Efficacy and Safety of Ticagrelor and Clopidogrel in Patients with Stable Coronary Artery Disease Undergoing Percutaneous Coronary Intervention

Jianan Li, Hong Qiu, Lirong Yan, Tingting Guo, Yong Wang, Yang Li, Jianfeng Zheng, Yida Tang, Bo Xu, Shubin Qiao, Yuejin Yang and Runlin Gao

Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

**Aim:** The efficacy and safety of ticagrelor and clopidogrel in patients with stable coronary artery disease (SCAD) undergoing percutaneous coronary intervention (PCI) remain uncertain. Thus, this study aimed to compare the efficacy and safety of ticagrelor and clopidogrel in patients with SCAD treated with PCI.

**Methods:** A total of 9,379 patients with SCAD undergoing PCI who received dual antiplatelet therapy (DAPT) were consecutively enrolled in two groups, namely, ticagrelor (n=1,081) and clopidogrel (n=8,298) groups. Major adverse cardiovascular and cerebrovascular events (MACCEs) and bleeding events according to ticagrelor or clopidogrel use were compared.

**Results:** After propensity matching (n=1,081 in each group), ticagrelor was associated with fewer MACCEs (3.6% vs. 5.7%, hazard ratio [HR] = 0.62, 95% confidence interval [CI] 0.41–0.93, \( p = 0.019 \)), and the difference between ticagrelor and clopidogrel for bleeding events was nonsignificant (4.0% vs. 3.2%, HR = 1.24, 95% CI 0.79-1.93, \( p = 0.356 \)). On the other hand, the difference between ticagrelor and clopidogrel for net adverse clinical events was significant (4.1% vs. 6.0%, HR = 0.67, 95% CI 0.46–0.98, \( p = 0.039 \)). In a multivariate analysis, the use of ticagrelor, number of stents, previous history of diabetes, previous history of smoking, and ACC/AHA type B2 or C lesions were considered independent predictors of MACCEs, while radial artery access, previous history of stroke, and weight <60kg were independent predictors of bleeding events.

**Conclusions:** Ticagrelor was associated with a lower incidence of MACCEs without an increased risk of bleeding events in patients with SCAD receiving PCI.

**Key words:** Ticagrelor, Clopidogrel, Stable coronary artery disease, Percutaneous coronary intervention

**Introduction**

Clopidogrel and aspirin have long been used as the standard dual antiplatelet therapy (DAPT) for patients undergoing percutaneous coronary intervention (PCI). The antiplatelet effect of clopidogrel is slow, variable, and irreversible, and it is reported that approximately 15–30% of patients are nonresponsive to clopidogrel. The multifactorial phenomenon of clopidogrel hyporesponsiveness is associated with an increased risk of thromboembolic events after PCI. Ticagrelor is a reversible, nonthienopyridine, P2Y12 oral inhibitor that has a faster onset and offset of action and a higher inhibitory effect on platelet aggregation compared with clopidogrel, which requires metabolic activation through a multistep process involving multiple cytochrome P450 isoenzymes. Ticagrelor can bind directly to the P2Y12 receptor and inhibit platelet aggregation induced by...
adenosine diphosphate\(^9\).

The Platelet Inhibition and Patient Outcomes (PLATO) trial and other studies have compared the efficacy and safety of ticagrelor and clopidogrel in patients with acute coronary syndrome (ACS), acute myocardial infarction (AMI), ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or non-ST-segment elevation acute coronary syndrome (NSTE-ACS)\(^{10-14}\). No other previous study comprehensively evaluated the efficacy and safety of ticagrelor in patients with stable coronary artery disease (SCAD) for a 1-year follow-up period. Therefore, we sought to investigate the efficacy and safety of ticagrelor vs. clopidogrel in patients with SCAD undergoing PCI.

### Methods

#### Patients

A total of 9379 consecutive patients with SCAD who underwent PCI from January 2017 to December 2018 were enrolled in this single-center study. Patients were divided into two groups according to the medication at discharge, namely, the ticagrelor group (\(n=1,081\)) and the clopidogrel group (\(n=8,298\)). All patients were then followed up for 1 year. The inclusion criteria were as follows: patients aged \(\geq 18\) years, those with a confirmed final diagnosis of SCAD, those who underwent PCI with drug-eluting stent (DES), and those prescribed aspirin and a P2Y12 inhibitor (ticagrelor or clopidogrel) upon admission and at discharge. The exclusion criteria were as follows: patients who were diagnosed with ACS; those with unsuccessful PCI; those with acute or severe complications of PCI; those who needed long-term oral anticoagulant drugs; those who discontinued P2Y12 blockers or switched between ticagrelor and clopidogrel; those for whom aspirin, clopidogrel, or ticagrelor are contraindicated; and those with coagulopathy, severe liver and kidney dysfunction, active major bleeding, major surgical history within 3 months, severe valvular heart disease, dilated cardiomyopathy, hypertrophic cardiomyopathy, tumor, hyperthyroidism, pulmonary embolism, and other basic diseases. The study flowchart is shown in Fig. 1. The Fuwai Hospital approved this study (2018-WJY01), and the study protocol conforms to the ethical guidelines of the Declaration of Helsinki and its later amendments. Informed consent for access to their medical records during hospitalization was obtained from all patients.

#### Treatment

Dual antiplatelet agents were administered to all patients prior to the PCI, with a 300-mg loading dose of aspirin, a 300–600-mg loading dose of clopidogrel, or a 180-mg loading dose of ticagrelor. After PCI, patients received 100-mg aspirin once daily indefinitely and 75-mg clopidogrel once daily or 90-mg ticagrelor twice daily for at least 12 months. The antiplatelet agents were chosen based on the discretion of

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**Fig. 1.** Flow chart
individual cardiologists. According to the current standard procedure guidelines, all patients underwent coronary angiography during PCI. Interventional cardiologists identified specific PCI techniques and stent types for coronary lesions. All patients received standard care and medications for the secondary prevention of coronary artery disease.

Endpoints and Definitions
The primary efficacy endpoints were major adverse cardiovascular and cerebrovascular events (MACCEs), defined as the composite of all-cause death, myocardial infarction (MI), any revascularization, and stroke at 1-year follow-up. The secondary efficacy endpoints were all-cause death, cardiovascular death, MI, stroke, and stent thrombosis. MI was defined according to the universal definition. Any revascularization was defined as revascularization involving either the target or nontarget vessels. Stroke was defined as the focal loss of neurologic function caused by either ischemia or hemorrhage, with residual symptoms lasting at least 24 h or leading to death. Stent thrombosis was evaluated in accordance with the Academic Research Consortium criteria. The safety endpoints were thrombolysis in MI (TIMI) bleeding events, which include major and minor bleeding events. The net adverse clinical events were defined as the composite of all-cause death, MI, stroke, or TIMI major bleeding.

Statistical Analysis
Continuous variables with normal distributions were expressed as the mean ± standard deviation and were compared using Student’s t-test. Continuous variables with non-normal distributions were expressed as the median (interquartile range) and were compared using the Mann-Whitney U test. Meanwhile, categorical variables were expressed as numbers and percentages and were compared using the chi-square test or Fisher’s exact test. Propensity score was employed to minimize the impact of selection bias in the direct comparison between ticagrelor and clopidogrel. We used the 1:1 nearest neighbor matching to match the patients in each cohort, without replacement, with a caliper width of 0.2 of the standard deviation. Differences between the matched pairs were evaluated using the paired t-test or the Wilcoxon signed-rank test for continuous variables and McNemar’s test for categorical variables.

A Kaplan-Meier analysis was employed to establish survival plots with MACCEs or bleeding events, with the two groups compared using the log-rank test. The Cox regression model was used to estimate hazard ratios (HR) and 95% confidence intervals (CI). The independent predictors of efficacy and safety endpoints in the matched cohort were determined using a Cox proportional hazards regression model, including factors considered significant (p value < 0.1) by univariate analysis or deemed clinically important in the multivariate model. A p value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 25.0 (IBM) and STATA 12.0 (StataCorp).

Results
Patient Characteristics
A total of 9379 patients who underwent PCI from January 2017 to December 2018 were consecutively enrolled in this study, including patients with SCAD. Of these patients, 1081 received ticagrelor, and 8298 received clopidogrel. Table 1 lists the patients’ baseline characteristics. Patients with the following characteristics were more likely to receive ticagrelor: a previous history of hyperlipidemia, MI, PCI, congestive heart failure, a higher creatinine clearance and low-density lipoprotein cholesterol (LDL-C), a lower left ventricular ejection fraction, more ACC/AHA type B2 or C lesions and stents, longer total stent length, and the use of medications serving as proton pump inhibitors. However, older patients, patients with a previous history of stroke, and patients treated with the transradial approach were more likely to receive clopidogrel.

After propensity score matching was performed for all patients, 1081 matched pairs of patients were selected (Table 1). In these matched patients, no significant differences were observed between ticagrelor and clopidogrel for any baseline clinical and procedural characteristics and medications.

Efficacy Endpoints
The incidence of MACCEs in the ticagrelor group was significantly lower than that in the clopidogrel group (3.6% vs. 6.1%, log-rank test, p < 0.001) (Table 2, Fig. 2A). Patients in the ticagrelor group had lower rate of any revascularization than did those in the clopidogrel group (2.1% vs. 3.3%, p = 0.040; Table 2). No significant differences were observed in the incidences of all-cause death, MI, stroke, and stent thrombosis between the two groups (Table 2).

After propensity score matching, the incidence of MACCEs was significantly lower in the ticagrelor group than in the clopidogrel group (3.6% vs. 5.7%, log-rank test, p = 0.019) (Table 2, Fig. 2D). Ticagrelor was associated with lower incidences of all-cause death and cardiovascular death compared with clopidogrel.
### Table 1. Baseline clinical characteristics

|                      | All Patients | Propensity-matched patients | p value |
|----------------------|--------------|-----------------------------|---------|
|                      | Ticagrelor   | Clopidogrel                 |         |
|                      | (n = 1081)   | (n = 8298)                  |         |
|                      |              |                             |         |
| Male, n (%)          | 842 (77.9)   | 6315 (76.1)                 | 0.193   |
| Age (years)          | 57.8 ± 9.8   | 59.5 ± 9.9                  | <0.001  |
| Systolic blood pressure (mmHg) | 130.5 ± 15.4 | 131.1 ± 16.2               | 0.259   |
| Diastolic blood pressure (mmHg) | 78.5 ± 9.6   | 78.7 ± 10.0                | 0.570   |
| Heart rate (beats/min) | 70.1 ± 10.7 | 70.1 ± 10.9                | 0.895   |
| Height (cm)          | 168.8 ± 7.2  | 168.3 ± 7.3                 | 0.048   |
| Body weight (kg)     | 74.7 ± 12.7  | 74.0 ± 12.0                 | 0.052   |
| BMI (kg/m²)          | 26.2 ± 3.6   | 26.0 ± 3.4                  | 0.290   |
| Hypertension, n (%)  | 697 (64.5)   | 5335 (64.3)                 | 0.905   |
| Diabetes, n (%)      | 378 (35.0)   | 2754 (33.2)                 | 0.243   |
| Hyperlipidemia, n (%)| 761 (70.4)   | 5438 (65.5)                 | 0.001   |
| Smoker, n (%)        | 604 (55.9)   | 4720 (56.9)                 | 0.530   |
| MI, n (%)            | 229 (21.2)   | 1069 (12.9)                 | <0.001  |
| PCI, n (%)           | 368 (34.0)   | 1900 (22.9)                 | <0.001  |
| CABG, n (%)          | 18 (1.7)     | 120 (1.4)                   | 0.574   |
| Congestive heart failure, n (%) | 28 (2.6)       | 129 (1.6)                   | 0.013   |
| Stroke, n (%)        | 87 (8.0)     | 955 (11.5)                  | 0.001   |
| Peripheral vascular disease, n (%) | 54 (5.0)       | 452 (5.4)                   | 0.536   |
| COPD, n (%)          | 8 (0.7)      | 66 (0.8)                    | 0.847   |
| Chronic renal insufficiency, n (%) | 12 (1.1)       | 63 (0.8)                    | 0.223   |
| White blood cells (10^9/l) | 6.60 ± 1.68  | 6.58 ± 1.68                 | 0.971   |
| Total platelets (10^9/l) | 228.23 ± 67.6 | 225.25 ± 58.09             | 0.116   |
| Hemoglobin (g/l)     | 145.67 ± 15.18 | 146.25 ± 14.50            | 0.245   |
| Creatinine clearance (ml/min/1.73m²) | 94.19 ± 27.23 | 90.95 ± 26.44              | <0.001  |
| Blood glucose (mmol/l) | 6.40 ± 2.24  | 6.39 ± 2.16                 | 0.845   |
| LDL-C (mmol/l)       | 2.45 ± 0.92  | 2.43 ± 0.91                 | 0.007   |
| CK-MB (mg/ml)        | 12.11 ± 8.56 | 12.03 ± 8.96                | 0.776   |
| CRP (mg/l)           | 3.91 ± 5.19  | 3.96 ± 6.26                 | 0.818   |
| Troponin I (ng/ml)   | 0.07 ± 0.22  | 0.10 ± 0.67                 | 0.209   |
| Left ventricular ejection fraction (%) | 62.26 ± 6.71 | 62.89 ± 6.07               | 0.003   |
| Number of diseased vessels, n (%) |          |                             |         |
| One-vessel disease   | 544 (50.3)   | 4290 (51.7)                 | 0.395   |
| Two-vessel disease   | 298 (27.6)   | 2431 (29.3)                 | 0.239   |
| Three-vessel disease | 147 (13.6)   | 1004 (12.1)                 | 0.158   |
| Left main disease    | 92 (8.5)     | 573 (6.9)                   | 0.053   |
| ACC/AHA lesion classification, n (%) |          |                             |         |
| Type A or B1         | 196 (18.1)   | 1823 (22.0)                 | 0.004   |
| Type B2 or C         | 885 (81.9)   | 6475 (78.0)                 | 0.004   |
| Number of stents     | 1.97 ± 0.96  | 1.79 ± 0.87                 | <0.001  |
| Stent diameter (mm)  | 3.16 ± 0.54  | 3.13 ± 0.51                 | 0.088   |
| Total stent length (mm) | 37.91 ± 22.36 | 35.46 ± 20.45              | 0.001   |
| Radial artery access, n (%) | 969 (89.6)   | 7734 (93.2)                 | <0.001  |
| ACEI/ARB, n (%)      | 903 (83.5)   | 6788 (81.8)                 | 0.163   |
| Beta-blocker, n (%)  | 984 (91.0)   | 7493 (90.3)                 | 0.445   |
| Statin, n (%)        | 1079 (99.8)  | 8290 (99.9)                 | 0.401   |
| Calcium channel blockers, n (%) | 111 (10.3)    | 763 (9.2)                   | 0.254   |
| Proton pump inhibitor, n (%) | 544 (50.3)    | 3908 (47.1)                 | 0.046   |

Data are expressed as mean ± standard deviation, or number (percentage). 
BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; LDL-C, low density lipoprotein cholesterol; CK-MB, creatine kinase-MB; CRP, C-reactive protein; ACC/AHA, American College of Cardiology/American Heart Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
Multivariate Cox regression analysis demonstrated that the use of ticagrelor (HR 0.52, 95% CI 0.29–0.92, p=0.027), number of stents (HR=1.37, 95% CI 1.18–1.71, p=0.008), his-
grel groups (Table 2). The incidences of non-cardiovascular death, MI, stroke, any revascularization, and stent thrombosis were comparable between the ticagrelor and prasu-
adverse clinical events in the ticagrelor group was lower compared with that in the clopidogrel group (4.1% vs. 6.0%, log-rank test, \( p = 0.036 \)) (Table 2, Fig. 2F). On multivariate Cox regression analysis, the independent predictors of bleeding events include radial artery access (HR = 0.35, 95% CI 0.12–0.65, \( p = 0.002 \)) (Fig. 2B).

**Safety Endpoints**

The incidence of bleeding events was significantly higher in the ticagrelor group compared with that in the clopidogrel group (4.0% vs. 2.7%, log-rank test, \( p = 0.016 \)) (Table 2, Fig. 2B). The TIMI major bleeding rates tended to increase in the ticagrelor group compared with those in the clopidogrel group (1.7% vs. 1.0%, \( p = 0.046 \)) (Table 2). No significant difference was observed in net adverse clinical events between the two groups (4.1% vs. 4.7%, log-rank test, \( p = 0.350 \)) (Table 2, Fig. 2C).

After propensity score matching, no significant difference was observed in bleeding events between the two groups (4.0% vs. 3.2%, log-rank test, \( p = 0.332 \)) (Table 2, Fig. 2E). Moreover, no significant differences were observed in the rates of major and minor bleeding events between the ticagrelor and clopidogrel groups (Table 2). The incidence of net adverse clinical events in the ticagrelor group was lower compared with that in the clopidogrel group (4.1% vs. 6.0%, log-rank test, \( p = 0.036 \)) (Table 2, Fig. 2F). On multivariate Cox regression analysis, the independent predictors of bleeding events include radial artery access (HR = 0.35, 95% CI 0.12–0.65, \( p = 0.002 \)), stroke (HR = 1.73, 95% CI 1.25–2.37, \( p = 0.030 \)), and weight <60kg (HR = 2.57, 95% CI 1.39–3.89, \( p = 0.021 \)) (Fig. 3B).

**Discussion**

We sought to compare the efficacy and safety of using ticagrelor vs. clopidogrel in patients with SCAD. The main finding of this study is that the use of ticagrelor was associated with reduced ischemic risk and similar bleeding risk compared with the use of clopidogrel at 1-year follow-up. Patients discharged on ticagrelor had lower incidences of all-cause death, cardiovascular death, and net adverse clinical events, as well as similar rates of TIMI major or minor bleeding events.

Ticagrelor is a direct oral P2Y12 receptor antagonist that is used to prevent atherosclerotic thrombosis.
in patients with ACS. The efficacy and safety of ticagrelor in patients with ACS were investigated in the PLATO trial. Ticagrelor, in combination with aspirin, reduced the incidence of the composite of death from vascular causes, MI, or stroke compared with clopidogrel plus aspirin. No significant differences were observed in the incidence of major bleeding between the ticagrelor group and the clopidogrel group. Previous studies have compared the efficacy and safety of ticagrelor vs. clopidogrel in patients with ACS, AMI, STEMI, NSTEMI, and NSTE-ACS. However, there is currently no study comparing the efficacy and safety of ticagrelor vs. clopidogrel in patients with SCAD undergoing PCI. Until now, this is the first real-world study that comprehensively evaluated the efficacy and safety of ticagrelor in patients with SCAD at 1-year follow-up.

Ticagrelor is a reversible and direct-acting oral antagonist of P2Y12 inhibitors, providing greater, faster, and more consistent P2Y12 inhibition than clopidogrel. In the multicenter, randomized, double-blind ONSET/OFFSET study, patients with SCAD were randomized into the ticagrelor group and the clopidogrel group. Ticagrelor achieved more rapid and greater platelet inhibition (IPA) than clopidogrel at 0.5, 1, 2, 4, 8, and 24 h after loading and at 6 weeks (p < 0.0001). This inhibitory effect persists in the maintenance phase and was faster in offset after drug discontinuation (–1.04 vs. –0.48, p < 0.0001). In the RESPOND study, the antiplatelet effect of ticagrelor was similar in patients who were responsive vs. nonresponsive to clopidogrel. Other pharmacokinetic and pharmacodynamic studies have demonstrated that ticagrelor has a faster onset and greater IPA than clopidogrel.

Some studies showed that ticagrelor was associated with an increased risk of bleeding events compared with clopidogrel in patients with AMI, NSTEMI, and ACS. However, the PLATO study and other studies revealed that ticagrelor did not increase the bleeding risk compared with clopidogrel in patients with ACS, NSTE-ACS, and STEMI. Presently, the safety of ticagrelor in patients with different types of coronary artery disease undergoing PCI is controversial. However, this study was not a randomized study; thus, selection bias may affect the results in a meaningful way. In addition, some factors such as all Chinese patients with SCAD, age younger than those in other studies regarding ticagrelor, lower proportion of patients with chronic kidney disease, and weight less than 60 kg may be the reasons why the bleeding events were not higher in the ticagrelor group than in the clopidogrel group in our study.

Our study was based on Chinese patients with SCAD, but our results may be applied to East Asian patients. East Asians have unique characteristics: thrombogenicity, the inhibition of platelet P2Y12-receptor, and the tendency to have bleeding complications. It is well known that East Asians share a common genetic homogeneity. In addition, previous pharmacokinetic studies have shown that the levels of active metabolites for ticagrelor and prasugrel in East Asians are similar. Therefore, our findings may be generalized to East Asian patients.

Although there is no randomized clinical trial comparing the efficacy and safety of ticagrelor or prasugrel with clopidogrel in the treatment of patients with SCAD, when clopidogrel is inadequate or when the risk of ischemia increases significantly, ticagrelor or prasugrel can be used in selected patients with stable coronary artery disease (class of recommendation, IIb; level of evidence, C). Aggregometry studies have shown that prasugrel and ticagrelor have stronger antiplatelet effects than clopidogrel; however, the net clinical benefits of these new antiplatelet drugs in patients with SCAD (which may reduce ischemic events but not significantly increase bleeding) have not yet been confirmed. In addition, ticagrelor is used in patients with SCAD who receive PCI, and its use is increasing, especially in high-risk diabetic patients or in complex coronary artery disease. This real-world study will provide important insight into the efficacy and safety of ticagrelor in patients with SCAD.

Our study has several limitations. First, our study only has a small sample size and a short follow-up time; therefore, a larger and high-quality randomized controlled trial with longer follow-up periods to validate our findings is needed. Second, this was a nonrandomized study, which may lead to selection bias. Third, although we conducted a propensity matching analysis, unmeasured factors may still exist, and the possible effects of unmeasured residual confounding factors cannot be ruled out. Fourth, medication side effects during clinical follow-up were not evaluated. Finally, patients usually receive DAPT for at least 12 months after PCI, but the duration of DAPT for patients with SCAD became shorter in recent ESC, AHA, and JCS guidelines. Thus, shorter duration of DAPT may change our results. The optimal duration of DAPT in patients with SCAD who underwent PCI with DES is uncertain, and the optimal duration of DAPT needs to be proven by a large randomized controlled trial in the future.

**Conclusion**

Compared with clopidogrel, the use of ticagrelor...
in patients with SCAD undergoing PCI was associated with a lower incidence of MACCEs without an increased incidence of bleeding events. The results of our study warrant further investigations on the optimal use of ticagrelor in patients with SCAD undergoing PCI.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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