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Endovascular Treatment Strategies of Lower Extremity Peripheral Artery Disease: An Overall Assessment in Terms of Cost and Effectiveness

Rasit Dinc*

Business University of Costa Rica: San Jose, San José, CR

***Corresponding author:** Rasit Dinc, INVAMED RD Global Mutlukent Mah. 1961 Cd. No.27 06810 Cankaya/Ankara/Turkey, Tel: +90(312)2357735-36; E-mail: rasitdinc@hotmail.com

Abstract

Peripheral artery disease (PAD) affects the arteries that supply blood to the peripheral tissues, mainly legs and feet. Due to the high rates of morbidity and morbidity, heavy workload and high cost, this disease is a high burden in the public health system. It also become a growing problem depend on increasing risk factors such as old age (>65-years old), diabetes mellitus, hypertension, hyperlipidemia. Clinically, PAD varies from asymptomatic to life-threatening serious presentations. Intermittent claudication (IC) is the hallmark of symptomatic PAD. The other symptomatic presentations are acute limb ischemia (ALI) and critical limb ischemia (CLI), which both can result in serious mortality or morbidity.

The treatment modalities may be either conservative or revascularization purposes. The current clinical guidelines recommend a comprehensive program of guideline-directed medical therapy (GDMT). The conservative therapies consist of nonpharmacological approaches associated with lifestyle change such as smoking cessation, healthy diet, and regular physical exercise and pharmacological approaches including anticoagulant/antiplatelet.

For the revascularization, while bypass grafting was the main treatment strategy until now, endovascular treatments have increased in popularity in recent years.

The therapy selection should also be customized to individual risk factors because of the inadequate reporting of clinical outcomes and costs of the treatment modalities.

This article aims to inform on future treatment choice decision with a brief evaluation of the cost and effectiveness of minimal invasive endovascular and the other surgical interventions in the light of the current studies.

Keywords: Peripheral artery disease (PAD); Lower extremity; Revascularization; Treatment modalities; Endovascular therapy; Open surgery

Introduction

Vascular disease is any condition that affects blood circulation in the circulatory system, including arteries, veins or lymph vessels. Peripheral arterial disease (PAD), arterial diseases other than the coronary, is a global epidemic and become a growing problem due to increasing risk factors such as old age (>65-years old), diabetes mellitus, hypertension, hyperlipidemia, obesity, renal failure[1,2]. PAD most commonly affect extremities, especially the legs (lower extremity PAD=LE-PAD). The buildup of fatty plaque in the arteries is primarily cause. A narrowing or blocking slow down or block blood flow in the peripheral extremity arteries that carry blood from the heart to the extremities[3].

The prevalence of PAD in the United States at ≥40 years of age is estimated to be ≈7%, corresponding to 8.5 million adults, and 200 million people worldwide[4-6]. This disease is a high burden in the public health system due to an increased risk of major cardiovascular events, high rates of morbidity and an important cause of impaired quality-of-life[7,8]. The economic burden of this disease is often underestimated, while its annual cost exceeds $21 billion in the US alone[9-11].

PADs, can cause problems ranging from asymptomatic to life-threatening serious clinical presentations. Especially the cases of low clinical severity are underappreci-

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ated. A standardized terminology used to describe the patient's condition and type of lesion for PAD. Numerous classification schemes is used to classify the clinical, prognostic of LE-PAD or aiming research[12]. Class 1, 2 and 3 are being mild, moderate, and severe claudication respectively, and 4-6 are critical limb ischemias in clinical practice according to Rutherford classification[13].

Although LE-PAD is mostly asymptomatic. The clinical presentation can be seen as discomfort in the legs induced by exercise and relieved by rest, which prescribed as intermittent claudication (IC). IC is the most common clinical presentation and the hallmark of symptomatic PAD[14]. It is defined as fatigue, discomfort, cramping, or pain of vascular origin in the lower extremities that is consistently induced by exercise and consistently relieved within 10 minutes by rest[15]. The other symptomatic presentations are acute limb ischemia (ALI) and critical limb ischemia (CLI). ALI is the abrupt interruption of arterial blood flow to the extremity. It is characterized by pain, pulselessness, poikilothermia, paleness, paresthesia/paralysis (5P) clinical manifestations. It is a medical emergency and rapid diagnosis, and treatment are required to protect extremity as well as to prevent death due to systemic disease and/or metabolic anomalies due to tissue necrosis[16]. Whereas, CLI is the end stage of peripheral artery disease which is characterized by chronic (over 2 weeks) ischemic pain, nonhealing wound/ulcers and gangrene. CLI is associated with impaired quality of life, high rates of morbidity and mortality. Annual mortality rate is approximately 25%[15]. Up to 21% of patients with intermittent claudication may progress to CLI[17].

Patients with PAD should be treated to reduce cardiovascular ischemic and limb-related events and improve functional status of the limb. In order to decide the therapeutic strategy in PAD; the severity, location, and duration of the stenosis, the patient's complaints, and the risks and consequences of treatment are considered[18].

This review article aims to inform on future treatment choice decision for the patients of PAD. For this purpose, it briefly reviews the cost and effectiveness of minimal invasive endovascular and the other surgical interventions based on the clinical outcomes from published studies.

Treatment in Peripheral Artery Disease (PAD)

The patients with PAD are at increased risk for major adverse cardiac events (MACE), including myocardial infarction (MI), ischemic stroke, and cardiovascular death. They also carry risk for major limb events such as major amputations and acute limb ischemia. Again, even though it is usually benign, IC can progress to CLI[14,19,20]. So they should receive a comprehensive program of guideline-directed medical therapy (GDMT) to reduce the risk for MACE and major adverse limb events and that to improve functional status[1]. Treatment approaches address to relive the specific symptoms in any localization or to manage the patients with PAD against to the increased risk for any cardiovascular event. The therapy selection should also be customized to individual risk factors such as diabetes mellitus, hypertension[10]. American College of Cardiology/American Heart Association (ACC/AHA) guidelines currently recommend the evaluation of revascularization options for the management of PAD by a multidisciplinary approach of the care team[1,21].

Box-1. Clinical presentation and therapy modalities in lower extremity peripheral artery disease (LE-PAD)

Clinical presentation	Therapy modalities	
Asymptomatic	Conservative	Revascularization
Intermittent claudication (IC)	Nonpharmacological	Endovascular
Acute limb ischemia (ALI)	Pharmacological	Open surgery
critical limb ischemia (CLI)		

The current clinical guidelines mainly target wound healing and limb salvage as well as preventing cardiovascular ischemic events[22]. The treatment modalities are mainly used for conservative or revascularization purposes. While there are pharmacological and non-pharmacological methods for conservative treatment, minimally invasive endovascular and other surgical methods such as bypass and amputation are for revascularization[11,15].

Non-pharmacological Therapy

The experts and current guidelines strongly recommend lifestyle modifications for lower extremity PAD as the primary treatment strategies, including smoking cessation, healthy diet, weight loss and regular physical exercise[11,15]. The exercise therapy is known as structured exercise therapy (SET). Briefly, it can be defined as walking up to the point where claudication pain occurs and then resting for a short time until the pain subsides with a program based on behavioral change[23]. The observations with long-term, covering from 18 months to seven years, revealed that SET for patients with IC has a persistent benefit and is favorable in risk-benefit ratio[21]. Education of the patients about a healthy foot and recognition of foot infection is important to minimize tissue loss and against to new problems in their foots[24].

Pharmacological Therapy

Current pharmacological therapy (or secondary prevention medications) mainly includes antiplatelet therapy, anticoagulant therapy, statin therapy, antihypertensive therapy, and medications to improve circulatory flow[15].

Antiplatelet therapy (commonly aspirin or clopidogrel) has a significant role to reduce the risk of MI, stroke, and vascular death in patients with symptomatic PAD. They have been used as single, dual or triple antiplatelet therapies. Restenosis following revascularization therapy is a common and important problem. It is mainly due to excessive neointima formation. Therefore, the intraoperative and postoperative antiaggregant and antithrombotic agents are routinely used to prevent the restenosis-related events[25].

Lipid-lowering drugs (statin therapy) are indicated for all patients with PAD. Statin therapy reduces not only the risk of long-term adverse limb outcomes but also improve cardiovascular outcomes in patients with PAD[11,26].

Anticoagulation has been observed to reduce MACE and adverb limb events by improving patency[1,27]. AHA/ACC guidelines recommend the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers in patients with hypertension and PAD to reduce the risk of MACE. Pharmacotherapies should also be added for the additional risk factors such as diabetes mellitus, hyperlipidemia if they have[1].

The randomized controlled studies showed that sec-

ondary prevention medications show reduced morbidity and mortality rates in PAD[1,28,29].

Revascularization Therapies

Bypass (autologous or synthetic), endarterectomy and amputation are major invasive treatment strategies for PAD patients[30]. Bypass grafting has been the major treatment strategy until now in the treatment of symptomatic PAD[14]. However, bypass surgery requires prolonged recovery time, and it is frequently seen complications such as graft infection, thrombosis of the graft, distal embolization, and edema in the lower extremity[31].

The endovascular procedure, which has been developed more recently, is minimal invasive default strategy when comparing to the other surgical methods. Today, various devices used in endovascular treatment are available and new devices, and new generations of older devices continue to be added with the developing technology. Of these devices, stents, drug-eluting stents (DES), cutting balloons, and drug-coated balloons, fusible stents, and atherectomy devices are widely used. While atherectomy devices are generally used for high occlusions in the vasculatures caused by stenosis and hard calcific plaques, balloons or stents are used in cases with low levels of stenosis or soft lesions. Due to the anatomical variations of the arteries and status of the plaques and calcifications in the vasculatures, balloons and stents may sometimes be insufficient when used alone[32]. For this reason, the endovascular techniques are individualized based on lesion characteristics and the discretion of the surgeon[1,2,33]. Sometimes we should be aware of newly launched alternative opportunities. For example, calcified stenoses are more difficult to treat and decrease the effectiveness of drug-coated balloons and stents. A novel technology lithoplasty (shockwave application into vessel) seems like a good solution for calcified stenoses before angioplasty balloon inflation[34].

Revascularization for IC patients

Guidelines from the AHA/ACC1 and the Society for Vascular Surgery[19] recommend the best medical treatment as the first-line treatment for claudication. Only some of the patients with IC progress to CLI and a relatively low likelihood of limb loss associated with mild PAD[35,36]. Revascularization should be reserved for only refractory cases who don't derive adequate benefit from nonsurgical therapy with GDMT. Revascularization for this group patients aims to improve functional status and quality of life, rather than limb salvage. For this kind of patient with LE-PAD, revascularization therapy should not be limited for the ones who progressed to CLI.

Open surgical interventions are superior to those ones less invasive endovascular for the quality of life and patency. On the other hand, they have greater risk of perioperative adverse events. Therefore, the choice of revascularization methods should therefore be individualized based on the patient's goals, perioperative risk, and anticipated benefit[36].

Revascularization for CLI patients

Patients with CLI carry high risk for amputation and MACE. The aim in surgical or endovascular revascularization is to provide the blood flow to the foot, which will help preserving a functional limb. Medical therapy is also an important component for the patient with CLI in prevention of cardiovascular ischemic events[1,37].

Endovascular revascularization is an effective option for CLI patients as compared with the other surgical methods. The nature of the lesion plays an important role in which endovascular method to choose. Surgical procedures are reasonable for nonhealing wound/ulcers to establish a blood flow to the foot[38,39].

Revascularization for ALI patients

ALI is one of clinically devastating but the most treatable medical emergent forms of PAD. The urgency of treatment depends on the severity of ischemia in the limb. To provide rapid restoration of the arterial flow, revascularization should be carried out within 6 hours for immediately threatened limbs, while within 6 to 24 hours for viable limbs[40].

Catheter-guided thrombolysis can provide rapid restoration of arterial flow to a viable or immediately threatened limb. Otherwise, some situations such as inadequate conditions at the facilities, prolonged duration of ischemia and failure in the endovascular therapy can require amputation for treatment of ALI[41]. However, hybrid therapy, a combination of open and endovascular technique, may be best choice for multilevel occlusion situation.

There are several debates and studies according to the clinical outcomes of these procedures and their cost effectiveness were compared with each other in several studies[5,42-50].

Overview of Treatment Methods for Aspect of Cost Effectiveness

The criterion for effectiveness in treatment of patients with PAD is considered as successful revascularization to provide pain relief, wound healing, and functional limb salvage. Because an unwanted but common problem is restenosis occurred following an effective treatment procedure. Restenosis is defined as luminal diameter of the vessel narrowed by over 50%. The complex pathophysiologic mechanisms play role in the stenosis. Briefly, angioplasty, stent placement, or atherectomy cause mechanical injuries to the vessel result in stenosis. For these reasons, predicting functional outcomes to happen after revascularization procedures is difficult. Hence, revascularization may sometimes cause morbidity, which is associated with repeating hospital admissions, continuous outpatient care, and significant treatment and health care costs, and to death as well[51]. Based on all these data, The Global Vascular Guidelines (GVG) recommend a structured approach based on a three-step process for the best therapeutic selection to achieve the clinical goals: patient risk estimation, severity of limb disease, and anatomical pattern of PAD[19].

Box-2: The goals of the clinical treatment for patients with PAD[52]
Improve functional status
Preserve the limb
Prevent progression of atherosclerosis
Reduce cardiac and cerebrovascular mortality

It is important to document the possible clinical outcomes related with the current treatment methods for PAD. For the selection of the best treatment modality, it is crucial to

know this kind of clinical outcomes such as in-hospital mortality, recurrent ischemia, other vascular complications (bleeding, transfusion necessity etc.), requirement amputation, and restenosis related with applied treatment method[53]. Besides, the combination therapeutic strategies, which also called hybrid therapies, significantly contribute to improve clinical signs of PAD patients. There are some studies showing the combination therapies provide more quickly and greater improvement than the alone one[42,54,55]. For example, a combination stent plus atherectomy procedure not only improves patency of the vessel but also facilitates the replacement of stents and drug absorption by removing plaque[55].

Although it is not emphasized much, not only the clinical success but also the cost of the treatment method is important in the selection of the treatment method for the patients with PAD. Because the cost of routine treatment is quite high, and many facilities cannot have these opportunities. Furthermore, the above-mentioned adverse clinical results associated with the applied treatment method significantly affect the cost of treatment. Length of stay at the hospitals and discharge to a skilled nursing facility (SNF) also contributes significantly to the total costs of the procedures[56].

Besides, the issues affecting the cost are not limited to these, there are also other factors that should be considered: The all expenses incurred for the operating theater expenses (including all equipment used in the surgery, and personnel such as doctor, nurse, technicians etc. involved in the surgery), intensive care unit and subsequent inpatient ward services, medications, consultation activities, all laboratory and imaging services for diagnosis and follow-up have an important place in the treatment costs[2].

The success of treatment depends on the type of revascularization treatment, the features of lesion (degree, location, and length), the comorbid diseases of the patient, the physicians' experience, and the availability of equipment in the hospital[57,58]. Unfortunately, comprehensive data evaluating the risk-benefit and cost of therapeutic approaches in terms of advantages and disadvantages against each other is not available.

Endovascular vs Open Surgery

For severe PAD, revascularization therapy should be ensured either by endovascular technology or the other surgical repair[59]. In the treatment of symptomatic PAD, the main treatment strategy so far has been bypass grafting[3,11]. However, bypass surgery leads to a longer recovery time and higher complication rates[18]. On the other hand, endovascular treatment modalities have increased in popularity in recent years. Nonetheless, the optimal revascularization strategy for patients with PAD has not been well-documented to the extent of deciding a definitive treatment choice yet[59]. Both treatment methods have different advantages and disadvantages compared to each other.

In a large observational study which compared percutaneous intervention with surgical therapy in CLI patients, Agarwal et al reported that the percutaneous intervention was associated with reduced in-hospital mortality (2.34% versus 2.73%, P<0.001), length of stay (8.7 days versus 10.7 days, P<0.001) and decrease in leg amputation ratio despite similar rates of major amputation (6.5% versus 5.7%, P=0.75)[60].

Erdinc I (yet unpublished study) stated that length of stay in hospital are 2.3- and 5.7-days for endovascular and bypass treatments, respectively. In a study, Wiseman et al[59] showed that endovascular treatment is associated with improved amputation free survival compared to an open surgery. In addition, the endovascular therapies are less invasive. Taken together, endovascular therapeutic options have gained priority over surgical treatment options in recent years. Minor or major amputation operations are recommended when less invasive endovascular options failed[1,22]. In the United States, the rates of open bypass surgery and endovascular options for the treatment of patients with LE-PAD are approximately 40% and 60%, respectively[61].

A study by Wiseman et al[59], Kolte et al[62] and Davis et al[55] reported that endovascular treatment is associated with improved amputation free survival compared to an open surgery. On the contrary, there was no difference in amputation free survival overall in BASIL study, which is the most prominent randomized controlled trial[63]. In the CRITISCH Registry data, there was also no difference in 1 -year mortality and major amputation between endovascular and surgical revascularization of CLI patients[64].

Agarwal et al also reported a decline in cost of hospitalization ($31 679 versus $32 485, P<0.001)[60].

Tang et al study demonstrated that total length of stay in the hospital was significantly less in endovascular group than open surgical group. The initial cost of endovascular therapy was more expensive due to usage of the devices. However, the reduction in bed days, ICU utilization, and related hospital resources resulted in a significantly lower mean total cost per admission[2].

Another problem is that the underappreciated clinical and inadequate diagnostic evaluation can result in unnecessary amputation and morbidity[37].

Briefly, endovascular therapy has been increasingly attractive and widespread because of the lower morbidity and mortality[9]. Although long-term data are lacking, they look cost-effective[65]. A general negative aspect for endovascular therapy is that it may be less durable, requiring additional interventions to maintain limb salvage[9,63,66]. The choice of interventions should be individualized for each patient based upon multiple factors instead of generalizing it[59].

Standard Endovascular Devices vs Drug-Eluting/Coated Devices

The efficacy of endovascular versus open surgery revascularization remains unknown. Although endovascular methods have become widespread in PAD, the problem of restenosis has been a constant obstacle[67].

It is not available a comprehensive comparative proof for the best modality among the current endovascular therapeutic options in PAD patients. Nevertheless, drug-eluting stents or drug-coated balloons show promising results for decreasing restenosis rates. Limited studies show that the paclitaxel-eluting or paclitaxel-coated devices are superior to the standard devices in higher primary patency rate, better target lesion revascularization rate, and cost effectiveness[9,10,66,67]. Dake Ansel et al. have observed that the patency rates in paclitaxel coated stents and standard PTA were 83.1% and 32.8%, respectively. However, some reports imply that there are no significant differences of the risk of major amputation between two groups[68]. Again, some

studies have reported an increase of mortality in patients receiving paclitaxel drug-coated balloon/drug-eluting stent compared with controls[69].

When we look at costs of the specific endovascular interventions such as drug-coated balloons (DCB), drug-eluting stents (DES), bare metal stents (BMS) and balloon angioplasty (POBA), in a study, mean total 2-year cost of the drug-coated balloon/drug-eluting stent was found 700$ per patient lower when compared to standard PTA. In another study that DES was gradually and uniformly introduced into the population at a rate of 8%/year up to 48%/year, overall cost saving was 1688953,72$[10].

Unlike the angioplasty and stenting which push the plaque to the vessel wall, atherectomy which uses directional and rotational movements in combination with physical or ablative technics, takes out the plaque burden out of the vessel. Atherectomy can be used alone or in combination with stenting or angioplasty[70,71].

The effectiveness and cost of the devices has yet to be systematically understudied. For the above-mentioned reasons, use of these devices should be individualized carefully balancing the risks and benefits[69].

Box-3. Highlights in endovascular devices with vs without drug.
Endovascular interventions were found to be cost effective and superior in terms of clinical outcomes and cost effectiveness when compared to other treatment modalities in the treatment of peripheral artery disease.
Drug eluting stents (DES) are superior to other intervention methods in terms of primary patency which also means decrease in revascularization rate.
Drug eluting stents (DES) are cost effective compared to bare metal stents (BMS).
Drug coated balloons (DCB) are cost-effective compared to standard percutaneous transluminal angioplasty (PTA).
Limitation of this study

This review is not a systematic review study and is vulnerable to selection bias. For the best treatment modality for PAD patients, there is no comprehensive comparative proof study in term of their cost effectivity. The selection of the therapy strategy should be considered clinical characteristics of the patients and experience of the operating person.

Conclusion

Peripheric artery disease is an epidemic in global perspective. PAD. The prevalence of PAD is increasing in high-income countries. Additionally, PAD treatment is a significant burden to the payer.

Treatment approaches should relieve the specific symptoms in any localization or to manage the patients with PAD against the increased risk for any cardiovascular event. The therapy selection should also be customized to individual risk factors such as diabetes mellitus, hypertension. The physicians should consider revascularization for patients with lifestyle-limiting claudication and inadequate response to SET and medical treatment.

Because of the advantages of endovascular therapies on clinical outcomes and cost effectiveness compared with open surgery and amputation, upward trend of endovascular approach has been seen in recent years. When comparing different endovascular approaches, DES is superior to BMS in aspect of the cost-effectivity. DCB is also cost-effective compared to standard PTA. These results favor DES and DCB use in PAD management because of their cost-effectiveness and superiority in primary patency and clinical outcomes.

Patients with PAD need to a comprehensive therapy approach determined by a multidisciplinary team. Further clinical studies are required to assess patients' best therapy strategy.

List of Abbreviations: PAD: Peripheral artery disease,IC: Intermittent claudication (IC), ALI: Acute limb ischemia, CLI: Critical limb ischemia, GDMT: Guideline-directed medical therapy, LE-PAD: Lower extremity peripheral artery disease, MACE: Major adverse cardiac events, MI: Myocardial infarction, ACC/AHA: American College of Cardiology/American Heart Association, GVG: The Global Vascular Guidelines, SNF: Skilled nursing facility, CRITISCH Registry: Registry of First-Line Treatments in Patients with Critical Limb Ischemia), ICU: Intensive care unit, DCB: Drug-coated balloons, DES: Drug-eluting stents, BMS: Bare metal stents, POBA: Percutaneous old balloon angioplasty, PTA: Percutaneous transluminal angioplasty

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