

# Efficacy and safety of antiplatelet-combination therapy after drug-eluting stent implantation

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**Background/Aims:** Combination single-pill therapy can improve cost-effectiveness in a typical medical therapy. However, there is a little evidence about the efficacy and tolerability of combination single-pill antiplatelet therapy after percutaneous coronary intervention (PCI) with drug-eluting stents (DES).

**Methods:** From June to November 2012, in total, 142 patients who met the following criteria were enrolled: at least 18 years old; successful PCI with DES at least 3 months earlier; and regular medication of aspirin and clopidogrel with no side effects. After VerifyNow P2Y<sub>12</sub> and aspirin assays, the combination single pill of aspirin and clopidogrel was given and laboratory tests were repeated 6 weeks later.

**Results:** At baseline, the incidence of aspirin resistance, defined as aspirin reaction unit (ARU)  $\geq 550$ , was 9.2%, that of clopidogrel resistance, defined as P2Y<sub>12</sub> reaction unit (PRU)  $\geq 230$ , was 46.5%, and that of percent inhibition of PRU  $< 20\%$  was 32.4%. At follow-up, the incidence of resistance by ARU value was 7.0%, 50.0% by PRU value, and 35.9% by percentage inhibition of PRU, respectively. The mean values of ARU ( $431.5 \pm 63.6$  vs.  $439.8 \pm 55.2$ ;  $p = 0.216$ ) and PRU ( $227.5 \pm 71.4$  vs.  $223.3 \pm 76.0$ ;  $p = 0.350$ ) were not significantly different before versus after antiplatelet-combination single-pill therapy. Five adverse events (3.5%) were observed during the study period.

**Conclusions:** Combination single-pill antiplatelet therapy, which may reduce daily pill burden for patients after PCI with DES, demonstrated similar efficacy to separate dual-pill antiplatelet therapy.

**Keywords:** Aspirin; Clopidogrel; Drug combinations

## INTRODUCTION

The introduction of drug-eluting stents (DES) reduced the rates of restenosis after percutaneous coronary intervention (PCI) [1]. However, some problems remain, such as repeated revascularization and stent thrombosis, the incidences of which depend on patient and lesion characteristics [2,3].

Dual antiplatelet therapy with aspirin and clopidogrel is the standard regimen for prevention of thrombotic complications after DES implantation. Thus, current guidelines recommend dual antiplatelet therapy for at least 1 year [4]. Recently, a combination single pill of aspirin and clopidogrel was developed, and it is well known that combination single-pill therapy can improve patient adherence and cost-effectiveness [5,6].

Although this new combination antiplatelet pill has shown biological effects similar to those of typical dual antiplatelet medications in laboratory tests, there is a lack of clinical data in patients who had undergone DES implantation. We thus evaluated the efficacy and tolerability of combination single-pill antiplatelet therapy after DES implantation.

## METHODS

### Patients

From June to November 2012, in total, 142 patients who met the following criteria were enrolled prospectively after informed consent was obtained: 1) at least 18 years old; 2) successful PCI with DES at least 3 months earlier; and 3) regular medication of aspirin 100 mg (Aspirin protect, Bayer, Wuppertal, Germany; or Astrix, Boryung, Seoul, Korea) and clopidogrel 75 mg (Plavix, Bristol-Myers Squibb and Sanofi, Paris, France) with no side effects. Patients were excluded if they had any bleeding tendency or history of coagulopathy, the possibility of pregnancy or breast feeding, life expectancy of less than 1 year, hematological disease (e.g., neutropenia or thrombocytopenia), serious renal or liver dysfunction, hypersensitivity or allergy to antiplatelet drugs, history of stroke or transient ischemic attack within 6 months, or plans for major surgery within 6 months requiring antiplatelet drug discontinuation.

### Study protocol

Blood for tests including VerifyNow P2Y12 and aspirin assays (Accumetrics Inc., San Diego, CA, USA) was drawn in the morning after taking medications, including the dual antiplatelet regimen as usual, with water alone. Then, the combination single-pill of aspirin 100 mg and clopidogrel 75 mg (Superpirin, Myung In Pharmaceutical Co., Seoul, Korea) was given and laboratory tests were repeated 6 weeks later. Fig. 1 shows the flowchart of the study.

The primary outcome was change in P2Y12 reaction units (PRU) before versus after 6 weeks of combination single-pill antiplatelet therapy. Secondary outcomes were change in aspirin reaction units (ARU), incidence of drug resistance, daily pill burden, incidence of ma-

ior adverse cardiac events (MACE: death, myocardial infarction [MI], target lesion revascularization [TLR], or target vessel revascularization [TVR]), MI, TLR, TVR, stent thrombosis, ischemic stroke, and any possible drug-related adverse event, including bleeding events, neutropenia, thrombocytopenia, liver dysfunction, skin lesion, gastrointestinal dysfunction, and allergic reactions.

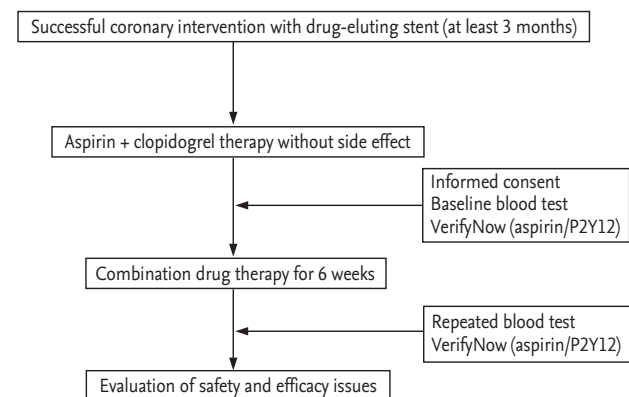
In evaluating platelet function, platelet reactivity  $\geq 230$  PRU was defined as clopidogrel resistance and ARU  $\geq 550$  as aspirin resistance. Clopidogrel resistance was also defined as percent inhibition of PRU  $< 20\%$  [7-9].

The study protocol was approved by the Ethics Committee at each participating site. Written informed consent was obtained from all patients prior to enrollment.

### Statistical analysis

For the calculation of study number, the standard deviation was assumed to be 20 and the difference between means to be 5. The power to detect a true difference was at least 80% and statistical significance was set at 5%. The estimated number of patients for an equivalence study was 140, including a 10% drop-out rate.

Data are expressed as frequencies for categorical variables and as mean  $\pm$  standard deviations (SDs) for continuous variables. Baseline and follow-up test results were compared with the paired *t* test or Wilcoxon



**Figure 1.** Schematic of the study design.

signed-rank test. *p* values were two-tailed, and *p* < 0.05 was considered to indicate statistical significance. Data were analyzed using the SPSS version 12.0 (SPSS Inc., Chicago, IL, USA).

**RESULTS**

Although, in total, 158 patients were screened, two and 14 patients did not complete study protocol due to a violations of inclusion criteria and loss of follow-up laboratory tests, respectively. The remaining 142 patients were included in the intention-to-treat analysis.

Table 1 summarizes the baseline characteristics. The

**Table 1. Baseline characteristics (n = 142)**

Characteristic	Value
Age, yr	63.9 ± 9.6
Male sex	99 (69.7)
Hypertension	72 (50.7)
Diabetes	32 (22.5)
Stroke	9 (6.3)
Diagnosis (at the time of stent implantation)	
STEMI	37 (26.1)
NSTEMI	28 (19.7)
Unstable angina	34 (23.9)
Angina pectoris	42 (29.6)
Silent ischemia	1 (0.7)

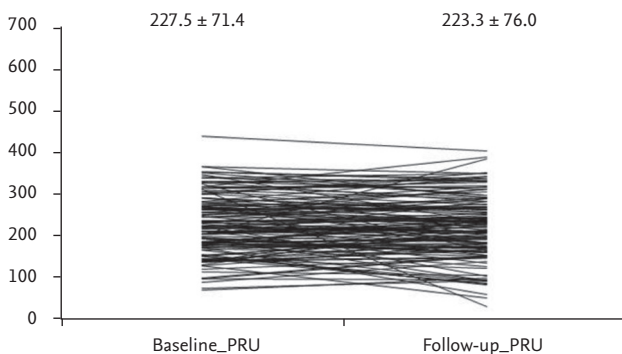
Values are presented as mean ± SD or number (%). STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-STEMI.

mean age was 63.9 ± 9.6 years, with 99 males (69.7%). There were 72 hypertensives (50.7%), 32 diabetics (22.5%), and 9 stroke (6.3%) cases. Almost half of the patients had presented with MI (n = 65, 45.8%). The total pill burden, defined as the total number of pills the patients took daily, was 4.97 ± 1.19 at baseline and 4.09 ± 1.20 at follow-up (*p* < 0.001).

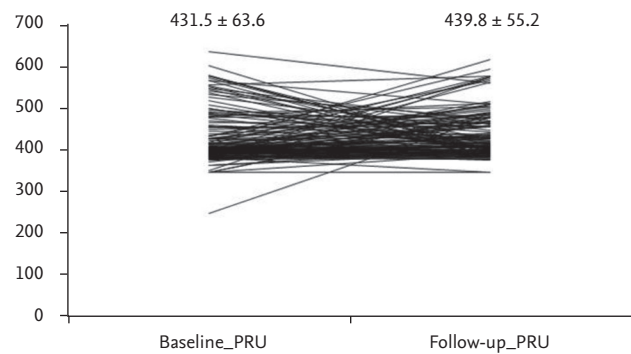
Serial changes in PRU values are shown in Fig. 2. The primary endpoint of PRU was not significantly different before versus after combination single-pill antiplatelet therapy (227.5 ± 71.4 vs. 223.3 ± 76.0; *p* = 0.350). ARU values were also similar between baseline and follow-up (431.5 ± 63.6 vs. 439.8 ± 55.2; *p* = 0.216) (Fig. 3).

The incidence of aspirin resistance was 9.2% at baseline and 7.0% at follow-up (*p* = 0.497). The incidence of clopidogrel resistance was 46.5% at baseline and 50.0% at follow-up (*p* = 0.555). Moreover, the incidence of clopidogrel resistance, defined as percent inhibition, was 32.4% at baseline and 35.9% at follow-up (*p* = 0.534) (Fig. 4). Considering the diverse cutoff values for clopidogrel resistance, there was no significant difference between baseline and follow-up (Table 2). Among patients who had clopidogrel resistance at baseline, 13.6% did not show resistance at follow-up. On the other hand, 18.4% showed clopidogrel resistance at follow-up although they did not show resistance at baseline. Comparing these incidences, there was no significant difference (*p* = 0.270).

There was no MACE during the study period. Five adverse events (3.5%) were observed: variceal bleeding, hematochezia, dyspnea on exertion, hand edema, and knee pain. In laboratory tests, including complete



**Figure 2.** Change in P2Y12 reaction unit (PRU). *p* = 0.350.



**Figure 3.** Change in aspirin reaction unit (ARU). *p* = 0.216.

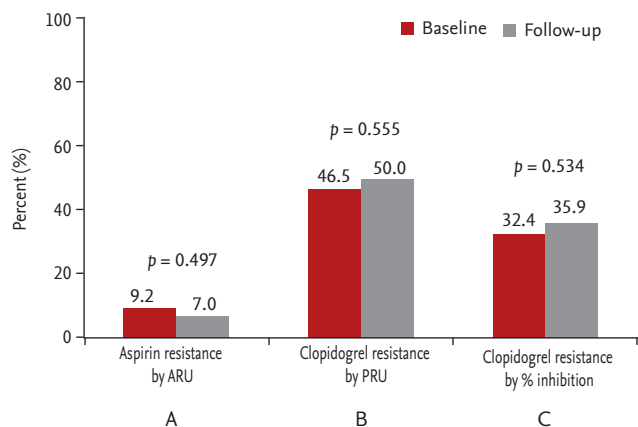
blood count, creatinine, liver enzymes, and cardiac enzymes, the values at follow-up were similar to those at baseline.

## DISCUSSION

The major finding in this study was that combination single-pill antiplatelet therapy showed similar antiplatelet action and tolerability compared with separate dual-pill antiplatelet therapy in patients who had undergone PCI with DES, although this was not a parallel study of two arms and no direct comparison was performed. To our knowledge, this is the first reported study to assess the efficacy and tolerability of combination single-pill antiplatelet therapy after PCI with DES.

The optimal duration of dual antiplatelet therapy after DES implantation is unknown. However, it has been reported that withdrawal of antiplatelet agents is

associated with increased risk of thrombotic complications. Thus, current guidelines for the use of antiplatelet agents recommend that patients receiving DES should take dual antiplatelet therapy for at least 12 months if not at high risk for bleeding [4]. Compared with separate dual-pill antiplatelet therapy, combination single-pill antiplatelet therapy is expected to have several beneficial effects that are commonly observed in combination pills for hypertension or dyslipidemia. First, the use of a combination single pill is associated with a greater likelihood of achieving treatment goals for cardiovascular risk factors. Combination therapy of antihypertensive agents showed a 30% increase in achieving blood pressure control compared with the separate dual-pill therapy, although the difference did not reach statistical significance (odds ratio [OR], 1.30; 95% confidence interval [CI], 0.98 to 1.71;  $p = 0.07$ ) [10]. In the treatment of concomitant hypertension and dyslipidemia, the mean Framingham estimated 10-year cardiovascular risk was reduced in patients receiving combination single-pill therapy [11]. In the present study, the combination single-pill antiplatelet regimen showed similar efficacy to the separate dual-pill regimen, although it did not achieve superiority. However, the treatment goal in antiplatelet therapy may differ from that of antihypertensive or lipid-lowering therapy in terms of not obtaining a more powerful effect but maintaining appropriate efficacy. Second, combination single-pill therapy can lower all-cause healthcare costs compared with patients receiving separate dual-pill therapy. A meta-analysis showed that strategies involving a combination single-pill regimen may reduce costs by minimizing the complexity of treatment regimens and thus improving adherence [12]. Third, simplifying the therapeutic regimen with single-pill therapy does enhance medication adherence [5,6]. In cohort studies on combination single-pill



**Figure 4.** Incidence of drug resistance. (A) Aspirin resistance, defined as aspirin reaction unit (ARU)  $\geq 550$ . (B) Clopidogrel resistance defined as P2Y12 reaction unit (PRU)  $\geq 230$ . (C) Clopidogrel resistance defined as percent inhibition of PRU  $< 20\%$ .

**Table 2. Incidence of clopidogrel resistance using various definitions**

Clopidogrel resistance	Baseline, %	Follow-up, %	p value
PRU $\geq 230$ [7]	46.5	50.0	0.555
PRU $\geq 252.5$ [14]	35.9	33.8	0.710
PRU $\geq 272$ [15]	28.2	24.6	0.491
PRU $\geq 282$ [16]	23.2	23.2	1.000

PRU, P2Y12 reaction unit.

therapy with antihypertensive agents, the use of single-pill therapy was associated with a increase in drug compliance, compared with the use of separate dual-pill therapy (OR, 1.21; 95% CI, 1.00 to 1.47) [10].

Recently, the European Society of Cardiology (ESC) guidelines suggested some tips that may help improve compliance with multiple drug therapies [13]. They include simplification of the dosing regimen by reducing daily doses and concomitant medications and the choice of cheaper alternatives, which can be obtained by prescribing combination single-pill regimens. Although the present study was not designed for a direct evaluation of drug adherence or compliance, the decrease in daily pill burden, which was achieved, would be expected to improve compliance and provide a benefit in clinical outcome, based on the studies about combination pills for hypertension or dyslipidemia. Although a therapeutic regimen with a combination single-pill therapy can improve clinical outcome by reducing pill burden, improving patient compliance, and lowering healthcare costs, these studies were limited to antihypertensive and lipid-lowering medications.

To our knowledge, no reported study has evaluated the tolerability and efficacy of combination single-pill antiplatelet therapy. Thus, this is the first study to assess the combination single-pill therapy of aspirin and clopidogrel.

In the present study, we investigated the impact of a combination single-pill of antiplatelet drugs on platelet function and clinical outcomes. Drug resistance, evaluated by ARU and PRU values, as well as % inhibition of PRU, was not significantly different before versus after combination single-pill antiplatelet therapy. Considering the various cut-off values according to ethnicity and clinical situations, we also evaluated the incidence of clopidogrel resistance by different criteria. When the definition according to the GRAVITAS (Gauging Responsiveness with a VerifyNow P2Y<sub>12</sub> assay: Impact on Thrombosis and Safety) trial was used [7], the incidence of clopidogrel resistance,  $\geq 230$  PRU, was similar between baseline and follow-up (46.5% vs. 50.0%;  $p = 0.555$ ). Considering another cutoff, derived from a study of Korean patients regardless of diagnosis [14], there was no significant difference in the incidence of  $\geq 252.5$  PRU (35.9% vs. 33.8%;  $p = 0.710$ ). According to the value from another study, which

enrolled patients regardless of renal function or diagnosis [15], the incidence of  $\geq 272$  PRU did not differ (28.2% vs. 24.6%;  $p = 0.491$ ). When the cutoff value of 282 was used, derived from primary PCI patients with high platelet reactivity and a proinflammatory state [16], the incidence of clopidogrel resistance was also identical. Indeed, the incidence of clopidogrel resistance was unchanged regardless of the definitions assessed here. Aside from effectiveness, the ratio of patients who are at high risk of bleeding was also not different before versus after combination single-pill antiplatelet therapy when the cutoff value was defined as  $\leq 85$  PRU (1.4% vs. 3.5%;  $p = 0.252$ ) [17]. Considering bleeding-related adverse events, there were two events during the study period. One patient who had not been diagnosed with liver disease and had normal liver function test results at the time of enrollment was hospitalized with upper gastrointestinal bleeding. Tests showed that the cause of the bleeding was liver cirrhosis with esophageal varix and she was treated with endoscopic ligation. Another patient experienced light episodes of hematochezia, which improved with no additional treatment. However, there was no cardiac event during the follow-up period.

The major limitations of the present study were that the insufficient number of subjects and the study period might not have been long enough to fully evaluate the clinical outcomes of combination single-pill antiplatelet therapy. Although improvement of adherence, by reducing the pill burden, is an important component in combination single-pill therapy, medication adherence was not evaluated because of the study design. Thus, we could only infer adherence indirectly from the decrease in pill burden. Thus, to generalize about the benefits of single-pill therapy, a study with longer follow-up and a larger number of patients may provide significant information regarding medication adherence and persistence. Also, each patient might have a different time interval from last medication to the blood tests although the condition was controlled somewhat by taking the medicine and conducting tests early in the morning. It is generally recommended to perform blood tests at a trough period (the low point of medication concentration in the blood just before the next dose) to consider the change of drug effects by process of time. Accordingly, the



timing of the platelet function tests could have affected the results.

The main finding was that combination single-pill therapy of aspirin and clopidogrel provided similar efficacy in terms of antiplatelet action compared with a two-pill regimen. Despite the importance of regular use of medication, patients who undergo PCI with DES are more likely to be prescribed a multiple-pill regimen and to receive a higher pill burden because of comorbidities. Thus, the results of the present study on a single-pill antiplatelet regimen are clinically relevant. In conclusion, combination single-pill therapy of aspirin and clopidogrel will contribute to reducing daily pill burden for high-cost patients while maintaining the effectiveness of antiplatelet action.

### KEY MESSAGE

1. Combination single-pill antiplatelet therapy showed similar effectiveness and tolerability compared with separate dual-pill antiplatelet therapy in patients who had undergone percutaneous coronary intervention with drug-eluting stents.
2. Combination single-pill therapy is expected to contribute to reducing daily pill burden for high-cost patients.

### Conflict of interest

No potential conflict of interest relevant to this article was reported although financial support from Myung In Pharmaceutical Company was given.

### Acknowledgments

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