



OPTIMIZING THE DOSE OF CLOPIDOGREL AND ASPIRIN IN ACUTE CORONARY SYNDROME

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Acute coronary syndrome (ACS), including unstable angina (UA) and myocardial infarction (MI), is one of the major causes of cardiovascular (CV) mortality in the United States. In 2011, more than 1.5 million Americans will experience ACS and 220,000 will die of an MI.¹ In 2007, coronary heart disease reached an estimated cost of \$151.6 billion dollars in the United States.¹ Due to the high possibility of reinfarction and death following ACS, optimizing pharmacotherapy can have a significant impact on reducing morbidity and mortality. A management goal in ACS is relief of ischemia by initiating pharmacological therapy with aspirin or clopidogrel.² The purpose of this article is to review the available literature regarding the dosing of aspirin and clopidogrel in ACS.

CURRENT RECOMMENDATIONS

The use of aspirin in patients with ACS is well established. Aspirin's clinical benefit in ACS is due to the irreversible inhibition of cyclooxygenase-1 (COX-1) enzyme and thus inhibition of platelet aggregation.² The 2007 ACC/AHA UA/NSTEMI guidelines recommend initiation of aspirin in the emergency department immediately upon diagnosis or suspicion of ACS. The initial recommended dose of aspirin is 163 to 325 mg, followed by a daily maintenance dose of 75 to 160 mg. The duration of therapy recommended is usually indefinite unless contraindications develop.² Practice guidelines recommend a higher daily maintenance dose (325 mg) for patients with bare-metal or drug

eluting stents.²

Clopidogrel, a thienopyridine, inhibits platelet aggregation by irreversibly antagonizing adenosine diphosphate (ADP) receptors on platelet surfaces.³ The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial demonstrated that clopidogrel 75 mg was at least as effective as aspirin 325 mg in reducing thrombotic events.⁴ However, the 2007 ACC/AHA UA/NSTEMI guidelines recommend the use of clopidogrel only in patients who are unable to tolerate aspirin (e.g. hypersensitivity) or who have major gastrointestinal contraindications.² The practice guidelines recommend a 300 mg loading dose for rapid platelet inhibition, followed by 75 mg daily.²

ASPIRIN DOSING

Numerous trials have established the benefit of aspirin in ACS. However the optimal dose of aspirin for safety and efficacy remains unclear. A meta-analysis conducted by the Antithrombotic Trialists' Collaboration indirectly compared various doses of aspirin with placebo. The meta-analysis demonstrated a 19% relative risk reduction in vascular events with aspirin doses of 500 to 1500 mg/day, 26% with aspirin doses of 160 to 325 mg/day, and 32% with aspirin doses of 75 to 150 mg/day.⁵ The meta-analysis concluded a similar risk of extracranial bleeding among patients

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Table 1 | Summary of clinical trials comparing efficacy of varying doses of aspirin.

Study (year)	Design	N	Primary Outcome	Groups	Results
CURE Peters, et al. ⁶ (2003)	Observational Study	12562	Composite CV death, nonfatal MI, or stroke	<ul style="list-style-type: none"> • Low: ≤ 100 mg ASA • Moderate: 101 -199 mg ASA • High: ≥200 mg ASA 	<ul style="list-style-type: none"> • Moderate vs. Low: OR 1.0 (95% CI, 0.82-1.23) • High vs. Low: OR 1.2 (95% CI, 1.08-1.51)
PCI-CURE Jolly, et al. ⁷ (2009)	Observational Study	2400 who underwent PCI	Composite CV death, nonfatal MI, or stroke	<ul style="list-style-type: none"> • Low: ≤ 100 mg ASA • Moderate: 101 -199 mg ASA • High: ≥200 mg ASA 	<ul style="list-style-type: none"> • Moderate vs. Low: OR 1.04 (95% CI, 0.71-1.52, p=0.85) • High vs. Low: OR 1.21 (95% CI, 0.89-1.54, p=0.23)
CHARISMA Steinhubl, et al. ⁸ (2009)	Post-Hoc Analysis	15,500	Composite CV death, nonfatal MI, or stroke at 28 months	<ul style="list-style-type: none"> • Low: 75-81mg ASA • Moderate: 100 mg ASA • High: 150-162 mg ASA 	<ul style="list-style-type: none"> • Moderate vs. Low: HR 0.95 (95% CI, 0.80-1.13) • High vs. Low: OR 1.0 (95% CI, 0.85-1.18)
CURRENT-OASIS 7 Mehta, et al. ⁹ (2010)	RCT	25,000	Composite CV death, nonfatal MI, or stroke at 30 days	<ul style="list-style-type: none"> • Low: 75-100mg ASA • High: 300-325 mg ASA 	<ul style="list-style-type: none"> • Low vs. High: HR 0.98 (95% CI 0.84-1.13, p=0.76)

ASA = aspirin; CV = cardiovascular; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; RCT = randomized controlled trial.

considered at high annual risk of vascular events due to pre-existing disease (e.g. previous occlusive event) at aspirin doses less than 325 mg/day.⁵ The meta-analysis supports the use of 75 to 150 mg daily aspirin for the prevention of major vascular events.

An observational analysis of the original CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial compared the efficacy of low (≤ 100 mg), moderate (101 to 199 mg) and high (≥ 200 mg) dose aspirin in preventing cardiovascular events (**Table 1**).⁶ No significant difference was observed in the incidence of CV death, non-fatal MI or stroke in patients receiving high dose aspirin versus low dose aspirin (adjusted OR 1.0, 95% CI 0.83 to 1.23). However, a significant difference occurred in patients receiving moderate versus low dose aspirin (adjusted OR 1.2, 95% CI 1.08 to 1.51).⁶ The incidence of major bleeding complications was significantly greater with increasing aspirin doses, with 1.9% occurring in the low dose group, 2.8% in the moderate dose group and 3.7% in the high dose group.⁶

Jolly, et al. conducted an observational analysis of the original CURE trial in patients undergoing percutaneous coronary intervention (PCI). Similar rates of CV death, MI or stroke were observed between the three aspirin groups 48 hours post-PCI and at 30 days.⁷ The incidence of CV death, MI or stroke at 12 months was 8.6% for the high dose, 7.4% for the moderate dose and 7.1% for the low dose aspirin group.⁷ The occur-

rence of major bleeding events at the end of follow-up for high, moderate and low dose aspirin was 3.9%, 1.5% and 1.9%, respectively (high- vs. low-dose HR 2.05, 95% CI 1.20 to 3.50, $p = 0.009$; moderate- vs. low-dose HR 0.78, 95% CI 0.34 to 1.77, $p = 0.55$).⁷

An analysis of the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial compared the efficacy of low dose (75 to 81 mg), moderate dose (100 mg) and high dose (150 mg to 162 mg) aspirin in preventing CV death, MI or stroke. The analysis determined the incidence of CV death, MI or stroke was similar between moderate compared with low dose (HR 0.95, 95% CI 0.80 to 1.13) and high compared with low-dose (HR 1.0, 95% CI 0.85 to 1.18).⁸ In addition, no statistically significant differences were observed in the occurrence of major bleeding between all three aspirin groups.⁸

Until recently, most of the available data for optimizing aspirin doses in patients with ACS has been derived from post-hoc analysis. The CURRENT OASIS-7 (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events-Seventh Organization to Assess Strategies in Ischemic Symptoms) trial is the first randomized study to assess the optimal dose of aspirin in patients with ACS undergoing invasive therapy. The authors compared the efficacy of high (300 to 325 mg) dose ASA versus low (75 to 100 mg) dose aspirin in preventing CV death, MI or stroke at 30 days.⁹ The in-

Table 2 | Summary of clinical trials comparing efficacy of clopidogrel loading doses.

Study (year)	Design	N	Primary Outcome	Groups	Results
ALBION Montalescot, et al. ¹⁰ (2006)	Randomized Study	103	Inhibition of platelet aggregation	<ul style="list-style-type: none"> • 300 mg LD • 600 mg LD • 900 mg LD 	<ul style="list-style-type: none"> • 600 mg vs. 300 mg, $p < 0.05$ • 900 mg vs. 300 mg, $p < 0.05$
PRACTICAL Yong, et al. ¹¹ (2009)	Randomized Study	124	PCI myonecrosis	<ul style="list-style-type: none"> • 300 mg LD • 600 mg LD 	<ul style="list-style-type: none"> • 600 mg vs. 300 mg, $p = 0.31$

LD = loading dose; PCI = percutaneous coronary intervention.

investigators found no significant difference between the two treatment groups. The primary outcome of CV death, MI or stroke occurred in 4.1% of the high dose aspirin group compared to 4.2% of the low dose aspirin group (adjusted HR 0.98, 95% CI 0.84 to 1.13, $p = 0.76$).⁹ The trial also demonstrated no statistically significant difference in the occurrence of major bleeding between the high dose and low dose aspirin group (adjusted HR 1.18, 95% CI 0.92 to 1.53, $p = 0.20$), however there was a statistically significant difference in the occurrence of minor bleeding between both groups (adjusted HR 1.18, 95% CI 1.03 to 1.36, $p = 0.019$).⁹

Most of the available data comparing low and high dose aspirin do not demonstrate a statistically significant difference in the incidence of CV death, non-fatal MI or stroke in patients with ACS. However, the available studies have established statistically significant differences in the incidence of major bleeding with increasingly higher aspirin doses. The optimal aspirin dose should not only be based on the beneficial effects of preventing a CV event but also on the likelihood of experiencing a potential adverse event.

CLOPIDOGREL LOADING DOSING

The CAPRIE trial has demonstrated that clopidogrel is as efficacious as aspirin in reducing the incidence of ischemic stroke, MI or vascular death in patients with atherosclerotic vascular disease.² Due to a slow onset of action, a loading dose of 300 mg is generally required to achieve rapid platelet inhibition.² Most studies evaluating the impact of high clopidogrel loading (600 to 900 mg) measure surrogate outcomes (such as platelet function or markers of platelet aggregation) to determine efficacy. There have been a few studies conducted in patients undergoing PCI that have examined the impact of higher clopidogrel (600 mg vs. 300 mg) loading doses.

The ALBION (Assessment of the best loading dose of clopidogrel to Blunt platelet activation, Inflammation and Ongoing Necrosis) trial was a small, random-

ized study conducted in patients hospitalized with NSTEMI (**Table 2**). The ALBION trial compared the effectiveness of clopidogrel 300 mg, 600 mg and 900 mg loading dose on platelet aggregation inhibition.¹⁰ Higher loading doses of 600 mg and 900 mg versus 300 mg produced significantly faster onset of platelet aggregation inhibition ($p < 0.05$).¹⁰ Additionally, greater loading doses significantly shorten the time to maximal platelet aggregation inhibition ($p = 0.04$). However, inflammatory markers were not significantly affected by increasing clopidogrel loading doses.¹⁰ There was no significant difference in the incidence of major adverse cardiac events and severe bleeding events between the three groups.¹⁰

Another randomized trial, PRACTICAL (Platelet Responsiveness to Aspirin and Clopidogrel and Troponin Increment after Coronary intervention in Acute coronary Lesions), compared the effects of 600 mg vs. 300 mg clopidogrel loading dose on platelet aggregation inhibition, myonecrosis and clinical outcomes in Non-ST elevation myocardial infarction patients undergoing PCI. The results from this trial demonstrated greater platelet aggregation inhibition with the 600 mg versus 300 mg clopidogrel loading dose. However, the incidence of post-PCI myonecrosis, major bleeding and clinical outcomes (ex. death, MI, stroke) was not significantly different between groups.¹¹

Unfortunately, most of the studies comparing the efficacy of clopidogrel loading doses have measured surrogate markers as opposed to clinical outcomes. These studies demonstrate greater platelet aggregation inhibition with higher loading doses. However these effects do not necessarily translate to significant improvement in clinical outcomes.

CLOPIDOGREL MAINTENANCE DOSING

A small, randomized trial evaluated the benefit of higher loading and maintenance doses of clopidogrel (**Table 3**). This study included 119 patients who were undergoing PCI in native coronary vessels.¹² The results from this study supported previous findings re-

garding greater inhibition of platelet aggregation with higher doses. The results also demonstrate a significantly higher inhibition of platelet aggregation 4 hours post-PCI in the high dose group compared with low dose group (10% vs. 27%, $p = 0.047$). The combined ischemic end-points at 30 days were statistically significantly different between the high (10.3%) and low (23.8%) dose group ($p = 0.04$).¹² However, the incidence of individual end points including AMI and target vessel revascularization were not significantly different between both groups. Moreover, major and minor bleeding at 30 days was similar in both groups.¹²

Another retrospective study conducted by Lemesle and colleagues compared the impact of high loading and maintenance dose clopidogrel on the composite end point of death, MI or in-stent thrombosis at 2 months. This study included 2,954 patients who underwent PCI with stent implantation.¹³ Patients were pretreated with either 600 mg clopidogrel loading dose followed by 150 mg/day for 15 days and then 75 mg thereafter, or 300 mg clopidogrel loading dose followed by 75 mg/day thereafter. At 2 months, the composite primary endpoint occurred in 6.3% of high-dose group versus 8.2% in the low dose group ($p = 0.46$).¹³ There was no statistically significant difference between the two groups in the rate of minor ($p = 0.221$) or major ($p = 0.224$) bleeding.¹³

The impact of high maintenance dose clopidogrel on CV death, MI or stroke at 30 days was tested by the

CURRENT-OASIS 7 trial.⁹ The trial enrolled 25,086 patients undergoing PCI. Patients were randomly assigned to double dose or standard dose clopidogrel and high dose versus low dose aspirin groups. Unlike previously mentioned studies, high maintenance dose clopidogrel was only continued for 7 days which was then followed by standard dosing of 75 mg/day.⁹ The results illustrated a significantly lower incidence of the primary outcome (a composite of CV death, nonfatal MI, or stroke at 30 days) in patients undergoing PCI who received double dose (3.9%) treatment compared to standard dose (4.5%) treatment ($p = 0.039$). There was also a significantly lower occurrence of the secondary outcome of a composite of CV death, nonfatal MI, stroke, or recurrent ischemia favoring high dose clopidogrel; however, in both cases, the difference was driven primarily by a lower rate of MI.⁹ There was no significant difference in the incidence of primary outcome between double (4.9%) and standard dose (4.3%) clopidogrel (HR 1.14, 95% CI 0.92-1.40, $p = 0.23$) in patients who did not undergo PCI. The authors also found no significant difference in the incidence of major bleeding using TIMI (Thrombosis in Myocardial Infarction) definitions between the double and standard dose groups; however, high dose clopidogrel resulted in a greater risk of major bleeds according to CURRENT definitions (1.6% vs. 1.1% for the comparison of high- to standard-dose clopidogrel; adjusted HR 1.41, 95% CI 1.09 to 1.83, $p = 0.009$).⁹

Table 3 | Summary of clinical trials comparing efficacy of clopidogrel maintenance doses.

Study (year)	Design	N	Primary Outcome	Groups	Results
Mohammed, et al. ¹² (2008)	Randomized Study	119 *undergoing PCI	Platelet aggregation, cardiac and bleeding events at 30 days	<ul style="list-style-type: none"> High: 600 mg LD + 75 mg BID Low: 300 mg LD + 75 mg daily 	<ul style="list-style-type: none"> IPA: High (10%) vs. Low (27%), $p = 0.047$ CV events: High (10.3%) vs. Low (23.8%), $p = 0.04$ AMI: High (7.8%) vs. Low (11.9%), $p = 0.27$ TVR: High (1.3%) vs. Low (4.8%), $p = 0.99$
Lemesle, et al. ¹³ (2009)	Retrospective Study	2,954 *undergone PCI	Death, MI or stent thrombosis at 2 months	<ul style="list-style-type: none"> High: 600 mg LD + 75 mg BID x 15 days, then 75 mg daily Low: 300 mg LD + 75 mg daily 	<ul style="list-style-type: none"> High (6.3%) vs. Low (8.2%), $p = 0.046$
CURRENT OASIS-7 Mehta, et al. ⁹ (2010)	Randomized-2x2 factorial trial	25086 *undergoing PCI	CV death, myocardial infarction or stroke at 30 days	<ul style="list-style-type: none"> High: 600 mg LD + 75 mg BID x 7 days, then 75 mg daily Low: 300 mg LD + 75 mg daily 	<ul style="list-style-type: none"> High (3.9%) vs. Low (4.5%), $p = 0.039$

AMI = acute myocardial infarction; BID = twice daily; CV = cardiovascular; IPA = inhibition of platelet aggregation; LD = loading dose; MI = myocardial infarction; PCI = percutaneous coronary intervention; TVR = target vessel revascularization.

In conclusion, higher loading and maintenance dose clopidogrel may confer a modest benefit in patients undergoing PCI. Furthermore, these higher doses generally were not associated with additional bleeding risks according to the commonly used TIMI definitions. Unfortunately, the benefit obtained from higher maintenance dose does not seem to apply to those not receiving PCI, as demonstrated by CURRENT-OASIS 7 trial. Further studies are needed to determine the benefit of higher clopidogrel maintenance doses in patients with ACS.

DUAL THERAPY: ASPIRIN PLUS CLOPIDOGREL

Given their two distinct mechanism of action, the combination of aspirin plus clopidogrel may be synergistic in ACS patients. The first trial to evaluate the impact of combination therapy in ACS patients was CURE.¹⁴ The study included 9,000 patients who were randomly assigned to the clopidogrel plus aspirin group or aspirin alone. The study's primary outcome was the composite of CV death, non-fatal MI, or stroke. The primary outcome occurred 9.3% in the combination group versus 11.4% in the aspirin alone group (RR 0.80, 95% CI 0.72 to 0.90, $p < 0.001$).¹⁴ The incidence of major bleeding was significantly higher in the combination group (3.7%) compared to aspirin alone group (2.7%; RR 1.38, 95% CI 1.13 to 1.67, $p = 0.001$).¹⁴ However, the incidence of life-threatening bleeding did not differ between both groups.

The PCI-CURE trial, evaluated the effects of combination therapy in patients from CURE who underwent PCI.⁷ The study demonstrated a significant reduction in the primary composite of CV death, MI or stroke in the clopidogrel plus aspirin group at 30 days. The PCI-CURE trial only showed significant differences in minor bleeding between both groups.⁷

Overall, the use of combination therapy with clopidogrel and aspirin may provide some additional benefits in patients with ACS but these benefits come at the expense of additional bleeding risk. Specifically, the combination therapy may increase the incidence of major bleeding as demonstrated by the CURE trial. However, whether an increased risk of major bleeding occurs in patients receiving PCI is not fully known, but may depend on the definitions used to assess major bleeding. Therefore, the initiation of combination therapy should be carefully based on a risk versus benefits ratio for an individual patient.

SUMMARY

The initiation of anti-platelet therapy can play an important role in the management of patients with

ACS. Aspirin doses between 75 and 325 mg are equally effective in preventing CV death, MI or stroke in patient with ACS. However, studies have consistently demonstrated a significantly greater incidence of major bleeding events with higher aspirin doses. As previously discussed, the administration of clopidogrel loading doses is necessary to obtain rapid platelet aggregation inhibition in ACS. Studies have demonstrated greater and faster onset of platelet aggregation inhibition with higher clopidogrel loading doses (e.g. 600 mg or 900 mg vs. 300 mg). Unfortunately, increasing only clopidogrel loading doses without increasing maintenance doses has not resulted in significant differences in inflammatory markers or clinical outcomes.

Studies evaluating higher loading and maintenance doses of clopidogrel (e.g. CURRENT-OASIS 7) have demonstrated significant decreases in the incidence of primary outcomes in patients receiving higher doses compared to standard doses. These studies have not demonstrated significant increasing in the occurrence of adverse events (except possibly for major bleeding) in patients receiving higher loading and maintenance doses of clopidogrel. However, similar results were not obtained in patients who did not undergo PCI. Finally, studies evaluating the combination therapy of aspirin plus clopidogrel showed significant decreases in the incidence of the primary outcome (e.g. composite of CV death, non-fatal MI or stroke) in patients receiving both aspirin and clopidogrel compared to aspirin alone. The use of dual therapy with aspirin and clopidogrel has resulted in significantly greater incidence of major bleeding events.



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