



Optimal pretreatment timing for high load dosing (600mg) of clopidogrel before planned percutaneous coronary intervention for maximal antiplatelet effectivity - VASP phosphorylation status laboratory substudy of the PRAGUE-8 study

¹Zuzana Motovska, ¹Petr Widimsky, ¹Robert Petr, ¹Dana Bilkova, ²Iuri Marinov, ³Stanislav Simek, ⁴Petr Kala
on behalf of the PRAGUE-8 study investigators

¹Third Medical Faculty Charles University & Univ. Hospital Kralovske Vinohrady, Prague; ²The Institute of Hematol. and Blood Transfusion, Prague;
³First Medical Faculty Charles University & General Univ. Hospital, Prague; ⁴Masaryk University & Univ. Hospital, Brno; Czech Republic;

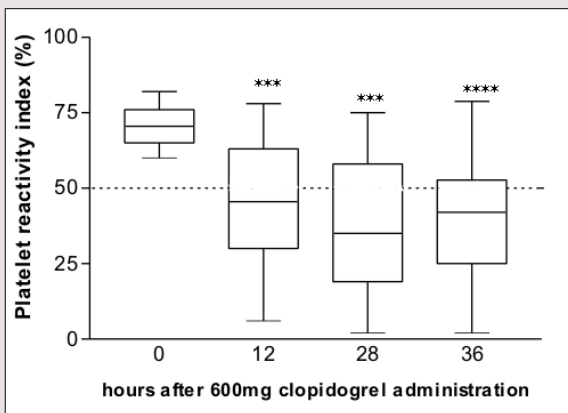


Figure 1. Time-dependent inhibition of platelet P2Y12 receptor (VASP phosphorylation state) after the clopidogrel 600 mg LD;

p=0.001 baseline mean PRI (%) vs. mean PRI (%) at 12h and 28h after LD; * p=0.002 baseline mean PRI (%) vs. mean PRI (%) at 36h after LD;

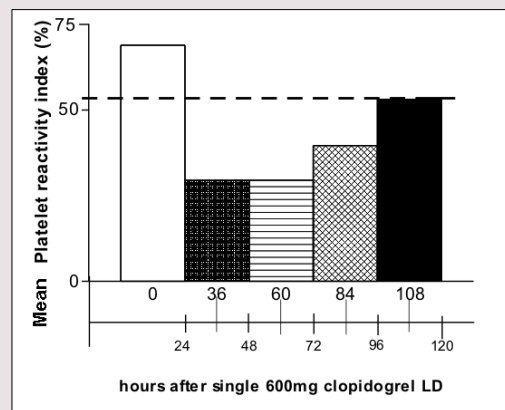


Figure 2. The recovery of ADP-mediated platelet activation after the 600 mg clopidogrel loading dose

Background The optimal timing for 600 mg clopidogrel pre-treatment before planned PCI in patients with stable coronary artery disease has never been tested in a randomized trial.

Methods The time course of platelet inhibition was investigated in 105 patients pre-treated with clopidogrel ≥ 6 h before the planned procedure. Flow cytometric analysis of the vasodilator stimulated phosphoprotein (VASP) phosphorylation state was done and a Platelet Reactivity Index (PRI) was calculated prior to treatment (baseline) and at 12, 28, 36, 60, 84 and 108 hours after the clopidogrel loading dose (LD) administration.

Results The maximal inhibition of platelet activation was seen at 28 h post administration (PRI mean $36 \pm 23\%$), and 2/3 of patients had PRI value $< 50\%$ (Figure 1). At 12 hours 47% of patients had PRI value $\geq 50\%$ (mean $45 \pm 21\%$). 600 mg of clopidogrel significantly suppressed platelet activation for 4 days (Figure 2). A correlation was between baseline PRI and its values by 28 hours ($rS = 0.48, p < 0.001$), between 12 h – 28 h the correlation was strong ($rS = 0.77, p < 0.001$).

Conclusion The time curve of clopidogrel efficacy was dependent on baseline platelet reactivity. Among stable CAD patients, pre-treatment with 600 mg of clopidogrel resulted in maximal antiplatelet efficacy one day after drug administration. Recovery of platelet activation was achieved on the 5th day after a high loading dose.

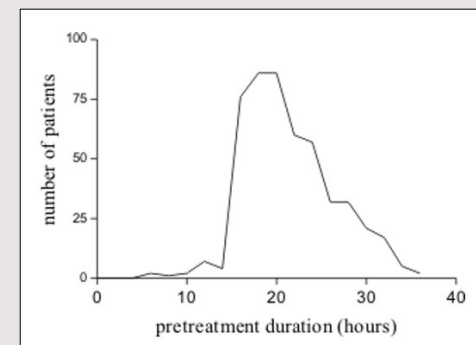


Figure 3. Frequency distribution of the 600 mg clopidogrel pre-treatment duration in PRAGUE-8 study

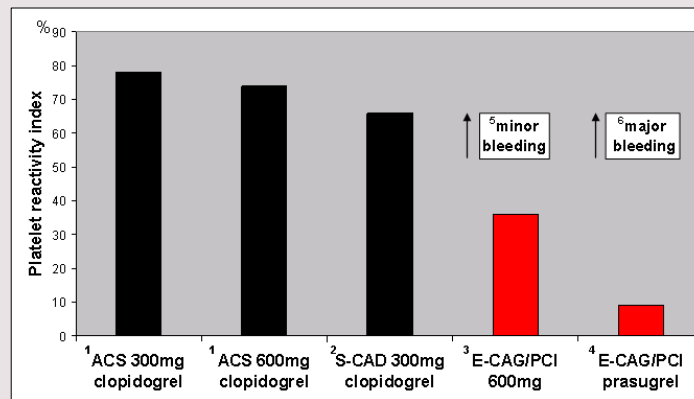


Figure 4. Dose dependent efficacy of clopidogrel and prasugrel in different patient population expressed as the mean of maximal decrease of platelet reactivity index (PRI) in patients with acute coronary syndromes (ACS) 6h after the drug administration, and in patients with elective coronary angiography/PCI (E-CAG/PCI) 24 h after the drug administration;

¹J Am Coll Cardiol. 2006; 48: 93; ²J Thromb Haemost 2007; 5:1630; ³Laboratory substudy of the PRAGUE-8 trial; ⁴Eur Heart J 2008; 29: 21; ⁵Eur Heart J. 2008;29:1495; ⁶NEJM 2007; 357: 2001

Clinical implication. The PRAGUE-8 trial randomized 1028 patients with stable angina to group A ('non-selective'—clopidogrel 600 mg >6 h before coronary angiography \pm PCI) or group B ('selective'—clopidogrel 600 mg in the cath-lab after coronary angiography, only in case of PCI). The mean time between clopidogrel administration and coronary angiography was 21 h and only in 4 (0.7%) patients, out of the entire pre-treated study population, had time intervals <12 h (Figure 3). However, as the main PRAGUE-8 trial results shown, the risk of bleeding associated with the full antiplatelet effect of 600 mg clopidogrel pre-treatment was not outweighed by the risk associated with coronary intervention on a stable atherosclerotic lesion. High (600 mg) loading dose of clopidogrel before elective CAG increased the risk of minor bleeding complications, while the benefit on periprocedural infarction was not significant.