Comparison of the efficacy of half ticagrelor loading doses and clopidogrel in elderly acute coronary syndrome patients in China

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Abstract

Purpose: To evaluate the effects of half-load doses (HLD) of ticagrelor and clopidogrel on elderly acute coronary syndrome patients (ACS) over a period of 90 days.

Methods: Seventy-four patients diagnosed as ACS were included in this trial. The patients were randomly distributed into group 1 (treated with HLD ticagrelor, 90 mg LD) and group 2 (treated with clopidogrel, 300 mg LD). The interaction of treatment effect was evaluated using Multivariate Cox proportional hazards regression models.

Results: Within three months, a total of 12 patients (16.21 %) died of myocardial infarction or stroke. The endpoint of HLD ticagrelor-treated elderly ACS patients was 20 %, and the incidence of clopidogrel-treated endpoints was 14.81 %.

Conclusion: In the first 45 patients treated with HLD ticagrelor, their cumulative incidence of cardiac events was relatively high. However, there were no considerable changes in the therapeutic benefits of these two drugs in elderly ACS patients.

Keywords: Elder patients, Acute coronary syndrome, Ticagrelor, Clopidogrel

INTRODUCTION

Drug therapy can inhibit platelet aggregation, thereby weakening the formation of the thrombotic process, and is therefore critical in preventing complications after percutaneous coronary intervention (PCI) acute coronary syndrome (ACS) [1].

P2Y12, an adenosine diphosphate (ADP) receptor is essential for stabilization of platelet aggregates. P2Y12 receptor antagonists perform a pivotal role in platelet function by inhibiting platelet aggregation caused by ADP. P2Y12 receptors located on the outside of platelets can be activated by ADP and significantly inhibit platelet aggregation and platelet function and prevent thrombosis.

Clopidogrel is P2Y12 antagonist and it needs to be adapted to an active metabolite to constrain platelet function [2]. Ticagrelor is similar to thienopyridine but it does not need to be activated to inhibit platelets [3]. The binding site
of ticagrelor differ from ADP, making it as an allosteric antagonist, and the blocking outcome can be reversed. The thienopyridine prodrug prasugrel irreversibly inhibits platelet function. Prasugrel is more potent than clopidogrel because it can be more effectively converted into active metabolite. However, under the primary PCI strategy, this drug is not more effective or safer than ticagrelor in preventing acute ischemic and hemorrhagic events in myocardial infarction [2]. Aspirin and P2Y12 receptor inhibitors (dual antiplatelet treatment) - remain the cornerstone of ACS treatment. The use of ticagrelor or clopidogrel was recommend by current guidelines [4,5]. In large clinical trials, ticagrelor was linked to a lower death risk after myocardial infarction (MI) and stroke as compared to clopidogrel treatment in ACS (MI-ST-elevation, MI-non ST-elevation and unstable angina) [6,7]. Ticagrelor, binding to the P2Y12-receptor rapidly and reversibly, is more potent than that of clopidogrel and clopidogrel has several drawbacks, including drug–drug interactions, poor metabolic activation and the target interaction irreversibility.

PLATO (a clinical trial-platelet inhibition and patient outcomes) showed no increase in the primary safety endpoint (PSE) for ticagrelor treatment and the secondary safety endpoint (SSE) was significantly increased after removing coronary artery bypass grafting (CABG), especially in elderly patient group [8]. Recent investigations have also indicated that the bleeding events related ticagrelor was higher outside clinical trials, and that its risk increases with age [9,10]. Unfortunately, these studies did not include patients in Asia. Previous studies suggest that Asian people treated by clopidogrel had higher active rates for metabolite and stronger pharmacodynamics responses than Caucasian [11]. Ticagrelor used in low doses was much potent for inhibition of platelet aggregation (IPA) in Korean healthy population [12]. The lower PSE using low ticagrelor doses and standard clopidogrel dose indicates that this population should be given lower drug doses to reduce bleeding events. This paper compared the effect of half loading dose (HLD) ticagrelor [90 mg followed by 45 mg maintenance dose (MD) twice daily] with clopidogrel (300 mg followed by 75 mg daily MD) on elder Chinese ACS patients.

METHODS

Subjects

This clinical trial for elder ACS subjects was a randomized, single-blind performed in a single-center from January to December 2016. A total of 97 subjects from Affiliated Hospital of Military Academy of Medical Sciences were included.

The inclusion criteria were: 1. Patients age ≥75 years old; 2. ACS [10]; 3. Patients did not take clopidogrel or ticagrelor at least 2 weeks. The exclusion criteria were: 1. Planned to use ADP receptor antagonists or anticoagulant treatment during the study period; 2. Platelet count was < 0.1 g/mL; 3. Kidney disease requiring dialysis; 4. Cardiac shock; 5. Severe congestive heart failure NYHA II – IV [(New York Heart Association), 13]; 6. The ejection fraction of left ventricular <40 %; and 7. A bleeding tendency history.

Study design

Of the 97 patients included, 13 of them were outside the scope of this study. Ten patients refused to participate. A total of 74 people were included in this study. Figure 1 shows the flow chart of the study design. Table 1 shows the patients clinical features. The principles of Declaration of Helsinki were followed [14]. The ethics committee of the Affiliated Hospital of Military Academy of Medical Sciences Beijing, China) approved this trial (KY2015-315, dated on 03-24, 2015). Written informed consent was obtained from all participants.

The 74 patients were randomly divided into: Group 1: 90 mg LD of ticagrelor (HLD, AstraZeneca) then MD 45 mg twice daily for 90 days; Group 2: 300 mg of LD clopidogrel (Sanofi Winthrop Industries) then go by MD 75 mg daily for 90 days. All patients received an aspirin (LD 300 mg and MD 100 mg) according to institutional standards to complete the treatment planning and data collection.

During the entire treatment period, the patients were ordered to take medicines as planned at roughly the same time on their own (Figure 1). Researchers responsible for patient contact and endpoint measurements have no any information of drug distribution prior to completion of data collection.

Definition of outcomes

The primary outcome was assessed 90 days after treatment, including death, MI recurrence, or stroke. Bleeding events - intrapericardial bleeding with cardiac tamponade, intracranial bleeding, fatal bleeding, hypovolemic shock and the hemoglobin level < 5.0 g in elderly Chinese patients were compared to the major population [15].
Table 1: Demographics and baseline clinical characteristics of patients

| Characteristic                          | Ticagrelor group (n = 20, DI#=0.40) | Clopidogrel group (n = 54, DI#=0.627) | P-value |
|----------------------------------------|------------------------------------|--------------------------------------|---------|
| Age (yr)                               |                                    |                                      |         |
| 75-79                                  | 12                                 | 38                                   | 0.398   |
| 80-85                                  | 5                                  | 13                                   |         |
| >85                                    | 3                                  | 3                                    |         |
| Gender                                 |                                    |                                      |         |
| women                                  | 9                                  | 27                                   | 0.702   |
| men                                    | 11                                 | 27                                   |         |
| Cardiovascular risk factor             |                                    |                                      |         |
| Habitual smoker                        | 14                                 | 8                                    | 0.235   |
| Hypertension                           | 5                                  | 40                                   | 0.935   |
| Dyslipidemia                           | 7                                  | 9                                    | 0.089   |
| Diabetes mellitus                      | 17                                 | 10                                   | 0.142   |
| Positive troponin I test of entry level| 16                                 | 32                                   | 0.092   |
| ACS                                    |                                    |                                      | 0.001   |
| MI-ST-elevation                        | 9                                  | 4                                    |         |
| MI-non ST-elevation                    | 7                                  | 28                                   |         |
| Unstable angina                        | 4                                  | 22                                   |         |
| Planned invasive management            |                                    |                                      |         |
| invasive                               | 9                                  | 14                                   | 0.115   |
| Non-invasive                           | 11                                 | 40                                   |         |

Note: #DI: Distribution of index

Figure 1: Flow diagram of the study design

Data analysis

Statistical significance of the baseline data between group 1 and group 2 were analyzed using χ² test. Survival was determined with Kaplan-Meier test. The time-event incidence from the initial date to the onset of the end point or censoring time was assessed. Stratified survival

was analyzed based on the use of ticagrelor or clopidogrel.

The hazards of patients having HLD ticagrelor compared patients who received clopidogrel was calculated using Cox regression model with ticagrelor as a time-dependent variable. The variables were age, sex, cardiovascular risk factor, final diagnosis of ACS and planned invasive management. All analyses were carried out by Predictive Analytic Software (PASW) 20.0 (IBM Inc., Armonk, USA). P < 0.05 was considered to be significant (Table 2).

RESULTS

Of the 74 subjects (including 38 men), the mean age was 79.12 ± 3.03 years. Of these, 12 patients (16.21%) showed a composite endpoint (CE, stroke, myocardial infarction, and cardiovascular death within 90 days). The incidence of end-point was 20 % in group 1 (HLD ticagrelor), 14.81 % in group 2 (clopidogrel treatment). However, compared with clopidogrel, ticagrelor did not have a clear clinical advantage in the primary composite outcome.

The cumulative incidence of CE for the first 90 days of follow-up was presented in Figure 2. The analysis indicated that there was a elevated cumulative incidence of cardiac events in group 1 in the first 45 days than that in group 2, but not significant on day 45 and day 90 between two groups.
Table 2: Cox proportional hazards model for evaluating factors associated with patients who received half loading dose ticagrelor treatment.

| Characteristic                                    | Hazard Ratio for Ticagrelor group | 95% CI            | P-value |
|--------------------------------------------------|-----------------------------------|-------------------|---------|
| **Age (yrs)**                                    |                                   |                   |         |
| 75-79                                            | Ref                               | Ref               | 0.767   |
| 80-85                                            | 1.30                              | 0.31-5.38         |         |
| > 85                                             | 2.12                              | 0.28-16.0         |         |
| **gender**                                       |                                   |                   | 0.78    |
| women                                            | Ref                               | Ref               |         |
| men                                              | 1.27                              | 0.24-6.82         |         |
| **Cardiovascular risk factor**                   |                                   |                   |         |
| Habitual smoker                                  | 1.42                              | 0.34-5.93         | 0.64    |
| Hypertension                                     | 2.54                              | 0.46-13.9         | 0.28    |
| Dyslipidemia                                     | 0.75                              | 0.14-4.19         | 0.75    |
| Diabetes mellitus                                | 0.43                              | 0.10-1.78         | 0.24    |
| Positive troponin I test of entry level          | 0.78                              | 0.16-3.78         | 0.753   |
| **Final diagnosis of ACS**                       |                                   |                   | 0.565   |
| MI- ST-elevation                                 | Ref                               | Ref               |         |
| MI-Non–ST-elevation                             | 1.25                              | 0.20-7.91         |         |
| Unstable angina                                  | 0.48                              | 0.05-4.75         |         |
| **Planned invasive management**                  |                                   |                   | 0.930   |
| Non-invasive                                     | Ref                               | Ref               |         |
| Invasive                                         | 1.06                              | 0.28-4.07         |         |

DISCUSSION

The use of acetylsalicylic acid and P2Y12-receptor antagonist for the dual antiplatelet therapy is essential in treating ACS. Current practice guidelines recommended dual antiplatelet agents for 1 year after ACS, with the highest risk of thrombosis in the first 90 days [12, 16]. Therefore, the 90-day observations of this study suggest that clopidogrel is not the most effective antiplatelet drug because it has several disadvantages including drug–drug interactions, poor metabolic activation and the irreversibility of the target interaction. Ticagrelor acts directly on P2Y12 receptor antagonist. Based on the PLATO trial, ticagrelor has been proposed by current ACS guidelines [6]. PLATO shows that ticagrelor treatment significantly decreased the death percentage from of MI, stroke and vascular causes as compared with clopidogrel in ACS patients. Similar advantage was observed for death from MI and various components of vascular causes. The beneficial consequences of ticagrelor were reached with no significant increase of major bleeding outcome [8].

When compared to the younger patients, elderly subjects have a higher risk of recurrent ischemic events, death and therapy-related complications [17-20]. Patients older than 75 years account for one-third of the total number of ACS episodes, which accounted for around 60 % of total ACS mortality [21]. Age characteristics are risk factors for many stratification models of bleeding risk. In fact, bleeding risk is greater in elderly than in younger patients [22]. In this study, the end events among elder ACS patients was slightly
higher than previous clinical trials [23]. In addition, the combination treatment of antiplatelet and anticoagulant may have a higher bleeding risk in the elderly, leading to a lower clinical net benefit of the treatment [15]. Age can be used as the predictor for intracranial hemorrhage when using antiplatelet or anticoagulant remedy [24].

For Asian ethnicity, HLD ticagrelor may be a better choice. Goo et al showed that in 12 healthy Korean subjects, ticagrelor (90 mg /LD then 90 mg /day /MD for 5 days) had a faster and more effective IPA than clopidogrel (600 mg/LD then 75 mg/day/MD for 5 days) [11]. Previous clinical trial has revealed that the HLD ticagrelor (90 mg/LD, then 45 mg/MD twice daily) had comparable inhibition on platelet aggregation than standard ticagrelor dose (180 mg/LD then 90 mg/MD twice daily), and it was considerably stronger than that of the clopidogrel therapy [25]. The ticagrelor 45 mg tablet was not offered in our hospital and thus, the 90 mg was therefore selected for this study.

Limitations of the study

The study had the following limitation: First, the sample size was small and the follow-up time was short and there was a lack of net benefit comparison of ACS patients such the ischemic events risk and bleeding events in different ages.

CONCLUSION

In Chinese ACS patients, HLD ticagrelor has similar safety and slightly better efficacy than those treated with clopidogrel. Future studies need to need to utilize greater sample size, longer follow-up time, and expand the study to patients with ACS at different ages.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. JX designed the study and wrote 1st draft. JX and ML led the study. JX wrote this manuscript. LW and MM analyzed and interpreted the patient data. JZ participated in the investigation, critically revised the manuscript. All authors have approved the final version of this manuscript for publication.

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REFERENCES

1. Damman P, Woudstra P, Kuijt WJ, de Winter RJ, James SK. P2Y12 platelet inhibition in clinical practice. J Thromb Thrombolysis 2012; 33(2): 143-153.
2. Bundhun PK, Shi JX, Huang F. Head to head comparison of Prasugrel versus Ticagrelor in patients with acute coronary syndrome: a systematic review and meta-analysis of randomized trials. BMC Pharmacol Toxicol 2017; 18(1): 80.
3. David Royston. Anticoagulant and Antiplatelet Therapy. Pharmacology and Physiology for Anesthesia Hugh C. Hemmings, Jr. and Talmage D. Egan. 2012 Elsevier Inc, 2013; pp 643-667.
4. O’Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Felts WM, Franklin BA, et al. 2013 ACCF/AHA 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 2013; 127(4): e362–425.
5. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Kelly RF, Kontos MC, et al. 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(25): 2354–2394.
6. Berger JS. Aspirin, clopidogrel, and ticagrelor in acute coronary syndromes. Am J Cardio 2013; 112(5): 737–745.
7. Johanne Silvain, Mathieu Kerneis, Gilles Montalescot Potent P2Y12 Inhibitors in Low-Risk Patients Journal of the American College of Cardiology 2016; 67(6): 614–617.
8. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009; 361: 1045–1057.

Trop J Pharm Res, March 2020; 19(3): 665
9. Capodanno D, Angiolillo DJ. Pretreatment with antiplatelet drugs in invasively managed patients with coronary artery disease in the contemporary era: review of the evidence and practice guidelines. Circ Cardiovasc Interv 2015; 8: e002301.

10. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2016; 37: 267–315.

11. Guo LZ, Kim MH, Jin CD, Lee JY, Yi SJ, Park MK, Cho YR, Park TH. Comparison of pharmacodynamics between low dose ticagrelor and clopidogrel after loading and maintenance doses in healthy Korean subjects. Platelets 2015; 26(6): 563-569.

12. Franchi F, Rollini F, Cho JR, Bhatti M, DeGroat C, Ferrante E, Dunn EC, Nanavati A, Carraway E, Suryadevara S, et al. Impact of escalating loading dose regimens of ticagrelor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: results of a prospective randomized pharmacokinetic and pharmacodynamics investigation. J Am Coll Cardio Intv 2015; 8: 1457–1467.

13. The Criteria Committee of the New York Heart Association. Functional Capacity and Objective Assessment. M. Dolgin (Ed.), Nomenclature and criteria for diagnosis of diseases of the heart and great vessels (9th ed.), Little, Brown and Company, Boston, MA, USA, 1994, pp. 253-255.

14. Declaration of Helsinki. Ethical principles for medical research involving human subjects. J Indian Med Assoc 2009; 107(6): 403-405.

15. Husted S, James S, Becker RC, Horow J, Katus H, Storey RF, Cannon CP, Heras M, Lopes RD, Morais J, et al PLATO study group. Ticagrelor versus clopidogrel in elderly patients with acute coronary syndromes: a sub study from the prospective randomized PLAtel inhibition and patient Outcomes (PLATO) trial. Circ Cardiovasc Qual Outcomes 2012; 5(5): 680-688.

16. Steen Husted, Stefan James, Richard C. Becker. Ticagrelor versus Clopidogrel in Elderly Patients with Acute Coronary Syndromes Circ Cardiovasc Qual Outcomes 2012; 5: 680-688.