COMMENTARY

Clopidogrel application: beyond coronary artery disease

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ABSTRACT

Dual antiplatelet therapy with aspirin and clopidogrel, a P2Y12 antagonist, is a cornerstone for treatment of patients with stroke, peripheral arterial disease and acute coronary artery disease, followed with or without percutaneous coronary intervention. In the present issue of Clinical Science, Giachini and co-workers found that clopidogrel could normalize the increased phenylephrine-induced vascular contraction and the impaired acetylcholine-induced vasodilation in mesenteric arteries from AngII (angiotensin II)-infused Sprague–Dawley rats. This might develop a new area for clopidogrel application; however, whether clopidogrel can improve arterial function in patients with hypertension or diabetes, or if clopidogrel outweights the beneficial effect of aspirin in those patients, remains an open field for future inquiry.

Platelets, normally circulating in resting form, respond to vascular injury by adhering to the damaged vessel wall. Activation results in their aggregation and thrombus formation. ADP, an important platelet agonist in vivo, has two types of receptors in the platelet plasma membrane: P2Y1 and P2Y12. P2Y12 is the predominant receptor involved in ADP-stimulated platelet aggregation and secretion [1].

The two currently FDA (Federal Drug Administration)-approved thienopyridine P2Y12 antagonists, ticlopidine and clopidogrel, metabolized into active metabolites through cytochrome P450 in the liver, irreversibly antagonize the P2Y12 receptor [2]. Ticlopidine, the first FDA-approved P2Y12 antagonist, has been largely replaced in clinical practice by clopidogrel because of more convenient dosing and fewer side effects.

Large multi-centre randomized controlled trials have demonstrated the beneficial effects of clopidogrel in patients with coronary artery disease. In patients with acute coronary syndrome, including unstable angina, ST-elevation or non-ST elevation myocardial infarction [3], CURE (Clopidogrel in Unstable angina to prevent Recurrent Events), COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) and CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy - Thrombolysis in Myocardial Infarction 28) trials found that clopidogrel, as compared with placebo, reduces by 20–31% the primary end point of myocardial infarction, stroke and cardiovascular death in a 12-month follow-up. In patients with stable cardiovascular disease or asymptomatic patients with multiple cardiovascular risk factors, there is no obvious reduction in the rate of myocardial infarction, stroke or death from cardiovascular causes, as compared with aspirin alone in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial. Moreover, clopidogrel increased the risk of moderate-to-severe bleeding.

Key words: ADP, angiotensin II, clopidogrel, endothelium, hypertension, mesenteric artery, P2Y receptor.

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; AngII, angiotensin II; CABG, coronary artery bypass grafting; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; CURE, Clopidogrel in Unstable angina to prevent Recurrent Events; FDA, Federal Drug Administration; 2-MeS-ADP, 2-methylthio-ADP; PAD, peripheral artery disease.

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The American College of Chest Physicians currently recommends the use of clopidogrel with aspirin in patients who undergo CABG (coronary artery bypass grafting) [4]. However, a recent systematic review of published articles on the use antithrombotic agents in patients who had CABG, including CURE, CAPRIE (Clopidogrel versus Aspirin in Patients at risk of Ischemic Events), CREDO (Clopidogrel for the Reduction of Events During Observation) and CHARISMA, does not show a clear clinical benefit of clopidogrel when given in addition to aspirin after CABG [4]. For those patients with stroke, owing to a lack of clinical-trial-based evidence, the AHA (American Heart Association)/American Stroke Association guidelines do not recommend the early administration of clopidogrel or aspirin. For the long-term secondary prevention of non-cardioembolic ischaemic stroke, the AHA recommends antiplatelet therapy using aspirin and/or clopidogrel [5]. The ACC (American College of Cardiology) and AHA have jointly published guidelines for the management of PAD (peripheral artery disease). Aspirin and clopidogrel are the only antiplatelet agents recommended for cardiovascular risk reduction in patients with PAD [6].

Besides the above-mentioned diseases, risk factors, including hypertension, diabetes, dyslipidaemia and smoking, also lead to artery dysfunction even at an early stage, e.g. increased arterial vasoconstriction or impaired vasodilation. In the present issue of Clinical Science, Giachini and co-workers [7] found that clopidogrel could normalize the increased phenylephrine-induced vascular contraction and impaired acetylcholine-induced vascular dilatation in mesenteric arteries from AngII (angiotensin II)-infused hypertensive rats. This finding might develop a new area for clopidogrel application, especially for those atherosclerotic risk factor diseases which impair artery function even at an early stage. In fact, there is increasing evidence using the beneficial effect of clopidogrel on endothelial function and hypertension [8]. A clinical study found that clopidogrel dose-dependently improved flow-mediated dilation of the brachial artery [9]. Besides preventing platelet aggregation, clopidogrel also increases endothelial NO bioavailability [10], decreases serum levels of CD40 ligand, CRP (C-reactive protein) and P-selectin, decreases platelet-leucocyte aggregate formation, and decreases pro-inflammatory and prothrombotic-related events in humans [8]. Beneficial effects of clopidogrel on inflammatory markers have been demonstrated across the spectrum of atherothrombotic disease and its risk factors (hypertension and diabetes, and patients with acute coronary syndrome, acute ischaemic stroke and those with PAD). Owing to the above-mentioned evidence and the clinical findings, ACC/AHA guidelines recommend that antiplatelet medication, including aspirin or clopidogrel, should be used for high-risk patients, especially for those with a 10-year risk of cardiovascular disease and stroke greater than 10%. The AHA/ACC recommends the use of clopidogrel in instances of aspirin allergy or intolerance. Owing to the lack of support from evidence-based medicine, whether clopidogrel can improve the arterial function in patients with hypertension or diabetes, or if clopidogrel outweighs the beneficial effects of aspirin in those patients, remains an open field of future inquiry.

To determine whether clopidogrel exerts its effect on vascular contraction/vasodilation via direct or indirect mechanisms, Giachini et al. [7] studied the effect of a P2Y12 agonist 2-MeS-ADP (2-methylthio-ADP). They showed that 2-MeS-ADP induced endothelium-dependent relaxation and vasoconstriction to the same degree in both vehicle and AngII-infused rats, indicating that the beneficial effects of clopidogrel on vascular function are independent of the P2Y12 receptor. NO and prostanoid synthesis inhibitors abolished the beneficial effect of clopidogrel, indicating an intermediary role of NO and prostanoids. One issue not addressed in the study by Giachini et al. [7] is whether or not clopidogrel altered the levels of NO and prostanoids in plasma or artery, which might provide the biochemical evidence for the beneficial effect of clopidogrel. Whether or not the beneficial effect of clopidogrel on vascular function is related to normalization of some humoral or hormonal factors involved in the pathogenesis of hypertension remains unclear.

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REFERENCES


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