VENOUS AND ARTERIAL CRITICAL ISSUES

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Risk factors that identify women at high risk of abdominal aneurysm (aortic or iliac) that should be considered for screening

Randomized controlled trials (RCTs) of population screening for abdominal aortic aneurysm (AAA) using ultrasound followed by surgical intervention when AAA maximum diameter reached 5-5.5 cm demonstrated that in men aged 65-80 years old, aneurysm related mortality was reduced by 40% (1-6). Based on the available data, screening is considered economically viable when the prevalence of AAA is 1.0% or higher (7). However, only one RCT included women and in this study there was no evidence of benefit (1, 8). In view of the low prevalence of AAA in women, this trial may have been underpowered. Indeed, epidemiological studies have found that the prevalence of AAA in women is nearly a quarter of that found in men (9, 10).

Risk factors reported to be associated with the presence of AAA in women screened with ultrasound are smoking, history of AAA in first degree relatives, atherosclerotic arterial disease, stroke, hypertension and hypertenstion (7,8). Currently, women are not included in AAA screening programs because this is considered as “not indicated or not economically viable” (8). The aim of our study was to determine (a) whether high risk groups can be identified with an abdominal aneurysm (AA) in this population and (b) the risk factors associating with the prevalence of AAA ≥ 3.0 cm or iliac aneurysm (IA) ≥ 1.8 cm in women screened with ultrasound.

METHOD

Demographic data and risk factors were collected from the first 50,000 females who attended for the Life-line Cardiovascular Screening in the UK. Ultrasound was used to screen for AAA or IA, ankle/brachial index (ABI) and carotid atherosclerosis. ECG was also used to detect the presence of atrial fibrillation.

RESULTS

The results demonstrated that the presence of an abdominal aneurysm (AA) (iliac or AAA) below the age of 65 was rare. The prevalence of AA increased with age from 0.27% in the 66-70 year age group to 0.74% in the 81-85 year age group. The prevalence of AA over the age of 85 was just over 1%.

Of the total 116 aneurysms identified, 34 were iliac with mean (SD) maximum diameter of 2.35 ± 0.25 cm and range 1.9-2.8 cm. Of these 12 (35%) had a maximum diameter of 2.5 cm or greater. The remaining 82 were AAA with mean (SD) maximum diameter of 3.82 ± 0.85 cm and range 3.0-6.3 cm. Of these 12 (14%) had a maximum diameter of 5.0 cm or greater.

In the age group of 66-85 there were 102 (0.41%) AA in 27,770 women. Age, history of MI or CAD, history of stroke/TIA, hypertension, hyperlipidemia, history of smoking 10 pack-years or more, family history of AAA, presence of atrial fibrillation (AF), ankle-brachial index less than 0.9, and carotid bifurcation atherosclerosis were associated with increased prevalence of AA.

The strongest risk factor was the presence of internal carotid stenosis ≥ 50%, followed by smoking and ABI < 0.9. Diabetes and ABI > 1.4 (data not shown) were not associated with AA.

This study shows that in women aged 66-85 a prevalence of AA greater than 1.0% is found in the presence of any of the following risk factors: history of MI (1.18%), history of Stroke/TIA (1.21%) and having smoked more than 10 pack-years (2.24%), ABI < 0.90 (2.04%), carotid artery stenosis >50% (3.61%) and AF (2.17%). Thus, the presence of any of the above could be considered as an indication to screen for AAA or iliac aneurysm.

In a multivariable linear logistic regression analysis using the significant risk factors based on the history, age U76, hypertension, pack years U10, family history of AAA and history of stroke/TIA were independent predictors of AA. Hyperlipidemia, family history of CAD and family history of stroke or TIA were not independent predictors of AA. This model had an ROC area under the curve of 0.725 (95% CI 0.673 to 0.777) and could identify 2,947 women who had AA (prevalence 1.39%). By adding ABI and AF which required a clinical examination and ECG the prediction improved to an ROC area under the curve of 0.745 (95% CI 0.693 to 0.797). This model could identify 3,693 women who had AAA (prevalence 1.40%).

CONCLUSION

The findings of this study have important implications for developing a screening selection plan for women over 65. Firstly, the presence of carotid stenosis U 50% (symptomatic or asymptomatic) in women identifies a group with a relatively high prevalence of 3.6%. This finding suggests that any patient known to have such a lesion should have screening with ultrasound to exclude the presence of abdominal aneurysm. The presence of any one or more of the 4 risk factors: history of MI, History of stroke/TIA, a smoking history of more than 10 pack-years and ABI < 0.9 can be used to develop targeted screening because of increased risk (> 1%). However, whether such screening will be associated with benefit can only be determined by RCTs and cost-benefit studies.

REFERENCES

Impact of modern intraoperative imaging during EVAR

ABSTRACT
This article will discuss the different new capabilities of modern intraoperative imaging systems and the effect their use has for the intraoperative guidance of the EVAR procedure and assessment of the final result.

INTRODUCTION
Endovascular Aneurysm Repair (EVAR) is completely dependent on imaging methods. High-quality preoperative imaging is crucial for the accurate planning of the procedure with dedicated software. Intraoperatively the imaging is required to guide the procedure, but it exposes the patients and operators to ionizing radiation. Moreover, patients are also exposed to nephrotoxic iodine contrast agents. Recently there has been increasing evidence of the advantages of the use of modern high-quality intraoperative imaging, not only in the guidance of the procedure but also for the assessment of the final result.

This article will discuss some of the different possibilities with modern intra-operative imaging during EVAR.

ARTICLE
Fusion Imaging
EVAR is performed with fluoroscopy guidance but the identification of the anatomical landmarks is mostly done with repeated angiographies identifying the aortic branches adjacent to the sealing zones in infrarenal and thoracic EVAR. Moreover, in more complex EVAR such as fenestrated and branched EVAR the aortic branches are involved in the repairs and even more angiographies will be needed. In recent years, one of the major advances in intraoperative imaging has been the possibility of dynamically overlying a 3-D reconstruction of the preoperative contrast-enhanced computer tomography (CTA) in the life fluoroscopy image obtained intraoperatively – fusion imaging. Initially, the technology was designed to have a cone beam intraoperative CT (CB-CT) done for the registration of the intraoperative patient position with the preoperative CTA. However, almost all angiographic systems are currently able to do the registration with 2 perpendicular fluoroscopy images avoiding thereby the radiation associated with the CB-CT. Another feature that has come with some of the systems is the possibility of marking the origin of the vessels of interest. This allows the operator to choose to keep the markings and avoid the overlay of a 3-D reconstruction on the fluoroscopy image, which could otherwise shadow the native fluoroscopy. Fusion imaging has been repeatedly shown to lead to decreased exposures to iodine contrast and radiation, mostly due to the decrease in the number of digital subtraction angiographies (DSA) needed. However, fusion imaging has not been shown to have the same universal effect on decreasing the operative time and fluoroscopy time as it would have been expected.4,6

Intraoperative Fluoroscopy
The guidance of the EVAR procedures with the fluoroscopy makes this the major source of radiation to the operators since they need to be close to the patient while instrumenting the different devices. On the contrary patients are also exposed during DSA when all the staff can move away from the patient, and thereby the source of radiation, which decreases the radiation exposure.4,5 (REF Cleveland) Decreasing the frame rate of the fluoroscopy has been demonstrated recently to be able to potentiate the advantages provided by fusion imaging in lowering intraoperative radiation exposure.4 Moreover, recent low dose settings for fluoroscopy and the introduction of crystalline silicone detectors in the angiography systems are also expected to increase even further the reduction in radiation exposure.

Low concentration iodine contrast agents
The exposure to nephrotoxic contrast agents has been a potential limitation of EVAR in patients with renal insufficiency. Carbon dioxide angiography has been proposed as an alternative in these cases, but the frame rate and radiation dosage of the DSA is higher with this setup. High-quality angiography systems has allowed the use of lower concentration contrast agents (140 mg iodine / ml) during EVAR with sustainable good quality angiographies. Moreover, this can be done in combination with the use of fusion imaging whereby the volume of contrast is also reduced, which potentiates the avoidance of nephrotoxicity.6

Cone Beam Computer Tomography
Modern angiographic equipments have the capacity of performing CB-CT, which consists in the multiplanar and 3-D reconstruction of a series of images obtained while the C-arm is rotated around the patient. This is of particular interest in assessing the final result of EVAR since it allows the identification of eventual findings not directly seen in the standard 2-D projections. This is particularly useful for the eccentric compression of the metallic structure of the stents in the iliac arteries6 and aortic visceral branches in more complex EVAR.5 The CB-CT can also be done with contrast-enhancement but the advantages in the detection of endoleaks are not as dramatic and protocols with a regular completion DSA and plain CB-CT have been proposed with good results.7 The use of CB-CT may allow the identification of impending failures that would otherwise only become apparent in the first postoperative CTA and lead to reinterventions that can currently be performed already intraoperatively.

CONCLUSION
Modern intraoperative imaging systems can currently decrease the exposure to ionizing radiation for patients and operators. Moreover, it also allows the reduction of the use of iodine contrast. The different technical methods have until recently been used separately, but the impact can be potentiated if all the capabilities are combined.6 Moreover, the use of 3-D and multiplanar diagnostic capacities has also been a major breakthrough in the assessment of the final result of the EVAR procedure. Modern intraoperative imaging methods are therefore an essential part of EVAR, especially in more complex procedures.

REFERENCES
How to improve outcomes in open repair for TAAA

INTRODUCTION

The most extensive forms of thoraco-abdominal aortic aneurysms (TAAA) include all critical arteries to the brain, spinal cord, intestinal organs, kidneys and extremities. Open repair of these extensive aneurysms is associated with very high morbidity and mortality because of the potential danger of end organ damage due to ischemia and malperfusion. Stroke, paraplegia, renal failure and intestinal infarction are the main catastrophes which can occur if the end organs are not efficiently protected.

STRATEGIES TO MINIMIZE ORGAN ISCHEMIA

Modern open TAAA repair is performed with extra-corporeal circulation (ECC), allowing distal aortic perfusion during aortic cross clamping. ECC also allows after-load reduction of the heart, cooling and rewarming of the body and adjusting hemodynamic constraints during the procedure. In addition, during cross clamping of the visceral aortic segment, selective organ perfusion can be performed via side arms of the ECC system. Using flow- and pressure measurements, all organs can be selectively perfused with optimal hemodynamic conditions. We have learned that the celiac axis and superior mesenteric artery need at least 1 liter per minute blood flow per artery. If lower, mucosal damage immediately occurs, which can be assessed by measuring elevated levels of fatty acid oxidase (1).

Monitoring of the brain and spinal cord can be performed by means of transcranial Doppler and EEG (brain) and motor evoked potentials (spinal cord). The technique of motor evoked potentials indicates spinal cord ischemia and urges the surgeon to clamp the aorta/graft is possible and to repair rather than replace the stent graft.

There is clear evidence that clinical outcome after aortic aneurysm repair with regards to morbidity and mortality is superior in high volume centers and high volume surgeons. The obvious reasons for this better outcome include routine exposure, frequent procedures, constant multidisciplinary discussions, familiarity with techniques and infrastructure and experience with management of complications.

In the ideal situation, an aortic center can manage all aortic pathologies from the aortic root to the level of the iliac bifurcation. This implies that the “aortic team” is a multidisciplinary team, including cardiothoracinc surgeons, vascular surgeons and interventional radiologists. In addition, anesthesiologists, perfusionists, neurophysiologists, intensive care physicians and genetic counselors should participate in this team. All team members gather once or twice a week in the dedicated “Aortic Conference” where all new and already treated patients are discussed.

An aortic center is a high volume center in which all above mentioned procedures are performed by a dedicated team with extensive experience and motivation. Community driven developments and political changes currently indicate the need for centralization of complex procedures. National cardiac and vascular societies will soon be confronted with the request to re-organize the system in order to fulfill the obligation to create high volume centers of excellence.

REFERENCES


The failing EVAR: tips and tricks

ABSTRACT

Since December 1995, we have implanted over 1000 EVAR (endovascular aneurysm repair) devices, mainly for abdominal AAA (Abdominal aortic aneurysm). Each patient has been followed up using standardized protocols and 19% have required re-interventions for failing stent grafts. Although most of these “failures” can be treated using endovascular techniques, a significant proportion requires surgery. This article describes the cohort of patients for whom open surgery was required to treat the “failing EVAR”. It outlines the results of open intervention and gives the author’s personal experience of the techniques required to manage this difficult patient group.

INTRODUCTION

The introduction of EVAR for the treatment of AAA has revolutionized the way in which we treat patients with aneurysmal disease, both in the abdominal and thoracic aorta. Nevertheless, the long-term follow up in the various EVAR trials has shown that the results of open surgery and EVAR are no different at 10 years 1,2. This is primarily because there is an attrition rate to EVAR with advancing time, with many grafts requiring secondary intervention to maintain AAA exclusion from the systemic circulation (and therefore prevent rupture). Although the majority of these interventions can be performed using endovascular / interventional techniques, we are now seeing a cohort of patients for whom there are no further endovascular options and open surgery is required.

METHODS

Between 1995 and 2015, 1100 EVAR grafts were deployed at the Freeman Hospital, 947 for abdominal and 161 for thoracic aortic disease. All patients received a CTA (computerized tomographic angiogram) and a plain abdominal x-ray at 1 month and then CTA/US (ultrasound) and x-rays yearly for life. When a ‘failing EVAR’ was identified a policy of early intervention was pursued, except for ‘benign’ type 2 endoleak (no sac expansion).

Failure was defined as disease progression with aortic neck and iliac expansion causing loss of end graft seal, limb occlusion/kinking, graft/stent dislocation/disintegration, endoleak and rupture.

RESULTS

During this timeframe, 303 re-interventions were performed in 212 patients (19%). Although many of these were in ‘early’ stent grafts, a significant proportion was seen in the newer devices, across the range of manufacturers.

If we exclude these early devices and consider the last 10 years of EVAR (2005-2015), follow up of 705 EVARs still reveals a re-intervention rate of 8% for Type I and Type III endoleaks. The median time to intervention was 20.9 months (1-96) with most (43) occurring within the first 2 years post implantation. Nevertheless, long term follow up identified 16 endoleaks developing at between 3 and 10 years post implantation. Although our unit has an endovascular first policy for these failing grafts, we also performed 46 open interventions. Open conversion was required in 26 of which 8 were for rupture, open banding in 15 and sac exploration and ‘fixing’ in 5.

All patients requiring open exploration of their failing stent grafts had expanding sacs, most with diagnosed type I and type III endoleaks. For those with no endoleak detected pre-operatively, all were found to have either significant endoleaks/ graft failure at operation. No cases of endotension were identified.

Open techniques for EVAR repair included, proximal banding, oversizing of significant endoleaks (I, II, III), sac plication and stent graft removal (figure 1) and replacement with Dacron grafts. The mortality associated with open conversion in this series was 10%. For this reason, all attempts were made not to clamp the aorta/graft is possible and to repair rather than replace the stent graft.

For patients with expanding sacs and no pre-operative identifiable endoleaks, at laparotomy the aortic aneurysm sac was palpated for identifiable thrill and latterly interrogated with intra-operative duplex. If flow within the sac was iden-
Fenestrated endograft in para-visceral penetrating aortic ulcer

ABSTRACT
Penetrating atherosclerotic ulcer (PAU) represent an aortic lesion that is still imperfectly understood. PAU are most frequently localized in the descending aorta, usually in the middle/distal third of it. Abdominal localization is unusual but increasingly diagnosed. Para-visceral PAU are even more infrequent representing a challenge, both for endovascular and open surgical repair.

Modern endovascular technologies offer a new less invasive approach for the treatment of para-visceral aorta. Fenestrated endograft overall appears to be an effective option in the treatment of this aortic district. Due to the relatively new introduction of fenestrated endograft and rarity of para-visceral PAU localization, English literature is poor about this subject. Aim of this paper is to briefly describe the pathology and gives a short review of the most recent literature with the options it takes.

INTRODUCTION
Penetrating atherosclerotic ulcers (PAUs) are described as ulceration of an aortic atherosclerotic plaque penetrating through the internal elastic lamina into the medial. PAUs are most frequently localized in the descending aorta while infrarenal aorta, aortic arch and suprarenal aorta represent less frequent localizations.1,2

PAU is typically diagnosed in elderly (>70 years old) characterized by multiple comorbidities that often limit treatment options. There is a lack in consensus about indication for surgical treatment of PAUs, because the natural history of this lesion is still poorly understood and characterized both by acute severe progression and asymptomatic stability.

When symptomatic, PAU are categorized as Acute Aortic Syndrome (AAS) as well as Aortic Dissections (AD) and Intra Mural Hematomas (IMH); in the AAS the PAU range between 2% and 7%.8 Most frequent presenting symptom for PAU is the acute chest or back inter-scapular pain and the risk in case of progression is represented by development of saccular aneurysms, AD-IMH and aortic rupture.

Due to its frequent short extension, PAU represent an ideal lesion to treat with standard endovascular therapy; the English literature widely describe thoracic endovascular aortic repair and abdominal endovascular aortic repair procedures for the treatment of thoracic and infrarenal PAU with optimal short and long term results both in symptomatic and asymptomatic patients but it lacks about suprarenal/para-visceral PAU reports. In this rare aortic PAU localization, open surgical repair (OSR) and hybrid repair are the historical technical choices. The use of the Chimney (Ch-EVAR) and fenestrated (FEVAR) technique seems to increase the chances of totally endovascular techniques in the treatment of para-visceral penetrating aortic ulcer.

DIAGNOSIS
PAU represents a severe life threatening aortic lesion. The number of diagnosis is growing rapidly due to the increasing number of diagnostic exams requested every day and the continuous improvement of imaging technologies. Although angiography was previously considered the standard of reference for the diagnosis of many aortic diseases5 is largely been replaced by CT angiography and magnetic resonance imaging (MRI) actually considered the gold standard for PAU diagnosis, preoperative evaluation and follow-up. The radiological aspect of these lesions has been described as a craterlike or focal outpouching of contrast in the atherosclerotic aortic wall6,7. Diagnosis can be accidental in totally asymptomatic patients being screened for other reason or in an acute manner, after symptoms presentation. Symptomatic PAU localized in the
thoracic aorta presents with the AAS’s classic symptom as continuous or remittent chest pain or back/inter-scapular pain; other less frequent symptoms include dyspnoea, haemoptysis and dysphagia due to oesophageal compression. Abdominal PAU are more often asymptomatic if compared with thoracic PAU. If symptomatic they usually present with acute abdomino lumbar pain.

**INCLUSION CRITERIA FOR PAU TREATMENT**

When PAU is complicated by pseudo-aneurysm formation, progression to an AD or IMH, contained aortic rupture or per- nal o lumbar pain.

**PARA-VISCERAL PENETRATING AORTIC ULCER**

Suprarenal/para-visceral PAU represent a more challenging scenario. They can be defined as penetrating atherosclerotic ulcers localized suprarenal or juxta-renal without a sufficient aortic neck length to deliver standard EVAR. In this case, OSR represents a valid option but it takes even more risks than OSR in thoracic and infrarenal district. Despite surgical and anesthesiological innovations in standard OSR, high-volume centres report perioperative mortality rates between 5% to 11.4%, paraplegia/paraparesis rates between 3.8% and 8.9%, and mortality due to disalysis in 4.9% to 6.5% of patients treated for thoraco-abdominal aortic pathologies.

Hybrid repair, consisting in visceral vessel surgical transposition achieved by minimally invasive surgical access followed by standard EVAR procedure, lowers the risk of OSR but remains technically challenging with a 30-day complications and mor- tality rate that remain significant. Literature reported 30-day mortality and morbidity ranging between 24,4% to 30% and 30% to 60% respectively9,10. Total endovascular repair recently emerged as an option for para-vascular aortic district due to the development of Ch-EVAR and FEVAR. Despite its technical complexity FEVAR can be proposed in the elective setting while Ch-EVAR is preferred in acute/subacute cases.

In this chapter we will discuss the use of FEVAR in the treat- ment of para-visceral penetrating aortic ulcer. While many less frequent symptoms include dyspnoea, haemoptysis and dysphagia due to oesophageal compression. Abdominal PAU are more often asymptomatic if compared with thoracic PAU. If symptomatic they usually present with acute abdomino lumbar pain.

**CONCLUSIONS**

Fenestrated endovascular aortic repair is a safe and effective technique for the treatment of para-visceral PAU. Despite several cases reported in literature the results in terms of technical success, 30-day mortality and morbidity and short-term results are encouraging. Endograft manufacturing lead time remains the main limitation to FEVAR.

**REFERENCES**


Table 1. Literature review on suprarenal/para-visceral penetrating aortic ulcer (PAU).

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Elective</th>
<th>Urgent/ Emergent</th>
<th>T5%</th>
<th>30-day Complication</th>
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<td>Tamer et al.</td>
<td>2016</td>
<td>7</td>
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Open Versus Endovascular Repair of Juxtarenal Aneurysms

Juxtarenal aneurysms are those AAA with a short neck below the renal arteries and most stent manufacturers still recommend a minimum neck length of 15mm for standard EVAR. Data from the Eurostar Registry in 2006 demonstrated a significantly higher risk of proximal Type I endoleak within 30 days of EVAR with a neck length of 10cm or less (10.9%) and also after one year follow-up with a neck length of 15mm or less (9.6%) compared to neck lengths >15mm (2.6% - 3.4%) 1. In order to achieve better proximal fixation, endovascular repair of juxtarenal AAA is now focussed on either FEVAR or EVAR/EVAS with chimney stents. The question arises through whether open surgery still has a place.

With regard to EVAR or EVAS using chimney stents, outcome data is limited but appears no worse than FEVAR 2. In the absence of an “on the shelf” fenestrated stent, the chimneys are a useful technique to deploy for endovascular ruptured AAA repair and may also be used in elective cases where the superior mesenteric artery is too close to the renal arteries to allow FEVAR with a scallop for the SMA.

In a recent meta-analysis of 2326 juxtarenal AAA repaired with either EVAR or repair, mortality was the same for both techniques at around 4% (P=0.822) and there was no difference in the risk of acute kidney injury at the time of surgery (11.4% FEVAR versus 13.9% open, P=0.542). Not all studies reported longer term renal outcomes, but in those that did, chronic renal failure was commoner after FEVAR (19.7%) than after open surgery (7.7%). Five year survival was also better after open surgery (73% versus 55% FEVAR), but this may reflect patient choice, it remains difficult to justify FEVAR for juxtarenal AAA repair in patients who are fit for open surgery. In those unfit for open repair or with a hostile abdomen from previous surgery, FEVAR clearly has a role.

REFERENCES

Chimney technique vs Fenestrated endografts results on renal perfusion

Abstract
Endovascular aortic repair (EVAR) is as effective as open surgical repair (OSR) in reducing aneurysm related mortality with inferior perioperative mortality. To preserve proximal sealing, fenestrated (F)- and chimney-graft (CG)-EVAR emerged but very few series described their impact on renal function. Thus, 1/3 of patients present with renal ischemic lesions after complex EVAR, caused by renal embolization (due to cannulation, stenting or aortic thrombus dislocation), renal artery thrombosis, or intentional coverage of accessory renal arteries. Contrast volume’s effects on acute kidney injury (AKI) disappear after adjustment for procedure time, suggesting that it is a marker for the complexity of endovascular repair and that patients undergoing complex procedures are at higher risk of renal function decrease. Concerns over target vessel patency and renal function impairment during follow-up seem unfounded given the current literature reports but long-term results of CG-EVAR are still awaited. Hence, both techniques should remain in the armamentarium of physicians treating complex aortic aneurysms.

Introduction
DEndovascular aortic repair (EVAR) proved to be as effective as open surgical repair (OSR) in reducing aneurysm related mortality with inferior perioperative mortality due to its less invasive nature. However, 40% of patients could not benefit from this treatment according to instructions for use (IFUs). To preserve proximal aortic sealing, two major techniques emerged, fenestrated (F)-EVAR with the use of side holes into the main aortic graft (fenestration and scallop), and chimney-graft (CG)-EVAR with the use of parallel stent grafts adjacent to the endograft’s main body, in order to maintain the perfusion to the renal and visceral arteries. CG-EVAR has gained increasing popularity. Its off-the-shelf availability allows emergent treatment and the use of low profile devices makes complex aneurysm EVAR possible even in hostile iliac accesses; contrary to F-EVAR, which requires a manufacturing delay of 8-12 weeks with limited availability in most countries, elevated price not to mention the need for greater endovascular expertise in terms of sizing, procedure planning and accurate device deployment. Nonetheless, very few series have described the impact of each technique on renal function.

ETIOLOGY OF RENAL IMPAIRMENT
Post-operative renal dysfunction is induced by complex and intricate multifactorial mechanisms such as pre-existing renal insufficiency and diabetes mellitus, leading to higher risk of contrast induced nephropathy, patient age >65 years and recent exposure to nephrotoxic agents. The pre-dominant cause for acute kidney injury (AKI) in emergent patients is acute tubular necrosis, as a result of hypoxic damage to nephrons, secondary to hypotension and hypovolemia, causing pre-renal insufficiency; while in elective procedures, contrast induced nephropathy (caused by increased intra-renal vasoconstriction and decreased medullary blood supply) and renal micro- and macro-embolization can lead to post-renal obstruction.

Indeed, about one-third of patients present with renal ischemic lesions after complex EVAR, caused by a variety of conditions, such as renal embolization (due to complex renal artery manipulation during cannulation and stenting or thrombus dislocation from a shaggy aorta during endovascular maneuvers), renal artery thrombosis, or intentional coverage of accessory renal arteries (ARA). Most cases show a volume of lesion under 25% but ARA coverage is the most common cause for renal infarction during EVAR with a 25% incidence. In accordance with a Society of Vascular Surgery consensus statement on the treatment of abdominal aortic aneurysms, only ARA ≤3 mm in diameter and supporting not more than one-third of renal parenchyma should be considered for ostium coverage to limit the risks for long-term renal function alteration. Larger renal infarction volumes are usually caused by per-operative complications (failed cannulation,......
renal artery dissection, stent occlusion/dislocation or perforation with the need for embolization). However, patients with renal infarction often present with worsening renal function in the postoperative period but not in the long-term.²

Moreover, some authors showed that although univariate analysis suggested a significant effect of contrast volume for the development of AKI and estimated glomerular filtration rate (eGFR) decrease during follow-up, this effect disappeared after adjustment for procedure time.³ This suggests that high contrast volume is a marker for the complexity of endovascular repair and that patients undergoing more complex procedures are at higher risk of renal function decrease. Furthermore, post-EVAR AKI was associated with a significantly higher risk for long-term renal function decrease.

INCIDENCE OF RENAL IMPAIRMENT

Saratzis et al. reported a substantial incidence of AKI after F-EVAR, with 18.8% as per the Acute Kidney Injury Network (AKIN) and Kidney Disease Improving Global Outcomes (KDIGO) criteria, associated with a significant drop in eGFR and a risk of progression towards permanent renal impairment as well as early and long-term mortality.⁴ A meta-analysis showed concerning results, with a 28% incidence of AKI after F-EVAR compared with 10% after OSR (p = 0.03).² F-EVAR led to a pooled proportion of eGFR drop >30% in 20% at 30 days and 8% at the end of follow-up, thus, demonstrating a significant peri-operative impact of F-EVAR on renal function but similar 1 year results compared with OSR. Comparable results were reported with CG-EVAR by Lee et al. with a 32.6% incidence of AKI and a chronic kidney disease (CKD) decline by 1 stage in 35.2% and by 2 stages in 5.4% during follow-up.²

These data raise the question of an eventual benefit of targeted AKI prevention strategies for complex aneurysms endovascular repair. Moreover, earlier diagnosis of renal dysfunction could help improve patient prognosis and life expectancy by allowing better-informed attempts to preserve renal function. Unfortunately, biomarkers of renal impairment are still limited by delayed biologic kinetic. Our vascular unit recently published the results of a retrospective observational study on the early impact of CG- versus F-EVAR on renal parenchymal vascularization and renal function by analyzing biochemical markers and renal resistive index (RRI) in asymptomatic patients contraindicated for OSR.⁵ Incidence of AKI post-F-EVAR was 32% and compared favorably with already published data. However, with CG-EVAR, the incidence was lower than most reported results (10%) and approached the results of post-operative OSR. Moreover, early repeated measures of RRI showed good sensitivity and specificity in predicting the risks of post-operative renal impairment and could be helpful in alerting the clinician to the risk of post-operative renal function degradation, allowing early implementation of a specific peri-operative renal protocol. Finally, there were no significant differences between RRI (used as a representation of renal parenchymal vascularization), eGFR, incidence of AKI or CKD between F-EVAR and CG-EVAR techniques. This absence of difference in terms of postoperative renal impairment and need for postoperative persistent dialysis was also supported in a metaanalysis.⁶

LONG-TERM RENAL ARTERY PATENCY

Another major concern, especially regarding CG-EVAR, is its possible inferiority in terms of long-term renal artery patency and the potential consequences over long-term renal function. As a matter of fact, after CG-EVAR, renal arteries are significantly more downward angulated and more curved at inspiration and expiration compared to F-EVAR.⁷ This is not an unexpected finding given that renal artery angioplasty serves as one of many variables in selecting appropriate endovascular strategy in complex aneurysms. However, this difference is a cause for concern over the long-term sustainability of the repair compared to the excellent long-term results of F-EVAR with target vessel’s patency of 93% and freedom from branch reintervention of 84% at 5-years in the most experienced center.¹¹ Yet, it is important to keep in mind that such results cannot be extrapolated to every vascular center.

On the other hand, the PERICLES registry reported the results of CG-EVAR in an impressive number of centers in Europe and the US. Even though techniques may be a little heterogeneous, those results may be interpreted as “real world data” and showed target vessel’s patency rates of 91.8% at 1-year and 87.0% at 5-years, which compares well with those of F-EVAR.⁸ The absence of significant difference between CG-EVAR and F-EVAR in terms of target vessel’s occlusions or stenosis was also reported in a recent meta-analysis.¹² Nevertheless, it seems important to mention that the reintervention rates, which could be considered as an indicator of successful endovascular treatment, were higher with F-EVAR (5.6% vs 11.7%, p = 0.001), and the reasons for reintervention were mainly endoleak or target vessel related.

CONCLUSION

CG-EVAR and F-EVAR both present with advantages and limits depending on the anatomy and clinical presentation of the patient. Concerns over target vessel patency and renal function impairment during follow-up seem unfounded given the current literature reports but long-term results of CG-EVAR are still awaited. Hence, both techniques should remain in the armamentarium of physicians treating complex aortic aneurysms.

References


16 VENOUS AND ARTERIAL CRITICAL ISSUES
Fenestrated and Branched Endografts: a personal view

ABSTRACT
In our institution we have experience of over 1000 EVAR (Endovascular Aneurysm Repair) procedures over a 20-year period. Follow up data suggests that these devices can fail in the longer term particularly in patients with short and angulated aortic necks. This paper describes our initial experience with fenestrated (fEVAR) and branched (bEVAR) stent grafts in an attempt to quality assure long term aneurysm sealing in the group of patients with peri and suprarenal abdominal aortic aneurysm (AAA). National commissioning policy for complex endografts will also be considered with recommendations for the establishment of a few high volume fEVAR and bEVAR endovascular centres in the UK.

INTRODUCTION
For AAA patients with short and angulated aortic necks (pararenal aortic aneurysms), follow up data would suggest that the longevity of EVAR is reduced. Manufacturers have issued instructions for use (IFUs) for their individual devices and do not recommend deployment outside of these strict criteria. Fenestrated and branched stent grafts were developed in the late 1990’s to treat patients with both juxtarenal and suprarenal AAA. Although there is a steep learning curve in the use of these devices, the early and mid term results are promising and many centres now deploy these complex stent grafts as the first line treatment of these complex aneurysms.

All patients have been followed up using standardized protocols of a CTA and plain x-rays at 30 days followed by yearly CT scans/plain x-rays.

METHODS
Between 2007 and 2015, all peri and suprarenal aortic aneurysms referred to our institution were considered for treatment using fenestrated and branched aortic stent grafts. Data were collected on a prospectively maintained database and analysed retrospectively with respect to technical success, morbidity and mortality. Results were compared to those of standard EVAR.

RESULTS
During this period 98 fenestrated (fEVAR) and 37 branched (bEVAR) devices were deployed along with 484 infrarenal EVARs. All deployments were successful on an intention to treat basis with no loss of target vessel. The in hospital mortality for the groups were fEVAR 2% (n=2), bEVAR 2.7% (n=1) and infra renal EVAR 0.4% (n=2). All patients receiving branched grafts also received protocolised spinal drains and aggressive blood pressure control on the intensive care unit for 48-72 hours post procedure. Despite this, 3 patients developed paraplegia. Two branched patients also developed renal failure, one requiring dialysis.

At follow up, there have been 2 target vessel losses, with no significant clinical consequences. At median follow up of 12 months (1-62) there has been one type 1 endoleak in each group and one type 3 endoleak in a patient receiving a combined fenestrated and branched device.

DISCUSSION
These results of 135 complex fenestrated and branched stent grafts deployed in a single unit over a 9 year period include our learning curve and confirm that the methodology is feasible and that the medium term results are good. Our morbidity and mortality results compare favourably with previously published series including those of Verhoeven et al. from Nuremberg who report a 30 day mortality of 0.7% and a pooled literature review by Katsarogis showing a 2.4% 30 day mortality for open, fenestrated and chimney repair of juxtarenal AAA.

Despite these excellent results, there are several difficulties associated with the widespread adoption of this technology. These are in relation to the cost of the devices and the time taken to manufacture the stent grafts themselves. In addition, many smaller hospitals are now wishing to perform these complex cases, despite lack of specific training. It is therefore important that this technology is introduced responsibly, perhaps to a few designated major endovascular centres in each country. In a survey of current practice in the UK conducted by Cross et al and published in the BJS in 2012, there was a wide variation in the perceived indications for complex stent grafts and consensus agreement on the role of fEVAR was only 68% amongst experts. More than 90 of UK centres performing fEVAR participated. The conclusion was that guidelines and recommendations should be developed on the indications for fEVAR to inform clinicians, commissioners and health economists.

The Department of Health in the UK subsequently set up a Vascular Clinical Reference Group. This includes representatives from each region within the UK and has a mandate to develop commissioning advice for the provision of vascular service. The Vascular Society of Great Britain and Ireland has strong input into this advice and one of its first publications was in April 2013 and entitled “Use of Complex Endovascular Stent Grafts in the Management of Abdominal Aortic Aneurysm” 4.

The findings of the group were that there were no randomised control trials comparing outcomes with open repair, no other reliable data that compare mortality after fenestrated graft repair with open repair, limited median and no long term data on safety and durability, no reported health economic analyses, no assessments of quality of life or resource utilisation and no data on which to base estimates of cost effectiveness.

Their recommendations were that there should be mandatory registry submission and network training opportunities. The grafts are expensive and therefore they should be targeted to those who are able to gain most benefit from their use and are not exposed to unknown risks. They suggested that complex endografts should only be used for patients with medium or high risk of open mortality (>5%) and for low risk patients with additional factors, which might effect morbidity (i.e. hostile abdomen). They should not be used for patients with a life expectancy of less than two years (cost effectiveness) or greater than 10 years (durability/radiation).

The recommendations of providers of complex endovascular stent graft services there were all fEVAR should be performed in major arterial arterial centres with a catchment population of 2 million and >100 aortic procedures annually. Decisions and deployments should be by multidisciplinary teams and training should be provided to those network interventionists wishing to perform their FEVARs in a major arterial centre.

At the moment in the UK, there are over 25 centres providing fEVAR. bEVAR is often in only small numbers. Only 3-4 centres perform over 20 cases per year and the recommendations of the commissioners needs to be enacted. The new commissioning criteria recommends an annual caseload of 24-30 complex endografts and the number of UK providers reduced to between 10-20.

These recommendations should be the same for the rest of Europe. Nevertheless, if we strive for endovascular only centres, the skills required for the open treatment of AAA will be lost not only to our Consultants but only to our trainees. In his commentary on Verhoefens recent paper, Dr von Allmen from Switzerland states “we should strive for dedicated aortic centres and not only endovascular centres, which would guarantee patient centres rather than procedure centred patient care”. Not all patients require EVAR and until the long term results of fEVAR and bEVAR are known it is important that treatment for AAA remains bespoke and matched to both the physiological and anatomical requirements of each of our patients.

REFERENCES
Management strategies for endoleaks type I and II

ABSTRACT
Endoleaks are the most common cause of EVAR failure. This article will summarize the different management alternatives for the treatment of type I and II endoleaks. Type I endoleaks have a general indication for treatment and are usually dealt by extending the sealing zone to another segment of the aorto-iliac arteries or improving the apposition of the stentgraft to the sealing zone. On the contrary type II endoleaks are only treated when aneurysm sac expansion occurs. For type II endoleaks the treatment of choice is usually embolization, which can be achieved either by translumbar or intra-arterial access, mostly depending on the origin of the endoleak. Considering the multitude of endovascular techniques available and the good results achieved, conversion to open repair is currently rarely needed.

INTRODUCTION
Endoleaks (EL) are still one of the main causes of failure after Endovascular Aneurysm Repair (EVAR), although several can be prevented by good patient selection. Different types of ELs have varying clinical consequences and therefore different management strategies have been recommended. This article will focus on the different options for the treatment of type I and II ELs after EVAR.

ARTICLE
Type I Endoleaks
Type I ELs are related to a failure of the sealing zones and constitute a failure of the EVAR and universal treatment has been recommended. Very small intraoperative type I ELs can seal without immediate clinical consequence, but there appears to be an increased risk of long-term failure. The risk of proximal endoleaks (type Ia) is greatly increased by selecting poor preoperative anatomies for standard infrarenal grafts. For this reason in the elective setting it is always preferable not to compromise with the sealing zones. On the contrary, in the emergency setting more liberal anatomies can be accepted in a damage control attitude.

Proximal Palmaz stents
One of the first strategies proposed for the sealing of intraoperative type la endoleaks has been the deployment of large balloon expandable stents at the proximal part of the endograft (Palmaz PMA1, Cordis Corp., Miami Lakes, FL, USA). These stents improve the apposition of the stentgraft to the proximal sealing zone and have been shown have good results on the short- and long-term. However, the clinical failure on the long-term in this group of patients is not insignificant (own data under peer review). For this reason this technique should be reserved as a bailout when type Ia EL occur and not as a complement to increase the anatomical suitability for standard infrarenal endografts. The main advantage of this technique is the quickness of it’s application, making it ideal for the treatment of intraoperative type la endoleaks during EVAR of ruptured aneurysms.

Endoanchors
A more recent alternative to improve the apposition and fixation of the proximal part of the endograft to the aortic neck has been the use of endoanchors (Aptus, Medtronic Cardiovascular, Santa Rosa, CA, USA). A trial has shown promising EL-free rates after one year for the prevention (97%) and treatment (77%) of type la endoleaks. However, long-term results are still missing and should become available from the ANCHOR registry.

Proximal extension
While the previous methods are aiming at improving the seal of the endograft at its current position another strategy to seal the type la endoleaks is to get a better seal at a more proximal position. This is can be done in the infrarenal segment if the graft was originally placed too low. However, if migration occurred due to poor quality of the neck or if there has been proximal disease progression, there will be the need to involve the visceral segment in the reconstruction with fenestrated and/or branched stentgrafts. These procedures are slightly more complex than the primary implantation of the same type of devices often due to the access and the presence of transrenal bare metal fixation stents. This has led to slightly lower technical success rate but still very good 30-day mortality rates. Until recently, these grafts were custom made which limited their use in the acute setting. However, currently there is an off-the-shelf thoracoabdominal branched device that can be used in some cases (t-branch, COOK Medical, Bjaeverskov, Denmark). Otherwise, chimney grafts are also a valid alternative, especially in the acute setting, with acceptable results that do not require such as extensive aortic coverage.

Distal extension
In parallel to the described above for the proximal zone, the distal zone can also be subject to the development of endoleaks (type Ib). These are usually dealt with by moving the sealing zone to a more distal position. Traditionally this has implied embolization of the internal iliac artery and extension of the stentgraft into the external iliac artery. However, and in order to avoid the risk of ischemic complications associated with the embolization, iliac branded devices are currently preferred whenever possible. This procedure is associated with very high success rates and patency.

Conversion to open repair
Conversion continues a valid alternative for the treatment of failed EVAR. It is associated good results but there is still an increased morbidity and mortality when compared to the endovascular alternatives. For this reason it is currently reserved for after failed endovascular re-do procedures and is therefore rarely needed.

Embolization of the type Ia endoleak
This technique has been reserved for the patients that are not candidates for any of the other alternatives. It is currently preferably performed with a liquid embolic agent (Onyx, Medtronic Cardiovascular, Santa Rosa, CA, USA) filling the endoleak channel parallel to the proximal part of the endograft. Only very limited results have been published (20 patients in 3 different series) with the promising results. However, this technique may have a more prominent role for the treatment of endoleaks following newer endovascular aneurysm sac sealing treatment where there are technical limitation for the other endovascular alternatives.
REFERENCES


ABSTRACT

Background. Para-anastomotic aneurysms (P-AAA) and proximal aortic aneurysmal evolution are challenging clinical scenarios, after previous aortic open (OR) or endovascular repair (EVAR). OR is technically demanding, and standard EVAR could be impossible due to the absence of proximal landing zone. The aim of the study is to report mid-term results of fenestrated/branched endografts (FB-EVAR) to treat proximal aortic lesions after previous aortic repair.

Methods. Since 2010, patients that underwent FB-EVAR after previous aortic repair were reviewed. Primary endpoints were Technical (TS) and Clinical (CS) success. Secondary endpoints were procedure-related events (endoleaks, target visceral vessels occlusions, mortality), mid-term survival and freedom from EVAR-related re-interventions.

Results. Forty patients (M:97%, age:75±5 years, ASA≥III:100%) were enrolled. Thirty (75%) underwent previous aortic OR and 10 (25%) standard EVAR. The mean time since the previous treatment was 12 years. The aortic lesions were thoracoabdominal aneurysms in 60% cases and juxta/para-renal aneurysms in 40% cases. The mean aortic aneurysm diameter was 67±2mm. All patients were at high-risk for OR and had anatomies precluding standard EVAR. TS was 95%; operative target vessel perfusion was 98.5%. Thirty-day mortality was 0%. CS was 80% because there was eight transient renal function worsening. One distal type I endoleak was detected and treated at 1-month. The mean follow-up was 2040±months. There were not proximal type I endoleaks, target visceral vessel occlusions or aneurysmal-related mortality. Survival at one year was 85±4%. One late FEVAR-related re-intervention occurred.

Conclusion. According to the reported data, FB-EVAR for treating P-AAA or proximal aortic aneurysmal degeneration after previous aortic OR/EVAR in high-risk patients is a safe/effective solution.

INTRODUCTION

Proximal para-anastomotic aortic aneurysms (P-AAA) or progressive aortic aneurysmal degenerations after a previous open (OR) or endovascular repair (EVAR) are considered challenging scenarios. Redo OR is technically demanding, and it is associated with not negligible peri-operative complications, while standard endografting could be not usually and safely performed due to the absence of a proximal landing zone.

Single and multi-centre experiences have suggested that fenestrated and branched endografts (FB-EVAR) are well-established options to treat primary juxta/para-renal (j/p-AAA) and thoracoabdominal aortic aneurysms (TAA)(table)10-11. Recently, few authors suggested FB-EVAR as a less invasive alternative to OR for treating P-AAA or progressive aortic aneurysmal degeneration after a previous aortic repair, even if additional technical difficulties were reported in comparison to primary FB-EVAR.

We want to report our experience in the treatment of P-AAA by FB-EVAR.

Management of para-anastomotic aortic aneurysms

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Patient selection

All the consecutive patients submitted to FB-EVAR, from 2010 and to 2016 were prospectively collected in an electronic dedicated database. The cases of FB-EVAR (with off-the-shelf or custom made devices, Cook Medical) after a previous aortic repair (previous OR and EVAR) were retrospectively evaluated. The demographic, cardiovascular risk factors were studied as well as the pre-operative morbidity and aortic-iliac morphological features.

Procedure

As previously reported10, the procedures were performed in the operating theatre with mobile angiographic C-arms (Ziehm Imaging GmbH, 150 Nürnberg, Germany) and from 2016 in a...
Dedicated hybrid room. In all cases of TAAA the cerebrospinal fluid (CSF) monitoring/drainage was used. Bilateral common femoral artery and proximal left brachial/axillary (when it is necessary) artery cut-down are performed under general anesthesia. The fenestrated-branched module is introduced via the femoral artery or surgical iliac conduit in cases with narrow or calcified iliac artery. The fenestrated/branched device is accurately positioned at the level of the visceral aortic vessels with angiographic check and fusion imaging. For fenestrated endografts, the graft is partially deployed, with the top cap and the reducing tie system still in place. A 20/22F sheath is inserted through the contralateral femoral artery and positioned inside the fenestrated module or at the aortic bifurcation. By using a floppy guide wire and various catheters, the fenestrations and the relative visceral arteries are cannulated. By using a stiff guide-wire (Cook, Rosen) a 55-cm-long 7F sheath (Cook, Flexor) is positioned in each visceral vessel. Bridging balloon-expandable stent-grafts (Advanta, Atrium, Hudson, NH, USA) are then advanced inside the 7F sheath. The reducing tie system and the proximal top cap are then deployed. The visceral bridging stent-grafts are deployed so that 4-5mm of each protrudes into the aortic lumen. Finally, these segments are flared by dilatation using a 10-12mm balloon to obtain a seal around the fenestrations of the device.

For branched endografts, the branch component is positioned so that the distal ends of the branches lie 15 to 20mm above the ostia of the target vessels. If the device has branches but not fenestrations, the bifurcated endograft/iliac extensions are deployed, the large femoral sheaths are removed and the anastomoses are closed. The arterial flow to the pelvis and lower limbs is corrected. In devices that incorporate a combination of branches and fenestrations, the fenestrations are completed as the first priority using the techniques described above and the large femoral sheaths are removed before the branches are completed. Through axillary arterial access, an 80-cm-long 8/10F sheath (Cook, Flexor) is advanced into the endograft, and each branch and its corresponding artery is catheterized, wired, and stented with a balloon-expandable stent-graft (Advanta; Atrium, Hudson, NH, USA). This sequence is completed one branch at a time. The stents are each deployed over a stiff wire, and a bare nitinol self-expandable stent can be added inside each covered stent to add stability and avoid kinks. Since 2012, we started to stage the TAAA procedure in order to reduce the risk of spinal cord ischemia.

Intra and Peri-operative results
Forty patients were enrolled in the study, 30 (75%) had previous aortic surgery and 10 (25%) previous EVAR treatment. The mean time of previous OR treatment was 12 years. The TS was achieved in 98% patients. The technical failure consists in a left renal artery stent.

Follow-up
The mean follow-up was 2040 months. Survival was 85% 4.5%, 65% 4 8%, and 65% 4 10%, at 12, 24 and 36 months, respectively. No late type I endoleaks, target visceral vessel occlusion or aneurysmal-related mortality occurred during the follow-up. One re-intervention occurred at 36-month of follow-up. For a type 3 endoleak from the celiac trunk and was successfully corrected. Freedom from re-interventions was 90% 4 5%, 90% 4 5% and 85% 4 7% at 12, 24 and 36 months, respectively. There were not cases of aneurysm enlargement and renal function worsening during the follow-up.

CONCLUSION
Even if planning and intra-operative technical difficulties were reported, FB-EVAR is a valid option to treat proximal para-anastomotic aneurysms or proximal aneurysmal degeneration after previous aortic surgery. According to the reported data, FB-EVAR can be considered safe and effective in high-risk patients in terms of technical success, early mid-term clinical success, AAA related mortality, visceral target vessels patency and FB-EVAR related re-interventions.
According to the majority of manufactures’ instructions for use referring to its length, diameter, angles and calcification/thrombosis than the open repair (OR) 1. The EVAR feasibility/early and late complications after EVAR 4, and severe neck morbidity 6, especially for high-surgical risk patients. This is the interventions and mortality 5. For these cases, the treatment regulation > 60º (SNA) can be associated with a higher incidence not be treated by standard EVAR as well as AAA with an infra-renal neck angle > 60º infra-renal neck wider than 28mm. The use of EVAR outside the IFU is considered off-label.

How to improve the EVAR outcomes in cases with hostile neck?

ABSTRACT
Data from randomized and controlled trial proved that the endovascular repair (EVAR) of the infra-renal abdominal aortic aneurysm (AAA) is associated with a lower 30-day morbidity/mortality than the open repair (OR) 1. The EVAR feasibility/efficacy depends on specific anatomical aortic-iliac features and the anatomic feature of the proximal sealing zone below the renal arteries is one of the main reasons for EVAR ineligibility/failure. The presence of a hostile infra-renal neck (-c) can hinder the technical procedure or lead to its failure. According to the majority of manufactures’ instructions for use (IFU), the AAA with an infra-renal neck length ≤10mm should not be treated by standard EVAR as well as AAA with an infra-renal neck angle > 60º and infra-renal neck wider than 28mm. The use of EVAR outside the IFU is considered off-label.

INTRODUCTION
In the early years of the millennium, a challenging infra-renal neck anatomy was responsible for EVAR ineligibility in the 45%-60% of the AAA 1. Chakir 2 defined the proximal ‘hostile neck’, referring to its length, diameter, angles and calcification/thrombosis, in order to estimate the risk of EVAR failure. Infra-renal neck length ≤10mm (SN-AAA) is an independent risk factor of early and late complications after EVAR 2, and severe neck angulation > 60º (SNA) can be associated with a higher incidence of proximal type I endoleak, proximal stent graft migration, re-interventions and mortality 1. For these cases, the treatment suggested as gold standard remains OR, which requires an infra-renal or supra-renal cross clamping 4, 5. Unfortunately, it has not a negligible rate of peri-operative mortality (0.8-6.8%) and morbidity 7, especially for high-surgical risk patients. This is the reason because over the last decade, the fenestrated endograft has become a valid alternative to OR since it offers, good early/mid-term results for short-neck or juxta-renal AAA 3.

Few papers, with small cohorts and early-results for AAA with infra-renal neck length ≤10mm 4 and for the influence of severe infra-renal aortic neck angulations (SNA) on EVAR outcome has been reported. In this paper we will report our experience with short and angulated infra-renal neck and our current algorithm related to AAA neck anatomy.

INFRARENAL SHORT-NECK
We recently reported the largest experiences in literature of SN-AAA treated by the off-label use of SF-EVAR 4 between 2005-2010: 60 patients with a mean follow-up of 51 418 months. All patients were unfit for OR and turned down for FEVAR for clinical (AAA with maximum diameter >65mm, symptomatic patients, AAA with growth >5mm/6months) or anatomical (proximal neck angles U 60º, renal artery unfit for FEVAR) reasons. In our study, the production delay was the reason of EVAR ineligibility for patients with symptomatic SN-AAA (7%), SN-AAA with diameter > 65mm (33%) and SN-AAA with rapid enlargement (25%). They were treated with 32 (53.3%) Zenith-Flex™ and 28 (46.7%) Medtronic Endurant™ endografts. Four (7%) intra-operative proximal cuff placements were performed to solve the caudal endograft migration and endoleak type I (ELI) (3/4 cases had a proximal neck anuagulations U60º). According to the Report- ing Standards for endovascular aneurysm repair of the American Society of Vascular Surgery, the technical success was 100%. According to the INTRAreanal Angulated-Neck.

In a recent experience 10, we carried out a retrospective analysis of the Anaconda™ Italian Registry to identify patients with and without SNA with the aim to evaluate the early and late outcome of EVAR using the Anaconda™ endograft in patients with severe proximal aortic neck angle and to compare the outcomes in patients with and without proximal neck angulations. Patients were stratified according the angle β (angle between the infra-renal neck and the longitudinal axis of the aneu- rysm), that can be deemed low (< 45°) mid (between 45° and 99°) and severe (> 95°). Groups were identified according to the presence of a severe (Group A; GA: U60º) and mild or low (Group B; GB: <45º) proximal neck angle. The endpoints were mortality, proximal type I endoleak (ELI), freedom from iliac leg thrombosis and conversion to open repair at 30-days and 3-years of follow-up for both groups. From September 2005 to December 2012, 1030 patients were enrolled in the Anaconda™ Italian Registry. Sixty-five cases (6.3%) were included in GA and 737 (71.5%) in GB. The main body was repositioned and balloononed in 35% and 9.2% of cases in GA and GB respectively. One proximal aortic cuff was deployed (1.5%). The 30-day mortality was 1.5%; 2 (3%) surgical conversions occurred. Five endoleaks were detected at 30 days: (1.5%) ELI and 4 (6%) endoleak type I (ELI). No main-body migration occurred. There were 2 deaths during the follow up, not AAA related. An elective conversion occurred at 3 years of fol- low up for a contained aortic rupture due to a persistent ELI. At 3 years of follow-up a significant AAA shrinkage was observed in 50% of cases; in 34.8% the AAA sac was stable.

We compared the results of GA and GB. In GA the main body repositioning was required in a significant large number of cases than in GB (GA:35% vs GB:7.0%; p<0.001). There were no differences in the main body balloononing and proximal cuff placement. There were no statistical differences regards the 30-day mortality (GA 1.5% vs GB 1.3%), ELI (GA 1.5% vs GB 0.8%), iliac leg thrombosis (GA 1.5% vs GB 1.4%) and conversion to open repair (GA 0.3% vs GB 0.6%). The 3-years survival was 95.4% in GA and 94.7% in GB (p=ns). At 3 years of follow up: freedom from ELI was 98.5% in GA and 97.8% in GB (p=ns); freedom from iliac limb occlusion was 95.4% in GA and 96.9% in GB (p=ns); freedom from conversion to open repair was 95.4% in GA and 98.5% in GB (p=ns). In a recent meta-analysis (7 studies, 1559 patients) Antoniou et al. 11 correlated the presence of an hostile proximal neck with more infra-operative inadequate approach, increased 30-day mortality, late ELI and AAA related mortality. In literature there are only few data regarding the results of EVAR in angled neck and they are taken by small and single-centre cohorts from report that no study severe angle separately but as a part of hostile neck anat- ony. In an analysis of the EUROSTAR, Hobo et al. 7 demonstrated a substantial increase in the incidence of early/late proximal ELI and re-interventions in patients with a severe proximal neck angle. Abuhrahma et al. 4 suggest that EVAR can be performed in
patients with an angulated neck but it is associated with an higher rate of early ELI (39%), proximal cuff placement (33%) and peri-operative complications (29%). They reported during the follow-up a freedom from late ELI of 64%.

In our previous report, we underlined how an AAA with a severe neck or iliac angulations can be treated by a ring-stent endograft with similar results to those of AAA with more favourable anatomy. We did not find any differences regarding early and late proximal ELI, endograft migration, AAA related mortality, iliac leg complications and freedom from reinterventions. These findings are confirmed also in the analysis from the Italian Anacopa registry. According to the Registry inclusion criteria all the patients have a neck length ≥ 15mm, so the angled neck is the only main hostile neck feature evaluated. According to reported results there is no difference in terms of early and late outcomes (ELI, mortality, conversion to open repair and iliac leg thrombosis) in patients with severe and favourable neck angle. These data can compare favourably with the results reported with the Endura™ endograft (Medtronic Vascular, Santa Rosa, CA, USA) from the ENGAGE investigators. A peculiar difference between GA and GB was due to the main body repositioning rate (GA: 35% vs GB: 20.7%; p: .008). This aspect is in line with the EUROSTAR analysis and with the AbuCorda’s report, that reported as an angled neck is associated to an increased risk of endograft migration and early and late mortality. The severe neck angle could reduce the accuracy of the endograft deployment. In these cases the possibility of the endograft repositioning is considered an important tool to achieve the sufficient sealing and the technical success. Reposi- tionable stent-graft systems allow the number of patients who can be effectively treated with EVAR as reported by Smets et al. As regards the long term outcomes, our results are encouraging in terms of technical success and freedom of endograft events whether the neck ≥ 1.5 cm and severe neck or iliac angulations can be treated by a ring-stent endograft with similar results to those of AAA with more favourable anatomy. The endograft re- positionability could be an important trick in cases with severe neck angle expanding the number of patients fit for EVAR.

CONCLUSION
Careful patient selection is crucial in reducing the risk of EVAR complications, and several criteria have been described to identify patients at high risk for failure. In our experiences the off label use of SF-EVAR in SN-AAA, with straight, not conical, with relative narrow aortic neck and 10-15mm aortic neck length, can be considered safe and effective in patients unfit for OR and FEVAR. For these cases, long-term data showed acceptable results in preventing the aneurysm rupture and the related mortality. According with our experience of EVAR with infrarenal fixation, AAA with neck length U 1.5 cm and severe neck angle can be treated by standard endograft with results comparable of those with favourable anatomy. The endograft re- positionability could be an important trick in cases with severe neck angle expanding the number of patients fit for EVAR.

REFERENCES

EVAR – RATIONALE AND LIMITATIONS
The aim for surgical management of abdominal aortic aneurysms (AAA) is to prevent aneurysm rupture and to achieve freedom of aneurysm growth and rupture. However, limitations of EVAR technology became obvious. First, those procedure-related such as endoleak, causing a recto flow into the aneurysmal sac, endoendastasis that is an increased sac pressure in the absence of demonstrable leak, migration of the endograft, structural failure leading to disconnection of the endograft components or its rupture. Second, disease related and the difficulty of the material to allow for the continui- aortic dilatation a process that is inherent to the nature of aneurysm disease. Direct arterial flow will increase sac pressur, will determine continuous expansion and will increase the risk of rupture. Evidence from trials and registries point out that long term durability of EVAR still represents a major concern, that surveillance is mandatory to detect and treat EVAR failures timely after and long-term interventions, which can be required in 30 to 40% of the patients.

In this chapter occlusive complications which essentially can be fixed by endovascular or less invasive open repair will not be dis- cussed. Our main concern will be aortic ruptures and the role of open conversion in two perspectives: first, because aortic rupture has been regarded as the ultimate failure of EVAR and second, because open conversion has traditionally been associated to its treatment or in attempts to correct EVAR failures. Early and late ruptures have been reported from early experiences to registries and RCT’s trials. van Marrewijk10 from the Eurostar registry col- lected between 1994 – 2000 identified, at 22 months, a rupture rate of 1.8% associated with type II endoleaks, 4% for types I and II endoleaks and 0.7% in patients without evidence of endoleaks. Other reports from the same registry12,13 identified 34/4291 (0.8%) ruptures at 18 months follow-up with 62% mortality rate. Endoleaks type I and II, migration and graft connection, fabric erosion and rupture were known factors associated to persistent increase in aneurysm size. Failure to attend regular surveillance was noted in 38% of those patients having a rupture. Also, data from the same registry suggested that aneurysms larger than 65mm had higher risk of late rupture and older generation de-
Vascular grafts in proximal type I endoleaks, use of endo-anchors to improve fixation, control of potential sources of endoleak type II through direct embolization of lumbar arteries and/or inferior mesenteric artery and intra-sac direct injection and/or embolization, are ingenious endovascular alternatives developed and used with success.

Open intervention with or without conversion to conventional repair still plays a role in 3 main situations: i) Aneurysm expansion associated with endoleaks after failure of endovascular attempts; ii) acute rupture and iii) endograft infection. It may consist in a) Opening of the sac (procedure) and surgical control of the origin of the endoleak; b) Partial explantation plus conventional repair and c) Total explantation with conventional surgical repair.

Figures have been used to correct persistent leaks as shown in fig. 2. They consist in opening the aneurysm sac, control the potential sources of bleeding without removal of the main endograft and closure of the sac in the usual fashion used in the conventional open repair.

Figure 2: A – Evidence of high intra-sac continuous flow from lumbar arteries (confirmed by aortography); B – Opened sac and suture of 3 pairs of bleeding lumbar arteries; closure of the sac over the endograft

During the last 10 years 4 patients with sac expansion and persistent isolated type II endoleaks were treated using this procedure, with no mortality or morbidity. One patient on dual anti-platelet therapy following PTCA with DES developed hypertensive episode complicated with severe hemorrhagic stroke and died 2 months after the procedure; in the remaining 3 with a mean follow-up of 16 months (1 to 36) there was no evidence of subsequent sac expansion and are fully asymptomatic. In fact, limited success and durability of endovascular treatment, whatever technique and materials used, have been reported by several authors.

Figure 3: Total explant of a Vanguard graft (3 yrs post-implantation)

Institutional Experience - Santa Maria Hospital: From 2009 to December 2015 5 patients were treated and their characteristics are summarized in Tables I and II:

Table I Characteristics of the patients with secondary ruptures

<table>
<thead>
<tr>
<th>Patient</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age @EVAR (yrs)</td>
<td>71</td>
<td>74</td>
<td>57</td>
<td>81</td>
</tr>
<tr>
<td>Age @rupture (yrs)</td>
<td>79</td>
<td>78</td>
<td>61</td>
<td>85</td>
</tr>
<tr>
<td>Time to rupture (yrs)</td>
<td>7</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Date of rupture</td>
<td>05-04-2009</td>
<td>14-07-2011</td>
<td>24-07-2011</td>
<td>23-10-2013</td>
</tr>
<tr>
<td>Gender</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Type of EVAR</td>
<td>aorto-biiliac and bilateral renal stenting</td>
<td>aorto-biiliac</td>
<td>aorto-uniliac left and femoro-femoral bypass</td>
<td>aorto-biiliac</td>
</tr>
<tr>
<td>Complications during the EVAR</td>
<td>No</td>
<td>?</td>
<td>No</td>
<td>endoleak at final angiography</td>
</tr>
<tr>
<td>Follow-up</td>
<td>aneurysm excluded, no growth</td>
<td>?</td>
<td>sac growth, no endoleak</td>
<td>sac growth, endoleak type II</td>
</tr>
<tr>
<td>Previous interventions</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
CTA performed on admission prior to repair; however, previous associated with migration in 2 were and they were identified on months. In all patients, endoleaks type I or III were present and 1 (patient 1) failed to attend the scheduled follow-up after 84 tula following repair with aorto-iliac unilateral endoprosthesis -7) and 1 patient presented also with an arteriovenous iliac fis-(57-81), time interval between EVAR and rupture was 4.6 yrs (4 ing had the initial treatment elsewhere; mean age was 72.8 yrs ment because of secondary ruptures following EVAR, 3 hav -ing had the initial treatment elsewhere; mean age was 72.8 yrs (57-81), time interval between EVAR and rupture was 4.6 yrs (4 -7) and 1 patient presented also with an arteriovenous iliac fis-tula following repair with aorto-iliac unilateral endoprosthesis plus crossover graft. 2 patients did not attend surveillance and 1 (patient 1) failed to attend the scheduled follow-up after 84 months. In all patients, endoleaks type I or III were present and associated with migration in 2 were and they were identified on CTA performed on admission prior to repair; however, previous presence of type II endoleaks was recognized only in 1 patient during surveillance and no other changes had been reported. Open conversion was performed in all: aortic control achieved in 4 by suprarenal clamping (in 2 it was suprarenal) and in 1 patient it was possible to do infrarenal clamping. Total graft explant was done in 2 patients and in 3 it was partial with suture of the Dacron graft to proximal component of the endograft as shown in fig.4, representing two different surgical options. Early mortality (<30days) was 40%; those who survived are well without any further complications.

All 5 patients were admitted through the emergency department because of secondary ruptures following EVAR, 3 having had the initial treatment elsewhere; mean age was 72.8 yrs (57-81), time interval between EVAR and rupture was 4.6 yrs (4 -7) and 1 patient presented also with an arteriovenous iliac fistula following repair with aorto-iliac unilateral endoprosthesis plus crossover graft. 2 patients did not attend surveillance and 1 (patient 1) failed to attend the scheduled follow-up after 84 months. In all patients, endoleaks type I or III were present and associated with migration in 2 were and they were identified on CTA performed on admission prior to repair; however, previous presence of type II endoleaks was recognized only in 1 patient during surveillance and no other changes had been reported. Open conversion was performed in all: aortic control achieved in 4 by suprarenal clamping (in 2 it was suprarenal) and in 1 patient it was possible to do infrarenal clamping. Total graft explant was done in 2 patients and in 3 it was partial with suture of the Dacron graft to proximal component of the endograft as shown in fig.4, representing two different surgical options. Early mortality (<30days) was 40%; those who survived are well without any further complications.

Table II: Mode of presentation and procedures performed

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause of rupture</td>
<td>Type IA endoleak with migration</td>
<td>Type IIIA</td>
<td>Type IB</td>
<td>Type IIIB</td>
</tr>
<tr>
<td>Presentation</td>
<td>Rupture</td>
<td>Rupture</td>
<td>iliac arteriovenous fistula</td>
<td>Rupture</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>185/89mmHg</td>
<td>Shock</td>
<td>132/66mmHg</td>
<td>140/65</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>8.4</td>
<td>11.4</td>
<td>14.4</td>
<td>11.6</td>
</tr>
<tr>
<td>Aortic control</td>
<td>Suprarenal</td>
<td>Suprarenal</td>
<td>Suprarenal</td>
<td>Infrarenal</td>
</tr>
<tr>
<td>Graft explant</td>
<td>total and removal of renal stents</td>
<td>Total</td>
<td>Partial distal</td>
<td>Partial distal</td>
</tr>
<tr>
<td>Reconstruction</td>
<td>tube graft bypass to the left renal artery</td>
<td>No</td>
<td>tube graft between the EVAR body and the femoro-femoral bypass</td>
<td>aorto-bifemoral</td>
</tr>
<tr>
<td>Survival</td>
<td>death @ 18 days</td>
<td>death intraoperative</td>
<td>alive @ 3 yrs</td>
<td>alive @ 1 yrs</td>
</tr>
</tbody>
</table>

Fig. 5 refers to patient 1 who had a previous EVAR and bilateral renal artery stent because of severe arterial hyperten-sion and renal artery stenosis who remained well and compli-ant with the surveillance program during 7 years; subsequently developed anemia, fever and loss of weight, was investigated elsewhere, missed the scheduled visits for follow-up and was finally referred to the emergency department because of sudden abdominal pain and aneurysm rupture. Total explant, left renal bypass and conventional aortic repair were achieved; no bacterial growth was obtained from the endograft and from sac content and wall, but no definitive infection could be ruled out. Patient developed left lower limb ischemia requiring ampu-tation, but refused treatment and died.

Endovascular treatment of acute ruptures is associated with high mortality and morbidity, comparable with open conversion: confirming that endovascular repair does not reduce the mortal-ity associated with these secondary ruptures. In a single center review, Klonaris et al reported hospital mortality of 33% when dealing with emergency treatment of ruptures as opposed to 5.6% when global results from both, elective and urgent re-pairs including elective complications were considered. Their indications were mainly associated with type II endoleaks with sac enlargement (present in 56%), reported a 46% failure rate of previous endovascular treatment of this complication, 33% had either partial or total endograft explant and in 27% its preserva-tion was the preferred option with control of the source of endoleak. Partial explant of the endograft has been suggested to reduce mortality and morbidity associated with a full removal of the endograft thus suggesting the value of a patient and device specific approach to open conversion.

Torney et al reported overall 30-day mortality was 17%, 99% in elective cases, 37% for urgent situations and 56% for sec-ondary ruptures and 60% in aorto-iliac fistulae, confirming the importance of early and elective intervention for EVAR failures. Endoleak was the most common indication for explant, with one or more endoleaks present in 82%. 22% of patients had partial explant with preservation of endograft segments. Other reasons mentioned for explant were infection (13%), acute thrombosis (4%), and claudication (7%); 47% required open conversion af-ter 48 months of initial EVAR, a fact that also confirms the im-portance of continuous and active surveillance program, for the entire life of the patient. In their report, survival was negatively affected by chronic obstructive lung disease (COPD), infection, need of visceral revascularization, renal insufficiency, emergency procedures and ruptures; better outcomes were confirmed in the presence of type II endoleak and if the operation was performed for sac enlargement without rupture. Open conversion with total explant of the endograft has been used in infected endografts, a clinical situation which has been progressively recognized. Total removal of the infected graft, debridement and in situ reconstruction with conventional tech-niques has been advocated with success, but new approaches combining endovascular re-lining and eventual debridement have been recently reported.

Operative technique is determined by the type of endograft fixation and also the type of aortic reaction, ranging from in-tense inflammation and fibrosis to aortic wall atrophy. For endografts with suprarenal fixation we preferred suprarenal clamping to gain control of the bleeding and if there is no evidence of leak at the proximal landing zone, both on pre-operative as-sessment and after careful mobilization of the endoprosthes, partial explant and anastomosis of the Dacron graft in the main component of the endograft has been performed successfully. Kelso reported that open conversion varied from 0.6 to 4.5% after EVAR and is associated with higher morbidity and mortality (10% in excess) when compared to OR in aortic rupt-
 Maintenance of experience and expertise in open AAA repair continues to be a requirement in all units dealing with AAA and should be taken into account in all training and educational programs in Vascular Surgery.

REFERENCES


Open approach to TAAA redo complex cases

INTRODUCTION
Elective repair of thoraco-abdominal aortic aneurysms (TAAA) is a great challenge for the patient and the surgical team. The best results are obtained in high volume centers in which an extensive infrastructure is in place including extra corporal circulation, neuromonitoring, dedicated anesthesia high level intensive care, and a multidisciplinary team.

Redo complex cases are even more demanding because patients already underwent previous surgical procedures. Therefore, they suffer most often from postoperative morbidities.

PATHOLOGIES
Redo complex cases following TAAA surgery comprise a wide spectrum. The spectrum not only varies in different pathologies but also in gradient of complexity. The most common problem is newly developed aneurysm formation proximal or distal to the already performed reconstruction. In addition, aneurysms can develop at the level of reattached arteries, most often button reimplantations, especially in patients suffering from connective tissue disease (CTD).

Other pathologies associated with previous TAAA surgery include aortic graft infection, aorto bronchial and aorto esophageal fistulae.

Since the introduction of endovascular modalities, conversion to open repair can be necessary because of type I endoleaks which cannot be corrected by endovascular means, migrated endografts, perforation with subsequent fistulae, infection and migration of the endograft can only be explanted safely if the aorta is cross clamped completely adhesive to the surrounding tissues, increasing the risk of lung injury and air leakage. Anastomotic aneurysms can often be repaired by endovascular means. If not, open repair requires dissection of more proximal or distal clamp positions, frequently including important side branches which have to be reimplanted.

The same accounts for conversion after TEVAR procedures: the endograft can only be explanted safely if the aorta is cross clamped proximal and distal to the anchoring parts of the endograft.

In post TAAA repair infection cases, either after open or endo procedures, the challenge is the material which has to replace the aorta. Since a few years we have moved away from artific holografts since we experienced deterioration of the tissue and encountered reinfection as well. We switched to large bovine pericardial patch material of which we create tube or bifurcated grafts. These can subsequently be used to replace the entire descending (figure) or abdominal aorta.

STRATEGIES
Obviously, before considering redo surgery, the patient has to be fully examined with regards to general, cardiac and pulmonary functions. We routinely perform echocardiography, coronary angiography (CT, MRA) and pulmonary function tests.

The main principle in these complex redo TAAA operations is to provide optimal protection to the organs. This means that extra corporal circulation is mandatory, including selective perfusion of target organs. Assessment of motor evoked potentials is used as a neuromonitoring technique to judge spinal cord function continuously.

Depending on the pathology, many considerations will also depend on the local situation. To start with, thoracotomy and/or laparotomy after previous local surgery can be hazardous due to adhesions. Especially in the chest, the left lung can be completely adhesive to the surrounding tissues, increasing the risk of lung injury and air leakage. Anastomotic aneurysms can often be repaired by endovascular means. If not, open repair requires dissection of more proximal or distal clamp positions, frequently including important side branches which have to be reimplanted.

How to shift the learning curve from the patient to the model - rationale and scope of the VASCULAR INTERNATIONAL training courses

ABSTRACT
Currently vascular surgical training has to cope with various challenges such as working time restrictions, significant reduction of open surgical training cases in many countries, an increasing diversity of open and endovascular procedures and distinct expectations by the trainees. Even more importantly both the patients and the public do not longer accept a “learning by doing” training philosophy leaving the learning curve on the patient’s side alone. The VASCULAR INTERNATIONAL (VI) Foundation and School aims to overcome these obstacles by training conventional vascular and endovascular techniques before they are applied on patients. In order to achieve largely realistic training conditions, lifelike pulsatile models with exchangeable synthetic arterial inlays were created to practise carotid endarterectomy and patchplasty, open AAA surgery and peripheral bypass surgery as well as for endovascular procedures e.g. EVAR, TEVAR and peripheral balloon dilatation and stenting, respectively. All models are equipped with a small pressure pump inside to create pulsatile flow conditions with variable peak pressures around 90 mmHg. The VI course schedule consists of a series of two-hour-modules, teaching different open or endovascular procedures step by step in a standardized way. The trainees practice in pairs with continuous supervision and intensive advice of highly experienced vascular surgeons (ratio trainer:trainee = 1:4). Several evaluations of these courses clearly show that tutor-assisted training on lifelike models is an educational-centred and motivated environment is associated with significant increase of general and specific vascular surgical technical competence within a short period of time. Future studies should evaluate whether these benefits positively influence the future learning curve of vascular surgical trainees. In addition it should be clarified to what extent sophisticated models are useful to assess the level of technical skills of vascular surgical residents at national or international board examinations. This article gives an overview of our experiences over 20 years of practical training on beginners and advanced vascular surgeons using lifelike pulsatile vascular surgical training models.

BACKGROUND
Due to a significant increase in vascular patients and a tremendous progress in open and endovascular surgical treatment modalities during the last years, vascular surgical has evolved into an attractive surgical specialty. This development is supported by substantial changes in curricula i.e. a 0-5 years scheme in the United States, and the foundation of vascular surgery as an independent specialty in many European countries. However vascular surgical training has to cope with significant challenges like working time restrictions in Europe and the US and – due to a dramatic increase of endovascular procedures - a significant reduction of open surgical cases suitable for training at many teaching hospitals. In addition there is an ongoing discussion whether surgeons are prepared properly for their job. Like in aviation and in virtu-
ally all other professions that are based on technical skills, the patients and the public do not longer accept "learning by do-ing". Training philosophy leaving the learning curve on the patient’s side alone. Consequently new training strategies and techniques focusing on simulation and closer supervision are mandatory.1,4

CURRENT CONCEPTS OF ADULT LEARNING
The widely accepted Fitts and Posner’s theory of motor skills acquisition is nicely transferable to vascular surgery since it discriminates between a cognitive, an associative and an autonomous stage.9 At the example of a leg bypass anastomosis the first two steps can be achieved by use of a structured clinical training alone or in combination of an intensive vascular training course. The third stage needs a repetitive performance of certain techniques, which supports the concept of deliberate practice by Ericsson.6

Since simulation courses outside the hospital cannot substitute training and practice at home they should clearly be able to support the cognitive and the associative stages of motor skill acquisition especially if training is performed by use of high fidelity models. As shown by Sidhu et al. realistic models are superior to simple plastic models. These authors randomized junior and senior residents to a three-hour training session to perform a graft-to-arterial anastomosis on plastic models or a high-fidelity model (human cadaver arm, brachial artery). One week later all participants had to perform a vascular anastomosis on a femoral artery on a live pig where both junior and senior residents showed a significantly better skill transfer from the bench model to live animals by practicing on high-fidelity models.12 As described below this study strongly supports the philosophy of VASCULAR INTERNATIONAL (VI) that training on largely realistic pulsatile models is superior to simple plastic models.

Besides the three stages of motor skills acquisition the Dreyfus and Dreyfus framework is considered as a suitable model of individual professional development through a series of five levels: novice, advanced beginner, competent, proficient, and expert.8 Just recently Mitchell showed that this concept can also be nicely applied to vascular surgery.10 Again vascular surgical simulation courses may be useful at almost every stage of an individual professional development. This is more or less self-evident for medical students or residents in their first years, but may also be applicable for competent or even proficient vascular surgeons if they aim to critically revise their own approaches and techniques or if they are interested in new techniques (like for example the eversion technique for CEA). Residents who are near to complete their training can also benefit significantly, especially when they are in front of a practical assessment like for example the practical examination held by the Section and Board of Vascular Surgery of the UEMS (Union of European Medical Specialists).10

PRINCIPLES OF THE VASCULAR INTERNATIONAL FOUNDATION AND SCHOOL
The main idea and mission of the VASCULAR INTERNATIONAL (VI) Foundation and School are passion for vascular surgical education and shifting the learning curve from the patient to the life-like training model’s. With maximised patient safety as priority, VI is aiming to constantly improve training in order to support safe and efficient open vascular and endovascular patient care.11 Basic principles include a standardized technical skills training by use of two-hour training modules, the use of life-like vascular models with pulsatile flow, team building and an ongoing scientific evaluation of the effectiveness of our courses. Founded by surgeons for surgeons, VI has run more than 150 national and international courses at different sites including Annual Meetings of the German Vascular Society (DGG), the European Society for Vascular Surgery (ESVS) and the Society for Vascular Surgery (SVS) in the US with over 2,500 participants from many Western and Eastern European countries, North and South America and the Middle East since 1991. The basic courses are aimed at beginners in vascular surgery and many other surgical disciplines, including cardiovascular surgery, trauma surgery, urology, gynecology, ENT, etc, while the master classes are suitable either for vascular surgical residents just before board examination or vascular surgeons who want to be re-trained in complex open and endovascular techniques. Since three years VI also offers courses for vascular and endovascular nurses and team training (nurse and surgeons). Furthermore VI organizes for many years an annual course to lower leg arteries on cadavers at the Albert-Ludwigs-University of Freiburg, Germany. Since 1991 VI is the only training organization in Europe that manufactures (www.vascular-international.org) and sold life-like models for endovascular procedures like EVAR, TEVAR and peripheral balloon dilatation and stenting, respectively. Since 1991 Basic open surgical procedures (suture and basic anastomotic techniques) are trained in a box model, in which vessel segments (calf aorta, veins etc) are inserted. To simulate a realistic practical open and endovascular training situation, a wide range of synthetic arterial inlays for carotid stenosis, aortic aneurysms and femoral bifurcation stenosis were designed. These inlay models are exchangeable in order to guarantee that every trainee is able to perform the complete operation by him- or herself. All models are equipped with a small pump inside to create pulsatile flow conditions with peak pressures around 90 mmHg within the inlays. The models have been constantly improved in terms of usability, durability and transportability and are individually available to equip training sites wherever needed, i.e. hospitals, industry or meetings. All models and inlays are commercially available (www.vascular-international.org).

Modular Course System: VI offers a wide spectrum of courses tailored to meet different training levels. The basic courses and training on largely realistic pulsatile anatomical open and endovascular surgical techniques, whereas the master classes cover all aspects of peripheral bypass surgery, access surgery, carotid surgery and stenting as well as open and endovascular aortic procedures. Absolute priority is given to practical training with step-by-step structured learning of open and endovascular procedures. In order to achieve a maximum training effect the basic and advanced training courses consist of several two-to-three-hour modules. Each module represents a complete open or endovascular procedure and follows an overall structure that includes the description of the target group, the educational objectives and the sequence of the procedure. The modular system permits to arrange target group oriented one-, two- or three-days courses for different training levels of the vascular specialist...

Practical training and course participants: Trainees practice in pairs on open vascular surgical models and in triples on endovascular models, respectively. Dressed in gloves and gowns they use original instruments, material and sutures. Each procedural step is demonstrated by the convenor at a separate table and transmitted to a video screen at every working place. The trainees have to follow the sequence of the procedure as demonstrated by the convenor. Experienced tutors advise the trainees to follow those instructions very carefully. A ratio of usually 1 tutor to 4 trainees allows permanent supervision and assistance. At the end of each module the tutors perform an assessment of the technical reconstruction and discuss with the trainees whether the educational objectives have been achieved...

The VI philosophy of practicing on largely realistic pulsatile vascular models in a standardized way was confirmed by a very recent randomized trial. 18 first-year surgical residents were taught technical aspects of a vascular anastomosis using femoral anastomosis simulation. One expert instructor taught a standardized anastomosis technique using the same method each time to one group over four sessions, while, similar to current vascular training, four different expert instructors each taught one session to the other (traditional) group. The technical skill assessment (OSATS, objective structured assessment of technical skill performance metrics) clearly showed that standardized teaching leads to significantly higher mean overall technical and global skill scores. Furthermore, the vast majority of trainees suggested a preference for a standardized approach.14

Theory: the practical training is supported by one-hour theory sessions dealing with: material science, surgical instruments, radiation protection, case discussions including patient selection for open or endovascular intervention, complication management, hemostasis etc. In addition each trainee is provided with a course-specific manual which explains each procedure in a stepwise fashion according to any given module. This supports the trainees to follow the training sequences not only during but also after the course if anyone wants to repeat the procedure.

EVALUATION OF PROCEDURES TRAINED BY VASCULAR INTERNATIONAL
Besides feedback-sessions and questionnaires before and after the course, several course elements have been evaluated systematically:

Vein patch plasty: before and after a 2.5 days basic course in open vascular surgical techniques 24 trainees were asked to perform a 5cm long vein patch plasty in a non-perfused calf aorta (running suture polypropylene 5/0). Procedure time and the overall quality of the patch scored from 0=catastrophic to 10=excellent were measured. All assessments were performed independently by two senior vascular surgeons. The results showed a significant reduction of procedure time from 14.8 (± 3.1) minutes to 14.1 (+/−2.2) minutes (p<0.001), as well as a significant improvement of the overall quality of the vein patch (score 5.2 before the course and 6.2 at the end of the course, p<0.05). These results were based on a very high inter-observer correlation between the two surgical assessors (r=0.8849).15

Open aortic repair: in another study the performance of 15 trainees on an infrarenal aortic anastomosis model (polyester tube graft 18mm, polypropylene 3/0) was evaluated at the beginning and the end of a three-day master class. Three experienced vascular surgeons assessed generic skills by use of OSATS and procedural skills with regard to overall technical quality and procedure time. Both assessments were measured Arterial 1 to 40 with a score of U4 representing competence. In addition, a video tape of the trainees was used for blinded assessment. The results showed that generic skills increased significantly from OSATS scores of 10.3 to 36.3 (median 17.3) before the course to 12 to 33 (median 26, p<0.006) at the end of the course. With respect to procedural skills the pre-course scores were low (median 17.3, 10 - 37) but improved to 25 (13.3 - 32) at the end of the course (p<0.004). Several operative components like front and back wall of the aortic anastomosis, needle and vessel handling, corner stitches and anastomotic apposition likewise improved significantly. Finally, trainees performed the aortic anastomosis significantly faster at the end of the course with a median time of 23 minutes before and 18 minutes after the course, respectively.16

Carotid endarterectomy (CEA) and patchplasty: In a prospective observational cohort analysis with pre- and post interventional measurements, 10 participants of a three-day master class with a personal experience of less than 10 CEAAs performed a conventional CEA with patch plasty on VI simulators. Primary endpoints were to assess any changes in the participants’ surgical skills and in the technical quality of their completed carotid patches documented by means of procedure-based assess-
Skills either in the operating theatre or on sophisticated training simulators for general and specific assessment is done by two independent experienced vascular surgeons. Using the example of the UEMS examinations, training courses are sparse. Nonetheless, more data are needed to recommend an evidence-based implementation of simulation courses for the future. The translation of course-mediated skills into performance forms (PBAs). Scores ranging from 1 (inadequate) to 5 (excellent). Again a significant improvement in the surgical skills tasks was observed with the mean score increase by 21.5% from 3.4 ± 0.9 to 4.2 ± 0.7 (p<0.001). Furthermore the mean score for the quality of the carotid patch increased by 27% from 3.5 ± 0.9 to 4.5 ± 0.8 (p<0.001).

**FUTURE DIRECTIONS**

For the future the translation of course-mediated skills into vascular surgical competence at the trainees’ “home hospital” has to be assessed in studies with a longitudinal design. There is evidence that the benefits of simulation courses and box trainers for laparoscopic, endourological and basic surgical techniques are related to an improved performance in the operating room. Unfortunately, transfer data for vascular surgical training courses are sparse. Nonetheless, this kind of evidence is necessary to diminish existing doubts that the vascular training courses do not have a significant positive impact on the vascular trainee’s further learning curve and ability to acquire new skills. Just recently external simulation courses were included in the surgical curriculum in Switzerland (J. Schmidli, personal communication). Nonetheless more data are needed to recommend an evidence-based implementation of simulation courses into national vascular surgical curricula.

The second major challenge in vascular surgical education is the assessment of technical skills at the end of the training period. Since the sheer number of procedures and years spent in a teaching hospital is no longer accepted as the only valid indicator for competence a move from volume- and time-based education to a competence-based education is necessary. Consequently such a move would include an assessment of technical skills either in the operating theatre or on sophisticated training models.

Today practical examinations are in place only in a few countries. Using the example of the UEMS examinations, trainees have to perform a bifurcated artery anastomosis, a saphenous junction ligation and an endovascular access to the renal artery. Assessment is done by two independent experienced vascular surgeons using a scoring system for general and specific surgical skills. Just recently the VI models were introduced very successfully into the UEMS examination.

The future of vascular surgery depends on properly trained young surgeons. Meanwhile it is internationally accepted that the frame conditions mentioned above demand a shift to novel training modalities. All national vascular surgical societies should focus on that issue by creating nationwide structures for training, competence assessment and credentialing. Unanimity should dominate to shift the vascular surgeon’s learning curve from the patient to the training model.

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**INTRODUCTION**

The Union Européenne des Médecins Spécialistes (UEMS) was created in 1958, and since the foundation the main objectives are to promote the highest level of patient care in the European Union (EU), to promote the harmonization of high-quality training programs within the various specialities throughout the EU and to facilitate the free exchange of training and work of trainees and medical specialists between the various member countries.

Since 2005 the Section of Vascular Surgery is independent and separate and according the statutes of the UEMS Section and Board of Vascular Surgery: “The main objective is to guarantee the highest standards of care in the field of Vascular Surgery within the EU, by ensuring that the training of the specialist doctor is raised to the highest possible level.”

The European Section and Board of Vascular Surgery (SBVS) shall achieve this by the following means:

1. The SBVS shall recommend the standards required for the training of their specialists and the maintenance of these standards;
2. The SBVS shall make proposals for the quality of training and for the syllabus and curriculum for vascular and endovascular surgery;
3. The SBVS shall recommend procedures to achieve the free movement of specialist doctors throughout the EU;
4. The SBVS shall recommend the criteria to which the training centres of their specialty should conform;
5. The SBVS shall examine the real content and quality of training in the different countries of the EU;
6. The SBVS shall facilitate the exchange of their specialist trainees between training centres of the various countries of the EU to ensure a better harmonization and quality of training;
7. The SBVS shall set up a system for “recognition of quality” in their specialty.”

**Why it makes sense to get certified on an european level?**

There are large differences in requirements and length of training in Vascular Surgery within the EU concerning the minimum training required (range 5-9 years), the program accreditation and trainee certification (national association, specialty society, government, university, specialty board, general medical council,...) and the national exit examinations required (written, oral, case load), which stresses the importance of harmonization in training and certification in Vascular Surgery within the EU.

Currently a European specialist qualification in any specialty, including vascular surgery, does not replace an accreditation by the national authorities, which is the primary specialist accreditation recognized by law by all member countries and in countries where there is a government approved national examination. The European examination cannot and should not be used to bypass national qualifications. Thus, the European Qualification, entailing those who pass the examination as Fellow of the European Board of Vascular Surgery (FEBSV), must be seen as a respected qualification and an European quality mark.

**EUROPEAN EXAMINATION AND FEBSV**

The motivations to organize European Examinations by our Section and Board of Vascular Surgery are: to harmonize knowledge and skills, to indicate that the candidate has passed a structured training program, to guarantee a minimal level of competence and to promote exchange between countries by establishing this standard: FEBSV (Fellow of the European Board of Vascular Surgery).

**1. ELIGIBILITY CRITERIA**

- To fulfill the FEBSV eligibility criteria the Applicants must:
- Be in possession of a CEST/ICT (Certificate of Completion of Specialist Training/Certificate of Completion of Training) or equivalent certificate in vascular surgery, or general surgery (in countries where vascular surgery is not yet an independent specialty);
Be eligible (within 6 months of application) for a valid national CCST/CCT or equivalent certificate in vascular surgery, or general surgery and must provide a signed confirmation by 2 trainers (in English).

2. LOGBOOK

In the Logbook open vascular and endovascular procedures for which the applicant is the principle operator are recorded individually. Although for privacy reasons patient identification should be removed, all procedures should be traceable with the possibility to be verified (e.g., date of procedure and patient gender and initials).

Definitions

A. An open vascular surgical procedure is a procedure that requires surgical exposure of one or more arteries or veins for:
1. The correction of arterial or venous diseases, deformities or defects.
2. The repair of arterial or venous injury.
3. The treatment of other diseases requiring arterial or venous reconstruction.

B. An endovascular surgical procedure is a procedure that requires the use of guide wires and/or catheters in one or more arteries or veins and fluoroscopy guidance for:
1. The correction of arterial or venous diseases, deformities or defects.
2. The repair of arterial or venous injury.
3. The treatment of other diseases requiring guide wire/catheter manipulations in arteries or veins.

C. The essential steps of an open or endovascular vascular procedure are
1. Exposure or acquisition of access.
2. Control or maintenance of access.
3. Final diagnosis.
4. Vascular intervention (removal, implantation, deformation, repair, replacement or reconstruction).
5. Confirmation of intended result.
6. Closure.

D. The principle operator for both open and endovascular procedures is the person who performs the majority of the essential steps of the procedure.

E. Open vascular and endovascular surgical procedures are both classified into three levels, based on how much specific training or experience would be required for a typical procedure of its kind:
1. Basic: procedures requiring little or no specific training or experience.
2. Intermediate: procedures requiring specific training or experience.
3. Advanced: procedures requiring advanced training or experience.

3. ORAL AND TECHNICAL SKILLS EXAMINATION

Currently the Oral and Technical skills examination is organized twice a year (in Maastricht at EVC and in September during the ESVS annual meeting). It is divided in five parts: clinical case analyses, academic viva, overall assessment, open technical skills assessment and endovascular skills assessment.

To reduce subjectiveness: the candidates have two assessors at each station; rotation of candidates around stations (in total 12 different examiners for the oral section plus 4 different examiners for the technical skills section); the clinical cases, academic paper and overall assessment are discussed prior to start of the exam with the examiners; the official language is English but the candidate can have linguistic help if needed.

Concerning Quality Assurance the FEBVS has been Quality assured by an external educationalist, each exam has a number of senior examiners who act as raying assessors and also assessors of the examiners; the Syllabus is available on the web (www.uemsvascular.com).

3.1 Clinical case analyses

Discussion of 4 clinical cases concerning AAA, Lower limb, Endovascular and Miscellaneous, 15 minutes each, by two examiners that must mark independently using a fixed marking scheme range 4-8 (overall professional capability / patient care; knowledge and judgement; quality of response), and the Pass mark is 6.

3.2 Academic Viva

Discussion of one paper, published in one of top-leading scientific journals in the field of vascular surgery, during 20 minutes, about methodology, statistics, quality of results and conclusions, relevance, by two examiners that must mark independently using a score system 4-8 and the Pass mark is 6.

3.3 Overall assessment

Questions about indications, guidelines, evidence, trials, during 30 minutes, by two examiners that must mark independently using a score system 4-8 and the Pass mark is 6.

3.4 Open Technical skills assessment

Three-station bench assessment: Carotid endarterectomy, Distal anastomosis and Aortic anastomosis, by two independent examiners in each station.

The rating scales are: Generic Surgical Skill (8 components, five point scale, generic) and Procedural Skill (unique to procedure, five point scale), with high inter-observer reliability and validity.

3.5 Endovascular skills assessment

By two independent examiners, using the STRESS - machine (Simulator for Testing Radiological and Endovascular Skills). IT is not a TRAINING but a TESTING machine (glass model) with simple objectives (catheter and guidewires); Contrast, Balloons and Stents are not necessary.

WHAT'S NEEDED

1. To promote the FEBVS as the specialty examination in countries where such an examination is not required yet;
2. To increase the participation of examiners from countries which adopt the FEBVS as their exit examination;
3. To improve examiner training and certification;
4. To institute regular statistical assessment of the exam.
5. To continue the development of the European Vascular Curriculum.

REFERENCES

INTRODUCTION

Our knowledge of the role of platelets in both physiological and pathophysiological haemostasis has grown vastly over the past few decades. Platelets have the ability to almost instantaneously identify and bind the collagen that is revealed upon vessel wall injury through the use of Von Willebrand factor (vWF). Platelet-platelet interaction then leads to adhesion and plug formation. Atherosclerotic plaque ruptures evoke a similar reaction, producing platelet-rich thrombi. Assays assessing the regulation of platelet function and activation yield the opportunity of monitoring and possibly guiding antiplatelet therapy effectively.

PLATELETS AND PLATELET ACTIVATION

Platelets play a major role in the progression of atherosclerosis and related cardiovascular events (CVEs). They can be activated via many pathways. Platelets are anucleate blood cells that originate from the cytoplasm of megakaryocytes in the bone marrow and circulate to ‘survey’ the integrity of the vascular endothelium, where they discriminate between normal endothelial cell lining and injured endothelium. In normal physiological conditions, platelets play a central role in haemostasis: a low platelet count (thrombocytopenia) or low platelet function (thrombocytopenia) will lead to bleeding complications, whilst excessive platelet counts or functioning leads to clotting, mainly in the arteries. After traumatic vascular injury, the loss of the endothelial cell barrier between extracellular matrix components and blood flow triggers platelet activation; primary platelet activation starts with platelet-binding to exposed collagen via GPIIIa and glycoprotein (GP)VI expressed on the platelet wall. This activates the integrin αIIbβ3, the production of thromboxane A2 (TxA2) and the release of c-de- and dense granules. Adenosine diphosphate (ADP), released from the dense granules initiates secondary platelet activation. ADP binds to P2Y1- and P2Y12 receptors on the platelet wall, enforcing the platelet activation. Concomitantly, the coagulation cascade and hence the serine protease (enzyme) thrombin (factor IIa) is synthesized. Thrombin increases secondary platelet activation by binding to the protease activated receptors (PAR)-1 and PAR-4. TxA2 acts on the platelet’s own thromboxane receptors and those of other platelets. These receptors trigger intraplatelet signalling, which converts cGMP (also known as glycoprotein Ibα and IIbα) receptor to their active form. cGMP binding further anchors the platelets to vWF for stabilization and to initiate aggregation. Activated αIIbβ3 on the surface of activated platelets allows them to bind fibrinogen, a rod-like protein with nodules on either end capable of binding αIIbβ3, allowing the platelets to aggregate.

ANTIPLATELET THERAPY

Antiplatelet therapy such as COX-1 (aspirin) or P2Y12 inhibitors (e.g. clopidogrel and ticagrelor) has become standard treatment in primary, secondary and periprocedural prevention of CVEs. A daily dose of antiplatelet medication prevents platelet activation and aggregation and thereby lowers the risk of thrombosis. Currently multiple different platelet aggregation inhibitors are available, they are subdivided by point of action. Aspirin, P2Y12 inhibitors and diprydamol are most widely used and studied.

• Aspirin, acetylsalicylic acid, is the most widely used and studied drug. It inhibits thromboxane aggregation by suppressing the production of the prostaglandin thromboxane A2 by irreversibly acetylating the enzyme cyclo-oxygenase 1 (COX1). needed for thromboxane A2 production). Although aspirin has a moderate effect, since it only targets the thromboxane - dependent pathway, it is very effective in preventing secondary CVEs; an odds reduction of 25% in subsequent CVEs was found through many studies by the Antithrombotics Trials' Collaboration.

• P2Y12 inhibitors, i.e. clopidogrel, prasugrel and ticagrelor are increasingly prescribed for secondary CVE prevention. Clopidogrel and prasugrel are pro-drugs that need metabolism to an active form. Ticagrelor does not. P2Y12 inhibitors block the ADP-pathway by irreversibly binding to the P2Y12-receptor. Clopidogrel is prescribed after myocardial or cerebral infarction and in severe peripheral arterial disease. Prasugrel is gaining popularity for its stronger platelet inhibiting and consistent effect. As opposed to clopidogrel, to which patients’ response vary widely. The risk of major bleeding is larger though. The benefit of ticagrelor is that it works almost instantly.

• Dipyridamole blocks the enzyme phosphodiesterase thereby increasing intracellular cAMP and cGMP, both platelet aggregation inhibitors. Dipyridamole is prescribed with aspirin for secondary prevention after cerebral infarction.

PLATELET REACTIVITY TESTING

The intensity of platelet activation can be tested (for different pathways) and is a predictor of cardiovascular outcome. There is a plethora of test commercially available. The reproducibility and applicability vary strongly between these tests. The current gold standard, light transmission platelet aggregation (LTA), is time consuming and requires experienced lab workers. Point of care tests (POCTs) like the VerifyNow, VASP or Multiplate, have been tested in many, mostly cardiologic, trials. No test proved to be superior in a recent extensive review and meta-analysis.

The choice of the test is still based on cost, experience and preference. Most used commercially available tests:

• LTA is the “gold standard” because of the long and broad experience with the use of this technique. It optically detects the formation of aggregates in platelet-rich plasma stimulated with manually added agonists. Because the LTA is a manually conducted test, the reproducibility between laboratories is low and the test is time consuming.

• The VerifyNow is an easy and rapid point-of-care test (POCT) to measure platelet inhibition in response to aspirin, P2Y12 inhibitors and GPIIb/IIIa-inhibitors based on optical light transmission. The results are congruent with LTA. Cut-off values have been defined for the prediction of thrombotic events following percutaneous coronary intervention (PCI). The VerifyNow is the most used diagnostic POCT to assess the effectiveness of antiplatelet therapy in individual patients.

• The Multiplate detects the change in electrical impedance resulting from the adhesion and aggregation of platelets on two metal sensor wires. When activated, platelets adhere to the sensor wires altering the impedance. The Multiplate can be used for both aspirin and P2Y12 monitoring and is semi-automatic. Manual preparation and pipetting of the agonists is necessary.

• Vasodilator-stimulated Phosphoprotein Phosphorylation Assay (VASP) is an intracellular platelet protein that is not phosphorylated under normal conditions. Persistent VASP phosphorylation is associated with an increased risk for ischaemic cardiovascular events. VASP phosphorylation is assessed using the phosphorylation detection kit (vasodilator-stimulated Phosphoprotein Phosphorylation Assay, Vasodilator-stimulated Phosphoprotein Phosphorylation Assay, VASP).
phosphorylation, measured with flow cytometry, correlates with P2Y12 receptor inhibition, reflecting the effect of the medical treatment. This makes the VASP assay only applicable for monitoring of P2Y12 inhibitors. Although the VASP is no POCT, it has a high sensitivity and specificity compared to the VerifyNow.

**HIGH ON TREATMENT PLATELET REACTIVITY**

Antiplatelet therapy is prescribed to prevent CVEs. Unfortunately, these events still occur. Both non-responsiveness and high on-treatment platelet reactivity (HTPR) have been linked to CVEs. High responders have a high risk of bleeding whilst low responders tend to clot. A recently published review showed that high-on-aspirin platelet reactivity (HAPR) had a prevalence of 22.2% in a pooled analysis of 102 studies containing a total of 44,098 patients with coronary artery disease (CAD), cerebrovascular disease (CVD) or peripheral arterial disease (PAD) treated with aspirin or aspirin and clopidogrel. The prevalence of non-responders for clopidogrel was even higher: 40.4% of patients were diagnosed with high-on-clopidogrel platelet reactivity (HCPR). This was associated with an increased risk of CVEs (RR 2.80, 95%CI: 2.40-3.27). Other studies have shown that the incidence of HAPR and HCPR is significantly higher in patients with chronic kidney disease and diabetes, both common risk factors in vascular surgery patients. HCPR can be caused by a mutation in the CYP2C19 gene. Cytochrome P450 2C19 (CYP2C19) enzymes are needed to metabolize clopidogrel. The cause of HAPR remains unknown, although evidence suggests a clinical relevance.

Identification of both high- and non-responders allows for patients at risk to receive “tailored antiplatelet therapy” to improve outcome. Guiding antiplatelet therapy by the absolute degree of platelet inhibition is expected to improve clinical outcome. Cardiologic trials investigating the role of tailored antiplatelet therapy (i.e., GRAVITAS, MADONNA, ARCTIC etc.) have been inconclusive so far. Although this may well be due to heterogeneity of the treatments and utilized platelet function assays.

**TIMING OF PLATELET REACTIVITY TESTING**

Most studies that investigate the potential benefit of personalized antiplatelet therapy use a single platelet reactivity test for treatment stratification, often obtained early after starting treatment with clopidogrel. Although data have demonstrated that the mean platelet function across a population is constant in different samples, these findings cannot exclude changes in platelet reactivity over time in individual patients. A subanalysis of the ELEVATE-TIMI 56 trial assessed platelet reactivity over time in individual patients. The platelet reactivity of patients taking clopidogrel (75 or 150 mg) was measured with the VerifyNow and VASP-assay at two time-points. Evaluating each patient individually, 15.7% of patients taking clopidogrel 75 mg and 11.4% of patients taking 150 mg changed their responder status when tested at 2 different time points (p < 0.001). Despite being treated with the same dose of clopidogrel, >40% of patients had a change in platelet reactive units (PRU) >40 on serial sampling, causing change in responder status in approximately 1 on 5 patients. Even though this study is a retrospective sub-analysis and has only two time points of platelet reactivity testing with no specification of the interval, it raises some questions as to the optimal timing for testing. Furthermore, several studies on healthy subjects, not on APT, have shown that platelet reactivity can vary significantly over time. These findings suggest that many physiological factors, other than medications, may affect platelet function over time even in healthy individuals. We can only speculate which mechanisms contribute to platelet activation variability. Potential factors might include either true alterations in platelet reactivity due to fluctuation in platelet production and expression of the P2Y12 receptor, changes in hepatic metabolism altering the level of clopidogrel bioactivation, unrecognized noncompliance, or artifactual changes in measurements due to biological or technical issues affecting the platelet reactivity tests.

**PERSPECTIVE: PERSONALIZED ANTIPLATELET THERAPY (PAPT)**

The association of HAPR and HCPR with an increased risk of thrombotic events sparked the concept of tailoring APT based on platelet reactivity measurements. Switching APT (to a higher dose or to other medicines) could result in less CVEs by lowering platelet reactivity, especially in high-risk patients. Not only HTPR should be an indicator to adjust APT. Low on-treatment platelet reactivity (LTPR) should also be considered a reason to tailor APT, due to the increased risk of bleeding. This suggests the presence of a therapeutic window for platelet reactivity with HTPR and LTPR at either end of the spectrum.

In order to effectively guide PAPT evidence must be generated to find a gold standard platelet function test. The mechanisms that cause variability between patients, within patients and between the tests must be explained. Well-designed randomised controlled trials will aid in identifying a POCT that can effectively guide antiplatelet therapy. Finding the platelet-fingerprint for each patient and tailoring their antiplatelet therapy might lower the CVE risk in vascular patients in the (near) future.

**REFERENCES:**


Acute limb ischemia in patients with malignancy

ABSTRACT
The association between cancer and thrombosis is well recognized. The pathogenesis of pro-thrombotic state in cancer is multifactorial and several factors like type of malignancy, presence of metastasis and chemotherapy influence the risk of thromboembolism. Arterial thromboembolic events (TEE) are less common compared to venous TEE, but carry significant morbidity and mortality. Currently there are no scoring systems or guidelines to identify high-risk patients and target prophylactic anticoagulation to prevent arterial thromboembolism. In our experience there was no significant difference in the 30-day amputation rate between patients treated conservatively and surgically. Acute limb ischaemia is a pre-terminal event with overall one-year mortality of 80%. Limb salvage is possible with conservative treatment and therapy should be directed at controlling the primary malignancy, metastasis and patients’ holistic needs.

INTRODUCTION
The association between cancer and thrombosis is well recognized and dates back to 1865 when Armand Trousseau first reported that spontaneous recurrent or migratory thrombophlebitis may be an indicator of an occult visceral malignancy. Although venous thromboembolism is the commonest clinical manifestation, the spectrum of disease can range from asymptomatic abnormal coagulation tests to massive thromboembolism. Compared to venous thrombosis, acute peripheral arterial thrombosis is less common, but can account up to 12% to 16% of patients presenting with acute limb ischaeemia and is associated with high morbidity and mortality. Similar to non-cancer patients, acute limb ischaemia in patients with malignancy can be embolic or thrombotic in nature. The sources of embolism in these patients include non-bacterial thrombotic endocarditis (NBTE), paradoxical embolus from deep venous thrombosis (DVT) through a patent foramen ovale or tumor-cell emboli. There is also an increased risk of in situ thrombosis due to the malignancy associated acquired thrombophilia. In recent years, an increased prevalence of antiphospholipid antibodies has been reported in patients with malignancy that might increase the risk of thrombosis. Extrinsic compression from tumor, immobility and low flow states due to sepsis (Chemotherapy induced immunosuppression), dehydration (Chemotherapy related vomiting and diarrhoea) can exacerbate the intrinsic hypercoaguable state, leading to thromboembolic events. In addition, treating malignancy with chemotherapy, hormonal therapy or radiotherapy can also increase the risk of thromboembolic events. In a large retrospective study, Moore et al reported a 11.3% incidence of arterial thromboembolic events in patients who had cisplatin based chemotherapy. Several other chemotherapeutic agents including Fluorouracil, Sunitinib and Gemcitabine are also associated with arterial ischemic events. An increased risk of peripheral arterial disease and venous thromboembolism is also noted in patients treated with androgen-deprivation therapy. The hypogonadism induced by these agents predisposes to metabolic syndrome, insulin resistance, diabetes and dyslipidaemia leading to increased cardiovascular mortality. The low testosterone is also associated with reduced fibrinolytic activity which predisposes these patients to thromboembolic events. Radiotherapy has multiple effects on the arterial system including: oxidative stress, endothelial damage, activation of coagulation cascade, arteritis and accelerated atherosclerosis. The commonest site of primary cancer was lung (28%, n=20), followed by GI tract malignancies (27%, n=19) (gastric = 6, Colo-rectal = 6, esophagus = 4 and opharynx = 3) and urogenital system (n = 14) (Prostrate = 3, Ovary = 2, testicular = 2, Vagina = 2, Bladder, Kidney, Penis, Cervix and Endometrium = each 1). Over half of the patients (56%) had metastasis involving lung, liver and/or bones at the time of presentation.

Like cancer pro-coagulant (CP) and heparanase that contribute to the hypercoaguable state. In view of this association between cancer and thrombosis several risk-scoring systems have been reported (1) Khouran, (2) Kroger and (3) Caprini. These risk assessment model were introduced to identify high-risk patients for venous thromboembolism. National and international guidelines recommend using such risk assessment tools to identify high-risk patients and target prophylactic anticoagulation. No such risk-scoring systems or guidelines are, however, currently available for identifying high-risk patients and preventing arterial thromboembolism. The optimal management of cancer patients presenting with acute limb ischaemia is controversial. Attempts to salvage the limb surgically can be futile with one-year amputation and/or mortality rates as high as 56% to 100%. In the study by Morris-Stiff and Lewis, in spite of having similar physical performance score at the time of surgery, compared to patients without malignancy, all the cancer patients who underwent surgical treatment died within 6 months. In the Thrombolysis or Peripheral Arterial Surgery (TOPAS) trial, 12% of patients in the thrombolysis arm and 11% in the surgical arm had concomitant cancer. Secondary analysis of the data revealed that cancer was an independent risk factor for increased morbidity and mortality. Thrombolysis is feasible in these patients but has similar outcomes compared to surgical intervention. In view of this poor outlook, anticoagulation and palliation may be an appropriate approach in several patients.

OUR EXPERIENCE
Between June 2010 and May 2015, 69 patients with known or occult malignancy were referred to the regional vascular unit with acute limb ischaemia. The median age was 71 years (range 41-94 years) and 54% were men (n = 36). Median follow up period was 71 days (range 2 to 582 days).

Timing of acute arterial ischemic event and cancer
In majority of the patients (43%, n = 30), the diagnosis of cancer had been made three months of prior to the presentation of acute limb ischaemia. In 24% (n=17) of patients, the diagnosis of cancer was made more than one year before the index event. Some of these patients had recurrence or metastasis at the time of presentation. In 6 patients (8%) cancer was diagnosed within 6 months of presenting with acute limb ischaemia.

Cancer profile and treatment
The commonest site of primary cancer was lung (28%, n=20) followed by GI tract malignancies (27%, n = 19) (gastric = 6, Colo-rectal = 6, esophagus = 4 and opharynx = 3) and urogenital system (n = 14) (Prostrate = 3, Ovary = 2, testicular = 2, Vagina = 2, Bladder, Kidney, Penis, Cervix and Endometrium = each 1). Over half of the patients (56%) had metastasis involving lung, liver and/or bones at the time of presentation.

In all the three patients diagnosed with prostate cancer had hormonal therapy. Seven patients (n=10%) had combined chemotherapeutic agents including Fluorouracil, Sunitinib and Gemcitabine are also associated with arterial ischemic events. Chemotherapy related vomiting and diarrhoea can exacerbate the intrinsic hypercoaguable state, leading to thromboembolic events. In a large retrospective study, Moore et al reported a 11.3% incidence of arterial thromboembolic events in patients who had cisplatin based chemotherapy. Several other chemotherapeutic agents including Fluorouracil, Sunitinib and Gemcitabine are also associated with arterial ischemic events. An increased risk of peripheral arterial disease and venous thromboembolism is also noted in patients treated with androgen-deprivation therapy. The hypogonadism induced by these agents predisposes to metabolic syndrome, insulin resistance, diabetes and dyslipidaemia leading to increased cardiovascular mortality. The low testosterone is also associated with reduced fibrinolytic activity which predisposes these patients to thromboembolic events. Radiotherapy has multiple effects on the arterial system including: oxidative stress, endothelial damage, activation of coagulation cascade, arteritis and accelerated atherosclerosis.

Site of thrombo-embolism
Four patients presented with acute upper limb ischaemia. The remaining sixty-five patients presented with lower limb symptoms. Arterial imaging, usually MRA revealed that multiple arterial segments were involved in majority of the patients with lower limb symptoms. The infra-popliteal territory (femoral, popliteal and crural segments) was the most common site (n=23), followed by aorto-iliac segment (n=21). Five patients presented with occluded grafts from previous surgery.

Intervention
Anticoagulation using intravenous heparin was initiated in all patients after diagnosing acute limb ischaemia. A total of thirty patients underwent surgical intervention to salvage the limb and the remaining thirty-nine patients were treated conservatively with anticoagulation in the form of treatment dose tinzaparin. In the surgical group, seventeen patients (24%) underwent endovascular intervention (stenting or angioplasty) while fourteen patients had radiotherapy alone as their primary treatment for cancer. Two thirds of the patients (n=16) who underwent chemotherapy had used platinum based regimens (Cisplatin, Carboplatin and Oxaliplatin) and in these fourteen patients (87%) had received platinum based regimens within the last three months of index event.

Vascular Profile
The vast majority of the patients (91%) did not have a previous history of peripheral vascular disease. Six patients had a previous history of peripheral vascular disease and five of them presented with occluded grafts (two infra-iliac grafts, one ilio-femoral graft and two infra-inguinal grafts).

Mode of presentation
In most cases (65%) patients presented acutely with symptoms of a acutely painful, cold and pale limb lasting less than 24 hours. The remaining patients presented with symptoms persisting for more than 24 hours (range 1-28 days, median 7 days).

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Outcomes (figure 1)
Four patients underwent amputation within 30 days of index event (two in the surgical group and two in the conservative group). The 30-day mortality was 23% (7 out of 30) in the surgical group and 46% (18 out of 39) in the conservative group. The overall one-year mortality was 80% in both the groups. Only six out of the thirty patients in the surgical group and nine out of the thirty-nine patients in the conservative group were alive at one year. The overall one-year mortality was 80% in both the groups. The initial one-year survival benefit seen in the surgical group at 30-days (77% versus 54%) was not sustained even in the mid-term with only 20% of the patients being alive at one year in both the groups.

DISCUSSION
Thromboembolic events are the second leading cause of death in patients with cancer and is the leading cause of death in patients with peripheral vascular disease. In spite of this well known association there is paucity of data regarding the pathogenesis, risk stratification and management of cancer patients presenting with acute limb ischaemia. To our knowledge, this is one of the largest case series exploring the outcomes of acute limb ischaemia in patients with cancer treated both surgically and conservatively. The results of this study confirm the high one-year mortality associated with acute limb ischaemia in patients with cancer, irrespective of the initial management option.

In these patients, limb salvage is possible with systemic anticoagulation and conservative approach. Only two patients underwent amputation in the conservative group with a similar amputation rate in the surgically treated patients. The initial survival benefit seen in the surgical group at 30 days (77% versus 54%) was not sustained even in the mid-term with only 20% of the patients being alive at one year in both the groups. Hence clinicians, when faced with a cancer patient with acute limb ischaemia, should consider the patient's general condition and over all prognosis in the decision making process. Patients should be informed about the overall prognosis and lack of survival benefit with intervention and palliative care teams should be involved early in their care.

Certain types of chemotherapy agents are known to have high incidence of thromboembolic events. In a large retrospective study, Moore et al20 have shown that cisplatin based chemotherapy regimens are associated with an 8% incidence of arterial TEE and up to 18% combined arterial and venous TEE rate. In our study, twenty percent of the patients had received platinum based chemotherapy within the last three months of the presenting index event. A standard or extended low molecular weight heparin (LMWH) prophylaxis in patients receiving platinum based chemotherapy seems plausible but is not of proven benefit. In elderly patients receiving bevacizumab (a vascular endothelial growth factor (VEGF) inhibitor), Perez and Lishie21 have shown that low dose aspirin can reduce the risk of cardiovascular complications. Prevention of radiation induced arteritis and thromboembolic events can be achieved by controlling the vascular risk factors like smoking, diabetes, hypertension, diet and healthy lifestyle modification, antiplatelet and statin therapy.

Finally, the role of newer oral anticoagulant drugs and the duration of LMWH treatment in preventing further thromboembolic events in these patients is yet to be elucidated.

RECOMMENDATIONS
Acute limb ischaemia is a poor prognostic sign in patients with malignancy. There was no significant difference in 30-day amputation rate or one year mortality rate between patients treated conservatively and surgically. Hence a conservative approach with (1) anticoagulation and or antiplatelets agents, (2) early communication with the oncology and palliative care teams about the vascular event are critical in establishing future management plans.

relations
Identification of predictive risk factors for peripheral microvascular complications in patients with Raynaud’s Phenomenon

BACKGROUND
Raynaud’s phenomenon (RP) is a well characterized common clinical disorder characterized by recurrent episodes of digital artery vasospasm triggered by exposure to cold or emotional stress. RP can be classified as primary (idiopathic) or secondary when associated to several diseases or conditions. The pathogenesis of RP is still not entirely clear or understood. Recent insights into the pathogenic mechanisms underlying RP, in particular vascular, neuronal and intravascular abnormalities, might help to identify crucial key points and potential targets for early therapeutic intervention.

It has been reported that 95% of patients with SSc, 20-30% of systemic lupus erythematosus (SLE), 20-30% of S. Sogren and 25% of Myositis(1) will have RP as the first clinical manifestation of disease. (Figure 1). The co-existence of RP, positive antinuclear antibody (ANA) and microvascular abnormalities diagnosed by nailfold videocapillaroscopy (NVC) is a core diagnostic triad of associated autoimmune CTD. Koening et al(2) demonstrated in prospective study of 586 patients followed up for 3,197 person years that the incidence of progression of isolated RP to new a digital tropic lesion occurred when a new digital tropic lesion occurred. If no RP developed, patients were seen on a regular basis at 3–6 months intervals, as indicated by disease severity. Final observation was in forth trimester of 2014. We had no patients lost during the entire course of our follow-up period.

Primary outcome was the occurrence of at least one or more new ischemic fingertip DU in the 3-year follow-up period. In addition we applied survival analysis to new occurrence of DU during the study period, regarding endothelium dysfunction (FMD, endothelin-1 (ET-1) and asymmetric dimethylarginine (ADMA) angiogenic biomarkers (vascular endothelial growth factor (VEGF), endostatin and endoglin) and microvascular damage (nailfold Video capillaroscopy (NVC) (Figure 3) and microangiopathy evolution score (MES)).

OBJECTIVES
Measure of disease activity can be used to describe and compare study populations as well as to identify potentially risk factors for microangiopathy. Given that research methods into new treatments for RP and DU are rapidly advancing, they could be used to determine eligibility and as a measure tool for outcome for new treatments and disease activity in clinical practice, helping to decide, whether the actual therapy gives satisfactory results or a more aggressive therapy is needed.

The main objectives of this thesis were: identification of risk factors for DU in patients with RP, and evaluate the risk of SSc patients to develop a first episode of DU or to have a recurrence of DU during a 3-year long follow-up period.

METHODS
This research study was designed to provide an analysis of the clinical characteristics, endothelial dysfunction parameters and vascular biomarkers in Raynaud patients. An effort was done to consolidate knowledge and contribute to the discussion of contradictory findings described in literature.

A prospective observational cohort study with a 3-year clinical follow-up was conducted to evaluate 109 selected patients attending the Multidisciplinary Raynaud Outpatient Clinic of the Center for Immunology at Centro Hospitalar do Porto in Portugal (77 SSc patients and 32 primary RP). Thirty-four healthy, sex/age matched, non-obese, without self-reported cardiovascular risk factors controls were invited to participate.

SSc patients were divided into two groups: DU group, that included 38 patients having an active ulcer at the beginning of our follow-up study, with or without a past history of DU and a group with no history of DU, that included 39 patients with no history of DU until enrolment.

Clinical and demographic parameters were analysed. Allen test, flow-mediated dilatation (FMD), nailfold videocapillaroscopy (NVC), autoantibody screening and endothelial dysfunction and angiogenesis vascular biomarkers were assessed in all patients and controls. When included in the study cohort, Patients were instructed to come to the hospital clinics when ever a new digital tropic lesion occurred. If no DU developed, patients were seen on a regular basis at 3–6 months intervals, as indicated by disease severity. Final observation was in the forth trimester of 2014. We had no patients lost during the entire course of our follow-up period.

Primary outcome was the occurrence of at least one or more new ischemic fingertip DU in the 3-year follow-up period. In addition we applied survival analysis to new occurrence of DU during the study period, regarding endothelium dysfunction (FMD, endothelin-1 (ET-1) and asymmetric dimethylarginine (ADMA) angiogenic biomarkers (vascular endothelial growth factor (VEGF), endostatin and endoglin) and microvascular damage (nailfold Video capillaroscopy (NVC) (Figure 3) and microangiopathy evolution score (MES)).

The institutional ethical review board of Centro Hospitalar do Porto approved this study. All subjects signed informed consent before inclusion in the study. Data were collected by analysis of clinical file data and by clinical interview.

RESULTS
As far as we know, this is first study that demonstrates that both endothelial dysfunction and an angiogenic stimulus are present in PRP. Clearly, our findings suggest that endothelial dysfunction suggested by increased serum levels of ET-1 as well as a pro-angiogenic state due to increased serum levels of VEGF might be triggered by the repeated bouts of vasospasms. However when comparing PRP and SRP SSc- associated without DU no major difference were found regarding the vascular biomarkers investigated. Table 1. Thus, a new and useful information coming out of this investigation is that severe oblitative peripheral vasculopathy is present only in SRP patients with DU as expressed by the increased peripheral resistance, low FMD response to shear stress, decreased PSV and EDV and high RI mostly consequent of the EC injury with endothelial dysfunction associated to an impaired angiogenesis.

As risk factors for DU in RP patients we identified that FMD, PSV and EDV were significantly lower in patients with DU when compared to SSc non-DU, primary RP and controls. Regarding qualitative NVC patterns statistically differences of FMD were found between groups. FMD, PSV and EDV were significantly lower in the late pattern compared to active pattern and early pattern. No differences found between active and early patterns. We observed a successive decrease of PSV and EDV and increases in vascular resistance, measured by resistive index (RI) with progression of microvascular damage diagnosed in NVC. Regarding vascular biomarkers, we report high serum levels of ET-1 and ADMA, low serum levels of VEGF and increased endoglin serum as independent risk factors of DU in patients.

In an attempt to determine potential predictive factors of appearance of new episodes of ischemic DU in secondary Raynaud, we identified as risk factors: history of at least one DU before enrolment, autoantibody anti-scleroderma-70, presence of telangectasia, NVC late pattern, high MES score, low FMD%, positive Allen test, and increased ET-1 serum levels. Multivariate Cox analysis confirmed increased MES score, low FMD%, increased ET-1 and ADMA serum levels as independent risk factors of the development of a new DU. With respect to angiogenic biomarkers only VEGF was identified as predictive risk factor for the occurrence of at least one new DU during the three-year follow-up period.

Patients with FMD levels ≤0.5% (p=0.000), ET-1 serum level > than 11.9 pmol/ml (p=0.020), ADMA serum levels > than 0.49 umol/l (p=0.079) and MES score greater than 2 (p=0.000) had significantly more new digital ulcers in 3-year survival analysis. Low VEGF serum levels ≤422.47 pg/ml had significantly more DU (p=0.028). (Figure 4).

Our study identified FMD=9.41% (HR: 0.37 95%CI: 0.14-0.99); ET-1=11.85 pmol/l (HR: 3.81 95%CI: 1.41-10.26) and late NVC pattern (HR: 2.29 95%CI: 0.97-5.38) as predictors of DU recurrence in the 3-year follow-up period and when estimating the probability of occurrence of first DU in naïve DU patients, only late NVC pattern (HR: 12.66 95%CI: 2.06-77.89) was an independent predictor.

CONCLUSIONS
In our investigation we confirmed that macrovascular disease, endothelium dependent flow-mediated dilatation, ET-1, microvascular damage detected in capillaroscopy as well as angiogenic
biomarker VEGF are risk factors for DU events. Late NVC pattern evidenced a robust behavior as predictor for new DU episodes, recurrent or first event. Additionally endothelial dysfunction parameters were strong predictors of DU recurrence.

REFERENCES
How to optimize the open distal revascularization for CLI patients

ABSTRACT
To optimize short and long term results in open distal revascularization we need experienced clinical judgment, creativity, technical precision and intensive postoperative care. This is why we must invest in details related with patient evaluation and surgical technique. These investments are highly cost effective for patients and for vascular surgery practice. In this presentation we will discuss this subject using our center experience supported by a review of literature.

INTRODUCTION
Critical limb ischemia (CLI) plays a very important problem in occupancy rates in most vascular surgery departments. This is related to the increase of life expectancy, increasing proportion of diabetic patients and prolonged admissions (mostly related to the extension of foot lesions). At the same time, as the proportion of diabetic patients is increasing, the needs for distal revascularization are growing up.

In this area, open surgery remains the gold standard in which vein grafts were used 59.1% and PTFE grafts in 40.9%; 136 distalateral revascularizations and 26 patients underwent redo procedures. The mean follow-up was 16.1 months and the mean age was 72.1 years; among the patients 71.0% had diabetes and 6.2% were in hemodialysis; vein grafts were used 59.1% and PTFE grafts in 40.9%; 136 distal and 50 ultradistal bypass procedures were done. The inflow and outflow arteries are described in chart 1 and 2.

RESULTS
Analyzing the entire group, there were 24 major amputations: 7 (4.4%) during the first month and 17 during the follow-up; 30 days mortality was 3.2%.

At the end of the follow-up the total amputation rate is 15.0% (17.1% in PTFE group and 12.7% in vein group), the overall survival is 80.7% and the amputation free survival is 74.5%.

DISCUSSION
Distal and ultradistal revascularizations are the last attempt to preserve limbs. All efforts in this area contribute to preserve patient autonomy and life expectancy.

In general preserving the limb we preserve quality of life and life itself. It is important to emphasize that even patients already amputated (single limb with CLI) are too much dependent of their unique limb. For bedridden patients, lower limbs are also important as they help moving in the bed, from bed to chair and help to prevent pressure sores. That is why all of these patients deserve a strong investment in limb preservation.

In our experience, to optimize distal and ultradistal revascularization it is important:

A - Full diagnostic and prognostic evaluation
1. Clinical evaluation (general condition, renal function, extension of foot lesions, knee function).
2. Duplex scan at the admission and before surgery, executed by experienced team (inflow and outflow vessels, veins to be used as grafts).
3. High quality angiography (if renal function allows).
4. Strong investment in limb preservation (together with patient opinion).

B - Select the correct revascularization procedure
1. Without wasting time (is foot).
2. Evaluate extension of foot lesions and pay attention to tarsus, inflow and outflow arteries, vein length and diameter.
3. In the absence of a good vein choose PTFE as alternative conduit.

C - Surgical technique
1. High qualified and motivated surgical team.
2. Be liberal in more distal inflow vessels (profunda, plantar and crural). Use Esmarch’s bandage.
3. Use Esmarch’s bandage for clampless distal anastomosis (Rutherford 5 and 6). In order to optimize results we need experienced clinical judgement, creativity, technical precision and intensive postoperative care. In our experience details such as experimented and motivated surgical team, high quality duplex scan and angiography, the use of Esmarch’s bandage for clampless distal anastomosis, the use of vein adjunctives in PTFE grafts, intensive follow-up program and the liberal use of oral anticoagulation, play all together an important role in the excellence of results.

BIBLIOGRAPHY

ARTICLE
Between March 2012 and March 2016, we performed in our center 186 consecutive open distal and ultradistal revascularizations in 145 patients (113 males and 32 females) all with CLI (Rutherford 5 and 6); 15 patients (8.1%) were submitted to bilateral revascularizations and 26 patients underwent redo procedures to treat failing grafts or occlusions; the mean follow-up was 16.1 months and the mean age was 72.1 years; among the patients 71.0% had diabetes and 6.2% were in hemodialysis; vein grafts were used 59.1% and PTFE grafts in 40.9%; 136 distal and 50 ultradistal bypass procedures were done. The inflow and outflow arteries are described in chart 1 and 2.
Drug-coated balloons or stents for femoro-popliteal lesions?

Obstructive disease of the superficial femoral and popliteal artery may present clinically as asymptomatic, intermittent claudication, rest pain or trophic lesions. Up to 70% of patients have localized disease causing limiting claudication for daily activities. The clinical manifestations will depend of the lesion and the degree of co-lateralization between the deep popliteal and femoral arteries. In patients with critical limb ischemia the goal is to solve the symptoms with a single, minimally invasive intervention.

The first step is to decide who need to be treated by an interventional therapy. The patients accepted to intervention are patients with critical ischemia and claudients with severe compromise of their quality of life after failed medical therapy.

The second step is to choose between endovascular and conventional surgical revascularization. This decision must be tailored individually, in accordance to the clinical risk of the patient, the characteristics of the lesion, the availability of great saphenous vein, the opinion of the patient, the expertise of the vascular surgeon and the hospital capability.

After choosing endovascular, different options are available, simple balloon angioplasty, bare metal stenting, drug eluting balloon (DEB) angioplasty or drug eluting stenting (DES). The expected results will be influenced by the technique, type of the lesion (stenosis/occlusion, calcification) and type of arteries involved. In all of them the big issue is restenosis (DES). The expected results will be influenced by the technical expertise and improvement of the hospital capability.

The technologies are similar in terms of the drug, as presently all available eluting technology uses paclitaxel as the active drug. Several trials and registries of drug eluting balloons (DEB) in primary lesions and restenosis showed favorable results in terms of late lumen loss, restenosis rate and target lesion revascularization compared with simple balloon angioplasty 1-12.

The drug eluting stent (DES) technology also showed excellent results in the treatment relatively short femoropopliteal lesions (5.6cm) in early clinical trials 1-2. In all papers published comparing drug eluting technology versus simple balloon angioplasty, the former performed always better. The target lumen revascularization rate at 12 months with DES is 2.4-15.4% with 27-48% in the simple balloon angioplasty groups 1-2,12-19.

The DES technology is scarcer in devices with published results. The target lesion revascularization of this technology ranges between 3.8 and 9% at 12 months20,21.

There is but one trial comparing DES versus DEB, but in the infrapopliteal sector. In this area the DES technology performs better with lower 6-month target lesion revascularization rate (7.7% vs 13.6%)22.

In the femoropopliteal sector there is but one meta-analysis that presents similar odds ratio in terms of restenosis with both DEB and DES (0.99) at 12-months23.

Nevertheless, the results will depend not only of the treatment technique used, but also if the lesion is stenotic or occlusive and its degree of calcification and fibrosis. The presence of disease in the popliteal artery and the number of permeable arteries in the leg and foot are also determining factors.

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Popliteal artery atherosclerotic obstruction: endovascular options

ABSTRACT
Successful endovascular intervention for femoral-popliteal (FP) arterial disease provides relief of claudication and offers limb salvage in cases of critical limb ischemia. Technologies and operator technique have evolved to the point where we may now provide effective endovascular therapy for a spectrum of lesions, patients, and clinical scenarios. Endovascular treatment of this segment offers a significant alternative to the surgical revascularization, and may confer improved safety for a wide range of patients, not solely those deemed high surgical risk. Although endovascular therapy of the segment has historically been hampered by high rates of restenosis, emergent technolo- gies including stents with new designs, drug- eluting stents, drug coated balloons, and perhaps bioabsorbable stent platforms, provide future hope for more durable patency in complex disease. By combining lessons learned emerging technologies, we may appropriately our application of endovascular therapy to provide optimal care to our patients.

INTRODUCTION
Peripheral artery disease (PAD), atherosclerosis of the lower extremity is prevalent affecting 14.5% of the population over the age of 70 (1). The most common arterial bed affected by PAD is the femoropopliteal segment. Most of patients are as- ymptomatic, but symptomatic patients with FP disease de- scribe symptoms ranging from walking impairment to critical limb ischemia (CLI). The recent guidelines formulated in the comprehensive Ameri- can College of Cardiology/American Heart Association 2005 Practice Guidelines for the Management of Patients With Periph- eral Arterial Disease (1) and the 2007 Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) (2) favored percutaneous transluminal angioplasty as the initial pre- ferred option for endovascular treatment of symptomatic femoropopliteal arterial lesions, with bail-out stent placement after a suboptimal or failed result from balloon dilation. More recent data, however, suggest that particular for longer lesions of the superficial femoral artery (SFA), patency rates after systematic primary stenting are significantly higher than after balloon dilation and provisional stenting (3). In fact, recent data from studies on nitinol stent implantation in the SFA have reported encourag- ing patency rates of 60% to 80% at 12 months (4-6).

On the basis of the available clinical evidence, implantation of the nitinol stents into the SFA has become a widely used techni- que overall, resulting in improved clinical outcome of percuta- neous procedures. By contrast, there is still a relative uncertain- tity about the role of endovascular stenting in the popliteal artery. Because scientific reports have traditionally Combined the popliteal artery with SFA, there is little specific information available on the outcome of endovascular techniques in the popliteal artery. In fact, patients with isolated popliteal disease are largely underrepresented in the available literature. The popliteal artery, unlike the SFA, has unique characteristics because if embryologically originates from the sacral system (7,8). Most important, this arterial segment is highly exposed to biomechanical forces resulting from the repetitive flexion of the knee (9-11). Concerns have been expressed that the implan- tation of stents, particularly in the popliteal artery, may be comp- licated by an unacceptable risk of stent fracture.

Although non-stent-based-solutions for the popliteal artery may seem appealing, very few data are available and stenting may still be required in a high percentage of patients after initial angioplasty procedures (8). Only one randomized multicenter trial (CTAP): Endovascular Treatment of Atherosclerotic Pop- liteal Artery lesions: balloon angioplasty vs. primary stenting has provided 2-years results after endovascular therapy of true popliteal artery beyond the proximal (PT) segment. This trial demonstrated that primary stenting achieves superior technical success and higher primary patency compared to PTA in popli- teal lesions only if provisional stenting during the index proce- dure is considered as TLR and loss patency; provisional stenting as part of a PTA strategy had equivalent 1-year patency. No mid-term follow-up data are available comparing different treat- ment modalities in popliteal artery lesions (12).

ARTICLE
There are only a few studies that exclusively address endovas- cular treatment options for PTA lesions (8-12). Scheinert et al. performed a retrospective, single-center analysis of 101 patients treated with a novel interwoven nitinol stent (NS). Mean lesion length was 58.4 mm. Primary and secondary patency rates at 1 year were 87.7% and 95.3%, and 2-year primary and secondary patency rates of 78.1% and 91.9%, respectively (13). However, it has to be mentioned that the registry was a single-center, self- reported, and not independently controlled trial, with all the at- tendant design-specific limitations. Nevertheless, the perfor- mance of this particular stent was also investigated in another retrospective registry by Goltz et al. that included patients with critical limb ischemia. Primary and secondary patency rates at 1 year in the 34 patients eligible for follow-up were 68.4% and 79.8%, respectively, and the TLR rate was 15.5% (14).

Seman et al. Compared PTA and atherectomy in a cohort of 65 patients with PA lesions. Because of residual stenosis or flow-limiting dissection, bailout stenting was performed in 45% and 6% of patients (P=0.005), respectively; however, 1-year primary patency rates were not significantly different between the study groups (73% versus 75%) (15). In another study by Jahnke et al., 86 patients with PA lesions were treated with ei- ther conventional PTA or cryoplasty. Bailout stent placement was needed in 45% (P=0.035), and primary patency rates were 66.2% and 79.3% (P=0.10), respectively (16).

Rastan et el. (17) performed a prospective, randomized tri- al that enrolled 246 patients (158 men; mean age 72 years) who were randomly assigned to receive nitinol stent (n=119) or PTA (n=127) for lesions averaging 42.3 mm in length. The primary patency rate was significantly higher in the stent group (64.2%) than in the PTA group (31.3%, P=0.0001). TLR rates were 22.4%, respectively (P=0.0001). When provisional stent placement in the PTA arm was not considered as TLR and loss in patency, the differences prevailed between the study groups but were not significant (64.2% vs. 56.1% for primary patency, respectively; P=0.44). In this trial, about the same percentage of patients in both groups (79%) showed a ≥1 class improve- ment in the Rutherford category 2 years after the index pro- cedure. Because of the comparable secondary patency rates in both study cohorts, no significant differences in the clinical endpoints, including changes in the Rutherford category, ABI, amputation rate and mortality could be detected between the study groups. Because there were significant number of CLI pa- tients enrolled into the trial, minor amputations occurred in 6 patients and major amputations were need in 2 patients. The limb salvage rates of 99.0% in the PTA group and 98.9% in the stent group are comparable to previous SFA and popliteal artery studies. This randomized, multicenter study demonstrated that provisional nitinol stenting achieves equivalent patency in comparison with primary stenting in the treatment of obstructive popliteal artery lesions. However, the 2-year results of this trial suggest the possibility of a shift toward higher patency rates in favor of primary stenting.

As also shown in the 1-year results of ETAP trial (12, 17) long lesions of the popliteal artery were at higher risk for restenosis at 2 year follow-up target, thus lesion length > 60 mm as an independent predictor of restenosis. Considering the high bio- mechanical stress next to the knee joint, the 4.6% stent fracture rate 6% in this trial supports observations that the fractures are rare events in second-generation nitinol stents even at midterm follow-up. Notably, the same stent type was used in the RESIL- IENT trial of patients with SFA lesions; their 3-year stent frac- ture rate was 4.1%. Moreover, in both trial, no correlation could be found between the incidence of stent fractures and either restenosis or TLR (17, 18).

Evidence regarding the use of DCB in popliteal artery the INPACT, Levant I, Biolux P-1 and Pacifier trial studies no study subgroups for popliteal artery treatment so far no evidence of the efficacy of DCB in treating occlusive disease of the popliteal artery.

In our experience period January 2004 to December 2014 we performed 501 revascularization procedures femoral-popliteal sector with combined treatment of superficial femoral artery and proximal popliteal 28% of procedures and treatment of popliteal isolated from 4.2% (21 cases). In the case of isolated popliteal disease we used the first choice of treatment and self- expanding stent implantation was to be placed at the target le- sion if there was a persistent stenosis of >30% after repeated and prolonged PTA or a flow-limiting dissection.

CONCLUSION
Regarding solutions for popliteal artery treatment may per- form the following considerations:
• Little scientific information available on the outcome of endovascular techniques in the popliteal artery.
• Scientifics reports have combined the popliteal artery with the superficial femoral artery.
• Patients with isolated popliteal disease are largely under- represented in the available literature.
• PTA with bailout stenting is an acceptable treatment for the popliteal artery, a third of patients will have restenosis within one year.
• New stent designs can potentially improve the outcome. But evidence is scarce to promote primary stent implan- tation.
• DCB can potentially improve the outcome and future studies should have to show efficacity in popliteal segment
PTA or drug-eluting stents for infrapopliteal lesions?

ABSTRACT

The endoluminal therapy for lower extremity occlusive disease has extraordinary evolved in the last decade and has become the first-line treatment for critical limb ischemia patients with below-the-knee arteries involvement. The armamentarium now available for the vascular interventionist is quite considerable. Several newer technologies, mainly drug coating for balloons and stents, have emerged trying to increase the patency of the plain old balloon angioplasty. In addition, some adjunctive endovascular devices have been shown to be feasible and safe in the infrapopliteal vessels, but have failed to show superior efficacy. Meanwhile, drug eluting stents have been showing the most promising outcomes, even if it is highly probable that the lesions treated in the published series and trials do not reflect “real-world” infrapopliteal lesions, especially in diabetics. As so, its use should still be reserved for anatomically favorable lesions in selected patients.

Several newer technologies, mainly drug coating for balloons and stents, have emerged trying to increase the patency of the plain old balloon angioplasty (POBA). In addition, some adjunctive endovascular devices, including atherectomy, laser, or cryoplasty have been shown to be feasible and safe in the infrapopliteal vessels, but have failed to show superior efficacy. Meanwhile, drug eluting stents have been showing the most promising outcomes, even if it is highly probable that the lesions treated in the published series and trials do not reflect “real-world” infrapopliteal lesions, especially in diabetics. As so, its use should still be reserved for anatomically favorable lesions in selected patients.

The previous reviewed meta-analyses also demonstrated significant benefit of DES over PTA for patency, reduced re-reintervention rates, and even for diminished major amputation rates, though, these results are not specific to CLI, as most studies have also included claudicant patients in their populations. Moreover, it is again highly probable that the lesions selected for DES placement do not reflect all the “real-world” infrapopliteal lesions seen in the majority of CLI patients, specially if diabetics (eg, fewer lesions, less pronounced lesions, less calcified). Several newer technologies, mainly drug coating for balloons and stents, have emerged trying to increase the patency of the plain old balloon angioplasty (POBA). In addition, some adjunctive endovascular devices, including atherectomy, laser, or cryoplasty have been shown to be feasible and safe in the infrapopliteal vessels, but have failed to show superior efficacy when compared with conventional, much less expensive therapies, even if the limited data of the observational surgical single center series is insufficient. Specifically considering drug eluting stents (DES), there is an randomized controlled trial and four meta-analyses evaluating the results of infrapopliteal DES versus POBA and bare-metal stents (BMS).

BARE-METAL STENTS

Bare-metal stents appeared to have little clinical advantage over successful simple balloon angioplasty in below-the-knee arteries, with an obvious increased cost of the procedure. Consequently, they should probably be reserved only for bailout situations after POBA such as flow-limiting dissections, recoil and calcified lesions, to allow patency salvage of the treated artery.

Conclusion

Endovascular approach is currently considered the first choice approach for below-the-knee arteries. Newer endovascular technologies have been developed to further improve patency rates and amputation-free rates, with DES having the most promising outcomes. Nevertheless, it is still early to advocate its ubiquitous use for infrapopliteal lesions, even if the available evidence indicates that they have superior results compared to POBA, even if predominantly concerning restenosis rates. As so, they should be reserved for anatomically favorable lesions, similar to those treated on the series and studies referred to in this article.

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What’s new with bioresorbable stents?

ABSTRACT
The bioresorbable stent is a old idea, with implantation of support after revascularization on peripheral arteries. But the evaluation in the follow up of the results in special in clinical studies is unknown. We have a clinical and experimental experience, in a prospective study with evaluation of implantation in superficial femoral sector in 6 cases of patients and a study with experimental implantation in pigs to level of iliac arteries. The results of both studies are no are better in comparison with the normal bare stent.

Key words: Endovascular, surgery, stent, bioresorbable

INTRODUCTION
Light maintaining patency achieved after the level of arteries peripheral arterial system is one of the objectives in the treatment of chronic occlusive disease. Have been tested and evaluated different systems without any achieve the ideal situation, being among these metal stent implantation and performance with balls and drug-imregnated stents. Implantation bioresorbable stent, for its mechanical action and the possible pharmacological or vasoactive substances, if compounds are impregnated, shown as a suggestive idea considering that the permanence of the implanted device would have a temporary presence until its reabsorption. On the one hand substances which would slow the progression of the disease at the level of the treated artery apply, performing a development prevention and even reversal of action in the process. This implies that if the disease progresses not there are remains of the previous treatment, having a similar initial situation, without the presence of metals or other devices inside of artery.

MATERIAL Y METHODS

Experimental study
We used the pig as an experimental animal implanted Remedy™ stent of 4 mm of diameter and 2 cm length, in the iliac artery in 6 animals and six animals were implanted with a stent supported by ball Herculink™ from Abbott Company, with similar characteristics in size than the resorbable implemented in the first group, by a standard technique femoral artery at the groin open approach. The valuation has been performed at three months, from the point of view ultrasound, IVUS, angiographic and histo-pathologic exam of the stent implantation, analyzing arterial sector.

RESULTS
Clinical study
The results show a permeability in 5 of the 6 patients, developing in one total occlusion of the vessel in the group of resorbable stent implantation. In the group of metallic stent placement, vessel patency undeveloped stenotic lesions remained. In two patients they have evolved with restenosis and three patients have remained permeable to the maximum evaluation period of 12 months. Fig 2

Experimental study
The results show the development of stenosis in the implantation of the stent in three animals, remaining permeable of arteries in three other animals. The histopathology study, showed the wall artery with structural changes at the level of development of fibrotic endarterial lesion with inflammatory processes. The permeability was 5 animals in each group, however, has developed stenotic lesions in two animals in which a resorbable stent was implanted. Fig 3

DISCUSSION
The idea of intraluminal implantation of devices that perform a function and then reabsorbs, has been developed for decades without achieving to date about effective result. The tests were performed at the level of the coronary and peripheral arteries, although venues have the common denominator of being carriers blood ducts have a different pathophysiology. The problem is that absorbable devices reabsorption disappears is performed by phagocytosis or by hydrolysis or more frequently, especially in the latter case if the implanted device structure is a chemical carrier. This means that there is a biological receptor activity locally by processes reabsorptive implanted device that creates local inflammatory conditions that induce processes of tissue retraction and fibrosis, bringing the beneficial effect of reabsorption induced void.

Developed studies have shown advantages over metal, especially because the materials used in the manufacture of the latter usually have low induction of biological rejection behavior as inert.

CONCLUSION
The reabsorptive stent has not offered better results than the metal or the clinical or experimental study and together comparative can be considered worst, to develop processes of restenosis in the case of patients and arterial fibrosis in experimental evaluated in studies histological pathologies.

REFERENCES
Long TASC D lesions stenting on SFA

ABSTRACT
Subintimal recanalization, re-entry devices and retrograde puncture have made percutaneous transluminal angioplasty (PTA) a seductive choice for TASC C and D lesions in the superficial femoral artery (SFA), especially in high-risk patients.

Long-term results reported lower primary patency but similar secondary patency rates compared to endovascular repair. Moreover, symptoms were not worsened in case of endovascular failure compared to bypass surgery failure and in-stent thrombosis did not jeopardize ulcer surgery, as early endovascular failure (≥200 days) only affects 30% of implantation sites for infrainguinal bypass surgery, without affecting distal run-off.

A recent update of the TASC II concluded that although the level of evidence is low, the initial recanalization strategy in the superficial femoral artery (SFA) is commonly used. Clinical outcomes with nitinol bare metal stents compared to PTA and drug eluting stents as well as heparin-bonded grafts showed really encouraging 12-month results with a 77.6% primary patency rate, 84.7% event-free survival rate, 85.4% freedom from target lesion revascularization (TLR) rate, and only 2.1% restenosis rate. However, it is limited by lesion lengths, calcifications with the subsequent risk of dissection, and occlusions.

Bare metal stents (BMSS)
Few studies focus on endovascular treatment for long SFA lesions (>15 cm) but current reports suggest that there are statistically superior patency and clinical outcomes with nitinol BMSS compared to PTA alone. However, the majority of series chooses primary patency rates as a primary endpoint, while it is now well established that it does not always correlate to clinical outcomes.

Our center recently regrouped and harmonized the results of 3 French centers and 2 Belgian centers, in order to obtain the largest series ever published on TASC C and D femoropopliteal lesions primary stenting (42.6% of patients in critical limb ischemia (CLI) with high technical success rates (95.0%). At 12 months, survival rate was 88.2%, primary and secondary patency rates were 60.0% and 75.7% respectively with a limb salvage rate of 95.5%. TASC C lesions showed significantly higher patency rates compared to TASC D lesions (82.1% vs. 44.0%; p = 0.0009).

In the literature, 12-month primary patency rates range from 44.0 to 92.4%; the lowest values are related to the longest lesion lengths and the highest number of stents per limb. Hence, clinical status (Claudication vs. CLI), lesion length and distal runoff appear to be independent restenosis risk factors. Thus, TASC D lesions in patients suffering from claudication are highly predictive of restenosis. Up today, there is no recommendation on the use of dual antiplatelet therapy after the treatment of long SFA lesions. However, most trials prescribed this therapy for at least 1 month in the post-operative period. Incidence of stent fractures varies between 2 to 65%, with higher rates in case of long stenting or high number of stents per lesion. Their consequences, especially in terms of patency rates, are debated. Some authors have reported their absence of contribution to restenosis, while others showed higher restenosis and reintervention rates. More importantly, limb salvage rates are to be taken cautiously since some studies give a limb salvage rate per overall included limbs and others per patient, minor and major amputations are not always differentiated and in some cases data are even pooled between claudiquants and CLI patients, thereby artificially increasing the rates. Knowing this, limb salvage rates for stented TASC D lesions are around 83% at 3 years.

Drug eluting stents (DESs)
Paclitaxel-coated nitinol DESs have demonstrated superiority over standard PTA up to 5 years with ZILVER-PTX (Cook Medical). Specific reports on TASC C and D lesions showed really encouraging 12-month results with a 77.6% primary patency rate, 84.7% event-free survival rate, 85.4% freedom from target lesion recanalization (TLR) rate, and only 2.1% restenosis rate. However, it was a single arm study and randomized trials are awaited to provide further knowledge on this interesting therapeutic option surrounding the results of bypass surgery.

Covered stents
The first generation of covered stents (Viabahn®, W. L. Gore & Associates, Flagstaff, AZ) showed no advantage over BMSSs in SFA lesions. Moreover, device modification at the edges and heparin-bonding showed significantly improved primary patency rates compared to BMSSs at 24 months (69.4 vs. 40.0%; p=0.004) for TASC C and D lesions in the VIATSTAR study but without a significant impact on clinical outcomes or TLR rate.

Recent developments in SFA stents
Dynamic forces (compression, torsion, bending, lengthening, and shortening) impose significant constraints in the setting of stent implantation, potentially causing kinking, compression, fracture, and accelerated restenosis. Stent technologies are constantly improving, tending towards increased durability and conformability with better long-term patency. An interwoven nitinol stent (Supera®, IDEV Technologies, Inc, Webster, TX) was developed to confer greater radial strength, flexibility, and fracture resistance. A single-center report on 78% TASC C or D lesions showed impressive results with cumulative primary patency rates of 85.6%, 83.1%, and 76.7% and secondary patency rates of 93.8%, 93.8%, and 89.3% at 12, 24, and 36 months respectively. No stent fractures were found and long lesions >30 cm showed equivalent patency compared to lesions of 1 to 15 cm and 15 to 30 cm.

Other stent designs are actually under investigation and could continue to improve outcomes of STA stenting:
- Tigris® (Gore & Associates), with nitinol wire frame, ePTFE coating and interconnecting
- SMART Flex® (Cordis Corporation), with helical strut bands and flex bridges for flexibility while maintaining longitudinal integrity.
- or BioMimics 3D® (Varyan Medical) stents, with helical design to promote laminar flow for instance.

“Full metal jacket” or “leave nothing behind” Nowadays, there is an increased popularity of the “leave nothing behind” concept and studies on drug coated balloons (DCBs) are a point of interest with 12-month patency rates of 65.2% in the Levant II study, and 82.6% in the IN-PACT SFA study. Nevertheless, those results are in no way comparable to actual series of long lesions treated by BMS implantation, as exclusion criteria for DCB studies are often represented by CLI, chronic total occlusions of lesions >10 cm. Moreover, unsuccessful pre-dilation (remaining stenosis >70% and/or flow limiting dissections) was a strict exclusion criterion and only optimal lesions were included. The RAPID trial is actually an ongoing study on DCB treatment in long SFA lesions. However, residual stenosis or flow limiting dissections remain a major pitfall in this type of strategy. Thus, a series combining this time the use of DCBs and systematic implementation of self-expanding nitinol BMSS in long lesions showed encouraging results in reducing restenosis and TLR at 12-month.

We believe that most TASC C and D lesions require mechanical stabilization. Yet, since long-segment stent implantation has many disadvantages, especially owing the high restenosis rate, a “less metallic implant” philosophy with drug coated balloons and additional focal scaffolding could represent an optimal strategy given current therapeutic options.

CONCLUSION
Endovascular repair has already outperformed synthetic bypass grafts in terms of patency and procedure-related complications. New technologies, including new-generation nitinol stents, DESs, heparin-bonded stent grafts, and DCBs, are increasingly approaching the results of vein bypass grafts. The prospective, randomized, multicentric ZILVERPASS study is...
now enrolling and will compare bypass surgery and endovascular repair by Zilver PTX® in TASC C and D lesions in order to assess if treatment strategy should be changed by proposing primary stenting for long lesions as first-line treatment. The primary endpoint will again be the primary patency at 12 months. One may nonetheless wonder if patency rates are the right choice to evaluate this kind of revascularization. Indeed, clinical improvement with walking distance improvement for patients suffering from claudication, or rest pain abolition as well as wound healing for CLI patients, seem to be the real efficiency criteria.

REFERENCES

CAROTID ULTRASOUND: current value in stroke risk stratification

Carotid ultrasound was introduced in the 1970s after a pioneer cooperation between physicists, engineers and doctors who developed new ultrasound-based techniques to non-invasively analyse the vascular system. These methods became, in the following years, essential for the diagnosis of vascular diseases and became cardinal for the specialty of Vascular Surgery. The present techniques of vascular diagnosis based in ultrasound use the Colour-flow Duplex Scan (CDFS) which includes high definition B-mode ultrasonographic evaluation, colour-flow mapping and Doppler curves which allow velocity measurements and contributes for stenosis stratification.

After forty years of its generalization, the assessment of the carotid atherosclerotic disease by CDFS remains a central technique for screening and characterization of arterial lesions and also for therapeutic decisions and interventional indications. Carotid ultrasound can evaluate the spectrum of atherosclerotic involvement from the early stages, where the wall thickening reflects the impact of the risk factors, to the advanced stages where plaque formation (with its different phenotypes) is the consequence of the evolution of the disease.

WHICH INFORMATION IS PROVIDED BY CAROTID ULTRASOUND?

IMT measurements.

Pignoli et al. reported in 1986 the visualization of the normal arterial wall using 2D-ultrasound and described a typical pattern that includes three echogenic lines (echogenic interfaces). The inner line (echogenic) corresponds to the lumen-intima interface, the second (echolucent) to most of the media and the third (echogenic) to the interface media-adventitia. The complex of the two inner lines was designated as intima-media thickness (IMT) and became a useful parameter for the assessment of the early impact of atherosclerotic disease on the arterial wall.

The increase in IMT measurements was established as a marker of the risk factors repercussion on the arteries, as a tool to study the progression and regression of atherosclerosis and also for therapeutic management. However, IMT is a rather imprecise parameter, due to its dependence on the operator and the equipment and the introduction of digital image.
processing methods represented a significant improvement allowing a more accurate standardization of the examinations. A number of research groups focused on the identification of the “active” carotid lesion using HDU with image processing assistance and found that it is possible to select groups of atherosclerotic plaques that are associated with increased risk of stroke in the follow-up.

Presently CFDs with plaque characterization seems to be helpful for clinical decisions in the identification of subgroups of asymptomatic patients with vulnerable or ruptured lesions where the stroke risk is higher and in the selection of the best treatment approach (endarterectomy for “active” lesions and stenting for stable plaques).

IMT AND CAROTID PLAQUES AS MARKERS OF CARDIOVASCULAR AND STROKE RISK.

Risk factors for cardiovascular events

The IMT normal values are dependent on the population under study and this explains why every evaluation of “abnormality” should take into account these populational differences.

The relevance of IMT as a marker of overall cardiovascular risk was studied in several populational settings (like Finland, United States, France, Netherlands, Sweden) and in general there was a clear association between increases in the IMT and the risk of myocardial infarct and stroke with impact on the morbidity and mortality specifically in the higher intervals of IMT (Kuopio, ARIC, CHS, CAPS, MDIC, Rotterdam, Three-City, Tromso, U-IMT Project Group). The presence of plaque, or as an extreme expression of IMT, was also relevant in terms of risk prediction but its value was better in women.

Despite the general concordance in the results, these studies used methodologies that were not uniform and these pitfalls are discussed below.

IMT vs. Plaque: a continuous of the same process or different phenotypes?

Recently, some authors reported that IMT and plaque formation may not be sequential stages of the same process but, instead, different phenotypes of the atherosclerotic disease. The basis for this new concept is the recognition that, unlike IMT which usually is an “organized” thickening of the wall, plaque expresses intimal thickening with foam cells, smooth muscle cells, macrophages and a lipid-necrotic core covered by a fibrous cap where it is not possible anymore to visualize the normal appearance of a normal wall. On the other hand, IMT is more related to smooth muscle hypertrophy and hypoplasia and may be induced just by chronic hypertension and age-related arterial stiffness while plaque is the ultimate expression of the atherosclerotic process.

Methodological problems of IMT-Plaque quantification.

The IMT quantification has been used in multiple studies but a detailed analysis of the methodology reveals significant heterogeneity in the criteria used to make the assessments and to define what is normal or abnormal. These differences can be responsible for some inaccuracy in defined the role of IMT as a new risk factor of cardiovascular events. Now there is a need to develop the capacity to identify high-risk individuals.

The main issues of IMT quantification are the following:

• Imaging one side of the neck or report bilateral measurements.
• Image one segment or multiple segments.
• Measurements only in the common carotid artery or also at the bulb and internal carotid artery?
• Measures as mean from various determinations or maximum values?
• Angle of incidence and phase of the cardiac cycle in which the measurement was taken not always reported.
• IMT considered as a continuous variable or as a categorical variable (which should be the cut-off?).
• Normal values in the population studied not always available.
• Differences in defining what plaque is: a cut-off of focal IMT increase or implies disorganization of the ultrasonic geometric structure of the arterial wall?
• Is the presence of a plaque an extreme value of the IMT (the IMT being the thickness of the plaque) or is it a separate entity and the IMT should be determined out of the plaque, in a spared zone of the arterial wall?
• Populational studies do not take into account plaque characterization.

Adding IMT-Plaque to the cardiovascular risk assessment scores using traditional risk factors increases its performance?

Once the IMT and Plaque risk prediction, some studies evaluated whether it provided additional prognostic benefit above the Framingham Risk Score (FRS) which incorporates the traditional risk factor information. The conclusion was that the improvement over FRS was moderate and sometimes even basically negligible. The explanation for this finding may be related to the non-uniform methodology mentioned above and also with the concept of IMT which is closely determined by the risk factors which are also independent determinants of advanced disease and events.

STROKE RISK STRATIFICATION BASED ON ULTRASOUND FINDINGS

IMT and risk of stroke

Beyond the relationship with future occurrence of myocardial infarct, the IMT increase and carotid plaque is also related with stroke and stroke recurrence. However, the overall carotid atherosclerotic burden when assessed by 3D methods seem to be a better predictor of stroke and these developments are expected to bring new insights in the future.

Degree of stenosis and risk if stroke

The decision on the appropriate treatment (medical or intervention) for carotid stenosis is dependent on the degree of stenosis defined in major trials for the management of symptomatic (NASCET, ECST) and asymptomatic disease (ACAS, ACST). The NASCET and ECST concluded for a clear benefit with surgery (carotid endarterectomy-CEA) in symptomatic patients with >70% stenosis. In patients with <50% stenosis, CEA did not provide any benefit and in the 50-70% group only the NASCET study (and not the ECST) concluded the CEA was beneficial.

In asymptomatic patients, the ACAS trial demonstrated a reduction in the relative risk of stroke in patients submitted to CEA over best medical treatment alone, but only for lesions associated to >50% stenosis. The ACST also confirmed a benefit of CEA in asymptomatic patients for stenosis higher than 80%. Adequate quantification of the degree of stenosis is therefore mandatory, particularly concerning 50%, 60% and 70% cut-offs. Despite an overall similarity between the results of NASCET and ECST for the threshold of 70%, major methodological differences were present in both trials as the stenosis quantification method in angiographies was substantially different and led to an underestimation of stenosis in the NASCET study when compared to the ECST.

The understanding of all these discrepancies is very important as the correct quantification of the degree of stenosis remains the main parameter used for therapeutic decision. The CDS examination is able, as discussed above, to accurately quantify the degree of stenosis and continues to an essential tool to stratify the risk of stroke and the indication for medical or interventional treatment.

Plaque structure and risk of stroke

The study of surgical specimens removed by CEA demonstrated that plaques may be very different and some features, like ulceration and intra-plaque haemorrhage, were more typical of symptomatic lesions. Other observations found that the culprit lesions of some coronary and cerebral ischaemic events were associated with moderate stenosis evidencing the morphology of atherosclerotic plaques in the pathogenesis of clinical complications. Data from the ECST reported that the neurologic risk at 2 years in the medical arm of the ECST was related, beyond the degree of stenosis, with the presence of plaque surface irregularities in angiographic examinations which was found to be an independent predictor of stroke risk. Similar observations came form the NASCET trial and the ACSCPT study.

Plaque characterization emerged as a strong research field and was able to identify those lesions associated with increased clinical risk and to select subgroups of carotid lesions associated with increased neurological risk. This is particularly important in asymptomatic patients to detect the lesions more prone to cause events in the future (asymptomatic plaques prone to become symptomatic).

Among the techniques developed to identify these lesions (angiography, intravascular ultrasound and the acoustic bio-imaging methods), HDU remains one of the most important due to its easy applicability in large groups of patients. The introduction of digital image processing methods also represented a significant improvement of accuracy and capability in identify the “active” plaque.

CONCLUSION

Carotid ultrasound techniques remain essential in the definition of stroke risk and the stratification of patients for the different treatment modalities in patients with carotid stenosis.

In patients without significant obstruction it gives relevant information about the ones at increased risk for future cardiovascular events. However, its ability to improve the discriminative power over the traditional risk factor scores seems to be moderate.

REFERENCES

What defines an unstable or vulnerable carotid plaque?

ABSTRACT
A significant carotid artery plaque is one of the main risk factors for cerebral ischemic events. The carotid revascularization is indicated to prevent future cerebral ischemic events and the stratification of carotid plaque in accordance to this risk is fundamental to avoid revascularization in patients with low risk, especially in the asymptomatic ones. This paper summarizes some of the main techniques to identify the unstable or vulnerable carotid plaque. In the symptomatic patients the plaque is considered vulnerable, however the revascularization needs to be in emergency setting for crescendo symptoms or in expedite time in presence of specific clinical risk factors (ABCD2 score).

INTRODUCTION
Biological carotid plaque evolution

The carotid atherosclerotic plaque growths during a long period and it is associated with several risk factors (hypertension, dyslipidemia, diabetes, smoke). The carotid bifurcation is associated with a reduced shear stress that allows a modification of the mediolaminar layer of the plaque, with increase of lipids accumulation and inflammatory cells that stimulate the micro vessel formation within the plaque. This inflammation inside the plaque determines the formation of a lipid-necrotic core and a reduction of fibrous cap thickness. The shift of a plaque from a stable to unstable structure depends on the extension of the above elements: the neo-angiogenesis and the high inflammation levels - due to the lipid accumulation and monocyte activation - led to haemorrhagic events inside the plaque and the rupture of the fibrous cap. The exposure of the elements inside the plaque to the blood flow cause thrombotic and embolic events that led to neurologic symptoms. The current researches are focused to individualize the biological elements of "vulnerability" by clinical or imaging evaluation, to find the higher risk patients for future neurologic events in particular in asymptomatic patients.

IDENTIFICATION OF UNSTABLE OR VULNERABLE CAROTID PLAQUE
Clinical evaluation: the symptomatic status
The first element to define an unstable/vulnerable plaque is the expression of neurologic symptoms. The type of the neurologic symptoms is the clearest element of vulnerability: transient ischemic attacks (TIA) in crescendo or stroke in evolution are due to multiple thrombus-embolic events that need a prompt intervention. The single TIA and stroke are also a clear element of plaque vulnerability and the intervention is necessary to prevent the recurrence of the symptoms (i.e. of the thrombus-embolic cerebral event), however several elements can be considered to stratify the risk of neurological symptoms recurrence. The ABCD² score system (Table 1 and 2) can be a useful tool to identify patients for a prompt revascularization. The timing of revascularization is fundamental and within 2-weeks from symptom manifestation, to find the higher risk patients for future neurologic events in particular in asymptomatic patients.

Plaque contrast enhanced ultrasound (CEUS)
The carotid plaque evaluation by CEUS is a relatively new tool to identify the level of plaque micro-vascularization. The identification of plaque neovascularization was identified as a significant predictor for symptomatic plaque or histological plaque vulnerability by histology analysis by several studies. In the study of Fagiolini et al. the presence of high value of carotid enhanced correlates with the plaque vulnerability by analysis of the specimen, neurologic symptoms and the presence of cerebrovascular lesion at preoperative computed tomography. CT scan and magnetic resonance imaging (MRI)
The development of higher sensitivity of carotid CT and MRI can be lead to identify the classical element of plaque vulnerability such as ulceration, extensive lipid-necrotic core and calcification that can by stratify the degree of vulnerability of the carotid plaque similarly to the DUS evaluation but with the advantage of the objectivity of the images and the absence of the limitation that can by stratify the degree of vulnerability of the carotid plaque similarly to the DUS evaluation but with the advantage of the objectivity of the images and the absence of the limitation of the operator-dependent results of the DUS.

CONCLUSION
The identification of high-risk plaque (vulnerable or unstable) is the main element of interest in the studies about asymptomatic carotid stenosis. The majority of asymptomatic carotid artery stenosis may not benefit from revascularization procedures if treated with best medical therapy, however some asymptomatic patients in best medical therapy can develop a neurological symptom. The vulnerable plaque identification is fundamental for asymptomatic patients and several imaging techniques are available but scarcely adopted in current clinical practice. The validation of these new tools for the vulnerable plaque identification must to be one of the most important topics for future researches.
REFERENCES

Table 1: ABCD2 score

<table>
<thead>
<tr>
<th>Factors</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Age &gt;60 years</td>
<td>1</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>1</td>
</tr>
<tr>
<td>Systolic Arterial Pressure (mmHg) &gt;140 mmHg</td>
<td></td>
</tr>
<tr>
<td>e/o Diastolic Arterial Pressure &gt; 90 mmHg</td>
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<tr>
<td>Clinical Manifestations</td>
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<td>Unilateral Ipostenia</td>
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</tr>
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<td>Speech dysfunction without ipostenia</td>
<td>0</td>
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<tr>
<td>Other</td>
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<td>Symptoms Duration</td>
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<tr>
<td>&gt; 60 min</td>
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<td>10-59 min</td>
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<td>&lt; 9 min</td>
<td>0</td>
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<td>Diabetes Mellitus</td>
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Table 2: 2-day stroke risk in according to the ABCD2 score

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<th>ABCD2 Score</th>
<th>2-Day Stroke Risk</th>
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<tbody>
<tr>
<td>0-3</td>
<td>1.0%</td>
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<tr>
<td>4-5</td>
<td>4.1%</td>
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<tr>
<td>6-7</td>
<td>8.1%</td>
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</table>

Table 3: Risk for neurological event expressed in percentage in bold (48-month follow-up)

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>History of contralateral TIs or stroke</th>
<th>DWAs present</th>
<th>Plaque area (mm²)</th>
<th>GSM</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;30</td>
<td>15-30</td>
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<td>&gt;80</td>
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<td>40-80</td>
<td>13.8</td>
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<td>&lt;40</td>
<td>7.4</td>
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<tr>
<td></td>
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<td>13.1</td>
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<td>13.1</td>
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<td>&gt;80</td>
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ECST: European carotid surgery trial; TIA: transient ischemic attack; DWAs: discrete white area; GSM: gray scale measurement
Can Carotid Surgery or Stenting Prevent Dementia?

There has long been an interest in the impact of carotid surgery on cognitive function, and our own unit published a review on this subject in 1998. More recently, it has been suggested that if carotid intervention were to prevent dementia, then that would be a justification to operate on asymptomatic patients.

Carotid stenosis may cause both cerebral hyperperfusion and microembolisation, which theoretically might aggravate vascular dementia. Unfortunately it is difficult to prove causation. The risk factors for carotid stenosis and dementia are virtually identical ie hypertension, diabetes, hypercholesterolaemia and smoking. Not all patients with dementia have carotid stenosis, and in one study the incidence of carotid stenosis was the same in both patients with dementia and in age, sex and geographical area matched controls (26% vs 20%, NS). Intracranial microemboli are detected more frequently by transcranial Doppler in patients with dementia and in age, sex and geographical area matched controls (26% vs 20%, NS), 2. Intracranial microemboli are detected more frequently by transcranial Doppler in patients with dementia and in age, sex and geographical area matched controls (26% vs 20%, NS). 2. Intracranial microemboli are detected more frequently by transcranial Doppler in patients with dementia and in age, sex and geographical area matched controls (26% vs 20%, NS).

If impaired cognitive function were due to cerebral hyperperfusion, then carotid intervention might be expected to improve cognition. Unfortunately the wide variation in studies performed in this area prevents suitable meta-analysis, although most suggest no effect. Often different cognitive tests are used and there are no control groups. No account is taken of the effect of mood/depression on the test performance, although they do require active participation by the patient. Many tests of cognitive function improve with practice, thus post-operative improvement may simply be a test-retest phenomenon. Many studies showing reduced cognition after surgery relate only to the first week, where the impact of anaesthesia, analgesia and pain may confound the outcome. There are no long term studies comparing the incidence of dementia on operated patients compared to non-operated patients with carotid stenosis, although the ACST1 investigators are currently considering long-term follow-up of their original cohorts to study this.

At present, no definite conclusion can be made regarding the effect of carotid intervention on cognitive function.

REFERENCES

Importance of Mechanisms of procedural stroke in carotid revascularization: data from ICSS and ACST

WHAT IS THE KEY MESSAGE OF THIS PAPER
Stroke is a complication of carotid revascularisation that limits the benefit of the procedure in overall stroke prevention. In order to decrease the risk of revascularisation it is important to understand the mechanism of stroke. In ICSS in which symptomatic patients were treated with carotid artery stenting (CAS) or carotid endarterectomy (CEA), one third of the procedural strokes were caused by periprocedural haemodynamic disturbances. In ACST-1 the perioperative stroke rate was low. Most strokes occurred on the day of the procedure and were caused by thrombosis or thrombotic occlusion of the ipsilateral carotid artery. The analyses in these two randomized controlled trials emphasize the importance of immediate assessment of the treated carotid artery in case of the occurrence of cerebral deficit after CEA, and careful attention to applied surgical technique. Further, careful attention to blood pressure control could potentially lower the incidence of procedural stroke.

This chapter is based on two publications:
• A Hubers3; GJ de Borst3; D.J. Thomas3; F.L.Moll3; R. Bulbulia4, A. Halliday5 on behalf of ACST-1 collaborative group. The mechanism of procedural stroke following carotid endarterectomy within the Asymptomatic Carotid Surgery Trial I (ACST-I). Accepted for publication Cerebrovasc Dis 2016.

INTRODUCTION
Stroke is a feared complication of carotid revascularisation that limits the benefit of the procedure in overall stroke prevention. Large randomised clinical trials have shown that patients treated with carotid artery stenting (CAS) have a higher risk of stroke within 30 days of intervention than patients treated with carotid endarterectomy (CEA). This difference in procedural stroke is mostly attributed to an excess of minor non-disabling strokes. In these recent trials, the operative risk of CEA was significantly lower than the 7% risk of stroke or death within 30 days of treatment reported in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST). In contrast, mid- and long-term results of these randomized trials comparing CAS versus CEA show that the risk of stroke beyond the operative period is similar between both treatment arms. As a consequence, improvement in surgical and stenting techniques to further decrease procedural stroke risks would clearly increase the absolute benefit of carotid revascularisation. The main suggested causes of stroke related to carotid endarterectomy are embolization, intraoperative hyperperfusion, thrombotic occlusion of the ipsilateral or contralateral carotid artery, or hyperperfusion syndrome. The International Carotid Stenting Study (ICSS) was a large randomized controlled clinical trial that compared CAS and CEA in recently symptomatic patients. The prevalence of severe asymptomatic carotid stenosis (ACS) in the general population ranges from 0% to 3.1% and patients with this lesion are at a modest but increased risk of future ipsilateral stroke. The Asymptomatic Carotid Surgery Trial I (ACST-I) showed that CEA reduces stroke risks in patients with severe ACS younger than 75 years of age. Benefit of CEA can only be realised when
periprocedural event rates are low. Within ICSS and ACST-1 we assessed the clinical characteristics of the procedural strokes in order to better understand the nature and mechanism of these adverse events related to the recanalisation procedure.

**ICSS & ACST-1**

Outcome events

The methods applied for the analyses within the ICSS and ACST-1 trial were comparable but differed in detail. The exact protocols for these sub-analyses can be studied in the original papers by Huibers et al. Major outcome events were adjudicated by an independent endpoint committee that was unaware of treatment allocations. Stroke was defined as a rapidly developing clinical syndrome of focal disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin. Stroke was considered procedural if the event occurred at any time between initiation of the recanalisation (day 0) and day 30 after recanalisation. Stroke was classified as disabling if there was an increase in the modified Rankin score to 3 or more, attributable to the event 30 days after onset.

For the present analysis, the technical data forms completed by the surgeon or interventionalist at the time of the procedure were reviewed along with the carotid and brain imaging to determine the most likely mechanism of stroke. The technical forms recorded the techniques used for endarterectomy or stenting and also recorded complications occurring during the procedure or immediately afterwards, including events such as hypertension or asystole. In addition, the available clinical data described above to assess the likely procedural stroke mechanism according to the following classification, in ischaemic stroke: (1) carotid-embolic (2) haemodynamic (3) thrombosis or occlusion of the carotid artery (4) hyperperfusion (5) cardio-embolic (6) multiple or (7) undetermined.

Severity of stroke

Overall, the majority of strokes were classified as non-disabling (47/85 [55%]). Non-disabling strokes were more commonly seen in patients undergoing CEA (36/58 [62%]) compared to patients undergoing CEA (11/27 [41%]) (p=0.066). At day 0 of CAS, 28 of 43 (65%) strokes were non-disabling. In the CEA arm, strokes on day 0 were non-disabling in 5 of 12 (42%) patients and disabling or fatal in 7 of 12 (58%) patients (p=0.148).

Haemodynamic complications

Of the 55 patients in the CAS group 18 patients (33%) developed haemodynamic disturbances: hypertension (n=12), hypotension (n=7), new arrhythmia (n=2) and severe bradycardia (n=2). One patient developed both hypertension and severe bradycardia. Among the 22 patients in the CEA group, 11 patients (23%) developed haemodynamic disturbances: hypertension (n=6) and new arrhythmia (n=5). There was a significant difference in hypotension (p=0.012), hypertension (p=0.05) and new arrhythmia (p<0.008) between both treatment arms.

Technical difficulties

In five patients there were technical difficulties encountered during the procedure, of which 7 in the CAS arm, inability to advance the stent (1) or displacement of the stent (1) slow flow or filling defect (3) Bovine arch configuration and a tortuous carotid artery (1). In the 18 patients in the CAS group 16 (89%) had an obvious mechanism of stroke, was seen in 2 with a haemodynamic mechanism. In patients undergoing CEA, ischaemic stroke was caused by a haemodynamic mechanism (n=5), followed by cardio-embolic (4) or thrombosis or occlusion of the carotid (4). Within this surgical treatment arm three ischaemic strokes were caused by a cardio-embolism and another two by hyperperfusion. There was no statistically significant difference in ischaemic stroke mechanism between both treatment arms (p=0.479). Among the 7 haemorrhagic strokes we found hyperperfusion more often in the CAS arm (n=4) compared to the CEA arm (1). Overall, in 22 CEA patients with identified stroke mechanism, six (22%) had a postoperative stroke due to hyperperfusion.

There was a significant difference in stroke mechanism between ICSS and CEA for day 0 strokes occurring after the procedure (p<0.022). Overall, a trend was seen towards an increased rate of cardio-embolic and haemodynamic mechanism on day 0. For day 1-30 there was a trend towards an increased rate of thrombotic occlusion of the carotid (table 4). For both ischaemic and haemorrhagic strokes there was no significant difference in stroke mechanism between non-disabling and disabling.
The interobserver agreement for determination of stroke mechanism was 43/53 (81%). In 31 patients an obvious stroke mechanism was determined. Based on the available information in the remaining 22 patients we were able to determine a most likely mechanism in a further 10 patients. In the remaining 12 patients stroke mechanism remained undetermined. However, it was possible to determine the timing of onset of stroke in all cases within this analysis. Three of these out of 12 strokes (25%) with undetermined mechanism occurred intra-procedural and 9 post-procedural. In six strokes, stroke type (ischaemic or haemor- rhagic) was not determined by brain scans and are therefore excluded from the table. Out of 33 patients with ischaemic stroke, the following mechanisms were determined: thrombosis or occlusion of the carotid artery (9/33, 27%), carotid embol- ic mechanism (6/33, 18%), haemodynamic mechanism (4/33, 12%), cardio-embolic (3/33, 9%) or hyperperfusion (3/33, 9%). In the remaining 8 patients it was not possible to determine an obvious stroke mechanism. Stroke mechanism remained unde- termined in 6 patients with ischaemic stroke. Among 4 patients with haemorrhagic stroke, 3 were caused by hyperperfusion, in 1 patient stroke mechanism could not be determined. Five out of 6 (83%) strokes caused by a “carotid embolic” mecha- nism and 7 out of 9 (78%) strokes caused by “thrombosis or a thrombotic occlusion of the carotid artery” occurred on the day of the procedure. All strokes caused by hyperperfusion occurred within day 1-5.

DISCUSSION

In the present study we describe clinical characteristics and evaluated the cause of procedural strokes in symptomatic pa- tients with atherosclerotic carotid stenosis, undergoing CAS or CEA in the ICSS trial or CEA in asymptomatic patients in the ACST-1 trial. The substudy in ICSS is the first detailed report of the most likely pathophysiological mechanism of procedural stroke comparing both treatment arms in patients treated ei- ther by CAS or CEA. In the CAS group most strokes occurred on the day of the procedure, were predominately minor and most often caused by a haemodynamic mechanism. Strokes after CEA occurred more frequently in the postoperative phase, were predominately major and most often caused by hyperperfusion. Nearly all (97%) of the strokes associated with CAS were the result of infarction. In contrast, in the surgery arm a much larg- er proportion of patients (19%) suffered from a haemorrhagic stroke. Nearly all strokes occurred in the ipsilateral hemisphere; however a few strokes (6) developed in a cerebral territory not directly related to the treated carotid artery. Non-ipsilateral strokes can be addressed to catheter related disruption of the plaque in the aortic arch in patients undergoing CAS. The pos- sible mechanism for non-ipsilateral strokes following CEA is not always clear.

In ACST-1, the vast majority of strokes were ischaemic, non-dis- abling and ipsilateral to the carotid artery. More than half of the strokes occurred at the day of the procedure and were most often caused by thrombosis or thrombotic occlusion of the carotid artery.

Timing of stroke relative to the post-procedural time interval is of clinical importance in terms of understanding the underly- ing mechanism of stroke. We therefore made a clear distinction between strokes that were apparent during the procedure or at awakening versus those strokes that occurred after a symptom free interval. These analyses have several limitations. First of all, due to its retrospective character we were unable to identify the exact timing of stroke in a small number of patients. Secondly, in ICSS, and ACST-1 no standard neurological assessment by a stroke physician or neurologist was performed until 1 month post-revascularisation, although patients were seen by physician earlier than one month post revascularisation if they suffered from a procedural stroke. As a consequence, minor signs and symptoms of cerebral deficit could have been missed. Third, in a small subset of patients we were not able to conclude on the underlying mechanism of stroke. However, most of these strokes occurred on day 0, reaffirming the importance of thorough technique and close patient monitoring during the procedure and in the early post-procedural period. In future studies and to draw comparison and pooling of data, it is of importance to score procedural strokes according to the same method used in this paper. Further, in our opinion, every patient with carotid intervention related stroke should undergo imaging of his brain to exclude haemorrhage and have imaging of the carotid artery tract to affirm patency of the treated artery.

CONCLUSION

The mechanism of stroke following carotid intervention is di- rected and differs from a trial on symptomatic patients, haemodynamic disturbance showed to be the most relevant mechanism both in CAS and CEA. We identified preventable causes of stroke in one third of the patients treated with CAS and CEA. This suggests that careful attention to blood pressure control could lower the incidence of procedural stroke. In ACST-1 the periprocedural stroke rate was low. Most strokes occurred on the day of the procedure and were caused by thrombosis or thrombotic occlusion of the ipsilateral carotid artery. The analyses in these two randomized controlled trials emphasize the importance of imme- diate assessment of the treated carotid artery in case of the occurrence of cerebral deficit after CEA, and careful attention to applied surgical technique.
Emergency CEA for patients with a stroke in evolution - when is it indicated and how should it be performed?

Stroke in evolution (SIE) are defined as an acute neurologic deficit progressing within hours or days after the initial diagnosis to a greater deficit after waxing and waning of signs without disappearance of the deficit. Since 10 to 20% of all ischemic strokes are associated with a stenosis or an occlusion of the extracranial carotid artery the question arises whether an emergency treatment of an acute embolizing or occluding extracranial carotid lesion is clinically reasonable.

The organization of stroke units have considerably improved stroke care over the last decades. One key point is the availability of high quality brain imaging tools, which can visualize very nicely the mismatch between the already established ischemic core if the brain infarction and surrounding areas which are hypoperfused but not definitely lost. The area of this penumbra region occurs when blood flow is below 10 to 15 mL/100 g/min. At this point electrical communication between neurons fails to exist. If blood flow is below 10 to 12 mL/100g/min neuronal death will occur inevitably. However, any decision making in these patients is still hampered by a significant delay of a precise diagnosis, which usually lasts several hours (cerebral ischemia does not hurt). This implies that a relevant portion of patients still present with an already established major ischemic brain infarction. Due to a very high risk of cerebral bleeding, these patients are unfortunately no candidates for any revascularization option (e.g. systemic or local thrombolysis or emergency thrombectomy).

Based on very disappointing surgical experiences from the 1960s and 1970s any concept of emergency revascularization of acute occlusions of the internal carotid artery (ICA) is still considered with great scepticism. However, recent randomized trials on stent retriever systems (ESCAPE, EXTEND-IA, MR CLEAN, REVSTAT, SWIFT PRIME) have demonstrated unanimously that patients with an acute ischemic stroke could benefit significantly from systemic thrombolysis plus early endovascular thrombectomy if the procedure is done within 6 to 8 hours after the initial onset of symptoms. Key for success was an overall recanalization rate of 80% and more, regardless of whether the ICA was occluded or not.

Since the advantage of early revascularization in the treatment of ischemic strokes is evident now, the question arises whether emergency CEA still plays a role in this field. In Germany all carotid interventions (both CEA and CAS) have to be documented in a nationwide carotid registry. Out of 182,033 procedures performed between 2009 and 2014, 5,058 patients (68% male) were diagnosed with a SIE. 3,176 patients were treated by CEA (mean age 71 years) and 1,882 by CAS (documented only between 2012 and 2014, mean age 66.5 years). The in-hospital rates of any strokes and deaths were 9% in the CEA group and 11.7% in the patient group treated by CAS. The vast majority of strokes were assessed as being major (modified Rankin Scale >3 or more).

Based on own experiences with emergency CEs in more than 200 patients the following technical rules should be respected: general anaesthesia (GA) is preferred, because stroke patients are often not able to cooperate in a proper way. Whether GA has also positive effects on brain tissue is still a matter of debate. After skin incision a “no-touch-technique” of the carotid bifurcation is absolutely mandatory to prevent any intraoperative embolization. Clamping of the common carotid artery (CCA)
should be applied as soon as possible. The carotid bifurcation should be opened by a standard longitudinal incision. The systemic blood pressure should be elevated up to 180 mmHg to support the collateral blood flow and to increase the back flow from the intracranial ICA which supports the retrograde flushing of a distal ICA thrombus. Catheter thrombectomies have to be done very carefully to avoid any damage to the distal ICA (e.g. local dissection, a-v-fistula to the jugular vein). If there is any suspicion of remaining clots an on-table-angiography is recommended before removing the CCA clamp. In general a carotid shunt should be inserted as soon as possible to restore proper antegrade blood flow to the brain. After that CEA, of the embolizing/occluding lesion and patch closure can be performed in a standard fashion. In any case a completion on-table angiography in an antegrade and a lateral view is necessary. If possible, this angiography should be assessed by the operating surgeon and collaborating neuroradiologists together, to prove that the ICA and the first segments of the anterior and middle cerebral arteries are patent. If there are any doubts a selective catheter angiography should be performed immediately, possibly in conjunction with catheter thrombectomy. If emergency CEA is performed in an Hybrid OR, these optional steps could also be done intraoperatively.

In summary emergency CEA still has a place in the modern armamentarium of the treatment of carotid-related SIE. Patients with a small ischaemic core and surrounding zones of critical hypoperfusion might be proper candidates. Furthermore the following features qualify for an emergency CEA: known high-grade severely calcified ICA stenosis, floating thrombus at the carotid bifurcation, failed endovascular therapy, contraindications for thrombolysis, evidence of a patent M1 segment of the middle cerebral artery, unavailability of an endovascular specialist with neuroradiological expertise. Since neurologists have a better insight into the natural history of these patients all steps have to be done in close cooperations with stroke physicians. Further clinical trials and registries should focus on more specific clinical and morphological variables to even better define the optimal choice for open or endovascular emergency treatment of carotid-related strokes.

Burden of Venous Diseases

**ABSTRACT**

In the last years, many studies have appeared that show the prevalence of venous diseases worldwide, namely the chronic venous diseases (CVD), their impact on the quality of life of the people affected and the economic costs involved. However, in spite of these efforts more than a decade has passed and venous diseases continue to be seen by the patients and the Health Services as having lower social relief, a benign nature, little impact on people’s lives and not causing mortality. The author thinks that this mindset has to be changed so that more attention is given to the acute forms of the disease (venous thromboembolism-VTE), to reduce the impact of the CVD, which is the most significant in terms of prevalence and economic costs, but with less impact as to mortality.

It is the only possible way to make people generally aware of the social importance of this pathology and its true burden.

**ARTICLE**

In the last decade several papers have been published throughout the world, especially in the western world, where the epidemiological importance, the impact on the quality of life and the costs of the healthcare of the CVD are shown. However, these striking and significant efforts that have gradually been changing the way the health authorities and the users themselves look at this condition, have had little result, because the venous disease is still considered a minor problem today.

If this is due, on the one hand, to the gap that exists between the symptoms and the clinical manifestations in the chronic forms, on the other hand, we think we need to change the message that is passed on in terms of public health.

It is noticeable that the vascular disorders that cause mortality have more attention from the health services and that unfortunately the disease leads only to an increase of morbidity, in spite of the striking high costs involved. In our opinion, in social terms the message to demonstrate the burden of the venous diseases, has indeed to be stressed.

Venous diseases in the acute form are potentially fatal, and venous thromboembolism (deep vein thrombosis – DVT and pulmonary embolism – PE) should be emphasized when speaking of these situations and of the burden of the disease. Then we should look at the immense social and economic repercussions of the post thrombotic syndrome (PTS) and the difficulties of treatment.

Finally we must talk about the CVD, unquestionably the most common situation with the worst economic impact prognosis, but less relevant in terms of mortality. Only by giving evidence that venous diseases originate increased mortality is it possible, in the author’s vision, to get the health institutions to change their behavior patterns and increase attention to the venous pathology, which, in terms of prevalence, is comparable to arterial hypertension.

VTE, encompassing both DVT and PE, is the third most common cardiovascular condition, contributing to the global burden of the disease. VTE is the leading cause of premature death and disability among hospital-associated adverse events.

In Europe, estimates range from 650,000 to one million people experiencing either a DVT or PE each year and up to half a million die from events related to these conditions.

Age is an important risk factor for the development of DVT both in men and women. A comprehensive systematic review reported the incidence of DVT as 2-3 per 10,000 person years at age 30–49, increasing markedly to 20 per 10,000 person years at age 70–79.

Cancer is another important factor in VTE. The risk of VTE in cancer patients is increased by seven-fold, with approximately 5-20% of all cancer patients developing VTE and this is one of the main causes of mortality in this type of patients.

Another important aspect is that the incidence rates of this condition are higher for women during the childbearing ages, whereas after 45 years of age the incidence is higher amongst men.
This is a potentially preventable disease but the costs have to be well planned by the health services. The new oral anticoagulants (DOACS) can probably change the burden of this part of the pathology but undoubtedly with a marked increase in costs.

Just to have an idea, in 28 European Community countries VTE generates treatment costs ranging from €1.5 to €3.2 billion, hospital-associated costs from €0.10 to €0.97 billion and indirect costs from €0.2 to 5.1.8-11

Another important aspect was that the number of cases tends to increase despite prevention campaigns, with import future implications (fig 1).10,11

The costs of late sequels of DVT and PE are more difficult to estimate.10 To 70% of the DVT patient (depending on the PTS definition) developed symptomatology and there are 6 to 11% of severe forms. The prevalence of venous leg ulcers in these patients can change from 3-8%.1,3,6

The costs are very significant. The average cost of treating primary DVT has been reported at $6000 per DVT. PTS complications were found to add a further 75% to the cost of primary DVT, estimated at $4300.1,11

The estimated annual direct cost of PTS symptoms is $200 million; indirect costs are even more staggering, with two million workdays lost annually because of leg ulceration. However, these studies do not yet reflect the costs of endovascular treatment that many of these situations involve, which undoubtedly with a marked increase in costs.

Venous ulcers affect 1-2% of the UK population and are a cause of significant morbidity, particularly in the elderly, where the prevalence can increase up to 5%. These are a significant concern as they may be very difficult to treat with recurrence rates as high as 50% at five years, with significant social implications.1,12

Another aspect that significantly influences the burden of this disease is its progressive nature. The Bonn Vein study found that over six years, the progression of C2 disease to higher CEAP classes was 32% in patients with saphenous reflux and 19.8% for those with non-saphenous reflux.13,14

Based on the Edinburgh Vein Study, other authors conclude that nearly half of the general population with chronic venous disease deteriorated during 13 years, and almost one third with varicose veins developed skin changes of CVI, increasing their risk of ulceration. Age, family history of varicose veins, history of deep venous thrombosis, overweight, superficial reflux, especially in the small saphenous vein and with deep reflux, might influence the risk of progression.10,12

This suggests that if left untreated, a significant number of patients will move along the spectrum of venous disease from varicose veins to edema, progressing to skin changes and ultimately, ulceration. This has important implications in terms of health economic factors and healthcare planning and highlights the importance of an early prevention of the disease, because one of the most important points is that the number of procedures for varicose veins in the western countries, certainly tends to increase the economic implications.

Age and the obesity pandemic are also factors positively associated with this condition which worsen the prognosis of the disease in the next years, since an increase of the life expectancy in the developed countries is expected and consequently an increase in the number of patients with CVD.

Studies have shown that QoL, including mental health, is significantly worse in patients with varicose veins and correlates with CEAP class. This is supported by findings suggesting that QoL individuals with venous ulceration is comparable to that of patients with congestive cardiac failure, suggesting that the more advanced the class of disease, the more burdensome CVD is to the patient.13,15

In conclusion, we can say that venous diseases in their acute and chronic forms can lead to mortality and intense morbidity, with a significant socioeconomic burden that should be addressed by health services at the same level as other diseases with similar social impact.

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How to manage COs patients

ABSTRACT

Aim: To suggest how to manage a COs patient, i.e., a patient complaining of leg symptoms but presenting with no visible or palpable signs.

Methods: A research was made through Medline and Embase databases to identify articles on this topic.

Results: Very few articles were identified. Only in the recent Vein Consult Program, the COs patient was well documented regarding its prevalence, gender repartition, risk factors, investigations and treatment.

Suggestions for management of COs patients: According to the clinical status and information provided by instrumental investigations, recommendations for treatment are suggested.

INTRODUCTION

The COs patient is described in the CEAP classification which encompasses all the venous disorders as a patient presenting with venous symptoms, but without visible or palpable sign.

Aim. The aim of this article is to suggest how to manage a COs patient.

Methods. A research was made through Medline and Embase databases to identify articles on this topic, using the following keywords: COs, treatment and venous symptoms, treatment and COs, compression and COs, dietary advice and COs, venoactive drugs and COs.

Results. Very little literature was produced on this specific type of patients. The prevalence of COs patients has been evaluated in various surveys and established around 20% of adult populations in surveyed countries. The Vein Consult Program provided many data on this CEAP clinical class: in the COs population of the survey, the most frequent complaints were ‘heavy legs’, reported by 58%; ‘pain in the legs’, reported by 52%; ‘night cramps’, reported by 32%; and ‘sensation of swelling’, reported by 29%. Despite being reported less frequently by the COs patients, the symptom distribution and ranking were similar to those of symptomatic subjects in the C1 to C4 population of the survey, except that night cramps ranked higher in the COs compared with the others. The mean number of reported symptoms was lower in the COs population compared with the C4-C6 population (21.31; P <0.0001).

Among the COs patients a duplex scan investigation was performed in 14%. The majority were found to have reflux, which was mostly superficial, but an appreciable percentage (18%) had deep reflux. COs individuals were younger compared with the C1 to C6 subjects (48.6 ± 55.5 years), with a lower body mass index (25.76 ± 27.24 kg/m2). They also had fewer chronic venous disorders (CVDs) risk factors.

Of all screened women, 18.5% were at the COs stage. 22.4% of screened men. Whatever the age group, men were more likely to be assigned to the COs class of the CEAP than women, except in the 18-34 age bracket. Although the quality of life of COs subjects was impaired, they were often not considered to have CVDs by GPs (25.5% in COs; 71% in the total survey). From the data provided by the Vein Consult Program we know that COs patients are undertreated (only 13% received lifestyle advice).

In order to manage them, we suggest some recommendations for identifying, classifying and treating them.

Pathophysiological hypotheses regarding the COs patients and their management.

The fact that leg symptoms are neither specific nor pathognomonic of a venous disease makes the identification of COs patients uneasy. Not only such symptoms can stem from other diseases or disorders, but chronic venous disorders can be combined with others diseases in some patients, particularly in the older ones. The first step is to eliminate non venous disorders by relying on history, clinical examination and appropriate investigations that may detect neurologic, rheumatologic, and/or various other causes.

According to the CEAP COs patient description, two subgroups of patients can be identified: those with no anomaly on routine instrumental investigation that could be classified as COs, and the others with pathophysiologic anomalies in an anatomical territory that are then identified as COs, or COs plus CVDs.

To help care providers in this field, an international consensus meeting on venous symptoms (called SYM Vein meeting) was held with the aim to solve the ambiguities on venous symptoms. The SYM Vein document analyzed the different situations in all CEAP classes, but we will focus on COs patient.

Leg symptoms are highly likely to be venous and a venous dysfunction is identified: the management of these patients depends on the pathophysiologic detected anomaly and on the symptoms severity. If the operative treatment of the physiopathological dysfunction is minimvasive, the treatment may be performed as first step. Conversely if the symptoms are moderate and the correction of the physiopathologic disorder needs a more invasive treatment, for example iliac vein compression stenting a conservative treatment, as described in the next paragraph, should be prescribed first.

Leg symptoms are highly likely to be venous, but a venous dysfunction is not detected on routine investigation. It must be kept in mind that routine investigations including duplex scan are unable to assess great saphenous veins tributaries beyond first order saphenous tributary and we know that reflux may be present in these tributaries without great saphenous incompetence.

In this case after routine duplex scan the patient is recorded COs, although he is in reality COs, or COs and CVDs if the patient has an isolated reflux in the tributaries beyond first order saphenous tributary.

Another hypothesis is proposed by a muscovite team. According to this team, reflux in the great saphenous vein is intermittent, occurring at the end of the day or after a long time in orthostatic position. Depending on the time of investigation, the COs patient could be classified either COs, or COs plus CVDs. For symptomatic patients with no venous dysfunction identified on routine duplex scan examination, we recommend a conservative treatment using:

- lifestyle advice despite they are difficult to follow in some professional activity.
- compression therapy despite the long-term compliance to such treatment is poor.
- venoactive drugs which efficacy has been widely studied in symptomatic patients.
- if conservative treatment is insufficient to improve the patient's status, complementary instrumental investigations must be undertaken to try identify localized reflux or vein compression. From the data provided by the Vein Consult Program we know that COs patient are undertreated (only 13% received lifestyle advice).

CONCLUSION

COs patients are presently underdiagnosed and undertreated. To improve the status of COs patients, prospective studies are needed to:

- elucidate their pathophysiology.
- develop new appropriate investigations.
- determine what treatments are the most cost effective.

REFERENCES

Value Of A Diagnostic Score Ascribing Leg Symptoms To Chronic Venous Disorders In Patients Undergoing Surgery For Varicose Veins

BACKGROUND
A diagnostic score ascribing leg symptoms to chronic venous disorders has been described by Carpentier associating four combined criteria: A: heaviness; B: itching/restless syndrome/phlebalgia; C: worsened by hot/improved by cold; D: not worsened by walking), each criteria varying from 0 to 1 (total score 0-4), with a threshold level > 3 showing a high specificity and a fair sensibility for chronic venous disorders (CVD). The aim of this study was to evaluate the preoperative clinical and hemodynamic relevance of this venous symptoms ascribing score (VSAS), and its postoperative evolution in patients undergoing surgery for varicose veins.

METHOD
This prospective study has included during 7 months consecutive patients with unilateral varicose veins without deep veins insufficiency, treated by surgery. We gathered the clinical, anatomical and hemodynamic preop data of the patients. The VSAS have been routinely evaluated pre and postoperatively. The importance of the varicose reservoir (VR) was evaluated through the number of zones treated by phlebectomy (NZT).

RESULTS
We included 149 patients (123 females, 26 males, mean age 55.1 years) for whom 149 lower limbs (LLs) have been operated on. The frequency of CEAP class C2 was 95.9%, symptoms were present in 83.8% of the cases, and a reflux on the saphenous vein (SV) was observed in 65.7% of the LLs. The preop VSAS was > 3 in 68% of the cases. The surgical treatment was done by isolated phlebectomy in 88.6% of the cases and by stripping of the SV in 11.4%. Patients with a preop VSAS > 3 were significantly younger (53.23 yrs vs 59.08 yrs, p=0.016), with a more frequent CEAP class C2 (95.8% vs 55.1%, p=0.0001). A VSAS > 3 was not correlated to the presence or not of a reflux on the SV (40.6% vs 48.37% NS) or to the extension of the VR (NZT=8.1 vs 7.0 NS). The VSAS was significantly reduced after the surgery (VSAS <3: 17% at 1 month postop vs 68% in preop). A VSAS>0 has progressively increased during the first year of follow-up(47% at 1 month, 59% at 3 months and 85% at 1 year).

CONCLUSION
This scoring system showed that the preoperative symptoms were highly ascribable to CVD in patients operated on for varicose veins. After the surgical treatment the score was significantly reduced, reflecting the efficacy of the surgery for symptoms ascribing score (VSAS=0 has progressively increased during the first year of follow-up). A VSAS > 3 was not correlated to the presence or not of a reflux on the SV or to the extension of the VR (NZT=8.1 vs 7.0 NS). The VSAS was significantly reduced after the surgery (VSAS <3: 17% at 1 month postop vs 68% in preop). A VSAS=0 has progressively increased during the first year of follow-up(47% at 1 month, 59% at 3 months and 85% at 1 year).

REFERENCE

How to ensure the success of sclerotherapy?

ABSTRACT
Sclerotherapy is a safe and efficient technique in the treatment of varicose veins of the lower limbs. Historically, it has been used for over a century but it is mainly since the advent of ultrasound guidance and sclerosing foam that it has been the subject of numerous scientific studies. It has become indispensable in the therapeutic arsenal against varicose veins.

However, to ensure the success of sclerotherapy, this must be practised according to certain rules of good practice, governed by the respect of guidelines and international recommendations. We report on 10 basic rules to respect for an optimal use of sclerotherapy.

1. The respect of prerequisites and of training. The operator needs to have had good training, specific to the practice of visual sclerotherapy and ultrasound guided sclerotherapy, and therefore must also possess the necessary prerequisites (a good knowledge of venous diseases, a good practice of venous Duplex Ultrasound).

2. The planning of the injections. The direct needle puncture allows for the action of the foam on the venous walls to be optimized, given that the sclerosing agent is extremely vulnerable once in contact with blood.

3. The choice of concentration of the sclerosing product is determined according to the diameter of the venous segment to be treated, which is measured while the patient is standing up.

4. The planning of the injections. The injections are administered from the zones of reflux which are highest up, towards the distality, and from the largest varicose veins to the smallest ones.

5. The choice of concentration of the sclerosing product is determined according to the diameter of the venous segment to be treated, which is measured while the patient is standing up.

6. The volume injected is determined by the occurrence of a spasm in the target vein and by the homogenous and compact filling of this vein by the sclerosing foam (criteria of judgment: ultrasound image in B-mode, following the injection). The volumes injected are dosed and graduated so as to avoid overdosing (as opposed to administering a ‘bolus’ dose at a single point of injection).

7. The technique used. The direct needle puncture allows for optimal precision.

8. Ultrasound guidance should be used as soon as it is technically possible. Echo-sclerotherapy implies permanent ultrasound monitoring throughout the procedure, but also beforehand (during the assessment-location phase; the safety and pertinence of puncture sites), and afterwards (monitoring of the foam distribution and the occurrence of a spasm in the vein being treated).

9. The indications. These must be targeted correctly, technically, large saphenous veins (>6 mm) can be treated, but may provoke more recanalizations.
10. The follow-up on the assessment of efficiency after the foam sclerotherapy must not be performed too soon (at least 6 weeks post injection).

CONCLUSION
The optimization of the treatment of varicose veins by sclerotherapy necessitates a skilled operator, good quality foam, which is injected quickly after its manufacture and administered in the most pertinent area tactically, commencing from the top, with injections being performed according to the direct needle puncture technique and under permanent ultrasound guidance. The doses must be adapted to each given case.

BIBLIOGRAPHY

INTRODUCTION
Deep vein valve reconstruction is a kind of surgery aims to correct deep venous reflux. It deserved to patients affected by chronic venous insufficiency (CVI), not responding to conservative or with low compliance for compression and eligible for deep venous surgery.

INDICATIONS
Deep venous surgery needs an accurately patients selection and a corrected indications.
First of all, it is necessary to identify the etiology of deep reflux, since different are the results and therefore different are the indications.
According to CEAP classification, deep venous pathology recognize three classical etiologies: primary (Ep), secondary (Es) and congenital (Ec).

PRIMARY DEEP VENOUS INSUFFICIENCY
In primary deep venous insufficiency (PDVI) usually valves are present but malfunctioning and it is possible to restore valve function. Valvuloplasty technique represent the best option.
Given that PDVI is frequently associated with superficial venous incompetence, should we first treat the deep venous reflux or the superficial reflux? We know that in primary insufficiency we can obtain the competence of the deep venous system only by treating the superficial system, because the deep reflux represents, in certain cases, a functional overload of the deep system when associated with a significant superficial reflux.
However, in almost half of the patients the deep venous reflux persists after superficial venous system treatment and the result will be a varicose recurrence. To explain these different situations we must distinguish two anatomical conditions: PDVI with symmetrical cusps and PDVI with asymmetrical cusps. Infact, in presence of symmetrical insertion of the cusps, the treatment of superficial system is advisable because the reduction of deep overload is able to restore the valve competence. Otherwise, when cusps present an asymmetrical insertion, this anatomical anomaly impedes the restoration of valve competence, even reducing the deep overload. In a case, deep valve reconstruction should be consider the first indication to treatment.
In summary, in PDVI deep venous surgery is based on an accurate diagnosis of the valve morphology, because on the latter is based the strategy of treatment.

SECONDARY DEEP VENOUS INSUFFICIENCY
In secondary deep venous insufficiency (SDVI), well known as post-thrombotic syndrome (PTS), valve cusps appear usually destroyed. Superficial and perforators incompetence are frequently associated. It is fundamental not to focus the attention on superficial venous system or perforators, but to consider the venous system as a single unit, because the biggest mistakes in phlebology come from obstinacy in treating a specific sector of the vein system. PTS is a complex pathology characterized by two principal hemodynamic disorders: increased resistance to flow, due to stenosis (obstruction), intralumenal synechiae and rigidity of the venous wall, and reflux, due to valve damage. Obstruction and reflux can be isolated (1/3 of cases) or associated (2/3 of cases), in the same site or in different site. Usually obstruction is located at iliac level, while reflux involve femoro-popliteal level. First of all, it is crucial to identify or to exclude an associated obstruction, because obstacle to flow can be more significant than reflux. Obstruction should be treated first and subsequently we can consider if necessary the correction of deep venous reflux.
In summary, in SDVI the rule is to perform one action and wait. infact the hemodynamic reset will be obtained within a few months, given that the re-equilibrium of the leg is obtained through the re-equilibrium of the microcirculatory system. It is mandatory to evaluate the new obtained assessment before applying deep venous reconstructive surgery.

Who Needs Deep Vein Valve Reconstruction?

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CHIEF OF VASCULAR SURGERY
DEPARTMENT OF CARDIOVASCULAR SURGERY
HESPERIA HOSPITAL MODENA (ITALY)
CONGENITAL DEEP VENOUS INSUFFICIENCY

In congenital deep venous insufficiency (CDVI), usually identify as valve agenesia, superficial reflux and deep venous reflux are associated. Valve agenesia is a rare condition characterized by the absence of valve in the entire venous tree. It involves young patients with severe CVI and low level of quality of life. Any attempt to be radical in the ablation of varicose vein usually fails and the treatment of superficial system should be reserved to significant varicose veins with trophic lesion in the bed of the reflux. Valvuloplasty is not performable and other direct surgical options may obtain transitory results. So, we apply first two indirect actions: ensure a functional and efficacious flow by treating first the proximal obstruction frequently associated and increase the calp pump efficacy. The need to treat the deep system through a direct approach is reserved to C4b-C6 patients. Given that in PTS and in valve agenesia it is not possible to perform a direct valve repair, other surgical options such as valve transposition, valve transplant and neovale are considered.

Valve transposition consists in transposing a devalvulated segment below a valvulated one, usually employing profunda vein or saphenous vein. This technique offers good results but it is seldom applicable due to anatomic adverse conditions, such as incompetence of the profunda vein or saphenous vein.

Valve transplant aims to insert a segment with a competent valve, usually the axillary or the brachial vein, inside an incompetent axis. Adverse anatomical conditions due to discrepancy in caliber between the two segment, often make this technique unfeasible.

Neovale reconstruction aims at creating a flap by dissection of the vein wall, in order to obtain a new valve working as an antireflux mechanism. Neovale is not a standardizable technique, depending on the features of the vein wall.

PATIENTS SELECTION AND EVALUATION

The indication to treatment is based on patient selection and diagnostic protocol. Diagnostic protocol is applied in any patient eligible for deep vein reconstruction with improbable quality of life and not responding or not compliant to compression therapy. Patients selection considers C4-C6 patients presenting PTS and/or deep venous reflux and/or superficial reflux with suspected PTS and/or with undetected reflux; C3 patients where no superficial incompetence has been detected; C2 patients with multiple varicose recurrences.

Diagnostic protocol involves ultrasound (US) evaluation, air plethysmography, venography and IVUS. US is not exhaustive in detecting both reflux and obstruction and II and III level investigations are mandatory. Air plethysmography can provide functional data correlated with calf pump efficiency and parameters (VFl, EF, Rf) particularly useful in follow up evaluation. Venography and IVUS are the gold standard for detecting proximal obstruction and reflux. In cases of suspected anatomical anomalies, CT scan or MRI could be useful.

CONCLUSIONS

Deep vein valve reconstruction is a safe and efficacy surgical approach in the treatment of CVI. It requires a careful patient selection in dedicated deep venous reconstructive Center and expertise vascular surgeon.

In most cases we won’t heal the patient but simply improve his conditions. A close follow up is required for prevented and early detected secondary hemodynamic disorders which can reduce the efficacy of the first intervention.

REFERENCES


Does prescription of medical compression prevent postthrombotic syndrome after proximal DVT?

ABSTRACT

Aim: The aim of this review is to try to explain the controversy by critical analysis of published randomized controlled trials on the value of elastic compression stockings in the treatment of acute proximal deep vein thrombosis in prevention of postthrombotic syndrome.

Methods: A research was made through Medline and Embase databases to identify previously randomized controlled trials (RCTs) on the topic.

Results: We identified six RCTs including the SOX trial.

Conclusion: Prescription of elastic compression stockings for the prevention of postthrombotic syndrome is now in doubt. Immediate compression after diagnosis of acute deep vein thrombosis to prevent swelling and reduce pain, permitting early ambulation in combination with adequate anticoagulation has proven benefit, although a secondary analysis of the SOX trial refutes this belief. Continued long-term compression treatment is questioned.

Table 1 (cut)

<table>
<thead>
<tr>
<th>Article</th>
<th>Type of study</th>
<th>Patients #</th>
<th>DVT location</th>
<th>Type of compression or no compression</th>
<th>F-U duration</th>
<th>Date of initial compression</th>
<th>Adherence to treatment criteria</th>
<th>Type of assessment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brandjes DPM et al.</td>
<td>Single centre</td>
<td>194/194</td>
<td>Proximal DVT</td>
<td>No more information</td>
<td>2Y</td>
<td>2-3 W after DVT</td>
<td>Always 76% Usually 16.7% Never or occasionally 73%</td>
<td>Brandjes Scoring System</td>
<td>Moderate or Mild Severe</td>
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Abbreviations: CS=compression stockings; DVT=deep venous thrombosis; W=week; Y=year

Introduction: Until 2014 medical compression was considered necessary for preventing postthrombotic syndrome (PTS) after proximal deep venous thrombosis (DVT), but the SOX trial, a randomized controlled trial (RCT) published by a recognized epidemiologist group casted a serious doubt on this assertion.1 Aim: The aim of this review is to underline the controversy of this article by comparing its conclusion to those of previously reported RCTs on the topic.

Methods: A research was made through Medline and Embase databases to identify previously randomized controlled trials (RCTs) on the topic.

Results: Six RCTs on compression for proximal DVT to prevent PTS were identified.4,6 Their analyses according to date publication are displayed in tables 1 to 6.
Table II Ginsberg 1

<table>
<thead>
<tr>
<th>Article</th>
<th>Type of study Patients #</th>
<th>DVT location</th>
<th>Type of compression or no compression</th>
<th>F-U duration</th>
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<th>Adherence to treatment criteria</th>
<th>Type of assessment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>Single centre Asymptomatic patients with deep venous valve incompetence # 10</td>
<td>No compression</td>
<td>Global Rating questionnaire at baseline and 3-M interval. Failure was defined as: - Pain and/or swelling not improved or worse after the first 3-M treatment interval - Symptomatic deterioration during 2 successive treatment intervals - Pain and swelling not - Symptoms causing 5 or more days of work absenteeism or inability to perform housework during 3-M interval. - Veins ulcers</td>
<td>Presence of PTS 5%</td>
<td></td>
<td></td>
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<tr>
<td>Study 2</td>
<td>Single centre Asymptomatic patients with venous valve incompetence # 47</td>
<td>No compression</td>
<td>Placebo stockings with no homodynamic effect (T 3 sizes too large)</td>
<td>No information</td>
<td></td>
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<tr>
<td>Study 3</td>
<td>Single centre Asymptomatic PTS with venous valve incompetence # 35</td>
<td>No compression</td>
<td>Placebo stockings (Gr II)</td>
<td>Compressions at 3-Y</td>
<td></td>
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</tbody>
</table>

Abbreviations: AK= above knee ; BK= below knee ; CS= compression stockings ; D=day; DVT= deep venous thrombosis ; M= month ; PTS= postthrombotic syndrome; W= week ; Y= year

Table III Partsch 4

<table>
<thead>
<tr>
<th>Article</th>
<th>Type of study Patients #</th>
<th>DVT location</th>
<th>Type of compression or no compression</th>
<th>F-U duration</th>
<th>Date of initial compression</th>
<th>Compliance</th>
<th>Type of assessment</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>Partsch 4 et al</td>
<td>Single centre 33 included</td>
<td>Iliac extension 50%</td>
<td>Group I: 10 bed rest, no compression for 9 days; Group II: 26 (13 Unis 10, 13 CS) Early ambulation and compression</td>
<td>2 years</td>
<td>As soon as DVT was diagnosed</td>
<td>Up-to-the time of FU CS was worn by 79% in group 1 versus 50% in group 2+3</td>
<td>Villalta score</td>
<td>Gr 3 mean score 8.2, 21% patients score &lt;5, Gr 2+3 mean score 5.1/6/26 patients score &lt;5</td>
</tr>
</tbody>
</table>

Abbreviations: EC=Elastic compression ; DVT= deep venous thrombosis ; F-U= follow-up; PTS= postthrombotic syndrome; Y= year

Table IV. Prandoni 5

<table>
<thead>
<tr>
<th>Article</th>
<th>Type of study Patients #</th>
<th>DVT location</th>
<th>Type of compression or no compression</th>
<th>F-U duration</th>
<th>Date of initial compression</th>
<th>Adherence to treatment criteria</th>
<th>Type of assessment</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>Prandoni P et al</td>
<td>Single centre 180</td>
<td>Iliac Vein O EVF ?</td>
<td>CS 5-10mm Hg popliteal, femoral veins 20-40mm Hg # 90 vs. No compression (Gr 2, # 90)</td>
<td>4-10 days (average 1W after DVT)</td>
<td>Adherence 90% of patients wear compression 80% of daytime hours</td>
<td>Villalta-Prandoni Scale</td>
<td>Villalta score Gr 3</td>
<td>0-4: 71% 5-9: 26% 10: 1% C1: 29.1-0.84, P&lt; 0.001 Gr 2</td>
</tr>
</tbody>
</table>

Abbreviations: CTV= common femoral vein; D=day; DVT= deep venous thrombosis; W= week; Y= year

Table V. Aschwanden 6

<table>
<thead>
<tr>
<th>Article</th>
<th>Type of study Patients #</th>
<th>DVT location</th>
<th>Type of compression or no compression</th>
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<th>Type of assessment</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>Aschwanden M et al</td>
<td>Single centre 90</td>
<td>Iliac extension 91% (11.8%) Common femoral vein 26.9% Femoral vein 42.5% Iliac vein 24.3%</td>
<td>CS for 6 months</td>
<td>For all patients Exclusion C4. Then C1 CS</td>
<td>No compression</td>
<td>Gr 1 2 Y Gr 2 2 Y</td>
<td>CS for 6 months No compression or worse after the first 6-M DVT. After 6 months, adherence to compression was 91.6%</td>
<td>P=NS</td>
</tr>
<tr>
<td>Aschwanden M et al</td>
<td>Multicentre 826</td>
<td>Iliac extension</td>
<td>CS 30-40 mmHg</td>
<td>2.9 Y after DVT</td>
<td>Compression adherence 86.4% 3 or more days/W 7Y 55.6% 3 or more days/Y</td>
<td>Villalta's scale Ginsberg’s criteria VEINES-QOL/SSF-36 VENES-QOL/Sym</td>
<td>Cumulative incidence of PTS 14.7% Gr 2 P= 0.058</td>
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Abbreviations: CS= compression stockings ; DVT= deep venous thrombosis; M= month; W= week; Y= year

Table VI. Aschwanden 6

<table>
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<tr>
<th>Article</th>
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<th>Type of assessment</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Kahn SK et al</td>
<td>Multicentre 866</td>
<td>Iliac extension</td>
<td>CS 30-40 mmHg</td>
<td>2 Y after DVT</td>
<td>Compression adherence 86.4% 3 or more days/W 7Y 55.6% 3 or more days/Y</td>
<td>Villalta’s scale Ginsberg’s criteria VEINES-QOL/SSF-36 VENES-QOL/Sym</td>
<td>Cumulative incidence of PTS 14.7% Gr 2 P= 0.058</td>
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Abbreviations: CTV= common femoral vein; D=day; DVT= deep venous thrombosis; W= week; Y= year

TABLES ANALYSIS

i) The only one, which provides precise data on iliofemoral DVT is the Kahn’s article. 1 This issue is crucial as we know that this location is responsible of the most severe PTS. 12

ii) There is a consensus that Villalta score is appropriate to measure outcome after treatment, 11 but it has been used only in 3 RCTS. 6,6 Knowing that Brandjes score is similar to the Villalta one. Quality of Life (QoL) score has been used only in Kahn’s RCT. 1 The discrepancy makes it difficult to compare the outcome of the 6 RCTs.

iii) Ginsberg and Aschwanden RCTs are less informative as patients are not assessed at the time of diagnosis of DVT, but included in the studies after 12 and 6 months, respectively, but they still provide interesting information.

To summarize Brandjes and Prandoni 4 concluded that elastic compression could prevent PTS if compliance was very high, but they did not report on the number of iliofemoral DVT. Conversely Kahn 5 in her large RCT did not find any benefit using compression. However, the location of iliofemoral DVT was reported, but the compliance was low.

The Ginsberg’s trial is not easy to analyze as it is divided into three studies and it is difficult to determine if the patients wore compression the first year after initial DVT. Consequently Ginsberg’s conclusion i.e. “most patients do not have PTS 1 year after proximal DVT and do not require stockings” must be interpreted with reservations. 2

Partsch’ RCT conclusion i.e. « immediate mobilization with compression the first year after initial DVT. Consequently Ginsberg’s trial is not easy to analyze as it is divided into three studies and it is difficult to determine if the patients wore compression the first year after initial DVT. Consequently Ginsberg’s conclusion i.e. “most patients do not have PTS 1 year after proximal DVT and do not require stockings” must be interpreted with reservations. 2

DISCUSSION

As pointed in the 6th Pacific Vascular Symposium the term proximal DVT is not satisfactory as this heading encompasses any DVT from the popliteal to the inferior vena cava. 12 Obviously we cannot put in the same basket a DVT affecting the popliteal or femoral vein with the one involving the iliofemoral axis in terms of possible future development of PTS. Similarly, an isolated femoral vein obstruction cannot be compared to iliofemoral occlusion.
CONCLUSION: In the assessment of efficacy after the The available data does not allow one to draw an unambiguous conclusion about the long-term durability of pharmacological DVT that is responsible for the most severe PTS. This point is crucial, as we know that the conclusion gives better results in selected patients in terms of PTS occurrence compared to anticoagulation. Therefore, it is essential to prompt and safe initiation of full-dose anticoagulation to decrease morbidity and mortality.

Therefore, it is essential to prompt and safe initiation of full-dose anticoagulation to decrease morbidity and mortality.

The doses must be adapted to each given case.

BIBLIOGRAPHY


REFERENCES


Efficacy of DOACs in acute phase of DVT

The acute phase of venous thromboembolism (VTE) is the first 5-10 days following the presentation of a deep-vein thrombosis (DVT) or pulmonary embolism (PE), when there is an evident risk of extension, recurrence, hemodynamic compromise and death. Therefore, it is essential the prompt and safe initiation of full-dose anticoagulation to decrease morbidity and mortality.

The direct oral anticoagulants (DOACs) are shifting the setting of acute VTE management. These agents have predictable pharmacodynamics and pharmacokinetics, rapid-onset of action and shorter half-lives, with fewer drug-drug and drug-food interactions. Notwithstanding the use of DOACs should still only be used in appropriate clinical situations.

Table 1. Summary of phase 3 trials of direct oral anticoagulants for acute treatment of venous thromboembolism (from Hills and Crowther, 2015)
In the last years, 6 phase 3 trials with 27,023 patients with venous VTE have compared with the standard treatment (LMWH plus VKAs) (table 1). All DOACs demonstrated noninferiority against VKAs in the acute treatment (figure 1) and clear superiority against placebo in the extended treatment. DOACs and VKAs have similar efficacy in the treatment of acute symptomatic VTE with a significant reduction in the risks of major bleeding (intracranial bleeding, fatal bleeding, and clinically relevant non major bleeding occurred significantly less in DOACs beneficiaries). The efficacy and safety of DOACs were consistent in patients with PE, DVT, increased body weight, moderate renal chronic disease, older and patients with cancer.

Although the mean population age and the inclusion and exclusion criteria were similar across the studies, they differed in other aspects (e.g. study design and acute treatment strategies). DOACs simplify VTE treatment because they are administered in fixed doses and no routine monitoring is needed. Rivaroxaban and apixaban were tested as a single-drug approach, whereas in the dabigatran and edoxaban studies, initial bridging with parenteral agents was employed (figure 2).

DOACs, in Europe and in the United States, are approved for the treatment of DVT and/or PE and the prevention of VTE. Treatment with LMWH is still the main option for pregnancy-related VTE. Although the encouraging results in subgroup studies, further data are needed to clarify the efficacy and safety of DOACs in the management of patients with cancer and with different levels of renal impairment.

The efficacy of NOACs in inherited or acquired thrombophilias are scarce, although numerous patients with undiagnosed thrombophilia have been enrolled in phase 3 studies. We accept the use of NOACs in patients with uncomplicated thrombophilias (e.g. heterozygous factor V Leiden or heterozygous prothrombin gene mutation), but we should be more reluctant - and, in this way, require more evidence -, for instance, in the treatment of antiphospholipid syndrome (APS) or heparin-induced thrombocytopenia (HIT). Real-world studies in unselected patient populations may help to address potential gaps on the clinical use of DOACs, as well as providing support to clinicians on the applicability of clinical trial data to the patients of our daily practice.

REFERENCES
Safety profile of DOACs for long-term prevention of DVT recurrence

ABSTRACT
Venous thromboembolism (VTE) is associated with a risk of recurrence, and thus it is a common clinical challenge to decide whether anticoagulation should be stopped or continued. This review summarizes risk factors for the risk of recurrence and risk factors for bleeding. The available evidence shows that the risk of major bleeding is the decreased with the use of direct oral anticoagulants (DOACs) compared to vitamin K antagonists (VKAs). This improved benefit-risk ratio allows prolonged anticoagulation in patients considered at risk for recurrent VTE.

INTRODUCTION
Venous thromboembolism (VTE), including both deep vein thrombosis (DVT) and pulmonary embolism (PE) occurs at an incidence of 1–2.5 cases of VTE per 1,000 persons per year. Acquired and genetic risk factors are known to contribute to this risk. In patients with cancer associated thrombosis, treated with VKA the risk of recurrence is greatly increased, compared to patients without underlying cancer; at the same time, the risk for major bleeding is increased compared to non-cancer patients.

Risk factor for recurrence of venous thromboembolism
During clinical practice, the most challenging decision is whether to stop anticoagulation or continue with extended anticoagulant treatment: On one hand there is an annual risk of 1 to 12% risk of major bleeding with continued VKA therapy; on the other hand, after discontinuation, the risk of VTE recurrence is around 7 to 10% during the first 6 months after discontinuation of anticoagulant treatment, depending on underlying risk factors. The risk of recurrence is higher in patients with unprovoked, idiopathic events as compared to those with provoked VTE.

Risk for bleeding high low
Quality of OAC poor Well controlled
Residual thrombus no yes
Severe Thrombophilia no yes
Patient preference pro against
Recurrence event no yes
DVT distal proximal
Thrombus load small extended, PE
Gender female male
Cause of initial VTE Triggered No trigger
Underlying risk factor temporary permanent

Table 1: Patient characteristics to be considered for prolonging or shortening of anticoagulant treatment. Modified from 1.

Table 2: Risk factors for major bleeding with VKA treatment 1.

Risk factors for bleeding with anticoagulant treatment

**Vitamin K antagonists**
Risk factors for bleeding with anticoagulant treatment are summarized in table 2. Patients with no risk factors are considered to be at low (1.6%) risk of bleeding during the first three months of anticoagulation, while the presence of one risk factor leads to a doubling of this risk over the first three months; with two or more risk factors, the bleeding risk increases to 12.8%. The annual risk of bleeding is 0.8%, 1.6% and 6.5% with zero, one or two and more risk factors, respectively. Of note, the risk factor “would not be applicable to patients on DOAC treatment.”

Direct oral anticoagulants (DOACs)
Meta-analysis comparing DOACs to the traditional treatment of LMWH overlapping with VKA have shown that the treatment with a DOAC significantly reduced the risk of major bleeding (RR 0.67, 95% CI 0.45-0.93), and in parallel, intracranial, fatal, and clinically relevant non-major bleeding occurred significantly less in DOAC recipients.

Comparative studies of extended anticoagulant therapy have been conducted for rivaroxaban, apixaban and dabigatran with the aim of assessing efficacy and safety in long-term treatment regimens for 6-18 months beyond the initial treatment period (10-12). These placebo-controlled randomized trials showed a high efficacy of DOAC treatment without a significant increase of major bleeding compared to placebo.
With the availability of four different DOACs, a potential dose reduction over time, taking into consideration the patient’s risk of recurrence and bleeding, the treatment can be tailored to the individual patient. On the other side, the available treatment options will become increasingly more complex and possibly more confusing for both doctor and patient. It is important to become acquainted with the wide spectrum of treatment options, to provide our patients with the best benefit-risk of anticoagulant treatment.

### Outlook

With the introduction of DOACs the risk of major bleeding in the long-term anticoagulation of VTE has been significantly reduced compared to the traditional treatment with VKA, thus offering the promise of prolonged anticoagulation and protection from recurrent VTE in high-risk patients, without an increase of bleeding complications. In a new therapeutic concept is the possibility of reducing the intensity of anticoagulation with the use of a prophylactic dose of a DOAC, as has been shown successfully in the Amplify Extension Study, and is presently safe for those patients with an increased risk of recurrence. A similar concept is presently studied in the ongoing Einstein Choice Study.

**Table 3.** Phase III extended treatment studies of direct oral anticoagulants versus placebo for the long-term prevention of recurrent symptomatic venous thromboembolism

<table>
<thead>
<tr>
<th>Study</th>
<th>DOAC</th>
<th>n</th>
<th>Duration (months)</th>
<th>Primary efficacy results</th>
<th>Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>EINSTEIN EXT(10)</td>
<td>Rivaroxaban 20 mg od</td>
<td>1,986</td>
<td>6 or 12</td>
<td>Placebo: 73%</td>
<td>Placebo: 0%</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban 7.5 mg bid</td>
<td>2,482</td>
<td>12</td>
<td>Placebo: 16.6%</td>
<td>Placebo: 0.5%</td>
</tr>
<tr>
<td>AMPLIFY-EXT(11)</td>
<td>Apixaban 2.5 mg bid</td>
<td>1,343</td>
<td>6</td>
<td>Placebo: 5.6%</td>
<td>Dabigatran: 0.3%</td>
</tr>
<tr>
<td></td>
<td>Apixaban 5 mg bid</td>
<td>1,343</td>
<td>6</td>
<td>Placebo: 5.6%</td>
<td>Dabigatran: 0.3%</td>
</tr>
</tbody>
</table>

**Figure 1:** The risk of recurrence of venous thromboembolism (VTE) is particularly high during the acute phase; it remains high, particularly after idiopathic VTE. Over time, the risk gradually decreases. Accordingly, during the initial phase an intensive anticoagulant treatment is required, followed by maintenance treatment. For extended treatment, a less active anticoagulation, i.e. prophylactic dose, may be sufficient. Modified from 14.
Thrombophilia and NOACs

Thrombophilia is defined as an inherited or acquired predisposition to thrombosis. It seems particularly important in relation to venous thromboembolism (VTE), as the incidence rate of VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), is higher in patients with thrombophilia than in general population.

Inherited thrombophilias mostly considered to be associated with VTE include the deficiencies of the natural anticoagulants antithrombin, protein C and protein S, and the increase of procoagulant proteins due to the presence of F5G1691A (FVR506Q, factor V Leiden) and F2G20210A (prothrombin) gene mutations. However, there is a risk gradient for VTE, which is higher in carriers of AT, PC, and PS deficiencies and those who are homozygous or carriers of multiple abnormalities (high-risk thrombophilia) and moderate in heterozygous carriers of FV or PT20210A (mild thrombophilia). Internationally, guidelines do not consider routine testing to be justified among unselected patients with VTE. Testing should preferentially target young individuals (i.e. aged less than 50 years) with a first episode of venous thrombosis (unprovoked or provoked by minor risk factor or oestrogen-related), those with recurrent events, and those with a strong family history of VTE.

Antiphospholipid Syndrome (APS) is an important acquired thrombophilia, characterized by vascular thrombosis and/or pregnancy morbidity, in the presence of persistent circulating anti-phospholipid antibodies (aPL). When considering APS, the laboratory evaluation should include detection of Lupus anticoagulant (LA), anti-cardiolipin (ACL) or anti-β2 glycoprotein-1 antibodies. These tests must be performed twice, 12 weeks apart, and be positive on both occasions to confirm the clinical diagnosis. Primary APS affects less than about 0.5% of the general population. However, patients with APS are at an approximately 16-fold increased risk of VTE.

The management of thromboembolic disease in patients with thrombophilia is, generally, not different from that in patients without thrombophilia. The goal of therapy is to prevent thrombus extension or embolization and to prevent early and late episodes of recurrent VTE. Anticoagulation is the cornerstone of VTE treatment, usually divided in 2 phases: active treatment for 3 months and extended treatment for a longer period that has to be defined case-by-case. Traditionally, treatment occurs in 2 overlapping steps. It starts with a rapidly-acting parenteral anticoagulant, usually low-molecular-weight heparin (LMWH), which is overlapped with a vitamin K antagonist (VKA), such as warfarin. When the anticoagulant response with warfarin is therapeutic, as evidenced by an international normalized ratio (INR) between 2 and 3, LMWH is stopped and warfarin is continued as long-term therapy for a minimum of 3 months. The subsequent anticoagulation aims to prevent recurrent episodes of thrombosis, and the decision to stop or continue treatment depends on the balance between the risk of recurrence and the risk of bleeding.

Although current therapy is effective and safe, these conventional anticoagulants present several disadvantages. These limitations led to the development of new oral anticoagulants (NOACs), which reversibly inhibit specific coagulation proteins and produce a more predictable anticoagulant response. NOACs offer a convenient and attractive approach to the treatment of VTE since they are given orally in a fixed dose, do not require routine laboratory monitoring, have fewer drug-drug interactions than oral VKA and there are no dietary restrictions. Because of their rapid onset of action, the NOACs have the potential to enable all-oral regimens, which can replace parenteral anticoagulants and warfarin for active and extended VTE treatment, thereby simplifying VTE treatment.

The four main NOACs currently approved for treatment of VTE are dabigatran (a direct thrombin inhibitor), rivaroxaban, apixaban and edoxaban (all direct Factor Xa inhibitors), and all 4 agents have been compared with conventional anticoagulant therapy for the treatment of acute symptomatic VTE, in the RE-COVER I and II, EINSTEIN-DVT and PE, AMPLIFY, and Hokusai-VTE trials, respectively. Overall, NOACs are, at least, as effective as conventional treatment for VTE and are associated with less bleeding. Rivaroxaban, apixaban, and dabigatran were also evaluated for extended treatment and compared with placebo in the double-blind EINSTEIN-Extension, AMPLIFY-Extension, and RE-SONATE trials, respectively. All trials demonstrated superiority of the NOACs over placebo for the prevention of recurrent VTE and are associated with low rates of major bleeding. Dabigatran was also compared with warfarin for extended VTE treatment in the RE-MEDY trial, and demonstrated non-inferiority compared with warfarin and major bleeding was reduced by 50% with dabigatran.

The use of NOACs represents an important step forward in the management of VTE and may therefore reduce the significant burden on patients with VTE.

However, some limitations to these studies can be pointed out. Certain patient populations were not well represented, such as patients with thrombophilia. None of the clinical trials evaluating NOACs in VTE have been conducted to specifically evaluate NOACs in thrombophilia. The proportion of patients entered into each of the VTE trials evaluating NOACs with a known thrombophilia were as follows: Dabigatran trials: RE-COVER: 9.3%, RE-COVER II: 6.7%, RE-SONATE: 11.5%, RE-MEDY: 18.4%; Rivaroxaban: Rivaroxaban: EINSTEIN-DVT: 6.46%, EINSTEIN-EXT: 8.1%, EINSTEIN PE: 5.36%; Apixaban trials: AMPLIFY: 2.46%. The number of patients with thrombophilia included in clinical trials was low, not allowing an accurate evaluation of efficacy and safety of NOACs in this setting. However, the importance of this group of patients, it was performed a post-hoc subgroup analysis data from RE-MEDY, RE-COVER, RE-COVER II, and RE-SONATE trials, to investigate the efficacy of dabigatran versus warfarin in patients with and without thrombophilia (congenital or acquired) at baseline. The frequencies of VTE/VTE-related death, and of PE, were similar for dabigatran and warfarin in patients with thrombophilia who were receiving extended treatment for VTE. Treatment efficacy was not significantly affected by the presence of thrombophilia.

Antiphospholipid syndrome, as stated above, is associated with a high risk of thromboembolic disease. Clinical management of patients with APS aims mainly at avoiding thrombotic and/or obstetric recurrences. The current mainstay of the treatment of thrombotic APS is long-term anticoagulation with oral vitamin K antagonists (VKAs) such as warfarin with a target in INR of 2.5 (range 2.0-3.0) for patients presenting with a first VTE event, or a recurrent VTE event occurring whilst off anticoagulation. However, VKAs present particular problems in patients with APS. First, VKA monitoring in patients with aPL can be complicated by the variable responsiveness of thromboplastin reagents to lupus anticoagulant (LA), which may in turn potentially influence the validity of the INR in patients with APS. Second, LA detection in patients on VKAs may be problematic because of the prolonged baseline clotting time. This potentially limits the ability to diagnose APS in patients on VKAs and also to monitor APS status in those with an established diagnosis. In clinical trials, thromboembolism (venous and arterial thrombosis combined) recurred in 12.5% to 15.0% of patients with APS annually receiving dose-adjusted warfarin targeting an INR of 2 to 3, but one-half occurred when their INR was below the pre-defined target range. In a large population based observational registry of patients with APS, within 5 years, 25% developed thrombosis, despite most receiving anticoagulation. Although NOAC were apparently an attractive option for APS patients, reports on its efficacy are controversial. Among patients with acute VTE, approximately 10% have APS, and it is therefore likely that some patients with APS were included in NOACs VTE trials. However, aPL status was not systematically documented in these trials, and the results may therefore not be directly generalizable to patients with APS where there remains an unmet need.

Only a few case series with a limited number of patients with APS treated with NOACs were reported. A descriptive analysis of 26 patients for a median time of 19 months with either dabigatran or rivaroxaban, showed only one relapse. In another series of 12 patients, 2 had recurrent VDT within the first months after starting rivaroxaban. In another series of 35 patients treated with rivaroxaban, none presented with recurrent thrombotic events after a follow-up of 10 months. Another group reported a series of 8 patients with APS that failed to achieve thrombosis prevention during rivaroxaban use.

Clinical trials are being conducted to evaluate efficacy and safety of NOACs in APS patients. Rivaroxaban in Antiphospholipid Syndrome (RAPS) is a phase II/III prospective, randomized controlled non-inferiority open-label clinical trial in patients with thrombotic APS, with or without SLE, currently receiving warfarin therapy. The primary aim is to demonstrate that the intensity of anticoagulation achieved with rivaroxaban is not inferior to that of warfarin. Secondary aims are to compare rates of recurrent thrombosis and bleeding, and the QoL in patients on rivaroxaban with those on warfarin.

Another trial, named TRAPS (Rivaroxaban in Thrombotic Antiphospholipid Syndrome), will include patients with clinical manifestations of APS, including arterial events and/or pregnancy morbidity. In the TRAPS trial, only patients with triple positivity will be eligible.

Apixaban for the Secondary Prevention of Thrombosis Among Patients With Antiphospholipid Syndrome (ASTRO-APS) is a prospective, randomized, blinded phase IV study designed to estimate event rates of efficacy and safety of apixaban compared with usual care for the prevention of recurrent thrombosis among patients with APS.

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REFERENCES