The year in cardiology 2015: peripheral circulation

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Preamble

In 2015, the interest of carotid intima-media thickness to reclassify individual risk is challenged, but this vascular marker could remain interesting for younger subjects. In a middle-aged Spanish cohort, the coexistence of several peripheral plaques is frequent, with the ilio-femoral plaques having the best correlation with coronary calcium. Regarding asymptomatic carotid stenosis (ACS), multi-modality imaging presents increasing interest to depict those requiring revascularization.

The understanding of genetic subtypes of aortic diseases has improved during this year, although the lack of clinical benefits of losartan in Marfan syndrome tempered the enthusiasm triggered by previous data. Similarly, new trials failed to limit the expansion of abdominal aortic aneurysms by pharmacotherapy.

In the lower limbs, the epidemiology of amputations in Europe is better understood, highlighting the burden of lower extremities artery disease (LEAD). In claudicants, the non-inferiority of (supervised then unsupervised) exercise to revascularization of femoral artery disease (LEAD) is better understood, highlighting the burden of lower extremities artery disease (LEAD). In claudicants, the non-inferiority of (supervised then unsupervised) exercise to revascularization of femoral artery disease (LEAD) is better understood, highlighting the burden of lower extremities artery disease (LEAD).

The public awareness of venous thrombo-embolism (VTE) is low, compared with other cardiovascular conditions and needs public sensitization. High levels of D-dimers detected in a community-dwelling cohort are associated with increased risk of VTE. When VTE occurs, screening for occult cancer using abdominal/pelvic CT does not improve patient’s prognosis. In case of deep vein thrombosis (DVT) at high risk of embolization, systematic insertion of a vena cava filter in addition to anticoagulation is useless. In case of a first unprovoked pulmonary embolism (PE), the extension of anticoagulation to 24 months compared with 6 months did not improve the outcome beyond this period.

Vascular biomarkers

The interest of C-IMT is challenged in the light of recent data questioning its ability to reclassify the risk. Interestingly, however, C-IMT thickness was associated with cardiovascular events in adults aged <45 in a multicentre study spanning 16.3 years of follow-up. While the study was unable to provide information on the incremental value of C-IMT beyond conventional risk factors, it opens a window of scrutiny of this biomarker in subjects who are not yet eligible for standard cardiovascular risk screening (since cardiovascular risk scoring systems are applicable to, individuals mostly aged >40). The potential of vascular imaging is highlighted through the concept of carotid plaque burden. The Biobild Study, which followed 5808 asymptomatic adults for almost 3 years, showed that plaque burden (assessed by a novel 3D technique) improved prediction of cardiovascular events and reclassification (by 23%) beyond conventional risk factors, to a magnitude similar to coronary artery calcification.

Among other vascular markers, the interest of the ankle-brachial index has been confirmed by a study in a Spanish community-dwelling cohort, showing its abilities beyond the Framingham risk score to reclassify intermediate-risk subjects in a wide age range (35–74 years). Cost-effective analyses are warranted to define the optimal roles of these complementary techniques.

In a large cohort of men and women aged 40–54, the systemic extent of atherosclerosis in the carotid, abdominal aortic, and ilio-femoral territories by 2-/3-dimensional ultrasound and coronary artery calcification by computed tomography was evaluated. Most participants at high Framingham risk score risk had subclinical disease; interestingly enough, extensive atherosclerosis was also present in a substantial number of low-risk individuals, suggesting added value of imaging of coronary and peripheral arteries for diagnosis and prevention. Importantly, compared with aorta and carotid plaques, ilio-femoral plaques were best correlated with coronary calcium.

New mechanisms for renal dysfunction are proposed through aortic stiffening. An increase in aortic flow reversal (i.e. retrograde flow from the descending thoracic aorta toward the aortic arch), caused by aortic stiffening and impedance mismatch, reduces antegrade flow into the kidney and thereby deteriorates renal function.
In a thorough approach, vascular biomarkers for primary and secondary prevention were critically appraised, and their potential integration into clinical practice was assessed in a collaborative position paper (Table 1).6

**Carotid arteries disease**

Carotid artery duplex ultrasonography (CUS) is not recommended for syncope workup. A retrospective study in 495 patients showed that findings could barely explain syncope in 2% of cases. Nevertheless, CUS allows cardiovascular risk factors management optimization, respectively, in 57 and 33% of patients with known or newly detected atherosclerosis.7 In Europe, 21% of patients had systemic hypertension, and 31% had diabetes mellitus. Among them, 8.6% had the index carotid occluded during follow-up. Only one patient (0.3%) had a stroke at the time of the occlusion and three others (0.9%) had an ipsilateral stroke during follow-up, all before 2005. Stenosis severity or contralateral occlusion did not predict the risk of cerebrovascular events.10 Yet, it is of outmost importance to identify high-risk lesions or patients who may benefit from revascularization. In two large biobanks, the histological characteristics of 1640 carotid plaques showed that the 5-year stroke risk was related to plaque thrombus, fibrous content, macrophage infiltration, high microvessels density, and overall plaque instability.11 This association was not observed for cap thickness, calcification, intraplaque haemorrhage, or lymphocyte infiltration.

Multi-modality imaging can increasingly help the clinician to decide carotid revascularization in case of high-risk ACS. A study in 1356 patients showed that CUS imaging allows to assess plaque microvascularization, plaque echogenicity, surface irregularity, and intraplaque haemorrhage, all predictive for high risk for embolization.12 High-resolution MRI can also assess plaque components and total plaque burden, as confronted to surgically removed carotid plaques histology.13 While the availability and cost-effectiveness of MRI may be hurdles for its generalized use for cardiovascular risk assessment, its high accuracy and reliability suggest major abilities for risk stratification, which could even be potentially cost-effective.14 Finally, in patients with ≥70% carotid stenosis, (18)F-FDG PET/CT showed an increased FDG uptake and inflammation in patients with symptomatic carotid stenosis compared with asymptomatic patients.15 All these markers of high-risk plaque still need confirmation in trials assessing their use in the risk assessment strategies.

In CADISS (Cervical Artery Dissection in Stroke Study), a randomized controlled trial, Markus et al.16 found no difference in efficacy of antiplatelet and anticoagulant drugs to prevent stroke and death in patients with symptomatic carotid and vertebral artery dissection, but neurologic events were rare in both groups (Table 1). Although the low number of events (0.8%) does not allow to draw any definitive conclusion, antiplatelet treatments seem safer, more convenient, and less costly.

The long-term outcome of the 1713 patients randomized between carotid stenting (CAS, n = 855) vs. endarterectomy (CEA, n = 858) for symptomatic carotid stenosis in the International Carotid Stenting Study (ICSS) was recently published (Table 2).17 The cumulative 5-year risk of fatal or disabling stroke did not differ significantly between the stenting vs. the endarterectomy groups [hazard ratio (HR) 1.06, 95% CI 0.72–1.57, P = 0.77]. However, the occurrence of any stroke was significantly more frequent in the stenting group than in the endarterectomy group (119 vs. 72 events), with 5-year cumulative risk 15.2 vs. 9.4%, (HR 1.71, 95% CI 1.28–2.30, P < 0.001). Carotid stenting was associated with a higher procedure-related and long-term risk of non-disabling stroke than CEA. These findings should be weighed against the risk of procedural myocardial infarction, cranial nerve palsy, and access-site haematoma associated with CEA. Despite the lack of difference in Rankin scale scores between the two groups, subtle differences in functional outcome between the treatment groups cannot be ruled out. Interestingly, the MRI substudy of ICSS18 has shown that new ischaemic brain lesions discovered on diffusion-weighted imaging (DWI) after CAS were more frequent than after CEA and seem

Table 1 **Usefulness of vascular biomarkers for primary and secondary CVD prevention**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Recommendation</th>
<th>Level of evidence</th>
<th>Incremental value to risk scores</th>
<th>Ease of use</th>
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</thead>
<tbody>
<tr>
<td>Ankle-brachial index</td>
<td>Ilb</td>
<td>A</td>
<td>+++</td>
<td>+++</td>
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<td>Arterial stiffness</td>
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<tr>
<td>Carotid-femoral pulse wave velocity</td>
<td>Ilb</td>
<td>A</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Brachial-ankle pulse wave velocity</td>
<td>Iib</td>
<td>B</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Carotid ultrasonography</td>
<td>Ilb</td>
<td>A</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Central haemodynamics/wave reflections</td>
<td>Iib</td>
<td>B</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Endothelial function</td>
<td></td>
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<td></td>
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<tr>
<td>Flow-mediated dilatation</td>
<td>III</td>
<td>B</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Endothelial peripheral arterial tonometry</td>
<td>III</td>
<td>C</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

Proposed by the European Society of Cardiology working group on Peripheral Circulation and endorsed by the ARTERY Society. Adapted from Vlachopoulos et al.6 (+) fair; (++) moderate; (+++) good; (++++) very good. Modified from Ref. 6.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Type and aim</th>
<th>Challenger</th>
<th>Reference</th>
<th>n</th>
<th>Setting (indication)</th>
<th>Primary endpoint</th>
<th>Main hypothesis validated?</th>
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<tbody>
<tr>
<td>Carotid arteries</td>
<td></td>
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<tr>
<td>CADISS</td>
<td>Open: antiplatelet vs. anticoagulant drugs in extracranial carotid and vertebral dissection</td>
<td>Anticoagulant drug</td>
<td>Antiplatelet therapy</td>
<td>250</td>
<td>Extracranial vertebral and carotid dissection with TIA or stroke</td>
<td>Ipsilateral stroke or death</td>
<td>No</td>
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<tr>
<td>ICSS</td>
<td>Open: Long-term outcomes after stenting vs. endarterectomy</td>
<td>CAS</td>
<td>CEA</td>
<td>1708</td>
<td>Symptomatic carotid stenosis</td>
<td>Fatal or disabling stroke in any territory</td>
<td>No</td>
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<tr>
<td>SONOBUSTER trial</td>
<td>Blinded: Sonolysis to reduce silent brain damage after carotid revascularization</td>
<td>Sonolysis</td>
<td>Control group (Sham)</td>
<td>242</td>
<td>Patients with carotid stenosis &gt;70%</td>
<td>Reduction of symptomatic or asymptomatic brain damage on MRI</td>
<td>Yes</td>
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<tr>
<td>Illuminati et al.</td>
<td>Open: Pre-operative coronary angiography + revasc prior to CEA</td>
<td>CEA + systematic coronary angiography</td>
<td>CEA without coronary angiography</td>
<td>416</td>
<td>Patients undergoing CEA, no clinical CAD</td>
<td>Myocardial infarction</td>
<td>Yes</td>
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<tr>
<td>Aorta</td>
<td></td>
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<tr>
<td>Forteza et al.</td>
<td>Double blind: To limit thoracic aortic expansion in MFS patients</td>
<td>Losartan (up to 100 mg o.d.)</td>
<td>Atenolol (up to 100 mg o.d.)</td>
<td>140</td>
<td>MFS patients with aorta Ø &lt;45 mm</td>
<td>Maximal aorta diameter increase indexed by BSA</td>
<td>No</td>
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<td>Marfan Sartan trial</td>
<td>Double blind: To limit thoracic aorta expansion in MFS patients</td>
<td>Losartan (50 or 100 mg o.d.)</td>
<td>Placebo</td>
<td>253</td>
<td>MFS</td>
<td>Normalized change rate in aortic root diameter</td>
<td>No</td>
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<tr>
<td>AORTA trial</td>
<td>Double blind: To limit the expansion of small AAA</td>
<td>Pemirolast (10/25/40 mg/day)</td>
<td>Placebo</td>
<td>326</td>
<td>Patients with AAA 30–49 mm</td>
<td>Aortic maximal diameter rate (ultrasound)</td>
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<td>IMPROVE trial</td>
<td>Open: EVAR vs. OS for rAAA</td>
<td>EVAR-first strategy</td>
<td>OS-first strategy</td>
<td>631</td>
<td>Patients with rAAA</td>
<td>Mortality</td>
<td>No</td>
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<tr>
<td>Lower extremities artery disease</td>
<td></td>
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<tr>
<td>CLEVER (18 months)</td>
<td>Open: Supervised exercise vs. stenting vs. OMC in claudication</td>
<td>Supervised exercise</td>
<td>Stenting/OMC</td>
<td>111</td>
<td>Moderate–severe IC due to aorto-iliac lesions</td>
<td>Peak walking time at 18 months</td>
<td>Yes: Supervised exercise and stent superior to OMC</td>
</tr>
<tr>
<td>SUPERB</td>
<td>Open: Safety and efficacy of interwoven-wire nitinol stent for FP lesions</td>
<td>Intervenous-wire nitinol stent implantation</td>
<td>Performance goal for PTA based on meta-analysis</td>
<td>264</td>
<td>Rutherford class 2–4 FP lesions</td>
<td>Efficacy: 1-year primary patency; Safety: 30-day combined death, amputation, TLR</td>
<td>Efficacy: Yes; Safety: Yes</td>
</tr>
<tr>
<td>EXCITE-ISR</td>
<td>Open: excimer laser atherectomy + PTA vs. PTA for FP in-stent restenosis</td>
<td>Excimer laser atherectomy + PTA + bailout stenting</td>
<td>PTA + bailout stenting</td>
<td>250</td>
<td>Rutherford class 2–5, SFA in-stent restenosis</td>
<td>TLR at 6 months</td>
<td>Yes</td>
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<tr>
<td>RELINE</td>
<td>Open: Stent graft vs. PTA for in-stent SFA restenosis</td>
<td>Heparin-bonded stent</td>
<td>PTA + bailout stenting</td>
<td>83</td>
<td>Rutherford class 2–5, SFA in-stent restenosis</td>
<td>Primary patency at 1 year</td>
<td>Yes</td>
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<tr>
<td>LEVANT II</td>
<td>Open: DEB vs. PTA for FP lesions</td>
<td>DEB</td>
<td>PTA</td>
<td>476</td>
<td>Rutherford class 2–5 FP lesions</td>
<td>Efficacy: 1-year primary patency; Safety: death, index-limb amputation/reevaluation</td>
<td>Efficacy: Yes; Safety: Yes</td>
</tr>
<tr>
<td>IN.PACT SFA I (2 years)</td>
<td>Open: DEB vs. PTA for FP lesions</td>
<td>DEB</td>
<td>PTA</td>
<td>331</td>
<td>Rutherford class 2–4 FP lesions</td>
<td>Efficacy: 1-year primary patency; Safety: death, clinically driven TVR, major amputation, thrombosis</td>
<td>Efficacy: Yes; Safety: Yes</td>
</tr>
</tbody>
</table>
to be a marker of increased risk for recurrent cerebrovascular events. New ischaemic DWI lesions after intervention were found in 50 and 16.8% of the cases after CAS and CEA, respectively. In the CAS group, recurrent stroke or TIA occurred more often among DWI+ patients than among DWI− patients. In patients undergoing CEA, neither the presence nor the number of DWI lesions was associated with the risk of future cerebrovascular events. In a post hoc analysis, no significant difference regarding the risk of peri-procedural DWI lesions was found between patients undergoing CAS under monotherapy vs. dual antiplatelet therapy, but the study was not adequately powered to demonstrate such a difference. This trend was confirmed in another randomized controlled trial. New infarctions on MRI were found more frequently after CAS than after CEA (49 vs. 25%, P = 0.002). Lesions were significantly greater after CAS. Cognitive tests showed similar performances between the two groups.

To avoid brain lesions during revascularization, cerebral sonolysis has been proposed (Table 2). This is a new method for acceleration of artery recanalization already judged as effective during the management of acute stroke. The SONOBUSTER trial randomized 242 patients undergoing CEA or CAS because of >70% internal carotid stenosis between sonolysis and a sham group. New post-procedural brain ischaemic lesions detected on MRI were significantly less frequent in the sonolysis group than in the control group (31 vs. 47%, P = 0.018). Sonolysis and CEA were identified as independent predictors of reduced brain ischaemic risk. A larger multicentre trial is necessary to confirm these engaging results.

A systematic review tested the hypothesis of an improvement in procedural risk following CAS over time. This study comes after some industry-funded registries in patients qualified as high risk for CEA, suggesting significant reduction in procedural risks after CAS. The authors reviewed large administrative registries involving >1 500 000 procedures. Carotid stenting was associated with non-fatal stroke or death rates exceeding the recommended 3% threshold risk in 9/21 registries involving ‘average risk for CEA’ asymptomatic patients. In symptomatic patients, CAS was associated with post-operative death or non-fatal stroke rates exceeding 6% in 13/18 registries and 10% in 5/18 registries involving ‘average risk for CEA’ symptomatic patients. Three registries reported post-operative death or non-fatal stroke rates for CAS in ‘high risk for CAS symptomatic patients’ ranging from 7.9 to 14.4%, definitely worse than those reported by centres of excellence for CAS. In these three registries, CEA was performed with a procedural death or non-fatal stroke rates ranging from 1.5 to 7%. These contemporary data suggest that post-operative death or non-fatal stroke rates following CAS remain significantly higher than after CEA and often exceed accepted thresholds, with no evidence of sustained decline in procedural risk after CAS.

Regarding the coronary risk of patients undergoing CEA, the long-term results of a randomized controlled trial assessing the benefits of systematic pre-operative coronary angiography before elective CEA in patients with unknown coronary artery disease showed that systematic coronary angiography prior to CEA followed by selective PCI or CABG significantly reduced the incidence of late MI (HR = 0.078, 95% CI 0.024–0.256, P < 0.001) and improved long-term survival compared with the group not receiving a systematic coronary angiography. These results are in contradiction with
Aortic diseases

The interaction between the aorta and cardiac diseases are of increasing interest. Transcatheter aortic valve replacement offers a unique model to reveal the reciprocal interaction of left ventricular function and arterial elastic properties. Valvular replacement acutely increases waves travelling from the left ventricle towards the periphery (previously ‘tapered’ by the valvular obstruction), confronting the arterial tree to higher systolic and pulse pressure. This leads to passive increase in arterial stiffness, which, in turn, limits the procedure’s acute afterload relief and calls for medical therapy supplementation aiming at arterial de-stiffening. Other data establish a relationship between aortic stiffening and the use of vitamin K antagonists (VKA). In patients with renal failure under haemodialysis, those under VKA showed increased aortic stiffening, and those without VKA had increased stiffening in case of poor vitamin K status. The VivaK trial is launched to assess whether vitamin K supplementation in these patients is able to slow aortic stiffening.

Major steps on the understanding and management of aortic disease related to genetic disorders have been taken; ACTA2 (actin, α-2, smooth muscle, aorta) is now known as the most frequently mutated gene causing familial thoracic aortic aneurysms and dissection, responsible for 12–21% of familial cases. The other manifestations of this mutation include livedo reticularis, iris flocculi, and patent ductus arteriosus in some members. In a large series of individuals with ACTA2 mutations (277 cases), the cumulative lifetime risk of an aortic event is estimated at 76%. Events are mostly aortic dissections (type A in two-thirds), with 25% mortality. This study depicted some mutations (disrupting p.R179 and p.R258) as at lower risk than average.

Data from in vitro to clinical studies suggested beneficial effects of angiotensin receptor blockers to slow aneurysmal evolution of the thoracic aorta in the Marfan syndrome, but the enthusiasm has been tempered after the publication of two trials with negative results (Table 2). The first compared losartan vs. atenolol to slow ascending aorta enlargement in 140 patients with Marfan syndrome equally randomized between the two groups. After 3 years, the progression rate did not significantly differ between the two groups. Similarly, the Marfan Sartan trial failed to demonstrate the superiority of Losartan over placebo to limit aortic growth and avoid clinical events in these patients over 3 years, despite an average systolic blood pressure drop of 5 mmHg. The results from a consortium set-up to collect data from all controlled trials on angiotensin receptor blockers in Marfan patients are awaited.

In the German Registry for Acute Type A Aortic Dissection, the prognostic consequences of pre-operative malperfusion (one-third of cases) has been highlighted. The 30-day mortality, at 12% in the absence of any malperfusion, increased almost by 10% for each number of systems affected, reaching 43% when three systems were involved. Further studies are needed to delineate anatomic patterns for a more accurate risk stratification of patients with aortic dissection.

A collaborative registry on aortic iatrogenic dissection during interventional coronary angiography prior to vascular surgery and need further confirmation.
confirmed through the analysis of data from Medicare beneficiaries between 2001 and 2008.42

There is an increasing interest for the use of EVAR in case of ruptured AAA. However, the 1-year results of the multicentre randomized IMPROVE trial had not shown any superiority of EVAR-first strategy over surgery OS in case of ruptured AAA. (Table 2).43 There were indications that quality of life and cost were in favour of endovascular-first strategy. Among the morphological characteristics of the lesion, shorter necks were associated with increased mortality in case of OS and disqualified EVAR.44 The results of this trial are supported by a registry of all consecutive ruptured AAA cases \( (n = 467) \) in 10 hospitals of the Amsterdam area between 2004 and 2011. During a follow-up of 5 years after discharge, the survival rates were similar (EVAR: 36%, OS:38%, \( P > 0.2 \)).45 The rates of freedom from re-intervention were 66% for EVAR and 90% for OS, although the difference was not significant after adjustments to confounding factors. Nonetheless, it should be emphasized that the use of EVAR for ruptured AAA is limited in the real world, needing 24-h access to an expert team, and OS remains yet the treatment of reference in this life-threatening situation.

**Lower extremities artery disease**

A retrospective, cross-sectional study among 3406 patients undergoing endovascular therapy showed significant association of age, male gender, diabetes, and renal failure with the likelihood of critical limb ischaemia (CLI). Smoking was associated with intermittent claudication rather than CLI.46

Non-invasive imaging is the method of choice to assess LEAD. The analysis of the Medicare Part B databases between 2002 and 2013 showed an increased utilization of MR angiography (MRA), CT angiography (CTA) but also subtraction angiography (DSA) from 2002 to 2006. Among radiologists the rate of DSA decreased by 75% from 2002 to 2013. The overall utilization of DSA has risen sharply among cardiologists and surgeons because of interventional procedures.47

The epidemiology of amputations is poorly studied even in Europe. From 2006 to 2012, lower limb amputations were identified among 80 German statutory health insurance companies covering 4 million individuals nationwide.48 The rates of at least 1 lower limb amputation were stable over time at 0.04% in the entire population. In 2012, the incidence for minor amputation was 0.03%.

Extrapolated to the German population in 2012, there were 49 150 cases and 32 767 persons with amputations. A study in the whole population in Hungary had not shown any significant evolution in the incidence of amputations between 2004 and 2012.49 During this period, 76 798 lower limb amputations occurred, including 38 200 major amputations. The major lower limb amputation incidence for the overall period was 42.3/100 000 in the total population and 317.9/100 000 in diabetic population. The epidemics of LEAD-related amputations should be considered as major as other cardiovascular events. Appallingly, in many cases, amputations are still performed without pre-operative assessment of the vasculature, as pointed out by the analysis of data from the largest public health insurance in Germany, highlighting the poor adherence to guidelines (Figure 1).50

Intermittent claudication (IC) caused by aorto-iliac disease can be managed with supervised exercise, unsupervised exercise, optimal medical therapy, and revascularization. The 18-month results of the CLEVER trial showed that a 6-month program of supervised exercise followed by unsupervised exercise is as effective as stenting in improving walking ability, although ABI values and quality of life measures are better after stenting (Table 2).51

The results of bare nitinol stent implantation in the femoropopliteal arteries are still jeopardized by the high rate of in-stent restenosis; very promising results were reported for an interwoven nitinol wire stent in the SUPERB trial, a prospective, multicentre, single-arm study.52 Primary patency and freedom from target lesion revascularization (TLR) at 12 months were 78.9 and 88.9%, respectively, in the absence of stent fractures. Considering the lack of efficacy of simple balloon angioplasty (PTA) for the treatment of femoro-popliteal in-stent restenosis, interesting data from two recent small RCTs should be highlighted. The EXCITE-ISR trial randomized 250 patients 2:1 to adjunctive laser atherectomy or PTA with bailout stenting; freedom from TLR at 6 months was 78.1 vs. 68.7% (\( P < 0.05 \)) in favour of atherectomy (not considering bailout stenting as a TLR).53 However, the advantage was limited to the perioperative period. Similarly, the RELINE trial showed that the use of heparin-bonded stent graft yielded a 1-year primary patency of 74.8 vs. 37.0% for PTA with bailout stenting (\( P < 0.001 \)) and a freedom from TLR of 79.9 vs. 42.2% (\( P < 0.001 \)).54

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**Figure 1** Vascular procedures in amputated patients. In a subgroup analysis, patients with critical limb ischaemia (Rutherford Categories 4, 5, and 6) who underwent an amputation during index hospitalization were selected. From these 4298 patients, 45% \( (n = 1917) \) underwent a surgical and/or endovascular revascularization procedure (Rx) during index hospitalization (in part in combination with a diagnostic angiography). Another 11% \( (n = 494) \) received a diagnostic angiography (Angio). But 44% \( (n = 1887) \) received neither angiography nor revascularization. From these latter 1887 patients, 316 patients had received a revascularization or a diagnostic angiography during the 2 years before amputation, but the remaining 1571 patients (37%) with critical limb ischaemia were amputated without any revascularization or diagnostic angiography neither during index hospitalization nor 2 years before. Reprinted with kind permission from Reinecke et al.50

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**Table 2** Proportion of patients undergoing endovascular therapy among amputated patients. The year in cardiology 2015

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**Table 2** Proportion of patients undergoing endovascular therapy among amputated patients. The year in cardiology 2015
efficacy of these treatment options for in-stent restenosis should now be tested against the use of drug-eluting balloons (DEB).

In 2015, a few RCTs were published comparing DEB with PTA for femoro-popliteal arteries. The largest RCT is the LEVANT-II, which randomized in a 2:1 ratio 476 patients in Rutherford class 2–5 to Lutonix DEB or PTA; the study met the primary objectives both for efficacy (1-year primary patency 65.2 vs. 52.6% for DEB and PTA, respectively; \( P = 0.02 \)) and safety (freedom from the composite of perioperative death and 12-month index-limb-related death, index-limb amputation, and reintervention 83.9 vs. 79.0%; \( P = 0.005 \) for non-inferiority). However, there were no significant differences in TLR (12.3 vs. 16.8%, \( P = 0.21 \)) and functional outcomes, possibly because of the low rate of TLR in the PTA arm, deriving from the exclusion of lesions likely to require stenting after initial predilatation. So far, the LEVANT-II is the largest and best-designed RCT on DEB, with blinding of patients, follow-up investigators, and core laboratory evaluators. This trial strengthens the advantages of DEB over PTA reported at 1 year in the IN.PACT SFA I trial, presented in the last year review,\(^\text{56,57}\) late confirmed at 2 years in terms of primary patency (78.9% vs. 50.1%; \( P < 0.001 \)), TLR (91 vs. 28.3%; \( P < 0.001 \)), and vessel thrombosis (1.5 vs. 3.8%; \( P = 0.24 \)).\(^\text{58}\) Recently, the 5-year results of the THUNDER trial, the first pivotal RCT on DEB, were published;\(^\text{59}\) although underpowered for the assessment of long-term clinical outcomes, this study showed for the first time the persistence of the advantage of DEB over PTA in terms of freedom from TLR (79 vs. 44%; \( P = 0.0005 \)), in the absence of drug-related local vessel abnormalities. The consistency of the results supports the use of DEB over PTA when indicated for femoro-popliteal disease.

For infrapopliteal arteries, the EXPAND trial (Table 2) compared primary nitinol BMS implantation to PTA with bailout stenting in patients with severe IC or CLI.\(^\text{60}\) This small RCT did not reach the planned sample size owing to slow enrolment and did not show statistically different clinical outcomes at 1 year, in terms of sustained clinical improvement (increase in Rutherford category ≥ 2: 74.3 vs. 68.6%, \( P > 0.2 \)), freedom from TLR (76.6 vs. 77.6%, \( P > 0.2 \)), and amputation (8.9 vs. 13.2%, \( P > 0.2 \)).

**Venous thrombo-embolism**

Public awareness of VTE including DVT and PE is low (44 and 54%, respectively), and lower than that of heart attack (88%), stroke (85%), or hypertension (90%).\(^\text{61}\) This underlines the need for campaigns to raise public awareness of VTE and reduce the burden of a largely preventable disease.

D-dimer (DD) testing is a useful tool in the diagnostic work-up for acute VTE, particularly because of its sensitivity, since a negative DD test formally rules out VTE. A recent large population-based prospective study showed that higher basal plasma DD levels in the general population were associated with greater risk of VTE risk over a median of 17 years follow-up (HR 3.5, highest vs. lowest DD quintile for the first 10 years of follow-up). Elevated DD may represent a marker of contributors to thrombosis, although elevated DD are not specific to VTE.\(^\text{62,63}\) Atrial fibrillation (AF) also seems to confer an increased VTE risk. In a large population-based cohort study, VTE risk was increased eight-fold in the first 6 months following AF diagnosis (HR 8.44), this was true for both DVT and PE. However, beyond 6 months after AF diagnosis, only the risk of PE remained significantly higher. Intra-atrial stasis and thrombus formation, haemodynamic changes, or delays in initiation of therapy after diagnosis may partly explain the increased VTE risk in this specific population.\(^\text{64}\)

There is no clinically significant benefit of screening for occult cancer using CT of the abdomen and pelvis in patients with a first unprovoked VTE. The multicentre, randomized, controlled SOME trial compared the utility of systematic abdominal and pelvis CT scan on top of conventional screening based on basic blood testing, chest radiography, and screening for breast, cervical, and prostate cancer.\(^\text{65}\) Among 854 patients, 3.9% had a new diagnosis of cancer between randomization and 1-year follow-up. There was no significant difference between the two groups in terms of mean time to cancer diagnosis or cancer-related mortality.

The utility of inferior vena cava filters (VCFs), retrievable or not, appears to be limited. This has been addressed by the multicentre, randomized, controlled PREPIC-2 study,\(^\text{66}\) which included patients with PE and lower limb DVT and presenting a high risk of recurrence (Table 2). In the group of patients assigned to filter implantation in addition to anticoagulation, VCF was removed after 3 months. There was no significant difference in PE recurrence rate, symptomatic DVT, major bleeding or death compared with patients treated with anticoagulation alone.

In a retrospective cohort of VTE patients receiving long-term warfarin for secondary prophylaxis, bridge therapy prior to surgery or invasive procedures was associated with a 17-fold higher bleeding risk during warfarin interruption. No difference in VTE recurrence rates was observed between patients with vs. without bridge therapy. In most cases, bridge therapy may be unnecessary, and studies identifying patients at high risk of VTE recurrence are needed.\(^\text{67}\)

Optimal anticoagulant therapy duration remains debated. A recent multicentre, randomized trial, PADIS-PE, evaluated the impact of an additional 18 months treatment with warfarin vs. placebo, after an initial 6 months non-randomized treatment period following a first episode of unprovoked PE (Table 2).\(^\text{68}\) During the additional 18 months of therapy, the VTE recurrence rate was reduced by 85%, at the cost of a moderate increase in major bleeding risk. However, the benefit was not maintained at 24 months after discontinuation of prolonged anticoagulation. These results suggest that long-term anticoagulation may be more appropriate than temporary treatment prolongation in patients experiencing first episode of symptomatic unprovoked PE. Selection of patients with a first unprovoked VTE episode who can safely stop anticoagulation should not rely on DD testing alone.\(^\text{69}\) The risk of recurrence in patients with two consecutive negative DD tests at 1-month interval is not low enough to justify discontinuation of anticoagulant therapy in men, or in women with non-oestrogen-therapy-related VTE. Based on these results, the role of DD as a tool for identifying patients in whom anticoagulation may be stopped warrants further tailoring.

Direct oral anticoagulants are increasingly preferred for VTE treatment. Their efficacy and safety profile compared with VKAs is established, but their widespread use is hampered by a lack of specific antidotes. This problem may soon be moot. A placebo-controlled, double-blind Phase 1 trial showed that humanized monoclonal antibody idarucizumab induced immediate, complete, dose-dependent, and sustained reversal of dabigatran-induced anticoagulation in healthy volunteers. The drug was well tolerated, and no serious or clinically relevant safety concerns were reported.\(^\text{70}\)
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