ORIGINAL RESEARCH

Impact of Baseline Anemia in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention: A Prespecified Analysis From the VALIDATE-SWEDEHEART Trial

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***Background*—**The impact of baseline anemia in a contemporary acute coronary syndrome (ACS) population undergoing percutaneous coronary intervention in the era of predominant radial artery access, potent P2Y12 inhibition, and rare use of glycoprotein IIb/IIIa inhibitors has not been adequately studied.

***Methods and Results*—**ACS patients who underwent percutaneous coronary intervention between 2014 and 2016 in the VALIDATE-SWEDEHEART (Bivalirudin Versus Heparin in ST-Segment and Non–ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies Registry) trial without missing values for hemoglobin were included (n=5482). Mortality, myocardial reinfarction, and major bleeding at 180 days were assessed using Cox regression models and propensity score matching. All studied comorbidities were more common in ACS patients who had anemia (n=792). ACS patients with anemia had higher rates of 180-day mortality (6.9% versus 2.1%; hazard ratio, 1.9; 95% CI, 1.3–2.7; $P<0.001$), myocardial reinfarction (4.3% versus 1.9%; hazard ratio, 1.7; 95% CI, 1.1–2.7; $P=0.013$), and major bleeding (13.4% versus 8.2%; hazard ratio, 1.3; 95% CI, 1.0–1.6; $P=0.041$). The results were most evident in patients with a hemoglobin value <100 g/L, who had a nearly 10 times higher mortality rate.

***Conclusions*—**Baseline anemia in ACS patients undergoing percutaneous coronary intervention, treated according to current practice including routine radial artery access, constitutes a high-risk feature for both ischemic events, bleeding events, and mortality. A multidisciplinary approach is warranted to maximize benefit and minimize patient risk.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT02311231. **(*J Am Heart Assoc*. 2019;8: e012741. DOI: 10.1161/JAHA.119.012741.)**

Key Words: acute coronary syndromes • anemia • mortality • VALIDATE-SWEDEHEART

Despite advances in the field of acute coronary care, major bleedings following percutaneous coronary intervention (PCI) still constitute a major clinical problem.[1] It has been suggested that a major bleeding carries the same prognostic impact as a new myocardial infarction (MI) during the first year after an acute coronary syndrome (ACS).[2] The HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial demonstrated more than a decade ago that bivalirudin reduced mortality in patients with ST-segment–elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention, compared with heparin plus glycoprotein IIb/IIIa inhibitors (GPIs).[3] This was in part due to a reduction in major bleedings.[3,4] Both non–access site and access site major bleedings increase mortality; however, radial artery access essentially removes the risk of excess

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Accompanying Tables S1 and S2 and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012741

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Clinical Perspective

What Is New?

- Baseline anemia in acute coronary syndrome patients who undergo percutaneous coronary intervention and are treated according to current practice with >90% use of radial artery access, >97% potent P2Y12 inhibitors during percutaneous coronary intervention, and <3% glycoprotein IIb/IIIa inhibitors was associated with higher rates of 180-day mortality, myocardial reinfarction, and major bleeding.
- Patients with severe anemia (a hemoglobin value <100 g/L) had a nearly 10 times higher mortality rate, 6 times higher rate of myocardial reinfarction, and 3 times higher rate of major bleeding at 180 days.

What Are the Clinical Implications?

- Our results indicate that anemia constitutes a high-risk feature in patients with acute coronary syndromes, despite treatment with contemporary therapies, including high use of radial artery access.
- In complex patients with anemia and concomitant coronary disease, a multidisciplinary approach is warranted to maximize benefit and minimize patient risk.

mortality associated with major access site bleedings.[5,6] In parallel with the increased use of radial artery access, acute medical care of ACS patients has also improved with the advent of potent P2Y12 inhibitors.[7,8]

Baseline anemia, defined according to the World Health Organization,[9] is present in nearly 20% of ACS patients.[10,11] ACS patients with anemia are older and more often present with previous cardiovascular disease, diabetes mellitus, a history of major bleeding, and malignancy, compared with those without anemia.[10–19] Having anemia at baseline therefore identifies both patients at high risk of bleeding and those at high risk for ischemic events. In fact, anemia in ACS patients is not only associated with overall increased mortality and bleeding but in some studies also associated with increased rates of MI.[10,11]

The vast majority of studies investigating the impact of baseline anemia on hard clinical events have been performed in an era of either extensive GPI use or with limited radial artery use. The recent VALIDATE-SWEDEHEART (Bivalirudin Versus Heparin in ST-Segment and Non–ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies Registry) trial compared bivalirudin to heparin monotherapy in ACS patients undergoing PCI.[20] The patients enrolled in the trial constituted a modern ACS population with high use of radial artery access (90.3%) as well as high use of modern P2Y12 inhibitors (ticagrelor 94.9%, prasugrel 2.1%, or cangrelor 0.3%). Furthermore, only bailout use of GPI was allowed (2.6%).[20] The impact of anemia at baseline in such a patient cohort, treated according to contemporary strategies has so far not been adequately assessed. The aim of the current study was therefore to evaluate the prognostic value of baseline anemia in ACS patients enrolled in the VALIDATE-SWEDEHEART trial.

Methods

Study Population

Data, methods and materials used to conduct this research can be made available after clearance by the VALIDATE steering committee. The study design of the VALIDATE-SWEDEHEART trial has already been described in detail.[20,21] In short, VALIDATE-SWEDEHEART was a registry-based, multicenter, prospective, randomized, controlled, and open-label clinical trial evaluating the efficacy and safety of heparin monotherapy versus bivalirudin in ACS patients undergoing PCI. The trial included patients presenting with STEMI or non-STEMI (NSTEMI) between 2014 and 2016 and for whom PCI was planned at one of the 25 participating Swedish centers. Treatment with ticagrelor, prasugrel, or cangrelor before PCI was mandatory and only bailout use of GPI was allowed. The SWEDEHEART registry was used as case-report form for randomization and for follow-up. A total of 6006 patients underwent randomization in the VALIDATE-SWEDEHEART trial, and all patients without missing values for hemoglobin (n=5482) were included in the present study (Figure 1). Baseline anemia was defined in accordance with the World Health Organization as a hemoglobin value <130 g/L for men and <120 g/L for women.[9] The hemoglobin values in the cohort represent the first acquired hemoglobin for each patient, meaning that the blood tests were performed at the

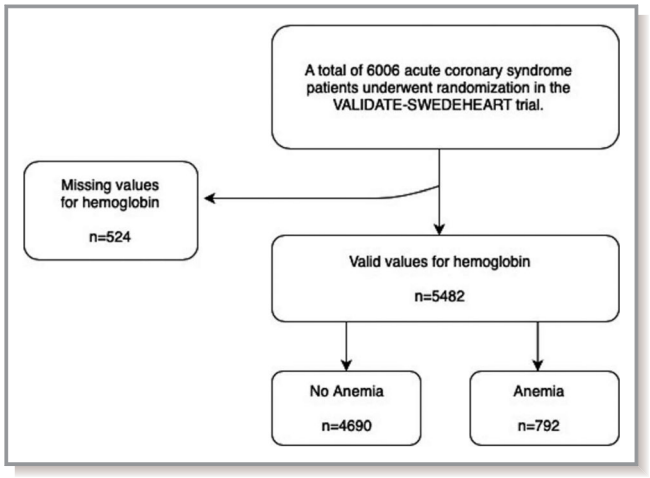

Figure 1. Flowchart of study inclusion.

emergency department on arrival or in relation to the PCI procedure in those STEMI patients who went directly to the catheterization lab. The VALIDATE-SWEDEHEART trial and subgroup analyses were approved by the ethics committee at Lund University and the Swedish Medical Products Agency. All patients provided written informed consent to participate in the trial.

End Points

The primary end point was death from any cause at 180 days. Secondary end points were myocardial reinfarction, major bleeding, definite stent thrombosis, and stroke at 180 days. MI was defined according to the third universal definition,[22] and major bleeding was defined as type 2, 3, or 5 according to the Bleeding Academic Research Consortium scale.[20] Further analyses were done on cause of death, divided into cardiovascular death, fatal bleeding, or other causes.

End point screening and adjudication

Research nurses screened for clinical end point events by contacting the patients or first-degree relatives by telephone 7 and 180 days after PCI. If a patient was suspected to have had a clinical end point event (ie, death, myocardial reinfarction, major bleeding, or stroke), the patient's healthcare records were subjected to central blinded adjudication to determine both the cause of the event and the date of the event according to prespecified criteria. Time to event was calculated using calendar days with date of randomization as time point zero. If the patient or relatives could not be contacted after the nurses had placed repeated telephone calls and mailed a letter, information was collected through review of hospital records.[20]

Statistical Analyses

Differences between categorical variables were analyzed with the chi-square test and continuous variables were compared using the Mann–Whitney *U* test. Kaplan–Meier event rates were analyzed to compare unadjusted primary and secondary end points between groups. Patients who were lost to follow-up were censored at the last contact with the patient.[20] Adjustments for confounders were made using multivariable Cox regression models as well as propensity score matching. We also performed landmark analyses for mortality and major bleeding to distinguish between short- and long-term effects. Statistical significance was defined as a 2-tailed $P<0.05$. Analyses were performed in IBM SPSS (Armonk, NY: IBM Corp.) (version 25), R (R Foundation for Statistical Computing, Vienna, Austria) (version 3.4.4), Stata (Statacorp, TX) (GraphPad Software, San Diego, California USA) (version 15.1), or GraphPad Prism (version 8.0.2).

Propensity score matching

A propensity score (PS) for baseline anemia was calculated using the variables age, sex, STEMI, medical history of kidney dysfunction, diabetes mellitus, coronary artery disease, and heart failure to achieve a good balancing of baseline differences. PS matching was performed in a 1:1 fashion. End points were subsequently analyzed using univariable Cox regression. In separate sensitivity analyses, downstream adjustments were made for body mass index (BMI).

Multiple imputation and subsequent multivariable Cox regression

Baselines differences that were associated with anemia and with worse clinical outcomes were identified a priori and adjusted for. These variables were age, sex, BMI, STEMI, medical history of kidney dysfunction, hyperlipidemia, hypertension, diabetes mellitus, current smoking, coronary artery disease, stroke, heart failure, Killip class, hours from symptom onset to PCI, radial artery access during PCI, use of potent P2Y12 inhibitors (ticagrelor, prasugrel, or cangrelor) during PCI, and blood transfusion during the hospital stay. In the original data set, 1440 (26.3%) cases had missing values for at least 1 of these variables. Data were assumed to be missing at random, based on Little's Missing Completely at Random test as well as logistic regression modeling. Multiple imputation was performed for missing data by using 10 imputations and 10 iterations for every imputation. In subsequent multivariable Cox regression analysis, adjustments were made for all variables mentioned above. Kidney dysfunction was defined as an estimated glomerular filtration rate <60 mL/min per 1.73 m^2. Coronary artery disease was defined as previous MI, previous PCI, or previous coronary artery bypass grafting. The multivariable Cox regression model for mortality was tested for proportionality of hazards using Schoenfeld residuals.

Results

Patient Characteristics

Baseline anemia was present in 792 of 5482 ACS patients (14.4%). Patients with anemia were older ($P<0.001$), more often women ($P=0.034$), and had a lower BMI compared with patients without anemia ($P<0.001$; Table 1). Furthermore, patients with anemia more often had kidney dysfunction, hyperlipidemia, previous hypertension, diabetes mellitus, current smoking, previous coronary artery disease, previous stroke, or a history of heart failure (all $P<0.001$). Patients with anemia also more frequently presented with STEMI and Killip class 3 or 4 than patients without anemia ($P<0.001$). The time from symptom onset to PCI did not significantly differ between nonanemic and anemic patients when analyzing

Table 1. Characteristics of Patients With Acute Coronary Syndromes With and Without Anemia

	No Anemia* (n=4690)	Anemia* (n=792)	*P* Value	Missing or Unknown, n (%)
Hemoglobin, median (IQR)	145 (137–154)	118 (112–125)	<0.001	0 (0.0)
Age, y				0 (0.0)
Median (IQR)	67 (59–74)	74 (67–81)	<0.001	
≥65, n (%)	2695 (57.5)	642 (81.1)	<0.001	
Female, n (%)	1217 (25.9)	234 (29.5)	0.034	0 (0.0)
BMI, median (IQR)	27 (25–30)	26 (23–28)	<0.001	563 (10.3)
Medical history, n (%)				
Kidney dysfunction	598 (12.8)	244 (30.8)	<0.001	8 (0.1)
Hyperlipidemia	1419 (30.3)	299 (37.8)	<0.001	43 (0.8)
Hypertension	2351 (50.4)	475 (60.3)	<0.001	27 (0.5)
Diabetes mellitus	702 (15.0)	198 (25.0)	<0.001	14 (0.3)
Current smoker	1174 (25.7)	146 (19.1)	<0.001	142 (2.6)
CAD	847 (18.1)	221 (27.9)	<0.001	56 (1.0)
Previous MI	690 (14.7)	183 (23.1)	<0.001	
Previous PCI	639 (13.6)	156 (19.7)	<0.001	
Previous CABG	200 (4.3)	66 (8.3)	<0.001	
Stroke	170 (3.6)	51 (6.5)	<0.001	26 (0.5)
Heart failure	142 (3.0)	60 (7.6)	<0.001	120 (2.2)
STEMI, n (%)	2365 (50.4)	457 (57.7)	<0.001	0 (0.0)
Killip class 3 or 4, n (%)	38 (0.8)	13 (1.6)	0.024	0 (0.0)
Hours from symptoms to PCI				592 (10.8)
STEMI, median (IQR)	3 (2–6)	3 (2–6)	0.482	
NSTEMI, median (IQR)	31 (18–57)	35 (18–64)	0.177	
Randomized to heparin, n (%)	2372 (50.6)	385 (48.6)	0.306	0 (0.0)
Potent P2Y12 inhibitors during PCI, n (%)	4566 (98.9)	749 (96.9)	<0.001	92 (1.7)
Radial access, n (%)	4276 (91.2)	680 (85.9)	<0.001	0 (0.0)
Peak high-sensitivity cardiac troponin T, median (IQR)	628 (146–2490)	1013 (169–3251)	0.001	1475 (26.9)
LVEF during hospital stay, n (%)			<0.001	700 (12.8)
≥50%	2672 (65.0)	371 (55.4)		
49%–40%	879 (21.4)	174 (26.0)		
39%–30%	451 (11.0)	91 (13.6)		
<30%	110 (2.7)	34 (5.1)		
Blood transfusion during hospital stay, n (%)	4 (0.1)	4 (0.5)	0.013	39 (0.7)
Discharge medications, n (%)				
Aspirin	4483 (97.0)	713 (93.2)	<0.001	104 (1.9)
Other antiplatelets			<0.001	97 (1.8)
Clopidogrel	339 (7.3)	92 (12.0)		
Prasugrel	46 (1.0)	9 (1.2)		
Ticagrelor	4160 (90.0)	639 (83.5)		

Continued

Table 1. Continued

	No Anemia* (n=4690)	Anemia* (n=792)	*P* Value	Missing or Unknown, n (%)
Warfarin or NOAC	291 (6.3)	69 (9.0)	0.014	102 (1.9)
ACEI or ARB	4106 (88.9)	651 (85.1)	0.009	98 (1.8)
Beta-blockers	4217 (91.3)	652 (85.2)	<0.001	98 (1.8)
Statins	4522 (97.9)	732 (95.7)	<0.001	97 (1.8)

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NOAC, novel oral anticoagulant; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.
*Baseline anemia was defined in accordance with the World Health Organization as a hemoglobin value <130 g/L for men and <120 g/L for women.

STEMI (median time, 3 hours in both groups) and NSTEMI patients separately (31 hours versus 35 hours, respectively). Radial access PCI and potent P2Y12 inhibitors were less frequently used in patients with anemia (P<0.001). Patients with anemia had a higher median peak value of high-sensitivity cardiac troponin T and a lower left ventricular ejection fraction during their hospital stay than patients without anemia (both P=0.001). Furthermore, patients with anemia more often received blood transfusion (P=0.013). At discharge, patients with anemia less often received evidence-based discharge medications such as aspirin and ticagrelor (Table 1). After PS matching, baseline variables were equalized between groups (Table 2). However, differences remained regarding BMI (which was analyzed in separate sensitivity analyses).

Mortality

Patients with ACS and anemia at baseline had a higher unadjusted mortality rate at 180 days compared with patients without anemia (6.9% and 2.1,% respectively; P<0.001; Figure 2A). After multiple imputation, and subsequent multivariable adjustments for confounding factors, patients with anemia still had a higher hazard ratio (HR) for 180-day mortality (HR, 1.9; 95% CI, 1.3–2.7; P<0.001). Results were consistent in the PS matched cohort (HR, 2.3; 95% CI, 1.4–3.7; P=0.001; Table 3; Figure S1A).

Myocardial Reinfarction

Patient with ACS and anemia more often experienced myocardial reinfarction (4.3% versus 1.9%; P<0.001; Figure 2B). Results were unchanged after multiple imputation with multivariable adjustments (HR, 1.7; 95% CI, 1.1–2.7; P=0.013) as well as in PS matched patients (HR, 2.0; 95% CI, 1.1–3.7; P=0.022; Table 3; Figure S1B).

Major Bleeding

ACS patients with anemia experienced higher rates of major bleeding than patients without anemia (13.4% versus 8.2%; P<0.001; Figure 2C). Results were consistent after multiple imputation with multivariable adjustments (HR, 1.3; 95% CI, 1.0–1.6; P=0.041) and in PS matched patients (HR, 1.4; 1.0–1.9; P=0.037; Table 3; Figure S1C).

Other End Points

No difference was found in event rates of definite stent thrombosis between patients with and without anemia (0.8% and 0.6%, respectively; P=0.46; Figure 2D). PS matching showed similar results (HR, 1.5; 95% CI, 0.4–5.4; P=0.51; Figure S1D). However, patients with anemia experienced higher rates of stroke (2.0% compared with 0.7%; P<0.001; Figure 2E), which was consistent in PS matched patients (HR, 2.9; 95% CI, 1.0–8.0; P=0.042; Table 3; Figure S1E).

Sensitivity and Subgroup Analyses

Landmark analyses in patients who survived the first 7 days were performed (Figure 3). Both mortality (4.5% versus 1.2%; P<0.001) and major bleeding (6.9% versus 4.9%; P=0.026) were significantly increased in the 7-day landmark analyses for ACS patients with anemia. The mortality curve also showed continued separation over time (Figure 3A). Results were also consistent when anemia was stratified according to severity (Figure 4). Patients with anemia with a hemoglobin <100 g/L had a nearly 10 times higher mortality rate, 6 times higher rate of myocardial reinfarction, and 3 times higher rate of major bleeding, compared with patients with normal hemoglobin values. High hemoglobin values (>150 g/L) were not associated with worse outcome compared with normal hemoglobin values. Hemoglobin was also analyzed as a continuous variable for patients with a hemoglobin value between 90 (to exclude outliers, based on visual inspection of a histogram of the hemoglobin level distribution) and 140 (as greater hemoglobin levels have previously been associated with increased risk of adverse

Table 2. Patient Characteristics After Propensity Score Matching

	No Anemia (n=762)	Anemia* (n=762)	*P* Value
Hemoglobin, median (IQR)	142 (135–151)	118 (112–125)	<0.001
Age, y			
Median (IQR)	74 (67.75–81)	74 (67–81)	0.518
≥65, n (%)	628 (82.4)	617 (81.0)	0.466
Female, n (%)	231 (30.3)	225 (29.5)	0.737
BMI, median (IQR)	27 (24–30)	26 (23–28)	<0.001
Medical history, n (%)			
Kidney dysfunction	236 (31.0)	236 (31.0)	>0.999
Hyperlipidemia	283 (37.4)	289 (38.4)	0.690
Hypertension	478 (63.1)	451 (59.5)	0.155
Diabetes mellitus	165 (21.7)	189 (24.8)	0.145
Current smoker	128 (17.3)	138 (18.8)	0.453
CAD	195 (25.6)	213 (28.0)	0.298
Stroke	38 (5.0)	49 (6.5)	0.217
Heart failure	56 (7.3)	60 (7.9)	0.699
STEMI, n (%)	441 (57.9)	436 (57.2)	0.796
Killip class 3 or 4, n (%)	13 (1.7)	13 (1.7)	>0.999
Hours from symptoms to PCI			
STEMI, median (IQR)	3 (2–6)	3 (2–6)	0.743
NSTEMI, median (IQR)	33 (21–62)	34 (18–64)	0.647
Potent P2Y12 inhibitors during PCI, n (%)	734 (98.1)	720 (96.8)	0.097
Radial artery access, n (%)	677 (88.8)	655 (86.0)	0.089
Peak high-sensitivity cardiac troponin T, median (IQR)	763 (161–3252)	1017 (184–3217)	0.388
LVEF during hospital stay, n (%)			0.854
≥50%	380 (57.2)	356 (55.4)	
49%–40%	161 (24.2)	169 (26.3)	
39%–30%	90 (13.6)	85 (13.2)	
<30%	33 (5.0)	33 (5.1)	
Blood transfusion during hospital stay, n (%)	2 (0.3)	4 (0.5)	0.434

BMI indicates body mass index; CAD, coronary artery disease; IQR, interquartile range; LVEF, left ventricular ejection fraction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.
*Baseline anemia was defined in accordance with the World Health Organization as a hemoglobin value <130 g/L for men and <120 g/L for women.

events).[12] This analysis yielded an HR of 0.95 (95% CI, 0.93–0.96; $P<0.001$) for each grams per liter increase of hemoglobin with regard to 180-day mortality. In patients with baseline anemia, randomized treatment (heparin versus bivalirudin) did not affect rates of mortality ($P=0.36$), myocardial reinfarction ($P=0.89$), or major bleeding ($P=0.92$) at 180 days (Table S1). Patients with anemia did not seem to benefit more from radial artery access during PCI than patients without anemia regarding 180-day mortality ($P_{interaction}=0.437$) or major bleeding ($P_{interaction}=0.254$). Results after PS matching did not change when downstream adjustments were made for BMI (Table S2). Moreover, we analyzed causes of death and found that patients with anemia were 3 times as likely to die from cardiovascular causes, 5 times as likely to die from fatal bleeding, and 4 times as likely to die from other causes (noncardiovascular and nonfatal bleeding; Table 4). Among the patients with anemia who died within 180 days (n=54), fatal bleeding and other causes (non-cardiovascular and nonfatal bleeding) represented a larger proportion of deaths than for patients without anemia who experienced death (n=96; Figure 5).

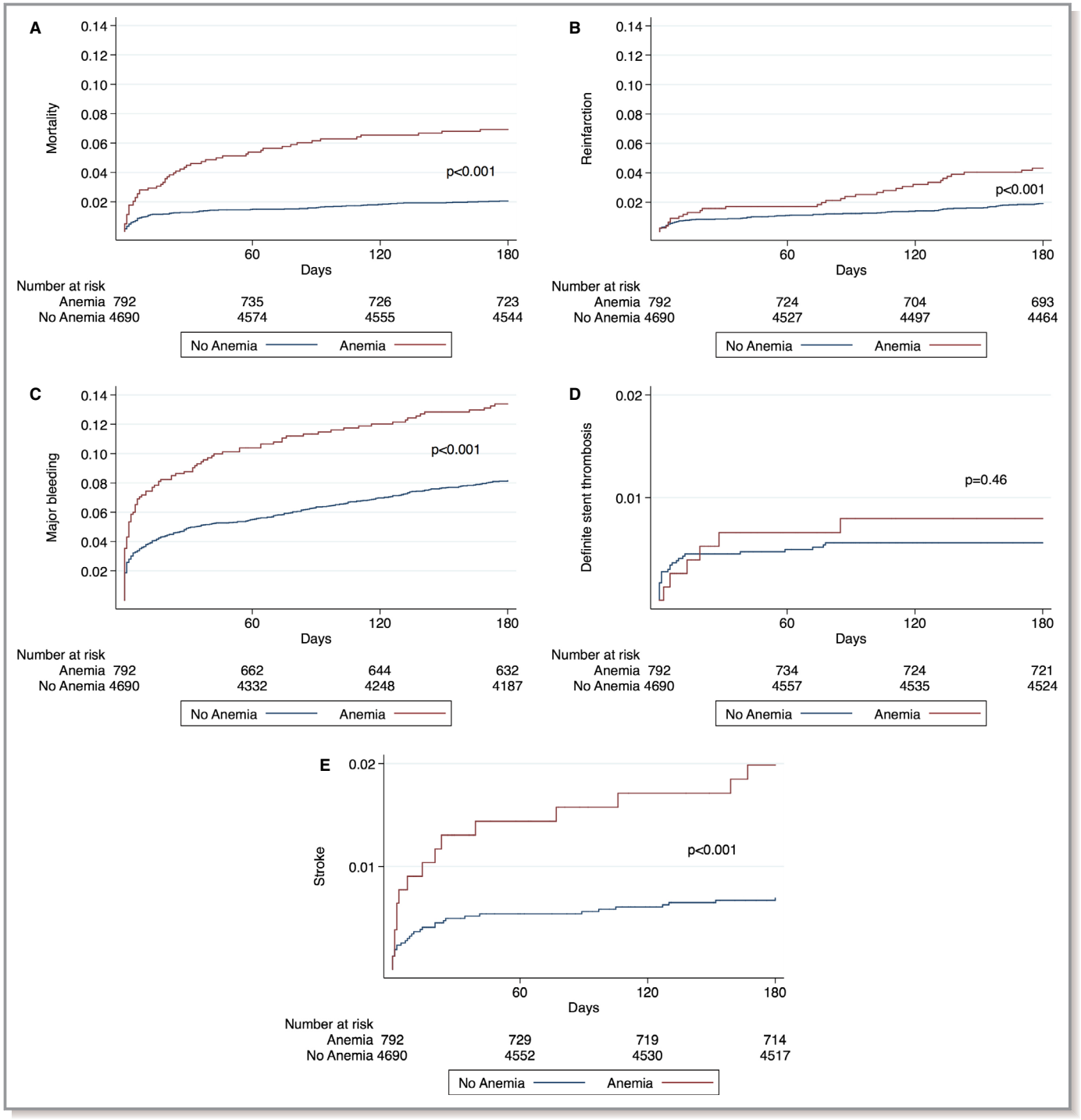

Figure 2. Kaplan–Meier failure functions for mortality (**A**), myocardial reinfarction (**B**), major bleeding (**C**), definite stent thrombosis (**D**), and stroke (**E**), at 180 days in acute coronary syndrome patients with and without anemia.

Discussion

The main findings of our study were that baseline anemia in patients with ACS, treated according to contemporary practice with radial artery access, mandatory use of modern P2Y12 inhibitors, and low use of GPI, was associated with a large excess risk of mortality at 180 days. Patients with anemia also experienced higher risk of myocardial reinfarction as well as major bleeding and stroke. No difference in definite stent thrombosis was seen. The results were consistent over time in landmark analyses. A strong correlation between anemia severity and

Table 3. End Points at 180 Days

	No Anemia (n=4690)	Anemia* (n=792)	95% CI	*P* Value	Missing or Unknown, n (%)
Mortality					
Kaplan–Meier event rates, n (%)	96 (2.1)	54 (6.9)		<0.001	0 (0.0)
Unadjusted HR	1.0	3.4	2.5–4.8	<0.001	0 (0.0)
Multivariable adjusted HR after multiple imputation	1.0	1.9	1.3–2.7	<0.001	0 (0.0)
Propensity score matching HR	1.0	2.3	1.4–3.7	0.001	0 (0.0)
Reinfarction					
Kaplan–Meier event rates, n (%)	88 (1.9)	32 (4.3)		<0.001	0 (0.0)
Unadjusted HR	1.0	2.3	1.5–3.4	<0.001	0 (0.0)
Multivariable adjusted HR after multiple imputation	1.0	1.7	1.1–2.7	0.013	0 (0.0)
Propensity score matching HR	1.0	2.0	1.1–3.7	0.022	0 (0.0)
Major bleeding†					
Kaplan–Meier event rates, n (%)	377 (8.2)	102 (13.4)		<0.001	0 (0.0)
Unadjusted HR	1.0	1.7	1.4–2.1	<0.001	0 (0.0)
Multivariable adjusted HR after multiple imputation	1.0	1.3	1.0–1.6	0.041	0 (0.0)
Propensity score matching HR	1.0	1.4	1.0–1.9	0.037	0 (0.0)
Definite stent thrombosis					
Kaplan–Meier event rates, n (%)	26 (0.6)	6 (0.8)		0.460	0 (0.0)
Propensity score matching HR	1.0	1.5	0.4–5.4	0.510	0 (0.0)
Stroke					
Kaplan–Meier event rates, n (%)	32 (0.7)	15 (2.0)		<0.001	0 (0.0)
Propensity score matching HR	1.0	2.9	1.0–8.0	0.042	0 (0.0)

HR indicates hazard ratio.
*Baseline anemia was defined in accordance with the World Health Organization as a hemoglobin value <130 g/L for men and <120 g/L for women.
†Major bleeding was defined as 2, 3, or 5 on the Bleeding Academic Research Consortium scale.

increased mortality, myocardial reinfarction, and major bleeding rates was seen, with especially a hemoglobin level <100 g/L being associated with an overall high clinical event rate. All causes of death (cardiovascular death, fatal bleedings, and other causes of death) were increased.

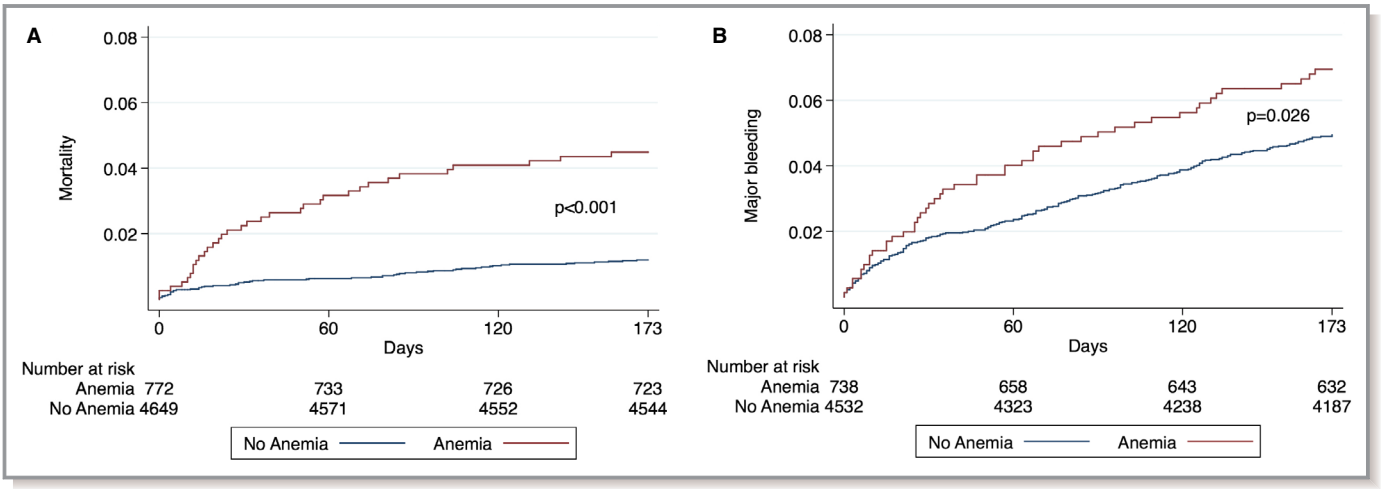

Figure 3. Landmark analysis at 7 days, for mortality (**A**) and major bleeding (**B**), in acute coronary syndrome patients with and without anemia.

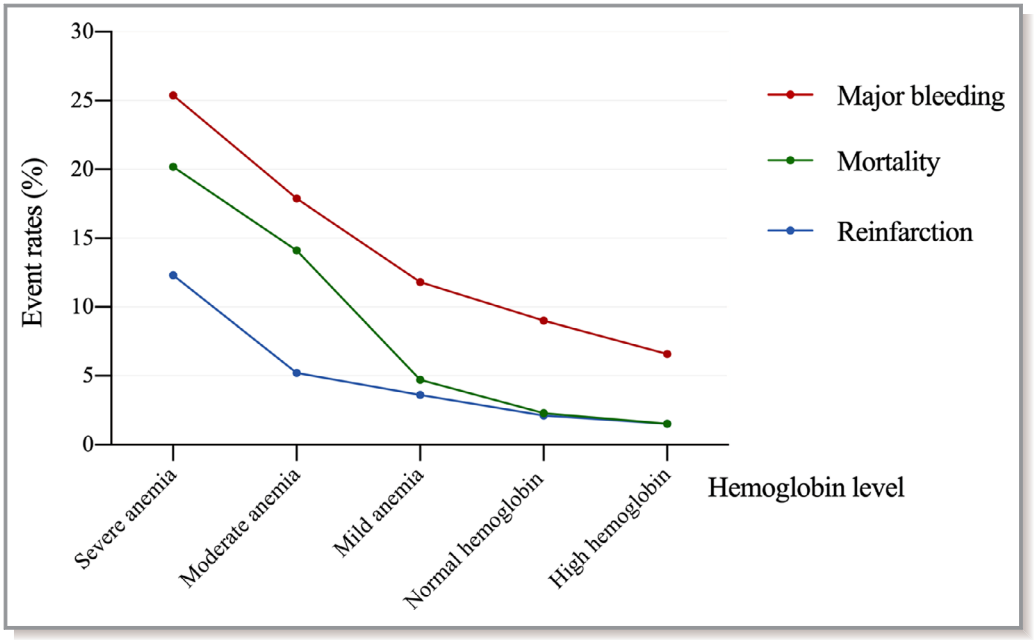

Figure 4. Event rates at 180 days for mortality (green), reinfarction (blue), and major bleeding (red), stratified by hemoglobin level categories in acute coronary syndrome patients: severe anemia (hemoglobin <100 g/L); moderate anemia (hemoglobin 100–109 g/L); mild anemia (hemoglobin 110–129 g/L for men and 110–119 g/L for women); normal hemoglobin (130–150 g/L for men and 120–150 g/L for women); and high hemoglobin (>150 g/L).

Results in Context With Previous Studies

The association between baseline anemia and mortality has been studied and validated in several trials, both in the general population[23] and in coronary artery disease.[10–19] However, these trials have mostly been performed in an era of extensive usage of GPI, which currently is not recommended as standard practice because of excess bleeding risk.[24] Furthermore, these studies were carried out when the radial artery was not the default access route.[24] Both reducing the use of GPI and using primarily the radial artery as access route has in multiple randomized trials been associated with less serious bleedings.[3,6] However, the usage of more potent P2Y12 inhibition could in theory increase bleeding rates, especially in patients with anemia.[7,8] Therefore, we aimed to evaluate how baseline anemia translates into hard clinical outcomes in an era of >90% radial artery access and only bailout use of GPI (<3%) but with modern P2Y12 inhibition. Our results indicate that baseline anemia still constitutes a highly predictive factor for total mortality in this clinical setting. Regarding myocardial reinfarction, previous studies have reported conflicting data. Whereas some studies report an increase in myocardial reinfarction,[10,11,14] some studies do not show any association.[12,13,17,25] Our results indicate an increase in myocardial reinfarction in patients with baseline anemia. We also found that the left ventricular ejection fraction of patients with anemia during their hospital stay was lower compared with that of patients without anemia, which might be indicative of a larger infarct size or area at ischemic risk. Likewise, patients with anemia had higher peak values of high-sensitivity cardiac troponin T, which is a strong predictor of infarct size and systolic dysfunction at 6 months.[26] Moreover, we found an increase in bleeding events in patients with anemia, despite low use of GPI and >85% radial artery access in this patient group. Notably, the bleeding risk was particularly high in patients with a hemoglobin value <100 g/L, which is consistent with the PRECISE-DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) risk score.[27] The landmark analyses suggest that there is a continued increased bleeding risk even after the acute phase of MI. However, the majority of bleedings occurred within the first week, despite the default radial access use and low GPI use. Some studies have shown a J-shaped association between hemoglobin levels and outcomes.[12] However, this could not be demonstrated from our data, where only low hemoglobin levels appeared to be linked with worse outcomes. Caution should be applied when adding potent antithrombotic agents to patients with anemia during their hospital stay. However, this must be balanced with the increased risk of MI of this patient group.

Mechanisms Behind Mortality, Myocardial Reinfarction, and Major Bleeding

Baseline hemoglobin level may be a surrogate marker of comorbidities, such as malignancies, that are associated with increased bleeding rate as well as risk of thromboembolic

Table 4. Causes of Death for Acute Coronary Syndrome Patients With and Without Anemia

	No Anemia (n=4690)	Anemia* (n=792)	95% CI	*P* Value
Cardiovascular death cause				
Kaplan–Meier event rates, n (%)	75 (1.6)	40 (5.2)		<0.001
Unadjusted HR	1.0	3.3	2.2–4.8	<0.001
Fatal bleeding				
Kaplan–Meier event rates, n (%)	5 (0.1)	4 (0.5)		0.009
Unadjusted HR	1.0	4.9	1.3–18.1	0.018
Other death cause				
Kaplan–Meier event rates, n (%)	16 (0.3)	10 (1.4)		<0.001
Unadjusted HR	1.0	3.9	1.8–8.6	0.001

HR indicates hazard ratio.
*Baseline anemia was defined in accordance with the World Health Organization as a hemoglobin value <130 g/L for men and <120 g/L for women.

events.[28] Anemia could also be a marker of inflammatory disorders that are in turn associated with increased ischemic risk.[28,29] Furthermore, anemia could also be suggestive of an ongoing occult gastrointestinal bleeding or an increased propensity for bleeding attributable to coagulopathies.[11] In accordance with this, fatal bleeding was in our study 5 times more common in patients with anemia. Moreover, patients with anemia more often received blood transfusion, which has previously been described as a possible independent factor for mortality in ACS patients.[30] Other stipulated mechanisms behind anemia and ischemic outcomes could be a decreased oxygen-carrying capacity of the blood that predisposes for ischemia and arrhythmias.[12] Our data suggest that patients with anemia also receive less optimal guideline-directed discharge medication, including aspirin and potent P2Y12 inhibitors, which could predispose to downstream ischemic events. The factors mentioned above may explain our finding that cardiovascular death causes were 3 times as frequent in patients with anemia. This could also be explained by a higher comorbidity burden of cardiovascular risk factors, or discontinuation of antiplatelet therapy due to bleeding events in patients with anemia, which may generate consequential ischemic complications.[31] Interestingly, radial access was less often used in patients with anemia, highlighting that patients with anemia are a sicker group, where puncture of the radial artery to a lesser degree was deemed possible. This may be attributable to more extensive arteriosclerosis or hemodynamic instability in this patient group, and therefore a femoral approach might have been preferred.

Limitations

Our study is an observational study, and causality between anemia and worse outcomes is therefore uncertain. Furthermore, a larger sample size including more patients with anemia could have shed further light on the topic of anemia and clinical outcomes. More background knowledge of cause of anemia could have added more information on mechanisms behind anemia and worse clinical outcomes. In addition, we

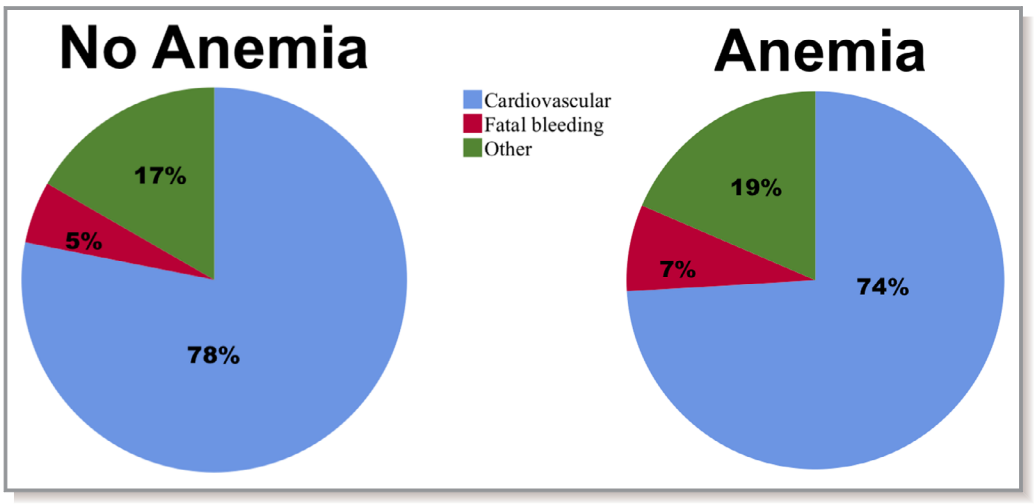

Figure 5. The causes of death for acute coronary syndrome patients who died within 180 days from their index myocardial infarction (n=150). Patients are divided into those who presented without baseline anemia (n=96) and with baseline anemia (n=54).

lacked data on some potential confounders, including malignancy, coagulopathies, and inflammatory disorders, which could have contributed to the higher event rates in patients with anemia. Finally, the hemoglobin value is subject to natural variation due to variation of the intravasal plasma volume that is subject to dehydration/diuretics as well as volume infusion.

Conclusions

Our results indicate that anemia constitutes a high-risk feature in patients with acute coronary syndromes despite treatment with contemporary therapies, including high use of radial artery access, potent P2Y12 inhibitors, and low use of GPI. Especially anemia with a hemoglobin <100 g/L, constitutes a strong negative predictive sign with a substantially increased risk of death, myocardial reinfarction, and major bleeding. The mechanisms are likely multifactorial: Anemia can both be a marker of a sicker patient cohort and have direct physiological consequences, but it may also lead to a lesser degree of guideline-stipulated discharge medications. Nevertheless, in complex patients with anemia and concomitant coronary disease, a multidisciplinary approach is warranted to maximize benefit and minimize patient risk.

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Supplemental Material

Table S1. Kaplan-Meier event rates for patients with and without anemia who received heparin vs bivalirudin.

	No Anemia n=4690		p-value	Anemia n=792		p-value
	Heparin n=2372	Bivalirudin n=2318		Heparin n=385	Bivalirudin n=407	
Mortality n(%)	51(2.2)	45(2.0)	0.617	23(6.1)	31(7.8)	0.364
Reinfarction n(%)	52(2.2)	36(1.6)	0.106	16(4.4)	16(4.2)	0.889
Major bleeding n(%)	192(8.2)	185(8.1)	0.850	50(13.4)	52(13.3)	0.917

*Baseline anemia was defined in accordance with WHO as a hemoglobin value <130 g/L for men and <120 g/L for women. †Major bleeding was defined as 2, 3, or 5, on the Bleeding Academic Research Consortium scale.

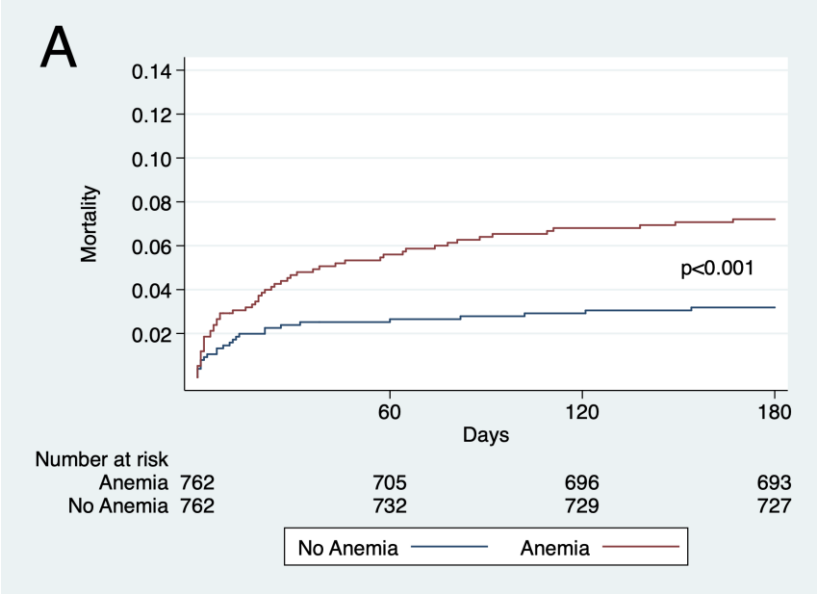
Table S2. Sensitivity analyses for endpoints at 180 days after propensity score matching with downstream adjustments for body mass index (BMI).

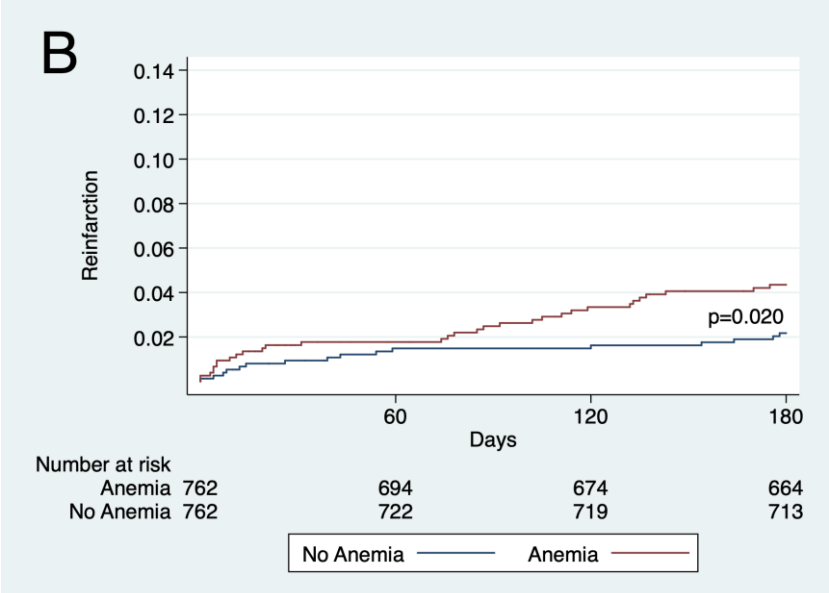
	No Anemia n=4690	Anemia n=792	95% CI	p-value	Missing or unknown n(%)
Mortality - hazard ratio	1.0	2.2	1.3-3.8	0.002	156(10.2)
Reinfarction – hazard ratio	1.0	2.2	1.2-4.2	0.013	156(10.2)
Major bleeding – hazard ratio	1.0	1.4	1.0-1.9	0.041	156(10.2)
Definite stent thrombosis – hazard ratio	1.0	1.0	0.3-3.9	0.979	156(10.2)
Stroke – hazard ratio	1.0	2.7	0.9-7.6	0.066	156(10.2)

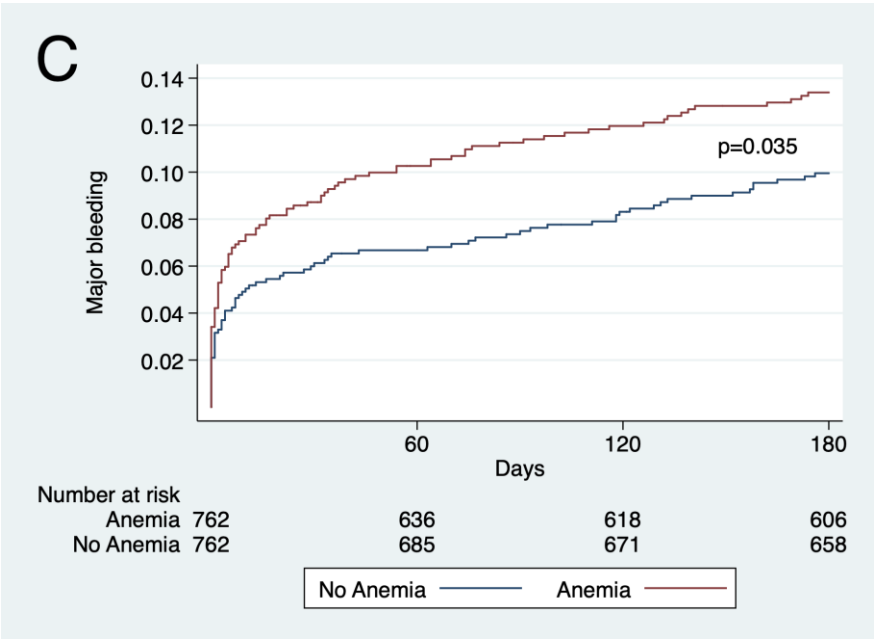
*Baseline anemia was defined in accordance with WHO as a hemoglobin value <130 g/L for men and <120 g/L for women. Major bleeding was defined as 2, 3, or 5, on the Bleeding Academic Research Consortium scale.

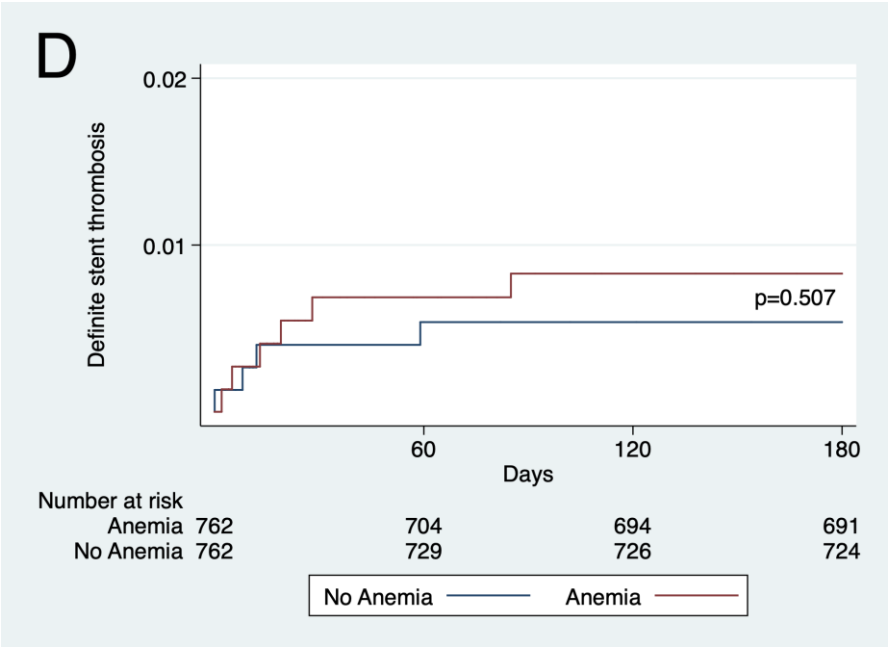
†Abbreviations: CI=confidence interval

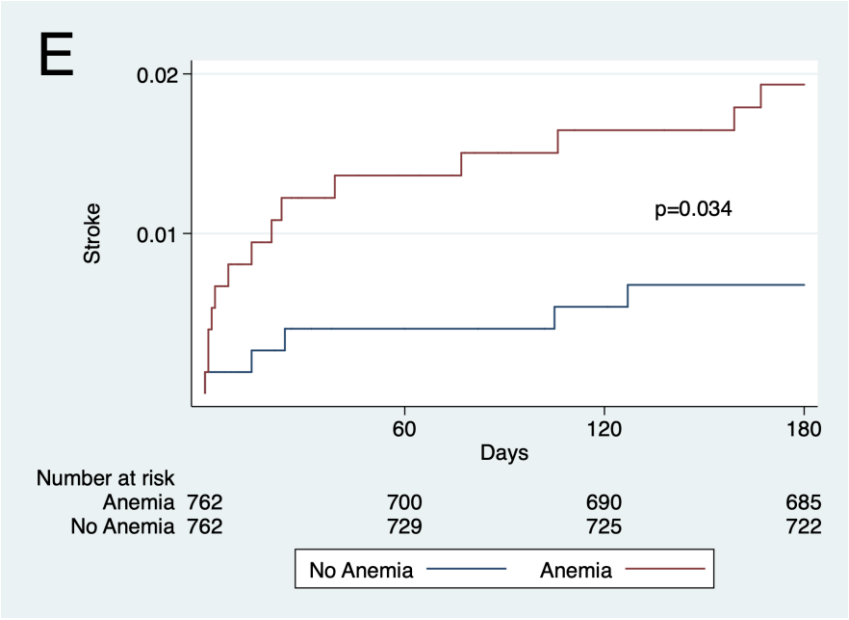
Figure S1. Kaplan-Meier failure functions for mortality (A), myocardial reinfarction (B), major bleeding (C), definite stent thrombosis (D), and stroke (E), at 180 days in acute coronary syndrome patients with and without anemia after propensity score matching.






C
0.14
0.12
0.10
0.08
0.06
0.04
0.02
Major bleeding
p=0.035
60
120
180
Days
Number at risk
Anemia 762 636 618 606
No Anemia 762 685 671 658
No Anemia
Anemia


D
0.02
0.01
Definite stent thrombosis
p=0.507
60
120
180
Days
Number at risk
Anemia 762 704 694 691
No Anemia 762 729 726 724
No Anemia
Anemia


E
0.02
0.01
Stroke
p=0.034
60
120
180
Days
Number at risk
Anemia 762 700 690 685
No Anemia 762 729 725 722
No Anemia
Anemia