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Outcomes After Transcatheter Mitral Valve Repair in Patients With Renal Disease

Insights From the Society of Thoracic Surgeons/American College of Cardiology National Cardiovascular Data Registry Transcatheter Valve Therapy Registry

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BACKGROUND: Renal disease is associated with poor prognosis despite guideline-directed cardiovascular therapy, and outcomes by sex in this population remain uncertain.

METHODS AND RESULTS: Patients (n=5213) who underwent a MitraClip procedure in the National Cardiovascular Data Registry Transcatheter Valve Therapy registry were evaluated for the primary composite outcome of all-cause mortality, stroke, and new requirement for dialysis by creatinine clearance (CrCl). Centers for Medicare and Medicaid Services–linked data were available in 63% of patients (n=3300). CrCl was <60 mL/min in 77% (n=4010) and <30 mL/min in 23% (n=1183) of the cohort. Rates of primary outcome were higher with lower CrCl (>60 mL/min, 1.4%; 30–<60 mL/min, 2.7%; <30 mL/min, 5.2%; dialysis, 7.8%; *P*<0.001), and all low CrCl groups were independently associated with the primary outcome (30–<60 mL/min: adjusted odds ratio, 2.32; 95% CI, 1.38–3.91; <30 mL/min: adjusted odds ratio, 4.44; 95% CI, 2.63–7.49; dialysis: adjusted hazards ratio, 4.52; 95% CI, 2.08–9.82) when compared with CrCl >60 mL/min. Rates of 1-year mortality were higher with lower CrCl (>60 mL/min, 13.2%; 30–<60 mL/min, 18.8%; <30 mL/min, 29.9%; dialysis, 32.3%; *P*<0.001), and all low CrCl groups were independently associated with 1-year mortality (30–<60 mL/min: adjusted hazards ratio, 1.50; 95% CI, 1.13–1.99; <30 mL/min: adjusted hazards ratio, 2.38; 95% CI, 1.78–3.20; adjusted hazards ratio: dialysis, 2.44; 95% CI, 1.66–3.57) when compared with CrCl >60 mL/min.

CONCLUSIONS: The majority of patients who undergo MitraClip have renal disease. Preprocedural renal disease is associated with poor outcomes, particularly in stage 4 or 5 renal disease where 1-year mortality is observed in nearly one-third. Studies to determine how to further optimize outcomes in this population are warranted.

Key Words: creatinine ■ kidney ■ mitral valve ■ mortality ■ risk factor

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WHAT IS KNOWN

- Preoperative renal dysfunction is a risk factor for mortality in patients undergoing mitral valve surgery.
- Anatomic features of the mitral valve apparatus in patients with renal disease make surgical mitral repair or replacement less feasible.

WHAT THE STUDY ADDS

- Preprocedural renal disease is common and a significant independent predictor for adverse outcomes after transcatheter mitral valve repair, both in-hospital and on follow-up.
- One-year mortality is observed in ≈1 in 5 patients with stage 3 renal disease and almost 1 in 3 patients with stage 4 or 5 renal disease at the time of transcatheter mitral valve repair.

Preoperative renal disease is a risk factor for mortality in patients undergoing mitral valve surgery.[1–3] In patients with end-stage renal disease, in-hospital mortality occurs in a little <1 in 5 patients, and all-cause mortality at 1-year follow-up occurs in almost 40% of patients who undergo valve surgery.[4] Furthermore, the high prevalence of mitral annular calcification in renal disease makes surgical mitral repair or replacement less feasible, and this mitral annular calcification is also associated with an increased risk of peri-surgical complications.[5–7] Given the high-risk clinical and anatomic profile of patients with severe mitral regurgitation and renal disease, traditional surgical options may not be ideal, and alternative transcatheter-based options may be considered.[8]

However, outcomes data in patients with renal disease undergoing transcatheter mitral valve repair (TMVr) remain limited. These patients are underrepresented in clinical trials of TMVr, and reports from subsequent registry-based data may be underpowered.[8–12] The Society of Thoracic Surgeons (STS)/American College of Cardiology Transcatheter Valve Therapy registry provides an opportunity to examine the largest population of patients with renal disease undergoing TMVr. The primary aim of this study was to determine major adverse outcomes in patients with preprocedural renal disease who undergo TMVr.

METHODS

Study Cohort

Between November 2013 and June 2016, 5737 patients from 204 hospitals in the United States underwent TMVr with a MitraClip device (Abbott Vascular, Abbott Park, IL) and were included in the STS/American College of Cardiology Transcatheter Valve Therapy registry. Participation in this registry is required for hospitals Centers for Medicare and Medicaid Services (CMS) reimbursement, and, therefore, all regions of the country are represented. However, claims of patients with Medicare Advantage are not available to the public or for research purposes, and, therefore, these patients are not included in the CMS-linked cohort of this study. The Duke Clinical Research Institute serves as the data analysis center and has institutional review board approval to analyze the aggregate deidentified data for research purposes. Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the National Cardiovascular Data Registry at cvquality@acc.org

In the current analysis, patients with missing data on components of the Cockroft-Gault equation to calculate estimated creatinine clearance (CrCl; n=33), missing data on in-hospital death status (n=1), age <65 years (n=462), and prior TMVr (n=28) were excluded. The final cohort for the in-hospital analysis consisted of 5213 index procedure patients from 204 hospitals. Patients from the STS/American College of Cardiology Transcatheter Valve Therapy registry were linked to CMS administrative claims data using CMS-provided direct patient identifiers. CMS-linked clinical outcomes data at 30 days and 1 year were available in 3300 patients from 194 hospitals. (Figure 1)

Primary and Secondary Outcomes

The primary outcome was in-hospital major adverse events defined as a composite of all-cause mortality, stroke, and new requirement for dialysis in the overall study cohort. Stroke was defined per the Mitral Valve Academic Research Consortium criteria and adjudicated by a board-certified cardiologist at the Duke Clinical Research Institute.[13] New requirement for dialysis is only applicable to those patients with no prior dialysis, and, therefore, the denominator of the rate only includes patients without prior dialysis.

Secondary outcomes included all-cause mortality, readmission because of heart failure, any bleeding event, and mitral valve reintervention at 30-day and 1-year follow-up in the CMS-linked cohort. International Classification of Disease codes for these CMS-linked secondary clinical outcomes are shown in Appendix I in the Data Supplement. A board-certified cardiologist at the Duke Clinical Research Institute adjudicated all site-reported valve-related events.

Other Outcomes

Other outcomes included the following in-hospital events in the overall study cohort defined according to the Mitral Valve Academic Research Consortium criteria[13]: major vascular access site complication, major bleeding event, adverse event related to device or delivery system (single leaflet device detachment, complete detachment of leaflet clip, device embolization, delivery system component embolization, device thrombosis, and other device/delivery system related event), mitral valve reintervention, unplanned other cardiac surgery or intervention, and successful deployment of clip. Site-reported degree of mitral regurgitation and mean mitral gradient were also evaluated on postprocedure and 30-day echocardiogram in the overall study cohort.

Statistical Analyses

Continuous variables are presented as median (interquartile range), and categorical variables are presented as proportion (n). Differences in baseline characteristics and outcomes were compared across CrCl groups (CrCl >60 mL/min, stages 1–2; CrCl 30–≤60 mL/min, stage 3; CrCl ≤30 mL/min, stages 4–5; on dialysis, stage 5) by χ^2 rank based group means score statistic (Kruskal-Wallis equivalent) for continuous variables and Pearson χ^2 test for categorical variables. Missing categorical variables were imputed using the fully conditional method, with the discriminant function allowing all continuous and categorical variables to be predictors for imputation. Continuous variables were imputed using the predictive mean matching method, which generates imputed variables consistent with observed values. Five data sets were created in the imputation phase. These datasets were analyzed separately, and estimates from each imputed dataset were pooled into a single set of statistics.

Variables associated with in-hospital major adverse events were assessed in the overall cohort using a logistic regression model and presented as odds ratios (95% CIs). The variables considered for univariate analysis are shown in Appendix II in the Data Supplement. The final model was adjusted for demographics (age, sex, white race, body mass index) and variables with 2-sided significance level of ≤0.1 on univariate analysis that were also thought to potentially affect the primary outcome–based on biomedical knowledge (CrCl, prior coronary artery bypass graft surgery, prior stroke, severe chronic lung disease, presence of cardiogenic shock within 24 hours, and postprocedure mitral regurgitation). The Generalized Estimating Equation method with exchangeable working correlation structure was used to account for within-hospital clustering.

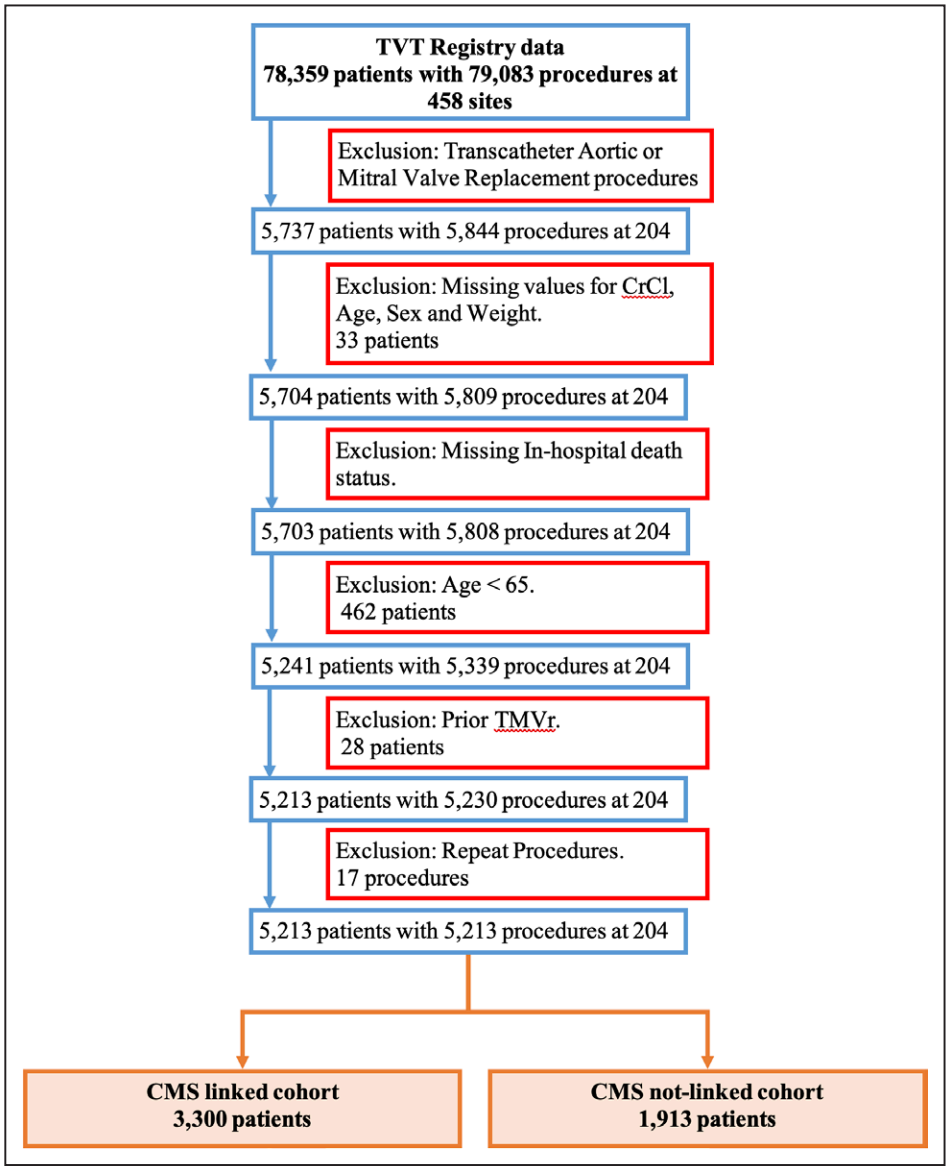

Figure 1. Study cohort.
CMS indicates Centers for Medicare and Medicaid Services; CrCl, creatinine clearance; TAVR, transcatheter aortic valve replacement; TMVR, transcatheter mitral valve repair; and TVT, Transcatheter Valve Therapy.

Table 1. Baseline Characteristics of Patients Undergoing a MitraClip Procedure Stratified by CrCl Rate

	CrCl >60 mL/min (n=1203)	CrCl 30 to ≤60 mL/min (n=2827)	CrCl ≤30 mL/min (n=1029)	On Dialysis (n=154)	*P* Value
Age, y	77 [71–82]	83 [78–87]	85 [81–89]	73 [70–81]	<0.001
Male sex (%)	66.0 (794)	51.6 (1460)	39.8 (410)	61.0 (94)	<0.001
Race (%)					<0.001
White	93.5 (1125)	91.9 (2598)	89.0 (916)	79.9 (123)	
Black	3.7 (44)	4.2 (120)	5.6 (58)	11.7 (18)	
Asian	0.9 (11)	2.1 (60)	3.8 (39)	5.8 (9)	
Native American	0.4 (5)	0.4 (10)	0.2 (2)	1.9 (3)	
Pacific Islander	0.2 (3)	0.4 (12)	0.6 (6)	0	
Ethnicity (%)					
Hispanic	5.2 (62)	4.3 (121)	4.1 (42)	5.8 (9)	0.48
Body mass index, kg/m^2	28.2 [25.1–32.8]	24.6 [22.0–27.7]	22.6 [19.9–25.6]	25.0 [20.9–27.7]	<0.001
Medical history (%)					
Prior myocardial infarction	29.6 (356)	25.3 (716)	25.9 (266)	35.7 (55)	0.002
Prior PCI	33.0 (397)	30.4 (859)	29.2 (300)	37.0 (57)	0.054
No. of prior cardiac surgeries					<0.001
Prior CABG	34.8 (419)	28.5 (807)	28.0 (288)	29.9 (46)	<0.001
0	57.1 (687)	63.6 (1799)	65.1 (670)	60.4 (93)	
1	33.7 (405)	27.2 (769)	26.1 (269)	33.8 (52)	
>2	6.7 (80)	6.2 (174)	6.7 (69)	4.5 (7)	
Prior mitral valve surgery	2.6 (31)	2.1 (59)	1.4 (14)	1.3 (2)	0.20
Diabetes mellitus	29.3 (353)	24.5 (694)	22.0 (226)	44.8 (69)	<0.001
Atrial fibrillation/flutter	64.8 (779)	65.1 (1839)	66.1 (680)	54.5 (84)	0.046
Prior stroke	10.9 (131)	10.3 (292)	8.7 (90)	9.7 (15)	0.39
Severe chronic lung disease	15.5 (186)	9.6 (272)	7.6 (78)	19.5 (30)	<0.001
Hostile chest	8.8 (106)	7.3 (206)	6.8 (70)	10.4 (16)	0.14
Current smoker (within 1 y)	6.1 (73)	4.5 (128)	2.9 (30)	7.1 (11)	0.002
Clinical presentation (%)					
NYHA Class IV within 2 wk	76.9 (925)	78.0 (2205)	74.1 (763)	63.6 (98)	<0.001
Cardiogenic shock within 24 h	1.0 (12)	0.9 (26)	1.4 (14)	4.5 (7)	<0.001
Cardiac arrest within 24 h	0.3 (4)	0.2 (7)	0.2 (2)	0	0.84
Patient predicted mortality at 30-day, STS 2007 model (MV replacement; %)	5.7 [3.9–8.3]	9.2 [6.8–12.7]	16.0 [11.9–21.3]	24.4 [17.8–33.2]	<0.001
Patient predicted mortality at 30-day, STS 2007 model (MV repair; %)	3.7 [2.4–5.6]	6.1 [4.3–8.8]	10.6 [7.8–15.5]	21.6 [15.6–31.4]	<0.001
Left main stenosis ≥50% (%)	9.3 (112)	7.9 (224)	7.0 (72)	7.1 (11)	0.33
No. of diseased coronary arteries (%)					0.009
0	40.4 (486)	43.2 (1222)	43.5 (448)	32.5 (50)	
1	14.0 (169)	14.4 (406)	13.9 (143)	14.3 (22)	
2	13.4 (161)	13.1 (371)	10.3 (106)	14.3 (22)	
3	26.0 (313)	22.6 (640)	22.6 (233)	27.3 (42)	
Left ventricular internal systolic dimension, cm	3.8 [3.2–4.6]	3.5 [2.9–4.4]	3.5 [2.8–4.2]	4.1 [3.3–5.0]	<0.001
Left ventricular internal diastolic dimension, cm	5.4 [4.7–6.0]	5.0 [4.5–5.7]	4.9 [4.3–5.5]	5.3 [4.8–6.1]	<0.001
Mitral stenosis (%)	5.6 (67)	5.0 (141)	5.7 (58)	4.6 (7)	0.80
Mitral valve disease cause (%)					
Functional mitral regurgitation	17.5 (211)	15.9 (449)	15.2 (156)	23.4 (36)	0.04
Degenerative mitral regurgitation	85.3 (1026)	88.2 (2494)	88.0 (906)	83.1 (128)	0.02

(*Continued*)

Table 1. Continued

	CrCl >60 mL/min (n=1203)	CrCl 30 to ≤60 mL/min (n=2827)	CrCl ≤30 mL/min (n=1029)	On Dialysis (n=154)	*P* Value
Endocarditis	0.3 (4)	0.3 (8)	0.2 (2)	0	0.84
Other	2.3 (28)	2.3 (65)	2.4 (25)	3.2 (5)	0.90
Procedure status (%)					0.007
Elective	91.9 (1106)	90.9 (2570)	88.5 (911)	85.1 (131)	
Urgent	7.6 (92)	8.5 (241)	10.9 (112)	12.3 (19)	
Emergent/salvage	0.4 (5)	0.4 (12)	0.5 (5)	1.9 (3)	
No. of clips deployed					0.11
0	2.2 (27)	2.7 (76)	1.7 (18)	1.9 (3)	
1	50.7 (610)	53.1 (1501)	56.2 (578)	59.1 (91)	
2	40.4 (486)	38.0 (1073)	34.4 (354)	31.2 (48)	
3+	5.2 (63)	5.1 (144)	5.5 (57)	5.2 (8)	

Categorical variables are shown as proportion (n) and compared across CrCl groups by Pearson χ^2 test. Continuous variables are shown as median [interquartile range] and compared across CrCl groups by χ^2 rank based group means score statistic (Kruskal-Wallis equivalent). CABG indicates coronary artery bypass graft; CrCl, creatinine clearance; MV, mitral valve; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and STS, Society of Thoracic Surgery.

The strengths of association between CrCl and all-cause mortality on 30-day and 1-year follow-up in the CMS-linked population were assessed using a Cox proportional hazards model and presented as hazard ratios (95% CIs). Differences in all-cause mortality at 30-day and 1-year follow-up across CrCl groups were assessed by the log-rank test and presented as Kaplan-Meier curves.

The strengths of association between CrCl and other clinical outcomes on 30-day and 1-year follow-up in the CMS-linked population were assessed using a Fine and Gray's subdistribution hazards model. For 30-day readmission because of heart failure and any bleeding event, the assumption of proportional hazards did not hold for patients on dialysis, and hazard ratios were provided for ≤10 and >10 days postprocedure (arbitrary value). For 1-year mitral valve reintervention, the assumption of proportional hazards did not hold for patients on dialysis, and hazard ratios were provided for ≤3 and >3 months postprocedure (arbitrary value).

The hazards models were adjusted for demographics (age, sex, race, body mass index) and variables with 2-sided significance level of ≤0.1 on univariate analysis that were also thought to potentially affect 30-day and 1-year outcomes based on biomedical knowledge (prior coronary artery bypass graft surgery, prior stroke, severe chronic lung disease, New York Heart Association classification within 2 weeks of the procedure, presence of cardiogenic shock, presence of endocarditis, procedure status, and postprocedure mitral regurgitation). Because of very few mitral valve reintervention events at 30-day follow-up, the hazards ratio for this variable only adjusted for age and body mass index. The marginal model approach was used to account for within-hospital clustering for all time-to-event analyses.

A separate analysis was conducted to evaluate the incidence of acute kidney injury (AKI) and strength of association between AKI and outcomes. AKI was defined by the Mitral Valve Academic Research Consortium definition, and the strength of association between AKI and all-cause mortality on 30-day and 1-year follow-up in the CMS-linked population were also assessed using a Cox proportional hazards model as described above.[13] However, the assumption of proportional hazards did not hold for patients with AKI, and hazard ratios were provided for ≤10 and >10 days postprocedure (arbitrary value) for 30-day all-cause mortality and for ≤3 and >3 months postprocedure (arbitrary value) for 1-year all-cause mortality. Similarly, the strength of association between AKI and other clinical outcomes on 30-day and 1-year follow-up in the CMS-linked population were also assessed using a Fine and Gray's subdistributional hazards model as described above.

Separate analyses were also conducted to evaluate the strength of association between baseline renal function and clinical outcomes in the CMS-linked population as described above among patients who achieved at least acceptable reduction in mitral regurgitation per Mitral Valve Academic Research Consortium criteria (≥2 levels of reduction in mitral regurgitation from baseline) and by cause of mitral regurgitation (degenerative or functional).[13]

Finally, to determine which variables were independently associated with 1-year all-cause mortality by CrCl groups in the CMS-linked population, a Cox proportional hazards model was used. The model was adjusted for variables that were thought to potentially affect 30-day and 1-year outcomes based on biomedical knowledge (age, sex, white race, body mass index, prior cardiac surgery, prior stroke, severe chronic lung disease, and cardiogenic shock within 24 hours). Given the fewer events in the dialysis population, the model was only adjusted for age, prior stroke, and cardiogenic shock within 24 hours. The marginal model approach was used to account for within-hospital clustering.

Significance was tested at a 2-sided alpha level of 0.05. All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc, Cary, NC).

Table 2. Short-Term Outcomes After a MitraClip Procedure Stratified by CrCl Rate

	CrCl >60 mL/min (n=1203)	CrCl 30 to ≤60 mL/min (n=2827)	CrCl ≤30 mL/min (n=1029)	On Dialysis (n=154)	*P* Value
Primary outcome (%)					
Composite of in-hospital all-cause mortality, stroke, or new requirement for dialysis	1.4 (17)	2.7 (77)	5.2 (53)	7.8 (12)	<0.001
Secondary in-hospital outcomes (%)					
All-cause mortality	1.2 (15)	2.1 (59)	4.0 (41)	6.5 (10)	<0.001
Stroke	0.2 (3)	0.5 (15)	0.9 (9)	1.3 (2)	0.14
New requirement for dialysis (among patients not currently on dialysis)	0.2 (3)	0.6 (18)	1.4 (14)	…	0.006
Major vascular access site complication	0.3 (4)	0.4 (10)	0	0	0.25
Other in-hospital outcomes (%)					
Major bleeding event	1.8 (22)	3.1 (88)	3.4 (35)	3.2 (5)	0.10
Adverse event related to device or deliver system	2.1 (25)	2.2 (62)	1.7 (18)	3.2 (5)	0.63
Mitral valve reintervention	0.7 (9)	0.4 (11)	1.0 (10)	0.6 (1)	0.17
Unplanned other cardiac surgery or intervention	1.2 (15)	1.2 (35)	1.1 (11)	1.9 (3)	0.83
Deployment of clip (%)	96.3 (1159)	96.1 (2718)	96.1 (989)	95.5 (147)	0.96
Echocardiographic outcomes: postprocedure					
≤Mild mitral regurgitation (%)	64.3 (673)	59.8 (1445)	54.8 (478)	59.7 (74)	<0.001
Mean mitral gradient, mm Hg	4 [3–6]	4 [3–6]	4 [3–6]	5 [3–6]	0.03
Echocardiographic outcomes: 30-day	(n=657)	(n=1517)	(n=530)	(n=66)	
≤Mild mitral regurgitation (%)	54.2 (356)	46.8 (710)	42.3 (224)	47.0 (31)	<0.001
Mean mitral gradient, mm Hg	4 [3–5]	4 [3–6]	4 [3–6]	5 [4–7]	0.002

Categorical variables are shown as proportion (n) and compared across CrCl groups by Pearson χ^2 test. Continuous variables are shown as median [interquartile range] and compared across CrCl groups by χ^2 rank based group means score statistic (Kruskal-Wallis equivalent). CrCl indicates creatinine clearance.

RESULTS

Baseline Characteristics of the Overall Study Cohort

Of the 5213 patients who met study criteria, 23% (n=1203) had CrCl >60 mL/min, 54% (n=2827) had CrCl >30 but ≤60 mL/min, 20% (n=1029) had CrCl ≤30 mL/min, and 3% (n=154) were on dialysis.

Baseline characteristics stratified by CrCl are shown in Table 1. Of the patients who underwent TMVr, those with CrCl ≤60 mL/min but not on dialysis were older, more likely to be of female sex or nonwhite race, and with a lower body mass index than those with CrCl >60 mL/min. These patients with CrCl ≤60 mL/min but not on dialysis also had fewer comorbidities (lower frequency of prior cardiac surgeries, diabetes mellitus, severe chronic lung disease, and current tobacco use) but still had a significantly higher 30-day STS-predicted mortality, than those with CrCl >60 mL/min.

Patients with CrCl ≤60 mL/min but not on dialysis also had a smaller left ventricular cavity and were more likely to have a degenerative cause of mitral regurgitation than patients with CrCl >60 mL/min. Although the majority of TMVr were performed electively, this was less likely in patients with CrCl ≤60 mL/min than those with CrCl >60 mL/min. There was no difference in the number of clips deployed across CrCl groups.

Table 3. Independent Variables Associated With the Primary Outcome (In-Hospital Major Adverse Events Defined as a Composite of All-Cause Mortality, Stroke, and New Requirement for Dialysis)

Variable	Adjusted Odds Ratio (95% CI)	*P* Value
Baseline renal function		
CrCl >60 mL/min	Reference	
CrCl 30–60 mL/min	2.42 (1.42–4.11)	0.0011
CrCl ≤30 mL/min	4.71 (2.77–8.01)	<0.0001
On dialysis	4.93 (2.33–10.5)	<0.0001
Prior stroke	1.83 (1.16–2.90)	0.001
Severe chronic lung disease	1.94 (1.25–3.01)	0.003
Cardiogenic shock within 24 h	13.1 (6.88–25.0)	<0.0001
Postprocedure mitral regurgitation		
None/trace/trivial/moderate	Reference	
Moderate-severe/severe	5.23 (3.48–7.86)	<0.0001

Logistic regression model adjusted for CrCl, age, sex, white race, body mass index, prior coronary artery bypass graft surgery, prior stroke, severe chronic lung disease, presence of cardiogenic shock within 24 h, and postprocedure mitral regurgitation. CrCl indicates creatinine clearance.

Table 4. Clinical Outcomes After a MitraClip Procedure Stratified by CrCl Rate in Patients With Data Linked to the Centers for Medicare and Medicaid Services Database

	CrCl >60 mL/min (n=718)	CrCl 30 to ≤60 mL/min (n=1821)	CrCl ≤30 mL/min (n=665)	On Dialysis (n=96)	*P* Value
30-day outcomes (%)					
All-cause mortality	3.3 (24)	4.4 (81)	6.6 (44)	13.5 (13)	<0.001
New requirement for dialysis*	0.3 (2)	0.7 (13)	1.5 (10)	…	0.01
Readmission because of heart failure	4.5 (32)	4.4 (81)	6.5 (43)	6.3 (6)	<0.001
Any bleeding event	5.4 (39)	9.1 (165)	11.1 (74)	11.5 (11)	<0.001
Mitral valve reintervention	2.2 (16)	1.5 (28)	1.8 (12)	1.0 (1)	<0.001
1-year outcomes (%)					
All-cause mortality	13.2 (95)	18.8 (343)	29.9 (199)	32.3 (31)	<0.001
New requirement for dialysis*	0.8 (6)	1.5 (28)	3.8 (25)	…	<0.001
Readmission because of heart failure	16.7 (120)	17.0 (309)	25.7 (171)	17.7 (17)	<0.001
Any bleeding event	13.1 (94)	17.5 (319)	22.1 (147)	26.0 (25)	<0.001
Mitral valve reintervention	6.3 (45)	5.5 (101)	5.9 (39)	9.4 (9)	<0.001

Categorical variables are shown as proportion (n) and compared across CrCl groups by Pearson χ^2 test. CrCl indicates creatinine clearance.
*Among patients not currently on dialysis.

In-Hospital Outcomes in the Overall Study Cohort

The primary composite outcome of in-hospital all-cause mortality, stroke, and new requirement for dialysis was increased in patients with CrCl ≤60 mL/min compared with those with CrCl >60 mL/min, and this was driven by higher in-hospital mortality rate (Table 2). Independent variables associated with the primary outcome in a multivariable model included prior stroke, severe chronic lung disease, cardiogenic shock within 24 hours, procedural indication of endocarditis, more than moderate mitral regurgitation postprocedure, and nonelective procedure status (Table 3).

Echocardiographic Outcomes in the Overall Study Cohort

Postprocedure echocardiogram was performed in 85.5% (n=4458) of patients in the overall study cohort, and a 30-day echocardiogram was performed in 65.4% (n=2770) of patients eligible for 30-day follow-up (n=4234). Data for patients with versus without an available postprocedural echocardiogram are shown in Tables I and II in the Data Supplement. Patients with CrCl ≤60 mL/min had a significantly lower frequency of mitral regurgitation quantified as mild or less in degree on follow-up compared with patients with CrCl >60 mL/min, whereas patients on dialysis had a significantly higher mean gradients across the mitral valve compared with patients not on dialysis (Table 2; Figure I in the Data Supplement).

Baseline Characteristics of the CMS-Linked Study Cohort

CMS-linked data were available in 63.3% (n=3300) of the overall study cohort (n=5213). Among the CMS-linked cohort, 22% (n=718) had CrCl >60 mL/min, 55% (n=1821) had CrCl >30 but ≤60 mL/min, 20% (n=665) had CrCl ≤30 mL/min, and 3% (n=96) were on dialysis. Patients with versus those without available CMS-linked data were older, less likely to be of minority race or Hispanic ethnicity, and less likely to have diabetes mellitus or prior stroke. Patients with CMS-linked data, however, did have higher STS-predicted mortality at 30-day compared with patients who did not have available CMS-linked data. Finally, patients with CMS-linked data were more likely to have degenerative mitral regurgitation and a clip deployed compared with patients who did not have available CMS-linked data. (Table III in the Data Supplement)

Clinical Outcomes on Follow-Up in the CMS-Linked Study Cohort

Clinical outcomes were significantly higher with lower CrCl on both 30-day and 1-year follow-up when compared with CrCl >60 mL/min (Table 4). All-cause mortality occurred in nearly a third of patients with CrCl ≤30 mL/min or on dialysis at 1-year follow-up (Figure 2). After multivariable adjustment, patients on dialysis were significantly associated with higher rate of all-cause mortality, whereas patients with CrCl ≤30 mL/min and those on dialysis were significantly associated with higher rate of any bleeding event, at 30 days when compared with patients with CrCl >60 mL/min (Table 5). However, at 1-year follow-up, all CrCl groups ≤60 mL/min were significantly associated with all-cause mortality and any bleeding event when compared with patients with CrCl >60 mL/min (Table 5). Only patients with CrCl ≤30 mL/min not on dialysis were significantly associated with readmission because of heart failure, whereas only patients on dialysis (when time ≥3 months) were significantly associated

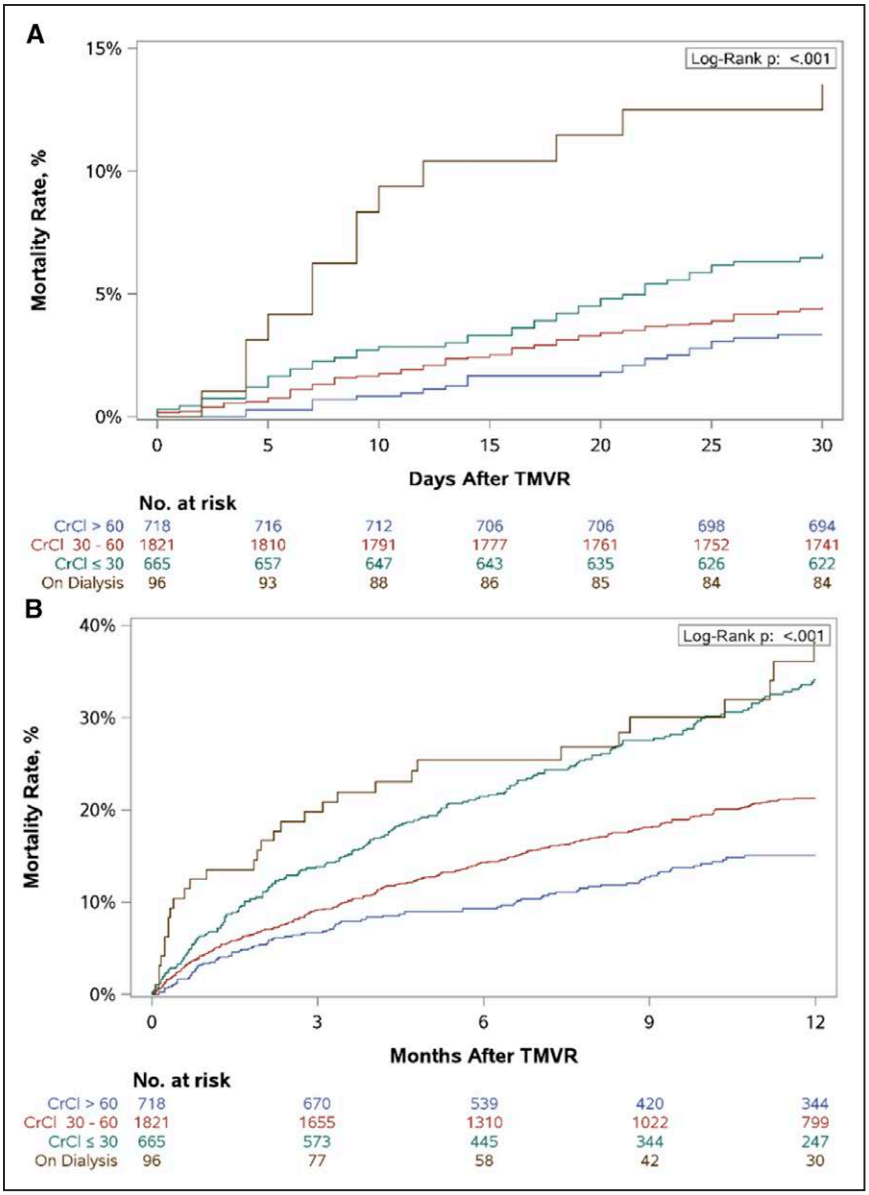

Figure 2. Kaplan Meier estimates of all-cause mortality stratified by creatinine clearance (CrCl) rate.
All-cause mortality shown at (**A**) 30-day and (**B**) 1-year follow-up. TMVR indicates transcatheter mitral valve repair.

with mitral valve reintervention, at 1 year when compared with patients with CrCl >60 mL/min (Table 5).

AKI occurred in 13% of the CMS-linked cohort (n=425). Patients who developed AKI were associated with significantly increased risk of mortality, readmission because of heart failure, and any bleeding event at 30-day and 1-year follow-up when compared with those who did not develop AKI (Table 5).

A majority of the patients in the CMS-linked cohort achieved acceptable reduction in mitral regurgitation (85%, n=2798), but only a minority could be further categorized as optimal reduction in mitral regurgitation (16%, n=516). The associations between baseline renal function and clinical outcomes at 1 year among patients who achieved acceptable reduction in mitral regurgitation are shown in Table 6.

Of the CMS-linked cohort, 79% (n=2608) had cause identified as degenerative mitral regurgitation only, whereas 7% (n=231) had cause identified as functional mitral regurgitation only. The 9.3% of the cohort (n=307) that were identified to have both degenerative and functional mitral regurgitation were excluded from the current subgroup analysis. The associations between baseline renal function and clinical outcomes at 1 year by cause of mitral regurgitation are shown in Table IV in the Data Supplement. Findings in the degenerative mitral regurgitation subgroup were similar to the overall cohort. The functional mitral regurgitation subgroup was significantly underpowered but demonstrated a significant unadjusted association between patients with CrCl ≤30 mL/min but not on dialysis and both all-cause mortality and readmission because of heart failure at 1-year follow-up.

Finally, in the evaluation of variables independently associated with 1-year all-cause mortality, only severe chronic lung disease (adjusted hazards ratio

Table 5. Associations Between Different CrCl Groups, as well as AKI, and Clinical Outcomes at 30-Day and 1-Year Follow-Up

Variable	Adjusted Hazards Ratio (95% CI)	*P* Value
30-day follow-up		
All-cause mortality		
CrCl >60 mL/min	Reference	
CrCl 30–60 mL/min	1.28 (0.78–2.10)	0.33
CrCl ≤30 mL/min	1.61 (0.98–2.65)	0.06
On dialysis	3.31 (1.79–6.13)	<0.001
AKI		
When time in days ≤10	13.90 (8.64–22.4)	<0.001
When time in days >10	7.49 (5.05–11.1)	<0.001
Readmission because of heart failure		
CrCl >60 mL/min	Reference	
CrCl 30–60 mL/min	0.94 (0.62–1.43)	0.78
CrCl ≤30 mL/min	1.29 (0.74–2.27)	0.37
On dialysis		
When time in days ≤10	2.39 (0.84–6.83)	0.10
When time in days >10	0.68 (0.16–2.94)	0.60
AKI	2.25 (1.5–3.21)	<0.001
Any bleeding event		
CrCl >60 mL/min	Reference	
CrCl 30–60 mL/min	1.75 (0.89–3.42)	0.10
CrCl ≤30 mL/min	2.08 (1.02–4.26)	0.045
On dialysis		
When time in days ≤10	1.19 (0.49–2.90)	0.71
When time in days >10	4.18 (1.36–12.8)	0.01
AKI	1.84 (1.41–2.41)	<0.001
Mitral valve reintervention*		
CrCl >60 mL/min	Reference	
CrCl 30–60 mL/min	0.55 (0.26–1.14)	0.11
CrCl ≤30 mL/min	0.66 (0.31–1.42)	0.29
On dialysis	0.39 (0.05–3.03)	0.37
AKI	2.81 (1.56–5.06)	<0.001
1-year follow-up		
All-cause mortality		
CrCl >60 mL/min	Reference	
CrCl 30–60 mL/min	1.50 (1.13–1.99)	0.005
CrCl ≤30 mL/min	2.38 (1.78–3.20)	<0.001
On dialysis	2.44 (1.66–3.57)	<0.001
AKI		
When time in months ≤3	6.33 (5.10–7.84)	<0.001
When time in months >3	1.85 (1.43–2.40)	<0.001
Readmission because of heart failure		
CrCl >60 mL/min	Reference	
CrCl 30–60 mL/min	1.12 (0.89–1.40)	0.33
CrCl ≤30 mL/min	1.81 (1.40–2.35)	<0.001
On dialysis	1.11 (0.69–1.78)	0.68
AKI		
When time in months ≤3	2.00 (1.57–2.54)	<.001
When time in months >3	0.70 (0.46–1.06)	0.09
Any bleeding event		
CrCl >60 mL/min	Reference	
CrCl 30–60 mL/min	1.43 (1.03–2.00)	0.03
CrCl ≤30 mL/min	1.84 (1.25–2.72)	0.002
On dialysis	2.11 (1.31–3.41)	0.002
AKI	1.44 (1.17–1.75)	<0.001
Mitral valve reintervention		
CrCl >60 mL/min	Reference	
CrCl 30–60 mL/min	0.96 (0.66–1.39)	0.82
CrCl ≤30 mL/min	1.19 (0.78–1.82)	0.42
On dialysis		
When time in months ≤3	0.56 (0.13–2.46)	0.45
When time in months >3	3.09 (1.29–7.39)	0.01
AKI	1.21 (0.74–1.97)	0.45

Cox proportional hazards model (for all-cause mortality) and Fine and Gray's subdistribution hazards model (for other clinical outcomes) adjusted for age, sex, race, body mass index, prior coronary artery bypass graft surgery, chronic lung disease, New York Heart Association classification within 2 wk of the procedure, presence of cardiogenic shock, prior stroke, presence of endocarditis, post-procedure mitral regurgitation, and procedure status. AKI indicates acute kidney injury; and CrCl, creatinine clearance.

*Adjusted for age and body mass index only.

[aHR], 1.88; 95% CI, 1.41–2.50; *P*<0.001) and cardiogenic shock within 24 hours (aHR, 4.23; 95% CI, 1.96–9.11; *P*<0.001) were significantly associated with 1-year mortality in patients with CrCl 30 to 60 mL/min, whereas only cardiogenic shock within 24 hours (aHR, 3.16; 95% CI, 1.54–6.49; *P*=0.002) was significantly associated with 1-year mortality in patients with CrCl ≤30 mL/min. In the dialysis subgroup, both prior stroke (aHR, 3.08; 95% CI, 1.10–8.61; *P*=0.03) and cardiogenic shock within 24 hours (aHR, 8.17; 95% CI, 2.08–32.1; *P*=0.003) were significantly associated with 1-year mortality.

DISCUSSION

This large observational analysis of outcomes after TMVr with the MitraClip device among patients with varying degrees of renal function demonstrated several key findings. First, significant preprocedural renal disease was common among patients undergoing TMVr. Second, the presence of preprocedural renal disease was associated with an independent increased risk of in-hospital major adverse events, as well as all-cause mortality and any bleeding event at 1-year follow-up.

Table 6. Associations Between Different CrCl Groups and Clinical Outcomes at 1-Year Follow-Up Among Patients With at Least Acceptable Reduction in Mitral Regurgitation

Variable	Adjusted Hazards Ratio (95% CI)	*P* Value
All-cause mortality		
CrCl >60 mL/min	Reference	
CrCl 30–60 mL/min	1.57 (1.14–2.16)	0.006
CrCl ≤30 mL/min	2.45 (1.80–3.34)	<0.001
On dialysis	2.01 (1.25–3.21)	0.004
Readmission because of heart failure		
CrCl >60 mL/min	Reference	
CrCl 30–60 mL/min	1.07 (0.86–1.34)	0.54
CrCl ≤30 mL/min	1.73 (1.33–2.25)	<0.001
On dialysis	1.22 (0.70–2.11)	0.49
Any bleeding event		
CrCl >60 mL/min	Reference	
CrCl 30–60 mL/min	1.38 (1.04–1.84)	0.03
CrCl ≤30 mL/min	1.81 (1.28–2.55)	<0.001
On dialysis	2.06 (1.23–3.44)	0.006
Mitral valve reintervention		
CrCl >60 mL/min	Reference	
CrCl 30–60 mL/min	1.07 (0.65–1.77)	0.80
CrCl ≤30 mL/min	1.35 (0.83–2.19)	0.22
On dialysis		
When time in months ≤3	0.67 (0.09–5.00)	0.69
When time in months >3	4.86 (1.87–12.6)	0.001

Cox proportional hazards model (for all-cause mortality) and Fine and Gray's subdistribution hazards model (for other clinical outcomes) adjusted for age, sex, race, body mass index, prior coronary artery bypass graft surgery, chronic lung disease, New York Heart Association classification within 2 wk of the procedure, presence of cardiogenic shock, prior stroke, presence of endocarditis, post-procedure mitral regurgitation, and procedure status. CrCl indicates creatinine clearance.

Patients with a CrCl ≤30 mL/min not on dialysis had a similar hazards ratio as those on dialysis with 1-year mortality rates of about 30% in both groups. Third, the development of AKI after TMVr is significantly and independently associated with poor clinical outcomes at both 30-day and 1-year follow-up.

The current report demonstrated that more than three-quarters of patients undergoing TMVr in the United States have renal disease, and a little less than a quarter of them have stage 4 or 5 renal disease. Patients with renal disease are often underrepresented in pivotal trials of cardiovascular interventions.[14] The initial EVEREST (Endovascular Valve Edge-to-Edge Repair Study) registry of the MitraClip device excluded patients with renal disease, and only 3.3% of the randomized EVEREST II trial's cohort had renal disease.[8,10] Although subsequent registries consisted of a higher proportion of patients with renal disease undergoing TMVr than prior randomized trials (23% of the 78 patients in the EVEREST II High-Risk Study, 30.5% of the 628 patients in the European Sentinal Registry, and 41.6% of the 567 patients in the ACCESS-Europe registry), the current cohort remains the largest evaluated to date.[9,11,12]

With the commercial availability of the MitraClip device, it is important to identify patients who may or may not benefit from this treatment strategy. A pooled analysis of patients in the EVEREST II trials demonstrated all-cause mortality rates of 21% and 26% in patients with stage 3, 4, or 5 renal disease at baseline.[15] In the current study, all-cause mortality was increased among patients with versus those without baseline renal disease even after multivariable adjustment, with 1-year mortality observed in ≈1 in 5 patients with stage 3 renal disease and almost 1 in 3 patients with stage 4 or 5 renal disease. Furthermore, this significantly increase risk of all-cause mortality and any bleeding among patients with stage 3, 4, or 5 baseline renal disease was observed even among patients with an acceptable reduction in mitral regurgitation. The poor prognosis observed at 1 year is likely to be because of the morbidity and mortality associated with renal disease, rather than a lack of treatment efficacy because the rates of all-cause mortality observed across the different stages of renal disease in the current study are similar to those observed with other cardiovascular therapies.[16,17] A recent analysis of patients undergoing transcatheter aortic valve replacement demonstrated a 1-year all-cause mortality rate of 22% in stage 3 renal disease and 31% in stage 4 or 5 renal disease.[16,17] In the setting of percutaneous coronary intervention, 5-year all-cause mortality in patients with chronic renal disease is 27% when compared with 11% in those with normal renal function.[16,17] Furthermore, there also seems to be a significant decrease in all-cause mortality over time in patients who undergo mitral valve surgery.[3,4] One large single-center study of patients undergoing mitral valve surgery reported persistently lower survival rates over time in patients on dialysis versus those not on dialysis (59.2% versus 89.5% at 1-year, 42.3% versus 84.4% at 2 years, and 28.9% versus 78.4% at 5 years follow-up).[4] It is unclear from this study, however, why the increased adverse events observed among patients with baseline renal disease at both in-hospital and 1-year follow-up are not observed at 30-day follow-up.

Other causes of mortality in this population may be postulated. In the current study, there was a significantly independent association between impaired renal function and bleeding events across all stages of renal disease. Bleeding events are a known complication of renal disease because of underlying abnormalities in platelet biology and the coagulation cascade, as well as independently predict mortality in cardiovascular disease.[18–20] Other potential causes of mortality may relate to calcification of the valvular apparatus. Data from the Framingham Offspring Study demonstrated the presence

of mitral annular calcification in patients with renal disease before the onset of end-stage renal disease.[21] The presence of both renal disease and mitral annular calcification was associated with a significantly increased risk of mortality, possibly because of resultant valvular abnormalities or extension of calcium into the adjacent conduction system. Alternatively, systemic inflammation may lead to valvular calcification and is associated with an increased risk of both all-cause and cardiovascular-related mortality in patients with renal disease.[22] Histology data demonstrate evidence of increased inflammation on surgically removed heart valves in patients with versus without end-stage renal disease.[23] In the current study, patients with versus those without preprocedural renal disease were more likely to have more than mild residual mitral regurgitation and higher mean gradients across the mitral valve on follow-up. However, the association between baseline renal disease and 1-year mortality was observed even among patients with acceptable reduction in mitral regurgitation.

Finally, the current study also reports a significant independent association between the development of AKI after TMVr and major adverse outcomes on both 30-day and 1-year follow-up. This is not a new finding when compared with the surgical literature.[24,25] One single-center study reported AKI and AKI requiring dialysis in 4% and 2.5% of patients undergoing valve surgery, respectively.[24] The development of AKI was associated with a markedly increased rate of mortality on long-term follow-up. The authors also demonstrated that AKI was more likely to develop in patients with a preoperative creatinine level of >1.4 mg/dL. However, the definition of AKI varies across the surgical literature, and, therefore, a direct comparison to the rate of AKI observed in this cohort is not feasible.

Limitations

There are several limitations of this study, including those inherent to a retrospective observational study design. However, the National Cardiovascular Data Registry system that includes the STS/American College of Cardiology Transcatheter Valve Therapy registry has a long track record of data quality and management and <1% of patients excluded from the current analysis because of missing baseline variables.[26] Second, only two-thirds of the patients were CMS-linked. However, CMS administrative claims data have nearly 100% long-term follow-up. Third, postprocedural changes in quality of life were not evaluated. However, patients with CrCl ≤30 mL/min, but not on dialysis, continued to have a significantly higher rate of readmission because of heart failure compared with those with CrCl >60 mL/min. Fourth, measures of frailty that predict outcomes but are not evaluated by the STS Predicted Risk of Mortality model were not consistently captured. Fifth, only a single preprocedural creatinine was evaluated; it remains unclear if this represents chronic renal function or acute renal insufficiency. In addition, data on medications that may affect renal function, as well as hemodynamic data, were not available. Given the lack of need for contrast with TMVr, some patients may have undergone the procedure when in acute renal failure. Finally, echocardiographic data were not reviewed by an independent core laboratory, and detailed data on mitral valve anatomy (eg, mitral leaflet calcification, leaflet tethering, mitral annular calcification) were missing in more than a third of the patients. Nonetheless, this is the largest outcomes-based analysis of a real-world population with varying degrees of renal function undergoing TMVr to date.

Conclusions

Preprocedural renal disease is common among patients undergoing TMVr and associated with increased major adverse outcomes after TMVr both in-hospital and on follow-up; 1-year all-cause mortality is >30% with stage 4 or 5 renal disease. This adverse association is observed even among patients with an acceptable reduction in mitral regurgitation and particularly prevalent in patients who develop AKI after TMVr. These data should be incorporated in the patient selection and shared decision-making process. Further studies investigating both the underlying mechanism of poorer outcomes after TMVr patients with renal disease, as well as prospective evaluation of the optimal mitral valve treatment strategy in this high-risk subgroup, are warranted.

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