Comparison of dual antiplatelet therapy prescribed as one-pill versus two-pill regimen

A pooled analysis of individual patient data from the three MR-CAPCIS trials

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Summary

Fixed-dose combination (FDC) drugs can simplify the medication regimen and potentially improve adherence. However, evidence is lacking about the efficacy and safety of FDC drugs of clopidogrel plus aspirin. Individual data from the three independent MR-CAPCIS trials were pooled and analysed. In those trials, subjects who had been treated with either dual antiplatelet therapy (DAPT) or aspirin alone after drug-eluting stent (DES) implantation were randomly assigned to one-pill or to two-pill DAPT group. Platelet reactivity was measured with VerifyNow-P2Y12 and aspirin point-of-care assays at baseline and eight weeks after treatment. In the present study, primary efficacy endpoint was changes in platelet reactivity unit (PRU) between baseline and eight weeks. A total of 965 subjects were analysed. In prior clopidogrel and aspirin users, PRU was well maintained regardless of switching to either one-pill or two-pill DAPT (ΔPRU=0.4 vs 0.0, p=0.939). In prior aspirin users, PRU was decreased by 73.7 in one-pill DAPT and 77.5 in two-pill DAPT group, with no differences between them (p=0.499). The incidence of high on-treatment platelet reactivity at eight weeks, defined as PRU≥235 in Western people, was 34.8% in one-pill DAPT group and 37.6% in two-pill DAPT group (p=0.380), and that defined as PRU≥275 in Oriental people was 17.7 vs 21.7% (p=0.129). Independent predictors of high platelet reactivity on clopidogrel were female gender, increasing age, and diabetes. Study drugs were well tolerated. In conclusion, FDC one-pill DAPT showed similar efficacy to two-pill DAPT in terms of platelet reactivity in patients receiving DES in Korea.

Keywords

Aspirin, clopidogrel, dual antiplatelet therapy, fixed-dose combination

Introduction

Drug-eluting stents (DES) have shown dramatic efficacy in reducing restenosis and need for repeat revascularisation after percutaneous coronary intervention (PCI) compared with bare metal stents (1). However, concerns still remains about the risk of late and very late stent thrombosis associated with DES due to delayed vascular healing, although safety profile of new-generation DES has been much improved (2). Dual antiplatelet therapy (DAPT) plays a central role for the prevention of thrombotic complications after DES implantation. Therefore, it is recommended that DAPT should be given for at least six to 12 months after DES implantation in patient with stable coronary artery disease (3, 4).

Premature discontinuation of DAPT is a strong predictor for the occurrence of stent thrombosis, and a greater effort should be made to eliminate premature cessation of DAPT (5). Fixed-dose
combination (FDC) drugs can simplify the medication regimen and potentially improve drug adherence (6). Recently, several FDC drugs of clopidogrel and aspirin were developed by pharmaceutical companies in South Korea. However, evidence is lacking about the efficacy and safety of FDC drugs of clopidogrel plus aspirin in patients treated with DES. The purpose of the present study is to evaluate the efficacy and safety of dual antiplatelet therapy prescribed as one-pill versus standard two-pill regimen in a broad patient population receiving DES.

Methods

Study design

We pooled and analysed the individual data from the three independent MR-CAPCIS (Multicenter Randomized trial to assess the efficacy of Combination formula of Aspirin Plus clopidogrel In patients with coronary Stents) trials with very similar study design, which were conducted at 19 sites in South Korea. In those trials, subjects who had been treated with either DAPT or aspirin alone after DES implantation were randomly assigned to one-pill DAPT or to two-pill DAPT group. FDC drugs of clopidogrel and aspirin, used in each trials, were manufactured respectively from three different companies in South Korea (Jeil, CJ, and Hanmi pharmaceutical companies). All the included studies were approved by the institutional review board of each center and were conducted in accordance with the Declaration of Helsinki and consistent with the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice.

Study population

In MR-CAPCIS trials, patients aged 20 to 85 years were eligible to participate if they had been diagnosed as having coronary artery disease, underwent drug-eluting stent implantation, and taken aspirin or aspirin plus clopidogrel for more than three months in a stable condition. Patients were excluded from the studies if they 1) were not received drug-eluting stents or PCI was failed; 2) were taking or had taken other anti-platelets or anticoagulants for >2 weeks within the prior 30 days; 3) had a history of alcohol abuse or intoxication; 4) had hypersensitivity to clopidogrel or aspirin; 5) had abnormal laboratory results that indicated liver disease (serum glutamic oxaloacetic transaminase and glutamate pyruvate transaminase >5 times the upper normal limit); 6) had abnormal laboratory results that indicated renal disease (serum creatinine >3 times the upper normal limit); 7) had blood coagulation disorders, uncontrolled severe hypertension, active bleeding, or history of severe bleeding, such as
intracranial haemorrhage or ulcer bleeding; 8) were pregnant, breastfeeding, or not using effective methods of contraception; 9) had other contraindications to the study drug; or 10) had participated in another clinical study within four weeks before the start of the studies.

**Study procedures and follow-up**

The study flow is shown in▶Figure 1. After screening procedure, patients were stratified according to the prior antiplatelet therapy status. Stratum I was composed of patients who were treated with clopidogrel and aspirin, whereas stratum II consisted of patients prescribed with aspirin after DAPT treatment for at least one year. In both strata, patients were randomly assigned in a 1:1 fashion to a treatment group (one-pill DAPT, aspirin 100 mg and clopidogrel 75 mg daily) or to a control group (two-pill DAPT, aspirin 100 mg daily and clopidogrel 75 mg daily). Allocation to study group in each trial was uniformly determined by interactive web response service using random numbers created by SAS randomisation software (SAS Institute, Cary, NC, USA). Although each trial was open labelled, randomisation was blinded to those analysing the data.

At the day of randomisation, baseline data including vital signs, physical examinations, and laboratory tests were collected.
in both study groups. VerifyNow assay (Accumetrics Inc, San Diego, CA, USA), a point-of-care assay using whole blood, was used to measure antiplatelet activity of clopidogrel and aspirin. Follow-up information were collected at intervals of four weeks. At four weeks, the occurrence of adverse events (AE) was surveyed by telephone calls with patients. At eight weeks, data were obtained during clinic visits regarding AE, drug adherence as well as vital signs, physical examinations, and laboratory tests including the VerifyNow assay. Serious AE such as death, myocardial infarction, or stroke were reported immediately by the principal investigators of each centre directly to the coordinating centre.

Study endpoints

The primary efficacy endpoint of this study was the change in P2Y12 reaction units (PRU), calculated by baseline PRU minus post-treatment PRU. The secondary efficacy endpoints were the change in aspirin reaction units (ARU) and change in % P2Y12 inhibition between baseline and eight weeks of treatment. In addition, we compared the drug adherence which was measured by pill count returned from study participants at the end of study. The safety endpoints were incidences of major adverse cardiac and cerebrovascular events (MACCE), which was the composite of all-cause death, myocardial infarction, and stroke, as well as incidences of adverse events.

Myocardial infarction was defined according to the Third Universal Definition of Myocardial Infarction (7). Stroke was defined as an acute onset of a focal neurologic deficit presumed of vascular origin lasting for ≥24 hours. Adverse events (AE) were any untoward medical occurrences during study drug administration. Drug-related AE were judged by investigators and serious AE were any AE resulting in death, disability, or hospitalisation.

### Results

#### Patients

A total of 972 patients from 19 sites in South Korea were screened from November, 2012 to July, 2013, in whom DES was implanted for the treatment of coronary artery disease. Of these, seven participants met exclusion criteria and remaining 965 were divided into stratum I and II according to the prior antiplatelet agents used (Figure 1). In stratum I, 490 subjects (50.8%) under DAPT were randomly allocated to either one-pill DAPT group (n = 244) or

#### Statistical analysis

The analyses for baseline characteristics, safety endpoints, and drug adherence were based on a modified intention-to-treat analysis set, which included all randomised patients except those who had not taken any study drug, had newly recognised exclusion criteria, and had no safety data collected. Continuous variables are presented as mean ± standard deviation, and were compared with the Student’s t-test or Mann-Whitney test, according to distribution. Categorical variables are expressed as numbers and percentages, and were compared using the Chi-square test or Fisher’s exact test, depending on sample size. The comparisons of efficacy endpoints were performed using the Student’s t-test or Mann-Whitney test, according to distribution. A multivariate logistic regression analysis was used to identify independent predictors for high platelet reactivity to clopidogrel or aspirin. Factors entered into the multivariate model were those with p-value less than 0.10 from univariate analyses. A two-tailed p-value of < 0.05 was considered statistically significant. All statistical analyses were performed with R Statistical Software version 3.0.3 and IBM SPSS version 21.0 (IBM Corp., New York, NY, USA).

### Table 2: Study efficacy endpoints.

<table>
<thead>
<tr>
<th>Prior antiplatelet agents</th>
<th>STRATUM 1</th>
<th></th>
<th>STRATUM 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clopidogrel + Aspirin</td>
<td></td>
<td>Aspirin</td>
<td></td>
</tr>
<tr>
<td>Allocated antiplatelet agents</td>
<td>One-pill DAPT (N = 225)</td>
<td>Two-pill DAPT (N = 235)</td>
<td>One-pill DAPT (N = 226)</td>
<td>Two-pill DAPT (N = 225)</td>
</tr>
<tr>
<td>Change in PRU</td>
<td>0.4 ± 48.6</td>
<td>0.0 ± 47.4</td>
<td>0.939</td>
<td>-73.7 ± 58.9</td>
</tr>
<tr>
<td>Pre-treatment PRU</td>
<td>204.5 ± 64.1</td>
<td>207.4 ± 67.3</td>
<td>0.640</td>
<td>287.2 ± 65.6</td>
</tr>
<tr>
<td>Post-treatment PRU</td>
<td>204.9 ± 70.9</td>
<td>207.4 ± 75.2</td>
<td>0.711</td>
<td>213.4 ± 75.2</td>
</tr>
<tr>
<td>Change in ARU</td>
<td>1.0 ± 90.6</td>
<td>11.2 ± 96.5</td>
<td>0.243</td>
<td>-5.0 ± 83.5</td>
</tr>
<tr>
<td>Pre-treatment ARU</td>
<td>469.5 ± 74.7</td>
<td>456.1 ± 73.9</td>
<td>0.052</td>
<td>474.7 ± 59.6</td>
</tr>
<tr>
<td>Post-treatment ARU</td>
<td>470.1 ± 66.4</td>
<td>467.3 ± 78.4</td>
<td>0.628</td>
<td>469.6 ± 69.6</td>
</tr>
<tr>
<td>Change in %P2Y12 inhibition</td>
<td>-0.1 ± 15.5</td>
<td>-0.4 ± 16.0</td>
<td>0.835</td>
<td>22.0 ± 18.7</td>
</tr>
<tr>
<td>Pre-treatment % P2Y12 inhibition</td>
<td>28.7 ± 19.2</td>
<td>28.3 ± 18.4</td>
<td>0.795</td>
<td>5.1 ± 7.3</td>
</tr>
<tr>
<td>Pre-treatment % P2Y12 inhibition</td>
<td>28.6 ± 21.3</td>
<td>27.9 ± 20.8</td>
<td>0.698</td>
<td>27.0 ± 19.9</td>
</tr>
</tbody>
</table>

Data are mean ± SD. ARU = aspirin reaction unit; DAPT = dual antiplatelet therapy; PRU = P2Y12 reaction unit.
two-pill DAPT (n = 246). In stratum II, 475 (49.2%) under aspirin monotherapy were randomized to either one-pill (n = 237) or two-pill DAPT group (n = 238). Among 965 subjects, 948 were included in the modified intention-to-treat analysis set and 911 had follow-up platelet-function tests.

The mean age of study subjects was 64.1 ± 10.5 years, 75.5% were men, and 28.0% had diabetes. About half of patients had stable angina (52.2%) and 37.9% presented with acute coronary syndrome. After randomisation, both treatment groups were well balanced with regard to baseline demographic and laboratory characteristics in stratum I as well as in stratum II (▶Table 1).

**Efficacy endpoints**

▶Table 2 provides comparisons of efficacy endpoints. The PRU was well maintained in stratum I who took DAPT before enrollment regardless of randomisation into one-pill DAPT or two-pill DAPT (0.4 vs 0.0, p = 0.939; ▶Figure 2A). There was no difference between the two different DAPT regimens. In stratum II who took aspirin alone before enrollment, PRU was decreased by about 75 after eight weeks of treatment with either one-pill or two-pill DAPT, which was comparable to each other (-73.7 vs -77.5, p = 0.499; ▶Figure 2B). Change of individual
Table 3: Study safety endpoints.

<table>
<thead>
<tr>
<th>Prior antiplatelet agents</th>
<th>STRATUM 1 Clopidogrel + Aspirin</th>
<th>P-value</th>
<th>STRATUM 2 Aspirin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocated antiplatelet agents</td>
<td>One-pill DAPT (N = 240)</td>
<td>Two-pill DAPT (N = 241)</td>
<td>One-pill DAPT (N = 232)</td>
<td>Two-pill DAPT (N = 235)</td>
</tr>
<tr>
<td>MACCE</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>1.000</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MI</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>All AE</td>
<td>42 (17.6)</td>
<td>39 (16.3)</td>
<td>0.792</td>
<td>24 (10.3)</td>
</tr>
<tr>
<td>Drug-related AE</td>
<td>7 (2.9)</td>
<td>3 (1.3)</td>
<td>0.221</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>5 (2.1)</td>
<td>5 (2.1)</td>
<td>1.000</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

Values are n (%). AE = adverse event; DAPT = dual antiplatelet therapy; MACCE = major adverse cardiac and cerebrovascular event; MI = myocardial infarction.

Table 4: Incidence of high platelet reactivity at eight weeks using various definitions.

<table>
<thead>
<tr>
<th>High Platelet Reactivity</th>
<th>One-pill DAPT (N = 451), %</th>
<th>Two-pill DAPT (N = 460), %</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRU ≥ 235</td>
<td>34.8</td>
<td>37.6</td>
<td>0.380</td>
</tr>
<tr>
<td>PRU ≥ 275</td>
<td>17.7</td>
<td>21.7</td>
<td>0.129</td>
</tr>
<tr>
<td>% inhibition ≤ 15%</td>
<td>28.8</td>
<td>32.8</td>
<td>0.191</td>
</tr>
<tr>
<td>ARU ≥ 550</td>
<td>17.1</td>
<td>18.9</td>
<td>0.470</td>
</tr>
</tbody>
</table>
| ARU = aspirin reactivity unit; DAPT = dual antiplatelet therapy; PRU = P2Y12 reactivity unit. 

PRU values from baseline to eight weeks were demonstrated in Suppl. Figure 1 (available online at www.thrombosis-online.com). For the change in ARU, it was similar between the two groups in stratum I (1.0 vs 11.2, p = 0.243; Figure 3A) as well as in stratum II (-5.0 vs -5.3, p = 0.970; Figure 3B). Regarding to the change in % P2Y12 inhibition, it was negligible in stratum I who took DAPT before enrollment and there was no difference between one-pill versus two-pill regimen (-0.1 % vs -0.4 %, p = 0.835; Suppl. Figure 2A, available online at www.thrombosis-online.com). In stratum II who took aspirin alone before enrollment, one-pill or two-pill DAPT achieved the comparable % P2Y12 inhibition (22.0 % vs 21.5 %, p = 0.815; Suppl. Figure 2B, available online at www.thrombosis-online.com). Short-term compliance to study medication was excellent in both one-pill and two-pill DAPT group (95.7 % vs 96.4 %, p = 0.195; Suppl. Table 1, available online at www.thrombosis-online.com).

When we compared the antiplatelet activity of FDC drugs from three different companies, the reduction of PRU after switch from aspirin monotherapy to one-pill DAPT was comparable to each other. The mean change in PRU between baseline and eight weeks of treatment was -75.4 with FDC drug produced by Jeil pharmaceutical company, -81.7 with CJ, and -62.0 with Hanmi (p = 0.173; Suppl. Table 2, available online at www.thrombosis-online.com). In addition, the change in PRU after switch from conventional DAPT (clopidogrel plus aspirin) to one-pill DAPT was also similar among three different FDC drugs (0.0 with Jeil vs -3.6 with CJ vs 6.0 with Hanmi, p = 0.549; Suppl. Table 2, available online at www.thrombosis-online.com).

Safety endpoints

The incidences of MACCE and AE are shown in Table 3. In stratum I, MACCE occurred in one patient (0.4 %) treated with one-pill DAPT (1 myocardial infarction), and in none of the patients treated with two-pill DAPT (p = 1.000). In stratum II, no cases of MACCE occurred in one-pill DAPT group and one case of MACCE (1 ischaemic stroke) in two-pill DAPT group (p = 1.000).

A total of 138 patients (14.6 %) experienced any types of adverse events. The rate of adverse events was similar between one-pill vs two-pill DAPT group in both stratum I (17.6 % vs 16.3 %, p = 0.792) and in stratum II (10.3 % vs 14.1 %, p = 0.273). The incidences of drug-related adverse events as well as serious adverse events were also similar between the two groups in both stratum.

Incidences of high platelet reactivity after eight weeks of treatment

We compared incidences of high platelet reactivity after eight weeks of treatment between the two treatment groups. When high platelet reactivity during treatment with clopidogrel was defined as ≥ 235 PRU, ≥ 275 PRU, or ≤ 15 % inhibition according to the various definitions (8–11), the incidences of high on-clopidogrel platelet reactivity was numerically greater in the patients with two-pill DAPT than in those with one-pill DAPT, but this differences did not reach statistical significance (Table 4 and Figure 4). When high on-aspirin platelet reactivity was defined as ≥ 550 ARU (12), the incidences of aspirin resistance was similar between the two groups (17.1 % vs 18.9 %, p = 0.470).
Clinical features of patients with high on-treatment platelet reactivity

Clinical characteristics between those with and without high on-clopidogrel platelet reactivity were analysed using 275 as cut-off value (Suppl. Table 3, available online at www.thrombosis-online.com). Patients with high platelet reactivity to clopidogrel therapy were older (62.7 ± 10.5 years vs 69.1 ± 9.2 years, p < 0.001) and were more likely to have hypertension (58.2 % vs 73.9, p < 0.001), diabetes (26.2 % vs 37.8 %, p = 0.002), chronic kidney disease (26.6 % vs 52.8 %, p < 0.001) and stable angina (49.1 % vs 66.1 %, p < 0.001). In contrast, they had less frequency of male gender (84.7 % vs 42.2 %, p < 0.001), cigarette smoking (22.8 % vs 10.0 %, p<0.001), and history of myocardial infarction (7.0 % vs 2.8 %, p = 0.035). Regarding aspirin resistance, however, clinical features between those with and without high ‘on-aspirin’ platelet reactivity were comparable to each other except that those with high on-aspirin platelet reactivity were older (63.6 ± 10.5 vs 65.6 ± 10.4, p = 0.035). To determine the independent predictors for high platelet reactivity to clopidogrel or aspirin, a multivariate logistic regression analysis was performed (Suppl. Table 5, available online at www.thrombosis-online.com). In results, independent predictors for high on–clopidogrel platelet reactivity were female gender (HR 6.03, CI 4.08–8.92, p < 0.001), increasing age (hazard ratio [HR] 1.45 for 10 years, confidence interval [CI] 1.20–1.70, p < 0.001), and diabetes (HR 1.54, CI 1.04–2.29, p = 0.032). However, there were no independent predictors for high on-aspirin platelet reactivity. Furthermore, independent predictors for poor response to both clopidogrel and aspirin (PRU ≥ 275 and ARU ≥ 550) were old age (HR 1.55 per 10 years, CI 1.08–2.04, p = 0.021) and female gender (HR 4.72, CI 2.33–9.56, p < 0.001).

Discussion

In the present study, we compared the efficacy and safety of DAPT prescribed as fixed-dose combination one-pill drug with those of standard two-pill regimen in patients receiving DES. Treatment with one-pill DAPT for eight weeks showed similar efficacy to two-pill DAPT regarding change in PRU, regardless of the prior antiplatelet agents used. Proportions of on-treatment high platelet reactivity, defined by various cut-off values, were also similar between the two treatment groups. In addition, the incidence of major adverse cardiac and cerebrovascular events and that of adverse events were also comparable between the two groups.

It is recommended to maintain dual antiplatelet agents for 6-12 months after DES implantation, and adherence to DAPT is a crucial factor for the prevention of thrombotic complications including late and very late stent thrombosis. FDC drugs are designed to simplify the medication regimen and can improve drug adherence (6, 13). Recently, Castellano et al. reported that complexity of drug treatment is associated with poor medication adherence, and demonstrated in a randomised trial that the use of one-pill combination strategy can improve drug adherence significantly by 22 % compared with the three drugs given separately for secondary prevention following acute myocardial infarction (14). For these reasons, one-pill DAPT can improve adherence after DES implantation, which might leads to better clinical outcome under the

![Figure 4: Distribution of platelet reactivity after eight weeks of treatment with one-pill vs two-pill dual antiplatelet therapy (DAPT). Incidences of high on-clopidogrel platelet reactivity (PRU ≥ 275, or PRU ≥ 235) were not different between one-pill DAPT and two-pill DAPT regimen (A). Incidences of high on-aspirin platelet reactivity (ARU ≥ 550) were also similar between the two regimens (B).](https://www.thrombosis-online.com)
assumption that one-pill DAPT has similar efficacy to two-pill DAPT.

In our study, one-pill DAPT showed similar antiplatelet action to two-pill DAPT, in terms of change in PRU and ARU, in patients who had been treated with either clopidogrel plus aspirin or aspirin only. In addition, changing to one-pill DAPT from conventional two-pill DAPT caused no change in PRU in prior clopidogrel and aspirin users (ΔPRU = 0.4 ± 48.6, p = 0.913 by paired t-test). Concerning drug adherence, it is of note that adherence to study medications was excellent in both groups and no significant differences were found between them (95.7% in one-pill DAPT group vs 96.4% in two-pill DAPT group, p = 0.195). We believe that this result was driven mainly by meticulous counseling of the patients regarding the importance of DAPT in each centre. However, there are several issues that need to be considered when interpreting the results of drug adherence because numerous factors can potentially influence the adherence. Pill counts has been shown to have a positive impact on patients’ adherence that it may be overestimated (15). Planned visits and returning unused medications can cause an attention bias in that patients tend to pay more attention to take medications in the days immediately before the visits. Moreover, patients are tempted to discard unused medicines before visits. In our study, the study period was too short to see the differences in drug adherence between one- vs two-pill DAPT.

When considering non-adherence, however, abrupt discontinuation of one-pill DAPT would be more detrimental than that of two-pill DAPT. If the patients stop taking medications for any reason, the clinical consequences of discontinuation of one-pill DAPT might be worse than stopping one of two pills of DAPT, especially in terms of stent thrombosis. This issue should be evaluated in the long-term follow-up, although our results showed that there were no differences in the rates safety outcomes.

As high platelet reactivity during antiplatelet therapy has the prognostic value in patients undergoing coronary stenting (16, 17), we evaluated the incidence of high platelet reactivity after eight weeks of treatment. When high platelet reactivity during treatment with clopidogrel was defined as ≥ 235 PRU, the proposed cut-off value in the Western population (8, 9, 18), the incidence of clopidogrel resistance was similar between the two groups (34.8% vs 37.6%, p = 0.380). However, platelet reactivity after clopidogrel therapy in the present study was higher than what has been reported previously in the Western population, which is in accordance with previous data from our group and other Korean studies (10, 19). Therefore, we analysed the incidence of high platelet reactivity using an another cut-off value of 275 that could predict thrombotic events such as myocardial infarction or stent thrombosis for one year after DES implantation (10), and the results showed no significant differences between one-pill vs two-pill DAPT groups (17.7% vs 21.7%, p = 0.129). One interesting finding was that the incidence of high platelet reactivity after clopidogrel therapy in one-pill DAPT group showed a statistically insignificant but numerically lower trend than two-pill DAPT group regardless of the various cut-off values, although mean PRU measurements were about the same between the two groups. This finding needs to be confirmed by larger trials. Apart from efficacy, the proportion of patients at risk of bleeding should be assessed as the more effective the antiplatelet agent, higher the risk of bleeding. When enhanced responders who are at risk of bleeding were defined as PRU ≤ 85 (20), the incidence of patients at risk of bleeding after clopidogrel treatment was also not different between the two groups (4.4% in one-pill DAPT vs 4.8% in two-pill DAPT, p = 0.802). During the study period, seven cases of bleeding events occurred (2 in one-pill DAPT vs 5 in two-pill DAPT) but there were no cases of serious bleeding which required blood transfusion. In short, both regimens showed an optimal efficacy in about 75% of patients, whereas an insufficient efficacy (PRU ≥ 275) was found in about 20% and an excessive effect (PRU ≤ 85) in 5% of patients receiving DES.

Inter-individual variability in response to clopidogrel have been reported and high platelet reactivity to clopidogrel treatment has been repeatedly shown to be associated with increased risk for thrombotic complications (18, 21). In the present study, patients with high platelet reactivity to clopidogrel therapy showed several clinical features. Old age, female gender, non-smoking, hypertension, diabetes mellitus, and chronic kidney disease were associated with high on-clopidogrel platelet reactivity, which was consistent with our previous report (22). Of these factors, female gender, increasing age, and diabetes mellitus were the independent predictors for high ‘on-clopidogrel’ platelet reactivity. In contrast, clinical factor associated with high ‘on-aspirin’ platelet reactivity was only old age that was not an independent predictor in the multivariate analysis. Furthermore, clinical factors for poor response to both clopidogrel and aspirin (PRU ≥ 275 and ARU ≥ 550) were also identified (Suppl. Table 4 and Suppl. Figure 3, available online at www.thrombosis-online.com). Old age, female gender, chronic kidney disease, non-smoking, and stable angina were associated with hypo-responsiveness both to clopidogrel and aspirin, which were similar to those of high on-clopidogrel platelet reactivity. Among these, age and female gender were the independent predictors. Taken together, inter-individual variability of DAPT is determined mainly by clopidogrel resistance which should be a target for more tailored antiplatelet treatment.

Study limitations
The present study has several limitations. First, the follow-up duration of this study was not long enough to compare the clinical
outcomes and drug adherence between one-pill DAPT and two-pill DAPT groups. Second, we used pill counts as an indicator for drug adherence, which may overestimate patients’ adherence. Third, FDC drugs of clopidogrel and aspirin in this study were manufactured from three different pharmaceutical companies, thus these drugs had different combination formula and clopidogrel had different salt. Nonetheless, FDC drugs (one-pill DAPT) from three different companies showed similar efficacy to each other when compared with clopidogrel plus aspirin. Fourth, estimated health care costs reduced by one-pill DAPT were not calculated, which is one of the expected benefits of FDC drugs. In addition, the findings of this study were confined to South Korea, and all the subjects were East Asians. Therefore, the effects of FDC drugs of clopidogrel and aspirin based on East Asians may limit its potential generalisability to other Western countries.

Conclusion

Fixed-dose combination one-pill DAPT showed similar efficacy to two-pill DAPT regarding inhibition of platelet reactivity. However, the applicability to other Western countries and for long-term use remains to be confirmed.

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Conflicts of interest

None declared.

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