Acute Coronary Syndromes

A Randomized Comparison of High Clopidogrel Loading Doses in Patients With Non–ST-Segment Elevation Acute Coronary Syndromes

The ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis) Trial

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OBJECTIVES   We sought to compare the antiplatelet effects of three clopidogrel loading doses (LDs).

BACKGROUND   Administration of a 300-mg clopidogrel LD is beneficial in situations requiring rapid platelet inhibition. Whether higher LDs can provide further benefits remains unknown.

METHODS   Patients (n = 103) with non–ST-segment elevation acute coronary syndromes were randomized to receive a 300-mg, 600-mg, or 900-mg clopidogrel LD, given on top of other standard therapy (including acetylsalicylic acid). The main outcome measure was inhibition of adenosine diphosphate-induced inhibition of platelet aggregation (IPA); inhibition of platelet activation, inflammatory markers, troponin I release, and major adverse cardiac events also were evaluated; all measures were blindly evaluated.

RESULTS   Compared with the 300-mg LD, greater doses were associated with significantly greater platelet inhibition, with dose-effect relationships observed for onset of action, maximal plateau, 24-h areas under the curves of IPA, and rates of low IPA ($<$10% at 6 h), using 20 μmol/l major adverse cardiac events. A significant dose-response was also observed for the vasodilator-stimulated phosphoprotein index, a measure of $P2Y_{12}$ receptor inhibition. Similar but nonsignificant trends were observed for troponin release and major adverse cardiac events. Bleeding rates were similar in each group.

CONCLUSIONS   In low-to-moderate risk patients with non–ST-elevation acute coronary syndromes, clopidogrel LDs $>$300 mg provide a faster onset of action, a higher IPA plateau, and greater reductions in platelet activation during the first 24 h. A 900-mg LD may induce a greater antiplatelet effect than 600 mg, when compared with the standard 300-mg regimen. These findings require further clinical confirmation.   (J Am Coll Cardiol 2006;48:931–8) © 2006 by the American College of Cardiology Foundation

Optimal and rapid inhibition of platelet function is an important therapeutic goal for the management of patients with acute coronary syndromes and in those undergoing percutaneous coronary intervention (PCI). In the case of antiplatelet therapy with clopidogrel, a $P2Y_{12}$ adenosine diphosphate (ADP)-receptor antagonist, this has traditionally been achieved by initiating treatment with a 300-mg

oral loading dose (LD) to reduce the time to onset of action from a few days to a few hours (1), with a significant clinical benefit in addition to acetylsalicylic acid (ASA), in various situations (2–10).

However, the slow onset of action still remains a question in the urgent care setting and/or PCI and has led several groups to conduct small randomized studies evaluating greater LDs (i.e., 400 to 600 mg) of clopidogrel. Most of these studies have suggested that greater LDs reduce the time to achieve optimal inhibition of platelet aggregation (IPA) (11–13), although divergent results have also been published (14,15). Recent data also have suggested an incremental benefit of a 600-mg LD (compared with the standard 300-mg LD) on the release of cardiac markers after PCI (13,16). These studies typically have been single center and open label, with a limited number of sampling time points; all have used clopidogrel LDs $\leq$600 mg.

To address the question of the optimal clopidogrel LD rigorously, we performed a randomized, multicenter,

Abbreviations and Acronyms

ADP	= adenosine diphosphate
ASA	= acetylsalicylic acid
AUC	= area under the inhibition of platelet aggregation curve
GP	= glycoprotein
IPA	= inhibition of platelet aggregation
LD	= loading dose
LMWH	= low molecular weight heparin
MACE	= major adverse cardiac events
MFI	= median fluorescence intensity
NSTE-ACS	= non–ST-segment elevation acute coronary syndrome
PA	= platelet aggregation
PAI	= plasminogen activator inhibitor
PCI	= percutaneous coronary intervention
PGE$_1$	= prostaglandin E1
sCD40L	= soluble CD40 ligand
VASP	= vasodilator-stimulated phosphoprotein
vWF Ag	= von Willebrand factor antigen

parallel-group evaluation of the effects of three different clopidogrel LDs, testing a dose as high as 900 mg. In this dose-ranging study, multiple sampling time points were used to precisely determine the onset of action and the timing of the maximal effect on inhibition of platelet function with the different LDs. Although evaluation of platelet aggregation (PA) was the primary objective of the study, platelet activation and markers of inflammation and necrosis also were evaluated during the first 24 h. To avoid any interaction of PCI on the kinetics of all these markers, it was decided to study patients with non–ST-segment elevation acute coronary syndrome (NSTE-ACS) before they presented to the catheterization laboratory. Finally, ischemic and bleeding events were closely monitored during a month of follow-up.

METHODS

Study design. The ALBION (Assessment of the best Loading dose of clopidogrel to Blunt platelet activation, Inflammation and Ongoing Necrosis) trial was a randomized, parallel-group study of patients hospitalized with NSTE-ACS with a blinded evaluation of the primary end point and all biological secondary end points. The study was conducted at seven cardiology centers in Paris, France, according to the principles of the Helsinki Declaration and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for Good Clinical Practice. Approval was obtained from the Pitié-Salpêtrière University Hospital Ethics Committee, and patients provided written informed consent.

Major inclusion criteria were: 1) age >18 and ≤85 years; 2) ischemic symptoms (onset <48 h) and at least one of the following: electrocardiogram ST-segment or T-wave changes or positive troponin; 3) treatment at hospital admission with 250 to 500 mg of oral or intravenous ASA

and low molecular weight heparin (LMWH); and 4) an assignment for clopidogrel treatment.

Major exclusion criteria were: 1) catheterization performed before randomization or scheduled to be performed <24 h after randomization; 2) contraindication to LMWH, clopidogrel, or ASA; 3) severe hypertension; 4) platelet count <100,000/mm^3; 5) neutrophil count <1800/mm^3; 6) increased risk of bleeding; and 7) recent (within 10 days) or planned use of nonpermitted concomitant medications (any antiplatelet agent other than ASA, oral anticoagulants, hirudin, nonsteroidal anti-inflammatory drugs). In case of emergent PCI or glycoprotein (GP) IIb/IIIa inhibitor use during the 24-h study period, the patient was excluded from the analysis.

Treatment and follow-up. Using central randomization, patients were allocated to receive a 300-, 600-, or 900-mg oral clopidogrel LD on the morning of day 1. Twenty-four hours after the LD, all patients were started on a regimen of clopidogrel 75 mg/day and ASA ≤100 mg/day. Low molecular weight heparin was administered twice daily. All study medication was administered on an open-label basis. Patients were followed up at 30 (±7) days to record clinical outcome and adverse event reporting.

Processing of samples. To ensure prompt sample transfer and assaying, patients could only be randomized if the baseline blood sample was to be taken between 7 AM and 11 AM between Monday and Friday. The blood samples were transferred by the delivery service to the central laboratory, arriving within 1 h of venipuncture. Platelet aggregometry and flow cytometry tests were blindly performed immediately upon receipt.

Assay methods. Aggregometry, flow cytometry, measurements of inflammatory biomarkers, and markers of myonecrosis at all time points during the 24 h were processed in the core laboratory that was blinded to the treatment received.

ADENOSINE DIPHOSPHATE-INDUCED PLATELET AGGREGATION. Platelet-rich plasma was obtained by centrifugation of citrated whole blood at 100 *g* for 15 min at room temperature. Platelet-poor plasma was obtained by further centrifugation at 1000 *g* for 20 min. In vitro PA in platelet-rich plasma was measured at 37°C in an aggregometer (Model 490-4D, Chrono-Log Corporation, Kordia, the Netherlands) following the optical aggregometry method of Born (17). Platelet aggregation was induced by the addition of ADP (Chrono-Par, Kordia, the Netherlands) at final concentrations of 5 μmol/l and 20 μmol/l, and PA parameters were measured on samples obtained at baseline, 0.5 h, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, and 24 h. Inhibition of platelet aggregation (%) at time Tx was (intensity of aggregation at T baseline) − (intensity of aggregation at Tx)/(intensity of aggregation at T baseline).

FLOW CYTOMETRY. Flow cytometry measurements were performed at the same nine time points. All flow cytometric studies were conducted on a FACScalibur flow cytometer