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Appropriateness of diagnostic and therapeutic pathways in patients with vascular disease

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Foreword

The unsuitability of requests for vascular diagnosis, which in some specialised laboratories reaches as much as 40% of the overall activity, is one of the causes that generates the well-known plethora of waiting lists. However, it is not the only cause. The old concept of "everyone has the right to a Doppler", the influence of mass media on the usefulness of an early diagnosis in vascular disease and an increase in induced requests from a high-quality offer certainly play their parts.

Among the possible organisational interventions, the distinction between urgent, relatively urgent and non-urgent procedures, in relation to the gravity of the clinical picture of the patient, seems at the moment to be the most promising.

The Hospital and Health Care Units of Padua have been considering this aspect since 2004, entrusting a commission which brings together all the vascular diagnostic experts present in the territory with the task of drawing up priority tables for the procedure of vascular diagnostics. The document elaborated by the experts was then discussed with the general practitioners (GP) of the territory for their consideration.

On the basis of this experience it was decided to approach other provinces in the region and on the request of some Health Authorities involved in the reorganisation deliberated by the Veneto Regional Committee n. 3535 of November 12, 2004, concerning the timeliness in the supply of the service, the "ANGIOVENETO" Working Group was formed to re-examine the contents of the Padua document in the light of different operating situations.

This present document is intended to reach two specific goals:

— offer the GP of the Veneto Region a guide for suitable management of vascular diseases;

— indicate the general procedures of intervention that can be expected from a specialist.

The working group proposes periodic revision of the document based on new scientific evidence which may emerge in the near future and on the basis of suggestions that colleagues and all health workers might want to give.

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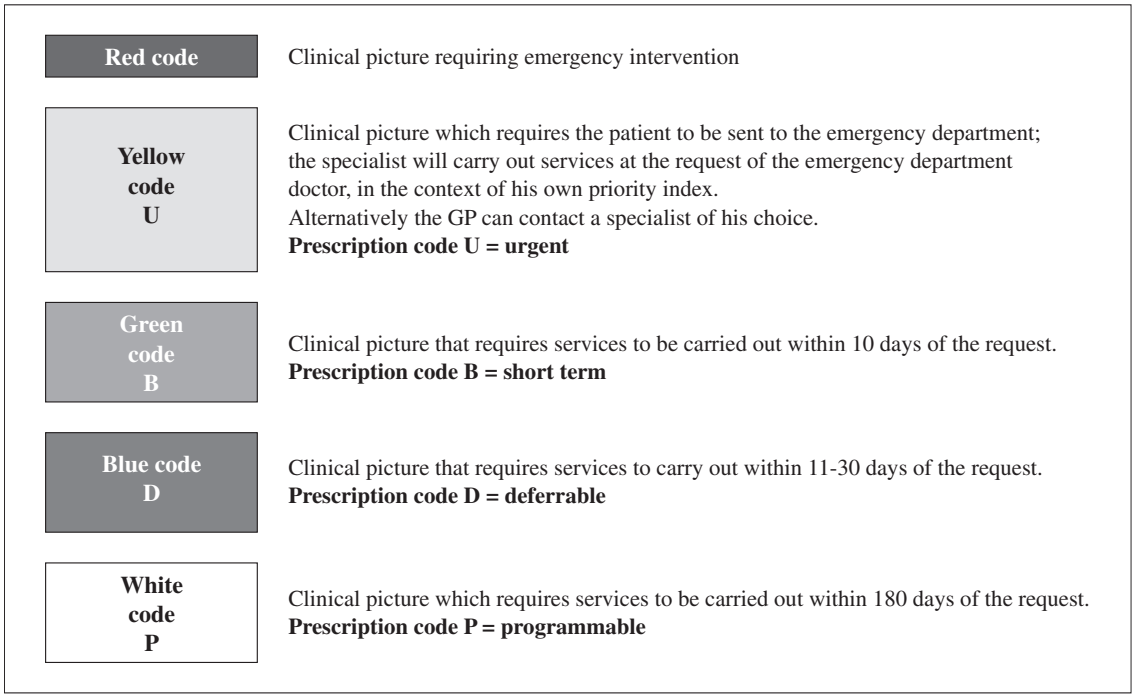

Figure 1.—Codes.

So that the initiative has the efficacy hoped for, however, the operative sharing between the GP and the specialist, while indispensable, is not enough. Two other conditions are necessary:

— adequate organisation of the system of access to the health structures providing the services;

— their tested operative quality.

As far as the first aspect is concerned it is necessary that the Unified Appointment Centres bring their information systems into line with the new timing criteria proposed by the Veneto Region and acknowledged in full by the present document, reserving preferential channels and places for the most urgent services.

The operative quality of the structure should be ensured by the presence of specialists (angiologists and vascular surgeons) who have undergone a specific training programme. However, considering that vascular diagnostic activity is also provided by other specialists, the working group suggests considering qualitatively reliable those laboratories that conform to the directives for execution and reporting proposed by the Italian Vascular Diagnostic Society (SIDV-GIUV) and that follow or have followed the programme of accreditation to excellence of the Italian Society of Angiology and Vascular Pathology (SIAPAV) with relative certification.

Quality medical treatment

The GP and the specialist are the two principal references to ensure that patients with vascular disease get the best medical treatment.

In order to achieve this, it is necessary that the single roles and the collaborative relationship between the two professional figures are agreed upon.

The role of the general practitioner in the management of patients with vascular disease

a) Diagnosis or clinical suspect of vascular disease.

TABLE I.—*Symptoms of cerebral ischemia.*

Carotid territory
— Motor disturbance (mono, hemi contralateral)
— Paresthesia (mono, hemi contralateral)
— Amaurosis fugax
— Facial paresis
— Aphasia e dysarthria
Vertebrobasilar territory
— Dizziness (associated with other symptoms)
— Disturbance of balance
— Drop attack
— Diplopia
— Dysarthria

b) Initial therapeutic approach.
c) Request for instrumental exams:
— for differential diagnosis;
— for further therapeutic approaches;
— on the indication of other specialists.
d) Request for specialist consultation:
— for further diagnostic study;
— for specific specialist therapy.
In short:
— general clinical evaluation;
— basic medical therapy;
— identification of cases to be referred to a specialist;
— follow-up.

The role of the specialist in the management of patients with vascular disease

a) First examination, often at the request of the GP.
b) Controls, often at the request of the specialist himself.
c) Therapeutic suggestions.
d) Execution of instrumental examinations.
e) Drawing up a programme for further diagnostic study.
f) Provision of specialist therapy.
In short:
— detailed diagnosis;
— specialist therapy;
— management of difficult cases;
— follow-up.

The relationship between general practitioner and specialist

GP → specialist:
— request for specialist services;
— precise diagnostic request;
— history useful for evaluation.
Specialist → GP:
— detailed diagnostic report (any therapeutic suggestions);
— reason for any further examinations and/or specialist visits;
— suggestions for a therapeutic strategy and tactics for the common management of difficult cases.

Appropriateness of choices in the clinical picture of patients with vascular disease

In acknowledging what is required from the deliberation of the Regional Committee, the document proposes the identification of assistance priorities based on the appropriateness of choices from the clinical picture of the patient, adopting a colour code corresponding to the timeliness of provision of the procedure, and the new regional prescription forms.
The colour codes are as follows (Figure 1).

Grade of recommendation according to the type of documented evidence

Grade of recommendation
Type of documented evidence:
A. At least one randomised clinical trial of high statistical or analytical value.
B. Randomised clinical trial with lower statistical value.
C. Non-randomised study of single groups Descriptive studies or cases studies. Reports on single cases.

Pathology of the supra-aortic arteries

Stroke is the third cause of death after cardiovascular disease and cancer causing 10-12% of all deaths and is the principal cause of disabling.
The prevalence of stroke in the elderly population (aged 65-84 years) is 6.5%.

Ischemic stroke represents the most common form of ictus (80%).

Every year there are 194 000 cases of stroke, of which 80% are first time episodes. This figure is sure to increase with demographic evolution.

The number of patients disabled by stroke is about 900 000, another figure which is sure to increase.

In about 1/3 of cases, ischemic stroke is due to atherosclerosis of the supra-aortic arteries (SAoA), a situation that benefits selectively from an early diagnosis for the by now consolidated possibility of a reduction in morbidity and mortality by means of carotid revascularisation in cases of stenoses ≥70%.[1-3]

The risk of stroke after transient ischemic attack (TIA) or a minor stroke is high (10-20% in the 90 days following it), above all in the first 48 h (about 5-10%).[4-10]

In particular, patients with carotid arteriopathy have a high risk of early relapse after TIA. In patients with hemispheric TIA and ipsilateral carotid arteriopathy (stenosis 50-99%) the risk of stroke at 90 days is equal to 20.1%, while the risk in the first 48 h is 5.5% (independently of the degree of stenosis).[10]

As was said above, TIA correlated with a high-grade carotid stenosis (≥70%) means a higher risk of stroke compared to a sustained condition of a light carotid stenosis (<50%).[2] In particular, the risk after 3 years of homolateral stroke or death is 30-35% in patients with carotid stenosis ≥70%.[2, 3] The risk of stroke in patients with carotid atherosclerosis is correlated not only to the grade of stenosis, but also to the composition of the plaque and therefore to its morphology (hypoechogenicity, lack of homogeneity, surface irregularities).[11-15]

Carotid arteriopathy is frequently found in the normal population, especially in the elderly and/or patients with other morbid conditions such as peripheral arteriopathy, diabetes mellitus, hypertension, ischemic cardiopathy,[16] retinal vascular occlusion,[17] and in patients after irradiation of the neck.[18]

The symptoms suggestive of vascular-cerebral pathology are reported in Table I and Table II and can be transient in character (TIA) or permanent (stroke).[1]

TABLE II.—*Non-acceptable symptoms for TIA.*

Non-focal symptoms
- — Loss of consciousness
- — Sensation of instability
- — Generalised debility
- — Mental confusion
- — Loss or reduction of visus associated with a reduced level of knowledge
- — Incontinence of faeces and urine

One of the following symptoms if isolated
- — Dizziness
- — Diplopia
- — Dysphagia
- — Loss of balance
- — Tinnitus
- — Symptoms of sensitivity limited to a part of a limb or the face
- — Scintillating scotoma
- — Transient global amnesia
- — Drop attack
- — Dysarthria

Appropriateness of examinations in pathologies of the supra-aortic arteries

Indications for the execution of a colour-Doppler (CD) of the SAoA (evaluation of the common, external, internal carotid, subclavian and vertebral arteries) according to the gravity of the clinical picture. The exam is completed with the bilateral measurement of the brachial arterial pressure (Table III).

Management of carotid arteriopathy [1, 19] (Table IV and V)

Frequency of controls in patients with carotid arteriopathy (Grade C) (Table VI)

Further checks should be requested from the specialist according to the necessity of further diagnostic study or for the planning of a possible intervention, where prescribed by the GP on the indication of the specialist (*Grade C*):

— transcranial Doppler and CD (to be executed after CD SAoA);

— angio-MR (SAoA + intracranial circle, MR cerebral parenchyma);

— angio-CT (SAoA + intracranial circle, CT cerebral parenchyma);

— angiography (SAoA + intracranial circle).

TABLE III.—*Appropriateness of examinations in pathologies of the supra-aortic arteries.*

— Stroke (Grade A)	Red code
— 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) (Grade A) — Symptoms suggestive of TIA or minor stroke in the carotid or vertebrobasilar areas, lasting less than 7 days (Grade A) — Pulsative laterocervical swelling (Grade C)	Yellow code
— Symptoms suggestive of TIA and/or minor stroke, in the carotid or vertebrobasilar areas, lasting more than 7 days (Grade A)	Green code (within 10 days)
— Asymptomatic patients, candidates for surgical intervention or coronarography (check-list) (Grade C) — Laterocervical murmur in patients with higher cardiovascular risk (Grade C) — Suspected subclavian steal syndrome (Grade C)	Blue code (11-30 days)
— Asymptomatic or symptomatic patients with symptoms lasting more than 30 days (Grade C) - Age > 65 years (also without symptoms suggestive of atherosclerotic disease or atherosclerotic risk factors) - Age < 65 years with one or more of the following conditions: - previous stroke or TIA - previous myocardial infarction - atherosclerosis in other areas (coronary, peripheral arteries) - presence of risk factors (smoking, diabetes, hypertension, dyslipidemia) - abdominal aortic aneurism - retinal vascular occlusion - radiating neck therapy - laterocervical or supraclavicular heart murmurs — Follow-up of patients subjected to thrombendarterectomy (TEA) or carotid stents (Grade C)	White code (within 180 days)

Indications for transcranial Doppler and CD: [21]

— patients with symptomatic or asymptomatic cerebral-vascular insufficiency to highlight:

- endoluminal lesions of the monitorisable intracranial vessels (Grade B);
- cerebral vasomotion reserve and residue functionality of the intracranial cerebral circulation (especially polygon of Willis) (*Grade B*);
- intracranial repercussions of extracranial lesions or subclavian steal symptoms (*Grade C*);
- risk of microembolic events in subjects who have potentially embolic lesions (*Grade B*);
- suspected coexistence of aneurysms and/or intracranial arteriovenous malformation (*Grade C*);

— subjects with suspected right-left cardiac shunt;

— subjects with subarachnoid haemorrhage for the evaluation of possible vasospastic phenomena.

Pathology of the arteries of the lower limbs

Occlusive peripheral arterial disease (PAD) may be acute or chronic. Acute PAD is acute limb ischemia (embolism, thrombosis). Chronic PAD is characterized by a chronic evolution, a stability in the phase of intermittent claudication, a risk of amputation and death in advanced stages.[22, 23]

Acute limb ischemia (Table VII)

Peripheral arterial disease

PAD is caused by atherosclerosis in more than 80% of cases and represents one of the three main localizations.

Prevalence in the general population varies from 0.6% to 6% based on diagnostic examination.[24] Recent studies based on ankle-brachial index (ABI) show that PAD affects 12% of the adult population and 20% of individuals over 70 years of age.[25]

TABLE IV.—*Management of symptomatic carotid stenosis.*

Stenosis < 50%	Correction of risk factors, medical therapy (Grade A), surveillance every 6 months (Grade C)
Stenosis 50-69%	
— Age < 75 years — Female sex — Focal symptoms lasting more than 3 months — Hyperechogenic, homogeneous, regular surface plaque	Correction of risk factors, medical therapy (Grade A), surveillance every 6 months (Grade C)
— Age > 75 years — Male sex — Focal symptoms lasting less than 3 months — Hypoechogenic, nonhomogeneous, irregular surface plaque	Consider TEA or carotid stenting (Grade B)
Stenosis ≥70%	Open (Grade A) or endovascular (Grade B) [20] revascularization If not revascularization, surveillance every 3 months in the first year, successively every 6 months (Grade C)

TEA: thromboendarterectomy.

TABLE V.—*Management of asymptomatic carotid stenosis.*

Stenosis <50%	Correction of risk factors, medical therapy (Grade A), surveillance once yearly (Grade C)
Stenosis 50-59%	Correction of risk factors, medical therapy (Grade A), surveillance every 6 months (Grade C)
Stenosis ≥60%	Consider TEA or carotid stenting (Grade A) (degree of stenosis deduced from recent studies; definitive cut-off in process of definition)

TEA: thromboendarterectomy.

In spite of the fact that diagnosis of PAD does not require expensive procedures, PAD is still underdiagnosed. It is important to ameliorate this aspect, because PAD is associated with increased cardiovascular mortality, with a risk of death that is six times higher compared to the general population.[22, 26]

The most diffuse classifications are those of Fontaine [27] and Rutherford,[28] both of which are equally valid (Table VIII).

The former classification identifies 4 stages of PAD:

1st stage: asymptomatic;

2nd stage: claudication;

3rd stage: rest pain;

4th stage: skin wound and gangrene.

The 2nd stage can be further subdivided into 2nd stage A and 2nd stage B, which are characterised by an absolute claudication distance (ACD) that is greater than or less than 200 m, respectively.

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

Table VIII shows the two classifications, signs and symptoms, and pathophysiologic mechanisms.

The 1st stage is defined as 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 intermittent claudication (IC) (2nd stage).

The pathophysiology of 1st stage is characterised by the presence of atherosclerotic plaques and the activation of inflammatory processes, with the release of substances that mediate leukocyte-leukocyte and/or leukocyte-endothelium interactions. Such molecular and cellular interactions promote successive

TABLE VI.—*Frequency of controls in patients with carotid arteriopathy.*

— Asymptomatic, age >65 years without risk factors, with CD of the SAoA negative at previous visit	5 years
— Asymptomatic, age >65 with risk factors	Once yearly
— Intima: media thickness	2 years
— Asymptomatic stenosis < 50%	Once yearly
— Symptomatic stenosis < 50% — Asymptomatic stenosis 50-59%	6 months
— Symptomatic stenosis 50-99% — Asymptomatic stenosis≥60%	Specialist consultation
— Carotid occlusion	Once yearly or every 2 years if normal contralateral carotid According to severity of contralateral stenosis
— High risk plaques (hypoechogenic, non-homogeneous, irregular surface) Previous intervention on carotid plaques	6 months
— TEA or carotid stent	1st control within 3 months, 2nd control within 9 months, successively every 12 months

leukocyte activation involving deposition of chemokines on the endothelial surface and facilitate adhesion and migration of leukocytes to subendothelial tissues.[29] Activation of an inflammatory response at the level of plaques leads to local complications (plaque rupture and thrombosis)[30, 31] and systemic dissemination of pro-inflammatory molecules (high-risk plaques) that can induce complications at other vascular sites (Tables IX, X).[32-35]

The 2nd stage is characterised by IC, defined as the presence of repetitive, painful cramping of leg muscles that occurs during walking or climbing stairs and goes away upon resting.

The further division into subgroups 2nd A and 2nd B in the Fontaine classification, and especially in the 3 categories of Rutherford's classification, is quite useful as the natural history of the arteriopathy in patients with more impairing ACD is decidedly more severe.

Patients with mild claudication (2nd stage A, ACD greater than 200 m) remain stable in about 75% of cases [36-39] and the presence of claudication has an important clinical role as an indicator of global cardiovascular risk (myocardial infarction and stroke). The natural history of patients with moderate claudication (ACD less than 200 m) and especially that of patients with severe claudication (ACD less than 100 m) indicates a higher cardiovascular risk and an elevated risk of progression of local disease (Tables XI, XII, XIII, XIV).[23, 40]

The 3rd stage (ischemic rest pain) corresponds to grade II, category 4 in the Rutherford scheme; the 4th stage (ischemic cutaneous lesions) corresponds to Rutherford grade III. Since 1989,[41] the definitions of chronic critical ischemia of lower limbs or critical limb ischemia (CLI) have been combined according to collectively accepted terminology.

CLI is defined as the presence of persistent rest pain lasting longer than 15 days that requires regular analgesic treatment, which may or may not be associated with ischemic cutaneous lesions.

In spite of the fact that the term CLI is comprehensive of very different clinical pictures, that often require personal management, it does draw the attention of physicians to the criticalness of the clinical picture, with elevated risk of amputation and death.

TABLE VII.—*Acute limb ischemia.*

Acute ischaemia	Red code (emergency services)
— When to suspect	— Recent absence of arterial pulses — Pallor of the limb (cyanosis in patches) — Hypothermia (thermal touch; in respect to the contralateral limb) — Paresthesia and lack of sensibility — Reduction of motor function
— Differential diagnosis	— Heart failure in patients with PAD — Acute venous thrombosis — Acute compressive neuropathy
— Non atherosclerotic causes of acute ischaemia	— Arterial traumas (also iatrogenic) — Aortic dissection — Vasculitis with thrombosis — Idiopathic thrombosis (thrombophilia) — Entrapment of popliteal artery or popliteal cyst with thrombosis — Vasospasm with thrombosis (ergotism)
— Causes of acute ischaemia in patients with atherosclerosis	— Thrombosis in arterial stenosis (thrombosis on plaque) — Thrombosis of arterial bypass — Heart embolism, atheroembolism — Thrombosis of popliteal aneurysm

The stages of rest pain could be further distinguished according to the way in which pain manifests itself:

3rd stage A: rest pain only in a horizontal position that goes away when the limb hangs loose;

3rd stage B: persistent rest pain.

However, at present the distinction between these two clinical conditions does not lead to different therapeutic strategies. Thus, for simplicity, a general definition of rest pain is used.

The 4th stage on the Fontaine classification (ischemic skin wounds or gangrene) is comparable to category 5 or 6 in the Rutherford scheme, since the entity of cutaneous necrosis strongly affects therapy and therapeutic timing. Cutaneous lesions require particular attention due to the possibility of bacterial infection, thus influencing the treatment strategy (Table XV).

MEASUREMENT AND RELIABILITY OF THE ANKLE-BRACHIAL INDEX

In diabetic patients, an ABI greater than 1.3 is frequent because of the presence of Mönckeberg medial calcification of arteries, which renders the tibial arteries non-compressible.

In these cases, international guidelines suggest that the Toe Systolic Blood Pressure (TSBP)[43, 44] should be measured.

In Italy, this test is used less frequently and is not always reliable; therefore, in accordance with the Interdisciplinary Group of the Diabetic Foot,[45] it is suggested that the CD should be performed (Table X).

MEASUREMENT OF WALKING CAPACITY

Measurement of walking capacity is useful for assessment of disabilities and for monitoring the stability, improvement, or worsening of the clinical picture with respect to the natural history of the disease and its treatment.

The treadmill test is the most widely used method for measuring walking capacity, although its wide-scale utilisation is unfeasible due to organization or costs.

Valid alternatives to assess clinical status that are more feasible in a surgery include:

— the six-minute walking corridor test (6WCT): the patient walks in a corridor of known length for 6 min or until the occurrence of leg pain; distance and time are reported;

— Walking Impairment Questionnaire

TABLE VIII.—*Classification of PAD according to Fontaine and Rutherford.*

Fontaine		Signs and symptoms	Pathophysiology	Rutherford		
Stage	Clinic			Clinic	Grade	Category
1st	Asymptomatic (silent arteriopathy)	Fortuitous discovery of aortic and iliac calcifications	Atherosclerotic Plaques High-risk plaques Inflammation of atherosclerotic plaques Atherothrombosis	Asymptomatic (silent arteriopathy)	0	0
2nd A	Mild claudication	ACD > 200 m Recovery T < 2 min	Discrepancy between oxygen demand and arterial supply	Mild claudication	I	1
2nd B	Moderate or severe claudication	ACD < 200 m Recovery T > 2 min	Higher discrepancy between oxygen demand and arterial supply	Moderate claudication	I	2
		ACD < 100-80 m Recovery T > 2 min	Highest discrepancy between oxygen demand and arterial supply + acidosis	Severe claudication	I	3
3rd	Ischaemic rest pain	Ischaemic rest pain	Severe skin hypoxia and acidosis Infection	Ischaemic rest pain	II	4
4th	Ischaemic 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

Recovery T: recovery time.

(WIQ): specific instrument for the evaluation of the walking capacity.[46]

The WIQ quantifies walking performance by evaluating three different parameters:

— distance (normal minimal score 70);

— velocity (normal minimal score 40);

— stair climbing (normal minimal score 60).

In clinical practice it is sufficient to evaluate the walking capacity (also by GP) using the 6WCT, and to use the treadmill test only under the following conditions:

— 1 month before and after revascularization procedures;

— before and after physical training programmes;

— clinical evaluation of the efficacy of pharmacological therapy;

— discrepancies between the clinical picture and the results of diagnostic examinations.

Nocturnal pain of lower limbs or light cutaneous lesions may not be ischemic, especially in diabetic patients. In these cases of uncer-

TABLE IX.—*Silent peripheral arterial disease.*

Silent arteriopathy - Fontaine 1st stage	Rutherford 0/0	White code (within 180 days)
When to suspect	— Asymptomatic subjects with fortuitous discovery of aorta and iliac plaques or calcification of arterial wall — Age >70 years — Diabetic patients age > 50-69 years — Asymptomatic absence of lower limb pulse	
Epidemiology	— Prevalence 12-20% — Risk of progression to severe claudication: - 25% in 2-5 years - 6-10% in 12-18 months [40, 42] — Marker of global CV risk (at 5 years): [22, 25, 26] - nonfatal CV events 5% - CV mortality 30%	
Required examinations	— ABI measurement; if indicated, CD lower limbs	
Management	— Confirmed diagnosis: investigation and treatment of risk factors, additional studies as for patients with claudication	
Follow-up	— Unconfirmed or uncertain diagnosis: surveillance once yearly or every 2 years	

ABI: ankle-brachial index; CV: cardiovascular; PAD: peripheral arterial disease.

TABLE X.—*Meaning of ABI.*

ABI	Meaning
>1.30	— Not reliable (perform CD)
>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, likely with multiple lesions along the arterial trunk

tainty, it is reasonable to perform all diagnostic examinations indicated for moderate or severe claudication, as well as transcutaneous measurement of the pO_2, which is internationally accepted for evaluation of the status of cutaneous microcirculatory perfusion. This test is very useful for staging cutaneous ischemia and assesses outcome in terms of limb salvage or of carrying out amputation.[52, 53]

Patients undergoing intensive pharmacological treatment should be referred to an Angiology or Vascular Surgery Unit for better management of PAD.[54]

Peripheral arteriopathy in diabetic patients

PAD is one of more frequent complications of diabetic macroangiopathy, in which the male/female ratio of 3:1 found in nondiabetic PAD is reduced to 2:1 or even 1:1.

More than 8% of diabetic patients at the time of diagnosis of diabetes already have PAD.[55]

Management of diabetic patients is different from that of non-diabetic patients because the first symptom of diabetic PAD is often the occurrence of cutaneous lesions owing to the minor relevance of intermittent claudication (higher pain threshold, combined with neuropathy).

This difference means that a careful vascular surveillance of the diabetic patient must be carried out by the GP, by the centres for the prevention and cure of the diabetic foot and by the territorial structures and hospitals of Angiology and Vascular Surgery Units.

The GP must make periodic controls of the presence of arterial pulses and/or vascular bruits, the walking ability and the trophic state of the skin,[56, 57] requesting and carrying out personally the measurement of the ABI when a reduction in pulsation is revealed,

TABLE XI.—*Mild claudication.*

Mild claudication - Fontaine 2st stage	Rutherford I/1	White code (within 180 days)
When to suspect	— Pain in legs that occurs during walking > 200 m and disappears after resting, with recovery time <2 minutes — Pain in the legs after climbing more than two flights of stairs	
Epidemiology		
	— Prevalence 12-20% — Risk of progression to severe claudication: - 25% in 2-5 years - 6-10% in 12-18 months [40, 42] — Marker of global CV risk (at 5 years):[22, 25, 26] - nonfatal CV events 5% - CV mortality 30%	
Required examinations (Grade A)	— ABI measurement; if indicated, CD lower limbs — CD SAoA — CD abdominal aorta — Cardiological examination for coronary artery disease — Assessment of walking capacity (optional)	
Management		
(Grade A)	Goals: — Slow disease progression and prevention of fatal and non-fatal CV events: - correction of risk factors - antithrombotic (antiplatelet) drugs	
(Grade B/C)	— Improvement of walking capacity: - supervised physical training - drugs for claudication	
Follow-up	— Surveillance once yearly after two controls with stable functional and clinical parameters — Surveillance of SAoA and abdominal aorta following specific criteria (see relative paragraphs) — Specialist consultation (angiologist or vascular surgeon) [Blue code (11-30 days)] in case of progressive disease	

ABI: ankle-brachial index; CV: cardiovascular; SAoA: supra-aortic artery.

the presence of a bruit or the reduction in walking capacity (evaluation of 1st level).

Further investigation of 2nd level (CD) and 3rd level (angiography, angio-MR, angio-CT) will be adopted where appropriate according to the suggestions of the flow chart reported below (Figure 2).

In the case of occurrence of cutaneous ulcers it is suggested to proceed directly to an evaluation of 3rd level in order to provide the patient with the most suitable treatment in the shortest possible time.

The surveillance is referred to the GP and/or the centre for the prevention and cure of the diabetic foot. All diabetic patients whose disease goes back more than 20 years should undergo a vascular evaluation of 1st and 2nd level at least once and be included in a specific follow-up according to the results.[58]

Pathology of the abdominal aorta (aneurysms)

Although it is quite frequent, the pathology of the abdominal aorta gives few signs and symptoms that can indicate it at an early stage.

Thirteen percent of patients affected by PAD present an aneurysm of the abdominal aorta (AAA),[59] while the data relative to the association of arterial hypertension with AAA are very variable in different studies. The only certain datum is that the relative risk of

TABLE XII.—*Moderate claudication.*

Moderate claudication - Fontaine stage 2nd B	Rutherford I/2	White code (within 180 days)
When to suspect	— Pain in legs that occurs during walking < 200 m and disappears after resting, with recovery time >2 minutes — Pain in legs climbing fewer than two flights of stairs	
Epidemiology	— Prevalence 12-20% — Risk of progression to severe claudication: - 25% in 2-5 years - 6-10% in 12-18 months [40, 42] — Marker of global CV risk (at 5 years): [22, 25, 26] - non-fatal CV events 5% - CV mortality 30%	
Required examinations	— ABI measurement	
(Grade A)	— CD lower limbs to assess indications for endovascular procedures: - investigation into site and extension of stenosis or obstruction - investigation into collateral vessels (test of deep femoral artery)	
(Grade C)	— Assessment of walking capacity	
(Grade A)	— CD SAoA	
(Grade A)	— CD abdominal aorta	
(Grade A)	— Cardiological examination for coronary artery disease	
Management	Goals:	
(Grade A)	— Slow disease progression and prevention of fatal and non-fatal CV events: - correction of risk factors - antithrombotic (antiplatelet) drugs	
(Grade B/C)	— Improvement in walking capacity: - supervised physical training - 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 specific criteria (see relative paragraphs) — Specialist consultation (angiologist or vascular surgeon) [Blue code (11-30 days)] in case of progressive disease	

ABI: ankle-brachial index; CV: cardiovascular; SAoA: supra-aortic artery.

AAA is high in subjects with a family history of the same pathology.

It is also useful for the evaluation to include the measurement of the diameter (Ø) of the non-aneurysmatic aorta and the calculation of the ratio Ø aneurism / Ø native aorta as there are important differences between populations (Ø 21.4 mm in the population of Western Australia,[60] 17 mm in the Brazilian population [61] and 18.4 mm in the Danish population[62]). In the absence of relevant epidemiological data that can identify a sure reference cut-off, a ratio around 2 would suggest careful surveillance, while a value of 2.5 would be an indication of surgery.[63]

Appropriateness of examinations in the pathology of the abdominal aorta

Indications on the execution of CD of the abdominal aorta (*Grade A*) according to the clinical picture are reported in Table XVI. The examination is to be completed with CD of the iliac axes and measurement of the ABI.

TABLE XIII.—*Severe claudication.*

Severe claudication - Fontaine stage 2ndt B	Rutherford I/2	Blue code (11-30 days)
When to suspect	— Pain in legs that occurs during walking < 80-100 m and disappears after resting, with recovery time > 2 minutes — Pain in legs climbing less than one flight of stairs	
Epidemiology	— Global CV risk: 20% mortality in 3 years — Local risk of limb involvement: - 40% evolution in CLI in 6-18 months - 35% amputation within 2 years	
Required examinations* (Grade A)	— ABI measurement — CD of lower limbs to assess: - investigation into site and extension of stenosis or obstruction - investigation into collateral vessels (test of deep femoral artery) — Angiography: determine the indications and possibility of revascularization procedures (open or endovascular)	
(Grade B/C)	— Assessment of walking capacity	
(Grade A)	— CD SAoA	
(Grade A)	— CD abdominal aorta	
(Grade A)	— Cardiological examination for coronary artery disease	
Management:		
(Grade A)	— Open or endovascular revascularization (favourable angiographic picture)	
(Grade A)	— Improvement in walking capacity: - supervised physical training - drugs for claudication	
(Grade C)	— Correction of risk factors and modification of lifestyle	
(Grade A)	— Antithrombotic (antiplatelet) drugs	
Follow-up	— Surveillance every 3 months — Surveillance every 6 months, after two controls with stable functional and clinical parameters — Surveillance of SAoA and abdominal aorta following specific criteria (see relative paragraphs) — Specialist consultation (angiologist or vascular surgeon) [Green code (within 10 days)] in case of progressive disease	

* Considering the difficulties in obtaining all the diagnostic information necessary in a reasonably short time, the GP is advised to refer the patient to a vascular clinic or vascular care unit for a clinical and instrumental consultation, which should be performed within 30 days [Blue code (11-30 days)]. ABI: ankle-brachial index; CV: cardiovascular; SAoA: supra-aortic artery.

TABLE XIV.—*Sudden appearance of severe claudication.*

Sudden appearance of severe claudication	Yellow code

Further examinations are to be requested by the specialist in relation to the necessity of further diagnostic study or for the planning of a possible vascular or endovascular surgical operation, where prescribed by the GP on the indication of the specialist (Grade C):

— angio-spiral CT (with 3 mm sections) with 3D elaboration;

— angio-MR;

— angiography.

Management of patients with abdominal aortic aneurysm [64] and frequency of controls (Table XVII)

Pathology of the renal arteries

From 30% to 40% of patients with PAD suffer from stenoses of the renal arteries, independently of the presence of renovascular hypertension, and the progression of the stenoses is verified in about 20% of cases per year,[66] the risk of progression being highest among those with a stenosis greater than 60%, hypertension and diabetes.[67] The evaluation of this compartment is therefore:

— advisable at least once in the diagnostic programme for PAD,

— to be recommended in case of the coexistence of arterial hypertension or renal insufficiency (RI) in PAD.

The main causes of stenoses of the renal arteries are atherosclerosis (about 90% of the

TABLE XV.—*Critical limb ischemia.*

Critical limb ischemia - Fontaine stage 3rd - 4th	Rutherford II/4-III/5-III/6	Green code (within 10 days)
When to suspect	— Chronic ischemic rest pain of lower limbs (Rutherford II/4), requiring regular analgesic drugs — Cutaneous ulcers leg related to PAD (Rutherford III/5) — Extensive cutaneous ulcers or gangrene of the forefoot or foot attributable to objectively proven PAD (Rutherford III/6) — Pain in legs after very short walking distances	
Epidemiology	— Incidence: 450 cases/year/million inhabitants [47] — Relative risk of amputation: - nonrevascularized 50% - revascularized 26% — Relative risk of death: - nonrevascularized 50% - revascularized 18% [48, 49] — Outcome after amputation: - total autonomy 33% - partial autonomy 33% [50] - death 33%	
Required examinations (Grade A)	— None — Refer patients directly to a vascular medicine or vascular surgery unit	
Management:		
(Grade A)	— Open or endovascular revascularization	
(Grade A)	— Intensive pharmacological treatment [51]	
(Grade A)	— Supervised physical training for rehabilitation or therapy for claudication	
(Grade C)	— Drugs for claudication	
(Grade A)	— Correction of risk factors and antithrombotic (antiplatelet) drugs	
Follow-up:	Once no longer critical, very frequent control visits, with frequency related to clinical stability. — Stabilised PAD: follow-up procedures as for moderate claudication — Persistent CLI: monthly surveillance and repeated cycles of aggressive treatment, assessing the possibility of revascularization	

CLI: critical limb ischemia; PAD: peripheral arterial disease.

cases), usually found in males, smokers, those with arteriopathy and those over 50 years old, and fibromuscular dysplasia (10% of cases), usually found in women between the ages of 15 and 50.

The clinical suspect of renal artery stenosis derives from the combination of signs (Table XVIII), which taken singularly have little predictive value.

Appropriateness of examinations in pathology of the renal arteries

Indications for CD of the renal arteries according to the clinical picture (Table XIX).

Frequency of controls in patients with stenoses of the renal arteries (Table XX)

Pathology of the celiac tripod and mesenteric arteries

The prevalence of atherosclerotic alterations in the celiac tripod and mesenteric arteries has little clinical relevance; the examination in this compartment should be carried out only if there is a well-grounded clinical suspect of *angina abdominis* (Table XXI).

Pathology of the veins of the lower limbs

Instrumental diagnostics with Doppler ultrasound or CD in venous pathology are

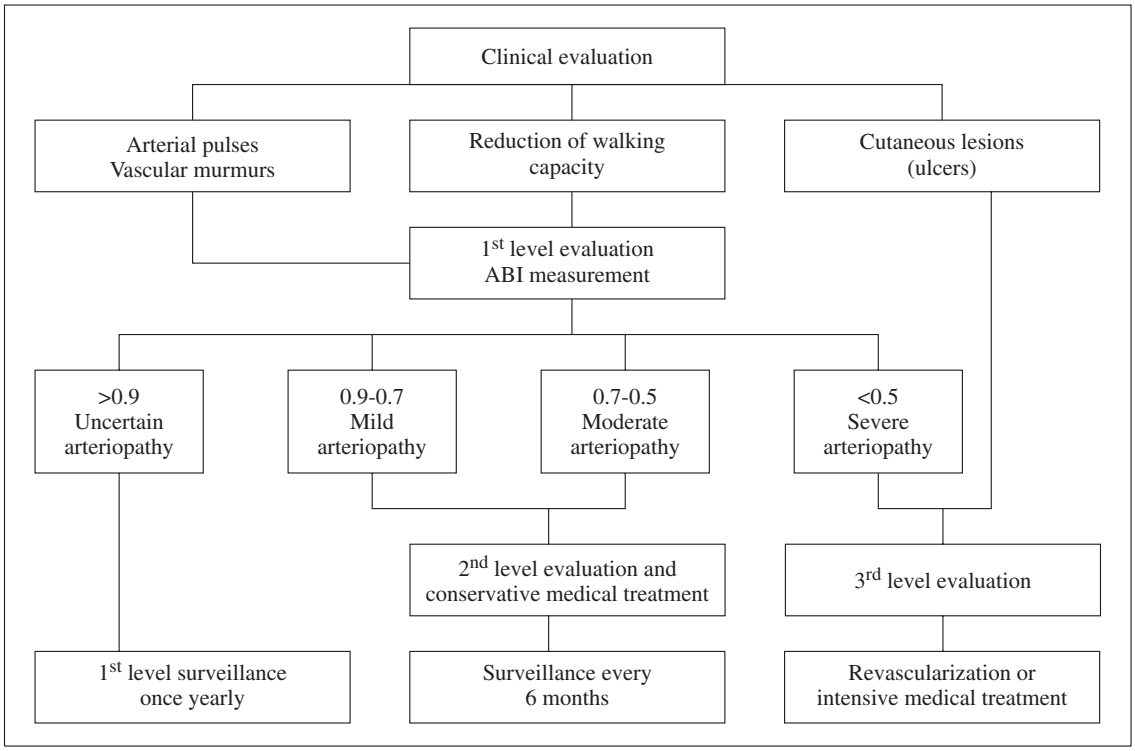

Figure 2.—Flow-chart for management of peripheral arterial disease in diabetic patients.

aimed principally at thrombotic pathology and chronic venous insufficiency.

Thromboembolic venous disease

Thromboembolic venous disease (TEV) is a clinical-anatomic condition which consists of a thrombotic pathology in the deep venous circle (DVT) of the lower limbs, associated or otherwise with pulmonary embolism (Tables XXII, Table XXIII).

Given that the different centres have different protocols with various therapeutic possibilities and the timeliness of the controls depends on both these variables, it is strongly recommended that a specialist angiology examination is requested to exclude both thrombosis and other similar pathologies.

Management of DVT can be made using the schemes given below (Tables XXIV, XXV and XXVI).

Superficial venous thrombosis
(Table XXVII)

Chronic venous insufficiency

The most frequent symptoms found in patients with chronic venous insufficiency (CVI) are a sense of heaviness in the lower limbs, made worse with prolonged orthostatism, evening edema or subedema (signs from stockings), a persistent sense of restlessness in the legs for which it is not easy to find relief.

From the physiopathologic point of view CVI is characterised by a difficult venous return to the lower limbs, stasis, venous hypertension, increase in the capillary permeability, inflammatory activation and stimulation of the subcutaneous pain receptors .

Etiologically CVI may be primitive, that is linked to a non-corrected varicose disease, or secondary to a post-thrombotic syndrome.[86] Unfortunately none of the above mentioned symptoms is pathognomonic of CVI, but may

TABLE XVI.—*Appropriateness of the abdominal aorta examination.*

Clinical picture	Code
Abdominal pain in the presence of:	
— Known AAA	Red code
— Pulsing abdominal mass	Yellow code
— Absence of femoral pulse not previously noted (suspect ascendant aortic thrombosis) — Pulsing abdominal mass In case of confirmed AAA and/or aneurysm of the iliac axes, it is advisable to refer the patient for specialist consultation	Green code (within 10 days)
— Iliac Doppler indicative of upstream hemodynamic stenosis — Blue toe syndrome	Blue code (11-30 days)
— When the presence of AAA cannot be clinically excluded — Age > 50 years with family history of AAA — Presence of peripheral or carotid arteriopathy — Occasional aortic calcifications — Age > 65 years (males) — Age < 65 years with risk factors (smoking, diabetes, hypertension, dyslipidemia) — Follow-up in patients with aortic endoprosthesis	White code (within 180 days)

TABLE XVII.—*Management of AAA and frequency of controls (Grade A).*

Ø* 30-39 mm	Surveillance once yearly
Ø ≥40 mm	Surveillance every 6 months
Ø ≥48 mm	Angio-CT or angio-MR (intervention)
Ø with accelerated growth (10 mm/year or 7 mm/6 months)	Angio-CT or angio-MR (intervention)
Asymptomatic without risk factors and negative echo-CD for AAA	Follow-up not indicated
Asymptomatic with risk factors and negative echo-CD for AAA	Surveillance every 3 years
Ratio Ø AAA / Ø non-aneurysmatic aorta > 2	Surveillance every 6 months
Ratio Ø AAA / Ø non-aneurysmatic aorta > 2.5	Angio-CT or angio-MR (intervention)
Subjects with aortic endoprosthesis	1, 3, 6, 9, 12 months after the procedure; then surveillance once yearly [65]

Ø: diameter.

also be seen in other morbid conditions. For this reason the classifying of CVI cannot be only clinical, even though the diagnosis of varices certainly does not impose difficulties.

The aims of clinical and instrumental evaluation in a patient with CVI are:

1. confirmation of the CVI diagnosis;

2. identification of the condition of primitive or secondary CVI;

3. identification of the state of compensated or non-compensated CVI;

4. evaluation of the indications for surgical treatment and its outcome.

1) Confirmation of the diagnosis of CVI

The first approach is certainly through natural history. The history must be suitably guided with specific questions aimed at recognising the presence, even if remote,

TABLE XVIII.—*Clinical and laboratory signs of renovascular disease.*[68, 69]

History
- — Sudden appearance of hypertension, especially before 30 years of age or after 50-55 years (before 50 years it suggests fibromuscular dysplasia, above 50 years atherosclerotic disease) or worsening of a condition of hypertension previously under control
- — Family history negative for essential hypertension
- — 3rd grade hypertension or unresponsive to medical therapy (at least 3 drugs), associated or not with RI
- — Episodes of recurrent pulmonary edema without any evident cardiac anomaly or dysfunction
- — Atrophic kidney or asymmetry of the dimensions of the two kidneys (about 1.5-2 cm) associated or otherwise with hypertension
- — Presence of compartmental atherosclerotic vascular lesions
- — Smoking habit
- — RI following the use of ACE-inhibitors or angiotensin II blockers
- — RI unjustified by other pathologies associated or otherwise with hypertension

Physical examination
- — Systolic-diastolic abdominal bruit
- — Test results suggestive of carotid or peripheral arteriopathy
- — 3rd or 4th grade retinopathy

Laboratory tests
- — Unexplained hypokalemia with high potassiuria
- — Proteinuria
- — High plasma renin activity

RI: renal insufficiency.

TABLE XIX.—*Appropriateness of examinations in pathology of the renal arteries.*

— *Screening for renovascular pathology in patients with hypertension and/or RI and/or PAD* Suspect of stenosis of the renal arteries based on the clinical and laboratory characteristics listed in Table XVIII according to clinical judgement (in patients with PAD screening is advisable at least once during the diagnostic programme for PAD and is recommended if it coexists with arterial hypertension and/or RI)	White code (within 180 days)

RI: renal insufficiency; PAD: peripheral arterial disease.

TABLE XX.—*Frequency of controls in patients with stenoses of the renal arteries.*

— Stenosis of the renal artery < 60%	— Once yearly
— Stenosis of the renal artery > 60%	— Every 6 months
— Patients who have undergone stenting of the renal artery	— At 1, 3, 6, 12 months after the procedure and successively once yearly controls

TABLE XXI.—*Angina abdominis.*

CD of the mesenteric arteries (with test of stimulation of a meal) — Exclusively in case of well-grounded suspect of "angina abdominis"	Green code (within 10 days)

of events that facilitate or trigger off DVT (*e.g.* swollen leg after plaster cast, an operation, giving birth, a long confinement to bed), and at evaluating the time of the appearance of the symptoms and signs, and their presence in both legs or just one (suspect secondary CVI).

The physical examination does not present difficulties, but it should be carried out according to the CEAP classification (Table XXVIII).

As well as noting the presence of single alterations given in the classification it should be noted that in primary CVI (often bilateral)

TABLE XXII.—*Thromboembolic venous disease.*

Epidemiology

The incidence of DVT and pulmonary embolism in the general population varies according to the case records, exceeding in any case 1 per 1 000. TEV is more and more frequently met in clinical practice inside and outside hospital because of: extension of surgical operations to a wider band of the population, lengthening of the average life-time, lengthening of the survival of patients with neoplasia, increase in traumatic pathologies (road accidents, sports, etc.).[70-76]

The greater diagnostic possibilities with non-invasive, repeatable examinations and the greater knowledge of the problem on the part of doctors are two other factors which may have some impact on such frequency.

In the large majority of cases pulmonary embolism is associated with the presence of DVT in the lower limbs.

When to suspect

The symptoms and clinical signs which lead to clinical suspect of DVT are as follows:

— pain at rest and/or when walking
— edema
— cutaneous hyperesthesia
— reddening and other alterations in colour of the cute
— presence of a cutaneous venous reticulum

These are non-specific signs and therefore the clinical suspect of DVT must always be confirmed by the results of diagnostic tests.

Examinations to request

In the instrumental diagnosis of TEV, CD is considered the principal means of investigating venous thrombosis of the lower limbs (Grade A).[73-81]

Associated investigations. In recent years many studies have been carried out with the aim of identifying the best diagnostic approach, that is the one able to give an early, accurate diagnosis reducing the number of ultrasonographies and controls. These studies are based on the dosing of D-dimer, which is the product of degradation of stabilised fibrin, and on the a priori clinical probability.[82-85]

DVT: deep venous thrombosis; TEV: thromboembolic venous disease.

the superficial venous system is twisted and dilated, while in secondary CVI (usually in one leg only) the superficial venous system may be normal or dilated and is not usually very twisted.

2) Identification of the conditions of primary or secondary CVI

The clinical orientation deduced from the natural history and physical examination of the patient must be confirmed with a CD which must examine all three venous compartments, superficial, deep and perforating.

In primary CVI the superficial venous system, as was already said, is twisted and dilated, with a significant saphenous back flow. The venous valves are present (except in cases of primitive agenesia), mobile, but incontinent. The deep venous system is integral except in cases of old, non-treated varicose disease. The perforating system may be continent or incontinent depending on the evolutionary stage of the disease.

In secondary CVI the superficial system is integral in the initial stages of the disease (recent post-thrombotic syndrome, DVT not older than 4-6 years); in the later stages there may be dilatation (post-thrombotic or post-phlebitic varices), but the course of the disease is prevalently straightforward. The valves are mobile and continent, except in the most advanced stages of the disease.

The deep system may have parietal thrombotic residues or a complete recanalisation (valvular stumps) with consequent incontinence (back flow).

The perforating system may be continent or incontinent according to the evolutionary stage of the disease.

The CD examination must be completed with a careful hemodynamic study, evaluating the direction of the flow and back flow and identifying the supply circulation (venous mapping). This evaluation, which should be part of all venous CD examinations of the lower limbs, is indispensable in pre-operative evaluation.

TABLE XXIII.—A priori *clinical probability of deep venous thrombosis.*

GP	Given the difficulty of a clinical diagnosis of DVT the GP is advised to take a standardised approach using the Wells score (clinical probability) [85]		
	Wells score		
	— Active cancer	1	
	— Paralysis, paresis or plaster cast of the lower limb		1
	— Recent confinement to bed and/or major surgery		1
	— Localized tenderness along the distribution of the deep vein system		1
	— Swelling of the entire limb	1	
	— Increase in the circumference of the calf (> 3cm compared to the healthy limb)		1
	— Pitting edema of the symptomatic limb		1
	— Collateral superficial veins (non varicose)		1
	— Previously documented DTV		1
	— Alternative diagnosis		-2
	Likely DTV		≥2
	Unlikely DTV		<2
	As soon as the doctor decides on this basis that the suspect of DTV is valid, we consider that he should be given the maximum possible help (Yellow code).		

TABLE XXIV.—*Management of deep venous thrombosis.*

Suspect DVT or Relapse DVT	Casualty Department or specialist CD Start therapy with EBPM	Yellow code
Negative CD Likely DVT or positive D-dimer	GP Therapeutic indications + programmed control in 3-7 days	Green code (within 10 days)
Positive CD	DVT confirmed: hospitalisation or home management; short term control	Blue code (11-30 days)

TABLE XXV.—*Frequency of controls for patients with deep venous thrombosis.*

— DVT in treatment	— At 3rd, 6th and 12th month
— After suspension of anticoagulation therapy	— Every 6 months for 2 years

3) Identification of the state of compensated or uncompensated CVI

The diagnosis of compensated or uncompensated CVI depends on the extent of the venous hypertension and the efficiency of the venous muscle pump. The clinical picture CEAP C3 (edema) and C4 (cutaneous alterations) lead to suspect of an uncompensated CVI. The edema is correlated with an increase in the capillary permeability, and the cutaneous alterations with inflammatory activation (dermatitis) and with an increased erythrocytic diapedesis (ochre dermatitis).

However, since the cutaneous alterations once started do not regress and therefore do not modify a C4 diagnosis, an instrumental evaluation of this condition can be usefully made.

The phlebodynamometry is an obsolete exam from a clinical point of view, even

TABLE XXVI.—*Criteria for home therapy for deep venous thrombosis.*

Criteria for exclusion

Patients who, wherever the thrombosis is localised, present one or more of the following conditions:

1) alcoholic or uncooperative patients
2) patients with other affections that require hospitalisation
3) patients with strong suspect of occult neoplasia
4) patients with symptoms of pulmonary embolism (that is with the presence of manifest symptoms, whereas asymptomatic pulmonary embolism revealed in scintigraphy, very common in patients with thrombosis, is not a counter indication for home treatment);
5) patients with a high risk of bleeding due to the effect of anticoagulant therapy;
6) patients living too far from the hospital
7) elderly people living alone
8) patients for whom it is not possible to monitor home, oral anticoagulant therapy

Conditions for home treatment

1) Instrumental diagnosis of DVT
2) Instructions for the patient concerning what the therapy involves which he or she will have to manage in part
3) Quick and easy access in case medical advice is needed
4) Constant availability of medical staff or paramedical staff
5) Control of the platelet count after about 5 days to check any possible development of platelet disorders induced by heparin, which would require immediate suspension of the medicine and hospitalisation of the patient (if the treatment was initially at home) to deal with the case
6) The possibility that the start and continuation of the anti-coagulant therapy can be directly managed from the base clinic

TABLE XXVII.—*Superficial venous thrombosis.*

— Superficial venous thrombosis	— The treatment and control of superficial venous thrombosis (SVT) vary considerably, according to the site and spread. In SVT of the saphenous vein to the thigh it should be noted that the incidence of pulmonary embolism is higher than one might think (33%). If CD is necessary, as indicated below, an angiology examination is strongly recommended.	
— GP	— Clinical diagnoses and start of treatment and follow-up	
	With the exception of:	
SVT of the trunk, ascending towards the inguen or the popliteal cavity	— Specialist chosen through direct contact	
SVT with suspect association and/or extension to the deep veins	— Emergency Department → Specialist	Yellow code
SVT + significant risk factors for DVT		
Persistent SVT or worsening despite therapy	Specialist - CD	Green Code (within 10 days)
SVT controls to change dressings, prescriptions for elastic stockings, suspension of therapy	Specialist - CD	Blue code (11-30 days)

CD: colour Doppler; GP: general practitioner; DVT: deep venous thrombosis.

though its invasiveness is relatively modest. Equivalent information can be obtained with infrared photoplethysmography (infrared-PPG) also known as light reflection rheography, which evaluates the extent of the emptying of the subpapillary venous plexus induced by contraction of the calf muscles, and the refilling time.

TABLE XXVIII.—. *CEAP classification (C = clinical data).*

Class	Signs	Symptoms
C0	No visible signs of venous disease	With or without symptoms [S] o [A]
C1	Reticular veins and/or telangectasias	With or without symptoms [S] o [A]
C2	Trunk varices	With or without symptoms [S] o [A]
C3	Edema	With or without symptoms [S] o [A]
C4	Cutaneous signs of venous stasis (dermatitis, eczema)	With or without symptoms [S] o [A]
C5	Cutaneous signs of venous stasis + healed ulcer	With or without symptoms [S] o [A]
C6	Cutaneous signs of venous stasis + active ulcer	With or without symptoms [S] o [A]

S: symptomatic; A: asymptomatic.

TABLE XXIX.—*Management of chronic venous insufficiency.*

CEAP C0 / C1	Diagnosis and treatment responsibility of GP CD and PPG are not indispensable; useful for: — differential diagnosis — serious symptoms (PPG) — screening in the presence of risk factors (family history, occupational risk)	White code (within 180 days)
CEAP C2	CD and PPG (evaluation of surgical indications and/or planning of a treatment programme for the varices)	
CEAP C3 / C4 / C5	CD and PPG Request specialist consultancy	
CEAP C6	CD and PPG CD Specialist consultancy and treatment	Green code (within 10 days)

CD: colour Doppler; PPG: photoplethysmography.

A refilling time of less than 15-20 s is indicative of a hemodynamically significant back flow.

4) Evaluation of the indications for surgical treatment and its outcome

The "surgical" treatment of CVI has as its main aim the elimination of a significant hemodynamic back flow. Today there are numerous ways of operating, but these are not the concern of this document. Nevertheless, some references are useful and can be summarised as follows:

— total surgical ablation (long saphenous stripping) is at present little used;

— operations must not only correct the back flow, but also ensure the best possible venous return and try to save the saphenous apparatus useable for arterial or coronary vascular surgery;

— endovascular procedures (laser, radiofrequencies) are becoming more and more reliable, and are particularly useful in case of marked cutaneous suffering;

— secondary CVI does not usually have indications for surgery, except for corrections limited to the compartment such as the closing of incontinent and hemodynamically unfavourable perforating veins or the closing of the so called "nutritional veins" in case of an active ulcer caused by phlebostasis.

TABLE XXX.—*Acute ischemia of the upper extremities.*

When to suspect	— Absence of arterial pulse (not previously noted) — Pallor of the limb — Hypothermia — Paresthesia and hypoesthesia — Loss of function	
Differential diagnosis	— Acute venous thrombosis — Acute compressive neuropathy	
Causes	— Acute venous thrombosis — Atherothrombosis — Peripheral embolism — Arterial traumas — Aortic dissection — Vasculitis — Thrombophilia	
Management	— Send the patient to Emergency Department	Yellow code

TABLE XXXI.—*Deep venous thrombosis of the upper extremities.*

When to suspect	— Edema of the whole limb — Reddening or pallor of the limb — Turgidity of the superficial venous vessels — Pain	
Differential diagnosis	— Acute arterial ischemia — Acute compressive neuropathy	
Cause	— Idiopathy — Thrombophilia — Traumas of the upper extremities — Excessive straining of the limb (thrombosis from exertion) — Presence of venous catheters — Thoracic outlet syndrome	
Management	— Send the patient to Emergency Department	Yellow code

As has already been mentioned the preoperative evaluation cannot be made without CD venous mapping. PPG may be useful in a preventative evaluation of the hemodynamic efficacy of the operation, by means of the execution of the test after the exclusion (with a tourniquet) of the venous segment on which the operation is to be performed. A reduction in refilling time and an improvement in the muscular emptying after muscular contraction are predictive of a good hemodynamic gain.

CVI is often considered to be a pathology of little importance because its natural course is not aggravated by the risk of death. This position is, however, wrong because the disease is disabling [87-91] and significantly compromises the quality of life of the patient from clinical stage 3 onwards, and in stages C5-C6 reaching a degree of compromise equivalent to those of serious chronic diseases such as COPD, diabetes and cardiac failure.[92]

A close collaboration between the specialist and the GP is fundamental for the best management of a patient with CVI.

The clinical evaluation of the patient can certainly be referred to the GP, who will request confirmation or further specialist study according to the stratification of the gravity of the CEAP clinical picture and to the aims of treatment, as set out below (Table XXIX).

TABLE XXXII.—*Thoracic outlet syndrome.*

When to suspect	— Tumefaction of the upper limb — Venous congestion — Paresthesia in particular positions (e.g. sleeping position) — Asthenia e cutaneous pallor due to exertion with the arm raised — Axillary thrombosis	
Differential diagnosis	— Mediastinal mass — Lymph node compression — Bone neoplasia or metastases — Stiff neck	
Causes	— Muscular compression (scalene) — Supernumerary ribs	
Diagnoses	— Specialist examination with the execution of a stimulus manoeuvre (Grade C) — CD (Grade C) — X-ray of cervical column (Grade C) — Angio-CT or angio-MR, on the indications of the specialist (Grade C) — Angiography in patients with venous or arterial pathology who are candidates for an operation if the non-invasive diagnostic is not adequate (Grade C)	White code (within 180 days)
Therapy	— Avoid physical activity for muscular strengthening or hypertrophy — Specific gymnastics for the support of the thoracic girdle — Physio-kinesitherapy — Surgical intervention (supernumerary ribs and scalene)	

CD: colour Doppler.

FREQUENCY OF CONTROLS

Controls should be programmed by the specialist.

After a surgical procedure it is advisable to carry out CD and PPG in the immediate post-operative period and then after 3-4 months.

An instrumental anatomic-functional evaluation is recommended for each worsening of the clinical picture, such as a change in CEAP class or a change from an asymptomatic to a symptomatic condition.

The best method for following the efficacy of a conservative treatment with elastic contention and drugs is four-monthly or six-monthly execution (according to the gravity) of PPG.

Venous and arterial pathology of the upper extremities and thoracic outlet syndrome

Pathologies of the upper extremities are less frequent than those of the lower limbs. Among these the main ones are distal vascular syndromes (Raynaud's phenomenon and acrocyanosis) and the thoracic outlet syndrome (stenosis or arterial obstruction, intermittent compression, venous thrombosis).[93] Subclavian-axillary venous thromboses are also relatively frequent from traumas (thromboses from exertion in sport), central venous catheters, pace-makers,[94, 95] lymph node compression and neoplastic infiltrations. The complications of arterial-venous *fistulae* for dialysis should also be noted.

The principal diagnostic method is CD.[96, 97] Other investigations, which according to the pathology have the purpose of defining and characterising the diagnosis, are X rays of the cervical spine (supernumerary ribs), angio-CT and angio-MR. Angiography is instead only indicated in patients with venous or arterial pathologies candidates for surgical intervention.

The study of the digital arteries and the palmar arch can be carried out both with a Doppler CW and Doppler ultrasound or with plethysmography, in normal conditions and with the Allen test. It can be completed with

TABLE XXXIII.—*Raynaud's phenomenon*.

When to suspect	— Episodes of pallor of one or more fingers with hypothermia and hypoesthesia triggered off by stress or hypothermia followed by recovery of vascularisation (Raynaud's phenomenon)	
Differential diagnoses	— Carpal tunnel syndrome and other entrapment neuropathies — Other distal syndromes (acrocyanosis, erythromelalgia)	
Causes	— Idiopathic — Drugs and toxins (ergotamine, cisplatin, beta-blockers, oral contraceptives, cocaine etc.) — Vibration traumas — Polyneuropathy — Collagen and autoimmunity diseases — Hematologic diseases (polycythemia, cryoglobulinemia, lymphomas etc.) — Atherosclerotic or microembolic arterial occlusions	
Diagnoses	— Specialist examination (Grade C) — Echo-colour-Doppler (Grade C) — Plethysmography (photoplethysmography or strain gauge plethysmography) with physical (hot and cold stimulation) or pharmacological tests (Grade C) — Capillaroscopy (scleroderma pattern) (Grade A) — Autoantibody determination (Grade A)	White code (within 180 days)
Therapy	— Treatment of the underlying pathology (if present) — Avoid triggering or favourable factors (cold, smoking, vibration traumas, sports which traumatise the hands etc.) — Autogenous training, biofeedback — Connective massage — Medical therapy (calcium antagonists, alpha-blockers, nitroglycerine creams, ACE-inhibitors, ketanserin, vasoactive drugs, prostanoids, etc.) — Sympatholytic drugs or sympathectomy in selected cases	

physical tests (hot and cold stimulation) or pharmacologist tests, using plethysmography (photoplethysmography). In some situations, for the study of microcirculation capillaroscopy may be useful.

Colour-Doppler of the arterial circulation of the upper extremities

Evaluation with CD is indicated in the following cases:

— study of the aneurysmatic pathologies or compressive pathologies causing ischemic phenomena;

— diagnosis of stenosis or obstruction of the innominate-proximal subclavian compartment (with possible hemodynamic involvement of the vertebral axes);

— control of the revascularisation (mostly post-traumatic);

— the preparation and monitoring of arterial-venous *fistulae* for dialysis.

Light reflection plethysmography

Light reflection photoplethysmography is complementary to the other diagnostic exams in the study of the pathology of obstructed venous drainage of the upper extremities.[98]

Digital photoplethysmography

Photoplethysmography[99-101] is used as a complementary, integrative method for the study of both functional (Raynaud's phenomenon, acrocyanosis) and organic arteriopathy, because it can highlight a condition of rigidity or arterial-capillary spasm at an early stage.

Morphological capillaroscopy of the ungual fold

Capillaroscopy is a harmless, non-invasive investigation and therefore easily repeatable,

TABLE XXXIV.—*Vasomotor disorders.*

When to suspect	— Change in cutaneous colour and/or temperature usually of the hands and fingers in situations of nervous tension, hypothermia (acrocyanosis) or environmental hyperthermia (erythromelalgia)	
Differential diagnosis	— Raynaud's phenomenon	
Causes	— Idiopathic — Medicines (anti-hypertensive drugs, vasodilators, etc.) — Neurovegetative dystonia — Polyneuropathy — Hypertensive or hypotensive syndromes — Diabetes mellitus — Hematologic diseases (polycythemia, cryoglobulinemia, lymphomas etc.)	
Diagnoses	— Specialist examination (Grade C) — Plethysmography (photoplethysmography o strain gauge plethysmography) with physical (hot and cold stimulation) or pharmacological tests (Grade C) — Colour-Doppler (Grade C)	White code (within 180 days)
Therapy	— Treatment of the underlying pathology (if present) — Avoid triggering or favourable factors (cold, smoking, drugs etc.) — Autogenous training, biofeedback — Connective massage	

which allows the study *in vivo* of microcirculation. Unlike other techniques, such as the Doppler laser and the light reflection plethysmography, which evaluate the total compartmental flow, the capillaroscopy selectively investigates the nutritional circle. The possible applications of morphological capillaroscopy are numerous in that it is well-known how alterations in microcirculation represent the final stage of ischemic damage in both arterial and venous pathologies and are the common denominator of metabolic pathologies such as diabetes, and rheumatic pathologies such as connective tissue disorders from autoimmunity.[102-104]

In clinical practice, capillaroscopy finds its principal investigative application in the screening of patients who present acral vasomotor disturbances, such as the Raynaud's phenomenon and acrocyanosis.[105-108]

See Tables XXX, XXXI, XXXII, XXXIII and XXXIV for acute ischemia of the upper extremities, deep venous thrombosis of the upper extremities, thoracic outlet syndrome, Raynaud's phenomenon and vasomotor disorders, respectively.

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Appropriatezza del percorso diagnostico e terapeutico nel paziente vasculopatico

Premessa

La "non appropriatezza" delle richieste di diagnostica vascolare, che in alcuni laboratori specialistici raggiunge anche il 40% di tutta l'attività, è una delle cause che generano la ben nota pletora delle liste di attesa. Non è certo la sola. L'antico concetto "un Doppler non si nega a nessuno", l'influenza dei mass media sull'utilità di una diagnosi precoce di vasculopatia, l'aumento della richiesta indotto da un'elevata qualità dell'offerta giocano certamente il proprio ruolo.

Tra gli interventi organizzativi possibili, la distinzione tra procedure urgenti, relativamente urgenti e non urgenti, in relazione alla gravità del quadro clinico del paziente, sembra al momento essere quello più promettente.

L'Azienda Ospedaliera e l'Azienda ULSS di Padova hanno affrontato quest'aspetto sin dal 2004, affidando a una commissione che riuniva tutti gli esperti di diagnostica vascolare presenti sul territorio il compito di redigere delle tabelle di priorità delle procedure di diagnostica vascolare. Il documento elaborato dagli esperti è stato successivamente discusso con i medici di medicina generale (MMG) del territorio per la definitiva condivisione.

Sulla base di quell'esperienza, si è voluto estenderne la condivisione anche ad altre province regionali e su sollecitazione di alcune Direzioni Sanitarie a loro volta coinvolte nel riassetto organizzativo dalla deliberazione della Giunta della Regione Veneto n. 3535 del 12 Novembre 2004, relativa alla tempestività nell'erogazione delle prestazioni, si è costituito il

Gruppo di Lavoro "ANGIOVENETO" che ha riesaminato i contenuti del documento padovano alla luce delle diverse realtà operative.

Il presente documento desidera cogliere due obiettivi specifici:

— offrire al MMG della Regione Veneto una guida per un appropriato management delle malattie vascolari;

— indicare le procedure generali di intervento che egli dovrebbe attendersi da parte dello specialista.

Il Gruppo di Lavoro si propone la revisione periodica del documento in base a nuove evidenze scientifiche che dovessero emergere nel futuro prossimo e in base ai suggerimenti che i colleghi e tutti gli operatori sanitari volessero proporre.

Perché l'iniziativa abbia l'efficacia sperata, tuttavia, la condivisione operativa tra MMG e specialista, pur se indispensabile, non è sufficiente. Sono necessarie altre due condizioni:

— l'adeguamento organizzativo del sistema di accesso alle strutture sanitarie eroganti le prestazioni;

— la loro provata qualità operativa.

Per quanto concerne il primo aspetto è necessario che i Centri di Prenotazione Unificata adeguino i loro sistemi informatizzati ai nuovi criteri di tempistica proposti dalla Regione Veneto e totalmente recepiti dal presente documento, riservando dei canali preferenziali e dei posti riservati per le prestazioni più urgenti.

La qualità operativa delle strutture dovrebbe essere assicurata dalla presenza di specialisti (angiologo e chirurgo vascolare) che abbiano svolto un preciso training formativo. Tuttavia, considerato che l'attività di diagnostica vascolare viene erogata anche da altri specialisti, il Gruppo di Lavoro suggerisce di considerare qualitativamente affidabili quei laboratori che seguano le direttive di esecuzione e di refertazione proposte dalla Società Italiana di Diagnostica Vascolare (SIDV-GIUV) e che seguano o abbiano seguito il programma di accreditamento di eccellenza della Società Italiana di Angiologia e Patologia Vascolare (SIAPAV), con la relativa certificazione.

Trattamento medico di qualità

Il MMG e lo specialista sono i due principali riferimenti perché il paziente vasculopatico riceva un trattamento medico di qualità ("best medical treatment").

Perché questo si possa realizzare è necessario che i singoli ruoli e i rapporti collaborativi tra le due figure professionali siano ampiamente condivisi.

Ruolo del medico di medicina generale nella gestione del paziente vasculopatico

a) Diagnosi o sospetto clinico di malattia vascolare.

b) Approccio terapeutico iniziale.

c) Richiesta di esami strumentali:

— per diagnosi differenziale;

— per ulteriori approcci terapeutici;

— su indicazione di altri specialisti.

d) Richiesta di consulenza specialistica:

— per approfondimento diagnostico;

— per terapie specialistiche specifiche.

In sintesi:

— valutazione clinica generale;

— terapia medica di base;

— individuazione dei casi da avviare allo specialista;

— follow-up.

Ruolo dello specialista nella gestione del paziente vasculopatico

a) Prima visita, spesso su richiesta del MMG.

b) Visite di controllo, spesso su richiesta dello stesso specialista.

c) Suggerimenti terapeutici.

d) Esecuzione di esami strumentali.

e) Formulazione del percorso di approfondimento diagnostico.

f) Erogazione delle terapie specialistiche.

In sintesi:

— diagnosi circostanziata;

— terapia specialistica;

— gestione dei casi complessi;

— follow-up.

Rapporti tra medico di medicina generale e specialista

MMG → specialista:

— richiesta della prestazione specialistica;

— quesito diagnostico preciso;

— dati anamnestici utili alla valutazione.

Specialista → MMG:

— referto diagnostico dettagliato (eventuali suggerimenti terapeutici);

— motivazione di eventuali ulteriori esami e/o visite specialistiche;

— suggerimenti di strategia e tattica terapeutica per la gestione comune dei casi complessi.

Triage di gravità dei quadri clinici del paziente vasculopatico

Nel recepire i desiderata della deliberazione della Giunta Regionale, il documento propone l'identificazione delle priorità assistenziali in base a un triage di gravità del quadro clinico del paziente, adottando dei codici colore corrispondenti alla tempestività di erogazione delle procedure, e alla modulistica del nuovo ricettario regionale.

I codici colore adottati sono i seguenti (Figura 1).

Grado di raccomandazione in base al tipo di evidenza documentata

Grado di raccomandazione
Tipo di evidenza documentata
A) Almeno un trial clinico randomizzato di alto valore statistico o meta-analisi
B) Trial clinico randomizzato con più basso valore statistico
C) Studi di singoli gruppi non randomizzati
Studi descrittivi o di casistica
Rapporti su singoli casi

Patologia dei tronchi sopraortici

L'ictus è la terza causa di morte dopo le malattie cardiovascolari e le neoplasie causando il 10-12% di tutti i decessi per anno e rappresenta la principale causa di invalidità.

Il tasso di prevalenza di ictus nella popolazione anziana (età 65-84 anni) è del 6,5%.

L'ictus ischemico rappresenta la forma più frequente di ictus (80%).

Ogni anno si verificano 194 000 ictus, di cui 80% sono nuovi episodi. Tale dato è destinato ad aumentare con l'evoluzione demografica.

Il numero di pazienti invalidati per ictus è di circa 900 000 persone, dato anche questo destinato ad aumentare.

In circa 1/3 dei casi l'ictus ischemico è dovuto ad aterosclerosi dei tronchi sopraortici, situazione che beneficia in modo selettivo di una diagnosi precoce per la possibilità ormai consolidata di una riduzione di morbilità e mortalità previa rivascolarizzazione carotidea in caso di stenosi ≥ 70% [1-3].

Il rischio di ictus dopo TIA o minor stroke è elevato (10-20% nei 90 giorni successivi), soprattutto nelle prime 48 h (circa 5-10%) [4-10].

In particolare, i pazienti con arteriopatia carotidea hanno un rischio elevato di recidive precoci dopo TIA. Nei pazienti con TIA emisferico e arteriopatia carotidea ipsilaterale (stenosi 50-99%) il rischio di ictus a 90 giorni è pari al 20,1%, mentre il rischio nelle prime 48 h è del 5,5% (in maniera indipendente dal grado di stenosi) [10].

Come detto sopra, il TIA correlato a una stenosi carotidea di grado elevato (≥ 70%) comporta un rischio di ictus superiore rispetto a una condizione sostenuta da una stenosi carotidea lieve (< 50%)[2]. In particolare, il rischio a 3 anni di ictus omolaterale o morte è del 30-35% nei pazienti con stenosi carotidea ≥ 70% [2, 3].

Il rischio di ictus in pazienti con aterosclerosi carotidea è correlato non solo al grado di stenosi, ma anche alla composizione della placca e quindi alla sua morfologia (ipoecogenicità, disomogeneità, irregolarità di superficie) [11-15].

L'arteriopatia carotidea si riscontra frequentemente nella popolazione normale, soprattutto negli anziani e/o nei pazienti con altre condizioni morbose come l'arteriopatia periferica, il diabete mellito, l'ipertensione, la cardiopatia ischemica [16], l'occlusione vascolare retinica [17], e nei pazienti dopo terapia radiante al collo [18].

I sintomi suggestivi di patologia cerebro-vascolare sono riportati nella Tabella I e nella Tabella II e possono essere a carattere transitorio (TIA) o permanente (ictus) [1].

Triage di gravità nella patologia dei tronchi sopraortici

Indicazione all'esecuzione dell'eco-color-Doppler dei tronchi sopraortici (TSA) (valutazione delle arterie carotidi comuni, esterne, interne, succlavie e vertebrali) in base alla gravità del quadro clinico. L'esame va completato con la misurazione bilaterale della pressione arteriosa omerale (Tabella III).

Management dell'arteriopatia carotidea (Tabelle IV e V) [1, 19]

Periodicità dei controlli nei pazienti con arteriopatia carotidea (*Grado C*) (Tabella VI)

Ulteriori accertamenti vanno richiesti dallo specialista in relazione alla necessità di un approfondimento diagnostico o per la pianificazione di un eventuale intervento, ovvero prescritti dal MMG su indicazione dello specialista (*Grado C*):

— Doppler ed eco-color-Doppler transcranico (vanno eseguiti dopo l'eco-color-Doppler TSA);

— angio-RMN (tronchi sopraortici + circolo intracranico, RMN parenchima cerebrale);

— angio-TC (tronchi sopraortici + circolo intracranico, TC parenchima cerebrale);

— angiografia (tronchi sopraortici + circolo intracranico).

Indicazioni a Doppler ed eco-color-Doppler transcranico [21]:

— pazienti con insufficienza cerebrovascolare sintomatica o asintomatica per evidenziare:

- lesioni endoluminali dei vasi intracranici monitorizzabili (*Grado B*);
- riserva vasomotoria cerebrale e funzionalità residua della circolazione cerebrale intracranica (soprattutto poligono di Willis) (*Grado B*);
- ripercussioni intracraniche di lesioni extracraniche o di sindromi da furto della succlavia (*Grado C*);
- rischio di eventi microembolici in soggetti portatori di lesioni potenzialmente emboligene (*Grado B*);
- sospetto di coesistenti aneurismi e/o malformazioni arterovenose intracraniche (*Grado C*);

— soggetti con sospetto shunt cardiaco destro-sinistro;

— soggetti con emorragia subaracnoidea per la valutazione di eventuali fenomeni vasospastici.

Patologia delle arterie degli arti inferiori

La patologia delle arterie degli arti inferiori può essere acuta e cronica; la prima si manifesta con un

quadro di ischemia acuta (embolia, trombosi), la seconda (arteriopatia obliterante periferica, AOP) è caratterizzata da un'evoluzione cronica, abbastanza stabile nel tempo nella fase di claudicazione intermittente, che negli stadi avanzati manifesta un'accelerazione evolutiva con rischio di amputazione e di morte [22, 23].

Ischemia acuta degli arti inferiori (Tabella VII)

Arteriopatia obliterante degli arti inferiori

L'AOP in oltre l'80% dei casi è dovuta all'aterosclerosi, della quale rappresenta una delle tre localizzazioni principali.

La prevalenza nella popolazione generale varia dallo 0,6 al 6% a seconda dello strumento utilizzato per il suo riconoscimento [24]. Utilizzando come strumento diagnostico la misura dell'indice pressorio caviglia/braccio (*ankle-brachial index*, ABI), studi recenti indicano una prevalenza del 12% nella popolazione adulta con punta del 20% nella popolazione con età superiore a 70 anni [25].

Nonostante il suo riconoscimento non richieda procedure costose, la diagnosi di AOP è attualmente sottostimata, e un impegno adeguato a migliorare questa lacuna è giustificato dell'elevato rischio relativo di mortalità cardiovascolare, maggiore di sei volte rispetto alla popolazione di pari età senza AOP [22, 26].

Le classificazioni più diffuse sono quella di Fontaine [27] e quella di Rutherford [28]. Sono entrambe valide (Tabella VIII).

La prima distingue l'AOP in 4 stadi:

1) asintomatico;
2) claudicazione;
3) dolori a riposo;
4) gangrena.

Lo stadio 2°, a sua volta, è distinto in due sottogruppi: stadio 2° A e stadio 2° B, rispettivamente con autonomia di marcia (distanza assoluta di claudicazione, ACD) superiore o inferiore a 200 m.

La classificazione di Rutherford può essere considerata una rivisitazione della prima, 43 anni dopo, tenendo conto delle nuove conoscenze in tema di epidemiologia, fisiopatologia, possibilità di rivascolarizzazione, e risultati clinici del paziente. Essa distingue tre gradi e sei categorie.

La Tabella VIII riporta sinotticamente le due classificazioni, i segni e i sintomi, e la principale alterazione fisiopatologica di ogni stadio.

Il 1° stadio è definito come lo stadio asintomatico, nel quale le lesioni della parete arteriosa (calcificazioni, placche) sono già presenti, ma non inducono ancora sintomi.

Il paziente con sintomi occasionali (sforzi eccezionali) che talvolta è stato indicato come 1° stadio va considerato a tutti gli effetti un paziente claudicante (2° stadio).

La fisiopatologia del 1° stadio è dominata dalla presenza della placca aterosclerotica e dall'attivazione infiammatoria che rilascia microparticelle che mediano delle interazioni cellulari leucocita-leucocita e leucocita-endotelio. Queste interazioni molecolari e cellulari promuovono un'ulteriore attivazione leucocitaria mediante la deposizione di chemochine sull'endotelio, facilitando l'adesione dei leucociti sull'endotelio e la loro migrazione nei tessuti sottoendoteliali [29]. L'attivazione infiammatoria locale è responsabile delle complicanze locali della placca (trombosi su placca) [30,31] e della disseminazione sistemica di molecole proinfiammatorie (placca a rischio) che possono indurre complicanze di placche anche in altre sedi dell'albero vascolare (Tabella IX, X) [32-35].

Il 2° stadio è lo stadio della claudicazione intermittente (CI), definita come dolore crampiforme ai muscoli dell'arto inferiore (coscia o gamba) che compare durante la deambulazione o salendo le scale, che si manifesta ogni volta che si ripete il medesimo sforzo, e che recede prontamente con la cessazione dello sforzo.

La suddivisione nei sottogruppi 2° A e 2° B e soprattutto nei tre sottogruppi di Rutherford appare molto appropriata perché la storia naturale dei pazienti con ACD maggiormente compromessa è decisamente più grave.

Il paziente con claudicazione lieve (stadio 2° A con ACD > 200 m) infatti è destinato a rimanere stabile in circa il 75% dei casi [36-39], e la malattia ha un ruolo clinico importante come marker di rischio cardiovascolare (CV) globale (infarto miocardico e ictus).

La storia naturale del paziente con claudicazione moderata (ACD < 200 m) e ancor più con claudicazione severa (ACD < 100 m) è gravata da un rischio cardiovascolare maggiore e da un rischio elevato di progressione della malattia locale (Tabelle XI, XII, XIII, XIV) [23, 40].

Il 3° stadio (dolore ischemico a riposo), corrispondente al grado II categoria 4 di Rutherford, e il 4° stadio (lesioni ischemiche cutanee), corrispondente alla categoria III di Rutherford, dal 1989 [41] vengono riuniti nella definizione di ischemia cronica critica dell'arto inferiore (ICCAI) o critical limb ischaemia (CLI) secondo la dizione inglese ormai universalmente utilizzata.

La CLI è definita dalla presenza di dolori a riposo persistenti da più di due settimane, che richiede un regolare trattamento analgesico, associata o meno a lesioni ischemiche cutanee (Tabella XV).

Nonostante raggruppi quadri clinici molto differenti tra loro, che richiedono spesso un management personalizzato, il termine di CLI ha il pregio di richiamare subito l'attenzione del medico sulla criticità del quadro clinico, con rischio elevato di amputazione e di morte.

Sul piano clinico lo stadio dei dolori a riposo meriterebbe di essere distinto a seconda della modalità di comparsa del dolore:

3° A: dolore a riposo soltanto in posizione orizzontale, che scompare con l'arto penzoloni;

3° B: dolore a riposo persistente.

Tuttavia, poiché le due condizioni cliniche non comportano strategie terapeutiche differenti, per motivi di semplificazione della classificazione si preferisce mantenere soltanto l'indicazione generica di dolori a riposo.

Lo stadio delle lesioni ischemiche cutanee, al contrario, merita di essere distinto nei sottogruppi suggeriti dalla classificazione di Rutherford perché l'entità della necrosi cutanea condiziona procedure e tempi terapeutici differenti. Tra le caratteristiche fisiopatologiche delle lesioni cutanee cui prestare particolare attenzione va ricordata l'infezione batterica che spesso condiziona il trattamento e il risultato.

Affidabilità dell'indice pressorio caviglia/braccio

Il riscontro di un ABI > 1,30 è frequente nei pazienti diabetici a causa dell'incompressibilità delle arterie tibiali per la presenza di mediocalcinosi di Monckeberg.

Le linee guida internazionali in questa evenienza suggeriscono di eseguire la misura della pressione arteriosa all'alluce (*toe systolic blood pressure*, TSBP) [43, 44].

Questa procedura in Italia è poco diffusa e per alcuni versi non supera totalmente l'inaffidabilità; per tale motivo, in accordo con il Gruppo Interdisciplinare sul Piede Diabetico [45], si suggerisce di procedere a un esame eco-color-Doppler (Tabella X).

Test del cammino

La valutazione della capacità deambulatoria è utile per valutare l'handicap del paziente e monitorarne la stabilità, il miglioramento o il peggioramento in relazione alla storia naturale e al trattamento eseguito.

Il metodo più accreditato è l'esecuzione del test del cammino su tappeto ruotante (treadmill test) che tuttavia presenta difficoltà oggettive di realizzazione su larga scala, soprattutto per motivi organizzativi e di costo.

Valide alternative di facile realizzazione sono:

— 6 min Walking Corridor Test (6WCT): test della marcia spontanea in un corridoio di lunghezza nota, da continuare per 6 min o fino alla comparsa del dolore al polpaccio che costringe ad arrestare la prova, e annotando la distanza percorsa e il tempo;

— Walking Impairment Questionnaire (WIQ): questionario specifico sulla deambulazione [46].

Il WIQ quantifica la performance deambulatoria in tre dimensioni differenti:

— distanza (valori normali di score fino a 70);

— velocità (valore normale fino a 40);

— scale (valore normale fino a 60).

Nella pratica clinica è sufficiente valutare la capacità di marcia (anche da parte del MMG) con il 6WCT, riservando l'esecuzione del treadmill test alle seguenti condizioni:

— prima e dopo 1 mese dall'esecuzione di procedure di rivascolarizzazione;

— prima e dopo programmi di traning fisico controllato;

— studi clinici che valutano l'efficacia di farmaci sulla deambulazione;

— quando esista discrepanza tra il quadro clinico ed i risultati degli esami diagnostici.

I dolori a riposo notturni possono essere non di origine ischemica, e così anche le lesioni cutanee minime, soprattutto nei pazienti diabetici; in questi casi dubbi oltre agli esami indicati per la claudicazione moderata e/o severa, è anche indicata la misura della pressione transcutanea di ossigeno per la valutazione del grado di ischemia, esame accreditato internazionalmente per valutare la perfusione microcircolatoria cutanea, molto utile per la stadiazione dell'ischemia cutanea, la predittività dell'outcome di salvataggio d'arto, e la scelta del livello di amputazione [52, 53].

Il trattamento farmacologico intensivo, come tutto il management del paziente con arteriopatia periferica, deve essere demandato a "strutture dedicate" impegnate a tempo pieno nella diagnosi e nella cura delle vasculopatie al fine di garantire le migliori possibilità di successo [54].

Arteriopatie periferiche nel paziente diabetico

L'AOP è anche una delle manifestazioni più frequenti della macroangiopatia diabetica, che ne riduce anche il rapporto maschi/femmine dal 3:1 delle AOP non diabetiche a 2:1 e anche 1:1.

Oltre l'8% dei pazienti diabetici al momento della diagnosi di diabete ha già una AOP documentabile [55].

L'approccio al paziente diabetico presenta alcune peculiarità rispetto al non diabetico perché il sintomo d'esordio di una AOP diabetica è spesso la comparsa di ulcerazioni cutanee a causa della minore rilevanza della claudicazione intermittente (più elevata soglia al dolore, concomitanza della neuropatia).

Queste peculiarità impongono un'attenta sorveglianza vascolare del paziente diabetico che deve essere realizzata in modo univoco dal MMG, dai Centri per la Prevenzione e Cura del Piede Diabetico, dalle strutture territoriali e ospedaliere di Angiologia e Chirurgia Vascolare.

Il MMG dovrà controllare periodicamente la presenza dei polsi arteriosi e/o di soffi vascolari, la capacità deambulatoria e lo stato trofico della cute [56, 57], richiedendo o effettuando personalmente la misura dell'ABI quando rilevasse una riduzione della pulsatilità, la presenza di un soffio o la riduzione della capacità deambulatoria (valutazione di 1° livello).

Gli approfondimenti di 2° livello (eco-color-Doppler) e 3° livello (angiografia, angio-RMN, angio-TC) saranno adottati, di volta in volta, secondo i suggerimenti dell'algoritmo sotto riportato (Figura 2).

Nel caso di comparsa di ulcere cutanee si suggerisce di accedere direttamente ad una valutazione di 3° livello nell'intento di fornire al paziente il più opportuno trattamento nei tempi più brevi.

La sorveglianza è demandata al MMG e/o ai Centri per la Prevenzione e la Cura del Piede Diabetico. Tutti i diabetici la cui malattia dati da più di venti anni dovrebbero essere sottoposti a una valutazione vascolare di 1° e 2° livello almeno una volta ed essere inseriti, a seconda del risultato, negli specifici follow-up [58].

Patologia dell'aorta addominale (aneurismi)

Pur essendo abbastanza frequente, la patologia dell'aorta addominale è povera di segni e sintomi che orientino precocemente in tal senso.

Il 13% dei pazienti affetti da arteriopatia periferica presenta un aneurisma dell'aorta addominale (AAA) [59], mentre i dati relativi all'associazione ipertensione arteriosa – AAA sono alquanto variabili nei vari studi. L'unico dato certo è che il rischio relativo di AAA è elevato nei soggetti con familiarità per la stessa patologia.

È utile che la valutazione comprenda anche la misura del diametro (Ø) dell'aorta non aneurismatica ed il calcolo del rapporto Ø aneurisma / Ø aorta nativa a causa di importanti differenze di popolazione (Ø 21,4 mm nella popolazione dell'Australia occidentale [60], 17 mm nella popolazione brasiliana [61] e 18,4 mm in quella danese [62]). In assenza di dati epidemiologici rilevanti che identifichino un sicuro cut-off di riferimento, un rapporto intorno a 2 dovrebbe suggerire una stretta sorveglianza, mentre il valore di 2,5 dovrebbe rappresentare il livello di indicazione chirurgica [63].

Triage di gravità nella patologia dell'aorta addominale

Indicazione all'esecuzione dell'eco-color-Doppler dell'aorta addominale (*Grado A*) secondo il quadro clinico. L'esame va completato con eco-color-Doppler degli assi iliaci e misurazione dell'ABI (Tabella XVI).

Ulteriori accertamenti vanno richiesti dallo specialista in relazione alla necessità di un approfondimento diagnostico o per la pianificazione di un eventuale intervento di chirurgia vascolare od endovascolare, ovvero prescritti dal MMG su indicazione dello specialista (*Grado C*):

— angio-TC spirale (con sezioni di 3 mm) con elaborazione 3D;
— angio-RMN;
— angiografia.

Management del paziente con aneurisma dell'aorta addominale [64] e periodicità dei controlli (Tabella XVII)

Patologia delle arterie renali

Il 30-40% dei pazienti con arteriopatia periferica è portatore di stenosi delle arterie renali, indipendentemente dalla presenza di ipertensione renovascolare, e la progressione della stenosi si verifica in circa il 20% dei casi per anno [66], essendo il rischio di progressione più alto tra quelli con una stenosi superiore al 60%, ipertesi e diabetici [67]. La valutazione di questo distretto è pertanto:

consigliabile almeno una volta nell'iter diagnostico dell'arteriopatico periferico;

da raccomandare in caso di coesistenza di ipertensione arteriosa o di insufficienza renale (IR) nell'arteriopatico periferico.

Le cause principali della stenosi delle arterie renali sono l'aterosclerosi (circa 90% dei casi), generalmente in uomini, fumatori, arteriopatici, con più di 50 anni, e la displasia fibromuscolare (10% dei casi), in genere in donne di età compresa fra 15 e 50 anni.

Il sospetto clinico di una stenosi delle arterie renali deriva dall'insieme di caratteristiche suggestive (Tabella XVIII), che, considerate singolarmente, hanno un basso valore predittivo.

Triage di gravità nella patologia delle arterie renali

Indicazione all'eco-color-Doppler delle arterie renali secondo il quadro clinico (Tabella XIX).

Periodicità dei controlli nei pazienti con stenosi delle arterie renali (Tabella XX)

Patologia del tripode celiaco e delle arterie mesenteriche

La prevalenza di alterazioni aterosclerotiche nel tripode celiaco e nelle arterie mesenteriche è clinicamente poco rilevante; l'esame di questo distretto va eseguito soltanto nel fondato sospetto clinico di *angina abdominis* (Tabella XXI).

Patologia delle vene degli arti inferiori

La diagnostica strumentale con eco-Doppler o eco-color-Doppler nella patologia venosa è indirizzata principalmente alla patologia trombotica e all'insufficienza venosa cronica.

Malattia tromboembolica venosa

La malattia tromboembolica venosa (TEV) è una condizione anatomo-clinica costituita da una patologia trombotica a carico del circolo venoso profondo degli arti inferiori, associata o meno a embolia polmonare (Tabelle XXII, XXIII).

Dato che i vari centri si rifanno a protocolli diversi con varie possibilità terapeutiche e le tempistiche dei controlli dipendono da entrambe queste variabili, si raccomanda caldamente di richiedere anche la

visita specialistica angiologica sia per escludere la trombosi sia per escludere altre patologie che la simulano.

In linea di massima per la diagnosi e terapia di TVP prossimale ci si rifà allo schema sotto riportato (Tabelle XXIV, XXV e XXVI).

Trombosi venosa superficiale (Tabella XXVII)

Insufficienza venosa cronica

I sintomi più frequentemente riferiti dai pazienti con insufficienza venosa cronica (IVC) sono il senso di pesantezza agli arti inferiori, accentuato dall'ortostatismo prolungato, l'edema o il subedema serotino (segno del calzino), un senso persistente di irrequietezza delle gambe che non trovano facilmente riposo.

Dal punto di vista fisiopatologico la IVC è caratterizzata da difficoltoso ritorno venoso agli arti inferiori, stasi, ipertensione venosa, aumento della permeabilità capillare, attivazione infiammatoria e stimolazione degli algo-recettori sottocutanei.

Sotto il profilo etiologico può essere primitiva, legata cioè a una malattia varicosa non corretta, ovvero secondaria a una sindrome post-trombotica [86]. Purtroppo nessuno dei sintomi sopra indicati è patognomonico della IVC ma può manifestarsi anche in altre condizioni morbose, e per tale motivo la tipizzazione della IVC non può essere soltanto clinica, anche se la diagnosi di varici non pone certamente delle difficoltà.

Gli obiettivi della valutazione clinica e strumentale in un paziente con IVC sono:

1) conferma della diagnosi di IVC;

2) identificazione della condizione di IVC primitiva o secondaria;

3) identificazione dello stato di IVC compensata o scompensata;

4) valutazione dell'indicazione al trattamento chirurgico e predittività della sua efficacia.

1) Conferma della diagnosi di IVC

Il primo approccio è certamente anamnestico. L'anamnesi deve essere opportunamente guidata con specifiche domande volte a riconoscere la presenza, anche alquanto remota, di eventi facilitanti o scatenanti una TVP (ad esempio gamba gonfia dopo un'ingessatura, un intervento, un parto, un periodo di allettamento prolungato), e a valutare l'epoca della comparsa dei sintomi e dei segni, e la loro presenza bilaterale o monolaterale (sospetto di IVC secondaria).

L'esame obiettivo non presenta difficoltà, ma si suggerisce di condurlo secondo lo schema della classificazione CEAP (Tabella XXVIII).

Oltre ad annotare la presenza delle singole alterazioni previste dalla classificazione è bene tener presente che nella IVC primitiva (spesso bilaterale) il sistema venoso superficiale si presenta tortuoso e dilatato, mentre nella IVC secondaria (di solito monolaterale) il sistema venoso superficiale può essere normale o dilatato e generalmente è poco tortuoso.

2) Identificazione della condizione di IVC primitiva o secondaria

L'orientamento clinico desunto dall'anamnesi e dall'esame obiettivo del paziente deve essere confermato da un eco-color-Doppler che deve esaminare tutti i tre distretti venosi, superficiale, profondo e perforante.

Nella IVC primitiva il sistema venoso superficiale, come già detto, si presenta tortuoso e dilatato, con un significativo reflusso safenico. Le valvole venose sono presenti (salvo i casi di agenesia primitiva), mobili, ma incontinenti. Il sistema venoso profondo è integro, salvo i casi di antica malattia varicosa non trattata. Il sistema perforante può essere continente o incontinente a seconda dello stadio evolutivo della malattia.

Nella IVC secondaria il sistema superficiale è integro nelle fasi iniziali della malattia (sindrome post-trombotica recente, TVP non più antica di 4-6 anni); nelle fasi avanzate può presentare delle dilatazioni (varici post-trombotiche o post-flebitiche), ma il decorso è prevalentemente rettilineo. Le valvole sono mobili e continenti, ad eccezione delle fasi molto avanzate della malattia.

Il sistema profondo può presentare dei residui trombotici parietali o una ricanalizzazione completa. Le valvole appaiono immobili e rimaneggiate dal processo di ricanalizzazione (monconi valvolari), con conseguente incontinenza (reflusso).

Il sistema perforante può essere continente o incontinente a seconda dello stadio evolutivo della malattia.

L'esame eco-color-Doppler deve essere completato da un preciso studio emodinamico, valutando la direzionalità del flusso e dei reflussi ed identificando i circoli di supplenza (mappaggio venoso). Questa valutazione, che dovrebbe far parte di tutti gli eco-color-Doppler venosi degli arti inferiori, è indispensabile nella valutazione preoperatoria.

3) Identificazione dello stato di IVC compensata o scompensata

La diagnosi di IVC compensata o scompensata dipende dall'entità dell'ipertensione venosa e dalla efficienza della pompa muscolo-venosa. I quadri clinici CEAP C3 (edema) e C4 (alterazioni cutanee) fanno sospettare una IVC scompensata. L'edema è, infatti, correlato con l'aumento della permeabilità capillare, e le alterazioni cutanee con l'attivazione infiammatoria (dermite) e con l'aumentata diapedesi eritrocitaria (dermite ocra).

Tuttavia, poiché le alterazioni cutanee una volta instaurate non regrediscono e dunque non modificano la diagnosi C4, è opportuno valutare strumentalmente questa condizione.

La flebodinamometria è un esame obsoleto sul piano clinico, anche se la sua invasività è relativamente modesta. Informazioni equivalenti possono ottenersi con la fotopletismografia infrarossa (infrared-PPG) nota anche come reografia a luce riflessa, che valuta

l'entità dello svuotamento dei plessi venosi subpapillari indotto dalla contrazione dei muscoli del polpaccio, e il tempo di riempimento venoso ("refilling time").

Un tempo di riempimento inferiore a 15-20 s è indicativo della presenza di un reflusso emodinamicamente significativo.

4) Valutazione dell'indicazione al trattamento chirurgico e predittività della sua efficacia

Il trattamento "chirurgico" della IVC ha come obiettivo principale l'eliminazione del reflusso emodinamicamente significativo. Le attuali modalità di intervento sono molteplici, ed esulano dalle finalità di questo documento. Alcuni riferimenti sono tuttavia utili e possono essere così sintetizzati:

— l'ablazione chirurgica totale (stripping safenico lungo) è attualmente poco eseguita;

— gli interventi devono non solo correggere il reflusso ma anche assicurare il miglior ritorno venoso possibile e tentare di risparmiare il "patrimonio safenico" utilizzabile per chirurgia vascolare arteriosa o coronarica;

— le procedure endovascolari (laser, radiofrequenza) mostrano una sempre maggiore affidabilità, e sono particolarmente utili in caso di marcata sofferenza cutanea;

— la IVC secondaria di solito non ha indicazione chirurgica, salvo correzioni molto distrettuali, come la chiusura di perforanti incontinenti ed emodinamicamente sfavorevoli o la chiusura delle cosiddette "vene nutrici" in caso di ulcera flebostatica attiva.

Come già accennato la valutazione preoperatoria non può prescindere dal mappaggio venoso eco-color-Doppler.

La PPG può essere utile nel valutare preventivamente l'efficacia emodinamica dell'intervento, mediante l'esecuzione del test dopo esclusione (mediante laccio emostatico) del segmento venoso su cui si intende intervenire. Una riduzione del "refilling time" e un miglioramento dello svuotamento muscolare dopo contrazione muscolare sono predittivi di un buon guadagno emodinamico.

La IVC è spesso considerata una patologia di scarso rilievo perchè la sua storia naturale non è gravata da un rischio di mortalità. Questa posizione è tuttavia errata perchè la malattia è invalidante [87-91] e compromette in modo significativo la qualità di vita del paziente a partire dalla fase clinica C3, e raggiungendo in C5-C6 un grado di compromissione sovrapponibile a quella di importanti malattie croniche come la BPCO, il diabete e lo scompenso cardiaco [92].

Una stretta collaborazione tra lo specialista ed il MMG è fondamentale per la miglior gestione del paziente con IVC.

La valutazione clinica del paziente può essere senz'altro demandata al MMG, il quale richiederà le conferme o gli approfondimenti specialistici in base alla stratificazione della gravità del quadro clinico CEAP e agli obiettivi di trattamento, secondo quanto di seguito indicato (Tabella XXIX).

PERIODICITÀ DEI CONTROLLI

I controlli vanno programmati dallo specialista.

Dopo una procedura chirurgica è opportuno eseguire eco-color-Doppler e PPG nell'immediato postoperatorio e dopo 3-4 mesi.

Una valutazione anatomo-funzionale strumentale è opportuna a ogni peggioramento del quadro clinico, come il cambio di classe CEAP o anche il passaggio da una condizione asintomatica a una sintomatica.

Il metodo migliore per seguire l'efficacia di un trattamento conservativo con contenzione elastica e farmaci è l'esecuzione quadrimestrale o semestrale (a seconda della gravità) della PPG.

Patologia arteriosa e venosa degli arti superiori e dello stretto toracico superiore

Le patologie vascolari degli arti superiori sono meno frequenti rispetto a quelle degli arti inferiori. Tra di esse le principali sono le acrosindromi vascolari (sindrome di Raynaud e acrocianosi) e la sindrome dello stretto toracico superiore (stenosi od ostruzioni arteriose, compressioni intermittenti, trombosi venose) [93]. Relativamente frequenti pure le trombosi venose succlavio-ascellari da trauma (trombosi da sforzo degli sportivi), da catetere venoso centrale, da pace-maker [94, 95], da compressioni linfonodali e da infiltrazioni neoplastiche. Da ricordare inoltre le complicanze delle fistole artero-venose per la dialisi.

La metodica diagnostica principale è l'eco-color-Doppler [96, 97]. Altre indagini, che a seconda delle patologie hanno lo scopo di definire e caratterizzare la diagnosi, sono la Rx-grafia del rachide cervicale (costa soprannumeraria), l'angio-TC e l'angio-RMN. L'angiografia è invece indicata solo nei pazienti con patologia arteriosa o venosa destinati ad intervento chirurgico.

Lo studio delle arterie digitali e dell'arcata palmare può essere effettuato sia con Doppler CW che con eco-Doppler o con pletismografia, in condizioni normali e con test di Allen. Può essere completato con test fisici (stimolazione calda e fredda) o farmacologici, utilizzando la pletismografia (fotopletismografia). In alcune situazioni, per lo studio del microcircolo, può essere utile la capillaroscopia.

Eco-color-doppler del circolo arterioso degli arti superiori

La valutazione con eco-color-Doppler è indicata nei seguenti casi:

— lo studio della patologia aneurismatica o compressiva alla base di fenomeni ischemici;

— la diagnosi di stenosi o ostruzioni del distretto anonimo-succlavio prossimale (con eventuale coinvolgimento emodinamico degli assi vertebrali);

— il controllo delle rivascolarizzazioni (il più delle volte post-traumatiche);

— la preparazione e il monitoraggio delle fistole artero-venose per la dialisi.

Pletismografia a luce riflessa

La fotopletismografia a luce riflessa è complementare agli altri esami diagnostici nello studio della patologia da ostacolato scarico venoso dell'arto superiore [98].

Fotopletismografia digitale

La fotopletismografia [99-101] viene utilizzata come metodica complementare e integrativa nello studio delle arteriopatie sia funzionali (malattia di Raynaud, acrocianosi) che organiche, per la sua possibilità di evidenziare in fase precoce una condizione di rigidità o di spasmo arteriolo-capillare.

Capillaroscopia morfologica della plica ungueale

La capillaroscopia è un'indagine non invasiva, innocua, quindi facilmente ripetibile, che consente lo studio in vivo del microcircolo. A differenza di altre tecniche, quali il laser Doppler e la pletismografia a luce riflessa, che valutano il flusso totale distrettuale, la capillaroscopia indaga selettivamente il circolo nutrizionale. Le possibili applicazioni della capillaroscopia morfologica sono numerose, in quanto è ben conosciuto come le alterazioni del microcircolo rappresentano la via finale del danno ischemico sia in corso di patologia arteriosa che venosa, il denominatore comune di patologie metaboliche, quali il diabete, e reumatiche, quali le connettiviti su base autoimmune [102-104].

Nella pratica clinica, la capillaroscopia trova la sua principale applicazione come indagine di screening nei pazienti che presentano disturbi vasomotori acrali, quali il fenomeno di Raynaud e l'acrocianosi [105-108].

Ischemia acuta dell'arto superiore (Tabella XXX)

Trombosi venosa profonda dell'arto superiore (Tabella XXXI)

Sindrome dello stretto toracico superiore (Tabella XXXII)

Fenomeno di Raynaud (Tabella XXXIII)

Acrosindromi vascolari (acrocianosi, eritromelalgia) (Tabella XXXIV)