ORIGINAL RESEARCH

Prognostic Impact of Baseline Hemoglobin Levels on Long-Term Thrombotic and Bleeding Events After Percutaneous Coronary Interventions

Kazuya Nagao, MD; Hirotoshi Watanabe, MD; Takeshi Morimoto, MD; Tsukasa Inada, MD; Fujio Hayashi, MD; Yoshihisa Nakagawa, MD; Yutaka Furukawa, MD; Kazushige Kadota, MD; Takashi Akasaka, MD; Masahiro Natsuaki, MD; Ken Kozuma, MD; Kengo Tanabe, MD; Yoshihiro Morino, MD; Hiroki Shiomi, MD; Takeshi Kimura, MD; on behalf of the CREDO-Kyoto PCI/CABG Registry Cohort-2, RESET, and NEXT Investigators*

Background—Association of baseline hemoglobin levels with long-term adverse events after percutaneous coronary interventions has not been yet thoroughly defined. We aimed to assess the clinical impact of baseline hemoglobin on long-term ischemic and bleeding risk after percutaneous coronary intervention.

Methods and Results—Using the pooled individual patient-level data from the 3 percutaneous coronary intervention studies, we categorized 19 288 patients into 4 groups: high-normal hemoglobin (≥14.0 g/dL; n=7555), low-normal hemoglobin (13.0–13.9 g/dL in men and 12.0–13.9 g/dL in women; n=5303), mild anemia (11.0–12.9 g/dL in men and 11.0–11.9 g/dL in women; n=4117), and moderate/severe anemia (<11.0 g/dL; n=2313). Median follow-up duration was 3 years. Low-normal hemoglobin, mild anemia, and moderate/severe anemia correlated with significant excess risk relative to high-normal hemoglobin for GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries Trial) moderate/severe bleeding, with adjusted hazard ratios of 1.22 (95% CI, 1.04–1.44), 1.73 (95% CI, 1.47–2.04), and 2.31 (95% CI, 1.92–2.78), respectively. Moderate/severe anemia also correlated with significant excess risk relative to high-normal hemoglobin for the ischemic composite end point of myocardial infarction/ischemic stroke (adjusted hazard ratio, 1.33; 95% CI, 1.11–1.60), whereas low-normal hemoglobin and mild anemia did not. However, the excess risk of low-normal hemoglobin, mild anemia, and moderate/severe anemia relative to high-normal hemoglobin remained significant for ischemic stroke and for mortality.

Conclusions—Decreasing baseline hemoglobin correlated with incrementally higher long-term risk for major bleeding, ischemic stroke, and mortality after percutaneous coronary intervention. Even within normal range, lower baseline hemoglobin level correlated with higher ischemic and bleeding risk. **(*J Am Heart Assoc*. 2019;8:e013703. DOI: 10.1161/JAHA.119.013703.)**

Key Words: anemia • bleeding • hemoglobin • ischemia • percutaneous coronary interventions

From the Department of Cardiovascular Center, Osaka Red Cross Hospital, Osaka, Japan (K.N., T.I., F.H.); Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan (H.W., H.S., T.K.); Department of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya, Japan (T.M.); Department of Cardiovascular and Respiratory Medicine, Shiga University of Medical Science, Otsu, Japan (Y.N.); Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital, Kobe, Japan (Y.F.); Department of Cardiology, Kurashiki Central Hospital, Kurashiki, Japan (K. Kadota); Department of Cardiovascular Medicine, Wakayama Medical University, Wakayama, Japan (T.A.); Department of Cardiovascular Medicine, Saga University, Saga, Japan (M.N.); Department of Cardiology, Teikyo University Hospital, Tokyo, Japan (K. Kozuma); Department of Cardiology, Mitsui Memorial Hospital, Tokyo, Japan (K.T.); and Department of Cardiology, Iwate University Hospital, Morioka, Japan (Y.M.).

Accompanying Appendix S1, Data S1, Tables S1 through S4, and Figures S1 through S3 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013703

*A complete list of the RESET and NEXT Investigators can be found in the Supplemental Material.

Correspondence to: Takeshi Kimura, MD, Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan. E-mail: taketaka@kuhp.kyoto-u.ac.jp

Received June 21, 2019; accepted September 23, 2019.

Clinical Perspective

What Is New?

- One third of patients undergoing percutaneous coronary intervention had anemia, as defined per the World Health Organization criteria.
- Moderate/severe anemia (hemoglobin <10.9 g/dL) was associated with a markedly higher risk for long-term ischemic and bleeding events, as well as mortality.
- Even mild anemia (hemoglobin 11.0–12.9 g/dL for men and 11.0–11.9 g/dL for women) and low-normal hemoglobin (hemoglobin 13.0–13.9 g/dL for men and 12.0–13.9 g/dL for women) correlated with significantly higher risk for ischemic stroke, serious bleeding events, such as GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries Trial) moderate bleeding, and mortality compared with high-normal hemoglobin (hemoglobin ≥14.0 g/dL).

What Are the Clinical Implications?

- Given the excess bleeding and ischemic risk of even a small decline in hemoglobin at the threshold of 14 g/dL, we might as well pay attention to the preprocedural hemoglobin value as an indicator of long-term clinical outcomes in patients planned for percutaneous coronary intervention.
- Future studies would be warranted to address the optimal antithrombotic therapy in patients with anemia who have both high ischemic and bleeding risk.

Anemia is highly prevalent in patients with cardiovascular diseases.[1–3] Among patients undergoing percutaneous coronary interventions (PCIs), preexisting anemia is known to correlate with a higher risk of short- and long-term mortality,[4,5] major adverse cardiovascular events,[6] and major in-hospital bleeding complications.[7,8] To date, most studies have used the conventional World Health Organization (WHO) thresholds of anemia (<13.0 g/dL for men and <12.0 g/dL for women)[7,9]; however, as the WHO definition of anemia encompasses a wide range of hemoglobin values, the severity of anemia (ie, mild, moderate, or severe) should be taken into consideration for the precise risk estimation. In addition, the threshold hemoglobin value correlating with the increased ischemic and/or bleeding risk after PCI could be higher than the WHO criteria of anemia; the different levels of baseline hemoglobin value, even among patients without anemia, might influence on the long-term ischemic and bleeding outcome. Hence, this study aims to comprehensively assess the clinical impact of the levels of baseline hemoglobin on long-term ischemic and bleeding risk after PCI.

Methods

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

Using the pooled individual patient-level data, we constructed a pooled database of 3 Japanese PCI studies, which were conducted after the introduction of a drug-eluting stent (DES): CREDO-Kyoto (Coronary Revascularization Demonstrating Outcome Study in Kyoto) PCI/CABG (Coronary Artery Bypass Grafting) Registry Cohort-2,[10] RESET (Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent Trial),[11] and NEXT (NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-Eluting Stent Trial)[12] (Figure 1). The design and major results of all studies have been described previously.[10–12] CREDO-Kyoto enrolled consecutive patients undergoing first PCI or CABG during the study period. In RESET and NEXT, patients scheduled for PCI with DES were to be enrolled without any exclusion criteria. Therefore, there were no exclusion criteria relevant to the current topic. The relevant review boards at all participating centers for each study approved each research protocol for the 3 studies. Because of retrospective enrollment, the requirement for written informed consent from patients was waived in the CREDO-Kyoto PCI/CABG Registry Cohort-2; however, we excluded those patients who refused participation in the study when contacted for follow-up. Written informed consent was obtained from all study patients in RESET and NEXT. Among 19 489 patients undergoing PCI enrolled in all 3 studies combined, the present study population included 19 288 patients from 122 Japanese PCI centers, after excluding 201 patients whose baseline hemoglobin value was unavailable (Figure 1). The follow-up durations were 5 years in the CREDO-Kyoto PCI/CABG Registry Cohort-2 and 3 years in the RESET and NEXT. In this study, the follow-up was censored at 3 years to standardize the follow-up duration across 3 studies.

We attained procedural anticoagulation with unfractionated heparin following the local site protocols. Of note, neither glycoprotein IIb/IIIa inhibitor nor bivalirudin was used in any patient. The recommended antiplatelet regimen comprised aspirin (≥81 mg/d) indefinitely and thienopyridines (75 mg of clopidogrel or 200 mg of ticlopidine daily) for ≥3 months for DESs and ≥1 month for bare-metal stents. However, the actual duration of dual-antiplatelet therapy (DAPT) was left to the discretion of each attending physician. Likewise, duration of triple antithrombotic therapy of DAPT and warfarin was left to the discretion of each attending physician. The status of antiplatelet therapy was assessed throughout the follow-up period using the same method across all 3 studies. We

defined the discontinuation of DAPT as persistent, if either aspirin or thienopyridine was discontinued for ≥2 months.

Anemia was defined by the standard WHO classification: no anemia (hemoglobin ≥13.0 g/dL for men and ≥12.0 g/dL for women); mild anemia (hemoglobin 11.0–12.9 g/dL for men and 11.0–11.9 g/dL for women); moderate anemia (hemoglobin 8.0–10.9 g/dL); and severe anemia (hemoglobin <8.0 g/dL).[9] Patients without anemia were further subdivided into 2 groups: high-normal hemoglobin (hemoglobin ≥14.0 g/dL) and low-normal hemoglobin (hemoglobin 13.0–13.9 g/dL for men and 12.0–13.9 g/dL for women). The cutoff value of hemoglobin 14.0 g/dL was selected considering the distribution of hemoglobin value and ease for clinical application. We compared the baseline characteristics and clinical outcomes across the 4 groups, including the high-normal hemoglobin, low-normal hemoglobin, mild anemia, and moderate/severe anemia groups.

Definition of Clinical Outcome Measures

In this study, the primary ischemic outcome measure was a composite of myocardial infarction (MI) and ischemic stroke (fatal or nonfatal), whereas the primary bleeding outcome measure was GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial) moderate/severe bleeding (severe, life-threatening intracerebral bleeding or bleeding that caused substantial hemodynamic compromise needing treatment; and moderate, bleeding that needed transfusion).[13] The secondary outcome measures included all-cause death, cardiovascular death, noncardiovascular death, MI, definite stent thrombosis, stroke, ischemic stroke, hemorrhagic stroke, GUSTO severe bleeding, GUSTO moderate bleeding, gastrointestinal bleeding, intracranial bleeding, any coronary revascularization, and heart failure hospitalization. Intracranial bleeding included both hemorrhagic stroke and traumatic brain injury. Detailed definitions of the clinical events can be found in Data S1. An independent clinical event committee in each study adjudicated all the end point events.

Statistical Analysis

Categorical variables are expressed as number and percentage and compared across baseline hemoglobin groups using the χ^2 test. Continuous variables are expressed as mean with SD or median with interquartile range and compared across baseline hemoglobin groups using the ANOVA or the Kruskal-Wallis test, depending on their distributions. We estimated the cumulative 3-year incidence with the Kaplan-Meier method and assessed the differences across baseline hemoglobin groups by the log-rank test. We also performed a landmark analysis at 30 days after index PCI. Surviving patients within 30 days were included for the analysis beyond 30 days. Using the multivariable Cox proportional hazard models, the risks of low-normal hemoglobin, mild anemia, and moderate/severe anemia relative to high-normal hemoglobin (reference) on the outcome measures were expressed as hazard ratios and their 95% CIs. We used a dummy code variable for low-normal hemoglobin, mild anemia, and moderate/severe anemia to assess the hazard ratios relative to high-normal hemoglobin. Corroborating our previous study,[14] we included 34 clinically relevant factors (Table 1) as the risk-adjusting variables and incorporated the centers and studies as the stratification variables in the multivariable Cox proportional hazard models. We also treated the 4 groups of anemic status as an ordinal variable and estimated the linear trend in the same multivariable Cox proportional hazard models. To determine the risks for hemorrhagic stroke and intracranial bleeding, we constructed parsimonious models with the clinically relevant 13 risk-adjusting variables (Table 1) because of a small number of patients with event. Proportional hazard assumptions for the risk-adjusting variables were assessed on the plots of log (time) versus log (−log [survival]), stratified by the variable and verified to be acceptable. We also conducted the subgroup analyses for the primary bleeding outcome measure. The same 34 risk-adjusting variables used in the entire cohort were included in the multivariable Cox proportional hazard models. For the subgroup analyses stratified by warfarin use, atrial fibrillation, shock, malignancy, and platelet count, we constructed parsimonious models with the same 13 risk-adjusting variables used in the parsimonious models in the entire cohort because of a small number of patients with outcome. Furthermore, we conducted a sensitivity analysis in which we combined high-normal hemoglobin group and low-normal hemoglobin group into one group (no anemia group), so that we could evaluate the risk of mild and moderate/severe anemia relative to no anemia, as defined per the conventional WHO criteria. We also performed another sensitivity analysis in which we divided the high-normal hemoglobin group further into very high hemoglobin group (hemoglobin ≥16 g/dL) and high-normal hemoglobin group (hemoglobin 14.0–15.9 g/dL) and evaluated the risk of very high hemoglobin, mild anemia, and moderate/severe anemia using high-normal hemoglobin group as the reference. All analyses of the Cox proportional hazard model with stratification were performed with SPSS, version 19 (IBM Corporation, Armonk, NY). All other analyses were performed with JMP, version 10.0, software (SAS Institute Inc, Cary, NC) and GraphPad Prism 6.05 (GraphPad Software, Inc, La Jolla, CA). In this study, all reported P values were 2 tailed, and we considered $P<0.05$ as statistically significant.

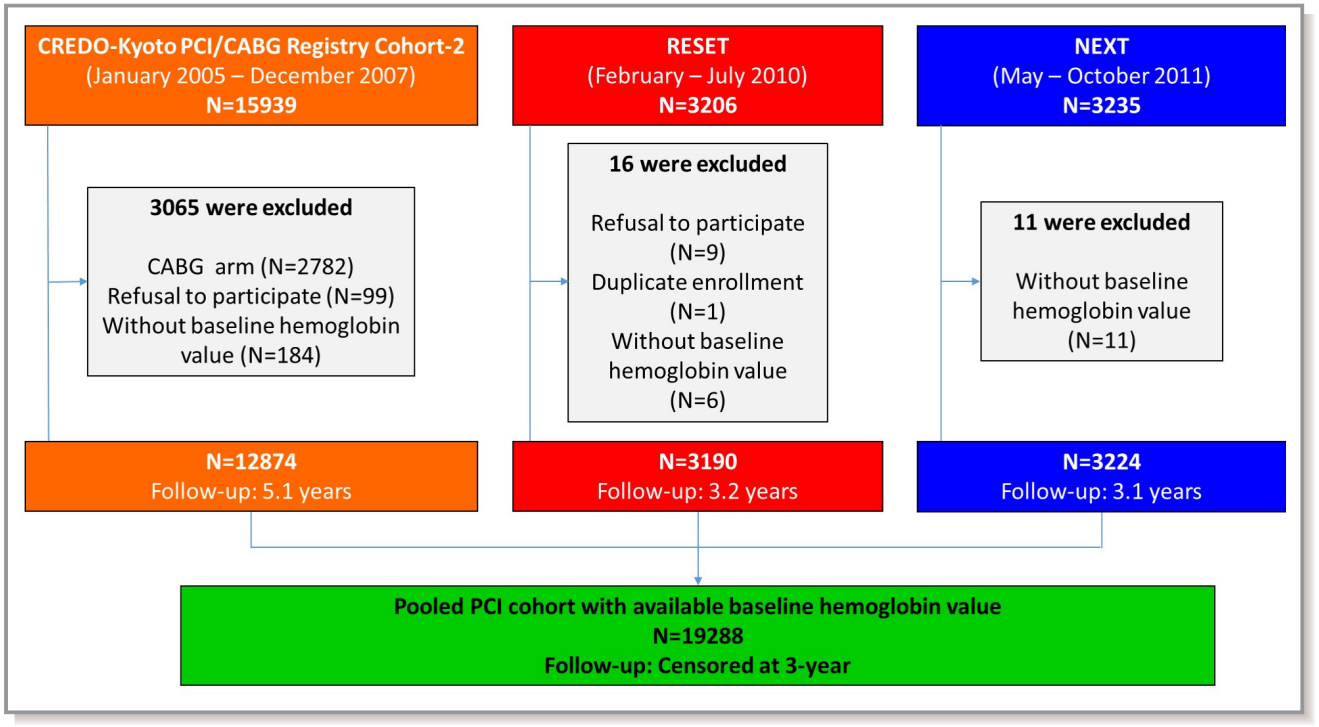


Figure 1. Study flow. CABG indicates coronary artery bypass grafting; CREDO-Kyoto PCI/CABG Registry, Coronary Revascularization Demonstrating Outcome Study in Kyoto Percutaneous Coronary Intervention/CABG Registry; NEXT, NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-Eluting Stent Trial; RESET, Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent Trial.

Results

Baseline Characteristics Based on the Levels of Hemoglobin

In the entire study population, the median baseline hemoglobin value measured on median 1 (interquartile range, 0–5) day before index PCI was 13.4 (interquartile range, 12.1–14.6) g/dL. Overall, 6430 patients (33.3%) had anemia: mild (N=4117; 21.3%), moderate (N=2152; 11.2%), or severe (N=161; 0.8%). Among the remaining 12 858 patients without anemia, the median baseline value of hemoglobin was 14.2 g/dL; the baseline hemoglobin was ≥14 g/dL in 7555 patients. Accordingly, the study population consisted of the 4 groups: high-normal hemoglobin (≥14.0 g/dL) group: N=7555 (39.2%); low-normal hemoglobin (13.0–13.9 g/dL in men and 12.0–13.9 g/dL in women) group: N=5303 (27.5%); mild anemia (11.0–12.9 g/dL in men and 11.0–11.9 g/dL in women) group: N=4117 (21.3%); and moderate/severe anemia (<11.0 g/dL) group: N=2313 (12.0%) (Figure 2).

The baseline patient characteristics were markedly different across the 4 groups. Overall, with decreasing hemoglobin value, incrementally higher proportion of patients had advanced age, lower body mass index, and comorbidities, including hypertension, diabetes mellitus, end-stage renal disease not on dialysis with an estimated glomerular filtration rate <30 mL/min per 1.73 m^2, and malignancy. In addition, the proportions of patients with a history of heart failure, multivessel disease, reduced left ventricular ejection fraction, history of MI, stroke, peripheral vascular disease, and atrial fibrillation were incrementally higher with the increasing severity of anemia (Table 1). Conversely, the proportion of patients who presented as having acute MI was higher in the high-normal group compared with that in the other 3 groups. For the lesion and procedural characteristics, the target lesion was more likely to be right coronary artery lesion, restenotic lesion, aortic ostial lesion, and bifurcation lesion with increasing severity of anemia. In addition, the prevalence of cilostazol use was higher in the high-normal group than in the other 3 groups, whereas the prevalence of statin use was higher in the high- and low-normal groups compared with the mild and moderate/severe anemia groups. In all 4 groups, <10% of patients received warfarin, with no significant difference across the groups. Furthermore, the prevalence of calcium channel blockers, nitrates, and histamine-2 receptor blocker or proton-pump inhibitor use was incrementally higher with the increasing severity of anemia (Table 1).

Long-Term Ischemic Outcomes Based on the Levels of Hemoglobin

Median follow-up duration was 3 years; clinical follow-up at 3 years was completed in 94.6% of patients overall. The rate of

persistent discontinuation of DAPT through 3-year follow-up was only slightly, but significantly different across the 4 groups (Figure S1). Median (interquartile range) duration of DAPT was 571 (67–1095) days, 674 (91–1095) days, 630 (106–1095) days, and 439 (45–1095) days in the high-normal hemoglobin, low-normal hemoglobin, mild anemia, and moderate/severe anemia groups, respectively ($P<0.001$).

The cumulative 3-year incidence of the primary ischemic outcome measure (a composite of MI and ischemic stroke) was incrementally higher with decreasing baseline hemoglobin (Figure 3A). After adjusting for confounders, the excess risk of the moderate/severe anemia group relative to the high-normal hemoglobin group remained significant for the primary ischemic outcome measure, whereas it was no longer significant in the low-normal hemoglobin and mild anemia groups (Table 2 and Figure 4). However, the adjusted risk for ischemic stroke was significantly higher in the low-normal hemoglobin, mild anemia, and moderate/severe anemia groups than in the high-normal hemoglobin group, whereas decreasing baseline hemoglobin did not affect the risk for MI (Table S1).

Long-Term Bleeding Outcomes Based on the Levels of Hemoglobin

The cumulative 3-year incidence of the primary bleeding outcome measure was incrementally higher with decreasing baseline hemoglobin (Figure 3B). After adjusting for confounders, the excess risk of the low-normal hemoglobin, mild anemia, and moderate/severe anemia groups relative to the high-normal hemoglobin group remained highly significant for the primary bleeding outcome measure and GUSTO moderate bleeding (Table 2, Figure 4, and Table S1). The moderate/severe anemia group was also associated with significant excess risk for intracranial bleeding (Table S1). By the landmark analysis at 30 days after index PCI, the cumulative 3-year incidence of the primary bleeding outcome measure was incrementally higher, with decreasing baseline hemoglobin both within and beyond 30 days (Figure S2A). Adjusted excess risk of the mild and moderate/severe anemia groups relative to the high-normal hemoglobin group for the primary bleeding outcome measure remained significant both within and beyond 30 days, whereas the risk of the low-normal hemoglobin group was significant within 30 days, but it was no longer significant beyond 30 days (Figure S2B).

For the relationship between bleeding events and DAPT status, 68% (952 events) of the primary bleeding events occurred while under DAPT. The proportion of primary bleeding events while under DAPT to all primary bleeding events was incrementally higher with the decreasing baseline hemoglobin (Figure S3A). The proportion of primary bleeding events that needed blood transfusion and distribution of bleeding sources was not significantly different across the 4 groups (Figure S3B and S3C).

Long-Term Mortality Based on the Levels of Hemoglobin

The cumulative 3-year incidence of all-cause death was also incrementally higher with decreasing baseline hemoglobin. After adjusting confounders, the excess risk of the low-normal hemoglobin, mild anemia, and moderate/severe anemia groups relative to the high-normal hemoglobin group remained significant for all-cause death, driven by the excess risk for both cardiovascular and noncardiovascular death (Table S1).

Subgroup Analysis

There was significant interaction between those subgroup factors, such as sex, shock, renal function, and atrial fibrillation, and the effect of hemoglobin levels on the primary bleeding outcome measure. The effect of decreasing baseline hemoglobin on the primary bleeding outcome measure was more prominent in men, patients without shock, patients with estimated glomerular filtration rate $\geq$60 mL/min per 1.73 m^2, and patients without atrial fibrillation. There was no interaction in other subgroups, such as age, body mass index, malignancy, platelet counts, use of histamine-2 receptor blocker or proton-pump inhibitor, DAPT score, and use of DES (Figure 5). Of note, despite difference in baseline clinical and procedural characteristic between CREDO-Kyoto PCI/CABG Registry Cohort-2 and RESET/NEXT (Table S2), there was no significant interaction between the study and the effect of hemoglobin levels on the primary bleeding outcome measure (Figure 5).

Sensitivity Analysis

In the sensitivity analysis with 3 groups (ie, no anemia [combination of high-normal and low-normal hemoglobin], mild anemia, and moderate/severe anemia), adjusted excess risk of moderate/severe anemia relative to no anemia remained significant for both the primary ischemic and bleeding outcome measures, whereas the risk of mild anemia relative to no anemia remained significant for the primary bleeding outcome measure, but not for the primary ischemic outcome measure (Table S3). In the sensitivity analysis with 5 groups (ie, very high hemoglobin, high-normal hemoglobin, low-normal hemoglobin, mild anemia, and moderate/severe anemia), adjusted excess risk of moderate/severe anemia relative to high-normal hemoglobin remained significant for both the primary ischemic and the bleeding outcome measures, whereas the risk of mild anemia and low-normal

Table 1. Baseline Clinical and Procedural Characteristics and Medications

Variables	High-Normal Hemoglobin (Hemoglobin ≥14 g/dL) (N=7555; 39.2%)	Low-Normal Hemoglobin (13 g/dL ≤ Hemoglobin < 14 g/dL for Men and 12 g/dL ≤ Hemoglobin <14 g/dL for Women) (N=5303; 27.5%)	Mild Anemia (11 g/dL ≤ Hemoglobin <13 g/dL for Men and 11 g/dL ≤ Hemoglobin <12 g/dL for Women) (N=4117; 21.3%)	Moderate/Severe Anemia (Hemoglobin <11 g/dL) (N=2313; 12.0%)	*P* Value
Hemoglobin, median (IQR), g/dL	14.9 (14.4–15.7)	13.3 (13–13.6)	11.9 (11.5–12.5)	10 (9.2–10.6)	<0.001
Clinical characteristics					
Age, mean (SD), y	63.7 (10.4)	69.8 (9.5)	72.5 (9.2)	74.1 (9.8)	<0.001
≥75 y*,†	1115 (15)	1783 (34)	1888 (46)	1270 (55)	<0.001
Men*,†	6898 (91)	2953 (56)	3097 (75)	1245 (54)	<0.001
Body mass index, mean (SD), kg/m^2	24.8 (3.3)	23.9 (3.5)	23 (3.4)	22.3 (3.6)	<0.001
<25kg/m2*,†	4338 (57)	3540 (67)	3096 (75)	1858 (80)	<0.001
Clinical presentation					
Acute myocardial infarction*,†	2395 (32)	1199 (23)	843 (20)	511 (22)	<0.001
ST-segment–elevation myocardial infarction	2069 (27)	1010 (19)	696 (17)	411 (18)	<0.001
Hypertension*	6026 (80)	4329 (82)	3398 (83)	1990 (86)	<0.001
Diabetes mellitus	2824 (37)	2018 (38)	1777 (43)	1137 (49)	<0.001
Insulin therapy*	384 (5)	407 (8)	439 (11)	422 (18)	<0.001
Lipid-lowering therapy	3011 (40)	2513 (47)	1733 (42)	822 (36)	<0.001
Current smoker*	2992 (40)	1135 (21)	821 (20)	393 (17)	<0.001
History of heart failure*	946 (13)	770 (15)	834 (20)	831 (36)	<0.001
Multivessel coronary disease*	3757 (50)	2733 (52)	2305 (56)	1392 (60)	<0.001
Mitral regurgitation grade 3/4*	125 (2)	165 (3)	158 (4)	172 (7)	<0.001
Left ventricular ejection fraction, mean (SD), %	58.9 (12.4)	60.4 (12.3)	58.5 (13.3)	56.4 (13.8)	<0.001
Left ventricular ejection fraction ≤40%	540 (9)	352 (8)	383 (11)	270 (14)	<0.001
Prior myocardial infarction*,†	1112 (15)	839 (16)	810 (20)	472 (20)	<0.001
Prior percutaneous coronary intervention	993 (13)	867 (16)	898 (22)	432 (19)	<0.001
Prior coronary artery bypass grafting	80 (1)	80 (2)	106 (3)	57 (2)	<0.001
Prior stroke*,†	593 (8)	527 (10)	545 (13)	384 (17)	<0.001
Hemorrhagic stroke	81 (1)	84 (2)	69 (2)	47 (2)	0.002
Ischemic stroke	526 (7)	457 (9)	488 (12)	343 (15)	<0.001
Peripheral vascular disease*	370 (5)	352 (7)	431 (11)	378 (25)	<0.001
Estimated glomerular filtration rate <30 mL/min per 1.73 m^2, not on dialysis*	58 (0.8)	91 (2)	184 (4)	345 (15)	<0.001
Dialysis*,†	23 (0.3)	67 (1)	258 (6)	471 (20)	<0.001
Atrial fibrillation*,†	552 (7)	389 (7)	358 (9)	249 (11)	<0.001
Platelets, median (IQR), $\times 10^9$/L	207 (174–245)	206 (173–245)	198 (173–245)	203 (159–254)	<0.001

Continued

Table 1. Continued

Variables	High-Normal Hemoglobin (Hemoglobin ≥14 g/dL) (N=7555; 39.2%)	Low-Normal Hemoglobin (13 g/dL ≤ Hemoglobin < 14 g/dL for Men and 12 g/dL ≤ Hemoglobin <14 g/dL for Women) (N=5303; 27.5%)	Mild Anemia (11 g/dL ≤ Hemoglobin <13 g/dL for Men and 11 g/dL ≤ Hemoglobin <12 g/dL for Women) (N=4117; 21.3%)	Moderate/Severe Anemia (Hemoglobin <11 g/dL) (N=2313; 12.0%)	*P* Value
Chronic obstructive pulmonary disease*	218 (3)	174 (3)	149 (4)	72 (3)	<0.001
Liver cirrhosis*,†	120 (2)	92 (2)	97 (2)	70 (3)	<0.001
Malignancy*,†	398 (5)	394 (7)	483 (12)	347 (15)	<0.001
DAPT score, mean (SD)	1.2 (1.4)	0.6 (1.4)	0.5 (1.5)	0.6 (1.6)	<0.001
≥2	3115 (41)	1354 (26)	987 (24)	609 (26)	<0.001
Procedure characteristics					
Stent use	7198 (95)	5070 (96)	3945 (96)	2186 (95)	0.09
Drug-eluting stent*,†	4832 (64)	3675 (69)	3001 (73)	1572 (68)	<0.001
Sirolimus-eluting stent	3082 (41)	2164 (41)	1646 (40)	919 (40)	0.68
Paclitaxel-eluting stent	229 (3)	172 (3)	136 (3)	80 (3)	0.71
Everolimus-eluting stent	1089 (14)	910 (17)	826 (20)	389 (17)	<0.001
Biolimus-eluting stent	520 (7)	501 (9)	450 (11)	220 (10)	<0.001
Bare-metal stent	2857 (38)	1689 (32)	1170 (28)	735 (32)	<0.001
No. of target vessels, mean (SD)	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)	0.26
No. of target lesions, mean (SD)	1.4 (0.7)	1.4 (0.7)	1.4 (0.7)	1.4 (0.7)	0.79
Target of LAD	4453 (59)	2975 (56)	2213 (54)	1227 (53)	<0.001
Target of proximal LAD*	4220 (56)	2822 (53)	2109 (51)	1182 (51)	<0.001
Target of right coronary artery	2771 (37)	2011 (38)	1695 (41)	943 (41)	<0.001
Target of left circumflex coronary artery	2126 (28)	1486 (28)	1079 (26)	585 (25)	0.01
Target of unprotected left main coronary artery*	217 (3)	178 (3)	131 (3)	113 (5)	<0.001
Target of chronic total occlusion*	805 (11)	531 (10)	411 (10)	231 (10)	0.54
Target of restenotic lesion	258 (3)	238 (4)	234 (6)	132 (6)	<0.001
Target of bifurcation*	2282 (30)	1542 (29)	1175 (29)	657 (28)	0.16
Side-branch stenting*	265 (4)	206 (4)	142 (3)	82 (4)	0.63
Target of aortic ostium	117 (2)	127 (2)	106 (3)	94 (4)	<0.001
Use of intravascular ultrasound	4038 (53)	3058 (58)	2500 (61)	1300 (56)	<0.001
Total stent length, mean (SD), mm	35.0 (27.1)	35.2 (27.2)	36.0 (27.8)	35.7 (26.5)	0.24
>28 mm*	3243 (43)	2283 (43)	1788 (43)	1075 (46)	0.02
Minimum stent size, mean (SD), mm	3.0 (0.4)	2.9 (0.4)	2.9 (0.4)	2.9 (0.4)	<0.001
<3.0 mm*	2922 (39)	2452 (46)	1844 (45)	1052 (45)	<0.001
Medication at discharge					<0.001
Aspirin	7487 (99)	5242 (99)	4074 (99)	2276 (98)	0.04

Continued

Table 1. Continued

Variables	High-Normal Hemoglobin (Hemoglobin ≥14 g/dL) (N=7555; 39.2%)	Low-Normal Hemoglobin (13 g/dL ≤ Hemoglobin < 14 g/dL for Men and 12 g/dL ≤ Hemoglobin <14 g/dL for Women) (N=5303; 27.5%)	Mild Anemia (11 g/dL ≤ Hemoglobin <13 g/dL for Men and 11 g/dL ≤ Hemoglobin <12 g/dL for Women) (N=4117; 21.3%)	Moderate/Severe Anemia (Hemoglobin <11 g/dL) (N=2313; 12.0%)	*P* Value
Thienopyridines	7410 (98)	5205 (98)	4035 (98)	2241 (97)	0.002
Ticlopidine	5089 (67)	3245 (61)	2396 (58)	1415 (61)	<0.001
Clopidogrel	2290 (30)	1942 (37)	1622 (39)	826 (36)	<0.001
Cilostazol*,†	1274 (17)	687 (13)	556 (14)	307 (13)	<0.001
Warfarin*,†	622 (8)	390 (7)	359 (9)	189 (8)	0.10
Statins*	4894 (65)	3328 (63)	2275 (55)	1033 (45)	<0.001
β Blockers*	2536 (36)	1629 (31)	1361 (33)	791 (34)	0.002
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers II*	4519 (60)	3058 (58)	2500 (61)	1358 (59)	0.01
Calcium channel blockers*	2870 (38)	2286 (43)	1851 (45)	1033 (45)	<0.001
Nitrates*	2428 (32)	1721 (32)	1362 (33)	783 (34)	0.41
H2B or PPI‡	3386 (53)	2391 (54)	1915 (58)	1185 (62)	<0.001

Data are expressed as number (percentage) of patients unless otherwise indicated. DAPT indicates dual-antiplatelet therapy; H2B, histamine-2 receptor blocker; IQR; interquartile range; LAD, left anterior descending coronary artery; PPI, proton-pump inhibitor.

*Thirty-four variables incorporated into the multivariable analysis as the full-adjusting model.

†Thirteen variables incorporated into the multivariable analysis as the parsimonious model for hemorrhagic stroke and intracranial bleeding.

‡Data were available in 16 093 patients (83%).

hemoglobin relative to high-normal hemoglobin remained significant for the primary bleeding outcome measure, but not for the primary ischemic outcome measure (Table S4). Adjusted excess risk of very high hemoglobin relative to high-normal hemoglobin was not significant for both the primary ischemic outcome measure and the primary bleeding outcome measure (Table S4).

Discussion

The primary findings in this study are as follows: (1) One third of patients undergoing PCI had anemia, as defined per the WHO criteria. (2) With the increasing severity of anemia, patients trended to be older, have lower body mass index, and have more severe comorbidities. (3) Moderate/severe anemia was associated with a markedly higher risk for ischemic and bleeding events, as well as mortality. (4) Even mild anemia and low-normal hemoglobin correlated with significantly higher risk for ischemic stroke, serious bleeding events, such as GUSTO moderate bleeding, and mortality.

Corroborating the prior studies of patients undergoing PCI,[15] the incidence of anemia in this study was 33%, which is considerably higher than that reported in patients in a primary care setting,[16] possibly reflecting the higher prevalence of comorbidities predisposing to anemia in patients with coronary artery disease. Indeed, we observed that patients with lower hemoglobin correlated with more advanced age, lower body mass index, history of heart failure, and more severe comorbidities, including diabetes mellitus, reduced renal dysfunction, peripheral vascular disease, and history of malignancy.

Consistent with previous studies,[7,8] this study demonstrated a robust and strong correlation between the baseline hemoglobin levels and the subsequent bleeding outcome. Even a mild degree of anemia was associated with marked excess risk for major bleeding compared with high-normal hemoglobin. Most strikingly, even among patients without anemia, the lower level of baseline hemoglobin value was associated with higher long-term bleeding risk. The findings corroborated and expanded a previous report in patients with acute coronary syndromes, demonstrating that the 30-day rates of major bleeding progressively increase from the highest (>16 g/dL) to the lowest (10 g/dL) levels of baseline hemoglobin.[17] In patients with lower baseline hemoglobin levels, even a small decrease in hemoglobin might lead to transfusion at an earlier stage, which might result in increased bleeding events. Indeed, the incidence of GUSTO moderate bleeding (bleeding that needs transfusion) was incrementally

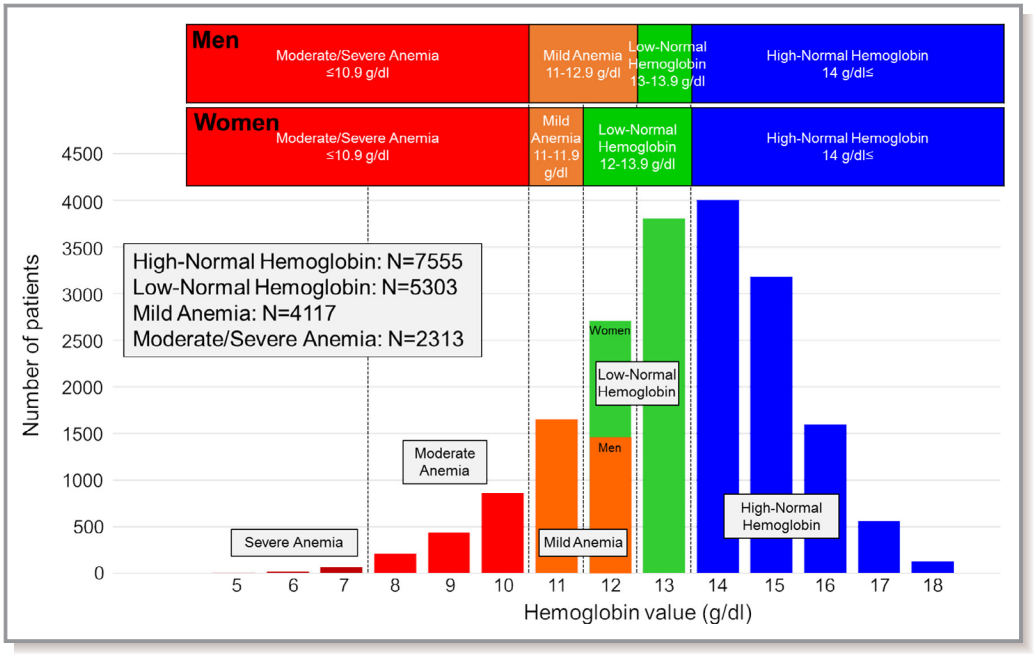
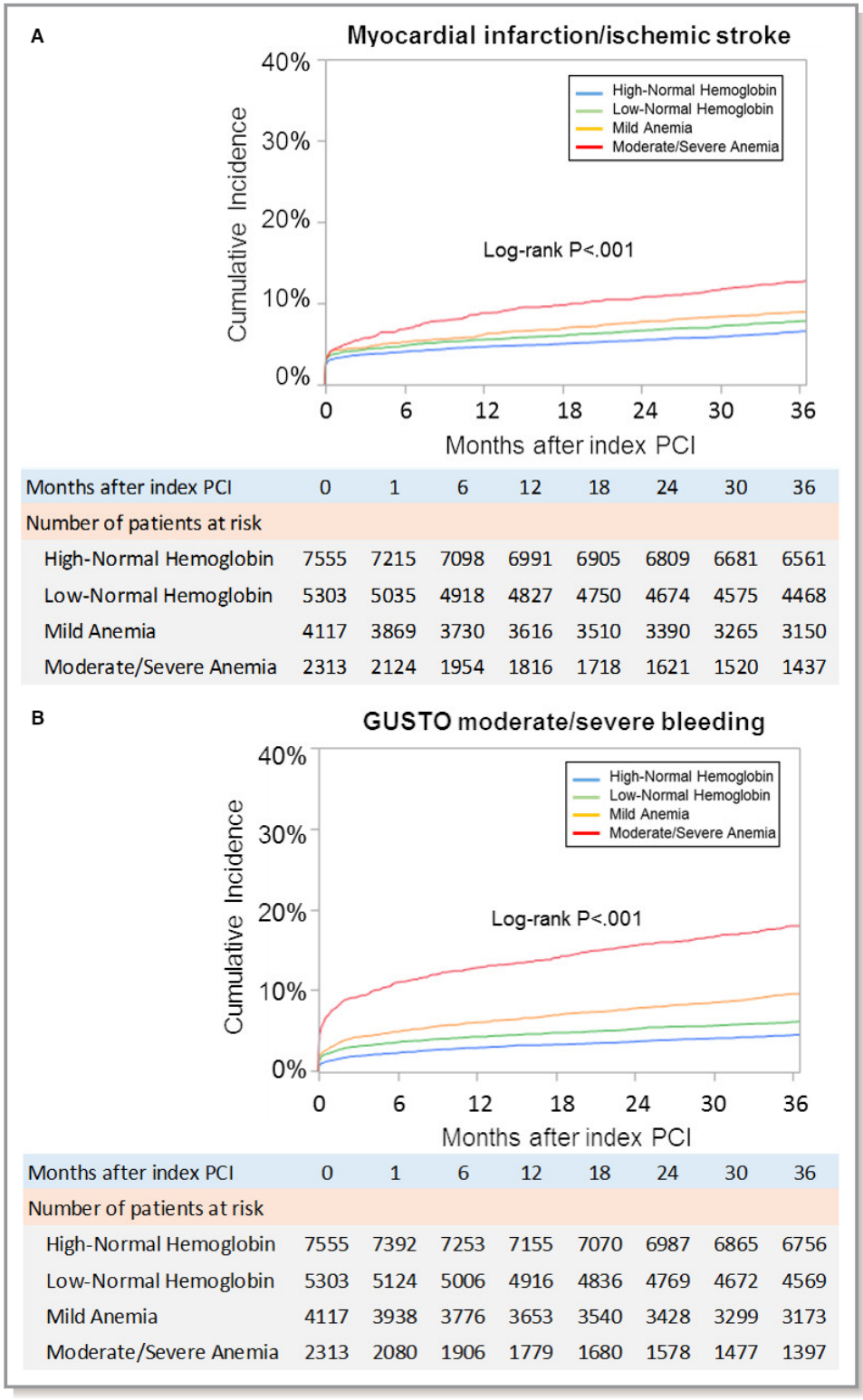


Figure 2. Distribution of hemoglobin at the baseline. All patients were categorized into 4 groups: high-normal hemoglobin (≥14.0 g/dL), low-normal hemoglobin (13.0–13.9 g/dL for men 12.0–13.9 g/dL for women), mild anemia (hemoglobin 11.0–12.9 g/dL for men and 11.0–11.9 g/dL for women), and moderate/severe anemia (hemoglobin <10.9 g/dL).

higher with the increasing severity of anemia in this study. In addition, preprocedural anemia could result from the presence of long-standing unrecognized hemorrhagic diathesis, which could result in an increased future risk for bleeding. Of note, the presence of a small decline in hemoglobin might often be regarded as "not severe" and dismissed. However, given the excess bleeding risk of even a small decline in hemoglobin at the threshold of 14 g/dL, we might as well pay attention to the low-normal hemoglobin value as an indicator of high bleeding risk in patients planned for PCI.

Previous studies in the eras of bare-metal stent have shown that baseline anemia was associated with increased risk of in-hospital or short-term (<30 days) incidence of MI or recurrent ischemia.[5,18,19] More recent study, including 6528 patients treated with DES with 4-year follow-up, demonstrated that the patients with baseline severe anemia (5.5% of the entire cohort) were associated with increased risk of MI compared with no/mild anemia.[4] In the present study, moderate/severe anemia was associated with excess risk for the long-term ischemic outcome measure, but this was driven by higher incidence of ischemic stroke rather than MI. The discrepancy of the results might be caused by the different categorization of severity of anemia. We combined moderate anemia group and severe anemia group into one group because proportion of patients with severe anemia in our study was small (<1%). Rather, our study more focused on the patients with mild anemia or without anemia. We observed that even mild anemia and low-normal hemoglobin were associated with significant excess risk relative to high-normal hemoglobin for the ischemic stroke. Several underlying mechanisms are plausible. As the tissue oxygen supply is limited because of the reduced hemoglobin value, patients would be more susceptible to ischemic events.[20] Alternatively, patients with anemia might exhibit a hypercoagulable state, which could exacerbate the risk of ischemic events.[21] Furthermore, advanced age and comorbidities related to anemia might result in the higher incidence of ischemic events. High ischemic and bleeding events, along with anemia-related comorbidities, could likely underlie the correlations between low hemoglobin levels and mortality. Unlike some previous studies dominantly enrolling the patients with acute coronary syndrome and examining short-term outcomes,[15,17,19] those with hemoglobin >16 g/dL in the present study did not appear to be at significantly increased risk for the long-term bleeding and ischemic outcomes relative to those with hemoglobin 14.0 to 15.9 g/dL.

In this study, we found that the rate of persistent discontinuation of DAPT through 3-year follow-up was only slightly different across the 4 groups, suggesting that baseline severity of anemia might not be taken into consideration in the decision making for DAPT duration. We are confronted with a difficult situation in deciding the intensity of antithrombotic therapy of patients with anemia who have both high ischemic and bleeding risk. The current guidelines generally



Months after index PCI	0	1	6	12	18	24	30	36
Number of patients at risk								
High-Normal Hemoglobin	7555	7215	7098	6991	6905	6809	6681	6561
Low-Normal Hemoglobin	5303	5035	4918	4827	4750	4674	4575	4468
Mild Anemia	4117	3869	3730	3616	3510	3390	3265	3150
Moderate/Severe Anemia	2313	2124	1954	1816	1718	1621	1520	1437

Months after index PCI	0	1	6	12	18	24	30	36
Number of patients at risk								
High-Normal Hemoglobin	7555	7392	7253	7155	7070	6987	6865	6756
Low-Normal Hemoglobin	5303	5124	5006	4916	4836	4769	4672	4569
Mild Anemia	4117	3938	3776	3653	3540	3428	3299	3173
Moderate/Severe Anemia	2313	2080	1906	1779	1680	1578	1477	1397

Figure 3. Kaplan-Meier curves for the primary ischemic and bleeding outcome measure. **A**, Myocardial infarction or ischemic stroke. **B**, GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries Trial) moderate/severe bleeding. PCI indicates percutaneous coronary intervention.

Table 2. Clinical Outcome Through 3 Years

Variable	High-Normal Hemoglobin	Low-Normal Hemoglobin	Mild Anemia	Moderate/Severe Anemia
Myocardial infarction/ischemic stroke				
Cumulative 3-y incidence (%)	486 (6.6)	405 (7.8)	352 (9.0)	265 (12.7)
Unadjusted HR (95% CI), *P* value	Reference	1.20 (1.05–1.37), *P*=0.007	1.38 (1.20–1.58), *P*<0.001	1.96 (1.68–2.27), *P*<0.001
Adjusted HR (95% CI), *P* value	Reference	1.14 (0.99–1.32), *P*=0.07	1.16 (1.00–1.35), *P*=0.05	1.33 (1.11–1.60), *P*=0.003
GUSTO moderate/severe bleeding				
Cumulative 3-y incidence (%)	329 (4.5)	316 (6.1)	374 (9.6)	383 (18.0)
Unadjusted HR (95% CI), *P* value	Reference	1.39 (1.19–1.62), *P*<0.001	2.20 (1.89–2.55), *P*<0.001	4.42 (3.81–5.12), *P*<0.001
Adjusted HR (95% CI), *P* value	Reference	1.22 (1.04–1.44), *P*=0.02	1.73 (1.47–2.04), *P*<0.001	2.31 (1.92–2.78), *P*<0.001

The outcomes were adjusted by 34 full-adjusting covariates listed in Table 1. GUSTO indicates Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial; HR, hazard ratio.

recommend less intensive antithrombotic therapy in patients with high bleeding risk.[22,23] Future studies would be warranted to address the optimal antithrombotic therapy in patients with anemia.

Limitations

This study has several limitations. First, this study did not address the causes of anemia. In addition, anemia was

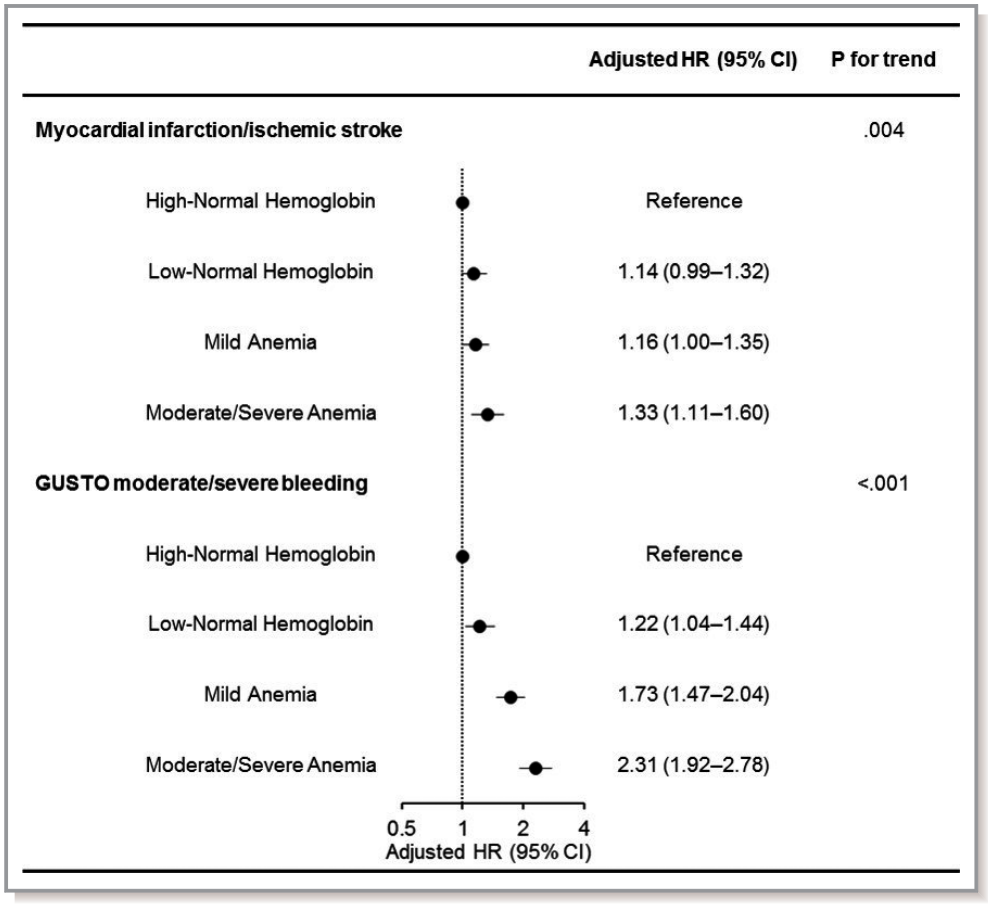


Figure 4. A hazard ratio plot showing the adjusted excess risk of the low-normal hemoglobin and mild and moderate/severe anemia groups relative to high-normal hemoglobin group for the primary ischemic and bleeding outcome measures. We included 34 clinically relevant factors indicated in Table 1 as the risk-adjusting variables and incorporated the centers and studies as the stratification variables in the multivariable Cox proportional hazard models. GUSTO indicates Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries Trial; HR, hazard ratio.

A

Variable	Number of patients	Cumulative 3-year incidence (%)	Hazard Ratio (95% CI)	P value	P value for Interaction
Age					.20
<75					
High-Normal Hemoglobin	6440	255 (4.0)	Reference		
Low-Normal Hemoglobin	3520	188 (5.3)	1.26 (1.03-1.55)	.03	
Mild Anemia	2229	185 (8.3)	1.78 (1.45-2.19)	<.001	
Moderate/Severe Anemia	1043	167 (16)	2.29 (1.77-2.95)	<.001	
>=75					
High-Normal Hemoglobin	1115	74 (6.6)	Reference		
Low-Normal Hemoglobin	1783	128 (7.2)	1.07 (.79-1.45)	.66	
Mild Anemia	1888	189 (10)	1.5 (1.14-1.99)	.004	
Moderate/Severe Anemia	1270	216 (17)	2.07 (1.55-2.78)	<.001	
Sex					.03
Men					
High-Normal Hemoglobin	6898	283 (4.1)	Reference		
Low-Normal Hemoglobin	2953	150 (5.1)	1.2 (0.98-1.48)	.08	
Mild Anemia	3097	285 (9.2)	2.01 (1.68-2.42)	<.001	
Moderate/Severe Anemia	1245	206 (16.5)	2.68 (2.14-3.35)	<.001	
Women					
High-Normal Hemoglobin	657	46 (7)	Reference		
Low-Normal Hemoglobin	2350	166 (7.1)	.98 (.7-1.37)	.92	
Mild Anemia	1020	89 (8.7)	1.07 (0.74-1.55)	.74	
Moderate/Severe Anemia	1068	177 (16.6)	1.52 (1.06-2.19)	.02	
Body-mass index					.77
<25					
High-Normal Hemoglobin	4338	204 (4.7)	Reference		
Low-Normal Hemoglobin	3540	223 (6.3)	1.18 (.96-1.44)	.11	
Mild Anemia	3096	289 (9.3)	1.68 (1.38-2.04)	<.001	
Moderate/Severe Anemia	1858	321 (17.3)	2.26 (1.83-2.8)	<.001	
>=25					
High-Normal Hemoglobin	3217	125 (3.9)	Reference		
Low-Normal Hemoglobin	1763	93 (5.3)	1.4 (1.04-1.88)	.03	
Mild Anemia	1021	85 (8.3)	1.91 (1.4-2.59)	<.001	
Moderate/Severe Anemia	455	62 (13.6)	2.47 (1.67-3.67)	<.001	
Acute coronary syndrome					.49
No					
High-Normal Hemoglobin	4492	154 (3.4)	Reference		
Low-Normal Hemoglobin	3707	182 (4.9)	1.27 (1.01-1.59)	.04	
Mild Anemia	2931	233 (8.0)	1.88 (1.51-2.34)	<.001	
Moderate/Severe Anemia	1583	229 (14.5)	2.55 (1.99-3.27)	<.001	
Yes					
High-Normal Hemoglobin	3063	175 (5.7)	Reference		
Low-Normal Hemoglobin	1596	134 (8.4)	1.15 (.89-1.47)	.28	
Mild Anemia	1186	141 (11.9)	1.44 (1.12-1.85)	.004	
Moderate/Severe Anemia	730	154 (21.1)	1.75 (1.31-2.34)	<.001	
ST-segment elevation myocardial infarction					.16
No					
High-Normal Hemoglobin	5486	200 (3.7)	Reference		
Low-Normal Hemoglobin	4293	212 (4.9)	1.17 (.95-1.43)	.14	
Mild Anemia	3421	285 (8.3)	1.80 (1.48-2.20)	<.001	
Moderate/Severe Anemia	1902	299 (15.7)	2.49 (2.00-3.10)	<.001	
Yes					
High-Normal Hemoglobin	2069	129 (6.2)	Reference		
Low-Normal Hemoglobin	1010	104 (10.3)	1.34 (1.01-1.78)	.04	
Mild Anemia	696	89 (12.8)	1.47 (1.09-2.00)	.01	
Moderate/Severe Anemia	411	84 (20.4)	1.77 (1.24-2.54)	.002	

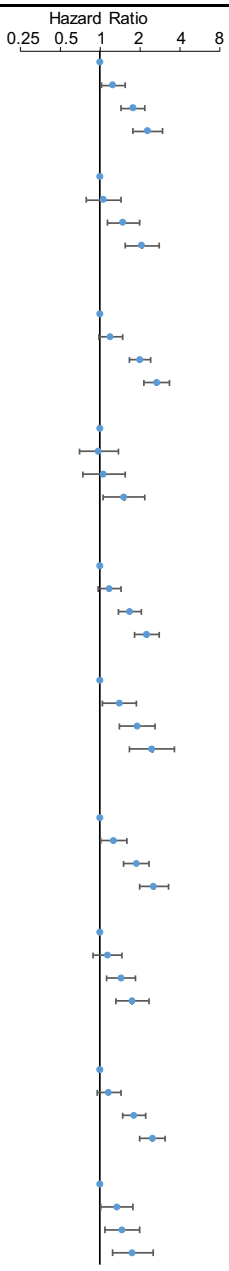


Figure 5. Subgroup analyses for the primary bleeding outcome in the clinically relevant subgroups. **A**, Hazard ratio of low-normal hemoglobin, mild anemia, and moderate/severe anemia relative to high-normal hemoglobin and *P* value for interaction between subgroup factors and the effect of hemoglobin levels on the primary bleeding outcome measure. The same 34 risk-adjusting variables used in the entire cohort were included in the multivariable Cox proportional hazard models. **B**, Continued, *We constructed parsimonious models with the 13 risk-adjusting variables used in the parsimonious models in the entire cohort. **C**, Continued, *We constructed parsimonious models with the 13 risk-adjusting variables used in the parsimonious models in the entire cohort. CREDO-Kyoto indicates Coronary Revascularization Demonstrating Outcome Study in Kyoto; DAPT, dual-antiplatelet therapy; H2B, histamine-2 receptor blocker; NEXT, NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-Eluting Stent Trial; PPI, proton-pump inhibitor; RESET, Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent Trial.

B

Variable	Number of patients	Cumulative 3-year incidence (%)	Hazard Ratio (95% CI)	P value	P value for Interaction
Shock*					<.001
No					
High-Normal Hemoglobin	7287	271 (3.7)	Reference		
Low-Normal Hemoglobin	5112	273 (5.3)	1.34 (1.12-1.60)	.001	
Mild Anemia	3934	328 (8.3)	2.00 (1.69-2.38)	<.001	
Moderate/Severe Anemia	2132	334 (15.7)	3.19 (2.64-3.85)	<.001	
Yes					
High-Normal Hemoglobin	210	58 (21.6)	Reference		
Low-Normal Hemoglobin	191	43 (22.5)	.98 (.62-1.57)	.94	
Mild Anemia	183	46 (25.1)	1.21 (.77-1.91)	.41	
Moderate/Severe Anemia	181	49 (25.0)	.1.32 (.80-2.17)	.28	
Estimated glomerular filtration rate					.01
>=60 ml/min/1.73m^2					
High-Normal Hemoglobin	5625	188 (3.3)	Reference		
Low-Normal Hemoglobin	3486	171 (4.9)	1.3 (1.03-1.63)	.03	
Mild Anemia	2009	140 (7)	1.78 (1.4-2.27)	<.001	
Moderate/Severe Anemia	644	87 (13.5)	2.88 (2.14-3.87)	<.001	
<60 ml/min/1.73m^2 or HD					
High-Normal Hemoglobin	1930	141 (7.3)	Reference		
Low-Normal Hemoglobin	1817	145 (8)	1.04 (.81-1.33)	.76	
Mild Anemia	2108	234 (11.1)	1.6 (1.28-2)	<.001	
Moderate/Severe Anemia	1669	296 (17.7)	2.22 (1.76-2.79)	<.001	
Atrial fibrillation*					.007
No					
High-Normal Hemoglobin	7003	286 (4.1)	Reference		
Low-Normal Hemoglobin	4914	269 (5.5)	1.24 (1.04-1.48)	.04	
Mild Anemia	3759	322 (8.6)	1.82 (1.53-2.17)	<.001	
Moderate/Severe Anemia	2064	335 (16.2)	2.55 (2.09-3.11)	<.001	
Yes					
High-Normal Hemoglobin	552	43 (7.8)	Reference		
Low-Normal Hemoglobin	389	47 (12.1)	1.19 (.73-1.91)	.49	
Mild Anemia	358	52 (14.5)	1.45 (.91-2.31)	.12	
Moderate/Severe Anemia	249	48 (19.3)	1.28 (.74-2.21)	.38	
Malignancy*					.50
No					
High-Normal Hemoglobin	7157	294 (4.1)	Reference		
Low-Normal Hemoglobin	4909	286 (5.8)	1.26 (1.06-1.50)	.009	
Mild Anemia	3634	318 (8.8)	1.77 (1.49-2.11)	<.001	
Moderate/Severe Anemia	1966	315 (16)	2.28 (1.87-2.79)	<.001	
Yes					
High-Normal Hemoglobin	398	35 (8.8)	Reference		
Low-Normal Hemoglobin	394	30 (7.6)	.93 (.54-1.58)	.78	
Mild Anemia	483	56 (11.6)	1.46 (.91-2.36)	.12	
Moderate/Severe Anemia	347	68 (19.6)	2.22 (1.36-3.64)	.001	
Platelet count*					.23
>=150x10^9/L					
High-Normal Hemoglobin	6746	273 (4)	Reference		
Low-Normal Hemoglobin	4685	274 (5.8)	1.41 (1.18-1.69)	<.001	
Mild Anemia	3421	288 (8.4)	2.04 (1.70-2.44)	<.001	
Moderate/Severe Anemia	1826	288 (15.8)	3.24 (2.65-3.96)	<.001	
<150x10^9/L					
High-Normal Hemoglobin	797	56 (7)	Reference		
Low-Normal Hemoglobin	606	42 (6.9)	.89 (.58-1.36)	.58	
Mild Anemia	689	85 (12.3)	1.62 (1.13-2.34)	.009	
Moderate/Severe Anemia	477	94 (19.7)	2.09 (1.42-3.08)	<.001	

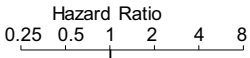


Figure 5. continued.

C

Variable	Number of patients	Cumulative 3-year incidence (%)	Hazard Ratio (95% CI)	P value	P value for Interaction
H2B or PPI					.95
No					
High-Normal Hemoglobin	3056	143 (4.7)	Reference		
Low-Normal Hemoglobin	2031	135 (6.6)	1.32 (1.02-1.70)	.03	
Mild Anemia	1405	141 (10)	1.78 (1.37-2.30)	<.001	
Moderate/Severe Anemia	724	134 (18.5)	2.52 (1.88-3.39)	<.001	
Yes					
High-Normal Hemoglobin	3386	147 (4.3)	Reference		
Low-Normal Hemoglobin	2391	153 (6.4)	1.30 (1.01-1.65)	.04	
Mild Anemia	1915	184 (9.6)	1.88 (1.48-2.38)	<.001	
Moderate/Severe Anemia	1185	211 (17.8)	2.58 (1.97-3.36)	<.001	
Warfarin*					.13
No					
High-Normal Hemoglobin	6933	285 (4.1)	Reference		
Low-Normal Hemoglobin	4913	278 (5.7)	1.35 (1.13-1.61)	.001	
Mild Anemia	3758	325 (8.7)	2.01 (1.69-2.39)	<.001	
Moderate/Severe Anemia	2124	348 (28.2)	3.25 (2.69-3.92)	<.001	
Yes					
High-Normal Hemoglobin	622	44 (7.1)	Reference		
Low-Normal Hemoglobin	390	38 (9.7)	1.16 (.72-1.88)	.54	
Mild Anemia	359	49 (13.7)	2.06 (1.31-3.25)	.002	
Moderate/Severe Anemia	189	35 (21.1)	1.59 (.89-2.85)	.12	
DAPT score					.08
>=2					
High-Normal Hemoglobin	3115	124 (4)	Reference		
Low-Normal Hemoglobin	1354	95 (7)	1.50 (1.12-2.00)	.007	
Mild Anemia	987	99 (10)	1.94 (1.44-2.62)	<.001	
Moderate/Severe Anemia	609	111 (18.2)	2.50 (1.77-3.54)	<.001	
<2					
High-Normal Hemoglobin	4440	205 (4.6)	Reference		
Low-Normal Hemoglobin	3949	221 (5.6)	1.08 (.88-1.32)	.46	
Mild Anemia	3130	275 (8.8)	1.59 (1.30-1.93)	<.001	
Moderate/Severe Anemia	1704	272 (16)	2.23 (1.79-2.77)	<.001	
Drug-eluting stent					.24
No					
High-Normal Hemoglobin	2723	164 (6.2)	Reference		
Low-Normal Hemoglobin	1628	149 (9.5)	1.26 (.99-1.60)	.06	
Mild Anemia	1116	159 (15.3)	1.83 (1.44-2.33)	<.001	
Moderate/Severe Anemia	741	178 (27.0)	2.52 (1.92-3.31)	<.001	
Yes					
High-Normal Hemoglobin	4832	165 (3.5)	Reference		
Low-Normal Hemoglobin	3675	167 (4.7)	1.16 (.92-146)	.20	
Mild Anemia	3001	215 (7.5)	1.62 (1.30-2.03)	<.001	
Moderate/Severe Anemia	1572	205 (14.0)	2.12 (1.65-2.73)	<.001	
Study					.82
CREDO-Kyoto 2					
High-Normal Hemoglobin	5430	270 (5)	Reference		
Low-Normal Hemoglobin	3470	261 (7.5)	1.28 (1.07-1.54)	.008	
Mild Anemia	2461	285 (11.6)	1.78 (1.48-2.13)	<.001	
Moderate/Severe Anemia	1513	294 (19.4)	2.32 (1.88-2.86)	<.001	
RESET/NEXT					
High-Normal Hemoglobin	2125	59 (2.8)	Reference		
Low-Normal Hemoglobin	1833	55 (3.1)	.98 (.66-1.45)	.92	
Mild Anemia	1656	89 (5.6)	1.46 (1.02-2.10)	.04	
Moderate/Severe Anemia	800	89 (12.0)	2.12 (1.41-3.17)	<.001	

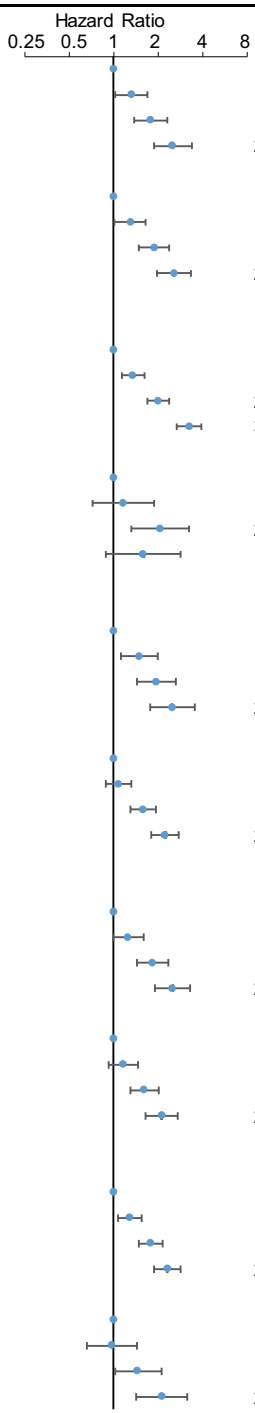


Figure 5. continued.

evaluated only at baseline. Some patients might have subclinical causes of bleeding, such as subclinical malignancies, that could lead to anemia later on. However, long-term change in hemoglobin and its correlation with the prognosis remain unclear. Second, we did not have the reference for the low-normal and high-normal hemoglobin groups; the current

study does not provide the definite threshold of hemoglobin to stratify the long-term ischemic and bleeding events. Nevertheless, the patients with low-normal hemoglobin still face marked excess risk for bleeding and stroke compared with those with high-normal hemoglobin. Third, despite comprehensive statistical adjustment for potential confounders and a wide range of interaction tests, unmeasured confounders could still have affected the study results. Finally, several patients in this study underwent PCI using bare-metal stent, the first-generation DES, and older antiplatelet agents, which are less frequently used in the current practice. In addition, the duration of DAPT was considerably long in the current study because the importance of DAPT has been stressed in each study era, whereas the results of randomized clinical trials of DAPT duration after PCI have not been published.[24,25] Thus, findings in this study should be cautiously applied to the current practice.

Conclusions

Decreasing baseline hemoglobin was associated with incrementally higher long-term risk for not only major bleeding, but also ischemic stroke and mortality after PCI. Even among patients without anemia, the lower level of baseline hemoglobin value was associated with higher long-term ischemic and bleeding risk.

Sources of Funding

CREDO-Kyoto PCI/CABG (Coronary Revascularization Demonstrating Outcome Study in Kyoto Percutaneous Coronary Intervention/Coronary Artery Bypass Grafting) Registry Cohort 2 is funded by Pharmaceuticals and Medical Devices Agency in Japan, RESET (Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent Trial) by Abbott Vascular Japan, Co, Ltd, and NEXT (NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-Eluting Stent Trial) by Terumo Japan, Co, Ltd.

Disclosures

Dr Kozuma reports honoraria from Abbott Vascular, Daiichi Sankyo, and Sanofi. Dr Tanabe reports honoraria from Abbott Vascular, Terumo Japan, Daiichi Sankyo, Sanofi, and AstraZeneca Japan. Dr Morino reports honoraria from Abbott Vascular and Terumo Japan. The remaining authors have no disclosures to report.

References

1. Karkouti K, Wijeysundera DN, Beattie WS. Risk associated with preoperative anemia in cardiac surgery: a multicenter cohort study. *Circulation*. 2008;117:478–484.
2. Peterson PN, Magid DJ, Lyons EE, Clarke CL, Zeng C, Fitzgerald A, Lindenfeld J, Kosiborod M, Brand D, Masoudi FA. Association of longitudinal measures of hemoglobin and outcomes after hospitalization for heart failure. *Am Heart J*. 2010;159:81–89.
3. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. *J Am Coll Cardiol*. 2002;39:1780–1786.
4. Pilgrim T, Vetterli F, Kalesan B, Stefanini GG, Raber L, Stortecky S, Gloekler S, Binder RK, Wenaweser P, Moschovitis A, Khattab AA, Buellesfeld L, Zwahlen M, Meier B, Juni P, Windecker S. The impact of anemia on long-term clinical outcome in patients undergoing revascularization with the unrestricted use of drug-eluting stents. *Circ Cardiovasc Interv*. 2012;5:202–210.
5. Voeltz MD, Patel AD, Feit F, Fazel R, Lincoff AM, Manoukian SV. Effect of anemia on hemorrhagic complications and mortality following percutaneous coronary intervention. *Am J Cardiol*. 2007;99:1513–1517.
6. Kitai Y, Ozasa N, Morimoto T, Bao B, Furukawa Y, Nakagawa Y, Kadota K, Yanagita M, Shizuta S, Kimura T. Prognostic implications of anemia with or without chronic kidney disease in patients undergoing elective percutaneous coronary intervention. *Int J Cardiol*. 2013;168:5221–5228.
7. Kwok CS, Tiong D, Pradhan A, Andreou AY, Nolan J, Bertrand OF, Curzen N, Urban P, Myint PK, Zaman AG, Loke YK, Mamas MA. Meta-analysis of the prognostic impact of anemia in patients undergoing percutaneous coronary intervention. *Am J Cardiol*. 2016;118:610–620.
8. Ali ZA, Poludasu S, Qureshi YH, Krishnan P, Ali AA, Tatonetti N, Downey P, Zalewski A, Nazif T, George I, Mandava A, Baber U, Dangas G, Mehran R, Kini AS, Sharma SK. Impact of major bleeding on long-term mortality in anemic versus nonanemic patients undergoing percutaneous coronary intervention using bivalirudin. *Am J Cardiol*. 2014;113:1481–1486.
9. Nutritional anaemias: report of a WHO scientific group. *World Health Organ Tech Rep Ser*. 1968;405:5–37.
10. Kimura T, Morimoto T, Furukawa Y, Nakagawa Y, Kadota K, Iwabuchi M, Shizuta S, Shiomi H, Tada T, Tazaki J, Kato Y, Hayano M, Abe M, Tamura T, Shirotani M, Miki S, Matsuda M, Takahashi M, Ishii K, Tanaka M, Aoyama T, Doi O, Hattori R, Tatami R, Suwa S, Takizawa A, Takatsu Y, Takahashi M, Kato H, Takeda T, Lee JD, Nohara R, Ogawa H, Tei C, Horie M, Kambara H, Fujiwara H, Mitsudo K, Nobuyoshi M, Kita T. Long-term safety and efficacy of sirolimus-eluting stents versus bare-metal stents in real world clinical practice in Japan. *Cardiovasc Interv Ther*. 2011;26:234–245.
11. Kimura T, Morimoto T, Natsuaki M, Shiomi H, Igarashi K, Kadota K, Tanabe K, Morino Y, Akasaka T, Takatsu Y, Nishikawa H, Yamamoto Y, Nakagawa Y, Hayashi Y, Iwabuchi M, Umeda H, Kawai K, Okada H, Kimura K, Simonton CA, Kozuma K. Comparison of everolimus-eluting and sirolimus-eluting coronary stents: 1-year outcomes from the randomized evaluation of sirolimus-eluting versus everolimus-eluting stent trial (RESET). *Circulation*. 2012;126:1225–1236.
12. Natsuaki M, Kozuma K, Morimoto T, Kadota K, Muramatsu T, Nakagawa Y, Akasaka T, Igarashi K, Tanabe K, Morino Y, Ishikawa T, Nishikawa H, Awata M, Abe M, Okada H, Takatsu Y, Ogata N, Kimura K, Urasawa K, Tarutani Y, Shiode N, Kimura T. Biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent: a randomized, controlled, noninferiority trial. *J Am Coll Cardiol*. 2013;62:181–190.
13. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med*. 1993;329:673–682.
14. Ito S, Watanabe H, Morimoto T, Yoshikawa Y, Shiomi H, Shizuta S, Ono K, Yamaji K, Soga Y, Hyodo M, Shirai S, Ando K, Horiuchi H, Kimura T. Impact of baseline thrombocytopenia on bleeding and mortality after percutaneous coronary intervention. *Am J Cardiol*. 2018;121:1304–1314.
15. Numasawa Y, Ueda I, Sawano M, Kuno T, Kodaira M, Noma S, Suzuki M, Miyata H, Fukuda K, Kohsaka S. Relation of baseline hemoglobin level to in-hospital outcomes in patients who undergo percutaneous coronary intervention (from a Japanese multicenter registry). *Am J Cardiol*. 2018;121:695–702.
16. Endres HG, Wedding U, Pittrow D, Thiem U, Trampisch HJ, Diehm C. Prevalence of anemia in elderly patients in primary care: impact on 5-year mortality risk and differences between men and women. *Curr Med Res Opin*. 2009;25:1143–1158.
17. Bassand JP, Afzal R, Eikelboom J, Wallentin L, Peters R, Budaj A, Fox KA, Joyner CD, Chrolavicius S, Granger CB, Mehta S, Yusuf S. Relationship between baseline haemoglobin and major bleeding complications in acute coronary syndromes. *Eur Heart J*. 2010;31:50–58.
18. McKechnie RS, Smith D, Montoye C, Kline-Rogers E, O'Donnell MJ, DeFranco AC, Meengs WL, McNamara R, McGinnity JG, Patel K, Share D, Riba A, Khanal S, Moscucci M. Prognostic implication of anemia on in-hospital outcomes after percutaneous coronary intervention. *Circulation*. 2004;110:271–277.
19. Sabatine MS, Morrow DA, Giugliano RP, Burton PB, Murphy SA, McCabe CH, Gibson CM, Braunwald E. Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. *Circulation*. 2005;111:2042–2049.

20. Levy PS, Quigley RL, Gould SA. Acute dilutional anemia and critical left anterior descending coronary artery stenosis impairs end organ oxygen delivery. *J Trauma*. 1996;41:416–423.
21. Smith KJ, Bleyer AJ, Little WC, Sane DC. The cardiovascular effects of erythropoietin. *Cardiovasc Res*. 2003;59:538–548.
22. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Juni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018;39:213–260.
23. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC Jr. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;68:1082–1115.
24. Bittl JA, Baber U, Bradley SM, Wijeysundera DN. Duration of dual antiplatelet therapy: a systematic review for the 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2016;134:e156–e178.
25. Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, Spertus JA, Steg PG, Cutlip DE, Rinaldi MJ, Camenzind E, Wijns W, Apruzzese PK, Song Y, Massaro JM, Mauri L. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA*. 2016;315:1735–1749.

Supplemental Material

Appendix

List of the participating centers and the investigators

CREDO-Kyoto registry cohort-2

Kyoto University Hospital: Takeshi Kimura
Kishiwada City Hospital: Mitsuo Matsuda, Hirokazu Mitsuoka
Tenri Hospital: Yoshihisa Nakagawa
Hyogo Prefectural Amagasaki Hospital: Hisayoshi Fujiwara, Yoshiki Takatsu, Ryoji Taniguchi
Kitano Hospital: Ryuji Nohara
Koto Memorial Hospital: Tomoyuki Murakami, Teruki Takeda
Kokura Memorial Hospital: Masakiyo Nobuyoshi, Masashi Iwabuchi
Maizuru Kyosai Hospital: Ryozo Tatami
Nara Hospital, Kinki University Faculty of Medicine: Manabu Shirotani
Kobe City Medical Center General Hospital: Toru Kita, Yutaka Furukawa, Natsuhiko Ehara
Nishi-Kobe Medical Center: Hiroshi Kato, Hiroshi Eizawa
Kansai Denryoku Hospital: Katsuhisa Ishii
Osaka Red Cross Hospital: Masaru Tanaka
University of Fukui Hospital: Jong-Dae Lee, Akira Nakano
Shizuoka City Shizuoka Hospital: Akinori Takizawa
Hamamatsu Rosai Hospital: Masaaki Takahashi
Shiga University of Medical Science Hospital: Minoru Horie, Hiroyuki Takashima
Japanese Red Cross Wakayama Medical Center: Takashi Tamura
Shimabara Hospital: Mamoru Takahashi
Kagoshima University Medica and Dental Hospital: Chuwa Tei, Shuichi Hamasaki
Shizuoka General Hospital: Hirofumi Kambara, Osamu Doi, Satoshi Kaburagi
Kurashiki Central Hospital: Kazuaki Mitsudo, Kazushige Kadota
Mitsubishi Kyoto Hospital: Shinji Miki, Tetsu Mizoguchi
Kumamoto University Hospital: Hisao Ogawa, Seigo Sugiyama
Shimada Municipal Hospital: Ryuichi Hattori, Takeshi Aoyama, Makoto Araki
Juntendo University Shizuoka Hospital: Satoru Suwa

RESET Trial

Caress Sappro Tokeidai Memorial Hospital: Kazushi Urasawa, Ryoji Koshida
Teine Keijinkai Hospital: Mitsugu Hirokami
Cardio-vascular Center Hokkaido Ohno Hospital: Takehiro Yamashita, Masato Nagashima
Caress Sappro Hokko Memorial Hospital: Yoichi Nozaki
Hokkaido Social Insurance Hospital: Keiichi Igarashi, Jungo Furuya

Aomori Prefectural Central Hospital: Fuminobu Yoshimachi, Yukinori Sakamoto
Iwate Prefectural Central Hospital: Akihiro Nakamura, Shigefumi Fukui
Iwate Medical University Hospital: Tomonori Itoh
Sendai Kosuei Hospital: Naoto Inoue, Kaname Takizawa
Tohoku Kousei Nenkin Hospital: Yoshiaki Katahira, Takao Nakano
Sendai Open Hospital: Atsushi Kato
Iwaki Kyoritsu General Hospital: Yoshito Yamamoto, Tomohiro Tada
Fukushima Medical University Hospital: Yasuchika Takeishi, Kazuhiko Nakazato
Hoshi General Hospital: Mikihiro Kijima, Yuichi Ujiie
Ohta Nishinouchi Hospital: Nobuo Komatsu, Goro Ishida
Saiseikai Kurihashi Hospital: Yoshimi Ota, Atsushi Honda
Saitama Cardiovascular And Respiratory Center: Makoto Muto, Tetsuya Ishikawa
Dokkyo Medical University Koshigaya Hospital: Takaaki Komatsu
Jikei University Kashiwa Hospital: Mitsuyuki Shimizu, Yoshiki Uehara
Juntendo University Hospital: Hiroyuki Daida, Katsumi Miyauchi
Sakakibara Memorial Hospital: Tetsuya Sumiyoshi, Ryuta Asano
NTT Medical Center Tokyo: Masao Yamasaki
The Cardiovascular Institute Hospital: Junji Yajima, Ryuichi Funada
Mitsui Memorial Hospital: Kengo Tanabe, Masanori Taniwaki
Tokyo Medical University Hospital: Nobuhiro Tanaka, Masashi Ogawa
Teikyo University Hospital: Akiyoshi Miyazawa, Ken Kozuma, Nobuaki Suzuki
Tokyo Women's Medical University Hospital: Nobuhisa Hagiwara, Fumiaki Mori
The Jikei University Hospital: Takayuki Ogawa, Kazuo Ogawa
Juntendo University Nerima Hospital: Masataka Sumiyoshi, Shinya Okazaki
Tokyo Metropolitan Hiroo General Hospital: Tamotsu Tejima, Yasuhiro Tanabe
St. Luke's International Hospital: Yutaro Nishi
Itabashi Chuo General Hospital: Hiroshi Ohta
Saiseikai Yokohama-city Eastern Hospital: Toshiya Muramatsu, Hiroshi Ishimori
Yokohama Rosai Hospital: Kenichi Kato, Kazuhiko Yumoto
Tokai University Hospital: Yoshihiro Morino
Yokohama City University Medical Center: Kazuo Kimura, Kiyoshi Hibi
Kitasato University Hospital: Taiki Tojo, Takao Shimohama
Kanazawa Cardiovascular Hospital: Masanobu Namura, Yuki Horita
University of Fukui Hospital: Jong-Dae Lee, Akira Nakano
Fukui Cardio Vascular Center: Sumio Mizuno, Katsushi Misawa
Juntendo University Shizuoka Hospital: Satoru Suwa
Shizuoka City Shizuoka Hospital: Tomoya Onodera, Ryosuke Takeuchi

Shizuoka General Hospital: Osamu Doi, Satoshi Kaburagi
Okamura Memorial Hospital: Yasuhiro Tarutani
Seirei Hamamatsu General Hospital: Hisayuki Okada
Hamamatsu Medical Center: Masakazu Kobayashi, Yohei Takayama
Toyohashi Heart Center: Takahiko Suzuki, Masashi Kimura
Aichi Medical University Hospital: Takayuki Ito, Hiroaki Takashima
Tosei General Hospital: Hiroshi Asano
Nagoya Daini Red Cross Hospital: Haruo Hirayama, Mamoru Nanasato, Yasushi Tatematsu
Toyota Memorial Hospital: Hisashi Umeda
Nagoya Kyoritsu Hospital: Toru Aoyama
Fujita Health University Hospital: Yukio Ozaki, Hiroyuki Naruse
Matsusaka Chuo General Hospital: Masatoshi Miyahara
Nagai Hospital: Kozo Hoshino
Mie University Hospital: Takashi Tanigawa
Mie Heart Center: Hideo Nishikawa, Hiroyuki Suzuki
Yokkaichi Social Insurance Hospital: Masaki Kawamura
Koto Memorial Hospital: Teruki Takeda
Shiga University of Medical Science Hospital: Takashi Yamamoto
Kyoto University Hospital: Takeshi Kimura, Hiroki Shiomi
Mitsubishi Kyoto Hospital: Shinji Miki, Tetsu Mizoguchi
National Hospital Organization Kyoto Medical Center: Mitsuru Abe
Kyoto Second Red Cross Hospital: Hiroshi Fujita
Sakurabashi Watanabe Hospital: Kenji Fujii
Osaka City General Hospital: Akira Itoh, Kazuhiro Osawa
Osaka Saiseikai Noe Hospital: Shunsuke Take, Shiho Koyama
Osaka City University Hospital: Minoru Yoshiyama, Satoshi Nishimura
Osaka Red Cross Hospital: Tsukasa Inada, Fujio Hayashi
National Cerebral and Cardiovascular Center: Hiroshi Nonogi, Eiji Tada
Sumitomo Hospital: Yuji Yasuga, Nobuhiro Mitsusada
Higashisumiyoshi Morimoto Hospital: Yuji Sakanoue
Kansai Denryoku Hospital: Katsuhisa Ishii, Kazuaki Kataoka
Kobe City Medical Center General Hospital: Makoto Kinoshita
Kobe University Hospital: Junya Shite, Hirotoshi Hariki
Kansai Rosai Hospital: Masaaki Uematsu, Masaki Awata
Hyogo Prefectural Amagasaki Hospital: Yoshiki Takatsu, Ryoji Taniguchi
Hyogo College of Medicine Hospital: Motomaru Masutani
Tenri Hospital: Yoshihisa Nakagawa, Hirokazu Kondo

Nara Medical University Hospital: Shiro Uemura, Kenichi Ishigami
Japanese Red Cross Society Wakayama Medical Center: Takashi Tamura, Hiroki Sakamoto
Wakayama Medical University Hospital: Takashi Akasaka, Hironori Kitabata
Tottori University Hospital: Masahiko Kato, Yoshiyuki Furuse
Matsue Red Cross Hospital: Kinya Shirota, Asao Mimura
The Sakakibara Heart Institute of Okayama: Keizou Yamamoto, Hiroyuki Takinami
Kurashiki Central Hospital: Kazushige Kadota, Hiroyuki Tanaka
Kawasaki Medical School Hospital: Hiroyuki Okura, Yoji Neishi
Okayama University Hospital: Hiroshi Ito, Yoshiki Hata
Hiroshima City Hospital: Masaharu Ishihara, Kazuoki Dai
Fukuyama Cardiovascular Hospital: Seiichi Haruta, Hideo Takebayashi
Tsuchiya General Hospital: Mamoru Toyofuku
Chikamori Hospital: Kazuya Kawai, Shuichi Seki
University Of Occupational And Environmental Health Japan: Shinjo Sonoda, Yoshitaka Muraoka
Kurume University Hospital: Takafumi Ueno, Seiji Kanaya
Kokura Memorial Hospital: Masashi Iwabuchi, Shinichi Shirai
Kouseikai Hospital: Yoshihiro Iwasaki
Saiseikai Kumamoto Hospital: Koichi Nakao
Kumamoto Rousai Hospital: Toshiyuki Matsumura, Sei Nakata
Miyazaki Medical Association Hospital: Yoshisato Shibata, Nehiro Kuriyama
Kagoshima Medical Center: Hitoshi Nakashima, Yasuhisa Iriki

NEXT Trial

Caress Sappro Tokeidai Memorial Hospital: Kazushi Urasawa, Ryoji Koshida
Oji General Hospital: Katsuhisa Ishii, Nobuo Kato
Hokkaido Junkanki Hospital: Daisuke Hotta, Masaru Yamaki
Teine Keijinkai Hospital: Mitsugu Hirokami
Cardio-vascular Center Hokkaido Ohno Hospital: Takehiro Yamashita, Masato Nagashima
Caress Sappro Hokko Memorial Hospital: Yoichi Nozaki
Japan Community Health Care Organization Hokkaido Hospital: Keiichi Igarashi, Jungo Furuya
Aomori Prefectural Central Hospital: Fuminobu Yoshimachi, Dai Miura, Yoshihisa Aida, Yukinori Sakamoto, Atsushi Konta
Iwate Prefectural Central Hospital: Akihiro Nakamura, Shigefumi Fukui, Sohta Nakajima
Iwate Medical University Hospital: Tetsuya Fusazaki
Tohoku Pharmaceutical University Hospital: Yoshiaki Katahira, Takao Nakano
Sendai Open Hospital: Atsushi Kato, Toru Takii

Iwaki Kyoritsu General Hospital: Yoshito Yamamoto, Tomohiro Tada
Fukushima Medical University Hospital: Yasuchika Takeishi, Kazuhiko Nakazato
Saiseikai Kurihashi Hospital: Yoshimi Ota, Atsushi Honda
Saitama Cardiovascular and Respiratory Center: Tetsuya Ishikawa, Takuro Fujii
Dokkyo Medical University Koshigaya Hospital: Takaaki Komatsu
New Tokyo Hospital: Sunao Nakamura, Naoyuki Kurita
Juntendo University Hospital: Hiroyuki Daida, Katsumi Miyauchi
Sakakibara Memorial Hospital: Itaru Takamisawa
NTT Medical Center Tokyo: Masao Yamasaki
The Cardiovascular Institute Hospital: Junji Yajima, Shingo Tanaka, Ryuichi Funada, Nobuhiro Murata
Mitsui Memorial Hospital: Kengo Tanabe, Yoshifumi Nakajima
Tokyo Medical University Hospital: Nobuhiro Tanaka, Masashi Ogawa, Naotaka Murata
Teikyo University Hospital: Ken Kozuma, Nobuaki Suzuki
Tokyo Women's Medical University Hospital: Nobuhisa Hagiwara, Fumiaki Mori, Junichi Yamaguchi
Juntendo University Nerima Hospital: Masataka Sumiyoshi, Kenji Inoue, Shinya Okazaki
Itabashi Chuo Medical Center: Hiroshi Ohta
Saiseikai Yokohama-city Eastern Hospital: Toshiya Muramatsu, Hiroshi Ishimori
Kanto Rosai Hospital: Atsuo Namiki
Yokohama Rosai Hospital: Kenichi Kato, Kazuhiko Yumoto
Tokai University Hospital: Nobuhiko Ogata, Shou Torii
Yokohama City University Medical Center: Kazuo Kimura, Kiyoshi Hibi
Kitasato University Hospital: Taiki Tojo, Takao Shimohama
Kanazawa Cardiovascular Hospital: Masanobu Namura, Yuki Horita
University of Fukui Hospital: Jong-Dae Lee, Hiroyasu Uzui, Akira Nakano
Fukui Cardiovascular Center: Sumio Mizuno, Katsushi Misawa
Ogaki Municipal Hospital: Hiroaki Mukawa, Yohei Shibata, Kazushi Terada
Juntendo University Shizuoka Hospital: Satoru Suwa
Shizuoka General Hospital: Osamu Doi, Hideaki Moriwaki, Hiroki Sakamoto
Okamura Memorial Hospital: Yasuhiro Tarutani
Seirei Hamamatsu General Hospital: Hisayuki Okada
Hamamatsu Medical Center: Masakazu Kobayashi, Terumori Sato, Yohei Takayama
Aichi Medical University Hospital: Hiroaki Takashima, Takayuki Ito, Amano Tetsuya
Tosei General Hospital: Masayoshi Ajioka, Yosuke Murase, Yusuke Sakamoto
Toyota Memorial Hospital: Hisashi Umeda, Kazutaka Hayashi
Fujita Health University Hospital: Yukio Ozaki, Hiroyuki Naruse

Japanese Red Cross Nagoya Daini Hospital: Haruo Hirayama, Yasushi Tatematsu, Hiroki Kamiya
Chubu Rosai Hospital: Tetsuya Amano, Tomohiro Yoshida, Tadayuki Uetani
Nagai Hospital: Kozo Hoshino
Mie University Hospital: Takashi Tanigawa, Toshiki Sawai
Mie Heart Center: Hideo Nishikawa, Hiroyuki Suzuki
Japan Community Health Care Organization Yokkaichi Hazu Medical Center: Masaki Kawamura, Takashi Yamanaka
Koto Memorial Hospital: Teruki Takeda
Shiga University of Medical Science Hospital: Takashi Yamamoto
Kyoto University Hospital: Takeshi Kimura, Masahiro Natsuaki, Hou Heigen, Hirotoshi Watanabe
Mitsubishi Kyoto Hospital: Shinji Miki, Tetsu Mizoguchi, Masashi Kato
National Hospital Organization Kyoto Medical Center: Masaharu Akao, Mitsuru Abe
Kyoto Second Red Cross Hospital: Hiroshi Fujita
Osaka University Hospital: Shinsuke Nanto, Masahiro Kumada, Kouichi Tachibana, Keita Okayama
Sakurabashi Watanabe Hospital: Kenshi Fujii
Osaka City General Hospital: Akira Itoh, Takahiro Naruko, Kei Yunoki
Osaka Saiseikai Noe Hospital: Shunsuke Take, Yoshihiro Kato, Shiho Koyama
Osaka City University Hospital: Takao Hasegawa, Tomokazu Iguchi
Osaka Red Cross Hospital: Tsukasa Inada, Fujio Hayashi
National Cerebral and Cardiovascular Center Hospital: Hiroki Sakamoto, Satoshi Yasuda
Sumitomo Hospital: Yuji Yasuga, Nobuhiro Mitsusada
Higashisumiyoshi Morimoto Hospital: Yuji Sakanoue
Bell Land General Hospital: Toru Kataoka
Kobe City Medical Center General Hospital: Natsuhiko Ehara
Kobe University Hospital: Toshihiro Shinke, Takumi Inoue, Junya Shite, Akihide Konishi
Kansai Rosai Hospital: Masaki Awata, Takayuki Ishihara
Hyogo Prefectural Amagasaki Hospital: Yoshiki Takatsu, Ryoji Taniguchi
Hyogo College of Medicine Hospital: Motomaru Masutani, Masaharu Ishihara
Tenri Hospital: Yoshihisa Nakagawa, Toshihiro Tamura
Japanese Red Cross Society Wakayama Medical Center: Takashi Tamura, Yuichi Kawase, Mamoru Toyofuku
Wakayama Medical University Hospital: Takashi Akasaka, Yasushi Ino, Hironori Kitabata
Tottori University Hospital: Masahiko Kato, Yoshiyuki Furuse
Matsue Red Cross Hospital: Kinya Shirota

The Sakakibara Heart Institute of Okayama: Atsushi Hirohata, Eiki Hirose
Kurashiki Central Hospital: Kazushige Kadota, Seiji Habara
Kawasaki Medical School Hospital: Hiroyuki Okura, Yoji Neishi
Hiroshima City Hospital: Masaharu Ishihara, Yasuharu Nakama
Fukuyama Cardiovascular Hospital: Hideo Takebayashi, Kenji Goto
Tsuchiya General Hospital: Nobuo Shiode, Masaya Otsuka, Mamoru Toyofuku
Iwakuni Clinical Center: Satoru Sakuragi
Chikamori Hospital: Kazuya Kawai, Shuichi Seki
University of Occupational and Environmental Health Japan: Shinjo Sonoda, Yoshitaka Muraoka
Fukuoka Wajiro Hospital: Taro Saito, Yoritaka Otsuka
Kurume University Hospital: Takafumi Ueno, Yoshiaki Mitsutake, Hidetoshi Chibana
Kokura Memorial Hospital: Masashi Iwabuchi, Shinichi Shirai
Kouseikai Hospital: Yoshihiro Iwasaki, Masahiko Ishizaki
Saiseikai Kumamoto Hospital: Koichi Nakao, Shinzo Miyamoto
National Hospital Organization Kumamoto Medical Center: Kazuteru Fujimoto
Kumamoto Rousai Hospital: Toshiyuki Matsumura, Takuo Tsurugi
Miyazaki Medical Association Hospital: Yoshisato Shibata, Nehiro Kuriyama
Tenyokai Central Hospital: Hiroshi Yamaguchi, Junichiro Takaoka, Nobuhiko Atsuchi
National Hospital Organization Kagoshima Medical Center: Hitoshi Nakashima, Tetsuro Kataoka, Keisuke Kusumoto

List of clinical research coordinators

Research Institute for Production Development

Saori Tezuka, Yumika Fujino, Misato Yamauchi, Naoko Okamoto, Miya Hanazawa, Risa Kato, Miyuki Tsumori, Masayo Kitamura, Itsuki Yamazaki, Chikako Hibi, Yuki Sato, Satoko Nishida, Yui Kinoshita, Hitomi Sasae, Yuriko Uchida, Asuka Takahashi, Emi Takinami, Yuko Yamamoto, Mai Yoshimoto, Izumi Miki, Asuka Saeki, Sachiko Maeda, Saeko Minematsu.

Data S1.

Supplemental Methods

Definitions of clinical events

MI was adjudicated with the definition of ARTS (Arterial Revascularization Therapies Study) in the CREDO Kyoto PCI/CABG registry cohort-2 and with the definition of ARC (Academic Research Consortium) consensus criteria for clinical end points in the RESET and NEXT.[1,2] The definitions for the endpoints other than MI were consistent across the 3 studies. Death was regarded as cardiovascular in origin unless obvious non-cardiovascular causes could be identified. Any death during the index hospitalization was regarded as cardiovascular death.Stroke was defined as ischemic or haemorrhagic stroke either occurring during the index hospitalization or requiring hospitalization with symptoms lasting >24 hour. Haemorrhagic infarction was classified into ischemic stroke based on its primary cause. Stent thrombosis was defined according to the definition of the ARC consensus.[2]

Table S1. Relationship between baseline Hb value and the secondary outcome measures through 3 years.

	High-normal Hb	Low-normal Hb	Mild anemia	Moderate/Severe anemia
All-cause death				
Cumulative 3-year incidence (%)	338 (4.5)	346 (6.6)	565 (14.0)	620 (27.4)
Unadjusted HR (95% CI), P value	Reference	1.47 (1.27–1.71), P<.001	3.21 (2.81–3.68), P<.001	6.89 (6.04–7.87), P<.001
Adjusted HR (95% CI), P value	Reference	1.21 (1.03–1.42), P=.018	1.93 (1.67–2.24), P<.001	2.56 (2.17–3.01), P<.001
Cardiovascular death				
Cumulative 3-year incidence (%)	218 (2.9)	221 (4.2)	299 (7.5)	375 (17.3)
Unadjusted HR (95% CI), P value	Reference	1.46 (1.21–1.76), P<.001	2.61 (2.19–3.11), P<.001	6.29 (5.32–7.44), P<.001
Adjusted HR (95% CI), P value	Reference	1.12 (0.92–1.37), P=.26	1.52 (1.25–1.84), P<.001	1.92 (1.56–2.36), P<.001
Non-cardiovascular death				
Cumulative 3-year incidence (%)	150 (2.1)	155 (3.1)	312 (8.1)	313 (15.4)
Unadjusted HR (95% CI), P value	Reference	1.49 (1.19–1.87), P<.001	4.05 (3.33–4.92), P<.001	8.19 (6.75–9.95), P<.001
Adjusted HR (95% CI), P value	Reference	1.30 (1.03–1.65), P=.028	2.46 (2.00–3.04), P<.001	3.76 (2.98–4.75), P<.001

Table S1. Relationship between baseline Hb value and the secondary outcome measures through 3 years (continued)

	High-normal Hb	Low-normal Hb	Mild anemia	Moderate/Severe anemia
Myocardial Infarction				
Cumulative 3-year incidence (%)	338 (4.6)	261 (5.0)	234 (5.9)	158 (7.4)
Unadjusted HR (95% CI), P value	Reference	1.11 (0.94–1.30), P=.22	1.30 (1.10–1.54), P=.002	1.62 (1.34–1.96), P<.001
Adjusted HR (95% CI), P value	Reference	1.03 (0.86–1.22), P=.77	1.11 (0.93–1.34), P=.25	1.14 (0.90–1.44), P=.27
Definite stent thrombosis				
Cumulative 3-year incidence (%)	80 (1.1)	48 (0.9)	30 (0.8)	26 (1.2)
Unadjusted HR (95% CI), P value	Reference	0.86 (0.60–1.23), P=.40	0.71 (0.46–1.07), P=.09	1.14 (0.73–1.78), P=.56
Adjusted HR (95% CI), P value	Reference	1.14 (0.77–1.68), P=.52	0.95 (0.60–1.50), P=.83	1.71 (0.99–2.95), P=.06
Stroke				
Cumulative 3-year incidence (%)	207 (2.8)	198 (3.9)	181 (4.8)	155 (7.8)
Unadjusted HR (95% CI), P value	Reference	1.38 (1.14–1.68), P=.001	1.69 (1.38–2.06), P<.001	2.83 (2.30–3.48), P<.001
Adjusted HR (95% CI), P value	Reference	1.28 (1.04–1.58), P=.02	1.29 (1.03–1.60), P=.03	1.62 (1.25–2.10), P<.001

Table S1. Relationship between baseline Hb value and the secondary outcome measures through 3 years (continued)

	High-normal Hb	Low-normal Hb	Mild anemia	Moderate/Severe anemia
Ischemic stroke				
Cumulative 3-year incidence (%)	151 (2.1)	162 (3.2)	136 (3.6)	111 (5.6)
Unadjusted HR (95% CI), P value	Reference	1.55 (1.24–1.93), P<.001	1.73 (1.38–2.19), P<.001	2.76 (2.16–3.53), P<.001
Adjusted HR (95% CI), P value	Reference	1.50 (1.18–1.91), P=.001	1.37 (1.07–1.77), P=.01	1.71 (1.27–2.31), P<.001
Hemorrhagic stroke*				
Cumulative 3-year incidence (%)	57 (0.8)	39 (0.8)	47 (1.2)	45 (2.4)
Unadjusted HR (95% CI), P value	Reference	0.94 (0.66–1.48), P=.94	1.59 (1.08–2.33), P=.02	2.98 (2.02–4.41), P<.001
Adjusted HR (95% CI), P value	Reference	0.86 (0.56–1.33), P=.49	1.22 (0.12–1.86), P=.34	1.71 (1.07–2.76), P=.03
GUSTO moderate bleeding				
Cumulative 3-year incidence (%)	184 (2.5)	191 (3.7)	226 (5.8)	244 (11.5)
Unadjusted HR (95% CI), P value	Reference	1.50 (1.22–1.84), P<.001	2.36 (1.94–2.86), P<.001	4.93 (4.07–5.97), P<.001
Adjusted HR (95% CI), P value	Reference	1.40 (1.13–1.74), P=.002	2.07 (1.68–2.57), P<.001	2.89 (2.28–3.68), P<.001

Table S1. Relationship between baseline Hb value and the secondary outcome measures through 3 years (continued)

	High-normal Hb	Low-normal Hb	Mild anemia	Moderate/Severe anemia
GUSTO severe bleeding				
Cumulative 3-year incidence (%)	156 (2.1)	140 (2.7)	170 (4.4)	158 (7.7)
Unadjusted HR (95% CI), P value	Reference	1.29 (1.03–1.63), P=.03	2.09 (1.68–2.59), P<.001	3.75 (3.00–4.67), P<.001
Adjusted HR (95% CI), P value	Reference	1.08 (0.85–1.38), P=.53	1.46 (1.15–1.85), P=.002	1.74 (1.32–2.29), P<.001
Gastrointestinal bleeding				
Cumulative 3-year incidence (%)	111 (1.5)	106 (2.1)	160 (4.2)	133 (6.5)
Unadjusted HR (95% CI), P value	Reference	1.38 (1.06–1.80), P=.02	2.78 (2.18–3.54), P<.001	4.50 (3.50–5.79), P<.001
Adjusted HR (95% CI), P value	Reference	1.32 (1.00–1.75), P=.05	2.21 (1.69–2.88), P<.001	2.83 (2.07–3.86), P<.001
Intracranial bleeding*				
Cumulative 3-year incidence (%)	75 (1.0)	60 (1.2)	69 (1.8)	65 (3.4)
Unadjusted HR (95% CI), P value	Reference	1.15 (0.82–1.62), P=.41	1.78 (1.28–2.47), P=.001	3.30 (2.37–4.60), P<.001
Adjusted HR (95% CI), P value	Reference	1.02 (0.71–1.46), P=.91	1.34 (0.94–1.90), P=.10	1.94 (1.30–2.88), P=.001

Table S1. Relationship between baseline Hb value and the secondary outcome measures through 3 years (continued)

	High-normal Hb	Low-normal Hb	Mild anemia	Moderate/Severe anemia
Any coronary revascularization				
Cumulative 3-year incidence (%)	2081 (28.3)	1330 (26.0)	1089 (28.2)	600 (29.9)
Unadjusted HR (95% CI), P value	Reference	0.90 (0.84–0.96), P=.002	0.98 (0.91–1.06), P=.64	1.05 (0.96–1.15), P=.29
Adjusted HR (95% CI), P value	Reference	0.99 (0.92–1.07), P=.99	1.06 (0.97–1.15), P=.19	0.99 (0.89–1.11), P=.86
HF hospitalization				
Cumulative 3-year incidence (%)	205 (2.8)	195 (3.8)	291 (7.6)	296 (14.8)
Unadjusted HR (95% CI), P value	Reference	1.37 (1.13–1.67), P=.002	2.77 (2.32–3.31), P<.001	5.62 (4.70–6.72), P<.001
Adjusted HR (95% CI), P value	Reference	1.18 (0.96–1.46), P=.12	1.93 (1.58–2.34), P<.001	2.33 (1.86–2.92), P<.001

* For these outcomes, 13 variables listed in Table 1 were incorporated into the multivariable analysis as the parsimonious models. Other than those, the outcomes were adjusted by 34 full-adjusting covariates listed in Table 1.

CI, confidence interval; GUSTO, The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HF, heart failure; HR, hazard ratio.

Table S2. Baseline clinical and procedural characteristics across the studies.

	Total *N*=19288	**CREDO-Kyoto PCI/CABG registry Cohort-2** *N*=12874 (66.8%)	**NEXT** *N*=3224 (16.7%)	**RESET** *N*=3190 (16.5%)	***P* for difference across the studies**
Clinical characteristics					
Age, mean (SD), years	68.5 (10.7)	68.2 (11.1)	69.2 (9.8)	69.1 (9.7)	<.001
≥75 years	6056 (31)	4015 (31)	1039 (32)	1002 (31)	0.52
Men	14193 (74)	9255 (72)	2488 (77)	2450 (77)	<.001
Body mass index, mean (SD), kg/m^2	23.9 (3.5)	23.7 (3.5)	24.2 (3.6)	24.3 (3.6)	<.001
<25	12832 (67)	8817 (69)	2047 (64)	1968 (62)	<.001
Clinical presentation					
Acute myocardial infarction	4948 (26)	4607 (36)	154 (5)	187 (6)	<.001

Table S2. Baseline clinical and procedural characteristics across the studies (continued)

	Total	CREDO-Kyoto PCI/CABG registry Cohort-2	NEXT	RESET	*P*
ST-segment elevation myocardial infarction	4186 (22)	3952 (31)	102 (3)	132 (4)	<.001
Hypertension	15743 (82)	10562 (82)	2629 (82)	2552 (80)	.03
Diabetes mellitus	7756 (40)	4839 (38)	1482 (46)	1435 (45)	<.001
Insulin therapy	1652 (9)	977 (8)	338 (11)	337 (11)	<.001
Lipid-lowering therapy	8079 (42)	4145 (32)	2006 (62)	1928 (60)	<.001
Current Smoker	5341 (28)	4093 (32)	591 (18)	657 (21)	<.001
History of heart failure	3381 (18)	2582 (20)	383 (12)	416 (13)	<.001
Multivessel coronary disease	10187 (53)	7096 (55)	1598 (50)	1493 (47)	<.001
Mitral regurgitation grade 3/4	620 (3)	514 (4)	61 (2)	45 (1)	<.001

Table S2. Baseline clinical and procedural characteristics across the studies (continued)

	Total	CREDO-Kyoto PCI/CABG registry Cohort-2	NEXT	RESET	*P*
Left ventricular ejection fraction, mean (SD), %	58.9 (12.8)	58.5 (13.2)	59.8 (11.8)	59.7 (12.1)	<.001
Left ventricular ejection fraction ≤40%	1545 (10)	1114 (11)	206 (7)	225 (8)	<.001
Prior myocardial infarction	3233 (17)	1354 (11)	913 (29)	966 (30)	<.001
Prior percutaneous coronary intervention	3190 (17)	0 (0)	1628 (51)	1562 (49)	<.001
Prior coronary artery bypass grafting	323 (2)	0 (0)	162 (5)	161 (5)	<.001
Prior stroke	2049 (11)	1364 (11)	344 (11)	341 (11)	0.98
Peripheral vascular disease	1369 (7)	950 (7)	139 (4)	280 (9)	<.001
Estimated glomerular filtration rate <30ml/min/1.73m^2, not on dialysis	678 (4)	524 (4)	82 (3)	72 (2)	<.001
Dialysis	819 (4)	457 (4)	189 (6)	173 (5)	<.001

Table S2. Baseline clinical and procedural characteristics across the studies (continued)

	Total	CREDO-Kyoto PCI/CABG registry Cohort-2	NEXT	RESET	*P*
Atrial fibrillation	1548 (8)	1103 (9)	213 (7)	232 (7)	<.001
Hb, median (IQR), g/dL	13.4 (12.1-14.6)	13.6 (12.2-14.8)	13.1 (11.9-14.3)	13.3 (11.9-14.4)	<.001
Platelet, median (IQR), 10^9/L	204 (170-245)	208 (173-249)	194 (164-234)	200 (166-238)	<.001
Chronic obstructive pulmonary disease	613 (3)	468 (4)	71 (2)	74 (2)	<.001
Liver cirrhosis	379 (2)	332 (3)	23 (1)	24 (1)	<.001
Malignancy	1622 (8)	1170 (9)	240 (7)	212 (7)	<.001
DAPT score, mean (SD)	0.82 (1.46)	0.8 (1.4)	0.9 (1.5)	0.9 (1.5)	<.001
≥2	6065 (31)	3950 (31)	1059 (33)	1056 (33)	.005
Procedure characteristics					

Table S2. Baseline clinical and procedural characteristics across the studies (continued)

	Total	CREDO-Kyoto PCI/CABG registry Cohort-2	NEXT	RESET	*P*
Stent use	18399 (95)	12016 (93)	3213 (100)	3170 (99)	<.001
Drug-eluting stent	13080 (68)	6703 (52)	3211 (100)	3166 (99)	<.001
Sirolimus-eluting stent	7811 (41)	6232 (48)	2 (0)	1577 (49)	<.001
Paclitaxel-eluting stent	617 (3)	612 (5)	0 (0)	5 (0)	<.001
Everolimus-eluting stent	3214 (17)	3 (0)	1611 (50)	1600 (50)	<.001
Biolimus-eluting stent	1691 (9)	80 (1)	1611 (50)	0 (0)	<.001
Bare metal stent	6451 (34)	6421 (50)	14 (0)	16 (1)	<.001
Number of target vessels, mean (SD)	1.3 (0.5)	1.4 (0.6)	1.1 (0.4)	1.1 (0.3)	<.001
Number of target lesions, mean (SD)	1.4 (0.7)	1.5 (0.8)	1.3 (0.5)	1.2 (0.5)	<.001

Table S2. Baseline clinical and procedural characteristics across the studies (continued)

	Total	CREDO-Kyoto PCI/CABG registry Cohort-2	NEXT	RESET	*P* for difference across the studies
Target of LAD	10868 (56)	7757 (60)	1551 (48)	1560 (49)	<.001
Target of proximal LAD	10333 (54)	7371 (57)	1478 (46)	1482 (47)	<.001
Target of right coronary artery	7420 (39)	5339 (42)	1065 (33)	1016 (32)	<.001
Target of left circumflex coronary artery	5276 (27)	3625 (28)	835 (26)	816 (26)	.002
Target of unprotected left main coronary artery	639 (3)	472 (4)	91 (3)	76 (2)	<.001
Target of chronic total occlusion	1978 (10)	1501 (12)	246 (8)	231 (7)	<.001
Target of restenotic lesion	862 (5)	0 (0)	432 (13)	430 (14)	<.001
Target of bifurcation	5656 (29)	4162 (32)	785 (24)	709 (22)	<.001

Table S2. Baseline clinical and procedural characteristics across the studies (continued)

	Total	CREDO-Kyoto PCI/CABG registry Cohort-2	NEXT	RESET	*P*
Side-branch stenting	695 (4)	611 (5)	44 (1)	40 (1)	<.001
Target of aortic ostium	444 (2)	168 (1)	156 (5)	120 (4)	<.001
Use of intravascular ultrasound	10896 (57)	5429 (42)	2828 (88)	2639 (83)	<.001
Total stent length, mean (SD), mm	35.3 (27.2)	37.0 (30.0)	32.9 (20.6)	31.1 (19.1)	<.001
>28 mm	8389 (44)	5897 (46)	1280 (40)	1212 (38)	<.001
Minimum stent size, mean (SD), mm	2.9 (0.4)	2.9 (0.5)	2.9 (0.4)	2.9 (0.4)	.008
<3.0 mm	8270 (43)	5284 (41)	1563 (49)	1423 (45)	<.001
Medication at discharge					
Aspirin	19288 (99)	12687 (99)	3217 (100)	3175 (100)	<.001

Table S2. Baseline clinical and procedural characteristics across the studies (continued)

	Total	CREDO-Kyoto PCI/CABG registry Cohort-2	NEXT	RESET	*P*
Thienopyridines	18891 (98)	12517 (97)	3206 (99)	3168 (99)	<.001
Ticlopidine	12145 (63)	11289 (88)	443 (14)	413 (13)	<.001
Clopidogrel	6680 (34)	1198 (9)	2731 (85)	2751 (86)	<.001
Cilostazole	2824 (15)	2436 (19)	195 (6)	193 (6)	<.001
Warfarin	1560 (8)	1058 (8)	240 (7)	262 (8)	.34
Statin	11530 (60)	6612 (51)	2450 (76)	2468 (77)	<.001
Beta-blockers	6317 (33)	3912 (30)	1216 (38)	1189 (37)	<.001
Angiotensin converting enzyme inhibitors/angiotensin receptor blockers	11435 (59)	7498 (58)	1980 (61)	1957 (61)	<.001

Table S2. Baseline clinical and procedural characteristics across the studies (continued)

	Total	CREDO-Kyoto PCI/CABG registry Cohort-2	NEXT	RESET	*P*
Calcium channel blockers	8040 (42)	5182 (40)	1452 (45)	1406 (44)	<.001
Nitrates	6294 (33)	4595 (36)	808 (25)	891 (28)	<.001
H2B or PPI	8877 (55)	6641 (52)	2236 (69)	unavailable	<.001

Data are expressed as number (%) of patients unless otherwise indicated.

DAPT, dual antiplatelet therapy; Hb, hemoglobin; H2B, histamine-2 receptor blocker; LAD, left anterior descending coronary artery; PPI, proton-pump inhibitor.

Table S3. Sensitivity analysis: Clinical outcome across no anemia (a composite of high-normal Hb andlow-normal Hb), mild anemia and moderate/severe anemia.

	NO anemia (a composite of high-normal Hb and low-normal Hb)	Mild anemia	Moderate/Severe anemia
Hemoglobin	Males:≥13.0 g/dL Females:≥12.0 g/dL	Males:11.0–12.9 g/dL Females:11.0–11.9 g/dL	<11.0 g/dL
Patient Number (%)	12858 (67)	4117 (21)	2313 (12)
Myocardial infarction/Ischemic stroke			
Cumulative 3-year incidence (%)	891 (7.1)	352 (9.0)	265 (12.7)
Unadjusted HR (95% CI), P value	Reference	1.27 (1.13-1.44), P<.001	1.81 (1.58-2.08), P<.001
Adjusted HR (95% CI), P value	Reference	1.09 (0.95-1.24), P=.22	1.23 (1.04-1.45), P=.02
GUSTO moderate/severe bleeding			
Cumulative 3-year incidence (%)	645 (5.1)	374 (9.6)	383 (18.0)
Unadjusted HR (95% CI), P value	Reference	1.89 (1.67-2.15), P<.001	3.81 (3.36-4.33), P<.001
Adjusted HR (95% CI), P value	Reference	1.56 (1.36-1.79), P<.001	2.06 (1.76-2.40), P<.001

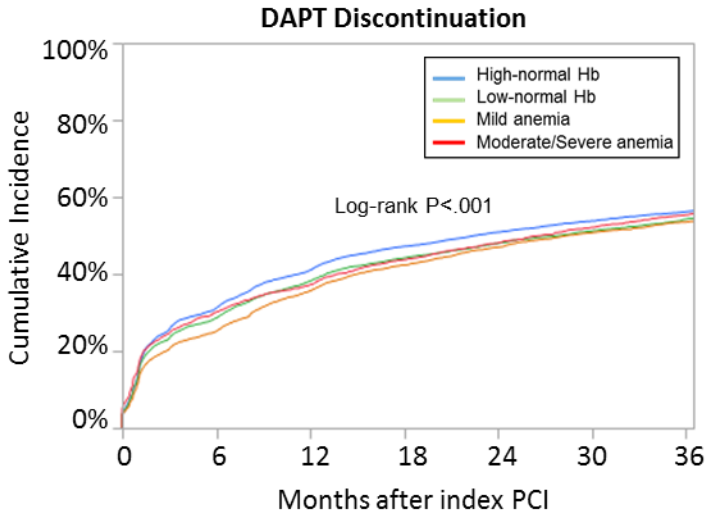
GUSTO, The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HR, hazard ratio

Table S4. Sensitivity analysis: Clinical outcome across very high Hb, high-normal Hb, low-normal Hb, mild anemia and moderate/severe anemia

	Very high Hb	High-normal Hb	Low-normal Hb	Mild anemia	Moderate/Severe anemia
Hemoglobin	≥16.0 g/dL	14.0–15.9 g/dL	Males:13.0–13.9 g/dL Females:12.0–13.9 g/dL	Males:11.0–12.9 g/dL Females:11.0–11.9 g/dL	<11.0 g/dL
Patient Number (%)	1357 (7)	6198 (32)	5303 (27)	4117 (21)	2313 (12)
Myocardial infarction/Ischemic stroke					
Cumulative 3-year incidence (%)	79 (5.9)	407 (6.6)	405 (7.6)	352 (8.6)	265 (11.5)
Unadjusted HR (95%CI), P value	0.89 (0.69-1.13), P=.34	Reference	1.18 (1.02-1.35), P=.02	1.35 (1.17-1.56), P<.001	1.92 (1.64-2.24), P<.001
Adjusted HR (95% CI), P value	0.88 (0.69-1.13), P=.32	Reference	1.12(.97-1.30), P=.13	1.14 (.98-1.33), P=.09	1.30 (1.08-1.58), P=.006
GUSTO moderate/severe bleeding					
Cumulative 3-year incidence (%)	60 (4.4)	269 (4.3)	316 (6.0)	374 (9.1)	383 (16.6)
Unadjusted HR (95%CI), P value	1.03 (0.77-1.35), P=.85	Reference	1.40 (1.19-1.65), P<.001	2.21 (1.89-2.58), P<.001	4.44 (3.80-5.20), P<.001
Adjusted HR (95% CI), P value	0.92 (0.69-1.22), P=.56	Reference	1.20(1.01-1.43), P=.03	1.71 (1.44-2.03), P<.001	2.28 (1.89-2.76), P<.001

GUSTO, The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HR, hazard ratio

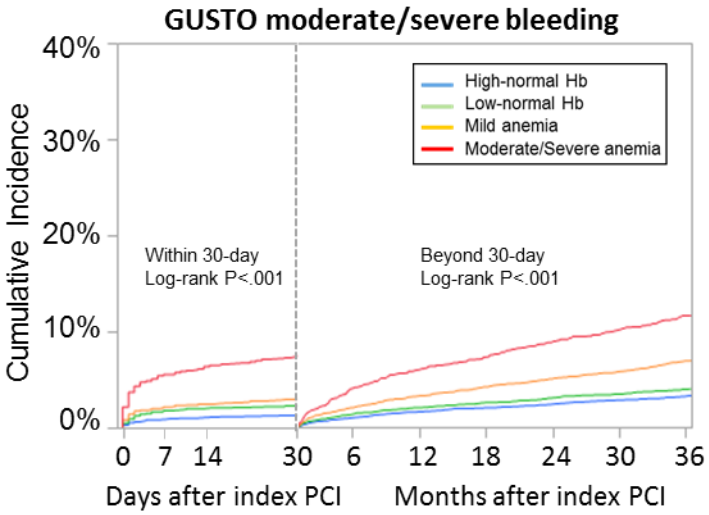
Figure S1. The Kaplan–Meier curves for the persistent discontinuation of dual antiplatelet therapy among patients with high-normal Hb, low-normal Hb, mild, and moderate/severe anemia.



Months after index PCI	0	1	6	12	18	24	30	36
Number of patients at risk								
High-normal Hb	7555	6484	5085	4317	3817	3514	3243	3013
Low-normal Hb	5303	4557	3688	3152	2812	2599	2380	2174
Mild anemia	4117	3570	2941	2475	2164	1956	1754	1595
Moderate/Severe anemia	2313	1876	1449	1250	1074	941	824	732

DAPT, dual antiplatelet therapy; Hb, hemoglobin; PCI, percutaneous coronary intervention.

Figure S2A. Thirty-day landmark analysis of the primary bleedinh outcome measure.



Days or Months after index PCI	0	7	14	30	6	12	18	24	30	36
Number of patients at risk										
High-normal Hb	7555	7455	7423	7458	7315	7211	7126	7041	6923	6816
Low-normal Hb	5303	5183	5157	5224	5090	4996	4917	4844	4750	4645
Mild anemia	4117	3999	3970	4039	3859	3731	3615	3501	3365	3241
Moderate/Severe anemia	2313	2165	2132	2221	2006	1784	1773	1663	1557	1469

In this analysis, surviving patients with hemorrhagic events within 30 days were also included in the number at risk beyond 30 days.

Figure S2B. A hazard ratio plot showing the adjusted excess risk of the low-normal Hb, mild and moderate/severe anemia groups relative to high-normal Hb group for the primary bleeding outcome measure within and beyond 30 days.

HR, hazard ratio; CI confidence intervals

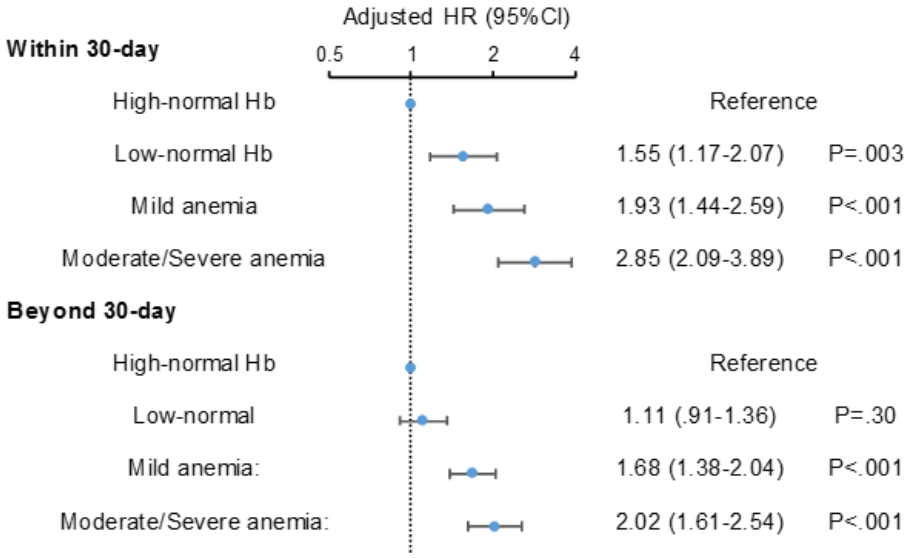
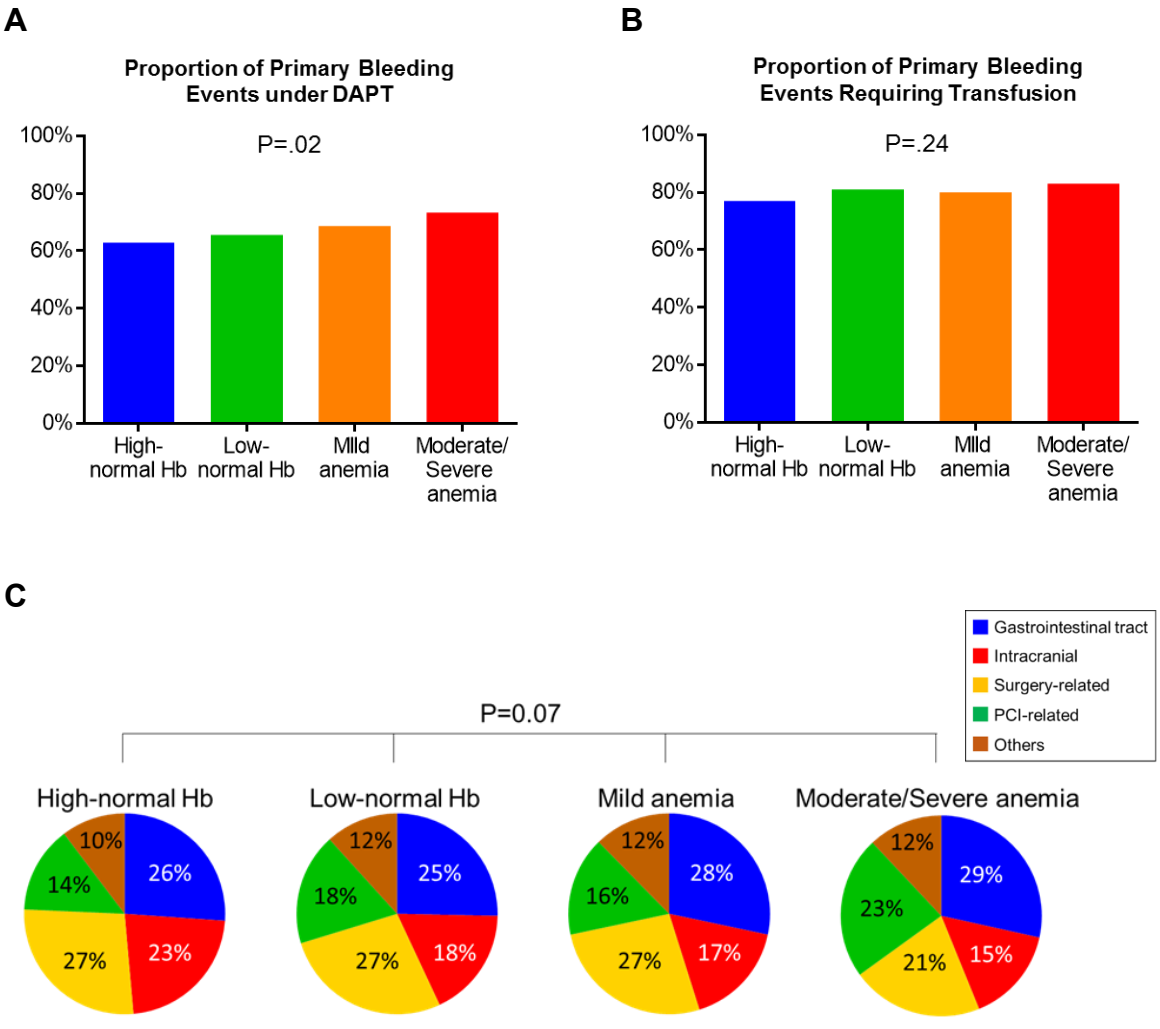


Figure S3.

A. **The proportion of primary bleeding events while under DAPT to all primary bleeding events.** DAPT, dual antiplatelet therapy; Hb, hemoglobin.
B. **The proportion of primary bleeding events requiring blood transfusion to all primary bleeding events.**
C. **The proportion of bleeding sources.**



Supplemental References:

1. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schönberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med. 2001;344:1117–1124.
2. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, Van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: A case for standardized definitions. Circulation. 2007;115:2344–2351.