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Long-Term Safety and Efficacy of Prolonged Dual Antiplatelet Therapy according to Baseline Anemia after Percutaneous Coronary Intervention

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Purpose: We aimed to evaluate the outcomes of prolonged dual antiplatelet therapy (DAPT) depending on baseline anemia after percutaneous coronary intervention (PCI).
Materials and Methods: Among the 1470 study participants, 448 (30.5%) were classified as having baseline anemia. We categorized the study population according to baseline anemia and DAPT duration: ≤12-month (m) DAPT (n=226) vs. >12-m DAPT (n=222) in anemic patients, and ≤12-m DAPT (n=521) vs. >12-m DAPT (n=501) in non-anemic patients.
Results: During a follow-up of 80.8 (interquartile range 60.6–97.1) months, anemic patients showed a higher incidence of major adverse cardiovascular and cerebrovascular events (MACCEs) (26.9% vs. 17.1%, $p<0.001$) and major bleeding (9.8% vs. 5.1%, $p=0.006$). Among the non-anemic patients, prolonged DAPT was associated with a reduced rate of MACCEs [inverse probability of treatment weighting (IPTW) adjusted hazard ratio (HR), 0.78; 95% confidence interval (CI), 0.63–0.96; $p=0.019$] without an increase in major bleeding (IPTW adjusted HR, 1.12; 95% CI, 0.75–1.68; $p=0.574$). However, prolonged DAPT was not related to the incidence of MACCEs (IPTW adjusted HR, 1.11; 95% CI, 0.88–1.39; $p=0.387$), with increased major bleeding (IPTW adjusted HR, 2.01; 95% CI, 1.32–3.06; $p=0.001$) among anemic patients.
Conclusion: Although extended DAPT led to a reduction in MACCEs in non-anemic patients, it was related to increased major bleeding without reducing MACCEs in anemic patients.

Key Words: Anemia, dual antiplatelet therapy, percutaneous coronary intervention, treatment outcome

INTRODUCTION

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is mandatory for patients with coronary artery disease (CAD) after percutaneous coronary intervention (PCI). Although DAPT effectively reduces the thrombotic risk in the early period after PCI, the bleeding risk exceeds the ischemic risk with prolonged DAPT. Therefore, the optimal duration of DAPT, with a balance between ischemic benefits and bleeding risk, is debated. The DAPT study demonstrated that prolonged DAPT was associated with a reduced rate of major adverse cardiovascular and cerebrovascular events (MACCEs) and stent thrombosis.[1] In real-world practice, prolonged DAPT also reduced ischemic events, such as non-fatal myocardial infarction (MI), target lesion revascularization (TLR), and stent thrombosis.[2] Furthermore, several reports have suggested that prolonged DAPT has ischemic benefits, especially for high-risk patients

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receiving complex PCI.[3,4] Based on these findings, prolonged DAPT is frequently prescribed considering the patients' ischemic risk and procedure complexity. Anemia is a frequent condition that occurs in approximately 10%–20% of patients with CAD requiring PCI.[5,6] Baseline anemia is a well-known risk factor for future adverse clinical outcomes after PCI, including both bleeding and ischemic events.[7,8] Some observational data have shown that lesion complexity is more common in anemic patients.[9] However, anemia is an obstacle for prolonged DAPT, considering the increased risk of bleeding. There are limited data on the outcomes of prolonged DAPT depending on baseline anemia after PCI. Therefore, we aimed to evaluate the long-term safety and efficacy of prolonged DAPT depending on baseline anemia after PCI.

MATERIALS AND METHODS

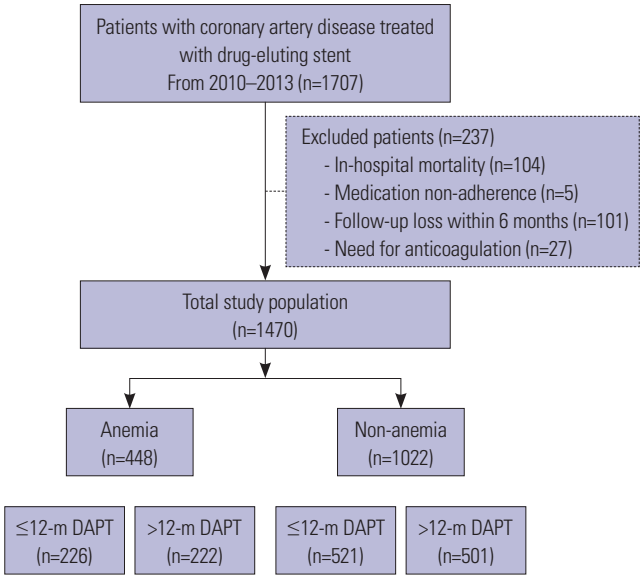
Study population and design

We analyzed the clinical and procedural data of 1707 patients with CAD who received PCI, from the medical database of the Yeungnam University Medical Center PCI registry from January 2010 to December 2013. After excluding patients with in-hospital mortality (n=104), those with non-adherence to DAPT (n=5), those who were lost to follow-up within 6 months (n=101), and those who required anticoagulation immediately after PCI (n=27), a total of 1470 patients were included in the final analysis. We categorized the study population into the following four groups according to baseline anemia before the procedure and DAPT duration after PCI: anemia and ≤12-m DAPT (n=226), anemia and >12-m DAPT (n=222), non-anemia and ≤12-m DAPT (n=521), and non-anemia and >12-m DAPT (n=501). According to the criteria of the World Health Organization (WHO), anemia is defined as a hemoglobin concentration of <13 g/dL for male and <12 g/dL for female.[10] Fig. 1A outlines the study population selection process.

All patients underwent laboratory examination, including a measurement of the hemoglobin level before PCI. Data regarding the baseline medical history, medications, angiographic findings, revascularization procedure, and clinical outcomes were collected from the patients' electronic medical records. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The Institutional Review Board at our institute approved this study (IRB No. 2019-09-077-001) and waived the requirement for patient informed consent due to the retrospective nature of the study.

Procedure and clinical follow-up

All study patients received at least 100 mg of aspirin and a total of 300 mg of clopidogrel as a loading dose before PCI, followed by a maintenance dose of 75 mg of clopidogrel. For patients presenting with acute coronary syndrome, ticagrelor was administered at a loading dose of 180 mg, followed by a dose of 90 mg twice daily according to the current guidelines.[11,12] Whether to maintain clopidogrel or ticagrelor was based on the physician's discretion. Angioplasty was performed based on angiographic findings of ≥70% or ≥50% diameter stenosis on coronary angiography with evidence of myocardial ischemia, such as a positive stress test or functional significance using fractional flow reserve. An intra-arterial bolus of 5000 IU of heparin was administered after the placement of the sheath, and additional heparin was injected to maintain an activated clotting time of >250 s. PCI procedures were performed using the current conventional technique. Briefly, after pre-dilation with a plain balloon, drug-



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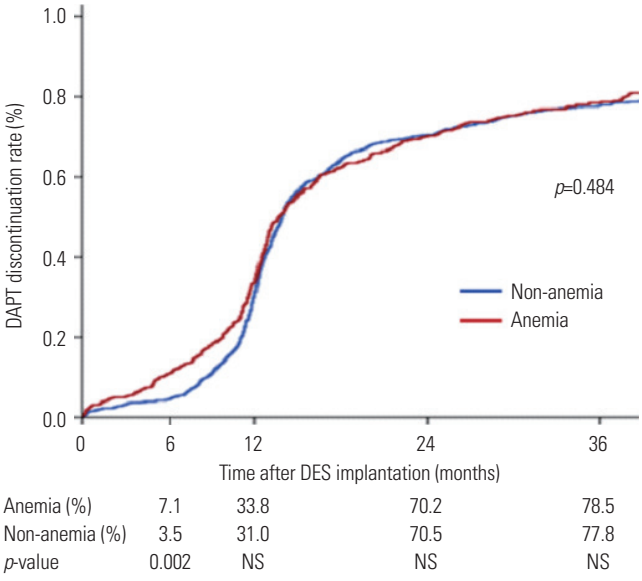

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Fig. 1. Study population. (A) Study population selection process. (B) DAPT continuation rate between patients with and without anemia. DAPT, dual antiplatelet therapy; DES, drug-eluting stent.

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eluting stent (DES) implantation was performed together with adjuvant dilation with a noncompliant balloon if significant residual stenosis was noted. The type of DES was decided based on the attending physicians' discretion. After successful intervention, DAPT with a combination of aspirin and a P2Y12 inhibitor was maintained for at least 6 months in patients with stable angina and 12 months in patients with acute coronary syndrome. All study participants received cardiovascular medications, including beta-blockers, renin-angiotensin system antagonists, and lipid-lowering drugs, unless indicated otherwise. The DAPT duration of individual patients was decided by each physician based on ischemic or bleeding risk. All patients were followed up within 1 month of the procedure and every 3–6 months thereafter. Follow-up coronary angiography was conducted if clinically indicated.

Study objectives and definitions

The objectives of our study were as follows: 1) to evaluate the long-term effects of baseline anemia after PCI and the best cut-off value of hemoglobin to predict adverse clinical outcomes, and 2) to investigate the long-term safety and efficacy of prolonged DAPT according to baseline anemia. The lesion morphology classification was determined according to the American College of Cardiology and American Heart Association (ACC/AHA) lesion classification.[13] Multivessel disease was defined as the presence of >70% luminal diameter stenosis in two or more major epicardial arteries. We also defined complex PCI related with high risk of ischemic events based on the previously published reports.[2-4] Complex PCI was defined as a procedure with at least one of the following angiographic characteristics: three-vessel disease, chronic total occlusion, total stent length ≥60 mm, or bifurcation stenting with two stents. For patients with multiple target lesions, complex PCI was decided based on more severely affected vessels. We calculated the DAPT score and the Predicting Bleeding Complication in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) score using an online calculator (DAPT score: http://tools.acc.org/DAPTriskapp/#!/content/calculator/; PRECISE-DAPT score: http://www.precisedaptscore.com/predapt/).[14,15]

Study endpoints

The primary endpoint of the study was MACCEs, a composite of cardiac death, non-fatal MI, repeat target vessel revascularization (TVR), and stroke.[16] Deaths with no other explanation were considered cardiac deaths. MI was defined according to the third universal definition of MI.[17] TVR was defined as any repeat PCI of the target vessel or bypass surgery of the target vessel performed for restenosis or other complications of the target vessel. All revascularizations were considered clinically indicated if follow-up angiography showed a percent diameter stenosis ≥70% or ≥50% as assessed by quantitative coronary angiographic analysis with either ischemic symptoms or a positive stress test. Stroke was defined as a sudden focal neurologic deficit of presumed cerebrovascular etiology that persisted beyond 24 h and had no other identifiable cause. Brain imaging (computed tomography or magnetic resonance imaging) was conducted for all suspected strokes. The secondary endpoints were bleeding events, TLR, stent thrombosis, and all-cause mortality. All bleeding events were classified as either major or minor, according to the definition of thrombolysis in MI.[18] Major bleeding included any intracranial bleeding, clinically overt signs of hemorrhage associated with a drop in hemoglobin >5 g/dL, and fatal bleeding resulting in death within 7 days. TLR was defined as repeat revascularization of the lesion within 5 mm of the stented lesion or bypass surgery of the stented vessel. Stent thrombosis was defined as definite or confirmed thrombotic occlusion of a previously implanted stent by angiography. All endpoint events were adjudicated by three analysts who were blinded to both the clinical and angiographic information.

Statistical analysis

Data are expressed as number (%), mean±standard deviation, or median [interquartile range (IQR)]. Continuous variables were compared using the Student's t-test or one-way analysis of variance, and categorical data were compared using the chi-square statistics or Fisher's exact test. Event-free survival was analyzed using the Kaplan-Meier survival curves according to baseline anemia and DAPT duration. The differences between event-free survival curves were compared using the log-rank test. The hazard ratios (HRs) for MACCEs and major bleeding events for each patient were calculated according to the baseline hemoglobin level. Correlation and linear regression analyses were used to compare the baseline hemoglobin levels and adverse outcomes, including MACCEs and major bleeding. We calculated the HRs for MACCEs using a Cox regression model with univariate analysis. Variables that achieved a p-value <0.10 in the univariate analysis were entered into the multivariate analysis and the variables used to calculate the adjusted HR of MACCEs, cardiac death, and major bleeding according to anemia and DAPT duration. The variables that achieved p-values <0.10 in the univariate analysis are shown in Supplementary Table 1 (only online). To reduce the impact of differences in baseline and angiographic characteristics between the groups on the study endpoints, we adjusted for confounding factors using the inverse probability of treatment weighting (IPTW).[19] For IPTW adjustment, we used significant variables associated with anemia in logistic regression modeling as follows: age, sex, hypertension, diabetes, dyslipidemia, and chronic kidney disease. Standardized mean differences after IPW adjustment were less than 0.10 across all matched covariates, indicating successful balance between comparator groups. Statistical analyses were performed using SPSS version 20.0.0 (IBM Corp., Armonk, NY, USA) and SAS (SAS Institute Inc., Cary, NC, USA). p-values <0.05 were considered statistically significant.

RESULTS

Baseline and angiographic characteristics

The baseline and angiographic characteristics of the study population are summarized in Table 1. Compared to patients without anemia, patients with anemia were older (62.0±10.9 years vs. 68.5±9.4 years, p<0.001) and had a higher prevalence of cardiovascular risk factors, such as hypertension, diabetes, and chronic kidney disease. Patients with anemia were mostly female compared to those without (36.4% vs. 25.3%, p<0.001). The baseline hemoglobin level was significantly lower in patients with anemia than in those without (11.3±1.3 g/dL vs. 14.4±1.2 g/dL, p<0.001). Compared to patients without anemia, those with anemia showed significantly lower DAPT scores (2.14±1.23 vs. 1.80±1.28, p<0.001) and higher PRECISE-DAPT scores (12.33±6.45 vs. 23.03±12.26, p<0.001). In patients with anemia, the DAPT discontinuation rate at 6 months after PCI was significantly higher than that in patients without anemia (7.1% vs. 3.5%, p=0.002). After 6 months, the DAPT discontinuation rate was similar between patients with and without anemia (Fig. 1B).

The target vessel was not significantly different between patients with and without anemia, but patients with left main disease tended to receive prolonged DAPT. Severe angiographic finding, such as type C lesion, were more common in patients with anemia than in those without (28.8% vs. 20.0%, p<0.001), according to the ACC/AHA lesion classification. Moreover, patients with anemia were more likely to undergo complex PCI than patients without anemia (38.4% vs. 27.2%, p<0.001), mainly due to three-vessel disease and multiple long stenting.

Clinical outcomes

We evaluated the incidence of adverse clinical outcomes at the median follow-up duration of 80.8 (IQR, 60.6–97.1) months. The long-term clinical outcomes according to anemia and DAPT duration are summarized in Table 2. The incidence of MACCEs was significantly higher in the anemia group than in the non-anemia group (26.9% vs. 17.1%, p<0.001). Major bleeding events were also more frequently observed in the anemia group than in the non-anemia group (9.8% vs. 5.1%, p=0.006). Patients without anemia who received >12-m DAPT showed a lower frequency of MACCEs than those who received ≤12-m DAPT and patients with anemia who received ≤12-m or >12-m DAPT (15.6% vs. 18.7% vs. 27.0% vs. 26.7%, respectively, p<0.001). The difference in MACCEs was mostly driven by the incidence of cardiac death and non-fatal MI. Although prolonged DAPT showed a trend toward a decreased rate of MACCEs in patients without anemia (15.6% vs. 18.7%, p=0.061), the MACCE rate was similar between ≤12-m and >12-m DAPT in patients with anemia (Fig. 2). There was a significant linear negative correlation between the incidence of MACCEs and baseline hemoglobin (R=-0.431, p<0.001) (Fig. 3A). The cut-off value of baseline hemoglobin for predicting MACCEs was 13.8 g/dL. The incidence of major bleeding and baseline hemoglobin were also negatively correlated (R=-0.204, p<0.001) (Fig. 3B), and the cut-off value of baseline hemoglobin for major bleeding was 14.4 g/dL.

The adjusted HRs of "hard" endpoints, MACCEs, cardiac death, and major bleeding according to anemia and DAPT strategy are described in Table 3. Considering the patients without anemia who received ≤12-m DAPT as a reference, >12-m DAPT was associated with a reduced rate of MACCEs (IPTW adjusted HR, 0.777; 95% CI, 0.630–0.959; p=0.019) with no increase in major bleeding events. However, patients with anemia who received ≤12-m DAPT showed an increased rate of MACCEs (IPTW adjusted HR, 1.360; 95% CI, 1.095–1.687; p=0.005). Furthermore, patients with anemia who received >12-m DAPT showed an increased rate of cardiac death (IPTW adjusted HR, 2.130; 95% CI, 1.099–4.127; p=0.025) and major bleeding (IPTW adjusted HR, 2.005; 95% CI, 1.317–3.055; p=0.001).

DISCUSSION

In this study, we found a significant linear negative correlation between the incidence of MACCEs or major bleeding events and baseline hemoglobin levels. Our study showed that the prevalence of baseline anemia was 30.5%, and among patients with anemia, 49.6% received >12-m DAPT considering their lesion complexity. However, the incidence of MACCEs did not decrease with prolonged DAPT among patients with baseline anemia. Furthermore, prolonged DAPT was associated with an increased rate of cardiac death and major bleeding in patients with anemia, even after adjustment for baseline and angiographic characteristics.

From our real-world PCI registry, the incidence of anemia was 30.5%. The incidence of anemia from other East Asian data was reported as approximately 30%–40%,[20-22] which was higher than that in Western countries.[6,23] Current guidelines regarding DAPT duration after PCI are mostly based on large-scale randomized trials and mainly consist of patients without high bleeding risk. Furthermore, current guidelines do not specifically mention an appropriate DAPT duration for patients with anemia, and only suggest that anemia could be a risk factor for bleeding events. Indeed, the current guidelines might be insufficient to determine the appropriate DAPT duration for East Asia, which has a higher incidence of anemia. Our study showed that prolonged DAPT was associated with an increased rate of cardiac death and major bleeding without a decrease in the rate of MACCEs in patients with anemia. Our study suggests the need for specified guidelines regarding DAPT duration after PCI, especially for patients with anemia.

A previous large-scale analysis of the clinical impact of the baseline hemoglobin level after PCI showed that decreasing baseline hemoglobin levels correlated with incrementally higher rates of ischemic and major bleeding events.[20] Our data also showed a strong linear negative correlation between MACCEs or major bleeding and baseline hemoglobin level. The correla-

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Table 1. Baseline and Angiographic Characteristics

Variables	Anemia		Non-anemia		*p* value
	≤12-m DAPT (n=226)	>12-m DAPT (n=222)	≤12-m DAPT (n=521)	>12-m DAPT (n=501)	
Baseline characteristics					
Age, yr	68.2±9.6	68.8±9.3	62.4±10.7	61.7±11.2	<0.001
Female	80 (35.4)	83 (37.4)	136 (26.1)	123 (24.6)	<0.001
Hypertension	151 (66.8)	132 (59.5)	263 (50.5)	232 (46.3)	<0.001
Diabetes	91 (40.3)	106 (47.7)	165 (31.7)	157 (31.3)	<0.001
Dyslipidemia	145 (64.2)	145 (65.3)	381 (73.1)	377 (75.2)	0.003
Chronic kidney disease	10 (4.4)	9 (4.1)	4 (0.8)	4 (0.4)	<0.001
Smoking	120 (53.1)	132 (59.5)	310 (59.5)	321 (64.1)	0.045
Previous PCI	24 (10.6)	22 (9.9)	37 (7.1)	46 (9.2)	0.356
Previous MI	13 (5.8)	8 (3.6)	24 (4.6)	30 (6.0)	0.512
Old CVA	34 (15.0)	30 (13.5)	53 (10.2)	52 (10.4)	0.158
Clinical presentation					0.082
Stable angina	103 (45.6)	112 (50.5)	202 (38.8)	211 (42.2)	
Unstable angina	26 (11.5)	30 (13.5)	68 (13.1)	65 (13.0)	
Acute MI	97 (42.9)	80 (36.0)	251 (48.2)	225 (44.9)	
LVEF, %	54.5±10.5	55.3±11.1	57.1±29.9	55.6±10.5	0.399
Laboratory finding					
Hemoglobin, g/dL	11.3±1.4	11.3±1.2	14.4±1.2	14.5±1.3	<0.001
Creatinine, mg/dL	1.42±1.59	1.47±1.45	0.98±0.57	1.05±0.67	<0.001
Total cholesterol, mg/dL	172.36±44.11	169.47±44.31	193.34±43.11	196.11±99.02	<0.001
LDL-cholesterol, mg/dL	99.40±43.57	98.05±40.45	114.59±39.92	117.12±108.06	0.001
HDL-cholesterol, mg/dL	44.81±21.5	41.99±11.2	44.76±11.99	46.16±12.57	0.005
Triglyceride, mg/dL	137.87±94.89	144.49±123.39	171.3±122.6	176.37±139.91	<0.001
DAPT duration, days	349.3±271.4	1166.1±840.2	358.5±228.1	1261.0±877.5	<0.001
DAPT score	1.81±1.26	1.80±1.31	2.11±1.22	2.18±1.25	<0.001
PRECISE-DAPT score	22.49±13.10	23.58±11.35	12.02±6.57	12.65±6.30	<0.001
Angiographic characteristics					
Target vessel					
LM	11 (4.9)	18 (8.1)	18 (3.5)	35 (7.0)	0.026
LAD	118 (52.2)	138 (62.2)	297 (57.0)	288 (57.5)	0.208
LCX	75 (33.2)	66 (29.7)	142 (27.3)	157 (31.3)	0.334
RCA	95 (42.0)	88 (39.6)	186 (35.7)	169 (33.7)	0.126
Involved vessel					<0.001
1-vessel	110 (48.7)	103 (46.4)	331 (59.7)	263 (52.5)	
2-vessel	82 (36.3)	76 (34.2)	169 (32.4)	170 (33.9)	
3-vessel	34 (15.0)	43 (19.4)	41 (7.9)	68 (13.6)	
Multivessel disease	116 (51.3)	119 (53.6)	210 (40.3)	238 (47.5)	0.002
Stent type					0.478
1st generation DES	18 (8.0)	10 (4.5)	36 (6.9)	31 (6.2)	
2nd generation DES	208 (92.0)	212 (95.5)	485 (93.1)	470 (93.8)	
Reference vessel diameter, mm	2.93±0.43	2.98±0.45	3.04±0.51	3.07±0.51	0.002
Minimal lumen diameter, mm	0.24±0.20	0.23±0.19	0.21±0.21	0.22±0.21	0.296
Diameter stenosis, %	88.5±9.9	88.3±10.3	89.4±9.9	88.6±10.6	0.424
Lesion length, mm	21.8±10.8	22.1±12.0	20.5±10.8	21.4±11.4	0.428
Acute gain, mm	2.82±0.43	2.86±0.48	2.96±0.47	2.95±0.47	<0.001
Chronic total occlusion	13 (5.8)	15 (6.8)	22 (4.2)	31 (6.2)	0.425
Bifurcation PCI					
1-stent	42 (18.6)	52 (23.4)	107 (20.5)	121 (24.2)	0.283
2-stent	6 (2.7)	5 (2.3)	10 (1.9)	16 (3.2)	0.621

Table 1. Baseline and Angiographic Characteristics (continued)

Variables	Anemia		Non-anemia		*p* value
	≤12-m DAPT (n=226)	>12-m DAPT (n=222)	≤12-m DAPT (n=521)	>12-m DAPT (n=501)	
ACC/AHA lesion description					0.002
Type A or B	163 (72.1)	156 (70.3)	424 (81.4)	394 (78.6)	
Type C	63 (27.9)	66 (29.7)	97 (18.6)	107 (21.4)	
In-stent restenosis	17 (7.5)	9 (4.1)	19 (3.6)	36 (7.2)	0.032
Complex PCI*	83 (36.7)	89 (40.1)	123 (23.6)	155 (30.9)	<0.001
Total stent number, n	1.47±0.77	1.55±0.84	1.38±0.72	1.43±0.72	0.047
Stent diameter, mm	3.09±0.4	3.12±0.44	3.22±0.7	3.17±0.44	0.040
Total stent length, mm	34.5±21.8	34.9±23.1	30.5±19.3	32.8±20.8	0.018

DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; MI, myocardial infarction; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; LDL, low density lipoprotein; HDL, high density lipoprotein; LM, left main; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; DES, drug-eluting stent; ACC/AHA, American College of Cardiology/American Heart Association.
Data are presented as mean±standard deviation or n (%).
*Complex PCI was defined as composite of three-vessel disease, chronic total occlusion, total stent length ≥60 mm, or bifurcation two stent.

Table 2. Clinical Outcomes according to Anemia and the Duration of DAPT

Variables	Anemia		Non-anemia		*p* value
	≤12-m DAPT (n=226)	>12-m DAPT (n=222)	≤12-m DAPT (n=521)	>12-m DAPT (n=501)	
MACCE	49 (27.0)	48 (26.7)	81 (18.7)	72 (15.6)	<0.001
Cardiac death	7 (3.5)	10 (5.5)	7 (1.7)	5 (1.0)	0.012
Non-fatal MI	13 (8.1)	9 (4.7)	26 (6.4)	15 (3.1)	0.019
TVR	19 (11.3)	13 (7.2)	31 (7.2)	35 (7.4)	0.284
Stroke	16 (8.4)	22 (13.1)	41 (9.4)	32 (7.3)	0.078
All-cause mortality	16 (8.1)	14 (8.8)	16 (3.8)	14 (3.4)	0.003
TLR	14 (8.1)	6 (3.5)	26 (6.1)	20 (4.3)	0.030
Stent thrombosis	5 (2.9)	2 (0.9)	12 (2.8)	4 (0.8)	0.045
Any bleeding	28 (17.5)	33 (19.7)	46 (10.7)	55 (13.8)	0.036
Major bleeding	12 (7.9)	18 (11.6)	22 (5.3)	19 (5.0)	0.035

DAPT, dual antiplatelet therapy; MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; TVR, target vessel revascularization; TLR, target lesion revascularization.
Data are presented as n (%).

tion coefficient for the correlation between MACCEs and baseline hemoglobin (R=-0.431) was greater than that for the correlation between major bleeding and baseline hemoglobin (R=-0.204), which indicates that the baseline hemoglobin level had a stronger relationship with MACCEs than with major bleeding. For patients with CAD who received PCI, bleeding events can lead to vicious cycle related to ischemic events, such as hemoglobin loss, antiplatelet therapy cessation, or stent thrombosis. This indicates that major bleeding is one of the risk factors for future MACCE occurrence. Our plot analysis of adverse events and baseline hemoglobin showed a cut-off value of 13.8 g/dL for predicting MACCEs and 14.4 g/dL for predicting major bleeding. However, the current WHO definition of anemia in women is a hemoglobin level below 12.0 g/dL. From our data, women without anemia who had baseline hemoglobin levels between 12.0 g/dL and 13.8 g/dL might also have a risk for future MACCEs or bleeding events. Immediate correction of anemia might be considered due to the strong correlation between baseline anemia and future adverse clinical events. However, the correction of anemia by blood transfusion is also associated with an increased risk of mortality and major adverse cardiovascular events.[24] Even though anemia is associated with future adverse clinical events, anemia correction should be carefully considered for individual patients with anemia. It is necessary to conduct a prospective randomized control trial on the methods of anemia correction for patients requiring PCI.

Our study showed that patients with anemia showed more complex angiographic findings, such as multivessel disease and type C lesions, and more frequently received complex PCI compared to patients without anemia. Another large single-center study also showed that patients with anemia had higher SYNTAX scores and a higher incidence of type B2/C lesions.[9] Many previous reports regarding the association between anemia and clinical outcome after PCI have not shown detailed angiographic and procedural descriptions. In this regard, our study could provide mechanistic insight into the correlation between anemia and future MACCEs. Patients with anemia and CAD are more likely to have a complex angiographic anatomy, which leads to future ischemic events. Furthermore, anemia can also

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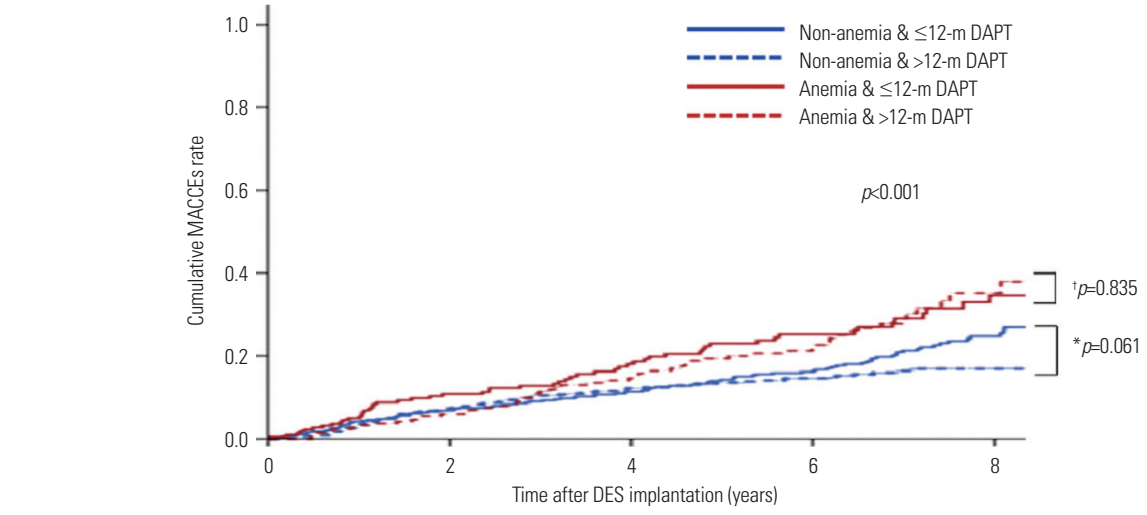

Non-anemia & ≤12-m DAPT	521	438	371	288	113
Non-anemia & >12-m DAPT	501	451	385	307	101
Anemia & ≤12-m DAPT	226	182	134	95	41
Anemia & >12-m DAPT	222	201	149	111	27

Fig. 2. Kaplan-Meier survival curves according to anemia and the duration of dual antiplatelet therapy. **p*-value between ≤12-m and >12-m DAPT in patients without anemia, †*p*-value between ≤12-m and >12-m DAPT in patients with anemia. MACCE, major adverse cardiovascular and cerebrovascular event; DAPT, dual antiplatelet therapy; DES, drug-eluting stent.

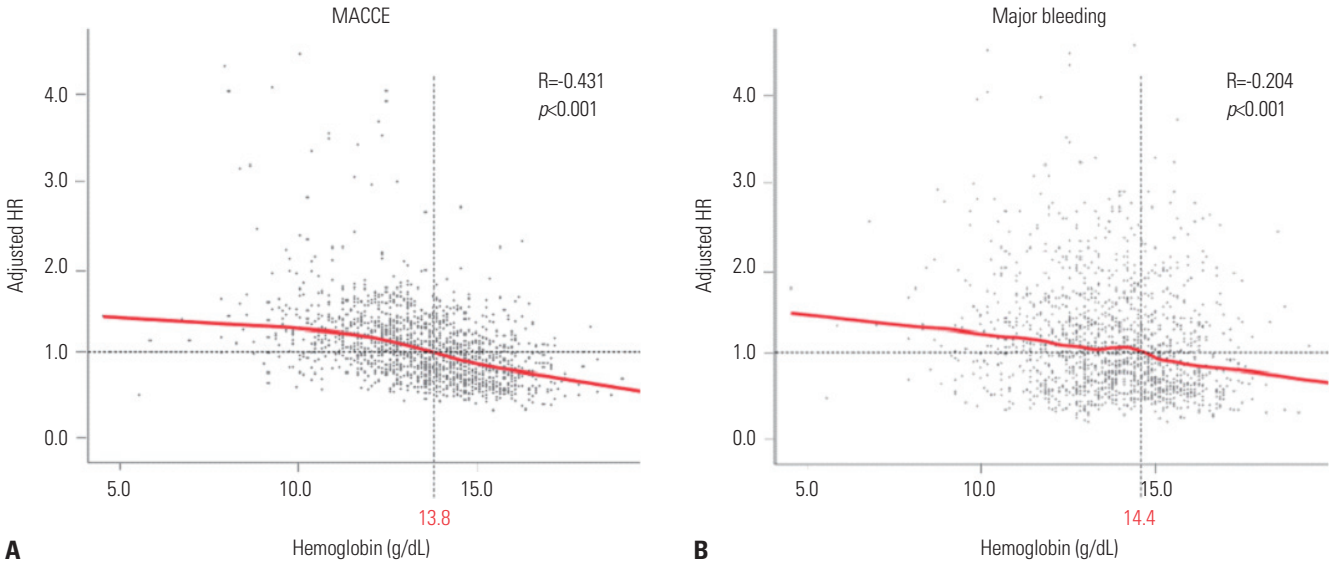

Fig. 3. Correlation between the incidence of adverse clinical outcomes and baseline hemoglobin. (A) There was a significant linear negative correlation between the incidence of MACCEs and baseline hemoglobin. (B) The incidence of major bleeding and baseline hemoglobin was also negatively correlated. MACCE, major adverse cardiovascular and cerebrovascular event; HR, hazard ratio.

cause a mismatch between oxygen supply and demand, which is an essential mechanism of type 2 MI.[25] Several studies on the optimal DAPT duration after PCI have suggested that the ischemic benefit with prolonged DAPT was higher in patients who received complex PCI.[3,4] However, these studies were based on randomized control; as a result, patients with a high risk of bleeding, such as those with baseline anemia, might have been excluded. Based on our findings, even after adjustment for angiographic findings, prolonged DAPT was not associated with a reduced rate of MACCEs in patients with anemia who received complex PCI, but was associated with increased rates of cardiac death or major bleeding. In other words, prolonged DAPT was not appropriate for patients with baseline anemia regardless of lesion complexity.

In our study, the DAPT score of patients with anemia was significantly lower than that of those without (1.80±1.28 vs. 2.14±1.23, $p<0.001$). According to the DAPT score, patients with anemia were recommended a standard DAPT duration for 12 months. However, the DAPT score system does not have any criteria for baseline anemia.[14] The PRECISE-DAPT score of patients with

Table 3. Adjusted HRs of MACCE, Cardiac Death, and Major Bleeding according to Anemia and DAPT Duration

	MACCE		Cardiac death		Major bleeding	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Non-anemia & ≤12-m DAPT	Reference					
Non-anemia & >12-m DAPT						
Unadjusted HR	0.753 (0.559–1.014)	0.062	0.891 (0.322–2.461)	0.824	1.060 (0.598–1.878)	0.843
Adjusted HR	0.764 (0.566–1.029)	0.077	0.873 (0.316–2.416)	0.794	1.084 (0.610–1.927)	0.784
IPTW adjusted HR	0.777 (0.630–0.959)	0.019	0.885 (0.431–1.817)	0.794	1.123 (0.750–1.680)	0.574
Anemia & ≤12-m DAPT						
Unadjusted HR	1.493 (1.078–2.068)	0.016	2.446 (0.918–6.520)	0.074	1.634 (0.840–3.176)	0.148
Adjusted HR	1.249 (0.888–1.757)	0.201	1.705 (0.616–4.717)	0.304	1.354 (0.674–2.722)	0.395
IPTW adjusted HR	1.360 (1.095–1.687)	0.005	1.517 (0.731–3.146)	0.063	1.422 (0.908–2.228)	0.124
Anemia & >12-m DAPT						
Unadjusted HR	1.451 (1.045–2.016)	0.026	3.007 (1.847–7.635)	0.021	2.096 (1.140–3.851)	0.017
Adjusted HR	1.105 (0.778–1.569)	0.576	2.008 (0.727–5.546)	0.179	1.840 (0.970–3.490)	0.062
IPTW adjusted HR	1.105 (0.881–1.385)	0.387	2.130 (1.099–4.127)	0.025	2.005 (1.317–3.055)	0.001

MACCE, major cardiovascular and cerebrovascular event; DAPT, dual antiplatelet therapy; HR, hazard ratio; IPTW, inverse probability treatment weight; CI, confidence interval.

anemia was higher than that of those without (23.03±12.26 vs. 12.33±6.45, $p<0.001$), which indicates that patients with anemia had high bleeding risk features according to the PRECISE-DAPT score system. However, the PRECISE-DAPT score of patients with anemia was below the cut-off value of 25 points for deciding short DAPT. Several studies on the external validation of the DAPT score showed that this score system could not be successfully generalized in real-world practice.[26,27] Our study results suggest that the PRECISE-DAPT score system also requires extensive external validation for practical use in real-world populations.

Our study had some limitations. First, this study was based on single-center PCI registry data, and it had some intrinsic limitations related to its retrospective nature. However, our cardiovascular center is one of the highest-volume PCI centers in the Korean Society of International Caridology.[28] Due to the retrospective design, there were significant differences in baseline and angiographic characteristics between patients with and without anemia. However, we performed IPTW adjustment to reduce the impact of differences in baseline and angiographic characteristics. Furthermore, our study aimed to evaluate the incidence of anemia and its clinical impact in a real-world population that required PCI. Our study retrospectively categorized the study population according to DAPT duration: ≤12-m and >12-m of DAPT. However, the DAPT duration of patients who classified as >12-m DAPT might be too long compared to contemporary practice. Second, our data did not include information about temporary DAPT cessation due to anemia during the study period. However, a previous study suggested that baseline anemia did not modify the risk of clinical outcomes associated with any DAPT cessation.[23] Furthermore, the DAPT discontinuation rate was similar between patients with and without anemia during the study period. Our study enrolled some patients who received first-generation DES. However, the incidence of first-generation DES implantation was relatively low (6.5%), and there was no statistically significant difference between the four study groups. Fourth, our study did not analyze blood transfusion in patients with severe anemia; indeed, our hospital did not routinely conduct blood transfusion, especially for patients with CAD who requred PCI.

In conclusion, even though patients with anemia had more complex angiographic findings compared to those without, the incidence of MACCEs was not decreased by prolonged DAPT among patients with baseline anemia. Furthermore, prolonged DAPT was associated with an increased rate of cardiac death and major bleeding in patients with anemia, even after adjusting for baseline and angiographic characteristics. Our results suggest the importance of an individualized DAPT duration for anemic patients with a complex anatomy.

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AUTHOR CONTRIBUTIONS

Conceptualization: Jung-Hee Lee. Data curation: Hun-Tae Kim and Jung-Hee Lee. Formal analysis: Hun-Tae Kim. Investigation: Jung-Hee Lee, Jong-Ho Nam, Chan-Hee Lee, Jang-Won Son, Ung Kim, Jong-Seon Park, and Dong-Gu Shin. Methodology: Jung-Hee Lee. Project administration: Hun-Tae Kim and Jung-Hee Lee. Resources: Jung-Hee Lee, Jong-Ho Nam, Chan-Hee Lee, Jang-Won Son, Ung Kim, Jong-Seon Park, and Dong-Gu Shin. Software: Jung-Hee Lee. Supervision: Jung-Hee Lee. Validation: Jung-Hee Lee. Visualization: Hun-Tae Kim and Jung-Hee Lee. Writing—original draft: Hun-Tae Kim. Writing—review & editing: Jung-Hee Lee, Jong-Ho Nam, Chan-Hee Lee, Jang-Won Son, Ung Kim, Jong-Seon Park, and Dong-Gu Shin. Approval of final manuscript: all authors.

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