Consensus Document on Intermittent Claudication from the Central European Vascular Forum (C.E.V.F.) - 3rd revision (2013)

with the sharing of the Mediterranean League of Angiology and Vascular Surgery, and the North Africa and Middle East Chapter of International Union of Angiology

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This paper is the review of the Consensus Document on Intermittent Claudication of the Central European Vascular Forum (CEVF), published in 2008, and and shared with the North Africa and Middle East Chapter of International Union of Angiology and the Mediterranean League of Angiology and Vascular Surgery. The Document presents suggestions for general practitioners and vascular specialists for more precise and appropriate management of PAD, particularly of intermittent claudication, and underlines the investigations that should be required by GPs and what the GP should expect from the vascular specialist (angiologist, vascular surgeon). The idea of the Faculty is to produce a short document, which is an easy reference in daily clinical practice, both for the GPs and vascular specialists.

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The following text does not repeat the cultural background already expressed and discussed in the previous paper,[1] to which we refer also for references. The references given in this paper are only those in support of the new suggestions.

1. Classifications of peripheral arterial disease

The most well-known classifications of peripheral arterial disease (PAD) are those of Fontaine and Rutherford, both of which are equally valid.

Fontaine's classification identifies four stages: 1st, asymptomatic (asy-PAD); 2nd, claudication; 3rd, rest pain; 4th, skin wound and gangrene. The 2nd stage can be further subdivided into stages 2nd A and 2nd B, distinguishing the minor or major impairment in walking capacity.

Rutherford's classification could be considered as a modernization of the Fontaine scheme and was formulated 43 years later, based on new information concerning epidemiology, pathophysiology, possibility of revascularization and clinical results. Rutherford's classification divides PAD into 3 grades and 6 categories (Table I).

2. Asymptomatic PAD

The asy-PAD (Fontaine's 1st stage and Rutherford Grade 0 and category 0) indicates the asymptomatic presence of arterial lesions (calcifications, plaques). Patients with occasional symptoms (*e.g.* after exceptional physical stress), sometimes misclassified as 1st stage, should be considered as having 2nd stage.

Asy-PAD should be suspected in asymptomatic individuals for whom occasional changes in arterial walls are present (calcifications, isolated plaques), in all subjects over 70 years, in those aged 50 to 69 years with history of smoking or diabetes mellitus (DM), in individuals less than 50 years with DM and any one other atheroscle-

TABLE I.—*Classification of peripheral arterial disease according to Fontaine and Rutherford.*

Fontaine		Signs & symptoms		Pathophysiology		Rutherford Category
Stage	Clinic			Clinic	Grade	
1st	Asymptomatic	Fortuitous discovery of aortic & iliac calcifications	ATS plaque Risk plaque Inflammation of ATS plaque Atherothrombosis	Asymptomatic	0	0
2nd A	Mild claudication	ACD>200 m recovery T<2 min	Discrepancy between oxygen request and arterial supply	Mild claudication	I	1
2nd B	Moderate or severe claudication	ACD<200 m recovery T>2 min	Higher discrepancy between oxygen request and arterial supply	Moderate claudication	I	2
		ACD<100-80 m recovery T>2 min	Highest discrepancy between oxygen request and arterial supply and acidosis	Severe claudication	I	3
3rd	Ischemic rest pain	Rest pain	Severe skin hypoxia and acidosis	Ischemic rest pain	II	4
4th	Ulceration or gangrene	Necrosis	Severe skin hypoxia and acidosis Infection	Minor tissue loss	III	5
		Gangrene	Severe skin hypoxia and acidosis Infection	Major tissue loss	III	6

rosis risk factor (smoking, dyslipidemia, hypertension, or hyperhomocysteinemia) and in individuals with known atherosclerotic coronary, carotid, or renal artery disease.

Also subjects over 50 years with metabolic syndrome [2] should be investigated for Asy-PAD.

Any 3 of the following 5 criteria constitute diagnosis of metabolic syndrome:

— elevated waist circumference ≥94 cm (increased risk), ≥102 cm (high risk) in men;

— elevated waist circumference ≥80 cm (increased risk), ≥ 88 cm (high risk) in women;

— elevated triglycerides (≥150 mg/dL or 1.7 mmol/L or on drug treatment for elevated triglycerides);

— reduced HDL-C (≤ 40 mg/dL or 1.03 mmol/L in men, ≤50 mg/dL or 1.3 mmol/L in women or on drug treatment to reduce cholesterol);

— elevated blood pressure (≥130 mmHg systolic blood pressure or ≥85 mmHg diastolic blood pressure or on antihypertensive drug treatment in a patient with a history of hypertension);

— elevated fasting glucose (≥100 mg/dL or 5.56 mmol/L) or type 2 DM, or on drug treatment for elevated glucose.

Asy-PAD is diagnosed by measurement of the Ankle-Brachial Index (ABI), at rest and after exercise; an ABI<0.9 is considered indicative of PAD.

Additional diagnostic tests, such as those carried out for 2nd stage [color flow duplex sonography (CFDS) of supra-aortic arteries (SAoA), abdominal aorta and cardiac examination] may be useful, even if not expressively indicated.

If the diagnosis is confirmed, it is advisable to proceed with the identification and correction of other risk factors. The prescription of antiplatelet therapy, at the moment is controversial.

In cases that the diagnosis of Asy-PAD is not confirmed, a follow-up visit is recommended after 2-3 years in the presence of risk factors.

3. Mild claudication

Mild claudication is defined as the appearance of muscular cramps of the lower limbs (buttock, thigh, calf) climbing more than two flights of stairs, or walking more than 200 m. It is very important that the general practitioner (GP) verifies if the same symptoms are always present following similar exercise.

In patients with mild claudication, it is necessary to further assess local symptoms and determine the presence of vascular lesions at sites other than the arterial trunk of the legs, due to the well-known overlapping of atherosclerotic lesions.

3.1 Appropriate investigations in mild claudication

The following diagnostic investigations are indicated:

— measurement of the ABI. If the ABI is non-diagnostic, with discrepancy between clinical findings and ABI value, it should be repeated after exertion;

— CFDS of the supra-aortic arteries (SAoAs), as their involvement is present in 13-18% of patients with PAD;

— CFDS of the abdominal aorta, as aortic abdominal aneurism (AAA) is present in about 5-10% of patients with PAD. Moreover, non-stenosing lesions of the abdominal aorta may be responsible for severe cutaneous ischemia of the lower limbs (blue toe syndrome, athero-embolism, etc.);

— cardiological investigations (ECG, echocardiogram) should always be performed in patients with IC, as coronary involvement is present at least in one third of patients with PAD. If patients with PAD complain also of symptoms evoking coronary artery disease (CAD), handgrip or echo stress test, dipyridamole thallium scintigraphy and, when indicated, coronary angiography should be performed in view of possible coronary revascularization.

A CFDS of the lower limbs is usually not required to manage mild claudication, nevertheless, especially in young claudicant patients, it may be advised to better define the anatomy and functionality of the arteriopathy.

3.2 Management of mild claudication

The goals of the management of mild claudication are the following:

— to prevent major cardiovascular events (fatal and non-fatal);

— to slow the progression of local and/or systemic disease;

— to improve walking capacity.

Such objectives can be realized only by drastic modifications in lifestyle (first and foremost stop smoking), correction of risk factors and specific pharmacological treatment.

3.2.1 Lifestyle modifications

First and foremost it is necessary to stop smoking and avoid the use of tobacco in any form. Regular physical activity, walking at least thirty minutes a day at a steady pace, it is strongly recommended, along with a low caloric intake diet.

3.2.2 Correction of risk factors

Diabetes mellitus. Fasting blood glucose levels should be reduced to 80-120 mg/dL (4.44-6.66 mmol/L), while after meals should be <180 mg/dL (9.99 mmol/L), and glycosylated hemoglobin values <6.5% of total hemoglobin. In these patients, particular attention should be given to the care of feet in order to reduce the risk of infection, avoiding the worsening of the ischemic disease.

Hypertension. Blood pressure should be well controlled using angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or calcium antagonists, by maintaining systolic values less than 140 mmHg. Diastolic values should be always <90 mmHg, except in diabetic patients, in whom values <85 mmHg are recommended.[3, 4]

Hypercholesterolemia. It should be treated in an aggressive manner, according with the assessment of cardiovascular (CV) risk. Treatment must also include adequate dietary considerations and, if necessary, pharmacological intervention with statins in order to reduce the values of cholesterol-LDL (C-LDL) <70 mg/dL (1.8 mmol/L).

In patients at very high CV risk, when the target level cannot be reached, it is recommended, at least, a ≥50% reduction. High-risk individuals can be detected on the basis of established CV diseases, diabetes mellitus, moderate to severe renal disease, very high levels of individual risk factors or a high score risk.[5]

Statins also reduce non-fatal cerebro- and cardiovascular events and mortality, independently of the cholesterol-lowering effect. This activity is due to the pleiotropic effects of these drugs, with anti-inflammatory effects and stabilization of the atherosclerotic plaque.[6, 7]

Kidney function should be monitored because chronic renal insufficiency is independently associated with PAD and future PAD events.[8]

3.2.3 Drugs in mild claudication

All patients with mild IC should take aspirin (100-300 mg o.d.) or other antiplatelet therapy, as ticlopidine (250-500 mg o.d.) or clopidogrel

(75 mg o.d). In PAD patients with type 2 DM, platelets have been shown to be hyper-reactive, with increased production of thromboxane A2. In these patients, aspirin or clopidogrel resistance *ex vivo* is frequently found. In the very rare case of resistance to both drugs, picotamide, a dual inhibitor of TXA2 synthase and receptor antagonist, could be used, because it is effective and safe (loading dose 300 mg t.d.s. for 1-2 weeks; maintenance dose 300 mg o.d or b.d.)

TABLE II.—*Appropriateness of CFDS investigation of the supra-aortic arteries (SAoA) and frequency of control visits.*

CFDS of SAoA is indicated in the following Clinical Frameworks	
- Crescendo TIA 2 or more episodes attributable to TIA within 24 hours, or 3 episodes in 72 hours, with complete resolution of symptoms between episodes	Grade A hospital
- Symptoms suggestive of TIA in the carotid or vertebro-basilar areas started less than 7 days	emergency room
- Pulsatile laterocervical swelling	Grade C hospital emergency room (ask for thoracic CT)
- Symptoms suggestive of TIA and/or minor stroke, in the carotid or vertebro-basilar areas started more than 7 days	Grade A within 10 days
- Asymptomatic patients, candidates for major surgical intervention or coronary angiography (check list) - Neck bruits - Suspected subclavian steal syndrome	Grade A within 30 days
- Symptomatic patients, with symptoms started from more than 30 days	Grade C within 30 days
- Asymptomatic patients - Age >65 years with risk factors for atherosclerosis - Patients with previous stroke, previous myocardial infarction, atherosclerosis in other areas (coronary, peripheral arteries), abdominal aortic aneurism, retinal vascular occlusion, radiation neck therapy; - Patients with laterocervical or supraclavicular murmurs; - Follow-up after surgery or endovascular procedures of SAoA	Grade C within 180 days
Frequency of the control visit (degree of carotid stenosis assessed with ultrasound criteria)	
- Asymptomatic patient: age>65 years without risk factors for atherosclerosis and with CFDS of the SAoA negative at previous visit	After 5 years
- Carotid stenosis <20%	18 - 24 months (depending on risk factors control)
- Carotid stenosis 20-49%	1 year
- Carotid stenosis 20-49%, with echolucent plaque (I & II Lusby's type) or with very irregular surface (suggestive of ulcer)	6 months
- Carotid stenosis 50-69%	6 months
- Carotid stenosis 50-69%, with echolucent plaque (I & II Lusby's type) or with very irregular surface (suggestive of ulcer)	3-4 months
- Carotid stenosis >70%	Specialist consultation
- Carotid occlusion, with normal contralateral carotid	1 year
- Carotid occlusion, with stenosis of contralateral carotid	According to severity of stenosis
- Carotid plaque, after previous surgery or endovascular procedures	According to severity of stenosis
- Follow-up after surgery or endovascular procedures of SAoA	1st control within 3 months 2nd control within 9 months successively: every 12 months

The disability associated with mild claudication generally allows an acceptable quality of life for most patients and often the correction of risk factors is sufficient to improve walking capacity.

Whenever specific needs exist, additional interventions (drugs and physical activity) can be performed in order to improve the walking distance and quality of life as described below.

3.4 Follow-up of patients with mild claudication

Patients with mild claudication having stable functional and anatomic parameters after two successive control visits should be re-evaluated annually by measurements of ABI and walking ability (6 minutes walking test). In case of worsening of these parameters and clinical features, CFDS of lower limb's arteries is indicated.

TABLE III.—*Appropriateness of CFDS investigation of the abdominal aorta and frequency of control visits.*

CFDS of abdominal aorta is indicated in the following clinical frameworks	
- Age >50 years with family history of AAA - presence of arterial disease in other districts - occult discovery of aortic calcifications - Age >65 years (males) - Age >50 years with risk factors	Within 180 days
- Iliac Doppler signal indicative of upstream hemodynamic stenosis - Blue toe syndrome	Within 30 days
- Bilateral absence of femoral pulse (suspect ascending aortic thrombosis) - pulsatile abdominal mass	Within 10 days
In case of confirmed AAA, follow indication for management, or refer patient for specialist consultation	Specialist consulting
- Abdominal pain	Hospital emergency room
in the presence of pulsatile mass	Hospital emergency room
in the presence of known AAA	Call emergency intervention
Frequency of control visits and management	
- diameter between 30 and 39 mm	12 months
- >40 mm	6 months
- >55 mm (if diameter of the proximal normal aorta is <2 cm we suggest to use the ratio: AAA / not aneurysmatic aorta)	Angio-CT, angio-MRI (intervention)
- >40 mm with accelerated growth: 10 mm/year or 7 mm/6 months	Angio-CT, angio-MRI (intervention)
Asymptomatic patients without risk factors and negative previous CFDS	Follow-up not indicated
Asymptomatic patients with risk factors and negative previous CFDS	3 year 5 years after 2nd negative CFDS
Ratio: AAA / not aneurysmatic >2.0	6 months
Ratio: AAA / not aneurysmatic >2.5	Angio-CT, angio-MRI (intervention)

Regarding the periodic examination control of the SAoA and the abdominal aorta, the recommended follow-up times are detailed in Tables II, III.

If the clinical picture has changed, with a sudden reduction in walking capacity or the appearance of cyanosis and rest pain (even if intermittent) the patient should undergo specialist evaluation at least within 10 days.

4. Moderate claudication

Moderate claudication is defined as the appearance of muscular cramps of the lower limbs (buttock, thigh, calf) climbing less than two flights of stairs, or walking less than 200 m.

The cardiovascular mortality and morbidity outcomes do not differ from those of mild claudication, but the PAD outcome is different, with a 6-10% risk of progression to severe claudication in 12-18 months.

4.1 Appropriate investigations in moderate claudication

The same diagnostic procedures as in mild claudication are indicated, with a few differences, regarding the measurement of walking capacity and CFDS.

The measurement of walking capacity at least by 6 MWT (6 minutes of walking test, test of spontaneous walking capacity measurement) is strongly recommended,[1] because it is the more reliable indicator of the ambulatory disability, very useful for prescribing or not a revascularization procedure and for organizing a supervised physical training program, as well as for the follow-up of PAD.

The CFDS of the lower limbs, assessing the anatomy and hemodynamics of the arterial tree, will determine possible indications for endovascular revascularization. The investigation should be extended to all the arterial axis of the limb, up to the metatarsal arteries, with detailed description of the arterial lesions (site, length and extension of stenosis or obstruction), and effectiveness of collateral vessels, and distal run-off.

4.2 Management of moderate claudication

Correction of lifestyle and risk factors, as well as pharmacological therapy is similar to those indicated for mild claudication. These treatments should be associated with physical exercise and drugs that improve walking capacity.

4.2.1 Physical training

In moderate claudication, the clinical advice to perform regular physical activity must become a real therapeutic prescription, with the specific indication of intensity and duration.[1, 9]

4.2.1a Supervised Protocol

Day 0 (the day before starting a physical training program).

1) Warm-up 10 min on bicycle exercise, without load;

2) Maximal treadmill (diagnostic) test: constant load (speed: 3.2 km/h; slope: 12-15%); parameters: ICD, ACD, recovery time (RT);

3) Assessment of walking capacity: 1 h after maximal treadmill test, submaximal treadmill (speed: 1.5 km/h; slope: 6±2%) or spontaneous walking without slope, measuring the absolute walking capacity; the same settings will be used for training session.

Day 1-8.

1) Warm-up 10 min on bicycle exercise without load;

2) single training session: patient walks until 60-70% of measured walking capacity (sub maximal test);

3) resting and restore period: standing or sitting for 1 min or until the patient can restart the walking (indicative setting could be a period equal to RT measured during the maximal treadmill test);

4) daily training session: exercise-rest-exercise pattern should be repeated, reaching the 1-2 km of walk, or at least 30 min of effective walking time;

5) cool-down: sitting rest until the normalization of all cardiovascular parameters.

Day 9.

1) New assessment of walking capacity: submaximal treadmill test or spontaneous walking without slope (same settings utilized on day 0);

2) recalculation of single exercise load: patient walks until 60-70% of new walking performance (incremental protocol of the training program);

3) resting and restore period as well as daily training session remain unchanged.

At 6 weeks.

Maximal treadmill test to assess the new initial claudication distance (ICD), absolute claudication distance (ACD), recovery time (RT).

4.2.1b Home program (advised protocol)

The patient is advised to continue a daily regular physical activity, following the style utilized during the supervised period.

Every month the maximal walking capacity should be verified by the patient himself, who should be referred to the specialist if the walking capacity has worsened.

4.2.2 Alternative Methods to improve walking ability

Although physical training is universally recognized as the most efficacious means for improving the walking capacity in claudicant patients, the use of this modality in clinical practice remains limited, because of the small number of centers dedicated to vascular rehabilitation, their long distance from the residence of the patients, and the frequent co-morbidity (osteoarthritic, cardiac and respiratory diseases) that do not allow for effective exercise. In these cases, valid alternative methods may be adopted, as pharmacological intravenous infusion,[10] and some physical tools. Among these are encouraged intermittent pneumatic compression (IPC) and transcutaneous electrical stimulation.

The IPC device (ArterialAssist®) incorporates a foot, ankle and calf cuff that is inflated with a frequency of 3 impulses/min up to a pressure of 120-140 mmHg. The pressure rises within about 0.3 seconds and holds for 3 seconds while the delay between the inflation of the foot/ankle and calf is 1 second. During deflation the pressure in the device returns to 10 mmHg, for 17 seconds. The recommended duration of treatment is 3 hours per day or more, for a minimum of 3 months. All studies in claudicants demonstrated a significant improvement of both ICD and ACD.[11-13] IPC may also be indicated when revascularization is not indicated and in critical leg ischemia.[14]

The frequency rhythmic electrical modulation system (FREMS™) stimulation is a transcutaneous electrical stimulation characterized by impulses variable in frequency and duration. It has been used especially in the treatment of diabetic neuropathy, with significant improvement on pain control and the speed of nerve conduction. In patients with intermittent claudication (IC) the FREMS™ has shown a significant improvement of ICD, and qualitative improvement of microcirculation, miming the effects of exercise, while the effect on the ACD was not significant. However, when it was applied in addition to a protocol of supervised physical training, it was able to enhance the effectiveness on both the ICD and ACD in comparison to the control group. However, the results on ICD remain more significant.[15]

4.2.3 Drugs improving walking ability

The drugs that are supported by adequate scientific evidence for their beneficial effects and are currently recommended for improving the walking capacity appear below:

a) *Cilostazol*, an inhibitor of type III phosphodiesterase, with vasodilative and antiplatelet activity;

b) *Naftidrofuryl*, a serotonin receptor antagonist, which improves aerobic metabolism in hypoxic tissues;

c) *Pentoxifylline*, a methylxanthine derivative, which improves anomalous erythrocyte deformability and reduces the levels of fibrinogen and platelet aggregation. It improves the symptoms of claudication in about 20% of patients within 6 months of treatment. The recent guidelines indicate for this drug a marginal role in claudicants, but it remains utilized by many doctors.

d) *L-propionyl-carnitine* (LPC), a metabolic drug with beneficial effects on the walking capacity in patients with IC by favoring the clearance of excess acetylcarnitine which is present in patients with reduced muscular performance, and by providing additional energy to ischemic muscles. This drug, when administered by intravenous infusion (600 mg/day) during training programs, enhances the effectiveness of exercise, especially in moderate and severe claudication.[10] It is recommended as an alternative to training in patients in whom exercise is not feasible for any reason.

In addition, for some drugs used in the correction of risk factors, such as statins [16, 17] (atorvastatin [18, 19] and simvastatin [20]) and ramipril,[21-23] has been demonstrated that there is an increase

in the walking capacity, due to their pleiotropic effect.

4.3 Follow-up of patients with moderate claudication

Patients with moderate claudication having stable functional and anatomic parameters after two successive control visits should be followed every six months by measurements of ABI and walking ability (6 MWT).

The follow-up of these patients requires greater attention regarding the possible appearance of symptoms and signs indicating progression of the disease. In this light it is important to take into consideration the ABI<0.5, glycated hemoglobin >8 mg% in diabetic patients, persistence of risk factors (especially smoking), heart failure, chronic renal insufficiency.

In case of evolutive clinical features (reduction of walking ability, onset of intermittent cyanosis and/or rest pain) it is advisable to refer the patient to a vascular specialist (VS), within a maximum of 30 days. In case of development of claudication at few steps, the patient should be referred immediately to the vascular unit or to the emergency room.

4.3.1 PAD and cancer

In the past decade an association between atherosclerosis and cancer, due to common cellular and molecular pathways (genetic predisposition, oxidative stress, diet, and risk factors, smoking, mutagens, cell proliferation), has been reported.[24,25] In a sudden and unreasoned clinical worsening of PAD in patients with best medical treatment who have achieved their therapeutic targets, the suspicion of an occult malignancy should be considered, although current evidence do not allow any recommendation in this regard.

In addition, cancer and chemotherapy may predispose patients to acute arterial ischemia. However, until now, this event, which was considered as a manifestation of pre-terminal cancer, seems to benefit from revascularization procedures, in terms of limb salvage and survival of the patient.[26]

5. Severe claudication

Severe claudication is defined as the presence of typical symptoms of IC that occur when climbing less than one flight of stairs or walking less than 100 m. It is associated with a 3-year mortality rate of 20%, and a very high risk of local limb worsening. Forty per cent of cases progress to critical limb ischemia (CLI) in 6-18 months and 35% require major amputation within 24 months. Due to the high risk of progression in CLI and systemic cardiovascular risk, severe claudication requires important and urgent diagnostic procedures.[27, 28]

In current clinical practice, severe claudication is often referred to as disabling claudication. Using these terms as synonymous is a semantic error, which should be avoided. Severe claudication indicates an objective group of claudicant patients with a well-defined walking capacity. Instead the term of disabling claudication indicates a subjective feature, a claudication that impacts the daily living activities. A 150 m ACD can provide a satisfactory quality of life for patients over 70 years old, but can be considered incapacitating for people 50 years old, with different personal and professional requirements. As this status could represent a priority indication for revascularization, the diagnosis of disabling claudication must be carried out objectively by measuring the deterioration of the quality of life.

5.1 Appropriate investigations in severe claudication

The main diagnostic target is to determine the critical levels of limb perfusion (ankle pressure ≤60 mmHg, $TcPO_2$≤40-35 mmHg, occlusion of one or two arteries of the leg). The main investigation methods are the extensive and detailed CFDS of lower limbs, angiography magnetic resonance imaging (angio-MRI), angiography computerized tomography (angio-CT), angiography and the $TcPO_2$ (transcutaneous partial pressure of oxygen; transcutaneous oxygen; transcutaneous oximetry). The measurement of walking ability is also relevant. CFDS of the SAoA and abdominal aorta as well as cardiac investigations must always be considered.

The priority of performing various procedures

cannot be predetermined because it depends on anatomical and clinical characteristics of the framework and the available resources.

For these reasons, it is recommended that the patient with severe claudication, such as the one with critical ischemia, is investigated at a vascular center, able to implement in a short time all the diagnostic and therapeutic procedures needed. The GP is invited to refer the patient to his/her own specialized units of reference (for details on the investigation tests, see § 8).

5.2 Management of severe claudication

Once a complete clinical and laboratory evaluation has confirmed the critical and progressive worsening of perfusion, the first option to consider is revascularization, taking into account all the possible procedures (endovascular, open surgery, hybrid), especially in case of stenotic or isolated lesions in arteries that do not cross arthroses. When revascularization is not indicated (multiple and extended hemodynamic lesions, relevant co-morbidities), conservative treatment requires the prescription of a personalized program of physical training, and drug treatment using drugs that are already indicated for moderate claudication.

5.3 Follow-up of patients with severe claudication

Patients with severe claudication not submitted to revascularization should be checked every three months (from GPs or vascular specialists) by measurement of ABI and assessment of their walking capacity. The check-up can be repeated every six months in case of clinical improvement confirmed by two subsequent visits with stable parameters.

During intervals, the patients remain entrusted to their GP, who will have to monitor carefully the clinical framework and the effectiveness of aggressive treatment of risk factors.

In case of progression of the clinical picture, with sudden reduction of walking capacity, onset of cyanosis and/or rest pain (even intermittent), it is advisable to refer urgently (within 10 days) the patient to a specialized center.

If the reduction of walking capacity is within the framework of *restricted claudication* (claudication after a few steps), it is advisable to refer the patient immediately to the reference vascular center or the emergency room.

As for the periodic inspection of the SAoA and the abdominal aorta, it is advisable to follow the directions provided for these anatomical areas (Tables II, III).

6. Diabetic PAD

Tha PAD is also one of the most frequent manifestations of diabetic macroangiopathy, which reduces the male/female ratio from 3:1 to 2:1 found in PAD without diabetes, and often even more to 1:1.

Diabetic PAD shows some peculiar epidemiological, anatomical and clinical characteristics, which makes it different from the atherosclerotic PAD.[29]

Epidemiology: in diabetic patients the appearance of PAD occurs a decade earlier than in non-diabetic patients.

Anatomy: diabetic PAD affects the medium and small-diameter arteries (distal part of the superficial femoral artery, popliteal and below the knee arteries), with a relative minor aorto-iliac involvement compared with non diabetic PAD, showing also a greater tendency to calcification in the tunica media. Furthermore, the frequently found lesions in the deep femoral arteries diminish the capability for collateralization**.**

Clinical status: there are differences in the clinical features regarding signs and symptoms. Diabetic PAD remains for years as asymptomatic. The claudication has a lower prevalence compared to non-diabetic, as a result of the high pain-threshold and of the sedentary lifestyle, typical in the majority of diabetics. When present, claudication does not manifest as pain, but as weakness of the diseased leg, causing disability for walking.

It is not unusual the first symptom of the PAD in the diabetic to be the appearance of skin ulceration due to thromboembolic events, macro and/or microcirculatory, that seem to arise from a clear sky, because of the lack of relevant IC.

The ischemic skin ulcerations in CLI, are very frequent in diabetic patients (about 60% of all patients with CLI) and the heavy outcome of the CLI mentioned in § 8, is even more severe in diabetic patients (co-existing neuropathy and ease

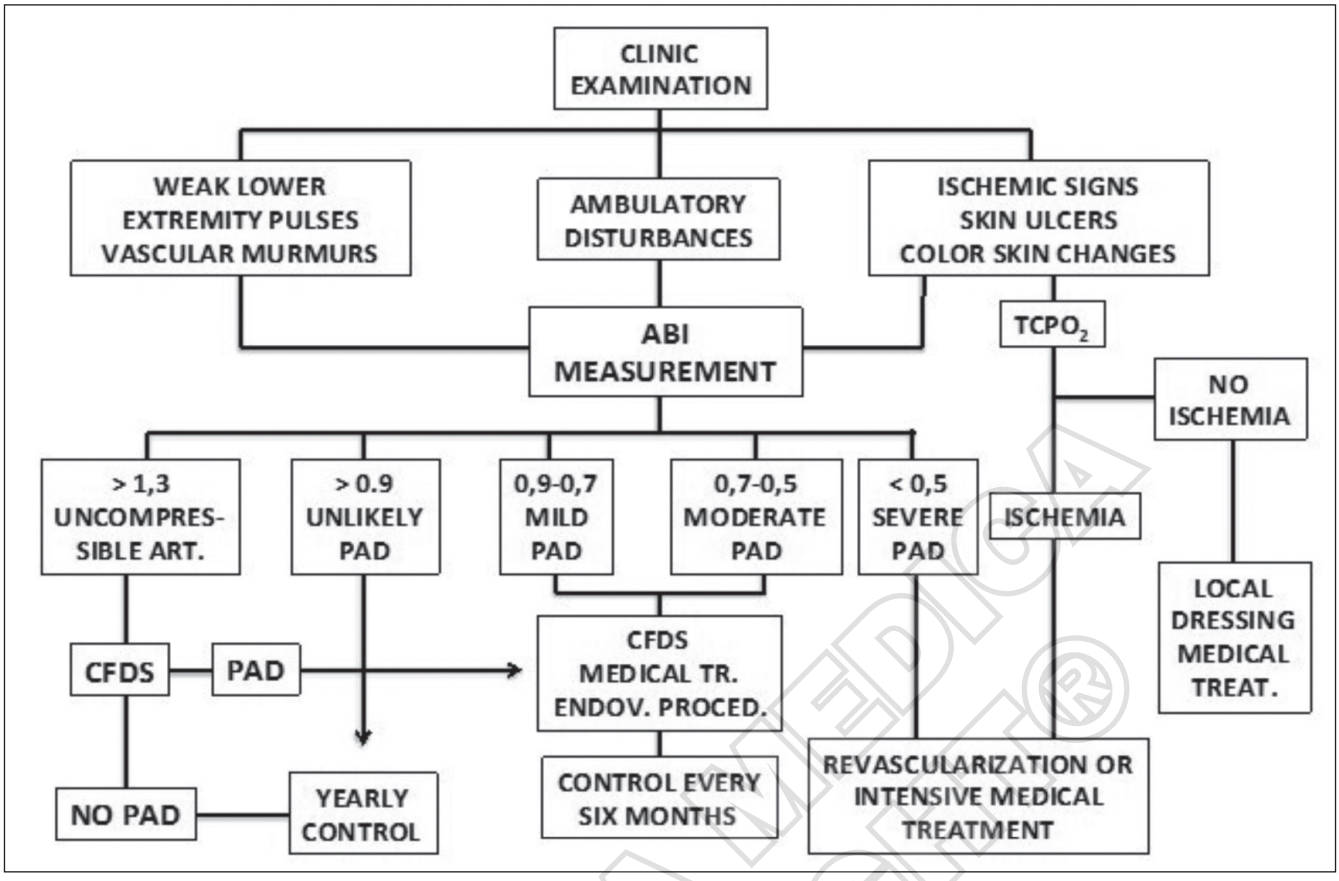

Figure 1.—Surveillance Strategy in Diabetic Patient.

of infection), that increases the risk of amputation and/or death.

However, it should be mentioned that skin ulceration in diabetic patients may also be non-ischemic. It is possible, an accidental injury of the skin of the lower limbs (traumatic ulcer) to show little tendency towards healing (poor efficacy of growth factors, the presence of protein glycation, and overlap of infection), mimicking a CLI framework that will not be confirmed by further investigations.

The high prevalence of PAD in diabetic patients requires a careful surveillance of these patients with the final goal of early diagnosis, aiming in slowing the progression of the disease and especially in reducing the occurrence of major cardiovascular events (myocardial infarction and/or stroke) either fatal or non-fatal.

To submit all diabetic patients to a vascular assessment by CFDS of the lower limbs is, however, unfeasible for the considerable expenditure of human and economic resources. To overcome the impasse is appropriate to stratify the roles of the various levels of care, with appropriate diagnostic procedures performed by properly trained staff.

The initial approach is the task of GPs and diabetologists, who both have a closer contact with the diabetic population, while the VS is responsible for more proper vascular investigation (CFDS, $TcPO_2$, vascular imaging).

Only a close co-operation between these three physicians will ensure a proper management of the patient with DM and his vascular events, with the different levels of intervention summarized in the algorithm shown in Figure 1.

All diabetic patients with long lasting disease, should receive adequate vascular investigations. Furthermore, given the preventive role of many actions outlined in Figure 1, the vascular investigations should be extended to patients with symptoms and signs of endothelial dysfunction (high Body Mass Index [BMI], altered waist/hip ratio, presence of microalbuminuria or erectile dysfunction.)

The GP and the diabetologist will periodically check on these patients, the presence of arterial pulses, vascular murmurs, walking ability, and trophic status of the skin. In case of reduction of pulsatility, presence of murmurs or reduction of walking ability, ABI should be measured. According to the ABI value, they will refer the patient to the VS, which will continue the diagnostic process according to the aforementioned algorithm.

However, it should be noted that frequently in patients with DM (but also with renal insufficiency or other diseases causing vascular calcification) the tibial arteries at the ankle become non-compressible and this produces a false elevation of the ABI which could exclude the presence of PAD. If ABI is greater than 1.3, additional non-invasive diagnostic tests should be performed. International guidelines suggest in these cases the measurement of toe systolic pressure. This procedure, however, is rarely done because most of the specialists prefer to perform directly and immediately an extensive CFSD of the lower limbs.

In case of skin ulcers a $TcPO_2$ measurement [30] is suggested, aiming to verify the ischemic nature of skin ulceration and provide the patient with the most appropriate treatment as soon as possible.

6.2 Management and follow-up of diabetic PAD

The management and follow-up of diabetic PAD is the same as in non-diabetic arteriopathy. More attention must address the balance of hyperglycemia and dyslipidemia.

All patients with PAD and DM need to stop smoking and keep the C-LDL less than 70 mg/dL.

When this target cannot be reached it is recommended that the initial level of C-LDL is at least halved. Blood pressure should be controlled to <140/85 mmHg. Antiplatelet therapy is recommended in all patients with symptomatic PAD and DM,[31] unless contraindicated for any reason. Also the management of diabetic CLI follows the same directions, mentioned above, looking carefully to the prevention and/or the appropriate treatment of infection.

6.3 Diabetic skin ulcers

Ischemia, neuropathy and infection are the pathophysiological triad of the d*iabetic foot*, defined by the world health organization (WHO) as *a condition of infection, ulceration and/or destruction of deep tissues, associated with neurological abnormalities and various degrees of peripheral vascular disease of the lower limbs.* The current trend is to modify this definition as *foot with anatomical and functional alterations determined by PAD and/or diabetic neuropathy*, including, with a clear purpose of prevention, not only patients with lesions in place but also those at risk for ulceration.[32]

As already indicated, all patients with diabetic skin ulcers should be subjected to the measuring of $TcPO_2$, to verify the ischemic pathogenesis of the disease.

If ischemia is confirmed (CLI), revascularization as well as local treatment of the wound and an intensive pharmacological treatment are indicated.

Conversely, if the skin wound is a pressure one (neurotrophic) or traumatic ulcer, orthoses for bone alterations, and local care are indicated. In case of infection, antibiotic treatment, local and/or systemic, is required.

Nevertheless, to avoid further ischemic complications, possible revascularization may be considered in patients with non-ischemic diabetic foot ulcers,[33] if CFDS and other imaging methods show the presence of severe arterial disease.

7. Revascularization in patients with intermittent claudication

In patients with mild claudication, considering the aforementioned clinical epidemiology, revascularization is very rarely indicated.

In moderate claudication, the possibility to carry-out revascularization may be considered whenever the best medical treatment (physical training, antiplatelet drugs, as well as drugs for claudication) does not lead to improvement or stabilization of PAD.

In patients with disabling claudication (objectively diagnosed, see § 5) that impacts their activities of daily live, with culprit lesions located at the aorta/iliac arteries, revasculariza-

tion should be considered as the first therapeutic option, along with the risk factor management, after detailed discussion with the patient of the risk-benefit ratio.[34]

In severe claudication, revascularization procedures should be considered carefully.

It is noteworthy that patients' request itself cannot be considered as the only criterion for revascularization.

An accurate assessment of the risks of the procedures should always be performed. In such cases, the patient should be evaluated by CFDS and other imaging investigations (angio-RMI, angio-CT and angiography) of the lower limbs arteries, assessing the anatomic conditions of the arterial tree.

Revascularization (open or endovascular) should be performed only if the anatomy is favorable (single or sequential obstruction; aortic, iliac or femoral involvement) with good distal run-off.

Endovascular revascularization has developed rapidly during the past decade, and a great number of patients can now be offered the less invasive treatment option. An increasing number of centers nowadays favor an endovascular first approach due to reduced morbidity and mortality, compared with vascular surgery. However, the selection of the most appropriate revascularization strategy has to be determined on a case-by-case basis in a specialized vascular center in close cooperation with an endovascular specialist and a vascular surgeon. The main issues to be considered are the anatomical suitability, comorbidities, local availability and expertise, and the patient's preference.

If revascularization is indicated, it should be performed in specialized vascular centers, and an endovascular-first strategy is mostly recommended.[34]

The expansion of endovascular therapy has prompted many physicians to consider more liberal indications for percutaneous intervention. However, evidence for any long-term benefit of revascularization over supervised exercise and best medical therapy is inconclusive, especially in patients with mild to moderate claudication. In a recent study, supervised exercise resulted in superior treadmill walking performance compared to endovascular treatment with stents, even for those with aortoiliac peripheral artery disease.[35]

The faculty of this consensus document suggests that the clinical indication criteria should not change because of the presumed lesser invasiveness of the endovascular procedures. The clinical features, possible complications, natural history of the disease, alternative methods of treatment and patients' informed consent, should also be taken into account.

If the disease is extensive, with limited run-off, revascularization is not indicated and the patient must be persuaded to follow an adequate program of physical training accompanied by appropriate pharmacological therapy.

When endovascular procedures have been undertaken, pharmacological treatment is recommended to prevent early failure because of thrombosis at the site of intervention. Standard therapy is heparinization during the procedure, and life-long antiplatelet medications. Despite lack of data from large randomized studies after infrainguinal angioplasty and stenting, the faculty of this consensus document recommends (by extrapolating results from experience in the coronary arteries) a dual antiplatelet therapy (aspirin and a thienopyridin) after infra-inguinal bare-metal-stent implantation. Aspirin (75-100 mg/day) could be used for a lifetime, clopidogrel from one to three months, at a dose of 75 mg/day. According to the last recommendations of the ACCP, due to lack of evidence, they suggest single antiplatelet therapy.[36] However, the authors of this document recommend dual antiplatelet therapy.

8. Critical limb ischemia

We conclude this document on intermittent claudication with a paragraph on critical limb ischemia, just to underline the need for an early specialist consultation. The diagnosis of CLI should be suspected in the presence of the following symptoms:

a) night-time rest pain of lower limbs (Fontaine stage 3rd; Rutherford grade II, category 4), lasting longer than 15 days which requires regular analgesic treatment;

b) minimal ischemic cutaneous lesions (Fontaine stage 4th; Rutherford grade III, category 5);

c) extended cutaneous lesions or gangrene (Fontaine stage 4th; Rutherford grade III, category 6).

The grouping of stages 3rd and 4th together

in the Fontaine classification and of the corresponding Rutherford categories has the advantage of focusing the attention of both GPs and specialists on the clinical condition, which is associated with an elevated risk of amputation and death.

The yearly incidence of CLI in Europe is around 450 cases per one million inhabitants. The relative risk of major limb amputation reaches 50% in patients that do not undergo revascularization and is 26% in individuals that are subjected to revascularization, while the relative risk for death is 50% and 18%, respectively. On the other hand, amputation is accompanied by a very poor prognosis: 1/3 of amputated patients die within 1 year, 1/3 achieves partial autonomy and only 1/3 obtains complete autonomy.[37, 38]

The appropriate management requires intervention by open, endovascular or hybrid revascularization followed by pharmacological treatment to maintain the patency of the bypass. Supervised physical training, drugs for claudication, antiplatelet therapy, and correction of risk factors and lifestyle modification are always advocated.

GPs should immediately refer the patient with suspected CLI to a vascular center (angiology, vascular medicine or vascular surgery units).

Many vascular specialists suggest to adopt the same strategy of management in patients with CLI, those with a few steps claudication, as well as patients with severe claudication, because all these conditions show the same critical aspects of CLI.

8.1 Diagnostic pathway of CLI

As already mentioned, for severe claudication, the main diagnostic pathway determines the degree of criticality of the limb perfusion, by morphological and hemodynamic assessment of arterial tree.

The CFDS must accurately define the anatomy and hemodynamics. The investigation should be extended to the whole arterial axis of the limb, down to the metatarsal arteries, describing the number and location of stenosis or obstruction (single block, sequential blocks, or multiple and extended blocks), collateral arteries and distal run-off. In most cases the examination will highlight multiple and extensive stenosis and obstruction.

To facilitate the therapeutic choice the following framework is suggested:

— Single or double sequential lesions (aorto-iliac, iliac-femoral, femoral-popliteal) with good run-off;

— Multiple and extensive lesions (aortic, iliac,

TABLE IV.—*Strategic and tactical suggestions for the treatment of CLI.*[35]

Hemodynamic	Clinical presentation	Treatment
1) Single or double sequential lesions 2) Good run-off (favorable hemodynamic)	1) Rest pain 2) Small skin ulcers 3) Digital necrosis 4) Forefoot necrosis	Primary revascularization
1) Multiple and extended lesions 2) Visible plantar arch 3) Adequate run-off (favorable hemodynamic)	1) Rest pain 2) Small ischemic lesions 3) Only toes affected	1) Intensive treatment 2) Revascularization in case of failure
1) Multiple and extended lesions 2) Visible plantar arch 3) Adequate run-off (favorable hemodynamic)	Forefoot gangrene	1) Primary revascularization 2) Forefoot amputation 3) Intensive treatment
1) Multiple and extended lesions 2) No visible plantar arch 3) Poor run-off	1) Digital necrosis 2) Forefoot necrosis	1) Intensive treatment 2) Amputation of necrotic parts 3) Attempt revascularization in case of failure 4) Eventual major amputation

femoral, popliteal and arteries of the leg), with visible plantar arch, and good or adequate run-off;

— Multiple and extensive lesions (aortic, iliac, femoral, popliteal and arteries of the leg), with no visible plantar arch and poor run-off.

The run-off is defined as good, adequate or poor, depending on the patency of three, two or only one (even none) of leg arteries. This is the translation of the angiographic classification of Rutherford.[39]

The faculty of this document did not consider necessary to include the angiographic scores proposed later.[40, 41]

Other imaging methods are angiography, angio-MRI and angio-CT.

Angiography should be reserved exclusively to the *pre-revascularization time*, carried out simultaneously with an endovascular procedure or open surgery. Its use during the diagnostic assessment of the patient is very rare. When indicated, angiography should be performed with an arterial digital technique; it should be very selective, acquiring images even in long time, to see all distal parts of the tibial arteries and plantar arch.

Angio-MRI can study well the perfusion of the arterial tree, and it is suitable mainly for the study of aortic and iliac inflow, which CFDS-information is lacking, or when an overview is required.

Conversely, angio-CT can also study very well the arterial wall. Finally, it is very important to plan the strategies and tactics of revascularization, especially in endovascular approach (*i.e.* stents, sub-intimal angioplasty). However, the definition of run off is still poor with the above mentioned techniques, and angiography is often required.

All of these methods use contrast media; gadolinium for the MRA and iodine media for the angio-CT and angiography. Gadolinium should not be administered to patients with severely impaired renal function (glomerular filtration rate, GFR<30 mL/min) because of the risk of nephrogenic systemic fibrosis (NSF). The use of iodinated contrast agents is not recommended if serum creatinine is >350 mol/L (3.98 mg/dL). The stimulation of diuresis by adequate hydration reduces nephrotoxicity.

Skin perfusion can be measured by $TcPO_2$. The measurement can be performed along the entire surface of the skin of the lower limb, but the choices of treatment are based on the values of the forefoot. A $TcPO_2$ <30-25 mmHg confirms the severity of PAD and the criticality of skin perfusion. Clinical judgment could be facilitated by the simultaneous transcutaneous measurement of carbon dioxide ($TcPCO_2$).

8.2 Management of CLI

Revascularization (endovascular or surgical) is the primary option of treatment. However, even if technically possible, revascularization procedures are not always recommended, because of hemodynamic conditions that are not favorable. Table IV shows some operative strategies.[42]

In case of single or double sequential hemodynamic lesions (aorto-iliac, iliac, femoral, femoro-popliteal) with good run-off, associated with rest pain, small skin ulcers and digital or forefoot necrosis, primary revascularization is always indicated.

In case of multiple and extended hemodynamic lesions (aortic, iliac, femoral, popliteal, and arteries of the leg) with visible plantar arch and adequate run-off (favorable hemodynamic condition), associated with rest pain and ischemic skin lesions, not extensive or involving only the toes, the Padua protocol suggests a pharmacological conservative treatment, reserving revascularization as a spare option, just in case of failure. Other teams, considering the favorable anatomy, think that revascularization is the treatment of first choice, but a primarily conservative treatment is also justified. These are two tactics of a common strategy, and their use depends on the preferences and attitudes of each team.

In a similar framework with favorable hemodynamic, associated with gangrene of the forefoot, then revascularization with forefoot amputation is indicated, followed by intensive pharmacological treatment.

In the case of multiple and extended lesions (aortic, iliac, femoral, popliteal, and arteries of the leg, with no visible plantar arch and poor run-off, associated with digital or forefoot necrosis), pharmacological conservative treatment is indicated with associated amputation of the necrotic parts.

Primary amputation. It is defined as the ampu-

tation of the ischemic lower limb, without making any attempt to revascularization or conservative treatment.

Despite the clinical presentation, epidemiology indicates shorter survival in patients amputated for CLI compared to non-amputees (revascularized or under conservative treatment).[43, 44] However, the possibility to perform primary amputation must be considered in some cases. The main indications are extended necrotic lesions of the limb, paralyzed limbs or ankylosis, and in all conditions in which revascularization or conservative treatment cannot guarantee the recovery of a limb able to ensure at least a self-sufficient upright position.[45, 46] Primary amputation, therefore, should be considered in dependent patients.[47, 48] However, the Faculty of this document does not believe that the *not self-sufficiency* may be the only parameter on making this decision.

Finally, the decision to amputate and the choice of the level of amputation should take into consideration the potential healing, the possibility of prosthesis and relative ambulatory rehabilitation, in order to obtain a satisfactory quality of life.[49]

8.2.1 Conservative treatment of CLI

As mentioned above, revascularization (endovascular, open surgery or hybrid) treatment option is the priority in case of CLI. However, there are patients in whom revascularization is not possible or advisable, for either technical reasons (rarely), or due to high risk of failure of the procedure, as well as severe comorbidity, (high deterioration of physical conditions-reduced level of autonomy). In these patients, conservative treatment is indicated.

The goals of conservative treatment are pain relief, prevention of amputation, healing or significant improvement of skin lesions, increase in survival, with reduced risk of major cardiovascular events.

The strategies to be adopted are many (*intensive treatment*), from adequate hydration to optimal treatment of co-morbidities, use of prostanoids, anticoagulants, analgesics, antibiotics, as well as the use of hyperbaric oxygen therapy and spinal cord stimulation.[50]

Prostanoids should be administered in a protected environment (day service, day hospital or hospitalization). Reliable patients, well educated about the possible side effects, with adequate family support, and the specialized unit always available, it is possible to treat them by continuous infusion of iloprost by an elastomeric pump for a period of 3-5 days. It is an off-label use that the unit of care should always declare.[51]

It has recently been proposed treatment with intravenous administration of propionyl-carnitine (LPC, 600 mg/day) in combination with prostanoids, with expected improvement of pain and skin lesions in the short and medium-term.[52] The rationale of the proposal is due to the cytoprotective effect of the LPC on ischemia-reperfusion injury.[53]

The available reported results of this kind of management, demonstrated a 9% incidence of amputations after two years, with 13% mortality in one year, reaching 24% at two years, which is well below the relevant rates of the international literature.[54]

The improvement of these results is due to the characteristics of management rather than the efficacy of a single drug, and especially to the strict follow-up with clinical and laboratory means monthly (or more frequent in case of recent worsening or clinical instability).

8.3 Follow-up of patients with CLI

Care units for the conservative treatment of severe PAD and CLI must be totally dedicated to the treatment of vascular disease (unit of angiology and vascular medicine), with ready availability of beds and close cooperation with a radiological and surgical team, and other specialists.

The patient with CLI in conservative treatment is a very frail patient and requires very detailed care (outpatient, day hospital, hospitalization) with easy possibility to switch from one type of service to another, in a very short time. These patients should be *taken in charge* by a dedicated care-unit, able to provide all the diagnostic and therapeutic procedures necessary from time to time, and especially to ensure an adequate and careful follow-up.

Also is essential a close collaboration between GPs and the specialist of care-unit, who have to share methods and aims of conservative treatment, and inform each other about the patient's condition.

The patient discharged to family members/carers should be properly educated about the signs and symptoms of clinical worsening (increased pain, worsening of ischemic lesions); the care-unit should provide a dedicated call service. The follow-up should include a fortnightly telephone interview and a clinical and laboratory control at least once a month.

Once the critical status has been over, very close control visits are recommended until clinical stability will be reached. In case of stabilization of PAD, the follow-up procedures are the same as in moderate claudication. In case of persisting CLI, a monthly surveillance is advisable as well as repeated cycles of intensive treatment, searching for new options for revascularization.

9. Conclusive remarks

The prognosis of patients with lower extremity PAD is characterized by an increased risk for cardiovascular ischemic events due to concomitant coronary artery disease and cerebrovascular disease.[1, 4] These cardiovascular ischemic events are more frequent than ischemic limb events in any lower extremity PAD cohort (asy-PAD, atypical leg pain or classic claudication, or CLI).

For this reason the patient with PAD, and particularly with intermittent claudication, must be carefully followed by the GP and the vascular specialist, regarding both the local evolution of the disease and the global cardiovascular risk. Summarizing all of the suggestions in the previous paragraphs, the faculty of this consensus document wishes to provide the following recommendations. The class of recommendation and level of evidence are those adopted by the European Society of Cardiology:[33]

9.1. Asy-PAD

Recommendations Class I

1. A history of walking impairment, claudication, ischemic rest pain, and/or non-healing wounds is recommended as background for a standard clinical review for adults older than 50 years who have atherosclerosis risk factors as well as for adults greater than 70 years. (*Level of Evidence: C*)

2. People with asy-PAD should be identified by measurement of the ABI and should receive all therapeutic interventions known to diminish their increased risk for myocardial infarction (MI), stroke, and death. (*Level of Evidence: B*)

3. Smoking cessation, lipid lowering drugs, diabetes and hypertension treatment are recommended for individuals with asymptomatic lower extremity PAD. (*Level of Evidence: B*)

4. Antiplatelet therapy is indicated for individuals with asymptomatic lower extremity PAD to reduce the risk of adverse cardiovascular ischemic events. (*Level of Evidence: C*)

Recommendations Class IIa

1. An exercise ABI measurement can be useful to diagnose lower extremity PAD in individuals who are at risk for lower extremity PAD, who have a normal ABI (0.91 to 1.30), and are without classic claudication symptoms, as well as they have no other clinical evidence of atherosclerosis. (*Level of Evidence: C*)

9.2. Intermittent claudication

Recommendations Class I

1. Patients with symptoms of intermittent claudication should undergo a vascular physical examination, including measurement of the ABI. (*Level of Evidence: B*)

2. In patients with symptoms of intermittent claudication, the ABI should be measured after exercise if the resting index is normal. (*Level of Evidence: B*)

3. Smoking cessation, lipid lowering, as well as diabetes and hypertension treatment according to current guidelines is recommended for individuals with intermittent claudication. (*Level of Evidence: B*)

4. Antiplatelet therapy is indicated in all patients with intermittent claudication, to reduce the risk of adverse cardiovascular ischemic events. (*Level of Evidence: C*)

5. Patients with intermittent claudication, before considering the possibility of revascularization, either endovascularly or surgically, should:

(a) have received supervised physical training and pharmacotherapy for impaired walking ability, and have performed at least six

months of best physical and pharmacological therapy;

(b) receive adequate best medical treatment (antiplatelet drugs, statins and ACE inhibitors) and treatments aimed at changing the global cardiovascular risk;

(c) also they should be carefully assessed for the degree of disability by appropriate questionnaires that measure the quality of life, and be educated to objectively quantify their own deterioration in ambulatory performance;

(d) have a favorable anatomy for revascularization with good run-off, high probability of success and low risk of failure. (*Level of evidence: C*)

10. Faculty of 3rd revision of CEVF Consensus Document on Intermittent Claudication

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