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Renal function changes associated with transcatheter aortic valve-in-valve for prosthetic regurgitation compared to stenosis☆

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ABSTRACT

Background: Renal dysfunction is frequently encountered in patients with aortic prosthesis degeneration requiring valve-in-valve (VIV) transcatheter aortic valve replacement (TAVR). The effect of VIV TAVR on renal function in patients with bioprosthetic aortic regurgitation (AR) and stenosis (AS) is unknown.
Objectives: The aims of this study were to describe the change in renal function after VIV TAVR and to compare differences in renal function changes in those with predominant prosthetic regurgitation compared to stenosis.
Methods: All VIV TAVR between June of 2014, and October 2019 (n = 141) at a single institution were reviewed. Baseline renal function parameters including estimated glomerular filtration rate (eGFR) were compared with post-discharge follow-up values in both prosthetic AR and AS patient groups. Linear regression analysis was performed to determine correlates of renal function change.
Results: Mean baseline eGFR was lower in the AR group (55 SD21 vs. 64 SD24 ml/min/1.73 m^2 $p = 0.0495$). At post-discharge follow-up there was an increase in mean eGFR in the AR group which was not present in the AS group (8 SD12 vs. 0 SD11 ml/min/1.73 m^2 respectively $p = 0.0006$). There were strong correlations between change in creatinine ($\beta = -0.57$, $R^2 = 0.64$, $p < 0.0001$) and BUN ($\beta = -0.61$, $R^2 = 0.51$, $p < 0.0001$), and pre-procedure values in the AR group.
Conclusions: Patients who underwent VIV TAVR for AR experienced significant improvement of renal function at post-discharge follow-up. More advanced renal dysfunction at baseline was associated with greater improvement in renal function at post discharge in AR patients.

1. Introduction

Surgical aortic valve replacement (SAVR) is increasingly performed with bioprosthetic aortic valves as opposed to mechanical aortic valves [1,2]. The limited longevity of bioprostheses when compared to mechanical prostheses often necessitates repeat intervention for prosthetic structural valvular degeneration. Repeat SAVR may be associated with increased morbidity and mortality, especially when higher risk patient characteristics including advanced age, female sex, advanced NYHA functional classification and chronic kidney disease (CKD) are present [3,4].

Since the first valve-in-valve (VIV) transcatheter aortic valve replacement (TAVRs) in 2007 [5,6], VIV TAVR has increasingly become an accepted therapy for structural valvular degeneration of bioprosthetic aortic valves, with demonstrated safety and efficacy in registry data [7], where baseline CKD was present in 46.5% of patients undergoing VIV TAVR [8]. Given the association of baseline CKD with post-procedure acute kidney injury following TAVR [9], and the association of acute kidney injury with poor outcomes [10], CKD can sometimes be perceived as a complicating factor in performing TAVR. Contrary to this concern, recent data suggests that renal function is more likely to improve or remain unchanged after TAVR for native valve

Abbreviations: AR, Aortic Regurgitation; AS, Aortic Stenosis; CKD, Chronic Kidney Disease; eGFR, Estimated Glomerular Filtration Rate; POD, post-operative day; TAVR, Transcatheter Aortic Valve Replacement; VIV, Valve in Valve.

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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aortic stenosis (AS) [11]. However, the effect of VIV TAVR on renal function is unknown in patients with degenerated aortic bioprostheses with regurgitation and/or stenosis. Accordingly, the aims of this study were to firstly describe the change in renal function after VIV TAVR and secondly, compare renal function changes with VIV TAVR in those with predominant prosthetic regurgitation compared to stenosis. Finally, we aimed to identify parameters that correlate with change in renal function after VIV TAVR.

2. Methods

2.1. Subjects and sample

A retrospective review of the medical records was conducted for all VIV TAVRs between June of 2014, and October 2019, at Mayo Clinic (Rochester, MN). All patients had prior surgical or transcatheter AVR, and exclusion criteria included chronic hemodialysis and congenital myopathies that result in errors in conventional measures of renal function. Patients were classified as having significant aortic regurgitation (AR) if they had moderate or more AR by echocardiography, all other patients were classified as undergoing VIV TAVR primarily for AS. The study was reviewed and approved by the institutional review board.

2.2. Data collection

Baseline pre-procedure renal function including the Creatinine and BUN was collected for each patient, eGFR was calculated using the abbreviated modification of diet in renal disease study equation. Degree of AR was measured by transthoracic and/or transesophageal echocardiography and was collected from the intra-procedural, pre-deployment echocardiogram. Pre and post deployment diastolic blood pressure by invasive hemodynamic measurement were collected. Post-procedure creatinine, BUN and calculated eGFR were collected on post-operative day 1, and on the first renal function panel that was available post discharge within 90 days. Acute kidney injury (AKI) was defined as per Kidney Disease Improving Global Outcomes (KDIGO) guidelines as a rise in serum creatinine by 0.3 mg/dL within 48 h, increase in serum creatinine by 1.5 times the baseline within 7 days, or decrease in urine output to <0.5 ml/kg/hr for a period of 6 h [12].

2.3. Statistical analysis

Baseline characteristics were compared between the two groups using two-sample t-tests for continuous variables, and Pearson chi-squared tests for categorical variables. Within each group paired t-tests were performed comparing pre-procedure creatinine, BUN and eGFR, with post procedure values on post-op day 1 and post discharge when available. Mcnemar-Bowker tests were used as a paired analysis to assess change in CKD stage pre-procedure and post-discharge in both the AR and AS groups. Additionally, change in creatinine, BUN and eGFR from pre-procedure to post-op day 1 and post-discharge, were compared between the two groups using 2 sample t-tests. Linear regression analyses by least squares method were performed for change in renal parameters with both change in diastolic blood pressures and pre-procedure degree of AR. Linear regression analyses were also performed between changes in renal parameters post-discharge with their respective pre-procedure baselines. Propensity score matching was conducted between the two groups, and statistical analyses listed above were conducted to reassess the matched baseline characteristics, and change in renal function parameters. JMP version 14.1.0, BlueSky Statistics version 7.40 and SPSS v.25 were used for all statistical analysis.

3. Results

A total of 143 patients underwent VIV TAVR, of these patients 2 were excluded (one due to a long-standing history of end stage renal disease requiring chronic hemodialysis, and the other due to a congenital myopathy resulting in low muscle mass which made traditional markers of renal function unreliable). All patients had either prior SAVR (n = 127), or prior TAVR (n = 14). Of the patients analyzed, 103 (73%) were classified as having significant prosthetic AR while 38 (27%) primarily had prosthetic AS.

3.1. Baseline characteristics

Baseline patient characteristics are shown in Table 1. When compared to the AS group that underwent VIV TAVR, the AR group had a significantly higher mean creatinine (1.48 SD 0.64 vs. 1.19 SD 0.41 mg/dL; p = 0.0017), and BUN (32 SD 18 vs. 23 SD 9 mg/dL; p = 0.0003) and were more likely to be male (87% vs 66%; p = 0.0034). The mean eGFR was significantly lower in the AR group (55 SD 21 vs. 64 SD 24 ml/min/1.73 m^2; p = 0.0495). Baseline pre-procedure CKD stages are displayed in Table 1 between the two groups. Pearson chi-square test of homogeneity demonstrated no significant difference between the two groups in distribution of baseline CKD stage (p = 0.35).

The AR group had 5 (5%) patients with class I symptoms, 16 (16%) patients with class II, 60 (58%) with class III symptoms, and 22 (22%) with class IV symptoms. The AS group had no patients with class I symptoms, 3 (8%) with class II symptoms, 32 (84%) with class III symptoms, and 3 (8%) with class IV symptoms. A Pearson chi-square test for homogeneity demonstrated a significant difference between the two groups in distribution of NYHA functional class (p = 0.033). There was no significant difference between the AR and AS groups in regards to volume of contrast used for the procedure (43.2 ml SD 41 vs. 43.2 SD 31.6 respectively; p = 1). As expected, the AR group had a significantly lower mean AV gradient when compared to the AS group (23.8 mmHg SD 11.1 vs. 44.8 mmHg SD 11.5, p < 0.001). Likewise, the mean aortic valve area (AVA) was significant higher in the AR group when compared to the AS group (1.7 cm^2 SD 0.69 vs. 0.89 cm^2 SD 0.21, p < 0.001). Overall, there were 7 identified cases (6.8%) of mixed valvular disease in the AR group with AVA < 1.0 cm^2. Additional baseline characteristics were similar between the two groups (Table 1).

Peri-procedural outcomes are detailed in Table 2. In total, 4 (2.8%) patients had peri-procedural stroke with no differences between the AR and AS groups (p = 0.93). Nine (6%) patients had major bleeding requiring transfusion with no difference between the two groups (p = 0.27). Likewise, there were no significant differences between the AR and AS groups with regards to need for pacemaker (9% vs 11% respectively; p = 0.74) or vascular injury requiring surgery (3% vs 0 respectively; p = 0.23). One (1%) patient suffered an in-hospital mortality in the AR group while there were no in-hospital mortalities in the AS group (p = 0.54)

3.2. Change in renal function with VIV

The paired *t*-test results for both groups are shown in Table 3 and Fig. 1. In the AR group the creatinine decreased significantly from baseline for both post-operative day (POD) one and at post-discharge follow up (-0.18 SD 0.29 and −0.22 SD 0.44 mg/dL respectively; p < 0.0001). Consequently, the AR group demonstrated an increase in eGFR for both POD 1 and post-discharge follow up when compared to baseline (10 SD 12 and 8 SD 12 ml/min/1.73 m^2 respectively; p < 0.0001). Additionally, the BUN on average decreased in the AR group on both POD 1 (-5 SD 7 mg/dL; p < 0.0001) and at post discharge (-5 SD 14 mg/dL; p = 0.006) when compared with baseline. Within the AS group paired analysis demonstrated significant decrease in creatinine (-0.1 SD 0.16 mg/dL; p = 0.0004), BUN (-2 SD 4 mg/dL; p = 0.002) and increase in eGFR (10 SD 19 ml/min/1.73 m^2; p = 0.002) on POD 1 when compared to baseline. However, at post discharge follow up there was no significant change in creatinine (0.0035 SD 0.27 mg/dL; p = 0.94), eGFR (0 SD 11 ml/min/1.73 m^2; p = 1) or BUN (2 SD 10 mg/dL; p = 0.4) when compared with baseline. Within the AR group, there were two

Table 1
Baseline Characteristics.

	Aortic Regurgitation (n = 103)	Aortic Stenosis (n = 38)	p-value
Age	78 SD 11	78 SD 10	0.82
Sex			0.0034
M	90 (87%)	25 (66%)	
F	13 (13%)	13 (34%)	
Race			
White	98 (95%)	37 (97%)	0.88
Black	1 (1%)	0 (0%)	
Hispanic	2 (2%)	1 (3%)	
Native American	1 (1%)	0 (0%)	
South Asian	1 (1%)	0 (0%)	
Creatinine (mg/dL)	1.48 SD 0.64	1.19 SD 0.40	0.0017
eGFR (ml/min/1.73m^2)	55 SD 21	64 SD 24	0.0495
BUN (mg/dL)	32 SD 18 (n = 100)	23 SD (n = 30)	0.0003
CKD Stage			
I	3 (3%)	4 (11%)	0.35
II	38 (37%)	16 (42%)	
IIIa	32 (31%)	7 (18%)	
IIIb	22 (21%)	9 (24%)	
IV	7 (7%)	2 (5%)	
V	1 (1%)	0	
Previous Aortic Surgery			0.26
SAVR	91 (88%)	36 (95%)	
TAVR	12 (12 %)	2 (5%)	
Peripheral Arterial Disease	54 (52%)	24 (63%)	0.26
History of smoking	5 (5%)	0 (0%)	0.17
Hypertension	90 (87%)	36 (95%)	0.21
Diabetes	24 (23%)	12 (32%)	0.32
History of Stroke	13 (13%)	2 (5%)	0.21
Prior myocardial infarction	28 (27%)	8 (21%)	0.46
Chronic lung disease			
None	45 (44%)	13 (34%)	0.47
Mild	22 (22%)	9 (24%)	
Moderate	16 (16%)	10 (26%)	
Severe	19 (19%)	6 (16%)	
Ejection Fraction	52% SD 12	54% SD 12	0.35
NYHA Functional Class			
I	5 (5%)	0 (0%)	0.033
II	16 (16%)	3 (8%)	
III	60 (58%)	32 (84%)	
IV	22 (22%)	3 (8%)	
STS Risk Score	7.7 SD 4.48 (n = 93)	8.4 SD 5.12 (n = 37)	0.49
BMI (Kg/m^2)	29 SD 12	32 SD 7	0.11
TAVR Implanted			
Self Expanding	35 (34%)	14 (37%)	0.75
Balloon Expanding	68 (66%)	24 (63%)	
Access Used			
Transfemoral	98 (95%)	35 (92%)	0.5
Transapical	3 (3%)	3 (8%)	
Transaxillary	1 (1%)	0	
Transcaval	1 (1%)	0	
Volume of contrast used (mL)	43.2 SD 41 (n = 93)	43.2 SD 31.6 (n = 32)	1.0
Aortic Valve Mean Gradient (mmHg)	23.8 SD 11.1	44.8 SD 11.5	<0.001
Aortic Valve Area (cm^2)	1.7 SD 0.69	0.89 SD 0.21	<0.001

Abbreviations: BMI = Body Mass Index, BUN = Blood urea nitrogen, CKD = Chronic Kidney Disease, eGFR = Estimated Glomerular Filtration Rate, NYHA = New York Heart Association, SAVR = Surgical Aortic Valve Replacement, STS = Society of Thoracic Surgeons, TAVR = Trans-Catheter Aortic Valve Replacement

Table 2
Peri-procedural Outcomes.

	Aortic Regurgitation	Aortic Stenosis	p-Value
Stroke	3 (3%)	1 (3%)	0.93
Major bleed requiring blood transfusion	8 (8%)	1 (3%)	0.27
Need for Pacemaker	9 (9%)	4 (11%)	0.74
Vascular Injury Requiring Repair	3 (3%)	0	0.23
In-Hospital Mortality	1 (1%)	0	0.54

Table 3
Mean change in renal parameters with matched paired and 2 sample t-Test analysis.

	Aortic Regurgitation	Paired analysis p-value	Aortic Stenosis	Paired analysis p-Value	2 sample t-Test p-value
Mean Change in Creatinine POD1	−0.18 SD 0.29 (n = 101)	<0.0001	−0.1 SD 0.16 (n = 37)	0.0004	0.06
Mean Change in Creatinine Post discharge	−0.22 SD 0.44 (n = 90)	<0.0001	0.00351 SD 0.27 (n = 37)	0.94	0.0007
Mean Change in eGFR POD1	10 SD 12 (n = 101)	<0.0001	10 SD 19 (n = 37)	0.0018	0.93
Mean Change in eGFR Post discharge	8 SD 12 (n = 90)	<0.0001	0 SD 11 (n = 37)	1.0	0.0006
Mean Change in BUN POD1	−5 SD 7 (n = 96)	<0.0001	−2 SD 4 (n = 30)	0.0022	0.01
Mean Change in BUN Post discharge	−5 SD 14 (n = 68)	0.0058	2 SD 10 (n = 25)	0.40	0.0163

Abbreviations: BUN = Blood Urea Nitrogen, eGFR = Estimated Glomerular Filtration Rate, POD1 = Post-Operative Day 1

cases of patients who required hemodialysis pre-procedure and had significant renal recovery post procedure to allow discontinuation of renal replacement therapy. Paired analyses using Mcnemar-Bowker tests to assess change in CKD stage pre-procedure and post-discharge are demonstrated in Fig. 2. In the AR group there was significant improvement in CKD stage from pre-procedure to post discharge ($\chi^2 = 22.7$; p = 0.002). However, in the AS group there was no significant change in CKD stage observed at post discharge follow-up when compared to baseline ($\chi^2 = 2.3$; p = 0.801).

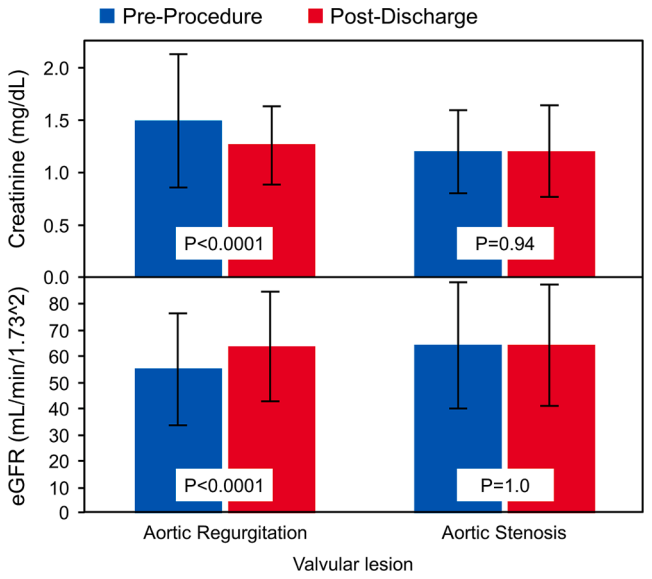

Fig. 1. Mean Creatinine and eGFR pre-procedure and post-discharge. **Legend:** The bar charts represent mean eGFR and mean creatinine in the AS and AR subgroups at both pre-procedure (blue bars) and post-discharge (red bars). The p-values represent paired t-tests performed comparing pre-procedure and post-discharge values in both groups. **Abbreviations:** eGFR = Estimated Glomerular Filtration Rate, AR = Aortic Regurgitation, AS = Aortic Stenosis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3. Comparison in renal function changes according to prosthetic lesion

Data comparing mean change in renal function parameters is found in Table 3. In comparing mean change in creatinine at POD 1 and post-discharge follow up, AR patients had a trend towards greater decrease in creatinine at POD 1 compared to the AS patients (-0.18 SD 0.29 vs −0.1 SD 0.16 mg/dL respectively; $p = 0.06$), the larger decrease in creatinine for the AR group was sustained to post discharge as well and was statistically significant (-0.22 SD 0.44 vs 0.0035 SD 0.27 mg/dL respectively; $p = 0.0007$). Mean change in eGFR was similar between the AR and AS groups at POD 1 (10 SD 12 vs. 10 SD 19 ml/min/1.73 m^2 respectively; $p = 0.93$). However, at post discharge there was a sustained increase in mean eGFR in the AR group whereas the change in eGFR was not sustained in the AS group (8 SD 12 vs. 0 SD 11 ml/min/1.73 m^2 respectively; $p = 0.0006$). Furthermore, mean change in BUN was greater in the AR group than the AS group on both POD 1 (-5 SD 7 vs −2 SD 4 mg/dL respectively; $p = 0.01$) and at post-discharge follow up (-5 SD 14 vs 2 SD 10 mg/dL respectively; $p = 0.016$).

3.4. Adverse renal effects following VIV

Of all 141 patients that were included in the study 8 (5.7%) developed AKI. 5 of the cases of AKI were in the AR group, of which one patient transiently required hemodialysis post procedure. All 5 of these CIN cases experienced full recovery of renal function with post-discharge renal function parameters that were improved compared to pre-procedure baselines in 4 of them. There were 3 patients within the AS group that developed AKI, none of them required dialysis.

3.5. Relationship between renal function and Aortic Regurgitation

Linear regression models were created by the ordinary least squares method and are displayed in Table 4. A linear regression model demonstrated a negative correlation between baseline degree of AR and change in creatinine post discharge ($\beta = -0.49$, $R^2 = 0.058$; $p = 0.0061$), and a positive correlation was noted between change in eGFR post discharge and degree of AR ($\beta = 1.53$, $R^2 = 0.062$; $p = 0.0049$). There was no significant relationship between change in diastolic blood pressure and change in post discharge creatinine, post discharge eGFR, and change in BUN. There were strong correlations between change in creatinine ($\beta = -0.57$, $R^2 = 0.64$; $p < 0.0001$), eGFR ($\beta = -0.19$, $R^2 = 0.11$; $p = 0.0016$) and BUN ($\beta = -0.61$, $R^2 = 0.51$; $p < 0.0001$), and their respective pre-procedure values in the AR group. There was no significant relationship between post-discharge change in creatinine, and BUN, and their respective pre-procedure values in the AS group. There was a significant negative relationship between post discharge change in eGFR and its pre-procedure baseline in the AS group ($\beta = -0.14$, $R^2 = 0.11$; $p = 0.04$).

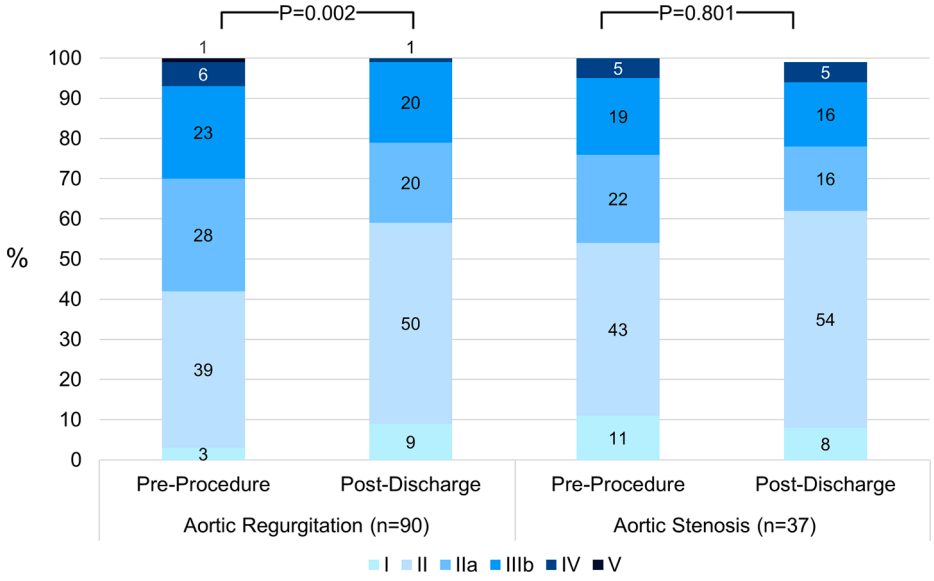

Fig. 2. CKD Stage Pre-Procedure and Post-Discharge. **Legend:** The stacked bar charts represent the CKD stage distribution both pre-procedure and post-discharge in those patients that post-discharge data was available. The p-values correspond with Mcnemar-Bowker tests which were performed comparing pre-procedure and post-discharge CKD stage in both groups. **Abbreviations:** CKD = Chronic Kidney Disease, AR = Aortic Regurgitation, AS = Aortic Stenosis.

Table 4
Linear regression analyses for change in renal function parameters.

	Beta coefficient	R^2	F	p value
Degree of AR on change in eGFR (post-discharge)	1.53 (n = 127)	0.062	8.2	0.0049
Degree of AR on change in BUN (post-discharge)	−1.24 (n = 93)	0.036	3.36	0.07
Degree of AR on Change in Creatinine (post-discharge)	−0.49 (n = 127)	0.058	7.79	0.0061
Diastolic blood pressure on change in eGFR (post-discharge)	0.13 (n = 88)	0.015	1.29	0.26
Diastolic blood pressure on change in BUN (post-discharge)	−0.12 (n = 62)	0.012	0.7	0.405
Diastolic blood pressure on change in Creatinine (post-discharge)	−0.004 (n = 88)	0.012	1.02	0.32
Pre-procedure eGFR on change in eGFR (post-discharge)				
Aortic Regurgitation	−0.19 (n = 90)	0.11	10.57	0.0016
Aortic Stenosis	−0.14 (n = 37)	0.11	4.5	0.0407
Pre-procedure BUN on Change in BUN (post-discharge)				
Aortic Regurgitation	−0.61 (n = 68)	0.51	68.28	<0.0001
Aortic Stenosis	−0.097 (n = 25)	0.0058	0.13	0.72
Pre-procedure Creatinine on Change in Creatinine (post-discharge)				
Aortic Regurgitation	−0.57 (n = n = 90)	0.64	156.66	<0.0001
Aortic Stenosis	−0.14 (n = 37)	0.043	1.57	0.22

Abbreviations: AR = Aortic Regurgitation, BUN = Blood Urea Nitrogen, eGFR = Estimated Glomerular Filtration rate

3.6. Propensity score matching

Propensity score matching was conducted between the two groups in order to address potential confounders. Between the two groups there were 34 patients in each group that were found to be good matches on baseline characteristics as seen in Table 5. The mean changes in renal parameters as well as paired analyses of the pre and post procedure renal functions in the AR and AS matched groups are shown in Table 6. Paired analysis again demonstrated a significant improvement in creatinine and eGFR respectively at post discharge (-0.11 SD 0.23 mg/dL, p = 0.013 and 4.5 ml/min/1.73 m^2 SD 9.1, p = 0.0095) in the AR group however, there was no noted improvement in BUN (0 SD 7.9 mg/dL, p = 1). The paired analysis demonstrated no noted significant improvement in creatinine, eGFR or BUN at post discharge follow up in the AS group. When comparing the mean change in renal function parameters between the two matched groups there was noted to be greater improvements in renal function parameters (creatinine and eGFR) on average in the AR group when compared to the AS patients however these improvements were not statistically significant.

4. Discussion

The primary findings of this study are that (1) patients with prosthetic AR undergoing VIV TAVR present with more advanced renal insufficiency and worse NYHA symptoms compared to patients with prosthetic AS, (2) renal function improves acutely with VIV TAVR for both prosthetic AR and AS, with sustained improvements in patients with prosthetic AR at post-discharge follow-up and (3) degree of renal function improvement was proportional to severity of renal dysfunction in patients with prosthetic AR. Despite more advanced renal dysfunction at baseline, prosthetic AR patients experience significant improvements

Table 5
Baseline Characteristics After Propensity Score Matching.

	Aortic Regurgitation (n = 34)	Aortic Stenosis (n = 34)	p-Value
Age	78.5 SD 8.44	78.5 SD 10.9	1.00
Sex			
M	27 (79.4%)	24 (70.6%)	0.40
F	7 (20.6%)	10 (29.4%)	
Race			
Hispanic	0 (0.0%)	1 (2.9%)	0.37
Native American	1 (2.9%)	0 (0.0%)	
White	33 (97.1%)	33 (97.1%)	
Pre-Procedure Creatinine (mg/dL)	1.3 SD 0.42	1.2 SD 0.40	0.26
Pre-Procedure eGFR (ml/min/1.73m^2)	57.5 SD 19.26	62.5 SD 9.46	0.34
Pre-Procedure BUN (mg/dL)	31.1 SD 31.1 (n = 33)	23.6 SD 9.46 (n = 27)	0.06
CKD Stage Pre-Procedure			
I	1 (2.9%)	2 (5.9%)	0.92
II	15 (44.1%)	15 (44.1%)	
IIIa	9 (26.5%)	7 (20.6%)	
IIIb	8 (23.5%)	8 (23.5%)	
IV	1 (2.9%)	2 (5.9%)	
Previous Valve Replacement			
SAVR	33 (97.1%)	32 (94.1%)	0.55
TAVR	1 (2.9%)	2 (5.9%)	
Peripheral arterial disease	22 (64.7%)	21 (61.8%)	0.80
Smoker	2 (5.9%)	0 (0.0%)	0.15
Hypertension	33 (97.1%)	32 (94.1%)	0.55
Diabetes	11 (32.4%)	10 (29.4%)	0.79
Stroke	2 (5.9%)	1 (2.9%)	0.55
Prior Myocardial Infarction	10 (29.4%)	8 (23.5%)	0.58
Chronic Lung Disease			
None	9 (26.5%)	12 (35.3%)	0.74
Mild	8 (23.5%)	9 (26.5%)	
Moderate	9 (26.5%)	8 (23.5%)	
Severe	8 (23.5%)	5 (14.7%)	
Ejection Fraction	54.5 SD 10.1	53.4 SD 12.7	0.70
NYHA Functional Class			
II	3 (8.8%)	3 (8.8%)	1.0
III	28 (82.4%)	28 (82.4%)	
IV	3 (8.8%)	3 (8.8%)	
STS Risk Score	8.1 SD 4.31	8.4 SD 5.26	0.79
BMI (Kg/m^2)	30.4 SD 6.85	31.4 SD 7.13	0.55
TAVR Received			
Self Expanding	12 (35.3%)	14 (41.2%)	0.62
Balloon Expanding	22 (64.7%)	20 (58.8%)	
Access Route			
Transapical	1 (2.9%)	3 (8.8%)	0.30
Transfemoral	33 (97.1%)	31 (91.2%)	
Volume of Contrast (mL)	40.2 SD 38.6	38 SD 28.2	0.79

Abbreviations: BMI = Body Mass Index, BUN = Blood urea nitrogen, CKD = Chronic Kidney Disease, eGFR = Estimated Glomerular Filtration Rate, NYHA = New York Heart Association, SAVR = Surgical Aortic Valve Replacement, STS = Society of Thoracic Surgeons, TAVR = Trans-Catheter Aortic Valve Replacement

Table 6
Mean change in renal parameters with matched paired and 2 sample t-Test analysis after propensity score matching.

	Aortic Regurgitation	Paired analysis p-value	Aortic Stenosis	Paired analysis p-Value	2 sample t-Test p-value
Mean Change in Creatinine Post discharge	−0.11 SD 0.23 (n = 31)	0.013	−0.02 SD 0.25 (n = 33)	0.68	0.15
Mean Change in eGFR Post discharge	4.5 SD 9.1(n = 31)	0.0095	0.94 SD 10.2 (n = 33)	0.60	0.14
Mean Change in BUN Post discharge	0 SD 7.9 (n = 22)	1.0	2.1 SD 10.8 (n = 23)	0.36	0.47

Abbreviations: BUN = Blood Urea Nitrogen, eGFR = Estimated Glomerular Filtration Rate.

in renal function post VIV TAVR, likely reflecting increased renal perfusion due to improved forward stroke volume resulting from correction of AR. These findings have implications for patient management, especially in patients with more advanced renal dysfunction, in whom there may be clinical hesitancy to perform contrast-requiring interventions.

In patients with prosthetic AR undergoing VIV TAVR, baseline renal parameters correlated significantly with change in renal parameters at post-discharge follow up. Higher creatinine and BUN at baseline in this group was strongly associated with a larger improvement in these parameters respectively at post-discharge follow up. Likewise, a lower baseline eGFR was associated with a larger improvement in eGFR at post-discharge follow up. These findings emphasize the importance of considering the impact of prosthetic AR on renal function, and suggests that renal function is likely to improve in this group with VIV TAVR, particularly in those with more advanced CKD. Though there were also negative correlations between baseline renal function parameters and changes in these parameters post discharge in the AS group, in regards to BUN and creatinine these were not statistically significant. Pre-procedure eGFR in the AS group had modest negative correlation with change in eGFR post-discharge, suggesting similar associations in the AS compared to the AR group. It is possible that more favorable baseline renal function, and smaller sample size in the AS group resulted in less ability to detect improvement in renal function in this study. There was a modest association between the degree of AR at baseline and renal recovery during long term follow up in both groups.

Another important observation of this study is that VIV TAVR, regardless of mechanism of bioprosthetic dysfunction, is associated with a low risk of worsening renal function regardless of baseline CKD stage. This finding is concordant with published data showing low risk of acute kidney injury in conventional TAVR for treatment of native aortic valve stenosis [13]. Distinct changes in renal function following VIV TAVR occurred between the two groups in our study. The notable greater improvement in renal function with TAVR and association of this improvement with more advanced pre-procedure renal dysfunction at baseline in AR patients, suggests a component of cardiorenal syndrome that is unique to the AR group. In support of this hypothesis, AR is commonly employed in animal models for studying both type 1 and 2 cardiorenal syndrome [14,15]. Though there is a paucity of data available on response of renal function to aortic valve replacement for AR, significant improvement in renal function after SAVR for AR has been recognized [16]. Although this study did not demonstrate an association between the change in diastolic blood pressure (a marker of AR severity and prognosis [17]) and change in renal function, acute correction of AR is known to be associated with significant improvements in cardiac output, and decreased venous congestion that may result in improved renal perfusion.

To address potential confounding variables propensity score matching was conducted using baseline characteristics. In the process of finding suitable matches the pre-procedure renal function parameters became more balanced between the two groups. With this the difference in mean change in renal function parameters between the two groups was not statistically significant. We suspect that this is largely due to a greater proportion of patients with advanced renal dysfunction in the AR group being excluded when the matched pairs were made. As mentioned above our analysis showed that those with worse baseline renal function had greater improvement in renal function at post discharge follow up in the AR group but not the AS group. Therefore, it is not surprising that when these patients with likely significant cardiorenal syndrome are excluded from analysis that the effect of VIV TAVR on change in renal function parameters is reduced. Nevertheless, the paired analysis of the matched groups again demonstrated a significant improvement in creatinine and eGFR at post discharge follow up in the AR group that was not present in the AS group. This suggests that even when controlling for differences in baseline renal function, those who have VIV TAVR for predominant AR have a small but significant improvement in renal function at post discharge followup while those who undergo it for AS do not.

4.1. Study limitations

The retrospective nature of this study lends to the possibility of underlying selection bias. In particular, baseline characteristics demonstrated a significantly higher proportion of male patients in the AR group when compared to the AS group. Higher creatinine levels in male patients may be a confounder when comparing creatinine in the two groups. For this reason, we calculated and collected data on eGFR in both groups to control for this confounder. Additionally, pre-procedure renal function parameters including creatinine, BUN and the calculated eGFR were based on single values as an assumption of baseline. However, this assumption reflects clinical practice where often clinicians may have only one reference in "baseline" renal parameters to make judgements on the safety of TAVR. Furthermore, the presence of cardiorenal syndrome in these patients may result in acute kidney injury which is a departure from baseline renal function, and is best demonstrated on the immediate pre-procedure measures of renal function. Another limitation of this study is the lack of available information on the duration of patient symptoms prior to undergoing the procedure, leading to potential lead-time bias. Particularly the fact that AR is often more difficult grade and diagnose than AS may lead to those with AR presenting at a more advanced stage of disease.

5. Conclusion

Despite more advanced baseline renal dysfunction, patients who underwent VIV TAVR for prosthetic AR experienced significant improvement in renal function that was sustained in outpatient follow up compared to patients who had VIV for prosthetic stenosis.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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References

[1] J.M. Brown, S.M. O'Brien, C. Wu, J.A. Sikora, B.P. Griffith, J.S. Gammie, Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database, J. Thorac. Cardiovasc. Surg. 137 (1) (2009) 82–90, https://doi.org/10.1016/j.jtcvs.2008.08.015.

[2] M. Alkhouli, F. Alqahtani, A. Kawsara, S. Pislaru, H.V. Schaff, R.A. Nishimura, National Trends in Mechanical Valve Replacement in Patients Aged 50 to 70 Years, J. Am. Coll. Cardiol. 76 (22) (2020) 2687–2688, https://doi.org/10.1016/j.jacc.2020.09.608.

[3] C.W. Akins, M.J. Buckley, W.M. Daggett, A.D. Hilgenberg, G.J. Vlahakes, D. F. Torchiana, J.C. Madsen, Risk of Reoperative Valve Replacement for Failed Mitral and Aortic Bioprostheses, Ann. Thorac. Surg. 65 (6) (1998) 1545–1552.

[4] W.R. Jamieson, L.H. Burr, R.T. Miyagishima, et al., Re-operation for bioprosthetic aortic structural failure - risk assessment, Eur. J. Cardiothorac. Surg. 24 (6) (2003) 873–878, https://doi.org/10.1016/s1010-7940(03)00566-9.

[5] T. Walther, J. Kempfert, M.A. Borger, J. Fassl, V. Falk, J. Blumenstein, M. Dehdashtian, G. Schuler, F.W. Mohr, Human minimally invasive off-pump valve-in-a-valve implantation, Ann. Thorac. Surg. 85 (3) (2008) 1072–1073, https://doi.org/10.1016/j.athoracsur.2007.12.040.

[6] P. Wenaweser, L. Buellesfeld, U. Gerckens, E. Grube, Percutaneous aortic valve replacement for severe aortic regurgitation in degenerated bioprosthesis: the first valve in valve procedure using the Corevalve Revalving system, Catheter. Cardiovasc. Interv. 70 (5) (2007) 760–764, https://doi.org/10.1002/ccd.21300.

[7] D. Dvir, J.G. Webb, S. Bleiziffer, M. Pasic, R. Waksman, S. Kodali, M. Barbanti, A. Latib, U. Schaefer, J. Rodés-Cabau, H. Treede, N. Piazza, D. Hildick-Smith, D. Himbert, T. Walther, C. Hengstenberg, H. Nissen, R. Bekeredjian, P. Presbitero, E. Ferrari, A. Segev, A. de Weger, S. Windecker, N.E. Moat, M. Napodano, M. Wilbring, A.G. Cerillo, S. Brecker, D. Tchetche, T. Lefèvre, F. De Marco, C. Fiorina, A.S. Petronio, R.C. Teles, L. Testa, J.-C. Laborde, M.B. Leon, R. Kornowski, Transcatheter aortic valve implantation in failed bioprosthetic surgical valves, JAMA 312 (2) (2014) 162, https://doi.org/10.1001/jama.2014.7246.

[8] D. Dvir, J. Webb, S. Brecker, S. Bleiziffer, D. Hildick-Smith, A. Colombo, F. Descoutures, C. Hengstenberg, N.E. Moat, R. Bekeredjian, M. Napodano, L. Testa, T. Lefevre, V. Guetta, H. Nissen, J.-M. Hernández, D. Roy, R.C. Teles, A. Segev, N. Dumonteil, C. Fiorina, M. Gotzmann, D. Tchetche, M. Abdel-Wahab, F. De Marco, A. Baumbach, J.-C. Laborde, R. Kornowski, Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-in-valve registry, Circulation 126 (19) (2012) 2335–2344, https://doi.org/10.1161/CIRCULATIONAHA.112.104505.

[9] R. Bagur, J.G. Webb, F. Nietlispach, E. Dumont, R. De Larochelliere, D. Doyle, J.-B. Masson, M.J. Gutierrez, M.-A. Clavel, O.F. Bertrand, P. Pibarot, J. Rodes-Cabau, Acute kidney injury following transcatheter aortic valve implantation: predictive factors, prognostic value, and comparison with surgical aortic valve replacement, Eur. Heart J. 31 (7) (2010) 865–874, https://doi.org/10.1093/eurheartj/ehp552.

[10] A.J. Muñoz-García, E. Muñoz-García, M.F. Jiménez-Navarro, A.J. Domínguez-Franco, J.H. Alonso-Briales, J.M. Hernández-García, E. de Teresa-Galván, Clinical impact of acute kidney injury on short- and long-term outcomes after transcatheter aortic valve implantation with the CoreValve prosthesis, J. Cardiol. 66 (1) (2015) 46–49, https://doi.org/10.1016/j.jjcc.2014.09.009.

[11] R.J. Cubeddu, C.R. Asher, A.M. Lowry, E.H. Blackstone, S.R. Kapadia, M.C. Alu, V. H. Thourani, M.J. Mack, S.K. Kodali, H.C. Herrmann, J. Forcillo, V.C. Babaliaros, C. M. Devireddy, S.C. Malaisrie, C.J. Davidson, W.A. Jaber, M.B. Leon, L.G. Svensson, Impact of Transcatheter Aortic Valve Replacement on Severity of Chronic Kidney Disease, J. Am. Coll. Cardiol. 76 (12) (2020) 1410–1421, https://doi.org/10.1016/j.jacc.2020.07.048.

[12] Kidney Disease Improving Global Ouctomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf, 2012 (accessed 29 December 2021).

[13] K. Shah, Z. Chaker, T. Busu, R. Shah, M. Osman, F. Alqahtani, M. Alkhouli, Meta-Analysis Comparing Renal Outcomes after Transcatheter Versus Surgical Aortic Valve Replacement, J. Interv. Cardiol. 2019 (2019) 1–9, https://doi.org/10.1155/2019/3537256.

[14] Y. Funahashi, S. Chowdhury, M.B. Eiwaz, M.P. Hutchens, Acute Cardiorenal Syndrome: Models and Heart-Kidney Connectors, Nephron 144 (12) (2020) 629–633, https://doi.org/10.1159/000509353.

[15] K. Rafiq, T. Noma, Y. Fujisawa, Y. Ishihara, Y. Arai, A.H.M.N. Nabi, F. Suzuki, Y. Nagai, D. Nakano, H. Hitomi, K. Kitada, M. Urushihara, H. Kobori, M. Kohno, A. Nishiyama, Renal sympathetic denervation suppresses de novo podocyte injury and albuminuria in rats with aortic regurgitation, Circulation 125 (11) (2012) 1402–1413, https://doi.org/10.1161/CIRCULATIONAHA.111.064097.

[16] E. Hryniewiecka, T. Hryniewiecki, J. Różański, T. Pilecki, R. Zagożdżon, T. Orłowski, M. Gołębiowski, L. Pączek, K. Mucha, B. Foroncewicz, Reversal of stage 5 chronic kidney disease by aortic valve replacement in kidney transplant recipient: a case report, BMC Cardiovasc. Disord. 20 (1) (2020), https://doi.org/10.1186/s12872-020-01328-0.

[17] J.C. Vogt, H.I. Michelena, R.A. Nishimura, V.T. Nkomo, S.V. Pislaru, G.S. Reeder, C.S. Rihal, M.F. Eleid, Diastolic blood pressure predicts outcomes after aortic paravalvular leak closure, Catheter. Cardiovasc. Interv. 97 (1) (2021), https://doi.org/10.1002/ccd.28890.