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Efficacy and safety of ticagrelor versus clopidogrel with different dosages in acute coronary syndrome patients with high GRACE and CRUSADE scores

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ABSTRACT

Objective: To investigate the efficacy and safety of ticagrelor and different dosages of clopidogrel after acute coronary syndrome.
Methods: We compared different antiplatelet strategies for the prevention of cardiovascular events in 1939 patients admitted to the hospital with an acute coronary syndrome undergoing percutaneous coronary intervention (PCI).
Results: At 24 months, a survival analysis showed that ticagrelor and double-dose clopidogrel decreased the incidence of MACCE (a composite of all-cause death, myocardial infarction (MI), target vessel revascularization and stroke) ($p < 0.001$, $p = 0.012$, respectively). Although double-dose clopidogrel obviously increased the risk of major bleeding ($p < 0.001$), a similar result was not observed in the ticagrelor group ($p = 0.398$). These two stronger antiplatelet strategies also decreased the incidence of myocardial infarction ($p = 0.004$ and 0.045, respectively). The advantages of ticagrelor are also evident in the endpoints of all cause death and target vessel revascularization. The NACCE (a composite of all-cause death, MI, stroke and major bleeding) rate was also reduced in the ticagrelor group ($p = 0.004$).
Conclusions: In PCI patients with a high ischemic and bleeding risk, the ticagrelor antiplatelet strategy significantly reduced the MACCE rate without increasing the risk of major bleeding. A decreased MACCE rate was also observed in patients administered the double dosage of clopidogrel, but the bleeding risk was increased compared with the control group.

1. Introduction

In patients with acute coronary syndrome (ACS), dual antiplatelet therapy (DAPT) has been the cornerstone strategy.[1,2] However, several studies have shown that a clopidogrel loading dose >300 mg resulted in high platelet inhibition, a faster onset of action, and fewer poor responders in both clopidogrel-naïve and clopidogrel-treated patients.[3–5] The efficacy of clopidogrel is variable due to different transformations of the prodrug to its active metabolite that occur in patients; the approved 75 mg clopidogrel maintenance dose achieves a modest antiplatelet effect, but a poor response to clopidogrel remains a concern, the prevalence of which has been reported in up to 44% of patients.[6,7] Studies have shown an improvement in platelet inhibition and a reduction in response variability with 150 mg compared to 75 mg clopidogrel.[6,8,9] Although clinical outcome data with high-dose clopidogrel are limited, the use of 150 mg clopidogrel daily as the maintenance dose is increasing.

Ticagrelor, a reversible and direct-acting oral antagonist of the adenosine diphosphate receptor P2Y12, provides faster and more consistent platelet inhibition than clopidogrel. In the PLATO trial,[10] which involved 18,624 ACS patients, ticagrelor and clopidogrel were compared for the prevention of cardiovascular events, and the results showed that ticagrelor significantly reduced the number of composite ischemic endpoint events, cardiac death and myocardial infarction without an increased rate of major bleeding.

Most patients with ACS have comorbidities and risk factors that greatly increase their risk of ischemic or bleeding events; therefore, assessing the patient's overall benefit–risk profile is vital when considering their long-term antithrombotic treatment strategy. Several risk scores have been developed based on various

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parameters.[11–13] From the ischemic risk perspective, a more effective antiplatelet agent, such as ticagrelor and prasugrel, could reduce the number of major adverse cardiac and cerebrovascular events (MACCE) among patients with high ischemic risk.[14–16] Additionally, these new antiplatelet agents may increase the rate of achieving safe endpoints for those with a high bleeding risk.[17] However, during the process of identifying real high-risk patients, physicians are often caught in the dilemma that patients with high ischemic risk typically have a high bleeding risk. The reason for this situation may be that risk factors involved in the ischemic model are also factors involved in the bleeding model. For patients with high ischemic and bleeding risk, it is challenging to determine the optimal antiplatelet therapy.

In this retrospective study, we compared ticagrelor (90 mg twice daily) and clopidogrel (75 or150 mg daily) for the prevention of cardiovascular events and safety in high ischemic and bleeding risk patients who presented with ACS and underwent a percutaneous coronary intervention (PCI).

2. Material and methods

2.1. Study design and patients

Patients diagnosed with ACS that underwent a PCI in our hospital were continuously included. The study disposition and screening process are shown in Fig. 1. In brief, a total of 8809 post-PCI patients from March 2013 to January 2016 were included into the risk model to calculate their risk scores (Fig. 1). 1939 patients with high ischemic and bleeding risk were included into three groups according to their antiplatelet strategy: standard antiplatelet therapy (patients received clopidogrel with a loading dose of 300 mg followed by 75 mg daily with aspirin 100 mg daily for 12 month, followed with clopidogrel 75 mg daily), double-dose clopidogrel (patients received clopidogrel with a loading dose of 300 mg followed by 75 mg daily with aspirin 100 mg daily for 12 month, followed with clopidogrel 150 mg daily, the Double group) and ticagrelor therapy (patients received ticagrelor with a loading dose of 180 mg followed by 90 mg twice daily with aspirin 100 mg daily for 12 month, followed with ticagrelor 90 mg twice daily, the Ticagrelor group). The exclusion criteria also included any history of surgical procedures within the past year, hematological disorders, concomitant therapy with a strong cytochrome P-450 3A4 inhibitor or inducer, antiplatelet strategy change and pregnancy. The study was approved by the institutional ethics committee, and all participants provided written informed consent. All authors vouch for the accuracy and completeness of the data and analyses.

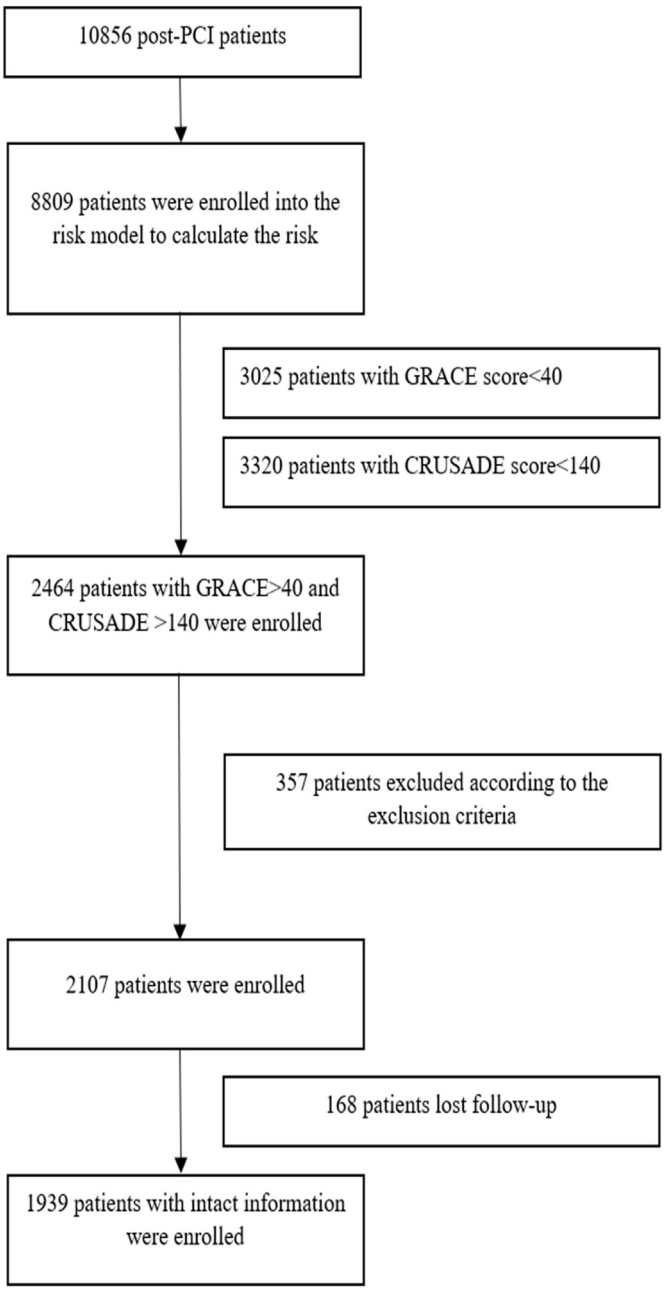

Fig. 1. Flow Diagram of our study. Of all 10,856 patients, 2047 patients were excluded with incomplete information, 3025 patients with GRACE score<40 and 3320 patients with CRUSADE score <140. Among 2464 patients with GRACE>40 and CRUSADE>140, 357 patients were excluded according to the excluded criteria. 168 patients lost during the follow-up period. And 1939 patients were finally enrolled into the result analysis.

2.2. Endpoints

The primary efficacy endpoint was MACCE (supplementary material). Another endpoint was a composite of net adverse clinical and cerebral events (NACCE: a composite of all-cause death, MI, stroke and major bleeding).[18] Other efficacy endpoints include stent thrombosis.

The safety end point was bleeding complications that were classified according to the Thrombolysis In Myocardial Infarction (TIMI) criteria[19,20] (supplementary material). The health status of all patients was assessed using the Seattle Angina Questionnaire (SAQ) (supplementary material).

2.3. Data collection and follow-up

We recorded patients' baseline clinical characteristics and risk factors, including smoking, hypertension, diabetes, prior myocardial infarction and previous incidence of stroke or transient ischemic attack. Follow-up information was collected, according to a clinically designed questionnaire, every three months for two years after discharge. Additionally, medication adherence and the presence of MACCE were investigated. The SAQ was also completed by our patients, and detailed information was collected.

2.4. Statistical analysis

All continuous variables are presented as the mean ± SD, and analysis of variance was used to compare means across multiple groups. Noncontinuous and categorical variables are presented as frequencies or percentages and were compared using the Chi-

square test. The time-dependent analysis was used for the comparison of the primary endpoint. The absolute differences on MACCE between groups and the corresponding 95% confidence intervals were reported. The Kaplan–Meier curve method was used to calculate time to clinical endpoints, and the log-rank test was used to compare the survival curves. The Cox proportional hazards model was further applied to estimate the potential factors involved in the interaction analysis. Statistical interactions between the clinical factors and antiplatelet strategies were tested by multiple regression models. Otherwise specified, a 2-sided P value < 0.05 was considered to indicate statistical significance. Statistical analysis was performed using STATA software V.12.0 version and R version 3.4.

3. Results

We continuously recruited 1939 patients diagnosed with acute coronary syndrome undergoing PCI from March 2013 to January 2016. All patients met the criteria of a GRACE score >140 and a CRUSADE score >40. Among the 1939 patients with intact follow-up information, 684 were assigned to the standard group, 532 to the double group, and 723 to the ticagrelor group. The baseline and procedural characteristics are shown in table 1.

3.1. Clinical outcomes

Clinical outcomes at 12 months is shown in Supplementary Material Table 1. Compared with the standard group, the risk of MACCE at 12 months was not different in the ticagrelor group and double group (ticagrelor group: HR: 0.846, 95% CI: 0.586–1.222; double group: HR: 1.161, 95% CI: 0.805–1.674, p = 0.256). Ticagrelor and double-dose clopidogrel significantly decreased the risk of cardiovascular death compared with standard clopidogrel after 12-month follow up (ticagrelor group: HR: 0.523, 95% CI: 0.321–0.853; double group: HR: 0.560, 95% CI: 0.331–0.949, p = 0.013).

Table 1
Baseline characteristics of the study sample.

Characteristics	Clopidogrel 75 mg daily (n = 684)	Clopidogrel 150 mg daily (n = 532)	Ticagrelor 90 mg twice daily (n = 723)	P value
Age(yr)	68.7(8.44)	70.5(7.70)	69.7(7.56)	<0.001
Age≥75yr-no/total no. (%)	166(24.3)	139(26.1)	197(27.2)	0.439
Male sex-no/total no. (%)	338(49.4)	249(46.8)	316(43.7)	0.099
BMI, kg/m^2	25.26 ± 2.59	25.13 ± 1.51	24.80 ± 2.34	<0.001
Cardiovascular risk factors				
Hypertension (%)	424(62.0)	328(61.7)	475(65.7)	0.233
Diabetes mellitus (%)	353(51.6)	306(57.5)	383(53.0)	0.107
Insulin requiring (%)	138(20.1)	117(21.9)	159(21.9)	0.647
Dyslipidemia (%)	424(61.9)	345(64.8)	498(68.8)	0.024
Smoker (%)	362(52.9)	303(57.0)	398(55.0)	0.370
Previous MI (%)	163(23.8)	117(22.0)	169(23.4)	0.741
Previous vascular disease (%)	217(31.7)	156(29.3)	209(28.9)	0.473
Clinical presentation				
Heart rate (beat/min)	81.39 ± 15.02	80.57 ± 15.56	80.27 ± 15.79	0.379
Systolic blood pressure (mmHg)	121.6 ± 17.30	120.3 ± 17.56	119.5 ± 17.62	0.094
Diastolic blood pressure (mmHg)	70.21 ± 28.7	68.78 ± 9.36	68.08 ± 9.16	0.094
Laboratory vales				
Hct	0.342 ± 0.05	0.346 ± 0.056	0.342 ± 0.049	0.282
Hemoglobulin (g/l)	143.86 ± 25.59	138.20 ± 21.98	137.75 ± 27.04	<0.001
PLT (× 10^9/l)	196.49 ± 46.77	195.68 ± 46.79	191.53 ± 41.73	0.090
eGFR (ml/min)	104.7 ± 29.11	102.09 ± 31.23	105.13 ± 30.63	0.177
GRACE scores	166.34 ± 16.9	168.22 ± 16.25	167.3 ± 16.46	0.121
CRUSADE scores	44.25 ± 3.93	44.41 ± 3.75	44.05 ± 3.91	0.266
Medical history				
ACEI/ARB (%)	558(81.6)	430(80.8)	562(77.7)	0.165
β-blockers (%)	630(92.1)	478(89.8)	643(88.9)	0.122
Lipid-lowering agent (%)	616(90.1)	473(88.9)	657(90.9)	0.518
Tirofiban (%)	436(63.7)	376(70.7)	479(66.3)	0.038
LMWH (%)	598(87.4)	482(90.5)	672(92.9)	0.002
Killip classification (%)				0.016
I	431(63.0)	316(59.4)	447(61.8)	
II	159(23.2)	157(29.5)	160(22.1)	
III	66(9.6)	40(7.5)	89(12.3)	
IV	28(4.1)	19(3.6)	27(3.7)	
PCI indication				0.018
STEMI (%)	408(59.6)	329(61.8)	479(66.3)	
Non-STEMI (%)	189(27.6)	120(22.6)	151(20.9)	
Unstable Angina (%)	87(12.7)	83(15.6)	93(12.9)	
Total No. of stents	1.66(0.64)	1.72(0.68)	1.80(0.71)	<0.001
Total stented length, mm				
TVD (%)	180(26.3)	190(35.7)	228(31.5)	0.002
Target vessel				
LAD	293(42.8)	233(43.7)	311(43.0)	0.940
LCX	224(32.7)	161(30.2)	187(25.8)	0.016
RCA	253(36.9)	178(33.4)	274(37.8)	0.248
Bypass graft	14(2.0)	21(2.9)	16(3.0)	0.492
LM involved	96(14.0)	102(19.2)	132(18.3)	0.033
Radial artery access	637(93.1)	483(92.4)	672(92.9)	0.247

BMI: Body Mass Index, MI: Myocardial Infarction, Hct: hematocrit, PLT: platelet, eGFR: estimated glomerular filtration rate, ACEI: Angiotensin-Converting Enzyme Inhibitors, ARB: angiotensin receptor blocker, LMWH: low molecular weight heparin , PCI: Percutaneous coronary intervention, STEMI:ST-Segment elevation myocardial infarction, TVD: triple vessel disease; LM: left main artery, LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery.

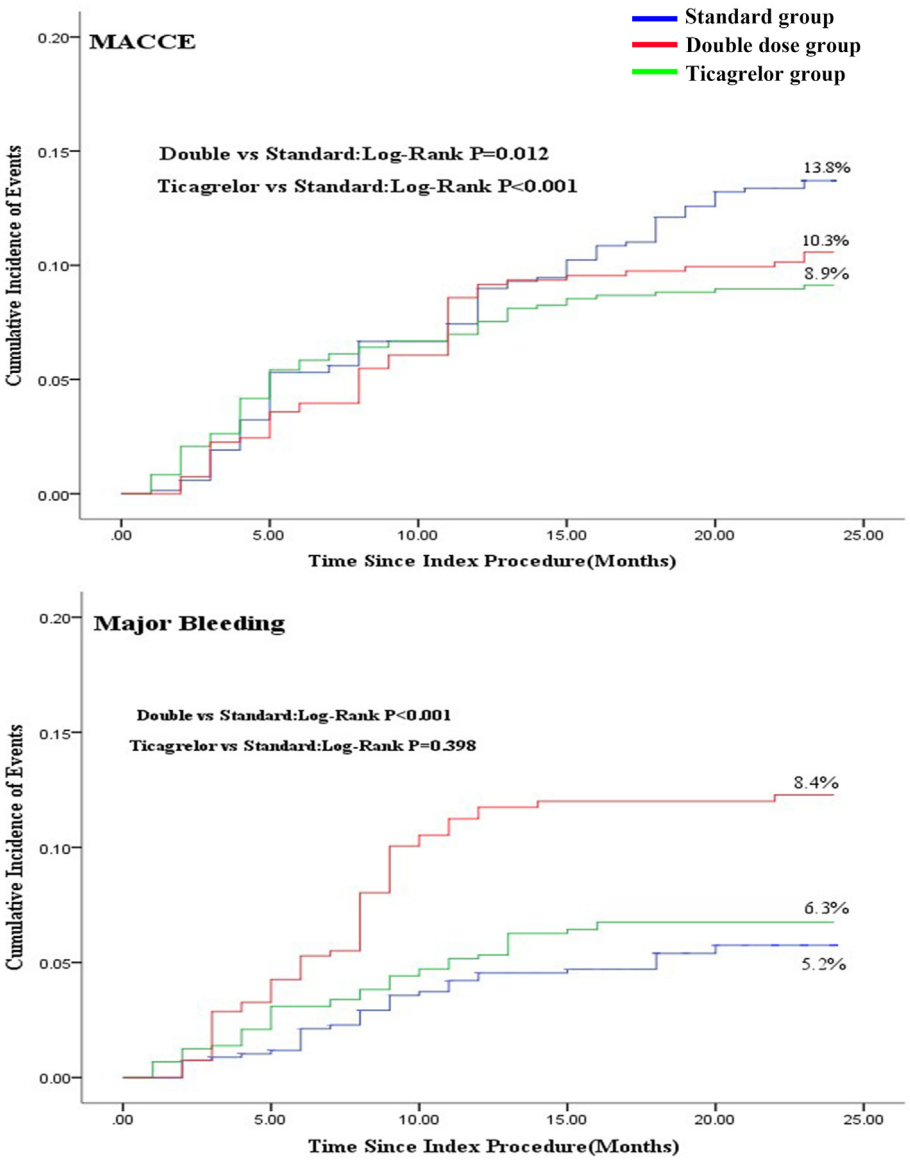

Fig. 2. Cumulative Kaplan–Meier Estimates of the Occurrence of Primary Endpoints (MACCE) and Major Bleeding Endpoint. MACCE = major adverse cardiac and cerebrovascular events.

The risk of all-cause death, myocardial infarction (MI), target vessel revascularization (TVR), stent thrombosis and stroke did not differ significantly among the three groups. Double-dose clopidogrel could significantly increase the risk of major bleeding (HR:2.183, 95% CI:1.436–3.319, p < 0.001), but this increased risk was not observed in the ticagrelor group. A difference in the risk of NACCE was not detected in the three groups. Ticagrelor and double-dose clopidogrel increased the risk of minor bleeding after 12-month follow up (ticagrelor: HR:2.401, 95% CI: 1.704–3.384, double: HR: 1.848, 95% CI:1.316–2.595, p < 0.001).

The risk of MACCE of ticagrelor group was lower than that in the standard group (hazard ratio [HR]: 0.716, 95% CI: 0.514–0.999) (Supplementary Table 2), demonstrating the superiority of the ticagrelor strategy compared with standard DAPT in the decrease of MACCE risk. Regarding the double group, the MACCE rate was lower than that of the standard group (HR: 0.637, 95% CI: 0.464–0.873). Fig. 2 shows the cumulative Kaplan–Meier estimates of MACCE and TIMI-defined major bleeding. The risk of all-cause death (double vs standard: HR: 0.837, 95%CI: 0.585–1.197, ticagrelor vs standard: HR:0.571, 95%CI: 0.396–0.824), cardiovascular death (double vs standard: HR: 0.515,95%CI: 0.317–0.837, ticagrelor vs standard: HR: 0.482, 95%CI: 0.308–0.755) and MI (double vs standard: HR: 0.651,95%CI: 0.425–0.997, ticagrelor vs standard: HR: 0.556, 95%CI: 0.370–0.835) showed significant differences among the three groups at the 24-month follow-up (Supplementary Table 2). A significantly decreased risk of NACCE was detected in the ticagrelor group (HR: 0.646, 95% CI: 0.488–0.856) compared to that of the standard group, but not in the double group compared with that of the standard group (HR: 1.136, 95% CI: 0.874–1.476) (Supplementary Table 2). The risk of target vessel revascularization (double vs standard: HR: 0.815, 95% CI: 0.485–1.367, ticagrelor vs standard: HR:0.613, 95%CI: 0.368–1.022), stent thrombosis (double vs standard: HR: 0.897, 95% CI: 0.512–1.571, ticagrelor vs standard: HR:0.607, 95%CI: 0.305–1.208) and stroke (double vs standard: HR: 1.021,95%CI: 0.539–1.935, ticagrelor vs standard: HR: 0.888, 95%CI: 0.481–1.639) did not differ significantly among the three groups (Fig. 3, Supplementary Table 2).

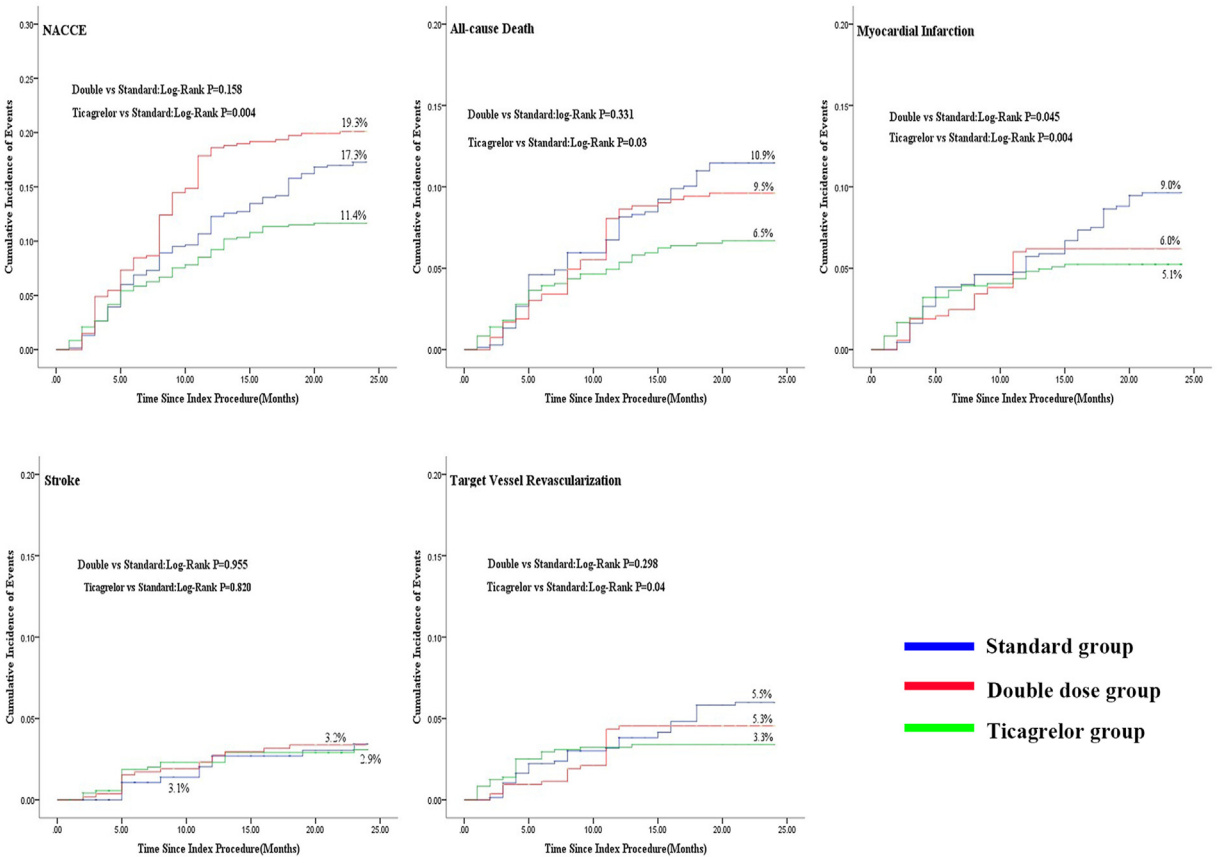

Fig. 3. Cumulative Kaplan–Meier Estimates of the Occurrence of Adverse Events. Cumulative event curves through 24 months of NACCE (A), all-cause death (B), myocardial infarction (C), stroke (D), and target vessel revascularization (E). NACCE = net adverse clinical and cerebral events.

3.2. Bleeding

The risk of TIMI-defined major bleeding was similar between the standard group and the ticagrelor group (HR: 1.205, 95% CI: 0.779, 1.864) (Supplementary Table 2) but not between the standard group and the double group (HR: 2.292, 95% CI: 1.512, 3.475). The risk of TIMI-defined minor bleeding increased in both the double group and ticagrelor group compared with the standard group (HR: 2.272, 95% CI: 1.681–3.069; HR: 1.514, 95% CI: 1.123–2.040, respectively).

3.3. Subgroup analysis of endpoints

In the following analysis, we analyzed the relationship of different clinical factors to different antiplatelet strategies and the impact on efficacy and safety endpoints. Regarding the efficacy endpoints, we first identified the potential clinical factors associated with MACCE using a Cox multivariate analysis, and the related factors are shown in table 2. Four factors, including renal function, history of MI, triple vessel artery disease and the usage of tirofiban, were associated with MACCE. The stratified analyses revealed that participants with an eGFR<90 ml/min/1.73 m^2 exhibited a lower ischemic rate in the ticagrelor group compared with in the standard group (HR: 0.616, 95% CI: 0.387–0.981, p = 0.049). In addition, patients with a previous MI could benefit from stronger antiplatelet treatments (ticagrelor group: HR: 0.635, 95% CI: 0.424–0.95; double group: HR: 0.590, 95% CI: 0.373–0.935, p = 0.027). Similar results were also observed in patients with triple vessel artery disease (p < 0.001) and the usage of tirofiban (p < 0.001). For the safety endpoints (table 3), three factors were identified to be related to bleeding events. Among these factors, participants aged >70 years accounted for a higher bleeding rate in the double group compared with in the standard group (HR: 2.264, 95% CI: 1.553–3.30, p < 0.001). Additionally, patients receiving the GPIIb/IIIa agent tirofiban exhibited an increased bleeding risk in the double group (HR: 2.633, 95% CI: 1.901–3.646, p < 0.001). In both the ticagrelor and double group, patients receiving LMWH typically exhibited an increased risk of bleeding compared with those in the standard group (ticagrelor group: HR: 1.353, 95% CI: 1.020–1.794; double group: HR: 2.397, 95% CI: 1.818–3.159, p < 0.001).

3.4. SAQ

With respect to the quality of life according to the SAQ in the treatment subgroups, as presented in Supplementary Table 3 and Figure 4, there was abundant evidence of significant differences among the three groups throughout the whole follow-up process (p < 0.001). Regarding other domains of health status, we did not observe any difference among the three groups in the first 6 months, but as the length of follow-up increased, a difference was gradually observed.

4. Discussion

This study demonstrated that, compared to standard DAPT and double-dose clopidogrel, the use of ticagrelor in patients with high ischemic and bleeding risk can significantly reduce the rate of MACCE, a composite of all-cause death, myocardial infarction,

Table 2
Association between antiplatelet strategies and ischemic risk according to baseline characteristics.

subgroup	T	S	D	Hazard Ratio(95%CI) T vs S	Hazard Ratio(95%CI) D vs S	P	P for interaction
Age							0.117
>70 years old	309	245	210	0.575(0.364,0.909)	0.606(0.365,1.005)	0.032	
<70 years old	414	439	322	0.735(0.471,1.147)	0.912(0.582,1.429)	0.392	
Sex							0.375
Male	316	338	249	0.643(0.383,1.079)	1.015(0.675,1.526)	0.151	
Female	407	346	283	0.666(0.444,1.001)	0.486(0.295,0.800)	0.011	
eGFR							0.003
≥90 ml/min/1.73m^2	508	467	332	0.748(0.481,1.162)	0.861(0.533,1.391)	0.432	
<90 ml/min/1.73m^2	215	217	200	0.616(0.387,0.981)	0.620(0.388,0.993)	0.049	
BMI							0.247
≥24 kg/m^2	438	479	432	0.809(0.569,1.150)	0.634(0.435,0.924)	0.058	
<24 kg/m^2	285	205	100	0.452(0.212,0.964)	1.444(0.690,3.023)	0.017	
DM							0.858
No	340	331	226	0.583(0.358,0.949)	0.639(0.373,1.097)	0.061	
Yes	383	353	306	0.746(0.488,1.141)	0.857(0.555,1.324)	0.399	
Previous MI							<0.001
No	554	521	415	0.666(0.395,1.123)	1.043(0.632,1.720)	0.207	
Yes	169	163	117	0.635(0.424,0.950)	0.590(0.373,0.935)	0.027	
Smoking							0.899
No	325	322	229	0.785(0.444,1.389)	1.053(0.590,1.877)	0.595	
Yes	398	362	303	0.604(0.411,0.897)	0.631(0.417,0.953)	0.016	
Angiopathy							0.477
No	514	467	376	0.553(0.329,0.931)	1.407(0.902,2.194)	0.002	
Yes	209	217	156	0.826(0.551,1.238)	0.331(0.184,0.597)	0.001	
Diagnosis							0.364
STEMI	479	408	329	0.811(0.559,1.176)	0.884(0.592,1.321)	0.539	
NSTEMI	151	189	120	0.468(0.206,1.063)	0.226(0.067,0.761)	0.022	
UA	93	87	83	0.199(0.057,0.697)	0.824(0.369,1.840)	0.040	
LM involved							0.959
No	591	588	430	0.527(0.283,0.983)	1.047(0.587,1.867)	0.057	
Yes	132	96	102	0.687(0.474,0.997)	0.604(0.395,0.924)	0.032	
Triple vessel artery							<0.001
No	495	504	342	0.712(0.461,1.099)	0.890(0.565,1.402)	0.306	
Yes	228	180	190	0.566(0.354,0.907)	0.550(0.335,0.905)	0.019	
β-blocker							0.832
No	80	54	54	0.712(0.380,1.335)	0.332(0.139,0.789)	0.044	
Yes	643	630	478	0.607(0.418,0.882)	0.879(0.610,1.268)	0.030	
Tirofiban							<0.001
No	244	248	156	0.841(0.511,1.384)	1.349(0.841,2.165)	0.145	
Yes	479	436	376	0.601(0.395,0.915)	0.460(0.271,0.781)	0.005	

T: ticagrelor group; S: standard group; D: double group; STEMI: ST-Segment elevation myocardial infarction; UA: Unstable Angina; LMWH: low molecular weight heparin; eGFR: evaluated glomerular filtration rate; LM: left main artery; BMI: Body Mass Index; MI: Myocardial Infarction; DM: diabetes mellitus; STEMI:ST-Segment elevation myocardial infarction; UA: unstable angina.

target vessel revascularization and stroke. A similar benefit was also observed for the reduction in NACCE. In addition, the beneficial effects of the ticagrelor strategy were achieved without a significantly increased risk of major bleeding. Although the double-dosage clopidogrel strategy showed a trend of reduced MACCE rates, it did not achieve significant improvement in clinical outcomes. In patients receiving antiplatelet treatment, the evaluation of antiplatelet therapies has been largely focused on reducing ischemic event occurrence (efficacy). However, bleeding (safety) has also become an increased risk with the emergence of more potent antiplatelet drugs and strategies. The balance between the risk reduction in ischemic events and the increase risk of bleeding events has attracted more attention in recent years, leading to the introduction of the novel clinical composite endpoint “net adverse clinical events”. Accordingly, the present study not only focused on the efficacy of intensive antiplatelet therapy but also paid attention to safety.

For ACS patients, understanding the predictive factors for ischemia and bleeding is important in light of the multiple studies that have firmly established the strong link between complications of drugs and procedures and subsequent mortality in these patients when treated with PCI. Many risk models involve similar clinical factors, such as age, renal function, and sex. However, patients with high ischemic risk usually have a high bleeding risk, which is consistent with our data. Current post-PCI antiplatelet therapy tried to make a balance between ischemia and bleeding. For patients with high ischemic risk, many physicians would like to adjust the antiplatelet strategy to a double dose of clopidogrel added to aspirin, whereas some experts may question this approach and advise them to undergo CYP2C19 genetic testing. This information is subsequently used in the decision to switch from clopidogrel to a more potent agent. However, according to a study performed in 2016, Jacob et al did not support routine CYP2C19 genetic testing in this population.[21] Previous efforts have explored new post-PCI antiplatelet strategies, including double-dosage clopidogrel and triple antiplatelet therapy that added cilostazol or replaced clopidogrel with potent P2Y12 inhibitors (prasugrel or ticagrelor).[8,22] Although meta-analysis of these pilot studies showed that a double dosage of clopidogrel lowered the incidence of post-PCI adverse events, its effect is controversial.[23] In the GRAVITAS trial, a high dosage of clopidogrel was ineffective in reducing the 6-month composite ischemic event occurrence. In our trial, we observed no benefit from double-dosage clopidogrel with regard to the ischemic endpoints. Gilles et al compared prasugrel with high-dose clopidogrel in acute coronary syndrome. The results showed that in ACS patients, a 10 mg prasugrel maintenance dose resulted in significantly increased platelet inhibition compared with that of clopidogrel at twice its approved maintenance dose.[24] A clinical

Table 3
Association between antiplatelet strategies and bleeding risk according to baseline characteristics.

subgroup	T	S	D	Hazard Ratio(95%CI) T vs S	Hazard Ratio(95%CI) D vs S	P	P for interaction
Age							<0.001
>70 years old	309	245	210	1.275(0.862,1.886)	2.264(1.553,3.30)	<0.001	
≤70 years old	414	439	322	1.246(0.596,2.606)	2.262(1.084,4.718)	0.101	
Killip class							0.152
I	447	431	316	1.032(0.725,1.470)	2.725(1.975,3.758)	<0.001	
II	160	159	157	1.360(0.804,2.301)	1.745(1.049,2.901)	0.099	
III	89	66	40	1.644(0.779,3.473)	1.956(0.831,4.607)	0.274	
IV	27	28	19	2.551(0.941,6.913)	0.663(0.133,3.30)	0.073	
Smoking							0.221
No	325	322	229	1.316(0.889,1.947)	1.954(1.315,2.906)	0.003	
Yes	398	362	303	1.178(0.829,1.673)	2.442(1.755,3.398)	<0.001	
Angiopathy							0.142
No	514	467	376	1.306(0.935,1.825)	2.846(2.073,3.908)	<0.001	
Yes	209	217	156	1.193(0.783,1.818)	1.427(0.923,2.206)	0.278	
Diagnosis							0.298
STEMI	479	408	329	1.540(1.093,2.170)	2.531(1.796,3.566)	<0.001	
NSTEMI	151	189	120	0.797(0.453,1.404)	1.996(1.221,3.263)	0.002	
UA	93	87	83	0.963(0.505,1.834)	1.845(1.024,3.323)	0.039	
Tirofiban							<0.001
No	244	248	156	1.066(0.707,1.608)	1.797(1.189,2.717)	0.065	
Yes	479	436	376	1.389(0.988,1.953)	2.633(1.901,3.646)	<0.001	
LWMH							<0.001
No	51	86	50	0.718(0.339,1.521)	1.612(0.846,3.072)	0.086	
Yes	672	598	482	1.353(1.020,1.794)	2.397(1.818,3.159)	<0.001	

T: ticagrelor group; S: standard group; D: double group; STEMI: ST-Segment elevation myocardial infarction; UA: Unstable Angina; LMWH: low molecular weight heparin.

trial registered in China[25] showed that a dual-loading dose of antiplatelet therapy was associated with an increased major bleeding risk but not with a decreased MACCE among patients 75 years old undergoing PCI. In our study, we found that ticagrelor may reduce the incidence of ischemic events at 24 months but that its efficacy at 12 months showed no significantly decreased risk of MACCE. For the cardiovascular death, we observed statistical significance at both the 12-month and 24-month follow ups. Strong antiplatelet therapy is typically beneficial in the first year but not in the second year. This difference may be explained by the characteristics of the patients. In this study, we enrolled patients with a high risk of ischemia and bleeding, and there has been no previous study on this topic. The underlying mechanisms may require more studies and higher-level evidence. For the safety endpoints, ticagrelor increased the incidence of minor bleeding throughout the entire follow-up period, and similar results were observed in the double-dose clopidogrel group. However, the rate of minor bleeding in the second year was lower (28.5%, 10.7% and 12.9% respectively), so bias may exit due to the low incidence.

5. Study limitations

Despite the encouraging findings, our study has some limitations. First, this is a single-center retrospective observation trial. A multicenter design could provide more convincing data, especially for this head-to-head comparison trial on intensified strategies and there may be some inevitable bias by adopting the questionnaire, in addition, we could not analyze the impact of change of drug type or duration on patients' outcomes. Second, in our study, we employed GRACE and CRUSADE scores to identify patients with high ischemic and bleeding risk. However, no clinical score model is suitable for Chinese patients, which may cause bias in the results. Third, in this trial, although we mentioned above that genetic testing was not necessary in the general population, the percentage of patients who underwent a platelet function test and genotype test was low given the high ischemic risk of our patients. Thus, we could not use this limited information to draw a conclusion on whether the negative effect of double dose clopidogrel was attributed to a high prevalence of the CYP2C19 loss-of-function genotype is increased approximately two-fold in the Asian population compared to that of the Caucasian population, thus contributing to the high prevalence of low clopidogrel responsiveness in Asians.[26]

6. Conclusion

In landmark PCI patients with high ischemic and bleeding risk, the ticagrelor antiplatelet strategy significantly reduced the MACCE rate and increased quality of life without increasing the risk of major bleeding. A decreased rate of MACCE was observed in patients treated with a double dosage of clopidogrel, but the bleeding risk was greater than that in the control group.

Declaration of competing interest

All authors declared that there was no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2021.02.002.

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