Int J Clin Exp Med 2019;12(1):1289-1298
www.ijcem.com /ISSN:1940-5901/IJCEM0077305

Original Article

Investigation of efficacy and safety of ticagrelor in elderly patients with acute coronary syndrome

Yang Liu, Heng-Liang Liu, Zhen-Xuan Hao, Qi Chen, Dan-Li Wang, Jin-Rui Ji, Jing Liu, Sheng-Hao Zhang

Department of Cardiology, Zhengzhou People's Hospital, Southern Medical University, Zhengzhou 450000, China

Received September 3, 2017; Accepted September 10, 2018; Epub January 15, 2019; Published January 30, 2019

Abstract: Objective: This study aims to investigate the efficacy and safety of dual antiplatelet therapy (DAPT) with ticagrelor and aspirin in elderly patients with Acute Coronary Syndrome (ACS). Methods: A total of 432 patients with ACS who underwent Percutaneous coronary intervention (PCI) were enrolled into the study. These patients were divided into three groups, according to age: non-elderly group (age: <60 years old, n=167), elderly group (age: 61-79 years old, n=209), and very elderly group (age: ≥80 years old, n=56). TIMI blood flow grade, TIMI myocardial perfusion grade (TMPG), major complications, 1-year follow-up bleeding events and the primary endpoint were observed and investigated after treatment with DAPT after PCI. Results: TIMI blood flow, TMPG, reinfarction during hospitalization, post-infarction angina pectoris, severe arrhythmia, incidence of cardiac function and cardiogenic shock (Killip III or above), incidence of total, severe and moderate bleeding events, and the primary and secondary endpoints at 1-year follow-up in the very elderly group were significantly higher, compared with the elderly group and non-elderly group. Conclusions: The probability of complications and hemorrhage was high in very elderly patients with ACS after DAPT with ticagrelor and aspirin following PCI.

Keywords: Elderly, acute coronary syndrome, percutaneous coronary intervention, antiplatelet, hemorrhage, complications

Introduction

The pathological basis [1] of acute coronary syndrome (ACS) is total or subtotal vessel occlusion resulting from unstable plaque rupture, platelet activation, aggregation and adhesion. Percutaneous coronary intervention (PCI) is one [2] of the most effective therapies for ACS. Acute and subacute stent thrombosis are the main causes [3, 4] of most severe complications and major adverse cardiac events (MACE) after PCI in patients with ACS. Dual antiplatelet therapy (DAPT) with clopidogrel and aspirin is the foundation [5-7] for antiplatelet therapy after PCI. However, some patients may experience severe thrombosis complications due to clopidogrel resistance, thereby increasing the incidence of MACE after PCI in patients with ACS. The antiplatelet effects of ticagrelor is faster and more effective than clopidogrel, which increases coronary artery flow [8-10], and significantly reduces the incidence of post-PCI thrombotic complications and MACE in patients with ACS. Furthermore, it has been recommended as a first-line drug [11-14] for the treatment of ACS in patients in post-PCI antiplatelet therapy by national and international guidance.

The Platelet Inhibition and Patient Outcomes (PLATO) trial indicated that the incidence of major bleeding did not significantly increase [11-13] in the ticagrelor group, compared with the clopidogrel group. However, only 5.9% of the subjects enrolled in that trial were Asians, in which Chinese subjects accounted for 2%. Clopidogrel resistance more easily occurs in Asian populations due to the influence of CYP2C19 gene polymorphism. The Acute Myocardial Infarction Registry (KAMIR) trial revealed that risk of bleeding in the ticagrelor group significantly increased, compared with that in the clopidogrel group, especially in elderly patients (>75 years old) and patients with low-body weight (weight: <60 kg) [15]. The present study mainly aimed at discussing the efficacy and safety of DAPT with ticagrelor and aspirin after PCI in Chinese elderly patients with ACS.

Study subjects

A total of 432 patients with ACS, who underwent PCI at the Emergency Department and were admitted to the Coronary Care Unit (CCU) of our hospital between January 2013 and March 2016, were enrolled as study subjects. These patients were divided into three groups according to age: non-elderly group, <60 years old (mean age: 52.3 ± 5.7 years old), 167 patients (124 male patients and 43 female patients); elderly group, 61-79 years old (mean age: 68.6 ± 6.9 years old), 209 patients (143 male patients and 66 female patients); very elderly group, ≥80 years old (mean age: 84.6 ± 3.2 years old), 56 patients (32 male patients and 24 female patients). The inclusion criteria applied for these ACS patients were based on the European Guidance of ACS 2015 [7]. The present study conforms to the Declaration of Helsinki, and was approved by the Ethics Committee of Zhangzhou People's Hospital.

Inclusion criteria for ACS patients: (1) patients who were more than 18 years old, visited a doctor within 48 hours after onset of symptoms (ST-segment elevation myocardial infarction (STEMI) patients visited a doctor within 12 hours after onset of symptoms), and agreed to undergo CAG and/or PCI; (2) STEMI: patients who presented with a level of troponin T (cTnT) higher than the upper limit of normal laboratory value and in accordance with the evolution law of STEMI enzymology, and met at least one of the following conditions: the duration of symptoms of myocardial ischemia was ≥20 minutes at rest, two or more adjacent limbs leads presented with continuous ST-segment elevation ≥1 mm (0.1 mv), precordial lead presented with ST segment elevation ≥1-3 mm (V1-V3 was ≥0.3 mV, V4-V6 was ≥0.1 mv); there was new complete left bundle branch block; there were new emerged pathological Q waves; there was imaging evidence of abnormal segmental wall motion of survival myocardium; angiography confirmed a new complete occlusion of the coronary artery; (3) non-ST-segment elevation myocardial infarction (NSTEMI): patients presented with a level of cTnT higher than the upper limit of normal laboratory value at least one time, and met at least one of the following conditions: the duration of symptoms of myocardial ischemia was ≥10 minutes at rest, two or more adjacent limbs leads presented with continuous ST-segment reduction ≥1 mm (0.1 mv), (4) patients with unstable angina pectoris (UA): the cTnT level was normal, new angina pectoris occurred within one month, or original angina pectoris aggravated within one month, and met at least one of the following conditions: the duration of symptoms of myocardial ischemia was ≥10 minutes at rest, two or more adjacent limbs leads presented with ST-segment reduction ≥1 mm, or two or more adjacent limbs leads presented transient ST-segment elevation ≥1 mm, or reduced or inverted T-waves.

The following patients were excluded: (1) patients with sick sinus syndrome (SSS) or a heart rate of <55 bpm before enrollment, or an electrocardiogram (ECG) with the first degree of atrioventricular block or above; (2) patients with contraindications and drug allergies due to the use of ticagrelor; (3) patients with peptic ulcer and gastrointestinal bleeding within six months; (4) patients with moderate and severe hepatopathy, bleeding and coagulation disorders, and malignant tumors; (5) patients with uric acid nephropathy; (6) patients who were planning to undergo coronary artery bypass graft within seven days after admission; (7) patients whose blood platelet count was <100× 10^9/L; (8) patients who have received clopidogrel treatment within the past 30 days; (9) patients suffering from bronchial asthma or chronic obstructive pulmonary disease (COPD); (10) patients who have a past history of intracranial hemorrhage.

Research methods

An aspirin loading dose of 300 mg was immediately given for chewing after admission, followed by 100 mg *qd* for maintenance. Then, a ticagrelor loading dose of 180 mg was given for chewing, followed by 90 mg *bid* for maintenance. Subsequently, conventional administration of statins, angiotensin converting enzyme inhibitor and β receptor blockers, and nitrates were given. The first 18-lead ECG examination was completed within 10 minutes after admission, as well as electrocardiograph monitoring, oxygen uptake, emergency check of myocardial enzyme, cTnT, type B brain natruretic peptide (BNP), blood routine, coagulation function, electrolyte, renal function, eight preoperative items, random blood sugar, blood grouping, medical history inquiries, past medical history,

medications and allergic history. If the first ECG interpretation was STEMI or cTnT results upon admission suggested STEMI, the patient was immediately elected for the operation; and an informed consent was obtained from the patient prior to participation into the present study. Renal function and ECG were reviewed after the operation. Furthermore, myocardial enzyme and cTnT were rechecked at 6, 12, 18 and 24 hours after admission. If emergency biochemical results did not meet the inclusion criteria, it would be considered as a wrong inclusion, and the patient would drop out. If STEMI could not be diagnosed through the first ECG and the emergency check of cTnT and myocardial enzyme, ECG would be rechecked after 10 and 30 minutes, and cTnT and myocardial enzyme would be detected after six hours. If STEMI and NSTEMI were diagnosed, the patient would be assigned the same as above. If a patient was diagnosed with UA, whether the patient should be included was determined after should be returned to the emergency biochemical findings were returned, then coronary angiography (CAG) was checked. CTnT, myocardial enzyme, renal function and ECG would be reviewed after the operation.

PCI method

The Judksin method was used for CAG, with a puncture approach in the left and right radial arteries or femoral arteries. At the end of the radiography, the catheter was guided to reach the opening of the coronary artery, and the wire was guided to reach the distal-end *via* culprit artery. With respect to patients with STEMI, if thrombus shadows were macroscopically observed, a thrombus aspiration tube would be used for thrombus suction (5, 4 and 0 patients underwent thrombus suction in the three groups, respectively). Coronary blood flow was determined *via* repeat radiography. PTCA + stent implantation or direct stenting was performed according to pathological changes. All stents used in the operation were drug eluting stents. If macroscopic thrombus shadows and no-reflow and slow flow was found during the operation, 10 μg/kg of tirofiban was given for coronary intra-arterial injection. This was finished within three minutes, then venous pumping was continued at a dose of 0.15 μg/(kg·min) for 24 hours. Only culprit vessels were treated during emergency PCI in patients with STEMI. If other vessels needed to be treated, a second elective operation would be performed after 10-14 days.

Observation indicator

Observational indexes within 30 days and duration of hospital stay: The data on age, gender, heart rate, systolic pressure, serum creatinine, cardiac function Killip grading, ECG ST-segment changes, myocardial necrosis markers, hematokrit (HCT), past history of vascular disease and diabetes, and the determination of whether or not sudden cardiac arrest occurred were collected; and statistical analysis was performed to calculate the Global Registry of Acute Coronary Events (GRACE) score [16] and CRUSADE score [17]. The SYNTAX score [18] was worked out based on the patient's CAG results. The data on hospital stay, the number of implanted stents, and the diameter and length (if two or more non-series stents are implanted, the total length of the implanted stents would be the sum of the length of those implanted stents, while if two or more series stents are implanted in the target lesion, the total length of these implanted stents would be the total length of the diameter of each two series of stents minus 3 mm) of the implanted stents were collected. The incidence of adverse events during hospitalization, electively repeated PCI, post-infarction angina, reinfarction during hospitalization, severe arrhythmia (emerging atrial fibrillation or atrial flutter of hemodynamic instability, high-grade atrioventricular block, sustained ventricular tachycardia and ventricular fibrillation, excluding reperfusion arrhythmia during the PCI operation), and cardiac function and cardiogenic shock with a Killip class of ≥III were also collected. The Thrombolysis in Myocardial Infarction (TIMI) blood flow grade after PCI, and TIMI myocardial perfusion grade (TMPG) of infarction-related vessels were recorded.

One-year follow-up indexes: All patients included in the present study were followed up for 12 months. The follow-up period started from the date when the patient participated in the study until the date the patient was admitted for 12 months. Immediately after the initial medication, at six weeks, six months and 12 months after the medication, the follow-up were conducted through rehospitalization, outpatient

Table 1. The general clinical data of the 3 groups were compared

Project	Non elderly control group (A group, 167)	Elderly group (B group, 209)	Venerable age group (C group, 56)	P
Male (%)	124 (74.25)	143 (68.42)	32 (57.14)[a]	0.004
Age (year)	52.3 ± 5.7	68.6 ± 6.9[a]	84.6 ± 3.2[a,b]	0.000
Blood pressure (%)	39 (23.35)	103 (49.28)[a]	35 (62.5)[a]	0.000
Smoking history (%)	67 (40.12)	87 (41.63)	13 (23.21)[a,b]	0.038
Hyperlipidemia (%)	67 (40.12)	102 (48.8)	25 (44.64)	0.243
Serum creatinine (mmol/L)	81.2 ± 11.2	86.6 ± 12.5	85.0 ± 16.3	0.783
STEMI (%)	135 (80.84)	137 (65.55)[a]	27 (48.21)[a,b]	0.000
NSTEMI (%)	10 (5.99)	31 (14.83)[a]	22 (39.29)[a,b]	0.000
UA (%)	22 (13.17)	41 (19.62)	7 (12.50)	0.175
GRACE integral				
Low risk (<85 branch) (%)	24 (14.37)	21 (10.05)	2 (3.57)[a]	0.069
Moderate risk (85~133 branch) (%)	42 (25.15)	39 (18.66)	6 (10.71)[a]	0.05
High-risk (>133 branch) (%)	101 (60.05)	149 (71.29)[a]	48 (85.71)[a,b]	0.001
CRUSADE integral				
Very low risk (1-20 branch) (%)	11 (6.59)	19 (9.09)	4 (7.14)	0.654
Low risk (21-30 branch) (%)	108 (64.67)	121 (57.89)	29 (51.79)	0.178
Moderate risk (31-40 branch) (%)	36 (21.56)	41 (19.62)	17 (30.36)	0.223
Moderate risk (41-50 branch) (%)	9 (5.39)	13 (6.22)	4 (7.14)	0.088
Very high-risk (>51 branch) (%)	2 (1.20)	3 (1.44)	2 (3.57)	0.456

Note: Compare with group A, [a]P<0.05; compare with group B, [b]P<0.05. STEMI: ST segment elevation myocardial infarction; NSTEMI: non ST segment elevation myocardial infarction; UA: unstable angina pectoris.

visit and phone call, respectively. The endpoint events and related biochemical criterion were recorded. Patients who could not be contacted for three times were considered lost to follow-up.

Primary endpoints: cardiovascular (CV) death, and myocardial infarction (MI) or stroke.

Secondary endpoints: Effectiveness and safety endpoints. Specifically, effectiveness endpoints include all-cause death, repeat revascularization of target vessels, in-stent thrombosis, heart-related rehospitalization, and transient ischemic attack.

Safety endpoint refers to the occurrence of bleeding complications; that is, the incidence of some adverse events including severe bleeding (intracranial hemorrhage or alimentary tract hemorrhage, circulation instability due to massive hemoptysis, hemoglobin decrease by ≥5 g/dl, and hematocrit decrease by ≥15%), moderate bleeding (hemoptysis, hematemesis volume ≥100 ml/d, melena, gross hematuria, etc.), and mild bleeding (hemoptysis, hematemesis volume <100 ml/d, hematoma at the site of puncture, skin ecchymosis, mucous membrane, and gum bleeding and microscopic hematuria).

Statistical method

Data were analyzed using SPSS 18.0 statistical software, and results were expressed as x ± standard deviation (SD). Count data was evaluated using X^2-test, and ANOVA was used for the measurement data. P<0.05 was considered statistically significant.

Results

Comparison of common clinical information among the three groups

Among these three groups, differences in hyperlipidemia, the concentration of serum creatinine, and the proportion of patients with UA were statistically significant (P<0.05). Specifically, the male proportion and the number of smoking patients were markedly lesser in the very elderly group than in the non-elderly and elderly groups, but the proportion of NSTEMI patients was significantly higher than in the elderly and very elderly groups (P<0.05). Fur-

Table 2. Comparison of characteristics of coronary artery lesions in 3 groups (%)

Lesion characteristics	Non elderly control group (A group, 167)	Elderly group (B grou, 209)	Venerable age group (C grou, 5)	P
Single vessel disease	85 (50.90)	83 (39.71)	10 (17.86)[a,b]	0.000
Double vessel disease	61 (36.53)	45 (21.53)[a]	12 (21.43)[a]	0.004
Three vessel disease	21 (12.57)	81 (38.76)[a]	34 (60.71)[a,b]	0.000
Merge left main pathology	4 (2.39)	8 (3.83)	6 (10.71)[a,b]	0.025
SYNTAX integral	17.98 ± 6.93	17.86 ± 7.25	24.82 ± 7.92[a]	0.001
Use IIb/IIIa antagonists (%)	39 (23.35)	30 (14.35)[a]	2 (3.57)[a,b]	0.001
TIMI Classification				
Preoperative 0~1 level	137 (82.04)	166 (79.43)	29 (51.79)[a,b]	0.000
Postoperative 3 level	163 (97.0)	189 (90.43)[a]	45 (80.35)[a,b]	0.000
Postoperative TMPG level				
0~1 level	3 (1.80)	10 (4.78)	5 (8.93)[a]	0.444
2 level	11 (6.59)	22 (10.53)	10 (17.86)[a]	0.048
3 level	153 (91.62)	177 (84.69)[a]	41 (73.21)[a,b]	0.002
Number of stents implanted in each patient ($\bar{x}$ ±s)	1.59 ± 0.32	1.61 ± 0.52	1.60 ± 0.29	0.725
Mean vessel diameter (mm, $\bar{x}$ ±s)	2.72 ± 0.40	2.71 ± 0.52	2.71 ± 0.39	0.632
Stent insertion length (mm, $\bar{x}$ ±s)	24.19 ± 5.67	25.01 ± 6.96	23.87 ± 6.73	0.712

Note: Compare with group A, [a]P<0.05; compare with B group, [b]P<0.05.

thermore, the proportion of STEMI patients was significantly higher in the non-elderly group than in the elderly and very elderly groups. On the contrary, the proportion of hypertension patients was obviously lower than in the non-elderly and very elderly groups (P<0.05). In terms of GRACE score, the proportion of patients at high risk significantly exceeded the proportion in the non-elderly group (P<0.05), the proportion of patients at extremely high risk was obviously higher than that in the non-elderly and elderly groups (P<0.05), and the same proportion of patients was higher in the elderly group than in the non-elderly group (P>0.05). The difference in CRUSADE score of patients at extremely low risk, low risk, moderate risk, high risk and extremely high risk among these three groups was not statistically significant (P>0.05) (**Table 1**).

Characteristics of coronary artery lesions among these three groups of patients

There was no statistical difference in the number of implanted stents, diameter of blood vessels with target lesions, and length of implanted stents during PCI among the three groups. Compared with the non-elderly and elderly groups, triple-vessel disease, combined left main coronary artery lesions and SYNTAX score were significantly higher in the very elderly group, while the application proportion of IIb/IIIa receptor antagonist, TIMI 3 blood flow and TMPG 3 myocardial perfusion after PCI were obviously lower (P<0.05) (**Table 2**).

Hospitalization duration, PCI features and complication incidence among the three groups

In the very elderly and elderly groups, mean hospitalization duration and elective repeat PCI during hospitalization were higher than in the non-elderly group (P<0.05), while the incidence of re-infarction during hospitalization, postinfraction angina, severe arrhythmia and cardiac function and cardiogenic shock with a Killip grade of ≥III was greater in the very elderly group than in the non-elderly and elderly groups (P< 0.05) (**Table 3**).

Comparison of bleeding incidence, one-year follow-up results and effectiveness end points among the three groups

A total of 401 patients were successively followed up with a success rate of 92.82%. At the end of follow-up, the incidence of total, severe and moderate bleeding was significantly greater in the very elderly group than in the non-elderly group (P<0.05), while the difference in the incidence of mild bleeding among the three groups was not statistically significant. Furthermore, the incidence of both primary and secondary endpoints was obviously higher in the very elderly group than in the non-elderly and elderly groups (P=0.000) (**Table 4**).

Table 3. Length of hospital stay and complication rate of the 3 groups were compared

Project	Non elderly control group (A group, 167)	Elderly group (B group, 209)	Venerable age group (C group, 56)	P
Average length of stay (d)	8.1 ± 1.7		13.3 ± 2.8[a]	0.036
Hospitalization for two times (%)	8 (4.79)	13 (6.22)	7 (12.5)[a]	0.125
Post infarction angina pectoris (%)	9 (5.39)	13 (6.22)	8 (14.29)[a,b]	0.065
Re infarction (%)	1 (0.60)	1 (0.48)	3 (5.36)[a,b]	0.008
Severe arrhythmia (%)	11 (6.59)	11 (5.26)	9 (16.07)[a,b]	0.019
KillipIII level above heart function (%)	4 (2.40)	6 (2.87)[a]	6 (10.71)[a,b]	0.011
PCI Cardiogenic shock after operation (%)	0 (0)	1 (0.48)	3 (5.36)[a,b]	0.000

Note: Compare with group A, [a]P<0.05; compare with B group, [b]P<0.05.

Table 4. The incidence of bleeding and the results of 1 year follow-up were compared between the 3 groups

Project	Non elderly control group (A group, 155)	Elderly group (B group, 193)	Venerable age group (C group, 53)	P
Number of bleeding cases	10 (6.45)	25 (12.95)[a]	10 (18.87)[a,b]	0.026
Severe bleeding	0	1 (0.52)	2 (3.77)[a]	0.019
Moderate bleeding	1 (0.65)	2 (1.04)	3 (5.66)[a,b]	0.026
Mild bleeding	9 (5.81)	22 (11.40)	5 (9.43)	0.191
Primary endpoint	1	4 (2.07)	6 (11.32)[a]	0.000
Cardiovascular death	0	1 (0.52)	3 (5.66)[a,b]	0.001
Miocardial infarction	1 (0.65)	2 (1.04)	1 (1.89)	0.732
Apoplexy	0	1 (0.52)	2 (3.77)[a]	0.019
Secondary validity endpoint	6 (3.87)	15 (7.77)	19 (35.85)[a,b]	0.000
All causes of death (including bleeding, death)	0	2 (1.04)	5 (9.43)[a,b]	0.000
Stent thrombosis	1 (0.65)	0	1 (1.89)	0.213
Target blood vessel revascularization	2 (1.29)	6 (3.11)	2 (3.77)	0.454
Cardiac readmission	3 (1.94)	6 (3.11)	9 (16.98)[a,b]	0.000
Transient ischemic attack	0	1 (0.52)	2 (3.77)[a]	0.019

Note: Compare with group A, [a]P<0.05; compare with B group, [b]P<0.05.

Discussion

ACS is a series of clinical syndromes that include STEMI, NSTEMI and unstable angina (UA) [3, 4]. The specific process is that the unstable plaque rupture induces blood platelets to activate, aggregate and release vasoactive substances, and the resulting acute thrombosis induces acute myocardial ischemia. Clopidogrel combined with aspirin has always been one of important measures for treating ACS [5-7]. Recently, it has been found that clopidogrel needs go through two levels of liver enzyme-mediated metabolism, and slowly takes effect. Moreover, the difference in its curative effect among individuals is relatively significant. As a result, the incidence of MACE after PCI is increased [8, 9]. CYP2C19 gene polymorphism is an important genetic factor for clopidogrel antiplatelet response. However, the new type of receptor antagonist, ticagrelor, can directly work without liver enzyme activation, and has a rapider antiplatelet effect. Its effectiveness is independent of the CYP2C19 gene polymorphism [8-13]. The PLATO trial indicated that [4] compared with clopidogrel, ticagrelor significantly reduced the incidence of primary composite endpoints within one year, but the difference in fatal hemorrhage and massive hemorrhage was not statistically significant. At present, ticagrelor has been recommended by several guidelines as a class I therapy for ACS patients [5-7].

The elderly, especially those in the advanced stage, suffer from a large number of ACS complications, have complex vasculopathy and have poor tolerance to various medicines. Moreover, the incidences of both thrombosis and hemorrhage during antiplatelet therapy are significantly higher in these patients, compared to non-elderly patients. Furthermore, no-reflow

and slow-flow would occur at a larger incidence during emergency PCI. Postoperatively, there are some disadvantages, including increase in MACE, more complications, poor prognosis and high mortality rate [19]. The present study shows that the incidence of hypertension and NSTEMI in advanced patients was significantly greater than that in non-elderly patients and elderly patients, while the incidence of STEMI was obviously lower than that in non-elderly patients and elderly patients. This indicates that as age increases, hazardous factors would gradually increase. There are few patients with typical STMI, but there are larger numbers of patients with NSTEMI. Moreover, it has been indicated that operation risk and postoperative complications would be increased.

The feature of coronary artery lesions is another important index to evaluate the operation success rate, intraoperative and postoperative complications, and MACE [21-23]. GRACE score can be used to systematically and accurately screen out patients at high risk, which has a remarkable practical value to the predication of case fatality rate both during hospitalization and after discharge [16]. SYNTAX score can be used to evaluate the complexity of unprotected left main lesions and triple-vessel disease according to CAG radiographic results, and is an important basis for guiding PCI or CABG. According to the research data compared with non-elderly patients, for advanced and elderly patients, both the preoperative GRACE score and SYNTAX score of coronary artery lesions after angiography are obviously higher. These are important indexes of poor prognosis for advanced patients.

One objective of emergency PCI is to restore the forward flow of the infarction-related artery to TIMI 3. However, it was found that after PCI restores epicardial blood flow to TIMI 3, the myocardial tissues of 25-30% of patients are not effectively re-perfused; that is, the slow flow and no-reflow phenomenon [19, 20]. In fact, successful perfusion at the myocardial tissue level is the final standard of a successful reperfusion. As the standard of myocardial perfusion at tissue level, TMPG consists of perfusing and emptying of contrast agents in myocardial tissues, which can more accurately evaluate the perfusion at the myocardial tissue level [19]. For patients with TIMI 3 epicardial coronary artery blood flow, the mortality of TMPG 0-1 (microvascular occlusion) patients was significantly higher than in patients with TMPG 2-3 [3, 4, 19, 20]. Therefore, the combined use of TIMI blood flow and TMPG is an effective index to forcefully evaluate myocardial reperfusion. This revealed that according to the research data, there was no significant difference in the number, mean diameter and length of the implanted stent among very elderly, elderly and non-elderly patients. However, the proportion of TIMI blood flow III and TMPG III after PCI was found to significantly decrease, which may have resulted from complex coronary artery lesions, long surgical duration, great difficulties and poor endothelial function in very elderly patients.

After PCI, on the basis of DAPT, and in combination with the IIb/IIIa antagonist applied, myocardial perfusion may be significantly improved to reduce the incidence [3, 19, 20] of complications and MACE in the perioperative period. It has been shown in the data of the present study that the proportion of applied tirofiban was obviously lower in the very elderly group than in the elderly group, which may have caused the significant reduction in TIMI blood flow grade III and TMPG grade III. Due to the reduced effective myocardial reperfusion after PCI, the incidence of re-infarction during hospitalization, post-infraction angina, severe arrhythmia, cardiac function and cardiogenic shock with a Killip class of ≥III, and secondary elective PCI during hospitalization significantly increased; and the mean length of hospital stay was prolonged.

GRACE score is positively correlated with MACE after PCI [16], and CRAUSADE score is mainly used as an evaluation index for risk of bleeding. In the GRACE score, risk factors should be graded such as heart rate, systolic blood pressure, serum creatinine, heart failure and ischemia events. Similarly, these should be regarded as risk factors of bleeding in the CRUSADE score. In addition, ischemic risk factors also include aged, chronic kidney disease, renal insufficiency, diabetes and previous myocardial infarction, which are risk factors for bleeding. Accordingly, it has been shown that in patients with PCI, ischemia and hemorrhage were closely correlated and contradictory.

The present study shows that DAPT with ticagrelor and aspirin significantly reduced the inci-

dence of ischemic events, compared with the treatment of clopidogrel. However, the incidence of bleeding events presents an increasing trend [13, 24]. In the PEGASUS-TIMI 54 trial, although there was no significant difference in the incidence of intracranial hemorrhage when compared with the ticagrelor and placebo groups, the incidence of massive hemorrhage refined by TIMI significantly increased [12]. In the PLATO trial, there was no significant difference [16] in the complications of bleeding between Asians and Africans. However, when compared among Asians, especially European and American East Asians, there was a lower incidence of potential ischemic events after DAPT with ticagrelor and aspirin in these populations, but there was a higher probability of bleeding [25, 26]. In the present study, based on the GRACE score, it was shown that high-risk patients were significantly more in very elderly patients than in elderly and non-elderly patients. However, there was no significant difference in CRUSADE risk score among these three groups. The proportion of the IIb/IIIa receptor antagonist application significantly decreased, but the probability of bleeding increased. This indicates that age is an independent risk factor of bleeding. In addition, the female proportion was higher in the very elderly group than in the elderly and non-elderly groups. Accordingly, based on the CRUSADE risk score, it was shown that the female gender is one of the important risk factors, and the reason for increased bleeding. After a 1-year follow-up, it was found that the incidences of primary endpoint events and the secondary endpoint significantly increased in the very elderly group. This indicate that there are significantly higher incidences of ischemic events, bleeding events and CV deaths for one-year and all-cause death in patients with ACS after PCI in the very elderly group, compared with the non-elderly and elderly groups.

Limitations of the study: This study focused on DAPT with ticagrelor and aspirin. However, no comparisons with clopidogrel were performed. Furthermore, the sample size was small. Tirofiban was combined when used in the control group, but no strict control standards were set. Further controlled studies are being undertaken by the authors to resolve these existing limitations.

Acknowledgements

Construction project of innovative scientific and technological talents in Zhengzhou (096SYJH-331144).

Disclosure of conflict of interest

None.

Address correspondence to: Heng-Liang Liu, Department of Cardiology, Zhengzhou People's Hospital, Southern Medical University, 33 Yellow River Road, Zhengzhou 450000, China. Tel: +86371 67077035; Fax: +86 371 67077635; E-mail: lhldoc@163.com

References

[1] Libby P. Current concepts of the pathogenesis of acute coronary syndromes. Circulation 2001; 104: 365-72.

[2] Wessler JD, Stant J, Duru S, Rabbani L, Kirtane AJ. Updates to the ACCF/AHA and ESC STEMI and NSTEMI guidelines: putting guidelines into clinical practice. Am J Cardiol 2015; 115: 23A-8A.

[3] Liu Y, Liu H, Hao Z, Geng G, Chen Q, Han W, Jia K, Zhou Y. Efficacy and safety of different doses of tirofiban combined with ticagrelor on diabetic patients with AMI receiving in emergency percutaneous coronary intervention (PCI). Int J Clin Exp Med 2015; 8: 11360-9.

[4] Liu HL, Liu Y, Hao ZX, Geng GY, Zhang ZF, Jing SB, Ba N, Guo W. Comparison of primary coronary percutaneous coronary intervention between diabetic men and women with acute myocardial infarction. Pak J Med Sci 2015; 31: 420-5.

[5] China Society of Cardiology of Chinese Medical Association. Guideline on the diagnosis and therapy of ST-segment elevation myocardial infarction. Zhonghua Xin Xue Guan Bing Za Zhi 2015; 43: 380-93.

[6] Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ; ACC/AHA Task Force Members; Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the american college of cardiology/american heart association task force on practice guidelines. Circulation 2014; 130: 2354-94.

[7] Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C,

Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S; ESC Scientific Document Group. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the european society of cardiology (ESC). Eur Heart J 2016; 37: 267-315.

[8] Husted S, van Giezen JJ. Ticagrelor: the first reversibly binding oral P2Y12 receptor antagonist. Cardiovasc Ther 2009; 27: 259-74.

[9] VAN Giezen JJ, Nilsson L, Berntsson P, Wissing BM, Giordanetto F, Tomlinson W, Greasley PJ. Ticagrelor binds to human P2Y (12) independently from ADP but antagonizes ADP-induced receptor signaling and platelet aggregation. J Thromb Haemost 2009; 7: 1556-65.

[10] Armstrong D, Summers C, Ewart L, Nylander S, Sidaway JE, van Giezen JJ. Characterization of the adenosine pharmacology of ticagrelor reveals therapeutically relevant inhibition of equilibrative nucleoside transporter 1. J Cardiovasc Pharmacol Ther 2014; 19: 209-19.

[11] Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009; 361: 1045-57.

[12] Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015; 372: 1791-800.

[13] Kang HJ, Clare RM, Gao R, Held C, Himmelmann A, James SK, Lim ST, Santoso A, Yu CM, Wallentin L, Becker RC; PLATO Investigators. Ticagrelor versus clopidogrel in asian patients with acute coronary syndrome: a retrospective analysis from the platelet Inhibition and patient outcomes (PLATO) trial. Am Heart J 2015; 169: 899-905.

[14] Goto S, Huang CH, Park SJ, Emanuelsson H, Kimura T. Ticagrelor vs. clopidogrel in japanese, korean and taiwanese patients with acute coronary syndrome--randomized, double-blind, phase III PHILO study. Circ J 2015; 79: 2452-60.

[15] Park KH, Jeong MH, Ahn Y, Ahn TH, Seung KB, Oh DJ, Choi DJ, Kim HS, Gwon HC, Seong IW, Hwang KK, Chae SC, Kim KB, Kim YJ, Cha KS, Oh SK, Chae JK. Comparison of short-term clinical outcomes between ticagrelor versus. clopidogrel in patients with acute myocardial infarction undergoing successful revascularization; from Korea acute myocardial infarction registry-nationg, Institute of health. Int J Cardiol 2016; 215: 193-200.

[16] Bekler A, Altun B, Gazi E, Temiz A, Barutçu A, Güngör Ö, Özkan MT, Özcan S, Gazi S, Kırılmaz B. Comparison of the GRACE risk score and the TIMI risk index in predicting the extent and severity of coronary artery disease in patients with acute coronary syndrome. Anatol J Cardiol 2015; 15: 801-6.

[17] Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby KL, Wang TY, Gibler WB, Ohman EM, Roe MT, Pollack CV Jr, Peterson ED, Alexander KP. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines) bleeding score. Circulation 2009; 119: 1873-82.

[18] Schwietz T, Spyridopoulos I, Pfeiffer S, Laskowski R, Palm S, DE Rosa S, Jens K, Zeiher AM, Schächinger V, Fichtlscherer S, Lehmann R. Risk stratification following complex PCI: clinical versus anatomical risk stratification including" post PCI residual SYNTAX-score" as quantification of incomplete revascularization. J Interv Cardiol 2013; 26: 29-37.

[19] Liu Y, Liu HL, Geng GY, Ba N, Jing SB, Guo W, Zhang ZF. Effects of coronary arterial injection of tirofibanon diabetes mellitus complicated with acute myocardial infarction in the elderly. Acta Cardiol Sin 2013; 29: 550-6.

[20] Chen Q, Liu Y, Liu HL. Effects of intracoronary tirofiban administration on diabetes mellitus complicated by acute myocardial infarction in female patients undergoing emergency percutaneous coronary intervention. Int J Clin Exp Med 2016; 9: 11966-73.

[21] Bhatt DL, Hulot JS, Moliterno DJ, Harrington RA. Antiplatelet and anticoagulation therapy for acute coronary syndromes. Circ Res 2014; 114: 1929-43.

[22] Goto S, Huang CH, Park SJ, Emanuelsson H, Kimura T. Ticagrelor vs. clopidogrel in japanese, korean and taiwanese patients with acute coronary syndrome - randomized, doubleblind, phase III PHILO study. Circ J 2015; 79: 2452-60.

[23] Hiatt WR, Fowkes FG, Heizer G, Berger JS, Baumgartner I, Held P, Katona BG, Mahaffey KW, Norgren L, Jones WS, Blomster J, Millegård M, Reist C, Patel MR; EUCLID Trial Steering Committee and Investigators. Ticagrelor versus clopidogrel in symptomatic peripheral

artery disease. N Engl J Med 2017; 376: 32-40.
[24] Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009; 361: 1045-57.
[25] Levine GN, Jeong YH, Goto S, Anderson JL, Huo Y, Mega JL, Taubert K, Smith SC Jr. Expert consensus document: world heart federation expert consensus statement on antiplatelet therapy in east asian patients with ACS or undergoing PCI. Nat Rev Cardiol 2014; 11: 597-606.
[26] Li H, Guo J, Carlson GF, Teng R. Pharmacodynamics, pharmacokinetics, and safety of ticagrelor in chinese patients with stable coronary heart disease. Br J Clin Pharmacol 2016; 82: 352-61.