Relation of Preprocedural Hemoglobin Level to Outcomes After Percutaneous Coronary Intervention

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Adverse effects have been reported in patients with preprocedural anemia after percutaneous coronary intervention (PCI), but data regarding the relation between elevated hemoglobin (Hb) level and post-PCI prognosis remain limited. This study assessed the impact of elevated Hb on major adverse cardiac and cerebrovascular event (MACCE) at 12 months, a composite of all-cause mortality, nonfatal myocardial infarction, and ischemic stroke after PCI. We pooled patient-level data from four Korean multicenter drug-eluting stent registries from 2010 to 2016. In total, 5,107 patients were divided into 5 categories according to the baseline Hb level (<10, 10 to 12.9, 13 to 14.9, 15 to 16.9 and ≥17 g/dl). Patients with higher Hb levels were significantly younger, predominantly male, current smokers with higher body mass index, and more frequent dyslipidemia. Hypertension, diabetes, chronic kidney disease, and cerebrovascular accident were more prevalent in lower Hb groups. Categorically, a U-shaped curvilinear relation was observed between baseline Hb and clinical outcomes showing significantly higher MACCE rate in <10g/dl (hazard ratio [HR], 4.62 [2.81 to 7.68]) and ≥17 g/dl (HR, 4.06 [1.57 to 10.5]) groups compared with the reference group (13 to 14.9 g/dl), especially in men. In nonanemic patients (Hb ≥13 g/dl), adjusted HRs of MACCE, mortality, and stroke were significantly higher in ≥17 g/dl group than in the reference group. Furthermore, ≥17 g/dl was an independent predictor for MACCE and all-cause mortality after PCI. In conclusion, not only low Hb but also elevated Hb of ≥17 g/dl was significantly associated with higher MACCE rates and all-cause mortality after PCI. An appropriate treatment strategy for patients with high Hb level should be identified through future studies. **(Am J Cardiol 2019;124:1319−1326)**

Previous studies have shown that a low baseline hemoglobin (Hb) level is related to a greater risk of adverse clinical outcomes after percutaneous coronary intervention (PCI).[1−4] Although the relation between Hb and post-PCI outcomes has been shown to be not linear,[3,5] data regarding the precise relation is scarce, and the significance of a high Hb level on post-PCI outcomes is unclear. Although hematocrit or Hb level is not regarded as a traditional cardiovascular risk factor, a high hematocrit is related to increased blood viscosity leading to endothelial injury and rupture of vulnerable plaques through the increase of shear forces.[6,7] Additionally, a high hematocrit may directly promote acute thrombus formation, and an increased risk of thromboembolic events exists in patients with polycythemia.[8] Therefore, we sought to assess whether patients with poorly controlled polycythemia are at a greater risk of adverse outcomes after PCI.

Materials

Our data was derived from 4 different Korean multicenter drug-eluting stent (DES) registries which have been summarized previously.[9] The detailed information about each registry and participating institutes is supplied in Supplementary Data. These registries included patients who needed DES implantation without specific inclusion or exclusion criteria, reflecting real-world treatment practices and outcomes in Korean post-PCI patients. Among 5,712 patients who were enrolled in the Korean DES registries, 308 patients with missing data on basic information and 111 patients who were lost to follow-up before 12 months were excluded from the present analysis. And 186 patients who were not treated with a new-generation DES were excluded to minimize bias regarding stent generation.

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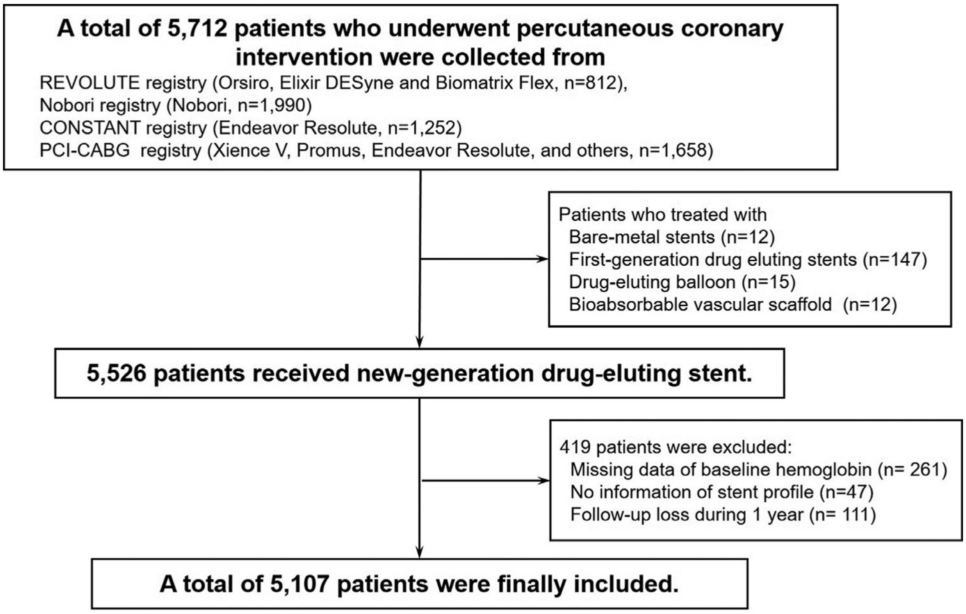

Figure 1. Study flow. CONSTANT = clinical, optical coherence tomography, and angiographic outcomes following Resolute zotarolimus-eluting stent implantation for patients with or without diabetes mellitus; PCI-CABG registry = clinical outcomes of percutaneous coronary intervention versus coronary artery bypass graft for multivessel disease; REVOLUTE = registry to evaluate clinical outcomes following new-generation drug-eluting stents.

Finally, 5,107 consecutive patients who underwent PCI and completed the 1-year follow-up were examined in this study (Figure 1). The enrolled patients were categorized into 5 groups according to the baseline Hb level (<10, 10 to 12.9, 13 to 14.9, 15 to 16.9, and ≥17 g/dl) that could easily be contrasted with anemia in routine clinical practice. The study protocol was approved by the institutional review board at each participating site, and all participants provided written informed consent.

The primary end point was the occurrence of major adverse cardiac and cerebrovascular events (MACCE) at 12 months, a composite of all-cause mortality, nonfatal myocardial infarction (MI), and ischemic stroke. The secondary end point was all-cause mortality at 12 months. Clinical events were defined according to the Academic Research Consortium.[10] Stent thrombosis was defined as definite or probable stent thrombosis.[10] Clinical outcomes were assessed 1-year post-PCI, either through a visit to the clinic or a telephone interview.

Loading and maintenance dose of anticoagulation or antiplatelets during and after procedure were followed usual guideline. Details of the intervention, such as lesion predilation, poststent dilation, and the application of mechanical support or concomitant medication, were left to the discretion of the operator. Chronic kidney disease (CKD) was defined as a baseline estimated glomerular filtration rate of <60 ml/min/1.73 m^2. Severe calcification was defined as calcification involving both sides of the arterial wall that was noted without cardiac motion before contrast injection.

Data are reported as mean ± standard deviation for continuous variables and as number and percentage for categorical variables. Baseline characteristics in the groups were analyzed using one-way analysis of variance or Mann-Whitney *U* test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables. Kaplan-Meier survival analysis using the log-rank test was used to compare the cumulative incidence of MACCE and all-cause mortality in the groups. Hazard ratios (HR) for the primary end point and for all end points were calculated through multivariable analyses using a Cox proportional hazards model. The Hb category (13 to 14.9 g/dl) with the highest number of patients that included the average baseline Hb in the total cohort was defined as the reference group for these analyses. Multivariable logistic regression analysis was performed to determine predictors for the occurrence of MACCE. Statistical comparisons were performed using SPSS, version 23.0 (IBM Corp., Armonk, New York). All tests were 2-sided, and p <0.05 was considered statistically significant.

Results

The distribution of baseline Hb levels (mean, 13.4 ± 2.0 [3.6 to 19.8] g/dl) in the subjects is shown in supplemental Figure 1. Baseline characteristics of the patients according to baseline Hb levels are summarized in Table 1. Compared with patients with lower Hb level, patients with higher Hb levels were younger, predominantly male, and current smokers with a higher body mass index. The rate of co-morbidities, including hypertension, diabetes, CKD, and cerebrovascular accidents was significantly higher in patients with lower Hb levels, whereas dyslipidemia tended to be more frequent in those with higher Hb levels. At clinical presentation, acute coronary syndrome, especially ST-elevation MI was more frequent in patients with higher Hb levels. The proportion of decreased ejection fraction (EF) below 40% was higher in patients with Hb level of <10 and ≥17 g/dl than in the other groups, representing an inverse J-shape pattern. Angiographic findings showed that the prevalence of multivessel disease and severe calcification were significantly higher with decrease in Hb level. Conversely, a thrombus

Table 1
Baseline characteristics according to baseline hemoglobin level

Variables	Hemoglobin (g/dl) at baseline					p Value
	<10 (n = 295)	10 to 12.9 (n = 1,599)	13 to 14.9 (n = 2,051)	15 to 16.9 (n = 1,055)	≥17 (n = 107)	
Age (years)	69.1 ± 10.1	69.7 ± 9.6	64.5 ± 10.6	58.7 ± 10.8	54.3 ± 11.4	<0.001
Men	162 (54.9%)	777 (48.6%)	1,570 (76.5%)	1,008 (95.5%)	107 (100%)	<0.001
Body mass index (kg/m^2)	23.6 ± 3.6	24.0 ± 3.5	24.6 ± 3.0	25.2 ± 3.0	25.9 ± 3.3	<0.001
Hypertension	228 (77.8%)	1,136 (71.4%)	1,293 (63.4%)	581 (55.5%)	56 (52.3%)	<0.001
Diabetes mellitus	186 (63.3%)	710 (44.6%)	720 (35.2%)	301 (28.8%)	26 (24.3%)	<0.001
Dyslipidemia	186 (63.3%)	1,098 (68.8%)	1,427 (70.0%)	766 (73.2%)	76 (71.0%)	0.020
Current smoker	41 (13.9%)	210 (13.4%)	549 (27.4%)	410 (39.5%)	59 (56.7%)	<0.001
Previous smoker	58 (19.7%)	282 (18.0%)	468 (23.4%)	267 (25.7%)	21 (20.2%)	<0.001
Smoking status (pack-years)	37.7 ± 25.0	35.7 ± 23.3	34.6 ± 21.3	32.9 ± 21.8	28.3 ± 13.7	0.109
Chronic kidney disease	128 (43.5%)	179 (11.3%)	52 (2.6%)	9 (0.9%)	3 (2.8%)	<0.001
Chronic obstructive lung disease	13 (4.4%)	42 (2.6%)	46 (2.3%)	16 (1.5%)	2 (1.9%)	0.052
Previous PCI	56 (19.0%)	337 (21.1%)	418 (20.4%)	221 (21.0%)	15 (14.0%)	0.447
Previous MI	26 (8.8%)	118 (7.4%)	147 (7.2%)	84 (8.0%)	5 (4.7%)	0.630
Previous bypass surgery	10 (3.4%)	43 (2.7%)	35 (1.7%)	16 (1.5%)	2 (1.9%)	0.076
Previous CVA	46 (15.6%)	205 (12.9%)	209 (10.3%)	59 (5.7%)	7 (6.5%)	<0.001
Clinical presentation						
Stable coronary artery disease	131 (44.4%)	856 (53.8%)	1,041 (51.0%)	435 (41.4%)	33 (31.1%)	<0.001
Acute coronary syndrome	164 (55.6%)	735 (46.2%)	1,002 (49.0%)	615 (58.6%)	73 (68.9%)	<0.001
Unstable angina pectoris	70 (23.7%)	422 (26.5%)	572 (28.0%)	283 (27.0%)	17 (16.0%)	0.055
NSTEMI	80 (27.1%)	200 (12.6%)	230 (11.3%)	129 (12.3%)	21 (19.8%)	<0.001
STEMI	14 (4.7%)	113 (7.1%)	200 (9.8%)	203 (19.8%)	35 (33.0%)	<0.001
Cardiogenic shock	3 (1.0%)	13 (0.8%)	8 (0.4%)	4 (0.4%)	1 (0.9%)	0.301
Laboratory data						
White blood cell count (K/mm^3)	7.97 ± 3.70	7.57 ± 3.08	7.88 ± 2.89	8.74 ± 3.27	9.81 ± 3.29	<0.001
Platelet count (K/mm^3)	229.9 ± 108.5	240.5 ± 82.1	237.2 ± 68.3	233.3 ± 66.0	223.7 ± 51.1	0.017
Low-density lipoprotein cholesterol (mg/dl)	81.7 ± 36.0	90.4 ± 33.9	98.7 ± 35.3	106.8 ± 35.9	113.4 ± 43.4	<0.001
High-density lipoprotein cholesterol (mg/dl)	36.4 ± 11.0	41.1 ± 10.9	42.3 ± 11.1	41.9 ± 10.0	40.5 ± 9.1	<0.001
Serum Creatinine (mg/dl)	3.6 ± 3.3	1.6 ± 3.0	1.1 ± 2.1	1.1 ± 3.3	1.0 ± 0.3	<0.001
C-reactive protein (mg/l)	18.5 ± 40.5	10.1 ± 29.2	4.6 ± 12.0	4.6 ± 18.7	10.4 ± 29.5	<0.001
Ejection fraction (%)	49.1 ± 16.2	55.4 ± 18.3	55.9 ± 17.8	55.0 ± 17.1	53.0 ± 15.6	<0.001
Ejection fraction <40%	62 (23.8%)	177 (12.9%)	156 (9.0%)	77 (8.5%)	14 (14.4%)	<0.001
Medication at discharge						
Statins	240 (81.9%)	1,370 (86.2%)	1,846 (90.2%)	970 (92.1%)	99 (93.4%)	<0.001
Beta blockers	170 (67.7%)	803 (65.0%)	1,021 (65.0%)	574 (65.5%)	68 (71.6%)	0.667
Angiotensin converting enzyme or angiotensin receptor blockers	152 (65.5%)	730 (61.6%)	945 (62.9%)	539 (65.3%)	76 (83.5%)	0.001
Clopidogrel	287 (97.2%)	1,570 (98.2%)	2,016 (98.3%)	1,034 (98.0%)	104 (97.2%)	0.963
Ticagrelor	4 (1.4%)	27 (1.7%)	35 (1.7%)	21 (2.0%)	2 (1.9%)	0.868
Antiplatelet agents at 12 months						
Dual antiplatelet therapy	111 (58.7%)	554 (56.4%)	720 (56.7%)	401 (56.5%)	40 (52.6%)	0.930
Aspirin	244 (82.7%)	1,332 (83.3%)	1,719 (83.8%)	894 (84.7%)	88 (82.2%)	0.867
Clopidogrel	185 (62.7%)	352 (63.5%)	1,302 (63.5%)	666 (63.1%)	64 (59.7%)	0.889
Ticagrelor	2 (0.7%)	11 (0.7%)	14 (0.7%)	11 (1.0%)	2 (0.2%)	0.868

Data are presented as mean ± standard deviation or number (%).

CVA = cerebrovascular accident; MI = myocardial infarction; NSTEMI = non-ST elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST elevation myocardial infarction.

was more frequently observed angiographically with increasing Hb level (Table 2).

At 12 months, unadjusted risks of the primary and secondary outcomes were significantly different in Hb groups with a similar pattern. The incidence of MACCE and all-cause mortality gradually decreased with increasing Hb level (from <10 to 16.9 g/dl), but steeply increased at a level of ≥17.0 g/dl (Figure 2). Adjusted HRs for MACCE and its individual components according to baseline Hb level are shown in Figure 3. The risks of MACCE were lowest in patients with Hb levels of 13 to 14.9 g/dl and significantly increased in those with Hb below 13 g/dl and in the Hb ≥17 g/dl group showing a "U-shape" curve. A consistent pattern was observed in all-cause mortality and cardiac mortality according to Hb groups. The risks of nonfatal MI and ischemic stroke tended to increase in the Hb <10 and ≥17 g/dl groups than in the reference group but did not reach statistical significance. In the subgroup analyses, similar trend was observed in men, but not in women (supplemental Figure 2).

Additionally, we assessed the effect of high Hb level on clinical outcomes in patients without anemia (Hb of

Table 2
Angiographic and procedure characteristics according to baseline hemoglobin level

Variables	Hemoglobin (g/dl) at baseline					p Value
	<10 (n = 295)	10 to 12.9 (n = 1,599)	13 to 14.9 (n = 2,051)	15 to 16.9 (n = 1,055)	≥17 (n = 107)	
Angiographic characteristics						
Multivessel coronary disease	209 (71.1%)	1,157 (72.8%)	1,358 (66.7%)	655 (62.6%)	63 (60.6%)	<0.001
Left main lesions	21 (7.1%)	155 (9.7%)	200 (9.8%)	88 (8.3%)	9 (8.4%)	0.441
Severe calcification	57 (19.3%)	172 (10.8%)	138 (6.7%)	53 (5.0%)	3 (2.8%)	<0.001
Bifurcation	52 (18.3%)	334 (21.9%)	413 (21.0%)	214 (21.0%)	24 (23.1%)	0.711
Thrombus	10 (5.2%)	83 (7.9%)	144 (10.3%)	133 (18.2%)	25 (34.7%)	<0.001
Procedure characteristics						
Vascular access						<0.001
Radial approach	40 (22.6%)	374 (36.8%)	541 (42.4%)	320 (49.0%)	30 (43.5%)	
Femoral approach	136 (76.8%)	642 (63.1%)	732 (57.4%)	332 (50.8%)	38 (55.1%)	
Procedure success	292 (99.3%)	1,581 (99.2%)	2,028 (99.4%)	1,046 (99.6%)	106 (99.1%)	0.795
Number of coronary arteries treated						0.480
1	228 (77.3%)	1,195 (74.7%)	1,514 (73.8%)	806 (76.4%)	81 (75.7%)	
2 or 3	67 (22.7%)	404 (25.3%)	537 (26.2%)	249 (23.6%)	26 (24.3%)	
Total number of stents implanted	1.5 ± 0.7	1.5 ± 0.6	1.5 ± 0.7	1.4 ± 0.6	1.4 ± 0.6	0.305
Multiple stenting	113 (38.3%)	626 (39.1%)	797 (38.9%)	378 (35.8%)	39 (36.4%)	0.458
Total stent length (mm)	35.0 ± 19.6	33.8 ± 18.1	33.3 ± 18.2	31.7 ± 17.2	32.0 ± 17.8	0.013
Mean stent diameter (mm)	3.1 ± 0.8	3.1 ± 0.8	3.1 ± 0.4	3.1 ± 0.4	3.1 ± 0.4	0.202
Intra-aortic balloon pump	1 (0.6%)	23 (2.3%)	31 (2.5%)	13 (2.0%)	4 (6.0%)	0.146

Data are presented as mean ± standard deviation or number (%).

≥13 g/dl), and the results are reported in Table 3. When patients with a baseline Hb of 13 to 14.9 g/dl were considered as the reference group, HRs of MACCE, cardiac mortality, stent thrombosis and ischemic stroke tended to gradually increase with increasing Hb level, and patients with Hb ≥17 g/dl had significantly higher rates of MACCE, ischemic stroke, all-cause mortality, and cardiac mortality. Regarding nonfatal MI, a trend toward an increasing HR in the Hb ≥17 g/dl group was observed but without statistical significance. The observed relation trend between Hb level and clinical outcomes was unchanged in subgroup analyses of both patients with MI and those with non-MI (supplemental Table 1).

Multivariable Cox regression analysis after adjustment for confounding factors showed that Hb ≥17 g/dl was significantly associated with a higher incidence of MACCE in the

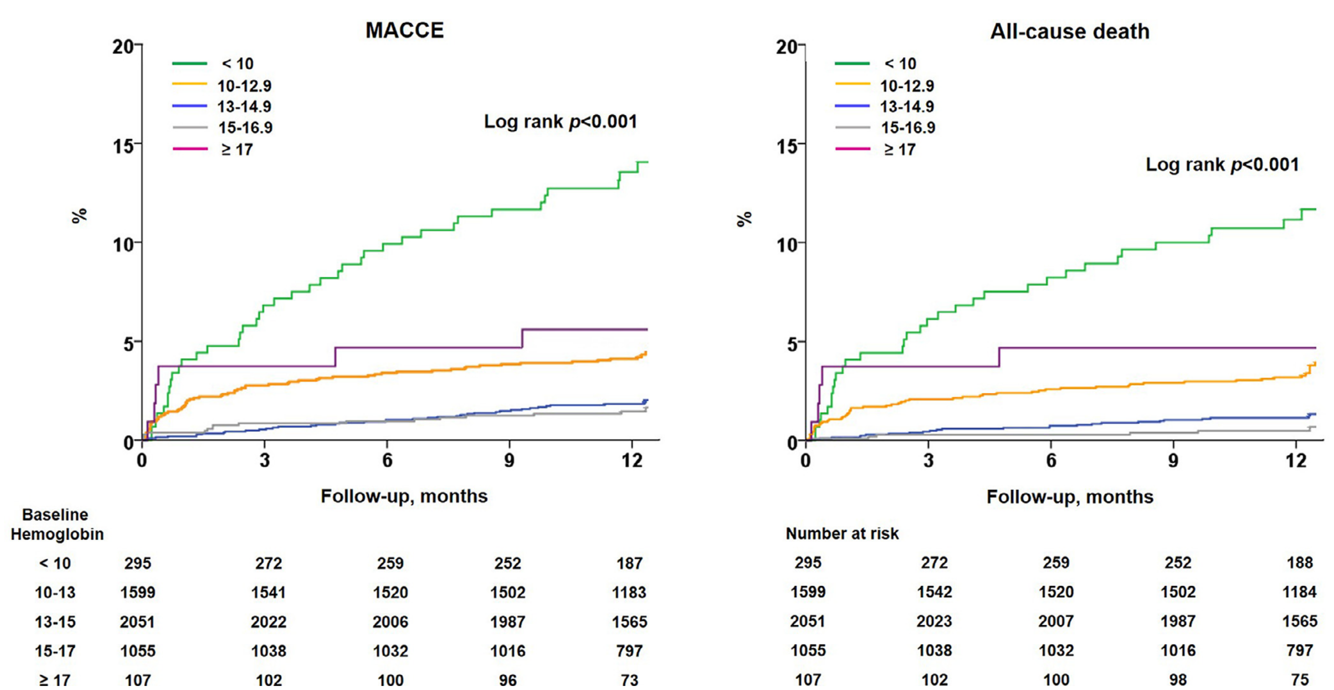

Figure 2. Kaplan-Meier curves of 12-month MACCE and mortality according to baseline hemoglobin groups. MACCE = major adverse cardiac and cerebrovascular event(s).

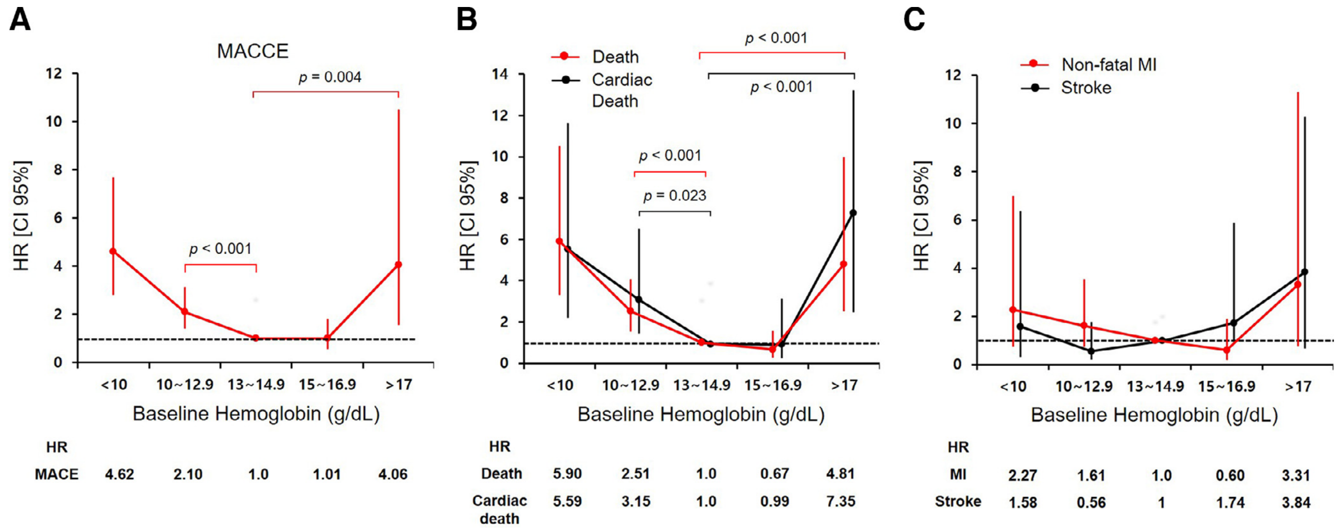

Figure 3. Multivariable adjusted risk of (*A*) MACCE, (*B*) all-cause mortality and cardiac mortality, and (*C*) nonfatal MI and ischemic stroke. Hemoglobin level of 13 to 14.9 g/dl is used as a reference. Model adjusted for age, sex, body mass index, hypertension, diabetes, dyslipidemia, chronic kidney disease, current smoking status, previous cerebrovascular accident, acute coronary syndrome, and multivessel disease. CI = confidence interval; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular event(s); MI = myocardial infarction.

cohort (Table 4). Other important predictors for MACCE included age, Hb <10 g/dl, hypertension, CKD, and EF <40%. Concerning all-cause mortality, Hb ≥17 g/dl remained a significant independent predictor along with age, low body mass index, Hb <10 g/dl, hypertension, CKD, and EF <40%.

Discussion

In this analysis of real-world Korean DES registries, we found for the first time a relation between an elevated Hb level of more than 17 g/dl, and adverse clinical outcomes

Table 3
Clinical outcomes for 12 months after PCI according to baseline hemoglobin in patients without anemia (hemoglobin of ≥13 g/dl)

	No. of events	Event rate (%)	Age- and sex-adjusted		Multivariable-adjusted*	
			HR (95% CI)	p Value	HR (95% CI)	p Value
MACCE						
13-14.9	42	2.0	Reference		Reference	
15-16.9	18	1.7	1.11 (0.61-2.02)	0.728	1.25 (0.65-2.40)	0.496
≥17	8	7.5	4.88 (1.87-12.77)	0.001	4.36 (1.26-15.10)	0.020
All-cause mortality						
13-14.9	27	1.3	Reference		Reference	
15-16.9	7	0.7	0.65 (0.27-1.57)	0.335	0.86 (0.34-2.18)	0.745
≥17	5	4.7	7.73 (2.85-20.99)	<0.001	7.56 (2.04-27.98)	0.002
Cardiac mortality						
13-14.9	10	0.5	Reference		Reference	
15-16.9	4	0.4	0.84 (0.23-2.99)	0.782	1.14 (0.29-4.48)	0.854
≥17	4	3.7	15.15 (4.45-51.58)	<0.001	17.54 (3.97-57.55)	<0.001
Nonfatal MI						
13-14.9	14	0.7	Reference		Reference	
15-16.9	5	0.5	0.65 (0.19-2.28)	0.504	0.33 (0.04-2.16)	0.216
≥17	2	1.9	5.56 (1.16-26.54)	0.031	3.18 (0.37-27.21)	0.291
Stent thrombosis						
13-14.9	1	0	Reference		Reference	
15-16.9	3	0.3	5.85 (0.61-56.25)	0.126	4.78 (0.39-58.48)	0.221
≥17	3	2.8	57.75 (6.01-555.20)	<0.001	33.27 (2.34-472.96)	0.010
Ischemic stroke						
13-14.9	8	0.4	Reference		Reference	
15-16.9	7	0.7	2.79 (0.95-8.23)	0.063	4.23 (1.29-13.91)	0.018
≥17	1	0.9	5.83 (0.67-50.26)	0.109	13.08 (1.27-77.74)	0.031

Event rates were calculated by Kaplan-Meier analysis.

CI = confidence interval; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular event; MI = myocardial infarction; PCI = percutaneous coronary intervention

* Adjusted for age, sex, body mass index, hypertension, diabetes, dyslipidemia, current smoking, chronic kidney disease, previous cerebrovascular accident, acute coronary syndrome, left ventricular systolic dysfunction, and multivessel disease.

Table 4
Predictors for 12-month MACCE and all-cause mortality after PCI

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
MACCE predictors				
Age per 1 year	1.06 (1.04-1.08)	<0.001	1.05 (1.03-1.07)	<0.001
Male	1.20 (0.86-1.67)	0.281	1.34 (0.86-2.07)	0.195
Body mass index per 1 kg/m^2	0.90 (0.86-0.94)	<0.001	0.95 (0.90-1.01)	0.121
Hemoglobin <10 g/dl	4.96 (3.497.04)	<0.001	3.00 (1.78-5.06)	<0.001
Hemoglobin ≥17 g/dl	1.78 (0.95-3.35)	0.079	2.98 (1.02-9.72)	0.041
Hypertension	1.62 (1.16-2.26)	0.005	1.85 (1.12-3.05)	0.016
Diabetes	1.92 (1.44-2.56)	<0.001	1.06 (0.70-1.60)	0.601
Dyslipidemia	0.76 (0.56-1.02)	0.068	1.06 (0.70-1.60)	0.774
Chronic kidney disease	4.14 (2.94-5.82)	<0.001	1.72 (1.02-2.89)	0.041
Previous CVA	2.27 (1.59-3.24)	0.001	1.37 (0.84-2.22)	0.208
Current smoking	1.19 (0.93-1.57)	0.096	1.11 (0.75-1.63)	0.609
LVEF <40%	3.74 (2.68-5.20)	<0.001	3.27 (2.15-4.96)	<0.001
Acute coronary syndrome	1.71 (1.27-2.31)	<0.001	1.30 (0.88-1.92)	0.192
Multivessel disease	1.55 (1.10-2.18)	0.012	1.28 (0.81-2.03)	0.292
LDL level (mg/dl)	1.00 (1.00-1.01)	0.001	1.00 (0.99-1.00)	0.172
Mortality predictors				
Age per 1year	1.08 (1.06-1.10)	<0.001	1.06 (1.03-1.08)	<0.001
Male	1.20 (0.82-1.78)	0.352	1.38 (0.83-2.30)	0.217
Body mass index per 1 kg/m^2	0.87 (0.82-0.92)	<0.001	0.92 (0.86-0.99)	0.030
Hemoglobin <10 g/dl	5.83 (3.94-8.65)	<0.001	3.35 (1.86-6.04)	<0.001
Hemoglobin ≥17 g/dl	1.92 (0.96-4.69)	0.053	4.59 (1.37-15.37)	0.014
Hypertension	1.45 (0.99-2.12)	0.059	1.76 (1.00-3.10)	0.049
Diabetes	2.03 (1.45-2.87)	<0.001	1.13 (0.71-1.78)	0.607
Dyslipidemia	0.64 (0.45-0.90)	0.011	0.90 (0.57-1.44)	0.670
Chronic kidney disease	4.17 (2.79-6.24)	<0.001	1.90 (1.06-3.42)	0.032
Previous CVA	2.01 (1.30-3.10)	0.002	1.30 (0.74-2.30)	0.365
LVEF <40%	4.26 (2.91-6.23)	<0.001	3.69 (2.30-5.90)	<0.001
Acute coronary syndrome	1.95 (1.37-2.79)	<0.001	1.40 (0.88-2.22)	0.156
Multivessel disease	1.42 (0.96-2.11)	0.081	1.11 (0.66-1.86)	0.687
LDL level (mg/dl)	0.99 (0.99-1.00)	0.014	1.00 (0.99-1.00)	0.577

CI = confidence interval; CVA = cerebrovascular accident; HR = hazard ratio; LDL = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; MACCE = major adverse cardiac and cerebrovascular event; PCI = percutaneous coronary intervention.

after PCI. After adjustments for confounding factors, a strong U-shape relation between baseline Hb and adverse events was revealed and patients with both low Hb and increased Hb were at a higher risk of MACCE and mortality. When we performed sensitivity analyses after excluding patients with anemia (Hb level of <13 g/dl), patients with Hb ≥17 g/dl experienced significantly more frequent MACCE, all-cause mortality, cardiac mortality, and ischemic stroke than those in the reference group (Hb of 13 to 14.9 g/dl). Furthermore, Hb level of ≥17 g/dl was an independent predictor of MACCE and all-cause mortality at 12 months.

Although it is widely recognized that preprocedural anemia is associated with poor outcomes after PCI in patients with various forms of ischemic heart disease,[2,3,11] relation between polycythemia and adverse outcomes after PCI has not previously been reported. Several observational studies indicated that a high hematocrit level might increase the risk of MI, stroke, and cardiovascular mortality in a general healthy population.[12−14] Some studies reported that frequent blood loss through voluntary blood donations reduced the risk of MI in middle-aged men.[15] Recently, data from a Japanese registry showed a reverse J-shaped relation between baseline Hb level and adverse in-hospital outcomes after PCI showing a trend of an increased risk in patients with elevated Hb levels.[5] They divided patients into 5 groups according to 2-g/dl increments in their Hb levels (from <10 to >16 g/dl) but did not showed statistically significant increase in risk in patients with Hb above 16 g/dl. In our cohort, we observed that Hb level of more than 17 g/dl was more predictive of poor PCI outcomes than was Hb level of ≥16 g/dl.

Interestingly, our data show that patients with anemia and those with polycythemia (Hb ≥17 g/dl) have different risk factors. Patients with anemia were more likely to be women, older, and have diabetes, CKD, cerebrovascular accident, and severe calcification on a stenotic lesion, whereas, those with elevated Hb of ≥17 g/dl tended to be male, younger, smokers with lower high-density lipoprotein cholesterol, higher low-density lipoprotein cholesterol (LDL-C), elevated white blood cell count and c-reactive protein, more frequent ST-elevation MI, and thrombi (supplemental Figure 2.). These observations indicated that polycythemia might be linked with impaired lipid metabolism, inflammatory reaction, and plaque rupture.

There are some possible mechanistic explanations of these observations. Experimental studies have shown that whole blood viscosity increases almost exponentially with increasing hematocrit when the hematocrit is greater than 50%, especially in a low-shear rate condition as in a microcirculation by increasing microvascular resistance.[16] Furthermore, polycythemia reduces the oxygen delivery index (calculated as the ratio of hematocrit to whole blood viscosity), causing tissue level hypoxia.[16,17] Hyperviscosity may also lead to direct endothelial injury and trigger the rupture of vulnerable plaques by elevating endothelial shear stress. Some coronary imaging studies have reported that the plaque rupture site is frequently located at the proximal shoulder of the plaque where the wall shear stress is focally elevated.[18] In contrast, at the distal shoulder of the plaque where the blood flow is slow and turbulent, both low shear stress and increased blood viscosity can promote endothelial cell proliferation, monocyte recruitment, platelet aggregation, and subsequent thrombus formation.[19] Consistent with these findings, the prevalence of ST-elevation MI and angiographical thrombus was progressively higher with increasing Hb categories in this study. Moreover, polycythemia can be related with excess total body iron which plays a role in oxidative damage to LDL-C. The accumulation of oxidized lipids induces endothelial cell damages, and inflammatory cell attraction, and consequently promotes the progression of atherosclerosis.[20] Our data show that patients with polycythemia tended to be younger and are related with lower high-density lipoprotein cholesterol, higher LDL-C, and elevated inflammatory marker compared with those with normal Hb level. Although we did not measure ferritin or transferrin saturation, our data suggest that adverse lipid metabolism, inflammation, and oxidative stress in patients with polycythemia might be attributed to excess stored body iron. So, we represented possible suggestive mechanisms of polycythemia to MACCE after PCI in supplemental Figure 3.

Our findings indicate that patients with polycythemia seem to need different strategies after PCI. Currently, therapeutic phlebotomy is recommended in all polycythemia vera patients to reduce the risk of thrombosis. Several previous studies have reported the cardiovascular protective effect of phlebotomy or isovolemic hemodilution in high-risk patients with coronary and peripheral artery diseases.[21−24] Phlebotomy or hemodilution resulting in improved blood viscosity and red cell aggregation, reduction of ferritin and oxidative stress could have a positive effect on clinical outcomes.[24,25] Although conflicting results exist,[26] a stratified and tailored approach, including controlled phlebotomy in patients with polycythemia may be warranted to improve prognosis after PCI.

Our study has several limitations. First, because this study involved prospective registry-based analyses, detailed date regarding etiologies of anemia or polycythemia, the cause of noncardiac death, bleeding events, and information concerning transfusion were lacking. Second, as our findings were based on a single measurement of preprocedural Hb level, fluctuations in Hb before and after PCI, or during the duration of follow-up, which could have affected clinical outcomes, were not evaluated. Third, the effect of centers which can influence the post-PCI outcomes was not indicated. Lastly, our focus on patients with particularly high Hb more than 17 g/dl involved relatively small number of our cohort.

In conclusion, an elevated Hb level of more than 17 g/dl is independently associated with unfavorable 1-year clinical outcomes after PCI. Therefore, initial assessment of Hb level is crucial and combined polycythemia should be considered as a risk factor of future ischemic events in patients undergoing PCI. Various preventative strategies to reduce adverse outcomes in these patients should be established in the future.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.07.056.

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