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Management of Peripheral Artery Disease with Medial and Intimal Calcification

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ABSTRACT

Peripheral artery disease (PAD) is a complex condition characterized by atherosclerotic plaque and medial arterial calcification (MAC), which can lead to thrombotic events and nonhealing wounds. MAC is prevalent in small and mid-sized arteries of the lower limbs and is often seen in patients with diabetes, advanced age, or chronic kidney disease. Its presence is strongly correlated with increased arterial stiffness and reduced blood flow, which can cause dysfunctional tissue perfusion. The extent of medial calcification independently predicts worse long-term limb outcomes, including higher rates of major amputation and mortality among PAD patients. Medial calcification is associated with systemic factors such as chronic kidney disease, diabetes, hypercalcemia, and elevated phosphate or parathyroid hormone levels.

Diagnosis involves anatomic and functional evaluations, including history-taking, physical examination, and diagnostic testing. Management of claudication and CLTI involves assessing walking capacity, asymptomatic patients at an elevated risk for cardiovascular events, and a multidisciplinary approach to manage risk factors. Endovascular development in the current era includes angioplasty, stenting, atherectomy, and drug-eluting balloon, but cardiovascular consequences elevate procedure risks and treatment failures.

Removing lower extremity vascular calcification may improve vascular remodelling and drug delivery. The latest endovascular treatments for medial artery calcification and intimal arterial calcification using IVL have shown promising early results for managing challenging calcified lesions. Longer-term studies and further real-world registry data will continue to refine its role in clinical practice.

BACKGROUND

Peripheral artery disease (PAD) comprises many phenotypes, including atherosclerotic plaque and medial arterial calcification (MAC). These traits generate thrombotic events that result in nonhealing wounds and ischemia.[1] Calcified peripheral artery disease (PAD), specifically medial artery calcification (MAC), is increasingly recognized as a critical factor negatively impacting limb survival outcomes according to recent studies and reviews. Medial calcification is especially prevalent in small and mid-sized arteries of the lower limbs and is often seen in patients with diabetes, advanced age, or chronic kidney disease. Its presence is strongly correlated with increased arterial stiffness and reduced blood flow, which can cause dysfunctional tissue perfusion independent of atherosclerotic burden.[2, 3]

Numerous clinical investigations have demonstrated that the extent of medial calcification independently predicts worse long-term limb outcomes, including higher rates of major amputation and mortality among PAD patients. For example, higher tibial artery calcification scores are linked to more severe limb ischemia and poorer prognosis after endovascular therapies, serving as better predictors of amputation risk compared to the ankle-brachial index (ABI). In patients with chronic limb-threatening ischemia, advanced foot artery calcification further stratifies amputation risk among vulnerable populations like diabetics.[3] A post-mortem examination of femoropopliteal arteries revealed that MAC was present in 46% of individuals aged 13 to 82 years, highlighting the inconsistencies in PAD diagnosis. Finding peripheral artery disease (PAD) early is difficult because affordable and simple tests, like the ankle-brachial index, might not work well for patients with chronic kidney disease (CKD) or diabetes mellitus (DM), which are major causes of artery hardening and make treatments more complicated.[4]

The recent studies and clinical guidelines shows that medial calcification in PAD is a significant, independent contributor to poor limb survival outcomes, suggesting a pressing need for new diagnostic tools and therapeutic strategies addressing calcification alongside vascular occlusion. This research is to examine the anatomical and functional evaluation, as well as the management of peripheral artery disease with calcification.

OBJECTIVE

Intimal calcification is indeed a feature of plaque disease resulting from atherosclerosis, chronic inflammation, necrosis, and subsequent healing processes. This calcification develops within diseased arterial intima where there is accumulation of lipid, inflammatory cells, and necrotic debris. Intimal calcification is actively driven by an inflammatory cascade mediated by macrophages, cytokine release, and death of both smooth muscle cells and macrophages, which release matrix vesicles that serve as nuclei for crystal and bone-like tissue formation within the intima. Intimal calcification tends to cause arterial lumen narrowing and can contribute to plaque instability, implicating it in acute vascular diseases such as myocardial infarction and stroke.[5-7]

Medial calcification, on the other hand, represents wall disease and is a result of metabolic and degenerative changes in vascular smooth muscle cells, which undergo phenotypic transformation into osteoblast-like cells. This process occurs in the medial layer of the artery independent of atherosclerotic plaque formation or lipid accumulation. Medial calcification is associated with systemic factors such as chronic kidney disease, diabetes, hypercalcemia, and elevated phosphate or parathyroid hormone levels. It leads to increased arterial stiffness without necessarily causing flow-limiting stenosis. Clinically, medial calcification is most notorious for decreasing arterial compliance and is often seen in Mönckeberg sclerosis. Unlike intimal calcification, which develops in response to plaque pathology, medial calcification is a chronic, active process resembling bone formation and generally lacks the inflammatory and lipid-rich environment of the intimal process.[8]

The differences aetiology, Pathophysiology, Mechanism, Clinical Consequence and Imaging between medial and intimal calcification can be seen in the table 1 below.

Tabel 1 The differences aetiology, Pathophysiology, Mechanism, Clinical Consequence and Imaging between medial and intimal calcification

Feature	Intimal Atherosclerotic Calcification	Medial Arterial Calcification (MAC)
Anatomical Layer	*Intima* (the innermost layer of the artery, site of atherosclerotic plaques)	*Media* (the smooth muscle layer of the arterial wall, between the intima and adventitia)
aetiology	Atherosclerosis, inflammation, necrosis, healing	Metabolic/degenerative (CKD, diabetes, aging)
Pathophysiology	Occurs within atherosclerotic plaques as part of the chronic inflammatory, lipid-driven process	Occurs independently of atherosclerosis, as a degenerative or metabolic process affecting the vascular smooth muscle and elastic lamina
Primary Mechanism	Inflammation + lipid accumulation → necrosis → calcification within necrotic core	Vascular smooth muscle cell (VSMC) osteogenic differentiation and apoptosis → deposition of calcium in elastic fibres
Appearance (Histologic/Imaging)	Patchy, irregular, often nodular; associated with necrotic core and cholesterol clefts	Diffuse, linear, concentric ("pipe-stem") calcification along the medial layer
Arteries Affected	Large and medium-sized arteries (e.g., coronary, carotid, aorta)	Medium and small muscular arteries (e.g., tibial, femoral, radial, sometimes coronary)
Clinical Consequence	Plaque rupture → thrombosis, ischemic events (Acute Myocardial Infarct, stroke)	Increased arterial stiffness → elevated pulse pressure left ventricular hypertrophy, impaired perfusion in diabetes/CKD
Key Associations	Classic atherosclerotic risk factors: dyslipidaemi hypertension, smoking, aging	Diabetes mellitus, chronic kidney disease, aging, mineral metabolism disorders (↑ phosphate, ↓ fetuin-
Molecular Drivers	Macrophages, oxidized LDL, inflammatory cytokines (IL-1β, TNF-α)	Osteogenic signaling in VSMCs: Runx2, BMP-2, Wnt/β catenin, oxidative stress
Calcification Morphology	*Microcalcification* (unstable plaques) → *macrocalcification* (stable plaques)	*Linear or concentric* medial layer calcification without plaque involvement
Imaging/Detection	Prominent on imaging, affects intervention	Sometimes difficult to detect, found on histology

Intimal and medial calcifications represent distinct diseases with different pathophysiological mechanisms, clinical implications, and therapeutic considerations.

Pathophysiological Mechanisms :

Intimal Calcification : This develops within areas of atherosclerotic plaque, triggered by endothelial dysfunction, lipid accumulation, inflammation, necrosis, and subsequent healing. Macrophages and smooth muscle cells within the plaque die, releasing extracellular vesicles and apoptotic bodies that serve as nucleation sites for calcium crystal deposition. The process is driven by chronic inflammation, oxidative stress, and promotes further vessel injury and plaque instability.[7]

Medial Calcification : This affects the media (middle layer) of the arterial wall and results primarily from metabolic or

degenerative changes, including vascular smooth muscle cell transformation into osteoblast-like cells. Calcium is deposited in the absence of cholesterol or inflammatory cell accumulation. Conditions such as diabetes, chronic kidney disease, and disturbances in calcium-phosphate metabolism accelerate medial calcification, further contributing to matrix remodelling and arterial stiffness.[7]

Clinical Implications :

Intimal Calcification : Associated with arterial narrowing and unstable plaques, it increases the risk of acute events like myocardial infarction or stroke. Microcalcifications within plaques heighten the chance of rupture and thrombosis, while macrocalcifications are linked to stable, but stiff, arteries.[5]

Medial Calcification : Typically does not restrict blood flow or cause plaque rupture, but raises arterial stiffness significantly. This is linked to hypertension, left ventricular hypertrophy, heart failure, and chronic vascular disease, especially in the context of metabolic syndromes or aging.[7]

Diagnosis Vascular intimal and medial calcification in showed in

- CT or angiography:
  - Intimal: irregular, focal, discontinuous calcification (along plaque edges).
  - Medial: smooth, circumferential, tubular calcification ("railroad track" pattern on x-ray or CT).
- Histology:
  - Intimal: calcified necrotic core under fibrous cap.
  - Medial: calcium deposits along elastic laminae, often continuous.

Clinical Significance Intimal calcification in coronary arteries constitutes a component of the atherosclerotic burden and affects plaque stability and treatment strategy (e.g., necessity for atherectomy or intravascular lithotripsy). In peripheral or diabetic arteries, medial calcification significantly enhances arterial stiffness and results in non-compressible vessels (high ABI >1.3). Both conditions can coexist, particularly in elderly or people with chronic kidney disease or diabetes.

Therapeutic Considerations

Intimal Calcification : Strategies target atherosclerosis and inflammation—statins, antiplatelet agents, blood pressure control, and lifestyle modifications. Monitoring and intervention focus on stabilizing plaques and reducing rupture risk.[5]

Medial Calcification: Approaches involve controlling metabolic disorders—managing phosphate, calcium balance, and parathyroid hormone levels. Addressing underlying CKD or diabetes is also crucial. Unlike plaque disease, current therapies for medial calcification are limited and largely preventive.[5]

Imaging and IVUS/OCT, CT Angiography and Floroscopy correlation between intimal and medial calcification in PAD can be described in the table 2 below.

Table 2 Intimal and Medial calcification in PAD by IVUS, OCT, CT Angiography, Fluoroscopy

Feature	Intimal Atherosclerotic Calcification	Medial Arterial Calcification (MAC)
Anatomical location	Within the intima, usually overlying the necrotic co or fibrous cap	Within the media, external to the intima, along the elas lamina
IVUS (Intravascul Ultrasound)	Appears as bright, highly echogenic areas wi acoustic shadowing within or protruding into t lumen.- Often eccentric (one side of the vessel Associated with plaque burden.	Circumferential, continuous echogenic ring along ves wall.- Concentric pattern, smooth contour.- Usua separate from lipid or plaque.- May not cause lumi narrowing.
OCT (Optical Coheren Tomography)	Calcification = signal-poor region with sharp borde within the plaque.- Usually superficial or deep intima, irregular shape.- May have overlying th fibrous cap.	Deep, circumferential signal-poor band with sha borders, often beneath intima, without lipid pool or c rupture.- Sometimes described as “double ring” or “tra track” pattern
CT Angiography / Plain X-ra	Irregular, patchy, spotty calcifications followi plaque contours.- May appear focal along vessel wa or nodular.	Linear, concentric, continuous calcification (“pipe-ste appearance).- Especially visible in tibial, femoral, a radial arteries.- Produces railroad-track sign on pla radiographs.
Angiography (fluoroscopy)	May show irregular lumen contour, stenosis ulceration.	Vessel often appears patent (no stenosis) but rigid, po compliance during ballooning.
IVL (Intravascular Lithotrip response	Effective if calcium is superficial and eccentr fragmentation improves vessel compliance.	May require higher energy; calcium distributed deep and circumferentially—more resistant to dilation.
Functional effect	Reduces luminal diameter, risk of rupture a thrombosis.	Causes arterial stiffness, high pulse pressure, and diffic vessel compliance (e.g., balloon recoil).

Table 3 Concept Pathology and Imaging in Calcified Peripheral Artery Disease

Concept	Intimal	Medial
Process	Atherogenesis → necrosis → dystrophic calcification	VSMC osteogenic differentiation → matrix mineralization
Morphology	Focal, nodular, irregular	Linear, concentric, continuous
Imaging	Eccentric, spotty, luminal	Concentric, circumferential, mural
Clinical Parallel	Plaque burden, stenosis, rupture risk	Vessel stiffness, noncompressible arteries, CKD/diabetes

The concept of imaging with pathology between medial and intimal calcification can be seen in the table 3 below, which shows that there are significant differences.

Practical Interpretation in clinical IVUS or OCT, Coronary arteries : 1) Intimal calcification → guides atherectomy or IVL decisions , 2) Superficial or thick calcium arcs seen on OCT often indicate heavily calcified plaques needing modification before stenting, 3) Medial calcification less common, but may be seen in CKD or older patients, complicating vessel expansion.

Different treatments for Peripheral Artery Disease in IVUS or OCT showed : MAC (Medial Artery Calcification) dominates — e.g., below-knee vessels in diabetes or ESRD. MAC management causes balloon resistance and poor recoil response despite no true stenosis.

In Description Image in IVUS showed in Figure 1 , "C" = Calcium in Circle → Medial Calcified Vessel and "Half-moon" = Calcium in Plaque → Intimal Calcified Vessel.

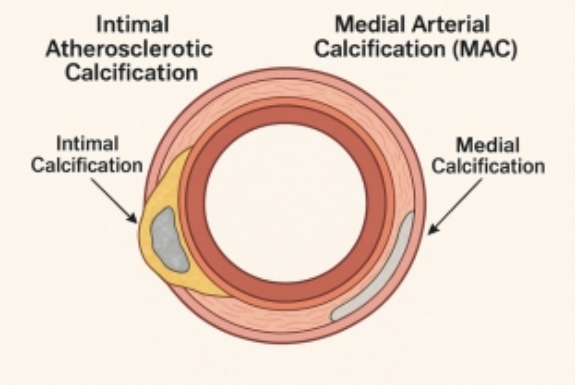


Figure 1 Description Calcified Vessel in IVUS

DISCUSSION

Diagnosis Anatomic and Functional Assessment of PAD:

The PAD assessment involves both anatomical and functional evaluations, including history-taking, physical examination, and diagnostic testing. Based on the acquired data, the classification determines the most effective treatment alternatives for optimal patient outcomes.

A.I. Anatomic Assessment

Anatomic assessment focuses on common disease sites in patients with PAD (Figure 1). The American Heart Association (AHA) recommends employing duplex ultrasonography, CT angiography, or MRA of the lower extremities to identify the location and severity of stenosis in patients with symptomatic PAD who may require revascularization. Comparable patient attributes have likewise demonstrated advantages from invasive angiography.[9] Furthermore, regional perfusion and oxygenation evaluation is an essential element of therapeutic protocols predicated on angiosomal flow disruption patterns.[10]

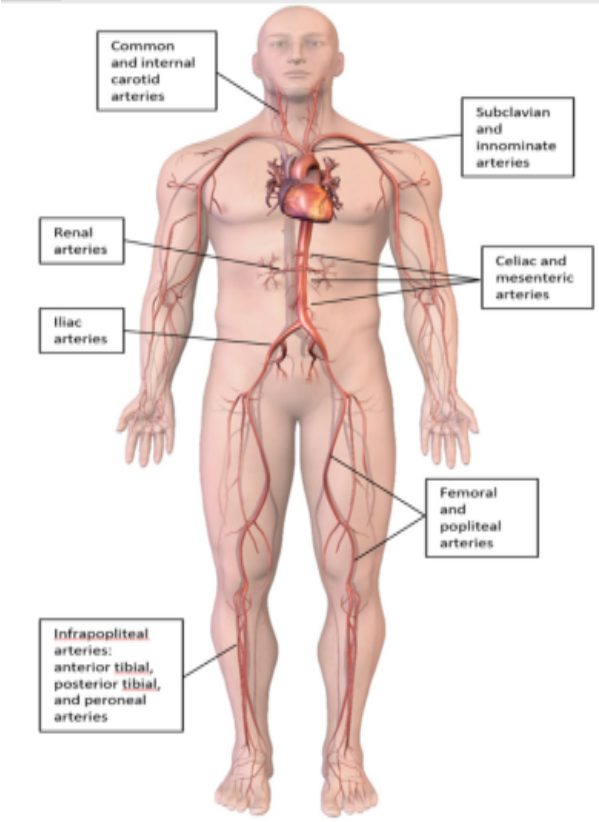
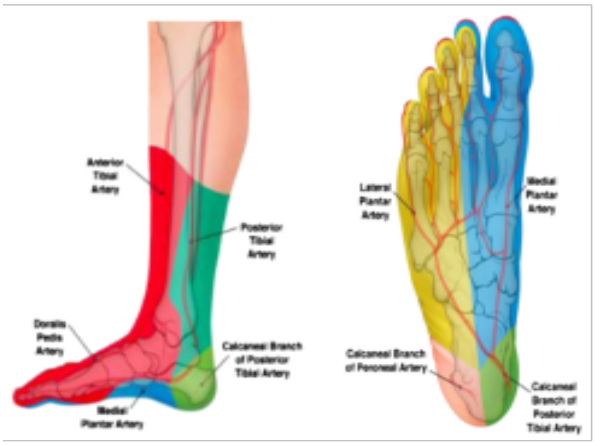


Figure 1 Common sites of disease in patients with peripheral artery disease.

Figure 2. Common PAD sites in patient.[11]

Angiosome are six anatomical regions supplied by principal artery networks, initially delineated through arterial dissection and post mortem dye injection. They offer more comprehensive data than ABI, which may be normal or noncompressible in around 30% of individuals with Chronic Limb Threatening Ischemia (CLTI). [10] Acquaintance with the Angio some concept is associated with substantial evidence indicating that Angiosome-directed revascularization enhances wound healing rates

and thereby reduces the incidence of major amputations more effectively. The Angiosome is illustrated in Figure 3.



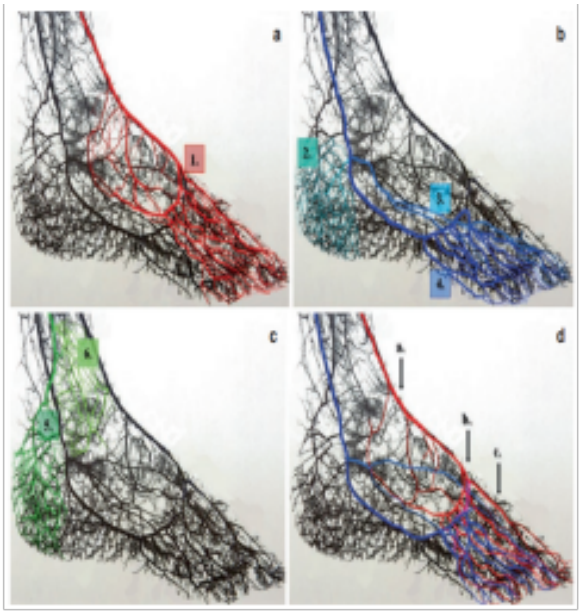


Figure 3. Angiosome distribution on foot[12]
a) dorsalis pedis angiosome originated from 1. Anterior tibialis artery ; Dorsalis pedis angisome consusted of 3 angiosome in ; figure b) the branch from posterior tibialis artery, 2. Medial calcaneus angiosome, 3. Angiosome medial plantar, and 4. Plantaris lateralis angiosome; figure c) angiosome originated from the branch of perionealis artery which are 5. Calcaneus lateralis artery angiosome and 6. Angiosome branch from anterior perforator; figure d) communication of main artery from dorsalis pedis artery and plantaris pedis a dorsalis pedis communication (tibialis anterior flow) and plantaris artery (tibialis posterior flow), b) communication of flow among middle foot flow among dorsalis pedis, plantaris pedis across perforator metatarsalis, c) communication amomg branches of arteries placed on forefoot amomg anterior metatarsalis and posterior digitalis

A.II. Functional Assessment

Identifying Population at Risk

Assessment should include individuals at risk for PAD along with symptoms. Table 4 shows the "at risk" population based on the epidemiologic evidence-based medicine.

Age ≥ 65 years
Age 50 - 64 years (Risk Factors for atherosclerosis :e.g diabetes mellitus, history of smoking, hyperlipidemia hypertension or family history of PAD)
Age <50 years with diabetes, + 1 additional risk factor
Leg symptoms with exertion (suggestive of claudication)
Ischemic rest pain
Abnormal lower extremity pulse examination
Known atherosclerotic eg coronary, carotid, subclavian, renal mesenteric artery stenosis, or AAA

Source : Hirsch AT, et al.[13]
Table 4 . Individuals at risk for PAD

Collecting Historical and Physical Examination Information

It is important to recognize the unique pulse palpation sites during a physical examination: femoral, popliteal, dorsalis pedis, and posterior tibial artery. The auscultation effort concentrates on the femoral artery.[14]

In individuals with a history or physical examination finding indicative of PAD, a resting ABI, with or without segmental pressures and waveforms, is advised for diagnostic confirmation. The recommendation also pertains to patients at risk for PAD who exhibit no symptoms upon history or physical examination. Physicians should classify resting ABI as abnormal (<0.90), borderline (0.91-0.99), normal (1.00-1.40), or noncompressible (>1.40).[9] This explanation can be seen from the anamnesis or historical findings and physical examination in the table 5 below.

Historical findings	Physical Examination Findings
Claudication	Abnormal pulses
Atypical lower extremity symptoms	Audible bruits
Impaired walking function	Nonhealing lower extremity ulcers
Ischemic rest pain	Lower extremity gangrene
Nonhealing wounds	Elevation pallor or dependent rubor
	Delayed capillary refill
	Cool extremities

Table 5. Anamnesis findings and physical examination findings suggestive of PAD[14]

Physiological Assessment in Patients:

Physiological testing encompasses several assessments, including toe-brachial index (TBI), exercise treadmill ankle-brachial index (ABI) testing, TBI with waveform analysis, transcutaneous oxygen measurement (TcPO2), and skin perfusion pressure (SPP).

Confirmation of diagnosis:

The American Heart Association (AHA) recommends the Toe-brachial index (TBI) as subsequent physiological assessment when the ABI exceeds 1.40. To validate symptomatic yet normal or borderline resting ABI, an exercise treadmill ABI may be conducted as a physiological

assessment. The AHA specifically advises this for patients with exertional, non-joint-related leg discomfort.[9, 14]

Identifying the Location and Scope of Disease:

In individuals exhibiting normal or borderline Ankle-Brachial Index (ABI) alongside nonhealing wounds or gangrene, it is prudent to identify Critical Limb Threatening Ischemia (CLTI) utilizing Toe-Brachial Index (TBI) with waveforms, Transcutaneous Partial Pressure of Oxygen (TcPo2), or Skin Perfusion Pressure (SPP). The identical procedure is applicable to patients exhibiting aberrant or noncompressible ABI in cases of nonhealing wounds or gangrene. This is intended as an assessment of local perfusion.[9] The normal value of TcPo2 is greater than 50 mmHg at the foot level. A skin perfusion pressure below 30 mmHg provides 85% sensitivity and 73% specificity for diagnosing CLTI. Coronary Artery Disease (CAD) and Peripheral Artery Disease (PAD) have similar parallels in their evaluation, as demonstrated in Table 6.

Coronary Artery Disease	Peripheral Artery Disease
EKG	ABI
Echo	PVR / Segmental Pressures
Stress Test	Treadmill Test
CT Angiography, Angiography Invasive	Ultrasound Duplex, CT Angiography, MR Angiography Angiography Invasive

Table 6 Similarities investigation diagnosis Coronary Artery Disease and Peripheral Artery Disease

Peripheral Artery Disease has many differential diagnoses which can be seen in the table 7 below

Condition	Location	Characteristic	Effect of Exercise	Effect of Rest	Effect of Position	Other Characteristics
Symptomatic Baker's cyst	Behind knee, down calf	Swelling, tenderness	With exercise	Also present at rest	None	Not intermittent
Venous claudication	Entire leg, worse in calf	Tight, bursting pain	After walking	Subsides slowly	Relief speeded by elevation	History of iliofemoral deep vein thrombosis; edema; signs of venous stasis
Chronic compartment syndrome	Calf muscles	Tight, bursting pain	After much exercise (jogging)	Subsides very slowly	Relief with rest	Typically heavy muscled athletes
Spinal stenosis	Often bilateral buttocks, posterior leg	Pain and weakness	May mimic claudication	Variable relief but can take a long time to recover	Relief by lumbar spine flexion	Worse with standing and extending spine
Nerve root compression	Radiates down leg	Sharp lancinating pain	Induced by sitting, standing, or walking	Often present at rest	Improved by change in position	History of back problems; worse with sitting; relief when supine or sitting
Hip arthritis	Lateral hip, thigh	Aching discomfort	After variable degree of exercise	Not quickly relieved	Improved when not weight bearing	Symptoms variable; history of degenerative arthritis
Foot/ankle arthritis	Ankle, foot, arch	Aching pain	After variable degree of exercise	Not quickly relieved	May be relieved by not bearing weight	Symptoms variable; may be related to activity level or present at rest

Source : Gerhad-Herman et al[9]
Table 7. Differential diagnosis of non-PAD related leg pain.

A.III. The result-finding assessment

Following the assessment of findings, subsequent steps involve establishing diagnoses and categorizing the stage of PAD disease. Alternative diagnoses for leg pain or claudication, despite normal physiological testing, encompass benign tumors, neurological conditions, and musculoskeletal factors. Variations can be made based on location, characteristics, symptoms, and the relative effects of positional changes. The finding assessment diagnosis PAD showed in Table 8.

The post-diagnosis staging system is utilized to establish the suitable revascularization strategy. Various classifications are present, each with distinct measurement objectives and methodologies. Rutherford, Fontaine, and SVS WIFI all classify PAD clinically; however, Fontaine is recommended solely for research purposes and assesses patient performance according to four clinical stages. The SVS WIFI classification provides a comprehensive evaluation of wounds and determines CLI severity by considering factors such as wound condition and foot infection, which indicate the risk of amputation and treatment options. Refer to Table 5 for additional information regarding disease staging systems. Similarities and differences exist between PAD and CAD showed in Table 9.

Name	Scope	Description	Advantages	Disadvantages
Clinical staging systems				
Fontaine	All PAD	Four broad clinical stages; asymptomatic to tissue loss	Simple for description and basic clinical algorithms	Inadequate discrimination between key subsets
Rutherford et al[225]	All PAD	Seven clinical stages (R0-R6); 3 for IC and 2 stages comprising CLTI	In longstanding use in clinical research and trials	Inadequate discrimination within the CLTI spectrum (R5, R6)
SVS WIFI[226]	CLTI only	"TNM"-like scheme based on wound, ischemia, foot infection. Combinations are grouped into 4 clinical stages based on expected amputation risk	Comprehensive for the universe of patients with extremity wounds, neuroischemia	Complex, new, requires more validation. Only covers the subset of PAD with CLTI
Anatomic staging systems				
Bollinger et al[227]	Infrainguinal	13 individual segments are scored, then summed	Captures overall disease burden; correlated with major CV events and survival	Not useful for defining revascularization strategies
TASC II[50,228]	Aorto-iliac and Infrainguinal	Lesion complexity graded A-D for each specific segment (AI, FP, TP)	Useful for comparing devices/interventions in a specific lesion type or segment	Does not combine segments into overall patterns of disease thus less useful for revascularization planning or comparison across strategies
Graziani et al[229]	Infrainguinal; diabetes focused	7 patterns of disease described; focused on diabetic patients with foot ulcers	Prevalence of patterns across subgroups can be compared	Not readily applied to revascularization planning or outcomes comparison
GLASS[23]	Infrainguinal*; CLTI focused	Complexity of disease patterns combining above and below the knee lesions are summarized into 3 overall stages based on defining a primary target artery pathway (TAP)	Directly relevant to revascularization planning, and for comparison between strategies in patients with CLTI	Not well validated. Currently does not incorporate pedal disease into stages

CLTI indicates chronic limb-threatening ischemia; GLASS, Global Limb Anatomic Staging System; PAD, peripheral artery disease; SVS WIFI, Society for Vascular Surgery Threatened Limb Classification System (wound, ischemia, foot infection; WIFI); and TASC, Trans-atlantic Societal Consensus.
*Simple descriptive stages are provided for AI disease and for pedal disease within GLASS.

Table 8. Staging Systems in PAD.

CAD	PAD	Management
Guideline-directed medical therapy	Optimal medical therapy	Antithrombotic, lipid-lowering, antihypertensive and glycaemic control agents
Lifestyle management	Lifestyle management	Smoking cessation, dietary intervention, weight management, exerci
Stable angina	Claudication	Conservative symptom management with revascularisation reserved for significant symptoms
Acute coronary syndrome	Chronic limb-threating ischaemia and chronic mesenteric ischaemia	Revascularisation generally preferred over medical therapy alone
ST-elevation myocardial infarction	Acute limb ischaemia and acute mesenteric ischaemia	Urgent or emergent revascularisation
Stent versus coronary bypass surgery	Endovascular versus surgical revascularisation	Multidisciplinary approach to balance anatomic complexity, periprocedural complications, risk of repeat revascularisation and patient's preference

CAD, coronary artery disease; PAD, peripheral artery disea

Diagnosis	Analogy	Outcome	Urgency
Claudication : Disabling Lifestyle limiting	*Angina*	Patency (Quality of life)	*Whenever*
Critical Limb Ischemia : Tissue loss / Ischemia Rest Pain Refractory infection	*ACS*	Limb Salvage (Amputation Free Survival / Wound Healing)	*Now*

Source : Tran, et al.11

Table 9. Parallel concepts in care in patients with CAD and PAD along with revascularization indication concept11

B. Management of Claudication and Critical Limb Ischemia

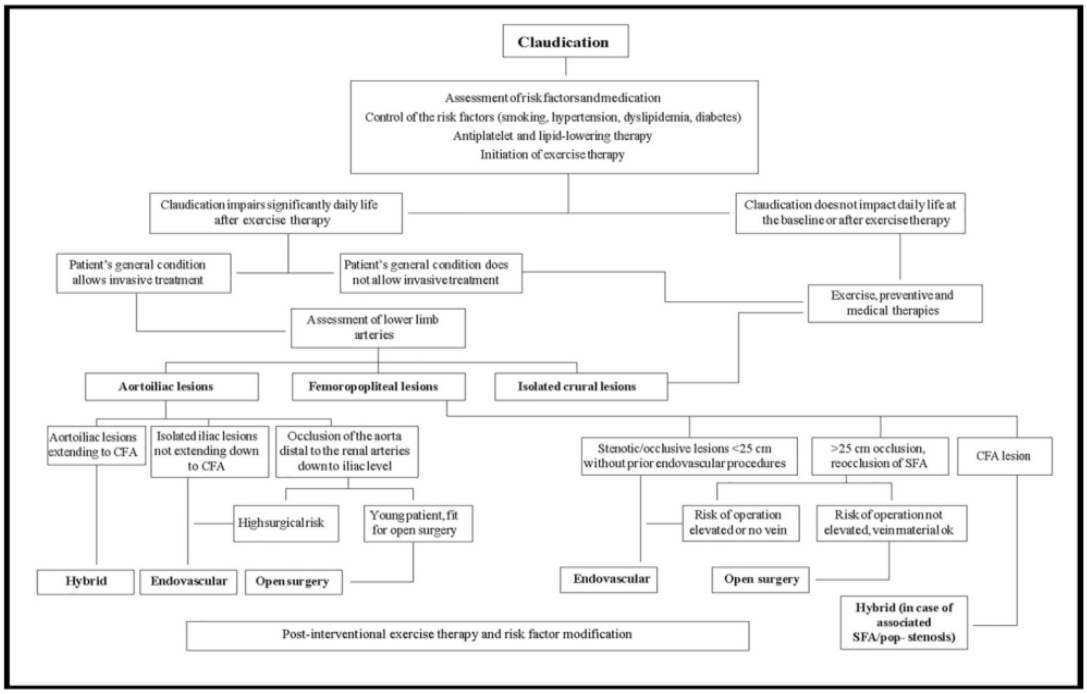
The majority of patients with peripheral artery disease (PAD) have no symptoms. Assessment of walking capacity is essential for the detection of clinically masked peripheral artery disease (PAD). Asymptomatic patients with peripheral artery disease (PAD) are at an elevated risk for cardiovascular (CV) events and can benefit from various CV preventive strategies, particularly rigorous management of risk factors. Antithrombotic therapies are recommended for patients exhibiting symptoms of peripheral artery disease (PAD). Their use in asymptomatic patients has not demonstrated any proven benefit. Anatomical imaging test data must be analyzed alongside symptoms and hemodynamic tests before making treatment decisions.

Timely identification of tissue loss and infection is crucial, necessitating referral to a vascular specialist for limb preservation through a multidisciplinary strategy. Acute limb ischemia accompanied by neurological deficit requires prompt revascularization.

Endovascular therapy and open surgery exhibit limited durability and may entail mortality and morbidity; hence, they should be reserved for patients unresponsive to medicinal treatment or experiencing disabling symptoms. A study of 12 trials including 1,548 patients indicated that both endovascular therapy and open surgery enhanced claudication symptoms and quality of life relative to medicinal therapy alone. Open surgery may lead to extended hospitalizations and increased complication rates compared to endovascular therapy; yet, it offers superior durability of patency.

Cardiovascular prevention and exercise training are essential for controlling intermittent claudication. Revascularization may be advised if everyday activities are significantly hindered, with the site and extent of arterial lesions influencing revascularization alternatives. The claudication management algorithm is illustrated in Figure 4.

Figure 4. Management of Claudication Algorithm



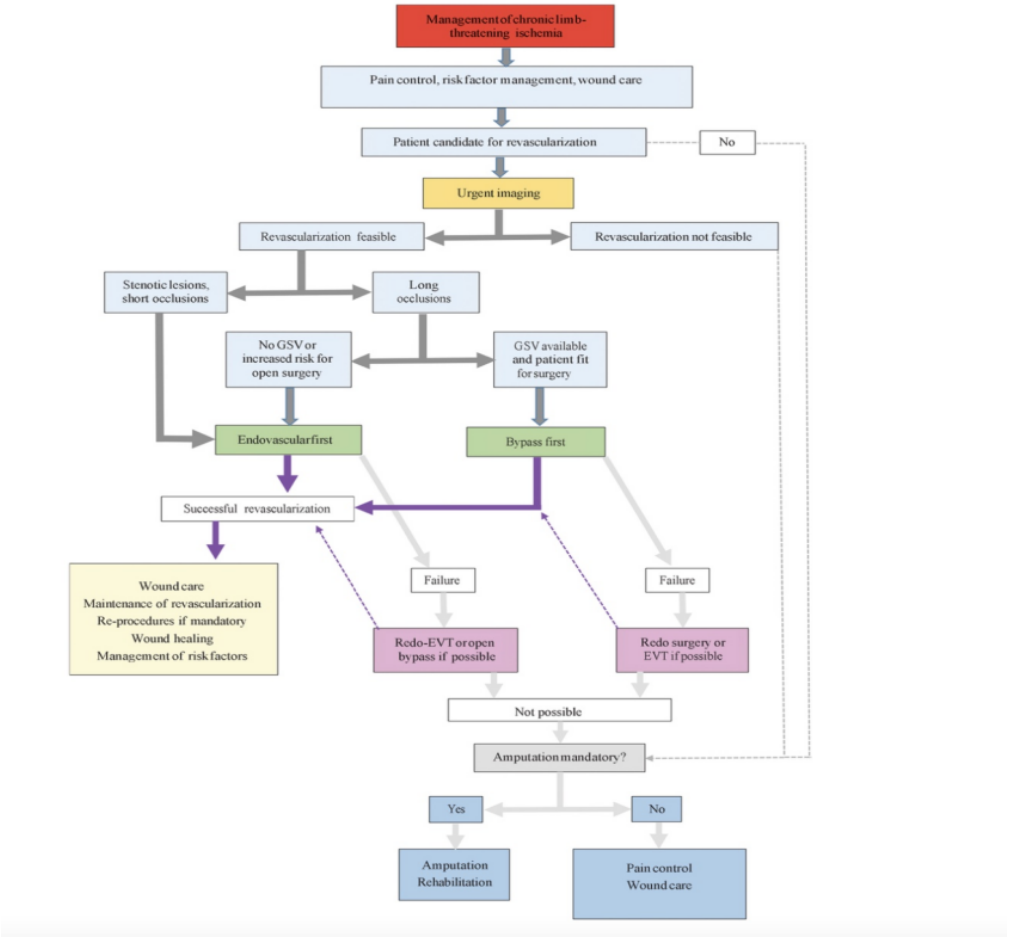
*) EVT = Endovascular Therapy ; GSV = Great Saphenous vein ; CFA = Common Femoralis Artery ; SFA = Superfisialis Femoral Artery

Chronic limb-threatening ischaemia (CLTI) delineates clinical patterns associated with compromised limb viability due to various reasons. Risk stratification is based on the severity of ischemia, wounds, and infection. Revascularization is necessary to prevent limb loss, although certain patients may retain their legs for extended durations despite the lack of revascularization. All patients with chronic limb-threatening ischemia (CLTI) must get optimal medical therapy (OMT) alongside risk factor modification. Glycaemic management is crucial for individuals with diabetes to enhance limb-related outcomes, such as reduced rates of major amputation and improved patency following infrapopliteal revascularisation. Management of CLTI is illustrated in Figure 5 below.

C. PAD Calcification

Calcification in the lower extremities predominantly occurs in the media. This pattern differs from that of coronary arteries. It may contribute to arterial stiffness, which affects pedal perfusion and potentially influences the severity of PAD symptoms. The degree of functional impairment in patients with PAD exhibits a limited correlation with anatomical assessments of plaque burden, and the response to therapy has been demonstrated to be diverse. The correlation between arterial calcification and symptoms of peripheral artery disease remains unexamined. Calcification of lower extremity arteries is associated with the severity of ischemia in patients with peripheral artery disease, as categorized by Rutherford's classification. This discovery may elucidate the diversity in the presentation of PAD patients and bolster initiatives to create clinical medicines focused on mitigating calcification and enhancing outcomes.

Figure 5. Management of Chronic Limb Threatening Ischemia (CLTI)



*) EVT = Endovascular Therapy ; GSV = Great Saphenous vein

Figure 6 Schematic diagram depicting multiple mechanism leading to vascular calcification

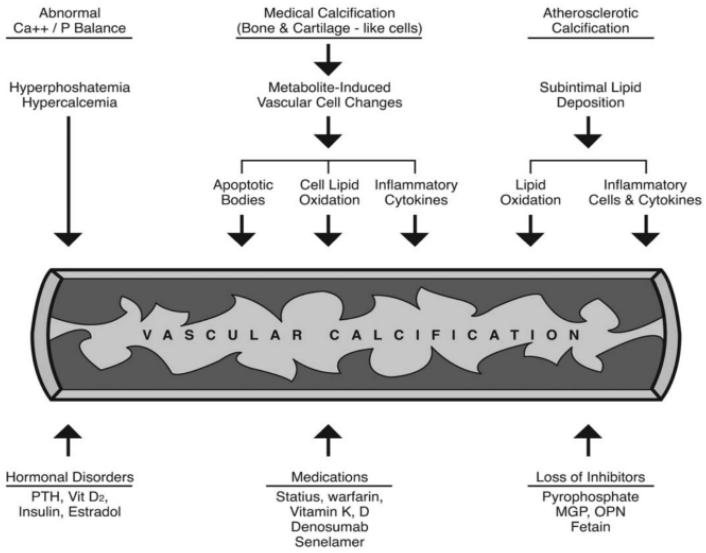
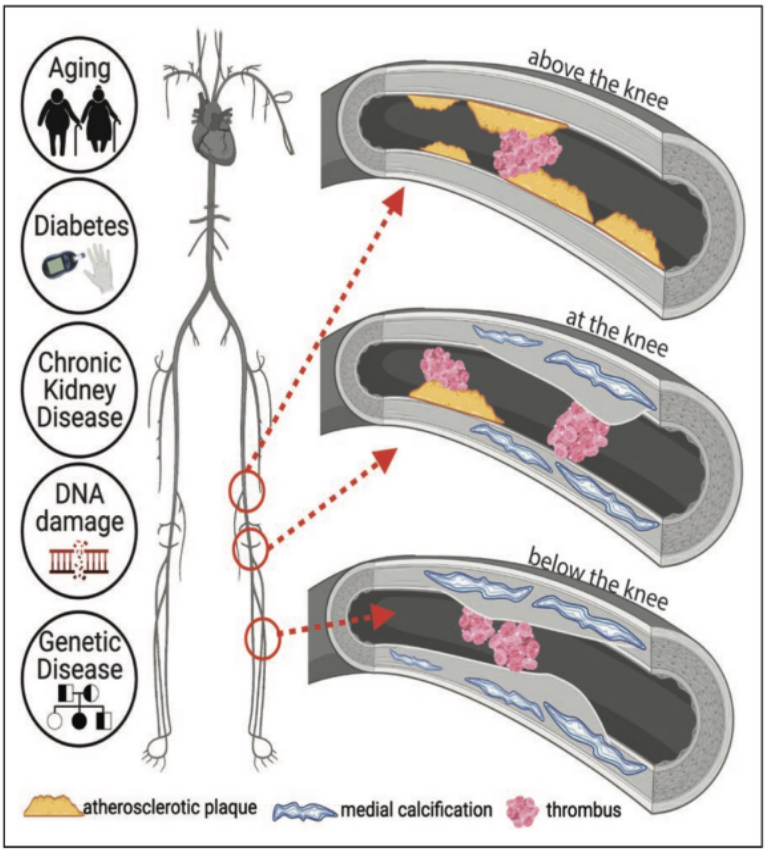


Fig. 1. Schematic diagram depicting multiple mechanisms leading to vascular calcification.

Figure 7 Peripheral Artery Disease stems from reduced blood flow the lower extremities and historically has been attributed to atherosclerotic plaques



Emerging clinical and genetic data show that medial arterial calcification (MAC) alone can lead to vaso-occlusion. The molecular mechanisms driving MAC pathogenesis are distinct from the pathway driving atherosclerotic plaque calcification. While both atherosclerotic plaque and MAC cause PAD, the vasculature above the knee is more prone to former, and vessels below the knee the latter. Future studies must focus on developing non invasive tools for physicians to determine whether PAD in a particular patient stems from atherosclerosis, MAC, or both, such that therapies (ie, statins) are targeted properly to maximize patients outcomes. Futhermore, defining the distinct molecular mechanisms driving MAC may uncover novel therapeutic targets

Intimal calcification and medial artery calcification (MAC) both contribute to nonhealing wounds and critical limb ischemia (CLI); however, they represent different pathological conditions mediated by distinct mechanisms. While most studies on vascular calcification use atherosclerotic disease models, we now recognize MAC as a factor in CLI and thromboocclusive events. Therefore, it is essential to create experimental models and methodologies tailored to the onset and advancement of MAC pathogenesis. Future research should aim to determine if PAD symptoms come from atherosclerotic plaque or MAC and clarify specific disease processes for targeted treatment approaches, using biomarkers or noninvasive imaging. Figures 6 and 7 elucidate the origin of calcifications in peripheral artery disease (PAD).

Emerging clinical and genetic data show that medial arterial calcification (MAC) alone can lead to vaso-occlusion. The molecular mechanisms driving MAC pathogenesis are distinct from the pathway driving atherosclerotic plaque calcification. While both atherosclerotic plaque and MAC cause PAD, the vasculature above the knee is more prone to former, and vessels below the knee the latter. Future studies must focus on developing non invasive tools for physicians to determine whether PAD in a particular patient stems from atherosclerosis, MAC, or both, such that therapies (ie, statins) are targeted properly to maximize patients outcomes. Futhermore, defining the distinct molecular mechanisms driving MAC may uncover novel therapeutic targets

Management of calcification in peripheral artery disease (PAD) differs greatly depending on whether the calcium is intimal (atherosclerotic) or medial (Mönckeberg's sclerosis). Managing medial and intimal calcification in peripheral artery disease (PAD) involves a combination of medical risk factor modification and emerging endovascular strategies, tailored to the underlying pathophysiology of each calcification type.[15]

C.1. Medial Calcification Management in PAD

Medial artery calcification (MAC), also known as Mönckeberg sclerosis, is linked to factors such as diabetes, chronic kidney disease, and certain medications like

warfarin that reduce levels of calcification inhibitors such as matrix Gla protein. Management includes:

Stopping or avoiding medications that worsen MAC, such as warfarin, especially in high-risk patients.

Intensifying control of diabetes, phosphate balance, and secondary hyperparathyroidism in patients with chronic kidney disease.

Regular monitoring using imaging, as MAC often contributes to arterial stiffness and poor endovascular outcomes.

Endovascular techniques such as intravascular lithotripsy, which use pressure waves to disrupt calcific deposits, and specialized balloons and atherectomy devices may help treat MAC in select patients.

There is ongoing research on agents that target vascular smooth muscle cell differentiation and mineralization pathways, but no widely approved targeted pharmacologic therapy exists currently.

C.2. Intimal Calcification Management in PAD

Intimal calcification is associated with obstructive atherosclerotic plaque and atherothrombotic risk. Management includes:

Aggressive risk factor modification: Smoking cessation, lipid-lowering therapy, blood pressure control, antiplatelet agents, and glycemic control.

Endovascular and surgical interventions are influenced by the presence and extent of intimal calcification, which may limit stent expansion or angioplasty success.

Intravascular imaging (IVUS, OCT) is important to differentiate between medial and intimal calcification before intervention, as they predict technical success and complications differently.

Newer device-based solutions such as intravascular lithotripsy are used in both intimal and medial calcification but require individualized assessment.

General Principles management PAD for intimal and medial calcification include :

Lifestyle modification and management of systemic disease factors are crucial for both types of calcification.

Interventional strategies should be chosen based on detailed imaging, as technical success and patency rates are lower in heavily calcified arteries.

Current guidelines emphasize the use of mechanical plaque modification and facilitate optimal outcomes in endovascular treatment when severe calcification is present.

Overall, management is multifactorial, involving both medical therapy and emerging interventional techniques tailored according to whether calcification is medial or intimal.

C.3. Endovascular development in the current era

Patients with claudication and critical limb ischemia, who are unresponsive to conservative treatment, undergo endovascular revascularization. Modalities include angioplasty, stenting, atherectomy, and drug-eluting balloon. These techniques are recognized for relieving clinical ischemia and facilitating revascularization; nonetheless, cardiovascular consequences elevate procedure risks and treatment failures. It affects guidewire navigation in stenotic regions and elevates the pressure necessary for balloon dilation; hence, it increases the risk of artery wall dissection and perforation. Stenting may fail to achieve complete expansion, resulting in restenosis and complicating subsequent interventions. Vessel Calcification diminish the effectiveness of drug-coated balloons (DCBs) due to the absorption of antiproliferative drugs, as revealed by Fanelli et al.

Atherectomy can be used as an alternative in lesions with vessel calcification . There are multiple available methods, including excisional atherectomy that cuts plaques directionally and may be preferred in eccentric lesions. However, this technique carries a risk of distal debris embolization, so distal filter devices are frequently used to prevent this.[16]

Another method uses rotational aspiration/atherectomy catheters, which have a fast-cutting drill that can go through severe blockages and blood clots. Examples of such catheters include the Jetstream atherectomy system (Boston Scientific Corporation) or Rotarex S (BD Interventional). These systems remove debris through continuous suction, which decreases embolization and minimizes the need for distal filters. An alternative mechanism is laser atherectomy, which acts through two mechanisms : high-energy light to ablate plaques and calcification, and light energy that is absorbed by blood/contrast, exerting a mechanical effect. Rotational and orbital atherectomy use spinning or moving diamond-coated tools to remove hard plaque, which makes it possible to use a lower-pressure balloon for a more effective angioplasty. Even though atherectomy might lower the need for stents compared to using PTA to prepare the blood vessel, it hasn't been thoroughly researched in patients with severe cardiovascular lesions, which makes it hard to create treatment guidelines for these patients.[17]

Angiography has several limitations, including the potential to underestimate vessel size, plaque morphology, and various factors, such as the presence of calcium and thrombus, plaque vulnerability, true lesion length, stent expansion and apposition, residual narrowing post-intervention, and the presence or absence of dissections. Intravascular ultrasound (IVUS) serves as a critical adjunctive tool, offering accurate imaging and facilitating interventional procedures to enhance outcomes. IVUS-guided treatment demonstrates improved outcomes relative to therapy guided solely by angiography. IVUS is essential in all endovascular procedures to enhance outcomes related to target vessel revascularization (TVR) and in-stent restenosis (ISR) and achieve high technical success rates.

Intravascular lithotripsy (IVL) followed by balloon angioplasty is a new way to treat hard calcium deposits in blood vessels. It uses shockwaves to break up these deposits by applying very high pressure (50 atm) to the vessel wall through a balloon filled with fluid that is inflated at a lower pressure. Originally used in urology to fragment kidney stones, this action allows for facilitated balloon expansion and a decreased risk of arterial dissection and perforation. We also hypothesize that the in situ fragmentation of the calcium will enhance the delivery of antiproliferative medications by DCB. In the DISRUPT PAD III trial, patients were randomized between IVL with DCB versus standard PTA with DCB in patients with moderate to severely calcified PAD. The primary outcome was procedural success (< 30% residual stenosis without flow-limiting dissection), which was achieved in 68% of patients in the IVL group and 52% in the PTA group. Additionally, there was a relative risk reduction of 77% for type C and D dissections, resulting in reduced stent placement. The long-term success of IVL as an adjunct to DCB effectiveness is still pending, with one-year results regarding the patency of treated stenosis yet to be reported. Figure 8 shows the algorithm for treating PAD by classification using endovascular revascularization.

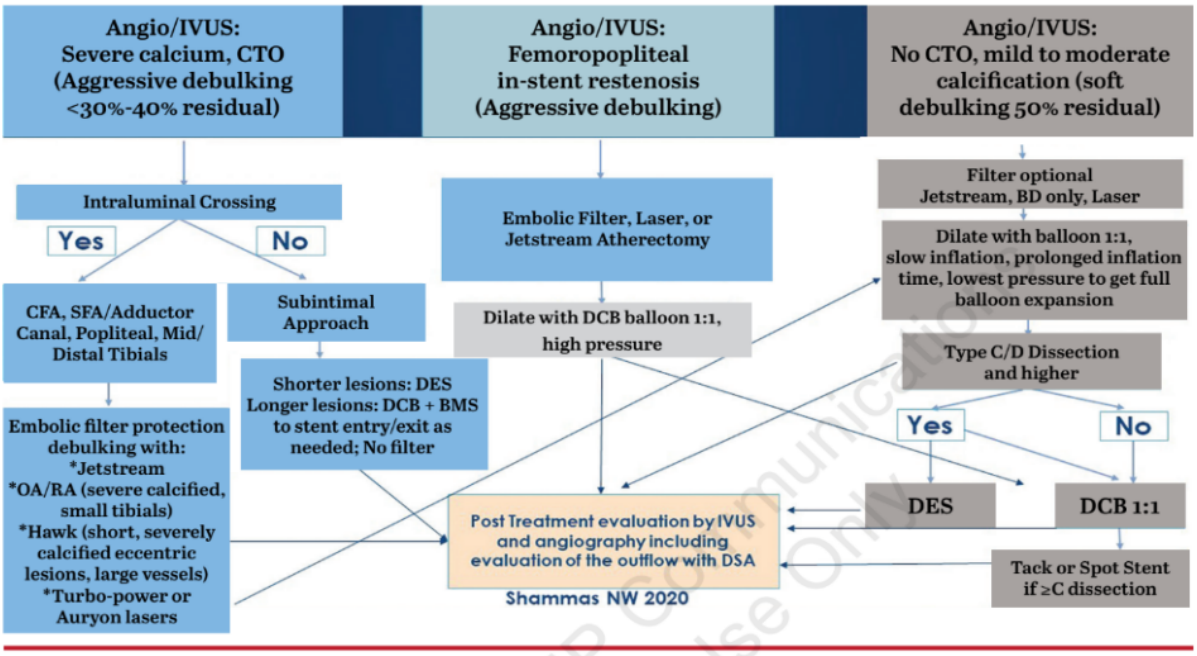


Figure 8 Algorithm Peripheral Artery Disease with calcification
Source: Shammas N,W 2020 16

The pathophysiology, clinical impact and management differences in intimal and medial calcification, showed Table 10 :

Table 10. pathophysiology, clinical impact and management differences in intimal and medial calcification

Type of Calcification	Pathology	Clinical Problem
Intimal Calcification	Occurs within atherosclerotic plaque (intima). Associated with inflammation, lipid, necrosis, and luminal narrowing.	Flow-limiting stenosis → ischemia, ulcer, claudication.
Medial Calcification (MAC)	Involves vascular smooth muscle and elastic lamina. N stenosis but causes vessel rigidity and stiffness.	Arterial noncompliance, high pulse pressure, poor perfusion, and balloon-resistant lesions.

Clinical objective management calcification in peripheral artery disease showed Table 11:

Table 11. Clinical objective management calcification in peripheral artery disease

Goal	Intimal Calcification	Medial Calcificati (MAC)
Revascularization	Restore lumen paten (treat stenosis/occlusion).	Improve complian and flow whe necessary, oft without true stenosis
Biomechanical	Modify calcified plaq to allow ste expansion.	Overcome w stiffness and rec during intervention.
Systemic	Aggressively mana atherosclerotic risk.	Control metabolic/mineral imbalance (CK diabetes).

C.4. Endovascular Management based in Medial and Intimal Vessel Calcification in PAD :

C.4.1 Intimal Calcification (Plaque-based)

Problem : Rigid, eccentric, or nodular calcium impedes balloon expansion and stent delivery.

Approach:

Lesion Preparation (Plaque Modification):

Atherectomy (orbital, rotational, directional):

Debulk superficial or nodular calcium.

Particularly useful for eccentric or focal calcification.

Intravascular Lithotripsy (IVL):

Uses acoustic pressure waves to fracture deep calcium; preserves soft tissue.

Useful for circumferential or deep intimal calcium.

Specialty Balloons:

Scoring or cutting balloons → focal calcium disruption.

Adjunctive Treatment:

Drug-coated balloon (DCB) to reduce restenosis.

Self-expanding stent if recoil or dissection occurs.

Imaging Guidance:

IVUS or OCT to identify calcium arc, depth, and thickness.

Determines whether atherectomy or IVL is required.

Clinical Example : Calcified femoropopliteal plaque → rotational atherectomy → DCB → optimal lumen gain.

C.4.2 Medial Arterial Calcification (Mönckeberg's sclerosis)

Problem : Vessel wall is circumferentially rigid; lumen may be preserved but resistant to dilation and recoil-prone.

Approach :

Endovascular Options:

IVL (Intravascular Lithotripsy):

Most effective for deep, concentric calcium in media.

Improves vessel compliance without dissection.

High-pressure or ultra-noncompliant balloons:

Sometimes required but risk of rupture.

Avoid excessive atherectomy:

Medial calcium is deep ; atherectomy targets intima → limited benefit, higher risk.

If Revascularization Needed:

DCB or stent post-IVL if lumen gain inadequate.

Use imaging guidance to avoid over-dilation.

Non-Endovascular Medical Measures:

Control phosphate, calcium-phosphate product, and PTH in CKD.

Use vitamin K and avoid excessive vitamin D analogs.

Emerging therapies: sodium thiosulfate, SNF472 (calcium chelator in trials).

All explanations of PAD classification management described above can be summarized in the table 12 below.

Table 12 Management of Intimal and Medial Calcification in PAD

Parameter	Intimal Calcification	Medial Calcification (MAC)
Location	Intima (plaque)	Media (wall)
Cause	Atherosclerosis	Metabolic (DM, CKD)
Main issue	Stenosis, occlusion	Stiffness, recoil
Imaging	Eccentric, nodular	Circumferential, linear
Endovascular tools	Atherectomy, IVL, scoring/cutting balloons	IVL, high-pressure balloon
Medical therapy focus	Lipid lowering, antiplatelets	Mineral metabolism, CKD management
Outcome measure	Lumen gain, patency	Compliance, pulse pressure, flow

The established management approach for peripheral artery disease states that if a lesion calcified is present in the intima, the plaque should be treated through debulking, modification, and lumen opening. If lesion calcified in the medial, treat the wall for fracture or soften calcium, restore compliance, optimize systemic metabolism Tips and Trick Management of Medial and Intimal Calcification in Peripheral Artery Disease showed in Figure 9

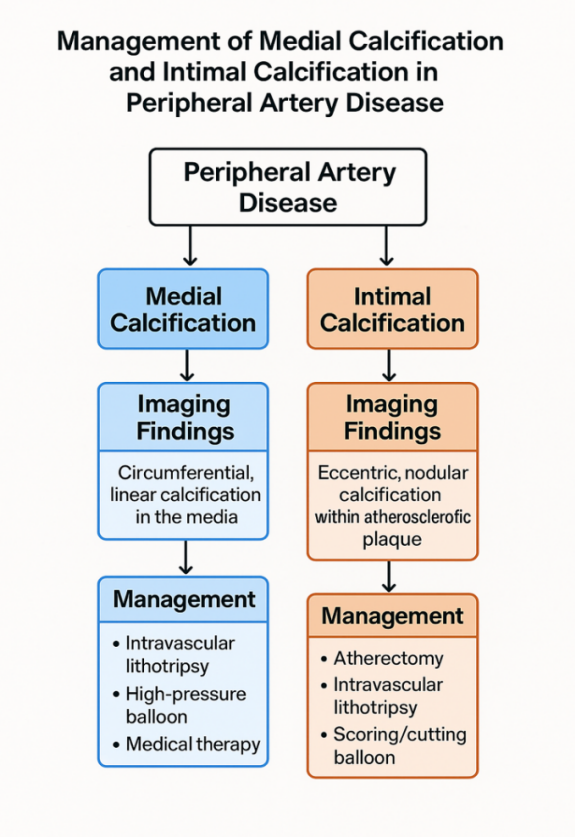


Figure 9 Management of Medial and Intimal Calcification in Peripheral Artery Disease

The latest endovascular treatments for medial artery calcification (MAC) have focused on device-based mechanical interventions, particularly intravascular lithotripsy, which shows promising early results for managing challenging calcified lesions.[18-20]

Intravascular Lithotripsy (IVL) adapts shockwave technology used in kidney stone treatment, delivering sonic pressure pulses via a special balloon catheter to selectively fracture both superficial and deep arterial calcium while minimizing trauma to soft tissues. Recent registries and clinical trials, such as DISRUPT PAD III, demonstrate that IVL achieves high technical success, with lower rates of flow-limiting dissection and need for bailout stenting compared to conventional angioplasty and improves luminal gain with sustained benefit at 6 months. IVL is especially valuable for MAC, which is more difficult to treat with standard high-pressure balloons or atherectomy due to the depth and circumferential nature of medial deposits.[19-21]

Atherectomy devices—especially orbital, directional, or laser atherectomy—have been used to debulk calcified tissue, but evidence specifically targeting medial calcification is limited; these are more established for intimal or mixed calcified lesions.[22] Research continues into combining vessel preparation with IVL, atherectomy, and drug-coated balloons (DCBs) to maximize long-term patency and reduce restenosis risk by removing or modifying the calcium barrier.[15, 20] Rotational atherectomy and other "plaque-modifying" modalities are subject of ongoing investigation for safety and efficacy in MAC, often used in conjunction with IVL or DCBs.[18, 23]

IVL provides durable benefit in maintaining vessel patency , low rates of adverse events (MAEs), minimizing complications, and improving limb outcomes (high rates of limb salvage and amputation-free survival at 12 months) for PAD patients with severe calcification (in chronic limb-threatening ischemia and intermittent claudication), improvement in clinical measures (ABI, walking distance) and repeat revascularizations with results out to 1-2 years post-intervention that compare favourably with other modalities. Longer-term studies and further real-world registry data will continue to refine its role in clinical practice.[24]

Emerging research includes the use of novel pharmacologic strategies—such as inhibitors of vascular smooth muscle cell mineralization and agents that affect bone mineralization—as adjuncts to mechanical therapy, but currently no medical therapy can reverse MAC in peripheral arteries.[25] Ongoing clinical trials and genetic studies may yield more targeted approaches, but at present, IVL combined with adjunct technologies represents the leading endovascular approach for MAC. [18, 20]

FUTURE DIRECTION

Calcification in PAD is common and associated with higher mortality, amputation risk, and poor revascularization success. Treatment challenges include imaging, lesion preparation, and calcification-specific interventions.

It will prioritize personalized, patient-centered approaches, stratifying patients by calcification burden, choosing appropriate devices, combining endovascular, stem cell / genomic cell and surgical interventions.

CONCLUSION

Peripheral Artery Disease (PAD) can result in severe outcomes, including stroke, amputation, and vascular mortality. Diagnosis and treatment can be challenging due to the disease's broad spectrum. Management of PAD with medial arterial calcification, intimal medial calcification, and superficial calcification have different causes, mechanisms, diagnoses, endovascular management, and outcomes. Removing lower extremity vascular calcification may improve vascular remodelling and drug delivery. The latest endovascular treatments for medial artery calcification (MAC) and intimal arterial calcification using IVL have shown promising early results for managing challenging calcified lesions.

ACKNOWLEDGEMENTS

None Stated

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