

Editorial

Comments on the 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases



Comentarios a la guía ESC 2017 sobre el diagnóstico y tratamiento de la enfermedad arterial periférica

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INTRODUCTION

Since 2011, the Spanish Society of Cardiology (SEC) has had a policy of endorsing all the clinical practice guidelines published by the European Society of Cardiology (ESC). In an effort to increase awareness of the guidelines, they are translated into Spanish and published in *Revista Española de Cardiología* along with comments from a group of Spanish experts that highlight the most noteworthy aspects, criticize the limitations, and adapt the recommendations to everyday clinical practice in Spain.

This article contains the comments on the recently published ESC guidelines on the diagnosis and treatment of peripheral vascular diseases,¹ developed in collaboration with the European Society for Vascular Surgery (ESVS). The Guidelines Committee set up a working group composed of SEC members to comment on the guidelines. These guidelines update the first ESC clinical practice guidelines on peripheral vascular disease (PVD) published in 2011.² Although PVD may appear to be beyond the scope of cardiology, nothing could be further from the truth. The guidelines stress the importance of increasing cardiologists', vascular surgeons' and other physicians' awareness and knowledge of the common nature of arteriosclerotic disease and the risk factors in the different vascular territories, including extracranial carotid and vertebral disease. For example, they recommend screening for PVD in patients with cardiac or cerebrovascular disease, and vice versa, because these 2 locations are the most common causes of mortality in patients with PVD. The collaboration with the ESVS is also relevant, because vascular surgeons are increasingly more involved in treatment, not only for revascularization, but also epidemiological aspects and the medical treatment of arterial disease. The document contains a table titled "What is new in the 2017 PAD guidelines?" plus some key messages at the start of each chapter, by way of an introduction. Another

interesting feature is the "questions and answers" section, only available in the additional online material, which includes 14 short clinical cases that clearly and specifically illustrate the practical application of the guideline recommendations. Below are the comments on the most important aspects, following the same order as the guideline sections.

EPIDEMIOLOGY AND RISK FACTORS

The section on epidemiology and prognosis has few additions and no notable updates. There is more information on the epidemiology of PVD in the additional material published along with the guidelines.¹ Diabetes, smoking, hypertension, dyslipidemia, age, and male sex are highlighted as the classical risk factors whose relative importance can vary depending on the vascular territory. The document does not mention the role of other potential risk factors such as sedentary lifestyle, obesity, racial components, atmospheric pollution, and industrialization, which may play a role in the development of atherosclerosis.³ The guidelines note that there are few data on the incidence and prevalence of PVD in Europe, although recent studies show that the prevalence of PVD has increased in recent years, especially in middle- and low-income countries.⁴ We should not forget that between 40% and 80% of individuals with PVD are asymptomatic and that prevalence varies enormously with age and other population characteristics. For example, the prevalence of an ankle-brachial index (ABI) ≤ 0.9 in men older than 60 to 65 years in countries such as Germany and Sweden is around 18%.⁵ The authors of the guidelines note the significant lack of epidemiological information on PVD in women. Although Spain is not mentioned, there are some publications that contain a similar or slightly lower prevalence.⁶

There are few updates on prognosis in these guidelines. The presence of a pathological ABI doubles the 10-year mortality risk, mainly due to coronary and cerebrovascular disease, which highlights the need for optimal medical treatment with exhaustive control of cardiovascular risk factors for patients with a diagnosis of PVD.

GENERAL ASPECTS

There are no significant changes regarding the general focus of diagnosis and treatment. The guidelines recommend a complete

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clinical history and examination, including detailed assessment of all vascular territories, vascular risk factors and symptoms. They reaffirm the recommendation for physical activity based on the 2010 position paper of the European Association of Preventive Cardiology⁷ (EAPC), but in the general section, the recommended type, intensity, and duration of activity is not specified. Given that the recommendations in the various other sections tend to involve a multidisciplinary approach to diagnosis and treatment, this section is missing a direct reference to the usefulness of cardiac rehabilitation programs in these patients. The guidelines stress the importance of measuring blood pressure in both arms during the physical examination, in light of evidence that a difference of > 15 mmHg increases mortality and acts as a vascular risk factor.

The diagnostic methods section stresses the appropriate use of ABI, which is useful, inexpensive, and noninvasive. There is a table describing who should have an ABI measurement, how to measure it, and how to interpret the results, which encourages better training in the technique. The ABI is becoming increasingly relevant as a marker of atherosclerotic disease, and the recommendation to measure it is not limited to patients in whom there is clinical suspicion, but also applies to "at risk" patients. Similarly, duplex ultrasound is given increasing importance in confirming the diagnosis, and its usefulness for screening different territories and for follow-up of revascularization procedures is noted. There are no major changes from previous guidelines regarding the usefulness of ultrasound, computed tomography (CT) angiography, and magnetic resonance (MR) angiography. CT-angiography remains the investigation with the highest resolution, with the limitation of contrast-related risks, which can be reduced with adequate fluids and, as recently found, pretreatment with statins.⁸ MR-angiography is an alternative to avoid such complications, although it has other limitations, such as lower resolution and being contraindicated in severe renal failure.

Regarding treatment approach, the guidelines only dedicate one line to the reminder that treatment starts with lifestyle changes, control of risk factors, and physical activity. It is unusual that there are no general recommendations on physical activity. Later in the guidelines the main recommendations from the 2016 cardiovascular prevention guidelines are reiterated.^{9,10} For example, the recommendation on cholesterol cutoff values is now < 70 mg/dL, and, for individuals with baseline levels of 70-135 mg/dL, a reduction of at least 50%. For the first time the guidelines recommend, with a Ia evidence level, use of statins in lower extremity arterial disease (LEAD) to improve walking distance. They also describe the additional benefits of evolocumab when added to statins found in the FOURIER trial.¹¹ Smoking cessation is essential, with a Ib recommendation, to reduce mortality in all patients with peripheral arterial disease. For the first time, protection against passive smoking is emphasized. For arterial hypertension, they suggest a reduction to below 140/90 mmHg (140/85 mmHg in diabetes), but without going below 110 mmHg to avoid a "J-shape" effect.

It is interesting to see that beta-blockers have been removed from the table of recommendations, although opinion is unchanged on their usefulness and the absence of contraindications in peripheral vascular disease. However, the guidelines do recommend considering stopping them in critical limb ischemia. In their place, angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) have been added to the table as first-line treatment for hypertensive patients with PVD.

For the treatment of diabetes, strict glycemic control is stressed, although the previous glycated hemoglobin value of < 6.5% in general has been removed, due to evidence of associated morbidity risk. The new guidelines are lacking a chapter on diabetes, given its significant involvement in PVD and, in particular, the advances in the field and the changes in treatment strategy in recent years. There is no reference to the vascular side effects of the newer antidiabetic drugs.^{12,13}

ANTITHROMBOTIC TREATMENT IN PERIPHERAL ARTERIAL DISEASE

Regarding antithrombotic treatment in patients with carotid disease, the recommendation tables in the 2011 guidelines² did not stipulate systematic antiplatelet therapy, whereas the new guidelines do. It should be given indefinitely and as single antiplatelet therapy in symptomatic stenosis (I A), and to be considered in asymptomatic patients with at least moderate stenosis (IIa C), as prevention mainly against myocardial infarction, since no clear reduction has been demonstrated in risk of stroke. The recommendations are unchanged for dual antiplatelet therapy (DAPT) in the first month after carotid stenting (I B) and antiplatelet monotherapy indefinitely after carotid endarterectomy (I A).

The recommendation tables for antithrombotic treatment in lower extremity arterial disease are new compared with the 2011 recommendations. Probably the most important point is that they do not recommend systematic antiplatelet therapy in patients with asymptomatic disease isolated to this region (III A), given its apparent lack of benefit. However, for symptomatic patients, there is a clear recommendation for indefinite single antiplatelet therapy (I A), and also after revascularization surgery (I C), especially if an infra-inguinal bypass has been performed (I A); anticoagulation should be considered if there is a venous graft (IIb B). One of the most debated topics in vascular surgery is the treatment regimen to be established after endovascular treatment in the lower extremities, especially at an infra-inguinal level, regarding the use and duration of DAPT. The various devices and techniques used and the different anatomical and clinical inclusion criteria greatly complicate the comparison of outcomes of the different antiplatelet regimens. The most widely agreed recommendation is DAPT for at least the first month after the procedure (IIa C) and indefinite single antiplatelet therapy thereafter. The preferential use of clopidogrel over aspirin (IIb B) is debated, despite the results of the CAPRIE trial.¹³

Last, regarding antithrombotic treatment for patients requiring anticoagulation, the most important recommendation is the introduction of the CHA₂DS₂-VASc score (I A) for oral anticoagulation. In cases of endovascular therapy, the guidelines recommend evaluating DAPT plus oral anticoagulation or oral anticoagulation alone, according to bleeding risk.

EXTRACRANIAL CAROTID AND VERTEBRAL ARTERIAL DISEASE

The guidelines' recommendations on imaging tests in carotid disease have maintained the recommendation for duplex ultrasound as the first option (I B), but there are new recommendations, depending on the type of treatment that is to be given: assessment of the aortic arch and extracranial circulation in cases that are to be stented (I B), with computed tomography (CT) or magnetic resonance (MR) (I B recommendation), as well as confirmation of the severity of stenosis with CT or MR in cases that are to undergo endarterectomy (I B). Of note is the increasingly restrictive use of digital subtraction angiography in the diagnosis of carotid stenosis, to be considered only if there is a discrepancy between imaging findings.

There are no new recommendations on revascularization and the recommendation to use protection devices when implanting carotid stents has been maintained, moving from IIb B to IIa C. One of the bigger changes in the 2017 guidelines regards treatment of asymptomatic carotid stenosis. In previous guidelines,² the recommendation was to consider endarterectomy for patients with asymptomatic stenosis > 60% in centers with validated outcomes (risk of stroke/death < 3%) and with life expectancy > 5 years (IIa A), or stenting as an alternative in high-volume centers (IIb B). Following the latest results of recent studies and after demonstration of the benefit of optimal medical treatment in recent years in patients with asymptomatic carotid stenosis, stratification of stroke risk is recommended in these patients (based on clinical parameters and imaging), and endarterectomy is only to be

considered for patients with stenosis of 60% to 99% and high risk of stroke (IIa B), while stent implantation should be considered for patients with high surgical risk (IIa B), always in accredited centers and when life expectancy is > 5 years.

In the treatment of symptomatic stenosis, there are no major changes from the previous guidelines, except that, in the criteria for endarterectomy and for stenting, they have included outcome validation (rate of stroke/death < 6%) in these patients. The recommendation for early revascularization in symptomatic patients (in the first 14 days after symptom onset) has also been maintained, although there is some debate regarding performing this immediately (in the first 7 days), due to potential cerebral reperfusion syndrome. In the section on vertebral artery stenosis, there are no differences in treatment compared with the 2011 guidelines.²

UPPER EXTREMITY ARTERIAL DISEASE

There are some differences from the previous guidelines regarding the treatment of upper extremity disease. In symptomatic patients, the recommendation for revascularization is not as strong as before (being relegated from I C to IIa C), probably due to the mid- to long-term results of endovascular treatment in this area, which were not as favorable as expected. For the same reason, endovascular treatment is now not recommended as the first option, but rather endovascular technique or open surgery should be weighed up depending on the patient's surgical risk and the anatomical characteristics of the lesion (IIa C). The revascularization criteria are unchanged for asymptomatic patients (existing or planned mammary vein graft, hemodialysis access, or bilateral lesions that make blood pressure measurement difficult).

MESENTERIC ARTERIAL DISEASE

Unlike the 2011 guidelines, the 2017 version includes, for the first time, recommendations on the diagnosis and treatment of acute mesenteric ischemia, probably because of the progressive increase in the detection of this condition brought about by the wider availability of abdominal CT-angiography (recommendation I C) in emergency departments, as well as the use of D-dimer in the diagnostic workup (IIa B). Of note, endovascular treatment is recommended as the first option in ischemia of thrombotic origin (IIa B), and open and endovascular surgery should be considered for embolic etiology. Although laparotomy after endovascular treatment is not essential in patients with acute bowel ischemia, it is often necessary to inspect the bowel. After open revascularization, second look laparotomy is also indicated. There are no major changes in the diagnostic process of chronic mesenteric ischemia. As an essential recommendation, in patients with symptomatic chronic ischemia, surgery should not be delayed to improve the patient's nutritional state (III C).

RENAL ARTERY DISEASE

There are few changes regarding the treatment of renal stenosis. The guidelines reinforce the used of duplex ultrasound as the first diagnostic option, CT-angiography and MR-angiography as confirmation, and digital subtraction angiography if there is discrepancy between imaging findings or when endovascular treatment is planned. The benefits of endovascular treatment are increasingly questioned, and systematic revascularization of renal stenosis is strongly discouraged (III A), to be considered only in selected cases (fibromuscular dysplasia–stenting is discouraged in this situation–acute pulmonary edema, or heart failure).

LOWER EXTREMITY ARTERIAL DISEASE

In the section on the clinical presentation and natural history, a very interesting new concept since the previous guidelines is

introduced, on “masked” lower extremity arterial disease in patients who appear asymptomatic but in whom assessment of potential claudication symptoms is difficult. Such patients may present with critical ischemia as the first manifestation, so emphasis is placed on the detection of LEAD using ABI and especially on prophylaxis against minor trauma that can then lead to trophic disorders that confer a higher risk of losing the limb.

Regarding diagnostic tests, there are no changes to the recommendations regarding ABI as the first option in screening and diagnosis, and alternative methods in cases of extensive calcification with ABI > 1.40 (I C). However, the recommendation tables no longer contain (although it is mentioned in the text) consideration of treadmill testing both in patients with atypical symptoms and in the follow-up after treatment, which was included in the 2011 guidelines² (IIa A–B) and in the 2016 AHA/ACC American guidelines¹⁴ (I B). Also of note is the disappearance of the 2011 recommendation to use segmental pressures and pulmonary function tests to complete the noninvasive workup of these patients (I B), which was also present in the 2015 north American SVS guidelines¹⁵ (II C). Duplex ultrasound is reinforced as the first-line imaging technique for confirming the diagnosis (I C) and for assessment of the saphenous vein for possible grafting. It should be performed along with CT or MR to plan revascularization options (I C), with results always assessed together with clinical signs and symptoms and noninvasive tests to plan the revascularization. As in other territories, the systematic use of digital subtraction angiography for surgical or endovascular planning is becoming increasingly limited, except for the detailed assessment of infrapopliteal vessels or when immediate endovascular treatment is planned. One of the major changes in the guidelines is the recommendation to consider abdominal aortic aneurysm screening in these patients (IIa C).

In the treatment of intermittent claudication, the concept of systematically starting with conservative treatment has been kept. Control of cardiovascular risk factors continues to be emphasized. In medical treatment, the recommendation for antiplatelet agents remains, and there are new strong recommendations for statins (I A) and physical exercise, preferably supervised (I A). For the first time in the guidelines, a section is dedicated to exercise in intermittent claudication, which is indicated in the tables with a Ia recommendation. They propose 3-month rehabilitation programs that include a minimum of 3 hours per week walking up to the maximal or submaximal distance tolerated. For the first time they suggest cycling, strength training and upper arm exercise for patients who cannot walk. The benefit is becoming increasingly relevant in quality of life questionnaires, and it is made easier by improvements in technology that allow exercise tracking on patients' own mobile devices. Only in cases of lack of clinical improvement with conservative treatment and in cases where claudication limits the patient's daily activities should revascularization be considered.

In critical ischemia, the WIfI classification¹⁶ (W: wound; I: ischemia; fl: foot infection) has been demonstrated to be essential for stratifying risk of amputation, as in addition to ischemia it includes parameters such as infection and tissue status (I C). Whenever possible, systematic revascularization is recommended in patients with critical ischemia (I B). Unlike the 2011 guidelines, in which endovascular treatment was considered the first-line treatment for these patients (IIb B), the new guidelines do not specify endovascular or open surgery as first line.

Until now, the anatomical classification of the TASC¹⁷ and subsequent TASC-2 trials has been used to make recommendations on revascularization in patients with lower extremity ischemia.¹⁸ The confusion with the new classification and the difficulty in some cases in assigning certain patients to one category or another led to considerable criticism, which is probably why, unlike the 2011 guidelines, the new version does not use this classification to determine recommendations.

Because of the good outcomes of endovascular treatment in the aorto-iliac segment, demonstrated several years ago, the guidelines have maintained the recommendation for their use, essentially in non-extensive lesions (I C), in patients with serious comorbidity (IIa B), performed by experts and without compromising a possible open surgical treatment (IIb B), and systematically with stenting (IIa B). Open surgical treatment is reserved for patients with extensive lesions (IIa B) or lesions affecting the aorta as far as the renal arteries (IIa C), and hybrid treatment should be considered for iliofemoral occlusions (IIa C). In summary, in the aorto-iliac segment, the tendency is towards endovascular treatment, but surgical risk and the anatomy of the lesions should always be taken into account.

In the femoro-popliteal segment, the outcomes of endovascular treatment are much less clearly defined, due to the generally diffuse involvement of this segment and the different forces of traction, rotation, flexion, and so on, to which the superficial femoral artery is subject. Because of the wide heterogeneity of studies of this anatomical site, the evidence is rather limited. The recommendations are also based on the anatomy of the lesions and the surgical risk, although in this segment the presence of a vein suitable for use in bypass is essential (I A).

In infrapopliteal disease, as mentioned before, angiographic assessment at this site, and especially of the foot, should be considered prior to revascularization (IIa C). Unlike the 2011 guidelines, in which endovascular treatment was considered the first option (IIa C), the current recommendation is for venous bypass (I A) in the infrapopliteal segment due to its better long-term outcomes; the endovascular option should be considered if there is no available venous graft or for patients with very high surgical risk. Finally, given the lack of evidence on outcomes, and while new studies are awaited, neither angiogenesis nor stem cell therapy are indicated (III B).

The guidelines state that acute limb ischemia with neurological deficit mandates urgent surgery but that surgery can be delayed by a matter of hours if there is no neurological deficit, allowing more complete patient workup. The use of thrombolysis, although included in the algorithm in the new guidelines, is not included in the recommendations tables, unlike in the 2011 guidelines (I B).

MULTIVESSEL ARTERIAL DISEASE

Regarding multivessel arterial disease and the value of carotid screening in patients requiring coronary revascularization (CABG), the current recommendation is to only screen patients with a recent neurological event, a stroke or transient ischemic attack in the last 6 months (I B), and it should be considered in patients older than 70 years with multivessel coronary artery disease, carotid bruit or lower extremity disease (the previous guidelines recommended systematic screening for this subgroup). In the treatment of carotid stenosis in patients requiring CABG, a new inclusion is treatment stratification based on the presence of recent neurological symptoms: if present, revascularization should be considered in patients with stenosis of 50% to 99% (IIa B), with endarterectomy as the first option (IIa B). Systematic revascularization is not advised in patients without neurological symptoms (III B), and should only be considered in severe bilateral stenosis or severe stenosis with occlusion of the contralateral carotid artery (IIb B), and for patients with severe stenosis and high-risk anatomical or clinical characteristics (IIb C).

CARDIAC CONDITIONS IN PATIENTS WITH PERIPHERAL ARTERIAL DISEASE

In the section on screening and treatment of lower extremity arterial disease in patients with coronary disease, there are some interesting new recommendations, particularly regarding establishing a good collaboration between the cardiologist, interventionalist, cardiac surgeon and vascular surgeon, which should result in fewer

complications and allow more holistic treatment. In this section, the guidelines neglect to mention the I A indication for cardiac rehabilitation following cardiac events.

In patients with carotid stenosis who are candidates for revascularization, those with concomitant severe coronary disease should be considered for coronary angiography screening (IIb B). Last, there is a new section, not present in the 2011 guidelines, relating to noncoronary cardiac disease in patients with lower extremity arterial disease, such as heart failure, atrial fibrillation or valvular heart disease, as well as the indications in transcatheter cardiological procedures (transcatheter aortic valve implantation [TAVI]). Of note is the recommendation to perform a full vascular study in patients who are candidates for heart transplant or ventricular assist devices (I C), screening for LEAD in patients with heart failure (IIb C) due to potential "masked" arterial disease, oral anticoagulation in patients with AF and LEAD based on the CHA₂DS₂-VASc score (I A), as well as screening for LEAD in patients requiring arterial access such as TAVI (I C).

GAPS IN THE EVIDENCE

The most notable gaps in scientific evidence were in the following aspects: arterial disease in women, risk stratification in asymptomatic carotid stenosis, when to schedule carotid revascularization following stroke, DAPT after endovascular treatment (duration), risk stratification in renal stenosis, long-term results of drug treatments in superficial femoral arterial disease and the need for full screening in peripheral arterial disease and its benefits.

AFTER THE GUIDELINES

Shortly after these guidelines were published, 2 highly relevant studies were published, which is seems appropriate to comment on here. The first found that the combination of low-dose rivaroxaban (2.5 mg twice daily) with aspirin 100 mg daily significantly reduced major cardiovascular events and events related to lower extremity ischemia, such as amputations, in patients with peripheral arterial disease.¹⁹ The second found that evolocumab, a PCSK9 inhibitor, significantly reduced the risk of cardiovascular events in patients with peripheral arterial disease.²⁰

CONFLICTS OF INTEREST

V.A. Arrarte: remuneration for presentations and consultancy from Amgen, MSD, Boehringer and Bayer; payment of travelling expenses, accommodation and meeting attendance from MSD.

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