



Research Article

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Improvement in renal functions with transcatheter aortic valve implantation

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Abstract

Background & Objectives In recent years, emerging transcatheter aortic valve implantation (TAVI) has become an alternative for surgery. However, with advanced age, several co-morbid factors together with contrast agent usage can cause deterioration in renal function and increase in the risk of acute kidney injury (AKI) with poor prognosis in patients with AKI. Therefore, many patients cannot benefit from this treatment. In this study, we aim to examine the effects of TAVI on renal functions. **Methods and Results** Seventy patients, mean age of 77.6 years, underwent TAVI between July 2011 and December 2012. Estimated glomerular filtration rate (eGFR) was calculated by using the Cockcroft and Gault Formula. Patients were monitored for 48 h for urine output. Stage 1 AKI, according to the VARC-2 AKIN system, developed in only five (7.1%) of the patients after the procedure. There was a statistically significant increase between the mean 1st month eGFRs before (68.2 vs. 61.0, $P < 0.01$) and after (68.2 vs. 63.6, $P < 0.05$) the TAVI in the cohort. After TAVI (48.5 mL/min, $P < 0.01$) and the 1st month (52.1 mL/min, $P < 0.01$), the eGFR of the 36 (51.4%) patients diagnosed with chronic kidney disease before the procedure showed a statistically significant increase in renal functions. The hospital mortality rate was higher in the group which developed AKI ($P < 0.01$). First month eGFR showed a more statistically significant increase than pre-TAVI eGFR (62.8 and 69.8, $P < 0.05$, respectively) in AKI developing patients and this difference - though statistically not significant - continued into the sixth month. **Conclusions** In this study, we showed that the treatment of aortic stenosis through TAVI allows improvement of renal functions, and that AKI rates will be lower with careful patient selection, proper pre-procedural hydration, and careful use of contrast agent.

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1 Introduction

With increasing life expectancy, the prevalence of aortic stenosis (AS) also increases. Surgical aortic valve replacement (s-AVR) is performed with lower operative mortality in the absence of serious co-morbid conditions with both a recovery in symptoms and prolonged life expectancy observed in patients who undergo s-AVR. Nonetheless, 30% of patients cannot undergo AVR due to left ventricular dysfunction, advanced age and co-morbid conditions.^[1,2] Transcatheter aortic valve implantation (TAVI), first performed on a human being in 2002, developed rapidly and has be-

come an important treatment option for inoperable, or high-risk AS patients. According to Placement of AoRtic TraNscathetER Valves (PARTNER), in the only randomized clinical study conducted on this subject, TAVI is superior to medical treatment in inoperable patients and it is an important alternative for s-AVR in high-risk patients.^[3,4]

Although it is a less invasive procedure than surgery, the risk of acute kidney injury (AKI) has increased due to several co-morbidities, such as advanced age, diabetes mellitus (DM), peripheral arterial disease, hypertension; besides coronary angiography (CAG), multi-slice computed tomography (MSCT) and contrast agents used during the procedure. Some studies showed that after s-AVR, AKI is observed at 25% and is related to poor clinical course.^[5,6] In recently studies, AKI is detected in 12%–57% of patients and associated with a 2–6 fold increase in the mortality rate in the short-long term follow up.^[3,4,7–9] Nevertheless, the wide incidence of AKI is that there are several definitions for AKI. In the PARTNER study, this rate also ranges

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Table 1. Acute kidney injury (VARC-2 AKIN classification).

| | |
|---------|---|
| Stage 1 | At serum creatinine: 150%–199% (1.5–1.99 increase for basal) or increase 0.3 mg/dL or urine output < 0.5 mL/kg per hour within > 6 h and < 12 h |
| Stage 2 | At serum creatinine: 200%–299% (2.0–3.0 increase for basal) or urine output < 0.5 mL/kg per hour within > 12 h and < 24 h |
| Stage 3 | <p>At serum creatinine: ≥ 300% (2.0–2.99 increase for basal) or with at least 0.5 mg/dL increase in serum creatinine ≥ 4.0 mg/dL</p> <p>Urine output < 0.3 mL/kg per hour at the end of ≥ 24 h</p> <p>Anuria after ≥ 12 h</p> <p>Creatinine increase must be within 48 h</p> <p>Stage 3 must be accepted regardless other criteria in patients performed renal replacement treatment</p> |

between 1.1% and 28% (AKI creatinine > 3 mg/dL).^[3,4] Therefore, the original Valve Academic Research Consortium (VARC) definition, which uses the modified RIFLE criteria (risk (R), injury (I), and failure (F), sustained loss (L) and end-stage kidney disease (E)), is suggested for AKI.^[10] However, the later RIFLE version modified with VARC-2 and the new Acute Kidney Injury Network (AKIN) system which includes Kidney Disease Improving Global Outcomes (KDIGO) that is accepted by nephrology communities are recommended (Table 1).^[11]

In this study, we aimed to evaluate the renal functions with TAVI and the effects of proper patient selection, the timing of hydration and the procedure, and the effect of the TAVI procedure on renal functions in patients with severe AS.

2 Methods

In our clinic, patients with AS were evaluated by the heart team and were excluded for TAVI according to logistic EuroSCORE or Society of Thoracic Surgeons (STS) score and the European and American guidelines.^[12,13] These exclusion criteria are the following: estimated life expectancy < 1 year, improvement of quality of life by TAVI unlikely because of co-morbidities, severe primary associated disease of other valves with a major contribution to the symptoms of the patient, that can be treated only by surgery, inadequate annulus size (< 18 mm, > 29 mm), thrombus in the left ventricle, active endocarditis, elevated risk of coronary ostium obstruction, plaques with mobile thrombi in the ascending aorta, or arch, for transfemoral/subclavian approach: inadequate vascular access (vessel size, calcification, tortuosity).^[12] TAVI was performed on 70 patients with high-risk for s-AVR, or were inoperable, due to severe calcified AS and co-morbid reasons between July 2011 and December 2012. All of the TAVI patients in-

cluded in the study for evaluating renal functions. Transthoracic echocardiography (TEE) was applied to 68 patients before the procedure. Two patients were excluded for TEE because one of them suffered from esophageal stricture and the remaining had esophageal varicose. TAVI was considered to be appropriate for the patients by the heart team. All the patients were informed in advance and ethical approval (approval number 2011–68) was obtained from the ethics committee of the hospital.

Estimated glomerular filtration rate (eGFR) was calculated by measuring the serum creatinine (SCr) before the procedure, 48 h after the procedure, 1–6 and 12th months and applying the Cockcroft and Gault formula^[14] (CGF, eGFR: (140–age) × bodyweight / 72 × SCr (for women × 0.85)). Patients were monitored for 48 h for urine output. Chronic kidney disease (CKD) was described as eGFR < 60 mL/min. AKI was defined according to the AKIN system (Table 1) in the latest VARC-2 classification. Before TAVI, all patients were applied TEE and MSCT and the valve morphology, aortic annulus, coronary ostium-annulus distance, calcification, situation of peripheral arteries and whether there additional pathology were assessed. The patients were applied peripheral aorta-ilio-femoral angiography, MSCT and TAVI by using non-ionic lower osmolar radio-iodine contrast agent with at least two days intervals in line with their basal renal functions. Before the contrast treatment, metformin treatment was discontinued for the patients with diabetes and for those who had heart failure one day before and one day after the procedure, 50 mL/h intravenous saline infusions were applied. To those who didn't have heart failure, saline infusion rate was 100 mL/h. Four patients were applied subclavian TAVI, one was applied transaortic TAVI, and 65 were applied transfemoral TAVI. TAVI was applied to 66 patients under general anesthesia, four patients were applied under local anesthesia. In 58 cases, a vascular closure device was used and in the

rest, surgical cut-down was applied. During the procedure, the active clotting time of the patients was heparinized so that it would be 250–300 s. Aortic arch angiography was applied for a suitable valve implantation position. But before the TAVI, the suitable position was assessed by TEE and MSCT in order to lessen the amount of contrast used in the aortic arch angiography. On 44 patients, 23 mm, 25–26 mm, and 29 mm Edwards SAPIEN XT (Edwards Lifesciences, Irvine, CA, USA) valves were used. After the TAVI, the patients were applied control peripheral aorta-ilio-femoral angiography.

Statistical analysis was performed using SPSS 17.0 statistical software packages (SPSS Inc., Chicago, IL, USA). Continuous variables were compared using the unpaired *t*-test for parametric variables or the Mann–Whitney *U*-test for non-parametric variables, respectively. Descriptive statistics for categorical data of groups were compared with the Fisher's exact test. Data were expressed in dependency on the test used as the mean \pm SD (parametric), median and 25th and 75th percentiles (non-parametric) or *n* (%) (categorical data), whereas figures represent the mean \pm SE of mean. Odds ratios (OR) and corresponding 95% confidence intervals (95% CI) are reported, *P* < 0.05 was considered statistically significant.

3 Results

Seventy patients have undergone TAVI in our clinic. The group consisted of 51 females and 19 males. The patients' basic characteristics and data about TAVI procedure are given in Table 2. The average valve area was determined as 0.6 cm² and mean gradient was 52.8 mmHg in echocardiography. The average STS score of the patients was 7.7, mean logistic EuroSCORE was 21.7%, and 85% of them were in moderate and high risk groups according to SUR-TAVI risk model. The mean age was 77.6 years and 67.1% of them had coronary artery disease, 80.0% had hypertension, 41.4% had peripheral artery disease, and 27.1% had DM. The average follow-up period was 9 months (1–17 months). In terms of renal functions, six months of follow-up period was assessed. The mean usage of contrast agents during the TAVI procedure was 209.5 mL and discharge time was 5.5 days. Stage 1 AKI according to VARC-2 AKIN system developed in only five (7.1%) of the patients after the procedure. One of these patients was the transaortic TAVI. The patients were divided two groups: AKI group and non-AKI group. No statistically significant difference was observed between the baseline characteristics and procedural features of AKI group and non-AKI group (Table 2). The patients' average mean aortic valve gradient

was 9.2 mmHg after the TAVI. No moderate, or severe, paravalvular aortic regurgitation was detected. There was no incidence of stroke pre- and post-TAVI. The surgical closure for femoral artery was applied on 14% patients. There were peripheral artery complications which were managed well in 4 patients (2 dissections, 2 hematomas). Four patients need pacemaker implantation after TAVI. After the procedure, there were 5 mortality cases (3 during the procedure), and 2 patients died of non-cardiac reasons within 30 days. Two of these five patients were in the group AKI. In the non-AKI group, 30% of the patients received blood transfusions, while in the AKI group the percentage was 20% (one patient). In the non-AKI group, 17.7% of the patients undergoing blood transfusion were given more than \geq 2 units of erythrocyte suspension. None of the patients after the TAVI needed renal replacement therapy. Mean SCr of all patients pre and post-TAVI were 1.02 ± 0.4 mg/dL and 0.98 ± 0.3 mg/dL, respectively and there was no statistically difference (*P* = 0.13). The mean eGFR of pre- and post-TAVI were 59.5 ± 21.1 and 62.0 ± 21.4 , respectively, with no statistically difference (*P* = 0.11). However, there was a statistically significant increase between the mean eGFR of patients who reached one month in the follow-up period and mean eGFR of pre-TAVI (68.2 and 61.0, *P* = 0.005) and post-TAVI (68.2 and 63.6, *P* = 0.03). Also, when compared the AKI groups with non-AKI ones, we see that there was no significant difference between any parameter, except post-TAVI eGFR (63.9 ± 20.9 vs. 41.38 ± 12.8 , *P* = 0.01). The post-TAVI difference between eGFRs of both groups is not seen in the first and sixth months (Table 3 and Figure 1). So, an improvement in renal functions was observed in the first month in all patients. This recovery was also observed in the group with worse renal functions before TAVI. Mean eGFR of the 36 patients (51.4%) who were defined as CKD was 42.8 mL/min. Post-TAVI (48.5 mL/min, *P* = 0.004) and 1st month (52.1 mL/min, *P* < 0.0001) eGFRs showed statistically significant increase in this group of patients as well. In-patient mortality rate had higher statistically significance in the group developing AKI (non-AKI: 4.6% vs. AKI: 40%, *P* = 0.003). Three patients who developed AKI and were discharged did not develop any in-hospital complications, and the eGFR at the 1st month showed statistically significant increase compared to pre-TAVI eGFR (62.8 and 69.8, *P* = 0.04). This difference continued in the sixth month although not statistically significant. This indicates that, though patients with deteriorating renal functions in the post-TAVI period have a higher risk of complication, if AS is fixed in the follow-up period, their renal functions seem to improve.

Table 2. Basal characteristics and procedural features.

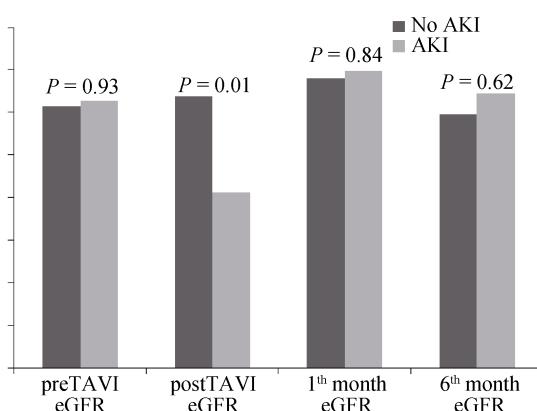
| Characteristics | All patients n = 70 | Non-AKI n = 65 | AKI n = 5 | P value |
|---|------------------------|-------------------|--------------|---------|
| Male/Female | 19/51 | 19/46 | 0/5 | 0.15 |
| Age, yrs | 77.6 | 77.5 | 78.2 | 0.84 |
| BMI, kg/m ² | 27.6 | 27.8 | 25.3 | 0.54 |
| NYHA class II, n | 7 | 7 | 0 | |
| NYHA III, n | 47 | 44 | 3 | 0.52 |
| NYHA IV, n | 16 | 14 | 2 | |
| STS | 7.7 | 7.8 | 5.4 | 0.32 |
| SURTAVI, n | | | | |
| Lower risk | 10 | 9 | 1 | |
| Middle risk | 18 | 17 | 1 | 0.91 |
| High risk | 42 | 39 | 3 | |
| EuroScore, % | 21.7 | 22 | 16.8 | 0.48 |
| Concomitant co-morbid situations, % | | | | |
| Coronary artery disease | 67.1 | 67.3 | 60 | 0.97 |
| Hypertension | 80 | 78.5 | 100 | 0.26 |
| Diabetes mellitus | 27.1 | 27.7 | 20 | 0.71 |
| Hyperlipidemia | 45.7 | 46.2 | 40 | 0.79 |
| Smoker | 17.1 | 18.5 | 0 | 0.29 |
| COPD | | | | |
| Mild | 31.4 | 32.3 | 20 | |
| Moderate | 40 | 41.5 | 20 | 0.26 |
| Severe | 28.6 | 26.2 | 60 | |
| Peripheral artery disease | 41.4 | 43.1 | 20 | 0.31 |
| Atrial fibrillation | 24.3 | 26.2 | 0 | 0.18 |
| Echocardiography parameters | | | | |
| TEE aortic annulus diameter, cm | 20.1 | 20.9 | 20.3 | 0.34 |
| Maximal gradient, mmHg | 85.2 | 84.3 | 97.2 | 0.13 |
| Mean gradient, mmHg | 52.8 | 52.3 | 58.4 | 0.33 |
| LVEF, % | 54.5 | 54.1 | 60.6 | 0.32 |
| AVA, cm ² | 0.6 | 0.6 | 0.5 | 0.15 |
| Aortic regurgitation (advanced), n | 1 | 1 | 0 | 0.93 |
| Peak systolic pulmonary arterial pressure, mmHg | 46.2 | 45.4 | 55 | 0.10 |
| Procedural features | | | | |
| Local anesthesia | 4 | 4 | 0 | 0.56 |
| Femoral approach method, % | | | | |
| Vascular closure | 82.8 | 90 | 60 | 0.52 |
| Surgery cut-down | 17.2 | 10 | 0 | |
| Subclavian approach, n | 4 | 4 | 0 | |
| Transaortic approach, n | 1 | 0 | 1 | |
| Valve size, n | | | | |
| 23 mm | 44 | 40 | 4 | |
| 26 mm | 25 | 24 | 1 | 0.70 |
| 29 mm | 1 | 1 | 0 | |
| Process period, min | 67 | 76.3 | 60.5 | 0.35 |
| Mean, mL | 209.5 | 209 | 210 | 0.98 |
| Transfusion after process, % | 28.6 | 30 | 20 | 0.63 |
| ≥ 2 unit erythrocyte suspension | 17.9 | 17.7 | 20 | 0.40 |
| Discharging period after treatment, day | 5.5 | 5.6 | 4.3 | 0.51 |

AVA: aortic valve area; BMI: body mass index; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; STS: Society of Thoracic Surgeons; TEE: transesophageal echocardiography.

Table 3. Comparing renal functions between groups.

| | All patients, n = 70 | Non-AKI, n = 65 | AKI, n = 5 | P |
|------------------------------------|-------------------------|--------------------|---------------|------|
| SCr before TAVI, mg/dL | 1.0 ± 0.4 | 1.03 ± 0.4 | 0.83 ± 0.2 | 0.25 |
| eGFR before TAVI, mL/min | 59.5 ± 21.1 | 61.5 ± 26.4 | 62.8 ± 22.7 | 0.93 |
| SCr after TAVI, mg/dL | 0.98 ± 0.3 | 0.96 ± 0.4 | 1.22 ± 0.2 | 0.14 |
| eGFR after TAVI, mL/min | 62.0 ± 21.4 | 63.9 ± 20.9 | 41.3 ± 12.8 | 0.01 |
| 1 st month SCr, mg/dL | 0.97 ± 0.3 | 0.93 ± 0.3 | 0.80 ± 0.1 | 0.34 |
| 1 st month eGFR, mL/min | 68.2 ± 24.3 | 68.1 ± 24.9 | 69.8 ± 3.7 | 0.84 |
| 6 th month SCr, mg/dL | 1.0 ± 0.4 | 1.0 ± 0.4 | 0.97 ± 0.2 | 0.59 |
| 6 th month eGFR, mL/min | 59.8 ± 19.2 | 59.5 ± 19.5 | 64.5 ± 6.7 | 0.62 |

Data are presented as mean ± SD. AKI: Acute kidney injury; eGFR: estimated glomerular filtration rate; SCr: Serum Creatinine; TAVI: transcatheter aortic valve implantation.

**Figure 1.** Comparing renal functions between groups with and without AKI. AKI: acute kidney injury; eGFR: estimated glomerular filtration rate; TAVI: transcatheter aortic valve implantation.

4 Discussion

In our study, we determined the post-procedure rate of AKI according to VARC-2 AKIN system as 7.1%. In our assessment which involved all the patients, we found that after the TAVI on renal functions, eGFR showed a statistically non-significant increase and that there was a statistically significant increase in the 1st month. Besides, it has been determined that this improvement in renal functions is more prominent in the group of patients who are regarded as the CKD. Furthermore, it is shown that with the removal of AS from the group that developed AKI after the TAVI, a significant improvement in renal function was achieved in the 1st month.

AS is a degenerative disease whose prevalence among the elderly is growing gradually, and decreases life expec-

tancy once it has become symptomatic. Its definite treatment is aortic valve replacement. However, due to frequent co-morbid conditions with advanced age, the rate of patients who cannot undergo s-AVR is between 30% and 40%.^[1,2] First application on human beings started in 2002, and quickly reached place in the real world, TAVI took its place on the latest valve guide of European Society of Cardiology (ESC) as an alternative for s-AVR in high-risk patients.^[12] Despite all these developments, some groups of patients cannot get enough benefit from this treatment due, especially, to the presence of many co-morbid conditions that cause renal dysfunction with advanced age, and leads to avoidance from performing on these patients. About patients who carry many risk factors for development of AKI which is a sign of post-procedure poor prognosis, we need to be careful in appropriate patient selection, adequate hydration, and careful use of contrast to minimize the risk. In PARTNER, which is the only available randomized controlled study, patients with serious renal failure are excluded and there is insufficient data about them. Incidence of AKI in different proportions is determined due to the inefficiency in the definition of AKI. AKI incidence rate ranging from 12%–57% is determined as 21% in a new multi-centered study involving 995 patients.^[15] We determined the AKI incidence at a relatively lower level than many other studies (7.1%) by using the latest VARC-2 AKIN criteria, and none of our patients needed renal replacement. It is clearly shown in many studies that AKI causes serious increase in morbidity and mortality in patients who underwent TAVI.^[3,5,8,16,17] In our study, 2 out of 5 patients who developed AKI showed in-hospital mortality.

Though the underlying reason for AKI is unknown, its results appear from the cumulative effect of many factors. These factors are: contrast induced nephropathy, hemodynamic instability during in-procedure and post-procedure rapid pacing, calcification during valve implantation or cholesterol embolism, vascular bed catheter manipulations and blood transfusion.^[16,18–20] In addition to these, advanced renal reserve due to advanced age and renovascular atherosclerosis, decreased renal perfusion depending on AS and the use of diuretic and vasoactive agents are other co-morbid factors. Furthermore, the reported results support underlying patho-physiological cardio-renal syndrome (CRS). CRS occurs when acute or chronic heart, or kidney, disorder affects the other organ hemodynamically and neurohormonally. Type 2 CRS is characterized with the progressive renal dysfunction caused by cardiac dysfunction. Severe AS and low cardiac output and the decrease in renal perfusion activate the renin-angiotensin-aldosterone system and cause systemic inflammation, increased sympathetic activation, re-

duction of nitric oxide, endothelial dysfunction, tissue hypoperfusion and renal parenchymal fibrosis.^[20] Intervention in AS stops this procedure and provides progression in renal functions. In our study, in the 1st and 6th months after TAVI, improvement in renal functions was recorded both the overall patients and the group developing AKI and also in the CKD group who initially had poor renal functions. The mechanisms of the growth in morbidity and mortality are: (1) fluid retention with AKI, (2) metabolic acidosis and cardiac dysfunction, and (3) arrhythmia caused by electrolyte imbalance (type 3 CRS). Although contrast agents are important risk factors, no difference in terms of amount of contrast was determined in both of our patient groups. We use the methods of TEE, MSCT and aortic arch angiography to determine a suitable position for the valve. We are trying to decrease the amount of contrast agents in the aortic arch angiography by evaluating both TEE and MSCT very well. Also, CAG, MSCT and TAVI procedure are conducted in separate sessions, and with proper hydration depending on the state of renal function. Another important AKI risk factor shown in many studies is transapical approach.^[17,20,21] Diffuse atherosclerosis, calcification embolism, anesthesia and procedure related hypotension in transapical procedures increase this risk. Although we did not have any transapical procedures in our study, one of the patients developing AKI was one performed with transaortic approach. Though blood transfusion was a serious risk factor, the number of patients developing AKI was limited and there was no difference in blood transfusion between the two groups. Careful patient selection is necessary in terms of blood transfusion for these patients.

In conclusion, TAVI is a developing treatment method that promises to create an alternative for surgery in the treatment of patients with symptomatic and severe AS. It will be applied more safely when the advancements in technology bring better closure systems, procedural techniques and peri-procedural treatments. With this study, we showed that AS treatment by TAVI improves renal functions and AKI rates decrease by careful patient selection, proper pre-procedural hydration, and careful use of contrast. However, the reliability of TAVI will be more clearly revealed with randomized, controlled studies involving more patients and longer follow up periods.

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