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 (ΔMPA_{20}) between baseline and switching values.

RESULTS—TRIPLE versus DOUBLE showed greater ΔMPA_{20} (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 ΔMPA_{20} 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 $P2Y_{12}$ 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.

RESEARCH DESIGN AND METHODS

—This ACCEL-DM (Adjunctive Cilostazol versus double-dose ClopidogrEL in Diabetes Mellitus) study was a subanalysis of T2DM Korean patients who were recruited from prospective, randomized, platelet-function studies. T2DM was defined according to the criteria of American Diabetes Association (7). The local ethics committee approved the study protocol, and signed informed consent was obtained from all patients. Patients receiving elective PCI received a 300-mg clopidogrel loading dose at least 12 h before PCI or were receiving chronic clopidogrel therapy (75 mg/d ≥5 days). Patients with acute myocardial infarction (AMI) patients being treated with emergency PCI received a 600-mg clopidogrel loading dose, followed by clopidogrel (75 mg/d) for at least 5 days before randomization. After randomization, the TRIPLE group received cilostazol (100 mg b.i.d.), clopidogrel (75 mg/d), and aspirin (200 mg/d) for 30 days. The DOUBLE group received

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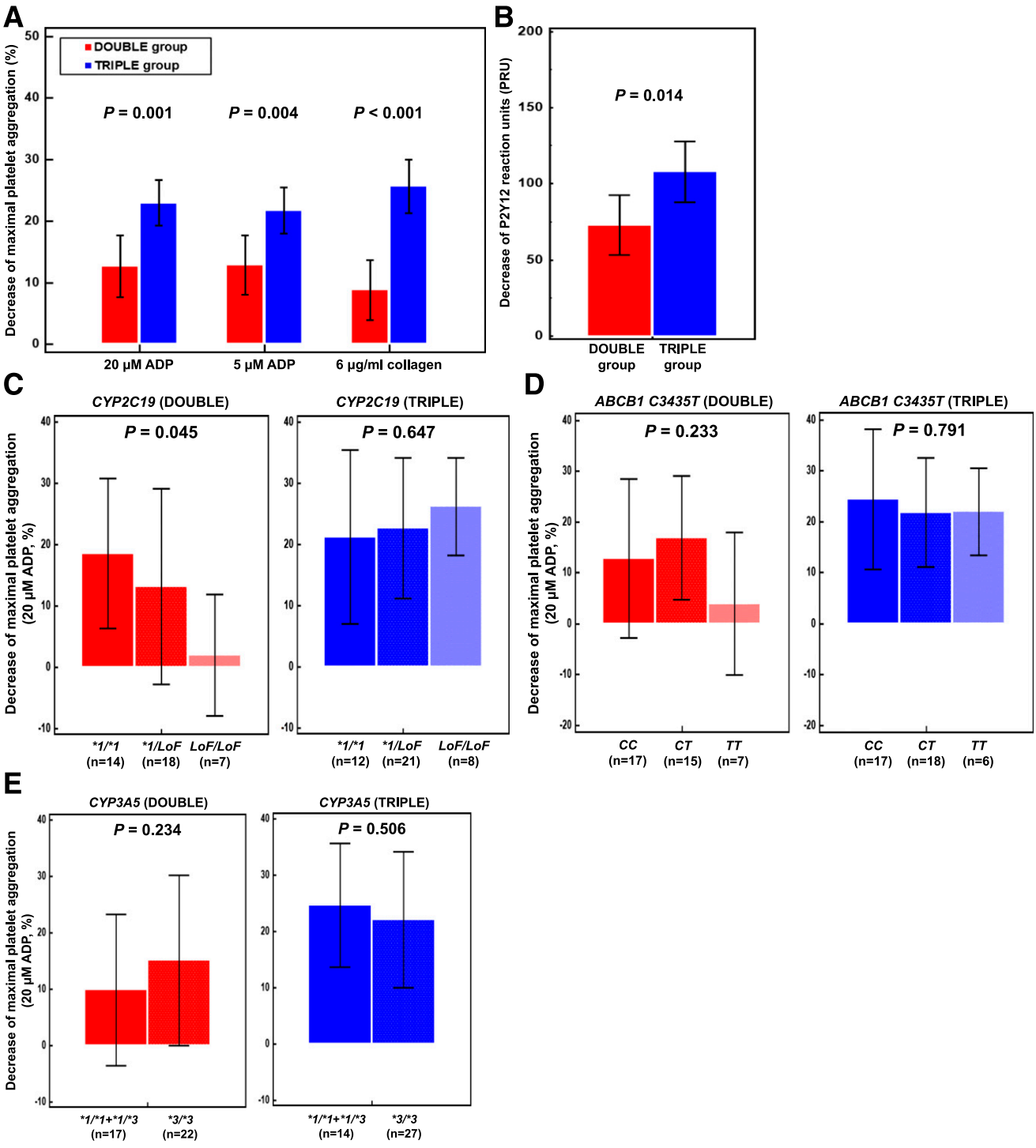

Figure 1—*Decreases of maximal platelet aggregations* (A) *and P2Y12 reaction units* (B) *between baseline and the 30-day follow-up. Decreases of 20 μmol/L ADP-induced maximal platelet aggregation by double-dose clopidogrel* (left bars, *red*) *or adding cilostazol* (right bars, *blue*)*:* CYP2C19 (C), ABCB1 C3435T (D), *and* CYP3A5 (E) *genotypes. Results are expressed as means with the 95% CIs (error bars).*

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 maximal 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 difference in 20 μmol/L ADP-induced maximal aggregation of 15% with a power of 90%, a two-sided $\alpha = 0.05$, 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 χ^2 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 characteristics 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 occurred during the study period. Baseline platelet reactivity and HPR prevalence before 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 ($P \leq 0.124$; Supplementary Table 2).

TRIPLE was associated with a greater ΔMPA_{20ADP} of 22.9 ± 11.6% compared with 12.7 ± 15.5% for DOUBLE (difference, 10.2% [95% CI 4.2–16.3%]; $P < 0.001$; Fig. 1*A*). Other changes of LTA-based PAs also showed the same results ($P \leq 0.021$). TRIPLE achieved a higher ΔPRU of 108 ± 63 compared with 73 ± 61 for DOUBLE (difference, 35 [7–62]; $P = 0.014$; Fig. 1*B*). 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-function (*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. 1*C–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 characteristics or genetic polymorphisms significantly influenced the effect of adding cilostazol (Fig. 1*C–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 influenced by genetic variations and demographic characteristics and that the double-dose clopidogrel effect is significantly 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 comparable platelet inhibition among the *CYP2C19*2* homozygotes (12).

A recent meta-analysis demonstrated that the addition of cilostazol might reduce 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 itself increases the activity of inflammation, oxidative stress, and coagulation activity, which can increase the influence of platelet reactivity on clot formation (15). The inhibitory effect of cilostazol on PDE3, together with its effect on signaling through adenosine, prostaglandin, and nitric oxide on platelets, vascular smooth muscle cells, endothelium, 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 together, 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 future 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 unknown 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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