AUCTORES
Globalize your Research

Journal of Clinical Cardiology and Cardiovascular Interventions
Kun Lian, Chengxiang Li and Qingyi Wang *

Open Access

Research Article

Ticagrelor Versus Clopidogrel in the treatment of Elderly Chinese Chronic Total Occlusion Patients Undergoing Percutaneous Coronary Intervention

Peng Han [1,2#], Ying Liang [3#], Suining Xu [4,2#], Shuai Zhao [2], Yan Chen [5], Ziwei Wang [6], Yuhao Chen [6], Boda Zhu [6], Zhilin Sha [6], Anxin Shen [6], Feng Tao [7], Qin Wang [8], Qiong Wang [2], Genrui Chen [2,9], Zhijun Tan [3], Li Yang [2], Haokao Gao [2], Chengxiang Li [2*], Qingyi Wang [10*] and Kun Lian [2*]

[1]Department of Cardiology, 981 Hospital of Joint Logistics Support Force, Chengde, Hebei 067000, P. R. China.

[2]Department of Cardiology, Xijing Hospital, Airforce Military Medical University, Xi'an, Shaanxi 710032, P. R. China.

[3]Department of Health Statistics, The Airforce Military Medical University, Xi'an, Shaanxi 710032, P. R. China.

[4]Department of Cardiology, The First Affiliated Hospital of Xi'an Medical University, Xi'an, Shannxi 710077, P. R. China.

[5]Department of Cardiology, No.971 Hospital of the PLA Navy, Qingdao, Shandong 266071, P. R. China.

[6]Cadet Brigade, School of Basic Medicine, Airforce Military Medical University, Xi'an, Shannxi 710032, P.R. China.

[7]Department of Naval Medicine, Naval Medical University, Shanghai 200433, P. R. China.

[8] Department of Pharmacogenomics, The Airforce Military Medical University, Xi'an, Shaanxi 710032, P. R. China.

[9]Department of Cardiology, Hanyin County People's Hospital, Ankang, Shaanxi 725100, P. R. China

[10]School of Basic Medicine, Airforce Military Medical University, Xi'an, Shannxi 710032, P.R. China.

[#]Peng Han, Ying Liang, and Suining Xu contributed equally to this work.

***Corresponding Author: Kun Lian,** Department of Cardiology, Xijing Hospital, Airforce Military Medical University, 169 West Changle Road, Xi'an, Shaanxi 710032, P.R. China, **Chengxiang Li**, Department of Cardiology, Xijing Hospital, Airforce Military Medical University, 169 West Changle Road, Xi'an, Shaanxi 710032, P.R. China and **Qingyi Wang,** School of Basic Medicine, Airforce Military Medical University, 169 West Changle Road, Xi'an, Shaanxi 710032, P.R. China.

Received Date: March 08, 2022; Accepted Date: March 14, 2022; Published Date: March 21, 2022

Citation: Peng Han, Ying Liang, Suining Xu, Shuai Zhao, Yan Chen. et all (2022). Ticagrelor Versus Clopidogrel in the treatment of Elderly Chinese Chronic Total Occlusion Patients Undergoing Percutaneous Coronary Intervention. *J. Clinical Cardiology and Cardiovascular Interventions*, 5(4); DOI:**10.31579/2641-0419/259**

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.

Objective: This study was designed to investigate the effectiveness and safety of Ticagrelor in comparison with Clopidogrel as an add-on therapy to Aspirin for elderly Chinese CTO patients who underwent elective PCI.

Materials and Methods: We retrospectively enrolled 504 CTO patients (aged ≥75 years) who received PCI from December 2009 to May 2020 and DAPT for up to 12 months. The effectiveness endpoints were evaluated by major adverse cardiac events (MACE) including 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, as was evidenced in our study, were older, and 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＞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) showed no significant difference. After clinical characteristics balanced matching by inverse probability of treatment weighting (IPTW) model, we found that Ticagrelor had an unfavorable effect on reducing the incidence of bleeding with the IPTW model (IPTW-OR, 1.81, 95% CI: 1.18-2.76, P=0.006).

Conclusions: Clopidogrel and Ticagrelor present similar effectiveness and safety to elderly Chinese CTO-PCI patients, yet Ticagrelor should be prescribed with caution to patients with a high bleeding risk.

Keywords: ticagrelor; clopidogrel; aged cto patients; percutaneous coronary intervention; chronic total occlusion

1. Introduction

Coronary chronic total occlusion (CTO) is observed in approximately 15-25% of coronary artery disease (CAD) patients who underwent prior coronary angiography [1,2]. Guidelines recommend selective percutaneous coronary intervention (PCI) to CTO patients to improve their symptoms and quality of life, as well as survival rates [3,4]. Intensive dual antiplatelet therapy (DAPT) is recommended for CTO-PCI patients to reduce potential thrombosis induced by complex lesions and frequent stent placement of CTO [5,6]. Tough continuous antiplatelet therapy is also associated with increased bleeding, more concern is given for delivering DAPT medication to elderly CTO-PCI patients to balance bleeding and ischemia, as the elderly population over 75 years has a much higher risk of bleeding. Nevertheless, given that traditional clinical randomized controlled trials seldom had elderly CTO patients as their subjects, data on elderly CTO-PCI patients' DAPT is scarcely available.

As the most commonly used DAPT drugs, Ticagrelor has faster action and stronger antiplatelet effect, and its effect is reversible compared with Clopidogrel [7]. Chinese CTO-PCI patients were reportedly showed lower MACE incidence and higher bleeding incidence after receiving normal dose of Ticagrelor, compared with Clopidogrel in Chinese CTO-PCI patients [8],. Unfortunately, no data concerning the elderly patients was found.

Considering the profound potential value of identifying how different DAPT strategies affect elderly CTO-PCI patients, this study was designed to investigate the effectiveness and safety of Ticagrelor in comparison with Clopidogrel as an add-on therapy to Aspirin for elderly Chinese CTO patients who received PCI.

2. Materials and Methods

Study design

This study was conducted in the Department of Cardiology, Xijing Hospital from December 2009 to May 2020 and aimed to compare the effectiveness and safety of Ticagrelor versus Clopidogrel in elderly Chinese CTO patients who 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 were prescribed DAPT for up to 12 months, and were retrospectively enrolled in the study. Among the 504 patients, with 30 lost in follow-up, eventually 474 patients were included in this study. These patients were initiated on DAPT prior to PCI, among whom 320 took Clopidogrel with a 300mg loading dose followed by a dose of 75 mg daily, while the other 154 patients took 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. Inclusion criteria included: 1) were aged ≥75 years old; 2) validated with CTO by coronary angiography; 3) received PCI successfully; 4) signed the informed consent. Exclusion criteria included: 1) underwent conservative oral anticoagulation therapy; 2) exhibited PCI contraindications; 3) displayed P2Y12 inhibitors contraindications; 4) with high risk of bleeding diathesis or coagulation disorder; 5) diagnosed with dialysis-dependent renal failure or liver cirrhosis; 6) refused to participate in this study by the patient. Clinical baseline, angiographic and procedural data were collected and recorded.

Study endpoints and definitions

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 effectiveness 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 [9].

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), left circumflex artery (LCX) and right coronary artery (RCA). The diagnosis of MI was based on the Fourth Universal Definition of MI [10]. Clinically driven revascularization was defined as any reintervention because of symptoms [11]. The safety endpoints were evaluated by the incidence of bleeding: Bleeding Academic Research Consortium (BARC) type 1, 2, 3, or 5 [12]. 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 ≥3 g/dL, significant bleeding requiring blood transfusion, and fatal bleeding [13].

Statistical analysis

This is a single-center, retrospective cohort study. Continuous variable was described as mean ± 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, diastolic blood pressure (DBP), hyperlipidemia, prior PCI, glucose (GLU), total cholesterol (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (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.

3. Results

Clinical baseline, angiographic and procedural baseline characteristics

In this study, a total of 504 CTO patients (≥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**).

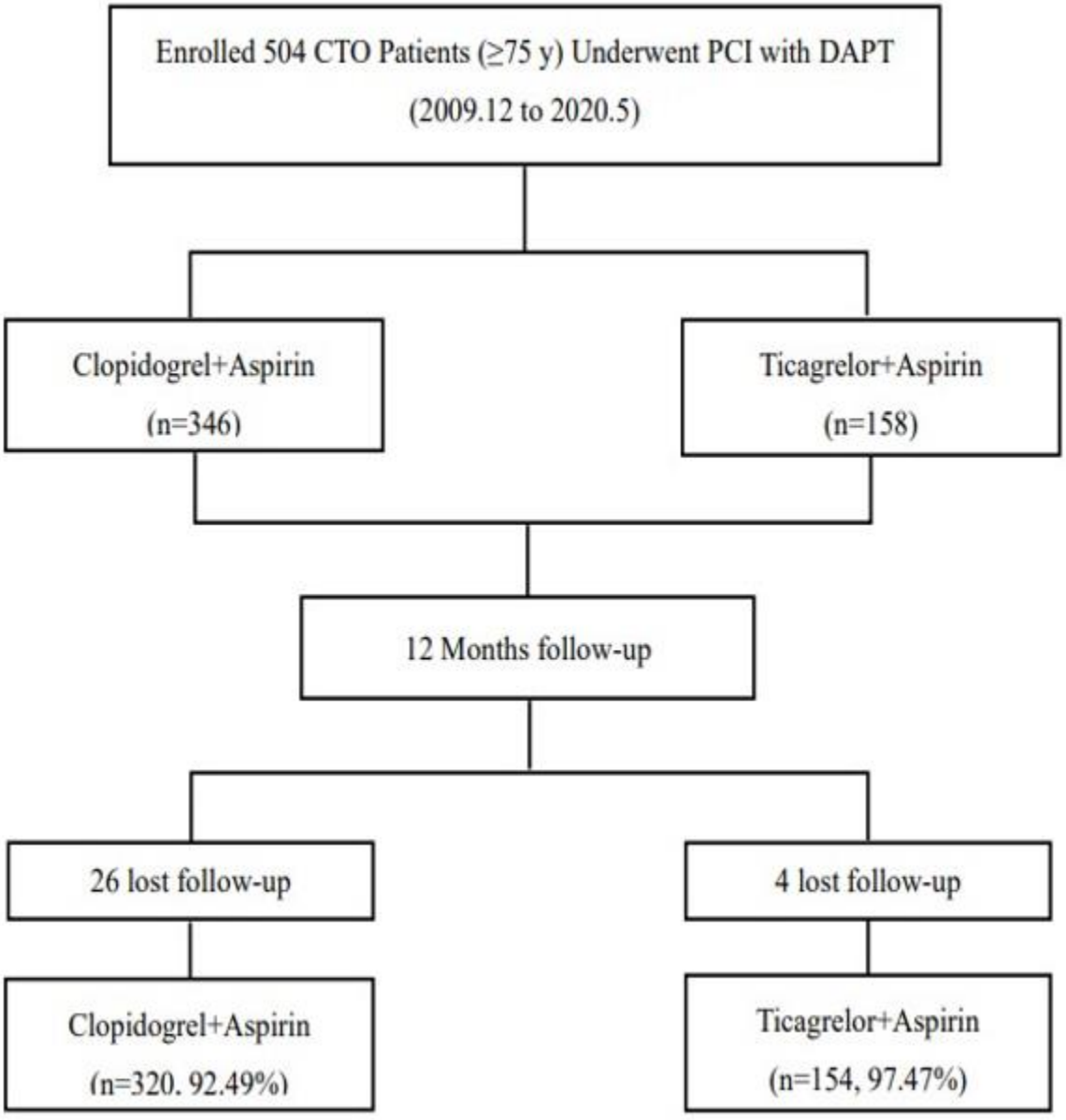

Figure 1: *Study workflow*

In terms of clinical baseline characteristics, compared with the patients in Ticagrelor group, those in Clopidogrel group were older (80.45±4.23 vs. 79.18±3.59, P=0.001) and had a higher percentage of BMI (24.14±3.49 vs. 22.82±4.75, P=0.003), more elevated diastolic blood pressure

(74.53±10.16 vs. 71.82±9.85, *P*=0.007) and higher HDL-C (1.92±0.87 vs. 1.05±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±3.49 vs. 22.82±4.75, *P*=0.003), TG (1.31±0.78 vs. 1.48±0.85, *P*=0.037) and LDL-C (1.22±0.71 vs. 1.96±0.75, *P*<0.001). There were no significant differences among the other clinical characteristics (*P*＞0.05 for all) (**Table 1**).

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 before PCI			
WBC (10^9/L)	6.65±2.19	6.87±3.79	0.420
RBC (10^{12}/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 (10^9/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 amiotransferase; 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 1: *Clinical baseline characteristics (n=474)*

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**).

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.

Table 2. *Angiographic and procedural characteristics*

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 ($P>0.05$), the individual components in the two groups were not significantly different either. 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**).

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

Table 3: *Efficacy and safety points*

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**).

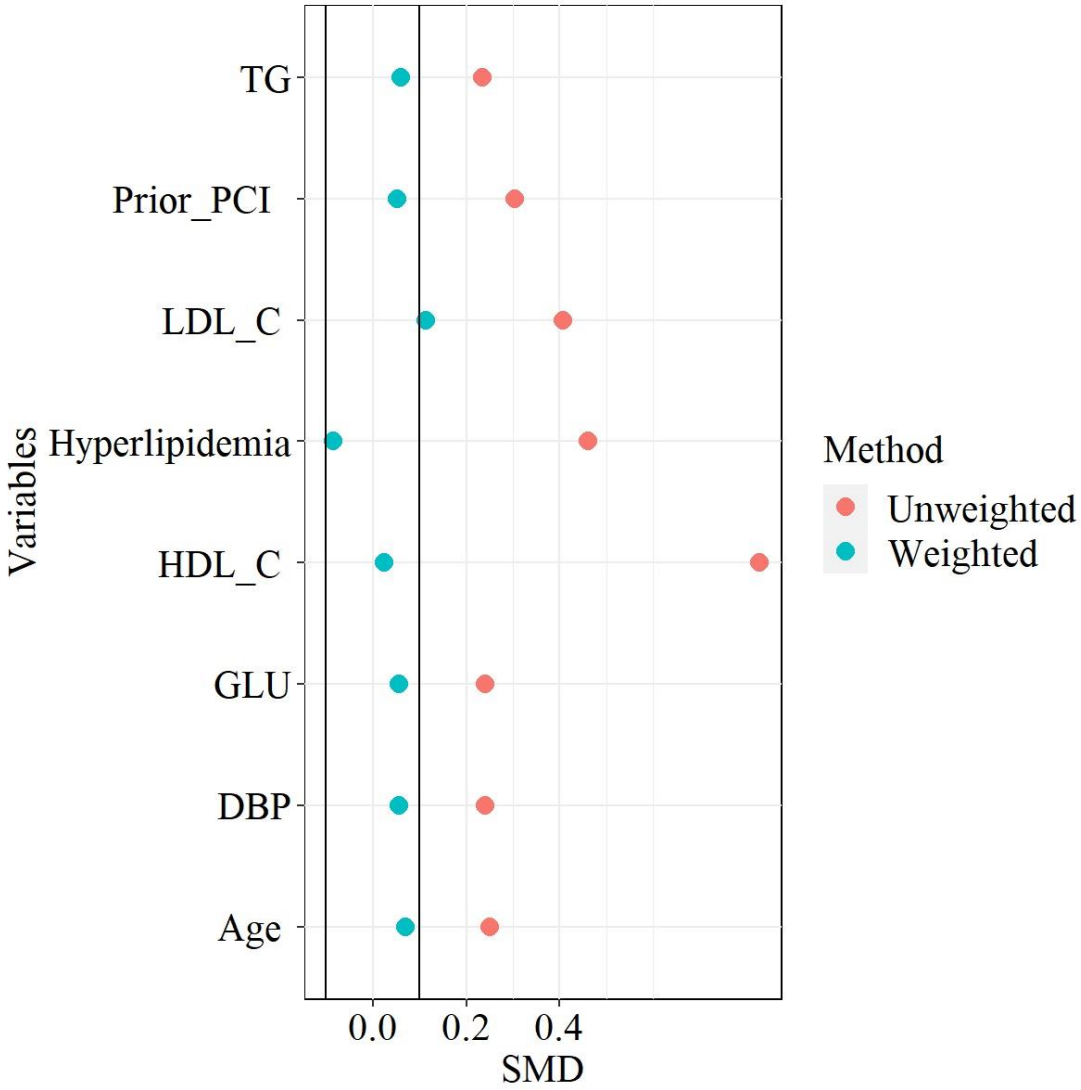

Figure 2: *Standardized mean differences weighted and unweighted propensity score matching for the corresponding variable*

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**).

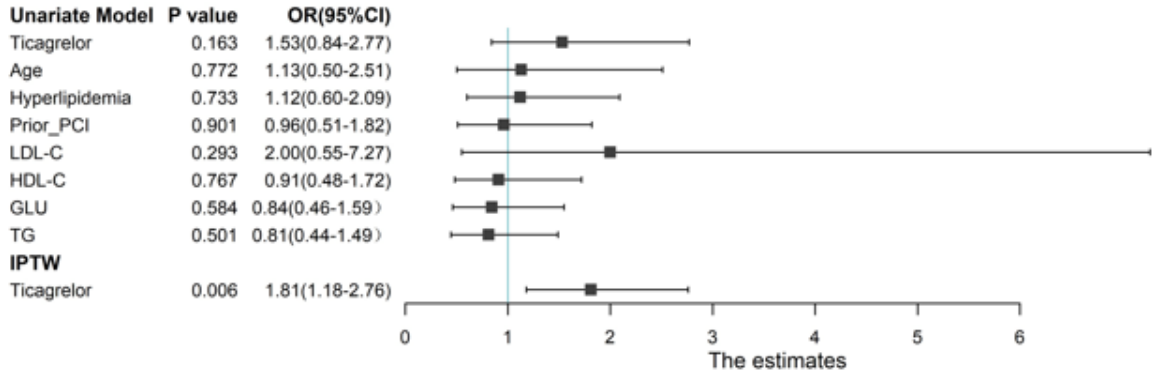

Figure 3: *Univariate analysis and IPTW estimate of ticagrelor (vs. clopidogrel) on the occurrence of bleeding.*

4. Discussion

PCI has been applied to CTO at high success rates [14], but CTO-PCI patients presented with higher ischemic incidence because of more complex lesions. Therefore, prolonged DAPT duration is usually recommended for these patients [2,5]. Elderly CTO-PCI patients are also exposed to high risks of bleeding [15], which makes it vitally important to balance both thrombose and hemorrhage for CTO-PCI patients to ensure a desirable prognosis. Previous studies indicated that clinical improvement showed up, regardless whether the DAPT duration was >12 months or not after PCI in CTO patients [16,17]. Considering the reasons above, the duration of DAPT in this study was determined as 12 months. DAPT, which comprises aspirin and a P2Y12 inhibitor, reduces coronary ischemic events after PCI by preventing both stent thrombosis and non-culprit segments thrombosis via antiplatelet aggregation. 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 [5, 6].

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) [18,19]. In the ESTATE study that enrolled Taiwan acute coronary syndrome (ACS) patients, the patients 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), than those taking Clopidogrel, and the incidence of all bleeding was similar (19.6% vs. 14.3%, P=0.13) [20]. 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%) [18,19], and the ESTATE study included 269 (28.99%) Chinese patients older than 75 years [20]. In these studies, data concerning CTO patients was absent, and Chinese elderly patients accounted only for a small number of the subjects enrolled. Consequently, these studies could hardly represent Chinese elderly CTO population.

In the present study, all the patients were aged ≥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 effectiveness but worse safety in comparison with Clopidogrel in our study.

Clopidogrel was reported to have similar MACE but higher bleeding incidence than Ticagrelor for patients after PCI [21-23]. An “East Asian paradox” was known for pointing out that East Asian patients have lower ischemic but higher bleeding risk after PCI [24]. In the PHILO trial which targeted mostly Japanese patients, compared with Clopidogrel, Ticagrelor was found 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) [25]. The TICAKOREA trial indicated that 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) than the Clopidogrel group, 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) [26]. 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) [27]. In consistent with the previous studies, our findings also validated the perception that East Asian patients receiving Ticagrelor medication have a higher incidence of bleeding complications, especially minor bleeding.

Some study had data concerning DATP of CTO-PCI patients, however, no subjects of DATP of CTO-PCI patients who aged ≥75 years was reported. In the GF-APT registry, stable coronary artery disease patients who undergoing complex PCI got higher risk of MACEs (11.2% vs. 8.6%) and similar risk of major bleeding (0.6% vs. 0.9%) after 12-months use of Clopidogrel compared with Ticagrelor, and Ticagrelor had higher minor bleeding risk (1.2% vs. 3.4%), 34.1% of the patients in the study were CTOs [28]. This supports our result that Ticagrelor medication has a higher incidence of minor bleeding. One research into Chinese CTO patients who underwent PCI compared the incidences of overall MACE, major bleeding and minor bleeding in normal Ticagrelor dose group and Clopidogrel group, which were (7.3% vs. 14.2%), (4.1% vs. 0.6%) and (23.4% vs. 11.9%), respectively [8]. This indicates that normal dose Ticagrelor triggered 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 ≥70 years with non-ST-elevation acute coronary syndrome (NSTE-ACS), the primary bleeding incidence was higher in Ticagrelor group (24% vs. 18%, P=0.02), and no significant differences was detected in the incidence of cardiovascular death, MI, and stroke between the two groups (11% vs. 12%, P=0.71) [29], which are align with the conclusion that Clopidogrel tend to induce high bleeding risks in elderly NSTE-ACS patients. The MACE incidence in the POPular AGE study largely coincided with that in our study, whereas the MACE incidence of Ticagrelor group in other studies 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, Kamir-NIH study and GF-APT registry 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.

Taken together, DAPT after PCI can benefit aged CTO-PCI patients, and Ticagrelor showed similar MACE but higher incidence of bleeding, especially minor bleeding (BARC 1 bleeding) in contrast to Clopidogrel. As the bleeding events were not clinically relevant, Clopidogrel and Ticagrelor are considered with similar effectiveness and safety in elderly Chinese CTO-PCI patients. However, Ticagrelor should be prescribed cautiously to patients with a high bleeding risk. This study shed lights in potential clinical application of Clopidogrel and Ticagrelor. Still, a further prospective, multi-center and large-scale trials are required to verify the effectiveness and safety of Ticagrelor and Clopidogrel in elderly CTO patients who underwent PCI.

Study Limitations

The study still maintains a few limitations. As a single center retrospective study but with a small sample size, the selection bias was hardly avoidable and the methodological biases exist. Additionally, cardiovascular death was not identified and separately analyzed in our follow-up, with the CTO score, opening techniques or the occurrence of stroke, not considered. More, analysis of effectiveness end points wasn’t adjusted accordingly, given the unavailability of nonfatal MI date and clinically driven revascularization. Lastly, therapeutic agents such as β-blocker were not included in this study, and neither did we evaluate the major adverse

effects of P2Y12 inhibitors including dyspnea, hyperuricemia, and asymptomatic heart block.

Conclusions

This clinical study demonstrated that Clopidogrel and Ticagrelor have similar effectiveness and safety to elderly Chinese CTO-PCI patients in improving their prognosis, yet Ticagrelor should be prescribed with caution to eliminate potential bleeding.

List of 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; **IPTW:** inverse probability of treatment weighting; **CAD:** coronary artery disease; **MI:** myocardial infarction; **DES:** drug-eluting stents; **TIMI:** Thrombolysis In Myocardial Infarction; **LM:** left main artery； **LAD:** left anterior descending artery; **LCX:** left circumflex artery; **RCA:** right coronary artery; **BARC:** Bleeding Academic Research Consortium; **DBP:** diastolic blood pressure; **Glu:** glucose; **TG:** total cholesterol; **LDL-C:** low-density lipoprotein cholesterol; **HDL-C:** high-density lipoprotein cholestero; **SMD:** standardized mean differences; **IPTW:** inverse probability of treatment weighting; **ADP:** adenosine diphosphate; **ACS:** acute coronary syndrome; **CABG:** coronary artery bypass grafting; **HR:** hazard ratio; **AMI:** acute myocardial infarction; **MVD:** multivessel disease; **NSTE-ACS:** non-ST-elevation acute coronary syndrome.

Ethics Approval and Consent to Participate

Declarations

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 analyzed in the current study are available from the corresponding author on reasonable request.

Funding

This work was supported by Shaanxi Province Key Research and Development Program General Project—Social Development (2018SF-153), Xi'an Science and Technology Project (20YXYJ0003(4)), New Clinical Technology and New Business of Xijing Hospital (XJGX15Y39), Bethune-Merck Diabetes Research Foundation (G2017044).

Conflict of Interest

The authors have no conflicts of interest to declare.

References

1. Fefer P, Knudtson ML, Cheema AN, et al. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. J Am Coll Cardiol. 2012;59(11):991-997.
2. Galassi AR, Werner GS, Boukhris M, et al. Percutaneous recanalisation of chronic total occlusions: 2019 consensus document from the EuroCTO Club. EuroIntervention. 2019;15(2):198-208.
3. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40(2):87-165.
4. Christakopoulos GE, Christopoulos G, Carlino M, et al. Meta-analysis of clinical outcomes of patients who underwent percutaneous coronary interventions for chronic total occlusions. Am J Cardiol. 2015;115(10):1367-1375.
5. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J, 2018, 39(3): 213-260.
6. Yong Huo, Young-Hoon Jeong, Yanjun Gong, et al. 2018 update of expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. Science Bulletin. 2019; 64: 166-179.
7. 2012 Writing Committee Members, Jneid H, Anderson JL, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/Non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation, 2012. 126(7): 875-910.
8. Wang Y, Zhao HW, Wang CF, et al. Efficacy and safety of standard and low dose Ticagrelor versus Clopidogrel in east Asian Patients with chronic total occlusion undergoing percutaneous coronary intervention: a single center retrospective study. BMC Cardiovasc Disord. 2020;20(1):109.
9. Hicks KA, Mahaffey KW, Mehran R, et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. J Am Coll Cardiol, 2018. 71(9): 1021-1034.
10. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction guidelines. Eur Heart J 2018; 40: 237-269.
11. Scheinert D, Micari A, Brodmann M, et al. Drug-Coated Balloon Treatment for Femoropopliteal Artery Disease. Circ Cardiovasc Interv, 2018. 11(10): e005654.
12. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation, 2011. 123(23): 2736-2747.
13. Choi JH, Seo JM, Lee DH, Park K, Kim YD. Clinical utility of new bleeding criteria: a prospective study of evaluation for the Bleeding Academic Research Consortium definition of bleeding in patients undergoing percutaneous coronary intervention. J Cardiol. 2015;65(4):324-329.
14. Lee SW, Lee PH, Ahn JM, et al. Randomized Trial Evaluating Percutaneous Coronary Intervention for the Treatment of Chronic Total Occlusion. Circulation. 2019;139(14):1674-1683.
15. Costa F, Van Klaveren D, Feres F, et al. Dual Antiplatelet Therapy Duration Based on Ischemic and Bleeding Risks After Coronary Stenting. J Am Coll Cardiol. 2019;73(7):741-754.
16. Sachdeva A, Hung YY, Solomon MD, McNulty EJ. Duration of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention for Chronic Total Occlusion. Am J Cardiol. 2020;132:44-51.
17. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Thorac Cardiovasc Surg,

2016. 152(5): 1243-1275.
18. Husted S, James S, Becker RC, et al. Ticagrelor versus Clopidogrel in elderly patients with acute coronary syndromes: a substudy from the prospective randomized PLATelet inhibition and patient Outcomes (PLATO) trial. Circ Cardiovasc Qual Outcomes, 2012. 5(5): 680-688.
19. Kang HJ, Clare RM, Gao R, et al. Ticagrelor versus Clopidogrel in Asian patients with acute coronary syndrome: A retrospective analysis from the Platelet Inhibition and Patient Outcomes (PLATO) Trial. Am Heart J, 2015. 169(6): 899-905.e1.
20. Chen IC, Lee CH, Fang CC, et al. Efficacy and safety of Ticagrelor versus Clopidogrel in acute coronary syndrome in Taiwan: A multicenter retrospective pilot study. J Chin Med Assoc, 2016. 79(10): 521-530.
21. Silvain J, Lattuca B, Beygui F, et al. Ticagrelor versus Clopidogrel in elective percutaneous coronary intervention (ALPHEUS): a randomised, open-label, phase 3b trial. Lancet. 2020;396(10264):1737-1744.
22. You SC, Rho Y, Bikdeli B, et al. Association of Ticagrelor vs Clopidogrel With Net Adverse Clinical Events in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. JAMA. 2020;324(16):1640-1650.
23. Turgeon RD, Koshman SL, Youngson E, et al. Association of Ticagrelor vs Clopidogrel with Major Adverse Coronary Events in Patients with Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. JAMA Intern Med. 2020;180(3):420-428.
24. Kang J, Kim HS. The Evolving Concept of Dual Antiplatelet Therapy after Percutaneous Coronary Intervention: Focus on Unique Feature of East Asian and "Asian Paradox". Korean Circ J. 2018;48(7):537-551.
25. Goto S, Huang CH, Park SJ, Emanuelsson H, Kimura T. Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome -- randomized, double-blind, phase III PHILO study. Circ J. 2015;79(11):2452-2460.
26. Park DW, Kwon O, Jang JS, et al. Clinically Significant Bleeding With Ticagrelor Versus Clopidogrel in Korean Patients With Acute Coronary Syndromes Intended for Invasive Management: A Randomized Clinical Trial. Circulation. 2019;140(23):1865-1877.
27. Ahn JH, Ahn Y, Jeong MH, et al. Ticagrelor versus Clopidogrel in acute myocardial infarction patients with multivessel disease; From Korea Acute Myocardial Infarction Registry-National Institute of Health. J Cardiol. 2020;75(5):478-484.
28. Xi Z, Li J, Qiu H, et al. Ticagrelor vs. Clopidogrel After Complex Percutaneous Coronary Intervention in Patients With Stable Coronary Artery Disease. Front Cardiovasc Med. 2021;8:768190.
29. Gimbel M, Qaderdan K, Willemsen L, et al. Clopidogrel versus Ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): the randomised, open-label, non-inferiority trial. Lancet. 2020;395(10233):1374-1381.

DOI: 10.31579/2641-0419/259