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Review Article
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Antithrombotic Treatment for Symptomatic Peripheral Artery Disease

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Single antiplatelet therapy with aspirin or clopidogrel is widely used in the prevention of adverse cardiovascular and limb events in patients with symptomatic peripheral artery disease (PAD). However, the risk of these events remains high, and the most optimal antithrombotic therapy for PAD is still uncertain. We conducted a literature search to identify the major clinical trials on therapeutic approaches in the prevention of adverse events in patients with PAD. This article provides an overview of the clinical trials that have evaluated the efficacy and safety of intensified antithrombotic strategies for PAD. Due to the heterogeneity of patient populations and the variable definitions of clinical outcomes used in different clinical studies, it was difficult to make direct comparisons between the study results. Although a number of choices are now available, the risk-benefit of each antithrombotic regimen for patients with PAD must be carefully considered.

Key Words: Antithrombotic treatment • Peripheral artery disease

INTRODUCTION

Peripheral artery disease (PAD) is usually caused by atherosclerotic obstruction of major arteries supplying the extremities, with lower leg arteries being most commonly affected. A common symptom of PAD is painful aching in the leg muscles triggered by physical activity, known as intermittent claudication. Chronic or critical limb ischemia (CLI) is an advanced stage of PAD. It presents with resting pain, ulceration, gangrene and/or tissue loss of lower extremities. Patients diagnosed with CLI are at increased risk of major amputation, impaired physical function, and a substantial reduction in the quality of life.[1,2] PAD patients may also present with acute atherothrombotic occlusions resulting in acute limb ischemia (ALI) when there is a sudden decrease in limb perfusion that threatens the immediate viability of the affected limb. PAD is not only associated with limb-related complications, but also carries a high risk of cardiovascular (CV) morbidity and mortality due to concomitant atherosclerotic disease in other vascular beds and coexisting risk factors.[3-5] In the 8273 PAD patients included in the Reduction of Atherothrombosis for Continued Health (REACH) registry, 62% also had atherosclerosis in other arterial territories.[5] In the 13885 PAD patients recruited in the Examining Use of Ticagrelor in Peripheral Artery Disease (EUCLID) trial, 44% had polyvascular disease, of whom 19% had PAD plus coronary artery disease (CAD), 15% had PAD plus cerebrovascular disease (CVD), and 10% had PAD plus both CAD and CVD.[6] In the REACH registry, the 1-year event rate of CV death, myocardial infarction (MI), stroke or hospitalization for atherothrombotic events was the highest in patients with PAD, and the risk of these events increased with the number of involved arterial territories.[3] The EUCLID trial also demonstrated

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that the risks of adverse cardiac events and lower extremity revascularization were higher in patients with polyvascular disease than in those with PAD alone.[6]

DISEASE BURDEN AND RISK

PAD affects around 13% of the Western population over the age of 50 years and up to 20% of patients over the age of 75.[7-9] A global study revealed that from 2000 to 2010, the number of individuals with PAD increased by 28.7% in low-income or middle-income countries and by 13.1% in high-income countries,[10] and that as of 2010, more than 200 million people worldwide were believed to be living with PAD.[10] Besides an aging population trend observed in Asia, the rising prevalence rates of diabetes and end-stage renal disease have also contributed to the increase in the burden of PAD in this region.[11,12] In Taiwan, the number of PAD cases receiving percutaneous transluminal angioplasty (PTA) increased 15-fold from 600/year in 2000 to 9100/year in 2011, reflecting that PAD poses a real threat to public health.[13] Recently, advances have been made in the devices used for PTA in the management of PAD.[14] Despite the increasing use of PTA and device improvement in Taiwan, the number of limb amputations for PAD is still high, ranging from 4100 to 5100 cases per year with no decreasing trend from 2000 to 2011.[13] More importantly, the clinical outcomes are poor after revascularization procedures for patients with symptomatic PAD, with around about 10% of these patients being hospitalized within 1 year after the index limb revascularization procedure for ALI, major amputation or surgical peripheral revascularizations.[15] In addition, almost 40% of all patients have been reported to require hospitalization for all causes within 1 year, with one-half being limb-related and one-third being CV disease-related events.[15] Although there has been much progress in the devices and techniques used for revascularization of PAD, these studies demonstrate that there is still significant room for improvement with regards to medical therapies to further reduce limb and CV adverse events.

SINGLE ANTIPLATELET STRATEGY

The high burden and risk of PAD warrants the development of more effective and evidence-based medical therapies to improve clinical outcomes. However, progress has been relatively slow. Medical treatment of PAD begins with risk factor management including control of hypertension, diabetes, hypercholesterolemia and smoking cessation. Aspirin is the conventional antiplatelet agent used to prevent CV events in patients with symptomatic PAD,[16,17] however more potent antiplatelet agents have been tested in clinical trials. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial included 19185 patients with either MI, ischemic stroke or symptomatic PAD, and found that when compared with aspirin, clopidogrel led to a slight reduction in the primary composite endpoint of major adverse cardiac events (MACEs) including MI, ischemic stroke, and vascular death [relative risk reduction 8.7%, 95% confidence interval (CI) 0.3-16.5].[18] Subgroup analysis of PAD patients (n = 6452) in the CAPRIE study demonstrated that clopidogrel conferred a greater benefit than aspirin with a 24% risk reduction of MACEs.[18] However, the CAPRIE trial did not specifically report limb outcomes or bleeding events in the PAD subgroup. Current American College Cardiology (ACC)/American Heart Association (AHA) guidelines recommend that either aspirin or clopidogrel should be used in patients with symptomatic PAD.[19] The European Society of Cardiology (ESC) guidelines further recommend that clopidogrel may be preferred over aspirin.[20] The EUCLID trial compared ticagrelor versus clopidogrel in 13885 patients with symptomatic PAD. The study showed that ticagrelor did not reduce the risk of stroke, MI or CV death compared with clopidogrel. In addition, the risks of hospitalization for ALI and lower limb revascularization were similar between groups. Thrombolysis in myocardial infarction (TIMI) major bleeding was also similar.[21]

DUAL ANTIPLATELET STRATEGY

Combination antiplatelet agent therapy has also been tested in clinical trials. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial randomized selected patients with established CV disease or multiple risk factors to receive aspirin plus clopidogrel or aspirin monotherapy.[22] The results of the CHARISMA trial demonstrated that dual antiplatelet therapy (DAPT) re-

duced the primary endpoint (MI, stroke, or CV death) only in the subgroup of patients with established CV disease, but not in patients only with risk factors.[22] A post hoc analysis of the 3096 PAD patients in the CHARISMA trial showed no significant difference of the primary endpoint between DAPT and aspirin groups. There was only a non-significantly lower rate of peripheral arterial bypass surgery in the DAPT group (p = 0.07), and the risk of leg amputation was similar.[23] The rate of severe or moderate bleeding defined by the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) criteria did not differ significantly between groups, however the risk of GUSTO mild bleeding was significantly increased in patients receiving DAPT. Using a more potent antiplatelet strategy, the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin — Thrombolysis In Myocardial Infarction 54 (PEGASUS-TIMI 54) trial randomized 21162 patients with MI occurring 1 to 3 years before enrollment to receive aspirin plus ticagrelor (60 mg or 90 mg bid) or aspirin monotherapy.[24] Overall, DAPT with aspirin and ticagrelor significantly reduced the risks of CV death, MI, or stroke compared to aspirin, but increased the risks of bleeding and dyspnea.[24,25] Among the included patients, 1143 (5%) had prior PAD.[26] In these PAD patients, aspirin plus ticagrelor 60 mg [hazard ratio (HR) 0.69, 95% CI 0.47-0.99] but not 90 mg (HR 0.81, 95% CI 0.57-1.15) significantly decreased the rate of MACEs. In addition, major adverse limb events (MALEs), defined as ALI or peripheral revascularizations for ischemia, were reduced by aspirin plus ticagrelor 90 mg (HR, 0.49, 95% CI 0.30-0.81), but not by 60 mg (HR 0.81, 95% CI 0.53-1.24). Moreover, no significant increase in TIMI major bleeding was observed in those who received aspirin plus ticagrelor 60 mg (HR 1.18, 95% CI 0.29-4.70) or 90 mg (HR 1.46, 95% CI 0.39-5.43) compared to aspirin monotherapy.[26] However, considering that the number of patients was small (approximately 370 patients) in each ticagrelor dose group, larger studies are necessary to confirm the beneficial effect of this DAPT strategy.

DOUBLE THERAPY STRATEGY

Data from previous clinical trials suggest that intensely targeting the antiplatelet pathway only provides limited protective effects for PAD patients at high risk of CV events. The residual risk seen with antiplatelet therapy has prompted the search for alternative antithrombotic therapies. The development of the non-vitamin K dependent oral anticoagulant (NOAC), rivaroxaban, has provide an opportunity to test the effect of a double therapy strategy with aspirin plus low dose rivaroxaban on vascular protection. The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial recruited 27395 patients with chronic CAD and/or PAD who did not require DAPT according to current clinical practice guidelines.[27] The patients were randomized to either one of three regimens: rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily) alone, or aspirin (100 mg once daily) alone. Compared with aspirin monotherapy, the primary endpoints of MI, stroke, or CV death were significantly reduced in the aspirin plus rivaroxaban (2.5 mg twice daily) group but not in the rivaroxaban (5 mg twice daily) group. In the secondary endpoints of ischemic stroke, MI, CV death or ALI, both the aspirin plus rivaroxaban (2.5 mg twice daily) group and rivaroxaban (5 mg twice daily) group showed benefits over aspirin monotherapy.[27] The Warfarin Antiplatelet Vascular Evaluation trial showed that a combination of a vitamin K antagonist with antiplatelet therapy was not more effective than antiplatelet monotherapy in preventing MI, stroke, or CV death in PAD patients and only increased the risk of life-threatening bleeding.[28] The results of the COMPASS trial suggested a potential role of NOACs in the management of PAD.

Among all patients in the COMPASS trial, 7470 had PAD which was defined as symptomatic PAD, CAD with an ankle brachial index (ABI) < 0.90 and carotid stenosis with previous carotid revascularization or asymptomatic carotid artery stenosis of at least 50%. In PAD subgroup analysis, the risk of MACEs was reduced by 28% (HR 0.72, 95% CI 0.57-0.90) in patients treated with rivaroxaban 2.5 mg twice daily plus aspirin compared with aspirin alone.[29] For limb outcomes in PAD, double therapy with rivaroxaban and aspirin reduced the risk of MALEs (defined as ALI, CLI or major vascular amputations) by 46% (HR 0.54, 95% CI 0.35-0.84), ALI by 44% (HR 0.56, 95% CI 0.32-0.99), and major amputation by 70% (HR 0.30, 95% CI 0.11-0.80).[29] In terms of safety, the risk of

Table 1. Efficacy and safety of intensified antithrombotic therapy in patients with PAD

Clinical trials	Clopidogrel vs. Aspirin (CAPRIE trial)[18]	Ticagrelor (90 mg bid) vs. Clopidogrel (EUCLID trial)[21]	Aspirin + Clopidogrel vs. Aspirin (CHARISMA trial)[22,23]	Aspirin + Ticagrelor (60 mg or 90 mg bid) vs. Aspirin (PEGASUS trial)[24,26]	Aspirin + Rivaroxaban (2.5 mg bid) vs. Aspirin (COMPASS trial)[27,29]
Included patients	Prior MI, IS or PAD (PAD group, n = 6,452)	PAD (n=13,885)	Prior MI, IS or PAD (PAD group, n=3,096)	Prior MI (PAD group, n=1,143)	CAD and/or PAD (PAD group, n=7,470)
Follow-up time	Mean 1.91 years	Median 30 months	Median 28 months	Median 33 months	Mean 23 months
MACE	MACE: Vascular death, MI, or IS Overall ↓8.7% (event rate/yr 5.32% vs. 5.83%, p = 0.043) PAD group ↓24% (event rate/yr 3.71% vs. 4.86%, p = 0.0028)	MACE: CV death, MI, or IS No reduction (event rate/yr 4.47% vs. 4.36%, p = 0.65)	MACE: CV death, MI, or any stroke No reduction in PAD group (event rate 7.6% vs. 8.9%, p = 0.183)	MACE: CV death, MI, or any stroke In PAD group, ↓31% in 60 mg (event rate 14.1% vs. 19.3%, p = 0.045) and no significant reduction in 90 mg (event rate 16.3% vs. 19.3%, p = 0.24)	MACE: CV death, MI, or any stroke ↓28% in PAD group (event rate 5% vs. 7%, p = 0.0047)
Limb outcome	Not reported in PAD group	No reduction in ALI (event rate 1.7% vs. 1.7%, p = 0.85) and lower limb revascularization (event rate 12.2% vs. 12.8%, p = 0.30)	Nonsignificant lower rate of peripheral arterial bypass surgery (event rate 3.8% vs. 5.1%, p = 0.07)	↓51% in ALI or peripheral revascularization in 90 mg (event rate 0.32% vs. 0.71%, p = 0.005) and no significant reduction in 60 mg (event rate 0.60% vs. 0.71%, p = 0.33)	↓46% in major adverse limb events, including ALI, CLI or major amputation (event rate 1% vs. 2%, p = 0.0054)
Amputation	Not reported in PAD group	Not reported	No reduction in PAD group (event rate 0.8% vs. 1.1%, p = 0.356)	1 case in placebo, 1 case in 60 mg and 0 case in 90 mg group	↓60% in all vascular amputation (event rate < 1% vs. 1%, p = 0.0069) and ↓70% in major amputation (event rate < 1% vs. 1%, p = 0.011)
Bleeding	Not reported in PAD group	No increase in TIMI major bleeding (evet rate 1.6% vs. 1.6%, p = 0.49)	No significant difference in GUSTO severe (event rate 1.7% vs. 1.7%, p = 0.901) and moderate bleeding (event rate 2.5% vs. 1.9%, p = 0.259). GUSTO mild bleeding was significantly increased (event rate 34.4% vs. 20.8%, p < 0.001)	No increase in TIMI major bleeding in both doses (60 mg, event rate 1.6% vs. 1.6%, p = 0.82; 90 mg event rate 1.8% vs. 1.6%, p = 0.57)	Modified ISTH major bleeding was significantly increased (event rate 3% vs. 2%, p = 0.0089) but no significant increase in fatal bleeding and intracranial hemorrhage (Both event rate < 1% vs. < 1%)

ALI, acute limb ischemia; CAD, coronary artery disease; CAPRIE, Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; CLI, chronic or critical limb ischemia; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; CV, cardiovascular; EUCLID, Examining Use of Ticagrelor in Peripheral Artery Disease; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; IS, ischemic stroke; ISTH, International Society on Thrombosis and Hemostasis; MACE, major adverse cardiac events; MI, myocardial infarction; PAD, peripheral artery disease; PEGASUS, Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin; TIMI, thrombolysis in myocardial infarction.

total major bleeding defined by the modified International Society on Thrombosis and Hemostasis (ISTH) criteria was significantly increased in the patients who received aspirin plus rivaroxaban (2.5 mg twice daily), however the rates of fatal bleeding and intracranial hemorrhage were similar between groups.[29] In the 6391 patients with lower extremity PAD in the COMPASS study, further analysis showed that MALEs were a grave prognostic factor in patients with PAD of the lower extremities.[30] Overall, the risk of subsequent hospitalization after MALEs during 1 year of follow-up was high at up to 61.5%. Patients with MALEs not only had a higher risk of subsequent hospitalization, but also increased risks of amputation and mortality. Rivaroxaban 2.5 mg twice daily plus aspirin significantly decreased the risk of MALEs by 43%, total amputations by 58% and peripheral vascular interventions by 24% compared with aspirin monotherapy.[30] Double therapy with rivaroxaban 2.5 mg twice daily plus aspirin may provide a new horizon for PAD treatment.

Among the 6391 patients with PAD of the lower extremities in the COMPASS study, the risk of MALEs was significantly associated with the severity of PAD. The incidence of MALEs was the highest in the patients with prior peripheral revascularization or amputation followed by the patients with symptomatic PAD but no history of amputation or revascularization. The patients with asymptomatic PAD had the lowest risk of MALEs.[31] Severe ischemia symptoms (Fontaine classification III or IV), prior amputation and prior peripheral revascularization were the three major independent predictors of MALEs in these patients.[30] Antithrombotic strategies in these high-risk PAD groups are especially important. The ongoing VascularOutcomes studY of ASA alonG with rivaroxaban in Endovascular or surgical limb Revascularization for Peripheral Artery Disease (VOYAGER PAD) trial is a randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of rivaroxaban (2.5 mg twice daily) plus aspirin versus aspirin monotherapy in symptomatic PAD patients undergoing peripheral surgical and/or endovascular revascularization.[32] The primary endpoint of the VOYAGER PAD trial includes both CV events (MI, ischemic stroke, and CV death) and also limb events (ALI and major amputation). The study results will further extend our understanding about the most appropriate management for these groups of PAD patients in the near future.

CONCLUSIONS

This review article highlights the significant burden of PAD and its related adverse cardiac and limb outcomes. Table 1 summarizes the results of clinical trials with regards to the efficacy and safety of intensified antithrombotic therapy in patients with PAD. Vascular protection provided by traditional single antiplatelet therapy for PAD is not adequate, as the risks of CV- and limb-related adverse events are still very high, especially in those with severe ischemic symptoms who have already had limb events. There is an urgent need for a better treatment options to improve the clinical outcomes of PAD patients.

CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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