

# The year 2017 in cardiology: aorta and peripheral circulation

Victor Aboyans<sup>1,2\*</sup>, Sigrid Braekkan<sup>3</sup>, Lucia Mazzolai<sup>4</sup>, Henrik Sillesen<sup>5</sup>,  
Maarit Venermo<sup>6</sup> and Marco De Carlo<sup>7</sup>; on behalf of the ESC Working Group  
on Aorta and Peripheral Vascular Diseases

<sup>1</sup>Department of Cardiology, Dupuytren University Hospital

<sup>2</sup>Martin Luther King Ave., Limoges, France; Inserm 1094, Limoges School of Medicine, Ave Dr. Marcland, 87025 Limoges, France;

<sup>3</sup>K.G. Jebsen Thrombosis Research and Expertise Center (TREC), Department of Clinical Medicine, UiT – The Arctic University of Norway, Hansine Hansens veg 18, 9037, Tromsø, Norway;

<sup>4</sup>Division of Angiology, Department of Heart and Vessel, Lausanne University Hospital, Ch du Mont-Paisible 18, Lausanne, 1011, Switzerland;

<sup>5</sup>Department of Vascular Surgery, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, Copenhagen, 2100, Denmark;

<sup>6</sup>Department of Vascular Surgery, Helsinki University Hospital, Haartmaninkatu 4, FI-00290 Helsinki, Finland;

<sup>7</sup>Cardiac Catheterization Laboratory, Cardiothoracic and Vascular Department, Azienda Ospedaliero-Universitaria Pisana, via Paradisa, Pisa, Italy

## Preamble

More than 83 million people live with cardiovascular (CV) disease in the ESC member countries, with peripheral vascular diseases as the most predominant condition (more than 35 million) followed by ischaemic heart disease (>29 million), underlining the public health burden of the former in our continent (1).

The ESC collaborated with European Society of Vascular Surgery (ESVS) to publish the most comprehensive guidelines document on the management of peripheral arterial diseases (PADs), encompassing all the peripheral territories (2). Compared to the 2011 version, major changes regard risk stratification for patients with asymptomatic carotid disease, and those with critical limb-threatening ischaemia (CLTI), and a new specific chapter on cardiac diseases in patients with PADs. Any presentation of PADs is associated with a very high risk for CV events, and all patients require best medical therapy for secondary prevention. In this respect, the VIVA (3) and COMPASS (4) trials are definitely the two seminal randomized controlled trials (RCTs) of the year. The VIVA trial demonstrated the interest of multiple vascular screening to improve population longevity (Table 1) (3). Over 50,000 Danish men were randomized to receive an invitation for vascular screening or not. Vascular screening consisted of arm blood pressure and ankle-brachial index (ABI) measurement, and abdominal

aorta ultrasound. Positive cases were invited to consult their general practitioners, while large abdominal aorta aneurysm (AAA) were referred to vascular surgeons. After 4.4 years, the mortality was significantly lower in the screening group (Table 1). The number needed to screen to prevent one death was 169, far below the one necessary for any cancer screening.

The COMPASS trial randomized 27,395 patients either with coronary artery disease (CAD) or PADs [lower-extremity artery disease (LEAD) or carotid stenosis or prior carotid revascularization] to three different antithrombotic strategies. In the pre-defined sub-analysis of patients with PADs, the results were consistent with those obtained in the entire population (Table 1): the combination of rivaroxaban 2.5 mg b.i.d. + aspirin 100 mg was associated with a significant 28% reduction of a combination of CV death, myocardial infarction, or stroke and a 46% reduction of major adverse limb events (MALE), including amputation, as compared to aspirin 100 mg (4). Bleeding events were higher under the combination therapy, except for fatal bleeding. The net benefit including ischaemic and major bleeding events remained in favour of the combination strategy. The clinical implication for the management of these patients needs further analyses to select specific subgroups with an optimal benefit/risk ratio (RR). Also, the external applicability of these results is important; among REACH participants with LEAD, 68% were COMPASS-compatible, fulfilling

**TABLE 1.** Summary of major randomized trials in peripheral intervention in 2017

<b>Trial's acronym (or first author)</b>	<b>Type and aim of the study</b>	<b>Challenger (n)</b>	<b>Reference (n)</b>	<b>Setting (indication)</b>	<b>Primary outcome (+secondary outcomes of interest)</b>
<b>Multiple localization</b>					
COMPASS-PAD (4)	Double-blind: interest of low-dose rivaroxaban (alone or with aspirin) in patients with PADs	Rivaroxaban 2.5 mg x2 + Aspirin 100mg (R+A: 2492) or Riva 5 mg x2 (R: 2474)	Aspirin 100mg (A: 2504)	LEAD (past revascularization, claudication with proven LEAD, or CAD with ABI < 0.90) or carotid disease (past revascularization or carotid stenosis > 50%)	CV death, MI or Stroke: R+A vs. A = -28% (P = 0.0047); R vs. A = -14% (P = 0.19) -46% reduction of MALE for R+A vs. A. +61% bleeding risk, but not fatal bleeding.
VIVA (3)	Open: interest of vascular screening in general population	Screening for hypertension, LEAD and AAA (25,078)	No screening (25,078)	Men aged 65–74 years in Central Denmark	Mortality (HR 0.93; 95% CI: 0.88–0.98)
<b>Carotid artery disease</b>					
Moresoli (5)	Meta-analysis: CAS versus CEA in patients with asymptomatic carotid stenosis	CAS (1881)	CEA (1138)	Asymptomatic carotid stenosis	Any peri-procedural stroke and long-term stroke (RR 1.24; 95% CI: 0.76–2.03) or death (RR 1.72; 95% CI: 0.95–3.11)
<b>Lower extremities artery disease</b>					
EMPA-REG (LEAD subgroup) (6)	Double-blind: efficacy and safety of empagliflozin on top of standard care in type 2 diabetic patients with LEAD	Empagliflozin (982)	Placebo (479)	LEAD (past revascularization or amputation, stenosis > 50%, or ABI < 0.90)	CV death: HR, 0.57; 95%CI: 0.37–0.88. -38% all-cause mortality reduction No increased risk of amputation.
FOURIER (LEAD subgroup) (7)	Double-blind: interest of evolocumab on top of statins to reduce cardiovascular events	Evolocumab (1856)	Placebo (1780)	Claudication and ABI < 0.85 or prior revascularization	Composite: CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization: -21% (P < 0.01). MALE also reduced by -42% (P < 0.01)
ICE (8)	Open: SES vs. BES for iliac occlusive disease	SES (340)	BES (320)	Moderate to severe claudication caused by iliac artery stenosis or occlusion	Binary restenosis at 12 months 6.1% (SES) vs. 14.9% (BES) P = 0.006
ISAR-STATH (9)	Open: endovascular techniques for superficial femoral artery revascularization	DCB + stent (48) or atherectomy (52)	BMS (55)	stenosis or occlusion of superficial femoral artery	(1) Diameter stenosis in percentages measured by angiography 34%. 56% vs. 55%; P = 0.009 and 0.007; (2) Binary restenosis rate 7.23% vs. 22.52% vs. 24.54%; P = 0.0017 PEB + stent vs. BA + stent

TABLE 1. Continued

Trial's acronym (or first author)	Type and aim of the study	Challenger (n)	Reference (n)	Setting (indication)	Primary outcome (+secondary outcomes of interest)
ILLUMENATE pivotal (10)	Single-blind: DCB vs. PTA in femoropopliteal disease	DCB (200)	PTA (100)	Rutherford Class 2–4 LEAD caused by femoropopliteal stenosis or occlusion	(1) Composite: 12 months of freedom from device and procedure-related 30 days of death, and from target limb major amputation and CD-TLR: 92.1% vs. 83.2% P=0.001; 12 months <sup>a</sup> primary patency 76.3% vs. 57.6% P=0.003
ILLUMENATE EU (11)	Single-blind: DCB vs. PTA in femoro-popliteal disease	DCB (222)	PTA (72)	Moderate to severe claudication or ischemic rest pain caused by femoro-popliteal stenosis or occlusion	(1) Composite: 30 days of freedom from device- and procedure-related death, and 12 months <sup>b</sup> from target limb major amputation and CD-TLR: 94.1% vs. 83.3%. (2) Primary patency 12 months <sup>b</sup> and freedom from CD-TLR 83.9% vs. 60.6% P=0.001
Venous thrombo-embolic disease					
EINSTEIN-choice (12)	Double-blind: Efficacy & safety of two doses of rivaroxaban vs. aspirin in long-term after VTE	Rivaroxaban 10 mg OD (R10: 1127)	Aspirin 100 mg OD (A: 1131)	After 6–12 months of anticoagulation for acute DVT or PE	Symptomatic recurrent fatal or nonfatal VTE
		Rivaroxaban 20 mg OD (R20: 1107)			R20 vs. A: –66% (P<0.001) R10 vs. A: –74%(P<0.001)
					No significant increase major bleeding risk
ATTRACT (13)	Open <sup>c</sup> : efficacy and safety of pharmaco-mechanical thrombolysis to prevent PTS after proximal DVT	Pharmaco-mechanical thrombolysis + anticoagulation (337)	Anticoagulation (355)	Post-thrombotic syndrome between 6 and 24 months	No significant difference in PTS rates (47% in the pharmacomechanical-thrombolysis group vs. 48% in the control group; P=0.56)
PEITHO (long-term results) (14)	Double-blind: long-term efficacy and safety of thrombolysis for intermediate-risk PE	Tenecteplase (506)	Placebo (499)	Intermediate-risk PE<5 days and RV dysfunction and/or troponin release	Median FU 37 months: No significant difference in terms of mortality, residual dyspnoea, and chronic thrombo-embolic pulmonary hypertension

A: aspirin; AAA: abdominal aorta aneurysm; BES: balloon-expandable stent; CAD: coronary artery disease; CAS: carotid artery stenting; CD: clinically driven; CEA: carotid endarterectomy; CV: cardiovascular; DCB: drug-coated balloon; DES: drug-eluting stent; DVT: deep-vein thrombosis; HR: hazard-ratio; LEAD: lower-extremities artery disease; MALE: major adverse limb events; MI: myocardial infarction; PADs: peripheral arterial diseases; PTA: plain balloon angioplasty; PTS, post-thrombotic syndrome; R: rivaroxaban, R+A: rivaroxaban plus aspirin; RR: relative risk; SES: self-expandable stent; SFA: superficial femoral artery; TLR: target lesion revascularization.

<sup>a</sup>Defined as absence of target lesion restenosis, measured by duplex ultrasonography-derived peak systolic velocity ratios $\leq$ 2.5 and freedom from CD-TLR.

<sup>b</sup>Defined as the absence of target lesion restenosis on duplex ultrasound (peak systolic velocity ratio $\leq$ 2.5).

<sup>c</sup>With blinded assessors.

inclusion, and exclusion criteria (15). The main reason for not being COMPASS-compatible was a high-bleeding risk. Hence, the bleeding risk stratification is of paramount importance.

## Other specific studies in lower-extremity artery disease

The 2017 ESC guidelines (1) emphasize the optimal management of risk factors in patients with PADs. A new analysis of the FOURIER trial underscored the importance of lowering LDL-cholesterol in patients with LEAD, with significant benefits with evolocumab, a PCSK-9 inhibitor (*Table 1*) (7). This new analysis in patients with LEAD showed similar benefits in terms of CV events reduction, and a significant reduction of MALE. This is the first trial showing the benefits of a lipid-lowering drug to reduce MALE, including amputation.

Many patients with LEAD are diabetic. Recently strikingly positive results on the CV benefits of sodium glucose co-transporter 2-inhibitors have been presented, although concerns were raised regarding the increased risk of amputation (mostly minor) with canagliflozin (16). A new analysis of patients with LEAD enrolled in the EMPA-REG trial confirmed the benefits of empagliflozin in terms of mortality and CV events (*Table 1*), without any difference in amputation rates as compared to placebo (6). The need for improved diabetes care was underlined by a recent registry on 15,332 CLTI patients (47% diabetic), showing that in spite of a 60% higher risk of infection and 40% higher amputation rate (both in-hospital and at 4-year follow-up), diabetic patients were revascularized less often (46% vs. 54%,  $P < 0.001$ ) (17).

In another review of 60,998 hospitalizations of patients undergoing revascularization or amputation in the USA for CLTI, the 30-days readmission rate was 20%, mainly due to infections, persistent CLTI symptoms, cardiac conditions, and procedural complications (18).

Regarding revascularization, the Iliac, Common and External Artery Stent Trial (ICE) is the first RCT to compare balloon-expandable (BES) vs. self-expandable stents (SES) (8). Among 660 patients undergoing iliac stenting, 1-year binary restenosis was significantly lower after SES as compared to BES (*Table 1*). Furthermore, freedom from target lesion revascularization (TLR) was higher in the SES group, with no difference in peri-procedural complications or functional outcome. At the femoro-popliteal level, new evidence regarding device choice came from a network meta-analysis (6091 patients) (19). Five endovascular strategies were compared: bare metal stent (BMS), covered metal stent (CMS), drug-eluting stent (DES), drug-coated balloon (DCB), and plain balloon angioplasty (PTA). Drug-coated balloon, DES, and CMS offered a significant reduction in 1-year TLR vs. PTA (68%, 58%, and 48%, respectively). Additionally, DCB significantly reduced TLR

also vs. BMS (53%), appearing the preferable revascularization device. The advantages of DCB were confirmed in ISAR-STATH, an RCT randomizing 155 patients to three different strategies: DCB + BMS, PTA + BMS, or directional atherectomy (9). The primary endpoint was significantly lower for DCB + BMS than PTA + BMS, as well as 2-year TLR (*Table 1*). Further evidence favouring DCB over PTA comes from the ILLUMENATE pivotal (10) and ILLUMENATE EU (11) which randomized 300 and 222 patients, respectively, to DCB or PTA; primary patency was significantly higher for DCB in both trials (*Table 1*).

Cardiac risk should be assessed in patients undergoing vascular surgery (2). In a nationwide US registry of patients undergoing non-cardiac surgery, peri-operative myocardial infarction occurred in 2% of patients with vascular surgery, among the highest risks compared to other types of non-cardiac intervention [odds ratio (OR) 1.56, 95% confidence interval (95% CI) 1.52–1.59] (20). Through a propensity-matched analysis, the registry suggests that invasive management of peri-operative myocardial infarction would improve outcomes; this deserves a trial enrolling patients with PADs.

## Carotid artery disease

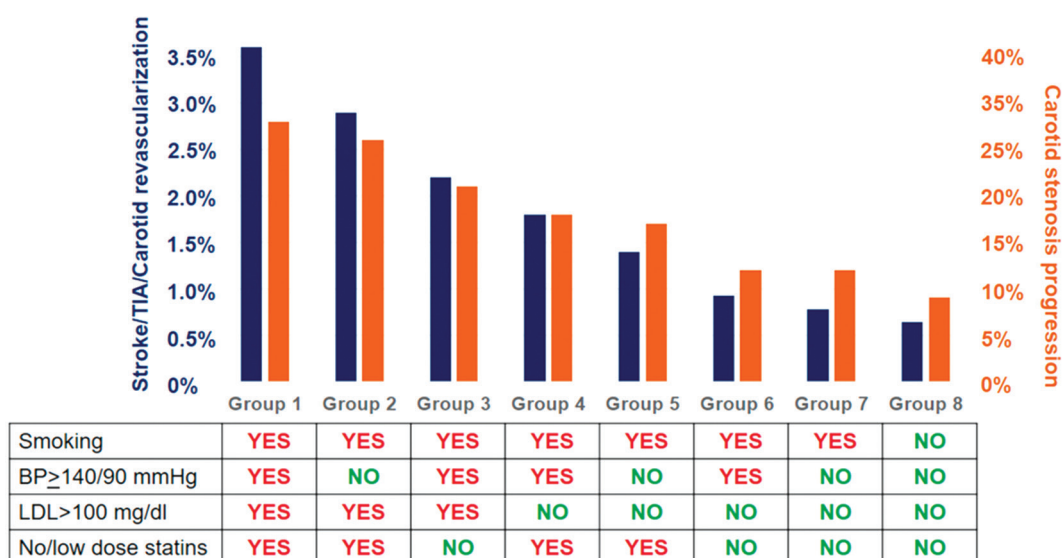
### Optimal medical management

Patients with asymptomatic carotid artery stenosis should benefit from best medical therapy (1). This has recently been confirmed in 864 patients with 50–69% or 70–99% carotid artery stenosis (21). Altogether, 4929 carotid ultrasound studies were performed on 1439 carotid arteries over 6.5 years. Ischaemic stroke/transient ischemic attack (TIA) and carotid revascularization occurred in 12.2% and progression of the stenosis in 21.5% of patients. The quality of risk factors control were independent predictors for the stenosis progression or occurrence of stroke/TIA (*Figure 1*) (21).

### Revascularization

A meta-analysis of five RCTs including 3019 asymptomatic patients compared carotid artery stenting (CAS) to surgery (CEA) (5). After CAS, the risk of any peri-procedural stroke and non-disabling stroke as well as the composite of any peri-procedural stroke or death was increased with borderline statistical significance (*Table 1*). There was a trend for less peri-procedural myocardial infarctions after CAS. There was no significant difference regarding incident long-term stroke between the two techniques.

Women are at increased risk of peri-operative stroke, but gender-specific data are sparse. In the National Surgical Quality Improvement Program database (5620 CEA and 141 CAS), the early post-operative outcomes in women with symptomatic carotid artery stenosis were compared. During the first 30 days, MACE occurred in 12.2% and 5.2%, respectively after CAS and



**FIGURE 1.** Neurologic ischaemic events and stenosis progression in patients with asymptomatic carotid stenosis according to the quality of risk factors management. Adapted from Shah et al (21). BP, blood pressure; TIA, transient ischemic attack  
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CEA ( $P < 0.001$ ) (22). In a propensity-matched analysis including 125 pairs, the 30-day incidence of post-operative MACE in the CAS group was 11.2% vs. 4.0% after CEA (OR: 2.8;  $P = 0.04$ ). This is in favour of CEA as the preferred option in women.

Early revascularization after an ischaemic stroke/TIA is recommended in case of carotid stenosis, but the influence of the timing on revascularization techniques has been poorly studied. In a pooled analysis of individual data of 4138 patients from four RCTs, the risk of stroke or death after CAS was higher than after CEA in those treated within 7 days (8.3% vs. 1.3%, RR 6.7; 95% CI: 2.1–21.9, adjusted for age, sex, and type of qualifying event) (23). These results favour of CEA in the early days after a neurologic ischaemic event.

In a German registry (2009–14), a total of 13,086 CAS procedures were analysed (24). In-hospital stroke or death occurred in 2.4% (1.7% in asymptomatic and 3.7% in symptomatic patients). The multivariable analysis showed the use of an embolic protection device was an independent predictor of lower in-hospital rates of stroke or death (adjusted RR 0.65; 95% CI: 0.50–0.85), major stroke or death (adjusted RR 0.60; 95% CI 0.43–0.84), and stroke (adjusted RR 0.57; 95% CI: 0.43–0.77). This supports the recent recommendations in favour of embolic protection device during CAS (2).

Current practice of carotid revascularization was evaluated in 12 countries (25). Among 58,607 treated cases, the largest national and international variation was seen in indications: overall, about half of the patients were asymptomatic (48%), but this varied from 0% (Denmark) to 73% (Italy). National variation between centres was even bigger and was the highest in Austria

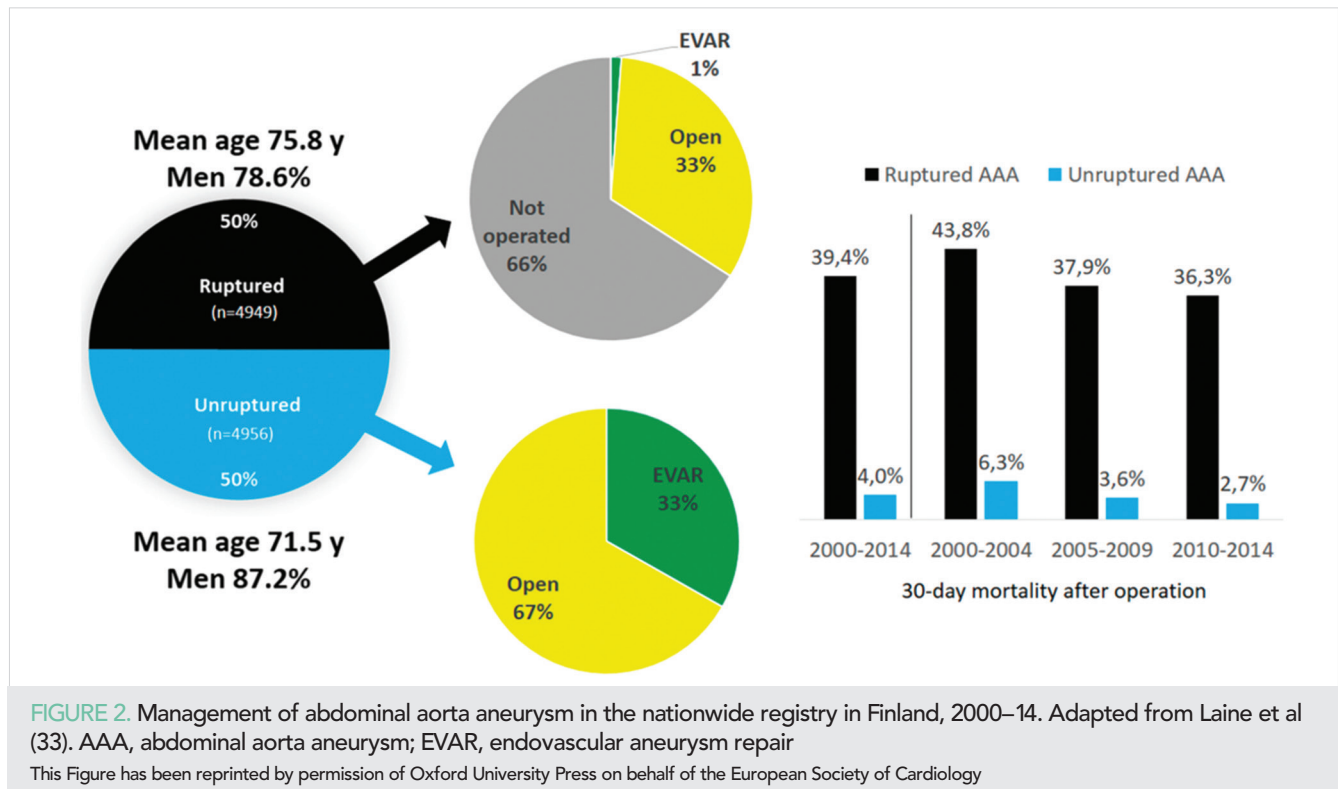
(0–72%), Hungary (5–55%), and the USA (0–100%). The odds for revascularization for asymptomatic carotid stenosis were much higher in countries where fee per case is paid to the operator (OR 5.8, 95% CI 4.4–7.7). Among asymptomatic patients CAS was used most often in Sweden (26%) while some countries (Finland, Iceland) did not use CAS at all. An international effort is necessary to homogenize guidelines and practices globally.

## Aorta

### Thoracic aorta

Echocardiography remains the most frequent imaging method to assess the proximal aorta. The diameter varies according to the cardiac cycle, site, and mode of measurement as well as age and body size. In the multicentre collaborative NORRE study including more than 700 healthy individuals, the normal reference ranges for the proximal aorta dimensions have been set (26).

Two studies from the Multi-Ethnic Study of Atherosclerosis reported on aortic calcification on computed tomography (CT): the first assessed the ascending aorta calcium and showed that this condition is rare in general population (3.4%) (27). The ascending aorta calcium density was inversely correlated with CV events, even after adjustments for risk factors and the coronary artery calcium. The second study focused on those with coronary artery calcium score of zero and found no additional prognostic information from ascending aorta calcium (28). A magnetic resonance imaging study showed the prognostic interest of the aortic arch pulse-wave velocity, a marker of aortic stiffness, in middle-age (45–54 years) subjects, but not at older ages (29).



Regarding aortic events, so far only the aortic diameter is considered as a risk marker from imaging for aortic dissection. Two independent case-control studies, comparing patients with type-B aortic dissection (TB-AD) with controls, suggest that beyond the diameter, the age-related elongation of the aortic arch is also associated with increased risk of TB-AD (30, 31).

### Abdominal aorta

After screening, small AAAs require follow-up of the diameter, typically assessed by 2D ultrasound (US). Using 3D-US for assessment of AAA volume in 179 patients with small AAAs, it was found that 3D-US was accurate in assessing both diameter and volume as compared to CT (32). During follow-up, 40% patients classified as stable according to the diameter actually presented a volume growth highlighting the higher sensitivity of this new method.

Data from one of the most comprehensive and nationwide registries in Europe come from Finland, showing the improvement in the prognosis of patients with unruptured and ruptured AAA during the last 2 decades (Figure 2) (33). The VascuNet network analysed differences in AAA interventional methods and outcomes in 83,253 patients through 11 countries during the 2005–09 and 2010–13 periods (34). The proportion of octogenarians operated increased between the two periods from 18.5% to 23.1% ( $P < 0.0001$ ) and similarly the proportion of patients treated with endovascular aneurysm repair (EVAR) increased from 44.3% to 60.6% ( $P < 0.0001$ ). Mortality for EVAR decreased from 1.5%

to 1.1% ( $P < 0.0001$ ), but the outcome worsened for open repair from 3.9% to 4.4% ( $P = 0.008$ ).

In some countries, AAAs are repaired by EVAR at a lower diameter than recommended in guidelines. Based on data from almost 40,000 Medicare patients undergoing EVAR from 2001 to 2008, earlier AAA repair by 5 mm has major consequences, with 22% excess EVAR procedures and 42% and 37% increase in open and endovascular re-interventions (35). The cost per saved AAA rupture was estimated to be 1 million USD.

After EVAR lifelong surveillance is necessary and CT-angiography has been the preferred modality, while ultrasound duplex scanning (DUS) with and without contrast enhancement (CEUS) is an alternative. A Cochrane review of 42 studies (36) concluded that both DUS and CEUS have high specificity for identification of endoleaks; however, CEUS is more sensitive and can be routinely used, with CT scan only when endoleak is suspected.

### Venous thromboembolism

After an acute episode of venous thromboembolism (VTE) anticoagulation is indicated for at least 3 months (37). Optimal anticoagulation duration, beyond the initial period remains uncertain. Prandoni et al. showed that anticoagulation in patients with a first episode of proximal DVT, based on the assessment of residual vein thrombosis and serial D-dimer, leads to an overall annual rate of recurrent VTE  $< 5\%$  (38). However, in

**TABLE 2.** Characteristics included in the risk prediction scores for cancer-related venous thromboembolism (VTE)

	<b>Khorana</b>	<b>Vienna CATS</b>	<b>PROTECHT</b>	<b>CONKO</b>
Very high-risk tumours (pancreatic or gastric cancer) <sup>a</sup>	2	2	2	2
High-risk tumours (lung, gynaecological, lymphoma, bladder, or testicular cancer)	1	1	1	1
Pre-chemotherapy haemoglobin <10 g/dL or use of erythropoietin stimulating agents	1	1	1	1
Pre-chemotherapy white blood cell count >11 × 10 <sup>9</sup> /L	1	1	1	1
Pre-chemotherapy platelet count ≥350 × 10 <sup>9</sup> /L	1	1	1	1
Body mass index >35 kg/m <sup>2</sup>	1	1	1	
D-dimer >1.44 µg/mL		1		
Soluble P-selectin ≥53.1 ng/mL		1		
World Health Organization (WHO) performance status ≥2				1
Gemcitabine chemotherapy			1	
Platinum-based chemotherapy			1	
Cut-off for classification of high-risk patients (points)	≥3	≥5	≥3	≥3

Numbers represent the value attributed to each characteristic in the scores.  
<sup>a</sup>The Vienna CATS also included brain cancer as a high-risk site.

men this strategy needs further assessment. Several prediction rules are proposed to identify patients at high risk of recurrence (39). The REVERSE II study prospectively validated the 'men continue and HERDOO2' clinical prediction rule (40). This allows identifying low-risk women, following a first unprovoked VTE, who can safely discontinue anticoagulation once the initial treatment is completed (3.0% recurrence per patient-year in low-risk women). No predictors for low risk of recurrence were found in men. The decision on whether to discontinue anticoagulation should therefore be individually tailored and balanced against bleeding risk.

Once the decision to extend anticoagulant treatment is taken, common agreement is to continue with the initial compound. The latest EINSTEIN-CHOICE trial (12) showed that standard (20 mg o.d.) and lower dose rivaroxaban (10 mg o.d.), significantly reduced the risk of recurrence compared to aspirin, without significant increase in bleeding rates (*Table 1*).

In patients with proximal DVT treated with DOACs, persistence of residual vein thrombosis is likely to occur less frequently than in patients treated with conventional anticoagulation. These results may have implications for the prognosis of patients with DVT (41).

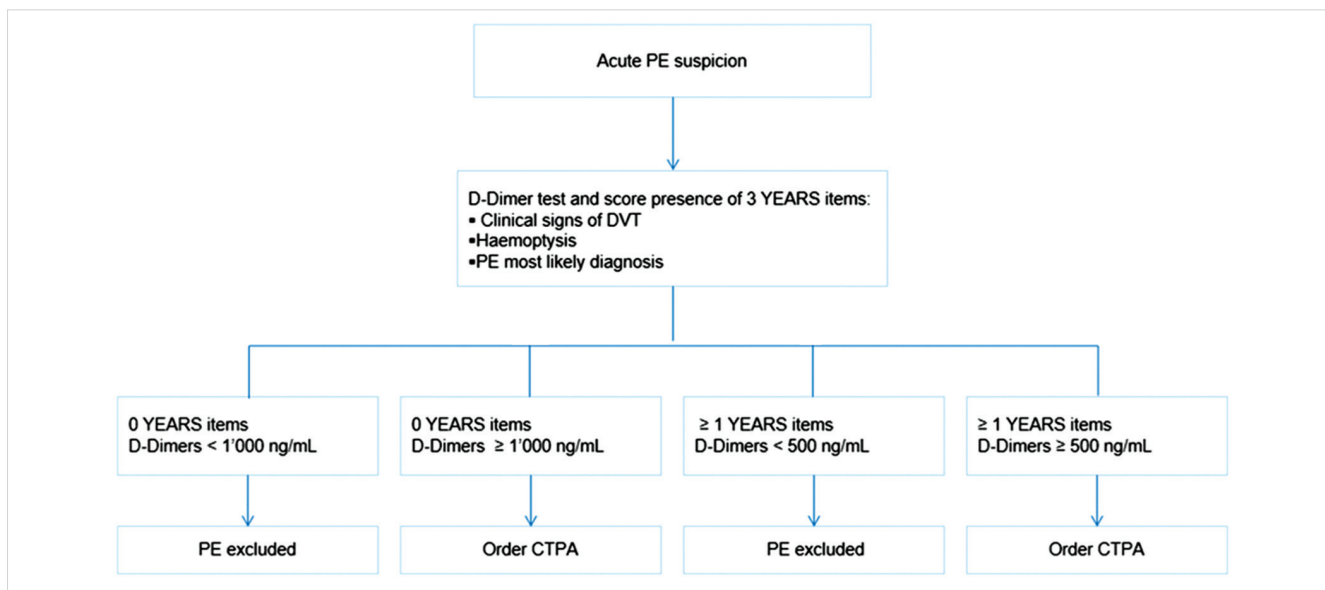
According to current guidelines, adjuvant catheter-directed thrombolysis may be considered in selected patients with acute ilio-femoral DVT, if performed in experienced centres, to diminish risk of post-thrombotic syndrome (PTS). However, the recently published ATTRACT trial (692 patients) failed to show the additional interest of catheter-directed thrombolysis to decrease the risk of PTS, but did result in a higher risk of major bleeding (13). While the PTS severity score was lower in the pharmacomechanical group, this did not affect improve the quality of life of the patients. There was no difference according to the site of DVT (57% had ilio-fe-

moral DVT). The overall results are in contradiction with a smaller trial reported previously in favour of pharmacomechanical intervention, with decreased risk of PTS after 5 years of follow-up (42). Further trials, focused on ilio-femoral DVT, are required.

The clinical usefulness of VTE risk prediction scores in ambulatory cancer patients is debated. A cohort of 876 cancer patients compared several scores (*Table 2*) (43). All models performed poorly (c-statistics: 0.50–0.57), indicating the need for improvements before these models can be considered in clinical practice. Identifying predictors for VTE recurrence in cancer patients remains a challenge. In two cohorts of patients with cancer-associated VTE, the modified Ottawa score showed modest discriminating power and was unable to predict the risk of VTE recurrences (44, 45).

Diagnostic algorithms are frequently used to identify patients in whom pulmonary embolism (PE) can be ruled out without the use of computed tomography pulmonary angiography (CTPA). In a study of 3465 patients with suspected PE, the YEARS decision rule (based on three clinical items combined with two D-dimer cut-offs) yielded a 14% decrease in CTPA examinations compared to conventional strategies (*Figure 3*) with a negative predictive value of 99.4% (46). Whether negative CTPA is sufficient to exclude PE in patients with likely pretest probability is debated. Pulmonary embolism was excluded with CTPA in 37% of patients with likely clinical probability, and the 3-month VTE risk was 0.6%, indicating that a negative CTPA safely excludes PE in this patient group (47).

The prevalence of PE in patients presenting with syncope has been highly debated this year, following the PESIT trial, reported last year (39), describing a 17% rate of PE in syncope cases referred to emergency rooms, after excluding cases with evident aetiology.



**FIGURE 3.** The YEARS diagnostic strategy in case of suspicion for pulmonary embolism. CTPA, computed tomography pulmonary angiography; DVT, deep vein thrombosis; PE, pulmonary embolism

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A meta-analysis including 6608 emergency department patients and 975 patients hospitalized for syncope reported a PE prevalence <1% (48). Two other studies reported a PE prevalence of 1.4% among patients with syncope (14, 49). Routine screening for PE in all patients presenting with syncope may not be justified.

The PEITHO trial investigated long-term prognosis in patients with intermediate-risk PE randomized to receive thrombolysis or placebo (50). Thrombolytic treatment did not decrease long-term mortality rates, persisting dyspnoea, chronic thromboembolic pulmonary hypertension, or right ventricular dysfunction.

### Conflict of interest

V.A.: AstraZeneca, Bayer, Boehringer-Ingelheim, Novartis, Pfizer/BMS Alliance, Sanofi. S.B.: none. L.M.: Bayer, Pfizer/BMS Alliance, Sanofi. H.S.: Amgen,

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