Cilostazol to Overcome High On-Treatment Platelet Reactivity in Korean Patients Treated With Clopidogrel and Calcium-Channel Blocker

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Current oral antiplatelet therapy mainly targets the inhibition of cyclooxygenase-1 (COX-1) and the P2Y₁₂ receptor in patients with acute coronary syndrome (ACS) and those treated with percutaneous coronary intervention (PCI).¹ Despite proven clinical efficacy, the persistent ischemic event occurrence (~10%) suggests that dual antiplatelet therapy (DAPT) has reached a ceiling in its effect in attenuating thrombotic events and that some ischemic events are mediated by other pathways (non-COX-1 and non-P2Y₁₂). However, the addition of inhibitors of the platelet thrombin receptor² or coagulation factor³ to DAPT has not been clearly demonstrated to be effective in reducing ischemic event occurrence and has been associated with increased bleeding risk.

Article p2581

Phosphodiesterases (PDEs) are potential targets for inhibition to attenuate adverse cardiovascular events in patients with coronary artery disease (CAD).⁴ The platelet cyclic adenosine 3',5'-monophosphate (cAMP) and cyclic guanosine 3',5'-monophosphate (cGMP) stimulate protein kinases that are critical for regulating cellular function. PDEs convert cAMP and cGMP to inactive 5'-AMP and 5'-GMP, and influence downstream intracellular signaling. PDEs consist of 11 broad families (PDE1–PDE11), and their distribution and function differ according to species.⁴ Cilostazol is a dual inhibitor of PDE3 and adenosine reuptake that may have an important role in reducing ischemic events associated with CAD (Table 1). Cilostazol is a widely used selective and reversible inhibitor of PDE3, which is highly expressed in myocardial and vascular smooth muscle cells (VSMCs) and platelets. Cilostazol also inhibits adenosine reuptake into erythrocytes, endothelial cells, muscle cells, and platelets, thereby increasing interstitial and circulatory adenosine levels at clinically relevant concentrations (~3 μmol/L).⁵ Adenosine activates G-protein-coupled adenosine receptors, possesses a wide range of biological activities and influences cell survival through pre- and post-conditioning processes. In platelets and VSMCs, the interaction of adenosine with G_s-coupled adenosine A₂ receptors results in increased intracellular cAMP. Thus, cilostazol can increase the production and also inhibit the breakdown of cAMP in platelets and VSMCs. In contrast, adenosine mainly

acts on G_i-coupled adenosine A₁ receptors in cardiac myocytes and reduces cAMP generation, which counteracts the cAMP elevation by PDE3 inhibition in the heart. This unique feature may contribute to the observed safety profile of cilostazol, and several studies have suggested a beneficial effect of cilostazol in arrhythmia prevention.⁶

In this issue of the Journal, Lee et al provide more evidence regarding the benefit of adding cilostazol to DAPT ["triple antiplatelet therapy" (TAPT)] in reducing post-PCI clinical events.⁷ In the primary analysis of the CILON-T (influence of Cilostazol-based triple antiplatelet therapy ON ischemic complication after drug-eluting stent implantation) trial,⁸ TAPT did not show superiority in reducing the composite of adverse cardiovascular outcomes after drug-eluting stent implantation despite greater reduction in platelet reactivity assessed by the VerifyNow P2Y₁₂ assay [~45 P2Y₁₂ reaction units (PRU)] compared with DAPT. In the current post hoc analysis of the CILON-T trial, the investigators divided the cohort into 4 groups based on calcium-channel blocker (CCB) prescription and the type of antiplatelet therapy in a 2×2 factorial manner. A significantly greater level of platelet reactivity at discharge was observed in patients treated with CCB and DAPT together compared with DAPT alone (251 vs. 226 PRU; P=0.008), but not in patients treated with TAPT (215 vs. 203 PRU; P=0.294). The composite of cardiac death, non-fatal myocardial infarction and ischemic stroke at 6 months post-PCI was increased in patients treated with CCB in the DAPT group (4.9% vs. 0.9%, P=0.016), but not in the TAPT group (0% vs. 1.8%, P=0.346). CCB use without concomitant cilostazol use was a significant predictor of total thrombotic events, and the addition of cilostazol to DAPT was associated with reduced clinical event occurrence in patients taking CCB (P=0.027 for thrombotic events). This analysis is consistent with earlier findings that adding cilostazol to DAPT following PCI may be beneficial in high-risk patients.⁹

The current study findings are interesting and may be clinically relevant. The same investigators first reported that coadministration of the cytochrome P450 (CYP) 3A4 inhibitor may attenuate clopidogrel response and result in worsened clinical outcomes particularly in patients with the CYP3A5*3/*3 genotype.¹⁰ The latter observation is supported by the findings of the current study. Further support for this observation comes from

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Table 1. Pharmacokinetics, Pharmacodynamics and Mechanisms of Cilostazol^{4–6,18,22}

Drug name	6-[4-(1-cyclohexyl-1 <i>H</i> -tetrazol-5-yl)butoxy]-3,4-dihydro-2(1 <i>H</i>)-quinolinone		
Chemical structure
Mechanism	Inhibition of phosphodiesterase 3 (platelets, VSMC, heart, and adipocytes)→increased cAMP		
Metabolism	Inhibition of adenosine uptake (erythrocytes, platelets, muscle cells, and endothelial cells)→increased adenosine Extensively metabolized by liver *OPC-13015: mainly produced by <i>CYP3A4</i> *OPC-13213: mainly produced by <i>CYP3A5</i> and <i>2C19</i>		
Maximal concentration	3–3.65 h		
Maximal effect	≈6 h (platelet inhibition)		
Excretion	Urine (74%), feces (20%)		
Target effect		PDE3-dependent (cAMP)	PDE3-independent
1. Antiplatelet effect		O	O (adenosine)
2. Vasodilatory effect (VSMC relaxation)		O	O (adenosine)
3. Antiproliferative effect (control of VSMC proliferation and migration)		O	O (adenosine)
4. Effect on endothelial dysfunction (NO release)		Δ	Δ (PGE ₁ , PGI ₂ , Sirt 1)
5. Antiatherogenic effect (decrease of adhesion molecules, control of inflammatory cells and cytokines, etc)		Δ	–
6. Control of dyslipidemia (decrease of triglyceride, and increased HDL-cholesterol and apolipoprotein A ₁)		Δ (lipoprotein lipase)	–
7. Protection against ischemia-reperfusion injury (cytoprotection)		–	Δ (adenosine)
8. Positive chronotropic effect		O	–
Negative chronotropic effect		–	Δ (adenosine)

O, definite; Δ, proven by several studies; VSMC, vascular smooth muscle cell; cAMP, cyclic adenosine-monophosphate; *CYP*, cytochrome P450; PDE, phosphodiesterase; NO, nitric oxide; HDL, high-density lipoprotein; PG, prostaglandin; SIRT, sirtuin.

Table 2. Pharmacokinetics of Cilostazol, and Its Active Metabolites Following Oral Administration of 100 mg Cilostazol Before and After Erythromycin Co-Administration²⁰

Parameter	Cilostazol		OPC-13015		OPC-13213	
	Before	After	Before	After	Before	After
<i>t</i> _{max} (h)	4±2	5±3	7±3	13±9	5±2	46±3
<i>C</i> _{max} (μg/L)	621±172	886±198 (↑ 47%)	129±39	95±28 (↓ 24%)	61±20	78±30 (↑ 29%)
AUC _t (μg/L·h)	8,917±3,252	16,770±9,475 (↑ 87%)	2,667±1,546	2,828±2,165 (↑ 8%)	584±273	1,280±484 (↑ 141%)

*t*_{max}, time to reach maximum plasma concentration; *C*_{max}, maximum plasma concentration; AUC_t, area under the plasma concentration-time curve t.

a novel in vitro pharmacodynamic assay, which demonstrated that *CYP3A4/5* isoenzymes play a significant role in both hepatic oxidation steps of clopidogrel.¹¹ Among subjects homozygous for *CYP2C19**1, Koreans displayed significantly lower *CYP2C19* enzyme activity than Swedes ($P<0.000001$),¹² which may imply that *CYP3A4/5* enzyme activity plays a more important role in clopidogrel metabolism among Koreans.

The addition of cilostazol in PCI-treated patients has been shown to reduce major cardiovascular events such as mortality, myocardial infarction and stent thrombosis.^{7,9} Although the vasodilatory and antiproliferative effects of cilostazol have been proposed to explain its clinical benefit,^{9,13} reduction in these ischemic events are unlikely to be explained by these mechanisms only. To date, several studies have demonstrated that adding cilostazol to DAPT significantly enhances platelet inhibition.^{14–16} Compared with double-dose clopidogrel therapy (150 mg/day), TAPT was associated with a greater decrease in adenosine diphosphate (ADP)-induced platelet aggregation.^{14,15} The latter observation has been consistently observed in various high-risk clinical settings (ACS, diabetes, and complex PCI), including the carriage of the *CYP2C19* loss-of-function allele.^{15,16} In addition, Yang et al¹⁷ reported that platelets expressed the adenosine A_{2b} receptor, which was upregulated under stress in vivo. Adenosine A_{2b} receptor stimulation was associated with decreased expression of the P2Y₁ ADP receptor, implying that adenosine acts in platelets beyond its immediate influence on adenosine reuptake and platelet aggregation. This finding again supports the influence of adenosine on

in vivo platelet aggregation. Taken together, it is important to note that the in vivo antithrombotic effect of cilostazol may not be completely reflected by the ex vivo platelet function test.

The interaction between cilostazol and CCB at the hepatic isoenzyme level cannot be overlooked. The decrease in platelet reactivity by the addition of cilostazol seems to differ between patients with and without CCB coadministration (at discharge: ≈37 vs. 22 PRU, and at 6-month: ≈52 vs. 41 PRU).⁷ Although cilostazol is a direct-acting drug, the 2 major metabolites of cilostazol, OPC-13015 (mainly produced by *CYP3A4*) and OPC-13213 (mainly produced by *CYP3A5* and *2C19*), account for approximately 50% of PDE3 inhibition.¹⁸ Single nucleotide polymorphisms (SNPs) of *CYP2C19* and *CYP3A5* thus may influence the pharmacokinetic and pharmacodynamic properties of cilostazol.^{16,19} Suri et al demonstrated that maximum plasma concentrations of cilostazol and OPC-13213 increased significantly, whereas OPC-13015 concentrations decreased significantly (all $P<0.001$), following erythromycin coadministration in healthy volunteers receiving cilostazol (Table 2).²⁰ It has been demonstrated that OPC-13015 is 3-fold more potent in inhibiting platelet reactivity than cilostazol, whereas OPC-13213 is 3-fold less potent than cilostazol.¹⁸ Taking these findings together, CCB coadministration may moderately enhance the antiplatelet effect of cilostazol.

The current post hoc analysis by Lee et al has several limitations. A great body of data has demonstrated the reduced pharmacodynamic and clinical efficacy of clopidogrel in PCI-treated patients carrying the *CYP2C19* loss-of-function allele.²¹

Although demonstrating the relation of platelet reactivity to the occurrence of clinical events in patients receiving TAPT, the authors should have included the demographic variables, drug–drug interactions and SNPs as a combined variable. The investigators did not mention the time of blood sampling for platelet function measurement after the last-dose administration. In a healthy volunteer study using pharmacokinetic–pharmacodynamic model (a single dose of 100 mg cilostazol),²² peak cilostazol concentration was achieved at 3.65 h, but maximal platelet inhibition was at 6.05 h after cilostazol administration. The maximum pharmacodynamic effect was observed ≈8 h after clopidogrel loading.²³ Because the pharmacodynamic effect of each drug in TAPT can vary, even during maintenance treatment, the specific sampling time may be important for reducing possible confounders. Finally, platelet reactivity was similar or increased after 6-month therapy compared with platelet reactivity measured at discharge. This is not in agreement with other pharmacodynamic studies in which a decrease in platelet reactivity (≈40 PRU) was reported.^{24–26}

The current post hoc analysis has provided more insight regarding the potential benefits of adding cilostazol to DAPT, a strategy that may overcome the limitations of clopidogrel–drug interactions, enhance platelet inhibition, and reduce the occurrence of post-PCI ischemic/thrombotic events without an increase in bleeding risk. However, we must keep in mind that an ex vivo platelet function test alone may not completely reflect the pleiotropic effects of cilostazol therapy.

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