**REVIEW**

**Current and emerging drug treatment strategies for peripheral arterial disease**

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**Abstract**

**Introduction**: Peripheral artery disease (PAD) is a prevalent but underdiagnosed manifestation of atherosclerosis that has a worse prognosis than coronary artery disease. Patients with PAD are at heightened risk of both systemic cardiovascular adverse events, as well as limb-related morbidity. There is insufficient awareness of its clinical manifestations, including intermittent claudication and critical limb ischemia and of its risk of adverse cardiovascular and limb outcomes.

**Areas covered**: Current knowledge concerning medications and their mechanism of action, landmark trials and the evidence base behind the most commonly utilised pharmacological therapy including but not limited aspirin, clopidogrel, ticagrelor, warfarin, rivaroxaban, statins, angiotensin converting enzyme inhibitors, Evolocumab and Ezetimibe.

**Expert opinion:** Relative to coronary artery disease, peripheral artery disease is an undertreated and under investigated condition**.** The majority of the evidence base in the management of PAD is extrapolated from data subsets of large trials examining different conditions. This creates a paucity of management decisions based on trials powered for outcomes in PAD.

**Keywords**: Peripheral Arterial Disease, Intermittent claudication, lower extremity arterial disease, antiplatelet therapy, anticoagulation therapy

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| List of abbreviations as they appear in the article | |
| PAD | Peripheral vascular disease |
| CAD | Coronary artery disease |
| CVD | Cerebrovascular disease |
| OR | Odds ratio |
| HR | Hazard ratio |
| ARR | Absolute risk reduction |
| RRR | Relative risk reduction |
| CLI | Critical limb ischemia |
| ABI | Ankle-Brachial Index |
| CLIPS | Critical Leg Ischaemia Prevention Study |
| POPADAD | Prevention of progression of arterial disease and diabetes |
| ESC | European society of cardiology |
| AAA | Aspirin for Asymptomatic Atherosclerosis |
| CI | Confidence interval |
| CAPRIE | Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events |
| MI | Myocardial infarction |
| PLATO | Platelet inhibition and patient Outcomes |
| ACS | Acute coronary syndrome |
| EUCLID | Examining Use of Ticagrelor in Peripheral Artery Disease |
| CHARISMA | Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance |
| DAPT | Dual antiplatelet |
| ASPIRE-PAD | Antiplatelet Strategy for Peripheral Arterial Interventions for Revascularization of Lower Extremities |
| LONGDAPTPAD | Effects of Prolonged DAPT After Lower Extremity Percutaneous Transluminal Angioplasty in Patients With Lower Extremity-PAD |
| WAVE | Warfarin Antiplatelet Vascular Evaluation |
| OAC | Oral anticoagulation |
| COMPASS | Cardiovascular outcomes for people using anticoagulation strategies |
| VOYAGER-PAD | Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD (Peripheral arterial disease) |
| RCT | Randomized control trial |
| ePAD | Edoxaban in Peripheral Arterial Disease |
| INVEST | International verapamil-SR/Trandolapril |
| ACEI | Angiotensin converting enzyme inhibitors |
| ONTARGET | Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial |
| 4S | Scandinavian Simvastatin Survival Study |
| HPS | Heart Protection Study |
| REACH | Reduction of Atherothrombosis for Continued Health |
| IDEAL | Incremental Decrease in Events through Aggressive Lipid Lowering |
| IMPROVE-IT | Improved Reduction of Outcomes: Vytorin Efficacy International Trial |
| PCSK9 | proprotein convertase subtilisin-kexin type 9 |
| FOURIER | Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk |
| ODYSSEY OUTCOMES | Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab |

**Article highlights**

* Peripheral artery disease (PAD) is a prevalent but underdiagnosed manifestation of atherosclerosis that has a worse prognosis than coronary artery disease. PAD is estimated to affect 10-15% of the general population with an estimated prevalence of around 200million worldwide. The strongest risk factor is smoking followed by diabetes. The majority patients are asymptomatic with only around 10-30% exhibiting symptoms of intermittent claudication. There is currently no universal screening programme for PAD
* Antiplatelet medication has demonstrated great efficacy in the management of PAD. Aspirin provides relatively weak antiplatelet inhibition via antagonism of platelet cyclooxygenase-1. Aspirin has demonstrated a significant reduction vascular events in symptomatic PAD patients. There is currently no evidence that aspirin helps asymptomatic patients. Clopidogrel is a thienopyridine derivative whose active metabolic specifically and irreversibly inhibits the P2Y12 subtype of adenosine diphosphate receptor. Clopidogrel has demonstrated efficacy and has evidence of improved outcomes as compared to aspirin. Ticagrelor is an alternative thienopyridine derivative to clopidogrel. Ticagrelor failed to demonstrate any benefit as a combination therapy with aspirin compared to aspirin alone. There is some evidence that dual antiplatelet therapy may be beneficial in the context of patients having undergoing below knee surgical bypass.
* The role of oral anticoagulation (OAC) in PAD in less well established. Warfarin is a vitamin-K antagonist that inhibits the synthesis of clothing factors II, VII, IX, X, as well as protein C and protein S. Warfarin has failed to demonstrate benefit in the treatment of PAD patients. Rivaroxaban is an alternative OAC that works through inhibition of factor Xa. Low dose rivaroxaban in combination with aspirin has demonstrated improved outcomes as compared to aspirin monotherapy
* Risk factor reduction in the form of treatment of hypertension and hypercholesterolemia with Angiotensin converting enzyme inhibitors/Angiotensin receptor blockers and statin medications has demonstrated improved outcomes from both in terms of major acute cardiovascular events and walking distance
* Ezetimibe inhibits the absorption of cholesterol from the small intestine but selectively blocking the NPC1L1 protein in the jejunal brush border. Ezetimibe has demonstrated improved outcomes in combination with a statin as compared to a statin alone. Evolocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9) and lowers low-density lipoprotein cholesterol levels. Evolocumab has demonstrated improved outcomes in combination with a statin as compared to a statin alone.
* There are several medications with a potential effect on walking and/or claudication distance. The medications with the most evidence behind them include cilostazol, naftidrofuryl, pentoxifylline, inositol, buflomedil, glyceryl trinitrate, carnitine and propionyl-L-carnitine.

**1.0 Introduction and epidemiology**

Peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis in the arterial system, excluding those that supply the heart (coronary artery disease, CAD), or the brain (cerebrovascular disease, CVD) 1. Other terms used for this condition are peripheral vascular disease, peripheral arterial occlusive disease, and lower extremity arterial disease. Atherosclerotic plaques cause arterial stenosis and/or occlusion in PAD, and in doing so are a great cause of morbidity and mortality. PAD can be viewed as a marker of atherosclerotic disease burden and is associated with increased mortality from cardiovascular and cerebrovascular causes 2.

PAD is estimated to affect 10-15% of the general population 3 with an estimated prevalence of around 200million worldwide. This increases with age affecting 20% of those above the age of 80 4. Approximately 50% of PAD patients are asymptomatic, leading to under-diagnosis and under-treatment of the disease 5. Of note, PAD more commonly affects the lower limbs as compared to the upper limbs 6.

In this review article, PAD will refer to atherosclerotic disease of the lower extremity, including the aortoiliac, femoropopliteal, and infrapopliteal arterial segments, which comprises its most prevalent form 2. The focus of this article is to review the literature with regards to current and emerging drug treatment strategies for PAD.

**1. 1 Risk factors**

The development of PAD is multifactorial with various implicated risk factors 7. Consistently the single strongest predictive risk factor has been shown to be smoking, accounting for over 50% of disease burden 8 with an odds ratio (OR) of around 1.42 – 2.72 depending on the population studied 9. Furthermore, smoking exhibits a dose-response relationship with PAD with persistence of high risk in former smokers 8.

In terms of risks, diabetes mellitus is a close second to smoking with a similar risk profile (OR 1.47 – 1.88) and is more likely to be asymptomatic given possible co-existence of peripheral neuropathy 8. The duration and severity of diabetes has been directly correlated with the incidence and severity of PAD with every 1% increase in glycosylated haemoglobin increasing the risk of PAD by 2% 10, 11. Other vascular risk factors including but not limited to hypertension, hypercholesterolemia and chronic kidney disease have also been linked as aetiological agents 9. There is also evidence that blood markers of inflammation such as C-Reactive Protein, D-dimer & fibrinogen are associated with PAD and worsen outcomes 12-14.

**1.2 Clinical manifestation and prognosis**

PAD symptomology often falls into 3 clinical patterns 15: Classic intermittent claudication is thought to affect 10-30% of people. This is characterized exertional discomfort in one or both legs, which occurs with exercise and is relieved by with rest. The site of the pain can often indicate the location of the disease. Atypical leg pains affect 20-40% of patients. The largest cohort of 50% are thought to be asymptomatic 16. The mortality risk of patients presenting with intermittent claudication is double that of asymptomatic patients 17.There are multiple classification systems for these patterns of symptoms in chronic PAD18. The two most utilised are the 1954 Fontaine19 and the 1986 Rutherford classification20 and its 1997 revision21. Both have been utilised widely in clinical settings to direct patient management as well as for research purposes. The Fontaine classification is solely based on clinical symptoms, without other diagnostic tests. The Rutherford classification is more detailed and describes acute and chronic limb ischaemia separately. It also associates clinical symptoms with objective findings - ankle-brachial index (ABI), pulse volume recordings and vascular Doppler ultrasound.  The Rutherford classification for chronic limb ischemia can be viewed in table 1.

Prognosis in PAD can be divided into outcomes for the affected limb and outcomes for the patient generally. Overall PAD can be viewed as a proxy for global atherosclerotic disease elsewhere, including CVD and CAD. Patients with PAD have increased rates of ischemic stroke, myocardial infarction (MI) and cardiovascular death 22, 23. Within five years of diagnosis, 10-15% of patients with intermittent claudication will die from cardiovascular disease 24. Some 60% of patients with PAD suffer from co-existent ischemic heart disease and 30% from CVD 25. The long term prognosis of PAD has been shown to be worse than CAD (Hazard ratio, HR:2.4, P=0.01) 26. Untreated, PAD can progress to locally compromised arterial blood supply resulting in severe pain, ulcers or gangrene and acute limb ischemia necessitating urgent revascularisation therapy to prevent limb loss 27. The natural history of critical limb ischemia (CLI) is well documented. At 1 year, 25% of patients will be dead, 30% will have undergone amputation, and 45% will be alive with both limbs 24. More than 60% of patients with CLI will be dead at 5 years 28. Currently, there are no predictive formulae that allow the clinician to estimate the level of risk of an individual patient with intermittent claudication to progress to CLI or the time scale in which this is likely to occur 29. Some patients even develop CLI as a first presenting symptoms of PAD without ever having suffered intermittent claudication. Pharmacological therapy has been demonstrated to reduce the risk of asymptomatic PAD becoming symptomatic and improve overall prognosis once symptomatic.

**1. 3 Diagnosis and screening**

It has proven difficult to identify patients who may benefit from treatment. This is compounded by the absence of trials screening the general population 30. Several consensus documents and practice guidelines recommend screening for the presence of PAD using the ABI in patients >65 years old or those who are >50 years of age with a history of diabetes or smoking 31, 32. The goal is to identify and treat patients with increased cardiovascular risk. However, these consensus documents and guidelines have not been adopted everywhere due to the limited evidence for screening 33.

Careful history and clinical examination in combination with an ABI remain the initial means of diagnosing PAD in high risk individuals 34. An ABI test is the ratio of blood pressure at the ankle to blood pressure at the arm. It should always be done in cases of suspected PAD, but it has limitations. Although a value of ≤0.9 or less is diagnostic of PAD, falsely elevated (>1.2) and unreliable values are often seen in patients with diabetes and renal failure because of arterial calcification. There is a strong and consistent relationship between an abnormal ABI and the presence of coronary or cerebrovascular disease 22, 35. However, screening alone with ABI is currently not recommended based on the available evidence 36.

**1.4 Management**

The pharmacological management of PAD is largely dependent on what stage of the disease it is. There has been no demonstratable benefit to the treatment of asymptomatic PAD 37. The recommendation is that pharmacological management should be initiated once patients presented with symptoms such as intermittent claudication. Treatment options emerging from large trials revolve around anti-platelet, anti-coagulation & lipid lowering therapies.

**2.0 Anti-platelet therapy**

Table 2 demonstrates the evidence base underlying the antiplatelet and anticoagulation medications in PAD. Figure 1 demonstrates anti-platelet therapies and their mechanism of action.

**2.1 Aspirin**

Aspirin provides relatively weak antiplatelet inhibition via antagonism of platelet cyclooxygenase-1. The efficacy of aspirin is well validated in symptomatic PAD. In symptomatic PAD data for the efficacy of aspirin comes largely from a landmark 2002 metanalysis from the Antithrombotic Trialists’ Collaboration that looked at all antiplatelet agents in 9214 patients and demonstrated a proportional reduction of 23% in serious vascular events: nonfatal MI, nonfatal stroke, or vascular death (P=0.004) 38 over a 2 year period. The 2007 CLIPS trial (Critical Leg Ischaemia Prevention Study) looked into the utility of aspirin vs placebo in prevention of major acute cardiovascular events (MACE) in randomized control trial (RCT) of 366 PAD patients 39. This demonstrated that aspirin had a relative risk reduction (RRR) in MACE of 64% (P=0.22) over a mean follow up period of 20.7 months.

The lack of effectiveness of aspirin in asymptomatic PAD largely comes from the POPADAD (prevention of progression of arterial disease and diabetes) 40 & AAA (Aspirin for Asymptomatic Atherosclerosis) 37 trials. The largest metanalysis on the topic reviewed 5269 patients from 18 trials and demonstrated that aspirin monotherapy resulted in a non-significant reduction in cardiovascular events (Absolute event rate 8.2% vs 9.6% relative risk: 0.75; 95% confidence interval [CI]: 0.48 to 1.18); however, there was a significant reduction in nonfatal stroke (32 of 1516 vs 51 of 1503, HR: 0.64; 95% CI: 0.42 to 0.99; P - 0.04) and no statistically significant differences in all-cause or cardiovascular mortality, MI, or major bleeding 41. These results are in line with emerging data suggesting aspirin is not useful in primary prevention of cardiovascular mortality in healthy older adults or diabetics 42, 43. The role of differing doses of aspirin in PAD is not yet clear and may benefit from further trials. However, a 2017 metanalysis demonstrated that analysis by the dose of aspirin used did not show any evidence of effect 44.

**2.2 Clopidogrel**

Clopidogrel is a thienopyridine derivative whose active metabolic specifically and irreversibly inhibits the P2Y12 subtype of adenosine diphosphate receptor. The data supporting clopidogrel use is largely derived from the 1997 trial CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events). In this study, aspirin monotherapy was compared to clopidogrel monotherapy in a cohort of 19,185 patients with ischemic stroke, recent MI, or symptomatic PAD 45. CAPRIE demonstrated a significant reduction among symptomatic PAD patients on clopidogrel vs aspirin (Annual event rate of 4.86% vs 3.71%, RRR of 23.8%, P= 0.00028) and no major differences in terms of safety over a mean follow up period of 1.9 years. Based on these data clopidogrel remains the single antiplatelet agent of choice in symptomatic PAD patients in the latest iteration of the 2017 European Cardiology Society (ESC) PAD guidelines 31.

**2.3 Ticagrelor**

Ticagrelor is an alternative thienopyridine derivative to clopidogrel. Ticagrelor was first evaluated in the 2015 PLATO trial (Platelet inhibition and patient Outcomes) which randomized patients with recent acute coronary syndrome (ACS) to either clopidogrel or ticagrelor with background aspirin 46. The primary outcome was a composite of death from vascular cases, MI, or stoke at 12 months. This had occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those receiving clopidogrel (HR, 0.84; 95% CI, 0.77 to 0.92; P<0.001) 46. This trial demonstrated superiority of ticagrelor over clopidogrel in the prevention of fatal and non-fatal cardiovascular events with ACS. In a post-hoc subgroup analysis of 1,144 PAD patients in the PLATO trial there was no added benefit to dual therapy with ticagrelor and aspirin as compared to aspirin monotherapy (18% vs 20.6%, HR: 0.85 95% CI 0.64-1.11; P = 0.99) 47 ~~the reduction in ischemic events with ticagrelor was consistent with the overall trial results however did not reach statistical significance~~. These findings raise the possibility of ticagrelor as a possible treatment for patients with PAD and coexisting CAD, although well-powered trials would be required to test this hypothesis.

The ad-hoc analysis of the PLATO trial set the scene for the 2017 EUCLID trial (Examining Use of ticagrelor in Peripheral Arterial disease) 48. This was a randomized, blinded, double dummy trial comparing ticagrelor monotherapy vs clopidogrel monotherapy in 13,5885 patients with PAD. This demonstrated no significant difference between ticagrelor vs clopidogrel in the primary endpoint of cardiovascular death, MI, or ischemic stroke (10.6% vs 10.8%, HR, 1.02; 95% CI 0.92 to 1.13; P=0.65).

**2.4 Dual antiplatelet therapy (DAPT)**

The role of DAPT is well established in acute MI. However, the role of DAPT in PAD is less clear. The question of the utility of DAPT was first evaluated in the 2009 CHARISMA trial (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) 49 which investigated the role of DAPT in a broad high-risk population for atherosclerotic disease. A post-hoc subgroup analysis in 3096 patients with symptomatic (2838) or asymptomatic (258) PAD. The primary endpoint was rates of cardiovascular death, MI, or stroke. The primary endpoint occurred in 7.6% in the clopidogrel plus aspirin group and 8.9% in the placebo plus aspirin group (HR, 0.85; 95% CI, 0.66-1.08; P = 0.18). This was at the expense of a minor increase in bleeding 50.

In 2015 Armstrong et al 51 performed an observational cohort analysis that included 629 patients with claudication or CLI on DAPT or aspirin monotherapy and followed them up for 3 years. This demonstrated a significant reduction in MACE in patients taking DAPT vs aspirin monotherapy (20% vs 28%, HR:0.65; 95% CI: 0.44 to 0.96; p = 0.03) compared with those taking aspirin monotherapy. The contrast between the results of this study and CHARISMA may be partly due to inclusion of a higher-risk group of patients with severe PAD, with more than half of the patients presenting with CLI. There is likely to be a discrepancy based partially on bias inherent to observational cohort studies. Consistent with these differences, the overall event rates in CHARISMA were much lower.

The 2010 CASPAR trial (Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Arterial Disease) 52 evaluated the role of DAPT vs aspirin monotherapy in 851 patients undergoing below knee surgical bypass for CLI and followed them up for 3 years. In a prespecified subgroup analysis, there was a significant benefit of DAPT in patients treated with prosthetic grafts (N=125) (35% RRR, HR: 0.65; 95% CI: 0.45 to 0.95; p = 0.025) but not in those treated with vein grafts. Median duration of follow-up was 364 days. The primary efficacy endpoint was a composite of index-graft occlusion or revascularisation, above-ankle amputation of the affected limb, or death. In 2015 DAPT was further evaluated in the PEGASUS-TIMI (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction) trial 53. This trial had 3 arms, ticagrelor 90mg with aspirin, ticagrelor 60mg with aspirin and aspirin with placebo. They examined the utilisation of DAPT in patients with MI 1-3 years previously and followed them up for a median of 33 months. Subgroup analysis of 1143 patients with symptomatic PAD demonstrated an absolute risk reduction of 4.1% (HR: 0.69 p = 0.045) in MACEs for patients on DAPT compared with aspirin and placebo. Importantly, this group also had a significant 35% relative risk reduction in acute limb ischemia or peripheral revascularization for ischemia (HR: 0.65; 95% CI: 0.44 to 0.95 p=0.026) 54 over the 3 year follow up period. However, there was a 0.12% absolute excess of major bleeding. A 2016 retrospective analysis of 57,041 patients from around 370 hospitals undergoing lower limb revascularization demonstrated DAPT had a survival benefit for patients with CLI undergoing bypass (5 years, 70% vs 66%, p = .04) and endovascular intervention (5 years, 71% vs 67%, p = 0.01). This benefit was not seen in patients with claudication (bypass, 89% vs 88%, p = 0.36: endovascular intervention, 87% vs 85%, p = 0.46)55. A 2017 metanalysis of DAPT failed to demonstrate a benefit for patient’s (7.6% versus 8.9%; OR= 0.84; 95% CI 0.65–1.08; P=0.18) whilst demonstrating a significantly increased risk of bleeding as compared to monotherapy (1.47% vs. 0.88%; OR= 1.65; 95% CI 1.23 – 2.21 P=0.001) 56.

As of 2020 there are no other published head-to-head trials comparing monotherapy to DAPT in PAD patients. There are two ongoing studies ASPIRE-PAD (Antiplatelet Strategy for Peripheral Arterial Interventions for Revascularization of Lower Extremities) 57 and LONGDAPTPAD (Effects of Prolonged DAPT After Lower Extremity Percutaneous Transluminal Angioplasty in Patients With Lower Extremity-PAD) 58 should shed more light on the topic once the trials are finished in June/July 2020.

**2.5 Vorapaxar**

Vorapaxar is a thrombin receptor antagonist and exerts its antiplatelet effect by inhibiting thrombin-related platelet aggregation. Its different mechanism of action affords it the advantage of not prolonging bleeding time as compared to other antiplatelet agents 59.

Vorapaxar was tested vs placebo in the 2016 TRA2P-TIMI 50 trial (Thrombin Receptor Antagonist for Secondary Prevention-Thrombolysis in Myocardial Infarction Study Group) 60 in addition to standard antiplatelet therapy in secondary prevention in 3787 symptomatic PAD patients. Vorapaxar did not reduce the risk of MACE (11.3% vs 11.9%; HR, 0.94; 95% CI, 0.78-1.14; P=0.53) but significantly reduced the risk of acute limb ischaemia (2.3% vs. 3.9%; HR: 0.58; 95% CI: 0.39 to 0.86; p = 0.006) and peripheral revascularization (18.4% vs. 22.2%; HR: 0.84; 95% CI: 0.73 to 0.97; p = 0.017) This benefit was observed irrespective of the underlying mechanism of acute limb ischaemia, including surgical graft thrombosis and native vessel thrombosis. These beneficial effects were counterbalanced by an increased risk of bleeding (7.4% vs 4.5%; HR, 1.62; 95% CI, 1.21-2.18; P=0.001) 61. The increased risk of intracranial bleeding in patients with prior stroke was profound enough to warrant interruption of the trial by the data safety monitoring board in that population 62. The 2014 TRACER trial (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) further corroborated these negative findings in a subgroup of 936 symptomatic PAD patients in a double blind randomized cohort with similar MACE rates in the Vorapaxar vs placebo group (21.7% vs 24.8%, HR 0.85, P=0.78) 63.

**3.0 Oral Anti-coagulation (OAC)**

**3.1 Warfarin**

Warfarin is a vitamin-K antagonist that inhibits the synthesis of clothing factors II, VII, IX, X, as well as protein C and protein S. A 2006 metanalysis of 9 trials looking at 4889 patients with PAD and OAC concluded that the trials were heterogenous and inconclusive, however it demonstrated that OACs significantly reduced the risk of graft occlusion (19% vs 25%, OR = 0.63, 95% CI 0.44-0.89) at the expense of an increase in the risk of major haemorrhage and that there was no mortality benefit 64. The authors then proceeded to publish the 2007 WAVE trial (Warfarin Antiplatelet Vascular Evaluation) 65 looking into the utility of OACs in PAD. A total of 2161 patients were randomly assigned to aspirin monotherapy or aspirin and warfarin combination therapy. The results demonstrated that there was no statistical significance in the addition of warfarin when it came to outcomes from MACE (12.2% vs 13.3%, RR = 0.92; 95% CI, 0.73 to 1.16; P=0.48) however there was a significantly increased risk of life-threatening bleed (4% vs 1.2%, RR, 3.41; 95% CI, 1.84 to 6.35; P<0.001) in the group receiving dual therapy 65.

**3.2 Rivaroxaban**

Rivaroxaban is an alternative OAC that works through inhibition of factor Xa. The utility of Rivaroxaban in PAD was first demonstrated in 2017 in the COMPASS trial (Cardiovascular outcomes for people using anticoagulation strategies) 66. This was a RCT of 27,395 patients with stable CAD, PAD, or both assigned to either aspirin monotherapy, low-dose rivaroxaban (2.5mg twice daily) combined with aspirin, high-dose rivaroxaban alone, or aspirin plus high-dose rivaroxaban. A total of 7470 participants had PAD with a median duration of follow up of 21 months. The primary outcome was a composite of MACE. The trial ended early due to the overwhelming efficacy in reducing the primary outcome demonstrated by the dual aspirin & low-dose rivaroxaban cohort as compared to the aspirin only cohort (4.1% vs 5.4% HR, 0.76, CI, 0.66-0.86, P<0.001). There was a higher risk of major bleeding in the dual therapy cohort (3% vs 2%, HR 1.61, 95% CI 1.12−2.31, P = 0.0089), but no excess in fatal or critical organ bleeding.

The 2020 VOYAGER-PAD trial (Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD) was a RCT of 6,564 patients undergoing lower limb revascularisation randomized post-operatively to low-dose twice daily (2.5mg) rivaroxaban and aspirin or placebo and aspirin 67. The primary efficacy outcome was a composite of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes. At 3 years the primary outcome had occurred in 17.3% of the active group and 19.9% in the control group (HR, 0.85, 95% CI, 0.76 to 0.96; P = 0.009). This benefit occurred at the cost of significantly higher incidence of major bleeding (as defined by the International Society on Thrombosis and Haemostasis) with no excess Intracranial bleeding or fatal bleeding.

**3.3 Edoxoban**

Edoxoban is an alternative factor Xa inhibitor to rivaroxaban. The 2018 ePAD trial (Edoxaban in Peripheral Arterial Disease) was a RCT looking into the utility of edoxoban & aspirin treatment compared to aspirin & clopidogrel in 203 patients following femoropopliteal endovascular treatment. This small trial failed to demonstrate a statistically significant difference in bleeding or graft restenosis (30.9% vs 34.7%; RR 0.89, 95% CI 0.59 to 1.34, p=0.643) between both cohorts 68.

**4.0 Anti-hypertensive therapy**

Table 3 demonstrates the evidence base underlying the antihypertensive medications in PAD.

**4.1** **Angiotensin converting enzyme inhibitors (ACEI)/Angiotensin receptor blockers (ARB)**

The evidence base for utilisation of ACEIs in PAD started in 2000 with data derived from the landmark HOPE trial (Heart Outcomes Prevention Evaluation) 69. A total of 9297 patients (of whom 3099 had PAD as defined by a low ABI) were enrolled comparing the use of ramipril to placebo in patients with cardiovascular disease without heart failure with reduced ejection fraction. A post hoc analysis found that patients with PAD benefited from a significant reduction in the primary outcome of cardiovascular death, MI, or stroke as did those patients without PAD. In those without symptoms and an ABI <0.6, the primary outcome occurred in 16.4% in the ramipril arm versus 22% in the placebo arm (HR 0.77, 95% CI 0.55-1.09). This effect was seen in both symptomatic (20.1% vs 25.8%, HR 0.75, 95% CI 0.61-0.98) and asymptomatic PAD across a range of ABI values 70. Patients were followed up for a mean duration of 4.5 years. In 2008 the ONTARGET investigators (Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial) compared in a prospective RCT of 3468 patients with PAD Ramipril vs Telmisartan (ARB) vs a combination of both 71. The results found no significant difference in MACE between all 3 groups (16.5% in the ramipril group, 16.7% in the telmisartan group, and 16.3% in the combination-therapy group.) but a higher rate of adverse events in the combination group after a 56 month median follow up period. The results of ONTARGET and other studies 72 suggest a class effect to the mechanism of action of ARB/ACEI’s in PAD. The effect seems to not just be limited to a reduction in MACE, but there is a strong evidence base for an increase in walking time and reduction in pain. The strongest evidence for this comes from a 2013 RCT of 212 symptomatic PAD patients randomized to Ramipril or Placebo. This demonstrated that among patients with intermittent claudication, 24-week treatment with ramipril resulted in significant 75 second increase (95% CI, 60-89 (P < .001) in pain-free and maximum treadmill walking times compared with placebo 73. A 2013 metanalysis of 6 RCTs compromising of 621 patients looking into this further corroborated these findings 74. The benefit of ACEI/ARBs has also been demonstrated in the context of CLI where use has been demonstrated to result in significantly lower rates of MACE (HR 0.76, 95% CI 0.58-0.99, p=0.04) and overall mortality (HR 0.71, 95% CI 0.53-0.95, p=0.02) 72. A 2020 metanalysis of 19 observational studies looking at 26,985 patients with CLI split into 12,292 patients on statins and 12,513 patients not on statins looked at the effect of statin therapy in the context of CLI. It demonstrated that patients treated with statins were 25% less likely to undergo amputation (HR 0.75; 95% CI: 0.59-0.95) and 38% less likely to have a fatal event (HR 0.62; 95% CI: 0.52-0.75)75.

The 2010 INVEST trial (International verapamil-SR/Trandolapril) 76 demonstrated in post-hoc analysis of 2699 patients that a J-shaped relationship existed between blood pressure and cardiovascular events. Outcomes were observed to be best between a treated systolic of 135-145 mmHg and a diastolic of 60-90 mmHg. Interestingly, this J-shaped relationship was not observed for patients without PAD. The authors concluded that PAD patients may require a different blood pressure target as compared to non-PAD patients.

Nevertheless, the evidence for ACEI/ARBs isn’t all positive. A post-hoc sub analysis of the 2014 ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) 77 and a subgroup analysis of VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) 78 did not show a significant reduction in primary end points of MACE, respectively, with ACE inhibitor or ARB over other antihypertensive classes in subgroup analysis of patients with symptomatic PAD. This suggests that a predominant if not all of the effect of ACEI/ARBs is linked to blood pressure control. Data by Mehler et al from 2003 looking at antihypertensive medication in diabetic patients demonstrated no difference in outcomes between patients randomized to ACEI or nisoldipine (calcium channel blocker) 79. The 2017 ESC guidelines recommended ACEI/ARBs as first line therapy for patients with PAD and hypertension on this basis 31.

**5.0 Cholesterol reduction**

Elevated lipids and lipoproteins including cholesterol are associated with increased risk of cardiovascular disease including PAD80. Current guidelines suggest PAD is equivalent to a history of CAD/CVD with respect to cholesterol lowering therapies and therefore should be treated aggressively 2, 31. Table 4 demonstrates the evidence base underlying the lipid reducing medications in PAD

**5.1 Statin therapy**

Statin therapy has the largest evidence base in PAD of the cholesterol lowering medications 81, 82. The majority of the data in support of statin use in patients with PAD are derived from subgroup analyses of larger clinical trials. In 1998 a retrospective analysis of the 4S (Scandinavian Simvastatin Survival Study) was the first to demonstrate that in CAD patients, treatment with simvastatin reduced the incidence or progressive intermittent claudication by 38% over a median follow up of 5.4 years 83. Since then several trials have demonstrated the efficacy of a variety of statins. The first prospective trial demonstrating the efficacy of cholesterol reduction in PAD patients was in 2006. This was a prospective observation cohort study in 2420 PAD patients of which 581 had hypercholesterolemia. Following adjustment for risk factors they demonstrated an all cause reduction in mortality (HR 0.46, P<0.001) in patients with PAD treated with a variety of statins 84.

The HPS (Heart Protection Study) in 2007 randomized subset of 6748 PAD patients to simvastatin vs placebo. Overall, there was a 22% (26.4% versus 32.7%, P<0.001) relative reduction in the rate of first major vascular event with simvastatin versus placebo over a 5 year mean follow up period 85. This benefit has also been seen in retrospective analysis of patients with advanced PAD, including CLI 86. Data from the 2014 REACH (Reduction of Atherothrombosis for Continued Health) 87 registry demonstrated that in patients with PAD, statin therapy was associated with a 17% decrease (19.6 vs. 20.3%; HR, 0.83; 95% CI, 0.73–0.96; P=0.01) in adverse CV event rate. Furthermore, statin therapy was also associated with a significant reduction at 4-years of rates of ischemic amputation (3.8 vs. 5.6%; HR, 0.64; 95% CI, 0.48–0.86; *P* = 0.0027) 87. Data from prospective cohort studies has demonstrated that statin therapy has beneficial effects beyond lipid-lowering properties only and should be considered in all patients with PAD 88. This trial demonstrated that the beneficial effects of higher statin doses and lower target LDL cholesterol levels were independent of each other and independent of the presence of clinical risk factors, ABI values, electrocardiography, and propensity scores for statin therapy 88.

A 2007 metanalysis of 18 trials and 10049 PAD patients demonstrated no benefit of lipid lowering in patients with PAD with regards to MACE. This was largely as a result of one trial showing a detrimental effect of lipid lowering therapy using cholestyramine. When excluding this trial, lipid lowering significantly reduced cardiovascular events (odds ratio 0.74, 95% CI 0.55–0.98) 88. In 2015, the IDEAL trial (Incremental Decrease in Events through Aggressive Lipid Lowering) 89 demonstrated in a cohort of 8,888 post MI patients (of which 374 had PAD) randomised to high-dose atorvastatin (80mg) compared to normal dose simvastatin (20-40mg) and found a lower incidence of the development of PAD (2.2% vs 3.2%, HR=0.70, 95% CI 0.53 to 0.91; p=0.007) in the trial population and a non-significant trend lower rates of major coronary events (14.4% vs 20.1%, HR=0.68, P=0.13) in the PAD population.

**5.2 Ezetimibe**

Ezetimibe inhibits the absorption of cholesterol from the small intestine but selectively blocking the NPC1L1 protein in the jejunal brush border 90. This decreases the amount of cholesterol normally available to liver cells, leading them to absorb more from circulation, thus lowering levels of circulating cholesterol Combination therapy of simvastatin and Ezetimibe was evaluated in 2016 in the IMPROVE-IT trial (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) 91. This was a RCT of 18144 patients randomized to ezetimibe/simvastatin vs placebo/simvastatin which demonstrated that 1930 high risk patients (18% with PAD) experienced the greatest benefit from ezetimibe 92.

**5.3 Evolocumab**

Evolocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9) and lowers low-density lipoprotein cholesterol levels by approximately 60% 93. The FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) 94 in 2017 was a double blind prospective RCT of 27564 patients with and without PAD that randomised patients on statin therapy to Evolocumab or placebo. A total of 3642 patients had a background of PAD and sub-analysis of this cohort demonstrated a 3.5% ARR (HR 0.79, 95% CI 0.66-0.94, P=0.0098) in the primary end point of cardiovascular events (MI, death, stroke, hospitalization for unstable angina, and coronary revascularization) compared with a 1.6% ARR in patients without PAD 95.

**5.4 Alirocumab**

The 2019 ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) 96 looked into the utility of Alirocumab in patients with non-coronary atherosclerosis post MI. This was a subset analysis of 1,554 patients with PAD & CVD, which demonstrated that in in patients with both PAD & CAD there was no significant difference in the addition of Alirocumab in combination therapy with a statin (ARR -0.5% HR 1.03 P=0.06).

**6. Pharmacotherapy to improve claudication**

There are several medications with a potential effect on walking and/or claudication distance. The medications with the most evidence behind them include cilostazol, naftidrofuryl, pentoxifylline, inositol, buflomedil, glyceryl trinitrate, carnitine and propionyl-L-carnitine. However, objective documentation of such an effect is limited. The beneficial effects on walking distance are mild to moderate 97.

Cilostazol is a phosphodiesterase inhibitor with multiple adverse side effects that has been evaluated in a 2014 metanalysis of 15 RCT’s with a total of 3718 patients vs placebo. It demonstrated that Cilostazol improves mean walking distance by 31.41 meters (P<0. 00001) compared to placebo 98. Pentoxifylline is a theophylline derivative which was reviewed in a 2015 metanalysis of 3377 patients which concluded that there was a lack of high quality evidence required to say if there was a beneficial effect 99. Naftidrofuryl is a 5-HT2 antagonist with few adverse side effects that was assessed in a 2009 met-analysis consisting of 7 RCT’s and 1083 patients and demonstrated a ratio of final maximal walking distance over baseline maximal walking distance after use of naftidrofuryl compared with placebo of 1.4 100. Interestingly, a 2009 metanalysis demonstrated that of all the medications utilised for increasing walking distance, statins were the most successful with an average increase in mean walking distance of around 160 meters 97.

**7. 0 Expert opinion**

PAD is an increasingly common and unrecognised manifestation of atherosclerotic vascular disease. PAD patients are at increased risk of systemic ischemic events, associated with comorbid CAD or CVD. Most patients are asymptomatic, if symptoms do occur, the main presentation is intermittent claudication which is associated with a reduction in mobility and quality of life. A review of the literature demonstrates that symptomatic patient’s prognosis benefits from multiple pharmacologic therapies such as antiplatelet, anticoagulation and anti-lipid medication. There is also a role for medications that improve walking distance without changing prognosis. PAD continues to be underdiagnosed and undertreated when compared to CAD 101. Most deaths in PAD are attributable to cardiovascular disease and these outcomes are worse compared with CAD patients 26. There is compelling evidence demonstrated in the trials reviewed for specific medical management improving clinical outcomes. However, pharmacological treatments are greatly underutilised, with one study demonstrating in a population of 11,134 patients that around 24% of PAD patients were not on any statins, compared to their CAD counterpart where 100% were on a statin therapy 102. The study also demonstrated that CAD patients were treated to lower lipid targets. They hypothesized that doctors are more aggressive with lipid control in patients with CAD compared with patients with PAD alone 102. A 2012 study utilising the Danish nationwide administrative registries identified 2 groups with incident PAD: PAD alone (n=34,160) and PAD with history of coronary artery disease (CAD) (n=9570). With the use of a comparator with incident CAD alone (n=154,183). They demonstrated that at 18 months post diagnosis the use of cardioprotective medication in the PAD alone group vs the CAD alone group was substantially lower (any antiplatelet, 53% versus 66%; statins, 40% versus 52%; angiotensin-converting enzyme inhibitors, 20% versus 29%) 103. Compounding this problem is that large registries have demonstrated that around 50% of patients are not adherent to their medications and that this worsens with increasing poly vascular disease burden 104. The reason for this level of underutilisation and lack of adherence is unclear and likely to be multifactorial. Large contributors may include that PAD patients are less aware of their condition and its outcomes as compared to CAD patients 105. The lack of awareness of the gravity of PAD and the lack of clear guidelines of how to effectively screen patients and which patient’s benefit from treatment are problems that need to be overcome.

There is a paucity in the literature with regards to high quality research specifically looking at the PAD population. Whilst this has improved in recent year, most data guiding treatment decisions is derived from subsets of patients suffering with PAD enrolled in trials for CAD/CVD. Inherent to the use of a smaller subset of data, they are more likely to be underpowered and less likely to demonstrate significant results or to capture data outcomes relevant in PAD. There is a need for additional, independent, comparative, randomized multicentre studies specifically powered for outcomes in the PAD population. Additionally, medications designed to improve quality of life would be ground-breaking. Moving forward there needs to be a coordinated effort to develop a registry of PAD patients in order to provide real world assessment of clinical outcomes. Other gaps in the literature that need to be investigated further include the role of DAPT in PAD, optimal screening programmes to identify patients who may benefit from treatment and the benefit of screening other locations for atherosclerotic disease (such as CAD) once PAD is identified.

Based on the current evidence base our treatment recommendations are separate depending on the absence or presence of symptoms:

1. Asymptomatic patients should have aggressive risk factor control
2. Symptomatic patient should be treated with aspirin in combination with low dose rivaroxaban with a statin ± trial of naftidrofuryl

The arena for effective management of PAD has changed so dramatically over the last decade that it requires a multidisciplinary approach with multimodal interventions. There has been a logarithmic growth in pharmacological and surgical therapy and physician ability to deal with this condition thanks to a growing number of high-quality trials. The optimal treatment of an individual patient involves a combination of exercise, pharmacological therapy, and in a small minority revascularization therapy (endovascular or open surgery). The goal for the future should be early identification of the PAD patient so that progression to CLI and amputation can be prevented and appropriate therapy to prevent MACE can be implemented.

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**Conflicts of interest**

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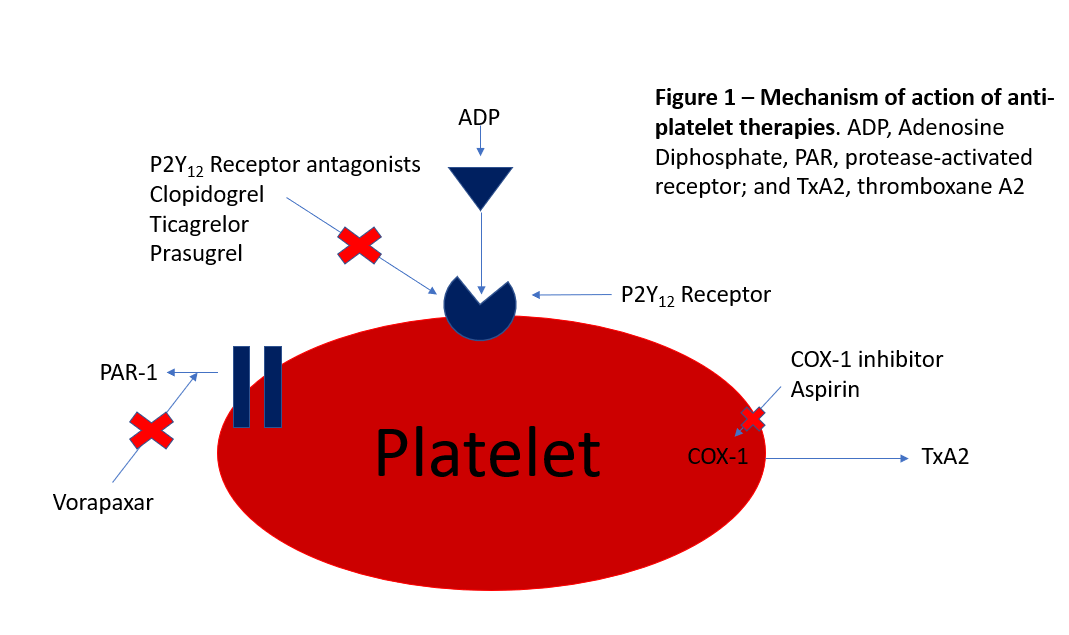
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| Table 1 – Rutherford classification for chronic lower limb peripheral arterial disease20, 21 | | | |
| Grade | Category | Clinical criteria | Objective criteria |
| 0 | 0 | Asymptomatic | Normal treadmill or reactive hyperaemia test |
| 1 | Mild claudication | Completes treadmill exercise; ABI after exercise > 50 mm Hg but at least 20 mm Hg lower than resting value |
| I | 2 | Moderate claudication | Between categories 1 and 3 |
| 3 | Severe claudication | Cannot complete standard treadmill exercise, and ABI after exercise < 50 mm Hg |
| II | 4 | Ischemic rest pain | Resting ABI < 40 mm Hg, flat or barely pulsatile ankle or metatarsal PVR; TP < 30 mm Hg |
| III | 5 | Minor tissue loss: ischemic ulceration not exceeding ulcer of the digits of the foot | Resting ABI < 60 mm Hg, ankle or metatarsal PVR flat or barely pulsatile; TP < 40 mm Hg |
| 6 | Major tissue loss; severe ischemic ulcers or frank gangrene | Same as category 5 |
| Abbreviations: ABI, ankle-brachial index; PVR, pulse volume recording; TP, toe pressure. | | | |

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| Table 2 – Antiplatelet and oral anticoagulation in PAD | | | | | | |
| Agent | Study, year | Patient population | Intervention | Outcome | Results | Interpretation |
| Aspirin | ATC 38, 2002 | Meta-analysis, 9214 PAD patients | Antiplatelet vs control | Vascular events | 23% risk reduction, P=0.004 over 2 years | Antiplatelet therapy reduces rates of serious vascular outcomes |
| CLIPS 39,  2007 | 366 PAD patients | Aspirin Vs placebo | Vascular events | 64% RRR, HR, 0.36; P=0.022 | Aspirin decreases the rate of major  vascular events in symptomatic PAD |
| POPADAD 40, 2008 | 1,276 diabetic patients with asymptomatic PAD | Aspirin Vs placebo | MACE and critical leg ischaemia | 18.2% vs. 18.3%, HR 0.98, p=0.022 | Aspirin is not beneficial in asymptomatic PAD |
| AAA trial 37, 2010 | 3,350 asymptomatic PAD patients | Aspirin Vs placebo | Fatal or non-fatal coronary events; stroke; revascularization | 13.7 vs 13.3 events per 1000 years, HR 1.03 (95% CI  0.84–1.27) | Aspirin is not beneficial in asymptomatic PAD |
| Clopidogrel | CAPRIE 45, 1997 | Subset of 6,452 PAD patients | Aspirin Vs Clopidogrel | MACE | 4.86% vs 3.71, HR, 0.76; P=0.0028 | Clopidogrel is superior to aspirin |
| Ticagrelor | PLATO 46, 2015 | Subset of 1,144 PAD patients | Aspirin/Ticagrelor Vs Aspirin/Clopidogrel | MACE | 18% vs 20.6%, HR: 0.85  P = 0.99 | No significant difference between treatment |
| EUCLID 48, 2017 | 13,885 PAD patients | Ticagrelor Vs Clopidogrel | MACE | 10.6% vs 10.8%, HR 1.02 P=0.65 | No difference between Ticagrelor or clopidogrel in PAD |
| Vorapaxar | TRACER 63, 2014 | Subset of 936 PAD patients | Vorapaxar Vs placebo | CVD death, MI, stroke, recurrent ischemia with rehospitalization, or urgent revascularisation | 21.7% vs 24.8%, HR 0.85  P=0.78 | There is no difference between Vorapaxar and placebo |
| TRA2P-TIMI 50 60, 2016 | Subset of 3,787 PAD patients | Vorapaxar Vs placebo (on top of single antiplatelet) | MACE | 11.3% vs 11.9%; HR, 0.94; P=0.53 | There is no difference between Vorapaxar and placebo |
| Acute limb Ischemia | 2.3% vs. 3.9%; HR: 0.58; p = 0.006 | Vorapaxar significantly reduces rates of acute limb ischemia |
| DAPT | CHARISMA 50, 2009 | Subset of 3,096 PAD patients | Aspirin/Clopidogrel Vs Aspirin |  | 7.6% vs 8.9%, HR, 0.85  P = 0.18 | No significant difference between DAPT and aspirin monotherapy |
| PEGASUS-TIMI 54, 2015 | Subset of 1,143 PAD patients | Ticagrelor/  aspirin vs aspirin | MACE | 4.1% ARR, HR: 0.69  p = 0.045 | Addition of ticagrelor to aspirin in PAD patients reduces MACE |
| Armstrong et al 51, 2015 | 629 PAD patients | Aspirin Vs DAPT | MACE | 20% vs 28%, HR:0.65  p = 0.03 | Addition of DAPT reduces MACE |
| Warfarin | WAVE 65, 2007 | 2,161 PAD patients | Aspirin vs Aspirin/Warfarin | MACE | 12.2% vs 13.3%, HR: 0.92  P=0.48 | No evidence that addition of warfarin reduces MACE |
| Rivaroxaban | COMPASS 66, 2017 | 7,470 PAD patients | Aspirin/Rivaroxaban Vs Aspirin | MACE | 4.1% vs 5.4%, HR: 0.76, P<0.001 | Aspirin & Rivaroxaban is superior to Aspirin alone in reduced MACE |
| VOYAGER-PAD67, 2020 | 6,564 PAD patients undergoing revascularisation | Rivaroxaban/aspirin vs placebo/aspirin | composite of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes | 17.3% vs 19.9%, HR, 0.85; P = 0.009 | Rivaroxaban and aspirin is superior to aspirin alone in patients undergoing lower limb revascularisation |
| Edoxoban | ePAD 68, 2018 | 203 patients post femoropopliteal endovascular treatment | Edoxoban/Aspirin Vs Clopidogrel/aspirin | Incidence of restenosis/reocclusion events | 30.9% vs 34.7% in re-occlusion rates p=0.643 | Non-significant trend towards lower re-occlusion rates with Edoxoban/Aspirin |
| ATC, Antithrombotic Trialists’ Collaboration; CLIPS, Critical Leg Ischaemia Prevention Study; POPADAD, prevention of progression of arterial disease and diabetes; AAA, Aspirin for Asymptomatic Atherosclerosis; CAPRIE, Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events; PLATO, Platelet inhibition and patient Outcomes; EUCLID, Examining Use of ticagrelor in PAD; TRACER, Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome; TRA2P-TIMI 50, Thrombin Receptor Antagonist for Secondary Prevention-Thrombolysis in Myocardial Infarction Study Group 50; CHARISM, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; PEGASUS-TIMI, Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction; WAVE, Warfarin Antiplatelet Vascular Evaluation; COMPASS, Cardiovascular outcomes for people using anticoagulation strategies; VOYAGER-PAD, Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD (Peripheral arterial disease); ePAD, Edoxaban in Peripheral Arterial Disease; HR, Hazard Ratio; PAD, Peripheral Arterial Disease; MACE, Major Adverse Cardiac Events; MI, Myocardial Infarction; CVD, Cerebrovascular disease. | | | | | | |

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| Table 3 – Antihypertensive medications in PAD | | | | | | |
| Agent | Study, year | Patient population | Intervention | Outcome | Results | Interpretation |
| Ramipril | HOPE 70, 2004 | Subset of 3099 PAD patients | Ramipril Vs Placebo | MI, Stroke & Cardiovascular death | 20.1% vs 25.8%, HR 0.75, 95% CI 0.61-0.98, P<0.001 | Ramipril is an effective treatment strategy in PAD |
| Telmisartan | ONTARGET 71, 2008 | Subset of 3468 PAD patients | Ramipril Vs Telmisartan | Death from cardiovascular causes, MI, stroke, or hospitalization for heart failure | RR 1.01  P = 0.003 | There is no difference between Ramipril or Telmisartan |
| Valsartan | VALUE 78, 2006 | Subset of 2,114 PAD patients | Valsartan Vs Amlodipine | cardiac morbidity and mortality | 13.4% vs 13.6%. P = 0.633 | There is no difference in outcome between Valsartan or Amlodipine |
| Calcium channel blockers Vs Beta blockers | INVEST 76, 2010 | Subset of 2699 PAD patients | Verapamil SR±Trandolapril Vs Atenolol±Hydrochlorothiazide | Death, nonfatal MI, or nonfatal stroke | 15.5% vs 17.1%, HR: 0.89; P=0.21 | There is no difference between a Verapamil SR±Trandolapril Vs Atenolol±Hydrochlorothiazide strategy in outcomes |
| Chlorthalidone | ALLHAT 77, 2014 | Subset of 830 PAD patients | Chlorthalidone Vs Amlodipine | MACE | HR 0.86  P=0.099 | Chlorthalidone, amlodipine, and lisinopril performed similarly |
| Chlorthalidone Vs Lisinopril | HR 0.98  P=0.847 |
| HOPE, Heart Outcomes Prevention Evaluation; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; VALUE, Valsartan Antihypertensive Long-term Use Evaluation; INVEST, The International Verapamil SR-Trandolapril Study; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; HR, Hazard Ratio; RR, Relative Risk; MACE, Major Adverse Cardiac Events; MI, Myocardial Infarction; PAD, Peripheral Arterial Disease | | | | | | |

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| Table 4 – Lipid lowering therapy in PAD | | | | | | |
| Agent | Study, year | Patient population | Intervention | Outcome | Results | Interpretation |
| Simvastatin | 4S 83, 1998 | 4,444 adults with previous MI and/or Angina | Simvastatin Vs Placebo | Development of intermittent claudication | 38% reduction in development of intermittent claudication over 5.4 years | Statin therapy stops progression of PAD |
| Simvastatin | HPS 85, 2007 | Subset of 6748 PAD patients | Simvastatin Vs Placebo | Major Vascular event | 26.4% versus 32.7%,  P=0.0001 over 5 years | Simvastatin reduces major vascular  events in patients with PAD |
| Atorvastatin | IDEAL 89, 2015 | Subset of 374 PAD patients | High dose Atorvastatin Vs usual dose Simvastatin | Major coronary event | 14.4% vs 20.1%, HR=0.68, P=0.13 | High-dose atorvastatin is superior to usual-dose simvastatin in preventing PAD |
| Development of PAD | 2.2% vs 3.2%, HR=0.70, 95% CI 0.53 to 0.91; p=0.007 |
| Ezetimibe | IMPROVE-IT, 2016 92 | Subset of 1930 PAD patients | Ezetimibe+  simvastatin  vs placebo+  simvastatin | MACE, unstable angina  requiring hospitalization,  or coronary  revascularization | HR 0.92  ARR 4.2% | PAD patients benefit from the addition of Ezetimibe on top of normal statin thearpy |
| Evolocumab | FOURIER 95,  2018 | Subset of 3642  PAD patients | Evolocumab+  statin vs  placebo+  statin | MACE, unstable angina  requiring hospitalization,  or coronary  revascularization | HR, 0.79  P=0.0098 | Evolocumab  decreases the rate of major cardiovascular  events in PAD  patients |
| Alirocumab | ODYSSEY  OUTCOMES 96, 2019 | Subset of 1554 PAD & CAD | Alirocumab+  statin vs  placebo+  statin | Death from coronary heart  disease, nonfatal MI,  ischemic stroke, or  unstable angina  requiring hospitalization | 3.5% ARR, HR 0.79, 95% CI 0.66-0.94, P=0.0098 | Alirocumab therapy on addition to Statin therapy does not result in a significant reduction in MACE. |
| 4S, Scandinavian Simvastatin Survival Study; HPS, Heart Protection Study; IDEAL, Incremental Decrease in Events through Aggressive Lipid Lowering; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; MI, Myocardial Infarction; PAD, Peripheral Arterial Disease; RRR, Relative Risk Reduction; ARR, Absolute Risk Reduction; CAD, Coronary artery disease; CVD, Cerebrovascular disease; HR, Hazard Ratio/. | | | | | | |