Pharmacodynamic Effect of Cilostazol Plus Standard Clopidogrel Versus Double-Dose Clopidogrel in Patients With Type 2 Diabetes Undergoing Percutaneous Coronary Intervention

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OBJECTIVE—To determine the effect of adding cilostazol (100 mg b.i.d.) to standard-dose clopidogrel (75 mg/d) (TRIPLE) compared with double-dose clopidogrel (150 mg/d) (DOUBLE) and the influence of the cytochrome P450 (CYP2C19*2/*3, CYP3A5*3) and ATP-binding cassette subfamily B1 (ABCB1 C3435T) genetic polymorphisms in type 2 diabetes (T2DM) patients.

RESEARCH DESIGN AND METHODS—T2DM patients were treated with TRIPLE (n = 41) or DOUBLE (n = 39) after percutaneous coronary intervention. Conventional aggregometry and VerifyNow were performed at baseline and at 30 days. The primary end point was absolute change in 20–μM ADP-induced maximal platelet aggregation (ΔMPA20) between baseline and switching values.

RESULTS—TRIPLE versus DOUBLE showed greater ΔMPA20 (22.9 ± 11.6 vs. 12.7 ± 15.5%; difference, 10.2% [95% CI 4.2–16.3]; P < 0.001). Carriage of one (β coefficient, −5.4%; P = 0.162) and two CYP2C19 loss-of-function allele(s) (−8.3%; P = 0.007) were associated with lower ΔMPA20 in DOUBLE–treated patients, but not in TRIPLE–treated patients.

CONCLUSIONS—Among T2DM patients, adding cilostazol achieves greater platelet inhibition compared with clopidogrel (150 mg/d), which is not influenced by genetic polymorphisms.

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Patients with type 2 diabetes (T2DM) have greater morbidity and mortality from cardiovascular disease than patients without T2DM. Moreover, increased short- and long-term ischemic event occurrences have been observed in diabetes patients treated with percutaneous coronary intervention (PCI) (1). Dual-antiplatelet therapy with aspirin and a P2Y12 inhibitor has been the mainstay to prevent ischemic events among T2DM patients undergoing PCI. However, the antiplatelet and clinical responses to clopidogrel in PCI-treated patients can be influenced by several single nucleotide polymorphisms of the gene encoding cytochrome P450 (CYP2C19*2/*3, CYP3A5*3) and the ATP-binding cassette gene B1 (ABCB1) (2,3).

Cilostazol is a dual-inhibitor of phosphodiesterase type 3 (PDE3) and adenosine reuptake in endothelium, vascular smooth muscle cells, inflammatory cells, and platelets (4). These pleiotropic effects, in addition to platelet inhibition, may affect the occurrence of atherothrombosis in cilostazol-treated patients. The pharmacodynamic and clinical benefit of cilostazol is more prominent in high-risk settings, particularly in diabetes patients (4,5). Cilostazol maintains intraplatelet cyclic AMP levels, which are markedly abnormal in diabetes patients, making them more susceptible to cilostazol effects (5). However, cilostazol metabolism also shows the substantial interindividual variability via CYP3A5 and CYP2C19 polymorphisms (6).

The current analysis evaluated the antiplatelet effect of adding cilostazol (TRIPLE) or double-dose clopidogrel (150 mg/d) (DOUBLE) compared with standard-dose clopidogrel in high-risk T2DM patients undergoing PCI. We also assessed the influence of single nucleotide polymorphisms on the effect of these regimens.
clopidogrel (150 mg/d) and aspirin (200 mg/d) for 30 days.

Blood samples for platelet function were collected immediately before elective PCI or at least 5 days later after emergency PCI, and 2–6 h after the last dose at the 30-day follow-up. Light transmittance aggregometry (LTA) and VerifyNow (Accumetrics, San Diego, CA) were used as previously described (8). Platelet aggregation (PA) values (maximal and 5-min final) induced by ADP (5 and 20 μmol/L) or collagen (6 μg/mL) were determined using an AggRAM aggregometer (Helena Laboratories Corp., Beaumont, Texas). Absolute changes in PA (ΔPA) were defined as changes of values between baseline and 30-day follow-up: ΔPA = baseline PA – 30-day PA.

CYP2C19 genotyping used the ABI SNaPshot reaction. Genotyping for CYP3A5*3 and ABCB1 C3435T was
performed using the TaqMan method (Applied Biosystems, Foster City, CA).

The primary end point was the absolute change in maximal PA induced by 20 
μmol/L ADP (ΔMPA_{20ADP}). High on-
treatment platelet reactivity (HPR) was defined as 5 μmol/L ADP-induced max-
imal PA >46% (LTA) or P2Y12 reaction units (PRU) >235 (VerifyNow) (9).

The sample size calculation was based on 
an earlier observed difference in 20 μmol/L 
ADP-induced maximal PA after adding 
cilostazol or doubling of the clopidogrel 
dose (8). At least 38 patients in each group 
were needed to detect an absolute differ-
ence in 20 μmol/L ADP-induced maximal 
aggregation of 15% with a power of 90%, a 
two-sided α = 0.05, and a SD of 0.2.

Continuous variables were compared 
using the Student t test, Mann-Whitney U 
test, or one-way ANOVA; categoric variables 
were compared using χ² or the Fisher exact 
test. To evaluate the effect of covariates on 
ΔMPA_{20ADP}, a multivariate linear regression 
analysis was performed including variables 
showing P < 0.2 in univariate analysis. 
Analyses were performed with SPSS 18.0 
software (SPSS, Inc., Chicago, IL), and 
P < 0.05 was considered significant.

RESULTS—Among 80 T2DM patients 
with available genotype, 39 were admitted 
for AMI and 77 were treated with a 
drug-eluting stent. Baseline characteris-
tics were well matched (Supplementary 
Table 1). In the TRIPLE group (n = 41), 
there were five cases of transient headache 
and three cases of palpitation for 3–5 days 
after the study was initiated regimen. In 
the DOUBLE group (n = 39), two patients 
presented with transient headache and 
two with gastrointestinal discomfort. These 
adverse events were well tolerated overall, 
and no major ischemic or bleeding events 
ocurred during the study period. Baseline 
platelet reactivity and HPR prevalence be-
fore randomization did not differ between 
the TRIPLE (n = 41) and DOUBLE (n = 39) 
groups. At the 30-day follow-up, platelet 
reactivity and the prevalence of HPR in 
the TRIPLE group was consistently lower 
than in the DOUBLE group (P = 0.124; 
Supplementary Table 2).

TRIPLE was associated with a greater 
ΔMPA_{20ADP} of 22.9 ± 11.6% compared 
with 12.7 ± 15.5% for DOUBLE (differ-
ence, 10.2% [95% CI 4.2–16.3%]; P < 0.001; Fig. 1A). Other changes of LTA-
based PAs also showed the same results 
(P = 0.021). TRIPLE achieved a higher 
ΔPRU of 108 ± 63 compared with 73 ± 61 
for DOUBLE (difference, 35 [7–62]; 
P = 0.014; Fig. 1B). Furthermore, a significant 
decrease in prevalence of HPR was observed with TRIPLE compared with 
DOUBLE based on the criteria of LTA 
(61.0% vs. 20.5%; P < 0.001) and VerifyNow 
(58.5 vs. 33.3%; P = 0.024).

Carriage of the CYP2C19 loss-of-
fraction (LoF) allele (*2 or *3) was relatively 
high, with 39 intermediate (48.8%) and 15 poor (18.7%) metabolizers 
(Supplementary Table 3). In the DOUBLE 
group, ΔMPA_{20ADP} was associated with 
only the number of the CYP2C19 LoF alleles 
(Fig. 1C–E). Compared with noncarriers, 
carriers of one (*β coefficient, −5.4% [SE 
4.7%]; P = 0.162) and two CYP2C19 LoF 
alleles (−8.3% [2.7%]; P = 0.007) showed 
reduced values of ΔMPA_{20ADP} (Supplementary 
Table 4). None of the clinical character-
istics or genetic polymorphisms significantly 
influenced the effect of adding cilostazol 
(Fig. 1C–E, Supplementary Table 5).

CONCLUSIONS—To the best of our 
knowledge, the ACCEL-DM study is the 
first to compare the pharmacodynamic 
effect of TRIPLE versus DOUBLE in high-
risk T2DM patients after PCI (10). This 
study demonstrated that the antiplatelet 
effect of adding cilostazol is not influ-
enced by genetic variations and demo-
graphic characteristics and that the 
double-dose clopidogrel effect is signi-
ficantly influenced by the CYP2C19 LoF 
variant, which is in line with the recent 
pharmacokinetic and pharmacodynamic 
studies (11,12). A recent study suggested 
that tripling the maintenance dose of 
clopidogrel (225 mg/d) in the CYP2C19*2 
 heterozygotes achieved levels of platelet 
reactivity similar to the standard 75-mg 
dose in noncarriers, but the maintenance 
dose (300 mg/d) did not result in com-
parable platelet inhibition among the 
CYP2C19*2 heterozygotes (12).

A recent meta-analysis demonstrated 
that the addition of cilostazol might re-
duce long-term mortality by 31% over 
control in PCI-treated patients, without 
the increase of bleeding (13). Despite the 
same HPR during clopidogrel therapy, 
the linked magnitude of HPR to post-
PCI ischemic events appeared greater 
in the diabetic cohort compared with 
the nondiabetic cohort (14). Diabetes it-
self increases the activity of inflamma-
tion, oxidative stress, and coagulation 
activity, which can increase the in-
fluence of platelet reactivity on clot forma-
tion (15). The inhibitory effect of 
cilostazol on PDE3, together with its ef-
fect on signaling through adenosine, 
prostaglandin, and nitric oxide on plate-
lets, vascular smooth muscle cells, endo-
thelium, and inflammation cascades are 
likely to contribute to its overall clinical 
benefits in diabetes patients (4). In addition, 
the antiplatelet effect of adding 
cilostazol appears not to be influenced 
by the CYP2C19 genotype. Taken to-
gether, adding cilostazol may be a safe 
and commendable antiplatelet regimen 
to reduce PCI-related clinical events. 
However, this concept, which is based 
on several transitional research projects, 
needs to be validated by large-scale fu-
ture clinical trials.

This study has several limitations. 
First, this study was a subgroup analysis 
with a relatively small number of patients. 
Because the genetic effect in response to 
treatments was evaluated with exploratory 
purposes, this analysis should be conceived 
as a “proof of concept” investigation. 
Second, this study was performed using 
candidate gene analysis, and other un-
known genetic variants may be relevant 
in cilostazol and clopidogrel responses. 
Finally, this study may have overestimated 
the antiplatelet effect of each treatment 
because platelet reactivity after PCI can 
vary over time. However, the observed 
change between baseline and the 30-day 
follow-up was 73 PRU in the DOUBLE 
group, which was similar with ~80 PRU 
result observed from the previous study 
(11).

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