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The Effects of Aspirin and Clopidogrel Response on Myonecrosis After Percutaneous Coronary Intervention

A BRIEF-PCI (Brief Infusion of Intravenous Eptifibatide Following Successful Percutaneous Coronary Intervention) Trial Substudy

Jacqueline Saw, MD, Cameron Densem, MD, Simon Walsh, MD, Percy Jokhi, MD, PhD, Andrew Starovoytov, MD, Rebecca Fox, MSc, Graham Wong, MD, Christopher Buller, MD, Donald Ricci, MD, G. B. John Mancini, MD, Anthony Fung, MBBS

Vancouver, British Columbia, Canada

Objectives The purpose of this study was to evaluate the effects of aspirin and clopidogrel response on myonecrosis after percutaneous coronary intervention (PCI) with glycoprotein (GP) IIb/IIIa blockade.

Background Aspirin and clopidogrel resistance is increasingly recognized, but its effects on PCI outcomes with GP IIb/IIIa blockade are unknown.

Methods This was a prospective, pre-specified substudy of the BRIEF-PCI (Brief Infusion of Intravenous Eptifibatide Following Successful Percutaneous Coronary Intervention) trial, which randomized 624 patients to 18-h or <2-h eptifibatide infusion after uncomplicated PCI. To be eligible, patients must have been pre-treated with aspirin (≥5 days) and clopidogrel (75 mg/day ≥5 days, 300 mg loading ≥6 h, or 600 mg loading ≥2 h) and must not have received GP IIb/IIIa inhibitors within 48 h. Verify-Now Aspirin and Clopidogrel ($P2Y_{12}$) assays were performed at baseline before PCI. Patients with aspirin reaction unit (ARU) ≥550 were labeled as aspirin resistant. Clopidogrel low-responders were defined as those in the lowest quartile of platelet inhibition. The primary end point was the prevalence of myonecrosis within 24 h after PCI.

Results We enrolled 209 patients into our substudy, of which 185 had aspirin response assessed, 198 had clopidogrel response assessed, and 174 had both assessed. There were 4.9% who were aspirin resistant. Clopidogrel low-responders were defined as those in the lowest quartile with platelet inhibition <19%. Only 1.1% had both aspirin resistance and low clopidogrel response. There was no difference in myonecrosis prevalence among aspirin-resistant compared with aspirin-sensitive patients (11.1% vs. 27.8%, $p = 0.259$) or among clopidogrel low-responders compared with clopidogrel responders (23.5% vs. 29.3%, $p = 0.433$).

Conclusions Aspirin and clopidogrel response did not affect myonecrosis prevalence amongst patients who received eptifibatide for PCI. (J Am Coll Cardiol Intv 2008;1:654–9) © 2008 by the American College of Cardiology Foundation

From the Division of Cardiology, Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia, Canada.

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Variability in response to aspirin and clopidogrel is increasingly recognized in cardiovascular medicine. However, the clinical relevance and importance of this variability and nonresponse to these agents remain contentious. Furthermore, there is no established standard for tests for diagnosing antiplatelet therapy nonresponse. Several central laboratory and point-of-care assays have been used to assess varying physiologic aspects of platelet response to these agents. However, none of these tests correlate well with each other for diagnosing nonresponse, and none have definitively been shown to predict adverse clinical events when nonresponse was found. Nevertheless, such technical limitations have not dampened the enthusiasm of clinicians to identify patients with suboptimal antiplatelet response, because the potential consequence of nonresponse could be a catastrophic cardiovascular event.

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The enthusiasm to evaluate aspirin and clopidogrel response is most compelling in the setting of interventional cardiology, because both these agents are used adjunctively after coronary stent placement to prevent stent thrombosis. There have been 3 recent publications that evaluated myonecrosis prevalence after percutaneous coronary intervention (PCI) according to aspirin and clopidogrel response, but controversial results were reported (1–3). Notably, none of the patients in these studies received a glycoprotein (GP) IIb/IIIa inhibitor during the PCI. This is pertinent, because GP IIb/IIIa inhibitors are potent platelet antagonists that are frequently used as a component of the "triple antiplatelet armamentarium" during PCI to reduce periprocedural cardiovascular events. We hypothesized that GP IIb/IIIa blockade would minimize any clinical impact of aspirin and clopidogrel nonresponse. We therefore evaluated the effects of aspirin and clopidogrel response on the prevalence of myonecrosis after PCI in the presence of GP IIb/IIIa blockade.

Methods

We designed a prospective, pre-specified substudy of the BRIEF-PCI (Brief Infusion of Intravenous Eptifibatide Following Successful Percutaneous Coronary Intervention) trial, because all patients received a GP IIb/IIIa inhibitor. In short, the BRIEF-PCI trial was a randomized, double-blinded controlled trial comparing an abbreviated <2-h infusion of eptifibatide (Integrilin, Schering Corporation, Kenilworth, New Jersey) with a standard 18-h infusion among 624 patients who underwent an uncomplicated PCI (4). To be eligible for this substudy, patients must have been pre-treated with aspirin (≥81 to 325 mg daily for at least 5 days) and clopidogrel (received 75 mg/day for ≥5 days or 300-mg loading dose ≥6 h prior or 600-mg loading dose ≥2 h prior). Patients were excluded if they received a GP IIb/IIIa inhibitor within 48 h; had a recent (<48 h) ST-segment elevation myocardial infarction (MI); had visible coronary thrombus; received bivalirudin; required unprotected left main intervention; required use of ablative or thrombectomy devices; had allergy or intolerance to aspirin, thienopyridines, or eptifibatide; or had unsatisfactory PCI results. Anticoagulant during the PCI was either unfractionated heparin (50 to 70 IU/kg) or enoxaparin. Intravenous eptifibatide was administered before the first balloon inflation as a double-bolus of 180 μg/kg (10 min apart) followed by an infusion of 2 μg/kg/min.

The VerifyNow Aspirin and Clopidogrel ($P2Y_{12}$) assays (Accumetrics Inc., San Diego, California) were performed at baseline before PCI and administration of eptifibatide. Whole blood samples were collected into Vacuette tubes (Gernie, Monroe, North Carolina) containing 3.2% sodium citrate. The sample tubes were gently inverted several times and incubated at room temperature for at least 10 min. The assay cartridges were then inserted into the instrument, followed by the insertion of the sample tubes into the cartridges. These assay cartridges contain fibrinogen-coated beads and platelet agonists (the aspirin assay contains arachidonic acid, and the clopidogrel assay contains adenosine diphosphate [ADP]/prostaglandin E1 [PGE1] and isothrombin receptor activating protein [TRAP]). Activated platelets in whole blood bind and aggregate the fibrinogen-coated beads in proportion to the number of expressed GP IIb/IIIa receptors, with consequent increase in light transmittance. This change in optical signal is reported as aspirin reaction unit (ARU) and $P2Y_{12}$ reaction unit by the aspirin and clopidogrel assays, respectively. The $P2Y_{12}$ assay also reports "percent inhibition (%)," which is the percent change from baseline aggregation calculated from the $P2Y_{12}$ reaction unit result and the baseline result from the TRAP channel. Patients with ARU ≥550 were labeled as aspirin resistant. Clopidogrel low-responders were defined as those belonging to the lowest quartile of platelet inhibition.

Abbreviations and Acronyms

ARU = aspirin reaction unit
CK-MB = creatine kinase-myocardial band
GP = glycoprotein
PCI = percutaneous coronary intervention
TRAP = thrombin receptor activating protein
Tn-I = troponin-I

Laboratory tests including troponin-I (Tn-I), total creatine kinase, and creatine kinase-myocardial band (CK-MB) were performed at baseline, at 6 to 8 h after PCI, and the following day (18 to 24 h). Patients were followed by a research coordinator during hospital stay and contacted by telephone at 30 days. The study protocol was approved by the University of British Columbia Ethics Review Board, and all patients provided written informed consent before participation in the study. The study was funded by Interventional Cardiology Research at Vancouver General Hospital.

The primary end point was the prevalence of myonecrosis within 24 h after PCI, which was defined as Tn-I elevation ≥0.26 g/L in patients with normal baseline Tn-I. In patients with elevated baseline Tn-I, CK-MB >3 times upper limit of normal and >50% above baseline was used. We also assessed secondary end points of CK-MB elevation >3 times upper limit of normal, clinical end point of death, MI, and urgent target vessel revascularization at 30 days, REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events) major and minor bleeding events (5), and blush score before and after PCI (6).

Statistical analysis. Hypothesis tests were done with 2-sided tests at the 5% significance level. Baseline characteristics were compared with chi-square and Fisher exact tests for discrete variables and Wilcoxon rank-sum test for continuous variables. Statistical comparisons of primary and secondary end points were performed with Pearson's chi-square test for categorical data and Mann Whitney test for continuous variables. Interactions were tested with logistic regression, incorporating terms for randomized treatment assignment (abbreviated vs. standard eptifibatide duration), aspirin response, and clopidogrel response. A sample size of 204 was determined to be required—assuming clopidogrel low-responder prevalence of 25% and myonecrosis prevalence of 40% after PCI in responders—to detect an absolute difference of 20% from low-responders, with 5% alpha and 80% power. The SPSS 13.0 statistical software (SPSS, Chicago, Illinois) was used.

Results

We enrolled 209 patients into the BRIEF-PCI substudy from March 2005 to May 2007 at the Vancouver General Hospital, British Columbia, Canada. All patients received intravenous eptifibatide. Of these patients, 185 had baseline

Table 1. Baseline Characteristics

Characteristics, % (n) or Mean ± SD	All Patients (n = 209)	Aspirin Resistant (n = 9)	Aspirin Sensitive (n = 176)	Clopidogrel Low-Responder (n = 51)	Clopidogrel Responder (n = 147)
Age (yrs)	61.3 ± 9.9	63.6 ± 10.9	61.1 ± 10.0	60.6 ± 9.5	61.8 ± 10.2
Male	80.9% (169)	88.9% (8)	81.3% (143)	82.4% (42)	82.3% (121)
Body mass index (kg/m^2)	28.4 ± 5.0	29.1 ± 7.1	28.3 ± 4.7	30.3 ± 5.3*	27.8 ± 4.7*
Prior PCI	22.5% (47)	22.2% (2)	22.2% (39)	29.4% (15)	19.7% (29)
Prior CABG	4.8% (10)	0.0% (0)	5.1% (9)	7.8% (4)	2.7% (4)
Prior MI	30.6% (64)	33.3% (3)	30.7% (54)	39.2% (20)	27.9% (41)
Diabetes mellitus	14.8% (31)	22.2% (2)	14.2% (25)	19.6% (10)	14.3% (21)
Hypertension	57.4% (120)	66.7% (6)	58.0% (102)	64.7% (33)	53.7% (79)
Hyperlipidemia	78.9% (165)	88.9% (8)	79.5% (140)	68.6% (35)	82.3% (121)
Active smoker	23.0% (48)	44.4% (4)	22.2% (39)	21.6% (11)	23.8% (35)
PAD	5.3% (11)	11.1% (1)	6.3% (11)	2.0% (1)	6.8% (10)
ACS	57.4% (120)	44.4% (4)	59.1% (104)	60.8% (32)	53.7% (79)
Baseline laboratory results					
Creatinine	93.1 ± 20.5	91.0 ± 17.3	93.0 ± 20.7	98.2 ± 23.9	91.6 ± 19.7
Hemoglobin	144.4 ± 13.8	141.5 ± 12.2	144.4 ± 13.8	146.0 ± 15.8	143.9 ± 13.3
Platelet	237.6 ± 58.9	248.9 ± 67.5	236.4 ± 59.4	222.9 ± 56.1	242.8 ± 60.2
CRP	7.0 ± 14.6	7.0 ± 7.7	7.2 ± 16.1	14.7 ± 25.9*	4.5 ± 6.7*
Pre-procedural medications					
CCB	16.7% (35)	0.0% (0)	15.9% (28)	17.6% (9)	17.0% (25)
ACE inhibitors	71.3% (149)	66.7% (6)	72.2% (127)	72.5% (37)	70.1% (103)
Beta blockers	90.9% (190)	88.9% (8)	93.2% (164)	98.0% (50)*	87.8% (129)*
Statins	87.6% (183)	66.7% (6)	89.2% (157)	88.2% (45)	87.8% (129)
Procedural characteristics					
Integrilin 18 h	49.3% (103)	66.7% (6)	50.0% (88)	52.9% (27)	48.3% (71)
Integrilin duration (h)	8.9 ± 8.3	12.1 ± 8.4	9.0 ± 8.3	9.2 ± 8.3	8.7 ± 8.3
# of vessels treated	1.3 ± 0.5	1.2 ± 0.4	1.3 ± 0.5	1.3 ± 0.6	1.2 ± 0.5
# of lesions treated	1.7 ± 0.9	1.4 ± 0.7	1.7 ± 1.0	1.9 ± 1.2	1.6 ± 0.8
DES used	36.8% (77)	33.3% (3)	35.8% (63)	39.2% (20)	36.7% (54)
AHA B2 or C lesion	64.8% (114)	44.4% (4)	64.7% (114)	61.0% (25)	66.4% (83)

*$p < 0.05$.

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; AHA = American Heart Association; CABG = coronary artery bypass surgery; CCB = calcium-channel blocker; CRP = C-reactive protein; DES = drug-eluting stent; MI = myocardial infarction; PAD = peripheral arterial disease.

aspirin response assessed, 198 had clopidogrel response assessed, and 174 had both assessed. The baseline characteristics are reported in Table 1, with patients segregated into groups according to aspirin and clopidogrel response. Aspirin-resistant patients had similar baseline characteristics compared with aspirin-sensitive patients. Clopidogrel low-responders tended to have higher body-mass index, higher baseline C-reactive protein level, and greater beta-blockade use, compared with clopidogrel responders. The majority of our patients received clopidogrel 75 mg/day for at least 5 days (78.9%). Only 13.9% received clopidogrel 300-mg loading at least 6 h previously, and only 7.2% received clopidogrel 600-mg loading at least 2 h previously.

According to our criteria, 4.9% of patients were aspirin resistant. Figure 1 shows the distribution of ARU in our substudy patients. Clopidogrel low-responders were defined as those belonging to the lowest quartile with platelet inhibition <19% (Fig. 2). Only 1.1% of patients were both aspirin resistant and clopidogrel low-responders. There was no difference in the primary end point of myonecrosis among aspirin-resistant compared with aspirin-sensitive patients (11.1% vs. 27.8%, p = 0.259) or among clopidogrel low-responders compared with clopidogrel responders (23.5% vs. 29.3%, p = 0.433) (Table 2).

We also segregated aspirin and clopidogrel response into quartiles of ARU and platelet inhibition, respectively, and found no difference in the prevalence of myonecrosis between different quartiles (Figs. 3 and 4). Likewise, there was no difference among patients who received different clopidogrel loading regimens (75 mg/day for ≥5 days or 300-mg loading dose ≥6 h prior or 600-mg loading dose ≥2 h prior), with respect to platelet inhibition achieved (p = 0.839) or prevalence of myonecrosis with PCI (p = 0.985).

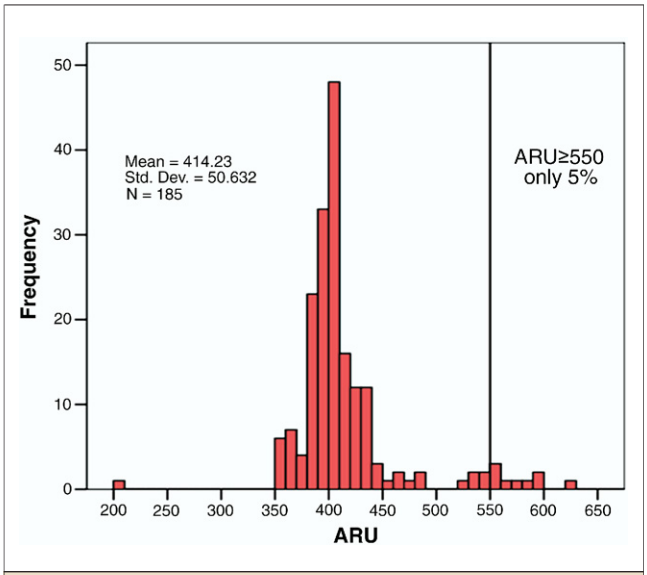

Figure 1. Aspirin Response

Distribution of the aspirin reaction unit (ARU) with the VerifyNow Aspirin assay.

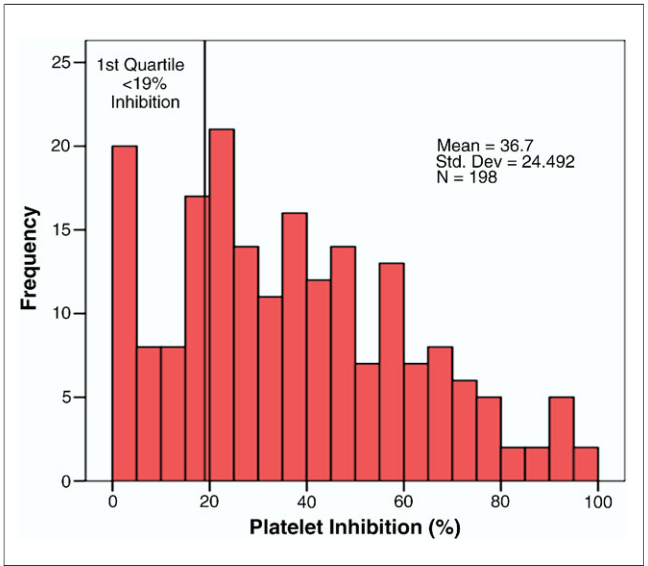

Figure 2. Clopidogrel Response

Distribution of platelet inhibition (%) with the VerifyNow Clopidogrel ($P2Y_{12}$) assays. Patients in the lowest quartile had <19% platelet inhibition.

There were also no differences in the secondary end points of CK-MB elevation, clinical 30-day death, MI and urgent target vessel revascularization event-rates, REPLACE-2 major or minor bleeding events (Table 2), and blush score before and after PCI, when comparing between aspirin-resistant and -sensitive patients and between clopidogrel low-responders and responders.

Because patients were randomized to different durations of eptifibatide infusion, we tested for interactions between the randomized assignment of eptifibatide duration (<2 h vs. 18 h) and aspirin and clopidogrel response. We found no significant interaction between aspirin resistance and randomized treatment (p = 0.999) or between clopidogrel low-response and randomized treatment (p = 0.448) on the prevalence of myonecrosis.

Discussion

Our study demonstrated that the prevalence of myonecrosis was not affected by the response to aspirin and clopidogrel amongst patients who also received eptifibatide during PCI. Likewise, the short-term clinical event-rates were not affected by aspirin and clopidogrel response in this cohort. Therefore, it seems that the effects of GP IIb/IIIa blockade with eptifibatide were sufficiently potent such that even lack of adequate response to aspirin and/or clopidogrel before PCI did not jeopardize the short-term results of PCI.

Aspirin and clopidogrel resistance had been associated with higher rates of adverse clinical outcomes after PCI (1,2). However, our study suggests that the clinical impact

Table 2. Prevalence of Myonecrosis and Secondary End Points

	Aspirin Resistant	Aspirin Sensitive	p Value	Clopidogrel Low Responder	Clopidogrel Responder	p Value
Myonecrosis	11.1% (1/9)	27.8% (49/176)	0.259	23.5% (12/51)	29.3% (43/147)	0.433
CK-MB >3× ULN	11.1% (1/9)	2.3% (4/176)	0.112	3.9% (2/51)	2.1% (3/146)	0.467
REPLACE-2 major bleeding	0.0% (0/9)	2.3% (4/176)	0.648	3.9% (2/51)	2.7% (4/147)	0.667
REPLACE-2 minor bleeding	22.2% (2/9)	22.2% (39/176)	0.996	17.6% (9/51)	29.3% (43/147)	0.125
30-day death, MI, urgent TVR	11.1% (1/9)	2.3% (4/176)	0.112	2.0% (1/51)	2.7% (4/147)	0.766

CK-MB = creatine kinase-myocardial band; MI = myocardial infarction; REPLACE = Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events; TVR = target vessel revascularization; ULN = upper limit of normal.

of aspirin or clopidogrel resistance was blunted amongst patients undergoing PCI who also received GP IIb/IIIa inhibitors. This suggests that routine evaluation for aspirin or clopidogrel response might not be necessary in this cohort. Correspondingly, a GP IIb/IIIa inhibitor could be used to ensure low periprocedural myonecrosis and clinical adverse events in patients in whom aspirin and/or clopidogrel resistance is suspected.

Our study expands on the 3 previously published studies on this topic, none of which incorporated the use of GP IIb/IIIa inhibitors (1–3). Moreover, these previous trials have demonstrated conflicting results with respect to the impact of aspirin and clopidogrel resistance on the prevalence of myonecrosis after PCI. Chen et al. (1) assessed 151 patients who underwent nonurgent PCI and found 19.2% of patients to be aspirin resistant on the basis of the Accumetrics VerifyNow Aspirin assay. Compared with patients who were aspirin responders, aspirin-resistant patients did have a higher prevalence of CK-MB and Tn-I elevation after PCI. Lev et al. (2) assessed 150 patients who underwent elective PCI. They found 12.7% of patients to be aspirin resistant with both the VerifyNow Aspirin assay and light transmittance aggregometry. They also found 24% of patients to be clopidogrel resistant with light transmittance aggregometry. Aspirin-resistant patients had a higher prevalence of CK-MB elevation after PCI; however, there was only a trend to higher prevalence of CK-MB elevation in clopidogrel-resistant patients. Finally, Buch et al. (3) assessed 330 patients who underwent elective PCI. They found no correlation between aspirin and clopidogrel response to Tn-I or CK-MB release with PCI, with the VerifyNow Aspirin and $P2Y_{12}$ assays.

We used the VerifyNow Aspirin and $P2Y_{12}$ assays to assess for aspirin and clopidogrel response, because these assays have been approved for clinical use, with rcal useesults that are rapidly available at the bedside and require minimal technical manipulation of the whole blood samples. With this assay, we found that only approximately 5% of our patient population was aspirin resistant (ARU ≥550).

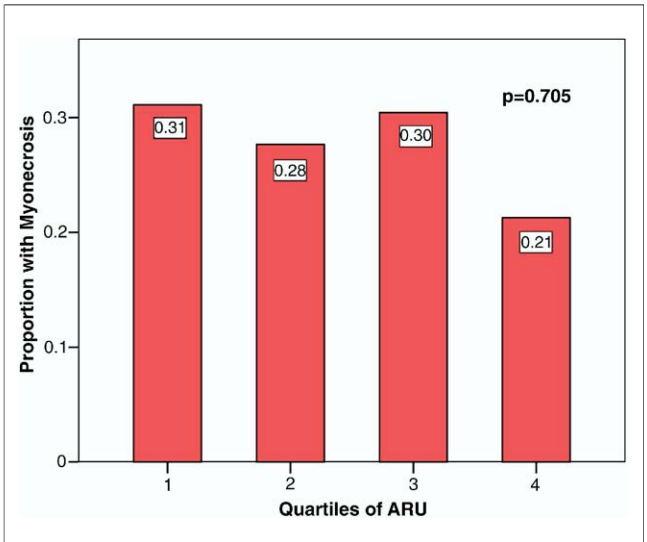

Figure 3. ARU Quartiles and Myonecrosis Prevalence

Prevalence of myonecrosis according to quartiles of aspirin reaction unit (ARU) with the VerifyNow Aspirin assay.

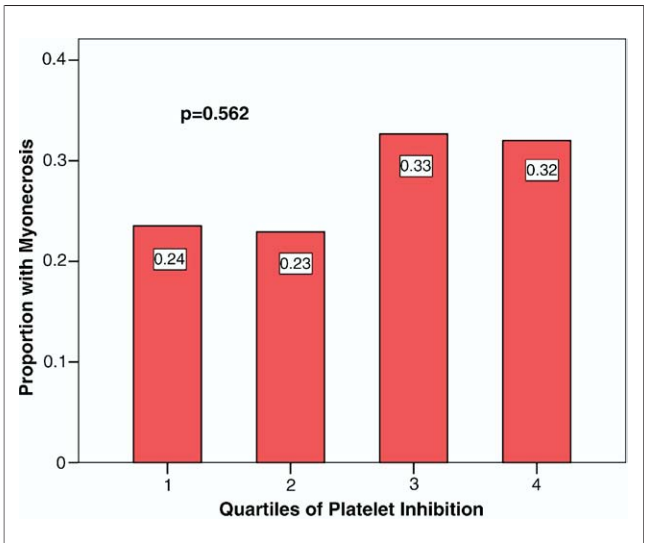

Figure 4. Platelet Inhibition Quartiles and Myonecrosis Prevalence

Prevalence of myonecrosis according to quartiles of platelet inhibition with the VerifyNow Clopidogrel ($P2Y_{12}$) assays (1st quartile corresponds to the lowest quartile of platelet inhibition).

However, there is no manufacturer's threshold identified for clopidogrel resistance. Thus, we allocated measured platelet inhibition into quartiles, and clopidogrel low-responders were defined as those belonging to the lowest quartile of platelet inhibition. With these definitions, we found that only 1.1% of patients were both aspirin resistant and a low-responder to clopidogrel.

Study limitations. We included only a small patient population in our substudy. The observed prevalence of myonecrosis (28.2% in this substudy) was lower than anticipated, and thus the lack of difference in myonecrosis prevalence between the groups evaluated might be due to the study being underpowered. Moreover, the lower prevalence of aspirin resistance (4.9%) in our patient population further reduced our study's power to assess aspirin-resistant patients. We could only use the VerifyNow assays for aspirin and clopidogrel response, due to funding limitations. We did not use light transmittance aggregometry to assess for aspirin and clopidogrel platelet response, because this technique requires a designated platelet laboratory with dedicated technical personnel to prepare platelet rich plasma, which are both time intensive and costly. Likewise, we did not perform flow-cytometry assessments of platelet receptor expression or use other point-of-care devices (e.g., PFA-100) due to cost constraints. Several authors have shown that platelet function tests correlate poorly amongst themselves (7–9), and thus the proportion of patients who were aspirin- or clopidogrel-resistant in our study could have been different with other assays, which might have altered our study conclusions. However, we believe that the VerifyNow assays were well-suited for our study, because they are the most commonly used point-of-care platelet assays currently available and were used in all 3 studies that had previously evaluated myonecrosis prevalence during PCI (1–3). Finally, we assessed only procedural and short-term 30-day clinical end points and thus do not know the long-term effects of aspirin and clopidogrel response on cardiovascular events.

Conclusions

Among patients undergoing uncomplicated PCI with eptifibatide, the response to aspirin and clopidogrel did not seem to affect periprocedural myonecrosis prevalence.

Reprint requests and correspondence: Dr. Jacqueline Saw, Division of Cardiology, Vancouver General Hospital, 2775 Laurel Street, 9th Floor, Vancouver, BC, V5Z 1M9, Canada. E-mail: jsaw@interchange.ubc.ca.

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Key Words: aspirin ■ clopidogrel ■ PCI ■ resistance.