A Randomized Comparison Study Assessing the Impact of Cilostazol on the Heart Rate and Arrhythmias by 24-Hour Ambulatory Holter Electrocardiographic Monitoring after Drug-Eluting Stent Implantation for Coronary Artery Disease

Results from the CILOHA (The randomized prospective impact of CILOstazol associated with Heart rate and Arrhythmias after percutaneous coronary intervention) Trial

Beom-June Kwon¹, Su-Hyun Lee², Dong-Bin Kim², Hun-Jun Park², Sung-Won Jang², Sang-Hyun Ihm², Hee-Yeol Kim² and Ki-Bae Seung²

¹Department of Cardiology, Seogwipo Medical Center, Jeju, Republic of Korea
²Department of Cardiology, College of Medicine, Catholic University of Korea, Seoul, Republic of Korea

Aims: Cilostazol may have a positive chronotropic or pro-arrhythmic effect. However, there have been no randomized trials to confirm these effects.

Methods: This randomized prospective trial compared dual (DAT, aspirin and clopidogrel, n=114) versus triple antiplatelet therapy (TAT, DAT plus cilostazol, n=113) at baseline and after six months in patients receiving intracoronary drug-eluting stents (DES). The primary endpoint was the 24-hour heart rate (24h-HR) at six months determined using 24h-Holter ECG monitoring. The secondary endpoints were the 24h-HR ≥70 bpm, 24h-HR increase ≥5 bpm and the counts or presence of arrhythmias.

Results: At six months after DES implantation, the 24h-HR (73 [68-83] vs. 68 [62-75] bpm, p<0.001), presence of a 24h-HR ≥70 bpm (71.4 vs. 47.1%, p<0.001) and presence of a 24h-HR increase ≥5 bpm (44.8 vs. 24.5%, p=0.002) were significantly higher for the TAT group than for the DAT group. A multivariate analysis showed that the use of cilostazol (OR: 3.10, p=0.035) and a baseline 24h-HR ≥70 bpm (OR: 4.60, p<0.001) were strong predictors of a 24h-HR increase ≥5 bpm. However, there were no significant intergroup differences in arrhythmias.

Conclusions: Cilostazol appears to result in an increase in the 24h-HR after DES implantation. Therefore, some caution should be exercised regarding the use of cilostazol in patients with tachycardia, when planning DES implantation.


Key words: Arrhythmia, Cilostazol, Heart rate, Holter ECG monitoring, Percutaneous coronary intervention

Introduction

The resting heart rate has been shown to be a potent predictor of major cardiovascular events in both the general population¹ and in patients with various cardiovascular diseases²-⁴. Furthermore, the exercise and recovery heart rates are powerful predictors of overall mortality⁵-⁶. The heart rate is incorporated in prognostic scores such as the global registry of acute coronary events (GRACE) risk score⁷. An analysis of the baseline heart rate as a continuous variable showed that, for every five beat per minute (bpm)
increase, there was an 8% increase in cardiovascular death, a 16% increase in admission to the hospital for congestive heart failure (CHF), a 7% increase in admission to the hospital for myocardial infarction (MI) and an 8% increase in coronary revascularization\(^9\). A baseline resting heart rate of 70 bpm or greater versus less than 70 bpm was associated with an increased risk for cardiovascular death, admission for CHF or MI and coronary revascularization in patients with stable coronary artery disease (CAD) and left ventricular (LV) systolic dysfunction\(^9\).

Cilostazol is an oral selective phosphodiesterase-type III (PDE-III) inhibitor commonly used for its potent effects on vasodilation and antiplatelet aggregation in patients with peripheral arterial disease\(^9\). In patients with long lesions\(^9\) and type 2 diabetes mellitus\(^10\) after the implantation of a drug-eluting stent (DES), adjunctive cilostazol (triple antiplatelet therapy, TAT) on top of the standard dual antiplatelet therapy (aspirin plus clopidogrel therapy, DAT) was found to be associated with improved clinical outcomes due to a decreased need for revascularization. Recent meta-analyses reported that TAT was associated with a significant reduction in target lesion revascularization (TLR) and target vessel revascularization (TVR) during a mid-term follow-up (1- to 12-month)\(^11\). Therefore, TAT was associated with a significant reduction in major adverse cardiac events (MACEs), mainly due to the reduction in TLR and TVR. However, there was not a significant difference in the MI and mortality, and data regarding the TLR and TVR at long-term intervals (≥12 months) have been limited and inconclusive\(^11\).

For patients with acute coronary syndromes, cilostazol reduced the 12-month cardiac and cerebral events after percutaneous coronary intervention (PCI), especially for patients with high-risk profiles\(^12\). However, another trial showed that cilostazol had no effects on clinically-driven TLR, or on MACEs in the real-world all-comer patient population after DES implantation, despite the greater reduction of platelet reactivity by the addition of cilostazol to conventional DAT\(^13\). Therefore, the clinical implication of adjunctive cilostazol may differ according to the study design and patients’ characteristics.

The increase in the level of cyclic adenosine monophosphate (cAMP) in nodal cells caused by cilostazol could cause adrenergic stimulation, resulting in a positive chronotropic effect\(^13\,14\). Considering that the advantages of using cilostazol, such as the reduction in the risk of TLR and TVR, did not definitely translate into any clinically meaningful benefits, including the risk of MI and mortality, detrimental tachycardia and tachyarrhythmia caused by cilostazol might be an important explanation for this lack of benefit. However, the data are still limited regarding whether cilostazol might induce tachycardia and tachyarrhythmias after DES implantation, and evidence is lacking from randomized trials that have evaluated the safety of this agent, especially using 24-hour ambulatory Holter electrocardiographic (ECG) monitoring. Accordingly, the aim of the present clinical trial was to assess the safety of TAT versus DAT after DES implantation, in terms of the heart rates and arrhythmias.

### Methods

#### Patients

The CILOHA trial was a prospective, open-label randomized trial with blinded evaluation performed between March 2010 and February 2012 at three centers in South Korea: St. Paul’s Hospital, Bucheon St. Mary’s Hospital and Seoul St. Mary’s Hospital, which are all associated with the Catholic University of Korea. This study included patients ≥18 years of age with angina pectoris, a positive stress test, myocardial infarction and/or native coronary lesions undergoing PCI with DES. Patients were excluded if they had contraindications to the use of aspirin, clopidogrel or cilostazol; a left ventricular ejection fraction <30%; were in a bed-ridden state; had persistent atrial fibrillation, an atrial flutter, a history of ventricular tachycardia or ventricular fibrillation; had a pacemaker or implantable cardioverter-defibrillator or had undergone cardiac re-synchronization therapy; if they had uncorrected hematological disease; hepatic dysfunction; were receiving treatment with an anti-arrhythmia drug; were receiving treatment with warfarin or antiplatelet agents other than aspirin or clopidogrel; had an expected survival <1 years from a non-cardiac disease or had inability to follow the study protocol. The respective institutional review boards at each of the three centers approved the protocol. All patients gave written informed consent.

#### Randomization and Procedures

All patients received aspirin and clopidogrel before PCI with a loading dose of aspirin (300 mg) and clopidogrel (300 to 600 mg) and were maintained on daily aspirin (100 mg daily) and clopidogrel (75 mg daily) for at least six months. Coronary stenting was performed according to the standard PCI technique\(^15\). The choice of the type of DES was made by the individual physicians. Angiographic success was defined as an in-segment final diameter stenosis <30%
as determined by a quantitative angiographic analysis.

After DES implantation, patients were randomly allocated at a 1:1 ratio to either the TAT (aspirin, clopidogrel, and cilostazol) group or the DAT (aspirin and clopidogrel) group using sealed envelopes containing a computer-generated randomization sequence. The TAT group received a loading dose of cilostazol at 200 mg after the baseline 24-hour Holter ECG monitoring, and then 100 mg twice daily for at least six months, in addition to conventional DAT.

All baseline 24-hour Holter ECG monitoring periods were started within 72-hour after successful PCI when the patients could walk and participate in their usual activities. Subsequently, the TAT group received additional cilostazol upon completion of the baseline 24-h Holter ECG monitoring. At six months, repeat 24-hour Holter ECG monitoring was performed for both groups in an outpatient clinic. The recruitment flow is illustrated in Fig. 1.

The 24-hour Ambulatory Holter Electrocardiographic Monitoring

The continuous 24-hour ECG recordings were obtained using modified V1, V5 and aVF leads. Because bipolar leads were used, the output was the potential difference between the positive and negative inputs. The positive electrodes were placed in the conventional positions of V1 and V5 for the modified V1 and V5 leads, respectively. The negative electrode was placed on the upper end of the sternum.

All patients were instructed to rest or sleep during the nighttime and to maintain their usual activities during the daytime. During the 24-hour monitoring period, each patient maintained a personal log, in which the times of specific activities and symptoms were recorded.

The 24-hour Holter ECG recordings were analyzed by experienced Holter technicians and cardiologists who were blinded to the clinical data. Initially, all beats were automatically categorized into different classes on the basis of morphology using advanced software algorithms (Model 563 AccuPlus™ Holter Analysis System). The technician or cardiologist confirmed that the classes were correctly identified. Additional manual correction was performed before data transmission.

The following data were reported and compared between the baseline and six-month recording, using the 24-hour ambulatory Holter ECG monitoring: (1) 24-hour average heart rate (bpm), presence of a heart rate ≥70 bpm, presence of a heart rate increase ≥5 bpm at the six-month follow up compared to the baseline heart rate; (2) the presence of a premature ventricular complex (PVC), the 24-hour total counts of PVCs, the presence of frequent PVCs (>10 beats per hour), the presence and total counts of PVC couplets, the maximal counts of PVCs per hour, the mean counts of PVCs per 1000 beats; (3) the presence of non-sustained (<30 seconds) ventricular tachycardia (NS-VT, three or more consecutive PVCs at a rate of >100 bpm); (4) the presence of complex arrhythmias, defined as more than 10 PVCs per hour (frequent PVC) and/or any number of PVC couplets and/or of runs of NS-VT; (5) the presence of sustained ventricular tachycardia (VT); (6) the presence of a premature atrial complex (PAC), the 24-hour total counts of PACs, the presence of and total counts of PAC couplets, the maximal counts of PACs per hour, the mean counts of PVCs per 1000 beats; (7) the presence and frequency (number of episodes/24-hour) of supraventricular tachycardia (SVT, three or more consecutive PACs at a rate of >100 bpm) and their maximum length (number of beats/episode).

The 24-hour average heart rate was calculated as the total number of normal beats in sinus rhythm (three consecutive normal beats) divided by the recording duration after correction for noise and episodes of non-sinus rhythm. Arrhythmias (PVC, NS-VT, VT, APC, and SVT) were assessed if the signals were of sufficiently high quality for analysis.

Other Assessments

Alcohol intake was considered to be present in patients with weekly alcohol consumption, irrespective of the type of alcoholic beverage and the intensity of alcohol use. Conventional transthoracic echocardiography was performed. The Gensini’s score was used to calculate the severity of CAD.

Study Endpoints

The primary endpoint of the trial was the 24-hour average heart rate obtained from the 24-hour Holter ECG monitoring at the six-month follow-up after DES implantation. The secondary endpoints included the maximum and minimum heart rates, the incidence of a heart rate ≥70 bpm, heart rate increases above 5 bpm, the PVC (presence, total count, maximum count per hour and mean count per 1000 beats), PVC couplets (presence and total count), presence of NS-VT, presence of VT, PAC (presence, total count, maximum count per hour and mean count per 1000 beats), PAC couplets (presence and total count) and SVT (presence, total count and longest beat) from the 24-hour Holter ECG monitoring at the six-month follow-up examination after DES implantation.

The efficacy and safety assessments included
Statistical Analysis

We assumed that there would be a difference of 5 bpm in the 24-hour average heart rate at six months after the index procedure between the two groups, because such a difference has been demonstrated to

assessments of the MACEs (cardiac death, nonfatal myocardial infarction or TLR), the incidence of major bleeding based on the Thrombolysis In Myocardial Infarction guidelines\(^\text{17}\) and the drug discontinuation at six months.
have prognostic significance, as mentioned above. A priori calculations suggested that a sample size of 198 patients was required to obtain a power of 80% to detect a 5 bpm difference for the primary endpoint between the two groups using a two-tailed test at the 0.05 significance level, with an intergroup sampling ratio of 1:1. The total sample size required was estimated to be 220 patients for the trial with the expectation of a 10% drop-out rate.

All of the data were analyzed according to the intention-to-treat principle. The baseline characteristics of patients were analyzed between the groups. The normality of the distribution was assessed by the Kolmogorov-Smirnov test. Continuous variables with a normal distribution were expressed as the means ± standard deviation (SD) and were compared using an unpaired t-test. When they were not normally distributed, the values were analyzed after log transformation and were presented as medians and interquartile ranges. Categorical variables were expressed as frequencies (percentages) and were compared using the χ² test or the Fisher exact test (if there was an expected cell value < 5). The change in the 24-hour average heart rate from the baseline to the follow-up were compared with paired t-tests in each group, and the mean difference with the 95% confidence interval is shown. A multivariate logistic regression analysis was performed to identify predictors of a 24-hour average heart rate increase ≥ 5 bpm at the six-month follow-up using a forward conditional method, including eligible variables as covariates.

A two-tailed p value < 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS for Windows (SPSS Inc., Chicago, IL, USA), version 15 software program.

**Results**

**Baseline Characteristics**

There were no significant intergroup differences in any of the baseline clinical characteristics (Table 1), angiographic and procedural characteristics (Table 2) or clinical diagnosis and profiles of medication at discharge (Table 3).

**The 24-hour Average Heart Rate with TAT Versus DAT**

The follow-up 24-hour Holter ECG monitoring was performed in 92.9% of the cases in the TAT group and 89.5% of those in the DAT group (p = 0.360) (Table 4). No significant differences existed between the two groups at baseline. At six months, the 24-hour average heart rate was significantly higher in the TAT group than in the DAT group (73 [68-83] bpm vs. 68 [62-75] bpm, p < 0.001). The heart rate at six months significantly increased compared with the baseline heart rate in the TAT group, but this did not occur in the DAT group. The change in the 24-hour average heart rate from the baseline to the follow-up was significantly different between the two groups. The follow-up minimum heart rate was significantly higher in the TAT group than in the DAT group. Furthermore, the rates of patients with a heart rate ≥ 70 bpm (71.4% vs. 47.1%, p = 0.001) and the presence of a heart rate increase ≥ 5 bpm at six months were significantly higher in the TAT group than in the DAT group (44.8% vs. 24.5%, p = 0.002).

**Premature Ventricular Complex, Nonsustained Ventricular Tachycardia and Sustained Ventricular Tachycardia in the Patients Treated with TAT Versus DAT**

There were no significant intergroup differences at baseline (Table 5). In addition, presence of PVC, the 24-hour total counts of PVC, the presence of frequent PVCs, the presence of PVC couplets, the total counts of PVC couplets, the maximum counts of PVCs per hour, the mean counts of PVCs per 1000 beats, the presence of NS-VT and the presence of complex arrhythmia did not differ significantly between the groups at the follow-up. VT did not occur in either group.

**Premature Atrial Complex and Supraventricular Tachycardia in the Patients Treated with TAT Versus DAT**

The two groups had similar characteristics of PAC and SVT both at baseline and at the follow-up (Table 6). There was a trend toward a lower presence of PAC couplets at the follow-up for the TAT group compared with the DAT group (41.9% vs. 54.9%, p = 0.061). Overall, TAT did not seem to have an adverse effect on PAC or SVT.

**Predictors of the Incidence of a 24-hour Average Heart Rate Increase ≥ 5 bpm at the Follow-up in a Multivariate Analysis**

The independent predictors of a 24-hour average heart rate increase ≥ 5 bpm at follow-up were cilostazol use (odds ratio [OR]: 3.10, 95% CI: 1.08 to 8.89) and a 24-hour average heart rate < 70 bpm at baseline (OR: 4.60, 95% CI: 1.61-13.14) in the multivariate logistic regression analysis, which evaluated cilostazol use, age, sex, body mass index, current smoker status, hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, the hemoglobin level, high-
of MACEs and major bleeding did not significantly differ (Table 8). As expected, drug discontinuation was significantly higher for the TAT group compared to the DAT group (6.2% vs. 0.9%, p=0.035).

**Discussion**

The main novel finding of this trial is that TAT was associated with a significant increase in the 24-hour average heart rate, an increased 24-hour min-

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### Table 1. The baseline clinical characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Triple antiplatelet group (n=113)</th>
<th>Dual antiplatelet group (n=114)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.5 ± 9.9</td>
<td>63.5 ± 9.8</td>
<td>0.979</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>73 (64.6)</td>
<td>65 (57.0)</td>
<td>0.242</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.5 ± 2.9</td>
<td>24.7 ± 3.1</td>
<td>0.673</td>
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<tr>
<td>Current smoking status, n (%)</td>
<td>42 (37.2)</td>
<td>32 (28.1)</td>
<td>0.144</td>
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<tr>
<td>Alcohol intake, n (%)</td>
<td>52 (46.0)</td>
<td>46 (40.4)</td>
<td>0.389</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>128 ± 19</td>
<td>127 ± 19</td>
<td>0.825</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>76 ± 12</td>
<td>74 ± 12</td>
<td>0.172</td>
</tr>
<tr>
<td>Resting heart rate on ECG (bpm)</td>
<td>68 ± 11</td>
<td>69 ± 13</td>
<td>0.519</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior myocardial infarction, n (%)</td>
<td>13 (11.5)</td>
<td>8 (7.0)</td>
<td>0.243</td>
</tr>
<tr>
<td>Prior revascularization, n (%)</td>
<td>12 (10.6)</td>
<td>7 (6.1)</td>
<td>0.223</td>
</tr>
<tr>
<td>Prior cerebrovascular disease, n (%)</td>
<td>11 (9.7)</td>
<td>17 (14.9)</td>
<td>0.236</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>12 (10.6)</td>
<td>12 (10.5)</td>
<td>0.982</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>78 (69.0)</td>
<td>77 (67.5)</td>
<td>0.810</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>45 (39.8)</td>
<td>40 (35.1)</td>
<td>0.461</td>
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<tr>
<td>Hyperlipidemia, n (%)</td>
<td>66 (58.4)</td>
<td>72 (63.2)</td>
<td>0.464</td>
</tr>
<tr>
<td>Metabolic syndrome, n (%)</td>
<td>59 (52.2)</td>
<td>50 (43.9)</td>
<td>0.208</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hemoglobin (mg/dL)</td>
<td>13.4 ± 1.9</td>
<td>13.0 ± 1.8</td>
<td>0.819</td>
</tr>
<tr>
<td>Platelet count (×10^9/mm³)</td>
<td>240 ± 70</td>
<td>246 ± 66</td>
<td>0.572</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>124 ± 53</td>
<td>123 ± 46</td>
<td>0.875</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>176 ± 39</td>
<td>182 ± 40</td>
<td>0.269</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>42 ± 13</td>
<td>44 ± 15</td>
<td>0.266</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>155 ± 101</td>
<td>142 ± 74</td>
<td>0.311</td>
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<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>105 ± 31</td>
<td>111 ± 35</td>
<td>0.190</td>
</tr>
<tr>
<td>eGFR by the MDRD formula (mL/min/1.73 m²)</td>
<td>69.8 ± 23.8</td>
<td>73.4 ± 23.5</td>
<td>0.293</td>
</tr>
<tr>
<td>Hs-CRP (mg/dL)</td>
<td>0.58 ± 1.28</td>
<td>0.76 ± 1.40</td>
<td>0.367</td>
</tr>
<tr>
<td>Echocardiographic indices</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>60.6 ± 12.8</td>
<td>62.1 ± 9.5</td>
<td>0.338</td>
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<tr>
<td>LVEF &lt; 45%, n (%)</td>
<td>20 (17.7)</td>
<td>14 (12.3)</td>
<td>0.253</td>
</tr>
<tr>
<td>RWMA, n (%)</td>
<td>26 (23.0)</td>
<td>19 (16.7)</td>
<td>0.231</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>108 ± 33</td>
<td>115 ± 39</td>
<td>0.257</td>
</tr>
<tr>
<td>Left ventricular hypertrophy, n (%)</td>
<td>30 (26.5)</td>
<td>31 (27.2)</td>
<td>0.913</td>
</tr>
</tbody>
</table>

Data are given as n (%) or means ± SD. HDL = high-density lipoprotein; LDL = low-density lipoprotein; eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease Study Group; Hs-CRP = high sensitive-C reactive protein; LVEF = left ventricular ejection fraction; RWMA = regional wall motion abnormality; LVMI = left ventricular mass index; LVH = left ventricular hypertrophy.
Our findings have important implications. First, to our knowledge, this trial is the first to specifically examine the association between cilostazol and either the 24-hour average heart rate or tachyarrhythmias after DES implantation, using 24-hour Holter ECG monitoring. Second, despite the use of negative chronotropic drugs, such as beta-blockers (BB), or in some cases, non-dihydropyridine calcium channel blockers (CCB), cilostazol still had a positive chronotropic effect after DES implantation. Third, the deleterious effect of cilostazol on the 24-hour average heart rate did not translate to an increased risk of pro-arrhythmic effects, such as PVC, NS-VT or VT. Fourth, we measured the heart rate changes and other arrhythmia incidence at six months compared to the patients in the DAT group. This result was supported by the findings of a multivariate analysis showing that cilostazol use was a predictor of a 24-hour average heart rate increase of at least 5 bpm among various confounding factors. However, TAT did not seem to be associated with an increased risk of PVC, NS-VT, VT, PAC or SVT compared to DAT. Based on these findings, it is reasonable to believe that using cilostazol in addition to DAT may contribute to a positive chronotropic effect without any pro-arrhythmic action after DES implantation.

Table 2. The angiographic and procedural characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Triple antiplatelet group</th>
<th>Dual antiplatelet group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=113)</td>
<td>(n=114)</td>
<td></td>
</tr>
<tr>
<td>Gensini's score</td>
<td>26.6 ± 24.7</td>
<td>23.5 ± 20.2</td>
<td>0.318</td>
</tr>
<tr>
<td>Visible thrombus, n (%)</td>
<td>12 (10.6)</td>
<td>15 (13.2)</td>
<td>0.555</td>
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<tr>
<td>Chronic total occlusion, n (%)</td>
<td>22 (19.5)</td>
<td>19 (16.7)</td>
<td>0.583</td>
</tr>
<tr>
<td>Target lesion involving the left main artery, n (%)</td>
<td>5 (4.4)</td>
<td>5 (4.4)</td>
<td>0.989</td>
</tr>
<tr>
<td>Use of a glycoprotein IIb/IIIa inhibitor, n (%)</td>
<td>9 (8.0)</td>
<td>8 (7.0)</td>
<td>0.786</td>
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<tr>
<td>Total stents per patient, n</td>
<td>1.5 ± 0.8</td>
<td>1.5 ± 0.8</td>
<td>0.853</td>
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<tr>
<td>Multivessel stenting, n (%)</td>
<td>42 (37.2)</td>
<td>37 (32.5)</td>
<td>0.456</td>
</tr>
</tbody>
</table>

Data are given as n (%) or means ± SD.
Gensini’s score was calculated to assess the severity of coronary artery disease.

Table 3. The clinical diagnosis and medication profile at discharge

<table>
<thead>
<tr>
<th></th>
<th>Triple antiplatelet group</th>
<th>Dual antiplatelet group</th>
<th>p</th>
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</thead>
<tbody>
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<td></td>
<td>(n=113)</td>
<td>(n=114)</td>
<td></td>
</tr>
<tr>
<td>Clinical diagnosis, n (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Stable angina</td>
<td>51 (45.1)</td>
<td>55 (48.2)</td>
<td>0.350</td>
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<tr>
<td>Unstable angina</td>
<td>34 (30.1)</td>
<td>25 (21.9)</td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>28 (24.8)</td>
<td>34 (29.8)</td>
<td></td>
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<tr>
<td>Medication at discharge</td>
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<tr>
<td>ARB</td>
<td>44 (38.9)</td>
<td>35 (30.7)</td>
<td>0.193</td>
</tr>
<tr>
<td>ACEi</td>
<td>40 (35.4)</td>
<td>48 (42.1)</td>
<td>0.300</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>88 (77.9)</td>
<td>85 (74.6)</td>
<td>0.558</td>
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<tr>
<td>DH CCB</td>
<td>20 (17.7)</td>
<td>26 (22.8)</td>
<td>0.338</td>
</tr>
<tr>
<td>NDH CCB</td>
<td>6 (5.3)</td>
<td>9 (7.9)</td>
<td>0.433</td>
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<td>Thiazide or diuretic</td>
<td>18 (15.9)</td>
<td>15 (13.2)</td>
<td>0.554</td>
</tr>
<tr>
<td>Anti-angina drug</td>
<td>65 (57.5)</td>
<td>57 (50.0)</td>
<td>0.256</td>
</tr>
<tr>
<td>Statin</td>
<td>101 (89.4)</td>
<td>106 (93.0)</td>
<td>0.338</td>
</tr>
<tr>
<td>Hypoglycemic agent, n (%)</td>
<td>29 (25.7)</td>
<td>25 (21.9)</td>
<td>0.509</td>
</tr>
<tr>
<td>Proton pump inhibitor, n (%)</td>
<td>10 (8.8)</td>
<td>15 (13.2)</td>
<td>0.300</td>
</tr>
</tbody>
</table>

Data are given as n (%).

ARB = angiotensin II receptor blockers; ACE = angiotensin-converting enzyme; DH-CCB = dihydropyridine calcium channel blocker; NDH CCB = non-dihydropyridine calcium channel blocker.
Increased heart rates have been shown to be associated with endothelial dysfunction, the severity and progression of atherosclerosis and plaque disruption. In addition, a large number of patients with lower heart rates had developed collateral vessels in a previous study, potentially decreasing the ischemic burden. Increasing heart rates in the setting of CAD could produce myocardial ischemia due to a reduction in the coronary supply resulting from the shortened duration of diastole, as well as by the increase in oxygen demand. A high resting heart rate is a predictor of the total and cardiovascular mortality in patients with CAD, and the reduction in the resting heart rate could be a major determinant of the clinical benefit observed in post-MI patients. In contrast, the relationship between the presenting heart rate and cardiovascular outcomes has a ‘J-shaped’ curve (higher event rates at very low and high heart rates) in patients with non-ST-segment elevation acute coronary syndromes. Among hypertensive patients with even higher resting heart rates, BBs were not superior to CCBs for reducing cardiovascular events despite a more marked reduction in the heart rate. Moreover,

Table 4. A comparison of the 24-hour average heart rate determined by 24-hour Holter ECG monitoring between the triple antiplatelet therapy and dual antiplatelet therapy groups

<table>
<thead>
<tr>
<th></th>
<th>Triple antiplatelet group</th>
<th>Dual antiplatelet group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=113)</td>
<td>(n=114)</td>
<td></td>
</tr>
<tr>
<td>Patients at the six-month follow-up Holter, n (%)</td>
<td>105 (92.9)</td>
<td>102 (89.5)</td>
<td>0.360</td>
</tr>
<tr>
<td>24-hour average HR (bpm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>71 (63-80)</td>
<td>70 (63-79)</td>
<td>0.288</td>
</tr>
<tr>
<td>At follow-up</td>
<td>73 (68-83)*</td>
<td>68 (62-75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change</td>
<td>2 (0 to 5)*</td>
<td>-1 (~3 to 1)</td>
<td>0.033</td>
</tr>
<tr>
<td>p=0.027</td>
<td>p=0.306</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hour maximum HR (bpm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>101 (94-116)</td>
<td>105 (96-116)</td>
<td>0.611</td>
</tr>
<tr>
<td>At follow-up</td>
<td>110 (101-127)</td>
<td>113 (97-126)</td>
<td>0.260</td>
</tr>
<tr>
<td>24-hour minimum HR (bpm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>52 (48-58)</td>
<td>56 (50-61)</td>
<td>0.491</td>
</tr>
<tr>
<td>At follow-up</td>
<td>58 (51-67)*</td>
<td>51 (46-63)</td>
<td>0.001</td>
</tr>
<tr>
<td>Presence of a HR ≥70 bpm, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>66 (58.4)</td>
<td>59 (51.8)</td>
<td>0.314</td>
</tr>
<tr>
<td>At follow-up</td>
<td>75 (71.4)*</td>
<td>48 (47.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of a HR increase ≥5 bpm at follow-up, compared to baseline, n (%)</td>
<td>47 (44.8)*</td>
<td>25 (24.5)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data are given as medians (interquartile range), n (%) or mean differences (95% CI).

1 Log-transformed data

HR= heart rate
*p < 0.05 (compared with dual antiplatelet therapy), *p < 0.05 (compared with the baseline within-group).
Table 5. Comparisons of the findings of a premature ventricular complex, nonsustained ventricular tachycardia, and sustained ventricular tachycardia by 24-hour Holter ECG monitoring between the triple antiplatelet therapy and dual antiplatelet therapy groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Triple antiplatelet group (n = 113)</th>
<th>Dual antiplatelet group (n = 114)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of PVC, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>86 (76.1)</td>
<td>86 (75.4)</td>
<td>0.907</td>
</tr>
<tr>
<td>At follow-up</td>
<td>76 (72.4)</td>
<td>78 (76.5)</td>
<td>0.500</td>
</tr>
<tr>
<td>Total counts of PVCs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3 (0-95)</td>
<td>2 (0-12)</td>
<td>0.215</td>
</tr>
<tr>
<td>At follow-up</td>
<td>6 (0-111)</td>
<td>4 (0-56)</td>
<td>0.167</td>
</tr>
<tr>
<td>Presence of frequent PVCs, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>18 (15.9)</td>
<td>12 (10.5)</td>
<td>0.229</td>
</tr>
<tr>
<td>At follow-up</td>
<td>21 (20.0)</td>
<td>13 (12.7)</td>
<td>0.159</td>
</tr>
<tr>
<td>Presence of PVC couplets, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>18 (15.9)</td>
<td>11 (9.6)</td>
<td>0.156</td>
</tr>
<tr>
<td>At follow-up</td>
<td>15 (14.3)</td>
<td>12 (11.8)</td>
<td>0.590</td>
</tr>
<tr>
<td>Total counts of PVC couplets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0.094</td>
</tr>
<tr>
<td>At follow-up</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0.305</td>
</tr>
<tr>
<td>Maximum counts of PVCs per hour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2 (0-20)</td>
<td>1 (0-4)</td>
<td>0.451</td>
</tr>
<tr>
<td>At follow-up</td>
<td>3 (0-18)</td>
<td>2 (0-10)</td>
<td>0.391</td>
</tr>
<tr>
<td>Mean counts of PVCs per 1000 beats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0 (0-1)</td>
<td>1 (0-0)</td>
<td>0.186</td>
</tr>
<tr>
<td>At follow-up</td>
<td>1 (0-1)</td>
<td>0 (0-1)</td>
<td>0.180</td>
</tr>
<tr>
<td>Presence of NS-VT, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3 (2.7)</td>
<td>3 (2.6)</td>
<td>0.991</td>
</tr>
<tr>
<td>At follow-up</td>
<td>4 (3.8)</td>
<td>7 (6.9)</td>
<td>0.328</td>
</tr>
<tr>
<td>Presence of complex arrhythmia, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>26 (23.0)</td>
<td>19 (16.7)</td>
<td>0.231</td>
</tr>
<tr>
<td>At follow-up</td>
<td>28 (26.7)</td>
<td>22 (21.6)</td>
<td>0.392</td>
</tr>
<tr>
<td>Presence of VT, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>–</td>
</tr>
<tr>
<td>At follow-up</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>–</td>
</tr>
</tbody>
</table>

Data are given as n (%) or medians (interquartile range).

†Log-transformed data
PVC = premature ventricular complex; NS-VT = nonsustained-ventricular tachycardia; complex arrhythmia defined as a presence of frequent PVCs and/or any number of PVC couplets and/or runs of NS-VT, sustained ventricular tachycardia.

the magnitude of the exercise-induced increase in heart rate does not represent a risk factor for total mortality in middle-age men. Thus, the clinical significance of the heart rate is a matter of ongoing debate.

Ventricular arrhythmia remains a marker of electrical instability. The LV performance is depressed during PVCs due to the loss of atrioventricular and ventricular synchronicity. Ventricular arrhythmias are not only associated with marked impairment of the LV systolic function, but also with diastolic filling and relaxation. PVCs are a common form of arrhythmia that may trigger more serious arrhythmic events, such as VT or ventricular fibrillation. The presence of PVCs has been found to be an independent risk factor for sudden death, especially in patients after MI. Although PDE-III inhibitors could be beneficial by causing positive inotropy, those may also be detrimental by re-inducing PVCs in the setting of a chronic myocardial insult. In our trial, cilostazol did not appear to be associated with an increased risk for ventricular tachycardia or PVCs. These non-signifi-
The present trial also demonstrated that there were no significant differences in the PVC, NS-VT or VT between the two groups of patients. Several potential mechanisms by which cilostazol did not contribute to the pro-arrhythmic effect may explain these findings. First, cilostazol affects the cardiac electrophysiological properties by increasing the inward Ca$^{2+}$ current and decreasing the outward potassium current, thus minimizing the induction of ventricular arrhythmia\textsuperscript{19}. Second, the inhibitory effect of cilostazol on adenosine uptake could lead to lower intracellular adenosine levels, resulting in decreased cAMP levels\textsuperscript{38}. Thus, this effect could attenuate the inotropic effect compared with other PDE3 inhibitors. Third, unlike other PDE-III inhibitors, cilostazol affects the PDE-III A patients\textsuperscript{37}.

The present trial also demonstrated that there were no significant differences in the PVC, NS-VT or VT between the two groups of patients. Several potential mechanisms by which cilostazol did not contribute to the pro-arrhythmic effect may explain these findings. First, cilostazol affects the cardiac electrophysiological properties by increasing the inward Ca$^{2+}$ current and decreasing the outward potassium current, thus minimizing the induction of ventricular arrhythmia\textsuperscript{19}. Second, the inhibitory effect of cilostazol on adenosine uptake could lead to lower intracellular adenosine levels, resulting in decreased cAMP levels\textsuperscript{38}. Thus, this effect could attenuate the inotropic effect compared with other PDE3 inhibitors. Third, unlike other PDE-III inhibitors, cilostazol affects the PDE-III A patients\textsuperscript{37}.

Other PDE-III inhibitors, such as milrinone and vesnarinone, were previously reported to be associated with increased mortality in patients with CHF and reduced systolic LV function, despite the benefits from positive inotropy\textsuperscript{36}. The increase in mortality was attributed to an increase in sudden death, presumed to be due to ventricular tachycardia or fibrillation and newly developed atrial arrhythmia (fibrillation or flutter)\textsuperscript{36}. According to the US Food and Drug Administration, all PDE-III inhibitors, including cilostazol, are contraindicated in all patients with chronic CHF because of the recognition that these agents increased the mortality rates in this subpopulation of cardiac patients\textsuperscript{37}.

Table 6. Comparison of the incidence of premature atrial complex and supraventricular tachycardia between the triple antiplatelet therapy and dual antiplatelet therapy groups as detected by the 24-hour Holter ECG monitoring

<table>
<thead>
<tr>
<th>Variables</th>
<th>Triple antiplatelet group</th>
<th>Dual antiplatelet group</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of PAC, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>107 (94.7)</td>
<td>110 (96.5)</td>
<td>0.509</td>
</tr>
<tr>
<td>At follow-up</td>
<td>102 (97.1)</td>
<td>99 (97.1)</td>
<td>0.971</td>
</tr>
<tr>
<td>Total counts of PACs\textsuperscript{1}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>17 (4-57)</td>
<td>19 (6-57)</td>
<td>0.648</td>
</tr>
<tr>
<td>At follow-up</td>
<td>17 (6-74)</td>
<td>20 (11-65)</td>
<td>0.779</td>
</tr>
<tr>
<td>Presence of PAC couplets, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>57 (50.4)</td>
<td>53 (46.5)</td>
<td>0.551</td>
</tr>
<tr>
<td>At follow-up</td>
<td>44 (41.9)</td>
<td>56 (54.9)</td>
<td>0.061</td>
</tr>
<tr>
<td>Total counts of PAC couplets\textsuperscript{1}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
<td>0.647</td>
</tr>
<tr>
<td>At follow-up</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0.259</td>
</tr>
<tr>
<td>Maximum counts of PACs per hour\textsuperscript{1}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4 (2-12)</td>
<td>4 (2-10)</td>
<td>0.917</td>
</tr>
<tr>
<td>At follow-up</td>
<td>4 (2-20)</td>
<td>4 (2-10)</td>
<td>0.589</td>
</tr>
<tr>
<td>Mean counts of PACs per 1000 beats\textsuperscript{1}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0.441</td>
</tr>
<tr>
<td>At follow-up</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0.850</td>
</tr>
<tr>
<td>Presence of SVT, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>45 (39.8)</td>
<td>38 (33.3)</td>
<td>0.310</td>
</tr>
<tr>
<td>At follow-up</td>
<td>33 (31.4)</td>
<td>32 (31.4)</td>
<td>0.993</td>
</tr>
<tr>
<td>Frequency of SVTs\textsuperscript{1}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0.676</td>
</tr>
<tr>
<td>At follow-up</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0.401</td>
</tr>
<tr>
<td>Maximum length of SVTs (if SVT was present)\textsuperscript{1}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4 (3-7)</td>
<td>4 (4-7)</td>
<td>0.438</td>
</tr>
<tr>
<td>At follow-up</td>
<td>5 (3-10)</td>
<td>6 (3-11)</td>
<td>0.708</td>
</tr>
</tbody>
</table>

Data are given as n (%) or medians (interquartile range).
\textsuperscript{1}Log-transformed data
PAC = premature atrial complex; SVT = supraventricular tachycardia.
isofrom of the enzyme, which is selectively localized in the microsomal fraction. Moreover, some studies have shown that cilostazol had anti-arrhythmgic or therapeutic neutrality in arrhythmias. Additionally, cilostazol was reported to prevent episodes of VF or failed to prevent them in Brugada patients. Therefore, it has been difficult to conclude whether cilostazol exerts anti-arrhythmgic, neutral or arrhythmgic effects.

**Study Limitations**

There are several potential limitations associated with our study. First, despite the prospective, randomized design, this trial was open label. To minimize the potential biases in the open label design, we made use of a central randomization system, and the analysts of the 24-hour Holter ECG monitoring and members of the clinical events committee were unaware of the patient group assignments. Second, the study population was not powered to confirm the effect of cilostazol on malignant tachyarrhythmias, such as NS-VT and VT or MACEs. The adverse clinical outcomes beyond increasing the heart rate itself therefore remain unclear. Third, the long-term effects of cilostazol on the heart rates and tachyarrhythmias remain unclear after the six-month follow-up or when cilostazol is discontinued. Fourth, the type of DES was not restricted by protocol, but was chosen at the discretion of the individual interventionists. This might have introduced a possible bias. Fifth, there was no explicit description of the comparable activity levels for the baseline and follow-up Holter ECG recordings. For more confident data, the patients’ activities need to be regulated to the same extent during both recordings. Furthermore, baseline Holter ECG monitoring was carried out in an inpatient clinic, whereas the follow-up data were collected in an outpatient clinic. Sixth, whether these results can be generalized to other ethnicities beyond Koreans and other East Asians is speculative. Moreover, it is unclear whether the clinical impact of the chronotropic effects of cilostazol might be dependent on the patients’ characteristics and risks. Finally, studies including cilostazol with newer antiplatelet therapies, such as prasugrel and ticagrelor, are needed in the future.

**Conclusions**

Cilostazol as an adjunct to DAT appears to increase the 24-hour average heart rates after DES implantation without increasing the risk of tachyarrhythmias. It remains unclear whether the risk of the positive chronotropic effects of cilostazol may out-

### Table 7. The predictors of the incidence of a 24-hour average heart rate increase ≥5 bpm at the follow-up by the multivariate analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cilostazol use</td>
<td>3.10</td>
<td>1.08-8.89</td>
<td>0.035</td>
</tr>
<tr>
<td>24-hour average heart rate &lt;70 bpm at baseline</td>
<td>4.60</td>
<td>1.16-13.14</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Baseline cilostazol use, age (≥65 or <65 yr), sex, body mass index (≥25 or <25 kg/m²), current smoker status, hypertension, diabetes mellitus, hyperlipidemia, estimated glomerular filtration rate (≥60 or <60 mL/min/1.73 m²), hemoglobin (mg/dL), high-sensitive C-reactive protein (mg/dL), left ventricular ejection fraction (≥45 or <45 %), left ventricular hypertrophy, use of negative chronotropic drugs (beta blocker or non-dihydropyridine calcium channel blocker), and presence of 24-hour average heart rate <70 bpm were entered in a forward conditional method.

### Table 8. The clinical outcomes during the follow-up and the adverse drug effects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Triple antiplatelet group (n=113)</th>
<th>Dual antiplatelet group (n=114)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>8 (7.1)</td>
<td>9 (7.9)</td>
<td>0.816</td>
</tr>
<tr>
<td>TIMI major bleeding</td>
<td>0 (0.0)</td>
<td>1 (0.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Drug discontinuation</td>
<td>7 (6.2)*</td>
<td>1 (0.9)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Data are given as n (%).
MACE = major adverse cardiac events including cardiac death, non-fatal myocardial infarction, and target lesion revascularization; TIMI = Thrombolysis in Myocardial Infarction.
*p < 0.05 (compared with dual antiplatelet therapy)
weigh the benefits after DES implantation. Nevertheless, some caution should be exercised regarding the use of cilostazol in patients with tachycardia when planning DES implantation.

Conflicts of interest

None.

References

40) Szel T, Antzelevitch C: Abnormal repolarization as the basis for late potentials and fractionated electrograms recorded from epicardium in experimental models of brugada syndrome. J Am Coll Cardiol, 2014; 63: 2037-2045