

# World Journal of *Cardiology*

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### REVIEW

- 562 Sudden cardiac death in patients with rheumatoid arthritis  
*Masoud S, Lim PB, Kitas GD, Panoulas V*

### MINIREVIEWS

- 574 Vascular complications of transcatheter aortic valve replacement: A concise literature review  
*Chaudhry MA, Sardar MR*
- 583 Peripheral interventions and antiplatelet therapy: Role in current practice  
*Singh P, Harper Y, Oliphant CS, Morsy M, Skelton M, Askari R, Khouzam RN*
- 594 Is Entresto good for the brain?  
*Patel N, Gluck J*
- 600 Cardiac and pericardial tumors: A potential application of positron emission tomography-magnetic resonance imaging  
*Fathala A, Abouzied M, AlSugair AA*

### SYSTEMATIC REVIEWS

- 609 Hand dysfunction after transradial artery catheterization for coronary procedures  
*Ul Haq MA, Rashid M, Kwok CS, Wong CW, Nolan J, Mamas MA*
- 620 Infective endocarditis and thoracic aortic disease: A review on forgotten psychological aspects  
*Suárez Bagnasco M, Núñez-Gil IJ*

### CASE REPORT

- 629 Endovascular treatment of paravisceral mycotic aneurysm: Chimmeny endovascular sealing the end of de road  
*Rabellino M, Moltini PN, Di Caro VG, Chas JG, Marechino R, Garcia-Monaco RD*
- 634 Percutaneous closure of congenital Gerbode defect using Nit-Occlud® Lê VSD coil  
*Phan QT, Kim SW, Nguyen HL*

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## Peripheral interventions and antiplatelet therapy: Role in current practice

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### Abstract

Peripheral arterial disease (PAD) is a common disorder associated with a high risk of cardiovascular mortality and continues to be under-recognized. The major risk factors for PAD are similar to those for coronary and cerebrovascular disease. Management includes exercise program, pharmacologic therapy and revascularization including endovascular and surgical approach. The optimal revascularization strategy, endovascular or surgical intervention, is often debated due to the paucity of head to head randomized controlled studies. Despite significant advances in endovascular interventions resulting in increased utilization over surgical bypass, significant challenges still remain. Platelet activation and aggregation after percutaneous transluminal angioplasty of atherosclerotic arteries are important risk factors for re-occlusion/restenosis and life-threatening thrombosis following endovascular procedures. Antiplatelet agents are commonly prescribed to reduce the risk of myocardial infarction, stroke and death from cardiovascular causes in patients with PAD. Despite an abundance of data demonstrating efficacy of antiplatelet therapy in coronary artery disease and cerebrovascular disease, there is a paucity of clinical information, clinical guidelines and randomized controlled studies in the PAD population. Hence, data on antiplatelet therapy in coronary interventions is frequently extrapolated to peripheral interventions. The aim of this review article is to elucidate the current data on revascularization and

the role and duration of antiplatelet and anticoagulant therapy in re-vascularized lower limb PAD patients.

**Key words:** Peripheral arterial disease; Peripheral vascular disease; Antiplatelet therapy; Revascularization

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**Core tip:** Peripheral arterial disease (PAD) is nearly a pandemic disorder which carries a high morbidity and mortality. Treatment includes risk factor modification, revascularization whenever feasible and medical management including antiplatelet therapy being a crucial element. Despite improvements in endovascular techniques and equipment for revascularization in PAD patients, current data regarding antiplatelet therapy in this population is limited. Our objective is to consolidate the current data on role and duration of antiplatelet and anticoagulant therapy in re-vascularized lower limb PAD patients.

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## INTRODUCTION

Peripheral arterial disease (PAD) represents a major clinical problem affecting millions of people worldwide, which carries high morbidity and mortality and an increased risk of major adverse cardiovascular events including myocardial infarction (MI), stroke, premature death and impaired quality of life. The incidence of PAD is globally estimated to be between 3% and 12%<sup>[1-3]</sup>. This incidence has increased to as high as 29% in low to middle income areas, becoming one of the global problems of the 21<sup>st</sup> century<sup>[4]</sup>. Atherosclerosis in the peripheral arteries is a chronic, slowly developing disorder causing narrowing of the arteries. Depending on the degree of narrowing, clinical presentations vary from classic intermittent claudication, exercise limitations, or ischemic pain, to lower extremity ulceration or gangrene of the toes from chronic limb ischemia. Other patients found to have PAD from ankle brachial index (ABI) screening can remain asymptomatic throughout their life. Occasionally, acute events occur, frequently associated with thrombosis, embolism and/or major arterial occlusion.

Therapy for PAD includes both a pharmacologic and revascularization approach if possible. Antiplatelet therapy is the cornerstone of pharmacologic therapy in addition to risk factor reduction. The purpose of this paper is to discuss revascularization strategies and review clinical trial data for antiplatelet therapy in

patients with PAD.

## REVASCULARIZATION STRATEGY: ENDOVASCULAR THERAPY VS SURGICAL BYPASS

The optimal treatment strategy, endovascular or surgical intervention, is often debated due to the lack of head to head randomized controlled studies. Of the studies conducted, most are underpowered and lack uniform endpoint definitions making a direct comparison among studies difficult<sup>[5]</sup>.

Remarkable advancement in technology in the past decade has shifted the paradigm of revascularization strategies in PAD from an open surgical approach to percutaneous endovascular treatments including percutaneous atherectomy, percutaneous transluminal angioplasty (PTA) and stenting. Analysis conducted by Goodney *et al*<sup>[6]</sup>, provides statistical evidence based on Medicare claims between 1996 and 2006 that endovascular interventions are now performed more commonly than bypass surgery. The rate of major lower extremity amputation declined significantly more than 25% and endovascular interventions increased more than threefold [138 to 455 per 100000; relative risk (RR) = 3.30; 95%CI: 2.9-3.7], while surgery decreased by 42% (219 to 126 per 100000; RR = 0.58; 95%CI: 0.5-0.7)<sup>[6]</sup>. However, caution must be used to interpret this data as more research is warranted to determine if there is an association between lower extremity vascular procedures and improved rates of limb salvage in this population.

The BASIL trial was first published in 2005 followed by an intention-to-treat analysis published in 2010 evaluating amputation-free survival and overall survival. This was a prospective randomized controlled trial comparing the effectiveness of endovascular therapy vs open surgical approach in patients with severe limb ischemia due to infra-inguinal disease. Similar short term outcomes were found comparing both treatment modalities<sup>[7,8]</sup>. However, data also suggests that the results of angioplasty are less durable than that of surgical grafting. The primary patency rate after angioplasty is greatest for lesions in the common iliac artery and decreases distally. Additionally, the rates of patency are lower in cases with increasing lesion length, multiple and diffuse lesions, poor-quality run-off and in patients with concomitant diabetes and renal failure<sup>[9]</sup>.

The BEST-CLI trial is currently underway and designed to clarify this clinical conundrum for critical limb ischemia patients. This is a multi-center trial with a planned enrollment of 2100 patients that includes interventional cardiologists, interventional radiologists and vascular surgeons. The trial emphasizes a team based treatment approach and will compare patients eligible for both endovascular and open surgical bypass. All contemporary endovascular therapeutic modalities

**Table 1 Results of clinical trials initially designed for patients with coronary artery disease, with subgroup analysis in peripheral arterial disease**

Clinical trial	No. of patients	Patient population	Drugs studied	Primary end point	Outcomes
PEGASUS TIMI-54 subgroup analysis <sup>[40]</sup> (2016)	1143	CAD and concomitant PAD	Ticagrelor 90 mg BID + aspirin <i>vs</i> Ticagrelor 60 mg BID + aspirin <i>vs</i> Placebo + aspirin	Cardiovascular death, MI and stroke  Acute limb ischemia and peripheral revascularization for ischemia	15.2% in ticagrelor (pooled group) and 19.3% in placebo. ARR 4.1% in ticagrelor (pooled group) 60 mg dose more beneficial (ARR of 5.2%)  0.46% in ticagrelor (pooled group) and 0.71% in placebo (HR 0.65; 95%CI: 0.44-0.95; <i>P</i> = 0.026)
PLATO-subgroup analysis <sup>[32]</sup> (2015)	1144	CAD and concomitant PAD	Ticagrelor <i>vs</i> clopidogrel	Cardiovascular death, MI and stroke	18% in ticagrelor group and 20.6% in clopidogrel group (HR: 0.85; 95%CI: 0.64-1.11; <i>P</i> = 0.99)
TRA 2P-TIMI 50 <sup>[35]</sup> (2012)	26449	Previous history of MI or ischemic stroke within the previous 2 wk-12 mo or PAD	Vorapaxar <i>vs</i> placebo	Cardiovascular death, MI, and stroke	9.3% in vorapaxar group and 10.5% in placebo ( <i>P</i> < 0.001)  Subgroup analysis in PAD patients showed no difference between groups for the primary endpoint  Rate of intracranial hemorrhage (1% vorapaxar <i>vs</i> 0.5% placebo; <i>P</i> < 0.001)  6.8% in clopidogrel plus aspirin group and 7.3% in aspirin group ( <i>P</i> = 0.22)  Subgroup analysis in PAD patients: no benefit was derived from dual antiplatelet therapy
CHARISMA <sup>[38]</sup> (2006)	15603	Patients with either clinically documented vascular disease or risk factors for atherothrombotic disease	Aspirin plus clopidogrel <i>vs</i> aspirin monotherapy	MI, stroke or cardiovascular death	RRR of 8.7% clopidogrel group ( <i>P</i> = 0.043; 95%CI: 0.3-16.5)  Subgroup analysis in PAD patients: 23.8% RRR in clopidogrel over aspirin ( <i>P</i> = 0.0028; 95%CI: 8.9-36.2)
CAPRIE <sup>[15]</sup> (1996)	19185	Recent MI, recent ischemic stroke or symptomatic PAD	Aspirin <i>vs</i> clopidogrel	MI, stroke and vascular death	

MI: Myocardial infarction; PAD: Peripheral arterial disease; ARR: Absolute risk reduction; RRR: Relative risk reduction.

and surgical bypass conduits will be compared and chosen by enrollment site and physician preference. The revascularization strategy will be selected for each case in a specialized vascular center in close cooperation with an endovascular specialist and a vascular surgeon<sup>[10]</sup>.

## ANTIPLATELET THERAPY

Platelets have a fundamental role in the development of atherothrombosis<sup>[11]</sup>. Although percutaneous revascularization therapies have evolved significantly with dramatic improvement in interventional devices and techniques, the most appropriate antiplatelet therapy regimen in PAD is understudied compared to the coronary artery disease (CAD) population. Multiple antiplatelet agents have been studied in the PAD population, including aspirin, the combination of aspirin and dipyridamole, clopidogrel, ticagrelor, cilostazol and vorapaxar. Results from randomized clinical trials in patients with CAD and subgroup analysis in the PAD population and PAD alone are summarized in Tables 1 and 2 respectively. Given the number of agents studied, there is a wide discrepancy in the management of patients with PAD. Meta-analysis conducted by the Antithrombotic Trialists Collaboration Group in 2002 evaluated 287 randomized studies, and concluded that antiplatelet therapy reduced the risk of

serious vascular events (non-fatal MI, non-fatal stroke, or vascular death) by about 23%, not just among the population with unstable angina, acute MI or stroke but also among patients with CAD, PAD, and those at high risk of embolism<sup>[12]</sup>.

## ASPIRIN

Aspirin is a commonly used antiplatelet agent, which irreversibly inhibits the cyclooxygenase-1 and 2 enzymes resulting in decreased formation of thromboxane A<sub>2</sub>, thus inhibiting platelet aggregation. However, compelling evidence to support a reduction in cardiovascular events in the setting of PAD is lacking<sup>[12]</sup>. In a meta-analysis published by Berger *et al.*<sup>[13]</sup> in 2009, 18 trials comprising 5269 participants with PAD were evaluated. Cardiovascular events occurred at a rate of 8.9% (251/2823 subjects) in the aspirin or aspirin plus dipyridamole group and 11% (269/2446 subjects) in the control group (95%CI: 0.76-1.04). This finding was a 12% relative risk reduction in non-fatal MI, non-fatal stroke and cardiovascular death with aspirin, but it failed to reach statistical difference<sup>[13]</sup>. Despite these results, aspirin (dose 75-325 mg) is given a class I recommendation in the 2016 AHA/ACC PAD guidelines for management of symptomatic patients largely due to benefit of aspirin in other vascular diseases<sup>[3,14]</sup>.

**Table 2** Results of clinical trials designed for patients with peripheral arterial disease

Clinical trial	No. of patients	Patient population	Drugs studied	Primary end point	Outcomes
COMPASS <sup>[44,45]</sup> (2017)	27402	Peripheral arterial disease or coronary artery disease	Rivaroxaban plus aspirin or rivaroxaban alone <i>vs</i> aspirin alone	Myocardial infarction, stroke, CV death and the time from randomization to the first occurrence of major bleeding	Preliminary results: Trial stopped prematurely. One of rivaroxaban arms proved to be superior to aspirin alone No disclosed information on the primary bleeding endpoint or the regimen that showed superiority to aspirin alone
EUCLID <sup>[41]</sup> (2016)	13885	PAD (ABI $\leq$ 0.80 or prior (> 30 d) revascularization of the lower extremities)	Ticagrelor <i>vs</i> clopidogrel	CV death, MI, or ischemic stroke	10.8% in ticagrelor group <i>vs</i> 10.6% in clopidogrel group ( $P = 0.65$ )
MIRROR <sup>[39]</sup> (2012)	80	PAD treated with endovascular therapy	Dual antiplatelet therapy (aspirin plus clopidogrel) <i>vs</i> aspirin monotherapy	Local concentrations of platelet activation markers $\beta$ -thromboglobulin and CD40L	Reduced peri-interventional platelet activation and improved functional outcome in the dual antiplatelet therapy group
Berger <i>et al</i> <sup>[13]</sup> (Meta-analysis-2009)	5269	PAD (patients with claudication, those undergoing percutaneous intervention or bypass surgery, and asymptomatic patients with an ABI of 0.99 or less)	Aspirin or combination of aspirin plus dipyridamole <i>vs</i> placebo	Composite end point of non-fatal MI, nonfatal stroke, and CV death	8.9% in aspirin or combination of aspirin and dipyridamole, 11% in placebo (95%CI: 0.76-1.04)
WAVE <sup>[43]</sup> (2007)	2161	PAD (atherosclerosis of the arteries of lower extremities, carotid arteries or subclavian arteries)	Antiplatelet agent plus oral anticoagulant <i>vs</i> antiplatelet therapy in patients with PAD	CV death, MI and stroke	12.2% in combination therapy group and 13.3% in antiplatelet therapy alone (95%CI: 0.73 to 1.16; $P = 0.48$ )
Thompson <i>et al</i> <sup>[29]</sup> (Meta-analysis-2002)	2702	PAD (stable, moderate to severe claudication)	Cilostazol <i>vs</i> placebo	MWD, pain free walking distance	MWD: 44% and 50% (cilostazol 50 mg and 100 mg respectively) and 21.4% in placebo ( $P < 0.05$ ) Pain-free walking distance: 60% and 67% (cilostazol 50 and 100 mg respectively) and 40% in placebo group ( $P < 0.05$ )
BOA <sup>[42]</sup> (2000)	2690	Patients undergone infra-inguinal bypass surgery	Warfarin <i>vs</i> aspirin	Graft occlusion	No observed difference in warfarin compared to aspirin (HR = 0.95; 95%CI: 0.82-1.11)

ABI: Ankle brachial index; CV: Cardiovascular; HR: Hazard ratio; MI: Myocardial infarction; MWD: Mean walking distance.

## CLOPIDOGREL

Clopidogrel is a thienopyridine derivative which inhibits platelet activation by adenosine diphosphate (ADP). There is data to support the effectiveness of clopidogrel as monotherapy in PAD. The first trial to establish this benefit was the CAPRIE trial, a randomized, blinded trial which compared the relative efficacy of clopidogrel (75 mg once daily) and aspirin (325 mg once daily) in patients with high risk of ischemic events. It included 19185 subjects (recent MI, recent ischemic stroke or symptomatic PAD), followed over 1-3 years with mean follow up of 1.9 years. There was a statistically significant 8.7% relative risk reduction ( $P = 0.043$ ; 95%CI: 0.3-16.5) in the composite endpoint of MI, stroke and vascular death in the clopidogrel group. In a subgroup analysis of the PAD population from the CAPRIE trial, the average event rate per year was 3.71% in the clopidogrel arm compared to 4.86% in the

aspirin arm, resulting in a 23.8% relative risk reduction ( $P = 0.0028$ ; 95%CI: 8.9-36.2)<sup>[15]</sup>. This outcome provides support for the inclusion of clopidogrel as a class I recommended antiplatelet agent in the 2016 AHA/ACC guidelines for the management of PAD<sup>[3]</sup>.

We are currently in an era where individualized antiplatelet therapy is becoming an important concept due to the fact that significant major adverse cardiovascular events (MACE) still occur despite clopidogrel use<sup>[16]</sup>. It is possible that clopidogrel resistance due to poor metabolism may contribute to this problem<sup>[17,18]</sup>. Clopidogrel resistance has been demonstrated in populations of patients also identified to have risk factors for PAD, including diabetics<sup>[19]</sup>, smokers<sup>[20]</sup>, and chronic kidney disease patients<sup>[21]</sup>. Doubling the dose of clopidogrel in these patients has proved ineffective<sup>[22]</sup>. In these cases, a more potent P2Y<sub>12</sub> inhibitor such as prasugrel or ticagrelor should be considered as these agents have enhanced platelet inhibition<sup>[23,24]</sup>. This

concept has been validated by Spiliopoulos *et al*<sup>[25]</sup>, who measured platelet reactivity after switching from clopidogrel to ticagrelor in clopidogrel resistant patients and found a significant response in platelet inhibition.

## DIPYRIDAMOLE AND ASPIRIN

The role of dipyridamole, an inhibitor of platelet adenosine uptake, in the management of PAD is debatable. Numerous small studies have shown benefit of combining dipyridamole and aspirin compared to aspirin alone<sup>[26,27]</sup>. The ESPRIT trial published in 2006 was a large randomized controlled trial which compared the efficacy of aspirin and dipyridamole combination therapy against aspirin alone to prevent vascular events within six months after ischemic stroke or TIA. The primary outcome was the composite of death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding, which occurred at a rate of 13% in the aspirin and dipyridamole group and 16% aspirin alone group [hazard ratio (HR) = 0.80, 95%CI: 0.66-0.98; absolute risk reduction 1.0% per year, 95%CI: 0.1-1.8]<sup>[28]</sup>. However, it is uncertain if dipyridamole monotherapy would be superior to aspirin since there is no data available. Additionally, this study was not conducted in the PAD population.

## CILOSTAZOL

Cilostazol, a unique antiplatelet agent, is a phosphodiesterase III inhibitor which reversibly inhibits platelet aggregation and also possesses vasodilatory and antiproliferative properties. It has been widely studied in PAD. A meta-analysis of 8 randomized trials including 2702 PAD subjects with claudication found improvement in maximum and pain-free treadmill walking distance with cilostazol. The mean walking distance of patients taking cilostazol 50 and 100 mg twice daily increased by 44% and 50%, respectively compared to 21.4% in placebo ( $P < 0.05$ ). The pain-free walking distance increased by 60% and 67% in the cilostazol 50 and 100 mg twice daily groups respectively, compared to 40% in the placebo group ( $P < 0.05$ )<sup>[29]</sup>. Hence cilostazol has class IA recommendation to improve symptoms and walking distance in patients with claudication<sup>[3]</sup>. There are some available studies that support an additional value of cilostazol in reducing restenosis and repeat revascularization following endovascular therapy, although these studies are very small and thus hypothesis generating<sup>[30,31]</sup>.

## TICAGRELOR

Ticagrelor is a cyclopentyltriazolopyrimidine which reversibly binds to the platelet ADP P2Y<sub>12</sub> receptor, unlike the thienopyridines. Ticagrelor is metabolized by Cytochrome P450 3A4/5. Its metabolite AR-C124910XX is equally active and potent, reversibly interacting with the platelet P2Y<sub>12</sub> ADP receptor, resulting in the

inhibition of platelet aggregation. Ticagrelor has been reported to have a faster onset of action compared to clopidogrel and, like prasugrel, results in greater platelet inhibition than clopidogrel.

The PLATO trial established the benefit of ticagrelor over clopidogrel in the ACS population. In this study, 18624 ACS patients with or without ST-segment elevation were randomized to receive ticagrelor (180 mg loading dose, then 90 mg twice daily) or clopidogrel (300-600 mg loading dose, then 75 mg daily). All patients received low dose aspirin (75-100 mg daily), although 325 mg was permitted for 6 mo following PCI with stenting. There was a significant reduction in the rate of death from vascular causes, MI, or stroke with ticagrelor compared to clopidogrel (9.8% vs 11.7%,  $P < 0.001$ ), although the rate of non-CABG related major bleeding was higher (4.5% vs 3.8%,  $P = 0.03$ )<sup>[23]</sup>. An analysis of the PLATO population ( $n = 1144$ ) with concomitant PAD, found similar results to the overall trial although it did not reach statistical significance. It also showed a significantly higher rate of the primary endpoint compared to patients without PAD<sup>[32]</sup>.

The recently published EUCLID trial is a direct comparison of ticagrelor and clopidogrel in the PAD population. This is a large, multicenter, randomized, parallel blinded study that enrolled 13885 patients 50 years or older with PAD defined as ABI  $\leq 0.80$  or prior ( $> 30$  d) revascularization of the lower extremities. Patients were randomized to ticagrelor 90 mg twice daily ( $n = 6930$ ) or clopidogrel 75 mg daily ( $n = 6955$ ) and followed for 30 mo. The primary outcome of the study was the incidence of cardiovascular death, MI, or ischemic stroke, which occurred at a rate of 10.8% of the ticagrelor group and 10.6% of the clopidogrel group ( $P = 0.65$ ). There was also no noted difference in secondary outcomes including acute limb ischemia and major bleeding between the two groups. Not surprisingly, there was a higher rate of medication discontinuation in the ticagrelor group due to dyspnea. In summary, among patients with symptomatic PAD, ticagrelor was not superior to clopidogrel in preventing MACE<sup>[33]</sup>.

The THEMIS Study (Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study) is another ongoing trial which is evaluating the efficacy of ticagrelor vs placebo, in addition to standard care including aspirin, for the long-term prevention of major vascular events in patients with type 2 diabetes and coronary atherosclerosis<sup>[34]</sup>.

## VORAPAXAR

Vorapaxar is a protease activator receptor-1 (PAR-1) antagonist, inhibiting the interaction of thrombin with the PAR-1 receptor, thus inhibiting platelet aggregation. The Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic events-Thrombolysis in Myocardial Infarction 50 (TRA



2P-TIMI 50) trial published was a double blinded placebo controlled trial which evaluated vorapaxar for the secondary prevention of atherothrombosis. It included 26449 subjects with a previous history of MI or ischemic stroke within the previous 2 wk-12 mo or PAD, randomized to either vorapaxar 2.5 mg daily or placebo. Concomitant antiplatelet therapy was permitted. The primary endpoint included a composite of cardiovascular death, MI and stroke. Results revealed that the composite endpoint occurred in 9.3% of patients receiving vorapaxar vs 10.5% of patients receiving placebo (HR = 0.87; 95%CI: 0.80-0.94;  $P < 0.001$ ). Subgroup analysis in the PAD population showed no difference in the primary endpoint, however the vorapaxar group showed a significant reduction in limb ischemic events (vorapaxar 2.3% vs placebo 3.9%; HR = 0.58; 95%CI: 0.39-0.86;  $P = 0.006$ ) and the need for peripheral artery revascularization (vorapaxar 18.4% vs placebo 22.2%; HR = 0.84; 95%CI: 0.73-0.97;  $P = 0.017$ ). However, the clinical benefit offered by vorapaxar was offset by a significant increase in the rate of intracranial hemorrhage (vorapaxar 1% vs placebo 0.5%,  $P < 0.001$ )<sup>[35]</sup>.

## DUAL VS MONO ANTIPLATELET THERAPY

Data behind optimal antiplatelet therapy following peripheral endovascular treatment is limited. A recent meta-analysis reviewed dual vs mono antiplatelet therapy trials after endovascular therapy in coronary, carotid and peripheral vascular territories. The authors did not find conclusive data proving superiority of dual antiplatelet therapy over monotherapy in peripheral vascular interventions, however they did note the paucity of data in this regard<sup>[36]</sup>.

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance trial compared the effect of combination aspirin and clopidogrel vs aspirin monotherapy in patients with either clinically documented vascular disease or risk factors for atherothrombotic disease. It included 15603 patients randomized to either clopidogrel (75 mg/d) plus low dose aspirin (75-162 mg) or placebo plus low dose aspirin for a mean follow up of 28 mo. Dual antiplatelet therapy did not significantly reduce the rate of MI, stroke or cardiovascular death (6.8% in clopidogrel plus aspirin group and 7.3% in aspirin monotherapy group,  $P = 0.22$ )<sup>[37]</sup>. In a subgroup analysis of patients with symptomatic PAD, no benefit was derived from dual antiplatelet therapy<sup>[38]</sup>.

The MIRROR study was a randomized double blinded trial, enrolling only 80 patients, which assessed the influence of dual antiplatelet therapy with aspirin and clopidogrel vs aspirin alone on local platelet activation in patients with PAD treated with endovascular therapy. Primary endpoints were local concentrations of platelet activation markers  $\beta$ -throm-

boglobulin and CD40L and the rate of clopidogrel resistance. Secondary endpoints included the clinical development of target lesion revascularization (TLR), stenosis, ABI, adverse events and days spent in hospital because of TLR, 6 mo after the intervention. The duration of therapy was 6 mo post intervention and results showed reduced peri-interventional platelet activation and improved functional outcome in the dual antiplatelet therapy group. The median peri-interventional concentration of  $\beta$ -TG was 224.5 vs 365.5 ( $P = 0.03$ ) in the clopidogrel and placebo group respectively. The concentration of CD40L was 127 in the clopidogrel group and 206.5 in the placebo group ( $P = 0.05$ )<sup>[39]</sup>.

Finally, the combination of ticagrelor and aspirin was studied against aspirin alone in the PEGASUS-TIMI 54 trial to evaluate the benefit of prolonged treatment with dual antiplatelet therapy. A total of 21162 patients with a history of myocardial infarction 1 to 3 years prior, were randomized to receive placebo or two different regimens of ticagrelor, 60 mg twice daily or 90 mg twice daily. All patients were recommended to take aspirin, with 97% taking aspirin 75-100 mg daily. The trial continued for a median of 33 mo with a primary composite endpoint of cardiovascular death, MI or stroke. The rate of the primary endpoint was 9.04% in the placebo (aspirin only) arm, 7.77% in the ticagrelor 60 mg arm and 7.85% in the ticagrelor 90 mg arm ( $P = 0.004$  ticagrelor 60 mg vs placebo;  $P = 0.008$  ticagrelor 90 mg vs placebo). This benefit was counterbalanced by a significant increase in TIMI major bleeding with both ticagrelor groups compared to placebo<sup>[40]</sup>.

The symptomatic PAD population from this trial included 1143 patients and was separately analyzed. As expected, the PAD population had a higher rate of major cardiovascular events compared to the population without PAD (19.3% vs 8.4%,  $P < 0.001$ ). Both ticagrelor groups had a lower incidence of the primary endpoint compared to placebo, but only the 60 mg arm had a statistically significant reduction. There was no difference in the rates of major bleeding between the three groups, although the numbers of patients in each group were small<sup>[41]</sup>.

## ROLE OF ANTICOAGULANT THERAPY

### Vitamin K antagonists

There is limited information describing the role of oral anticoagulation, with or without antiplatelet therapy, in patients with PAD. Warfarin and acenocoumarol, both vitamin K antagonists, have been studied in a few PAD population based studies. The Dutch Bypass Oral Anticoagulants or Aspirin (BOA) trial evaluated anticoagulation with warfarin (INR goal 3.0-4.5) compared to aspirin 80 mg daily in 2690 patients undergoing infra-inguinal bypass surgery. There was no observed difference in the patency rates with warfarin

compared to aspirin, respectively (HR = 0.95; 95%CI: 0.82-1.11). Subgroup analysis revealed that patients with vein grafts benefited from lower rates of graft occlusion (HR = 0.69; 95%CI: 0.54-0.88) in the warfarin group. However, patients with prosthetic grafts experienced higher rates of graft occlusion on warfarin (HR = 1.26; 95%CI: 0.82-1.11). As predicted, the warfarin population experienced an increased number of major bleeding episodes compared to aspirin (HR = 1.96; 95%CI: 1.42-2.71). The BOA trial reiterated that only selected patients with PAD stand to benefit from chronic warfarin therapy, particularly patients undergoing lower extremity bypass with vein grafts<sup>[42]</sup>.

The WAVE trial compared the efficacy and safety of combination therapy with an antiplatelet agent (aspirin 81-325 mg, ticlopidine or clopidogrel) and a vitamin K antagonist (warfarin or acenocoumarol) (target INR, 2.0 to 3.0) to antiplatelet therapy (aspirin, ticlopidine or clopidogrel) alone in patients with PAD. Results showed that the use of combination therapy did not prevent major cardiovascular complications to a greater extent than antiplatelet therapy alone (combination therapy group 12.2% and antiplatelet therapy alone 13.3%; 95%CI: 0.73-1.16;  $P = 0.48$ ). Instead, combination therapy was associated with a significantly higher incidence of life-threatening bleeding (4.0% vs 1.2%; 95%CI: 1.84-6.35;  $P < 0.001$ ) and moderate bleeding (2.9% vs 1.0%; 95%CI: 1.43-5.58;  $P = 0.002$ )<sup>[43]</sup>. Due to lack of evidence to support any benefit of the addition of warfarin to antiplatelet therapy in the reduction of thrombotic events in patients with PAD, oral anticoagulant therapy is highlighted as a class III (no benefit and possible harm) recommendation in the most recent AHA/ACC guidelines<sup>[3]</sup>.

## DIRECT ACTING ORAL ANTICOAGULANT AGENTS

Studies are currently ongoing to investigate the potential role of direct acting oral anticoagulant agents (DOAC) (dabigatran, rivaroxaban, apixaban and edoxaban) therapy in the PAD population. Apixaban, edoxaban and rivaroxaban are all factor Xa inhibitors, while dabigatran is a direct thrombin inhibitor. Preliminary results from the Cardiovascular Outcomes for People using Anticoagulation Strategies trial have recently been released, following early termination due to clinical benefit. In this study, 27402 patients with documented atherosclerosis (coronary and/or peripheral) were randomized to either 2.5 mg of rivaroxaban twice-daily plus aspirin 100 mg daily, 5 mg rivaroxaban twice-daily monotherapy or aspirin 100 mg once daily monotherapy. Primary endpoints were defined as the time from randomization to the first occurrence of either myocardial infarction, stroke or cardiovascular death and the time from randomization to the first occurrence of major bleeding. The primary efficacy outcome data was not released, but the

company stated that the trial reached its prespecified criteria for superiority in at least one of the rivaroxaban-based arms compared to aspirin alone. Bleeding information was not disclosed, although the company release mentioned "confirmation of the existing safety profile"<sup>[44,45]</sup>. In a similar trial, edoxaban, a once-daily factor Xa inhibitor is being evaluated in a randomized multicenter study in patients with PAD to assess the efficacy of its addition to aspirin compared to a clopidogrel plus aspirin regimen in preventing stenosis or occlusion in patients undergoing femoro-popliteal endovascular intervention<sup>[46]</sup>.

## ANTIPLATELET THERAPY AND PATENCY POST PERIPHERAL ENDOVASCULAR TREATMENT

Restenosis after percutaneous transluminal angioplasty is a major limitation for favorable outcomes, and is influenced by a number of factors such as vascular inflammation, platelet activation and aggregation. Data on post endovascular intervention duration of treatment with antiplatelet therapy is insufficient. There is high rate of re-occlusion and target lesion stenosis post angioplasty. Patency rate after PTA is impacted by variables; such as length of diseased segments, severity of the disease in run-off arteries, the number of lesions treated and presence of cardiovascular risk factors<sup>[1,47]</sup>.

The ideal antiplatelet regimen and appropriate duration of treatment has not been well validated in clinical trials. The combination of aspirin and dipyridamole trended toward a superior impact on patency after femoro-popliteal angioplasty compared with vitamin K antagonists at 3, 6, and 12 mo. Aspirin 50 to 300 mg, with or without dipyridamole, given before femoro-popliteal endovascular treatment, reduced the incidence of re-occlusion at 6 and 12 mo without any safety concerns when compared with no therapy or vitamin K antagonists<sup>[48]</sup>. The Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularization study which was designed to assess the efficacy and safety of this regimen after femoro-popliteal PTA was stopped prematurely because of insufficient randomization numbers. Off-label use of dual antiplatelet therapy in many patients led to its failure. The combination of clopidogrel and aspirin showed higher inhibition of platelets before and after angioplasty in patients undergoing endovascular intervention for claudication<sup>[49]</sup>. As mentioned previously, in the MIRROR study, treatment with clopidogrel and aspirin reduced target lesion revascularization improving the patency of treated lesions and decrease the need for revascularization<sup>[39]</sup>.

Lower extremity bypass is another important treatment for patients with symptomatic PAD when less-invasive endovascular procedures are not an

**Table 3** Current available guidelines addressing antiplatelet therapy for peripheral arterial disease

Class of recommendation	Guidelines
Class Ia	Aspirin in daily doses of 75 to 325 mg or clopidogrel 75 mg/d is recommended to reduce the risk of MI, stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD
Class IIa	Antiplatelet therapy is reasonable to manage asymptomatic individuals with an ABI less than or equal to 0.90 to reduce the risk of MI, stroke, or vascular death
Class IIb	Dual-antiplatelet therapy (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization

PAD: Peripheral arterial disease; MI: Myocardial infarction.

option because of anatomic or technical considerations. Graft failure is related to multiple factors including type of graft material, site of anastomosis, rate of stenosis, type of antiplatelet used post procedure and duration of medical treatment post intervention. Prosthetic grafts with anastomosis to the tibial arteries seem to have highest rate of failures. Most grafts fail in the first two years, mainly attributed to graft stenosis<sup>[50]</sup>.

Antiplatelet therapy with aspirin improves grafts patency and limb salvage. Patients receiving a prosthetic graft were more likely to benefit from administration of antiplatelet agents than those treated with a venous graft<sup>[51]</sup>. Risk of graft occlusion while on single antiplatelet therapy; typically aspirin, still remains high. Incidence reported to be 15% per year when a vein is used and 20% with synthetic material (polytetrafluoroethylene) rising to 45% and 75%, respectively, for below-knee grafts<sup>[52,53]</sup>. In the CASPAR trial, combination of aspirin and clopidogrel showed statistically significant decrease in prosthetic graft failure with decreasing rate of occlusion and amputation to levels similar to those seen with venous grafts<sup>[54]</sup>.

## DISCUSSION

### Current practice

Dual antiplatelet therapy is often used in patients undergoing infra-inguinal angioplasty and stenting as mentioned in a survey by Allemang *et al*<sup>[55]</sup> from the vascular surgery community itself, which revealed that the most common antiplatelet therapy after lower extremity endo-luminal therapy was a combination of aspirin and clopidogrel. Duration of therapy also varied, with 1 to 3 mo as the most common time frame. Therapy use increased with distal endovascular treatment and with the placement of stents and there was no consensus over the duration of therapy<sup>[55]</sup>. However, there is no robust data to support such practice. Rationale for shorter duration of antiplatelet therapy post endovascular interventions in patients with PAD is primarily drawn from the fact that there is endothelial damage from balloon angioplasty and stenting is generally reserved as a last resort for treating flow limiting localized complications. However, in the current era, peripheral vascular intervention invariably involves atherectomy and significantly longer length of lesions

compared to those seen in the coronary realm. This translates to more extensive endothelial damage and subsequent re-endothelialization which would make longer duration of dual antiplatelet therapy appear intuitive.

### Current guidelines

The recently updated AHA/ACC guidelines for the management of patients with PAD, recommend either aspirin in daily doses of 75 to 325 mg or clopidogrel 75 mg per day as safe and effective antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD (class IA). A Class IIa recommendation is given for considering antiplatelet therapy to manage asymptomatic individuals with an ABI less than or equal to 0.90. Dual antiplatelet therapy with aspirin and clopidogrel may be reasonable after lower extremity revascularization (class IIb), due to the lack of well designed, large clinical trials<sup>[3]</sup>. A summary of the current AHA/ACC Guideline recommendations for antiplatelet therapy in PAD is provided in Table 3.

## CONCLUSION

There have been significant advances in open surgical and endovascular modalities for the treatment of peripheral vascular disease. Long term patency rates for either modality continue to improve, however, randomized controlled trial data comparing the two options head to head are lacking. There appears to be a consensus emerging that endovascular therapy when feasible should be attempted first, although robust randomized data is still needed to support this approach. With contemporary atherectomy techniques, drug coated balloons and stents, a bigger armamentarium is available for immediate and long term success of endovascular therapy. Similarly there is lack of data regarding post intervention medical therapy. Although dual antiplatelet therapy with aspirin and clopidogrel is commonly used, the duration of such therapy is highly variable without a strong recommendation in practice guidelines. Practice patterns for dual antiplatelet therapy are influenced and extrapolated from data available for PCI. It is apparent that there is paucity of clinical trial data for the treatment of peripheral vascular disease

and subsequent care. Additional data is warranted from large scale multicenter randomized controlled trials and observational studies to assess the optimal medical treatment and duration of medical therapy across the spectrum of PAD.

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