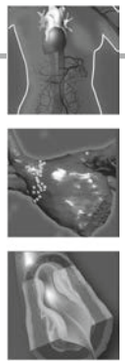

Is a higher loading dose of clopidogrel more effective during primary angioplasty for patients with STEMI?

Evaluation of: Patti G, Bárczi G, Orlic D *et al.* Outcome comparison of 600 and 300 mg loading doses of clopidogrel in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: Results from the ARMYDA-6 MI randomized study. *J. Am. Coll. Cardiol*. 58, 1592–1599 (2011). Primary angioplasty remains the mainstay of therapy for patients with ST-elevation myocardial infarction. Given the high prothrombotic state and large thrombotic burden in these patients, there is need for more rapid and potent platelet inhibition. To date, there have been several observational studies and one randomized trial supporting the notion that clopidogrel 600 mg compared with 300 mg improves outcomes. The ARMYDA-6 trial is the first randomized trial comparing clopidogrel 600 mg versus 300 mg specifically in a population with ST-elevation myocardial infarction. The authors found that a 600 mg loading dose of clopidogrel was associated with a significant reduction in the infarct size. While the clinical results are far from conclusive, the totality of available data support the use of a 600 mg loading dose as the optimal dose of clopidogrel in patients undergoing primary percutaneous coronary intervention. Now, with the availability of newer, more potent $P2Y_{12}$ inhibitors, large trials comparing these newer agents against clopidogrel 600 mg are needed in this population.

KEYWORDS: clopidogrel ▪ primary percutaneous coronary intervention ▪ ST-elevation myocardial infarction

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Primary percutaneous coronary intervention (PCI) is the main stay of treatment for patients with ST-elevation myocardial infarction (STEMI). These patients have an especially high prothrombotic milieu, due to their large thrombotic burden and the disruption of vascular endothelium during PCI. Clopidogrel, which acts on the $P2Y_{12}$ receptor on the surface of platelets and inhibits their activation, has proven to be beneficial in placebo-controlled trials of medically treated STEMI and those undergoing PCI for stable angina or non-STEMI [1,2]. However, its optimal use, in terms of timing and dosing, has never been properly studied in large-scale randomized trials in a pure primary PCI population. The ARMYDA-6 trial evaluated the effect of using clopidogrel 600 mg as loading dose versus the use of 300 mg on the outcomes after PCI in patients with STEMI.

Summary of methods & results

In this international, multicenter, randomized, and prospective trial, the authors evaluated two loading doses of clopidogrel – 300 or 600 mg – in the setting of primary PCI for patients presenting with STEMI. A total of 201 patients who met inclusion criteria were randomized to immediate 300 mg (n = 98) or 600 mg (n = 103) loading doses. The primary end point was the evaluation of the infarct size, defined as the area under the curve of CK-MB and troponin I. Secondary end points included thrombolysis in myocardial infarction (TIMI) flow pre- and post-PCI, left ventricular ejection fraction at discharge by transthoracic echocardiography, major adverse cardiovascular events (MACE) at 30 days, bleeding and entry site complications.

Clinical and procedural characteristics were appropriately matched for in the 600 and 300 mg loading dose groups. In the high dose clopidogrel group, the infarct size, as measured by the area under the curve, was significantly lower compared with the 300 mg cohort (CK-MB 2070 vs 3049 ng/ml; $p = 0.0001$; troponin I 255 vs 380 ng/ml; $p < 0.0001$). The secondary end points which included TIMI flow pre-PCI (not significant) and post-PCI TIMI flow <3 was significantly lower ($p = 0.031$) in the 600 mg group, ejection fraction at discharge was better in the 600 mg group ($p = 0.026$); however, 30-day MACE incidence was barely statistically significant with a p value of 0.049.

Based on the above results, the authors of the ARMYDA-6 trial concluded that pretreatment with a loading dose of clopidogrel 600 mg significantly reduced the infarct size, may improve

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TIMI flow post PCI and left ventricular ejection fraction at discharge, and may reduce 30-day clinical events.

Discussion

Optimizing blood flow in diseased coronary arteries is the core principle behind PCI. Unfortunately, disruption of vascular endothelium during PCI creates a local environment conducive to thrombosis, which leads to further myocardial damage if not adequately addressed. Hence in patients with STEMI undergoing PCI, there is a need for rapid and potent platelet inhibition. But what 'potent' really means remains poorly understood, as GPIIb/IIIa antagonists are strikingly more potent inhibitors of platelet aggregation than clopidogrel, yet that doesn't appear to translate into improved clinical efficacy [1].

Randomized, placebo-controlled trial data supporting clopidogrel use in the treatment of STEMI patients comes from two trials, both of which excluded primary PCI. In the CLARITY trial, all patients received fibrinolytic therapy before protocol-mandated angiography [2]. This trial randomized 3491 STEMI patients under the age of 75 years, to receive a clopidogrel 300 mg loading dose followed by 75 mg daily, versus placebo. The primary outcomes of death, myocardial infarction (MI) or target vessel occlusion at angiography were reduced by 36% ($p < 0.01$) in the clopidogrel arm. In the COMMIT trial, 45,852 STEMI patients, who were either treated with fibrinolytics or received no reperfusion therapy, were randomized to clopidogrel 75 mg daily without a loading dose or placebo [3]. Randomization to clopidogrel was associated with a 9% relative risk reduction in death, recurrent MI or stroke.

While there are no randomized trial data supporting clopidogrel loading pre- versus post-primary PCI, a meta-analysis consisting of 8429 patients clearly supported the benefit of pretreatment with a loading dose of clopidogrel in patients undergoing primary PCI. Those pretreated with clopidogrel had higher rates of initial coronary patency (34.3%; 95% CI: 32.9–35.8) compared with those who did not (25.8%; 95% CI: 24.5–27.1). Pretreatment with clopidogrel was also noted to be an independent predictor of improved clinical outcomes [4]. However, this study did not examine the effect of dosing on the above results.

In STEMI patients undergoing emergent PCI, the beneficial effect of a loading dose of clopidogrel 600 mg compared with a 300 mg loading dose has been noted in several observational studies. A prospective observational study of 255 consecutive patients presenting with STEMI undergoing primary PCI, examined procedural angiographic end points and 1-year MACE with 600 and 300 mg loading doses given prior to PCI. Patients who received 600 mg had a significantly higher survival free of MACE (hazard ratio [HR]: 0.57; 95% CI: 0.33–0.98; $p = 0.04$) compared with the lower loading dose [5]. In a *post hoc* observational analysis of patients with STEMI undergoing primary PCI, enrolled in the HORIZONS-AMI study, a loading dose of clopidogrel 600 mg was noted to reduce 30-day ischemic events compared with a dose of 300 mg. Interestingly, and somewhat counterintuitively, patients who received a 600 mg loading dose also experienced less bleeding, which might suggest that they were just a 'less sick' cohort overall. Hence, the authors noted that despite the use of multivariate and propensity analysis, it is unknown if unmeasured cofounders were still present [6].

A 2 × 2 factorial, randomized CURRENT OASIS-7 study investigated optimal doses of aspirin and clopidogrel in patients with acute coronary syndrome. A subgroup analysis including 6346 STEMI patients undergoing primary PCI found a 37% reduction in MI at 30 days in patients who received clopidogrel 600 mg followed by 150 mg daily for 7 days, compared with those randomized to 300 mg followed by 75 mg daily (0.63, 95% CI: 0.41–0.94) [101]. There was also a 46% reduction in definite stent thrombosis with a HR of 0.54 (95% CI: 0.35–0.84). While these are some of the strongest data available supporting a 600 mg loading dose among patients undergoing primary PCI, the results of the STEMI subset need to be carefully interpreted until published in their entirety and it must be recognized that the potential benefits of the loading dose versus the higher early maintenance dose cannot be differentiated.

The use of newer, more potent $P2Y_{12}$ inhibitors shows substantial promise in patients undergoing primary PCI. The TRITON study, a subgroup analysis of 3534 STEMI patients, not all of whom were primary PCI patients, showed a significant reduction in 30-day cardiovascular death, nonfatal MI and nonfatal stroke with prasugrel compared with clopidogrel (6.5 vs 9.5%, respectively) with a HR of 0.68 (95% CI: 0.54–0.87; $p = 0.0017$) [7,8]. At 15 months, the effect of prasugrel

persisted with an absolute risk reduction of 1.3% in the primary PCI group and 4.6% in the secondary group [7,9]. Another new, reversible $P2Y_{12}$ inhibitor, ticagrelor, was studied in comparison with clopidogrel in the randomized, double blind PLATO trial [10]. The results of subgroup analysis of 7544 STEMI patients enrolled in the PLATO trial showed a nominal reduction in the primary end point (MI, cardiovascular death and stroke) with ticagrelor compared with clopidogrel (HR: 0.87; 95% CI: 0.75–1.01; p = 0.07), although there were significant reductions in several important secondary end points, including MI alone (HR: 0.80; p = 0.03), total mortality (HR: 0.82; p = 0.05) and definite stent thrombosis (HR: 0.66; p = 0.03). These results fully support the notion that more potent $P2Y_{12}$ inhibition improves outcomes in STEMI patients treated by PCI.

ARMYDA-6, although small, is the first prospective randomized trial that compared the 600 mg versus 300 mg loading dose of clopidogrel, specifically in STEMI patients undergoing primary PCI. The study was well designed, with appropriate inclusion and exclusion criteria and effective randomization. Infarct size was measured using surrogate laboratory markers instead of more accurate modalities such as MRI. Known clinical and procedural variables were adequately matched. As noted by the authors, the study included a small number of patients and hence was not powered to reliably make clinical conclusions. It is important to recognize that the markedly higher event rates in the 300 mg arm were much higher than would be expected, suggesting that by chance, this cohort may have had a greater degree of coronary disease or greater degrees of at risk myocardium, which indicated the need for a more cautious interpretation of the results. Further large studies are needed to confirm the findings of this study.

Future perspective

ARMYDA-6 confirmed the findings of several previously published observational studies and subsets of randomized trials that a loading dose of clopidogrel 600 mg is more effective than 300 mg. While it would be ideal to definitively confirm these results in a trial adequately powered for clinical end points, at this time trials comparing clopidogrel 600 mg against prasugrel or ticagrelor loading and determining the optimal time of administration seem much more clinically relevant.

Executive summary

- There is a need for rapid and potent platelet inhibition in patients with ST-elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention.
- A loading dose of clopidogrel 600 mg has been shown to be more beneficial than 300 mg in several observational studies and the results of ARMYDA-6 support these earlier findings.
- Newer, more rapid, potent and consistent $P2Y_{12}$ inhibitors such as ticagrelor and prasugrel show promise for improving outcomes in STEMI patients with relatively safe short-term bleeding profiles.
- Further large-scale randomized controlled trials comparing new $P2Y_{12}$ inhibitors with clopidogrel in patients with STEMI patients undergoing primary percutaneous coronary intervention are warranted.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

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