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Efficacy and safety of ticagrelor versus clopidogrel with different dosage in high-risk patients with acute coronary syndrome

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ABSTRACT

Background: Dual antiplatelet therapy is recommended as a standard antiplatelet strategy in acute coronary syndrome. For those with reduced pharmacologic response to clopidogrel, strengthening antiplatelet therapy (clopidogrel 150 mg daily) may reduce adverse clinical events. Ticagrelor is a direct-acting inhibitor of the adenosine diphosphate receptor P2Y12 that has a more rapid onset and offset than clopidogrel.
Methods: In this retrospective study, we compared ticagrelor (180 mg loading dose 90 mg twice daily thereafter), clopidogrel (300 mg loading dose, 75 mg or 150 mg daily thereafter) for the prevention of cardiovascular events in 273 high-risk patients admitted to coronary care unit with acute coronary syndrome.
Results: The rate of IST in hospital was significantly reduced in patients of ticagrelor group comparing with those receiving clopidogrel 75 mg (0.69% vs 8.2%, $p = 0.009$). Moreover, the TVR rate was less in the ticagrelor group than clopidogrel 75 mg group (2.7% vs 13.1%, $p = 0.007$) 6 months follow-up. The incidence of MACCE has no difference between the two clopidogrel groups. Kaplan–Meier analysis of MACCE-free indicated that there was no difference between the three groups. Ticagrelor significantly increased the rate of minor bleeding compared with clopidogrel 75 mg daily during hospital (45.5% vs 26.2%,$p = 0.012$) and 6-month follow-up (66.9% vs 45.9%,$p = 0.004$).Bleeding-free prognosis was significantly better in the clopidogrel 75 mg daily group.
Conclusions: In patients with acute coronary syndrome undergoing PCI, the rate of in-stent thrombosis and TVR were significantly reduced treated with ticagrelor compared with clopidogrel 75 mg daily, without an increase of overall major bleeding, but with an increase of minor bleeding.

1. Introduction

In patients with acute coronary syndrome (ACS), dual antiplatelet therapy with aspirin and clopidogrel has been the cornerstone strategy [1,2]. The efficacy of clopidogrel is variable due to different transformation of the prodrug to active metabolite in different patients, and clopidogrel resistance [3,4] may increase the risk of stent thrombosis and myocardial infarction [5,6]. The polymorphisms of cytochrome P450 2C19 might be one of the factors influencing the individual susceptibility [7,8]. A strategy of raising the dose of clopidogrel may help to overcome poor response to the agent and improve clinical outcome [9,10]. However, the bleeding risk may also increase with double dose of clopidogrel.

Ticagrelor is a reversible and direct-acting antagonist of the adenosine diphosphate receptor P2Y12, providing faster, and more consistent platelet inhibition than clopidogrel. In PLATO trial [11], involving 18,624 ACS patients, ticagrelor and clopidogrel were compared for the prevention of cardiovascular events, and the results showed that ticagrelor significantly reduced the composite ischemic end point events, cardiac death and myocardial infarction without an increase of the rate of major bleeding.

In this retrospective study, we compared ticagrelor (90 mg twice daily), clopidogrel (75 mg daily), and clopidogrel (150 mg daily) for the prevention cardiovascular events and safety in patients presented with ACS and underwent percutaneous coronary intervention (PCI).

2. Material and methods

2.1. Study design and patients

The ACS patients admitted in Coronary Care Unit and underwent PCI in our hospital were continuously enrolled. The exclusion criteria included history of surgical procedures within the past year, hematological disorders, concomitant therapy with a strong cytochrome P-450 3A4 inhibitor or inducer, and pregnancy. We recorded patients' baseline

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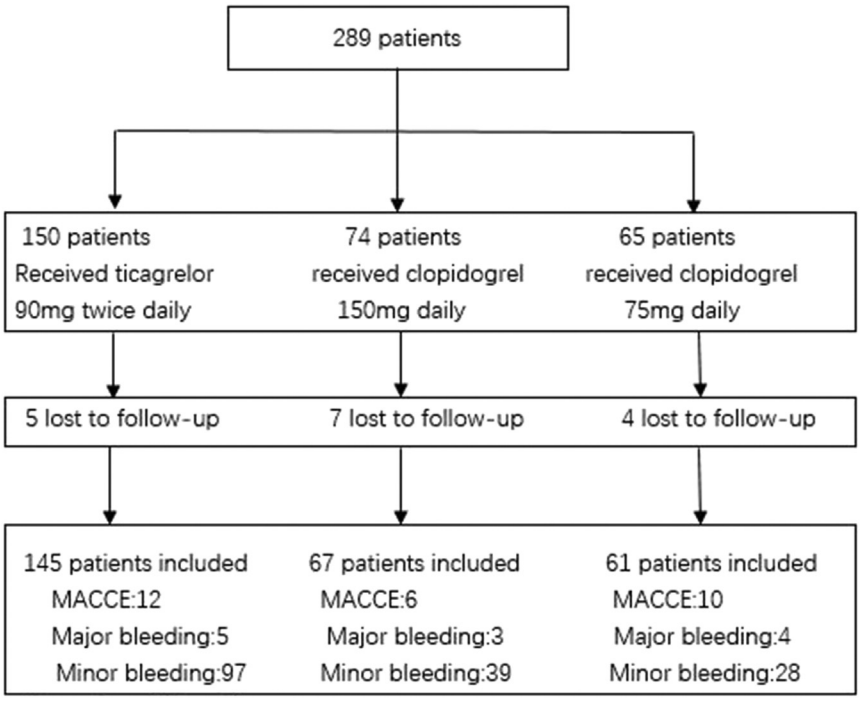

Fig. 1. Trial profile.

clinical characteristics and the risk factors including smoking, dyslipidemia, hypertension, diabetes, prior myocardial infarction and previous history of stroke or transient ischemic attack. The GRACE and CRUSADE score were also calculated for each patient.

Out of the 289 patients enrolled, 16 of them were lost in follow-up and 273 patients were finally included in the study. One hundred and forty-five of them received ticagrelor with a loading dose of 180 mg followed by a maintaining dose of 90 mg twice daily, 67 patients received clopidogrel with a loading dose of 300 mg followed by 150 mg daily and 61 patients received the same loading dose of clopidogrel but followed by a dose of 75 mg daily. All patients received aspirin at a dose of 100 mg daily unless they could not tolerate the drug. For those who had not previously been receiving aspirin, a loading dose of 300 mg was preferred loading dose.

2.2. End points

The efficacy end point was a composite of death from cardiovascular diseases, nonfatal myocardial infarction, nonfatal stroke, in-stent thrombosis (IST) and target vessel revascularization (TVR) during the follow-up, i.e., major adverse cardiac and cerebral events (MACCE). Cardiovascular death was defined as death related to cardiac causes or stroke. Myocardial infarction was defined as either the development of new pathologic Q wave in at least 2 contiguous leads, or in the absence of pathologic Q waves, an elevation in cardiac biomarkers levels to more than twice the upper limit of normal unrelated to either PCI-S or coronary bypass surgery [12]. Stroke was defined as permanent focal neurologic dysfunction caused by an ischemic or hemorrhagic event, with residual symptoms lasting at least 24 h or leading to death. Evaluation for in-stent thrombosis (IST) was performed according to the Academic Research Consortium criteria [13], we adopted definite and probable IST in this study. Target vessel revascularization was defined as re-intervention driven by any lesion located in the stented vessel, the indication for repeating revascularization was based on angina symptoms and a significant angiographic stenosis(>50% diameter stenosis).

The safety end point was bleeding complications that were classified according to Thrombolysis In Myocardial Infarction (TIMI) criteria [14,15]. Major life threatening bleeding including: (1)fatal bleeding; (2)intracranial bleeding; (3) intrapericardial bleeding with cardiac tamponade; (4) hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery, a decline in the hemoglobin level of 5.0 g per deciliter or more.

Table 1
Baseline characteristics of each treatment group.

	Ticagrelor (n = 145)	Clopidogrel 150 mg (n = 67)	Clopidogrel 75 mg (n = 61)	P value
Age (years)	61.9(11.7)	57.0(11.6)	65.0(13.1)	0.252
Male (%)	99 (68.3%)	45 (67.2%)	45 (73.8%)	0.675
Diabetes (%)	55(37.95%)	15 (22.4%)	21 (34.4%)	0.081
Hypertension (%)	89 (61.4%)	31 (46.3%)	35 (57.4%)	0.118
Smoking (%)	80 (55.2%)	44 (65.7%)	34 (55.7%)	0.33
Previous MI (%)	22 (15.2%)	9 (13.4%)	13 (22.9%)	0.288
Lipid disorder (%)	28 (19.3%)	16 (23.8%)	14 (22.9%)	0.702
Stroke(%)	33 (22.7%)	11 (16.4%)	19 (31.1%)	0.141
eGFR <60 ml/min (%)	42 (28.9%)	20 (29.8%)	25 (40.9%)	0.221
ACEI/ARB (%)	119 (82.1%)	52 (77.6%)	41 (67.2%)	0.06
β-Blocker (%)	113 (77.9%)	51 (76.1%)	32 (52.4%)	0.01
PPI (%)	80 (55.2%)	38 (56.7%)	31 (50.8%)	0.782
Lipid-lowering agent (%)	138 (95.2%)	64 (95.5%)	59 (96.7%)	0.87

ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin II receptor blocker; PPI: proton-pump inhibitor.

Table 2
Procedural characteristics among the patients with different antiplatelet therapy.

	Ticagrelor (n = 145)	Clopidogrel 150 mg (n = 67)	Clopidogrel 75 mg (n = 61)	P value
PCI indication				0.528
STEAMI (n, %)	116(80%)	58(86.5%)	46(75.4%)	
Non-STEMI (n, %)	18(12.4%)	6(8.9%)	8(13.1%)	
Unstable Angina (n, %)	11(7.6%)	3(4.5%)	7(11.5%)	
GRACE score	151.09(34.18)	145.94(31.24)	158.04(38.03)	0.139
GRUSADE score	33.28(11.87)	31.43(11.49)	36.65(14.05)	0.053
Tirofiban (%)	97 (66.9%)	54 (80.6%)	38 (62.3%)	0.055
LMWH (%)	139 (95.8%)	64(95.5%)	54 (88.5%)	0.061
Multi-vessels disease (%)	2.15(0.83)	1.59(0.73)	1.85(0.81)	0.31
Total No. of stents (%)	1.68(0.83)	1.38(0.65)	1.70(0.78)	0.048
PCI vessel				0.775
LAD	84 (57.9%)	39 (58.2%)	39 ((63.9%))	
LCX	12(8.3%)	8 (11.9%)	4(6.6%)	
RCA	49(33.8%)	20 (29.9%)	18(29.5%)	
No. of vessels treated				0.061
1	123 (84.8%)	64 (95.5%)	52 (85.2%)	
2	19 (13.1%)	3 (4.5%)	9 (14.8%)	
3	3(2.1%)	0(0.0%)	0(0.0%)	

LMWH: low molecular weight heparin; PCI: percutaneous coronary intervention; LAD: left anterior descending; LCX: left circumflex coronary artery; RCA: right coronary artery.