

## "Blood transfusion and the risk of acute kidney injury after transcatheter aortic valve implantation"

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### Abstract

Background: Blood transfusion is associated with acute kidney injury (AKI) after transcatheter aortic valve implantation (TAVI). We sought to elucidate in more detail the relation between blood transfusion and AKI and its effects on short- and long-term mortality. Methods and Results: Nine hundred ninety-five patients with aortic stenosis underwent TAVI with the Medtronic CoreValve or the Edwards Valve in 7 centers. AKI was defined by the Valve Academic Research Consortium (absolute increase in serum creatinine  $\geq 0.3$  mg/dL [ $\geq 26.4$   $\mu\text{mol/L}$ ] or  $\geq 50\%$  increase  $< 72$  hours). Logistic and Cox regression was used for predictor and survival analysis. AKI occurred in 20.7% (n=206). The number of units of blood transfusion  $< 24$  hours was the strongest predictor of AKI ( $\geq 5$  units, OR, 4.81 [1.45-15.95], 3-4 units, OR, 3.05 [1.24-7.53], 1-2 units, OR, 1.47 [0.98-2.22]) followed by peripheral vascular disease (OR, 1.48 [1.05-2.10]), history of heart failure (OR, 1.43 [1.01-2.03]), leucocyte cou...

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## Blood Transfusion and the Risk of Acute Kidney Injury After Transcatheter Aortic Valve Implantation

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**Background**—Blood transfusion is associated with acute kidney injury (AKI) after transcatheter aortic valve implantation (TAVI). We sought to elucidate in more detail the relation between blood transfusion and AKI and its effects on short- and long-term mortality.

**Methods and Results**—Nine hundred ninety-five patients with aortic stenosis underwent TAVI with the Medtronic CoreValve or the Edwards Valve in 7 centers. AKI was defined by the Valve Academic Research Consortium (absolute increase in serum creatinine  $\geq 0.3$  mg/dL [ $\geq 26.4$   $\mu\text{mol/L}$ ] or  $\geq 50\%$  increase  $\leq 72$  hours). Logistic and Cox regression was used for predictor and survival analysis. AKI occurred in 20.7% (n=206). The number of units of blood transfusion  $\leq 24$  hours was the strongest predictor of AKI ( $\geq 5$  units, OR, 4.81 [1.45–15.95], 3–4 units, OR, 3.05 [1.24–7.53], 1–2 units, OR, 1.47 [0.98–2.22]) followed by peripheral vascular disease (OR, 1.48 [1.05–2.10]), history of heart failure (OR, 1.43 [1.01–2.03]), leucocyte count  $\leq 72$  hours after TAVI (OR, 1.05 [1.02–1.09]) and European System for Cardiac Operative Risk Evaluation (EuroSCORE; OR, 1.02 [1.00–1.03]). Potential triggers of blood transfusion such as baseline anemia, bleeding-vascular complications, and perioperative blood loss were not identified as predictors. AKI and life-threatening bleeding were independent predictors of 30-day mortality (OR, 3.15 [1.56–6.38], OR, 6.65 [2.28–19.44], respectively), whereas transfusion ( $\geq 3$  units), baseline anemia, and AKI predicted mortality beyond 30 days.

**Conclusions**—AKI occurred in 21% of the patients after TAVI. The number of blood transfusions but not the indication of transfusion predicted AKI. AKI was a predictor of both short- and long-term mortality, whereas blood transfusion predicted long-term mortality. These findings indicate that outcome of TAVI may be improved by more restrictive use of blood transfusions. (*Circ Cardiovasc Interv*. 2012;5:680-688.)

**Key Words:** acute kidney injury ■ anemia ■ blood transfusion ■ predictors  
■ transcatheter aortic valve implantation

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.<sup>1</sup> Despite its minimally invasive nature, TAVI is invariably associated with a number of complications that may affect outcome. Some of these complications are clinically manifest during the procedure for which immediate actions are taken, whereas others such as acute kidney injury (AKI) are detected later and may have silent, but harmful, prognostic effects. AKI is reported in 12% to 57% of the patients who undergo TAVI and is associated with a

2- to 6-fold increased risk of death during short- and long-term follow-up.<sup>2–10</sup>

At present, the pathophysiologic mechanisms of AKI after TAVI are unclear. Some studies suggest a direct relation between perioperative blood transfusion and AKI.<sup>5,6,10</sup> This may be explained by the fact that in association with the transfusion of red blood cells (RBC) a number of other cellular and molecular substances are administered that either directly or indirectly (eg, inflammation) induce kidney damage,<sup>11</sup> yet one may question whether the triggers for blood transfusion, such as perioperative blood loss because of bleeding-vascular

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### WHAT IS KNOWN

- Perioperative blood transfusion has been associated with acute kidney injury after transcatheter aortic valve implantation.

### WHAT THE STUDY ADDS

- Blood transfusion was the most important factor associated with acute kidney injury whereas potential triggers of transfusion, such as baseline anemia, vascular-bleeding complications, blood loss, or severe hypotension, were not.
- Patients with anemia had less decline in hemoglobin after transcatheter aortic valve implantation but received more transfusions as compared with patients without anemia.
- Acute kidney injury was a predictor of both short- and long-term mortality whereas blood transfusion predicted long-term mortality.

complications may also play a role. This also holds for the presence of baseline anemia, impaired kidney function, and other procedural factors such as changes in cardiovascular hemodynamics during TAVI.<sup>7,12</sup> We, therefore, sought to explore in more detail the relation between blood transfusion and AKI after TAVI relative to a number of baseline and procedural variables in a series of 995 patients in addition to the effects of blood transfusion and AKI on mortality.

## Methods

### Patients

Between November 2005 and January 2012, 1050 patients with aortic stenosis underwent TAVI with the Medtronic CoreValve System (Medtronic Inc) or the Edwards SAPIEN Valve (Edwards Life Sciences) in the Erasmus Thoraxcenter, Rotterdam, The Netherlands (n=220); Quebec Heart and Lung Institute, Quebec City, Quebec, Canada (n=216); University Hospital Bonn, Bonn, Germany (n=182); University Hospital Maastricht, Maastricht, The Netherlands (n=145); University Hospital Saint-Luc, Brussels, Belgium (n=122); University Hospital Antwerp, Antwerp, Belgium (n=97); and Angiografía de Occidente, Cali, Colombia (n=68). Patients on chronic hemodialysis (n=35) and those who died within 72 hours precluding creatinine measurements during the first 3 days after TAVI (n=23—including 3 patients on chronic hemodialysis [causes of death are listed in online-only Data Supplement]) were excluded from the study. The final study population consisted, therefore, of 995 patients.

In each institution, patients with symptomatic aortic stenosis were screened at the outpatient clinic during which a structured interview, physical examination, ECG, and blood sampling were performed. Invasive diagnostic workup included a left heart catheterization (performed by the referring institution in most patients) to determine the coronary anatomy and hemodynamic status; echo-(Doppler) cardiography (transthoracic or transesophageal), contrast angiography, or contrast enhanced multisliced CT were performed >2 weeks before TAVI to assess the valvular and vascular anatomy and to define the vascular access strategy (transfemoral, transapical, transsubclavian, transaortic). Treatment eligibility was based on previously described patient-selection criteria, and final acceptance for TAVI was established by Heart Team consensus.<sup>13</sup>

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. This study complies with the Declaration of Helsinki.

### Procedure

TAVI was performed under general or local anesthesia using the Medtronic CoreValve System (26, 29, or 31 mm) or Edwards SAPIEN Valve (20, 23, or 26 mm) via a transfemoral, transapical, transsubclavian, or transaortic approach of which details have been described previously.<sup>14–18</sup> Details of the prehydration protocol for the various institutions are summarized in online-only Data Supplement.

The amount of contrast and the occurrence of life-threatening arrhythmias (any episode of ventricular tachycardia, ventricular fibrillation, asystole requiring vasopressive drugs, electric defibrillation, or cardiopulmonary resuscitation), any complication leading to severe sustained hypotension, postimplantation balloon dilation, and (Valve Academic Research Consortium-defined) bleeding and vascular complications were recorded during or immediately after TAVI.<sup>19</sup>

After the procedure, patients were extubated in the catheterization room or after transfer in the cardiac care unit shortly after the procedure or later if clinically indicated. Antiplatelet therapy after Medtronic CoreValve System and Edwards SAPIEN Valve implantation 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 to cover the time with subtherapeutic INR levels. Oral anticoagulation was resumed shortly after TAVI.

### Laboratory Measurements and AKI Definition

Preoperative serum creatinine (SCr) values were used to calculate the baseline SCr clearance using the Cockcroft and Gault equation: SCr clearance (mL/min)=(140–age)×weight (kg)÷72×SCr (mg/dL) (×0.85 for women).<sup>20</sup> Chronic kidney disease (CKD) was defined as a calculated SCr clearance <60 mL/min.<sup>21,22</sup> Patients with CKD were further classified in tertiles to examine the effect of mild (45.0–60.0 mL/min), moderate (35.0–44.9 mL/min), and severe CKD (<35 mL/min).

AKI was defined according to the Valve Academic Research Consortium recommendations as an absolute (≤72 hours) reduction in kidney function and defined as: (1) an absolute increase in the highest value of SCr ≥0.3 mg/dL (≥26.4 μmol/L) or (2) a percentage increase in the highest value of SCr ≥50% (1.5-fold from baseline). AKI severity was further classified as stage I (increase in SCr of 150%–200% or increase of ≥0.3 mg/dL ≥26.4 μmol/L), stage II (increase in SCr of 200%–300%), or stage III (increase in SCr of ≥300% or increase of ≥4.0 mg/dL [≥354 μmol/L]) with an acute increase of ≥0.5 mg/dL (44 μmol/L). Patients receiving renal replacement therapy (hemodialysis, peritoneal dialysis, or hemofiltration) during hospitalization or within 30 days after the procedure were considered to be classified as stage III.<sup>19</sup>

Preoperative hemoglobin (Hb) values were used to define baseline anemia according to the American College of Physicians and WHO criteria as a Hb level <13 g/dL in men and <12 g/dL in women.<sup>23</sup> Patients with anemia were classified in tertiles to assess the effects of mild (12.0–12.99 g/dL in men; 11.30–11.99 g/dL in women), moderate (10.80–11.99 g/dL in men; 10.23–11.29 g/dL in women), and severe anemia (<10.80 g/dL in men, <10.23 g/dL in women).

Data on RBC transfusions were recorded by the institution's blood bank laboratory and used to determine the corrected Hb drop ≤24 hours after TAVI according to the modified Landefeld equation.<sup>24,25</sup> In this equation 1 unit of packed RBCs is considered to represent 1 g/dL of Hb and, therefore, the net Hb drop corresponds to the addition of the number of packed RBC to the baseline-minus-measured nadir Hb.<sup>12</sup>

### Follow-Up

After hospital discharge, mortality data were collected by contacting the civil registries or the referring physician or general practitioner

**Table 1. Baseline Characteristics of Patients With and Without AKI After TAVI**

	Entire Cohort (n=995)	No AKI (n=789)	AKI (n=206)	P Value
Age, y, median (IQR)	82 (77–86)	82 (78–86)	82 (77–86)	0.42
Male sex, no (%)	497 (50)	393 (50)	104 (50)	0.86
Height, cm, mean±SD	164±10	164±10	165±10	0.31
Weight, kg, mean±SD	72±15	71±15	73±16	0.092
Body mass index, mean±SD	26.4±5.0	26.3±4.8	26.9±5.5	0.14
Body surface area, mean±SD	1.79±0.21	1.79±0.21	1.82±0.22	0.097
New York Heart Association class ≥III, no (%)	806 (81)	631 (80)	175 (85)	0.11
Previous cerebrovascular event, no (%)	198 (20)	155 (20)	43 (21)	0.71
Previous myocardial infarction, no (%)	262 (26)	201 (26)	61 (30)	0.23
Previous coronary artery bypass graft surgery, no (%)	267 (27)	214 (27)	53 (26)	0.68
Previous percutaneous coronary intervention, no (%)	303 (31)	239 (30)	64 (31)	0.83
Congestive heart failure, no (%)	577 (58)	442 (56)	135 (66)	0.010
Diabetes mellitus, no (%)	274 (28)	218 (28)	56 (27)	0.90
Hypertension, no (%)	772 (78)	603 (76)	169 (82)	0.085
Peripheral vascular disease, no (%)	301 (30)	222 (28)	79 (39)	0.004
Chronic obstructive pulmonary disease, no (%)	281 (28)	217 (28)	64 (31)	0.31
Creatinine, median (IQR)	100 (81–129)	99 (81–126)	106 (80–139)	0.12
Chronic kidney disease, no (%)*				
Mild*	243 (24)	198 (25)	45 (22)	0.40
Moderate*	250 (25)	203 (26)	47 (23)	
Severe*	242 (24)	184 (23)	58 (28)	
Hemoglobin, mean±SD	12.2±3.8	12.2±4.2	12.0±1.7	0.42
Anemia, no (%)†				
Mild†	200 (20)	157 (20)	43 (21)	0.82
Moderate†	192 (19)	150 (19)	42 (20)	
Severe†	175 (18)	136 (17)	39 (19)	
Leucocyte count (×10 <sup>9</sup> cells/L), mean±SD	7.3±2.0	7.3±2.2	7.2±2.1	0.55
Atrial fibrillation, no (%)	265 (27)	209 (27)	56 (27)	0.82
Permanent pacemaker, no (%)	133 (13)	100 (13)	33 (16)	0.21
Left ventricular ejection fraction ≤35%, no (%)	157 (16)	116 (15)	41 (20)	0.068
Aortic valve area, cm <sup>2</sup> , mean±SD	0.66±0.19	0.66±0.20	0.66±0.17	0.89
Peak gradient, mean±SD	71±25	71±25	71±26	0.93
Mitral regurgitation grade ≥III, no (%)	118 (12)	102 (13)	16 (8)	0.041
Aortic regurgitation grade ≥III, no (%)	86 (9)	71 (9)	15 (7)	0.44
Logistic Euroscore, median (IQR)	17 (11–30)	15 (10–28)	22 (12–35)	<0.001

AKI indicates acute kidney injury; TAVI, transcatheter aortic valve implantation; and IQR, interquartile range.

\*Chronic kidney disease was defined as a calculated creatinine clearance <60 mL/min; mild 45.0 to 60.0 mL/min, moderate 35.0 to 44.9 mL/min and severe <35 mL/min.

†Anemia was defined as Hb <13 g/dL in men and <12 g/dL in women,<sup>23</sup> mild anemia 12.0 to 12.99 g/dL in men and 11.30 to 11.99 g/dL in women, moderate anemia 10.80 to 11.99 g/dL in men and 10.23 to 11.29 g/dL in women, and severe anemia <10.80 g/dL in men and <10.23 g/dL in women.

and was complete in 98.4% of the 937 patients who survived the first 30 days (median [interquartile range] follow-up time; 12 [4–23] months). Death at any time during the follow-up period was classified as cardiac or noncardiac according to the Valve Academic Research Consortium criteria.<sup>19</sup>

### Statistical Analysis

Details of data completeness and management are summarized in online-only Data Supplement. Categorical variables are presented as frequencies and percentages and were compared with the  $\chi^2$  test or Fisher exact test. The normality of distributions was assessed with

the Shapiro-Wilk test; comparison of continuous variables was done by using the Student *t* test or Wilcoxon rank-sum test when appropriate. A stepwise logistic regression analysis including all variables from Tables 1 and 2 exhibiting  $P<0.10$  in the univariable analysis was used to determine the predictive factors of AKI and 30-day mortality. Two interaction terms were tested to evaluate synergistic effects of (1) baseline anemia and Hb drop ≤24 hours and (2) baseline CKD and contrast load.<sup>10</sup> A stepwise Cox regression analysis including all variables from Tables 1 and 2 exhibiting  $P<0.10$  in the Cox univariable analysis was used to determine the predictive factors of long-term mortality in patients who survived the first 30 days after TAVI (landmark analysis). For the purpose of this

**Table 2. Perioperative Results for Patients With and Without AKI After TAVI**

	No AKI (n=789)	AKI (n=206)	P Value
<b>Intraoperative or ≤24 h</b>			
Access strategy, no (%)			
Transfemoral	561 (71)	130 (63)	0.002
Transapical	210 (27)	67 (33)	
Transsubclavian	18 (2)	6 (3)	
Transaortic	0	3 (2)	
Circulatory support, no (%)	20 (3)	9 (4)	0.16
Prosthesis size, mm, no (%)*			
20, 23, 26	517 (66)	146 (71)	0.12
29, 31	272 (34)	59 (29)	0.12
Any complication leading to severe sustained hypotension, no (%)	24 (3)	8 (4)	0.54
Life-threatening arrhythmia, no (%)	29 (4)	10 (5)	0.44
Postimplantation balloon dilation, no (%)	130 (16)	39 (19)	0.41
Contrast volume, mL, mean±SD	142±97	158±96	0.052
Duration of procedure, min, mean±SD	99 (70–156)	105 (70–173)	0.32
Major vascular complication, no (%)	55 (7)	26 (13)	0.008
Bleeding complication, no (%)			
Life threatening or major, no (%)	104 (13)	37 (18)	0.080
Life threatening	39 (5)	15 (7)	0.19
RBC transfusion, no (%)			
None	632 (80)	133 (64)	<0.001
1–2 units	137 (17)	54 (26)	
3–4 units	14 (2)	11 (5)	
≥5 units	6 (1)	8 (4)	
Hemoglobin drop—uncorrected for RBC TF, g/dL, mean±SD	2.3±4.1	2.3±1.7	0.94
Hemoglobin drop—corrected for RBC TF, g/dL, mean±SD	2.7±4.3	3.2±2.7	0.12
<b>Postoperative ≤72 h</b>			
Serum creatinine (μmol/L), median (IQR)			
Preprocedural	99 (81–126)	106 (80–139)	0.12
Postprocedural	83 (67–106)	172 (122–229)	<0.001
Creatinine clearance (mL/min), mean±SD			
Preprocedural	48±20	50±27	0.49
Postprocedural	63±37	33±29	<0.001
Leucocyte count (×10 <sup>9</sup> cells/L), mean±SD			
Preprocedural	7.3±2.2	7.2±2.1	0.55
Postprocedural	11.7±4.8	13.0±4.9	0.001
Hemoglobin (g/dL), mean±SD			
Preprocedural	12.2±4.2	12.0±1.7	0.42
Postprocedural	9.4±1.5	9.1±1.5	0.011
RBC transfusion, no (%)			
None	515 (65)	98 (48)	<0.001
1–2 units	209 (27)	63 (31)	

(Continued)

**Table 2. (Continued).**

	No AKI (n=789)	AKI (n=206)	P Value
3–4 units	49 (6)	28 (14)	
≥5 units	16 (2)	17 (8)	
<b>In-hospital</b>			
<b>Echocardiography</b>			
Peak gradient, mean±SD	19±11	19±12	0.99
Mitral regurgitation grade ≥III, no (%)	62 (9)	10 (6)	0.21
Aortic regurgitation grade ≥III, no (%)	40 (6)	10 (5)	0.96
Length of stay (days), median (IQR)	10 (6–14)	13 (8–22)	<0.001
<b>Mortality</b>			
≤30 days	28 (4)	30 (15)	<0.001
≤30 days cardiac	14 (2)	17 (8)	<0.001
>30 days†	140 (18)	59 (34)	<0.001
>30 days cardiac‡	61 (8)	26 (15)	<0.001

AKI indicates acute kidney injury; TAVI, transcatheter aortic valve implantation; RBC, red blood cell; TF transfusion.

\*One patient did not receive a valve due to aborted TAVI after failed introduction of 18F sheath.

†N=937 patients survived >30 days after TAVI of which 199 patients died at a median of 12 (IQR: 4–23) months after TAVI.

‡The cause of death was missing or unknown in 27 of the 199 deaths (14%; n=8 in AKI group, n=19 in no AKI group).

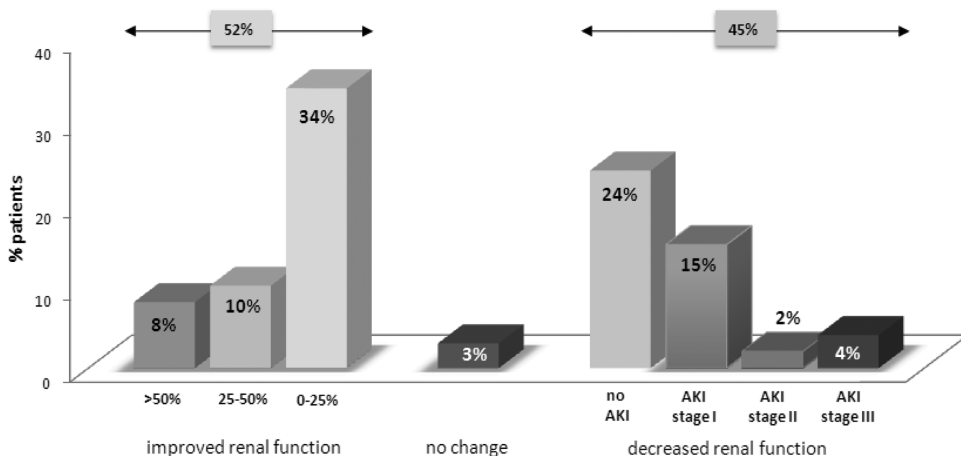
study, RBC transfusion was forced into the multivariable analyses for predictors of AKI, whereas both RBC transfusion and AKI were forced into the multivariable analyses of 30-day and late mortality, irrespective of the P value obtained from the univariable analyses. Variables included in the multivariable model for the prediction of AKI, 30-day mortality, and long-term mortality are listed in online-only Data Supplement. Results are reported as adjusted OR or hazard ratio (HR) with a 95% CI. Survival curves for time-to-event variables were constructed on the basis of all available follow-up data in patients who survived the first 30 days after TAVI (landmark analysis) with the use of Kaplan–Meier estimates and were compared with the log-rank test. Patients lost to follow-up (1.6%) 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. All statistical analyses were performed with SPSS software (version 17).

### Results

The baseline patient characteristics and perioperative details of the total population and of the patients with and without AKI are summarized in Tables 1 and 2, respectively. AKI occurred in 20.7% (n=206) of the patients of whom 3.1% (n=31) received renal replacement therapy. Details of AKI (stages I–III) and other changes in renal function are depicted in Figure 1. Patients with AKI had a significantly higher mortality at 30 days and during follow-up (Table 2).

### Predictors of AKI

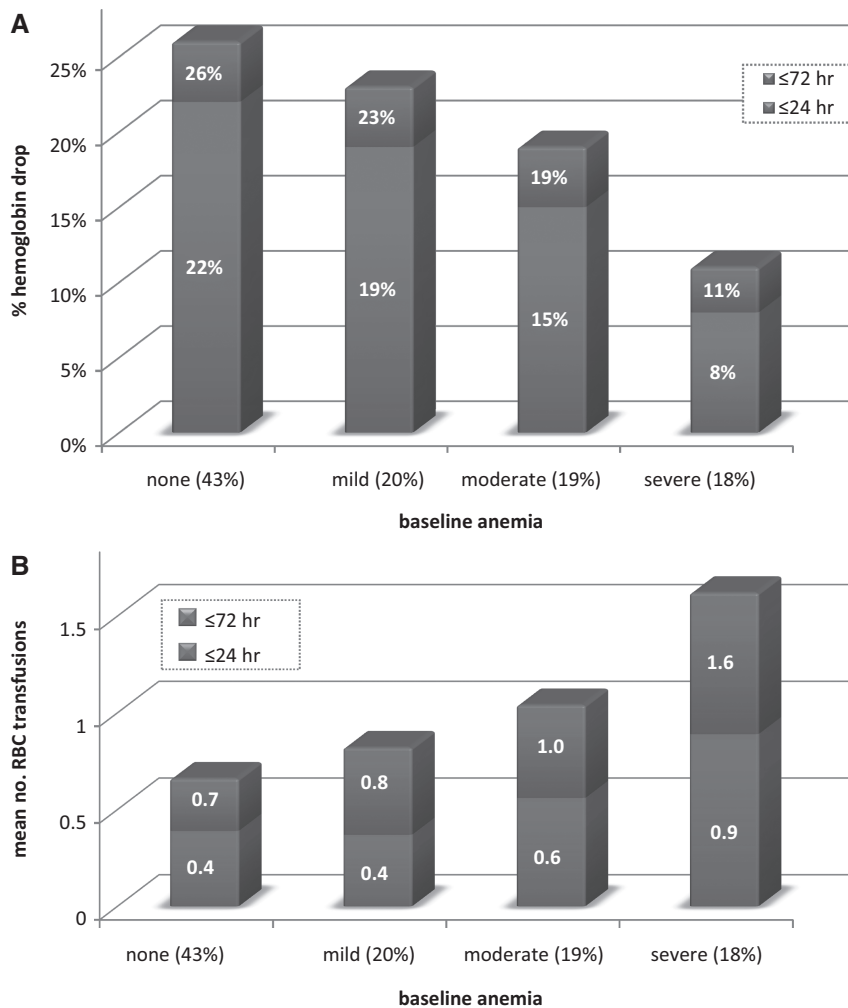
By univariable analysis, patients with AKI had a higher prevalence of congestive heart failure (66 versus 56%, P=0.010) and peripheral vascular disease (39 versus 28%, P=0.004) explaining a higher operative risk (Logistic EuroSCORE 22



**Figure 1.** Changes in creatinine  $\leq 72$  hours after transcatheter aortic valve implantation.

versus 15%,  $P < 0.001$ , Table 1). They also more often underwent transapical TAVI (33 versus 27%,  $P = 0.002$ ) and suffered more major vascular complications (13 versus 7%,  $P = 0.008$ , Table 2). Despite the latter, there was no difference in perioperative blood loss (corrected Hb drop) between patients with and without AKI, yet patients with AKI received significantly more blood transfusions within 24 and 72 hours after TAVI. Because baseline anemia might affect the decision to administer blood transfusion, the mean Hb drop and number of blood

transfusions for patients with no and with various degrees of baseline anemia was analyzed (Figure 2A–2B); patients with severe baseline anemia had 2.4 times less blood loss but on average received 2.3-fold more units of blood transfusions in comparison with patients without anemia before TAVI ( $P < 0.001$ ). Neither contrast use ( $P = 0.052$ ) nor any of the interaction terms (baseline anemia and Hb drop  $\leq 24$  hours,  $P = 0.31$ ; baseline CKD and contrast load,  $P = 0.10$ ) were significantly associated with AKI.



**Figure 2.** Mean percent Hb drop and mean number of blood transfusions  $\leq 24$  and  $\leq 72$  hours after transcatheter aortic valve implantation (TAVI) grouped according to various degrees of baseline anemia. Baseline anemia was defined as Hb  $< 13$  g/dL in men and  $< 12$  g/dL in women<sup>23</sup>; mild anemia 12.0 to 12.99 g/dL in men and 11.30 to 11.99 g/dL in women, moderate anemia 10.80 to 11.99 g/dL in men and 10.23 to 11.29 g/dL in women, and severe anemia  $< 10.80$  g/dL in men and  $< 10.23$  g/dL in women. Hb indicates hemoglobin. **A**, Mean percent Hb drop  $\leq 24$  and  $\leq 72$  hours after TAVI. Percent Hb drop  $\leq 24$  h = (baseline Hb – nadir Hb  $\leq 24$  h) / (baseline Hb); Percent Hb drop  $\leq 72$  h = (baseline Hb – nadir Hb  $\leq 72$  hours) / (baseline Hb). **B**, Mean number of blood transfusions  $\leq 24$  and  $\leq 72$  hours after TAVI. AKI indicates acute kidney injury.

**Table 3. Independent Predictors of AKI After TAVI**

Variable	OR (95% CI)	P Value
RBC transfusion ≤24 h		
None	Reference	0.003
1–2 units	1.47 (0.98–2.22)	0.064
3–4 units	3.05 (1.24–7.53)	0.015
≥5 units	4.81 (1.45–15.95)	0.010
Peripheral vascular disease	1.48 (1.05–2.10)	0.026
Congestive heart failure	1.43 (1.01–2.03)	0.042
Maximum leucocyte count ≤72 h (per 10 <sup>9</sup> cells/L increase)	1.05 (1.02–1.09)	0.001
Logistic EuroSCORE (per % increase)	1.02 (1.00–1.03)	0.006

AKI indicates acute kidney injury; TAVI, transcatheter aortic valve implantation; RBC, red blood cell.

In a descending order of the magnitude of the OR, we found by multivariable analysis that the number of units of blood transfusion ≤24 hours was the strongest predictor of AKI (≥5 units, OR, 4.81 [1.45–15.95]; 3–4 units, OR, 3.05 [1.24–7.53]; 1–2 units, OR, 1.47 [0.98–2.22]), followed by peripheral vascular disease (OR, 1.48 [1.05–2.10]), congestive heart failure (OR, 1.43 [1.01–2.03]), leucocyte count ≤72 hours after TAVI (OR, 1.05 [1.02–1.09]), and Logistic EuroSCORE (OR, 1.02 [1.00–1.03]). Potential triggers of blood transfusion such as baseline anemia, bleeding-vascular complications, and perioperative blood loss (corrected Hb drop) were not identified as independent predictors of AKI (Table 3).

**Prognostic Implications**

Independent predictors of 30-day mortality consisted of perioperative life-threatening bleeding (OR, 6.65 [2.28–19.44]), aortic regurgitation post-TAVI (OR, 4.80 [1.78–12.96]), AKI (OR, 3.15 [1.56–6.38]), leucocyte count ≤72 hours (OR, 1.13 [1.06–1.20]), and Logistic EuroSCORE (OR, 1.04 [1.02–1.06], Table 4). Mortality during follow-up in patients who survived the first 30 days was determined by a mix of patient-related variables and by the administration of blood transfusion for ≤72 hours (≥5 units, HR, 2.54 [1.34–4.81], 3–4 units, HR, 2.03

**Table 4. Independent Predictors of Mortality ≤30 Days After Transcatheter Aortic Valve Implantation**

Variable	OR (95% CI)	P Value
Life-threatening bleeding	6.65 (2.28–19.44)	0.001
Post operative aortic regurgitation grade ≥III	4.80 (1.78–12.96)	0.002
Acute kidney injury	3.15 (1.56–6.38)	0.001
Maximum leucocyte count ≤72 h (per 10 <sup>9</sup> cells/L increase)	1.13 (1.06–1.20)	<0.001
Logistic EuroSCORE (per % increase)	1.04 (1.02–1.06)	<0.001
RBC transfusion ≤24 h		
None	Reference	0.72
1–2 units	0.76 (0.33–1.75)	0.51
3–4 units	0.31 (0.03–3.06)	0.31
≥5 units	1.01 (0.15–6.73)	0.99

**Table 5. Independent Predictors of Mortality >30 Days After Transcatheter Aortic Valve Implantation**

Variable	HR (95% CI)	P Value
RBC transfusion ≤72 h		
None	Reference	0.004
1–2 units	1.32 (0.94–1.86)	0.11
3–4 units	2.03 (1.26–3.24)	0.003
≥5 units	2.54 (1.34–4.81)	0.004
Baseline anemia		
None	Reference	0.005
Mild	0.85 (0.54–1.34)	0.48
Moderate	1.49 (1.01–2.20)	0.043
Severe	1.75 (1.18–2.60)	0.005
Acute kidney injury	1.57 (1.13–2.17)	0.007
Peripheral vascular disease	1.69 (1.25–2.30)	0.001
Congestive heart failure	1.62 (1.16–2.26)	0.004
Male sex	1.53 (1.14–2.06)	0.005
Atrial fibrillation	1.46 (1.06–1.99)	0.019

RBC denotes red blood cell.

[1.26–3.24], 1–2 units, HR, 1.32 [0.94–1.86]) in addition to AKI (HR, 1.57 [1.13–2.17], Table 5). Kaplan–Meier survival estimates for increasing severity of AKI, baseline anemia, and number of transfusions are shown in Figure 3.

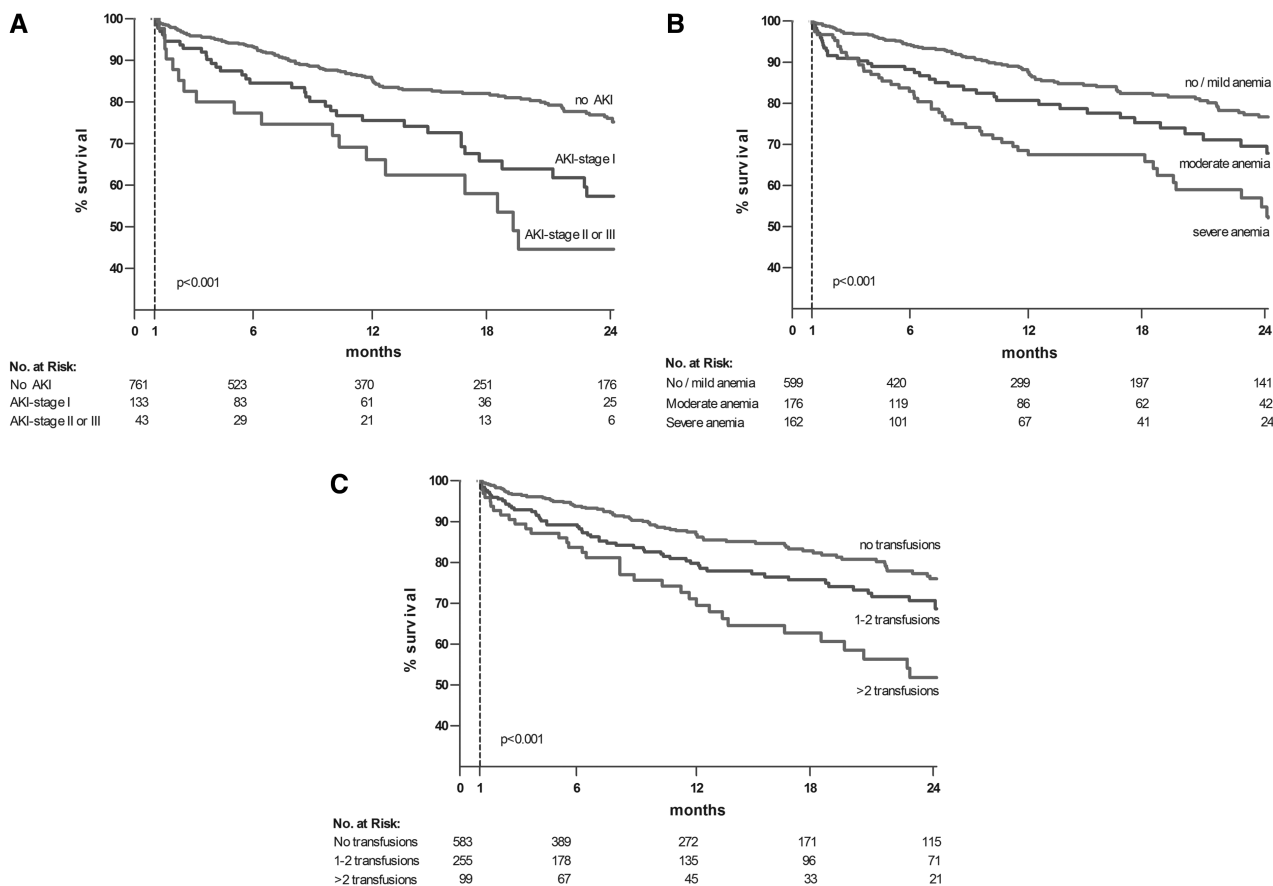
**Discussion**

In this multicenter study including 995 patients who underwent TAVI we found that AKI occurred in 21% of the patients and that the number of perioperative blood transfusions was the strongest predictor of AKI but not the clinical indications of transfusion (ie, baseline anemia, perioperative vascular-bleeding complications, or blood loss). AKI was a predictor of both short- and long-term mortality, whereas blood transfusion predicted long-term mortality.

The frequency of AKI after TAVI has been reported to vary between 12% and 57% in previous but smaller series of patients using various definitions of AKI.<sup>2–10</sup> The herein reported point estimate of 21% most likely reflects the incidence of AKI encountered in clinical practice, given the sample size and the multicenter nature of this study. Irrespective of the true value, AKI poses a clinical problem as it is associated with an increased mortality at 30 days and beyond. This has also been shown by others and suggests that the outcome of TAVI may be improved by—among others—implementing all measures to prevent AKI.<sup>5–10</sup>

For that purpose it is essential to understand the pathophysiologic mechanism(s) of AKI after TAVI. Unfortunately, a clinical study such as this one cannot do so, yet the analysis of the association between AKI and patient- and procedure-related variables that are readily available (eg, patient demographics) or subject to change or improvement (eg, execution of procedure) may be helpful.

With respect to execution of the procedure, the findings of this study indicate that AKI and, therefore, outcome may be improved by a more careful use of blood transfusions. As mentioned, the number of blood transfusions was found



**Figure 3.** Time-to-event curves for selected risk factors in patients who survived the first 30 days after transcatheter aortic valve implantation (TAVI) (landmark analysis). Event rates were calculated with the use of Kaplan–Meier methods and compared with the use of the log-rank test. **A**, Time-to-event curves for patients without acute kidney injury (AKI), AKI-stage I and with AKI-stage II or III after TAVI. **B**, Time-to-event curves for patients without transfusions, 1–2 transfusions and with >2 transfusions ≤72 h after TAVI. **C**, Time-to-event curves for patients with no and various degrees of baseline anemia. Baseline anemia was defined as Hb <13 g/dL in men and <12 g/dL in women<sup>23</sup>; mild anemia 12.0 to 12.99 g/dL in men and 11.30 to 11.99 g/dL in women, moderate anemia 10.80 to 11.99 g/dL in men and 10.23 to 11.29 g/dL in women, and severe anemia <10.80 g/dL in men and <10.23 g/dL in women. Hb indicates hemoglobin.

to be the strongest predictor of AKI with a distinct gradient of risk. The relation between AKI and transfusion is consistent with other reports that studied patients who underwent TAVI or cardiac surgery,<sup>5,6,10,26,27</sup> yet, such a strong relationship between AKI and the number of transfusions has not been reported. Noteworthy, we also found that the clinical triggers upon which one may decide to administer blood during TAVI were not associated with AKI. If true, this suggests that one should be more restrictive in the use of blood transfusions during TAVI and that the need of unequivocal criteria for the decision of blood transfusion is advocated. This is illustrated by the findings that patients without anemia had a 2.4 times greater Hb drop in comparison with patients with severe baseline anemia. This may be explained by a different patient and procedure planning in addition to differences in the execution of TAVI (ie, control of hemostasis) in patients with different baseline risks. Interventions that reduce perioperative transfusions may protect against AKI, especially in anemic patients.<sup>27</sup>

The absence of a relationship between AKI and the indications for transfusion in addition to the fact that we did not find a relationship between AKI and periprocedural complications leading to hypotension supports a direct harmful effect of transfusion on

the kidneys. It is known that preserved RBCs suffer structural or functional changes including reduced deformability and increased aggregability, all of which—particularly in older patients with impaired renal function—might induce (further) renal dysfunction.<sup>28</sup> Also the coadministration of proinflammatory molecules may play a role either directly or indirectly by inducing inflammation.<sup>29</sup> This may explain the relation found in this and other studies between postoperative leucocyte count and AKI.<sup>4,6,10,30</sup>

At variance with percutaneous coronary intervention (PCI),<sup>31</sup> we found a borderline association between contrast load and AKI in the univariable analysis, yet contrast load was not found to be an independent predictor. The absence of an association cannot be explained by a restrictive use of contrast in the present population considering the mean values and standard deviations (142±97 and 158±96 mL) although this may be an issue of sample size as a result of which a significant statistical difference was not detected. The current findings suggest that unlike PCI, contrast has only a minor effect on the development of AKI in patients who undergo TAVI.

With respect to the patient-related variables and, thus, patient selection, it is unlikely that we will exclude patients with peripheral vascular disease because TAVI was specifically developed for patients who are too high a risk for aortic



valve replacement. These patients often have widespread atherosclerosis including the peripheral circulation. It remains to be seen how additional pre- and postoperative care may avoid AKI such as optimal perioperative hydration.

Apart from perioperative blood transfusion and AKI, we found a number of other predictors of early and late mortality after TAVI. In accordance with previous series, we found severe bleeding and postoperative aortic regurgitation to be associated with a 5-fold increased risk of early death,<sup>32</sup> whereas severe baseline anemia, peripheral vascular disease, heart failure, male sex, and atrial fibrillation were independent predictors of late death.<sup>12,33,34</sup> These findings confirm the importance of appropriate patient selection to improve outcome after TAVI.

### Limitations

This multicenter observational assessment in a large series of patients may estimate the frequency of AKI and its predictors but it cannot elucidate the precise pathophysiologic mechanism(s). This is needed to propose in greater detail improvements in patient and procedure planning and execution in addition to eventual changes in postoperative care. We also acknowledge the formulation of the research question during and after the data collection and the absence of a pre-specified case report form. As a result, despite a high degree of completeness (online-only Data Supplement), the timing of the collection of the individual variables may not be consistent, which may affect the precision of the current findings. In addition, there was no uniform protocol of blood transfusion, as a result of which we were not able to unravel the true triggers of transfusion, thereby precluding specific propositions of improvement.

### Conclusions

AKI occurred in 21% of the patients after TAVI. The number of blood transfusions, but not the indication of transfusion, predicted AKI. AKI was a predictor of both short- and long-term mortality, whereas blood transfusion predicted long-term mortality. These findings indicate that the outcome of TAVI may be improved by a more restrictive use of blood transfusions.

### Disclosures

Dr Rodés-Cabau is a consultant for and received funding from Edwards Lifesciences Inc; Drs Kefer and van Garsse are physician proctors for Edwards Lifesciences Inc; Drs Bosmans and de Jaegere are physician proctors for Medtronic CoreValve Inc, MN.

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