

# Ticagrelor Versus Clopidogrel in The Treatment of Elderly Chinese Chronic Total Occlusion Patients Undergoing PCI

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## Research Article

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# Abstract

**Background:** Taking thrombosis and bleeding risks into consideration, little real world study data is available to dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) in elderly Chinese chronic total occlusion (CTO) patients.

**Methods:** We assigned 504 CTO patients aged  $\geq 75$  years who successfully underwent PCI from December 2009 to May 2020. The patients were randomized to Clopidogrel and Ticagrelor group and received DAPT for up to 12 months. Efficacy endpoints were evaluated by major adverse cardiac events (MACE) consisting of all-cause death, nonfatal myocardial infarction (MI) and clinically driven revascularization. The safety endpoints were recorded as the incidence of Bleeding Academic Research Consortium (BARC) bleeding.

**Results:** Patients in Clopidogrel group were older, they had a higher percentage of BMI, diastolic blood pressure and HDL-C than those in Ticagrelor group. Clopidogrel group had a lower percentage of hyperlipidemia, prior PCI, glucose, TG and LDL-C. No significant difference was found as to the Angiographic and procedural characteristics ( $P \geq 0.05$  for all). After 12 months' follow-up, the incidence of MACE (12.19% vs. 11.04%,  $P=0.763$ ) and bleeding (9.38% vs. 13.64%,  $P=0.205$ ) had no significant difference. After clinical characteristics balanced matching by IPTWs model, we found that Ticagrelor had an unfavorable effect on reducing the incidence of bleeding with the IPTWs model (IPTW-OR, 1.81, 95% CI: 1.18-2.76,  $P=0.006$ ).

**Conclusions:** This clinical study demonstrated that Clopidogrel should be recommended to elderly CTO patients after PCI, especially those with a high bleeding risk.

**Trial registration:** The study protocol was approved by the Ethics Committee of Air Force Medical University (KY20172019-1).

## Background

Coronary CTO is observed in approximately 15-25% of CAD patients have undergone prior coronary angiography [1, 2]. Guidelines recommend selective PCI to CTO patients to improve their symptoms and quality of life, and patients who undergo successful CTO-PCI have higher survival rates [3, 4]. As CTO lesions are complex and intraoperative stent placement is frequent, the risk of thrombosis is high; therefore, intensive DAPT is recommended for CTO-PCI patients to prevent stent thrombosis [5, 6]. However, continuous antiplatelet therapy is also associated with increased bleeding risk, leading to the necessity to balance the risk of bleeding and ischemia. As the elderly population over 75 years has a much higher risk of bleeding, more concern is needed for the adjustment of DAPT medication to elderly CTO-PCI patients. Consequently, it is of great significance to investigate the efficacy and safety of different DAPT strategies for elderly CTO-PCI patients. However, traditional clinical randomized controlled trials seldom focused on elderly CTO patients, and data on Chinese elderly CTO patients after PCI is scarcely available. In addition, most CTO-PCI DAPT studies focused on duration rather than medication

selection, which makes current clinical studies of Chinese elderly CTO-PCI patients' DAPT medication selection underrepresented.

Ticagrelor and Clopidogrel are two of the most commonly used DAPT drugs. Compared with Clopidogrel, Ticagrelor has faster action, stronger antiplatelet effect and its effect is reversible [7]. A study on Chinese CTO-PCI patients investigated the efficacy and safety of Ticagrelor and Clopidogrel, in which there were three groups (Ticagrelor group of 90 mg twice daily, Ticagrelor group of 60 mg twice daily, and Clopidogrel group of 75 mg once daily). The major adverse cardiac and cerebral events (MACCE, all-cause mortality, target vessel revascularization, stent thrombosis, nonfatal MI, and nonfatal stroke), major bleeding and minor bleeding incidence were separately 7.3% vs. 6.4% vs. 14.2%, ( $P=0.023$ ), 4.1% vs. 0.6% vs. 0.6%, ( $P=0.016$ ) and 23.4% vs. 12.4% vs. 11.9%, ( $P=0.004$ ) [8]. These results indicate that Ticagrelor with normal dose has lower incidence of MACE but higher bleeding incidence compared with Clopidogrel in Chinese CTO-PCI patients. However, the study did not reveal information on elderly patients, and there is no study related to elderly CTO patients' DAPT. Therefore, it of necessity to investigate elderly CTO-PCI patients.

Herein, the current study is designed to assess the efficacy and safety of Ticagrelor in comparison with Clopidogrel on a background of Aspirin for elderly Chinese CTO patients who have undergone prior PCI.

## Methods

### Study design

This study was conducted in the department of cardiology, Xijing Hospital from December 2009 to May 2020 to compare the efficacy and safety of Ticagrelor versus Clopidogrel in elderly Chinese CTO patients who previously underwent elective PCI with drug-eluting stents (DES). PCI success was assessed by the interventional cardiologist performing the procedure. The study protocol was approved by the Ethics Committee of Air Force Medical University (KY20172019-1). Written informed consents were obtained from all participants.

### Study participants

From December 2009 to May 2020, a total of 504 CTO patients who successfully underwent elective PCI followed by DAPT for up to 12 months were consecutively enrolled in the study and randomized to treatment with Ticagrelor or Clopidogrel. Of the 504 patients, 30 were lost to follow-up, and eventually 474 patients were included in this study. For these participants, 320 of them took 100mg Aspirin and Clopidogrel with a 300mg loading dose followed by a dose of 75 mg daily, while the other 154 patients took 100mg Aspirin and Ticagrelor with a loading dose of 180 mg followed by a dose of 90 mg twice daily. All the patients took Aspirin at a dose of 100 mg daily. CTO was defined as angiographic evidence of total occlusion with complete interruption of anterograde blood flow (Thrombolysis In Myocardial Infarction (TIMI) flow grade 0) with an estimated duration of >3 months via previous angiograms, angina symptoms and a history of MI [2]. Coronary arteries measured were proximal left main artery (LM), left

anterior descending artery (LAD), right coronary artery (RCA) and left circumflex artery (LCX). Inclusion criteria included: 1) age  $\geq 75$  years old; 2) confirmed with CTO by coronary angiography; 3) successful PCI; 4) informed consent signed by the patient. Exclusion criteria included: 1) conservative oral anticoagulation therapy; 2) PCI contraindications; 3) P2Y12 inhibitors contraindications; 4) high risk of bleeding diathesis or coagulation disorder; 5) dialysis-dependent renal failure or liver cirrhosis; 6) refusal to participate in this study by the patient. Clinical, angiographic and procedural baseline data were collected and recorded.

## Study end points

Clinical follow-up was carried out by telephone interviews and outpatient visits. The follow-up period started from the date of DAPT use after PCI and ended when any study outcome first occurred or at 12 months after PCI. Inpatient observation and outpatient visits were scheduled for patients being regularly followed up in our hospital, while telephone calls were made for patients without regular medical follow-up. The incidence of end points was collected in medical records by a predefined questionnaire, in which health status, physical examinations, vital signs as well as laboratory assessments were simultaneously recorded. The efficacy endpoints in this study were evaluated by the occurrence of MACE, i.e., the composite of all-cause death, nonfatal MI and clinically driven revascularization. All-cause death was defined as death from any cause, which was ascertained without adjudication<sup>[9]</sup>. MI was defined as the presence of recurrent cardiac ischemic symptoms, new Q waves in  $\geq 2$  contiguous electrocardiographic leads or an elevation of creatine kinase (CK) level or its MB isoenzyme (CK-MB) to at least 3 times the upper limit of normal in 2 plasma samples<sup>[10]</sup>. Clinically driven revascularization was defined as any reintervention because of symptoms<sup>[11]</sup>. The safety endpoints were evaluated by the incidence of bleeding: Bleeding Academic Research Consortium (BARC) type 1, 2, 3, or 5<sup>[12]</sup>. Type 1 is inactive bleeding. Type 2 is active bleeding requiring evaluation or intervention by medical personnel, which differs from Type 3, Type 5 and bleeding related to coronary artery bypass graft. Type 3 is heavy bleeding as well as intracranial bleeding with significant hemoglobin reduction to 5g/dl, which requires blood transfusion. For Type 5, it refers to potential or qualitative fatal bleeding. The major bleeding events, which are the equivalent of BARC 3 and 5, include gastrointestinal bleeding, intracranial hemorrhage, hemoglobin decrease of  $\geq 3$  g/dL, significant bleeding requiring blood transfusion, and fatal bleeding<sup>[13]</sup>.

## Statistical analysis

Continuous variable was described as mean  $\pm$  SD or median and interquartile spacing, and categorical variable as number (percentage). Differences in continuous and categorical variables between groups were analyzed with Mann–Whitney U-test and Chi-square test respectively, and  $P < 0.05$  was considered to be statistically significant. Univariate logistic regression models were developed to explore the effect of treatment. To validate the effects of treatment groups on the incidence of bleeding, a propensity score weighting method was adopted according to the results of univariate factor comparison and literature reports. A logistic model was used to calculate propensity score, in which the dependent variable was Ticagrelor group and the covariates included age, DBP, hyperlipidemia, prior PCI, GLU, TG, LDL-C and HDL-C. Standardized mean differences (SMD) ( $< 0.20$  is indicative of good balance) were calculated to

evaluate the balance of the inverse probability of treatment weighting (IPTW) model. Finally, the IPTW odds ratio (IPTW-OR) was derived for Ticagrelor group.

## Results

### Clinical, angiographic and procedural baseline characteristics

In this study, a total of 504 CTO patients ( $\geq 75$  years) were prescribed with DAPT for 12 months after PCI from December 2009 to May 2020. During this period of time (12 months after PCI), 30 patients were lost to follow-up, and in the end 474 CTO patients were included in the study (Figure 1). In terms of clinical baseline characteristics, compared with the patients in Ticagrelor group, those in Clopidogrel group were older ( $80.45 \pm 4.23$  vs.  $79.18 \pm 3.59$ ,  $P=0.001$ ) and had a higher percentage of BMI ( $24.14 \pm 3.49$  vs.  $22.82 \pm 4.75$ ,  $P=0.003$ ), more elevated diastolic blood pressure ( $74.53 \pm 10.16$  vs.  $71.82 \pm 9.85$ ,  $P=0.007$ ) and higher HDL-C ( $1.92 \pm 0.87$  vs.  $1.05 \pm 0.29$ ,  $P<0.001$ ). A lower percentage of patients in Clopidogrel group had hyperlipidemia (22.50% vs. 43.51%,  $P<0.001$ ) and prior PCI (25.63% vs. 39.61%,  $P=0.003$ ), and they had lower glucose ( $24.14 \pm 3.49$  vs.  $22.82 \pm 4.75$ ,  $P=0.003$ ), TG ( $1.31 \pm 0.78$  vs.  $1.48 \pm 0.85$ ,  $P=0.037$ ) and LDL-C ( $1.22 \pm 0.71$  vs.  $1.96 \pm 0.75$ ,  $P<0.001$ ). There were no significant differences among the other clinical characteristics ( $P>0.05$  for all) (Table 1). For CTO lesion characteristics, no significant differences were found as to the CTO lesions of coronary arteries (LM, LAD, RCA, and LCX), number of treated vessels, number of stents or total stent length ( $P>0.05$  for all) (Table 2).

Table 1  
Baseline clinical characteristics (n=474)

Variable	Clopidogrel (n=320)	Ticagrelor (n=154)	P value
Age, years	80.45±4.23	79.18±3.59	0.001
Male, %	230 (71.88)	115 (74.68)	0.582
BMI	24.14±3.49	22.82±4.75	0.003
Heart rate, beats/min	73.15±12.33	72.24±10.74	0.437
SBP, mmHg	130.02±22.71	128.39±25.38	0.487
DBP, mmHg	74.53±10.16	71.82±9.85	0.007
Smoking, %	87 (27.19)	33 (21.43)	0.215
Medical history			
Hypertension, %	192 (60.00)	85 (55.19)	0.322
Diabetes mellitus, %	90 (28.13)	48 (31.17)	0.518
Hyperlipidemia	72(22.50)	67 (43.51)	<0.001
Valvular heart disease, %	2 (0.63)	0	1.000
Atrial fibrillation, %	12 (375)	4 (2.60)	0.598
Stroke, %	33 (10.31)	19 (12.34)	0.532
Chronic kidney diseases, %	8 (2.50)	8 (5.19)	0.172
Peripheral arterial disease, %	2 (0.63)	0	1.000
Family history of CAD, %	0	2 (1.30)	0.105
Prior MI, %	15 (4.69)	10 (6.49)	0.511
Prior PCI, %	82 (25.63)	61 (39.61)	0.003
Prior CABG, %	8 (2.50)	2 (1.30)	0.511
Laboratory data			
WBC (10 <sup>9</sup> /L)	6.65±2.19	6.87±3.79	0.420

Abbreviations: CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; BMI, Body Mass Index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; RBC, red blood cell; Hb, Hemoglobin; PLT, blood platelet ; Ccr, creatinine clearance; BUN, blood urea nitrogen; UA, uric acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Alb, albumin; Glu, Glucose; TC, triglyceride; TG, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction.

Variable	Clopidogrel (n=320)	Ticagrelor (n=154)	P value
RBC (10 <sup>12</sup> /L)	4.24±0.61	4.24±0.53	0.946
Hb (g/L)	131.19±18.45	129.87±17.01	0.457
PLT (10 <sup>9</sup> /L)	177.32±67.05	189.04±60.24	0.066
Creatinine (μmol/L)	108.20±52.01	114.93±82.86	0.288
Ccr (ml/min)	49.09±13.88	46.40±13.54	0.104
BUN (mmol/L)	5.89±2.20	6.06±1.97	0.655
UA (μmol/L)	311.00±289.95	313.27±89.20	0.930
ALT (U/L)	20.00 (16.75)	21.00 (11.00)	0.578
AST (U/L)	20.00 (13.00)	16.00 (12.85)	0.177
Alb (g/L)	38.49±4.99	37.96±3.94	0.363
Glu (mmol/L)	6.19±2.42	6.97±3.04	0.007
TC (mmol/L)	3.64±1.07	3.52±0.89	0.236
TG (mmol/L)	1.31±0.78	1.48±0.85	0.037
LDL-C(mmol/L)	1.22±0.71	1.96±0.75	<0.001
HDL-C(mmol/L)	1.92±0.87	1.05±0.29	<0.001
NT-proBNP (pg/ml)	598.30 (1415.98)	661.50 (2065.50)	0.229
LVEF (%)	52.17±9.36	51.12±9.29	0.303

Abbreviations: CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; BMI, Body Mass Index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; RBC, red blood cell; Hb, Hemoglobin; PLT, blood platelet ; Ccr, creatinine clearance; BUN, blood urea nitrogen; UA, uric acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Alb, albumin; Glu, Glucose; TC, triglyceride; TG, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction.

Table 2  
Angiographic and procedural characteristics

Variable	Clopidogrel (n=320)	Ticagrelor (n=154)	P value
CTO Lesion characteristics, %			
LM	2 (0.63)	0	1.000
RCA	149 (46.56)	76 (49.35)	0.624
LAD	158 (49.38)	71 (46.10)	0.556
LCX	96 (30.00)	53 (34.42)	0.343
Number of treated CTO vessels, %			
1	308 (96.25)	144 (93.51)	0.242
2	12 (3.75)	9 (5.84)	0.342
3	0	1 (0.65)	0.325
Number of stents	2.42±1.16	2.40±1.15	0.842
Total stent length, mm	61.13±34.18	61.36±36.55	0.948
Abbreviations: CTO, chronic total occlusion; LM, left main; LAD, left anterior descending; RCA, right coronary artery; LCX, left circumflex.			

## Clinical outcomes on follow-up

After 12 months' follow-up, the incidence of MACE was 12.19% in Clopidogrel group and 11.04% in Ticagrelor group, with no statistical significance ( $P>0.05$ ). The individual components in the two groups were not significantly different either, which included all-cause death (10.94% vs. 11.04%), nonfatal MI (0.31% vs. 1.30%) and clinically driven revascularization (0.94% vs. 0). The total bleeding rate (9.38% vs. 13.64%) and BARC 1 bleeding (8.13% vs. 12.99%) of Clopidogrel group were lower than those of Ticagrelor group, but with no statistical significance ( $P>0.05$ ) (Table 3). Considering that the factors that might be related to bleeding were not balanced, the IPTW model was used to balance the clinical characteristics from the two groups (Figure 2). The characteristics were significantly balanced after matching, and it was found that compared with Clopidogrel, Ticagrelor had an adverse impact on the reduction of the incidence of bleeding with the IPTW model (IPTW-OR: 1.81, 95% CI: 1.18-2.76,  $P=0.006$ ) (Figure 3).

Table 3  
Efficacy and safety points

Variable	Clopidogrel (n=320)	Ticagrelor (n=154)	P value
MACE, %	39 (12.19)	17 (11.04)	0.763
All-cause death, %	35 (10.94)	17 (11.04)	1.000
Nonfatal myocardial infarction, %	1 (0.31)	2 (1.30)	0.248
Clinically driven revascularization, %	3 (0.94)	0	0.554
Bleeding, %	30 (9.38)	21 (13.64)	0.205
BARC 1, %	26 (8.13)	20 (12.99)	0.100
BARC 2, %	2 (0.63)	0	1.000
BARC 3, %	0	0	
BARC 5, %	2 (0.63)	1 (0.65)	1.000

## Discussion

PCI is feasible for CTO with high success rates<sup>[14]</sup>, but CTO-PCI patients have higher ischemic risk because of more complex lesions. Therefore, prolonged DAPT duration is recommended for these patients<sup>[2, 5]</sup>. Elderly CTO-PCI patients are also at high risk of bleeding<sup>[15]</sup>, which makes it vitally important to balance the risks of both thrombosis and hemorrhage for CTO-PCI patients to ensure a desirable prognosis. Previous studies indicated that the improvement of clinical outcomes was irrespective of whether the duration of DAPT after PCI in CTO patients was >12 months or not<sup>[16, 17]</sup>. Considering the reasons above, the duration of DAPT in this study was determined as 12 months. DAPT, which comprises aspirin and a P2Y12 inhibitor, prevents both stent thrombosis and non-culprit segments thrombosis via antiplatelet aggregation to reduce coronary ischemic events after PCI. As P2Y12 inhibitors recommended by many guidelines, Ticagrelor and Clopidogrel can prevent adenosine diphosphate (ADP) dependent activation of platelet aggregation by binding to the P2Y12 receptor<sup>[5, 6]</sup>.

According to the results of the PLATO trial, compared with Clopidogrel, Ticagrelor showed a lower incidence of endpoint events including cardiovascular death, MI and stroke (9.8% vs. 11.7%,  $P<0.001$ ) without increasing bleeding risk (11.6% vs. 11.2%,  $P=0.43$ )<sup>[18, 19]</sup>. In the ESTATE study that enrolled Taiwan acute coronary syndrome (ACS) patients, compared with patients taking Clopidogrel, those who took Ticagrelor had a lower incidence of MI, stroke, or vascular death endpoints with marginal statistical significance (7.1% vs. 11.6%,  $P=0.07$ ), and the incidence of all bleeding was similar (19.6% vs. 14.3%,  $P=0.13$ )<sup>[20]</sup>. Among these studies, more than 80% patients received invasive therapies (PCI or coronary artery bypass grafting (CABG)). The PLATO trial contained 587 Chinese patients (3.1%) and also 2878 elderly patients (15.45%)<sup>[18, 19]</sup>, and the ESTATE study included 269 (28.99%) Chinese patients older than

75 years<sup>[20]</sup>. In these studies data concerning CTO patients was absent, and Chinese elderly patients accounted only for a small number of the subjects enrolled in the studies. Consequently, these studies could hardly be representative of Chinese elderly CTO patients.

In the present study, all the patients were aged  $\geq 75$  years and underwent PCI with DES. After 12-month DAPT, the incidence of MACE in Ticagrelor group was lower than that in Clopidogrel group (11.04% vs. 12.19%), but the incidences of overall bleeding (13.64% vs. 9.38%) and BARC 1 bleeding (12.99% vs. 8.13%) were higher in Ticagrelor group, with no statistical significance for all the differences. After balancing clinical characteristics of the two groups, the difference of bleeding incidence was found to be statistically significant. This indicates that Ticagrelor has similar effect in reducing MACE but higher bleeding risk for Chinese elderly CTO-PCI patients. Thus, Ticagrelor showed similar efficiency but worse safety in comparison with Clopidogrel in our study.

Several studies showed that Clopidogrel had similar MACE but higher bleeding incidence than Ticagrelor for patients after PCI<sup>[21–23]</sup>. There is a “East Asian paradox” which describes that East Asian patients have lower ischemic but higher bleeding risk after PCI<sup>[24]</sup>. In the PHILO trial which targeted mostly Japanese patients, compared with Clopidogrel, Ticagrelor was associated with higher incidence of overall bleeding events (23.8% vs. 14.7%, hazard ratio (HR): 1.72; 95% CI: 1.23-2.40) and minor bleeding events (15.2% vs. 9.2%, HR: 1.75; 95% CI: 1.15-2.67), and the incidence of ischemic events (the composite of MI, stroke or vascular-cause death) is not significantly different (9.0% vs. 6.3%, HR: 1.47; 95% CI: 0.88-2.44)<sup>[25]</sup>. The TICAKOREA trial indicated that in comparison with Clopidogrel group, Ticagrelor group had higher incidence of clinically significant bleeding (11.7% vs. 5.3%,  $P=0.002$ ) and minor bleeding (5.2% vs. 1.3%,  $P=0.02$ ), and the incidence of cardiovascular death, MI and stroke was not significantly different between the two groups (9.2% vs. 5.8%,  $P=0.07$ )<sup>[26]</sup>. The Kamir-NIH study based on East Asian population showed that Ticagrelor reduced the risk of ischemic event with statistical significance (8.6% vs. 11.9%,  $P=0.018$ ), but it had a significantly higher bleeding risk than Clopidogrel (10.8% vs. 4.8%,  $P<0.001$ ) for patients with acute myocardial infarction (AMI) and multivessel disease (MVD)<sup>[27]</sup>. These studies support the perception that East Asian patients with the medication of Ticagrelor have a higher incidence of bleeding complications, especially minor bleeding, which is consistent with our findings.

There are few studies aiming at DAPT for Chinese CTO patients or elderly patients who underwent PCI, let alone post-PCI patients with CTO who aged  $\geq 75$  years in China. In a study on Chinese CTO patients who underwent PCI, the incidences of overall MACE, major bleeding and minor bleeding in normal Ticagrelor dose group and Clopidogrel group were (7.3% vs. 14.2%), (4.1% vs. 0.6%) and (23.4% vs. 11.9%), respectively<sup>[8]</sup>. This indicates that normal dose Ticagrelor renders lower incidence of MACE but higher bleeding incidence compared with Clopidogrel for Chinese CTO patients. According to the POPular AGE study involving 1002 patients (aged  $\geq 70$  years) with non-ST-elevation acute coronary syndrome (NSTEMI-ACS), the primary bleeding outcome incidence was higher in Ticagrelor group (24% vs. 18%,  $P=0.02$ ), and there were no significant differences as to the incidence of cardiovascular death, MI, and stroke between

the two groups (11% vs. 12%,  $P=0.71$ ) [28], which is in favor of the conclusion that Clopidogrel is recommended for elderly NSTEMI-ACS patients with a high bleeding risk.

The MACE incidence in the POPular AGE study is similar to that in our study, whereas in other studies the MACE incidence of Ticagrelor group is lower than that in our study. This might be attributed to the greater complexity of lesions of elderly CTO patients, which leads to higher MACE risks. The bleeding incidence in Ticagrelor group in our study is higher than those in the TICAKOREA trial and Kamir-NIH study but is lower than incidences in other studies. This may be partly due to the research bias brought by small sample size as well as the differences of baseline and procedure characteristics between the groups that might affect the comparison of the endpoints.

It is found that DAPT after PCI can benefit elderly CTO-PCI patients, and Ticagrelor showed similar MACE and higher incidence of bleeding, especially minor bleeding (BARC 1 bleeding) compared with Clopidogrel; therefore, we believe Clopidogrel has similar efficiency and better safety for elderly Chinese CTO-PCI patients. As Ticagrelor has higher bleeding incidence, it should be prescribed with caution to patients with a high bleeding risk. This study may make potential contribution to clinical practice, but it is essential to carry out a further prospective, multi-center and large-scale study to compare the efficacy and safety outcomes of Ticagrelor and Clopidogrel in elderly Chinese CTO patients who underwent PCI.

## Study limitations

There are several limitations in the current study. Firstly, it was a single center study with a small sample size, in which the selection bias was hardly avoidable. Secondly, we did not distinguish cardiovascular death in our follow-up, and we did not assess CTO score, opening techniques or the occurrence of stroke. Thirdly, owing to the unavailability of the information on the date of nonfatal MI and clinically driven revascularization, we did not adjust the analysis of efficacy end points accordingly. Fourthly, we did not include other related therapeutic agents such as  $\beta$ -blocker and other drugs, and we did not evaluate the major adverse effects of P2Y12 inhibitors including dyspnea, hyperuricemia, and asymptomatic heart block.

## Conclusions

This clinical study demonstrated that in the improvement of elderly Chinese CTO patients' prognosis, Clopidogrel is found to be more desirable for elderly Chinese CTO patients after PCI because of lower incidence of bleeding events. Consequently, Clopidogrel should be recommended for elderly CTO patients after PCI, especially patients with a high bleeding risk.

## Abbreviations

DAPT: dual antiplatelet therapy; PCI: percutaneous coronary intervention; CTO: chronic total occlusion; MACE: major adverse cardiac event; MI: myocardial infarction; BARC: Bleeding Academic Research Consortium; DES: drug-eluting stents; TIMI: Thrombolysis In Myocardial Infarction; LM: left main artery

LAD: left anterior descending artery; RCA: right coronary artery; LCX: left circumflex artery; CK: creatine kinase; CK-MB: creatine kinase MB isoenzyme; SMD: standardized mean differences; IPTW: inverse probability of treatment weighting; ADP: adenosine diphosphate; ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; AMI: acute myocardial infarction; MVD: multivessel disease; NSTEMI: non-ST-elevation acute coronary syndrome.

## **Declarations**

### **Ethics approval and consent to participate**

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Air Force Medical University (KY20172019-1). Written informed consents were obtained from all participants.

### **Consent for publication**

The consent was obtained from all authors for publication of this study.

### **Availability of data and materials**

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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### **Conflict of interest statement**

The authors have no conflicts of interest to declare.

### **Authors' contributions**

Peng Han contributed to the original draft writing and editing of the work; Suining Xu contributed to the design and editing; Ying Liang and Zhijun Tan contributed to the statistical analyses; Shuai Zhao, Yan Chen, Ziwei Wang, Yuhao Chen, Boda Zhu, Zhilin Sha and Anxin Shen contributed to the data curation; Feng Tao contributed to the language editing; Qin Wang, Qiong Wang, Genrui Chen, Li Yang and Haokao Gao contributed to the review and editing; Kun Lian and Chengxiang Li contributed to the project administration and supervision. All authors read and approved the final manuscript.

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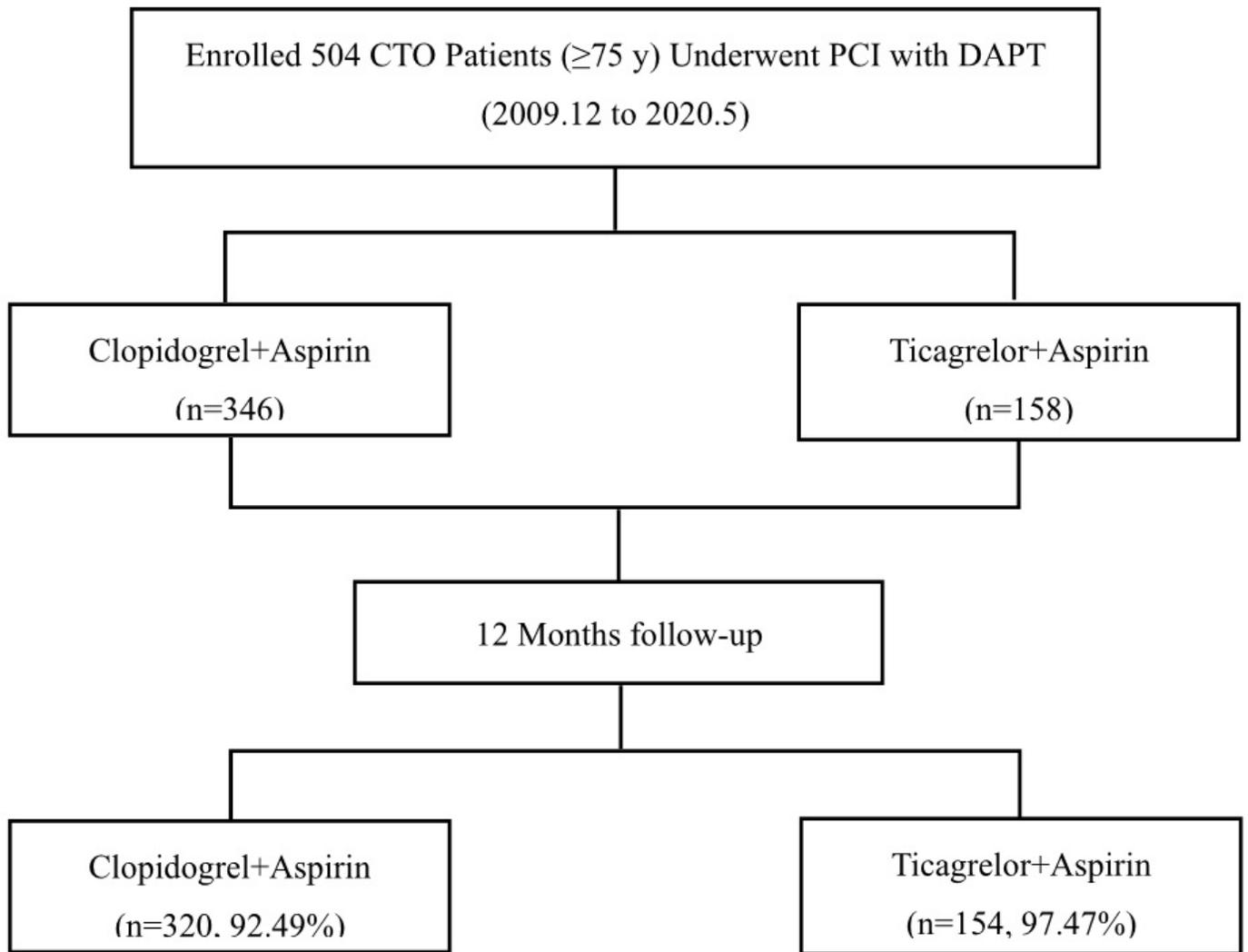
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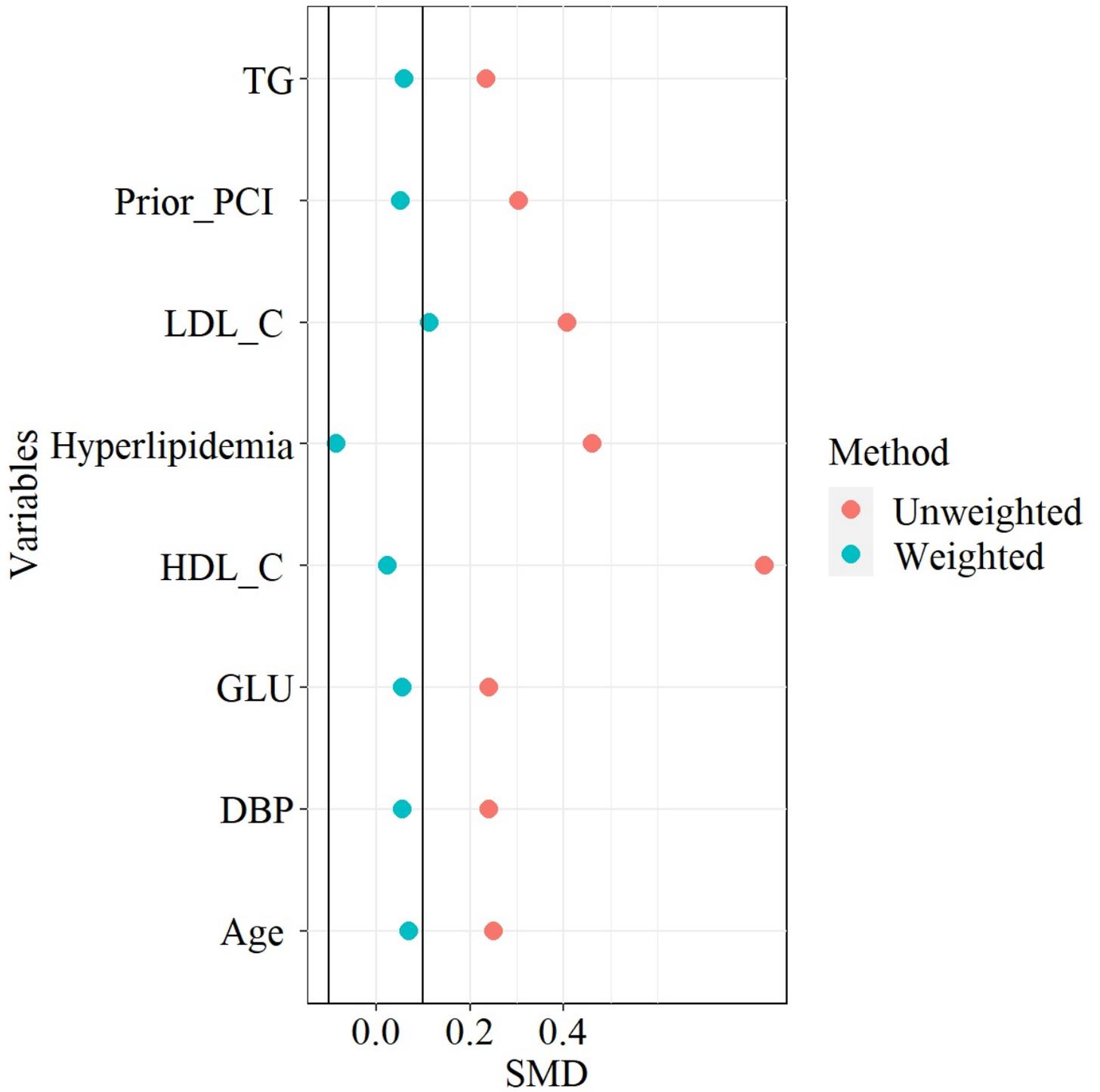
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## Figures



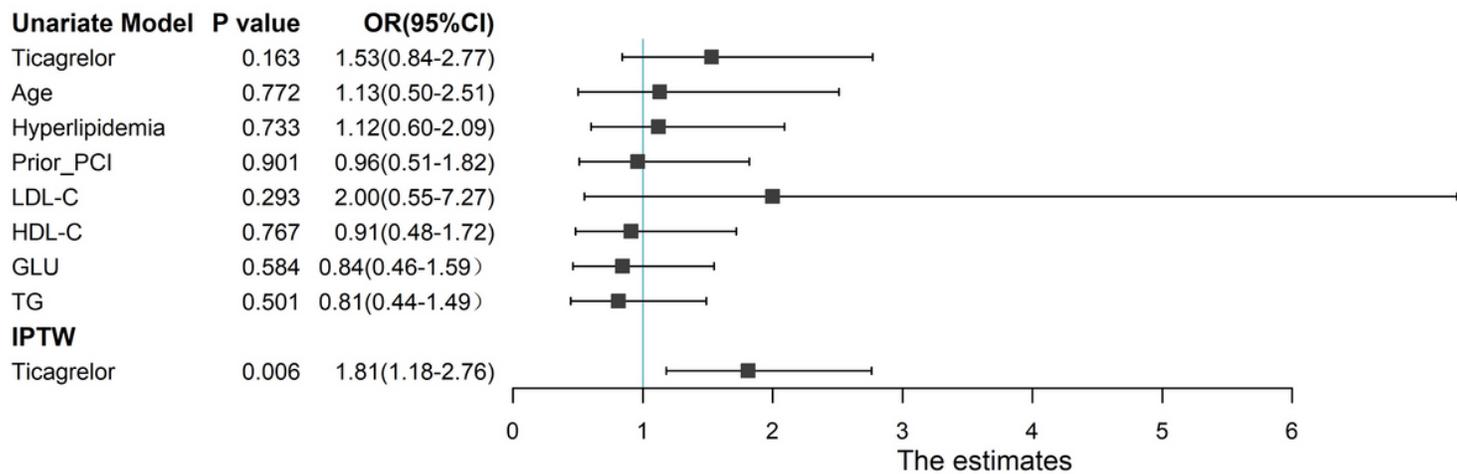
**Figure 1**

Study workflow



**Figure 2**

Standardized mean differences weighted and unweighted propensity score matching for the corresponding variable



**Figure 3**

Univariate analysis and IPTWs estimate of ticagrelor (vs. clopidogrel) on the occurrence of bleeding