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ORIGINAL ARTICLE
Valvular Heart Disease

Identification of Anemia for Predicting Mid-Term Prognosis After Transcatheter Aortic Valve Implantation in Japanese Patients

— Insights From the OCEAN-TAVI Registry —

Hiroshi Onoda, MD, PhD; Hiroshi Ueno, MD, PhD; Teruhiko Imamura, MD, PhD; Yohei Ueno, MD; Hiroyuki Kuwahara, MD, PhD; Mitsuo Sobajima, MD, PhD; Koichiro Kinugawa, MD, PhD; Norio Tada, MD; Toru Naganuma, MD; Masahiro Yamawaki, MD; Futoshi Yamanaka, MD; Shinichi Shirai, MD; Kazuki Mizutani, MD; Minoru Tabata, MD, PhD; Kensuke Takagi, MD; Yusuke Watanabe, MD; Masanori Yamamoto, MD, PhD; Kentaro Hayashida, MD, PhD; the OCEAN-TAVI Investigators

Background: Patients with anemia have a poor prognosis following transcatheter aortic valve implantation (TAVI). Given the unique distribution of hemoglobin levels in the Japanese cohort, the optimal cut-off hemoglobin value may help stratify Japanese patients' mortality following TAVI.

Methods and Results: Data of patients who underwent TAVI were collected from the prospective multicenter Optimized transCathEter vAlvular iNtervention (OCEAN)-TAVI Registry. Receiver operating characteristic analysis was used to calculate a hemoglobin cut-off value to stratify 2-year mortality following TAVI. In all, 2,588 patients (mean [±SD] age 84.4±5.2 years, 795 men) were included in the study. Of these patients, 909 (35.1%) had anemia, which was defined as hemoglobin <10.9 g/dL for men and <10.4 g/dL for women. The presence of anemia, uniquely defined for the Japanese cohort, was independently associated with 2-year mortality following TAVI, with an odds ratio of 1.77 (95% confidence interval 1.39–2.25) adjusted for 14 other clinical variables.

Conclusions: The existence of anemia, uniquely defined for the Japanese cohort, was associated with mid-term mortality following TAVI.

Key Words: Aortic stenosis; Prognosis; Transcatheter aortic valve implantation

Transcatheter aortic valve implantation (TAVI) is an alternative treatment for patients with aortic stenosis (AS) who are at high risk of surgical aortic valve replacement (SAVR).[1] In addition, TAVI is as safe and effective as SAVR in low-risk patients.[2,3]

Anemia is a common comorbidity in elderly patients undergoing TAVI. In general, anemia is an independent risk factor of mortality in the elderly cohort.[4] Previous studies reported that anemia was one of the predictors of short-term mortality following TAVI.[5–8]

Most studies investigating the relationship between anemia and prognosis following TAVI use the World Health Organization (WHO) criteria to define anemia, namely hemoglobin <13.0 g/dL in men and <12.0 g/dL in women.[9]

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Second Department of Internal Medicine, University of Toyama, Toyama (H.O., H.U., T.I., Y.U., H.K., M.S., K.K.); Department of Cardiology, Sendai Kousei Hospital, Sendai (N.T.); Department of Cardiology, New Tokyo Hospital, Matsudo (T.N.); Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto (T.N., F.Y.); Department of Cardiology, Saiseikai Yokohama-City Eastern Hospital, Yokohama (M. Yamawaki); Department of Cardiology, Shonan Kamakura General Hospital, Kamakura (F.Y.); Department of Cardiology, Kokura Memorial Hospital, Kitakyushu (S.S.); Division of Cardiology, Department of Medicine, Faculty of Medicine, Kindai University, Osakasayama (K.M.); Department of Cardiovascular Surgery, Tokyo Bay Urayasu Ichikawa Medical Center, Urayasu (M.T.); Department of Cardiology, Ogaki Municipal Hospital, Ogaki (K.T.); Department of Cardiology, Teikyo University School of Medicine, Tokyo (Y.W.); Department of Cardiology, Toyohashi Heart Center, Toyohashi (M. Yamamoto); Department of Cardiology, Nagoya Heart Center, Nagoya (M. Yamamoto); and Department of Cardiology, Keio University School of Medicine, Tokyo (K.H.), Japan

K.K., K.H. are members of *Circulation Reports*' Editorial Team.

Mailing address: Hiroshi Ueno, MD, PhD, Second Department of Internal Medicine, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan. E-mail: hueno@med.u-toyama.ac.jp

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Table 1. Baseline Characteristics, Procedural Data and Clinical Outcomes of Patients With and Without Anemia

	Anemia (n=909)	No anemia (n=1,679)	P value
Patient characteristics			
Age (years)	85.3±5.2	83.9±5.2	<0.001
Female sex	655 (72.1)	1,138 (67.8)	0.024
BSA (m^2)	1.40±0.16	1.45±0.17	<0.001
BMI (kg/m^2)	21.5±3.4	22.6±3.7	<0.001
NYHA Class III or IV	567 (62.4)	754 (44.9)	<0.001
Clinical frailty scale			
1–4	606 (66.7)	1,299 (77.3)	
5, 6	248 (27.2)	334 (19.9)	
7, 8	55 (6.1)	46 (2.7)	
Logistic EuroScore (%)	14.4 [9.5–22.7]	12.3 [7.9–19.9]	<0.001
STS score (%)	7.7 [5.4–11.4]	5.9 [4.2–8.6]	<0.001
Diabetes	180 (19.8)	375 (22.3)	0.13
Dyslipidemia	347 (38.2)	767 (45.7)	<0.001
Hypertension	706 (77.7)	1,284 (76.5)	0.49
Chronic kidney disease	729 (80.2)	1,080 (64.3)	<0.001
Coronary artery disease	345 (38.0)	609 (36.3)	0.40
Atrial fibrillation	201 (22.1)	348 (20.7)	0.41
Peripheral vascular disease	138 (15.2)	239 (14.2)	0.51
Previous cerebrovascular accident	95 (10.4)	206 (12.2)	0.38
COPD	132 (14.5)	253 (15.1)	0.71
Previous CABG	58 (6.4)	111 (6 .6)	0.82
Active malignancy	48 (5.3)	76 (4.5)	0.55
Echocardiographic characteristics			
LVEF (%)	59.4±12.3	59.2±12.9	0.68
Aortic valve area (cm^2)	0.6±0.2	0.6±0.2	0.29
Peak velocity (m/s)	4.6±0.80	4.5±0.8	0.01
Mean gradient (mmHg)	52.0±18.6	49.8±18.0	0.004
Aortic regurgitation III or IV	106 (11.7)	168 (10.0)	0.19
Mitral regurgitation III or IV	125 (13.7)	166 (9.9)	0.003
Laboratory results			
Hb (mg/dL)	9.5±0.8	12.2±1.2	<0.001
Creatinine (mg/dL)	1.2±0.7	0.9±0.4	<0.001
BNP (ng/mL)	359 [169–704]	232 [99–490]	<0.001

Values are given as the mean±SD, n (%), or median [interquartile range]. BMI, body mass index; BNP, B-type natriuretic peptide; BSA, body surface area; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; Hb, hemoglobin; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.

In contrast, in the Japanese elderly cohort, anemia is defined as hemoglobin <11.0 g/dL.[10] The optimal cut-off value for hemoglobin to significantly stratify post-TAVI mortality remains unknown.

In this study we investigated the implication of anemia, stratified according to the statistically calculated cut-off value, on mid-term mortality following TAVI.

Methods

Study Population and Design

We analyzed data from the Optimized transCathEter vAlvular iNtervention (OCEAN)-TAVI Registry, an ongoing Japanese multicenter TAVI registry. In all, 2,588 patients with severe AS who underwent TAVI at 14 Japanese centers (University of Toyama of Medicine, Teikyo University School of Medicine, Kokura Memorial Hospital, Kishiwada Tokushukai Hospital, Sendai Kousei Hospital, Saiseikai Yokohama-City Eastern Hospital, New Tokyo Hospital, Shonan Kamakura General Hospital, Osaka City University Graduate School of Medicine, Tokyo Bay Urayasu-Ichikawa Medical Center, Ogaki Municipal Hospital, Toyohashi Heart Center, Nagoya Heart Center, and Keio University School of Medicine) between October 2013 and May 2017 were prospectively included in this registry. The inclusion criteria of this registry have been reported elsewhere.[11,12]

Patient selection for TAVI was determined by the heart team in each center. TAVI was performed using an Edwards Sapien XT/3 (Edwards Lifesciences, Irvine, CA, USA) or the Medtronic CoreValve/Evolut R System (Medtronic, Minneapolis, MN, USA). Approach sites and devices depended on the size, calcification, and tortuousness of the artery.

The OCEAN-TAVI registry is registered with the University Hospital Medical Information Network (ID: UMIN000020423). This registry was approved by each local ethics committee and all patients provided informed

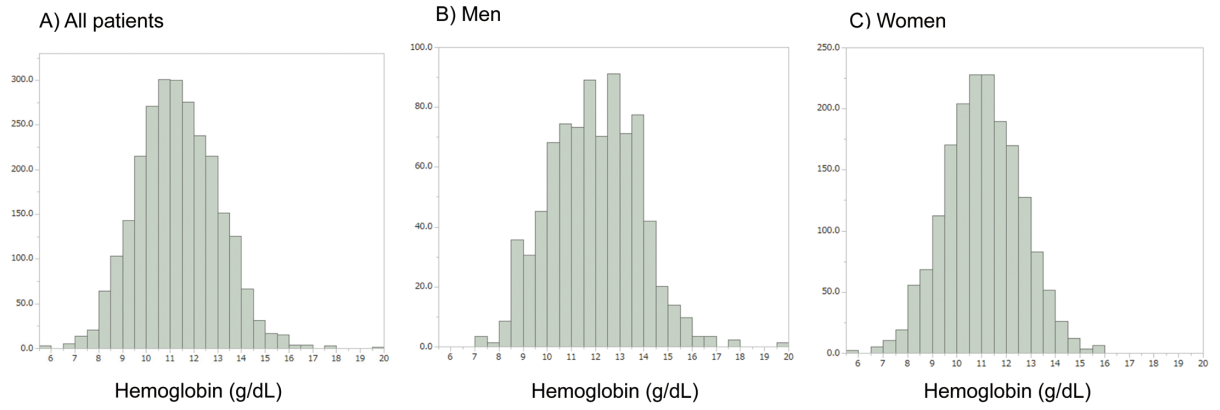

Figure 1. Distribution of preoperative hemoglobin concentrations before transcatheter aortic valve implantation in (**A**) all patients and (**B**) men and (**C**) women separately.

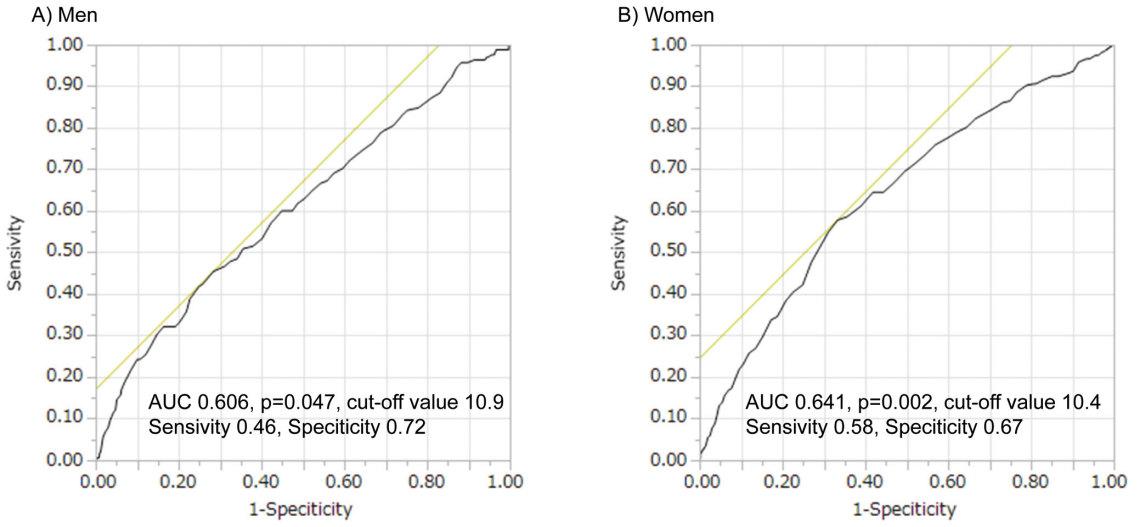

Figure 2. Receiver operating characteristic curve analysis of hemoglobin levels for predicting all-cause mortality after transcatheter aortic valve implantation in (**A**) men and (**B**) women.

consent before study enrollment.

Definitions of Anemia and Data Collection

Receiver operating characteristic (ROC) curve analysis was used to calculate the hemoglobin cut-off value to stratify all-cause death, and the patient cohort was stratified according to this cut-off value.

Information on demographic, laboratory, and echocardiographic characteristics before and after the procedure was collected. Blood transfusions were performed at the discretion of attending physicians. All outcomes and procedural complications were defined according to the Valve Academic Research Consortium-2 criteria.[13]

Endpoints and Statistical Analysis

The primary endpoint was all-cause mortality following TAVI. All statistical analyses were performed using JMP® 14 (SAS Institute, Cary, NC, USA). Two-sided $P<0.05$ was considered significant.

Continuous variables are presented as the mean±SD or as the median and interquartile range (IQR). Parametric data were compared using unpaired t-tests. Non-parametric data were compared using the Mann-Whitney U-test. Categorical data are presented as counts and percentages, and were compared using the Chi-squared test or Fisher's exact test, as appropriate.

Prognostic outcomes were estimated using the Kaplan-Meier method and compared between the 2 groups using a log-rank test. Logistic regression analysis was used to investigate the effect of different covariates on 2-year mortality after TAVI. Variables that differed significantly between patients who were alive or had died at 2 years were included in the multivariate analysis.

Table 2. Periprocedural Parameters in Patients With and Without Anemia

	Anemia (n=909)	No anemia (n=1,679)	P value
Procedural data			
Transfemoral approach	750 (82.5)	1,417 (84.4)	0.21
Edwards SAPIEN valve series	791 (87.0)	1,454 (86.7)	0.79
Medtronic CoreValve series	118 (13.0)	224 (13.3)	0.79
Procedure time (min)	82.5±44.0	79.9±46.3	0.18
Conscious sedation	205 (22.6)	405 (24.1)	0.37
In-hospital complications			
Device success	840 (92.9)	1,546 (92.4)	0.64
In-hospital death	36 (4.0)	34 (2.0)	0.004
Length of stay in ICU (days)	1 [1–3]	1 [1–2]	0.002
Conversion to open surgery	9 (1.0)	16 (1.0)	0.93
Major stroke	18 (2.0)	37 (2.2)	0.71
Life-threatening or major bleeding	179 (19.7)	218 (13.0)	<0.001
Major vascular complication	53 (5.8)	60 (3.6)	0.009
Acute kidney injury	138 (15.2)	151 (9.0)	<0.001
Aortic regurgitation III or IV	21 (2.3)	28 (1.7)	0.25
New pacemaker implant	76 (8.4)	135 (8.0)	0.78
New atrial fibrillation	34 (3.8)	68 (4.1)	0.70
Blood transfusion	386 (42.8)	362 (21.6)	<0.001
Blood transfusion (units)	0 [0–2]	0 [0–0]	<0.001
Minimum Hb after TAVI (mg/dL)	8.6±1.1	9.9±1.4	<0.001

Values are given as the mean±SD, n (%), or median [interquartile range]. Hb, hemoglobin; ICU, intensive care unit; TAVI, transcatheter aortic valve implantation.

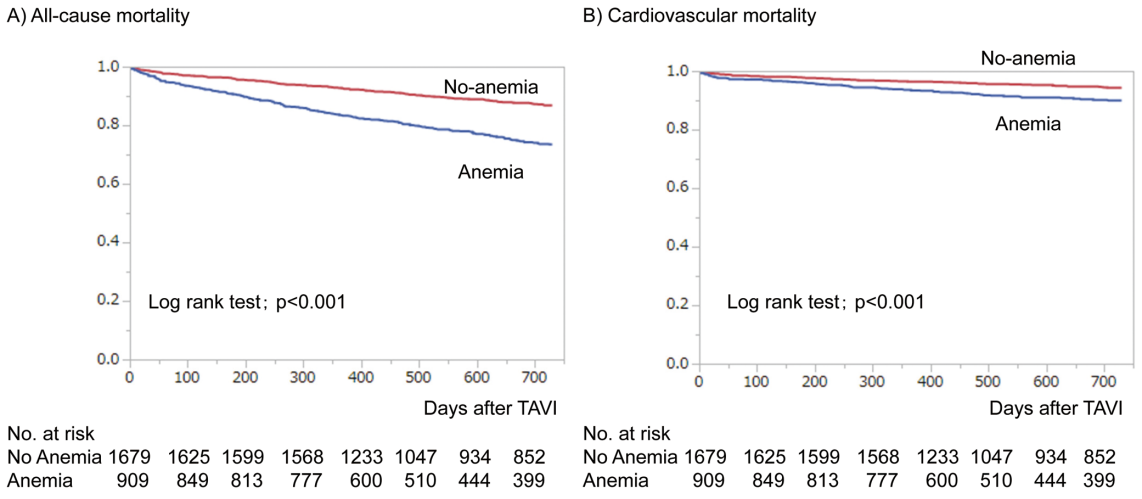

Figure 3. Kaplan-Meier estimates of (**A**) all-cause mortality and (**B**) cardiovascular mortality after transcatheter aortic valve implantation (TAVI) in patients with anemia based on the definition determined in the present study (i.e., hemoglobin <10.9 g/dL for men and <10.4 g/dL for women).

Results

Baseline Characteristics

Baseline characteristics are summarized in **Table 1**. The mean age of patients was 84.4 years, 69% were women, the mean body surface area (BSA) was 1.43 m^2, and the median logistic EuroScore was 12.8%.

Defining the Anemic Population

The mean preoperative hemoglobin concentration was 11.3±1.1 g/dL in all patients, and 11.8±1.8 g/dL in men and 10.9±1.5 g/dL in women. The distribution of preoperative hemoglobin concentrations is shown in **Figure 1**.

ROC analysis indicated a hemoglobin cut-off value for anemia of 10.9 g/dL in men and 10.4 g/dL in women (**Figure 2**), with areas under the curve of 0.606 (P=0.047) and 0.641 (P=0.002) in men and women, respectively.

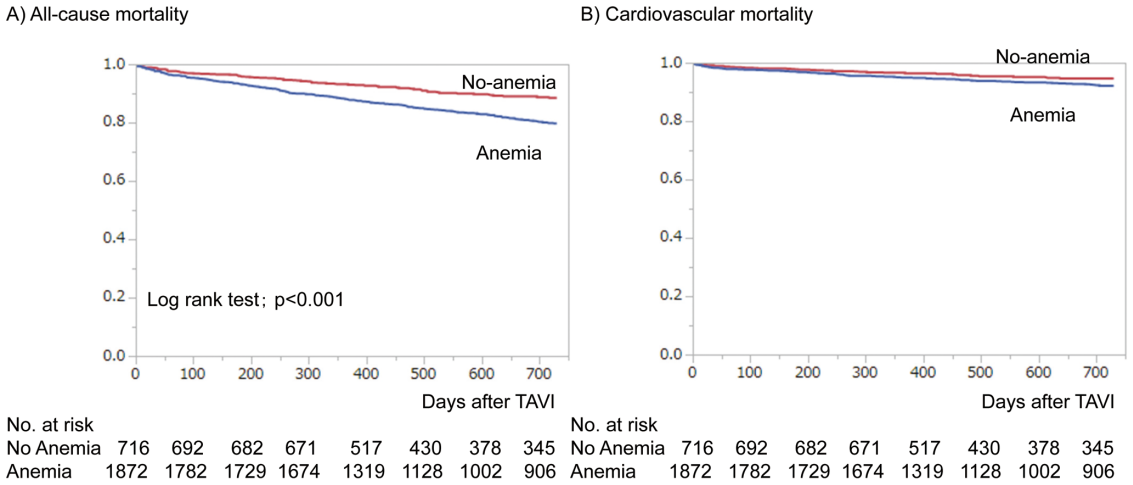

Figure 4. Kaplan-Meier estimates of (**A**) all-cause mortality and (**B**) cardiovascular mortality after transcatheter aortic valve implantation (TAVI) in patients with anemia according to the World Health Organization definition[9] (i.e., hemoglobin <13.0 g/dL in men and <12.0 g/dL in women).

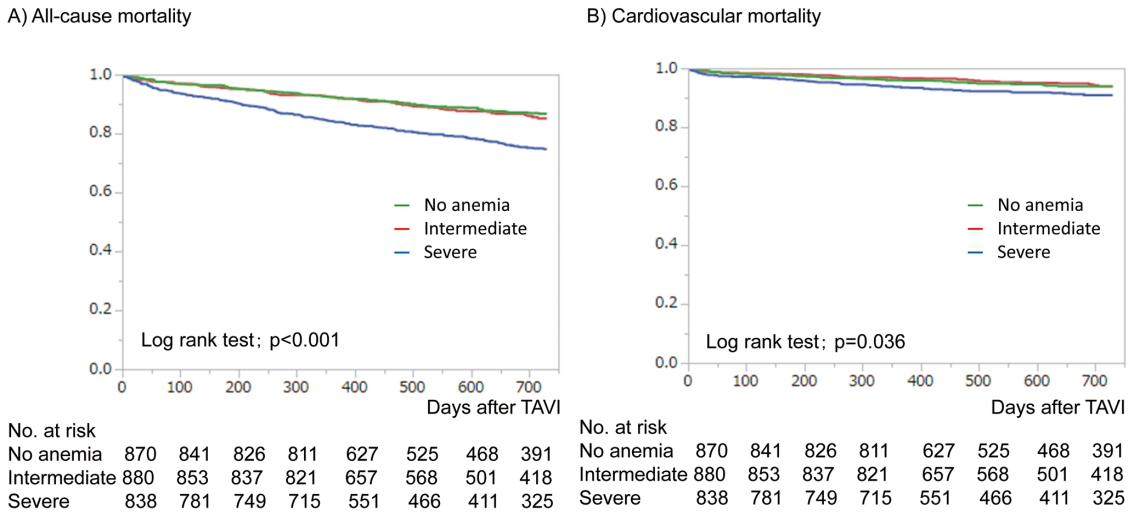

Figure 5. Kaplan-Meier estimates of (**A**) all-cause mortality and (**B**) cardiovascular mortality after transcatheter aortic valve implantation (TAVI) in patients with anemia according to hemoglobin tertiles: severe, hemoglobin <10.5 g/dL; intermediate, hemoglobin 10.5–11.9 g/dL; no anemia, hemoglobin >11.9 g/dL.

There were 909 patients (35.1%) in the anemia group (hemoglobin <10.9 g/dL in men and <10.4 g/dL in women) and 1,679 patients (64.9%) in the non-anemic group.

Comparisons of Patient Characteristics

Patients with anemia were older and had a lower BSA (P<0.001 for all; **Table 1**). The prevalence of frail patients was higher in the anemia group.

Patients with anemia had an overall worse clinical profile, with a higher Society of Thoracic Surgeons score and logistic EuroScore, a higher prevalence of New York Heart Association Class III or IV and chronic kidney disease (CKD), and higher plasma B-type natriuretic peptide and serum creatinine concentrations (P<0.001 for all).

Measurement of transthoracic echocardiograms revealed that patients with anemia had higher peak velocity, a higher mean pressure gradient at the aortic valve, and a higher prevalence of mitral regurgitation of Grade III or higher (P<0.05 for all).

Periprocedural Outcomes

Procedure-related findings are presented in **Table 2**. Most patients were treated by the transfemoral approach using the Edwards SAPIEN valve series. There were no significant

Table 3. Multivariate Logistic Regression Analysis for the Association Between 2-Year Morality and Clinical Findings

	OR (95% CI)	P value
Patient characteristics		
Male sex	1.64 (1.28–2.11)	<0.001
NYHA Class III or IV	1.45 (1.14–1.85)	0.003
Logistic EuroScore (per 1% increase)	1.02 (1.01–1.02)	<0.001
Dyslipidemia	0.63 (0.50–0.80)	<0.001
Creatinine (per 1-mg/dL increase)	1.39 (1.15–1.68)	<0.001
Coronary artery disease	1.06 (0.82–1.35)	0.64
Atrial fibrillation	1.05 (0.80–1.37)	0.73
Peripheral vascular disease	1.42 (1.05–1.92)	0.02
Previous cerebrovascular accident	0.91 (0.64–1.29)	0.59
COPD	1.41 (1.06–1.89)	0.02
Anemia (study criteria)	1.77 (1.39–2.25)	<0.001
Echocardiographic characteristics		
Aortic valve mean gradient (per 1-mmHg increase)	0.99 (0.99–1.00)	0.02
Preoperative mitral regurgitation III or IV	1.05 (0.75–1.47)	0.78
Procedural data		
Transfemoral approach	0.88 (0.65–1.18)	0.40
Blood transfusion	1.88 (1.46–2.40)	<0.001

CI, confidence interval; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; OR, odds ratio.

differences in procedural characteristics between the anemia and non-anemic groups.

Although no significant differences were observed in procedural success rates between the 2 groups, the incidence of acute kidney injury (AKI), life-threatening or major bleeding, and major vascular complications was significantly higher in the anemia group (P<0.05 for all). Furthermore, the post-procedural stay in the intensive care unit was longer in the anemia group (P=0.002).

Although blood transfusion rates were higher in patients with anemia (42.8% vs. 21.6%; P<0.001), their hemoglobin levels remained lower throughout the hospital course compared with patients without anemia (8.6 vs. 9.9 g/dL; P<0.001).

Two-Year All-Cause Mortality

Anemic patients had significantly higher in-hospital mortality (4.0% vs. 2.0%; P=0.004). In addition, 2-year all-cause mortality was significantly higher in the anemia than non-anemic group (17.9% vs. 13.2%; P<0.001; **Figure 3A**). A similar trend was observed for 2-year cardiovascular mortality (P<0.001; **Figure 3B**).

The patient cohort was also stratified using the WHO criteria (i.e., hemoglobin <13.0 g/dL for men and <12.0 g/dL for women). These criteria significantly stratified all-cause mortality (P<0.001; **Figure 4A**), but not 2-year cardiovascular mortality (P=0.052; **Figure 4B**).

A 3-group comparison of hemoglobin tertiles (<10.5, 10.5–11.9, and >11.9 g/dL) showed similar trends: the group with severe anemia (first tertile) had significantly higher 2-year all-cause mortality (**Figure 5A**) and cardiovascular mortality (**Figure 5B**) than the other two groups.

The presence of anemia as defined in this study was associated with 2-year all-cause mortality with an odds ratio of 1.77 (95% confidence interval 1.39–2.25) after adjusting for the other 14 baseline characteristics that were significantly different between patients who were alive and deceased at 2 years (**Table 3**).

Causes of Death

At 2 years, all-cause deaths were recorded for 212 of 909 patients with anemia and 190 of 1,679 patients without anemia. Cardiovascular death was the dominant cause of death (76/212 in the anemia group, 81/190 in the non-anemic group), followed by infections (n=78), malignancy (n=48), and renal failure (n=18).

Discussion

In this multicenter study, anemia, statistically defined as hemoglobin <10.9 g/dL for men and <10.4 g/dL for women, was associated with 2-year all-cause mortality among 2,588 patients who underwent TAVI.

Optimal Hemoglobin Cut-Off Value

Previous studies conducted in Western countries also demonstrated that anemia was associated with short- and mid-term clinical outcomes following TAVI.[5–8] In these studies, the baseline mean hemoglobin levels ranged between 11.9 and 13.1 g/dL, which are relatively higher than those in the present study conducted in Japan (i.e., 11.3 g/dL). The WHO definition of anemia is higher still: 13.0 g/dL for men and 12.0 g/dL for women.[9]

Given our findings that the WHO definition of anemia did not significantly stratify patients' clinical outcomes, the cut-off values of the WHO definition may rather overestimate the post-TAVI prognosis and the cut-off values we propose in this study may be more appropriate to risk stratify the Japanese cohort of patients who undergo TAVI. For example, when a male patient has a hemoglobin concentration of 12.0 g/dL, he is assigned as anemic according to the WHO definition (<13.0 g/dL), but no anemic (>10.9 g/dL) with a lower mortality risk according to our findings in this study.

Anemia and AKI

The direct or indirect effects of anemia on outcomes are not well understood. One of the dominant reasons why anemia is associated with mortality following TAVI could be the increased incidence of AKI, which has a considerable association with mortality. The detailed mechanism remains unknown, but renal ischemia caused by reduced oxygen supply due to anemia may be one possible explanation.[14] A recent study also reported the association between post-TAVI anemia and AKI, as well as 1-year mortality.[6]

Anemia and Blood Transfusion

Blood transfusion was another significant risk factor for 2-year mortality following TAVI. It has been reported that blood transfusion facilitates systemic inflammation, which can contribute to the progression of renal injury, causing AKI and increasing post-TAVI mortality.[6,15,16] To improve post-TAVI clinical outcomes, unnecessary blood transfusions are best avoided.

Anemia and CKD

In this study, patients with anemia were more likely to have CKD, and elevated serum creatinine was an independent prognostic factor. Patients with CKD undergoing TAVI have a high incidence of in-hospital complications, such as bleeding and AKI, and CKD is known to contribute to a poor prognosis after TAVI.[17,18]

Although renal anemia is one of the causes of anemia complicated with CKD, its prevalence among all cases of anemia observed before TAVI remains unknown. It was reported that approximately 79% of TAVI anemic patients had iron-deficiency anemia.[8] However, it is unclear how preoperative determination of the cause of anemia (e.g., iron deficiency, vitamin deficiency, renal anemia) may affect prognosis following TAVI.

Future Directions

The findings of this study will help risk stratification before TAVI. Of note, as demonstrated in this study, the impact of hemoglobin values may vary according to ethnicity, and unique hemoglobin cut-off values for different populations should be used for risk stratification.

Urena et al reported that treatment with a combination of erythropoietin and iron replacement did not reduce the 30-day mortality following TAVI in anemic patients.[19] Whether aggressive treatment of anemia targeting our novel hemoglobin cut-off values would improve post-TAVI clinical outcomes needs to be determined in future studies. Sodium-glucose cotransporter 2 inhibitors and hypoxia-induced factor prolyl hydroxylase inhibitors increase endogenous erythropoietin.[20,21] The prognostic implication of the aggressive correction of anemia using these agents also remains to be determined.

Study Limitations

This study has several limitations. First, we used a different definition of anemia from the WHO due to the unique distribution of hemoglobin in the Japanese population. The applicability of our definition to other ethnicities and countries remains unknown. Second, the cause of anemia may affect the outcome, but the data in the OCEAN-TAVI Registry could not assess the cause of anemia. However, because 80.2% of patients in the anemia group had CKD, renal anemia may be the main cause. Third, the findings of this study are limited to mid-term results. Fourth, we did our best to adjust for other parameters, but other uninvestigated parameters may be confounders with the existence of anemia. We observed only the association between anemia and 2-year mortality, and their causality remains unknown. The factors that influence prognosis after TAVI are multifactorial, and anemia is important, but not the only factor.

Finally, the areas under the curve in the ROC analyses were not extremely high. It should be noted that there are many factors contributing to mortality following TAVI and anemia is just one. Given its relatively high specificity, our definition of anemia could be particularly useful in identifying high-risk patients after TAVI.

Conclusions

Using a definition of anemia of <10.9 g/dL hemoglobin in men and <10.4 g/dL hemoglobin in women, we found that anemia was significantly associated with post-TAVI all-cause mortality and cardiovascular mortality in Japan.

Acknowledgments

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Disclosures

M. Yamamoto, N.T., T.N., S.S., K.M., M.T., H.U., and Y.W. are clinical proctors for Edwards Lifesciences and Medtronic. K.T. and K.H. are clinical proctors of Edwards Lifesciences. K.K., K.H. are members of *Circulation Reports*' Editorial Team. The remaining authors have nothing to disclose.

IRB Information

The study protocol and associated documents were approved by the Ethics Committee at the University of Toyama Hospital on October 4, 2018 (Reference code: H30-81).

Data Availability

The deidentified participant data will not be shared.

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