# Triple antithrombotic therapy in patients undergoing percutaneous coronary intervention: balancing between ischemia and bleeding

## Konstantinos C. Koskinas, Lorenz Räber

Department of Cardiology, University Hospital of Bern, Bern, Switzerland
*Correspondence to:* Lorenz Räber, MD, PhD. Department of Cardiology, University Hospital of Bern, Bern, Switzerland. Email: Lorenz.raeber@insel.ch.
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We appreciate the commentary by Dr. Shah and colleagues (1) on our paper assessing the duration of triple antithrombotic therapy among patients undergoing percutaneous coronary interventions (PCI) (2). As pointed by the authors, antithrombotic management of patients who undergo PCI with stent implantation and have concomitant indication for long-term oral anticoagulation (OAC) is a common clinical dilemma. While a so-called triple therapy with a combination of dual antiplatelet therapy (DAPT) plus warfarin has been the standard of care in these patients, it results in a higher risk of bleeding compared with less intensive antithrombotic regimens (3). Between the Scylla of ischemic and atherothrombotic risk and the Charybdis of hemorrhage, the question regarding the optimal treatment in this challenging group of patients remains largely unanswered.

When seeking the "optimal" antithrombotic strategy in this setting, several aspects need to be addressed. First, is triple therapy, or a less-intensive (dual) antithrombotic regimen associated with better clinical outcomes? Second, if dual therapy with a single antiplatelet agent is opted, should we choose clopidogrel or a novel, more potent P2Y12 inhibitor? Third, is warfarin or a novel OAC (NOAC) better—and if it is a NOAC, then which one and at what dose? Fourth, assuming that we have identified the "optimal" combination, how long should patients receive this treatment before transition to a less intensive antithrombotic regimen can be recommended? And finally, is there an optimal type, dose, and duration

of antithrombotic therapy that fits all patients, or should treatment rather be tailored to individual patient characteristics? Clearly, no single study—no matter how well designed or adequately powered—will be able to address all (or even most of) these questions.

Because only few randomized controlled trials have addressed this challenging topic to date, current guidelines are largely based on observational studies and expert opinion (3,4). The WOEST randomized trial focused on the intensity of antithrombotic treatment—triple *vs.* dual therapy (5). It compared clopidogrel alone *vs.* the combination of clopidogrel plus aspirin in 573 warfarin-treated patients who underwent PCI. The study found lower rates of any bleeding, similar rates of rates of ischemic evens (although clearly underpowered for these endpoints), and lower mortality in the warfarin plus clopidogrel arm. The findings were intriguing, but could not ensure that there is no excess of stent thrombosis when aspirin is omitted (5). The ISAR TRIPLE trial addressed the question of treatment duration (6). It compared 6-week *vs.* 6-month treatment with triple therapy in 604 patients undergoing PCI with drug-eluting stents (DES). At 9 months, the primary composite (ischemic and bleeding) endpoint did not differ between groups, overall supporting the feasibility of an abbreviated duration of triple therapy following PCI by current standards (6). More recently, the PIONEER AF-PCI trial focused primarily on the type of OAC—warfarin *vs.* a NOAC (7). It assessed 2,124 patients randomized in a 1:1:1 ratio to three regiments: low-

dose rivaroxaban (15 mg daily) plus a P2Y12 inhibitor for 12 months; very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT; or standard therapy with vitamin K antagonist plus DAPT. Not unexpectedly, both schemata including rivaroxaban were associated with a lower rate of clinically significant bleeding compared with standard triple therapy (warfarin plus DAPT) (7), and they also resulted in fewer recurrent hospitalizations (8). The study added to the results of WOEST regarding the safety of omitting aspirin from triple therapy (bleeding reduction) but had at least two notable limitations: (I) it was not powered to address efficacy, i.e., ischemic events (stent thrombosis and stroke); and (II) findings based on a very low dose of rivaroxaban that is not clinically approved are not directly applicable to current clinical practice.

Against this background, our study from the Bern PCI Registry (NCT02241291) focused on the comparison of short (1 month) *vs.* longer (median, 3 months) duration of triple therapy, i.e., warfarin combined with aspirin plus clopidogrel in the vast majority of patients (2). We found no significant differences with regard to bleeding, ischemic, and net clinical outcomes between the 2 groups. These findings need to be interpreted in view of the fact that treatment duration was determined according to clinical judgment, such that—not unexpectedly—patients who received triple therapy for only one month were more frequently female with stable coronary artery disease, had higher HAS-BLED scores, and were more commonly treated with balloon angioplasty alone or placement of bare-metal rather than drug-eluting stents. Notwithstanding limitations common to all observational studies, these findings extend previous evidence by supporting a role of shorter, patient-tailored DAPT durations in the management of patients on OAC undergoing coronary interventions, and by substantiating current, largely consensus-based recommendations regarding the length of triple therapy in this clinical setting.

Defining the optimum balance between too much *vs.* too little anticoagulant and antiplatelet therapy in patients with indication for both treatments remains a conundrum. While the combination of a vitamin-K antagonist with DAPT has been the standard of care (albeit not supported by concrete evidence), the field is changing: new-generation DES have reduced the risk of stent thrombosis compared with earlier devices (9), and NOACs appear to be at least as efficient for stroke prevention but safer than warfarin (associated with fewer intracranial bleedings) in patients with atrial fibrillation (10). Because patients are not identical with respect to their underlying ischemic or bleeding risks,

it is reasonable to assume that different patients may benefit from different variations of triple (or dual) therapy regarding components, dosage, and duration of treatment. Randomized trials are currently underway testing NOACs in various combinations with single or dual antiplatelet agents (REDUAL-PCI: NCT02164864; ENTRUST-AF-PCI: NCT02866175; and AUGUSTUS: NCT02415400). Until more evidence is available to advance current knowledge and better inform our practice, clinical judgment will be required to determine the best possible regimen for these patients. In this context, accounting for clinical scores that reflect bleeding (HASBLED score) or ischemic risk (the CHA2DS2-VASc score) to tailor the intensity of treatment, and shortening the length of triple therapy in patients estimated to be more prone to bleeding appear to be reasonable approaches.

## Acknowledgements

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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