

Aspirin and clopidogrel resistance in patients with diabetes mellitus

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We read with interest the review paper on aspirin and clopidogrel resistance by Wang et al.¹ We agree that it is an emerging entity with important clinical implications. Nevertheless, we were surprised that very little emphasis was put on the antiplatelet agent resistance of diabetic patients. Only one short sentence mentioned that hyperglycaemia may decrease the effectiveness of antiplatelet therapy by increasing reactive oxidant species. Still the specific case of diabetic patients is of major interest as diabetes mellitus, especially type 2 diabetes, is an increasing cause of cardiovascular disease worldwide. Antiplatelet therapy is a cornerstone in the prevention and treatment of cardiovascular disease in any at-risk individual, including patients with diabetes. However, recent observations showed that patients with diabetes may show both acetylsalicylic acid (aspirin)² and clopidogrel³ resistance.

Placebo-controlled randomized clinical trials with aspirin in the diabetic population are scarce. However, post hoc analysis of large clinical studies of primary and secondary prevention consistently showed a less-effective cardiovascular protection by aspirin when compared with results observed in the non-diabetic population.² A so-called aspirin resistance assessed by an in vitro platelet aggregation test was present in almost 20 % of diabetic patients, more in those with type 2 than in those with type 1 diabetes.^{2,4} Although we are at the very beginning of complete understanding of 'aspirin resistance', several potential molecular mechanisms of this phenomenon in diabetes have been evidenced.^{2,4} Diminished susceptibility of various platelet proteins and receptors on blood platelet membranes to acetylation, because of glycation due to high ambient glucose, might determine platelet 'insensitivity to aspirin' in diabetic patients. Although higher concentrations of aspirin could counteract the effects of hyperglycaemia,⁴ it has been suggested that one simple mean to overcome aspirin resistance might be to increase the daily dosage of aspirin from 100 to 300 mg among diabetic patients.² However, recent guidelines still recommend 100–162 mg/day.

Although patients with type 2 diabetes seem to benefit most from clopidogrel, a P2Y₁₂ receptor antagonist, compared with aspirin, they still show a reduced responsiveness to clopidogrel compared with non-diabetic patients.⁵ Insulin-treated patients with type 2 diabetes have greater ADP-induced platelet aggregation compared with non-insulin-treated diabetic patients while on dual aspirin–clopidogrel oral therapy.³ The alteration of the P2Y₁₂-dependent pathway of platelet reactivity in patients with diabetes might partially explain the negative results of CHARISMA.⁶ In this trial, 42% of the 15 603 randomized patients had diabetes (17% insulin-treated), with no significant better cardiovascular protection by the clopidogrel plus aspirin combination vs. aspirin alone. Whether more potent P2Y₁₂

antagonism using a higher maintenance dose of clopidogrel or novel antagonists will be able to inhibit more efficiently the upregulated P2Y₁₂ pathway in platelets of patients with type 2 diabetes is currently under investigation. Similarly, the potential add-on value of thiazolidinediones (glitazones) to antiplatelet agents also deserves further studies.² In the future, individualized and more aggressive antiplatelet therapeutic approaches should be considered to provide further protection to these high-risk patients with diabetes mellitus.

References

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