

The year in cardiology: aorta and peripheral circulation

The year in cardiology 2019

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Received 11 October 2019; revised 29 November 2019; editorial decision 11 December 2019; accepted 11 December 2019; online publish-ahead-of-print 6 January 2020

Preamble

Similar to previous years,^{1–3} the current article reviews groundbreaking science published 2019 in the area of aortic and peripheral arterial diseases (PAD) as well as venous thromboembolic disease (VTE) that will affect our daily clinical practice. With the growing recognition of PAD, it will be necessary to consolidate imprecisions in terminology. Many are used to the acronym PAD for atherosclerotic disease of the lower extremity arteries. Others have used the same acronym to qualify atherosclerotic disease of the lower extremity arteries and carotid arteries. In the current article and in line with the European Society of Cardiology (ESC) guidelines,⁴ we have stringently used the specific terms lower extremity arterial disease (LEAD) and reserved PAD as the umbrella term encompassing all arterial diseases other than aorta and coronaries.

Vascular biology/translational research

The extent to which genetic factors contribute to PAD development and if they are shared or distinct between LEAD, cerebral, and coronary arteries are largely unknown. In a genome-wide association study in the Million Veteran Program, ~32 million DNA sequence variants were tested for PAD (31 307 cases, 211 753 controls) and combined with electronic health records.⁵ The results were

replicated in an independent sample from the UK Biobank. They identified 19 LEAD loci (18 not previously reported): 11 loci were associated with disease in three vascular beds (coronary, cerebral, and lower extremity), including LDLR, LPL, and Lp(a) (*Take home figure*); 4 loci appeared to be specific for LEAD, including F5 p.R506Q (Factor V Leiden variant), highlighting the pathogenic role of thrombosis in LEAD and supporting Factor Xa inhibition as a therapeutic strategy.

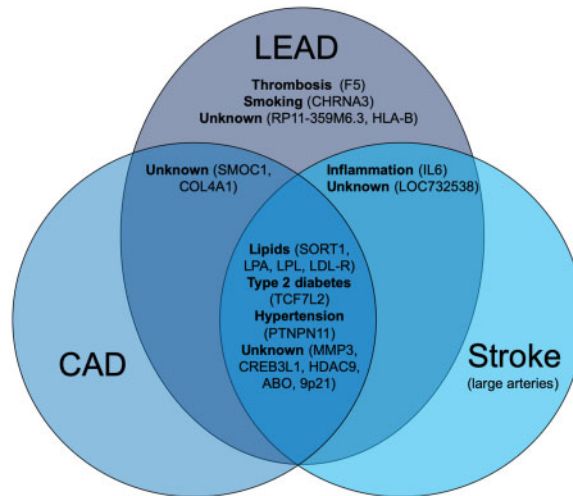
Despite the fact that numerous long non-coding RNAs (lncRNA) have been identified, only a few of them have been studied with respect to endothelial cell homeostasis or vascular disease development. One of them, the pro-angiogenic lncRNA MANTIS, may be clinically relevant in carotid disease.⁶ In fact, the protective effects of laminar flow and statins are, at least in part, attributed to the expression of MANTIS. The mechanisms involve epigenetic rearrangements and the transcription factors Krüppel-like factor 2 and 4. As induction of MANTIS mimics the beneficial effects of statins on endothelial function, the authors proposed that strategies to increase MANTIS might improve vascular function in patients not responding to statin therapy.

The transcriptional activity of nuclear receptors that regulate key pathophysiological processes in atherosclerosis development is controlled by the nuclear receptor corepressors (NCOR), scaffolding proteins that form the basis of large corepressor complexes. Oppi *et al.*⁷ investigated the role of NCOR1 in atherogenesis. Myeloid cell-specific deletion of NCOR1 in LDL receptor knockout mice

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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Take home figure Lower extremity artery disease (LEAD) risk variants and mechanistic overlap with coronary artery disease (CAD) and large artery stroke. Venn diagram of each of the 19 LEAD risk loci in a based on their association with LEAD ($N = 31\,307$ LEAD cases and $211\,753$ controls), CAD ($N = 111\,216$ CAD cases and $248\,081$ LEAD controls), and large artery stroke ($N = 7393$ large artery stroke cases and $628\,737$ controls) using logistic regression. Each locus is stated next to the plausible relationship with the underlying risk factor and the loci names are based on the nearest genes. Figure adapted from Ref.⁵

aggravated atherosclerosis development. Macrophage NCOR1-deficiency led to increased foam cell formation, enhanced expression of pro-inflammatory cytokines, and atherosclerotic lesions characterized by larger necrotic cores and thinner fibrous caps. The immunometabolic effects of NCOR1 were mediated via suppression of peroxisome proliferator-activated receptor gamma (PPAR γ) target genes in mouse and human macrophages, which lead to an enhanced expression of the CD36 scavenger receptor and subsequent increase in oxidized LDL uptake in the absence of NCOR1. Interestingly, in human atherosclerotic plaques, the expression of NCOR1 was reduced, whereas the PPAR γ signature was increased, and this signature was more pronounced in ruptured compared with non-ruptured carotid plaques. The data suggest that stabilizing the NCOR1-PPAR γ binding could be a promising strategy to block the pro-atherogenic functions of plaque macrophages and lesion progression.

Radiotherapy-induced cardiovascular disease (CVD) is an emerging problem in a growing population of cancer survivors where traditional vascular treatments have limited benefits. Using a translational approach, it was now shown that human irradiated blood vessels exhibit elevated levels of inflammation signals associated with inflammatory activation long after radiotherapy, and similar changes occurred in a mouse model of localized irradiation to the heart and carotids.⁸ In the model, the localized inflammatory response was ameliorated by an interleukin (IL)-1 receptor antagonist. Clinical studies in humans now need to evaluate IL-1 blockade as a potential treatment of radiotherapy-induced CVD.

Subjects with Lp(a) elevation have increased arterial wall inflammation and cardiovascular risk. Stiekema et al.⁹ evaluated whether evolocumab, which as opposed to statins lowers both LDL-cholesterol and Lp(a), attenuates arterial wall inflammation in the index vessel (carotid or thoracic aorta) in patients with elevated Lp(a) (>200 mg/dL). In this

multicentre, randomized, double-blind, placebo-controlled study, 129 patients were randomized to monthly subcutaneous evolocumab 420 mg or placebo. Compared with placebo, evolocumab reduced LDL-cholesterol by 60.7% [95% confidence interval (CI) 65.8–55.5] and Lp(a) by only 13.8% (95% CI 19.3–8.5). Importantly, arterial wall inflammation [assessed by [(positron emission tomography with 2-deoxy-2-[fluorine-18]-fluoro-D-glucose integrated with computed tomography)] ^{18}F -FDG PET/CT] was not significantly altered with evolocumab at Week 16. This supports that, beyond economic issues, statins remain the first pillar of lipid-lowering therapies, which ties in with current lipid guidelines.¹⁰

Another large study characterized serum metabolic signatures associated with atherosclerosis in the carotid and coronary arteries and subsequently their association with incident CVD among 3867 participants from the *Multi-Ethnic Study of Atherosclerosis* (MESA), with replication among 3569 participants from the Rotterdam and *LOLIPOP* studies.¹¹ They showed that 30 ^1H NMR (proton nuclear magnetic resonance spectroscopy) measured metabolites were associated with coronary artery calcium and/or carotid intima-media thickness. Metabolites associated with atherosclerosis were largely consistent between the carotid and coronary vascular beds and predominantly tag pathways that overlap with the known cardiovascular risk factors: disturbances in lipid and carbohydrate metabolism, branched chain, and aromatic amino acid metabolism, as well as oxidative stress and inflammatory pathways.

Vascular biomarkers and cardiovascular risk

Multimodality vascular assessment enables to evaluate the atherosclerotic process and the cardiovascular risk. In a population-based

study¹² using hybrid ¹⁸F-FDG PET and magnetic resonance imaging (MRI), arterial inflammation was detected in 48% of participants of 40–54 years of age, increasing steadily by the number of risk factors. Aortic, carotid, and/or iliofemoral plaques were present in 90% of cases, but most inflammation was depicted in the plaque-free zones. Inflammation was present only in 11% of plaques, suggesting arterial inflammation in early stage of atherosclerosis process. An experimental study went one step further and developed an integrative multiparametric PET/MRI protocol that allows non-invasive assessment of different processes relevant to atherosclerosis progression.¹³ Using clinically approved nanobody radiotracers, they were able to study different biomarkers of atherosclerosis progression, namely vascular cell adhesion molecule-1, lectin-like oxidized low-density lipoprotein receptor-1, and macrophage mannose receptor, that correlated with histopathological findings in mice and rabbits.

Atherosclerosis is even identifiable in adolescence, especially in case of unhealthy lifestyle: in an observational study¹⁴ including 1266 young participants aged 13–17 years, aortic stiffness, estimated by carotid-femoral pulse-wave velocity (cfPWV) was proportionally increased by the tobacco smoking and alcohol drinking intensities, with a strong potentiation when both were combined (Figure 1). At these ages, smoking and drinking cessation lead to normalization of cfPWV. In the other lifespan tip, vascular markers could be useful to downgrade the estimated risk in elderly people who would have an indication for statins based on risk scores, highly affected by age. In a cohort of 5805 healthy elderly participants (mean age 69 years), normal (<10) coronary calcium score and no carotid plaque on ultrasound were the most powerful vascular markers to downgrade the predicted cardiovascular risk, with respective net reclassification index of 0.29 and 0.14, avoiding unnecessary statin prescription in 34% and 21% of cases.¹⁵

Ultrasound vascular imaging can efficiently improve patients' adherence to medical advice for healthy lifestyle. The *Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention* (VIPVIZA) open controlled trial¹⁶ randomized 3532 individuals >40 years attending a screening programme; the control group received regular risk factors screening and guidelines-based management but the results of carotid ultrasound were not disclosed, while the intervention group received, along with their general practitioners, a pictorial presentation of the carotid ultrasound results, including colour-scaled presentations of vascular age based on intima-media thickness, and plaque identification. A nurse called 2–4 weeks later to reassure participants and provide any information needed. The same pictorial information was repeated after 6 months. The baseline Framingham risk score (FRS) and SCORE were respectively at 12.9 and 1.28. At 1 year, both scores were significantly lower in the intervention group (−1.07, $P=0.0017$ for FRS and −0.16, $P=0.001$ for SCORE), with more striking results in the high-risk group (−2.16 and −2.85, respectively). The persistence of these results and their consequences on CVD events need further evaluation.

Cerebrovascular disease

Excessive arterial pulsatility may contribute to cognitive decline and risk of dementia via damage to the fragile cerebral microcirculation. As part of the Whitehall II study,¹⁷ peak forward-travelling

compression wave intensity (FCWI) was assessed using Duplex ultrasound within the common carotid arteries in 3191 individuals (mean age = 61 years; 75% male) and serial measures of cognitive function were taken at baseline and almost 10 years later. Higher FCWI at baseline was associated with accelerated cognitive decline during follow-up and this association was largely driven by cognitive changes in individuals with the highest FCWI. Compared to other participants, this group was approximately 50% more likely to exhibit cognitive decline, even after adjustments for multiple potential confounding factors.

While intensive lipid lowering is recommended after transient ischaemic attack (TIA) and ischaemic stroke the target level for LDL to reduce cardiovascular events after stroke has not been well studied. In a parallel group trial, 2860 patients with recent ischaemic stroke or TIA and evidence for cerebrovascular and coronary artery atherosclerosis were randomized to either LDL target of <70 mg/dL or 90–110 mg/dL with a statin, ezetimibe, or both.¹⁸ During a mean follow-up of 3.5 years, major cardiovascular events occurred less in the lower target group [8.5% vs. 10.9%; hazard ratio (HR) 0.78 (95% CI 0.61–0.98)].

Patients with high stroke risk and atrial fibrillation who are unsuitable for oral anticoagulants (OACs) require alternative stroke prevention strategies. The multicentre, non-randomized, first-in-human clinical *Carotid Artery Implant for Trapping Upstream Emboli for Preventing Stroke in Atrial Fibrillation Patients* (CAPTURE) trial sought to determine the feasibility and safety of a novel permanent coil filter directly placed into both common carotid arteries designed to capture emboli >1.4 mm in diameter.¹⁹ Patients received aspirin/clopidogrel for 3 months, and aspirin thereafter. In three centres, 25 patients with atrial fibrillation, with CHA₂DS₂-VASc ≥2, who were unsuitable for OACs and had no carotid stenosis >30% were enrolled. The procedure success was 92%; 1 patient had unilateral deployment. There were no device/procedure-related major adverse events. After 6-month mean follow-up, asymptomatic thrombi were detected in four patients (one bilateral, four unilateral) and the thrombi dissolved with subcutaneous heparin. Permanent carotid filter placement for stroke prophylaxis seems technically feasible and safe. Larger studies and a comparison with the use of left atrial appendage occluders are necessary.

Aortic disease

A common challenge in the emergency room is to distinguish patients with symptoms suggestive of acute aortic syndrome (AAS) requiring a computed tomography scan, from others. In a study of 839 patients attending the emergency room with suspected AAS, focused cardiac ultrasound, integrated into a strategy including clinical assessment and (for low-risk patients) D-Dimer testing, enabled the correct identification of all patients with aortic dissection (AD), although the upper border of the 95% CI was 1.2%.²⁰ These findings confirm the importance of transthoracic echocardiography in the diagnostic strategy of AAS as suggested in the last ESC guidelines.²¹

The term AAS has become commonplace, but constitutes a range of disease entities, which may not have the same pathophysiological mechanisms, responses to treatment or outlook. Among 1012 patients, those with intra-mural haematoma (IMH) ($n=340$) had a

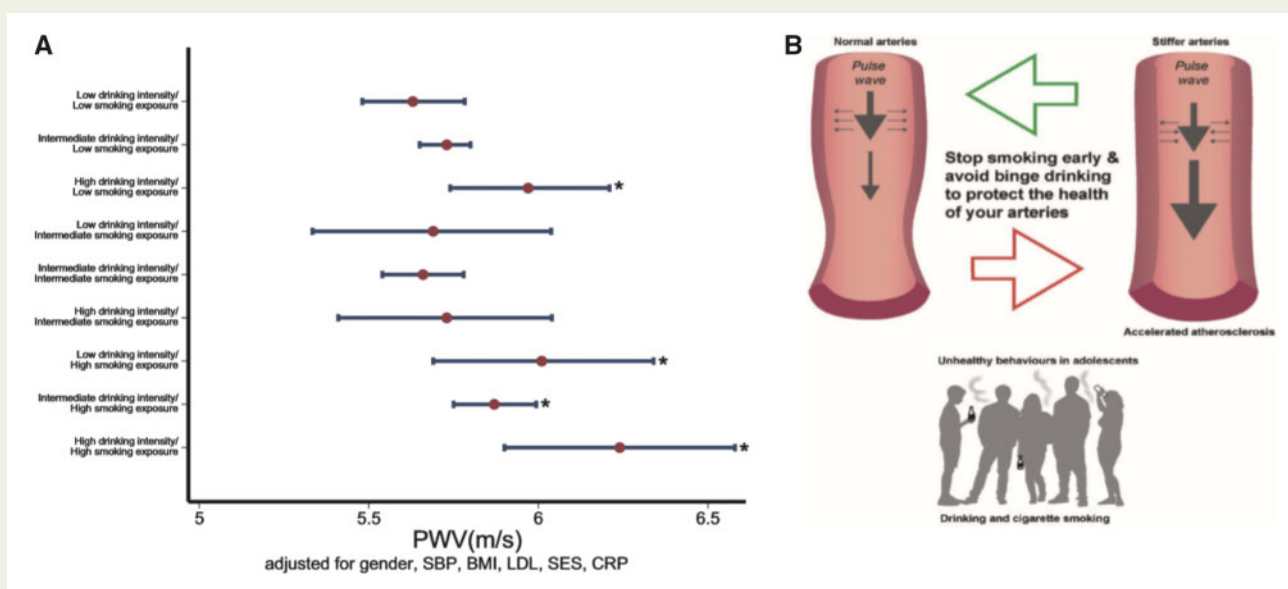


Figure 1 (A) The combined effect of smoking over lifetime and intensity of drinking on arterial stiffness. The combination of high-intensity drinking with lifetime smoking exposure is shown. Pulse wave velocity measurements are expressed as mean values and 95% confidence intervals around the mean on the x-axis. The participants who had 'high' drinking intensity and 'high' smoking exposure had the highest pulse wave velocity compared with the 'low lifetime smoking exposure' and 'low drinking intensity'. * $P < 0.05$. (B) Unhealthy behaviours in adolescents (drinking and cigarette smoking) are associated with increased carotid to femoral pulse wave velocity (stiffer arteries) and accelerated atherosclerosis. Stopping smoking in adolescents and reducing binge drinking has potential for reversibility of arterial stiffening. Reproduced with permission from Ref.¹⁴

much better short- and long-term mortality than those patients with AD ($n = 672$).²² Taking the Type B IMH in-hospital mortality, estimated at 1.5%, as reference, the overall crude in-hospital mortality of Type A AD was 15.0% with an adjusted hazard ratio (aHR) of 30.4; compared to Type A IMH mortality of 8.0% (aHR 4.85) and Type B AD mortality of 5.0% (aHR 3.51).

Identifying patients with Marfan syndrome at particular risk of AD is currently based on the absolute diameter of the aorta, the growth rate, and the presence/absence of a family history of AD. A novel additional approach may be the evaluation of the longitudinal strain of the proximal aorta by MRI (Figure 2A).²³ Higher strain rates were associated with more rapid aortic expansion and appeared to predict clinical outcomes. If proximal aortic strain is reproducible and if these findings are replicated in larger cohorts, this may help to inform the need for, and timing of, surgery in these patients.

Complex flow patterns are identified in the true and often the false lumen after AD. A better understanding of these flow dynamics may explain the differing behaviour of ADs over the long term. Recent insights into this process have become available from detailed study categorizing flow patterns using echo Doppler. The potential for prognostic implications is discussed (Figure 2B).²⁴

The optimal management of descending thoracic aortic aneurysms is controversial. A retrospective study on a propensity-adjusted population of Medicare beneficiaries found lower perioperative and overall mortality in patients undergoing thoracic endovascular aortic repair (TEVAR) compared to open repair, but with a higher risk of reintervention.²⁵ The odds of perioperative mortality were greater for open surgical repair and depended on the centre volume: high-volume centre, odds ratio (OR) 1.97 (95% CI 1.5–2.6); low-volume

centre, OR 3.62 (95% CI 2.9–4.5). The restricted mean survival time difference favoured TEVAR at 9 years, -209 days (95% CI -299 to -120 days) for open surgical repair. The risk of reintervention was lower for open surgical repair, HR 0.40 (95% CI 0.34–0.60).

In the last ESC guidelines on the management of aortic diseases,²¹ both open surgery and endovascular aneurysm repair (EVAR) of abdominal aneurysms received Class I recommendation, based on several head-to-head trials enrolling patients with suitable anatomy for both options. While, in the short term, EVAR was associated with lower mortality, this difference was gradually annihilated over time, while in turn, EVAR requested repeated X-ray exposure and reinterventions for endoleaks. The results of very long-term follow-up (14 years) of the *Open vs. Endovascular Repair (OVER)* trial²⁶ are interesting in that they show no mortality or secondary procedure difference beyond the first years. These results support current recommendations; importantly, mortality was largely not aneurysm-related (only 2.7%, mostly post-operative), and mostly due to cardiovascular causes, emphasizing the need for maximal preventive measures in these patients. Finally, gender-specific evidence is still lacking, as women constituted <10% of all participants.

Lower extremity artery disease

Lower extremity arterial disease is an increasing public health problem according to the latest global epidemiology report.²⁷ In 2010, LEAD, defined as ABI ≤ 0.9 , affected 202 million subjects worldwide; this number increased by 22% to 237 million in 2015. The overall prevalence in subjects aged ≥ 25 years was 5.6% (95% CI 3.8–8.6),

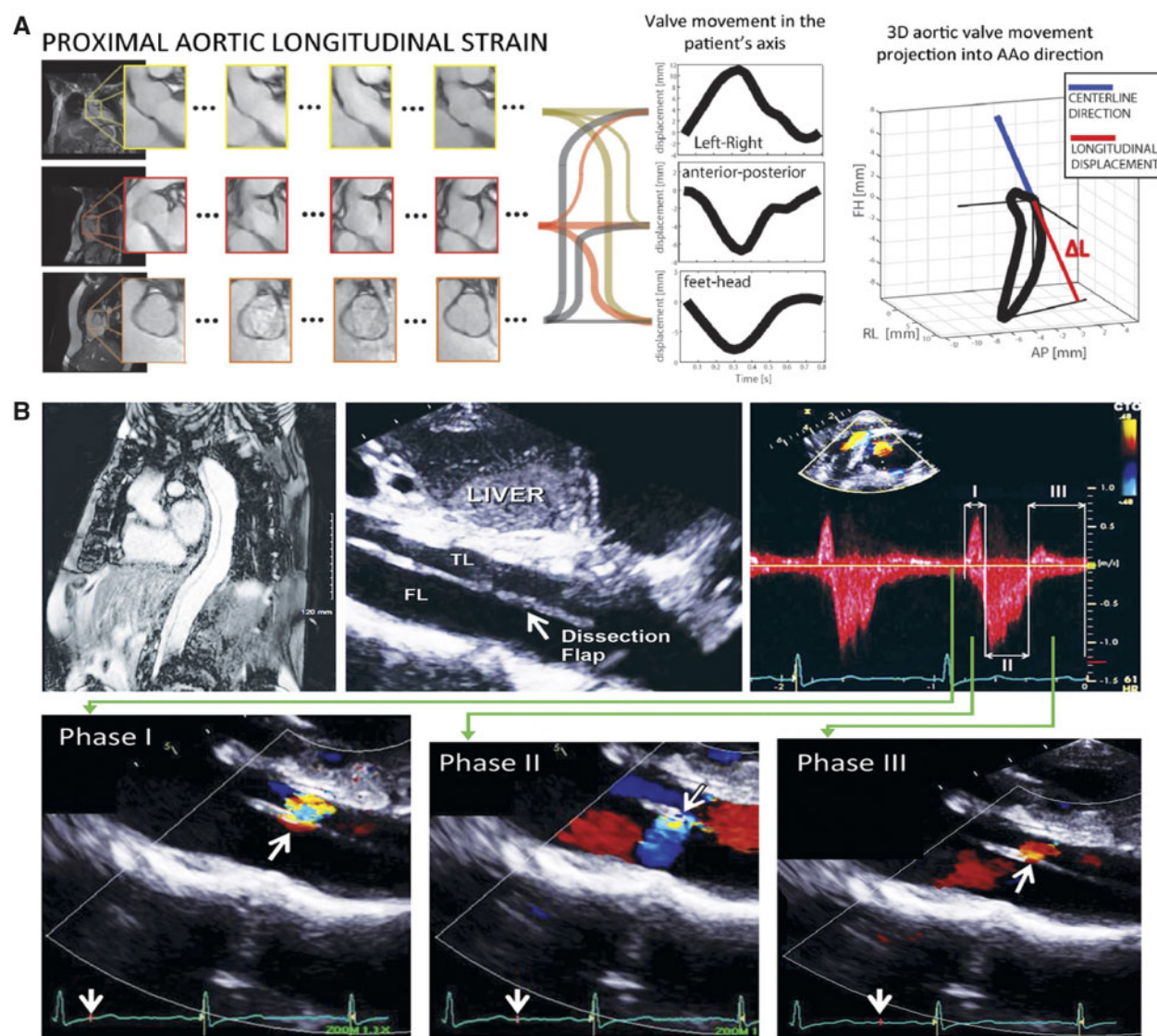


Figure 2 New imaging techniques for risk stratification in patients with aortic diseases (A) methods for proximal longitudinal strain measurement by magnetic resonance imaging.²³ (B) Doppler approach to flow in aortic dissection. Reproduced with permission from Ref.²⁴

higher in high-income countries than in low- and middle-income countries (LMIC) (7.4% vs. 5.1%), although the vast majority of patients (73%) lived in LMIC. This prevalence was similar between sexes, with higher rates of young (<50 years) patients in LMIC.

The association of LEAD with major adverse cardiovascular events (MACE) is well documented, whereas its association with limb events is less clear. In the *Veterans Aging Cohort Study*, including 125 674 subjects without history of prior amputation, the incidence of amputation over a median of 9.3 years of follow-up was 1.2 per 1000 person-years.²⁸ The presence of LEAD conferred a 13.9-fold increase in amputation risk, but microvascular disease (MVD), defined as retino-, neuro-, and/or nephropathy, was also associated with a 3.7-fold risk increase, and the combination of LEAD and MVD lead to a 22.7-fold increased risk. Importantly, MVD alone was associated with 15% of all below-the-knee amputations.

Among the 13 885 patients with an ABI ≤ 0.8 or prior lower extremity revascularization (LER) randomized to ticagrelor vs. clopidogrel in the *Examining Use of Ticagrelor in Peripheral Artery Disease* (EUCLID) trial, the rate of acute limb ischaemia (ALI) requiring hospitalization was 0.8 per 100 patient-years, with no difference between treatment arms.²⁹ Acute limb ischaemia was strongly associated with subsequent MACE (aHR 1.4, 95% CI 1.0–2.1), all-cause mortality (aHR 3.3, 95% CI 2.4–4.6), and major amputation (aHR 34.2, 95% CI 9.7–20.8). Previous LER, baseline atrial fibrillation, and baseline ABI ≤ 0.60 were independent predictors of ALI. In this trial, a second analysis showed that 12.5% of patients experienced LER during the trial.³⁰ Independent predictors of post-randomization LER were prior history and type of prior LER ($P < 0.0001$), living in North America or Europe ($P < 0.0001$), presence of limb symptoms at baseline (HR 1.3; 95% CI 1.2–1.5), diabetes (HR 1.3; 95% CI 1.1–1.4), and smoking (HR

1.2; 95% CI 1.1–1.4). Cardiac and limb events were numerically higher in patients undergoing surgical procedures, but surgical patients experienced fewer LERs after the index LER.

A growing proportion of ALI hospitalizations occurs in cancer patients who experience arterial thromboembolism. In the population-based *Surveillance Epidemiology and End Results-Medicare* linked dataset, 374 331 patients ≥ 67 years with primary diagnosis of breast, lung, prostate, colorectal, bladder, uterine, pancreatic, gastric cancer, or non-Hodgkin lymphoma were identified.³¹ The risk of arterial thromboembolic events began to increase 150 days before the date of cancer diagnosis in older patients and peaked in the 30 days before cancer diagnosis, when 0.62% of patients suffered an arterial thromboembolic event vs. 0.11% in control subjects (OR 5.63; 95% CI 5.07–6.25).

Lipid lowering is a key element of LEAD treatment.⁴ The 2019 ESC guidelines recommend a LDL-cholesterol reduction of $\geq 50\%$ and a goal of < 55 mg/dL (1.4 mmol/L) for LEAD patients, to be achieved with statins, plus ezetimibe and PCSK9 inhibitors if needed.¹⁰ A recent pre-specified analysis of the *Evaluation of CV Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab* (ODYSSEY OUTCOMES) trial further supports these recommendations.³² After a median follow-up of 2.8 years, the 1554 patients with atherosclerotic disease in two or three vascular beds (coronary, lower limb, and/or cerebrovascular) showed a significantly larger absolute risk reduction with alirocumab, as compared to patients with isolated coronary artery disease (CAD). The absolute risk reduction regarding MACE was 1.9% (95% CI -2.4% to 6.2%) and 13.0% (95% CI -2.0% to 28.0%) for two and three vascular beds, respectively, whereas regarding all-cause mortality was 1.3% (95% CI -1.8% to 4.3%) and 16.2% (95% CI 5.5–26.8%), respectively.

Another pillar of the medical treatment of LEAD is optimal control of arterial hypertension.^{4,33} A recent analysis from the *Atherosclerosis Risk in Communities* (ARIC) study evaluated the impact of different stages of hypertension on the development of LEAD.³⁴ During a median follow-up of 25.4 years, a systolic blood pressure (BP) ≥ 140 mmHg or diastolic BP ≥ 90 mmHg was associated with higher rate of incident LEAD diagnosis (HR 2.40; 95% CI 1.72–3.34), independent of the use of anti-hypertensive medications. Higher BP categories showed significant associations with incident LEAD starting from 120 to 129 mmHg for systolic BP and ≥ 90 mmHg for diastolic BP. These data emphasize the need for BP control to prevent the development of LEAD.

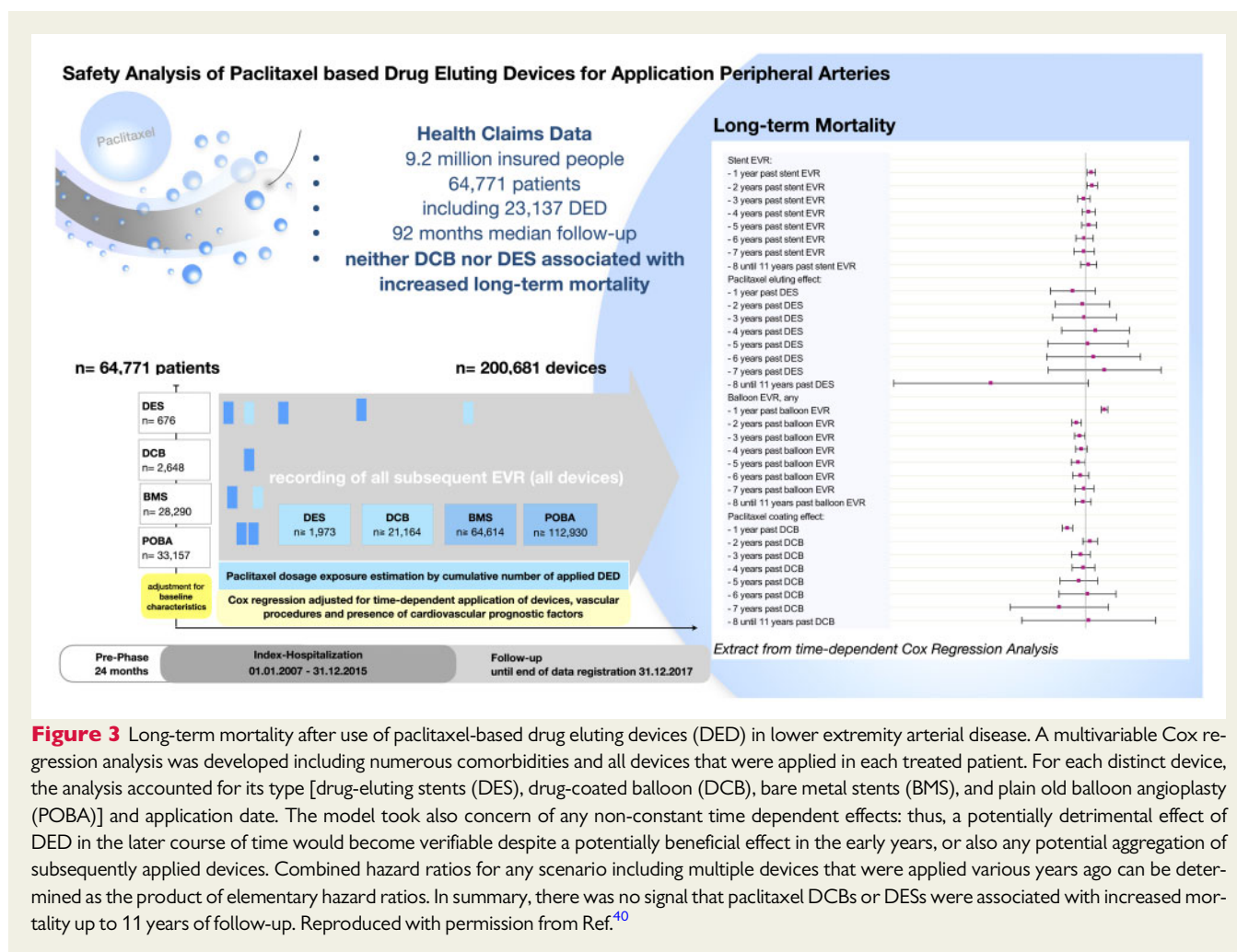
While supervised exercise training is a mainstay of the management of claudication,⁴ low adherence rates limit its clinical application. In a randomized study, 156 participants were allocated to supervised treadmill exercise, supervised resistance training, or oral advice about nutrition and training.³⁵ After 6 months, the 6-min walk distance improved only in the treadmill exercise group (36.1 m, 95% CI 13.9–58.3), but at 12 months neither treadmill nor resistance significantly differed from baseline or control (walking distance: +7.5 m and +6.1 m). These results highlight the need for long-term supervised exercise programmes to maintain benefits. Additionally, a systematic review of 84 studies reported that alternative training modalities (circuit exercise, low-pain and pain-free walking, resistance training, upper/lower limb ergometry, and pole striding) had significantly higher adherence and completion rates vs. traditional exercise training (85.5% vs. 77.6%, and 86.6% vs. 80.8%, respectively).³⁶

In lack of randomized controlled trials (RCTs), a large gap in evidence regards the best revascularization strategy in chronic limb threatening ischaemia (CLTI). In a retrospective analysis, 16 800 patients with CLTI who had first surgical LER (36%) were compared to those with first endovascular LER (64%).³⁷ The endovascular group was younger, but suffered from more comorbidities, including renal failure (36% vs. 24%), CAD (34% vs. 32%), heart failure (19% vs. 15%), and diabetes (65% vs. 58%; all $P < 0.05$). In a propensity-matched analysis, a surgery-first strategy was associated with worse amputation-free survival (HR 1.16, 95% CI 1.13–1.20), while an endovascular-first strategy was associated with higher reintervention rates (HR 1.19, 95% CI 1.14–1.23) after 80 months of follow-up. Mortality was similar between groups (HR 0.94, 95% CI 0.89–1.11). These results suggest that an endovascular-first approach might be preferable regarding amputation-free survival.

Several trials have shown the superiority of drug-eluting stents (DES) and drug-coated balloons (DCBs) vs. plain balloon angioplasty (PTA) in patients with femoropopliteal disease.^{1–3} The 5-year results of the IN.PACT SFA trial showed the persistence of clinical benefits, with 74.5% freedom from clinically driven target lesion revascularization with DCBs vs. 65.3% with PTA ($P = 0.020$), although this benefit was non-significant in diabetics (70.3 vs. 64.4%, $P = 0.24$).³⁸ The clinical use of paclitaxel-eluting devices was dramatically interrupted in November 2018 by the unexpected results of a meta-analysis including 28 RCTs with a total of 4432 patients.³⁹ The study described a two-fold increase in all-cause mortality between 2 and 5 years of follow-up with paclitaxel-eluting DES/DCBs (HR 1.93, 95% CI 1.27–2.93), and a causal link between paclitaxel dose and mortality was hypothesized. These findings raised great concern, halted enrolment in RCTs on paclitaxel-eluting devices, and prompted a worldwide call for high-quality data collection and analysis. Most recently, a confutation of the above-mentioned study came from a large analysis of German health claims data, investigating long-term mortality with paclitaxel-eluting devices from 2007 until present in 64 771 patients undergoing 107 112 endovascular procedures.⁴⁰ The use of paclitaxel-eluting devices was not associated with any signal of increased mortality up to 10 years of follow-up (Figure 3).

Venous thromboembolism

In 2019, the ESC issued updated guidelines for management of patients with acute pulmonary embolism (PE).⁴¹ Key points include use of age-adjusted D-dimer cut-off in preclinical risk assessment. Furthermore, categorization of PE events in 'provoked' and 'unprovoked' is no longer suggested. Rather, occurrence of index event in presence of 'reversible risk factor', or in absence of any 'identifiable risk factor' is suggested for patient stratification and guidance of treatment duration. For the first time, direct oral anticoagulants (DOACs) are recommended over vitamin K antagonists for PE treatment in eligible patients as for patients with atrial fibrillation. A reduced dose of apixaban or rivaroxaban for extended anticoagulation should be considered after the first 6 months of treatment. Edoxaban or rivaroxaban should be considered as an alternative to low molecular weight heparin in patients with non-gastrointestinal cancer who experience VTE. A new recommendation (class IIa, level A) proposes that carefully selected, low-risk PE patients should be considered for early



discharge and home treatment, as long as proper outpatient care and anticoagulant therapy are possible (Figure 4). A recent prospective multicentre single-arm trial further corroborates this recommendation. Low-risk PE patients (no HESTIA criteria present, and absence of right ventricle enlargement/dysfunction) were early discharged (maximum of two nights in hospital) for home treatment with rivaroxaban. The study was prematurely terminated because of low symptomatic VTE recurrence and PE-related death rates (0.6%; one-sided upper 99.6% CI 2.1%), and low bleeding episodes (1.2%) at 3 months from diagnosis.⁴³ Careful selection of low-risk PE patients is key in successful home treatment; in this regard, clinical severity scores alone may not be sufficient to identify such low-risk group especially with regard to subclinical right ventricular dysfunction exclusion. Therefore, combining right ventricular assessment to clinical criteria further allow proper risk stratification as recently suggested by Barco et al.⁴⁴

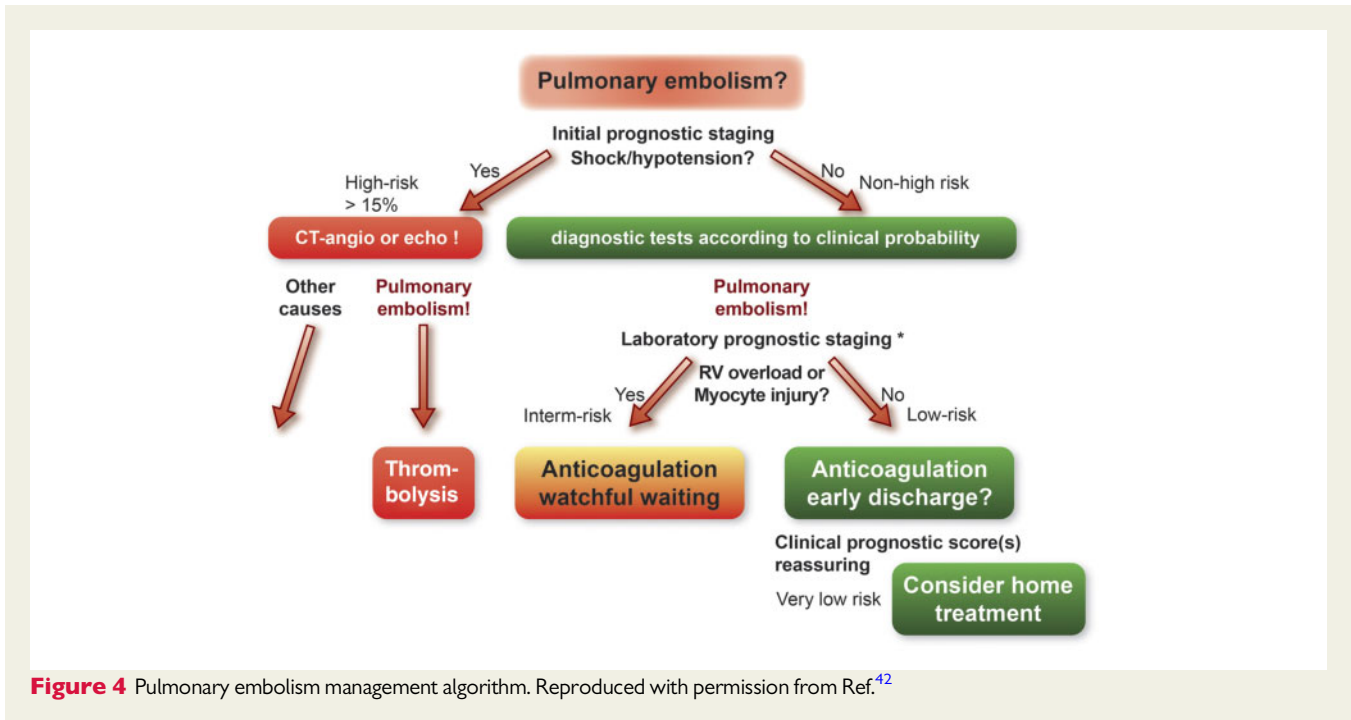
The diagnosis of PE during pregnancy is challenging with wide pregnancy-related and PE suspicion symptoms overlap. Overall PE prevalence is however low thus exposing patients to unnecessary imaging tests. The 2019 ESC PE guidelines propose a dedicated diagnostic algorithm for suspected PE in pregnancy using stratification tools based on clinical presentation, D-Dimer testing, and

compression ultrasonography of lower extremities. The pregnancy adapted YEARS algorithm, which takes into account these three parameters, was recently shown to safely rule out PE across all trimesters of pregnancy avoiding a significant number of imaging tests.⁴⁵

Management of vein thrombosis at unusual sites is challenging in practice. Whether patients with isolated distal deep vein thrombosis (IDVT) should be systematically treated with anticoagulation is still questioned. It is suggested to stratify patients with IDVT in high- and low-risk of recurrence.⁴⁶ Those at high risk should be anticoagulated as for proximal deep vein thrombosis.⁴⁷ With this regard, recent prospective registries suggested that patients with IDVT may be treated with DOACs although data from clinical trials are still missing.^{48,49}

Perspectives

Exciting new scientific data published in 2019 shed more light on the nuances of atherosclerosis among the different peripheral vascular territories. The year 2020 is highly awaited for vascular specialists, with the completion of the *Vascular Outcomes study of ASA along with rivaroxaban in endovascular or surgical limb revascularization for peripheral artery disease (VOYAGER PAD)* study, evaluating the efficacy and safety of rivaroxaban 2.5 mg b.i.d. together with aspirin in reducing the risk



of major thrombotic vascular events in subjects with symptomatic LEAD undergoing surgical or endovascular revascularization (NCT02504216). Additionally, further data will become available addressing the safety of paclitaxel-coated technology for LEAD revascularization. In the field of VTE, data from the CARAVAGGIO study (NCT03045406), comparing apixaban to dalteparin, for the treatment of acute VTE in cancer patients, are awaited.

Conflict of interest: C.H. reports research grants from Deutsche Forschungsgemeinschaft, Mitsubishi Cleansui, Wild Blueberry Association of North America, National Processed Raspberry Council, University of Surrey, Philips, Cranberry Institute, Rheacell; personal fees from Bayer, Novo Nordisk, Profil Institute outside the submitted work. J.J.F.B. reports grants and personal fees from Bayer and Rexgenero, personal fees from Amgen, outside the submitted work. M.D.C. reports personal fees from Bayer and Sanofi, outside the submitted work. H.R. reports grants from Bard, Biotronik, Bayer, personal fees from Diaplan, MedUpdate, Daichi Sankyo, and NeoVasc, personal fees and other support from NovoNordisk; other support from Bristol Myers Squibb and Pfizer; grants, personal fees, and other support from Pluristem outside the submitted work and is the senior author of a manuscript which is presented/reviewed in this article. A.P. reports personal fees from Actelion Pharmaceuticals Ltd and from Bristol-Myers Squibb Pharmaceuticals Limited, outside the submitted work. V.A. declares personal fees from Amgen, Bayer, Novartis, NovoNordisk, BMS/Pfizer alliance, and Sanofi, as speaker or advisor. L.M. and I.B. have declared no conflict of interest.

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