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Use of Proton Pump Inhibitors Is Associated With Anemia in Cardiovascular Outpatients

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Background: Proton pump inhibitors (PPI) are frequently prescribed in combination with aspirin for preventing peptic ulcer in patients with atherosclerotic diseases. In contrast, long-term use of PPI has been suggested to be associated with iron or vitamin B_{12} deficiency. The effect of PPI on hemoglobin (Hb) concentration, however, has not been clarified in cardiovascular outpatients.

Methods and Results: We retrospectively investigated the clinical characteristics of 278 continuous outpatients who received blood test including complete blood count and serum creatinine concentration (mean age, 69.9±10.8 years; male, 68.7%). The frequency of anemia was 51% in patients receiving PPI and 19% in those not receiving PPI (chi-squared test, P<0.001). On multivariate analysis female sex (P<0.001), peripheral artery disease (P=0.003), PPI (P=0.003), low white blood cell count (P=0.004), old age (P=0.007), and low estimated glomerular filtration rate (P=0.010) were independently associated with low Hb. Among these patients, we investigated the change in Hb after the initiation of PPI in 36 patients for whom data on Hb level within 1 year before and within 1 year after the initiation of PPI were available. Mean decrease in Hb after the initiation of PPI was 0.38±0.87 g/dl (95% confidence interval: −0.67 to −0.09 g/dl).

Conclusions: Use of PPI was associated with anemia in Japanese cardiovascular outpatients. (*Circ J* 2015; **79:** 193−200)

Key Words: Anemia; Cardiovascular disease; Hemoglobin; Proton pump inhibitor

Proton pump inhibitors (PPI) are one of the most widely used medications worldwide. Although these drugs are considered safe and have been approved for long-term use, some long-term safety concerns have been raised, such as respiratory infection, Clostridium difficile infection, vitamin B_{12} deficiency, and bone fracture. Iron deficiency anemia is also a concern.[1] Gastric acid plays an important role in iron absorption because ferric iron is not soluble at high pH. Furthermore, Marcuard et al reported that PPI decreased the absorption rate of vitamin B_{12}.[2]

The risk of peptic ulcer complications, particularly bleeding, has been raised in association with aspirin use, and the odds ratio (OR) of bleeding in an epidemiologic study was 2.4.[3] In that same study, use of PPI was associated with a decrease of 80% in the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin. Thus, some PPI were indicated for the prevention of gastroduodenal ulcer relapse during aspirin therapy, and guidelines advocate the use of PPI in a wide group of patients with atherosclerosis.[4] Therefore, PPI are frequently prescribed for cardiovascular outpatients. Furthermore, given that novel anticoagulant drugs have been marketed,[5–7] chronic use of PPI might increase in patients with cardiovascular disease. In contrast, cardiovascular outpatients have an increased risk of developing heart failure due to the frequent complications of hypertension or ischemic heart disease. Anemia is a factor indicating poor outcome in both patients with heart failure with a reduced ejection fraction and heart failure with a preserved ejection fraction.[8–10] Moreover, anemia has been shown to predict mortality in patients undergoing their first coronary revascularization.[11] Therefore, appropriate care should be taken if PPI cause anemia in cardiovascular outpatients.

This retrospective study was thus designed to determine how PPI influence blood hemoglobin (Hb) level in cardiovascular outpatients.

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Table 1. Clinical Patient Characteristics

Clinical characteristics	All	No acid suppression agent	Patients with H_2-blocker	Patients with PPI	P-value
n	278	166	24	88	
Age (years)	69.9±10.8	68.4±11.5	73.4±8.4	71.8±9.6*	0.015
Male gender	191 (68.7)	115 (69.3)	18 (75.0)	58 (65.9)	0.675
BMI (kg/m^2)	23.8±3.9	24.1±4.1	22.9±3.0	23.5±3.7	0.251
SBP (mmHg)	131.4±20.1	133.5±19.8	129.7±20.1	127.9±20.4	0.130
DBP (mmHg)	76.0±12.8	77.2±13.6	72.6±10.0	74.6±11.6	0.155
Heart rate (beats/min)	73.9±13.2	75.1±13.7	70.8±11.2	72.2±12.6	0.237
RBC ($10^4/\mu l$)	443.7±58.4	454.3±57.5	445.3±43.4	423.4±58.6**	<0.001
Hb (g/dl)	13.6±1.8	14.0±1.7	13.4±1.5	12.8±1.8**	<0.001
Ht (%)	41.0±5.1	42.2±4.9	40.7±4.2	38.9±5.2**	<0.001
MCV (fl)	92.6±5.3	93.0±5.1	91.5±5.1	92.1±5.7	0.233
MCH (pg)	30.6±1.9	30.9±1.7	30.2±2.1	30.2±2.3*	0.011
MCHC (g/dl)	33.1±1.0	33.2±1.0	33.0±1.0	32.8±1.1**	0.003
WBC ($10^2/\mu l$)	60.3±17.1	60.8±17.5	61.9±13.7	59.1±17.2	0.685
Plt ($10^4/\mu l$)	19.3±5.5	19.3±5.7	19.9±3.8	18.9±5.3	0.712
eGFR (ml·min^{-1}·1.73 m^{-2})	65.8±21.2	69.2±20.5	64.3±15.6	59.8±22.7**	0.003
UA (mg/dl)	5.8±1.6	5.8±1.4	5.6±1.5	6.0±1.8	0.448
Na (mEq/L)	139.9±2.7	140.2±2.0	139.7±1.9	139.4±3.7	0.093
K (mEq/L)	4.3±0.4	4.3±0.4	4.2±0.4	4.3±0.4	0.308
Cl (mEq/L)	104.3±2.9	104.4±2.4	103.9±2.5	104.2±3.7	0.668
Comorbidity					
History of gastroduodenal ulcer†	21 (7.6)	11 (6.6)	3 (12.5)	7 (8.0)	0.587
Reflux esophagitis†	25 (9.0)	10 (6.0)	1 (4.2)	14 (15.9)*	0.022
Hypertension	193 (69.4)	115 (69.3)	14 (58.3)	64 (72.7)	0.398
Diabetes mellitus	104 (37.4)	58 (34.9)	13 (54.2)	33 (37.5)	0.191
Dyslipidemia	160 (57.6)	95 (57.2)	12 (50.0)	53 (60.2)	0.662
Heart failure	59 (21.2)	28 (16.9)	4 (16.7)	27 (30.7)*	0.032
Angina pectoris	81 (29.1)	43 (25.9)	8 (33.3)	30 (34.1)	0.352
Old MI	81 (29.1)	34 (20.5)	9 (37.5)	38 (43.2)**	<0.001
History of PCI	78 (28.1)	34 (20.5)	8 (33.3)	36 (40.9)**	<0.001
Cerebral infarction	27 (9.7)	13 (7.8)	3 (12.5)	11 (12.5)	0.436
Cerebral hemorrhage	5 (1.8)	1 (0.6)	1 (4.2)	3 (3.4)	0.183
Dementia	3 (1.1)	2 (1.2)	–	1 (1.1)	0.980
PAD	22 (7.9)	8 (4.8)	2 (8.3)	12 (13.6)	0.046
Medication					
Statins	126 (45.3)	67 (40.4)	8 (33.3)	51 (58.0)*	0.013
Uric acid-lowering agents	38 (13.7)	25 (15.1)	1 (4.2)	12 (13.6)	0.348
Oral hypoglycemic agents	59 (21.2)	30 (18.1)	10 (41.7)*	19 (21.6)	0.030
Insulin	7 (2.5)	4 (2.4)	–	3 (3.4)	0.818
ARB	148 (53.2)	81 (48.8)	10 (41.7)	57 (64.8)	0.026
Diuretics	83 (29.9)	39 (23.5)	7 (29.2)	37 (42.0)**	0.009
ACEI	41 (14.7)	29 (17.5)	2 (8.3)	10 (11.4)	0.277
Calcium channel blockers	120 (43.2)	72 (43.4)	13 (54.2)	35 (39.8)	0.449
β-blockers	134 (48.2)	66 (39.8)	15 (62.5)	53 (60.2)**	0.003
Other antihypertensive agents	16 (5.8)	12 (7.2)	–	4 (4.5)	0.490
Antiplatelet agents	146 (52.5)	69 (41.6)	14 (58.3)	63 (71.6)**	<0.001
Aspirin	130 (46.8)	58 (34.9)	13 (54.2)	59 (67.0)**	<0.001
DPI	51 (18.3)	19 (11.4)	6 (25.0)	26 (29.5)**	0.001
Warfarin	61 (21.9)	28 (16.9)	4 (16.7)	29 (33.0)*	0.010
Warfarin+DPI	9 (3.2)	3 (1.8)	2 (8.3)	4 (4.5)	0.169

Data given as mean±SD or n (%). Differences in continuous and categorical variables among 3 groups were assessed using 1-way ANOVA and chi-squared test, respectively. *P<0.05, **P<0.01 compared with no acid suppression agent (1-way ANOVA followed by Tukey post-hoc test or chi-squared test followed by Bonferroni correction). †Diagnosed on gastrointestinal fiberscopy. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; DPI, dual platelet inhibitor; eGFR, estimated glomerular filtration rate; H_2-blocker, histamine type 2 receptor blocker; Hb, hemoglobin; Ht, hematocrit; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; Plt, platelet; PPI, proton pump inhibitor; RBC, red blood cells; SBP, systolic blood pressure; statins, HMG-CoA reductase inhibitor; UA, uric acid; WBC, white blood cells.

Methods

Subjects

We retrospectively investigated continuous outpatients who visited the Cardiovascular Division, Department of Internal Medicine, Hyogo College of Medicine Hospital from February 2011 to October 2012 for the treatment of cardiovascular disease (ischemic heart disease, heart failure, peripheral artery disease, cerebrovascular disease, cardiomyopathy, and arrhythmia) or risk factors of cardiovascular disease (hypertension, dyslipidemia, diabetes mellitus, and hyperuricemia), and who underwent complete blood count (CBC) and measurement of serum creatinine. We reviewed patient demographics, comorbidity, and medication in their medical records. Exclusion criteria were as follows: history of digestive system surgery, malignancy, hemodialysis, aplastic anemia, hemolytic anemia, major bleeding within 1 year, inflammatory disease, connective tissue disease, and use of erythropoietin, vitamins, iron or folic acid preparations. A Japanese equation was used to calculate estimated glomerular filtration rate (eGFR): eGFR ($ml \cdot min^{-1} \cdot 1.73\,m^{-2}$)=194×serum creatinine$^{-1.094}$×age$^{-0.287}$(×0.739 if female).[12] Diabetes mellitus was defined as fasting plasma glucose ≥126 mg/dl, HbA1c ≥6.5%, or use of anti-diabetic medication. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or use of anti-hypertensive medication. Dyslipidemia was defined as low-density lipoprotein cholesterol ≥140 mg/dl, high-density lipoprotein cholesterol <40 mg/dl, triglyceride ≥150 mg/dl, or use of anti-dyslipidemia medication. Anemia was defined according to the World Health Organization criteria (Hb <13 g/dl in men, <12 g/dl in women).

Next, we examined the change in Hb level after the initiation of PPI in patients who did not have heart failure and whose medication was not changed except for the initiation of PPI between the CBC before and after the initiation of PPI. They underwent CBC at least once within 1 year before, and again within 1 year after the initiation of PPI. To calculate the change in Hb after the initiation of PPI, the average Hb level within 1 year after the initiation of PPI was subtracted from that within 1 year before the initiation of PPI.

This study was approved by the Ethics Committee of Hyogo College of Medicine and the Ethics Committee of Hyogo University of Health Sciences.

Statistical Analysis

Data are given as mean±SD. Differences in categorical variables between groups were assessed using chi-squared test. Differences in continuous variables between groups were assessed using unpaired Student's t-test or 1-way analysis of variance (ANOVA) followed by Tukey post-hoc test. Regarding continuous variables, the correlation between each variable was examined using Pearson's correlation analysis. Multiple regression analysis and logistic regression analysis were used to identify variables that might predict Hb level and anemia, respectively. Factors with P<0.10 on univariate analysis were selected as independent factors in multivariate analysis. Hb level before and after the initiation of PPI was compared using paired t-test. Differences were considered statistically significant for P<0.05. All calculations and analyses were performed using Ekuseru-Toukei 2010 (Social Survey Research Information).

Table 2. Correlation With Hemoglobin

Factor	R	P-value
Age	−0.361	<0.001
BMI	0.210	0.001
SBP	0.084	0.194
DBP	0.207	0.001
Heart rate	−0.125	0.078
WBC	0.169	0.005
Plt	0.054	0.372
eGFR	0.337	<0.001
UA	−0.033	0.633
Na	0.141	0.023
K	−0.079	0.207
Cl	−0.083	0.184

Pearson's correlation analysis. Abbreviations as in Table 1.

Results

Univariate Factors Associated With Hb

We screened 634 patients, and 278 patients were enrolled. Table 1 lists the clinical characteristics, comorbidities, and medications. The reasons for PPI prescription were as follows: reflux esophagitis (n=85), use of antiplatelet agents (n=63), history of gastroduodenal ulcer (n=30), and use of warfarin (n=7). When reflux esophagitis and gastroduodenal ulcer were diagnosed on gastrointestinal fiberscopy, they were analyzed as factors for Hb concentration and anemia. PPI users tended to be older, had worse renal function, and had a higher rate of treatment with diuretics, antiplatelet agents or warfarin, and had a higher prevalence of comorbidities (Table 1). Among them, there were 36 patients who underwent CBC at least once within 1 year before, and again within 1 year after the initiation of PPI.

On Pearson's correlation analysis the following continuous variables correlated significantly with Hb level: age, body mass index (BMI), DBP, white blood cell (WBC), eGFR, and serum Na concentration (Table 2). Among categorical variables, the following were associated with Hb on unpaired Student's t-test: gender, heart failure, peripheral artery disease, and use of PPI, diuretics, or antiplatelet agents (Table 3).

Multivariate Factors Associated With Hb

Multiple regression analysis was performed to examine the factors associated with Hb level, using the following factors with P<0.1 on univariate analysis: age, gender, BMI, DBP, WBC, eGFR, Na, heart rate, heart failure, peripheral artery disease, and use of PPI, diuretics, and antiplatelet agents. Female sex, peripheral artery disease, use of PPI, low WBC, old age, and low eGFR were independently associated with low Hb (Table 4).

Factors Associated With Anemia

Table 5 lists differences of clinical characteristics between patients with anemia and those without anemia. Among continuous variables, the following were significantly different between patients with and those without anemia on unpaired Student's t-test: age, BMI, SBP, DBP, WBC, platelet, eGFR, uric acid, and serum Na and K concentration. Among categorical variables, the following factors were significantly different between patients with anemia and those without anemia on chi-squared test: gender, history of gastroduodenal ulcer, heart

Table 3. Effects of Medication and Comorbidity on Hb Concentration

Clinical characteristics	Hemoglobin (g/dl)		P-value
	(+)	(−)	
Male (+)/Female (−)	14.1±1.7	12.5±1.6	<0.001
Comorbidity			
History of gastroduodenal ulcer	13.9±1.3	13.5±1.9	0.452
Reflux esophagitis	13.4±1.9	13.6±1.8	0.559
Hypertension	13.6±1.9	13.6±1.9	0.968
Diabetes mellitus	13.4±1.8	13.7±1.8	0.234
Dyslipidemia	13.5±1.7	13.6±2.0	0.878
Heart failure	13.1±2.1	13.7±1.8	0.022
Angina pectoris	13.5±1.8	13.6±1.9	0.798
Old MI	13.6±1.9	13.5±1.8	0.631
History of PCI	13.8±1.8	13.5±1.9	0.143
Cerebral infarction	13.2±1.9	13.6±1.8	0.303
Cerebral hemorrhage	12.9±2.5	13.6±1.8	0.418
Dementia	12.2±1.5	13.6±1.8	0.187
PAD	12.2±2.0	13.7±1.8	<0.001
Medication			
Proton pump inhibitor	12.8±1.8	13.9±1.7	<0.001
H_2-blockers	13.4±1.5	13.6±1.9	0.696
Statins	13.7±1.8	13.5±1.9	0.408
Uric acid-lowering agent	14.0±2.0	13.5±1.8	0.132
Oral hypoglycemic agent	13.4±1.7	13.6±1.9	0.482
Insulin	12.8±1.8	13.6±1.8	0.277
ARB	13.5±1.9	13.6±1.8	0.799
Diuretics	13.0±2.0	13.8±1.7	<0.001
ACEI	13.9±2.1	13.5±1.8	0.251
Calcium channel blocker	13.6±1.8	13.5±1.9	0.879
β-blocker	13.6±2.0	13.5±1.7	0.757
Other anti-hypertensive agent	13.3±2.1	13.6±1.8	0.559
Antiplatelet agent	13.3±1.8	13.8±1.8	0.039
Aspirin	13.4±1.8	13.7±1.8	0.199
DPI	13.3±2.0	13.6±1.8	0.194
Warfarin	13.5±2.0	13.6±1.8	0.909
Warfarin+DPI	13.6±2.0	13.6±1.8	0.993

Data given as mean±SD. Differences in continuous variables between groups were assessed using unpaired Student's t-test. Abbreviations as in Table 1.

Table 4. Multivariate Factors Associated With Hb Concentration

Factor	β	P-value
Gender (male)	0.367	<0.001
PAD	−0.191	0.003
PPI	−0.178	0.003
WBC	0.185	0.004
Age	−0.173	0.007
eGFR	0.164	0.010
BMI	0.088	0.158
DBP	0.082	0.184
Diuretics	−0.082	0.218
Na	0.064	0.275
Heart rate	−0.057	0.348
Antiplatelet agents	0.026	0.671
Heart failure	−0.008	0.903

Abbreviations as in Table 1.

failure, peripheral artery disease, and use of PPI, diuretics, β-blockers, antiplatelet agents, aspirin, or dual platelet inhibitors (DPI).

In order to examine the factors associated with anemia, logistic regression analysis was performed using the following factors with P<0.1 on univariate analysis: age, gender, BMI, SBP, DBP, WBC, platelet, eGFR, uric acid, serum Na and K concentration, history of gastroduodenal ulcer, diabetes mellitus, heart failure, peripheral artery disease, and use of PPI, oral hypoglycemic agents, β-blockers, and antiplatelet agents. Use of aspirin and DPI were excluded because it is a confounding factor for the antiplatelet agent. Similarly, use of diuretics was excluded because it is a confounding factor for heart failure. Use of PPI, low eGFR, old age, and low WBC were independently associated with anemia (Table 6).

Acid Suppression Agents and Incidence of Anemia

The frequency of anemia according to WHO criteria was 51% in patients receiving PPI (n=88), and 19% in those not receiving PPI (n=190; chi-squared test, P<0.001). In patients who

Table 5. Clinical Characteristics vs. Presence of Anemia

Clinical characteristics	With anemia	Without anemia	P-value
n	81	197	
Age (years)	75.4±9.7	67.7±10.4	<0.001
Male gender	50 (61.7)	141 (71.6)	0.019
BMI (kg/m^2)	23.1±4.0	24.2±3.9	0.038
SBP (mmHg)	127.0±21.5	133.3±19.3	0.026
DBP (mmHg)	71.8±12.0	77.8±12.7	<0.001
Heart rate (beats/min)	75.7±14.6	73.2±12.6	0.237
Hb (g/dl)	11.4±1.1	14.4±1.2	<0.001
WBC ($10^2/\mu$l)	56.4±17.0	61.9±16.9	0.015
Plt ($10^4/\mu$l)	18.0±5.4	19.8±5.4	0.013
eGFR (ml·min^{-1}·1.73 m^{-2})	52.1±20.3	71.5±19.0	<0.001
UA (mg/dL)	6.2±2.0	5.7±1.3	0.040
Na (mEq/L)	139.0±3.9	140.2±1.8	<0.001
K (mEq/L)	4.4±0.4	4.3±0.3	0.022
Cl (mEq/L)	104.3±3.9	104.3±2.3	0.921
Comorbidity			
History of gastroduodenal ulcer	2 (2.5)	19 (9.6)	0.045
Reflux esophagitis	10 (12.3)	15 (7.6)	0.249
Hypertension	59 (72.8)	134 (68.0)	0.476
Diabetes mellitus	37 (45.7)	67 (34.0)	0.077
Dyslipidemia	43 (53.1)	117 (59.4)	0.352
Heart failure	29 (35.8)	30 (15.2)	<0.001
Angina pectoris	27 (33.3)	54 (27.4)	0.384
Old MI	29 (35.8)	52 (26.4)	0.146
History of PCI	23 (28.4)	55 (27.9)	1.000
Cerebral infarction	11 (13.6)	16 (8.1)	0.183
Cerebral hemorrhage	3 (3.7)	2 (1.0)	0.150
Dementia	2 (2.5)	1 (0.5)	0.204
PAD	14 (17.3)	8 (4.1)	<0.001
Medication			
Proton pump inhibitor	45 (55.6)	43 (21.8)	<0.001
H_2-blocker	8 (9.9)	16 (8.1)	0.643
Statins	35 (43.2)	91 (46.2)	0.692
Uric acid-lowering agent	14 (17.3)	24 (12.2)	0.256
Oral hypoglycemic agent	23 (28.4)	36 (18.3)	0.076
Insulin	4 (4.9)	3 (1.5)	0.199
ARB	44 (54.3)	104 (52.8)	0.895
Diuretics	42 (51.9)	41 (20.8)	<0.001
ACEI	14 (17.3)	27 (13.7)	0.460
Calcium channel blocker	39 (48.1)	81 (41.1)	0.290
β-blockers	50 (61.7)	84 (42.6)	0.005
Other antihypertensive agent	6 (7.4)	10 (5.1)	0.571
Antiplatelet agent	55 (67.9)	91 (46.2)	0.001
Aspirin	48 (59.3)	82 (41.6)	0.008
DPI	21 (25.9)	30 (15.2)	0.042
Warfarin	22 (27.2)	39 (19.8)	0.203
Warfarin+DPI	3 (3.7)	6 (3.0)	0.723

Data given as mean±SD or n (%). Differences in continuous and categorical variables between groups were assessed using unpaired Student's t-test and chi-squared test, respectively. Abbreviations as in Table 1.

did not receive PPI, the frequency of anemia was 17% in patients not taking acid suppression agents (n=166), whereas it was 33% in patients taking histamine H_2-receptor blocker (n=24). The differences in frequency of anemia among the 3 groups were statistically significant only between patients who received PPI and those who received no acid suppression agents (chi-squared test followed by Bonferroni correction, P<0.001). **Figure** shows the effect of acid suppression agents on Hb and mean corpuscular volume (MCV). Mean Hb was 12.8±1.8 g/dl in patients with PPI, 13.4±1.5 g/dl in patients with H_2-blocker, and 14.0±1.7 g/dl in patients with no acid suppression agents (P<0.001, PPI vs. no acid suppression

Table 6. Logistic Regression: Factors Associated With Anemia

Factor	β	P-value
PPI	0.893	<0.001
eGFR	−1.078	0.005
Age	0.737	0.025
WBC	−0.733	0.031
PAD	0.507	0.082
Antiplatelet agents	−0.446	0.168
Na	−0.365	0.185
Plt	0.309	0.269
UA	−0.327	0.317
Diabetes mellitus	0.372	0.323
β-blocker	0.275	0.352
Heart failure	0.249	0.361
DBP	−0.303	0.384
K	−0.196	0.493
Gender (male)	−0.172	0.506
Oral hypoglycemic agents	0.169	0.640
SBP	−0.073	0.839
BMI	0.040	0.888
History of gastroduodenal ulcer	−0.013	0.990

Abbreviations as in Table 1.

agents; 1-way ANOVA followed by Tukey post-hoc test), whereas MCV was not significantly different between the 3 groups.

Decrease in Hb After Initiation of PPI

Among 278 patients, we examined the change in Hb after the initiation of PPI in 36 patients who underwent CBC at least once within 1 year before and again 1 year after the initiation of PPI. We compared average Hb level within 1 year before initiation of PPI and that within 1 year after the initiation of PPI. Hb, mean corpuscular Hb concentration, platelets and red blood cells significantly decreased after the initiation of PPI (Table 7). Decrease in average Hb was 0.38±0.87 g/dl (95% confidence interval: –0.67 to –0.09 g/dl). Serum creatinine increased after initiation of PPI, but the change in Hb was not correlated with the change in creatinine (r=–0.13, P=0.44).

Discussion

In order to verify the association between PPI and anemia, we retrospectively investigated the clinical characteristics of 278 continuous outpatients who visited the Cardiovascular Division of Hyogo College of Medicine Hospital. The frequency of anemia was significantly higher in patients receiving PPI than in those receiving no PPI. Multivariate analysis confirmed that PPI treatment was independently associated with low Hb and anemia. Moreover, decrease in average Hb during 1 year after PPI treatment was 0.38±0.87 g/dl, which was significantly greater than the reported annual decrease in Hb of 0.08–0.04 g/dl/year for men and 0.05–0.04 g/dl/year for women.[13] These findings suggest that PPI decrease Hb. It is possible that PPI were prescribed to the patients with peptic ulcer and that the peptic ulcer itself caused anemia, but patients with major bleeding within 1 year were excluded from the present study and history of peptic ulcer was not associated with low Hb in the present subjects. Thus, we think that PPI treatment, not gastrointestinal bleeding, caused anemia. The present findings suggest that PPI use is one of the causes of cryptogenic anemia in cardiovascular outpatients. PPI should be continued, however, in most patients who take antiplatelet agents or anticoagulants. First, PPI have been clearly demonstrated to prevent gastrointestinal bleeding among pa-

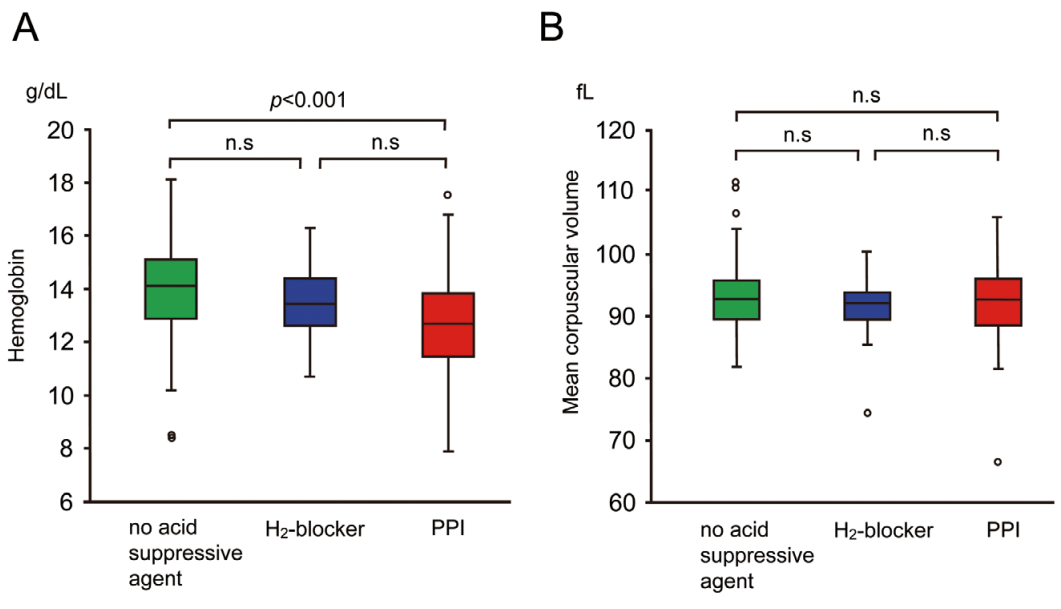

Figure. Box plot of (A) hemoglobin and (B) mean corpuscular volume vs. acid suppression agent. Box, interquartile range; horizontal line within box, median; whiskers, smallest and largest non-outlier values; open circles, outliers. PPI, proton pump inhibitor.

Table 7. Changes in Hematological Parameters After Initiation of PPI

	Before initiation of PPI	After initiation of PPI	P-value
Hb (g/dl)	13.5±1.9	13.1±1.9	0.013
MCH (pg)	30.7±1.7	30.6±1.7	0.311
MCHC (g/dl)	33.1±0.9	32.9±0.9	0.017
MCV (fl)	92.9±4.0	92.9±3.9	0.863
Plt ($10^4/\mu l$)	19.7±3.4	18.8±3.1	0.014
RBC ($10^4/\mu l$)	439.6±54.9	429.4±51.9	0.048
WBC ($10^2/\mu l$)	65.3±20.0	62.2±17.2	0.216
Cr (mg/dl)	0.86±0.26	0.95±0.32	<0.001

Data given as mean±SD. Hb before and after the initiation of PPI was compared using paired t-test. Cr, creatinine. Other abbreviations as in Table 1.

tients receiving antiplatelet agents and anticoagulants.[14,15] The COGENT study showed that omeprazole inhibited gastrointestinal events among patients receiving aspirin and clopidogrel in coronary artery disease.[16] Second, Chitose et al confirmed that PPI were safe to use for cardiovascular events using P2Y12 receptor antagonists in Japanese patients.[17] In their study, a total of 1,270 patients taking dual antiplatelet therapy, aspirin and thienopyridine, were enrolled and divided into 2 groups according to use of PPI. They concluded that intake of PPI was not associated with an increased risk for adverse clinical outcome in patients treated with stent placement. In the present subjects, the prevalence of history of gastroduodenal ulcer was similar in patients with and those without PPI despite the higher rate of aspirin use in patients with PPI than in those without PPI. Gastroduodenal ulcer might have been prevented by the PPI in the present study.

PPI have been suggested to cause anemia by several mechanisms. One is suppression of iron absorption. Iron is an essential molecule for cellular physiology, and body iron content is tightly regulated. Because no efficient pathway exists for iron excretion, body iron is regulated primarily at the level of dietary iron absorption.[18,19] Dietary iron in 2 forms, ferric iron (non-haem) and ferrous iron (haem), is absorbed using distinct transmembrane transport systems consisting of 3 elements: a specific transport protein complex; an enzyme changing the oxidative iron state; and regulatory proteins. Non-haem ferric iron is converted into ferrous iron by reducing enzyme duodenal cytochrome b and absorbed through divalent metal transporter-1 on the cell membrane of the intestinal epithelium.[20–24] Gastric acid assists in the dissociation of iron salts from food and the reduction of ferric iron to the more soluble ferrous iron.[25] Krieg et al verified that high pH in the stomach is associated with iron deficiency anemia, using mice with loss-of-function mutation in the α subunit of H^+,K^+-ATPase.[26] Another mechanism is suppression of vitamin B_{12} absorption. Gastric acid also facilitates the release of vitamin B_{12} bound to proteins within ingested foodstuffs to permit binding to R-proteins for eventual absorption in the terminal ileum.[25] Given that PPI are potent gastric acid secretion inhibitors, a decrease in gastric acid secretion due to PPI may affect the absorption of iron and vitamin B_{12}, and long-term use of PPI may result in anemia. The frequency of anemia in patients who received histamine H_2-blocker tended to be lower than in PPI users and higher than in patients without acid suppression agents, even though these differences did not reach statistical significance. These findings suggest that PPI induces anemia via pH-dependent mechanisms.

With regard to the impact of PPI on iron absorption, however, conflicting results have been reported depending on the disease: for example, PPI had no impact on iron absorption in patients with Zollinger-Ellison syndrome,[27] whereas they inhibited iron absorption in patients with hemochromatosis.[28] PPI treatment was associated with anemia but not with low MCV in the present subjects. These findings suggested that both iron deficiency and vitamin B_{12} deficiency contributed to the development of anemia.

Given that anemia is directly involved in oxygen transport capacity, it is highly likely to be associated with cardiac function. We have previously reported that anemia was associated with high brain natriuretic peptide concentration in the general population.[29] Anemia, occurring in as much as 56.7% of cases of chronic heart failure in Japan, has proven to be an independent risk factor for all-cause mortality, cardiac death, and readmission for exacerbation of heart failure.[30] Therefore, drug-induced anemia should not be neglected in cardiovascular outpatients, who are often at high risk of heart failure. Accumulation of iron in excess has been implicated in the risk of cardiovascular disease or cancer through increased iron catalyzed free radical-mediated oxidative stress.[31,32] Moreover, under physiological conditions, a high concentration of Hb causes stroke and myocardial infarction via thrombus formation. Thus, the effects of long-term PPI on morbidity and mortality in patients with cardiovascular diseases remain to be elucidated. Large-scale prospective studies investigating the prognostic impact of long-term use of PPI in cardiovascular out patients are warranted.

Although Ajmal et al reported that inhibitors of the renin-angiotensin system (RAS) such as angiotensin-converting enzyme inhibitor or angiotensin receptor blocker were associated with lower Hb,[33] RAS inhibitors were not associated with anemia in the present subjects. The present study may not have had sufficient statistical power to detect effects of RAS inhibitors on Hb level because of the small sample size. Effects of RAS inhibitors should be examined in a larger subject group in Japan.

Conclusions

PPI use was associated with decreased Hb in Japanese cardiovascular outpatients. The long-term impact of PPI-associated anemia in these patients remains to be elucidated.

Study Limitations

The present study had several limitations. Thorough examination of the gastrointestinal tract was not done in all patients. Latent gastrointestinal bleeding might cause anemia in patients

with PPI. Second, serum iron, ferritin, and vitamin B_{12} concentration were not examined. Other unknown mechanisms might contribute to anemia associated with PPI.

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Disclosures

No conflicts of interest declared.

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