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Do we have a unified consensus on antithrombotic management of PAD?

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Abstract

Peripheral artery disease (PAD) is one of the most frequent manifestations of atherosclerosis with high rates of morbidity and mortality. Platelets and coagulation are involved in the progression of atherosclerosis and thromboembolic complications. PAD patients have increased pro-thrombotic potential, which includes platelet hyperaggregability and increased pro-coagulant state. Therefore, antithrombotic treatment is of utmost importance for the prevention of cardiovascular events in this group of patients.

Aspirin is the basic antiplatelet drug, but with limited efficacy in PAD. In contrast to coronary artery disease, its effect on the prevention of cardiovascular events in PAD has been limited proven. Particularly in asymptomatic PAD, there is no evidence for risk reduction with aspirin. Clopidogrel and ticagrelor are more effective than aspirin. Clopidogrel is thus an effective alternative to aspirin for prevention of cardiovascular events in symptomatic PAD. In patients who are non-responders to clopidogrel, ticagrelor is indicated.

Dual antiplatelet treatment (DAPT) with aspirin and ticagrelor in patients with coronary artery disease and concomitant PAD significantly decreased the rate of major adverse cardiovascular events, including adverse limb events. However, in the CHARISMA trial, aspirin and clopidogrel were not more effective than aspirin alone and increased bleeding complications. Therefore, DAPT seems effective only in PAD accompanied by coronary artery disease.

Anticoagulant treatment for symptomatic PAD with vitamin K antagonists alone or in combination with aspirin is not more effective than single antiplatelet treatment but increases the rate of major bleeding. Low dose rivaroxaban combined with aspirin in PAD patients significantly reduces cardiovascular events, including limb-threatening ischemia and limb amputations.

Anticoagulation and antiplatelet treatment after percutaneous or surgical revascularization of PAD improve the patency of treated vessels. Aspirin with or without dipyridamole improved patency of infra-inguinal by-pass grafts at one year. The combination of clopidogrel with aspirin was more effective than aspirin alone in the prevention of prosthetic graft occlusions in patients undergoing below-knee by-pass-grafting. Oral vitamin K antagonists were not more effective than aspirin in the prevention of infra-inguinal by-pass occlusion. The combination of low dose rivaroxaban and aspirin was effective in preventing major adverse cardiovascular

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events and adverse limb events after infrainguinal endovascular or surgical revascularization in patients with intermittent claudication. However, the data on antithrombotic treatment after revascularization for limb-threatening ischemia is scanty and inconclusive.
In conclusion: Antithrombotic treatment of PAD is a cornerstone for the management of these patients. Antiplatelet drugs prevent the initiation and progression of atherosclerosis and are effective also in the prevention of thromboembolic events. Simultaneous use of antiplatelet and anticoagulation drugs is accompanied by an increased risk of bleeding. However, combined treatment with aspirin and low-dose rivaroxaban is more effective than single antithrombotic treatment and safer than full-dose combined treatment.

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Introduction

Cardiovascular atherosclerotic diseases are the leading cause of morbidity and mortality in developed and developing countries. Peripheral artery disease (PAD) represents one of the most frequent manifestations of atherosclerosis with heightened morbidity and mortality. The mortality risk is more than doubled in symptomatic PAD patients compared to subjects without PAD and is increased by the severity of the disease [1]. Prevention of progression of local disease and future cardiovascular events represents the main objective of PAD treatment [2,3]. Similarly, as in other atherosclerotic diseases prevention of PAD consists of controlling risk factors (e.g. smoking, diabetes, hypertension, dyslipidemia) and prevention of disease progression using antithrombotic drugs: antiplatelets and anticoagulants [4].

Platelets and coagulation play a very important role in the genesis, progression of atherosclerosis, and thromboembolic complications. Platelets are known to contribute to the early stages of atherosclerosis such as endothelial dysfunction [5], and also to final events such as rupture of vulnerable plaque [6]. Platelets participate in atherogenesis by chemokine release [7], a surface association to oxidized LDL [8], the release of microparticles [9], and release inflammatory mediators [10].

Evidence is also accumulating on the involvement of coagulation proteins in atherosclerosis and atherothrombosis. Coagulation proteins not only play a role in fibrin formation and platelet activation but also mediate various biological and pathophysiologic processes, which activate protease-activated-receptors (PARs). Therefore, in patients with atherosclerotic disease, despite antiplatelet therapy, the residual atherothrombotic risk remains substantial [11].

Observational studies have shown that PAD patients have increased prothrombotic potential, which includes platelet hyperagregability and increased levels of some clotting factors. Patients with lower limb PAD have higher baseline collagen-induced aggregation compared to healthy controls and also in comparison to coronary artery disease patients PAD patients manifest platelet hyperagregability [12]. Further, a higher percentage of platelets expressing P-selectin on their surface was found in PAD patients compared to healthy controls [13]. Platelet activity as assessed by flow cytometry and aggregation increased with the progression of the severity of PAD [14]. Enhanced platelet activation in PAD patients may substantially contribute to adverse outcomes and may partially explain non-responsiveness to aspirin in these patients.

Studies also indicated that PAD patients have increased pro-coagulant state and decreased fibrinolytic potential [4]. It was shown that particularly patients with severe PAD have enhanced thrombin activation, which could be a consequence of the pro-inflammatory state of this group of patients [15]. These findings underline the importance of antithrombotic treatment in PAD, suggesting combined treatment with antiplatelet and anticoagulant drugs.

Most trials evaluating antithrombotic therapy in PAD have limited value because of the small sample size, heterogeneity of the study population, and different endpoints. Statements of guidelines on the management of PAD are mostly based on data derived from subgroup analyses of large randomized trials including patients with different forms of atherosclerotic disease [16]. There are some discrepancies between the actual European Society for Cardiology (ESC)[2] and American Heart Association/American College of Cardiology (AHA/ACC)[17] guidelines. Therefore, this article aims to comment on existing guidelines and upgrade them with recent findings.

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Antiplatelet treatment of asymptomatic PAD

Patients with asymptomatic PAD are at increased risk for ischemic events in the coronary, cerebrovascular, and lower extremity arteries.[18,19] However, in asymptomatic PAD, there is no evidence for risk reduction with aspirin. Patients with diabetes who had reduced ankle-brachial pressure index (≤ 0.99) but no symptomatic cardiovascular disease, did not benefit from aspirin 100 mg daily. There was no difference in the incidence of cardiovascular events (lethal and nonlethal myocardial infarction (MI), stroke, cardiovascular mortality) or major amputations compared to placebo.[20] Similar results were found in a general population cohort, aged 50-75 years at inclusion, without overt cardiovascular disease but with decreased ankle-brachial pressure index (≤ 0.95). After a mean follow-up of 8.2 years, there was no difference between the aspirin group and the placebo group in the primary composite end-point (fatal or nonfatal coronary events, stroke, or revascularization), no difference in the secondary endpoint (angina pectoris, claudication, or transient ischemic attack), and no difference in all-cause mortality.[21] No other antiplatelet agent has been systematically evaluated in patients with asymptomatic PAD.[22]
The European Society for Cardiology and European Society for Vascular Medicine guidelines on PAD advise against antiplatelet treatment of patients with asymptomatic PAD [2,23].

Antithrombotic treatment for symptomatic PAD

Antiplatelet therapy is widely used in the prevention of adverse cardiovascular events in patients with symptomatic PAD. However, the risk of these events remains high, and the optimal antithrombotic therapy for PAD is still uncertain.

Single antiplatelet therapy

Management of PAD is based on comprehensive risk factor management including smoking cessation and control of hypertension, diabetes, and hypercholesterolemia. Aspirin is still the most frequently used antiplatelet agent for the prevention of cardiovascular events in patients with symptomatic PAD [24]. A meta-analysis of 42 trials comprising 9,214 patients with symptomatic PAD demonstrated that antiplatelet treatment was associated with a 23% lower odds of serious vascular events. However, in the trials included, aspirin was used only by approximately ¼ of patients. The meta-analysis of Berger and co-workers that included more than 5,000 individuals examined the efficacy of aspirin with or without dipyridamole compared with placebo in PAD patients.[25] It was shown that in patients with PAD, treatment with aspirin alone or in combination with dipyridamole was not effective in the prevention of cardiovascular events, and non-fatal stroke was the only significantly reduced end-point.[25]
Based on the available data, the U.S. Food and Drug Administration has not approved aspirin for PAD [26]. Therefore, it is a question ~~of~~ whether aspirin can still be recommended as the drug of choice for the management of patients with PAD? [27]
In the context of single antiplatelet therapy of symptomatic PAD, the $P2Y_{12}$ inhibitors clopidogrel and ticagrelor have been studied. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial which included 19,185 patients with either MI, ischemic stroke, or symptomatic PAD, clopidogrel was compared to aspirin. The subgroup analysis of

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PAD patients (n=6,452) demonstrated that clopidogrel was significantly more effective than aspirin with an additional 24% risk reduction of major adverse cardiovascular events (MACE). On this foundation, both the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) guidelines favor the use of clopidogrel.[2,17] Recently, the EUCLID trial (Examining Use of Ticagrelor in Peripheral Artery Disease), investigated the efficacy of ticagrelor in comparison to clopidogrel. The study included 13,885 patients with PAD with a mean follow-up of 2.5 years. No significant difference in MACE between ticagrelor and clopidogrel treatment arms was found.[28] Major bleeding rates or limb revascularizations were similar between the groups. Therefore, the efficacy and safety profile of ticagrelor was comparable to clopidogrel in PAD patients. It was concluded that in patients with PAD who are non-responders to clopidogrel, ticagrelor monotherapy may be considered as an effective alternative.[29] The preferred use of clopidogrel was confirmed in an extensive network meta-analysis, where also trials examining the potential additional benefits of voraxapar or picotamide, and combinations with dipyridamole or ticlopidine were included.[30] However, another recently published systematic review didn't confirm the superiority of clopidogrel over aspirin as a single antiplatelet agent in patients with chronic PAD.[31]

Non-responsiveness to antiplatelet therapy

Although the guidelines unequivocally recommend the use of either clopidogrel or aspirin for the management of patients with PAD, it is also well documented that a significant number of patients suffer from so-called "antiplatelet non-sensitivity". For aspirin, the ineffectiveness of platelet inhibition was found in up to 30-60% of patients.[32] The exact mechanism of this phenomenon is not entirely understood, but it can be described as either pharmacokinetic or pharmacodynamic.[33,34] The terms "aspirin resistance" and "clopidogrel resistance" are used to describe patients with higher platelet reactivity than the reference range despite antiplatelet therapy, who are therefore exposed to a greater risk for ischemic events. [35,36] A meta-analysis of studies analyzing aspirin or clopidogrel resistance showed that aspirin and clopidogrel resistance is significantly associated with CV events at a population level (relative risk of 2.09 and 2.80, respectively).[37] Besides drug resistance to prevent platelet activation, other factors like platelet hyperactivity, increased rate of platelet turnover, increased rate of drug metabolism and excretion, drug to drug interactions, malabsorption, as well as poor patient compliance determine the efficacy of some antiplatelet drugs.[33,34,38] Therefore, instead of "resistance" the term "non-responsiveness" is better suited. It also explains the absence of a definite relationship between laboratory findings of platelet function and clinical outcomes.[39] Nevertheless, it seems plausible that non-responsiveness to aspirin depends also on the type of atherosclerotic disease. There is evidence that the adverse effects of antiplatelet resistance are especially pronounced in PAD.[35] Patients with PAD are at the highest risk for cardiovascular events because of their huge atherosclerotic burden, which constantly contributes to platelet activation and thromboxane production via contact activation and turbulent flow.[13]

How to overcome non-responsiveness to aspirin and clopidogrel?

First, it is important to check and eliminate all factors independent of the metabolism of the antiplatelet drugs which can affect drug efficacy, like non-compliance, and to identify other factors that could influence the effect of aspirin or clopidogrel, like the presence of diabetes, kidney disease, inflammation and obesity, which are characterized by increased platelet

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aggregation.[40] In some patients, drug non-responsiveness may be a temporary manifestation and within seven days, both aspirin and clopidogrel (without a loading dose) reach a steady-state drug level. [41] One of the approaches to overcome antiplatelet non-responsiveness is to increase the drug dose.[42] In diabetic patients, 100 mg of aspirin was demonstrated as too low, and increasing the dose to 300 mg led to significantly increased platelet inhibition.[43] Increased loading and maintenance doses of clopidogrel also have been found to decrease the "resistance" in comparison to lower doses.[44] One of the options to improve the management of antiplatelet non-responsiveness is the use of the Bochum Clopidogrel and Aspirin Plan (BOCLA-Plan), incorporating a test and treatment strategy. It was shown that this strategy effectively eliminated aspirin non-responsiveness by dose modification.[45] It was also shown that twice-daily enteric-coated aspirin at 100 mg dose was superior to once-daily aspirin at 200 mg dose, which was in turn superior to a once-daily dose of 100 mg of a plane or enteric-coated aspirin[46]. Finally, one of the solutions to antiplatelet drug non-responsiveness is to add another antiplatelet drug to induce the additive effect. In summary, to achieve the desired pharmacological effect of the antiplatelet therapy, it is important to consider personalization of the treatment by monitoring both antiplatelet sensitivity, where the choice of the laboratory method may be important, as well as the patient compliance.[37,39,47]

Dual antiplatelet strategy (DAPT)

The combination of antiplatelet therapy was investigated in different clinical trials. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance (CHARISMA) trial randomly assigned 15,603 patients with established CV disease or multiple risk factors, either to aspirin and clopidogrel or aspirin monotherapy.[48] DAPT reduced the primary end-points (MI, stroke, or CV death) only in the subgroup of patients with established CV disease. Also in the subgroup of PAD patients (3,096 in this study), the CHARISMA trial showed no significant difference in primary end-point in DAPT and aspirin group. A non-significantly lower rate of peripheral arterial by-pass surgery was registered in the DAPT group (p=0.07). However, the risk of leg amputation was similar.[49] In the DAPT group, mild bleeding was significantly increased. The Trial Heart Attack Using Ticagrelor Compared to Placebo on Background of Aspirin – Thrombolysis In Myocardial Infarction 54 (PEGASUS-TIMI 54) included 21,162 patients who suffered MI of whom 1,143 (5%) had prior PAD. In this trial, the effect of aspirin plus ticagrelor was compared to aspirin monotherapy.[50] In the PAD group of patients, the combination of aspirin plus + 160 mg of ticagrelor (but not 90 mg of ticagrelor) significantly decreased the rate of MACE.[51] Also, major adverse limb events were reduced in patients with dual antiplatelet treatment. No significant differences in major bleeding were observed between groups.

In the study of Platelet Inhibition and Patient Outcomes (PLATO), the efficacy of ticagrelor with aspirin was compared to clopidogrel with aspirin in patients who had acute coronary syndrome.[52] In a sub-group analysis of 7,144 PAD patients, MACE were non-significantly lower in the ticagrelor group compared with the aspirin group.[53]

In two coronary trials Prolonging Dual Antiplatelet Treatment after Grading Stent Induced Intimal Hyperplasia Study (PRODIGY) a long versus short duration of DAPT after coronary stenting in patients with stable coronary artery disease or acute coronary syndromes were compared.[54] In the PRODIGY trial, clopidogrel with aspirin for 24 months in comparison to 6 months did not significantly reduce MACE but doubled the risk of bleeding. However, in the

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subgroup of PAD patients, there was a significant reduction of MACE with the long-term treatment group. [55]

Protease-activated receptor1 antagonists

Thrombin activates platelets through two protease-activated receptors (PARs), PAR-1 and PAR-4.[56] Selective PAR-1 blockade results in potent inhibition of thrombin-induced platelet aggregation.[57] Vorapaxar is an oral competitive PAR-1 antagonist that inhibits thrombin-induced platelet aggregation. The effect of Vorapaxar in conjunction with other antiplatelet agents was examined in the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events – Thrombolysis In Myocardial Infarction (TRA-2*P-TIMI50) and Thrombin Receptor Antagonists for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) studies.[56,58] In the sub-group of PAD patients in the TRA-2°P-TIMI50 trail, Vorapaxar did not significantly reduce MACE.[59] However, Vorapaxar did reduce the risk of several adverse limb events including the development of acute limb ischemia and peripheral revascularization. [60] In TRACER Study, 936 patients with PAD were included. There was no significant reduction in MACE and a non-significant reduction in peripheral revascularization procedures as well as lower extremity amputation in the sub-group of PAD patients treated with Vorapaxar. [61]

Anticoagulation and new oral anticoagulants on top of antiplatelets

Beyond platelets, other mechanisms are involved in thrombus formation, particularly coagulation. In this regard, ~~an~~ increasing interest has been focused on pharmacological approaches to inhibit coagulation in addition to antiplatelet therapy, referred to as dual antithrombotic pathway inhibition (DAPI).[62] In addition to platelets, thrombi contain fibrin which is produced by the coagulation pathway.[63] Coagulation factors, particularly factor Xa and thrombin are critical for platelet activation and development of inflammation which promotes thrombus formation. Thrombin activates platelet receptors PAR-1 and PAR-4 as key mechanisms of platelet activation. For these reasons, inhibitors of different coagulation factors were used for thrombotic risk reduction.

In the past, the effect of classical anticoagulant drugs, like warfarin (vitamin K antagonists) in addition to aspirin and other antiplatelet drugs was investigated. A combination of warfarin and antiplatelet agent (aspirin, ticlopidine, or clopidogrel) versus antiplatelet treatment alone was studied in the Warfarin and Antiplatelet Vascular Evaluation (WAVE) trial.[64] No significant differences in the primary outcome including MI, stroke, or severe lower extremity ischemia were observed among patients receiving warfarin plus antiplatelet therapy compared to antiplatelet therapy alone. However, an increased risk of life-threatening bleeding was observed in the warfarin plus antiplatelet group compared to antiplatelet therapy alone. These findings indicate that there is no benefit of the addition of warfarin to antiplatelet therapy for the reduction of thrombotic events in patients with PAD. Therefore, moderate-intensity warfarin treatment would be acceptable only in the presence of co-existing indications such as atrial fibrillation or recent venous thrombosis. Otherwise, there is no indication for full-dose oral anticoagulation with vitamin K antagonists in patients with PAD.[23]

The efficacy of warfarin in the PAD population has also been evaluated following surgical revascularization to maintain graft patency. The Dutch Bypass, Oral Anticoagulants or Aspirin (BOA) trial evaluated anticoagulation with warfarin vs. aspirin 80 mg daily.[65] There was no difference in the patency rates with warfarin compared to aspirin, respectively. However,

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subgroup analyses revealed that patients with vein grafts benefited from lower rates of graft occlusion with warfarin monotherapy. Patients treated with warfarin experienced an increased number of major bleeding compared to aspirin. [66]

The recent introduction of novel anticoagulants (especially dabigatran, rivaroxaban, and apixaban) and their proven effect in the management of atrial fibrillation and venous thromboembolism have stimulated the idea of anticoagulant use for secondary prevention in patients with atherosclerotic disease.[67] Direct oral anticoagulants (DOACs) have some advantages in comparison to vitamin K inhibitors. They selectively inhibit factor Xa or thrombin and indirectly inhibit platelet activation.[68] For these reasons, particularly factor Xa inhibition in combination with antiplatelets is a promising approach to thrombotic risk reduction. This idea was tested in the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) Trial which randomized 27,395 individuals with coronary artery disease or peripheral artery disease to three treatment arms: 5 mg rivaroxaban daily, 2.5 mg rivaroxaban twice daily plus 100 mg aspirin daily or aspirin alone.[69] Approximately 91% of patients had a history of coronary artery disease and 27% had PAD. The patients who received DAPI had a 24% reduction in the primary MACE and 18% lower all-cause mortality. The greatest effect of combined treatment represented the reduction of stroke (by 42%). The benefits were consistent across all clinical subgroups with either coronary artery disease or PAD or both. In the subgroup analysis of COMPASS which included 6,391 patients with PAD, low-doses of rivaroxaban combined with aspirin reduced major adverse limb events by 43%, amputations by 58%, and fatal peripheral vascular outcomes by 24%. A significant increase in major bleeding without a difference in the fatal or intracranial bleeding was observed in the group treated with rivaroxaban on top of aspirin.[70] Despite the increase in bleeding in patients treated with low-dose rivaroxaban plus aspirin, net clinical benefit was favorable, particularly in the high-risk subgroups and in those with multiple risk factors.[2]

The effect of combined anticoagulant and antiplatelet treatment was also investigated in the VOYAGER-PAD trial in 6,564 patients who had undergone infrainguinal percutaneous or surgical revascularization for disabling claudication. The patients were randomized to rivaroxaban 2.5 mg twice daily plus aspirin or the placebo and aspirin.[71] The primary efficacy outcome included acute limb ischemia, major amputation of limb for vascular causes, MI, ischemic stroke, or cardiovascular death.[72] Rivaroxaban significantly reduced the major outcomes including limb ischemia, major amputation as well as myocardial infarction, ischemic stroke, and cardiovascular death compared with aspirin alone. In the rivaroxaban group, major bleeding was increased, but there was no excess of fatal or intracranial bleeding events.[73]

Antiplatelet therapy in prevention of cardiovascular events in diabetes

An excessive mortality and morbidity rate has been reported in patients with both types of diabetes mellitus.[74] Aspirin is generally effective in preventing cardiovascular events, but the efficacy of aspirin and other antiplatelet drugs has been suggested to be low in diabetic patients. In the Antithrombotic Trialists Collaboration analysis, antiplatelet treatment in diabetic patients did not achieve a statistically significant reduction of major vascular events.[75] Recent evidence indicates that newer antiplatelet drugs may be more effective in the prevention of death and morbidity in diabetic patients, particularly in diabetics with PAD. The

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effect of picotamide – a combined inhibitor of thromboxane A2 synthase and receptor was investigated in the DAVID study.[76] In this multicentric randomized trial, picotamide was compared with aspirin for prevention of mortality and MACE in diabetics with PAD. The cumulative incidence of the two years overall mortality was significantly lower among patients who received picotamide than in those who received aspirin. 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), ticagrelor demonstrated reduced rates of MACE. The overall opinion is that is wise to weigh the cardiovascular risk of diabetes mellitus before prescribing antiplatelet medication and to estimate the risk of bleeding.

Antithrombotic therapy in prevention of adverse limb events

Current guidelines recommend the use of antiplatelet treatment in patients with PAD to reduce the risk of myocardial infarction, stroke, and vascular death.[2] However, there is no recommendation for antithrombotic treatment to reduce major adverse limb events in PAD patients. Little attention was paid to limb outcomes and most studies were underpowered to detect the effects on limb outcomes.[77] Currently, sub-group analysis of studies dealing with events in cardiovascular patients showed the importance of antithrombotic therapies on limb outcomes. The PEGASUS-TIMI [54] trial investigated the efficacy of ticagrelor vs. placebo added to aspirin. DAPT using ticagrelor plus aspirin compared with aspirin alone reduced MACE without increasing major bleeding events.[50] More intense antithrombotic therapy (ticagrelor plus aspirin) was more effective in reducing the need for limb revascularization and limb amputation. Further, the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Study which compared combined (low-dose rivaroxaban plus aspirin) treatment with aspirin monotherapy, again showed that intensive antithrombotic treatment prevents significantly more adverse limb events: amputations and fatal peripheral vascular outcomes. Similarly, the Vascular Outcomes Study of ASA Along With Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease (VOYAGER-PAD) trial confirmed that combined treatment with aspirin and rivaroxaban is more effective than aspirin alone in the prevention of vascular events.[72] A recent meta-analysis which included seven randomized studies enrolling 30,447 patients with PAD found that more intense antithrombotic therapy reduces the risk of limb amputation and revascularization as well as stroke at the price of an increased risk of bleeding events.[77]

Anticoagulation and antiplatelet treatment after percutaneous and surgical revascularization of PAD

Despite the benefits of endovascular or open intervention, recurrence rates of occlusions of the treated arteries remain high in the long term, which makes the use of complementary antithrombotic treatment essential for prolonging vessel patency and reducing the need for multiple interventions. However, the level of evidence of the effects of antithrombotic treatment is limited.[78] Few controlled studies exist on antithrombotic regimens in PAD patients undergoing peripheral revascularization.

Antiplatelet agents reduced the risk of major adverse cardiovascular or cerebrovascular events (MACE) by 22% in patients undergoing peripheral arterial grafting for PAD.[24]

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Furthermore, a recent Cochrane review suggested a benefit of aspirin with or without dipyridamole on infrainguinal bypass graft patency at 1 year.[79] The protective effect of aspirin was more pronounced in patients receiving prosthetic grafts than vein grafts.

In the Clopidogrel and Acetyl Salicylic Acid in Bypass Surgery for Peripheral ARterial Disease (CASPAR) trial the efficacy of dual antiplatelet therapy with clopidogrel plus aspirin versus aspirin alone was compared in patients undergoing below-the-knee bypass grafting.[80] After 1-year follow-up, there was no difference in the composite rate of graft occlusion, revascularization, amputation, or death between the 2 arms (35.1% for clopidogrel plus aspirin vs. 35.4% for aspirin). A subgroup analysis by type of graft showed a benefit of clopidogrel plus aspirin in patients who received prosthetic grafts. Any bleeding was higher with clopidogrel plus aspirin than with aspirin alone (16.7% vs. 7.1%, respectively), although no significant differences were observed in the rates of severe bleeding between the two arms.

The Dutch BOA (Bypass Oral anticoagulants or Aspirin) trial randomized patients undergoing infrainguinal bypass to high-intensity anticoagulation with phenprocoumon or acenocoumarol versus aspirin.[81] Overall rates of graft occlusion were similar between the 2 arms; however, subgroup analysis indicated anticoagulation was associated with better vein graft patency. Major bleeding including intracranial hemorrhage was higher with anticoagulation than with aspirin.

A Cochrane meta-analysis identified 3 trials that compared high dose aspirin plus dipyridamole with placebo in patients undergoing endovascular revascularization for PAD.[82] Aspirin plus dipyridamole was associated with superior patency at 6 months.

The phosphodiesterase 3 inhibitor cilostazol, which has antiplatelet properties, has also been studied in small controlled trials of PAD patients undergoing endovascular revascularization; however, convincing data for its efficacy are lacking.[83]

The combination of antiplatelet and anticoagulant treatment with aspirin plus betrixaban in a small study of 129 patients was shown to have overall superior efficacy, with no difference in bleeding incidence, compared to aspirin alone. The effects were significant for restenosis, limb salvage, survival rates, and cumulative rates of above ankle amputation or death.[84]

DAPT with aspirin and clopidogrel is suggested for at least 1 month following stent implantation, regardless of stent type, or with aspirin and ticagrelor in PAD patients with previous myocardial infarction. Treatment with DAPT (cilostazol plus aspirin) following endovascular intervention seems superior to aspirin monotherapy for the prevention of restenosis in femoropopliteal segments in critical limb ischemia [83], but not in infra-popliteal segments.[85]

Antithrombotic treatment after revascularization of critical limb ischemia (CLI)

The majority of published reviews focus on evaluating antithrombotic treatment for PAD in general, however, specific data on CLI are sparse.[86] Only a few studies were dedicated to CLI and even those usually included a mixture of CLI and claudication patients.[87] Therefore, reliable data regarding antithrombotic therapy for CLI following endovascular procedures do not exist.[4,16,88]

Some studies suggested that dual antiplatelet therapy reduces post-surgical restenosis and amputation for diabetic patients, without increasing major bleeding incidences, compared to single antiplatelet therapy. Treatment with DAPT might provide better outcomes than monotherapy following endovascular intervention for CLI, but the ideal treatment should be tailored to the individual patient.[89] Therefore, the efficacy of aspirin in patients with CLI

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remains elusive and may be related to under-representation of CLI in clinical trials of PAD, inefficient aspirin metabolism (i.e., aspirin resistance), and inappropriate dosing.[90]

Choice of antithrombotic therapy on the dependence of clinical stages of PAD and accompanied atherosclerotic diseases

Antithrombotic therapy should be individualized and based on clinical presentation and extension of atherosclerotic disease. [29]

- **Patients with asymptomatic PAD (low ABI):**
  Antithrombotic treatment including antiplatelets is not indicated,
- **Asymptomatic PAD patients with a history of clinically manifested coronary or cerebrovascular disease**:
  Aspirin or P2Y12 inhibitors (e.g., clopidogrel) or both in patients with ischemic events within the past 12 months.
- **Symptomatic PAD patients who do not have clinically manifested coronary or cerebrovascular disease:**
  Aspirin or clopidogrel is indicated to reduce MACE.[91] As there is a lack of evidence for aspirin in this group of patients, other antiplatelet agents including clopidogrel which significantly reduce MACE are the first choice for treatment of symptomatic PAD. Ticagrelor monotherapy can be considered as an effective alternative to clopidogrel.
- **Symptomatic PAD patients who have clinically manifested coronary or cerebrovascular disease:**
  Single-drug therapy with aspirin or clopidogrel. Treatment with dual antiplatelet therapy with clopidogrel and aspirin is not more effective than aspirin alone and causes more major bleeding.[48]
  Combined treatment with low-dose rivaroxaban and aspirin represents an option for the treatment of patients with a high ischemic and low bleeding risk.
- **Patients with PAD at higher risk for ischemic limb events** (severe leg disease, ABI <0.60) may benefit from vorapaxar added to other antiplatelet therapy.
- **The optimal antithrombotic therapy for patients with critical limb** ischemia remains unclear and is currently under investigation.

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