Original article

Blood Transfusion and Outcome After Transfemoral Transcatheter Aortic Valve Replacement

Clinical trial registration: ClinicalTrials.gov Identifier: NCT03385915

Running title: Blood transfusion in TAVR

Pasi Maaranen,[1] MD, Annastiina Husso,[2] MD, PhD, Tuomas Tauriainen,[3] MD, PhD, Asta Lahtinen,[3] MD, Antti Valtola,[2] MD, Tuomas Ahvenvaara,[3] MD, Marko Virtanen,[1] MD, Teemu Laakso,[4] MD, Eeva-Maija Kinnunen,[4] MD, PhD, Sebastian Dahlbacka,[4] MD, PhD, Tatu Juvonen,[4] MD, PhD, Timo Mäkikallio,[5] MD, PhD, Maina P. Jalava,[6] MD, Jussi Jaakkola,[6] MD, PhD, Juhani Airaksinen,[6] MD, PhD, Tuija Vasankari,[6] MSc, Stefano Rosato,[7] MSc, Mikko Savontaus,[6] MD, PhD, Mika Laine,[4] MD, PhD, Peter Raivio,[4] MD, PhD, Matti Niemelä,[5] MD, PhD, Ari Mennander,[1] MD, PhD, Markku Eskola,[1] MD, PhD, Fausto Biancari,[3,6] MD, PhD.

[1]Heart Hospital, Tampere University Hospital, Tampere; [2]Heart Center, Kuopio University Hospital, Kuopio; [3]Department of Surgery, Oulu University Hospital and University of Oulu; [4]Heart Center, Helsinki University Hospital, Helsinki; [5]Department of Internal Medicine, Oulu University Hospital, Oulu; [6]Heart Center, Turku University Hospital and Department of Surgery, University of Turku, Turku, Finland and [7]National Centre of Global Health, Istituto Superiore di Sanità, Rome, Italy.

Disclosure of potential conflicts of interest: Dr. Mikko Savontaus is proctor for Medtronic, the relationship is significant; Dr. Mika Laine is proctor for Boston Scientific, the relationship is significant. The other coauthors do not have any conflict of interest related to this study. Sources of funding and support: this study was not supported by any external funding.

Corresponding Author:
Prof. Fausto Biancari,
Heart Center,
Turku University Hospital,
PO Box 52, 20521 Turku
E-mail: faustobiancari@yahoo.it

Abstract

Objective: We aimed to investigate the prognostic impact of red blood cell (RBC) transfusion on the outcome after transfemoral transcatheter aortic valve replacement (TAVR).

Design: Nationwide, retrospective, observational multicenter study.

Setting: Five University Hospitals.

Participants: The nationwide FinnValve registry included data from 2130 patients who underwent TAVR for aortic stenosis from 2008 to 2017. After excluding patients who underwent TAVR through non-transfemoral accesses, 1818 patients were selected for this analysis.

Intervention: TAVR with or without myocardial revascularization.

Measurements and Main Results: During the study period, 293 patients (16.1%) received RBC transfusion and the time-trend analysis showed that the rates of RBC transfusion decreased significantly from 27.5% in 2012 to 10.0% in 2017 ($p<0.0001$). RBC transfusion was associated with higher 30-day mortality (crude rates, 6.8% vs. 0.9%, adjusted OR 8.47, 95%CI 3.86-18.60), late mortality (crude 5-year mortality rates, 60.5% vs. 40.4%, adjusted OR 1.57, 1.23-2.00) as well as increased risk of stroke, acute kidney injury, renal replacement therapy and prolonged hospital stay compared to patients who did not receive blood transfusion. The risk of early and late adverse events increased significantly by increasing amount of transfused RBC units and when operation for excessive bleeding was necessary. Consistently with these findings, postoperative hemoglobin drop and nadir level were associated with higher early and late mortality.

Conclusions: This study showed that, despite a high prevalence of preoperative anemia, TAVR can be performed with a rather low rate of RBC transfusion. Patients who received blood transfusion after TAVR had an increased risk of early and late adverse events. These adverse effects were particularly evident with increasing amount of RBC transfusion and operations for excessive bleeding.

Key-words: Transcatheter aortic valve replacement; TAVI; SAVR; Aortic stenosis; Blood transfusion.

Recent studies from nationwide registries reported a three- to six-fold increase in the use of transcatheter aortic valve replacement (TAVR) procedures for severe aortic stenosis (AS) during the last years.[1,2] The widespread use of TAVR paralleled with a larger number of patients being referred for invasive treatment of AS with a documented improvement of early and mid-term survival.[2] Interestingly, these studies showed a significant decrease in the rates of red blood cell (RBC) transfusion after TAVR during the most recent years.[1-3] Still, a few previous studies[4-8] documented a high frequency of RBC transfusion after TAVR with a negative impact on the outcome. However, most of these studies were institutional series of limited size with short follow-up and without a throughout analysis of important bleeding-related variables such as the amount of RBC transfusions, need of operation to treat severe bleeding or drop of hemoglobin level. We aimed to investigate the impact of these parameters on patient outcome in a nationwide TAVR registry.

MATERIALS AND METHODS

Study Population

The FinnValve registry is a nationwide registry registered in ClinicalTrials.gov (Identifier: NCT03385915), which retrospectively collects data from consecutive and unselected patients who underwent TAVR or surgical aortic valve replacement with a bioprosthesis for severe AS with or without myocardial revascularization at all five Finnish university hospitals (Helsinki, Kuopio, Oulu, Tampere and Turku) from January 2008 to October 2017. During the study period, both TAVR and surgical aortic valve replacement were performed only in these university hospitals. A limited number of TAVR procedures have been performed in three central hospitals without on-site cardiac surgery over a short period of time when temporarily allowed by the national authorities. Data from these central hospitals were not collected in to

this registry to avoid bias related to procedures performed outside a heart team environment. This study was approved by the Institutional Review Board of each participating center.

The inclusion criteria for this study were 1) transfemoral TAVR for AS with or without aortic valve regurgitation; 2) patients aged >18 years; and 3) primary TAVR with or without concomitant coronary revascularization. The exclusion criteria were 1) prior TAVR or surgical intervention on the aortic valve; 2) transcatheter or surgical procedure for isolated aortic valve regurgitation; 3) acute endocarditis and/or 4) TAVR performed through other than transfemoral access.

Data was collected retrospectively into an electronic case report form by cardiologists, cardiac surgeons and research nurses. Data underwent robust checking of its completeness and quality. Data on mortality was retrieved from the national registry Statistics Finland, which is based on death certificates reviewed by local authorities. Based on this, follow-up was considered complete for all patients, but for those not residing in Finland whose follow-up was truncated at hospital discharge.

Transfusion policy

The criteria for blood transfusion in this study were not pre-specified. However, during the study period, all centers adopted a policy of transfusing RBC when hemoglobin was ≤9.0 g/dL during the day of procedure and ≤8.0 g/dL during the subsequent days.

Definition Criteria of Baseline Risk Factors

Baseline variables were defined according to the EuroSCORE II criteria.[9] The operative risk of these patients was stratified according to the EuroSCORE II and the Society of Thoracic Surgeons (STS)[10] risk scores. Severe frailty was defined according to the Geriatric Status Scale (GSS) and herein is defined as GSS grades 2-3 as

proposed by Rockwood et al.[11] Anemia was defined according to the World Health Organization criteria, i.e. <12 g/dL in women, <13 g/dL in men. Coronary artery disease was defined as any stenosis ≥50% of the main coronary branches. Selected valve prostheses were the following third generation TAVR prostheses and their variants: Evolut R (Medtronic, Minneapolis, MN, USA), Sapien 3 (Edwards, irvine, CA, USA), Acurate Neo (Boston Scientific, Marlborough, MA, USA) and Lotus (Boston Scientific, Marlborough, MA, USA).

Stratification of the Severity of Perioperative Bleeding

The severity of perioperative bleeding were stratified according to different criteria as follows: 1) any RBC transfusion; 2) amount of transfused RBC units perioperatively and during the index hospitalization; 3) transfusion of ≥4 RBC units and/or any operation for intrathoracic or access site bleeding; 4) increasing amount of RBC transfusions, i.e. no RBC transfusion, 1-2 RBC units, 3-4 RBC units; >4 RBC units; 5) the Valve Academic Research Consortium-2 (VARC-2) major and life-threatening bleeding[12]; 6) operation for any bleeding; 7) operation for any peripheral bleeding; 8) postoperative hemoglobin nadir level; and 9) postoperative hemoglobin drop during the index hospitalization. The definition of VARC-2 bleeding[12] were based on hemoglobin drop, the amount of RBC transfusions and need of any surgical, endovascular or drainage procedure for excessive bleeding. Data on the amount of blood transfusion were retrieved from Institutional blood service electronic registry and this information is considered complete in all patients.

Outcome measures

The primary outcome of this study were 30-day and mid-term all-cause mortality. The secondary outcomes were stroke, acute kidney injury, de novo renal replacement therapy, atrial fibrillation and postoperative length of stay in the hospital where the index procedure was performed. Stroke was defined as any focal or global neurological deficit lasting 24 hours or longer with a new brain infarct or hemorrhage detected at

neuroimaging, or a neurological deficit resulting in death. Furthermore, data on vascular complications as well as operations for intrathoracic or peripheral bleeding were recorded. Major vascular complications were defined according to the VARC-2 definition criteria.[12] Acute kidney injury was defined according to the KDIGO classification criteria as any increase in serum creatinine ≥3.0 times the baseline level or serum creatinine increase ≥26.5 µmol/l and/or de novo renal replacement therapy during the index hospitalization.[13]

Statistical Analysis

Statistical analysis was performed using SAS statistical package, version 9.2 (SAS Institute Inc, Cary, NC), SPSS v. 25.0 statistical software (IBM Corporation, New York, USA) and Stata v. 15.1 statistical software (StataCorp LLC, Texas, USA). Statistical analyses were performed by the senior author (F.B.) with large experience in biostatistics and by a biostatistician (S.R.) with expertise in cardiovascular diseases. The normal distribution of continuous variables was assessed with the Shapiro-Wilk test which showed that none of the continuous variables, but baseline hemoglobin were normally distributed. The Mann-Whitney *U*-test, Student's T-test, Fisher's exact test and Chi-square test were used for univariate analysis. Time trend was assessed by the linear-by-linear association test. Logistic regression with backward selection was used to identify the risk factors independently associated with RBC transfusion including in the regression model the covariates with $p<0.05$ in univariate analysis as listed in Table 1. Extracardiac arteriopathy was forced in to this model. Discrimination and calibration of the logistic regression models were estimated by the Hosmer-Lemeshow's test and the receiver operating characteristics (ROC) curve analysis. Cox proportional hazards analyses with backward selection were employed for risk estimation of mid-term mortality. The identified risk factors are as follows and they were employed for all risk adjusted analysis: age, gender, baseline hemoglobin level, baseline estimated glomerular filtration rate, diabetes, pulmonary disease, oxygen therapy, atrial fibrillation, GSS frailty grades 2-3, active malignancy, urgent or emergency procedure, left ventricular ejection fraction

≤50%, and third generation prostheses. The proportional hazards assumption was met according to the test based on Schoenfeld residuals (p=0.578) as well as by graphical assessment of the ln-ln plot of the survival curves of patients with and without blood transfusion adjusted for the aforementioned covariates. Time-varying hazard ratios were estimated for RBC transfusion, number of RBC units transfused, and more than 4 RBC units transfused and/or any operation for bleeding. Interaction tests for RBC transfusion with anemia, coronary artery disease, surgical versus percutaneous femoral artery access, selected third generation prostheses, and STS score <3% or > 3% were performed with a statistical significance set at p<0.1. Mixed-effect logistic regression was performed to estimate the risk of 30-day mortality adjusted for the aforementioned covariates and any interinstitutional differences in patient blood management. A one-to-one propensity score matching was performed to adjust the cohorts of patients who received or not RBC transfusion for baseline and operative covariates using the nearest neighbor method with a caliper of 0.2 of the standard deviation of the logit of the propensity score (i.e. 0.2). A propensity score was calculated by including the covariates listed in Table 1. After matching, we evaluated the balance between the matched cohorts with analysis of the standardized differences. A standardized difference ≤0.10 was considered as an acceptable balance between the study cohorts. Paired tests were used to compare the outcomes of interest in these matched cohorts. All tests were two-sided and p<0.05 was set for statistical significance.

RESULTS

Study Population and Main Outcomes

The FinnValve registry includes data from 6463 patients who underwent primary TAVR (2130 patients) and surgical aortic valve replacement (4333 patients) with a bioprothesis for severe AS. Out of 2130 TAVR patients, no data on blood transfusion was available in 35 patients and were excluded from this study. After excluding patients who underwent TAVR through non-transfemoral accesses, 1818 patients were selected

for this analysis. The characteristics of these patients are summarized in Table 1, and the main outcomes of this series are summarized in Table 2. During the study period, 293 patients (16.1%) received RBC transfusion and the time-trend analysis showed that the rates of blood transfusion decreased significantly through the years, from 27.5% in 2012 to 10.0% in 2017 (Linear-by-linear association test, p<0.0001, Fig. 1).

In brief, transfusion of 1-2, 3-4 and >4 RBC units occurred in 10.5%, 2.8% and 2.9% of patients respectively. Operation for intrathoracic for bleeding was performed in 0.6% of patients, surgical/endovascular procedure for peripheral bleeding in 3.7% of patients and any operation for bleeding in 4.2% of patients. VARC-2 major bleeding occurred in 24.1% of patients and VARC-2 life-threatening bleeding occurred in 6.0% of patients. Reoperation for bleeding and/or transfusion of >4 RBC units was observed in 6.4% of patients. After TAVR, the mean nadir hemoglobin level was 10.3±1.6 g/dL and the mean drop of hemoglobin level was 2.2±1.3 g/dL.

Logistic regression showed that female gender (19.3% vs. 11.9%), low baseline hemoglobin (mean, 11.6 vs. 12.7 g/dL), extracardiac arteriopathy (19.9% vs. 15.5%), first-second generation prostheses vs. third generation prostheses (24.6% vs. 13.0%), urgent/emergency procedure (27.1% vs. 15.3%), and preoperative use of aspirin (19.4% vs. 13.1%) were independent predictors of RBC transfusion after TAVR (Hosmer-Lemeshow's test, p=0.478, area under the ROC 0.735, 95%CI 0.705-0.766) (Tab. 1). When anemia was included in to this regression model instead of baseline hemoglobin, it was an independent predictor of RBC transfusion (crude rates, 23.0% vs. 10.3%, OR 2.61, 1.99-3.42). Logistic regression model including the aforementioned covariates along with any minor or major vascular complications according to the VARC-2 criteria showed that the latter was associated with an excessive risk of RBC transfusion (crude rates, 52.9% vs. 10.9%, OR 10.10, 95%CI 7.24-14.10).

Early Outcomes

RBC transfusion was associated with increased 30-day mortality (crude rates, 6.8% vs. 0.9%, adjusted OR 8.47, 95%CI 3.86-18.60, missing data in 5 patients, 0.3%) (Tab. 2). When the year of procedure was included in to the regression model, the risk estimate of RBC transfusion for 30-day mortality did not change markedly (adjusted OR 8.49, 95%CI 3.85-18.87; when adjusted for years 2008-2014 vs. 2015-2017: OR 8.41, 95%CI 3.82-18.50). Similarly, RBC transfusion increased the risk of stroke, acute kidney injury, de novo renal replacement therapy, new atrial fibrillation and prolonged hospital stay (Tab. 2). The risk of these early adverse events increased along with the amount of transfused RBC units also when adjusted for multiple covariates (Tab. 3). Thirty-day mortality increased significantly with increasing amount of RBC transfusion, particularly when operation for excessive bleeding was necessary (Tab. 4). Consistently with these findings, postoperative hemoglobin level drop and nadir were independent predictors of 30-day mortality (Tab. 4). Mixed-effect logistic regression adjusted for multiple variables and participating centers showed that 30-day mortality was significantly increased in patients who received RBC transfusion (OR 8.47, 95%CI 3.86-18.60) compared to those who did not received RBC transfusion (Tab. 2). Similarly, mixed-effect logistic regression showed that increasing amounts of RBC transfusion (1-2 RBC units, OR 2.92, 95%CI 0.97-8.84; 3-4 RBC units, OR 14.82, 95%CI 4.91-44.70; > 4 RBC units, OR 22.98, 95%CI 8.62-61.20) were associated with increased 30-day mortality (Tab. 3).

Late Outcome

The mean follow-up of this study was 2.0±1.6 years (range, 0-9.6 years). The adjusted impact of RBC transfusion, increasing amount of RBC transfusion, VARC-2 major and life-threatening bleeding as well as transfusion of more than four units of RBC and/or any operation for bleeding on late all-cause mortality are summarized in Table 4 and Figure 2. When the year of procedure was included in to the regression model, the risk of late mortality after RBC transfusion did not change markedly (adjusted HR 1.56, 95%CI 1.22-2.01; when adjusted for years 2008-2014 vs. 2015-2017: HR 1.61, 95%CI 1.25-2.06). Late all-cause mortality was

increased significantly along with the amount of transfused RBC units, particularly when operation for excessive bleeding was necessary (Tab. 4). Consistently with these findings, also postoperative hemoglobin level drop and nadir were independent predictors of late all-cause mortality (Tab. 4).

The time-varying hazard ratio for all-cause mortality decreased markedly during the first year after the procedure for any RBC transfusion, increasing amount of RBC units transfused as well as for transfusion of more than four units of RBC, but then the negative prognostic impact of these variables remained constant along the years (Fig. 3).

Interaction Analyses

Interaction tests showed that there was a significant interaction between anemia and RBC transfusion in predicting 30-day mortality (p=0.088). No significant interaction was observed between RBC transfusion and variables of interests in predicting the primary outcomes.

Propensity Score Matching Analysis

Propensity score matching provided 281 pairs of patients with all baseline covariates having a standardized difference ≤0.10 (Tab. 5), but coronary artery disease (standardized difference, 0.130, p=0.124) and new oral anticoagulants (standardized difference, 0.199, p=0.038). These matched cohorts had similar STS score (mean, 5.2% vs. 5.3%, p=0.429, standardized difference, 0.013) and EuroSCORE 2 (mean, 7.2% vs. 7.6%, p=0.808, standardized difference, 0.048) (Tab. 5). Among these propensity matched pairs, patients who received RBC transfusion after TAVR had significantly increased risk of 30-day (7.1% vs. 0%, p<0.0001) and late mortality (at 5-year, 59.1% vs. 43.3, p=0.008), acute kidney injury, renal replacement therapy, atrial fibrillation as well as longer hospital stay (Tab. 6). Patients who received RBC transfusion had a numerically increased risk of stroke (6.4 vs. 3.6%, p=0.170), but the difference did not reach statistical significance (Tab. 6)

DISCUSSION

The main findings of the present study are that: 1) despite the high prevalence of anemia (46%), this nationwide study showed that RBC transfusion was necessary in only 16% of patients after TAVR; 2) the frequency of RBC transfusion dramatically decreased during the years, likely because of improved results with most recent TAVR prostheses and changes in perioperative antithrombotic treatment; 3) preoperative anemia, extracardiac arteriopathy and antithrombotic therapy are potential targets to reduce the risk of perioperative bleeding and RBC transfusion; 4) RBC transfusion after TAVR is an independent predictor of early and late adverse events; 5) the risk of adverse events was particularly evident in patients who required multiple RBC transfusion and any operation for bleeding; 6) consistently with these findings, postoperative hemoglobin level drop and its nadir were independent predictors of early and late mortality.

Previous studies documented rates of blood transfusion after TAVR of 25% to 39% in series with a prevalence of anemia ranging from 45% to 57%.[5-8] The present study documented a rate of RBC transfusion of 16% in the context of a prevalence of anemia of 46%. These figures suggested that, despite a lack of a policy of preoperative optimization of hemoglobin, in this nationwide series the risk of severe bleeding requiring transfusion was rather low and decreased over time. Similar findings were observed in a recent study from the National Inpatient Sample which reported a rate of blood transfusion decreasing from 30% in 2012 to 10% in 2015.[3] Such improvements might be secondary to the knowledge of the prognostic importance of severe bleeding, which is thoroughly documented in adult cardiac surgery, as well as to advances in patient selection, transcatheter technology and perioperative antithrombotic policies. Indeed, a drop in the use of blood transfusion was observed particularly from 2015 to 2017 along with the introduction of third generation TAVR prostheses and likely with consolidated experience with this procedure in all participating centers. However, in our country a drop of blood transfusion was observed

during the last few years also after surgical aortic valve replacement[2] and this might be related to improved reduced perioperative blood losses and patient blood management during the recent years.

It is worth noting that herein extracardiac arteriopathy and access site bleeding requiring operative treatment were independent predictors of blood transfusion. These findings suggest that adequate planning of the access site is of crucial importance to prevent significant bleeding and to reduce the exposure to blood products. Still, in the setting of significant atherosclerosis of the iliac and femoral arteries, transaortic access might not reduce the risk of perioperative bleeding.[14] A recent study showed a rate of blood transfusion as high as 30% also with the transcaval approach.[15] Early experience suggests that transcarotid access,[16] but not the trans-subclavian access,[17] may reduce the risk of major bleeding after TAVR. In the near future, further studies on extra-femoral peripheral access will elucidate whether these routes may reduce the risk of vascular complications and perioperative bleeding.

The prevalence of anemia in patients undergoing TAVR may reach 60%[18] and it is associated with higher risk of blood transfusion and mortality.[19] Intuitively, preprocedural treatment of anemia could seem a sound policy to prevent perioperative anemia and the need of blood transfusion. However, the efficacy and safety of treating anemia before TAVR is controversial[20,21] and further studies are needed to get conclusive results on the efficacy of this important component of patient blood management.

The negative prognostic effect of blood transfusion has been largely demonstrated in cardiac surgery,[22] whereas only a few studies of small size investigated this issue in patients undergoing TAVR.[4-8,23,24] This setting provides important advantages in investigating the effect of transfusions in patients undergoing cardiovascular interventions. Indeed, the minimally invasive nature of TAVR allows a more reliable evaluation of the effects of perioperative anemia and blood transfusion without the confounding effect of significant hemodilution and other detrimental effects of cardiopulmonary bypass seen in patients undergoing cardiac surgery. Herein, we have demonstrated that the negative effect of blood transfusion was independent of

other significant comorbidities as shown by regression analyses adjusted by significant comorbidities (Tabs. 2 and 3) as well as by propensity score matching analysis (Tabs. 5 and 6). The evidence of a prognostic effect of postoperative nadir and drop of hemoglobin on the early and late mortality further strengthened these findings (Tab. 4). The time-varying hazard ratio analysis showed that the adjusted risk of all-cause mortality decreased during the first year after the procedure for any RBC transfusion, increasing amount of RBC units transfused as well as for transfusion of more than four units of RBC, but later the negative prognostic impact of these variables remained constant along the years (Fig. 3).

The present analysis confirmed that blood transfusion, particularly when multiple RBC units are transfused and/or operation for bleeding was necessary, increases the risk of stroke and acute kidney injury (Tabs. 2 and 3). Blood transfusion is a well-known risk factor for acute kidney injury in patients undergoing TAVR,[5,23,24] but less is known about its impact on stroke.[23,25] These two end-organ complications may share the same pathogenetic mechanisms possibly triggered by reduced oxygen delivery secondary to severe anemia as well as immune-mediated reactions associated with blood transfusion. These early end-organ complications are in turn associated with increased risk of late mortality. The transfusion-related immunomodulation may further compromise the recovery of patients receiving blood products by producing acute, sub-acute, and chronic effects on macrophage function.[26]

The present study has some limitations inherent to all retrospective analyses. RBC transfusions were performed without pre-specified treatment criteria and the magnitude of bias cannot be determined at this stage. However, these results suggest that the risk of adverse events increased when multiple RBC units were transfused and when any operation for excessive bleeding was necessary. Furthermore, separate analyses showed that both nadir and drop of hemoglobin levels were independent predictors of early and late mortality, which suggest the prognostic importance of perioperative anemia. Indeed, contrary to patients undergoing surgical aortic valve replacement, the risk of hemodilution secondary to fluid therapy is minimal in patients undergoing TAVR and any postoperative drop of hemoglobin level occurring in these patients

mostly reflects the amount perioperative blood loss. Despite these limitations, this nationwide registry provides data from a rather large number of unselected patients offering an excellent view to evaluate the results of TAVR. Data retrieved from a central national registry strengthened the validity of survival analyses. In conclusion, this nationwide registry showed that, despite a high prevalence of preoperative anemia, TAVR can be performed with a rather low rate of RBC transfusion. RBC transfusion had a significant impact on early and mid-term outcomes of these patients, and the adverse effects were particularly evident with increasing amount of RBC transfusions and operations for excessive bleeding. These findings suggest there is a need of studies evaluating the efficacy and safety of preprocedural treatment of anemia and of strategies to reduce access site bleeding during TAVR.

References

1. Stortecky S, Franzone A, Heg D, et al. Temporal trends in adoption and outcomes of transcatheter aortic valve implantation: a Swisstavi registry analysis. Eur Heart J Qual Care Clin Outcomes. 2019 (in press)

2. Mäkikallio T, Jalava MP, Husso A, et al. Ten-year experience with transcatheter and surgical aortic valve replacement in Finland. Ann Med. 2019 (in press)

3. Arora S, Strassle PD, Qamar A, et al. Trends in inpatient complications after transcatheter and surgical aortic valve replacement in the transcatheter aortic valve replacement era. Circ Cardiovasc Interv. 2018;11:e007517.

4. Escárcega RO, Lipinski MJ, Magalhaes MA, et al. Impact of blood transfusions on short- and long-term mortality in patients who underwent transcatheter aortic valve implantation. Am J Cardiol. 2015;115:93-9.

5. Apostolidou E, Aronow HD, Beale CE, et al. Association between red blood cell transfusion and clinical outcomes among patients undergoing transcatheter aortic valve replacement. Ann Thorac Surg. 2019;107:1791-8.

6. Mayr NP, Wiesner G, Hapfelmeier A, et al. Periprocedural transfusion in patients undergoing transfemoral transcatheter aortic valve implantation. Catheter Cardiovasc Interv. 2018; 92: 141– 148.

7. Seiffert M, Conradi L, Terstesse AC, et al. Blood transfusion is associated with impaired outcome after transcatheter aortic valve implantation. Catheter Cardiovasc Interv. 2015;85:460-7.

8. Konigstein M, Havakuk O, Arbel Y, et al. Impact of hemoglobin drop, bleeding events, and red blood cell transfusions on long-term mortality in patients undergoing transaortic valve implantation. Can J Cardiol. 2016;32:1239.e9-1239.e14.

9. Nashef SA, Roques F, Sharples LD, et al. EuroSCORE II. Eur J Cardiothorac Surg. 2012;41:734-44.

10. The Society of Thoracic Surgeons. Online STS adult cardiac surgery risk calculator. 2017. http://riskcalc.sts.org/stswebriskcalc/#/. Accessed October 7, 2018.

11. Rockwood K, Stadnyk K, MacKnight C, et al. A brief clinical instrument to classify frailty in elderly people. Lancet. 1999;353:205-6.

12. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Thorac Cardiovasc Surg. 2013;145:6-23.

13. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Section 2: AKI Definition. Kidney Int Suppl. 2012;2:19-36.

14. Chollet T, Marcheix B, Boudou N, et al. Propensity-matched comparison of clinical outcomes after transaortic versus transfemoral aortic valve replacement. EuroIntervention. 2018;14:750-757.

15. Lederman RJ, Babaliaros VC, Rogers T, et al. The fate of transcaval access tracts: 12-month results of the prospective NHLBI transcaval transcatheter aortic valve replacement study. JACC Cardiovasc Interv. 2019;12:448-456.

16. Overtchouk P, Folliguet T, Pinaud F, et al. Transcarotid approach for transcatheter aortic valve replacement with the Sapien 3 prosthesis: a multicenter French registry. JACC Cardiovasc Interv. 2019;12:413-419.

17. Amat-Santos IJ, Rojas P, Gutiérrez H, et al. Transubclavian approach: A competitive access for transcatheter aortic valve implantation as compared to transfemoral. Catheter Cardiovasc Interv. 2018;92:935-944.

18. Takagi H, Hari Y, Kawai N, Ando T; ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. Meta-nnalysis of impact of anemia and hemoglobin level on survival after transcatheter aortic valve implantation. Am J Cardiol. 2019;123:306-314.

19. D'Errigo P, Biancari F, Rosato S, et al. Transcatheter aortic valve implantation compared with surgical aortic valve replacement in patients with anaemia. Acta Cardiol. 2018;73:50-59.

20. Urena M, Del Trigo M, Altisent OA, et al. Combined erythropoietin and iron therapy for anaemic patients undergoing transcatheter aortic valve implantation: the EPICURE randomised clinical trial. EuroIntervention. 2017;13:44-52.

21. Shuvy M, Mewa J, Wolff R, et al. Preprocedure anemia management decreases transfusion rates in patients undergoing transcatheter aortic valve implantation. Can J Cardiol. 2016;32:732-8.

22. Dyke C, Aronson S, Dietrich W, et al. Universal definition of perioperative bleeding in adult cardiac surgery. J Thorac Cardiovasc Surg. 2014;147:1458-1463.

23. Tchetche D, Van der Boon RM, Dumonteil N, et al. Adverse impact of bleeding and transfusion on the outcome post-transcatheter aortic valve implantation: insights from the Pooled-RotterdAm-Milano-Toulouse In Collaboration Plus (PRAGMATIC Plus) initiative. Am Heart J. 2012;164:402-9.

24. Nuis RJ, Rodés-Cabau J, Sinning JM, et al. Blood transfusion and the risk of acute kidney injury after transcatheter aortic valve implantation. Circ Cardiovasc Interv. 2012;5:680-8.

25. Brascia D, Garcia-Medina N, Kinnunen EM, et al. Impact of transfusion on stroke after cardiovascular interventions: meta-analysis of comparative studies. J Crit Care. 2017;38:157-163.

26. Youssef LA, Spitalnik SL. Transfusion-related immunomodulation: a reappraisal. Curr Opin Hematol. 2017;24:551-557.

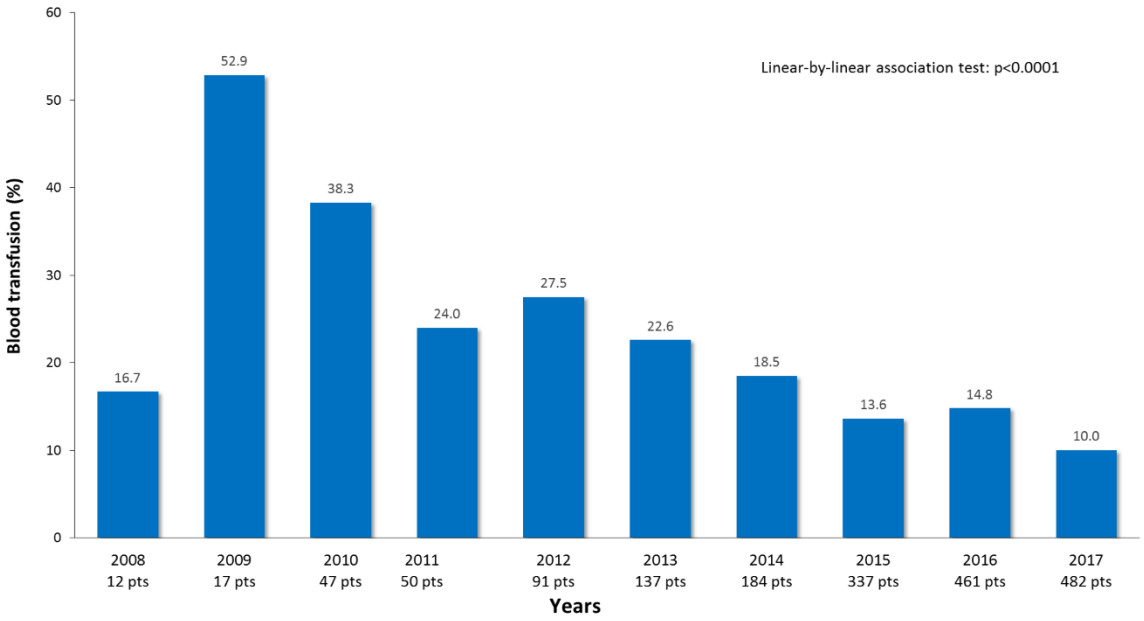

Figure 1. Rates of blood transfusion along the study period.

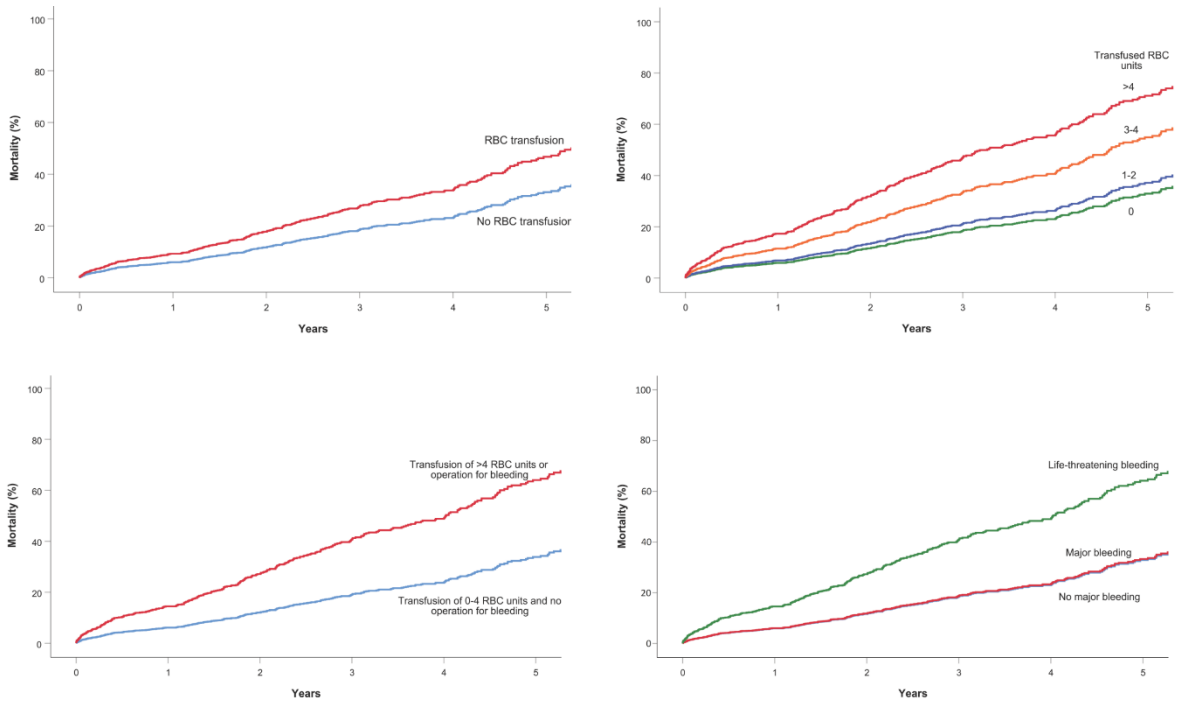

Figure 2. Adjusted late mortality according to red blood cell transfusion, and transfusion of more than four units of red blood cells and/or any operation for bleeding. RBC, red blood cell.

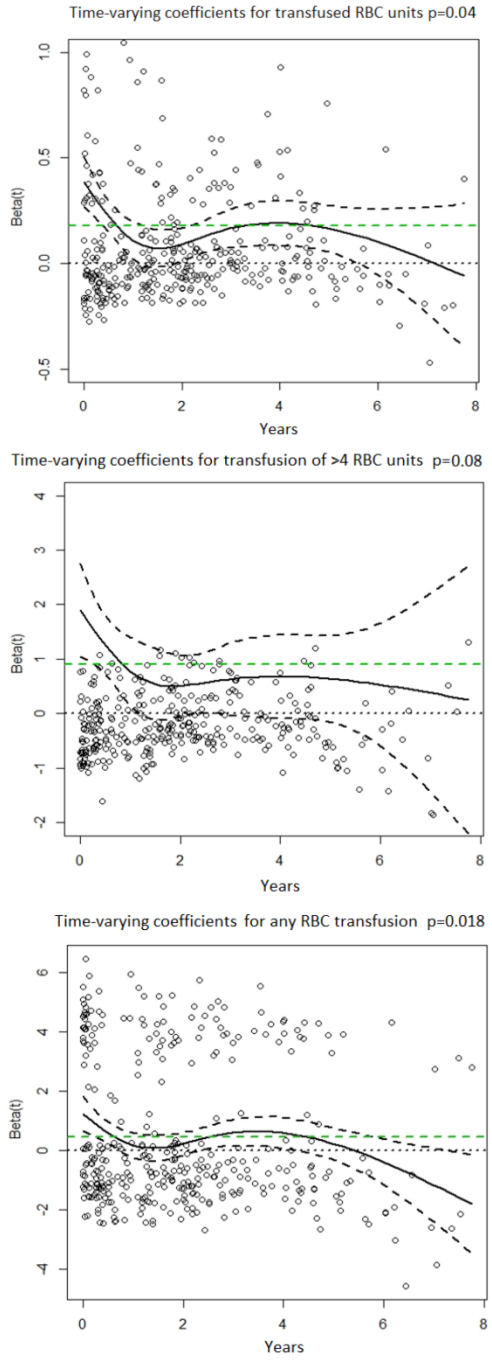

Figure 3. Time-varying hazard ratios for red blood cell transfusion, number of red blood cell units transfused, and transfusion of more than four units of red blood cells and/or any operation for bleeding RBC, red blood cell.

Table 1. Characteristics of patients who underwent transcatheter aortic valve replacement and predictors of red blood cell transfusion.

Characteristics	Overall series 1818 patients	No RBC transfusion 1525 patients	RBC transfusion 293 patients	Univariate analysis p-value	Multivariate analysis Odds ratio, 95%CI
Age, mean (years)	81.6±6.4	81.5±6.3	82.2±6.7	0.045	
Female, n (%)	1030 (56.7)	831 (54.5)	199 (67.9)	<0.0001	1.56, 1.17-2.07
Body mass index, mean (kg/m^2)	27.2±4.9	27.3±4.8	26.7±5.3	0.053	
Hemoglobin, mean (g/dL)	12.5±1.5	12.7±1.5	11.6±1.5	<0.0001	0.96, 0.95-0.96
Anemia, n (%)	829 (45.6)	638 (41.9)	191 (65.2)	<0.0001	*2.61, 1,99-3.42*
eGFR, mean (ml/min/1.73 m^2)	66±23	66±22	62±24	0.001	
Dialysis, n (%)	19 (1.0)	13 (0.9)	6 (2.0)	0.065	
Active malignancy, n (%)	290 (16.0)	58 (3.8)	13 (4.4)	0.289	
Diabetes, n (%)	497 (27.3)	423 (27.7)	74 (25.3)	0.383	
Transient ischemic attack or stroke, n (%)	321 (17.7)	266 (17.4)	55 (18.8)	0.585	
Pulmonary disease, n (%)	370 (20.4)	303 (19.9)	67 (22.9)	0.243	
Oxygen therapy, n (%)	10 (0.6)	9 (0.6)	1 (0.3)	1.000	
Frailty GSS grades 2-3, n (%)	260 (14.3)	220 (14.4)	40 (13.7)	0.729	
Extracardiac arteriopathy, n (%)	277 (15.2)	222 (14.6)	55 (18.8)	0.066	1.51, 1.06-2.16
LVEF ≤50%, n (%)	471 (25.9)	402 (26.4)	69 (23.6)	0.323	
Atrial fibrillation, n (%)	785 (43.2)	666 (43.7)	119 (40.6)	0.333	
NYHA class 4, n (%)	207 (11.4)	161 (10.6)	46 (15.7)	0.011	
SPAP, n (%)				0.022	
31-55 mmHg	747 (41.1)	620 (40.7)	127 (43.3)		
>55 mmHg	232 (12.8)	183 (12.0)	49 (16.7)		
Porcelain aorta, n (%)	82 (4.5)	68 (4.5)	14 (4.8)	0.809	
Coronary artery disease, n (%)	495 (27.2)	407 (26.7)	88 (30.0)	0.239	
Recent myocardial infarction, n (%)	40 (2.2)	30 (2.0)	10 (3.4)	0.122	
Acute heart failure ≤60 days/crit. preop. state, n (%)	208 (11.4)	161 (10.6)	47 (16.1)	0.007	
Prior PCI, n (%)	382 (21.0)	307 (20.1)	75 (25.6)	0.035	
Prior cardiac surgery, n (%)	313 (17.2)	272 (17.8)	41 (14.0)	0.111	
Permanent pace-maker, n (%)	175 (9.6)	154 (10.1)	21 (7.2)	0.119	
Urgent/emergency procedure, n (%)	129 (7.1)	94 (6.2)	35 (11.9)	<0.0001	1.59, 1.02-2.49
Concomitant PCI, n (%)	91 (5.0)	67 (4.4)	24 (8.2)	0.006	
Selected prostheses,[a] n (%)	1329 (73.1)	1157 (75.9)	172 (58.9)	<0.0001	0.48, 0.37-0.63
Surgical femoral a. access, n (%)	290 (16.0)	225 (14.8)	65 (22.2)	0.001	
Antithrombotic treatment					
Aspirin, n (%)	884 (48.6)	713 (46.8)	171 (58.4)	<0.0001	1.48, 1.14-1.94
Warfarin, n (%)	661 (36.4)	563 (36.9)	98 (33.4)	0.258	
NOAC, n (%)	81 (4.5)	73 (4.8)	8 (2.7)	0.118	
Heparin, n (%)	113 (6.2)	84 (5.5)	29 (9.9)	0.004	
Clopidogrel/ticagrelor, n (%)	252 (13.9)	198 (13.0)	54 (18.4)	0.013	
Dual antiplatelet treatment, n (%)	178 (9.8)	135 (8.9)	43 (14.7)	0.002	
EuroSCORE II, mean (%)	6.7±6.9	6.4±6.3	8.3±9.3	<0.0001	
STS Score, mean (%)	4.5±3.2	4.3±2.7	5.5±5.0	<0.0001	

Continuous variables are reported as means±standard deviation as well as median and interquartile range. Categorical variables as counts and percentages. Clinical variables are according to the EuroSCORE II definition criteria. RBC, red blood cell; CI, confidence interval; eGFR, glomerular filtration estimated according to the MDRD equation; LVEF, left ventricular ejection fraction; Frailty, GSS grades 2-3; SPAP, systolic pulmonary artery pressure; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; NOAC; new oral anticoagulant; [a], selected valve prostheses were the following third generation TAVR prostheses and their variants: EvolutR, Sapien 3, Acurate Neo and Lotus.

Table 2. Crude rates and risk adjusted estimates of adverse events in patients receiving or not blood transfusions after transcatheter aortic valve replacement.

Outcomes	Overall series 1818 patients	No RBC transfusion 1525 patients	RBC transfusion 293 patients	Univariate analysis p-value	Adjusted analysis Risk estimate, 95%CI
Mortality (%)				<0.0001	1.57, 1.23-2.00
30-day	1.9	0.9	6.8		
1-year	7.8	6.6	13.6		
2-year	15.4	13.3	25.0		
3-year	24.8	21.7	37.7		
4-year	31.1	27.7	44.3		
5-year	45.0	40.4	60.5		
Stroke, n (%)	45 (2.5)	27 (1.8)	18 (6.1)	<0.0001	3.97, 2.02-7.82
KDIGO acute kidney injury,[a] n (%)	105 (5.9)	55 (3.7)	50 (17.7)	<0.0001	5.54, 3.46-8.88
Renal replacement therapy,[a] n (%)	8 (0.4)	2 (0.1)	6 (2.1)	<0.0001	16.13, 2.32-112.38
Atrial fibrillation,[b] n (%)	109 (10.6)	77 (9.0)	32 (18.4)	<0.0001	2.18, 1.35-3.56
Hospital stay, mean (days)	5.1±4.4	4.4±3.4	8.6±6.6	<0.0001	3.87, 3.34-4.39

Continuous variables are reported as means±standard deviation as well as median and interquartile range. Categorical variables as counts and percentages. RBC, red blood cell; CI, confidence interval; KDIGO, Kidney Disease: Improving Global Outcomes. Risk estimates are odds ratios, hazard ratios or coefficients with 95% confidence interval (CI); [a], excluding patients with preoperative estimated glomerular filtration rate <15 ml/min/m^2 or dialysis; [b], excluding patients with any preoperative atrial fibrillation.

Table 3. Crude rates and risk adjusted estimates of adverse events according to increasing amount of blood transfusions after transcatheter aortic valve replacement.

Outcomes	No RBC transfusion 1525 patients	RBC transfusion 1-2 units 190 patients	RBC transfusion 3-4 units 51 patients	RBC transfusion >4 units 52 patients	P-value
Mortality (%)					
30-day	0.9	2.6	11.8	17.3	
1-year	6.6	8.1	19.9	25.3	
2-year	13.3	19.2	33.0	38.8	
3-year	21.7	32.6	41.4	54.5	
4-year	27.7	41.4	45.9	54.5	
5-year	40.4	58.0	62.9	69.7	
Adjusted risk estimates	Reference	1.16, 0.85-1.58	2.00, 1.27-3.13	3.11, 2.05-4.72	<0.0001
Stroke, n (%)	27 (1.8)	9 (4.7)	1 (2.0)	8 (15.4)	
Adjusted risk estimates	Reference	2.85, 1.24-6.58	1.08, 0.14-8.34	11.47, 4.70-27.98	<0.0001
KDIGO acute kidney injury,[a] n (%)	55 (3.7)	20 (10.7)	13 (26.5)	17 (37.0)	
Adjusted risk estimates	Reference	2.66, 1.44-4.91	8.31, 3.85-17.96	17.85, 8.62-36.95	<0.0001
Renal replacement therapy,[a] n (%)	2 (0.1)	1 (0.5)	2 (4.0)	3 (6.1)	
Adjusted risk estimates	Reference	1.66, 0.87-31.97	21.40, 1.90-241.46	61.66, 6.59-576.46	0.001
Atrial fibrillation,[b] n (%)	77 (9.0)	10 (8.8)	6 (21.4)	16 (50.0)	
Adjusted risk estimates	Reference	0.83, 0.41-1.71	2.57, 0.98-6.79	11.50, 5.36-24.68	<0.0001
Hospital stay, mean (days)	4.4±3.4	7.0±4.5	10.5±7.5	12.7±9.5	
Adjusted risk estimates	Reference	2.22, 1.61-2.83	5.63, 4.52-6.72	7.86, 6.78-8.94	<0.0001

Continuous variables are reported as means±standard deviation as well as median and interquartile range. Categorical variables as counts and percentages. Risk estimates are odds ratios, hazard ratios or coefficients with 95% confidence interval (CI). RBC, red blood cell; KDIGO, Kidney Disease: Improving Global Outcomes; [a], excluding patients with preoperative estimated glomerular filtration rate <15 ml/min/m^2 or dialysis; [b], excluding patients with any preoperative atrial fibrillation.

Table 4. Risk estimates of 30-day and late mortality according to different parameters of perioperative bleeding related variables.

Outcomes	
30-day mortality	Odds ratio, 95%CI
RBC transfusion	8.47, 3.86-18.60
VARC-2 severity of bleeding	
None or minor bleeding	*Reference cat.*
Major bleeding	2.15, 0.85-5.47
Life threatening bleeding	17.57, 7.37-41.89
Number of RBC units transfused (per unit)	1.48, 1.32-1.65
None	*Reference cat.*
1-2 units	2.92, 0.97-8.84
3-4 units	14.82, 4.91-44.70
>4 units	22.98, 8.63-61.21
Transfusion of >4 RBC units or operation for bleeding	7.35, 3.33-16.26
Any operation for bleeding	7.59, 3.18-18.13
Operation for peripheral bleeding	4.37, 1.57-12.13
Nadir hemoglobin (per g/dL)	0.94, 0.91-0.97
Drop in hemoglobin (per g/dL)	1.88, 1.41-2.52
Late mortality	Hazard ratio, 95%CI
RBC transfusion	1.57, 1.23-2.00
VARC-2 severity of bleeding	
None or minor bleeding	*Reference cat.*
Major bleeding	1.02, 0.80-1.30
Life threatening bleeding	2.58, 1.86-3.58
Number of RBC units transfused (per unit)	1.20, 1.14-1.26
None	*Reference cat.*
1-2 units	1.16, 0.85-1.58
3-4 units	2.00, 1.27-3.13
>4 units	3.11, 2.05-4.72
Transfusion of >4 RBC units or operation for bleeding	2.12, 1.53-1.65

Any operation for bleeding	1.94, 1.30-2.88
Operation for peripheral bleeding	1.76, 1.23-2.51
Nadir hemoglobin (per g/dL)	0.98, 0.97-0.99
Drop in hemoglobin (per g/dL)	1.18, 1.08-1.29

RBC, red blood cell, CI, 95% confidence interval.

Table 5. Characteristics of propensity score matched pairs of patients who received or not blood transfusions after transcatheter aortic valve replacement.

Characteristics	No RBC transfusion 281 patients	RBC transfusion 281 patients	Univariate analysis p-value	Standardized differences
Age, mean (years)	82.1±6.5	82.1±7.8	0.818	0.006
Female, n (%)	188 (66.9)	189 (67.3)	0.928	0.008
Body mass index, mean (kg/m^2)	26.9±5.1	26.8±5.3	0.787	0.024
Hemoglobin, mean (g/dL)	116±14	117±15	0.562	0.051
Anemia, n (%)	188 (66.9)	179 (63.7)	0.425	0.067
eGFR, mean (ml/min/1.73 m^2)	63±24	62±24	0.726	0.006
Dialysis, n (%)	5 (1.8)	5 (1.8)	1.000	0.000
Active malignancy, n (%)	14 (5.0)	13 (4.6)	0.844	0.017
Diabetes, n (%)	72 (25.6)	68 (24.2)	0.696	0.039
Transient ischemic attack or stroke, n (%)	52 (18.5)	53 (18.9)	0.914	0.009
Pulmonary disease, n (%)	58 (20.6)	62 (22.1)	0.681	0.035
Oxygen therapy, n (%)	2 (0.7)	1 (0.4)	0.563	0.049
Frailty GSS grades 2-3, n (%)	38 (13.5)	39 (13.9)	0.902	0.010
Extracardiac arteriopathy, n (%)	45 (16.0)	53 (18.9)	0.374	0.075
LVEF ≤50%, n (%)	63 (22.4)	64 (22.8)	0.920	0.009
Atrial fibrillation, n (%)	99 (35.2)	112 (39.9)	0.257	0.096
NYHA class 4, n (%)	35 (12.5)	39 (13.9)	0.618	0.042
SPAP, n (%)			0.889	0.041
31-55 mmHg	126 (44.8)	123 (43.8)		
>55 mmHg	39 (13.9)	43 (15.3)		
Porcelain aorta, n (%)	10 (3.6)	13 (4.6)	0.523	0.053
Coronary artery disease, n (%)	98 (34.9)	81 (28.8)	0.124	0.130
Recent myocardial infarction, n (%)	10 (3.6)	10 (3.6)	1.000	0.000
Acute heart failure ≤60 days/crit. preop. state, n (%)	41 (14.6)	40 (14.2)	0.904	0.010
Prior PCI, n (%)	71 (25.3)	70 (24.9)	0.922	0.008
Prior cardiac surgery, n (%)	31 (11.0)	38 (13.5)	0.368	0.076
Permanent pace-maker, n (%)	21 (11.0)	21 (11.0)	1.000	0.000
Urgent/emergency procedure, n (%)	30 (10.7)	28 (10.0)	0.782	0.023
Concomitant PCI, n (%)	23 (8.2)	22 (7.8)	0.876	0.013
Selected prostheses,[a] n (%)	173 (61.6)	169 (60.1)	0.730	0.029
Surgical femoral a. access, n (%)	57 (20.3)	58 (20.6)	0.917	0.009
Antithrombotic treatment				

Aspirin, n (%)	178 (63.3)	118 (58.0)	0.195	0.109
Warfarin, n (%)	86 (30.6)	93 (33.1)	0.526	0.053
NOAC, n (%)	1 (0.4)	8 (2.8)	0.038	0.199
Heparin, n (%)	29 (10.3)	24 (8.5)	0.470	0.061
Clopidogrel/ticagrelor, n (%)	50 (17.8)	49 (17.4)	0.912	0.009
Dual antiplatelet treatment, n (%)	41 (14.6)	38 (13.5)	0.716	0.030
EuroSCORE II, mean (%)	7.2±6.9	7.6±7.9	0.808	0.048
STS Score, mean (%)	5.2±3.6	5.3±4.6	0.429	0.013

Continuous variables are reported as means±standard deviation as well as median and interquartile range. Categorical variables as counts and percentages. Clinical variables are according to the EuroSCORE II definition criteria. RBC, red blood cell; CI, confidence interval; eGFR, glomerular filtration estimated according to the MDRD equation; LVEF, left ventricular ejection fraction; Frailty, GSS grades 2-3; SPAP, systolic pulmonary artery pressure; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; NOAC; new oral anticoagulant; [a], selected valve prostheses were the following third generation TAVR prostheses and their variants: EvolutR, Sapien 3, Acurate Neo and Lotus.

Table 6. Adverse events in propensity score matched pairs of patients who received or not blood transfusions after transcatheter aortic valve replacement.

Outcomes	No RBC transfusion 281 patients	RBC transfusion 281 patients	Univariate analysis p-value
Mortality (%)			0.008
30-day	0	7.1	<0.0001
1-year	5.9	13.5	
2-year	12.7	24.9	
3-year	22.8	36.0	
4-year	25.3	43.0	
5-year	43.3	59.1	
Stroke, n (%)	10 (3.6)	18 (6.4)	0.170
KDIGO acute kidney injury,[a] n (%)	12 (4.4)	46 (17.0)	<0.0001
Renal replacement therapy,[a] n (%)	1 (0.4)	10 (3.6)	<0.0001
Atrial fibrillation,[b] n (%)	79 (28.1)	111 (39.5)	0.005
Hospital stay, mean (days)	4.7±3.0	8.5±6.2	<0.0001

Continuous variables are reported as means±standard deviation as well as median and interquartile range. Categorical variables as counts and percentages. RBC, red blood cell; CI, confidence interval; KDIGO, Kidney Disease: Improving Global Outcomes. Risk estimates are odds ratios, hazard ratios or coefficients with 95% confidence interval (CI); [a], excluding patients with preoperative estimated glomerular filtration rate <15 ml/min/m^2 or dialysis; [b], excluding patients with any preoperative atrial fibrillation.