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RESEARCH PAPER

In-hospital outcomes of ticagrelor versus clopidogrel in patients 75 years or older with acute coronary syndrome: findings from the Improving Care for Cardiovascular Disease in China (CCC)–Acute Coronary Syndrome Project

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Abstract

Background: The evidence for the comparative effectiveness and safety of ticagrelor versus clopidogrel in older patients with acute coronary syndrome (ACS) is limited, especially in the acute phase of ACS. This study aimed to compare the in-hospital outcomes of ticagrelor versus clopidogrel in older patients with ACS.
Methods: Hospitalised ACS patients aged ≥75 years who were recruited to the Improving Care for Cardiovascular Disease in China-ACS project between November 2014 and December 2019 and received aspirin and $P2Y_{12}$ receptor inhibitors within 24 h after first medical contact were included. The primary outcomes were in-hospital major adverse cardiovascular events (MACE) and major bleeding. Multivariable Cox regression was performed to evaluate the comparative effectiveness and safety of ticagrelor and clopidogrel. Inverse probability of treatment weighting (IPTW) and propensity score matching analyses were performed to evaluate the robustness of the results.
Results: Of 18,244 ACS patients, 18.5% received ticagrelor. Multivariable-adjusted analysis revealed comparable risks of in-hospital MACE between patients receiving ticagrelor and clopidogrel (hazard ratio [HR] 1.12, 95% confidence interval [CI] 0.92–1.35). However, ticagrelor use was associated with 45% higher risk of in-hospital major bleeding compared with clopidogrel use (HR 1.45, 95% CI 1.09–1.91). Similar results were found in the IPTW analysis.
Conclusions: ACS patients aged ≥75 years receiving ticagrelor during the acute phase had similar risk of in-hospital MACE, but higher risk of in-hospital major bleeding compared with those receiving clopidogrel. More evidence is needed to guide the use of $P2Y_{12}$ receptor inhibitors during hospitalisation in older patients with ACS.
Clinical Trial Registration: URL: http://www.clinicaltrials.gov. Unique identifier: NCT02306616.

Keywords: acute coronary syndrome, older people, antiplatelet therapy, in-hospital major adverse cardiovascular events, in-hospital bleeding

Key points

- Evidence for the comparative effectiveness and safety of ticagrelor versus clopidogrel in older acute coronary syndrome (ACS) patients is limited.
- acute coronary syndrome (ACS) patients aged ≥75 years receiving ticagrelor had similar risk of in-hospital major adverse cardiovascular events (MACE) compared with those receiving clopidogrel.
- Older acute coronary syndrome (ACS) patients receiving ticagrelor had higher risk of in-hospital major bleeding compared with those receiving clopidogrel.
- More evidence is needed to guide the use of P2Y12 receptor inhibitors during hospitalization in acute coronary syndrome (ACS) patients aged ≥75 years.

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor is strongly recommended in the guidelines for patients with acute coronary syndrome (ACS) during the acute phase [1–6]. Compared with clopidogrel, ticagrelor provides faster, greater and more consistent platelet inhibition effects [7]. Findings from the Platelet Inhibition and Patient Outcomes (PLATO) study demonstrated that ticagrelor significantly reduced the risk of death from vascular causes, myocardial infarction or stroke without an increase in major bleeding during 12 months of follow-up in patients with ACS compared with clopidogrel [8]. Thus, the latest guidelines including the guideline for ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation ACS (NSTE-ACS) from the

European Society of Cardiology (ESC), the guideline for NSTE-ACS from the American College of Cardiology/American Heart Association (AHA) and the guideline for STEMI from the Chinese Society of Cardiology (CSC) consistently recommend ticagrelor over clopidogrel, irrespective of age [2, 4–6].

Patients aged ≥75 years account for a substantial proportion of those hospitalised for ACS, and the number and percentage of older ACS patients will continue to increase because of population ageing [9]. Compared with younger patients, older patients have higher risks of both ischemic and bleeding events [10, 11]. The benefit-risk scenario related to antiplatelet drugs may differ between older and younger patients with ACS. In 2016, a randomised controlled trial (RCT) carried out in 200 patients aged ≥65 years found that ticagrelor significantly reduced the risk of ischemic events without increasing the risk of major bleeding. However, another small RCT found that clopidogrel was non-inferior to ticagrelor for a combined endpoint of ischemic and bleeding events, but significantly reduced the risk of bleeding among NSTE-ACS patients aged ≥70 years [12, 13]. Subgroup analyses from RCTs and observational studies have also provided conflicting results [14–17], thus provoking some uncertainties for the selection of $P2Y_{12}$ receptor inhibitors in older patients. Furthermore, all of these studies focused on the 1-year outcomes after discharge. The evidence for the comparative effectiveness and safety of ticagrelor and clopidogrel during the acute phase of ACS among older patients is limited. Therefore, in this study, we compared the in-hospital outcomes of ticagrelor versus clopidogrel in contemporary real-world ACS patients aged ≥75 years.

Methods

Data source

The Improving Care for Cardiovascular Disease in China (CCC)-ACS project is a nationwide registry of the AHA and CSC. Details regarding the project design have been published [18]. Briefly, the project was initiated in November 2014. In total, 159 tertiary hospitals and 82 secondary hospitals were recruited across mainland China. Each month, the first 20–30 eligible patients at tertiary hospitals and 10–20 eligible patients at secondary hospitals with a principal discharge diagnosis of ACS were consecutively recruited. A web-based data collection platform was used to collect data with standardised definitions. Multiple strategies including regular on-site quality audits and real-time validation checks were used to ensure the completeness and quality of the data. This study complied with the Declaration of Helsinki.

Study population

From November 2014 to December 2019, 19,242 hospitalised ACS patients aged ≥75 years who received DAPT within 24 h of first medical contact were recruited to the CCC-ACS project. We excluded patients who received warfarin within 2 weeks before admission ($N = 174$) and patients who switched between ticagrelor and clopidogrel during hospitalisation ($N = 824$). Finally, 18,244 patients were included. Patients were divided into the ticagrelor and clopidogrel groups according to the $P2Y_{12}$ receptor inhibitor they received. After a one-time loading dose (if administered), patients received maintenance doses during hospitalisation. The flow chart of the selection of the study population is presented in Supplementary Figure 1.

Definitions of in-hospital outcomes

In-hospital major adverse cardiovascular events (MACEs) were defined as the composite outcome of cardiac death, re-infarction, and stroke during hospitalisation. Major bleeding was defined as any one of the following bleeding events: (i) fatal bleeding, (ii) intracranial bleeding, (iii) retroperitoneal bleeding, (iv) any bleeding resulting in a decline in haemoglobin level of ≥5 g/dL, (v) bleeding requiring surgical intervention or (vi) transfusion with overt bleeding [19, 20]. Any clinically relevant bleeding was defined as all documented bleeding events including intracranial bleeding, retroperitoneal bleeding, gastrointestinal bleeding, skin or mucosa bleeding, access-site bleeding and bleeding at other sites, or a decline in haemoglobin level of ≥3 g/dL. Other outcomes included ischemic MACE (defined as the composite outcome of cardiac death, re-infarction and ischemic stroke), re-infarction, stroke and death during hospitalisation.

Definitions of other variables

The transfer status of the patients indicated whether they were transferred to the hospital from other facilities. Current smokers were defined as patients who smoked within the preceding year. Hypertension was defined as a history of hypertension, the receipt of antihypertensive therapy or presence of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on admission. Diabetes mellitus was defined as a history of diabetes mellitus, the receipt of oral hypoglycaemic drug or insulin therapy or presence of fasting blood glucose ≥7.0 mmol/L (126 mg/dL) or haemoglobin A1c ≥6.5%. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease Study equation [21]. A loading dose of aspirin was defined as a dose ≥150 mg. A loading dose of a $P2Y_{12}$ receptor inhibitor was defined as a clopidogrel dose ≥300 mg or a ticagrelor dose ≥180 mg. The percutaneous coronary intervention (PCI) status during the current hospitalisation was classified as no PCI performed, timely PCI and other PCI. Timely PCI was defined for patients with STEMI and NSTE-ACS according to the current guideline recommendations [5, 6]. For patients with STEMI, timely PCI was defined as primary PCI within 90 min of first medical contact. For patients with NSTE-ACS, timely PCI was defined based on their risk stratification. The risk

Table 1. Characteristics of patients according to the receipt of different $P2Y_{12}$ receptor inhibitors

	Original population			IPTW			Propensity score 1:1 matching		
Characteristics	Clopidogrel (*N* = 14,678)	Ticagrelor (*N* = 3,566)	ASD,%	Clopidogrel (*N* = 14,694)	Ticagrelor (*N* = 3,563)	ASD,%	Clopidogrel (*N* = 3,274)	Ticagrelor (*N* = 3,274)	ASD, %
Age, years	80.4 ± 4.2	79.9 ± 4.0	12.4	80.3 ± 4.1	80.3 ± 4.2	0.4	80.0 ± 3.9	80.0 ± 4.0	0.9
Female	6,289 (42.9)	1,406 (39.4)	6.9	6,215 (42.3)	1,518 (42.6)	0.6	1,265 (38.6)	1,299 (39.7)	2.1
STEMI	7,450 (50.8)	2,507 (70.3)	40.8	8,022 (54.6)	1,955 (54.9)	0.5	2,274 (69.5)	2,301 (70.3)	1.8
Transferred	5,209 (35.5)	1,122 (31.5)	8.6	9,536 (35.1)	2,205 (38.1)	6.3	2,228 (31.9)	2,230 (31.9)	0.1
Heart rate (bpm/min)	78.8 ± 18.2	78.7 ± 18.1	0.6	78.8 ± 18.2	79.3 ± 18.2	2.5	79.0 ± 18.5	78.7 ± 18.2	1.6
Systolic blood pressure	133.4 ± 24.9	130.6 ± 25.8	11.2	133.0 ± 25.1	131.7 ± 25.5	5.1	131.6 ± 25.4	130.9 ± 26.0	3.0
Cardiovascular risk factors									
Current smokers	2,985 (20.3)	782 (21.9)	3.9	2,993 (20.4)	738 (20.7)	0.9	724 (22.1)	726 (22.2)	0.1
Hypertension	11,105 (75.7)	2,637 (74.0)	3.9	11,075 (75.4)	2,697 (75.7)	0.7	2,460 (75.1)	2,416 (73.8)	3.1
Diabetes mellitus	7,077 (48.2)	1,732 (48.6)	0.7	7,089 (48.2)	1,735 (48.7)	0.9	1,596 (48.8)	1,578 (48.2)	1.1
Medical history									
Myocardial infarction	1,684 (11.5)	267 (7.5)	13.6	1,565 (10.7)	349 (9.8)	2.8	233 (7.1)	218 (6.7)	1.8
Previous PCI	1,472 (10.0)	256 (7.2)	10.2	1,403 (9.6)	353 (9.9)	1.3	223 (6.8)	208 (6.4)	1.9
Heart failure	777 (5.3)	88 (2.5)	14.6	695 (4.7)	159 (4.5)	1.3	80 (2.4)	76 (2.3)	0.8
Peripheral vascular disease	251 (1.7)	37 (1.0)	5.8	230 (1.6)	53 (1.5)	0.7	35 (1.1)	35 (1.1)	<0.1
COPD	627 (4.3)	103 (2.9)	7.4	589 (4.0)	127 (3.6)	2.4	81 (2.5)	100 (3.1)	3.5
Chronic kidney disease	517 (3.5)	74 (2.1)	8.7	475 (3.2)	130 (3.7)	2.3	76 (2.3)	65 (2.0)	2.3
Ischemic stroke	1,896 (12.9)	362 (10.2)	8.7	1,814 (12.4)	385 (10.8)	4.9	339 (10.4)	338 (10.3)	0.1
Haemorrhagic stroke	132 (0.9)	16 (0.5)	5.5	119 (0.8)	33 (0.9)	1.2	13 (0.4)	15 (0.5)	0.9
Medication before admission									
Aspirin	3,842 (26.2)	575 (16.1)	24.8	3,565 (24.3)	844 (23.7)	1.4	428 (13.1)	406 (12.4)	2.0
Clopidogrel	2,608 (17.8)	127 (3.6)	47.3	2,207 (15.0)	504 (14.1)	2.5	120 (3.7)	126 (3.9)	1.0
Ticagrelor	45 (0.3)	240 (6.7)	35.4	259 (1.8)	56 (1.6)	1.6	42 (1.3)	35 (1.1)	2.0
β blocker	1,592 (10.9)	246 (6.9)	13.9	1,442 (9.8)	348 (9.8)	0.2	195 (6.0)	174 (5.3)	2.8
Statin	3,046 (20.8)	421 (11.8)	24.4	2,757 (18.8)	656 (18.4)	0.9	304 (9.3)	278 (8.5)	2.8
Severe conditions at admission									
Heart failure	1,843 (12.6)	350 (9.8)	8.7	1,811 (12.3)	500 (14.0)	5.0	355 (10.8)	333 (10.2)	2.2
Cardiac arrest	192 (1.3)	68 (1.9)	4.8	208 (1.4)	49 (1.4)	0.3	60 (1.8)	61 (1.9)	0.2
Cardiac shock	448 (3.1)	176 (4.9)	9.7	527 (3.6)	126 (3.6)	0.2	164 (5.0)	160 (4.9)	0.6
Laboratory tests									
eGFR, mL/min per 1.73 m^2*	64.6 (46.0–83.2)	67.4 (48.6–86.4)	11.5	64.9 (46.5–83.4)	63.8 (44.0–83.3)	4.0	66.3 (48.5–85.6)	67.2 (48.3–86.4)	2.4
LDL-C, mmol/L	2.6 ± 0.9	2.7 ± 1.0	8.5	2.6 ± 0.9	2.6 ± 1.0	1.6	2.7 ± 0.9	2.7 ± 1.0	0.4
Haemoglobin, g/L	125.5 ± 20.0	127.9 ± 19.9	11.7	126.0 ± 19.9	125.3 ± 20.5	3.3	127.7 ± 19.9	127.8 ± 19.9	0.5
In-hospital medication									
ACEI/ARB	7,150 (48.7)	1,544 (43.3)	10.9	7,017 (47.8)	1,692 (47.5)	0.5	1,468 (44.8)	1,438 (43.9)	1.8
β blocker	7,649 (52.1)	1,753 (49.2)	5.9	7,579 (51.6)	1,894 (53.2)	3.2	1,662 (50.8)	1,604 (49.0)	3.5
Statin	13,983 (95.3)	3,392 (95.1)	0.7	13,996 (95.3)	3,405 (95.6)	1.4	3,113 (95.1)	3,114 (95.1)	0.1
Glycoprotein IIb/IIIa inhibitors	2,482 (16.9)	926 (26.0)	22.2	2,788 (19.0)	680 (19.1)	0.3	864 (26.4)	842 (25.7)	1.5
Anticoagulant therapy			14.5			7.0			6.2
None	4,304 (29.3)	1,010 (28.3)		4,220 (28.7)	940 (26.4)		849 (25.9)	903 (27.6)	
Unfractionated heparin	263 (1.8)	137 (3.8)		312 (2.1)	75 (2.1)		124 (3.8)	95 (2.9)	
Low-molecular-weight heparin	9,579 (65.3)	2,320 (65.1)		9,660 (65.7)	2,451 (68.8)		2,219 (67.8)	2,185 (66.7)	
Fondaparinux sodium	398 (2.7)	59 (1.7)		366 (2.5)	71 (2.0)		49 (1.5)	56 (1.7)	
others	134 (0.9)	40 (1.1)		135 (0.9)	26 (0.7)		33 (1.0)	35 (1.1)	
Loading doses of aspirin	5,601 (38.2)	2,302 (64.6)	54.7	6,343 (43.2)	1,623 (45.6)	4.8	2,104 (64.3)	2,146 (65.6)	2.7
Loading doses of $P2Y_{12}$ receptor inhibitors	5,719 (39.0)	2,680 (75.2)	78.6	6,775 (46.1)	1,680 (47.2)	2.1	2,438 (74.5)	2,475 (75.6)	2.6
PCI status			39.9			3.4			2.1
No PCI performed	6,711 (45.7)	996 (27.9)		6,183 (42.1)	1,493 (41.9)		906 (27.7)	923 (28.2)	
Timely PCI	2,251 (15.3)	910 (25.5)		2,554 (17.4)	615 (17.3)		831 (25.4)	834 (25.5)	
Other PCI	4,824 (32.9)	1,352 (37.9)		4,979 (33.9)	1,243 (34.9)		1,262 (38.6)	1,259 (38.5)	
PCI performed with detailed information unavailable	892 (6.1)	308 (8.6)		977 (6.7)	211 (5.9)		275 (8.4)	258 (7.9)	
CABG	67 (0.5)	12 (0.3)	1.9	67 (0.5)	9 (0.3)	3.2	17 (0.5)	10 (0.3)	3.3

Abbreviations: IPTW, inverse probability of treatment weighting; ASD, absolute standardised difference; STEMI, ST-segment elevation myocardial infarction; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft. [a]Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease Study equation.

stratification criteria proposed by the 2020 ESC guideline for patients with NSTE-ACS were used to classify patients as 'very high risk,' 'high risk' or 'low risk' according to their clinical profile. The detailed criteria are presented in the Supplementary Material. Timely PCI for patients with NSTE-ACS was defined as PCI within 2 h for patients at very high risk, PCI within 24 h for patients at high risk and PCI at any time for patients at low risk [6].

Statistical analysis

The patients' characteristics in different groups were presented as the mean ± standard deviation or median (interquartile range) for continuous variables and number (percentage) for categorical variables, and compared using absolute standardised differences.

The Kaplan–Meier method was used to estimate the cumulative event rates, and log-rank test was performed to test the differences between groups. Multivariable Cox proportional hazards models were performed to evaluate the comparative effectiveness and safety of ticagrelor and clopidogrel, with hazard ratio (HR) and 95% confidence interval (CI) reported. Variables adjusted in the models included ACS type, age, sex, transfer status, heart rate, eGFR, baseline haemoglobin, low-density lipoprotein cholesterol, hypertension, diabetes mellitus, history of myocardial infarction, heart failure, haemorrhagic stroke, ischemic stroke, chronic kidney disease, peripheral vascular disease, and chronic obstructive pulmonary disease, previous PCI, preadmission use of aspirin, clopidogrel, ticagrelor, β-blockers, and statins, acute heart failure at admission, cardiac shock at admission, cardiac arrest at admission, in-hospital medications including angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, β-blockers, statins, glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, and anticoagulants, PCI status during the current hospitalisation, loading status of aspirin; and loading status of $P2Y_{12}$ receptor inhibitors. The majority of the patients (84%) were hospitalised for ≤15 days, with small number of patients at each day after 15 days; therefore, the Kaplan–Meier analysis and Cox regression analysis were performed based on a 15-day observation.

To evaluate the robustness of the results from Cox regression analysis, inverse probability of treatment weighting (IPTW) and propensity score matching analyses were also performed [22]. For every patient, the propensity score, reflecting the probability of receiving ticagrelor conditional on the covariates, was estimated using logistic regression models. The variables included in the models are presented in the Supplementary Materials. For the IPTW analysis, stabilised weights based on the propensity scores were computed for the patients. The computation methods are presented in the Supplementary Materials. For the propensity score matching analysis, the patients in the ticagrelor and clopidogrel groups were 1:1 matched in a random order based on the propensity scores using the nearest-neighbour approach with a calliper of 0.02 and without replacement.

Table 2. Event number and rate of in-hospital outcomes

In-hospital outcomes	Original population			IPTW analysis			Propensity 1:1 matching analysis		
	Clopidogrel (*N* = 14,678)	Ticagrelor (*N* = 3,566)	*P*	Clopidogrel (*N* = 14,694)	Ticagrelor (*N* = 3,563)	*P*	Clopidogrel (*N* = 3,274)	Ticagrelor (*N* = 3,274)	*P*
MACE	671 (4.6)	182 (5.1)	0.177	701 (4.8)	162 (4.5)	0.552	160 (4.9)	163 (5.0)	0.864
Ischemic MACE	611 (4.2)	161 (4.5)	0.349	642 (4.4)	143 (4.0)	0.357	147 (4.5)	147 (4.5)	1.000
Re-infarction	83 (0.6)	18 (0.5)	0.661	100 (0.7)	16 (0.5)	0.110	15 (0.5)	15 (0.5)	1.000
Stroke	133 (0.9)	33 (0.9)	0.913	131 (0.9)	39 (1.1)	0.277	27 (0.8)	27 (0.8)	1.000
Any clinically relevant bleeding events	956 (6.5)	291 (8.2)	0.001	978 (6.6)	264 (7.4)	0.108	227 (6.9)	259 (7.9)	0.131
Major bleeding	285 (1.9)	94 (2.6)	0.009	282 (1.9)	91 (2.6)	0.017	58 (1.8)	80 (2.4)	0.058
Non-CABG-related major bleeding	281 (1.9)	93 (2.6)	0.009	278 (1.9)	89 (2.5)	0.022	56 (1.7)	79 (2.4)	0.046
All-cause death	544 (3.7)	155 (4.4)	0.074	581 (4.0)	142 (4.0)	0.958	139 (4.3)	144 (4.4)	0.761
Cardiac death	497 (3.4)	144 (4.0)	0.058	533 (3.6)	133 (3.7)	0.783	126 (3.9)	133 (4.1)	0.657

Abbreviations: IPTW, inverse probability of treatment weighting; MACE, major adverse cardiovascular events; CABG, coronary artery bypass graft.

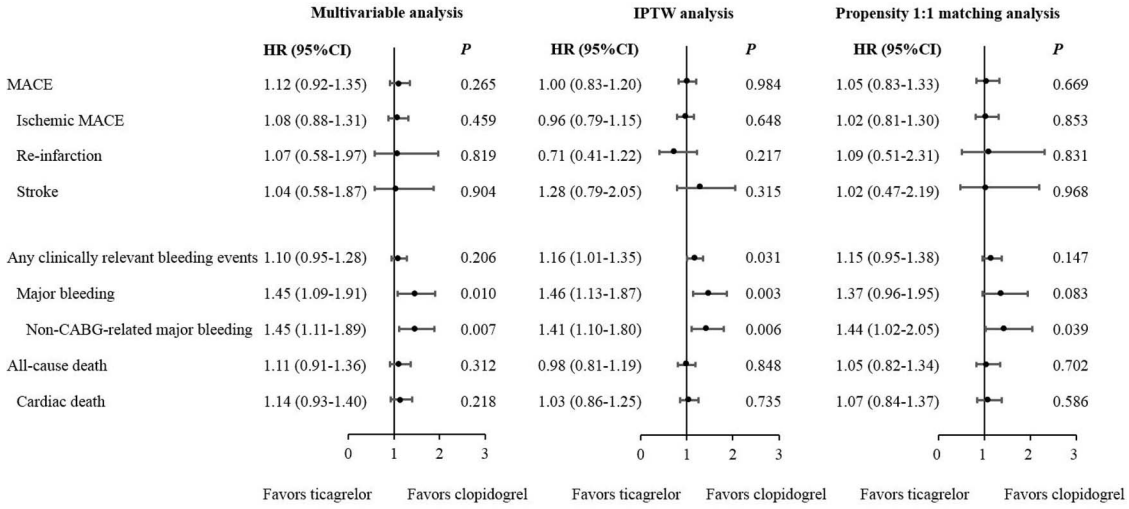


Figure 1. The associations between ticagrelor use and in-hospital outcomes as compared with clopidogrel use Abbreviations: IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiovascular events; CABG, coronary artery bypass graft.

Variables with missing values were imputed using a sequential regression multiple imputation method by IVEware software version 0.2 (Survey Research Center, University of Michigan, Ann Arbor, MI, USA) and are summarised in Supplementary Table 1. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). A two-tailed P value of < 0.05 was considered statistically significant.

Results

Patients' characteristics

Of 18,244 patients included in the study, 18.5% ($n = 3,566$) received ticagrelor and 81.5% ($n = 14,678$) received clopidogrel. An upward trend in the use of ticagrelor was observed from 2014 to 2019 (Supplementary Figure 2). About 75.2% of the patients on ticagrelor received loading doses, versus 39.0% of those on clopidogrel. Compared with patients receiving clopidogrel, those receiving ticagrelor were younger, had fewer comorbidities and more likely to be STEMI, and receive GPIIb/IIIa inhibitors, loading doses of aspirin and timely PCI during hospitalisation (Table 1). Among patients receiving PCI, 98.4% in the ticagrelor group and 96.6% in the clopidogrel group received drug-eluting stents, respectively (Supplementary Table 2). The proportion of patients receiving proton pump inhibitors was 65.2% in the clopidogrel group and 71.0% in the ticagrelor group (Supplementary Table 3).

Comparison of in-hospital MACE between the ticagrelor and clopidogrel groups

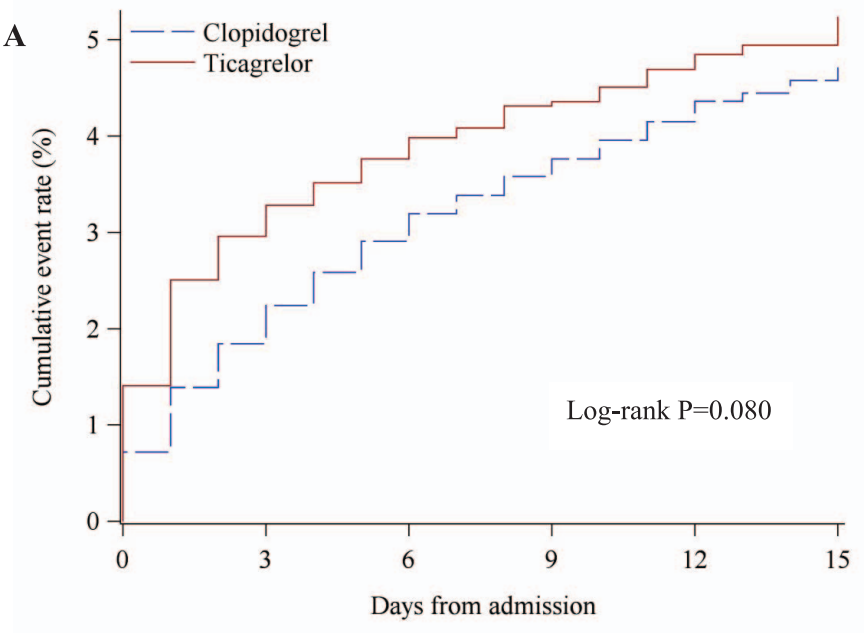
The incidence of MACE during hospitalisation was 5.1% (182 events) in the ticagrelor group and 4.6% (671 events) in the clopidogrel group (Table 2). Multivariable Cox regression analysis revealed no significant association between ticagrelor use and in-hospital MACE compared with clopidogrel use (HR = 1.12, 95% CI = 0.92–1.35, $P = 0.265$) (Figure 1).

After IPTW or propensity score matching, all of the patients' characteristics were balanced between the ticagrelor and clopidogrel groups (Table 1). There were no significant differences in the incidence of in-hospital MACE between the ticagrelor and clopidogrel groups (IPTW analysis: 4.5 vs. 4.8%, $P = 0.552$; HR = 1.00, 95% CI = 0.83–1.20; propensity score matching analysis: 5.0 vs. 4.9%, $P = 0.864$; HR = 1.05, 95% CI = 0.83–1.33) (Table 2, Figure 1). The Kaplan–Meier analysis also showed no significant differences in the cumulative 15-day event rates of MACE between the two groups in the pseudo-population after IPTW or the propensity score-matched population (Figure 2).

Comparison of bleeding outcomes between the ticagrelor and clopidogrel groups

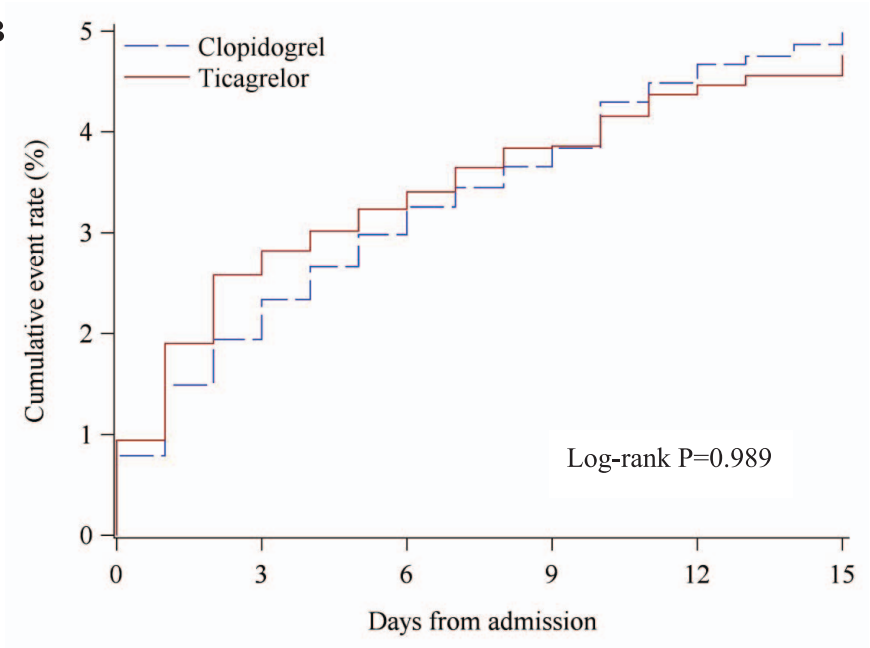
The incidence of major bleeding during hospitalisation was 2.6% (94 events) in the ticagrelor group and 1.9% (285 events) in the clopidogrel group (Table 2). After multivariable adjustment, ticagrelor use was associated with 45% higher risk of major bleeding (HR = 1.45, 95% CI = 1.09–1.91, $P = 0.010$) compared with clopidogrel use (Figure 1).

In the pseudo-population after IPTW, in-hospital major bleeding occurred significantly more often in the ticagrelor group than in the clopidogrel group (2.6 vs. 1.9%, $P = 0.017$; HR = 1.46, 95% CI = 1.13–1.87) (Table 2, Figure 1). A significantly higher cumulative 15-day event rate of major bleeding in the ticagrelor group compared with the clopidogrel group was also observed in the Kaplan–Meier curves in the pseudo-population after IPTW. In the propensity score-matched population with limited sample size, the incidence of in-hospital major bleeding remained higher in the



Number at risk:

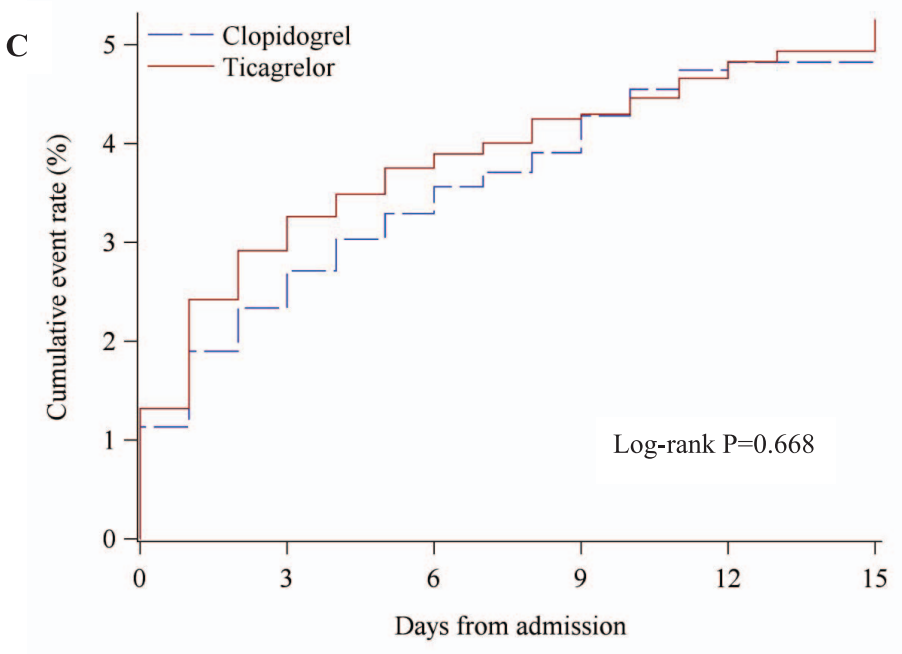
Clopidogrel	14625	14041	12632	9157	5412	2928
Ticagrelor	3553	3346	3022	2207	1239	649



Number at risk:

Clopidogrel	14644	14044	12661	9197	5390	2887
Ticagrelor	3554	3371	3014	2187	1262	728

Figure 2. Cumulative Kaplan–Meier estimates of the MACEs during the 15-day in-hospital period in (A) the whole study population, (B) pseudo-population after IPTW and (C) propensity score-matched population.



Number at risk:

Clopidogrel	3264	3116	2852	2072	1189	638
Ticagrelor	3265	3079	2782	2045	1140	595

Figure 2. Continued.

ticagrelor group, but without statistical significance (2.4 vs. 1.8%, $P = 0.058$; HR = 1.37, 95% CI = 0.96–1.95) (Table 2, Figure 1). The Kaplan–Meier curves also showed a non-significant higher cumulative event rate of in-hospital major bleeding in the ticagrelor group compared with the clopidogrel group (Figure 3).

Comparison of in-hospital mortality between the ticagrelor and clopidogrel groups

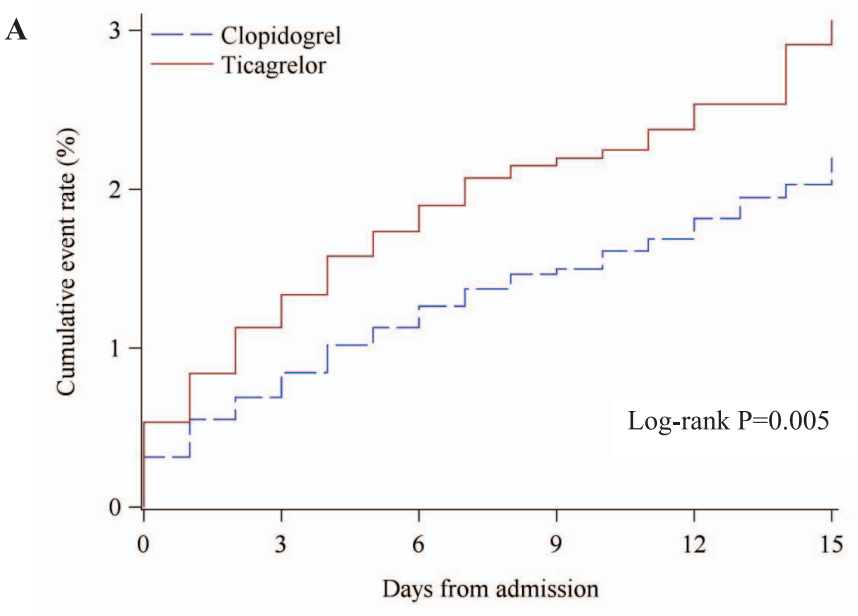
The in-hospital all-cause mortality was 4.4% (155 events) in the ticagrelor group and 3.7% (544 events) in the clopidogrel group (Table 2). No significant association was observed between ticagrelor use and all-cause death (HR = 1.11, 95% CI = 0.91–1.36, $P = 0.312$) in the multivariable-adjusted analysis (Figure 1).

In the IPTW or propensity score matching analysis, there were no significant differences in all-cause mortality between the ticagrelor and clopidogrel groups (IPTW analysis: 4.0 vs. 4.0%, $P = 0.958$; HR = 0.98, 95% CI = 0.81–1.19; propensity score matching analysis: 4.4 vs. 4.3%, $P = 0.761$; HR = 1.05, 95% CI = 0.82–1.34) (Table 2, Figure 1).

Discussion

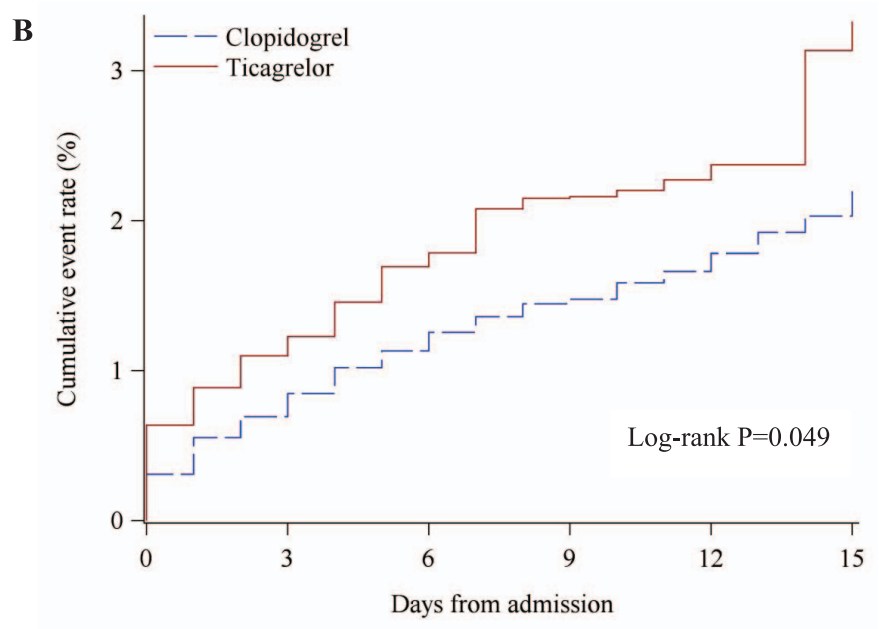
Based on data from contemporary real-world patients with ACS, we found that patients aged ≥75 years with ACS receiving ticagrelor during the acute phase had similar risk of in-hospital MACE consisting of cardiac death, re-infarction and stroke, but higher risk of in-hospital major bleeding compared with those receiving clopidogrel.

A few studies comparing the 1-year outcomes of ticagrelor versus clopidogrel in older ACS patients have reported similar results to those in our study. The POPular AGE study revealed that clopidogrel reduced the risk of PLATO major or minor bleeding by 29% without increasing the composite outcome of all-cause death, myocardial infarction, stroke and bleeding during 12 months of follow-up [12]. Another RCT carried out in Korean patients with ACS found that ticagrelor significantly increased the risk of clinically significant bleeding by 126%, with no interaction between patients younger or older than 65 years [23]. Similarly, the SWEDEHEART registry found that among patients aged ≥80 years with myocardial infarction, ticagrelor and clopidogrel had comparable ability to prevent the ischemic outcome of death, readmission for myocardial infarction and stroke. However, ticagrelor was associated with 17% and 48% higher risks of death and bleeding, respectively, at 1 year after discharge [16]. Other studies have showed inconsistent results. A small RCT found that ticagrelor significantly reduced the composite outcome of cardiovascular death, myocardial infarction and stroke without an increased risk of bleeding at the 1-year follow-up among ACS patients aged ≥65 years [13]. Similarly, subgroup analysis from the PLATO trial revealed



Number at risk:

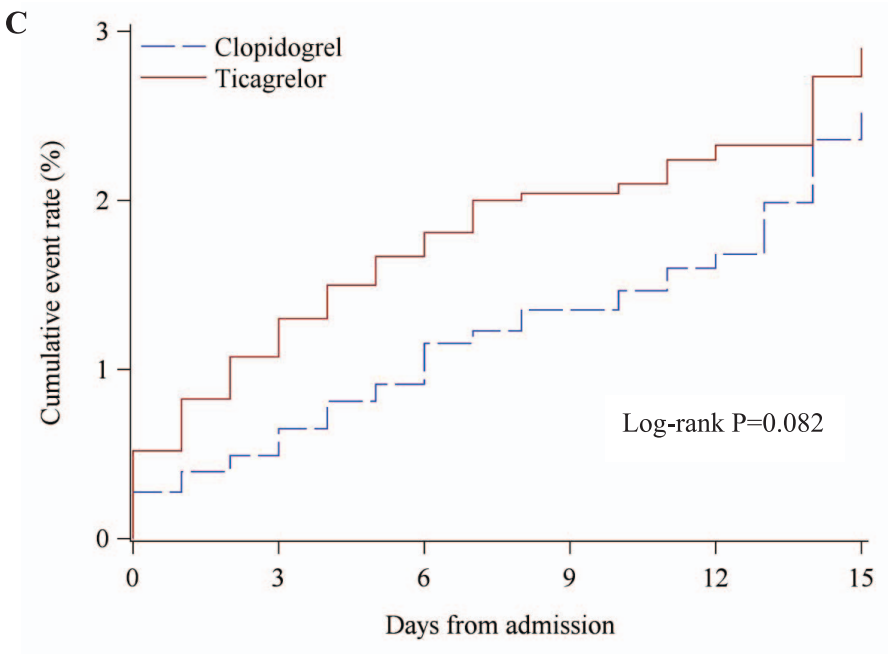
Clopidogrel	14657	14097	12637	9142	5397	2907
Ticagrelor	3562	3350	3007	2185	1218	633



Number at risk:

Clopidogrel	14673	14096	12659	9179	5374	2864
Ticagrelor	3561	3377	2993	2162	1246	714

Figure 3. Cumulative Kaplan–Meier estimates of major bleeding during the 15-day in-hospital period in (A) the whole study population, (B) pseudo-population after IPTW and (C) propensity score-matched population.



Number at risk:

Clopidogrel	3272	3132	2855	2066	1188	626
Ticagrelor	3271	3080	2767	2025	1121	579

Figure 3. Continued.

a consistent benefit of ticagrelor over clopidogrel in reducing the risk of thrombotic outcomes in patients older or younger than 75 years [24]. Two observational studies among older ACS patients treated with PCI also found that ticagrelor was associated with a lower risk of composite ischemic outcomes or mortality without a significant increase in the risk of bleeding within 1 year [15, 17]. The inconsistencies in these findings may arise from several aspects. First, the studies were carried out in different populations, and interethnic differences in the thrombogenicity and pharmacodynamic profiles of $P2Y_{12}$ receptor inhibitors are known to exist. Second, unlike the patients included in the PLATO trial and Bermen registry, among whom bare-metal stent implantation was widely performed, almost all patients underwent PCI in our study and in the POPular AGE study received drug-eluting stents. Compared with bare-metal stents, drug-eluting stents were demonstrated to significantly reduce the risk of subsequent thrombotic events [25], which may reduce the need for potent antiplatelet therapies. Third, different age cutoffs were adopted in different studies to define older patients. The baseline risks of ischemic and bleeding events associated with age-related conditions may differ among studies.

Older age is associated with a series of physiological changes that can affect the pharmacokinetics of antiplatelet drugs. Adverse drug–drug interactions are more pronounced in older patients because of comorbidities and receipt of multiple medications [26]. All of these changes may result in increased risks of adverse events, including bleeding, in older patients. Previous studies demonstrated that age was an independent predictor of intracranial haemorrhage in patients receiving thrombolytic or anticoagulant therapy [27, 28]. In patients treated with antiplatelet drugs, the risk of major bleeding increased steeply with age, with the 10-year risk of major bleeding being 2.1-fold higher in patients aged ≥75 years than in younger patients, and disabling or fatal bleeding being more frequent in older patients [29]. Ischemic and bleeding events should both be considered seriously when choosing the optimal antiplatelet therapy for patients, because they are associated with an increased risk of all-cause mortality [30, 31]. In patients with ACS receiving DAPT, the impact of bleeding on death was gradually heightened as the severity of bleeding events increased. The risk of death associated with recurrent myocardial infarction was higher than that of mild-to-moderate bleeding and similar to that of severe, non-intracranial bleeding, whereas the risk of death following BARC 3c bleeding was 3.5-fold higher than that following myocardial infarction [31]. Thus, the increased risk of in-hospital major bleeding associated with ticagrelor use in our study represents a significant risk for patients because it may be associated with long-term mortality.

Our study should be interpreted within the context of its limitations. First, although we used multivariable Cox regression models, IPTW analysis and propensity score matching analysis to adjust for confounders related to demographics, medical history and treatment before and during the current hospitalisation, residual confounding may exist because of the observational study design. Second, all patients in our study were Chinese, and generalisation to non-East Asian patients may require further research.

The growing number of ACS patients aged ≥75 years in clinical practice poses great demands for high-quality evidence to guide the selection of $P2Y_{12}$ receptor inhibitors in these patients. However, findings from RCTs that mainly enrolled younger patients may not be applicable to older patients. Our study was by far the largest study to compare the in-hospital outcomes of ACS patients aged ≥75 years receiving ticagrelor versus clopidogrel. Our findings provide important preliminary evidence on the benefit-risk scenario in patients aged ≥75 years with ACS receiving ticagrelor compared with clopidogrel, which is inconsistent with evidence from RCTs that included few ACS patients aged ≥75 years and the relevant guideline recommendations [2, 4–6]. These findings require further validation by other large pragmatic studies, because it may not be feasible to conduct RCTs in ACS patients aged ≥75 years.

Conclusions

Patients aged ≥75 years with ACS receiving ticagrelor during the acute phase had similar risk of in-hospital MACE consisting of cardiac death, re-infarction and stroke, but higher risk of in-hospital major bleeding compared with those receiving clopidogrel. More evidence is needed to guide the use of $P2Y_{12}$ receptor inhibitors during hospitalisation in older patients with ACS.

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Declaration of Conflicts of Interest: Dr Fonarow reports consulting for Abbott, Amgen, AstraZeneca, Bayer, Cytokinetics, Janssen, Medtronic, Merck, and Novartis. The other authors have no conflicts of interest to declare.

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