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Original Research

Severity of and Recovery From Anemia After Transcatheter Aortic Valve Replacement: An Analysis of the PARTNER Trials and Registries

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ABSTRACT

Background: Anemia is associated with increased mortality in patients undergoing transcatheter aortic valve replacement (TAVR); however, data on the effect of the severity of and recovery from anemia on clinical outcomes are limited. This study examined the impact of the severity of and recovery from anemia after TAVR.

Methods: Patients with symptomatic, severe aortic stenosis across all surgical risk groups from the Placement of Aortic Transcatheter Valves (PARTNER) I, II, and III trials and registries who underwent TAVR were analyzed. Baseline anemia was defined as mild (hemoglobin [Hb] level $\geq$11.0 g/dL and $<$13.0 g/dL for men and $\geq$11.0 g/dL and $<$12.0 g/dL for women) and moderate-to-severe anemia (Hb level $<$11.0 g/dL). Recovery from anemia was defined as an increase of $\geq$1 g/dL in the Hb level. Patients with missing Hb information and major bleeding within 30 days were excluded. The association of the severity of and recovery from anemia with clinical outcomes was analyzed using multivariable Cox proportional hazards regression models. The primary outcome was 1-year all-cause mortality.

Results: The Kaplan-Meier estimate for 1-year all-cause mortality was 5.4%, 8.2%, and 14.5% in patients with no, mild, and moderate-to-severe anemia, respectively ($P < .001$). Recovery from anemia at 30 days occurred in 8.4% (229/2730) of all patients. Compared with those without baseline or 30-day anemia, patients with recovery from anemia had similar 1-year mortality (hazard ratio, 1.02; CI, 0.50-2.08; $P = .96$), whereas those without recovery from anemia had higher 1-year mortality (hazard ratio, 1.82; CI, 1.17-2.85; $P = .009$).

Conclusions: In patients undergoing TAVR, moderate-to-severe anemia is independently associated with increased 1-year mortality, and recovery from anemia after TAVR is associated with favorable outcomes. Further efforts are needed to determine whether preprocedural correction of anemia improves post-TAVR outcomes.

Abbreviations: AS, aortic stenosis; CEC, clinical events committee; Hb, hemoglobin; HF, heart failure; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement.

Keywords: anemia; anemia recovery; aortic stenosis; transcatheter aortic valve implantation; transfusion.

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Introduction

Patients with severe aortic stenosis (AS)—a common valvular disorder among elderly populations[1–4]—are at the risk of anemia because of associated comorbidities, including acquired type 2A von Willebrand syndrome due to excessive shearing of the stenotic aortic valve, and gastrointestinal bleeding due to intestinal angiodysplasia (Heyde syndrome).[5–8] The presence of baseline anemia and its severity have been linked with poor outcomes in patients undergoing surgical aortic valve replacement (SAVR), including an independent association with 30-day and long-term mortality.[9,10] A similar association of adverse outcomes with baseline anemia has been reported in patients undergoing transcatheter aortic valve replacement (TAVR).[11–16] Most of these studies were derived from small, single-center series that treated mainly high-risk patients and did not evaluate outcomes by the severity of anemia.[12,14–17] Furthermore, data on recovery from anemia after correction of valvular stenosis are scarce.[6,17] The objectives of this study were to determine the prevalence and severity of baseline anemia in patients undergoing TAVR and examine the association of the severity of and recovery from anemia with outcomes after TAVR.

Materials and methods

Study design and population

The study cohort consisted of treated patients with a low, intermediate, and high surgical risk undergoing TAVR from the Placement of Aortic Transcatheter Valves (PARTNER) I, II, and III trials and registries (including PARTNER IIA trial and both PARTNER II SAPIEN 3 High- and Intermediate-risk registries).[1–3,18–20] Detailed descriptions of the trial designs as well as the inclusion and exclusion criteria have been published previously.[1–3,18–20] Across all PARTNER trials and registries, the institutional review boards of each site approved the study protocol and patient enrollment, and all patients enrolled provided written informed consent.

The key exclusion criteria specific to the current analysis were anemia (hemoglobin [Hb] level <9 mg/dL), thrombocytopenia (platelet count <50,000 cells/mm^3), and history of bleeding diathesis or coagulopathy. Additional exclusion criteria for the current study were as follows: (1) patients with missing preprocedural or 30-day Hb values and (2) patients with major, disabling, or life-threatening bleeding within 30 days after TAVR. Patients eligible for this subanalysis were evaluated based on the severity of anemia at baseline and changes in anemia at 30 days. Baseline anemia was defined using the World Health Organization criteria, yielding 3 groups: no anemia, mild anemia (Hb level, 11.0-13.0 g/dL for men and 11.0-12.0 g/dL for women), and moderate-to-severe anemia (Hb level <11.0 g/dL).[21] The changes in anemia were evaluated across 4 groups: no anemia at either time point, no anemia at the baseline and mild-to-moderate anemia at 30 days ("new anemia"), baseline anemia with recovery at 30 days, and baseline anemia without recovery at 30 days. Recovery from anemia was defined as an increase of ≥1 g/dL in the Hb level.[17,21] The sample size determination is presented in Supplemental Figure S1.

Study end points

The primary end point was 1-year all-cause mortality. The secondary end points were heart failure (HF)-related rehospitalization and a composite of all-cause mortality and HF-related rehospitalization at 1 year. HF-related rehospitalizations were determined based on clinical events committee (CEC)-adjudicated rehospitalization definitions for each study[1–3,18–20]; patients whose rehospitalization was CEC adjudicated as HF related and met the CEC rehospitalization definition from their trial (eg, symptoms of AS from PARTNER I) were considered to have HF rehospitalization in this study.

Statistical analysis

The baseline patient, echocardiographic, and procedural characteristics were compared based on the severity of anemia at the baseline and changes in anemia at 30 days. Categorical variables are presented as incidences and were compared using the Pearson χ^2 test. Continuous variables are presented as mean ± standard deviation and were compared using the Student *t* test for 2 groups and 1-way analysis of variance for ≥3 groups. Kaplan-Meier estimates were used for the 1-year time-to-event end points and compared using the log-rank test. The patients were censored until their last known follow-up time, which was defined as the time of death, study exit, or up to 1 year, whichever was earlier.

Multivariable Cox proportional hazards regression models were used to assess the association of the severity of anemia (reference = no anemia) with outcomes. The multivariable models were adjusted for covariates with P <.15 in a univariate Cox regression model using backward stepwise selection. The initial covariate list can be found in Table 1. We additionally used a competing risk model for 1-year HF hospitalization events to address the competing risk caused by death. Because the Hb level cutoffs for mild anemia are different in men and women, we performed subgroup analyses to examine the association between baseline anemia and outcomes by sex.

Table 1. List of covariates used in the regression models.

Initial covariates for univariate Cox regression model	Candidate variables for multivariable logistic regression model (selected a priori for model inclusion)
Age	Age (per 10 y)
Sex	Sex
BMI	BMI (per 5 kg/m^2)
Baseline creatinine	Baseline anemia severity
STS risk score	STS risk score
NYHA functional class	NYHA functional class
CAD	CAD
Prior PCI	Prior PCI
Prior MI	Prior MI
Prior CABG	Prior CABG
Prior CVA	Prior CVA
PVD	PVD
Diabetes mellitus	Diabetes mellitus
COPD	COPD
Atrial fibrillation	Atrial fibrillation
CKD	CKD
Liver disease	Liver disease
Permanent pacemaker	Permanent pacemaker
Frailty	Frailty
AV area	AV area
AV mean gradient	AV mean gradient (per 10 mm Hg)
LV mass	LV mass
LVEF	LVEF (per 5%)
Moderate-to-severe mitral regurgitation	Mitral regurgitation
Platelet count	Platelet count
TAVR access site	Transfemoral access
PVR at 30 d	Moderate-to-severe PVR at 30 d
	Anticoagulant medication at discharge
	Antiplatelet medication at discharge
	Transfusion during index hospitalization

AV, aortic valve; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; PVR, paravalvular regurgitation; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement.

We used multivariable logistic regression models to identify the independent predictors of recovery from anemia at 30 days after TAVR. The candidate variables were selected a priori for inclusion in the multivariable logistic regression model (Table 1). The outcome analysis involving changes in anemia was performed starting 30 days after TAVR because patients with missing 30-day Hb values were excluded.

We performed restricted cubic spline analyses to examine the association of baseline Hb levels and changes in Hb levels (as continuous variables) with outcomes. Because blood transfusion could influence recovery from anemia and its outcomes, sensitivity analyses were performed after excluding patients who received a blood transfusion after TAVR. Lastly, we performed additional analyses in patients with or without late bleeding complications. Late bleeding complications were defined as any bleeding event beyond 30 days that met the following criteria: (1) bleeding that caused mortality, new hospitalization, or prolonged hospitalization for >24 hours because of treatment; (2) bleeding that required pericardiocentesis or an open and/or endovascular procedure for repair or hemostasis; (3) bleeding that led to a permanent disability (eg, blindness, paralysis, and hearing loss); or (4) bleeding that required a transfusion of >3 units of blood within 24 hours.[22] This definition was applied to the whole patient cohort as a binary variable, and the interaction between late bleeding complications and anemia was tested. The interaction tests were performed between the anemia variables and cohort to examine the poolability of the study results.

All statistical analyses were performed using the SAS software, version 9.4. All the tests were 2 sided, and a P value of <.05 ($P_{interaction}$ < .1) was considered statistically significant. All the analyses were post hoc, with no multiplicity adjustment, and are considered exploratory.

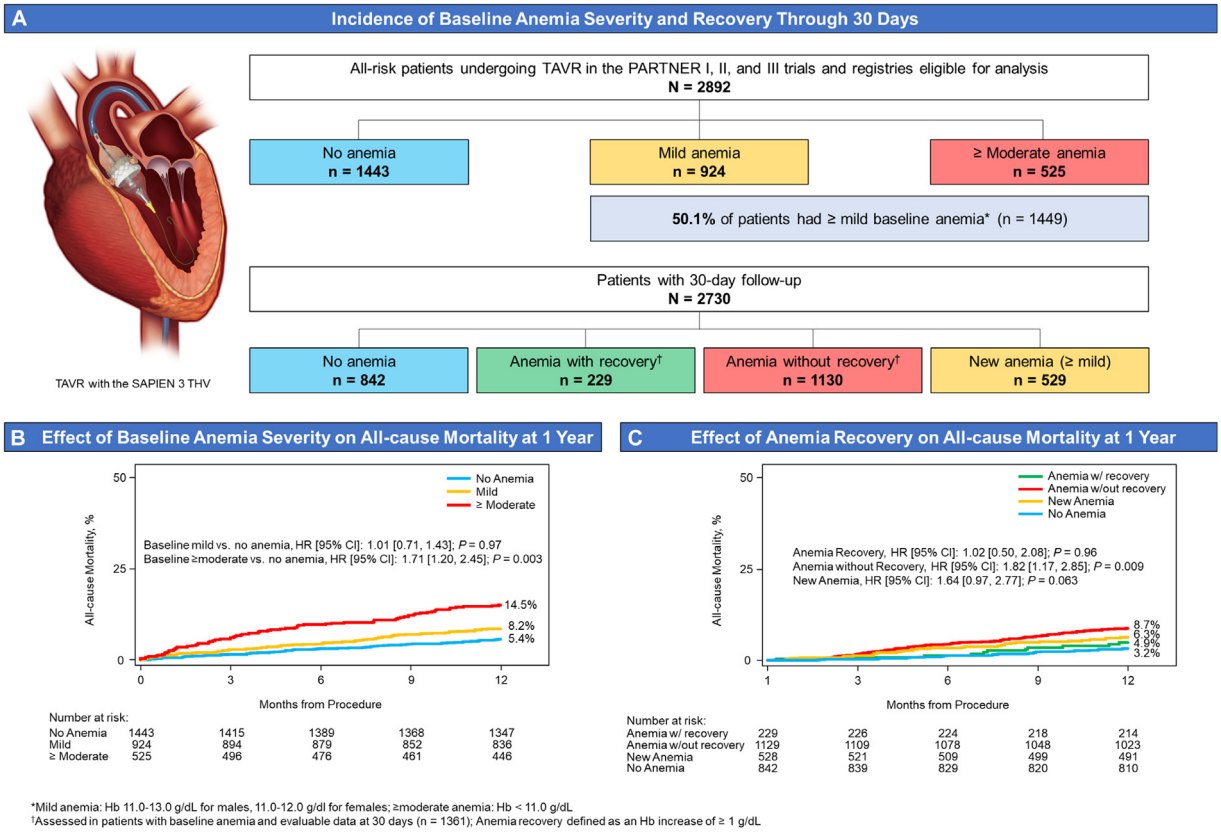
Results

Baseline characteristics

The study included 2892 patients across the spectrum of surgical mortality risk who underwent TAVR for symptomatic severe AS, of whom 1449 (50.1%) had baseline anemia (Central Illustration). Of the patients with anemia, 924 (63.8%) had mild and 525 (36.2%) had moderate-to-severe anemia. The patients with mild and moderate-to-severe anemia were older; had higher Society of Thoracic Surgeons scores; and had a higher prevalence of comorbidities such as prior myocardial infarction, diabetes, chronic kidney disease, and frailty than those without anemia (Table 2). The patients with anemia were prescribed antiplatelet medication less frequently at discharge than those without anemia. Blood transfusion during the index hospitalization was more frequent in the patients with moderate-to-severe anemia prior to TAVR. There were minor differences in baseline characteristics between patients with recovery from anemia and those without recovery from anemia, including male sex, Society of Thoracic Surgeons score, and postprocedural transfusion during the index hospitalization (Supplemental Table S1).

Association of the severity of baseline anemia with outcomes

The Kaplan-Meier estimate for the primary end point of 1-year all-cause mortality was 5.4%, 8.2%, and 14.5% in the patients with no anemia, mild anemia, and moderate-to-severe anemia, respectively



*Mild anemia: Hb 11.0-13.0 g/dL for males, 11.0-12.0 g/dl for females; ≥moderate anemia: Hb < 11.0 g/dL
†Assessed in patients with baseline anemia and evaluable data at 30 days (n = 1361); Anemia recovery defined as an Hb increase of ≥ 1 g/dL

Central Illustration.

This figure summarizes the key finding from the study. (**A**) Cohort formation and identification of patients with anemia from the Placement of Aortic Transcatheter Valves (PARTNER) trials and registries. Time-to-event curves and hazard ratios for 1-year all-cause mortality for the (**B**) severity of and (**C**) recovery from anemia. Hb, hemoglobin; HR, hazard ratio; TAVR, transcatheter aortic valve replacement; THV, transcatheter heart valve.

Table 2. Baseline characteristics by severity of baseline anemia.

	No anemia	Mild anemia	≥Moderate anemia	*P* value[a]
Male	844/1443 (58.5%)	657/924 (71.1%)	259/525 (49.3%)	<.001
Age, y	79.4 ± 0.20 (7.59)	81.8 ± 0.23 (6.98)	81.4 ± 0.35 (7.92)	<.001
BMI, kg/m^2	29.6 ± 0.16 (5.89)	28.3 ± 0.20 (6.19)	28.4 ± 0.31 (7.04)	<.001
Baseline creatinine, mg/dL	1.0 ± 0.01 (0.31)	1.2 ± 0.01 (0.42)	1.3 ± 0.02 (0.48)	<.001
STS score	5.0 ± 0.08 (2.96)	6.5 ± 0.12 (3.56)	7.7 ± 0.17 (3.87)	<.001
Baseline NYHA class (I/II)	508/1443 (35.2%)	232/924 (25.1%)	78/525 (14.9%)	<.001
Baseline 6-min walk test, m	241.8 ± 3.67 (135.24)	192.6 ± 4.12 (120.21)	148.9 ± 5.32 (113.44)	<.001
Baseline KCCQ overall summary score	58.6 ± 0.63 (22.47)	53.7 ± 0.81 (23.52)	46.2 ± 1.02 (22.23)	<.001
Previous CAD	828/1441 (57.5%)	623/924 (67.4%)	343/525 (65.3%)	<.001
Previous PCI	365/1441 (25.3%)	294/924 (31.8%)	160/525 (30.5%)	.001
Previous MI	215/1442 (14.9%)	157/924 (17.0%)	103/525 (19.6%)	.038
Previous CABG	303/1443 (21.0%)	288/923 (31.2%)	146/525 (27.8%)	<.001
Previous CVA	123/1443 (8.5%)	97/924 (10.5%)	45/525 (8.6%)	.23
Peripheral vascular disease	346/1442 (24.0%)	248/922 (26.9%)	136/521 (26.1%)	.26
Diabetes mellitus	447/1443 (31.0%)	363/924 (39.3%)	218/525 (41.3%)	<.001
COPD	362/1437 (25.2%)	318/920 (34.6%)	171/523 (32.7%)	<.001
Atrial fibrillation	418/1401 (29.8%)	307/876 (35.0%)	162/481 (33.7%)	.026
Chronic kidney disease				
Normal or high eGFR, ≥90 mL/min/1.73 m^2	179/1442 (12.5%)	81/924 (8.8%)	34/524 (6.5%)	<.001
Mildly decreased eGFR, 60-89 mL/min/1.73 m^2	698/1442 (48.4%)	349/924 (37.8%)	149/523 (28.4%)	
Mildly-to-moderately decreased eGFR, 45-59 mL/min/1.73 m^2	385/1442 (26.7%)	267/924 (28.9%)	160/523 (30.5%)	
Moderately-to-severely decreased eGFR, 30-44 mL/min/1.73 m^2	159/1442 (11.0%)	177/924 (19.2%)	130/523 (24.8%)	
Severely decreased eGFR, 15-29 mL/min/1.73 m^2	21/1442 (1.5%)	50/924 (5.4%)	51/523 (9.7%)	
Liver disease	19/1443 (1.3%)	9/924 (1.0%)	8/525 (1.5%)	.62
Hypertension	13,144/1443 (91.1%)	852/922 (92.4%)	483/525 (91.8%)	.51
Permanent pacemaker	159/1443 (11.0%)	140/924 (15.2%)	58/525 (11.0%)	.007
Frailty	91/1434 (6.3%)	82/904 (9.1%)	76/509 (14.9%)	<.001
Baseline aortic valve area, cm^2	0.7 ± 0.01 (0.18)	0.7 ± 0.01 (0.17)	0.7 ± 0.01 (0.17)	.003
Baseline aortic valve mean gradient, mm Hg	46.0 ± 0.35 (13.24)	44.9 ± 0.42 (12.65)	46.3 ± 0.63 (14.35)	.08
Baseline LV mass, g	222.5 ± 2.00 (72.05)	233.4 ± 2.49 (71.16)	238.2 ± 3.45 (75.03)	<.001
Baseline LVEF, %	58.7 ± 0.34 (12.73)	56.2 ± 0.45 (13.36)	55.8 ± 0.59 (13.26)	<.001
Baseline mitral regurgitation	113/1377 (8.2%)	119/866 (13.7%)	77/503 (15.3%)	<.001
Platelet count, /mL	201,492.1 ± 1671.20 (63,417.58)	201,517.8 ± 2093.18 (63,592.74)	213,618.9 ± 3638.24 (83,283.14)	<.001
Transfemoral approach	1305/1443 (90.4%)	797/924 (86.3%)	446/525 (85.0%)	<.001
Antiplatelet medication at discharge	1164/1443 (80.6%)	655/924 (70.9%)	330/525 (62.7%)	<.001
Anticoagulant medication at discharge	359/1443 (24.9%)	210/924 (22.7%)	116/525 (22.1%)	.31
Postprocedural transfusion during index hospitalization	8/1443 (0.6%)	8/924 (0.9%)	40/525 (7.6%)	<.001
Postprocedural transfusion during index hospitalization (no. of units)	1.6 ± 0.57 (1.51)	1.1 ± 0.13 (0.35)	1.3 ± 0.16 (1.00)	.69

Descriptive statistics are presented as n or N (%) for categorical variables and mean ± standard error (standard deviation) for continuous variables.
BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons.
[a] *P* values were based on the χ^2 test for categorical variables and analysis of variance test for continuous variables.

(*P* < .001 from the log-rank test; Figure 1A). Similarly, compared with the patients with no anemia at the baseline, those with mild or moderate-to-severe anemia at the baseline had significantly higher rates of 1-year HF rehospitalization (4.3%, 8.3%, and 8.9% in the groups with no, mild, and moderate-to-severe anemia, respectively) and the composite of all-cause mortality and HF rehospitalization at 1 year (8.9%, 14.3% and 20.4% in the groups with no, mild, and moderate-to-severe anemia, respectively) (both *P* < .001 from the log-rank test; Figure 1B, C). The competing risk analysis for 1-year HF rehospitalization showed the event rate to be 4.3%, 8.1%, and 8.4% in the groups with no, mild, and moderate-to-severe anemia, respectively (*P* < .001).

In the multivariable analyses, moderate-to-severe anemia was associated with an increased risk of 1-year all-cause mortality (adjusted hazard ratio [HR], 1.71; 95% CI, 1.20-2.45; *P* = .003) and the composite of all-cause mortality and HF-related rehospitalization (adjusted HR, 1.60; 95% CI, 1.21-2.12; *P* = .001) (Figure 1A-C). The 1-year all-cause mortality showed an HR of 0.91 (95% CI, 0.83-0.99; *P* = .036) with every 1-g/dL increase in Hb value (Supplemental Table S2). The subgroup analyses showed similar findings in men and women ($P_{interaction}$ > .05) (Supplemental Table S3). In the overall cohort, mild anemia was associated with an increased risk of HF-related rehospitalization (adjusted HR, 1.48; 95% CI, 1.04-2.11; *P* = .03) but was not associated with either all-cause mortality or the composite of mortality and HF-related rehospitalization. There was no statistically significant interaction between the severity of baseline anemia and the cohort, indicating the poolability of the results ($P_{interaction}$ > .1). Furthermore, there was no statistically significant interaction between the severity of baseline anemia and late bleeding complications in terms of 1-year mortality ($P_{interaction}$ = .11) (Supplemental Table S4). In the competing risk analysis for 1-year HF rehospitalization, the adjusted HR was 1.50 (95% CI, 1.05-2.14; *P* = .025) when the patients with mild anemia and those with no baseline anemia were compared and 1.37 (95% CI, 0.86-2.18; *P* = .19) when the patients with moderate-to-severe anemia and those with no baseline anemia were compared.

Recovery from anemia and its association with outcomes

A total of 2730 patients (1371 with no anemia at the baseline and 1359 with baseline anemia) had Hb level information at 30 days of follow-up and were included in the anemia recovery analysis. Of the 1371 patients with no anemia at the baseline, 529 (38.6%) developed

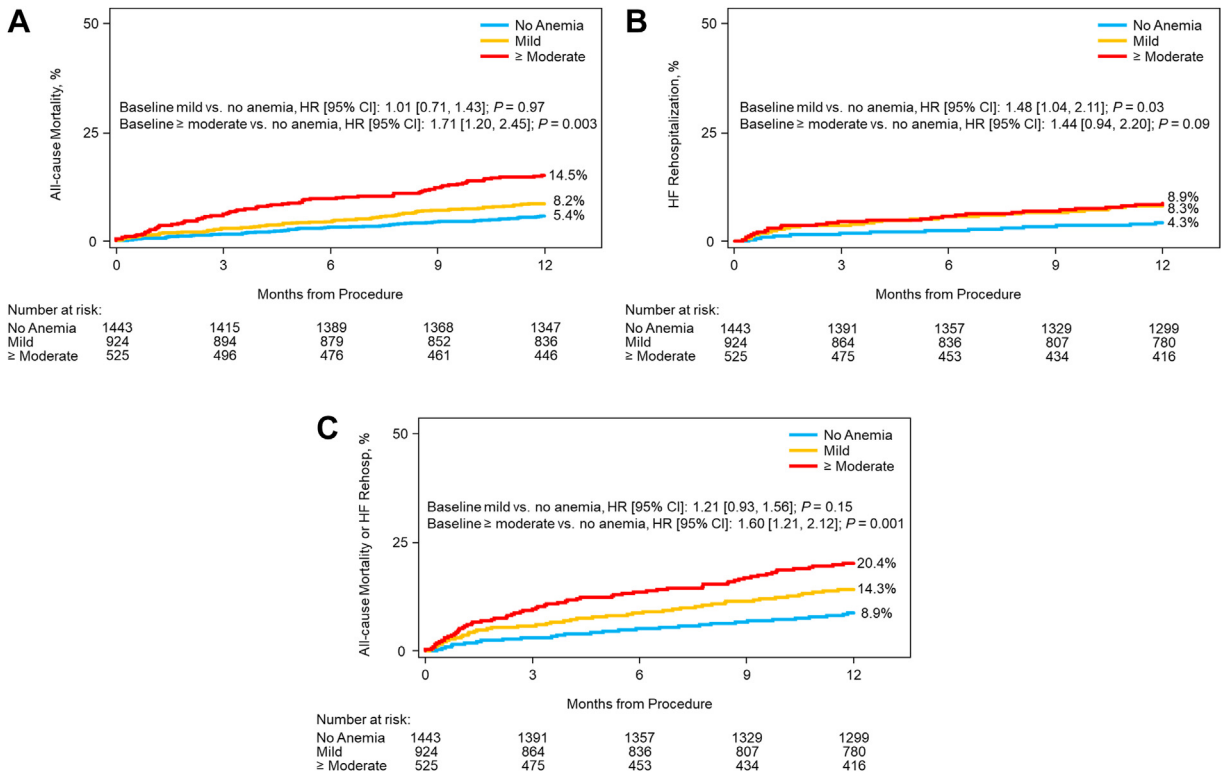


Figure 1.

One-year outcomes by severity of anemia. Time-to-event curves for (**A**) 1-year all-cause mortality, (**B**) heart failure (HF)-related rehospitalization, and (**C**) composite of all-cause mortality and HF-related rehospitalization after transcatheter aortic valve replacement in patients with no anemia, mild anemia, and moderate-to-severe anemia. HF-related rehospitalization was defined as rehospitalization that met both the rehospitalization definitions from the trial[1–3,18–20] and was clinical events committee adjudicated as HF related. The adjusted hazard ratios were compared with those of the no baseline anemia category. HR, hazard ratio.

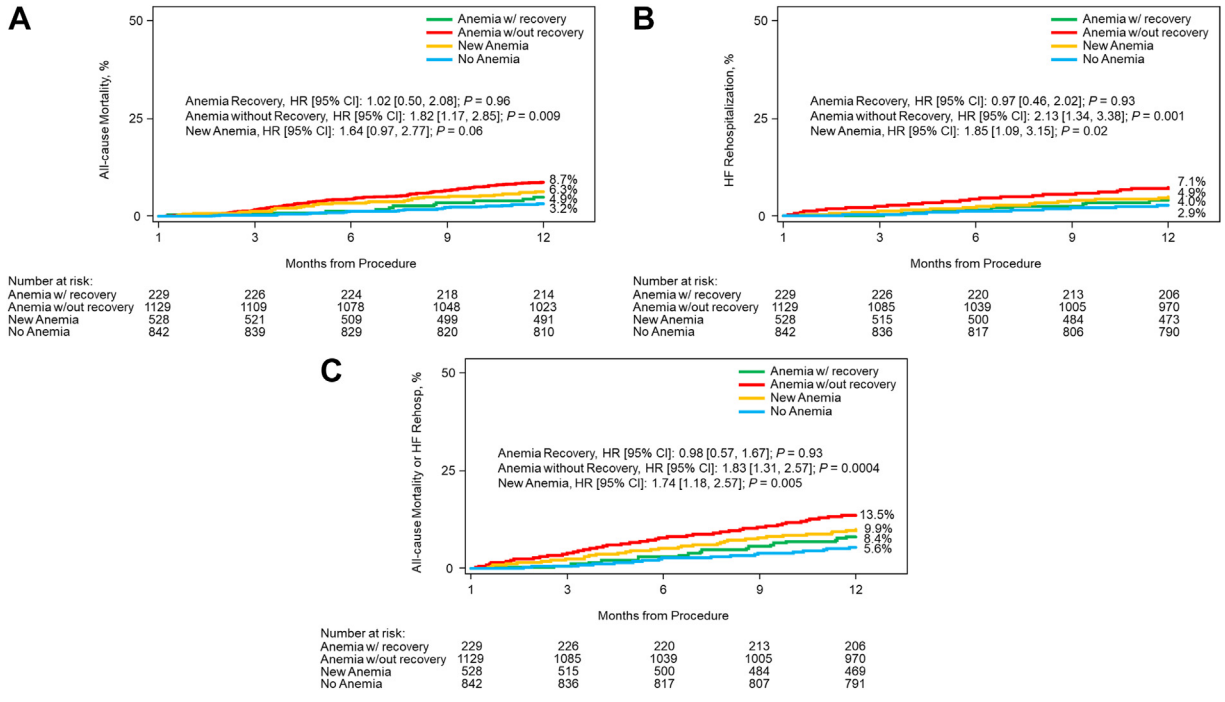


Figure 2.

One-year outcomes by recovery of anemia. Time-to-event curves for (**A**) 1-year all-cause mortality, (**B**) heart failure (HF)-related rehospitalization, and (**C**) composite of all-cause mortality or HF-related rehospitalization after transcatheter aortic valve replacement in patients with no anemia, anemia with recovery, anemia without recovery, and new anemia at 30 days. The results are based on a 30-day landmark analysis. HF-related rehospitalization was defined as rehospitalization that met both the rehospitalization definitions from the trial[1–3,18–20] and was clinical events committee adjudicated as HF related. The adjusted hazard ratios were compared with those of the no baseline or 30-day anemia category. HR, hazard ratio.

new anemia at 30 days of follow-up. Of the 1359 patients with anemia at the baseline, 229 (16.9%) experienced recovery from anemia at 30 days.

In the multivariable analysis, moderate-to-severe anemia at the baseline (odds ratio [OR], 2.18; 95% CI, 1.61-2.95; $P < .001$) and higher mean aortic valve gradients (OR per 10 mm Hg, 1.13; 95% CI, 1.02-1.25; $P = .02$) were independently associated with recovery from anemia (Supplemental Table S5). Of the 525 patients with moderate-to-severe anemia, 40 (7.6%) received a blood transfusion (Table 2), and 14 out of the 229 (6.1%) patients with recovery from anemia received a blood transfusion (Supplemental Table S1). No statistically significant interactions between baseline anemia and the cohort were detected, indicating the poolability of ORs for recovery from anemia ($P_{interaction} = .40$).

In the multivariable Cox regression analyses, baseline anemia without recovery was associated with increased 1-year all-cause mortality (HR, 1.82; 95% CI, 1.17-2.85; $P = .009$), and patients with new anemia at 30 days showed a similar but statistically nonsignificant trend for 1-year all-cause mortality (HR, 1.64; 95% CI, 0.97-2.77; $P = .063$) compared with those with no anemia (Figure 2A). Similarly, anemia without recovery was also associated with increased HF-related rehospitalization (HR, 2.13; 95% CI, 1.34-3.38; $P = .001$) and the composite of all-cause mortality and HF-related rehospitalization (HR, 1.83; 95% CI, 1.31-2.57; $P = .0004$) (Figure 2B, C). The sensitivity analyses, after the exclusion of patients who received a blood transfusion, showed similar results (Supplemental Table S6). There was no significant interaction between recovery from anemia and late bleeding complications in terms of 1-year mortality ($P_{interaction} = .74$; Supplemental Table S7). Similarly, although there was no statistically significant interaction between baseline anemia and late bleeding complications ($P_{interaction} = .11$; Supplemental Table S7), it is possible that moderate-to-severe anemia at the baseline was associated with higher mortality in patients without late bleeding complications (HR, 1.96; 95% CI, 1.34-2.86; $P = .0005$) but not in those with late bleeding complications (HR, 0.54; 95% CI, 0.17-1.72; $P = .30$).

Examination of continuous changes in the Hb level showed a decrease in the HRs for 1-year all-cause mortality (HR, 0.88; 95% CI, 0.78-0.99; $P = .032$) and HF-related rehospitalizations (HR, 0.75; 95% CI, 0.67-0.84; $P < .001$) with each 1-unit increase in or recovery of the Hb levels from the baseline to 30 days (Supplemental Figure S2A-C and Supplemental Table S2).

Discussion

In this study of patients undergoing TAVR across the spectrum of surgical risk, we reported the following key findings: (1) ~50% of the patients had baseline anemia; (2) the presence of moderate-to-severe anemia at the baseline was independently associated with poor outcomes at 1 year; (3) recovery from anemia occurred in 8.4% (229/2730) of all patients and 16.9% (229/1359) of all anemic patients at 30 days; yet, only 6.1% of the patients received a blood transfusion; and (4) anemia without recovery and new anemia at 30 days were associated with worse outcomes compared with no anemia; however, there was no significant association of recovery from anemia with any adverse 1-year outcomes.

Other studies have underscored the association of the severity of anemia with adverse outcomes in higher-risk populations. Nuis et al[12] demonstrated that patients undergoing TAVR with an Hb level of <10 g/dL had higher 1-year mortality than those with an Hb level of ≥10 g/dL. Similarly, in a study by Nagao et al,[11] in all patients with severe AS undergoing either SAVR or TAVR, moderate-to-severe anemia at baseline was associated with a higher risk of mortality and HF hospitalization. A recent analysis from the Optimized Transcatheter Valvular Intervention Registry also found that severe anemia, defined as an Hb level of <10.5 g/dL, was associated with significantly higher all-cause and cardiovascular mortality.[13] In a large, multicenter cohort with independent clinical outcome adjudication, we confirmed that baseline anemia and its severity are associated with increased mortality and rehospitalization after TAVR, and we extended the results of previous studies to lower-risk populations undergoing TAVR.[11–17,21,23,24]

Anemia may represent a marker of frailty, poor nutritional status, or a myriad of comorbidities such as kidney disease, cancer, and gastrointestinal pathologies known to negatively impact clinical outcomes.[25,26] It is, therefore, expected that baseline anemia would be associated with adverse outcomes, not only after TAVR but also across a multitude of cardiovascular diseases, including HF, and in those undergoing other percutaneous and surgical cardiac procedures.[11,27–29] However, anemia may have direct deleterious effects on the cardiovascular system, which might be related to inadequate systemic oxygen delivery, compensatory high cardiac output, tachycardia, and resultant myocardial ischemia,[30,31] and, in turn, causally mediate an increased risk of death and rehospitalization.

Although cross-sectional analyses are confounded by a strong correlation of anemia with clinical comorbidities, frailty, and nutritional status, longitudinal assessment of anemia addresses these shortcomings. Specifically, associations of recovery from anemia with outcomes similar to those in nonanemic patients and those with new and persistent anemia with poor outcomes suggest that anemia, per se, leads to poor outcomes and has clinically relevant implications on the management of anemia in patients with AS undergoing TAVR. In addition, the impact of late bleeding complications was shown in the current analysis because patients with no late bleeding complications, with underlying moderate-to-severe anemia at the baseline, were associated with higher mortality; however, a similar association was not seen in patients with late bleeding complications likely because late bleeding complications by themselves are associated with increased mortality regardless of the baseline Hb levels.[22] The beneficial impact of the identification and correction of anemia has been demonstrated in patients with HF with a reduced ejection fraction in multiple studies.[32,33] Clinical guidelines recommend intravenous iron as the preferred mode for the correction of iron-deficiency anemia in patients with HF.[34,35] Iron deficiency is present in more than half of all patients undergoing TAVR.[23] However, the clinical benefit of correction of iron-deficiency anemia prior to TAVR is unclear and warrants further investigation. A small (n = 48), randomized, double-blind trial of erythropoietin + iron supplementation versus a placebo in patients undergoing TAVR did not lead to improvement in 30-day mortality or the number of red blood cell transfusions.[36] Several ongoing randomized clinical trials are investigating whether the correction of iron-deficiency anemia prior to TAVR using various intravenous iron formulations leads to improved outcomes (NCT04346004, NCT04797832, and NCT04786769).

In the current analysis, we found that 15.7% of the patients had recovery from anemia at 30 days; yet, only 6.1% of the patients with recovery from anemia received a blood transfusion. The pathophysiologic mechanism of recovery from anemia is unclear; however, our finding of an association of higher baseline aortic valve gradients with recovery from anemia suggests that it contributes to reversal of the type 2A acquired von Willebrand syndrome of AS after TAVR.[6,7] High aortic valve pressure gradients generate greater shear stress, which contributes to increased proteolysis of von Willebrand Factor multimers and leads to dysfunction in as many as 42% of patients with severe AS.[37] The von Willebrand multimers have been reported to normalize after both TAVR and SAVR,[37,38] with a consequent reduction in occult or overt bleeding events after valve replacement.[39] Further study is warranted to clarify the mechanisms of recovery from anemia after TAVR.

Study limitations

This was a retrospective post hoc analysis of the PARTNER trials and is subject to inherent limitations. The current analysis was mostly limited

to mild and moderate anemia because patients with severe anemia (Hb level <9 g/dL) were excluded from the PARTNER trials. Recovery from anemia was assessed only at 30 days, which may be too short a duration to assess the full impact of Hb recovery after TAVR. Data regarding the manner of Hb recovery are not differentiated in terms of therapies utilized for Hb recovery, ie, blood transfusions, iron supplementations, or erythropoietin. Similarly, hematologic laboratory testing relating to the etiology of anemia and acquired von Willebrand disease was not available.

Conclusion

Our study showed that among patients with severe symptomatic AS undergoing TAVR, ~50% have at least mild anemia. The presence of moderate-to-severe anemia is associated with increased risks of 1-year mortality and HF-related hospitalization. Among patients with anemia who undergo TAVR, ~15.7% experience recovery of their Hb levels within 30 days. Anemic patients without recovery of Hb or with new anemia have worse 1-year outcomes after TAVR, whereas those with Hb recovery have outcomes similar to those without anemia. Further studies are needed to understand the pathophysiologic underpinnings of the association of anemia and recovery from anemia with outcomes after TAVR and determine whether the correction of anemia before TAVR favorably impacts postprocedural outcomes.

Declaration of competing interest

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Ethics statement and patient consent

Across all PARTNER trials and registries, the institutional review boards of each site approved the study protocol and patient enrollment, and all patients enrolled provided written informed consent.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2022.100531.

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