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On-Treatment Platelet Reactivity is a Predictor of Adverse Events in Peripheral Artery Disease Patients Undergoing Percutaneous Angioplasty

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WHAT THIS PAPER ADDS

On-treatment platelet reactivity, the so called antiplatelet resistance, has been associated with cardiovascular events in patients with coronary artery disease undergoing PCI. In the present study of PAD patients, the entity of platelet inhibition on dual antiplatelet therapy is associated not only with thrombotic, but also with bleeding complications, suggesting that a "therapeutic window" exists, within which the predicted risk of ischaemic and bleeding complications is the lowest. Future studies are needed to evaluate the potential utility of assessing platelet function, in the clinical setting of PAD, to ensure the patient is given the best tailored antiplatelet therapy.

Objectives: Few data are available on the association between a different entity of platelet inhibition on antiplatelet treatment and clinical outcomes in patients with peripheral artery disease (PAD). The aim of this study was to evaluate the degree of on-treatment platelet reactivity, and its association with ischaemic and haemorrhagic adverse events at follow up in PAD patients undergoing percutaneous transluminal angioplasty (PTA).

Methods: In this observational, prospective, single centre study, 177 consecutive patients with PAD undergoing PTA were enrolled, and treated with dual antiplatelet therapy with aspirin and a P2Y12 inhibitor. Platelet function was assessed on blood samples obtained within 24 h from PTA by light transmission aggregometry (LTA) using arachidonic acid (AA) and adenosine diphosphate (ADP) as agonists of platelet aggregation. High on-treatment platelet reactivity (HPR) was defined by LTA $\geq$ 20% if induced by AA, and LTA $\geq$ 70% if induced by ADP. Follow up was performed to record outcomes (death, major amputation, target vessel re-intervention, acute myocardial infarction and/or myocardial revascularisation, stroke/TIA, and bleeding).

Results: HPR by AA and HPR by ADP were found in 45% and 32% of patients, respectively. During follow up (median duration 23 months) 23 deaths (13%) were recorded; 27 patients (17.5%) underwent target limb revascularisation (TLR), two (1.3%) amputation, and six (3.9%) myocardial revascularisation. Twenty-four patients (15.6%) experienced minor bleeding. On multivariable analysis, HPR by AA and HPR by ADP were independent predictors of death [HR 3.8 (1.2–11.7), $p = .023$ and HR 4.8 (1.6–14.5), $p = .006$, respectively]. The median value of LTA by ADP was significantly lower in patients with bleeding complications than in those without [26.5% (22–39.2) vs. 62% (44.5–74), $p < .001$). LTA by ADP $\leq$ 41% was independently associated with bleeding HR 14.6 (2.6–24.0), $p = .001$] on multivariable analysis.

Conclusions: In this study a high prevalence of on-clopidogrel and aspirin high platelet reactivity was found, which was significantly associated with the risk of death. Conversely, a low on-clopidogrel platelet reactivity was associated with a higher risk of bleeding. These results document that the entity of platelet inhibition is associated with both thrombotic and bleeding complications in PAD patients.

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INTRODUCTION

Peripheral artery disease (PAD) is most commonly caused by atherosclerosis, and is characterised by an increased risk of myocardial infarction, stroke, and cardiovascular death.[1] Given the markedly elevated cardiovascular risk among patients with PAD, antiplatelet therapy would be expected to be of great benefit. However, there is little evidence that antiplatelet therapy can alter the natural history of PAD, both in asymptomatic and symptomatic patients, and which antiplatelet agent could be the best option is not well defined. Although dual antiplatelet therapy (DAPT) is generally recommended after peripheral vascular intervention, this is largely based on extrapolation from coronary percutaneous intervention data.[2] In this setting a different entity of on-treatment platelet function inhibition is associated with different clinical outcomes. Several studies have demonstrated that high on-treatment platelet reactivity (HPR), so called antiplatelet resistance, is associated with an increased risk of ischaemic complications (especially stent thrombosis),[3–5] and there is a growing body of evidence that, on the contrary, low on-treatment platelet reactivity (LPR) could be associated with bleeding risk.[6] High on-aspirin platelet reactivity measured by light transmission aggregometry (LTA) induced by arachidonic acid (HPR by AA) and high on-clopidogrel platelet reactivity measured by LTA induced by adenosine diphosphate (ADP) (HPR by ADP) have been used to defined the variable responses to antiplatelet therapy in major clinical studies. Concerning the role of HPR in PAD, few data are available in the literature. HPR on-clopidogrel has been associated with an increased risk of adverse events (cardiovascular death, major amputation, and re-intervention) during follow up in patients with PAD undergoing percutaneous transluminal angioplasty (PTA).[7–9] The role of so called aspirin resistance in PAD is not completely defined; indeed, available studies are not homogenous in terms of clinical presentation of the disease, time of blood sampling, and methods used for the determination of HPR on-aspirin therapy.[10–17]

The aim of this study was to evaluate the degree of on-treatment platelet reactivity, and the association between the entity of platelet inhibition and ischaemic and haemorrhagic adverse events at follow up, in patients with PAD undergoing PTA with or without stenting.

MATERIALS AND METHODS

Study population

The study enrolled 177 PAD patients (118 males, median age 75 years) undergoing primary and elective PTA, with or without stenting, who were referred to the University Hospital of Florence, Italy from January 2012 to December 2013. Inclusion criteria were ankle brachial index (ABI) <0.9 or >1.3 and age >18 years. Patients aged <18 years and/or unable to sign the informed consent were excluded. A platelet count $<100 \times 10^9$/L, a haemoglobin <9 g/dL, and a haematocrit $<$ 28% were additional exclusion criteria. The study was approved by the local ethics committee. All patients gave written informed consent.

Percutaneous transluminal angioplasty and antiplatelet management

All interventions were performed according to current standards, and the use and type of stent implanted was at the discretion of the operator. All patients, unless they were already on antiplatelet therapy for a previous coronary revascularisation, underwent a P2Y12 inhibitor loading dose. Patients were discharged on DAPT with a P2Y12 inhibitor and aspirin. Clopidogrel was the first choice P2Y12 inhibitor (according to the guidelines) unless patients were on treatment with prasugrel or ticagrelor for a recent acute coronary syndrome. Aspirin, 100—325 mg once daily, was recommended for an indefinite period, and a P2Y12 inhibitor for at least 6 months.

Platelet function assessment

Platelet function was assessed by light transmission aggregometry (LTA) (APACT4, Helena Laboratories, Milan, Italy), performed on platelet rich plasma, using AA and ADP as agonists of platelet aggregation. Blood samples anticoagulated with 0.109 M sodium citrate (ratio 9:1) were obtained within 24 h of PTA. Platelet rich plasma, obtained by centrifuging whole blood for 10 min at 200 g, was stimulated with 1 mM AA and 10 μM ADP. According to literature data, HPR was defined by LTA $\geq$ 20% if induced by AA, and LTA $\geq$70% if induced by ADP.[18]

Follow up

Follow up was performed to record the occurrence of ischaemic and bleeding events. All patients had scheduled examinations at 1, 6, and 12 months and then annually thereafter. Adherence to antiplatelet treatment was assessed during scheduled or unscheduled examinations. All other possible information derived from hospital readmission or by the referring physician, relatives, or municipality live registries was collected.

Outcomes

The study's outcomes were death, major amputation, target vessel re-intervention (TVR), acute myocardial infarction and/or myocardial revascularisation, stroke/TIA, and bleeding, classified as major and non-major according to the TIMI classification.[19]

Statistical analysis

Statistical analysis was performed using the software package SPSS 20 (SPSS Inc., Chicago, Il, USA). Discrete data were summarised as frequencies, and continuous data were expressed as means and standard deviations or medians and interquartile ranges (IQRs), as appropriate. The χ^2 test was used for comparison of categorical variables, and the unpaired two tailed Student *t* test or Mann—Whitney rank sum test were used to test differences among continuous variables. The ability of platelet aggregation values by ADP and AA to predict outcomes was examined by receiver operating characteristics (ROC) curves. ROC curves were

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