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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.