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Review Article

A NARRATIVE REVIEW OF ASSESSMENT AND MANAGEMENT OF PERIPHERAL ARTERIAL DISEASE: ESSENTIAL KNOWLEDGE FOR CARDIOLOGISTS, BIHAR, INDIA.

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Abstract

The term "peripheral artery disease" (PAD) refers to a group of atherosclerotic arterial illnesses that impact arteries other than the coronary ones and cause significant morbidity and mortality in the cardiovascular system. Cardiologists are essential to the diagnosis and treatment of PAD because of their knowledge in cardiovascular disease management. The aim of this review article is to present a thorough overview of PAD assessment and management from the viewpoint of a cardiologist. It covers imaging, general treatment modalities, diagnosis, epidemiology, and particular concerns for the many anatomical locations affected by PAD. The review highlights how critical it is to identify common risk factors for PAD patients, including diabetes, dyslipidemia, smoking, hypertension, and autoimmune diseases. Ankle brachial index (ABI), imaging modalities, and assessments of upper extremity, mesenteric, carotid, renal, and lower extremity peripheral artery disease are all important in making the diagnosis. Depending on the demands of each patient, treatment options include lipid-lowering medications, antiplatelet, antithrombotic, and antihypertensive therapies. Novel treatments like icosapent ethyl and low-dose rivaroxaban have the potential to lower cardiovascular events in PAD patients. Trials are still underway to determine the best course of action for managing PADs. The study emphasizes the debate surrounding paclitaxel-coated devices in femoropopliteal treatments and the necessity of a multidisciplinary strategy in managing Critical Limb-Threatening Ischemia (CLTI). Due to their extensive experience in treating cardiovascular disorders, cardiologists are ideally suited to spearhead developments in PAD research and treatment. As a result, cardiologists are better prepared to diagnose and treat patients with PAD. This study highlights the value of individualized care and further research to improve the quality of care for PAD patients.

Keywords: *Peripheral Artery Disease, Ankle Brachial Index, Cardiovascular Risk Management, Critical Limb-Threatening Ischemia, Novel PAD Treatments*
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Introduction

Peripheral Artery Disease (PAD) refers to atherosclerotic narrowing or blockage in non-coronary arteries throughout the body, affecting arteries in various areas like the limbs, carotid, vertebral, coeliac, mesenteric, and renal arteries. It is a manifestation of systemic atherosclerosis, leading to increased cardiovascular morbidity and mortality, along with a decreased quality of life. Cardiologists, given their expertise in managing heart disease, play a crucial role in screening, diagnosing, and treating PAD. While clinical evidence for PAD is not as extensive as that for coronary artery disease (CAD), the treatment goals remain similar: preventing ischemic events through lifestyle changes and medical therapy, and considering revascularization when appropriate. This article offers a comprehensive overview of PAD assessment and treatment from a cardiologist's perspective.

The key questions identified for this review center around understanding the most effective strategies for diagnosing and treating PAD from a cardiologist's perspective. Firstly, how do current imaging techniques and diagnostic tools like the Ankle Brachial Index (ABI) improve the early detection and assessment of PAD in various anatomical locations? Secondly, what are the general and specific treatment modalities, including lifestyle changes, pharmacotherapy, and revascularization techniques, that yield the best outcomes for patients with PAD, considering the varied presentations and severities of the disease? Thirdly, how do risk factors such as diabetes, dyslipidemia, and smoking influence the management and prognosis of PAD, and what strategies can cardiologists employ to mitigate these risks? Additionally, the review seeks to explore the potential and challenges of novel treatments like icosapent ethyl and low-dose rivaroxaban in reducing cardiovascular events in PAD patients. Finally, it questions the role of a multidisciplinary approach, particularly in managing complex cases like Critical Limb-Threatening Ischemia (CLTI), and how cardiologists can spearhead advancements in PAD research and treatment to provide individualized, effective care.

Methodology

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An extensive literature search was conducted across various medical databases, including PubMed, MEDLINE, EMBASE, and the Cochrane Library. The search was aimed at identifying articles, studies, and trials published in English from inception to the present date. Keywords used in the search included "Peripheral Arterial Disease," "PAD management," "cardiovascular risk," "cardiologist's perspective," "ankle-brachial index," "imaging in PAD," "antiplatelet therapy," "lipid-lowering therapy," and "novel treatments for PAD."

The selection criteria were focused on high-quality studies, review articles, clinical guidelines, and randomized controlled trials that provide significant evidence and insights into the assessment and management of PAD. Priority was given to articles that specifically discussed the role of cardiologists in managing PAD, novel diagnostic approaches, and advanced treatment modalities. Exclusion criteria included non-English articles, studies with incomplete data, and outdated or superseded studies.

Epidemiology Of Pad

The epidemiological characteristics pertaining to diverse patterns of peripheral artery disease (PAD), including upper extremity artery disease, carotid artery disease, mesenteric artery disease, lower extremity artery disease, and renal artery disease, exhibit variations across different populations. All individuals exhibit shared risk factors, namely hypertension, smoking, dyslipidemia, diabetes, and autoimmune/inflammatory conditions. The identification and assessment of these risk factors holds paramount importance in the comprehensive management of PAD patients. Isolated PAD is recognized as an autonomous cardiovascular risk factor, while individuals with concurrent vascular disease in multiple anatomical regions are associated with the most elevated risk of cardiovascular complications. However, upon the diagnosis of PAD in a specific region, the screening for asymptomatic atherosclerosis in other anatomical sites does not alter the course of treatment. In patients presenting with notable CAD, the implementation of proactive ultrasound screening for PAD has not demonstrated definitive advantages when compared to conventional medical therapy [1]. In individuals deemed suitable for coronary artery bypass grafting (CABG), who frequently undergo carotid ultrasound examinations, there exists a dearth of substantial evidence to substantiate the implementation of preventive carotid revascularization in the absence of neurological symptoms.

Diagnosis And Assessment Of Pad

In conjunction with routine cardiac evaluations, it is imperative to inquire about potential neurological manifestations, such as arm discomfort during physical exertion, dizziness, or vertigo. These symptoms may serve as indicators of underlying carotid, vertebral, or upper extremity PAD. The presence of abdominal pain following the consumption of food should elicit a heightened sense of suspicion regarding the potential involvement of mesenteric disease. The imperative nature of conducting screenings for claudication and slow-healing extremity wounds cannot be overstated, as it plays a pivotal role in the timely identification and subsequent mitigation of tissue loss and the need for amputation. The assessment of pulses and auscultation for bruits in all vascular territories is of paramount importance. The measurement of blood pressure in bilateral upper extremities holds significant clinical importance, as it allows for the assessment of potential variations between the arms. Notably, a discernible discrepancy of 15 mm Hg in systolic blood pressure readings between the two arms may serve as an indicative marker for the presence of subclavian artery disease.

Ankle Brachial Index

The ankle brachial index (ABI) is a commonly utilized diagnostic tool in the medical field for the identification of PAD that affects the lower extremities. The procedure involves the division of the maximum ankle systolic blood pressure, acquired using a cuff and Doppler, by the maximum arm systolic blood pressure. A value of ABI less than 0.9 is suggestive of obstructive disease, while a value exceeding 1.4 indicates arterial stiffening due to calcification. In patients who exhibit claudication symptoms, the application of exercise treadmill ABI or pedal plantarflexion ABI has demonstrated an increase in sensitivity.

In individuals of advanced age, those with diabetes, or those suffering from chronic kidney disease, it is possible for the ABI to exhibit an elevation as a result of calcification. The measurement of the toe brachial index (TBI) can be utilized for the purpose of confirmation, whereby a value of less than 0.7 is generally regarded as indicative of an abnormal condition. Toe brachial index (TBI) holds particular significance in individuals presenting with limb-threatening ischemia. Additional perfusion measurements, such as transcutaneous oxygen pressure and skin perfusion pressure, play a crucial role in informing revascularization decisions in these particular cases.

Imaging

DUS is effective for PAD screening, especially in carotid and lower extremities, but its accuracy varies with operator expertise and patient factors. CTA is commonly used for comprehensive vascular visualization but has drawbacks like cost, limited functional data, radiation exposure, and contrast agent use. It excels in diagnosing diseases like vertebral, subclavian, mesenteric, aorto-iliac, and renal

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artery disease. MRA's usefulness in PAD is limited due to motion artifacts, poor small vessel imaging, and difficulty visualizing stents. Iodinated contrast is avoided in moderate CKD and poses higher risks in advanced CKD and ESRD patients due to nephrogenic systemic fibrosis concerns. Invasive angiography with digital subtraction angiography is the gold standard for diagnosis, mainly for cases requiring endovascular revascularization. Carbon dioxide serves as a safer contrast agent alternative for advanced kidney disease patients during endovascular procedures [2].

General Treatment Modalities

The utilization of tobacco is recognized as a potent risk factor in the pathogenesis, advancement, and reappearance of PAD subsequent to revascularization procedures. The therapeutic advantages of smoking cessation are comparable to those of numerous pharmacological interventions. Patients diagnosed with PAD should be provided with tailored guidance regarding lifestyle modifications, akin to individuals suffering from CAD [3]. These recommendations encompass structured exercise regimens, dietary interventions, and weight management strategies.

Antiplatelet And Antithrombotic Therapy

Aspirin is a common treatment for symptomatic PAD, with ESC guidelines favoring clopidogrel based on CAPRIE trial findings. DAPT is used post-revascularization, but no specific agent or duration is established. Warfarin's efficacy varies compared to aspirin or DAPT post-bypass graft. Ticagrelor, often used in acute coronary syndrome, doesn't offer significant benefits over clopidogrel in peripheral artery disease.

Vorapaxar, a pharmacological agent classified as a thrombin receptor antagonist, exhibits a relatively modest recommendation of ACC class IIb in the medical community. However, its utilization is restricted due to the heightened propensity for bleeding complications, without concomitant substantial reduction in cardiovascular events. Cilostazol is a pharmacological agent that is commonly prescribed for the management of claudication, a condition characterized by pain and cramping in the lower extremities during physical activity. However, it is important to note that despite its widespread use, cilostazol has demonstrated restricted effectiveness and is associated with a notable incidence of discontinuation due to adverse reactions. The utilization of pentoxifylline is currently not recommended.

Future guidelines may consider low-dose rivaroxaban, an oral factor Xa inhibitor. COMPASS and VOYAGER-PAD trials show reduced ischaemic events with aspirin plus low-dose rivaroxaban, albeit with a slightly higher non-fatal bleeding risk [4].

Antihypertensive Therapy

There exists a plethora of compelling evidence substantiating the efficacy of treating hypertension in order to mitigate the occurrence of cardiovascular events. Moreover, contemporary guidelines have advocated for a more stringent approach towards blood pressure management. Nevertheless, persistent concerns have arisen regarding the potential impact of aggressive antihypertensive therapy on limb perfusion in individuals with obstructive PAD, despite the absence of substantial evidence supporting this notion in any extensive study. The management of blood pressure ought to adhere to established clinical guidelines, with the selection of particular therapeutic agents being determined by the patient's concurrent medical conditions. It is noteworthy that the administration of ACE inhibitor (ACEI) has demonstrated a reduction in overall mortality among individuals with PAD, regardless of whether they exhibit symptoms or not. This finding was observed in the HOPE (Heart Outcomes Prevention Evaluation) trial.

Lipid-Lowering Therapy

Statins have been shown to effectively mitigate the risk of stroke and heart attack in patients with ischemic heart disease through their cholesterol-lowering properties and various pleiotropic effects. Simvastatin exhibits a notable reduction in major cardiovascular events among individuals diagnosed with PAD. The administration of PCSK-9 antibodies, such as evolocumab, has been shown to confer notable advantages to individuals diagnosed with CAD as well as isolated PAD. These benefits manifest in the form of a reduction in MACE and significant occurrences of major limb events [5]. Alirocumab demonstrates the most substantial risk reduction in individuals afflicted with polyvascular disease. The potential therapeutic effects of icosapent ethyl in the context of PAD are currently being assessed.

Carotid Artery Disease

Approximately 10% to 20% of thromboembolic strokes arise from notable extracranial carotid artery disease, typically characterized by a stenosis exceeding 50%. Revascularization is contraindicated for carotid arteries that are near-occluded or occluded. Early revascularization is imperative in cases of symptomatic carotid artery stenosis, particularly when performed within a 14-day timeframe following the event. Carotid endarterectomy (CEA) has demonstrated superiority over medical therapy as a standalone intervention [6]. The management of asymptomatic carotid disease remains a subject of ongoing debate and controversy within the medical community. Revascularization is indicated in asymptomatic patients presenting with stenosis ranging from 60% to 99% along with concomitant risk factors. The ongoing clinical trials

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will facilitate the determination of the optimal therapeutic approach. The comparative analysis between CEA and carotid artery stenting (CAS) reveals that CAS is associated with an elevated risk of stroke and mortality, while concurrently presenting a reduced risk of perioperative MI. Cardiac ablation procedures, commonly referred to as CAS, are recommended to be conducted exclusively in specialized medical facilities under the supervision of experienced healthcare professionals [7]. The risk associated with prophylactic CAS procedures in asymptomatic patients is reported to be less than 3%, while for symptomatic patients, the risk is documented to be less than 6%. Transcarotid artery revascularization (TCAR) is an emerging hybrid modality, albeit necessitating additional validation of its advantages. Revascularization of vertebral artery disease should be judiciously considered, as the efficacy of stenting remains limited and is accompanied by heightened risks.

Upper Extremity Pad

Atherosclerotic PAD affecting the upper extremities predominantly manifests in the left subclavian artery, with subsequent occurrences observed in the right subclavian artery and innominate artery. The presence of a SBP difference exceeding 15mm Hg between the upper extremities is indicative of suspicion for the condition under consideration. In more severe instances, symptoms are known to manifest. The clinical presentation may encompass upper extremity claudication, vertebral basilar steal syndrome, coronary steal phenomenon in individuals with internal mammary artery coronary bypass grafts, or dysfunction of dialysis access. Revascularization is recommended in cases of symptomatic disease or in instances where CABG is planned with the utilization of the internal mammary artery. The utilization of endovascular intervention employing a stent that can be expanded via a balloon is frequently favored as the initial course of action owing to its notable efficacy and enduring rates of vessel patency [8].

Mesenteric Artery Disease

Mesenteric ischemia, whether acute or chronic, is rare but life-threatening, requiring urgent intervention. Chronic mesenteric artery disease presents with postprandial abdominal pain, weight loss, and GI disturbances, usually when two of the three main arteries are significantly compromised. Revascularization is essential for symptomatic patients, with a preference for endovascular stenting in older, comorbid individuals [9]. Surgery offers better symptom relief and patency but entails longer recovery and hospital stays.

Acute mesenteric ischemia often results from superior mesenteric artery embolisms, demanding swift diagnosis and treatment to reduce mortality risk. Patients experience severe and disproportionate abdominal pain. D-dimer is sensitive but not specific. The choice of treatment depends on local expertise, with open surgery favored for its comprehensive bowel examination and potential for hybrid revascularization during laparotomy.

Renal Artery Disease

Atherosclerotic renal artery stenosis (RAS) represents the predominant etiology underlying the development of renovascular hypertension in the adult population. Fibromuscular dysplasia (FMD) stands as the predominant etiology in the younger female population. RAS precipitates renal hypoperfusion, thereby triggering the renin-angiotensin-aldosterone system (RAAS) and subsequently inducing systemic hypertension. The management of atherosclerotic RAS necessitates the implementation of strategies aimed at controlling blood pressure, administering statins, and employing antiplatelet therapy. Individuals diagnosed with bilateral RAS may be prescribed ACEIs or angiotensin receptor blockers (ARBs) as part of their treatment regimen, while ensuring diligent monitoring of renal function.

Three pivotal randomized controlled trials (RCTs), namely STAR, the ASTRAL, and CORAL, have yielded inconclusive evidence regarding the superiority of revascularization compared to medical therapy [10]. However, these trials have been subject to scrutiny due to certain limitations in their study designs and the inclusion of patients with moderate disease severity. Renal revascularization ought to be contemplated for carefully chosen instances, including FMD, recurrent cardiac insufficiency, unresponsive hypertension, or advancing renal failure accompanied by renal ischemia. The utilization of endovascular intervention is favored as a result of its demonstrated reduction in both morbidity and mortality rates. The confirmation of lesion significance can be achieved through the assessment of translesional systolic pressure gradient or renal fractional flow reserve. Additionally, the prediction of kidney viability and response to revascularization can be determined by evaluating the renal resistive index obtained through ultrasound imaging.

Lower Extremity Pad—Claudication

Claudication symptoms generally remain stable, with a minority progressing to CLTI. Supervised exercise therapy, along with medical treatment, is essential but often limited in availability. Revascularization is considered if claudication significantly affects one's life despite exercise therapy [11]. The choice between surgical and endovascular revascularization depends on anatomy and local expertise.

For aorto-iliac disease, endovascular treatment is preferred due to high stent patency rates. Common femoral artery disease is often managed with surgical endarterectomy,

known for its effectiveness and safety. The decision for femoropopliteal disease hinges on occlusion complexity, vein conduit presence, and surgical risk. Autologous vein grafts offer superior long-term patency in surgical bypass. If opting for endovascular treatment, preserving landing zones for potential future bypass grafts is crucial.

Lower Extremity Pad—Chronic Limbthreatening Ischaemia

CLTI, an advanced PAD form, presents as rest pain, ulcers, or gangrene, leading to significant morbidity and mortality. Fontaine and Rutherford classifications are limited in assessing amputation risk. The WIFI system offers a comprehensive assessment and aids decision-making. The debate on "endovascular first" or "surgical bypass first" approaches continues, with ongoing trials like BEST-CLI and BASIL-2 seeking clarity [12].

Amputation, a last resort, may be necessary in severe cases, but exhaustive revascularization efforts should precede it. CLTI requires a multidisciplinary approach involving various specialists, infrastructure, and a specialized vascular team to optimize care, improve outcomes, and reduce costs.

Acute Limb Ischaemia

Acute limb ischemia (ALI) in patients represents a critical subset necessitating prompt evaluation and intervention, commonly arising from embolic or thrombotic etiologies. The prompt initiation of heparin anticoagulation is recommended. In contrast to ST-elevation myocardial infarction (STEMI), the administration of systemic thrombolysis is not deemed appropriate for ALI. The timeliness of revascularization is contingent upon the presence and severity of sensory and motor impairments [13]. The available options for viable limb treatment include catheter-based thrombolysis, ultrasound-accelerated catheter-based thrombolysis, and surgical or percutaneous thrombectomy. Previous studies failed to consider contemporary thrombectomy systems, which have demonstrated remarkable efficacy in the removal of thrombi. The involvement of surgeons is imperative irrespective of the chosen technique, owing to the possibility of reperfusion injury in patients experiencing prolonged ischemia. In such cases, fasciotomies are necessary to mitigate the risk of developing compartment syndrome.

Paclitaxel Controversy

DCBs and DESs that have been coated with paclitaxel have gained significant popularity in the management of femoropopliteal PAD owing to their enhanced efficacy in maintaining primary patency. Nevertheless, a meta-analysis conducted in 2018 has brought forth apprehensions regarding the potential for heightened mortality rates associated with the utilization of paclitaxel-coated devices during femoropopliteal interventions [14]. Warnings were issued by regulatory agencies, resulting in a decrease in usage and the suspension of RCTs such as BASIL-3 and SWEDEPAD. Additionally, conflicting evidence has surfaced. The safety profile of paclitaxel-coated devices remains uncertain [15]. The delicate task of striking a balance between enhanced patency and the potential risk of mortality poses a significant challenge, particularly in patients with CLTI. In this patient population, the utilization of paclitaxel-coated therapy is favored due to the considerable morbidity associated with recurrent ischemic events.

Conclusion

Although there are several shared risk factors, the clinical manifestation of different types of PAD exhibits considerable diversity. It is recommended that all patients presenting with symptomatic PAD be prescribed a comprehensive treatment plan that encompasses lifestyle modification, antithrombotic therapy, lipid-lowering therapy, as well as appropriate management of hypertension or diabetes. The determination regarding revascularization should prioritize patient-centricity and necessitate comprehensive multidisciplinary deliberation. Due to the extensive range of pathological conditions, there persist numerous lacunae in the existing body of evidence. RCTs frequently lag behind the swift progression of methodologies and technological advancements. Numerous similarities can be observed in the provision of medical care for patients with cardiac conditions and patients with vascular conditions. Cardiologists possess a distinctive vantage point that enables them to deliver the utmost quality of care to individuals afflicted with PAD and spearhead forthcoming investigations and advancements in the field.

Limitations

The limitations of this review on the assessment and management of Peripheral Arterial Disease (PAD) primarily include its reliance on published studies and trials, which may not capture the full spectrum of emerging treatments and diagnostics due to publication lag. Additionally, the variability in PAD presentation and treatment responses across different populations might not be fully addressed due to the heterogeneity of included studies. The review's focus on cardiologist perspectives might also limit the exploration of interdisciplinary approaches.

Implications for future research

Future research for the review article should focus on validating the most effective diagnostic tools for early PAD detection, assessing the long-term safety and efficacy of novel treatments like icosapent ethyl and low-dose rivaroxaban, and exploring personalized medicine

approaches. Studies should also investigate the impact of socioeconomic factors on PAD treatment outcomes and the benefits of a multidisciplinary approach in patient care. Additionally, the safety and effectiveness of paclitaxel-coated devices require further long-term examination. These areas are crucial for enhancing PAD management and patient outcomes.

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List of abbreviations
PAD- Peripheral Artery Disease
ABI- Ankle Brachial Index
CLTI- Critical Limb-Threatening Ischemia
CAD- Coronary artery disease
CABG- coronary artery bypass grafting
TBI- toe brachial index
ACEI- ACE inhibitor
CEA- Carotid endarterectomy
CAS- carotid artery stenting
TCAR- Transcarotid artery revascularization
RAS- renal artery stenosis
RAAS- renin-angiotensin-aldosterone system
FMD- Fibromuscular dysplasia
ARBs- ACEIs or angiotensin receptor blockers
RCTs- randomized controlled trials
ALI- Acute limb ischemia
STEMI- ST-elevation myocardial infarction

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The authors have no competing interests to declare.

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