the authors investigated the clinical efficacy of prasugrel in clopidogrel nonresponders undergoing percutaneous coronary intervention (PCI) with drug-eluting stents. As stated by the authors, clopidogrel nonresponse or high on-treatment platelet reactivity (HTPR) after a clopidogrel loading dose has been identified as a major risk factor for recurrent ischemic events in acute coronary syndrome patients undergoing PCI. It is associated with an increased risk of cardiovascular (CV) death, myocardial infarction, and stent thrombosis (2). Consistent with the results of this study, a meta-analysis by Aradi et al. (3) suggested that HTPR was associated with a 3.35-fold increase in CV mortality. This issue is very relevant because a large majority of patients undergoing PCI are currently treated with clopidogrel despite its limitations.

However, the RECLOSE 3 trial has methodological limitations that distort its conclusion. First, as stated by the authors, it is a historical cohort comparison with the RECLOSE 2 (REsponsiveness to CLOpidogrel and Stent Thrombosis 2) trial, which represents the "control" group of clopidogrel nonresponders. However, the RECLOSE 2 trial was already an interventional trial in which clopidogrel nonresponders had an increase in their clopidogrel maintenance dose in order to reach a platelet reactivity (PR) <70% on an adenosine diphosphate test. This group of patients therefore cannot represent a valid clopidogrel nonresponders group. Second, the RECLOSE 3 trial population, unlike that of the RECLOSE 2 trial, included stable patients who are at low risk of events and in whom HTPR has limited prognosis implications (4). This could skew the results despite adjustments, and they should have been excluded from the analysis.

Third, in the present study, there are 2 limitations to the antiplatelet therapy protocol proposed. First, no prasugrel loading dose was used. It is well demonstrated that most events related to HTPR are early events, including periprocedural events, and therefore a prasugrel loading dose should have been used to optimize PR inhibition (3). In addition, the duration of dual antiplatelet therapy is not provided. After publication of the DAPT trial, it could be postulated that a difference in the duration of dual antiplatelet therapy between the 2 groups may have contributed to the observed difference in outcome (5).

Another major limitation lies in the fact that bleeding events were not reported. In fact, prasugrel is associated with a significant increase in major bleeding events in ACS patients undergoing PCI, which could offset its potential benefit on ischemic events. Balancing ischemic and bleeding events is critical to improve outcomes in patients undergoing PCI.

Finally, several studies have investigated the potential of PR monitoring in order to improve the outcome in patients with HTPR undergoing PCI. However, although small studies had promising results, large-scale randomized trials failed to show any difference in outcome. An adequately designed and powered trial is still warranted to provide a safe and efficient alternative to clopidogrel in patients with HTPR. Selection of patients and of the intervention to overcome HTPR will be critical in this lasting odyssey.

*Laurent Bonello, MD, PhD
Françoise Dignat-George, PhD
Marc Laine, MD

*MARS Cardio Cardiology Department
Hopital Universitaire Nord
Chemin des Bourrely
13015 Marseille
France
E-mail: laurentbonello@yahoo.fr

http://dx.doi.org/10.1016/j.jcin.2015.10.017

Please note: Dr. Bonello has received honoraria from AstraZeneca and Eli Lilly and research grants from AstraZeneca. The other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Valenti R, Marcucci R, Comito V, et al. Prasugrel in clopidogrel non-responders undergoing percutaneous coronary intervention: the RECLOSE (REsponsiveness to CLOpidogrel and StEnt Thrombosis) 3 study. J Am Coll Cardiol Intv 2015;8:1563–70.

2. Tantry US, Bonello L, Aradi D, et al., Working Group on On-Treatment Platelet Reactivity. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol 2013;62:2261–3.

3. Aradi D, Komócsi A, Vorobcsuk A, et al. Prognostic significance of high on-clopidogrel platelet reactivity after percutaneous coronary intervention: systematic review and meta-analysis. Am Heart J 2010;160:543–51.

4. Park DW, Ahn JM, Song HG, et al. Differential prognostic impact of high on-treatment platelet reactivity among patients with acute coronary syndromes versus stable coronary artery disease undergoing percutaneous coronary intervention. Am Heart J 2013;165:34–42.

5. Mauri L, Kereiakes DJ, Yeh RW, et al., DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371:2155–66.

REPLY: Personalized Antiplatelet Therapy: The Odyssey Continues

We appreciate the interest of Dr. Bonello and colleagues in our paper on the RECLOSE-3 (REsponsiveness to CLOpidogrel and StEnt Thrombosis 3) study (1). However, all their comments and criticisms

reveal a misunderstanding of the paper because all the points they raised were already discussed and clarified in the paper. First, the aim of the study was to test the hypothesis that nonresponsiveness to clopidogrel is a modifiable risk factor and not the comparison of prasugrel with clopidogrel, and ethical issues make unlikely the possibility to perform a randomized study using clopidogrel in the control arm in clopidogrel nonresponders. Second, in the RECLOSE-2 study, as well as in the GRAVITAS (Gauging Responsiveness with a VerifyNow P2Y12 Assay: Impact on Thrombosis and Safety) trial, tailored therapy with an increased dose of clopidogrel in clopidogrel nonresponders had some effect on in vitro tests, but no clinical benefit (2,3). Thus, the historical cohort of the RECLOSE-2 trial may be used as the control arm. Third, the differences in baseline characteristics between the 2 patients groups were rigorously considered in the multivariable analyses. Fourth, the duration of prasugrel treatment, as well as the major and minor bleeding events, was clearly reported, with an increase in minor bleeding rate in prasugrel-treated patients, whereas no difference between groups was revealed in major bleeding, and the last finding supports the safety profile of prasugrel in clopidogrel nonresponders. Finally, the demonstration that high residual platelet reactivity on clopidogrel is a modifiable risk factor puts an end to what Dr. Bonello and colleagues define inappropriately as an odyssey.

Renato Valenti, MD
***David Antoniucci, MD**
*Division of Cardiology
Careggi Hospital
Viale Pieraccini 17
Florence I-50134
Italy
E-mail: david.antoniucci@virgilio.it

http://dx.doi.org/10.1016/j.jcin.2015.10.015

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Valenti R, Marcucci R, Comito V, et al. Prasugrel in clopidogrel non-responders undergoing percutaneous coronary intervention: the RECLOSE (REsponsiveness to CLOpidogrel and StEnt Thrombosis) 3 Study. J Am Coll Cardiol Intv 2015;8:1563–70.

2. Parodi G, Marcucci R, Valenti R, et al. High residual platelet reactivity after clopidogrel loading and long-term cardiovascular events among patients with acute coronary syndromes undergoing PCI. JAMA 2011;306:1215–23.

3. Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. JAMA 2011;305:1097–105.

Cerebral Embolization After Implantation of a Balloon-Expandable Aortic Valve Without Prior Balloon Valvuloplasty

When Is Doing Less More?

Transcatheter aortic valve replacement (TAVR) is an established therapeutic option for patients with severe symptomatic aortic stenosis. However, the periprocedural stroke rate continues to be relatively high, ranging between 3% and 5% in randomized clinical trials and large registries (1,2). Despite the evolution of the transcatheter valve, delivery system design, and procedural techniques, stroke rates have not diminished. Additionally, studies that have utilized diffusion-weighted magnetic resonance imaging have demonstrated a high rate of silent cerebral emboli upwards of 70% during TAVR (3). Although these findings may reflect, to some extent, the nature of TAVR in a high-risk patient with multiple comorbidities, this may also reflect a fundamental limitation of the procedure. In fact, transcranial Doppler studies during TAVR have highlighted the occurrence of cerebral embolization at virtually all of the time points during the procedure but seem most frequent during valve positioning and implantation, suggesting a mechanical interaction between the transcatheter valve and the native aortic valve. In particular, procedural variables suggest that mechanical factors such as balloon post-dilation, valve dislocation or embolization, or the need for a second valve are associated with a higher cerebrovascular event rate (4). Additionally, these studies have identified the lowest number of transcranial Doppler events occurring during balloon aortic valvuloplasty (BAV).

Given these considerations, we read with much interest the recent paper by Bijuklic et al. (5) in *JACC: Cardiovascular Interventions* evaluating the effect of TAVR without versus with prior BAV on the risk of cerebral embolization in 87 patients who received a balloon-expandable valve. Their procedural success rate was 93.5% with and 98.2% without BAV, and procedure duration and contrast volume were significantly lower without BAV. The incidence of new cerebral ischemic lesions in the total cohort was 66.7%. Compared with patients with BAV, those without BAV had a significantly higher total volume