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TECHNICAL NOTE

Personalized Antiplatelet Therapy Following Endovascular Revascularization in Peripheral Artery Occlusive Disease: A Novel Concept

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Case: A 73 year old patient with a longstanding history of peripheral artery occlusive disease (PAOD) presented with an acute on chronic progression of symptoms, based on a long occlusion of the superficial femoral artery (SFA), which was treated by thrombosuction, percutaneous transluminal angioplasty, and SFA stenting. Post-procedural dual antiplatelet therapy was initiated and subsequently adjusted based on platelet reactivity testing.
Discussion: Increasingly complex arterial lesions are treated by an endovascular approach; however, long-term patency rates are often disappointing. In order to optimize the patency rates (dual) antiplatelet therapy is initiated. It is known that a substantial proportion of patients have high platelet reactivity despite the use of antiplatelet drugs. Several methods have been published to test the individual response to different antiplatelet drugs. There is evidence that adjusting antiplatelet therapy based on platelet reactivity testing results in a reduction of cardiovascular events and bleeding complications; however, the optimal test and the exact role of personalized antiplatelet therapy in PAOD is currently unknown.
Conclusion: Although some important hurdles should be overcome before routine implementation, the concept of post-procedural antiplatelet therapy in patients with PAOD is advocated in order to optimize the results of endovascular interventions, as apparent from the presented case.

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CASE

A 73 year old male with acute progression of chronic peripheral artery occlusive disease (PAOD) Rutherford stage 5, visited the outpatient clinic of a tertiary vascular referral center. The patient had a medical history of kidney transplantation, stage 3 chronic kidney disease (CKD), deep venous thrombosis complicated by a pulmonary embolism, and intermittent claudication for which he had undergone stenting of both common iliac arteries 10 years earlier and had been prescribed aspirin. A digital subtraction angiography (DSA) was performed, which revealed a 23 cm long occlusion of the superficial femoral (SFA) and proximal anterior tibial artery (Fig. 1A). Thrombosuction (AngioJet, Boston Scientific, Marlborough, MA, USA) and subsequent percutaneous transluminal angioplasty (PTA) of the SFA were performed (Fig. 1B). Because of multilevel residual stenoses, three self expandable stents and a balloon expandable stent were placed in the SFA over a total length of 27 cm with satisfactory results (no residual stenosis >30%). After the procedure, dual antiplatelet therapy (DAPT) was initiated: clopidogrel (loading dose 300 mg) was added to the aspirin. The next day a VerifyNow $P2Y_{12}$ assay (Accumetrics, San Diego, CA, USA) and a CYP2C19 polymorphism DNA test (Spartan RX CYP2C19, Spartan Bioscience Inc., Ottawa, Canada) were performed, which showed 0% platelet inhibition and two loss of function CYP2C19 alleles, respectively, which suggested that clopidogrel was not effective. Therefore, clopidogrel was switched to the stronger $P2Y_{12}$ inhibitor, prasugrel. A VerifyNow showed an effective platelet inhibition on prasugrel (41% inhibition, PRU 171). At the 6 month follow up the patient did not report any pain, and duplex ultrasound confirmed patency of the stents without restenosis.

Endovascular revascularization

Nowadays, minimally invasive endovascular techniques are often the first line of therapy in PAOD. The choice of the specific endovascular technique depends on various factors,

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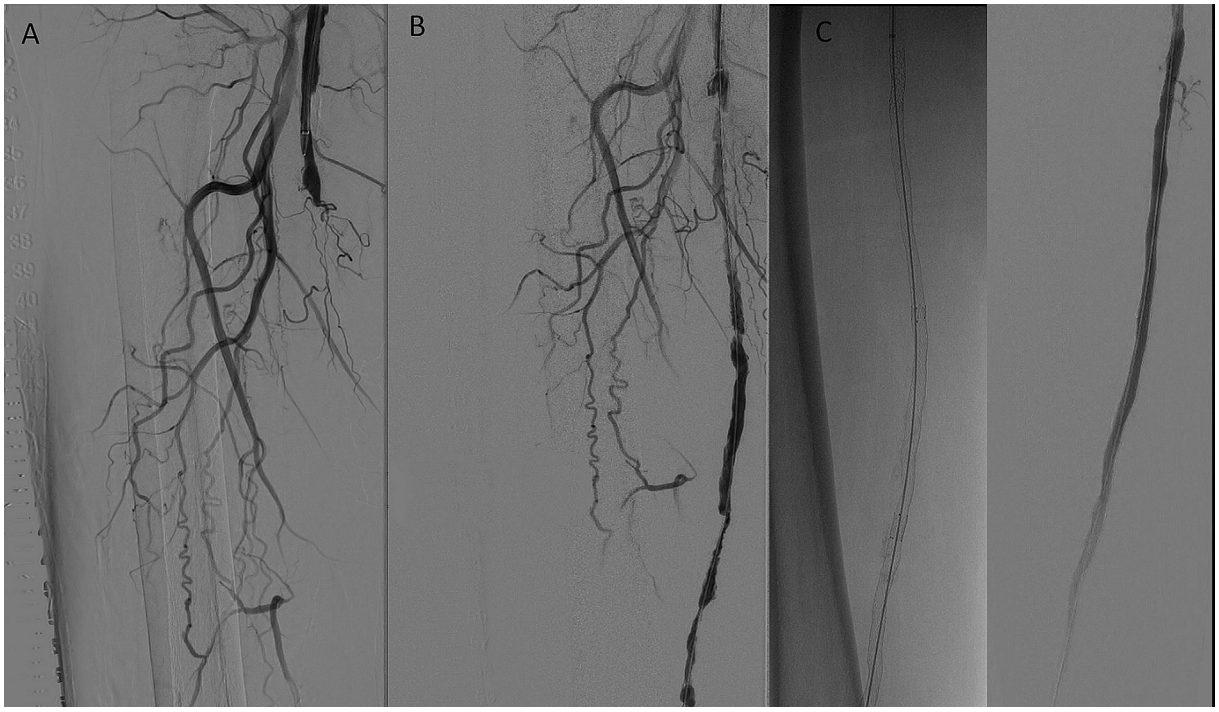

Figure 1. (A) Digital subtraction angiography (DSA), which shows a 23 cm occlusion in the superficial femoral artery. (B) DSA after two thrombosuctions with the Angiojet catheter. (C) DSA after percutaneous transluminal angioplasty and stenting.

such as the cause, length and degree of stenosis or occlusion, and the duration of the occlusion. Mechanical thrombectomy or thrombosuction is most effective in removing fresh thrombi, causes minimal peripheral embolization, and is less time consuming than medicinal thrombolysis.[1] PTA is usually the preferred choice in limited disease such as stenosis or occlusions up to 10 cm in length and stenting is advised when there is a residual stenosis of $\geq$30—50% or a flow limiting dissection.[2,3]

One year primary patency rates of balloon angioplasty in long femoral occlusions vary from 27% to 43.5%,[4] which is improved by the use of drug eluting balloons (primary patency up to 76.1%).[5] Primary patency at 1 year for stenting of long femoral occlusions varies from 64.8% to 66% and secondary patency rates vary between 70% and 83%, which depends on the characteristics of the atherosclerotic lesion and type of stent.[5—8] Because of the acute on chronic presentation in the current case, due to a total and likely recent occlusion of the SFA, mechanical thrombectomy followed by PTA and stenting due to residual multilevel stenosis was chosen.

Post-procedural antiplatelet therapy

The fast and continuous evolution of endovascular technologies allows for successful revascularization of increasingly complex atherosclerotic lesions. Lifelong antiplatelet therapy (APT) is generally recommended to promote patency after peripheral endovascular interventions of the femoropopliteal segment, although no evidence based guidelines exist.[1] Nowadays, many different types of antiplatelet regimen are used (Table 1). Studies on APT in patients with PAOD have major limitations due to small study populations and potential risk of bias.[9] This lack of high quality evidence leads to a great (inter)national variety in the administered APT, duration of treatment, and platelet reactivity test used to assess the effect of APT.[10] In cardiology trials, a relative risk reduction of secondary cardiovascular events (cardiovascular death, myocardial infarction or any revascularization) of around 30% is seen when adding clopidogrel to aspirin after percutaneous coronary intervention (PCI).[11—13] It is not known exactly whether this is the case in PAOD; however, a similar risk reduction is assumed.

Prior to PTA and stenting of femoropopliteal arteries, a loading dose of clopidogrel is often added to aspirin, and DAPT is continued for 1—3 months after PTA. The rationale for this practice is largely based on extrapolation of data derived from percutaneous coronary interventions (PCIs), and is not supported by international guidelines.[1,14]

The patient in this case received a loading dose of 300 mg of clopidogrel after the procedure followed by a maintenance dose of 75 mg once daily for 6 months. Several recent cardiology trials suggest that a loading dose of 600 mg might be more effective in preventing major adverse cardiac events, without increasing the risk of bleeding.[15] However, for PAOD patients there is no evidence that suggests superiority of a higher loading dose.

Analogous with observations in patients undergoing PCI, a natural variation in response to APT can be expected among patients undergoing peripheral revascularization. A recently published review showed that high on aspirin platelet reactivity (HAPR) occurred in 22.2% of the patients in a pooled analysis of 102 studies containing a total of

Table 1. Different types of antiplatelet regimens.

Class	Drugs	Mechanism of action	Pros	Cons
Cyclo-oxygenase inhibitors	Aspirin Carbasalate calcium Triflusidal	Irreversibly inhibits the enzyme COX, resulting in reduced platelets production of thromboxane A_2 (powerful vasoconstrictor that lowers cyclic AMP and acts as secondary platelet activator)	Economical Also analgesic, anti-inflammatory and antioxidant properties	Risk of gastrointestinal bleeding Resistance
P2Y12 inhibitors (Thienopyridines)	Clopidogrel	Binds irreversibly to the ADP receptors (P2Y12 receptors), ensuring a inhibition of the ADP pathway Prodrug that needs to be metabolized via the CYP by the liver	Economical	Requires CYP2C19 for its metabolization Slow onset of action Inter-individual variability
	Prasugrel	Same mechanism of action as clopidogrel/ticlopidine Needs transformation to an active metabolite via the CYP system in a similar manner to clopidogrel	Faster onset of action than clopidogrel No effect of CYP2C19 genotype on clinical cardiovascular event rates	Increased bleeding risk in patients >75 years, <60 kg and/or with CVA/TIA in medical history More expensive than clopidogrel
	Ticlopidine	Same mechanism of action as clopidogrel/prasugrel	Suitable when aspirin has failed or is not tolerated.	Rare, but serious side effects of neutropenia and TTP
P2Y12 inhibitors (Nucleotide analogues)	Ticagrelor	Reversible P2Y12 receptor antagonists. Unlike the thienopyridines, ticagrelor is not a prodrug and does not require metabolic activation	More effective than thienopyridines in prevention of vascular death, MI, or stoke	Twice daily administration Increased bleeding risk
	Cangrelor	Same mechanism of action as ticagrelor	Fast acting drug, suitable for bridging surgery patients who require P2Y12 inhibition	IV administration
Phosphodiesterase inhibitors	Cilostazol	Inhibits phosphodiesterase enzymes that break down cAMP, (resulting in increasing cellular cAMP levels and thereby blocking of platelet aggregation response to ADP) and/or cGMP	Effective in increasing pain free walking distance in patient with CI	Dangerous with heart failure
	Dipyridamole	Same mechanism of action as cilostazol	Effects of dipyridamole and aspirin on platelet behaviour are additive	High dose causes vasodilatation Twice daily administration
Glycoprotein IIb/IIIa inhibitors	Abciximab Eptifibatide Tirofiban	Blocks GPIIb/IIIa, the platelets receptor for fibrinogen and von Willebrand factor	Rapid onset of action	IV administration

ADP = adenosinediphosphate; cAMP = cyclic adenosine monophosphate; cGMP = Cyclic guanosine monophosphate; CI = claudication intermittens; COX = cyclo-oxygenase inhibitors; CVA = cerebrovascular accident; CYP = cytochromes P450; GPIIb/IIIa = glycoprotein IIb/IIIa; IV = intravenous; TIA = transient ischemic accident; TTP = thrombotic thrombocytopenic purpura.

44,098 patients with coronary artery, cerebrovascular, or peripheral arterial disease who had been treated with aspirin with or without clopidogrel.[16] Patients with HAPR had an increased risk of future cardiovascular events (combined endpoint of cardiovascular death, myocardial infarction, stent thrombosis, stroke, acute limb ischemia, peripheral revascularization, and acute peripheral occlusion; RR 2.09, 95% CI 1.77−2.47). The number of non-responders for clopidogrel was even higher: 40.4% of patients were diagnosed with high on clopidogrel platelet reactivity (HCPR), which was also associated with an increased risk of cardiovascular events (RR 2.80, 95% CI 2.40−3.27). Furthermore, the incidence of HAPR and HCPR is significantly higher in patients with chronic kidney disease and diabetes mellitus, both common risk factors in PAOD.[17,18]

Platelet reactivity testing

Multiple tests are available for measuring platelet reactivity (Table 2); the different tests measure diverse pathways of thrombus formation and the reproducibility and applicability vary strongly between these tests.[19] To date, none of the available tests has proven its superiority in predicting thrombotic or bleeding events. However the VerifyNow, a commercially available point of care test, shows congruent results with the light transmittance aggregometer and is widely studied in clinical trials.[16]

Personalized antiplatelet therapy

The association of HAPR and HCPR with increased risk of thrombotic events sparked the concept of tailoring APT based on platelet reactivity measurements. The basis of the concept is that switching APT (to a higher dose or other APT) with the aim of achieving lower platelet reactivity would result in fewer thrombotic events, especially in high risk patients, such as patients with diabetes mellitus or renal failure. Multiple studies suggest that not only high platelet reactivity (HPR) should be an indicator to adjust APT, but that low platelet reactivity (LPR) should also be considered as a reason to adapt APT due to the increased risk of gastrointestinal and intracerebral bleeding complications.[20,21] These data suggest the presence of a therapeutic window for platelet reactivity with HPR at one end and LPR at the other end of the spectrum.

The data on HPR and LPR might elicit the idea that simply testing platelet reactivity in response to antiplatelet agents and adjusting the regimen based on the results will lead to improved clinical outcomes. However, the clinical benefit of tailoring APT based on platelet function tests in patients undergoing PCI has shown disappointing results thus far. Two major trials (GRAVITAS, $n = 2{,}214$[22] and ARCTIC, $n = 240$[23]) showed no difference in their primary composite endpoint (death of cardiovascular causes, non-fatal acute myocardial infarction, and ST elevation) or bleeding complications after 6 months in GRAVITAS and 1 year in ARCTIC, when comparing standard APT with tailored APT. However, a few smaller studies showed a beneficial effect of tailored versus standard APT on a composite endpoint (e.g. cardiac death, stent thrombosis, recurrent ACS, recurrent PCI <1 year) without any difference in bleeding complications.[24−27] The two largest trials included a low risk population, counteracted HPR primarily with a higher dose of the same APT instead of switching APT, and used a single platelet reactivity test, which could have resulted in the lack of effect of tailored APT.

PAPT in patients with PAOD

Most research regarding personalized antiplatelet therapy (PAPT) has been performed in patients with coronary artery disease (CAD) undergoing PCI. Randomized controlled trials to investigate the potential benefit of PAPT in patients with PAOD are mandatory. However, several questions need to be answered before this treatment strategy can be implemented in clinical trials.[28]

1. What is the incidence of HAPR and HCPR in patients with PAOD?
2. Is high and low platelet reactivity in patients with PAOD related to the occurrence of respectively thrombotic or bleeding events during follow up?
3. What are the optimal cut off values of different platelet reactivity tests to predict thrombotic or bleeding events?
3. Does HPR change over time and what is the optimal moment for platelet reactivity testing?
4. What is the optimal alternative APT for patients with PAOD displaying HAPR or HCPR?

Importantly, low patency rates after PTA leave room for randomized controlled trials to prove significant benefit of PAPT compared with standard care after the questions above are answered. Since the risk of hemorrhagic complications might increase with the use of novel and dual APT, the use of a combined clinical benefit endpoint, comprising both thrombotic and bleeding events, would be advised in potential future trials.

CONCLUSION

Technological improvements in the endovascular armamentarium have made increasingly complex atherosclerotic lesions eligible for endovascular interventions, which has led to a mainly endovascular first strategy in PAOD. However, the patency rates of endovascular procedures still leave room for improvement and optimization of post-procedural medical therapy, including personalized APT, is therefore essential. Current evidence regarding the optimal APT after peripheral endovascular revascularization is inconclusive. It is reasonable to expect that personalized APT, based on platelet reactivity measurements, may improve outcomes. However, some important conditions should be fulfilled prior to routine implementation of personalized APT in clinical practice, such as determination of the optimal platelet reactivity test, and the optimal type and duration of (D)APT.

Table 2. Commonly used platelet reactivity test.

Platelet reactivity testing	Technique	Pros	Cons
VerifyNow	Platelets are stimulated with agonists, causing platelet activation and precipitating to the fibrinogen coated beats in the cartridges. Degree of platelet is based on remaining optical light transmittance through the cartridges	Easy and rapid point of care test Aspirin, P2Y12, and GPIIb/IIIa inhibitor monitoring	Cut off values differ per patient population Low correlation with golden standard (LTA)
Light transmittance aggregometry (LTA)	Citrated whole blood is centrifuged, resulting PRP and PPP. After stimulation of the platelets with agonists, formed aggregates modify optical density of the samples, expressed as % platelet aggregation	Gold standard due to long lasting experience	Manually conducted test therefore reproducibility between laboratories is low Time consuming
Platelet function analyzer (PFA)	Blood is aspirated at high shear rates through cartridges with either collagen and epinephrine or collagen and ADP, which induce platelet adhesion, activation and aggregation. This leads to rapid occlusion of the aperture and cessation of blood flow, defined as closure time	Rapid and automatic	Originally designed as screening instrument for thrombopathy and thus better standardized compared to monitoring of APT
Multiplate	Activated platelets, after stimulation with agonists, adhere to metal sensor wires and electrical resistance increases	Aspirin and P2Y12 monitoring	Semi-automatic; preparation of the agonists and pipetting is necessary to perform the tests
Vasodilator stimulated phosphoprotein (VASP)-phosphorylation assay	ADP inhibits VASP (an intracellular platelet protein) phosphorylation through the P2Y12 receptor. Persistent VASP phosphorylation, as measured with flow cytometry, correlates with P2Y12 receptor inhibition, reflecting the effect of the P2Y12 inhibitor	Standardized kit	Only applicable for monitoring of P2Y12 inhibitors Time consuming

ADP = adenosinediphosphate; APT = antiplatelet therapy; PRP = platelet rich plasma; PPP = platelet poor plasma.

In conclusion, although some important hurdles should be overcome prior to routine implementation, the concept of individualized medicine regarding the type of endovascular intervention is advocated, but foremost post-procedural APT in patients with PAOD to optimize the results of endovascular interventions, as apparent from the presented case.

CONFLICT OF INTEREST

None.

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