ARTERIAL DISEASES SHORT REVIEW

Uptodate on lower extremity arterial disease- A review

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Abstract Atherosclerotic cardiovascular disease (ASCVD) is defined as coronary heart disease (CHD), cerebrovascular disease, or Lower Extremity Arterial Disease (LEAD) also named peripheral arterial disease (PAD). ASCVD is considered to be of atherosclerotic origin and is the leading cause of morbidity and mortality mainly for individuals with diabetes mellitus (DM). Although the prognosis of LEAD is relatively benign regarding viability and survival of the affected limb, all patients with LEAD are at increased risk of myocardial infarction, ischemic stroke and cardiovascular death. Several studies indicated a two- to three-fold greater mortality in patients with LEAD than in age-matched controls with normal ankle-brachial index (ABI), with a five-year mortality of about 30% in patients with LEAD. LEAD is rapidly progressing worldwide due to demographic expansion, aging, increasing prevalence of tobacco smoking, sedentarity, hypertension, dyslipidemia, and type 2 diabetes. Among PWT2D the occurrence of LEAD is associated with a high risk of morbidity compared with people without diabetes. Pharmacological management in LEAD patients should include: lipid-lowering treatment, anticoagulant and anti-platelet treatment, vascular pleiotropic treatment and antihypertensive treatment. The non-pharmacological management of LEAD patient is the foundation of the therapeutic process and translates into reduced cardiovascular (CV) risk, improved prognosis, and better patients functioning. Modification of the risk factors profile may contribute to the reduction of the severity and progression of atherosclerosis as well as to a delay in the onset of complications. Study results show that the management of LEAD patients, both non-pharmacological and pharmacological is less intensive than the management of patients with coronary artery disease or cerebrovascular disease.

Keywords Lower extremity arterial Disease, Atherosclerosis, Peripheral arterial disease, Diabetes mellitus, Vascular treatments

Introduction

Atherosclerosis is considered a generalized disease. Similar or identical etiopathogenetic mechanisms and risk factors are involved in various atherosclerotic diseases, and the positive effects of preventive measures on atherogenesis in different parts of the arterial system were shown. However, until now, great emphasis has been placed on the aggressive pharmacological management of coronary artery disease (CAD), while less attention has been paid to the management of peripheral arterial disease (LEAD), despite its significant morbidity and mortality. Data on the efficacy of preventive measures in LEAD patients have mostly been gained from subgroup analyses from studies devoted primarily to the management of coronary patients. These data have shown that treatment of risk factors for atherosclerosis with drugs can reduce cardiovascular events also in patients with LEAD. However, effects of some preventive procedures in LEAD patients differ from coronary patients[1-2].

Although the prognosis of LEAD is relatively benign regarding viability and survival of the affected limb, all patients with LEAD are at increased risk of myocardial infarction, ischemic stroke and cardiovascular

death. Several studies indicated a two- to three-fold greater mortality in patients with LEAD than in age-matched controls with normal ankle-brachial index (ABI), with a five-year mortality of about 30% in patients with LEAD[3].

Epidemiology and risk factors

LEAD affects over 40 million people in Europe[4] and appears to be 2 to 4 times more prevalent in people with type 2 diabetes (PWT2D) than in the general population[5]. Its prevalence ranges from 1.2% to 20% according to its definition. In the Action in Diabetes and Vascular Disease (ADVANCE) trial, the baseline prevalence of LEAD was 4.6%[6, 7]. In the same trial, the incidence of LEAD was reported in 1.2 per 100 patient-years when it was 3.7 per 100 in the Fremantle Diabetes Study. The prevalence of LEAD rise up to 20% when its occurrence rely on an abnormal ankle-brachial index (ABI)[7].

LEAD prevalence and incidence in PWT2D are strongly associated with the classical cardiovascular risk factors and diabetes duration7). The results of the UKPDS (UK Prospective Diabetes Study) have shown a prevalence of 1.2% at diagnosis and 12.5% after 18 years of diabetes evolution[8].

LEAD is rapidly progressing worldwide due to demographic expansion, aging, increasing prevalence of tobacco smoking, sedentarity, hypertension, dyslipidemia, and type 2 diabetes[4]. Among PWT2D the occurrence of LEAD is associated with a high risk of morbidity compared with people without diabetes. The evidence show that LEAD is associated with a 4 to 5 folds increased risk of non-traumatic lower limb amputation (LLA), cardiovascular disease (CVD), and mortality[9]. However, it remains less studied than other diabetes related complications and only rare randomized control trial have evaluated it as a primary outcome.

Among PWT2D, 5-year mortality after non-traumatic major amputations of the lower extremity is very high[10]. Whether it is a below-the-knee or above-the-knee amputation, mortality ranges from 40 to 82% to 40 to 90% respectively[11].

Primary and secondary prophylaxis

LEAD patients need intensive prevention and management of risk factors. Cigarette smoking is one of the most important risk factors for peripheral arterial disease. Smoking increases the risk of LEAD by several fold and is a more influential risk factor for LEAD than for coronary artery disease. Smoking is associated with severity of LEAD, a higher amputation rate, peripheral bypass occlusion and mortality[12]. Multiple pathophysiologic mechanisms may account for the prevalence of atherosclerosis in cigarette smokers. These include abnormalities of endothelial function, lipoprotein metabolism, coagulation, and platelet function. Smoking cessation decreases the risk of cardiovascular morbidity and mortality, and may improve functional capacity in patients with LEAD. Therapies to promote smoking cessation include counselling, nicotine replacement, and bupropion. Smoking cessation as a modifiable risk factor in patients with LEAD is of utmost importance[10].

Hyperlipoproteinaemia is also a relevant risk factor for LEAD. Hypercholesterolemia was found in 45% to 59% of symptomatic LEAD patients, and a significant benefit of statin treatment on cardiovascular and cerebrovascular events has been shown in this group of patients. Routine statin use in vascular patients, either managed conservatively or undergoing open surgical or endovascular procedures, is associated with several beneficial effects[13]. A meta-analysis, the Cholesterol Treatment Trialists' Collaboration, showed that each 1.0-mmol/L decrease in low-density lipoprotein cholesterol by statin treatment is associated with a 12% reduction in all-cause mortality[13].

The extent to which LDL values should be lowered in LEAD patients remains unclear, no prospective interventional studies have so far been carried out in LEAD alone patients. Beside statins PCSK9 inhibitors were shown to be effective in management of hypercholesterolemia in LEAD patients. The Fourier study[14] which enrolled 27,564 patients of which 13.2 % (3,642) had symptomatic LEAD, all of whom were on statin therapy evaluated benefit in the preplanned LEAD subgroup. The full study of evolocumab, showed a significant decrease in the combined CV endpoints of MI, stroke, and death. In the LEAD subgroup, evolocumab significantly reduced the primary end- points[14].

European Society of Vascular Medicine has updated evidence on the management on dyslipidaemia in patients with LEAD[15]. Guidelines recommend a low-density lipoprotein cholesterol (LDLC) goal of more than 50% reduction from baseline and <1.4 mmol/L (<55 mg/dL) in LEAD patients. As demonstrated by randomized controlled trials, lowering LDL-C not only reduces cardiovascular events but also major adverse limb events, including amputations, of the order of 25%. Addition of ezetimibe or a PCSK9 inhibitor further decreases the risk of cardiovascular events, and PCSK9 inhibition has also been associated with reduction in the risk of MALE by up to 40%. Furthermore, statin- based treatment improved walking performance, including maximum walking distance, and pain-free walking distance[15].

Hypertension is one of the most important risk factors for atherosclerotic disease, including LEAD. In patients with preclinical and clinical stages of LEAD,

hypertension was found in 50% to 92%. Follow-up data from the Framingham Study found a 2.5- to 4-fold increased risk of LEAD in men and women with hypertension[16]. Nevertheless, not all studies have demonstrated a clear relation between hypertension and LEAD. However, most of the findings support that the presence of hypertension additionally increases the risk of cardiovascular events in LEAD patients, as was confirmed in the SHEP (Systolic Hypertension in the Elderly Programme) study, where a low ankle-brachial index (<0.9) in an older population in conjunction with hypertension predicted a two- to three-fold increased risk of cardiovascular mortality.

Any class of antihypertensive drugs can be used to treat hypertension in most patients with LEAD, including beta blockers. Although a meta-analysis of 11 randomized control studies showed that beta (β) adrenergic blocker therapy did not worsen intermittent claudication[17], starting the treatment of hypertension in LEAD patients with (β) blockers can provoke the onset of intermittent claudication and vasospasms.

(β) Blockers should be carefully prescribed to LEAD patients with critical limb ischemia and vasospastic disorders. Dihydropyridine calcium channel blockers are appropriate for hypertensive patients with LEAD. Carvedilol and nebivolol are also effective drugs. However, in patients with LEAD, there is no conclusive, outcome-related data favouring the use of carvedilol or nebivolol over other beta blockers. ACE inhibitors exert various beneficial actions on the cardiac and vascular structure and function, beyond their blood pressure-lowering effects[18].

The antiatherogenic effect of the ACE inhibitor ramipril was confirmed in the Heart Outcomes Prevention Evaluation (HOPE) study, where ramipril provided equal relative protection against myocardial infarction, stroke and cardiovascular death in patients with LEAD as in other high-risk groups[19]. The absolute benefit of ramipril was greater in patients with a reduced ankle-brachial pressure index than in those with a normal ankle-brachial pressure index.

In people with obesity, the accumulation of dysfunctional perivascular adipocytes is associated with an increased systemic inflammation and higher level of ED[19]. Hypertension is associated with higher circulating levels of paracrine factors like ET-1, a potent vasoconstriction factor, in response to endothelial cell damage[20] or exercise induced ischemia[21].

Apart from smoking, diabetic metabolic disorders are the most important risk factors for LEAD progression. Every HbA1c increase in the magnitude of 1 % is associated with a 28 % increase in the relative risk for manifest LEAD. Diabetes elevates the risk of LEAD by a factor of 3 to 4 and the risk of claudication by a factor of 2. A subgroup analysis of United Kingdom Prospective Diabetes Study (UKPDS) showed a lower amputation rate with lower levels of HbA1c[8]. Among type 2 patients with diabetes under intensified treatment the Steno-2 study observed a 25 % relative risk reduction in amputation rates and a 10 % decrease in vascular interventions over 7 years[22].

Therefore, it is recommended that patients with diabetes should be screened for LEAD and all LEAD patient should be screened for diabetes and effectively treated in the case of a proven diagnosis of diabetes.

The antiplatelet drugs represent one of the basic options for the management of patients with various atherosclerotic diseases. Aspirin is the oldest and most often prescribed antiplatelet drug. The efficacy of aspirin depends probably on the type or location of atherosclerotic disease. It seems that it is most effective in coronary patients with clinically unstable disease, and its efficacy is uncertain in LEAD patients.

One of the first meta-analyses[23] indicated that antiplatelet drugs also significantly reduce cardiovascular events in patients with LEAD. However, only one third of the LEAD patients included in this meta-analysis were treated with aspirin, while the rest received other antiplatelet drugs.

Also meta-analysis of randomized trials of the efficacy of aspirin for the prevention of cardiovascular events was performed in patients with LEAD only. Randomized trials of aspirin therapy with or without dipyridamole involved 5269 individuals. Aspirin therapy alone or in combination with dipyridamole did not significantly decrease the primary endpoints of cardiovascular events (non-fatal myocardial infarction, non-fatal stroke and cardiovascular death). Only a significant reduction in non-fatal stroke was observed[24].

The effect of aspirin on cardiovascular events in patients with preclinical LEAD was studied in the Aspirin for Asymptomatic Atherosclerosis (AAA) trial[25]. This double-blind randomized controlled trial included 3350 subjects with a low ankle-brachial index (ABI) (≤0.95). Participants were followed for 8.2 years. No statistically significant difference in endpoints was found between the subjects treated with aspirin (100 mg) and the placebo group.

Clopidogrel and ticagrelor were shown to be more effective than aspirin. Clopidogrel is thus an effective alternative to aspirin for prevention of cardiovascular events in symptomatic LEAD. In patients who are non-responders to clopidogrel, ticagrelor is indicated. Dual antiplatelet treatment (DAPT) with aspirin and ticagrelor

in patients with coronary artery disease and concomitant LEAD significantly decreased the rate of major adverse cardiovascular events, including adverse limb events[26]. However, in the CHARISMA trial, aspirin and clopidogrel were not more effective than aspirin alone[27].

The new antiplatelet drugs prasugrel, ticagrelor and picotamide seem to be more effective than aspirin in LEAD patients, particularly in diabetic patients with LEAD. A novel antagonist of protease-activated receptor (PAR)-1, to the primary receptor for thrombin on human platelets, on vascular endothelium and smooth muscle cells was used in patients with different atherosclerotic disease. Vorapaxar in LEAD patients did not reduce the risk of cardiovascular death, myocardial infarction or stroke[28]. However, vorapaxar significantly reduced the rates of hospitalization for acute limb ischemia and peripheral artery revascularization. The beneficial effects of PAR-1 antagonists on vascular events were accompanied by an increased risk of bleeding[28].

Regarding to anticoagulants and combination with antiplatelets, there is no indication for full dose INR lowering oral anticoagulation with vitamin K antagonists in patients with LEAD, provided that there is no acute embolic event. However, the effect of a low dose antithrombotic therapy with the new oral anticoagulants in combination with ASA has been investigated. In the COMPASS trial which included patients with CAD and LEAD, rivaroxaban and aspirin alone and in combination were studied. Those assigned to rivaroxaban (2.5 mg twice daily) plus ASA 100 mg daily, had a 24 % better total survival and cardiovascular outcome but more major bleeding events than those assigned to aspirin alone[29].

Rivaroxaban (5 mg twice daily) alone did not result in better cardiovascular outcomes than aspirin alone and resulted in more major bleeding events. The net benefit was 22 % overall risk reduction of the stable CAD/LEAD population. Besides the 28 % general survival benefit, an additional significant (46 %) reduction in major adverse limb events including major amputation for ASA 100 mg/d combined with rivaroxaban 2 × 2.5 mg /d compared to ASA 100 mg/d and placebo was seen[29].

LEAD patients and diabetes mellitus

Early detection of lower extremity arterial disease (LEAD), before the onset of symptoms is mostly desirable in case of Diabetes Mellitus (DM) and highly wanted to prevent the occurrence of diabetic foot[30].

There has been continued debate regarding the reliability of vascular screening in diabetes. International guidelines recommend to regularly inspect and examine the at-risk foot[30]. The American Diabetes Association suggests to perform an exhaustive interview including history of decreasing walking speed, leg fatigue, and claudication as well as a clinical evaluation of the vascular status31). Foot examination should include inspection of the skin, examination of eventual deformities, and 10-g monofilament or vibration testing to evaluate the presence of sensory deficit. Vascular status should include palpation of pedal pulse. To grade LEAD presentation, ADA recommend to use the Fontaine or Rutherford classification[31].

Candidates for ultrasound or advanced LEAD testing include those with atypical LEAD symptoms or absence of pulse at lower extremities and abnormal ankle-brachial index or any occurrence of foot problems.

Conservative treatment of Lower Extremity Arterial Disease

Lifestyle management remains the cornerstones of diabetes management. Patients should be guided to benefit of preventive care services, smoking cessation counseling and nutritional therapy optimization. A comprehensive approach to the reduction in risk of diabetes-related complications is recommended.

The non-pharmacological management of LEAD patient is the foundation of the therapeutic process and translates into reduced cardiovascular (CV) risk, improved prognosis, and better patients functioning[32-34]. Modification of the risk factors profile may contribute to the reduction of the severity and progression of atherosclerosis as well as to a delay in the onset of complications. Study results show that the management of LEAD patients, both non-pharmacological and pharmacological is less intensive than the management of patients with coronary artery disease or cerebrovascular disease[35].

The non-pharmacological management for all types of atherosclerotic disease is mostly related to lifestyle modification, such as smoking cessation, improved physical activity and loos of body weight[36-39].

Smoking cessation is recommended in all LEAD patients. Those who smoke or use other forms of tobacco should be educated at every visit regarding the need to quit smoking. Smoking LEAD patients should be helped with an established plan to quit smoking consisting of pharmacotherapy (i.e. varenicline, bupropion and/or nicotine replacement therapy) and/or referral for a smoking cessation program. LEAD patients should avoid exposure to environmental smoke at work, home, and public spaces[39, 40].

In patients with intermittent claudication the walking exercise is the most effective, non-invasive therapy for improving maximal and pain free walking distances.

While both home-based and supervised treadmill walking exercise have been shown to improve pain-free and maximal walking distance in LEAD, most randomized trials of walking exercise in patients with PAD have studied supervised treadmill exercise[41-43]. Alternative cardio workout strategies such as upper body ergometry, cycling and walking until pain occur or low-intensity training, preventing moderate to maximum claudication, may be beneficial in symptomatic patients[43]. At least 150 minutes of moderate-intensity aerobic training per week (30 minutes 5 times a week) or 75 minutes of high-intensity aerobic training per week (15 minutes 5 times a weak) or a combination of the above are proposed[44].

LEAD patients are recommended to follow healthy diet. The low saturated fat content, with particular focus on whole-grain products, vegetables, fruit, and fish should be the base of daily diet[44].

Currently, no data from controlled, randomized clinical trials are available to suggest any benefits from any particular lifestyle modification dedicated to LEAD patients so as to reduce the mortality rate and incidence of CV events. Therefore, it is suggested that patients should follow the recommendations for the entire high cardiovascular risk population.

Numerous groups of drugs were analyzed in terms of their vascular pleiotropic and protective character.

The most extensively studied for this indication are cilostazol, naftidrofuryl, pentoxiphylline, buflomedyl, carnitine, and propionyl-L-carnitine. The beneficial impact of the aforementioned substances is usually mild to moderate and highly variable depending on the type of the study. No evidence was provided for these agents to significantly alter the outcome prognosis.

In recent years, sulodexide, as a mixture of glucosaminoglycans from porcine intestinal mucosa containing fast-moving heparin (80%) and dermatan sulfate (20%) is reaching a growing importance in LEAD treatment. The drug is targeting the inflammatory response, endothelial dysfunction and the associated changes within the extracellular matrix as well as modulating the coagulability of blood[45-49].

In vivo, sulodexide has been shown to promote arterial relaxation via a mechanism involving endothelium-dependent NO production. Results from clinical studies demonstrated that the activity of sulodexide is multidirectional and includes an effect on the hemostasis system, a reduction in thrombin generation, a profibrinolytic effect, and inhibition of pro-coagulation microparticle generation. It also has a documented effect on normalization of blood viscosity and lipid levels[45-49].

References

1) American Diabetes Association Economic costs of diabetes in the U.S. in 2017. Diabetes Care 2018;41: 917- 928.

2) Poredoš P, Jezovnik MK, Do the Effects of Secondary Prevention of Cardiovascular Events in PAD Patients Differ from Other Atherosclerotic Disease? Int. J Mol Sci, 2015; 16: 14477-89.

3) Grenon SM, Owens CD, Alley H, et al. n-3 Polyunsaturated fatty acids supplementation in peripheral artery disease: the OMEGA-PAD trial.. Vasc Med. 2013 Oct; 18(5):263-74.

4) Fowkes, F. G., Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet 2013;382 (9901):1329-40.

5) Criqui, M. H.,Matsushita K, Aboyans V et al. Lower Extremity Peripheral Artery Disease: Contemporary Epidemiology, Management Gaps, and Future Directions: A Scientific Statement From the American Heart Association. Circulation 2021;144 (9):e171-e191.

6) Mohammedi, K., M. Woodward, Y. Hirakawa, S. Zoungas, S. Colagiuri, P. Hamet, S. Harrap, N. Poulter, D. R. Matthews, M. Marre, J. Chalmers, and Advance Collaborative Group. Presentations of major peripheral arterial disease and risk of major outcomes in patients with type 2 diabetes: results from the ADVANCE-ON study. Cardiovasc Diabetol 2016;15 (1):129.

7) Norman, P. E., W. A. Davis, D. G. Bruce, and T. M. Davis. Peripheral arterial disease and risk of cardiac death in type 2 diabetes: the Fremantle Diabetes Study. Diabetes Care 2006;29 (3):575-80.

8) Adler A, Stevens RJ, Neil A, et al. UKPDS 59: Hyperglycemia and Other Potentially Modifiable Risk Factors for Peripheral Vascular Disease in Type 2 Diabetes. Diabetes Care 2002; 25: 894-9.

9) Jude, E. B., S. O. Oyibo, N. Chalmers, and A. J. Boulton.. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. Diabetes Care 2001;24(8):1433-7.

10) Stern, J. R., C. K. Wong, M. Yerovinkina, S. J. Spindler, A. S. See, S. Panjaki, S. L. Loven, R. F. D'Andrea, Jr., and R. Nowygrod. A Meta-analysis of Long-term Mortality and Associated Risk Factors following Lower Extremity Amputation. Ann Vasc Surg 2017;42:322-327.

11) Thorud, J. C., B. Plemmons, C. J. Buckley, N. Shibuya, and D. C. Jupiter. Mortality After Nontraumatic Major Amputation Among Patients With Diabetes and Peripheral Vascular Disease: A Systematic Review. J Foot Ankle Surg 2016;55(3):591-9.

12) Frank U, Nikol S, Belch J. 5 Conservative treatment for PAD - Risk factor management. Vasa. 2019 Dec;48(Suppl 102):1-12.

13) Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174000 participants in 27 randomised trials. The Lancet 2015;385:1397-405.

14) Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. New Engl J Med 2017; 376: 1713-22.

15) Belch JJF, Brodmann M, Baumgartner I, et al. Lipid-lowering and anti-thrombotic therapy in patients with peripheral arterial disease. Vasa 2021; 50: 401-11.

16) Makin, A., G.Y. Lip, S. Silverman, et al., Peripheral vascular disease and hypertension: a forgotten association? J Hum Hypertens, 2001;15(7): 447-54.

17) Diehm C, Pittrow D, Lawall H. Effect of nebivolol vs. hydrochlorothiazide on the walking capacity in hypertensive patients with intermittent claudication. J Hypertens. 2011 Jul;29(7):1448-56.

18) Östergren J, Sleight P, Dagenais G, et al. for the HOPE study investigators, Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease, European Heart Journal, 2004;25(1):17–24.

19) Kim, H. W., E. J. Belin de Chantemele, and N. L. Weintraub. Perivascular Adipocytes in Vascular Disease. Arterioscler Thromb Vasc Biol 2019;39 (11):2220-2227.

20) Xu, M., Y. P. Lu, A. A. Hasan, and B. Hocher. Plasma ET-1 Concentrations are Elevated in Patients with Hypertension - Meta-Analysis of Clinical Studies. Kidney Blood Press Res 2017;42 (2):304-313.

21) Mangiafico RA, Malatino LS, Spada RS et al. Treadmill exercise-induced release of endothelin-1 in patients with peripheral arterial occlusive disease at Fontaine stage IIb. Int Angiol 2010;19 (1):14-7.

22) Gaede P, Lund-Andersen H, Parving HH, et al. Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes. New Engl J Med 2009; 358: 580-91.

23) Antithrombotic trialists Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients BMJ; 2002: 324: 71-86.

24) Berger JS, Krantz MJ, Kittelson JM, Hiatt WR. Aspirin for the Prevention of Cardiovascular Events in Patients With Peripheral Artery Disease: A Meta-analysis of Randomized Trials. JAMA. 2009;301(18):1909–1919.

25) Fowkes FGR, Price JF, Stewart MCW, et al. Aspirin for Prevention of Cardiovascular Events in a General Population Screened for a Low Ankle Brachial Index: A Randomized Controlled Trial. JAMA. 2010;303(9):841–848.

26) McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. Am J Med 2006;199:624–38.

27) Bhatt DL, Fox KAA, Hacke W et al. Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. New Engl J Med 2006; 354: 1706-17.

28) Huynh, K. Vorapaxar for the treatment of PAD. Nat Rev Cardiol 2016;13, 184.

29) Eikelboom JW, Connolly SJ, Bosh J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. New Engl J Med 2017; 377: 1319-30.

30) Schaper NC, Van Netten JJ, Apelqvist J and Iwgdf Editorial Board. Practical Guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). Diabetes Metab Res Rev 2020;36 Suppl 1:e3266.

31) Standards of Medical Care in Diabetes—2022 Abridged for Primary Care Providers. Clin Diabetes 2022;40(1):10–38.

32) Sartipy, F., F. Lundin, E. Wahlberg, and B. Sigvant. Cardiovascular long-term outcome and prophylactic treatment patterns in peripheral arterial disease in a population-based cohort. Eur Heart J Qual Care Clin Outcomes 2019;5 (4):310-320.

33) Aboyans V. et al; 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). European Heart Journal (2018) 39, 763–821.

34) Jawien A. et al; Recommendations for the management of lower extremity artery disease (LEAD) based on ESVS/ESC 2017 guidelines. Position document of PTChN, PTNT, PTLR and SFSN PTK experts. Acta Angiologica 2019;25(4):219-269.

35) Cassar K et al. Management of secondary risk factors in patients with intermittent claudication. Eur J Vasc Endovasc Surg. 2003; 26(3): 262–266.

36) McDermott MM et al. Atherosclerotic risk factors are less intensively treated in patients with peripheral arterial disease than in patients with coronary artery disease. J Gen Intern Med. 1997; 12(4): 209–215.

37) Meijer WT et al. Determinants of peripheral arterial disease in the elderly: the Rotterdam study. Arch Intern Med. 2000; 160(19): 2934–2938.

38) Fowkes FG et al. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. Am J Epidemiol. 1992; 135(4):331–340.

39) Kannel WB, McGee DL. Update on some epidemiologic features of intermittent claudication: the Framingham Study. J Am Geriatr Soc. 1985; 33(1): 13–18.

40) Törnwall ME et al. Prospective study of diet, lifestyle, and intermittent claudication in male smokers. Am J Epidemiol. 2000; 151(9): 892–901.

41) Gerhard-Herman MD et al. 2016 AHA/ACC Guideline on the management of patients with lower peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017; 69(11):e71–e7e126.

42) Housley E et al. Physical activity and risk of peripheral arterial disease in the general population: Edinburgh Artery Study. J Epidemiol Community Health. 1993;47(6): 475–480.

43) Piepoli MF et al. ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). BMJ. 2004; 328(7433):189.

44) Regensteiner JG et al. Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials. J Am Geriatr Soc. 2002; 50(12):1939–1946.

45) Carroll B. J. et al; Sulodexide in venous disease. Journal of Thrombosis and Haemostasis, 2019;17:31–38.

46) Raffetto J. D. et al; Sulodexide Promotes Arterial Relaxation via Endothelium-Dependent Nitric Oxide-Mediated Pathway. Biochem Pharmacol. 2019 August;166:347–356.

47) Mattana P et al. Vascular pathologies and inflammation: The anti-inflammatory properties of sulodexide. Italian Journal of Vascular and Endovascular Surgery. 2012;19:1–7.

48) Gaddi A. V. et al; Sulodexide improves pain-free walking distance in patients with lower extremity peripheral arterial disease: A systematic review and meta-analysis. JRSM Cardiovasc Dis. 2020 Feb 14;9:2048004020907002.

49) Bignamini A. et al; Sulodexide for Diabetic-Induced Disabilities: A Systematic Review and Meta-Analysis. Adv Ther (2021) 38:1483–1513.