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Original article

Impact of chronic kidney disease on platelet inhibition of clopidogrel and prasugrel in Japanese patients

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ABSTRACT

Background: The impact of chronic kidney disease (CKD) on the antiplatelet effect of clopidogrel and low-dose (3.75 mg) prasugrel in Japanese patients is largely unknown.
Methods: A total of 53 consecutive Japanese patients with stable coronary artery disease who received aspirin and clopidogrel were enrolled, and categorized by estimated glomerular filtration rate (eGFR): CKD group (n = 15, eGFR < 60 ml/min/1.73 m^2) and non-CKD group (n = 38, eGFR ≥ 60 ml/min/1.73 m^2). Clopidogrel was switched to 3.75 mg prasugrel. Platelet reactivity measurement using the VerifyNow P2Y12 assay (Accumetrics, San Diego, CA, USA) was performed at baseline (on clopidogrel) and day 14 (on prasugrel).
Results: The VerifyNow P2Y12 reaction units (PRU) during clopidogrel therapy was significantly higher in the CKD group than that in the non-CKD group (185.2 ± 51.1 PRU vs. 224.3 ± 57.0 PRU, p = 0.02), whereas, the PRU with the prasugrel therapy in the CKD group and non-CKD group were not significantly different (149.9 ± 51.1 PRU vs. 165.3 ± 61.8 PRU, p = 0.36). The PRU was significantly lower with the prasugrel therapy compared to that with the clopidogrel therapy both in the CKD group and in the non-CKD group.
Conclusions: Antiplatelet effect of clopidogrel but not prasugrel is attenuated in patients with CKD. Prasugrel achieves a consistently lower platelet reactivity compared with clopidogrel regardless of the presence of mild to moderate CKD.

Introduction

Patients with chronic kidney disease (CKD) account for an increasing percentage of the population undergoing percutaneous coronary intervention (PCI) [1]. Furthermore, CKD is associated with a worse prognosis in patients undergoing PCI [2–7], which is possibly due to insufficient platelet inhibition in antiplatelet therapy [8–10].

The platelet inhibition by clopidogrel varies widely and high residual platelet reactivity (HPR) after treatment with clopidogrel has been suggested to be an independent risk factor for cardiovascular events in patients undergoing stent implantation [11,12]. Prasugrel is a third-generation thienopyridine antiplatelet that achieves greater platelet inhibition with less variability between patients than does clopidogrel [13]. The dose of prasugrel in Japanese patients was determined as approximately one-third of that used in other countries, considering the higher average age, lower body weight, and increased bleeding risk compared to Western patients [14]. However, few data are available on platelet reactivity after the treatment of clopidogrel or prasugrel in the presence or absence of CKD undergoing PCI and stenting.

We, therefore, performed this analysis to investigate whether concomitant CKD affected the platelet reactivity under the treatment of clopidogrel and prasugrel in Japanese patients with coronary artery disease undergoing stent implantation.

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Materials and methods

Study design and patients

This was a post hoc analysis of a single-center, prospective study designed to compare the antiplatelet effect of changing from 75 mg clopidogrel to 3.75 mg prasugrel in Japanese patients undergoing coronary stenting (UMIN 000014528). The primary analyses of the study have been already published [15]. In brief, between July 2014 and November 2014, the study prospectively enrolled 53 patients who were between 20 and 80 years of age and treated with daily aspirin and clopidogrel for ≥14 days before or after PCI for stable coronary artery disease. The exclusion criteria were as follows: severe renal insufficiency [estimated glomerular filtration rate (eGFR) ≤ 30 ml/min/1.73 m^2]; an acute coronary syndrome event, PCI or coronary artery bypass graft surgery within the previous 4 weeks; contraindications to prasugrel; severe liver dysfunction; body weight ≤50 kg; platelet counts $\leq 10 \times 10^4$; and pregnancy. Patients were also excluded if they received other antithrombotic agents and were at high risk of bleeding.

Patients who received aspirin (100 mg daily) and clopidogrel (75 mg daily) for ≥14 days underwent a platelet function test, measuring P2Y12 reaction units (PRU) using the VerifyNow P2Y12 assay (Accumetrics, San Diego, CA, USA). Clopidogrel was then changed to 3.75 mg prasugrel (maintenance dose in Japanese patients). At day 14, the platelet function test was performed, and thereafter, direct switching from the prasugrel to 75 mg clopidogrel was performed. At day 28, patients underwent a platelet function test again. Aspirin and other medications remained unchanged throughout the study period. One patient dropped out after day 14 visit and did not receive the last (i.e. day 28) platelet function test. For purposes of the present analysis, we used 53 paired PRU measurements at study entry (on clopidogrel therapy) and at day 14 (on prasugrel maintenance therapy) of the 53 patients.

The original protocol was approved by the institutional review boards at Chiba University Hospital and the study was conducted in accordance with regulatory standards and ethical guidelines for clinical studies rooted in the Declaration of Helsinki. The data center in Chiba University Hospital collected and managed data. We sought no further ethics board review for the current analysis, because each patient provided written informed consent for the original study and the analysis was done using the anonymous data originally collected.

CYP2C19 genotyping

Genotyping of *CYP2C19*2* (rs4244285, c681G > A) and *CYP2C19*3* (rs4986893, c636G > A) was performed using GTS-7000 (Shimadzu Corp., Kyoto, Japan), with 1 μL of the rest of whole blood used for laboratory testing as described previously [15]. The use of blood samples for genotyping was approved (approval No. 511) by the Biomedical Research Ethics Committee of the Graduate School of Medicine, Chiba University, in accordance with the Ethics Guidelines for Human Genome and Gene Analyses Research in Japan.

Study endpoints

The primary purpose of this study was to investigate whether the presence of concomitant CKD impacted on antiplatelet effect of clopidogrel or prasugrel, with respect to the PRU values. We defined CKD as eGFR <60 ml/min/1.73 m^2 in this study [16].

Statistical analysis

Continuous variables are presented as mean ± SD and were compared with paired or unpaired Student's *t* test or analysis of variance (ANOVA) as appropriate. Categorical variables are presented as counts and percentages and were compared by means of the Fisher's exact test. Multivariable linear regression models were used to assess whether CKD was an independent predictor of antiplatelet effects of the drugs. PRU was used as a dependent variable, and the presence of CKD, CYP2C19 poor metabolizer (PM) genotype, and variables with a significant difference between the CKD and non-CKD group such as age, gender, body mass index and comorbidities were considered for inclusion into the model as independent variables. Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). A value of $p < 0.05$ was considered significant.

Results

Patient characteristics are presented in Table 1. The study population comprised 38 patients (72%) without and 15 patients (28%) with CKD. The mean eGFR in the CKD and non-CKD group were 79.6 ± 13.3 ml/min/1.73 m^2 and 51.5 ± 6.5 ml/min/1.73 m^2, respectively ($p < 0.001$). Patients in the CKD group were older compared to the non-CKD group. There were no patients with a history of primary kidney disease or kidney transplantation. There was no significant difference in the distribution of *CYP2C19* genotypes between the 2 groups.

The PRU values in the CKD and non-CKD group during prasugrel and clopidogrel therapy are shown in Fig. 1. During clopidogrel therapy, the PRU in the CKD group was significantly higher compared to the non-CKD group. The PRU with prasugrel was not

Table 1
Patient characteristics.

	Overall	CKD	Non-CKD	*p*-value
Age (years)	66.6 ± 9.2	70.8 ± 8.1	65.0 ± 9.1	0.04
Male	47 (89%)	14 (93%)	33 (87%)	0.66
Body mass index (kg/m^2)	24.3 ± 3.0	24.6 ± 3.1	24.2 ± 3.1	0.69
eGFR (ml/min/1.73 m^2)	71.7 ± 17.4	51.5 ± 13.4	79.6 ± 13.4	<0.001
CKD stage				
1	6 (11%)	–	6 (16%)	–
2	32 (60%)	–	32 (84%)	–
3a	13 (25%)	13 (87%)	–	–
3b	2 (4%)	2 (13%)	–	–
Proteinuria	2 (4%)	2 (13%)	0 (0%)	0.02
Coronary risk factors				
Hypertension	37 (70%)	13 (87%)	24 (63%)	0.11
Dyslipidemia	40 (75%)	12 (80%)	28 (73.7)	0.74
Diabetes	21 (40%)	6 (40%)	15 (40%)	>0.99
Current smoker	8 (15%)	1 (7%)	7 (18%)	0.42
Prior myocardial infarction	18 (34%)	2 (13%)	16 (42%)	0.06
Prior ischemic stroke	2 (4%)	0 (0%)	2 (5%)	>0.99
Prior PCI	53 (100%)	15 (100%)	38 (100%)	–
Prior CABG	2 (4%)	1 (7%)	1 (3%)	0.49
Medication				
Aspirin	53 (100%)	15 (100%)	38 (100%)	–
ACE inhibitors	15 (28%)	2 (13%)	13 (34%)	0.18
ARB	4 (8%)	9 (60%)	12 (32%)	0.07
β-Blockers	31 (58%)	8 (53%)	23 (61%)	0.76
Ca channel blockers	25 (47%)	9 (60%)	16 (42%)	0.36
Statins	48 (91%)	11 (73%)	37 (97%)	0.01
Proton pump inhibitors	39 (74%)	11 (73%)	28 (74%)	>0.99
CYP2C19 genotype				>0.99
EM	17 (32%)	5 (33%)	12 (32%)	
IM	26 (49%)	7 (47%)	19 (50%)	
PM	10 (19%)	3 (20%)	7 (18%)	

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EM, extensive metabolizer (*1/*1); IM, intermediate metabolizer (*1/*2 or *1/*3); PCI, percutaneous coronary intervention; PM, poor metabolizer (*2/*2, *2/*3 or *3/*3).

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