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ORIGINAL RESEARCH

Outcomes of Surgical Mitral and Aortic Valve Replacements Among Kidney Transplant Candidates: Implications for Valve Selection

David K. Ngendahimana, PhD; Salil V. Deo, MD; Varun Sundaram, MD; Krista L. Lentine, MD, PhD; Charles A. Herzog, MD; Laith Al Dahabreh, MD; Titte R. Srinivas, MD; Kenneth D. Chavin, MD, PhD; Nagaraju Sarabu, MD, MPH

BACKGROUND: Limited literature exists that evaluated outcomes of kidney transplant–eligible patients who are having dialysis and who are undergoing valve replacement. Our main objective in this study was to compare mortality, reoperation, and bleeding episodes between bioprosthetic and mechanical valve procedures among kidney transplant–eligible patients who are having dialysis.

METHODS AND RESULTS: We studied 887 and 1925 dialysis patients from the United States Renal Data System, who underwent mitral valve replacement and aortic valve replacement (AVR) after being waitlisted for a kidney transplant (2000–2015), respectively. Time to death, time to reoperation, and time to bleeding requiring hospitalizations were compared separately for AVR and mitral valve replacement. Kaplan–Meier survival curves, Cox proportional hazards model for time to death, accelerated time to event model for time to reoperation, and counting process model for time to recurrent bleeding were used. There were no differences in mortality (hazard ratio [HR], 0.92; 95% CI, 0.77–1.09) or risk of reoperation or risk of significant bleeding events between bioprosthetic and mechanical mitral valve replacement. However, mechanical AVR was associated with a modestly significant less hazard of death (HR, 0.83; 95% CI, 0.74–0.94) compared with bioprosthetic AVR. There were no differences in time to reoperation, or time to significant bleeding events between bioprosthetic and mechanical AVR.

CONCLUSIONS: For kidney transplant waitlisted patients who are on dialysis and who are undergoing surgical valve replacement, bioprosthetic and mechanical valves have comparable survival, reoperation rates, and bleeding episodes requiring hospitalizations at both mitral and aortic locations. These findings emphasize that an individualized informed decision is recommended when choosing the type of valve for this special group of patients having dialysis.

Key Words: end-stage renal disease ■ kidney transplant ■ survival ■ United States Renal Data System ■ valve replacement

Valvular heart disease is highly prevalent in patients with end-stage kidney disease (ESKD) and has been identified in up to 14% of the patients.[1] The presence of valvular heart disease confers an increased risk of mortality in ESKD[2] and ESKD adversely influences outcomes following surgical valve replacement (VR).[3] The recommendations for choice of valve type during surgical VR for patients with ESKD varied by era. In 1998, Bonow et al recommended that mechanical VR is more appropriate based on anecdotal reports that bioprosthetic valves undergo faster degeneration in patients with ESKD because of impaired calcium homeostasis.[4] However, a USRDS (United States Renal Data System)–based registry analysis of >5000 patients with ESKD who underwent VR reported a 2-year risk of death, which

Correspondence to: Nagaraju Sarabu, MD, MPH, Transplant Institute, 11100 Euclid Ave, Cleveland, OH 44106. E-mail: nagaraju.sarabu@uhhospitals.org

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CLINICAL PERSPECTIVE

What Is New?

- This retrospective large registry database reports comparative outcomes (mortality, reoperation rates, and bleeding episodes) of surgical bioprosthetic and mechanical valve replacements among a special population with end-stage kidney disease, those who are waiting for a kidney transplant (KT).
- Mortality, reoperation rates, and bleeding episodes were comparable between bioprosthetic and mechanical valve replacements for patients with end-stage kidney disease who are waiting for a KT.
- Prospective kidney transplantation after surgical valve replacement among those who are waiting for a kidney transplant is associated with a remarkable decrease in the hazard of death at >4-fold.

What Are the Clinical Implications?

- The recent recommendation made by the American College of Cardiology/American Heart Association in 2017 that choice of bioprosthetic versus mechanical for valve replacement should be a shared decision between patient and providers for the general population is also supported in the context of patients with end-stage kidney disease who are waitlisted for KT.
- KT waitlisted patients with end-stage kidney disease requiring valve replacement will benefit from subsequent KT and hence KT is a viable option for patients with end-stage kidney disease who have undergone valve replacement.

Nonstandard Abbreviations and Acronyms

aHR	**adjusted hazards ratio**
AVR	**aortic valve replacement**
bAVR	**bioprosthetic aortic valve replacement**
bMVR	**bioprosthetic mitral valve replacement**
ESKD	**end-stage kidney disease**
KT	**kidney transplantation**
mAVR	**mechanical aortic valve replacement**
mMVR	**mechanical mitral valve replacement**
MVR	**mitral valve replacement**
USRDS	**United States Renal Data System**
VR	valve replacement

was no different between bioprosthetic and mechanical VR (relative risk [RR], $_{0.90}0.98_{1.07}$).[5] Accordingly, the American College of Cardiology/American Heart Association 2006 guidelines did not recommend a preference for choice of valve.[6] Subsequently, 2 systematic reviews concluded that bioprosthetic valves may be preferred since bioprosthetic valves undergo degeneration at low rates, mechanical valves have anticoagulation risks, and both valves have comparable survival rates.[7,8] The most recent American College of Cardiology/American Heart Association guidelines recommend valve selection solely based on shared decision making, which should involve discussion of risks of anticoagulation with mechanical valves versus risks of degeneration with bioprosthetic valves and consider patient preference.[9]

Previous literature evaluating outcomes from VR among patients with ESKD have limitations. Most of the studies included all patients on dialysis, with no specific analyses of those who are transplant eligible and subsequently undergo kidney transplantation (KT). Abbott et al reported that while valvular heart disease was a barrier to KT, receiving VR was not.[10] On the other hand, Sharma et al showed that among patients with a functioning KT who underwent VR, bioprosthetic valves had marginal survival benefit compared with mechanical valves. However, studies are lacking evaluating outcomes of VR among waitlisted dialysis patients, who represent a special subset because they are screened by transplant centers and generally not waitlisted if they have active infection, malignancy, substance abuse, uncontrolled psychiatric illness, nonadherence, and significantly shortened life expectancy.[11] In 2016, 81 418 patients on dialysis were on the waitlist and 20 161 KT were performed in the United States.[1] It has been shown that waitlisted patients on dialysis and KT recipients have up to 3 times and 4 times lower mortality, respectively, compared with the general dialysis population.[12] For the patients with ESKD in the United States who began dialysis in 2011, 5-year survival was 42% to 52%, compared with 77% to 84% for those who received a KT in the same year.[1] Previous studies are also limited by a shorter follow-up period (mean of 2 years), which is much less than the average life expectancy of patients with ESKD following KT.[3] Accordingly, the pattern of complications including bleeding, valve degeneration, infective endocarditis, etc may be expected to be different in patients with ESKD listed for transplant.

To help address these knowledge gaps, we performed a large cohort study using the national USRDS to investigate mortality, reoperation rates, and bleeding complications associated with surgical and transcutaneous VR among patients who were dialysis dependent and on the waitlist.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the USRDS at usrds@usrds.org.

The study protocol was approved by the University Hospitals Cleveland Medical Center Institutional Review Board and requirement for informed consent was waived. Data were extracted from the USRDS, which is a US national registry representing >94% of patients with ESKD and includes linked Medicare administrative claims.[13] The enrollment period was from January 1, 2000 to September 30, 2015. We identified all adults (age >18 at ESKD diagnosis), who received dialysis for at least 90 days before the hospitalization for VR surgery between January 1, 2000 and September 30, 2015, were waitlisted for KT before VR surgery, and who were primary Medicare beneficiaries (Figure 1). The observation period was from the date of valvular surgery (ie, enrollment date) and until death or the last date of the study period (ie, September 30, 2015).

Exposure

The type of prosthetic valve used for VR was ascertained by *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) procedure codes: 35.21 and 35.22 for bioprosthetic aortic valve replacement (bAVR) and mechanical aortic valve replacement (mAVR), respectively, and 35.23 and 35.24 for bioprosthetic mitral valve replacement (bMVR) and mechanical mitral valve replacement

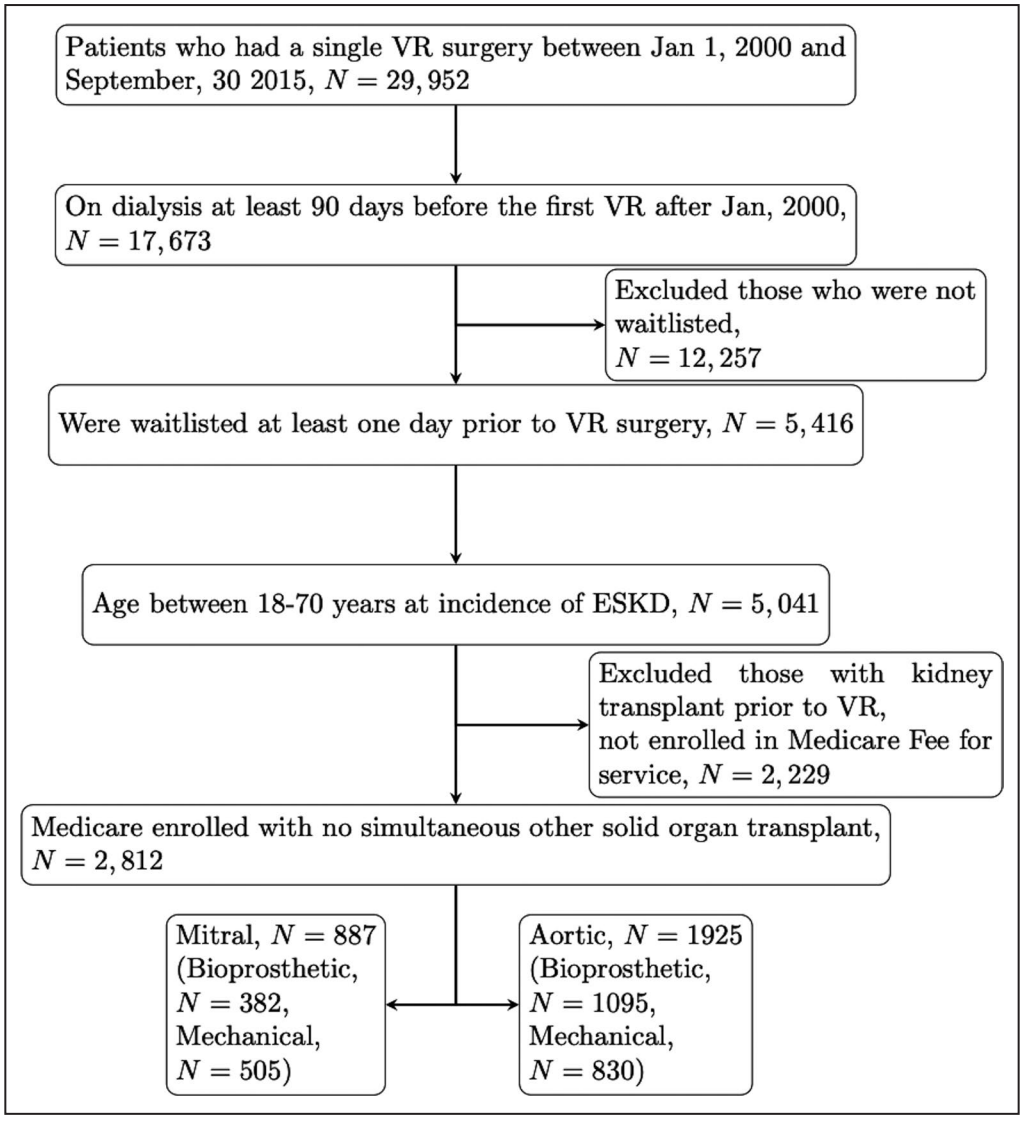

Figure 1. Flow chart of study participants selection.
ESKD indicates end-stage kidney disease; and VR, valve replacement.

(mMVR). We identified those who underwent transcatheter aortic valve replacement using the codes 35.05 and 35.06 and included these patients in the bAVR group.

Outcomes

The main outcomes were mortality, reoperation for second VR (ascertained by the same *ICD-9-CM* codes as above), and bleeding episodes requiring hospitalizations (ascertained by *International ICD-9-CM* codes, Table S1): hemorrhage of gastrointestinal tract, acute blood loss anemia, hemorrhage-unspecified, subdural hemorrhage, subarachnoid hemorrhage, and hemorrhage complicating a procedure or intracerebral hemorrhage. The USRDS collects "death" from multiple sources and that information is almost 100% for the cohort.[14] If "death" was not available in the USRDS by the end of the study period, it was assumed that the patient was alive by the end of the study period. For reoperation and bleeding events, we assumed that if the billing codes were not in the database, those respective events did not occur. It was a fair assumption because discontinuation of Medicare is rare.[15] In addition, we also compared causes of death between bioprosthetic and mechanical VR.

Covariates

Patient baseline demographic and clinical characteristics included age, sex, race, ethnicity, body mass index, cause of renal failure, dialysis access used for first dialysis, and initial mode of dialysis (peritoneal and hemodialysis) at the time of initiation of dialysis. Since comorbid conditions greatly impact the survival of patients undergoing dialysis, we utilized a previously developed comorbid profiling methodology based on *ICD-9-CM* diagnosis and procedure codes in the Medicare Part A institutional claims.[16] These included a diagnosis of cancer, diabetes mellitus, atherosclerotic heart disease, congestive heart failure, cerebrovascular accident and transient ischemic attack, peripheral vascular disease, other cardiac diseases, and chronic obstructive pulmonary disease before VR surgery. Concomitant coronary artery bypass graft surgery occurring on the same day as VR surgery was also identified.

Statistical Analysis

Analysis was performed separately for Mitral Valve Replacement (MVR) and aortic valve replacement (AVR). Baseline characteristics were compared between bioprosthetic and mechanical VR, using χ^2 for categorical variables and parametric *t* test or nonparametric Kruskal–Wallis test for continuous variables. We compared time to death and time to reoperation for another VR between bioprosthetic and mechanical using Kaplan–Meier survival curves and log-rank test. For both these outcomes, time zero was the time of VR and they were right censored at the end of the study period, which was September 30, 2015. KT after VR was modeled as time-dependent covariate. We used univariate and multivariate Cox proportional hazards models to estimate impact of valve type on time to death. Time to reoperation was examined using a semiparametric accelerated failure time model given the violation of the proportional hazard assumption and was also censored at the time of death. Additionally, the semiparametric version of the accelerated failure time was selected to avoid misspecification of the error distribution leading to bias in our estimates.[17] Reoccurrence of bleeding, with the same definition of time zero and censoring as reoperation, was investigated using the counting process model by Andersen-Gill, an extension of the Cox regression model.[18] For the purpose of this analysis, bleeding episodes were truncated at 4. Multiple imputation using the fully conditional specification implemented by the chained equations algorithm[19] was performed for missing body mass index data of 7 patients (0.01). Distribution of causes of death between bioprosthetic and mechanical VR was compared using χ^2 test. Statistical analyses were performed using SAS Version 9.3 (SAS Institute, Cary NC) and R version 4.0.2.

RESULTS

Baseline Characteristics

For the MVR cohort, there were 382 patients who received bMVR and 505 patients who received mMVR. For the MVR cohort, median (interquartile range) follow-up times were 1.35 (0.28–2.70) years for bMVR and 1.5 (0.37–3.41) years for mMVR. A higher proportion of those who received bMVR were older than 50 years, had atherosclerotic heart disease, and had simultaneous coronary artery bypass grafting compared with those who received mMVR (Table 1). For the AVR cohort, there were 1095 (11 with transcatheter aortic valve replacement) and 830 patients who underwent bAVR and mAVR, respectively. For the AVR cohort, median (interquartile range) follow-up times were 1.31 (0.42–3.02) years for bAVR and 1.95 (0.64–4.35) years for mAVR. A higher proportion of those who received bAVR were also older than 50 years, had higher prevalence of cancer, diabetes mellitus, atherosclerotic heart disease, congestive heart failure, chronic obstructive pulmonary disease, and had a higher body mass index than those who received mAVR (Table 1). In addition, patients were more likely to have received

Table 1. Demographic Characteristics of Patients on Dialysis on the Kidney Transplant Waitlist With Valve Replacement Between 2000 and 2015

Variables	Mitral		Aortic	
	Bioprosthetic (%) (N=382)	Mechanical (%) (N=505)	Bioprosthetic (%) (N=1095)	Mechanical (%) (N=830)
>50 y	62.0*	39.0*	79.1*	60.1*
Race				
Black	54.7	49.7	66.5	62.0
White	38.0	44.6	27.7	31.0
Other†	7.3	5.7	5.8	7.0
Hispanic ethnicity				
Hispanic	84.0	82.6	87.7	84.5
Non-Hispanic	8.4	11.5	7.3	9.9
Not specified	7.6	5.9	5.0	5.7
BMI, kg/m^2	30.02 (6.97)	29.59 (7.13)	30.85 (7.07)*	29.98 (6.50)*
Primary cause of renal disease				
PKD	4.2	3.8	3.7	3.5
DM	39.8	36.4	41.7	39.8
glomerulonephritis	15.2	15.4	15.4	18.9
Hypertension	25.7	26.7	26.3	26.0
Other	15.2	17.6	12.8	11.8
Medicaid and Medicare eligibility	9.4	13.5	8.6	9.0
Peritoneal dialysis	13.6	14.9	11.8	14.6
Cancer	5.5	4.6	8.0*	5.1*
DM	56.8	52.1	60.6*	52.7*
Atherosclerotic heart disease	69.6*	59.2*	78.8*	69.0*
Congestive heart failure	76.2	74.1	73.8*	68.1*
CVA/TIA	29.3	28.1	24.0	18.0
Peripheral vascular disease	40.1	36.2	45.2	41.7
Other cardiac disease	96.9	96.6	96.2	94.7
Chronic obstructive pulmonary disease	34.0	30.5	32.7*	27.6*
Kidney transplant	11.8*	15.8*	18*	23.1*
Year of surgery				
2000–2010	39.3*	47.3*	36.9*	51.8*
2011–2015	60.7*	52.3*	63.1*	49.2*
Coronary artery bypass grafting	31.2*	23.2*	35.9	36.4

Values are column percentages for all variables, except for body mass index (BMI), which are mean (SD). CVA/TIA indicates cerebrovascular accident/transient ischemic attack; DM, diabetes mellitus; and PKD, polycystic kidney disease.

* Statistically significant differences, $P<0.05$.

†American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, Other or Multiracial, Unknown.

bioprosthetic valves, both in mitral and aortic positions, if the valve replacement was more recent (2011–2015 versus 2000–2010).

Rates of Kidney Transplantation

During the follow-up period, for the MVR cohort, 125 (32.7%) patients had at least 1 KT (45 in bMVR and 80 in mMVR) with median time to first transplant 1.11 years in bMVR and 1.66 years in mMVR. During the follow-up period, for the AVR cohort, 389 (35.5%) patients had at least 1 KT (197 in bAVR and 192 in mAVR) with median time to first transplant of 1.12 years in bAVR and 1.03 years in mAVR.

Time to Death

During the study period, 235 patients in bMVR and 297 patients in mMVR died. Survival rates at 1, 3, and 5 years were 61%, 36%, and 19%, respectively for bMVR and 66%, 43%, and 30%, respectively, for mMVR (Figure 2A). In the univariate Cox model, those who received mMVR

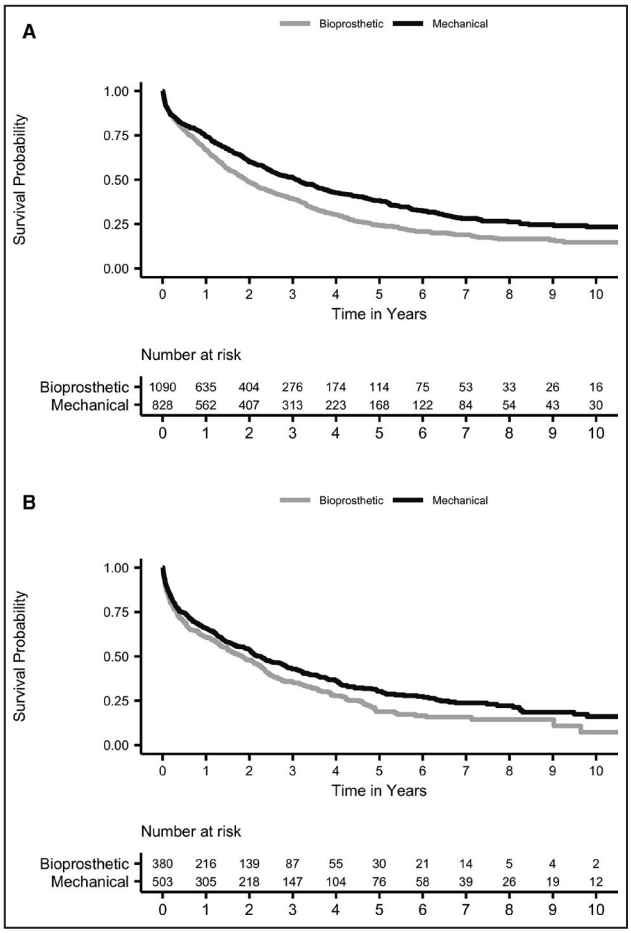

Figure 2. Unadjusted all-cause mortality-free survival, for patients on the kidney transplant waitlist with dialysis and valve replacement (VR) between 2000 and 2015, by valve type[§]: (A) mitral valve replacement (MVR) and (B) aortic valve replacement (AVR).
[§]The numbers at risk at time zero are slightly lower than the whole cohort in Table 1 because of exclusion of 4 MVR cases (2 bioprosthetic MVR and 2 mechanical MVR cases) and a total of 7 AVR (5 bioprosthetic AVR and 2 mechanical AVR cases) because these cases were considered to have a data entry error since date of VR was indicated as occurring after death.

were 20% less likely to die (hazard ratio [HR], $_{0.68}0.80_{0.94}$), which was statistically significant, compared with those who received bMVR. In the multivariate model, there was no statistically significant difference in mortality rates between bMVR and mMVR (adjusted hazard ratio [aHR], $_{0.78}0.93_{1.10}$). Risk factors for higher hazard of death among the MVR cohort included diabetes mellitus (aHR, $_{1.10}1.85_{3.12}$) and hypertension (aHR, $_{1.02}1.69_{2.82}$) as the causes of ESKD, compared with polycystic kidney disease, atherosclerotic heart disease (aHR, $_{1.02}1.25_{1.54}$), and chronic obstructive pulmonary disease (aHR, $_{1.02}1.21_{1.45}$). Among the factors that were associated with lower hazards of death, receiving a KT, compared with remaining on dialysis, had the strongest association at 83% reduction (aHR, $_{0.12}0.17_{0.24}$). Other factors that were associated with lower hazards of death were Black race versus White race (aHR, $_{0.63}0.76_{0.92}$) and Hispanic versus non-Hispanic ethnicity (aHR, $_{0.51}0.69_{0.92}$) (Table 2). Cardiovascular causes of death were the most common (44%) in both bMVR and mMVR, followed by unknown and infectious causes. There was no significant difference in the distribution of causes of death between bMVR and mMVR (Table S2).

During the study period, 606 patients in bAVR and 466 patients in mAVR died. Survival rates at 1, 3, and 5 years were 67%, 39%, and 24%, respectively for bAVR and 75%, 51%, and 38%, respectively for mAVR (Figure 2B). In the univariate Cox model, those who received mAVR had 27% less hazard of death (HR, $_{0.65}0.73_{0.82}$), which was statistically significant, compared with those who received bAVR. This relationship remained significant in the multivariate model, and mAVR was associated with lower hazard of death (aHR, $_{0.73}0.82_{0.93}$). Other notable variables that were associated with higher hazard of death included age >50 years (aHR, $_{1.02}1.18_{1.36}$), history of cerebrovascular accident or transient ischemic attack (aHR, $_{1.06}1.22_{1.40}$), and having chronic obstructive pulmonary disease (aHR, $_{1.02}1.15_{1.31}$). Receiving a KT after VR was associated with 89% lower hazard of death (aHR, $_{0.08}0.11_{0.14}$) and being of Hispanic ethnicity was associated with 18% lower hazard of death (aHR, $_{0.58}0.72_{0.89}$) (Table 2). Cardiovascular causes were again the most common cause of death in both bAVR and mAVR (45%), followed by unknown and infection with no significant differences in distribution of causes of death between both groups (Table S2).

Time to Reoperation

Reoperation incidence was 6% at 10 years for bMVR, compared with 9% for mMVR, which was not statistically significant (Figure 3A). The mean time to reoperation for the mMVR group was similar to that of the bMVR group, which is not statistically significant (mMVR versus bMVR estimated [adjusted] ratio of geometric means of time to reoperation is $\exp^{-0.01}$=0.99). Having MVR after 2010 was associated with longer time to reoperation for repeat MVR. Having peritoneal dialysis and other cardiac disease were associated with a shorter time to MVR reoperation. Reoperation rates were 11% at 10 years for bAVR, compared with 6% for mAVR, respectively (Figure 3B). Receiving bAVR versus mAVR did not significantly change time to reoperation. In the multivariate adjusted models, while receiving a KT had no significant effect for the hazard of reoperation for MVR, it was associated with delay in time to reoperation for AVR (estimated [adjusted] ratio geometric means of time to reoperation for those who receive KT after AVR was 1.95 [$\exp^{0.67}$]) (Table 3).

Time to Hemorrhage

In the MVR cohort, the mean number of bleeding reoccurrences was 2.30 and 2.45 per patient for bMVR

Table 2. Unadjusted and Adjusted All-Cause Mortality HR for Patients on the Kidney Transplant Waitlist With Dialysis and Valve Replacement Between 2000 and 2015

Variables	Mitral		Aortic	
	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
Type of valve				
Mechanical	0.80 (0.68, 0.94)†	0.93 (0.78, 1.10)	0.73 (0.65, 0.82)†	0.82 (0.73, 0.93)†
Bioprosthetic				
>50 y (%)		1.09 (0.90, 1.30)		1.18 (1.02, 1.36)†
Race (%)				
Black		0.76 (0.63, 0.92)†		0.91 (0.79, 1.04)
Other‡		0.95 (0.68, 1.32)		1.10 (0.87, 1.4)
White (ref.)				
Hispanic ethnicity (%)				
Hispanic		0.69 (0.51, 0.92)†		0.72 (0.58, 0.89)†
Not specified		1.02 (0.73, 1.44)		0.77 (0.58, 1.03)
Non-Hispanic				
BMI, mean (SD)		0.99 (0.98, 1.01)		1 (0.99, 1.01)
Primary cause of renal disease				
DM		1.85 (1.10, 3.12)†		0.93 (0.67, 1.28)
Glomerulonephritis		1.38 (0.82, 2.33)		0.76 (0.55, 1.06)
Hypertension		1.69 (1.02, 2.82)†		0.73 (0.53, 1)
Other		1.48 (0.88, 2.50)		0.86 (0.61, 1.21)
PKD (ref.)				
Peritoneal dialysis (%)		0.91 (0.70, 1.16)		1.18 (0.99, 1.4)
Cancer		1.40 (0.98, 2.00)		1.05 (0.84, 1.32)
DM		1.15 (0.91, 1.46)		0.97 (0.83, 1.13)
Atherosclerotic heart disease		1.25 (1.02, 1.54)†		1.08 (0.92, 1.26)
Congestive heart failure		1.15 (0.94, 1.42)		1.02 (0.89, 1.17)
CVA/TIA		1.16 (0.96, 1.40)		1.22 (1.06, 1.4)†
Peripheral vascular disease (%)		0.90 (0.75, 1.08)		1.08 (0.96, 1.22)
Other cardiac disease		1.07 (0.65, 1.78)		0.95 (0.72, 1.25)
Chronic obstructive pulmonary disease		1.21 (1.02, 1.45)†		1.15 (1.02, 1.31)†
Valve replacement surgery occurring between 2011 and 2015		0.91 (0.76, 1.10)		1.13 (0.99, 1.28)
Coronary artery bypass grafting		0.99 (0.81, 1.21)		1.05 (0.92, 1.19)
Kidney transplant		0.17 (0.12, 0.24)†		0.11 (0.08, 0.14)†

BMI indicates body mass index; CVA/TIA, cerebrovascular accident/transient ischemic attack; DM, diabetes mellitus; HR, hazard ratios; and PKD, polycystic kidney disease.

*Hazards ratio adjusted for age category (<50 years or at least 50 years), year of valve replacement surgery, race, ethnicity, BMI, primary cause of renal disease, dialysis type, whether patient had coronary artery bypass graft, comorbidity status (ie, cancer, DM, atherosclerotic heart disease, congestive heart failure, CVA/TIA, peripheral vascular disease, other cardiac disease, chronic obstructive pulmonary disease) and subsequent kidney transplant.

†Statistically significant differences, $P<0.05$.

‡American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, Other or Multiracial, Unknown.

and mMVR, respectively for the entire follow-up period. For the AVR, the mean number of bleeding episodes was 2.30 and 2.42 per patient for the follow-up period for bAVR and mAVR, respectively. For patients with MVR and patients with AVR, risk of bleeding associated with bioprosthetic and mechanical valves was not significantly different (aHR, $_{0.8}1.03_{1.31}$ and aHR, $_{0.82}0.94_{1.09}$, respectively) (Table 4).

DISCUSSION

In this retrospective registry analysis of adult US patients with ESKD, who were waitlisted for KT, were Medicare beneficiaries, and underwent valve replacement, we identified the following important findings: (1) Older patients with a higher comorbidity burden are more likely to receive bioprosthetic valves for both

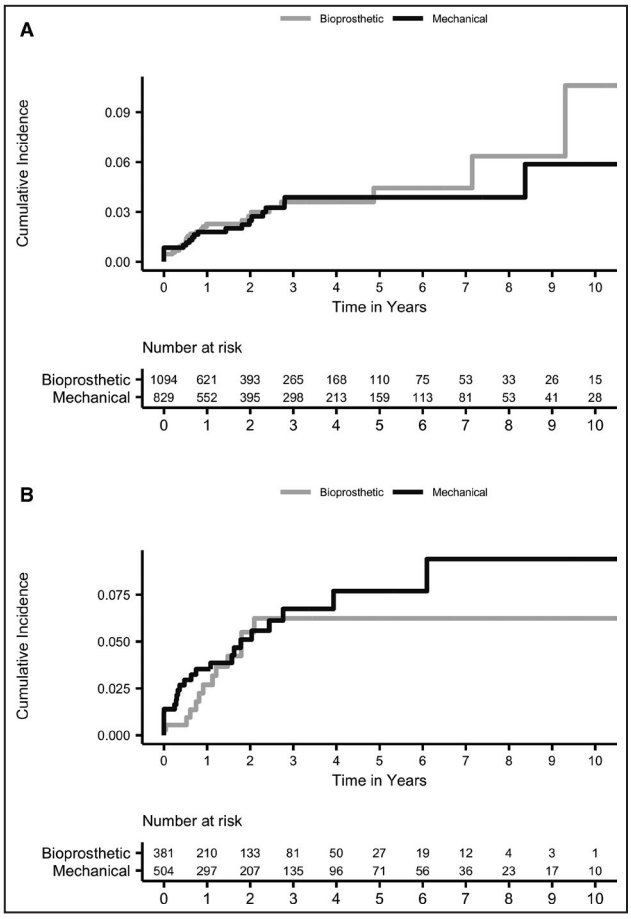

Figure 3. Unadjusted estimated cumulative incidence of reoperation, for patients on the kidney transplant waitlist with dialysis and valve replacement (VR) between 2000 and 2015, by valve type[§]: (A) mitral valve replacement (MVR) and (B) aortic valve replacement (AVR).

[§]The numbers at risk at time zero are slightly lower than the whole cohort in Table 1 because of exclusion of 2 MVR cases (1 bioprosthetic MVR case and 1 mechanical MVR case) and 2 AVR (1 bioprosthetic AVR case and 1 mechanical AVR case) because these cases were considered to have a data entry error since date of reoperation was indicated as occurring before first VR.

MVR and AVR. (2) The adjusted all-cause survival was no different between mechanical and bioprosthetic for MVR but was modestly better for mAVR than bAVR. (3) Reoperation rates were <10% and did not differ between mechanical and bioprosthetic valves for both MVR and AVR. (4) The risk of bleeding associated with bioprosthetic and mechanical valves was also not significantly different in both locations. (5) Receiving KT after valve replacement was associated with a remarkably lower hazard of death for both MVR and AVR, decreased reoperation rates for AVR (but not for MVR), and increased bleeding episodes requiring hospitalization for both MVR and AVR, compared with remaining on dialysis.

Our observation of younger age and lesser comorbidity among those who received mechanical valves resonated with many prior studies of patients with ESKD.[5,20,21] Poor survival of patients in our study, especially in the first year after VR (61%–75%), was also reflected in previous studies.[5,21–23] We observed similar overall survival rates between mechanical versus bioprosthetic VR, at mitral location but a modest reduction in death (18%) with mAVR compared with bAVR, after adjustment for known confounders. Previous literature studying long-term survival among patients with ESKD included all prevalent patients with dialysis and studied MVR and AVR as 1 group. In our recent systematic review that included 15 retrospective studies (2000–2015) with 5523 mechanical valves and 1600 bioprosthetic valves, valve choice did not influence long-term mortality (aHR, $_{0.73}0.87_{1.04}$).[8] In a study that included 1335 recipients of KT who underwent VR (966 mechanical and 369 bioprosthetic) and had a 2-year median follow-up, Sharma et al showed that bioprosthetic valves were associated with a modest but significant survival benefit (aHR, $_{0.70}0.83_{0.99}$).[24] Findings on overall survival in our study are generally consistent with previous literature with minor caveats, which may be attributed to residual confounding or random statistical variations. Since patients with mAVR were significantly younger, had less cardiovascular disease burden, had lower prevalence of chronic obstructive pulmonary disease, higher rates of KT, and the fact that the effect estimate is marginally significant, we believe that the finding of statistically significant survival benefit associated with mAVR compared with bAVR is reflective of selection bias. Our study adds to the currently existing literature by reporting survival outcomes on a special dialysis population (ie, those who are waitlisted for a KT). The 30% to 35% KT rates in our study cohort were lower than the 50% KT rates in the general waitlisted patients,[25] which is probably because of the higher comorbidity burden of our patients. By virtue of our study's novel design, we were also able to show that KT after VR was associated with a profound reduction in mortality of up to 5-fold. However, it should also be noted that receiving KT is likely associated with selection bias, which may have contributed to this remarkable association with improved survival.

Our rates of reoperation were higher than the previously reported 7%[23] and 2%[21] reoperation rates for structural valve degeneration, likely because we did not limit indication for reoperation as structural degeneration and also because of censoring at death, which is a competing risk. Our finding that time to reoperation was no different between bioprosthetic and mechanical valves is different from the pooled estimates in our systematic review, where bioprosthetic valves were associated with lesser relative risk for reoperation (adjusted RR: $_{0.11}0.32_{0.91}$).[8] Reasons

Table 3. Unadjusted and Adjusted Valve Replacement Effect on Reoperation for Patients on the Kidney Transplant Waitlist With Dialysis and Valve Replacement Between 2000 and 2015

Variables	Mitral		Aortic	
	Unadjusted Effect Estimate (SE)	Adjusted Effect Estimate (SE)*	Unadjusted Effect Estimate (SE)	Adjusted Effect Estimate (SE)*
Valve type				
Mechanical	−0.22 (0.27)	−0.01 (0.2)	0.03 (0.22)	0.27 (0.21)
Bioprosthetic (Ref.)				
Over 50 y		0.3 (0.25)		0.54 (0.21)†
Year of valve replacement surgery				
Between 2011 and 2015		0.92 (0.22)†		0.66 (0.19)†
Between 2000 and 2010 (ref.)				
Race, %				
Black		−0.38 (0.21)		0.35 (0.28)
Other§		0.2 (0.4)		0.55 (0.85)
White (ref.)				
Hispanic ethnicity (%)				
Hispanic		−0.24 (0.28)		0.3 (0.29)
Not specified		−0.74 (0.39)		0.01 (0.42)
Non-Hispanic (ref.)				
BMI, mean (SD)		0.02 (0.02)		0.03 (0.02)
Primary cause of renal disease				
DM		0.66 (0.57)		−0.7 (0.54)
Glomerulonephritis		0.56 (0.62)		−0.11 (0.48)
Hypertension		0.48 (0.54)		−0.31 (0.46)
Other		0.45 (0.53)		−0.12 (0.48)
PKD (ref.)				
Peritoneal dialysis (%)		−0.62 (0.24)†		0.38 (0.24)
Coronary artery bypass grafting		0.62 (0.25)		0.45 (0.21)†
Comorbidities‡				
Cancer		0.36 (0.45)		−0.08 (0.3)
DM		−0.24 (0.32)		0.7 (0.24)
Atherosclerotic heart disease		−0.37 (0.27)		−0.35 (0.23)
Congestive heart failure		−0.02 (0.25)		0.76 (0.19)†
CVA/TIA		−0.02 (0.2)		−0.58 (0.21)†
Peripheral vascular disease		0.3 (0.23)		0 (0.22)
Other cardiac disease		−4.7 (0.61)†		−0.52 (0.48)
Chronic obstructive pulmonary disease		0.2 (0.19)		0.2 (0.25)
Kidney transplant		0.19 (0.29)		0.67 (0.22)†

Effect estimates, from accelerated failure time model, indicate the degree to which exposures slow down (or speed up) time to reoperation. Positive estimates indicate increase in time to next reoperation. Exponentiation of these coefficients approximates ratio of mean time to reoperation associated with a covariate. BMI indicates body mass index; CVA/TIA, cerebrovascular accident/transient ischemic attack; DM, diabetes mellitus; and PKD, polycystic kidney disease.

*Estimate (acceleration factor) adjusted for age category (<50 years or at least 50 years), year of valve replacement surgery, race, ethnicity, BMI, primary cause of renal disease, dialysis type, whether patient had coronary artery bypass graft, comorbidity status (ie, cancer, DM, atherosclerotic heart disease, congestive heart failure, CVA/TIA, peripheral vascular disease, other cardiac disease, chronic obstructive pulmonary disease), and subsequent kidney transplant.

†Coefficients are statistically significantly different from zero ($P<0.05$).

‡Reference for each comorbidity is absence of the comorbidity.

§American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, Other or Multiracial, Unknown.

for this difference, while not clear, may be because of nonspecific selection of reoperations, study design, and differences in duration of follow-up. An interesting finding in our study was that KT was associated with delay in time to reoperation in the AVR group, which may be explained by improvement in biochemical mediators of calcification after KT[26] and lower rates of endocarditis among patients with KT.[27] Finally, we did not find any difference in significant bleeding episodes that required hospitalizations between

Table 4. Unadjusted and Adjusted Valve HR for Bleeding Reoccurrence for Patients on the Kidney Transplant Waitlist With Dialysis and Valve Replacement Between 2000 and 2015

Variables	Mitral		Aortic	
	Unadjusted HR	Adjusted HR*	Unadjusted HR	Adjusted HR*
Valve type				
Mechanical	0.94 (0.76, 1.18)	1.03 (0.8, 1.31)	0.84 (0.73, 0.96)	0.94 (0.82, 1.09)
Bioprosthetic (ref.)				
>50 y (%)		1.02 (0.81, 1.29)		1.08 (0.92, 1.26)
Year of valve replacement surgery				
Between 2011 and 2015		1.18 (0.89, 1.56)		1.37 (1.18, 1.6)†
Between 2000 and 2010 (Ref.)				
Race (%)				
Black		0.84 (0.67, 1.07)		0.93 (0.79, 1.09)
Other‡		0.95 (0.56, 1.59)		1.18 (0.9, 1.54)
White (ref.)				
Hispanic ethnicity (%)				
Hispanic		0.67 (0.48, 0.94)		0.81 (0.64, 1.03)
Not specified		0.83 (0.41, 1.7)		0.61 (0.45, 0.83)†
Non-Hispanic (ref.)				
BMI, mean (SD)		0.98 (0.97, 1)		1.01 (1, 1.02)
Primary cause of renal disease				
DM		1.46 (0.87, 2.45)		1.21 (0.82, 1.77)
Glomerulonephritis		1.34 (0.8, 2.25)		1.2 (0.84, 1.73)
Hypertension		1.55 (0.93, 2.59)		1.12 (0.78, 1.61)
Other		1.63 (0.97, 2.73)		1.21 (0.81, 1.8)
PKD (ref.)				
Peritoneal dialysis (%)		1.07 (0.79, 1.44)		0.92 (0.75, 1.14)
Coronary artery bypass grafting		0.92 (0.71, 1.2)		1.09 (0.93, 1.28)
Cancer		0.92 (0.44, 1.93)		1.14 (0.88, 1.48)
DM		0.96 (0.75, 1.23)		1.02 (0.83, 1.25)
Atherosclerotic heart disease		0.98 (0.79, 1.22)		0.84 (0.71, 1)
Congestive heart failure		1.23 (1, 1.5)		1.05 (0.9, 1.22)
CVA/TIA		0.97 (0.77, 1.23)		1.07 (0.91, 1.25)
Peripheral vascular disease		1 (0.77, 1.3)		1.08 (0.95, 1.23)
Other cardiac disease		1.65 (1.03, 2.64)		1.05 (0.78, 1.42)
Chronic obstructive pulmonary disease		1.26 (1.01, 1.57)†		1.03 (0.89, 1.2)
Kidney transplant		1.67 (1.31, 2.12)†		1.6 (1.38, 1.87)†

BMI indicates body mass index; CVA/TIA, cerebrovascular accident/transient ischemic attack; DM, diabetes mellitus; HR, hazard ratios; and PKD, polycystic kidney disease.

*Hazard ratio adjusted for age category (<50 years or at least 50 years), year of valve replacement surgery, race, ethnicity, BMI, primary cause of renal disease, dialysis type, whether patient had coronary artery bypass, comorbidity status (ie, cancer, DM, atherosclerotic heart disease, congestive heart failure, CVA/TIA, peripheral vascular disease, other cardiac disease, chronic obstructive pulmonary disease) and subsequent kidney transplant.

†Statistically significant differences, $P<0.05$.

‡American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, Other or Multiracial, Unknown.

mechanical and bioprosthetic VR for both MVR and AVR. This finding is different from what our systematic review had previously reported, where we noted that the mechanical VR group had higher bleeding risk compared with the bioprosthetic group (19.6% versus 6.9%). Again, reasons for this are not entirely clear but the way we analyzed our bleeding outcome as time to recurrent significant bleeding requiring hospitalization may explain the difference and also because of censoring at death, which is a competing risk. Interestingly, KT was associated with increased risk for bleeding events requiring hospitalization, which was probably because of hospitalization for KT surgery and perioperative bleeding episodes.

Our study has several strengths. It extends the existing literature on outcomes of patients with ESKD with

surgical valve replacement to a special subset of those who are waitlisted for KT. Since single-center studies would not have a sufficient number of such patients, utilization of a national registry made it possible to perform a robust analysis. In addition, using a longer time span of 15 years (2000–2015) also ensured an adequate number of subjects. Our study also has limitations, including those of retrospective observational designs and registry-based studies. We tried to overcome confounding for selection of type of valve by multivariate modeling and by imputation method for missing data. Nevertheless, there might still have been residual confounding. In addition, censoring at the time of death for time to reoperation and time to recurrent bleeding may have inflated the rates of these events. However, since time to death was similar overall between bioprosthetic and mechanical valves, we do not think the conclusions from our analyses would be different if time to death was modeled as competing risk. Transcatheter aortic valve replacement is emerging as a treatment of choice for AVR. Since we had only a few patients with ESKD with transcatheter aortic valve replacement, who subsequently received KT, we had included these into the bAVR. Our study cohort was limited to Medicare beneficiaries and findings have to be interpreted with caution when being generalized to a managed care population.

In conclusion, among patients receiving dialysis who are waitlisted for kidney transplant, mechanical and bioprosthetic valves have comparable outcomes in terms of survival, reoperation rates, and bleeding risks after MVR and AVR. Notwithstanding selection bias, KT after valve replacement is associated with better survival, and may be associated with decreased risk of valve reoperation, compared with remaining on dialysis and hence is a viable treatment option for patients receiving dialysis with history of valve replacement and who are deemed acceptable for KT. Future studies should explore the role of nonsurgical valve replacement in this special population.

ARTICLE INFORMATION

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Affiliations

From the National Center for PTSD, Veterans Health Administration, Menlo Park, CA (D.K.N.); Division of Cardiac Surgery, Louis Stokes Veterans Affairs Medical Center, Cleveland, OH (S.V.D.); Division of Cardiology, Department of Medicine, University Hospitals Cleveland Medical Center, Cleveland, OH (V.S.); Center for Abdominal Transplantation, Saint Louis University, St. Louis, MO (K.L.L.); Division of Cardiology, Department of Internal Medicine, Hennepin Healthcare and University of Minnesota, Minneapolis, MN (C.A.H.); and Transplant Institute, University Hospitals Cleveland Medical Center, Cleveland, OH (L.A.D., T.R.S., K.D.C., N.S.).

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None.

Supplementary Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. International Classification of Diseases 9th version diagnosis and procedure codes used to identify bleeding episodes and covariates.

Bleeding Outcome	
Type of Bleeding	**ICD 9 Code**
GI tract	578.9
Acute blood loss anemia	285.1
Unspecified	459
Subdural hemorrhage	852
Hemorrhage complicating a procedure	998.11
Intracerebral hemorrhage	431
Comorbid Conditions	
Cancer	140-208
Diabetes	250
Atherosclerotic heart disease	410-414
Congestive Heart Failure	425, 428, 402.X1
CVA/TIA	430-438
PVD	440-444, 447, 451-453, 557
Other cardiac	420-424.9, 426-427, 429, 785.0- 785.3
COPD	491-494, 496, 510, 781.5
CABG	36.1X

GI: Gastrointestinal, CVA/TIA: Cerebrovascular accident/Transient Ischemic Attack, PVD: Peripheral Vascular Disease, COPD: Chronic Obstructive Pulmonary Disease, CABG: Coronary Artery Bypass Graft.

Table S2. Causes of death for Kidney Transplant Waitlisted Dialysis Patients with Valve Replacement between 2000 and 2015.

	Mitral			**Aortic**		
	Type, n (%)		p-value	Type, n (%)		p-value
Cause of Death	Bioprosthetic	Mechanical	0.51	Bioprosthetic	Mechanical	0.61
Cardiovascular	103 (43.8)	129 (43.4)		275 (45.4)	212 (45.5)	
Infection	42 (17.9)	54 (18.2)		68 (11.2)	53 (11.4)	
Malignancy	< 11*	< 11*		< 45*	< 45*	
Withdrawal	< 11*	< 11*		< 11*	< 11*	
Other	22 (9.4)	27 (9.1)		60 (9.9)	55 (11.8)	
Unknown	59 (25.1)	71 (23.9)		151 (24.9)	116 (24.9)	

*: Absolute numbers are masked to protect patient identity.