Perioperative treatment and optimal medical therapy for endovascular interventions

1

Zoltan Jambrik

During the last decades, the therapeutic strategy of peripheral artery disease (PAD) has shifted continuously toward endovascular modalities; however, the optimal medical treatment has remained essential in the everyday routine. It should be considered that the long-term clinical benefit of an endovascular catheter-based procedure is strongly related to the well-tailored pharmacological (as well as non-pharmacological, but non-interventional) management. The comprehensive treatment recommendation for PAD was published in 2019 by the *European Journal of Vascular Medicine*'s board with cooperation of the national societies of the field. This didactic overview and guideline of the treatment options is useful during every stage of the treatment of a patient with PAD.[1] The principles of PAD management are focused on progression, cardiovascular events, pain, and quality of life issues. The treatment should be started in asymptomatic patients with a PAD diagnosis based on imaging and/or functional testing (*e.g.*, ankle-brachial index [ABI] measurement). It has been accepted since the "getABI" study published by Diehm *et al.*[2] that the ABI has a good correlation with mortality even in patients with no symptoms. According to the cited guidelines, the optimal medical treatment has its own purpose to slow down/stop the progression, to reduce the rate of thromboembolic events, and to improve quality of life. The pharmacological agents of diabetes mellitus, hypertension, and hyperlipidemia must be strictly involved as recommended in the specific guidelines of each mentioned concomitant diseases.

PRE- AND PERIPROCEDURAL THERAPEUTIC CONSIDERATIONS

Platelet inhibition in peripheral artery disease: Asymptomatic or symptomatic patients

All patients with PAD might be a potential candidate to receive pre-, peri-, and postprocedural thrombocyte aggregation inhibition

therapy. Platelet inhibition is an effective protective measure against thromboembolic event in secondary prevention. However, the beneficial effect of acetylsalicylic acid (ASA) in primary prevention has not been proven yet in PAD, although life-long thrombocyte aggregation inhibition therapy is effective to prevent coronary artery disease or cerebrovascular events. Considering the CAPRIE study results, the preference might be given to clopidogrel over ASA. While the combination of ASA and clopidogrel is commonly used in cardiology (in patients with myocardial infarction [MI] treated with or without the endovascular technique), there is no reliable evidence that this approach is useful in PAD. So far, the more potent platelet aggregation inhibition agents (such as ticagrelor) have not shown superiority over clopidogrel in patients with PAD. However, in cohort of high-risk patients with PAD and prior MI, the potential benefit of the ASA and ticagrelor combination has been suggested. The advantages of the combination after 3 years are still uncertain.[3]

From the European guideline, it can be concluded that every symptomatic patient with PAD must receive long-term platelet aggregation inhibition treatment. On the other hand, asymptomatic patients with PAD do not benefit from thrombocyte aggregation inhibition treatment according to the *European Journal of Vascular Medicine*'s board's guidelines (III/A recommendation level). However, the 2016 American Heart Association (AHA)/American College of Cardiology (ACC) "Lower Extremity PAD Guideline" is a little bit more permissive: in asymptomatic patients with PAD (ABI≤0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death (IIa C-EO) and in asymptomatic patients with borderline ABI (0.91-0.99), the usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death is uncertain (IIb B-R).[4] Exclusively in patients with diabetes and PAD, low-dose ASA administration reduces neither the rate of cardiovascular events nor the rate of loss of extremity. In summary, regarding asymptomatic patients with PAD, the benefit of antiplatelet therapy in reducing peripheral arterial events has only been evidenced for patients treated by invasive endovascular method.

In a clinical trial, high-dose ASA or low-dose ASA with dipyridamole provided a better patency rate, whereas high-dose ASA showed a statistically significant improvement in patients who had undergone a percutaneous procedure. However, in the light of indirect evidence, it is widely accepted in clinical practice that low-dose ASA is as effective as high-dose ASA and associated with a lower bleeding risk (I B).

Dual antiplatelet therapy (DAPT) has become routine in the medications that patients with PAD take after undergoing an endovascular procedure. However, there are only conflicting or insufficient data about this treatment pattern. In the MIRROR study, DAPT was better than ASA alone and a longer treatment period (1 year) was more favorable than a shorter one (6 months), if the reintervention on the target lesion was in focus.[5] It should be mentioned that this study was statistically underpowered for such clinical events and the study did not have a primary clinical endpoint. Rather, the endpoints were the local concentration of platelet-activating β-thromboglobulin, cluster of differentiation of 40 ligand (CD40L), and the rate of clopidogrel resistance.

If we consider the common pathophysiological basis of the atherosclerosis and the data on coronary arteries, temporary dual platelet aggregation with a combination of ASA 100 mg/day and clopidogrel 75 mg/day may be safe and useful in the absence of evidence concerning the

peripheral vasculature. It should be maintained at least 1 month after balloon angioplasty, and at least 3 months after stent or covered stent implantation. Ticagrelor failed to show significant benefit on the cardiovascular outcome compared with clopidogrel in a large-scale study dedicated for patients with PAD (EUCLID). By common sense, even without solid evidence, in patients with PAD and clopidogrel resistance, ticagrelor might be used to replace clopidogrel.

Anticoagulation with heparins

Based on observations of the pathology of chronic limb ischemia (CLI) – the most severe form of PAD – in three fourths of cases intraluminal thrombus formation can be detected. Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are potent anticoagulants, while both have some antithrombotic and antiproliferative features. In the everyday routine treatment, UFH is administered immediately before and during the endovascular intervention. The aim of heparin use is to prolong the activated clotting time (ACT) to 200-250 seconds.[6] There is a small study with nadroparin, a LMWH, that showed a lower re-occlusion rate at 6 months after the intervention.[7] Long-term use (3 months) of another LMWH (dalteparin) may be beneficial only in patients with CLI due to the longer, more complex lesions, the higher rate of chronic total occlusion, or remaining thrombus in the treated area.

Oral anticoagulants

If no other indication emerges (cardiac, non-vascular, hematological, etc.), the administration of a vitamin K antagonist oral anticoagulant is not encouraged by the guidelines due to lack of evidence. Regarding the novel direct oral anticoagulants, as suggested in the COMPASS trial, the recently published VOYAGER study found a more favorable outcome with 2×2.5 mg rivaroxaban + ASA *versus* ASA alone in patients with PAD and revascularization. The bleeding risk was similar in the two groups.[8] The summary of current recommendation of antithrombotic and anticoagulation regime is shown in Table 1.I.

Cilostazol

As an oral phosphodiesterase 3 (PDE) inhibitor, cilostazol improves the maximal walking distance and the absolute claudication distance in patients with PAD manifested in the lower

Table 1.I. *Antiplatelet and anticoagulation strategy according to the ESC Guidelines.*

	Monotherapy	Dual antiplatelet therapy	Oral anticoagulant therapy
Recommendation in PAD patients	With symptoms	With ACS, prior MI or after revascularization	With atrial fibrillation, mechanical artificial valve, or after revascularization
First choice drug	Clopidogrel	ASA + clopidogrel	VKA or NOAC (as required for the non-PAD concomitant disease)

extremities. Its beneficial effects can stem from increasing cyclic adenosine monophosphate (cAMP) levels in vascular smooth muscle cells and thrombocytes, which increase endothelial function (relaxation) and decrease the platelet activity on aggregation. The clinical impact of cilostazol can range from improving limb salvage through freedom from leg amputation to the lower rate of clinical need of target-level revascularization after percutaneous transluminal angioplasty (PTA). This might be explained by the lower occurrence of restenosis. Cilostazol can reduce in-stent restenosis after peripheral vascular interventions. In five retrospective case registries and two small prospective studies, there was a reduced restenosis rate after treatment with cilostazol.[9] In a large, retrospective observation trial in patients after endovascular treatment of a lower extremity, cilostazol use was associated with improved 1-year freedom from amputation. Patients with renal failure and diabetes also demonstrated a significant benefit from taking cilostazol.[10]

Medications to withdraw before intervention

In general, most of the usual medications a patient with PAD takes should be continued at the periprocedural stage. There are some data indicating that a sudden stop to taking a beta-blocker or statin might be the cause for some complications, such as tachycardia or acute coronary syndrome. Statin withdrawal may increase the frequency of MI and death after MI, while the inflammatory parameters and endothelial function can show rapid deterioration. A complex treatment (statins, beta blocker, angiotensin-converting enzyme [ACE] inhibitors, antiplatelet agents, etc.) is often recommended in this populations with a high cardiovascular burden based on current evidence.

Some treatments should be considered for a perioperative break, such as anticoagulants and metformin. Anticoagulants must be carefully managed. The old-fashioned K-vitamin antagonist (KVA) should be stopped several days before the procedure. The time range depends on the actual effect of the KVA (measured as the international normalized ratio [INR]) and its type: Acenocoumarin usually requires a 2-day drug-free period, but warfarin should be stopped 4-5 days prior to the day of admission/procedure. If the INR result on the morning of PTA is less than 2, there is no absolute contraindication for the intervention. In the case of radial access, a higher INR value can be acceptable because of the lower bleeding risk. Currently, the more frequent use of distal radial access for certain types of endovascular procedures may suggest a lower bleeding complication rate. The direct oral anticoagulants such as rivaroxaban, apixaban, and edoxaban are metabolized quickly, and a 24 hour-period without them before endovascular therapy is sufficient in a patient with a low bleeding risk. In the case of dabigatran, the withdrawal time before the procedure depends on the kidney function: if creatinine clearance is <50 mL/minutes, a withdrawal of 3-5 days is required, while those with good kidney function should have a withdrawal of 1-2 days.

Metformin is a widely used first-line oral antidiabetic drug that most patients with PAD take (related to the high frequency of diabetes mellitus in patients with vascular diseases). Metformin can exert a harmful effect by facilitating contrast-media-induced renal dysfunction. Withdrawal of metformin should be considered 48 hours before angiography or PTA.

OPTIMAL MEDICAL TREATMENT AFTER ENDOVASCULAR INTERVENTION: RISK FACTOR MANAGEMENT

Lipid-lowering therapy in dyslipidemia

It is widely accepted that increased serum total cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, or lipoprotein(a) concentrations and decreased high-density lipoprotein (HDL) levels can be potent contributors to the development of PAD. In the case of established PAD, the use of statins (such as a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor) prevents additional cardiovascular thromboembolic events and reduces morbidity and mortality. As secondary prevention, statins must be taken by every patient with PAD who does not have intolerance to this class of drugs.

Unfortunately, there is no randomized study about what cholesterol or LDL level should be reached after a peripheral endovascular procedure. We may export cut-off LDL levels that patients should reach during treatment from studies on patients with high cardiovascular risk. In patients at high risk, the acceptable LDL level after any cardiovascular event is <1.4 mmol/L. According to the "2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce Cardiovascular Risk," the presence of peripheral disease indicates a very-high cardiovascular risk status.

Currently, the advantageous effects of statins on ongoing PAD are indisputable. Based on several retrospective studies, intensive statin therapy (20-40 mg rosuvastatin or 40-80 mg atorvastatin) not only reduces the cardiovascular mortality but can prevent limb loss due to decreased amputation rate with relative risk reduction between 18% and 35%. A meta-analysis of 22 observational studies and two randomization trials with more than 268,000 patients with PAD concluded there was a significantly better outcome for patients taking high-dose statins. Specifically, the all-cause mortality and amputation rates showed an important and impressive decline. Unfortunately, these patients had not undergone endovascular procedures, so these data cannot be directly incorporated to our routine with post-PTA patients with PAD.[11]

Ezetimibe and evolocumab, proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors, can also be used as alternative (in the case of statin intolerance) or additional (to reach the target LDL level) therapeutic options. However, one may speculate that the effect of ezetimibe might depend on the concomitant statin therapy. On the other hand, the FOURNIER study in the PAD subgroup of the evolocumab arm showed a 42% reduction in the major adverse limb event rate (acute limb ischemia, major amputation, or urgent peripheral revascularization for ischemia) besides the benefit on the combined cardiovascular endpoint (MI, stroke, and death).

Angiotensin-converting enzyme inhibitors

Because hypertension is a well-known risk factor of PAD (and other manifestations of atherosclerosis), its treatment has remained a critical issue. The target blood pressure is <140/90 mmHg. ACE inhibitors function as a basic element of hypertension treatment, while

in patients with CLI they also decrease major adverse cardiovascular events (MACE) and overall mortality. On the other hand, ACE inhibitors have no effect on the major adverse limb event rate or the need for amputation. There are data about beneficial effect of ramipril on increasing pain-free and maximum walking time in patients with PAD. In one of the largest trials with ramipril (HOPE), ABI<0.90 was a strong predictor of MACE independently of the presence of symptoms. In this PAD subgroup, the benefit of ramipril treatment was twice as large as in patients with normal ABI. Hypotension as a side effect of ACE inhibitors has been observed after endovascular intervention, but without an increased occurrence of stroke, MI, death, or kidney failure. The current evidence does not support or preclude ACE inhibitor use specifically for patients with PAD, but the dedicated treatment of a risk factor is fundamental, recommended as a IIa treatment by AHA/ACC.

Diabetes mellitus

Diabetes mellitus one of the most prominent contributors to atherosclerosis as well as PAD. Maintaining blood glucose or glycated hemoglobin (HbA1c) below the recommended level is a cornerstone of the treatment for patients with diabetes mellitus. Moreover, a 1% increase in HbA1c was associated with 14.2% major cardiac event in the PAD subgroup of the EUCLID study. However, in a meta-analysis of randomized trials, intensive glucose control did not decrease the risk of PAD. Despite the robust beneficial evidence of various antidiabetic drugs on preventing cardiovascular events in patients with diabetes mellitus, the specific agent for lowering PAD-related adverse events has not yet been determined.

CONCLUSIONS

As observed in a nationwide Danish longitudinal cohort study, improving secondary prevention (including medical treatment) after an endovascular procedure is associated with a reduction in all adverse outcomes. Unfortunately, the rate of major amputations is not among the benefits.[12] It is clear that adherence to guideline-recommended medical therapy is crucial for better outcomes in PAD management. Nonetheless, it should be kept in mind, that the use of potent medical therapy as well as non-pharmacological options is still a challenging phase of patient care after percutaneous peripheral artery intervention.

REFERENCES

1. Frank U, Nikol S, Belch J, *et al.* ESVM Guideline on peripheral arterial disease. Vasa 2019;48:1–79.
2. Diehm C, Lange S, Darius H, *et al.* Association of low ankle brachial index with high mortality in primary care. Eur Heart J 2006;27:1743–9.
3. Bonaca MP, Bhatt DL, Storey RF, *et al.* Ticagrelor for Prevention of Ischemic Events After Myocardial Infarction in Patients With Peripheral Artery Disease. J Am Coll Cardiol 2016;67:2719–28.
4. Gerhard-Herman MD, Gornik HL, Barrett C, *et al.* 2016 AHA/ACC Guideline on the Management of Patients with Lower Extremity Peripheral Artery Disease: Executive Summary. Circulation 2017;135:e686–725.
5. Tepe G, Bantleon R, Brechtel K, *et al.* Management of peripheral arterial interventions with mono or dual antiplatelet therapy – the MIRROR study: a randomised and double-blinded clinical trial. Eur Radiol 2012;22:1998–2006.

6. Norgren L, Hiatt WR, Dormandy JA, *et al.* Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg 2007;33:S1–75.
7. Schweizer J, Müller A, Forkmann L, *et al.* Potential use of a low-molecular-weight heparin to prevent restenosis in patients with extensive wall damage following peripheral angioplasty. Angiology 2001;52:659–69.
8. Bonaca MP, Bauersachs RM, Anand SS, *et al.* Rivaroxaban in Peripheral Artery Disease after Revascularization. N Engl J Med 2020;382:1994–2004.
9. Warner CJ, Greaves SW, Larson RJ, *et al.* Cilostazol is associated with improved outcomes after peripheral endovascular interventions. J Vasc Surg 2014;59:1607–14.
10. Neel JD, Kruse RL, Dombrovskiy VY, *et al.* Cilostazol and freedom from amputation after lower extremity revascularization. J Vasc Surg 2015;61:960–4.
11. Sofat S, Chen X, Chowdhury MM, *et al.* Effects of Statin Therapy and Dose on Cardiovascular and Limb Outcomes in Peripheral Arterial Disease: A Systematic Review and Meta-analysis. Eur J Vasc Endovasc Surg 2021;62:450–61.
12. Sřgaard M, Nielsen BP, Skjřth F, *et al.* Temporal Changes in Secondary Prevention and Cardiovascular Outcomes After Revascularization for Peripheral Arterial Disease in Denmark A Nationwide Cohort Study. Circulation 2021;143:907–20.

Practical perioperative non-invasive assessment before intervention

2

Adam L. Jermendy

Non-invasive evaluation of vascular diseases has long been established as a reliable and accurate gatekeeper to invasive interventional procedures. Its usefulness in patient screening, stratification, and selection has been demonstrated. The non-invasive techniques used in the everyday clinical setting may vary according to local availability, institutional practices, and the level of expertise. Furthermore, the proper method to choose depends on the vascular territory in question. Generally, we can differentiate two broad categories: functional and anatomical tests. The most widespread and clinically used functional testing method is assessment of the ankle-brachial index (ABI). Anatomical tests include duplex ultrasonography (DUS), computed tomography angiography (CTA), and magnetic resonance angiography (MRA). Each test has its own advantages and disadvantages, which are discussed in this chapter. By using them according to the clinical question and in concordance with each other, each component may constitute an accurate and highly reproducible examination.

STANDARD NON-INVASIVE FUNCTIONAL TESTING MODALITIES

The use of the ABI has long been the first line in the examination of lower extremity atherosclerotic disease. Resting ABI measurement should be performed in patients with a history of peripheral artery disease (PAD) or after a physical examination suggestive of PAD.[1] It is obtained by measuring the systolic blood pressure in both brachial arteries and taking the higher value, which is then divided by the systolic blood pressure in both ankles (the higher value of the dorsalis pedis and posterior tibial arteries). The supine position and the use of a Doppler device is recommended to achieve higher diagnostic accuracy. The ABI as a first-line test in the diagnostic evaluation of