Atherosclerosis 290 (2019) 52–58

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Clinical outcomes after ticagrelor and clopidogrel in Chinese post-stented patients

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HIGHLIGHTS

- Ticagrelor is not superior to clopidogrel in the Chinese population.
- Ticagrelor decreased the risk of short-term thrombotic events in Chinese patients.
- Ticagrelor increased the risk of BARC type 2 bleeding compared to clopidogrel.

ARTICLE INFO

Keywords:
Clopidogrel
Ticagrelor
Acute coronary syndrome
Percutaneous coronary intervention
Clinical outcomes

ABSTRACT

Background and aims: International guidelines recommend ticagrelor over clopidogrel as preferred antiplatelet agent in patients following coronary stenting. However, no large real-life evidence is available in East Asians in general, and Chinese in particular, with regard to associated clinical outcomes. The present study aimed to assess the early and delayed outcomes after ticagrelor *versus* clopidogrel in post stenting Chinese patients.

Methods: We conducted the pre-specified interim analysis of Comparison Of Efficacy and Safety Between TIcagrelor and Clopidogrel In Chinese (COSTIC), the ongoing prospective, observational, single-center trial. Primary outcomes include first occurrence of myocardial infarction, stroke, vascular death and Bleeding Academic Research Consortium (BARC) scale bleeding event. Propensity score matching (PSM) was carried out to adjust for differences in baseline characteristics between treatment arms.

Results: In total, 4,465 patients were enrolled. After PSM, the patients prescribed with ticagrelor had a lower incidence of primary efficacy endpoint relative to those with clopidogrel (0.6% *vs.* 1.4%, HR = 0.44, 95%CI: 0.22–0.89, $p = 0.019$) at 1 month, but similar at 7 days, 6 months and 12 months. Further analysis indicated that the difference only exists in the subgroup of acute myocardial infarction (AMI) patients. With regard to safety, ticagrelor consistently increased the risk of BARC type 2 bleeding compared to clopidogrel at 1 month, 6 months and 12 months.

Conclusions: These preliminary data indicate that ticagrelor is superior to clopidogrel with regard to major vascular thrombotic outcomes at 1 month, especially in the AMI population, but both groups are similar at 7 days, 6 months and 12 months. Ticagrelor consistently caused significantly more BARC type 2 bleeding.

1. Introduction

Percutaneous coronary intervention (PCI) via the implantation of intracoronary stents is the established and conventional reperfusion technique for restoration of coronary artery blood flow and survival benefit in patients with acute coronary syndromes (ACS) [1]. However, an elevated risk of repeated thrombosis exists, justifying protection with $P2Y_{12}$ inhibitors such as clopidogrel, prasugrel, or ticagrelor [2].

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https://doi.org/10.1016/j.atherosclerosis.2019.09.011
Received 3 May 2019; Received in revised form 16 September 2019; Accepted 20 September 2019
Available online 21 September 2019

Specifically, defective genotypes, such as CYPC19*2, lead to poor response to clopidogrel and are common, with frequencies ranging from 20 to 30% in Caucasians, 30–45% in African-Americans, and up to 50–65% in East Asians [3]. Studies in Western cohorts suggested that ticagrelor induces a faster, consistent, and more potent inhibition of platelet activity than clopidogrel, while prasugrel is not available in China. Additionally, the Phase III Platelet Inhibition and Patient Outcomes (PLATO) trial demonstrated that ticagrelor in combination with low dose aspirin significantly reduced the rate of thrombotic outcomes in predominantly Caucasian ACS patients relative to clopidogrel, without increasing the rate of major bleeding events [4,5]. These data have favored the recommendation of the superiority of ticagrelor over clopidogrel post-stenting [1]. However, later evidence somewhat challenged the applicability of such universal guidelines for East Asians, since the Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH) and the phase III study from Japan (PHILO) studies reported that ticagrelor did not significantly reduce the rates of cardiovascular death, myocardial infarction or stroke, but caused more bleeding than clopidogrel [6,7]. In addition, our previous work prospectively evaluated the modulating effects of 13 variants associated with clopidogrel efficacy, including CYP2C19*2, in 5820 Chinese ACS patients, and found that there was no significant associations between the variants and risk of cardiovascular events [8]. Overall, the East Asian "paradox" clearly indicated less ischemia, but more bleeding hazards [9], arousing our question on whether ticagrelor is still superior to clopidogrel in Asian patients due to predominantly lower weighted patients, or/and inherent genetic variation different from the Western counterparts [8]. In 2014, the Word Heart Federation also delineated the differences in risk profiles between Caucasians and East Asians for ischemia and bleeding. However, till date, very few large studies have compared hard outcomes rather than biomarkers between ticagrelor and clopidogrel in the Asian cohorts. Aside from any safety and efficacy considerations, Asian patients are also likely to benefit from clopidogrel in terms of healthcare costs since numerous generic formulations are broadly available. Cost-effectiveness data are also inconclusive since some evidence suggests clopidogrel benefits [10], equality [11], or inferiority [12] for post-stenting strategies. Thus, there is an urgent unmet need to assess the short- and long-term outcomes after clopidogrel and ticagrelor in patients with ACS undergoing PCI. We designed and implemented the Comparison Of Efficacy and Safety Between TIcagrelor and Clopidogrel (COSTIC) study to evaluate the short-term (7 days and 1-month) and delayed (6-months and 12-months) outcomes in Chinese patients.

2. Materials and methods

Comparison Of Efficacy and Safety Between TIcagrelor and Clopidogrel In Chinese (COSTIC) patients is an ongoing prospective, observational, single-center registry study (NCT03239067) designed to compare short- and long-term safety and efficacy outcomes between ticagrelor and clopidogrel. The trial started in August 2014, and is planned to be completed in July 2020. ACS patients undergoing PCI who were prescribed with either ticagrelor or clopidogrel were consecutively enrolled in the study. Medication choice was at physicians' discretion. The study was designed in accordance with the Declaration of Helsinki and is consistent with the International Committee on Harmonization, Good Clinical Practice (ICH-GCP) guidelines and applicable regulatory requirements. The institutional review board approved the study (TJ-C20160202) and all participants provided written informed consent.

From the planned pool of 9000 patients, the current pre-specified interim analyses (> 50% enrollment), 4668 patients were diagnosed with ACS underwent PCI, and screened for inclusion into the COSTIC study between August 2014 and October 2017, at Tongji Hospital, Wuhan, China. Diagnosis of ACS was determined based on clinical presentation, ST-segment anomalies on ECG, and a positive biomarker test, based on the AHA/ACC Guidelines [13,14]. Forty-seven patients were not prescribed with ticagrelor or clopidogrel, 28 patients were excluded for life-threatening complications, 59 patients were found with metastatic cancer and 69 patients were lost to follow-up. The trial algorithm and patient flow chart are presented in Supplementary Fig. 1.

Of the 4465 patients recruited, 2030 patients were on ticagrelor maintenance dose and 2435 patients were on clopidogrel maintenance dose. 101 (2.2%) patients prematurely discontinued the medication before the 6-month time point (47 for clopidogrel and 54 for ticagrelor), 16 did not receive aspirin due to drug intolerance and 44 failed to recall BARC bleeding time (41 for BARC type 2 bleeding and 3 for BARC type 3 bleeding).

The course of treatment during hospitalization was recorded in a medical chart. After discharge, all surviving patients underwent face-to-face interviews, phone calls, or/and chart reviews at 7 days, 1 month, at 6 months and at 12 months. In addition, independent research personnel extracted baseline clinical characteristics from a centralized hospital database and adjudicated patients' data accordingly.

The primary efficacy endpoint was defined as a composite of vascular death, myocardial infarction (MI) and stroke. Vascular death was defined as death from a cardiovascular causes or cerebrovascular causes and any death without another known cause. The definition of MI was consistent with the Third Universal Definition of MI [15]. Stroke was defined as rapid loss of neurologic function caused by an ischemic central nervous system event documented by imaging, with residual symptoms lasting at least 24 h from time of onset or resulting in death. Secondary efficacy endpoints were defined as a composite of all-cause death, MI or stroke, a composite of vascular death, MI, stroke, recurrent cardiac ischemia or other arterial thrombotic events, MI alone, cardiovascular death alone, stroke alone, and all-cause death. Safety endpoint was bleeding of type 2 or higher according to the Bleeding Academic Research Consortium (BARC) criteria [16]. Major bleeding was defined as BARC type 3, 4 and 5 bleeding. An independent blinded central committee adjudicated all suspected endpoint events.

The subgroup analysis was performed by dividing the whole cohort into unstable angina (UA) group and acute myocardial infarction (AMI) group. The UA group consists of 2791 patients before PSM and 2201 patients after PSM while the AMI group consists of 1674 patients before PSM and 1465 patients after PSM.

Moreover, to identify the factors other than treatment of ticagrelor or clopidogrel affecting outcomes of the ACS cohort, we compared risks of primary endpoint events among groups based on the baseline characteristics (age, sex, smoking, hypertension, diabetes mellitus, dyslipidemia, thrombolytic therapy before PCI, coronary artery bypass graft [CABG], arrhythmia, three vessels disease, Killip class, prior MI, prior stroke, prior bleeding, peripheral arterial disease, chronic renal disease, chronic obstructive pulmonary disease, chronic gastritis, peptic ulcer and diagnosis of ACS). Specifically, considering the multiple comparison, Bonferroni correction was applied to adjust the p values.

Data are presented as mean ± SD for continuous variables and as percentages for categorical variables. Student-t test or Mann–Whitney test were used to compare continuous variables depending on their distribution. Chi-square test was used to compare categorical variables. For efficacy endpoints, Kaplan–Meier (KM) survival curves were constructed and compared by log-rank test. Additionally, multivariate Cox regression model was used to estimate hazard ratios for efficacy outcomes. For bleeding endpoints, hazard ratios based on logistic regression applied to assess differences between clopidogrel and ticagrelor arms. For multivariate Cox regression and logistic regression models, a threshold of 0.05 was set to choose appropriate predictors using a backward stepwise strategy. Additional propensity score matching (PSM) was introduced to balance clinical factors related to treatment selection. Variables associated with both group assignments as well as outcome variables, such as age, sex, cardiovascular risk factors (such as smoking, hypertension, diabetes mellitus and dyslipidemia), medical history of thrombolytic therapy before PCI, CABG, Killip class, arrhythmia, three-vessel disease, prior MI, prior stroke, prior bleeding, peripheral arterial disease, chronic renal disease, chronic obstructive pulmonary disease, chronic gastritis and peptic ulcer, diagnosis of ACS, characteristics of PCI (such as artery access, gensini score, no of

Table 1
Baseline characteristics based on treatment group.

	Pre PSM			Post PSM		
	Clopidogrel group (N = 2435)	Ticagrelor group (N = 2030)	*p* value	Clopidogrel group (N = 1833)	Ticagrelor group (N = 1833)	*p* value
Age, mean ± SD	61.22 ± 10.49	59.37 ± 10.21	< 0.001	60.35 ± 10.62	59.86 ± 10.12	0.157
Males, n (%)	1696 (69.7)	1552 (76.5)	< 0.001	1356 (74.0)	1373 (74.9)	0.520
Cardiovascular risk factor, n (%)						
Smoker	901 (37.0)	846 (41.6)	0.001	748 (40.8)	737 (40.2)	0.711
Hypertension	1474 (60.5)	1213 (59.8)	0.602	1108 (60.4)	1115 (60.8)	0.813
Diabetes mellitus	635 (26.1)	616 (30.3)	0.002	512 (27.9)	531 (29.0)	0.487
Dyslipidemia	473 (19.4)	415 (20.4)	0.396	373 (20.3)	365 (19.9)	0.742
Other medical histories, n (%)						
Thrombolytic therapy before PCI	48 (2.0)	50 (2.5)	0.264	43 (2.3)	38 (2.1)	0.574
CABG	11 (0.5)	6 (0.3)	0.399	7 (0.4)	6 (0.3)	0.781
Arrhythmia	210 (8.6)	136 (6.7)	0.017	128 (7.0)	130 (7.1)	0.897
Three vessels disease	28 (1.1)	26 (1.3)	0.690	23 (1.3)	24 (1.3)	0.883
Killip class > 2	160 (6.6)	170 (8.4)	0.022	131 (7.1)	141 (7.7)	0.529
Prior MI	174 (7.1)	162 (8.0)	0.293	135 (7.4)	145 (7.9)	0.534
Prior stroke	179 (7.4)	103 (5.1)	0.002	110 (6.0)	101 (5.5)	0.523
Prior bleeding	49 (2.0)	23 (1.1)	0.020	21 (1.1)	23 (1.3)	0.762
Peripheral arterial disease	443 (18.2)	351 (17.3)	0.432	325 (17.7)	321(17.5)	0.862
Chronic renal disease	115 (4.7)	96 (4.7)	0.992	88 (4.8)	87 (4.7)	0.938
Chronic obstructive pulmonary disease	58 (2.4)	25 (1.2)	0.005	30 (1.6)	25 (1.4)	0.497
Chronic gastritis	101 (4.1)	106 (5.2)	0.089	90 (4.9)	94 (5.1)	0.762
Peptic ulcer	57 (2.3)	38 (1.9)	0.280	40 (2.2)	34 (1.9)	0.481
Diagnosis of ACS, n (%)			< 0.001			0.122
ST-elevation MI	409 (16.8)	552 (27.2)		394 (21.5)	440 (24.0)	
Non–ST-elevation MI	354 (14.5)	359 (17.7)		310 (16.9)	321 (17.5)	
Unstable angina	1672 (68.7)	1119 (55.1)		1129 (61.6)	1072 (58.5)	
Characteristics of PCI						
Artery access, n (%)			0.517			0.992
Radial artery	2265 (93.0)	1871 (92.2)		1698 (92.6)	1693 (92.4)	
Brachial artery	85 (3.5)	72 (3.5)		61 (3.3)	63 (3.4)	
Femoral artery	83 (3.4)	86 (4.2)		73 (4.0)	76 (4.1)	
Ulnar artery	2 (0.1)	1 (0.0)		1 (0.1)	1 (0.1)	
Gensini score	50.45 ± 34.83	63.45 ± 38.67	< 0.001	56.56 ± 35.81	60.65 ± 37.43	0.001
No of stents, mean ± SD	1.75 ± 0.93	1.98 ± 1.05	0.02	1.88 ± 0.98	1.93 ± 1.02	0.128
Total length of stents, mean ± SD	46.27 ± 28.04	52.99 ± 31.25	< 0.001	50.02 ± 29.37	51.51 ± 30.42	0.132
TIMI flow after PCI, n (%)			0.787			0.980
TIMI 1	1 (0.0)	1 (0.0)		1 (0.1)	1 (0.1)	
TIMI 2	14 (0.6)	15 (0.7)		12 (0.7)	13 (0.7)	
TIMI 3	2420 (99.4)	2014 (99.2)		1820 (99.3)	1819 (99.2)	
Other discharge medication, n (%)						
aspirin	2430 (99.8)	2022 (99.6)	0.244	1829 (99.8)	1825 (99.6)	0.247
statin	2415 (99.2)	2010 (99.0)	0.563	1816 (99.1)	1815 (99.0)	0.865
ACEI	1695 (69.6)	1562 (76.9)	< 0.001	1374 (75.0)	1385 (75.6)	0.674
beta blocker	1823 (74.9)	1619 (79.8)	< 0.001	1446 (78.9)	1445 (78.8)	0.968
nitrate	636 (26.1)	426 (21.0)	< 0.001	415 (22.6)	402 (21.9)	0.606
diuretics	197 (8.1)	181 (8.9)	0.324	162 (8.8)	157 (8.6)	0.770

PSM, propensity score matching; SD, standard deviation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; MI, myocardial infarction; ACS, acute coronary artery syndrome; ACEI, angiotensin converting enzyme inhibitor.

stents, total length of stents and TIMI flow after PCI) and use of concomitant medication such as ACEI, beta blockers and nitrates were used to estimate the propensity score. Using the nearest neighbor matching without replacement approach, we performed 1:1 PS matching using 0.2 as the considered caliper distance. Absolute standardized differences of less than 10% for each covariate indicated a small imbalance. For matched pair comparisons, the paired *t*-test or paired sample Wilcoxon's signed rank test was used for continuous variables and McNemar's test was used for categorical variables. All comparisons were two-tailed, and $p < 0.05$ was considered as statistically significant. Statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Baseline characteristics of all patients pre and post PSM by treatment group are showed in Table 1. Clopidogrel patients were older, with mean age of 61.22 ± 10.49 years *versus* ticagrelor (59.37 ± 10.21 years; $p < 0.001$). The patients were predominantly male, including 1696 (69.7%) in the clopidogrel group and more (76.5%) in the ticagrelor group ($p < 0.001$). Among qualifying ACS, STEMI or non-STEMI were more frequent in the ticagrelor group ($p < 0.001$). Additionally, the prevalence of smokers and diabetics was higher in the ticagrelor group compared with the clopidogrel group ($p < 0.05$). In addition, relative to the clopidogrel group, a larger proportion of patients in the ticagrelor group had a history of stroke ($p = 0.002$) and chronic obstructive pulmonary disease ($p = 0.005$). Doctors preferred prescribing ticagrelor in patients with Killip class > 2 ($p = 0.022$) and patients with higher Gensini score ($p < 0.001$), more stents ($p < 0.001$) and greater total length of stents ($p < 0.001$). Patients with history of prior bleeding were prescribed with clopidogrel more often ($p = 0.020$). Prescriptions of ticagrelor combined with ACEI, beta-blocker and nitrate were more common, in contrast to clopidogrel ($p < 0.001$). PSM based on the 31 variables identified 1833 matched pairs of patients. Post PSM, the two treatment groups were better balanced with respect to all covariates except that ticagrelor patients still had higher Gensini score ($p = 0.001$; Table 1).

Of the 1833 pairs of patients matched by PSM, patients prescribed with ticagrelor and patients with clopidogrel had similar cumulative 7-day incidence of the primary efficacy endpoint (composite of vascular death, MI

Table 2
Efficacy endpoints of 7-day, 1-month, 6-month and 12-month time points after PSM.

	Ticagrelor group	Clopidogrel group	Hazard ratio for ticagrelor group	*p* value
	(n = 1833)	(n = 1833)	(95% CI)	
7 days				
Primary endpoint: composite of death from vascular causes, MI, or stroke — no./total no. (%)	5 (0.3)	8 (0.4)	0.62 (0.20–1.91)	0.404
Composite of death from any cause, MI, or stroke — no./total no. (%)	6 (0.3)	9 (0.5)	0.67 (0.24–1.87)	0.440
1 month				
Primary endpoint: composite of death from vascular causes, MI, or stroke — no./total no. (%)	11 (0.6)	25 (1.4)	0.44 (0.22–0.89)	0.019
Secondary endpoints- no./total no. (%)				
Composite of death from any cause, MI, or stroke	16 (0.9)	28 (1.5)	0.57 (0.31–1.05)	0.069
Composite of death from vascular causes, MI, stroke, recurrent ischemia, TIA, or other arterial thrombotic events	40 (2.2)	48 (2.6)	0.89 (0.59–1.36)	0.391
MI	3 (0.2)	3 (0.2)	0.75 (0.17–3.34)	0.702
Death from vascular causes	8 (0.4)	18 (1.0)	0.58(0.30–1.13)	0.056
Stroke	1 (0.1)	4 (0.2)	0.25 (0.03–2.23)	0.179
Death from any cause	14 (0.8)	24 (1.3)	0.58 (0.30–1.13)	0.103
6 months				
Primary end point: composite of death from vascular causes, MI, or stroke — no. of patients (%)	33 (1.8)	42 (2.3)	0.78 (0.50–1.24)	0.295
Secondary end points — no. of patients (%)				
Composite of death from any cause, MI, or stroke	43 (2.3)	46 (2.5)	0.93 (0.62–1.41)	0.743
Composite of death from vascular causes, MI, stroke, recurrent ischemia, TIA, or other arterial thrombotic events	115 (6.3)	127 (6.9)	0.79 (0.50–1.24)	0.435
MI	10 (0.5)	4 (0.2)	2.50 (0.78–8.00)	0.110
Death from vascular causes	20 (1.1)	35 (1.9)	0.57 (0.33–0.99)	0.042
Stroke	5 (0.3)	7 (0.4)	0.71 (0.23–2.24)	0.558
Death from any cause	30 (1.6)	39 (2.1)	0.77 (0.48–1.24)	0.274
12 months				
Primary end point: composite of death from vascular causes, MI, or stroke — no. of patients (%)	54 (2.9)	61 (3.3)	0.88 (0.61–1.27)	0.507
Secondary end points — no. of patients (%)				
Composite of death from any cause, MI, or stroke	70 (3.8)	67 (3.7)	1.04 (0.75–1.46)	0.806
Composite of death from vascular causes, MI, stroke, recurrent ischemia, TIA, or other arterial thrombotic events	166 (9.1)	173 (9.4)	0.96 (0.78–1.19)	0.213
MI	15 (0.8)	11 (0.6)	1.36 (0.63–2.96)	0.435
Death from vascular causes	28 (1.5)	46 (2.5)	0.61 (0.38–0.97)	0.035
Stroke	14 (0.4)	14 (0.4)	0.99 (0.47–2.08)	0.987
Death from any cause	44 (2.4)	52 (2.8)	0.84 (0.56–1.26)	0.405

CI, confidence interval; TIA, transient ischemic attack.

or stroke) and the secondary efficacy endpoint (composite of death from any cause, MI, or stroke), 0.3% in the ticagrelor group *vs.* 0.4% in the clopidogrel group ($p = 0.404$) and 0.3% in the ticagrelor group *vs.* 0.5% in the clopidogrel group ($p = 0.440$), respectively (Table 2).

The 1-month incidence of primary efficacy endpoint was 0.6% in the ticagrelor group and 1.4% in the clopidogrel group (HR, 0.44; 95% CI: 0.22–0.89, $p = 0.019$; Fig. 1 and Table 2). The 1-month incidence of secondary efficacy endpoint was not significantly different between the two treatment arms but a propensity that more events occurred in the clopidogrel group relative to the ticagrelor group was observed (1.5% in clopidogrel group and 0.9% in ticagrelor group, $p = 0.069$; Table 2). Similarly, there was also a trend that more vascular death events occurred in the clopidogrel group compared to the ticagrelor group ($p = 0.056$; Table 2).

The PSM analysis revealed that at 6-month time point and 12-month point, the incidence of primary and secondary endpoints in the clopidogrel group was not significantly different from the ticagrelor group with an exception that patients taking clopidogrel had a 1.9% 1-month and a 2.5% 6-month incidence of vascular death compared with 1.1% and 1.5% in those taking ticagrelor ($p = 0.042$ and $p = 0.035$, respectively; Table 2).

The incidence of primary and secondary endpoints without PSM in the 4465 patients was consistent with the analysis after PSM (Supplementary Table 1).

Based on the BARC bleeding scale criteria, bleeding events were classed into BARC type 2 bleeding and major bleeding, which was defined as BARC type 3 to 5 bleeding.

For major bleeding endpoints before PSM, the incidence at 6-month and 12-month endpoints tended to be numerically higher in the ticagrelor group without PSM ($p = 0.093$ and $p = 0.084$, respectively; Supplementary Table 2) but it is not statistical significant and the differences were further attenuated after PSM ($p = 0.192$ and $p = 0.136$, respectively; Table 3 and Fig. 2).

With regard to BARC type 2 bleeding events, the risk of bleeding was significantly higher in the ticagrelor group through the time points without PSM ($p = 0.020$ for 7-day, $p = 0.007$ for 1-month, $p = 0.003$ for 6-month and $p < 0.001$ for 12-month; Supplementary Table 2). After PSM, the significance of 1-month, 6-month and 12-month time points remained ($p = 0.036$, $p = 0.003$ and $p < 0.001$, respectively; Table 3 and Fig. 2) while the risk of BARC type 2 bleeding only showed a numerically difference between the treatment arms, but there is no statistical significance.

In addition, we did subgroup analysis based on types of ACS in the matched individuals after PSM and the whole population was divided into two subgroups, the subgroups of UA patients and AMI patients.

The subgroup of UA patients consisted of 1129 individuals prescribed with clopidogrel and 1072 with ticagrelor while the subgroup of AMI patients comprised 704 patients taking clopidogrel and 761 taking ticagrelor. The subgroup analysis revealed that the 1-month incidence of primary endpoint in patients prescribed with clopidogrel from the AMI subgroup was significantly higher compared to those with ticagrelor, 2.7% and 1.2%, respectively ($p = 0.035$; Supplementary Fig .2). Patients taking clopidogrel and those taking ticagrelor from the AMI group had a similar 12-month incidence of primary endpoint ($p = 0.411$; Supplementary Fig .2). In the UA subgroup, the two treatment groups had similar low 1-month and 12-month incidences of primary efficacy endpoint. ($p = 0.180$ and $p = 0.775$, respectively; Supplementary Fig .2).

Except for treatment with $P2Y_{12}$ receptor antagonists, the risk of primary endpoint events among groups regarding baseline characteristics was compared and we found that there was a significantly higher

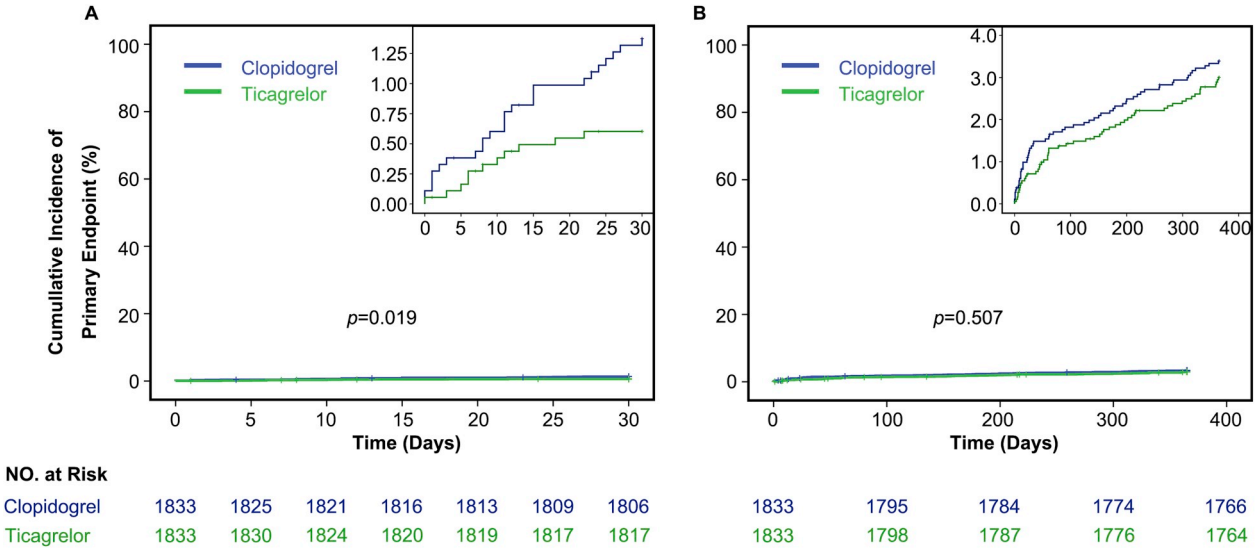

Fig. 1. Time-to-event curves for primary efficacy endpoint after PSM.
Compared to the ticagrelor group, the risk of primary efficacy endpoint at 1-month time point was significantly higher in the clopidogrel treatment group in acute coronary artery syndrome population (A) while at the 12-month time point (B) it was similar between the two treatment arms. Insets represent the time-to-event curves at different scales.

risk in patients with Killip class III or IV, and patients with chronic renal disease (p = 4.90E-12 and p = 1.13E-6; Supplementary Table 3). Patients were divided into three groups based on age, and those older than 65 years had the highest risk compared to the other two groups (p = 1.16E-6; Supplementary Table 3). As for types of ACS, acute ST-elevation MI patients were at the highest risk, followed by non–ST-elevation MI patients (p = 5.98E-6; Supplementary Table 3).

4. Discussion

This single-center large study directly compared the outcomes between ticagrelor and clopidogrel in Chinese ACS patients undergoing PCI. In contrast to previous studies conducted in the predominantly Caucasian cohorts, our results demonstrated that treatment with ticagrelor only confers significant efficacy benefits (composite of vascular death, MI and stroke) over clopidogrel at 1-month follow-up, specifically in AMI patients. We also reported that treatment with ticagrelor was accompanied by significantly more frequent BARC type 2 bleeding events relative to clopidogrel when assessed by BARC bleeding criteria, the Standardized Bleeding Definitions for Cardiovascular Clinical Trials.

Previous studies have shown lower prevalence of primary and secondary thrombotic endpoints but more bleeding in Chinese ACS patients undergoing PCI compared to Caucasians for both drugs, which was likely to stem from genetic differences between populations, now known as the East Asian “paradox” [9,17,18] which are supported by the index data.

There are few important considerations to be yielded from the current dataset analyses. First, the sample size of the interim COSTIC trial cohort is sufficient to conduct such analyses and detect trends or/and significant differences.

Second, there was a consistent trend towards numerically less vascular endpoints after ticagrelor, although only the difference reached significance for primary efficacy outcome at 1-month time point. It will be important to see if the trend will exist after the full COSTIC dataset is analyzed. Interestingly, further analysis of secondary efficacy endpoints also revealed a consistent mortality reduction after ticagrelor in COSTIC similar to PLATO at 6-month and 12-month endpoint. The condition might be explained by the stronger and faster platelet inhibition of ticagrelor compared to clopidogrel in healthy and stable coronary artery disease patients [5,19,20]. In the ONSET/OFFSET Study by Steen et al. [5], ticagrelor achieved more rapid and potential platelet inhibition than clopidogrel before 2 weeks, while at day 28, platelet inhibition caused by clopidogrel and ticagrelor achieved a steady state. Similarly, Long et al. [21] evaluated the pharmacodynamics responses to

Table 3
BARC bleeding at 7-day, 1-month, 6-month and 12-month time points after PSM.

	Ticagrelor group (n = 1833)	Clopidogrel group (n = 1833)	Hazard ratio for ticagrelor group (95% CI)	p value
7 days				
Major bleeding[a], n (%)	5 (0.3)	2 (0.1)	2.50 (0.49–12.92)	0.256
Bleeding BARC type 2, n (%)	23 (1.3)	13 (0.7)	1.78 (0.90–3.52)	0.094
1 month				
Major bleeding[a], n (%)	7 (0.4)	5 (0.3)	1.40 (0.44–4.42)	0.563
Bleeding BARC type 2, n (%)	26 (1.4)	13 (0.7)	2.01 (1.03–3.93)	0.036
6 months				
Major bleeding[a], n (%)	23 (1.3)	15 (0.8)	1.54 (0.80–2.96)	0.192
Bleeding BARC type 2, n (%)	44 (2.4)	20 (1.1)	2.23 (1.31–3.80)	0.003
12 months				
Major bleeding[a], n (%)	39 (2.1)	27 (1.5)	1.45 (0.89–2.39)	0.136
Bleeding BARC type 2, n (%)	61 (3.3)	28 (1.5)	2.22 (1.41–3.49)	< 0.001

BARC, Bleeding Academic Research Consortium.
[a] Major bleeding was defined as BARC type 3, 4 and 5 bleeding.

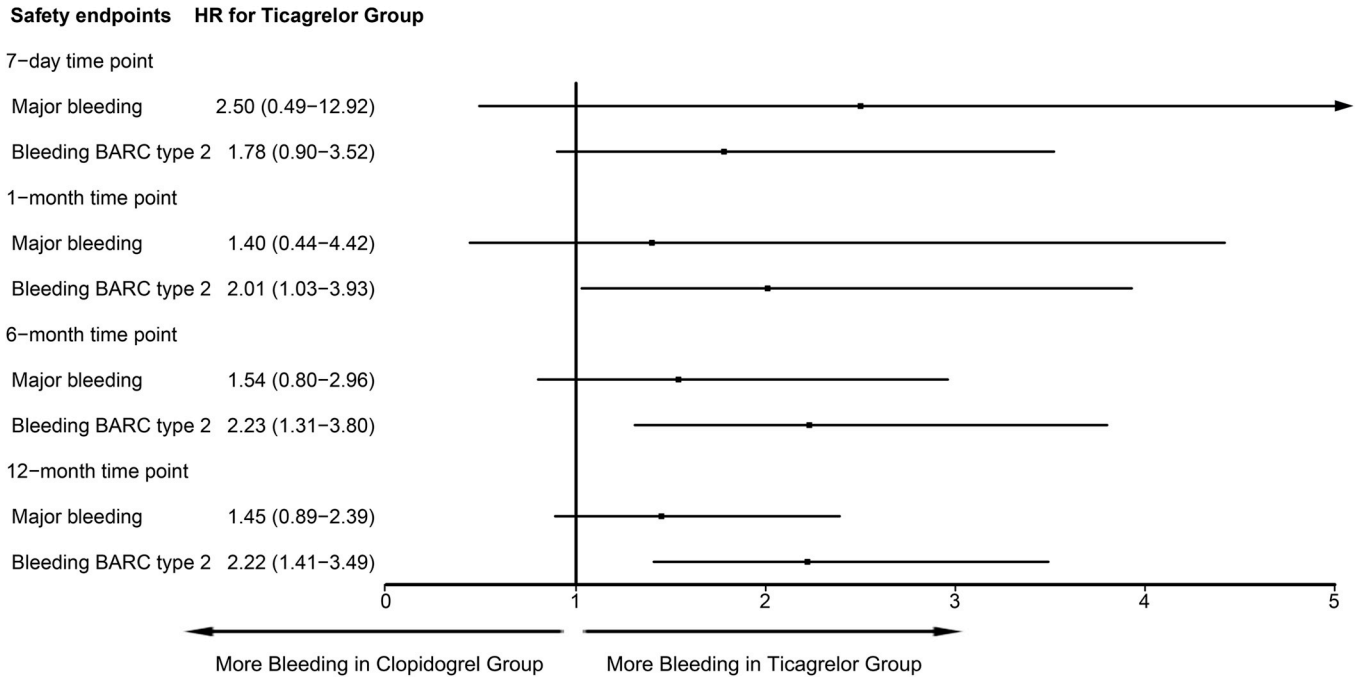

Fig. 2. Comparison of bleeding risk in patients treated with ticagrelor *vs.* clopidogrel after PSM.
There is a propensity for more major bleeding events in the ticagrelor group than in the clopidogrel group through the follow-up time points, but the difference is not statistically significant. At 1-month, 6-month and 12-month time points, the risk of bleeding BARC type 2 was significantly higher in the ticagrelor group. BARC, Bleeding Academic Research Consortium; major bleeding, BARC type 3 to 5 bleeding.

ticagrelor and clopidogrel in Korean subjects and found that low loading and maintenance doses of ticagrelor are still superior to clopidogrel regarding platelet inhibition.

In addition, the subgroup analysis revealed that UA patients taking either ticagrelor or clopidogrel had a low risk of thrombotic events while AMI patients with clopidogrel were at higher risk relative to those with ticagrelor.

Moreover, patients who were older, diagnosed as Killip class III or IV, with chronic renal disease and AMI patients should be paid more attention as they are at high risk of thrombotic events.

Third, with regard to BARC type 2 bleeding risks either before or after PSM, clopidogrel was overwhelmingly safer than ticagrelor. The BARC categorization is a new objective, hierarchically graded, consensus classification for bleeding, which is proposed by several experienced groups, with end points in cardiovascular taken into consideration. The BARC bleeding definition is practical and easy to use, based on data that can be readily available on site, monitored and adjudicated. The higher risk of BARC type 2 bleeding in ticagrelor is consistent with the KAMIR-NIH study in the Korean population. Considering the impact of bleeding on clinical outcomes that bleeding increased the risk of mortality [22], ticagrelor might be used under close monitoring or lower dose.

Finally, the indication-seeking PHILO study found that differences in primary and secondary efficacy and safety outcomes in Asian patients (predominantly Japanese), albeit not significant, were superior for clopidogrel over ticagrelor at 12 months post randomization [7], while the index dataset exhibits mixed directions in preventing thrombosis (numerically favoring ticagrelor), and associated bleeding risks (significantly less for clopidogrel). In addition, the KAMIR-NIH study conducted in Asian patients also reported superior responses to clopidogrel over a 6 month time period [6]. The disparity between outcomes reported in these different studies implies that other factors may exist, which could account for these differences, an area which warrants further research and careful examination of the completed (n = 9,000) COSTIC dataset. The excess of bleeding after ticagrelor is important due to the established link towards a higher risk of major adverse cardiovascular events after PCI [23,24]. Specifically, the earlier such drug discontinuations occurs, the higher the risk of occurrence of vascular events, with the highest risk within the first 7 days after the start of antiplatelet therapy disruption [24]. Therefore, the issue of increased BARC type 2 bleeding caused by ticagrelor is of great concern to cardiologists because this potentially has a detrimental effect on the patients' well-being.

4.1. Strengths and limitations

Large sample size, conducting a study in a frame of a single busy cardiac catheterization laboratory with uniformed approaches, very careful follow-up, and registration in the US federal database are obvious assets. Single clinical centre environment also reduces variability of interventional techniques and enforces uniformed outcome assessments. Each outcome was clinically verified and confirmed by an adjudication committee.

There are limitations worth mentioning. Among the most important limitations are the non-randomized design that COSTIC is an observational study, and still existing background differences between the COSTIC arms, despite propensity matching techniques. It should be emphasized that there might be important confounders to our analysis potentially impacting the conclusions. Limited by cost-effectiveness in a "real world" environment, most Holter monitoring merely lasted 24 h; therefore, we did not evaluate the incidence of bradyarrhythmia in COSTIC. Moreover, as with any conventional antiplatelet trials, with very few anecdotal exceptions, definite compliance with drugs via their plasma metabolite level assessments was not done. Finally, our study was conducted exclusively in a Chinese cohort, so extrapolation of these facts to other ethnicities seems premature.

These preliminary data from prespecified analyses of the COSTIC trial indicate that in Chinese patients undergoing PCI, treatment with ticagrelor significantly reduces the risk of vascular death, MI or stroke compared with clopidogrel during 1 month, especially in AMI patients, and the risk of vascular death during delayed follow-up (6-month and 12-month endpoint). Nevertheless, treatment with ticagrelor is not superior to clopidogrel in a delayed follow-up regarding the primary efficacy outcome, and consistently increased the risk of BARC type 2 bleeding at 1-month, 6-month and 12-month time points.

Clinical trial registration

URL: https://www.clinicaltrials.gov. Unique Identifier: NCT03239067.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Financial support

This work was supported by National Key R&D Program of China (NO. 2017YFC0909400) and NSFC project (No. 91839302 and 91439203).

Author contributions

Yang Sun and Chenze Li: statistical analysis and draft of the manuscript; Lina Zhang, Ting Yu and Heng Ye: follow –up data acquisition and critical review of the manuscript throughout the editorial process; Bo Yu and Min Tao: data acquisition, data interpretation and critical review of the manuscript throughout the editorial process; Jiangang Jiang, Jiangtao Yan and Hesong Zeng: study concept and design, critical review of the manuscript throughout the editorial process, and approval of the final manuscript draft submitted for publication. Xiaoqing Shen and Dao Wen Wang: study concept and design, data acquisition, data interpretation, critical review of the manuscript throughout the editorial process, and approval of the final manuscript draft submitted for publication.

Acknowledgments

We thank Amit Bhat (Indegene Pvt. Ltd., Bangalore) for providing medical writing and editorial support for the development of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.09.011.

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