

Transcatheter Aortic Valve Replacement

Prevalence, Factors Associated With, and Prognostic Effects of Preoperative Anemia on Short- and Long-Term Mortality in Patients Undergoing Transcatheter Aortic Valve Implantation

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Background—There is scant information on the prevalence and factors associated with preoperative anemia in patients undergoing transcatheter aortic valve implantation (TAVI) and whether it is associated with mortality. We sought to determine the prevalence and factors associated with preoperative anemia in addition to the prognostic effects of the various levels of preoperative hemoglobin level on mortality in patients undergoing TAVI.

Methods and Results—Ten-center observational study encompassing 1696 patients with aortic stenosis who underwent TAVI was conducted. Anemia was defined by the World Health Organization criteria (hemoglobin <12.0 g/dL in women and <13.0 g/dL in men). The prevalence of preoperative anemia was 57%. Patient-related factors associated with preoperative anemia were (descending order of odds ratio [95% confidence interval]) as follows: anemia-related medication (4.90 [3.08–7.80]), history of heart failure (1.77 [1.43–2.20]), male sex (1.69 [1.32–2.16]), mitral regurgitation grade ≥III (1.61 [1.15–2.25]), history of malignancy (1.44 [1.03–2.09]), and peripheral vascular disease (1.33 [1.04–1.70]). The creatinine clearance was inversely associated with preoperative anemia (odds ratio, 0.92 [0.87–0.97]). In multivariable analyses, preoperative anemia was not associated with 30-day mortality (1.72 [0.96–3.12]; $P=0.073$) but showed the strongest association with 1-year mortality with a hazard ratio (95% confidence interval) of 2.78 (1.60–4.82) in patients with hemoglobin <10 g/dL. Patients with anemia received ≥1 blood transfusion 2× more often, but the indication of transfusion was unrelated to overt bleeding in 60%. Blood transfusion was associated with mortality at 30 days (odds ratio, 1.25 [95% confidence interval, 1.08–3.67]) and during follow-up (hazard ratio, 1.09 [95% confidence interval, 1.03–1.14]).

Conclusions—Preoperative anemia is prevalent in >50% of patients undergoing TAVI. Various baseline factors were related to anemia, which in turn was associated with 1-year mortality. Patients with anemia received more transfusions but mostly for indications unrelated to overt bleeding, whereas transfusion was independently associated with both early and 1-year mortality. These findings indicate that optimization of baseline factors related to preoperative anemia, in addition to more strict criteria of the use of blood products, may improve outcome after TAVI. (*Circ Cardiovasc Interv.* 2013;6:625-634.)

Key Words: anemia ■ blood transfusion ■ hemoglobin

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WHAT IS KNOWN

- Preoperative anemia is a common finding in elderly patients, in patients with heart disease, and in patients undergoing percutaneous and surgical cardiac interventions.

WHAT THE STUDY ADDS

- Preoperative anemia is prevalent in more than half of patients undergoing transcatheter aortic valve implantation.
- Various baseline factors are associated with anemia, which in turn is strongly associated with 1-year mortality but not with early mortality.
- Patients with anemia receive more transfusions mostly for indications unrelated to overt bleeding, whereas transfusion is independently associated with both early and 1-year mortality.

Transcatheter aortic valve implantation (TAVI) is increasingly used to treat patients with aortic stenosis who are considered at high risk for surgical aortic valve replacement.^{1,2} These patients, therefore, often have preexisting comorbid conditions that may affect outcome, offsetting treatment effects.

Anemia is a common finding in (elderly) patients and has been shown to be an independent risk factor for early and late mortality in the general and elderly population,^{3,4} in patients with coronary artery disease including acute coronary syndrome⁵ and heart failure,^{6,7} and in patients undergoing percutaneous and surgical cardiac interventions.^{8–13}

In a recent study including 118 patients who underwent TAVI, preoperative anemia was seen in half of the patients and was associated with increased 1-year mortality.¹⁴ Yet, the relationship between the degree of preoperative anemia and the effect of confounders because of differences in baseline risk between patients with and without anemia on outcome need further elucidation. In addition, no data are available describing the causes of anemia in this population. Such information may be helpful because the measures aimed at correcting or treating anemia, and its cause may conceptually improve operative outcome.¹⁵

We, therefore, sought to determine the prevalence and associated factors of preoperative anemia in addition to the effects of the various levels of preoperative hemoglobin (Hb) concentration on short- and long-term mortality in a series of 1696 patients undergoing TAVI.

Methods

Study Population

The study population stems from a cohort of 1706 patients who underwent TAVI with the Medtronic CoreValve System (Medtronic Inc, Minneapolis, MN), the Edwards SAPIEN or SAPIEN XT Valve (Edwards Lifesciences, Irvine, CA), or the Direct Flow Valve (Direct Flow Medical, Inc, Santa Rosa, CA) from November 2005 to March 2013 in the following institutions: (1) Rotterdam Thoraxcenter,

the Netherlands (n=322); (2) Quebec Heart and Lung Institute, Canada (n=287); (3) University Hospital Bonn, Germany (n=255); (4) Bergmannsheil, Ruhr-University Bochum, Germany (n=202); (5) University Hospital Maastricht, the Netherlands (n=145); (6) University Hospital Saint-Luc, Belgium (n=122); (7) University Hospital Antwerp, Belgium (n=120); (8) Angiografia de Occidente, Colombia (n=93); (9) Royal Perth Hospital, Australia (n=90); and (10) Hospital Clínico Universitario de Valladolid, Spain (n=70). Patients with missing baseline Hb values (n=10) were excluded, resulting in a final study population consisting of 1696 patients.

In accordance with the institutions' policies, every patient gave written informed consent for TAVI and the use of anonymous clinical, procedural, and follow-up data for research in accordance with institutional review board approval.

Procedure

Planning and execution of TAVI have been described previously.¹⁶ All procedures were performed under local or general anesthesia using the Medtronic CoreValve System (valve sizes 23, 26, 29, and 31 mm), the Edwards SAPIEN or SAPIEN XT Valve (valve sizes 23, 26, and 29 mm), or the Direct Flow Valve (valve sizes 24 and 25 mm). After TAVI, antiplatelet therapy consisted of clopidogrel 75 mg for 6 months and aspirin 80 to 100 mg indefinitely. Patients on oral anticoagulant therapy before TAVI received periprocedural therapeutic anticoagulation with unfractionated heparin or low-molecular-weight heparin in combination with either clopidogrel or aspirin. Oral anticoagulation was resumed shortly after TAVI.

Definitions and Data Collection

In each hospital, blood samples for hematology and chemistry were taken before and at fixed intervals ≤ 72 hours after TAVI and included the nadir Hb concentration, maximum serum creatinine, and maximum leukocyte count. Preoperative anemia was defined according to the American College of Physicians and World Health Organization criteria as a preoperative Hb level <12.0 g/dL in women and <13.0 g/dL in men.¹⁷ Patients were also divided into categories of 1.0-g/dL Hb increments from <10.0 to ≥ 15 g/dL to assess the dose-dependent effects of decreased versus normal preoperative Hb level on mortality.

Preoperative serum creatinine values were used to calculate the baseline serum creatinine clearance using the Cockcroft and Gault equation.¹⁸ In accordance with the Kidney Disease Outcomes Quality Initiative guidelines, preoperative kidney function was classified as stage I (>90 mL/min per 1.73 m²), stage II (60–89 mL/min per 1.73 m²), stage III (30–59 mL/min per 1.73 m²), stage IV (15–29 mL/min per 1.73 m²), and stage V (<15 mL/min per 1.73 m²), with stage $\geq$ II indicating chronic kidney disease.¹⁹

After TAVI, the nadir Hb concentration was determined ≤ 24 and ≤ 72 hours after TAVI and was used to define the Hb decline relative to the patient's preoperative Hb value. The number of units of blood transfusions was determined at 4 time intervals: before and at ≤ 24 hours, >24 to ≤ 72 hours, and >72 hours after TAVI. Details of the indications of blood transfusions, in addition to the time of onset of the indications, were documented and used to determine whether there was an overt bleeding source that was defined by a clinically visible bleeding source or imaging-documented bleeding (ie, angiography, computed tomography, echo of blood vessels, or other organs). All end points were defined according to the Valve Academic Research Consortium recommendations.²⁰

Follow-up

Follow-up data on patient mortality were collected from the civil registries or the referring physician or general practitioner and was complete for all the patients at 30 days after TAVI and for 99.3% at follow-up (median, 356 [interquartile range, 90–680] days). Of all 449 patients who died during follow-up, the cause of death was confirmed in 88.4%, unknown in 7.3%, and missing/not assessed in 4.2%. The cause of death grouped according to the presence of preoperative anemia is listed in the online-only Data Supplement and

Table 1. Baseline Characteristics of Patients Undergoing Transcatheter Aortic Valve Implantation Grouped According to the Presence of Preoperative Anemia

	Entire Cohort (n=1696)	No Anemia (n=727)	Anemia (n=969)	P Value
Age, y, mean±SD	81±7	80±7	81±7	0.001
Male, n (%)	884 (52)	343 (47)	541 (56)	<0.001
Height, mean±SD, cm	165±9	166±9	165±10	0.055
Weight, mean±SD, kg	72±15	74±15	71±14	0.002
Body mass index, mean±SD, kg/m ²	26.5±4.8	26.8±5.0	26.3±4.7	0.049
Body surface area, mean±SD, m ²	1.81±1.80	1.83±0.22	1.80±0.20	0.002
New York Heart Association class ≥III, n (%)	1416 (84)	584 (80)	832 (86)	0.002
Previous cerebrovascular event	311 (18)	121 (17)	190 (20)	0.12
Previous myocardial infarction	438 (26)	174 (24)	264 (27)	0.12
Previous coronary artery bypass graft surgery	411 (24)	184 (25)	227 (24)	0.38
Previous percutaneous coronary intervention	533 (32)	210 (29)	323 (33)	0.054
History of heart failure, n (%)	962 (57)	337 (47)	625 (65)	<0.001
Diabetes mellitus, n (%)	477 (28)	187 (26)	290 (30)	0.057
Hypertension, n (%)	1300 (77)	553 (76)	747 (77)	0.62
Peripheral vascular disease, n (%)	473 (28)	168 (23)	305 (32)	<0.001
Chronic obstructive pulmonary disease, n (%)	473 (28)	196 (27)	277 (29)	0.46
Atrial fibrillation, n (%)	476 (28)	186 (26)	290 (30)	0.049
Permanent pacemaker, n (%)	216 (13)	82 (11)	134 (14)	0.12
History of malignancy, n (%)				
All	197 (12)	72 (10)	125 (13)	0.057
Gastrointestinal or hematologic	63 (4)	20 (3)	43 (4)	0.069
Anemia-related medication				
All	164 (10)	24 (3)	140 (14)	<0.001
Iron supplements	120 (7)	17 (2)	103 (11)	
Erythropoietin	20 (1.2)	5 (1)	15 (2)	
Blood transfusions	12 (0.7)	1 (0.1)	11 (1)	
Combination therapy*	8 (0.4)	1 (0.1)	7 (1)	
Laboratory results				
Creatinine, median (IQR), μmol/L	99 (80–128)	93 (78–116)	105 (84–138)	<0.001
Creatinine clearance, mean±SD, mL/min	50±22	54±22	47±22	<0.001
Hemoglobin, mean±SD, g/dL	12.1±1.7	13.6±1.0	11.0±1.1	<0.001
Leukocyte count (×10 ⁹ /L), mean±SD	7.3±2.2	7.4±2.0	7.2±2.3	0.039
Echocardiography				
Left ventricular ejection fraction, mean±SD	52±14	53±14	52±15	0.11
Aortic valve area, mean±SD, cm ²	0.68±0.20	0.68±0.19	0.68±0.20	0.74
Peak gradient, mean±SD	72±25	72±23	72±26	0.70
Mitral regurgitation grade ≥ III, n (%)	216 (13)	66 (9)	150 (16)	<0.001
Aortic regurgitation grade ≥ III, n (%)	137 (8)	51 (7)	86 (9)	0.16
Logistic EuroSCORE, median (IQR)	19.0 (11.0–30.7)	17.0 (10.1–26.0)	20.8 (12.4–33.5)	<0.001

EuroSCORE indicates European System for Cardiac Operative Risk Evaluation; and IQR, interquartile range.

*Ferrofumarate/erythropoietin treatment (n=4) and ferrofumarate/blood transfusion treatment (n=4).

classified as cardiovascular or noncardiovascular in accordance with the Valve Academic Research Consortium criteria.²⁰

Statistical Analysis

Details of data completeness and management are summarized in the online-only Data Supplement. Categorical variables are summarized as frequencies and percentages and were compared using the χ^2 test or Fisher exact test. The Shapiro–Wilk test was used to test for a

normal distribution of continuous variables, and comparison of continuous variables was performed using the Student *t* tests or Wilcoxon rank-sum test when appropriate. The factors associated with preoperative anemia were assessed using forward stepwise logistic regression analyses, including all variables from Table 1 with *P*<0.10 in the univariable analysis. Associations with 30-day and cumulative 1-year mortality after TAVI were assessed by, respectively, forward stepwise logistic and Cox regression analyses, including all variables from

Table 2. Perioperative Results of Patients Undergoing Transcatheter Aortic Valve Implantation Grouped According to the Presence of Preoperative Anemia

	No Anemia (n=727)	Anemia (n=969)	P Value
Intraoperative or ≤24 h			
Early experience, n (%) [*]	134 (18)	192 (20)	0.48
Device, n (%)			
Medtronic CoreValve	444 (61)	572 (59)	0.41
Edwards Sapien	275 (38)	391 (41)	0.28
Direct Flow Medical	6 (0.8)	2 (0.2)	0.081
Access strategy, n (%)			
Transfemoral	565 (78)	719 (74)	0.16
Transapical	140 (19)	202 (21)	
Trans-subclavian	13 (2)	31 (3)	
Transaortic	8 (1)	16 (2)	
Circulatory support, n (%)	21 (3)	27 (3)	0.90
Prosthesis size, n (%) [†]			
20, 23, 25 mm	152 (21)	198 (21)	0.82
26, 29, 31 mm	573 (79)	767 (80)	
Postimplantation balloon dilation, n (%)	104 (14)	177 (18)	0.030
Duration of procedure, min, mean±SD	121±74	112±65	0.022
Hemoglobin, g/dL, mean±SD			
Preprocedural	13.6±1.0	11.0±1.1	<0.001
Postprocedural	10.9±1.7	9.5±1.3	<0.001
Decline	2.7±1.5	1.5±1.4	<0.001
Blood transfusion, n (%)			
None	624 (86)	686 (71)	<0.001
1–2 U	69 (10)	223 (23)	
3–4 U	14 (2)	42 (4)	
≥5 U	20 (3)	18 (2)	
Postoperative ≤72 h			
Serum creatinine, median (IQR), μmol/L			
Preprocedural	93 (78–116)	105 (84–138)	<0.001
Postprocedural	90 (73–119)	100 (75–139)	<0.001
Creatinine clearance, mean±SD, mL/min			
Preprocedural	54±22	47±22	<0.001
Postprocedural	58±38	53±39	0.017
Leukocyte count (×10 ⁹ /L), mean±SD			
Preprocedural	7.4±2.0	7.2±2.3	0.039
Postprocedural	11.8±4.2	11.7±6.0	0.65
Hemoglobin, mean±SD, g/dL			
Postprocedural	10.31±1.7	9.0±1.3	<0.001
Decline	3.3±1.5	2.0±1.3	<0.001
Blood transfusion, n (%)			
None	569 (78)	519 (54)	<0.001
1–2 U	102 (14)	307 (32)	
3–4 U	27 (4)	98 (10)	
≥5 U	29 (4)	45 (5)	

(Continued)

Table 2. Continued

	No Anemia (n=727)	Anemia (n=969)	P Value
In-hospital results			
Echocardiography			
Peak gradient, mean±SD	18±9	18±10	0.24
Mitral regurgitation grade ≥III, n (%)	45 (7)	102 (12)	0.001
Aortic regurgitation grade ≥III, n (%)	37 (5)	52 (6)	0.72
Length of stay, median (IQR), d	8 (6–14)	10 (7–16)	<0.001
In-hospital complications			
Mortality (≤30 d)[‡]			
All-cause	36 (5)	92 (10)	<0.001
Cardiovascular	25 (3)	63 (7)	0.005
Noncardiovascular	11 (2)	28 (3)	0.061
Myocardial infarction (periprocedural, ≤72 h)	15 (2)	12 (1)	0.18
Cerebrovascular complications			
Major stroke	14 (2)	28 (3)	0.21
Minor stroke	12 (2)	5 (1)	0.020
TIA	8 (1)	5 (0.5)	0.17
Vascular complication, n (%)			
Major	59 (8)	92 (10)	0.32
Minor	70 (10)	84 (9)	0.50
Bleeding complication, n (%)			
Life-threatening or disabling	32 (4)	41 (4)	0.86
Major	47 (7)	83 (9)	0.11
Minor	54 (7)	86 (9)	0.28
Acute kidney injury, n (%)			
Stage 1	87 (12)	120 (12)	0.80
Stage 2	10 (1)	20 (2)	0.29
Stage 3	24 (3)	42 (4)	0.28
Combined 30-day safety end point	125 (17)	222 (23)	0.004

IQR indicates interquartile range; and TIA, transient ischemic attack.

^{*}Early experience represents the first 33 patients in each center who underwent transcatheter aortic valve implantation.²¹[†]Six patients did not receive a valve because of death before valve insertion.[‡]The cause of death was missing in 1 patient who died ≤30 days.

Tables 1 and 2 with $P<0.10$ in the univariable analyses.²¹ An exception was made for aortic regurgitation after TAVI, which was forced into the multivariable model independent of the P value (which proved to be 0.12), given its established predictive effect on 1-year mortality.^{22–27} The relationship between low preoperative Hb level and outcome was assessed by forcing this variable into the model of 30-day and 1-year mortality both as a continuous and a dichotomous variable (anemia). This was also done for Hb coded as a multicategory predictor in 1-g/dL increments, with the Hb category exhibiting the lowest event rate used as the reference group.⁵ Interaction terms were tested to evaluate the potential additive and synergistic harmful effects of baseline anemia and Hb decline at ≤24 and ≤72 hours after TAVI. Variables included in the multivariable model of determinants of preoperative anemia, 30-day mortality, and 1-year mortality are listed in the online-only Data Supplement. Results are reported as adjusted odds ratio (OR) or hazard ratio (HR) with a 95% confidence interval (CI). Kaplan–Meier methods were used to illustrate the timing of events during follow-up; statistical assessment was performed

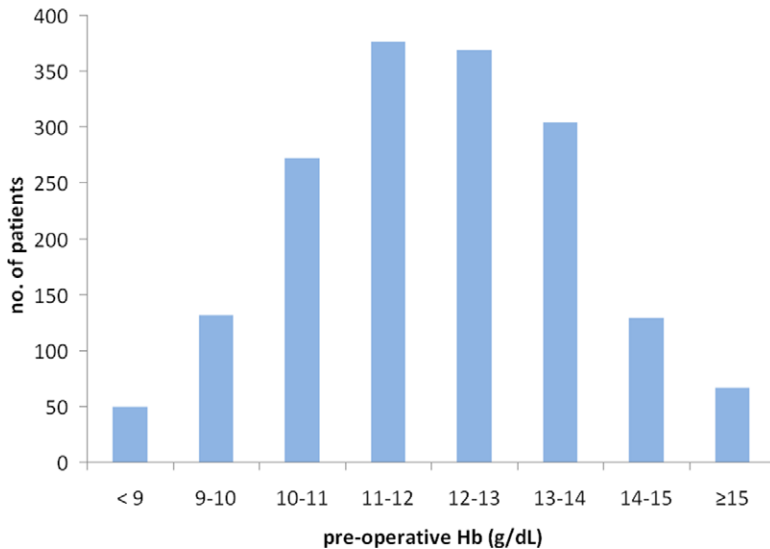


Figure 1. Distribution of preoperative hemoglobin concentration in patients undergoing transcatheter aortic valve implantation.

by the log-rank test. Patients lost to follow-up (0.7%) were considered at risk until the date of last contact at which point they were censored. A 2-sided $P < 0.05$ was considered to indicate significance, and all statistical analyses were performed with SPSS software version 20.0 (IBM, Chicago, IL).

Results

The overall prevalence of preoperative anemia was 57% and varied between 42% and 67% in the participating hospitals. The mean preoperative Hb concentration was 12.1 ± 1.7 g/dL (range, 7.2–17.5 g/dL). The distribution of preoperative Hb concentration is presented in Figure 1.

Factors Associated With Anemia

Baseline patient characteristics and operative details of the 1696 patients are summarized in Tables 1 and 2. Patients with anemia were older (81 versus 80 years; $P < 0.001$), more frequently men (56% versus 47%; $P < 0.001$), and had a lower

body mass index (26.3 versus 26.8 kg/m²; $P = 0.049$) and body surface area (1.80 versus 1.83 m²; $P = 0.002$). They were also more symptomatic (New York Heart Association class $\geq$ III, 86% versus 81%; $P = 0.002$), more often had a history of heart failure (65% versus 47%; $P < 0.001$) and chronic treatment for anemia (14% versus 3%; $P < 0.001$), and had a higher prevalence of peripheral vascular disease (32% versus 23%; $P < 0.001$), atrial fibrillation (30% versus 26%; $P = 0.049$), and mitral regurgitation grade $\geq$ III (16% versus 9%; $P < 0.001$) but showed a lower preoperative creatinine clearance (47 versus 54 mL/min; $P < 0.001$) and leukocyte count (7.2 versus 7.4×10^9 cells/L; $P = 0.037$). They, therefore, had a higher estimated operative risk (logistic European System for Cardiac Operative Risk Evaluation [EuroSCORE]: 21% versus 17%; $P < 0.001$) compared with patients without anemia. The baseline patient characteristics associated with preoperative anemia by multivariable analysis are shown in Table 3. As shown

Table 3. Multivariable Logistic Regression Analysis for Factors Associated With Preoperative Anemia in Patients Undergoing Transcatheter Aortic Valve Implantation

	Entire Cohort (n=1696)		No Chronic Use of Anemia-Related Medication (n=1532)	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Categorical variables				
Anemia-related medication	4.90 (3.08–7.80)	<0.001	NA	NA
History of heart failure	1.77 (1.43–2.20)	<0.001	1.85 (1.48–2.30)	<0.001
Male sex	1.69 (1.32–2.16)	<0.001	1.69 (1.31–2.18)	<0.001
Preoperative mitral regurgitation grade $\geq$ III	1.61 (1.15–2.25)	0.005	1.61 (1.14–2.28)	0.007
History of malignancy	1.44 (1.03–2.09)	0.033	1.63 (1.15–2.32)	0.006
Peripheral vascular disease	1.33 (1.04–1.70)	0.023	1.32 (1.03–1.70)	0.030
Continuous variables				
Preoperative creatinine clearance (per 10 mL/min increase)	0.92 (0.87–0.97)	0.001	0.91 (0.86–0.96)	<0.001
Preoperative leukocyte count (per 1×10^9 cells/L increase)	0.95 (0.91–0.99)	0.034	0.95 (0.90–0.99)	<0.001
Logistic EuroSCORE (per 1% increase)	1.01 (1.00–1.02)	0.017	1.01 (1.00–1.02)	0.012

CI indicates confidence interval; and EuroSCORE, European System for Cardiac Operative Risk Evaluation.

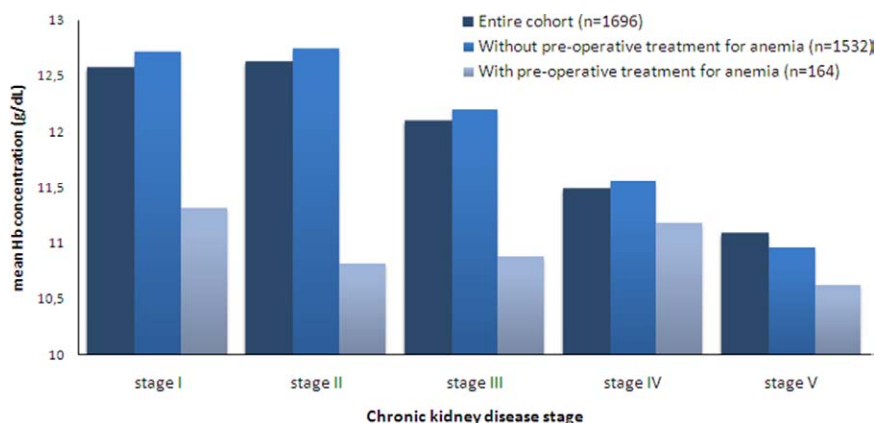


Figure 2. Preoperative hemoglobin concentration per category of kidney dysfunction in patients undergoing transcatheter aortic valve implantation in the entire cohort and in patients with and without drugs for the treatment of anemia. Preoperative kidney function was classified according to the Kidney Disease Outcomes Quality Initiative guidelines as stage I (>90 mL/min per 1.73 m²), stage II (60–89 mL/min per 1.73 m²), stage III (30–59 mL/min per 1.73 m²), stage IV (15–29 mL/min per 1.73 m²), and stage V (<15 mL/min per 1.73 m²).

in Figure 2, the severity of kidney dysfunction was inversely proportional to the Hb concentration in the overall cohort, except in patients who were on chronic treatment for anemia.

Preoperative Anemia and Transfusions

A total of 694 patients (41%) underwent ≥ 1 blood transfusion during or after TAVI. Figure 3A shows that patients with anemia consistently had ≥ 1 U of blood transfusions 2 $\times$ more frequently before and at each time interval after TAVI compared with patients without anemia ($P<0.001$). As shown in

Figure 3B, the indication of blood transfusion was more often not related to an overt bleeding source in patients with anemia (60% versus 46%; $P<0.001$). Details of the indications of transfusion therapy are listed in Table 4; the most frequent indication was operative blood loss in patients with anemia and access site complication in nonanemic patients.

Thirty-Day Mortality

Thirty-day all-cause mortality was 5% in patients without and 10% in patients with anemia ($P<0.001$). Associations with

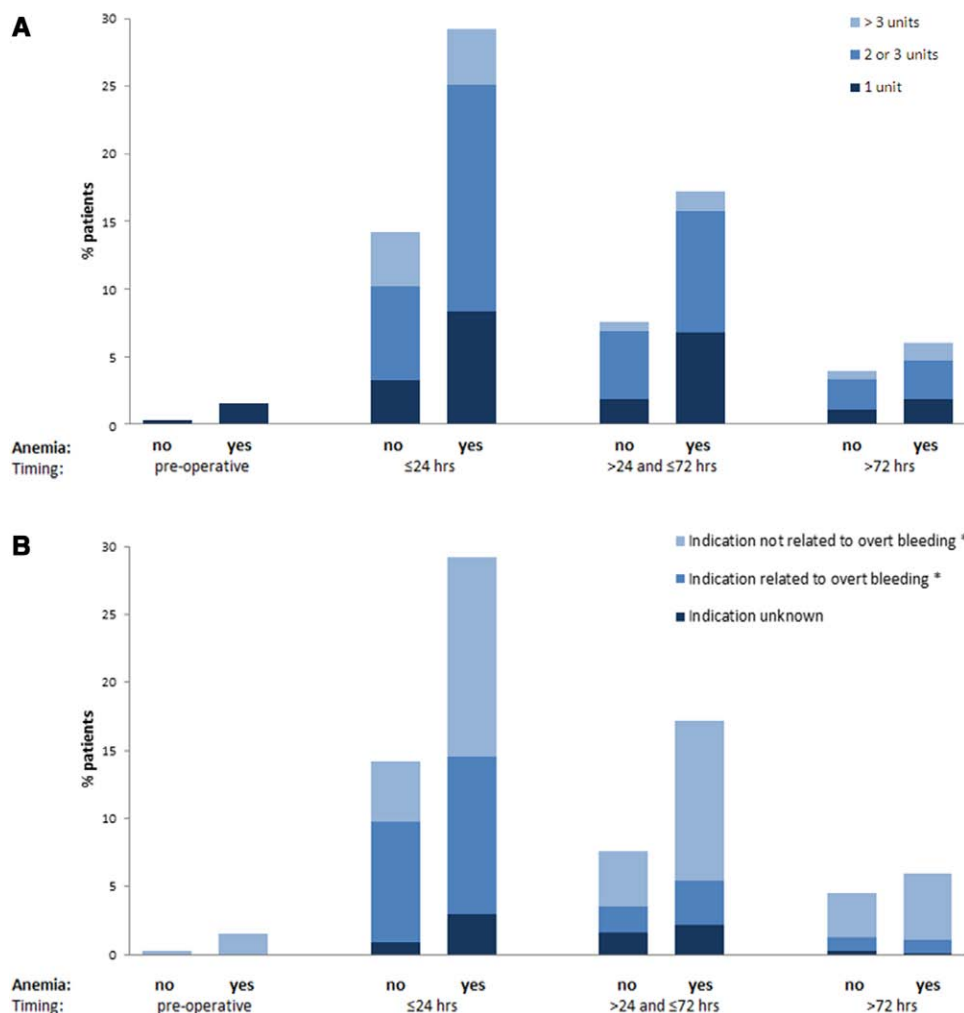


Figure 3. A, Timing and number of blood transfusions in patients undergoing transcatheter aortic valve implantation grouped according to the presence of preoperative anemia. **B,** Timing of the indication of blood transfusion therapy in patients undergoing transcatheter aortic valve implantation grouped according to the presence of preoperative anemia. Analysis includes 1 (ie, the first) indication of blood transfusion per patient (a second indication was found in 33 [5%] and 103 [11%] patients without and with anemia, respectively [$P<0.001$]). *Overt bleeding is defined by a clinically visible bleeding source or imaging-documented bleeding (ie, angiography, computed tomography, echo of blood vessels, or other organs).

Table 4. Blood Transfusion Indications During and After Transcatheter Aortic Valve Implantation Grouped According to the Presence of Preoperative Anemia

Indication	Entire Cohort (n=1696)	No Anemia (n=727)	Anemia (n=969)	P Value
Related to overt bleeding	240 (14)	86 (12)	154 (16)	<0.001
Access site complication	151 (10)	52 (7)	99 (10)	0.028
Transfemoral	128 (8)	45 (6)	83 (9)	0.067
Transapical	14 (1)	4 (0.6)	10 (1)	0.28
Cardiac tamponade	24 (1)	12 (2)	12 (1)	0.48
Late-onset hematoma near access site	14 (1)	5 (0.7)	9 (1)	0.59
Retroperitoneal hemorrhage	11 (0.6)	6 (1)	5 (0.5)	0.43
Gastrointestinal bleeding	7 (0.4)	2 (0.3)	5 (0.5)	0.71
Hematuria	5 (0.3)	1 (0.1)	4 (0.4)	0.40
Hemothorax	5 (0.3)	2 (0.3)	3 (0.3)	1.0
Cardioversion to surgical valve replacement	4 (0.2)	2 (0.3)	2 (0.2)	0.77
Jugular vein bleeding	4 (0.2)	0	4 (0.4)	0.14
Other*	15 (1)	4 (0.6)	12 (1.2)	0.15
Not related to overt bleeding	387 (23)	85 (12)	302 (31)	<0.001
Operative blood loss	223 (13)	42 (6)	181 (19)	<0.001
Hemoglobin decline without bleeding source	164 (10)	43 (6)	121 (13)	<0.001
Unknown	67 (4)	15 (2)	52 (5)	0.001

Analysis includes only 1 indication of blood transfusion per patient (a second indication was found in 33 [5%] and 103 [11%] patients without and with anemia, respectively [$P<0.001$]).

*Hemolysis (n=2), intubation complicated with pharynx bleeding (n=2), bleeding after thrombolysis (n=2), pocket hematoma after pacemaker implantation (n=2), dialysis-related blood loss (n=1), preoperative gastrointestinal bleeding (n=1), surgical intervention peripheral vessels (n=1), intracranial bleeding (n=1), sepsis (n=1), annular rupture (n=1), and liver laceration after chest compression (n=1).

30-day all-cause mortality are shown in Table 5. With respect to the dichotomous variables, postoperative aortic regurgitation grade $\geq$ III (OR, 5.07; 95% CI, 2.02–12.65) showed the strongest association with 30-day mortality followed by—in descending order of odds—acute kidney injury (OR, 3.21; 95% CI, 1.83–5.64), male sex (OR, 2.25; 95% CI, 1.25–4.06), postoperative mitral regurgitation (OR, 2.13; 95% CI, 1.06–4.27), and preoperative atrial fibrillation (OR, 2.03; 95% CI, 1.16–3.53), whereas preoperative anemia was not related to mortality (OR, 1.72; 95% CI, 0.96–3.12). With respect to continuous variables, the administration of every unit of blood transfusion was associated with a 25% higher risk of 30-day mortality, whereas every 1% increase in logistic EuroSCORE increased the risk of death by 3%. The peak aortic valve gradient before TAVI proved to have an inverse relationship with mortality.

One-Year Mortality

At 1 year, all-cause mortality was 21% in patients without and 31% in patients with anemia ($P<0.001$); patients with anemia more frequently died because of pneumonia ($P=0.024$). Associations with all-cause mortality during follow-up by multivariable analysis are shown in Table 6. With respect to the dichotomous variables, a significant and inverse relationship was found between the severity of preoperative Hb level and mortality during follow-up. In particular, patients with a preoperative Hb level <10 g/dL had a 2.8-fold higher risk of dying during the follow-up period, whereas patients with a preoperative Hb level between 10 to 11 and 11 to 12 g/dL had a 2.5- and 1.9-fold high risk, respectively. Postoperative acute kidney

injury (HR, 1.97; 95% CI, 1.53–2.54) and preoperative atrial fibrillation (HR, 1.77; 95% CI, 1.41–2.23), in addition to aortic regurgitation grade $\geq$ III (HR, 1.66; 95% CI, 1.09–2.53), male sex (HR, 1.53; 95% CI, 1.22–1.93), history of malignancy (HR, 1.51; 95% CI, 1.12–2.04), and history of peripheral vascular disease (HR, 1.34; 95% CI, 1.05–1.70), were also associated with 1-year mortality. Similar to 30-day mortality, the administration of blood transfusion was related to mortality during follow-up; every unit of transfusion was associated with a 9% increase in risk of late death. This also accounted for leukocyte count after TAVI and logistic EuroSCORE (ie, 5% increase in risk of late death for every 1% increase in logistic EuroSCORE), whereas left ventricular ejection fraction, body mass index, and peak gradient proved to have an inverse relationship with 1-year mortality. Kaplan–Meier estimates of survival of patients without and with preoperative anemia are shown in Figure 4.

Discussion

In this multicenter study encompassing 1696 patients who underwent TAVI, we found that preoperative anemia was present in 57% of patients with an equal distribution of its prevalence in the participating institutions (range, 42%–67%). Factors related to the presence of anemia included history of heart failure, male sex, preoperative mitral regurgitation, history of malignancy, peripheral vascular disease, and kidney dysfunction. Despite differences in baseline characteristics between patients with and without preoperative anemia, multivariable analyses showed that preoperative anemia was associated with 1-year mortality (10% and 31%, respectively).

Table 5. Multivariable Logistic Regression Analysis for Associations With 30-Day Mortality After Transcatheter Aortic Valve Implantation

Determinant	Odds Ratio (95% CI)	P Value
Preoperative anemia	1.72 (0.96–3.12)	0.073
Preoperative hemoglobin (per 1 g/dL increase)	0.90 (0.77–0.77)	0.20
Postoperative aortic regurgitation grade $\geq$ III	5.07 (2.02–12.65)	0.001
Acute kidney injury, stages I–III	3.21 (1.83–5.64)	<0.001
Male sex	2.25 (1.25–4.06)	0.007
Postoperative mitral regurgitation grade $\geq$ II	2.13 (1.06–4.27)	0.034
Preoperative atrial fibrillation	2.03 (1.16–3.53)	0.013
Blood transfusion $\leq$ 24 h (per 1 U increase)	1.25 (1.08–3.67)	0.004
Maximum leukocyte count $\leq$ 72 h (per 1×10^9 cells/L increase)	1.10 (1.05–1.16)	<0.001
Logistic EuroSCORE (per 1% increase)	1.03 (1.02–1.04)	<0.001
Preoperative peak gradient (per 10 mm Hg increase)	0.84 (0.74–0.96)	0.008

CI indicates confidence interval; and EuroSCORE, European System for Cardiac Operative Risk Evaluation.

Furthermore, a significant inverse relationship was found between the severity of preoperative anemia (ie, serum Hb level) and mortality during follow-up. This was, in particular, the case for patients with an Hb <10.0 g/dL. We also found that patients with preoperative anemia received more units of blood transfusions before and at 24 and 72 hours after TAVI mostly in the absence of overt bleeding, whereas administration of blood transfusion was associated with 1-year mortality in a dose-dependent manner.

Prevalence and Factors Associated With Anemia

The prevalence of anemia of 57% reported herein is higher than that demonstrated in patients with acute coronary syndrome or congestive heart failure and in patients undergoing percutaneous coronary intervention or cardiac surgery ($\leq 41.9\%$).^{5,7–9,13} This is most likely explained by differences in patient characteristics. Patients who are referred for TAVI are older and, therefore, more often have associated cardiac and noncardiac chronic disease or comorbid conditions, which both may explain a higher prevalence of anemia in these patients.^{4,28,29} In accordance with 4 previous studies that reported the cause or determinants of anemia in patients with heart disease, we found kidney impairment and peripheral vascular disease to be related to preoperative anemia.^{7,12,15,30} These and almost all other factors associated with anemia in the present analysis are common in patients with anemia and frequently seen in patients who currently undergo TAVI. For instance, we found a prevalence of chronic kidney disease in 60% of the patients, heart failure in 57%, peripheral vascular disease in 28%, and malignancy in 12%. A prevalence of 57% of anemia is, therefore, not surprising. The information of the presence of anemia and its associated conditions may help to improve patient selection and planning of TAVI. It is conceivable that the optimization of some of the baseline conditions that are associated with anemia may positively affect outcome (eg, optimization of heart failure, prehydration).

Table 6. Multivariable Cox Regression Analysis for Associations With Cumulative 1-Year Mortality After Transcatheter Aortic Valve Implantation

Determinant	Hazard Ratio (95% CI)	P Value
Preoperative anemia	1.42 (1.12–1.81)	0.004
Preoperative hemoglobin (per g/dL increase)	0.87 (0.81–0.94)	<0.001
Preoperative hemoglobin category, g/dL*		
≥ 15 vs 14 to 15 (n=66)	1.26 (0.60–2.62)	0.54
14 to 15 (n=129)	Reference	
13 to 14 vs 14 to 15 (n=304)	1.66 (0.97–2.84)	0.063
12 to 13 vs 14 to 15 (n=369)	1.44 (0.84–2.49)	0.19
11 to 12 vs 14 to 15 (n=376)	1.87 (1.10–3.19)	0.021
10 to 11 vs 14 to 15 (n=272)	2.49 (1.46–4.23)	0.001
<10 vs 14 to 15 (n=180)	2.78 (1.60–4.82)	<0.001
Acute kidney injury, stages I–III	1.97 (1.53–2.54)	<0.001
Preoperative atrial fibrillation	1.77 (1.41–2.23)	<0.001
Postoperative aortic regurgitation grade $\geq$ III	1.66 (1.09–2.53)	0.019
Male sex	1.53 (1.22–1.93)	<0.001
History of malignancy	1.51 (1.12–2.04)	0.007
Peripheral vascular disease	1.34 (1.05–1.70)	0.020
Blood transfusion $\leq$ 24 h (per 1 U increase)	1.09 (1.03–1.14)	0.001
Preoperative left ventricular ejection fraction (per 10% increase)	0.90 (0.83–0.98)	0.011
Body mass index (per 1 kg/m ² increase)	0.97 (0.95–0.99)	0.036
Maximum leukocyte count $\leq$ 72 h (per 1×10^9 cells/L increase)	1.05 (1.02–1.07)	<0.001
Logistic EuroSCORE (per 1% increase)	1.01 (1.0–1.02)	0.009

CI indicates confidence interval; and EuroSCORE, European System for Cardiac Operative Risk Evaluation.

*To establish the dose-dependent effect of decreased vs normal preoperative hemoglobin values (≤ 14 to 15 g/dL) on cumulative 1-year mortality, hazard ratio values of decreased hemoglobin levels are shown in steps of 1 g/dL, and each was compared with patients with hemoglobin values between 14 and 15 g/dL.

Prognostic Effects of Preoperative Anemia and Blood Transfusions

The main objective of the present study was to assess whether preoperative anemia was independently associated with (short- and long-term) mortality rather than being a marker of disease. For that purpose, multivariable analyses were performed. With respect to 30-day mortality, preoperative anemia was not independently associated with 30-day mortality ($P=0.073$). Several postoperative complications (in particular, valve dysfunction [ie, aortic regurgitation] and renal failure) and a few baseline variables (such as male sex and preoperative atrial fibrillation) showed a stronger relationship with mortality. We could not study the association between the severity of preoperative anemia (ie, Hb levels) and 30-day mortality because of a low absolute number of deaths in some of the Hb categories. Yet, what we perceive as an even more important clinical observation is that patients with preoperative anemia receive more units of blood transfusion during the perioperative period and that every unit of transfusion is associated with a 25% increase in risk of 30-day mortality, which was also found in the assessment of long-term mortality albeit that the association was

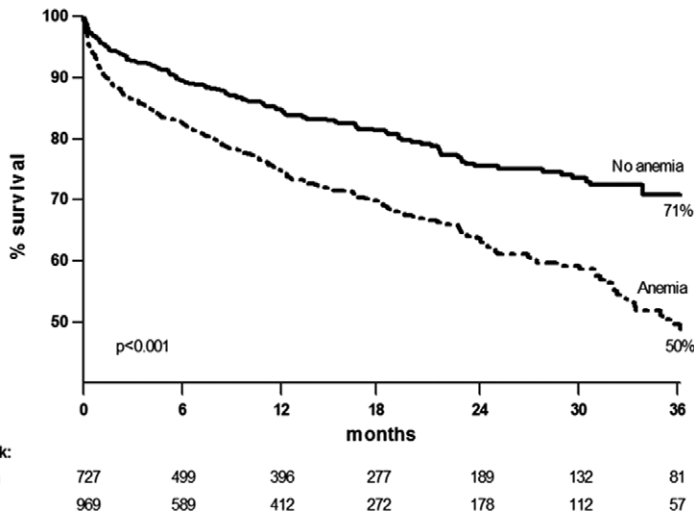


Figure 4. Kaplan-Meier survival estimates.

less pronounced (increase in risk of 9% per transfusion). In this study, the possibility of heterogeneity in timing of the collection of data in each institution precluded an accurate estimation of the total blood loss calculated by the Landefeld equation (which assumes that the net Hb decline corresponds to the addition of the number of blood transfusion to the baseline minus measured postoperative nadir Hb).³¹ Yet, in accordance with our previous findings,³² the current results show that patients with anemia had a smaller postoperative Hb drop but received significantly more frequent and also more units of blood transfusions compared with patients without anemia (Figure 3). Also, the indication of blood transfusion was not related to an overt source of bleeding in ≈60% of patients with anemia. Therefore, in the context of the significant and inverse relationship between blood transfusion and mortality, the biggest gain is to be expected from a more restrictive use of blood transfusions in addition to the need of uniform criteria for the use of blood products. The optimization of baseline factors related to preoperative anemia, in addition to measures aimed at correcting or treating anemia and its cause, may conceptually also reduce the use of perioperative blood transfusions.

In essence, the same observations were made when studying the associations with mortality during follow-up. The difference, however, was the significant inverse relationship between the severity of preoperative anemia (ie, Hb level) and late death, in particular when the Hb level was <10 g/dL. Preoperative anemia defined by the World Health Organization criteria had a weak association, whereas—in descending order of hazard—acute kidney injury, postoperative aortic regurgitation, and a few baseline patient-related variables such as preoperative atrial fibrillation, male sex, and peripheral vascular disease were more strongly associated with late death.

Limitations

Preoperative anemia was associated with short- and long-term mortality by multivariable analysis. Yet, it should be acknowledged that a multivariable analysis does not disclose the nature (eg, causal) of the observed relationship. Also, despite the fact that the factors associated with anemia were searched by reviewing all medical charts, it is unknown how many factors in how many patients remained undetected. Based on the

results of the present study, it is plausible that a more restrictive use of blood transfusion may be beneficial. Yet, the study does not allow to make proposals of a more restrictive transfusion protocol.

Disclosures

Dr Rodés-Cabau is a consultant for and received funding from Edwards Lifesciences Inc. Drs Kefer, van Garsse, and Yong are physician proctors for Edwards Lifesciences Inc. Drs Bosmans and de Jaegere are physician proctors for Medtronic CoreValve Inc, Minneapolis, MN. Other authors have no conflicts to report.

References

- Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597–1607.
- Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187–2198.
- Sarnak MJ, Tighiouart H, Manjunath G, MacLeod B, Griffith J, Salem D, Levey AS. Anemia as a risk factor for cardiovascular disease in The Atherosclerosis Risk in Communities (ARIC) study. *J Am Coll Cardiol*. 2002;40:27–33.
- Izaks GJ, Westendorp RG, Knook DL. The definition of anemia in older persons. *JAMA*. 1999;281:1714–1717.
- Sabatine MS, Morrow DA, Giugliano RP, Burton PB, Murphy SA, McCabe CH, Gibson CM, Braunwald E. Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. *Circulation*. 2005;111:2042–2049.
- Tang YD, Katz SD. Anemia in chronic heart failure: prevalence, etiology, clinical correlates, and treatment options. *Circulation*. 2006;113:2454–2461.
- Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure. *Circulation*. 2003;107:223–225.
- Lee PC, Kini AS, Ahsan C, Fisher E, Sharma SK. Anemia is an independent predictor of mortality after percutaneous coronary intervention. *J Am Coll Cardiol*. 2004;44:541–546.
- Zindrou D, Taylor KM, Bagger JP. Preoperative haemoglobin concentration and mortality rate after coronary artery bypass surgery. *Lancet*. 2002;359:1747–1748.
- Karkouti K, Wijeyesundera DN, Beattie WS; Reducing Bleeding in Cardiac Surgery (RBC) Investigators. Risk associated with preoperative anemia in cardiac surgery: a multicenter cohort study. *Circulation*. 2008;117:478–484.

11. Shander A, Knight K, Thurer R, Adamson J, Spence R. Prevalence and outcomes of anemia in surgery: a systematic review of the literature. *Am J Med*. 2004;116(suppl 7A):S8S–69S.
12. Pilgrim T, Vetterli F, Kalesan B, Stefanini GG, Räber L, Stortecky S, Gloeckler S, Binder RK, Wenaweser P, Moschovitis A, Khattab AA, Buellesfeld L, Zwahlen M, Meier B, Jüni P, Windecker S. The impact of anemia on long-term clinical outcome in patients undergoing revascularization with the unrestricted use of drug-eluting stents. *Circ Cardiovasc Interv*. 2012;5:202–210.
13. Carrascal Y, Maroto L, Rey J, Arévalo A, Arroyo J, Echevarría JR, Arce N, Fulquet E. Impact of preoperative anemia on cardiac surgery in octogenarians. *Interact Cardiovasc Thorac Surg*. 2010;10:249–255.
14. Van Mieghem NM, Nuis RJ, Tzikas A, Piazza N, Schultz C, Serruys PW, de Jaegere PP. Prevalence and prognostic implications of baseline anaemia in patients undergoing transcatheter aortic valve implantation. *EuroIntervention*. 2011;7:184–191.
15. Karski JM, Mathieu M, Cheng D, Carroll J, Scott GJ. Etiology of preoperative anemia in patients undergoing scheduled cardiac surgery. *Can J Anaesth*. 1999;46:979–982.
16. Cribier A, Eltchaninoff H, Tron C, Bauer F, Agatiello C, Nercolini D, Tapiero S, Litzler PY, Bessou JP, Babaliaros V. Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience. *J Am Coll Cardiol*. 2006;47:1214–1223.
17. Nutritional anaemias. Report of a WHO scientific group. *World Health Organ Tech Rep Ser*. 1968;405:5–37.
18. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41.
19. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, De Zeeuw D, Hostetter TH, Lameire N, Eknoyan G. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2005;67:2089–2100.
20. Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, Krucoff MW, Mack M, Mehran R, Miller C, Morel MA, Petersen J, Popma JJ, Takkenberg JJ, Vahanian A, van Es GA, Vranckx P, Webb JG, Windecker S, Serruys PW. Standardized endpoint definitions for Transcatheter Aortic Valve Implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *J Am Coll Cardiol*. 2011;57:253–269.
21. Nuis RJ, van Mieghem NM, van der Boon RM, van Geuns RJ, Schultz CJ, Oei FB, Galema TW, Raap GB, Koudstaal PJ, Geleijnse ML, Kappetein AP, Serruys PW, de Jaegere PP. Effect of experience on results of transcatheter aortic valve implantation using a Medtronic CoreValve System. *Am J Cardiol*. 2011;107:1824–1829.
22. Gotzmann M, Lindstaedt M, Mügge A. From pressure overload to volume overload: aortic regurgitation after transcatheter aortic valve implantation. *Am Heart J*. 2012;163:903–911.
23. Rodés-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Feindel CM, Osten M, Natarajan MK, Velianou JL, Martucci G, DeVarennes B, Chisholm R, Peterson MD, Lichtenstein SV, Nietlispach F, Doyle D, DeLarochelière R, Teoh K, Chu V, Dancea A, Lachapelle K, Cheema A, Latter D, Horlick E. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. *J Am Coll Cardiol*. 2010;55:1080–1090.
24. Sinning JM, Hammerstingl C, Vasa-Nicotera M, Adenauer V, Lema C, Caviguano SJ, Scheer AC, Hausen S, Sedaghat A, Ghanem A, Müller C, Grube E, Nickenig G, Werner N. Aortic regurgitation index defines severity of peri-prosthetic regurgitation and predicts outcome in patients after transcatheter aortic valve implantation. *J Am Coll Cardiol*. 2012;59:1134–1141.
25. Walther T, Simon P, Dewey T, Wimmer-Greinecker G, Falk V, Kasimir MT, Doss M, Borger MA, Schuler G, Glogar D, Fehske W, Wolner E, Mohr FW, Mack M. Transapical minimally invasive aortic valve implantation: multicenter experience. *Circulation*. 2007;116(11 suppl):I240–I245.
26. Moat NE, Ludman P, de Belder MA, Bridgewater B, Cunningham AD, Young CP, Thomas M, Kovac J, Spyt T, McCarthy PA, Wendler O, Hildick-Smith D, Davies SW, Trivedi U, Blackman DJ, Levy RD, Brecker SJ, Baumbach A, Daniel T, Gray H, Mullen MJ. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. *J Am Coll Cardiol*. 2011;58:2130–2138.
27. De Jaegere PP, Piazza N, Galema TW, Otten A, Soliman OI, Van Dalen BM, Geleijnse ML, Kappetein AP, Garcia HM, Van Es GA, Serruys PW. Early echocardiographic evaluation following percutaneous implantation with the self-expanding CoreValve Revalving System aortic valve bioprosthesis. *EuroIntervention*. 2008;4:351–357.
28. Wenaweser P, Pilgrim T, Kadner A, Huber C, Stortecky S, Buellesfeld L, Khattab AA, Meuli F, Roth N, Eberle B, Erdös G, Brinks H, Kalesan B, Meier B, Jüni P, Carrel T, Windecker S. Clinical outcomes of patients with severe aortic stenosis at increased surgical risk according to treatment modality. *J Am Coll Cardiol*. 2011;58:2151–2162.
29. Nuis RJ, Dager AE, van der Boon RM, Jaimes MC, Caicedo B, Fonseca J, van Mieghem NM, Benitez LM, Umana JP, O'Neill WW, de Marchena E, de Jaegere PP. Patients with aortic stenosis referred for TAVI: treatment decision, in-hospital outcome and determinants of survival. *Neth Heart J*. 2012;20:16–23.
30. Kulier A, Levin J, Moser R, Rumpold-Seitlinger G, Tudor IC, Snyder-Ramos SA, Moehle P, Mangano DT; Investigators of the Multicenter Study of Perioperative Ischemia Research Group; Ischemia Research and Education Foundation. Impact of preoperative anemia on outcome in patients undergoing coronary artery bypass graft surgery. *Circulation*. 2007;116:471–479.
31. Landefeld CS, Cook EF, Flatley M, Weisberg M, Goldman L. Identification and preliminary validation of predictors of major bleeding in hospitalized patients starting anticoagulant therapy. *Am J Med*. 1987;82:703–713.
32. Nuis RJ, Rodés-Cabau J, Sinning JM, van Garsse L, Kefer J, Bosmans J, Dager AE, van Mieghem N, Urena M, Nickenig G, Werner N, Maessen J, Astarci P, Perez S, Benitez LM, Dumont E, van Domburg RT, de Jaegere PP. Blood transfusion and the risk of acute kidney injury after transcatheter aortic valve implantation. *Circ Cardiovasc Interv*. 2012;5:680–688.