Progress in aorta and peripheral cardiovascular disease research

Lucia Mazzolai1*, Adriano Alatri1, Alessandra Bura Rivi`ere 2, Marco De Carlo 3, Christian Heiss 4, Christine Espinola-Klein 5, Oliver Schlager 6, Henrik Sillesen 7, Daniel Staub 8, Jose´ F. Rodriguez-Palomares 9, Aline Verstraeten 10, and Victor Aboyans 11; on behalf of the WG on aorta and peripheral vascular diseases

1Division of Angiology, Heart and Vessel Department, Lausanne University Hospital (CHUV), Lausanne, Switzerland; 2Division of Vascular Medicine, Heart, Vessels and Metabolisms Department, Toulouse University Hospital, Toulouse, France; 3Cardiothoracic and Vascular Department, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; 4Department of Clinical and Experimental Medicine, Faculty of Health and Medical Sciences, University of Surrey, Guildford GU2 7XH, UK; 5Section Angiology, Department of Cardiology, Cardiology I, University Medical Center Mainz, Mainz, Germany; 6Division of Angiology, Department of Medicine II, Medical University of Vienna, Waehringer Gu¨rtel 18-20, 1090 Vienna, Austria; 7Department of Vascular Surgery, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; 8Division of Angiology, University Hospital Basel, University of Basel, Basel, Switzerland; 9Cardiology Department, Hospital General Universitari Vall d’Hebron, Vall d’Hebron Research Institute (VHRI), CIBER-CV, Barcelona, Spain; 10Centre of Medical Genetics, Faculty of Medicine and Health Sciences, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium; and 11Department of Cardiology, Dupuytren-2 University Hospital, and Inserm 1094 & IRD, Limoges University, Limoges, France

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Abstract

Although coronavirus disease 2019 seems to be the leading topic in research number of outstanding studies have been published in the field of aorta and peripheral vascular diseases likely affecting our clinical practice in the near future. This review article highlights key research on vascular diseases published in 2020. Some studies have shed light in the pathophysiology of aortic aneurysm and dissection suggesting a potential role for kinase inhibitors as new therapeutic options. A first proteogenomic study on fibromuscular dysplasia (FMD) revealed a promising novel disease gene and provided proof-of-concept for a protein/lipid-based FMD blood test. The role of NADPH oxidases in vascular physiology, and particularly endothelial cell differentiation, is highlighted with potential for cell therapy development. Imaging of vulnerable plaque has been an intense field of research. Features of plaque vulnerability on magnetic resonance imaging as an under-recognized cause of stroke are discussed. Major clinical trials on lower extremity peripheral artery disease have shown added benefit of dual antithrombotic (aspirin plus rivaroxaban) treatment.

Keywords

Aorta • Peripheral artery disease • Venous thromboembolism • COVID • Antithrombotics

1. Introduction

The year 2020 was overshadowed by the spread of the novel coronavirus disease 2019 (COVID-19). Four months after the first cases in China, Varga et al. 1 described the involvement of the vascular endothelium in patients with COVID-19.

Nevertheless, the year 2020 was also characterized by outstanding publications in the field of aortic and peripheral vascular diseases, potentially improving the clinical management in the future.

This article summarizes the main findings from key studies published in 2020 on the basic science, epidemiology, imaging, and clinical trials addressing aortic and peripheral arterial and venous diseases. A specific chapter on vascular complications secondary to COVID-19 infection is also addressed. For this review, the authors performed a systematic review of published research papers in major vascular areas (arterial, venous, aorta, basic science, clinical trials, and COVID). The final selection was discussed within the group through a consensus.

2. Basic science

2.1 Aortic aneurysm and dissection

In 2020, multiple putative aortic aneurysm and dissection (AoAD) therapeutic targets were identified, two of which are detailed here.
In two small-scale case–control cohorts, a common missense variant in the alcohol-metabolizing aldehyde dehydrogenase 2 protein (ALDH2 p.Glu504Lys; gnomAD v2.1.1 MAFtotal: 1.8% vs. MAFAsians: 10.1%) previously linked to increased coronary artery disease risk, was suggested to be associated with protection from AoAD. Further proof of a direct relationship between ALDH2 activity and AoAD risk was next pursued in two different AoAD mouse models. In angiotensin II- or 3-aminopropionitrile fumarate-infused mice, ALDH2 inhibition by the isoflavone daidzin was shown to partially rescue the aortopathy phenotype as demonstrated by mitigation of elastic fibre fragmentation, near-normalization of aortic wall thickness, and a concomitant reduction in the incidence of AoAD. Further disentanglement of molecular mechanisms underlying this protective effect exposed a critical role for miR-31-5p-dependent inhibition of the pathological contractile-to-synthetic vascular smooth muscle cell (VSMC) phenotype switch. Specifically, ALDH2 loss-of-function represses the expression of miR-31-5p, which results in elevated myocardin levels and, consequently, increased expression of the VSMCs’ contractile apparatus genes (i.e. α-SMA, SM22-a, and calponin).

AoAD is also an important complication of the vascular Ehlers–Danlos syndrome (vEDS), caused by heterozygous mutations in the collagen Type III alpha 1 chain (COL3A1) gene. Contrary to some other heritable aortopathies (e.g. Marfan syndrome), vEDS-related dissections or ruptures can occur without prior aneurysm formation, and involve also muscular arteries. Bowen et al. created two vEDS mouse models (Col3a1<sup>−/−</sup> and Col3a1<sup>1938del+</sup>) corresponding to known human vEDS-causing mutations and presenting with sudden death due to aortic dissection or rupture in the absence of prior dilatation and major architectural wall deterioration. Comparative aortic transcriptome analysis of mutant mice and their wild-type (WT) littermates suggested excessive signalling through the PLC/IP3/PKC/ERK axis as a key disease culprit. Whereas administration of blood pressure-lowering agents such as beta-blockers did not improve survival rates, pharmacological treatment with ERK1/2 or PKC<sub>b</sub> inhibitors (i.e. riboxistaurin, cobimetinib, and hydralazine) improved survival from 52% to 90–97%, confirming considerable translational weight to the transcriptome findings. Similar to humans, pregnancy/lactation- and male puberty-associated exacerbation of aortic dissection/rupture risk were observed in the vEDS mice, all of which could be rescued by oxytocin and androgen signalling attenuation, respectively. Altogether, these studies put forward ALDH2, miR-31-5p, and the PLC/IP3/PKC/ERK axis as novel targets for AoAD prevention and, in the latter case, emphasized the role of androgen signalling and breastfeeding (oxytocin) in vEDS-related aortic dissection/rupture risk.

Niacin is known to prevent atherosclerosis via anti-inflammatory effects by activating the G protein-coupled receptor GPR109A on immune cells. An experimental study in mice indicates now that niacin could prevent abdominal aortic aneurysm (AAA) development independent of GPR109A. The authors show that niacin markedly blunted AAA formation in two mouse models (angiotensin II and CaCl<sub>2</sub>) with lower inflammatory responses and matrix degradation. Importantly, deletion of GPR109A gene did not prevent the protective effects. Nicotinamide led to very similar results with increases in NAD<sup>+</sup> concentrations and Sirt1 activity suggesting that both niacin and nicotinamide could become novel therapeutic agents to prevent AAA. Nicotinamide or related molecules may have the advantage of not causing flushing, a side effect of niacin linked to GPR109A.

2.2 Fibromuscular dysplasia

Fibromuscular dysplasia (FMD) affects predominantly middle-aged women and causes stenosis, tortuosity, aneurysm, and/or dissection of medium-sized arteries. It is often asymptomatic, and its aetiology poorly understood. A first FMD plasma proteomics and lipidomics study in 90 multifocal FMD patients and 100 age-sex-matched control individuals revealed differential abundance of 105 proteins and 16 lipid sub-classes (particularly triglycerides and fatty acids). Of these, 37 proteins and 10 lipid sub-classes were confirmed as being up- or downregulated in an independent validation cohort of 23 FMD patients and 28 controls. Using machine learning approaches, a combined protein and lipid signature reaching, respectively, a sensitivity and specificity of 78.3% and 64.3% was developed. Additionally, protein quantitative trait locus mapping and subsequent Bayesian network classification suggested CD2AP, PODXL2, and TACC3 to be upstream of FMD development and, therefore, to be candidate disease drivers. Moreover, an independent genetic association study in 506 FMD patients and 876 healthy individuals revealed a significant relationship between single-nucleotide polymorphisms in the upstream region of CD2AP expressed by endothelial cells of medium-sized arteries. Like PODXL2, CD2AP has been suggested to play a role in vascular leucocyte adhesion and rolling, and increased FMD risk [top-hit: rs9296551; ~odds ratio (OR) 1.36]. This first proteogenomic FMD study revealed a promising novel disease gene and provided proof-of-concept for a protein/lipid-based FMD blood test.

2.3 Atherosclerosis

Chronic inflammation and autoimmunity play important roles in the atherosclerosis development and stability of atherosclerotic plaques. Recently, relevance of co-stimulatory immune checkpoint protein glucocorticoid-induced tumour necrosis factor receptor family-related protein (GITR) in atherogenesis has been shown. GITR is known for activating and regulating effects on T cells. A novel role of GITR is proposed, in driving myeloid cell recruitment and activation in atherosclerosis, thereby inducing plaque growth and vulnerability. GITR expression was elevated in carotid endarterectomy specimens from 100 patients with symptomatic carotid disease vs. those extracted from asymptomatic patients (n = 93). GITR was essentially found in macrophages, endothelial cells, and T cells, and similar patterns were also observed in femoral endarterectomy samples. GITR expression correlated with signs of plaque vulnerability. Furthermore, patients with cardiovascular (CV) disease showed elevated soluble plasma GITR levels compared to healthy controls. In 28-week-old Girt<sup>−/−</sup>Apo<sup>e<sup>−/−</sup></sup> mice extension of aortic atherosclerosis was reduced, and plaques showed a more stable phenotype with fewer macrophages, smaller necrotic core, and a thicker fibrous cap. Lymphocytes were not affected by GITR deficiency. Monocyte and macrophage cell migration, activation, and mitochondrial function were differently modulated in Apoe<sup>−/−</sup> and Girt<sup>−/−</sup>Apo<sup>e<sup>−/−</sup></sup> mice. In Girt<sup>−/−</sup>Apo<sup>e<sup>−/−</sup></sup> mice, monocytes showed decreased integrins and reactive oxygen species (ROS) levels as well as reduced endothelium recruitment. Along the same line, macrophages showed reduced migratory capacity and lower cytokines production. Altogether (Figure 1), these data indicate that GITR plays a pivotal role and is a potential therapeutic target in atherosclerosis.

Cell membrane exteriorization of phosphatidylycerine and phosphatidylethanolamine (PE) occurring during apoptosis within plaques contributes to several high-risk features of vulnerable plaque. Recently, molecular imaging with PE-avid radiolabeled oxytetracycline in experimental atherosclerotic lesions was investigated in rabbits. The <sup>99m</sup>Tc-oxytetracycline uptake was two-fold higher in the test group of 21 rabbits on high-fat diet for 16 weeks vs. 6 rabbits on normal chow (controls) and 6 negative radiotracer control animals (<sup>99m</sup>Tc-linear oxytetracycline without PE-binding capability). On histology, oxytetracycline uptake
correlated to lesion severity and macrophage burden. This study represents a notable step towards atherosclerosis molecular imaging using radiolabeled oxytetracycline to localize lipid-rich areas with high levels of apoptotic macrophages in an experimental model. Further clinical studies in humans are awaited to detect vulnerable high-risk plaques.

A few interesting papers highlighted the important and complex role of NADPH oxidases in vascular physiology beyond their role as ROS producers and atherosclerosis mediators. A review of a large body of literature shows that endothelial cell differentiation requires ROS and NADPH oxidases (Nox1, 2, 4, and 5) and these are important local modulators of the signalling networks regulating differentiation of stem cells to endothelial cells.8

Understanding the specific roles of NADPH oxidases may also help to further develop cell-based therapies. For instance, in cord blood-derived endothelial colony-forming cells, Nox4 could be a future therapeutic target as it enhances the reparative functions of these cells supporting the creation of a pro-reparative microenvironment and effective post-ischaemic revascularization.9 The requirement for Nox4-derived ROS in vivo was highlighted by a mouse study demonstrating that Nox4-derived H2O2 plays a key role in exercise-induced vascular adaptations.10 Exercise led to an increased H2O2 release in the aorta of WT mice with adaptations of the eNOS and Ppargc1a pathway, and intracellular calcium release. In Nox4−/− mice, the physical activity performance and vascular protective effects of exercise were inhibited.

3. Epidemiology and prevention

A recent analysis from the Framingham Heart Study and the Danish nationwide administrative registries showed strong familial association of aortic aneurysm.11 Children of parents with aorta sized in the upper quartile (adjusted for age, sex, and body surface area) had a three-fold increased risk of being themselves in that aortic diameter upper quartile. Additionally, first-degree relatives of patients with ascending aortic aneurysm had a 6.7-fold increased risk in developing an ascending aortic aneurysm, and a 9.2-fold risk for aortic dissection. These observations support the use of systematic screening for aortic diseases in affected families.12

Patients with lower extremity artery disease (LEAD) have a high risk for major adverse cardiovascular events (MACE) and major adverse limb events (MALE). Recent analysis of UK electronic health reports showed a 15% decrease in LEAD incidence between 2006 and 2015 [from 236 to 202 per 100,000 person-years; adjusted incidence rate ratio (IRR) 0.85, 95% confidence interval (CI) 0.82–0.88]. However, CV mortality for incident LEAD did not decline significantly (adjusted IRR 0.84, 95% CI 0.70–1.00), at variance with the significant 43% fall in mortality for incident coronary artery disease.13

New insights on the pathophysiological mechanisms underlying the dismal prognosis of patients with chronic limb-threatening ischaemia come from a study demonstrating the association between CD34+ cell migration and long-term CV mortality. In coculture, CD34+ cells imprinted naive endothelial cells, increasing apoptosis and reducing network formation.14 An altered paracrine signalling from CD34+ cells to the endothelium may contribute to the increased CV risk in these patients.

The lack of improvement in CV prognosis of LEAD patients extends also to limb prognosis, as demonstrated by a new analysis from the 2017 Global Burden of Disease study.15 Data from 16 European countries, Canada, Australia, and the USA between 1990 and 2017 showed wide
time trend variability among countries and between sexes regarding amputa-
tion proximal to toes, in the absence of uniform improvements. New data on the impact of revascularization on limb prognosis in claudi-
cants were reported in a retrospective analysis of 11 887 elective endo-
vascular procedures. One-year amputation rate was 1.1%; independent predictors of major amputation were congestive heart fail-
uire (OR 6.5, 95% CI 2.4–17.2), American Society of Anesthesiologists Class IV (OR 9.3, 95% CI 1.9–44.9), non-white race (OR 3.3, 95% CI 1.5–
7.4), and tibial-level intervention (OR 6.3, 95% CI 1.5–26.1).

Women were previously considered to have poorer prognosis when
affected by LEAD, but this has been contradicted by two recent post hoc
analyses of large randomized-controlled studies (RCTs). In the EUCLID
(Examing Use of Ticagrelor in PAD) trial, women with LEAD were at
lower risk for MACE compared with men [9.5% vs. 11.2%; adjusted haz-
ard ratio (HR) 0.77; P = 0.37]. Similarly, in the COMPASS
(Cardiovascular Outcomes for People Using Anticoagulant Strategies)
trial, women had similar rates for MACE and major bleeding. There
were no sex-related interaction regarding the benefits in reducing
MACE under low-dose rivaroxaban plus aspirin vs. aspirin alone
(women: HR 0.72; men: HR 0.76; Pinteraction = 0.75) or major bleeding
(women: HR 2.22; men: HR 1.60; Pinteraction = 0.19).

Benefits of a more potent antithrombotic therapy in LEAD patients
were recently confirmed in a meta-analysis encompassing seven RCTs
comparing various antithrombotic regimens. More vs. less intense
antithrombotic therapy reduced significantly the risk of limb revasculari-
zation, limb amputation, and stroke (Figure 2), without significant effects
on myocardial infarction and CV death, but at cost of increased risk of
(major) bleeding, highlighting the importance of individualized risk/bene-
fit assessment.

4. Imaging

The largest diameter of the aorta is considered as the main risk factor
for aortic rupture and dissection and, therefore, this criterion is recom-
ended to guide interventions. However, the measurement of aortic di-
ameter (especially at the aortic root) has multiple limitations. Several
imaging techniques and measurement protocols exist suggesting that
established thresholds of aortic diameters might not be fully adequate.
Therefore, it is highly recommended to be very exhaustive when per-
forming aortic measurements, indicating in detail the methodology used.

To overcome these limitations, new parameters have been recently
introduced. Ascending aortic length (length > 13 cm) has been associ-
ated with a five-fold increase in aortic events (rupture, dissection, or
death). Furthermore, increased aortic stiffness (aortic strain reduction)
correlated with higher incidence of dissection or surgery in Marfan
patients. A recent study showed that both ascending aortic length and
volume improve prediction of aortic dissection in case of ascending aor-
tic aneurysms. Patients (n = 25) with type A acute aortic dissection
who had a computed tomography (CT) within the prior 2 years were
compared to those with thoracic aortic aneurysm and no-acute aortic
dissection (n = 75), and healthy controls (n = 258). Aortic diameter was
similar between patients with and without acute aortic dissection (45 vs.
46 mm, respectively, P = 0.079), as well as aortic volume (126 vs.
124 cm³, respectively, P = 0.075) as well as aortic volume (126 vs.
124 cm³, respectively, P = 0.075), as well as differences in aortic length (90 vs.
84 mm, respectively, P = 0.031). Aortic volume and length showed, re-
spectively, a five-fold and a seven-fold sensitivity in predicting acute aor-
tic dissection while the aortic length presented 70% positive predictive
value.

Not only the carotid artery stenosis severity, but also the atheroscle-
rotic plaque composition and morphology are increasingly recognized as
important features determining stroke risk. High-resolution, contrast-en-
hanced carotid magnetic resonance imaging (MRI) enables non-invasive
characterization of carotid artery plaques (CAP), including features of
plaque vulnerability as intraplaque haemorrhage, thin and/or ruptured fi-
brous cap, large lipid-rich and/or necrotic core, and mural thrombus.
The CAPIS study investigated a causal role between complicated CAP
and specific MRI plaque features with cryptogenic stroke. Using a sub-
tle prospective study, 234 patients with acute ischaemic stroke restricted
to single carotid artery territory on brain MRI, and unilateral or bilateral
CAP were recruited. Among patients with cryptogenic stroke (n = 104),
prevalence of ipsilateral complicated CAP on MRI was significantly higher
ipsilateral (31%) vs. contralateral to the infarct (12%; P = 0.0005). The
prevalence of ipsilateral complicated CAP in cryptogenic stroke was also
significantly higher than in patients with cardioembolic or small vessel
stroke (15%; P = 0.02), but significantly lower than in those with large ar-
tery stroke and ipsilateral 50–69% carotid stenosis (68%; P = 0.003).
These finding substantiate the role of complicated non-stenotic CAP
with imaging features of plaque vulnerability on MRI as an under-recog-
nized cause of stroke. Further studies are needed to determine a possi-
bile interventional approach in patients with such lesions.

Non-invasive assessment of limb perfusion and its impact in predicting
wound healing and amputation outcome could be of particular impor-
tance in patients with critical limb ischaemia (CLI). Different methods for
skin or muscle perfusion imaging have been developed, using hyperspec-
tral, laser Doppler, MR-based methods, and contrast-enhanced ultra-
sound techniques, with poor clinical application. In a prospective study
of 25 patients with diabetes and CLI, pedal perfusion was assessed be-
fore and after revascularization, using ⁹⁹mTc-tetrofosmin single-photon-
emission computed tomography (SPECT)/CT perfusion imaging of seg-
mented angiosomes of the foot. SPECT/CT detected a significantly
higher at 3 and 12 months after revascularization. The amputation-free survival rate was significantly
higher at 3 and 12 months for high-perfusion than low-perfusion

Figure 2 Forest plot of risk of adverse events with more intense vs.
less intense antithrombotic therapy in patients with lower extremity ar-
tery disease. The 95% CIs are denoted by lines (modified from Savarese
et al.). CI, confidence interval; CV, cardiovascular.
responders to revascularization. Therefore, SPECT/CT imaging could provide new prognostic information on regional perfusion response to lower extremity revascularization.

5. Clinical trials

5.1 Aorta

Several clinical trials have been published in 2020 (Table 1). The TEDY study investigated whether telmisartan 40 mg daily could slow small AAAs growth, as measured by ultrasound and CT scanning. Among the 207 patients included in the intention-to-treat analysis, no significant difference in ultrasound-assessed AAA growth rates was found among those under telmisartan (1.68 mm/year) vs. placebo (1.78 mm/year, \(P = 0.66\)). Similarly, telmisartan did not significantly affect AAA growth assessed by CT-measured AAA diameter or volume. The presence of mural thrombosis is considered as contributive to the AAA growth. The TicAAA study, randomized 144 patients with AAA to receive either ticagrelor 90 mg twice daily or placebo. After 12 months, the AAA volume growth rate assessed by MRI did not differ between the ticagrelor and the placebo groups (9.1% vs. 7.5%, \(P = 0.205\)). Neither the AAA diameter nor the intraluminal thrombus volume change differed between treatment groups.

Both TEDY and TicAAA trials were of short duration (1 year) and potential benefits with longer treatment durations need further investigations. In addition, the percentage proportion of female patients was low (TEDY 12%, TicAAA 4.2%), which does not allow any conclusion with respect to sex differences in treatment effects.

5.2 LEAD

The VOYAGER trial tested whether rivaroxaban 2.5 mg b.i.d. + aspirin 100 mg (dual pathway inhibition, DPI) was superior to aspirin 100 mg alone (control) in preventing thrombotic events after lower limbs revascularization. This multicentre, prospective RCT included 6564 patients (26% females) undergoing infra-iliac arterial revascularization. Primary efficacy outcome was a composite of acute limb ischaemia, major amputation for vascular causes, myocardial infarction, ischaemic stroke, or death from CV causes. It occurred in 17.3% patients in the DPI vs. 19.9% in the control group (HR 0.85, 95% CI 0.76–0.96; \(P = 0.009\)). The most frequent component of the primary endpoint, acute limb ischaemia, occurred in 5.2% in the DPI and 7.8% in the control group (HR 0.67, 95% CI 0.55–0.82). No heterogeneity with respect to patients’ sex was reported. TIMI major bleeding occurred in 2.65% patients in the DPI and in 1.87% in the control group (HR 1.43, 95% CI 0.97–2.10; \(P = 0.07\)). Overall, for every 10 000 patients treated for 1 year DPI would prevent 181 primary efficacy outcome events at the cost of 29 principal safety outcome events. The rate of the combined cumulative incidence of recurrent VTE or major bleeding was observed between both arms. The rate of the combined cumulative incidence of recurrent VTE or major bleeding did not differ between groups.

Together with previous trials, the Caravaggio trial further promotes the use of direct oral anticoagulants in patients with cancer. Clinicians should take into consideration individual bleeding risks, concomitant medication, and cancer types (e.g. patients with brain tumours, known intracerebral metastases, or acute leukaemia were excluded from Caravaggio) in cancer patients with VTE.

5.3 Venous thromboembolism

The Caravaggio study was a prospective open-label non-inferiority RCT comparing apixaban to dalteparin in 1155 cancer patients (51% females) with a venous thromboembolism (VTE) episode. Recurrent VTE occurred in 5.6% in the apixaban group and 7.9% in the dalteparin group (HR 0.63, \(P < 0.001\) for non-inferiority, \(P = 0.09\) for superiority). In patients <65 years apixaban was more effective than dalteparin in the prevention of recurrent VTE. No difference in major bleeding was observed between both arms. The rate of the combined cumulative incidence of recurrent VTE or major bleeding did not differ between groups.

The OASIS-4 trial demonstrated that ticagrelor reduced the risk of major adverse cardiovascular events in patients with stable coronary artery disease. Together with previous trials, the Caravaggio trial further promotes the use of direct oral anticoagulants in patients with cancer. Clinicians should take into consideration individual bleeding risks, concomitant medication, and cancer types (e.g. patients with brain tumours, known intracerebral metastases, or acute leukaemia were excluded from Caravaggio) in cancer patients with VTE.

5.4 Proprotein convertase subtilisin/kexin type 9 inhibition in VTE and LEAD

Proprotein convertase subtilisin/kexin type 9 (PCSK9) degrades low-density lipoprotein cholesterol (LDL-C) receptors and subsequently raises LDL-C. Modulation of VTE (deep vein thrombosis or pulmonary embolism) and LEAD (CLI, limb revascularization, or amputation for ischaemia) by PCSK9 inhibitors was assessed through prespecified analysis of two large clinical trials. The ODYSSEY-OUTCOMES trial compared alirocumab to placebo in 18,924 patients with recent acute coronary syndrome and uncontrolled dyslipidaemia with maximum-tolerated statin treatment. After a median follow-up of 2.8 years, LEAD-related events occurred in 246 patients and VTE events in 92 patients. Alirocumab significantly reduced the risk of LEAD events (HR 0.69; \(P = 0.004\)). The reduction was proportional with baseline lipoprotein(a) (\(P_{\text{trend}} = 0.03\), but not with LDL-C levels (\(P_{\text{trend}} = 0.50\)). Fewer, although non-significant, VTE events were recorded in the alirocumab group (HR 0.67; \(P = 0.06\)). VTE risk was numerically higher in the highest baseline quartile of lipoprotein(a) without significant trend across quartiles (\(P_{\text{trend}} = 0.22\)) and without association with baseline quartile of LDL-C (\(P_{\text{trend}} = 0.85\)). A post hoc analysis of the FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) also assessed the VTE risk in 27,564 patients with stable atherothrombosis and hyperlipidaemia on statin therapy, randomized to evolocumab or placebo. After a median follow-up of 2.2 years, the risk of VTE was...
| Trial | Type and aim | Comparison | N  | Setting (indication) | Primary endpoint | Main hypothesis validated? |
|-------|--------------|------------|----|----------------------|------------------|---------------------------|
| **Aorta** | | | | | | |
| TEDY26 | Multicentre RCT to assess the effect of telmisartan on aneurysm growth in patients with AAA | Telmisartan vs. placebo | 210 | Patients with AAA (diameter 35–49 mm) | Between treatment group difference in AAA growth over 2 years | No: [-0.11 mm (-0.60 to 0.38), \(P = 0.66\)] |
| TicAAA27 | Multicentre RCT to assess the effect of ticagrelor on aneurysm growth in patients with AAA | Ticagrelor vs. placebo | 144 | Patients with AAA (diameter 35–49 mm) | Between treatment group difference in change of AAA volume (MRI measurement) after 1 year | No: [baseline-adjusted mean ratio (ticagrelor/placebo) 1.013 (0.993–1.034), \(P = 0.205\)] |
| **Peripheral vascular diseases** | | | | | | |
| VOYAGER PAD28 | Multicentre RCT to assess dual pathway inhibition after peripheral revascularization in LEAD | Aspirin + rivaroxaban vs. aspirin + placebo | 65.64 | Symptomatic LEAD with peripheral revascularization | All-cause mortality | Yes: HR 0.85 (0.76–0.96), \(P = 0.0085\) |
| SWEDEPAD29 | Multicentre open-label, registry-based RCT to assess all-cause mortality after the use of paclitaxel-coated devices after peripheral revascularization in LEAD | Paclitaxel-coated devices vs. uncoated devices | 2289 | Symptomatic LEAD with peripheral revascularization | All-cause mortality | No: HR 1.06 (0.92–1.22) |
| ODYSSEY OUTCOMES30 (prespecified analysis) | Prespecified analysis of multicentre RCT to assess the effect of alirocumab on the occurrence of LEAD events and VTE | Alirocumab vs. placebo | 18 924 | Patients with recent ACS and elevated levels of lipoproteins despite intensive or maximum-tolerated statin treatment | Occurrence of LEAD events (critical limb ischaemia, limb revascularization, amputation for ischaemia) and VTE (DVT or PE) within the trial period (median duration of follow-up: 2.8 years) | Yes: combined endpoint LEAD + VTE HR 0.69 (0.55–0.86), \(P < 0.001\) (LEAD only HR 0.69 (0.54–0.89), \(P = 0.004\); VTE only HR 0.67 (0.44–1.01), \(P = 0.06\)) |
| FOURIER31 (post hoc analysis) | Post hoc analysis of multicentre RCT to assess the effect of evolocumab on the occurrence of VTE | Evolocumab vs. placebo | 27 564 | Patients (≥40 to ≤85 years of age) with cardiovascular disease and additional predefined cardiovascular risk factors | Occurrence of DVT or PE within the trial period (median duration of follow-up: 2.2 years) | Yes: HR 0.71 (0.50–1.00), \(P = 0.05\) |
| CARAVAGGIO32 | Multicentre RCT to compare the efficacy of apixaban with dalteparin in the risk reduction of recurrent VTE in cancer | Apixaban vs. dalteparin (non-inferiority of apixaban) | 1170 | Cancer patients with symptomatic or incidental DVT or PE | Recurrent VTE within 6 months | Yes: HR 0.63 (0.37–1.07), \(P < 0.001\) |

AAA, abdominal aortic aneurysm; ACS, acute coronary syndrome; ALI, acute limb ischaemia; DVT, deep vein thrombosis; HR, hazard ratio; LEAD, lower extremity artery disease; MI, myocardial infarction; MRI, magnetic resonance imaging; PAD, peripheral arterial disease; PE, pulmonary embolism; RCT, randomized-controlled study; VTE, venous thromboembolism.
reduced under evolocumab (HR 0.71; P = 0.05). There was no relation between baseline LDL-C levels and magnitude of VTE risk reduction. In patients with higher baseline lipoprotein(a) levels, evolocumab reduced VTE risk by 48% (HR 0.52; P = 0.017), whereas, in those with lower baseline lipoprotein(a) levels, evolocumab had no effect on VTE risk (P_{interaction} = 0.087 for HR; P_{heterogeneity} = 0.037 for absolute risk reduction). There was a significant interaction between baseline lipoprotein(a) concentrations and magnitude of VTE risk reduction (P_{interaction} = 0.04).

In both trials, female patients as well as non-white patients were underrepresented. Nevertheless, when combining data from both trials in a meta-analysis, a 31% relative risk reduction in VTE was observed with PCSK9 inhibition vs. placebo (HR 0.69; P = 0.007).

In conclusion, PCSK9 inhibition reduce the risk of LEAD events and could reduce VTE risk. However, further specific studies are required to confirm this class effect.

6. COVID

Although COVID-19 is primarily known as a respiratory disease caused by the SARS-CoV-2 virus, vascular complications including coagulopathy, arterial ischaemic events, and VTE are also common. Indeed, hyperinflammatory and prothrombotic states characterize COVID-19 disease. Vascular endothelial cells play a pivotal role in the COVID-19 disease pathophysiology, both as target organ and as contributing contributor to inflammation and thrombosis. SARS-CoV-2 infects directly the endothelium via the angiotensin-converting enzyme 2 receptor inducing endotheliitis. The systemic cytokine storm induced by SARS-CoV-2 virus affects also the endothelium. These changes result in endothelium dysfunction, likely contributing to poor patient outcome (Figure 3).

COVID-19 is associated with high VTE prevalence. In a recent meta-analysis, including 48 observational studies (18,093 patients) reporting VTE incidence in hospitalized patients with COVID-19, overall VTE incidence was 17.0%, with 7.1% in patients admitted to the ward and 27.9% in those admitted to the intensive care unit. Most of these patients were receiving pharmacological prophylaxis, suggesting the need for intensive anticoagulation. A number of studies, evaluating optimal dose and course of thromboprophylaxis in hospitalized COVID-19 patients, are ongoing.

Several autopsy studies contributed to clarify the pathophysiology of COVID-19 disease. Ackermann et al. evaluated features of seven lungs from COVID-19 infected patients, to those of patients died from acute respiratory distress syndrome secondary to influenza A (H1N1), and control lungs of age-matched uninfected patients. Both COVID-19 and H1N1 influenza patients shared some histologic pattern such as diffuse alveolar damage with perivascular T-cell infiltration. However, COVID-19 patients presented a typical pattern including severe endothelial injury associated with intracellular SARS-CoV-2 virus, and disrupted endothelial cell membranes. In addition, COVID-19 lungs showed widespread

Figure 3 Potential endothelial dysregulation by SARS-CoV-2 (reproduced with permission from Evans et al. 39). ACE2, angiotensin-converting enzyme 2 receptor; ROS, reactive oxygen species.
vascular thrombosis with microangiopathy and occlusion of alveolar capillaries. Finally, significant angiogenesis was shown in the lungs of affected patients. In light of these findings, many of the pulmonary embolisms described in the literature in COVID-19 patients may actually be episodes of in situ thrombosis.

Finally, concomitant CV disease or risk factors may aggravate the clinical course of COVID-19 disease as shown in a number of meta-analyses. Evaluating 25 studies and 65,484 patients, Sentongo et al.42 showed the association of CV disease and 10 pre-existing comorbidities with COVID-19 mortality. Compared to those without comorbidities, risk of death was significantly higher in patients with CV disease (RR 2.25), hypertension (RR 1.82), diabetes (RR 1.48), congestive heart failure (RR 2.03), chronic kidney disease (RR 3.25), and cancer (RR 1.47).42

7. Conclusions
During this very special past year, a number of studies paved the way towards a better understanding of several vascular diseases, including atherosclerosis, FMD, aneurysms, and elastopathies, identifying new targets for diagnosis or therapy. In the clinical field, several seminal trials filled the big gap of knowledge on the use of antithrombotic therapies in vascular diseases. COVID-19, the unpredicted ‘guest-star’ of research in 2020 showed major repercussions in the CV system, and here again, the better understanding of its pathophysiology and extensive use of antithrombotic therapies improved the outcome of millions of patients within <10 months although optimal antithrombotic dosage in these patients remains to be determined.

Authors’ contributions
L.M. and V.A. conceived and designed the manuscript, drafted the manuscript, and revised it for important intellectual content. A.A., A.B.R., M.D.C., C.H., C.E.-K., O.S., H.S., J.R.P., and A.V. made substantial contributions to the conception and design of the manuscript, and drafted the manuscript or revised it for important intellectual content. All authors approved the final version of the manuscript and agreed to be accountable for the work.

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