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## Risk of acute kidney injury in patients with severe aortic valve stenosis undergoing transcatheter valve replacement

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### Abstract

**Background.** Transcatheter aortic valve implantation (TAVI) for high-risk and inoperable patients with severe aortic stenosis is an emerging procedure in cardiovascular medicine. Little is known of the impact of TAVI on renal function.

**Methods.** We analysed retrospectively renal baseline characteristics and outcome in 58 patients including 2 patients on chronic haemodialysis undergoing TAVI at our institution. Acute kidney injury (AKI) was defined according to the RIFLE classification.

**Results.** Fifty-eight patients with severe symptomatic aortic stenosis not considered suitable for conventional surgical valve replacement with a mean age of  $83 \pm 5$  years underwent TAVI. Two patients died during transfemoral valve implantation and two patients in the first month after TAVI resulting in a 30-day mortality of 6.9%. Vascular access was transfemoral in 46 patients and transapical in 12. Estimated glomerular filtration rate (eGFR) increased in 30 patients (56%). Fifteen patients (28%) developed AKI, of which four patients had to be dialyzed temporarily and one remained on chronic renal replacement therapy. Risk factors for AKI comprised, among others, transapical access, number of blood transfusions, postinterventional thrombocytopenia and severe inflammatory response syndrome (SIRS).

**Conclusions.** TAVI is feasible in patients with a high burden of comorbidities and in patients with pre-existing end-

stage renal disease who would be otherwise not considered as candidates for conventional aortic valve replacement. Although GFR improved in more than half of the patients, this benefit was associated with a risk of postinterventional AKI. Future investigations should define preventive measures of peri-procedural kidney injury.

**Keywords:** acute kidney injury; severe inflammatory response syndrome; transcatheter aortic valve implantation

### Introduction

Despite the proven benefit of surgical valve replacement, almost one-third of patients with severe valvular heart disease (VHD) do not undergo intervention because of end-stage disease, advanced age and multiple comorbidities, including chronic kidney disease (CKD) [1]. Transcatheter aortic valve implantation (TAVI) for high-risk patients has emerged as a new therapeutic option, first reported in 2002 by Cribier [2]. Meanwhile, more than 2000 TAVI have been performed using a transfemoral or a transapical approach in patients with an estimated excessive perioperative risk or in those with contraindications for conventional surgical aortic valve replacement [3–10]. Information about the impact of TAVI on renal function is scarce. Two studies have reported the necessity of renal replacement therapy (RRT) as a postoperative outcome in a total of 9 from 69 patients

being treated with haemofiltration [11,12]. In the study of Svensson, 15 out of 40 patients undergoing TAVI died. Six of these patients had renal failure [6]. In all of these reports, renal failure was not defined, pre-existing impaired renal function was not specified and information about pre- and postinterventional GFR in the remaining patients was missing. Thus, no systematic renal data in patients after TAVI are available. We therefore analysed our cohort of TAVI patients with respect to pre- and postinterventional renal function and assessed risk factors for acute kidney injury (AKI).

## Subjects and methods

From August 2007 to September 2008, TAVI was performed in 58 patients with severe symptomatic aortic stenosis not considered suitable for conventional surgical valve replacement (Table 1). The patients underwent diagnostic left and right heart catheterization prior to TAVI. Procedures were performed in the catheterization laboratory under local anaesthesia. Vascular access was obtained through the common femoral artery or through the ventricular apex using a 6 cm intercostal incision. In the case of transfemoral access, either a self-expanding valve prosthesis (CoreValve prosthesis, CoreValve Inc., Irvine, CA, USA) or a balloon-expandable (Edwards Lifesciences, Irvine, CA, USA) valve prosthesis was used. In the case of the transapical approach, balloon-expandable valve prosthesis (Edwards Lifesciences, Irvine, CA) was employed. The procedures were performed using high-quality fluoroscopic guidance with the use of non-ionic contrast media. The primary endpoint of the present study was renal outcome; secondary endpoints included 30-day mortality. Medical records were reviewed by F.A., an investigator independent of the cardiology and cardiovascular surgery team, for procedural success, mortality, hospitalization time, RRT, renal function, comorbidities, medication and routine laboratory investigations. Estimated glomerular filtration rate (eGFR) was calculated with the simplified Modification of Diet in Renal Disease (MDRD) formula. Urine analysis was performed on the day of admission with Combur10 Test®. AKI was defined according to RIFLE classification [13]. Due to incomplete data of urinary output, we did not include this variable for the purpose of classification. Creatinine concentrations before TAVI were available in all patients. Daily creatinine measurements were available on  $5.3 \pm 1.6$  days during the 7 day interval after TAVI. Proteinuria was defined as a protein concentration  $>15$  mg/dl in random urine samples. The need for dialysis was predicted according to the bedside risk algorithm of Mehta [14]. During the first 7 days after TAVI, blood count and C-reactive protein (CRP) were recorded. Thrombocytopenia was defined as a platelet count  $<140 \times 10^9/l$ . Leucocyte counts  $<4.0$  and  $>12$  were considered pathologic and possibly SIRS related.

Statistical analysis was performed with GraphPadPrism version 5.01 and SAS 9.2 for Windows (SAS Institute Inc., Cary, NC, USA); the Mann-Whitney *U*-test was applied for non-parametric data to compare groups; the chi-square analysis and Fischer's exact tests were considered for discrete data. Spearman's correlation coefficient was used to establish associations. Univariate and multivariate logistic regressions were done using the SAS logistic procedure. Stepwise selection was used for model selection.

## Results

TAVI was performed in 58 patients with severe symptomatic aortic stenosis not considered suitable for conventional surgical valve replacement (Table 1). Successful implantation of the device was achieved in 56 of 58 patients (97%). The mean aortic valve gradient declined from  $51.2 \pm 17$  mmHg to  $9.4 \pm 4.9$  mmHg. One patient required extracorporeal cardiac support during the intervention. Two patients died during the intervention. Another two patients died in the first 30 days after TAVI. Thirty-day mortality was 6.9% in all patients and 50% in patients with postoper-

**Table 1.** Baseline characteristics of the patients before transaortic valve implantation

Patients	All	With AKI	Without AKI
Number of patients	58	15	39
Age (years) (mean $\pm$ SD)	$83 \pm 5$	$83 \pm 6$	$83 \pm 5$
Female sex, <i>n</i> (%)	34 (59)	8 (53)	23 (59)
Hypertension, <i>n</i> (%)	49 (83)	14 (93)	31 (79)
Diabetes mellitus, <i>n</i> (%)	12 (21)	5 (33)	5 (13)
Coronary artery disease, <i>n</i> (%)	30 (52)	9 (60)	20 (51)
Peripheral vascular disease, <i>n</i> (%)	21 (36)	8 (53)	11 (28)
NYHA class I+II, <i>n</i> (%)	12 (21)	2 (13)	9 (23)
NYHA class III and IV, <i>n</i> (%)	46 (79)	13 (87)	30 (77)
Left ventricular EF%, (mean $\pm$ SD)	$49 \pm 15$	$49 \pm 17$	$49 \pm 15$
Logistic EuroSCORE%, (mean $\pm$ SD) <sup>a</sup>	$27 \pm 16$	$25 \pm 10$	$27 \pm 17$
Creatinine ( $\mu$ mol/l) (mean $\pm$ SD)	$123 \pm 88$	$123 \pm 72$	$104 \pm 42$
eGFR, ml/min/1.73 m <sup>2</sup> (mean $\pm$ SD)	$55 \pm 26$	$57 \pm 33$	$58 \pm 22$
eGFR $< 60$ ml/min/1.73 m <sup>2</sup> , <i>n</i> (%)	35 (60)	9 (60)	22 (56)
ESRD, before TAVI, <i>n</i> (%)	2 (0.04)	0	0
Proteinuria, $>150$ mg/l, <i>n</i> (%)	11 (19)	4 (27)	7 (18)
Predicted need for dialysis (%) (mean $\pm$ SD) <sup>b</sup>	$3.1 \pm 4.0$	$4.7 \pm 5.7^*$	$2.5 \pm 3.2$

A total of 58 patients were analysed. Two patients died during the procedure and two were already on chronic haemodialysis before the intervention. Thus, 54 patients were considered for the analysis of the impact of TAVI on renal function.

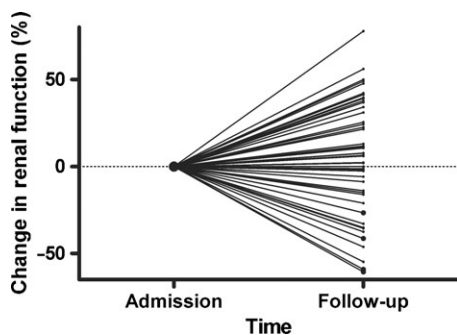
\**P*  $< 0.05$  in patients with AKI versus without AKI.

<sup>a</sup>Logistic EuroSCORE indicates the predicted mortality in case of cardiac surgery [25].

<sup>b</sup>Analysis without the two patients on dialysis.

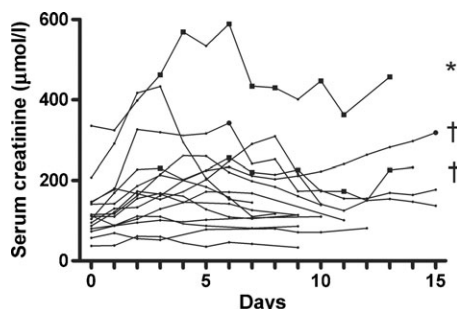
ative need for dialysis. The preprocedural renal function in the four patients who died in the first month was not lower than in those who did not die.

Two patients were on chronic haemodialysis prior to TAVI and survived the intervention without adverse events. Accordingly, 54 patients were available for the analysis of the impact of TAVI on renal function. From admission to Day 7 after TAVI, eGFR increased in 30 patients, declined in 21 and remained unchanged in 3 patients (Figure 1). Following TAVI, 15 of 54 patients (28%) developed AKI according to the RIFLE criteria. The baseline characteristics of the patients with and without AKI were comparable except for a significantly higher predicted probability of postoperative need for dialysis [14] (Table 1). According to the RIFLE criteria, seven patients were at risk (13.0%), four patients had injury (7.4%) and four showed failure (7.4%). The time course of renal function after TAVI in patients with AKI is shown in Figure 2. Three patients with failure and one with injury (hypervolaemia) had to undergo dialysis. One of these four patients remained on chronic haemodialysis therapy and two died. The valve was replaced more frequently by the transapical approach in patients who subsequently developed AKI (Table 2). As compared with patients



**Fig. 1.** Percentage change of renal function (eGFR) from the day before the intervention and Day 7 after TAVI, or at discharge if earlier, in all 54 patients analysed for the impact of TAVI on renal function. GFR increased in 30 patients, declined in 21 and remained unchanged in 3 patients. ● indicates the patients with dialysis treatment after TAVI.

without AKI, patients with AKI had a higher maximal postinterventional serum creatinine concentration, lower minimal eGFR and a more pronounced decline in eGFR. Patients with AKI had a lower haemoglobin concentration, received a higher number of blood cell transfusion units, encountered more frequently thrombocytopenia postpro-



**Fig. 2.** Time course of renal function as assessed by serum creatinine concentration after TAVI in the 15 patients with AKI. ■ indicates days on which haemodialysis was performed; † indicates patients who died during hospitalization; \*patient remained on chronic haemodialysis after TAVI.

cedurally, had a higher incidence of pathological leucocyte count compatible with SIRS and an increased length of hospital stay (Table 2). Volume of contrast media used ( $242 \pm 101$  ml versus  $262 \pm 104$  ml), procedural success (100% versus 100%), preinterventional ( $45 \pm 16$  mmHg versus  $52 \pm 16$  mmHg) and postinterventional aortic valve gradients ( $9.7 \pm 5.7$  mmHg versus  $9.4 \pm 4.8$  mmHg), maximal postinterventional CRP concentrations ( $126 \pm 77$  mg/l versus  $101 \pm 66$  mg/l) and 30-day mortality (13.3% versus 0%) were not statistically significantly different in patients with AKI than in those without it.

Univariate logistic regression analysis revealed a possible association of AKI with the apical versus transfemoral approach ( $P < 0.003$ ), thrombocytopenia ( $P < 0.02$ ), administered blood cell transfusion units (0 versus 1 to 2 versus  $>3$ ,  $P < 0.02$ ), pathological leucocyte count ( $P < 0.002$ ) and CRP concentration on Day 1 after TAVI ( $P < 0.06$ ). The small number of studied patients limited the possibilities for extensive multivariate regression analysis. Nevertheless, combining all the above-mentioned variables into a multivariate logistic regression model and using stepwise selection revealed that AKI was definitively related to the apical approach ( $P < 0.03$ ), thrombocytopenia ( $P < 0.03$ ) and pathological leucocyte count ( $P < 0.01$ ). A significant correlation was found between the minimal postinterventional thrombocyte count and change in eGFR from Day 2 compared to baseline ( $r = 0.37$ ,  $P = 0.0079$ ).

## Discussion

TAVI is a new treatment option for patients with severe aortic stenosis at an increased risk for conventional surgery [3–9]. In the present study, we analysed renal outcome in 54 high-risk patients undergoing TAVI at a single centre. Two patients on chronic haemodialysis were also followed up. Both patients were successfully treated. Based on the available literature, a total of three dialysis patients have previously been reported treated with TAVI; the survival

**Table 2.** Outcome after transcatheter valve replacement

Patients	All	With AKI	Without AKI	<i>P</i> -value <sup>a</sup>
Number of patients	58	15	39	
Renal function				
Maximal serum creatinine ( $\mu\text{mol/l}$ ) (mean $\pm$ SD)	$163 \pm 130$	$239 \pm 143$	$111 \pm 48$	0.0003
Minimal GFR, ml/min/1.73 m <sup>2</sup> (mean $\pm$ SD)	$46 \pm 24$	$30 \pm 22$	$54 \pm 21$	0.001
Decrease in GFR (%) (mean $\pm$ SD)	$18 \pm 22$	$49 \pm 14$	$6 \pm 8$	$<0.0001$
Access				
Transfemoral, <i>n</i> (%)	46 (79)	8 (53)	36 (92)	0.003
Transapical, <i>n</i> (%)	12 (21)	7 (47)	3 (8)	0.003
Minimal haemoglobin (mg/dl) (mean $\pm$ SD)	$93 \pm 13$	$88 \pm 9$	$96 \pm 14$	0.02
Transfusion units, <i>n</i> (mean $\pm$ SD)	$2.1 \pm 3.9$	$3.7 \pm 4.2$	$1.7 \pm 3.9$	0.007
Minimal thrombocyte count, 10 <sup>9</sup> /l (mean $\pm$ SD)	$139 \pm 60$	$114 \pm 30$	$150 \pm 67$	0.04
Thrombocytopenia, <i>n</i> (%)	34 (59)	13 (87)	19 (49)	0.01
Pathological leucocyte count, <i>n</i> (%)	23 (41)	10 (67)	11 (28)	0.01
Days of hospitalization, median (range)	11 (5–50)	18 (10–50)	11 (5–32)	0.0003

A total of 58 patients were analysed. Two patients died during TAVI and two were already on chronic haemodialysis before the intervention. Thus, 54 patients were considered for the analysis of the impact of TAVI on renal function.

<sup>a</sup>*P* AKI versus without AKI.

<sup>b</sup>Leucocyte count  $>12$  G/l and  $<4$  G/l were considered pathologic.

rate could not be derived from the publications [11,12]. Given the limited number of dialysis patients undergoing treatment with TAVI, the utility of TAVI as a treatment option has to be determined in a prospective study in dialysis patients. Severe aortic stenosis with left ventricular failure is one mechanism responsible for an impaired glomerular filtration rate. Unsurprisingly, eGFR was higher in more than one-half of the patients 7 days after the procedure, and TAVI has to be considered as a useful therapeutic option to improve renal function in this patient population. Conversely, TAVI may impair renal function, either transiently or definitely, in some patients. About one-fourth of our patients developed AKI and 7.4% required RRT. In comparison, the need for RRT in surgical aortic valve replacement is estimated to be 4.5% [15]. This population is not comparable with our patients as comorbidities and pre-existing CKD were more frequently observed in our population.

As compared with the transfemoral technique, the transapical approach was more often associated with AKI. Given the small number of patients, we can only speculate on the mechanisms for this difference. The most likely explanation is more prominent generalized arteriosclerosis and more advanced disease in transapical patients, since tortuous iliac vessels not allowing safe peripheral arterial catheterization, excessive calcification of the ascending aorta or the aortic arch was the reason for choosing the transapical approach.

Platelets decreased significantly in all patients after TAVI. The platelet count correlated with the decrease in GFR, and minimal postprocedural platelet counts were significantly lower in patients with AKI than without. Moreover, thrombocytopenia was an independent risk factor for AKI in multivariate analysis. Thrombocytopenia is a well-known feature after cardiovascular surgery, mainly attributed to mechanical destruction of platelets, haemodilution in the extracorporeal circuit (ECC), drugs and intravascular coagulation [16]. The incidence of acquired thrombocytopenia in our patients was high (59%) and in line with the high incidence of thrombocytopenia observed in a group of 25 patients undergoing percutaneous CoreValve implantation with extracorporeal percutaneous femoro-femoral bypass [9]. In the latter group, one patient died of fatal disseminated intravascular coagulation. Our patients, however, had no cardiopulmonary bypass support except for one. Intravascular coagulation is an established mechanism for AKI. Thus, it is a potential mechanism accounting for AKI in the present cohort probably induced by the valve itself. We cannot rule out that the lower thrombocyte counts in AKI patients are caused by the larger periprocedural blood loss, as AKI patients had a higher amount of transfusion units. Blood transfusion is a known risk factor for AKI [17,18]. In the present study, however, neither minimal postinterventional haemoglobin nor the amount of transfused units were related to AKI in the multivariate analysis. Thus, we do not consider blood loss to be the main cause of AKI in our patients.

Another potential mechanism for AKI is SIRS. Following TAVI, some patients had fever without clear focus and all patients showed an increase in CRP concentrations (mean  $\pm$  SD CRP concentration before TAVI  $12 \pm 18$  mg/dl versus after TAVI  $108 \pm 69$  mg/dl,  $P < 0.0001$ ). This increase

in CRP was higher than that reported after percutaneous coronary intervention ( $\sim 2$  mg/dl) and surgical valve replacement ( $\sim 66$  mg/dl) [19–21]. Moreover, a pathological leucocyte count as seen in SIRS was an independent risk factor for AKI in multivariate analysis. The mechanisms for these observations are not known and therefore must be investigated in the future.

Patients were not evaluated prospectively for typical clinical findings of atheroembolism and eosinophilia after the intervention was assessed only in some of the patients. Thus, we can only speculate whether atheroembolism was another cause of AKI in some patients.

The mechanisms of AKI following TAVI deserve consideration for future preventive strategies. First, contrast media with the potential to induce acute tubular necrosis should be used at low doses. Intravenous hydration, an established preventive measure for contrast media nephrotoxicity, is probably not applicable given the restricted cardiac performance of these patients. Although controversial, immediate dialysis after the interventions might be an option for reducing contrast media toxicity [22–24]. Second, the mechanism of SIRS in this subset of patients is unclear and should be elucidated. Third, the requirement for blood cell transfusions has to be diminished.

In conclusion, the present observation demonstrates that transcatheter aortic valve implantation is feasible in patients not qualifying for open heart surgery, including patients on haemodialysis, with a high rate of procedural success and a 30-day mortality lower (7%) than predicted by risk scores (27%). Improvement of eGFR was seen in the majority of patients. The incidence of AKI (27%) was associated with the transapical approach, requirement of blood transfusions, thrombocytopenia, pathological leucocyte counts and SIRS. Future investigations have to focus on the preventive mechanisms for AKI in patients who should receive this promising alternative and less invasive valve replacement procedure.

*Conflict of interest statement.* P.W. and S.W. received a consultant fee from CoreValve Inc., Irvine, CA, USA. The results presented in this paper have not been published previously in whole or part.

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## The Hannover Dialysis Outcome study: comparison of standard versus intensified extended dialysis for treatment of patients with acute kidney injury in the intensive care unit

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### Abstract

**Background.** Increasing the dose of renal replacement therapy has been shown to improve survival in critically ill patients with acute kidney injury (AKI) in several smaller European trials. However, a very recent large multicentre

trial in the USA could not detect an effect of dose of renal replacement therapy on mortality. Based on those studies, it is not known whether a further increase in dialysis dose above and beyond the currently employed doses would improve survival in patients with AKI. We therefore aimed to