Cilostazol Eliminates Adverse Smoking Outcome in Patients With Drug-Eluting Stent Implantation – Analysis of Longer-Term Follow-up of the CILON-T Randomized Trial –

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**Background:** The present study investigated whether cilostazol can eliminate adverse smoking outcome after percutaneous coronary intervention (PCI).

**Methods and Results:** A total of 914 patients with successful drug-eluting stent (DES) implantation were randomly assigned to dual antiplatelet therapy (DAT; aspirin and clopidogrel, n=457) or to triple antiplatelet therapy (TAT; DAT with cilostazol, n=457). The effect of smoking on 2-year major adverse cardio/cerebrovascular events (MACCE) in both the TAT and DAT groups was evaluated. Total MACCE were not significantly different between the 2 anti-platelet regimens (9.8% in TAT vs. 11.4% in DAT groups, P=0.45), but the adverse effects of smoking on clinical outcome were different between DAT vs. TAT. Current smokers had a higher prevalence of MACCE than non-smokers in the DAT group (16.7% vs. 9.5%, P=0.04). In the TAT group, however, the adverse effect of smoking was abolished (9.2% vs. 10.1%, P=0.85). Regarding the effects of smoking on the antiplatelet effects of DAT or TAT, post-treatment platelet reactivity (in P2Y₁₂ reaction units; PRU) in current smokers was not significantly lower than that in non-smokers in the DAT group, whereas, in the TAT group, it was significantly lower than that of non-smokers (189±88 vs. 216±89 PRU, P=0.01).

**Conclusions:** Adverse clinical effects of smoking may be eliminated by the addition of cilostazol to DAT after DES implantation. This may be due to the stimulation of cilostazol's antiplatelet effects by smoking. (*Circ J* 2014; 78: 1420–1427)

**Key Words:** Cilostazol; Percutaneous coronary intervention; Platelet function test; Smoking
to DAT, but the TAT regimen itself did not reduce ischemic events at 6 months after PCI with DES when compared to DAT, because there were a substantial number of patients who still had high PRU even under TAT, and experienced ischemic events. In contrast, baseline high post-treatment platelet reactivity (PPR), represented by PRU, was identified as an independent predictor of 6-month ischemic events in that study. A recent meta-analysis also confirmed the importance of baseline PPR in predicting clinical outcome.

Smoking has been advocated as a major risk factor for coronary artery disease. It has been reported that smoking is associated with a 2–4-fold increased risk of coronary events including sudden cardiac death, and worsens outcomes after PCI or coronary bypass surgery. Therefore, smoking is a major concern for clinicians treating patients with coronary artery disease. Practical interventions that effectively reduce the risk of smoking, however, are still underdetermined. As we previously reported, PPR as assessed using PRU may be affected by smoking status. Current smoking significantly decreased PRU in a genotype-dependent manner, which could be reversed when smoking is stopped. Therefore, the prognostic meaning of PPR should be evaluated in terms of smoking status, given that smoking status confounds PPR.

The present study was performed to determine (1) whether a 6-month addition of cilostazol to DAT has a potential legacy effect beyond the period of its use; (2) whether cilostazol can eliminate adverse smoking outcome; and (3) whether the prognostic meaning of PPR (according to PRU) is dependent on smoking status, through analysis of the 2-year clinical results from the CILON-T (Influence of CILostazol-based triple antiplatelet therapy ON ischemic complication after drug-eluting stent implantation) trial.

Methods

Study Protocol

The CILON-T trial, a prospective, open-label randomized trial performed at 5 Korean centers, was conducted to investigate the safety and efficacy of TAT (DAT with cilostazol) vs. DAT in reducing 6-month major adverse cardiovascular/cerebrovascular events (MACCE), a composite of cardiac death, non-fatal myocardial infarction (MI), ischemic stroke and target lesion revascularization (TLR) in real-world all-comer patients receiving PCI with DES. The study protocol was approved by the Institutional Review Board of each hospital and informed consent was obtained from each participant. A detailed study protocol has been published, and registered at http://clinicaltrials.gov/(NCT00776828).

Before PCI, loading doses of aspirin (300 mg) and clopidogrel (300–600 mg) were given to patients who had not taken these medications before. After PCI, aspirin (100 mg daily) and clopidogrel (75 mg daily) were given to all patients for at least 6 months. Patients were randomly assigned to TAT or DAT. Patients in the TAT group received a loading dose of cilostazol 200 mg immediately after PCI, and then 100 mg twice daily for 6 months in addition to conventional DAT. Coronary stenting was performed using standard PCI techniques. Information on smoking status was obtained from all patients. Patients who smoked any kind of tobacco on a daily basis within 3 months of index PCI were considered as current smokers, whereas all other patients were considered as non-smokers. Most current smokers (n=198, 86.4%) continued smoking until hospitalization, but stopped during hospitalization. The mean duration of hospitalization was 3 days.

Platelet Function Test

PPR was assessed using the VerifyNow P2Y12 system (Accumetrics, San Diego, CA, USA). This assay mimics turbidometric aggregation and utilizes disposable cartridges containing 20µmol/L ADP and 22nmol/L PGE1. Aggregation testing using ADP as a sole agonist activates P2Y1 and P2Y12 purinergic signaling; adding PGE1 increases the specificity of the test for P2Y12 signaling. In a separate channel of the cartridge in which iso-TRAP (thrombin receptor-activating peptide) is
### Table 1. Baseline Subject Characteristics

| Characteristics     | Total (n=914) | DAT (n=457) | TAT (n=457) | P-value | DAT (n=457) | TAT (n=457) | P-value | Current smoker | DAT (n=120) | TAT (n=337) | Non-smoker | P-value | Current smoker | TAT (n=109) | Non-smoker | P-value |
|---------------------|---------------|-------------|-------------|---------|-------------|-------------|---------|----------------|-------------|-------------|------------|---------|----------------|-------------|------------|---------|
| Age (years)         | 62.8±9.2      | 62.9±9.6    | 0.89        |         | 59.1±10.0   | 64.0±8.6    | <0.001  | 58.8±10.5      | 64.3±8.8    | <0.001      |           |         | 59.1±12.0     | 64.0±8.6    | <0.001    |         |
| Male                | 313 (69.4)    | 311 (68.2)  | 0.69        |         | 115 (95.8)  | 206 (61.1)  | <0.001  | 102 (93.6)     | 207 (59.5)  | <0.001      |           |         | 104 (93.4)    | 196 (60.5)  | <0.001    |         |
| BMI (kg/m²)         | 24.8±3.1      | 25.0±3.4    | 0.34        |         | 24.8±3.2    | 24.8±3.0    | 0.94    | 24.5±2.8       | 25.1±3.5    | 0.07        |           |         | 24.5±2.8      | 25.1±3.5    | 0.07      |         |

#### Previous history

|                      | DAT (n=429) | TAT (n=429) | P-value | DAT (n=429) | TAT (n=429) | P-value | Current smoker | TAT (n=109) | Non-smoker | P-value |
|----------------------|-------------|-------------|---------|-------------|-------------|---------|----------------|-------------|------------|---------|
| Hypertension         | 304 (67.4)  | 294 (64.5)  | 0.35    | 72 (61.0)   | 234 (69.4)  | 0.05    | 59 (54.1)      | 237 (68.1)  | 0.01        |         |         |
| Diabetes             | 144 (31.9)  | 167 (36.6)  | 0.13    | 36 (30.0)   | 107 (31.8)  | 0.72    | 36 (33.0)      | 133 (38.2)  | 0.32        |         |         |
| Dyslipidemia         | 177 (39.2)  | 200 (43.9)  | 0.15    | 46 (38.3)   | 135 (40.1)  | 0.74    | 38 (34.9)      | 161 (46.3)  | 0.03        |         |         |
| PCI                  | 38 (8.4)    | 31 (6.8)    | 0.35    | 9 (7.5)     | 29 (8.6)    | 0.70    | 7 (6.4)        | 25 (7.2)    | 0.78        |         |         |
| CABG                 | 13 (2.9)    | 8 (1.8)     | 0.25    | 0 (1.8)     | 12 (3.6)    | 0.04    | 2 (1.8)        | 7 (2.0)     | >0.99       |         |         |

#### Current smoker

|                      | DAT (n=457) | TAT (n=457) | P-value | Current smoker | TAT (n=109) | Non-smoker | P-value |
|----------------------|-------------|-------------|---------|----------------|-------------|------------|---------|
| No. stents per lesion| 1.2±0.4     | 1.2±0.5     | 0.46    | 1.2±0.4        | 1.2±0.5     | 0.46       | 1.2±0.5  | 0.97        |

Data given as mean±SD or n (%). ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, aldosterone receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; DAT, dual antiplatelet therapy; HDL-C, high-density lipoprotein cholesterol; LAD, left anterior descending artery; LCX, left circumflex artery; LDL-C, low-density lipoprotein cholesterol; LMC, left main coronary artery; MLD, minimum luminal diameter; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; PPI, proton pump inhibitor; RCA, right coronary artery; TAT, triple antiplatelet therapy; TC, total cholesterol; ZES, zotarolimus-eluting stent.
used as an agonist, a baseline value for platelet inhibition (%) without having to wean the patient off antiplatelet treatment was obtained. The VerifyNow P2Y12 assay reported the result as PRU, which was obtained at discharge after the index procedure.

### Study Endpoints and Clinical Follow-up

The primary 2-year outcome was the composite of MACCE including cardiac death, non-fatal MI, ischemic stroke, and clinically driven TLR. Secondary endpoints were all-cause death, and each component of the primary endpoint at 2 years. The cause of death was regarded as cardiovascular unless there was documented evidence of a clear non-cardiovascular cause. MI was defined as creatinine kinase myocardial band ≥3-fold the upper limit of normal. Ischemic stroke was defined as a new focal neurologic deficit of vascular origin lasting at least 24 h that was proven to be non-hemorrhagic on either computed tomography or magnetic resonance imaging. TLR was considered clinically driven when it was associated with typical symptoms on clinical assessment, typical signs on the stress test, or ≥70% diameter stenosis on angiographic follow-up. Clinical follow-up was done by office visit or telephone contact at 1, 3, 6 and 12 months and every 3 months thereafter. Follow-up coronary angiography was performed at 6 months, or earlier if indicated by clinical symptoms or evidence of myocardial ischemia. Follow-up angiography was usually done between 5 and 9 months after PCI. Drug compliance and adverse events were assessed at every visit during the clinical follow-up period.

### Statistical Analysis

Data are given as mean±SD or percentage. Patients were grouped according to antiplatelet regimen (TAT vs. DAT), smoking status (current smoker vs. non-smokers) or both. Continuous variables were compared using Student’s t-test, and categorical variables were compared using chi-squared or Fisher’s exact test. Cumulative event rates during the 2-year follow-up period were analyzed using the Kaplan-Meier method, and the differences between rates were assessed on log-rank test. In order to assess the differential effects of smoking according to time course, landmark analysis was performed at 5 and 9 months after PCI because repeat revascularization was usually performed between 5 and 9 months after index PCI. Multivariable Cox proportional hazard models were used to determine independent predictors for clinical events. The incidence of events according to PRU tertile was estimated on chi-squared test of linear-by-linear association. Two-tailed P<0.05 was considered statistically significant. All data were analyzed using SPSS for Windows 17.0 (Chicago, IL, USA).

### Results

Among 915 patients enrolled in the CILON-T trial, 1 patient in the DAT group was excluded due to follow-up loss, and finally 914 were analyzed in this study (Figure 1). Baseline clinical characteristics according to antiplatelet (DAT vs. TAT) and smoking status (current smoking vs. and non-smoking) are listed in Table 1. Two hundred and twenty-nine patients (25.0%) were identified as current smokers. There were no significant differences in baseline characteristics between the TAT and DAT groups. Current smokers were younger and men were predominant in both the DAT and TAT groups. In the DAT group, previous history of coronary bypass surgery was more frequent in non-smokers, and bifurcation lesions in current smokers. In the TAT group, the proportions of patients with hypertension, dyslipidemia and multi-lesion intervention were higher in non-smokers than in current smokers.

All patients took aspirin during the study period. A small proportion of patients (8.1%) continued cilostazol for >6 months after index PCI. There was no difference in the proportion of patients taking cilostazol >6 months after PCI between smokers and non-smokers (P=0.24). Approximately half of the patients (49.9%) continued clopidogrel >6 months after PCI, and there was no difference in the proportion of patients taking clopidogrel >6 months after PCI between smokers and non-smokers (P=0.11), as well as between the DAT and TAT groups (P=0.73).

### Impact of Smoking Status on 2-Year Clinical Outcome and PPR

Clinical outcome is presented in Table 2. During the 2-year follow-up period, MACCE occurred in 52 patients (11.4%) in the DAT group and in 45 patients (9.8%) in the TAT group, which was not statistically significant (P=0.45). Also, there were no significant differences between the 2 groups in the secondary endpoints, such as death, MI, ischemic stroke, TLR, or any of these events combined in all patients. The impact of smoking on clinical outcome in both the DAT and DAT group was analyzed. In the DAT group, the MACCE rate of smokers was significantly higher than that of non-smokers (16.7% vs. 9.5%, P=0.04). The increased MACCE rate in smokers was mainly

### Table 2. Clinical Outcome During 2-Year Follow-up

| Variable                        | Total (n=914) | DAT (n=457) | TAT (n=457) | P-value |
|---------------------------------|--------------|------------|------------|---------|
| Primary endpoint                |              |            |            |         |
| CD, MI, ischemic stroke and TLR | 52 (11.4)    | 45 (9.8)   | 0.45       |         |
| Current smoker                  | 20 (16.7)    | 32 (9.5)   | 0.04       |         |
| Non-smoker                      | 10 (9.2)     | 35 (10.1)  | 0.85       |         |
| Secondary endpoint              |              |            |            |         |
| Death                           | 12 (2.6)     | 7 (1.5)    | 0.24       |         |
| CD                              | 3 (0.7)      | 2 (0.4)    | 0.65       |         |
| MI                              | 8 (1.8)      | 6 (1.3)    | 0.57       |         |
| Ischemic stroke                 | 6 (1.3)      | 7 (1.5)    | 0.79       |         |
| TLR                             | 41 (9.1)     | 32 (7.0)   | 0.25       |         |
| CD and ischemic stroke          | 17 (3.7)     | 15 (3.3)   | 0.71       |         |

Data given as n (%). CD, cardiac death; MI, myocardial infarction; TLR, target lesion revascularization. Other abbreviations as in Table 1.
DAT). The mean PRU of all the study patients at discharge was 221 ± 86. In the DAT group, smoking status did not significantly affect PRU. In the TAT group, however, smokers had significantly lower PRU than non-smokers (189 ± 88 vs. 216 ± 89, P=0.01; Figure 2C).

Among current smokers, the MACCE rate was lower in the TAT group than in the DAT group (9.2% vs. 16.7%) with marginal significance (P=0.09). There was no difference in the MACCE rates between TAT and DAT in non-smokers (9.5% vs. 10.1%, P=0.80; Table S1).

Smoking Status Determines Prognostic Value of Baseline PPR for 2-Year Clinical Outcome After PCI

In order to assess the influence of smoking on the prognostic power of PPR, we compared the clinical outcomes among the 3 subgroups according to PRU tertiles of baseline PPR both in smokers and non-smokers (Table 3). In non-smokers, the highest PRU tertile had the highest MACCE (14.5% in the highest vs. 11.2% in the middle vs. 6.7% in the lowest, P=0.02) and the highest TLR (11.2% in the highest vs. 6.8% in the middle vs. 5.0% in the lowest, P=0.03). In smokers, however, baseline PRU tertile did not affect clinical outcome (P=0.53), suggesting that smoking status may confound the association driven by the higher TLR (15.3% vs. 6.9%, P=0.01) or MI (3.3% vs. 1.2%, P=0.13). Such an adverse impact of smoking on clinical outcome disappeared, however, in the TAT group (9.2% vs. 10.1%, P=0.85). Cumulative MACCE rates were compared using Kaplan-Meier analysis. In the DAT group, MACCE rates were higher in current smokers than in non-smokers (log-rank P=0.03; Figure 2). This difference was eliminated in the TAT group (log-rank P=0.80; Figure 2B). When we compared the MACCE rates between subjects who had never smoked (n=466) and active smokers who continued smoking until hospitalization (n=198), the MACCE rate was significantly higher in active smokers than in smokers in the DAT group (log-rank P=0.01). The MACCE rates, however, were similar between never smokers and active smokers in the TAT group (log-rank P=0.60; Figure S1).

Landmark analysis showed that adverse smoking effects were significant between 5 and 9 months (log-rank P=0.03), and this smoking hazard was abolished by cilostazol (log-rank P=0.77). There was no difference in the clinical outcomes between smokers and non-smokers regardless of cilostazol use, before 5 months and after 9 months of index PCI (Figure S2).

The VerifyNow P2Y12 assay was performed at discharge after index PCI in 716 patients (n=355 in TAT, n=361 in DAT). The mean PRU of all the study patients at discharge was 221±86. In the DAT group, smoking status did not significantly affect PRU. In the TAT group, however, smokers had significantly lower PRU than non-smokers (189±88 vs. 216±89, P=0.01; Figure 2C).

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Cilostazol Eliminates Smoking Risk

Discussion

The main findings of the present study are: (1) the addition of cilostazol for 6 months to DAT did not reduce 2-year MACCE compared to DAT after DES implantation, negating the legacy effect of cilostazol; (2) smokers had poorer clinical outcome than non-smokers in the DAT group, while smokers had similar outcome to non-smokers in the TAT group, suggesting that cilostazol helps to eliminate adverse smoking outcome or MACCE at 2 years after DES implantation; and (3) the predictive power of PPR on 2-year MACCE was maintained in non-smokers, but lost by smoking.

Influence of Antiplatelet Regimen, TAT, on Clinical Outcome After PCI

There are 2 important factors that affect prognosis after PCI: antiplatelet regimen, and actual platelet reactivity after treatment. In our previous short-term analysis of the CILON-T ran-

between baseline PPR and clinical outcome.

Independent Prognostic Factors for 2-Year Clinical Outcome After PCI

Multivariate Cox proportional hazard regression analysis was performed with relevant factors that were considered to be of potential significance to investigate independent prognostic factors (Table 4). In all subjects, the independent predictor for 2-year MACCE was lesion length (hazard ratio [HR] of long lesion ≥28 mm, 1.77; 95% confidence interval [CI]: 1.10–2.84, P=0.02). The use of cilostazol and baseline PPR were not associated with MACCE in all patients. In non-smokers, however, baseline PPR was a significant predictor of 2-year MACCE (the highest vs. the lowest tertile of PRU: HR, 2.13; 95% CI: 1.03–4.39, P=0.04). Such a prognostic value of baseline PPR for 2-year outcome was cancelled out by smoking in current smokers (the highest vs. the lowest tertile of PRU, HR: 1.28, 95% CI: 0.42–3.86, P=0.65).

### Table 4. Independent Predictors for 2-Year Composite Clinical Outcome†

| Variable                             | Total (n=716) | Current smoker (n=180) | Non-smoker (n=536) |
|--------------------------------------|--------------|------------------------|--------------------|
|                                      | HR (95% CI)  | P-value                | HR (95% CI)        | P-value                |
|                                      | P-value      |                        | P-value            |                        |
| Age ≥65 years                         | 1.12 (0.68–1.83) | 0.64                   | 0.69 (0.24–1.93)  | 0.48                   |
|                                      |              |                        | 1.37 (0.76–2.49)  | 0.28                   |
| Female sex                            | 0.79 (0.33–1.06) | 0.60                   | 0                   | 0.98                   |
|                                      |              |                        | 0.62 (0.33–1.15)  | 0.13                   |
| Diabetes                              | 1.49 (0.91–2.43) | 0.10                   | 1.49 (0.58–3.84)  | 0.39                   |
|                                      |              |                        | 1.50 (0.84–2.67)  | 0.17                   |
| Hypertension                          | 0.80 (0.49–1.34) | 0.41                   | 0.70 (0.27–1.79)  | 0.46                   |
|                                      |              |                        | 0.83 (0.44–1.57)  | 0.58                   |
| Hypercholesterolemia                  | 1.01 (0.62–1.64) | 0.94                   | 1.92 (0.75–4.87)  | 0.16                   |
|                                      |              |                        | 0.86 (0.48–1.53)  | 0.86                   |
| Previous MI                           | 0.26 (0.03–1.92) | 0.26                   | 0                   | 0.98                   |
|                                      |              |                        | 0.34 (0.04–2.48)  | 0.28                   |
| Lesion length ≥28 mm                  | 1.77 (1.10–2.84) | 0.02                   | 2.37 (0.94–5.95)  | 0.64                   |
|                                      |              |                        | 1.64 (0.92–2.89)  | 0.08                   |
| Reference vessel diameter <2.75mm    | 1.32 (0.82–2.13) | 0.24                   | 0.99 (0.40–2.44)  | 0.98                   |
|                                      |              |                        | 1.50 (0.85–2.64)  | 0.16                   |
| Multi-lesion intervention            | 0.93 (0.57–1.53) | 0.79                   | 1.30 (0.50–3.35)  | 0.58                   |
|                                      |              |                        | 0.85 (0.47–1.54)  | 0.60                   |
| Use of cilostazol                    | 0.80 (0.49–1.29) | 0.36                   | 0.66 (0.25–1.74)  | 0.40                   |
|                                      |              |                        | 0.92 (0.52–1.62)  | 0.92                   |
| PRU level at discharge               |              |                        |                    |                        |
| 1st tertile                          | 1            | –                      | 1                   | –                      |
| 2nd tertile                          | 1.18 (0.63–2.20) | 0.59                   | 0.89 (0.32–2.97)  | 0.98                   |
|                                      |              |                        | 1.53 (0.72–3.28)  | 0.26                   |
| 3rd tertile                          | 1.76 (0.97–3.20) | 0.06                   | 1.28 (0.42–3.86)  | 0.65                   |
|                                      |              |                        | 2.13 (1.03–4.39)  | 0.04                   |

†Cardiac death, non-fatal MI, ischemic stroke and TLR. CI, confidence interval. Other abbreviations as in Tables 1–3.

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Table 3. Clinical Outcome According to Baseline PRU

| Event | CD, MI, stroke, TLR | CD, MI, stroke | TLR |
|-------|---------------------|---------------|-----|
| Total (n=716) |                     |               |     |
| 1st tertile (0–184) (n=238) | 22 (9.2) | 6 (2.5) | 17 (7.1) |
| 2nd tertile (185–264) (n=239) | 27 (11.3) | 11 (4.6) | 18 (7.5) |
| 3rd tertile (≥265) (n=239) | 34 (14.2) | 10 (4.1) | 28 (11.7) |
| P-value | 0.11 | 0.32 | 0.1 |

Current smoker (n=180)

| Event | CD, MI, stroke, TLR | CD, MI, stroke | TLR |
|-------|---------------------|---------------|-----|
| 1st tertile (0–182) (n=60) | 9 (15.0) | 2 (3.3) | 6 (10.0) |
| 2nd tertile (183–252) (n=60) | 8 (13.3) | 2 (3.3) | 7 (11.6) |
| 3rd tertile (≥253) (n=60) | 7 (11.6) | 0 | 7 (11.6) |
| P-value | 0.75 | 0.21 | 0.77 |

Non-smoker (n=536)

| Event | CD, MI, stroke, TLR | CD, MI, stroke | TLR |
|-------|---------------------|---------------|-----|
| 1st tertile (0–187) (n=178) | 12 (6.7) | 3 (1.7) | 9 (5.0) |
| 2nd tertile (188–272) (n=179) | 20 (11.2) | 8 (4.4) | 12 (6.8) |
| 3rd tertile (≥273) (n=179) | 26 (14.5) | 9 (5.0) | 20 (11.2) |
| P-value | 0.03 | 0.09 | 0.07 |

Data given as n (%).

PRU, P2Y12 reaction unit. Other abbreviations as in Tables 1,2.
domized trial, baseline PPR was an independent predictor of 6-month ischemic events, whereas antiplatelet regimen TAT was not, because addition of cilostazol in TAT decreased PRU only by 30,19 which was a smaller decrement compared with the more than 100 by prasugrel or 150 by ticagrelor.19 Therefore, the addition of cilostazol in TAT could not significantly reduce the number of patients with high PPR, which is the most important factor associated with actual ischemic events. Several studies have reported the beneficial effects of TAT with cilostazol on cardiovascular outcome that persisted long after discontinuation of its use.20,21 Various activities of cilostazol, besides platelet inhibition, including improved endothelial function, suppression of inflammatory response and reduced neointimal formation,3,4 provide the rationale for a possible legacy effect of TAT. In the present study, however, clinical events at 2 years after DES implantation were not different between the TAT and DAT groups. This finding is in line with recent meta-analyses showing that cilostazol did not reduce mortality or MI at any point during the follow-up between 6 months and 2 years.22,23

Several studies have shown that adding cilostazol to DAT after DES implantation decreased angiographic restenosis compared with DAT.8,9,24 This beneficial effect of cilostazol was more prominent in patients with long coronary lesions and in diabetic patients.9,23 Cilostazol use, however, was not associated with reduction of TLR at 6-month or 2-year follow-up in the present study, and TAT failed to show a beneficial effect even when the patients were stratified according to diabetes or lesion length (data not shown). These null results might have been due to several causes, such as the insufficient numbers of patients with low event rates, the existence of substantial numbers of resistant patients even against TAT, and the possible chronotropic side-effect of cilostazol, which has been already described.19

Protective Effect of Cilostazol Against Adverse Smoking Outcome
Smoking is associated with increased cardiovascular morbidity and mortality by increasing blood pressure and coronary vascular resistance, reducing oxygen delivery, and accelerating platelet aggregation, inflammation and endothelial dysfunction.12–14 Consistent with these findings, the present MACCE rates were higher in current smokers than in non-smokers in the DAT group. This unfavorable effect of smoking, however, was eliminated in the TAT group, suggesting the beneficial effect of cilostazol in current smokers. The mechanisms underlying this effect of cilostazol associated with smoking remain unknown. Nevertheless, there are several possible explanations. In the present study, smoking significantly reduced PPR only in the TAT group but not in the DAT group, and therefore the data support the hypothesis that current smoking stimulates the antiplatelet action of cilostazol. Cigarette smoking is an inducer of cytochrome P450 (CYP)1A2 that transforms clopidogrel into its active metabolite. Therefore, smoking increases the antiplatelet activity of clopidogrel.25 Smoking, however, did not increase PPR in the DAT group in the present study. We think that this may be due to the small number of good responders with a favorable genetic CYP1A2 enzyme status that is associated with increased clopidogrel response among smokers.16 The major pharmacologically active metabolites of cilostazol are also produced via various CYP isoenzymes including CYP1A2.26,27 Although there has been a lack of data on changes in the pharmacokinetics of cilostazol due to smoking, we can consider the possibility that smoking potentially interacts with cilostazol by increasing its active metabolism, resulting in higher plasma concentration. In addition, given the present result of a higher TLR rate in current smokers than in non-smokers in the DAT group but not in the TAT group, an important role of cilostazol in inhibiting vascular smooth cell proliferation and neointimal formation in current smokers can be suggested. Moreover, from the results of previous studies,28,29 improvement of endothelial cell function by cilostazol in current smokers can be suggested as another potential mechanism. Further studies are needed to confirm these hypotheses. The present results suggest that cilostazol may be considered for the improvement of outcome, especially in smokers after DES implantation.

Prognostic Value of PPR
Previously, in the CILON-T trial, we showed that baseline PPR estimated by PRU was an independent predictor of 6-month MACCE in patients with DES implantation.10 In the present study, however, the prognostic power of PPR was weakened. There was a trend in that the 2-year event rate was higher in the upper tertile of PRU on multivariate analysis, with marginal significance. It seems that the relatively small number of ischemic events limited the statistical power and ability to detect the relationship. Interestingly, when we categorized the subjects according to smoking status, the predictive power of PPR changed. PPR had a significant impact on clinical outcome in non-smokers but not in current smokers. It is possible that the prognostic impact of PPR may be disturbed by various factors associated with active smoking, such as promotion of thrombosis, inflammation and endothelial dysfunction.12–14 In addition, non-smokers may have wide inter-individual variability in the inhibitory effect of clopidogrel, whereas current smokers may have a good response to clopidogrel and less variability of clopidogrel response between subjects. Thus, in non-smokers, the wide range of PPR might be an important determinant to predict MACCE at 2 years. Therefore, tailored application of PPR to non-smokers would be useful to predict long-term outcomes after DES implantation. Further studies are warranted to confirm this idea.

Persistent Risk Factor for Outcome: Long Lesion ≥28 mm
Long lesion length was identified as an independent predictor of 6-month thrombotic events among patients with DES implantation in the CILON-T trial.10 Long lesion length remained as a main risk factor for future cardiovascular events at 2 years after DES implantation in the present study. The relationship between lesion length and adverse events after PCI has been well-described. Longer lesions require treatment with longer balloons and stents, leading to greater arterial injury that is often associated with poorer outcome after stent implantation.30

Study Limitations
The present study had several limitations. First, the study drugs were given in an open-label manner, introducing a possible bias. Second, despite the relatively large sample size, the present study was underpowered to prove meaningful differences, especially in cardiac death and MI between the 2 groups. For a similar reason, multivariate analysis indicated that some of the clinical parameters did not have significance as predictors of 2-year clinical outcome. Third, we did not check the PRU level at 2 years, which would have been helpful in evaluating the legacy effect of cilostazol. Last, smoking status or smoking cessation was not evaluated throughout the clinical follow-up period.
Conclusions
The addition of cilostazol for 6 months to DAT did not reduce 2-year MACCE compared to DAT after DES implantation, negating the legacy effect of cilostazol. Cilostazol, however, had a beneficial effect in eliminating unfavorable smoking outcome. In addition, baseline PPR was identified as an important factor predicting 2-year MACCE only in non-smokers but not in current smokers, suggesting the confounding effect of smoking on the association between PPR and clinical events.

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Supplementary Files
Supplementary File 1
Figure S1. Comparisons of 2-year clinical outcomes between active and never smokers using Kaplan-Meier curves.
Figure S2. Landmark analysis showing differential impact of smoking on clinical outcome according to time course after index PCI.
Table S1. Clinical outcome during 2-year follow-up
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