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Editorial

# Antiplatelet Drugs and Endothelial Function

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Antiplatelets drugs, particularly cilostazol, an inhibitor of phosphodiesterase Ⅲ (PDE Ⅲ), are widely used for the treatment of ischemic stroke, transient ischemic attack, and peripheral arterial disease (PAD). The use of cilostazol reduces cardiovascular morbidity and mortality in patients with PAD as well as in patients with coronary artery disease (CAD)[1]. Although the mechanisms underlying the antiatherogenic effects of cilostazol remain unclear, cilostazol-induced improvement in endothelial function should contribute to the reduction in cardiovascular events. Endothelial dysfunction is the initial step in the pathogenesis of atherosclerosis, leading to cardiovascular events[2]. CAD is also associated with endothelial dysfunction mediated through reduced nitric oxide (NO) bioavailiability[3]. In a pathophysiological state of endothelial function, disruption of a balance between antithrombosis and pro-thrombosis leads to platelet aggregation. The use of cilostazol is expected to prevent cardiovascular events through an improvement in endothelial function. Indeed, previous studies have shown that cilostazol improves endothelial function both in smokers and patients with silent cerebral lacunar infarcts with hypercholesterolemia[4, 5].

Although the precise mechanism of cilostazol-induced improvement in endothelial function has not been fully clarified, it is believed that cilostazol increases NO production by an increase in endothelial NO synthase (eNOS) activity and decreases NO inactivation by a decrease in oxidative stress. Under a physiological condition, a normal interaction between platelets and endothelial cells is maintained by vasoactive agents and cytokines derived from cells and binding of their receptors. Cilostazol inhibits PDE Ⅲ in platelets through an increase in adenosine 3′,5′-cyclic monophosphate (cAMP) content and activation of protein kinase A, resulting in antiplatelet aggregation. It is expected that cilostazol restores an abnormal interaction between platelets and endothelial cells. Inhibition of PDE Ⅲ by cilostazol in vascular smooth muscle cells induces peripheral vasodilation through an increase in cAMP content and activation of protein kinase A, resulting in an increase in shear stress. Shear stress increases NO production through the activation of the Akt/PI3 pathway in endothelial cells. In addition, Kawabe-Tako *et al.*[6] reported that cilostazol promoted the mobilization of endothelial progenitor cells (EPCs) from bone marrow and endothelial regeneration in a rat carotid balloon injury model. In a clinical setting, Ueno *et al.*[7] showed a cilsotazol-induced increase in the number of circulating EPCs in patients with diabetes who had cerebral ischemia. Repair and regeneration of endothelial cells induce an increase in NO production from endothelial cells, and increased NO contributes to an increase in the number and enhancement of the function of EPCs, resulting in a benign circle between NO and EPCs. Rho-associated kinase (ROCK), one of the first downstream targets of the small GTP-binding protein Rho A, plays an important role in the regulation of vascular smooth muscle contraction, endothelial function, and many cellular functions. Activation of the RhoA/ROCK pathway impairs NO bioavailability through the downregulation of eNOS mRNA stability and inhibition of eNOS protein phosphorylation at Ser 1177 via the Akt/PI3K pathway[8]. It is likely that there is an

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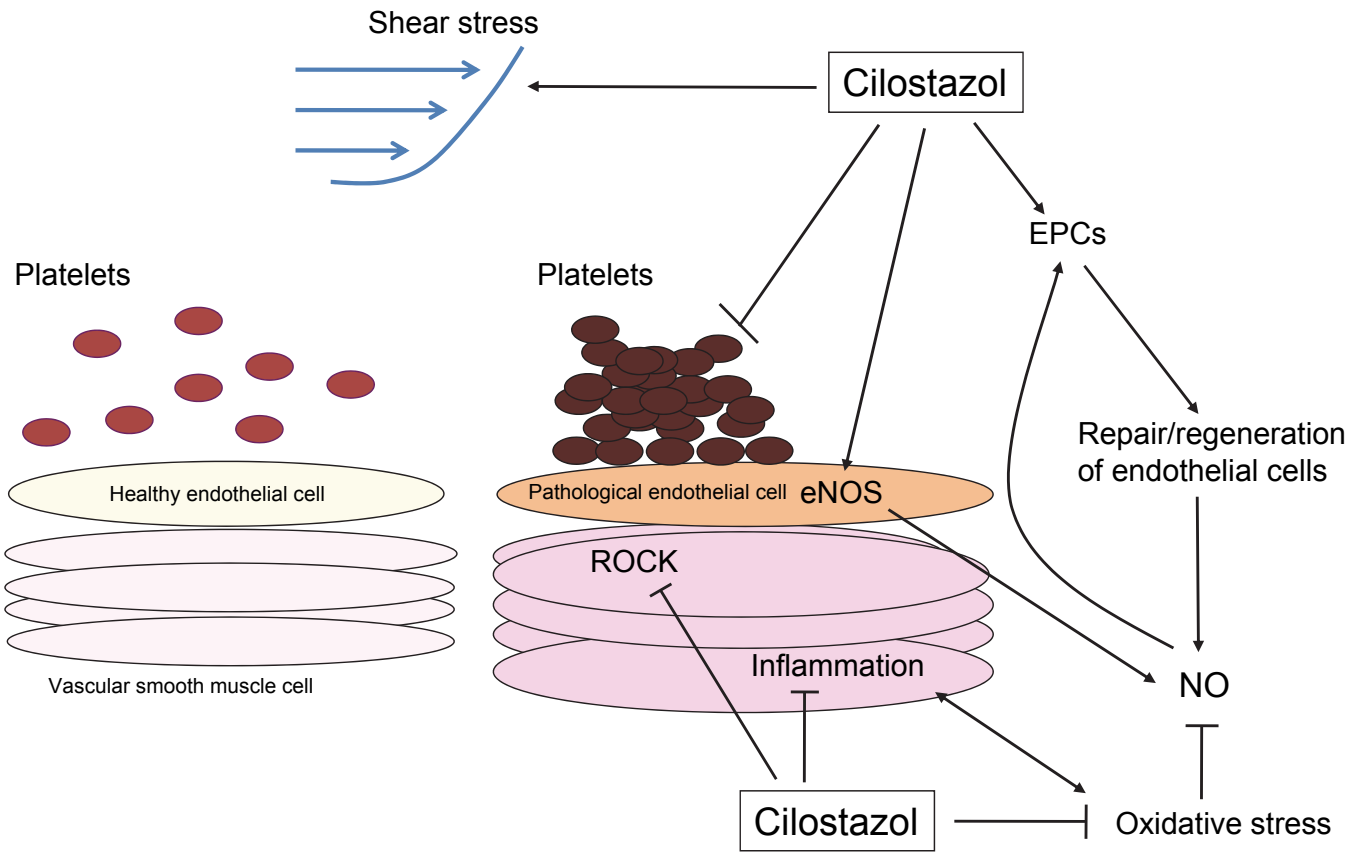


**Fig. 1.** Putative mechanisms by which cilostazol improves and augments endothelial function. eNOS, endothelial nitric oxide synthase; EPC, endothelial progenitor cells; ROCK, rho-associated kinase.

interaction between ROCK activity and eNOS activity. Sheu *et al.*[9] showed that cilostazol suppresses ROCK-related protein expression in leukocytes in patients with PAD. Therefore, the inhibition of ROCK activity by cilostazol is related to the activation of the eNOS/NO pathway. Cilsotazol also has an antiinflammatory property and may reduce the inflammation-related increase in oxidative stress in vascular smooth muscle cells and endothelial cells. These findings suggest that cilostazol increases NO production and decreases NO inactivation, leading to an increase in NO bioavailability. The putative mechanisms by which cilostazol improves and augments endothelial function is shown in **Fig. 1**.

In this issue, Mori *et al.*[10] reported that cilostazol did not alter flow-mediated vasodilation (FMD) in patients with CAD, while percent changes in baseline and maximal brachial artery diameters significantly increased after cilostazol treatment for 6−9 months. Although the precise reasons for the discrepant results of previous studies and the study by Mori *et al.* remain unclear, clisotazol-induced enlargement of baseline brachial artery diameter should be a key point of unchanged FMD. As described in the Limitations section, baseline brachial artery diameter is a predominant predictor of FMD. It is difficult to interpret the results for FMD when brachial artery diameter is changed after interventions. In addition, there is concern that cilostazol has no or little beneficial effects on endothelial function in the advanced stage of atherosclerosis.

Unfortunately, there is little information on the effects of antiplatelet drugs such as aspirin, clopidogrel, beraprost sodium, sarpogrelate hydrochloride, abciximab, and eicosapentaenoic acid as well as cilostazol on endothelial function. Future studies are needed to determine whether each antiplatelet drug improves endothelial function in a large population.

## Conflict of Interest

No conflict of interest.

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