ORIGINAL RESEARCH

Early Rapid Decline in Kidney Function in Medically Managed Patients With Atherosclerotic Renal Artery Stenosis

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***Background*—**Early rapid declines of kidney function may occur in patients with atherosclerotic renal artery stenosis with institution of medical therapy. The causes and consequences are not well understood.

***Methods and Results*—**Patients enrolled in the medical therapy–only arm of the CORAL (Cardiovascular Outcomes With Renal Artery Lesions) study were assessed for a rapid decline (RD) in estimated glomerular filtration rate (eGFR), defined as a ≥30% decrease from baseline to either 3 months, 6 months, or both. In the medical therapy–only cohort, eGFR was available in 359 subjects at all time points, the subjects were followed for a median of 4.72 years, and 66 of 359 (18%) subjects experienced an early RD. Baseline log cystatin C (odds ratio, 1.78 [1.11–2.85]; P=0.02), age (odds ratio, 1.04 [1.00–1.07]; P<0.05), and Chronic Kidney Disease Epidemiology Collaboration creatinine eGFR (odds ratio, 1.86 [1.15–3.0]; P=0.01) were associated with an early RD. Despite continued medical therapy only, the RD group had an improvement in eGFR at 1 year (6.9%; P=0.04). The RD and nondecline groups were not significantly different for clinical events and all-cause mortality (P=0.78 and P=0.76, respectively). Similarly, renal replacement therapy occurred in 1 of 66 (1.5%) of the RD patients and in 6 of 294 (2%) of the nondecline patients. The regression to the mean of improvement in eGFR at 1 year in the RD group was estimated at 5.8±7.1%.

***Conclusions*—**Early rapid declines in kidney function may occur in patients with renal artery stenosis when medical therapy is initiated, and their clinical outcomes are comparable to those without such a decline, when medical therapy only is continued. **(*J Am Heart Assoc*. 2019;8:e012366. DOI: 10.1161/JAHA.119.012366.)**

Key Words: cardiovascular disease • renal • renal artery stenosis • renal disease • renovascular • renovascular hypertension

Renal artery stenosis (RAS) is a common problem, especially in older people over the age of 70 years.[1] Renal dysfunction is commonplace, and there is a strikingly high rate of adverse cardiovascular events and mortality in patients with impaired kidney function and renal artery stenosis.[2] A number of studies have evaluated the factors that predict an improvement in kidney function after renal artery revascularization, commonly measured with estimates of glomerular filtration rate (GFR).[3,4]

One such factor is a rapid decline (RD) in kidney function, and as a result, some authors have suggested that an RD in kidney function is an indication for stent revascularization.[3,4] The utility of an RD in GFR as an indication for revascularization in medically managed patients has risen in importance since 3 randomized trials have demonstrated that medical therapy without revascularization is the preferred treatment for most patients with atherosclerotic RAS.[5–7]

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Accompanying Table S1 and Figures S1, S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012366

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Clinical Perspective

What Is New?

- Although large randomized studies such as ASTRAL (Angioplasty and Stenting for Renal Artery Lesions) and CORAL (Cardiovascular Outcomes With Renal Artery Lesions) have demonstrated the noninferiority of best medical therapy to that of best medical therapy+stenting, physicians still continue to consider a sudden deterioration of renal function in a medically managed patient with renal atherosclerosis as an indication to place a stent.

What Are the Clinical Implications?

- This analysis of the CORAL data set strongly suggests that best medical therapy (without stenting) should be continued in such patients.

We sought to determine the frequency of RD of kidney function in medically managed RAS patients and to examine the clinical outcomes with continued medical therapy. To perform this analysis, we used data from the CORAL (Cardiovascular Outcomes With Renal Artery Lesions)[5] clinical trial to evaluate rapid changes in estimated glomerular filtration rate (eGFR) occurring within the first 6 months of medical management in patients with RAS.

Methods

Patient Population

CORAL (NCT00081731) is a prospective, international, multicenter clinical trial that randomly assigned 931 participants with atherosclerotic RAS who received optimal medical therapy to stenting versus no stenting. Randomization occurred from May 2005 through January 2010. Optimal medical therapy for CORAL, including the use of antihypertensives, antiplatelet therapy, angiotensin receptor blockers, angiotensin converting enzyme inhibitors, and statins, has been previously published,[5,8] as has the importance of optimal medical therapy in treating atherosclerotic RAS.[9–11] The full CORAL data set is on the National Heart, Lung, and Blood Institute website (https://biolincc.nhlbi.nih.gov/studies/coral/), where investigators can request access to the data.

All enrolling centers obtained institutional review committee approval and followed institutional and study guidelines. All participating subjects provided written informed consent. The results of the study have been previously described.[5] Patients with RAS of at least 60% were eligible if they had hypertension while receiving ≥2 antihypertensive agents or had an eGFR <60 mL/min per 1.73 m^2. Angiograms were analyzed for verification of stenosis by the Angiography Core Lab for the study at the University of Virginia.

Study Aim

The current study sought to examine changes in kidney function within the medical therapy–only group. The primary aims were to (1) examine factors that predict RD of kidney function within the first 6 months of medical therapy and (2) determine the clinical outcomes of patients with early RD of kidney function.

Estimation of GFR

eGFR was assessed using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations at baseline, 3 and 6 months, and every 6 months for the duration of follow-up.[12]

Rapid Decline

RD was a dichotomous outcome and was defined as a ≥30% decrease in eGFR from baseline to either 3 months, 6 months, or both intervals.[13] Nondecline (ND) was defined as those patients who did not demonstrate an RD.

Statistical Analysis

Continuous data were tested for goodness of fit to the normal distribution using the Shapiro–Wilk test. If not normally distributed, the log-transformation of the variable was assessed for normality. Continuous data are presented as mean± SD of the untransformed or log-transformed version or, if neither were normally distributed, as median with interquartile range. Categorical data are presented as frequency and percent. Comparisons of continuous data were evaluated using 2-sample t tests or Wilcoxon rank sum test. For categorical variables, the chi-square test or, if the frequency of counts for some factors was low (≤5), Fisher exact test was used to compare groups. Statistical significance was defined as a $P<0.05$. All analyses were performed using R software (version 3.0.0) and SAS (version 9.3).

Multiple Variable Models and Longitudinal Analysis

Analysis was performed comparing the RD and ND groups on each baseline characteristic, one at a time, using ANOVA adjusting for age and sex. A stepwise logistic regression with group (RD versus ND) as the outcome was then used to further identify characteristics significantly related to group membership. The model was examined for discriminate ability using area under the curve from receiver operating characteristic analysis and the Hosmer-Lemeshow goodness-of-fit test to assess model fit.

Stepwise multivariate linear regression analysis was used to examine the independent predictors of percentage change in eGFR at 1-year follow-up and to assess the safety and clinical benefit of continued medical therapy. The covariates in the model included reference baseline GFR, rapid decline, sex, age, urine albumin to creatinine ratio (UACR), and cystatin C, and were selected by the stepwise method with the Akaike information criterion. The effect of RD on kidney function over time was estimated by applying the generalized linear mixed model with time (continuous variable) as a random coefficient. In models with an overall significant effect over time, post hoc tests were performed to determine which time-related pairs were significant. Bonferroni adjustment was used to avoid the potential for inflated type I errors. All multivariable models were tested for interaction between predictors and were found to be nonsignificant.

Regression to the Mean

We chose to test for regression to the mean (RTM), as it can lead to overestimation of the treatment effect if not properly adjusted. The nonparametric empirical likelihood method[14] and kernel density estimation[15] were applied to assess the RTM effect on follow-up repeated measurements of eGFR for both the RD and ND groups. Percentage change in eGFR within 6 months became the baseline reference value against which repeated measurements of eGFR were compared. ANCOVA was used for comparison between the groups considering the substantial decline in eGFR in the RD group.[16]

Clinical Event Analysis

The primary outcome was the composite end point defined as the first occurrence of any secondary end points: cardiovascular or renal death, myocardial infarction, stroke, congestive heart failure, or progressive renal insufficiency (≥30% decline in GFR sustained over a period of 6 months) and permanent renal replacement). All-cause mortality was also evaluated as an outcome. Events occurring within 6 months, before the establishment of the RD or ND reference baseline, were censored. These patients were included in the analysis of RD and for follow-up events. The time-to-event analysis used the first event after the 6-month reference baseline.

The predicted probability of the binary occurrence of the composite end point was calculated using logistic regression with adjustment for age, sex, baseline log urine albumin-to-creatinine ratio (LUACR), and baseline log cystatin C. Receiver operating characteristic was used to summarize the model performance. Time to event for the composite and mortality end points was examined using log-rank estimates to compare the RD and ND groups. Hazard ratios were calculated using the Cox proportional-hazards model adjusted for age, sex, and baseline LUACR and cystatin C. Model diagnostics were performed using the Cox-Snell residual plot test to check for goodness of fit. The proportional hazards assumption tests from the R function cox.zph in the survival package for all the survival models had $P>0.05$, indicating that the null hypothesis of proportional hazards was not rejected. The extended Cox model was used to test for interaction among model predictors and time. The time-dependent covariates were generated by building interactions of the predictors and a function of survival time and were included in the models. The P values for all time-covariate interactions in the survival models were >0.05, confirming the null hypothesis assumption of proportional hazards and indicating that the fitted Cox regression hazard models are adequate.

Results

There were 472 patients randomized to medical therapy only in the CORAL clinical trial. For this analysis of the medical therapy–only cohort, eGFR was available in 359 subjects at all relevant time points (baseline, 3 and 6 months, and 1 year). Patients who did not have all estimates relative to determining their decline status were excluded: CKD-EPI creatinine eGFR at baseline, 3 or 6 months, and 1 year. Sensitivity analysis was performed and confirmed that the cohort of patients with missing data was comparable to patients without missing data on baseline characteristics (Table S1). Analyzable subjects were followed for a median of 4.72 (interquartile range, 2.03) years. The average age was 69±9 years, 49% were male, and 7% were Hispanic/Latino. The baseline eGFR was 58±21 mL/min, and the median UACR was 20.7±66.5 μg/mg. The average systolic blood pressure was 150±23 mm Hg, and diastolic blood pressure was 78±13 mm Hg.

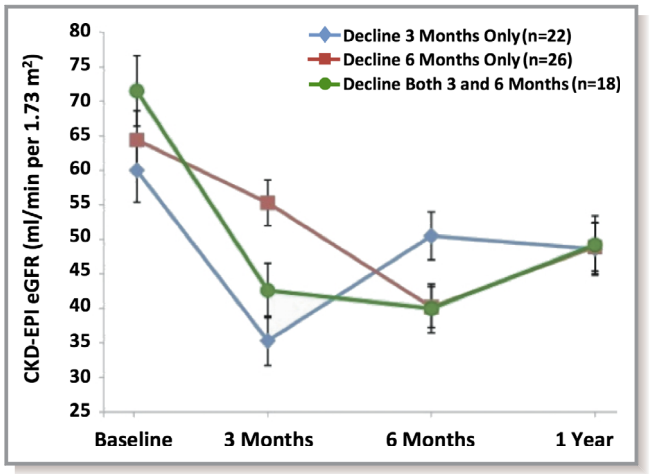


Figure 1. CKD-EPI eGFR of subjects with rapid decline from baseline to 1 year. Rapid decline within 6 months contains 3 mutually exclusive groups: decline at 3 months only, decline at 6 months only, and decline at both 3 and 6 months. Mean±SE at each time period are given. CKD-EPI indicates Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

Table 1. Baseline Clinical Characteristics of Patients With an Early Rapid Decline of Kidney Function (>30% Within 6 Months of Baseline) and Those Without an Early Rapid Decline of Kidney Function

Baseline Characteristics*	Rapid Decline (n=66)	No Rapid Decline (n=294)	*P* Value
Demographic/physical examination			
Age, y	71.5±7.8	69.5±9.3	0.07
Male sex	33 (50)	143 (49)	0.89
Black race	5 (8)	18 (6)	0.59
Hispanic/Latino	3 (5)	16 (5)	>0.99
Height, inches	65.8±3.8	66.0±4.2	0.72
Weight, lb	178.2±42.5	176.8±34.6	0.80
BMI, kg/m^2	29.9±6.9	29.5±5.9	0.67
Systolic BP, mm Hg	154.2±23.9	148.6±22.7	0.08
Diastolic BP, mm Hg	77.4±15.4	78.0±12.7	0.77
Laboratory values (assessed by core lab)			
Creatinine, mg/dL	1.2±0.5	1.2±0.5	0.94
Cystatin C, mg/L	1.4±0.5	1.3±0.5	0.16
MDRD-eGFR, mL/min per 1.73 m^2	62.2±23.1	61.2±22.9	0.74
CKD-EPI creatinine formula	58.9±21.6	58.2±21.2	0.80
CKD-EPI cystatin C formula	57.9±23.5	61.7±22.3	0.22
CKD-EPI creatinine-cystatin C formula	58.7±22.7	60.0±21.9	0.68
Urine albumin to creatinine ratio, μg/mg†	3.8±1.8	3.3±1.6	0.05
Urine albumin to creatinine ratio, μg/mg‡	29.7±131.1	18.6±43.4	0.03
Risk factors/indications			
Peripheral vascular disease	27 (41)	151 (52)	0.13
Hyperlipidemia	58 (88)	265 (92)	0.34
Prior myocardial infarction	20 (31)	87 (30)	0.88
Prior transient ischemic accident	16 (24)	56 (19)	0.40
Angina	8 (13)	38 (15)	0.84
Cardiovascular disease	38 (62)	169 (62)	>0.99
Diabetes mellitus	26 (39)	98 (33)	0.39
Congestive heart failure	6 (9)	46 (16)	0.24
Chronic kidney disease	40 (61)	185 (63)	0.78
CKD stage			
Mild	28 (42)	95 (33)	0.12
Moderate	26 (39)	131 (45)	0.49
Severe	5 (8)	16 (5)	0.27
Renal dysfunction	20 (31)	70 (24)	0.27
Smoking	17 (26)	89 (30)	0.55
Premature coronary artery disease	15 (27)	95 (38)	0.16
Bilateral disease	12 (24)	38 (21)	0.70
% Stenosis	66.8±12.6	67.8±11.8	0.59
Medication use			
Diuretic	27 (44)	119 (45)	>0.99
β-blocker	36 (57)	127 (48)	0.21
α-blocker	13 (20)	40 (14)	0.25
αβ-blocker	5 (8)	29 (10)	0.65
Calcium-channel blocker	28 (51)	97 (40)	0.17
Renin inhibitor	1 (2)	2 (1)	0.46
Vasodilator	3 (5)	9 (3)	0.47
Nitrate	11 (17)	56 (20)	0.61
ACEI/ARB	59 (92)	232 (90)	0.81
Antiplatelet agent	41 (73)	172 (74)	0.87
Statin	38 (68)	149 (66)	0.88
Total all medications	2.2±1.5	2.1±1.6	0.40

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index (weight in kilograms divided by the square of the height in meters); BP, blood pressure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, modified diet in renal disease.

*Data are expressed as the mean±SD or number (percentage). Comparisons were evaluated using a 2-sample t test for continuous data or Fisher's exact test for categorical data.

†Urine albumin-to-creatinine ratio (UACR) is measured as the log of UACR.

‡UACR is measured as median± interquartile range.

RD and ND Groups

In the medical therapy–only cohort of CORAL, 66 of 359 (18%) subjects experienced an early RD. We identified 3 mutually exclusive groups: 3-month decline only (n=22), 6-month decline only (n=26), or decline at both 3 and 6 months (n=18) (Figure 1). All other subjects, those without a decline in eGFR ≥30%, were classified as nondecline (293/359; 82%). The mean percentage change of eGFR from baseline to within 6 months for the RD group was −40.0±7.7% and −7.0±15.8% for the ND group.

Factors That Predict RD of eGFR

The RD and ND groups were very similar as measured by baseline characteristics, including demographic, physical examination, laboratory values, risk factors, and medication use (Table 1). UACR was the only univariate factor that was significantly

different between the RD and ND groups (29.7±131.1 versus 18.6±43.4 μg/mg, respectively; *P*=0.03).

Stepwise logistic regression was then employed to identify factors associated with an RD within 6 months. The overall model was significant with adjustment for age and sex, while stepwise selection, forcing in age and sex, was used to identify other factors to include in the model. The baseline factors log of cystatin C (odds ratio, 1.78 [1.11–2.85]; *P*=0.02,), age (odds ratio, 1.04 [1.00–1.07]; *P*<0.05), and CKD-EPI creatinine eGFR (odds ratio, 1.86 [1.15, 3.0]; *P*=0.01) were found to be significant predictors of an early RD. To place this in context, a 1-SD increase in the log of cystatin C was associated with a 78% increase in the odds of experiencing a rapid decline in eGFR within 6 months, and a 1-SD increase in baseline eGFR was related to an 86% increase of odds for a rapid decline. LUACR, in the logistic regression analysis, was marginally significant (*P*=0.07) but was not included in the final model (Figure 2). The appropriateness of the model was validated by area under the curve (0.66) from receiver operating characteristic analysis and the Hosmer-Lemeshow goodness-of-fit test (*P*=0.51).

Effect of Early RD on eGFR at 1 Year and Later

The relationship between an early RD and kidney function at 1 year, measured as percentage change of eGFR from the 6-month reference baseline, was examined (Table 2). An early RD, despite continued medical therapy only, was associated with an improvement in eGFR at 1 year (6.9%; *P*=0.04), as was baseline LUACR (−1.8%; *P*=0.007), and baseline cystatin C (14.2%; *P*<0.001). In this regard, the presence of an early RD accounted for a subsequent 6.9% improvement in eGFR at 1 year compared with the ND group. Overall, baseline LUACR predicted a 1.8% decline in eGFR at 1 year per 1-unit increase in LUACR, while baseline cystatin C predicted a 14.2% increase in eGFR per 1-unit increase in cystatin C. The RD group also had a greater improvement in eGFR at 1 year compared with the ND group by analysis of least square means (11.9±3.0% versus 5.0±1.2%; *P*=0.04).

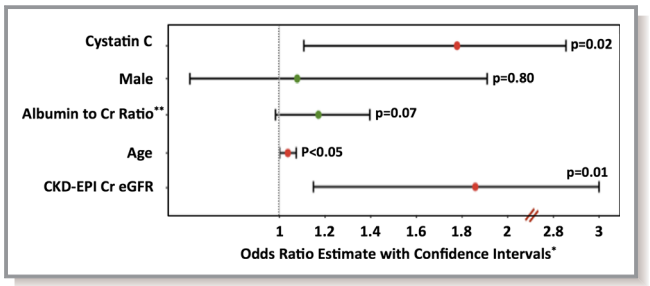


Figure 2. Baseline predictors of rapid decline in CKD-EPI eGFR within 6 months. Odds ratios with CIs from logistic regression. The odds ratios for cystatin C and CKD-EPI Cr eGFR are shown per 1-SD-unit increase in each factor. CKD-EPI indicates Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

Table 2. Predictors of 1-Year GFR Percentage Change After Rapid Decline Using Multivariable Linear Regression Adjusted for Age and Sex

Predictors	Estimate	Std. Error	*P* Value
CKD-EPI Cr eGFR (reference value)*	−0.132	0.07	0.055
Rapid decline (yes)	6.94	3.43	0.043
Sex (male)	2.66	2.01	0.186
Age, y	−0.10	0.11	0.358
Albumin-to-creatinine ratio (log)	−1.81	0.67	0.007
Cystatin C (log)	14.22	3.22	<0.001

CKD-EPI indicates Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.
*Within 6 months decline in eGFR.

A generalized linear mixed model was used to estimate the longitudinal effect of an RD to 5-year follow-up (Figure 3A and 3B). Based on the observed eGFR, the groups were similar at baseline, but the RD group had worse renal function from the onset of decline within 6 months and through 5-year follow-up compared with the ND group (*P*<0.001; Figure 3A, Figure S1). However, subjects with RD had significant and sustained improvement in percentage change of eGFR from the reference baseline (within 6 months) that was maintained through 5-year follow-up compared with the ND group (*P*<0.001; Figure 3B).

Clinical Outcomes of Patients With and Without an Early RD in eGFR

Comparisons of the RD and ND groups using log-rank test were not significantly different for composite end point outcomes and all-cause mortality (*P*=0.78 and *P*=0.76, respectively). Occurrence of an RD in eGFR did not have a higher hazard ratio for clinical events or mortality in Cox proportional hazard models adjusted for age, sex, and baseline LUACR (respectively, 0.93; 95% CI, 0.56–1.54; *P*=0.77; and 0.74; 95% CI, 0.34–1.60; *P*=0.45) (Figure 4A and 4B). Similarly, renal replacement therapy occurred in 1 of 66 (1.5%) of the RD patients and in 6 of 294 (2%) of the ND patients. In contrast, in the adjusted Cox models, age and baseline LUACR represented a significant hazard for clinical events. Overall, the suitability of the adjusted Cox models was confirmed using the log likelihood ratio test (*P*<0.001 and *P*=0.0002, respectively.)

Other clinical outcomes evaluated over time, by RD status, were systolic blood pressure, diastolic blood pressure, and LUACR (Figure S2A through S2C). Longitudinal analysis using mixed model repeated measures, with time considered as a categorical factor, demonstrated lower systolic blood pressure for subjects with RD at 6-month follow-up (*P*=0.012) but was not different at other time points (*P*=0.19, Figure S2A).

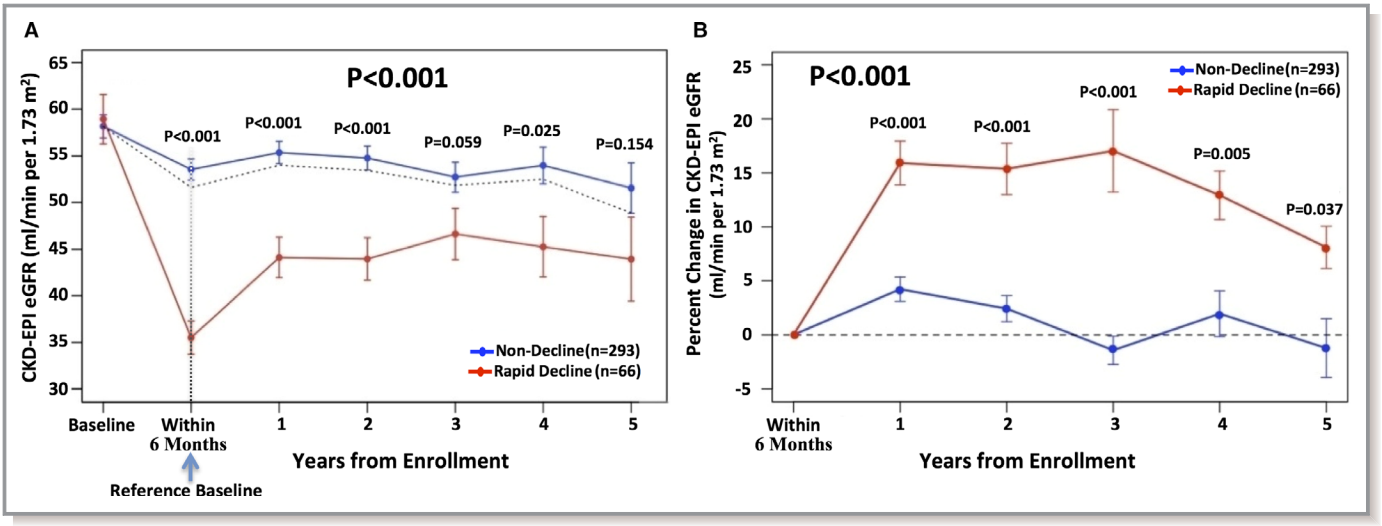
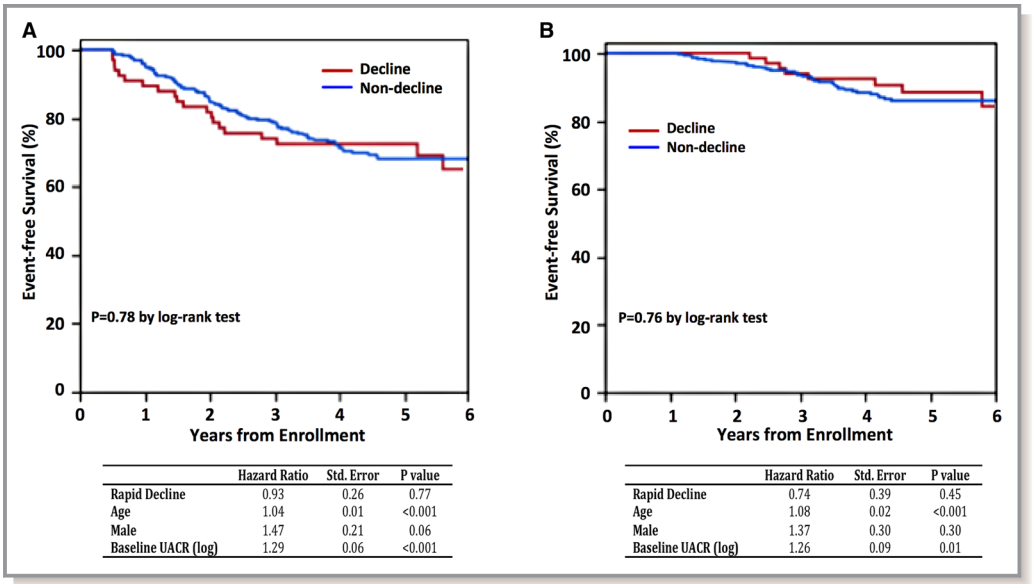


Figure 3. Longitudinal effect of rapid decline on CKD-EPI eGFR. **A**, Demonstrates that the observed eGFR for both the rapid decline and nondecline groups are similar at baseline and the dashed line for the whole population trends with the nondecline group. Overall, the rapid decline group had worse renal function from the onset within 6 months through 5 years of follow-up than the nondecline group (P<0.001). **B**, The rapid decline group had consistent significant improvement in eGFR over 5 years (P<0.001) and at each time period compared with the nondecline group. Means±SE at each time period are compared using the Student t test. CKD-EPI indicates Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

Diastolic blood pressure was significantly lower in the RD group when all follow-up times were considered (P=0.04) and was significant at 6 months (P<0.001; Figure S2B). LUACR was higher at baseline in the RD subjects (P=0.042) but was not different thereafter in follow-up (P=0.95; Figure S2C).

Regression to the Mean

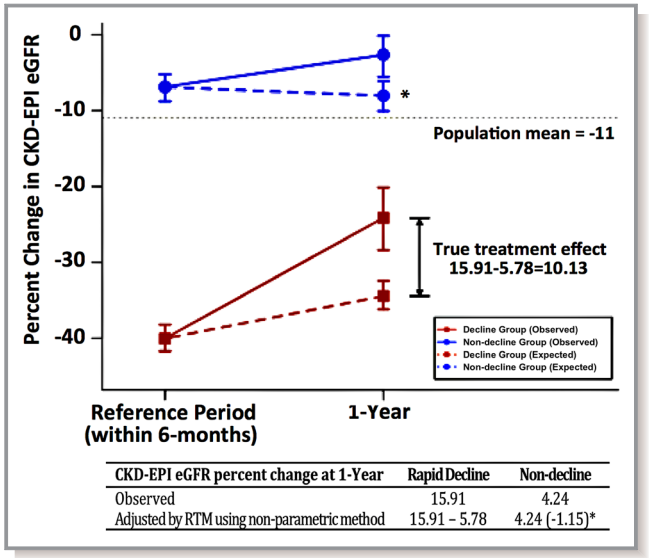
In the RD group, CKD-EPI e-GFR increased by 15.9±16.5% at 1 year. The RTM effect was estimated at 5.8±7.1%; therefore, after adjusting for the RTM effect, the 1-year CKD-EPI e-GFR increased by 10.1±18.0%. In the ND group, CKD-EPI e-GFR



	Hazard Ratio	Std. Error	P value
Rapid Decline	0.93	0.26	0.77
Age	1.04	0.01	<0.001
Male	1.47	0.21	0.06
Baseline UACR (log)	1.29	0.06	<0.001

	Hazard Ratio	Std. Error	P value
Rapid Decline	0.74	0.39	0.45
Age	1.08	0.02	<0.001
Male	1.37	0.30	0.30
Baseline UACR (log)	1.26	0.09	0.01

Figure 4. Kaplan–Meier survival curves and Cox proportional hazards models adjusted by age, sex, and baseline albumin to creatinine ratio (log) for composite clinical outcomes and all-cause mortality. **A**, Compares decline status survival curves that are not significant by the log-rank test for the composite end points (P=0.78), and a rapid decline in eGFR did not convey a higher hazard for occurrence of clinical events using Cox proportional hazards model. **B**, The rapid decline group was not significantly different by log-rank test (P=0.76), and had a similar hazard ratio for all-cause mortality compared with the nondecline group. eGFR indicates estimated glomerular filtration rate.



CKD-EPI eGFR percent change at 1-Year	Rapid Decline	Non-decline
Observed	15.91	4.24
Adjusted by RTM using non-parametric method	15.91 – 5.78	4.24 (-1.15)*

Figure 5. Medical therapy treatment effect after adjustment for regression to the mean on 1-year eGFR percent change in the rapid decline and nondecline groups. The 1-year percentage change in eGFR adjusted for RTM in the RD group was 10.13; RTM did not occur in the ND group and the observed percent change of 4.24 was not adjusted. There is a significant difference between the 1-year percent change in eGFR adjusted RTM in the RD group and the unadjusted 1-year eGFR in the ND group ($P<0.001$). CKD-EPI indicates Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ND, nondecline; RD, rapid decline; RTM, regression to the mean.

increased by 4.2±19.3% and no RTM effect was detected (Figure 5). The difference between the adjusted CKD-EPI eGFR percentage change in the RD group and the unadjusted eGFR in the ND group was significant ($P<0.001$).

Discussion

In the current study, we identified that early RD in kidney function was commonplace during the institution of aggressive medical management of patients with atherosclerotic RAS. By multivariable analysis, age and baseline kidney function were indicative of those likely to experience an early RD. Interestingly, though, patients who experienced this appeared to do reasonably well, and in fact had an improvement in kidney function by 1 year that was sustained over 5 years of follow-up. Thus, the current analysis indicates that early RD in kidney function for patients with atherosclerotic RAS after the institution of medical therapy are relatively common. Furthermore, the long-term clinical outcomes are similar, with no difference in mortality or event-free survival, with continued medical therapy only.

Recent studies, including ASTRAL, STAR (stent placement and blood pressure and lipid lowering for the prevention of renal dysfunction caused by atherosclerotic ostial stenosis of the renal artery), and CORAL have demonstrated equivalent results with the use of medical therapy alone when compared with stenting and medical therapy for patients with atherosclerotic RAS. Previous studies suggested that patients who were treated medically and experienced an early RD in kidney function were likely to experience an improvement in kidney function if they underwent stent treatment. Our current analysis now adds that patients who continue medical therapy alone often experience an improvement in kidney function.[17] These results are useful in that they should prevent unnecessary stenting in this patient population. Simply, an early RD in renal function with medical treatment may not be an indication for stenting.

Furthermore, it is important to note the effect of regression to the mean in this analysis. Regression to the mean is a statistical phenomenon wherein more extreme values will move closer to the mean over time upon remeasurement. In this analysis, the RD group represents the extreme values that are more likely to regress toward the mean and experience an improvement in kidney function on remeasurement, even in the absence of a change in treatment.

A limitation of the current work is that there were few patients in the study who had advanced kidney disease, stage IV or greater. Thus, in these subjects, no conclusion should be made.

Conclusion

The current analysis demonstrates that early rapid declines in kidney function occur in some patients with RAS when medical therapy is initiated and that their clinical outcomes are comparable to those without such a decline when treated with medical therapy only.

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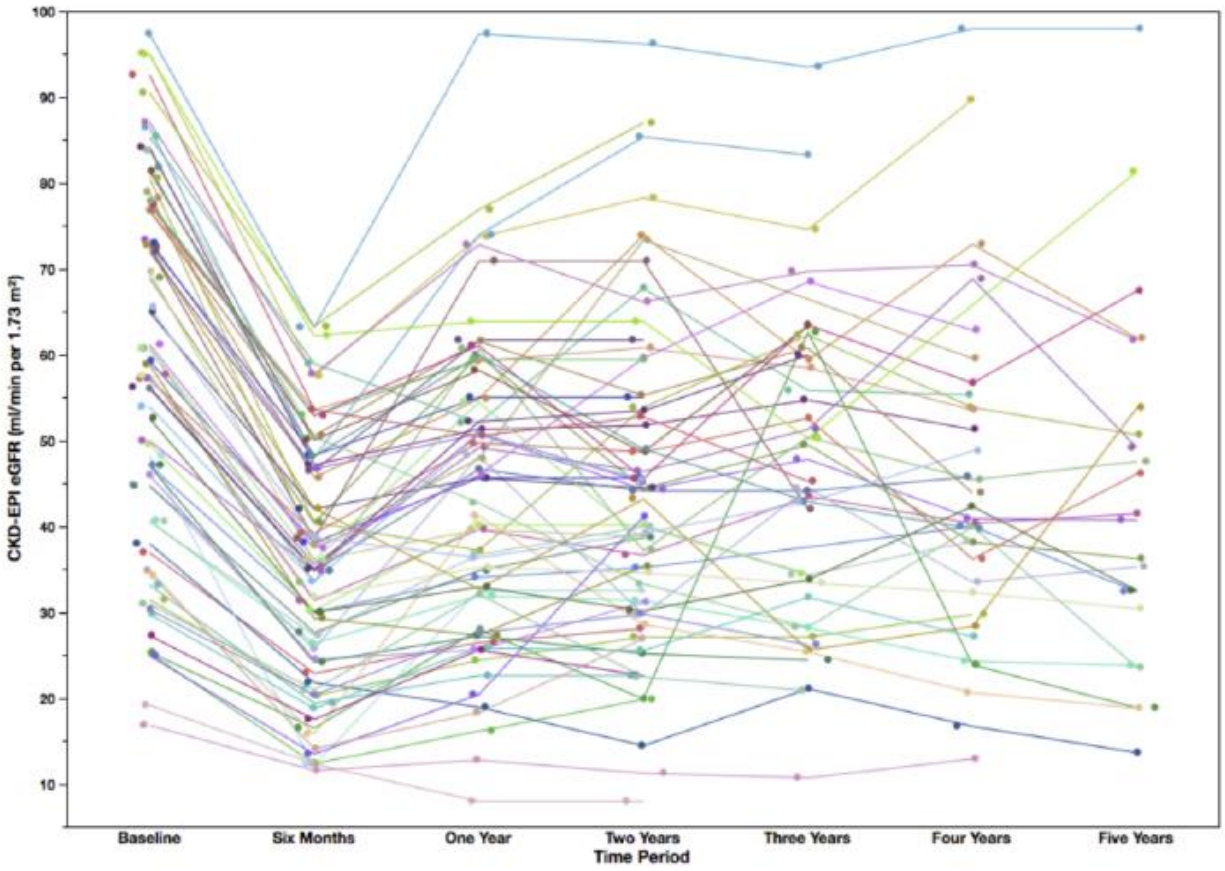
SUPPLEMENTAL MATERIAL

Table S1. **Comparison of Patients with Incomplete Data with Studied Patients.**

Baseline Characteristics*		Not Missing (n=359)	Missing (n=113)	P-value
Demographic/physical examination				
Age (yr)		69.9± 9.0	68.4±8.5	0.11
Male sex		176(49)	51(45)	0.52
Black race		23(6)	11(10)	0.30
Hispanic/Latino		19(5)	13(12)	0.03
Height (in)		66.0± 4.2	65.6±4.2	0.40
Weight (lb)		177.0± 36.1	174.6±40.3	0.58
BMI (kg/m^2)		29.5±5.9	29.4±5.9	0.87
Systolic BP (mmHg)		149.7± 23.0	152.7±22.9	0.22
Diastolic BP (mmHg)		77.9± 13.3	80.6±13.8	0.07
Laboratory values (assessed by core lab)				
Creatinine (mg/dl)		1.2±0.5	1.2±0.4	0.97
Cystatin C (mg/L)		1.3±0.5	1.3±0.5	0.24
MDRD-eGFR (ml/min per 1.73 m^2)		61.4±22.9	60.1±23.4	0.66
CKD-EPI creatinine formula		58.3±21.3	57.4±21.6	0.73
CKD-EPI cystatin C formula		61.0±22.6	57.7±23.0	0.22
CKD-EPI Creatinine- cystatin C formula		59.7±22.1	57.5±22.8	0.41
Urine albumin to creatinine ratio (ug/mg)**		3.4±1.6	3.7±1.7	0.09
Risk factors/indications				
Peripheral vascular disease		177(50)	61(55)	0.38
Hyperlipidemia		322(91)	97(87)	0.21
Prior myocardial infarction		106(30)	34(31)	0.91
Prior transient ischemic accident		72(20)	19(18)	0.68
Angina		45(14)	12(13)	>0.99
Cardiovascular disease		206(62)	69(67)	0.41
Diabetes mellitus		123(34)	38(36)	0.82
Congestive heart failure		51(14)	18(17)	0.54
Chronic kidney disease		225(63)	70(62)	0.91
CKD Stage	Mild	123(34)	33(30)	0.42
	Moderate	157(44)	42(38)	0.32
	Severe	21(6)	5(5)	0.81
Renal Dysfunction		90(25)	28(25)	>0.99
Smoking		105(29)	45(41)	0.03
Premature Coronary Artery Disease		110(36)	33(36)	>0.99
Bilateral disease		50(21)	16(21)	>0.99
% Stenosis		75.7±10.8	76.2±10.4	0.65
Medication Use				
Diuretic		145(44)	40(39)	0.42
β-Blocker		162(50)	52(51)	0.82
α-Blocker		53(15)	18(17)	0.76
$\alpha\beta$-Blocker		34(10)	12(11)	0.71
Calcium-channel blocker		125(42)	31(33)	0.15
Renin inhibitor		3(1)	0(0)	>0.99
Vasodilator		12(3)	9(8)	0.06
Nitrate		67(20)	20(20)	>0.99
ACE/ARB		165(50)	44(44)	0.26
Antiplatelet agent		212(74)	61(66)	0.14
Statin		186(66)	61(68)	>0.99
Total all medications		2.1±1.6	2.0±1.6	0.52

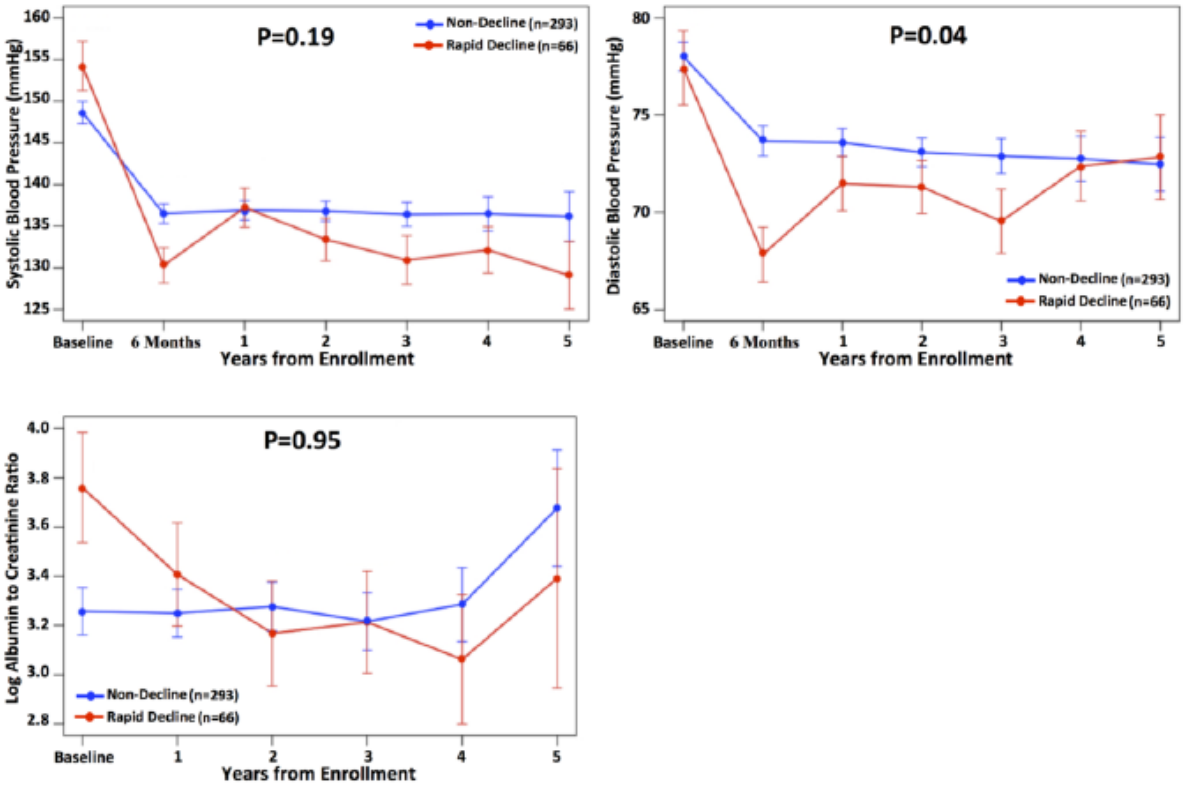
*Data are expressed as the mean ± SD or number (percentage). Comparisons were evaluated using two sample t-test for continuous data or Fisher's exact test for categorical data.
**Urine albumin to creatinine ratio (UACR) is measured as the log of UACR
yr, year; in, inch; lb, pound; BMI, body mass index ((weight in kilograms divided by the square of the height in meters); BP, blood pressure; MDRD , Modified Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; CKD, Chronic kidney disease; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; β-Blocker, beta adrenergic blocker; α-Blocker, alpha blocker; and $\alpha\beta$-Blocker, alpha-beta blocker.

Figure S1. Rapid decline patients CKD-EPI eGFR longitudinal response.



The observed trend of longitudinal improvement in eGFR after six-months for patients experiencing rapid decline demonstrates stable renal function out to 3-years follow-up and beyond.

Figure S2 a-c. Longitudinal effect of rapid decline status on clinical outcomes.



Graphs represent the following: a) systolic blood pressure (mmHg); b) diastolic blood pressure (mmHg); and c) albumin to creatinine ratio (log). Mean ± SE for baseline through 5-year follow-up are given.