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Clinical Research

Transcatheter Aortic Valve Replacement Outcomes in Patients With Native vs Transplanted Kidneys: Data From an International Multicenter Registry

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ABSTRACT

Background: Chronic kidney disease (CKD) has a negative impact on outcomes after transcatheter aortic valve replacement (TAVR). Data on outcomes in renal transplant recipients (RTRs) undergoing TAVR are scarce. We compared the outcomes in RTRs undergoing TAVR with matched patients who have native kidneys and similar kidney function.

Methods: This retrospective cohort study used data from 16 TAVR centres (13,941 patients). The study cohort included 216 patients (72 RTRs and 144 matched controls).

Results: The mean estimated glomerular filtration rate (eGFR) was 39.2 ± 23.6 vs 44.5 ± 23.6 mL/min for RTRs and control patients

RÉSUMÉ

Introduction : La néphropathie chronique a un effet négatif sur les résultats du remplacement valvulaire aortique par cathéter (RVAC). Les données sur les résultats des receveurs d'une greffe du rein qui se prêtent à un RVAC sont rares. Nous avons comparé les résultats de receveurs d'une greffe du rein qui se prêtent à un RVAC et de patients appariés ayant encore leurs propres reins et dont la capacité fonctionnelle rénale était similaire.

Méthodologie : Cette étude de cohorte rétrospective a utilisé les données de 16 centres de RVAC (13 941 patients). La cohorte de l'étude comprenait 216 patients (72 receveurs d'une greffe du rein et 144 témoins appariés).

Chronic kidney disease (CKD) is associated with aortic valve calcification, and increased prevalence and faster progression of aortic stenosis (AS).[1] Within the AS population, CKD is associated with reduced survival[2,3] and increased surgical risk; up to 50% of patients with AS and advanced CKD (stage 3-5) are not referred for surgical aortic valve replacement

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(*P* = 0.149), with a similar CKD stage distribution. After TAVR, the eGFR declined among RTRs but remained stable for up to 1 year in controls (*P* = 0.021). Long-term hemodialysis was required in 19 (26.4%) RTRs and 20 (13.8%) controls (hazard ratio [HR] = 2.09 95% confidence interval [CI], 1.03-3.86; *P* = 0.039) and was most often initiated during the periprocedural period (14 RTRs vs 16 controls; *P* = 0.039). After a median follow-up of 2.3 years, risk of death (29.2% vs 31.9%) and death/hemodialysis (40.3% vs 36.8%) was similar between the groups. The contrast volume/eGFR ratio was the strongest predictor of hemodialysis initiation (odds ratio [OR] = 1.64; 95% CI, 1.36-1.97 per 1 unit increase; *P* < 0.001), with a greater effect among RTRs than controls (*P* for interaction = 0.022).

Conclusion: s: TAVR appears safe in RTRs with mortality rates similar to matched patients with native kidneys. However, RTRs carry an increased risk of progressive renal impairment and need for hemodialysis initiation after TAVR. Our data highlight the importance of minimizing contrast load during TAVR, particularly in RTRs.

Résultats : Le taux de filtration glomérulaire estimé (TFGe) moyen a été de 39,2 ± 23,6 ml/min chez les receveurs d'une greffe du rein et de 44,5 ± 23,6 ml/min chez les témoins (*p* = 0,149), la distribution des stades de la néphropathie chronique étant similaire entre les groupes. Après le RVAC, le TFGe a diminué chez les receveurs d'une greffe du rein, mais est resté stable pendant une période maximale de 1 an chez les témoins (*p* = 0,021). Dix-neuf receveurs d'une greffe du rein (26,4 %) et 20 témoins (13,8 %) ont nécessité une hémodialyse à long terme (rapport des risques instantanés : 2,09; intervalle de confiance [IC] à 95 % : 1,03 − 3,86; *p* = 0,039); l'hémodialyse a été le plus souvent entreprise durant la période péri-procédurale (14 receveurs d'une greffe du rein et 16 témoins; *p* = 0,039). Après un suivi médian de 2,3 ans, le risque de décès (29,2 % vs 31,9 %) et de décès/hémodialyse (40,3 % vs 36,8 %) était similaire entre les groupes. Le rapport volume d'agent de contraste/TFGe a été le facteur de prédiction le plus robuste de l'instauration de l'hémodialyse (risque relatif approché : 1,64; IC à 95 % : 1,36 − 1,97 par palier d'augmentation de 1 unité; *p* < 0,001), l'effet étant plus important chez les receveurs d'une greffe du rein que chez les témoins (*p* pour l'interaction = 0,022).

Conclusions : Il semble que le RVAC soit sûr chez les receveurs d'une greffe du rein, les taux de mortalité étant semblables à ceux observés chez les patients appariés possédant encore leurs propres reins. Les receveurs d'une greffe du rein sont néanmoins exposés à un plus grand risque d'insuffisance rénale progressive et d'hémodialyse après le RVAC. Nos données soulignent l'importance de réduire au maximum le volume d'agent de contraste utilisé pendant le RVAC, particulièrement chez les receveurs d'une greffe du rein.

(SAVR).[4-6] Transcatheter aortic valve replacement (TAVR) may be an alternative for such patients,[7-10] but the post-TAVR outcomes among patients with CKD are worse than in patients with normal renal function.[11]

Renal transplant recipients (RTRs) constitute a unique subgroup within the CKD population. Even though RTRs show marked improvement in renal function post transplant, this is not associated with regression of valvular disease, and the improved survival of RTR over the past decade[12] means that it is all the more likely that these patients will eventually require aortic valve intervention. Their rates of mortality and complications are higher following SAVR.[13,14] One small-scale study suggested that TAVR may be superior to SAVR for RTRs with severe AS,[15] but no large scale dataset is available regarding the prevalence of RTRs within the TAVR population or their renal and overall outcomes compared with the general AS population or AS+CKD population.

In this study, we aimed to determine the prevalence of RTRs within the TAVR population, describe their characteristics, and compare their outcomes with matched patients who have native kidneys. Our primary interest was to examine whether renal transplantation is associated with worse renal outcomes (renal function as measured by estimated glomerular filtration rate [eGFR]), CKD stage, and need for hemodialysis) following TAVR compared with patients who had similar renal function but native kidneys.

Materials and Methods

This study was a retrospective cohort study based on data from 16 TAVR centres in Europe, North America, and Israel.

Study population

Each participating centre identified all RTRs who underwent TAVR and, according to predetermined matching as described below, selected matched control patients with native kidneys who underwent TAVR at the same centre. Two control patients were selected for every RTR. RTRs were identified using the comorbidity records included in each centre's TAVR database and the renal transplantation status confirmed in each patient's electronic medical record (EMR). Inclusion criteria were TAVR after renal transplantation, stable renal function (no change in CKD stage) during the 3 months before TAVR, and follow-up data available on renal function 90 and 365 (±14) days post-TAVR (unless deceased). Patients were excluded if they experienced allograft rejection before undergoing TAVR (eg, required dialysis in the 3 months prior to TAVR), had other significant valve disease, or had previously undergone SAVR (valve-in-valve TAVR). Control patients were selected using the following matching criteria: Society of Cardiothoracic Surgeons (STS) score (± 1 point), CKD stage (± 1 stage, or ± 15 mL/min if normal renal function) according to the CKD-Epidemiology Collaboration [EPI] equation,[16] gender, access route (femoral/nonfemoral), valve type (Sapien/CoreValve, Edwards Lifesciences, Corp, Irvine, CA), diabetes mellitus status, frailty status (as defined in each centre), and procedure date (± 12 months). The control cases were selected at each participating centre; control cases were required to fulfill the matching criteria on CKD stage, STS score, procedural date, and at least 2 of the 4 remaining matching criteria.

Study endpoints

Our study used 4 sets of endpoints: renal function, periprocedural/in-hospital clinical endpoints, intermediate-term clinical endpoints, and indices of valvular function at longest

available follow-up. Renal endpoints were eGFR and CKD stage following TAVR (at hospital discharge and 90 and 365 days post-TAVR). Periprocedural/in-hospital clinical endpoints included death, myocardial infarction (MI), need for periprocedural hemodialysis, major vascular complications, cerebrovascular accident/transient ischemic attack (CVA/TIA), and major bleeding according to the VARC definitions when applicable.[17] Additional periprocedural/in-hospital endpoints included greater than mild paravalvular leak (PVL), need for pacemaker implantation (PMI), infection, and bacteremia. Clinical endpoints from discharge up to the end of follow-up included death, need for long-term hemodialysis, and a composite of the 2. The valvular function was assessed by peak and mean aortic valve gradient (AVG) at longest available follow-up. See Supplemental Table S1 for the definitions used to define frailty and relevant periprocedural outcomes.

Data collection

Each of the participating centres maintains a prospective database of all TAVR patients treated at that centre. Data on baseline demographic, clinical, and procedural characteristics, renal function during admission and at discharge, and hospital outcomes were extracted from these databases. Data on survival postdischarge were retrieved from each patient's EMR and cross-referenced with each centre's TAVR database. Data on follow-up echocardiography were extracted from each centre's echocardiography database. Data on the need for initiation of hemodialysis were extracted from each patient's EMR. In addition, a complete review of each patient's cardiology and nephrology (when available) clinic records were reviewed to ascertain the data retrieved from the TAVR database and EMRs.

To assemble a unified database for the study, a uniform case report form was prepared and sent to all participating centres. All data required for the study were transferred to the uniform form and sent back to the first author (G.W.), who compiled the final database used for the statistical analysis.

Statistical methods

Baseline patient characteristics are presented as mean and standard deviation or median and interquartile (IQR) range, as appropriate. Proportions are used to describe categorical variables. Baseline characteristics were compared between the RTRs and control group using the Students' *t*-test, Mann–Whitney U-test, or χ^2 test, as appropriate.

To assess post-TAVR changes in renal function, we used a repeated measures mixed model[18] to compare the overall change in eGFR across the 4 time points (baseline, discharge, 90 and 365 days post-TAVR). Between-group comparisons of the distribution of CKD stages and the fraction of patients whose CKD stage worsened at each follow-up were performed using the χ^2 test.

Between-group comparisons of the rates of periprocedural/in-hospital outcomes were performed using the χ^2 test. We also fit a multivariate adjusted logistic regression model to calculate the odds ratio (OR) for the risk of any periprocedural/in-hospital endpoint for RTRs compared with control patients. To identify independent predictors of requiring periprocedural hemodialysis, we fit a multivariate adjusted logistic regression model.

Covariates for the regression models for periprocedural outcomes consisted of 5 variables: 3 that were predefined (STS score, DM status, and access route) owing to their known effect on periprocedural TAVR outcomes, and 2 additional variables (age and AVA) for which significant differences were found between the RTRs and control groups. The regression model used to identify independent predictors of the need for periprocedural dialysis included the same 5 covariates and 2 additional variables (CKD stage and contrast volume/eGFR ratio) identified using a forward stepwise selection process. The variables identified as independent predictors of the need for periprocedural hemodialysis were than examined for interaction with RTR status.

To analyze long-term outcomes, we generated Kaplan–Meier curves by plotting the cumulative rates of overall mortality, need for long-term hemodialysis, and a composite of the two after TAVR. These data were compared between the 2 groups, using the log-rank test. We also fit a multivariate adjusted Cox regression model to calculate the hazard ratio (HR) for the 3 outcomes for RTRs compared with control patients with adjustment for age. All analyses were performed at 1-year intervals for up to 3 years and for the longest available follow-up. All regression models were fit using Firth's penalized likelihood ratio.[19]

For patients with echocardiography data available during follow-up, we compared the average AVG (both peak and mean) between the RTRs and control patients using the independent sample Students' *t*-test. All analyses were performed using SPSS version 25.0 0 (IBM, Armonk, New York) and R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Sixteen TAVR centres from Europe (8), North America (5), and Israel (3), representing a total of 13,941 TAVR patients, took part in the study. A total of 72 RTRs underwent TAVR at these centres between November 9, 2008 and March 15, 2017, constituting 0.52% of the overall TAVR volume at these centres (median fraction, 0.53%; range, 0.16%-1.6%). For each RTR, we identified 2 matched controls who had native kidneys at the time of TAVR at the same centre as described above. Our final cohort included 216 patients (72 RTRs and 144 control patients).

Baseline characteristics

Baseline characteristics are presented in Table 1. The mean eGFR was 39.2 ± 23.6 mL/min in the RTR group vs 44.5 ± 23.6 mL/min in the control group ($P = 0.149$). The 2 groups did not differ significantly in distribution of CKD stage. RTRs were younger (72.5 ± 9.2 vs 81.2 ± 10.6 years, $P < 0.01$) with a larger aortic valve area (0.78 ± 0.19 vs 0.65 ± 0.18 cm^2, $P < 0.01$). All other characteristics were similar in the 2 groups.

Renal outcomes

Renal outcomes are illustrated in Figure 1 and Supplemental Figures S1 and S2. Among the control patients, eGFR remained stable for 1 year of follow-up: 44.5 ± 23.6, 46.9 ± 21.2, 47.5 ± 19.8, and 47.1 ± 21.1 mL/min at

Table 1. Patient characteristics

	Control patients (144)	Transplanted patients (72)	*P*
Age (years)	81.2 ± 10.6	72.5 ± 9.2	< 0.01
Female	43 (34.2%)	24 (37.5%)	0.654
Age at renal transplantation (years)	NA	59.7 ± 18.4	
Years from transplantation to TAVR	NA	12.8 ± 7.4	
Dialysis pre-transplant	NA	(80.3%)	
Diabetes mellitus	40 (32.2%)	17 (31.9%)	1.000
Hypertension	112 (87.7%)	56 (88.9%)	0.774
Atrial fibrillation	52 (43.8%)	24 (36.1%)	0.308
Chronic lung disease	30 (24.0%)	13 (20.8%)	0.732
Frailty	63 (57.5%)	38 (69.5%)	0.143
Coronary disease	73 (58.2%)	34 (55.6%)	0.771
Peripheral vascular disease	32 (26.0%)	19 (31.9%)	0.527
STS	6.86 ± 4.1	7.1 ± 4.5	0.744
NYHA III–IV	111 (77.4%)	50 (69.1%)	0.222
Baseline creatinine (mg/dL)	2.1 ± 1.5	2.5 ± 1.9	0.114
Baseline eGFR (mL/min)	44.5 ± 23.6	39.2 ± 23.6	0.149
CKD stage			
1	6 (4.2%)	2 (2.7%)	0.597
2	21 (14.5%)	11 (15.3%)	
3	70 (48.6%)	32 (44.4%)	
4	31 (21.5%)	16 (22.2%)	
5	16 (11.2%)	11 (15.3%)	
Aortic valve area (cm^2)	0.65 ± 0.18	0.78 ± 0.19	< 0.01
Peak valve gradient (mm Hg)	73.9 ± 21.9	74.8 ± 26.6	0.804
Mean valve gradient (mm Hg)	44.7 ± 14.6	44.6 ± 16.7	0.956
Bicuspid aortic valve	1 (0.7%)	1 (1.4%)	0.729
Ejection fraction (%)	51.9 ± 13.6	56.8 ± 11.6	0.111
Transfemoral access	94 (76.0%)	50 (80.6%)	0.494
General anesthesia	58 (48.3%)	25 (43.1%)	0.475
Contrast volume (mL)	113.4 ± 55.5	108.9 ± 50.2	0.584
Contrast volume/eGFR	2.5 ± 1.2	2.8 ± 1.6	0.305
Contrast volume/eGFR > 3.5	39 (31.2%)	28 (44.8%)	0.093
Valve type			0.631
Sapien	36 (34.9%)	20 (30.6%)	
CoreValve	63 (47.3%)	34 (54.2%)	
Other	25 (17.8%)	8 (15.2%)	
Immunosuppression			
Tacrolimus	NA	26 (45.8%)	
Cyclosporine	NA	18 (26.4%)	
Azathioprine	NA	4 (5.6%)	
Mycophenolate mofetil	NA	32 (54.2%)	
Steroids	NA	40 (70.6%)	
Steroid dose (prednisone equivalent, mg)	NA	5.2 ± 2.5	
Hospital days (total length of stay)	11.4 ± 3.2	12.2 ± 4.1	0.827

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement.

baseline, discharge, and 90 and 365 days post-TAVR, respectively. In contrast, RTRs exhibited a progressive decrease in eGFR post-TAVR: 39.2 ± 23.6, 36.8 ± 22.2, 32.1 ± 18.0, and 37.8 ± 21.4 mL/min at baseline, discharge, and 90 and 365 days post-TAVR, respectively. The repeated measurement mixed model confirmed a significant between-group difference in eGFR change over time ($P = 0.021$ for the time × RTR status interaction; Fig. 1). Both at discharge and 365 days post-TAVR, RTRs had a worse distribution of CKD stage and higher risk of worsening CKD stage (Supplemental Figures S1 and S2).

Periprocedural/in-hospital outcomes

Table 2 presents the periprocedural/in-hospital outcomes. The rates of the composite periprocedural/in-hospital endpoint were similar: 29.2% (21/72) of RTRs and 23.6% (34/144) of control patients ($P = 0.412$). After adjusting for age, diabetes status, aortic valve area, access route, and STS score, the OR for periprocedural/in-hospital outcome was 1.29 (95% CI, 0.64-2.66; $P = 0.504$). Regarding individual endpoints, periprocedural hemodialysis initiation was required for 14/72 (19.4%) patients in the RTR group compared with 16/144 (11.1%) patients in the control group ($P = 0.039$) after adjusting for age, diabetes status, aortic valve area, access route, STS score, CKD stage, and contrast volume/eGFR ratio. The OR for requiring periprocedural hemodialysis in the RTR group was 2.08 (95% CI, 1.25-2.51; $P = 0.046$). In all cases for which periprocedural/in-hospital hemodialysis was required, the baseline CKD stage was 3 or higher. In RTRs, hemodialysis was required in 3/32 (12.5%), 6/16 (37.5%), and 5/11 (45.4%) patients with baseline CKD stage 3, 4, and 5, respectively. The corresponding figures in the control patients were 3/70 (4.2%), 8/31 (25.1%), and 5/16 (31.1%) patients with baseline CKD stage 3, 4, and 5, respectively. As expected, baseline CKD had a significant impact on the risk of

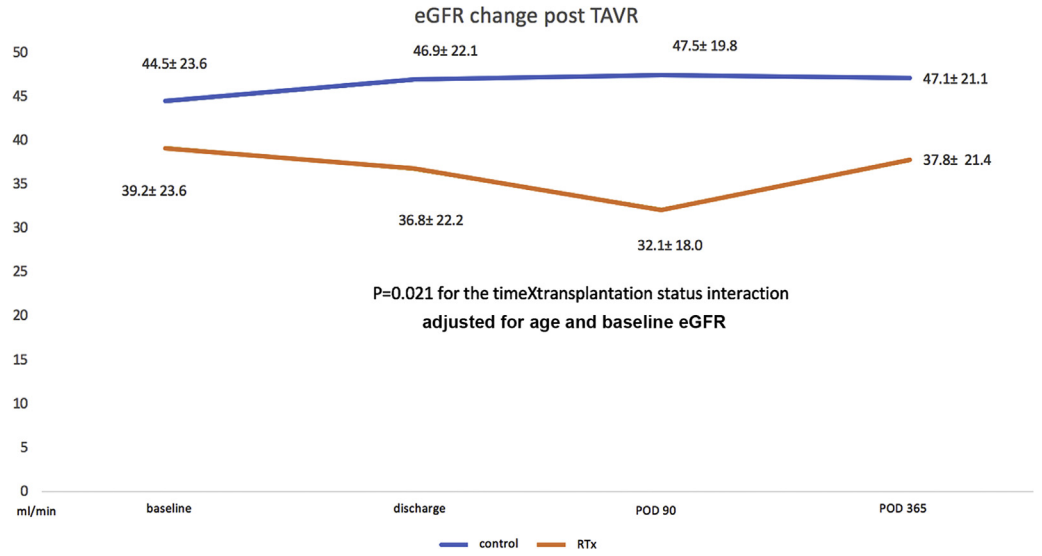

Figure 1. Change in estimated glomerular filtration rate (eGFR) up to 1 year after transcatheter aortic valve replacement (TAVR). Mean eGFR of transplanted patients (**orange**) and control patients (**blue**) at baseline, discharge, and 90 and 365 days post-TAVR.

requiring hemodialysis ($P < 0.001$) in both the RTR and control groups. Within each CKD category, the risk of hemodialysis was numerically greater in the RTR group, but the difference was not significant (stage 3: HR, 2.31; 95% CI, 0.44-8.34; $P = 0.322$; stage 4: HR, 1.81; 95% CI, 0.41-7.90; $P = 0.436$; and stage 5: HR, 1.75; 95% CI, 0.36-8.42; $P = 0.485$). The only other independent predictor of the need to initiate periprocedural hemodialysis was the ratio of contrast volume to eGFR (OR, 1.64; 95% CI, 1.36-1.97 per 1 unit increase; $P < 0.001$). The effect was more prominent in the RTR group (OR, 3.08; 95% CI, 1.38-6.91 per 1 unit increase; $P = 0.006$) compared to the control group (OR, 1.43; 95% CI, 1.19-1.71 per 1 unit increase; $P < 0.001$), with a significant interaction (P for interaction $= 0.022$). When analyzed as a categorical variable, a ratio >2.5 had an OR of 23.05 (95% CI, 8.18-27.23; $P < 0.001$) for risk of initiation of periprocedural hemodialysis. The distribution of the composite outcome of periprocedural complications and the need for periprocedural hemodialysis stratified by contrast volume/eGFR ratio tertiles are presented in Supplemental Table S2. In addition, the rate of more than mild PVL was significantly higher in the RTR group (22.2% (16/72) vs 11.1% (16/144) in the control group; $P = 0.042$). The incidence of all other periprocedural endpoints, including death (n = 3 RTRs and n = 4 control patients) were similar in both groups (Table 2).

Table 2. In-hospital outcomes

	Control (n = 144)	Transplanted (n = 72)	PV
Composite endpoint*	34 (23.6%)	21 (29.2%)	0.412
Dialysis	16 (11.1%)	14 (19.4%)	0.039
MI	0 (0%)	0 (0%)	NA
Vascular complications	7 (4.9%)	6 (8.3%)	0.326
CVA/TIA	4 (2.8%)	2 (2.8%)	1.000
PMI	20 (13.9%)	11 (15.5%)	0.836
Bleeding	13 (9.0%)	12 (16.7%)	0.289
Infection	8 (5.5%)	7 (9.8%)	0.264
Bacteremia	3 (2%)	3 (4.2%)	0.399
Death	4 (2.8%)	3 (4.2%)	0.687
> Moderate PVL	16 (11.1%)	16 (22.5%)	0.042

Adjusted odds ratio (OR) of 1.29 (95% confidence interval [CI], 0.64-2.66; $P = 0.504$) for the composite endpoint. Adjusted for age, diabetes status, aortic valve area, access route, and STS score and using Firth penalized likelihood ratio. Adjusted OR of 2.08 (95% CI, 1.25-2.51; $P = 0.046$) for periprocedural dialysis. Adjusted for age, diabetes status, aortic valve area, access route, and Society of Thoracic Surgeons (STS) score, chronic kidney disease stage and contrast volume/eGFR ratio Firth penalized likelihood ratio.

CVA/TIA, cerebrovascular accident/transient ischemic attack; MI, myocardial infarction; PMI, pacemaker implantation; PVL, paravalvular leak.

*Death/MI/need for dialysis/major vascular complications/major bleeding/CVA/TIA.

Need for long-term hemodialysis

Of the 30 patients (14 RTR and 16 control) who required periprocedural hemodialysis, only 3 (1 RTR and 2 controls) were able to discontinue hemodialysis after discharge; the other 27 patients remained on permanent hemodialysis. None of these patients underwent subsequent renal transplantation. After discharge, 6 additional RTRs and 6 additional control patients required initiation of long-term hemodialysis ($P = 0.372$).

Midterm clinical outcomes

Midterm outcomes are presented in Figure 2 and Table 3. Figure 2 also presents Kaplan–Meier curves for long-term mortality. After a median follow-up of 2.5 years (IQR, 1.5-4.6 years) in the RTR group and 2.2 years (IQR, 1.5-5.5 years) in the control group ($P = 0.293$), 21/72 (29.2%) RTRs and 46/144 (31.9%) control patients had died. Unadjusted log-rank comparisons revealed similar rates of death in the 2 groups at any stage. Adjustment for age revealed consistent results (Fig. 2A).

At the longest available follow-up, 19/72 (26.4%) RTRs and 20/144 (13.8%) control patients required permanent hemodialysis (log-rank $P = 0.036$). Compared with control patients, RTRs had a HR of 2.09 (95% CI, 1.03-3.86;

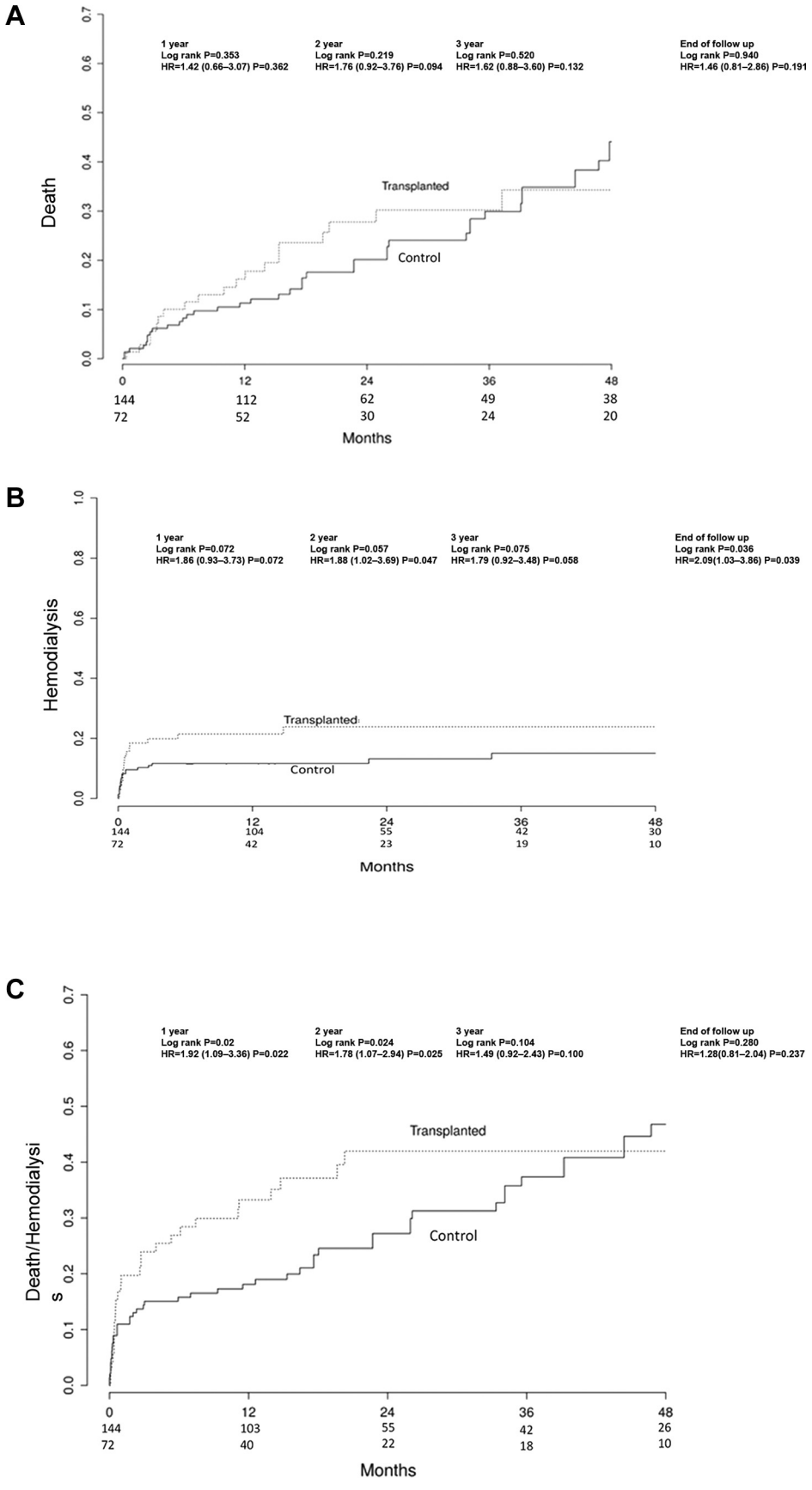

Figure 2. Kaplan—Meier curves for long-term outcomes. **(A)** mortality, **(B)** need for long-term hemodialysis, and **(C)** a composite of the 2. Unadjusted and age-adjusted comparisons are presented for each of the first 3 years of follow-up and the overall follow-up. HR, hazard ratio.

Table 3. Midterm outcomes

	Control (n = 144)	Transplanted (n = 72)	Log-rank *P*	Hazard ratio*
1 year				
Death	16 (11.1%)	12 (16.6%)	0.353	1.42 (0.66-3.07) $P = 0.362$
Hemodialysis	17 (11.8%)	16 (22.2%)	0.072	1.86 (0.93-3.73) $P = 0.072$
Death/hemodialysis	26 (18.1%)	24 (33.3%)	0.020	1.92 (1.09-3.36) $P = 0.022$
2 years				
Death	24 (16.6%)	18 (25.0%)	0.219	1.76 (0.92-3.76) $P = 0.094$
Hemodialysis	18 (12.5%)	17 (23.6%)	0.057	1.88 (1.02-3.69) $P = 0.047$
Death/hemodialysis	34 (23.6%)	28 (38.9%)	0.024	1.78 (1.07-2.94) $P = 0.025$
3 years				
Death	31 (21.5%)	19 (26.4%)	0.520	1.62 (0.88-3.60) $P = 0.132$
Hemodialysis	19 (13.2%)	17 (23.6%)	0.075	1.79 (0.92-3.48) $P = 0.058$
Death/hemodialysis	41 (28.5%)	28 (38.9%)	0.104	1.49 (0.92-2.43) $P = 0.100$
End of follow-up				
Death	46 (31.9%)	21 (29.2%)	0.940	1.46 (0.81-2.86) $P = 0.191$
Hemodialysis	20 (13.8%)	19 (26.4%)	0.036	2.09 (1.03-3.86) $P = 0.039$
Death/hemodialysis	53 (36.8%)	29 (40.3%)	0.280	1.28 (0.81-2.04) $P = 0.237$

*Adjusted for age.

$P = 0.039$) for requiring long-term hemodialysis. Analysis at 1-year intervals revealed a borderline significant unadjusted risk for hemodialysis in the RTRs (log-rank $P = 0.072$ at 1 year, 0.057 at 2 years, and 0.075 at 3 years) and a consistent trend toward higher adjusted HRs for dialysis at each time point (1 year: HR, 1.86; 95% CI, 0.93-3.73; $P = 0.072$; 2 years: HR, 1.88; 95% CI, 1.02-3.69; $P = 0.047$; and 3 years: HR, 1.79; 95% CI, 0.92−3.48; $P = 0.058$; Fig. 2B).

Overall, at the end of follow-up, 29/72 (40.3%) of RTRs and 53/144 (36.8%) of control patients were either dead or receiving permanent hemodialysis (log-rank $P = 0.280$; HR, 1.28, 95% CI, 0.81-2.04; $P = 0.237$). During the first 2 years of follow-up, RTRs had an increased risk of this composite endpoint (1 year: HR, 1.92; 95% CI, 1.09-3.36, $P = 0.022$; 2 years: HR, 1.78; 95% CI, 1.07-2.94; $P = 0.025$; Fig. 2C).

Predictors of midterm mortality

Initiation of long-term hemodialysis was the strongest independent predictor of long-term mortality within the entire cohort (HR, 2.81; 95% CI, 1.05-7.52; $P = 0.039$). Other predictors of mortality included frailty (HR, 2.11; 95% CI, 1.03-4.33; $P = 0.042$) and higher STS score (HR, 1.13; 95% CI, 1.06-1.21 per point; $P < 0.01$).

Echocardiographic follow-up

Follow-up data on valve function were available for 67/72 (94%) RTRs and 104/144 (78%) control patients. After a median follow-up of 290 (IQR, 51-442) days from TAVR, no significant difference was found between the control and RTR groups regarding peak (18.7 ± 9.1 vs 16.8 ± 7.5 mm Hg, respectively, $P = 0.167$) or mean (10.2 ± 5.3 vs 8.9 ± 3.8 mm Hg, respectively, $P = 0.98$) aortic valve gradient.

Discussion

In the current study, we aimed to describe the characteristics and outcomes of RTRs undergoing TAVR. RTRs constituted approximately 0.5% of the TAVR population; these patients were younger and had a larger valve area than the overall TAVR population. TAVR in RTRs appears to be safe in regard to periprocedural/in-hospital outcomes and effective based on mortality and is comparable with TAVR in patients with native kidneys and similar baseline characteristics. However, examination of renal outcomes revealed consistently worse results in RTRs than in patients with native kidneys. Unlike the control group, the RTR group did not have improved/stabilized eGFR following TAVR. The RTR group also had a higher likelihood of CKD category deterioration up to 1 year after TAVR. Most importantly, the RTRs had a significantly greater risk of requiring hemodialysis initiation due to TAVR, which most often resulted in loss of renal allograft function and necessitated long-term renal replacement therapy with hemodialysis.

The relationship between CKD and TAVR outcomes is a subject of considerable interest. There are 2 main concerns when considering the pros and cons of TAVR in patients with CKD. First, CKD is a well-recognized risk factor for both overall and cardiovascular morbidity and mortality.[20] Not surprisingly, most evidence indicates that advanced CKD is an independent predictor of worse outcomes following AVR,[11,21] including both TAVR and SAVR. However, given the dismal prognosis of patients with both severe AS and advanced CKD following conservative treatment, AVR should not be denied *a priori* simply based on renal function. Data suggest that both SAVR and TAVR are associated with significant benefit compared with conservative treatment in terms of mortality.[22,23]

Second, TAVR entails exposure to several risk factors for acute kidney injury (AKI) including contrast material, hemodynamic changes, bleeding, hospital stay, and infection; AKI complicates up to 18% of TAVR cases, 34% among patients with CKD.[24] A substantial proportion of these patients eventually require hemodialysis, with increased risk associated with decreasing baseline renal function.[25] Both periprocedural AKI and the need for initiation of hemodialysis are associated with increased short- and long-term mortality.[24,25] In light of the markedly decreased quality of life associated with hemodialysis,[26] the benefit gained by treating the valvular disease may be reduced or completely abolished. This issue is even more critical among RTRs. Repeat transplantation is much less likely for patients with renal function loss in an allograft compared with patients with loss of native kidney function;[12] thus, the long-term consequences of hemodialysis reinitiation are far worse than CKD in patients with native kidneys.

To optimize clinical outcomes, one must recognize the unique features of RTRs with severe AS and understand the

various risks and benefits they face when undergoing TAVR. Although RTRs constitute only a small proportion of the TAVR population (0.5%, according to our data), renal transplantations are increasingly common, and improved care of these patients results in better post-transplant survival. Thus, it is likely that the presence of RTRs among TAVR patients will increase in the future.

We think that several important lessons can be learned from our results. First, with regards to baseline characteristics, RTRs were roughly a decade younger than patients with similar renal function. This is not surprising, as CKD accelerates progression of AS.[1] Moreover, although their significantly younger age should be associated with better post-TAVR prognoses, RTRs mortality was similar to the matched control group after adjusting for age. This suggests that the RTRs were "biologically" older than their chronological age, which should be acknowledged by multidisciplinary TAVR teams when assessing candidates for this procedure. The prevalence of more than moderate PVL in our cohort was high (15%) and significantly higher in RTRs, who also had significantly larger AVA than control patients. Taken together, these findings suggest that accurate prosthetic valve sizing is more challenging in patients with CKD, especially in RTRs, probably due to the difficulty in accurately assessing valves that are severely calcified, as is usually the case with patients who have CKD.[1] Another possible explanation for suboptimal valve sizing in RTR is underuse of cardiac computed tomography (CT) as part of the assessment workup to reduce the exposure to contrast material as much as possible. However, this is probably relevant to previous eras in the TAVR evolution and less likely to have an effect in the age when CT assessment has become the norm for preprocedural planning. The higher prevalence of PVL did not result in increased mortality, likely due to the limited sample size and relatively short follow-up. However, the detrimental effects of post-TAVR PVL are well recognized,[27] and efforts should be made to avoid suboptimal valve results.

Regarding renal outcomes, our results clearly showed that RTRs had a significantly increased risk of renal function deterioration, including a roughly doubled risk of requiring long-term hemodialysis compared with patients who had similar eGFRs but native kidneys. Although long-term survival did not significantly differ between the 2 groups, RTRs had a higher mortality risk for the first 3 years of follow-up, and the risk was almost twice that of patients with native kidneys. The Kaplan−Meier curves showed a late "catch up" in mortality among the control patients (Fig. 2A), which is probably attributable to the fact that the average age of these patients was almost a decade higher than the RTRs group. Similarly, examining the chance of survival without requiring long-term hemodialysis revealed that RTRs had a lower likelihood of event-free survival during the first 2 years (almost double the risk of a clinical outcome compared with controls). The risk attenuated and lost significance with longer follow-up, likely due to the increased late mortality among control patients. As our main focus was on renal outcomes, given that overall mortality or mortality/need for hemodialysis at longest available follow-up did not differ between the groups and the *P* values of the 1-, 2-, and 3-year interval analyses were all very close to the 0.05 significance level, these results may be an incidental finding and be viewed cautiously.

Previous studies reported a post-TAVR hemodialysis incidence of up to 3%,[24,25] with an HR of 3.5 among patients with CKD.[25] In our cohort, RTRs had an almost 8-fold greater requirement for hemodialysis than reported in the overall TAVR population and an almost 3-fold increase compared with patients with CKD undergoing TAVR. This probably stems from the lower renal reserves of RTRs compared with patients who have native kidneys, even with similar eGFRs. The high risk for dialysis in our control group (11.1%) is explained by the much higher proportion of patients with stage 4 to 5 CKD in our control group compared with previous studies (33% vs 17%).[25] Notably, initiation of hemodialysis after TAVR is associated with a significantly reduced quality of life and substantially increased risk of death (HR of 2.8 in our study, with similar results reported by Ferro et al.[25]). This increased risk should be considered and discussed with patients during the evaluation for TAVR, as it may have great impact on their likelihood of gaining benefit from the procedure. Importantly, RTRs with CKD stage 1 to 3 had substantially better rates of long-term mortality (18.3%), less than half the rate of mortality of patients with CKD stages 4 to 5, and comparable with the mortality rate in the overall TAVR population. These data indicate that, among RTRs with reasonable renal function, TAVR is associated with significant clinical benefit.

Our data suggest that the ratio of contrast volume to eGFR was the most significant predictor of the need for periprocedural hemodialysis, which almost always resulted in permanent loss of autonomous renal function. Although this was true among patients with native kidneys and those with allografts, the impact was significantly greater in RTRs. This finding is in line with current evidence regarding risk of AKI following angiography[28] and highlights the need to use measures to minimize contrast volume in RTRs undergoing TAVR, such as fusion imaging for valve implantation and transesophageal echocardiography to evaluate post-implantation regurgitation, as well as exploring possible hydration protocols and means of renal protection during TAVR, as has been done in the PCI population.[29-31] The importance of minimizing the use of contrast material is highlighted by the fact that the mean volume was just above 100 mL, and yet the rates of hemodialysis were substantial. This, in turn, highlights the importance of considering the contrast volume/eGFR ratio rather than absolute contrast volume in patients with CKD.

Finally, the long admission period in our cohort (12 days) is another indication of the complex nature of the patients and high rate of periprocedural complications, some of which (PMI, initiation of dialysis, vascular complications, infection/bacteremia) would be expected to prolong the hospital stay significantly. Although not having an impact on clinical benefit, the high rate of periprocedural complicationsand consequently the long admission period for RTR has bearing on the cost effectiveness of TAVR in these patients. As previously reported in both the United States[32,33] and Canada,[34] TAVR is cost effective in both high- as well as intermediate-risk patients. This cost effectiveness, however, is based on cost savings in terms of admission length and periprocedural complications in favour of TAVR, balancing the increased up-front additional costs of the TAVR valve. Given our data, this may not apply to RTR.

Limitations

Our study has several limitations. The sample size was modest, but it was reflective of the frequency of RTRs within the TAVR population and was similar to studies in other populations with significant noncardiac comorbidities and undergoing TAVR.[35] We did not use propensity score matching for the selection of control patients, but they were still selected using uniform criteria relating to the major characteristics expected to affect the examined outcomes; out of 27 variables presented in Table 1, the RTR and control groups differed in only 2 (age and AVA), which attests to the validity of our control-group selection. The retrospective design renders our results prone to confounding, even with the use of matching and multivariate adjustment. Our follow-up period for renal outcomes was only 1 year post-TAVR. We did not include data on other parameters of renal function, such as proteinuria, which is known to have a significant effect on the progression of renal disease.[36] We could not examine the risk/benefit profile of SAVR/TAVR in RTRs because this was beyond the scope of our intended aims, especially as the high mortality rates of RTRs undergoing valve surgery have already been described,[13] and the preliminary data available on the advantages of TAVR over SAVR in these patients are limited.[15] We did not assess stroke, heart failure, or any other possible long-term endpoints except for mortality and initiation of hemodialysis. Finally, because we performed multiple analyses and did not specify a primary endpoint or performed power calculations for any of the endpoints, our results should be considered exploratory and hypothesis generating and require confirmation from larger adequately powered studies.

Conclusions

RTRs constitute a small proportion of the TAVR population and have several distinctive characteristics. Although their prognosis regarding mortality and valve performance was equivalent to patients with similar renal function, they exhibited a higher risk of adverse renal outcomes. Unlike patients with native kidneys, RTRs continued to have deterioration of renal function after TAVR and had a substantial risk of post-TAVR initiation of hemodialysis. Minimizing the contrast volume used during TAVR appears to be crucial to avoid adverse renal outcomes in these patients. Further research is required to examine the risk/benefit profile of RTRs undergoing TAVR.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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