Impact of Transcatheter Aortic Valve Replacement on Severe Aortic Stenosis with Chronic Kidney Disease

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Abstract

Introduction: We hypothesize that although patients with chronic kidney disease (CKD) are at risk of short- and long-term adverse outcomes following TAVR, the determinants of change in renal function and long-term clinical outcomes are not well defined and may be multifactorial.

Methods: From January 2013 to December 2020, a total of 380 consecutive patients with severe valvular aortic stenosis (AS), who had been referred to the TAVR multidisciplinary team, were recruited. The study excluded patients with end-stage renal disease requiring chronic dialysis (N=31). Procedural and clinical outcomes of all patients were followed up by the heart valve team according to the Valve Academic Research Consortium-2 consensus document.

Results: Compared to patients without CKD and patients with CKD stage 1-2, patients with CKD stage 3-5 were significantly older (P<0.001), had more comorbidities, poor baseline clinical status and significantly higher Society of Thoracic Surgeons predicted risk of mortality (STS-PROM) score (P<0.001) and frailty score (P<0.001). The three groups showed no significant difference in device or procedural success rates. Acute kidney injury (AKI) was documented for 19.0%, renal function improvement for 5.7%, and unchanged renal function for 75.3% of the global cohort. Significantly more patients with CKD stage 3-5 at baseline suffered from AKI after TAVR (no CKD vs. CKD stage 1-2 vs. CKD stage 3-5 = 20% vs. 13% vs. 25%, respectively, P= 0.027) and renal function improvement (no CKD vs. CKD stage 1-2 vs. CKD stage 3-5 = 0% vs. 0% vs. 13%, respectively, P<0.001). Multivariate analysis revealed that higher baseline STS-PROM and frailty score, the presence of peripheral vascular disease and the need for emergency hemodynamic support during TAVR were independent predictors of developing AKI; while higher baseline STS-PROM and frailty score, the presence of 30-day stroke or major vascular access complications independently predicted long-term adverse outcomes.

Conclusions: Our data demonstrated that in patients with CKD and AS undergoing TAVR, renal function was more likely to stay the same or improve, rather than worsen. Perhaps it is not the renal disease per se, but the accompanying comorbidities and the presence of periprocedural complications that drive the development of AKI and adverse outcomes after TAVR.

Key words: transcatheter aortic valve replacement, chronic kidney disease, acute kidney injury, clinical outcomes, prognosis

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Introduction

With the aging of the population and the emergence of transcatheter aortic valve replacement (TAVR) as a therapeutic option for patients with aortic stenosis (AS), clinicians increasingly face challenging scenarios resulting from the intersection of AS, the frailty of the elderly and multiple comorbidities that may influence health status, procedural risk estimates and anticipated benefit from TAVR.[1,2]

Chronic kidney disease (CKD) is one of the more prevalent comorbidities in patients undergoing TAVR. Chronic kidney disease stage 3-5 and end-stage renal disease (ESRD) on dialysis are associated with increased mortality or a greater incidence of adverse events (specifically major stroke, bleeding and vascular complications).[3-11] Moreover, acute kidney injury (AKI), and new renal replacement therapy (RRT) post-TAVR are associated with higher risk-adjusted in-hospital mortality in patients in the "no CKD" and "CKD" groups.[6] Although CKD and ESRD may not be absolute contraindications to TAVR, it is generally believed that valve repair with TAVR may come at the cost of injuring the kidneys. There is even some controversy as to whether we should perform TAVR in every AS patient with CKD, especially those who are on dialysis.[10-12]

Notably, the results from some of the studies evaluating the impact of baseline renal function on outcomes after TAVR are conflicting.[13-15] A meta-analysis study demonstrated that the association between advanced CKD and increased mortality or a greater incidence of adverse events was found only in high-surgical-risk patients who underwent TAVR. Advanced CKD is not associated with increased mortality or poorer safety outcomes in low- to intermediate-risk patients. The authors speculate that perhaps it is not renal disease per se that limits clinical benefit, but rather the accompanying comorbidities that drive outcome differences.[7] Moreover, in patients with severe AS undergoing TAVR, even those with baseline impaired renal function, the CKD stage is more likely to stay the same or improve, rather than worsen.[16-19] It is postulated that AS may contribute to the cardiorenal syndrome that improves with TAVR.[16-19] However, more evidence is needed to validate these hypotheses.

We hypothesized that, although patients with baseline renal impairment are at risk for short- and long-term mortality following TAVR, the determinants of change in renal function and long-term clinical outcomes are not well defined and may be multifactorial. The objectives of the study were to: 1) assess change in renal function following TAVR; 2) identify pre-TAVR and procedural variables associated with the development of AKI after TAVR- and 3) identify variables associated with long-term major adverse cardiac and cerebral events (MACCE) after TAVR.

Materials and methods

Patient population

From January 2013 to December 2020, a total of 380 consecutive patients with severe AS, who would be at intermediate or high risk if undergoing conventional cardiac surgery with sternotomy and cardiopulmonary bypass, were referred by a multidisciplinary heart team to undergo TAVR in a high-volume center in Taiwan. This study excluded patients with ESRD requiring chronic dialysis (N=31). Finally, a total of 349 patients were included in the present study.

In our institution, a multidisciplinary, shared decision-making approach is adopted for all patients considering aortic valve replacement, with the implementation of best practices to ensure patient goals and preferences are incorporated into final decision-making. The present study was approved by the Institutional Review Board of Cheng Hsin General Hospital under the No. (769) 109A-09, and the individual consent requirement for this retrospective analysis was waived.

TAVR procedures

The decision as to whether TAVR would be performed, and which type and size of prosthesis was to be used, was made at the heart team's discretion. Decisions were made based on pre-procedural computed tomography (CT) scans performed on all patients. All implantations were performed in a hybrid theater, and almost all patients of the study population were treated under general anesthesia.

In our institution, the default strategy for all patients was the transfemoral (TF) approach. TF TAVR was conducted using percutaneous closure devices, or after surgical cut-down of the femoral artery in cases with vessel calcification or severe obesity. If TF access was not feasible because of diseased peripheral vessels, alternative access (trans-carotid, trans-subclavian, transapical, or direct aortic implantation) was considered, whereby we followed the recommendations from previous reports.[20] In most cases, after balloon valvuloplasty had been done during rapid ventricular pacing, valve deployment was performed under fluoroscopy.

Post TAVR, all patients were referred to the intensive care unit and monitored for at least 1 day, whereby heart rate monitoring was continued until discharge. For the purpose of platelet inhibition, aspirin (100 mg per day) was dispensed to all patients. An additional dose of 75 mg of clopidogrel was administered post-procedure for 3 months in most cases. Patients with an indication for anticoagulant therapy received clopidogrel and warfarin or a direct oral anticoagulant without aspirin.

Follow-up and data collection

Echocardiography and clinical follow-up were performed before and after the operation. Echocardiographic studies performed at baseline and after TAVR were evaluated according to the criteria established by the American Society of Echocardiography.[21] Predicted patient operative mortality after TAVR was calculated using the Society of Thoracic Surgeons predicted risk of mortality (STS-PROM).

All patients were followed up by the heart team through telephone interviews and office visits. Data were prospectively collected and entered into our heart valve replacement database. Median (25^{th} ,75^{th} quartiles) follow-up was 575 (173, 1012) days for the study patients.

Definitions

Severe AS was defined as severe stenosis of the aortic valve with aortic valve area <1.0 cm^2 determined by transthoracic echocardiography, with or without aortic valve regurgitation.

According to the Valve Academic Research Consortium-2 consensus document[22], device success was defined as: 1) absence of procedural mortality; 2) correct positioning of a single prosthetic heart valve into the proper anatomical location, and 3) intended performance of the prosthetic heart valve (no prosthesis-patient mismatch and mean aortic valve pressure gradient [PG] <20 mmHg or mean peak velocity <3 m/s, and no moderate or severe prosthetic valve regurgitation).

Procedural success was defined as the achievement of a successful deployment of the TAVR device and retrieval of the delivery system in the absence of mortality, conversion to surgical aortic valve replacement, or myocardial infarction (MI). The implantation depth in the present study was measured perpendicular to the plane of the valve, as the distance from the distal part of the transcatheter heart valve to the noncoronary cusp.

CKD stages were classified according to the National Kidney Association as: Stage 1 (eGFR ≥90 ml/min per 1.73 m2); Stage 2 (eGFR 60 to 89 ml/min per 1.73 m2); Stage 3A (eGFR 45 to 59 ml/min per 1.73 m2); Stage 3B (eGFR 30 to 44 ml/min per 1.73 m2); Stage 4 (eGFR 15 to 29 ml/min per 1.73 m2), and Stage 5 (eGFR <15 ml/min per 1.73 m2).[23] The eGFR was calculated by the Cockcroft-Gault formula.

The main renal endpoint of this study was the change in renal function from baseline to ≤72 hours post-TAVR. AKI was defined according to the VARC-2 definition as an absolute increase in

serum creatinine ≥0.3 mg/dL (≥26.4 mmol/L) or ≥50% increase in serum creatinine up to 72 hours after TAVR.[22] Improvement of renal function after TAVR was defined as: 1) an absolute decrease of ≥50% in serum creatinine (≥50% decrease compared with baseline) up to 72 hours after the procedure, or 2) an improvement of ≥25% in eGFR over 72 hours after the procedure, or 3) a decrease of ≥0.3 mg/dL in serum creatinine over 72 hours post-TAVR. Patients with unchanged renal function were those who had neither AKI nor improvement of renal function post-TAVR.

The major cardiac and cerebral adverse events (MACCE) were defined as a composite of all-cause mortality, major stroke and non-fatal MI during long-term follow-up. Other safety endpoints at 30 days included New York Heart Association (NYHA) functional class III/IV heart failure, life-threatening bleeding, AKI-stage 3, major vascular complications, paravalvular leaks and the need for permanent pacemaker implantation for complete heart block.

Statistical analysis

Data were transferred from the database to the Statistical Program for Social Sciences program (version 18.0 for Windows, SPSS Inc., Chicago, IL, USA). Univariate comparisons of demographic, procedural and outcome parameters between these two groups were made. Continuous variables were expressed as mean ± standard deviation and were compared using the Student's t-test or the Wilcoxon rank sum test. Categorical variables were presented as percent frequency and compared using the Pearson's chi-square test or the Fisher's exact test. Logistic regression analysis was used to identify the predictors of development of AKI after TAVR in the study patients.

For the survival analysis, the TAVR patients were divided into two groups, depending on whether or not MACCE occurred during follow-up. Univariate comparisons of clinical characteristics and laboratory measurements between the two groups were conducted using appropriate tests. The independent predictors of MACCE in the study patients were determined using multivariate Cox proportional hazards analyses. Variables with a P-value <0.1 in the univariate analysis were included in the multivariate model, in addition to the presence of AKI vs. unchanged or improved renal function after TAVR, and important covariables associated with poor outcome, i.e., STS-PROM score, left ventricular ejection fraction and baseline CKD ≥stage 3.

Two-sided $P<0.05$ was considered statistically significant for all analyses.

Results

Baseline characteristics of the study patients (Table 1)

Baseline demographic and clinical characteristics among the study patients with no CKD, CKD stage 1-2, and CKD stage 3-5 at baseline are summarized in Table 1.

Compared to patients without CKD (mean age 75 ± 11 years) and patients with CKD stage 1-2 (mean age 77 ± 9 years), patients with CKD stage 3-5 (mean age 81 ± 7 years) were significantly older ($P<0.001$). The prevalence of diabetes mellitus ($P<0.001$), known coronary artery disease ($P=0.006$), prior MI ($P=0.026$), prior percutaneous coronary intervention ($P=0.043$), carotid artery disease ($P=0.016$), prior stroke ($P=0.006$), peripheral vascular disease ($P=0.016$) and prior atrial fibrillation ($P=0.026$) was highest in patients with CKD stage 3-5.

More patients with CKD stage 3-5 presented with NYHA functional class III/IV Heart failure ($P=0.047$). Compared to patients without CKD and those with CKD 1-2, patients with CKD stage 3-5 had significantly higher STS-PROM score ($P<0.001$) and frailty score ($P<0.001$) values.

Baseline CT measurements of the study patients (Table 2)

The baseline CT measurements showed no significant differences among the 3 groups. However, patients with CKD stage 3-5 had less

Table 1. Baseline characteristics of the study patients

	No CKD (N = 46)	CKD 1-2 (N = 155)	CKD 3-5 (N = 148)	P value
Age, yrs.	75 ± 11	77 ± 9	81 ± 7	<0.001
Male, n (%)	19 (41%)	79 (51%)	71 (48%)	0.510
Body mass index, kg/m^2	24.4 ± 5.6	24.5 ± 3.9	24.9 ± 4.0	0.610
Body surface area, m2	1.6 ± 0.2	1.6 ± 0.2	1.6 ± 0.2	0.420
Systemic hypertension, n (%)	29 (63%)	108 (70%)	113 (76%)	0.167
Diabetes mellitus, n (%)	15 (33%)	43 (28%)	76 (51%)	<0.001
Dyslipidemia, n (%)	28 (61%)	77 (50%)	78 (53%)	0.409
Current smoker, n (%)	6 (13%)	7 (5%)	10 (7%)	0.122
Coronary artery disease, n (%)	25 (54%)	88 (57%)	108 (73%)	0.006
Previous myocardial infarction, n (%)	3 (7%)	4 (3%)	15 (10%)	0.026
Previous percutaneous coronary intervention, n (%)	10 (22%)	49 (32%)	60 (41%)	0.043
Previous coronary artery bypass grafting, n (%)	2 (4%)	16 (10%)	10 (7%)	0.321
Previous valve surgery, n (%)	2 (4%)	4 (3%)	3 (2%)	0.686
Carotid artery disease, n (%)	4 (9%)	25 (16%)	38 (26%)	0.016
Previous stroke, n (%)	2 (4%)	16 (10%)	30 (20%)	0.006
Peripheral vascular disease, n (%)	14 (30%)	37 (24%)	58 (39%)	0.016
Previous atrial fibrillation / atrial flutter, n (%)	12 (26%)	33 (21%)	52 (35%)	0.026
Previous permanent pacemaker implantation, n (%)	1 (2%)	14 (9%)	16 (11%)	0.198
Chronic obstructive pulmonary disease, n (%)	11 (24%)	19 (12%)	23 (16%)	0.152
Porcelain aorta, n (%)	3 (7%)	3 (2%)	8 (5%)	0.198
Heart failure, NYHA functional class III/IV, n (%)	41 (89%)	137 (88%)	142 (96%)	0.047
Syncope, n (%)	7 (15%)	27 (17%)	24 (16%)	0.926
STS-PROM score, %	6.2 ± 4.1	6.6 ± 6.4	13.9 ± 10.1	<0.001
Frailty score	2.2 ± 1.2	2.0 ± 1.1	2.7 ± 1.0	<0.001

CKD: chronic kidney disease; NYHA: New York Heart Association; STS-PROM: Society for Thoracic Surgery-probability of mortality score.

frequent bicuspid anatomy (P=0.008), and their sino-tubular junction diameters (P=0.006) and sinus of Valsalva diameters (P=0.047) were significantly smaller compared to the other 2 groups. Moreover, iliofemoral arterial disease was most prevalent in patients with CKD stage 3-5.

Procedural characteristics and immediate complications (Table 3)

The technical aspects of the procedure and procedural outcomes are presented in Table 3.

Significantly more CoreValve/Evolut R valves and significantly less Sapien XT/Sapien 3 valves were implanted in patients with CKD stage 3-5. The valve sizes were similar among the 3 groups. TAVR procedures were conducted via TF, trans-subclavian and trans-aortic approaches with self-expanding valves. The balloon-expandable valves were implanted via TF, transapical or trans-aortic access. The final implantation depth below the annulus was similar in the 3 patient groups.

There were no significant differences

Table 2. Baseline computed tomographic measurements of the study patients

	No CKD (N = 46)	CKD 1-2 (N = 155)	CKD 3-5 (N = 148)	P value
Perimeter of aortic annulus, mm	74.7 ± 7.4	74.8 ± 8.7	73.4 ± 7.1	0.549
Aortic annulus diameter (P), mm	23.8 ± 2.3	23.8 ± 2.8	23.4 ± 2.3	0.542
Area of aortic annulus, mm^2	431.4 ± 86.0	434.0 ± 103.6	414.5 ± 82.4	0.404
Aortic annulus diameter (A), mm	23.3 ± 2.3	23.4 ± 2.7	22.9 ± 2.2	0.429
Bicuspid morphology, n (%)	11 (24%)	47 (30%)	24 (16%)	0.015
Severe annular or leaflet calcification, n (%)	12 (41%)	44 (43%)	24 (35%)	0.616
Severe LVOT calcification, n (%)	0 (0%)	1 (1%)	0 (0%)	0.623
LVOT, mm	23.5 ± 2.5	23.2 ± 2.9	22.9 ± 2.6	0.522
Sino-tubular junction diameter, mm	29.1 ± 3.8	29.0 ± 4.2	27.1 ± 3.2	0.006
Sinus of Valsalva diameter, mm	31.9 ± 2.3	31.4 ± 3.8	30.3 ± 3.4	0.047
Left coronary height, mm	13.4 ± 3.0	14.0 ± 3.3	13.3 ± 3.1	0.287
Right coronary height, mm	17.2 ± 4.8	16.5 ± 3.4	15.7 ± 3.0	0.130
Left common iliac artery (MLD), mm	7.5 ± 1.7	7.7 ± 2.0	6.8 ± 1.9	0.022
Left external iliac artery (MLD), mm	6.5 ± 1.4	6.6 ± 1.4	6.3 ± 1.1	0.438
Left common femoral artery (MLD), mm	6.7 ± 1.5	6.8 ± 1.3	6.3 ± 1.2	0.030
Right common iliac artery (MLD), mm	7.3 ± 2.0	7.9 ± 1.7	6.8 ± 1.8	0.001
Right external iliac artery (MLD), mm	6.7 ± 1.5	6.8 ± 1.3	6.3 ± 1.3	0.063
Right common femoral artery (MLD), mm	7.1 ± 1.3	7.0 ± 1.5	6.3 ± 1.4	0.012

A: area-derived; CKD: chronic kidney disease; LVOT: left ventricular outflow tract; MLD: minimal luminal diameter; P: perimeter-derived.

Table 3. Procedural characteristics and immediate complications of the study patients

	No CKD (N = 46)	CKD 1-2 (N = 155)	CKD 3-5 (N = 148)	P value
THV valve type				
CoreValve/Evolut R, n (%)	12 (26%)	46 (30%)	63 (42%)	0.026
Sapien XT/Sapien 3, n (%)	31 (67%)	84 (54%)	68 (46%)	0.033
Lotus, n (%)	0 (0%)	9 (6%)	7 (5%)	0.253
Portico, n (%)	3 (7%)	16 (10%)	10 (7%)	0.476
THV valve size, mm				
≦ 23, n (%)	19 (41%)	57 (37%)	48 (32%)	0.498
25, 26, 27 n (%)	15 (33%)	64 (41%)	66 (45%)	0.353
＞ 27, n (%)	12 (26%)	34 (22%)	34 (23%)	0.841
Vascular access				
Trans-femoral, n (%)	41 (89%)	146 (94%)	133 (90%)	0.314
Trans-apical, n (%)	2 (4%)	3 (2%)	6 (4%)	0.506
Trans-subclavian, n (%)	2 (4%)	3 (2%)	0 (0%)	0.074
Direct aortic, n (%)	1 (2%)	1 (1%)	6 (4%)	0.140
Procedural outcomes				
Device success, n (%)	44 (96%)	143 (92%)	135 (91%)	0.616
Paravalvular leakage ≧ moderate, n (%)	0 (0%)	3 (2%)	4 (3%)	0.519
2nd device needed, n (%)	2 (4%)	7 (5%)	7 (5%)	0.993
post-TAVR trans-valvular PG ≧ 20mmHg, n (%)	1 (2%)	3 (2%)	4 (3%)	0.845
Procedural success, n (%)	46 (100%)	154 (99%)	146 (99%)	0.637
Conversion to SAVR, n (%)	0 (0%)	0 (0%)	0 (0%)	-
Coronary obstruction, n (%)	0 (0%)	1 (1%)	3 (2%)	0.389
Annulus rupture, n (%)	0 (0%)	0 (0%)	2 (1%)	0.255
Left ventricular rupture, n (%)	0 (0%)	1 (1%)	0 (0%)	0.534
Emergency CPB / ECMO, n (%)	2 (4%)	3 (2%)	2 (1%)	0.447
Implantation depth from annulus, mm	3.3 ± 2.4	3.4 ± 2.2	3.8 ± 2.3	0.175
Total contrast volume, c.c.	131.2 ± 76.0	122.0 ± 46.6	111.5 ± 43.9	0.039

CPB/ECMO: cardiopulmonary bypass/extracorporeal membrane oxygenation; PG: pressure gradient; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement; THV: transcatheter heart valve

in device or procedural success rates and the incidence of major intraoperative complications. Significantly less contrast medium was used in patients with CKD 3-5 (*P*=0.039).

Changes in renal function after TAVR in the study patients (Table 4)

AKI was documented for 19.0%, renal function improvement for 5.7%, and unchanged renal function for 75.3% of the global cohort. Significantly more patients with CKD stage 3-5 at baseline suffered from AKI after TAVR (no CKD vs. CKD stage 1-2 vs. CKD stage 3-5 = 20% vs. 13% vs. 25%, respectively; *P*=0.027). Similarly, renal function improvement was observed more frequently in patients with baseline CKD 3-5 (no CKD vs. CKD stage 1-2 vs. CKD stage 3-5 = 0% vs. 0% vs. 13%, respectively; *P*<0.001). That is, patients with CKD stages 3-5 were at the highest risk of AKI but also had the greatest potential for improvement in renal function.

Predictors of developing AKI after TAVR in the study patients (Table 5)

The multivariate logistic regression analysis showed that the odds ratio (OR) and the 95% confidence interval (95% CI) for the independent predictors of developing AKI after TAVR in the study patients were: the presence of peripheral arterial disease (OR: 2.523 [1.353-4.705]), higher STS-PROM score (OR: 1.054 [1.017-1.093]), higher frailty score (OR: 1.393 [1.002-1.937]) at baseline, and the need for emergency cardiopulmonary bypass/extracorporeal membrane oxygenation (CPB/ECMO) due to the occurrence of intra-operative complications (OR: 10.460 [1.642-66.655]).

It is noteworthy that the presence of CKD stage 3-5 at baseline is not an independent predictor of the development of AKI.

Thirty-day and long-term clinical outcomes of the study patients (Table 6)

The intensive care unit stays were significantly longer (no CKD vs. CKD stage 1-2 vs. CKD stage 3-5 = 1.9 ± 1.5 days vs. 2.1 ± 2.7 days vs. 4.9 ± 10.0 days, respectively; *P*<0.001).

Significantly fewer patients were in NYHA functional class I/II at 30 days after TAVR in the CKD 3-5 group (no CKD vs. CKD stage 1-2 vs. CKD stage 3-5 = 89% vs. 90% vs. 72%, respectively, *P*<0.001). At 30 days, the MACCE rate was significantly higher in the CKD stage 3-5 group (*P*=0.031), mainly driven by a higher all-cause mortality rate (*P*=0.046). Moreover, the CKD stage 3-5 group had a significantly higher rate of developing AKI stage 3 following TAVR (no CKD vs. CKD stage 1-2 vs. CKD stage 3-5 = 4% vs. 2% vs. 8%, respectively, *P*=0.044).

During the median follow-up of 575 days, a significantly higher rate of long-term MACCE (*P*<0.001) was found, mainly driven by both cardiac and non-cardiac death.

Independent prognostic determinants of composite MACCE by univariate and multivariate analysis (Table 7)

The TAVR patients were then divided into two groups, depending upon whether or not MACCE occurred during follow-up.

Table 4. Changes of renal function after transcatheter aortic valve replacement in the study patients

	No CKD (N = 46)	CKD 1-2 (N = 155)	CKD 3A (N = 68)	CKD 3B (N = 47)	CKD 4-5 (N = 33)	P valve
Acute kidney injury, n (%)	9 (20%)	20 (13%)	16 (24%)	9 (19%)	12 (36%)	0.025
Unchanged, n (%)	37 (80%)	135 (87%)	47 (69%)	31 (66%)	13 (40%)	<0.001
Improved, n (%)	0 (0%)	0 (0%)	5 (7%)	7 (15%)	8 (24%)	<0.001

Table 5. Independent predictors of developing acute kidney injury after transcatheter aortic valve replacement in the study patients

	AKI (+) (N = 66)	AKI (-) (N = 283)	Univariate P value	Multivariate P value
Baseline characteristics				
Age, yrs.	82 ± 6	78 ± 9	<0.001	
Male, n (%)	30 (46%)	139 (49%)	0.690	
Body mass index, kg/m^2	24.1 ± 4.0	24.8 ± 4.3	0.249	
Systemic hypertension, n (%)	48 (73%)	202 (71%)	0.946	
Diabetes mellitus, n (%)	36 (55%)	98 (35%)	0.004	
Dyslipidemia, n (%)	38 (58%)	145 (51%)	0.429	
Current smoker, n (%)	7 (11%)	16 (6%)	0.236	
Coronary artery disease, n (%)	51 (77%)	170 (60%)	0.014	
Previous myocardial infarction, n (%)	4 (6%)	18 (6%)	1	
Previous percutaneous coronary intervention, n (%)	28 (42%)	91 (32%)	0.150	
Previous coronary artery bypass grafting, n (%)	8 (12%)	20 (7%)	0.267	
Previous valve surgery, n (%)	4 (6%)	5 (2%)	0.121	
Carotid artery disease, n (%)	17 (26%)	50 (18%)	0.184	
Previous stroke, n (%)	11 (17%)	37 (13%)	0.572	
Peripheral vascular disease, n (%)	**36 (55%)**	**73 (26%)**	**<0.001**	**0.004**
Previous atrial fibrillation / atrial flutter, n (%)	25 (38%)	72 (25%)	0.060	
Previous permanent pacemaker implantation, n (%)	8 (12%)	23 (8%)	0.431	
Chronic obstructive pulmonary disease, n (%)	15 (23%)	38 (13%)	0.088	
Chronic kidney disease ≧ stage 3, n (%)	37 (56%)	111 (39%)	0.019	
Porcelain aorta, n (%)	5 (8%)	9 (3%)	0.197	
Heart failure, NYHA functional class III/IV, n (%)	66 (100%)	254 (90%)	0.014	
Syncope, n (%)	12 (18%)	46 (16%)	0.845	
STS-PROM score, %	**16.1 ± 11.0**	**8.1 ± 7.4**	**<0.001**	**0.004**
Frailty score	**3.0 ± 0.9**	**2.2 ± 1.1**	**<0.001**	**0.048**
Device characteristics				
Valve type				
Balloon-expandable valves, n (%)	27 (41%)	156 (55%)	0.052	
Valve size				
≦ 23 mm, n (%)	20 (30%)	104 (37%)	0.400	
25, 26, 27 mm, n (%)	30 (46%)	115 (41%)	0.564	
＞ 27 mm, n (%)	16 (24%)	64 (22%)	0.904	
Procedural outcomes				
Device success, n (%)	60 (91%)	262 (93%)	0.840	
Procedural success, n (%)	64 (97%)	282 (99%)	0.167	
Coronary obstruction, n (%)	2 (3%)	2 (1%)	0.340	
Annulus rupture, n (%)	2 (3%)	0 (0%)	0.042	
Left ventricular rupture, n (%)	1 (2%)	0 (0%)	0.427	
Emergency CPB/ECMO, n (%)	**4 (6%)**	**3 (1%)**	**0.034**	**0.013**
New left bundle branch block, n (%)	22 (33%)	92 (33%)	1	
Newly developed complete heart block, n (%)	4 (6%)	21 (7%)	0.904	
Total contrast volume, min	118.1 ± 52.8	118.9 ± 50.3	0.912	

CPB/ECMO: cardiopulmonary bypass/extracorporeal membrane oxygenation; NYHA: New York Heart Association.

The hazard ratio (HR) and the 95% confidence interval (95% CI) in the multivariate Cox proportional hazards analyses for the independent predictors of MACCE in the study patients were: higher baseline STS-PROM score (HR: 1.046 [1.025-1.067]), higher frailty score (HR: 1.545 [1.219-1.959]), and the presence of 30-day non-fatal stroke (HR: 10.449 [5.079-21.496]) or major vascular access complications (HR: 2.044 [1.094-3.818]).

Actually, the presence of CKD stage 3-5 at baseline and the development of AKI immediately after TAVR were not independent predictors of long-term adverse outcomes.

Table 6. Thirty-day and long-term clinical outcomes of the study patients

	No CKD (N = 46)	CKD 1-2 (N = 155)	CKD 3-5 (N = 148)	P value
Intensive care unit stay, days	1.9 ± 1.5	2.1 ± 2.7	4.9 ± 10.0	<0.001
Peri-procedural complications				
30-day NYHA functional class I/II, n (%)	41 (89%)	140 (90%)	107 (72%)	<0.001
30-day MACCE, n (%)	1 (2%)	4 (3%)	13 (9%)	0.031
All-cause mortality, n (%)	0 (0%)	2 (1%)	8 (5%)	0.046
Cardiac mortality, n (%)	0 (0%)	0 (0%)	3 (2%)	0.128
Non-fatal myocardial infarction, n (%)	0 (0%)	0 (0%)	0 (0%)	-
Non-fatal stroke, n (%)	1 (2%)	2 (1%)	6 (4%)	0.311
Other 30-day VARC complications				
Major or life-threatening bleeding, n (%)	2 (4%)	1 (1%)	4 (3%)	0.211
Major vascular access complication, n (%)	3 (7%)	8 (5%)	14 (10%)	0.344
Acute kidney injury, stage 1, n (%)	6 (13%)	10 (7%)	18 (12%)	0.177
Acute kidney injury, stage 2, n (%)	1 (2%)	7 (5%)	7 (5%)	0.745
Acute kidney injury, stage 3, n (%)	2 (4%)	3 (2%)	12 (8%)	0.044
Permanent pacemaker for CAVB, n (%)	2 (4%)	16 (10%)	24 (16%)	0.066
Long-term cumulative MACCE, n (%)	5 (11%)	35 (23%)	59 (40%)	<0.001
All-cause mortality, n (%)	4 (9%)	30 (19%)	52 (35%)	<0.001
Cardiac mortality, n (%)	0 (0%)	6 (4%)	16 (11%)	0.008
Non-fatal myocardial infarction, n (%)	0 (0%)	3 (2%)	0 (0%)	0.151
Non-fatal stroke, n (%)	1 (2%)	6 (4%)	12 (8%)	0.154

CAVB: complete atrio-ventricular block; MACCE: major adverse cardiac cerebral events; NYHA: New York Heart Association; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement; VARC: Valve Academic Research Consortium.

Table 7. Independent prognostic determinants of composite major adverse cardiac and cerebral events (MACCE) by univariate and multivariate analysis

	MACCE (+) (N = 99)	MACCE (-) (N = 250)	Univariate P value	Multivariate P value
Baseline characteristics				
Age, yrs.	82 ± 7	77 ± 9	<0.001	
Male, n (%)	54 (55%)	115 (46%)	0.186	
Body mass index, kg/m^2	24.0 ± 4.0	24.9 ± 4.3	0.051	
Systemic hypertension, n (%)	70 (71%)	180 (72%)	0.913	
Diabetes mellitus, n (%)	46 (47%)	88 (35%)	0.067	
Dyslipidemia, n (%)	57 (58%)	126 (50%)	0.275	
Current smoker, n (%)	10 (10%)	13 (5%)	0.154	
Coronary artery disease, n (%)	76 (77%)	145 (58%)	0.002	
Previous myocardial infarction, n (%)	10 (10%)	12 (5%)	0.111	
Previous percutaneous coronary intervention, n (%)	47 (48%)	72 (29%)	0.001	
Previous coronary artery bypass grafting, n (%)	8 (8%)	20 (8%)	1	
Previous valve surgery, n (%)	2 (2%)	7 (3%)	0.968	
Carotid artery disease, n (%)	27 (27%)	40 (16%)	0.024	
Previous stroke, n (%)	21 (21%)	27 (11%)	0.018	
Peripheral vascular disease, n (%)	46 (47%)	63 (25%)	<0.001	
Previous atrial fibrillation / atrial flutter, n (%)	36 (36%)	61 (24%)	0.034	
Previous permanent pacemaker implantation, n (%)	10 (10%)	21 (8%)	0.768	
Chronic obstructive pulmonary disease, n (%)	25 (25%)	28 (11%)	0.002	
Chronic kidney disease stage 3-5, n (%)	59 (60%)	89 (36%)	<0.001	
Porcelain aorta, n (%)	2 (2%)	12 (5%)	0.373	
Heart failure, NYHA functional class III/IV, n (%)	98 (99%)	222 (89%)	0.004	
Syncope, n (%)	19 (19%)	39 (16%)	0.514	
STS-PROM score, %	**15.6 ± 10.9**	**7.3 ± 6.4**	**<0.001**	**<0.001**
Frailty score	**3.0 ± 1.0**	**2.1 ± 1.1**	**<0.001**	**<0.001**

(Continued)

Table 7. Independent prognostic determinants of composite major adverse cardiac and cerebral events (MACCE) by univariate and multivariate analysis *(Continued)*

	MACCE (+) (N = 99)	MACCE (-) (N = 250)	Univariate P value	Multivariate P value
Device characteristics				
Valve type				
Balloon-expandable valves (Sapien XT/ Sapien 3), n (%)	35 (35%)	148 (59%)	<0.001	
Valve size				
≦ 23 mm, n (%)	27 (27%)	97 (39%)	0.057	
25, 26, 27 mm, n (%)	40 (40%)	105 (42%)	0.879	
＞ 27 mm, n (%)	32 (32%)	48 (19%)	0.013	
Procedural outcomes				
Device success, n (%)	87 (88%)	235 (94%)	0.088	
Procedural success, n (%)	97 (98%)	249 (99%)	0.404	
Coronary obstruction, n (%)	2 (2%)	2 (1%)	0.684	
Annulus rupture, n (%)	2 (2%)	0 (0%)	0.142	
LV rupture, n (%)	0 (0%)	1 (0.4%)	1	
Emergency CPB/ECMO, n (%)	3 (3%)	4 (2%)	0.663	
New left bundle branch block, n (%)	37 (37%)	77 (31%)	0.292	
Newly developed complete heart block, n (%)	8 (8%)	17 (7%)	0.851	
Total contrast volume, min	118.1 ± 54.7	119.0 ± 49.1	0.881	
Peri-procedural complications				
30-day NYHA functional class I/II, n (%)	57 (58%)	231 (92%)	<0.001	
30-day non-fatal myocardial infarction, n (%)	0 (0%)	0 (0%)	-	
30-day non-fatal stroke, n (%)	**9 (9%)**	**0 (0%)**	**<0.001**	**<0.001**
30-day acute kidney injury, n (%)	38 (38%)	28 (11%)	<0.001	
30-day major or life-threatening bleeding, n (%)	2 (2%)	5 (2%)	1	
30-day major vascular access complication, n (%)	**14 (14%)**	**11 (4%)**	**0.003**	**0.025**
30-day permanent pacemaker for CAVB, n (%)	16 (16%)	26 (10%)	0.191	

CAVB: complete atrio-ventricular block; CPB/ECMO: cardiopulmonary bypass/extracorporeal membrane oxygenation; NYHA: New York Heart Association.

Discussion

The main findings of our study are as follows:

(1) Although the presence of baseline CKD stage 3-5 is associated with the development of AKI after TAVR and a greater incidence of adverse events, it is not an independent predictor of AKI and MACCE.

(2) The development of AKI following TAVR is associated with increased incidence of adverse events. However, it is also not an independent predictor of MACCE.

(3) After TAVR, even with baseline impaired renal function, renal function was more likely to stay the same (75.3%) or improve (5.7%), rather than worsen (19.0%).

(4) The presence of peripheral vascular disease, higher STS-PROM score and frailty score at baseline, and the presence of immediate procedural complications needing emergency CPB/ECMO, are independent predictors of developing AKI after TAVR.

(5) The long-term adverse outcomes were independently determined by peri-procedural complications (stroke and major vascular complications within 30 days after TAVR), as well as poor baseline conditions (higher baseline STS-PROM score and frailty score).

It is generally believed that performing TAVR in aging patients with a high prevalence of CKD may come at a cost of injuring the kidneys. There is even some controversy as to whether we should do TAVR in every AS patient with CKD.[10-12] Notably, the results from studies evaluating the impact of baseline renal function on outcomes after TAVR are conflicting, whereby the association of CKD and clinical outcomes was not found to be significant by multivariate analyses.[13-15] Moreover, a meta-analysis demonstrated that the association between advanced CKD and increased mortality or a greater incidence of adverse events was found only in high-surgical-risk patients who underwent TAVR, but not in low- to intermediate-risk patients.[7] In the present study, we clearly demonstrated that patients with CKD stage 3-5 were significantly older, with more comorbidities and poor baseline conditions, i.e., more incident heart failure, higher STS-PROM score, and frailty score values. Although the presence of baseline CKD stage 3-5 is associated with the development of AKI after TAVR and a greater incidence of adverse events, it is not an independent predictor of AKI and MACCE. Furthermore, the development of AKI following TAVR is associated with increased incidence of adverse events. But it is also not an independent predictor of MACCE. Therefore, it is not renal disease per se that drives clinical outcome differences.

In line with the previous studies, our study also demonstrated that in patients with severe AS undergoing TAVR, even with baseline impaired renal function, CKD stage is more likely to stay the same or improve, rather than worsen.[16-19] After TAVR, AKI did occur in 19.0% of patients. However, renal function in most study patients remained unchanged (75.3%). It is noteworthy that, although patients with CKD stage 3-5 were more likely to develop AKI following TAVR, improvement of renal function was also seen in 5.7% of patients with CKD stage 3-5. We believe that AS, which contributes to the cardiorenal syndrome that improves with TAVR, may play an important role in TAVR induced renal function improvement.

Nevertheless, in logistic regression analysis, we found that the presence of previous peripheral vascular disease, higher STS-PROM score and frailty score at baseline, along with the presence of immediate procedural complications needing emergency CPB/ECMO were independent predictors of developing AKI after TAVR. It is well known that peripheral vascular disease is common among patients undergoing TAVR.[24] Previous studies have demonstrated that patients with peripheral vascular disease are at higher risk of significant vascular complications, many of which likely manifested as bleeding, resulting in AKI and other adverse events following TAVR.[24,25] In our series, the prevalence of peripheral vascular

disease was significantly higher in patients with CKD stage 3-5 (Tables 1 and 2) in addition to higher baseline STS-PROM score and frailty score, which may, to some extent, account for the higher incidence of adverse outcomes in the study patients. More importantly we found that the need for emergency CPB/ECMO for profound shock, especially in those who needed surgical bailout (3 left ventricular or annular ruptures and 1 acute coronary obstruction in the present study), is associated with poor outcomes, including AKI and new need for dialysis.[26]

It should be noted that AKI can occur in 9/46 (20%) of patients without CKD and 20/155 (13%) of patients with CKD stage 1-2 at baseline. These findings highlight the importance of trying our best to minimize the risk of AKI in the pre-procedure, intra-procedure and post-procedure phases, even when the patients' baseline renal function is within normal ranges or mildly impaired. Although the exact pathophysiology of AKI and contrast-induced nephrotoxicity remains elusive, reducing the total administered contrast volume is likely the most important modifiable factor to reduce the risk of AKI and contrast-induced nephrotoxicity.[27] For those with pre-existing severe renal dysfunction (GFR <30 mL/min), but who are not yet on hemodialysis, in whom contrast must be avoided, and those at high risk for renal dysfunction (GFR 30-50 mL/min or multiple risk factors), in whom contrast should be minimized, avoidance of exposure to contrast should take priority, unless it is absolutely necessary. Moreover, diligent planning in the pre-procedure phase, as well as modifications to the procedural steps in order to minimize contrast exposure along with continued monitoring post procedure, are of paramount importance and may potentially reduce the risk of AKI from contrast-induced nephrotoxicity in TAVR patients. As mentioned above, prevention and early recognition of any immediate complications of TAVR, such as hypotension from any cause (especially hypovolemia and bleeding, etc.), and the avoidance of nephrotoxic drugs, are all very important aspects of intra- and post-procedure care.[28]

Finally, we found in the present study that higher baseline STS-PROM score and frailty score, as well as the occurrence of peri-procedural complications (stroke and major vascular complications within 30 days after TAVR), are independently associated with long-term MACCE in terms of all-cause mortality, major stroke and non-fatal MI during long-term follow-up. Our findings are consistent with those reported in previous TAVR studies, showing that the clinical outcomes may be affected by procedural complications as well as baseline comorbidities.[29,30] Therefore, the bottom line is that CKD, and even ESRD, are not contraindications to TAVR. To achieve best possible outcomes for those patients with aortic stenosis and CKD undergoing TAVR, it is critically important for the heart team to pay great attention to proper patient selection, taking into consideration comorbidities and frailty, prevention of complications and hypotension during the procedure using best practices, and avoidance of concomitant use of nephrotoxic medications, including contrast medium.

Study Limitations

First of all, this was not a randomized trial. Therefore, it was subject to selection bias and unmeasured confounders. Second, considering the relatively small sample size and the fact that it was not a multi-center study, definitive conclusions cannot be drawn from the present study alone. Moreover, the statistical results may be affected by the relatively small sample size, for instance, the incidence of AKI is numerically higher in patients without CKD. Third, device selection was not randomized. Rather, it was at the operator's discretion and largely based on the operator's experience. This may have impacted the observed outcomes. Fourth, the study period was relatively long, across a period of more than 7 years. The evolution of patient selection, accumulation of operator/center experience,

improvements in transcatheter valve technology and the introduction of newer-generation device iterations, may all have contributed to the reduction of complication rates and improvement of TAVR results, making it difficult to estimate the real effect of each factor on overall TAVR outcomes. However, the present study does offer an opportunity to examine how the evolution of those factors affected the clinical outcomes of TAVR patients over time, and the impact of CKD on TAVR outcomes, in a "real-world" clinical setting of a single large volume center.

Conclusion

Aging patients undergoing TAVR have a high prevalence of CKD, which portends a poor prognosis. Despite technological advances and rapidly increasing clinical experience, AKI remains a relatively common complication following TAVR. However, neither pre-existing CKD nor TAVR-induced AKI were found to be independent predictors of adverse outcomes by multivariate analyses in the present study. Actually, poor baseline general conditions as well as the occurrence of 30-day stroke and major vascular complications after TAVR were independently associated with long-term MACCE. Therefore, strategies to scrutinize the risks of periprocedural complications and continuing efforts to seek to minimize these risks are imperative in patients with aortic stenosis and CKD undergoing TAVR.

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