Antithrombotic treatment for Peripheral Arterial Disease. The IMETHA updated Guidelines

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Peripheral Arterial Disease (PAD) is a chronic, progressively deteriorating atherothrombotic disease that causes narrowing or blockage of the vascular lumen of the arteries of the peripheral arterial circulation. Since 2013, the European Society of Cardiology has included in the definition of PAD the pathology of all peripheral arteries, except those of the heart, aorta and brain, and introduced the term Lower Extremity Artery Disease (LEAD), for peripheral obstructive artery disease that affects arteries from the aortic axis and peripheral, as it affects the majority of patients with PAD.[1] In 2017, the above definitions were adopted by the European Society of Vascular Surgery in the common guidelines issued for PAD.[1] LEAD can be present as an asymptomatic disease in many patients with atherosclerotic lesions in the peripheral arteries. In symptomatic patients, LEAD manifests initially as intermittent claudication, ie pain of the affected limb during walking (Intermittent Claudication; IC), which may gradually develop into severe intermittent claudication that limits daily activities, and results in critical illness; resting pain and / or gangrene (Critical Limb Ischemia; CLI). In 2019, the international "global" guidelines were published,[2] which also modified the above terminology from CLI to CLTI (Chronic Limb-Threatening Ischaemia, Chronic Ischemia that threatens the viability of the limb)

More than 20 million people in Europe have PAD, with a prevalence of 2.5% in people aged 40-59 and 15-20% in people over 70.[3,4] In addition to local manifestations of lower extremity perfusion, PAD is considered the clinical equivalent of Coronary Artery Disease (CAD) in terms of cardiovascular risk as it is associated with a high risk of acute myocardial infarction, ischemic stroke and general vascular death. Atherosclerosis affects more than one vascular bed, and in the case of LEAD it is very common to affect the coronary arteries, but also the cerebral circulation. Therefore, it is a poor prognostic indicator of mortality, as the survival of patients with PAD is reduced by 30-60% (depending on the stage of the disease), compared to the general population of similar age. At this point it should be noted that aneurysmal aortic disease, although it is no longer considered of atherosclerotic etiology, it is nevertheless considered equivalent to CAD and is associated with a high risk of myocardial infraction and stroke. Typically, the relative risk (RR) of cardiovascular death in patients with PAD is increased by about 6 times, while one year after the onset of CLI, 25% of patients have died and 25% have undergone major amputation.[4]

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IMETHA a Greek Institute on Thrombosis and Antithrombotic Therapy (ISETAT, Institute for the Study and Education on Thrombosis and Antithrombotic Therapy), aim to promote research and education, to keep up to date with developments in the field of thrombosis and antithrombotic therapy, to formulate recommendations for the use of antithrombotic drugs as well as to develop and coordinate research programs related to thrombosis and antithrombotic therapy.

IMETHA has recently published its updated recommendations on antithrombotic treatment of patients with LEAD, carotid disease and aortic aneurysm disease.

Weighing the evidence

The clinical practice recommendations in this document are presented using the European Society of Cardiology grading system.[1] For each recommendation, the letter A, B, or C indicates the level of current evidence guiding the recommendation (Table 1).

Depending on whether the recommendation is strongly supportive of an intervention, weakly supportive, or strongly against an intervention, each recommendation is categorised as either Class I, IIa/IIb, and III, respectively (Table 2). The lower the class number, the greater the evidence and/or general agreement in favour of an intervention.

Class of recommendation	*Definition*	
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful and effective	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/ efficacy of the given treatment or procedure	
Class IIa	Weight of evidence/ opinion is on favour of usefulness/ efficacy	Should be considered
Class IIb	Usefulness/ efficacy is less well established by evidence/ opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/ effective, and in some cases may be harmful	Is not recommended/ is not indicated

Table 1.

Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomized trial or large non-randomized studies
Level of evidence C	Consensus of experts opinion and/or small studies, retrospective studies and registries

Table 2.

LEAD - ABDOMINAL AORTIC ANEURYSM DISEASE

(LEAD: lower extremity arterial disease; AMI: acute myocardial infraction; AF: atrial fibrillation; DOAC: direct acting oral anticoagulants)

Recommendation	Class	Level of Evidence
Lifelong anti-platelet therapy is recommended in patients with symptomatic LEAD	I	A
In patients with symptomatic LEAD, combination treatment with aspirin (75–150 mg) and clopidogrel (75 mg) daily does not appear to be superior to monotherapy in terms of major cardiovascular events and carries a higher risk of bleeding. Therefore, dual antiplatelet treatment may only be given to selected symptomatic patients who are at particularly high risk for cardiovascular events and at the same time have a low risk of bleeding	IIb	C
In patients with symptomatic LEAD clopidogrel 75mg daily should be considered as a single antiplatelet treatment, as it appears to be superior to aspirin	IIa	B
In patients with symptomatic LEAD the combination of aspirin 100mg daily and rivaroxaban 2.5mg twice daily should be considered over monotherapy with aspirin (75-150mg), especially in those with concomitant coronary artery disease, diabetes mellitus, renal impairment, heart failure or previous interventions of revascularization and amputations, if the risk of bleeding is acceptable	IIa	B
In asymptomatic patients with diagnosed LEAD (ankle brachial index <0.9), lifelong antiplatelet therapy with aspirin (75-150mg) or clopidogrel (75mg) may be considered to decrease the risk of AMI, stroke, and vascular death	IIb	C
In patients with symptomatic LEAD and indication for chronic anticoagulation (AF, mechanical prosthetic valve or venous thromboembolic disease), anticoagulation (DOAC or coumarin anticoagulants) should be considered as monotherapy without the addition of antiplatelet treatment	IIa	B
In patients with symptomatic LEAD receiving chronic anticoagulation (due to AF, mechanical prosthetic valve or venous thromboembolic disease), the addition of an antiplatelet agent may only be considered for those patients at high risk for ischemia, which have a strong indication for antiplatelet treatment, always taking into consideration the patient's bleeding risk	IIb	C
Cilostazol at a dose of 50-100 mg twice daily increases the walking distance in symptomatic patients with LEAD in the intermittent claudication stage and may be administered in addition to the basic antiplatelet agent (clopidogrel or aspirin)	IIb	B
In patients with symptomatic LEAD, the addition of oral coumarin anticoagulants to the antiplatelet agent (aspirin or clopidogrel) is not superior to monotherapy with any of these agents, and could increase the risk of bleeding complications and therefore is not recommended	III	B
Patients with aortic aneurysm disease should receive lifelong antiplatelet treatment with aspirin 75–150mg daily	IIa	C

OPEN REPAIR FOR REVASCULARIZATION

(LEAD: lower extremity arterial disease; AF: atrial fibrillation; DOAC: direct acting oral anticoagulants)

Recommendation	Class	Level of Evidence
Patients with LEAD undergoing open surgery for revascularization should receive single antiplatelet therapy, with clopidogrel (75 mg daily) or aspirin (75-150 mg daily), which should be started before surgery and will be continued for life	IIa	B
Patients with LEAD undergoing open surgery for revascularization should receive a combination of rivaroxaban (2.5 mg twice daily) with aspirin (100 mg daily) as antithrombotic treatment, instead of monotherapy with aspirin, when their bleeding risk is acceptable	IIa	B
In patients with LEAD and indication for chronic anticoagulation (AF, mechanical prosthetic valve or venous thromboembolic disease) who undergo open surgery for revascularization, anticoagulation (DOAC or coumarin anticoagulants) should be continued as monotherapy, without the addition of antiplatelet treatment	IIa	B
Patients with LEAD who are at high risk for limb loss or thrombosis of revascularization procedure may receive antiplatelet treatment with combination of aspirin (75-150 mg daily) and clopidogrel (75 mg daily) for an early period after surgery (1-6 months), if the bleeding risk is acceptable	IIb	C
Patients with LEAD undergoing bypass surgery with a synthetic below-knee graft should be treated with aspirin (75-150 mg daily) and clopidogrel (75 mg daily) for 6 months, if the bleeding risk is acceptable	IIa	B
In patients with LEAD who undergo bypass surgery with a venous graft below the knee and are at high risk of limb loss or thrombosis of the vascularization procedure, high dose of oral coumarin anticoagulants may be given instead of antiplatelet treatment, as long as the bleeding risk is acceptable	IIb	B
Patients undergoing open surgery for an abdominal aortic aneurysm repair should receive antiplatelet treatment with aspirin 75-150 mg daily throughout the peri-operative period, that will be continue for life	IIa	C

ENDOVASCULAR PROCEDURES

(LEAD: lower extremity arterial disease)

Recommendation	Class	Level of Evidence
A single antiplatelet treatment is recommended for patients with LEAD undergoing endovascular intervention of the peripheral arteries, with clopidogrel (75 mg daily) or aspirin (75-150 mg daily), which will be started before surgery and will be continued for life	I	A
In patients with LEAD undergoing endovascular intervention of the peripheral arteries, dual antiplatelet therapy with aspirin (75-150 mg daily) and clopidogrel (75 mg daily) appears to be superior to monotherapy and should be administered to patients with acceptable bleeding risk, for a period of 1-6 months after intervention	IIa	B
Patients with LEAD undergoing endovascular intervention of the peripheral arteries, after the initial short interval of dual antiplatelet treatment, should receive antithrombotic therapy, with a combination of rivaroxaban (2.5 mg twice daily) and aspirin (100 mg), instead of long-term monotherapy with aspirin, if the bleeding risk is acceptable	IIa	B
After endovascular intervention in patients receiving chronic anticoagulation, the addition of an antiplatelet agent (clopidogrel or aspirin) should be considered for 1 month (up to 6 months) if the risk of bleeding is acceptable. In the long-term period, only chronic anticoagulation should be continued. If the risk of bleeding is high, chronic anticoagulation as monotherapy should be considered without the addition of an antiplatelet agent	IIa	C
Patients treated with endovascular aneurysm repair for abdominal aortic aneurysm should receive antiplatelet treatment with aspirin (75–150 mg daily) throughout the peri-operative period and for life	IIa	C

CAROTID ARTERY DISEASE

Asymptomatic patients

Recommendation	Class	Level of Evidence
In asymptomatic patients with a significant (> 50%) carotid stenosis, lifelong aspirin (75-150 mg daily) should be administered. In case of a contraindication to aspirin the administration of clopidogrel (75mg daily) should be considered as a reasonable alternative treatment	IIa	B
A combination treatment with aspirin and clopidogrel is not recommended in asymptomatic patients with a significant (> 50%) carotid stenosis	III	B

Symptomatic patients

Recommendation	Class	Level of Evidence
In symptomatic patients with carotid stenosis> 50% (recent transient ischemic attack or minor stroke), immediate initiation of dual antiplatelet treatment with clopidogrel (75 mg daily) and aspirin (75-150 mg daily) for 21 days is recommended. After that period, monotherapy antiplatelet treatment with clopidogrel or alternatively with aspirin is recommended for life	I	A
In symptomatic patients with carotid stenosis> 50% (recent transient ischemic attack or minor stroke), a combination of aspirin (75-150mg daily) and ticagrelor (90mg twice daily) may be given for 30 days when there is a contra-indication for clopidogrel, if the risk of bleeding is acceptable, and after that period monotherapy with aspirin is recommended for life	IIb	B
The use of coumarin anticoagulants instead of antiplatelet treatment is not recommended in patients with symptomatic carotid disease	III	B

DISSECTION OF INTERNAL CAROTID ARTERY

Recommendation	Class	Level of Evidence
In patients with dissection of internal carotid, the anticoagulation treatment with heparin initially and warfarin thereafter is not superior to antiplatelet treatment. Antiplatelet treatment with clopidogrel (75mg daily) or aspirin (75-150mg daily) or a combination of those, should be considered as the first choice of antithrombotic treatment based on simplicity of use and a possibly better bleeding risk profile in comparison to coumarin anticoagulants	IIa	B

ANTITHROMBOTIC TREATMENT FOR CAROTID ARTERY DISEASE INTERVENTION

Carotid endarterectomy

Recommendation	Class	Level of Evidence
In patients undergoing carotid endarterectomy, antiplatelet treatment with clopidogrel (75 mg daily) or aspirin (75-150 mg daily) is recommended before, during and after surgery	I	B
In symptomatic patients with carotid stenosis> 50% (recent transient ischemic attack or minor stroke) who are scheduled for carotid endarterectomy, immediate initiation of dual antiplatelet treatment with clopidogrel (75 mg daily) and aspirin (75-150 mg daily) should be administered up to the day of surgery (or up to 21 days after the episode), and since then single antiplatelet treatment should be continued with one of the two antiplatelets for life	IIa	B

Carotid artery stenting

Recommendation	Class	Level of Evidence
In patients undergoing carotid artery stenting, dual antiplatelet treatment with aspirin (75-150 mg daily) and clopidogrel (75 mg daily) is recommended	I	B
Dual antiplatelet treatment should be started at least 3 days before intervention and should be continued for 1 month; after that period single antiplatelet treatment with one of the two antiplatelet agents will be continued for life	IIa	B
In symptomatic patients with carotid stenosis> 50% (recent transient ischemic attack or minor stroke) who are scheduled for carotid artery stenting, immediate initiation of dual antiplatelet treatment with clopidogrel (75 mg daily) and aspirin (75-150 mg daily) should be considered, up to 1 month after surgery and since then single antiplatelet treatment will be continued with one of the two antiplatelet agents for life	IIa	B

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