

Triple Anti Platelet Therapy- Why and When?

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Optimal platelet inhibition is the desired goal in different cardiovascular indications, including acute coronary syndromes (ACS) and percutaneous coronary interventions (PCI). Since demonstration of antiplatelet effect of aspirin in 1960s, aspirin has been being used widely as an antiplatelet agent. However, 5 to 60% patients show decreased response to aspirin due to platelet resistance. Subsequently, in 1980s first generation platelet ADP antagonist ticlopidine and in 1990s second generation ADP antagonist clopidogrel were introduced. But within few years, clopidogrel non-responsiveness was identified in 5-25% of subjects. Combination of aspirin and clopidogrel was thought to be the optimum solution of this problem. But, up to 25% patients have high residual platelet reactivity despite dual antiplatelet therapy. Consequently, insufficient platelet inhibition may be an important factor for stent thrombosis and in-stent restenosis, as well as, for recurrence of ACS despite continued antiplatelet therapy. In a study on 215 patients undergoing DES-supported PCI for unprotected left main disease, clopidogrel non-responders had 4-fold increased risk of stent thrombosis and cardiac death as compared with clopidogrel responders. Only 36% of non-responders to a 600-mg loading dose of clopidogrel showed partial improvement in platelet inhibition when prescribed with 150 mg daily dose of clopidogrel or shifted to ticlopidine. Similar persistent high residual platelet reactivity after increasing the dose of clopidogrel was reported in case of stent thrombosis. In this disappointing background, came the concept of triple antiplatelet therapy. A number of antiplatelet agents including glycoprotein IIb/IIIa inhibitors and cilostazol were added to aspirin-clopidogrel combination. Glycoprotein IIb/IIIa inhibitors are mostly available in parenteral form and are unsuitable for long-term use. Moreover, they are associated with unacceptably high risk of bleeding. Addition of

cilostazol to the combination of aspirin and clopidogrel is a promising triple antiplatelet regimen. Cilostazol is an inhibitor of phosphodiesterase type III enzyme in both platelets and vascular smooth muscle cells. It has potential for inhibition of platelet aggregation and proliferative vessel response to coronary stent implantation. Both DECLARE [Drug-Eluting stenting followed by Cilostazol treatment reduces Late REstenosis]-Diabetes trial and DECLARE-Long trials showed superiority of triple antiplatelet therapy over dual antiplatelet therapy, specially in high-risk patients, in terms of angiographic late loss and rate of repeat revascularization. But, the more recent the CILON-T (Influence of CILostazol-based triple antiplatelet therapy ON ischemic complication after drug-eluting stent implantation) trial 2010, carried out in real-world patients undergoing PCI confirmed that triple antiplatelet treatment is associated with an increased platelet reactivity inhibition, but this effect did not translate into any clinical benefit. In the CILON-T Trial, no statistically significant differences were found in the rate of the composite primary end points of cardiovascular death, myocardial infarction, stroke, target vessel revascularization (8.5% in the triple antiplatelet therapy and 9.2% in the dual antiplatelet therapy). Also, a substantial percentage of patients randomized to triple antiplatelet therapy had still high residual platelet reactivity as assessed by VerifyNow assay. So, again the reality is far from the dream. Continued search for better antiplatelet inhibition led to development of newer molecules including Prasugrel, Ticagrelor, Cangrelor and Elinogrel. Prasugrel, a third-generation thienopyridine, has got faster onset of action, better oral bioavailability (80% vs. 10-20%), no CYP3A4-mediated drug interaction and is about 10 times more potent in comparison to clopidogrel. The Trial to assess improvement in Therapeutic Outcomes

by optimizing platelet Inhibition with prasugrel-Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) Trial involving 13,608 acute coronary syndrome patients undergoing PCI demonstrated statistically significant fewer non-fatal MI and stent thrombosis though at the cost of more bleeding. In July 2009, FDA approved prasugrel for reducing thrombotic cardiovascular events in patients with ACS who would undergo PCI. Very recently, high residual platelet reactivity has also been observed with prasugrel in a study carried out in Marseille, France. Ticagrelor, a non-thienopyridine reversible oral inhibitor of platelet P2Y₁₂ receptor, was associated with fewer death, MI and stroke in ACS patients undergoing PCI in the Platelet Inhibition and Patients Outcomes (PLATO) trial. It has been approved for clinical use in Europe, Canada, very recently, in the United States.

Ideal antiplatelet therapy is a long-felt demand for optimal management of coronary artery disease and cardiovascular interventions. Increasing the dose of individual antiplatelet drugs, replacement of one drug by another or increasing the number of antiplatelet drugs i.e. triple antiplatelet regimen could not achieve the goal of optimum platelet inhibition. The novel drugs, including third generation ADP P2Y₁₂ antagonists tend to overcome some of the limitations associated with the already-established agents by producing faster, more potent and less variable platelet inhibition. However, this apparent gain is often at the cost of greater risk of bleeding. Future research will further delineate the safety and efficacy of currently available drugs and open up avenues for optimal antiplatelet therapy.