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Bivalirudin and Clopidogrel With and Without Eptifibatide for Elective Stenting: Effects on Platelet Function, Thrombelastographic Indexes, and Their Relation to Periprocedural Infarction

Results of the CLEAR PLATELETS-2 (Clopidogrel With Eptifibatide to Arrest the Reactivity of Platelets) Study

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Objectives The primary objective of this study was to compare the effect of therapy with bivalirudin alone versus bivalirudin plus eptifibatide on platelet reactivity measured by turbidometric aggregometry and thrombin-induced platelet-fibrin clot strength (TIP-FCS) measured by thrombelastography in percutaneous coronary intervention (PCI) patients. The secondary aim was to study the relation of platelet aggregation and TIP-FCS to the occurrence of periprocedural infarction.

Background Bivalirudin is commonly administered alone to clopidogrel naïve (CN) patients and to patients on maintenance clopidogrel therapy (MT) undergoing elective stenting. The effect of adding eptifibatide to bivalirudin on platelet reactivity (PR) and TIP-FCS, and their relation to periprocedural infarction in these patients are unknown.

Methods Patients (n = 200) stratified to clopidogrel treatment status were randomly treated with bivalirudin (n = 102) or bivalirudin plus eptifibatide (n = 98). One hundred twenty-eight CN patients were loaded with 600 mg clopidogrel immediately after stenting, and 72 MT patients were not loaded. The PR, TIP-FCS, and myonecrosis markers were serially determined.

Results In CN and MT patients, bivalirudin plus eptifibatide was associated with markedly lower PR at all times (5- and 20-μM adenosine diphosphate–induced, and 15- and 25-μM thrombin receptor activator peptide–induced aggregation; $p < 0.001$ for all) and reduced mean TIP-FCS ($p < 0.05$). Patients who had a periprocedural infarction had higher mean 18-h PR ($p < 0.0001$) and TIP-FCS ($p = 0.002$).

Conclusions For elective stenting, the addition of eptifibatide to bivalirudin lowered PR to multiple agonists and the tensile strength of the TIP-FCS, 2 measurements strongly associated with periprocedural myonecrosis. Future studies of PR and TIP-FCS for elective stenting may facilitate personalized antiplatelet therapy and enhance the selection of patients for glycoprotein IIb/IIIa blockade. (Peri-Procedural Myocardial Infarction, Platelet Reactivity, Thrombin Generation, and Clot Strength: Differential Effects of Eptifibatide + Bivalirudin Versus Bivalirudin [CLEAR PLATELETS-2]; NCT00370045) (J Am Coll Cardiol 2009;53:648–57) © 2009 by the American College of Cardiology Foundation

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Ischemic complications during and after percutaneous coronary interventions (PCIs) are strongly influenced by platelet function (1). High post-PCI platelet reactivity (PR) to adenosine diphosphate (ADP) has been correlated with clinical events including periprocedural myocardial infarction and stent thrombosis (2–4). In a pharmacodynamic

study, eptifibatide administered with clopidogrel and heparin at the time of elective stenting produced consistent and superior platelet inhibition that was associated with lower periprocedural myonecrosis and inflammation marker release than was a strategy of clopidogrel and heparin alone (5,6). In addition to high PR to ADP, elevated maximum tensile strength of a thrombin-induced platelet-fibrin clot (TIP-FCS) measured by thrombelastography has also been strongly correlated with the occurrence of a 6-month post-PCI ischemic event (7).

Platelet function measurements were not performed in clinical trials that reported a noninferior anti-ischemic effect of bivalirudin therapy alone compared with heparin plus a glycoprotein (GP) IIb/IIIa inhibitor in patients treated with PCI (8,9). There are few studies reporting conflicting results regarding the potential antiplatelet effects of bivalirudin (10–13). In a recent study of PCI patients pretreated with a 600-mg clopidogrel load, administration of bivalirudin produced significant immediate additional suppression of ADP-induced platelet aggregation compared with that of unfractionated heparin (UFH) (12). In another study, therapy with bivalirudin or UFH in addition to eptifibatide and clopidogrel resulted in the same degree of platelet inhibition. Moreover, no significant differences occurred in the platelet inhibition between the bivalirudin and UFH alone groups (13). Thus, the effect of bivalirudin with and without a GP IIb/IIIa inhibitor on platelet function in PCI patients is unclear. Moreover, the effect of the latter regimens on TIP-FCS and the relation of TIP-FCS to periprocedural myonecrosis are completely unknown.

Therefore, the primary objective of the CLEAR PLATELETS-2 (Clopidogrel With Eptifibatide to Arrest the Reactivity of Platelets) study was to compare the effect of therapy with bivalirudin alone versus bivalirudin plus eptifibatide on platelet reactivity measured by turbidometric aggregometry and TIP-FCS measured by thrombelastography in PCI patients. The secondary aim was to study the relation of platelet aggregation and TIP-FCS to the occurrence of periprocedural infarction. Patients on long-term clopidogrel maintenance treatment (MT) and clopidogrel naïve (CN) patients loaded with high-dose clopidogrel immediately after stenting were studied, as both clinical scenarios are commonly encountered in daily practice in the U.S.

Methods

Patients. Two hundred consecutive stable patients undergoing PCI were enrolled in a 2-center, randomized, open-label study between March 2006 and December 2007. The study was approved by each of the local institutional review boards and was registered under http://www.clinicaltrials.gov (NCT00370045). The exclusion criteria were as follows: age <18 years old, a history of bleeding diathesis, acute myocardial infarction within 48 h, elevated cardiac markers (above upper limits of normal for the respective assay), cerebrovascular event within 3 months, chronic vessel occlusion, visible thrombus, illicit drug or alcohol abuse, prothrombin time >1.5 times control, platelet count <100,000/mm^3, hematocrit <30%, creatinine >2.0 mg/dl, and anticoagulation therapy or GP IIb/IIIa blocker use before the procedure.

Subjects were stratified according to clopidogrel therapy before PCI and randomized by a computer-generated assignment to eptifibatide plus bivalirudin (n = 98) or bivalirudin alone (n = 102), thus providing 4 treatment groups: 1) 600-mg clopidogrel plus bivalirudin (600 mg C + B); 2) 75-mg clopidogrel plus bivalirudin (75 mg C + B); 3) 600-mg clopidogrel plus bivalirudin plus eptifibatide (600 mg C + B + E); and 4) 75-mg clopidogrel plus bivalirudin plus eptifibatide (75 mg C + B + E). Clopidogrel naïve patients (n = 128) received treatment with 600-mg clopidogrel in the catheterization laboratory immediately after stenting, whereas patients currently on 75-mg MI (n = 72) did not receive a load. All patients on maintenance therapy had received daily clopidogrel for at least 2 weeks before enrollment. All patients were treated with at least 81-mg daily aspirin for at least 7 days before enrollment followed by 325-mg daily aspirin and 75-mg clopidogrel. Eptifibatide was administered using the ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor With Integrilin Therapy) study protocol as a double bolus (180 μg/kg) followed by an infusion (2 μg/kg/min) for 18 h after the procedure (14). Bivalirudin was administered according to the REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events-2) study protocol as a 0.75-mg/kg bolus followed by a 1.75-mg/kg/h infusion for the duration of the intervention (8).

Abbreviations and Acronyms

ADP = adenosine diphosphate
B = bivalirudin
C = clopidogrel
CK-MB = creatinine kinase-myocardial band
CN = clopidogrel naïve
E = eptifibatide
GP = glycoprotein
MT = clopidogrel maintenance treatment/therapy
PCI = percutaneous coronary intervention
PPACK = D-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone
PR = platelet reactivity
R = time to initial platelet-fibrin clot formation
TEG = thrombelastography
TIP-FCS = thrombin-induced platelet-fibrin clot strength
TRAP = thrombin receptor activator peptide
UFH = unfractionated heparin

Blood sampling. Baseline blood samples were obtained in the catheterization laboratory through the indwelling femoral vessel sheath and transferred to tubes anticoagulated with 75 μM D-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone (PPACK) (BIOMOL, Plymouth Meeting, Pennsylvania) for aggregation and flow cytometry studies. Blood samples for myocardial necrosis marker analyses and for thrombelastography were collected in Vacutainer tubes (Becton Dickinson, Franklin Lakes, New Jersey) containing 1.8-mg/ml dipotassium ethylene diamine tetraacetate and