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Strategy for the Treatment of Clopidogrel Low Responsiveness in Diabetes Mellitus and Stent Implantation

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Platelets play a central role in the pathogenesis of atherothrombosis.[1] Thus, achieving platelet inhibition is an important part of managing patients that have experienced an atherothrombotic event. Dual antiplatelet therapy with clopidogrel plus aspirin has been shown to markedly reduce ischemic events in patients undergoing percutaneous coronary intervention (PCI) and stenting.[2] Despite its proven benefit of dual antiplatelet therapy, diabetic patients remain at increased risk of recurrent ischemic events when compared to non-diabetic patients.

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Recent evidence suggests that diabetic patients are resistant or partially responsive to treatments with a dual antiplatelet effect (especially clopidogrel) which is related to poor clinical outcomes such as stent thrombosis and recurrent atherothrombotic events.[3][4] Yang et al.[5] previously reported that triple antiplatelet therapy (dual antiplatelet plus cilostazol) results in more potent inhibition of adenosine diphosphase (ADP) induced platelet aggregation than dual antiplatelet therapy in patients with diabetes and drug-eluting stent (DES) implantation. These results suggest that triple antiplatelet therapy is a treatment option for amelioration of low responsiveness to clopidogrel in diabetes mellitus (DM).

No treatments of clopidogrel low responsiveness in DM have been reported to date. An initial approach to clopidogrel low responsiveness was considered to be a correctable cause of resistance, including hyperglycemia, noncompliance, insulin resistance (metabolic syndrome) and drug interaction.

Currently, practical strategies to overcome clopidogrel low responsiveness include 1) addition of cilostazol, 2) increasing the dose of antiplatelet agents, and 3) the use of new drugs, such as prasugrel or ticagrelor.

Adding Cilostazol

Cilostazol is a potent oral antiplatelet agent with a rapid onset of action that selectively inhibits phosphodiesterase III and increases cyclic adenosine mono phosphate (cAMP) levels in platelets. The increase in cAMP blocks all activating pathways in platelets, including ADP-induced platelet activations.[6]

An OPTIMUS-2 study[7] of randomized crossover platelet function study in patients with type 2 DM and coronary artery disease following dual antiplatelet therapy revealed that the reduced platelet inhibition of P_2Y_{12} signaling can be enhanced by adjunctive treatment with cilostazol when compared with dual antiplatelet therapy. Thus, cilostazol led to significantly increased P_2Y_{12} platelet inhibition, as measured by flow cytometry and light transmission aggregometry. These findings were similar to the results of a study conducted by Yang et al. Several clinical studies have shown that triple antiplatelet therapy has better clinical outcomes than dual antiplatelet therapy in patients undergoing PCI and coronary stenting.

Lee et al.[8] compared the clinical benefit undergoing PCI between dual antiplatelet therapy (aspirin plus clopidogrel or ticlopidine, group I, n=1,597) and triple antiplatelet therapy (aspirin plus clopidogrel or ticlopidine plus cilostazol, group II, n=1,415) groups. They found that stent thrombosis within 30 days was significantly lower in group II (0.1%) than in group I (0.5%; p=0.024). Additionally, the independent predictors of stent throm-

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bosis were found to be primary stenting {hazard ratio (HR) 7.9, 95% confidence interval (CI) 2.0 to 30.8, p=0.003} and triple therapy (HR 0.12, 95% CI 0.015 to 0.98, p=0.048). They concluded that triple antiplatelet therapy more effectively prevented thrombotic complications after stenting without an increased risk of side effects when compared to dual antiplatelet. These bench and clinical data indicated that adjunctive treatment with cilostazol may improve platelet inhibition in diabetic patients.

Increasing Dose of Clopidogrel

A recent study was conducted to evaluate the efficiency of an 150 mg oral maintenance dose of clopidogrel.[9] Sixty patients that were pre-treated with 600 mg of clopidogrel and had a successful PCI after 12 hours were included in this trial. The patients were divided into groups that received one of two clopidogrel daily maintenance doses (75 or 150 mg) for 30 days in a double-blind randomized manner. Platelet function was evaluated 30 days after intervention by optical aggregometry and a VerifyNow P_2Y_{12} assay. Administration of an 150 mg oral maintenance dose of clopidogrel resulted in more intense inhibition of platelet aggregation than administration of the currently recommended 75 mg maintenance dose. An OPTIMUS study selectively examined type 2 DM[10] and found that the use of a large maintenance dose resulted in higher platelet inhibition than the 75 mg clopidogrel maintenance dose. Large scale clinical data (CURRENT/OASIS 7) was recently presented at the European Society of Cardiology (ESC) 2009 meeting. These data indicated that doubling the loading and maintenance doses of clopidogrel used to treat patients with acute coronary syndrome undergoing PCI significantly reduced stent thrombosis and cardiovascular events without inducing a significant increase in major bleeding. These data suggest that increasing the dose of clopidogrel may ensure an adequate platelet response.

Use of New Thienopyridines

Additional agents that might be potential alternatives to overcome the low responsiveness associated with clopidogrel such as pasugrel,[11] AZD 6140 (ticagrelor)[12] and cangrelor[13] are currently being evaluated in clinical trials.

Prasugrel is a new thienopyridine derivative that produces more potent platelet inhibition and a rapid onset of action that is associated with irreversible P_2Y_{12} receptor blockade. The latter properties of prasugrel may provide a superior alternative to clopidogrel, with less response variability and a decreased prevalence of non-responsiveness. Brandt et al.[11] compared the rate of onset, magnitude, and consistency of platelet inhibition after administration of prasugrel or clopidogrel to relate platelet inhibition to systemic exposure to each active metabolite. Inhibition of platelet aggregation after treatment with prasugrel was significantly higher (p<0.01) than after treatment with clopidogrel from 15 minutes through 24 hours due to ADP induced platelet aggregation. Moreover, the response to prasugrel was more consistent than the response to clopidogrel. These results suggest that treatment with 60 mg prasugrel results in more rapid, potent, and consistent inhibition of platelet function than treatment with 300 mg clopidogrel. A TRITON-TIMI 38 trial[14] compared the effects of prasugrel and clopidogrel in patients (n=13,608) with moderate to high risk acute coronary syndrome (ACS) who were undergoing PCI. A composite end point of death, myocardial infarction and stroke occurred in 12.1% of the clopidogrel group and 9.9% of the prasugrel group (HR: 0.81, p<0.001). However, major bleeding occurred in 1.8% of the clopidogrel group and 2.4% of the prasugrel group (HR 1.32, p=0.03).

Ticagrelor is an oral and reversible P_2Y_{12} receptor blocker that does not require hepatic conversion to an active metabolite and produces an overall superior ADP-induced platelet inhibition with less response variability than clopidogrel. Ticagrelor has fast onset and offset actions that may be advantageous in patients who have to undergo immediate surgery.[12] A PLATO trial (n=18,624) was conducted to compare treatment with ticagrelor (180 mg loading dose followed by 90 mg twice daily) to treatment with clopidogrel (300 to 600 mg loading dose followed by 75 mg daily) for the prevention of cardiovascular events and the results were recently presented at the ESC 2009 meeting. The primary composite of death, myocardial infarction and stroke was found to be reduced from 11.7% to 9.8% (HR, 0.84; p<0.001). In addition, the total mortality was reduced from 5.9% to 4.5% (p<0.001). However, there was no difference in total major bleeding between the two groups (11.6% vs. 11.2%; p=0.434).

Treatment with new thienopyridines instead of clopidogrel in patients with ACS or PCI may provide good results in cardiovascular disease (CVD) endpoints and potential alternatives to low responsiveness to clopidogrel.

REFERENCES

1) Ruggeri ZM. *Platelets in atherothrombosis. Nat Med 2002;8:1227-34.*
2) Steinhubl SR, Berger PB, Mann JT 3rd, et al. *Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411-20.*
3) Colwell JA, Nesto RW. *The platelet in diabetes: focus on prevention of ischemic events. Diabetes Care 2003;26:2181-8.*
4) Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. *Platelet function profiles in patients with type 2 diabetes and coronary artery disease on combined aspirin and clopidogrel treatment. Diabetes*

2005;54:2430-5.

5) Yang TH, Kim DI, Kim JY, et al. *Comparison of triple anti-platelet therapy (aspirin, clopidogrel, and cilostazol) and double antiplatelet therapy (aspirin and clopidogrel) on platelet aggregation in type 2 diabetic patients undergoing drug-eluting stent implantation. Korean Circ J 2009;39:462-6.*
6) Tanaka T, Ishikawa T, Hagiwara M, Onoda K, Itoh H, Hidaka H. *Effects of cilostazol, a selective cAMP phosphodiesterase inhibitor on the contraction of vascular smooth muscle. Pharmacology 1988;36:313-20.*
7) Angiolillo DJ, Capranzano P, Goto S, et al. *A randomized study assessing the impact of cilostazol on platelet function profiles in patients with diabetes mellitus and coronary artery disease on dual antiplatelet therapy: results of the OPTIMUS-2 study. Eur Heart J 2008;29:2202-11.*
8) Lee SW, Park SW, Hong MK, et al. *Triple versus dual antiplatelet therapy after coronary stenting: impact on stent thrombosis. J Am Coll Cardiol 2005;46:1833-7.*
9) von Beckerath N, Kastrati A, Wieczorek A, et al. *A double-blind, randomized study on platelet aggregation in patients treated with a daily dose of 150 or 75 mg of clopidogrel for 30 days. Eur Heart J 2007;28:1814-9.*
10) Angiolillo DJ, Shoemaker SB, Desai B, et al. *A randomized comparison of a high clopidogrel maintenance dose in patients with diabetes mellitus and coronary artery disease: results of the OPTIMUS (Optimizaing anti-Platelet Therapy In diabetes MellitUS) study. Circulation 2007;115:708-16.*
11) Brandt JT, Payne CD, Wiviott SD, et al. *A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. Am Heart J 2007;153:66, e9-16.*
12) Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. *Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. Eur Heart J 2006;27:1038-47.*
13) Fugate SE, Cudd LA. *Cangrelor for treatment of coronary thrombosis. Ann Pharmacother 2006;40:925-30.*
14) Wiviott SD, Braunwald E, McCabe CH, et al. *Prasugrel versus clopidogrel in patients with acute coronary syndrome. N Engl J Med 2007;357:2001-15.*