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## Transcatheter aortic valve implantation compared with surgical aortic valve replacement in patients with anaemia

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### ABSTRACT

**Objectives:** We compared the outcome of anaemic patients undergoing transcatheter (TAVI) and surgical aortic valve replacement (SAVR) for severe aortic valve stenosis.

**Methods:** Anaemic patients (haemoglobin <13.0 g/dL in men and <12.0 g/dL in women) undergoing TAVI and SAVR from the OBSERVANT study were the subjects of this analysis.

**Results:** Preoperative anaemia was an independent predictor of 3-year mortality after either TAVI (HR 1.37, 95% CI 1.12–1.68) and SAVR (HR 1.63, 95% CI 1.37–1.99). Propensity score matching resulted in 302 pairs with similar characteristics. Patients undergoing SAVR had similar 30-d mortality (3.6% versus 3.3%,  $p = .81$ ) and stroke (1.3% versus 2.0%,  $p = .53$ ) compared with TAVI. The rates of pacemaker implantation (18.6% versus 3.0%,  $p < .001$ ), major vascular damage (5.7% versus 0.4%,  $p < .001$ ) and mild-to-severe paravalvular regurgitation (47.4% versus 9.3%,  $p < .001$ ) were higher after TAVI, whereas acute kidney injury (50.7% versus 27.9%,  $p < .001$ ) and blood transfusion (70.0% versus 38.6%,  $p < .001$ ) were more frequent after SAVR. At 3-year, survival was 74.0% after SAVR and 66.3% after TAVI, respectively ( $p = .065$ ), and freedom from MACCE was 67.6% after SAVR and 58.7% after TAVI, respectively ( $p = .049$ ).

**Conclusions:** These results suggest that TAVI is not superior to SAVR in patients with anaemia.

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### KEYWORDS

Anaemia; anaemic; aortic valve stenosis; TAVR; TAVI; aortic valve replacement

## Introduction

Anaemia is associated with decreased early and late survival after cardiac surgery [1]. The negative prognostic impact of decreased preoperative levels of haemoglobin is likely due to a synergistic contribution of comorbidities underlying anaemia [2]. However, other mechanisms such as severe haemodilution during cardiopulmonary bypass (CPB) and the use of blood products to correct haemodilution and bleeding-related anaemia may be implicated [3]. Preoperative use of erythropoiesis-stimulating agents and iron would be logical measures to correct anaemia before cardiac surgery. Indeed, this approach along with meticulous surgical technique and reinfusion of shed blood allows transfusion-free cardiac surgery in Jehovah's Witnesses without compromising the outcome of these patients [4]. However, the perceived increased risk of thromboembolism related to a sudden increase of haemoglobin and the lack of data on the safety and efficacy of these strategies [5] along with the danger associated with delayed surgery

prevent the preoperative optimisation of the haemoglobin level in daily practice. Still, anaemia renders difficult the decision-making process in patients with severe aortic valve stenosis and may favour transcatheter aortic valve implantation (TAVI) with respect to surgical aortic valve replacement (SAVR), because of its related decreased risk of major bleeding and need for transfusions [6]. The prognostic impact of anaemia in patients undergoing aortic valve replacement and the potential benefits of TAVI over SAVR in anaemic patients are investigated in the present multicentre study.

## Methods

### Study design and data collection

OBSERVANT (OBServational Study of Effectiveness of avR-taVi procedures for severe Aortic steNosis Treatment) is a national observational, prospective, multicentre, cohort study that enrolled consecutive patients undergoing TAVI or SAVR for severe aortic

valve stenosis at 93 Italian cardiology/cardiac surgery centres between December 2010 and June 2012. Details on the study design, patient eligibility criteria and data collection modalities are reported elsewhere [7]. This study was coordinated by the Italian National Institute of Health and led in cooperation with the Italian Ministry of Health, the National Agency for Regional Health Services, Italian Regions, and Italian scientific societies and federations representing Italian professionals involved in the management of aortic valve stenosis. The complete list of executive working group, participating centres and investigators is reported in the Appendix. In the participating hospitals, both SAVR and TAVI could have been offered to patients with severe aortic valve stenosis. Data on demographic characteristics, health status prior to intervention, comorbidities, and complete information on the type of intervention were collected into a standardised online datasheet on a password-protected website. Collected data were stored and analysed at the Italian National Institute of Health. CoreValve (Medtronic, Minnesota, MN) and Sapien XT (Edwards Lifesciences, Irvine, CA) valve prostheses were implanted in these patients. Data auditing was performed by independent observers following specific standard operating procedures. They monitored the participating hospitals to assess the completeness of the enrolled cohort and compared the collected data with those of the original clinical records. The study protocol has been approved by the Ethics Committee of each participating centre and patients gave their informed consent to participate in this study.

### **Inclusion criteria**

The study population included consecutive adult patients admitted with a diagnosis of severe aortic valve stenosis (defined as an aortic valve area  $<1\text{ cm}^2$ , maximum aortic velocity  $>4\text{ m/s}$  or mean pressure gradient  $>40\text{ mmHg}$ ) and requiring aortic valve replacement. The aim of the present analysis was to evaluate the impact of anaemia on the outcome after TAVI and SAVR in separate cohorts. Anaemia was defined as a haemoglobin level  $<13.0\text{ g/dL}$  in men and  $<12.0\text{ g/dL}$  in women [8]. Anaemia was further classified into mild (haemoglobin  $11.0\text{--}12.9\text{ g/dL}$  in men and  $11.0\text{--}11.9\text{ g/dL}$  in women), moderate (haemoglobin  $8.0\text{--}10.9\text{ g/dL}$  in men and  $8.0\text{--}10.9\text{ g/dL}$  in women) and severe anaemia (haemoglobin  $<8.0\text{ g/dL}$  in men and women) according to the WHO criteria [8]. After assessing the impact of anaemia in these two cohorts, a comparative analysis of the immediate and intermediate outcome after TAVI and SAVR was

performed. In order to guarantee the comparability of the subjects undergoing TAVI or SAVR, patients with porcelain aorta, hostile chest and active endocarditis as well as those undergoing any combined coronary procedure, emergency procedure or a TAVI performed through a transapical approach were excluded from this analysis.

### **Outcome end points and follow-up**

Thirty-day and 3-year survival were the primary end points of this analysis. Secondary end points were in-hospital adverse events such as stroke, vascular complications, bleeding and acute kidney injury. Stroke was defined as any focal deficit lasting  $>24\text{ h}$ , or focal deficit lasting  $<24\text{ h}$  with positive neuro-imaging studies. Vascular complications were defined as any access site complication requiring surgical or percutaneous vascular intervention. Severity of bleeding was estimated as the proportion of patients who received red blood cell transfusion and as the number of units of transfused red blood cells. Acute kidney injury was classified in three stages according to the AKIN definition criteria and taking into consideration only the baseline and post-operative serum creatinine levels [9]. Other secondary outcome end points were major adverse cardiac and cerebrovascular events (MACCE) at 3 years. MACCE were defined as the composite end point including any of the following adverse events: death from any cause, stroke, myocardial infarction, percutaneous coronary intervention (PCI) and/or CABG. An administrative follow-up has been set up for each enrolled patient through a record linkage with the National Hospital Discharged Records database for in-hospital events and with the Tax Registry Information System for information on survival.

### **Statistical analysis**

The impact of anaemia on 3-year mortality was evaluated separately in the TAVI and SAVR cohorts by Cox proportional hazards analysis. A stepwise approach was used to select variables to be included in the model. Exploratory and interaction analyses were performed and showed that the TAVI cohort had a significantly higher operative risk than the SAVR cohort. Therefore, a propensity score matching method was employed to identify patients undergoing SAVR and TAVI with similar baseline characteristics [10]. The propensity score was estimated by a non-parsimonious logistic regression model with the treatment method as the dependent variable and the following variables as covariates: age, gender, body mass index, smoking

habit, frailty status, baseline haemoglobin, baseline albumin, previous percutaneous coronary intervention, previous balloon aortic valvuloplasty, previous cardiac surgery, previous operation on the aortoiliac arteries; chronic dialytic treatment, diabetes, chronic obstructive pulmonary disease, oxygen therapy, previous myocardial infarction, peripheral arteriopathy, estimated glomerular filtration rate, critical preoperative state, unstable angina, neurological dysfunction, pulmonary hypertension (systolic pulmonary arterial pressure >60 mm Hg), chronic liver disease, active neoplastic disease, New York Heart Association class, coronary artery disease, urgent operation, left ventricular ejection fraction, mitral valve regurgitation as well as mean and peak transvalvular gradient.

One-to-one propensity score matching was performed employing the nearest neighbour method and a caliper of 0.2 of the standard deviation of the logit of the propensity score [11]. To evaluate the balance between the matched groups, the *t*-test for paired sample for continuous variables, the McNemar test for dichotomous variables, the Stuart–Maxwell test for categorical variables and the analysis of the standardised differences after matching have been used. The same tests have been used to test differences in the early adverse events of propensity score matched groups. When a patient of a pair was lost to follow-up and the matched patient was still alive (or free from events when considering the MACCE outcome end point), the time of observation of both patients was truncated at the time of the last observation of the lost patient to guarantee the comparability between the two groups. Differences in the outcomes at 3 years have been evaluated by the Kaplan–Meier method with the Klein–Moeschberger stratified log rank test [12]. Tests were two-sided and a *p* < .05 was considered statistically significant. Statistical analyses were performed using the SAS statistical package, version 9.4 (SAS Institute Inc., Cary, NC).

## Results

The OBSERVANT study includes 7618 patients who underwent either TAVI or SAVR. For the purposes of this study, 5135 patients fulfilled the inclusion criteria and were the subjects of this analysis. From this cohort of patients, 3762 patients (73.3%) underwent SAVR and 1373 (26.7%) underwent TAVI. The prevalence of anaemia as defined by the WHO criteria was 58.3% in the TAVI group and 31.4% in the SAVR group. Separate multivariate analyses in the TAVI and SAVR cohorts showed that preoperative anaemia was an independent predictor of 3-year mortality after either

**Table 1.** Independent predictors of 3-year mortality after transcatheter (TAVI) and surgical aortic valve replacement (SAVR).

Variables	HR	(95%CI)	<i>p</i> value
<b>TAVI</b>			
Anaemia	1.37	(1.12–1.68)	.0024
Age	0.99	(0.98–1.01)	.3918
Female gender	0.72	(0.60–0.87)	.0008
Estimated glomerular filtration rate	0.99	(0.98–0.99)	<.0001
Active neoplastic disease	2.22	(1.55–3.18)	<.0001
Frailty (moderate–severe)	1.45	(1.19–1.78)	.0003
<b>New York Heart Association classes</b>			
Class 2	0.76	(0.49–1.19)	.2303
Class 3	0.88	(0.58–1.35)	.5546
Class 4	1.26	(0.79–2.02)	.3281
<b>SAVR</b>			
Anaemia	1.63	(1.34–1.99)	<.0001
Age	1.06	(1.05–1.08)	<.0001
Female gender	0.85	(0.70–1.04)	.1159
Prior interventions on the aortoiliac arteries	1.92	(1.14–3.23)	.0140
Pulmonary disease	1.77	(1.37–2.31)	<.0001
Estimated glomerular filtration rate	0.99	(0.99–1.00)	.0157
Dialysis	3.46	(1.83–6.54)	.0001
Chronic liver disease	1.82	(1.13–2.93)	.0135
Frailty (moderate–severe)	1.77	(1.28–2.44)	.0005
<b>Coronary disease</b>			
1 vessel	1.24	(0.89–1.73)	.1951
2 vessels	0.85	(0.47–1.55)	.5994
3 vessels	1.97	(1.15–3.38)	.0134

TAVI (HR 1.37, 95% CI 1.12–1.68) and SAVR (HR 1.63, 95% CI 1.37–1.99) (Table 1). These findings were confirmed in interaction analysis (TAVI, HR 1.38, 95% CI 1.13–1.68; SAVR, HR 1.70, 95% CI 1.40–2.07; interaction *p* value = .134).

Among anaemic patients, 1180 underwent SAVR and 800 underwent TAVI. Significant differences in baseline variables and operative risk were observed in these two cohorts (logistic EuroSCORE, TAVI  $14.6 \pm 12.5\%$  versus SAVR  $5.7 \pm 5.8\%$ , *p* < .001; EuroSCORE II, TAVI  $7.7 \pm 8.3\%$  versus SAVR  $3.0 \pm 3.5\%$ , *p* < .001). Therefore, a propensity score for estimation of the risk of being assigned to the TAVI or SAVR was calculated. Propensity score one-to-one matching resulted in 302 pairs without significant differences in baseline characteristics (Tables 2 and 3) as estimated by standardised differences (Figure 1). Only one of the covariates had a post-match standardised difference >10%, indicating an excellent covariate balance. The diameter of the aortic annulus significantly differed between the study groups likely because of differences in the methods of measurement (Figure 1).

## Outcomes

Early adverse events are summarised in Table 4. Thirty-day mortality was 3.6% after SAVR and 3.3% after TAVI (*p* = .81). Stroke rate was rather low and similar in the two study groups (SAVR, 1.3% versus TAVI 2.0%, *p* = .53). The rates of permanent pacemaker

**Table 2.** Baseline clinical characteristics of propensity score matched pairs of patients with anaemia undergoing transcatheter (TAVI) or surgical aortic valve replacement (SAVR).

	SAVR, n = 302	TAVI, n = 302	p value
Age (years ± SD)	80.0 ± 5.3	80.4 ± 6.5	.318
Male, n (%)	169 (56.0)	166 (55.0)	.803
Haemoglobin (g/dL)	10.6 ± 1.1	10.6 ± 0.9	.720
Severity of anaemia <sup>a</sup>			
Mild anaemia	183 (60.6)	178 (58.9)	.741
Moderate anaemia	118 (39.1)	124 (41.1)	
Severe anaemia	1 (0.3)	0	
BMI (kg/m <sup>2</sup> ± SD)	26.1 ± 4.1	26.3 ± 5.1	.569
Albumin (g/dL ± SD)	3.5 ± 0.9	3.5 ± 0.8	.479
Diabetes mellitus, n (%)	88 (29.1)	89 (29.5)	.930
eGFR (mg/min/1.73 m <sup>2</sup> ± SD)	57 ± 21	56 ± 22	.874
Chronic dialytic treatment, n (%)	9 (3.0)	7 (2.3)	.593
Smoking history, n (%)	34 (11.3)	30 (9.9)	.579
Neurologic dysfunction, n (%)	18 (6.0)	18 (6.0)	1.000
Chronic liver disease, n (%)	14 (4.6)	13 (4.3)	.835
Active neoplastic disease, n (%)	8 (2.6)	9 (3.0)	.796
Peripheral arteriopathy, n (%)	45 (14.9)	55 (18.2)	.286
Pulmonary disease, n (%)	72 (23.8)	69 (22.8)	.782
Pulmonary hypertension, n (%)	37 (12.2)	34 (11.3)	.705
Oxygen therapy, n (%)	9 (3.0)	9 (3.0)	1.000
Previous cardiac surgery, n (%)	29 (9.6)	31 (10.2)	.768
Previous op. on the aorta, n (%)	6 (2.0)	7 (2.3)	.782
Previous BAV, n (%)	12 (4.0)	12 (4.0)	1.000
Previous AMI, n (%)	32 (10.6)	38 (12.6)	.446
Previous PCI, n (%)	45 (14.9)	45 (14.9)	1.000
Coronary artery disease, n (%)	59 (19.5)	56 (18.5)	.519
One-vessel disease	28 (9.3)	33 (10.9)	
Two-vessels disease	15 (5.0)	14 (4.6)	
Three-vessels disease	16 (5.3)	9 (3.0)	
NYHA classes, n (%)			.976
I	17 (5.6)	15 (5.0)	
II	109 (36.1)	107 (35.4)	
III	144 (47.7)	147 (48.7)	
IV	32 (10.6)	33 (10.9)	
Unstable angina, n (%)	9 (3.0)	11 (3.2)	.655
Critical preoperative state, n (%)	9 (3.0)	8 (2.6)	.808
Frailty (moderate-severe), n (%)	47 (15.6)	48 (15.9)	.907
Urgent procedure, n (%)	9 (3.0)	10 (3.3)	.819
Logistic EuroSCORE I (% ± SD)	9.3 ± 8.0	9.4 ± 6.8	.853
Logistic EuroSCORE II (% ± SD)	4.8 ± 4.9	5.0 ± 4.3	.494

SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation; BMI: body mass index; AMI: acute myocardial infarction; eGFR: estimated glomerular filtration rate; PCI: percutaneous coronary intervention; BAV: balloon aortic valvuloplasty; NYHA: New York Heart Association.

<sup>a</sup>According to the World Health Organisation criteria (7). *p* values refer to McNemar test for dichotomous variables, Stuart–Maxwell test for categorical variables and *t*-test for paired sample for continuous variables.

implantation (18.6% versus 3.0%, *p* < .001), major vascular damage (5.7% versus 0.4%, *p* < .001), mild-to-severe paravalvular regurgitation (50.0% versus 9.8%, *p* < .001) and moderate-to-severe paravalvular regurgitation (6.3% versus 1.7%, *p* = .005) were significantly higher after TAVI compared with SAVR. However, the proportion of cardiogenic shock (2.0% versus 6.8%, *p* = .003), patients who received blood transfusion (38.6% versus 70.0%, *p* < .001), number of units of blood transfusion (mean 0.8 ± 1.5 versus 3.2 ± 3.8, *p* < .001) and acute kidney injury (AKIN stages 1–3: 27.9% versus 50.7%, *p* < .001) were significantly lower after TAVI compared with SAVR. These translated in a shorter stay in the intensive care unit after TAVI (mean

**Table 3.** Preoperative echocardiographic parameters of propensity score matched pairs of patients with anaemia undergoing transcatheter (TAVI) or surgical aortic valve replacement (SAVR).

	SAVR, n = 302	TAVI, n = 302	p value
LVEF, n (%)			.851
>50	234 (77.5)	230 (76.2)	
30–50	60 (19.9)	62 (20.5)	
<30	8 (2.6)	10 (3.3)	
Mitral valve regurgitation, n (%)			.708
Moderate	63 (20.9)	63 (20.9)	
Severe	8 (2.6)	4 (1.3)	
Aortic valve pattern			
Aortic valve area (cm <sup>2</sup> ± SD)	0.7 ± 0.2	0.7 ± 0.3	.542
Peak gradient (mmHg ± SD)	84 ± 24	83 ± 23	.525
Mean gradient (mmHg ± SD)	52 ± 16	51 ± 15	.606
Annulus diameter (mm ± SD)	21.1 ± 2.2	22.2 ± 2.1	<.0001

SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation; LVEF: left ventricular ejection fraction. *p* values refer to McNemar test for dichotomous variables, Stuart–Maxwell test for categorical variables and *t*-test for paired sample for continuous variables.

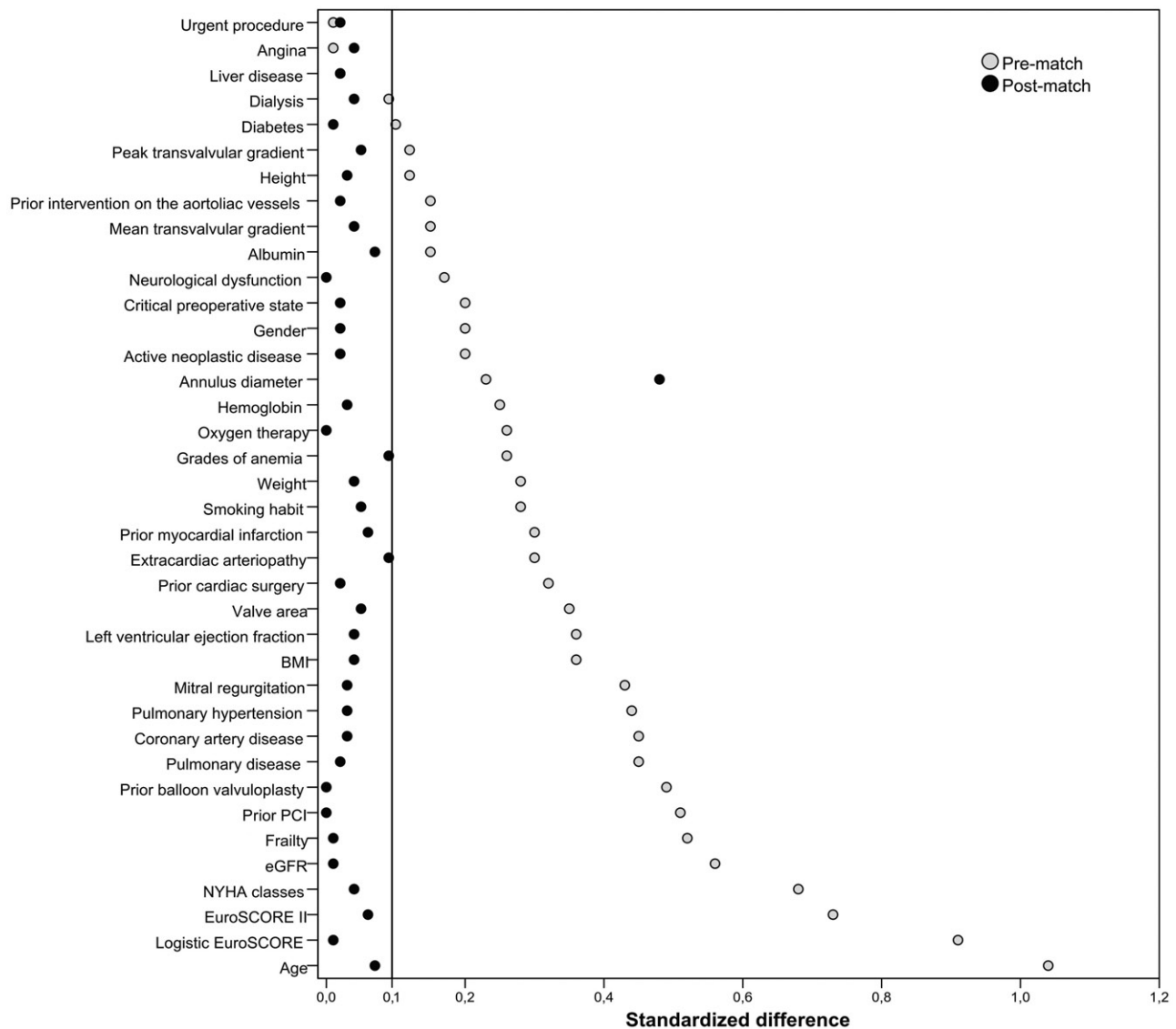
3.2 ± 4.3 versus 4.7 ± 9.6 d, *p* = .012). Furthermore, TAVI was associated also with lower mean transvalvular gradient (mean 10.6 ± 6.4 mmHg versus 13.2 ± 6.5 mmHg, *p* < .001) and peak transvalvular gradient (mean 19.5 ± 10.8 mmHg versus 24.5 ± 11.1 mmHg, *p* < .001).

Among these propensity score matched cohorts, 1-, 2- and 3-year survival was 83.6%, 79.8% and 74.0% after SAVR and 86.0%, 78.4% and 66.3% after TAVI, respectively (stratified log rank test, *p* = .065) (Figure 2). One-, two- and three-year freedom rates from MACCE were 79.8%, 74.7% and 67.6% after SAVR and 80.9%, 71.3% and 58.7% after TAVI, respectively (stratified log rank test, *p* = .049) (Figure 2). The incidence of adverse events (stroke, myocardial infarction and coronary revascularization) at 3-year follow-up is reported in Table 5.

## Discussion

The present study shows that preoperative anaemia is rather common in patients with severe aortic valve stenosis and this is likely due to the advanced age and associated comorbidities of this fragile patient population. Furthermore, Heyde's syndrome and coagulopathy may account as frequent causes of anaemia in patients with severe aortic valve stenosis [13]. In fact, the prevalence of anaemia in patients undergoing TAVI has been reported ranging from 42% to 67% in different centres [14–17] and it is higher than in patients undergoing general cardiac surgery, which has been estimated being 31% in a large UK study [18].

In the present study, anaemia had an independent, negative prognostic impact on mid-term outcome after either TAVI or SAVR. Also a few recent studies showed that preoperative anaemia before TAVI was associated with poorer mid-term survival [14,15,19],



**Figure 1.** Graphical representation of absolute standardised differences before and after propensity score matching comparing baseline covariates of patients undergoing transcatheter aortic valve implantation and surgical aortic valve replacement. Post-match standardised difference  $<0.1$  indicates excellent covariate balance.

and the adjusted risk estimates of 1-year mortality ranged from 1.44 to 2.10 [14,15]. Similarly, anaemia is associated with increased early and late mortality also after cardiac surgery [1,20–23]. Whether the negative effect of preoperative anaemia is related to suboptimal oxygen delivery and is aggravated by the use of blood transfusion or a combination of both is still a matter of debate [24]. In view of the significant prevalence of preoperative anaemia and the risk of severe bleeding and need of transfusion, a policy of optimisation of the haemoglobin level with administration of iron intravenously and erythropoiesis-stimulating agents would be a logical approach before aortic valve replacement. However, the lack of data on its safety formally prevents a widespread application of this strategy [25].

In this scenario of uncertainty regarding the treatment of preprocedural anaemia, anaemic patients with severe aortic valve stenosis may be assigned to a less invasive treatment such as TAVI in order to reduce the risk of significant bleeding and, consequently, the need of transfusion which are common during conventional cardiac surgery and the use of cardiopulmonary bypass. However, the present results indicate that, despite its minimally invasive nature, a large number of patients (39%) undergoing TAVI still required blood transfusion. The proportion of patients who received blood transfusion and their amount were anyway significantly larger in the SAVR cohort. In turn, patients undergoing conventional surgery had an increased rate of acute kidney injury and a longer stay in the intensive care unit, but they did not have

**Table 4.** Early outcome end points in propensity score matched pairs of patients with anaemia after transcatheter (TAVI) and surgical aortic valve replacement (SAVR).

Adverse events	SAVR, n = 302	TAVI, n = 302	p value
30-d mortality, n (%)	11 (3.6)	10 (3.3)	.808
Stroke, n (%)	4 (1.3)	6 (2.0)	.527
Valve migration, n (%)	0	5 (1.7)	.074
Cardiogenic shock, n (%)	20 (6.8)	6 (2.0)	.003
Cardiac tamponade, n (%)	12 (4.1)	8 (2.7)	.371
Permanent pacemaker, n (%)	9 (3.0)	55 (18.6)	<.0001
Major vascular damage, n (%)	1 (0.4)	16 (5.7)	<.0001
Infection			.266
Wound, n (%)	5 (1.7)	4 (1.2)	
Lung or other organs, n (%)	9 (3.1)	16 (5.6)	
Sepsis, n (%)	6 (2.1)	2 (0.7)	
Emergency PCI, n (%)	0	0	–
RBC transfusion, n (%)	203 (70.0)	112 (38.6)	<.0001
RBC transfusion (mean ± SD)	2.7 ± 3.6	0.8 ± 1.5	<.0001
RBC transfusion <sup>b</sup> (mean ± SD)	3.2 ± 3.8	1.1 ± 1.5	.002
Paravalvular regurgitation, n (%)	28 (9.3)	143 (47.4)	<.0001
Mild	23 (8.0)	125 (43.7)	
Moderate	3 (1.0)	18 (6.3)	
Severe	2 (0.7)	0	
AKIN stages	142 (50.7)	78 (27.9)	<.0001
Stage 1 <sup>a</sup>	85 (30.4)	54 (19.3)	
Stage 2 <sup>a</sup>	15 (5.3)	6 (2.1)	
Stage 3 <sup>a</sup>	42 (15.0)	18 (6.4)	
De novo dialysis, n (%) <sup>a</sup>	34 (11.8)	15 (5.2)	.005
Mean transvalvular gradient (mmHg ± SD)	13.2 ± 6.5	10.6 ± 6.4	<.0001
Peak transvalvular gradient (mmHg ± SD)	24.5 ± 11.1	19.5 ± 10.8	<.0001
ICU stay (days ± SD)	4.7 ± 9.6	3.2 ± 4.3	.012

SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation; PCI: percutaneous coronary intervention; ICU: intensive care unit; RBC: red blood cell; AKIN: Acute Kidney Injury Network.

<sup>a</sup>Excluding patients with previous dialysis. *p* values refer to McNemar test for dichotomous variables, Stuart–Maxwell test for categorical variables and *t*-test for paired sample for continuous variables.

<sup>b</sup>Excluding patients who did not receive red blood cell transfusion.

an increased risk of other major complications. Indeed, these results confirmed the particularly deleterious effect of severe haemodilution on post-operative renal function [26].

On the contrary, the risk of permanent pacemaker implantation (18.6% versus 3.0%,  $p < .001$ ), major vascular damage (5.7% versus 0.4%,  $p < .001$ ) and mild-to-severe paravalvular regurgitation (47.4% versus 9.3%,  $p < .001$ ) were significantly higher after TAVI compared with SAVR. At 3 years, TAVI was associated also with a significantly lower freedom from MACCE and a trend toward decreased survival. This is the first study comparing TAVI and SAVR in patients with anaemia and, therefore, no data are available to confirm and further interpret the present findings. We speculate that, despite the increased risk of bleeding and need of perioperative transfusion, conventional surgical treatment of severe aortic valve stenosis had a better survival and freedom from MACCE because of its related lower risk of paravalvular regurgitation and permanent pacemaker implantation. This may compensate for the higher renal risk related to haemodilution on

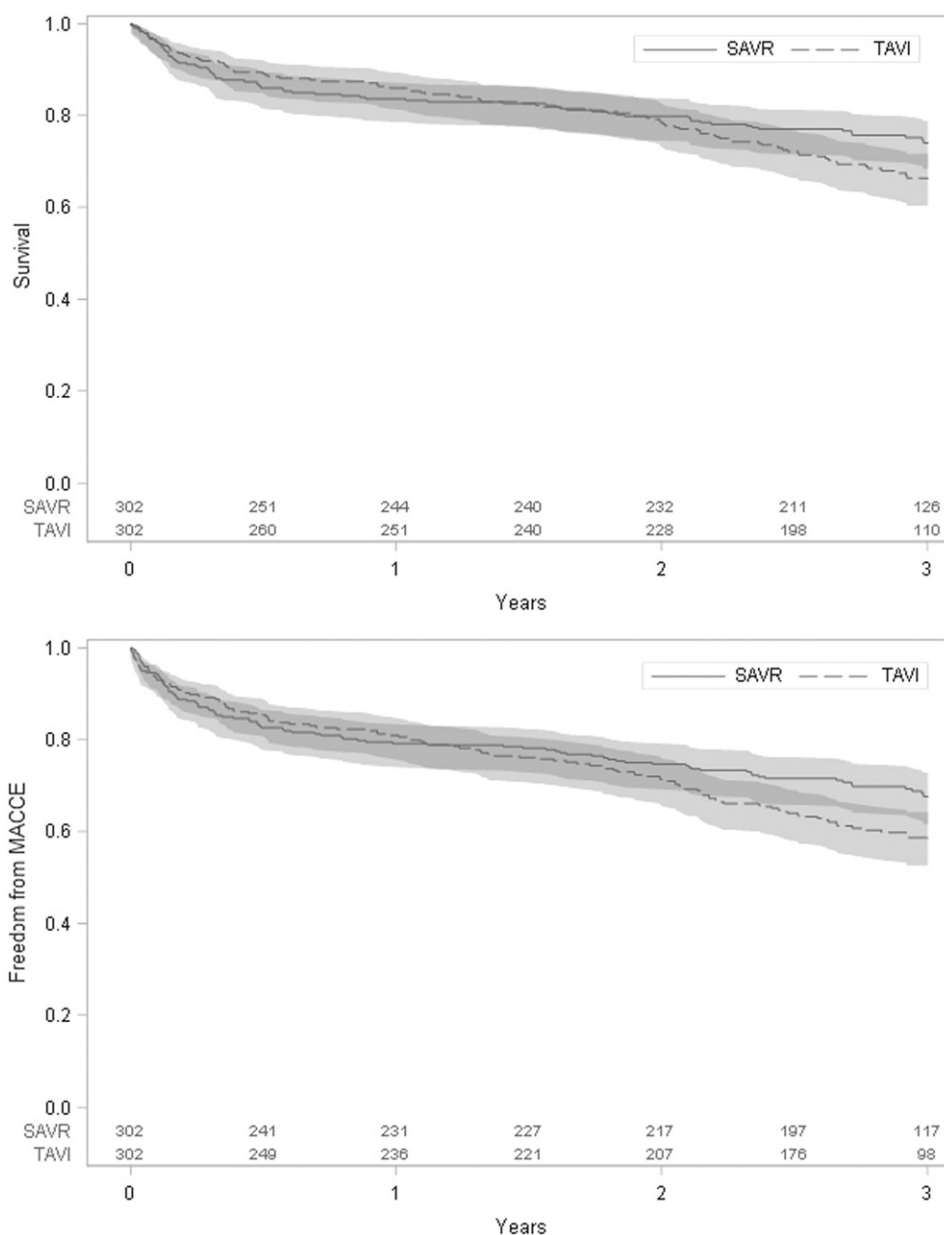
cardiopulmonary bypass. Furthermore, it is unclear whether these two treatment methods have a different impact on recovery of anaemia after aortic valve replacement. De Backer et al. [16] reported on anaemia recovery in only 40% of patients one year after TAVI. It is unknown whether paravalvular regurgitation, more frequently observed after TAVI, may have an effect on recovery of anaemia in these patients. On the contrary, SAVR has been shown to effectively revert coagulopathy and severe anaemia also in patients with Heyde's syndrome [27]. Further studies are needed to elucidate the effects of TAVI and SAVR on the recovery of anaemia and their impact on late outcome in anaemic patients.

### Study limitations

The results of this study can be affected by several limitations, which deserve to be acknowledged. First, this is not a randomised study and in order to compensate for the potential selection bias and differences in baseline characteristics we performed a propensity score matching. The results of propensity score matching may still be biased by confounders not taken into account in this study. However, conditions contraindicating SAVR were excluded from this analysis. Second, the definition of anaemia probably is not appropriate for patients undergoing major surgical procedures. However, the adopted cut-off of haemoglobin level has been widely in use in clinical research as a valid parameter for definition of anaemia and different degrees of anaemia were well balanced between the study groups. Third, we do not have data either on the perioperative nadir level of haemoglobin or after discharge. This limitation prevents analysis of the impact of severe perioperative anaemia and of persistent anaemia after the procedure on the early and late outcome. Fourth, this analysis does not take into account either any bleeding event or blood transfusion which might have resulted or worsened anaemia before TAVI and SAVR. Similarly, the lack of data on preoperative antithrombotic agents does not allow any analysis of the impact of these drugs on perioperative bleeding and other outcomes after TAVI and SAVR.

### Conclusions

In conclusion, the results of this study confirm that patients with anaemia have a poorer outcome after either TAVI or SAVR. The significant prevalence and negative prognostic impact of anaemia among patients requiring aortic valve replacement suggests



**Figure 2.** Intermediate survival (log-rank test by Klein–Moeschberger:  $p = .0075$ ) and freedom from major adverse cardiac and cerebrovascular events (MACCE) (log-rank test by Klein–Moeschberger:  $p = .0023$ ) in propensity score matched pairs of patients with anaemia after transcatheter (TAVI, dashed line) or surgical aortic valve replacement (SAVR, solid line) for severe aortic valve stenosis.

**Table 5.** Adverse events at 3 years after transcatheter (TAVI) and surgical aortic valve replacement (SAVR) in propensity score matched pairs of patients with anaemia.

Late events	SAVR, $n = 302$ (%)	TAVI, $n = 302$ (%)
Death from any cause	26.0	33.7
Stroke	6.9	12.2
Myocardial infarction	5.0	4.1
Coronary revascularization	2.3	1.4
MACCE	32.4	41.3

SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation; MACCE: major adverse cardiac and cardiovascular events (defined as the composite of death from any cause, stroke, acute myocardial infarction and/or coronary revascularization). Data are reported as actuarial estimates at the specific time point.

the urgent need of adequately performed studies to evaluate the benefit of preoperative optimisation of the haemoglobin level before TAVI and SAVR. The present results suggest that, despite a lower risk of perioperative blood transfusion and acute kidney injury, TAVI is not superior to SAVR in patients with anaemia.

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