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Rationale and Role of High Loading Dose Clopidogrel in Patients with Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

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ABSTRACT

Antiplatelet therapy, which reduces platelet activation and aggregation, is the corner stone of treatment for patients undergoing percutaneous coronary intervention (PCI). Clopidogrel is an established oral antiplatelet medication of thienopyridine class, which inhibits blood clots in coronary artery disease, peripheral vascular disease, and cerebrovascular disease. Many studies have revealed that high loading dose clopidogrel in patients undergoing PCI. This review article investigates the rationale and role of high loading dose clopidogrel in patients undergoing PCI.

Keywords: Clopidogrel; Antiplatelet Therapy; Percutaneous Coronary Intervention

1. Introduction

The term acute coronary syndrome (ACS) refers to any group of clinical symptoms compatible with acute myocardial ischemia and includes unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) [1]. Antiplatelet therapy, which reduces platelet activation and aggregation, integral steps in the formation of a thrombus after plaque disruption, is the corner stone of treatment for patients undergoing percutaneous coronary intervention (PCI) [2,3].

Clopidogrel is an established oral antiplatelet medication of thienopyridine class, which inhibits blood clots in coronary artery disease, peripheral vascular disease, and cerebrovascular disease. The active metabolite of clopidogrel inhibits platelet activation to a modest degree and with wide variability in platelet response by noncompetitively inhibiting the binding of adenosine diphosphate (ADP) to the P2Y12 receptor (ADP-receptor antagonist) that participates in the activation of the GP IIb/IIIa complex [4]. The use of clopidogrel (at a loading dose of 300 mg followed by a maintenance dose of 75 mg/day) is now a key component of treatment strategies used in the management of ACS, particularly for patients who undergo PCI and require peri- and postprocedural thrombus prevention. At this loading dose, inhibition of platelet aggregation to ADP is approximately 30%, and the time to peak effect is approximately 4 to 6 hours [5].

2. Clopidogrel in Acute Coronary Syndrome Risk Reduction

Two pivotal clinical trials-Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events (CAPRIE) and Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) have established the clinical benefits of clopidogrel [6].

Patients (n = 19,185) with atherosclerotic vascular disease, including recent myocardial infarction (MI), recent ischemic stroke (IS), or established peripheral artery disease (PAD) were evaluated in the CAPRIE study [6]. The annual IS and MI risk in clopidogrel treated group was 5.32%, and that in the aspirin treated group was 5.83% with a relative risk reduction of 8.7% vs. aspirin (p = 0.0431). The CURE trial was a double-blind, placebo-controlled, international, randomized trial of short- and long-term therapy with clopidogrel vs. placebo, in addition to aspirin and other contemporary therapies in patients with NSTE ACS. This trial [7] randomly assigned patients (n = 12,562) with UA or NSTEMI to receive either aspirin alone (75 - 325 mg/day) or aspirin plus clopidogrel (300 mg loading dose, then 75 mg/day). The incidence of cardiovascular death, MI, or stroke was

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20% lower for both low-risk and high risk patients who received aspirin plus clopidogrel (11.4%) than for those who received aspirin alone (9.3%; $p < 0.0001$). Benefit was seen as early as 24 hours after the initiation of treatment and continued throughout the trial's one year treatment period. The prespecified subgroup analysis, Percutaneous Coronary Intervention in the Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE), found that treatment with clopidogrel before PCI was also associated with a substantial benefit; the reduction in cardiac events was 31% at 30 days and at one year. Administration of clopidogrel therapy for a mean period of 8 months after PCI was also associated with a reduction in cardiovascular death, MI, or need for any revascularization ($p = 0.03$) [8].

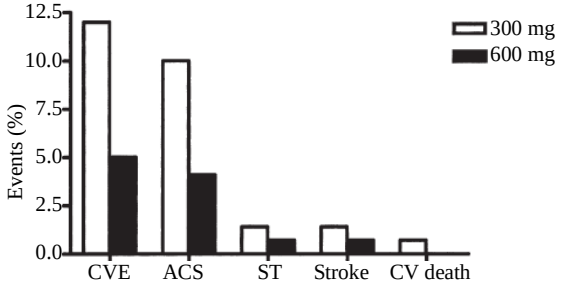
3. Role of High Loading Dose of Clopidogrel in ACS Patients Undergoing PCI

Based on the findings of PCI-CURE trial, the Clopidogrel for the Reduction of Events During Observation (CREDO) trial and the Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) trial, together with the results of a meta-analysis, the 2005 guidelines from the ACC, the AHA, and the Society for Coronary Angiography and Interventions contain a class I, level of evidence A recommendation for clopidogrel pretreatment before PCI [2-9]. Results of these large clinical trials in patients with ACS and stable angina revealed beneficial effects when patients were pretreated with 300 mg of clopidogrel 6 days before the intervention in the observational PCI-CURE trial [8], or 3 to 24 hours in the CREDO trial [10]. Based on these observations, current clinical guidelines recommend a 300 mg loading dose of clopidogrel to be administered the day before a planned PCI, or at least 6 hours before the intervention [2-10]. However, ischemic cardiovascular events still occur. The recurrences of ischemic cardiovascular events may be due to low response to antiplatelet therapy and inter-individual variability in platelet response to clopidogrel [11-15]. Considering these results, other therapeutic approaches should be considered for these low-responder patients, such as higher loading dose and or higher maintenance dose. Several studies have reported the relationship between clopidogrel resistance and recurrence of clinical outcomes and suggested that treatment with a higher loading dose and maintenance doses of clopidogrel may be more effective than a 300 mg loading dose. These studies also showed faster onset of action of 600 mg clopidogrel as compared with 300 mg loading dose [16- 20].

The Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty (ARMYDA-2) trial was the first randomized trial to evaluate the clinical significance of the emerging practice standard of high dose clopidogrel pretreatment. Patients (n = 255) scheduled to undergo PCI were randomized to receive a 600 mg or 300 mg loading dose of clopidogrel and aspirin. Treatments were administered 4 - 8 h prior to PCI. The primary endpoint, thirty day occurrence of death, MI, or target-vessel revascularization occurred only in 4% of patients in the 600 mg loading dose group where as it was 12% in the 300 mg loading dose group ($p = 0.041$). It was also observed that the high-loading regimen was associated with a 50% risk reduction of periprocedural MI ($p = 0.044$) [21].

A randomized prospective study evaluated the benefit (clinical outcomes) of a higher loading dose of clopidogrel on platelet aggregation and recurrent ischemic events for NSTE ACS patients undergoing coronary stenting. Patients were randomly received a 300 mg (n = 146) or 600 mg (n = 146) loading dose of clopidogrel at least 12 h before percutaneous coronary intervention. The ADP-induced platelet aggregation and expression of P-selectin were significantly lower in patients receiving 600 mg than in those receiving 300 mg. The cardiovascular outcomes of this study are presented in **Figure 1** [22]. However, despite the administration of a clopidogrel 600 mg loading dose and the routine use of 75 mg clopidogrel plus aspirin as a maintenance dose, recurrent ischemic cardiovascular events occurred [21,22].

HAN Ya-ling and co workers [23] conducted a study to evaluate the short-term efficacy and safety of a 150 mg maintenance dose of clopidogrel following a 600 mg loading dose in patients with ACS undergoing drug eluting stent implantation. A 600 mg loading dose was administered before PCI and patients were randomized to receive clopidogrel 75 mg or 150 mg for 30 days in addition to 300 mg aspirin daily. This study concluded that a high clopidogrel maintenance dose of 150 mg daily following a 600 mg loading dose for the first month after PCI procedure reduces the risk of stent thrombosis and is safe in patients with ACS undergoing drug eluting stent



ACS = acute coronary syndrome; CV death = cardiovascular death; CVE = cardiovascular events; ST = stent thrombosis. (Reproduced from [22]).

Figure 1. Clinical outcomes according to loading dose of clopidogrel.

implantation. A randomized, multi-center, parallel-group study (ALBION trial [Assessment of the best loading dose of clopidogrel to blunt platelet activation, Inflammation and Ongoing Necrosis]) evaluated the effects of three different loading doses of clopidogrel. Patients (n = 103) with non-ST-segment elevation acute coronary syndromes were randomized to receive a 300 mg, 600 mg, or 900 mg clopidogrel loading dose plus other standard therapy including aspirin. The results of this study demonstrated that clopidogrel loading doses of >300 mg can provide faster onset of action and greater levels of inhibition of platelet aggregation in patients with NSTE-ACS [24].

4. Conclusion

The review of published literatures shows that clopidogrel, an adenosine diphosphate receptor antagonist, achieves platelet inhibition with wide variability in response, and reduces the chances of death from cardiovascular causes, MI or stroke compared with placebo in patients with ST and non-ST segment elevation ACS. Currently, the 300 mg loading dose of clopidogrel given at least six hours before the procedure with a maintenance dose of 75 mg represents the conventional antiplatelet regimen before PCI. However, higher loading (up to 900 mg) and maintenance doses (150 mg) of clopidogrel given before PCI for NSTE ACS is safe and achieve greater degrees of platelet inhibition in a faster way than standard doses, and result in a decreased rate of ischemic events. The low risk of this pharmacological regimen may support its routine use in patients before planned coronary angioplasty and may influence practice patterns with regard to antiplatelet therapy before percutaneous intervention.

REFERENCES

[1] K. Amit and P. C. Christopher, "Acute Coronary Syndromes: Diagnosis and Management, Part I," *Mayo Clinic Proceedings*, Vol. 84, No. 10, 2009, pp. 917-38. doi:10.4065/84.10.917

[2] S. C. Smith, T. E. Feldman and J. W. Hirshfeld, "ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention)," *Circulation*, Vol. 113, No. 7, 2006, pp. 166-286.

[3] S. Silber, P. Albertsson and F. F. Aviles, "Guidelines for Percutaneous Coronary Interventions: The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology," *European Heart Journal*, Vol. 26, No. 8, 2005, pp. 804-847. doi:10.1093/eurheartj/ehi138

[4] M. D. Quinn, J. Martin, J. Desmond and M. D. Fitzgerald, "Ticlopidine and Clopidogrel," *Circulation*, Vol. 100, No. 15, 1999, pp. 1667-1672. doi:10.1161/01.CIR.100.15.1667

[5] S. D. Wiviott, D. Trenk and A. L. Frelinger, "Prasugrel Compared with High Loading- and Maintenance-Dose Clopidogrel in Patients with Planned Percutaneous Coronary Intervention: The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 Trial," *Circulation*, Vol. 116, No. 25, 2007, pp. 2923-2932. doi:10.1161/CIRCULATIONAHA.107.740324

[6] Caprie Steering Committee, "A Randomised, Blinded, Trial of Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE)," *The Lancet*, Vol. 348, No. 9038, 1996, pp. 1329-1339. doi:10.1016/S0140-6736(96)09457-3

[7] S. Yusuf, F. Zhao, S. R. Mehta, *et al*., "Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation," *The New England Journal of Medicine*, Vol. 345, No. 7, 2001, pp. 494-502. doi:10.1056/NEJMoa010746

[8] S. R. Mehta, S. Yusuf, R. J. Peters, *et al*., "Effects of Pretreatment with Clopidogrel and Aspirin Followed by Long-Term Therapy in Patients Undergoing Percutaneous Coronary Intervention: The PCI-CURE Study," *The Lancet*, Vol. 358, No. 9281, 2001, pp. 527-533. doi:10.1016/S0140-6736(01)05701-4

[9] S. B. King, S. C. Smith and J. W. Hirshfeld, "Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines," Vol. 117, No. 6, 2008, pp. 261-295.

[10] S. R. Steinhubl, P. B. Berger and J. T. Mann, "Early and Sustained Dual Oral Antiplatelet Therapy Following Percutaneous Coronary Intervention: A Randomized Controlled Trial," *Journal of the American Medical Association*, Vol. 288, No. 19, 2002, pp. 2411-2420. doi:10.1001/jama.288.19.2411

[11] P. A. Gurbel, K. P. Bliden and B. L. Hiatt, "Clopidogrel for Coronary Stenting: Response Variability, Drug Resistance, and the Effect of Pretreatment Platelet Reactivity," *Circulation*, Vol. 107, No. 23, 2003, pp. 2908-2913. doi:10.1161/01.CIR.0000072771.11429.83

[12] D. J. Angiolillo, A. Fernandez-Ortiz and E. Bernardo, "Identification of Low Responders to a 300-mg Clopidogrel Loading Dose in Patients Undergoing Coronary Stenting," *Thrombosis Research*, Vol. 115, No. 1-2, 2005, pp. 101-108. doi:10.1016/j.thromres.2004.07.007

[13] P. Järemo, T. L. Lindahl, S. G. Fransson and A. Richter, "Individual Variations of Platelet Inhibition after Loading Doses of Clopidogrel," *Journal of Internal Medicine*, Vol. 252, No. 3, 2002, pp. 233-238. doi:10.1046/j.1365-2796.2002.01027.x

[14] I. Muller, F. Besta and C. Schulz, "Prevalence of Clopidogrel Non-Responders among Patients with Stable Angina Pectoris Scheduled for Elective Coronary Stent Placement," *Thrombosis and Haemostasis*, Vol. 89, No. 5, 2003, pp. 783-787.

[15] V. L. Serebruany, S. R. Steinhubl and P. B. Berger, "Variability in Platelet Responsiveness to Clopidogrel among 544 Individuals," *Journal of the American College of Cardiology*, Vol. 45, No. 2, 2005, pp. 246-251. doi:10.1016/j.jacc.2004.09.067

[16] P. Barragan, J. L. Bouvier and P. O. Roquebert, "Resistance to Thienopyridines: Clinical Detection of Coronary Stent Thrombosis by Monitoring of Vasodilator-Stimulated Phosphoprotein Phosphorylation," *Catheterization and Cardiovascular Interventions*, Vol. 59, No. 3, 2003, pp. 295-302. doi:10.1002/ccd.10497

[17] P. A. Gurbel, K. P. Bliden and W. Samara, "Clopidogrel Effect on Platelet Reactivity in Patients with Stent Thrombosis: Results of the CREST Study," *Journal of the American College of Cardiology*, Vol. 46, No. 10, 2005, pp. 1827-1832. doi:10.1016/j.jacc.2005.07.056

[18] P. Wenaweser and O. Hess, "Stent Thrombosis is Associated with an Impaired Response to Antiplatelet Therapy Free," *Journal of the American College of Cardiology*, Vol. 45, No. 11, 2005, pp. 1748-1752. doi:10.1016/j.jacc.2005.01.058

[19] S. Matetzky, B. Shenkman and V. Guetta. "Clopidogrel Resistance is Associated with Increased Risk of Recurrent Atherothrombotic Events in Patients with Acute Myocardial Infarction," *Circulation*, Vol. 109, No. 25, 2004, pp. 3171-3175. doi:10.1161/01.CIR.0000130846.46168.03

[20] G. Montalescot, G. Sideris, C. Meuleman and C. Bal-dit-Sollier, "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," *Journal of the American College of Cardiology*, Vol. 48, No. 5, 2006, pp. 931-938. doi:10.1016/j.jacc.2006.04.090

[21] G. Patti, G. Colonna and V. Pasceri, "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," *Circulation*, Vol. 111, No. 16, 2005, pp. 2099-2116. doi:10.1161/01.CIR.0000161383.06692.D4

[22] T. Cuisset, C. Frere and J. Quilici. "Benefit of a 600-mg Loading Dose of Clopidogrel on Platelet Reactivity and Clinical Outcomes in Patients with Non-ST-Segment Elevation Acute Coronary Syndrome Undergoing Coronary Stenting," *Journal of the American College of Cardiology*, Vol. 48, No. 7, 2006, pp. 1339-1345. doi:10.1016/j.jacc.2006.06.049

[23] Y.-L. Han, B. Wang, Y. Li, K. Xu, *et al.*, "A High Maintenance Dose of Clopidogrel Improves Short-Term Clinical Outcomes in Patients with Acute Coronary Syndrome Undergoing Drug-Eluting Stent Implantation," *Chinese Medical Journal*, Vol. 122, No. 7, 2009, pp. 793-797.

[24] W. Rosamond, K. Flegal and G. Friday, "Heart Disease and Stroke Statistics—2007 Update: A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee," *Circulation*, Vol. 115, No. 5, 2007, pp. e69-e171. doi:10.1161/CIRCULATIONAHA.106.179918

