

The role of clopidogrel in cardiovascular diseases

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Clopidogrel is a second generation thienopyridine that requires hepatic cytochrome P450 mediated conversion to an active metabolite to specifically and irreversibly inhibit the platelet P2Y₁₂ receptor. The P2Y₁₂ receptor mediates the amplification of aggregation induced by adenosine diphosphate (ADP) and also other agonists. In addition, inhibition of P2Y₁₂ receptor has been shown to affect coagulation and inflammation [1]. Prevention of occlusive thrombus formation by inhibiting platelet function is the primary rationale for clopidogrel treatment. Indeed, the demonstration of significant clinical efficacy in major clinical trials led to the widespread use of clopidogrel and aspirin in the treatment of cardiovascular diseases [1].

Due to favorable side effects and a comparatively rapid onset of action, clopidogrel was preferred over ticlopidine to prevent the occurrence of stent thrombosis in patients undergoing stenting [2]. Since then the clinical efficacy of clopidogrel treatment has been demonstrated in various settings of cardiovascular diseases either as an alternative or complementary to aspirin. Based on the marginal superiority over aspirin and less frequent gastrointestinal bleeding observed in the CAPRIE (clopidogrel versus aspirin in patients at risk of ischemic events) trial, the United States Food and Drug Administration approved the use of a 75 mg/day dose of clopidogrel for patients with a history of recent heart attack, stroke, or established peripheral arterial diseases [3]. The important results of the CHARISMA trial indicated that dual antiplatelet therapy was not superior to aspirin alone in primary and secondary prevention of high risk patients. In the subset of patients with prior myocardial infarction (MI), ischemic stroke, or symptomatic peripheral arterial disease (PAD) a benefit was observed [4]. There are no large-scale prospective studies evaluating the utility of clopidogrel or dual antiplatelet therapy specifically in patients with peripheral arterial disease.

The clinical benefits due to the complementary effects of dual antiplatelet therapy was addressed in the secondary prevention trials. The most effective pharmacologic treatment to restore normal perfusion among ST-segment elevation-MI (STEMI) patients appears to be combination therapy of fibrinolytic therapy together with effective platelet inhibition [5].

The significant benefits of clopidogrel pretreatment in both the short term and long term were demonstrated in the meta-analysis of three major clinical trials including patients with STEMI [5]. The results of the meta-analysis support the initiation of clopidogrel pretreatment as early as possible for a wide range of patients from stable coronary artery diseases to STEMI, regardless of patients demographics or the use of GPIIb/IIIa blocker at the time of PCI [6]. Recent two important trials, Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction (CLARITY-TIMI) – 28 and Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) again confirmed the benefits of dual antiplatelet therapy in patients with STEMI together with fibrinolytic and heparin [5,7]. In the COMMIT trial, the benefit of 75mg/day clopidogrel treatment was observed even within 24 hours of treatment stressing the importance of early initiation of treatment [7].

Based on the significant reduction observed in the 12 month incidence of death, MI or stroke in acute coronary syndrome patients with unstable angina/non-ST-segment elevation (ACS-UA/NSTEMI), a loading dose of 300 mg followed by daily dose of 75 mg/day together with aspirin was considered the gold standard to prevent adverse cardiovascular events following PCI in ACS-UA/NSTEMI patients [8,9].

Although these studies strongly suggest the need for rapid and superior platelet inhibition in moderate to high-risk patients, uncertainty still remains for the optimal loading dose and timing of the initiation of loading. Therefore, the current guidelines from the AHA/ACC do not universally recommend pretreatment [10]. This is more important in patients who may have to undergo subsequent coronary artery bypass grafting (CABG). Based on the retrospective analysis of data suggesting the increased bleeding risk and need for blood transfusion among these patients, the ACC/AHA guidelines recommend a 5-day waiting period from the last dose [11]. However, a recent observational study suggested a similar post-operative bleeding rates in patients treated with or without clopidogrel [12].

The current recommended dose of clopidogrel is based primarily on clinical trial results and in comparison to the ticlopidine pharmacodynamic profile but not on assessment of the individual patient's response (a one size fits all principle) [13]. However, based on the *ex vivo* measurement of ADP-induced platelet aggregation, recent pharmacodynamic studies have revealed various limitations of clopidogrel therapy: 1) a delayed and irreversible pharmacodynamic response; 2) an overall modest degree of platelet inhibition (~30 to 50%); 3) dist-

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inert response variability with a substantial percentage of patients exhibiting non-responsiveness; 4) a potential influence of drug-drug interactions; and 5) the recent demonstration of an association between clinical adverse events including stent thrombosis and clopidogrel non-responsiveness [13].

Clopidogrel nonresponsiveness is dependent on time and dose. The mechanisms responsible for clopidogrel response variability and resistance are incompletely defined [13]. Several lines of evidences indicate that clopidogrel non-responsiveness is pharmacokinetic problem associated with insufficient active metabolite generation resulting in the overall modest degree of platelet inhibition [13]. The insufficient active metabolite generation is related to intestinal absorption, and functional and genetic variability in the cytochrome P450 isoenzymes. Use of a higher loading or maintenance doses of clopidogrel or new and more potent P2Y₁₂ receptor blockers such as prasugrel, cangrelor and AZD6140 are potential future alternative strategies [13]. The results of clinical trials investigating these drugs may entirely shift the treatment paradigm away from clopidogrel therapy.

Therefore, a modification of the treatment during stenting from the standard 300 mg dose to a higher 600 mg clopidogrel dose has occurred. The higher dose is associated with a more rapid onset of action, decreased incidence of clopidogrel nonresponsiveness, increased platelet inhibition and an increased inhibition of inflammatory marker release [13]. Similarly, increased inhibition of ADP-induced platelet aggregation was also observed with a 150 mg maintenance dose [14]. However, definitive large-scale clinical trials have not been conducted to establish the clinical utility and bleeding complications of higher clopidogrel loading or maintenance doses. Moreover, in patients not pretreated with clopidogrel, the addition of a GPIIb/IIIa inhibitor may be an important therapeutic consideration especially in high risk patients [15].

Another controversy surrounds patients on long term clopidogrel treatment and whether a loading dose should be administered prior to PCI. Currently, there is no recommendation for those patients who are already on clopidogrel treatment. Kastrati has shown that the administration of a loading dose to patients already treated with a maintenance dose is associated with additional platelet inhibition [16]. However, there are no prospective clinical trials to demonstrate the relevance of this laboratory finding.

Recent controversy has surrounded the duration of dual antiplatelet therapy for patients treated with drug eluting stents (DES) [17]. The current data suggest that premature discontinuation and resistance to antiplatelet therapy are important risk factors for stent thrombosis. Although indefinite treatment with dual antiplatelet therapy to prevent stent thrombosis has been advocated by some, the bleeding risks and cost are major concerns. Therefore, early identification of patients who are resistant to clopidogrel is being studied and drug eluting stents should be discouraged in patients who are not candidates for long-term dual antiplatelet therapy. The current recommendation is the uninterrupted dual antiplatelet

therapy for one year in patients treated with DES in whom the bleeding risk is acceptable [18].

Finally, there are emerging data from overall small studies demonstrating heightened thrombotic risk in patients with high platelet reactivity to ADP following coronary stenting [19]. The unresolved issue that remains is whether long-term superior inhibition of platelet aggregation by P2Y₁₂ inhibitors will lead to overall net clinical benefits. At this time there is a need for a definitive large scale trial designed to determine whether high platelet reactivity determined by an ex vivo test truly identifies the patient at risk for thrombotic events and whether there is a cutpoint associated with excessive bleeding. If the relation between high platelet reactivity and adverse ischemic events indeed exists, and if subsequent studies can demonstrate that lowering platelet reactivity in the individual patient leads to better outcomes, then the "one size fits all" approach to antiplatelet treatment that we currently employ will be replaced by personalized therapy.

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