Antiplatelet effects of ticagrelor versus clopidogrel after coronary artery bypass graft surgery: A single-center randomized controlled trial

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ABSTRACT

Objective: The study objective was to compare the onset of platelet inhibition (inhibition of platelet aggregation) between ticagrelor 90 mg twice per day and clopidogrel 75 mg once per day in patients receiving coronary artery bypass grafting.

Methods: In a single-center, randomized, open-label study, 140 patients receiving coronary artery bypass grafting were randomly assigned to the aspirin + ticagrelor group or the aspirin + clopidogrel group in a 1:1 ratio. Participants in the aspirin + ticagrelor group took aspirin 100 mg once per day and ticagrelor 90 mg twice per day. Participants in the aspirin + clopidogrel group took aspirin 100 mg once per day and clopidogrel 75 mg once per day. Platelet function was determined before study treatment (0 hours); at 2 hours, 8 hours, 24 hours, and 72 hours after medication; and during follow-up at 30 days after surgery.

Results: Inhibition of platelet aggregation at 2 hours after the first drug administration was greater for the aspirin + ticagrelor group than for the aspirin + clopidogrel group (34.2% [interquartile range, 9.1-66.0] vs 5.3% [interquartile range, -14.3-22.0], $P < .001$) and at all times in the study period ($P < .001$). More patients reached inhibition of platelet aggregation maximum within 24 hours in the aspirin + ticagrelor group than in the aspirin + clopidogrel group (52.9% vs 27.5%, $P = .006$). The average inhibition of platelet aggregation maximum from 2 to 24 hours was still greater in the aspirin + ticagrelor group than in the aspirin + clopidogrel group ($72.3\% \pm 15.4\%$ vs $49.2\% \pm 46.8\%$, $P < .001$). There were no differences in terms of bleeding or major adverse cardiac events between the 2 groups.

Conclusions: In patients receiving coronary artery bypass grafting, the onset of action was faster and the peak inhibition of platelet aggregation was higher with ticagrelor than with clopidogrel. (J Thorac Cardiovasc Surg 2019;158:430-7)

The trial flow diagram.

Central Message

In this randomized controlled trial of patients who underwent CABG, the onset of action was faster with ticagrelor than with clopidogrel, whereas the medication safety within 1 month was similar.

Perspective

Antiplatelet therapy is important for secondary prevention of CABG. However, despite the established comprehensive clinical use and benefit in patients undergoing CABG, AC therapy has limitations, including the failure to elicit a complete antiplatelet response. Ticagrelor is a promising antiplatelet agent, but its efficacy in patients undergoing CABG has been studied less in the literature.

See Commentaries on pages 438 and 440.

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Early graft occlusion is one of the major risk factors that negatively affects prognosis after coronary artery bypass grafting (CABG). Many factors, such as surgical trauma, cardiopulmonary bypass, and initial injury, contribute to platelet activation, which subsequently influences graft patency.^{1,2} Currently, early application of aspirin plus

Scanning this QR code will take you to the article title page to access supplementary information.

Abbreviations and Acronyms

ADP	= adenosine diphosphate
AT	= aspirin + ticagrelor
AC	= aspirin + clopidogrel
BARC	= Bleeding Academic Research Consortium
CABG	= coronary artery bypass grafting
DAPT	= dual antiplatelet therapy
IPA	= inhibition of platelet aggregation
ITT	= intention-to-treat
MACE	= major adverse cardiovascular events
MI	= myocardial infarction
PRI	= platelet reactivity index
VASP-P	= vasodilator-stimulated phosphoprotein phosphorylation

P2Y₁₂ receptor inhibitor, known as dual antiplatelet therapy (DAPT), after surgery has become a standardized prevention strategy for patients undergoing CABG.^{3,4}

DAPT, defined as medication of aspirin in combination with another antiplatelet drug, often consists of aspirin and clopidogrel, the effects of which were approved by a few studies.⁵⁻⁷ However, with more evidence coming out, it was found that the antiplatelet effect of clopidogrel varies significantly, and clopidogrel resistance was seen in approximately 30% of patients^{8,9}; thus, clopidogrel may not provide satisfactory antiplatelet effects in the early postoperative period.

Different from clopidogrel, which requires liver enzyme to be activated, ticagrelor is characterized by rapid onset of action and high inhibition of platelet aggregation (IPA), resulting in obvious pharmacokinetic advantages over clopidogrel.¹⁰ However, in patients receiving CABG who develop intense inflammatory reaction and activated platelet function postoperatively,^{11,12} it is unknown whether ticagrelor performs better than clopidogrel. We hypothesized that ticagrelor is not inferior to clopidogrel in terms of antiplatelet effects for patients receiving CABG. Therefore, we conducted a randomized controlled trial to compare pharmacokinetics and safety aspects between ticagrelor and clopidogrel at the early stage after CABG.

MATERIALS AND METHODS

Study Design

This study was an open-label, randomized, controlled clinical trial. Patients were randomly assigned to the aspirin + ticagrelor (AT) group or the aspirin + clopidogrel (AC) group in a 1:1 ratio immediately after CABG, according to the random table generated by SAS software (SAS Institute Inc, Cary, NC). All the subjects were numbered, and each subject was assigned a random number according to a random number table. The subjects were ordered according to the random number they received. The first 70 subjects were assigned to the AT group, and the last 70 subjects were

assigned to the AC group. The randomization was blinded to patients but not to operators. The study was approved by the ethics committee of Fuwai Hospital. The trial was registered on Clinicaltrials.gov (Registry Number NCT02330640). All participants gave written informed consent.

Between January 2016 and October 2016, we randomized 140 patients who underwent CABG. Patients were eligible if they met all of the following criteria: (1) treated by 2 designated surgeons who agreed to participate in this trial; (2) age 18 to 80 years; and (3) isolated CABG for the first time. Patients were not eligible if they had any 1 of the following conditions: (1) combined valvular surgery; (2) a second CABG; (3) emergency CABG, including selective CABG that transferred to emergency CABG; (4) serum creatinine greater than 130 $\mu\text{mol/L}$; (5) oral clopidogrel therapy within 5 days before the CABG; (6) oral anticoagulation therapy (warfarin) that cannot be withheld; (7) history of gastrointestinal, vaginal bleeding, postoperative gastrointestinal bleeding, or cerebral hemorrhage; (8) active pathological bleeding (eg, active gastroduodenal ulcer or cerebral hemorrhage); (9) uric acid nephropathy; (10) any other condition that may influence platelet count and function; (11) contraindication to aspirin, clopidogrel, or ticagrelor; (12) participants of other trials within 30 days before the CABG; or (13) plan of pregnancy within 12 months. The procedure on the patients will be stopped if any of the conditions occurred after the CABG procedure: (1) postoperative chest drainage greater than 200 mL/h for 2 hours or more; (2) need for reoperation for bleeding with cardiac tamponade; or (3) treated with intra-aortic balloon pump or extracorporeal membrane oxygenation after operation.

Data Collection

All the data were collected by trained clinical research staff, including research nurses or residents at Fuwai Hospital. The Case Report Forms were double entered into the database by trained technicians. Two auditors abstracted a random sample of 5% to 10% of medical records. The data submitted were compared with information in the medical records. When disagreement occurred, a supervisor adjudicated the variable to determine the final value.

As part of the current study protocol, all participants discharged alive were required to return for an outpatient follow-up visit at 1 month after surgery. For those who had reported any adverse events during the 1-month period, their medical records in the outpatient clinic were further reviewed for confirmation. For any major clinical events that were reportedly treated in other hospitals, patients were asked to give a copy of all relevant medical records by mail. Overall, the completion rate was 100%.

Procedures

Except study treatment, all randomized patients received the standard CABG protocol. Participants started study treatments after extubation. Participants in the AT group took aspirin 100 mg daily and ticagrelor 90 mg twice daily. Participants in the AC group took aspirin 100 mg daily and clopidogrel 75 mg daily. Because of the risk of bleeding from surgery, we did not give participants a loading dose.

Surgical Procedures

All surgeries were performed by 2 senior surgeons, with the same anesthesiologists and perfusionists. Standard techniques were adopted. In general, during off-pump CABG surgery, several cardiac positioning techniques and coronary artery stabilizers were adopted as previously described.¹³ On-pump CABG was performed with standard cardiopulmonary bypass techniques, using cold antegrade and retrograde blood cardioplegia, and moderate systemic hypothermia (30°C–34°C).

Outcome Measures

Because the onset of both agents was 2 hours after administration, the primary end point was defended as IPA at 2 hours after the first dose of study treatment. IPA was calculated as follows: IPA is platelet aggregation,

b is pre-dosing, and t is postdosing: $IPA\% = ((PAb-PA_t)/PAb) \times 100\%$. Platelet aggregation was measured by light-transmittance aggregometry at 2 hours in CABG recipients after the first dose of study drug. Secondary efficacy end points were the inhibition of platelet function measured by light-transmittance aggregometry at 0 hours, 8 hours, 24 hours, 3 days, and 30 days after the first dose of study drug; and the platelet reactivity index (PRI) at 0 hours, 2 hours, 8 hours, 24 hours, 3 days, and 30 days.

Safety measures included bleeding events according to the Bleeding Academic Research Consortium (BARC) definition (Table E1)¹⁴ and major adverse cardiovascular events (MACE). Considering the specificity of operation, the BARC type 1 or 2 bleeding events were not recorded in the early period of postoperation (7 days). MACE was a combination of all-cause mortality, myocardial infarction (MI), and repeat revascularization.

Blood Sample Collection and Platelet Function Test

Blood samples were collected from subjects for platelet function tests before study treatment (0 hours); at 2 hours, 8 hours, 24 hours, and 72 hours after medication; and during follow-up at 30 days after surgery. Two tubes of blood, 3 mL in each tube, were collected from peripheral veins; then, 109 mmol/L sodium citrate anticoagulant was added, giving a blood volume and anticoagulant ratio of 9:1. Two methods, namely, turbidimetry and measurement of vasodilator-stimulated phosphoprotein phosphorylation, were used to determine platelet function.

1. Turbidimetry. LBY-NJ4A Automated Platelet Aggregation Analyzer manufactured by Beijing Techlink Biomedical (Beijing, China) was used for analysis in this study. In principle, platelet aggregation rate was determined by turbidimetry. Adenosine diphosphate (ADP) 20 μ mol/L was added to platelet-rich plasma as an inducer to determine maximum platelet aggregation rate within 300 seconds.

2. Vasodilator-stimulated phosphoprotein phosphorylation assay. The VASP phosphorylation test was performed after blood collection by an experienced technician using Platelet VASP kits (Biocytex Co Ltd, Marseille, France) according to the instruction manual. Briefly, blood samples were mixed in vitro with ADP or prostaglandin E1. Each blood sample was incubated with a 16C2FITC antibody, followed by a goat anti-mouse fluorescence staining in isothiocyanate polyclonal reagent. Enzyme-linked immunosorbent assay was used to determine vasodilator-stimulated phosphoprotein phosphorylation on serine 239 of platelets in fresh whole blood. When prostaglandin E1 alone or together with ADP was added to the samples, optical density obtained at 450 nm was used to calculate PRI.

STATISTICS

Determination of Sample Size

The trial was designed to detect at least a 15% difference in the IPA at 2 hours between the 2 groups. We conservatively assumed the standard deviation of IPA was 30%. With a 2-sided .05 significance level and a 10% dropout rate, we calculated that 140 patients (70 patients in each group) would yield 80% power to detect that ticagrelor was superior to clopidogrel.

Statistical Analysis

The analysis was based on an intention-to-treat analysis that included patients who were randomized to a treatment group and contributed baseline data, regardless of whether patients received at least 1 dose of study drug or not. For the demographics and surgical characteristics, summary statistics were constructed by using frequencies and

proportions for categorical data and mean and standard deviation for continuous variables. The baseline variables were compared by *t* test or Wilcoxon rank-sum test for continuous variables or chi-square test or Fisher exact test for categorical variables, as appropriate.

For the primary analysis comparing the treatment effects, we did the test for normality, *t* test, and Wilcoxon rank-sum test to compare IPA at 2 hours between the groups (AT vs AC group). Without imputing missing observations for the primary analysis, the mixed-effects model for repeated measures was applied as a sensitivity analysis to examine the effect of missing data. To estimate global variation between groups, we fitted the mixed-effects model including fixed effects for treatment group, hour, and treatment group-by-hour interaction with random coefficients for the patient. According to the trend of change, we separately fitted 2 similar models with IPA values at 2, 8, and 24 hours, and at 24, 72, and 720 hours to obtain the slopes of onset and stable period. The multiple comparisons of IPA, within and between groups at each time from 2 to 720 hours, were performed using multiple test with Bonferroni-adjusted correction. The IPAm_{max} from 2 to 720 hours and the time to reach to IPAm_{max} were computed and compared between groups.

The analyses for the PRI were performed in the same manner as the IPA analysis except for computing PRI_{min} and time to reach to PRI_{min}, and chi-square test or Fisher exact test was conducted for comparing bleeding events and MACE between groups. Sensitivity analysis was conducted by excluding the 3 patients (2 patients declined follow-up, and 1 patient did not received the allocated treatment).

All statistical testing was 2 sided, at a significance level of .05, and all analyses used SAS version 9.4 (SAS Institute Inc) and estimated the mixed models and analysis of variance using the GLM procedure in SAS.

RESULTS

Demographics and Baseline Characteristics

From January 2016 to October 2016, 387 patients were evaluated for eligibility and 140 patients were randomized. One patient did not take the study treatment, and 2 patients were lost to follow-up (Figure 1). According to the principle of intention-to-treat analysis, all patient data are recorded and analyzed. Of the 140 patients randomized (70 in the AT group and 70 in the AC group), there was a good balance between the 2 groups with respect to baseline characteristics (Table 1). Mean age of patients was 59.5 years (± 9.2), and 24.8% were female. Four patients had Canadian Cardiovascular Society (CCS) class IV, and 18.2% of patients had New York Heart Association (NYHA) class III or IV. The preoperative platelet counts were not significantly different between the 2 groups. Some 81.4% of patients received off-pump CABG, and the graft numbers were not significantly different between the AT and AC groups (Table 1).

FIGURE 1. Study flow diagram. Flow chart of the study, including the number of screened patients, patients who withdrew, and patients who were in the final analysis. During the study period, 140 patients were eligible for this study. After 3 patients quit, we randomized the 137 patients to 2 groups: AT group (n = 70) and AC group (n = 67). IPA at 2 hours after the first dose of study treatment was the primary end point. AT, Aspirin + ticagrelor; AC, aspirin + clopidogrel; ITT, intention-to-treat.

Platelet Function

Overall, the 2 groups responded equally to aspirin. The primary end point for onset, IPA at 2 hours after the first drug administration, was greater for AT than for AC (median, 34.2%; interquartile range, 9.1-66.0 vs 5.3%; interquartile range, -14.3-22.0, $P < .001$; Table 2; $P < .01$ for the normality test) and at all times in the study period ($P < .001$; Figure 2, A). In the AT group, IPA did not differ between 24 and 72 hours, and between 72 and 720 hours after first administration, whereas in the AC group, IPA was greater at 720 hours than at 72 hours ($P < .001$; Video 1).

As shown in Figure 2, B, more patients reached IPAmx within 24 hours in the AT group than in the AC group (52.9% vs 27.5%, $P = .002$); the percentages of patients reaching IPAmx between 24 and 72 hours were not different between the 2 groups (AT vs AC: 17.1% vs 18.8%, $P = .825$); however, between 72 and 720 hours, more patients in the AC group reached IPAmx when compared with those in the AT group (AT vs AC: 30.0%

vs 53.6%, $P = .006$). The rate of onset slope of the antiplatelet effect curve as assessed by IPA from 2 to 24 hours after the first drug administration was greater in the AT group than in the AC group (0.9 ± 0.2 vs 0.5 ± 0.3 IPA/h, $P < .001$).

As is shown in Figure 3, A and B, more patients reached PRIm in within 24 hours in the AT group than in the AC group (48.6% vs 18.6%, $P < .001$); the percentages of patients reaching PRIm between 24 and 72 hours were not different between the 2 groups (AT vs AC: 31.4% vs 20.0%, $P = .122$); however, between 72 and 720 hours, more patients in the AC group reached PRIm when compared with those in the AT group (AT vs AC: 20.0% vs 61.4%, $P < .001$). The slope from 0 to 24 hours was less in the AT group than in the AC group (-0.019 ± 0.001 vs -0.003 ± 0.002 PRI/h, $P < .001$).

From 2 to 24 hours, both IPAmx and PRI were greater in the AT group than in the AC group: The median IPAmx

TABLE 1. Demographics, baseline characteristics, and surgical data

	AT (n = 70)	AC (n = 70)
Baseline characteristics		
Age (y) (mean $\pm$ SD)	58.6 $\pm$ 8.9	60.3 $\pm$ 7.5
Gender		
Male	77.1%, 54	72.9%, 51
Female	22.9%, 16	27.1%, 19
Weight	72.8 $\pm$ 11.1	71.8 $\pm$ 9.9
Hypertension	68.6%, 48	62.9%, 44
Hyperlipidemia	67.1%, 47	67.1%, 47
Diabetes mellitus	67.1%, 47	67.1%, 47
Previous AMI	35.7%, 25	40.0%, 28
PCI history	14.3%, 10	11.4%, 8
EF (%)	58.4 $\pm$ 10.6	59.4 $\pm$ 8.6
LVEDD (mm)	50.2 $\pm$ 6.3	49.5 $\pm$ 5.3
CCS class		
1	10.0%, 7	11.4%, 8
2	42.9%, 30	45.7%, 32
3	30.0%, 21	25.7%, 18
4	17.1%, 12	17.1%, 22
NYHA		
I (%)	7.1%, 5	12.9%, 9
II (%)	72.9%, 51	70.0%, 49
III (%)	17.1%, 12	15.7%, 11
IV (%)	2.9%, 2	1.4%, 1
Hemoglobin (g/L)	136.9 $\pm$ 14.5	132.6 $\pm$ 19.0
Platelet ($\times 10^9$ /L)	213.8 $\pm$ 64.3	211.3 $\pm$ 59.4
Prothrombin time (s)	14.5 $\pm$ 13.3	14.6 $\pm$ 13.4
Creatinine (mmol/L)	82.5 $\pm$ 15.5	83.8 $\pm$ 16.7
Preoperative medication		
Aspirin	58.6%, 41	54.2%, 38
β -blocker	100%, 70	100%, 70
ACEI/ARB	32.9%, 23	30%, 21
Calcium antagonist	51.4%, 36	61.4%, 43
Statins	71.4%, 50	68.6%, 48
Nitrates	88.6%, 62	92.3%, 65
euroSCORE II	1.2 $\pm$ 0.5	1.2 $\pm$ 0.7
STS score	0.7 $\pm$ 0.6	0.8 $\pm$ 0.6
Surgical data		
Surgical procedure		
On-pump	17.1%, 12	20%, 14
Off-pump	82.9%, 58	80%, 56
No. of grafts		
1	1.4%, 1	0%, 0
2	8.6%, 6	7.1%, 5
3	35.7%, 25	25.7%, 18
4	45.7%, 32	58.6%, 41
5	8.6%, 6	7.1%, 5
6	0.0%, 0	1.4%, 1

Values are mean $\pm$ SD or n (%). AT, Aspirin + ticagrelor; AC, aspirin + clopidogrel; SD, standard deviation; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; EF, ejection fraction; LVEDD, left ventricular end-diastolic diameter; CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; euroSCORE II, European System for Cardiac Operative Risk Evaluation; STS, Society of Thoracic Surgeons.

from 2 to 24 hours was still greater in the AT group than in the AC group (72.3% $\pm$ 15.4% vs 49.2% $\pm$ 46.8%, $P < .001$); however, the average time to reach to IPAmx from 2 to 720 hours was faster in the AT group than in the AC group (235.8 $\pm$ 320.0 hours vs 403.8 $\pm$ 343.1 hours, $P < .0016$).

The same results were observed with PRI examinations. The median PRImm from 0 to 24 hours was less in the AT group than in the AC group (0.1 $\pm$ 0.1 vs 0.8 $\pm$ 0.2, $P < .001$); the average time to reach to PRImm from 0 to 720 hours was faster in the AT group than in the AC group (174.7 $\pm$ 275.8 hours vs 457.7 $\pm$ 334.1 hours, $P < .001$).

Clinical Outcomes

No life-threatening bleeding (BARC type 4 and 5) was noted in the study period, and minor bleedings were not significantly different between the AT and AC groups: for type 1, 3 in the AT group and none in the AC group ($P = .24$); for type 2, 1 in the AT group and none in the AC group ($P = 1.00$); for type 3a, 1 in the AT group and 1 in the AC group ($P = 1.00$). Also, chest drainage volumes showed no significant difference between the 2 groups (Figure 4). No deaths, perioperative MI, or repeated revascularization occurred within 30 postoperative days. Length of hospital stay showed no significant difference between the AT and AC groups (7.3 $\pm$ 2.4 days vs 7.2 $\pm$ 2.2 days, $P = .68$).

DISCUSSION

The current study compared the pharmacokinetic characteristics and safety between ticagrelor and clopidogrel in patients receiving CABG. The results showed that ticagrelor had a quicker onset and higher peak platelet inhibition rate; meanwhile, there was no significant difference in bleeding events between the ticagrelor and clopidogrel groups.

For patients receiving CABG, it is crucial to initiate antiplatelet therapy as early as possible after the procedure. Mangano¹⁵ found that the mortality was significantly lower in patients who started aspirin therapy within 48 hours after surgery than those in the control group (1.3% vs 4.0%, $P < .001$). In fact, patients receiving CABG had abnormal activation of platelet function postoperatively, which persists until 30 days after the procedure.¹² Accordingly, multiple studies further evaluated the efficacy of the AC DAPT regimen, but the results were inconsistent, which may be related to the long peak time of clopidogrel and significant individual difference in efficacy.^{6,16}

Those limitations of clopidogrel make the timing of DAPT a concern for clinicians. As mentioned earlier, 30 days postoperation is a critical period for antiplatelet

TABLE 2. Platelet function test at various time points

	0 h	2 h	8 h	24 h	72 h	720 h	P*
IPA measures							<.0001
AT	—	34.2 (9.1-66.0)	63.4 (47.1-71.3)	65.2 (55.0-71.2)	61.6 (50.2-73.3)	64.7 (53.0-74.7)	
AC	—	5.3 (−14.3-22.0)	13.5 (−2.9-28.5)	21.2 (−8.7-37.8)	27.5 (2.1-55.0)	46.4 (23.1-71.1)	
P**	—	<.001	<.001	<.001	<.001	.001	
PRI measures							<.001
AT	0.8 (0.8-0.9)	0.5 (0.2-0.8)	0.2 (0.1-0.3)	0.2 (0.1-0.2)	0.1 (0.1-0.2)	0.2 (0.1-0.3)	
AC	0.8 (0.8-0.9)	0.8 (0.7-0.9)	0.8 (0.8-0.9)	0.8 (0.7-0.9)	0.5 (0.2-0.7)	0.3 (0.1-0.6)	
P**	1.0000	<.0001	<.0001	<.0001	<.0001	.0210	

Values are median (interquartile range). P* indicates P value of group-by-time interaction effect estimated by mixed-effects model. P** indicates P value of Bonferroni multiple-significance test correction. IPA, Inhibition of platelet aggregation; AT, aspirin + ticagrelor; AC, aspirin + clopidogrel; PRI, platelet reactivity index.

therapy because platelet functions are activated during this period. However, the slow onset may delay platelet inhibition and therefore negatively affect long-term prognosis. Ticagrelor may change this situation.

Unlike clopidogrel, ticagrelor is not a prodrug and its action does not rely on liver enzyme to convert it into an active drug, leading to significant improvement in bioavailability.¹⁰ The American Heart Association/American College of Cardiology guideline has included ticagrelor as the primary choice of antiplatelet drug for patients with acute coronary syndrome.^{3,17} But, it is yet to be determined whether the AT DAPT regimen can improve the efficacy of CABG. The PLATO subgroup study showed that the incidences of cardiac death and all-cause death were significantly lower in CABG recipients treated with ticagrelor than in the control group.¹⁸ Our study

examined platelet functions after CABG; the results showed that the mean IPA peak time was significantly faster in the AT group than in the AC group (235 vs 403 hours, $P = .0016$), and that the peak platelet inhibition rate in the AT group was approximately 1.5 times that in the AC group ($P < .001$). This finding provided theoretical support for the subgroup study results of PLATO.

When compared with the nonsurgical population in the ONSET/OFFSET study,¹⁹ participants in the current study had shorter platelet inhibition and decreased IPAmax and PRImax. This difference was more notable in patients undergoing coronary artery bypass receiving clopidogrel compared with the nonsurgical population receiving clopidogrel, indicating that ticagrelor is more suitable for antiplatelet purpose after CABG. Although the mechanism underlying this difference is still unknown, we supposed

FIGURE 2. IPA measured by light-transmittance aggregometry. A, IPA (%; ADP 20 μ mol/L; maximum extent) test at protocol time points. Data are expressed by median (interquartile range). IPA at 2 hours after the first drug administration was greater for AT than for AC. B, Distribution of the time to reach the IPAmax (%; ADP 20 μ mol/L; maximum extent). Different colors represent the proportion of patients who reached the IPAmax in 3 time slots: within 24 hours, 24 to 72 hours, or 72 to 720 hours. More patients reached IPAmax within 24 hours in the AT group than in the AC group (52.9% vs 27.5%, $P = .002$). IPA, Inhibition of platelet aggregation; AC, aspirin + clopidogrel; AT, aspirin + ticagrelor.

VIDEO 1. Dr Zhe Zheng introduces the main results and significance of the study. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)32786-7/fulltext](https://www.jtcvs.org/article/S0022-5223(18)32786-7/fulltext).

that this is related to an enhanced platelet activation in the surgical population.

The occurrence of postoperative bleeding events is another focus point in patients treated with ticagrelor after CABG. In a multicenter, randomized, controlled trial composed of 123 patients (stable angina), Gurbel and colleagues¹⁹ found that IPA declined significantly faster with ticagrelor than with clopidogrel after drug discontinuance, indicating that ticagrelor is safer in terms of bleeding events. However, our study observed no significant difference in chest drainage volume and total pleural fluid volume between the AT and AC groups 1 day after surgery. Similar

to our study, the study by Saw and colleagues²⁰ showed that no severe bleeding events (life-threatening hemorrhage or hemoglobin reduction >3 g/dL) occurred within 3 months as a result of postoperative application of ticagrelor after CABG, but the incidence of mild bleeding events was 10 times higher in the ticagrelor group than in the placebo group. Despite the suggested safety of ticagrelor application, finding a balance between anticoagulation and bleeding is still an important direction for further studies.

Study Limitations

Because this study conducted only a 1-month follow-up, the short observation time may have caused the negative results in comparison of deaths, perioperative MI, and repeated revascularization. Also, we used CT to analyze 1-month vein graft patency and found negative results (Table E2). As described in the “Materials and Methods” section, the primary end point of this study was pharmacokinetic comparison. An expanded sample size and extended follow-up period are required. In the meantime, the proportion of clopidogrel resistance was unknown in this study because the clopidogrel gene was not analyzed, which may affect the study results.

Another limitation of the current study is that the data had relative low statistical power to evaluate the impact of cardiopulmonary bypass on platelet function. As shown in Tables E3 to E10, the platelet function was not statistically different between patients receiving on-pump

FIGURE 3. PRI measured by vasodilator-stimulated phosphoprotein phosphorylation (VASP-P) levels. A, PRI measured by VASP-P levels at protocol time points. VASP-P levels tested by enzyme-linked immunosorbent assay. Data are expressed by median (interquartile range). More patients reached PRImin within 24 hours in the AT group than in the AC group (48.6% vs 18.6%, $P < .001$). The slope from 0 to 24 hours was less in the AT group than in the AC group (-0.019 ± 0.001 vs -0.003 ± 0.002 PRI/h, $P < .001$). B, Distribution of the time to reach PRImin. Different colors represent the proportion of patients who reached the PRImin in 3 time slots: within 24 hours, 24 to 72 hours, or 72 to 720 hours. PRI, Platelet reactivity index; AC, aspirin + clopidogrel; AT, aspirin + ticagrelor.

FIGURE 4. Postoperative thoracic drainage. Data are expressed by mean $\pm$ standard error of the mean. AT versus AC, $P = .771$. Chest drainage volumes were not significantly different in the 2 groups. AC, Aspirin + clopidogrel; AT, aspirin + ticagrelor.

CABG and patients receiving off-pump CABG. In the subgroup analysis in on-pump or off-pump patients, the onset of action was faster and the peak IPA was higher with AT than with AC.

CONCLUSIONS

In patients receiving CABG, the onset of action was faster and the peak IPA was higher with ticagrelor than with clopidogrel, whereas the medication safety within 1 month after surgery was similar between the 2 drugs.

Conflict of Interest Statement

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Key Words: CABG, dual antiplatelet therapy, platelet function, postoperation

TABLE E1. Standardized bleeding definitions for Bleeding Academic Research Consortium

Type 0:	No bleeding
Type 1:	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional.
Type 2:	Any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least 1 of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation.
Type 3	
Type 3a	Overt bleeding plus hemoglobin decrease of 3 to 5 g/dL* (provided hemoglobin decrease is related to bleed); any transfusion with overt bleeding.
Type 3b	Overt bleeding plus hemoglobin decrease 5 g/dL* (provided hemoglobin decrease is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid); bleeding requiring intravenous vasoactive agents.
Type 3c	Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal); subcategories confirmed by autopsy or imaging or lumbar puncture; intraocular bleed compromising vision.
Type 4:	CABG-related bleeding; perioperative intracranial bleeding within 48 h; reoperation after closure of sternotomy for the purpose of controlling bleeding; transfusion of 5 U whole blood or packed red blood cells within a 48-h period; chest tube output 2 L within a 24-h period.
Type 5:	Fatal bleeding.
Type 5a	Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious.
Type 5b	Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation.

Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2742, Table 3. CABG, Coronary artery bypass grafting.

TABLE E2. Computed tomography examination of venous graft patency rate

	Total (N = 357)	AC (N = 181)	AT (N = 176)	P value
Vein graft failure (% , n)	8.7%, 31	11.6%, 21	5.7%, 10	.0470
Vein graft occlusion (% , n)	3.9%, 14	3.9%, 7	4%, 7	.9574

The time of CT examination is 1 month after surgery. The vein graft failure refers to the presence of bridge vessel stenosis greater than 50% observed by CT. AC, Aspirin + clopidogrel; AT, aspirin + ticagrelor.

TABLE E3. Patient characteristics of groups by on/off pump

Variable	Overall (n = 140)	On pump (n = 26)	Off pump (n = 114)	P
Age (y) (mean ± SD)	59.5 ± 8.2	58.1 ± 8.2	59.8 ± 8.2	.4511
Gender (female)	25% (35)	7.7% (2)	28.9% (33)	.0239
Weight	72.3 ± 10.5	74.6 ± 12	71.8 ± 10.1	.2256
Hypertension	65.7% (92)	61.5% (16)	66.7% (76)	.6191
Diabetes mellitus	32.9% (46)	23.1% (6)	35.1% (40)	.2394
Previous AMI	37.9% (53)	42.3% (11)	36.8% (42)	.6041
EF (%)	58.9 ± 9.6	60.6 ± 8.8	58.5 ± 9.8	.2806
LVEDD (mm)	49.8 ± 5.8	50.2 ± 3.9	49.7 ± 6.1	.6598
CCS class				.6762
1	10.7% (15)	7.7% (2)	11.4% (13)	
2	44.3% (62)	53.8% (14)	42.1% (48)	
3	27.9% (39)	26.9% (7)	28.1% (32)	
4	17.1% (24)	11.5% (3)	18.4% (21)	
NYHA				.3742
I (%)	10% (14)	7.7% (2)	10.5% (12)	
II (%)	71.4% (100)	84.6% (22)	68.4% (78)	
III (%)	16.4% (23)	7.7% (2)	18.4% (21)	
IV (%)	2.1% (3)	0% (0)	2.6% (3)	
Hemoglobin (g/L)	134.7 ± 17	140.2 ± 12.8	133.5 ± 17.6	.0599
Platelet (*10 ⁹ /L)	223.3 ± 61.9	216 ± 61.1	225 ± 62.3	.4262
Prothrombin time (s)	14.5 ± 13.3	17.4 ± 22	13.9 ± 10.4	.1895
Creatinine (mmol/L) Preoperative medication	83.2 ± 16.1	86.6 ± 11.7	82.4 ± 16.8	.0465
Beta-blocker	100% (140)	100% (26)	100% (114)	
ACEI/ARB	31.4% (44)	30.8% (8)	31.6% (36)	.9360
Calcium antagonist	45% (63)	38.5% (10)	46.5% (53)	.4577
Statins	70.7% (99)	76.9% (20)	69.3% (79)	.4407
Nitrates	92.9% (130)	92.3% (24)	93% (106)	.9040
euroSCORE II	1.2 ± 0.5	1.2 ± 0.7	1.2 ± 0.5	.1418
STS score	0.7 ± 0.6	0.6 ± 0.3	0.8 ± 0.6	.1804
Treatment group (AT)	50% (70)	46.2% (12)	50.9% (58)	.6638
Surgical data				
Variable	Overall (n = 140)	On pump (n = 26)	Off pump (n = 114)	P
No. of grafts				.8809
1	0.7% (1)	0% (0)	0.9% (1)	
2	7.9% (11)	7.7% (2)	7.9% (9)	
3	30.7% (43)	38.5% (10)	28.9% (33)	
4	52.1% (73)	50% (13)	52.6% (60)	
5	7.9% (11)	3.8% (1)	8.8% (10)	
6	0.7% (1)	0% (0)	0.9% (1)	

SD, Standard deviation; AMI, acute myocardial infarction; EF, ejection fraction; LVEDD, left ventricular end-diastolic diameter; CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; euroSCORE, European System for Cardiac Operative Risk Evaluation; STS, Society of Thoracic Surgeons; AT, aspirin + ticagrelor.

TABLE E4. Platelet function test at various time points of groups by on/off pump

	0 h	2 h	8 h	24 h	72 h	720 h	<i>P</i> *
IPA measures							<.001
On pump	–	18.3 (–9.2-30.6)	30 (3.7-57.8)	53.2 (15.7-68.9)	47.7 (17.5-73)	69.9 (41.4-78.9)	
Off pump	–	20.6 (1.4-48.7)	46.6 (11.7-65.2)	49.6 (17.5-67.1)	53.5 (26.3-68.9)	57.3 (39.9-71.1)	
<i>P</i> **	–	1.0000	1.0000	1.0000	1.0000	1.0000	
PRI measures							<.001
On pump	0.9 (0.8-0.9)	0.8 (0.4-0.9)	0.8 (0.2-0.9)	0.6 (0.2-0.8)	0.2 (0.1-0.5)	0.3 (0.1-0.4)	
Off pump	0.8 (0.8-0.9)	0.7 (0.4-0.8)	0.4 (0.2-0.8)	0.3 (0.1-0.8)	0.2 (0.1-0.6)	0.2 (0.1-0.3)	
<i>P</i> **	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	

Values are median (25th-75th percentile). *P** indicates *P* value of group-by-time interaction effect estimated by mixed-effects model. *P*** indicates *P* value of Bonferroni multiple-significance test correction. *IPA*, Inhibition of platelet aggregation; *PRI*, platelet reactivity index.

TABLE E5. Baseline characteristics of off-pump subgroup

Variable	Overall (n = 114)	AT (n = 58)	AC (n = 56)	<i>P</i> value
Age (y) (mean ± SD)	59.8 ± 8.2	58.7 ± 9.1	60.9 ± 7.1	.3085
Weight	71.8 ± 10.1	73 ± 10.4	70.4 ± 9.7	.3060
EF (%)	58.5 ± 9.8	58.2 ± 10.8	58.8 ± 8.6	.9706
LVEDD (mm)	49.7 ± 6.1	50.3 ± 6.7	49.1 ± 5.5	.6619
Hemoglobin (g/L)	133.5 ± 17.6	135.9 ± 13.9	131 ± 20.5	.1990
Prothrombin time (s)	13.9 ± 10.4	14.8 ± 14.6	12.9 ± 0.6	.9638
Creatinine (mmol/L)	82.4 ± 16.8	82.7 ± 16.3	82 ± 17.5	.5903
euroSCORE II	1.2 ± 0.4	1.1 ± 0.4	1.2 ± 0.4	.5536
STS score	0.8 ± 0.6	0.7 ± 0.6	0.8 ± 0.6	.2208

AT, Aspirin + ticagrelor; AC, aspirin + clopidogrel; SD, standard deviation; EF, ejection fraction; LVEDD, left ventricular end-diastolic dimension; euroSCORE, European System for Cardiac Operative Risk Evaluation; STS, Society of Thoracic Surgeons.

TABLE E6. Inhibition of platelet aggregation of off-pump subgroup

Variable	Overall (n = 114)	AT (n = 58)	AC (n = 56)	<i>P</i> value
ipa_adp0-2	22.5 ± 35.1	36.6 ± 34.4	7.1 ± 28.9	<.0001
ipa_adp0-8	38.3 ± 34.1	57.6 ± 24.1	16.8 ± 30.7	<.0001
ipa_adp0-24	40.3 ± 34.2	61.4 ± 20	16.7 ± 31.3	<.0001
ipa_adp0-72	43.1 ± 32.3	58 ± 20.2	26.8 ± 35.2	<.0001
ipa_adp0-720	50.9 ± 32.6	59.8 ± 27.8	40.7 ± 35	.0020

P value is used multiple test by Bonferroni correction. AT, Aspirin + ticagrelor; AC, aspirin + clopidogrel.

TABLE E7. Platelet reactivity index of off-pump subgroup

Variable	Overall (n = 114)	AT (n = 58)	AC (n = 56)	P value
pri1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.2	1.0000
pri2	0.6 ± 0.3	0.5 ± 0.3	0.8 ± 0.2	<.0001
pri3	0.5 ± 0.3	0.3 ± 0.2	0.8 ± 0.2	<.0001
pri4	0.4 ± 0.3	0.2 ± 0.1	0.7 ± 0.2	<.0001
pri5	0.3 ± 0.3	0.1 ± 0.1	0.5 ± 0.3	<.0001
pri6	0.3 ± 0.2	0.2 ± 0.2	0.3 ± 0.3	.0222

P value is used multiple test by Bonferroni correction. AT, Aspirin + ticagrelor; AC, aspirin + clopidogrel.

TABLE E8. Baseline characteristics of on-pump subgroup

Variable	Overall (n = 26)	AT (n = 12)	AC (n = 14)	P value
Age (y) (mean ± SD)	58.1 ± 8.2	58.3 ± 8.2	58 ± 8.5	.9795
Weight	74.6 ± 12	71.8 ± 14.7	77.1 ± 8.9	.3030
EF (%)	60.6 ± 8.8	59.1 ± 9.6	61.9 ± 8.3	.4094
LVEDD (mm)	50.2 ± 3.9	49.3 ± 3.6	50.9 ± 4.2	.3509
Hemoglobin (g/L)	140.2 ± 12.8	141.7 ± 16.8	139 ± 8.5	.8569
Prothrombin time (s)	17.4 ± 22	12.9 ± 0.7	21.2 ± 29.9	.2069
Creatinine (mmol/L)	86.6 ± 11.7	81.8 ± 11.3	90.8 ± 10.8	.0760
euroSCORE II	1.1 ± 0.5	1.2 ± 0.5	1.2 ± 0.4	.6578
STS score	0.6 ± 0.3	0.7 ± 0.5	0.5 ± 0.2	.3961

AT, Aspirin + ticagrelor; AC, aspirin + clopidogrel; SD, standard deviation; EF, ejection fraction; LVEDD, left ventricular end-diastolic dimension; euroSCORE, European System for Cardiac Operative Risk Evaluation; STS, Society of Thoracic Surgeons.

TABLE E9. Inhibition of platelet aggregation of on-pump subgroup

Variable	Overall (n = 26)	AT (n = 12)	AC (n = 14)	P value
ipa_adp0-2	11.3 ± 38.8	41.2 ± 24.3	-12.2 ± 31.2	.0015
ipa_adp0-8	26.9 ± 43.6	57.5 ± 21.5	-1.4 ± 39.6	.0015
ipa_adp0-24	39.5 ± 45.1	69.8 ± 15.9	13.5 ± 46	.0020
ipa_adp0-72	44.6 ± 32.7	65 ± 19.9	27.1 ± 31.9	.0155
ipa_adp0-720	56.6 ± 34.2	58.9 ± 32.8	54.7 ± 36.6	1.0000

P value is used multiple test by Bonferroni correction. AT, Aspirin + ticagrelor; AC, aspirin + clopidogrel.

TABLE E10. Platelet reactivity index of on-pump subgroup

Variable	Overall (n = 26)	AT (n = 12)	AC (n = 14)	P value
pri1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	1.0000
pri2	0.7 ± 0.3	0.5 ± 0.3	0.8 ± 0.1	.1476
pri3	0.6 ± 0.3	0.3 ± 0.3	0.8 ± 0.1	.0012
pri4	0.5 ± 0.3	0.2 ± 0.1	0.8 ± 0.1	<.0001
pri5	0.3 ± 0.3	0.1 ± 0.1	0.5 ± 0.2	.0036
pri6	0.3 ± 0.2	0.2 ± 0.1	0.4 ± 0.3	1.0000

P value is used multiple test by Bonferroni correction. AT, Aspirin + ticagrelor; AC, aspirin + clopidogrel.