Circulation

ORIGINAL RESEARCH ARTICLE

Pharmacodynamic Effects of Switching From Ticagrelor to Clopidogrel in Patients With Coronary Artery Disease

Results of the SWAP (Switching Antiplatelet Therapy)-4 Study

BACKGROUND: Switching between different classes of $P2Y_{12}$ inhibitors, including de-escalation from ticagrelor to clopidogrel, commonly occurs in clinical practice. However, the pharmacodynamic profiles of this strategy have been poorly explored.

METHODS: This was a prospective, randomized, open-label study conducted in patients on maintenance dosing (MD) of aspirin (81 mg/d) and clopidogrel (75 mg/d). After a 7-day run-in with ticagrelor (180 mg loading dose [LD] followed by 90 mg twice daily MD), patients (n=80) were randomized into 1 of 4 groups: group A, clopidogrel 600 mg LD 24 hours after the last MD of ticagrelor (C-600 mg-24h); group B, clopidogrel 600 mg LD 12 hours after the last MD of ticagrelor (C-600 mg-12h); group C, clopidogrel 75 mg/d MD 24 hours after the last MD of ticagrelor (C-75 mg-24h); and group D, ticagrelor 90 mg twice daily MD (T-90 mg twice daily). MD of the randomized treatment was maintained for 10±3 days. Pharmacodynamic assessments were performed at baseline, after run-in, and at 2, 24, 48, and 72 hours and 10 days with $P2Y_{12}$ reaction units by VerifyNow; platelet reactivity index was assessed by vasodilator-stimulated phosphoprotein; and maximal platelet aggregation was determined by light transmittance aggregometry.

RESULTS: T-90 mg twice daily led to lower platelet reactivity than any clopidogrel regimen using all assays at all time points. $P2Y_{12}$ reaction unit levels were similar between the C-600 mg-24h (group A) and the C-75 mg-24h (group C) (P=0.29), including at 48 hours (primary end point; least mean difference, −6.9; 95% confidence interval, −38.1 to 24.3; P=0.66). $P2Y_{12}$ reaction unit levels were lower with C-600 mg-12h (group B) than with C-75 mg-24h (group C; P=0.024). Maximal platelet aggregation over time was lower with both C-600 mg-24h (group A; P=0.041) and C-600 mg-12h (group B; P=0.028) compared with C-75 mg-24h (group C). Platelet reactivity index profiles paralleled those observed with $P2Y_{12}$ reaction units. There were no pharmacodynamic differences for all tests between C-600 mg-24h (group A) and C-600 mg-12h (group B). In group C (C-75 mg-24h), platelet reactivity increased compared with baseline as early as 24 hours, reaching statistical significance at 48 and 72 hours and up to 10 days. These pharmacodynamic findings were delayed and blunted in magnitude with the administration of an LD, regardless of the timing of administration.

CONCLUSIONS: De-escalation from ticagrelor to clopidogrel therapy is associated with an increase in platelet reactivity. The use of an LD before the initiation of an MD regimen of clopidogrel mitigates these observations, although this is not affected by the timing of its administration after ticagrelor discontinuation.

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Clinical Perspective

What Is New?

- De-escalation consisting of a switch from ticagrelor to clopidogrel therapy is associated with an increase in platelet reactivity suggestive of a drug–drug interaction.
- Administration of a loading dose before the initiation of a maintenance dose regimen of clopidogrel mitigates these observations.
- Although delaying the timing of administration of a thienopyridine has been suggested as a strategy to overcome a drug–drug interaction during a switch from ticagrelor, this study did not show profiles of platelet reactivity to be affected by timing of loading dose administration after ticagrelor discontinuation.

What Are the Clinical Implications?

- The choice of $P2Y_{12}$-inhibiting therapy should be in line with guideline recommendations, and a strategy of de-escalation cannot be routinely recommended and should be avoided early after an acute coronary event, particularly in patients undergoing stent implantation.
- If there is a need to de-escalate from ticagrelor to clopidogrel, a 600-mg loading dose should be used except in patients switching therapy because of bleeding.
- Clopidogrel loading dose administration should occur when most feasible (12 or 24 hours after ticagrelor discontinuation) for the patient.

The recommended oral antiplatelet treatment regimen for patients presenting with acute coronary syndromes and for those undergoing percutaneous coronary intervention (PCI) is the combination of aspirin and a $P2Y_{12}$ receptor inhibitor.[1–3] Currently, 3 oral $P2Y_{12}$ receptor inhibitors are available for clinical use (clopidogrel, prasugrel, and ticagrelor), which has enabled physicians to switch among these therapies.[4,5] Among the switching opportunities, de-escalation (ie, switching from a more potent to a less potent agent) commonly occurs in clinical practice.[4,5] In general, reasons prompting the de-escalation of $P2Y_{12}$-inhibiting therapy include costs, side effects, and variations in ischemic and bleeding risk patterns over time.[4,5] However, pharmacodynamic investigations have suggested the potential for drug–drug interactions (DDIs), particularly when switching between different classes of $P2Y_{12}$ inhibitors (ie, from a nonthienopyridine to a thienopyridine).[4–11]

Ticagrelor is a first-in-class cyclopentyl triazolopyrimidine characterized by more potent pharmacodynamic effects compared with clopidogrel, a second-generation thienopyridine.[1] Despite the superiority of ticagrelor over clopidogrel in reducing ischemic events, many physicians often limit treatment duration with ticagrelor to just the early months or even weeks after an acute coronary syndrome.[4,5,12] However, the fast speed of offset of ticagrelor-induced antiplatelet effects after treatment discontinuation has brought into question how to maintain adequate levels of platelet inhibition in case of de-escalation to clopidogrel therapy.[13,14] Despite the common switching occurrence in clinical practice, the pharmacodynamic effects and optimal approach of switching from ticagrelor to clopidogrel remain poorly explored and represented the aim of this investigation.

METHODS

Study Design and Patient Population

The SWAP study (Switching Antiplatelet Therapy)-4 was a prospective, randomized, open-label, single-center study aimed at assessing the pharmacodynamic effects of switching from ticagrelor to clopidogrel in patients with coronary artery disease on a background of aspirin therapy (ClinicalTrials.gov identifier, NCT02287909). In particular, this study investigated how the pharmacodynamic effects of such a de-escalation strategy are affected by the use of a clopidogrel loading dose (LD) compared with a maintenance dose (MD) regimen and the impact of different timing of LD administration after discontinuation of ticagrelor treatment. Patients with coronary artery disease on maintenance (>30 days) therapy with aspirin (81 mg/d) and clopidogrel (75 mg/d) were screened for study eligibility (see the online-only Data Supplement for specific study inclusion and exclusion criteria). The study complied with the Declaration of Helsinki and was approved by the University of Florida Institutional Review Board, and all patients gave their written informed consent.

Patients meeting study entry criteria underwent a 7±2-day run-in phase with ticagrelor, which consisted of a switch from clopidogrel (75 mg/d MD) to ticagrelor (180 mg LD followed by 90 mg twice daily MD). After this run-in phase, with the use of a computer-based randomization system, patients were randomized (1:1:1:1) into 1 of the 4 following groups: group A, clopidogrel 600 mg LD 24 hours after the last MD of ticagrelor followed by 75 mg/d MD (C-600 mg-24h); group B, clopidogrel 600 mg LD 12 hours after the last MD of ticagrelor followed by 75 mg/d MD (C-600 mg-12h); group C, clopidogrel 75 mg/d MD 24 hours after the last MD of ticagrelor (C-75 mg-24h); and group D, continued ticagrelor 90 mg twice daily MD (T-90 mg twice daily). Randomized treatment was maintained for 10±3 days. Aspirin (81 mg/d) was maintained throughout the study. Compliance to treatment was assessed by pill count and patient interview. After completing the study, patients resumed the antiplatelet treatment regimen recommended by their treating physician. A flow diagram of the study is presented in Figure 1.

Blood Sampling and Pharmacodynamic Testing

Blood sampling for pharmacodynamic assessments was performed at the following time points: at baseline before

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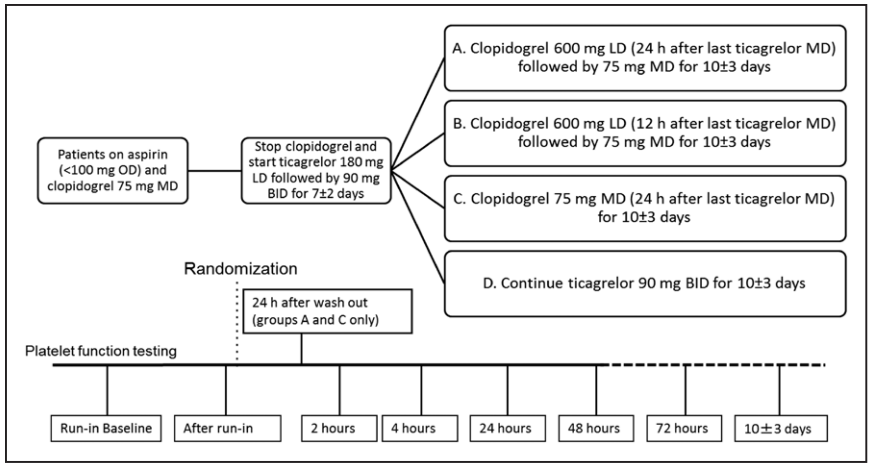

Figure 1. Study design.
BID indicates twice daily; LD, loading dose; MD, maintenance dose; and OD, once daily.

run-in (24 hours after the last clopidogrel MD to assess trough levels of platelet reactivity), after run-in (12 hours after the last ticagrelor MD of run-in period), 24 hours after washout (groups A and C only), and 2, 24, 48, and 72 hours and 10±3 days after randomization. Patients randomized to groups A and C, both requiring 24 hours' washout from last MD, were required to take their morning MD of ticagrelor after blood sample collection for their post–run-in phase and to return the next morning to receive the randomized treatment (these groups had a total of 8 blood sampling time points). Patients randomized to groups B and D initiated their randomized treatment the same morning of the post–run-in phase visit (these groups had a total of 7 blood sampling time points). A timetable of protocol procedures, including the timing of blood sampling, is summarized in the online-only Data Supplement (see Table I in the online-only Data Supplement).

Pharmacodynamic testing was performed by laboratory personnel blinded to treatment assignments. Pharmacodynamic testing included 3 different assays: VerifyNow $P2Y_{12}$ point-of-care testing (VN-$P2Y_{12}$), whole-blood vasodilator-stimulated phosphoprotein (VASP), and light transmittance aggregometry (LTA). In brief, the VN-$P2Y_{12}$ assay (Accriva, San Diego, CA) measures platelet-induced aggregation as an increase in light transmittance and reports results in $P2Y_{12}$ reaction units (PRUs).[6,15–17] VASP was measured by quantitative flow cytometry using commercially available, labeled monoclonal antibodies according to standard protocols (Biocytex Inc, Marseille, France) and quantified by the platelet reactivity index (PRI).[6,15–17] LTA was conducted with platelet-rich plasma by the turbidimetric method in a 2-channel aggregometer (Chrono-Log 490 model, Chrono-Log Corp, Havertown, PA) after 5 and 20 μmol/L ADP stimuli; curves were recorded for 6 minutes, and maximal platelet aggregation (MPA) was determined as percent change in light transmittance.[6,15–17] In line with expert consensus, high on-treatment platelet reactivity (HPR) was defined as follows: PRUs >208 (VN-$P2Y_{12}$), PRI >50% (VASP), MPA >59% (LTA 20 μmol/L ADP), or MPA >46% (LTA 5 μmol/L ADP).[18] Because MPA profiles using 5 μmol/L ADP were similar to those using 20 μmol/L ADP, only data for 20 μmol/L ADP are shown.

Ultimately, to define the impact of cytochrome P450 (CYP)2C19 genetic status on pharmacodynamic profiles associated with switching from ticagrelor to clopidogrel, genetic testing was performed in all patients at their baseline visit with the Spartan RX rapid genotyping device (Spartan Bioscience Inc, Ottawa, Canada).[19,20] This assay enables assessment of the following alleles: *1,*2,*3, and *17. Patients were classified according to the presence or absence of loss-of-function (LOF) alleles (*2 or *3) as follows: LOF homozygotes (*2/*2, *3/*3, or *2/*3), LOF heterozygotes (*1/*2, *1/*3, *2/*17, *3/*17), or non-LOF (*1/*1, *1/*17, or *17/*17).[19,20]

Sample Size Calculation and Study End Points

The primary end point was the comparison of PRUs assessed by VN-$P2Y_{12}$ at 48 hours after the switch from ticagrelor 90 mg twice daily between clopidogrel 600 mg LD administered 24 hours after the last ticagrelor MD (group A) and clopidogrel 75 mg MD administered 24 hours after the last ticagrelor MD (group C). We hypothesized that switching from ticagrelor to clopidogrel with an LD would mitigate the anticipated increase in platelet reactivity compared with no LD. The sample size was determined from the objective of establishing the superiority of this approach. Superiority was assessed with the 95% confidence interval of the difference in mean PRUs between these 2 groups. Under the assumption of a mean difference of 60 PRUs between groups and a common SD of 50 PRUs, a sample size of 16 patients per group would be required with a 95% power and an α of 0.05. Considering 4 arms of treatment and a possibility of having invalid data in 20% to 25% of patients because of technical issues or dropouts, we considered randomizing up to a total of 80 patients (20 patients per group) to ensure complete data. This sample size was calculated from previously published data.[13] Secondary end points included a comparison of PRUs (other than the primary end point), MPA, and PRI in all 4 groups at each time point and during the overall study time course; intragroup comparisons of platelet reactivity within each group; rates of HPR according to each platelet function assay (VN-$P2Y_{12}$, LTA, and PRI) in all 4 groups at each time point; and the impact of CYP2C19 LOF genetic status on pharmacodynamic parameters. Data from the intragroup comparisons were used to explore the presence of a DDI, which was defined as the presence of levels of platelet reactivity after de-escalation that were significantly higher than those at baseline while patients were on maintenance clopidogrel therapy. For all these analyses, we considered only

1 time point for post–run-in, which was the last time point before the administration of the randomized treatment: 12 hours after the last ticagrelor dose for groups B and D and 24 hours after the last ticagrelor dose for groups A and C. The safety population was composed of all patients exposed to at least 1 dose of study medication (any time from the run-in phase until completion of the study). The pharmacodynamic population included all patients who completed the run-in phase and received at least 1 dose of randomized study drug.

Statistical Analysis

Conformity to normal distribution was evaluated for continuous variables with the Kolmogorov-Smirnov test. For baseline characteristics, continuous variables are expressed as mean±SD, and categorical variables are expressed as frequencies and percentages. The χ^2 test or Fisher exact test was used as applicable to compare categorical variables between groups, and 1-way ANOVA was used to compare continuous variables. An ANCOVA method with a general linear model, with the baseline value of platelet reactivity used as a covariate, was used to evaluate the primary end point and all between-group comparisons at each single time point. A mixed between-within subjects ANCOVA with polynomial contrast, also adjusted for baseline platelet reactivity, was conducted with a general linear model to evaluate the overall difference between groups across time points. A repeated-measures ANOVA model was used to evaluate intragroup comparisons. This model was used to estimate the difference (Δ) in platelet reactivity between each time point and baseline (while patients were on maintenance clopidogrel therapy) to investigate the presence of a DDI. Because of the pharmacodynamic nature of the study, no adjustment for multiple comparisons was performed. The χ^2 test was used to compare rates of HPR among groups. An interaction analysis to assess the effects of LOF status on the main effect of treatment group was performed through a general linear model. Missing data (eg, because of hemolyzed blood samples, inability to draw blood, or dropouts) were not imputed. A 2-tailed value of $P<0.05$ was considered to indicate a statistically significant difference for all the analyses performed. Pharmacodynamic data are presented as least-squares mean and 95% confidence interval. Statistical analysis was performed with SPSS version 24.0 software (SPSS Inc, Chicago, IL).

RESULTS

Patient Population

Between June 2015 and August 2017, a total of 88 patients with coronary artery disease on maintenance therapy with aspirin and clopidogrel for at least 30 days agreed to participate in the study. One patient was excluded because of the presence of an exclusion criterion. Thus, 87 patients (safety population) entered the run-in phase, of whom 7 did not complete the phase (dyspnea, n=3; withdrawal of consent, n=3; development of non–study-related illness, n=1). Therefore, a total of 80 patients (pharmacodynamic population) were randomized (group A, n=20; group B, n=20; group C, n=20; group D, n=20). Overall, 4 patients withdrew from the study after randomization (need for PCI, n=1; inability to draw blood samples, n=1; noncompliance, n=2). Patient disposition is summarized in Figure 2. Demographic and baseline characteristics of the pharmacodynamic population are summarized in Table 1. No ischemic or *Bleeding* Academic Research Consortium type 2 to 5 bleeding events were observed in the safety population during the overall study time course; 1 patient had *Bleeding* Academic Research Consortium type 1 bleeding; 15 patients (18.75%) had dyspnea during the run-in phase with ticagrelor; and 2 patients had dyspnea after randomization (ticagrelor, n=1; clopidogrel, n=1).

Pharmacodynamic Findings

After the switch from clopidogrel to ticagrelor (run-in phase), platelet reactivity with all 3 pharmacodynamic assays was significantly reduced compared with baseline levels ($P<0.001$; Figures 3 through 5). Platelet reactivity remained significantly lower ($P<0.001$) in patients randomized to maintain ticagrelor therapy (group D) compared with any of the clopidogrel treatment arms (group A, B, or C) (Figures 3 through 5).

Pharmacodynamic profiles according to PRUs are illustrated in Figure 3. PRU levels were similar between C-600 mg-24h (group A) and C-75 mg-24h (group C) ($P=0.29$), including at 48 hours (primary end point; least mean difference, –6.9; 95% confidence interval, –38.1 to 24.3; $P=0.66$). PRU levels were lower over the study time course with C-600 mg-12h (group B) versus C-75 mg-24h (group C; $P=0.024$), with significant differences at 2 and 24 hours. There were no differences in PRU levels over time between C-600 mg-24h (group A) and C-600 mg-12h (group B; $P=0.26$).

Pharmacodynamic profiles according to MPA using 20 μmol/L ADP are illustrated in Figure 4. MPA over time was lower with both C-600 mg-24h (group A) ($P=0.041$) and C-600 mg-12h (group B; $P=0.028$) compared with C-75 mg-24h (group C), with significant differences at 24, 48, and 72 hours using a C-600 mg-24h regimen and at 2 and 24 hours using a C-600 mg-12h regimen. There were no differences in MPA levels between C-600 mg-24h (group A) and C-600 mg-12h (group B; $P=0.92$).

Pharmacodynamic profiles according to PRI are illustrated in Figure 5. Although at 24 hours PRI levels were lower in C-600 mg-24h (group A) compared with C-75 mg-24h (group C) ($P=0.025$), they were overall similar over the study time course ($P=0.21$). PRI levels were lower over the study time course with C-600 mg-12h (group B) versus C-75 mg-24h (group C; $P=0.006$), with significant differences at 2, 24, and 48 hours. There were no differences over time between C-600 mg-24h (group A) and C-600 mg-12h (group B; $P=0.15$), with

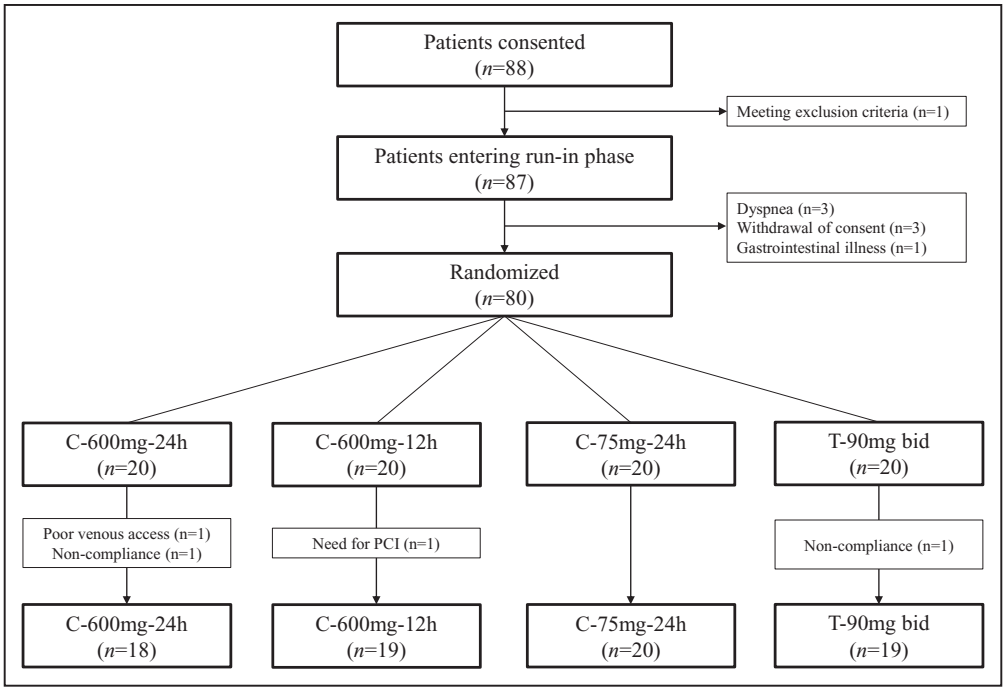

Figure 2. Patient disposition.
C-600mg-12h indicates clopidogrel 600 mg loading dose (LD) 12 hours after the last maintenance dose (MD) of ticagrelor; C-600mg-24h, clopidogrel 600 mg LD 24 hours after the last MD of ticagrelor; C-75mg-24h, clopidogrel 75 mg/d MD 24 hours after the last MD of ticagrelor; PCI, percutaneous coronary intervention; and T-90mg bid, ticagrelor 90mg twice daily MD.

significant differences only at a single time point (2 hours; *P*=0.027).

An intragroup analysis assessing platelet reactivity over time and comparison with baseline levels (before the run-in phase while patients were on maintenance clopidogrel therapy) allowed us to define whether exposure to ticagrelor interfered with clopidogrel-induced antiplatelet effects. Although levels of platelet reactivity increased over time when switching to clopidogrel, as would be anticipated with a de-escalation strategy, the magnitude of this effect was enhanced among subjects randomized to MD treatment (C-75 mg-24h) compared with patients in whom an LD was used (C-600 mg-24h and C-600 mg-12h; Figure 6). In particular, levels of platelet reactivity in patients randomized to group C (C-75 mg-24h) were increased compared with baseline as early as 24 hours and continued to increase up to 72 hours after randomization, reaching statistical significance at both the 48-hour (MPA and PRI) and 72-hour (PRUs, MPA, and PRI) time points. Although platelet reactivity declined after 72 hours, all pharmacodynamic measures (PRUs, MPA, and PRI) remained significantly higher than baseline even 10 days after randomization. These pharmacodynamic findings were delayed and blunted in magnitude with the administration of an LD. In fact, although levels of platelet reactivity were significantly lower 24 hours after randomization, they were similar to baseline after 48 hours and increased after 72 hours with C-600 mg-24h (PRI) and C-600 mg-12h (PRUs and MPA); platelet reactivity returned to levels similar to baseline after 10 days with the exception of PRI using C-600 mg-24h. De-escalation was also associated with an increase in HPR with time after randomization, although the proportion of patients with HPR did not exceed baseline levels (Table 2).

A total of 18 patients (22.8%) were carriers of a CYP2C19 LOF allele (Table 1). There was no interaction of LOF status on the effects of treatment group on measures of platelet reactivity based on PRUs and PRI during the overall study time course across groups and at the individual time points (data not shown). Only with measures of platelet reactivity by MPA was there a borderline interaction according to LOF status in the overall analysis across groups (*P*=0.047). In particular, compared with C-75 mg-24h, MPA was significantly lower across time points in non-LOF carriers in C-600 mg-24h (*P*=0.006) and C-600 mg-12h (*P*=0.004); among carriers of LOF, there were no differences between C-600 mg-24h and C-75 mg-24h (data not shown; *P*=0.89).

DISCUSSION

SWAP-4 is the first study to evaluate the pharmacodynamic impact of the timing and dosing of clopidogrel administration when de-escalating from ticagrelor therapy. Indeed, although a decrease in platelet inhibition is anticipated with de-escalation, defining the strategy associated with a less abrupt increase in platelet re-

Table 1. Baseline Characteristics of the Pharmacodynamic Population

Characteristics	C-600 mg-24h (n=20)	C-600 mg-12h (n=20)	C-75 mg-24h (n=20)	T-90 mg BID (n=20)	*P* Value
Age, y	62±7	65±8	63±9	58±9	0.09
Men, n (%)	11 (55)	15 (75)	13 (65)	12 (60)	0.59
BMI, kg/m^2	32±8	31±4	31±5	31±9	0.86
Race, n (%)					0.44
White	10 (50)	14 (70)	13 (65)	14 (70)	
Black	10 (50)	5 (25)	7 (35)	6 (30)	
Other	0 (0)	1 (5)	0 (0)	0 (0)	
Diabetes mellitus, n (%)	9 (45)	9 (45)	6 (30)	5 (25)	0.43
CKD, n (%)	3 (15)	2 (10)	0 (0)	1 (5)	0.31
Hypertension, n (%)	15 (75)	19 (95)	15 (75)	14 (70)	0.26
Dyslipidemia, n (%)	18 (90)	19 (95)	17 (85)	17 (85)	0.71
Smoking, n (%)	7 (35)	6 (30)	5 (25)	7 (35)	0.29
PAD, n (%)	4 (20)	3 (15)	3 (15)	3 (15)	0.97
Prior stroke, n (%)	6 (30)	1 (5)	4 (20)	3 (15)	0.21
Prior MI, n (%)	11 (55)	11 (55)	15 (75)	14 (70)	0.43
Prior PCI, n (%)	20 (100)	17 (85)	18 (90)	20 (100)	0.12
Prior CABG, n (%)	5 (25)	5 (25)	9 (45)	5 (25)	0.41
LOF allele, n (%)	6 (30)	0 (0)	5 (25)	7 (35)	0.04
Heterozygous	6 (30)	0 (0)	4 (20)	7 (35)	
Homozygous	0 (0)	0 (0)	1 (5)	0 (0)	
GOF allele, n (%)	0 (0)	1 (5)	0 (0)	2 (10)	0.89
Medications, n (%)					
OAD	3 (15)	7 (35)	2 (10)	4 (20)	0.22
Insulin	5 (25)	5 (25)	3 (15)	2 (10)	0.53
β-Blockers	15 (75)	17 (85)	19 (95)	16 (80)	0.36
ACEi/ARB	12 (60)	13 (65)	14 (70)	13 (65)	0.93
Statins	20 (100)	20 (100)	20 (100)	20 (100)	1
PPI*	5 (25)	4 (20)	5 (25)	4 (20)	0.96
Hemoglobin, g/dL	13.1±1.3	13.3±1.3	13.8±1.8	13.7±1.8	0.43
Creatinine, mg/dL	1.1±0.3	1.0±0.2	1.0±0.3	0.9±0.2	0.26
CrCl, mL/min	96±37	96±28	101±44	109±41	0.69
Hematocrit, %	39±4	40±3	42±5	41±4	0.32
Platelet count, 1000/mm^3	196±74	223±54	248±87	243±57	0.09

Data are presented as mean±SD or n (%). ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CrCl, creatinine clearance; C-600 mg-12h, clopidogrel 600 mg loading dose 12 hours after the last maintenance dose of ticagrelor; C-600 mg-24h, clopidogrel 600 mg loading dose 24 hours after the last maintenance dose of ticagrelor; C-75 mg-24h, clopidogrel 75 mg/d maintenance dose 24 hours after the last maintenance dose of ticagrelor; GOF, gain of function; LOF, loss of function; MI, myocardial infarction; OAD, oral antidiabetic drug; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; and T-90 mg BID, ticagrelor 90mg twice daily maintenance dose.

*No patient received omeprazole.

activity and ruling out a DDI is of utmost importance. Although the primary end point (superiority of C-600 mg-24h versus C-75 mg-24h after switching from ticagrelor on PRU levels) was not met, there are several key findings to this study. First, switching from ticagrelor to clopidogrel with an LD (before starting MD) was associated with greater levels of platelet inhibition during the first 48 hours compared with switching directly to an MD regimen (without an LD). Second, the pharmacodynamic profiles did not differ according to timing of administration of the LD (12 versus 24 hours after ticagrelor discontinuation). Third, the pharmacodynamic profiles of switching from ticagrelor to clopidogrel were suggestive of a DDI, which was mitigated

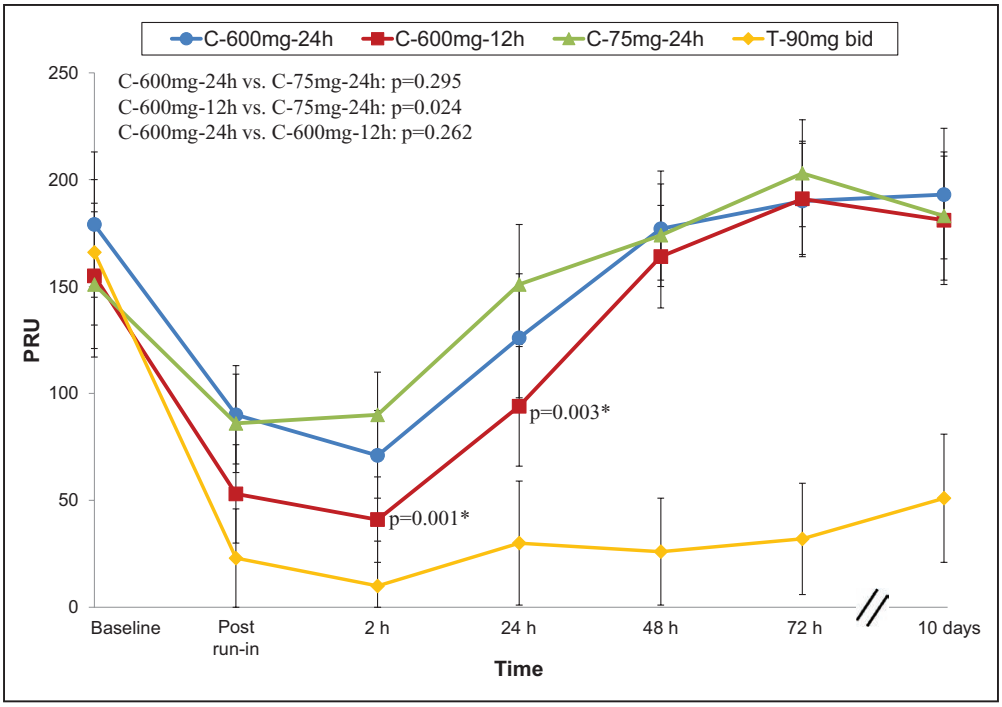

Figure 3. Pharmacodynamic profiles of switching from ticagrelor to clopidogrel measured by VerifyNow P2Y$_{12}$. Comparison of P2Y$_{12}$ reaction units (PRUs) among groups. *P* values represent the overall comparisons between groups during the overall study time course. Asterisks indicate *P* values that reach statistical significance between groups at the individual time points; values of *P*>0.05 are not presented. Data are presented as least-squares mean and 95% confidence interval. C-600mg-12h indicates clopidogrel 600 mg loading dose (LD) 12 hours after the last maintenance dose (MD) of ticagrelor; C-600mg-24h, clopidogrel 600 mg LD 24 hours after the last MD of ticagrelor; C-75mg-24h, clopidogrel 75 mg/d MD 24 hours after the last MD of ticagrelor; and T-90mg bid, ticagrelor 90mg twice daily MD. *Versus C-75mg-24h.

with the administration of an LD (regardless of timing of administration). Fourth,CYP2C19 genetic status did not appear to have any meaningful impact on the study findings. These pharmacodynamic findings have the following clinical implications: the choice of P2Y$_{12}$-inhibiting therapy should be in line with guideline recommendations,[2,3] and a strategy of de-escalation cannot be routinely recommended and should be avoided early after an acute coronary event, particularly in patients undergoing PCI. In line with expert consensus recommendations,[5] if there is a need to de-escalate from ticagrelor to clopidogrel, a 600-mg LD should be used except in patients switching therapy because of bleeding. Although expert consensus recommendations are that de-escalation should occur 24 hours after ticagrelor discontinuation,[5] the lack of significant differences in pharmacodynamic profiles according to timing of administration in this study suggests that LD administration should occur when most feasible (12 or 24 hours after ticagrelor discontinuation) for the patient.

The fast offset of the pharmacodynamic effects induced by ticagrelor (3–5 days) has raised concerns about a gap in platelet inhibition when switching to clopidogrel, particularly with the use of an MD regimen (without an LD), which requires at least 7 days to reach its full antiplatelet effects.[1,4,5,13] A gap in platelet inhibition could be detrimental in high-risk patients such as those who recently underwent stent implantation.[18,21] These concerns are further amplified by the fact that a DDI has been demonstrated in investigations assessing the pharmacodynamic effects of switching between different classes of P2Y$_{12}$ inhibitors (ie, from a nonthienopyridine to thienopyridine agent).[4–11] To this extent, the results of SWAP-2 and SWAP-4, both investigating a switch from a nonthienopyridine (ie, ticagrelor) to a thienopyridine (prasugrel and clopidogrel, respectively) agent, show consistent findings.[6] In fact, in both studies, switching to a thienopyridine using a MD regimen was associated with an increase in platelet reactivity over time, an observation that persisted with, although was hampered by, the administration of an LD. These findings suggest the presence of a DDI because of the inability of the active metabolite of clopidogrel to effectively bind with the P2Y$_{12}$ receptor during the first 24 to 72 hours after discontinuation of ticagrelor. In SWAP-4, even after 10±3 days of MD, levels of platelet reactivity remained elevated compared with baseline (before the run-in phase while patients were on maintenance clopidogrel therapy) when an LD was not used, indicating that for patients treated with a MD regimen, there was inadequate time for effective drug exposure to reach its full therapeutic effects. Our find-

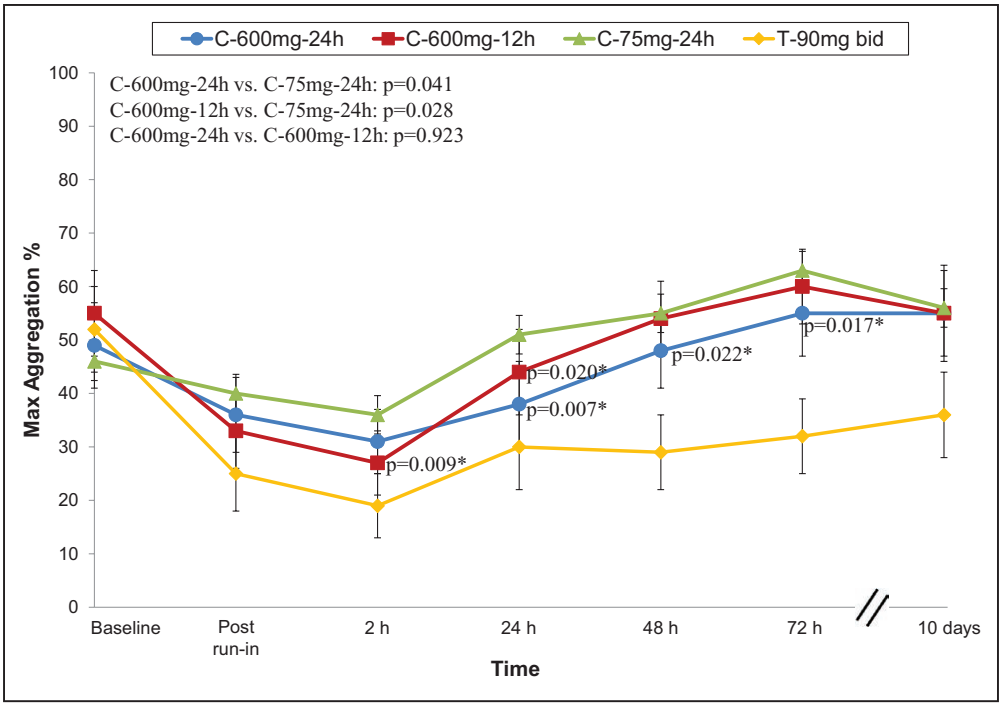

Figure 4. Pharmacodynamic profiles of switching from ticagrelor to clopidogrel measured by light transmittance aggregometry.

Comparison of maximal platelet aggregation among groups. *P* values represent the overall comparisons between groups during the overall study time course. Asterisks indicate *P* values that reach statistical significance between groups at the individual time points; values of *P*>0.05 are not presented. Data are presented as least-squares mean and 95% confidence interval. C-600mg-12h indicates clopidogrel 600 mg loading dose (LD) 12 hours after the last maintenance dose (MD) of ticagrelor; C-600mg-24h, clopidogrel 600 mg LD 24 hours after the last MD of ticagrelor; C-75mg-24h, clopidogrel 75 mg/d MD 24 hours after the last MD of ticagrelor; Max, maximum; and T-90mg bid, ticagrelor 90mg twice daily MD. *Versus C-75 mg-24h.

ings were consistent with the use of 3 different platelet function assays, providing support to our study conclusions. Overall, these pharmacodynamic observations suggest that repeated clopidogrel LD administrations may be required to allow an even less abrupt increase in platelet reactivity after de-escalation from ticagrelor therapy and to achieve more promptly the full therapeutic effects. Our study findings are in line with those from the only other randomized investigation assessing the pharmacodynamic effects of de-escalating from ticagrelor to clopidogrel therapy.[14] In this study, limited to a single platelet function assay, although patients treated with an LD of clopidogrel administered 12 hours after ticagrelor discontinuation had lower levels of platelet reactivity compared with those not treated with an LD during the first 48 hours, the primary end point of the study was not met.[14] However, the impact of differential timing of LD administration was not assessed, and the lack of a control group and a baseline reference did not allow the discernment of the presence of a DDI.[22]

Prior investigations hypothesized that switching at a later time frame from ticagrelor discontinuation (eg, 24 hours) would enable more time to wash out its effects, reducing the potential for any potential DDI.[5,6] This was the rationale for considering different timings of clopidogrel LD administration (12 and 24 hours) after discontinuation of ticagrelor treatment in SWAP-4. However, our study did not show any advantage on pharmacodynamic profiles associated with delaying clopidogrel LD administration. The mechanisms of such DDI remain unclear. They may reside in potential conformational changes at the $P2Y_{12}$ receptor level that persist beyond the half-life of ticagrelor, which would impede binding of the active metabolite of thienopyridines. This could explain why the pharmacodynamic effects of ticagrelor persist for 3 to 5 days after discontinuation despite its relatively short half-life (8–12 hours), the mechanisms of which are the subject of ongoing investigation.[1,13,23] Recently, the traditional concept that ticagrelor reversibly binds to a site distinct from that of ADP on the $P2Y_{12}$ receptor, acting through a noncompetitive, allosteric mechanism to prevent G-protein–mediated signal transduction after ADP binding, has been challenged.[24] In fact, some experiments suggest a competitive mode of antagonism by ticagrelor and inhibition of the ADP binding site.[25] Moreover, a mutagenesis analysis suggests the interaction of ticagrelor with the residue Cys194 of the receptor protein, which is in proximity to the agonist binding site, and to the residue Cys97,

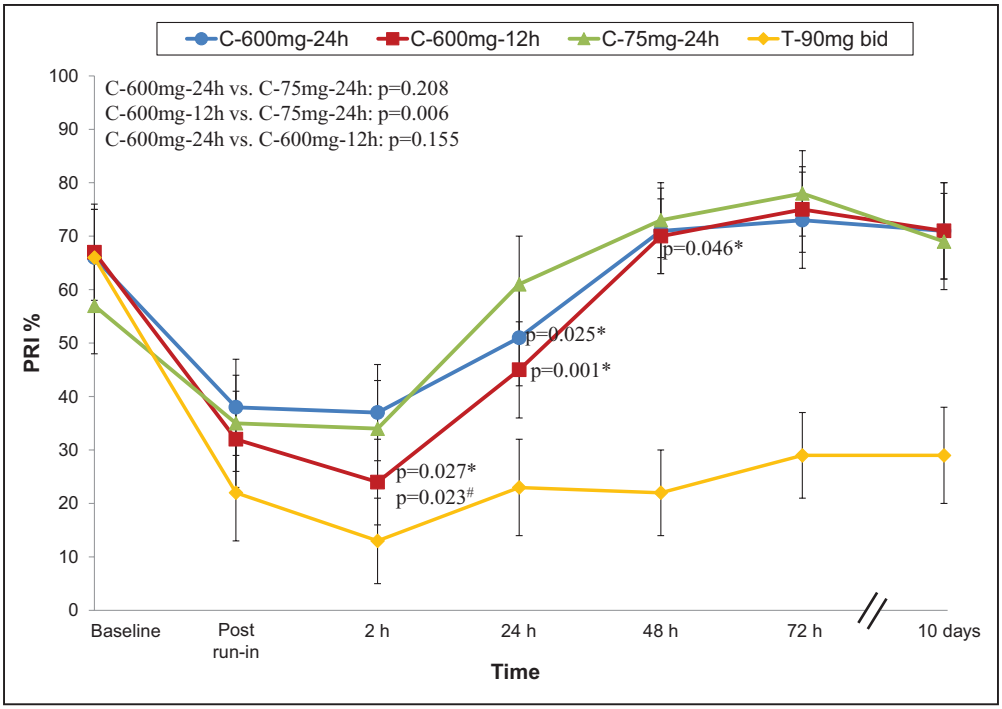

Figure 5. Pharmacodynamic profiles of switching from ticagrelor to clopidogrel measured by vasodilator-stimulated phosphoprotein.

Comparison of platelet reactivity index (PRI) among groups. *P* values represent the overall comparisons between groups during the overall study time course. Asterisks and hashtags indicate *P* values that reach statistical significance between groups at the individual time points; values of *P*>0.05 are not presented. Data are presented as least-squares mean and 95% confidence interval. C-600mg-12h indicates clopidogrel 600 mg loading dose (LD) 12 hours after the last maintenance dose (MD) of ticagrelor; C-600mg-24h, clopidogrel 600 mg LD 24 hours after the last MD of ticagrelor; C-75 mg-24h, clopidogrel 75 mg/d MD 24 hours after the last MD of ticagrelor; and T-90mg bid, ticagrelor MD 90 mg twice daily MD. *Versus C-75mg-24h. #Versus C-600mg-24h.

which interacts with the active metabolites of clopidogrel and prasugrel.[26,27]

The uptake of ticagrelor in clinical practice has increased over the past years, which also has led to a better definition of the factors associated with de-escalation, which include costs, side effects, and variations in ischemic and bleeding risk patterns over time.[4,5,28] The observation from clinical trials with prasugrel and ticagrelor showing that the greatest ischemic benefit of more potent $P2Y_{12}$ blockade is early after the index event when the risk of thrombotic complications is highest, whereas the risk of bleeding complications accrues with the prolongation of treatment,[29,30] has led investigations exploring outcomes associated with limiting treatment with the more potent agents to the first few weeks or months, followed by de-escalation to clopidogrel therapy.[31–33] Indeed, the evolution in stent technology contributing to stent designs associated with lower thrombotic risk and requiring shorter mandatory dual antiplatelet therapy duration has contributed to this pattern in clinical practice.[34] Dyspnea is also commonly present in ticagrelor-treated patients, as also observed in this study, and not infrequently is associated with treatment discontinuation.[12,35] Indeed, studies in which the timing of de-escalation was remote from the index event suggest this strategy to be safe, with outcomes driven largely by a reduction in bleeding without any tradeoff in efficacy.[31–33] However, in clinical practice, de-escalation often occurs early after the index event.[4,5] In addition to the anticipated inability to access the more potent $P2Y_{12}$ inhibitors because of costs, de-escalation to clopidogrel may occur as a result of early bleeds or need for use of oral anticoagulant therapy (eg, because atrial fibrillation becomes apparent during the hospital stay), in which case clopidogrel remains the $P2Y_{12}$ inhibitor of choice.[3,36] However, observational data suggest early de-escalation to be associated with an increased risk of adverse outcomes, which is in line with greater vulnerability of patients to an increase in platelet reactivity during this time frame.[37–39] It is also important to note that in the studies suggesting the safety of de-escalation, many patients were treated with prasugrel (including the only trial supporting the role of de-escalation guided by platelet function testing), which has an offset of pharmacodynamic effects much longer than that of ticagrelor and is of the same class (ie, thienopyridine) as clopidogrel, thus not leading to a DDI.[4,5,40] Details on the modality of switching

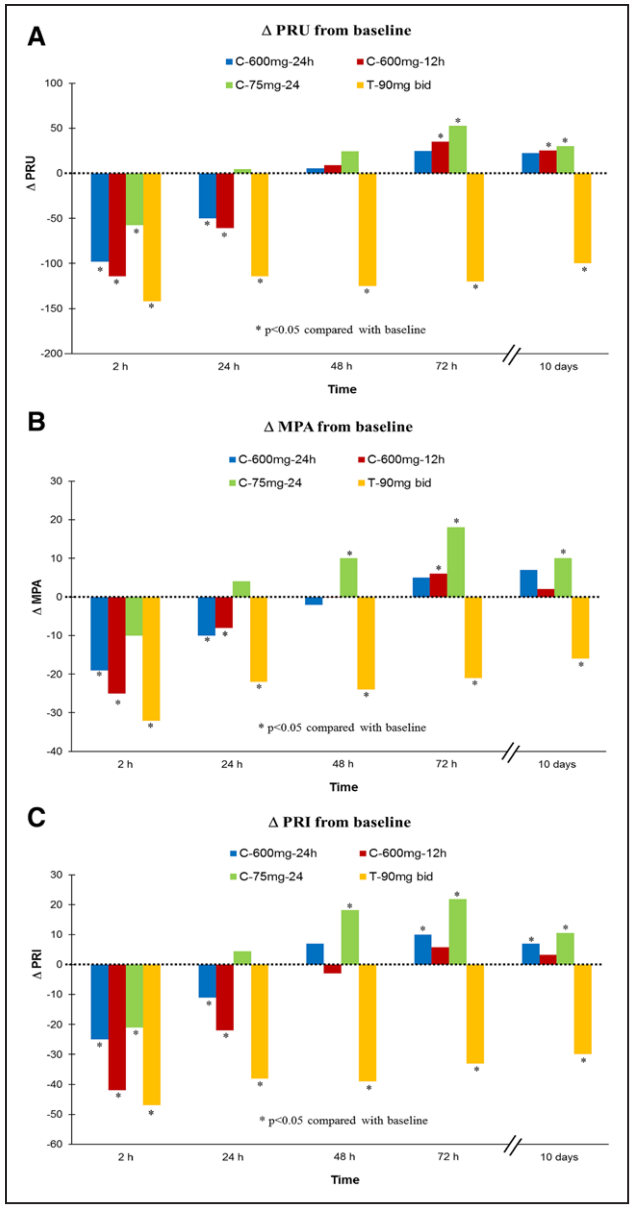

Figure 6. Intragroup comparisons of platelet reactivity assessed by multiple assays.
Intragroup analysis assessing platelet reactivity over time and how this compares with baseline levels while on clopidogrel maintenance therapy (before the run-in phase). Bar charts represent the difference (Δ) between each time point and baseline. Negative bar charts represent a reduction in platelet reactivity. Positive bar charts represent an increase in platelet reactivity. Δ Estimates are derived from the repeated-measures ANOVA model. Asterisks represent significant differences compared with baseline. **A**, Δ $P2Y_{12}$ reaction units (PRUs); **B**, Δ maximal platelet aggregation (MPA %); **C**, Δ platelet reactivity index (PRI %). C-600mg-12h indicates clopidogrel 600 mg loading dose (LD) 12 hours after the last maintenance dose (MD) of ticagrelor; C-600mg-24h, clopidogrel 600 mg LD 24 hours after the last MD of ticagrelor; C-75mg-24h, clopidogrel 75 mg/d (MD) 24 hours after the last MD of ticagrelor; and T-90mg bid, ticagrelor MD 90 mg twice daily MD.

Table 2. High On-Treatment Platelet Reactivity

	C-600 mg-24h, n (%)	C-600 mg-12h, n (%)	C-75 mg-24h, n (%)	T-90 mg BID, n (%)	*P* Value
PRUs >208					
Baseline	6 (30)	5 (25)	6 (30)	6 (30)	0.98
Post–run-in	0 (0)	2 (10)	1 (5)	0 (0)	0.94
2 h	0 (0)	0 (0)	2 (10)	1 (5)	0.30
24 h	2 (12)	0 (0)	4 (20)	1 (5)	0.15
48 h	4 (25)	5 (25)	7 (35)	0 (0)	0.06
72 h	7 (44)	8 (42)	9 (45)	0 (0)	0.006
10 d	10 (56)	7 (37)	6 (32)	1 (5)	0.012
MPA >59%					
Baseline	7 (35)	9 (45)	4 (20)	7 (35)	0.41
Post–run-in	0 (0)	2 (10)	2 (10)	1 (5)	0.51
2 h	0 (0)	0 (0)	2 (10)	0 (0)	0.11
24 h	2 (10)	3 (15)	8 (40)	2 (10)	0.054
48 h	5 (29)	9 (45)	10 (50)	0 (0)	0.005
72 h	8 (50)	10 (53)	13 (65)	1 (6)	0.002
10 d	9 (50)	7 (37)	9 (47)	3 (16)	0.12
PRI >50%					
Baseline	18 (90)	17 (85)	11 (55)	16 (80)	0.04
Post–run-in	7 (37)	3 (15)	6 (32)	1 (20)	0.06
2 h	5 (29)	1 (5)	6 (32)	0 (0)	0.01
24 h	9 (47.4)	10 (50)	12 (60)	2 (10)	0.01
48 h	14 (82)	16 (80)	18 (90)	0 (0)	<0.001
72 h	13 (87)	17 (94)	18 (95)	1 (6.3)	<0.001
10 d	16 (89)	16 (84)	15 (79)	3 (16)	<0.001

C-600 mg-12h indicates clopidogrel 600 mg loading dose 12 hours after the last maintenance dose of ticagrelor; C-600 mg-24h, clopidogrel 600 mg loading dose 24 hours after the last maintenance dose of ticagrelor; C-75 mg-24h, clopidogrel 75 mg/d maintenance dose 24 hours after the last maintenance dose of ticagrelor; MPA, maximal platelet aggregation with ADP 20 μmol/L; PRI, platelet reactivity index; PRU, $P2Y_{12}$ reaction unit; and T-90 mg BID, ticagrelor maintenance dose 90 mg twice daily maintenance dose.

(timing and dosing) from ticagrelor to clopidogrel in these clinical investigations are not fully reported. Indeed, more studies are warranted to better assess the safety and efficacy of a de-escalation strategy, including the impact of timing and the role of guidance by platelet function or genetic testing.[41–43]

Study Limitations

The present study was conducted in stable patients with coronary artery disease who were on dual antiplatelet therapy with aspirin and clopidogrel for at least 30 days and not in patients with a recent acute coronary syndrome or PCI on dual antiplatelet therapy with aspirin and ticagrelor. However, given the data showing an increase in ischemic events when switching early after an acute coronary syndrome/PCI and the potential

for a gap in platelet inhibition with de-escalation, there would have been ethical concerns about conducting this pharmacodynamic investigation in a more acute setting. It is also important to recognize that administering an LD of clopidogrel (when de-escalating from ticagrelor) in a real-world outpatient setting can be cumbersome compared with an inpatient setting. Although in our study switching to clopidogrel was associated with an increase in levels of platelet reactivity, the prevalence of HPR rates, which also increased over the study time course, did not exceed those observed at baseline (before the run-in phase while patients were on maintenance clopidogrel therapy). This in contrast to SWAP-2, in which both the absolute levels of platelet reactivity and the prevalence of HPR rates increased after the switch from ticagrelor to prasugrel.[6] These findings may be attributed to the fact that HPR rates at baseline in SWAP-4 were overall high, particularly with VASP-PRI. Indeed, HPR rates in patients treated with $P2Y_{12}$ inhibitors vary according to the assay used, and prior studies have consistently shown higher rates with VASP, suggesting the need for studies aimed at better defining HPR cutoff values.[17,18,44] In addition, the study was not powered to detect differences in HPR rates. Similarly, our study was powered to detect differences between C-600 mg-24h and C-75 mg-24h at the 48-hour time point. Therefore, all other study findings, including comparisons between other groups and at other time points and the impact of genetic status on pharmacodynamic measures, should be considered exploratory in nature and hypothesis-generating. Although the findings of the present study, in line with other pharmacodynamic investigations assessing a switch from a nonthienopyridine to a thienopyridine agent, suggest the presence of a DDI, the lack of pharmacokinetic assessments does not allow us to rule out other potential explanations. Therefore, we cannot exclude that our study findings are the result of differences in the duration of ticagrelor offset and clopidogrel onset of action. Indeed, pharmacokinetic measures of ticagrelor and its major metabolite and the active metabolite of clopidogrel would have provided some additional insights into our study findings. Ultimately, the sample size of the study does not allow the inference of any safety or efficacy considerations.

CONCLUSIONS

De-escalation from ticagrelor to clopidogrel therapy is associated with an increase of platelet reactivity suggestive of a DDI. Administration of an LD before the initiation of an MD regimen of clopidogrel mitigates these observations by delaying and hampering the increase in platelet reactivity. However, delaying the timing of LD administration after ticagrelor discontinuation did not improve the pharmacodynamic profile of such a de-escalation strategy. Larger studies are warranted to assess the safety and efficacy of de-escalation strategies.

ARTICLE INFORMATION

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The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

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Drs Franchi and Rollini performed statistical analysis. Dr Angiolillo handled funding and supervision. Dr Franchi and L. Been acquired the data. Drs Angiolillo, Rollini, and Franchi conceived and designed the research. Drs Franchi, Rollini, and Angiolillo drafted the manuscript. Drs Rivas Rios, Rivas, Agarwal, Kureti, Nagaraju, Wali, Shaikh, Briceno, Nawaz, Moon, Suryadevara, Soffer, Zenni, and Bass and L. Been made critical revisions to the manuscript for key intellectual content.

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Disclosures

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Pharmacodynamic Effects of Switching From Ticagrelor to Clopidogrel in Patients With Coronary Artery Disease: Results of the SWAP (Switching Antiplatelet Therapy)-4 Study

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SUPPLEMENTAL MATERIAL

Study population

Inclusion Criteria

Patients were screened at the outpatient cardiology clinics of University of Florida Health-Jacksonville and were considered eligible for the study if they met all of the following inclusion criteria: 1) angiographically documented CAD; 2) clinically stable on maintenance therapy with aspirin (81mg/day) and clopidogrel (75mg/day) for at least 30 days per standard of care; 3) age between 18 and 80 years old.

Exclusion Criteria

Patients were excluded if any of the following criteria were present: 1) history of intracranial bleeding; 2) known hepatic impairment; 3) active bleeding or propensity to bleed or blood dyscrasia; 4) platelet count $<80x10^6$/mL; 5) hemoglobin <10g/dL; 6) hemodynamic instability; 7) estimated glomerular filtration rate <30 mL/min; 8) use of oral anticoagulant therapy; 9) sick sinus syndrome or II or III degree AV block without pacemaker protection; 10) use of cytochrome P450 (CYP) 3Ainhibitors (ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir, and telithromycin) and inducers (rifampin, phenytoin, carbamazepine, and phenobarbital); 11) pregnant or lactating females.

Table S1. Summary of protocol procedures

	Screening		**V1** *Run-in Baseline*			**V2** *After 7±2 days Run-in$*				**V3** *After 24 hours wash-out$$*			**V4**	**V5**	**V6**	**V7**
	Consent	Baseline Labs*	PD testing	Genetic Testing	Study drug^	Baseline PD	Randomi-zation	Study drug	2 hrs PD†	Baseline PD†	Study drug	2 hrs PD†	24 hrs PD†	48 hrs PD†	72 hrs PD†	10±3 days PD†
Group A	X	X	X	X	X	X	X	X**		X	X***	X	X	X	X	X
Group B	X	X	X	X	X	X	X	X***	X				X	X	X	X
Group C	X	X	X	X	X	X	X	X**		X		X	X	X	X	X
Group D	X	X	X	X	X	X	X	X++	X				X	X	X	X

* Baseline labs obtained within the past 180 days will be considered valid for screening purposes. If baseline labs are not available, these will need to be obtained prior to considering a patient eligible for study entry and start the run-in phase (patients will have 90 days to enter the study).
^ Ticagrelor LD 180mg followed by 90mg BID MD for 7±2 days
† After Study Drug administration.
$ 12 hours after last ticagrelor 90-mg dose.
$$ 24 hours after last ticagrelor 90-mg dose.
Screening visit, V1, V2 and V4-V7 are common for all groups.
**At V2, group A and C will receive a 90-mg maintenance dose of ticagrelor.
*** Clopidogrel 600 LD
++ Ticagrelor 90mg BID for 10±3days
V3 will be needed only for group A and group C.

Group A: clopidogrel 600mg LD 24 hours after last MD of ticagrelor, followed by 75mg daily MD;
Group B: clopidogrel 600mg LD 12 hours after last MD of ticagrelor, followed by 75mg daily MD;
Group C: clopidogrel 75mg daily MD 24 hours after last MD of ticagrelor;
Group D: continue ticagrelor MD 90mg twice daily.
PD: pharmacodynamic; V: visit.