Randomized Controlled Double Blind Trial of High Loading Dose of Clopidogrel 600mg Versus the Conventional 300mg in Patients Undergoing Elective Percutaneous Coronary Intervention at the Philippine Heart Center

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Background **---** Aggressive anti-platelet therapy is needed in patients who underwent coronary angioplasty, hence the combination of Aspirin and Clopidogrel. A lot of studies were done internationally comparing conventional loading dose versus the higher loading dose, but we would like to test if their hypothesis would also apply to Filipinos, in terms of decreased major adverse cardiovascular events and bleeding rates. This study was done to compare 30 days outcome of patients receiving 600mg versus 300mg Clopidogrel loading dose prior to PCI. The primary endpoints that were determined in each study patient were the occurrence of death, post-procedural myocardial infarction, stroke and target vessel revascularization.

Methods **---** This is a randomized double blind trial involving patients for percutaneous coronary intervention (PCI). Subjects were randomized in a double blind fashion to receive either Clopidogrel 600 mg loading dose or Clopidogrel 300 mg loading dose given 4 to 6 hours prior to procedure. Complete blood count, Prothrombin time , partial prothrombin time, creatine kinase MB and troponin-I were measured at baseline; and CKMB and Troponin - I were repeated at 8 or 24 hours after intervention. The primary endpoints were the 30-day occurrence of death, myocardial infarction (MI), stroke or target vessel revascularization (PCI or CABG).

Results **---** A total of 115 patients scheduled to undergo percutaneous coronary intervention were randomized to a 600mg (n=58) or 300mg (n=57) group. The primary end point occurred in 51% of patients in the high loading dose versus 85 % of those in the conventional loading dose group (OR 0.19, 95% CI 0.08 to 0.46, P=0.000) and was due entirely to decreased rates of periprocedural MI in the higher loading arm. Troponin-I was significantly higher in the 300mg arm (4.3%) compared to the 600mg arm (2.5%) with a P value 0.007.

Conclusions **---** Pre-treatment with a 600mg loading dose of Clopidogrel 4 to 6 hours before the procedure is safe compared with the conventional 300mg dose, it significantly reduced the primary composite endpoint in the higher loading arm. It has greater significance in terms of lower periprocedural MI in patients undergoing percutaneous coronary intervention given 600mg loading dose of Clopidogrel. This study may support its routine use in elective coronary angioplasty, and have influence in future studies**. *Phil Heart Center J 2013;17(1):6-16.***

Key Words: Clopidogrel ■ Percutaneous Coronary Intervention ■ Electrocardiogram ■ Loading Dose

The pathophysiology of arterial thrombosis starts with platelet activation.[1] After plaque disruption, erosion or rupture, three important steps in the formation of platelet-rich thrombus. The first step is platelet adhesion mediated by proteins like von Willebrand factor that interacts with adhesive receptors that allows platelets to adhere to injured site. The second step is a platelet activation that involves a three-dimensional shape change of the platelet from a smooth discoid contour to spiculated form, which increases the surface area. Afterwards, there will be degranulation or secretion of alpha and dense granules within the platelet, thereby releasing pro-thrombotic, inflammatory and chemo-attractant mediators, which propagate, amplify, and sustain atherothrombotic process.[1]

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In clinical practice, anti-platelet therapy is one of the cornerstones of ACS therapy. Non-enteric coated should be chewed by patients who have not taken aspirin prior to presentation. Aspirin inhibits the cyclooxygenase pathway. If a patient is allergic to aspirin, patient may be given Clopidogrel, which inhibits ADP receptor; thereby, preventing platelet aggregation. The use of Clopidogrel loading doses higher than the standard 300 mg dose is becoming more common in percutaneous coronary intervention (PCI) in spite a scarcity of clinical evidence to support such a strategy.[2]

The clinical value of Clopidogrel therapy was established in a number of studies beginning with the CAPRIE trial of chronic Clopidogrel treatment in patients established with vascular disease. The CURE trial extended the benefits of Clopidogrel 75mg/day with 300mg loading dose in non-ST segment elevation acute coronary syndrome. COMMIT found that the addition of clopidogrel (75mg/daily) in ST elevation myocardial infarction was associated with a highly significant reduction in major adverse cardiovascular events (MACE).[3-5]

The United Laboratories studied the genetic variations in a human body called single nucleotide polymorphisms (SNP) that could determine the body's response to a certain drug. They have found out that 11.6% Filipinos are slow acetylators, meaning that drugs like anti-tuberculosis drugs could stay longer in the body, increasing the toxic effects of this drug.[6]

Pharmacological treatment prior to percutaneous intervention can reduce periprocedural myocardial infarction by improving the clinical outcomes as demonstrated by the ARMYDA trial (Atorvastatin for Reduction of MYocardial Damage during Angioplasty).[7] A study was done evaluating whether aggressive anti-platelet therapy, and at what dose would constitute the appropriate loading dose of anti-platelet prior to elective PCI entitled the ARMYDA-2 (Antiplatelet therapy for Reduction of Myocardial Damage during Angioplasty). The study proponents designed a randomized protocol to test the hypothesis of whether a high loading dose of Clopidogrel would influence outcome. This study was conceptualized because there was no available study comparing different loading dose of Clopidogrel in patients undergoing elective PCI

The ARMYDA-2 trial have demonstrated that by giving higher loading dose of Clopidogrel, there is better clinical benefit outcomes.[8] The benefits of high loading dose could be possibly due to decreasing periprocedural ischemia and distal embolization, protecting the microvascular bed, and counterbalancing the postprocedural "procoagulant status."[8] The study showed that whether you give the conventional loading dose of Clopidgrel 300mg versus the 600mg, there is no statistical difference in terms of bleeding; and a favorable outcome for the group given the higher loading dose in terms of reduction of MACE.

The current American College of Cardiology/American Heart Association guidelines for the treatment of unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI) recommend "initiation of Clopidogrel treatment in patients for whom percutaneous coronary intervention (PCI) is planned and who are not at high risk for bleeding."[2,9] Although doses from 300 mg to 600 mg loading dose of Clopidogrel has been recommended by the guidelines to achieve rapid onset of action, the bases for this recommendation are based from clinical trials that have evaluated the standard loading dose of 300 mg, followed by 75 mg daily dose.[10] Recent studies have shown that in subjects undergoing elective PCI who received 600 mg Clopidogrel loading dose, there has been reduced resistance, faster onset of action and greater platelet inhibition.[11,12]

The study done by Cuisset and colleagues demonstrated higher efficacy of 600 mg loading dose over 300 mg dose in terms of platelet reactivity and incidence of MACE in NSTEMI patients undergoing stenting procedure without a significant increase in bleeding complications.[13] Moreover, their study also showed biological and a clinical benefit of a higher loading dose of Clopidogrel.[13]

Some patients may experience ischemic symptoms after PCI because there are activated platelets seen in the vicinity of the stented coronary segment that could lead to occlusion of the stented vessel. Accordingly,

platelet inhibition with either a thienopyridine (ticlopidine or clopidogrel)[14,15] or glycoprotein IIb/IIIa receptor antagonists[13,14] has significantly reduced periprocedural myocardial injury and cardiac events, primarily in higher-risk patients. Clopidogrel is much better when compared to ticlopidine because it is associated with higher platelet inhibition, and it has a better safety profile.[14,15] The conventional loading dose of Clopidogrel based on early trials is 300mg in percutaneous intervention.[16,17] There have been reports that dose of 600mg is much better because of earlier and stronger inhibition of adenosine diphosphate (ADP)-induced platelet activation.[18]

The principal finding in the PREPAIR study, which was done in subjects undergoing elective angiography and PCI, is that inhibition of platelet aggregation was consistently better in the Clopidogrel 600 mg double bolus group.[19]

In the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS), an initial Clopidogrel loading dose of 300mg was considered more effective and equally safe as a non-loading scheme. Thus, 300mg loading dose of Clopidogrel became the standard initial treatment for patients who are to undergo PCI.[20] The dose of 300 mg of clopidogrel derives from dose finding data on healthy volunteers;[21] however, patients with coronary artery disease may have enhanced platelet reactivity as compared with healthy individuals, and so probably require more aggressive platelet inhibition.[22] A number of studies have suggested that Clopidogrel 300mg loading dose might not be enough, and that a higher loading dose may be required for it to be effective. Indeed a high loading dose (>300mg) might be beneficial on the premise that: (1) the slow onset of Clopidogrel, a higher dose would quicken its increase in concentration and effect on platelets; (2) a higher degree of platelet inhibition, as produced by larger loading, might further protect from periprocedural thrombotic events, thus yielding clinical benefits as well obviating the need for intravenous glycoprotein IIb/IIIa inhibitors in low risk patients; (3) higher loading doses might reduce the rate of non-responders, known to be at greater risk for periprocedural events. [23]

This study will try to evaluate improvement in the mortality and morbidity of pretreatment with a 600mg versus a 300mg loading dose of Clopidogrel for pre-PCI patients, for the primary endpoints post-procedural MI, stroke, target vessel revascularization, and death; and secondary endpoints: (1) any post-procedural increase of cardiac markers (Troponin-I and CKMB); (2) mean peak values of CKMB and troponin-I after intervention; and (3) occurrence of any of the hemorrhagic complications . There are a lot of studies done internationally comparing conventional loading dose (300mg) Clopidogrel versus the higher loading dose (600mg) Clopidogrel, and it showed favorable outcomes for the higher loading dose, and there was no significant difference regarding bleeding. This study would like to see the effect of higher loading dose of Clopidogrel on the incidence of MACE and bleeding complications among Filipinos undergoing percutaneous coronary intervention (PCI).

METHODOLOGY

This is a prospective randomized controlled double blind trial that was conducted at the Philippine Heart Center from January 2009 to September 2010 involving adults undergoing elective PCI. Excluded were those with contraindications to antithrombotic or antiplatelets therapy (including platelet count < 70 x 10^9/L); those who underwent coronary artery bypass grafting in the previous 3 months; those who had acute or recent myocardial infarction (within 14 days); those who had stroke within 3 months; those with overt malignancy; those with active bleeding or bleeding diathesis; those on oral anticoagulants with a warfarin derivative with international normalized ratio >1.5; those who received GpIIb/IIIa inhibitor within 30 days; those with thrombocytopenia (platelet count <100,000/mm^3); those with serum creatinine >1.8 mg/dl; those with severe liver disease resulting in abnormal bilirubin levels; those with known allergy to thienopyridines; and those subjects receiving investigational drug within 1 month. This study was approved by the Institutional Review Board, and informed consent was obtained from each subject prior to participation.

The flow of the study is illustrated in Figure 1. Eligible patients who had undergone coronary angiogram with significant coronary artery disease that were deemed responsible for myocardial ischemia and suitable for treatment with percutaneous intervention were enrolled and represent the study population. They were randomized to receive 300 mg Clopidogrel loading dose or 600 mg Clopidogrel loading dose. The person assigned to give the Clopidogrel sachet was not aware of the dose inside the sachet. The code of each sachet is known by one person only. Physicians performing the procedure and the follow-up assessor were not aware of the randomization assignment.

All patients without contraindications were pretreated before intervention with aspirin and they will receive aspirin indefinitely and continue Clopidogrel (75 mg/d) for up to 1 month and thereafter upon the discretion of the attending physician. It is within the discretion of the attending physician whether to use weight adjusted heparin or GpIIb/IIIa in each patient prior to angioplasty.

In all patients, blood samples were drawn before the procedure and 8-24 hours after the procedure to detect CK-MB (mass) and troponin I (mass).This is done to know if the patient had myocardial injury after the procedure. The samples were drawn into tubes without an anticoagulant, centrifuged for 10 minutes and was measured immediately. Serum cTn-I values were measured with an enzyme immunometric assay (VIDAS machine), while the CKMB values were measured using the VITROS machine. The upper limits of normal (ULN) value for cTn-I and CK-MB are 0-0.16 ng/ml, and 0-16 respectively. Biochemical analysis was performed by biochemists unaware of patients' therapies.

One-month clinical follow-up were obtained by office visit, follow up through telephone calls, text messaging thru cellphones, letters sent to all study patients and through patient's chart or their cardiologists. Patients were followed up 24 hours and 30 days after the procedure for the occurrence of any of the following: post-procedural MI, stroke, target vessel revascularization, death; any post-procedural increase of cardiac markers (Troponin-I and CKMB); mean peak values of CKMB and troponin-I after intervention; and occurrence of any of hemorrhagic complications.

Statistical analysis. The sample size needed was 112 patients at alpha=0.05, βeta =0.20 and at an assumed difference in mortality of 20 %. This assumption is based on the study done by Giuseppi Patti, et al, Randomized Trial of High Loading Dose of Clopidogrel for Reduction of Periprocedural Myocardial Infarction In Patients Undergoing Coronary Intervention (ARMYDA -2 Trial).[8]

The subjects were analyzed according to the group they were randomized. Continuous variables between groups were compared by T test for normally distributed values; otherwise the Mann-Whitney U test was used. Proportion was compared by x2 test or Fisher exact test when appropriate. Analysis was applied to the data with consideration of confounders if there were any.

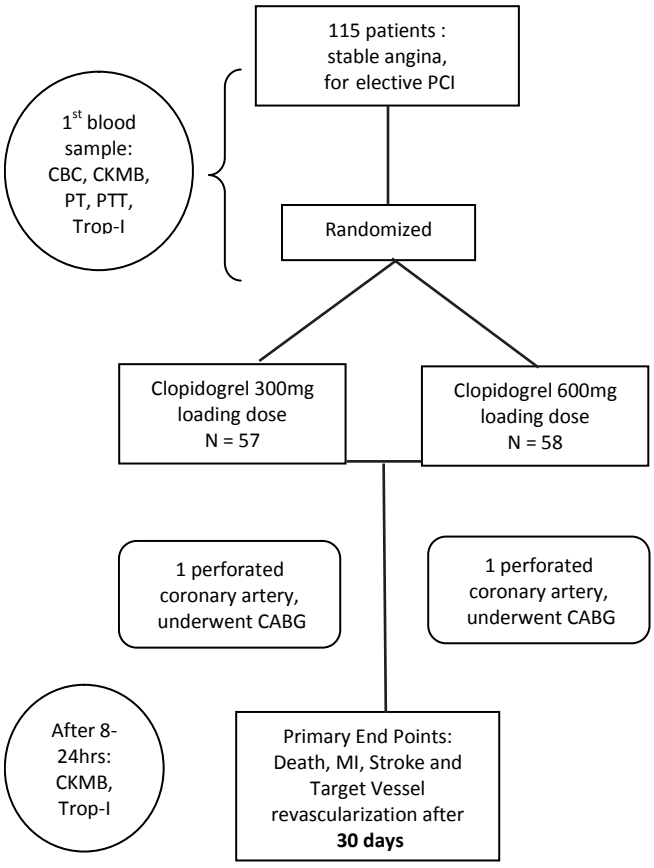


Figure 1. Flow of the study

RESULTS

From January 2009-September 2010, a total of 115 patients who fulfilled the enrollment criteria were randomized to a 600-mg (n-57) or 300-mg (n-58) arms before coronary angioplasty.

Table 1 shows the baseline characteristics. There is no statistical significant difference in terms of age (median age of 59y/o), sex, medications including history of intake of aspirin and Clopidogrel, presence of co-morbidities (hypertension, diabetes, dyslipidemia), previous history of myocardial infarction (MI) and revascularization (PCI or CABG), baseline white blood cell count, and segmenters, Prothrombin time and partial thromboplastin time.There were no confounders noted during statistical analysis. The baseline characteristics were found to be homogenous.

Table 2 shows the procedural features of both arms. There is no statistical significant difference in terms coronary artery involvement, number of vessels, type of intervention, number of stents, pre-dilations nor post-dilations, use of drug-eluting stent (DES), size of the stents used, duration of stent deployment or total ischemia of the procedures on both arms. Procedural success was attained in both groups except for one patient in the 300mg group, who upon doing the Fractional Flow Reserve diagnostic, was found to have insignificant lesion, and was sent home on medical therapy. Two patients (1 in each treatment arm), had coronary perforation during angioplasty and were immediately referred to a thoraco-vascular surgeon and underwent emergency coronary artery bypass successfully. The patient in the 300mg treatment had normal baseline and post-attempt angioplasty cardiac enzymes, while the patient in the 600mg had normal baseline cardiac enzymes but elevated enzymes post-attempt survey of the cardiac enzymes. The most common type of lesion found in both groups is the type B lesion, but this is not statistically significant. There were no confounders noted during statistical analysis.

Table 1. Baseline Characteristics of Patients Undergoing PCI Entrolled in the Study According to Loading Dose of Clopidogrel (PHC, 2011)

Characteristics	300mg Clopidogrel (n = 58)	600mg Clopidogrel (n = 57)	P-value
Age (mean, SD)	59 ±9.25	59 ±9.05	0.997
Gender			
Male	47(81)	46(81)	1.000
Female	11(19)	11(19)	1.000
Hypertension	54(93)	50(88)	0.361
Diabetes Mellitus	20(34)	21(37)	0.847
Dyslipidemia	43(74)	40(70)	0.681
Smoker (Current or past)	21(36)	29(51)	0.134
Medications:			
Statins	47(81)	50(88)	0.442
Beta Blockers	27(47)	31(54)	0.458
ACE Inhibitors*	12(21)	20(35)	0.099
ARB+	28(48)	18(32)	0.087
Duiretics	11(19)	5(9)	0.177
Calcium Blockers	21(36)	26(46)	0.346
ASA‡	39(67)	39(68)	1.000
Clopidogrel	38(66)	39(68)	0.843
Anti DM drugs§	16(28)	18(32)	0.686
Nitrates	25(43)	19(33)	0.339
Previous MI	17(29)	23(40)	0.244
Previous PCI	7(12)	3(5)	0.322
Previous Bypass Surgery	3(5)	2(4)	1.000
WBC¶	8.1(14)	8.1(14)	0.930
Segmenters	56.5(97)	55.1(97)	0.586
Prothrombin Time	94.5(2)	95.8(2)	0.605
Plasma Thromboplastin Time	37.1(64)	36.7(64)	0.789

Legend: * - Angiotensin converting enzyme inhibitor; + - Angiotensin receptor blockers; ‡ - Aspirin; § - anti Diabetes Mellitus; -¶ - white blood cell

Table 2. Procedural Features of Patients Undergoing PCI Enrolled in the Study According to Loading Dose of Clopidogrel (PHC, 2011)

Characteristics	300mg Clopidogrel (n = 58)	600mg Clopidogrel (n = 57)	P-value
Vessel Treated			
LAD*	47	48	0.806
LCX†	29	22	0.256
RCA‡	31	27	0.578
Number of Vessel involved			
1§	24	26	0.897
2‡	19	17	0.897
3¶	15	14	0.715
Restenotic lesions	4	4	1.000
Lesion type			
A#	9	7	0.817
B**	41	36	0.509
C††	3	2	1.000
A and B ‡‡	3	10	0.072
C and D§§	2	2	1.000
CTO (>3mos) ‖‖	1	2	0.616
Multivessel intervention	29	31	0.710
Type of intervention			
Balloon	57.4	58.6	0.833
Stent	56.5	59.5	0.612
Stent + rotablator	1	0	0.504
Bifurcations w/ kissing balloon	2	1	0.322
No stents / px	58	57	0.899
Stent dm (mm)	3.0	3.0	0.839
Total stent length	25.4	25.1	0.860
DES ¶¶	52	54	0.490
Direct Stenting	14	21	0.223
No of predilations	47	39	0.137
Stent deployment (pressure)	15.0	15.4	0.635
Duration of stent deployment	20.6	22.8	0.543
Total ischemia, s	42.4	42.4	0.995
Postdilation	14.5	14.9	0.867
Glycoprotein IIb/3a	58	57	NS
Abrupt vessel closure	58	57	NS

Legend: *- left anterior descending artery; †- left circumflex artery; ‡- right coronary artery; §- one coronary artery involved in the procedure; II- two coronary artery involved in the procedure; ¶- three two coronary artery involved in the procedure; #-Discrete (<10 mm), Concentric; readily accessible, <45degrees, smooth contour, little or no calcium, < than totally occlusive, no ostial location, no major side branch, absence of thrombus ; **-10-20 mm, eccentric; readily, >45-<90-degrees, irregular contour, mod-heavy calcification, < 3mos old total occlusion, bifurcation lesion requiring double guidewire; some thrombus present ; ††- 20 mm, >90-degrees, excessive tortuosity proximal segment, > 3mos old total occlusion, inability to protect major side branches, degenerated vein grafts w/ friable lesions; ‡‡- combination of A and B lesions; §§- combination of C and D lesions; II II-chronic total occlusion of the involved artery > 3months; ¶ ¶- drug eluting stent.

The primary composite endpoints that were analyzed in the study were death, post-procedural MI (troponin–I and CKMB), stroke and target vessel revascularization (PCI or CABG) after 30 days. There were occurrences of death (3%), target vessel revascularization (3%), and stroke (2%) in the conventional loading dose group; and only 2% for each said events in the higher loading dose arm. There were 74% who had increase in Troponin in the 300mg arm, and 49% in the 600mg arm, with a significantly statistical difference p-value of 0.007. With regards to CKMB, there was a greater elevation in the conventional loading arm, compared to the higher loading arm. The two patients in the 300mg arm who died were because of sepsis secondary to community acquired pneumonia and the second patient died due to cardiac dysryhthmia. The cause of death in the 600mg arm is because of intracranial hemorrhage. There was technical difficulty in inserting the wire because of tortuous abdominal artery aneurysm. There was an attempt on the second day but again the technical difficulty and the procedure was aborted. On that same day, patient was transferred to Neuro ICU because of intracranial bleeding and eventually succumbed. One patient in the 300mg Clopidogrel complained of numbness on the left side of the body with no motor deficit after 21 days of the procedure. The composite endpoint of the study showed favorable outcome for the 600mg arm, which has a 51% event rate compared to the 300mg arm, which had 85% event rate (p-value of 0.000).

Figure 3 is a Forest Plot that depicts all the primary endpoints and composite endpoint. Any box that is on the left side of the line favors the experimental drug (600mg Clopidogrel), and any box on the right favors the conventional loading dose (300mg Clopidogrel). Any box lines that transect the center line will have non-statistically significant value. The computation of all primary endpoints and the composite endpoint of all the events, which showed that the study favors the 600mg Clopidogrel loading dose compared to the 300mg Clopidogrel loading dose.

The box corresponding to the composite endpoint is noted to be on the left, with a relative risk of 19%, which means that there is 81% risk reduction of all primary endpoints given the high

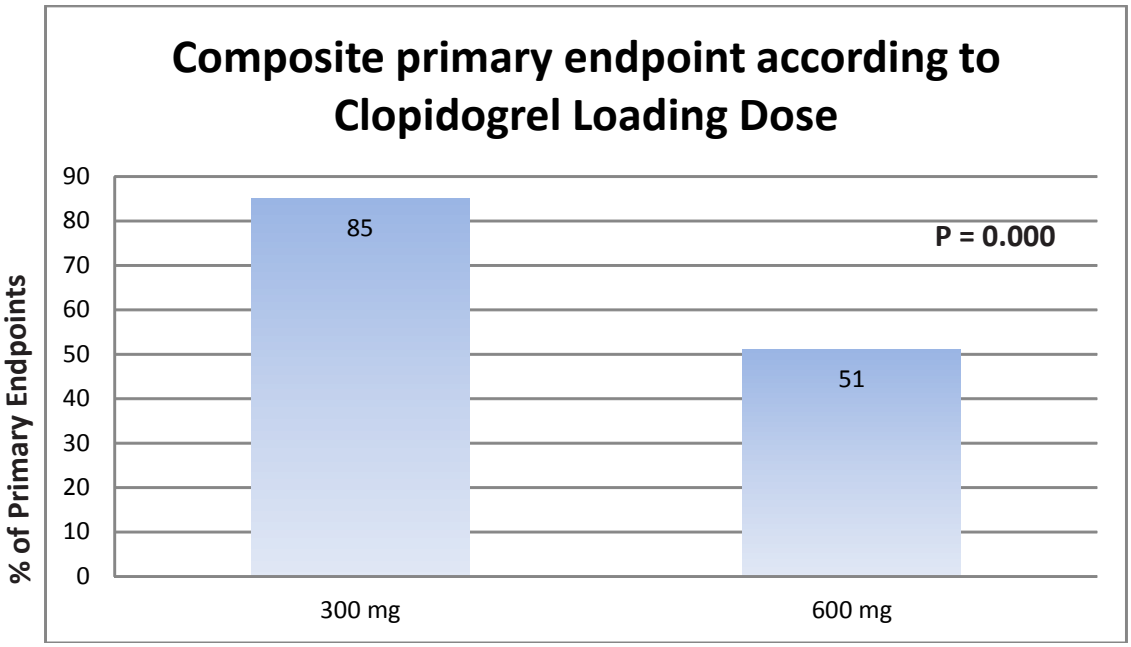
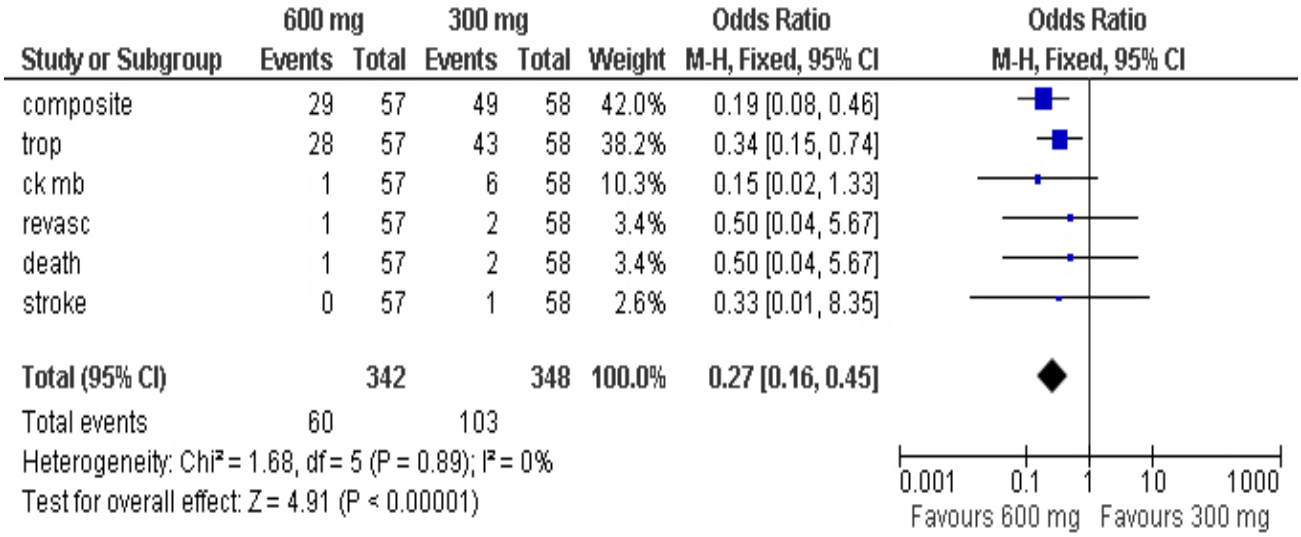


Figure 2. Composite study end points (30-day occurrence of death, myocardial infarction, stroke and target vessel revascularization) in patients receiving the 300-mg versus the 600-mg loading regimen of Clopidogrel. Numbers are expressed in percentages.



Legend: Ckmb (creatinine kinase-MB > 3x the ULN); revas (target vessel revascularization pertaining to repeat PCI or CABG within 30 days of follow up); trop (elevated Troponin-I, more than 0.16ng/ml); death(death of any cause); stroke (Cerebrovascular accident Infarct or Hemorrhage); composite (all the added events above)

Figure 3. Forrest Plot of all primary endpoints, including the primary composite endpoint.

loading dose with a 95% confidence interval of (0.08-0.46). The troponin-I, which is sensitive for acute coronary syndrome, is statistically significant in the Forest plot and the box corresponding to the event is found on the left side of the plot, which shows 66% risk reduction of primary endpoints, with a 95% confidence interval (0.15-0.74). Although the other primary endpoints are not statistically significant, there is a trend favoring the 600mg loading dose of Clopidogrel The summary plot, which is represented by the diamond figure, summarizes all the endpoints including the composite endpoint is favoring the high loading dose.

The number of subjects with elevated troponin I was significantly higher in the conventional loading arm than the 600mg loading arm (p-value of 0.007). Likewise, the number of subjects with elevation of CKMB level was 10% in the conventional loading group, compared to only 2% had enzyme elevation in the higher loading dose group, but it was not statistically significant. Even though it was not statistically significant, there is a trend of reduction of post-procedural myocardial infarction incidence in the 600mg arm.

The mean peak CKMB value is much lesser in the 600mg compared to the 300mg treatment arm, even though the p-value is only 0.911. There is not much difference in both treatment arms with regards to Troponin-I, as well. (Table 4).

There was no statistical difference in the major bleeding rates between the two groups. However, for the minor bleeding complications, the 600mg arm has a higher event rates compared to the conventional loading arm, but this is not statistically significant also. (Table 4)

DISCUSSION

This is the first randomized controlled double blind trial done in the Philippines, comparing the conventional loading dose (300mg) of Clopidogrel versus the high loading dose (600mg) of Clopidogrel in patients undergoing elective coronary angioplasty. The patients enrolled mostly were chronic stable angina patients.

Table 3. Primary Endpoints of Patients Undergoing PCI Enrolled in the Study According to Loading Dose of Clopidogrel (PHC, 2011)

Outcome	300mg Clopidogrel (n = 58)	600mg Clopidogrel (n = 57)	P-value
Target vessel revascularization	2(3)	1(2)	1.000
Post-procedural MI			
Troponin-I	43(74)	28(49)	0.007*
CKMB	6(10)	1(2)	0.512
Death	2(3)	1(2)	1.000
Stroke	1(2)	1(2)	1.000
Composite Endpoint	49(85)	29(51)	0.000*

Table 4. Secondary Endpoints of Patients Undergoing PCI Enrolled in the Study According to Loading Dose of Clopidogrel (PHC, 2011)

Outcome	300mg Clopidogrel (n = 58)	600mg Clopidogrel (n = 57)	P-value
Any post-procedural increase of cardiac markers			
Troponin I	43(74)	28(49	0.007*
CKMB	6(10)	1(2)	0.512
Mean peak values of cardiac enzymes after intervention			
CKMB	22.89	15.78)	0.911
Troponin-I	0.533	0.557	0.177
Hemorrhagic complcations			
major bleeding*	4(2)	3(2)	1.000
minor bleeding‡	4(2)	5(3)	0.073

* major bleeding defined as overt bleeding or intracranial hemorrhage

‡ minor bleeding defined as: entry-site complications (big-sized hematoma, pseudoaneurysm, and arteriovenous fistula

There are a lot of studies, like the ARMYDA-2 trial, showing that the higher the loading dose, the lesser is the ischemic events in the higher loading arm. As demonstrated in the study, there was a significant decrease of troponin-I, (which is sensitive for myocardial injury), in the 600mg arm after the procedure, hence lesser peri-procedural injury. Although with regards to CKMB, the result was not statistically significant, there was a trend that it was decreasing in the 600mg arm. Target vessel revascularization, stroke and death were much lesser in the 600mg arm. The composite primary endpoint of the study is statistically significant at a P-value of 0.000. A meta-analysis done by Lotrionte and colleagues[23] showed that the risk of bleeding is just the same for both treatment arms; so, this gives the physician or the angiographer much confidence that the risk is just the same for bleeding. Indeed, a high Clopidogrel loading dose (600 mg) might beneficial on the basis of 3 main premises: (1) given the slow onset of Clopidogrel, a higher dose would quicken its increase in concentration and effect on platelets; (2) a higher degree of platelet inhibition, as produced by larger loading, might further protect from periprocedural thrombotic events, thus yielding clinical benefits as well as obviating the need for intravenous glycoprotein IIb/IIIa inhibitors in low-risk patients; and (3) higher loading doses might reduce the rate of Clopidogrel non responders, known to be at greater risk for periprocedural adverse events.[23] The favorable effect of the high loading dose arm could be due to the fact, that Clopidogrel is a potent antiplatelet agent, inhibiting the ADP receptor and affecting intracellular signaling events that modulate ADP-induced platelet activation.[8] In our study it was also demonstrated that the risk of bleeding between the two groups are just similar.

Two studies done in patients who had acute coronary syndromes, have shown that pretreatment with Clopidogrel (given a mean of 6 days before intervention in the observational PCI-CURE [Percutaneous Coronary Intervention-Clopidogrel in Unstable Angina to prevent Recurrent Events] and 3 to 24 hours in the randomized CREDO-Clopidogrel for the Reduction of Events During Observation trial [14,16] may have beneficial effects, possibly by decreasing periprocedural ischemia and distal embolization, protecting the microvascular bed, and counterbalancing the post-procedural "procoagulant status."[9]

Many studies comparing conventional loading dose (300mg) versus higher loading dose, like the ARMYDA-2 trial have demonstrated that that pretreatment with a 600mg loading dose of Clopidogrel given 6 hours before the procedure is safe and, as compared with the 300mg dose, reduces periprocedural myocardial infarction and improves short-term prognosis in patients undergoing percutaneous revascularization.[9] In our study, the giving of loading dose is given between 6 to 8 hours, and showed similar results.

The main finding in our study is that high loading dose 600mg of Clopidogrel given to patients for elective coronary angioplasty are beneficial in terms of composite endpoint (death, stroke, myocardial infarction, target vascular revascularization). The computation for each primary endpoint, except for the Troponin level, showed no statistical difference, however there is trend demonstrating beneficial effects of the 600mg loading dose of Clopidogrel. And the composite endpoint showed there is statistical significant difference at a p-value of 0.000. Although there are new thienopyridines that are emerging like Prasugrel that has demonstrated that it has better efficacy of producing platelet inhibition, the drawback is the disadvantage of increase bleeding and limited by the age of the patient.[24]

There are limitations to this study. It does not include non-culprit IRA infarct-related artery), not all patients had undergone Fractional Flow Reserve (FFR); Hs-CRP was not determined; all patients included in this study are all elective case; HDL determination was not observed; and the 12L ECG (ST elevation in lead AVR) was not assessed. A characteristic pattern of ST segment depression in lead I, II and V4-6 and elevation in aVR has been shown to be of value in identifying high risk patients with three vessel or left main coronary artery disease.[25,26] Further refinement in this criteria has been made by the finding of lead aVR ST segment elevation greater than or equal to lead V1, distinguished left main coronary artery group from left anterior descending

group with 81% sensitivity and 80% specificity and 81% accuracy.[27] Determination of Clopidogrel resistance assay was not done, and is highly recommended.

In conclusion, higher loading dose of Clopidogrel in the 600mg loading arm improved mortality and morbidity in chronic stable angina patients that underwent or who will undergo elective coronary angioplasty, after 30 days.

Long term outcome of this kind of study (more than 1 month) is highly recommended, and greater sample size is also recommended. This study may support its routine use in elective coronary angioplasty, and may influence practice patterns here in the Philippines.

REFERENCES

1. Mehta SR, Yusuf S. Short- and long-term oral antiplatelet therapy in acute coronary syndromes and percutaneous coronary intervention. J Am Coll Cardiol, 2003; 41:79-88.
2. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlinn MD, Hochman JS et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—Summary article: A report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol 2002;40:1366–1374.
3. CAPRIE Steering Committee. A randomised blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996; 348: 1329-1339
4. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox K, for the CURE Investigators. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE). N Engl J Med 2001;345: 494-502
5. COMMIT Collaborative Group. Addition of clopidogrel to aspirin in 45 852 patients withacute myocardial infarction: randomised placebo-controlled trial. Lancet 2005; 366: 1607–21.
6. Unilab Probes Genes' LinktoTB.Treatmen.www.unilab.com.ph/consumer/health_news_details.asp?qqq=633
7. Pasceri V, Patti G, Nusca A, Pristipino C, Richichi G, Di Sciascio G; for the ARMYDA Investigators. Randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention: results from the ARMYDA (Atorvastatin for Reduction of MYocardial Damage during Angioplasty) study. Circulation. 2004;110:674–678.
8. 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 Trial. Circulation 2005;111:2009-2106.
9. Montalescot G, Sideris G, Meuleman C, Baldit-Sollier C, Lellouche N, Steq PG, et al. 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. J Am Coll Cardiol 2006; 48: 931–938.
10. Wolfram RM, Torguson RL, Hassani SE, 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 2006;97: 984–989.
11. Gurbel PA, Bliden KP, Hayes KM, Yoho JA, Herzoq WR, Tantry US. The relation of dosing to clopidogrel responsiveness and the incidence of high post-treatment platelet aggregation in patients undergoing coronary stenting. J Am Coll Cardiol 2005;45:1392–1396.
12. Gurbel PA, Bliden KP, Zaman KA, Yoho JA, Hayes KM, Tantry US, et al. 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. Circulation 2005;111:1153–1159.
13. Cuisset T, Frere C, Quilici J, Morange PE, Nait-Saidi L, Carvajal J, et al. Benefit of a 600mg loading dose of clopidogrel on platelet reactivity and clinical outcomes in patients with non-ST-segment elevation acute coronary syndrome undergoing coronary stenting. J Am Coll Cardiol 2006;48:1339–1345.

14. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK; for the Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE)Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneouscoronary intervention: the PCI-CURE study. Lancet 2001;358:527–533.
15. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH; for the CLASSICS Investigators. Double blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). Circulation 2002;102:624-629.
16. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C,Topol EJ; for the CREDO Investigators. Clopidogrel for the Reduction of Events During Observation: early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411–2420.
17. Braunwald E. Application of current guidelines to the management of unstable angina and non–ST-elevation myocardial infarction. Circulation 2003;108(suppl III):III-28 –III-37.
18. Muller I, Seyfarth M, Rudiger S, Wolf B, Pogatsa-Murray G, Scho¨mig A,Gawaz M. Effect of a high loading dose of clopidogrel on platelet function in patients undergoing coronary stent placement. Heart 2001;85:92–93.
19. L'Allier PL, Durroq G, Pranno N, Noble S, Ibrahim R, Greqoire JC, et al. Clopidogrel 600-Mg Double Loading Dose Achieves Stronger Platelet Inhibition Than Conventional Regimens (PREPAIR). J Am Coll Cardiol 2008; 51:1066-72.
20. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH; for the CLASSICS Investigators. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS). Circulation 2000; 102:624–629.
21. Cadroy Y, Bossavy JP, Thalamas C Sagnard L, Sakariassen K, Boneu B. Early potent antithrombotic effect with combined aspirin and LD of clopidogrel on experimental arterial thrombogenesis in humans. Circulation 2000;101:2823–2828.
22. Gorog P, Ridler CD, Rees GM, Kovacs IB. Evidence against hypercoagulability in coronary artery disease. Thromb Res 1995;79:377–385.
23. Lotrionte M, Biondi-Zoccai GG, Agostoni P, Abbate A, Angiolillio DJ, Valgimigli M, et al, Metaanalysis Appraising High Clopidogrel Loading in Patients Undergoing Percutaneous intervention. Am J Cardiol 2007;100;1199-1206.
24. Nicholas B Norgard and Mazen Abu-Fadel. Comparison of prasugrel and clopidogrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention. Vasc Health Risk Manag 2009; 5: 873–882.
25. Dassen W, Gorgles A, Mulleneers R, Karthaus V, Els HV, Talmon J. Development of ECG criteria to diagnose the number of narrowed coronary arteries in rest angina using self-learning techniques. J Electrocardiol 1994;27 Suppl:156-60.
26. Hori T, Kurosawa T, Yoshida M, Yamazoe M, Aizawa Y, Izumi T. Factors predicting mortality in patients after myocardial infarction caused by left main stem coronary artery occlusion. Significance of ST segment elevation in both aVR and aVL leads. Japan Heart J 2000;41:571-81.
27. Yamaji H, Iwasaki K, Kusachi S, Murakami T, Hirami R, Hina K, et al. Prediction of acute left main coronary artery obstruction by 12 lead electrocardiography. ST segment elevation in lead aVR with less ST segment elevation in lead V. J Am Coll Cardiol 2001;38(5):1348-54.