Chapter 5 is an excerpt from the Guideline on peripheral arterial disease. The correct citation is: European Society for Vascular Medicine (ESVM). Guideline on peripheral arterial disease. Vasa. 2019;48, Supplement 102, doi 10.1024/0301-1526/a000834.

5 Conservative treatment for PAD – Risk factor management

Ulrich Frank^a (Switzerland), Sigrid Nikol^a (Germany), and Jill Belch^a (UK) for the European Society of Vascular Medicine

PAD Guideline Writing Group

^aall co-first authors

ESVM Board Authors

Vinko Boc* (Slovenia), Marianne Brodmann (Austria), Patrick H Carpentier (France), Ali Chraim* (Ukraine), Caitriona Canning (Ireland); Evangelos Dimakakos* (Greece), Anders Gottsäter (Sweden), Christian Heiss (Germany), Lucia Mazzolai (Switzerland), Juraj Madaric* (Slovakia), Dan Mircea Olinic* (Romania), Zsolt Pécsvárady* (Hungary), Pavel Poredoš* (Slovenia), Isabelle Quéré (France), Karel Roztocil (ESVM President, Czech Republic), Agata Stanek (Poland), Dragan Vasic* (Serbia), Adriana Visonà (Italy), and Jean-Claude Wautrecht* (Belgium)

ESVM Country Society Authors

Miroslav Bulvas (Czech Republic), Mary-Paula Colgan (Ireland), Walter Dorigo (Italy), Graeme Houston (UK), Thomas Kahan (Sweden), Holger Lawall (Germany), Isak Lindstedt (Sweden), Guillaume Mahe (France), Romeo Martini (Italy), Giles Pernod (France), Stanislaw Przywara (Poland). Marc Righini (Switzerland), Oliver Schlager (Austria), and Piotr Terlecki (Poland)

*Indicates ESVM Board members who were also nominated by their Country Society as reviewers.

5.1 Objectives of conservative PAD treatment

The objectives of PAD treatment are to reduce the risk of future cardiovascular events (all Fontaine Stages) to improve walking performance, mobility and quality of life in Fontaine Stage II, and limb preservation, pain reduction and improved/ maintain quality-of-life in Fontaine Stages III and IV.

This chapter deals with cardiovascular risk and its management in patients with PAD.

5.2 Cardiovascular risk management in PAD

Basic conservative treatment consists in monitoring of and treatment for cardiovascular risk factors for

atherothrombosis. This covers regular physical activity, weight reduction in overweight patients, nicotine abstention in smokers, antiplatelet medication, as well as treatment for arterial hypertension, dyslipidemia and diabetes mellitus [113–117].

Recommendation	Class of recommendation	Level of evidence
Lifestyle changes are recommended in the presence of obesity and/or physical inactivity.	I	C

5.2.1 Smoking

Smoking is at present the most important risk factors for PAD. The corresponding amount of exposure (number of pack years) is associated with the severity of PAD, a higher amputation rate, peripheral prosthetic bypass occlusion and mortality [118, 119]. The rate of amputations is markedly increased among smokers. Smoking cessation has been evidenced to impact on progression of PAD [120, 121], yet its significance for walking performance in intermittent claudication is less definite.

The rate of abstinence can demonstrably be improved with nicotine replacement preparations, formal cessation programs and bupropion [122–124]. Regularly and medically addressing the problem, along with intensive supervision, is the key to withdrawal. Other options, including group therapy or nicotine replacement preparations, should also be considered and can be combined with one another.

5.2.2 Depression

The presence of concomitant reactive depression in patients with PAD has become increasingly important [125]. The development of depression appears to limit quality of life and walking performance to a significant extent. In turn, reduced walking performance may possibly have a causative effect on the development of reactive depressive conditions. Data from interventional studies of antidepressants or psychiatric treatment for patients with PAD have not yet become available.

Recommendation	Class of recommendation	Level of evidence
Smoking cessation (and abstinence from other drugs taken through smoke inhalation, e.g. cannabis) is recommended as being urgently required in all PAD stages.	I	A
It is recommended that smokers are to be provided with a cessation program consisting of medical supervision, group therapy and nicotine replacement considered.	I	A
In the absence of evidence on the long-term effects, it is recommended that eCigarettes should be considered to aid smoking cessation. In the light of adverse effects on the endothelium these should be a short interim activity to reduce habituation and making smoking cessation possible.	IIa	C

5.2.3 Dyslipidemia

Elevated total cholesterol concentrations, increased levels of low-density lipoprotein (LDL) cholesterol, triglyceride and lipoprotein (a), and decreased high-density lipoprotein (HDL) levels [126] are independent risk factors for the development of PAD. An inverse correlation has been shown between the level of LDL cholesterol and the ABI in patients with newly diagnosed PAD [127].

In the Heart Protection Study (HPS), simvastatin significantly lowered the rates of vascular and cardiac events in patients with PAD, irrespective of the presence of CAD at the beginning of the study [128–130]. This also applied to patients with so called ‘normal’ cholesterol values – indeed benefit was seen down to total cholesterol levels of 3.5 mmol/l. A cholesterol threshold value under which no benefit was detectable was not evidenced.

In prevention of vascular events and overall mortality, the most recent Cochrane analyses endorsed the benefits, cost efficiency and improved quality of life associated with statins, without accepting relevant undesirable effects even in low-risk patients [131].

The extent to which LDL values should be lowered in PAD patients remains unclear, no prospective interventional studies have so far been carried out in PAD alone patients. However, the results of the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) supported the “LDL hypothesis” and suggested monitoring and the reduction of LDL values in patients at a high risk of cardiovascular disorders. Further the Fourier study [132] which enrolled 27,564 patients of which 13.2 % (3,642) had symptomatic PAD, all of whom

were on statin therapy evaluated benefit in the preplanned PAD subgroup. The full study which was placebo controlled, of evolocumab, showed a significant decrease in the combined CV endpoints of MI, Stroke, and death (HR 0.80, 95 % CI 0.73–0.88) combined with a very good safety profile for very low levels of LDL. In the PAD subgroup, evolocumab significantly reduced the primary end point consistently in patients with PAD (hazard ratio [HR] 0.79; 95 % confidence interval [CI], 0.66–0.94, and also reduced the risk of major adverse limb events in all patients (HR, 0.58; 95 % CI, 0.38–0.88) [133]. This suggests that current targets are set to fall as these new drugs reach endpoint study conclusion.

The benefits of lipid lowering with statins and other lipid reducing agents in PAD is without doubt. Intriguingly, there is also some evidence in support of lipid lowering improving claudication. In the Scandinavian Simvastatin Survival Study (4S), simvastatin served to reduce the development of intermittent claudication in patients with coronary and stroke disease [128–134]. Further studies applying various doses of atorvastatin or simvastatin to treat patients with claudication yielded significantly improved pain-free or absolute walking distances compared to placebo after 3, 6, and 12 months. However, these studies examined small numbers of patient only [135–137].

Intensive statin therapy has been shown in retrospective studies to not only reduce CV mortality but also amputation [138, 139] and to enhance graft patency [140]. New data, recently available, shows that intensive statin therapy versus low intensity statin therapy better reduces adverse limb outcomes such as amputation [141].

Further consideration on additional therapy such as ezetimibe [142] and evolocumab [132], may need to be considered in this group which has such a high risk of further CV events.

The current European Society of Cardiology (ESC) guidelines recommend a lowering of LDL cholesterol depending on the overall cardiovascular risk to < 100 mg/dl (< 2.58 mmol/l) in high-risk patients and to < 70 mg/dl (< 1.81 mmol/l) in those at a very high risk including PAD patients (see the ESC Systematic Coronary Risk Evaluation [SCORE] system) [113]. To achieve these lower levels, monitoring of patient results, to ensure targets are reached, is crucial. Thus, it is not sufficient to merely start lipid lowering therapy, but the clinician must also ensure arrangements are in place for follow-up (e.g., in Primary Care) to ensure “treating to target”.

Identical target values can be recommended for women and men. However the current US guidelines have disassociated themselves from LDL titration as a target value [143]. PAD patients are considered very high-risk patients and are to be given “intensive” statin treatment with the aim to effectively and tolerably lower vascular risk. Medical Care has to focus on concordance, as non-adherence has shown to be a considerable problem in everyday practice.

Recommendation	Class of recommendation	Level of evidence
It is recommended that in patients with PAD, statins are indicated for the prevention of cardiovascular events. Statins reduce morbidity and mortality in PAD and are recommended for secondary prevention in all PAD patients who tolerate such medication.	I	A
It is recommended that Lipid levels are only important in terms of achieving recommended decreases, not as a value to decide whether or not to start a statin.	I	A
Based on the pleiotropic (multifactorial) and plaque-stabilizing effects of statins, statins should be considered for all PAD patients when tolerated, independent of LDL levels in all stages of disease.	IIa	C
It is recommended that in PAD patients, LDL should be lowered to 1.8 mmol/l (70 mg/dl) or reduced by $\geq 50\%$ if pretreatment values are 1.8–3.5 mmol/l (70–135 mg/dl)	I	A
A high dose of a potent statin is usually indicated, if tolerated, (eg 20–40 mg of rosuvastatin, 40–80 mgs and above atorvastatin or comparable doses of potent other statins).	I	A
A combination of a statin medication with ezetimibe can be considered to get better tolerance of the statin medication (with reduced doses) or to achieve the given target values in LDL-cholesterol.	IIa	B

The recent publication of the Fourier Study using the PCSK9 Inhibitor evolocumab, and its predefined sub-study of PAD [133], shows a significant decrease in both MACE and major adverse limb events (MALE). MACE in patients with PAD (hazard ratio [HR] 0.79; 95 % confidence interval [CI], 0.66–0.94 and without PAD (HR 0.86; 95 % CI, 0.80–0.93) and MALE (HR, 0.58; 95 % CI, 0.38–0.88; $P = 0.0093$).

61 % of PAD patients recruited had had an intervention, 40 % had diabetes, and the evidence showed the lower the LDL the better in terms of CV outcome with no lower limit being recommended and no overt side effects from this lower LDL. However, at present cost precludes us treating all patients, although a cost benefit analyses shows acceptable cost-effective thresholds [144] and so we recommend the following therapeutic strategy:

No data are available to evidence reduced morbidity and mortality by treating elevated triglyceride levels and low HDL cholesterol values.

Recommendation	Class of recommendation	Level of evidence
A PCSK9 inhibitor may be considered in PAD patients on maximum tolerated statin therapy, plus ezetimibe, who do not reach a target LDL.	I	B
In view of the primary prevention studies with statins and the known risk profile in asymptomatic PAD disease, consideration should be given to also treating asymptomatic PAD patients.	IIb	C

Nicotinic acid reduces femoral atherothrombosis and delays coronary atherothrombosis in patients with PAD [145], yet has no additional verified benefits compared to statins in terms of reduced clinical endpoints and so cannot be recommended [146]. Although, omega-3 fatty acids has shown no effect on platelet activation or inflammatory parameters in patients with PAD, positive data are available for other risk populations [147–149]. However, there are no positive endpoint studies for patients with PAD [150, 151].

Recommendation	Class of recommendation	Level of evidence
Nicotinic acid preparations are not recommended in the prevention of cardiovascular events in patients with PAD	III	A
Omega-3 fatty acids are not recommended in the prevention of cardiovascular events in patients with PAD.	III	A

5.2.4 Diabetes mellitus

Apart from smoking, diabetic metabolic disorders are the most important risk factors for PAD progression. Every HbA_{1c} increase in the magnitude of 1 % is associated with a 28 % increase in the relative risk for manifest PAD [152]. Diabetes elevates the risk of PAD by a factor of 3 to 4 and the risk of claudication by a factor of 2. A subgroup analysis of United Kingdom Prospective Diabetes Study (UKPDS) [40] in 3,884 patients showed a lower amputation rate with lower levels of HbA_{1c} and/or lower levels of chronic hyperglycemia [152]. Another study showed significantly reduced walking performance and lower-limb mobility in patients with diabetes with PAD compared with patients without diabetes with PAD [153].

Among type 2 patients with diabetes under intensified treatment (diabetes stabilization, CSE inhibitor i.e. statin and antiaggregant administration), the Steno-2 study observed a 25 % relative risk reduction in amputation rates and a 10 % decrease in vascular interventions over 7 years [154]. Both type 1 and type 2 patients with diabetes benefit from improved glucose stabilisation in terms of reduced PAD progression. Current guidelines issued by the

American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and the European Society of Cardiology recommend the formulation of individualised treatment objectives for HbA_{1c} together with the affected patients, considering the factors of age, comorbidity, hypoglycemic risk and patient's preference. The aim is an HbA_{1c} range of 6.5 % to 7.5 % to prevent subsequent complications [115, 155, 156]. In elderly vascular patients, a range of 7 % to 8 %, is seen as tolerable, while avoiding hypoglycemic events.

While 10-year follow-up data of the UKPDS has suggested a significant reduction in overall mortality, other studies have revealed no significant reduction in cardiovascular mortality by approximating the HbA_{1c} value to normal by way of intensified diabetes treatment. These include Action to Control Cardiovascular Risk in Diabetes (ACCORD [157]), Action in Diabetes and Vascular Disease: Preterax and Damicron Modified Release Controlled Evaluation (ADVANCE [158]), Veterans Affairs Diabetes Trial (VADT [159]), Action in Diabetes and Vascular Disease: Preterax and Damicron Modified Release Controlled Evaluation Post-trial Observational Study (ADVANCE-ON [160]).

The inconsistent database regarding the advantages of close-to-the-norm HbA_{1c} stabilization is the reason for querying the lowest possible HbA_{1c} target values and turning toward more individualised treatment strategies. Care for patients with vascular disorders and diabetic metabolic disorders requires interdisciplinary cooperation between vascular physicians and diabetologists.

Intentionally including pre-diabetes, the recent ESC/EASD guidelines classified patients with diabetes in groups at high and at very high risk for cardiovascular events. Individual specification of treatment objectives, measured according to HbA_{1c} values and the avoidance of hypoglycemia, is the most important aspect of anti-hyperglycemic treatment. In individual cases, lifestyle interventions and treatment for comorbidities are to be applied.

5.2.4.1 Antidiabetic therapy in PAD

When it comes to diabetic therapy, the glucocentric view is increasingly taking a back seat. Rather, the treatment of cardiovascular comorbidities is of increasing importance. However, this is where there are considerable differences between the individual antidiabetic substances.

Biguanides

Metformin is the first-line oral antidiabetic drug in diabetics with PAOD, although the data is thin in this respect. A recently published study again demonstrates the positive effect on CV survival, but not on extremity retention and patency after peripheral revascularization [161].

Sulfonylureas and Glinides

For both groups of substances no robust data on PAOD is available. Because of the relatively high risk of hypoglycemia and potential unfavorable effects in patients with coronary heart disease, these substances are hardly relevant [162].

DPP4 inhibitors

The cardiovascular endpoint studies SAVO-TIMI 53, EXAMINE, TECOS and CAROLINE show a non-inferiority of tested DPP4 inhibitors to the tested outcomes CV death, non-fatal myocardial infarction or stroke compared to placebo or glimepiride. In the SAVOR-TIMI 53 study, however, significantly more hospitalization for saxagliptin was observed because of heart failure, so this substance should be used with caution in patients with known heart failure. Cardiovascular superiority or benefits in the presence of concomitant PAD are not proven [163–167].

GLP1 agonists

Both liraglutide, dulaglutide and semaglutide have been shown to have a positive effect on cardiovascular events such as fatal and non-fatal myocardial infarction and non-fatal stroke versus placebo in endpoint studies [168–170]. In the LEADER study Liraglutide reduces the amputation rate.

For semaglutide, however, there is an increased rate of microvascular ocular complications in combination with insulin, which is why this GLP-1 agonist should not be used in patients with diabetic retinopathy [169].

Thiazolidinediones (PPAR γ agonists)

For Pioglitazone the PROACTIVE and the IRIS study show positive endpoint in cardiovascular survival in type 2 diabetes and prediabetic patients [171–175]. In the PROACTIVE trial, amputation was also considered the primary endpoint. Here, however, no significant advantage over the control group could be observed.

SGLT-2 inhibitors

For the substances empaglifozin, dapaglifozin and canaglifozin, the EMPAREG outcome study, the DECLARE-TIMI study and the CANVAS study provide data for positively influencing cardiovascular outcomes such as CV death, fatal and non-fatal myocardial infarction and stroke [176–179]. The EMPAREG outcome study furthermore revealed a significantly reduction in amputations in PAOD whereas for canaglifozin a significantly increased amputation rate (mainly toe amputations) was observed. Although these are retrospective subgroup analyses, the use of canaglifozin in patients with diabetes and PAOD is currently not recommended.

Insulin

For basal insulin therapy, no endpoint studies are available for patients with PAOD. Insulin should be used in type 2 diabetics just in case of present cardiovascular complications, if possible, only after an optimized oral or GLP-1 based therapy.

In summery only empaglifozin and liraglutid have been shown to reduce amputations. Therefore, these substances should be considered in addition to metformin in patients with diabetes with previously known PAD [180, 181]. Screening for diabetes in patients with PAD should be

carried out due to the close association between diabetes and PAD.

Recommendation	Class of recommendation	Level of evidence
It is recommended that patients with diabetes should be screened for PAD	I	B
It is recommended that all PAD patients should be screened for diabetes and effectively treated in the case of a proven diagnosis of diabetes. In type 2 diabetics in addition to metformin empagliflozin and/or liraglutid should be considered.	I	B
Appropriate diabetic control is recommended in patients with PAD.	I	B

5.2.5 Hypertension

Hypertension is associated with an increased prevalence of PAD [182]. The increase in risk is modest but the high prevalence of hypertension with increasing age makes the contribution of elevated blood pressure to incident PAD in the general population important. In men 40–79 years old the hazard ratio for incident PAD in the presence of hypertension was reported to be 2.42 [183], whilst a 20 mm Hg increase in systolic blood pressure was associated with a 62 % increased risk for PAD in a large population study [184].

Antihypertensive therapy unequivocally reduces cardiovascular events and mortality. Current evidence suggests a further benefit of reducing systolic blood pressure to lower values than previously recommended [185–187]. Thus, current guidelines recommend a target blood pressure, if tolerated, of 120–129/70–80 mm Hg in patients below 65 years, and 130–139/70–80 mm Hg for older patients (with no upper age limit), also in people with concomitant cardiovascular disease (including PAD) and diabetes [188, 189]. A systolic blood pressure below 120 mm Hg should not be targeted as it may increase the risk for acute coronary events and the risk of harm outweighs the benefits, in particular in patients with advanced CAD and in the old.

Angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), calcium antagonists, and diuretics are all suited for blood pressure lowering treatment in patients with PAD [188, 189]. ACE inhibitors and ARB have been shown to reduce cardiovascular events in patients with arterial peripheral vascular diseases [190–192]. ACE inhibitors were proposed to improve symptoms in patients with intermittent claudication [193] but this view has been revised [194] while the calcium antagonist verapamil was shown to prolong walking distance in patients with PAD [195]. Studies in hypertension show somewhat less reduction in cardiovascular events with beta blockers than with other antihypertensive drug classes. Of

note, beta blockers are well tolerated in PAD patients and are not contraindicated [196–198]. Thus, beta blockers are useful in PAD patients with concomitant cardiovascular disorders, where they are indicated.

Most patients require two or more drug classes to achieve target blood pressure. Thus, a blocker of the renin-angiotensin aldosterone system in combination with a calcium antagonist or a diuretic is recommended, adding the third drug, if needed, to achieve target blood pressure. If blood pressure remains uncontrolled adding spironolactone may be considered, which provides a greater reduction in blood pressure than adding an alpha blocker or a beta blocker [Williams 2015]. However, beta blockers are recommended when there are specific clinical indications.

Recommendation	Class of recommendation	Level of evidence
It is recommended that in patients with PAD and arterial hypertension, blood pressure should be treated to reduce cardiovascular events.	I	A
It is recommended that systolic blood pressure should be targeted to 120–129 mm Hg, if tolerated, in most hypertensive patients aged below 65 years, with or without cardiovascular disease.	I	A
It is recommended that systolic blood pressure should be targeted to 130–139 mm Hg, if tolerated, in older (65 years and above) hypertensive patients, with or without cardiovascular disease.	I	A
A diastolic blood pressure below 80 mm Hg should be considered for all hypertensive patients	IIa	B
Antihypertensive drug treatment should consider including an ACE inhibitors or an angiotensin receptor blocker	IIa	B

5.2.6 Platelet aggregation inhibitors in symptomatic PAD

The clinical significance of decreased platelet aggregation in the secondary prevention of atherothrombotic vascular disorders is undisputed. However, large convincing studies showing a benefit of aspirin (ASA) in the reduction of vascular lesions in PAD have not yet been carried out. This applies to both PAD and the inhibition of progression in peripheral atherothrombosis. A primary meta-analysis carried out by the Antithrombotic Trialists' Collaboration failed to detect a significant decrease in cardiovascular events in PAD patients who were taking ASA and who presented no further vascular lesions in other organs. So, while there are conclusive study results regarding the secondary prevention of cardiac and cerebrovascular events in patients with PAD with antiplatelet agents other than

Table 5.2.6. Recommendations on antithrombotic therapy in patients with Peripheral arterial disease.

Recommendation	Class of recommendation	Level of evidence
Lower extremity artery disease		
Long term SAPT is recommended in symptomatic patients	I	A
Long term SAPT is recommended in patients after revascularisation	I	C
Long term SAPT is recommended after infra-inguinal bypass surgery	I	A
In diabetic patients requiring SAPT clopidogrel may be preferred over aspirin [16, 179]	IIb	B
VKA may be considered after autologous infrainguinal bypass	IIb	B
DAPT at least 1 month after infrainguinal stent implantation	IIa	C
DAPT may be considered in below the knee prosthetic bypass graft	IIb	B
SAPT in asymptomatic patients	III	A
DAPT at least 1 month after drug coated balloon angioplasty	I	C
DAPT at least 3 months after drug eluting stent implantation	I	C
DAPT at least 3 months after covered stent implantation	I	C
Combination of aspirin (100 mg/d) and rivaroxaban (2 × 2.5 mg /d) in patients with symptomatic disease	IIa	B
Antithrombotic therapy for PAD Patients requiring oral anticoagulation (OAC)		
In patients with an indication for OAC, oral anticoagulation alone should be considered	IIa	B
After endovascular revascularisation aspirin or clopidogrel should be considered in addition to OAC for at least 1 month	IIa	B
After endovascular revascularisation OAC alone should be considered if bleeding risks are high	IIa	C
OAC and SAPT may be considered if ischemic risk is high or there is another firm indication for long term SAPT	IIb	C

AF = atrial fibrillation; CAS = carotid artery stenosis; CHA₂DS₂-VASc = Congestive heart failure, Hypertension, AGE ≥ 75 (2 points), Diabetes Mellitus, Stroke or TIA (2 points), Vascular disease, Age 65–74 years, Sex category; DAPT = dual antiplatelet therapy; LEAD = lower extremity artery disease; OAC = oral anticoagulation; PADs = peripheral arterial diseases; SAPT = single antiplatelet therapy.

aspirin, the data base regarding the primary prevention of peripheral arterial events is insufficient and in part contradictory [199–201].

In a subsequent meta-analysis including many platelet aggregation inhibitors (ASA, clopidogrel, ticlopidine, dipyridamole, picotamide), a 23 % reduction in the relative risk for ischemic events was seen in all patients with PAD [202] but most patients received ticlopidine in these studies.

The benefit of life-long antiplatelet treatment in patients with PAD to prevent CAD or cerebrovascular lesions does seem convincing [9, 16, 203]. Historically ticlopidine has been investigated in several studies in PAD patients and has shown to reduce the risk of MI, stroke and vascular death [204]. However, its benefits are limited by very frequent gastrointestinal side effects and potential side effects as neutropenia and thrombocytopenia. Therefore, clopidogrel, another thienopyridine derivative, has replaced ticlopidine. Clopidogrel was investigated in the CAPRIE study in which it proved efficacy in lowering the rates of MI, stroke and cardiovascular mortality. The overall benefit in the PAD subgroup compared with ASA was a 24 % relative risk reduction [203]. In terms of numbers needed to treat (NNT) and compared to ASA, this corresponds to a total of 87 patients treated with clopidogrel over three years to avoid one additional cardiovascular event. In the current ESC PAD guidelines, clopidogrel was therefore recommended over aspirin in PAD patients [12] (Table 5.2.6).

In the EUCLID study [205], ticagrelor and clopidogrel were equivalent in effect, though there were more drug discontinuations for side effects with Ticagrelor. Disappointingly, there was no ASA arm. However, the significance of the novel P2Y₁₂ adenosine receptor antagonists (prasugrel and ticagrelor) for PAD is still a matter of ongoing research. The daily dose of clopidogrel in secondary prophylaxis is 75 mg.

Based on the TRA 2P – TIMI 50 study, vorapaxar, a thrombin receptor (protease-activated receptor, PAR-1) antagonist, was granted approval in the US for the secondary preventive treatment of CAD and PAD (in combination with ASA or clopidogrel, to the exclusion of patients with cerebral arterial occlusive disease or a history of intracerebral bleeding due to the increased risk of cerebral bleeding in this patient group). Approval in Europe is limited to CAD. TRA 2P – TIMI 50 study yielded significant benefits in terms of vascular complications and mortality for patients with PAD and CAD treated with vorapaxar, a protease-activated receptor 1 (PAR1) antagonist, yet no gain for those presenting with cerebral arterial occlusive disease [206].

The combination of ASA and clopidogrel in high-risk patients with multiple risk factors and atherothrombotic manifestations (including PAD) – as well as in patients presenting with risk factors for cardiovascular disorders resulted in an increased bleeding risk and no benefit [207].

Combination treatment across the board has no statistically significant risk reductions in terms of MI, stroke or

Table 5.2.8. Preventive treatment for PAD and clinical benefits.

Treatment	Agent	Effect on morbidity and mortality*	Effect on PAD*	Effect on walking performance*	Effect on ABI
Smoking abstinence		Reduction of cardiovascular mortality			
Cholesterol lowering	Statin	12 % reduction in overall mortality	38 % reduction in the incidence of intermittent claudication	63 % increase in pain-free walking distances following 1 year of treatment	
	Ezetimibe	5 % risk reduction in combination with 40 mg simvastatin			
	Evolocumab	12 % risk reduction (95 % CI, 3 to 20) in the first year and 19 % risk reduction (95 % CI, 11 to 27) beyond the first year.			
Blood-pressure lowering	Beta blockers	53 % reduction in cardiovascular events			
	ACE inhibitors/ARBs	22 % reduction in risk of cardiovascular events		24 % improvement of pain-free walking distances; 17.5 % improvement of maximum walking distances	ABI increase from 0.59 to 0.64
Diabetes treatment		17 % reduction in risk of cardiovascular events	25 % reduction in major amputations		
Platelet inhibition	Clopidogrel	23.8 % reduction in risk of cardiovascular events			
ASA + DOAC	ASA 100 mg/d and rivaroxaban 2 × 2.5 mg/d	28 % net clinical benefit HR 0.80)	46 % reduction of major adverse limb events including major amputation (HR 0.54)		

Source: [216] (modified); *Relative risk reduction.

cardiovascular death. Therefore, combination treatment cannot be generally recommended for all patients with PAD. However, data from PEGASUS-TIMI 54 study [208, 209] prove that, in PAD patients with previous myocardial infarction, a selected high ischemic-risk subgroup, dual-antiplatelet therapy with aspirin and low-dose ticagrelor (60 mg b.i.d) is associated with a 5.2 % AR reduction in MACE and a reduction of MALE, while major TIMI bleedings were in excess of only 0.12 %. Therefore, DAPT with ticagrelor 60 mg b.i.d and aspirin may be considered in PAD patients with prior MI up to 3 years following the cardiac event. Evidence for prolonged treatment is currently lacking [12].

Evidence for dipyridamole in PAD is absent and is thus not indicated.

In summary, every symptomatic PAD patient should be given long-term treatment with platelet aggregation inhibitors, if there are no contraindications, as evidenced by the meta-analysis of the Antithrombotic Trialists' Collaboration and data from the Swedish Ticlopidine Multicentre Study (STIMS) and the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study [42, 199, 207].

Recommendation	Class of recommendation	Level of evidence
In patients with symptomatic PAD, platelet aggregation inhibitors are indicated for the secondary prevention of cardiovascular events. Clopidogrel may be preferred over aspirin.	I	A

5.2.7 Platelet aggregation inhibitors in asymptomatic PAD

In asymptomatic disease, there is no evidence for the use of aspirin. Patients with diabetes with asymptomatic PAD given 100 mg daily of ASA, have shown neither reduced rates of cardiovascular events (lethal and nonlethal MI, stroke, cardiovascular mortality) nor reduced rates of major amputations compared to placebo-treated patients [17, 200, 201]. Amongst other reasons, the authors attributed this result to the wide application of statins in this

high-risk group [167]. A large-scale, double-blind randomized population study covering a total of 28,980 Scottish residents found no clinically conspicuous cardiovascular disorders among 3,500 individuals with a decreased ABI score of ≤ 0.95 . After a median treatment and follow-up period of 8.2 years, administration of ASA 100 mg/day orally had yielded no difference in the rate of cardiovascular events compared to placebo [210]. The benefit of antiplatelet agents in reducing peripheral arterial events has only been evidenced for patients given invasive endovascular treatment [42, 204].

5.2.8 Anticoagulants

From a peripheral arterial perspective, there is no indication for full dose INR lowering oral anticoagulation with vitamin K antagonists in patients with PAD, provided that there is no acute embolic event. However, the effect of a low dose antithrombotic therapy with the new oral anticoagulants in combination with ASA has been investigated.

In the COMPASS Trial [211], evaluating patients with CAD, and CAD and PAD, rivaroxaban and aspirin alone and in combination were studied in patients with stable atherosclerotic vascular disease. Those assigned to rivaroxaban (2.5 mg twice daily) plus ASA 100 mg daily, had a 24 % better total survival and cardiovascular outcome (HR 0.76 (0.66–0.86)) but more major bleeding events than those assigned to aspirin alone (HR 1.70 (1.40–2.05)). Rivaroxaban (5 mg twice daily) alone did not result in better cardiovascular outcomes than aspirin alone and resulted in more major bleeding events. Clearly a decision weighing up risks of CV event vs bleeding is required. The net benefit was 22 % overall risk reduction of the stable CAD/PAD population.

Additional analysis of the PAD subgroup (stable PAD, CAD with asymptomatic PAD and stable carotid stenosis patients) in the Compass trial population [212, 213] revealed, besides the 28 % general survival benefit, an additional significant 46 % reduction in major adverse limb events including major amputation (HR 0.54 95 % CI 0.35–0.82) for ASA 100 mg/d combined with Rivaroxaban 2×2.5 mg /d compared to ASA 100 mg/d and placebo. The net benefit was 28 % risk reduction for the PAD subgroup of COMPASS compared to the 24 % MACE reduction in the CAPRIE subgroup [203]. Unfortunately, the comparator of the COMPASS trial was ASA instead of Clopidogrel.

Rivaroxaban was also shown to be effective in these patients when suffering from mild to moderate heart failure [214]. An additional clinical trial (Voyager PAD) [215] comparing ASA 100 mg/d with and without 2×2.5 mg rivaroxaban/d – including symptomatic PAD patients undergoing a surgical- or catheter-based intervention- is underway. Also, other new oral anticoagulants are being tested in a clinical phase 3 trial in combination with ASA in this patient population. Table 5.2.8 gives an overview of the benefits of consistent treatment for cardiovascular risk factors in patients with PAD.

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Recommendation	Class of recommendation	Level of evidence
Based on the results of the COMPASS trial, the combined therapy of ASA 100 mg/d and rivaroxaban 2×2.5 mg/d should be considered in PAD patients without a high risk of bleeding, or other contraindications.	Ila	B

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Correspondence address

Prof. Jill JF Belch FRCP, MD (Hons), FRS(E), FMedSci, OBE
Professor of Vascular Medicine
Ninewells Hospital and Medical School
Dundee DD1 9SY
United Kingdom

j.j.f.belch@dundee.ac.uk