Diabetic atherothrombosis: helpful adjunctive therapy

James H. Chesebro*

Cardiovascular Division, UMass Medical School and Memorial Medical Center, 55 Lake Ave N, Worcester, MA 01655-0002, USA

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This editorial refers to ‘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,’† by D.J. Angiolillo et al., on page 2202

About 90% of type 2 diabetes is attributed to excess weight, which is present in 1.1 billion adults worldwide, and in westernized urban populations the prevalence of diabetes ranges from 14 to 20%. Diabetic patients have more cardiovascular events, which are more severe, with increased morbidity and mortality. Diabetes mellitus and the adequacy of glycaemic control by lifestyle and medical therapy affect atherothrombosis via alteration of arterial rheology, the arterial wall substrate and blood thrombogenicity.

The rheology of blood flow in diabetics is worsened by physical obstruction and endothelial dysfunction causing vasoconstriction, which is, in part, worsened by decreased nitric oxide synthesis and increased thromboxane levels. Arterial plaque which is more prone to disruption and provides increased substrate for thrombosis, is worsened by a higher density of activated macrophages, tissue factor and glycosylated collagen in lesions from diabetics vs. non-diabetics. Diabetics have increased blood clotting, especially when their diabetes is poorly controlled, and often have increased serum fibrinogen, plasminogen activator inhibitor 1 (PAI-1), tissue-type plasminogen activator and coagulation factors II, V and VII, and increased numbers of glycoprotein receptors on platelets as well as increased D-dimer, von Willebrand factor antigen, anti-plasmin and decreased antithrombin III.

Thus, the problem of increased atherothrombosis with increased cardiovascular events in diabetics is multifactorial but, importantly, is also related to decreased intraplatelet cAMP levels, which contributes to the reduced platelet inhibition following P2Y12 receptor antagonist therapy with clopidogrel in diabetics, i.e. the reduced platelet inhibition is caused by dysregulation of intraplatelet signalling. Thus, it was logical to test cilostazol, which increases intraplatelet cAMP levels, in diabetic patients to see if treatment would enhance inhibition of P2Y12 receptor signalling and thus rationalize the addition of this therapy in order to reduce cardiovascular thrombotic events, including stent thrombosis and restenosis, in diabetics. A randomized crossover platelet function study by Angiolillo and colleagues in patients with type 2 diabetes mellitus and coronary artery disease on dual antiplatelet therapy with aspirin and clopidogrel shows that the reduced platelet inhibition of P2Y12 signalling can be enhanced by adjunctive treatment with cilostazol compared with dual antiplatelet therapy without cilostazol. Thus, cilostazol significantly increased P2Y12 platelet inhibition, as measured by flow cytometry and light transmission aggregometry, and it decreased P2Y12 platelet reactivity to a greater extent than occurred with dual clopidogrel and aspirin antiplatelet therapy without cilostazol.

Cilostazol reversibly inhibits phosphodiesterase III, the enzyme which degrades cAMP, and thereby increases cAMP in platelets and blood vessels (endothelial and smooth muscle cells), leading to inhibition of platelet aggregation and promotion of vasodilation, respectively. It is extensively metabolized by hepatic P450 enzymes, the metabolites being largely excreted in the urine. Two metabolites are active, one of which appears to account for at least 50% of the pharmacological activity (inhibition of phosphodiesterase III activity). Cilostazol and its active metabolites have elimination half-lives of about 11–13 h and the drug is therefore administered at 100 mg every 12 h. Vasodilation is greater in femoral beds than in the carotid, vertebral or superior mesenteric arteries, with no response in renal arteries (Physicians Desk Reference—Pletal tablets, Otsuka). Thus, cilostazol is currently approved by the FDA only for symptomatic relief of claudication in patients with peripheral vascular disease and in Japan for stroke prevention.

Cilostazol also reduces neointimal proliferation after coronary stenting. When added to dual antiplatelet therapy, cilostazol reduced restenosis after bare metal stenting (BMS) in diabetics and non-diabetics and patients with small vessels. Cilostazol significantly reduced late loss at 6 months after drug-eluting stent (DES) implantation and reduced the occurrence of target lesion revascularization and major adverse cardiac events in patients with long coronary lesions; 33% of the patients had diabetes.

* Corresponding author: Tel: +01 904 253 2000, Fax: +01 904 953 2911, Email: chesebj@ummhc.org
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In diabetic patients, triple antiplatelet therapy (aspirin, clopidogrel and cilostazol, n = 200) after DES implantation decreased angiographic restenosis and the extent of late loss, resulting in reduced risk of 9-month total lesion revascularization (TLR) compared with dual antiplatelet therapy (aspirin and clopidogrel, n = 200) (2.5 vs. 7.0%, P = 0.034). At 9 months, major adverse cardiac events, including death, myocardial infarction and TLR, tended to be lower in the triple antiplatelet than in the standard group (3.0 vs. 7.0%, P = 0.66). Meta-analysis of 23 randomized clinical trials (5428 patients) in whom a DES was implanted, with median follow-up of 6 months, showed significantly reduced binary angiographic restenosis [relative risk, RR = 0.60 (range, 0.49–0.73), P < 0.001] and reduced repeat revascularization [RR = 0.69 (0.55–0.86), P < 0.001]. Cilostazol appeared safe, with no significant increase in-stent thrombosis or bleeding. However, small study bias was evident for both restenosis endpoints. Thus, cilostazol appears effective and safe for reducing restenosis in both diabetic and non-diabetic patients with either BMS or DES.

Cilostazol is widely used in Asian countries for preventing coronary stent thrombosis. A non-randomized, open-label, retrospective study comparing dual antiplatelet therapy vs. triple antiplatelet therapy including cilostazol showed significantly lower stent thrombosis at 30 days in the triple therapy group (0.07%, 1 of 1415 patients) than in the dual therapy group (0.56%, 9 of 1597 patients) (P = 0.024), and triple therapy did not increase the risk of side-effects, including bleeding. Larger randomized clinical trials are needed, especially in diabetic patients, for evaluating coronary stent thrombosis and, in more North American and European patients, to evaluate restenosis. Triple antiplatelet therapy has not increased bleeding compared with dual antiplatelet therapy. Thus, triple antiplatelet therapy using cilostazol for 6–9 months appears useful and acceptable for reducing restenosis. However, more and larger randomized trials are needed to test the antithrombotic effectiveness of triple antiplatelet therapy including aspirin, clopidogrel and cilostazol. This could be compared with dual antiplatelet therapy with aspirin and clopidogrel and dual therapy with aspirin plus prasugrel for reducing myocardial infarction, stent thrombosis, and urgent target vessel revascularization, while also testing the safety of each treatment against bleeding.

Elimination or better control of diabetes also reduces atherothrombosis. Coordination therapies are therefore needed. These include lifestyle improvement with weight reduction (targeting a normal BMI of 25), which reduces the number of adipocytes and their production of retinol-binding protein-4, which causes insulin resistance with hyperglycaemia, dyslipidaemia with hypertiglyceridaemia, and low high-density lipoprotein cholesterol (HDL-C), endothelial dysfunction and increased systolic blood pressure. Daily walking exercise decreases the need for insulin, improves endothelial dysfunction, raises HDL-C and reduces hypertension, and, with normalization of body weight, should be a part of every cardiovascular rehabilitation programme. Additional diabetic therapy with the use of pioglitazone, an agonist of the peroxisome proliferator-activated receptor PPAR-γ, is anti-inflammatory, increases arterial cholesterol efflux and HDL-C synthesis, and causes significant reduction in all-cause mortality, non-fatal myocardial infarction and stroke in type 2 diabetics, while reducing the need to add insulin to glucose-lowering regimens compared with placebo.

Thus, although cilostazol appears useful for reducing restenosis after coronary stenting, in diabetics as well as other patients, and has a good potential for safely reducing thrombotic events in diabetics without enhancing bleeding, comprehensive treatment of type 2 diabetic patient should always include weight normalization and daily exercise, along with improved glycaemic control, including the recently studied thiazolidinedione pioglitazone, to maximize reduction of cardiovascular events.

Conflict of interest: none declared.

References