Letter to the Editor

Body mass index has no impact on platelet inhibition induced by ticagrelor after acute coronary syndrome, conversely to prasugrel

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Dual antiplatelet therapy with aspirin and clopidogrel has been considered as a cornerstone therapy after acute coronary syndrome (ACS) before new P2Y12 blockers demonstrated their clinical benefit in large randomized controlled trials [1,2]. European guidelines [3] recommended the use of prasugrel or ticagrelor in ACS patients as first choice, preferred with a higher level of evidence than clopidogrel (level B for both versus C). These drugs are characterized by a more rapid onset of action and a higher efficacy, inducing stronger platelet inhibition than clopidogrel. In recent years, obesity has become a major public health problem; obese patients exhibiting an unfavorable cardiovascular prognosis. The clinical relevance of platelet function testing has been well demonstrated for both ischemic and bleeding events with clopidogrel [4]. However several studies investigating platelet reactivity in patients treated with thienopyridines identified obesity as an important modulator of response to both clopidogrel [5] and prasugrel [6] and could suggest that antiplatelet therapy in this growing subgroup of patients should be optimized. Few studies have already suggested obesity as an independent factor that intervenes negatively in the clopidogrel responsiveness, which is not corrected by an increase of clopidogrel dosage [5,6]. However, our recent study clearly showed that this strategy is ineffective in the obese; we observed a significant linear relationship between body mass index (BMI) and the response to thienopyridines (clopidogrel 75 or 150 mg, or prasugrel 10 mg) [6]. Prasugrel appears to be a more effective alternative in case of obesity with significantly lower High on Treatment Platelet Reactivity (HTPR) rate than observed on clopidogrel. Nevertheless HTPR persists in some obese patients on prasugrel after an ACS. Ticagrelor proved his superiority on prasugrel concerning platelet inhibition after an ACS [7]. Therefore, the present biological study was designed to evaluate the impact of BMI on platelet inhibition induced by ticagrelor, in comparison with prasugrel, in patients undergoing percutaneous coronary intervention for ACS. All consecutive patients admitted for ACS with successful stent implantation in our institution were eligible. Patients were randomized and received a loading dose of ticagrelor 180 mg or prasugrel 60 mg and were treated at discharge with ticagrelor 90 mg twice a day or prasugrel 10 mg once. Non-inclusion criteria were a history of bleeding diathesis, prior stroke or transient ischemic attack, renal impairment (clearance <25 mL/min), severe hepatic impairment, and platelet count <100 G/L. All of them were reevaluated at one month during a follow up visit. Adherence to the therapy was systematically assessed at enrollment and at one month visit. Antiplatelet response was assessed one month after ACS with Platelet Reactivity Index VASP (PRI VASP). Patients were classified as obese depending on BMI (BMI ≥30 kg/m²). Overweight was defined by 25 ≤ BMI < 30 kg/m². HTPR was defined as PRI VASP > 50%, very low on treatment platelet reactivity (VLTPR) as PRI VASP ≤ 10% [8] and normo on treatment platelet reactivity as 10% < PRI VASP ≤ 50%. Obese patients were classified in two groups in which platelet reactivity was compared: obese without metabolic disorder according to NCEP III and obese with Metabolic syndrome determined by at least three of the five following criteria: waist circumference (>102 cm for male and >88 cm for female), hypertriglyceridaemia (triglycerides ≥1.7 mmol/L), low HDL-cholesterol (<1 mmol/L for male and <1.3 mmol/L for female), fasting glucose (≥6.1 mmol/L), and blood pressure (≥130 and/or ≥85 mm Hg). The Bleeding Academic Research Consensus definitions of bleeding were used [9]. Primary endpoints of the present study were defined as: correlation of degree of platelet inhibition and body mass index in patients treated with ticagrelor and prasugrel, one month after an ACS. Secondary endpoint consisted in the comparison between prasugrel and ticagrelor in obese patients. We
studied the impact of BMI and metabolic syndrome on platelet reactivity status according to antiplatelet therapy. The protocol was approved by the local medical ethics committee and conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained from each patient. The authors have certified full adherence with the principles of ethical publishing described in the International Journal of Cardiology. Statistical significance was defined as \( p < 0.05 \).

Between March and December 2013 186 patients were included after ACS, 93 patients were assigned to ticagrelor and 93 to prasugrel. No significant difference on basal characteristics was observed between the two cohorts. Of note, mean BMI was 26.5 ± 4.2 kg/m². 27 patients (15%) were defined as obese and 77 (41%) as overweight. 19 obese were defined as metabolic syndrome (11 on prasugrel and 9 on ticagrelor). All these patients received Aspirin 75 mg in association to P2Y12 inhibitor and all of them received a statin therapy, as well as proton pom inhibitor. We observed 13 bleeding complications (n = 24 patients). A majority of BARC1 bleedings were reported (83%). At one month, PRI VASP was 18.7 ± 11.5% on ticagrelor versus 34.0 ± 15.3% on prasugrel. Interestingly, only one patient was defined as HTPR (BMI = 24.6 kg/m²), 27 (29%) were classified as VLTPR on ticagrelor. On prasugrel we observed 13 HTPR patients (BMI = 28.9 kg/m²), 4 (4%) were classified as VLTPR. No significant correlation between BMI and platelet inhibition was observed (\( r = 0.04; p = 0.72 \)) on ticagrelor unlike prasugrel (\( r = 0.32; p < 0.01 \)) (Fig. 1A and B).

On ticagrelor, no difference is observed on PR between obese and non obese patients (\( p = 0.20 \)) and between overweight and non overweight patients (\( p = 0.49 \)). Inversely on prasugrel we reported significantly higher levels of PRI VASP in overweight patients (\( p < 0.001 \) compared with others) and obese patients (\( p < 0.01 \) compared with others) (Fig. 2).

PRI VASP comparison in obese patients reported significantly lower levels in ticagrelor treated patients (20.9 ± 2.8% vs. 45.9 ± 3.6%; \( p < 0.001 \)). Among the obese patients, we observed a strong impact of metabolic syndrome on response to prasugrel with significantly impaired response in obese with metabolic syndrome compared with obese without metabolic syndrome (Fig. 3). Interestingly, on ticagrelor this difference did not remain significant. Prasugrel is significantly associated with HTPR in obese (\( p < 0.01 \)) and overweight patients (\( p < 0.05 \)) in comparison with ticagrelor.

The present study investigates the impact of BMI on platelet inhibition induced by ticagrelor in comparison with prasugrel. Conversely to thienopyridine, no correlation was reported between BMI and PRI VASP on ticagrelor; obese patients do not express significantly higher level of platelet reactivity. Ticagrelor induces significantly higher platelet inhibition than prasugrel in obese patients. Antiplatelet management of ACS patients evolved and molecule choice has to integrate all individual co-factors, weighing up ischemic versus bleeding risk factors, providing a suitable treatment for each patient. In recent years, obesity has become a major public health problem and coronary artery disease is the primary cause of death in obese patients. Recent findings clearly supported the need for optimization of antiplatelet therapy and platelet function tests could help practitioners to identify ‘low responders’ as candidates for treatment adaptation. On thienopyridine a linear correlation between platelet reactivity and BMI is reported. The strategy consisting in increasing clopidogrel dosage or switching to prasugrel has clearly shown its limits, resulting in a large unprotected population. [6] Conversely on cyclopentyl-triazolo-pyrimidines (ticagrelor) obesity...
seems not to be a modulator of platelet inhibition as evidenced by the absence of correlation between BMI and PRI VASP. In obese patients we reported the superiority of ticagrelor on prasugrel concerning platelet inhibition with significantly lower levels of PRI VASP. We observed a significant impact of metabolic syndrome on platelet inhibition for patients treated with prasugrel, conversely to ticagrelor. A recent survey from our group proved that switching prasugrel low responders to ticagrelor leads to an adequate platelet inhibition, corresponding in switching from thienopyridine to cyclopentyl-triazolo-pyrimidines [10]. In daily practice, it is expected that switching therapy occurs frequently during in-hospital management of ACS patients, and a guided switching based on main clinical predictors of wrong response or/and platelet testing could be advocated for high risk patients. In the present study we observed that HTPR is really uncommon on ticagrelor, which also remains true in obese patients. In this perspective ticagrelor is an effective strategy for ACS management of obese patients and significantly less associated with high platelet reactivity in this population. Determination of ticagrelor effectiveness modulators is the next challenge in future ACS management.

In conclusion the present study suggests that platelet inhibition induced by ticagrelor is not correlated with BMI, unlike prasugrel. This highlights the potential value of ticagrelor in obese patients and suggests the potential benefit of tailored therapy based on BMI.

Declaration of conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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References