GLOBAL CARDIOLOGY SCIENCE & PRACTICE
A Qatar Foundation Academic Journal

OPEN ACCESS

Lessons from the trials

ARCTIC: Additional proof against antiplatelet adjusted therapy

Mahmoud Farouk Elmahdy[1,*], David Antoniucci[2]

[1]Aswan Heart Center, Aswan, Egypt
[2]Careggi Hospital, Florence, Italy
*Email: drmahmoudfarouk@yahoo.com

INTRODUCTION

The prognostic value of high platelet reactivity during treatment with aspirin and/or thienopyridine has been demonstrated repeatedly,[1–3] leading to the rationale for individualized antiplatelet therapy. Bedside tests have previously been used as screening tools to select patients with a poor response to clopidogrel in order to evaluate different treatments. However, conflicting results of such interventions have been reported in cohort studies and randomized studies.[4–8]

In randomized studies, the intensification of platelet inhibition in patients with a poor response to clopidogrel failed to improve outcomes when double doses of clopidogrel or prasugrel were used, whereas glycoprotein IIb/IIIa inhibition improved outcomes in these patients.[4,5]

ARCTIC STUDY

The Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting (ARCTIC) is a multicenter, randomized; open-label study, that was published in the New England Journal of Medicine in November 2012. The study was conducted to evaluate a strategy of systematic platelet-function monitoring for the purpose of adjusting treatment in patients with a poor response to aspirin, thienopyridine (clopidogrel or prasugrel), or both, as compared with a conventional approach in which similar treatment was given to all patients, without platelet-function assessment.[9]

The study enrolled 2440 patients scheduled for drug eluting stent (DES) implantation irrespective of the clinical presentation except for primary percutaneous coronary intervention for myocardial infarction with ST-segment elevation (STEMI), the planned use of glycoprotein IIb/IIIa inhibitors, long-term anticoagulation therapy, or those with bleeding diathesis. Eligible patients were randomly assigned to a strategy of platelet-function evaluation with adjustment of antiplatelet drugs and doses in patients with an inadequate platelet-inhibitory response (monitoring-group) or to a strategy of conventional treatment without platelet-function assessment (conventional-treatment group).

In the monitoring-group (1213 patients), platelet-function monitoring was performed with the use of the VerifyNow assay (Accumetrics) before stent implantation and the same measurements were repeated 2 to 4 weeks after stent implantation in order to adjust the maintenance therapy, if necessary. High on-clopidogrel platelet reactivity was defined by P2Y 12 reaction units (PRU) value >235 and/or a % inhibition $<15\%$, while high on-aspirin platelet reactivity was defined by an aspirin response units (ARU) value >550. If high platelet reactivity during treatment with aspirin was identified, intravenous aspirin was administrated. If high platelet reactivity during treatment with clopidogrel was identified, the protocol called for the administration of glycoprotein IIb/IIIa inhibitors and an additional loading dose of clopidogrel (at a dose of ≥ 600 mg) or a loading dose of prasugrel (at a dose of 60 mg) before the procedure, followed by a daily maintenance dose of 150 mg of clopidogrel or 10 mg of prasugrel after the procedure. At 14 to 30 days after stent implantation, patients with high platelet reactivity during treatment with clopidogrel were switched to prasugrel at a dose of 10 mg or received a 75-mg

http://dx.doi.org/10.5339/gcsp.2013.17
Submitted: 14 April 2013
Accepted: 19 May 2013

QSCIENCE.com
Member of Qatar Foundation

Cite this article as: Elmahdy M, Antoniucci D. ARCTIC: Additional proof against antiplatelet adjusted therapy, *Global Cardiology Science and Practice* 2013:17
http://dx.doi.org/10.5339/gcsp.2013.17

increase in the maintenance dose of clopidogrel; patients with low platelet reactivity during treatment with thienopyridine, defined as more than 90% inhibition, were switched to clopidogrel at a maintenance dose of 75 mg if they were receiving prasugrel at a dose of 10 mg or clopidogrel at a dose of 150 mg.

In the conventional-treatment group (1227 patients), patients underwent stent implantation without any platelet-function testing performed. The use of both aspirin and clopidogrel or prasugrel and the use of glycoprotein IIb/IIIa inhibitors were left to the physician's discretion. Baseline characteristics of the primary-analysis population were well matched between the two study groups.

The primary end point was the composite of death from any cause, myocardial infarction, stroke or transient ischemic attack, urgent coronary revascularization, and stent thrombosis. The main secondary efficacy end point was the composite of stent thrombosis (revascularized or not) and urgent revascularization. Other prespecified end points included the composite of death, recurrent acute coronary syndrome, or stroke; the composite of death or resuscitation after cardiac arrest; the composite of death or myocardial infarction; and each individual component of the primary end point. The main safety end point was defined as a major bleeding event, according to the percutaneous coronary intervention–specific definition set in the Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients, an International Randomized Evaluation (STEEPLE) trial.[10]

RESULTS

Approximately one third of the patients assigned to the monitoring-group had high platelet reactivity during treatment with clopidogrel before stent implantation; at the time of the procedure, 80.2% of these patients immediately received an additional loading dose of clopidogrel and 3.3% received an additional loading dose of prasugrel. High on-aspirin platelet reactivity was rare and led to the administration of an additional bolus of intravenous aspirin in four of five patients. When measurements of platelet reactivity were repeated 2 to 4 weeks later in the outpatient clinic, there was a reduction of approximately 50% in the percentage of patients who had a poor response to P2Y12 inhibitors (15.6%, vs. 34.5% at the time of the procedure; $p < 0.001$).

At 1 year of follow-up, the primary end point had occurred in 34.6% of patients in the monitoring-group and 31.1% of those in the conventional-treatment group ($p = 0.10$). The results were consistently similar for all secondary end points.

Bleeding events occurred in less than 5.0% of patients. The rate of major bleeding events did not differ significantly between the two groups (hazard ratio with monitoring, 0.70; 95% confidence interval [CI], 0.43 to 1.14). The results were similar for minor bleeding events.

WHAT HAVE WE LEARNED FROM ARCTIC?

First, ARCTIC confirmed that high platelet reactivity during treatment with aspirin is uncommon and can be overcome by the administration of an additional bolus of aspirin. In contrast, high platelet reactivity during treatment with clopidogrel is common and can be managed with an additional bolus of clopidogrel or prasugrel and by glycoprotein IIb/IIIa inhibition during the procedure.

Second, in the ARCTIC study, P2Y12 inhibition and glycoprotein IIb/IIIa inhibition were both intensified (when monitoring showed a poor response to clopidogrel) before stent placement (In contrast to the approaches used in previous studies) in order to prevent periprocedural events, and were continued after the intervention, and adjusted at 14 to 30 days to improve the long-term outcome. In addition, patients with a poor response to aspirin were simultaneously monitored and treated. Nevertheless, no hint of improvement in ischemic outcomes and no better safety outcomes with a strategy of monitoring and drug adjustment as compared with a conventional treatment strategy could be detected.

Third, although platelet function is almost a modifiable risk factor, but absence of an association between stronger antiplatelet therapy and ischemic outcomes has always been observed in randomized trials and the results of ARCTIC study suggests that this marker of risk has limited value in guiding therapeutic decisions.

Finally, there is an ongoing, randomized ANTARCTIC study (Assessment of a Normal versus Tailored Dose of Prasugrel after Stenting in Patients Aged >75 Years to Reduce the Composite of Bleeding, Stent Thrombosis and Ischemic Complications; ClinicalTrials.gov number, NCT01538446) will assess the value of platelet-function testing in older patients, with a focus on the prevention of bleeding events. In addition to the ongoing phase of the current study, ARCTIC-2 is designed to determine the

most effective duration of treatment; a second randomization for the continuation versus interruption of dual treatment occurred 1 year after the first randomization.

REFERENCES

[1] Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Ruven HJ, Bal ET, Deneer VH, Harmsze AM, van der Heyden JA, Rensing BJ, Suttorp MJ, Hackeng CM, ten Berg JM. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. *JAMA*. 2011;305(21):2172–2174.

[2] Buonamici P, Marcucci R, Migliorini A, Gensini GF, Santini A, Paniccia R, Moschi G, Gori AM, Abbate R, Antoniucci D. Impact of platelet reactivity after clopidogrel administration on drug-eluting stent thrombosis. *J Am Coll Cardiol*. 2007;49(24):2312–2317.

[3] Brar SS, ten Berg J, Marcucci R, Price MJ, Valgimigli M, Kim HS, Patti G, Breet NJ, DiSciascio G, Cuisset T, Dangas G. Impact of platelet reactivity on clinical outcomes after percutaneous coronary intervention: a collaborative meta-analysis of individual participant data. *J Am Coll Cardiol*. 2011;58(19):1945–1954.

[4] Cuisset T, Frere C, Quilici J, Morange PE, Mouret JP, Bali L, Moro PJ, Lambert M, Alessi MC, Bonnet JL. Glycoprotein IIb/IIIa inhibitors improve outcome after coronary stenting in clopidogrel nonresponders: a prospective, randomized study. *JACC Cardiovasc Interv*. 2008;1(6):649–653.

[5] Valgimigli M, Campo G, de Cesare N, Meliga E, Vranckx P, Furgieri A, Angiolillo DJ, Sabatè M, Hamon M, Repetto A, Colangelo S, Brugaletta S, Parrinello G, Percoco G, Ferrari R, Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel (3 T/2R) Investigators. Intensifying platelet inhibition with tirofiban in poor responders to aspirin, clopidogrel, or both agents undergoing elective coronary intervention: results from the double-blind, prospective, randomized Tailoring Treatment with Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel study. *Circulation*. 2009;119(25):3215–3222.

[6] Trenk D, Stone GW, Gawaz M, Kastrati A, Angiolillo DJ, Müller U, Richardt G, Jakubowski JA, Neumann FJ. A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents: results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) study. *J Am Coll Cardiol*. 2012;59(24):2159–2164.

[7] Price MJ, Berger PB, Teirstein PS, Tanguay JF, Angiolillo DJ, Spriggs D, Puri S, Robbins M, Garratt KN, Bertrand OF, Stillabower ME, Aragon JR, Kandzari DE, Stinis CT, Lee MS, Manoukian SV, Cannon CP, Schork NJ, Topol EJ. GRAVITAS Investigators Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA*. 2011;305(11):1057–1097.

[8] Aradi D, Komócsi A, Price MJ, Cuisset T, Ari H, Hazarbasanov D, Trenk D, Sibbing D, Valgimigli M, Bonello L, On behalf of the Tailored Antiplatelet Treatment Study Collaboration. Efficacy and safety of intensified antiplatelet therapy on the basis of platelet reactivity testing in patients after percutaneous coronary intervention: systematic review and meta-analysis. *Int J Cardiol*. 2012 Jun 15, [Epub ahead of print].

[9] Collet JP, Cayla G, Cuisset T, Elhadad S, Rangé G, Vicaut E, Montalescot G. Randomized comparison of platelet function monitoring to adjust antiplatelet therapy versus standard of care: rationale and design of the assessment with a double randomization of (1) a fixed dose versus a monitoring-guided dose of aspirin and clopidogrel after DES implantation, and (2) treatment interruption versus continuation, 1 year after stenting (ARCTIC) study. *Am Heart J*. 2011;161(1):5e5–12e5.

[10] Montalescot G, White HD, Gallo R, Cohen M, Steg PG, Aylward PE, Bode C, Chiariello M, King SB 3rd, Harrington RA, Desmet WJ, Macaya C, Steinhubl SR, for the STEEPLE Investigators. Enoxaparin versus unfractionated heparin in elective percutaneous coronary intervention. *N Engl J Med*. 2006; (355):1006–1017.