failure comprises a scarcity of pathways and guidance. An adequate facility must be constructed for scanning and nursing.

Optimal assessment and treatment pathways for recalcitrant leg ulcers

Thomas O'Donnell (Boston, MA, US)

Recalcitrant venous leg ulcers refer to ulcers that fail to heal within a specified time, the majority of which is within 6 months. Parkers et al¹ reviewed 27 studies to analyze significant risk factors for nonhealing venous leg ulcers by 6 months and potentially treatable causes were identified as increased size of the ulcer, long duration, deep venous disease, decreased ankle mobility, nutrition that leads to either an increased BMI or a deficiency, and heavy wound exudate. Mixed ulcers were excluded. The VIDIO study (Venogram vs IVUS for Diagnosing Iliac vein Obstruction)² showed that intravascular ultrasound is more sensitive for assessing treatable iliofemoral vein stenosis compared with multiplanar venography and it frequently led to revised treatment plans and the potential for improved clinical outcomes. Thomas O'Donnell's group also showed that vein valve transplantation is a durable procedure for preventing recurrent venous ulcers. Maleti's "neovalve open technique"³ succeeded in healing 88.8% of ulcers within a median of 12 weeks with no ulcer recurrence to date. An improvement in hemodynamic values (venous filling index, ejection fraction, and residual volume) was maintained during the follow-up phase.

References:

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2. Gagne PJ, Tahara RW, Fastabend CP, et al. Venography versus intravascular ultrasound for diagnosing and treating iliofemoral vein obstruction. *J Vasc Surg Venous Lymphat Disord.* 2017;5(5):678-687.
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Novel wound dressings to meet the challenge of recalcitrant venous ulcers

Keith Harding (Cardiff, UK)

Conventional management of vascular wounds includes keeping the wound clean, correcting moisture levels, supporting the stages of wound healing, treating infection, debriding nonviable tissue, and revascularizing if the ulcer is arterial or applying compression if the source is venous. A proportion of wounds do not respond to conventional management, which is a huge burden on the patient, needs district nurses, and primary care and outpatient services. Chronic wounds are usually a manifestation of an underlying disease process. A comprehensive assessment is the key to successful treatment. Underlying systemic, metabolic, and local factors must be assessed and addressed. These factors must be corrected, kept in balance, and maintained until the wound heals and then ways to influence or reduce must be considered.

A passive dressing is an ordinary dressing (eg, gauze) that covers and conceals the wound, an interactive dressing is capable of modifying the physiology of the wound environment to optimize healing by promoting debridement, enhancing granulation/re-epithelization, reducing exudate levels, and bacterial load, and a bioactive dressing delivers active substances, such as antimicrobials/antibiotics, which have a direct role in changing the chemical and cellular environment of the local wound, stimulating

healing. Current dressing categories are basic dressings, absorbent dressings, alginates, antimicrobials, films, foams, honey dressings, and hydrocolloids that obtain odor control, protease modulation, scar management, skin protection, and wound contact layers. Modern dressing types have their own shortcomings. Options of how to measure success in wound patients include healing of the wound, wound-free days, decrease in pain, odor, or exudate, eradication of infection, increase in the patient's quality of life, changes in the patient/care giver experience, and improved cost effectiveness.

Keith Harding stated that it is unrealistic to use complete healing as a primary outcome measure and that it is more appropriate to adopt a broader approach; several new options were discussed:

- Chitosan is the second most abundant naturally occurring carbohydrate polymer derived from chitin that is present in the shells of crustaceans. Chitosan has biocompatible, biodegradable, nontoxic, antimicrobial, hydrating, fibroblast-growth factor retaining, dermal fibroblasts stimulation, and deposition properties. It can potentially be developed into forms of dressings that can deliver inflammation regulatory peptides, such as neurotensin.
- The Neotherix scaffold is an electrospun scaffold made from a bioresorbable "suture" polymer of nano/micron scale fibers. The scaffold is attractive to healthy cells from adjacent tissue following creation of an acute wound. Fibroblasts migrate into scaffold and along the fibers to repair the wound.
- The SpinCare™ device obtains a no contact dressing for all clinical settings. It is applied 20 cm from the wound and offers excellent adherence to the wound bed.
- A color-changing dressing in the presence of an infection avoids the unnecessary use of antibiotics.
- Dressings for local pain relief include carboxymethyl cellulose dressings layered with ibuprofen, biocellulose wound dressing, sheet hydrogel dressings, and topical opioids.
- Topical O₂ systems: Natrox® Oxygen Wound Therapy is a class II medical device that consists of an O₂ generator, a delivery line, and a disposable wound interface. It runs off a battery and electrolyzes airborne moisture. Other topical O₂ systems are available and normobaric vs hyperbaric and gaseous O₂ vs carrier compounds are available. In general, most studies agree that topical O₂ shows promise. It should probably be part of our wound care armamentarium. It is not exactly clear how it works, but it seems to help with the healing pain. However, as with so much of wound healing, there is a paucity of large, high-powered, well-controlled trials.
- The geko™ is a daily disposable strap-on device that electrically stimulates the common peroneal. It induces muscle contractions and mimics the physiological effect of walking. This device is useful for a range of lower limb applications as well as venous leg ulcers (eg, mixed ulcers), postoperative edema, venous thromboembolism prophylaxis, and it has an effect on venous and arterial flow and microcirculation.
- Cold plasma can also be applied for ulcers. The interaction between cold plasma and biological material is deeply complex. The chemical character of the plasma has a large effect on the biological consequences.

From the scale of the problem of recalcitrant ulcers, novel approaches are needed.

V. Miscellaneous venous topics

Latest advances in managing C1 disease

Paul Pittaluga (Monaco, Monaco)

Sclerotherapy of telangiectasia and reticular veins is the oldest, but still the most common method of treatment. On one hand, it is simple, cheap, office-based, and requires no anesthesia. On the other hand, it needs several sessions, is not easy to perform, has variable results, and leads to pigmentation. The other option is skin laser because it requires no injections, it is office-based, it allows for the treatment of matting, and it is perceived as a modern technique; however, it is expensive, provides unequal results, and its efficacy is controversial. The modern approach includes radiofrequency ablation of the veins, but there is no clear data on efficacy. The surgical methods under local anesthesia are limited with the inability to remove the telangiectasia. The novel percutaneous surgical approach involves local anesthesia, driving the blood out from the vessel, and performing multiple focal destructions along the vessel with a specifically designed microinvasive tool. The tumescent anesthesia is injected just into the reticular layer of the skin (not papillary to avoid compression of the telangiectasia) to reduce the blood supply from the deeper vessels and keep the target vessels visible. The telangiectasias are interrupted by multiple microcuts and removed by slicing and emptying them. The procedure is fast and larger zones can be treated during the same session. The short-term results provide full disappearance of treated veins at 35 days.

New horizons for venous specialists

Sriram Narayanan (Singapore, Singapore)

Nonthrombotic iliac vein lesions may be responsible for most cases of chronic venous disease. The true prevalence of nonthrombotic iliac vein lesions is unknown. Nonthrombotic iliac vein lesions were observed in 23% to 32% of all cadavers, in 18% to 40% of patients with left lower limb deep vein thrombosis (DVT), but, by intravenous ultrasound, it may be found in 70% to 90% of all investigations. Pelvic congestion syndrome may be related to outflow obstruction (nonthrombotic iliac vein lesions, nutcracker syndrome, retro-aortic left renal vein) in 90% of cases or may be primarily due to an increase in ovarian, uterine, and pelvic vein volume during pregnancy and estrogen intake in 10% of cases.

Pelvic congestion syndrome affects 10% to 15% of women during their lifetime and may be associated with symptomatic pelvic venous hypertension that can manifest as pain, dysmenorrhea, bleeding, dyspareunia, or leg swelling and recurrent varicose veins in a specific localization (perineal, gluteal). Pelvic venous hypertension may be identified using a specifically designed questionnaire. If identified, it should be treated with ovarian vein embolization under intravascular ultrasound guidance, which can provide adequate sizing of the embolic device and confirm the nutcracker effect. The embolization may be completed by balloon-controlled foam sclerotherapy.

The same problem may be represented in men as corporal veno-occlusive erectile dysfunction. It usually occurs in 30 to 40 year old men with a varicocele that is idiopathic and lifestyle-related, sometimes after pelvic fracture and radical pelvic surgery. The incidence typically increases with age. To assess erectile function in such patients, the Sexual Health Inventory for Men (SHIM) may be used. Scores of 22 and lower suggest erectile dysfunction, with lower scores suggesting more severe forms. To verify the venous etiology of erectile dysfunction, a complex hemodynamic assessment may be performed, including measuring blood pressure in the arm and penis, calculating the penile-brachial index, measuring pulse volume by photoplethysmography on the thumb and penis, measuring peak systolic velocity and end-diastolic velocity on the 4 penile arteries by Doppler, as well as recording the erectile hardness score at 10 and 20 minutes after the corporal injection of prostaglandin. An end-diastolic velocity >5 cm/s with normal peak systolic velocity and penile-brachial index suggests a venous reason for the erectile dysfunction. This pathology may be treated with glue ablation of the deep dorsal venous bifurcation (GAVI technique) using a venesection and specific microcatheter under local anesthesia with sedation. The 6-month results from 19 patients demonstrate a significant improvement in the sexual status according to the SHIM score, an increase in the erectile hardness score, and a normalization of the end-diastolic velocity. Therefore, diagnosis and treatment of pelvic venous hypertension in women and men is a new horizon for venous specialists.

IVUS in venous interventions - reduction in radiation exposure

Narayan Karunanithy (London, UK)

Radiation exposure in complex venous interventions is significant. The radiation burden during a unilateral iliofemoral vein stent implantation may be as high as 32.4 Gy cm^2 , and it may be increased up to 60.8 Gy cm^2 during an inferior vena cava reconstruction. Considering that most of the patients undergoing such procedures are young (35 to 45 years old) and require additional preinterventional and postinterventional CT scans, the added lifetime cancer risk may be as high as 1:270 for iliofemoral stenting and 1:100 for inferior vena cava reconstruction. Therefore, decreasing radiation exposure is an important issue. IVUS can be used at all procedural steps, which not only reduces the radiation exposure, but also achieves more clinical efficacy. Intravascular ultrasound is better than phlebography for the assessment of lesion severity, as was demonstrated in the VIDIO study (Venogram vs Intravascular ultrasound for Diagnosing Iliac vein Obstruction). Moreover, at the base of the measurement of the stenosis area, it can predict clinical improvement after stenting. In addition, it can be used to assess lesion extension, to choose the proper size of the stent, and to control poststent deployment. Therefore, the routine use of the intravascular ultrasound will reduce radiation exposure and improve technical outcomes.

Where do we stand with IVC filters in 2019?

Richard McWilliams (Liverpool, UK)

In the last years, implantation of an inferior vena cava filter is associated with increased litigations resulting in multibillion dollar penalties for the manufacturers. At the same time, manufacturers are issuing safety notices calling physicians to inform the patients better about possible outcomes and complications of filter implantation, improve routine follow-

up, and increase the retrieval rate. However, there is a lack of clinical data on the current inferior vena cava filters. There are some ongoing studies, such as PRESERVE (PREdicting the Safety and Effectiveness of infeRior VEna cava filters), which is analyzing six different manufacturers, and CVC (Cook Inferior Vena Cava filter study), which is analyzing only the Tulip and Celect filters. The recently finished DENALI trial (a prospective, multi-center study of the Bard® DENALI™ retrievable inferior vena cava filter) on the Denali™ filter recruited 200 patients and demonstrated a good retrieval rate (121 removals of 124 attempts) during 5 to 736 days (mean, 201 days) after implantation without adjunctive use of loop snares or endobronchial forceps. However, the filter retrieval rate is relatively low due to organizational reasons. The main factors associated with low retrieval attempts are repeated surgery, long stays in the intensive care units, inter-hospital transfers, and an unstable address. At the same time, developing a proper inferior vena cava filter pathway increases the retrieval rate from 63% to 100% due to the absence of loss for follow-up patients. The other way for improvement is educating specialists on retrieval techniques with the emphasis on retrieval, properly following guidelines, and teamwork, as well as developing bioconvertible inferior vena cava filters. Data from the SENTRY trial (Study of the Novate SENTRY Bioconvertible Vena Cava Filter), a prospective, multicenter study with a 12-month follow-up, was published recently, demonstrating encouraging results.

The current and future role of medical apps in venous care

Oscar Johnson (London, UK)

There is an increasing number of smartphone users, meaning that the applications have a big potential for data storage and analysis, patient education and consultation, procedures and investigations, machine learning and virtual clinics, and a multidisciplinary team input. The potential concerns are access to technology, connectivity, technological literacy, financial ability, wellness to engage, accessibility, training and education, technical support, fueling the addiction, compatibility, access, data collection and storage, and security. Some applications already on the market are only related to clinical reference and scoring services. Therefore, the real potential of smartphone applications has still not been revealed. One application that is trying to overcome these limitations is the Leg Ulcer Pathway Audit (LUPA) from Guy's and St. Thomas Hospital (London, UK). It uses the Memopad Health monitoring application to improve remote patient healing monitor. It contains patient data and investigation timelines, and it is available on different platforms for the multidisciplinary team.

VI. Pelvic venous disease session

How to decide when pelvic venous reflux is clinically relevant and pelvic congestion syndrome

Neil Khilnani (New York, NY, US)

Pelvic venous reflux can be due to lower extremity and vulvar varicose veins. The symptoms can be lower limb swelling and/or claudication, left flank pain and/or hematuria. The new nomenclature for pelvic venous disorders consists of ovarian vein reflux, iliac vein reflux, renal vein compression, and iliac vein compression. The pathophysiology is clearly defined and inter-related and it can have an origin related to pelvic congestion, Nutcracker syndrome, and May-Turner syndrome. Pelvic venous disorders are relevant when it affects quality of life and it is necessary to treat to restore the health. In patients with pelvic venous reflux that is proven based on venogram data, pelvic pain predicts a pelvic venous disorder. The patient defines significance. Pelvic varicosities are often asymptomatic but can be the source of lower limb and vulvar varicosities. A total of 515 women with pelvic venous disorder, which was documented by venogram data, had lower extremity varicose veins that were mostly related to typical lower limb sources. Approximately 10% of lower extremity varicose veins have a pelvic origin, which are linked to pelvic escape points. There is little evidence to support primary embolization or stenting in varicose veins with a pelvic source. Only minimal improvement can be achieved for leg symptoms and lower extremity veins, but one study showed benefit for vulvar veins. Although there is not much literature supporting primary treatment of lower limb and vulvar varicose veins, these lower limb veins need treatment

VII. Lymphoedema session

Optimal lymphoedema diagnosis and management in 2019

Peter Mortimer (London, UK)

Genomic medicine is the future for the diagnosis and management of primary lymphedema and vascular anomalies. Genomic medicine is the use of the genomic information of an individual to guide their clinical care. Genomic information is the sequencing and analysis of an organism's entire DNA. Milroy disease is caused by a germ-line mutation in vascular endothelial growth factor receptor 3 (VEGFR3) that is associated with venous reflux and hydroceles in boys. Lymphedema distichiasis is caused by germ-line mutation in Forkhead Box C2 (FOXC2) that leads to a dominant hereditary lower limb lymphedema with onset at puberty and it is associated with varicose veins, cleft palate, ptosis, and congenital heart disease. Klippel-Trenaunay syndrome is caused by mosaic somatic mutations in the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) and AKT serine/threonine kinase 1 (AKT1) gene (RAS/MAPK pathway). A molecular (genomic) diagnosis can be made in 25% of primary lymphedema cases. Finding the gene permits an acquisition of knowledge concerning associated features (eg, venous or heart disease), allowing us to understand the gene function in the mechanism of disease, such as lymphatic valve failure, which provides information on the natural history of the disease (eg, FOXC2 can present at puberty [praecox] or later in life [tarda]). Germ-line mutations in VEGFR3, FOXC2, and gap junction protein gamma 2 (GJC2) cause hereditary human primary lymphedema and venous disease. FOXC2 causes deep venous reflux. Somatic mutations (eg, PIK3CA mutations), which is confined to the affected tissue, cause both venous and lymphatic malformations. In Klippel-Trenaunay syndrome (often caused by a PIK3CA mutation), the lymphatic anomaly may be significant, meaning that endovenous ablation may not reduce edema. Genotyping of affected tissue, where accessible, should therefore be a key element for management. The resulting genetic stratification may have prognostic value and it may serve to guide therapy.

A pragmatic approach to the assessment of swollen legs

Sarah Thomis (Leuven, Belgium)

The pathophysiology of edema includes increased capillary hydrostatic pressure, hypoalbuminemia (hence decreased oncotic capillary pressure), increased capillary permeability, and lymphatic obstruction (hence increased interstitial oncotic pressure). Causes of edema include venous edema resulting from chronic venous insufficiency and deep vein thrombosis, lymphedema, lipedema, and other causes, such as dependency edema, heart failure, kidney failure, and drugs. Lymphedema, chronic venous insufficiency, venous compression syndromes, strangulation edema, and trauma can cause unilateral edema, while heart failure, nephrotic syndrome, lipedema, lymphedema, chronic venous disease, dependency edema, idiopathic edema, and medications can cause bilateral edema. Anamnesis must contain time of onset and course, medical history for trauma, oncology, infection, medication, family history, immobility, cardiac or nephrotic problems, and associated symptoms, such as heaviness, tingling, and bruising. The clinical examination should investigate signs of venous insufficiency, such as varicose veins,

lipodermatosclerosis, and ulcers, arterial pulsations and capillary refill, skinfold thickness (Stemmer sign), and pitting sign. An ultrasound is used to rule out deep vein thrombosis, venous valve incompetence, and metastasis in the lymph nodes as well as to visualize skin thickness. Ultra-high frequency ultrasound is used to visualize lymph vessels. CT and MRI are used to visualize swollen lymph nodes, visualize lymphedema, lymph vessels without functional information, and as MR lymphangiography.

MR lymphoscintigraphy is used to quantify extraction from the injection point, arrival of the product in the lymph nodes at the groin/axilla, number of lymph nodes in the groin, dermal backflow, visualization of lymph nodes in the knee pit, and asymmetry. Lymphofluoroscopy is used to image the superficial lymphatic system (with a maximum depth of 2 cm) and it shows the architecture of lymphatics as well as the lymphatic system. Indications for lymphofluoroscopy are certain difficult-to-treat areas, deterioration of edema, and aid for surgical interventions and optimization of compression devices and lymph drainage.

VIII. Debates session

• The dangers of stenting for nutcracker syndrome far outweigh any benefits

For the motion

Gerard O'Sullivan (Galway, Ireland)

Venography and pressure gradient, noninvasive imaging, laboratory studies, clinical examination, and symptom history help achieve a diagnosis. Approximately 75% of patients <18 years old have complete resolution of their symptoms by using conservative treatment. Reed et al¹ showed that, at the 39-month follow-up, left renal vein transposition surgery results in 80% of patients having flank pain and 100% with hematuria improvement. Laparoscopic treatment and endovascular treatment, which achieves a 97% improvement in the symptoms, are other options. Dislodgement, complete migration, thrombosis, restenosis, vessel perforation, and visceral injury are complications of stenting. In conclusion, with current technology, stent placement is not safe in the medium or long term.

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Against the motion

Olivier Hartung (Marseille, France)

Nutcracker syndrome is an underdiagnosed disease. It is a functional pathology that is not life threatening and it does not carry the risk of renal insufficiency. Interventional treatment options are surgery and stenting. Endovascular treatment is quick and done under local anesthesia/sedation and by using a femoral or jugular approach. Stent migration was shown in 6.7% of the patients in the study by Wu et al;¹ which can occur early, but also as late as 5 months; 2 of the stents migrated into the heart. There are multiple surgical techniques, such as left renal vein (LRV) transposition, LRV transposition±patch/cuff, and LRV transposition+patch+stent, LRV-inferior vena cava bypass, left gonadal vein transposition, superior mesenteric artery transposition, autotransplantation, and nephrectomy. Surgery is invasive, but can be performed by mini laparotomy, laparoscopy-assisted surgery, total laparoscopic surgery, and robotic-assisted surgery, which reduces the length of stay and improves cosmetic results. Somehow, stenting is efficient in the treatment of residual stenosis/restenosis after a surgical procedure; however, in the Nutcracker syndrome where there is aortic prominence and kidney down into the lumbar fossae, the problems, such as indefinite size and length and lack of fixation, such as deployment in the first branch, make stents an unsure option. In the future, dedicated stents may solve these problems. In conclusion, in this functional disease, although there is a risk for stent migration and surgery is not perfect and invasive, all that is needed is a dedicated stent.

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• Aggressive thrombus removal for iliofemoral DVT is overutilised as most patients do not develop significant PTS

For the motion

Manj Gohel (Cambridge, UK)

Iliofemoral deep vein thrombosis (DVT) is an important and disabling condition that is associated with developing severe postthrombotic syndrome in some patients. Aggressive thrombus removal strategies can provide excellent technical and clinical success, but the question is how many cases of severe postthrombotic syndrome could be prevented with this approach. The CaVenT study (Catheter-directed Venous thrombolysis in acute iliofemoral vein Thrombosis) compared standard DVT treatment with adjunctive use of catheter-directed thrombolysis. The 5-year follow-up showed a significant reduction in the rate of postthrombotic syndrome (42.5% vs 70.8%) with very few cases of severe postthrombotic syndrome (4/37 vs 1/63) and no differences in terms of quality of life. The ATTRACT trial (Acute venous Thrombosis: Thrombus Removal with Adjunctive Catheter-directed Thrombolysis) compared different techniques of pharmacomechanical catheter-directed thrombolysis with standard treatment in patients with femoropopliteal and iliofemoral DVT and found no difference in the rate of postthrombotic syndrome as shown by the Villalta score between 6 and 24 months (47% vs 48%). The same results were found in the subgroup of patients with iliofemoral DVT (44% vs 45%). Despite some differences in the rate of moderate-to-severe postthrombotic syndrome (18% vs 28%) and severe postthrombotic syndrome (8.7% vs 15%), the number of patients with such complications was rather small and the number needed to treat to prevent one moderate or severe postthrombotic syndrome was 10. Thus, most patients with iliofemoral DVT do not develop significant postthrombotic syndrome, and aggressive treatment of this entire group would only prevent a small number of patients from developing postthrombotic syndrome.

Against the motion

Michael Lichtenberg (Arnsberg, Germany)

Thrombectomy is safe and effective because it decreases pain and swelling in the early period and reduces moderate-to-severe postthrombotic syndrome in the long-term follow-up. The maximal benefits of the thrombectomy may be observed with the use of mechanical or pharmacomechanical techniques in patients with a descending venous thrombus that occurs in the background of a venous obstruction. The standard conservative treatment with anticoagulants and compression stockings cannot prevent postthrombotic syndrome, especially after a proximal DVT. However, in the ATTRACT trial, adjunctive use of pharmacomechanical catheter-directed thrombolysis leads to a significant decrease in the incidence of moderate-to-severe postthrombotic syndrome (17.9% vs 23.7%), especially in patients with iliofemoral DVT (18.4% vs 28.2%). The main conditions to achieve good results from a thrombectomy include choosing the right patients

(ie, those with a descending DVT) using mechanical or pharmacomechanical techniques instead of catheter-directed thrombolysis, and treating the underlying pathology with venous stenting. The analysis of the BERN venous registry including only patients with descending DVT vs the CaVenT and ATTRACT trials (100% vs 48% and 57%, respectively) with the high rate of venous stenting (80% vs 17% and 30%, respectively) show the very low incidence of postthrombotic syndrome at 12 to 24 months (6% vs 41% and 47%, respectively). The results of the ASPIREX[®] device use from the Arnsberg registry support this evidence and provide a low incidence (36%) of postthrombotic syndrome at 12 months. Therefore, there is excellent evidence for thrombectomy of descending iliofemoral DVT, which is supported by the ATTRACT subanalysis and register studies and the novel thrombectomy devices have the potential to displace the standard pure catheter-directed thrombolysis techniques by providing better results with a one-step treatment approach.

