Journal of Cardiology 60 (2012) 7–11

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Comparison of early outcomes after primary stenting in Japanese patients with acute myocardial infarction between clopidogrel and ticlopidine in concomitant use with proton-pump inhibitor

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ARTICLE INFO

Article history:
Received 19 October 2011
Received in revised form 14 January 2012
Accepted 3 February 2012
Available online 21 March 2012

Keywords:
Proton-pump inhibitor
Thienopyridine
Acute myocardial infarction

ABSTRACT

Background: Recent studies have reported that concomitant use of clopidogrel with proton-pump inhibitors (PPIs) might decrease antiplatelet effects and increase the risk of adverse outcomes after coronary stenting. However, little is known about the difference between clopidogrel and ticlopidine in concomitant use with PPIs, especially within the Asian population.
Methods: We retrospectively analyzed 302 consecutive patients (248 males, mean age 66 ± 12 years) undergoing primary stenting for acute myocardial infarction from July 2006 to June 2010. PPIs were administered to 92% (278/302) of the patients. The patients were divided into two groups on the basis of clopidogrel (clopidogrel group, $n = 187$) or ticlopidine (ticlopidine group, $n = 91$) with PPI. Their characteristics, medications, and 30-day clinical outcomes were examined.
Results: There were no significant differences in 30-day major adverse cardiac events (cardiac death, non-fatal myocardial infarction, and definite stent thrombosis), bleeding events, and stroke between the two groups. The discontinuation of clopidogrel due to side effects was significantly less frequent than that of ticlopidine (1.1% vs 7.7%, $p = 0.003$, respectively).
Conclusion: Our findings suggest that concomitant use of clopidogrel with PPIs might be safer than ticlopidine with PPIs in patients undergoing primary stenting for acute myocardial infarction.

Introduction

Clopidogrel, an adenosine diphosphate receptor antagonist, is metabolized by P450 enzymes including cytochrome P450 2C19 (CYP2C19). It is widely prescribed to patients with acute coronary syndrome or undergoing percutaneous coronary intervention (PCI). Recent studies have suggested that proton pump inhibitors (PPIs) might reduce the antiplatelet effects of clopidogrel through inhibition of CYP2C19 [1–4]. In addition, several reports have shown that concomitant use of clopidogrel and PPIs is associated with an increased risk of adverse outcomes compared to use of clopidogrel without PPIs [3,5]. However clinical implications have not been consistent and are conflicting. The prevalence of CYP2C19 loss of function alleles has been shown to be much greater among Asians than among other populations [6], therefore potential drug interactions might be more apparent in Asian people.

On the other hand, ticlopidine, the predecessor of clopidogrel, is also related to CYP2C19 for metabolic transformation [7]. The rate of administration of ticlopidine has dramatically reduced due to its adverse side effects such as neutropenia and thrombocytopenic purpura [8]. There are few clinical reports on drug interactions between ticlopidine and PPIs, and little is known about the difference between clopidogrel and ticlopidine in concomitant use with PPIs. Therefore, the aim of this study was to compare clinical outcomes of Japanese patients with acute myocardial infarction (AMI) between clopidogrel and ticlopidine in concomitant use with PPIs.

Methods

Patients

This study included 302 consecutive patients undergoing primary percutaneous coronary intervention (PCI) for AMI from July 2006 to June 2010 at our hospital. The diagnosis of AMI (ST-elevation MI or non ST-elevation MI) was based on severe chest

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0914-5087/$ – see front matter
doi:10.1016/j.jjcc.2012.02.003

Table 1
Baseline clinical characteristics.

	Clopidogrel group (n = 187)	Ticlopidine group (n = 91)	p-Value
Age, y	66 ± 12	65 ± 13	0.23
Male, n (%)	152 (81)	74 (81)	0.99
Cardiovascular risk factors, n (%)			
Diabetes	74 (40)	39 (43)	0.6
Hypertension	121 (65)	47 (52)	0.04
Dyslipidemia	82 (44)	31 (34)	0.12
Current smoker	79 (42)	44 (48)	0.34
Hemodialysis	2 (1)	2 (2)	0.46
CKD (eGFR < 60 mL/min/1.73 m^2)	66 (35)	20 (22)	0.02
PreviousMI	14 (7)	8 (9)	0.71
PriorPCI	10 (5)	8 (9)	0.27
PriorCABG	2 (1)	1 (1)	0.98
GU/DU history, n (%)	9 (5)	10 (11)	0.06
Medications at discharge, n (%)			
Statin	174 (93)	85 (93)	0.91
ACEI/ARB	116 (62)	65 (71)	0.12
β-Blocker	93 (50)	46 (51)	0.9
Ca-antagonist	33 (18)	10 (11)	0.15
Use of aspirine, n (%)			
Aspirin	187 (100)	91 (100)	
Use of PPI, n (%)			
Lansoprazole	174 (93)	87 (96)	0.4
Others	13 (7)	4 (4)	

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; GU, gastric ulcer; DU, duodenal ulcer; ACEI, angiotension-converting enzyme inhibitor; ARB, angiotension receptor II blocker; PPI, proton-pump inhibitor.

pain at rest lasting longer than 30 min, typical electrocardiographic changes (ST-segment elevation, new left bundle branch block, or ST-segment depression), and/or elevation of creatine kinase and its isoenzyme to 2 times greater than the upper limit of normal. Patients with administration of fibrinolytic agents, cardiopulmonary arrest on arrival and without stenting were excluded from the study. All patients were treated with dual antiplatelet therapy [aspirin and thienopyridine (clopidogrel or ticlopidine)]. However, PPIs were not administered to 24 patients. Thus, a total of 278 patients were treated with primary PCI for AMI with concomitant use of thienopyridine and PPIs. The study subjects were allocated to two groups on the basis of clopidogrel with PPI (clopidogrel group, n = 187) or ticlopidine with PPI (ticlopidine group, n = 91).

Medication and PCI procedure

Patients were treated with clopidogrel 75 mg and aspirin 100 mg once daily in the clopidogrel group or ticlopidine 100 mg twice daily and aspirin 100 mg once daily in the ticlopidine group. From October 2007, clopidogrel has been available with health insurance in Japan and was basically prescribed after its introduction.

Activated clotting time was maintained over 250 s during the procedure. Coronary stent placement (bare metal stent or drug eluting stent) was at the discretion of the PCI operator.

Clinical outcomes

Complications including major adverse cardiac events (MACE) (cardiac death, non-fatal MI, and definite stent thrombosis) [9,10], bleeding events, stroke, and discontinuation of thienopyridine due to drug side effects were investigated at 30-day follow up. Non-fatal MI was defined as an event with a new elevation in serum creatine kinase and/or evolutionary ST elevation, development of new Q wave or left bundle branch block. Stroke was defined as persistent loss of neurological function developed after primary PCI and an acute lesion identified with magnetic resonance imaging. Bleeding event was divided into major bleeding or minor bleeding on the basis of thrombolysis in MI (TIMI) bleeding classification [major bleeding: intracranial hemorrhage or a > 5 g/dL decrease in hemoglobin concentration or a > 15% absolute decrease in hematocrit; minor bleeding: observed blood loss (a > 3 g/dL decrease in hemoglobin concentration or a > 10% decrease in hematocrit), no observed blood loss (a > 4 g/dL decrease in hemoglobin concentration or a > 12% decrease in hematocrit)] [11]. Deterioration of liver function was defined as elevation of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, or direct bilirubin at least twice the upper normal value.

Statistical analysis

Data are presented as mean ± SD. Categorical variables are expressed as count and percentages. Continuous data were compared by using Student's unpaired t test. Categorical data were compared by means of χ^2 test. A p-value <0.05 was considered statistically significant. All analyses were performed with the SPSS 17.0 software package (SPSS, Chicago, IL, USA).

Results

Patient characteristics

Baseline clinical characteristics in all patients are shown in Table 1. There were no significant differences in age, sex, qualifying event, coronary vessel treated, and medication between the two groups. With the exception of prevalence of hypertension and chronic kidney disease defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2, no significant differences were also observed in cardiovascular risk factors at entry into the study. The history of gastric ulcer or duodenal ulcer tended to be higher in the ticlopidine group than the clopidogrel group, but this difference was not statistically significant (p = 0.06).

Lesion and procedural characteristics are shown in Table 2. There were no significant differences in culprit lesions, frequency of intra-aortic balloon pump usage, angiographical results, or peak serum creatine kinase level between the two groups. Drug-eluting stents were implanted for most patients in both groups, and the rate was significantly higher in the ticlopidine group (p = 0.002).

Table 2
Lesion and procedural characteristics.

	Clopidogrel group ($n = 187$)	Ticlopidine group ($n = 91$)	p-Value
Lesion site, n (%)			
RCA	83 (44)	40 (44)	0.71
LAD	78 (42)	42 (46)	
LCX	15 (8)	6 (7)	
LMT	10 (5)	2 (2)	
SVG	1 (1)	1 (1)	
Multivessel disease, n (%)	110 (59)	45 (49)	0.14
TIMI grade before PCI (0/1/2/3), n	91/37/41/18	47/13/24/7	0.59
TIMI grade after PCI (0/1/2/3), n	1/1/12/173	0/0/9/82	0.57
PeakCK (IU/L)	2958 ± 2568	3189 ± 2800	0.49
IABP, n (%)	27 (14)	10 (11)	0.42
Stent type, n (%)			
DES	157 (84)	88 (97)	0.002
BMS	30 (16)	3 (3)	

RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; LMT, left main trunk; SVG, saphenous vein graft; TIMI, thrombolysis in myocardial infarction; PCI, percutaneous coronary intervention; CK, creatine kinase; IABP, intraaortic balloon pump; BMS, bare metal stent; DES, drug eluting stent.

Clinical outcomes

There were no significant differences in the occurrence of 30-day MACE, bleeding events, and stroke between the two groups (Table 3). The discontinuation of clopidogrel was significantly less frequent than that of ticlopidine (1.1% vs 7.7%, $p = 0.003$). The causes of thienopyridine discontinuation were skin disorder (rash) and deterioration of liver function. No patients developed neutropenia or thromobocytopenia. One patient had skin rash, and one patient had deterioration of liver function in the clopidogrel group. Four patients had skin rash, and three patients incurred deterioration of liver function in the ticlopidine group.

Discussion

To date, the difference between clopidogrel and ticlopidine in concomitant use with PPIs has not been clearly elucidated. We investigated early outcomes after primary PCI in Japanese patients with AMI between clopidogrel and ticlopidine in concomitant use with PPIs. Our study has produced a number of important findings. First, there were no significant differences in the occurrence of MACE, stroke, and bleeding between concomitant use of clopidogrel with PPIs and ticlopidine with PPIs in AMI patients undergoing primary coronary stenting. Second, the discontinuation of clopidogrel was significantly less frequent than that of ticlopidine in concomitant use with PPIs.

Clopidogrel combined with aspirin in patients undergoing PCI has been recommended because of its beneficial effects on reducing cardiovascular events [12–14]. It is well known that gastrointestinal hemorrhage is the most common serious bleeding complication from antiplatelet therapy [15], especially in acute coronary syndrome patients [16]. Therefore PPIs are often prescribed to avoid gastrointestinal tract bleeding while taking dual antiplatelet therapy. Recent studies, however, have suggested that PPIs might reduce the antiplatelet effects of clopidogrel through inhibition of hepatic cytochrome CYP2C19 [1,2,17–19]. In addition, concomitant use of clopidogrel and PPIs is associated with an increased risk of adverse outcomes compared with use of clopidogrel without PPIs [3,5]. In contrast, several studies have reported PPI use is not associated with an increased risk of cardiovascular events or mortality in patients with administration of clopidogrel [4,20,21]. To date, the clinical outcomes of various studies have shown conflicting results.

A large randomized trial has showed that there is no clinically relevant cardiovascular interaction between PPIs and clopidogrel whereas prophylactic use of a PPI reduces the rate of upper gastrointestinal bleeding [20]. A major limitation of the study was that 94% of the study population was white and CYP2C19 polymorphisms were not considered. The genotype of this enzyme has been classified into three groups: rapid extensive metabolizer, intermediate metabolizer, and poor metabolizer. There are genetically inter-ethnic differences in the frequencies of poor metabolizers of CYP2C19: 2.5% in the white American, 2.0% in the African American, 3.5% in the white European, 19.8% in the Chinese-Ham population, and 18.0–22.5% in the Japanese population [6]. Because of the much greater prevalence of CYP2C19 loss of function alleles among Asians compared to the other populations, the influence of drug interactions might be more apparent in Asian people. A Taiwanese population-based study has reported that the concomitant use of clopidogrel and PPIs is associated with an increased risk of rehospitalization and mortality in patients undergoing PCI [22]. In the light of CYP2C19 polymorphisms, a nationwide population study to investigate the influences of concomitant use of thienopyridine with PPI would be necessary.

On the other hand, a recent meta-analysis reported that summarized information from genetic association studies indicated that CYP2C19 had no major impact on the clinical efficacy of clopidogrel

Table 3
30-Day clinical outcomes.

	Clopidogrel group ($n = 187$) n (%)	Ticlopidine group ($n = 91$) n (%)	p-Value
MACE	9 (4.8)	6 (6.6)	0.54
Death	5	4	
Non fatal MI	4	2	
Stent thrombosis	4	2	
Stroke	2 (1.1)	3 (3.3)	0.19
Bleeding event	7 (3.7)	2 (2.1)	0.49
Major	5	2	
Minor	2	0	
Discontinuation of the drug	2 (1.1)	7 (7.7)	0.003

MACE, major adverse cardiac event; MI, myocardial infarction.

[23]. One metabolomic analysis suggests that clopidogrel is metabolized primarily by other enzymes but not by CYP2C19 [24]. There might be no racial difference relating to effect of clopidogrel.

We found that early outcomes after primary PCI in Japanese patients with AMI and concomitant use of clopidogrel and PPI were not significantly different from that of ticlopidine and PPI, and that the discontinuation of clopidogrel was significantly less frequent than that of ticlopidine. The safety and tolerability of clopidogrel has been found to be superior to that of ticlopidine. In addition, clopidogrel and ticlopidine have shown comparable efficacy with regard to cardiac events at 1-month after successful stenting [8]. Consistent with this previous finding, we showed that clopidogrel and ticlopidine in concomitant use with PPIs have equivalent effect regarding 30-day MACE in AMI patients undergoing primary stenting. With regard to stent thrombosis, the frequency in this study was about 2.1% in both groups. Compared to a large clinical trial (HORIZONS-AMI), the rate of stent thrombosis in HORIZONS-AMI trial was little different from that in this study [25]. We also demonstrated superiority of clopidogrel in safety and tolerability in concomitant use with PPIs.

Chronic kidney disease is associated with increased risk of cardiovascular events in patients with acute coronary syndrome. In patients with AMI treated with PCI, estimated creatinine clearance remains an independent predictor of short- and long-term mortality [26]. Given that the incidence of chronic kidney disease in the clopidogrel group was significantly higher compared to the ticlopidine group, this difference potentially influences the clinical outcomes. However, the occurrence of MACE was not significantly different between the two groups.

Regarding the stent type, the rate of bare-metal stent use in the clopidogrel group was higher than that in the ticlopidine group. However analysis without the patients implanted with a bare-metal stent also led to similar results.

There are several limitations to our study. First, we could not obtain sufficient data of the patients without PPIs. It would have been a better investigation if we could have analyzed 4 groups that included a control group. However PPIs are usually administered to high-risk patients such as AMI, therefore this study seems to reflect the real world. Second, because this single center study is retrospective, the study population consisted of consecutive patients and was relatively small and different in two groups. Large multicenter clinical investigations, especially in the Asian population, are required to address these issues. However, this is the first clinical outcome study in Japanese patients with AMI comparing clopidogrel with PPI and ticlopidine with PPI. It would be of benefit to accumulate data regarding these specific problems in the Asian population.

In conclusion, our findings suggest that concomitant use of clopidogrel with PPI might be safer in patients with AMI undergoing primary coronary stenting compared to that of ticlopidine with PPI.

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