EDITORIAL

Dual inhibition pathway after interventions for peripheral arterial disease

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The global burden of peripheral arterial disease (PAD) has been largely increased from 163 millions in 2000 to 202 millions in 2010 affecting mostly individuals from low or middle income countries.[1] Thus, the prevalence of PAD in individuals >55 years of age ranges from 9% to 23%.[2,3] However, only a small percentage of these individuals (5-10%) presents with the classic clinical symptoms of intermittent claudication; 30-50% experience various limb symptoms, while the remaining 40-65% are asymptomatic.[1,4]

Patients with PAD have a much higher 10-year cardiovascular mortality than age-matched controls without PAD (18.7% vs 4.4%), even after adjusting for traditional cardiovascular risk factors using the Framingham Risk Score.[5] The REACH registry, showed that patients with PAD are at high risk of major adverse cardiovascular events (MACE) and major adverse limb events (MALE) despite the current medical treatment that they are receiving.[6] A proportion of symptomatic PAD patients will need revascularization (surgical or endovascular) of the lower limbs during the following years after the initial diagnosis. Revascularization of PAD patients is associated with an increased risk of MALE and MACE. The analysis of such patients in Premier Healthcare Database showed that MALE increased rapidly post-procedure and then slowly after the first 12 months, while MACE increased steadily during the follow up period.[7] In the EUCLID trial,[8] it was also shown that following lower limb revascularization, there was an increased hazard for MACE and a markedly increased risk for MALE events (adjusted HR=13.9).

Best medical treatment and particularly antithrombotic one is of paramount importance for patients with PAD. The recent European Society for Vascular Surgery (ESVS) guidelines,[9] recommend long-term single antiplatelet treatment (SAPT) in patients with symptomatic PAD, with a class I recommendation. For patients that undergo a revascularization procedure, long-term SAPT is recommended (class IIb) based on a low level of evidence (C). On the other hand, dual antiplatelet therapy (DAPT) has been recommended in specific interventions, such as infra-inguinal stent implantation or below-the-knee bypass with a prosthetic graft, but still with moderate to low level of evidence. Therefore, there is a gap in the current literature and guidelines for antithrombotic strategies after peripheral revascularization to improve patency of the procedure and at the same time to reduce the increased risk of MACE and MALE after the intervention.

Indeed, the evidence on antithrombotic strategy demonstrating efficacy in reducing MACE and MALE after peripheral revascularization has not been satisfactory. Neither the CASPAR study[10] testing DAPT or the Dutch Bypass Oral Anticoagulants (BOA)[11] study testing warfarin showed any clear benefit regarding MALE and MACE in PAD patients after revascularization. In a recent systematic review of the literature, it was highlighted that there is scarce evidence on antithrombotic PAD treatment.[12] There is a considerable paucity of high-quality evidence on the optimal antithrombotic regimen for patients undergoing lower extremity revascularization, with no particular therapy shown to consistently improve patient outcomes.[12] On the other hand, in another recent systematic review and meta-analysis on antithrombotic therapy and MALE in patients with PAD, it was suggested that a more intense antithrombotic therapy reduces the risk of limb amputation and revascularization as well as stroke, with an increase in the risk of bleeding events.[13] However, in this study there is no specific recommendation.

In 2018, a sub-analysis of population of the Cardiovascular Events in Coronary or Peripheral Artery Disease (COMPASS)-PAD trial for MALE, confirmed the role of dual inhibition pathway (DIP) in reducing amputations and re-interventions in PAD.[14, 15] Low dose rivaroxaban (2.5mg x 2) plus aspirin (100mg x 1), treatment was associated with a reduction in MALE incidence of 43% and a decrease in total vascular amputations of 58%. Additionally, DIP treatment was associated with an increased risk of major bleeding.[16]

Most recently the Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD (VOYAGER PAD) trial published its outcomes.[17] This study was designed as a double-blind trial to test the hypothesis that rivaroxaban at 2.5 mg twice daily added to aspirin 100mg od, as compared with

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aspirin alone, would reduce the risk of a composite of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes in patients with symptomatic PAD who had undergone lower-extremity revascularization. Approximately two thirds of patients had been treated with an endovascular procedure (65%), and one third had been treated surgically (35%). It is of interest that in this study, the pre-defined use of clopidogrel was allowed in the discretion of the interventional physician. However, there was a nice balance between the patients that were on triple therapy and DAPT that helped in a valid sub-analysis in terms of clopidogrel use and its role.

The primary efficacy outcome was a composite of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or cardiovascular death. During 3 years of follow up the incidence of primary outcome was 17.3% for rivaroxaban group and 19.9% in the placebo group (hazard ratio, 0.85; 95% confidence interval [CI], 0.76 to 0.96; P=0.009). The incidence of the first five secondary outcomes in the testing hierarchy (acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or cardiovascular death) were all significantly lower in the rivaroxaban group than in the placebo group. The primary efficacy outcomes were consistent across subgroups (age, sex, body mass index, Glomerular filtration rate, diabetes mellitus, hyperlipidemia, smoking) and irrespectively of PAD characteristics (coronary artery disease, ankle brachial index, critical limb ischemia, concomitant clopidogrel use).

The principal safety outcome of thrombolysis in myocardial infarction (TIMI) major bleeding during 3 years of follow-up was higher in the rivaroxaban group (incidence 2.65% in comparison of 1.87% in the placebo group), however this difference was not statistically significant (hazard ratio, 1.43; 95% CI, 0.97 to 2.10; P = 0.07). Most importantly, intracranial hemorrhage occurred in 13 patients in the rivaroxaban group and in 17 patients in the placebo group, while fatal bleeding occurred in 6 patients in each group. In terms of subgroups analysis, interestingly, clopidogrel exposure was associated with higher rates of bleeding overall, particularly with longer durations (e.g. > 30 days). However, the safety of rivaroxaban plus aspirin versus aspirin alone was consistent regardless of background clopidogrel, while also the benefit of rivaroxaban plus aspirin versus aspirin alone was consistent regardless of background clopidogrel. More bleeding events may be associated with broad consequences, including discontinuation of therapies. In the absence of clear benefit, clopidogrel exposure along with aspirin and rivaroxaban should be minimized or avoided to reduce this risk.

This study estimated that for every 10,000 patients who were treated for 1 year, rivaroxaban at a dose of 2.5 mg twice daily added to aspirin would prevent 181 primary efficacy outcome events at the cost of 29 principal safety outcome events. The limitation of the trial was that the percentage of patients, who discontinued treatment prematurely, although relatively balanced between the groups, was higher than anticipated. Nonetheless, the high percentage of patients with premature treatment cessation may have attenuated the benefits observed in the intention-to-treat analysis, as suggested by the on-treatment analysis.

DIP therapy is the first antithrombotic regimen proven to offer significant benefit after peripheral revascularization in this large randomized clinical trial.[17] DIP was associated with a significant 15% reduction in risk of MACE and limb events, with no significant increase in TIMI major bleeding. The risk of acute limb ischemia was significantly reduced by 33% in patients receiving rivaroxaban plus aspirin compared with the group receiving aspirin alone. The results of VOYAGER PAD complement those of COMPASS, demonstrating consistent protection with DIP across the disease continuum in PAD. Thus, when a symptomatic PAD patient needs lower-extremity revascularization, it may be the right time to start this new DIP antithrombotic therapy, in order to improve post-intervention results in the early follow-up period, based on the VOYAGER PAD results and continue for life-long in order to sustain this outcome based on the COMPASS-PAD results.

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