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EDITORIAL COMMENT

Potent $P2Y_{12}$ Inhibitors in Low-Risk Patients

Is There a Medical Need?*

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The oral $P2Y_{12}$ inhibitors prasugrel and ticagrelor have demonstrated biological and clinical superiority over clopidogrel, with a faster onset of action and greater potency, which translate into improved clinical outcomes in patients with acute coronary syndrome (ACS) (1,2). They have very similar pharmacodynamics, and fit the need for expedited mechanical reperfusion in patients presenting with a partially occlusive thrombus in non–ST-segment elevation myocardial infarction (NSTEMI) or with a fully occlusive thrombus in ST-segment elevation myocardial infarction (STEMI). Whether these drugs are useful when there is no thrombus, no myocardial infarction (MI), and no emergency in patients presenting for a scheduled percutaneous coronary intervention (PCI), is unknown. Benefits observed with prasugrel and ticagrelor on stent thrombosis, major adverse cardiovascular events, and even mortality in ACS patients may not be found in lower-risk populations (3). Similarly, the latest European Society of Cardiology guidelines recommend ticagrelor in moderate- to high-risk ACS patients (e.g., with elevated troponin) (1), and a post hoc analysis of the PLATO (Platelet Inhibition and Patient Outcomes) study suggested little, if any, benefit in troponin-negative patients (4). European guidelines for stable coronary artery disease (CAD) consistently recommend clopidogrel only for coronary stenting in stable patients, and advise no pretreatment before a patient's coronary status and indication for revascularization are known (5).

However, knowing that the majority of these procedures are performed on an ad hoc basis and that some patients may be at high risk, prasugrel and ticagrelor have been given a class IIb recommendation, although acknowledging the critical absence of data (Level of Evidence: C). This uncertainty has led to great variations in practice. Off-label use of prasugrel and ticagrelor is increasingly frequent in elective PCI, especially when patients undergo high-risk elective procedures (left main stenting, bifurcations, multiple stenting, or any situation identified as high-risk for stent thrombosis) or present with high-risk features for ischemic events (advanced age, renal dysfunction, diabetes, genetic clopidogrel resistance, or absence of clopidogrel pre-treatment, among others). This has led investigators to design studies using prasugrel or ticagrelor in elective PCI.

In the PRASFIT-Elective (PRASugrel For Japanese PatIenTs with Coronary Artery Diseases Undergoing

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Elective PCI) study (6), patients scheduled for elective coronary artery stenting were randomized to receive either prasugrel (20-mg loading dose [LD]; 3.75-mg maintenance dose [MD]) or clopidogrel (300-mg LD; 75-mg MD) in a double-blind manner. The hypothesis that safety could be improved with a lower-dose regimen in the Japanese population was tested with these doses of prasugrel, 3 times lower than current doses approved in Western countries. Prasugrel's more rapid onset of action and greater potency compared with clopidogrel were preserved. The risk/benefit ratio was apparently optimized in this population, although the trial was not powered to demonstrate superior clinical efficacy. This experience is in addition to other randomized studies favorable to prasugrel (standard-dose regimen) in scheduled PCI (7–11). No such experience of dose lowering has been obtained with ticagrelor in elective PCI. On the contrary, doses higher than 180 mg have been tested without significant improvement of platelet inhibition (12). However, a lower MD of ticagrelor (60 mg twice a day) was tested in secondary prevention of MI with an optimized risk/benefit ratio (13).

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In this issue of the *Journal*, Angiolillo et al. (14) provide new information on the pharmacodynamics of ticagrelor (standard dose regimen), obtained in patients undergoing elective stenting. This randomized comparison with the standard of care (clopidogrel 600 mg) is a necessary preliminary step before larger clinical trials are performed. The investigators elegantly studied the biological effects of ticagrelor and clopidogrel in patients undergoing coronary angiography for suspected CAD or ACS, in whom ad hoc PCI was to be performed. These patients were not pre-treated with a $P2Y_{12}$ receptor inhibitor, as the coronary anatomy was not known and the

TABLE 1 Next Randomized Studies of Ticagrelor in Elective PCI and Stabilized ACS Treated by PCI

	ALPHEUS	TWILIGHT
Group	ACTION group at Pitié-Salpêtrière, Paris 6	Icahn School of Medicine at Mount Sinai, New York
Trial	Randomized	Randomized
Phase	4	4
Masking	Open label	Double-blind
Primary outcome measures	Ischemic event (PCI-related myocardial infarction (MI type 4) or injury [I])	Bleeding event (BARC 2, 3 or 5)
Safety outcome measures	Bleeding event (BARC 3 or 5)	Ischemic event (CV death, nonfatal MI, ischemic stroke or ischemia-driven revascularization)
Time frame post-PCI	48 h-30 days	3-15 months
Estimated enrollment	1,900	9,000
Centers	Multicenter-international	Multicenter-international
Treatment evaluated	Ticagrelor LD 180 mg, MD 90 mg bid	Ticagrelor 90 mg bid + placebo
Comparator	Clopidogrel LD (300-600 mg), MD (75-150 mg)	Ticagrelor 90 mg bid + aspirin 81mg
Population	Elective PCI with high-risk features	High-risk patients - Elective PCI or ACS treated by PCI with DES
Inclusion	Before PCI	After 3 months of DAPT
High-risk features required: - at least 1 for ALPHEUS - 1 clinical + 1 angiographic for TWILIGHT	Age >75 yrs Renal insufficiency (clearance <60 ml/min) Diabetes mellitus Overweight (BMI >30) History of ACS (in the past 12 months) Left ventricular ejection fraction <40% and/or prior episode of heart failure Multivessel disease Multiple stents needed or total stent length envisioned >30 mm Left main stenting Bifurcation stenting ACC/AHA type B2 and C lesion Stenting of venous or arterial coronary graft Undergoing nonemergent single or multiple site/vessel PCI during the same procedure	Adult patients ≥65 yrs of age Recent (≥3 days) presentation with ACS with clinical stabilization and decreasing cardiac enzymes Established vascular disease (previous MI, PAD, or CAD/PAD revascularization) Diabetes mellitus Chronic kidney disease (eGFR) <60 ml/min/1.73m^2 or creatinine clearance <60 ml/min Multivessel coronary artery disease Target lesion requiring total stent length >30 mm SYNTAX Score ≥23 Bifurcation lesions with Medina X, X, 1 classification requiring at least 2 stents Left main (≥50%) or proximal LAD (≥70%) lesion Calcified target lesion requiring atherectomy

ACC/AHA = American College of Cardiology/American Heart Association; ACS = acute coronary syndrome; ALPHEUS = Assessment of Loading with a new P2Y12 inhibitor or clopidogrel to Halt ischemic Events in patients Undergoing elective coronary Stenting; BARC = Bleeding Academic Research Consortium; bid = twice a day; BMI = body mass index; CAD = coronary artery disease; CV = cardiovascular; DAPT = Dual Anti-Platelet Therapy; DES = drug-eluting stents; eGFR = estimated glomerular filtration rate; LAD = left anterior descending; LD = loading dose; MD = maintenance dose; MI = myocardial infarction; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery; TWILIGHT = Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention trial.

treatment options not yet decided. This strategy is aligned with recent publications (15,16) and with both American and European guidelines (1,2,5). The investigators found that 2 h after the loading dose, $P2Y_{12}$-mediated platelet reactivity was lower in ticagrelor-treated patients than in clopidogrel-treated patients, and that the difference was already apparent at the end of PCI (average of 36 min after loading). They rightfully conclude that, in low-risk ACS patients undergoing ad hoc PCI, the ticagrelor LD provides more prompt and potent platelet inhibition and lower rates of patients with high platelet reactivity than the 600-mg clopidogrel LD. These data are very similar to the platelet sub-study of the ACCOAST (A Comparison of Prasugrel at PCI or Time of Diagnosis of Non-ST-Elevation Myocardial Infarction) trial, which showed that 1 h after prasugrel loading on the catheterization table, its platelet inhibitory effect was reached and was no different from the effect obtained in the group of patients loaded with prasugrel the day before (17).

Considering these pharmacodynamic results, PCI is performed without effective $P2Y_{12}$ inhibition at the time of stent implantation, and the potential impact on clinical outcomes is not yet known. Both the ACCOAST study in NSTEMI patients and the ATLANTIC (Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery) study in STEMI patients showed no advantage of earlier treatment on their primary endpoints, a composite clinical ischemic endpoint in ACCOAST and reperfusion endpoints in ATLANTIC (18,19). If anything, analysis of the 2 studies suggested that most events occurred after PCI, not during the procedure. Compared with clopidogrel, the rapid onset of action of ticagrelor and prasugrel and the immediate onset of action of cangrelor can prevent many of these events, particularly periprocedural MI and stent thrombosis (20,21). Similar considerations may apply to elective PCI, but need to be shown. The other concern, of course, is safety, as it would be unacceptable to reduce periprocedural MI at the cost of more major bleeding.

Elective PCI has become a safe procedure, especially with use of the latest generation of drug-eluting stents. Nonetheless, complications remain and can be considered frequent, but asymptomatic, when considering PCI-related myonecrosis/myocardial injury and, rare, but serious, when considering stent thrombosis, new MI, or stroke. All of these complications, including post-procedural myonecrosis, have been linked to patient prognosis (22). There is apparently room for improvement with the use of drugs such as ticagrelor in low-risk or stabilized ACS patients, as well as in stable CAD patients undergoing PCI. Two randomized clinical trials, TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention trial; NCT02270242) and ALPHEUS (Assessment of Loading with a new P2Y12 inhibitor or clopidogrel to Halt ischemic Events in patients Undergoing elective coronary Stenting; NCT02617290), explore this new frontier for $P2Y_{12}$ receptor inhibition in PCI patients. ALPHEUS compares ticagrelor and clopidogrel in elective PCI patients with high-risk features (e.g., diabetes, multivessel PCI, and so on), hypothesizing the superiority of ticagrelor to reduce the primary ischemic endpoint at 48 h (and 30 days), which includes asymptomatic peri-procedural complications that impair the prognosis of patients. The results of the study by Dr. Angiolillo et al. sustain our hypothesis that ticagrelor can blunt troponin release after PCI and prevent serious complications, such as stent thrombosis or MI. Crushed tablets will be used in ALPHEUS, as they improve the onset of action on platelet inhibition (23), and may help reach the study efficacy endpoint. In contrast, TWILIGHT is focused on safety and evaluates the use of ticagrelor alone compared with the combination of aspirin and ticagrelor during the post-PCI period (3 to 15 months), also considering elective PCI performed in patients with high-risk features (e.g., stabilized ACS, among others). These 2 trials are complementary, and both focus on a selected group of stable patients considered to be at high risk (**Table 1**). In the future, the change of paradigm for $P2Y_{12}$ inhibition in elective PCI may not concern all patients.

Elective PCI performed in stable CAD patients looks like a new potential indication for ticagrelor. There is a medical demand from physicians for intuitive protection when complex revascularization procedures are performed, a strategy somewhat supported by guidelines (7). Whether a medical need exists for patients will be known only after the results of the ongoing trials are published.

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