Triple troubles selecting optimal therapy for atrial fibrillation patients undergoing percutaneous coronary interventions

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In everyday clinical practice, over 80% of all patients with atrial fibrillation (AF) have an indication for an oral anticoagulant (OAC), and vascular disease may co-exist in ~30% of them [1]. Estimates suggest an AF prevalence of approximately 3% in adults [2], and ~20% of these require percutaneous cardiovascular interventions over time [3]. Hence ~1–2 million AF patients in Europe who are on OAC may undergo percutaneous coronary interventions (PCI), usually including stent implantation [4].

Antithrombotic therapy, with dual antiplatelet therapy (DAPT) consisting of low-dose acetylsalicylic acid and $P2Y_{12}$ platelet receptor inhibitor, is the mainstay to reduce the risk of recurrent ischaemic events during the first year after PCI [5], while OAC therapy is the cornerstone in the prevention of ischaemic stroke in AF patients, and it is able to prolong life in these patients [6]. Particular challenging in terms of antithrombotic treatment are patients who present with both AF and coronary artery disease who underwent PCI, since clinicians need to balance the triple risks of ischaemic stroke, recurrent cardiac ischaemia, and bleeding (Figure 1).

According to current guidelines, combination triple therapy (TT) with aspirin, clopidogrel and an oral anticoagulant (up to 6 months) is recommended either after an acute coronary syndrome (ACS), or after elective coronary stenting for stable coronary artery disease in AF patients at moderate or high risk of stroke [7].

This scenario requires careful consideration of antithrombotic therapy optimization because co-prescription of OAC with dual antiplatelet therapy increases the absolute risk of major haemorrhage [8] given the fact that, in addition to the risk of triple therapy itself, most often these patients are elderly with multiple comorbidities.

Data pertaining to this growing proportion of AF population are scarce due to the paucity of dedicated trials in patients who are difficult to enrol and less keen to participate in controlled randomized studies [9]. In addition, trials testing antithrombotic drugs usually exclude these patients according to the study protocols.

The first randomized controlled trials (RCTs) to address the optimal antiplatelet therapy in patients on OAC with a vitamin K antagonist (VKA) undergoing coronary stenting was the WOEST trial, which compared dual therapy (VKA plus clopidogrel) to triple therapy (VKA plus aspirin and clopidogrel) in 573 patients taking long-term OAC who received a coronary stent. Combination therapy with OAC and clopidogrel was associated with a significant reduction in the primary end point (any bleeding episode during 1-year follow-up), with no detectable increase in the rate of thrombotic events (especially stent thrombosis) [10]. However, some important issues limit the conclusions of the WOEST trial: only 69% of patients received OAC due to AF, most of the patients underwent elective PCI (70–75%), and the femoral approach was used in 74%, increasing access site-related bleeding; furthermore, the differences between dual and triple

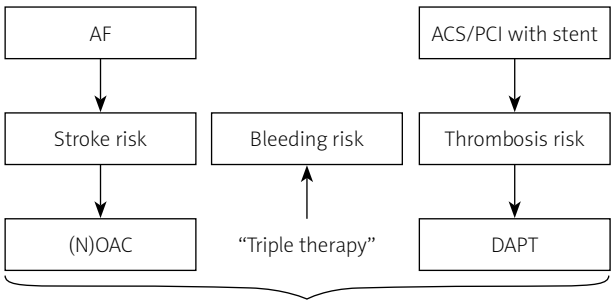

Figure 1. Antithrombotic strategies in atrial fibrillation patients undergoing percutaneous coronary interventions

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therapy for the primary end-point were driven by minor bleeding events; proton pump inhibitors (PPIs) were not used routinely, and in the TT arm DAPT was routinely continued for 12 months in all patients [4]. Finally, the study was powered to show superiority at the primary bleeding endpoint, but not to show non-inferiority at the secondary endpoint [4].

In this issue of "Advances in Interventional Cardiology" [11], the authors retrospectively evaluated the bleeding and the thromboembolic complications of a cohort of 136 patients with either paroxysmal or permanent non-valvular AF admitted for stable angina (SA) or myocardial infarction (MI) who underwent PCI. According to current guidelines, in all of these patients there was the indication for a VKA/novel oral anticoagulant (NOAC) due to AF and the indication for DAPT after PCI. The authors reported a rate of 6.6% of in-hospital thrombotic events and 12.3% during follow-up of 10.2 ±4.2 months, with no significant difference in occurrence of MI between patients who terminated any of the TT drugs prematurely and those who did not (6.8% vs. 8.5%, $p = 0.72$). On the other hand, they reported a 52% rate of bleeding during the hospital stay, and 34.6% in the follow-up period, with a significant difference in the major bleeding occurrence between those patients who continued TT vs. those who terminated any of the drugs prematurely, apparently confirming the evidence of previous studies.

The choice between different combinations of TT, with regard not only to the number and type of agents, but also to the dosage and length of the single drug, is a challenging decision for clinicians. The authors tried to find any clinical difference to guide this choice. Study participants were divided according to the use of VKA (group I), NOAC (group II) or low molecular weight heparin (LMWH; group III) as part of the TT. The study did not find any significant predictor for the selection of a particular anticoagulant as part of TT, but the efficacy, safety and convenience of NOAC as a part of TT was underlined, at the price of increased costs.

Recently published European Society of Cardiology guidelines for the management of atrial fibrillation recommend the use of NOACs at the lowest effective dose for stroke prevention [6], but at present there is no concluded randomized study comparing VKAs and NOACs in this field. Data on the safety of concomitant prescription of NOACs and antiplatelet drugs derived only from post hoc analyses of randomized trials of NOACs in non-valvular AF patients [12], and from studies of NOACs and antiplatelets in ACS/PCI patients [13]. While waiting for the results of the 4 ongoing large-scale outcome studies evaluating different combinations of NOACs or VKAs with antiplatelet therapy in AF patients undergoing stent PCI (PIONEER AF-PCI, RE-DUAL PCI, EVOLVE AF-PCI, and AUGUSTUS), the authors speculated that patients treated with NOACs as part of TT may experience less peripheral embolism than those treated with VKA.

An additional matter of debate is the choice of type of stent to be implanted in AF patients. In the cohort analyzed, a 2nd generation drug-eluting stent was implanted in the large majority (86.8%) of subjects, according to the data reported in the ZEUS study, in which zotarolimus-eluting stent implantation resulted in a lower risk of major adverse cardiac events compared with the bare metal stent in patients at high risk of bleeding or thrombosis [14].

Regarding the use of $P2Y_{12}$ inhibitors, currently only clopidogrel is recommended as a part of TT. Thus, in case of a recent AF onset in patients already treated with prasugrel or ticagrelor, switching to clopidogrel should be considered [15].

In conclusion, while waiting for the results of the ongoing randomized controlled trials, real life data are welcome for the prevention of triple trouble (recurrent cardiac ischaemia, bleeding and ischaemic stroke) in AF patients undergoing PCI. Published registry data reinforce the already existing evidence that TT is definitely associated with high risk of bleeding and should be maintained as short as possible.

Conflict of interest

Dr Parodi reported receiving consulting or lecture fees from Daiichi Sankyo/Eli Lilly, AstraZeneca, Bayer and The Medicine Company. Dr Scudiero declares no conflict of interest.

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