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Original article

Comparison of prasugrel versus clopidogrel in Korean patients with acute myocardial infarction undergoing successful revascularization

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ABSTRACT

Background: Although there have been several reports that prasugrel can improve clinical outcomes, the efficacy and safety of prasugrel is unknown in Korean patients with acute myocardial infarction (AMI) undergoing successful revascularization.

Methods: A total of 4421 patients [637 patients were prescribed prasugrel (60/10 or 5 mg, loading/maintenance dose) and 3784 patients clopidogrel (600 or 300/75 mg)] with AMI undergoing successful revascularization were enrolled from the core clinical cohort of Korea Acute Myocardial Infarction Registry-National Institute of Health.

Results: After propensity score matching (637 pairs), there were no significant differences in baseline clinical and procedural characteristics and in-hospital medications between the two groups. The primary efficacy endpoint, defined as the composite of cardiac death, MI, stroke, or target vessel revascularization at 6 months showed no significant difference between prasugrel and clopidogrel (2.4% vs. 2.9%, $p = 0.593$). Also, no difference was observed in the composite of cardiac death, MI, or stroke during hospitalization between two groups (0.8% vs. 0.9%, $p = 0.762$). However, the incidence of in-hospital Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding was significantly higher in prasugrel compared with clopidogrel (5.3% vs. 2.7%, $p = 0.015$). In multivariate linear regression analysis, trans-femoral intervention, use of glycoprotein IIb/IIIa inhibitors, use of calcium channel blocker, and use of prasugrel were independent predictors of in-hospital TIMI major or minor bleeding [odds ratio (OR) = 6.918; 95% confidence interval (CI) = 2.453–19.510, OR = 2.577; 95% CI = 1.406–4.724, OR = 4.016; 95% CI = 1.382–11.668, OR = 2.022; 95% CI = 1.101–3.714].

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Conclusions: Our study shows that the recommended dose of prasugrel had significantly higher in-hospital bleeding complications without reducing ischemic events compared with clopidogrel. However, further large-scale, long-term, randomized clinical trials are required to accurately assess the efficacy and safety of prasgurel and to find out the optimal dose for Korean AMI patients.

Introduction

Antiplatelet therapies play a central role for patients with coronary artery disease and have been developed to prevent thrombotic events without increasing the risk of bleeding over decades [1–3]. However, once it does occur, a thrombotic event is a serious complication and leads to high mortality in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI). Especially, as is well known, acute myocardial infarction (AMI) tends to have higher incidence of ischemic events than stable coronary artery disease after stent implantation [4,5]. Therefore, recent guidelines recommend that potent antiplatelet therapy is needed to prevent ischemic events in patients with AMI [6,7].

Prasugrel, a potent antiplatelet agent, is also an inactive prodrug, and has a more rapid onset of action and more potent platelet inhibition compared with clopidogrel [8–10]. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38 subgroup patients without previous stroke or transient ischemic attack (TIA), less than 75 years old, or more than or equal 60 kg body weight showed that prasugrel reduced ischemic events compared with clopidogrel without increasing TIMI major bleeding [11].

However, there were few data about the efficacy and safety of prasugrel in Korean patients with AMI. Therefore, the aim of this study was to compare the short-term clinical outcomes between prasugrel and clopiodogrel in Korean patients with AMI undergoing successful revascularization.

Materials and methods

Study population

The Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH) is a prospective, multicenter, web-based observational cohort study to develop the prognostic and surveillance index of Korean patients with AMI from 20 centers in Korea and has been supported by a grant of Korea Centers for Disease Control and Prevention since November 2011 [12].

We consecutively selected patients with AMI (ST- or non ST-segment elevation MI) who underwent successful PCI from the database of KAMIR-NIH. The diagnosis of AMI was based on the criteria for a third universal definition of myocardial infarction. Among them, we excluded the contraindications of prasugrel, known as patients $\geq$75 years of age, with body weight $<$ 60 kg or with prior TIA or stroke. Also, we excluded the patients receiving ticagrelor, those who discontinued antiplatelet agents during hospitalization, or those who underwent in-hospital switching between clopidogrel and prasugrel. The study protocols were approved by the ethics committee at each participating center, and followed the principles of the Declaration of Helsinki. All patients provided written, informed consent for participation in the registry. Trained study coordinators at each participating institution collected the data using a standardized format. Standardized definitions of all variables were determined by the steering committee board of KAMIR-NIH.

Intervention and medications

The choice of anti-platelet agents (clopidogrel or prasugrel), emergent or early invasive treatments strategies, vascular assess, pre-dilatation or post-dilatation, type of stents, use of peri-procedural glycoprotein IIb/IIIa inhibitors, and anti-thrombotic medications were determined based on the clinical status of AMI patient according to the clinical decision of operators in each institute. Anti-platelet agents were administered to all patients prior to the intervention, with aspirin 300 mg loading dose (LD) and clopidogrel 300 or 600 mg LD or prasugrel 60 mg LD. There was no restriction on the administration of prasugrel LD to the emergency room or the catheter room. PCI was performed in a standard and conventional manner. After the intervention, the patients received aspirin 100 mg once daily indefinitely and clopiodgrel 75 mg or prasugrel 10 mg or 5 mg once daily for at least one year. The maintenance doses (MD) of prasugrel and other medical treatments were also freely determined by the physician according to the patient's condition and the standard treatment regimen for patients with AMI.

Study endpoints

The primary efficacy end-point was major adverse cardiac events (MACE), defined as the composite of cardiac death, non-fatal MI, stroke, or clinically-driven target vessel revascularization (TVR) at 6-month follow-up. The secondary efficacy end-points were all-cause death, cardiac death, non-fatal MI, stroke, and definite stent thrombosis during hospitalization and the individual components of the primary efficacy composite end-point variable. The safety end-point was the composite of TIMI major or minor bleeding during hospitalization [13]. Clinically-driven TVR was defined as revascularization performed on the treated lesion or vessel of a patient who complained of clinical symptoms such as chest pain that had increased in frequency, duration, or intensity. Stroke was defined as a medical condition where blood flow to brain was interrupted, because of either ischemia or hemorrhage. The incidence of "definite" Stent thrombosis was recorded according to the Academic Research Consortium of Circulatory System Devices Panel Meeting, an advisory committee to the US Food and Drug Administration (FDA) in 2006.

Statistical analysis

Categorical variables were expressed as frequencies and percentages and continuous variables as mean $\pm$ SD. An analysis of categorical variables was performed using chi-square test or Fisher's exact test, as appropriate, and that of continuous ones using Student's *t*-test. The risk of an event in the prasugrel group relative to the clopidogrel group is presented as odd ratios (OR) or hazard ratios (HR) with 2-sided 95% confidence intervals (CI).

To minimalize the effect of selection bias in the direct comparison between clopidogrel and prasugrel, the propensity score was estimated using a multivariable logistic regression model, in which treatment status is regressed on the observed all baseline clinical, angiographic, and procedural characteristics. Thereafter, the patients receiving clopidogrel were 1-to-1 matched

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