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Lower limb interventions

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To my wife Krisztina, my family and my colleagues for their patience and support throughout this writing and for my teachers Kálmán Hüttl and László Pintér

Zoltán Ruzsa

To my Family, Friends and especially my teachers - Giancarlo Biamino and Andrej Schmidt

Stanislaw Bartuś

Introduction

Z. Ruzsa, S. Bartuś

In the recent years we have observed the rapid advance in the knowledge and treatment technologies of peripheral arteries disease. There is an increasing number of scientific data, especially from single center registries, on endovascular approach and the treatment of obstructive lesions is the object of fruitful discussions in the literature and during congresses. Over the past decade, the available literature on vascular interventions has vastly increased. We have attempted to provide in this book an introduction to the anatomy, imaging, clinical decision and complex techniques of peripheral artery circulation. The book is directed primarily to fellows in training, but it will also be useful for interventionists who are interested in learning new types of intervention such as endovascular procedures. The "Lower Limb Interventions" book is intended to be comprehensive in scope, yet its greater purpose is to simplify the clinical decision, to understand the role and technique of the intervention, and to give an up-to-date review of the literature.

The main parts of the book focuses on perioperative treatment and imaging, description of the devices and techniques used in peripheral vascular interventions.

In this book we tried to include the currently available evidence-based long-term results from the literature with practical comments. Because the amount of data coming from the big clinical multicenter trials is still very limited, some of the surgical techniques described in this book come from our clinical practice, but also from the experience of our teachers and long discussions during scientific meetings.

The new generation of dedicated peripheral stents, drug coated balloons, wires but also the new unconventional approaches indicate the potential direction for progress, development and improvement of long-term follow-up of the treatment. The goal of this book is to cover the different scientific and technical aspects in regards of the endovascular peripheral arteries treatment strategies including the most important regions of interventions. The text of the book is oriented for clinical practitioners and we hope it can also serve as a practical guide, particularly for fellows and young interventionalists.

We realize that our book does not contain all the important aspects of peripheral procedures and that some of the data we are providing today will rapidly be updated in the near future. All the readers are invited to contribute to the discussion and express their constructive criticism that will help all of us improving endovascular techniques.

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1 Perioperative treatment and optimal medical therapy for lower limb interventions

Z. Jambrik

Peripheral artery disease manifesting in lower limb arteries is a potential target of endovascular interventions and vascular surgical procedures. However, despite the rapidly growing importance and efficacy of catheter-based therapies, the optimal medical treatment requires an adjuvant to achieve the best angiographic and clinical outcome. It is clear that the lack of optimization of medical treatment options may have a disadvantageous impact on the short- and long-term vascular and clinical events. Furthermore, some medications can be a potential factor for severe complications during the percutaneous intervention and should be stopped before the intervention.

MEDICATIONS TO WITHDRAW BEFORE INTERVENTION

Generally, most of the usual medication of a PAD patient should be continued at the periprocedural stage. There are data suggesting that beta-blocker or statin therapy should not be stopped because they might be a cause of complications, including tachycardia or acute coronary syndrome. The statin withdrawal may result in increased myocardial infarction and increased mortality rate, while the inflammation parameters and endothelial function can show rapid deterioration. A complex treatment (statins, beta blockers, ACE inhibitors, antiplatelet agents, etc.) is often recommended in this population with high cardiovascular burden based on current data.

There are some treatments that should be considered for a perioperative brake, such as anticoagulants and metformin.

Anticoagulants require careful management. The K-vitamin antagonist (KVA) should be stopped several days before the procedure. The time range depends on the actual effect of the KVA (INR) and its type. Acenocoumarol usually requires a drug-free period of 2 days prior to the admission day. A patient on warfarin, however, requires a drug-free period of 4-5 days prior to the admission day. If the INR result on the morning of PTA is less than two, there is no absolute contraindication for the intervention. In the case of radial access, higher INR values can usually be acceptable because of the lower risk of bleeding.

The so-called novel anticoagulants, such as rivaroxaban, apixaban, and dabigatran are quickly metabolized, and can be stopped 24 hours before endovascular therapy.

Metformin is a widely used first-line oral antidiabetic drug that is prescribed to the majority of PAD patients (regarding the high frequency of diabetes mellitus in patients with vascular diseases). The withdrawal of metformin protects against contrast media-induced renal dysfunction. Withdrawal of metformin may be considered 48 hours before angiography or PTA. However, the newest data on the harmful potential of metformin are less clear. It is advised to make an individual decision for each patient based on their comorbidities, hydration state, actual renal function and the complexity of the current percutaneous intervention.

OPTIMAL MEDICATIONS

1. STATINS

The indefinite continuation of statin therapy in a patient who is already on statin at the time of PTA is a must. The statin therapy should also be initiated in all patients after any kind of vascular surgery (intervention) in order to protect against adverse cardiovascular events. The primary impact of statin is the lowering of serum lipids, while its pleiotropic effect may play a more important role. Anti-inflammation, improvement of endothelial function, stabilization of atheromatous plaque, and the inhibition of platelet reactivity lead to a favorable pattern in major cardiovascular events, morbidity, and mortality after (dominantly cardiac) interventions.

The beneficial effect of statins (as an inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase) allows for primary and secondary prevention in cardiovascular patients. Most of the randomized studies are conducted by enrolling patients with coronary artery disease; however, several observational databases provide coherent evidence of better cardiovascular outcomes (including mortality) in patients with PAD and statin therapy.

The relation of statin treatment with vascular procedures was investigated in a large randomized trial: DECREASE III (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography III). In DECREASE III, fluvastatin (in statin naïve subjects) reduced myocardial ischemia and cardiovascular mortality in patients that had undergone abdominal aortic aneurysm repair or arterial bypass compared to placebo. Atorvastatin also demonstrated similar changes in the combined endpoint (cardiac death, nonfatal MI, unstable angina pectoris, or ischemic stroke) in an RCT. The perioperative use of statins has been studied in the DREAM Trial (Dutch Randomized Endovascular Aneurysm Management), where statin therapy was associated with better long-term survival after both surgical and endovascular AAA management.

According to the above finding, the statin treatment is recommended by the current (2013) prevention guideline from ACC/AHA Guidelines for patients with cardiovascular disease (history of MI, acute coronary syndrome, coronary or arterial revascularization, cerebrovascular event, or PAD due to atherosclerosis). As high cardiovascular risk patients, PAD patients represent a target population for both perioperative and lifelong statin therapy. To summarize our knowledge about statin administration in the periprocedural setting of lower limb PTA, we can state that, despite the lack of lower limb PTA studies, robust supportive evidence is available that can be converted from cardiac or other kinds of vascular observations.

Based on these interpretations, the current 2016 AHA/ACC Lower Extremity PAD Guideline recommends treatment with a statin for all patients with PAD (I A).

2. THROMBOCYTE AGGREGATION INHIBITION

Patients with PAD are at increased risk for atherothrombotic events such as myocardial infarction or stroke. Antiplatelet therapy has been widely demonstrated as a beneficial option for general cardiovascular patients. There is a systemic review of 39 RCTs on thrombocyte aggregation in PAD patients that shows a relevant reduction (>20%) in non-fatal MI, non-fatal stroke, and vascular death compared to the patients receiving the placebo. All PAD patients should remain on thrombocyte aggregation therapy for a long time and it should be continued after arterial intervention.

Moreover, the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events) trial revealed the superiority of clopidogrel therapy *versus* ASA to prevent stroke, MI, or vascular death.

According to the current 2016 AHA/ACC Lower Extremity PAD Guideline:

- antiplatelet therapy with aspirin alone (75–325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce MI, stroke, and vascular death in patients with symptomatic PAD (I A);
- 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);
- 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).

The management of perioperative anti-platelet aggregation is less clear. There are no modern randomized trials defining optimal anti-platelet therapy after peripheral endovascular interventions.

There is no strong evidence that the initiation or continuation of antiplatelet medication in the perioperative period of non-cardiac or non-carotid surgery. However, no high-quality data are available related to lower limb endovascular interventions where there is a lower probability of bleeding complications.

DUAL ANTIPLATELET TREATMENT ˜DAPT°

The CHARISMA Trial (Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events) randomized patients with a prior stroke, MI, PAD, or multiple risk factors to low-dose aspirin (75 to 162 mg) or clopidogrel 75 mg plus aspirin. In the PAD subgroup, no difference was found after 2 years (median) following the composite endpoint (MI, stroke, or death from cardiovascular causes).

DAPT with aspirin and clopidogrel is not currently recommended for patients with PAD in the absence of a recent endovascular intervention. However, several observations suggest the beneficial effect of DAPT in patients with PAD undergoing endovascular interventions.

Based on the clinical practice and observational trials (in the case of limited RCTs), there are several general recommendations:

- aspirin therapy is sufficient after peripheral balloon angioplasty;
- aspirin monotherapy may be sufficient after atherectomy procedures;
- after femoropopliteal stenting, aspirin is continued for a minimum of 6 months (or lifelong) and clopidogrel is continued for 1–3 months;

- when paclitaxel-eluting femoropopliteal stents are used for 2 months of dual antiplatelet therapy, an indefinite aspirin course is suggested;
- drug-eluting stents are usually placed in the tibial vessels (because of similarities with coronary stenting situations) for one year of DAPT (however, there is no sufficient data on the clinical benefit).

The main conclusion, according to the periprocedural antiplatelet therapy, is that the individual bleeding risk should always be taken into consideration while tailoring the complex antiplatelet medication of a PAD patient after endovascular treatment.

3. POSTPROCEDURAL MANAGEMENT TO REDUCE THE RESTENOSIS RATE

The proliferation of the neointimal tissue at the site of vascular intervention may play a prominent role in the development of restenosis. A specific drug or treatment to avoid or at least decrease the restenosis rate after PTA would be ideal. However, there is no clear recommendation for an antiproliferation agent that can be useful in postprocedural circumstances.

Oral administration of rapamycin after coronary catheter-based intervention may reduce the restenosis rate, but there have not been any observations of its effects in patients after peripheral (including lower extremity) interventions. Moreover, the long-term impairment of the immune system as a logical consequence of the therapy might be a disadvantage to an immunosupressive state.

As an oral phophodiesterase 3 (PDE) inhibitor, cilostazol improves the maximal walking distance and the absolute claudication distance in patients with PA manifested on lower extremities. Its beneficial effects can originate from increasing the cAMP level in vascular smooth muscle cells and thrombocytes, which increases the endothelial function (mainly relaxation) and decreases the platelet activity on aggregation. The clinical impact of cilostazol includes improving limb salvage and preventing leg amputation, and lowering the clinical need for target level revascularization after PTA. This might be explained by the lower occurrence of restenosis. The cilostazol can reduce the in-stent restenosis after peripheral vascular interventions. A small RCT showed a significantly better patency rate of femoropopliteal stents at a 3-year follow-up in patients on cilostazol treatment compared with those receiving a placebo. Statistically favorable results were also found for re-stenosis 2 years after balloon angioplasty or stenting in the femoropopliteal region. In this case, freedom from revascularization was 86% and 63% in the cilostazol and placebo groups (P=0.038), respectively. An observational study after PTA of less complex lesions also achieved a 80% patency rate after a 4-year outcome. The effect of cilostazol can be observed 5 years after the femoropopliteal stenting. In this case, only a 31% re-stenosis rate was found.

In the case of a lack of heart failure (or reduced left ventricular function), 100 mg of cilastazol is recommended to improve symptoms and increase walking distance in patients with claudication (IA).

Combining cilastazol with other antiplatelet agents increases the rate of bleeding complications. However, in patients with low bleeding risk and high risk for restenosis, the co-administration of cilostazol and aspirin can be individually considered at a later phase after PTA. At this time, the routine administration of cilostazol is not supported by clear evidence.

4. PROSTANOIDS

Prostaglandin and prostacyclin are considered pharmacologic agents with multiple features improving circulation in patients with PAD via vasodilation and reduced platelet aggregation. There are no recommendations on the use of prostanoids for claudication or attempts to decrease the risk of amputation in CLI patients, but it can be administered (IIb) to alleviate ischemic rest pain or to facilitate ulcer healing in CLI.

5. ACE INHIBITORS

As hypertension is a well-known risk factor of PAD (and other manifestations of atherosclerosis as well), its treatment is one of the most important issues. ACE inhibitors act as a basic element of hypertension treatment, while they also decrease MACE and overall mortality in CLI patients. On the other hand, no effects on the major adverse limb event rate or need of amputation were observed. There is beneficial data addressing the use of ramipril for increasing pain-free walking time in PAD patients. Hypotension as a side effect of the ACE inhibitor has been observed after endovascular intervention, but without an increased occurrence of stroke, myocardial infarction, death, or kidney failure. Current evidence does not support or preclude ACE inhibitor use specifically for PAD patients, but the dedicated treatment of a risk factor is fundamental, including IIa treatment by AHA/ACC.

NON¸PHARMACOLOGICAL TREATMENT OPTIONS

Patient management should include smoking cessation, physical exercise, and diet with or without endovascular intervention in PAD patients. Physical exercise is a simple but useful method to improve endothelial function, muscle metabolism, exercise tolerance, and quality of life in PAD patients. Lipid and glycemic control in the diet should be considered as partial treatment of hyperlipidemia and diabetes mellitus. The current guideline supports a supervised physical exercise (walking) program as a Class IA recommendation for patients with PAD.[1-8]

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