Research Highlights

Highlights from the latest articles in anti-thrombotic and myocardial revascularization strategies in coronary artery disease

Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing PCI: the WOEST trial

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Evaluation of: 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, randomized, controlled trial. *Lancet* 381, 1107–1115 (2013).

Long-term treatment with anticoagulant treatment is indicated in patients with mechanical heart valves, and in most patients with atrial fibrillation [1]. Approximately one-third of these patients have concomitant significant coronary artery disease that may require percutaneous coronary intervention (PCI) with stenting, under which circumstances, double antiplatelet therapy with aspirin and clopidogrel is currently utilized to prevent stent thrombosis (ST). However, this combination of oral anticoagulants and dual antiplatelet therapy is associated with a high annual risk (4–16%) of fatal and nonfatal bleeding episodes [2]. Guidelines, based on expert consensus, recommend triple antithrombotic therapy, involving oral anticoagulants with a revised target international normalization ratio, aspirin, clopidogrel (for as short a time as possible), radial approach and extensive use of proton pump inhibitors; however, this strategy has not been prospectively validated [1].

Dewilde *et al.* published the randomized, open-label, multicenter, controlled WOEST trial in the *Lancet* recently [3]. They demonstrated that patients undergoing PCI had a significantly lower risk of bleeding complications at 1-year follow-up when treated with double therapy (oral anticoagulants and clopidogrel) compared with triple therapy (aspirin, clopidogrel and oral anticoagulation), with no evidence of an increased risk of thrombotic events.

A total of 573 patients were enrolled and 1-year follow-up was available for 563 (98.25%) patients. A total of 54 (19.4%) patients receiving double therapy, and 126 (44.4%) receiving triple therapy (hazard ratio [HR] 0.36; 95% CI: 0.26–0.50; p = 0.0001) experienced bleeding episodes. The combined secondary end point of death, myocardial infarction, stroke, target-vessel revascularization and ST was reported in 31 (11.1%) who received double therapy and in 50 (17.6%) patients who received triple therapy (HR: 0.60; 95% CI: 0.38–0.94; p = 0.025). The HR remained similar after correction for imbalance in baseline characteristics (0.56; 95% CI: 0.35–0.91). The authors conclude that aspirin use is not necessary in patients receiving oral anticoagulants and undergoing PCI.

In our opinion, the WOEST trial provides very important data, for this special population of patients, and insights into potential future directions without using aspirin for all patients after coronary stenting. Other potential considerations include: first, in the studied population, only 35% of patients used proton pump inhibitors, 25% of patients had a radial PCI and 30% of patients received a bare-metal stent. Bleeding episodes might have been prevented with an increased use of proton pump inhibitors, radial access for PCI and bare-metal stent

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used. Second, it would be extremely interesting to know, from the investigators, whether in those subgroups of patients, the double therapy is still safer and more effective than the triple therapy. Finally, *CYP2C19*2* and *CYP2C19*17* genotyping have not been evaluated in the study. Carriage of the *CYP2C19*2* loss-of-function allele has been repeatedly demonstrated to be associated with a reduced pharmacokinetic and pharmacodynamic response to clopidogrel, and with an increased risk of major adverse cardiovascular events, particularly ST [4,5]. On the other hand, the gain-of-function *CYP2C19**17 allelic variant has been reported to be associated with an enhanced response to antiplatelet treatment with clopidogrel, by means of a rapid metabolization of CYP2C19 substrates. Consequently, this may improve the prevention of major adverse cardiovascular events; however, it also increases the risk of bleeding, especially for homozygous (**17/*17*) allele carriers [6]. We appreciate that the mentioned genetic variations may have been homogeneously distributed in the studied population and may not have influenced the overall results of a large trial; however, we need to underline the necessity of *CYP2C19*2* and *CYP2C19*17* genotyping when use of clopidogrel is made. Finally, although the authors recognize that they do not have information on how much anticoagulation in the therapeutic range was achieved, it is well known that tight control of the international normalization ratio with a revised target during triple therapy could reduce the bleeding risk without an increase in stroke or ST.

Reference

1 Camm AJ, Kirchhof P, Lip GY *et al.* Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur. Heart J.* 31, 2369–2429 (2010).

2 Hansen ML, Sorensen R, Clausen MT *et al.* Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch. Intern. Med.* 170, 1433–1441 (2010).

3 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, randomized, controlled trial. *Lancet* 381, 1107–1115 (2013).

4 Simon T, Verstuyft C, Mary-Krause M *et al.* Genetic determinants of response to clopidogrel and cardiovascular events. *N. Engl. J. Med.* 360, 363–375 (2009).

5 Sibbing D, Stegherr J, Latz W *et al.* Cytochrome P450 2 C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. *Eur. Heart J.* 30, 916–922 (2009).

6 Sibbing D, Koch W, Gebhard D *et al.* Cytochrome 2 C19*17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. *Circulation* 121, 512–518 (2010).

Bedside monitoring to adjust antiplatelet therapy for coronary stenting (ARCTIC trial)

Evaluation of: Collet JP, Cuisset T, Rangé G *et al.*; ARCTIC Investigators. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N. Engl. J. Med.* 367, 2100–2109 (2012).

Dual antiplatelet therapy with aspirin and clopidogrel is recommended for the prevention of atherothrombotic events in patients who have acute coronary syndromes or are undergoing PCI [1,2]. However, despite such treatment, a substantial number of MACEs and especially ST still occur, which can partly be explained by the high on clopidogrel treatment platelet reactivity, present in about one-third of these patients [3–5]. Platelet-function testing can enable quantification of the degree of platelet reactivity during antiplatelet treatment and, potentially, the identification of patients in whom personalized antiplatelet therapy is necessary to minimize the risks of both ischemic and bleeding complications [6].

In the randomized, open-label, multicenter ARCTIC trial recently published in the *New England Journal of Medicine*, Collet *et al.* demonstrated that there were no significant improvements in clinical outcomes with platelet function monitoring and treatment adjustment for coronary stenting, as compared with standard antiplatelet therapy without monitoring [7].

The investigators randomly assigned 2440 patients scheduled for PCI were randomly allocated to a strategy of platelet-function monitoring, with drug adjustment in patients who had a poor response to antiplatelet therapy, or to a conventional strategy devoid of monitoring and drug adjustment. The primary end point was the composite of death, myocardial infarction, ST, stroke or urgent revascularization 1 year after stent implantation. The VerifyNow P2Y12 and aspirin point-of-care assays were used for patients in the monitoring group before stent implantation and in the outpatient clinic 2–4 weeks later. In the monitoring group, high platelet reactivity (platelet reaction units >235) in patients taking clopidogrel (34.5% of patients) or aspirin (aspirin reactions units >550; 7.6%) led to the administration of an additional bolus of clopidogrel, prasugrel, or aspirin along with glycoprotein IIb/IIIa inhibitors during the procedure. The primary end point was observed in 34.6% of the patients in the monitoring group, as compared with 31.1% of those in the conventional-treatment group (HR: 1.13, 95% CI: 0.98–1.29; p = 0.10). The main secondary end point, ST or any urgent revascularization, occurred in 4.9% of the patients in the monitoring group and 4.6% of those in the conventional treatment group (hazard ratio, 1.06, 95% CI: 0.74–1.52; p = 0.77). The rate of major bleeding events was not significantly different between groups. The authors conclude that their data do not support the routine use of platelet-function testing in patients undergoing coronary stenting.

Although the ARCTIC trial provides important information for the individualized, VerifyNow-guided, antiplatelet therapy in patients undergoing PCI with drug-eluting stents, few considerations should be mentioned: only 27.0% of patients presented with an acute coronary syndrome; no ST-segment elevation myocardial infarction patients included; different cut-off value might have been more discriminating (e.g., platelet reaction units of 208); only one platelet-function testing was used; and at the time of the procedure, 80.2% of the poor responders immediately received an additional loading dose of clopidogrel, and only 3.3% received an additional loading dose of prasugrel. A randomized study in acute coronary syndrome high-risk patients, with a cutoff value of 208 for platelet reaction units, more than one platelet-functions tests and switching to prasugrel or ticagrelor, and not clopidogrel reloading, is urgently needed.

Reference

1 Hamm C, Bassand JP, Agewall S *et al.* ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology. *Eur. Heart J.* 32, 2999–3054 (2011).

2 Steg PG, James SK, Atar D *et al.* ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). *Eur. Heart J.* 33, 2569–2619 (2012).

3 Ong AT, Hoye A, Aoki J *et al.* Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus or paclitaxel stent implantation. *J. Am. Coll. Cardiol.* 45, 947–953 (2005).

4 Geisler T, Zurn C, Simonenko R *et al.* Early but not late stent thrombosis is influenced by residual platelet aggregation in patients undergoing coronary interventions. *Eur. Heart J.* 31, 59–66 (2010).

5 Angiolillo DJ, Fernandez-Ortiz A, Bernardo E *et al.* Variability in individual responsiveness to clopidogrel: clinical implications, management and future perspectives. *J. Am. Coll. Cardiol.* 49, 1505–1516 (2007).

6 Breet NJ, van Werkum JW, Bouman HJ *et al.* Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. *JAMA* 303, 754–762 (2010).

7 Collet JP, Cuisset T, Rangé G *et al.*; ARCTIC Investigators. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N. Engl. J. Med.* 367, 2100–2109 (2012).

Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and PCI: the SYNTAX score II

Evaluation of: Farooq V, van Klaveren D, Steyerberg EW *et al.* Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 381, 639–650 (2013).

The anatomical SYNTAX score is used as a tool to help clinicians decide the best revascularization therapy in patients with complex coronary artery disease [1]. However, the absence of clinical parameters to tailor decision-making between coronary artery bypass graft surgery (CABG) and PCI is an important limitation.

The SYNTAX score II was developed as a result of the application of a Cox proportional hazards model to results of the randomized all-comers SYNTAX trial (n = 1800) [2]. The baseline features which bear strong associations with 4-year mortality in either or both of the CABG or PCI settings were added to the anatomical SYNTAX score. Comparisons of 4-year mortality predictions between CABG and PCI were made for each patient. SYNTAX score II contained eight predictors: anatomical SYNTAX score, age, creatinine clearance, left ventricular ejection fraction, presence of unprotected left main coronary artery disease, peripheral vascular disease, female sex and chronic obstructive pulmonary disease. SYNTAX score II predicted a significant difference in 4-year mortality between patients undergoing CABG and those undergoing PCI (p = 0.0037). In order to achieve similar 4-year mortality after CABG or PCI, younger patients, women and patients with reduced left ventricular ejection fraction required lower anatomical SYNTAX scores, whereas older patients, patients with unprotected left main coronary artery disease and those with chronic obstructive pulmonary disease, required higher anatomical SYNTAX scores. The incidence of diabetes was not significant for decision-making between CABG and PCI (p = 0.67).

SYNTAX score II provides a very important tool for clinicians to evaluate the importance of anatomical and clinical factors in the decision over the optimum revascularization technique for individual patients with complex coronary artery disease.

Reference

1 Sianos G, Morel MA, Kappetein AP *et al.* The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* 1, 219–227 (2005).

2 Farooq V, van Klaveren D, Steyerberg EW *et al.* Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 381, 639–650 (2013).