Clopidogrel pretreatment in primary percutaneous coronary intervention: Prevalence of high on-treatment platelet reactivity and impact on preprocedural patency of the infarct-related artery

José Luis Ferreiro*; Silvia Homs*; Javier Berdejo; Gerard Roua; Josep Gómez-Lara; Rafael Romaguera; Luis Teruel; Guillermo Sánchez-Élvia; Ana Lucrecia Marcano; Joan Antoni Gómez-Hospital; Dominick J. Angiolillo; Ángel Cequier

1Heart Diseases Institute, Bellvitge University Hospital – IDIBELL, University of Barcelona, L’Hospitalet de Llobregat, Barcelona, Spain; 2University of Florida College of Medicine-Jacksonville, Jacksonville, Florida, USA

Summary
To date, there is limited data on levels of platelet inhibition achieved in patients with ST-elevation myocardial infarction (STEMI) who are loaded with clopidogrel and aspirin (ASA) prior to undergoing primary percutaneous coronary intervention (P-PCI). The aim of this investigation was to evaluate the percentage of STEMI patients with high on-treatment platelet reactivity (HPR) to clopidogrel at the time of initiating P-PCI and its association with the initial patency of the infarct-related artery (IRA). This prospective pharmacodynamic study included 50 STEMI patients, previously naïve to oral antiplatelet agents, who received 500-mg ASA and 600-mg clopidogrel loading doses prior to P-PCI. Platelet function assessment was performed at the beginning of the procedure using various assays, including VerifyNow™ system (primary endpoint), light transmission aggregometry and multiple electrode aggregometry. The percentage of patients with suboptimal response to clopidogrel and ASA assessed with the VerifyNow™ system was 88.0% and 28.6%, respectively. Similar results were obtained with the other assays used. A higher percentage of patients with initial patency of the IRA was observed among those patients without HPR compared with those with HPR to clopidogrel (66.7% vs 15.9%; p=0.013), while no differences were observed regarding postprocedural angiographic or electrocardiographic outcomes. In conclusion, this study shows that a high percentage of STEMI patients have inadequate levels of clopidogrel-induced and, to a lesser extent, aspirin-mediated platelet inhibition when starting a P-PCI procedure, and suggests that a poor response to clopidogrel might be associated with impaired initial TIMI flow in the IRA.

Keywords
Clopidogrel responsiveness, ST-elevation myocardial infarction, antiplatelet therapy

Introduction
Dual antiplatelet therapy with aspirin (ASA) and a P2Y12 receptor blocker is currently the oral antiplatelet treatment of choice in patients suffering an acute coronary syndrome (ACS), including those with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (P-PCI) (1). Despite the introduction of novel and more potent P2Y12 receptor antagonists such as prasugrel and ticagrelor, clopidogrel is still broadly used in daily clinical practice including in the setting of P-PCI. Further, a considerable proportion of these patients are pretreated with a loading dose of clopidogrel at first medical contact with the emergency medical system (2). Importantly, clopidogrel pretreatment has shown to be of benefit in patients undergoing P-PCI (3-6). However, the pharmacodynamic (PD) efficacy of clopidogrel is subject to broad inter-individual variability (7) and a considerable proportion of patients, particularly in the setting of STEMI, present with high on-treatment platelet reactivity (HPR) (8, 9) which is associated with an increased risk of cardiovascular events (10).

To date, there is limited PD data in STEMI patients who have been pretreated with a loading dose (LD) of clopidogrel before undergoing P-PCI. The present study aimed to evaluate the percentage of STEMI patients with HPR at the very moment of initiating the procedure after receiving a LD of clopidogrel at the moment of diagnosis and its association with the initial patency of the infarct-related artery (IRA) in patients undergoing P-PCI as a reperfusion strategy.
Materials and methods

Subject population and study design

This is a prospective observational pharmacodynamics (PD) study that included consecutive patients admitted to a tertiary center with diagnosis of STEMI who received a 600-mg clopidogrel LD at the moment of diagnosis and prior to undergoing P-PCI. Patients could be first admitted at the emergency room of the tertiary hospital or quickly transferred by the emergency medical system from home or primary care centres (2). All patients were previously naïve to aspirin (acetylsalicylic acid, ASA) and clopidogrel. All patients were also treated with 500-mg ASA administered orally at the moment of diagnosis. Exclusion criteria were prior treatment with any antiplatelet agent, known allergies to aspirin or clopidogrel, cardiogenic shock, any active bleeding or malignancy, platelet count <100x10^3/µl, severe chronic kidney disease (creatinine clearance <30 ml/minute) and pregnant females. Technical procedures and drugs administration in the catheterisation lab were left at operator’s criteria according to standard clinical practice. Operators were unaware of the results of the platelet function assays. All patients received heparin (100 U/kg) at time of presentation per institution protocol, measuring activated-clotting time (ACT) when catheterisation is started, having an ACT target of 250-350 seconds (sec) and 200-250 sec in those receiving glycoprotein IIb/IIIa inhibitors (GPIs).

The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Bellvitge University Hospital. All subjects provided written informed consent to the study.

Endpoints, assessments of outcomes, and definitions

The primary endpoint was the evaluation of the association between clopidogrel HPR and patency of the IRA at the beginning of the procedure, which was evaluated with the Thrombolysis in Myocardial Infarction (TIMI) flow grade dichotomised into two arbitrary categories: poor flow (TIMI 0-1) vs good flow (TIMI 2-3). This categorisation was used because TIMI grade 2-3 flow allows complete visualisation of the distal area of the lesion, facilitating the procedure (11). Secondary endpoints were the post-procedural frequencies of a TIMI flow grade of 3, myocardial blush grade of 0 or 1, and complete resolution of ST-segment elevation.

TIMI flow grades were assessed as previously described (12): 0: no perfusion (no antegrade flow beyond the point of occlusion); 1: penetration without perfusion (the contrast material passes beyond the area of obstruction but “hangs up” and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cine run); 2: partial reperfusion (the contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction; however, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed is perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the culprit vessel, e.g. the opposite coronary artery or coronary bed proximal to the obstruction); and 3: complete perfusion (antegrade flow into the bed distal to the obstruction occurs as promptly as into the bed proximal to the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved bed in the same vessel or the opposite artery).

Myocardial blush grades were assigned as follows (13): 0: no myocardial blush; 1: minimal myocardial blush or contrast density; 2: moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery; and 3: normal myocardial blush or contrast density, similar to that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery.

A 12-lead electrocardiogram (ECG) was acquired at presentation and 60 to 90 minutes (min) after PCI, and the ST-segments of the postprocedural ECG were compared with those of the ECG at presentation. The degree of resolution of ST-segment elevation was categorized as complete (>70%), partial (30 to 70%), or none (<30%) (14).

Sample collection and platelet function assays

Blood samples for platelet function analyses were collected when arterial sheath to perform catheterisation was placed. All procedures were performed via radial artery access. The first 2-4 ml of blood were discarded to avoid spontaneous platelet activation. Samples were processed by trained laboratory personnel within 2 hours (h) after blood drawing. Platelet function assays included VerifyNow™ system, light transmission aggregometry and multiple electrode aggregometry (MEA).

VerifyNow assay

The VerifyNow (VN) assay is a rapid whole blood point-of-care device and was utilised according to the instructions of the manufacturer (Accumetrics, Inc., San Diego, CA, USA) as previously described (15). In brief, VN-P2Y12 assay mimics turbidometric aggregation and utilises disposable cartridges containing 20 µM adenosine diphosphate (ADP) and 22 nM PGE1. Aggregation testing using ADP as a sole agonist activates P2Y1 and P2Y12 purinergic signalling, while adding PGE1 increases the specificity of the test for P2Y12 signalling (16). In a separate channel of the cartridge in which iso-TRAP is used as an agonist, a baseline value for platelet function is obtained, enabling assessment of platelet inhibition without having to wean the patient off antiplatelet treatment. The VN-P2Y12 assay reports the results as P2Y12 reaction units (PRU) and percent inhibition of platelet aggregation (%IPA), which is calculated as ([baseline - PRU] / [baseline] × 100. In contrast to IPA values, which increase with decreasing platelet function, PRU values decrease with decreasing platelet function. A cut-off point of >240 PRUs was used to define clopidogrel HPR. Similarly, VN-ASA assay utilises disposable cartridges containing arachidonic acid (AA) and reports the results as Aspirin reaction units (ARU). ARU values decrease with enhanced aspirin-induced platelet inhibition. A cut-off value of >550 ARUs was used to define aspirin HPR.

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Light transmission aggregometry (LTA)

LTA was performed according to standard protocols as previously described (17). Briefly, blood-citrate tubes were centrifuged at 100 g for 10 min to recover platelet-rich plasma (PRP) and further centrifuged at 2,400 g for 15 min to recover platelet poor plasma (PPP). Platelet aggregation was assessed using PRP and PPP by the turbidometric method in a two-channel aggregometer (ChronoLog 490 Model, Chrono-Log Corp., Havertown, PA, USA). Light transmission was adjusted to 0% for PRP and to 100% for PPP for each measurement. Maximal platelet aggregation (MPA) was measured following stimuli with AA (1 mmol/l), and ADP (5 µmol/l). The cut-off values used to define HPR were MPA ≥20% for ASA, and >46% MPA using 5 µmol/l ADP for clopidogrel.

Multiple electrode aggregometry (MEA)

Blood was collected in hirudin-treated tubes. MEA was assessed in whole blood with the Multiplate™ analyzer (Dynabyte Medical, Munich, Germany) as previously described (18, 19). This instrument can perform up to five parallel aggregometry measurements assessing the change in impedance caused by the adhesion of platelets onto sensor units formed by silver-covered electrodes. Curves were recorded for 6 min and platelet aggregation was determined as area under the curve of arbitrary aggregation units (AU*min). In the present investigation, 6.4 µmol/l ADP was used as agonist. A cut-off value of >468 AU*min was used to define clopidogrel HPR.

Table 1: Clinical, angiographic and procedural characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=50)</th>
<th>HPR (n=44)</th>
<th>No HPR (n=6)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>59.7±11.2</td>
<td>59.7±11.7</td>
<td>59.7±6.7</td>
<td>0.998</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>38 (76.0)</td>
<td>32 (72.7)</td>
<td>6 (100)</td>
<td>0.314</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>22 (44.0)</td>
<td>19 (43.2)</td>
<td>3 (50.0)</td>
<td>~1</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>6 (12.0)</td>
<td>6 (13.6)</td>
<td>0 (0)</td>
<td>~1</td>
</tr>
<tr>
<td>Hyperlipidaemia, n (%)</td>
<td>20 (40.0)</td>
<td>17 (38.6)</td>
<td>3 (50.0)</td>
<td>0.672</td>
</tr>
<tr>
<td>Active smokers, n (%)</td>
<td>15 (30.0)</td>
<td>13 (29.5)</td>
<td>2 (33.3)</td>
<td>~1</td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
<td>6 (12.0)</td>
<td>6 (13.6)</td>
<td>0 (0)</td>
<td>~1</td>
</tr>
<tr>
<td>Time (min) from LD to P-PCI, median [IQT]</td>
<td>85.0 [60.0–121.3]</td>
<td>85.0 [65.0–120.0]</td>
<td>80.0 [38.8–131.3]</td>
<td>0.626</td>
</tr>
<tr>
<td>Total ischaemic time (min); median [IQT]</td>
<td>192.0 [133.8–305.0]</td>
<td>192.0 [141.3–300.0]</td>
<td>181.0 [82.5–463.8]</td>
<td>0.570</td>
</tr>
<tr>
<td>Origin</td>
<td></td>
<td></td>
<td></td>
<td>0.568</td>
</tr>
<tr>
<td>Emergency room</td>
<td>12 (24)</td>
<td>10 (22.7)</td>
<td>2 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Transferred by emergency system</td>
<td>38 (76)</td>
<td>34 (77.3)</td>
<td>4 (66.6)</td>
<td></td>
</tr>
<tr>
<td>Infarct-related artery, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.731</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>14 (28.0%)</td>
<td>12 (27.3)</td>
<td>2 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Left circumflex</td>
<td>6 (12.0%)</td>
<td>5 (11.4)</td>
<td>1 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>30 (60.0%)</td>
<td>27 (61.3)</td>
<td>3 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Number of diseased vessels, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.798</td>
</tr>
<tr>
<td>One</td>
<td>27 (54.0)</td>
<td>23 (52.3)</td>
<td>4 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Two</td>
<td>18 (36.0)</td>
<td>16 (36.4)</td>
<td>2 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Three</td>
<td>5 (10.0)</td>
<td>5 (11.3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Thrombus aspiration, n (%)</td>
<td>31 (62)</td>
<td>29 (65.9)</td>
<td>2 (33.3)</td>
<td>0.184</td>
</tr>
<tr>
<td>Periprocedural abciximab, n (%)</td>
<td>13 (26.0)</td>
<td>12 (27.3)</td>
<td>1 (16.7)</td>
<td>~1</td>
</tr>
<tr>
<td>Number of stents per patient, mean ± SD</td>
<td>1.2±0.6</td>
<td>1.2±0.6</td>
<td>1.0±0.0</td>
<td>0.438</td>
</tr>
<tr>
<td>Bare metal stents / total stents, n/n (%)</td>
<td>46/54 (85.2%)</td>
<td>40/48 (83.3)</td>
<td>6/6 (100)</td>
<td>~1</td>
</tr>
</tbody>
</table>

LD: loading dose; P-PCI: primary percutaneous coronary intervention.
Sample size

The primary endpoint of this study was the comparison of the initial TIMI flow of 2 to 3 in patients with and without HPR, as defined by the VN-P2Y12 assay. Assuming that 50% of patients were to present with HPR (8), a total of 46 patients would be needed to detect an absolute difference of 40% in the percentage of patients with poor initial TIMI flow, with 80% power and two-sided significance level of 0.05. Considering an approximate 8% dropout rate, inclusion of 50 patients was allowed to ensure that PD data from 46 patients was available.

Statistical analysis

Continuous variables were summarised by mean ± standard deviation (SD) or by median and interquartile range (IQR) if a normal distribution could be assumed or not, respectively. The Kolmogorov-Smirnov normality test was used to test such assumption. Categorical variables were expressed as frequencies and percentages and tested by means of the Chi-square test or Fisher’s exact test if application conditions were not fulfilled. A p-value <0.05 was considered statistically significant for all comparisons.

Logistic regression models (backward stepwise method) were used to evaluate the association between clopidogrel HPR and pre- and post-procedural endpoints. Each analysis included the variable of interest (initial TIMI flow dichotomised, final TIMI flow, final blush, and ST resolution) as the dependent variable and clopidogrel HPR status as the independent variable, adjusting by variables considered clinically relevant (age, body mass index [BMI], diabetes mellitus, smoking habit, time from LD to start of P-PCI, and time from onset of symptoms to start of P-PCI for all analyses, adding GPIs use during the procedure and thrombus aspiration for post-procedural endpoints) and baseline characteristics unbalanced between the two groups (p<0.20). Exploratory analyses of HPR to ASA and its association with the above mentioned endpoints were also performed.

Results

A total of 82 consecutive STEMI patients admitted to a tertiary centre with a diagnosis of STEMI who underwent P-PCI were prospectively screened, of whom 32 were excluded because of not fulfilling inclusion and exclusion criteria. Therefore, a total of 50 patients were included in the present analysis. Baseline demographics, procedural and angiographic characteristics of the overall population and according to HPR status are summarised in Table 1. The median time of clopidogrel pretreatment (time from LD administration to the beginning of the procedure) was 85 min [IQR 60.0 to 121.3]. There were no differences in time between patients with and without HPR (85.0 [65.0-120.0] vs. 80.0 [38.8-131.3]; p=0.626).

The percentage of patients with suboptimal response to clopidogrel assessed with the VN-P2Y12 was 88.0% (95% confidence interval [CI]: 76.2% to 94.4%). Distribution of clopidogrel-induced platelet reactivity is shown in Figure 1A. Consistent rates were obtained with the other platelet function assays used: 81.8% (95% CI: 68.0% to 90.5%) and 91.3% (95% CI: 79.7% to 96.6%) when evaluated with LTA and MEA, respectively. Although non-statistically significant differences in any clinical, angiographic or procedural variables were found according to HPR status, a numerical trend towards a greater use of thrombus aspiration and administration of abciximab during the procedure was observed in patients with HPR to clopidogrel defined by VN-P2Y12 (Table 1). A higher percentage of patients with good initial TIMI flow in the IRA was observed among patients without HPR compared...
with those with HPR (66.7% vs 15.9%). HPR was the only variable statistically significant in the multivariate analysis (p=0.013). No significant differences were seen in the post-procedural frequencies of final TIMI flow grade of 3 (83.3% vs 72.7%; p=0.578), myocardial blush grade of 0 or 1 (33.3% vs 63.6%, p=0.328), and complete resolution of ST-segment elevation (66.7% vs 43.2%; p=0.279) (Figure 2).

The percentage of patients with HPR to ASA was 28.6% (95% CI: 17.8% to 42.4%) and 38.1% (95% CI: 25.0% to 53.2%), assessed by VN-ASA (Figure 1B) and LTA, respectively. No significant differences regarding initial TIMI flow, final TIMI flow, myocardial blush grade and ST resolution were observed between patients with and without HPR to ASA (data not shown).

Discussion

The findings of the present investigation performed in STEMI patients undergoing P-PCI pretreated with a 600-mg LD of clopidogrel and 500-mg of ASA showed that: 1) a high percentage of STEMI patients have inadequate levels of clopidogrel-induced and, to a lesser degree, aspirin-mediated platelet inhibition, at the moment of starting the P-PCI procedure; and 2) inadequate levels of clopidogrel-induced platelet inhibition are associated with impaired initial TIMI flow in the IRA.

Clopidogrel pretreatment is associated with a lower risk of adverse ischaemic events in STEMI patients undergoing P-PCI (3-6). However, clopidogrel efficacy is well-known to be hampered by a broad variability in response that leads to a relatively high percentage of patients with suboptimal response or HPR, which is associated with worse clinical outcomes (20). One of the main limitations of clopidogrel is its delayed onset of action, even after a...
600-mg LD (21-23), which is of particular relevance in the setting of P-PCI given the need to minimise time delays between clinical presentation and mechanical reperfusion. In addition, prior investigations have shown that ACS is a predictor of diminished response to clopidogrel (24, 25). Notably, STEMI patients have higher rates of HPR than those with the other forms of ACS, as shown in a recent study by Bonello et al. (8). In line with this, Biscaglia et al. have recently reported that 90% of STEMI patients have negligible levels of platelet inhibition after pre-hospital administration of 600-mg clopidogrel, which confirm the results of the present investigation (26). These PD findings may also be attributed to impaired pharmacokinetics as a result of delayed intestinal absorption, which characterises STEMI patients, leading to impaired bioavailability of clopidogrel (27). This may occur due to selective shunting of blood to vital organs which may decrease gastrointestinal perfusion, or the elevated venous pressure and vasocostriction of peripheral arteries during STEMI that stimulates the release of atrial natriuretic peptide, which in turn inhibits permeability and intestinal motility (28, 29). Of note, inter-individual variability of intestinal absorption has been previously associated with variability in clopidogrel-induced platelet inhibition (22, 30).

An important and novel finding of the present investigation is the observed association between suboptimal response to clopidogrel and worse rates of IRA patency, which may have consequences in PCI procedures (e.g. higher use of bail-out GPIs or thrombectomy devices) and clinical outcomes. Although the initial patency of the culprit vessel has been reported to be higher in those patients that have received clopidogrel pretreatment prior to P-PCI (4), this is the first investigation, to the best of our knowledge, to observe an association between HPR at the beginning of the procedure and lower rates of initial patency of the IRA. Further, although non-statistically significant differences were found, a numerical trend towards better post-procedural angiographic (ST-segment resolution) outcomes was observed in the subset of patients without clopidogrel HPR, despite a higher use of thrombus aspiration devices and peri-procedural abciximab administration in the group of patient with HPR.

Overall, these results support the idea that an antithrombotic strategy with more potent antiplatelet efficacy than that achieved with standard clopidogrel therapy may be a better option in STEMI patients undergoing P-PCI (1, 7, 31, 32). In particular, two strategies must be considered appealing options in order to obtain greater antiplatelet effects and, thus, better outcomes than standard clopidogrel therapy in the STEMI scenario: 1) the use of the newer and more potent oral P2Y12 antagonists (prasugrel and ticagrelor); and 2) the use of intravenous agents, such as GPIs or cangrelor.

Newer and more potent oral antiplatelet agents with more rapid onset of action, such as prasugrel or ticagrelor, have demonstrated an important clinical benefit over clopidogrel in STEMI patients (33, 34). In line with this, a recent study by Nürenberg et al. performed in STEMI patients undergoing P-PCI found that the majority of subjects presented HPR to a 600-mg LD of clopidogrel 12-24 h after PCI, which corroborates the findings of the present investigation, and that this clopidogrel LD did not affect the PD efficacy of a 60-mg LD of prasugrel given afterwards (35). However, it is also important to note that studies evaluating the PD efficacy of prasugrel and ticagrelor in the setting of STEMI have also observed greater rates of HPR in the early hours post P-PCI than those reported in studies performed in non-STEMI patients (31, 36, 37). Remarkably, in a randomised PD study comparing ticagrelor vs prasugrel in STEMI patients undergoing P-PCI, both agents showed an important delay of action with HPR rates at 2 h after LD of 46.2% and 34.6% for ticagrelor and prasugrel, respectively (37). Further insights of the role of more potent P2Y12 inhibitors in STEMI will be provided with the ongoing ATLANTIC (A 30 Day Study to Evaluate Efficacy and Safety of Pre-hospital vs. In-hospital Initiation of Ticagrelor Therapy in STEMI Patients Planned for Percutaneous Coronary Intervention) trial, which is evaluating the efficacy and safety of pre-hospital compared to in-hospital administration of ticagrelor in addition to aspirin in STEMI patients with planned P-PCI (NCT01347580).

The delayed onset of action of oral antiplatelet agents in STEMI patients may explain the observed clustered events like stent thrombosis in the first hours post P-PCI (38), and reflects the need for more potent and quicker antithrombotic strategies, such as the use of intravenous agents, in this setting. In line with this observation, Valgimigli et al. observed that a significant number of STEMI patients undergoing P-PCI had suboptimal platelet inhibition after prasugrel administration for at least 2 h, which was reverted with simultaneous administration of high-dose bolus of tiroliban (39). The use of cangrelor, a very potent intravenous P2Y12 receptor blocker with a very short onset and offset of action (40, 41), might also be an attractive option in STEMI patients to achieve an early and strong platelet inhibition. The results of the recently presented phase III clinical trial CHAMPION (Cangrelor versus standard tTherapy to Achieve optimal Management of Platelet InhibitionON) – PHOENIX have shown a superior efficacy of cangrelor compared to clopidogrel in patients undergoing PCI, reducing ischaemic events at 48 h, and this effect was sustained through 30 days. Importantly, the benefit of cangrelor was consistent across the whole spectrum of PCI, including the subgroup of STEMI patients (42).

We acknowledge the inherent limitations of this investigation due to its observational design. Further, the small sample size of

What is known about this topic?
- Clopidogrel has a wide inter-individual variability in response.
- Clopidogrel has a limited efficacy on STEMI patients undergoing P-PCI due to its delayed onset of action and impaired bioavailability.

What does this paper add?
- A high percentage of STEMI patients have inadequate levels of clopidogrel-induced and, to a lesser degree, aspirin-mediated platelet inhibition at the moment of starting a P-PCI.
- A suboptimal response to clopidogrel may be associated with impaired initial patency of the infarct-related artery.
the study and, in particular, the very low number of patients without clopidogrel HPR at the beginning of the procedure makes it difficult to draw definitive conclusions regarding post-procedural outcomes and, therefore, these findings must be considered merely hypotheses-generating. In addition, the study was not powered to draw any conclusion on clinical outcomes during follow-up because of the small sample size. In fact, no patients in our study presented any ischaemic or bleeding events at 30-day follow-up. However, prior investigations have shown an association between clopidogrel responsiveness and adverse clinical outcomes in the setting of STEMI (10). Other limitations to be acknowledged are the lack of data on the novel platelet inhibitors prasugrel and ticagrelor, as well as having a single measurement of platelet function after loading. Indeed, having a second reassessment of platelet reactivity at a later time point would have been useful to prove that delayed absorption is the limiting step causing impaired clopidogrel efficacy. Finally, larger scale studies are warranted to define the clinical benefit of a tailored treatment strategy in STEMI patients based on the results of platelet function assays.

Conflicts of interest
José Luis Ferreiro (corresponding author) reports honoraria for lectures from Eli Lilly Co; Daichi Sankyo, Inc.; AstraZeneca. Dominick J. Angiolillo reports receiving: honoraria for lectures from Bristol Myers Squibb; Sanofi-Aventis; Eli Lilly Co; Daichi Sankyo, Inc.; AstraZeneca; consulting fees from Bristol Myers Squibb; Sanofi-Aventis; Eli Lilly Co; Daichi Sankyo, Inc.; The Medicines Company; Portola; Novartis; AstraZeneca; Merck; Evolva; Abbott Vascular; research grants from Bristol Myers Squibb; Sanofi-Aventis; GlaxoSmithKline; Otsuka; Eli Lilly Co; Daichi Sankyo, Inc., The Medicines Company; Portola; AstraZeneca. None of the other authors have conflicts of interest to report.

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