Aspirin Reload Before Elective Percutaneous Coronary Intervention

Impact on Serum Thromboxane B₂ and Myocardial Reperfusion Indexes

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Background—Microvascular obstruction seems to predict poor outcome in patients undergoing elective percutaneous coronary intervention (PCI), but the underlying mechanism is still unclear. We analyzed whether serum thromboxane B₂, a stable metabolite of thromboxane A₂, may be implicated in post-PCI microvascular obstruction.

Methods and Results—We enrolled 91 patients (74 males, 66±10 years) on chronic low-dose aspirin therapy (aspirin, 100 mg daily) scheduled for elective PCI and randomly assigned to receive aspirin reload (325 mg orally, n=46) or no reload (control group, n=45) ≥1 hour before elective PCI. Serum levels of thromboxane B₂, reperfusion indexes (corrected Thrombolysis In Myocardial Infarction frame count and myocardial blush grade), and serum cardiac troponin I were assessed before and after PCI. Serum thromboxane B₂ significantly increased after 120 minutes (P=0.0447) from PCI in control but not in aspirin reload group. After PCI, both groups showed a statistically significant reduction in corrected Thrombolysis In Myocardial Infarction frame count more evident in aspirin reload group (P=0.0023). Moreover, after PCI, 61% of patients allocated to aspirin reload and only 32% of patients allocated to control group reached normal microcirculatory reperfusion (myocardial blush grade=3); patients with myocardial blush grade=3 exhibited lower values of serum thromboxane B₂ compared with those with myocardial blush grade <3 (P=0.05). Periprocedural cardiac troponin I significantly increased (F=3.64; P=0.01334) and correlated with serum thromboxane B₂ (r=0.31; P=0.0413) in control but not in aspirin reload group. In addition, left ventricular ejection fraction significantly increased after PCI only in the aspirin reload group (P=0.0005).

Conclusions—Aspirin loading dose before elective PCI improves myocardial reperfusion and injury indexes, suggesting a possible role of platelet thromboxane A₂ in microvascular occlusion.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01374698.

(Circ Cardiovasc Interv. 2014;7:00-00.)

Key Words: angioplasty • aspirin • microcirculation

Optimal platelet inhibition is crucial to prevent procedural thrombotic complications and recurrent ischemic events in patients undergoing percutaneous coronary intervention (PCI).² Despite dual antiplatelet therapy with aspirin and thienopyridines and improved angiographic procedural technique, as recommended in PCI by international guidelines,² a residual risk of new major adverse cardiac events is still detectable.³

Among mechanisms investigated to explain this issue, an incomplete platelet inhibition and the so-called no-reflow phenomenon (ie, incomplete tissue perfusion, despite restoration of epicardial coronary artery patency) occurring in ≤40% of patients undergoing a successful primary PCI have been suggested to play a crucial role.³⁻⁷

Aspirin was the first antiplatelet drug with proven benefit in coronary artery disease (CAD).⁸⁻⁹ The antiplatelet effect of aspirin is because of the irreversible inhibition of platelet cyclooxygenase-1, the enzyme catalyzing the conversion of arachidonic acid to thromboxane A₂, a powerful aggregating and vasoconstrictive molecule. An almost complete suppression (>90%) of platelet cyclooxygenase-1 activity is required to prevent thromboxane A₂ formation and subsequent platelet aggregation/activation.¹⁰⁻¹³ Previous studies suggested...
WHAT IS KNOWN
- Impaired microcirculatory reperfusion may be detected in patients undergoing urgent or elective percutaneous coronary intervention and is usually called the no-reflow phenomenon.
- The mechanisms accounting for the no-reflow phenomenon are still unclear.

WHAT THE STUDY ADDS
- The results of this multicenter study showed that in patients undergoing elective percutaneous coronary intervention, preprocedural aspirin loading dose (325 mg) improves myocardial reperfusion and myocardial injury indexes.
- The study also suggests a role for platelet thromboxane A₂, as a mechanism eliciting incomplete microcirculatory coronary reperfusion and myocardial damage.

that platelets might be implicated in no-reflow phenomenon through microvascular obstruction by platelet aggregates and release of platelet-derived vasoactive and chemotactic mediators. Accordingly, in patients undergoing PCI for acute ST-segment–elevation myocardial infarction, plasma thromboxane B₂ levels were independent predictors of no-reflow and lack of ST-segment resolution, but it was unclear whether post-PCI platelet thromboxane B₂ biosynthesis was actually implicated in this phenomenon. We have recently demonstrated an incomplete inhibition of serum thromboxane B₂, which maximally reflects platelet thromboxane A₂ biosynthesis, in patients on chronic aspirin treatment undergoing PCI. Thus, we speculated that such incomplete inhibition might be implicated in impaired microcirculation reperfusion via thromboxane A₂ production, also after elective PCI. Accordingly, we tested the hypothesis that preprocedural aspirin oral loading dose (325 mg) could lower post-PCI serum thromboxane B₂ residual formation and improve reperfusion indexes compared with patients on chronic aspirin treatment without pre-PCI aspirin loading dose. To explore this issue, serum thromboxane B₂ and coronary reperfusion indexes were measured in patients on chronic aspirin treatment allocated to receive or not a pre-PCI aspirin loading dose.

Methods

Study Population
Preprocedural Aspirin reload for Native coronary disease Treated by Angioplasty: Reperfusion indexes Evaluation and Improvement (PANTAREI) study was a multicenter, randomized, clinical trial conducted in stable patients with CAD undergoing coronary revascularization procedures through angioplasty and stent implantation. From January 2011 to September 2012, consecutive stable patients with CAD aged from 18 to 85 years scheduled for elective diagnostic and intervention coronary procedure were considered for the enrollment in the present study. Patients were recruited from (1) Department of the Heart and Great Vessels Attilio Reale, SAPIENZA—University of Rome; (2) I Clinica Medica, SAPIENZA—University of Rome; and (3) Department of Interventional Cardiology, Santa Maria University Hospital, Terni, all in Italy.

Clinic and angiographic inclusion criteria to enter in the study were (1) stable angina with stress tests inducible myocardial ischemia; (2) de novo native coronary lesion with diameter stenosis ≥70% and <100%; (3) Thrombolysis In Myocardial Infarction flow grade ≥1; (4) reference lumen diameter equal or superior to 2.5 mm; and (5) lesion length ≤35 mm, which would be covered with ≥2 stent maximum. Moreover, only patients who affirmed being on 100 mg/daily oral aspirin for ≥7 days before PCI were considered eligible. Each patient was advised to take the last dose of oral aspirin the day before the index procedure. Exclusion criteria were acute coronary syndrome within 30 days, previous or planned administration of glycoprotein IIb/IIIa receptor antagonists, treatment with oral anticoagulant drugs, baseline levels of cardiac troponin I (cTnI) above the upper normal limit, stenosis located in venous or arterial by-pass grafts, target lesion localized inside a previously stented segment, renal insufficiency (glomerular filtration rate <50 mL/min), history of bleeding or peptic ulcers, thrombocytopenia (platelet count <100,000/mm³), and left ventricular ejection fraction <30%. The study complied with the Declaration of Helsinki and was approved by the institutional review committee, and the subjects gave informed consent.

Study Design
With the aim to evaluate the effect of aspirin reload on markers of platelet activation (ie, thromboxane B₂, serum levels), on indexes of reperfusion (ie, corrected Thrombolysis In Myocardial Infarction frame count [cTFC] and myocardial blush grade [MBG]), and on myocardial injury index (ie, serum cTnl) after PCI, we planned an interventional study. All eligible patients (Figure 1) were randomly assigned to receive 325 mg of aspirin (aspirin reload) or no reload (control group) ≥1 hour before PCI. A computer-generated random sequence was used for randomization, and randomization blocks were distributed to the centers. All participants were fasting for ≥12 hours. Blood samples were collected at baseline (before the start of procedure) and after 60 and 120 minutes from the end of procedure to measure thromboxane B₂. Moreover, cTnI was measured after 6, 12, and 24 hours from the end of procedure.

Cardiologists, unaware of clinical data, performed a 2-dimensional color Doppler trans thoracic echocardiogram at baseline and 72 hours after PCI, left ventricular ejection fraction (LVEF) was calculated by the biplane Simpson rule, as recommended by the American Society of Echocardiography. All recruited patients were followed up by cardiologist, according to the standard of Good Clinical Practice, for 1 year after PCI to verify adverse clinical outcomes.

Study End Points and Sample Size Calculation

Primary Objective
The primary end point was the evaluation of preprocedural aspirin reload effects on platelet activation after PCI. Thromboxane B₂ serum levels at the baseline and after 60 and 120 minutes from the end of PCI were measured.

Secondary Objectives
The secondary end points were the assessment of myocardial reperfusion indexes, such as cTFC and MBG, and LVEF changes occurring after elective PCI. Periprocedural myocardial damage was investigated at 6, 12, and 24 hours after the PCI, by plasma levels of cTnI.

Sample Size Calculation
We hypothesized a difference of 11 ng/mL in plasmatic thromboxane B₂ levels measured 120 minutes from the end of PCI when comparing the oral aspirin reload with the control group. We also assumed a SD of 15 ng/mL in each group. Based on these assumptions, this study needs 40 patients for each treatment arm for a power of ≥90% with a 2-sample t test at level 5%. Sample size calculation was performed using the software nQuery Advisor, version 5.0 (Statistical Solutions, Saugus, MA).
Laboratory Measurements

Blood samples were drawn from the antecubital vein with a 21-gauge needle and then mixed in a tube with 0.13 mmol/L sodium citrate (ratio 9:1). Samples were collected before and 60 and 120 minutes after the procedure. Blood samples were immediately centrifuged at 2000 rpm for 20 minutes at 4°C, and the supernatant was collected and stored at −80°C until measurement.

Thromboxane A2 serum levels were measured evaluating its stable metabolite thromboxane B2 by an enzyme immunoassay commercial kit (Amersham Pharmacia, Biotech, Little Chalfont, United Kingdom) and expressed as ng/mL. Intra- and interassay coefficients of variation for thromboxane B2 enzyme immunoassay kit were 4.0% and 3.6%, respectively.

cTnI levels were measured using an automated enzyme immunoassay system (Dimension RXL MAX, Siemens Healthcare Diagnostic, Eschborn, Germany) with the upper limit of normal being 0.08 ng/mL.

PCI Procedure

After collecting baseline blood samples to measure platelet activation markers and myocardial necrosis index, all procedures were performed according to standard practice. All patients declared in the cath laboratory, in the same day of PCI, that they have assumed the last dosage of aspirin (100 mg) the day before the index procedure. They also received 600 mg clopidogrel loading dose ≥3 hours before intervention, followed by 75 mg daily for ≥24 months. The interventional procedure was performed through radial (n=44) or femoral (n=56) percutaneous approach. After percutaneous access was obtained, an intravenous bolus of 5000 UI of unfractionated heparin was administered, with sufficient supplements (if necessary) to maintain an activated clotting time ≥250 seconds during the intervention. A baseline angiography of the involved vessel was performed in ≥2 near orthogonal views that showed the target lesion free of foreshortening or vessel overlap, using a 6Fr diagnostic catheter. The angiograms included ≥2 cm of catheter to allow for accurate quantitative coronary angiographic measurements.

The target lesion, classified according to standard American Heart Association/American College of Cardiology grading system, was crossed with a 0.014 exchange length guidewire, and a single predilatation, with an appropriately sized balloon, was performed by inflating the balloon to the nominal pressure. Immediately after balloon dilatation, a drug-eluting stent (Biomatrix, BIOSENSORS Europe SA, Morges, Switzerland) was implanted. Stent deployment was achieved with high-pressure balloon inflation (>15 atmosphere). Postdilation, balloon inflation time and inflation pressure were at operator’s discretion according to the lesion characteristics. Total balloon inflation time and maximum inflation pressure were recorded. No direct stenting was performed. The procedure was considered successful when stent placement was associated with a residual stenosis <30% and a Thrombolysis In Myocardial Infarction flow grade ≥3.

Angiographic Assessment

Angiograms recorded before and immediately after the procedure were assessed with the aid of the automated edge detection system (Centricity Cardiology CA 1000, GE Medical Systems, Milwaukee, WI). The same projections were used at all time points. The central filled nontapered catheter tip was used for calibration. Early lumen gain was calculated as the difference between minimal lumen diameter at the end of the intervention and before balloon predilation. During angiography, imaging was recorded from the time of first
injection of the coronary arteries until venous filling was observed and continued for ≥3 cardiac cycles at the washout phase. Epicardial coronary arteries were visualized in multiple views, including cranial and caudal angulations. Selective angiography was performed with an automatic injector (ACIST HD101, Eden Prairie, Minnesota), by using a total volume of 10 mL iopromide (Ultravist 370, Schering AG, Berlin, Germany), at a rate of 2.0 mL/s for left coronary arteries, and a total volume of 8 mL iopromide at a rate of 1.0 mL/s for right coronary arteries, at 450 pound-force per square inch. Two independent operators evaluated baseline and postinterventional cTFC and MBG. The readers were blinded to study group assignment. Digital angiograms were analyzed off-line with the use of an automated edge detection system (Cardiovascular Medical System, MEDIS Imaging Systems, Leiden, The Netherlands).

Corrected Thrombolysis In Myocardial Infarction Frame Count

The analysis of coronary flow was done according to the Thrombolysis In Myocardial Infarction frame count method by Gibson et al. Normal values were defined as follows: 36.2±2.6 frames for the left anterior descending coronary artery, 22.2±4.1 for the left circumflex artery, and 20.4±3.0 frames for the right coronary artery. Values above the normal frame count (mean+1SD) were considered suggestive for impairment of microcirculation.

Myocardial Blush Grade

The MBG20 was used to assess the filling and clearance of contrast in the myocardium. MBG, visually assessed, was defined as follows: 0, no myocardial blush or contrast density; 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, comparable with that obtained during angiography of a contralateral or ipsilateral non–infarct-related coronary artery. Operators performing PCI, as well as laboratory personnel, were blinded to treatment allocation.

Statistical Analysis

Treatment groups were compared with regard to discrete variables (MBG and all discrete variables in Tables 1 and 2) using χ² test or Fisher exact test for binary variables and with regard to continuous normal variables using Student paired or unpaired t-test (LVEF, baseline thrombocytopenia B2, serum levels, and all continuous variables in Tables 1 and 2). A difference in medians for baseline thrombocyan B2 was used as confirmatory analysis for cross-sectional endpoints (not shown) was assessed using Mann–Whitney rank-sum test. Spearman rank correlation was used to evaluate monotonicity of relationship between pairs of continuous variables (thrombocyan B2 versus cTnl changes, thrombocyan B2 versus LVEF).

Although adjusted thrombocyan B2 levels are fairly normal and have low SE, raw means might be not representative because of slightly large SD. For this reason, we also report median and interquartile range (IQR) below.

The difference in serum thrombocyan B2 (separately after 60 minutes or after 120 minutes) and cTFC levels between active and control groups was analyzed by means of ANCOVA. Unless otherwise stated, the treatment effect was evaluated after adjusting for the baseline levels of the outcome. At multivariate analysis, the treatment effect was also adjusted for other potential confounders. A forward stepwise procedure was used to select potential confounders, but because of randomization, none was found to be significant. The overall effect on thrombocyan B2 (jointly after 60 and 120 minutes) was analyzed by means of mixed effects models, in which a zero-centered normally distributed subject-specific intercept was used to tackle dependence arising from repeated measurements. Data are presented as mean (1 SD) or as median and IQR (25th, 75th percentile).

Results

A total of 100 of 302 consecutive screened patients, who met the enrollment criteria, were randomized to receive oral aspirin reload (325 mg) or no reload, immediately before the procedure (Figure 1, Consolidated Standards of Reporting Trials [CONSORT] flow diagram).

Two hundred two patients were excluded: 32 patients had 3-vessel disease (12 of them with left main involvement have been treated with elective by-pass surgery), 40 patients with ejection fraction <30% and diffused atherosclerotic disease, 28 patients had target lesion inside previously stented segments, 16 patients had target stenosis localized inside a previously implanted graft, 16 patients had target lesion localized inside a vessel with other occlusions not-to-be treated with the same stent(s) of the target lesion, 10 patients had renal insufficiency, 20 patients had unstable angina in the preceding 30 days with elevation of cTnl above the upper normal limit, and 8 patients had been treated with glycoprotein IIb/IIIa receptor antagonists.

Thirty-two patients dropped out of the study because they did not give the consent to proceed with aspirin reload and with the subsequent sampling, although they could potentially fall within study design. Also these patients declared, in the cath laboratory, in the same day of PCI that have assumed last dosage of aspirin (100 mg) the day before the index procedure and received 600 mg clopidogrel loading dose ≥3 hours before intervention, followed by 75 mg daily for ≥24 months. In these patients, demographic, clinical, and angiographic variables distribution were similar to those who entered in the study. These patients were all treated according to standard guidelines currently recommended. After PCI, 9 patients (n=4 aspirin reload group; n=5 control group) were excluded from the study: 4 patients had the need to cover a longer (>33 mm) segment, 3 patients with a bifurcation lesion had a flow-limiting dissection of the side branch that required stent deployment with final kissing balloon inflation, and 2 patients had a third stent implanted downstream of the treated target lesion (Figure 1).

Thus, a total of 91 consecutive patients (74 men and 17 women, mean age 66±10 years) fulfilling the study’s selection criteria were enrolled in the study (Figure 1). Forty-six patients were randomized to aspirin reload (325 mg) before the procedure, whereas 45 patients were assigned to control group. The enrolled patients completed all phases of the study.

In the overall population, comorbidities and cardiovascular risk factors were distributed as reported (Table 1): mean body mass index was 27.1±3.6 kg/m2, 30 (33%) patients had diabetes mellitus, 66 (72%) had dyslipidemia, 63 (69%) had hypertension, 34 (37%) patients were current smokers, 29 (32%) had cardiovascular family history, and 20 (22%) had previous vascular events. Baseline mean value of LVEF was 49.7±8.3%.

Mean angiographic index at epicardial level, expressed by cTFC, was 31.6±5.6 frames/s. MBG grade 1 was detected in 38 (42%), grade 2 in 47 (52%), and grade 3 in 6 (6%) patients. Before the PCI, mean serum thrombocyan B2 was 26.7±27.9 ng/mL (median [IQR]: 13.4 [7.3–43.2] ng/mL).

Table 1 shows baseline clinical characteristics of patients according to the randomization. Age, sex, risk factor distributions, and concomitant pharmacological treatment did not differ between the 2 groups. Baseline mean values of LVEF, as well as type of related vessel, American College of Cardiology/American Heart Association Lesion
Aspirin Reload in PCI

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Classification type, vascular access, stent diameter, total stent length, maximal inflation pressure, postdilatation, and procedure duration, did not differ between the 2 groups. cTFC and the MBG score before procedure were similar in both study arms (Table 2).

At baseline, thromboxane B_2 serum levels did not show significant differences between the 2 groups (control group: mean [SD] 21.8±19.9 ng/mL and median [IQR]: 10.8 (7.3–29.9) ng/mL; aspirin reload group: mean [SD] 30.3±32.1 ng/mL and median [IQR]: 17.2 (7.5–43.2) ng/mL; P=0.13 for difference in means; P=0.46 for difference in medians).

According to the randomization, in the control group there was a mean increase of thromboxane B_2 to 27.6±25.4 ng/mL after 60 minutes (P=0.12) and to 30.3±31.9 ng/mL after 120 minutes (P=0.0447) from PCI. The median (IQR) increase for the controls is 22.1 (7.0–38.3) after 60 minutes and 21.6 (7.5–44.5) ng/mL after 120 minutes.

Conversely, in patients who received aspirin reload, serum median thromboxane B_2 slightly decreased to 24.7±27.2 ng/mL after 60 minutes (P=0.15) and to 21.8±22.7 ng/mL after 120 minutes (P=0.0650). The median (IQR) was 13.4 (8.0–30.2) ng/mL after 60 minutes and 10.8 (8.0–24.0) ng/mL after 120 minutes. Aspirin reload and control group patients showed a mean change from baseline at 120 minutes of −10.3 and +8.7 ng/mL, respectively (P=0.0073, without baseline levels adjustment). Even after additionally adjusting for baseline levels, age, sex, and body mass index (which are not significant with P=0.50, 0.52, and 0.46, respectively), a difference of 11.92 (confidence interval: 3.6–23.47) ng/mL, P=0.0434, is observed at 120 minutes between aspirin reload and control group. If we use mixed effects models to analyze all repeatedly measured thromboxane B_2 serum levels, a global effect of 9.07 (confidence interval: 1.72–16.43) ng/mL, P=0.0158, is detected after adjusting for baseline measurements (where no additional potential confounders was found to be significant).

Table 1. Clinical Characteristics

<table>
<thead>
<tr>
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<th>ASA Reload Group (n=46)</th>
<th>Control Group (n=45)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66±8</td>
<td>66±12</td>
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<td>Male, n (%)</td>
<td>40 (87)</td>
<td>34 (76)</td>
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<td>Body mass index, kg/m²</td>
<td>27.2±4.0</td>
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<td>Diabetes mellitus, n (%)</td>
<td>15 (32)</td>
<td>16 (36)</td>
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<td>Hypertension, n (%)</td>
<td>31 (67)</td>
<td>32 (71)</td>
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<td>Hyperlipidemia, n (%)</td>
<td>33 (70)</td>
<td>33 (73)</td>
<td>0.7397</td>
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<td>Current smoker, n (%)</td>
<td>14 (30)</td>
<td>20 (44)</td>
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<tr>
<td>Previous cardiovascular events, n (%)</td>
<td>11 (23)</td>
<td>9 (20)</td>
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<td>Family history of cardiovascular disease, n (%)</td>
<td>12 (26)</td>
<td>17 (38)</td>
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<td>Baseline medications, n (%)</td>
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<tr>
<td>Statins</td>
<td>40 (85)</td>
<td>37 (82)</td>
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<td>Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers</td>
<td>35 (74)</td>
<td>39 (87)</td>
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<td>β-Blockers</td>
<td>17 (37)</td>
<td>19 (42)</td>
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<td>Calcium channel blockers</td>
<td>12 (26)</td>
<td>7 (16)</td>
<td>0.2373</td>
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<td>Oral hypoglicemic agents</td>
<td>12 (25)</td>
<td>12 (27)</td>
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<td>Insulin treatment</td>
<td>3 (6)</td>
<td>4 (9)</td>
<td>0.6504</td>
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</table>

Values are expressed as mean±SD. ASA indicates aspirin.

Table 2. Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ASA Reload Group (n=46)</th>
<th>Control Group (n=45)</th>
<th>P Value</th>
</tr>
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<tr>
<td>Treated vessel, n (%)</td>
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<td>Left main</td>
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<td>Left anterior descending</td>
<td>24 (52)</td>
<td>22 (49)</td>
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<tr>
<td>Left circumflex</td>
<td>7 (15)</td>
<td>5 (11)</td>
<td></td>
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<tr>
<td>Right coronary artery</td>
<td>14 (31)</td>
<td>17 (38)</td>
<td></td>
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<tr>
<td>Lesion type B2/C, n (%)</td>
<td>24 (52)</td>
<td>27 (60)</td>
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<td>Vascular access, n (%)</td>
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<tr>
<td>Radial</td>
<td>20 (43)</td>
<td>18 (40)</td>
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<td>Femoral</td>
<td>26 (57)</td>
<td>27 (60)</td>
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<td>Stent diameter, mm</td>
<td>3.1±0.4</td>
<td>3.2±0.4</td>
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<tr>
<td>Total stent length, mm</td>
<td>18±6</td>
<td>20±7</td>
<td>0.1232</td>
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<tr>
<td>Maximal inflation pressure (atmosphere)</td>
<td>15.7±1.4</td>
<td>16.2±1.6</td>
<td>0.1707</td>
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<td>Postdilatation, n (%)</td>
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<td>Procedure duration, min</td>
<td>52±8</td>
<td>55±7</td>
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<td>LVEF, %</td>
<td>50±9</td>
<td>49±8</td>
<td>0.0961</td>
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<td>cTFC before procedure, frames/s</td>
<td>31.0±5.6</td>
<td>32.3±5.5</td>
<td>0.5479</td>
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<td>MBG 1, n (%)</td>
<td>19 (41)</td>
<td>19 (42)</td>
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<tr>
<td>MBG 2, n (%)</td>
<td>24 (52)</td>
<td>23 (51)</td>
<td></td>
</tr>
<tr>
<td>MBG 3, n (%)</td>
<td>3 (7)</td>
<td>3 (7)</td>
<td></td>
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</table>

Values are expressed as mean±SD. ASA indicates aspirin; B2/C, type B lesion with ≥2 B characteristics or type C lesion according to American College of Cardiology/American Heart Association Lesion Classification; cTFC, corrected Thrombolysis In Myocardial Infarction frame count; LVEF, left ventricular ejection fraction; and MBG, myocardial blush grade.
No significant time trend ($P=0.75$) and interaction between treatment and time ($P=0.19$) were detected.

Before PCI, mean cTFC was similar between the 2 groups (Table 2; Figure 2). After PCI, both groups showed a statistically significant reduction in cTFC; in particular, in control group, this index significantly decreased from 32.3±5.5 (range: 22.0–44.0) to 27.7±4.8 (20.0–38.0) frames/s ($P<0.0001$) and in the aspirin reload group from 31.0±5.6 (22.0–39.0) to 25.0±4.3 (18.0–33.0) frames/s ($P<0.0001$). At the end of procedure, cTFC was significantly lower in the aspirin reload group (median [IQR]: −7 [3.5] frames/s) compared with the control group (−5 [6] frames/s; $P=0.19$; Figure 2).

Interestingly, 1 patient (2%) in control group and 6 patients (13%) in the aspirin reload group reached the lower risk ($\leq 20$ frames/s) cTFC class ($P<0.02$).

At baseline, MBG=2 was observed in 93% of patients in both groups. After PCI, 61% of patients allocated to aspirin reload group and 32% of patients allocated to control group reached MBG=3 ($P=0.0067$). Patients with MBG=3 showed lower values of serum thromboxane B$_2$ than those with MBG=3 (Figure 3A and 3B).

Baseline levels of cTnI were similar in both groups before PCI. As reported in Figure 4, we observed a periprocedural increase of cTnI, which, however, was higher in control group (mixed effect model with subject-specific random intercept, $P=0.046$). In addition, serum values of thromboxane B$_2$, recorded after 120 minutes from PCI, significantly correlated with cTnI changes from the baseline to 12 hours ($P=0.04$) in control group, whereas in aspirin reload group, no significant correlation has been found ($P=0.20$; $P=0.18$).

Finally, 72 hours after PCI, LVEF values did not change in control group (from 49±8%–48±7%; $P=0.10$), whereas they significantly increased in aspirin reload group (from 50±9% to 53±7%; $P=0.0005$); the difference between the 2 groups was significant (mean change from baseline at 72 hours of −1.95 and +3.15%, respectively, $P<0.001$). In aspirin reload group, LVEF mean changes from the baseline showed a significant inverse correlation with serum values of thromboxane B$_2$ after 120 minutes ($P=−0.32$; $P<0.03$).

### Adverse Cardiac Events

There were no adverse events during hospitalization in both groups. None of the patients died during the follow-up. No thrombosis-related events occurred after a mean time of 12±4 months after intervention. No major or minor bleeding occurred during and after PCI.

### Discussion

The present study provides evidence that aspirin reload before elective PCI improves myocardium reperfusion and myocardial injury indexes by blunting post-PCI increase of thromboxane B$_2$.

Impaired microcirculatory perfusion may be detected in patients undergoing urgent or elective PCI and is usually called no-reflow phenomenon.\textsuperscript{7} Depending on the population under

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**Figure 3.** Serum thromboxane B$_2$ according to myocardial blush grade (MBG) in control group (A) and in aspirin (ASA) reload group (B). Error plots definition: dot, mean value; box, SE from mean; and the whiskers, SD.

**Figure 4.** Serum cardiac troponin I levels before and after 6, 12, and 24 hours from percutaneous coronary intervention. Dot line represents aspirin reload group; full line represents control group. Data are presented as mean±SD (bars). A mixed effect model with subject-specific random intercept has been used for the statistical analysis ($P=0.0463$).
study and the diagnostic techniques used for its detection, the incidence of no-reflow ranges from 5% to 50%, and it is considered a hallmark of poor cardiovascular outcome. Several mechanisms seem to be involved in no-reflow phenomenon including thrombus embolization from epicardial artery and peripheral vasospasm as a consequence of reduced formation of vasodilating molecules such as nitric oxide or upregulation of vasoconstrictive molecules. A previous study demonstrated that in patients on chronic 100 mg aspirin treatment, serum thromboxane B2 is increased immediately after elective PCI. Our study hypothesis was that thromboxane B2 production was implicated in no-reflow phenomenon and that complete inhibition of thromboxane A2 could result in amelioration of microcirculatory perfusion after PCI. The results of the present study show that, compared with patients on chronic aspirin treatment, a loading dose of 325 mg of aspirin is able to blunt post-PCI increase of thromboxane B2. Coincidentally with the post-PCI reduction of thromboxane B2, we observed an improvement of microcirculatory reperfusion indexes, suggesting a potential role for thromboxane B2 in hampering reperfusion microvascular obstruction. Accordingly, 32% of patients on chronic treatment with aspirin showed post-PCI MBG=3, whereas, 61% of patients allocated to aspirin reload before PCI reached the normal reperfusion (MBG=3). Of note, patients who reached a normal microcirculatory perfusion exhibited significantly lower values of serum thromboxane B2 compared with those who did not, suggesting complete suppression of serum thromboxane as a prerequisite to improve post-PCI reperfusion in patients undergoing elective PCI. These findings are in agreement with data concerning patients receiving primary PCI for acute ischemia. In fact, Niccoli et al8 showed that in postprimary PCI plasma thromboxane B2 has a role in modulating myocardial reperfusion, suggesting post-PCI platelet cyclooxygenase-1 activation as a mechanism favoring myocardial vasoconstriction.

Several studies have shown a significant increase of myocardial injury biomarkers in a substantial proportion of patients undergoing elective PCI. Distal microembolization in coronary circulation has been considered the most frequent cause of peri-procedural cTnI increase during procedures of stent implantation in stable patients with CAD. Also, a peri-procedural cTnI elevation after stenting and impaired postprocedural myocardial reperfusion has been reported. Accordingly, we found an increase in peri-procedural cTnI that was particularly pronounced in the control group, indicating that aspirin reload may mitigate such phenomenon.

Notably, a loading dose of aspirin was also associated with a greater improvement of LVEF compared with control group. The present data do not permit to establish whether this association is dependent on reduction of myocardial injury or directly related to the improvement of coronary microcirculation.

This study has implications and limitations. Loading doses of aspirin are usually recommended in patients undergoing primary PCI but not in patients undergoing elective PCI. Also, a recent registry showed that in patients not on aspirin before PCI, across all presentations including stable CAD, there is an increased risk of mortality and stroke.

The positive effect on reperfusion indexes and myocardial necrosis markers suggests that a loading dose of aspirin may be indicated also in patients with stable CAD, but the lack of clinical end points supporting its role limits the study readiness for application.

In conclusion, loading doses of aspirin before elective PCI are associated with improvement in myocardial reperfusion and amelioration of myocardial necrosis indexes, suggesting platelet thromboxane A2 as a mechanism favoring this phenomenon. The clinical impact of these findings needs, however, to be examined by ad hoc designed prospective trials.

Acknowledgments

We want to thank Dott Patrizia Ferroni and Dott Marco Proietti for their fruitful suggestions.

Sources of Funding

This study was supported from grants from SAPIENZA—University of Rome (year: 2011—number: C26A11SR9Z).

Disclosures

None.

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Circ Cardiovasc Interv. published online July 29, 2014;
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circinterventions.ahajournals.org/content/early/2014/07/29/CIRCINTERVENTIONS.113.001197

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