Preliminary statement

The first Consensus Meeting on this topic was held in Abano Terme on 7th May 2005, during the 2nd International Educational Course of the Central European Vascular Forum (CEVF), sponsored by the Italian Pharmaceutical Company BIOFUTURA. There was no conflict of interest between the Faculty's Member and the Sponsor; no interference occurred between the Sponsor and the Faculty during the assessment of the Document. The intellectual property of the consensus document contents belongs only to the Faculty Members. The Sponsor also provided the publication of the Consensus Document (2006 Wolters Kluwer Health - Milano Roma) available on the website www.angio-pd.it.

The document was presented and shared with Italian Society for Angiology and Vascular Medicine, Czech Society of Angiology, Slovak Society for Angiology, Romanian Society for Vascular Surgery, and the translations in Italian, Check, Slovak and Romanian languages have been edited. In June 2006 it was presented during the 22nd world Congress of International Union of Angiology and the Mediterranean League of Angiology and Vascular Surgery.

This Document presents suggestions for General Practitioners for more precise and appropriate management of PAD, particularly of Intermittent Claudication, and underlines the investigations that should be required by GP and what the GP should expect from the vascular specialist (angiologist, vascular surgeon).

Introduction

Intermittent claudication (IC) is the major symptom of peripheral arterial disease (PAD) and is also an important marker of systemic atherosclerotic disease.

PAD affects 3% to 10% of the general population, increasing to 20% in individuals over 70 years of age.1-3 It is associated with increased cardiovascular morbidity and mortality,4-8 with a risk for death that is 3-6 times higher compared to the general population.

In spite of the fact that diagnosis of PAD requires only simple, non-invasive, and inexpensive pro-
cedures, PAD is still underdiagnosed and often goes untreated.9

In order to overcome these shortcomings, widespread screening programs should be implemented for all individuals over the age of 40-50 years, determining the presence of IC and checking for weak pulses in the lower extremities, and by measuring the ankle brachial pressure index (ABI).9, 10

Once identified, patients with PAD should undergo careful assessment of global cardiovascular risk, identifying possible risk factors and aggressively treating modifiable aspects, with the objective of slowing the evolution of local (worsening of claudication, appearance of critical ischemia, necessity of amputation) and systemic (prevention of myocardial infarction and stroke) disease.

This report presents suggestions for general practitioners (GP) for more precise and appropriate management of PAD, with particular reference to IC. The document suggests the investigations that should be requested by GP and the recommendations the GP should expect from the vascular specialist (angiologist, vascular surgeon).

Classifications of peripheral arterial disease

The most well known classifications are those of Fontaine et al.11 and Rutherford et al.,12 both of which are equally valid.

The former classification identifies four stages: 1st, asymptomatic; 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).

The 1st stage of Fontaine’s classification is defined as the asymptomatic presence of arterial lesions (calcifications, plaques). Patients with occasional symptoms (e.g. after exceptional physical stress), sometimes misclassified as stage 1st, should be considered as having stage 2nd. The pathophysiology of 1st stage is characterized by the presence of atherosclerotic plaques that may be followed by an activation of inflammatory processes, with the release of substances that mediates leukocyte-leukocyte and/or leukocyte-endothelium interactions, and activates platelet as well. Such molecular and cellular interactions promote successive leukocyte activation involving deposition of chemokines on the endothelial surface and facilitate adhesion and migration of leukocytes to subendothelial tissues.13 Activation of an inflammatory response at the site of plaques leads to local complications (plaque rupture and thrombosis)14, 15 and systemic dissemination of proinflammatory molecules (high-risk plaques) that can induce complications at other vascular sites.16-19

The 2nd stage is characterized by IC, defined as fatigue, discomfort, or frank pain that occurs in specific limb muscle group during effort due to exercise-induced ischemia (walking or climbing stairs) and goes away upon resting. Because of the difficulty to define in reliable way the ACD without specific measurements, GP is advised, during clinical history examination, to consider the patients’ capacity on climbing stairs and their limitations in life style.

The further division into subgroups 2nd A and 2nd B in the Fontaine classification, and especially in the three categories of Rutherford’s classification, is quite useful as the natural history of the arteriopathy in patients with greater ACD impairment is decidedly more severe.

Patients with mild claudication (2nd stage A, calf pain climbing more than two flight-stairs) remain stable in about 75% of cases20-23 and the presence of claudication has an important clinical role as an indicator of global cardiovascular risk (myocardial infarction and stroke).24 On the other hand, the natural history of patients with moderate claudication (2nd stage B, calf pain climbing less than two flight-stairs) is much more unfavorable, and even worsens if a severe claudication is present (calf pain climbing less than one flight-stairs), with an elevated risk of progression of local disease.25, 26

The 3rd stage in the Fontaine’s classification (ischemic rest pain) corresponds to grade II, category 4 in the Rutherford scheme. The stage 4th (ischemic cutaneous lesions) corresponds to Rutherford grade III. This grade III is divided in the categories 5 and 6, distinguishing the entity of skin necrosis (minor and major tissue loss). Since 1989, the definitions of chronic critical
ischemia of lower limbs or critical limb ischemia (CLI) have been combined according to collectively accepted terminology.\textsuperscript{27-29} CLI is defined as the presence of persistent limb pain that occurs at rest, lasting longer than 15 days that requires regular analgesic drugs (stage 3), with or without ulcers or gangrene attributable to objectively proven arterial occlusive disease (stage 4). The term CLI implies chronicity and is to be distinguished from acute limb ischemia.\textsuperscript{30, 31}

The term of CLI includes a great variability of clinical pictures which should require specific classification categories. In patients with rest pain, we could distinguish those with ankle pressure >50 mmHg, in which rest pain goes away when the limb is lowered, and clinical features which often regress back to stage 2\textsuperscript{nd} (A or B), from the patients with ankle pressure lower than 50 mmHg, with persistent rest pain when the limb is lowered and clinical features which often progress to the stage of skin damage (Fontaine 4\textsuperscript{th}, Rutherford III/5).

About the skin injury stage we could distinguish patients coming directly from stage 3\textsuperscript{rd} (Rutherford II/4) as evolution of the disease, with high trend to progression (Rutherford III/6) from the patients coming from the claudication stage after skin injury or trauma. These patients should not be classified as CLI, because the limb circulation is well compensated and the tendency for healing is good even without any revascularization. However, the definition of CLI, in spite of the melting-pot of clinical features must be maintained because it underscores the high risk of amputation and life.

\begin{table}[h]
\centering
\caption{Classification of peripheral arterial disease according to Fontaine and Rutherford.}
\begin{tabular}{|c|c|c|c|c|c|}
\hline
\textbf{Fontaine} & \textbf{Signs and symptoms} & \textbf{Pathophysiology} & \textbf{Rutherford} & \\
\cline{1-3}
\textbf{Stage} & \textbf{Clinic} & & & \\
\hline
1\textsuperscript{st} & Asymptomatic & & & \\
\hline
2\textsuperscript{nd} a & Mild claudication & ACD >200 m recovery t <2 min & Discrepancy between oxygen request and arterial supply & Mild claudication I I 1 \\
\hline
2\textsuperscript{nd} b & Moderate or severe claudication & ACD <200 m recovery t >2 min & Higher discrepancy between oxygen request and arterial supply & Moderate claudication I I 2 \\
\hline
& & ACD <100-80 m recovery t >2 min & Highest discrepancy between oxygen request and arterial supply, plus acidosis & Severe claudication I I 3 \\
\hline
3\textsuperscript{rd} & Ischemic rest pain & Rest pain & Severe skin hypoxia and acidosis & Ischemic rest pain II I 4 \\
\hline
4\textsuperscript{th} & Ulceration or gangrene & Necrosis & Severe skin hypoxia and acidosis infection & Minor tissue loss III I 5 \\
\hline
& & Gangrene & Severe skin hypoxia and acidosis infection & Major tissue loss III I 6 \\
\hline
\end{tabular}
\end{table}

ACD: absolute claudication distance.
Asymptomatic peripheral arterial disease

Asymptomatic lower extremity PAD (AsyPAD) (Fontaine stage 1; Rutherford grade 0, category 0) (Table II) 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, in individuals less than 50 years with diabetes and one other atherosclerosis risk factor (smoking, dyslipidemia, hypertension, or hyperhomocysteinemia) and in all people with known atherosclerotic coronary, carotid, or renal arterial disease.

Also subjects over 50 years with metabolic syndrome should be investigated for AsyPAD because a high prevalence of symptomatic and asymptomatic vascular disease has been demonstrated in such patients.32

Any 3 of 5 criteria constitute diagnosis of metabolic syndrome: elevated waist circumference (≥102 cm or ≥39.4 inches in men, ≥88 cm or ≥35 inches 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 for reduced HDL-C); 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 on drug treatment for elevated glucose).33

We do not have exact data concerning the prevalence of the AsyPAD, but it is estimated that for 100 patients with IC presenting to the doctor, there are another 100 people symptomatic too, but not presenting to the doctor and 300 people with asymptomatic lesions of the arterial walls of the lower limbs.4

Suspected AsyPAD is diagnosed by measurement of the ABI, at rest and after exercise; an ABI <0.9 is considered indicative of PAD. If the diagnosis is confirmed, it is advisable to proceed with the identification and correction of risk factors and with antithrombotic therapy.

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

In the last decade, all the efforts of angiologists and vascular doctors have already improved the poor prognosis of patients with PAD. The data from the REACH-registry34 show a 1-year cardiovascular death rate of 2.4% in PAD patients, calculating an about 12% death rate after 5 years. The Faculty of this Consensus Document would emphasize the importance of these data and of further increasing of our efforts.

In cases that the diagnosis of AsyPAD is not confirmed, a follow-up visit is recommended after 2-3 years in the presence of risk factors.
**Measurement and reliability of ankle brachial index**

The ABI is the ratio of systolic arterial pressure measured at the ankle to the brachial arterial systolic pressure.

Using a pocket-Doppler as a stethoscope, ankle (anterior and posterior tibial arteries) and brachial artery systolic blood pressures are measured. For each leg, the ABI can be calculated by dividing the highest systolic pressure at the ankle (using the highest value obtained from the anterior and posterior tibial arteries) by the highest recorded systolic pressure in either arm.

In healthy subjects, the ABI varies from 0.9 to 1.3. Values between 0.7 and 0.9 indicate the presence of mild PAD, while an ABI from 0.5 to 0.7 denotes moderate PAD. ABI values <0.5 indicate the presence of severe PAD with multiple obstructive lesions along the arterial tree (Table III).

Furthermore, in patients with diabetes, renal insufficiency or other diseases that cause vascular calcifications, the tibial vessels at the ankle become non compressible and this fact produces a false elevation of the ankle pressure which does not exclude the presence of PAD. These patients typically have an ABI >1.3 and additional non invasive diagnostic tests should be performed to evaluate the presence of PAD. The international guidelines suggest in these cases the measurement of the toe systolic blood pressure which does not exclude the presence of PAD.

The recent version of TASC II document suggests to increase the higher ABI normal value to 1.4. The Faculty of this Consensus Document maintains the previous statement to avoid the screening loss of several diabetic patients.

**Mild claudication**

Mild claudication (Fontaine stage 2ndA; Rutherford grade I; category 1) (Table IV) is defined as the appearance of muscular cramps of the lower limbs (buttock, thigh, calf) climbing more two flights of stairs, or walking more than 200 m. It is very important that the GP verifies if the same symptoms are always present following similar exercise.

The outcome of mild claudication is similar to that of AsyPAD, with a 25% risk at 2-5 years of progressing to more advanced stages; the prevalence is 3% at 40 years and 6% at 60 years. 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.

The following diagnostic examinations are indicated (grade A recommendation):

- measurement of the ABI, at rest and after exertion;
- CFDS of the supra-aortic arteries (SAoAs), as pathologies affecting cerebral arteries are present in 13-18% of patients with PAD;
- CFDS of the abdominal aorta as about 5-10% of patients with PAD carry aneurysms of the abdominal aorta, and because the aorta, which is the origin of arterial trunks of the lower limbs, may be the site of nonstenosing lesions which are responsible for severe cutaneous ischemia of the lower limbs (blue toe syndrome, atheroembolism, etc.);
- cardiological investigations for coronary artery disease (echocardiogram, ECG, dipyridamole thallium, handgrip or echo stress tests) should be performed and when indicated coronary angiography with the view to coronary revascularization should follow because significant coronary lesions are present in at least 1/3 of patients with PAD.

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

**Measurement of walking capacity**

The evaluation of patients with mild claudication should be completed by measurement of walking capacity. It is useful:

| Table III.—Meaning of ankle brachial index measurement. |
|---|---|
| ABI | Meaning |
| >1.3 | Unreliable measurement (perform CFDS) |
| >0.9 | Unlikely arteriopathy |
| 0.9-0.7 | Mild arteriopathy |
| 0.7-0.5 | Moderate arteriopathy with segmentary, stenotic and/or obstructive lesions |
| <0.5 | Severe arteriopathy with occlusive disease in more than one artery |

ABI: ankle brachial index; CFDS: color flow duplex scanning.
a) in establishing the diagnosis of PAD when resting measures of ABI are normal;
b) to objectively document the magnitude of limiting symptoms in patients with PAD and IC;
c) to objectively measure the functional improvement obtained in response to intervention;
d) to differentiate IC from pseudoclaudication;
e) to provide objective data that can demonstrate the safety of exercise and to individualize exercise prescription in patients with IC before the initiation of a formal program of exercise training.

**EXERCISE TREADMILL TEST**

This is the most widely used method for measuring walking capacity. The patient is requested to walk on a treadmill at different speeds and inclinations. The most commonly employed test is the protocol with speed between 1.5 and 2 mph (2.4-3 km/h) and inclination from 0% to 12%. The parameters measured are the distance walked before muscular symptoms appear without impeding walking (initial claudication distance [ICD] or pain free walking distance) and the distance at which the patient stops walking due to muscular cramps (absolute claudication distance [ACD] or maximal walking distance). The test has a certain degree of variability related to the attitude of the patient in using the treadmill that can be further influenced by the instructions given by the operator. In order to overcome some of these inconsistencies, a protocol has been proposed that foresees walking on a treadmill with a progressively increasing grade of slope.

However, in spite of initially promising results, no significant differences were noted between the reproducibility of the two tests.

Even though it is the most satisfactory method of measuring walking capacity, widespread utilization of the treadmill test is not feasible for several reasons, including:

- objective difficulties in walking on a treadmill at non-physiological velocities (low compliance, concomitant osteoarticular pathologies);
- risk of acute coronary insufficiency;
- practical grounds (the exam requires about 1 h, the constant presence of a physician for at least 30 min and the availability of specialized equipment for resuscitation such as cardiac monitoring and defibrillator).
Valid alternatives, more feasible for GPs, include the 6-Minute Walking Test (6MWT), and questionnaires such as the Walking Impairment Questionnaire (WIQ) or the Walking Edinburgh Questionnaire.

**SIX-MINUTE WALKING TEST (6MWT)**

The patient walks in a corridor of known length for 6 min at his/her maximal speed; stops are allowed. The total distance walked is recorded, better together with the total number of steps. If the patient can walk for 6 min without muscular cramps, the test is considered negative.47

**QUESTIONNAIRES**

The above-mentioned questionnaires are specific instruments for the assessment of quality of life in patients with IC, aimed to assess also the therapeutic outcomes. These questionnaires are also useful for initial clinical assessment in order to determine the presence or absence of claudication.

The WIQ quantifies walking performance by evaluating three different parameters: the distance (minimal normal score: 70), the velocity (minimal normal score: 40), and stair climbing (minimal normal score: 60). Scores lower than those reported suggest that the patient should take the 6MWT or the treadmill test.48-50

Considering the above, in clinical practice it is sufficient to evaluate the walking capacity using the 6MWT, and to use the treadmill test only before and after physical training programs, and in clinical trials.

*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 stopping smoking), correction of risk factors and specific pharmacological treatment.29

**CORRECTION OF RISK FACTORS**

Besides cigarette smoking, another important risk factor for PAD is diabetes mellitus. In diabetic patients, fasting blood glucose levels should be reduced to 80-120 mg/dL and after meals should be <180 mg/dL, with glycosylated hemoglobin values <7%.51 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.

As regards arterial hypertension, it must be adequately controlled and blood pressure values within 130/80 mmHg should be maintained using calcium antagonists or ACE inhibitors.52, 53 Treatment with ramipril (10 mg/day) has been associated with a significant reduction in cardiovascular death, stroke, and myocardial infarction54-56 also in patient with clinical as well as subclinical PAD independently from the presence of hypertension.57

Finally, hypercholesterolemia should be treated in an aggressive manner. Treatment must also include adequate dietary considerations and, if necessary, pharmacological intervention with statins in order to reduce the values of c-LDL <100 mg/dL. A large number of studies have demonstrated that in addition to significantly lowering hypercholesterolemia, statins also reduce cardiovascular mortality independently of the cholesterol-lowering effect.54, 56, 58 This activity is probably due to a reduction of inflammatory activation and stabilization of the atherosclerotic plaques. There are evidences that the cumulative survival of patients with high inflammation (high C-reactive protein, CRP) is worst than patients with low CRP. In patients with high CRP receiving statin therapy, the cumulative survival is slightly lower than patients with low CRP level.59

Kidney function should be monitored because chronic renal insufficiency is independently associated with PAD and future PAD events.60-62

**PHARMACOLOGICAL TREATMENT**

Elective pharmacological interventions for slowing the progression of disease include antiplatelet and anticoagulant agents. At present, these drugs are defined as anti-athero-thrombotic as they actively antagonise the pathophysiological mechanisms behind progression of local disease and its systemic localization, reducing the relative risk of cardiovascular morbidity and mortality.63, 64

The term atherothrombosis refers to the formation of atherosclerotic plaques, for which com-
**CFDS of SAoA is indicated in the following clinical pictures**

- Crescendo TIA
  - 2 or more episodes attributable to TIA within 24 h, or
  - 3 episodes in 72 h, with complete resolution of symptoms between episodes

- Symptoms suggestive of TIA in the carotid or vertebro-basilar areas started <7 days

- Pulsative latero-cervical swelling

- Symptoms suggestive of TIA and/or minor stroke, in the carotid or vertebro-basilar areas started >7 days

- Asymptomatic patients, candidates for major surgical intervention or coronaryography (check list)

- Neck bruits

- Suspected subclavian steal syndrome

- Symptomatic patients, with symptoms started from >30 days

- Asymptomatic patients
  - Age >65 y 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, radiating neck therapy;
  - Patients with latero-cervical or supraclavicular murmurs;
  - Follow-up after surgery or endovascular procedures of SAoA

**Frequency of the control visit (degree of carotid stenosis assessed with ultrasound criteria)**

- Asymptomatic patient: age >65 y without risk factors for atherosclerosis and with CFDS of the SaoA negative at previous visit

  - Carotid stenosis <20%
    - After 5 years

  - Carotid stenosis 20-49%
    - 1 year

  - Carotid stenosis 20-49%, with echolucent plaque (I e 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 e 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

**TABLE V.—Appropriateness of the supra-aortic arteries color flow duplex scanning investigation and frequency of control visits.**

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Emergency Room</th>
<th>Grade A</th>
<th>Grade C</th>
<th>Emergency Room</th>
<th>Grade A</th>
<th>Grade C</th>
<th>Grade A</th>
<th>Within 10 days</th>
<th>Grade A</th>
<th>Within 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency Room</td>
<td>Grade A</td>
<td>Within 10 days</td>
<td>Grade A</td>
<td>Grade A</td>
<td>Within 30 days</td>
<td>Grade A</td>
<td>Grade C</td>
<td>Grade C</td>
<td>Within 180 days</td>
<td>Grade C</td>
</tr>
<tr>
<td>Follow-up after surgery or endovascular procedures of SAoA</td>
<td>Specialist consultation</td>
<td>1 year</td>
<td>According to severity of stenosis</td>
<td>According to severity of stenosis</td>
<td>1st control within 3 months; 2nd control within 9 months; successively: every 12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CFDS: color flow duplex scanning; SAoA: supra-aortic arteries; TIA: transient ischemic attack.
Applications and thrombosis constitute a single process that is strictly related to the appearance of cardiovascular events (myocardial infarction, stroke, PAD, CLI). Such events affect large and medium-sized arteries along the entire vascular tree.

All patients affected with IC should take aspirin (100-300 mg/day) or other antiplatelet therapy. Ticlopidine reduces the need of revascularization procedures. Clopidogrel has been shown to reduce the relative risk of ischemic events (combined endpoint of IMA, ischemic stroke and vascular death) by 23.7% (confidence interval: 8.9-36.2; P=0.003) on PAD patients with respect to aspirin in the CAPRIE study. In patients with diabetes-associated PAD the efficacy in preventing major cardiovascular events provided by aspirin and, to a minor extent, by clopidogrel, is debated. Increased production of thromboxane A2 from platelets and other cells, also by alternative, aspirin insensitive pathways has been described, and aspirin or clopidogrel resistance ex vivo is frequently found. In a recent study, a dual inhibitor of TXA2 syn-

### TABLE VI.—Appropriateness of the abdominal aorta color flow duplex scanning investigation and frequency of control visit.

<table>
<thead>
<tr>
<th>CFDS of SAoA is indicated in the following clinical pictures</th>
<th>Frequency of control visits and management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;50 years with family history of AAA</td>
<td>Ø between 30 and 39 mm</td>
</tr>
<tr>
<td>Presence of arterial disease in other districts</td>
<td>Ø &gt;40 mm</td>
</tr>
<tr>
<td>Occasional discovery of aortic calcifications</td>
<td>Ø &gt;55 mm</td>
</tr>
<tr>
<td>Age &gt;65 years (males)</td>
<td>- if diameter of the proximal normal aorta is &lt;2 cm</td>
</tr>
<tr>
<td>Age &gt;50 years with risk factors</td>
<td>- we suggest to use the ratio Ø AAA/Ø not aneurysmatic aorta</td>
</tr>
<tr>
<td>Iliac Doppler signal indicative of upstream hemodynamic stenosis</td>
<td>Ø &gt;40 mm with accelerated growth: 10 mm/year or 7 mm/6 months</td>
</tr>
<tr>
<td>Blue toe syndrome</td>
<td>Frequency of control visits and management</td>
</tr>
<tr>
<td>Bilateral absence of femoral pulse (suspect ascending aortic thrombosis)</td>
<td>Ø ≥30 mm</td>
</tr>
<tr>
<td>Pulsing abdominal mass</td>
<td>Ø ≥40 mm</td>
</tr>
<tr>
<td>In case of confirmed AAA, follow indication for management, or refer patient for specialist consultation</td>
<td>Ø &gt;55 mm</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
</tr>
<tr>
<td>- in the presence of pulsing mass</td>
<td>- if diameter of the proximal normal aorta is &lt;2 cm</td>
</tr>
<tr>
<td>- in the presence of known AAA</td>
<td>- we suggest to use the ratio Ø AAA/Ø not aneurysmatic aorta</td>
</tr>
</tbody>
</table>

**CFDS:** color flow duplex scanning; **SAoA:** supra-aortic arteries; **AAA:** abdominal aortic aneurysm; **CT:** computed tomography; **MR:** magnetic resonance.

**Angio-CT:** abdominal aorta computed tomography; **Angio-MR:** abdominal aorta magnetic resonance.
thase and receptor antagonist, picotamide, sharply reduced mortality over aspirin in patients with PAD and associated type 2 diabetes,74 thus indicating that direct inhibitors of thromboxane may be advantageous in this condition. Picotamide is an effective and safe drug and can be used in PAD patients with type 2 diabetes where commercially available, as in Italy.

Unfortunately, the question could not be definitively solved by the quoted CLIPS66 trial, given the limited number of patients enrolled.

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 quality of walking as described below.

**Follow-up**

Patients with mild claudication having stable functional and anatomic parameters after two successive control visits should be re-evaluated annually by ABI measurements and 6MWT; in case of worsening of these parameters and clinical features CFDS is indicated as second level investigation. With regard to periodic examinations of the SAoA and the abdominal aorta, the recommended follow-up times are detailed in Tables V75 and VI.

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.

**Moderate claudication**

The distinction of Fontaine stage 2nd B into moderate claudication and severe claudication, as suggested by the Rutherford classification, represents one of the most important innovations of clinical epidemiology. Moderate claudication (Fontaine stage 2nd B; Rutherford grade I, category 2) (Table VII) should be suspected in subjects with muscular cramps of the lower limbs (gluteal, thigh, leg) after climbing less than two flights of stairs, or walking less than 200 m.

Systemic outcome does not differ from that of mild claudication, but the local outcome is different, with a 6-10% risk of progression to severe claudication in 12-18 months.

The same diagnostic procedures are indicated, with few differences. The first concerns the measurement of walking capacity (grade C recommendation, at this stage) is imperative in the light of carrying out a supervised physical training program. The second regards a detailed CFDS of lower limbs (measuring site, length and extension of stenosis or obstruction, and effectiveness of collateral vessels) to find indications and possibility for endovascular procedures.

**Management of moderate claudication**

Recommendations for management of moderate claudication by correction of risk factors and pharmacological therapy with antithrombotic agents are similar to those indicated for mild claudication. Improvements in walking capacity are also advocated, which in addition to having beneficial effects on the quality of life, most likely improve systemic disease as well. Antithrombotic treatment should be associated with physical exercise and drugs that improve walking capacity.

**Physical training**

Physical training is universally recognized as the most efficacious means for improving the walking capacity in patients with PAD, and should always be associated with pharmacological treatment as previously discussed.

The utility and efficacy of physical training has been demonstrated by several studies that however have been generally small and nonrandomized, along with a few meta-analyses.76-78 Many studies have also documented an improvement in general physical status with a reduction in cardiac frequency, respiration and oxygen consumption under the same work load.79, 80 Patients acquire the capacity to walk for longer distances and times at higher speeds.81

The improvement in walking capacity is independent of the presence of associated risk factors such as smoking,82 diabetes83 and other concomitant pathologies.

Supervised physical training, or training carried out at specialized centers under the supervi-
cision of expert staff, has been shown to be significantly better with respect to written or verbal advice (“stop smoking” and “keep walking”) to carry out regular physical activity.84-86 However, as home training is nonetheless preferable than the complete absence of physical exercise,84, 87, 88 and considering the organizational difficulties that supervised training necessitates, the most reasonable strategy at present appears to reserve supervised training to patients with moderate to severe IC, whilst home training is recommended for patients with mild claudication. Recently, a personalized home training program has been proposed that is guided by the pain threshold; such a home based program is a compromise between supervised physical training and mere advice to get more exercise.89, 90

In spite of being recommended by all guidelines, in clinical practice the use of physical training in claudicants remains low, and the adopted protocols show a great variability and often they are unclear, over all concerning the working load. The majority of papers and guidelines suggest to walk near-maximal pain,31, 91 and the TASC 2nd Document includes the high level of claudication pain during training session as predictor for good results.31 Considering the recent evidence about the significant increase of inflammation after the maximal exercise,91-97 the physical training in claudicants should utilize only the aerobic exercise, without reaching really the near maximal pain. Indeed, despite the definition near maximal pain, if we look at contents of the papers we find more prudence to describe the protocols, with the sug-

| TABLE VII.—Moderate claudication: Fontaine Stage 2B, Rutherford I/2. |
|-----------------|-----------------|-----------------|
| **When suspect** | Pain in the leg which occurs climbing less than two flight stairs and disappears after resting |
| **Epidemiology** | Prevalence: 40 y, 3%; 60 y, 6%; >70 y, 18-20% |
| | Worsening risk in severe claudication: |
| | - 25% in 2-5 years |
| | - 6-10% in 12-18 months |
| | Cardiovascular global risk 5 years: |
| | - non fatal CV events 5% |
| | - CV mortality 30% |
| **Examinations** | ABI measurement |
| **[Gr. A]** | CFDS of lower limbs to find |
| | - indications for endovascular procedures, assessing |
| | - site, length and extension of stenosis or obstruction |
| | - collateral vessels |
| **[Gr. C]** | Assessment of walking ability |
| **[Gr. A]** | CFDS supra-aortic arteries |
| **[Gr. A]** | CFDS abdominal aorta |
| **[Gr. A]** | Cardiac investigation |
| **Management** | Goals: slowdown of disease’s progression |
| | - prevention of fatal and not fatal CV events |
| | - improvement of walking ability |
| **[Gr. A]** | Slowdown of disease’s progression and prevention of CV events |
| | - correction of risk factors |
| | - antiplatelet drugs |
| **[Gr B]** | Improvement of walking ability |
| | - supervised physical training |
| **[Gr C]** | drugs for claudication |
| | - endovascular procedures for revascularization (if indicated, with assessment of risk/benefit ratio) |
| **Follow-up** | Surveillance every 6 months, after two controls with stable functional and clinical parameters |
| | Surveillance of SAoA and abdominal aorta following the specific criteria (Tables VII and VIII) |
| | Specialistic consulting (angiologist or vascular surgeon) in case of evolutive disease |

gestion that during the training patients should be encouraged to walk with a calf pain between mild to moderate intensity,\textsuperscript{35, 80, 98} and the TASC 2\textsuperscript{nd} Document reminds that patients should stop walking when claudication is considered moderate, and always avoiding excessive fatigue or discomfort.\textsuperscript{31}

To avoid misunderstandings on the terms, and protocols with high inflammatory risk, the Faculty of this Consensus Document proposes a shared and well defined short-course protocol, near maximal pain but without reaching it, effective as the longer ones, but with lower cost.\textsuperscript{99}

**Supervised Training Program 6 weeks, 3 days weekly (suggested protocol)**

**Day 0 (the day before to start Physical Training Program).**—1) Warm-up 10 min of 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.**—1) Warm-up 10 min of 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 resting until the normalization of all cardiovascular parameters.

**Day 9.**—1) New assessment of walking capacity: submaximal treadmill test or spontaneous walking without slope (same setting utilized the day 0); 2) recalculate the single exercise load: patient walks until 60-70\% of new walking performance (incremental protocol of the training program); 3) resting and restore period and daily training session remain unchanged.

**Day 18 (6 weeks).**—Maximal treadmill test to assess the new ICD, ACD, rt.

**Home program.**—The patients 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, referring to the specialist if the walking capacity is worsened.

The costs of this 6 weeks protocol in Italy varies from € 4,179 in Sicily and € 3,057 in Veneto, significantly lower than the estimated costs of 6 months protocols ($ 12 000 for unsupervised exercise, and $ 30 000 for the supervised training).\textsuperscript{100}

**Drugs improving the walking capacity**

During the last 50 years, several drugs have been proposed for improving walking capacity.\textsuperscript{101, 102} At present, however, only few of these agents are supported by adequate scientific evidence of their beneficial effects.

**Pentoxifylline** (a methylxanthine derivative) can improve anomalous erythrocyte deformability and reduces the levels of fibrinogen and platelet coagulation; 20\% of patients with PAD have improvement within 6 months of treatment, but the role of pentoxifylline as therapy for IC is marginal and not well established.\textsuperscript{30, 31}

**Naftidrofuryl**, a serotonin receptor antagonist, improves aerobic metabolism in hypoxic tissues. Several clinical controlled studies have reported significant positive results for both walking distances and quality of life. Other studies have reported conflicting results regarding its pharmacological efficacy.\textsuperscript{103, 104}

**Buflomedil** is an inhibitor of \(\alpha_1\) - and \(\alpha_2\)-adrenergic receptors, that acts as a calcium antagonist and reduces the vasoconstrictive response to various stimuli.\textsuperscript{99} Two non-recent controlled studies with relatively small sample populations suggested that administration of buflomedil leads to improvements in PAD,\textsuperscript{105} although these results have not been confirmed by more recent investigations.

**Cilostazol**, an inhibitor of type III phosphodiesterase, has vasodilative and anticoagulant activity.\textsuperscript{106} Some reports have indicated that it improves both ICD and ACD,\textsuperscript{107, 108} but currently this drug is only approved in some countries.

**L-propionyl-carnitine (LPC)** appears to have beneficial effects on the walking capacity in patients with IC by favoring the clearance of excess acetylcarnitine present in patients with reduced muscular performance.\textsuperscript{109, 110} This meta-
bolic effect is likely to be related to an anaplerotic mechanism, which is the capacity of LPC to furnish intermediate metabolites that are useful in bioenergetic processes through which LPC provides additional energy to ischemic muscles. In fact, ischemic limbs show a reduced metabolism of fatty acids and carnitine, similar to that seen in myocardial damage when primary carnitine deficits are present. In PAD, the carnitine deficit is correlated with severity of disease.

Several studies have demonstrated that LPC, in addition to being well-tolerated, leads to significant improvements in both the ACD and the quality of life. Moreover, a clinical pharmacologic study carried out in an in vivo human model of ischemia-reperfusion demonstrated that LPC protects vascular tissues and organs from ischemic injury.

Intravenous administration of LPC (600 mg/day) during physical training programs appears to further improve the efficacy of exercise in patients with moderate to severe IC. Other drugs active on the endothelial function, as mesoglycan and sulodexide, have been shown to improve walking capacity, but the number of published papers are not sufficient for strong recommendations.

Follow-up

Follow-up criteria for moderate claudication are essentially those indicated for mild claudication, but at shorter intervals, and require greater attention by the GP with regards to the possible appearance of symptoms that indicate progression of disease.

Markers of disease progression

The natural history of IC and its clinical epidemiology indicate that nearly 75% of patients with mild to moderate claudication will experience stabilization of disease; only 25% of these patients will progress to severe claudication and CLI. It is thus possible to define two forms of PAD.

The first relatively benign form is associated with walking difficulties that are not debilitating in the majority of patients, but nonetheless represent an important indicator of systemic cardiovascular risk, especially coronary. In contrast, the second form of PAD is more aggressive and is destined towards a progressive worsening of disease. Unfortunately, at present it is not possible to distinguish between the two forms during the claudication phase.

The factors contributing to PAD progression seems to be different in large vessels (cigarette smoking, lipids and inflammation) and in small vessels (diabetes), even if the major involvement of small vessels (under knee arteries) in diabetic did not show significant correlation with harder outcomes in the PAD of diabetic than no diabetic patients.

Several studies have suggested that long-term activation of inflammatory processes is an independent risk factor for cardiovascular events related with the progression of PAD. A recent paper suggests that the cytokines’ releasing trend after maximal exercise could be a better marker of disease progression. However, further investigations are needed in order to confirm this hypothesis.

To date, general risk factors for progression of PAD include:
- presence of multiple obstructions along the arterial trunk;
- ABI <0.5;
- presence of diabetes mellitus;
- persistence of risk factors (especially smoking);
- hyperhomocysteinemia;
- hyperviscosity (hematocrit) and hypercoagulability (fibrinogen);
- increased levels of CRP;
- heart failure;
- chronic renal insufficiency;
- PAD with progressively worsening symptoms.

Severe claudication

Severe claudication (Fontaine stage 2nd B; Rutherford grade I, category 3) is defined as the presence of symptoms typical of IC that occur climbing less than one flight 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 percent of cases progress to CLI in 6-18 months and 35% requires major amputation within 24 months.

Diagnostic procedures in these patients include extensive and detailed CFDS of the lower limbs,
treadmill test and imaging procedures (angio-RM, angio-TC, angiography) in addition to the assessment of the SAoA, abdominal aorta and cardiac assessments.

The management of these patients must have as primary consideration the possibility of revascularization (open or endovascular) without however disregarding supervised physical training in addition to antithrombotics, correction of risk factors and drugs for claudication. Prostaglandins have been proposed in the management of severe claudication to stabilize the disease as moderate claudication and postpone the revascularization procedures, but the overall evidence does not support this drug application as strong recommendation.

Considering the difficulty in obtaining all the results necessary for correct therapy, in a reasonable period of time, it is prudent that the GP sends the patient to urgent specialist consultation within 30 days.

In current clinical practice, severe claudication is often indicated as disabling claudication. Use this term as synonymous of severe claudication 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. Studies on the quality of life demonstrated that 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. This difference in subjective assessment of walking capacity as disability of patient should be carefully considered in the decision process for revascularization procedures.

The follow-up of patients with severe claudication requires frequent control visits, at least every 3 months. Controls could be performed on a 6 months’ basis if stable clinical and functional para-

<table>
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<th>TABLE VIII. — Severe claudication: Fontaine Stage 2B, Rutherford I/3.</th>
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<td>When suspect:</td>
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<tr>
<td>— Pain in the leg which occurs climbing less than one flight</td>
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<td>stairs and disappears after resting</td>
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<td>— Pain in the leg which occurs walking &lt;100 m, and disappears</td>
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<td>after resting</td>
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<tr>
<td>Epidemiology</td>
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<td>— Cardiovascular global risk: 20% mortality in 3 years</td>
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<td>— Local risk of the limb: 40% evolution in CLI in 6-18 months,</td>
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<td>35% amputation in 2 years</td>
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<td>Examinations*</td>
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<td>[Gr. A]</td>
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<tr>
<td>— ABI measurement</td>
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<td>— CFDS of lower limbs to find</td>
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<td>— Indications for endovascular procedures, assessing</td>
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<td>- Site, length and extension of stenosis or obstruction</td>
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<td>- Collateral vessels</td>
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<td>— Vascular imaging: finding the indications and possibility</td>
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<td>for revascularization procedures (open or endovascular)</td>
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<td>[Gr. B/C]</td>
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<tr>
<td>— Assessment of walking ability</td>
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<td>[Gr. A]</td>
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<td>— CFDS supra-aortic arteries</td>
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<td>— CFDS abdominal aorta</td>
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<td>— Cardiac investigation</td>
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<td>Management</td>
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<td>— Open or endovascular revascularization (see text)</td>
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<td>[Gr. A]</td>
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<td>— Improvement of walking ability</td>
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<td>[Gr. C]</td>
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<td>- supervised physical training</td>
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<td>- drugs for claudication</td>
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<td>[Gr. A]</td>
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<td>— Correction of risk factors</td>
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<td>- antiplatelet drugs</td>
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<td>Follow-up</td>
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<td>— Surveillance every 3 months</td>
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<td>— Surveillance every 6 months, after two controls with stable</td>
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<td>functional and clinical parameters</td>
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<td>— Surveillance of SAoA and abdominal aorta following the</td>
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<td>specific criteria (Tables VII and VIII)</td>
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<td>— Specialistic consulting (angiologist or vascular surgeon)</td>
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<td>in case of evolutive disease</td>
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*If is not possible to have in very short time all the required information for the best treatment, the GP is advised to directly address the patient to a Vascular Lab or Vascular Care Unit for a clinical and instrumental consulting, which should be realized within 30 days. Sudden Appearance of Severe Claudication immediately send the patient to Vascular Center or to Emergency Room. CLI: critical limb ischemia; ABI: ankle brachial index; CFDS: color flow duplex scanning; SAoA: supra-aortic arteries.
meters are observed after two successive control examinations.
In case of sudden appearance of claudication pain (few steps claudication) the patient must be referred to a Vascular Center or to Emergency Room immediately.

**Revascularization in patients with intermittent claudication**

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

In moderate claudication, due to the local risk of progression of disease, the possibility to carry out revascularization may be considered whenever the best medical treatment (physical training, antithrombotic drugs, drugs for claudication) does not lead to improvement or stabilization of PAD.

In severe claudication, revascularization procedures should be considered carefully.

If IC produces a significant compromise of the quality of life in occupational terms or limits ability to perform sports, the opportunity of revascularization could be considered also in moderate and mild claudication, overall in younger patients. 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 these cases, the Padua protocol provides a useful decisional flowchart (Figure 1).

Patient should be evaluated by CFDS and other imaging examinations (angio-RM, angio-TC and angiography) of the lower limbs arteries, assessing the anatomic conditions of the arterial tree.

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

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.

The revascularization is also indicated in the case of Leriche’s syndrome (even if with light claudication) if the aortic thrombosis is near the renal arteries or shows clear tendency toward ascending aortic thrombosis.

The relative easiness of endovascular procedures for revascularization could reduce the threshold for revascularization in claudicants, the indications could be less strict and the patients could be more demanding for interventions with quicker results.

The Faculty of this Consensus Document suggests that the clinical indication criteria should
When the endovascular procedures have been utilized, a pharmacological treatment is recommended to prevent early failure because of thrombosis at the site of intervention. Standard therapy is heparinization, and a life-long antiplatelet medication to promote patency. A large meta-analysis suggests that the double anti-aggregation therapy shows an increased long-term patency, but the TASC 2nd Document underscores that larger randomized trials will be necessary to make a firm recommendation. Despite the lack of data from large randomized studies after femoropopliteal angioplasty and stenting, the Faculty of this Consensus Document recommends (according to the experience in the coronaries) a dual antiplatelet therapy (aspirin and a thienopyridin) for at least 3 months after femoropopliteal stent implantation.

**Critical limb ischemia**

We conclude this Document on the Intermittent Claudication with a short section on critical limb ischemia, just to underline the need for an early specialist consultation. The diagnosis of CLI (Table IX) should be suspected in the presence of the following symptoms:

- nighttime rest pain of lower limbs (Fontaine stage 3rd; Rutherford grade II, category 4), lasting longer than 15 days and requiring regular analgesic treatment;
- minimal ischemic cutaneous lesions

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<th>TABLE IX.—Critical limb ischemia: Fontaine 3-4.</th>
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<td><strong>When suspect:</strong></td>
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<td><strong>Epidemiology</strong></td>
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<td><strong>Requiring examinations:</strong></td>
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<td><strong>Management:</strong></td>
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<td>[Gr. A]</td>
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<td>[Gr. C]</td>
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<tr>
<td><strong>Follow-up</strong></td>
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PAD: peripheral arterial disease; CLI: critical limb ischemia.
The grouping of stages 3rd and 4th together in the Fontaine classification and of the corresponding Rutherford categories,25, 26, 29 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.133 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.25, 134 On the other hand, amputation is accompanied by a very poor prognosis: 1/3 of amputated patients die within 1 year, 1/3 achieve partial autonomy and only 1/3 obtain complete autonomy.135

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

If the diagnostic imaging features (angio-RM and angiography) are unfavorable, the patient may be a candidate for intensive pharmacological therapy136 at dedicated centers specializing in vascular disease in order to provide the highest possibility of success.137

In the case of a definite diagnosis of CLI, the GP should immediately refer the patient to a Vascular Medicine (Angiology) or Vascular Surgery Unit (Vascular Center).

If the diagnosis is uncertain and the patient does not present particularly severe general symptoms, it is reasonable to corroborate the hypothesis of an ischemic cause for nocturnal pain or cutaneous lesions. In diabetic patients, for example, accidental skin lesions of lower limbs are often diagnosed as being related to CLI. In these cases, the GP should contact a specialist center to request an outpatient assessment, measuring the transcutaneous pO2, internationally accepted method to assess the microcirculatory perfusion. The exam is very useful for staging cutaneous ischemia and assesses outcome in terms of limb salvage or of carrying out amputation.138, 139

Many vascular specialists suggest to consider and manage as CLI also the patients with typical symptoms of claudication occurring after walking a very short distance (few steps claudication) and patients with severe claudication, because the same critical aspects of CLI are present in severe claudication.140

After the critical status has been overcome, very close control visits, until clinical stability has been reached, are recommended. In cases of stabilized PAD the follow-up procedures as in moderate claudication are indicated. In cases of persistent PAD, a monthly surveillance is advised and repeated cycles of intensive treatment, searching always for new options for revascularization.

**Glossary**

6MWT: 6 Minutes Walking Test (test of spontaneous walking capacity measurement).
AsyPAD: asymptomatic lower extremity peripheral arterial disease.
ABI: Ankle-Brachial Index;
ACD: absolute claudication distance (or MWD);
Advised physical training: advice regarding a home walking exercise training program;
CLI: critical limb ischemia;
CFDS: color flow duplex scanning;
CRP: C-reactive protein;
GP: general practitioner;
IC: intermittent claudication;
ICD: initial claudication distance (or PFWD) ;
MWD: maximal walking distance (or ACD) ;
LCP: L-propionyl carnitine;
PAD: peripheral arterial disease;
PFWD: pain free walking distance (or ICD);
SAoA: supra-aortic arteries;
Supervised physical training: walking exercise training program at specialized centers under the supervision of expert staff.
WIQ: Walking Impairment Questionnaire.

**References**


60. O’Hare AM, Rodriguez RA, Bacchetti P. Low ankle brachial index associated with rise in creatinine level over time. Arch Intern Med 2005;165:1481-5.


