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EDITORIAL

Influence of Platelet Reactivity on Outcome of Patients With Acute Myocardial Infarction Undergoing Primary Angioplasty

Giuseppe Patti, MD; Annunziata Nusca, MD

Dual antiplatelet therapy with aspirin and clopidogrel is a cornerstone in the management of patients undergoing percutaneous coronary interventions (PCI). However, cardiac events may occur even in patients on chronic antiplatelet therapy, because of the multifactorial pathogenesis of atherothrombosis and differences in the response to antiplatelet drugs; in particular, inter-individual variability in clopidogrel responsiveness has been widely noted and is a contemporary topic in interventional cardiology. Recent studies have demonstrated the prognostic effect of a low responsiveness to clopidogrel, identified as high residual platelet reactivity (HRPR) by platelet function tests, on short- and long-term clinical outcomes in patients undergoing PCI for stable angina or acute coronary syndromes.[1,2] Thus, a crucial point is the techniques of measuring platelet function, as well as the laboratory definitions of impaired response. Point-of-care assays of platelet function have become recently available, including the VerifyNow system, a rapid turbidimetry-based optical detection device.[3] If corroborated by results of definitive studies, use of those point-of-care assays might be integrated into routine clinical practice in order to achieve a risk stratification of patients undergoing PCI and to perform individualized therapy aimed at reducing the risk of both ischemic and bleeding events.

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In this issue of the Journal, Vavuranakis et al[4] explore the correlation between HRPR after clopidogrel loading, assessed by the VerifyNow assay, and angiographic endpoints in patients with ST-segment elevation myocardial infarction (STEMI) undergoing unexpectedly delayed primary PCI (time from first medical contact to balloon >2 h). All 74 patients enrolled in this prospective study had received a 600-mg clopidogrel loading dose before the intervention. HRPR was associated with angiographic detection of large thrombus burden in the culprit vessel, and, concordantly, lower platelet reactivity, expressed by P2Y12 Reaction Units (PRU) levels, was observed in patients with TIMI-flow grade 3 and normal myocardial blush grade after primary PCI; these results confirm the relevant role of platelet activation in the pathogenesis of acute MI, but also in determining procedural complications, such as distal microembolization and the no-reflow phenomenon, that may compromise the success rate of the primary intervention. Moreover, in a sub-study of the STRATEGY trial,[5] TIMI-flow grade <3, no-reflow and high corrected TIMI frame counts occurred more frequently in STEMI patients with elevated baseline platelet reactivity. In particular, in the setting of STEMI, increased platelet activation may be also caused by the short time between administration of antiplatelet drugs and the intervention, which may limit the effects of the antiplatelet agents, especially at standard doses; in such patients a relationship between platelet reactivity and the extent of myocardial necrosis has been also observed.[6] Platelet reactivity on admission significantly affects the risk of major adverse cardiac events (MACE) during follow-up after PCI, and may influence the angiographic success of the intervention.[5] Thus, evaluation of the individual response to antiplatelet agents might have a relevant prognostic role, especially in patients with acute coronary syndromes, in whom platelet inhibition represents an important target of treatment beyond pure mechanical intervention, and use of newer, more effective antiplatelet drugs, such as prasugrel,[7] may improve the degree of platelet inhibition and significantly decrease the incidence of ischemic events.

Recent studies were conducted to identify a clinically driven PRU threshold for predicting adverse clinical events after PCI, demonstrating a significant association between HRPR and worse prognosis. In our ARMYDA-PRO study,[2] HRPR after clopidogrel administration, measured by the VerifyNow assay at the time of intervention, was associated with a 6-fold higher incidence of 30-day MACE; a recent meta-analysis on 6 prospective studies[8] enrolling a total of 3,059 patients, showed that the optimal cut-off value to predict death, MI, or stent thrombosis during long-term follow-up after PCI was a PRU value >230, with corresponding sensitivity, specificity, positive predictive value, and negative predictive values of 55%, 65%, 11%, and 95%. In their study, Vavuranakis et al[4] explored the correlation between HRPR and angiographic endpoints in the setting of primary PCI for STEMI, identifying a threshold of ≥251.5 PRU as an independent predictor of thrombus grade C (OR=39.27); a significant relationship between HRPR and poorer clinical outcome in STEMI patients was also found in a recent observational, prospective investigation, in which baseline HRPR was associated with an adjusted 5- to 11-fold increase in the

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Department of Cardiovascular Sciences, Campus Bio-Medico University of Rome, Rome, Italy
Mailing address: Giuseppe Patti, MD, Department of Cardiovascular Sciences, Campus Bio-Medico University of Rome, Via Alvaro de Portillo, 200, 00128 Rome, Italy. E-mail: g.patti@unicampus.it
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risk of death, MI and target vessel revascularization at 1 year.[5] Thus, increasing data are now available for achieving a standardized definition of impaired clopidogrel response, as a result of the correlation between results of laboratory assays and clinical outcome. However, few studies have addressed the issue of whether individual clinical outcome may be modified when treatment is addressed according to the results of platelet function assays. In the GRAVITAS trial,[9] patients with HRPR, defined as PRU >230 measured within 24 h of PCI, were randomly assigned to high-dose (600 mg loading dose followed by 150 mg daily dose for 6 months) vs. standard-dose clopidogrel (no additional loading, and 75 mg daily); incidence of MACE at 6 months was similar in the 2 arms, without excessive bleeding in the high-dose group. However, in the hours after PCI there is a marked increase in platelet reactivity because of procedural platelet activation; thus, measurement of platelet reactivity when performed early after PCI is characterized by a low signal-to-noise ratio, and the results may not reflect the baseline individual degree of response to antiplatelet agents.[10] Accordingly, in the ARMYDA-PRO[2] and ARMYDA-BLEEDS[11] studies, only pre-intervention detection of on-treatment platelet reactivity predicted the risk of MACE for low-responders and the risk of bleeding for hyper-responders. The study by Vavuranakis et al[4] was not focused on clinical endpoints; however, the optimal PRU threshold identified in this study on STEMI patients was higher (PRU ≥251.5) than that observed in patients undergoing non-emergency PCI (PRU >230). A higher baseline platelet reactivity, as well as a low response to antiplatelet drugs, already described in STEMI patients, have been also identified in patients with diabetes mellitus;[12] thus, clinically driven thresholds of platelet reactivity might not be fixed and may vary according to clinical presentation or comorbidities. This intriguing concept, however, needs to be further investigated in specific studies.

Given the significant clinical impact of HRPR, which may be even more significant in the thrombogenic milieu of acute MI, an aggressive "antiplatelet strategy" has to be carefully considered in patients receiving primary PCI. STEMI patients present a higher platelet activation compared with stable syndromes and this may limit the effects of antiplatelet agents, especially at standard doses and when the time from antiplatelet therapy administration to PCI is reduced. In this clinical context, an "intense" platelet inhibition must be considered the "goal" strategy, and this may be obtained with higher doses of clopidogrel or, more consistently, with prasugrel. The extent of platelet inhibition after 300 mg clopidogrel in patients undergoing primary PCI may be variable and suboptimal, definitely far from 95%, the level assumed to be associated with better outcome, even when this loading dose was associated with glycoprotein IIb/IIIa inhibitors.[13] Moreover, the time to the peak antiplatelet effect after a 300-mg clopidogrel loading dose is at least 6–12 h, whereas a higher dose of 600 mg reduces this interval to 2 h and decreases the incidence of drug non-responsiveness.[13] Previous data have shown that a 600-mg clopidogrel loading dose consistently leads to greater platelet inhibition and reduces the incidence of MACE vs. the 300 mg regimen in patients with non-ST-segment elevation acute coronary syndromes and stable angina,[14] but the debate on the loading strategy of clopidogrel in patients with STEMI is still open. Observational studies evaluated 600 mg vs. 300 mg clopidogrel in patients undergoing primary PCI; in particular, an analysis from the randomized HORIZON AMI trial[15] demonstrated the superior efficacy of the higher regimen, with lower 30-day rate of mortality, reinfarction and stent thrombosis, and without excessive bleeding. In a recent multicenter randomized trial,[16] use of a 600-mg clopidogrel loading dose in STEMI patients undergoing primary PCI, as compared with the 300 mg strategy, decreased the infarct size, and improved post-procedural TIMI flow and left ventricular ejection fraction at discharge.

References

1. Aradi D, Komócsi A, Vorobcsuk A, Rideg O, Tokés-Füzesi M, Magyarlaki T, et al. Prognostic significance of high on-clopidogrel platelet reactivity after percutaneous coronary intervention: Systematic review and meta-analysis. *Am Heart J* 2010; **160:** 543–551.
2. Patti G, Nusca A, Mangiacapra F, Gatto L, D'Ambrosio A, Di Sciascio G. Point-of-care measurement of clopidogrel responsiveness predicts clinical outcome in patients undergoing percutaneous coronary intervention results of the ARMYDA-PRO study. *J Am Coll Cardiol* 2008; **52:** 1128–1133.
3. Michelson AD. Methods for the measurement of platelet function. *Am J Cardiol* 2009; **103:** 20A–26A.
4. Vavuranakis M, Vrachatis DA, Papaioannou TG, Archontakis S, Kalogeras KI, Kariori MG, et al. Residual platelet reactivity after clopidogrel loading in patients with ST-elevation myocardial infarction undergoing an unexpectedly delayed primary percutaneous coronary intervention: Impact on intracoronary thrombus burden and myocardial perfusion. *Circ J* 2011; **75:** 2105–2112.
5. Campo G, Valgimigli M, Gemmati D, Percoco G, Catozzi L, Frangione A, et al. Poor responsiveness to clopidogrel: Drug-specific or class-effect mechanism? Evidence from a clopidogrel-to-ticlopidine crossover study. *J Am Coll Cardiol* 2007; **50:** 1132–1137.
6. Frossard M, Fuchs I, Leitner JM, Hsieh K, Vlcek M, Losert H, et al. Platelet function predicts myocardial damage in patients with acute myocardial infarction. *Circulation* 2004; **110:** 1392–1397.
7. Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, et al; TRITON-TIMI 38 investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): Double-blind, randomised controlled trial. *Lancet* 2009; **373:** 723–731.
8. Brar SS, ten Berg J, Marcucci R, Price NJ, Valgimigli M, Kim HS, et al. Impact of platelet reactivity on clinical outcomes after percutaneous coronary intervention: Collaborative meta-analysis of individual participant data. *J Am Coll Cardiol* 2011 (in press).
9. Price MJ, Berger PB, Teirstein PS, Tanguay JF, Angiolillo DJ, Spriggs D, et al; GRAVITAS Investigators. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: The GRAVITAS randomized trial. *JAMA* 2011; **305:** 1097–1105.
10. Patti G, Pasceri V, Di Sciascio G. Standard- vs high-dose clopidogrel after percutaneous coronary intervention. *JAMA* 2011; **305:** 2520–2521.
11. Patti G, Pasceri V, Vizzi V, Ricottini E, Di Sciascio G. Usefulness of platelet response to clopidogrel by point-of-care testing to predict bleeding outcomes in patients undergoing percutaneous coronary intervention. *Am J Cardiol* 2011; **107:** 995–1000.
12. Mangiacapra F, Patti G, Peace A, Gatto L, Vizzi V, Ricottini E, et al. Comparison of platelet reactivity and periprocedural outcomes in patients with versus without diabetes mellitus and treated with clopidogrel and percutaneous coronary intervention. *Am J Cardiol* 2010; **106:** 619–623.
13. Ernst NM, Suryapranata H, Miedema K, Slingerland RJ, Ottervanger JP, Hoorntje JC, et al. Achieved platelet aggregation inhibition after different antiplatelet regimens during percutaneous coronary intervention for ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2004; **44:** 1187–1193.
14. Patti G, Colonna G, Pasceri V, Lassandro Pepe L, Montinaro A, Di Sciascio G. Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention: Results from the ARMYDA-2 study. *Circulation* 2005; **111:** 2099–2106.
15. Dangas G, Mehran R, Guagliumi G, Caixeta A, Witzenbichler B, Aoki J, et al; HORIZONS-AMI Trial Investigators. Role of clopidogrel loading dose in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty: Results from the HORIZONS-AMI trial. *J Am Coll Cardiol* 2009; **54:** 1438–1446.
16. Patti G, Bárczi G, Orlic D, Mangiacapra F, Colonna G, Pasceri V, et al. Outcomes comparison of 600 mg vs 300 mg loading dose of clopidogrel in patients undergoing primary percutaneous coronary interventions for ST-segment elevation myocardial infarction: Results from the Armyda 6 MI. *J Am Coll Cardiol* 2011 (in press).