

Comparison of 600 mg Versus 300 mg Clopidogrel Loading Dose for Patients With Ischemic Heart Disease: A Meta-Analysis of Randomized Controlled Trials

Gwen R. Marcellana, M.D | Emilio Jose Gravador, MD | Rodney Jimenez, MD |
Richard Henry Tiongco II, MD
St. Luke's Medical Center, Global City, Taguig City, Philippines

Correspondence:
Dr. Gwen R Marcellana.
St. Luke's Medical Center, Philippines.
Email: gmarcellana@stlukes.com.ph

DISCLOSURE: None

Abstract

INTRODUCTION: While a 600 mg loading dose (LD) of clopidogrel has demonstrated superior inhibition of platelet function compared to 300 mg LD, the clinical evidence supporting this superiority is limited. The debate centers on whether higher clopidogrel LD regimen in percutaneous coronary intervention (PCI) outperforms the standard 300 mg LD, with potential benefits being more pronounced in higher-risk patients. Balancing enhanced platelet inhibition to reduce ischemic events against the associated risk of increased bleeding remains a critical consideration in determining the optimal loading dose of clopidogrel for patients with ischemic heart disease.

METHODS: A systematic literature search for randomized clinical trials (RCTs) was performed comparing 600 mg with 300 mg LD of clopidogrel using PubMed, MEDLINE, Embase, Cochrane, Clinicaltrials.gov and HerdinPH. Studies included those between 2010 and 2023 involving human subjects. The primary efficacy endpoint was a 1-month rate of major adverse cardiac event (MACE) and the primary safety outcome was bleeding adverse effects.

RESULTS: Nine RCTs involving 29,827 patients were included in the efficacy analysis. Mean duration of follow-up was 30 days. Only eight studies were eligible for safety analysis. Compared with standard LD clopidogrel, high LD significantly reduced the incidence of overall MACE (OR: 0.82, 95% CI: 0.74-0.91, $p = 0.0002$), nonfatal myocardial infarction (OR: 0.56; 95% CI: 0.32-0.99, $p = 0.15$) and target vessel revascularization (OR: 0.63; 95% CI: 0.41-0.95, $p = 0.03$), without significant difference in terms of cardiac death (OR: 0.89; 95% CI: 0.76-1.04, $p = 0.15$) and stroke (OR: 0.92; 95% CI: 0.67-1.26, $p = 0.61$). However, major bleeding risk was higher in the 600 mg LD (1.9%; 261/13288) compared with 300 mg LD (2.4%; 328/13242) [OR: 1.27; 95% CI: 1.08-1.49, $p = 0.005$] without significant difference in minor bleeding (OR: 1.05; 95% CI: 0.94-1.17, $p = 0.35$).

CONCLUSION: The administration of 600 mg clopidogrel LD reduces the overall risk of MACE with associated increased risk of major bleeding.

BACKGROUND

The key principle in performing primary percutaneous coronary intervention (PPCI) is restoring and optimizing blood flow in diseased coronary arteries. The use of clopidogrel, a P2Y₁₂ receptor inhibitor on platelet surface has long been demonstrated to be efficacious in placebo-controlled studies in all spectrums of ischemic heart disease.^{1,2} The advantageous effects of clopidogrel pretreatment prior to PPCI was first introduced by the PCI-CURE study showing a reduction in cardiovascular (CV) death, myocardial infarction (MI), and target vessel revascularization (TVR) at 30 days at 4.5% in the clopidogrel versus 6.4% in the placebo group (relative risk 0.7, $p = 0.03$).³ This was followed by the CREDO study which assessed the impact of administering a loading dose of clopidogrel before the procedure showing tendency towards a decreased event rate when preloaded with a 300-mg clopidogrel dose.⁴ Rapid suppression of platelet activity on inhibition of platelet activity within the context of increased prothrombotic environment and disturbance of vascular endothelium during the percutaneous coronary

Published online: 29 May 2025
<https://doi.org/10.69944/pjc.ab9a6e6874>
<https://pjc.philheart.org>
ISSN: 0115-1029
e-ISSN: 2815-2123
Volume 53 Issue 1

This is an Open Access article under the Creative Commons Attribution-Non Commercial-ShareAlike 4.0 International License. CC BY-NC-SA 4.0. Please refer to <https://creativecommons.org/licenses/by-nc-sa/4.0/> for details.
Copyright (c) 2024 Philippine Heart Association

intervention (PCI) procedure and avoidance of subsequent cardiovascular ischemic events are the rationale for using a double dose of clopidogrel in acute coronary syndrome (ACS)/non-ACS patients undergoing primary coronary angioplasty.⁵

According to studies, the 600-mg loading dose (LD) of clopidogrel is linked to a more rapid onset of platelet inhibition,⁶⁻¹² establishing it as the preferred dose used for most patients with American College of Cardiology/American Heart Association (ACC/AHA) (2021)¹³ recommending use of the lower 300 mg LD generally reserved for older patients or those at higher risk of bleeding. The European Society of Cardiology guidelines (2018) recommend a 600 mg LD (Class IA)¹⁴ for elective stenting while the most recent 2023 guidelines for ACS recommend 300-600 mg loading when Prasugrel and Ticagrelor are unavailable, cannot be tolerated or contraindicated (Class IC).¹⁵

Several reports have suggested that a higher clopidogrel LD in comparison to a standard 300 mg LD may provide better protection and incremental benefit of improved platelet inhibition and enhanced responsiveness to clopidogrel in preventing cardiac death or non-fatal myocardial infarction without causing adverse events like increased bleeding. However, higher clopidogrel LD regimens were evaluated in several relatively small studies, and their clinical outcomes are conflicting or inconclusive.⁶⁻¹² A focus on 30-day major adverse cardiac event (MACE) outcomes was chosen due to its relevance in capturing early post-procedural ischemic events and complications, which are critical for evaluating the immediate efficacy and safety of different clopidogrel loading doses. The first month post-PCI represents a high-risk period for stent thrombosis, recurrent ischemia, and other adverse events, making it a clinically meaningful timeframe for assessing intervention-related outcomes. By synthesizing data from randomized trials, the analysis aims to provide a comprehensive comparison of the efficacy and safety of 600 mg versus 300 mg clopidogrel LD in optimizing outcomes for this high-risk patient population.

Objectives

The objective of this meta-analysis and systematic review is to validate current randomized trials that investigate the efficacy and safety of two clopidogrel loading regimens (600 mg vs 300 mg) in patients with ischemic heart disease treated with PPCI.

Specific Objectives:

1. To compare the primary efficacy outcome of one month rate of MACE of cardiac death, post-procedural myocardial infarction, stroke and urgent vessel revascularization.
2. To compare the primary safety outcome of bleeding adverse effects.

MATERIALS AND METHODS

Search Strategy

We identified five references through electronic searches of Medline/PubMed, Clinicaltrials.gov, Cochrane Library and

Herdin.ph from January 2015 up to October 2023. The reference list of articles was also included. The systematic literature review was performed independently by two investigators using the keywords and medical subject heading (MeSH) terms: “Clopidogrel 300 mg”, “Clopidogrel 600 mg”, and “Primary percutaneous coronary intervention”. A total of 97 articles were identified and 9 were included in the meta-analysis (Figure 1). The protocol for this systematic review is registered with PROSPERO (International Prospective Register of Systematic Reviews; Registration number: CRD42023438054). A systematic literature search was performed to identify optimal clopidogrel LD in patients undergoing PPCI. Studies were included if they were (1) controlled comparisons either through random allocation of high (600 mg) versus standard (300 mg) clopidogrel LD; (2) patients with coronary artery disease; and (3) scheduled for catheterization and/or PCI.

Study Selection

Electronic literature searches were done for RCTs involving adult ischemic heart disease (IHD) patients undergoing PPCI with 300 mg LD of clopidogrel compared to 600 mg. The primary study must address the primary efficacy outcome of cardiac death, post-procedural myocardial infarction, stroke and urgent vessel revascularization and primary safety outcome of bleeding adverse effects.

Studies were excluded if they were (1) non-randomized studies, 2) duplicate studies or (3) animal studies.

Data Collection and Analysis

Data extraction and quality assessment

After a systematic search of related literature, studies included were assessed individually based on their inclusion and exclusion criteria. Critical analysis of the primary and secondary outcomes, intervention, study population and comorbidities of participants was performed. Risk of bias assessment was done for each included study. Data extraction and quality assessment were independently conducted by two reviewers, GM and EG, to ensure accuracy and minimize bias. Quality assessment was done using the evaluation instrument recommended by Cochrane Collaboration for bias risk assessment.

Measures of treatment effect

Outcomes whether dichotomous or continuous were used to describe both primary and secondary outcomes between the groups. Analysis was conducted using the statistical package Review Manager Version 5.4.

Assessment of heterogeneity and reporting biases

Cochran's Q-test and I² statistics were used to assess statistical heterogeneity across studies. As a guide, I² values <25% indicates low, 25% to 50% moderate, >50% high heterogeneity. For categorical variables, Mantel-Haenszel effect model was used to calculate the pooled odds ratio for studies and associated 95% confidence intervals. A p-value of less than 0.05 was considered significant.

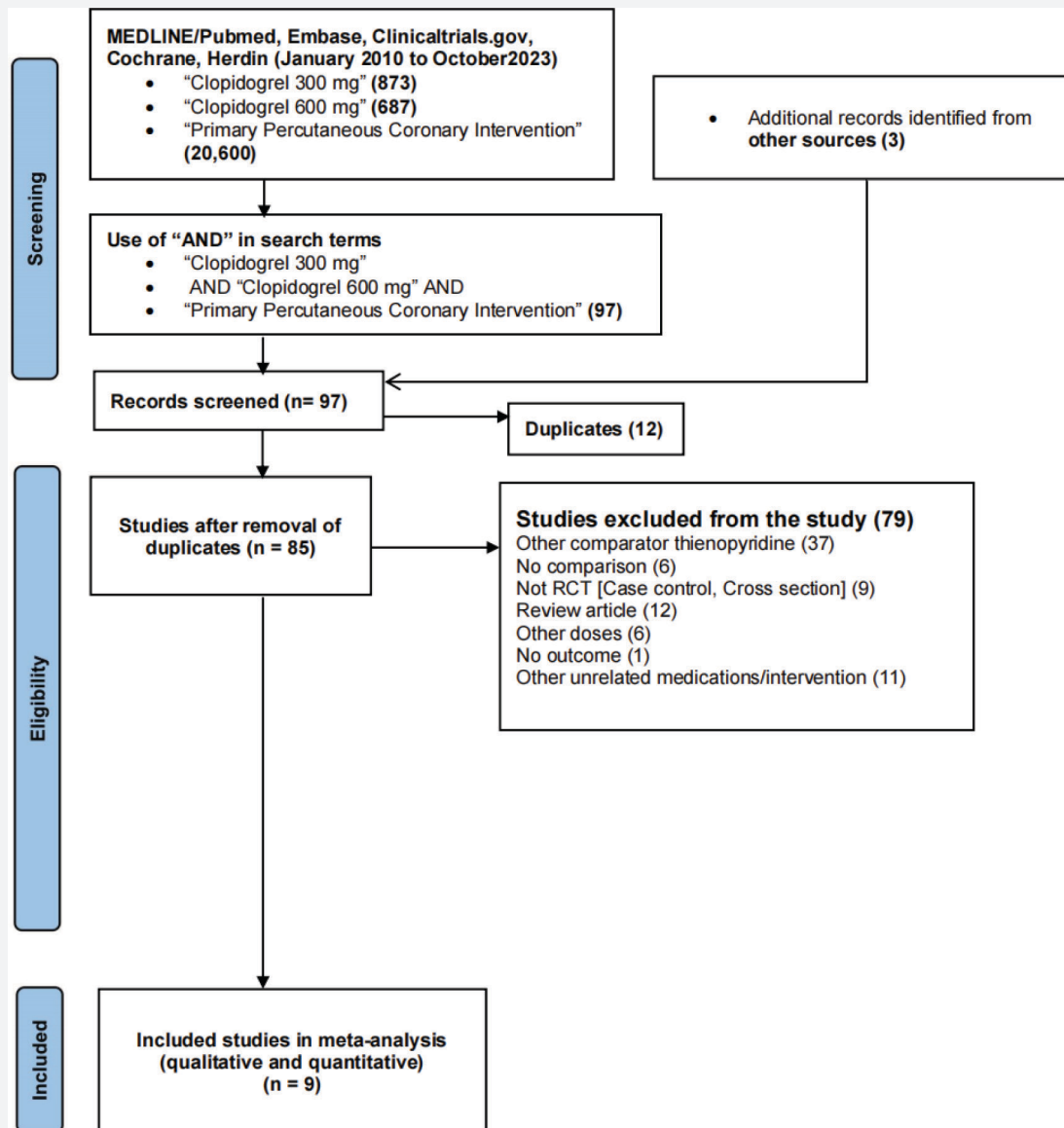
Search Methods:

Figure 1. PRISMA flow diagram showing the included and excluded studies at each stage of the selection process

Overview of the Included Randomized Control Trials

As shown in Table 1, the nine studies included adult patients' diagnosed with ischemic heart disease who were subjected to PPCI. The treatment arm consisted of 600 mg LD of clopidogrel while the control arm consisted of 300 mg LD. A total of 29,827 patients were included, with the largest population of 25,086 patients and smallest population of 69 patients. Average treatment and follow-up periods lasted for 30 days.

Characteristics of Studies

Risk of bias analysis was done on all nine studies (Figure 2a/2b) using the revised Cochrane risk-of-bias tool for randomized trials. The internal validity of included studies was appraised by two unblinded reviewers, with divergences resolved by

consensus, according to the methods of the Cochrane Collaboration. Disagreement was solved by discussing and involving a third author to reach a consensus on the final judgement.

The table on included trials (Figure 2a) presents a summary of the risk of bias assessment for the studies included in the analysis. It evaluates various domains of bias, such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. The risk of bias for each study is indicated using color-coded symbols: green (+) for low risk, yellow (?) for unclear risk and red (–) for high risk.

Table 1. Description of Included Studies

	Bantalla	Cuisset	Dangas	Fernandez	L'allier	Mehta	Montalescot	Patti, 2004	Patti, 2011
Treatment	57	146	2158	200	49	12520	34	126	103
Control	58	146	1153	200	49	12566	35	129	98
Blinding	Single	Single	Single	Single	Single	Double	Single	Double	No mention
Treatment/ Follow up	30 days	30 days	30 days	30 days	30 days	30 days	30 ± 7 days	30 days	30 days
Patient population	Stable CAD	NSTEACS	STEMI	Stable CAD	Stable CAD	ACS	NSTEACS	NSTEACS, Stable Angina	STEMI
Age (300)	59 ± 9.25	64.2 ± 10.3	60.5 (52.9–70.5)	64.3 ± 10.7	61.8	61.4	59.7	65 ± 10	65 ± 14
Age (600)	59 ± 9.05	65.2 ± 12.0	60.1 (52.2–69.3)	64.5 ± 10.9	61.9	61.3	62.8	63 ± 10	62 ± 11
Death	3	1	79	2	0	548	0	0	11
Myocardial Infarct	0	21	60	16	0	514	3	20	6
Stroke	1		22	0	0	129	0	0	1
Revascularization	3	1	72	0	0	0	1	1	8
Major Bleeding	0	0	131	12	0	0	0	0	4
Minor Bleeding	9	0	113	23	15	0	21	2	14

CAD - Coronary Artery Disease; ACS - Acute Coronary Syndrome; NSTEACS - Non-ST Elevation Acute Coronary Syndrome; STEMI - ST Elevation Myocardial Infarction (STEMI)

The risk of bias graph (Figure 2b) provides a visual summary of the proportion of studies judged to have low, unclear, or high risk of bias in each domain. The majority of studies show a low risk of bias for random sequence generation and blinding of outcome assessment. However, allocation concealment and selective reporting have a significant proportion of studies with unclear risk, while blinding of participants and personnel, as well as incomplete outcome data, exhibit some degree of high risk of bias.

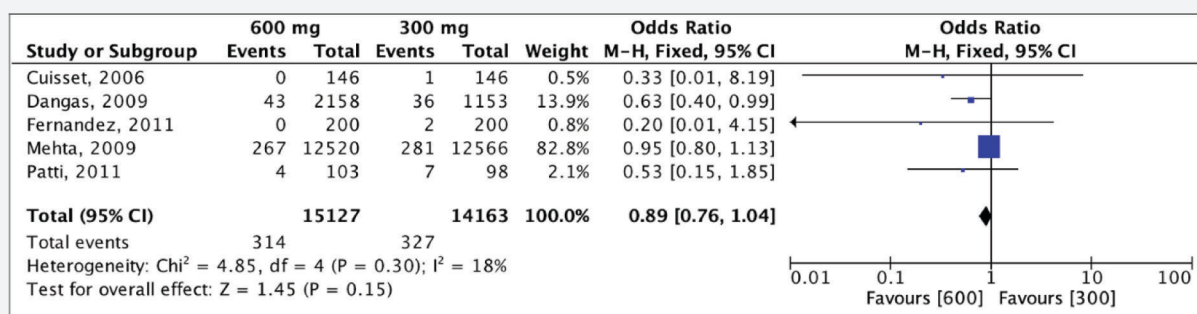
DATA ANALYSIS

Primary outcomes

Cardiac Death

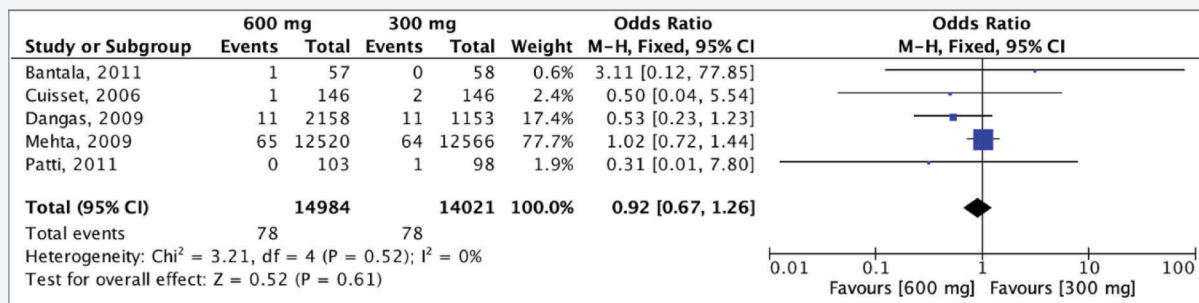
There was no statistically significant difference in terms of cardiac death (odds ratio of 0.89, 95% confidence interval 0.76 - 1.04, $p = 0.15$, $I^2 = 18\%$, 5 trials [29,290 patients], Forest plot 1.1) when comparing the use of 300 mg clopidogrel versus 600 mg clopidogrel. No significant heterogeneity was noted among the studies ($p = 0.30$, $I^2 = 18\%$).

Forest plot of comparison: 1.1 Cardiac Death



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bantala, 2011	+	?	+	?	+	?	?
Cuisset, 2006	+	?	?	+	+	?	?
Dangas, 2009	+	?	+	+	+	?	?
Fernandez, 2011	+	+	+	+	+	?	?
L'allier, 2007	+	?	?	+	+	?	?
Mehta, 2009	+	+	+	-	+	?	?
Montalescot, 2006	+	?	-	+	+	?	?
Patti, 2004	+	?	?	?	+	?	?
Patti, 2011	+	+	?	+	+	?	?

Figure 2a. Risk of bias summary of the included studies

Stroke**Forest plot of comparison: 1.2 Stroke**

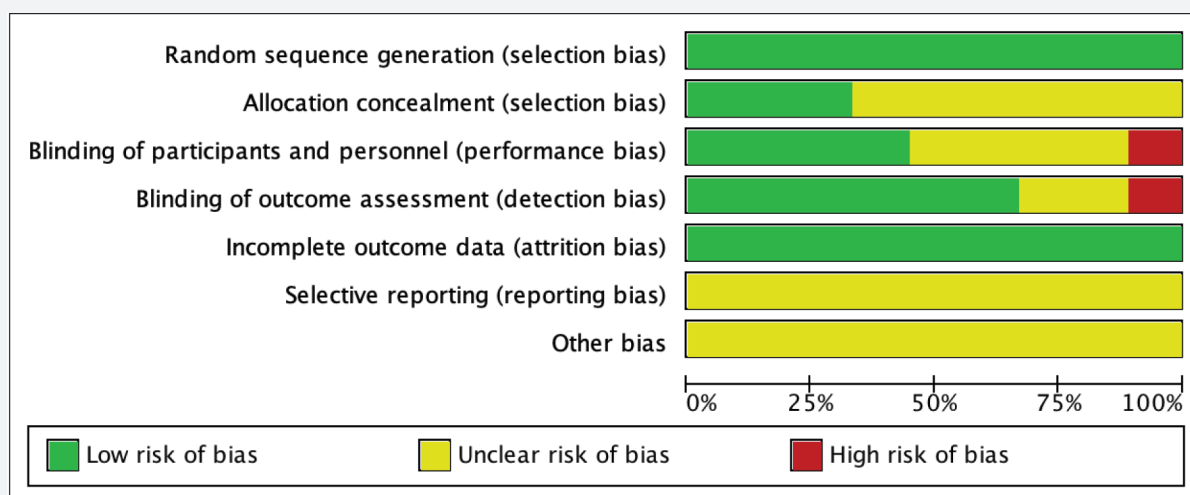


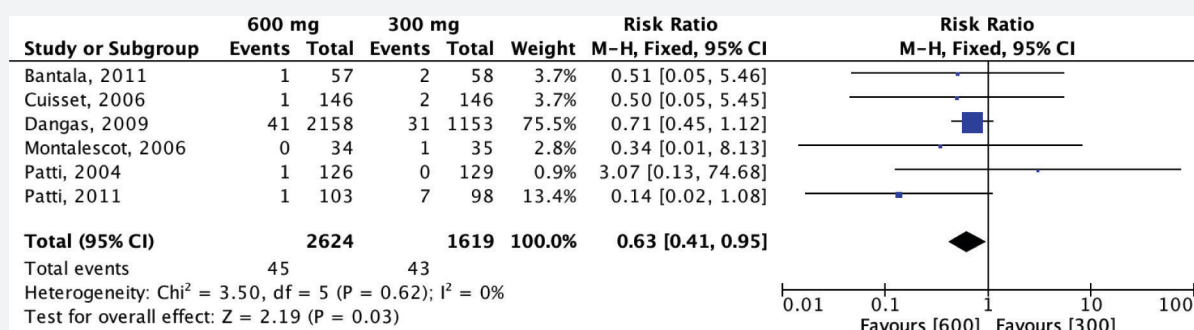
Figure 2b. Risk of bias graph: Review of author's judgments across different studies.

There was no statistically significant difference in terms of stroke (odds ratio of 0.92, 95% confidence interval 0.67 - 1.26, $p = 0.61$, $I^2 = 0\%$, 5 trials [28,905 patients], Forest plot 1.2)

when comparing the use of 300 mg clopidogrel versus 600 mg clopidogrel alone. No significant heterogeneity was noted among the studies ($p = 0.52$, $I^2 = 0\%$).

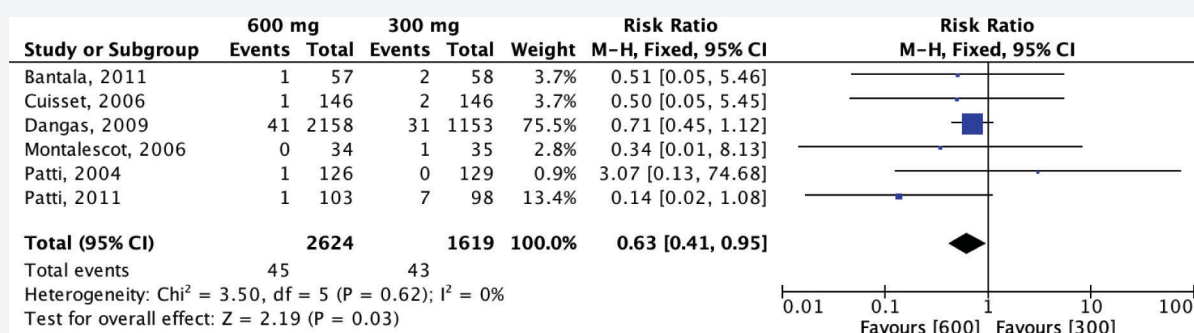
Myocardial Infarction

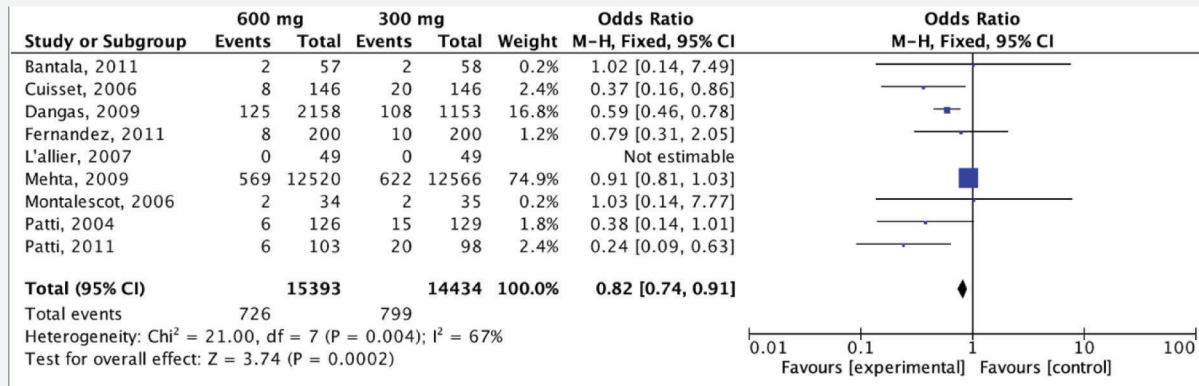
Forest plot of comparison: 1.3 Myocardial Infarction



Revascularization

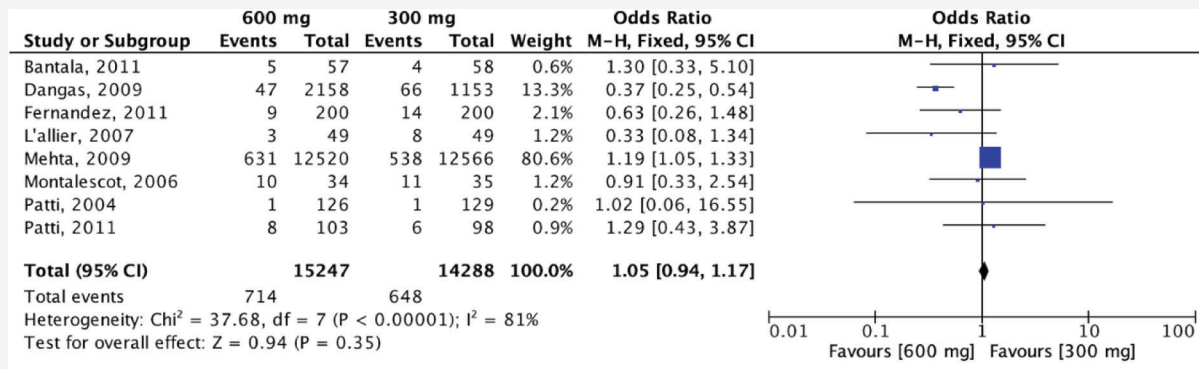
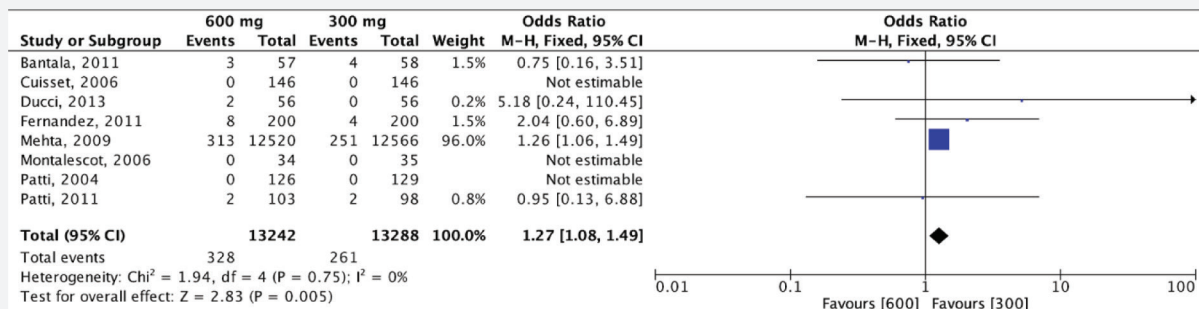
Forest plot of comparison: 1.4 Revascularization



Overall MACE**Forest plot of comparison: 1.5 Overall MACE**

The 600 mg LD significantly reduced the risk of myocardial re-infarction, (odds ratio of 0.78, 95% confidence interval 0.66 - 0.91, $p = 0.002$, $I^2 = 46\%$, 7 trials [29,614 patients], Forest plot 1.3), urgent need for revascularization (odds ratio of 0.63, 95% confidence interval 0.41 - 0.95, $p = 0.03$, $I^2 = 0\%$, 6 trials [4243

patients], Forest plot 1.4) and overall MACE (odds ratio of 0.82, 95% confidence interval 0.74 - 0.91, $p = 0.0002$, $I^2 = 67\%$, 8 trials [29,827 patients], Forest plot 1.5).

Secondary Outcomes:**Major Bleeding****Forest plot of comparison: 2.1 Major Bleeding****Minor Bleeding****Forest plot of comparison: 2.2 Minor Bleeding**

Major bleeding risk was higher in the 600 mg LD (1.9%; 261/13288) compared with 300 mg LD (2.4%; 328/13242) [OR: 1.27; 95% CI 1.08 to 1.49, $p = 0.005$, Forest plot 2.1] without significant difference in minor bleeding (OR: 1.05; 95% CI 0.94 to 1.17, $p = 0.35$, Forest plot 2.2).

DISCUSSION

Ensuring sufficient inhibition of platelets is crucial for the safety and success of PPCIs with the established gold standard of dual administration of aspirin and thienopyridines as antiplatelet therapy in individuals undergoing coronary stenting. In the early years, the gold standard of adjunctive antiplatelet therapy in ACS patients treated with or without interventional strategy was a LD of 300 mg clopidogrel.¹⁶

Achieving rapid, optimal platelet aggregation inhibition, however, is limited due to its complex metabolic pathway which takes around 4 hours to convert the drug to an active metabolite. Pharmacodynamic response to clopidogrel is also reported to be substantially variable because of low inhibition of adenosine diphosphate (ADP)-induced platelet aggregation or activation owing to genetic variations affecting the metabolic pathway.¹⁷ As patients often receive the clopidogrel LD just before PCI, there is a heightened risk of ischemic periprocedural events.¹⁸ Numerous investigations in both scientific research and clinical contexts have suggested that a 300 mg clopidogrel LD may not be sufficient, prompting consideration of more aggressive loading strategies.^{6,9,17-18}

As a result, various novel therapeutic approaches have been suggested to overcome the limitations of standard dosing. A high-dose (600 mg) clopidogrel has been used since, and has demonstrated the ability to achieve more rapid and potent inhibition of platelet aggregation, coupled with reduced incidence of resistance and recurrent events. The ESC 2023 Guidelines for the management of ACS indicates the use of clopidogrel at a LD of 300-600 mg followed by a maintenance dose of 75 mg in patients undergoing primary PCI, however, there are no class or level of recommendation in terms of either dosages.¹⁵ To date, there have been many significant research efforts dedicated to evaluating the functional and clinical implications of high clopidogrel LD regimens through analyzing the efficacy of a loading dose of 600 mg of clopidogrel.

The CURRENT-OASIS-7 trial found no significant difference between a 7-day high (600 mg) LD clopidogrel regimen and standard-dose 300 mg LD in terms of 30 days cardiovascular outcomes. However, the high dose group showed a higher incidence of major bleeding, significantly reduced incidence of stent thrombosis in patients undergoing PCI compared to the standard treatment. Subgroup analyses further indicated that the 7-day, 600 mg LD regimen was more effective than the standard-dose in reducing ischemic events and stent thrombosis in patients undergoing PCI for ACS.¹⁹ Similarly, the ARMYDA-6 MI trial noted reduced infarct size, lower thrombolysis in myocardial infarction (TIMI) flow Grade <3 after intervention, higher left ventricular ejection fraction at discharge,

and a lower 30-day MACE incidence for the 600 mg LD group. Safety profiles, including major bleeding and non-entry-site minor bleeding were similar between the two LD groups, suggesting that a higher equivalent LD of clopidogrel in urgent PCI for ST elevation myocardial infarction (STEMI) may improve outcomes without a significant rise in bleeding complications.²⁰

In contrast, the variability of outcomes across studies raises concerns regarding potential confounders influencing the observed heterogeneity in results. In the HORIZONS-AMI trial, the 600 mg LD was associated with significantly lower 30-day unadjusted rates of mortality, reinfarction and stent thrombosis, with a lower major bleeding rate and slightly lower minor bleeding rate compared to the 300 mg LD. It independently predicted a lower risk of 30-day MACE. However, other observational and registry-based studies, such as the Belgian registry by Mangiacapra, et al. and a Korean retrospective trial showed conflicting results regarding long-term benefits. While the higher-dose group consistently exhibited lower ischemic events, the absolute benefit varied widely depending on patient characteristics, procedural details and follow-up duration. In a Belgian registry study by Mangiacapra in 2010, the 600 mg LD group showed significantly better post-PCI outcomes, including lower rates of myocardial blush Grade 0 or 1 and less no-reflow phenomenon. At one year, the higher-dose group had a relatively lower MACE rate compared to the lower-dose group (17% vs. 27%).²² In a Korean retrospective trial with 171 STEMI patients undergoing primary PCI, the higher-dose group had significantly lower 30-day cumulative incidence of adverse events (1.4% vs. 11.2%), including no urgent target vessel revascularizations with no statistically significant difference in the incidences of major bleeding.²³

Based on these studies, the efficacy profile was reflected through a significant decrease in composite as well as individual outcomes of cardiovascular death, MI, or stroke with clopidogrel with cumulative evidence showing that the 600 mg LD is at least as effective as the 300 mg LD. Nonetheless, significant heterogeneity in study designs, patient populations and endpoint definitions contributes to the variability in reported benefits. This underlines the importance of individualized treatment approaches rather than a one-size-fits-all dosing strategy.

In terms of safety profiles, clopidogrel loading doses (600 mg vs 300 mg) were evaluated across multiple studies. Abuzahra, et al.²⁴ found no significant difference in major or minor bleeding at day 30 between the two groups, with one case of major bleeding reported in each group. Patti, et al. reported no significant increase in bleeding or entry-site complications at day 30, with two major bleeding episodes in both.¹⁰ Dangas, et al. observed no significant increase in bleeding rates with a higher LD, showing a major bleeding rate of 6.1% in the clopidogrel 600 mg LD group and 9.4% in the 300 mg LD group. In a retrospective study by Jung, et al. (2009), the 600 mg LD group did not exhibit a significant increase in major bleeding frequency compared to the 300 mg LD group. However, this study was considered less relevant due to

biases.²⁵ In contrast, the CURRENT-OASIS 7 trial reported a statistically significant increase in major bleeding (1.5%) in the clopidogrel 600 mg LD group compared to the 300 mg LD group (1.1%) in patients after PCI, highlighting that while a higher LD provides ischemic benefit, it may also come at the cost of increased bleeding risk.³

In our meta-analysis of nine RCTs involving 29,827 patients, comparing high LD clopidogrel with standard LD, it was found that the 600 mg LD significantly reduced the overall risk of MACE, nonfatal MI, and target vessel revascularization. However, there was no significant difference in cardiac death and stroke. Notably, substantial heterogeneity was detected in treatment effects across studies, likely due to differences in patient baseline characteristics, procedural approaches and follow-up durations. The 600 mg LD was associated with a higher risk of major bleeding compared to the 300 mg LD, while there was no significant difference in minor bleeding. The presence of significant heterogeneity suggests that a uniform treatment recommendation may not be appropriate, and clinicians should assess individual patient profiles, weighing ischemic and bleeding risks before choosing an optimal LD.

In conclusion, while the 600 mg clopidogrel LD reduces the overall risk of MACE, this benefit is counterbalanced by an increased risk of major bleeding. Therefore, clinicians should carefully weigh these considerations when deciding on the optimal LD for antiplatelet therapy in individuals undergoing PPCI, emphasizing the need for personalized and risk-stratified approaches in clinical practice. Future studies should focus on identifying patient subgroups that derive the greatest benefit from higher loading doses while minimizing bleeding complications.

REFERENCES

1. Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *JAMA* [Internet]. 2005;294(10):1224–32. Available from: <http://dx.doi.org/10.1001/jama.294.10.1224>
2. Ferguson JJ. Clopidogrel plus aspirin in patients with acute myocardial infarction treated with fibrinolytic therapy--CLARITY-TIMI 28. *Future Cardiol* [Internet]. 2005;1(5):605–10. Available from: <http://dx.doi.org/10.2217/14796678.1.5.605>
3. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* [Internet]. 2001;358(9281):527–33. Available from: [http://dx.doi.org/10.1016/S0140-6736\(01\)05701-4](http://dx.doi.org/10.1016/S0140-6736(01)05701-4)
4. Klès P. Results of the CREDO study: AHA Chicago, 18 November 2002. *Neth Heart J*. 2003;11(2):104–5.
5. Gulizia MM, Colivicchi F, Abrignani MG, Ambrosetti M, Aspromonte N, Barile G, et al. Consensus document ANMCO/ANCE/ARCA/GICR-IACPR/GISE/SICOA: Long-term antiplatelet therapy in patients with coronary artery disease. *Eur Heart J Suppl* [Internet]. 2018;20(Suppl F):F1–74. Available from: <http://dx.doi.org/10.1093/eurheartj/suy019>
6. Müller I, Seyfarth M, Rüdiger S, Wolf B, Pogatsa-Murray G, Schömig A, et al. Effect of a high loading dose of clopidogrel on platelet function in patients undergoing coronary stent placement. *Heart* [Internet]. 2001;85(1):92–3. Available from: <http://dx.doi.org/10.1136/heart.85.1.92>
7. von Beckerath N, Taubert D, Pogatsa-Murray G, Schömig E, Kastrati A, Schömig A. Absorption, metabolism, and antiplatelet effects of 300-, 600-, and 900-mg loading doses of clopidogrel: results of the ISAR-CHOICE (Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect) Trial: Results of the ISAR-CHOICE (intracoronary stenting and antithrombotic regimen: Choose between 3 high oral doses for immediate clopidogrel effect) trial. *Circulation* [Internet]. 2005;112(19):2946–50. Available from: <http://dx.doi.org/10.1161/CIRCULATIONAHA.105.559088>
8. Montalescot G, Sideris G, Meuleman C, Bal-Dit-Sollier C, Lellouche N, Steg PG, et al. ALBION Trial Investigators. ALBION Trial Investigators *J Am Coll Cardiol*. 2006;48:931–8.
9. Angiolillo DJ, Fernández-Ortiz A, Bernardo E, Ramírez C, Sabaté M, Bañuelos C, et al. High clopidogrel loading dose during coronary stenting: effects on drug response and interindividual variability. *Eur Heart J* [Internet]. 2004;25(21):1903–10. Available from: <http://dx.doi.org/10.1016/j.ehj.2004.07.036>
10. Patti G, Colonna G, Pasceri V, Pepe LL, Montinaro A, Di Sciascio G. Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention: results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study: Results from the ARMYDA-2 (antiplatelet therapy for reduction of MYocardial damage during angioplasty) study. *Circulation* [Internet]. 2005;111(16):2099–106. Available from: <http://dx.doi.org/10.1161/01.CIR.0000161383.06692.D4>
11. Gurbel PA, Bliden KP, Zaman KA, Yoho JA, Hayes KM, Tantry US. Clopidogrel loading with eptifibatide to arrest the reactivity of platelets: results of the Clopidogrel Loading With Eptifibatide to Arrest the Reactivity of Platelets (CLEAR PLATELETS) study: Results of the Clopidogrel Loading With Eptifibatide to Arrest the reactivity of Platelets (CLEAR PLATELETS) study. *Circulation* [Internet]. 2005;111(9):1153–9. Available from: <http://dx.doi.org/10.1161/01.CIR.0000157138.02645.11>
12. Wolfram RM, Torguson RL, Hassani S-E, Xue Z, Gevorkian N, Pichard AD, et al. Clopidogrel loading dose (300 versus 600 mg) strategies for patients with stable angina pectoris subjected to percutaneous coronary intervention. *Am J*

- Cardiol* [Internet]. 2006;97(7):984–9. Available from: <http://dx.doi.org/10.1016/j.amjcard.2005.10.064>
13. Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, et al. 2021 AHA/ACC/AASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: A report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation* [Internet]. 2021;144(22):e368–454. Available from: <http://dx.doi.org/10.1161/CIR.0000000000001029>
14. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* [Internet]. 2019;40(2):87–165. Available from: <http://dx.doi.org/10.1093/eurheartj/ehy394>
15. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J* [Internet]. 2023;44(38):3720–826. Available from: <http://dx.doi.org/10.1093/eurheartj/ehad191>
16. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* [Internet]. 2001;345(7):494–502. Available from: <http://dx.doi.org/10.1056/NEJMoa010746>
17. Brandt JT, Close SL, Iturria SJ, Payne CD, Farid NA, Ernest CS 2nd, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. *J Thromb Haemost* [Internet]. 2007;5(12):2429–36. Available from: <http://dx.doi.org/10.1111/j.1538-7836.2007.02775.x>
18. Pocock SJ, Mehran R, Clayton TC, Nikolsky E, Parise H, Fahy M, et al. Prognostic modeling of individual patient risk and mortality impact of ischemic and hemorrhagic complications: assessment from the Acute Catheterization and Urgent Intervention Triage Strategy trial: Assessment from the Acute Catheterization and Urgent Intervention Triage Strategy trial. *Circulation* [Internet]. 2010;121(1):43–51. Available from: <http://dx.doi.org/10.1161/CIRCULATIONAHA.109.878017>
19. CURRENT-OASIS 7 Investigators, Mehta SR, Bassand J-P, Chrolavicius S, Diaz R, Eikelboom JW, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med* [Internet]. 2010;363(10):930–42. Available from: <http://dx.doi.org/10.1056/NEJMoa0909475>
20. Patti G, Bárczi G, Orlic D, Mangiacapra F, Colonna G, Pasceri V. 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 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty Myocardial Infarction) Randomized Study. *Journal of the American College of Cardiology*. 2011;58(15):1592–9.
21. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, et al. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. *Lancet* [Internet]. 2011;377(9784):2193–204. Available from: [http://dx.doi.org/10.1016/s0140-6736\(11\)60764-2](http://dx.doi.org/10.1016/s0140-6736(11)60764-2)
22. Mangiacapra F, Wijns W, De Luca G, Muller O, Trana C, Ntalianis A, et al. Thrombus aspiration in primary percutaneous coronary intervention in high-risk patients with ST-elevation myocardial infarction: a real-world registry. *Catheter Cardiovasc Interv* [Internet]. 2010;76(1):70–76. Available from: <http://dx.doi.org/10.1002/ccd.22465>
23. Jung J-H, Min P-K, Lee S-H, Sung CW, Choi S, Cho JR, et al. Clopidogrel pretreatment before primary percutaneous coronary stenting in patients with acute ST-segment elevation myocardial infarction: comparison of high loading dose (600 mg) versus low loading dose (300 mg). *Coron Artery Dis* [Internet]. 2009;20(2):150–4. Available from: <http://dx.doi.org/10.1097/mca.0b013e3283262de2>
24. Abuzahra M, Pillai M, Caldera A, Hartley WB, Gonzalez R, Bobek J, et al. Comparison of higher clopidogrel loading and maintenance dose to standard dose on platelet function and outcomes after percutaneous coronary intervention using drug-eluting stents. *Am J Cardiol* [Internet]. 2008;102(4):401–3. Available from: <http://dx.doi.org/10.1016/j.amjcard.2008.03.073>
25. Dangas G, Mehran R, Guagliumi G, Caixeta A, Witzenbichler B, Aoki J, et al. Role of clopidogrel loading dose in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty: results from the HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trial. *J Am Coll Cardiol* [Internet]. 2009;54(15):1438–46. Available from: <http://dx.doi.org/10.1016/j.jacc.2009.06.021>