Clinical Trial/Experimental Study

Medicine®

OPEN

Platelet activity with hemoglobin level in patients with hemodialysis

Prospective study

Jae Min Kim, MD[a], Jin Sug Kim, MD[b], Hyung Oh Kim, MD[c], So Ra Lee, MS[c], Jae Hwan Rhew, MD[c], Jong Shin Woo, MD[c], Jang Hyun Cho, MD[a], Kyung Hwan Jeong, MD[b], Weon Kim, MD[c,*]

Abstract

Background: VerifyNow (VN; Accumetrics, San Diego, CA) P2Y12 reaction unit (PRU) has an inverse relation with hemoglobin level (Hb). Chronic kidney disease (CKD) is associated with low response to clopidogrel and low Hb. Our aim is to investigate the relation between PRU and Hb, and to assess whether Hb directly affects PRU or not in patients with CKD undergoing hemodialysis (HD).

Methods: We analyzed the relation between PRU and Hb in 43 HD patients and compared it with a control group of 127 patients with normal renal function. Both groups underwent percutaneous coronary intervention for stable coronary artery disease. We also compared PRU between the 2 groups considering Hb as a confounding factor.

Results: In the control group, Hb and PRU showed a significant inverse correlation (correlation coefficient $r = -0.340$; $P < .001$), but not in the HD group (correlation coefficient $r = -0.099$; $P = .53$). PRU was higher in the HD group than the control group after adjusting for the influence of Hb (299.2 [95% confidence interval: 278.4–316.7] vs 248.7 [95% confidence interval: 227.7–269.0]; $P < .001$), even after propensity score matching (299.2 [95% confidence interval: 278.4–316.7] vs 241.7 [95% confidence interval: 221.8–262.2]; $P < .001$).

Conclusions: PRU was higher regardless of lower Hb in CKD on HD patients than normal renal function patients. Therefore, Hb was not crucial factor to decide PRU in CKD on HD patients in this study.

Abbreviations: ACEi = angiotensin-converting enzyme inhibitor, ADP = adenosine diphosphate, ARB = angiotensin receptor blocker, BMI = body mass index, C = cholesterol, CAD = coronary artery disease, CKD = chronic kidney disease, Cr = creatinine, DM = diabetes mellitus, EPO = erythropoietin, Hb = hemoglobin, HD = hemodialysis, HDL = high-density lipoprotein, LDL = low-density lipoprotein, LOF = loss of function, LTA = light transmission aggregometry, PLT = platelets, PRU = P2Y12 reaction unit, PS = propensity score, TG = triglycerides.

Keywords: clopidogrel, hemodialysis, hemoglobin, platelet reactivity, P2Y12 reaction unit

1. Introduction

Clopidogrel has been widely prescribed to prevent major adverse cardiac events in coronary artery disease (CAD). But the response to clopidogrel has significant interindividual variation.[1,2] According to a meta-analysis, impaired platelet responsiveness to clopidogrel is associated with adverse clinical outcomes.[3]

Clopidogrel on-treatment platelet reactivity is affected by many factors such as genetic variations (CYP2C19), diabetes, female sex, smoking, and body mass index (BMI).[4] The VerifyNow (VN; Accumetrics, San Diego, CA) P2Y12 reaction unit (PRU) is an assay that measures the agglutination of fibrinogen-coated beads to stimulated platelets in citrated whole blood.[5] PRU has been used as a measure of residual platelet reactivity in patients taking P2Y12 receptor antagonists in practice. It has been reported that lower hemoglobin (Hb) or hematocrit level is associated with a higher VerifyNow PRU.[6–8] Usually, chronic kidney disease (CKD) patients are in a state of chronic anemia. There are several mechanisms; erythropoietin (EPO) deficiency, shortened red cell survival, retained inhibitors or toxic metabolites that inhibit erythropoiesis, and blood loss resulting from the qualitative platelet defect present in uremia.[9] In former study, we found that platelet responsiveness to clopidogrel is lower in patients with CKD than in patients with normal renal function.[10,11] However, there are no literature yet to confirm that Hb affects PRU in CKD on hemodialysis (HD) patients.

Editor: Salvatore De Rosa.

Data is available on request. Please contact the corresponding author.

The authors have no conflicts of interest to disclose.

[a] Division of Cardiology, Department of Internal Medicine, St. Carollo General Hospital, Suncheon-si, [b] Division of Nephrology, [c] Division of Cardiology, Department of Internal Medicine, Kyung Hee University Hospital, Kyung Hee University, Seoul, Republic of Korea.

[*] Correspondence: Weon Kim, Department of Internal Medicine, Kyung Hee University Medical Center, Kyung Hee University, 1 Hoegi-Dong, Dongdaemoon-Gu, Seoul, 130–702, Korea (e-mail: mylovekw@hanmail.net).

How to cite this article: Kim JM, Kim JS, Kim HO, Lee SR, Rhew JH, Woo JS, Cho JH, Jeong KH, Kim W. Platelet activity with hemoglobin level in patients with hemodialysis: Prospective study. Medicine 2020;99:10(e19336).

Received: 16 September 2019 / Received in final form: 28 January 2020 / Accepted: 29 January 2020

http://dx.doi.org/10.1097/MD.0000000000019336

The aim of this study was to analyze the relation between PRU and Hb level, and to assess whether Hb level directly affects PRU or not in patients with CKD undergoing HD.

2. Materials and methods

2.1. Patients

This PIANO (Effect of Platelet Inhibition According to Clopidogrel Dose in Patients with Chronic Kidney Disease)-9 CKD study is a single-center, nonrandomized, prospective analysis. Forty-three consecutive CKD patients undergoing chronic HD were enrolled as HD group, and 127 patients with normal renal function (estimated glomerular filtration rate >60 mL/min/1.73 m^2 and no proteinuria) were enrolled as the control group, from September 2009 to June 2011. Both groups underwent percutaneous coronary intervention (PCI) for stable CAD. Patients were screened for platelet reactivity if they took low-dose aspirin (100 mg/day) and clopidogrel (75 mg once daily maintenance dose) for at least 14 days as part of the standard treatment regimen. We also analyzed the relation between PRU value and Hb level in the HD group and control group. We also analyzed the relation between light transmission aggregometry (LTA) value and HD level.

The exclusion criteria were as follows: known allergy to aspirin or clopidogrel; concomitant use of other antithrombotic drugs (oral anticoagulants and dipyridamole); thrombocytopenia (platelet count <100,000/mL); liver disease (bilirubin >2 mg/dL); active bleeding or bleeding diathesis; concomitant use of a cytochrome P450 inhibitor or nonsteroidal anti-inflammatory drug; or recent treatment (<30 days) with a glycoprotein IIb/IIIa antagonist.

The study protocol was approved by the Institutional Ethics Committee, and all patients were exempted from informed consent for participation.

2.2. Platelet function measurements

Just before the HD sessions in HD patients, antecubital vein was used for each blood sample collection. The first 2 mL of blood was discarded to avoid spontaneous platelet activation, using multiple syringe sampling technique. Within 1 hour after blood draw the samples were processed.

For the HD group, 2 platelet function assays were performed. The first was LTA, and the second was the VerifyNow P2Y12 assay. The LTA of platelet-rich plasma was assessed by a turbidimetric method using a two-channel aggregometer (Chrono-Log Model 490; Chrono-Log Corp., Havertown, PA) after stimulation with 5 μmol/L adenosine diphosphate (ADP); aggregation percentages were recorded 7 minutes later. The VerifyNow P2Y12 assay estimates platelet-induced aggregation by recording increases in light transmittance; data are reported as both PRU and percentage inhibition. For the control group, the VerifyNow P2Y12 assay test was performed.

2.3. Statistical analysis

All statistical analyses were performed using SPSS for Windows version 20.0 (SPSS Inc, Chicago, IL) and R version 3.2.3. A two-sided $P < .05$ was considered significant. Continuous variables, presented as means ± standard deviations, were compared using unpaired Student t test. Categorical variables, presented as frequencies and percentages, were compared using the Chi-squared test or Fisher exact test as appropriate. For correlation analysis, Pearson correlation coefficient r was used. We used a propensity score (PS)-matched analysis to control confounding bias.[12] Many studies reported that platelet reactivity on clopidogrel is independently affected by diabetes, sex, BMI, smoking, CYP2C19 loss of function allele,[4,13] and Hb level.[7,8,14] So these variables were included on the PS. The patients were matched using pair matching (1:1 matching) and optimal matching method.

3. Results

3.1. Demographics and baseline characteristics

Baseline characteristics, risk factors of CAD, and concomitant medications of the study patients are shown in Table 1. In comparison to the control group, the HD group was younger, leaner, and showed lower Hb and cholesterol levels despite less statin use. Otherwise, there were no significant differences between the 2 groups.

3.2. Association between PRU and Hb

For all patients, there was a significant inverse correlation between PRU and Hb level ($r = -0.468$; $P < .001$) (Fig. 1A). Unstandardized regression coefficient calculated by univariate linear regression analysis was −18.2, which means that the PRU decreased by 18.2 units for every 1 mg/dL increase in Hb level. In the control group, there was also a significant inverse correlation between PRU and Hb level ($r = -0.340$; $P < .001$) (Fig. 1B). But in the HD group, PRU and Hb level showed no correlation ($r = -0.099$; $P = .53$) (Fig. 1C), and platelet aggregation value by LTA did not shown correlation ($r = 0.003$; $P = .98$) (Fig. 1D) with Hb level.

3.3. Hb-matched and PS-matched PRU

The HD group showed higher PRU (299.2 ± 67.3 vs 222.8 ± 69.0; $P < .001$) (Fig. 2A) and lower Hb level (11.2 ± 1.0 vs 13.7 ± 1.7; $P < .001$) (Fig. 2B) than the control group. Considering the significant relation between PRU and Hb, we compared the Hb-matched PRU between the 2 groups and found it to also be higher in the HD group than control group (299.2 [95% confidence interval: 278.4–316.7] vs 248.7 [95% confidence interval: 227.7–269.0]; $P < .001$) (Fig. 2C). PS-matched analysis considering diabetes, sex, BMI, smoking, CYP2C19 loss of function allele, and Hb showed higher PRU in the HD group than control group (299.2 [95% confidence interval: 278.4–316.7] vs 241.7 [95% confidence interval: 221.8–262.2]; $P < .001$) (Fig. 2D). Table 1 also shows PS-matched characteristics.

4. Discussion

4.1. PRU and Hb in HD patients

We demonstrated a significant inverse relation between PRU and Hb level in patients with normal renal function, which means that PRU increased as Hb level decreased. This finding coincides with results from previous studies.[7,8,15] We questioned that the inverse relation between PRU and Hb was similarly shown in

Table 1

Baseline demographics and clinical characteristics of the study population before and after propensity score matching.

	Total population			Propensity-matched population		
	Control (N = 127)	Hemodialysis (N = 43)	*P*	Control (N = 43)	Hemodialysis (N = 43)	*P*
Age (yrs)	65.0 ± 10.6	54.7 ± 14.4	<.001	69.5 ± 9.5	54.7 ± 14.4	<.001
*Male	79 (62.2%)	21 (48.8%)	.17	14 (32.6%)	21 (48.8%)	.19
*BMI (kg/m^2)	25.0 ± 3.3	23.4 ± 3.9	.01	24.1 ± 3.5	23.4 ± 3.9	.41
*DM	41 (32.3%)	9 (20.9%)	.22	10 (23.3%)	9 (20.9%)	>.99
Hypertension	89 (70.1%)	28 (65.1%)	.68	36 (83.7%)	28 (65.1%)	.08
Dyslipidemia	35 (27.6%)	11 (25.6%)	.96	14 (32.6%)	11 (25.6%)	.64
*Smoking	30 (23.6%)	9 (20.9%)	.88	2 (4.7%)	9 (20.9%)	.05
*CYP2C19 LOF allele	81 (63.8%)	24 (55.8%)	.46	27 (62.8%)	24 (55.8%)	.66
Laboratory findings						
*Hb (g/dL)	13.7 ± 1.7	11.2 ± 1.0	<.001	12.0 ± 1.2	11.2 ± 1.0	.01
PLT (10^3/mm^3)	240.9 ± 67.0	211.7 ± 68.8	.02	251.0 ± 80.3	211.7 ± 68.8	.02
Cr (mg/dL)	0.8 ± 0.2	10.5 ± 4.0	<.001	0.8 ± 0.3	10.5 ± 4.0	<.001
Total-C (mg/dL)	187.7 ± 42.2	145.7 ± 30.0	<.001	184.1 ± 47.7	145.7 ± 30.0	<.001
LDL-C (mg/dL)	116.1 ± 35.1	85.2 ± 27.2	<.001	113.8 ± 39.0	85.2 ± 27.2	<.001
HDL-C (mg/dL)	48.4 ± 19.1	49.2 ± 12.2	.75	47.9 ± 14.9	49.2 ± 12.2	.66
TG (mg/dL)	160.1 ± 123.9	98.6 ± 48.2	<.001	139.1 ± 72.8	98.6 ± 48.2	.01
Medications						
Beta blocker	62 (48.8%)	17 (39.5%)	.38	22 (51.2%)	17 (39.5%)	.39
ACEi or ARB	70 (55.1%)	24 (55.8%)	>.99	22 (51.2%)	24 (55.8%)	.83
CCB	43 (33.9%)	19 (44.2%)	.30	16 (37.2%)	19 (44.2%)	.66
Diuretics	12 (9.4%)	8 (18.6%)	.18	5 (11.6%)	8 (18.6%)	.55
Statin	117 (92.1%)	7 (16.3%)	<.001	39 (90.7%)	7 (16.3%)	<.001

Values are shown as mean ± standard deviation.

ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, C = cholesterol, CCB = calcium channel blockers, Cr = creatinine, DM = diabetes mellitus, Hb = hemoglobin, HDL = high-density lipoprotein, LDL = low-density lipoprotein, LOF = loss of function, PLT = platelets, TG = triglycerides.

* Variables included in the propensity score matching were diabetes, sex, BMI, smoking, CYP2C19 loss of function allele, and hemoglobin.

patients of impaired renal function. Pendyala et al[16] suggested that the PRU level was clearly influenced by a patient's baseline hematocrit, and there were inverse relation between them. Interestingly, 17% of CKD patients were included in their study. So, we newly assessed the relation of Hb and PRU in the CKD on HD patients. However, there was no inverse relation in the HD group by 2 different platelet activity measurement methods, VerifyNow P2Y12 assay and LTA.

4.2. Platelet activity in HD patients

Our data supported several previous studies that CKD patients had significantly higher PRU than patients with normal renal function.[18–21] Guo et al[21] suggested that renal impairment is associated with higher PRU and elevated major adverse cardiovascular events risks. Breet et al.[22] presented that CKD patients with higher PRU were associated high risk of cardiovascular events. Despite this significant implication of higher PRU in CKD patients, the mechanism or cause of the higher PRU has not been elucidated so far. We assumed that the lower Hb level could affect higher PRU in CKD patients, so we compared PRU after Hb level adjustment by PS-matching between 2 different renal function groups to offset the effect of lower Hb in CKD on HD patients. In addition, we also adjusted for other confounding factors such as sex, BMI, smoking, diabetes, and CYP2C19 loss of function allele as well as Hb, which could affect the PRU result.[4,15] Nevertheless, PRU was still higher in CKD on HD patients than normal renal function. Finally, our results implicated that not only the Hb level but other confounding factors mentioned above were not crucial factors for high PRU in CKD on HD patients.

4.3. Concept of enhanced platelet activity in HD patients

The CKD increases the risk of adverse cardiovascular outcomes after PCI.[21,23,24] The investigation about the reasons of enhanced platelet activity in HD patients could contribute to improve post-PCI cardiovascular outcomes. We already know that platelet responsiveness to clopidogrel is lower in patients with CKD than in patients with normal renal function.[10,11] Morel et al[25] summarize the putative mechanisms involved in impaired P2Y12 inhibition by thienopyridines in CKD as complex metabolism including hepatic conversion and intestinal absorption of clopidogrel that can be altered in uremia and accumulation of dinucleoside polyphosphates that act as partial agonists of the P2Y12 receptor, enhancing platelet turnover. Moreover, Stohlawetz el al[26] reported EPO that was routinely injected in CKD patients markedly enhances endothelial activation and platelet reactivity.

4.4. Emerging biomarkers for platelet activity

Recently, microRNAs, small noncoding RNAs that regulate gene expression, have been emerged as potential biomarkers for cardiovascular disease.[27,28] MicroRNAs also play a key role in atherosclerosis and platelet activation acting on not only intracellularly, but also extracellularly.[29–31] The blood level of specific circulating microRNAs correlate with platelet reactivity.[30] Further studies considering the role of microRNAs

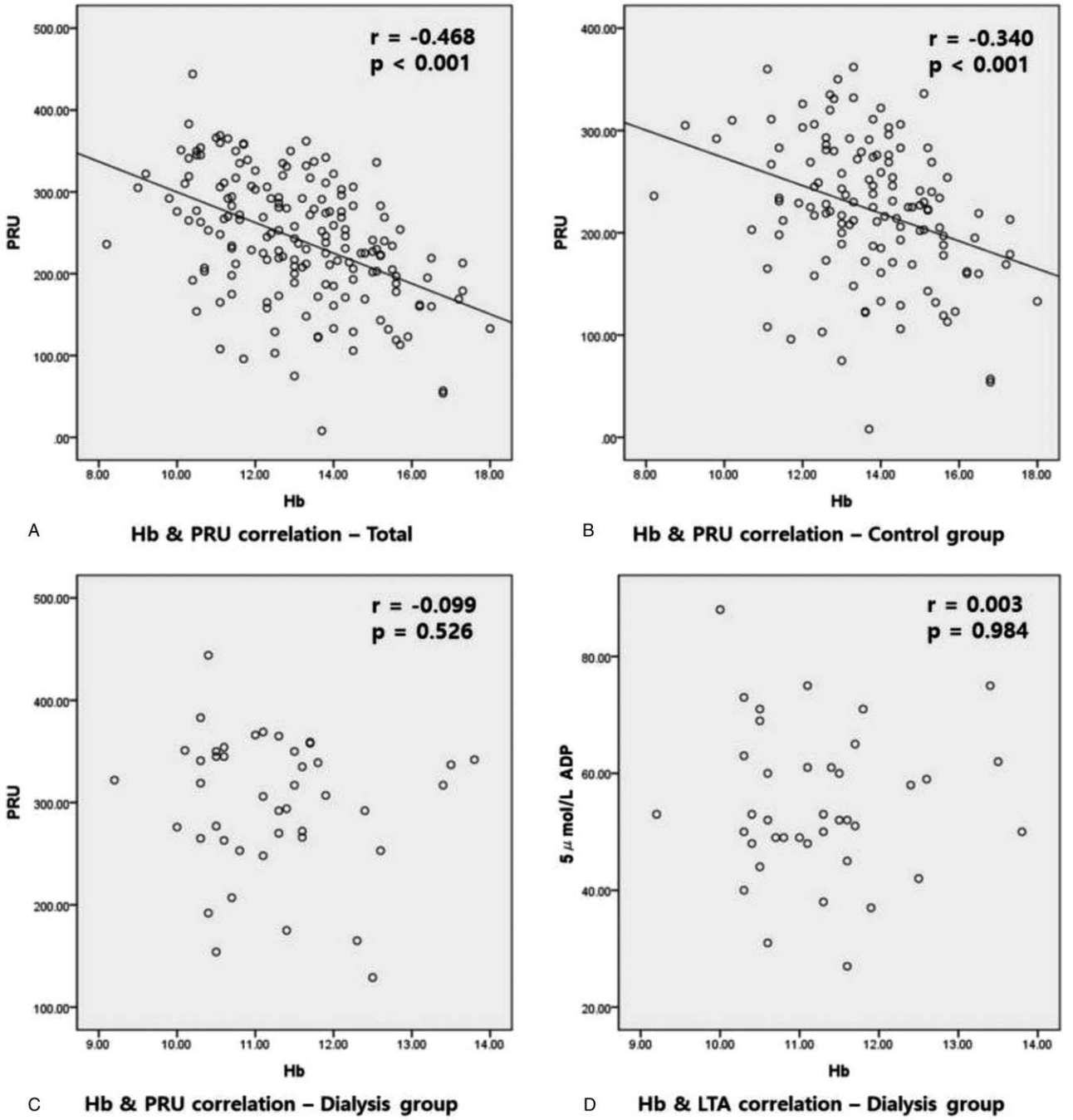

Figure 1. Relation among VerifyNow P2Y12 reaction unit (PRU), light transmission aggregometry (LTA) value, and hemoglobin (Hb) level. (A) Relation between PRU and Hb level in total patients. (B) Relation between PRU and Hb in the normal renal function group. (C) Relation between PRU and Hb in the hemodialysis group. (D) LTA value after stimulation with 5 μmol/L ADP. ADP = adenosine diphosphate, Hb = hemoglobin, LTA = light transmission aggregometry, PRU = P2Y12 reaction unit.

as platelet activity marker can elucidate the enhanced platelet activity in CKD patients.

4.5. Study strength and limitation

This was the first study to assess the relation between PRU and Hb level in patients with CKD undergoing HD. Previous articles excluded renal insufficiency, did not mention about renal function, or enrolled only a small proportion (17%) of CKD patients.[7,8,16,17] Furthermore, we newly found that PRU showed still higher level in CKD patients in spite of the PS matching with Hb and other confounding factors.

On the other hand, there are several limitations in our study. First, this study consisted of small number of patients in a single center with nonrandomized nature. Second, our study group contains only HD patients. Third, we could not confirm the key mechanism that affects PRU in HD patients. Further studies are

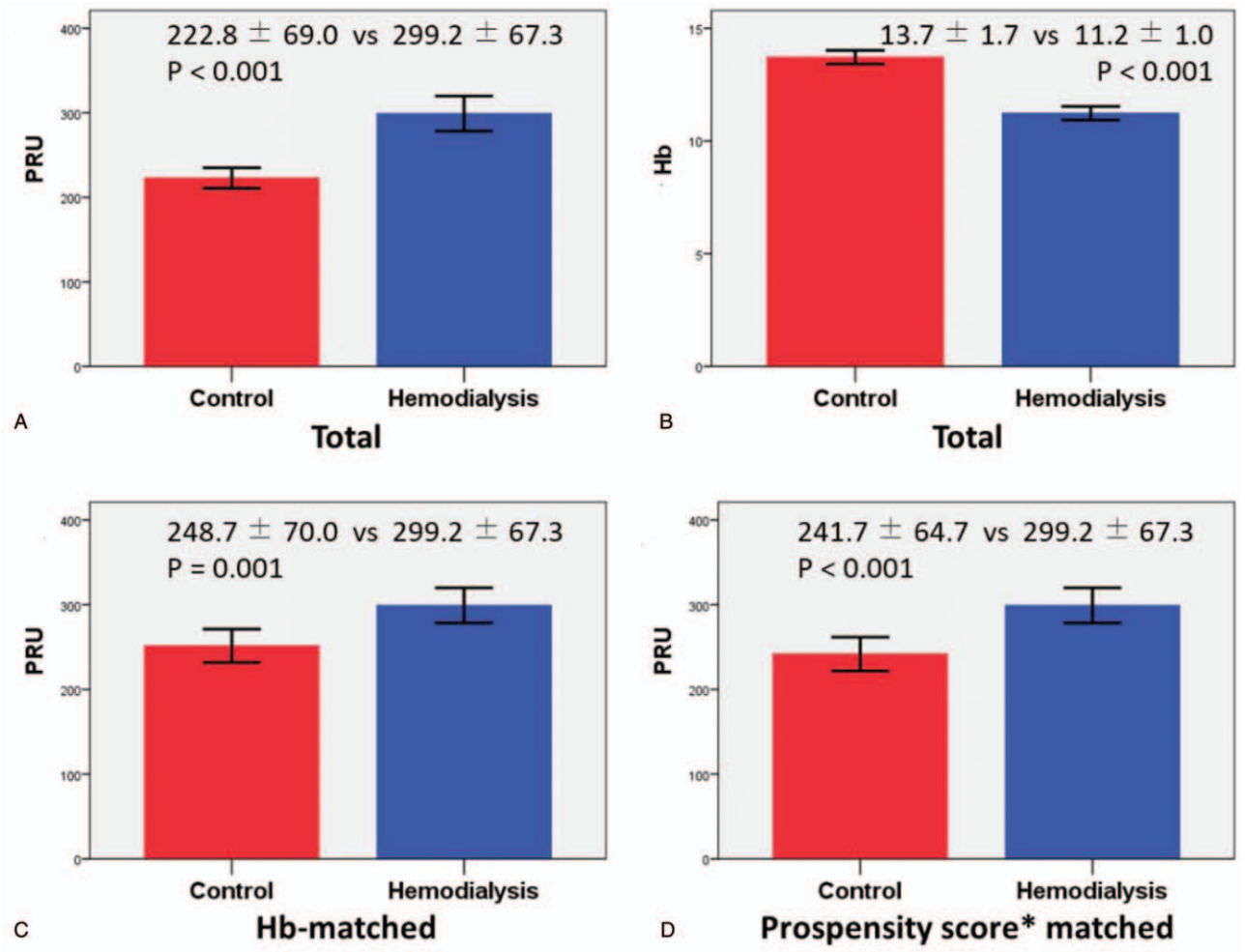

Figure 2. VerifyNow P2Y12 reaction unit (PRU) and hemoglobin (Hb) comparisons between the 2 groups, unadjusted, after propensity score matching. (A) Higher PRU in the hemodialysis group. (B) Lower level of Hb in the hemodialysis group. (C) Higher PRU in the hemodialysis group after Hb matching. (D) Higher PRU in the hemodialysis group after propensity score* matching for sex, BMI, smoking, diabetes, CYP2C19 loss of function allele, and hemoglobin level. Hb = hemoglobin, PRU = P2Y12 reaction unit.

necessary to reveal the cause of enhanced platelet reactivity in CKD on HD.

5. Conclusion

In conclusion, PRU showed higher level regardless of lower Hb in CKD on HD patients than normal renal function patients. Therefore, Hb was not crucial factor to decide PRU in CKD on HD patients in this study.

Author contributions

Conceptualization: Jae Min Kim, Jin Sug Kim, Jong Shin Woo, Weon Kim.
Data curation: Jae Min Kim, Jin Sug Kim, Hyung Oh Kim, Jong Shin Woo, So Ra Lee.
Formal analysis: Jae Min Kim, Hyung Oh Kim, Jong Shin Woo, Weon Kim.
Investigation: Jae Min Kim, Hyung Oh Kim, Jong Shin Woo, Weon Kim.
Methodology: Jae Min Kim, Weon Kim, Jae Hwan Rhew, Jang Hyun Cho, Kyung Hwan Jeong.
Project adminstration: Jae Min Kim, Jong Shin Woo, Weon Kim.
Supervision: Weon Kim, Jae Hwan Rhew, Jang Hyun Cho, Kyung Hwan Jeong.
Writing – original draft: Jae Min Kim, Jin Sug Kim, Jong Shin Woo, Weon Kim.
Writing – review & editing: Jae Min Kim, Jin Sug Kim, Jong Shin Woo, Weon Kim.
Weon Kim orcid: 0000-0003-1264-9870.

References

[1] Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. J Am Coll Cardiol 2007;49:1505–16.
[2] Serebruany VL, Steinhubl SR, Berger PB, et al. Variability in platelet responsiveness to clopidogrel among 544 individuals. J Am Coll Cardiol 2005;45:246–51.
[3] Aradi D, Kirtane A, Bonello L, et al. Bleeding and stent thrombosis on P2Y12-inhibitors: collaborative analysis on the role of platelet reactivity

for risk stratification after percutaneous coronary intervention. Eur Heart J 2015;36:1762–71.
[4] Park KW, Kim HS. Options to overcome clopidogrel response variability. Circ J 2012;76:287–92.
[5] Paniccia R, Antonucci E, Maggini N, et al. Comparison of methods for monitoring residual platelet reactivity after clopidogrel by point-of-care tests on whole blood in high-risk patients. Thromb Haemost 2010;104:287–92.
[6] Voisin S, Bongard V, Tidjane MA, et al. Are P2Y12 reaction unit (PRU) and % inhibition index equivalent for the expression of P2Y12 inhibition by the VerifyNow assay? Role of haematocrit and haemoglobin levels. Thromb Haemost 2011;106:227–9.
[7] Kim YG, Suh JW, Park JJ, et al. Different influences of hematocrit on the results of two Point-Of-Care platelet function tests, the VerifyNow assay and multiple electrode platelet aggregometry. PLoS One 2014;9: e114053.
[8] Kakouros N, Kickler TS, Laws KM, Rade JJ. Hematocrit alters VerifyNow P2Y12 assay results independently of intrinsic platelet reactivity and clopidogrel responsiveness. J Thromb Haemost 2013;11:1814–22.
[9] Eschbach JW. The anemia of chronic renal failure: pathophysiology and the effects of recombinant erythropoietin. Kidney Int 1989;35:134–48.
[10] Woo JS, Kim W, Lee SR, et al. Platelet reactivity in patients with chronic kidney disease receiving adjunctive cilostazol compared with a high-maintenance dose of clopidogrel: results of the effect of platelet inhibition according to clopidogrel dose in patients with chronic kidney disease (PIANO-2 CKD) randomized study. Am Heart J 2011;162:1018–25.
[11] Park SH, Kim W, Park CS, et al. A comparison of clopidogrel responsiveness in patients with versus without chronic renal failure. Am J Cardiol 2009;104:1292–5.
[12] Jin HY, Yang TH, Kim DI, et al. High post-clopidogrel platelet reactivity assessed by a point-of-care assay predicts long-term clinical outcomes in patients with ST-segment elevation myocardial infarction who underwent primary coronary stenting. Int J Cardiol 2013;167:1877–81.
[13] Lee JH, Ahn SG, Park B, et al. A pharmacodynamic study of the optimal P2Y12 inhibitor regimen for East Asian patients with acute coronary syndrome. Korean J Intern Med 2015;30:620–8.
[14] Stuart EA, King G, Imai K, et al. MatchIt: nonparametric preprocessing for parametric causal inference. J Stat Software 2011;42:
[15] Park KW, Park JJ, Jeon KH, et al. Clinical predictors of high posttreatment platelet reactivity to clopidogrel in Koreans. Cardiovasc Ther 2012;30:5–11.
[16] Pendyala LK, Loh JP, Lhermusier T, et al. Does baseline hematocrit influence the assays of on-treatment platelet reactivity to clopidogrel? Am Heart J 2014;168:545–51.
[17] Kim YG, Suh JW, Kang SH, et al. Cigarette smoking does not enhance clopidogrel responsiveness after adjusting VerifyNow P2Y12 reaction unit for the influence of hemoglobin level. JACC Cardiovasc Interv 2016;9:1680–90.
[18] Morel O, El Ghannudi S, Jesel L, et al. Cardiovascular mortality in chronic kidney disease patients undergoing percutaneous coronary intervention is mainly related to impaired P2Y12 inhibition by clopidogrel. J Am Coll Cardiol 2011;57:399–408.
[19] Gremmel T, Muller M, Steiner S, et al. Chronic kidney disease is associated with increased platelet activation and poor response to antiplatelet therapy. Nephrol Dial Transplant 2013;28:2116–22.
[20] Nishi T, Ariyoshi N, Nakayama T, et al. Impact of chronic kidney disease on platelet inhibition of clopidogrel and prasugrel in Japanese patients. J Cardiol 2017;69:752–5.
[21] Guo LZ, Kim MH, Shim CH, et al. Impact of renal impairment on platelet reactivity and clinical outcomes during chronic dual antiplatelet therapy following coronary stenting. Eur Heart J Cardiovasc Pharmacother 2016;2:145–51.
[22] Breet NJ, de Jong C, Bos WJ, et al. The impact of renal function on platelet reactivity and clinical outcome in patients undergoing percutaneous coronary intervention with stenting. Thromb Haemost 2014;112:1174–81.
[23] Best PJ, Lennon R, Ting HH, et al. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. J Am Coll Cardiol 2002;39:1113–9.
[24] Latif F, Kleiman NS, Cohen DJ, et al. In-hospital and 1-year outcomes among percutaneous coronary intervention patients with chronic kidney disease in the era of drug-eluting stents: a report from the EVENT (Evaluation of Drug Eluting Stents and Ischemic Events) registry. JACC Cardiovasc Interv 2009;2:37–45.
[25] Morel O, Muller C, Jesel L, et al. Impaired platelet P2Y12 inhibition by thienopyridines in chronic kidney disease: mechanisms, clinical relevance and pharmacological options. Nephrol Dial Transplant 2013;28:1994–2002.
[26] Stohlawetz PJ, Dzirlo L, Hergovich N, et al. Effects of erythropoietin on platelet reactivity and thrombopoiesis in humans. Blood 2000;95:2983–9.
[27] De Rosa S, Curcio A, Indolfi C. Emerging role of microRNAs in cardiovascular diseases. Circ J 2014;78:567–75.
[28] Pordzik J, Pisarz K, De Rosa S, et al. The potential role of platelet-related microRNAs in the development of cardiovascular events in high-risk populations, including diabetic patients: a review. Front Endocrinol (Lausanne) 2018;9:74.
[29] Sorrentino S, Iaconetti C, De Rosa S, et al. Hindlimb ischemia impairs endothelial recovery and increases neointimal proliferation in the carotid artery. Sci Rep 2018;8:761.
[30] Carino A, De Rosa S, Sorrentino S, et al. Modulation of circulating microRNAs levels during the switch from clopidogrel to ticagrelor. Biomed Res Int 2016;2016:3968206.
[31] Willeit P, Zampetaki A, Dudek K, et al. Circulating microRNAs as novel biomarkers for platelet activation. Circ Res 2013;112:595–600.