THE SUNSET OF TRIPLE ANTITHROMBOTIC THERAPY FOR ATRIAL FIBRILLATION PATIENTS

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Abstract

The management of Atrial Fibrillation (AF) in patients who have undergone Percutaneous Coronary Intervention (PCI) is challenging. The use of the triple antithrombotic therapy, including the combination of an anticoagulant plus DAPT, has been empirically used in clinical practice after PCI in patients with AF requiring oral anticoagulation. Although this triple antithrombotic therapy may minimize the risk of cerebrovascular and coronary ischemic events, it has been associated to at least a threefold increase in fatal and non-fatal bleeding complications. An appealing alternative strategy to reduce this bleeding risk may be to drop out one antiplatelet agent from the triple combination, thus composing a dual antithrombotic therapy. The safety and efficacy of this latter therapy regimen has been assessed in dedicated randomized trials, the evidence of which will be discussed in the present chapter.

The management of Atrial Fibrillation (AF) in patients who have undergone Percutaneous Coronary Intervention (PCI) is challenging. Oral anticoagulation is indicated in patients with AF for the primary and secondary prevention of stroke and systemic embolism, whereas Dual AntiPlatelet Therapy (DAPT) encompassing the combination of aspirin plus a P2Y12 inhibitor is indicated in patients who are undergoing PCI with stent implantation for the prevention of thrombotic complications. Thus the use of the triple antithrombotic therapy, including the combination of an anticoagulant plus DAPT, has been empirically used in clinical practice after PCI in patients with AF requiring oral anticoagulation. Although this triple antithrombotic therapy may minimize the risk of cerebrovascular and coronary ischemic events, it also has the potential to cause harm in a relevant proportion of patients. Indeed, com-

pared with oral anticoagulation therapy alone, the addition of DAPT to an oral anticoagulant agent is associated to at least a threefold increase in fatal and nonfatal bleeding complications [1-2]. Thus patients treated with a triple antithrombotic therapy should be considered at high risk of bleeding, prompting the implementation of strategies to minimize this risk. With this regard, European and North American consensus documents and guidelines, in principle, have recommended duration of triple therapy for the shortest time necessary. However, shortening the course of triple therapy does not appear to substantially reduce bleeding, as shown in the ISAR-TRIPLE trial, where no significant difference in the rates of overall major bleeding were observed between 6-week and 6-month triple therapy, peaked within the first 30 days of initiation of triple therapy [3]. Therefore, an appealing alternative strategy to reduce bleeding risk may be to drop out one antiplatelet agent from the triple combination, thus composing a dual antithrombotic therapy. The safety and efficacy of this latter therapy regimen has been assessed in dedicated randomized trials, the evidence of which will be discussed in the present chapter.

Randomized Trials assessing dual antithrombotic therapy

WOEST trial

The first study evaluating the cessation of aspirin after PCI while maintaining clopidogrel in combination with warfarin was the WOEST trial, which randomized 573 patients on oral anticoagulation (69% of patients had AF) to clopidogrel 75 mg/day alone (dual therapy) or to DAPT with aspirin 80mg/day plus clopidogrel (triple therapy) [4]. The assigned antiplatelet treatment was continued for at least one month, up to one year at the discretion of the operators, in patients who received a bare-metal stent for stable coronary disease. In patients with acute coronary syndromes (27% of patients) or who received drug-eluting stents (65% of patients), clopidogrel was given for at least one year. The PCI procedure was performed on oral anticoagulation therapy in half of the patients. Rates of the primary endpoint of any bleeding episodes assessed by several definitions at 1-year follow-up were significantly reduced in the dual therapy arm (19.5% vs. 44.9%; Hazard Ratio [HR] 0.36, 95% Confidence Interval [CI] 0.26-0.50; $p < 0.001$). The Thrombolysis In Myocardial Infarction (TIMI) major bleeding were numerically lower in the dual therapy group with no statistically significant differences. According to the Bleeding Academic Research Consortium (BARC) criteria, the difference in overall bleeding between the two groups was mostly driven by significant reduction in BARC 2 bleeds with dual therapy. The rates of the composite efficacy endpoint of death, myocardial infarction, stroke, target vessel revascularization, or stent thrombosis was significantly lower in the dual vs. triple therapy arm, driven by significant reduction in all-cause mortality (2.5% vs. 6.4%; $p = 0.027$) at one year. The WOEST trial has some limitations that should be considered in interpreting results and conclusions: only 69% of patients received anticoagulation due to AF; only 25% of patients underwent PCI for an acute coronary syndrome; the femoral approach was used in 74%, increasing access site bleeding; the differences between dual and triple therapy for the primary endpoint of "any bleeding" were mostly driven by events that could be considered cli-

nically minor; proton pump inhibitors were not routinely used; and finally, triple therapy was continued for 12 months against current recommendation on shortening the duration of triple therapy to 1-6 months. Therefore, the WOEST trial results did not change the 2016 European AF guidelines, which continued to support the use of the triple therapy for a limited period after PCI [5].

PIONEER AF-PCI trial

More recently, the PIONEER AF-PCI study randomized in a 1:1:1 ratio 2.124 patients with non-valvular AF who had undergone PCI with stent implantation to receive the following regimens: dual therapy with low-dose rivaroxaban (15 mg o.d.) plus a P2Y12 inhibitor (and no aspirin) for 12 months; triple therapy with very-low-dose rivaroxaban (2.5 mg b.i.d.) plus DAPT for 1, 6, or 12 months; or standard triple therapy with a dose-adjusted warfarin plus DAPT for 1, 6, or 12 months [6]. It is worth to mention that presentation with an acute coronary syndrome was about 50%, with STEMI about 12%, and a drug-eluting stent was implanted in 68% of participants. The P2Y12 inhibitor used for the majority of patients was clopidogrel (94%). The primary composite endpoint was the safety outcome of clinically significant bleeding, including TIMI major bleeding or minor bleeding or bleeding requiring medical attention. Rates of this latter safety endpoint were significantly lower in the two groups receiving rivaroxaban than in the group receiving standard triple therapy (16.8% in patients treated with rivaroxaban 15 mg and 18% in those treated with rivaroxaban 2.5 mg versus 26.7% in the warfarin group; HR 0.59, 95% CI 0.47–0.76; $P < 0.001$, and HR 0.63, 95% CI 0.50–0.80; $P < 0.001$, respectively). This difference in any bleeding was mostly driven by reductions in bleeding requiring medical attention, while major bleeding tended to be lower with rivaroxaban with no statistically significant difference. Of note, a relevant of patients (49%) in both DAPT groups continued triple therapy for 12 months. Moreover, an INR range of 2–3 was recommended, instead of 2–2.5, which may have increased bleeding in the warfarin group. Rates of Major Adverse Cardiovascular Event (MACE) including the composite of cardiac death, myocardial infarction, or stroke were similar in the three treatment groups. No differences in each components of MACE and in stent thrombosis were observed among groups; the number of secondary efficacy endpoint in this study was small, and the trial was not powered to establish either superiority or non-inferiority with regards to ischemic events and no firm conclusions regarding efficacy can be drawn from the PIONEER AF-PCI trial. Finally, the tested rivaroxaban dose of 15 mg once daily (or 10 mg once daily in those with moderate renal impairment) is not currently approved for the management of atrial fibrillation, and it remains unclear if this dose is protective in patients with high risk for thromboembolic stroke.

RE-DUAL PCI trial

In the RE-DUAL PCI trial, 2.725 patients with AF who had undergone PCI randomly received, in a 1:1:1 ratio, one of the following treatments: dual therapy with dabigatran at a dose of 110 mg twice daily plus a P2Y12 inhibitor (clopidogrel or ticagrelor); dual therapy with dabigatran at a dose of 150 mg twice daily plus a P2Y12 inhibitor; or triple therapy with warfarin plus a

P2Y12 inhibitor and aspirin for 1 month to 3 months [7]. An acute coronary syndrome was present in about half of patients, and a drug-eluting stent was used in 83% of PCI. The majority of patients received clopidogrel, and only 12.0% received ticagrelor. Of note, in the triple-therapy group, the mean percentage of time in the therapeutic INR range was 64%. The rate of the primary safety endpoint, the occurrence of International Society on Thrombosis and Hemostasis (ISTH) major or non-major clinically relevant bleeding, was lower in the 110-mg dual therapy group compared with overall triple therapy group (HR 0.52, 95% CI 0.42-0.63; P<0.001 for non-inferiority) and also in the 150-mg dual therapy group (HR 0.72, 95% CI 0.58-0.88; P<0.001 for non-inferiority) than in the corresponding triple therapy group (including only patients who had been eligible to be assigned to the 150-mg dual-therapy group). Both the ISTH and TIMI defined major bleeding were significantly lower with both dabigatran doses compared with triple therapy. Moreover, there were markedly lower rates of intracranial bleeding in the 110-mg and 150-mg dual-therapy groups (0.3% and 0.1%, respectively) than in the triple-therapy group (1.0%). The dual therapy with dabigatran (combined dose) was non-inferior to triple therapy with regards to the composite efficacy endpoint of death, myocardial infarction, stroke, systemic embolism, or unplanned revascularization. Rates of myocardial infarction and definite stent thrombosis tended to be slightly higher with dabigatran 110-mg dual therapy compared with triple therapy, while no differences in these latter events were observed between the 150-mg dual therapy and the triple therapy arms. Rates of death and stroke did not differ across groups. However, the RE-DUAL PCI trial was not powered to allow for efficacy comparisons of each dabigatran dose vs. warfarin, and for detecting differences in individual components of the composite efficacy endpoint.

Current European Guidelines

The most updated recommendations regarding the management of antithrombotic therapy in patients with AF who undergo PCI can be found within the recent European guidelines focused on DAPT, which were released in 2017 after the PIONEER AF-PCI trial [8]. This document provides the following main recommendations on triple or dual therapy:

- triple therapy with aspirin, clopidogrel, and oral anticoagulation should be considered for 1 month, irrespective of the type of stent used (Class IIa);
- longer duration of triple therapy up to 6 months should be considered in patients with high ischemic risk due to acute coronary syndrome or other anatomical/procedural characteristics that outweigh the bleeding risk (Class IIa);
- dual therapy with clopidogrel 75 mg/day and OAC should be considered as an alternative to 1-month triple antithrombotic therapy in patients in whom the bleeding risk outweighs the ischemic risk (Class IIa).

Therefore, according to the guidelines triple therapy should be used routinely and dual therapy should be restricted to selected patients with high bleeding risk. The RE-DUAL PCI trial provides further consistent evidence on the net clinical benefit of dual therapy, that should give cardiologists confidence to drop aspirin in case of higher bleeding risk. However, even after RE-DUAL PCI trial results, short triple therapy including the combination of aspirin, clo-

pidogrel and a non-vitamin K oral anticoagulant, should still remain a choice, especially in patients with high thrombotic risk, such as those treated for a myocardial infarction or those undergoing complex PCI.

REFERENCES

1) *Sorensen R, Hansen ML, Abildstrom SZ, et al*. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. Lancet 2009; 374:1967-74
2) *Dans AL, Connolly SJ, Wallentin L, et al*. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. Circulation 2013; 127:634-40
3) *Fiedler KA, Maeng M, Mehilli J, et al*. Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation: the ISAR-TRIPLE trial. J Am Coll Cardiol 2015; 65:1619-29
4) *Dewilde WJ, Oirbans T, Verheugt FW, et al*; WOEST Study Investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet 2013; 381:1107-15
5) *Kirchhof P, Benussi S, Kotecha D, et al*. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016; 37:2893-2962
6) *Gibson CM, Mehran R, Bode C, et al*. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med 2016; 375:2423-34
7) *Cannon CP, Bhatt DL, Oldgren J, et al*; RE-DUAL PCI Steering Committee and Investigators. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. N Engl J Med 2017; 377:1513-24
8) *Valgimigli M, Bueno H, Byrne RA, et al;* ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2017. [Epub ahead of print]