Osvrt na Smjernice za liječenje periferne arterijske bolesti Europskoga kardiološkog društva 2024.

Review of the 2024 European Society of Cardiology Guidelines for the management of peripheral arterial disease

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SAŽETAK: Periferna arterijska bolest česta je kardiovaskularna (KV) bolest udružena s povećanim rizikom od velikih neželjenih KV događaja i od velikih neželjenih događaja na ekstremitetima. Bolesnici mogu biti asimptomatski, a u simptomatskih se bolesnika mogu očitovati intermitetne klaudikacije ili kritična ishemija ekstremiteta. Prijeko je potreban holistički multidisciplinarni pristup koji uključuje pravodobnu dijagnozu, liječenje, praćenje i prevenciju. Inicijalni alat za postavljanje dijagnoze jest pedobrahijalni indeks. Liječenje uključuje modifikaciju životnoga stila i navika, farmakološko te endovaskularno i/ili kirurško liječenje.

SUMMARY: Peripheral arterial disease is a common cardiovascular disease associated with an increased risk of major adverse cardiovascular events and major adverse limb events. Patients can be asymptomatic, and symptomatic patients can present with intermittent claudication or critical limb ischemia. A holistic multidisciplinary approach that includes timely diagnosis, treatment, monitoring and prevention is necessary. The initial diagnostic tool is the ankle-brachial index. Treatment includes lifestyle and habits modification, pharmacological and endovascular and/or surgical treatment.

KLJUČNE RIJEČI: periferna arterijska bolest, pedobrahijalni indeks, veliki neželjeni kardiovaskularni događaj, veliki neželjeni događaj na ekstremitetima.

KEYWORDS: peripheral arterial disease, ankle-brachial index, major adverse cardiovascular event, major adverse limb event.

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Uvod

Periferna arterijska bolest (PAB) česta je kardiovaskularna bolest koja znatno povećava kardiovaskularni (KV) i ukupni morbiditet i mortalitet. Nažalost, bolesnici s PAB-om često su neprepoznati te nisu optimalno liječeni u usporedbi s bolesnicima koji imaju koronarnu bolest srca.

U bolesnika s PAB-om naglašena je važnost holističkog multidisciplinarnog pristupa, koji uključuje dijagnozu, liječenje, praćenje i prevenciju. Početni koraci u navedenom pristupu uključuju probir bolesnika koji su pod rizikom od PAB-a i pravodobno i optimalno farmakološko liječenje sa svrhom prevencije, redukcije velikih neželjenih kardiovaskularnih događaja (MACE) i velikih neželjenih događaja na ekstremitetima

Introduction

Peripheral arterial disease (PAD) is a common cardiovascular disease that significantly increases cardiovascular (CV) and overall mortality and morbidity. Unfortunately, in comparison with patients with coronary heart disease, PAD patients are often unrecognised and not optimally treated.

In patients with PAD, the importance of a holistic multidisciplinary approach, which includes diagnosis, treatment, monitoring and prevention, is emphasised. The initial steps are screening the patients at high risk and optimal pharmacological treatment introduction with the aim of preventing and reducing major adverse cardiovascular events (MACE) and major adverse limb

(MALE), poboljšanja preživljenja bolesnika, redukcije rizika od hospitalizacije, redukcije potrebe za endovaskularnom i/ili kirurškom intervencijom te poboljšanja kvalitete života i funkcijskoga statusa bolesnika.[1]

U užemu smislu bolest perifernih arterija podrazumijeva bolest perifernih arterija donjih ekstremiteta (**slika 1**). Rizični čimbenici za PAB isti su kao i za druga aterosklerotska vaskularna područja i uključuju čimbenike rizika na koje se ne može utjecati, poput dobi, spola i obiteljske anamneze, te čimbenike rizika na koje se može utjecati, kao što su pušenje, šećerna bolest, dislipidemija i arterijska hipertenzija. U bolesnika s aneurizmom abdominalne aorte (AAA) najvažniji su čimbenici rizika muški spol i pušenje. LDL kolesterol vodeći je čimbenik u nastanku aterosklerotske bolesti, uz šećernu bolest i izloženost duhanskom dimu, a svaki od navedenih rizik od nastanka PAB-a povećava 2 – 4 puta.

events (MALE), improving patient survival, reducing the risk of hospitalisation, reducing the need for endovascular and/or surgical intervention, and improving the patients' quality of life.[1]

More commonly, peripheral arterial disease is considered the disease of peripheral arteries of lower limbs (**Figure 1**). Risk factors for PAD are the same as for other atherosclerotic vascular territories and include non-modifiable risk factors such as age, sex and family history and modifiable risk factors such as smoking, diabetes, dyslipidemia and arterial hypertension. In patients with abdominal aortic aneurysm (AAA), the most significant risk factors are male gender and smoking. LDL cholesterol is the leading factor in the development of atherosclerosis, along with diabetes, arterial hypertension and smoking, and each of these increases the risk of developing PAD two to four times.

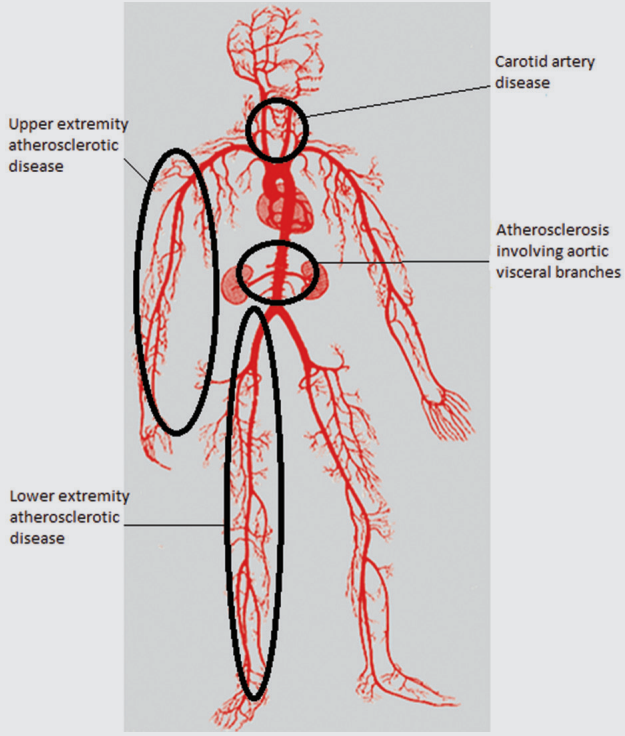

FIGURE 1. Sites of peripheral arterial atherosclerotic disease.

Pristup bolesniku s perifernom arterijskom bolešću

U početnome pristupu bolesniku s PAB-om prvi su koraci klinički i vaskularni pregled te laboratorijska analiza KV čimbenika rizika. Klinički pregled uključuje obiteljsku anamnezu na KV događaje, dosadašnje bolesti i simptome, dok fizikalni pregled koji uključuje palpaciju perifernih pulseva, auskultaciju femoralnog, karotidnog i abdominalnog područja i auskultaciju srca te pregled nogu i stopala. U sklopu laboratorijske obrade važno je odrediti kompletnu krvnu sliku, C-reaktivni protein (CRP), lipidogram, uključujući i Lp(a), glikemiju natašte i HbA1c, renalnu i jetrenu funkciju, elektrolite i koagulacijske parametre.

Approach to patients with peripheral arterial disease

In the initial approach to PAD patients, the first step is a clinical examination and laboratory analysis of CV risk factors. The clinical examination includes a family CV history, patient's history and symptoms, while the physical examination includes palpation of peripheral pulses, auscultation of the femoral, carotid and abdominal territories, auscultation of the heart, and an examination of the legs. As part of the laboratory workup, it is important to determine the complete blood count, C-reactive protein (CRP), cholesterol levels (including Lp(a)), fasting glycemia and HbA1c, renal and liver function, electrolytes and coagulation parameters.

Bolesnicima s PAB-om reducirana je hodna pruga, što dovodi do narušavanja funkcijskoga statusa, a samim time i kvalitete života. Zlatni je standard za procjenu hodne pruge test opterećenja. Bolesnici hodaju do maksimalne razine boli, što definira maksimalnu hodnu prugu, ali i naglašavaju početak boli i to označava crtu bezbolnog hoda. Alternativno, može se primjenjivati 6-minutni test hoda.

Pedobrahijalni indeks (ABI) jeftin je, jednostavan za primjenu i interpretaciju i široko rasprostranjen alat za dijagnozu i praćenje bolesnika s PAB-om. ABI u mirovanju ima 68 – 84 %-tnu osjetljivost i 84 – 99 %-tnu specifičnost za dijagnozu PAB-a. Vrijednost ABI-ja od ≤0,9 potvrđuje dijagnozu PAB-a, dok se za vrijednosti >1,4 uporabljuje pojam „nekompresibilne arterije" i povezan je s krutošću arterija u šećernoj bolesti, u težim oblicima bubrežnog zatajenja i u starijoj dobi. Obje su vrijednosti povezane s povećanim rizikom od KV događaja i smrti. Pri vrijednosti ABI-ja >1,4, preporučuje se primjena „toe-brachial" indeksa (TBI), tlaka na prstu (TP) ili *duplex* ultrazvuka. TBI mjeri tlak na palcu, drugom ili trećem prstu koristeći se laserskom doplerskom sondom ili pletizmografijom. Patološki je nalaz TBI-ja ≤0,7. U bolesnika s boli u ekstremitetu u naporu i urednim vrijednostima ABI-ja u mirovanju preporučuje se određivanje ABI-ja nakon vježbnja. Pozitivan test određen je padom arterijskog tlaka na gležnju >30 mmHg ili redukcijom vrijednosti ABI-ja >20 %. Mjerenje transkutanog tlaka kisika ($TcPO_2$) važno je za procjenu vijabilnosti tkiva, uz napomenu da na vrijednosti mogu utjecati debljina kože, temperatura sonde, upala i edem. Vrijednost $TcPO_2$ u mirovanju >30 mmHg pretkazatelj je cijeljenja rane, dok je vrijednost <10 mmHg povezana s lošijom prognozom cijeljenja rane i rizikom od amputacije.

Duplex ultrazvuk prvi je korak u obradi arterijske bolesti s pomoću kojeg se lokaliziraju i kvantificiraju vaskularne lezije. Osjetljivost je 88 %, a specifičnost 95 % u procjeni lezija >50 %. ABI i *duplex* ultrazvuk preporučeni su i za praćenje PAB-a nakon revaskularizacije.

S obzirom na povišen KV rizik, čak i u asimptomatskih bolesnika s PAB-om, važni su pravodobna dijagnoza, prevencija i kontrola KV čimbenika rizika. Preporuka je provesti probir s ABI ili TBI u bolesnika starijih od 65 godina s KV čimbenicima rizika (klasa preporuke II. a) ili u bolesnika starijih od 65 godina bez KV čimbenika rizika (klasa preporuke II. b). U bolesnika s AAA-om preporučuje se probir femoropoplitealnog područja *duplex* ultrazvukom u svrhu otkrivanja femoropoplitealne aneurizme. Probir asimptomatskih bolesnika sa stenozom karotidne arterije u općoj se populaciji ne preporučuje. Preporuka je *duplex* ultrazvukom ispitati stenozu karotida u bolesnika starijih od 60 godina s dva ili više KV čimbenika rizika, hipertenzijom i bolesti srca, koji su na programu hemodijalize, koji boluju od PAB-a, s poznatom koronarom bolesti srca (prije aortokoronarnoga premoštenja), sa šumom nad karotidnom arterijom i sa stanjem nakon provedenoga zračenja u području karotidne arterije.

Polivaskularna bolest definira se kao prisutnost simptomatske ateroskleroze u dvama ili više vaskularnih područja i česta je u bolesnika s aterosklerotskom bolesti. Nema dokaza da probir za asimptomatsku bolest u drugim (dodatnim) vaskularnim područjima poboljšava ishode bolesnika.

Periferna arterijska bolest može biti asimptomatska ili simptomatska i udružena s ranama na ekstremitetima. Dvije su podjele u široj uporabi, klasifikacija po Rutherfordu (ka-

PAD patients have a reduced walk distance, which leads to the impairment of the functional status, and thus the quality of life. The gold standard for evaluating a walk distance is the stress test. Patients walk up to the maximum level of pain, which defines the maximum walk distance, but also points out the time of pain onset, thus defining the pain-free walking distance. Alternatively, the six-minute walking test (6MWT) can be used.

The ankle-brachial index (ABI) is an inexpensive, easy to use and interpret and widely used tool for the diagnosis and monitoring of patients with PAD. Resting ABI has 68–84% sensitivity and 84–99% specificity for the diagnosis of PAD. A value of ABI ≤0.9 confirms the diagnosis of PAD, while values >1.4 require are considered "incompressible arteries" and are associated with arterial stiffness in diabetes, renal failure and older age. Both values are associated with an increased CV risk. With an ABI value >1.4, the recommendation is to use the toe-brachial index (TBI), toe pressure (TP) or duplex ultrasound. TBI measures pressure on the thumb, second or third toe using a laser doppler probe or plethysmography. The pathological finding of TBI is ≤0.7. In patients with limb pain during exercise and normal ABI values at rest, it is recommended to measure the ABI after exercise. A positive test is determined by a drop in ankle blood pressure >30 mmHg or a reduction in ABI value >20%. Measurement of transcutaneous oxygen pressure ($TcPO_2$) is important for assessing tissue viability, having in mind that values can be affected by skin thickness, probe temperature, inflammation, and edema. A resting $TcPO_2$ value >30 mmHg is a predictor of wound healing, while a value <10 mmHg is associated with a worse prognosis for wound healing and the risk of amputation.

Duplex ultrasound is the first step in the treatment of arterial disease in which vascular lesions are localised and quantified. The sensitivity is 88%, and the specificity 95% in the assessment of lesions >50%. ABI and duplex ultrasound are also recommended for monitoring PAD after revascularisation.

Considering the increased CV risk, even in asymptomatic PAD patients, timely diagnosis, prevention and control of CV risk factors are important. The recommendation is to perform screening with ABI or TBI in patients over the age of 65 with CV risk factors (class IIa recommendation) or in patients over the age of 65 without CV risk factors (class IIb recommendation). In patients with AAA, screening of the femoropopliteal area with duplex ultrasound is recommended in order to detect a femoropopliteal aneurysm. Screening of asymptomatic patients with carotid artery stenosis in the general population is not recommended. It is recommended to scan for carotid stenosis by duplex ultrasound in patients over the age of 60 with two or more CV risk factors, hypertension and heart disease, treated with hemodialysis, with diagnosed PAD, with known coronary heart disease (before coronary artery bypass grafting), with carotid murmur and after radiation of the carotid area.

Polyvascular disease is defined as the presence of symptomatic atherosclerosis in two or more vascular territories and is common in patients with atherosclerotic disease (**Figure 1**). There is no evidence that screening for asymptomatic disease in other (additional) vascular territories improves patient outcomes.

Peripheral arterial disease can be asymptomatic or symptomatic and can be associated with limb wounds. Two classifications are used – the Rutherford classification (categories 0–6) and the Fontaine classification (stages I–IV). Patients

tegorije 0 – 6) i klasifikacija po Fontaineu (stupnjevi I. – IV.). Bolesnici s asimptomatskom PAB nemaju tipične simptome, ali je nužno obratiti pozornost na bolesnike s ranama koji imaju maskirane simptome povezane s hodom zbog reducirane hodne pruge ili reduciran osjet boli. Simptomatska PAB (povezana s naporom) očituje se intermitentnim klaudikacijama ili kroničnim ranama bez kritično reducirane perfuzije ekstremiteta, dok se u nekih bolesnika mogu prezentirati atipični simptomi. Kronična ishemija s ugrozom ekstremiteta (CLTI) teži je oblik PAB-a s lošim ishodom ako se ne intervenira na arterijama ekstremiteta. Osim kliničkih obilježja koja uključuju ishemijsku bol u mirovanju, kronični ulkus (> 2 tjedna trajanja) ili gangrenu, važni su i hemodinamski pokazatelji koji uključuju tlak na gležnju <50 mmHg, TP <30 mmHg ili $TcPO_2$ <30 mmHg. U bolesnika s PAB-om i kroničnim ranama tzv. WifI klasifikacija služi za procjenu rizika od amputacije, a boduje se ovisno o vrsti rane, vrijednosti ABI-ja, AP-a i TP-a ili $TcPO_2$ te prisutnosti infekcije stopala.

Liječenje periferne arterijske bolesti

Liječenje PAB-a provodi se radi prevencije velikih KV događaja, sprječavanja događaja na ekstremitetu i poboljšanja kvalitete života. Svi bolesnici s detektiranom PAB moraju biti agresivno liječeni farmakološkim i nefarmakološkim mjerama koje dokazano imaju utjecaj na ishode bolesnika, a neovisno o inicijalnoj kliničkoj prezentaciji.

U navedeno se ubrajaju prestanak pušenja, dijetna prehrana i redukcija tjelesne mase te farmakološki posredovana optimizacija vrijednosti arterijskoga tlaka, lipida i glikemije te antitrombotska terapija. U bolesnika sa simptomatskim oblikom PAB-a potrebno je, uz spomenuto, provoditi i strukturirano vođene vježbe hodanja.

Vježbanje. Navedene se vježbe mogu provoditi u bolničkim i kućnim uvjetima, najmanje triput na tjedan, trajanja najmanje 30 minuta, tijekom barem 12 tjedana. Elementi uključeni u vježbe obično su blagog i umjerenog intenziteta, a radi smanjenja simptoma i KV rizika te povećanja kvalitete života, hodne pruge, funkcionalnoga statusa i osviještenosti bolesnika o vlastitoj bolesti. Ovisno o toleranciji bolesnika, intenzitet vježbi postupno se treba povećavati. Hodanje je najprihvaćeniji oblik vježbanja, ali u obzir dolaze i vježbe snage, vježbe na bicikl-ergometru ili kombinacija više različitih vježbovnih režima.

Antitrombocitno liječenje bolesnika s asimptomatskom PAB. Kao što je bilo poznato do sada, i dalje nema jasnog dokaza kako bolesnici s asimptomatskim PAB-om, unatoč reduciranom pedobrahijalnom indeksu, imaju prognostičke koristi ako su liječeni antitrombocitnom terapijom. Ne može se isključiti mogućnost povoljnoga djelovanja acetilsalicilatne kiseline (ASK) u određenim podskupinama bolesnika (npr. u bolesnika sa šećernom bolešću), a bolesnici s manifestnom aterosklerotskom bolešću na drugom vaskularnom području imaju indikaciju za antitrombocitno liječenje.[2]

Antitrombocitno liječenje bolesnika sa simptomatskom PAB. U bolesnika sa simptomatskim PAB-om antitrombotska terapija poboljšava KV prognozu i smanjuje rizik od razvoja KV događaja i događaja na ekstremitetu. Klopidogrel može imati prednost pred ASK-om. Ispitivanje *EUCLID* nije pokazalo veću korist od tikagrelora u usporedbi s klopidogrelom za smanjenje MACE-a ili velikih krvarenja. Kombinacija ASK-a i

with asymptomatic PAD do not have typical symptoms, but it is necessary to pay attention to patients with wounds, who have masked symptoms related to gait due to reduced walk distance or reduced pain sensation. Symptomatic PAD (exercise-related) presents with intermittent claudication or chronic wounds without critically reduced limb perfusion, while some patients may present with atypical symptoms. Chronic limb-threatening ischemia (CLTI) is a more severe form of PAD with a poor outcome if limb revascularisation is not performed promptly. In addition to clinical features including ischemic pain at rest, chronic ulcer (duration >2 weeks) or gangrene, hemodynamic parameters including ankle pressure <50 mmHg, TP <30 mmHg or $TcPO_2$ <30 mmHg are also important. In patients with PAD and chronic wounds, the so-called WifI classification serves to assess the risk of amputation, and is scored depending on the type of wound, ABI, AP and TP or $TcPO_2$ values, and the presence of foot infection.

Treatment of peripheral arterial disease

Treatment of PAD is carried out with the aim of preventing major CV events, preventing limb events and improving the quality of life. All patients with detected PAD must be aggressively treated with pharmacological and non-pharmacological measures that are proven to have an impact on patient outcomes, regardless of the initial clinical presentation.

The above includes: smoking cessation, dieting, weight reduction, and pharmacologically mediated optimisation of arterial pressure, cholesterol level, and glycemia values, as well as antithrombotic therapy. In patients with a symptomatic form of PAD, it is necessary, in addition to the above, to carry out structured and guided walking exercises.

Exercise. The mentioned exercises can be performed in hospital settings or at home, at least three times a week, for at least 30 minutes, during 12 weeks. The elements included in the exercises are usually of mild to moderate intensity, with the aim of reducing symptoms and CV risk and increasing the quality of life, walk distance, functional status and the patients' awareness of their own illness. Depending on the patients' tolerance, the intensity of the exercises should be gradually increased. Walking is the most accepted form of exercise, but strength exercises, exercises on a cycle-ergometer or a combination of several different exercise regimes are also considered.

Antiplatelet treatment of patients with asymptomatic PAD. There is still no clear evidence that patients with asymptomatic PAD, despite a reduced ankle-brachial index (ABI), have prognostic benefits if they are treated with antiplatelet therapy. The possibility of a beneficial effect of acetylsalicylic acid (ASA, aspirin) cannot be ruled out in certain subgroups of patients (e.g. in patients with diabetes), and patients with manifest atherosclerotic disease in another vascular territory have an indication for antiplatelet treatment.[2]

Antiplatelet treatment of patients with symptomatic PAD. In patients with symptomatic PAD, antiplatelet therapy improves CV prognosis and reduces the risk of CV events and limb events. Clopidogrel can have an advantage over aspirin. The EUCLID trial did not show a greater benefit of ticagrelor over clopidogrel in reducing MACE or major bleeding. The combination of aspirin and rivaroxaban in the so-called vas-

rivaroksabana u tzv. vaskularnoj dozi (2,5 mg dvaput na dan) učinkovitija je od same ASK za smanjenje MACE-a, MALE-a i akutne ishemije udova, uz napomenu o povećanom rizika od većih krvarenja, ali bez veće učestalosti intracerebralnih ili životno ugrožavajućih krvarenja.

Dvostruka antitrombocitna terapija (DAPT) indicirana je tijekom 1 – 3 mjeseca nakon endovaskularne terapije. Kombinacija ASK-a i rivaroksabana, uvedena nakon revaskularizacije, smanjila je učestalost MALE-a i MACE-a bez povećanja za život ugrožavajućih krvarenja, ali uz porast incidencije krvarenja prema ISTH (*International Society on Thrombosis and Haemostasis*) klasifikaciji, osobito kada je u kombinaciji primjenjivan i klopidogrel dulje od mjesec dana. U bolesnika koji imaju drugu indikaciju za oralnu antikoagulantnu terapiju (poput fibrilacije atrija ili mehaničkih zalistaka) i PAB antikoagulantna je terapija mandatorna, dok bi dodatna monoterapija antitrombocitnim lijekom nakon endovaskularnog liječenja trebala trajati 1 – 3 mjeseca.

Antihipertenzivna terapija. Nove Smjernice ESC-a za 2024. godinu o arterijskoj hipertenziji[3] preporučuju ciljne vrijednosti sistoličkoga tlaka od 120 do 129 mmHg za većinu odraslih ako se terapija dobro podnosi. U slučaju loše tolerancije terapije, cilj treba biti „najniži razumno ostvariv" arterijski tlak. Pacijenti s PAB-om i hipertenzijom imaju visok KV rizik te se preporučuju antihipertenzivni lijekovi poput ACE inhibitora, ARB-ova, beta-blokatora, diuretika i blokatora kalcijevih kanala. ACE inhibitori ili ARB-ovi trebaju biti prva linija liječenja radi smanjenja KV događaja, a kombinirana terapija može biti nužna za postizanje ciljnih vrijednosti arterijskoga tlaka.[4] Antihipertenzivno liječenje može produljiti hodnu prugu u bolesnika s PAB-om.

Hipolipemijska terapija. Bolesnici sa simptomatskim PAB-om često su nedovoljno i nezadovoljavajuće liječeni u usporedbi s onima koji imaju koronarnu bolest. Preporučuje se sniženje LDL kolesterola za više od 50 % od početne vrijednosti i postizanje ciljne razine LDL-C <1,4 mmol/L kako bi se smanjila smrtnost, infarkt miokarda i moždani udar, broj amputacija, a poboljšala hodna pruga. Statini su učinkoviti u smanjenju KV događaja i smrtnosti u bolesnika s PAB-om, čak i u uznapredovalim stadijima bolesti, a smanjuju i učestalost MALE-a. Ezetimib se može kombinirati sa statinima za poboljšanje rezultata liječenja u odabranih bolesnika s PAB-om, posebno kada ciljna razina LDL-a nije postignuta. Inhibitori PCSK9, kada se uporabljuju uz statine, dodatno smanjuju rizik od MACE-a i MALE-a, a poboljšavaju i hodnu prugu. U kliničkim ispitivanjima, uključujući i ona s PAB-om, inklisiran je pokazao smanjenje rizika od MACE-a za 26 %. Bempedoična kiselina, koja inhibira biosintezu kolesterola, smanjuje razinu kolesterola i može smanjiti učestalost MACE-a u bolesnika koji ne podnose statine. Iako fibrati nisu pokazali znatne koristi u smanjenju KV događaja u bolesnika s PAB-om, istraživanja sugeriraju da mogu imati ulogu u kontroli razina triglicerida.

Antidijabetici. Šećerna bolest znatno povećava rizik od PAB-a, a u bolesnika s PAB-om treba učiniti probir na šećernu bolest. Dijabetes je prisutan u 30 % bolesnika s intermitentnom klaudikacijom i 50 – 70 % onih s kritičnom ishemijom ekstremiteta. Preporučuje se postizanje razine HbA1c na manje od 7 % kako bi se izbjegla znatna hipoglikemija. U liječenju se preporučuju lijekovi s dokazanim KV prednostima, kao što su inhibitori SGLT2 i agonisti GLP-1, uz dodatak metformina

cular dose (2.5 mg twice daily) is more effective than aspirin alone in reducing MACE, MALE, and acute limb ischemia, bearing in mind an increased risk of major bleeding, but no higher incidence of intracerebral or life-threatening bleeding.

Dual antiplatelet therapy (DAPT) is indicated during one to three months after endovascular therapy. The combination of aspirin and rivaroxaban, introduced after revascularisation, reduced the frequency of MALE and MACE without increasing life-threatening bleeding, but with an increase in the incidence of bleeding according to the ISTH classification (International Society on Thrombosis and Haemostasis), especially when used in combination with clopidogrel for more than a month. In patients who have another indication for oral anticoagulant therapy (such as atrial fibrillation or mechanical valves) and PAD, anticoagulant therapy is mandatory, while additional antiplatelet monotherapy after endovascular treatment should last one to three months.

Antihypertensive therapy. The new 2024 ESC Guidelines on arterial hypertension[3] recommend target systolic pressure values of 120–129 mmHg for most adults, if therapy is well tolerated. In case of poor tolerance of the therapy, the goal should be the "lowest reasonably achievable" arterial pressure. Patients with PAD and hypertension have a high CV risk and antihypertensive drugs, such as ACE inhibitors, ARBs, beta-blockers, diuretics and calcium channel blockers are recommended. ACE inhibitors or ARBs should be the first-line treatment to reduce CV events, and combination therapy may be necessary to achieve target arterial pressure values.[4] Antihypertensive treatment can prolong walk distance in PAD patients.

Hypolipemic therapy. Patients with symptomatic PAD are often insufficiently and unsatisfactorily treated when compared to those with coronary artery disease. Lowering LDL cholesterol by more than 50% from baseline and achieving a target LDL-C level <1.4 mmol/L is recommended to reduce mortality, myocardial infarction and stroke, number of amputations, and improve walk distance. Statins are effective in reducing CV events and mortality in PAD patients, even in advanced stages of the disease, and they also reduce the incidence of MALE. Ezetimibe can be combined with statins to improve treatment outcomes in selected PAD patients, especially when target LDL levels have not been achieved. PCSK9 inhibitors, when used in addition to statins, further reduce the risk of MACE and MALE, and improve walk distance. In clinical trials, including those with PAD, inclisiran showed a 26% reduction in the risk of MACE. Bempedoic acid, which inhibits cholesterol biosynthesis, lowers cholesterol levels and can reduce the incidence of MACE in statin-intolerant patients. Although fibrates have not shown significant benefits in reducing CV events in patients with PAD, research suggests that they may have a role in controlling triglyceride levels.

Antidiabetics. Diabetes significantly increases the risk of PAD, and patients with PAD should be screened for diabetes. Diabetes is present in 30% of patients with intermittent claudication and 50–70% of those with critical limb ischemia. Achieving a HbA1c level below 7% is recommended to avoid significant hypoglycemia. Drugs with proven cardiovascular benefits, such as SGLT2 inhibitors and GLP-1 agonists, are recommended for treatment, with the addition of metformin as needed. Research shows that GLP-1RA (LEADER and SUSTAIN-6 trials) and SGLT2 inhibitors (EMPA-REG OUTCOME trial) reduce the risk of CV events in high-risk patients, while empagliflozin

po potrebi. Istraživanja pokazuju da GLP-1RA (istraživanja *LEADER* i *SUSTAIN-6*) i SGLT2 inhibitori (istraživanje *EMPA-REG OUTCOME*) smanjuju rizik od KV događaja u bolesnika s visokim rizikom, dok je empagliflozin pokazao smanjenje rizika od KV-a i ukupne smrtnosti u bolesnika sa šećernom bolešću tipa 2 i PAB-om. Iako su metformin i GLP-1RA povezani s smanjenjem rizika od MALE-a i MACE-a, važno je razmotriti individualizirane pristupe liječenju. SGLT2 inhibitori nisu znatno smanjili učestalost moždanog udara, ali postoje dokazi da metformin može smanjiti rast aorte u bolesnika s AAA-om. Praćenje dijabetičara s PAB-om ključno je zbog njihova visokog rizika od KV komplikacija.

Ostali lijekovi. Lijekovi poput verapamila, statina, antitrombocitnih lijekova i prostanoida mogu poboljšati duljinu bezbolne crte hoda u bolesnika s PAB-om, dok drugi lijekovi, poput cilostazola i naftidrofurila, nude znatnije produljenje crte bezbolnog hoda, ali bez bitnog utjecaja na KV ishode. Međutim, cilostazol može povećati rizik od krvarenja, što zahtijeva oprez u kombinaciji s drugim antitrombocitnim lijekovima.

Revaskularizacija. Metoda revaskularizacije dolazi u obzir u bolesnika s PAB-om u kojih je zbog klaudikacija narušena kvaliteta života i skraćena crta bezbolnog hoda ili imaju kroničnu ishemiju koja ugrožava ekstremitet (CLTI). Revaskularizacijsko liječenje, osim u slučaju CLTI-ja, nema bitnijih utjecaja na velike KV događaje i uputno ga je provesti nakon tri mjeseca optimalnoga medikamentnog liječenja i provedenih kontroliranih vježbi ako nisu ostvareni ciljevi. U asimptomatskih bolesnika revaskularizacijske metode nisu indicirane.

Aortoilijačne lezije mogu se učinkovito liječiti endovaskularnim i kirurškim metodama, pri čemu izbor ovisi o obilježjima lezije i riziku za bolesnika. Balonska angioplastika i primarno stentiranje pokazuju dugoročnu prohodnost uz nisku stopu komplikacija. Međutim, otvorena kirurgija pokazuje superiorniju ranu i srednjoročnu primarnu prohodnost, dok su sekundarne prohodnosti usporedive u objema terapijskim metodama.

Revaskularizacija femoropoplitealnih lezija prvotno bi trebala uključivati endovaskularno liječenje, čak i za složene lezije, osobito u bolesnika s visokim kirurškim rizikom. Unatoč izazovima održavanja dugoročne prohodnosti u femoropoplitealnoj regiji, uporaba balona koji otpuštaju lijekove poboljšalo je rezultate kod složenih lezija. Za razliku od prethodnih, u ovim smjernicama duljina lezije nije odlučujući kriterij za odabir modaliteta revaskualrizacije. Nakon početnih zabrinutosti oko materijala obloženih paklitakselom, analiza velikih nacionalnih baza podataka nije potvrdila raniju sumnju u povećanu smrtnost, što je dovelo do revizije stajališta FDA-a, koja sada ovakvu terapiju smatra sigurnom i učinkovitom. Kada je dostupna autologna vena i bolesnik ima nizak kirurški rizik, otvoreni kirurški pristup treba razmotriti nakon konzultacije s interdisciplinarnim vaskularnim timom. U bolesnika s teškom ishemijskom bolešću potkoljenična arterijska bolest (BTK) može se liječiti istodobno tijekom endovaskularnog zahvata na femoropoplitealnim arterijama.

Kronična ishemija koja ugrožava ekstremitet definirana je dugotrajnom hipoperfuzijom donjih udova, uzrokujući ishemijsku bol u mirovanju, rane koje ne cijele ili gangrenu. Dijagnostički kriteriji uključuju tlak na gležnju <50 mmHg, tlak na palcu <30 mmHg ili tkivnu oskimetriju <30 mmHg. Standardna ABI mjerenja mogu biti nepouzdana zbog arterija koje se ne mogu komprimirati, pa se preporučuju alternativne

shows a reduction in CV risk and overall mortality in patients with type 2 diabetes and PAD. Although metformin and GLP-1RA are associated with a reduction in the risk of MALE and MACE, it is important to consider individualised treatment approaches. SGLT2 inhibitors did not significantly reduce the incidence of stroke, but there is evidence that metformin can reduce aortic growth in patients with AAA. Monitoring of diabetic patients with PAD is essential because of their high risk of CV complications.

Other medications. Verapamil, statins, antiplatelets, and prostanoids can improve the length of the pain-free walk distance in PAD patients, while other drugs, such as cilostazol and naftidrofuryl, enable a significant prolongation of the pain-free walk distance, but without a significant impact on CV outcomes. However, cilostazol can increase the risk of bleeding, which requires caution when combined with other antiplatelet drugs.

Revascularisation. A revascularisation treatment is an option in PAD patients with impaired quality of life due to claudication and shortened pain-free walk distance or with chronic limb-threatening ischemia (CLTI). Revascularisation treatment, except in the case of CLTI, has no significant impact on major CV events and it is advisable to carry it out after three months of optimal medical treatment and controlled exercises, if the goals have not been achieved. In asymptomatic patients, revascularisation methods are not indicated.

Aortoiliac lesions can be effectively treated with endovascular and surgical methods, with the choice depending on lesion features and the risk for the patient. Balloon angioplasty and primary stenting show long-term patency with a low complication rate. However, open surgery shows superior early and medium-term primary patency, while secondary patencies are comparable in both therapeutic methods.

Revascularisation of femoropopliteal lesions should initially include endovascular treatment, even for complex lesions, especially in high-risk surgical patients. Despite the challenges of maintaining long-term patency in the femoropopliteal region, the use of drug-eluting balloons has improved outcomes in complex lesions. Unlike the previous ones, these guidelines state that the length of the lesion is not a decisive criterion for choosing the mode of revascularisation. After initial concerns about paclitaxel-coated materials, an analysis of large national databases did not confirm the earlier suspicion of increased mortality, leading to a revision of the FDA's position, which now considers the therapy safe and effective. If an autologous vein is available and the patient is at low surgical risk, an open surgical approach should be considered after consultation with an interdisciplinary vascular team. In patients with severe ischemic disease, below-the-knee (BTK) arterial disease can be treated simultaneously during endovascular surgery on femoropopliteal arteries.

Chronic limb-threatening ischemia (CLTI) is defined by long-term hypoperfusion of the lower limbs, causing ischemic pain at rest, non-healing wounds or gangrene. Diagnostic criteria include ankle pressure <50 mmHg, thumb pressure <30 mmHg, or tissue oximetry <30 mmHg. Standard ABI measurements can be unreliable due to non-compressible arteries, so alternative methods of perfusion assessment are recommended. For patients with CLTI, vascular imaging is mandatory to evaluate the possibilities of revascularisation, with additional digital subtraction angiography (DSA) to eval-

metode procjene perfuzije. Za bolesnike s CLTI-jem obvezna je vaskularna slikovna dijagnostika kako bi se procijenile mogućnosti revaskularizacije, uz dodatnu digitalnu suptrakcijsku angiografiju (DSA) za procjenu potkoljeničnih arterija. Obvezna se revaskularizacija preporučuje kako bi se obnovio protok krvi i smanjio rizik od amputacije. Usporedbe endovaskularnih pristupa i kirurških zahvata pokazale su slične stope preživljenja i amputacije, no kirurški zahvat ima dugoročne prednosti. Polivaskularna bolest zahtijeva individualan pristup s multidisciplinarnim timom, dok se hibridne metode mogu razmotriti za kombinirane lezije. U femoropoplitealnim lezijama potrebno je očuvati moguća mjesta za premosnice. Pri infrapoplitealnim lezijama endovaskularna je terapija prvi izbor, a angioplastika s običnim balonom pokazala se učinkovitom. U slučajevima ekstenzivne nekroze primarna amputacija može biti bolja opcija kako bi se izbjegle komplikacije.

Nakon revaskularizacije praćenje se preporučuje najmanje jednom godišnje, uključujući procjenu kliničkoga stanja, određivanje ABI indeksa i po potrebi ultrazvučne preglede.[5,6]

Među bolesnicima s PAB-om 20 – 30 % bolesnika ima disfunkciju lijeve klijetke, većinom povezanu s koronarnom bolesti srca. PAB i popuštanje srca neovisno su povezani s lošim ishodima i bolesnici s PAB koji imaju konkomitantno popuštanje srca imaju 30 % veći rizik od MACE-a i 40 % veći rizik od ukupne smrtnosti. Evaluacija funkcije lijeve klijetke u bolesnika s PAB-om može biti korisna za bolju stratifikaciju KV rizika i sveobuhvatno liječenje KV bolesti. Očekivano, prisutnost PAB-a u bolesnika s popuštanjem srca također je povezano s lošim ishodima.

Prevalencija fibrilacije atrija (FA) u bolesnika s PAB-om iznosi oko 12 %. U bolesnika s FA-om i PAB-om znatno je povećan rizik od ukupne smrtnosti, KV smrtnosti i MACE-a.[7] PAB je uključena u CHA_2DS_2-VASc bodovni sustav, što ističe prognostičku važnost PAB-a u bolesnika s FA-om.

uate the lower leg arteries. Mandatory revascularisation is recommended to restore blood flow and reduce the risk of amputation. Comparisons of endovascular approaches and surgery have shown similar survival and amputation rates, but surgery has long-term benefits. Polyvascular disease requires an individual approach with a multidisciplinary team, while hybrid methods can be considered for combined lesions. In femoropopliteal lesions, it is necessary to preserve possible sites for bypass grafts. For infrapopliteal lesions, endovascular therapy is the first choice, and balloon angioplasty has been shown to be effective. In cases of extensive necrosis, primary amputation may be a better option to avoid complications.

After revascularisation, monitoring is recommended at least once a year, including assessment of the clinical condition, determination of the ABI index and, if necessary, ultrasound examinations.[5,6]

About 20-30% of PAD patients have left ventricular dysfunction, mostly associated with coronary artery disease. PAD and heart failure are independently associated with poor outcomes and the PAD patients with concomitant heart failure have a 30% higher risk of MACE and a 40% higher risk of all-cause mortality. Evaluation of left ventricular function in patients with PAD can be useful for better CV risk stratification and comprehensive management of CV disease. As expected, the presence of PAD in patients with heart failure is also associated with poor outcomes.

The prevalence of atrial fibrillation (AF) in patients with PAD is about 12%. In patients with AF and PAD, the risk of all-cause mortality, CV mortality and MACE is significantly increased.[7] PAD is included in the CHA_2DS_2-VASc scoring system, which emphasises the prognostic significance of PAD in patients with AF.

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