Effect of aspirin versus cilostazol for inhibition of antiplatelet aggregation in type 2 diabetes mellitus patients (ESCORT-DM Study)

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Original investigation

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Abstract

Background

The role of aspirin in primary prevention of cardiovascular disease in patients with diabetes is controversial. In contrast, some studies have suggested beneficial effects of cilostazol on cardiovascular disease in patients with diabetes. Here we prospectively investigated the antiplatelet effects of cilostazol compared with aspirin in patients with diabetes and cardiovascular risk factors.

Methods

We randomly assigned 116 patients with type 2 diabetes and cardiovascular risk factors but no evident cardiovascular disease to receive aspirin at a dose of 100 mg or cilostazol at a dose of 200 mg daily for 14 days. The primary efficacy outcome was antiplatelet effects of aspirin and cilostazol assessed with the VerifyNow system (aspirin response units; ARU) and PFA-100 (closure time; CT). Secondary outcomes were changes of clinical laboratory data.

Results

The decrease of ARU (-0.4 ± 7.1% vs. -28.9 ± 9.9%, p < 0.001) and the increase of CT (25.7 ± 54.1% vs. 99.6 ± 63.5%, p < 0.001) were significantly greater in aspirin compared cilostazol. The prevalence of aspirin resistance was 7.5% according to VerifyNow (defined by ARU ≥ 550) and 18.9% according to PFA-100 (CT < 192 s). Compared with aspirin, cilostazol treatment was associated with increased HDL cholesterol (7.1 ± 12.7% vs. 4.2 ± 18.0%, p = 0.006) and decreased triglycerides (-9.4 ± 33.7% vs. 4.4 ± 17.57%, p = 0.016). However, there were no significant changes in total and LDL cholesterol, CRP level, and CD40 ligand between cilostazol and aspirin groups.

Conclusions

Aspirin showed better antiplatelet effects assessed with VerifyNow and PFA-100 compared with cilostazol. However, there were favorable changes in atherogenic dyslipidemia only in the cilostazol treatment group.

Trial registration

NCT02933788, dated october 14, 2016

Background

The balance of benefits and risks associated with usage of medication must be considered in various clinical situations. Aspirin has been shown to have an overall net clinical benefit (cardiovascular benefit vs. bleeding risk) when used for secondary prevention of atherosclerotic cardiovascular disease (ASCVD) in people with and without diabetes (1). However, aspirin as secondary prevention reduced the risk of
ASCVD in patients with diabetes by < 10% compared with a > 20% reduction in patients without diabetes (2). Furthermore, several randomized studies showed that the benefit of aspirin did not overcome the risk in primary prevention of ASCVD among patients with type 2 diabetes mellitus (3; 4).

The concept of “aspirin resistance” has been proposed to explain the poor response to aspirin to obtain adequate platelet inhibition in patients with type 2 diabetes mellitus (5; 6). Aspirin resistance is categorized as laboratory aspirin resistance, which is platelet reactivity not appropriately blocked by aspirin usage, and clinical aspirin resistance, which is failure of prevention of ASCVD events in patients taking aspirin (7). Various testing methods have been developed to evaluate aspirin resistance. Light or optical transmission aggregometry has suggested that 1 in 4 diabetic patients taking aspirin had resistance (8). If patients with diabetes do not respond to aspirin therapy, it may not be an adequate primary prevention therapy for patients with diabetes, and an alternative is needed.

Cilostazol, a reversible, selective inhibitor of phosphodiesterase 3, was shown to inhibit platelet activation in both in vitro and in vivo examinations (9). Cilostazol is broadly used for treatment of ischemic stroke, transient ischemic attack, and peripheral arterial disease (10). A previous open-label, single-arm, uncontrolled study showed that cilostazol significantly attenuated platelet activation, as measured using a laser light scattering aggregometer under no stimulation with exogenous agonists, in type 2 diabetes mellitus patients with insufficient platelet response to aspirin (11). However, no randomized study has yet compared anti-platelet activity between aspirin and cilostazol.

We performed the ESCORT-DM (Effect of aspirin versus cilostazol for inhibition of antiplatelet aggregation in type 2 diabetes mellitus patients) randomized trial to compare antiplatelet efficacy, cardiovascular risk markers, and safety between aspirin and cilostazol in high-risk Korean patients with type 2 diabetes mellitus.

**Methods**

**Study design and participants**

This study was a randomized, open label, active-controlled, parallel-group, multi-center study. Participants eligible for the study were patients aged 50 years or older with type 2 diabetes mellitus and one or more cardiovascular risk factors (family history of cardiovascular disease, hypertension, smoking history, dyslipidemia, and albuminuria) and without a high risk of bleeding. We excluded participants who were taking cilostazol or aspirin within one month before randomization. Other exclusion criteria included type 1 diabetes mellitus, secondary diabetes, or gestational diabetes; history of macrovascular complication including cardiovascular disease, cerebrovascular disease, and peripheral vascular disease; contraindicated for aspirin or cilostazol; clinically significant thyroid-stimulating hormone value outside the normal range; alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 times the upper limit of the normal range; alcohol intake greater than 30 g/day; presence of liver cirrhosis or tumor; continuous use (more than 2 weeks) of antithrombotic agents (Sarpogrelate, Beraprost, Indobufen, Triflusal, Clopidogrel, and Ticlopidine) or nonsteroidal anti-inflammatory drugs within one month or after...
randomization; current use of wafarin, dicoumarin derivatives, or digoxin; pregnant, nursing, or suspected of being pregnant; and history of gastrectomy. After screening, eligible and consenting participants underwent baseline evaluation (including anthropometric and lifestyle data, vital signs, medical history and concomitant medication, and venous blood and urine samples). All patients were then randomized into two groups: aspirin 100 mg quaque die (QD) or cilostazol 200 mg QD (1:1 matching). The randomization was based on the randomization table for each facility according to registration order. After a 14-day treatment period, participants visited the investigational site and underwent follow-up evaluation (vital signs and venous blood and urine samples); adverse reactions were reported, and the number of remaining pills was determined for evaluation of compliance.

The study was conducted at 2 university hospitals in Korea between October 2016 and July 2019 (ClinicalTrials.gov Identifier: NCT02933788). The study was conducted in accordance with the principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. All patients provided written informed consent prior to participation.

Study outcomes

The primary outcome measure of this study was change in platelet reactivity from baseline to day 14. Platelet reactivity was tested using the Platelet Function Analyzer 100 (PFA-100; Dade Behring, Miami, FL, USA) and the VerifyNow™ Aspirin instrument (Accumetrics Inc., CA, USA). The secondary outcome measures were changes in lipid profiles such as total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides; C-reactive protein (CRP) level; and cluster of differentiation 40 ligand (CD40L) after 14 days of treatment. Safety was assessed by recording major bleeding events (intracranial, gastrointestinal, or other), adverse events (AEs), complete blood count (CBC), blood urea nitrogen (BUN)-to-creatinine (Cr) ratio, and AST/ALT. Adherence to the trial regimen was assessed by pill count, and 70% and lower adherence was defined as nonadherence.

Anthropometric and laboratory measurements

Questionnaires for diabetes duration; current and past medication history; and past medical history for cardiovascular disease, alcohol history, and smoking status were completed. Anthropometric measures (height, weight, waist circumference), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, and clinical laboratory data were assessed at baseline and after 14 days of treatment. Venous blood and urine samples were obtained in the morning after a 12-h overnight fast and 2 h after intake of trial regimen. HbA1c level was measured using high performance liquid chromatography (HPLC). Serum insulin level was measured using an immunoradiometric assay. Insulin resistance was estimated using HOMA-IR, defined as [fasting plasma insulin (mU/L) × fasting plasma glucose (mmol/L)] / 22.5 (12). Beta-cell function was estimated using HOMA – beta, calculated as fasting plasma insulin (µU/ml) × 20/fasting plasma glucose (mmol/L) – 3.5 (12). Chemistry values were determined using standard assays in each local laboratory. Glomerular filtration rate (GFR) was estimated by the Modification of Diet in Renal Disease (MDRD) Study Group formula (13). The levels of CRP and CD40L were measured using
a high sensitivity enzyme-linked immunosorbent assay (ELISA) assay (R&D Systems, Minneapolis, MN, USA).

**PFA-100**

Blood was aspirated under constant vacuum from the sample reservoir through a capillary and a microscopic hole (147 um) in the membrane by PFA-100. Platelet activation evaluated by PFA-100 is based on co-stimulation of platelets by high shearing stress with a capillary and on the contact of platelets with a membrane coated with collagen and epinephrine to form a platelet plug within the hole. Platelet function was quantitated as the time necessary for thrombotic occlusion of a hole in a membrane coated with collagen and epinephrine (closure time; CT) (14). A CT of 193 sec or less indicated normal platelet function, whereas a CT over 300 sec was considered non-closure according to the manufacturer's cut-off values.

**VerifyNow™ Aspirin**

The VerifyNow system evaluates platelet activity by measuring the light absorbance through the sample. VerifyNow contains a lyophilized preparation containing human fibrinogen-coated beads that cross-links with activated platelets. When platelets become activated by the specific agonist, the fibrinogen-coated beads agglutinate with platelets, and light transmission increases. The VerifyNow aspirin test uses arachidonic acid as the specific agonist, which is converted by the cyclooxygenase-1 enzyme (the molecular target of aspirin therapy) into thromboxane A2. The data are output as aspirin response units (ARUs), and a cut-off value of ARU $\geq$ 550 was accepted to exclude aspirin-induced platelet aggregation according to the manufacturer's reference values.

**Statistical analysis**

The sample size was calculated based on previous studies. The change of platelet aggregation rate (D) between baseline and after administration of aspirin or cilostazol was defined as follows:

$$\text{change of platelet aggregation rate} = \frac{(\text{baseline rate}) - (\text{after administration rate})}{(\text{baseline rate})} \times 100$$

According to a previous study, the change of platelet aggregation rate with arachidonic acid after aspirin and cilostazol administration were 0.4504±0.3651 and 0.69 ± 0.4975, respectively (15). A sample size of 58 patients per trial group was estimated to provide the trial with 80% power (2-sided, 5% significance) while considering 10% dropout of study participants.

Categorical variables are expressed as frequency and percentage. Continuous variables are presented as mean ± SD. Continuous variables were analyzed for a normal distribution with the Shapiro–Wilks
goodness-of-fit test (using P-value < 0.1 as threshold). Only patients with drug adherence greater than 70% were considered for comparisons. Paired t-tests were used for comparison of normally distributed continuous variables in the same group. Wilcoxon tests were used for paired comparisons of continuous variables not following a normal distribution. The primary and secondary outcomes between the two groups were compared using repeated measures analysis of variance (ANOVA). Safety comparisons were assessed using Chi-square for proportions. All statistical analyses were performed using IBM SPSS software (IBM SPSS version 24.0, Chicago, IL, USA). Two-tailed values of P < 0.05 were considered statistically significant.

Results

A total of 127 subjects was screened, and 116 eligible subjects were randomly assigned to the aspirin group (n=58) or cilostazol group (n=58). Two subjects in the aspirin group withdrew consent before the baseline test. A total of 114 subjects (56 in aspirin group, 58 in cilostazol group; full analysis set, FAS) performed the baseline test. Demographic information and baseline characteristics of the FAS subjects enrolled in this study are summarized in supplementary table 1. The mean age of the study subjects was 60.0±6.6 years, and 76 subjects (66.7%) were men. There were no significant differences in baseline characteristics between groups (Supplementary table 1).

In the aspirin group, two patients were excluded due to side effects (abdominal pain = 1, thrombocytopenia = 1) and one patient due to low compliance. In the cilostazol group, 11 patients were excluded due to side effects (headache = 9, dizziness = 1, palpitations = 1) and 10 patients due to low compliance. A final 90 subjects (53 in the aspirin group, 37 in the cilostazol group; per protocol analysis set, PPS) completed the study (Supplementary figure 1). We analyzed the primary and secondary outcomes of the PPS (Supplementary table 2).

Effects of aspirin and cilostazol on platelet reactivity

The platelet reactivity change after 14 days of cilostazol or aspirin treatment was determined by changes in VerifyNow (ARU) and PFA-100 (CT) values (Table 1). In the cilostazol group, there was no significant ARU change after the 14-day treatment (mean change: -0.4±7.1%, p=0.632), but there was significant increase in CT (mean change: 25.7±54.1%, p=0.043) (Figure 1). In the aspirin group, there was a significant decrease in ARU after the 14-day treatment (mean change: -28.9±9.9%, p<0.001) and an increase in CT (mean change: 99.6±63.5%, p<0.001). Compared with the results in the cilostazol group, there was significant decrease in ARU (p<0.001) and increase in CT (p<0.001) after 14-day treatment in the aspirin group (Table 1). Aspirin resistance was defined as ARU ≥550 or CT <192 s, and the prevalence of aspirin resistance was 7.5% according to VerifyNow and 18.9% according to PFA-100.

Effects of aspirin and cilostazol on lipid profile, CRP, and CD40L

After 14 days of treatment, in the cilostazol group, there were significant changes in triglycerides (mean change: -9.4±33.7%, p=0.019) and HDL-cholesterol levels (mean change: 7.1±12.7%, p=0.001) but no
significant change in total cholesterol (mean change: 0.71±17.22%, p=0.979) or LDL-cholesterol (mean change: 0.89±27.60%, p=0.946) (Table 2). In the aspirin group, there was no significant change in total cholesterol (mean change: 1.93±17.57%, p=0.902), triglycerides (mean change: 4.4±17.57%, p=0.953), HDL-cholesterol (mean change: 4.2±18.0%, p=0.480), or LDL-cholesterol (mean change: 7.19±32.09%, p=0.399). Compared with results in the aspirin group, there were significant improvements of triglyceride (p=0.016) and HDL-cholesterol levels (p=0.006) in the cilostazol group but no difference in total cholesterol (p=0.956) and LDL-cholesterol levels (p=0.696) (Table 2). After the 14-day treatment, there was no significant change in CRP or CD40 ligand in either group compared with baseline and no significant difference in changes of CRP and CD40 ligand between the two groups (Table 2).

**Safety and AEs**

Safety and AEs are listed in Table 3. In both study groups, there were no serious AEs. However, the numbers of AEs leading to discontinuation of the trial regimen were higher in the cilostazol group (n=11) than in the aspirin group (n=2, p=0.01). The proportion of subjects with poor adherence was higher in the cilostazol group (n=10) than in the aspirin group (n=1, p=0.005). Headache was more common in the cilostazol group (27.6%) than in the aspirin group (1.8%, hazard ratio, 20.1; 95% confidence interval (CI), 2.7 to 164.4; p=0.004). Abdominal discomfort was similar in the cilostazol and aspirin groups (3.4% vs. 1.8%; hazard ratio, 1.47; 95% CI, 0.30 to 7.45; P=0.579). In the cilostazol group, common cold (1.7%), myalgia (3.4%), epistaxis (1.7%), palpitation (1.7%), and dizziness (1.7%) were reported. Decrease in PLT count (1.7%) caused discontinuation of the trial regimen in the aspirin group.

**Discussion**

This 14-day randomized trial revealed better ex vivo antiplatelet effects of aspirin as assessed with VerifyNow and PFA-100 compared with cilostazol in patients with type 2 diabetes mellitus. Regarding secondary outcomes, cilostazol significantly improved atherogenic dyslipidemia, with increased HDL-cholesterol level and decreased triglyceride level compared with aspirin treatment. Regarding AEs and adherence, aspirin showed better tolerability than cilostazol.

Few studies have compared the anti-platelet activity between aspirin and cilostazol. In a previous in vitro study, cilostazol inhibited adenosine diphosphate (ADP)-, collagen-, or arachidonic acid-induced platelet aggregation in a dose-dependent manner (16). In another in vitro study, the effects of 100 µmol/l aspirin and 10 µmol/l cilostazol were similar in inhibiting platelet aggregation (17). Only one randomized crossover study compared the ex vivo anti-platelet efficacy between aspirin and cilostazol (15). This comparative study in 12 healthy men showed that cilostazol was as effective as aspirin and clopidogrel in inhibiting ex vivo platelet aggregation, induced by the aggregation inducers ADP, collagen, epinephrine, and arachidonic acid, without prolonging bleeding time or changing the bleeding pattern compared with aspirin and clopidogrel (15). Platelet aggregation activity was measured in platelet-rich plasma at 37 °C using an aggregometer (CHRONO, 490 2D). However, in our study, the anti-platelet efficacy of aspirin was superior to that of cilostazol as assessed with the VerifyNow Aspirin system (p < 0.001) and PFA-100 (p <
0.001). The discrepancy between study results may be explained by the methodological differences in platelet function testing and the difference in populations (subjects with vs. without diabetes or medications such as statin), and further studies are needed.

Our study results indicated that cilostazol failed to show platelet aggregation inhibition as assessed with the VerifyNow Aspirin system (p = 0.632) but showed significant inhibition as assessed with PFA-100 (p < 0.001). These findings might be because the VerifyNow-Aspirin system is not adequate to assess the anti-platelet activity of cilostazol, as several previous studies failed to identify anti-platelet activity of cilostazol with the VerifyNow Aspirin system. In ex vivo studies, after a single oral uptake of cilostazol, the VerifyNow llb/llla test and the VerifyNow P2Y12 test detected a positive inhibitory effect of cilostazol, but the VerifyNow Aspirin test was not able to detect these results (18–20). Although cilostazol showed significant inhibition of platelet aggregation as assessed with PFA-100 (p < 0.001), it was inferior to aspirin (p < 0.001). In a previous animal model study, cilostazol showed anti-thrombotic effects in vivo at much lower plasma concentrations than the effective concentrations measured in ex vivo or in vitro aggregation tests using PFA-100 (21). Therefore, there is some possibility that PFA-100 as an ex vivo test underestimates the anti-platelet activity of cilostazol.

The prevalence of aspirin resistance in our study was 7.5% according to VerifyNow and 18.9% according to PFA-100, and these results are similar to a previous study. According to our previous study of 1056 type 2 diabetes mellitus patients from 11 hospitals, aspirin resistance measured in ARUs using VerifyNow was detected in 102 of 1045 subjects (prevalence 9.8%) and was associated with HDL-cholesterol (6). Another study of patients with type 2 diabetes mellitus reported that the prevalence of aspirin resistance measured by the PFA-100 system was 21.5% (22). These findings are consistent with our study results.

Our study showed that cilostazol treatment for only 14 days improved triglyceride and HDL-cholesterol levels. These results are consistent with our previous randomized, open, 36-month, multicenter trial that also showed improved triglyceride and HDL-cholesterol levels in the cilostazol treatment group compared with the aspirin treatment group (23), and other randomized studies showed similar results (24). However, CRP and CD40 ligand were unchanged in both groups in this study. Some studies reported that aspirin and cilostazol reduced CRP or CD40 ligand levels, but other studies reported no changes (25–27). These discrepancies could be due to several factors. These studies used heterogeneous and diverse populations, including healthy subjects, patients with diabetes, and patients with ischemic heart disease, and each study reported different baseline CRP and CD40 ligand levels. In addition, the duration of aspirin or cilostazol treatment varied among studies. In our study, the 14-day treatment period might be too short to detect changes of CRP and CD40 ligand levels by aspirin or cilostazol treatment.

Regarding safety and AEs, the aspirin group showed a lower rate of AEs and higher adherence to medication. Headache was most common side effect in the cilostazol group and caused many withdrawals from the study in this group (15.5%; 9/58 patients). This withdrawal rate was similar to that of a previous study (16%) (28). Although previous studies showed that headache due to cilostazol resolved after several weeks, our study was too short to observe this finding(28). Headache was
associated with low adherence to cilostazol in our studies. As this low adherence could result in low
efficacy of cilostazol compared with aspirin, we excluded patients with low adherence to trial regimens.

To our knowledge, this is the first randomized study comparing the safety of aspirin and cilostazol in type
2 diabetes mellitus patients and ex vivo antiplatelet efficacy evaluated by VerifyNow and PFA-100. The
strength of this study is its prospective and randomized design using the most popular point-of-care tests
(VerifyNow and PFA-100). This study also has some limitations. First, as the mechanisms of aspirin and
cilostazol are different, some platelet function tests were appropriate with some medication but
inappropriate with others. To overcome this problem, we used two popular platelet function tests based
on platelet aggregation (VerifyNow) or platelet adhesion under shear stress (PFA-100) (14). Second, the
short-term study period (14 days) can result in bias in evaluating safety. This short duration may not be
sufficient for development of major gastrointestinal bleeding, which is a common AE of aspirin (15),
although it was adequate to evaluate the primary outcome.

Conclusions

In summary, aspirin as assessed by VerifyNow and PFA-100 showed higher efficacy and tolerability
compared with cilostazol. However, the favorable changes in atherogenic dyslipidemia (triglycerides and
HDL cholesterol) only in the cilostazol treatment group indicate additional benefits with long-term
administration of cilostazol. We also anticipate synergistic effects of the combination of aspirin and
cilostazol on preventing ASCVD. A future study with long duration and another methodology to assess
the anti-platelet efficacy of cilostazol and aspirin is needed.

Abbreviations

adenosine diphosphate; ADP, adverse events; AEs, alanine aminotransferase; ALT, aspartate
aminotransferase; AST, aspirin response units; ARU, atherosclerotic cardiovascular disease; ASCVD, blood
urea nitrogen; BUN, closure time; CT, cluster of differentiation 40; CD40, complete blood count; CBC, C-
reactive protein; CRP, creatinine; Cr, diastolic blood pressure; DBP, enzyme-linked immunosorbent assay;
ELISA, full analysis set; FAS, glomerular filtration rate; GFR, high density lipoprotein; HDL, high
performance liquid chromatography; HPLC, low density lipoprotein; LDL, modification of Diet in Renal
Disease; MDRD, per protocol analysis set; PPS, quaque die; QD, systolic blood pressure; SBP

Declarations

Ethics approval and consent to participate: The institutional review board of each center approved the
protocol, and all patients provided written informed consent before participation in the study.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are
available from the corresponding author on reasonable request.
Competing interests: No potential conflict of interest relevant to this article was reported.

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Author contributions

- Design: Woo Je Lee, Cheol-Young Park
- Conduct/data collection: Woo Je Lee, Cheol-Young Park
- Analysis: Sang-Mo Hong
- Writing manuscript: SangMo Hong, Woo Je Lee, Cheol-Young Park

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**Tables**

Table 1. VerifyNow and PFA-100 value changes after 14 days of cilostazol or aspirin treatment.

|                      | Cilostazol group | Aspirin group | P-value |
|----------------------|-----------------|---------------|---------|
| **VerifyNow (ARU)**  |                 |               |         |
| Baseline             | 637±34          | 639±32        | 0.759   |
| 14 days              | 634±46          | 453±56        | <0.001  |
| Changes over 14 days (%) | -0.4±7.1       | -28.9±9.9†   | <0.001  |
| **PFA-100 (CT)**     |                 |               |         |
| Baseline             | 136±46          | 138±32        | 0.832   |
| 14 days              | 162±66          | 256±63        | <0.001  |
| Changes over 14 days (%) | 25.7±54.1*     | 99.6±63.5*   | <0.001  |

* P value <0.001
† P value <0.05
Table 2. Lipid profile, CRP, and CD40L level changes after 14 days of cilostazol or aspirin treatment.

|                      | Cilostazol group | Aspirin group | P-value |
|----------------------|------------------|---------------|---------|
| Total cholesterol (mg/dl) | Baseline        | 134±46        | 139±32  | 0.480  |
|                      | 14 days          | 134±33        | 138±32  | 0.576  |
|                      | Changes over 14 days (%) | 0.71±17.22   | 1.93±17.57 | 0.956  |
| Triglycerides (mg/dl)  | Baseline        | 116±68        | 147±75  | 0.044  |
|                      | 14 days          | 95±49         | 146±96  | 0.005  |
|                      | Changes over 14 days (%) | -9.4±33.7†  | 4.4±49.2 | 0.016  |
| HDL-cholesterol (mg/dl) | Baseline        | 54±12         | 52±20   | 0.607  |
|                      | 14 days          | 57±13         | 53±17   | 0.158  |
|                      | Changes over 14 days (%) | 7.1±12.7*    | 4.2±18.0 | 0.006  |
| LDL-cholesterol (mg/dl) | Baseline        | 76±27         | 77±29   | 0.834  |
|                      | 14 days          | 76±33         | 79±29   | 0.634  |
|                      | Changes over 14 days (%) | 0.89±27.60   | 7.19±32.09 | 0.696  |
| CRP (ng/ml)           | Baseline        | 1706±5355     | 902±1417 | 0.299  |
|                      | 14 days          | 952±1124      | 1285±3876 | 0.561  |
|                      | Changes over 14 days (%) | 68±162       | 175±1087 | 0.681  |
| CD40 ligand (pg/mL)   | Baseline        | 1992±1432     | 1747±1621 | 0.451  |
|                      | 14 days          | 2309±1593     | 1609±1524 | 0.042  |
|                      | Changes over 14 days (%) | 153.7±669.4  | 85.0±232.2 | 0.674  |
### Table 3 Adverse events

|                              | Cilostazol | Aspirin | p-value |
|------------------------------|------------|---------|---------|
| Serious adverse events       | 0          | 0       | N.S     |
| Adverse event leading to discontinuation of trial regimen | 11 (19.0%) | 2 (3.6%) | 0.01    |
| Poor adherence to trial regimen | 10        | 1       | 0.005   |
| Headache                     | 16 (27.6%) | 1 (1.8%) | 0.004   |
| Abdominal discomfort         | 2 (3.4%)   | 1 (1.8%) | 0.579   |
| Decrease PLT count           | 0          | 1 (1.8%) | N.S     |
| Common cold                  | 1 (1.7%)   | 0       | N.S     |
| Myalgia                      | 2 (3.4%)   | 0       | N.S     |
| Epistaxis                    | 1 (1.7%)   | 0       | N.S     |
| Palpitation                  | 1 (1.7%)   | 0       | N.S     |
| Dizziness                    | 1 (1.7%)   | 0       | N.S     |

### Figures

**Figure 1**

VerifyNow and PFA-100 value changes after 14 days of cilostazol or aspirin treatment.

### Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.
• SupplementaryTableEscort.docx