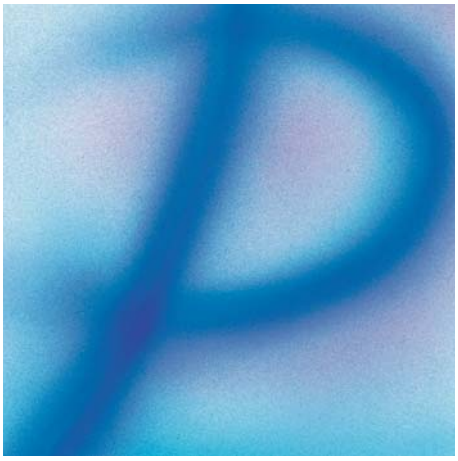
PHLEBOLYMPHOLOGY

ISSN 1286-0107

Special issue



Vol 20 • No.1 • 2013 • p1-84

AIMS AND SCOPE

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

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

Phlebolymphology is scientifically supported by a prestigious editorial board.

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

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

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Indexed in EMBASE, PASCAL, Index Copernicus, and Scopus.

ISSN 1286-0107

Phlebolymphology

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Report from the XXVth World Congress of the International Union of Angiology,

Prague, Czech Republic, July 1-5, 2012

XXV WORLD CONGRESS

of the International Union of Angiology

July 1-5, 2012

PRAGUE, CZECH REPUBLIC

Contents

Medical Reporters' Academy (MRA)

The reports from the XXVth World Congress of the International Union of Angiology (IUA) in Prague were prepared by the following members of the Medical Reporters' Academy (MRA):

- **Giuseppe CALANDRA** (Italy)
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Editorial

It was a great honor to welcome the one thousand physicians and scientists who participated in the XXVth World Congress of the International Union of Angiology (IUA) in Prague. The old European city of Prague, which is at the crossroads of many cultural influences and historical events, was also the ideal setting for the intensive exchanges that took place during the congress between worldwide vascular specialists and representatives of many vascular societies.

As well as lectures, round-table discussions, symposia, interactive teaching sessions, e-poster and free paper presentations, the IUA program included the presentation of new guidelines for the treatment and investigation of vascular diseases by several societies. Issuing guidelines is, of course, one of the leading missions of the IUA, but the dissemination of new, specialized knowledge among the multidisciplinary experts in the field is a continuous challenge that the IUA has to undertake.

Meetings like the XXVth World Congress of the International Union of Angiology (IUA) in Prague are among the most important ways of transmitting information and knowledge. This is a unique occasion to exchange with colleagues from all parts of the World.

The initiative of Servier to report on such an important congress, thereby keeping all venous specialists fully informed, meets the aims of the IUA. Bringing a group of young specialists of different geographical and disciplinary origins to the meeting, so that they can report on a wide selection of presentations, not only facilitates the dissemination of knowledge but also gives incentives to a new generation of specialists to keep going in the right direction. This report will allow those who could not attend the congress to read the highlights of the meeting and benefit from the outstanding presentations and discussions held during these 4 days. Written on the spot under the chairmanship of Andrew Nicolaides, this report should be greeted and encouraged.

We hope you enjoy the read.

Karel ROZTOCIL
President of the XXVth World Congress of the IUA

I. Arterial diseases

1.1. Aneurysms

The Amsterdam Ruptured Aneurysm Trial

W. Wisselink (The Netherlands)

A total of 116 patients with ruptured aneurysms, out of a population of 1.2 million inhabitants in the Amsterdam area, were treated during the period from 2004 to 2011.

After randomization, the authors treated 59 patients with open repair and 57 with endovascular aneurysm repair (EVAR). The hospitalization death rate was 21% in the EVAR group and 25% for the open repair group. They concluded that open repair was performed much better than expected and that open repair for ruptured aneurysms should not be abandoned.

Diagnosis and treatment of aortic aneurysm

Screening for abdominal aortic aneurysm

A. Jawien (Poland)

This latest meta-analysis, with at least 10 years of follow-up, suggests that screening reduces abdominal aortic aneurysm (AAA)–related mortality by 45%, with a strong reduction in all-cause mortality. Various national screening programs have been carried out. In the USA, AAAs were diagnosed in 5.1% of men of 65 to 75 years of age. In Northern Ireland, AAAs were detected in 5.4 % of men of 65 years of age. In Genoa, AAAs were found in 6.2% of males and females of 65 years of age or more. In Poland AAAs were detected in 5.7% of males of 60 years of age or more.

In the UK, AAA rate in patients of 65 years of age was 1.7%. The prevalence of AAA was lower than expected due to the younger age of this cohort.

In Sweden, AAAs were detected in 1.7% of 65-year-olds. In 3.3% of the examined men the aortic diameter was of 25 mm, while it was of 30 mm in 1.3%. The cut-off for further follow-up was 30 mm. An aorta with a diameter between 25 and 29 mm was classified as an «aneurysm in formation.»

Consensus exists across guidelines on the one-time screening of elderly men to detect and treat AAAs. Further studies are needed for other target groups, management of small AAAs, prediction models, and cost-effectiveness.

Pharmacological therapy for abdominal aortic aneurysm

D. Karetova (Czech Republic)

Abdominal aortic aneurysm (AAA) is a multifactorial complex disease involving genetic defects, inflammatory reactions, hemodynamical stress, and risk factors.

Comprehensive treatment includes smoking cessation, blood pressure control, dyslipidemia treatment, specific therapy (antiproteolytic/anti-inflammatory), statins, angiotensin II inhibitors. However, the only verified method for the prevention of AAA rupture is mechanic exclusion.

The aim of conservative therapy is the limitation of growth. In a meta-analysis including 14 studies, 13 different drugs belonging to 4 main drug classes were evaluated: β-blockers, antihypertensives, antibiotics, and statins.

Although propranolol showed no effect in aneurysm growth and impaired quality of life, it demonstrated a positive effect in perioperative cardiovascular risk reduction. There was no relationship between angiotensin receptor blockers or statins and AAA expansion rate. These drugs were recommended to patients with an AAA because of coexisting cardiovascular disease. Antibiotics like macrolides and tetracycline were studied in animal models for potential inhibitory effects on metalloproteinase activity. The significant changes in AAA expansion rates were controversial.

In conclusion, there is no specific proven medication to prevent AAA growth. Suboptimal «antiatherosclerotic» medication in patients with AAA, like statins and acetylsalicylic acid should be prescribed. Controlling hypertension is essential.

Role of conventional and endovascular treatment of abdominal aortic aneurysms.

P. Gloviczki (USA)

The management of abdominal aortic aneurysms (AAAs) has dramatically changed in the past decade. Nowadays, more than 60% of patients with AAA are treated with endovascular aneurysm repair (EVAR).

At Mayo Clinic, from 1996 to 2011 (3473 AAA patients), the use of EVAR increased compared with the use of open repair (OR). From 2007, EVAR was performed in 63% of patients. In 969 elective EVARs, the mortality rate at 30 days was 0.93%.

In the United States, from 1999 to 2008, the number of AAA repairs increased (+ 26.3%) while the risk-adjusted mortality rate decreased from 4.4% to 2.8 % (– 36%).

In a recent survey, survival at 8 years after open AAA repair and after EVAR showed an aneurysm-related survival of 93% and lower rates of complications and reinterventions for EVAR.

In a randomized trial, the early mortality rate with EVAR was 0.5%, while mortality at 2 years with EVAR was 7%. Procedure time, hospital stay, and blood loss were all reduced in patients undergoing EVAR. No major difference in morbidity, reinterventions, and erectile dysfunction were observed.

The data from high-risk patients in five FDA trials (565 EVAR patients, 61 OR controls) showed a mortality rate at 30 days of 2.9% with EVAR and 5.1% with OR. Aneurysm-related deaths at 4 years were 4.2% (EVAR) and 5.1% (OR).

Repair of AAA in high-risk patients provides excellent protection from AAA-related death at 4 years.

EVAR can be performed with a low rate of mortality and an acceptable rate of complications. EVAR is a less invasive procedure, thereby allowing treatment of high-risk patients with large aneurysms. However, long-term survival benefits, high costs, reintervention rates, and late rupture remain concerns.

1.2. Carotid stenosis

Medical management of carotid stenosis

R. C. Shields (USA)

R. C. Shields talked about the debate over the treatment of patients with asymptomatic carotid artery stenosis: should they be treated with an aggressive or a conservative approach?

Carotid disease is an important source of strokes (accounting to as many as 15% to 30% of them). The ACST trial (*Lancet* 2004 and 2010) shows a risk of stroke at 5 years of 6.9% for patients undergoing an immediate intervention and 10.9% in patients with deferred medical treatment, which rises to 13.4% and 17.9%, respectively, at 10 years. In those patients, the benefit of surgery was limited to males and those less than 75 years of age and the perioperative stroke and death rate was of 3.1%. The results of the CREST study (*New Engl J Med*) seem to be slightly superior in the carotid endarterectomy (CEA) group versus the carotid artery stenting (CAS) group.

The treatment of hypertension in carotid artery disease was the objective of the SECURE trial (*Circulation* 2001), which showed that ramipril significantly reduces carotid intimal medial thickness in 37% of cases; however, the clinical significance of this result is unclear. The HOPE trial (*New Engl J Med* 2000), another trial with ramipril versus placebo, showed a 32% reduction in the number of strokes in the treatment group.

If we focus on statins and the risk of stroke, the JUPITER trial (primary prevention) shows a hazard ratio of 0.52 with treatment, and in a meta-analysis of secondary prevention studies (*J Am Coll Cardiol* 2008) the reduction in stroke was 25. The ASTEROID trial, conducted with intravascular ultrasonography, showed that statins decrease plaque volume at 24 months in all age groups and in both sexes.

Antiplatelet therapy achieves primary risk reduction but its risks and benefits must be individually balanced.

Thus, with the best medical therapy, the annual risk of ipsilateral stroke is 0.4% to1.0 % in asymptomatic patients, and it is difficult for either CEA or CAS to improve on it.

What are the future directions? Surely, the new frontier is risk stratification, to identify those patients with increased risk of stroke for operative management,

with the use of inflammatory markers (hs-CRP, lipoprotein-associated phospholipase A2), carotid intimal medial thickness, and vulnerable plaque analysis.

In conclusion, medical management has become an indispensable part of the care of patients in every phase of carotid disease for primary prevention, secondary prevention, and perioperative management.

Can carotid intervention be dispensed of for asymptomatic disease? Possibly not, but we must determine who should receive surgery with the best medical possible treatment and who should receive conservative management alone.

The many facets of carotid disease.

Endarterectomy or stenting for carotid artery disease: current evidence and guidelines of the Society for Vascular Surgery

P. Gloviczki (USA)

Stroke occurs in 2.9% of high-risk patients and in 0.9% of low-risk patients, while death occurs in 0.6% of high-risk patients and in 0% of low-risk patients. Data from Maryland (USA) in the period 1994-2003 (23 237 carotid endarterectomies [CEA] by 438 surgeons) show an in-hospital stroke rate of between0.58% and 0.73%.

To compare carotid endarterectomy and stenting, Murad (*J Vasc Surg*, 2011) looked at different outcomes from the literature: risks of stroke, death, myocardial infarction, cranial nerve injuries, bleeding, wound complications, quality of life, and cost in 7484 patients data from different studies (Naylor, 1998; Alberts, 2001; Brooks, 2001, CAVATAS 2001; Yadev 2004; EVA-3S 2004; SPACE 2006; Ling 2006; BACASS 2006; Steinbauer 2008; CREST 2010; ICSS 2010).

Risks of stroke, death, and myocardial infarction: Results showed that carotid artery stenting (CAS) is associated with an increased risk of any type of stroke (relative risk, [RR], 1.45), a decreased risk of myocardial stroke (RR, 0.43), and a nonsignificant increase in deaths (RR, 1.45). There is a trend suggesting that CAS was more effective in patients <70 years of age. On the other hand, CAS is associated with 19 times more strokes than CEA, with 3 times more deaths, but with 10 times fewer myocardial infarctions than CEA. The conclusion of this study is that CAS significantly increases the risk of any type of stroke and decreases the risk of myocardial infarction.

Cost: Markov's analysis in symptomatic patients suitable for both CEA and CAS shows that CAS resulted in fewer quality-adjusted life years (8.97 vs 9.84) while the cost per patient was increased.

Therefore, given the current evidence, the United States Center for Medicare and Medicaid Services (CMS) has decided not to extend reimbursement for carotid artery angioplasty/stenting in patients with low or standard risk for carotid endarterectomy. However, this situation may change in the future.

In conclusion, in most patients with carotid stenosis who are candidates for intervention, CEA is preferred to CAS for the reduction of all-cause stroke and periprocedural death (grade 1, level of evidence B)

- CEA is preferred to CAS in patients aged >70 years of age (grade 1, level of evidence A).
- Carotid artery stenting (CAS) should be reserved for symptomatic patients with 50% to 99% stenosis who are at high risk for CEA for anatomical or medical reasons.
- There are insufficient data to recommend CAS as primary therapy for neurologically asymptomatic patients with 70% to 99% diameter stenosis.

Determination of the stability of atherosclerotic plaques in vivo and its clinical relevance

P. Poredos (Slovenia)

Carotid atherosclerosis causes 15% to 30% of acute ischemic strokes. In patients with asymptomatic carotid stenosis (ASCS), the average annual risk of stroke is up to 2% per year and the risk of coronary events is around 7%, while it rises to 20% in 3 months in symptomatic patients.

From the 10-year follow-up of theACST study, we know more about the natural history of carotid atherosclerosis. Of the 3210 followed-up patients, 50% had died at the end of the study, even in the younger groups (<75 years), stroke was the underlying cause in only 10%, and cardiovascular causes were responsible for almost 50% of total mortality.

The factors predicting the risk of ischemic cardiovascular events in asymptomatic carotid atherosclerosis are: severity of stenosis, progression of stenosis, structure of plaques, risk of atherosclerosis (systolic blood pressure, cholesterol, diabetes, smoking habits, and age), contralateral symptomatic carotid stenosis or occlusion, and silent ipsilateral cerebral infarctions. The risk of cardiovascular events increases with the grade of stenosis (up to 94%).

Atherosclerotic plaques, which are found in a majority of adults, represent a potential risk of vascular complications. The structure of plaque can be determined by ultrasound scan.

Geroulakos describes 5 types of plaques: type 1, uniformly echolucent; type 2, predominantly echolucent; type 3, predominantly echogenic; type 4, uniformly echogenic; and type 5, unclassified calcified plaque.

The histology of plaques is also related to embolic events and cerebrovascular complications. Echogenic and echolucent plaques have different compositions in terms of lymphocytes and macrophages, which determines their stability. Vulnerable carotid plaques are echolucent on ultrasound, have low gray-scale medians (GSM) and high concentration of inflammatory cells.

Take-home messages:

- Up to 30% of ischemic strokes are related to extracranial carotid atherosclerosis.
- As only a small portion of subjects with carotid atherosclerotic lesions develop cerebrovascular complications, it is important to identify those subjects at highest risk.
- The most significant predictors of cerebrovascular incidents are the degree of carotid stenosis, the structure of atherosclerotic lesions, and the degree of inflammation.
- Using new, noninvasive technologies (ultrasonography, positron emission tomography-computed tomography [PET/CT] scan), it is possible to identify the structure and stability of atherosclerotic plaques in vivo.
- It is expected that new diagnostic procedures will help identify those patients in whom intensive—including invasive—treatments would be most effective and indispensable.

Emergency carotid interventions

G. Szendro (Israel)

Emergency carotid endarterectomy (CEA) can be performed in several symptomatic situations: in crescendo transient ischemic attack (TIA), stroke in evolution, or within 48 hours of the index event; however, the risk of postoperative stroke (immediate or late) is higher.

The merits of emergency carotid revascularization for acute stroke and fluctuating neurological deficits is no longer controversial and is becoming increasingly common. The indications for this procedure are acute or fluctuating hemispheric symptoms, significant carotid stenosis, no cerebral hemorrhage, and stable cardiopulmonary state.

The combined risk of neurological and cardiac complications after carotid endarterectomy (CEA) for crescendo TIA is high but still acceptable considering the natural history of patients with unstable neurologic symptoms (combined stroke/death rate of 7% compared with 2.4% in elective cases). In Szendro's group, the combined stroke/death rate in the last 36 months in symptomatic patients was of only 1.5%.

Randomized trials confirmed the benefit of CEA in symptomatic patients with tight carotid stenosis. The timing of surgery in these patients is debated, the dilemma being the risk of recurrent stroke during the waiting period versus the risk of early intervention. There is a benefit from early intervention (<2 weeks). Two recent meta-analyses confirmed this with a stroke risk of 6.7% at 48 hours and 10 % at 7 days. The North Dublin population Stroke study reported a 5.6% rate of recurrent stroke at 72 hours with carotid stenosis being the only predictor.

However, so far no randomized controlled trial data support early CEA after an acute neurological event. In a systematic review, Rerkasem (*Stroke*, 2009) found no substantially elevated risk with early surgery in stable patients but found an elevated risk in patients with stroke in evolution or in crescendo TIAs. However, many other reports suggest a risk similar to that of stable patients. In their meta-analysis, Naylor and coworkers also reported a high rate of combined neurological and cardiac complications following urgent CEA for unstable neurological symptoms, and for crescendo TIA they found a 6.5% rate of perioperative stroke, a 9.0%rate of perioperative stroke and death, and a 10.9% rate of perioperative stroke, death, and major cardiac event. In patients with crescendo TIA and evolving stroke these risks rose to 16.9%, 20%, and 20.8%, respectively. Despite these numbers, most reports describe instantaneously improved neurological deficits and even full recovery in most cases of rescue CEA in selected patients. Intraoperative shunting is recommended although this recommendation is not evidence-based.

Carotid artery stenting (CAS) in emergency carotid stenosis is more controversial, because the safety and efficacy of urgent stenting have not been established and are usually not recommended in the acute setting. Sporadic reports show the feasibility and efficacy of urgent CAS, which can sometimes be helpful if combined with thrombolysis in acute symptomatic internal carotid artery occlusion.

Emergency intervention for internal carotid artery dissection could be performed with conservative treatment, open surgery, or CAS. Dissection can be spontaneous or post-trauma. There are very little controlled data, and most papers report case-controlled and observational studies.

Conservative options include anticoagulation, antiplatelet drugs, and thrombolysis (intravenous or intra-arterial). A meta-analysis (Georgiadis, *Neurology* 2009) showed no benefit for anticoagulation compared with aspirin in stroke prevention. This was confirmed in a meta-analysis including 762 patients (Menon, *J Neurosurg Psychiatry*, 2008), which concluded that there are no data to support the superiority of anticoagulants over antiplatelet therapy, that thrombolysis appears safe but that more data is required, and finally that stenting is technically possible although there is no data to demonstrate its efficacy.

Surgery or stenting should only be undertaken very rarely in case of stroke recurrence or to restore cerebral perfusion if irreversible infarction has not occurred. Aneurysmal intervention is very rarely needed (up to 50% of aneurysms resolve or shrink in size). Aneurysm enlargement is very rare (Redekop, *Can J Neurol Sci* 2008). The mechanisms of thrombolysis remain unclear.

Emergency thromboembolectomy: although cardioembolic internal carotid artery occlusion is very rare due to cardiac emboli, some incidents happen during hospitalization. Is there a place for urgent open embolectomy? There is a 100% technical success rate, with clinical improvement in high-risk selected patients. Embolectomy should be considered immediately in patients with atrial fibrillation and a very short clinical course (Murata, *Neurosurg Rev* 2010).

Mobile/unstable carotid plaques are very rare, could be spontaneous or post-trauma. Although acute thrombosis is rare, it can be treated with a conservative approach (antithrombotic drugs, antiplatelet or anticoagulation, stenting, and CEA). In asymptomatic cases, conservative therapy is the most common approach whereas CEA is recommended in symptomatic patients; CAS could be an option in several cases.

Vascular injuries in the cervico-thoracic region have a 25% mortality rate, so aggressive management of unstable patients is recommended. In stable patients, imaging is mandatory. Urgent surgery is used more frequently in case of penetrating neck trauma, which is characterized by the following hard signs: hemorrhage, expanding hematoma, bruit/thrill, absent pulse, and hemodynamic instability. The surgical principles include damage control, occasional temporary shunt, and balloon tamponade with Foley catheter. In 220 patients, Navsaria (*World J Surg* 2006) used 17 hemostatic balloons for18 stab wounds and found 3 arterial injuries by arteriography (open surgery on those cases). Balloon removal was successful after 72 hours in 13 cases and 1 patient underwent emergency surgery after removing the Foley.

Anticoagulation is the gold standard to reduce strokes in patients with blunt trauma. Of 643patients screened by angiography for carotid injury, 114 (18%) had carotid lesions. Anticoagulation was used in 73 patients (0 strokes); while in 41 patients, anticoagulation was not used (19 strokes).

False aneurysms are very rare, post-CEA there are less than 0.4% to 1%, and there are anecdotic cases post-CAS or post-trauma. The dangers are rupture, embolization, thrombosis, and compression. Infection occurs in one-third of cases. The recommended treatment is open surgery; CAS can be used as a bridging procedure though it can occasionally be definitive.

Combined carotid and coronary artery revascularization – should it be eliminated?

A. von Ristow (Brazil)

Atherothrombosis is a multifocal disease, and in a high proportion of cases, carotid occlusive disease and coronary artery disease coexist in the same patient.

In the presence of severe carotid occlusive disease and coronary artery disease, carotid endarterectomy (CEA) and coronary artery bypass graft surgery (CABG) have been employed either in sequence or simultaneously for more than 40 years. There are three traditional strategies. Staged CEA followed by CABG, combined CEA and CABG, or staged CABG followed by CEA. Carotid artery stenting (CAS) can be an alternative to CEA in several cases (usually prior to CABG).

But the additional carotid operation seems to put patients at increased risk of perioperative complications such as stroke and myocardial infarction when patients present with other associated clinical conditions. The risk of stroke in simultaneous CABG and valve replacement ranges from 4.2% to 13.0%. With CABG, the risk of stroke is of 3.0% in patients with unilateral >50% carotid stenosis, 5% in patients with bilateral stenosis, and rises to 7% in case of occlusion. For this

reason, most authors favor simultaneous CEA and CABG because stroke and 30-day mortality rates in selected centers range from 2.8% to 5.5% and 3.6% to 6.1%, respectively. However, in a systematic literature review, the combined rate of death, stroke, and myocardial infarction ranged from 9.7% to 17.7%.

In staged procedures, some patients die while waiting for the procedure. In 2006, Randall described that 5.7% of patients died prior to surgery and the total stroke and death rate at 30 days was 19.2% (Randall, *Stroke* 2006).

At Centervasc, after 2091 carotid revascularization procedures, the approach to the problem is to:

- Treat the symptomatic territory first, whenever possible.
- Perform simultaneous interventions only in unstable angina and severe carotid disease or coronary and cerebrovascular symptoms.

After initiating this strategy in 1988, staged CEA was performed and followed by CABG during the same hospital admission in 27 cases (without carotid operative mortality) and simultaneous CEA and CABG in 65 cases (which only prolonged the mean operative time by 45 min). There was no operative death, 5 cases of postoperative neurologic deficits (2 reversible and 3 irreversible with progression to death). The mortality after 30 days was 4.6%, and in these 3 patients the pump time was over 2 hours.

The overall incidence of stroke in CABG ranges from 1% to 2%; in patients with severe carotid disease, it can be up to 17%, but, despite this important correlation, only half of the strokes that occur during coronary surgery have a carotid etiology.

The etiology of perioperative stroke in CABG is multiple: embolism (air, calcium, aortic atheromatous debris, debris from extracorporeal circuits, thrombi…), aortic dissection, and hypotension.

If carotid stenosis is an important cause of stroke during open heart surgery, cerebral infarctions should be ipsilateral to the severely diseased vessel. Several studies have shown that this is not true. A severely narrowed or occluded carotid may in fact reduce embolization to the affected hemisphere.

The theoretic etiology of strokes during CABG include hypoperfusion (global or focal), and thromboembolic (heart or arterial) and hematologic etiology. During extracorporeal circulation, cerebral embolization seems unlikely. Perioperative hypotension may play an important role. Since hypotension is not totally preventable, all patients with high-grade carotid stenosis would be at risk. But the addition of a carotid intervention puts the patient at increased risk of preoperative complications.

In conclusion:

- Whenever possible, the symptomatic territory should be treated first.
- Simultaneous carotid and coronary revascularization should be undertaken in patients with symptoms in both territories.
- Symptomatic coronary patients with over 70% asymptomatic carotid stenosis, should also be operated simultaneously.
- The combination of CEA and CABG should not be abandoned, but should be restricted to specific situations—patients with unstable angina and severe carotid disease—and take place in centers having excellent results in both carotid and coronary surgery.

1.3. Restenosis

Vascular biology of restenosis.

S. Misra (USA)

The author presented his experience in the vascular biology of hemodialysis vascular access restenosis. He described the cost of vascular access–related morbidity (up to 1 billion US $) and the need to study the exact etiology of vascular access failure to determine therapeutic targets.

Vascular access placement induces changes (compliance mismatch, shear stress, hypoxic injury, and inflammatory mediators) that modulate the expression of genes and proteins in the veins (in the adventitia, media, and endothelium) leading to changes in fibroblasts to induce SMC differentiation, migration, and proliferation.

These changes can be studied in animal (pig, mouse, and rat) and human models of arteriovenous fistula stenosis by assessing macrophage infiltration and measuring the expression of HIF-1a, VEGEF-A, MMP-2, TIMP-1, and ADAMTS-1.

Identifying the pathological pathway could help choose the appropriate treatment. The most exciting options at the moment are the “limus” drugs and paclitaxel.

Restenosis after open carotid endarterectomy and after carotid stenting

P. Sedivy (Czech Republic)

From 1994 to 2011, the authors performed 4549 open carotid surgical procedures.

Restenoses of >70% were found in 186 cases(4.1%) after follow-up for 2 to156 months (median, 23 months). Restenosis was asymptomatic in 87% of patients and symptomatic in 13%. The authors reported a single TIA event in over 4549 procedures.

1.4. Peripheral arterial disease

Exercise prescription for peripheral arterial disease

T. G. Allison (US)

Exercise was presented as a therapeutic tool in patients with peripheral arterial disease who suffer from intermittent claudication. These patients have a high mortality.

The AHA/ACC Secondary Prevention Guidelines (2006 update) recommendations described peripheral arterial disease rehabilitation (a supervised program of exercise training) as the initial treatment modality for patients with intermittent claudication. (class 1, level A).

The exercise prescription for supervised endurance training in peripheral arterial disease with intermittent claudication must be carried out with a frequency of 3 to 5 times per week, on a treadmill, letting the patients walk until they experience the onset of ischemic pain, and repeating the exercise in successive periods of at least 50 minutes for each session.

The benefits of exercise training include improved walking distance and improved quality of life; however, there is no effect on the ankle brachial index (ABI). There are minimal increases in collaterals, which could demonstrate improved endothelial function, improved myocardial energetics, and reduced markers of systemic inflammation.

Risk factor management in patients with peripheral arterial disease (symposium of the vascular medicine section of the Royal Society of Medicine)

Risk stratification beyond Framingham. A practical approach.

A. Nicolaides (UK).

Prof Nicolaides talked about the 10-year cardiovascular risk in the general population according to population studies such as Framingham and PROCAM. He pointed out that this risk is age driven. For example, a 75-year-old male without risk factors is at high risk because of his age and a 40-year-old female with several risk factors may be at lower risk, again because of her age. However, it is this female who needs risk factor modification. Prof Nicolaides pointed out that only 50% of heart attacks occur in high-risk groups and that 40% of the individuals who suffer myocardial infarction (MI) do not have conventional risk factors.

In the PROCAM study only 6.5% of subjects in the general population were at high risk (risk >20% at 10 years), 14% of the population was at intermediate risk (10%-20% risk at 10 years) and the rest of the population (79.5%) was at low risk (risk < 10% at 10 years). However, the percentage of myocardial infarctions was equally distributed in the 3 groups: (33% occurred in the high-risk group, 35% in the intermediate-risk group, and 32% in the low-risk group). It is therefore necessary to develop a methodology and strategy to make better predictions.

There are three methods that can complement the Framingham risk score and can help reclassify patients into higher or lower risk categories: ankle brachial index (ABI), coronary artery calcium score (CACS), and ultrasound arterial scanning.

ABI is not useful below the age of 70 because it will be normal in the vast majority of people. CACS can improve prediction in individuals in the intermediate Framingham risk group, but has several disadvantages: it cannot identify those with noncalcified plaques, it is expensive, and individuals are subjected to high radiation. Ultrasound scanning is the most practical and useful of the three as an initial screening tool. The presence of carotid bifurcation or common femoral bifurcation atherosclerotic plaques allows reclassification of individuals into the high-risk group, even in the absence of risk factors. Its successful prediction has now been demonstrated in many prospective studies

- In individuals aged >40 years and at low Framingham risk should be screened with ultrasonography (both carotid and common femoral bifurcations):
  - The absence of plaques will confirm a low risk in 60% of cases. A repeat scan should be carried out 3 to 4 years later.
  - The presence of plaques will result in reclassification to a higher risk in 40% of cases. Individuals should be advised about risk factor modification and the presence of nonconventional risk factor (eg, hyperhomocysteinemia) should be investigated.
- Individuals aged >40 years and at intermediate Framingham risk at 10 years should be screened with ultrasonography (both carotid and common femoral bifurcations):
  - If plaques are present (in 80% of cases) aggressive risk factor modification is advised. Individuals with plaques should be told that the plaques should not be allowed to progress and that regression with treatment to target, which usually occurs in 28%, is associated with a 50% reduction in risk. Also, advise patients to have an annual ECG stress test.
  - If plaques are absent (in 20%) then CACS may be performed. It will allow reclassification to a lower- or higher-risk group with confidence.

Individuals aged >40 years and at high Framingham risk are advised to have aggressive risk factor modification according to current guidelines. Screening with ultrasound in order to follow plaque progression or regression is optional. It can be used to motivate individuals to adhere to prophylactic measures.

Inflammation markers and assessment of vascular risk

J. Belch (UK)

The association between the presence of intermittent claudication (IC) and survival were presented by the author. For the following risk factors the odds ratio are significantly increased: male gender, age, diabetes, hypertension,

hypercholesterolemia, and fibrinogen. Alcohol has a protective effect. The author described the different concepts and their relations:

- *Peripheral arterial disease and inflammation:* importance of the activity of white blood cells, E-selectin, C-reactive protein, and others. However, it is still unclear whether inflammation is a cause or a consequence.
- *Genetics:* there are studies showing the concordance of the ankle brachial index in twins, which suggests that genetic factors determine 48% of the variability in ankle brachial index scores after risk factor adjustment.
- *Infection and peripheral arterial disease risk:* smokers have more periodontal disease and *H. pylori* infection. It is not clear whether this is a cause or a consequence.
- *Autoimmune disease:* increased mortality in rheumatoid arthritis, sclerosis, and lupus (×3 to ×4) but the actual mechanism is still unclear.
- *Inflammation as an acute response to exercise and alteration in skeletal muscle structure* are recent findings but with unclear significance.

Is there any benefit from the management of dyslipidemia in peripheral vascular disease?

D. Mikhailibis (UK)

Prof Mikhailibis defended the increased use of aggressive approaches with statin treatment in order to decrease cardiac mortality with evident benefits even after short-term use. This treatment could also be positive in patients with decreased claudication and stroke. He mentioned that carotid plaque composition changes as a result of treatment with statins, and remarked on the significant decrease in intima media thickness and reduction in plaque with atorvastatin.

What is the effect of exercise on risk factor control?

G. Geroulakos (UK)

The use of exercise as a therapeutic tool was discussed. Leisure time plus activity could decrease the risk in coronary artery disease by 30% to 50% and this effect is linear. The effect of aerobic training is multifactorial: increased HDL-cholesterol, decreased triglycerides, improved glucose tolerance, decreased blood pressure (systolic and diastolic) in normal-weight or overweight normotensive and hypertensive patients. Exercise duration, but not intensity, was the most important element of success. Inflammatory and lipid changes during protracted exercise were studied in a 246-km race (spartathlon). Impressive but reversible changes were observed. In the current climate of global economic recession, physical exercise is perhaps one of the very few nonpharmacological interventions that has a very significant benefit by reducing cardiovascular and all-cause mortality at no or low cost.

Management of hypertension in patients with peripheral arterial disease

R. Cifkova (Czech Republic)

Prof Cifkova stated that the association between peripheral arterial disease and hypertension is underestimated and stressed the importance of hypertension treatment in order to decrease renal artery disease and cardiovascular mortality. She explained that only angiotensin-converting enzyme (ACE) inhibitors could increase walking distance. β-Blockers can be used in patients with peripheral arterial disease and there is no reason to restrict their use in the absence of other contraindications, especially in patients with critical ischemia where acute lowering of blood pressure is contraindicated.

1.5. Critical limb ischemia

Critical limb ischemia: open or endovascular approach?

N. Angelides (Cyprus)

Critical limb ischemia (CLI) is a severe arterial condition. One year after the initial diagnosis, only 56% of patients were alive with 2 viable legs, 26% had a major amputation, and 18% had died.

Progression of intermittent claudication to CLI occurs in less than 20% of nondiabetic patients whereas it occurs in more than 40% of patients with diabetes.

An initial endovascular attempt could be undertaken for all lesions (Trans-Atlantic Inter-Society Consensus [TASC] classification A to D) prior to any open surgery. Percutaneous catheter procedures are less traumatic, cheaper than surgery, and can be repeated with few complications. However the restenosis rate is still high (up to 30%).

The introduction of drug-eluting stents has partially solved the problem of early restenosis. These stents showed superiority to bare-metal stents in preventing tissue ingrowth even in the long term.

Drug-eluting balloons represent a novel option for the treatment of coronary and peripheral occlusive lesions. These balloons are coated with a drug that can be released when the balloon is expanded. The drug is absorbed in the wall of the vessel and can prevent tissue ingrowth. Drug-eluting balloons are mainly used in case of coronary in-stent restenosis, superficial femoral in-stent restenosis, as well as in distal blocked arteries. Some trials (THUNDER, PACIFIER, and LEVANT) are now in progress. LEVANT 1 and LEVANT 2 evaluated the safety and efficacy of Moxy drug–coated balloons in the treatment of femoro-popliteal segment occlusions and demonstrated that this coat strongly inhibits neointimal hyperplasia.

According to consensus documents, an open reconstructive procedure should be undertaken in patients with CLI when endovascular procedure has been unsuccessful and there is still a 25% of chance of saving the limb for a period of 1 year. The author has performed aorto-iliac bypass in TASC D and TASC C patients with tortuous and atherosclerotic arteries by means of a bifurcated prosthetic graft. The postoperative patency at 1 and 5 years is about 90% and 75%,

respectively. Femoral-popliteal bypass grafts were performed in patients with TASC D and C lesions with tortuous arteries with multilevel occlusions. A vein graft is always preferred. Polytetrafluoroethylene (PTFE) grafts are used for above-the-knee bypass because the results are good and the vein is preserved for a possible repeat surgery or for coronary vein bypass surgery. In case of graft occlusion, thrombolysis should be initiated as soon as possible. When there is no run off below the femoral artery, no tissue loss, nor rest pain, a primary amputation should be considered in order to avoid increased mortality and morbidity.

Percutaneous transluminal angioplasty versus primary stenting in below the knee arteries in critical limb ischemia

B. Brodman (Austria)

The value of primary balloon angioplasty in patients with critical limb ischemia (CLI) below the knee has already been reported; however, this is not the case for primary stent implantation.

The author reported a monocenter randomized controlled trial in 54 patients with CLI who had been treated by either percutaneous transluminal angioplasty (PTA) or stenting in the infrapopliteal arteries. They studied the effects of these treatments in terms of clinical benefits and rate of reobstruction at 1 year.

Clinical benefit was improved by at least one Rutherford classification in 81.5% of patients in the PTA group and by only 64.7% in the stent group. Similar positive results were observed for ulcer healing.

Reobstruction occurred in 39.4% of patients in the PTA group, compared with 66.7% in the stent group at 1 year of follow-up. The loss of primary patency as well as secondary patency was higher for the stent group after 1 year.

They concluded that PTA alone with the application of a modern hydrophilic balloon catheter is superior to primary stenting with expandable balloons.

Long-term results of intra-arterial infusion of autologous bone marrow mononuclear cells in patients with critical limb ischemia

M. Chochola (Czech Republic)

Critical limb ischemia (CLI) can lead to amputation in 25% of cases. Perfusion of bone marrow mononuclear cells (BMMC) is performed in order to achieve better angiogenesis.

In this study, intra-arterial infusion of BMMC was performed in 28 patients with severe CLI. Their clinical status and ankle brachial index (ABI) were evaluated every 6 months and their quality of life was assessed with the SF 36 questionnaire.

Only 2 major amputations were needed, with an improvement on defect healing and clinical status as well as on ankle brachial index (ABI), transcutaneous oxygen (TcpO2), and quality of life. After 5 years of follow-up, 14 patients had died (50%) due to multiple cardiovascular comorbidities. None of the surviving patients underwent major amputation.

This expensive therapeutic option could be suitable for the treatment of CLI in elective patients even if the long-term outcome is unfavorable due to the high mortality caused by cardiovascular comorbidities.

1.6. Stroke / atrial fibrillation

Differentiation of the newer oral anticoagulants for the management of stroke and atrial fibrillation

Pathogenesis and management of stroke. Impact of new oral anticoagulants

J. Biller (USA).

The pathogenesis of ischemic stroke includes various underlying diseases—large artery atherosclerosis, cardiac disease, small artery diseases, and other diseases such as the so-called cryptogenic stroke. Warfarin is effective in stroke prevention in patients at high risk of cardioembolic stroke, especially in those with nonvalvular atrial fibrillation but also in patients with recent myocardial infarction, dilative cardiomyopathy, mitral stenosis, mechanical prosthesis heart valve, or mechanical valve endocarditis. The risk profile of a patient can be calculated using a scoring system such as the CHADS2 or CHA2DS2VASc scores. Warfarin use significantly reduces the risk of all strokes, ischemic stroke, and all-cause mortality in comparison with antiplatelet therapy. However, there are no other potential indications for warfarin in the prevention of ischemic stroke.

At a high dose (150 mg twice daily), dabigatran was more effective than warfarin for the prevention of ischemic stroke, but at a low dose (110mg twice daily), it was equally as effective. However, the greatest efficacy in comparison with warfarin was reached at sites with poor international normalized ratio (INR) control. Both dabigatran and rivaroxaban have been approved for stroke prevention in patients with nonvalvular atrial fibrillation. Another oral anticoagulant, apixaban, is currently being reviewed by the American and European authorities for this indication.

Clinical efficacy and safety issues with newer anticoagulants in atrial fibrillation

S. Coccheri (Italy).

We will probably not have a head-to-head comparison of the new anticoagulants in the near future. According to the Euro Heart survey, 30% of high-risk patients with atrial fibrillation are undertreated, which means that the risk of ischemic stroke is twice higher. It is practically impossible to develop an absolutely safe anticoagulant. Attempts to introduce new anticoagulants were made with the goal of avoiding the need for laboratory monitoring and to maintain reasonable costs. The new anticoagulant drugs have some common properties (oral use, predictable dose-response, no need for laboratory monitoring, fixed or weight-adjusted dosage). On the other hand, there are also differences in the properties of these new drugs as well as differences in the design of phase3 clinical studies with new anticoagulants in atrial fibrillation patients. Indirect comparison of the new oral anticoagulants has shown that they differ in some aspects. In comparison with warfarin, intracranial bleeding was reduced by all of them, especially by apixaban. Concerning all-cause mortality, superiority to warfarin was proved only

for apixaban. When considering the number needed to treat (NNT) to prevent one stroke, high-dose dabigatran was the most effective. Rivaroxaban was less effective in secondary prevention but this finding might have been caused by a higher proportion of high-risk patients in the ROCKET-AF trial than in the other two atrial fibrillation studies.

In conclusion, careful reappraisal of the available data is needed before implementing these new drugs in routine clinical practice.

Impact of newer anticoagulants on the management of atrial fibrillation

J. Harenberg (Germany).

The three new anticoagulants proved their superiority or equivalence in comparison with well-controlled warfarin therapy. However, it is highly unlikely that a direct comparison of their efficacy will be performed in the near future due to cost issues and complicated logistics. The author presented a special statistical method for an indirect comparison—a network meta-analysis. The results of three atrial fibrillation studies were evaluated: RE-LY (compared dabigatran at high or low dose versus warfarin), ROCKET-AF (rivaroxaban versus warfarin), and ARISTOTLE (apixaban versus warfarin). They assessed similar outcomes: stroke, systemic embolism, major bleeding, intracranial bleeding, and mortality. Some significant differences were found:

- High-dose dabigatran was superior to low-dose dabigatran as well as rivaroxaban in preventing ischemic stroke.
- High-dose dabigatran was associated with a mild increase in the incidence of myocardial infarction when compared with rivaroxaban.
- Apixaban induced less major bleeding than high-dose dabigatran
- Low-dose dabigatran was associated with less major bleeding, less intracranial hemorrhage, but slightly more myocardial infarction cases than rivaroxaban
- No significant differences were found between low-dose dabigatran and apixaban.
- Apixaban caused less major bleeding and slightly less (borderline significance) intracranial hemorrhage than rivaroxaban.

In conclusion, apixaban and low-dose dabigatran seem to have reached the best risk-benefit ratio.

Safety of newer oral anticoagulants. What's new?

W. Leong (Canada)

There are many issues remaining concerning the new anticoagulants. Their potential advantage, ie, no need for laboratory monitoring, may lead to very infrequent contact between patients and physicians. Taking a closer look at the results of the RE-LY study, well-controlled warfarin therapy was as good as

dabigatran in stroke prophylaxis in patients with atrial fibrillation. In warfarin management, it is crucial to monitor the international normalized ratio (INR) carefully and reach the best possible time in the therapeutic range (TTR). Safety problems with the new anticoagulants are not negligible. In fact, specific patient populations may need laboratory monitoring but no reliable tests are currently available. In addition, no specific antidote has been developed so far. To date, clinical studies have excluded patients with specific problems (serious renal insufficiency, recent stroke). Some potential drug-drug interactions have also been reported with the new anticoagulants and uncertainty remains concerning the perioperative management of patients or the potential risk of combining these drugs with antiplatelet therapy. Therefore, warfarin will probably not become obsolete in the near future.

Invited discussion

B. Kaiser (Germany)

In the final discussion of the session, the speaker described the differences among the new anticoagulants—different targets, and different pharmacokinetic and pharmacodynamic properties—and reminded the audience of their safety issues—absence of a specific antidote, possible accumulation in patients with renal impairment or hepatic disease, and potential drug interactions. She came to the conclusion that at present, there is no simple answer to the question of which anticoagulant to choose for stroke prophylaxis in patients with atrial fibrillation.

High risk patients for stroke can now be identified using TCD, silent brain infarcts on CT or carotid plaque image analysis: where do we go from here?

A Nicolaides (UK)

In the last 5 years the therapeutic attitude toward asymptomatic carotid stenosis patients has changed because with the use of aggressive medical therapy the annual risk of ipsilateral stroke is now close to 1%. This makes routine carotid endarterectomy unjustified. However, if patient subgroups with sufficiently higher than average risk, despite optimal intervention, could be reliably identified, then carotid surgery may still be justified. Three methods can be used to identify patents at increased risk.

(a) The presence of micro-embolic signals (MES) (>2/hour) using transcranial Doppler (TCD).

The ACES multicenter study (467 patients with >70% stenosis with a mean follow-up of 2 years; Marcus, *Lancet Neurol* 2010) demonstrated an 8% annual ipsilateral stroke risk in patients with MES on TCD, in contrast to 1% in patient without MES. In a meta-analysis of all the published studies MES were present in 15% to 20% of patients with ACS and their presence identified a high-risk group. However, this group contained only 54% of the strokes, thus, 46% of the plaques that produced a stroke were missed. This means that many plaques rupture without producing MES. Perhaps only plaques with a thrombus on their surface produce MES.

(b) The presence of Silent CT-Brain Infarcts.

The prevalence of silent CT-brain infarcts in asymptomatic patients having carotid endarterectomy (>70% NASCET) was 14% in one study (Martin, *J Vasc Surg* 1991) and 18% in another (Cao, *J Vasc Surg* 1999). In a prospective study (ACSRS) with 8 years of follow-up in 572 patients with 60-99% NASCET stenosis, the presence of silent embolic infarcts identified a group that had an annual stroke risk of 3.6% in contrast to 1% in those without such infarcts (Kakkos, *J Vasc Surg* 2009). However, this high-risk group contained only 30% of the strokes. This means that 70% of the plaques that produced a stroke were missed. Perhaps many plaques rupture and produce a stroke without any previous emboli or infarcts.

(c) Texture analysis of ultrasonic images of plaques.

The relationship between hypoechoic plaques and increased risk of stroke was demonstrated in four prospective studies: Polack (*Radiology*, 1998) showed a relative risk (RR) of 2.8; in the Tromso Study (Mathiesen, *Circulation* 2001), the RR was 4.6; Gronholdt (*Circulation* 2001) found a RR of 3.1, and Hashimoto (*Cerebrovasc Dis* 2009) found a RR of 4.4. The last three studies used gray-scale median (GSM) as a measurement of plaque echodensity.

In the ACSRS study (1121 patients with a 4-year mean follow-up), severity of stenosis, history of contralateral transient ischemic attack/stroke, low GSM, increased plaque area, and discrete white plaque areas (DWA) without acoustic shadowing were independent predictors of risk. These predictors allowed risk stratification from 0.1% per year to 10% per year (Nicolaides, *J Vasc Surg* 2010).

The presence of juxtaluminal black areas without a visible echogenic cap (JBA) is associated with a necrotic core located at a juxtaluminal position on histology with a sensitivity of 84% and specificity of 75% (Sztajzel, *Stroke* 2005). In the ACSRS study, this new ultrasonic feature, JBA, could identify a high-risk group with an annual stroke rate of 4.1%. This group consisted of 22% of the population and contained (42/59) 71% of the ipsilateral hemispheric strokes that occurred during the 8-year follow-up (Kakkos, *J Vasc Surg* 2012).

User-friendly software for image analysis and training is now is available for vascular labs and risk stratification is within the ability of every vascular lab as long as referring doctors request it.

1.7. Others

Management of patients with polyvascular atherosclerotic disease

P. Poredos (Slovenia)

Atherosclerosis may be considered as a systemic (generalized) disease, and therefore:

- Patients with proven atherosclerotic disease are likely to have similar lesions in other vascular beds.
- With the progression of atherosclerosis, more vascular segments are affected and the prognosis worsens.

Advanced atherosclerosis is more widespread, and the prevalence of coronary heart disease (CHD) increases from 18% in patients with mild claudication to 48% in case of severe claudication (da Silva, 1981) and up to 90% if critical limb ischemia is present. The coincidence of peripheral arterial disease (PAD) and CHD depends on the type of diagnostic test. The rate of patients with concomitant PAD and CHD ranges from 20% to 50% if the diagnosis is based on history plus electrocardiogram (ECG) and from 80% to 90% if stress tests or angiography are used (Dormandy, 1992). This is of essential importance for prognosis. All-cause mortality after major vascular surgery depends on the number of vascular beds affected. In a study of 2933 patients, Kuijk (E*ur Heart J* 2010) showed that mortality increased linearly following parallel slopes (each one with an additional 15% increase in mortality) if 1, 2, or 3 vascular beds are affected. Mortality is mostly caused by cardiovascular events, as the REACH registry has showed.

Then, how to investigate patients with polyvascular disease? A systemic (global) disease may need a systemic (global) investigation, but advanced images of the whole body still have limitations; magnetic resonance imaging is expensive and time-consuming, computed tomography angiography produces radiation and contrast-related complications, and ultrasonography is time-consuming and some areas have limited accessibility. We must therefore choose from a number of basic investigations:

- In PAD patients we must use techniques for the identification of peripheral arterial lesions (Doppler, ultrasonography, angiography,…) and techniques for the recognition of atherosclerosis in other territories (electrocardiogram [ECG] and if necessary scintigraphy, exercise test, carotid ultrasound, and abdominal ultrasound).
- In CHD patients we must identify coronary lesions (ECG, stress test, coronarography) and search for atherosclerosis in other vascular beds (ankle brachial index [ABI], carotid bruit, and ultrasound).
- In cardiovascular disease (CVD) patients we must identify carotid lesions with ultrasonography and angiography and investigate other vascular beds with ECG and ABI.

For all patients we must remember the importance of ABI. This exploration must be performed in all patients with any atherosclerotic disease (CVD, CHD, and peripheral vascular disease [PVD]) particularly in those with polyvascular disease. It may be useful in subjects with no disease but with a high risk score.

What is the treatment for patients with polyvascular disease?

Risk factors should be managed and revascularization should be performed if needed.

The risk factors for atherosclerosis are multiple, and it is important to at least consider lifestyle (smoking, diet, and lack of exercise), hypercoagulable states, homocysteinemia, diabetes, obesity, genetics, hyperlipidemia, hypertension, age, gender, and infection. The REACH registry, with nearly 20 000 patients, has showed us that polyvascular disease patients have more risk factors (more weight for smoking, hypertension, and diabetes) than those with only one affected vascular bed. The control of risk factors in polyvascular disease must be more aggressive. The strategy is similar with medical therapy, so with more vascular beds involved, the treatment should be more aggressive.

There are differences in the relative weights of risk factors in the different vascular diseases:

- In CHD, hypercholesterolemia is the main risk factor, more so than smoking; the third risk factor is hypertension, while diabetes is the fourth.
- The risk factors for CVD are ranked as follows: hypertension > diabetes > dyslipidemia > smoking.
- For PAD, smoking is the main factor, followed by diabetes > hypercholesterolemia > hypertension.

On this basis, is the efficacy of the drugs used for the prevention of atherosclerosis comparable between different territories? Antiplatelet drugs seem to be more effective in the coronary bed (TRAN, *JAMA* 2004). From the CAPRIE study, we know that clopidogrel seems to be superior to aspirin in PAD, and aspirin is effective for prevention in CHD but not in PAD. Therefore, thienopyridines are probably the drugs of choice in PAD.

Statin trials in CHD have showed that a 1% reduction in LDL-cholesterol levels decreases cardiovascular events by 2%, and that secondary prevention of cardiovascular events in patients with PAD or stroke treated with statins decreases the number of cardiovascular events (Heart Protection Study, *Lancet* 2002). In fact, statin treatment provides benefits for all the vascular beds.

In patients with intermittent claudication, simvastatin 40 mg improves the pain-free walking distance (Mondillo, *Am J Med* 2003), which could be a pleiotropic effect of statins.

Angiotensin-converting enzyme (ACE) inhibitors: the HOPE study data demonstrate the absolute benefits of ramipril treatment in patients with multilevel disease.

β-Blocking agents are no longer contraindicated in patients with PAD, and could be prescribed in those with polyvascular disease.
Polyvascular disease patients undergoing revascularization are at increased risk for intraoperative complications related to atherosclerotic lesions in other territories; they have higher postoperative mortality rates, and invasive procedures may be limited due to multifocal limitations. Validated information is lacking regarding both the efficacy of these procedures in elderly patients and priority of revascularization.

Patients undergoing treatment for myocardial infarction (MI) have a 3-fold increased risk of in-hospital major events (7% to 20.4%) and mortality (3.7% to 13%) in case of associated PAD (Jeremias, *AJC* 2010), and the REACH registry (*JAMA* 2007) shows a 2-fold lower mortality for all causes such as CV death, myocardial infarction, and stroke in patients with disease in only one vascular bed compared with those with polyvascular disease .

How can we establish the priority of revascularization in patients with polyvascular disease? Surgical procedures (open or percutaneous) must first be performed in the territories with the most advanced atherosclerotic lesions and when atherosclerosis disease is the most life-threatening.

Revascularization priority should thus be given as follows:

I. Dissecting aortic aneurysm, acute myocardial infarction (ST-segment elevation myocardial infarction).

II. Acute coronary syndrome, symptomatic carotid stenosis, critical limb ischemia.

III. Asymptomatic critical carotid stenosis, asymptomatic AA (>4.5 cm) and limiting intermittent claudication.

When these conditions are concomitant, the priority must be to treat the carotid first, followed by the coronary and peripheral arteries later.

Upper extremity arterial disease: recent trials and future directions

R. F. Shepherd (USA)

Upper extremity arterial disease is less commonly encountered than disease of the lower members, with a wide range of diverse disorders and clinical presentations resulting from the large proximal arteries, smaller digital arteries, or the microvasculature.

Digital ischemia may be constant or episodic due to reversible vasospasm or fixed obstructive disease.

Reversible vasospasm is typical of Raynaud's phenomenon, persistent cyanosis, etc… but could be permanent in scleroderma and lead to critical ischemia.

To assess circulation deficits, noninvasive methods (laser Doppler, plethysmography, arterial waveforms, segmental blood pressure measurements, finger systolic pressure, basal and thermal challenge, and "cold" or "hot box") and imaging studies (contrast angiography, duplex ultrasonography, computed tomography angiography, magnetic resonance angiography) can be used.

- The treatment of Raynaud's remains unsatisfactory because only half of the patients respond to medication and there is poor correlation between the laboratory effect of a medication and clinical response. For this reason, there are multiple therapeutic options and different treatments.

- The few randomized studies that were carried out involved small numbers of patients. In up to 305 cases, the placebo effect was involved. In addition, there are differences in the response of primary and secondary Raynaud's.

- For the treatment of Raynaud's, the first step is to prevent vasospasm and improve distal blood flow. A wide range of drugs can be used:

- Direct vasodilators (nitroglycerin), usually in topical form (gel or patches). They can be effective in primary Raynaud's but their use is limited by side effects (headaches in up to 80% of cases, and hypotension). In a limited number of patients (10 with primary Raynaud's, 13 with scleroderma, 10 controls), Anderson (*Rheumatology* 2002) applied 2% topical glyceryl trinitrate to one finger, placebo treatment to a second finger, and left a third finger untreated. Scanning with laser Doppler to measure immediate baseline microvascular blood flow, at 10 and 20 minutes, Anderson found increases in flow in the three treated fingers.

- Calcium channel antagonists (nifedipine, amlodipine). Thompson reviewed18 studies, 13 studies assessing amlodipine vs placebo, and 5 other studies assessing a different CCB vs placebo, including a total of 348 patients with 10.8 attacks/week (*Rheumatology* 2005). Although he found a 35% reduction in the severity of attacks, the initial benefits were not sustained (tachycardia, headache, edema flushing).

- α-Blockers (a1): Minipress (prazosin), Cardura (doxazocin). Their secondary effects are similar to those of CCBs.

- Prostaglandins (iloprost, prostaglandin E1). They have vasodilatory and antiproliferative effects and inhibit platelet aggregation but they have side effects (headache, flush, nausea, and pulmonary edema). Wigley conducted a multicenter trial (*Ann Inter Med* 1994) that showed the benefits of iloprost in patients with systemic sclerosis in ulcer healing and improved Raynaud's scores by 39% (22% in the placebo group). Oral prostaglandins are not effective.

- Phosphodiesterase inhibitors. They inhibit cyclic GMP in vascular smooth muscle. They are useful for erectile dysfunction and pulmonary hypertension. In a single center study with 16 patients with secondary Raynaud's treated for 4 weeks with 50 mg sildenafil twice a day, laser Doppler showed improved capillary blood flow, a significant reduction in the number of attacks (36 vs 52), and ulcer healing.

- Antiplatelets and anticoagulants (Plavix, heparin).

- Agents improving endothelial function: bosentan, ET-1 receptor antagonist. As endothelin is a potent vasoconstrictor, its antagonist is used in pulmonary hypertension in patients with systemic sclerosis. The RAPID-1 and RAPID 2 trials (*Arthritis Rheum* 2004) have showed a role in Raynaud's. RAPID-1 evaluated the use of bosentan in 122 patients with systemic sclerosis in an international, multicenter, placebo-controlled, double-blind trial. Bosentan reduced the onset of new digital ulcers in 48% of patients but did not alter the time of healing. RAPID-2 (188 patients with secondary Raynaud's) showed a decrease in the number of new ulcers (1.9 vs 2.7). The use of this drug could be limited because it has a black box warning about potential liver toxicity (3-fold increase in liver enzymes in 11% of patients) and FDA pregnancy category X rating because it is very likely to result in major birth defects if used by pregnant women.

- Novel therapies:

  - Herbal preparations (*Gingko biloba*)

  - Fish oils (decrease thromboxane a2)

  - Losartan (angiotensin receptor blocker [ARB], antifibrotic)

  - Biofeedback (to raise digital temperature)

  - Traditional Chinese acupuncture

  - Spinal cord stimulation

  - Pneumatic compression: using an inflatable cuff around the arm with rapid, graduate, sequential, and pulsatile compression. The distal compartment is inflated to 95 mm Hg, 0.3 seconds later, the proximal compartment inflates to 85 mm Hg; after 2 seconds of compression, the cuff deflates and the cycle is repeat every 20 seconds. This device seemed to improve ulcer healing.

  - Botox, use of botulinum toxin type A has been reported by Neumeister (*Plast Reconstr Surg* 2009), in a retrospective study of 19 patients with ischemic hand pain. A total of 16 patients reported pain reduction and 12 (63%) remained free of pain 1 year later. Doppler showed increased tissue perfusion (from 48% to 425%). In a study of 11 patients with nonhealing ulcers, Van Beek (*Plast Reconstr Surg* 2007) showed healing in 9 of them and pain relief in all of them.

Loeys-Dietz syndrome: a case report and review of the literature.

M. G. Costopoulos (USA)

Loeys-Dietz syndrome can be confused with Marfan disease. The author presented the clinical case of a man aged 48 years with previous thromboembolic strokes currently treated with oral anticoagulation. The patient needed urgent repair of the ascending aorta due of a Stanford type A dissection from the origin of the artery to the iliac arteries with a St Jude aortic valve conduit. Genetic testing was positive for the presence of the *TGFBR-2* gene mutation. The patient was left with renal insufficiency. Physical examination was positive for thoracic kyphosis, pectus excavatum, and dolicocephaly.

This syndrome was described by Loeys and colleagues in 2008. It is transmitted genetically as an autosomal dominant disease and shows four specific features: aneurysm and dissection throughout the arterial tree, generalized arterial tortuosity, hypertelorism, and bifid uvula. These signs could be associated with sinus of Valsalva aneurysm, patent ductus arteriosus, atrial septal defects, bicuspid aortic valve, and other features (mental retardation, craniosynostosis, arachnocdactyly, joint laxity, malar hypoplasia, retrognathia, arched palate, blue sclera, easy bruising, dystrophic scars, translucent skin, cervical spine instability, scoliosis, and club foot deformity).

If there is cranio-facial involvement, the disease is named type I, as opposed to type II, which does not show cranio-facial involvement.

Phenotype similarities exist with Marfan disease, but in Loeys-Dietz syndrome, the aneurysms are more aggressive (ruptured and of smaller size) and biosynthesis of fibrillin-1 is normal. The explanation for the similar features between both diseases could be that both TGF-β and fibrillin-1 have a functional role in the synthesis of microfibrils.

There are also similarities with the Ehlers-Danlos type IV phenotype but type III collagen biochemistry is normal.

Treatment has poor results. Early intervention for aneurysmal disease and aggressive control of blood pressure must be performed.

Only two treatments are promising:

- Losartan (which could control arterial pressure and have a secondary effect by blocking TGF-β activity).
- Dexamethasone (which induces a beneficial upregulation in the expression of specific mRNAs leading to the normalization of elastic fiber production in fibroblasts with TGFBR-1 mutations and corrects the abnormal secretion of type 1 collagen in fibroblasts with TGFBR-2 mutations).

Dual antiplatelet therapy and proton pump inhibitors comedication- aren't we throwing the baby out with the bathwater?

J. Bultas (Czech Republic)

More than 30% of patients treated with dual antiplatelet therapy are cotreated with proton pump inhibitors (PPIs), but when these two types of drugs are combined, they are associated with reduced therapeutic effect and with increased cardiovascular risk (hazard ratio, 1.4 for cardiovascular mortality, myocardial infarction, or stroke). This effect seems to be smaller with rabeprazole and pantoprazole and could even disappear in as little as 12 hours if the drugs are discontinued. Another possibility is the use of new drugs that do not need bioactivation with CYP2C19, like ticagrelor, or have a pro-drug with PPI-resistant bioactivation, like prasugrel.

There is another question: do PPIs also interact with aspirin? The answer is yes. Aspirin needs an acid pH (<3.5) for its bioavailability and PPIs interact with its absorption. The antiplatelet effect of comedication is unpredictable.

Thus, patients with a high risk of bleeding could be treated by prasugrel or ticagrelor; *Helicobacter pylori* should be eradicated and PPI comedication should not be used. H_2 Inhibitors should be considered instead of a PPI. Pantoprazole could be an alternative.

Controlled compression ultrasound for peripheral and central venous pressure measurement.

C. Thalhammer (Switzerland)

Central venous pressure is a very important factor in the management of some intensive care patients, eg, patients with cardiac failure, volume overload, and sepsis. Until now, only invasive measurement has been possible. The authors presented a new noninvasive and simple method. They used a special device in connection with compression ultrasound. They compressed a superficial vein of the forearm with an ultrasound probe. They measured the lowest possible pressure necessary to fully compress the venous lumen, and based on this value and on the vertical distance between the site of measurement and the heart level, they calculated the central venous pressure.

They tested this method for peripheral venous pressure measurement in healthy volunteers with experimentally induced venous hypertension as well as for central venous pressure measurement in 50 intensive care patients with a central venous line. In both groups, they found a very good correlation between the results of invasive and noninvasive venous pressure measurements.

Noninvasive central venous pressure measurement by compression ultrasound – a step into real life.

M. Aschwanden (Switzerland)

Both the feasibility and the accuracy of the above described methods of noninvasive central venous pressure measurement with the use of compression ultrasound were tested. The results obtained with a high-end ultrasound machine and with portable ultrasound were compared. Further on, the differences in results between 2 groups of investigators were also compared: vascular specialists and nonvascular physicians who had completed a short training on this method. Both groups performed

measurements in 50 patients in an intensive care unit. The maximal time of measurement was 8 minutes, and feasibility ranged from 88% to 92%. No significant differences were found between the two types of ultrasound machines and the two groups of investigators. The authors concluded that compression ultrasound seems to be an effective method for noninvasive central venous pressure measurement in clinical practice.

Endovascular abdominal aortic surgery, our experience

P. Sedivy (Czech Republic)

The author related his experience in 990 cases of endovascular abdominal surgery.

Patients with special conditions were treated: 4% after open surgery and 3%with infected aneurysms.

In the patients with infected aneurysms, antibiotic therapy was given 2 to 4 weeks before the procedure and 4 to 6 weeks after. In the patients presenting *Salmonella* infection, the antibiotic was maintained in the long term after the procedure (12 months).

Robot-assisted vascular surgery, state of the art

P. Stadler (Czech Republic)

Robots represent the next step in minimally invasive surgery.

The authors used the Da Vinci robotic system between November 2005 and November 2011, performing 225 robotic-assisted laparoscopic aorto-iliac procedures.The clamping time was between 21 and 120 minutes according to the learning curve (ie, decreasing with experience). Conversion was made in 9 cases (3.8%)

The authors demonstrated the feasibility of this technique on aorto-iliac and hybrid procedures and in case of a difficult approach as for some visceral aneurysms, mammary artery aneurysms, and endoleak II – treatment.

II. Venous diseases

2.1. Venous thromboembolic diseases

2.1.1. Epidemiology

Venous thrombosis in hospitalized patients: a French epidemiological analysis

F. A. Allaert (France)

From 2005 to 2009, 693 997 deep venous thrombosis (DVT) or pulmonary embolisms (PE) were found during hospitalization in France. Prevalence was around 8.6% in a population of 43.5% males and 56.5% females.

DVT alone was responsible for 57.7% of cases, while PE, with or without DVT, accounted to 48.3% of cases.

The main reason for hospitalization was cardiovascular diseases (13.5%), tumors (10.6%), respiratory diseases (8.6%), and digestives diseases (6.4%).

Around 140 000 cases of DVT or PE are treated each year in French Hospitals. The mortality rate is close to 10 % for DVT and PE occurring during hospitalization.

Round-table discussion: acute venous thromboembolism in special populations. Lessons from the RIETE registry

In this session the authors reported data from RIETE (Registro Informatizado de la Enfermedad TromboEmbolica), an ongoing, multicenter, observational registry of consecutive patients with symptomatic, objectively proven, acute venous thromboembolism (VTE).

A. Visonà (Italy) stated that in elderly patients with dementia it is difficult to determine the correct incidence of venous thromboembolism (VTE). Impaired mobility causes increased VTE risk, while concomitant therapy results in increased bleeding risk. Moreover, the balance between the efficacy and safety of anticoagulants is uncertain. In a total of 30 895 patients, 1087 had dementia. During the 3-month study period 4.6% of these patients had fatal pulmonary embolism (PE), while, the incidence of PE in patients without dementia was 1.5%. Fatal bleeding occurred in 1.7% of patients with dementia, and in 0.6% of patients without dementia. Patients with dementia initially presenting with PE died from PE or bleeding in 9% and 2.2% of cases, respectively, and those initially presenting with deep venous thrombosis (DVT) alone died from PE and bleeding in 0.9% and 1.2% of cases, respectively. Patients with dementia had a 3-fold higher incidence of fatal PE and fatal bleeding than patients without dementia. With initial presentation of PE the risk of fatal PE in patients with dementia is 4-fold higher than that of fatal bleeding. With initial presentation of DVT alone, the risk of fatal PE is lower than the risk of fatal bleeding.

I. Tzoran (Israel) presented data about silent PE in patients with DVT. Major outcomes such as symptomatic PE or major bleeding occur within 90 days of DVT diagnosis. Out of 2375 patients with DVT, 842 had silent PE and among these, cancer was diagnosed in 33% of cases and prior VTE in 17%. The cumulative incidence of major bleeding events was higher in patients with no silent PE at baseline. DVT patients with silent PE at baseline had an increased incidence of symptomatic PE events. In DVT patients with no silent PE, the risk of major bleeding was higher than the risk of symptomatic PE. Screening for silent PE in DVT patients at increased risk for bleeding may be useful in some subgroups of patients.

P. Di Micco (Italy) reported some findings in patients with thrombocytopenia (platelet count < 80000) at onset of VTE. Thrombocytopenia is uncommon and usually associated with malignancy. Low molecular weight heparins are usually used at reduced doses while the use of fondaparinux is considered for long-term treatment. The outcome of patients with thrombocytopenia is poor and is associated with increased complications like fatal bleeding and fatal PE.

M. Monreal (Spain) examined the clinical presentation and outcome of patients with bleeding and VTE. A total of 6855 patients were enrolled in their study, 1635 of whom had comorbidities. In these patients, there were higher percentages of fatal bleeding (1.4% vs 0.3%) and fatal PE (4% vs 1.1%) compared with patients with no comorbidities within the 3 months of follow-up. In another study of 170 VTE patients with a recent major bleeding episode, with a follow-up of less than 3 months, fatal bleeding was found in 4% of patients, while fatal recurrent PE was found in 2.4%. In VTE patients with recent major bleeding, the incidence of cumulative survival decreased and cumulative new bleeding increased especially for gastrointestinal bleeding.

The risk of major bleeding (3.8%) and fatal PE (4.7%) was high in patients with hemorrhagic stroke who subsequently developed VTE.

L. Bertoletti (France) talked about chronic obstructive pulmonary disease (COPD) and VTE. COPD is a moderate VTE risk factor. Pulmonary embolism was the main clinical presentation of VTE in patients with COPD. COPD was associated with an increased risk of dying from fatal PE after an initial VTE event. Patients with COPD experienced higher rates of overall mortality and bleeding under thrombotic therapy during a 3-month follow-up. The therapeutic management of VTE remains a challenge with a higher risk of fatal PE and a higher risk of bleeding.

D. Jimenez (Spain) suggested that risk stratification models are useful. In particular, the simplified Pulmonary Embolism Severity Index (sPESI) is accurate and easy to use; within 3 months of follow up it may identify patients at low risk of death after a diagnosis of PE as well as patients with cancer and PE.

2.1.2. Risk factors

Thrombotic risk in cancer patients: need for stratification

I. Elalamy (France)

Tumors produce procoagulant factors (TF, mucins, APCR). Extrinsic factors like surgery and chemotherapy may play a role.

The incidence of deep venous thrombosis +pulmonary embolism during cancer ranges from 15% to 20%, and its prevalence is 4 to7 times higher.

According to guidelines, hospitalized patients with cancer should receive prophylaxis. It is important to adapt this prophylaxis to each phase of cancer progression (initial phase, during chemotherapy, remission).

Predicting the risk of recurrent venous thrombosis

P. A. Kyrle (Austria)

Venous thrombosis (VT) is a common disease that frequently recurs. Thrombotic risk assessment is important to balance the risks and benefits of anticoagulation treatment. Only patients at high risk of recurrence will benefit from long-term anticoagulation treatment, whereas it will expose low-risk patients to a risk of bleeding.

The risk of recurrence is high in patients in whom the initial VT was unprovoked (ie, the event occurred in the absence of a temporary risk such as surgery, trauma, pregnancy, or use of female hormones). The risk of recurrence was 25% in a cohort of patients from Austria with unprovoked VT or pulmonary embolism 5 years after the event and it increased with time. In contrast, patients who had VT after surgery or used female hormones were at a lower risk of recurrence.

In their study, Hull and colleagues reported that all the patients with recurrence of VT had had initial proximal deep thrombosis and that there was no recurrence in patients who had had distal deep vein thrombosis.

The low rate of recurrence in patients with isolated calf vein thrombosis has been confirmed by several other studies. Data from one study group showed that the risk of recurrence of VT is more than 2-fold higher in patients with symptomatic pulmonary embolism than in patients with isolated deep vein thrombosis.

The risk of recurrent VT is strongly predicted by the sex of the patients. Men with a first unprovoked VT have a nearly 4-fold increased risk of recurrence compared with women.

First conclusion: men who suffered from a first unprovoked VT, proximal VT/pulmonary embolism have a high risk of recurrence. In these patients, extended secondary prevention should be considered.

Residual vein thrombosis is a possible predictor of the recurrence of VT but it is modestly associated with an increased risk of recurrence and it is not a predictor

of recurrent VT in patients with unprovoked DVT. Moreover, the association with the risk of recurrence depends on the definition of residual vein thrombosis. It is premature to make a clinical decision on the basis of residual vein thrombosis measurement results.

Laboratory screening for thrombophilia to identify increased risk of VT has often been advocated and is now done on a routine basis around the world. However, there is no proof that thrombophilia screening helps prevent VT recurrence. VT has many causes and many patients have more than one abnormality and the effect of combined defects is not known. Routine testing of patients can lead to overtreatment or cause unnecessary concern. Furthermore, routine laboratory thrombophilia screening is no longer warranted.

D-dimer concentration is related to the occurrence of VT. In a meta-analysis of 7 randomized controlled trials including 1880 patients with first unprovoked VT, the annual recurrence rates were 8.9% in patients with high D-dimer levels, and 3.5% in patients negative for D-dimers. Results from two other trials showed that patients with a low D-dimer concentration have a low risk of recurrence.

In a prospective cohort study, 929 patients with a first unprovoked venous thrombosis or pulmonary embolism were followed up after discontinuation of anticoagulation treatment. The clinical variables were age, sex, location, and body mass index. The laboratory variables were: factor V Leiden (FV Leiden), prothrombin mutation, and D-dimer. Only the patient's sex, thrombosis location, and the concentration of D-dimer were related to an increased risk of VT recurrence.

In the future, D-dimer levels together with clinical risk factors could help establish rules to predict the risk of VT recurrence.

Treatment of venous thrombosis

S. Eichinger (Austria)

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are two manifestations of the same disorder: venous thromboembolism (VTE). Low-molecular-weight heparin is the treatment of choice for both DVT and PE. Secondary thromboprophylaxis with vitamin K antagonists should be started as soon as the diagnosis is confirmed. The dose of vitamin K antagonist should be adjusted to a target international normalized ratio (INR) of 2.5. For most patients with PE, thrombolysis is not recommended. Vena cava filters should be restricted to patients with active bleeding or risk of serious bleeding, and to those in whom PE has recurred despite adequate anticoagulation.

Duration of anticoagulation should be at least 3 months because shorter courses double the recurrence rates. More prolonged anticoagulation therapy should be considered in the presence of specific clinical risk factors. Global markers of coagulation, particularly D-dimers, may discriminate between low- and high-risk patients for the recurrence of VTE.

The new oral anticoagulants have the potential to simplify the long-term treatment of patients with VTE by obviating the need for periodic laboratory monitoring while being associated with a favorable benefit-to-risk ratio. They include compounds that inhibit factor Xa, such as rivaroxaban, and compounds that inhibit thrombin, such as dabigatran etexilate.

The results of the RECOVER and EINSTEIN randomized clinical trials, which studied initial and long-term treatment of VTE patients with dabigatran etexilate and rivaroxaban, respectively, have been reported. In RECOVER, the administration of dabigatran etexilate at the dose of 150 mg twice daily for 6 months in patients with acute VTE was found to be as effective as warfarin in patients who had been treated with heparins or fondaparinux for the initial 7 to 10 days and was associated with a statistically significant reduction in the incidence of major or clinically relevant bleeding complications. In EINSTEIN, the administration of rivaroxaban in patients with acute deep vein thrombosis from the beginning at the dose of 15 mg twice daily for 3weeks followed by 20 mg once daily for 3 to 12 months was found at least as effective and as safe as conventional enoxaparin-warfarin treatment. Of interest, rivaroxaban was found to be significantly more effective than comparators regarding the combined end point of recurrent VTE plus major bleeding. In addition, prolonging rivaroxaban at the dose of 20 mg once daily for an additional 6 to 12 months in patients who had received rivaroxaban or warfarin for at least 3 months achieved an 82% reduction in the risk of recurrent events over placebo and was associated with less than 1% major bleeding complications.

In the RE-MEDY trial, dabigatran demonstrated noninferiority to warfarin, with fewer bleeds, but there were more acute coronary syndrome events in the dabigatran group than in those taking warfarin.

The challenging aspects of treating VTE with the newer anticoagulants are: determining the optimal duration of anticoagulation, using a single-drug approach, patients at the extremes of age and bodyweight (advanced age, over/underweight), compliance and adherence, and monitoring.

2.1.3. Management

Venous thromboembolism prophylaxis in 2012, where we are and where are we going?

R. Hull (Canada)

Clinical trials differ from real life. The patients in trials are selected and have better care, the treatment is usually of short duration, and the studies have insufficient power to detect adverse effects. Clinical studies provide good evidence of the efficacy of a drug and support its labeling for a specific indication. The question is whether it is possible to generalize the results of a study. Postmarketing studies can then bring important signals and may sometimes lead to changes in prescribing information. Looking at the history of the development of the older anticoagulants approved for venous thromboembolism prophylaxis, one such case was enoxaparin. It caused bleeding in patients with renal insufficiency and intraspinal hematoma following epidural anesthesia with subsequent long-term or devastating paralysis. This led to labeling changes and black box warning from the FDA later on.

Another such case was fondaparinux. Shortly after its approval, there were several spontaneous reports of serious bleeding in patients with renal insufficiency or low body weight. Bleeding is the main safety issue with anticoagulants but in clinical studies, the patients with high bleeding risk are primarily excluded. However, later on, they may potentially be exposed to the drug without appropriate clinical experience. Because of this, the availability of an antidote seems to be a necessity for new anticoagulants. Contrary to the older anticoagulants, there are no specific antidotes for the new anticoagulants as yet, though some are currently under development. According to official reports, since its approval dabigatran has already been linked to 542 deaths, 3781 serious adverse events, and 2367 bleeding events. Moreover, a subanalysis of the RE-LY study revealed that for elderly patients, warfarin is safer. The other problem with all the new oral anticoagulants is the risk of overdose in patients with renal impairment or the potential drug interactions. In conclusion, it is still too early to say whether the new anticoagulants cause more or less bleeding than the older ones. Real-life practice teaches us that the results of clinical trials may not be sufficient and clinicians should consider additional factors before implementing these new drugs into their daily practice.

Controversies in the treatment of deep venous thrombosis

Part 1. Should we switch patients who are well-controlled on vitamin K-antagonists to new antithrombotic drugs?

For

M. Penka (Czech Republic)

The author demonstrated his opinion using one example of the therapeutic indications of anticoagulants: the prevention of strokes in patients with atrial fibrillation. Warfarin is effective in preventing strokes but only if the therapy is well managed and patients spend more than 75% of time in the therapeutic range of the international normalized ratio (INR). There are multiple factors contributing to changes in warfarin dosage. Limitations of warfarin include its multitarget mode of action, narrow therapeutic window, intra- and interpatient variability, the reluctance of physicians to prescribe it, and a dislike on the part of patients. On the other hand, the new oral anticoagulants are single-target drugs; their dosing is simple, they have only few interactions and have demonstrated very good efficacy and safety in phase 3 clinical trials in atrial fibrillation patients. In conclusion, the author found the current experience with the new drugs to be very convincing and according to him they will replace warfarin.

Against

E. Minar (Austria)

The opposing speaker chose another example of an indication for anticoagulation treatment—venous thromboembolism—and mentioned the results of phase 3 clinical studies with the new oral anticoagulants in venous thromboembolism treatment. Therefore, the two speakers only partially dealt with the same topic. However, some of their arguments targeted the same controversial issues, especially the bleeding risk inevitably associated with every anticoagulant. The effect of

warfarin can be controlled quite reliably and it is also possible to use lower INR targets in at-risk populations. However, patients with risk factors for bleeding have been excluded from clinical trials with new anticoagulants. Their short half-life and lack of need for regular monitoring may, in fact, be a problem in patients with poor compliance. Another source of problems is the potential fluctuation of renal function, especially in older fragile populations. There is also a lack of validated laboratory tests to measure the anticoagulation effect of new anticoagulants. Furthermore, their long-term effect is unknown, as is their cost-effectiveness and the risk of combining them with other antithrombotics. The author concluded with a slogan: "Never change a winning team."

Part 2. Percutaneous treatment of ileofemoral thrombosis

For

M. Rocek (Czech Republic)

The speaker briefly explained the techniques used for the interventional treatment of ileofemoral venous occlusion—catheter-directed local thrombolysis, mechanical thrombectomy, the combination of both techniques, and adjunctive techniques such as balloon angioplasty and stenting—and he mentioned some indications for inferior vena cava filter implantation. Several interesting cases of complicated but finally successful procedures were demonstrated. The author found endovascular treatment better than surgery due to its efficacy and safety and also the potential to shorten hospital stays.

Against

E. Minar (Austria)

The second speaker did not mention case reports but looked at the problem from a more general point of view. He mentioned the aims of the treatment of acute deep vein thrombosis (DVT)—the prevention of thrombus extension, pulmonary embolism, and postthrombotic syndrome (PTS). Unfortunately, there is only little data concerning PTS prevention. PTS may develop following proximal as well as distal DVT. The previous guidelines for antithrombotic therapy of the American College of Chest Physicians (ACCP) published in *Chest* in 2008 recommended to consider catheter-directed thrombolysis (CDT) for ileofemoral thrombosis. However, in the last ACCP guidelines (published this year) the authors suggest anticoagulation therapy alone over CDT. The speaker then demonstrated the results of some clinical studies of interventional therapy for ileofemoral thrombosis. He stated that most data were of low-quality and also stressed the small additional risk of bleeding associated with those interventional procedures. In his view, CDT is an alternative only for a minority of patients.

In the discussion, the participants expressed their opinion that interventional therapy should be an alternative especially in younger patients.

Part 3. Is routine testing for thrombophilia useful?

For

J. J. Michiels (The Netherlands)

The author cited the literature concerning the prevalence of thrombophilic defects in venous thromboembolism—not only deep vein thrombosis of the leg and pulmonary embolism, but also superficial thrombophlebitis, abdominal vein thrombosis, and even some cases of arterial thrombosis. The author named the tests that should be used in those patients. According to him, testing for thrombophilia is useful in some situations associated with increased thrombotic risk.

Against

S. Eichinger-Hasenauer (Austria)

The opposing speaker first explained the general rationale for carrying out tests. The condition tested should be frequent, the pathophysiology of the defect should be well understood, and a reliable test should be available. The main question, however, is whether the test result influences the treatment or management of the patient to his/her benefit.

For S. Eichinger, thrombophilia has a low prevalence and knowledge of the presence of a specific defect does not influence therapy. Thrombophilia testing is not useful even in the rare cases of thrombosis in unusual sites because their pathophysiology is not clearly understood. There is not enough data about the risk of venous thromboembolism recurrence in patients with thrombophilia. S. Eichinger does not consider thrombophilia testing useful in asymptomatic carriers either, because thrombotic risk may be adequately and simply derived from family history. Moreover, there are insufficient data on the efficacy and safety of low-molecular-weight heparin in asymptomatic carriers of thrombophilic defects during pregnancy.

Methodology of the international consensus on venous thromboembolism. The International Union of Angiology (IUA) guidelines on VTE.

A. Nicolaides (UK) summarized the rationale and methodology of the 2012 5th revision of the International Consensus Statement. The key questions are:

- What is the evidence? The evidence determines the grade of recommendation.
- In the absence of evidence, what new studies are needed?

The aims are to provide a clear and concise account of the evidence on the efficacy (or harm) of the various methods available for the prevention and management of venous thromboembolism (VTE). An additional aim is to provide recommendations based on such evidence.

Literature searches were performed by an independent agency (Pharmaceutical Strategic Initiatives). Only fully published, peer-reviewed papers of randomized comparisons were used to determine the level of evidence.

Randomized controlled trials (RCTs) with consistent results and systematics review provide high-level evidence. Single rigorously performed RCTs that are methodologically reliable and sufficiently large to give clear results and are applicable to most patients in most circumstances also provide high-level evidence. RCTs with less consistent results and with limited power or other methodological problems provide moderate-level evidence. Moderate-level evidence is also provided by RCTs results that are extrapolated to the target population from a different group of patients. Well-conducted observational studies with consistent results that are directly applicable to the target population provide low-level evidence. In the absence of evidence or in case of low-level evidence, the key questions that should be addressed by future studies need to be postulated.

Because the international consensus statement on venous thromboembolism is an international document not focused on the clinical practice of a single country or continent, and because of the variability in costs in different parts of the world, the authors have refrained from incorporating considerations of costs in their recommendations. They believe that decisions about costs and resource allocations for health care interventions are more appropriately made by individual health care systems as they may vary considerably between countries. Therefore, considerations of cost or cost-effectiveness are not considered in individual recommendations. However, recognizing that health care systems do not have unlimited resources, a section that summarizes the available evidence regarding the cost-effectiveness of primary prevention and treatment of VTE has been included. This section is for use by appropriate decision-makers.

Evidence is presented for outcomes such as the incidence of asymptomatic deep venous thrombosis at screening as well as symptomatic deep venous thrombosis or pulmonary embolism, fatal pulmonary embolism, overall mortality, and the development of the postthrombotic syndrome when available.

The American College of Chest Physicians (ACCP) consensus on VTE prevention and management

A. Comerota (USA) presented the methodology of the 2012 American College of Chest Physicians (ACCP) consensus. Panel members have changed from the previous guidelines. In this edition, methodologists, health economists, "frontline" clinicians, and experts have worked together.

Conflict-of-interest (COI) statements have an important role, to avoid circumstances (financial or intellectual) that might influence recommendations. For example, panelists with COI participated in discussions, but were excluded from voting on final recommendations.

Another difference was the use of electronic (rather than paper) publication and communication, which needed less time, was more easily searchable, had links

to additional sources, was less expensive and more environmentally friendly, and led to a yearly review of the evidence.

For most of items, the evidence is only 1B or 2B, with no 1A-level evidence. Changes in recommendations from the previous version were provided as examples. For example, anticoagulation alone over catheter-directed thrombolysis, operative venous thrombectomy, or systemic thrombolytic therapy (grade 2C), or recommendations against the use of vena cava filters in addition to anticoagulation in patient with acute deep venous thrombosis (grade 1B).

The need for harmonization of consensus opinions

A. Kakkar (UK) commented on the differences between the guidelines from both sides of the Atlantic using aspirin as an example. Harmonization of the way the evidence is assessed is necessary.

W. Leong (Canada) highlighted the limitations of guidelines in relation to ethnic diversity (pharmacogenetics) and differences in local standards of care (in developed or third-world countries, public or private health care, or in countries with no health care institutions, primary or secondary care, and professional types of qualification).

Globalization of venous thromboembolism guidelines

C. Carter (USA) presented the global issues of venous thromboembolism (VTE). Venous thromboembolism is the first cause of potentially preventable deaths in hospitalized patients and venous thromboembolism management is rated as the most effective patient safety practice for hospitals. He posed the question of how to improve their use of prophylaxis. Measures to increase adherence to guidelines could include professional public reporting, accountability for patient safety, or not covering the additional cost incurred for hospital-acquired venous thromboembolism in selected patients.

Management of venous thrombosis. From heparin to newer anticoagulants. What does the future hold?

V. Kakkar (UK) made a historical review of the anticoagulant treatment of deep vein thrombosis (DVT), which included the burden of venous thromboembolism (VTE), its current therapy, the newer anticoagulants, and unresolved issues.

The burden of thromboembolism is 300 000 deaths due to pulmonary embolism (PE) in the USA and 370 000 PE-related deaths per year in 6 European countries. The cost per VTE in Australia in 1 year is 1.5 million AUD (753 000€).

Appropriate initial treatment of DVT leads to prevention of fatal PE, reduced morbidity associated with acute leg or lung thrombus, prevention of recurrent VTE, and prevention of long-term sequelae.

It is important to consider venous thromboembolism as a chronic disease rather than an acute illness, with a high risk of recurrence during the first 6 to 12 months

after an acute episode, and with a cumulative rate of recurrence of about 25% at 5 years and 30% at 20 years. This recurrence is associated with a higher likelihood of postthrombotic syndrome and recurrent PE, which is fatal in about 4% to 9% of patients.

Vitamin K antagonists have been the most used alternative but have an unpredictable dose-response and need to be monitored to achieve therapeutic levels (international normalized ration [INR] of 2.0-3.0). Moreover, they have an important burden of complications (bleeding, drug interactions, and food effects). The duration of therapy depends on the causes and risk factors and varies from 3 months if risk factors are limited, to 6 months in first idiopathic VTE events, and 12 months in case of thrombophilia. High-risk patients with recurrent VTE or cancer may need lifelong treatment.

The new anticoagulants are expected to play an important role in treatment. They could provide similar or better therapeutic results with less complications and easy control (simple, single oral therapy administered in fixed-dose regimens for the initial and long-term treatment of DVT and PE). The likelihood of having improved benefit-risk profiles and efficacy in reducing the long term sequelae needs to be addressed.

Oral anti-IIa and anti-Xa drugs. Pharmacological and clinical differentiation and their impact on therapeutic outcome.
J. Fareed (USA)

The new oral anticoagulants seem to be very promising in comparison with warfarin. They differ from warfarin in many aspects—they work as direct inhibitors of specific coagulation factors, have an immediate onset of action, a fixed dosage, are eliminated from the body in 12 hours, have minimal drug and food interactions, and there is theoretically no need for laboratory monitoring. Nevertheless, warfarin has been used for 60 years in clinical practice while there is no experience with the long-term use of these new substances. Two main classes are the most developed—thrombin inhibitors (dabigatran etexilate) and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, etc…). All of them are candidates for use in several clinical situations—thromboprophylaxis in surgical (especially orthopedic) and medical patients, prophylaxis of stroke in atrial fibrillation, treatment of venous thromboembolism, and as part of the treatment of acute coronary syndrome. For these indications, they are undergoing or have even undergone phase 3 clinical studies and some of them have already been approved for clinical practice. Both dabigatran and rivaroxaban have obtained approval for thromboprophylaxis after major orthopedic surgery and for atrial fibrillation. However, dabigatran has failed to get FDA approval for acute coronary syndrome. Rivaroxaban seems very promising in the treatment of venous thromboembolism, with proven efficacy even in the initial phase of treatment, thereby giving the opportunity to avoid parenteral anticoagulation. Moreover, the extension of therapy with rivaroxaban beyond 6 to 12 months significantly reduced the rate of venous thromboembolism recurrence. Apixaban was recently evaluated by the FDA for atrial fibrillation but the decision was postponed as more data on clinical efficacy and safety is required. Edoxaban has been approved in Japan for atrial fibrillation and is currently being evaluated for further indications.

In conclusion, in spite of the advantages of the new oral anticoagulants, there are also some crucial safety issues—the absence of specific antidotes, no anticoagulant effect in case of missed doses, no test to monitor the anticoagulant effect and its intensity, difficulties in modulating dosage, relatively high discontinuation rates due to gastrointestinal distress, a reported 0.2% increase in the incidence of myocardial infarction, and a considerable increase in cost.

Safety issues with newer oral anticoagulant drugs (Symposium cosponsored by the North American Chapter of the International Union of Angiology)

C. Carter (USA) said that preapproval clinical trial safety data is not a substitute for postapproval safety monitoring. The APPRAISE 2 trial (apixaban vs placebo) was stopped prematurely due to an excess of clinically important bleeding in the apixaban arm without a counterbalancing reduction in ischemic events (7048 patients; median follow-up, 3.5 months; 412 primary events [44%]).

Many questions emerged following the ATLAS-51 trial (rivaroxaban 2.5 mg and 5 mg vs placebo + acetyl salicylic acid 75 mg). Rivaroxaban was effective in reducing the risk of the primary end point (composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in men and women but increased the risk of the primary end point in subjects with a history of ischemic stroke/transient ischemic attack. Rivaroxaban increased the risk of noncoronary artery bypass grafts–related thrombolysis in myocardial infarction and major bleeding in all subgroups except those with a history of chronic heart failure receiving rivaroxaban 2.5mg. Those at higher risk of bleeding were subjects >75 years of age, subjects weighing <60 kg or >90 kg, subjects with moderate renal impairment, and women.

In Japan, the occurrence of a number of cases of fatal hemorrhage in patients receiving dabigatran for the prevention of stroke and systemic embolism resulted in a strengthening of the advice for prescribers. These patients were all older than 75 years, with renal impairment and additional risk factors for bleeding, including concomitant medication.

From 2006 to 2012, the FDA submitted thousands of adverse event reports, a quarter of which were for dabigatran as well as generic and/or brand name drugs containing the same primary active ingredients (6090 gastrointestinal signs and symptoms, of which 4324 gastrointestinal hemorrhages).

We are in the early stage of market approval for the newer anticoagulants. Structured, well-conducted postapproval outcome research is desperately needed.

W. Leong (Canada) focused his presentation on the various safety aspects of treatment with the new oral anticoagulants.

It is difficult to verify patient compliance. Patients who use the new oral anticoagulants discontinue their medication in larger numbers than those treated with warfarin because of gastrointestinal symptoms. The administration of 2 daily

doses favors forgetfulness by the patient. Forgetting more than one dose can put the patient at prothrombotic risk. A "bad" warfarin patient will be a very "bad" dabigatran (rivaroxaban or apixaban) patient.

Some drug interactions often remain unknown. Pantoprazole reduces the plasma dabigatran concentration by up to 30%.

The combined use of dual antiplatelet therapy with warfarin is mandatory in certain thrombotic risk situations. In patients with atrial fibrillation the use of warfarin + aspirin + clopidogrel is associated with a more than 3-fold increased risk of nonfatal and fatal bleeding and this will probably also apply to the new the new anticoagulants. These strategies determine the potential increase in severe or moderate hemorrhagic events and even life-compromising events. There are insufficient studies to recommend a strategy at this point.

Monitoring is not recommended nor is it clinically useful for the new oral anticoagulants. However their anticoagulant effect must be controlled and there is no test to assess their effect or therapeutic range.

In renal failure their dose should be reduced or they should be discontinued. Nevertheless, there are no studies that clearly indicate the dose to use in these circumstances. If the partial thromboplastin time (PTT) of a dabigatran patient is>90 sec and his/her international normalized ratio (INR) is >1.5 there is a suspicion of overdosage or accumulation.

A survey from the Australian Government's Department of Health and Ageing reported that some bleeding adverse events occurred during the transition from warfarin to dabigatran. Many adverse events occurred with the reduced dosage regimen. For dabigatran, the most common type of serious bleeding was gastrointestinal bleeding.

Another survey from the Institute for Safe Medication Practices reported 932 serious adverse events (120 deaths, 25 cases of permanent disability, 543 cases requiring hospitalization) in patients using dabigatran. In the USA, from 2007 to 2009, 100 000 elderly patients were hospitalized per year for adverse drug reactions and the most commonly implicated medication was warfarin.

There is no evidence of an antidote for dabigatran, rivaroxaban, or apixaban. There is limited evidence with reversal strategies for rivaroxaban and dabigatran, in particular the use of plasma clotting factors to reverse the anticoagulant effect of rivaroxaban and the use of hemodialysis to remove dabigatran from the blood.

D. Hoppensteadt (USA) proposed to measure the effects of the oral anti-Xa agents (rivaroxaban and apixaban) and an anti-IIa agent (dabigatran) using the currently available assays (prothrombin time (PT), activated partial thromboplastin time [aPTT], amidolytic activity, Technothrombin thrombin generation assay) and a newly developed prothrombinase-induced clotting time assay (PiCT) in order to identify a clinically suitable test for monitoring the anticoagulant effects of these agents.

In the PT assay, responses showed assay-dependent variations: each reagent exhibited its own specific sensitivity to the different anticoagulants. Dabigatran produced the strongest anticoagulant activity whereas apixaban was relatively weaker. aPTT was relatively more sensitive to dabigatran and rivaroxaban while apixaban showed weaker anticoagulant responses with all reagents.

Amidolytic anti-IIa and Xa assays revealed the product-specific inhibition of these enzymes. Apixaban showed a relatively lower anti-Xa activity compared with rivaroxaban

In the PiCT test, all agents exhibited a concentration-dependent anticoagulant effect. The one-stage PiCT test showed the highest sensitivity to all 3 agents and was the only test where apixaban exhibited significant anticoagulant responses. The sensitivity limit of this assay was higher than for the other tests. In the thrombin generation assay, all agents showed a concentration-dependent inhibition of thrombin generation in both platelet-poor plasma and platelet-rich plasma. The relative inhibition in platelet-poor plasma was greater than in platelet-rich plasma.

These studies show that the PT and aPTT reagents exhibit wide variations and varying degrees of sensitivity to the new oral anticoagulants. The one- stage PiCT assay shows a higher sensitivity to all of the agents studied compared with the other clot-based tests and its use should be validated in clinical trials. The amidolytic anti-Xa and anti-IIa assays are relatively specific and are not affected by endogenous factors whereas the thrombin generation assays provide an overall anticoagulant/antithrombin potential test of plasma.

Thrombosis issues in surgical patients (Symposium of the International Surgical Thrombosis Forum)

Inhibition of FVIII with TB-402 for the prevention of venous thromboembolism after total knee and hip replacement: Phase I-II results

M. Tangelder (The Netherlands)

TB-402 is derived from an antibody that arose spontaneously during the treatment of hemophiliac patients and partially inhibits factor VIII (FVIII) activity. FVIII is an acute-phase protein with elevated activity after surgery; it is associated with a high risk of thrombosis. A partial inhibitor of FVIII activity may be an effective anticoagulant preserving partial coagulation activity.

The author presented the results of phase 1 and 2 trials investigating the use of a single dose of TB-402 for the prevention of venous thromboembolism (VTE) in patients after total knee and hip replacement.

Phase 1 trial: After total knee replacement, 316 patients were treated with a single dose of either TB-402 at a dose of 0.3 mg/kg, 0.6 mg/kg, or 1.2 mg/kg or enoxaparin 40 mg for at least 10 days.

Phase 2 trial: Prior to total hip replacement, 632 patients were treated either with a single dose of TB-402 (25 mg or 50 mg) 2 to 4 hours postoperatively, or rivaroxaban 10 mg for 20 to 35 days.

The primary efficacy outcome for both groups was total VTE. The safety outcome was the presence of major and nonmajor clinically relevant bleeding.

TB-402 was more effective than enoxaparin for the prevention of VTE (patients with a VTE, pooled data for TB-402, 21.7%; enoxaparin, 39.7%). The 0.3-mg/kg and 0.6-mg/kg doses had a bleeding risk comparable with that of enoxaparin, whereas the 1.2-mg/kg dose had a higher bleeding risk.

TB-402 is approximately as effective as rivaroxaban in preventing VTE after total hip replacement. No dose-response effect was found for the 25-mg and 50-mg doses. The bleeding risk with TB-402 is 4 to 5 times higher than for rivaroxaban. Based on these results, the further development of TB-402 was stopped.

Venous thromboembolism prophylaxis in spinal surgery

J. Fletcher (Australia)

The aim of this study was to establish the incidence of venous thromboembolism (VTE) in 366 patients undergoing elective spinal surgery. A venous duplex ultrasound was performed preoperatively, within 1 week postoperatively, and after 4 to 6 weeks. The median duration of the operation was 2.4 (0.6-3.5) hours. Mechanical prophylaxis was used in all patients and pharmacological prophylaxis in 48% of patients (low-dose unfractionated heparin in 27%, low-molecular-weight heparin in 25%). VTE incidence was 3.5% (in-hospital, 1.6 %; out-of-hospital, 1.9 %). The incidence of nonfatal pulmonary embolism was 0.6%. The risk of major bleeding increased 2.5 fold for every hour increase in the duration of the operation. Preoperative venous scans showed a high incidence (20%) of superficial thrombophlebitis in the small saphenous vein, which is likely to be related to preoperative immobility and lying supine due to back pain. In conclusion, vigorous perioperative mechanical prophylaxis minimizes VTE risk. The combined use of mechanical and pharmacological prophylaxis was safe and effective. The bleeding risk was related to the duration of the operation and not to the use of pharmacological prophylaxis.

Prophylaxis in high-risk abdominal surgery

A. Kakkar (UK)

The author examined trials from the last 40 years that dealt with thrombo-prophylaxis in surgical procedures. Low-dose unfractionated heparin proved its efficacy in the prophylaxis of postoperative venous thromboembolism (VTE) and against fatal pulmonary embolism (PE) in the 1970s. In the 1980s, low-molecular-weight heparin (LMWH) demonstrated its efficacy (versus placebo) in preventing VTE after major surgery. The effective once-daily dose of LMWH for

thromboprophylaxis in cancer surgery was established in 1995. Cancer operations have a higher risk of VTE and fatal PE. The @RISTOS study showed that VTE risk persists in cancer surgery patients and among them, 40% of VTEs were observed more than 21 days after cancer surgery. In ENOXACAN II, 332 patients undergoing cancer surgery received enoxaparin for 1 week followed by enoxaparin or placebo for another 21 days. At each follow-up, prolonged thromboprophylaxis was associated with a 60% reduction in the risk of DVT. Similar results were obtained in the FAME trial. In conclusion, primary prophylaxis is mandatory for surgical patients. There is increasing evidence of the benefits of extended postdischarge LMWH. VTE remains a serious disease in surgical cancer patients.

Home treatment of pulmonary embolism

J. Maly (Czech Republic)

Pulmonary embolism (PE) has long been considered a reason for hospitalization and its home treatment is relatively new and controversial. This possibility was first mentioned in 2003 by the British Thoracic Society, and then later on in 2008 by the European Society of Cardiology. The recent guidelines for antithrombotic therapy, published by the American College of Chest Physicians (ACCP) this year mentioned the possibility for outpatient treatment of PE in carefully selected patients.

Outpatient treatment may be understood as management of the patient on an outpatient-basis since the very beginning, or, more often, as an early discharge after a short hospital stay. Suitable patients are those with low-risk PE. In fact, many patients with deep vein thrombosis (DVT) have silent PE, and in many cases, this is not treated in hospital. In the first published studies of outpatient PE treatment, the exclusion criteria were chest pain, hypotension, and noncompliance. In the most recent studies, a more sophisticated selecting system was used. For example, one Dutch study used NT-proBNP as a risk marker with a cut-off value <500pg/ml for outpatient treatment. Up to 45% of patients were treated as outpatients and during the 3 months of follow-up, there were no cases of death, bleeding, or recurrence in this group. Another study—"OTPE"—used PESI (pulmonary embolism severity index), a semiquantitative risk scoring system to select patients with low-risk PE for home treatment and with this approach, the authors confirmed the noninferiority of outpatient treatment.

Besides NT-proBNP and PESI, there are more useful biomarkers and scoring systems—troponin I or T or simplified PESI.

In conclusion, outpatient treatment of PE is possible in low-risk patients with nonmassive PE. It is feasible and safe in selected patients. Validated methods for risk assessment and selection of patients are available. The new anticoagulants may in the future broaden the potential for the home treatment of PE but no data are available so far for this indication.

It is likely that up to 50% of PE patients will be candidates for the home treatment of PE.

The many facets of thrombosis

Interplay of inflammation and venous thrombosis

D. Wagner (USA)

Neutrophils release extracellular fibers composed of DNA, thereby forming a network called neutrophil extracellular traps (NETs). NET formation is induced by an infection and NETs should bind pathogens. However, NETs can bind platelets, which consequently become activated. In patients with deep vein thrombosis (DVT), an elevated level of circulating DNA was found in plasma, and this level correlated with the level of von Willebrand factor. This concept has been further investigated in experimental models of thrombosis. In the baboon thrombus, nuclear and extranuclear DNA was found. In a mouse model of thrombosis, venous flow restriction induced secretion from Weibel-Palade bodies and platelet-leucocyte adhesion.

It may be hypothesized that besides plasmin, DNAse and ADAMTS13 (von Willebrand factor cleaving protease) may be necessary for the lysis of thrombus.

Thrombotic thrombocytopenia purpura (TTP) is an example of thrombotic microangiopathy. NETs could be involved in its pathogenesis. Plasmatic DNA levels increase with TTP and decrease after plasma exchange therapy.

In conclusion, NET formation is a stimulus for platelet adhesion and thrombus formation. A better understanding of the interrelated pathogenesis of inflammation and thrombosis may improve the management of thrombosis.

Facts and controversies on the new anticoagulants

S. Coccheri (Italy)

According to the Euro Heart Survey, 30% of the patients with atrial fibrillation (AF) are undertreated, which doubles their risk of stroke. The results of the new oral anticoagulants (dabigatran at higher and lower doses, rivaroxaban, apixaban) in AF patients proved their noninferiority and even their superiority to warfarin. In addition, the results of studies in patients with venous thromboembolism (VTE) seemed promising, and even offered the possibility of treating VTE orally since the very beginning (shown for rivaroxaban). However, there are some concerns about safety in clinical practice. In comparative studies, intracranial bleeding was reduced with the newer anticoagulants compared with warfarin but gastrointestinal bleeding was slightly higher. In patients with renal impairment their dose must be reduced and there are very little or no data for very old patients. In addition, there are no tests available to precisely measure the anticoagulant effect. Problems may thus arise in emergency situations. So far, only one of the newly developed new anticoagulants (betrixaban) has a specific antidote.

In conclusion, patients must be carefully selected before treatment with new oral anticoagulants and they should remain under surveillance. Further registries and observational studies are necessary.

An update on the clinical development of defibrotide

D. Hoppensteadt (USA).

Defibrotide was developed 40 years ago. It is an agent with multiple actions: downregulation of thrombomodulin, vasodilatation at the microvascular level, release of TFPI (tissue factor pathway inhibitor), modulation of platelets and leucocytes, inhibition of factor Xa, and profibrinolytic effect. There are various potential indications of defibrotide: periphery artery disease, deep vein thrombosis, microangiopathy, and post–bone marrow transplant vasculopathy. Additional indications may include sepsis-associated coagulopathy, heparin-induced thrombocytopenia, ischemic stroke, senile dementia, and venoocclusive disease. It is effective in the pathology of arteries and veins as well as the microvasculature.

Generic and biosimilar low-molecular-weight heparins: need for global harmonization of the guidelines

C. Carter (USA).

Generic low-molecular-weight heparins (LMWH) may lead to potential cost savings. However, these drugs are used in critically ill patients and great care must be taken to avoid possible complications: bleeding, allergic reaction, a drop in platelet count, skin reaction, or even new thrombosis. In previous years, more than 1800 reports of adverse events caused by generic LMWHs were reported due to heparin contaminants (contamination of the raw heparin stock, respectively).

In various countries, there are different drug regulatory rules. A generic drug must usually prove "biosimilarity," which means that it must prove the absence of a clinically meaningful difference. The two main regulatory authorities in the world are the Food and Drug Agency and the European Medicines Agency. Following the scandal with contaminated heparin preparations, the rules have been changed; more evidence is required regarding the physical and chemical characteristics of the products, their bioavailability, efficacy, and safety. However, differences remain between the rules of the different regulatory authorities.

In conclusion, regulatory authorities should harmonize the approval process for complex biological drugs such as LMWH.

Heparin-induced thrombocytopenia and its management

I. Elalamy (France)

Heparin-induced thrombocytopenia is a paradoxical syndrome. This term may include heparin-induced thrombocytopenia as wells as heparin-induced thrombus generation or heparin-induced thrombosis. Its incidence is approximately 10 times higher after unfractionated heparin than after low-molecular-weight heparin (LMWH). Clinical manifestations include white (arterial) clots, deep vein thrombosis (DVT) or extension of DVT in spite of therapy, livedo reticularis, phlegmasia, ischemic gangrene, and bilateral adrenal hemorrhagic infarction. Heparin-induced skin necrosis is quite rare. The diagnosis of heparin-induced thrombocytopenia is difficult. Timing the kinetics of platelet count is very

important—the drop usually occurs 5 to 15 days after heparin or LMWH has been started. A special scoring system was proposed to assess the pretest probability. Laboratory tests include immunologic and functional assays. ELISA tests have a very high sensitivity but a low specificity. An immunochromatographic method is rapid and permanently available and is specific for IgG isotypes. Functional assays are not well standardized and are only performed in expert laboratories.

If heparin-induced thrombocytopenia is clinically suspected, heparin therapy must be suspended and immediately substituted with alternative anticoagulants (lepirudin, argatroban, fondaparinux); a survey of platelet count recovery and of the clinical signs of heparin-induced thrombocytopenia is recommended (4 "S": suspicion – suspension – substitution – survey).

Interrelationship between arterial atherosclerotic and venous thromboembolic disease

M. K. Jezovnik and P. Poredos (Slovenia)

Atherosclerosis and venous thromboembolism (VTE) were historically considered to be separate clinical entities. However, the concept of "white and red clot" is an oversimplification. Aspirin also works, to some degree, in venous thrombosis, while anticoagulants are being used in arterial diseases. In both arterial and venous thrombosis, the pathogenesis includes damage of the vessel wall, formation of thrombus, action of platelets, and coagulation factors. Autopsy findings have also proved the association of VTE with arterial diseases. In clinical studies, VTE was associated with a higher risk of subsequent cardiovascular events. There are also some common risk factors for both arterial and venous thrombosis.

This study evaluated the association between signs of preclinical atherosclerosis and VTE. In VTE patients, morphological, laboratory, and functional markers of preclinical atherosclerosis were measured (intima-media thickness in common carotid and femoral artery, inflammatory markers, markers of endothelial dysfunction, flow-mediated dilatation in brachial artery).

The authors found a significantly higher prevalence of the markers of preclinical atherosclerosis in VTE patients. The interrelation of both processes may be explained by the systemic inflammatory response.

A European perspective on generic anticoagulants drugs

W. Rakke (Germany)

Biological medicine uses active substances that are made by or derived from a living organism. Biosimilar products are products that are similar to original products of biological origin. They are not generic products and their immunogenic risk cannot be determined by pharmaceutical tests.

Heparin is sourced mainly from porcine intestinal walls. Due to this chemical heterogeneity, conventional pharmacokinetic studies cannot be performed. The essential requirements for generic LMWHs (European Medicines Agency guideline) are the following:

- Nonclinical studies.
- In vivo studies evaluating anti Xa and anti IIa.
- Toxicological studies that should last at least 4 weeks, with special emphasis on the determination of the effects on blood coagulation and homeostasis and on the potential development of osteoporosis.

Data on local tolerance can be collected as part of a repeat-dose toxicity study. A biosimilar medicinal product should show equivalent efficacy and safety to a reference product approved in the EU. The chosen reference product must be a medicinal product authorized in the European Community. Although it is generally expected that generic medicinal products are cheaper than the originals, the major problem of biosimilars is their development cost.

Contemporary outcome following catheter thrombolysis for iliofemoral deep vein thrombosis.

A. Comerota (USA)

Deep vein thrombosis (DVT) may have very important sequelae and may lead to valvular dysfunction, ambulatory venous hypertension, obstructive iliac lesion, calf muscle pump dysfunction, venous claudication, ulcerations. The risk of recurrence is high. Anticoagulation treatment alone does not always solve the problem. Venous thrombectomy can be an option.

Catheter-directed thrombolysis for iliofemoral deep venous thrombosis improves health-related quality of life as evidenced in a cohort study including 98 patients (68 treated with thrombolysis, 30 treated with anticoagulation alone) followed up for 16 to 22 months, using a validated health-related quality of life questionnaire. There was a significantly better improvement in health distress, postthrombotic symptoms, physical functioning, and stigma in the thrombolysis group compared with the heparin group (Comerota, *J Vasc Surg* 2000). In 2012, the same group found that postthrombotic morbidity correlates with residual thrombus following catheter-directed thrombolysis for iliofemoral deep vein thrombosis.

In the Scandinavian Randomized Trial, 63 patients with iliofemoral deep venous thrombosis were followed up at 6 months, 5 years, and 10 years and valve patency, postthrombotic morbidity, and complications were reported. The interventional approach showed a significant improvement on these criteria.

Another randomized trial was carried out in 35 eligible patients followed up for 6 months, of which 18 underwent thrombolysis and 17 had anticoagulation treatment alone (Eisharawy, *Eur J vasc Endovasc Surg* 2002). Patients with patent veins and normal valve function did not have postthrombotic syndrome and had a significantly reduced risk of recurrence.

In 2012, *The Lancet* published a randomized trial with a long-term outcome that compared additional catheter-directed thrombolysis (CDT) versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVen study). In 20 Norwegian Hospitals, Enden et al, treated 209 patients aged 18 to 75 years (101 catheter-directed thrombolysis). The follow-up of 24 months was achieved in 189 patients. Patients were assessed with the Villalta scale at 24 months and iliofemoral patency was assessed at 6 months. Both were significantly better in the catheter-directed thrombolysis group (66% vs 47% patency, and 41% vs 56% postthrombotic syndrome). The authors concluded that postthrombotic syndrome is directly associated with patency of the iliofemoral venous segment.

The presence of a residual "thrombus" on ultrasonography when warfarin is discontinued is associated with a substantially increased risk of recurrent thrombosis (Prandoni, *Arch Int Med* 2002). In a systematic review (Russell, *Am J Med* 2005) the quantitative assessment of thrombus burden predicted the outcome of treatment for venous thrombosis. The authors estimated that if residual thrombus is <50%, recurrence is 5%; however, when residual thrombus is >50%, recurrence can reach 50%.

In conclusion, iliofemoral DVT is associated with substantially increased postthrombotic morbidity if it is treated with anticoagulation alone. Catheter-directed thrombolysis for acute iliofemoral DVT is highly successful and is associated with a low risk of major bleeding.

Superficial thrombophlebitis: benign or serious?

Diagnostic algorithm for superficial thrombophlebitis

M. K. Jezovnik (Slovenia)

The diagnosis of superficial vein thrombophlebitis is established primarily on the basis of clinical signs. Nevertheless, clinical examination does not always reveal the true extent of superficial thrombophlebitis (ST), because clinical signs and symptoms of inflammation usually underestimate the true extent of the thrombus (Cochrane Database of Systematic Reviews 2012, *Eur J Vasc Endovasc J* 2005, *Ann Int Med* 2010, *Fam Pract* 2004, *VASA* 2004).

It has been established that up to 40% of patients with ST have concomitant DVT at the time of diagnosis. Up to 25% of concomitant DVT is not contiguous with ST but is in the contralateral limbs and in around 15% of patients there is propagation of ST to DVT. In addition, in 20% to 33% of patients, asymptomatic pulmonary embolism (PE) is present, while symptomatic PE is present in 2% to 13% of patients.

Venous ultrasonography can be used to objectively confirm the diagnosis of ST. Ultrasonographic investigation should be performed in patients with a clinical diagnosis of ST in the lower limb if SVT is above the knee, in case of edema of the whole leg, and in those with risk factors for venous thromboembolism.

Patients with isolated ST below the knee associated with varicose veins and with no risk factors for venous thromboembolism may not need ultrasonographic evaluation.

Duplex sonography–lead direct visualization of the thrombus inside the superficial venous system (homogeneous intraluminal material, increased venous diameter, and lack of compression) can show the relationship of the thrombus to the deep venous system and the simultaneous involvement of the deep venous system. This is useful for differential diagnosis (cellulitis, erythema nodosum, panniculitis, and lymphangitis).

A new consensus on management of superficial thrombophlebitis.

V. Stvrtinova (Slovakia)

The Consensus Proposal from the Central European Vascular Forum for Diagnosis and Treatment in Superficial Thrombophlebitis was published in *Acta Phlebologica* (2011) and can be summarized as follows:

- *Recommendation nº1*: Look carefully for risk factors of superficial thrombosis, especially for cancer, systemic disease, and thrombophilia.

- *Recommendation nº2:* Clinical investigation may underestimate the real extension of superficial thrombophlebitis, and does not give enough information on the status of the deep venous system; therefore, after clinical investigation it is important to perform duplex ultrasound investigation of the superficial and deep venous system too. In many cases, superficial thrombophlebitis (ST) is a banal condition, which resolves spontaneously. However, in recent years, a large number of deep venous thromboses concomitant with ST have been found due to systematic ultrasound investigation of the venous system.

- *Recommendation nº3:* Duplex ultrasound investigation should be done bilaterally—on both lower limbs—not only on the limb affected by ST.

- *Recommendation nº4*: It is necessary (mandatory) to perform duplex ultrasound investigation immediately after the clinical diagnosis of ST in the case of ST localized on the trunk of the greater saphenous vein, 10 cm or less from the sapheno-femoral junction, or on the trunk of the small saphenous vein, 10 cm or less from the sapheno-popliteal junction.

- *Recommendation nº5:* All patients with superficial thrombophlebitis should be treated with compression therapy.

- *Recommendation nº6:* In all cases of ST, immediate mobilization with elastic compression is necessary (mandatory). Patients should not to be confined to bed. Confinement to bed favors progression of the thrombus in both the superficial and the deep venous system.

- *Recommendation n°7*: Patients with ST, with an inflamed and thrombosed superficial vein larger than 5 cm on duplex ultrasound investigation should receive anticoagulant treatment with fondaparinux 2.5 mg for at least 45 days or with LMWH for 4 weeks. The dosage and duration of anticoagulation treatment depends on the concomitant diseases and other risk factors for VTE.

There are multiple drugs involved in the treatment of ST: anticoagulants, nonsteroidal anti-inflammatory drugs, topical local anti-inflammatory treatment (gel, cream, spray), venoactive drugs (in patients with varicose ST), antibiotics (in patients with septic ST), or corticosteroids (in patients with vasculitic and autoimmune syndromes), but evidence is lacking to support the choice of the best therapeutic option, dosage, or duration. Low-molecular-weight heparins are used in therapeutic or prophylactic dosages and with a duration ranging from 10 to 20 or 30 days. The Calisto study has showed that treatment with fondaparinux for 45 days is more effective than placebo (relative risk ratio, 85%) in reducing systematic thromboembolism and complications or death.

Compression in superficial thrombosis?

H. Partsch (Austria)

The main question is whether compression therapy can decrease the incidence of deep venous thrombosis, thrombus extension, and pulmonary embolism (objective signs), or pain (subjective symptoms). There are no randomized controlled trials that answer this question, because up to now trials have compared anticoagulation vs no anticoagulation. All trials included the use of stockings (not standardized) and there are no published studies comparing compression vs no compression. For this reason, further studies exploring these aspects are needed.

2.2. Chronic venous disease

2.2.1. Investigations

Venous hypertension in chronic venous insufficiency

M. Koster (Switzerland)

Venous insufficiency is a major health problem. In some patients, peripheral venous pressure measurement may be useful but due to its invasive nature (puncture of the superficial vein of the dorsal foot), it is not routinely performed. The authors tested a noninvasive method using compression ultrasound. They compressed the great saphenous vein above the medial ankle and compared the pressure necessary to fully compress the vein lumen in the supine position, at rest, and during a standardized Valsalva maneuver. They compared the results obtained in a group of patients with venous insufficiency and in 20 healthy controls. They excluded patients with a history of prior deep vein thrombosis. In the healthy subjects, no pressure difference was found at rest and during Valsalva maneuver. On the contrary, in patients with venous insufficiency the pressure was significantly higher during the maneuver. The authors concluded that compression ultrasound seems to be a promising method for noninvasive peripheral pressure measurement in patients with venous insufficiency. The research is ongoing.

In the discussion, H. Partsch commented on a possible disadvantage of the method: it does not enable continuous pressure measurement and only assesses reflux and not obstruction.

2.2.2. Conservative treatments

Recent developments with venoactive drugs and compression therapy in edema management

P. Carpentier (France) introduced the session by emphasizing the special place of edema in the clinical, etiological, anatomical, pathophysiological (CEAP) classification[1] and the Vein-Term definitions.[2] In these classifications, edema is at the turning point of the progression of chronic venous disease (CVD), being placed between the early stages and the occurrence of skin complications.

In the Venous Clinical Severity Score (VCSS), edema is also considered as a valuable sign that can progress with chronic venous disease severity and change with treatment. Therefore, edema assessment is part of the global sensitivity to clinical changes of the VCSS.

According to a further analysis of the Basel study database, there is a close relationship between the presence of edema and venous symptoms (unpublished results).

Achieving a comprehensive understanding of venous edema is challenging for various reasons. The first reason is a pathophysiological one. The molecular mechanisms leading to venous edema remain to be fully elucidated. Second, edema measurement is far from being straightforward, since many assessment methods have been tried but none, except the water displacement method, is validated. Until now, the "water boot" method remains the gold standard for edema assessment, despite the large variability in repeated measurements reported in the previous trials using this method. Third, treatment of edema and its associated symptoms is also challenging, as explained by **F. A. Allaert** (France) who presented a study of the efficacy of a 28-day treatment with ruscus extracts on venous symptom improvement and venous refilling time amelioration. Venous symptoms were assessed on a visual analogue scale (VAS) and daily activities were assessed with VCSS. Venous refilling time was measured using mercury strain-gauge plethysmography, and reflux was measured with duplex scan. Women aged from 18 to 50 years, assigned to the C2s or C3s classes of the CEAP classification, with no history of deep venous thrombosis, and no heart and/or kidney failure, were enrolled in the study. The study design was open and aimed at assessing clinical and plethysmographic parameters before and after treatment. A total of 65 patients, aged 38.1 $\pm$ 7.4 years, who had chronic venous disease for a mean of 22.8 years entered the study. A significant improvement in leg heaviness, pain, paresthesia, cramps, impatience, and pruritus was seen after treatment. Daily activities increased. With ruscus treatment, there was a correlation between improvement of symptoms and plethysmographic parameters, which increased from 11.7 s $\pm$ 4.0 to 13.8 s $\pm$ 4.4 ($P<.0001$).[3]

J. Chudek (Poland) reported that many chronic venous disease patients do not accept compression therapy. Previous epidemiological surveys have showed that less than 30% of patients with CVD accept to wear a compression device. In Poland, only 28% of women and 20% of men comply with compression therapy. In the US, the figures are almost the same with 27% of patients accepting to wear compression stockings.[4] The main reasons for noncompliance in the US were ranked as follows: not helpful, problems of arthritis, sweating, itching, not cosmetic, and high cost. In Poland, the reasons ranked differently: high cost, sweating, itching, not cosmetic, ulcer exudation, and difficulty to apply. Whatever the reason for noncompliance to compression therapy, those patients have to be treated and therefore, pharmacotherapy with venoactive drugs (VADs) is an alternative. It is also possible that patients are not adherent to VAD treatment. This was the aim of a survey performed between 2008 and 2009 in Poland, which enrolled 5134 patients compliant to compression therapy and 4663 who did not accept this type of therapy. It appeared that patients who were noncompliant to compression therapy used VADs significantly less frequently. Obesity, male gender, older age, and the presence of comorbidities influenced nonadherence to VADs.

A new concept of compression therapy consisting in a progressive compression with higher pressure at the calf level (26 mm Hg) than at the ankle (10 mm Hg)—in contrast with the 'degressive' classical compression—was presented by **P. Carpentier** (France). The efficacy of this new device on edema reduction was tested in a multicenter, randomized, double-blind study enrolling C3 patients with pitting edema and reflux and/or obstruction demonstrated with duplex scan. Its aim was to evaluate leg volume reduction between 7 and 30 days of "degressive" therapy, together with the subsequent volume control over a 3-month follow-up period. Leg volume was measured by water displacement. Patients in the treatment group used the "degressive" compression therapy and were compared with those wearing stockings as close as possible to 'placebo compression' in the control group. A total of 89 patients (29 men and 60 women), aged 62.1 $\pm$ 14.1 years, with a mean body mass index (BMI) of 30 were enrolled in the study. No statistical difference was seen between the groups in terms of age, gender proportion, BMI, weight, leg pain, and heaviness. A significantly higher decrease in leg volume was shown at day 7 in the treatment group over the control one (difference, 388 ml) and the volume steadily decreased over the 3-month follow-up period in both groups. Volume reduction was not negligible in the control group. Volume reduction was most important when edema was substantial at day 0, VAS was high, and treatment took place in summer. Why did the control group improve so much? Could it be due to the placebo effect, the stimulation of physical activity (showing the importance of the calf muscle pump in edema reduction)? Or perhaps because placebo compression was not just "placebo," which may partly explain the results. In conclusion, "progressive" stockings are able to rapidly (1 week) decrease edema.

G. Mosti (Italy) explained that "progressive" compression therapy may also help prevent edema. In 30 volunteers who mainly stood or sat for their entire work shifts, leg volume was assessed by water displacement at baseline—early in the morning—and at the end of the work shift, on 2 consecutive days. On one day, classical compression therapy was applied on one leg and a "progressive"

compression on the contralateral leg. On another day, no stockings were applied and the legs were left without therapy. Both legs and day sequences were randomized. No difference in leg volume (assessed as the difference between volume after wearing the stockings and baseline, and after wearing the stockings and no stockings) was seen between classical compression and "progressive" compression therapy. Occupational edema (assessed as the difference between leg volume at the end of the working shift and the morning) was significantly more reduced with "progressive" compared to classical compression therapy (-82% versus -69% respectively). "Progressive" compression therapy is more effective than classical compression in preventing occupational edema. Redistribution of leg fluid might be one of the explanations for the more effective edema reduction observed with "progressive" stockings.

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Hemodynamic performance using four compression stockings in postthrombotic syndrome correlates with the degree of reflux

C. R. Lattimer (UK)

Compression therapy is recommended after DVT but the class of compression and its length are not perfectly known. A longer and stronger compression could be the best but this remains to be confirmed. The aim of this study was to evaluate the effect of different classes of compression stockings on hemodynamics in postthrombotic syndrome patients.

A total of 40 legs with postthrombotic syndrome were tested with class-1, class-2, above-the-knee, and below-the-knee stockings. Duplex ultrasound and air plethysmography investigations were performed.

Hemodynamics were improved in 70% of the legs, irrespective of the class or length of stockings. The legs with the most severe reflux at baseline had the greatest reduction in the venous filling index. A better hemodynamic assessment method might help identify the most appropriate level of compression.

Controversies in compression therapy

Inelastic compression in mixed ulcers increases arterial inflow and venous output

G. Mosti (Italy), H. Partsch (Austria)

It is reported that 16% of venous ulcers are associated with arterial disease. Until now, the treatment of venous ulcers involved compression therapy but this was not recommended for arterial disease due to impairment of arterial inflow. The authors reported their experience in the treatment of mixed ulcers with compression therapy and defined the range of optimal compression pressure.

In 25 patients with mixed ulcers, they assessed skin flow in the peri-wound area and plantar surface of the first toe, toe pressure with laser-Doppler flowmetry, and venous pumping function (ejection fraction) with strain gauge plethysmography. They applied different ranges of pressure (baseline to 40-50 mm Hg). Patients presented a low mean ankle brachial pressure index (ABPI) (0.57 ± 0.09) and in 16 patients claudication occurred when walking less than 100 meters.

They observed that external compression of up to 40 mm Hg increases arterial flow and venous ejection fraction and concluded that compression therapy could be applied even in patients with arterial disease.

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Compression after deep venous surgery: for how long?

A. ten CATE-HOEK (The Netherlands)

Post-thrombotic syndrome (PTS) arises in 20% to 50% of patients after deep venous thrombosis, impairs quality of life, and increase costs. The origin of PTS is an increase in venous pressure due to obstruction or reflux after valve damage during recanalization. The prevention of recurrent DVT is based on the appropriate duration of anticoagulation and in some cases on the use of catheter-directed thrombolysis in the acute phase. The arbitrary duration of compression is usually of 2 years, started 10 days after diagnosis. The aim of this report was to determine the optimal duration of compression.

The authors concluded that 6 months of compression is sufficient to prevent PTS and that compression must be applied as soon as the diagnosis is made. In some cases, compression must be maintained for a prolonged period, depending on the Villalba score.

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When to use bandages or stockings in venous and lymphatic diseases?

H. Partsch (Austria)

The essential determinants of the efficacy of compression therapy are the pressure exerted and the elastic property of the material used. The main difference between the use of stockings and compression is the stiffness of bandages.

Computed tomography scan pictures showed that a minimum of 83 mm Hg elastic compression is needed to occlude the great saphenous vein in the thigh, whereas only 20 mm Hg is enough to compress the deep venous system in the calf.

The main aims of compression therapy are edema reduction and improvement of venous hemodynamics. Less pressure is needed to reduce edema and more pressure is needed to reduce the diameter of the leg veins in the upright position.

The author prefers using inelastic high pressure bandages in patients with long-standing leg ulcers and after endovenous or surgical abolition of venous reflux, deep venous thrombosis, or superficial thrombophlebitis, and for the initial treatment of lymphedema.

Compression stockings are preferred to maintain the good results achieved after inelastic high pressure bandages.

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2.2.3. Nonconservative treatments

Severely dilated truncal varicose veins treated with endovenous laser therapy

S. Kaspar (Czech Republic)

Endovenous laser therapy is not commonly used to treat severely dilated veins because of possible failure.

In this study, the author reported 224 procedures, performed either with Diode 980 or 1470 or Nd Yag 1320 nm lasers and under tumescent anesthesia. The treated great saphenous veins (GSV) and small saphenous veins (SSV) had diameters of more than 15 mm and more than 10mm, respectively. DVT and PE were not recorded during the follow-up (1 to 67 months). Bruising was found in 87% of cases and paresthesias (7%) were observed only after SSV treatment and resolved within 2 months. The total occlusion rate was 96%.

The author concluded that the procedure is safe and effective and could be performed even in severely dilated intrafascial veins. However, we should pay attention on how we perform tumescent anesthesia in order to decrease the risk of skin damage as well as nerves injuries, particularly in case of SSV treatment. Moreover, good compression and sufficient energy delivery are required to achieve good occlusion rates.

Radiofrequency ablation of the great saphenous vein as a part of the therapy of chronic venous insufficiency.

J. Marusiak (Czech Republic)

This retrospective study analyzed the results of stripping and radiofrequency ablation in 180 patients with varicose vein disease. Both groups were treated under general or spinal anesthesia, which was associated with local tumescent anesthesia only for the radiofrequency ablation group. Hematoma, paresthesia, infection, cosmetic results, and recurrence were analyzed. There were no statistical differences between the two groups concerning the number of complications and the rate of clinical or hemodynamic recurrence but the authors concluded that radiofrequency ablation is less painful and achieves a better quality of life.

It would have been interesting to compare cosmetic and quality of life results of two different surgical techniques but because of the use of tumescent local anesthesia in the radiofrequency ablation group no conclusions can be made for this study. We know that tumescent local anesthesia reduces hematoma and bruising, reduces pre- and postoperative pain, and has an impact on peri- and postoperative QOL.

Evaluation of the efficacy of adjunctive treatment with endovenous thermal ablation: a comparative study.

T. King (USA)

There are some controversies about the impact on health-related quality of life (QOL) of the concomitant or delayed treatment of symptomatic varicose veins during endovenous thermal ablation (ETA) for saphenous vein reflux. In this prospective comparative study, 156 patients were treated with ETA for great saphenous vein reflux. In group 1, 78 patients received delayed adjunctive treatment with foam and liquid sclerotherapy 4 to 6 months after ETA and in group 2, 78 patients received the same adjunctive treatment but simultaneously to ETA. The demographics, sapheno-femoral junction size, CEAP class, and Aberdeen Varicose Vein Questionnaire (AVVQ) score at baseline were similar in the 2 groups. In Group 2, the AVVQ scores were improved at 3 and 6 months and for group 1 the improvement was remarkable after undergoing delayed treatment. The author therefore concluded that there is no benefit in delaying adjunctive treatment for the management of residual symptomatic varicose veins after ETA.

This is in total accordance with the randomized controlled study of Carradice et al, which has shown that 66% of patients treated with ETA alone required secondary procedures on residual varicose vein tributaries after one year whereas only 0.04% of patients who had concomitant phlebectomy treatment required

secondary procedures. Moreover, quality of life in the concomitant treatment group was much better. We should never forget that patients come for the treatment of their varicose veins and not for the treatment of great saphenous vein reflux and we should pay much more attention to the patients' requests.

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Infrequent indications of endovenous laser therapy

S. Kaspar (Czech Republic)

Laser ablation of the anterior accessory great saphenous vein (AAGSV), small saphenous vein (SSV), or Giacomini vein (GV) are infrequent and rarely reported. The author reported his experience on the laser ablation of 142 SSV, 115 AAGSV, and 6 GV using 980- or 1470-nm diode or 1470-nm Nd YAg laser. Patients were assessed clinically and with duplex ultrasound. No severe complications were reported, some bruising resolved spontaneously, and transient paresthesia was observed in 7% of patients of the SSV group. The total occlusion rate was good.

The author concluded that endovenous laser therapy is safe and effective and could be routinely performed on AASV, SSV, and GV, which is not actually the case.

The use of tumescent local anesthesia could also decrease the risk of skin and nerve damage.

Low thrombotic risk following endovenous laser ablation for chronic venous disease

T. King (USA)

In a meta-analysis, the incidence of deep venous thrombosis after endovenous laser ablation (EVLA) was reported to range from 0% to 5.7%. In this retrospective case study, the author wanted to assess the immediate risk of venous thromboembolism (VTE) after EVLA for chronic venous disease.

A duplex ultrasound was performed 3 to7 days after 21 041 EVLA procedures and venous thromboembolism was found in only 0.29% of the cases while deep venous thrombosis was found in 44%, superficial thrombophlebitis in 23%, and pulmonary embolism in 11%.

The author concluded that there is a low incidence of venous thromboembolism after EVLA. He also concluded that thrombotic risk has a low level of predictability. Further studies are therefore required to determine predictive factors.

Management of chronic venous disease: current guidelines of the Society for Vascular Surgery (SVS) and of the American Venous Forum (AVF)

P. Glovicski (USA)

Why new guidelines? Because in these new guidelines, the evaluation process was perfected, the pathogenesis clarified, and the treatment revolutionized. The author reported the top 10 recommendations of the SVS and AVF guidelines.

1) The CEAP classification should be used to describe the severity of venous disease (grade 1B).

2) Patient evaluation should include duplex ultrasound scanning of the deep and superficial veins (duration of reflux > 0.5 s in superficial veins and >1.0 s in deep veins (grade 1A).

3) Compression therapy is suggested for patients with varicose veins (grade 2C).

4) The guidelines recommend against compression therapy as the primary treatment of varicose veins if the patient is a candidate for saphenous vein ablation (grade 2C).

5) Compression therapy should be used as the primary treatment in varicose ulcers (grade 1B).

6) For the treatment of an incompetent saphenous vein, endothermal ablation is recommended over high ligation and stripping (grade 1B).

7) Foam is an option for saphenous vein ablation (grade 2C).

8) Phlebectomy or sclerotherapy are recommended for varicose tributaries (grade 1B).

9) The guidelines are against the selective treatment of perforating veins in patients with simple varicose veins (grade 1B)

10) To decrease the recurrence of ulcers, ablation of the incompetent varicose vein should be performed (grade 1A)

The author concluded that the best treatment should be based not only on guidelines but also on physician experience and patient preferences.

2.3. Venous malformations

Arteriovenous malformations. General overview – how much do we know?

B. B. Lee (USA)

Arteriovenous malformation is one of various types of congenital vascular malformations with highly destructive potency. Arteriovenous malformations represent 10% to 20% of all congenital vascular malformations.

The classification of the embryologic subtypes of arteriovenous malformation distinguishes between truncular and extratruncular malformations in order to identify the risk involved in their clinical management (Hamburg Classification). Infiltrating extratruncular lesions are the most dangerous primitive type of congenital vascular malformations.

An early and aggressive approach is recommended after adequate diagnosis and proper classification of arteriovenous malformations.

Contemporary diagnosis. What is the best opinion?

R. Matassi (Italy)

Clinical examination alone does not give sufficient data for the complete diagnosis of arteriovenous malformations in the majority of cases. Therefore, the first noninvasive exam to be performed is a duplex scan, which should give data about flow (high flow, low flow, or no flow).

Plan radiography is the second less invasive exam; it gives information on the presence or absence of phleboliths.

Magnetic resonance imaging gives information on the site of the arteriovenous malformation, the presence of infiltration lesions, and vessel morphology.

Computed tomography is less clear except for the study of the main vessels.

Angiography is performed to confirm diagnosis or an indication for endovascular treatment.

Endovascular management of arteriovenous malformations. Is it a panacea?

P. Burrows (USA)

Primary embolization of arteriovenous malformations cures 40% of cases. Its symptoms can be controlled and palliated.

The best timing for endovascular treatment is in Schöbinger stage II or early stage III. Arterial embolization with tissue adhesives and arterial coils achieves proximal occlusion of the feeding arteries and is unlikely to produce good long-term results. Supraselective intranidal embolization with ethanol can produce better results and can occasionally be curative. It must be performed in stages, often for many months, to achieve closure.

Is ethanol still the gold standard for arteriovenous malformation treatment?

I. Baumgartner (Swizerland)

The majority of arteriovenous malformations are extratroncular. To achieve good results the nidus should be targeted.

Ethanol induces protein denaturation with subsequent wall denaturation. It provides the best outcome with minimal recurrence. The treatment should be performed precisely into the nidus either by direct puncture or transcatheter techniques. Multiple sessions are required. Preferably use 60% ethanol for lesions that are superficial and close to the nerves. Additional coil embolization may also be used. Steroids should be dispensed intravenously before and after treatment. Repeat sessions with single injections over several months are mandatory.

II.

First meeting of the Deep Venous Reconstructive Surgery in Chronic Venous Insufficiency (DVRS-CVI) CLUB

In the framework of the 13th meeting of the European Venous Forum,
28-30 June 2012, Florence, Italy

Contents

Editorial

As the President of the 13th meeting of the European Venous Forum held in Florence, it was a pleasure and honor to host the first meeting of the Deep Venous Reconstructive Surgery for Chronic Venous Insufficiency (DVRS-CVI). The idea for this meeting came about a few years ago, when Michel Perrin and Oscar Maleti dreamed of a DVRS Club open to everyone interested in this surgical challenge. It has now become a reality with the blessing of Andrew Nicolaides, General Secretary of the EVF.

It was a great privilege to listen to the presentations made by the pioneers of DVRS: Bob Kistner, who was the first surgeon to perform a valve plasty and later on, a valve transposition at the groin, and Seshradi Raju who performed the first axillary valve transplantation and the first stent for vein obstruction. European surgeons owe Michel Perrin for the promotion of DVRS in Western Europe and for encouraging new talents to emerge in deep vein surgery. Let's not forget Oscar Maleti and Marzia Lugli from Modena who successfully used the thickened wall of a postthrombotic vein to construct a neovalve. Such findings promote progress in venous surgery. Surgeons from both sides of the Atlantic Ocean met in Florence and delivered seventeen short presentations on all fields of DVRS, thereby giving a comprehensive review of the topic.

A selection of their abstracts is presented in this special issue. We hope you will enjoy reading it.

Giovanni Mosti
President of the EVF

OVERVIEW OF THE SESSION ON DEEP VENOUS RECONSTRUCTIVE SURGERY IN CHRONIC VENOUS INSUFFICIENCY

Robert L. Kistner (Honolulu, HI, USA)

It is a great honor to open this session devoted to deep vein surgical procedures for this distinguished audience. Dr Maleti and Dr Perrin have organized a series of rapid-fire presentations from authorities in different aspects of deep vein disease and during the next 2.5 hours we will be treated to a review of this whole field. My task is to set the stage for what we are about to hear.

The discussions that follow will describe surgical procedures that the majority of surgeons have never performed and that many believe to be seldom, if ever, indicated. The fact is that many of these techniques have been available for over 3 decades and have not been widely adopted so they have either failed the test of time or they have some other defect that makes them unpalatable. In response to this state of affairs a new "club" made up of persons who have actual experience in deep reconstruction called the DVRS-CVI club—you will recognize that this acronym stands for the title of this talk: Deep Venous Reconstructive Surgery for Chronic Venous Insufficiency. It is pronounced: 'Deevers-Civi Club'. This presentation today is the initial function of that group and your critical input following the session is urgently welcome.

The concept of deep vein reconstruction flies in the face of the taboos that dominated surgical thinking when I entered the surgical disciplines in the 1960s. The gospel at that time was to handle the veins with a "no-touch" technique—reminiscent of the no-touch technique of the "laying on of hands" used by some advocates of semi-spiritual healing. The concern was that the veins could not tolerate manipulation without developing thromboembolic complications. In retrospect, this was a state of irrational reaction to earlier experiences where the veins were traumatized without anticoagulation and without attention to already established principles of vascular surgery—these include provision for adequate inflow and outflow to the operative site and handling the vessels with vascular clamping, avoiding excessive stretching and torsion, and employing minimally clamping of the vessels under therapeutic levels of intraoperative anticoagulation. It is not that others had not experimented with surgery of the veins earlier—one can recall the description of venous transplantation in 1906 by Carrel and Guthrie, Trendelenburg in 1906, and Homans in 1934 with ligations of inferior vena cava and femoral veins, Lawen's description of thrombectomy in 1938, followed by Warren and Thayer's description of a sapheno-popliteal bypass in 1954, Palma's cross-femoral bypass in 1958, and Eiseman and Malette's folding of the veins to produce a competent valve in the 1950s. But all of these were whispers in the wind that failed to influence surgical practice immediately. The signal contribution of Bauer in the 1940s describing idiopathic (nonthrombotic) venous valve reflux was also largely ignored. All of this changed in the period from 1960 to 2000 when the earlier techniques of operating gently with proper instruments under anticoagulation using principles of vascular repair learned from arterial surgery were employed. By this time venography had been improved with better fluoroscopy techniques and the biggest boon of all to diagnosis and knowledge of the veins—the non-invasive ultrasound—came on the scene. A notable flurry of activity followed in many places around the globe during these years.

Surgical procedures to repair primary valvular reflux and others to manage postthrombotic disease by transposing or transplanting venous segments were devised, reported, and evaluated with small series of patients. Some of these proved to be reproducible by different surgeons in different parts of the world and the question of which patients should be candidates for the procedures became subject for debate. I believe the wider interest in deep vein surgery became stalled at that point in favor of the search for less invasive techniques and the romance of the interventional approach. Progress in the deep veins has continued with the description of the creation of the Maleti/Lugli neovalve and with deeper focus on the importance of restoring patency in the iliac vein by thrombectomy, angioplasty, and stenting. All of this you will hear in the next couple of hours.

So, where are we and Quo Vadis—where do we go from here? Is there a place for deep vein reconstruction? How should we evaluate the procedures to justify their risk and expense? Do we need a rash of prospective randomized trials costing millions of dollars and years of development? Is it possible to design these trials? Who would do them? Or is this even advisable now? Is the fact that there are sufferers from venous disease where clinical improvement provides the justification to perform relatively safe procedures while firm evidence is being accumulated?

Some things we know are needed are: basic science investigations into molecular, hematologic, and inflammatory aspects of venous and ulcer disease; safe thrombolytics to dissolve clots before they destroy the inside of the veins; a better understanding of the physiology of venous flow and the role of the venous valve; a much better awareness in the profession and in the public about venous disease; and the emergence of venous specialists who are experts in the natural history of chronic venous disease and can manage its medical and surgical aspects.

It is with these thoughts in mind that I am anxious to hear the papers that will follow. My hope is that their presentation in a concentrated session will stimulate some among the audience to use the present accomplishments as a prelude to their own future efforts to push the frontiers forward. We know that the presence of axial venous reflux and critical sites of obstruction in the veins will result in a progressive loss of quality of life. We know that the end stage of chronic venous disease is not the loss of the limb—rather it is the loss of the use of the limb, which amounts to a near-image of amputation.

Simply stated, the surgical intent is to interrupt the progressive development of disability from chronic venous disease in the safest and most effective way to preserve normal activity, free of discomfort and disability. The surgery of deep vein disease is properly done to adapt the venous system to the individual's way of life rather than having the person limit activities to meet the restrictions imposed by chronic venous disease.

A STRATEGY FOR THROMBUS REMOVAL FOR ACUTE ILIOFEMORAL DVT REDUCES POSTTHROMBOTIC SYNDROME

Anthony J. Comerota (Toledo, OH, USA)

Iliofemoral deep venous thrombosis is associated with severe postthrombotic morbidity when treated with anticoagulation alone. Catheter-directed thrombolysis (CDT), with or without the addition of mechanical techniques, is increasingly recommended for patients with iliofemoral DVT, although its effect on postthrombotic syndrome has not been well established. Recently, clinical observations from nonrandomized studies,[1] the report of a small randomized trial by Elsarawy et al,[2] and the recent publication of the CaVenT trial[3] all strongly support the concept that successful catheter-directed thrombolysis reduces postthrombotic morbidity.

Comerota et al[1] studied 71 consecutive patients with iliofemoral DVT who were treated with CDT. Pretreatment and posttreatment phlebograms were evaluated for quantity of residual thrombus by physicians blinded to clinical patient outcomes. Postthrombotic syndrome (PTS) was assessed using the Villalta score by examiners blinded to the phlebographic results. Patients who had ≥50% lysis had significantly lower Villalta scores (2.21) compared with those with <50% lysis (7.13; *P*=0.011). There was a direct and significant correlation of the CEAP class with the amount of residual thrombus at the completion of CDT and a direct linear correlation of Villalta score with residual thrombus. Elsharawy et al[2] demonstrated that there was significantly better patency and significantly better preservation of valve function when patients with iliofemoral DVT were randomized to CDT compared with those randomized to anticoagulation alone.

In their report of the CaVenT trial,[3] Enden and colleagues reported that there was significantly better iliofemoral venous segment patency with catheter-directed thrombolysis and significantly less postthrombotic syndrome in patients randomized to CDT.

The ATTRACT trial is ongoing, and when completed, it will be the largest study to date evaluating a strategy of thrombus removal with catheter-based techniques compared with anticoagulation alone in patients with acute iliofemoral DVT and those with acute femoral popliteal DVT.

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ULTRASOUND EVALUATION WITH B-FLOW DURING VALVE REPAIR

Fedor Lurie (Honolulu, HI, USA)

Duplex and triplex ultrasound scans are sufficient for addressing the most important questions prior to and after valve reconstruction surgery.

These include detection of significant reflux and/or obstruction, presence of valves, and their location. The limitations of conventional ultrasound techniques are:

1. Low reliability of valve visualization,

2. Low sensitivity in detection of limited reflux

3. Inability to detect valvular function in physiological conditions without forced reflux-provocation.

B-flow modality is angle-independent grayscale Doppler coding, which allows blood flow visualization without obstruction of the B-mode echo image. Use of B-flow improves valve detection and visualization, increases sensitivity of detection of limited reflux, and allows the study of valve function during physiologic flow.

During this presentation, we will demonstrate examples of identification of otherwise invisible-to-ultrasound valves, examples of valvular dysfunction that is difficult to diagnose by conventional techniques, and an example of intraoperative detection of residual limited reflux, its location and correction by guided stitching.

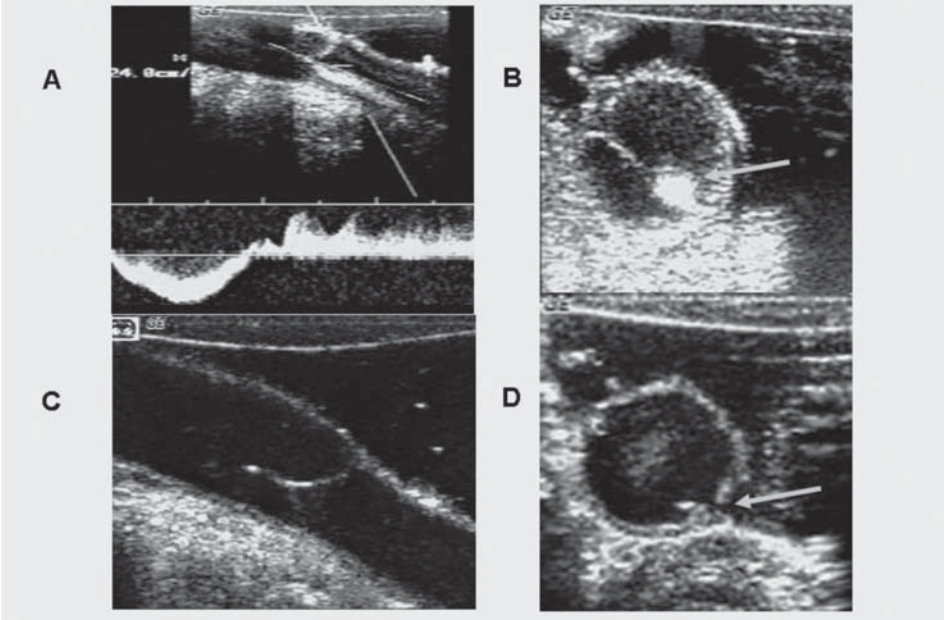

Figure 1. Intra-operative scan immediately after valvuloplasty shows remaining reflux (A). Transverse B-flow image (B) shows exact location of the gap between the cusps, allowing precise external placement of a stitch. B-flow images after the placement of an additional stitsch show absence of reflux (C,D).

DEEP VENOUS RECONSTRUCTIVE SURGERY FOR REFLUX IN PRIMARY VENOUS INSUFFICIENCY

Michel Perrin (Lyon, France)

Introduction. The effectiveness and usefulness of deep venous reconstructive surgery (DVRS) for primary deep reflux remain controversial.

Etiology and physiopathology. The most common etiology in deep venous reflux is the postthrombotic syndrome, but primary deep vein insufficiency is frequently overshadowed. Clinical examination frequently does not allow the distinction between superficial and deep venous insufficiency. In addition, primary reflux is difficult to identify from secondary deep reflux.

Investigations. Duplex scanning provides etiologic, anatomic, and hemodynamic information. Plethysmography gives information on the overall severity of venous disease, but not on its etiology and is not reliable for identifying the predominant component when superficial and deep insufficiencies are combined. It would seem logical to go beyond these investigations only in those patients in whom surgery for deep reflux may be considered. In the absence of contraindication, such as an ineffective calf pump, the following complementary investigations must be carried out: ambulatory venous pressure measurement and venography including ascending and descending phlebography.

Aim of DVRS. The goal of DVRS for reflux is to correct the reflux related to deep venous insufficiency at the subinguinal level. However, we must keep in mind that deep reflux is frequently combined with superficial and perforator reflux; consequently, all these mechanisms have to be corrected in order to reduce ambulatory venous pressure**.** Besides, primary deep venous obstruction should be associated with primary deep venous reflux

Surgical techniques can be classified into 3 groups

- Procedures with phlebotomy: internal valvuloplasty, transposition, transplantation, neovalve construction, and allografts.
- Procedures without phlebotomy, including banding and external valvuloplasty.
- Artificial valves inserted through vascular access.

Results

Outcomes of deep venous reconstructive surgery for primary deep reflux are difficult to assess as this surgery is frequently combined with superficial and perforator vein surgery, but both have usually been performed before as a first step.

In primary deep venous reflux the most frequent procedure is valvuloplasty, which is credited with achieving a good result in 70% of cases in terms of clinical outcome, defined as freedom from ulcer recurrence and reduction in pain, valve competence, and hemodynamic improvement over a follow-up period of more

than 5 years. Internal valvuloplasty is credited with better results than external valvuloplasty.

The **indication** for DVRS in deep reflux relies on clinical, hemodynamic, and imaging criteria.

- Clinical criterion: **C4b** and **C6** patients**.**
- Hemodynamic criterion: Axial reflux: uninterrupted retrograde venous flow from the groin to the calf. Axial reflux is important, segmental reflux is not.
- Imaging criterion: Venography is crucial to identify primary reflux and the station to be chosen.

When deep primary reflux is combined with superficial and perforator reflux they must be treated first, but we know from several studies that approximately half of the patients with deep axial reflux are not improved in the presence of chronic venous insufficiency.

When deep primary reflux is combined with obstruction, there is a large consensus for treating the obstruction first.

What remains controversial is the need to treat reflux as a second step.

Conclusion

- General practitioners as well as angiologists and vascular surgeons underdiagnose primary deep venous reflux.
- When identified, patients are treated by conservative treatment as very few doctors are aware of the possibilities offered by DVRS.
- Valve reconstruction for primary reflux is underused in selected cases, especially since it deserves a Grade 1A recommendation according to the 3rd edition of the Handbook of Venous Disorders.
- DVRS for primary reflux is not, however, often indicated and has to be performed in highly-specialized units.

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THE NEOVALVE: TECHNIQUES AND INDICATIONS

Oscar Maleti (Modena, Italy)

Neovalve construction is a technique aimed at creating an antireflux mechanism in patients affected by deep venous reflux whenever valvuloplasty is not feasible (postthrombotic syndrome and valve agenesis).

After attempting to restore the leg's hemodynamic equilibrium by correcting any proximal obstruction and/or superficial reflux that may be present, the failure of such conservative treatment should lead us to evaluate whether deep venous reconstruction is opportune.

Neovalve construction is one of three leading techniques: vein transposition, vein transplant, and neovalve construction itself. Neovalve construction can also be associated with endophlebectomy where necessary. Neovalve creation has undergone technical change over the years, from the first parietal dissection that created a bicuspid valve up to the most recent technical modification aimed at achieving a fluctuating flap.

Bicuspid parietal dissection aimed at mimicking the physiological human valve; however, given that it requires homogeneous wall thickness, it was not widely applicable due to wall fibrosis, which was frequently asymmetrical. For this reason constructing a monocuspid valve is the most feasible technique and it has demonstrated a performance comparable to that of a bicuspid valve.

The crucial difference is that the pocket is deeper in the monocuspid valve compared with the bicuspid valve, and this may increase the risk of readhesion. In order to avoid this eventuality, we introduced a modified technique in which the neovalve was fixed in a semi-open position to reproduce the physiological configuration of the valve.

Another challenge was the fact that particularly thin walls could impede parietal dissection. In selected cases we solved this problem by invaginating the entire vessel wall and reconstructing the pocket using a bovine pericardium patch. Subsequently, we paid particular attention to obtaining a thin flap in order to achieve greater mobility and thus efficacy.

This thin flap or leaflet was progressively increased from half of the circumference length to the entire circumference length, once again reconstructing the vein by means of a bovine pericardium or autologous venous tissue patch.

Finally, in another attempt to obtain a mobile leaflet that could work as a valve, we performed a parietal dissection on the opposite wall at the level of a venous collateral, which could create a competing flow inside the valve sinus.

Admittedly, since the venous collateral is inside the pocket of the valve, this technical solution does not reproduce the physiology of a human valve. However, there are two significant advantages: an extremely mobile flap and a washing-out action that prevents flap readhesion, venous stasis, and therefore also thrombosis.

The outcomes of the neovalve technique are excellent in the short term, good in the medium term, and similar to the other techniques in the long term. A progressive loss of function is reported.

However, the neovalve technique has shown that we can treat the deep venous system directly by open surgery without any fear of pulmonary embolism and deep venous thrombosis. Working as an antireflux mechanism, the neovalve allows the patient not only to benefit from a protracted ulcer-free period but also, principally, to maintain a protracted C4b-free period or at least gain a significant improvement in symptoms.

The downside of constructing a neovalve is that it is not an easy operation to perform and it cannot be standardized. Fortunately, currently available technology is already increasing the chances of performing this operation and a transcutaneous device is being developed that will simplify the procedure, making it easier to standardize.

From a clinical perspective, the indication to create a neovalve is broadly the same as the indication to perform deep venous reconstructive surgery in patients affected by PTS or valve agenesia whenever the following conditions are present:

- Failure to maintain the equilibrium of the leg by means of medical and compression therapy.
- Limited compliance with compression therapy.
- Inadequate results obtained by means of surgical correction or proximal obstruction correction.
- It is preferable to perform the operation in an active patient with efficient ambulation.

From a technical point of view, neovalve construction is indicated when a valvuloplasty or a valve transposition cannot be performed. Between vein transplant and neovalve construction, it is a question of choice.

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THE ROLE OF ENDOPHLEBECTOMY

Marzia Lugli (Modena, Italy)

The main characteristic alterations of postthrombotic syndrome are obstructive lesions, which determine obstacles to blood flow, and valve destruction, which causes reflux. These lesions are frequently associated. However, when combined, the respective roles and hierarchical relationship of these lesions have not been clearly established. The correction of obstruction provides clinical results such as the improvement of symptoms and restoration of the hemodynamic equilibrium of the leg.

Obstructive lesions above the inguinal ligament are commonly treated by means of venoplasty and stenting. This procedure is rarely employed below the ligament, even if in some situations stenting needs to be extended from the iliac segment to the common femoral vein. Indeed, the common femoral vein is a crucial area in determining the outflow of the leg.

The presence of a large amount of fibrotic tissue and the involvement of collateral vessel confluence, especially that of the deep femoral vein, suggest that open access surgery is the best surgical option. This intervention, known as "endophlebectomy," involves the disobliteration of chronically obstructed vein segments.

Endophlebectomy, which was first mentioned by Raju in association with a valve transplant, was later described as a stand-alone method by Puggioni and Kistner. Unlike endoarterectomy, endophlebectomy leaves intact a large part of the endothelium, thanks to the specific anatomo-pathological characteristics of endovenous fibrosis. For this reason, endophlebectomy has a low rate of thrombotic complications.

Although postthrombotic disease usually affects an entire venous segment, the strategic treatment of selected crucial areas may lead to restoring the hemodynamic equilibrium of the leg, which is the objective of endophlebectomy.

Since obstruction is usually concomitant with deep venous reflux, endophlebectomy can be associated with neovalve construction. These two surgical options are frequently integrated and the concomitant neovalve construction obviates the need for any subsequent intervention that may have been required in the event of persistent symptomatic reflux.

The indication criteria for endophlebectomy are difficult to define. Preoperative instrumental evaluation—both ultrasound and venography—usually underestimate

the amount of endovenous fibrotic tissue and there are no parameters to quantify its impact on venous inflow. Compared with common ultrasound, B-flow yields more information. Only intravascular ultrasonography can precisely evaluate the extent of the lesions but it is not easily performable at the above-mentioned sites.

Endophlebectomy is an operation that should be more widely indicated, both as a stand-alone technique and in association with angioplasty/stenting of proximal lesions or with deep venous reconstructive surgery.

Currently, there are no codified criteria for indicating the extent and location of the disobliteration to be performed, particularly below the inguinal ligament. As a result, it is essential to identify those areas that are crucial in restoring the leg to hemodynamic equilibrium.

Such codification will logically lead to the standardization of the endophlebectomy technique.

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VENOUS STENTING IN CHRONIC ILIAC VEIN OBSTRUCTION

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Venous stenting has emerged as a major modality of treatment for chronic venous disease. Routine use of intravascular ultrasonography for diagnostics has shown that obstructive lesions are often present in the iliac venous system at arterial crossover points in patients with advanced primary disease. The presence of reflux in association with postthrombotic disease is well established. Thus, iliac venous stenting appears to have a role in a wide spectrum of pathologies. More interestingly, substantial symptom relief including healing of venous ulceration occurs with iliac vein stenting alone in combined obstruction/reflux cases. In an

analysis of 528 limbs with combined pathology, 42% had axial reflux and 58% had reflux segment score ≥3. Nevertheless, clinical relief from the stent procedure alone was satisfactory with relief of pain, swelling, and ulcer healing of (cumulative) 74%, 62%, and 61%, respectively. Further correction of reflux was not necessary. The durable results from stenting alone, despite persistent uncorrected reflux, opens fundamental questions regarding pathophysiology in chronic venous disease.

A common pathway for venous pathology, be it obstruction, reflux, or both may be through oxygenation of the skin. Recently, it has become clear that a severe hypoxemia of about 50% compared with normal supine values occurs when assuming the erect position. Studies in a mechanical venous model suggest that reflux impacts the duration of arterial inflow occurring with calf pump action.

IVUS: SHOULD IT BE USED MORE FREQUENTLY?

Peter Neglén (Trimiklini, Cyprus)

The simple reply to the question stated in the title is: Yes. There is no doubt that intravascular ultrasonography (IVUS) best delineates intraluminal structures such as webs and trabeculations, thrombus, wall structure, and external compression *(Figure1)*. It is the gold standard for imaging the extent and severity of femoro-ilio-caval venous outflow obstruction, which makes it the premier diagnostic tool without any need to inject contrast dye. IVUS can also easily identify the anatomical location of the outflow by identifying the confluence of large tributaries.

There is no noninvasive or invasive test to detect a hemodynamically significant femoro-ilio-caval outflow obstruction. The pathophysiology of an outflow obstruction and the influence of length and degree of obstruction on venous hemodynamics are poorly understood. A >50% morphological obstruction of the cross-cut area in the pelvic outflow is presently considered significant and warrants stenting. This is an arbitrary number based on favorable clinical results after venoplasty and stent placement. Since there is no noninvasive accurate test, more or less invasive morphological investigations have to be utilized, such as venography, computed tomography venography, magnetic resonance venography and preferably IVUS *(Figure2)*.

Classic anterior-posterior venographic imaging of the ilio-femoral venous outflow has been shown to be inadequate; actually 25% of the venograms (n=304) were reported as "normal." Compared with IVUS findings, venograms underestimate the degree of stenosis by 30%. The sensitivity and negative predictive value to identify >70% diameter stenosis was 45% and 49%, respectively. In a group of 104 patients with >50% diameter stenosis detected by IVUS, the venogram revealed no stenosis in 17% and in an additional 41% an inaccurate location or extent of the stenosis was shown.

The sensitivity and negative predictive value was only 43% and 56%, respectively. By performing oblique views, the sensitivity and negative predictive value improved substantially to 63% and 68%, respectively (unpublished data), but are still insufficient.

There is no doubt that IVUS is superior to venogram. There are no comparative studies performed between CT-V/MR-V and IVUS.

IVUS is used not only to diagnose the severity, type, and extent of a venous outflow obstruction but also to guide the subsequent stent placement. The long-term patency of a stent is primarily dependent on an unobstructed outflow and brisk inflow of the stent module. IVUS is the only modality to identify segments free of significant occlusive postthrombotic disease, thus ensuring an adequate landing zone and patent outflow and inflow vessels. In a similar fashion, IVUS can differentiate between residual intraluminal thrombus and true underlying stenosis following early mechanical or lytic clot removal of the ilio-femoral segment. IVUS will ensure sufficient lysis and adequate stenting of the reveal chronic obstruction. Most IVC filters can now be placed bedside under IVUS guidance.

The major obstacle to a more frequent use of IVUS has been the cost of the catheters. When the manufacturers realize the increased need for IVUS investigations (a larger market), less expensive, simpler devices with fewer unnecessary bells and whistles will be produced, possibly based on laptop technology.

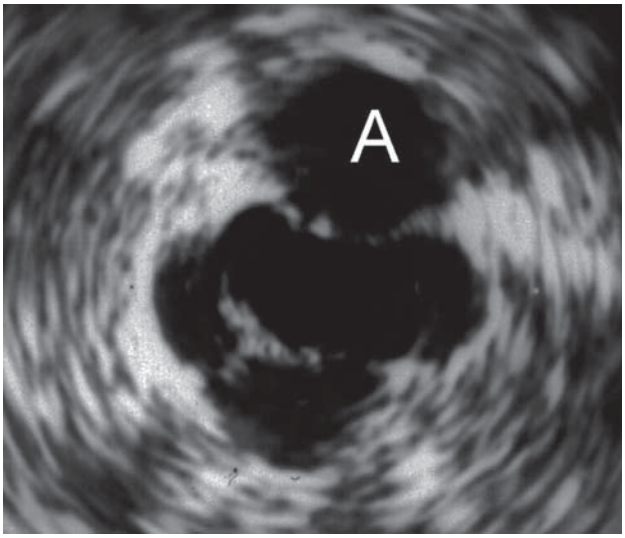

Figure 1. *The IVUS image shows the postthrombotic vein below the artery (A). The irregular vein is shown with surrounding fibrosis (increased echogenicity) and intraluminal trabeculations.*

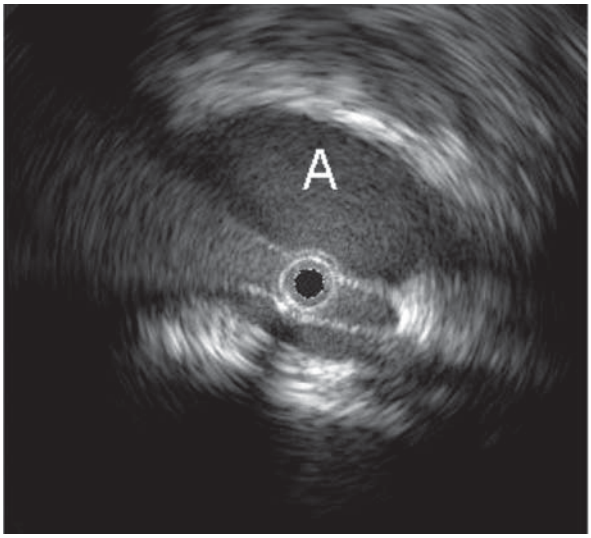

Figure 2. *The right common iliac artery (A) clearly markedly compresses the left common iliac vein (below). The black hole is the IVUS catheter.*

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