A Brief Overview of Medical Management Options in Peripheral Arterial Disease

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Abstract

Peripheral arterial disease (PAD) has significant mortality and morbidity along with poor quality of life yet not very well understood by the medical community, and it remains under diagnosed and less optimally treated medically. Optimized Medical treatment along with risk factor modification is the fundamental principle of PAD treatment. In this article, we reviewed the evidence-based medical management of PAD.

Keywords: Peripheral Arterial Disease; Transient Ischemic Attack; Dual Antiplatelet Therapy.

Introduction

Peripheral artery disease (PAD) is defined as the presence of stenosis or occlusion in aorta or arteries of limbs. The global burden of PAD is enormous, with more than 200 million people. This disease has significant disability and mortality. The incidence of morbidity and mortality has been increased tremendously in last recent years. Besides cardiovascular diseases such as coronary disease or stroke, smoking is the most important risk factor for PAD. Other risk factors include hypertension, hyperlipidemia, and advanced age. PAD is a marker of advanced arteriosclerosis overall, as shown by studies. In one big study REACH registry, approximately 25% of patients with PAD had a MI, 30% had angina, and 15% had a history of TIA. Peripheral artery disease is also especially important to diagnose because studies have shown that abnormal ankle-brachial index (ABI) is linked to increased mortality risk [1-3].

Medical therapy for PAD can be divided into two big categories. One category involves cardiovascular risk reduction, and the other involves improvement in leg symptoms. A brief review of all therapies is mentioned below.

Role of Antihyperlipidemic

The American College of Cardiology (ACC) recommends consider PAD equal to myocardial infarction or stroke regarding target LDL control; therefore, statins are the cornerstone of PAD medical management and have Class I indication to use in guidelines [5, 6]. The benefits of starting statin in PAD manifested very early on in the Heart Protection Study that showed the use of statin in PAD lead to a 24% relative risk reduction in events rate as compared to the control group [4]. REACH registry later also proved that the use of statin could decrease the incidence of critical limb ischemia, new limb revascularization, and amputation [2].

Regarding antihyperlipidemic therapy, the first-line drug is a high-intensity statin. Even after using a high-intensity statin, if serum LDL levels are not less than 70 mg/dL, there is a role of adding ezetimibe according to the IMPROVE-IT trial [7]. PCSK 9 inhibitors are also especially useful in PAD if LDL > 70 mg/dl after using high-intensity statin and ezetimibe, as demonstrated in the FOURIER study. In the FOURIER study, patients who had PAD and were treated with evolocumab showed a 3.5% absolute risk reduction in the primary endpoint of CV death, MI, or stroke. FOURIER study also showed a decrease in acute limb events (major amputation, acute limb ischemia or urgent revascularization) in patients who were on evolocumab as compared to placebo [8].

Role of antiplatelet

Antiplatelets also have a key role in the management of peripheral rial disease. Regarding aspirin, some studies initially did not show much benefit, but later studies showed benefits in terms of vascular death, stroke, and MI [9, 10].

In patients with atherosclerotic cerebrovascular disease (ASCVD), Clopidogrel was compared against aspirin in CAPRIE trial. This trial favored clopidogrel over aspirin in patients with peripheral artery disease; currently, guidelines had no preference of using clopidogrel in peripheral artery

disease patients over aspirin as a single antiplatelet agent [6]. With the advent of new P2Y12 inhibitors, ticagrelor was studied as compared to clopidogrel in the EUCLID trial. In this trial, ticagrelor was not found to be superior as compared to clopidogrel in terms of reduction of major cardiovascular events [12].

Role of dual antiplatelet therapy

The role dual antiplatelet therapy (DAPT) was studied in a patient population that also has PAD in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial. The primary outcome of the CHARISMA trial measured in terms of death, stroke, bleeding, and MI. This trial did not show any significant difference between DAPT vs. single antiplatelet therapy in the overall included population; currently, there is no convincing evidence of using dual antiplatelet therapy in a patient with PAD, and current guidelines have class IIb indication for using DAPT in PAD [13].

Role of anticoagulation

The role of anticoagulation in PAD was studied because pathological analysis of amputated limbs showed evidence of thrombosis [14]. Initially trial used warfarin. The result of these trials was not very promising, most likely due to poor compliance and a high discontinuation rate, and increased risk of fatal bleeding [15-17]. Later with the introduction of novel anticoagulation agents' further studies were done, and the COMPASS trial is one of the most important studies among them. In COMPASS trial patients were randomized into three categories. One group was treated with aspirin alone, the other group was treated with 5 mg rivaroxaban twice daily, and the third group received aspirin (100 mg) plus 2.5 mg rivaroxaban twice daily, cardiovascular death, stroke, or MI selected as primary outcomes. Rivaroxaban plus aspirin group showed 24% relative risk reduction as compared to aspirin group alone after following for 23 months. The sub-analysis also showed that a combination of rivaroxaban plus aspirin was also beneficial in decreasing major acute adverse limb events (acute limb ischemia or chronic limb ischemia requiring revascularization) [28]. From a bleeding perspective, the trial, as expected, did show there is more risk of non-fatal bleeding in rivaroxaban plus aspirin growth as compared to aspirin alone, no significant difference exists between two groups with regards to fatal bleeding [18]. Another trial, VOYAGER PAD, which was recently published in 2020, showed a beneficial effect of combining aspirin plus low-dose rivaroxaban (2.5 mg twice daily) versus aspirin alone. The primary endpoint in the VOYAGER trial was acute limb ischemia, major amputation, MI, ischemic, or CV death. Rivaroxaban group showed a 15 % relative risk reduction in the primary endpoint [19].

Role of vasodilator

Peripheral artery disease claudication due to decreased blood flow; therefore, drugs that can vasodilate the peripheral arteries are potentially beneficial. Two drugs were initially tried cilostazol and pentoxifylline. Currently, only cilostazol is used for this purpose and carries class IA indication in patients experiencing claudication in guidelines [6]. Its work-up by inhibiting phosphodiesterase inhibitor three and improved quality of life by decreasing claudication. It is especially important that cilostazol should not be given to heart failure patients because it can exacerbate heart failure [20, 21].

Role of supervised exercise therapy

Supervised exercise therapy 3-5 supervised sessions per week with a duration of 30 to 60 minutes showed tremendous improvement in maximal walking distance, and it is supported by literature [22].

Role of blood pressure control and smoking cessation

Blood pressure control is also especially important and patients with peripheral artery disease. The current European guidelines recommend blood pressure control of less than 140/90 mm of Hg, and ACC guidelines recommend treating blood pressure >130/80 mm of Hg. Regarding the choice of medication, ACE inhibitors are more preferred in guidelines with class II recommendations [6,24,25].

Among risk factor reduction, smoking cessation is crucially important because smoking increases the risk of PAD by 2-3 folds. Ideally, two methods, i.e., nicotine gum plus pharmacological approach, should be tried [26, 27].

Conclusion

In conclusion, peripheral artery disease, associated with significant mortality and morbidity along with a poor quality of life. All patients should have good hyperlipidemia control. Studies have shown the benefits of combining aspirin with low-dose rivaroxaban. Smoking cessation and participation in supervised exercise programs have long-term benefits [11,23]

Conflicts of Interest

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