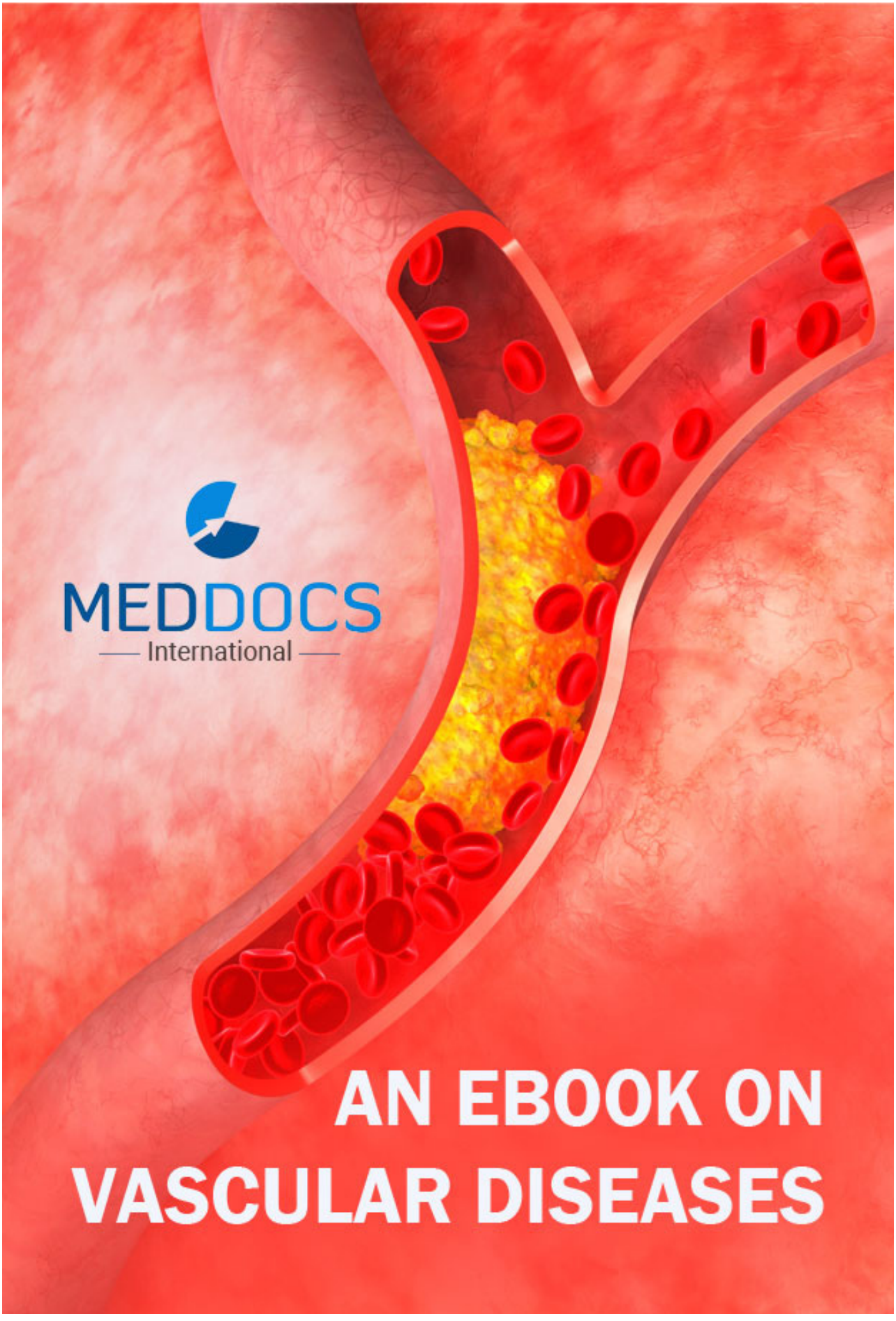

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AN EBOOK ON VASCULAR DISEASES

Infrapopliteal Occlusive Peripheral Arterial Disease

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Introduction

Peripheral Artery Disease (PAD) is defined as having partial or complete obstruction in one or more peripheral arteries. It is estimated that approximately 200 million people worldwide have lower limb PAD with a symptom spectrum ranging from asymptomatic to serious [1]. In the United States, the prevalence of lower limb PAD over 40 years old has been reported as 5.9%. In 1-2% of these patients, there are signs of chronic ischemia that threaten the extremity [2].

With increasing age, the incidence of lower extremity PAD increases. This increase, which is especially noticeable over 65, peaks at the age of 80 [3]. Approximately 1/3 of patients with lower extremity PAD have isolated Infrapopliteal (IP) disease. In the remaining 2/3, femoropopliteal and IP diseases are found in combination. Isolated IP disease occurs mainly in elderly patients (> 80 years), diabetic or dialysis-dependent patients, and survival rates without amputation are shorter than in the combined group [4].

Anatomy

The popliteal artery, which is the continuation of the superficial femoral artery, passes through the popliteal fossa and is divided into 2 branches, the Anterior Tibial Artery (ATA) and the Tibioperoneal Trunk (TPT), at the level of the distal end of the popliteal muscle. TPT continues as the Posterior Tibial Artery (PTA) and the Peroneal Artery (PA). ATA, proceeds as the DorsalisPedis Artery (DPA) in the dorsum of the foot (Figure 1).

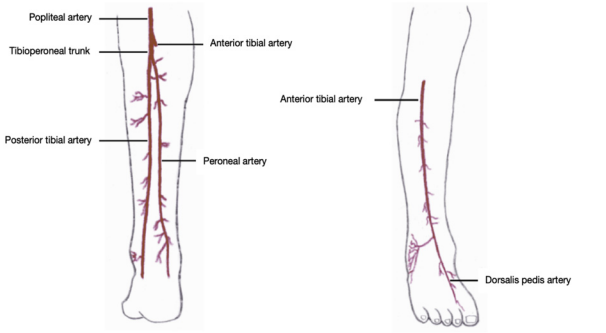

Figure 1: IP artery anatomy (posterior and anterior view-right lower extremity).

Popliteal artery has different variations in terms of branching pattern (**Figure 2**). These differences are important in planning the appropriate therapeutic intervention for both orthopedic and vascular interventions. By Kim and his friends, these variations were divided into 3 groups and 10 subgroups, creating a detailed identification system. Type 1 is the most common type where all branches are below the knee joint level, Type 2 is the type where all branches are above the knee joint level, Type 3 is defined as the type with hypoplasia and aplasia variations in all branches [5].

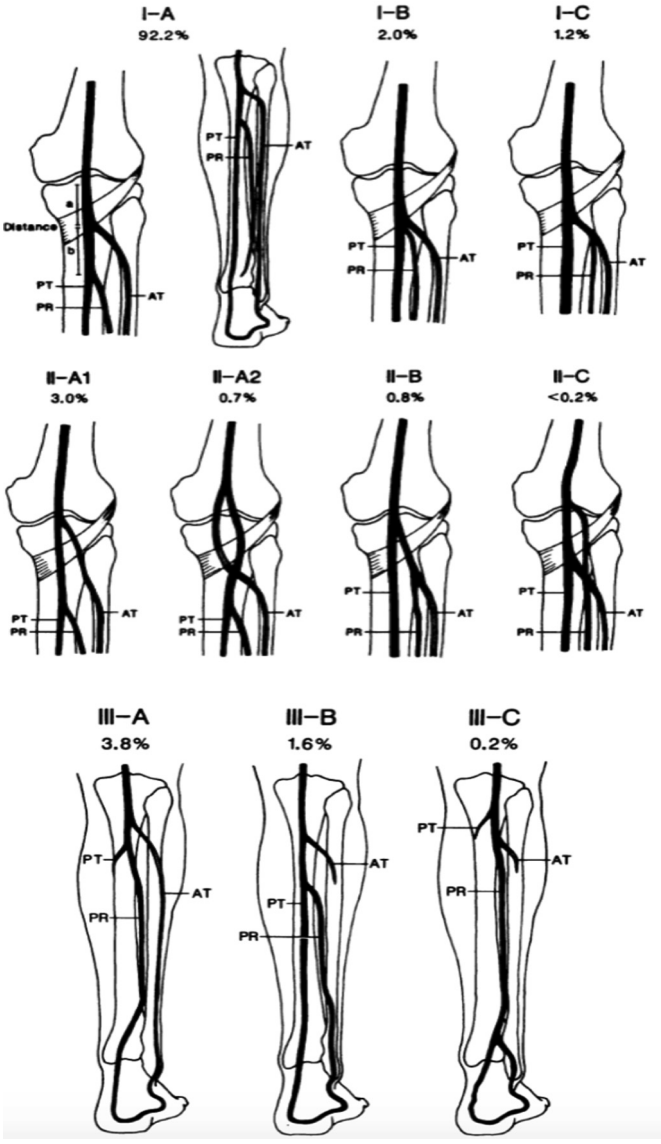

Figure 2: Popliteal artery anatomical variation subgroups [5].

Type 1A: Classic type (the most common).

Type 1B: Trifurcation.

Type 1C: PTA is the first branch. TBT continues as ATA and PA.

Type 2A-1: ATA separates from the knee joint level and proceeds in its normal course.

Type 2A-2: ATA progresses by curving towards the medial.

Type 2B: PTA is separated over the knee joint level.

Type 2C: PA is separated over the knee joint level. TBT continues as PTA and ATA.

Type 3A: Hypoplasia/aplasia of PTA. PA is more advanced.

Type 3B: Hypoplasia/aplasia of ATA. PA is more advanced. DPA originates from PA.

Type 3C: PTA and ATA are hypoplastic.

Angiosome concept

By introducing the term angiosome for the first time in 1987, Taylor and Palmar have identified areas of tissue that are perfused and drained by specific angiosomal vessels containing the skin, subcutaneous, fascia, muscle and bone [6].

Generally, there are 6 angiosomes originating from 3 main arteries in the ankle and foot region. ATA continues as DPA and supplies blood to the dorsum of the foot. PTA has 3 major branches and 3 angiosomes; the medial plantar artery supplies the blood to the instep, the lateral plantar artery supplies blood to the lateral midfoot and forefoot, and the medial calcaneal branch supplies blood to the heel area. PA has 2 major branches and 2 angiosomes. Anterior perforator branch provides blood flow to the ankle lateral region and the lateral calcaneal branch to the heel region. (Figure 3) There are also many collateral connections between the arteries responsible for the perfusion of these angiosomes [7,8].

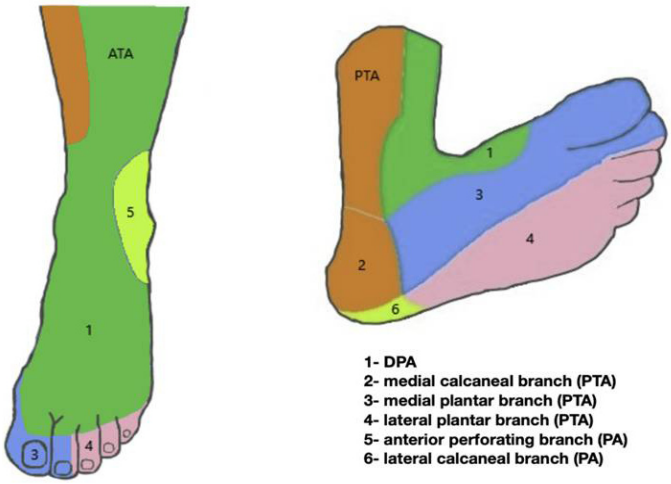

Figure 3: Distribution of angiosomes originating from ATA, PTA and PA.

It is widely accepted that angiosome-targeted revascularization is an effective method in providing blood flow to the ischemic lesion in patients with Chronic Limb-Threatening İschemia (CLTI). Especially in patients with diabetic and chronic renal failure where collateral circulation is poor, direct angiosome perfu-

sion gains importance.

In general, positive results are obtained in terms of wound healing, major amputation and amputation-free survival, with angiosome targeted Direct Revascularization (DR). Similar results can be achieved by İndirect Revascularization (IR) in the presence of collateral circulation. Although intervening with more than one artery by endovascular procedures seems to be a good option to provide adequate blood flow to the foot and affected angiosomes, no significant improvement in wound healing and amputation rates can be seen. Angiosome-targeted revascularization can be performed less frequently in bypass surgery because anastomosis is usually performed to the least affected artery with distal run-off to achieve a good patency rate [9].

In addition to the number of patent arteries under the knee, the distal run-off status and the presence of pedal arcus, the Wound Blush (WB), which is defined as an increase of contrast agent in the wound area after revascularization is an independent marker for ulcer healing. Additionally, in CLTI patients, all lesions may not be able to be intervened by endovascular intervention. In such cases, ulcer healing is likely with WB observation associated with high skin perfusion pressure, and the procedure may be terminated [10,11].

Risk factors

Diabetes mellitus (DM)

The prevalence of PAD is significantly higher in diabetic patients. It shows a more progressive course with the involvement of the distal arterial structures, leading to more serious clinical findings. This is due to the poor compliance of the distal arterial structures with revascularization compared to the proximal segments. Critical leg ischemia and limb loss rate are higher. Vascular involvement is more diffuse in diabetic patients with ischemic foot ulcers and is characterized by longer occlusive lesions, especially in the tibial arteries [12,13].

Smoking

It is the most important modifiable risk factor in the development of PAD. Compared to non-smokers, the risk of developing PAD is 4 times higher and the onset of symptoms occurs 10 years earlier. The progression to critical leg ischemia and amputation rate is significantly higher [14].

Hypertension (HT)

Almost all studies have revealed the relationship between HT and PAD. The incidence of HT in patients with PAD ranges from 50% to 92%. The relative risk for developing PAD is lower than for DM or smoking [14,15].

Hyperlipidemia (HL)

Increased cholesterol levels are associated with a 2-fold increase in the risk of developing claudication. More than 60% of patients with PAD have hypercholesterolemia. The prevalence of HL was defined as 77% in patients with PAD. In addition, every 10 mg / dl increase in total cholesterol level causes a 10% increase in the possibility of developing PAD [14].

Renal dysfunction

CLTI has worse results with End-Stage Renal Disease (ESRD). The rate of revascularization patency is low due to restenosis and thrombosis. In addition, the mortality and amputation rate is high. In patients with ESRD and multiple femoropopliteal occlusive lesions, the absence of evident flow in the below-knee arterial segments is called 'renal foot' [16].

-However, recently identified risk factors include increased inflammatory markers such as CRP, fibrinogen and homocysteine. In particular, hyperhomocysteinemia has been identified as an independent risk factor for PAD [17].

Etiology

a. Atherosclerosis

It is the most accused pathology in the etiology of lower limb PAD. It is especially seen in advanced age patients with risk factors such as DM and HT. It is typically characterized by eccentric plaques [18,19] (**Figure 4**).

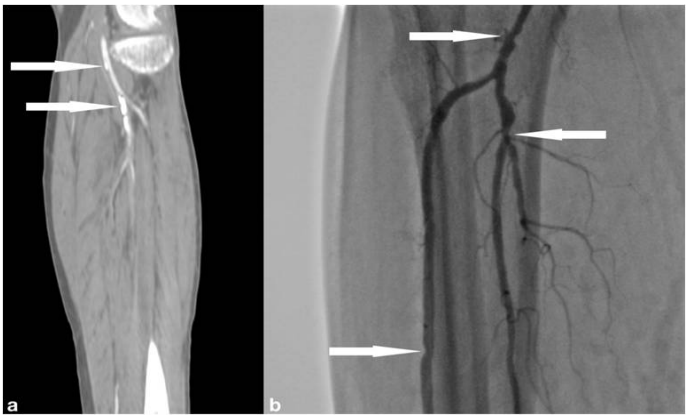

Figure 4: Eccentric plates (white arrows) at CT angiography section (a) PA and TPT level, digital substraction angiography (DSA) image (b) At PA, ATA and TPT level.

b. Non-atherosclerotic causes

Non-atherosclerotic causes should be considered in cases where there are no other signs of atherosclerosis and other atherosclerotic risk factors. In addition, if there is an incompatibility between symptoms and imaging techniques, alternative diagnoses should be considered except atherosclerosis. These include thromboangiitisobliterans, popliteal artery entrapment syndrome, fibromuscular dysplasia, cystic adventitial disease of popliteal artery, embolism from aortic or peripheral artery aneurysm and vasculitis [19,20].

Thromboanjiitis obliterans (Burger disease)

Segmental occlusive inflammatory disease of small/medium-sized limb arteries and veins. It is especially seen in the young adult population who smoke under the age of 45.

Popliteal artery entrapment syndrome

The surrounding anatomical structures make external compression due to the abnormal course of the popliteal artery. Recurrent trauma leads to the development of thrombosis or distal thromboembolism. Mild symptoms may be observed due to arterial collaterals developing in long-term cases.

Fibromuscular dysplasia

It is rare and may have iliac, femoral and popliteal artery involvement. As a result of arterial dissection or rupture, microemboli or critical leg ischemia findings may occur.

Cystic adventitial disease of popliteal artery

It occurs especially in middle-aged men and rarely causes

symptoms. As it can be seen in other regions such as external iliac, femoral, radial and ulnar artery, it mainly affects popliteal artery. It is defined as the luminal compression of mucoid cyst formation in the adventitia layer.

Aortic / Popliteal aneurysm

As a result of distal thromboembolism, it is characterized by acute limb ischemia or small gangrenous changes in the foot.

Behçet's disease

It is a type of vasculitis affecting many systems with arterial and vein involvement. It is reported that iliac, femoral, popliteal and PTA are also affected, although large arterial structures are typically involved. Isolated infrainguinal involvement is rare.

Other nonatherosclerotic occlusive causes also include occlusion due to vascular damage after blunt or penetrating trauma, thrombosis due to hypercoagulability, 'Blue-toe syndrome' due to cholesterol embolism from proximal atherosclerosis and peripheral embolism of cardiac origin [18].

Clinical features

Clinical findings vary from mild claudication to CLTI depending on the location and severity of arterial stenosis or occlusion. While many asymptomatic patients show a benign course, especially in smokers, patients accompanied by DM and renal failure may have a rapid progression.

Especially, infrapopliteal occlusive PAD occurs with rest pain, non-healing arterial ulcer and CLTI compared to iliofemoral arterial diseases. Rest pain occurs intermittently in the early stages of the disease and is called intermittent claudication. Patients typically try to keep their feet below the surface where they are to reduce symptoms. Symptoms of intermittent claudication, Thromboangiitisobliterans, popliteal artery aneurysm, fibromuscular dysplasia, popliteal artery entrapment syndrome and cystic adventitial disease of popliteal artery should be kept in mind In the differential diagnosis of patients [21].

Chronic limb threatening ischemia (CLTI)

Critical limb ischemia was first described in 1982 and has been used for a large patient population over the following years. As is known today, critical limb ischemia is associated with decreased quality of life, increased risk of amputation, and mortality. The outcomes of untreated critical leg ischemia are very poor [22].

It is a condition due to chronic and insufficient tissue perfusion characterized by resting pain that last longer than 2 weeks, healing ulcers and gangrene. It has a 1-2% prevalence in patients diagnosed with PAH. It is estimated that 5-10% of patients with asymptomatic PAD and intermittent claudication will have CLTI progression after a 5-year period [23].

Classification of symptoms

Rutherford and Fontaine are the most widely used symptom classification systems for years. The mild, moderate and severe claudication that defines walking impairment is determined by the performance of 5-minute treadmill test at 3.2 km/h at 12% slope in the Rutherford classification, and 200 meters in the Fontaine classification [24] (**Table 1**).

In addition to the severity of ischemia, wound characteristics and infection have also gained importance and The Vascular Surgery Association (SVS) defined a new classification system called WIFI (wound, ischemia, foot infection) in patients with critical leg ischemia for the purpose of determining the risk of amputation, selecting of treatment modality and estimating the prognosis before and after the treatment (**Table 2**).

Target population for WIFI classification includes any patient with;

- Ischemic resting pain, objective hemodynamic studies (ABI <0.4, AP <50 mmHg, TP <30 mmHg, $TcPO_2$ <20 mmHg).
- Presence of diabetic foot ulcer.
- Non-healing lower limb or foot ulceration of at least 2 weeks duration.
- Gangrene anywhere in the foot or lower limb [22].

Since each of the three categories (wound, ischemia, foot infection) has four degrees of severity, the classification system has theoretically 64 possible clinical combinations. These combinations are used to estimate amputation risk and revascularization benefit and necessity **(Table 3)**. Clinical stages and amputation risk in WIFI classification are shown in **Table 4**.

Table 1: Rutherford and Fontaine classification [21].

Rutherford classification			Fontaine classification	
Stage	**Category**	**Clinical features**	**Stage**	**Clinical features**
0	0	Asymptomatic	1	Asymptomatic
1	1	Mild claudication	2a	Mild claudication
1	2	Moderate claudication	2b	Moderate claudication
2	3	Severe claudication		
3	4	Rest pain	3	Rest pain
3	5	Minor tissue loss		
3	6	Major tissue loss	4	Ulcer and gangrene

Table 2: WIFI classification [22].

Components	Grade	Definition		
W (wound)	0	Rest pain (no wound, ulcer or gangrene)		
	1	Small, shallow ulser(s) on distal leg or foot, no gangrene		
	2	Deeper ulcer with exposed bone, joint or tendon on distal leg or foot; generally not involving the heet shallow hed! ulcer without calcaneal involvement, gangrenous changes limited to digits		
	3	Extensive, deep ulcer involving forefoot and/or midfoot; deep, full thicknes heel ulcer ± calcaneal involvement		
		Ankle-Brakial Index (ABI)	Ankle systolic pressure	Toe pressure, Transcutaneous oximetry(TePO2)
I (Ischemia)	0	≥80	>100 mm Hg	≥60 mm Hg
	1	0.6-0.79	70-100 mm Hg	40-59 mm Hg
	2	0.4-059	50-70 mm Hg	30-39 mm Hg
	3	≤0.39	<50 mm Hg	<30 mm Hg
F (Foot infection)	0	No symptoms or signs of infection		
	1	Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs)		
	2	Local infection (as described below) with erythema >2 cm, or involving structures deeper than skin and subcutaneous tissues (eg, abscess, osteomyelitis, septic arthritis, fascitis), and no systemic inflammatory response signs (as described below).		
	3	Local infection (as described below) with the signs of SIRS, as manifestec by two or more of the folowing: • Temperature >38 or <36C • Heart rate >90 beats/min • Respiratory rate >20 breaths/min or PaCO2 <32 mm Hg • White blood coll count >12,000 or <4000 cu/mm or 10% immature (band) • Forms		

Infection present, as defined by the presence of at least 2 of the following items:

-Local swelling or induration
-Erythema >0.5 to ≤2 cm around the ulcer
-Local tenderness or pain
-Local warmth
-Purulent discharge (thick, opaque to white, or sanguineous secretion)

SIRS: Systemic Inflammatory Response Syndrome

$PACO_2$: Partial pressure of Arterial Carbon dioxide

Table 3: a and b, estimation of risk/benefit [22].

a- Estimate risk of amputation at 1 year for each combination																
	I0				**I1**				**I2**				**I3**			
W0	VL	VL	L	M	VL	L	M	H	L	L	M	H	L	M	M	H
W1	VL	VL	L	M	VL	L	M	H	L	M	H	H	M	M	H	H
W2	L	L	M	H	M	M	H	H	M	H	H	H	H	H	H	H
W3	M	M	H	H	H	H	H	H	H	H	H	H	H	H	H	H
	FI0	FI1	FI2	FI3	FI0	FI1	FI2	FI3	FI0	FI1	FI2	FI3	FI0	FI1	FI2	FI3
b- Estimate likelihood of benefit of/requirement for revascularization																
W0	VL	VL	VL	VL	VL	L	L	M	L	L	M	M	M	H	H	H
W1	VL	VL	VL	VL	L	M	M	M	M	H	H	H	H	H	H	H
W2	VL	VL	VL	VL	M	M	H	H	H	H	H	H	H	H	H	H
W3	VL	VL	VL	VL	M	M	M	H	H	H	H	H	H	H	H	H
	FI0	FI1	FI2	FI3	FI0	FI1	FI2	FI3	FI0	FI1	FI2	FI3	FI0	FI1	FI2	FI3

W: Wound; I: Ischemia; FI: Foot Infection; VL: Very Low, L: Low, M: Moderate, H: High

Table 4: Clinical stages in WIFI classification [22].

Risk of amputation	Proposed clinical images	WIfI spectrum score
Very low	Stage 1	W0 I0 fI0,1 W0 I1 fI0 WI I0 fI0,1 W1 I1 fI 0
Low	Stage2	W0 I0 fI2 W0 II fII W0 I2 fI0,1 W0 I3 fI0 W1 I0 fI2 W1 I1 fI1 W1 I2 fI0 W2 I0 fI0/1
Moderate	Stage 3	W0 I0 fI3 W0 I2 fI1,2 W0 I3 fI1,2 W1 I0 fI3 W1 II fI2 W1 I2 fII W1 I3 fI0,1 W2 I0 fI2 W2 I1 fI0,1 W2 I2 fI0 W3 I0 fI0,1
High	Stage 4	W0 I1,2,3 fI3 W1 I1 fI3 W1 I2,3 fI2,3 W2 I0 fI3 W2 I1 fI2,3 W2 I2 fI1,2,3 W2 I3 fI0,1,2,3 W3 I0 fI2,3 W3 I1,2,3 fI0,1,2,3

Clinical stage 5 would signify an unsalvageable foot (most often because of wound extent or severity of infection)

Patient evaluation

In patients with PAD risk factors and symptoms such as claudication, resting pain, ulcer and gangrene, the entire cardiovascular system should be evaluated.

While fever is a marker of infected ulcer, tachycardia and tachypnea may support the diagnosis of deep tissue infection in the foot.

Depending on the duration and severity of PAD, there may be different findings in the physical appearance of the limb. With a significantly reduced blood flow, the skin becomes thin, dry, shiny and hairless. Hypertrophy and fragility appear on the nails. Unless there is bilateral PAD, the comparison of color and trophic changes between extremities can be a good marker in terms of PAD severity.

As a marker of perfusion, skin temperature is evaluated by gently palpating the skin and comparing it with other lower extremity. Ischemic extremity is cold and the level with temperature difference provides rough estimation of the level of occlusion. [25,26].

Buerger test

- In the supine position, elevation of the extremity permits the venous blood to drain.
- The limb is then placed in the dependent position, waiting the blood flow to return.
- The return time of the blood, which normally takes <20 sec, is an important marker for disease severity.
- The normal extremity will remain pink with elevation.
- In the presence of significant PAD, the foot becomes pale with elevation, and it may be red or cyanotic in the dependent position, depending on the skin temperature [25].

Patients with CLTI, especially those with diabetes, have signs of glove and socking neuropathy. These patients may be asymptomatic and may also have symptoms such as tingling, numbness, weakness, and burning pain in the feet and ankles. The presence of such a neuropathy is considered to be a major risk factor for tissue loss and should be carefully observed. It should be evaluated with the help of a diaposone whether there is a

loss of sense of vibration, which is an early finding [26].

Pulses

Palpations of the lower extremity distal pulses are indispensable in vascular examination. The patient must be in the supine position and rested for at least 15 minutes before the examination. It can provide information about the spread of the disease. It is usually characterized by weakening and complete loss in pulses below the stenosis/occlusion level.

Ulceration and gangrene

Ischemic ulcers are typically observed in areas where the arterial branches terminate. They start as small traumatic wounds and cannot heal due to insufficient blood flow. They are often found on the toes and between the fingers. They can also occur in the lateral malleolar and metatarsal heads, where the focal pressure is increased. When the blood supply is insufficient to supply the minimum metabolic needs, ischemic areas develop full-thickness skin necrosis and deeper tissues may also be involved. There is a clear demarcation line between viable and gangrenous tissue [25].

Diagnosis

A. Noninvasive tests

Evaluation of PAD begins with a detailed history and physical examination, and noninvasive tests are used to confirm clinical diagnosis and further define the level and extent of vascular pathology.

Indications

- screening of patients with risk factors for PAD,
- in the evaluation of acute changes as a result of thromboembolism,
- in order to confirm the diagnosis of arterial disease in patients with chronic symptoms or findings consistent with arterial pathology,
- in determining vascular injury,
- patient assessment prior to vascular procedures,
- for follow-up after vascular intervention

Ankle-brachial index

- It is an inexpensive and simple test used to confirm suspicion of lower limb PAD. It is found by the ratio of the highest systolic blood pressure measured from both ankles to the highest systolic blood pressure measured from both brachial regions. It is used to measure the severity of arterial disease and has predictive value for coronary and cerebrovascular disease. The patient must be rested for 15-30 minutes for an appropriate measurement (**Figure 5**).

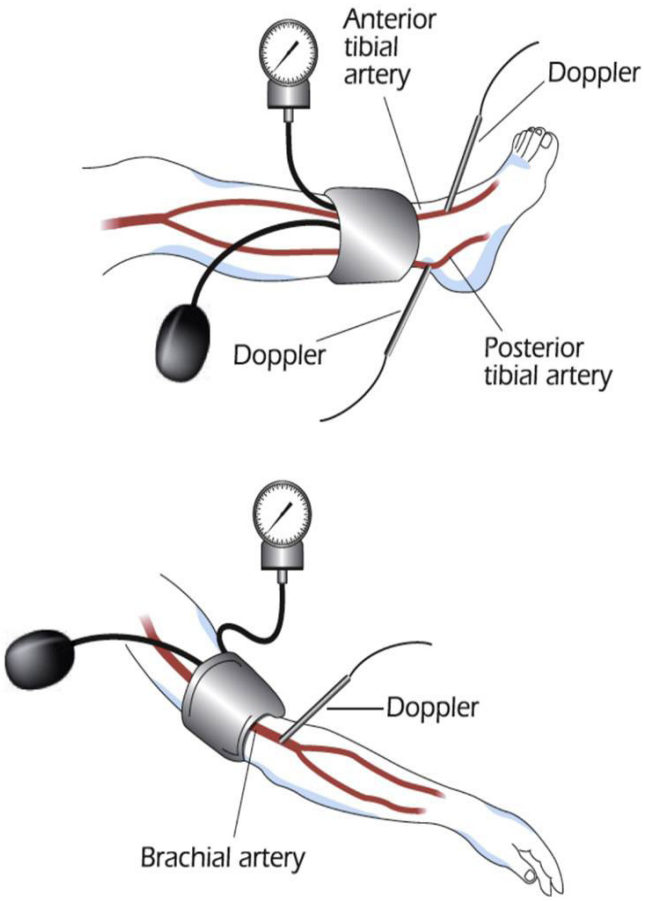

Figure 5: ABI measurement.

- ABI > 0.91 is considered normal. If there is claudication and resting ABI is normal, exercise test should be done.
- ABI > 1.3 indicates serious calcification and is associated with DM and end-stage renal failure. Calcified vessels are not normally compressed, and pressure measurements are higher than normal. In order to obtain more reliable results, additional tests such as transcutaneous O2 measurement, toe-brachial index, pulse volume records are required.
- ABI ≤ 0.90 is diagnostic in terms of occlusive arterial disease in symptomatic patients.
- ABI < 0.40 indicates critical ischemia and may be associated with rest pain, non-healing ulcers and gangrene.

Toe-brachial index

- It is a more reliable indicator of limb perfusion in patients with diabetes because small vessels in the toes are often protected from medial calcification.
- TBI is obtained by placing a pneumatic minicuff around the great toe.
- A photoplethysmographic or doppler flow detector is then used to evaluate the flow at the fingertip.
- The ratio of finger systolic pressure to highest systolic blood pressure measured from both brachial regions gives TBI.
- TBI of 0.7-0.8 is considered normal. Absolute finger pressure should be > 30 mmHg for wound healing, while it should be > 45-55 mmHg in diabetic patients.

Exercise test

- It is commonly used to confirm the diagnosis of lower extremity PAD in patients with claudication and normal resting ABI values.
- No change or a slight increase in ABI compared with baseline is interpreted as a normal exercise test.
- If the patient is symptomatic and there is no reduction in ankle pressure to explain symptoms, arterial obstruction should be excluded and other causes should be investigated.
- The exercise test is considered abnormal if there is a fall in the ankle systolic pressure by 20% more than the baseline, or a decrease below 60 mmHg, which takes longer than 3 minutes to recover.
- A failure to complete the exercise test due to symptoms and a fall in the ankle systolic pressure below 50 mmHg after exercise is defined as serious claudication.

$TcPO_2$

- It is used to assess local tissue perfusion, the healing potential of lower limb ulcers or amputation sites.
- A value of 60 mmHg at the foot level is considered normal.
- The factors limiting the accuracy of the test include tissue edema, skin temperature, emotional state (sympathetic vasoconstriction), inflammation and pharmacological agents.
- In the absence of diabetes and tissue edema, wounds are likely to heal if TcPO2 >40 mmHg.
- Values below 20 mmHg indicate severe ischemia and revascularization is required for wound healing.
- In addition, there are non-invasive tests such as segmental pressure measurements, doppler flowmetry, skin perfusion pressure measurement and plethysmography that are not routinely used by many clinics.

B. Imaging tests

Duplex ultrasound (DUS)

In patients with suspected occlusive arterial disease, non-invasive vascular assessment should be considered after the first physical examination. DUS comes first. It provides extensive information about arterial anatomy and hemodynamics. It provides segmental pressure recordings of lower extremities and malleolar artery flow measurement. It should be combined with ABI measurements. It has a 85-90% sensitivity and >95% specificity in detecting >50% stenoses. However, it is operator dependent and requires good training. It can not be used as a road map for the entire vascular structure. Other imaging tests are required when revascularization is planned. In addition, the preferred method for routine follow-up after revascularization is DUS [27,28].

Computed tomography angiography (CTA) and magnetic resonance angiography (MRA)

CTA and MRA are increasingly used for diagnostic and surgical planning. With multislice CTA, both excellent 3D images and information about the characteristics of the plaque are obtained. However, there are disadvantages such as high doses of contrast agents and radiation exposure. Patients with renal insufficiency carry a risk of contrast-associated nephropathy. MRA also provides 3D images, while its use is restricted in patients with metal implants and patients suffer claustrophobia [27,29].

DSA

It has been defined as the gold standard for detailed evaluation of arteries in patients with PAD. However, MRA and CTA are used instead of DSA owing to high sensitivity and specificity and non-invasive nature [30]. It is often used as a guide for percutaneous peripheral interventions or for the identification of patent arteries for distal bypass. In addition, since other imaging tests are insufficient in the determination of the ankle/pedal segments suitable for the distal bypass, it is preferred especially in patients with CLTI to evaluate the arteries below the knee. It carries a risk of complications such as contrast allergy, worsening of renal function, hemorrhage, pseudoaneurysm, A-V fistula, dissection and atheroemboli [27,28] CO_2 may be used as an alternative contrast agent in high-risk patients with reduced renal function.

Treatment

The aim

- Elimination of the pain
- Wound healing
- Protection of functional limb
- Improving the quality of life

A. Medical treatment

Smoking cessation

A lifetime smoker is 50% more likely to die from smoking, and the average lifespan is reduced by 10 years. In smokers, the 10-year risk of fatal cardiovascular disease nearly doubles. Relative risk < 50 years of age is five-fold higher in smokers than non-smokers. It has been shown that the risk of cardiovascular disease with smoking cessation reaches the risk of non-smokers within 10-15 years, but is never equalized. Patients should be absolutely motivated for smoking cessation. Smoking cessation programs should be initiated during the first admission to the hospital and should be continued for a long time after discharge. Drug therapies, such as nicotine replacement therapy, varenicline or bupropion, should be considered if motivational methods fail [31].

Diet and exercise

There is evidence that they affect the progression of atherosclerosis. Diets with high amounts of carbohydrates and saturated fats are associated with an increased risk of cardiovascular events. A decrease in plaque burden and cardiovascular events is observed with a diet that reduces the intake of saturated fats and increases omega-3 fatty acids and antioxidants. Patients should be encouraged to a low-fat or Mediterranean diet [26]. The aim of PAD treatment is to prevent cardiovascular events and improve the functional capacity of the lower limbs. Exercise therapy should be considered for all PAD patients and should be applied patient-specific. Supervised exercise sessions improve walking ability. Home-based exercise programs are an effective alternative for patients who are reluctant or unable to attend

supervised exercise sessions. Effective exercise programs suggest walking to near maximal pain, while evidence suggests that walking to the onset of ischemic leg pain is also beneficial [32].

Antihyperlipidemic therapy

Despite remarkable evidence and guideline recommendations, patient with PAD receive inadequate medical treatment and are less likely to receive statin therapy than patients with CAD. Especially in symptomatic PAD, high-dose statin therapy is recommended and reported to be associated with better survival and less major adverse cardiovascular events than low-dose statin therapy [33]. In the REACH study, which reported a 18% reduction in adverse outcomes including worsening of symptoms, peripheral revascularization and ischemic amputation, statin therapy not only reduced the risk of adverse cardiovascular events but also positively affected the prognosis of the extremity in PAD [34]. In addition, by giving statin therapy preoperatively and postoperatively, better limb results are obtained at the end of first year after endovascular or surgical procedures [35,36]. In all patients with PAD, serum LDL cholesterol levels should be <70 mg / dL (<1.8 mmol / L) or 50% if the baseline is between 70-135 mg / dL (1.8-3.5 mmol / L) [28] Statins are recommended for all patients regardless of their lipid levels. The maximum tolerated statin dose is the most reasonable option [37].

Antihypertensive treatment

Reducing systolic blood pressure leads to a decrease in cardiovascular events. In combination of PAD and HT, blood pressure should be <140/90 mmHg. Salt intake should be restricted and lifestyle should be regulated. Diuretics, beta blockers, ACE (angiotensin-converting enzyme) inhibitors and ARBs (angiotensin receptor blockers) can be administered in both monotherapy and combination. ACE inhibitors and ARBs can be preferred as first-line treatment in hypertensive patients due to their potential for peripheral arterial dilation [28].

Antidiabetic therapy

DM is an important risk factor for cardiovascular disease and PAD. The degree of vascular disease is associated with the duration and degree of hyperglycemia. Each 1% increase in glycolyzed hemoglobin (HbA1c) has been associated with a 28% increase in PAD incidence, regardless of other risk factors. Poor glycemic control correlates with decreased arterial patency rates and an increased risk of major adverse extremity outcomes. Therefore, strict glycemic control is required in all diabetic patients with PAD and glycemic goals must be personalized. In patients without high risk of hypoglycemia, the target HbA1c should be below 7.0%. Metformin is considered the best starting oral hypoglycemic agent [26,31,37].

Antiplatelet and anticoagulant therapy

Antiplatelet agents are used to prevent limb-related and general cardiovascular events. There are numerous antiplatelet treatment strategies, single, double and triple, and numerous studies investigating their superiority. There is no proven benefit of antiplatelet therapy in asymptomatic PAD. In symptomatic PAD, aspirin is known to significantly reduce the development of major cardiovascular events, and clopidogrel is superior to decreasing major cardiovascular events and cardiovascular mortality than aspirin [38,39]. It has been observed that there is a significant improvement in the prosthetic graft patency with aspirin after surgery [40]. However, in patients undergoing surgery, bilateral antiplatelet therapy has not been shown to have a significant advantage, and bleeding complications have been increased [41]. After endovascular interventions, regardless of stent type, bilateral antiplatelet therapy is recommended for at least 1 month (**Figure 6**).

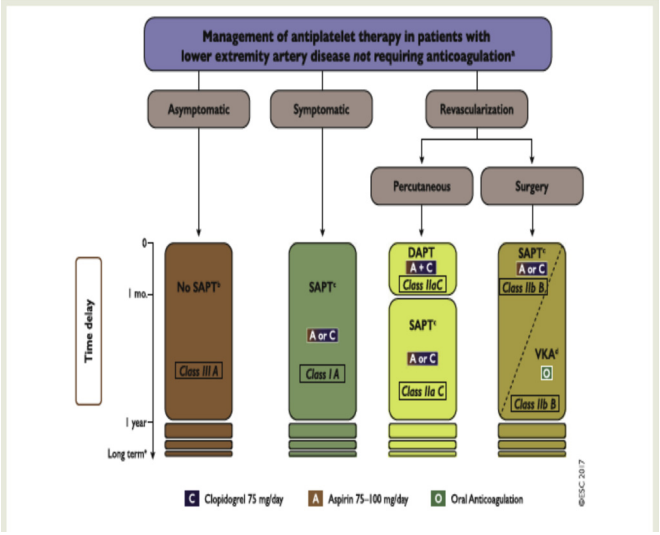

Figure 6: Antiplatelet treatment recommendations in lower limb PAD [28].

Antiplatelet therapy in patients with lower extreme artery disease. DAPT: Dual Antiplatelet Therapy: SAPT: Singlr Antiplatelet Therapy: VKA: Vitamin K Antagonist.

[a]e.g. concomitant AF or mechanical valve prosthesis.

[b]SAPT Should be considered if there is another concomitant atherosclerotic disease (e.g. coronory artery disease).

[c]DAPT may be considered in patients with recent acute coronary syndrome and/or precutaneous coronary intervention (<1 year).

[d]Evidence is week and bleeding doubles as compared to SAPT.

[e]Stands for as long as it is well tolerated.

In cases where long-term Oral Anticoagulants (OAC) are required, such as mechanical valve prosthesis or atrial fibrillation, OACs can be used alone. In these patients, single antiplatelet therapy (aspirin or clopidogrel) can be added to the treatment after endovascular interventions for at least 1 month if the risk of bleeding is low. The duration of treatment can be extended in patients with high ischemic risk (**Figure 7**).

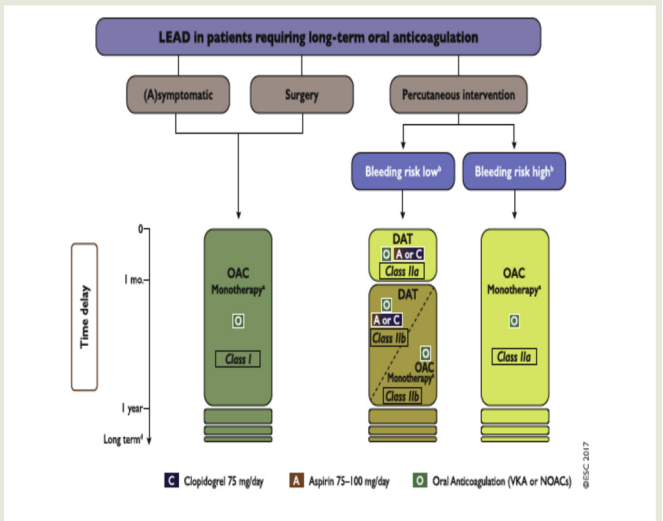

Figure 7: Antithrombotic treatment recommendations for PAD patients using OAC [28].

Antithrombotic therapy in patients with LEAD requiring oral anticoagulation. ACS: Acute Coronary Syndrome; CAD: Coronary Artery Disease; CLTI: Chronic Limb-threatening ischaemia; DAT: Dual Antithrombotic Therapy; LEAD: Lower Extremity artery Disease; NOACs: Non-vitamin K Oral Anticoagulants; OAC: Oral Anticoagulants; VKA: Vitamin K Antagonist.

[a]DAT may be considered in high ischaemic rick patients defined as prior stent thrombosis, acute limb ischaemia on OAC and concomitant CAD (recent ACS, stenting of the last patent coronary artery. multiple coronary vessel diseases in diabetic patients which incomplete revascularization).

[b]compared to the risk for stroke/CLTI due to stent/graft ocdusion.

[c]Stands for as long as it is well tolerated.

B. Revascularization

- In patients with infrapopliteal occlusive PAD, especially with CLTI, revascularization should be preferred in all functional patients. Regardless of the technique, modification of risk factors is important in the success of revascularization.
- Estimation of the operational risk and life expectancy has a critical role before revascularization. In risk classification models, while markers include advanced age (> 75-80), chronic kidney disease, coronary artery disease, congestive heart failure, DM, smoking, cerebrovascular disease, tissue loss, body mass index, dementia, and functional status, endpoints are defined as all-cause mortality, major amputation,amputation free survival, and perioperative events. However, a specific model is not recommended for evaluation.
- Urgent surgical debridement, including minor amputations and antibiotic therapy should be initiated in all suspected CLTI patients presenting with deep foot infection or wet gangrene. Limb staging should be repeated before the next important treatment decision [26].
- The anatomic pattern and severity of occlusive disease, the patient's functional status and medical comorbidities help define the most appropriate strategy for revascularization.
- In all CLTI patients who are candidates for limb salvage, the severity of the disease must be determined by clinical staging. Thus, estimation of benefit from revascularization becomes easier (**Figure 8**). For this purpose, current guidelines recommend WIFI classification, in which wound, ischemia and foot infection are evaluated.

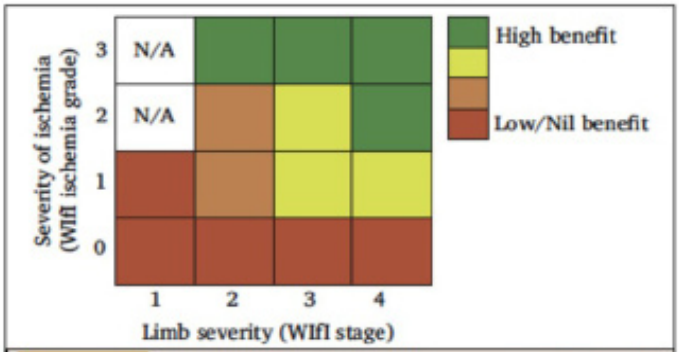

Figure 8: The effect of ischemia severity and the clinical stage on the benefit of revascularization [26].

The benefit of performimg revascularization in chronic limb-threatening ischemia (CLTI) increase with degree of ischemia [WIFI] stage). Wifi stage 1 limbs do not have advanced ischemia grades, denoted as applicable (N/A)

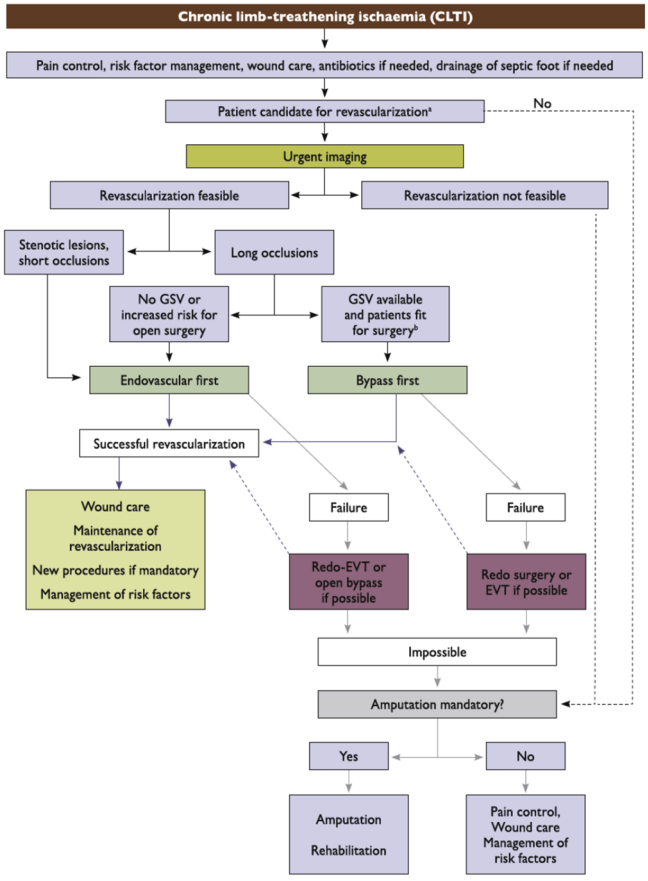

Figure 9: Management of critical limb ischemia [28].

a. In bedridden demented and/or frail patients, primary amputation should be considered.

b. In the absence of contra-indication for surgery and in the presence of adequate target for anastomosis/runoff.

Criteria for intervention

- The patient has symptoms that restricts his/her daily activities
- Inadequate response to exercise rehabilitation and pharmacological treatment
- If there is a vascular lesion that allows low-risk appropriate intervention with high probability of success in the early and late periods
- Providing symptomatic improvement

In recent years, there has been an increase in the number of patients undergoing endovascular interventions as the first step therapy due to continuous improvements in endovascular treatment results associated with improvements in endovascular techniques and materials. As a result, surgical interventions have been used less frequently.

Some surgeons advocate that the endovascular intervention can be used as the first step therapy and an unsuccessful intervention does not negatively affect the surgical results. However, the others think that unsuccessful endovascular intervention adversely affects limb prognosis.

In the BASIL-1 (Bypass versus Angioplasty in Severe Ischemia of the Leg) trial, which is the only randomized controlled study in the literature, a comparison of surgery and endovascular intervention was made as a primary treatment. According to the mid-term results, it was stated that there was no significant difference in terms of amputation-free survival, mortality and quality of life, and both interventions could be applied. However, it was reported that wound complications, hospital stay and hospital costs at 12th month were higher in the surgical group in the short term, and the rate of re-intervention was higher in the angioplasty group. In addition, endovascular intervention has been proposed as the first step in patients with life expectancy of less than 1-2 years and severe comorbidities [42].

According to current literature information, it is not proper to say that the best option for infrapopliteal occlusive PAD is surgical or endovascular intervention. When deciding on these two interventions, which have their own advantages and disadvantages, making a patient-specific assessment is the best option.

In stenotic lesions and short occlusions, endovascular intervention may be considered as the first choice. In long occlusions in the crural arteries, bypass surgery with autologous vein has a better long-term patency rate. Endovascular intervention may be selected in patients with an unsuitable autologous vein or at high surgical risk [28].

In current guidelines, it has been stated that angiosome-targeted revascularization should be considered especially in patients with severe wounds in the tarsal and calcaneal regions (class 2, level of evidence C) [26].

Surgery

By bypass procedures to infrapopliteal arteries are more complex and difficult than suprapopliteal ones. Therefore, surgical experience gains importance.

The presence of autologous vein graft, especially the great saphenous vein (GSV), plays a key role in bypass surgery and should be considered when making a revascularization decision in patients with average risk (estimated periprocedural mortality < 5% and estimated 2-year survival > 50%).

Contraindications

- Limited functional capacity
- Unsuitable arterial anatomy
- Restrictive medical risk factor (unstable CAD)
- Limited life expectancy
- Advanced gangrene and impossible limb salvage

During preoperative evaluation, information is obtained about the diameter, length and patency of the autologous vein graft to be used by vein mapping.

Frequently the ipsilateral GSV is used and the vein diameter should be > 3 mm. Alternatively, the contralateral GSV, the small saphenous vein, and the arm veins including the basilic and cephalic veins, can be used. Although the first choice is autologous vein grafts in patients who are canditate for infrapopliteal bypass, polytetrafluoroethylene (PTFE) grafts which has lower primary patency rates than vein grafts can also be used in cases where the appropriate graft cannot be found and there is no option for endovascular intervention.

Infrapopliteal bypass may not always be done in accordance with the angiosome concept. In this case, the most important factor in the selection of distal anastomosis region is the vessel quality and the best vessel that provides foot flow should be preferred.

Complications

- Graft thrombosis
- Hematoma
- Wound infection

Endovascular interventions

Previously, endovascular interventions were performed for the iliac arteries or those with PAD at high surgical risk. However, the indications were expanded over time. Thanks to the technological advantages including special catheters and guide wires and with the increased experience, almost all lesions have reached an endovascularly treatable potential. However, the success of the intervention depends on the complexity of the disease.

Intervention techniques

Balloon angioplasty

Balloon dilation is the stretching of the media and adventitia layer with intimal fracture. Severe fibrotic or excessively calcified lesions are more resistant to balloon dilatation, and intimal dissection or residual lesions may occur. If the lesion restricts blood flow or if there is > 30% residual stenosis, stenting should be performed.

- Standard balloons
- Drug-coated balloons: Used to reduce intimal hyperplasia
- Cutting balloons: It has 3 or 4 microsurgery blades, making incisions instead of intimal fractures. Its main purpose is to reduce the need for stents.
- Focal pressure and cryoplasty balloons: They are designed to reduce stent use and intimal hyperplasia. They have no proven effects.

Stenting

It is used to provide lumen patency by preventing recoil and by tracking down intimal flaps after balloon angioplasty.

- Bare metal stents
- Drug coated stents

Atherectomy

It is used to prevent late complications of stenting such as restenosis and fracture in severe calcific lesions.

Infrapopliteal interventions are applied especially in CLTI patients with tissue loss. These patients often need simultaneous femoropopliteal revascularization.

Isolated infrapopliteal lesions are rarely seen, especially in patients with diabetic and chronic renal failure.

Standard balloon angioplasty is the first step endovascular approach for anatomically appropriate infrapopliteal lesions. Usually, long balloons are used with longer inflation times to

minimize the possibility of dissection and residual lesions and the need for stents. The superiority of atherectomy over standard balloon angioplasty has not been proven. Although there are drug-coated balloon applications following atherectomy, comparative data are insufficient to show their superiority. Small studies reported the short-term benefits of drug-coated balloons in short tibial lesions, but it is not correct to generalize this data to the all CLTI patient population. Drug-coated stents may be preferred as a rescuing intervention after technical complications or after failed standard balloon angioplasty in short, proximal infrapopliteal lesions [26].

-In patients with ulcers that do not heal despite infrapopliteal intervention, inframalleolar intervention may also be considered as an option.

Complications

- Vascular rupture
- Dissection
- Branch occlusion
- Early and late occlusion
- Distal embolization
- Hematoma / pseudoaneurysm / thrombosis at the access site
- Acute kidney failure

Results

Surgery

In patients with infrapopliteal disease, GSV patency rate is higher at 1 and 2 years compared to other interventions. (87% at 1st year and 78% at 2nd). Prosthetic graft results are significantly worse than vein grafts in terms of amputation and patency rates at 2 years and longer follow-up, and higher limb loss rates are present. The superiority of autologous vein grafts in surgical interventions has been clearly stated [43]. However, studies showing that better patency rates were obtained by using PTFE grafts with 'vein cuff' and 'distal cuff' techniques, supports that prosthetic grafts can be used as an alternative when appropriate autologous vein grafts cannot be found [44,45].

Endovascular interventions

In a metaanalysis involving 52 studies with simple balloon angioplasty for infrapopliteal lesions, it has been reported that primary patency rate was 63.1%, re-intervention rate was 18.2%, major amputation rate was 14.9%, and all-cause mortality rate was 15.1% after 1 year. When the procedural results were evaluated, 91% technical success, 5.6% flow-limiting dissection and 9.1% stent requirement were determined [46].

In a metaanalysis conducted by Ipema et al., simple balloon angioplasty and drug-coated balloon angioplasty were compared at 12 months in terms of limb salvage (95.7% vs 94%), survival (92.9% vs 89.8%), restenosis (62% vs 32.9%) target lesion revascularization (27.8% vs 14%) and amputation-free survival (88.7% vs 82.5%). No statistically significant difference was found for all results, and the superiority of drug-coated balloon angioplasty to simple balloon angioplasty in infrapopliteal lesions could not be demonstrated [47].

In Cochrane analysis, in which all balloon angioplasty plus stent applications were compared with balloon angioplasty alone, it was revealed that the stents showed an instant success rate in achieving lumen patency, the technical success rate was higher, but there are no superiority in terms of patency at the 6th month and major amputation at the 12th month [48].

Drug-eluting stents have a better patency rate than bare metal stents in infrapopliteal arteries at the end of 1 year. (73% vs 50%) However, at the end of the third year, this rate decreases significantly. (49% vs 10%) In addition, there is no statistically significant difference between other endovascular intervention techniques in terms of major amputation and mortality [43]. In another study, drug-coated stents in the infrapopliteal region have not an advantage in the long term, although they have superiority in the first year [49]. However, Spreen et al. reported that drug-coated stents had better patency rates in infrapopliteal lesions both in the short and long term [50,51].

Another metaanalysis comparing endovascular intervention techniques was noted that drug-coated balloons showed encouraging results in terms of primary patency for infrapopliteal lesions in critical limb ischemia, and it was emphasized that it would be better than other treatment methods for target lesion revascularization. It has also been stated that drug-coated stents may be more advantageous than other methods in terms of technical success and major amputation [52].

Atherectomy devices are mainly used with balloon angioplasty and stents in complex lesions. It has been shown that using with simple balloon angioplasty does not provide any advantage in primary patency rates, has similar or even higher procedure complication rates, and provide no changes in amputation rates in long-term follow-up [53,54]. Furthermore, there are studies showing that the success of the procedure increases when it is combined with other endovascular intervention techniques, especially in cases where calcific load is high [55,56].

Other treatment options

Although risk factor modification and revascularization are performed as an optimal treatment in many patients, revascularization is not anatomically favorable in some patient groups. Amputation is the only option for them but they may also benefit from non-revascularization treatment options.

Spinal cord stimulation

By placing electrodes in the lumbar epidural space, the sensory fibers are stimulated with the help of a generator.

Mechanism:

- Release of vasodilator molecules that trigger a decrease in vascular resistance and relaxation in smooth muscle cells
- Increase in capillary flow
- Increase in skin temperature and TcPO2
- The popliteal artery, which is the continuation of the superficial femoral artery, passes through the popliteal fossa and is divided into 2 branches, the Anterior Tibial Artery (ATA) and the Tibioperoneal Trunk (TPT), at the level of the distal end of the popliteal muscle. TPT continues as the Posterior Tibial Artery (PTA) and the Peroneal Artery (PA). ATA, proceeds as the DorsalisPedis Artery (DPA) in the dorsum of the foot (Figure 1).Suppression of sympathetic vasoconstriction and pain conduction. Compared with conservative treatment, although spinal cord stimulation decreases pain and amputation rates, long-

term success in patients with CLTI is controversial due to the marked increase in treatment costs and complications [57,58].

Lumbar sympathectomy

It is the denervation of the lumbar sympathetic ganglion by surgical excision, laparoscopic retroperitoneal or percutaneous chemical blockade. With decreased sympathetic tone, there is an increase in blood flow in the subcutaneous arteriovenous vascular network. Although it is preferred for reducing symptoms in patients who cannot undergo revascularization, it has no effect in terms of limb salvage [59].

Intermittent pneumatic compression

An increase in arterial blood flow and collateral circulation in the distal extremity is aimed by creating arteriovenous pressure gradient. There are studies that report a decrease in ischemic pain and amputation rates, and an increase in ulcer healing. Although there is no definitive recommendation in current peripheral artery treatment guidelines, it can be used for symptomatic improvement in selected patients [60].

Hyperbaric oxygen therapy

Especially in the presence of diabetic foot ulcer, it increases the amount of oxygen in ischemic tissue, but there is no significant effect on wound healing, except for a decrease in major amputation rates. No clear benefit has been shown in CLTI patients. Therefore, it is not recommended for limb rescue purposes in the presence of severe ischemia [26,61].

Stem cell and gene therapy

Although there are many data that demonstrate functional improvement with reduction in ischemic symptoms and amputation rates, more extensive researches are needed to prove their effectiveness.

Pharmacotherapy

Prostanoids: (prostaglandin-E1, prostocycline, iloprost)

Impact mechanisms:

- Inhibition of platelet and leukocyte activation
- Inhibition of adhesion and aggregation of platelets
- Antiproliferative effect on endothelial cells

Prostanoids used in the treatment of ischemic pain also have significant effects on wound healing. However, they do not have a significant effect in terms of major amputation risk. They also have side effects such as headache, facial redness, nausea, vomiting and diarrhea [62].

Pentoxfylline: Pentoxifylline, a phosphodiesterase inhibitor, has effects such as increased erythrocyte elasticity, decreased blood viscosity and increased microcirculation. Although it is used for the first time in the treatment of intermittent claudication, there is no proven data on its effectiveness in critical limb ischemia [63].

Cilostazol: It causes platelet inhibition and vasodilation by phosphodiesterase-3 inhibition.

It provides an increase in microvascular circulation and skin perfusion pressure in ischemic extremities. It provides an improvement in amputation-free survival rates when combined with endovascular intervention. Although it is recommended for intermittent claudication, it has no proven effect in KETI patients. The most common side effect, headache, develops due to vasodilation [26,63].

Naftidrofuryl: It inhibits serotonin receptors in the damaged vessel wall, causing an increase in vasodilation, platelet and erythrocyte aggregation. Although there are studies showing increased walking distance compared to pentoxifylline and cilostazol, its effectiveness in critical leg ischemia has not been demonstrated [63-65].

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