Antithrombotic therapy is the cornerstone of the management of lower extremity arterial disease (LEAD), aiming to prevent both cardiovascular and limb events. Aspirin is the oldest and most widely used representative of the category. However, as Theodoridis et al rightfully remark, aspirin and antithrombotic therapy in general has been found to be effective only in patients with symptomatic LEAD. In asymptomatic LEAD, two trials, one in a general population aged 50 to 75 years with ABI <0.95 (Aspirin for Asymptomatic Atherosclerosis Trial) and another in diabetic patients aged >40 years with ABI <1.0 (PROPADAD Trial), have shown that aspirin compared with placebo did not result in a significant reduction in vascular events. In symptomatic LEAD, the evidence supporting the use of aspirin comes from a subgroup analysis of 6.263 patients with intermittent claudication, which was part of a large meta-analysis performed by the Antithrombotic Trialists Collaboration. Antiplatelet therapy significantly reduced major adverse cardiovascular events (MACE) by 23% (from 7.9% to 6.4%). Interestingly, the role of aspirin in chronic limb threatening ischemia (CLTI) as well as its role on the prevention of major adverse limb events (MALE) has never been studied.

Thienopyridines, on the other hand, represent the major rival of aspirin. A subgroup analysis of the CAPRIE trial, focusing on patients with symptomatic LEAD, showed that clopidogrel is superior to aspirin, reducing the annual relative risk of MACE by 23.8% (from 4.86% to 3.71%). Symptomatic LEAD was actually the only subgroup of atherosclerotic vascular disease in which clopidogrel was found to be more effective than aspirin. Once again, MALEs were not included on the outcome measures. The fact that the evidence supporting the use of clopidogrel over aspirin came from a post hoc analysis, which does not qualify as level I evidence, along with the relatively small absolute risk reduction (1.15% per year) prevented all scientific societies from issuing a clear-cut recommendation in favor of clopidogrel over aspirin in patients with symptomatic LEAD. Regarding the other thienopyridines, compared to clopidogrel in patients with symptomatic LEAD, ticagrelor was not found to be more effective in the EUCLID trial, whereas ticlopidine was associated with a higher rate of serious adverse events in the COOPER trial.

Having been established as the gold standard of the antithrombotic therapy for LEAD, aspirin subsequently served as the treatment of the control group against which various dual antiplatelet therapies (DAPT) were compared. The combinations of clopidogrel plus aspirin (CHARISMA trial) or voralapar plus aspirin (TRA 2°TIMI 50 trial) were not found to significantly reduce the rate of MACE in patients with LEAD, while they increased the rate of bleeding. Consequently, according to the European Society of Cardiology (ESC) and the European Society for Vascular Surgery (ESVS), DAPT (aspirin plus clopidogrel) for >1 month should be considered only after infra-inguinal stent implantation (Level of evidence: C) and may be considered after below-the-knee bypass with a prosthetic graft (level of evidence: B).

Similarly to DAPT, the combination of a coumadin plus an antiplatelet was not more effective than antiplatelet therapy alone in preventing MACE and was associated with an increase in life-threatening bleeding (WAVE trial). According to the 2017 ESC/ESVS guidelines, vitamin K antagonists in patients with LEAD may be considered only after autologous vein infra-inguinal bypass. On the other hand, in patients with LEAD who have an indication for oral anticoagulation (e.g. atrial fibrillation or mechanical prosthetic valve), oral anticoagulants alone should be considered.

The latest development on the subject of dual inhibition pathway, meaning the combination of antiplatelets and anticoagulants, is the administration of both aspirin and a low dose of rivaroxaban. The combination of rivaroxaban (2.5 mg twice a day) plus aspirin (100 mg once a day) compared with aspirin alone was evaluated in patients with peripheral arterial disease in the COMPASS trial and was found to significantly reduce both MACE (by 28%) and MALE (by 46%). The risk of bleeding was increased but the risk of fatal or critical organ bleeding was not. Despite the increased risk of bleeding, the net clinical benefit was in favor of the combination antithrombotic therapy. Taking into account the increased risk of bleeding, the option of dual inhibition therapy should be considered especially in high risk patients, such as smokers,
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betics and patients with critical limb ischemia or polyvascular disease. It should be noted that the ESC has already issued a guideline, according to which a combination of low-dose rivaroxaban and aspirin should be considered in patients with diabetes mellitus and chronic symptomatic LEAD without high bleeding risk. Another group of patients in whom dual inhibition therapy has proved to be preferable to single antiplatelet therapy is patients with LEAD who have undergone lower-extremity revascularization. In such patients, the VOYAGER trial has shown that the combination of rivaroxaban plus aspirin was associated with a significantly lower incidence of the composite outcome of MACE plus MALE than aspirin alone.

Although both COMPASS and VOYAGER represent major steps forward, there are several questions that remain unanswered, eg how would the combination of low-dose rivaroxaban and aspirin perform compared to clopidogrel instead of aspirin or compared to a combination of aspirin and clopidogrel.

Theodoridis et al are to be commended for summarizing all the above mentioned evidence supporting (or not) the use of various forms and combinations of antithrombotic therapy in patients with LEAD. The amount of data on which evidence-based decisions can be made gradually increases and their quality improves. At the same time, however, more questions are generated and more studies are needed to answer them.

REFERENCES