In-lab High Dose Clopidogrel Loading Before Percutaneous Coronary Intervention: Is It The Prime Time?

Milorad Tesic, MD and Goran Stankovic, MD, PhD
Department of Diagnostics and Catheterization Laboratories, Division of Cardiology, Clinical Center of Serbia, Medical School of Belgrade

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ABSTRACT

Clopidogrel pretreatment significantly improves outcome in patients undergoing percutaneous coronary intervention (PCI), but it is not well established if the ad hoc loading of clopidogrel before the PCI and after coronary angiography is efficient and safe for the patient. According to the results of PRAGUE-8 and ARMYDA-5 PRELOAD trials, in-lab loading with 600mg clopidogrel might be safe and effective alternative to pre-treatment given several hours before diagnostic angiography or PCI. Still there is concern about adequate platelet inhibition, which can be overcome either with new loading scenarios or introducing more potent, more predictable, faster onset antiplatelet drugs, such as prasugrel and ticagrelor. Although increasing evidence suggests a link between residual platelet reactivity and adverse clinical outcomes, large scale clinical trials are still necessary to determine whether changes in therapy based on results of platelet function testing improve clinical outcomes, and thus will determine whether broader use of platelet function testing in clinical practice is warranted.

INTRODUCTION

Since platelets have major role in pathogenesis of thrombosis, dual oral antiplatelet therapy including aspirin and thienopyridine has dramatically reduced the risk of vessel thrombosis after coronary stenting (1). The thienopyridine – clopidogrel inhibits irreversibly adenosine diphosphate (ADP) receptor which mediates platelet activation. Several clinical studies examined efficacy of clopidogrel treatment regimes in patients with coronary artery disease.

The first large trial of clopidogrel was the Clopidogrel versus Aspirin in Patients at Risk for further Ischemic Events (CAPRIE) in which patients with atherosclerotic vascular disease were randomised to either clopidogrel (75mg) or aspirin (325mg) daily with a mean follow up of two years (2).

Long-term administration of clopidogrel was more effective than long-term aspirin therapy in reducing the combined risk of ischemic stroke, myocardial infarction or vascular death with a favourable safety profile. In the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial, synergistic acting of aspirin and clopidogrel was evaluated and study demonstrated 20% reduction in the major cardiac events in the group who received dual antiplatelet therapy compared to aspirin alone (3).

Use of clopidogrel also improves clinical outcome in patients with ST-segment elevation myocardial infarction (STEMI) irrespective of the reperfusion strategy (4,5).

However there are number of growing issues regarding the degree of clopidogrel response, time of treatment, loading doses and related bleeding in patients undergoing percutaneous coronary intervention (PCI) (1). To shorten the duration of pre-treatment period, several trials have established the benefit of preloading with clopidogrel before PCI, indicating that two hours is the minimum pre-intervention interval that is necessary to achieve optimal inhibition of platelet aggregation (6,7).

Although this can be readily implemented in patients undergoing elective PCI, it is problematic when unplanned intervention is required in an urgent setting; and in a real-world setting only very few patients are actually scheduled for elective PCI, while most patients are scheduled for elective diagnostic coronary angiography (CAG) with immediate ad hoc PCI procedure when indicated.

In this review we analyse data from available studies regarding to the most common question regarding clopidogrel usage in everyday practice – safety and efficacy of in-lab clopidogrel loading before PCI and after diagnostic angiography.

CORRESPONDENCE

Goran Stankovic MD, PhD, FACC
Department of Diagnostics and Catheterization Laboratories, Division of Cardiology, Clinical Center of Serbia, 8 Koste Todorovica, 11000 Belgrade
Tel: +381-11-3613653
Email: gorastan@sbb.rs

CONFLICTS OF INTEREST

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Clopidogrel loading scenarios

Patients with STEMI and non-ST-segment elevation according to the PCI-CURE trial (3) and PCI- Clopidogrel as Adjunctive Reperfusion Therapy (PCI-CLARITY) trial (5), strongly support early clopidogrel initiation due to stronger baseline platelet activation and lower inhibition in response to antiplatelet drugs. While there are no doubts on the clinical benefit achieved with clopidogrel pre-treatment, a question that arises from this concern is whether the timing is necessary to achieve such a benefit. When administered without loading dose, 75mg daily, maximal inhibition of platelet aggregation is after 3-7 days (8). In the post-hoc analysis of a prospective, randomised Clopidogrel for the Reduction of Events During Observation (CREDO) trial, it was stated that 300 mg clopidogrel pre-treatment has a clinical benefit only if it is given at least 15 hours before the intervention.

Pre-treatment with the conventional 300 mg loading dose of clopidogrel is related with significant reduction of myocardial infarction and cardiovascular death after PCI at 30 days compared with a 300mg loading dose given at the time of the procedures (3,5). A higher loading dose with 600mg of clopidogrel causes an earlier and stronger platelet inhibition than the 300mg dose and the results of post hoc analysis of Intracoronary Stenting and Antithrombotic Regimen – Rapid Early Action for Coronary Treatment (ISAR-REACT) trial, in which all patients received 600mg loading dose between two and 24 hours before PCI, suggest that if a 600mg loading dose is chosen, no advantage is gained by increasing the pre-treatment duration beyond two hours (6).

In Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect (ISAR-CHOICE) trial, where 60 patients were randomised to either 300mg, 600mg or 900mg dose, authors stated that increasing the dose to 900mg has not been associated with any additional significant suppression of platelet function because of limited clopidogrel absorption (7).

Based on available clinical evidence ACC/AHA/SCAI 2009 focused updates of guidelines on PCI recommend that at least 300 to 600 mg of clopidogrel should be given as early as possible before or at the time of primary or non-primary PCI (9), while The European Society of Cardiology guidelines recommend that a 300mg loading dose of clopidogrel should be administered at least six hours before PCI (10). Physicians must take these recommendations into consideration while simultaneously dealing with the realities of clinical practice (11).

Clopidogrel pretreatment before diagnostic coronary angiography and ad-hoc percutaneous coronary intervention

In a real-world setting only very few patients are actually scheduled for elective PCI, while most patients are scheduled for elective diagnostic coronary angiography (CAG) with immediate ad hoc PCI procedure when indicated. If the result of angiography suggests that PCI is appropriate and when a strategy of standard pre-treatment can not be adopted clopidogrel loading with 600 mg at least two hours before the procedure is advised (9,10). In this sense ad hoc PCI is not recommended. The major question remains whether it is safe and useful to do pre-treatment with clopidogrel before diagnostic CAG to every patient, or to wait until the coronary angiogram is revealed? Potentially, in-lab or ad hoc strategy of loading clopidogrel might have benefits for patients if there is no indication for PCI, so patients are not exposed to aggressive antiplatelet medications and potential bleeding complications, or contrary, if there is a need for urgent surgical revascularisation it can be done without delay. Possible disadvantage of in-lab loading might be the increase of ischemic peri-procedural complications due to the fact that the full effect of clopidogrel is not yet achieved at the time of PCI (8). Routine clopidogrel pre-treatment before angiography was tested in the PRAGUE-8 trial, which included 1028 patients with stable angina submitted to diagnostic CAG (12).

In that study patients were randomised to receive either a 600mg clopidogrel loading dose more than six hours prior to procedure or a 600mg loading dose given in lab at the time of PCI following CAG. When the subgroup of patients who underwent PCI after diagnostic CAG (only 29 % of the initial cohort) was analysed, primary ischemic endpoint was not significantly different between those two groups (1.3% vs. 2.8%; P=0.43) (12). There was also a higher rate (6.5%) of minor bleeding complications in preload group compared to in lab group. Authors concluded that clopidogrel should be used in patients with chronic stable angina, before “planned elective PCI” as well as before “ad hoc PCI” but not before “planned elective CAG”. Importantly, sample size of this study was underpowered to detect differences in clinical outcome in the 298 patients undergoing PCI.

Two other studies tested in-lab clopidogrel loading exclusively in ad hoc PCI procedures. A recent study which included 199 patients who were loaded with 900mg of clopidogrel and then randomised to ad hoc PCI or delayed PCI (after two hours), didn’t show any difference in clinical end points between a strategy of delaying PCI for two hours and ad hoc PCI (13). But there is a concern of major bleeding rate probably due to high loading dose which was 3% in this study (13), compared to major bleeding rate of 1.5% after 300mg clopidogrel loading in PCI-CURE study (3). However, randomised trials generally exclude patients at highest risk of bleeding and may therefore underestimate the true frequency of bleeding associated with clopidogrel use in the general population.

The Antiplatelet therapy for Reduction of Myocardial Damage during Angioplasty (ARMYDA-5 PRELOAD) trial examined 409 patients with stable or unstable coronary syndromes randomised to receive a 600 mg dose of clopidogrel 4-8 h before PCI versus 600 mg given in the catheter laboratory after CAG and before ad hoc PCI. Results showed that clinical outcomes after in-lab loading strategy are comparable to that of the pre-treatment approach, with a similar 30-day incidence of adverse events, and, in particular, no significant difference in the rates of peri-procedural myocardial infarction (8.8% in-lab vs. 10.3% preload; P = 0.56) (14).

No bleeding differences (and no major bleedings) were observed in the two arms (in-lab: 5.4%; preload: 7.8%) (14). According to these results the in-lab loading strategy may prevent the need of preloading before CAG. When indicated, in-lab 600mg clopidogrel administration can be safe and effective alternative to pre-treatment given several hours before PCI.
Platelet function testing and clinical outcomes

In the ARMYDA-5 PRELOAD trial platelet reactivity testing was done at the randomisation, in the cath lab at the time of PCI, at two, eight and 24 hours after intervention by the VerifyNow P2Y12 assay in P2Y12 reaction units (PRU) (14). Baseline PRU levels were similar in both arms, but patient in in-lab arm showed higher platelet reactivity at the time of PCI (P=0.043) and after two hours (P=0.01) compared to preload arm. Afterward PRU levels in both arms were similar. It is interesting that although the PRU levels were significantly different during PCI and after two hours no excess ischemic events were observed in the in-lab arm of the study. Authors stated that the lack of influence in the clinical outcome is both due to similar baseline PRU levels and similar risk groups (14). Difference in the PRU levels at the time of PCI is caused by different timing of clopidogrel loading (14).

This is important issue, since during the critical two hours after PCI if the PRU levels are significantly higher in in-lab arm compared to the preload arm that can lead to early stent thrombosis. Nevertheless, this study serves the purpose of stimulating more and larger efforts to study the issue of clopidogrel platelet reactivity by developing either new regimens of the same drug or new drugs which have different, more predictable, and more powerful effects on platelet function, such as prasugrel or ticagrelor (11). With these new compounds, it may no longer be necessary to consider pre-treatment because of more rapid onset and more pronounced platelet inhibition than clopidogrel. However, large scale clinical trials are still necessary to determine whether changes in therapy based on results of platelet function testing improve clinical outcomes, and thus will determine whether broader use of platelet function testing in clinical practice is warranted.

CONCLUSION

According to the results of PRAGUE-8 trial and ARMYDA-5 PRELOAD trial in-lab clopidogrel loading might be safe and effective alternative to pre-treatment given several hours before PCI. Still there is concern about adequate platelet inhibition, which can be overcome either with new loading scenarios or introducing more potent, more predictable, faster onset antiplatelet drugs, such as prasugrel and ticagrelor. Increasing evidence suggests a link between platelet reactivity and adverse clinical outcomes, but large scale clinical trials are still necessary to determine whether changes in therapy based on results of platelet function testing improve clinical outcomes.

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