# Godina 2019. u kardiologiji: bolesti aorte i periferne cirkulacije

## The year in cardiology: aorta and peripheral circulation
## The year in cardiology 2019

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## Uvod

Kao i prethodnih godina,[1-3] trenutačni članak razmatra najvažnija znanstvena dostignuća objavljena tijekom 2019. u području bolesti aorte i bolesti perifernih arterija (PAD), kao i venske tromboembolijske bolesti (VTE) s utjecajem na našu svakodnevnu kliničku praksu. Uz sve veće prepoznavanje PAD-a bit će potrebno razjasniti nepreciznosti u terminologiji. Mnogi se akronimom PAD koriste za aterosklerotsku bolest arterija nogu. Drugi su pak isti akronim rabili za aterosklerotsku bolesti arterija nogu i karotidnih arterija. U ovom članku, i u skladu sa Smjernicama Europskog društva za kardiologiju (ESC),[4] strogo smo se koristili specifičnim izrazom arterijska bolest nogu (LEAD) i zadržali PAD kao općeniti pojam koji obuhvaća bolesti svih arterija, osim aorte i koronarnih arterija.

## 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.

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## Vaskularna biologija / translacijska istraživanja

U kojoj mjeri genski čimbenici pridonose razvoju PAD-a i jesu li isti kod LEAD-a te kod bolesti cerebralnih i koronarnih arterija, uglavnom nije poznato. U genomskom istraživanju *Million Veteran Program*, oko 32 milijuna varijanti sljedova DNA testirano je na PAD (31 307 slučajeva, 211 753 kontrola) u kombinaciji s elektroničkim zdravstvenim kartonima.[5] Rezultati su ponovljeni u neovisnom uzorku iz *UK Biobank*. Identificirali su 19 LEAD lokusa (18 ih prije nije bilo poznato): 11 lokusa bilo je povezano s bolešću u trima vaskularnim područjima (koronarni, cerebralni i donji ekstremiteti), uključujući LDLR, LPL i Lp(a) (**slika A** – središnja ilustracija – vidjeti u originalnom dokumentu); činilo se da su 4 lokusa specifična za LEAD, uključujući F5 p.R506Q (varijanta faktora V Leiden), ističući patogenu ulogu tromboze u LEAD-u i podržavajući inhibiciju faktora Xa kao terapijsku strategiju.

## 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) (**Figure 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.

**FIGURE A. Please see the original article (Eur Heart J. 2020 Jan 21;41(4):501-508b.).**

Unatoč činjenici da su identificirane brojne duge nekodirajuće sekvencije RNA (lncRNA), samo je nekoliko njih proučavano glede homeostaze endotelnih stanica ili razvoja vaskularnih bolesti. Jedna od njih, proangiogena lncRNA MANTIS, može biti klinički relevantna u karotidnoj bolesti.[6] Zapravo se zaštitni učinci laminarnog protoka i statina, bar djelomično, pripisuju ekspresiji MANTIS-a. Mehanizmi uključuju epigenetsko preuređivanje i transkripcijske čimbenike Krüppel-like faktor 2 i 4. Kako indukcija MANTIS-a oponaša blagotvorne učinke statina na endotelnu funkciju, autori su predložili da strategije povećanja ekspresije MANTIS-a mogu poboljšati vaskularnu funkciju u bolesnika koji ne reagiraju na terapiju statinom.

Transkripcijsku aktivnost nuklearnih receptora koji reguliraju ključne patofiziološke procese u razvoju ateroskleroze kontroliraju korepresori nuklearnih receptora (NCOR), proteini-skele koji čine osnovu velikih korepresorskih kompleksa. Oppi i sur.[7] istraživali su ulogu NCOR1 u aterogenezi. Brisanje NCOR1 specifičnih za mijeloidne stanice pogoršalo je razvoj ateroskleroze u miševa koji su imali inaktiviran LDL receptor. Nedostatak NCOR1 u makrofagima uzrokovao je povećano stvaranje pjenastih stanica i pojačanu ekspresije protuupalnih citokina i aterosklerotskih lezija karakteriziranih većim nekrotičnim jezgrama i tanjim vlaknastim čepovima. Imunometabolički učinci NCOR1 posredovani su suzbijanjem ciljnih gena receptora PPARγ u mišjim i ljudskim makrofagima, što uzrokuje pojačanu ekspresiju receptora pročišćivača CD36 i posljedično povećanje unosa oksidiranog LDL-a u odsutnosti NCOR1. Zanimljivo je da je kod aterosklerotskih plakova u ljudi ekspresija NCOR1 smanjena, dok je genska ekspresija PPARγ povećana, a taj je obrazac izraženiji u rupturiranom u usporedbi s nerupturiranim karotidnim plakom. Podatci pokazuju da bi stabiliziranje vezanja NCOR1-PPARγ moglo biti

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 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 (PPARγ) 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 PPARγ signature was increased, and this signature was more pronounced in ruptured compared

obećavajuća strategija za blokiranje proaterogenih funkcija makrofaga plaka i napredovanja lezije.

Kardiovaskularna bolest (CVD) izazvana radioterapijom problem je u nastajanju u sve većoj populaciji preživjelih od raka, gdje tradicionalni vaskularni tretmani imaju ograničene dobrobiti. Primjenom translacijskoga pristupa pokazano je da ozračene krvne žile ljudi pokazuju povišenu razinu proupalnih signala dugo nakon radioterapije, a slične promjene nastaju i u mišjem modelu lokaliziranog zračenja srca i karotida.[8] U modelu lokalizirani upalni odgovor ublažen je antagonistom interleukina (IL) -1. Klinička istraživanja u ljudima sada trebaju procijeniti je li blokada IL-1 potencijalna metoda liječenja CVD-a izazvana radioterapijom.

Ispitanici s povišenjem vrijednosti Lp(a) imali su povećanu upalu arterijskih stijenki  i povišeni kardiovaskularni rizik. Stiekema *i sur.*[9] istraživali su da li evolokumab, koji, za razliku od statina, snizuje i LDL kolesterol i Lp(a), ublažuje upalu arterijskih stijenki  u ciljnoj žili (karotide ili torakalna aorta) u bolesnika s povišenim Lp(a) (>200 mg/dL). U ovom multicentričnom, randomiziranom, dvostruko slijepom, placebom kontroliranom istraživanju, 129 ispitanika  randomizirano je na mjesečnu supkutanu primjenu evolokumaba 420 mg ili na placebo. U usporedbi s placebom, evolokumab smanjuje vrijednost LDL kolesterola za 60,7 % [95 %-tni interval pouzdanosti (CI) 65,8 − 55,5], a Lp(a) za samo 13,8 % (95% CI 19,3 − 8,5). Važno je da upala arterijske stijenke procijenjena pozitronskom emisijskom tomografijom s 2-deoksi-2-[fluor-18]-fluoro-D-glukozom(18F-FDG PET/CT) nije znatno izmijenjena u skupini liječenoj evolokumabom nakon 16 tjedana. To govori u prilog činjenici da su statini, osim zbog ekonomskih razloga, i dalje lijek prvog izbora u terapiji za snizivanje lipida, što je u skladu s trenutačnim smjernicama.[10]

Druga velika studija karakterizirala je metaboličke potpise u serumu povezane s aterosklerozom u karotidnim i koronarnim arterijama, a nakon toga njihovu povezanost s CVDom među 3867 sudionika istraživanja *Multi-Ethnic Study of Atherosclerosis*. Istraživanje je replicirano na 3569 sudionika iz istraživanja Rotterdam i *LOLIPOP*.[11] Mjerenje metabolita s pomoću 30 1H NMR (NMR spektroskopije) pokazalo je njihovu korelaciju s kalcijem unutar stijenki koronarnih arterija i/ili omjerom debljine intime i medije u karotidnim arterijama. Metaboliti povezani s aterosklerozom bili su u velikoj mjeri slični između karotidnih i koronarnih vaskularnih područja i pretežno označuju puteve koji se preklapaju s poznatim kardiovaskularnim čimbenicima rizika: poremećaji metabolizma lipida i ugljikohidrata, razgranani lanac i metabolizam aromatskih aminokiselina, kao i oksidativni stres i upalni putevi.

## Vaskularni biomarkeri i kardiovaskularni rizik

Multimodalne vaskularne pretrage omogućuju procjenu aterosklerotskih procesa i kardiovaskularnog rizika. U populacijskoj studiji[12], koja se koristila hibridnim 18F-FDG PET-om i magnetnom rezonancijom (MRI), arterijska je upala  otkrivena u 48 % sudionika u dobi od 40 do 54 godine; upala je bila u stalnom porastu kako se povećava broj čimbenika rizika. Aortni, karotidni i/ili iliofemoralni plakovi bili su prisutni u 90 % slučajeva, ali je većina upalnih procesa  prikazana u zonama bez plaka. Upala je bila prisutna samo u 11 % plakova, što upućuje na arterijsku upalu u ranome stadiju aterosklerotskog

with non-ruptured carotid plaques. The data suggest that stabilizing the NCOR1-PPARγ 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 inflammasome 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)] 18F-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 study[12] 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

procesa. Eksperimentalno istraživanje otišlo je korak dalje i razvilo integrativni multiparametrijski PET/MRI protokol koji omogućuje neinvazivnu procjenu različitih procesa važnih za progresiju ateroskleroze.[13] S pomoću klinički odobrenih, radioizotopom obilježenih, nanočestica mogli su proučavati različite biomarkere napredovanja ateroskleroze, i to: molekula vaskularne stanične adhezije-1, lektinu sličan oksidirani lipoproteinski receptor niske gustoće, kao i receptor manoze makrofaga, koji su u korelaciji s histopatološkim nalazima u miševa i zečeva.

Ateroskleroza se čak može prepoznati i u adolescenciji, posebno u slučaju nezdravog načina života: u opservacijskoj studiji[14] koja je uključivala 1266 mladih sudionika u dobi od 13 do 17 godina krutost aorte procijenjena brzinom karotidno-femoralnog pulsnog vala (cfPWV) razmjerno je povećana s obzirom na pušenje duhana i konzumaciju alkohola, uz jako potenciranje u kombinaciji obaju čimbenika (**slika 1**). U spomenutoj dobi prestanak pušenja i pijenja alkohola dovodi do normalizacije cfPWV-a. U drugoj krajnosti životnog vijeka vaskularni bi markeri mogli biti korisni za smanjenje procijenjenog rizika u starijih osoba koje bi inače imale indikaciju za statine na temelju rezultata kliničke procjene rizika koje se trenutačno primjenjuju, a koje su pod znatnim utjecajem dobi bolesnika. U skupini od 5805 zdravih starijih sudionika (prosječna dob 69 godina) normalna vrijednost (<10) koronarnog kalcija i nepostojanje karotidnog plaka na ultrazvuku bili su najmoćniji vaskularni biljezi za smanjivanje predviđenoga kardiovaskularnog rizika, s odgovarajućim netoindeksom reklasifikacije od 0,29 i 0,14, izbjegavajući nepotrebno propisivanje statina u 34 % i 21 % slučajeva.[15]

inflammation in early stage of atherosclerosis process. An experimental study went one step further and developed a 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 study[14] 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 *Vi-*
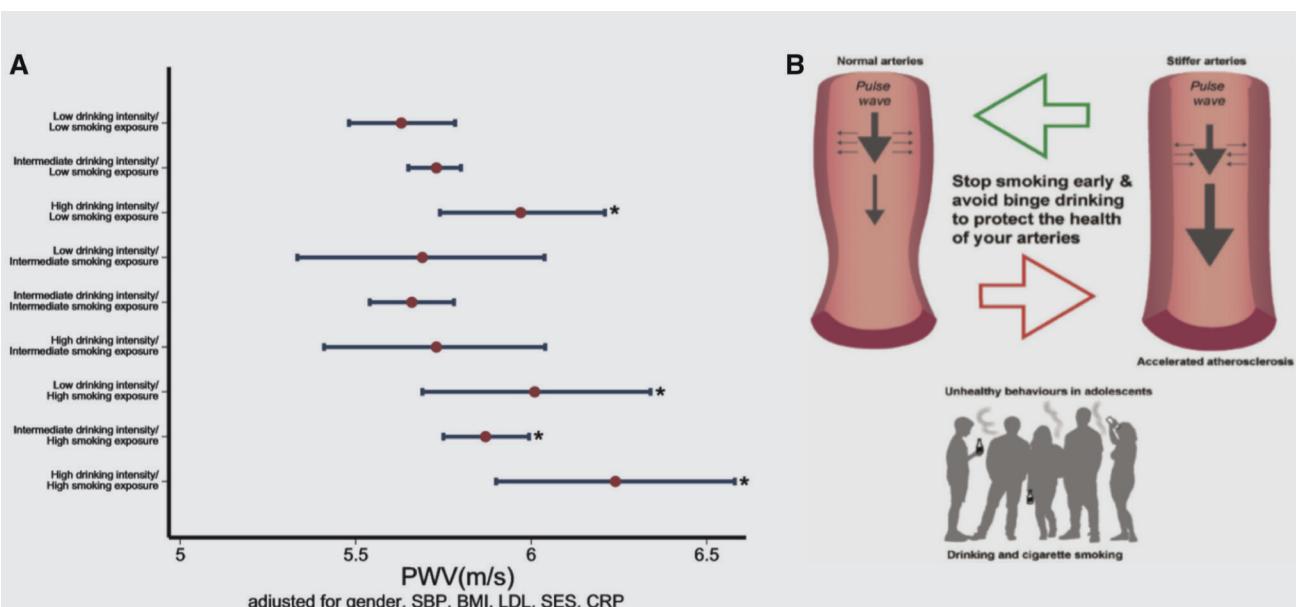


**FIGURE 1. (A) The combined effect of smoking over lifetime and intensity of drinking on arterial stiffness. The combination of high-intensity drinking with lifetime smoking exposure is shown. Pulse wave velocity measurements are expressed as mean values and 95% confidences intervals around the mean 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]**

Ultrazvučno vaskularno snimanje može učinkovito poboljšati suradljivost bolesnika i ustrajanje u zdravom načinu života. Istraživanje *Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention* (VIPVIZA) bilo je otvoreno, kontrolirano ispitivanje[16] u kojemu su randomizirana 3532 ispitanika starija od 40 godina koji su pohađali probirni program; u kontrolnoj skupini obavljena je redovita kontrola čimbenika rizika i liječenje temeljeno na smjernicama, ali im rezultati karotidnog ultrazvuka nisu obznanjeni, dok je u interventnoj skupini ispitanicima i liječnicima obiteljske medicine omogućen slikovni prikaz rezultata ultrazvuka karotida, uključujući prikaz vaskularne dobi zasnovanu na odnosu debljine intima-medija i identifikaciju plaka. Medicinska je sestra 2 – 3 tjedna poslije nazvala kako bi uvjerila sudionike i pružila sve potrebne informacije. Jednake slikovne informacije ponovile su se nakon 6 mjeseci. Osnovni rezultati procjene rizika prema Framingham (FRS) i SCORE tablicama bili su 12,9 i 1,28. U dobi od jedne godine oba su rezultata bila mnogo niža u interventnoj skupini (−1,07, P = 0,0017 za FRS i −0,16, P = 0,001 za SCORE) sa zamjetljivim rezultatima u skupini visokog rizika (−2,16 i −2,85, po skupinama). Postojanost ovih rezultata i njihove posljedice na neželjene kardiovaskularne događaje trebaju daljnju procjenu.

## Cerebrovaskularna bolest

Prekomjerna arterijska pulsatilnost može oštećenjem krhke moždane mikrocirkulacije pridonijeti padu kognitivnih funkcija i riziku od demencije. U sklopu istraživanja *Whitehall II*[17] određen je maksimalni intenzitet kompresijskog vala prema naprijed (FCWI) primjenom Duplex ultrazvuka, unutar zajedničkih karotidnih arterija u 3191 ispitanika (prosječna dob 61 godina; 75 % muškaraca), a serijske mjere kognitivne funkcije određene su na početku istraživanja i gotovo 10 godina poslije. Viši FCWI na početku istraživanja bio je povezan s ubrzanim kognitivnim padom tijekom praćenja, a ovu su povezanost velikim dijelom potaknule kognitivne promjene u pojedinaca s najvišim vrijednostima FCWI. U usporedbi s ostalim sudionicima, veća je vjerojatnost da će ova skupina pokazati kognitivni pad čak i nakon prilagođivanja višestrukim potencijalnim zbunjujućim čimbenicima.

Iako se preporučuje intenzivno snizivanje lipida nakon TIA-a i ishemijskog moždanog udara, ciljna razina LDL-a za smanjenje kardiovaskularnih događaja nakon moždanog udara nije dobro proučena. U paralelnom grupnom ispitivanju, 2860 bolesnika s nedavnim ishemijskim moždanim udarom ili TIA-om i dokazima ateroskleroze cerebrovaskularnih i/ili koronarnih arterija bilo je randomizirano na ciljne razine LDL-a od <70 mg/dL ili 90 – 110 mg/dL statinom, ezetimibom ili uz oba lijeka.[18] Tijekom prosječnog praćenja u trajanju od 3,5 godina veliki kardiovaskularni događaji odigrali su se rjeđe u skupini s nižom ciljnom razinom [8,5 % nasuprot 10,9 %; omjer opasnosti (HR) 0,78 (95 % CI 0,61 – 0,98)].

Bolesnici koji imaju visoki rizik od moždanog udara i fibrilaciju atrija, a nisu prikladni za liječenje oralnim antikoagulancijama (OAC) zahtijevaju alternativne strategije prevencije moždanog udara. Multicentrično, nerandomizirano, kliničko ispitivanje *Carotid Artery Implant for Trapping Upstream Emboli for Preventing Stroke in Atrial Fibrillation Patients* (CAPTURE) nastojalo je odrediti izvodljivost i sigurnost novoga trajnog filtra-zavojnice izravno smještenog u obje zajedničke karotidne arterije, dizajnirane za hvatanje embola promjera ve-

*sualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention* (VIPVIZA) open controlled trial[16] 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 ischemic 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 $CHA_2DS_2$-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

ćih od 1,4 mm.[19] Bolesnici su liječeni acetilsalicilatnom kiselinom (ASK) i klopidogrelom tijekom 3 mjeseca, a nakon toga samo primjenom ASK-a. U tri centra uključeno je 25 bolesnika s fibrilacijom atrija i $CHA_2DS_2$-VASc ≥2, koji nisu bili prikladni za OAC i nisu imali karotidnu stenozu >30 %. Uspjeh postupka bio je 92 %; 1 bolesnik imao je jednostranu implantaciju. Nije bilo većih neželjenih događaja vezanih za uređaj ili postupak. Nakon 6-mjesečnog praćenja otkriveni su asimptomatski trombi u četiri bolesnika (jedan bilateralni, četiri jednostrana) i trombi su otopljeni supkutanom primjenom heparina. Stalni karotidni filtri za profilaksu moždanog udara izgledaju tehnički izvedivo i sigurno. Potrebna su veća istraživanja i usporedba s uporabom okludera aurikule lijevog atrija.

## Bolesti aorte

Česti izazov u hitnoj službi jest detekcija i razlikovanje simptoma akutnog aortnog sindroma (AAS) od ostalih kliničkih stanja, za što je potrebno oslikavanje kompjutoriziranom tomografijom. U studiji na 839 bolesnika u hitnoj službi sa sumnjom na AAS, ciljani ultrazvuk srca, integriran u strategiju koja uključuje kliničku procjenu i (za bolesnike s niskim rizikom) određivanje razine D-dimera, omogućio je ispravnu identifikaciju svih bolesnika s disekcijom aorte (AD), iako je gornja granica 95 % CI bila 1,2 %.[20] Ovakvi nalazi potvrđuju važnost transtorakalne ehokardiografije u dijagnostičkoj strategiji AAS-a, kako je predloženo u posljednjim ESC-ovim smjernicama[21].

Izraz AAS postao je uobičajen, ali čini ga niz bolesti koje možda nemaju iste patofiziološke mehanizme, odgovore na liječenje ili prognozu. Među 1012 bolesnika, oni s intramuralnim hematomom (IMH) (n = 340) imali su mnogo nižu kratkoročnu i dugoročnu smrtnost od bolesnika s AD-om (n = 672).[22] Uključivanjem tipa B IMH-a u bolničku smrtnost, procijenjenu na 1,5 % kao referentnu vrijednost, ukupna smrtnost u bolnici zbog tipa A disekcije iznosila je 15 % s prilagođenim omjerom opasnosti (aHR) od 30,4; u usporedbi sa smrtnošću tipa A IMH-a od 8 % (aHR 4,85) i smrtnošću zbog tipa B disekcije od 5 % (aHR 3,51).

Prepoznavanje bolesnika s Marfanovim sindromom koji imaju povišen rizik od AD-a trenutačno se temelji na apsolutnom promjeru aorte, stopi rasta i prisutnosti/odsutnosti obiteljske anamneze o AD-u. Novi, dodatni pristup može biti procjena uzdužnog naprezanja proksimalne aorte s pomoću magnetne rezonancije (**slika 2A**).[23] Veće stope naprezanja povezane su s bržim proširenjem aorte i čini se da predviđaju kliničke ishode. Ako se procjena uzdužnog naprezanja proksimalne aorte pokaže reproducibilnom i ako se ovakvi nalazi uspiju replicirati u većim kohortama, ova bi metoda mogla pomoći u određivanju potrebe i vremena operativnog zahvata u ovakvih bolesnika.

Složeni obrasci protoka identificirani su u pravom, a često i u lažnom lumenu nakon AD-a. Bolje razumijevanje ove dinamike protoka može objasniti različita ponašanja AD-a tijekom dugoročnog praćenja. Nedavni uvidi u ovo zbivanje postali su dostupni iz detaljne studije kategoriziranja uzoraka protoka s pomoću Dopplera. O mogućnostima prognostičkih implikacija još se uvijek raspravlja (**slika 2B**).[24]

Optimalno je liječenje aneurizmi silazne torakalne aorte kontroverzno. Retrospektivna prilagođena studija populacije korisnika *Medicare* sustava utvrdila je niži perioperativni i ukupni mortalitet u bolesnika koji su podvrgnuti popravku torakalne aorte endovaskularnom protezom (TEVAR) u uspo-

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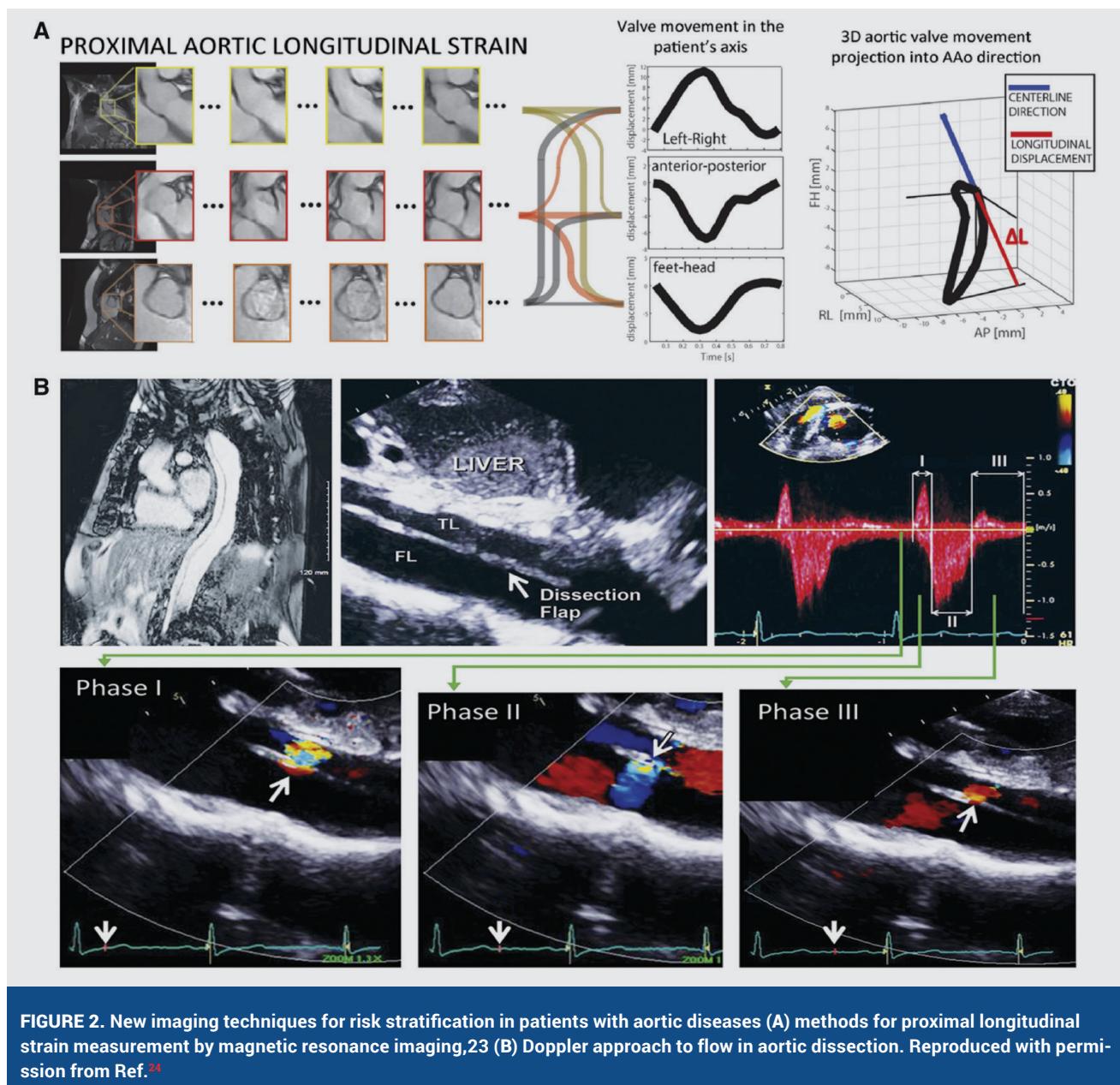
**FIGURE 2. New imaging techniques for risk stratification in patients with aortic diseases (A) methods for proximal longitudinal strain measurement by magnetic resonance imaging,23 (B) Doppler approach to flow in aortic dissection. Reproduced with permission from Ref.[24]**

redbi s otvorenim popravkom, ali s većim rizikom od ponovne intervencije.[25] Izgledi za perioperativnu smrtnost bili su veći za otvoreni kirurški popravak i ovisili su o volumenu centra: centri velikog volumena, omjer koeficijenta (OR) 1,97 (95 % CI 1,5 – 2,6); centri niskog volumena, OR 3,62 (95 % CI 2,9 – 4,5). Razlika prosječnog vremena preživljavanja pogodovala je TEVAR-u nakon 9 godina praćenja; −209 dana (95 % CI −299 do −120 dana) za otvoreni kirurški popravak. Rizik od ponovne intervencije bio je manji za otvoreni kirurški popravak, HR 0,40 (95 % CI 0,34 – 0,60).

U posljednjim Smjernicama ESC-a o liječenju bolesti aorte[21] otvorena operacija i endovaskularni popravak (EVAR) abdominalnih aneurizmi dobili su preporuku klase I, temeljenu na nekoliko izravnih uspoređivanja u koja su uključeni pacijenti s odgovarajućom anatomijom za obje mogućnosti. Iako je, kratkoročno, EVAR bio povezan s manjom smrtnošću, ta se razlika s vremenom postupno gubila, dok je, zauzvrat, EVAR zahtijevao

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) trial[26] 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.

ponovljenu izloženost zračenju i ponovnu intervenciju zbog mehaničkih komplikacija. Rezultati dugoročnog praćenja (14 godina) istraživanja *Open vs. Endovascular Repair* (OVER)[26] zanimljivi su po tome što ne pokazuju razliku u smrtnost ili u sekundarnim procedurama nakon prvih godina. Ovakvi rezultati podržavaju trenutačne preporuke; važno je da smrtnost uglavnom nije bila vezana za aneurizmu (samo 2,7 %, većinom postoperativno), a najviše je vezana za kardiovaskularne uzroke, što naglašava potrebu za maksimalnim preventivnim mjerama u ovih bolesnika. Konačno, još uvijek nedostaju dokazi o razlikama prema spolu, jer su žene činile <10 % svih sudionika.

## Bolesti arterija nogu

Arterijska bolest nogu sve je veći javnozdravstveni problem, prema najnovijemu svjetskom epidemiološkom izvješću.[27] Godine 2010. LEAD je definiran kao vrijednost ABI ≤0,9, a zahvaćao je 202 milijuna ispitanika širom svijeta; taj se broj u 2015. povećao za 22 %, na 237 milijuna. Ukupna prevalencija u ispitanika u dobi većoj od 25 godina bila je 5,6 % (95 % CI 3,8 – 8,6), veća u zemljama s visokim dohotkom nego u zemljama s niskim i srednjim dohotkom (LMIC) (7,4 % nasuprot 5,1 %), iako je velika većina bolesnika (73 %) živjela u LMIC. Prevalencija je bila slična među spolovima, s većom učestalošću mlađih (<50 godina) bolesnika u LMIC.

Povezanost LEAD-a s velikim neželjenim kardiovaskularnim događajima (MACE) dobro je dokumentirana, dok je njezina povezanost s događajima na donjim ekstremitetima manje jasna. U kohortnom istraživanju *Veterans Aging Cohort Study*, koje je uključivalo 125 674 ispitanika bez prethodne amputacije, učestalost amputacije u razdoblju praćenja od 9,3 godina bila je 1,2 na 1000 osoba po godini.[28] Prisutnost LEAD-a dala je 13,9 puta veći rizik od amputacije, ali mikrovaskularna bolest (MVD), definirana kao retinopatija, neuropatija i/ili nefropatija, također je bila povezana s porastom rizika od 3,7 puta, a kombinacija LEAD-a i MVD-a dovodi do 22,7 puta većeg rizika. Važno je da je i sama MVD bila povezana s 15 % svih potkoljeničnih amputacija.

Među 13 885 bolesnika s ABI-jem ≤0,8 ili prethodnom revaskularizacijom nogu (LER) randomiziranih na tikagrelor nasuprot klopidogrelu u ispitivanju *Examining Use of Ticagrelor in Peripheral Artery Disease* (EUCLID), učestalost akutne ishemije udova (ALI) koja je zahtijevala hospitalizaciju bila je 0,8 na 100 bolesnika po godini, bez razlike između ispitivanih skupina.[29] Akutna ishemija nogu bila je snažno povezana s naknadnim MACE-om (aHR 1,4, 95 % CI 1,0 – 2,1), ukupnom smrtnošću (aHR 3,3, 95 % CI 2,4 – 4,6) i velikim amputacijama (aHR 34,2, 95 % CI 9,7 – 20,8). Prethodna LER, fibrilacija atrija i početna vrijednost ABI-ja ≤0,60 bili su neovisni prediktori ALI. U tom ispitivanju, analiza podskupina pokazala je da je 12,5 % bolesnika imalo LER tijekom ispitivanja.[30] Neovisni prediktori postrandomizacijske LER bili su: anamnestički podatak i vrsta prethodne LER (P <0,0001), život u Sjevernoj Americi ili Europi (P <0,0001), prisutnost simptoma LEAD-a na početku istraživanja (HR 1,3; 95 % CI 1,2 – 1,5), dijabetes (HR 1,3; 95 % CI 1,1 – 1,4) i pušenje (HR 1,2; 95 % CI 1,1 – 1,4). Kardiološki i vaskularni događaji bili su brojčano učestaliji u bolesnika koji su bili podvrgnuti kirurškim zahvatima, ali su kirurški bolesnici imali manje reintervencija nakon inicijalne LER.

Sve veći udio hospitalizacija zbog ALI pojavljuje se u bolesnika s karcinomom koji imaju arterijsku tromboemboliju. U populacijskoj bazi podataka *Surveillance Epidemiology and*

## 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), 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 ≥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*

*End Results-Medicare* identificiran je 374 331 bolesnik u dobi ≥67 godina s primarnom dijagnozom neoplazme (dojke, pluća, prostate, kolorektalnog karcinoma, mokraćnoga mjehura, maternice, gušterače, karcinoma želudca) ili ne-Hodgkinova limfoma.[31] Rizik od arterijskih tromboembolijskih događaja počeo se povećavati 150 dana prije datuma postavljanja dijagnoze karcinoma u starijih bolesnika i dosegnuo je vrhunac 30 dana prije dijagnoze raka, kada je 0,62 % bolesnika pretrpjelo arterijski tromboembolički događaj u odnosu prema 0,11 % u kontrolnih ispitanika (OR 5,63; 95 % CI 5,07 – 6,25).

Snizivanje vrijednosti lipida ključan je element liječenja LEAD-a.[4] Smjernice ESC-a za 2019. preporučuju smanjenje vrijednosti LDL kolesterola za ≥50 % i ciljnu vrijednost <1,4 mmol/L za bolesnike s LEAD-om, što se treba postići s pomoću statina te uz ezetimib i inhibitore PCSK9 ako je to potrebno.[10] Nedavna analiza podataka iz studije *Evaluation of CV Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab* (ODYSSEY OUTCOMES) podržava ove preporuke.[32] Nakon medijana praćenja od 2,8 godina, 1554 bolesnika s aterosklerotskom bolešću u dvama ili trima vaskularnim područjima (koronarni, donji ekstremiteti i/ili cerebrovaskularni) zabilježeno je mnogo veće apsolutno smanjenje rizika u bolesnika liječenih alirokumabom u usporedbi s bolesnicima sa samo koronarnom bolesti srca (CAD). Apsolutno smanjenje rizika za MACE bilo je 1,9 % (95 % CI −2,4 % do 6,2 %) i 13,0 % (95 % CI −2,0 % do 28,0 %) za dva i tri vaskularna područja, dok je rizik od ukupne smrtnosti bio 1,3 % (95 % CI −1,8 % do 4,3 %) i 16,2 % (95 % CI 5,5 −26,8 %).

Drugi stup liječenja LEAD-a jest optimalna kontrola arterijske hipertenzije.[4,33] Nedavna analiza podataka iz studije *Atherosclerosis Risk in Communities* (ARIC) procijenila je utjecaj različitih stadija hipertenzije na razvoj LEAD-a.[34] Tijekom medijana praćenja od 25,4 godine sistolički tlak ≥140 mmHg ili dijastolički tlak ≥90 mmHg povezan je s višom učestalosti dijagnoze LEAD-a (HR 2,40; 95 % CI 1,72 – 3,34), neovisno o upotrebi antihipertenzivnih lijekova. Više kategorija arterijskoga tlaka pokazale su znatnu povezanost s pojavom LEAD-a počevši od 120 do 129 mmHg za sistolički tlak i ≥90 mmHg za dijastolički tlak. Ovi podatci naglašavaju potrebu kontrole arterijskoga tlaka kako bi se spriječio razvoj LEAD-a.

Iako je tjelesna aktivnost pod nadzorom temelj liječenja klaudikacija,[4] niska učestalost pridržavanja ograničava njezinu kliničku primjenu. U randomiziranoj studiji, 156 sudionika dodijeljeno je superviziranoj vježbi na pokretnoj traci, treningu snage pod nadzorom ili usmenim savjetima o prehrani i tjelesnoj aktivnosti.[35] Nakon 6 mjeseci, prijeđena udaljenost na 6-minutnom testu hoda poboljšala se samo u grupi na pokretnoj traci (36,1 m, 95 % CI 13,9 − 58,3), ali nakon 12 mjeseci ni traka ni trening snage znatno ne povećavaju prijeđenu udaljenost s obzirom na kontrole (udaljenost hoda: +7,5 m i +6,1 m). Ovi rezultati naglašavaju potrebu za dugoročnim nadziranim programima vježbanja. Usto, sustavni pregled 84 studije našao je da su alternativni modaliteti treninga (kružni aerobni trening, hodanje do granice bola, trening snage, ergometrija ruku/nogu i nordijsko hodanje) imali mnogo više stope pridržavanja i stope završetka u odnosu prema tradicionalnom vježbanju (85,5 % prema 77,6 %, i 86,6 % prema 80,8 %, po skupinama).[36]

U nedostatku randomiziranih kontroliranih ispitivanja (RCT), postoji velik jaz u dokazima za najbolju strategiju revaskularizacije u kroničnoj kritičnoj ishemiji nogu (CLTI). U retrospektivnoj analizi 16 800 bolesnika s CLTI-jem bolesnici koji su prvo kirurški revaskularizirani (36 %) uspoređeni su s

*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 bal-

onima s prvom endovaskularnom revaskularizacijom (64 %).[37] Endovaskularna skupina bila je mlađa, ali je imala više komorbiditeta, uključujući zatajenje bubrega (36 % prema 24 %), CAD (34 % prema 32 %), zatajivanje srca (19 % prema 15 %) i dijabetes (65 % prema 58 %; svi P <0,05). U „uparenoj" analizi kirurška je strategija bila povezana s kraćim vremenom bez amputacije (HR 1,16, 95 % CI 1,13 – 1,20), dok je endovaskularna strategija povezana s višim stopama reintervencije (HR 1,19, 95 % CI 1,14 – 1,23) nakon 80 mjeseci praćenja. Smrtnost je bila slična među skupinama (HR 0,94, 95 % CI 0,89 – 1,11). Ovakvi rezultati upućuju na prednost endovaskularnog pristupa što se tiče duljeg vremena bez amputacije.

Nekoliko je ispitivanja pokazalo superiornost stentova koji izlučuju lijek (DES) i balona obloženih lijekom (DCB) u usporedbi s običnom balonskom angioplastikom (PTA) u bolesnika s femoropoplitealnom bolešću.[1–3] Petogodišnji rezultati istraživanja IN.PACT SFA pokazali su trajnost kliničke dobrobiti, sa 74,5 % bolesnika bez potrebe za reintervencijom kod klinički vođene ciljane revaskularizacije lezija s DCBs u odnosu prema 65,3 % s PTA-om (P = 0,02), iako ta korist nije bila značajna u dijabetičara (70,3 prema 64,4 %, P = 0,24)[38]. Klinička uporaba materijala koji izlučuju paklitaksel dramatično je prekinuta u studenome 2018. neočekivanim rezultatima metaanalize koja

loon 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**).
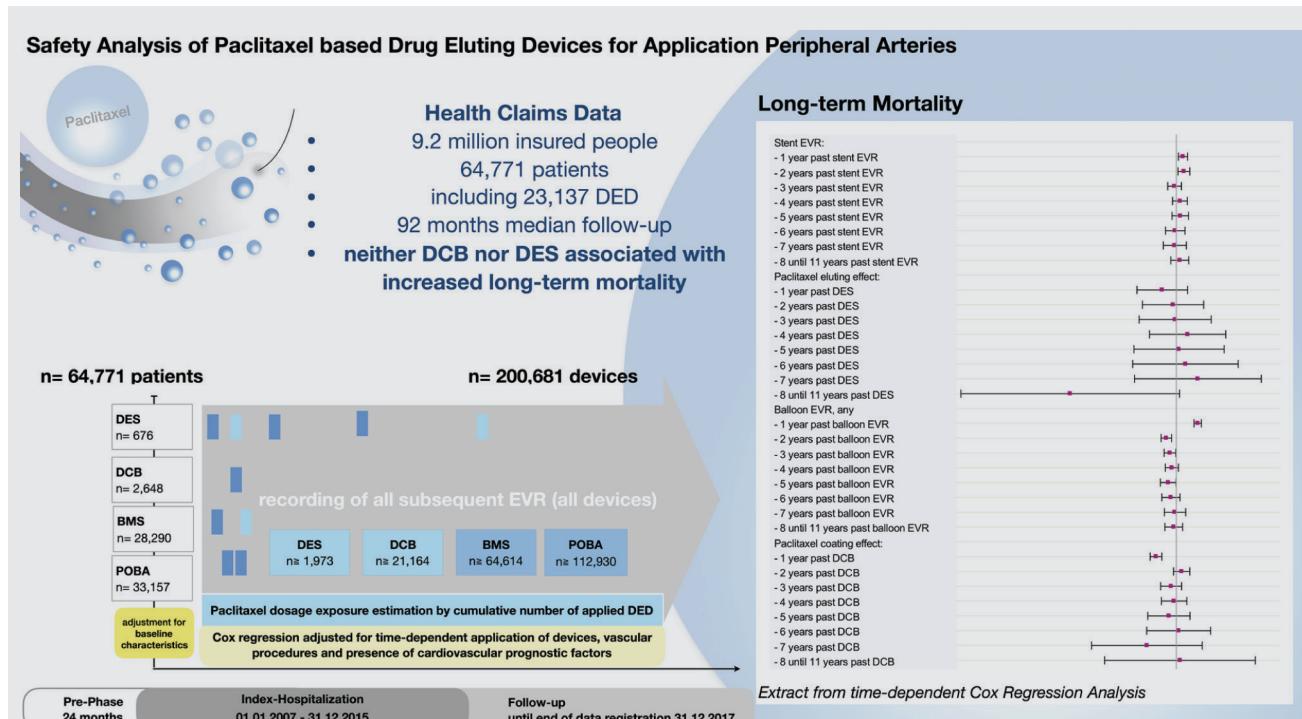


**FIGURE 3. Long-term mortality after use of paclitaxel-based drug eluting devices (DED) in lower extremity arterial disease. A multivariable Cox regression analysis was developed including numerous comorbidities and all devices that were applied in each treated patient. For each distinct device, the analysis accounted for its type [drug-eluting stents (DES), drug coated balloon (DCB), bare metal stents (BMS), and plain old balloon angioplasty (POBA)] and application date. The model took also concern of any non-constant time dependent effects: thus, a potentially detrimental effect of DED in the later course of time would become verifiable despite a potentially beneficial effect in the early years, or also any potential aggregation of subsequently applied devices. Combined hazard ratios for any scenario including multiple devices that were applied various years ago can be determined as the product of elementary hazard ratios. In summary, there was no signal that paclitaxel DCBs or DESs were associated with increased mortality up to 11 years of follow-up. Reproduced with permission from Ref[40]**

je uključila 28 RCT-a s ukupno 4432 bolesnika.[39] Studija je opisala dvostruko povećanje u ukupnoj smrtnosti između druge i pete godine praćenja s DES / DCB-ima koji izlučuju paklitaksel (HR 1,93, 95 % CI 1,27 – 2,93), a postavljena je sumnja na uzročnu vezu između doze paklitaksela i smrtnosti. Ovakvi su nalazi izazvali veliku zabrinutost, zaustavili prijavu RCT-a s materijalima koji izlučuju paklitaksel i potaknuli svjetski poziv za kvalitetno prikupljanje i analizu podataka. Nedavno je gore spomenuta studija opovrgnuta istraživanjem velike količine podataka njemačkih zdravstvenih osiguranika, koje je pokazalo da nema znatnog porasta u dugoročnoj smrtnosti u bolesnika s materijalima koji izlučuju paklitaksel od 2007. do danas, a riječ je bila o 64 771 ispitaniku, u kojih je bili provedeno ukupno 107 112 endovaskularnih postupaka.[40] Upotreba materijala koji izlučuju paklitaksel nije bila povezana s povećanom smrtnosti do 10 godina praćenja (**slika 3**).

## Venska tromboembolija

Godine 2019. izdane su ažurirane Smjernice ESC-a za liječenje bolesnika s akutnom plućnom embolijom (PE).[41] Ključne točke uključuju uporabu praga D-dimera prilagođena dobi bolesnika u pretkliničkoj procjeni rizika. Nadalje, više se ne predlaže kategorizacija PE događaja u 'provocirano' i 'neprovocirano'. Umjesto toga, preporučuje se registracija incidenta u prisutnosti „reverzibilnog čimbenika rizika" ili u odsutnosti bilo kojeg „prepoznatljivog čimbenika rizika" za stratifikaciju i usmjerivanje trajanja liječenja. Prvi put se više preporučuju izravne oralne antikoagulancije (DOAC) nego antagonisti vitamina K za liječenje PE-a u bolesnika s indikacijom, kao i u bolesnika s fibrilacijom atrija. Smanjena doza apiksabana ili rivaroksabana za produljenu antikoagulaciju treba se razmotriti nakon prvih 6 mjeseci liječenja. Edoksaban ili rivarok-

## 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 iden-
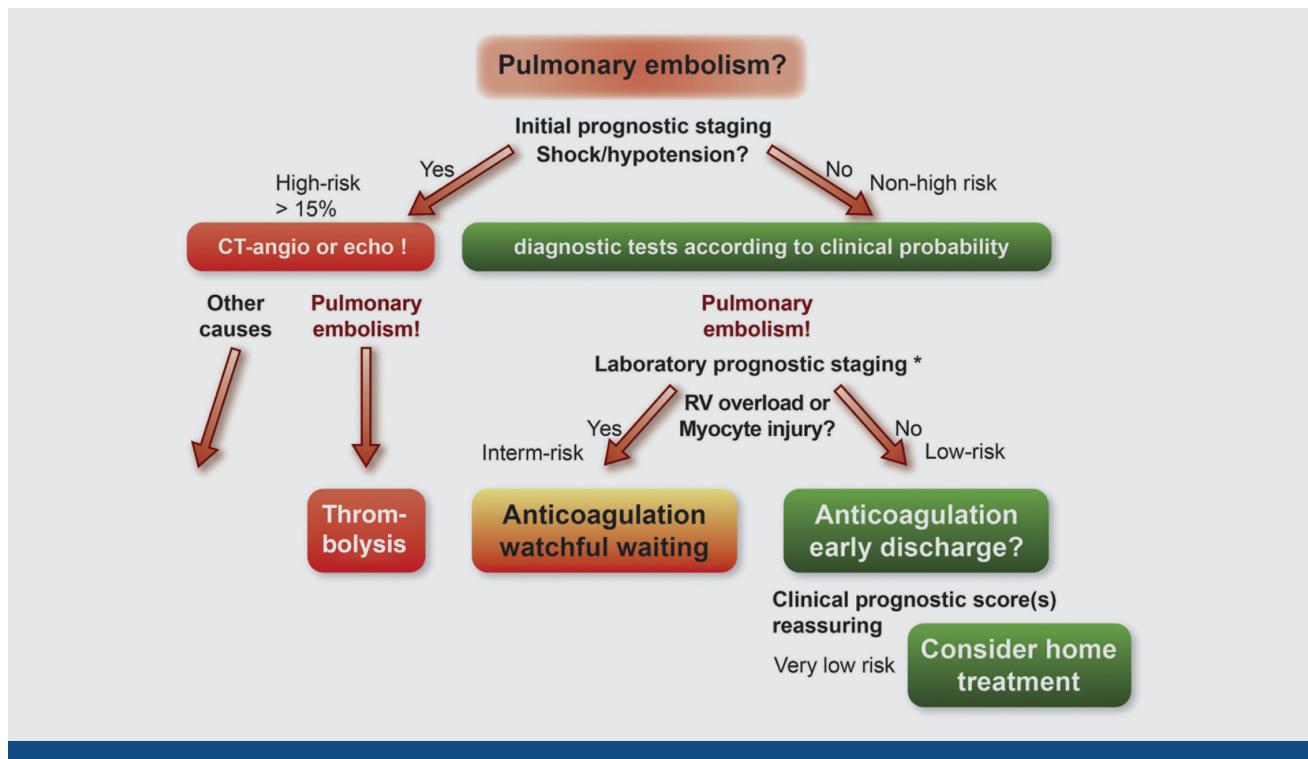


**FIGURE 4. Pulmonary embolism management algorithm. Reproduced with permission from Ref.[42]**

saban treba razmotriti kao alternativu niskomolekularnom heparinu u bolesnika s negastrointestinalnim karcinomom koji imaju VTE. Nova preporuka (klasa IIa, razina A) predlaže da se pažljivo odabrani pacijenti s PE-om s niskim rizikom razmotre za rani otpust i kućno liječenje, sve dok su mogući odgovarajuća ambulantna skrb i antikoagulantna terapija (**slika 4**). Nedavno prospektivno multicentrično istraživanje s jednim terapijskim krakom dodatno potvrđuje spomenutu preporuku. Bolesnici s PE-om niskog rizika (bez HESTIA kriterija i uz odsutnost dilatacije/disfunkcije desne klijetke) rano su otpušteni (najviše dvije noći u bolnici) na kućno liječenje rivaroksabanom. Studija je rano prekinuta zbog niskih simptomatskih recidiva VTE-a i smrtnosti povezane s PE-om (0,6 %; jednostrani gornji 99,6% CI 2,1%) i niskih epizoda krvarenja (1,2%) u 3 mjeseca od postavljanja dijagnoze.[43] Pažljiv odabir bolesnika s PE-om niskog rizika ključan je za uspješno ambulantno liječenje. S tim u vezi rezultati kliničke procjene rizika sami za sebe možda nisu dovoljni za identifikaciju skupine s niskim rizikom, posebno s obzirom na supkliničku disfunkciju desne klijetke. Stoga kombiniranje procjene sistoličke funkcije desne klijetke i kliničkih kriterija omogućuje daljnje ispravno stratificiranje rizika, kako su to nedavno predložili Barco *i sur.*[44]

Dijagnoza PE-a tijekom trudnoće izazovna je, uz široko preklapanje simptoma povezanih s trudnoćom i PE-om. Ukupna prevalencija PE-a ipak je niska pa su bolesnice često izložene nepotrebnim slikovnim testovima. Smjernice ESC-a za 2019. godinu predlažu namjenski dijagnostički algoritam za sumnju na PE u trudnoći s pomoću stratifikacijskih alata temeljenih na kliničkoj slici, vrijednostima D-dimera i kompresijskoj ultrasonografiji vena nogu. Trudnoći prilagođeni algoritam YEARS, koji uzima u obzir ova tri parametra, nedavno je pokazao da sigurno isključuje PE kroz sva tri tromjesečja trudnoće, izbjegavajući znatan broj slikovnih testova.[45]

Liječenje venske tromboze na neuobičajenim mjestima u praksi je zahtjevno. Još uvijek se postavlja pitanje trebaju li se pacijenti s izoliranom trombozom dubokih vena potkoljenica (IDDVT) liječiti sustavnom antikoagulantnom terapijom. Predlaže se stratificirati pacijente s IDDVT-om s obzirom na visok i nizak rizik od recidiva.[46] Oni s visokim rizikom trebaju se antikoagulirati kao i bolesnici s trombozom proksimalnih dubokih vena.[47] S tim u vezi nedavni prospektivni registri pokazuju da se pacijenti s IDDVT-om mogu liječiti DOAC-om, iako još uvijek nedostaju podatci iz kliničkih ispitivanja.[48,49]

## Perspektive

Uzbudljivi novi znanstveni podatci objavljeni 2019. godine osvijetlili su nijanse ateroskleroze među različitim perifernim vaskularnim teritorijima. Vaskularni stručnjaci željno iščekuju 2020. godinu. Bliži se završetak studije *Vascular Outcomes study of ASA along with rivaroxaban in endovascular or surgical limb revascularization for peripheral artery disease* (VOYAGER PAD) koja ocjenjuje učinkovitost i sigurnost rivaroksabana 2 x 2,5 mg zajedno s ASK-om u smanjenju rizika od većih trombotskih vaskularnih događaja u bolesnika sa simptomatskom LEAD koji su bili podvrgnuti kirurškoj ili endovaskularnoj revaskularizaciji (NCT02504216). Nadalje, postat će dostupni daljnji podatci koji se odnose na sigurnost materijala obloženih paklitakselom za revaskularizaciju kod LEAD-a. U području VTE čekaju se podatci iz studije *CARAVAGGIO* (NCT03045406), koja uspoređuje apiksaban i dalteparin za liječenje akutne VTE u pacijenata s malignim bolestima.

tify 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 (IDDVT) should be systematically treated with anticoagulation is still questioned. It is suggested to stratify patients with IDDVT 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 IDDVT 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.

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