Evaluation of Renal Function Before and After Percutaneous Mitral Valve Repair

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Background—Chronic kidney disease (CKD) is strongly related to outcome in cardiovascular diseases. The relationship between treatment of mitral regurgitation (MR) and renal function is not well described. We sought to evaluate renal function before and after mitral valve repair by the MitraClip device.

Methods and Results—Patients with moderate-to-severe or severe (3+ or 4+, respectively) MR by core laboratory determination who underwent transcatheter mitral valve repair with the MitraClip device in multicenter, investigational trials were included in this study. Estimated glomerular filtration rate (eGFR) was evaluated before and at hospital discharge, 30 days, 6 months, and 1 year after mitral valve repair. Eight hundred fifty-four patients with baseline mean eGFR 61.5±23.1 mL/min/1.73 m^2 were studied, including 438 (51.3%) with eGFR ≥60 mL/min/1.73 m^2 (CKD stage 1 or 2), 371 (42.6%) with eGFR 30 to 59 mL/min/1.73 m^2 (CKD stage 3), and 52 (6.1%) with eGFR <30 mL/min/1.73 m^2 (CKD stage 4 or 5). Baseline renal dysfunction was more prevalent in older patients with a history of heart failure, coronary artery disease, cerebrovascular disease, diabetes mellitus, hypertension, and atrial fibrillation. Baseline eGFR was associated with 1-year survival (P<0.001) after MitraClip repair. At 1-year follow-up, the mean change in eGFR for the overall cohort was −1.0±15.1 mL/min/1.73 m^2; for patients with CKD stage 1 or 2, stage 3, or stage 4 or 5, mean change was −4.1±16.6, +2.6±12.4, and +4.8±9.5 mL/min/1.73 m^2, respectively. Linear mixed effect modeling demonstrated a strong association between MR and eGFR, and a statistically significant improvement in eGFR in patients with CKD stage 4 or 5 associated with MR reduction to ≤2+ (P=0.007).

Conclusions—Renal dysfunction is associated with lower survival in patients with severe MR even after percutaneous mitral valve repair. Reduction in MR severity by the MitraClip device is associated with improvement in renal function at 1 year in patients with baseline renal dysfunction.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifiers: NCT00209274, NCT01931956, NCT01940120. **(*Circ Cardiovasc Interv*. 2015;8:e001349. DOI: 10.1161/CIRCINTERVENTIONS.113.001349.)**

Key Words: catheterization ■ kidney ■ mitral valve ■ valve

Renal function is strongly related to heart disease.[1–4] Mitral regurgitation (MR) is one of the most common valve lesions and is often progressive in nature.[5] In patients with severe MR, several hemodynamic abnormalities may occur, including increased left atrial pressure, pulmonary hypertension, and reduced left ventricular forward stroke volume,[6] leading to the development of heart failure. In addition, the presence and severity of MR has been found to be independently associated with worse renal function.[7]

The relationship between MR reduction and change in renal function has not been defined. Improvement in the hemodynamic abnormalities of chronic MR may affect renal function. Mitral repair with the MitraClip system has been used in patients with multiple comorbid medical conditions, including renal disease.[8,9] Because this percutaneous intervention does not involve cardiopulmonary bypass and uses no or minimal contrast administration, the acute effect of MR reduction alone on renal function may be more clearly assessed. Although the residual degree of MR by edge-to-edge repair using the MitraClip device is greater than achieved by mitral valve surgery,[10] the relationship between residual MR and renal function has not been investigated to date.

Received December 18, 2013; accepted December 15, 2014.

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The Data Supplement is available at http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.113.001349/-/DC1.

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WHAT IS KNOWN

- Chronic kidney disease is strongly associated with worse outcome in many cardiovascular diseases.

WHAT THE STUDY ADDS

- Chronic kidney disease severity by estimated glomerular filtration rate was strongly associated with worse 1-year survival after percutaneous mitral valve repair by the MitraClip device, even after adjusting for patient age and sex.
- Reduction in mitral regurgitation severity to moderate or less by MitraClip repair was associated with a small improvement in estimated glomerular filtration rate in patients with moderate or severe chronic kidney disease at baseline.

We hypothesized that a reduction in MR severity by percutaneous mitral repair is associated with improved renal function as measured by estimated glomerular filtration rate (eGFR) in patients with chronic kidney disease (CKD). The objectives of this study were (1) to evaluate clinical characteristics of patients with moderate-to-severe or severe (grade 3+ or 4+) MR and CKD; (2) to assess renal function at serial intervals to 1 year after transcatheter repair of MR with the MitraClip device as a function of baseline renal function; and (3) to explore the relationship between reduction in MR and change in eGFR.

Methods

Study Population

Patients enrolled in the Endovascular Valve Edge-to-Edge Repair Study trials (n=886) were included in this study. This cohort included patients treated with the MitraClip device in 3 separate studies: (1) EVEREST II randomized, controlled trial (ClinicalTrials.gov No. NCT00209274), a prospective, multicenter, randomized study of the MitraClip System in the treatment of MR, randomizing patients to MitraClip (n=178) or mitral valve surgery, (2) EVEREST II high risk registry study (n=78), a prospective multicenter study of the MitraClip System for the treatment of MR in high surgical risk patients, and (3) an ongoing, continued access prospective, multicenter study (REALISM) of the MitraClip System in a surgical population (nonhigh risk arm) and a high surgical risk population (high risk arm; n=630; Figure 1). Because of different inclusion and exclusion criteria for these studies, patients with baseline serum creatinine measurement >2.5 mg/dL were excluded from enrollment in the EVEREST II randomized trial and the nonhigh risk arm of the REALISM continued access registry.

Patients were eligible for MitraClip treatment if they had moderate-to-severe or severe (grade 3+ or 4+, respectively), chronic MR as described previously.[10] The study protocols were reviewed and approved by the institutional review board of each participating site, and all patients provided written informed consent for the procedure and follow-up.

Evaluation of Kidney Function

Serum creatinine measurements were performed per protocol at baseline (preprocedure), discharge, 30 days, 6 months, and 1 year after MitraClip procedure. eGFR was calculated post hoc according to Modification of Diet in Renal Disease Study Group formula:

Three categories of eGFR based on National Kidney Foundation recommendations were compared[11]: eGFR of ≥60 mL/min/1.73 m^2 (n=438) or CKD stage 1 or 2; eGFR of 30 to 59 mL/min/1.73 m^2 (n=364) or CKD stage 3; and eGFR <30 mL/min/1.73 m^2 (n=52) or CKD stage 4 or 5 CKD.[11] Calculation of eGFR at follow-up after MitraClip repair was adjusted for change in age. Stage 5 CKD patients already requiring renal replacement therapy at baseline (n=26) were excluded from the analysis.

Study Oversight

The monitoring, data collection, and analysis were performed by research personnel at Abbott Vascular in partnership with site investigators. The first author wrote the first draft of the article, with review and revision by all the coauthors. All the authors vouch for the accuracy of the data and analyses reported.

Statistical Analysis

Baseline clinical characteristics were summarized using means and standard deviations for continuous measures and counts and proportions for categorical measures. Comparison across stages of renal function was performed using analysis of variance for continuous variables and chi-square test of homogeneity for categorical variables. Mean change in eGFR between baseline and 1 year for the overall cohort was assessed using a paired t test. All P values and confidence intervals (CIs) were calculated using 2-sided tests, and a significance level of 0.05 was used to declare statistical significance for each analysis.

Paired eGFR and echocardiographic core laboratory measures of MR severity were analyzed over time, and linear mixed effect models were fit to evaluate the association between MR severity and eGFR. Repeated measures from individual patients were used to generate the models and a compound symmetrical covariance structure

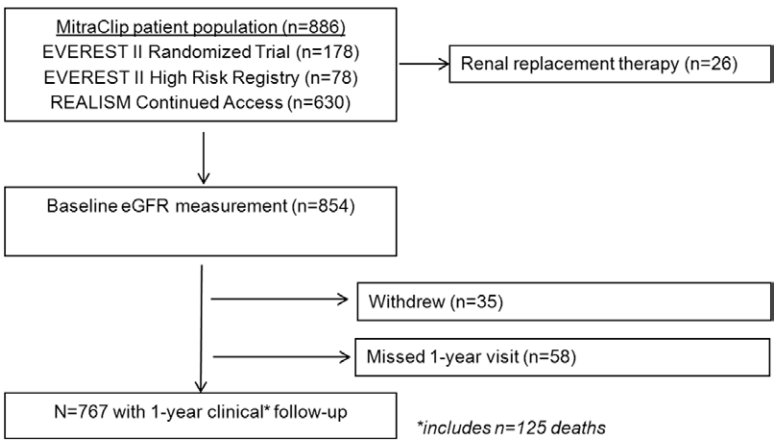


Figure 1. Study population of patients who underwent MitraClip repair of mitral regurgitation.

Table 1. Baseline Clinical Characteristics of the Overall Study Cohort and CKD Subgroups

Characteristic	All Patients (N=854)	CKD Stage 1 or 2 (N=438)	CKD Stage 3 (N=364)	CKD Stage 4 or 5 (N=52)	*P* Value
Age	73.5±11.8 (854)	70.4±12.9 (438)	76.6±9.4 (364)	77.2±11.5 (52)	<0.0001
Age ≥75 y	51.1% (436/854)	40.6% (178/438)	61.8% (225/364)	63.5% (33/52)	<0.0001
Male	59.0% (504/854)	65.1% (285/438)	54.9% (200/364)	36.5% (19/52)	<0.0001
History of heart failure	92.2% (787/854)	89.3% (391/438)	94.8% (345/364)	98.1% (51/52)	0.004
NYHA 3 or 4	67.8% (578/853)	59.5% (260/437)	74.5% (271/364)	90.4% (47/52)	<0.0001
Coronary artery disease	64.9% (553/852)	55.5% (243/438)	74.6% (270/362)	76.9% (40/52)	<0.0001
Prior myocardial infarction	34.5% (292/847)	26.8% (117/437)	42.7% (153/358)	42.3% (22/52)	<0.0001
Cerebrovascular disease	16.3% (139/854)	12.6% (55/438)	19.8% (72/364)	23.1% (12/52)	0.009
Previous cardiac surgery	40.3% (344/854)	33.1% (145/438)	48.1% (175/364)	46.2% (24/52)	<0.0001
Hypertension	82.0% (700/854)	75.8% (332/438)	87.4% (318/364)	96.2% (50/52)	<0.0001
Atrial fibrillation	56.3% (449/798)	45.8% (189/413)	66.3% (224/338)	76.6% (36/47)	<0.0001
Chronic obstructive lung disease	24.1% (205/852)	21.7% (95/438)	27.3% (99/362)	21.2% (11/52)	0.155
Diabetes mellitus	26.5% (226/853)	17.8% (78/438)	34.7% (126/363)	42.3% (22/52)	<0.0001
Left ventricular ejection fraction	52.6±13.6 (772)	55.3±12.5 (397)	50.0±14.0 (327)	47.2±15.0 (48)	<0.0001
Mitral regurgitation >2+	89.5% (740/827)	90.3% (381/422)	87.8% (310/353)	94.2% (49/52)	0.276
Degenerative pathogenesis of MR	50.9% (435/854)	61.9% (271/438)	40.1% (146/364)	34.6% (18/52)	<0.0001
Left ventricular end-diastolic diameter, cm	5.5±0.8 (814)	5.50±0.76 (417)	5.50±0.80 (346)	5.56±0.84 (51)	0.873
Left ventricular end-systolic diameter, cm	4.0±1.1 (785)	3.93±1.03 (400)	4.14±1.08 (334)	4.23±1.14 (51)	0.012
Left atrial volume, mL	91.5±43.7 (778)	90.9±41.1 (397)	91.7±44.8 (331)	95.1±54.7 (50)	0.805
Baseline serum creatinine, mg/dL	1.3±0.5 (853)	0.9±0.2 (437)	1.5±0.3 (364)	2.6±0.9 (52)	<0.0001
Body surface area, m^2	1.89±0.27 (854)	1.91±0.27 (438)	1.86±0.26 (364)	1.85±0.28 (52)	0.010
eGFR, mL/min/1.73 m^2	61.5±23.1 (854)	79.6±16.0 (438)	45.1±8.5 (364)	23.6±5.3 (52)	<0.0001

CKD Stage 1 or 2, eGFR ≥60 mL/min/1.73 m^2; CKD Stage 3, eGFR 30–59 mL/min/1.73 m^2; and CKD Stage 4 or 5, eGFR <30 mL/min/1.73 m^2. CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; MR, mitral regurgitation; and NYHA, New York Heart Association.

Table 2. Cardiac Medications at Baseline and 1 Year or Last Follow-Up

Medication Category	CKD Stage 1 or 2 (N=438)		CKD Stage 3 (N=364)		CKD Stage 4 or 5 (N=52)	
	Baseline	Follow-Up	Baseline	Follow-Up	Baseline	Follow-Up
ACEi/ARB	60.3%	65.3%	56.9%	56.9%	48.1%	46.2%
Anticoagulant	30.8%	31.3%	40.1%	44.5%	36.5%	32.7%
Antiarrhythmic	9.6%	16.2%	19.5%	20.6%	26.9%	25.0%
Antiplatelet	57.1%	62.6%	67.0%	61.0%	78.8%	57.7%
β-blocker	55.3%	63.5%	67.0%	67.9%	78.8%	73.1%
Calcium channel blocker	11.2%	15.8%	12.6%	14.8%	17.3%	15.4%
Diuretic	57.1%	61.0%	82.4%	75.5%	98.1%	73.1%
Nitrate	11.0%	13.7%	24.7%	25.0%	46.2%	36.5%

CKD Stage 1 or 2, eGFR ≥60 mL/min/1.73 m^2; CKD Stage 3, eGFR 30–59 mL/min/1.73 m^2; and CKD Stage 4 or 5, eGFR <30 mL/min/1.73 m^2. ACEi indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; and eGFR, estimated glomerular filtration rate.

was assumed to account for repeated measures within patient. The models were then used to estimate changes in eGFR associated with changes in MR severity between baseline and 1 year. The models included MR severity and the follow-up time period (days) as independent variables. Separate models were fit for patients within 3 CKD categories at baseline: CKD stage 1 or 2, stage 3, or stage 4 or 5. Model fit was evaluated by analyzing residuals; there was no evidence of lack of fit. Data on all patients, including those with missing values at ≥1 time points, were included in the models. Estimated mean changes together with 95% CIs are presented graphically by degree of renal dysfunction at baseline.

An exploratory analysis evaluating baseline clinical variables associated with an increase in eGFR of ≥5 mL/min/1.73 m^2 between baseline and 1 year was performed using a logistic regression model that included main effects only. Change in medication usage between baseline and 1 year or last follow-up was assessed using McNemar's test. Kaplan–Meier analyses of survival through 1 year after MitraClip repair were performed with stratification by degree of renal function at baseline. Survival across these strata was compared using the log-rank test. Cox proportional hazards modeling was performed to evaluate the association between severity of CKD and mortality after adjustment for age and sex. All statistical analyses were performed using PC SAS for Windows version 9.2 (SAS Institute, Cary, NC).

Results

The baseline clinical characteristics of the overall study cohort (n=854) are shown in Table 1. In general, patients were advanced in age, had a high prevalence of previous cardiac disease and advanced heart failure symptoms, as well as multiple comorbid medical problems. The vast majority had MR grade 3+ or 4+ by quantitative assessment by the echocardiography core laboratory. Baseline mean eGFR for the study population was 61.5±23.1 mL/min/1.73 m^2. The mean eGFR in patients with CKD stage 1 or 2 (n=438, 51.3%) was 79.6±16.0 mL/min/1.73 m^2 compared with 45.1±8.5 mL/min/1.73 m^2 for the patients with CKD stage 3 (n=364, 42.6%) and 23.6±5.3 mL/min/1.73 m^2 for the group with CKD stage 4 or 5 (n=52, 6.1%). In addition to expected older age (63.5% >75 years old) and more women (63.5%) in patients with CKD stage 4 or 5

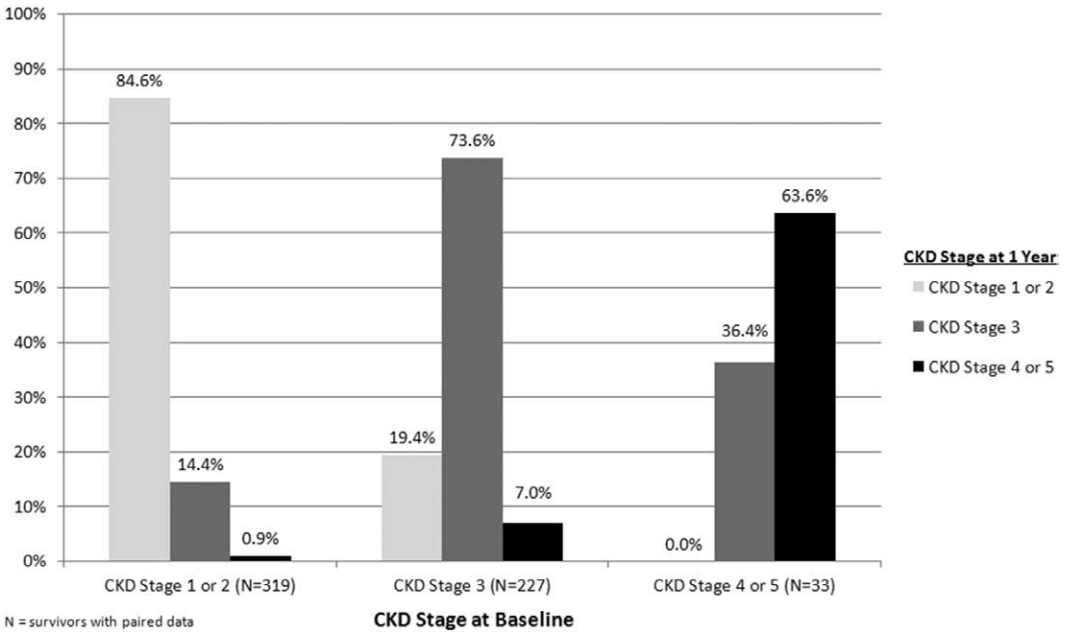


Figure 2. Paired comparisons of chronic kidney disease (CKD) severity across subgroups from baseline to 1 year.

disease, this subgroup had a lower percentage of degenerative MR (34.6%); lower left ventricular ejection fraction (LVEF; 47.2%); and had a higher prevalence of comorbid medical conditions, including advanced heart failure (New York Heart Association 3 or 4, 90.4%), diabetes mellitus (42.3%), coronary artery disease (76.9%), and history of atrial fibrillation (76.6%).

For baseline medications, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, diuretics, and antiplatelet agents were prescribed in the majority of patients, with a higher proportion of patients with severe CKD receiving these medications, except angiotensin converting enzyme inhibitors or angiotensin receptor blockers (Table 2).

In the overall cohort with paired baseline and 1 year data (n=579), mean change in eGFR was −1.0±15.2 mL/min/1.73 m^2 (*P*=0.10). Among patients with CKD stage 1 or 2 at baseline (n=319), the mean change in eGFR 1 year after MitraClip repair was −4.1±16.6 mL/min/1.73 m^2; among patients with CKD stage 3 at baseline (n=227), mean change in eGFR was +2.6±12.4 mL/min/1.73 m^2; and among patients with CKD stage 4 or 5 at baseline (n=33), the mean change in eGFR was +4.8±9.5 mL/min/1.73 m^2. Changes in eGFR across subgroups of baseline renal function are shown in Figure 2. Among patients with CKD stage 4 or 5 at baseline, 36.4% had improved to CKD stage 3 at 1 year after MitraClip repair.

The relationships between paired measurements of eGFR and severity of MR from baseline to 1 year follow-up after MitraClip repair are shown in Figure 3. For all subgroups of CKD, a modest, acute improvement in eGFR was seen before discharge. Using linear mixed effect models, the relationship between eGFR and MR severity was evaluated. Lower eGFR was strongly associated with MR 3 or 4+ severity in all 3 CKD categories (*P*<0.001). Reduction in MR severity from 3+/4+ at baseline to 1+/2+ at 1 year was significantly associated with an increase in eGFR among patients with CKD stage 3, 4 or 5 at baseline (Figure 4).

Clinical characteristics of patients who had improvement in renal function (defined as increase in eGFR ≥5 mL/min/1.73 m^2) compared with those whose eGFR did not improve are shown in Table 3. An exploratory, multivariable logistic regression analysis, including baseline age, New York Heart Association 3 or 4, atrial fibrillation, diabetes mellitus, coronary artery disease, LVEF, MR pathogenesis, diuretic, angiotensin converting enzyme inhibitor or angiotensin receptor blocker use, and MR severity ≤2+, was performed to assess variables associated with improvement in eGFR ≥5 mL/min/1.73 m^2. Only New York Heart Association 3 or 4 symptoms at baseline was independently associated with this degree of improvement in eGFR at 1 year (odds ratio 2.2; 95% CI, 1.41–3.57; *P*=0.007).

In an unadjusted analysis, 1-year survival was associated with baseline renal function (Figure 5). Kaplan–Meier estimates of mortality at 1 year was 15.0% of patients for the overall cohort, including 9.0%, 20.6%, and 26.0% of patients who died among CKD stages 1 or 2, stage 3, and stage 4 or 5, respectively (*P*<0.001). In Cox proportional hazards modeling, severity of CKD by subgroup remained associated with higher mortality after adjustment for age and sex (compared with CKD stage 1 or 2, hazard ratio, 2.35 [95% CI, 1.73–3.19] for CKD stage 3 and hazard ratio 3.8 [95% CI, 2.38–6.05] for CKD stage 4 or 5).

At 1-year follow-up, 217/569 (38.1%) patients had mild (1+) or less MR, 256/569 (45.0%) patients had moderate (2+) MR, and 96 (16.9%) patients had moderate-to-severe or severe (3 or 4+) MR by echocardiographic assessment. Among survivors with paired baseline and 1 year echocardiograms, reduction in left ventricular volumes, diameters, and left atrial volume were statistically significant (Table in the Data Supplement). Improvements in these measurements were evident across all CKD subgroups, with trends toward statistical significance in CKD stage 4 or 5 patients. Multiple cardiac medications were still prescribed in the majority of

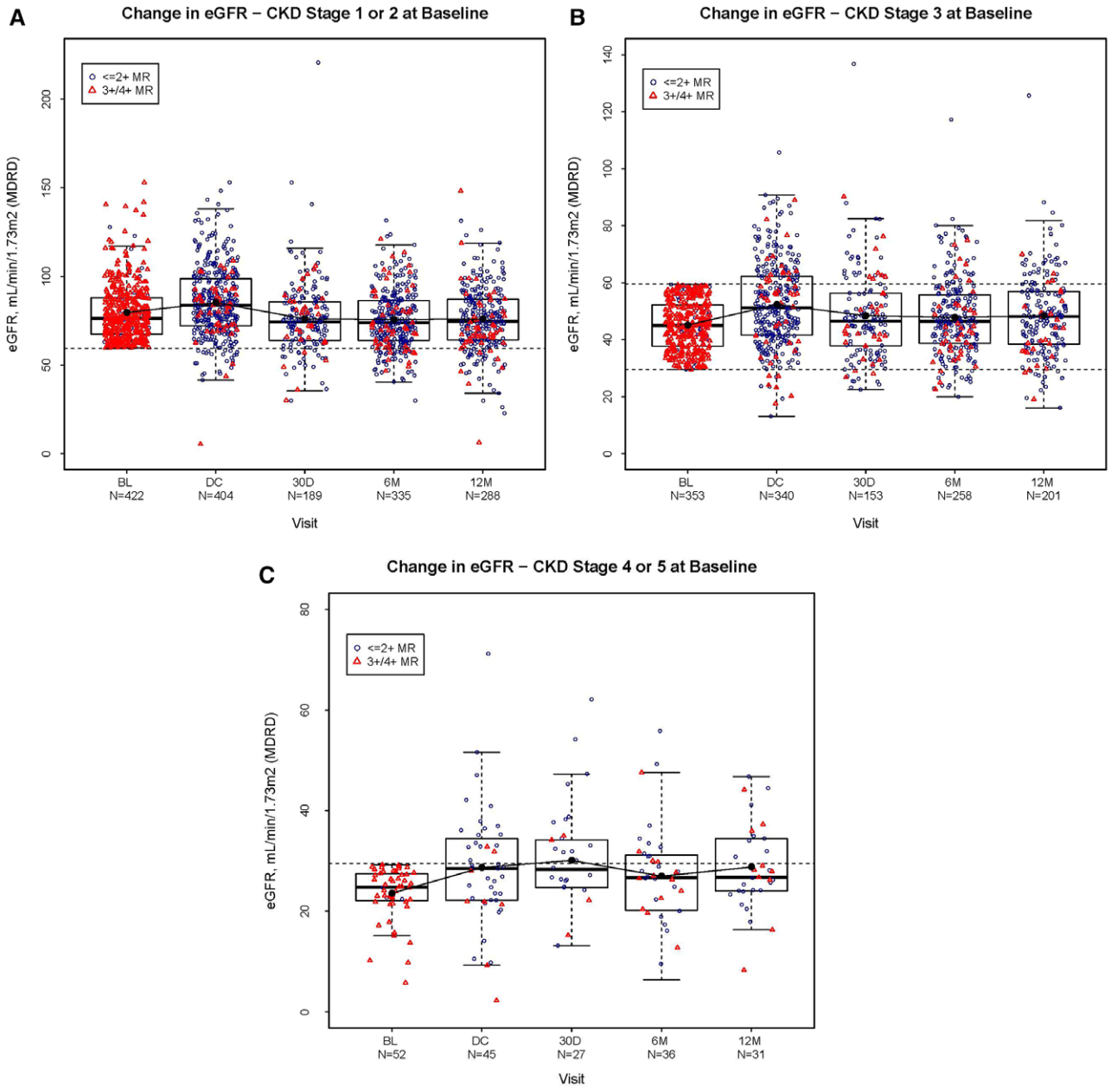


Figure 3. Estimated glomerular filtration rate (eGFR) and mitral regurgitation (MR) severity measurements during 1 year follow-up after MitraClip repair. **A**, Chronic kidney disease (CKD) Stage 1 or 2 (eGFR ≥60 mL/min/1.73 m^2) at baseline; **B**, CKD Stage 3 (eGFR 30–59 mL/min/1.73 m^2) at baseline; and **C**, CKD Stage 4 or 5 (eGFR <30 mL/min/1.73 m^2) at baseline. BL indicates baseline; and DC, discharge.

patients after MitraClip repair (Table 2), although there was a substantial decrease in the use of diuretics in patients with severe kidney disease at baseline (P<0.001).

Discussion

The main findings of this study are (1) the presence of CKD in patients with moderate-severe or severe MR is associated with higher prevalence of vascular disease (including coronary artery disease, prior myocardial infarction, and cerebrovascular disease) and hemodynamic abnormalities (such as advanced heart failure symptoms, lower LVEF, and atrial fibrillation); (2) the degree of renal dysfunction at baseline correlates with mortality at 1 year after percutaneous mitral valve repair; and (3) patients with severe kidney disease at baseline were more likely to have improvement in eGFR at 1 year after reduction in MR to moderate or less degree.

MR may result in significant hemodynamic abnormalities,[12] including reduced left ventricular systolic dysfunction, lower cardiac output, atrial fibrillation, and pulmonary hypertension. Although these factors may impair renal function, the current study highlights several other comorbid medical conditions that are associated with kidney disease in the setting of MR. The high prevalence of these other cardiovascular conditions, such as coronary and cerebrovascular disease, suggests that hemodynamic abnormalities of chronic MR may exacerbate renal dysfunction in patients with other risk factors. Importantly, severity of kidney disease at baseline was correlated with worse survival at 1 year even after reduction

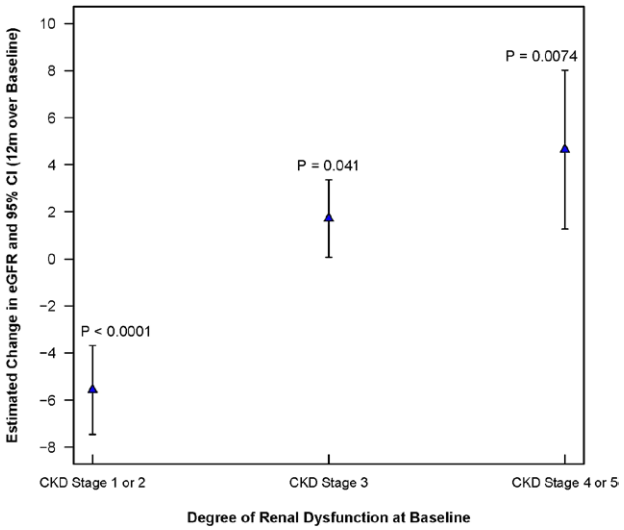


Figure 4. Mean change in eGFR at 1 year within chronic kidney disease (CKD) subgroups after MitraClip repair associated with mitral regurgitation (MR) reduction from 3+/4+ to 1+/2+.

in MR. This prognostic influence of preexisting renal dysfunction echoes its association with higher mortality in other cardiac conditions, including coronary artery disease,[13] left ventricular systolic dysfunction,[14] aortic valve stenosis,[15] and after cardiac surgery.[16] In a recent study of patients undergoing mitral valve repair for functional MR, patients with CKD stage 4 or 5 was associated with worse survival long term.[17]

Improvement in renal function has been reported after successful catheter ablation of atrial fibrillation, with freedom from recurrence of atrial arrhythmias as the only clinical variable associated with improved renal function at 1 year.[18] In the present study, although renal dysfunction was associated with many chronic, vascular conditions, our results suggest that reduction in MR severity by MitraClip repair is associated with an early improvement in eGFR. The time course of improvement in eGFR is consistent with previous reports of acute hemodynamic improvements after mitral valve repair with either the MitraClip device[19,20] or mitral valve surgery,[21] as well as the stability of these hemodynamic changes with evidence of left ventricular remodeling to 1 year follow-up.[22,23] The clinical benefit of percutaneous mitral valve repair in patients with more severe renal dysfunction mirrors the reduction in mortality or hospitalization described in patients with end-stage renal disease after surgical repair of functional MR.[17]

Although patients with baseline CKD stage 1 or 2 had a slight reduction in eGFR at 1 year after MitraClip therapy, patients with CKD stage 4 or 5 were more likely to have improvement rather than decline in eGFR. The change in eGFR associated with the reduction in MR to moderate or less was statistically significant in patients with CKD stage 3, 4 or 5. These results suggest that reduced eGFR at baseline may not be a fixed condition, but rather may identify patients whose renal function may improve to a greater extent from the hemodynamics benefits of MR reduction. The increase in eGFR after MR reduction observed in the severe renal dysfunction group statistically may reflect regression to the mean. However, the proportion of patients with improvement

Table 3. Baseline Clinical Characteristics of Patients With Improvement in Renal Function (Increase in eGFR ≥5 mL/min/1.73 m²) at 1 Year

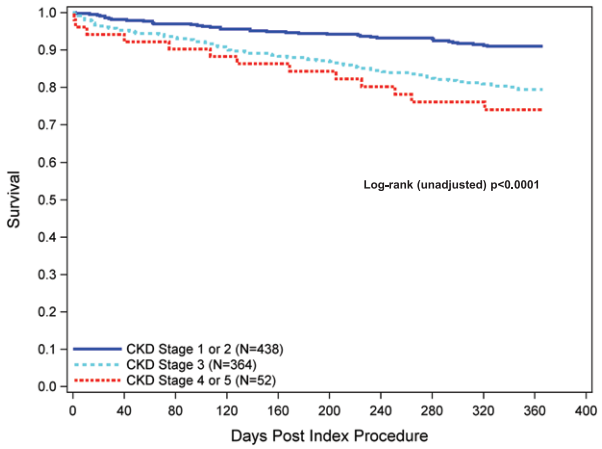
Baseline Characteristic	Improved eGFR	No Improvement	*P* Value
Age ≥75 y	48.9% (87/178)	48.1% (193/401)	0.928
Male	58.4% (104/178)	59.1% (237/401)	0.927
History of heart failure	92.1% (164/178)	90.3% (362/401)	0.535
NYHA 3 or 4	73.6% (131/178)	58.0% (232/400)	<0.001
Coronary artery disease	61.2% (109/178)	59.9% (240/401)	0.783
Prior myocardial infarction	28.4% (50/176)	29.6% (118/399)	0.842
Cerebrovascular disease	11.2% (20/178)	14.0% (56/401)	0.425
Previous cardiac surgery	37.1% (66/178)	37.7% (151/401)	0.926
Hypertension	78.7% (140/178)	81.0% (325/401)	0.499
Atrial fibrillation	55.7% (97/174)	52.6% (195/371)	0.520
Diabetes mellitus	25.3% (45/178)	24.9% (100/401)	0.918
LV ejection fraction	55.6±12.7 (164)	53.6±13.2 (372)	0.106
Mitral regurgitation >2+	88.3% (151/171)	91.5% (356/389)	0.272
Degenerative pathogenesis of MR	60.7% (108/178)	53.6% (215/401)	0.124
Baseline serum creatinine, mg/dL	1.3±0.6 (178)	1.2±0.5 (401)	0.003
Body surface area, m²	1.9±0.3 (178)	1.9±0.3 (401)	0.161
eGFR, mL/min/1.73 m²	57.3±20.5 (178)	66.2±23.7 (401)	<0.001
Left ventricular end-diastolic diameter, cm	5.4±0.8 (168)	5.5±0.8 (385)	0.052
Left ventricular end-systolic diameter, cm	3.8±1.0 (163)	4.0±1.1 (378)	0.059
Left atrial volume, mL	84.6±33.1 (162)	91.1±36.9 (372)	0.054

CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; LV, left ventricle; MR, mitral regurgitation; and NYHA, New York Heart Association.

from stage 4 or 5 to stage 3 CKD exceeded the proportions of patients who changed categories in other eGFR subgroups, suggesting that this observed improvement unlikely represented regression to the mean eGFR.

In addition, more advanced heart failure symptoms at baseline were also associated with improvement in eGFR at 1 year. In this cohort of patients, advanced heart failure symptoms represent a hemodynamic consequence of severe MR that may be reversible by sustained MR reduction. Longer term follow-up in the EVEREST II randomized trial has previously shown stable improvement in heart failure symptoms after MitraClip repair.[24] In the present study, the lower proportion of patients with severely reduced, baseline eGFR who were treated with diuretic medications at 1 year is consistent with reduced symptoms of heart failure and may be related to changes in eGFR. Furthermore, improvement in left ventricular and left atrial sizes at 1 year across CKD categories suggest reduction in adverse remodeling associated with severe MR and heart failure.

Renal dysfunction is common in patients with heart failure and left ventricular systolic dysfunction[14] and is multifactorial in pathogenesis. Although severity of baseline renal dysfunction was associated with lower LVEF in patients with MR, improvement in renal function was not related to



	Baseline	30 Days	6 Months	1 Year
CKD Stage 1 or 2				
# At risk	438	426	397	348
% Event-free	100%	98.2%	94.4%	91.0%
95% CI	-	[96.3%, 99.1%]	[91.8%, 96.2%]	[87.6%, 93.5%]
CKD Stage 3				
# At risk	364	345	311	247
% Event-free	100%	95.8%	88.0%	79.4%
95% CI	-	[93.2%, 97.5%]	[84.1%, 91.0%]	[74.5%, 83.5%]
CKD Stage 4 or 5				
# At risk	52	48	42	34
% Event-free	100%	94.2%	84.3%	74.0%
95% CI	-	[82.9%, 98.1%]	[70.9%, 91.9%]	[58.8%, 84.3%]

Figure 5. One-year survival as a function of baseline eGFR.

degenerative or functional pathogenesis of MR or baseline LVEF, although only a small percentage of patients had severe left ventricular systolic dysfunction. The ongoing randomized trial of MitraClip treatment of functional MR, Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) trial (NCT01626079), includes patients with renal dysfunction and heart failure.

This study has several limitations. Given the clinical characteristics of patients in this cohort from the EVEREST II trials, particularly advanced in age and with multiple comorbid conditions, the generalizability of these data is limited, and our findings may not be applicable to all patients with MR. As an observational, post hoc analysis, association between reduction in MR severity and changes in kidney function may not be causal because of potential confounding factors, including other differences in baseline clinical characteristics. The study population included several cohorts of patients treated with the percutaneous MitraClip repair system. Although all patients had quantitative assessment of MR severity by an echocardiographic core laboratory prior to treatment, clinical selection criteria for treatment with the MitraClip device was not uniform across these cohorts and selection bias may have influenced the results. Because of the small number of patients who underwent mitral valve surgery in the EVEREST II randomized trial with its inclusion criteria, assessment of renal function after mitral valve repair surgery as compared with MitraClip treatment was not performed. Therefore, it is not known whether more effective reduction in MR severity (to trace or no MR) is associated with greater absolute increase in eGFR. Renal function was assessed only by serial serum creatinine measurements, and the influence of duration of kidney disease on the observed change in eGFR after treatment of MR could not be determined. The clinical significance of the observed change in eGFR on longer term outcome is unclear. Survival bias may influence the reported change in eGFR in patients with baseline renal dysfunction, such that the improvement in eGFR may be overestimated in patients with follow-up measurements. However, the linear mixed effect models address this limitation by including all available measurements of serum creatinine and MR severity, including data from expired or withdrawn patients through their last available follow-up before death (eg, discharge, 30 days or 6 months as applicable) to provide a longitudinal evaluation of this relationship.

In conclusion, reduction in MR by percutaneous repair was associated with improvement in renal function in patients with more advanced CKD soon after MitraClip repair until last follow-up through 1 year. Although hypothesis generating, these results suggest that the hemodynamic improvements resulting after percutaneous mitral valve repair may improve renal function. Further studies of renal function after cardiac interventions and the influence on clinical outcome are needed.

Sources of Funding

Abbott Vascular.

Disclosures

Dr Wang has received research grants from Abbott, Edwards Lifesciences, Gilead Sciences, and American Heart Association (Mid-Atlantic Affiliate); Chithra Sangli is an employee of Abbott Laboratories; Dr Lim is a consultant for and has received research grants from Abbott; Dr Ailawadi has received research grants from AstraZeneca and has received consulting fees/honoraria from Abbott, Edwards, St. Jude and Atricure; Dr Kar has honoraria/institutional research support from Abbott; Dr Herrmann receives research funding to his institution from Abbott Vascular, Edwards Lifesciences, St Jude Medical, Medtronic, Gore, and Siemens, and he has equity in Microinterventional Devices; Dr Grayburn has received grants from Abbott Vascular, Medtronic, Baxter, ValTech Cardio, Guided Delivery Systems and consulting fees/honoraria from Abbott Vascular, Tendyne and Bracco Diagnostics; Dr Foster has received research grants from Abbott Vascular; Dr Weissman has received research grants from Edwards, Abbott, Sorin, St. Jude, Medtronic, Boston Scientific, MitraAlign, and Direct Flow; Dr Feldman is a consultant for and has received honoraria/institutional research support from Abbott, Boston Scientific, Edwards, and WL Gore. The other authors report no conflict.

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