Tolerating Increases in the Serum Creatinine following Aggressive Treatment of Chronic Kidney Disease, Hypertension and Proteinuria: Pre-Renal Success

Sheldon Hirsch^a Jackie Hirsch^a Udayan Bhatt^b Brad H. Rovin^b

^aLakeside Nephrology, Chicago, Ill., and ^bThe Ohio State University College of Medicine, Columbus, Ohio, USA

Key Words

Angiotensin-receptor blockers • CKD, aggressive treatment • CKD renin-angiotensin inhibitors • Creatinine renin-angiotensin inhibition • Renin-angiotensin system inhibitor • Retrospective study

Abstract

Background: Blood pressure (BP) reduction in patients with chronic kidney disease (CKD), particularly with a renin-angiotensin system inhibitor (RASi), commonly leads to an initial decrease in glomerular filtration rate. The current clinical guideline, based on studies with single RASi, is to tolerate an increase in the serum creatinine only up to 30%. This guideline has aptly guided CKD care for over a decade, but should be updated in the contemporary context of more aggressive RASi and diuretic use. **Methods:** This study is a retrospective review of 48 mostly African-American patients with CKD treated with multiple and/or high-dose renin-angiotensin system (RAS) inhibition and diuretics, targeting both low BP and reduction of urine protein. RASi was not reduced in response to initial increases in serum creatinine greater than 30%. **Results:** A clinically well-tolerated increase in serum creatinine over 30% during the first year occurred in 41% of the patients. Treatment was unaltered, and target goals for BP and urine protein were typically achieved. After the point of maximal serum creatinine in the first year,

these patients had minimal progression of disease over the next 6 years, with a long-term estimated glomerular filtration rate slope of only -0.52 ml/min/year/ 1.73 m². Only 25% progressed to end-stage renal disease or death. **Conclusion:** The 30% limitation to initial increases in the serum creatinine still pertains for single RASi at usual doses. However, favorable long-term outcomes suggest that initial increases over 30% should be tolerated in the context of dual goal-directed, more aggressive RASi and diuretic use.

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Introduction

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) lower systemic and intraglomerular pressure, often resulting in an initial increase in the serum creatinine [1–4]. This may also occur with non-renin-angiotensin system inhibitor (RASi) antihypertensives in patients with chronic kidney disease (CKD) [5, 6].

Bakris and Weir [1] made the landmark observation that the initial increase in serum creatinine following renin-angiotensin system (RAS) inhibition, in the absence of renal artery stenosis, non-steroidal use, or excessive diuresis, is less than 30%. Despite an early increase in serum creatinine, blood pressure (BP) control and RASi are

associated with improved long-term kidney function [1–6]. Thus, the National Kidney Foundation K/DOQI clinical guidelines recommend tolerating an increase of serum creatinine up to 30% following RASI, but decreasing or discontinuing RASI if serum creatinine increases more than 30% [7].

Since its initial description, the ‘30% rule’ has aptly guided RASI therapy. However, this guideline was derived from 1990s studies that used a single RASI at modest doses with achieved mean arterial BP 100 mm Hg or higher, and pertained only to the first 2 months after starting RASI [1]. Since then, BP goals have been lowered for proteinuric patients, and current clinical practice often involves multiple changes in medicines over a longer time period. The MDRD study [5, 8] suggested that a target BP of about 125/75 was beneficial to patients with proteinuria >1 g/day. A meta-analysis concluded that a systolic BP (SBP) goal of 110–120 mm Hg was beneficial for proteinuric patients [9]. Finally, long-term follow-up of the AASK cohort suggested that lower BP could benefit patients with a urine protein to creatinine ratio >0.22 [10].

Moreover, because initial and residual proteinuria correlate inversely with prognosis, several authorities and guidelines now advise reducing proteinuria in addition to lowering BP: a ‘dual goal’ approach [7, 11–13]. ‘Ultra-high’ doses and combinations of ACEIs, ARBs, mineralocorticoid receptor antagonists (MRA), and non-dihydropyridine calcium channel blockers (ndCCBs) are effective in reducing proteinuria, enabling clinicians to pursue these dual goals [14–18]. The randomized controlled ROAD trial found that adjusting an ACEI or an ARB to its maximal proteinuria-reducing dose led to greater maintenance of glomerular filtration rate (GFR) over 3.7 years of follow-up [19]. A ‘Remission Clinic’ in Italy targeted both a SBP of 120 mm Hg and urine protein <300 mg/day via sequential multi-RASI (ACEI, ARB, ndCCB) administration, and found an eightfold reduction of estimated GFR (eGFR) decline in non-diabetics compared with historically matched controls [18].

Achieving stringent goals for both BP and urine protein may require more aggressive use of diuretics, in addition to RASI. Diuretics are often effective antihypertensives in CKD due to the high prevalence of excess volume in these patients. They also potentiate the ability of RASIs to reduce urine protein, and loop diuretics help prevent hyperkalemia, enabling aggressive RASI.

Thus, CKD therapy has evolved from mono-ACEI treatment to a more complicated paradigm often characterized by aggressive treatment, potentially with mul-

tle medicines, and lower BP and proteinuria goals. Targeting lower BP and proteinuria goals with more aggressive RASI in combination with diuretics may result in initial elevations in the serum creatinine greater than 30%. These initial increases should not necessarily trigger a reflex to stop these therapies. The relationships between systemic BP and whole-kidney GFR, and intraglomerular pressure, renal plasma flow and single nephron GFR are linear outside the limited range of renal autoregulation in CKD [2, 20]. The 30% rule reflects the empiric observation that the addition of a single RASI with modest BP declines results in similarly modest declines in GFR (<30%). Greater decreases in BP and/or intraglomerular pressure with more intensive RASI (i.e. combinations and/or higher doses) and diuretics may be predicted to result in greater declines in GFR than that observed with single RASIs. No defining event occurs at the 30% point, or any other point; 30% is just a single point on a continuum relating declining hemodynamics to declining GFR. The observed decrease in GFR (whether <30% or >30%) reflects the extent of RASI and BP lowering that occurs. The empirically observed (<30%) decrease in GFR seen with single RASI does not mean that a larger decrease in GFR from more extensive treatment implies underlying renal vascular disease, other pernicious contributors, or worse long-term outcomes.

We present a retrospective study of aggressive BP and proteinuria control in a CKD cohort that suggests initial increases in serum creatinine over 30% are associated with the same apparently favorable long-term outcomes as for those patients with smaller initial increases.

Materials and Methods

All records, dating back to the year 2000, of a single nephrologist’s (S.H.) community-based urban renal clinic were reviewed. Patients were included if they presented with a serum creatinine of 1.4 mg/dl or more, or over ~1 g of proteinuria, were treated with RASI, and had regular follow-up for a minimum of 3.5 years. Patients with renal transplants or glomerular diseases treated with immunotherapy were excluded. Data were retrieved until the patient’s death, end-stage renal disease (ESRD) or final follow-up visit.

Pre-renal success was defined as an increase in the serum creatinine within the first year of treatment, following an increase (or sequential increases) in antihypertensive medicine(s) that was well tolerated by the patient and did not result in decreased treatment [21]. Excessive diuresis or RASI overtreatment was not presumed based solely on the increase in serum creatinine. The diagnosis of overtreatment (pre-renal failure) required specific evidence of hemodynamic compromise (including cramps, dizziness,

Fig. 1. The treatment algorithm used in the cohort. Patients were treated based on potassium and volume status. Secondary options are in parentheses. Spironolactone was only given up to 50 mg/day. Ultra-high doses of RASIs were allowed for residual proteinuria. JVD = Jugular venous distension.

weakness or objective findings such as tachycardia, BP below goal, or electrolyte abnormalities) in addition to the increased serum creatinine. The ‘over 30%’ (OT) cohort of pre-renal success patients were those whose serum creatinine increased over 30% after RASI therapy was intensified at the renal clinic. The remaining patients were termed the ‘under-30%’ (UT) cohort.

eGFR was calculated from the MDRD formula [22] at presentation and then as the mean of all subsequent eGFR measurements in sequential 6-month intervals. The long-term slope of eGFR was calculated from the highest serum creatinine in the first year to final follow-up.

BP and urine protein estimates (by commercial dipstick) were reported at presentation and approximately yearly intervals. A SBP of 125 mm Hg and a urine protein of ≤ 30 mg/dl were targeted. Since treatment decisions were based on SBP, diastolic BP was not always measured and is not reported.

Treatment decisions were guided at every visit by the current physical examination and potassium level (fig. 1), respecting the dynamic nature of these variables. With signs of volume excess (edema or jugular venous distension), either furosemide or spironolactone were added or increased (based on the serum potassium). If there were no signs of volume excess, and if the serum potassium was < 5 mEq/l, an ACEI or ARB was added or increased. If the potassium was > 5 mEq/l, then furosemide or ndCCBs were added or increased. In instances of residual proteinuria despite BP control, ‘ultra-high’ doses of RASIs were used (lisinopril 80 mg, losartan 200 mg, irbesartan 600 mg).

Baseline characteristics were compared by Fisher’s exact test for categorical variables or by Student’s *t* test. Time-to-event anal-

ysis was performed for the outcomes of a 20% further decline in GFR and of the occurrence of ESRD. The occurrence of a 20% further decline in GFR was defined as a 20% decline in GFR after the maximum serum creatinine within the first year. The outcome was present if the decline in GFR was present at two measurement points 6 months apart. Single variable time-to-event analysis was done using the log-rank test. Multivariate analysis was done using Cox proportional hazards regression after confirmation of the assumption of proportionality. Graphical analysis was done using Kaplan-Meier survival curves. The rate of decline in GFR was compared for the two groups using mixed effects linear regression. Specifically, the coefficient of the interaction term between the group variable and time was compared to null. This was done for the univariate situation. It was also done for a multivariate model with adjustments made for age, race, sex, and baseline GFR. All analyses were done using Stata 11 (Austin, Tex., USA).

Results

Initial Characteristics

As shown in table 1, patients were largely African-American, elderly, diabetic (62.5%), hypertensive (mean SBP 151.6 mm Hg), proteinuric (59.3% > 30 mg/dl) and with advanced CKD (mean eGFR 36.0 ml/min/1.73 m²). The OT cohort was more commonly female ($p = 0.008$) and had higher SBP ($p = 0.044$) than the UT group.

Treatment Profile

Most patients (77%) presented to the clinic already taking a RASI (table 2). By 1 year, all patients were given RASI (ACEI 79%, ARB 56%, ACEI+ARB 35%, MRA 25%), 56% of patients received dual or triple RASI, and 27% were prescribed an ‘ultra-high’ dose. There was no significant difference in the provision of ACEIs, ARBs, MRAs, ACEI+ARB, or ultra-high doses to the OT group versus the UT group either at presentation or after 1 year (table 2).

The OT patients were more commonly treated with furosemide at presentation, but this difference was lost after 1 year (table 2). The mean dose of furosemide was not significantly different between the two groups at presentation or at 1 year.

ndCCBs (29% of patients) and β -blockers (59%) were similarly distributed among subgroups (data not shown).

Clinical Course

The mean SBP in the entire cohort was 128.7 mm Hg after 1 year, and remained around or < 130 mm Hg throughout follow-up (fig. 2a). There was no significant difference in BP between the OT and UT groups (fig. 2b).

Table 1. Baseline demographics and clinical characteristics

	All patients	Diabetics only	Cr ↑ >30%	Cr ↑ <30%
Age, years	64.2 ± 11.5	66.5 ± 8.2	65.3 ± 11.8	63.4 ± 11.4
Patients	48	30	20	28
Male, %	58.3	46.7	35*	75
Diabetes, %	62.5	100	65.0	60.7
SBP, mm Hg	151.7 ± 23.6	151.4 ± 22.7	159.75 ± 26.8 ⁺	145.9 ± 19.6
eGFR, ml/min/1.73 m ²	36.0 ± 14.3	34.9 ± 12.3	35.9 ± 13.1	36.2 ± 15.2
Urine protein ≤30 mg/dl, %	41.7	46.7	50	35.6
Black, %	93.8	96.7	95	92.9

Values are means ± SD. * p = 0.008 vs. <30% ↑; ⁺ p = 0.044 vs. <30% ↑.

Urine protein decreased with treatment, with about 80% of patients in the entire cohort, and 85% of diabetics reaching ≤30 mg/dl after 3 years (table 3).

The rate of decline in eGFR (from time 0) for both the entire cohort and for those with diabetes was about 1.61 ml/min/year/1.73 m² over a mean follow-up of 73.4 months (range 42–123) (fig. 3a). The rate of decline in eGFR for the patients who presented with ≤30 mg/dl proteinuria was not significantly different than that of patients with higher levels of proteinuria (data not shown).

Serum creatinine increased in 83% of patients in the first year of treatment. The increase was greater than 30 in 41% of patients (median increase of 57.5%, range 31–164%). After the point of maximal serum creatinine (OT: mean 5.4 ± 3.3 months; UT: 7.4 ± 2.7 months), the long-term slope of eGFR was −0.52 and −1.39 ml/min/1.73 m² in the OT and UT groups, respectively (fig. 3b). After adjusting for age, race, sex, and baseline GFR, there was no statistical difference between the slope of the decline in GFR of the two groups (p = 0.228) after the point of maximal serum creatinine in the first year. No patient developed signs suggestive of underlying renal artery stenosis and no investigations were taken in this regard.

Using time-to-event analysis, the time to a 20% further decline in eGFR after the maximum serum creatinine in the first year was evaluated. No difference was found between the OT and UT groups using the log-rank test. A multivariate model was constructed using Cox proportional hazards regression. After adjusting for age, race, sex, and baseline GFR, no difference in time to progression was found between the OT and UT groups (HR = 0.60 with 95% CI 0.26, 1.35). A log-rank analysis showed no difference in time to ESRD for OT or UT subjects. A multivariate model was not done given the limited number of events.

Table 2. Medications at presentation and after 1 year

Medication/ timing	>30% (OT) (n = 20)	<30% (UT) (n = 28)	All patients (n = 48)
ACEI, %			
Presentation	60	67.8	64.6
After 1 year	75	82.1	79.2
ARB, %			
Presentation	35	14.3	22.9
After 1 year	65	50	56.3
MRA, %			
Presentation	5	0	2.1
After 1 year	25	25	25
Furosemide, %			
Presentation	70*	28.6	45.8
After 1 year	95	75	83.3
Furosemide dose, mg/day			
Presentation	74.3 ± 46.0	97.5 ± 95.3	82.7 ± 66.8
After 1 year	184.2 ± 143.7	139 ± 156.4	160.5 ± 150.3

* p = 0.04 vs. OT.

Table 3. Patients with urine protein at the goal of ≤30 mg/dl (values are %)

	All patients (n = 48)	Diabetics (n = 30)	>30% (n = 20)	<30% (n = 28)
Presentation	41.7	46.7	50	36
1 year	68.8	72.4	75	67
2 years	74.5	75.9	89.5	64
3 years	79.6	84.6	88.9	73
4 years	63.4	70.8	85.7	52

Fig. 2. SBP over time. **a** SBP in the entire cohort and in diabetic patients (DM). **b** SBP in OT and UT patients. The number of patients in each group remaining at each yearly time point is shown.

Fig. 3. Decline in kidney function over time. **a** Decline in kidney function in the entire cohort and in diabetic patients (DM). **b** Decline in kidney function in OT and UT patients. The number of patients in each group remaining at each yearly time point is shown.

Eight patients (16.7% of the entire group) progressed to ESRD. The patients who developed ESRD were older (mean 70.1 years), with lower initial eGFR (29.6 ml/min/1.73 m²), longer follow-up (mean 80.6 months), and their slope of mean eGFR decline was faster (−2.2 ml/min/1.73 m²/year; *p* = 0.038) than the non-ESRD group. Four patients (8.3%) died (of unknown etiology) during follow-up. Thus, 12 patients (25%) reached ESRD or death, similarly distributed between the OT and UT groups.

Adverse Events

Four patients discontinued ACEIs due to cough or allergic reactions. Hyperkalemia (>6.0 mEq/l) occurred in only 2.1% of over 800 measurements. In over 3,500 patient-months there were 3 known hospitalizations related to therapy – 2 from hypotension and 1 from hyperkalemia.

Discussion

Patients in this report were treated with aggressive RASI and furosemide, targeting currently recommended low BP and proteinuria goals. This often (41% of patients) resulted in initial increases in serum creatinine of more than 30%, but RASI was not decreased, contrary to current guidelines. These patients typically had several risk factors for progressive CKD, including diabetes, hypertension, and proteinuria, and 77% had already been treated with a single RASI and failed to achieve the dual treatment goals. Even with these unfavorable clinical characteristics, the decline in GFR was very slow at −1.61 ml/min/year/1.73 m² and was not different in patients with initial increases in serum creatinine over versus under 30%.

There was no concurrent control group for this study, but it is interesting to compare our results with studies of single RASI in proteinuric patients, and with African-American patients from the MDRD study. Despite similar baseline eGFR and targeted and achieved BPs, the decline in eGFR of African-American patients in the MDRD study was almost four times faster (−6.33 ml/min/year/1.73 m²) than observed in our cohort [5]. The difference is particularly notable as the MDRD had only 3% diabetic patients. In addition, only 25% of the patients in this study died or progressed to ESRD compared to 74% (mean follow-up of 6.2 years) of the patients in MDRD [8] and 73% of proteinuric patients in AASK (follow-up of 8.8–12.2 years) [10]. The MDRD and AASK cohorts were not matched historical controls, so we do not claim supe-

rior results. Nevertheless, the patients in our study were older, typically diabetic, more proteinuric than those in MDRD or AASK, and had higher initial BP than in the MDRD and lower initial eGFR than in AASK. Therefore, the low incidence of ESRD and death in our report supports the safe and effective use of high-dose RASI.

The outcomes reported here, along with results from the Remission Clinic [18] and the ROAD trial [19], suggest the strategy of targeting both low BP and urine protein with high-dose RASI and furosemide, and tolerating larger initial increases in serum creatinine, is promising and warrants further prospective study.

Patients in our cohort treated with dual ACE-ARB therapy (*n* = 17) achieved the same long-term results (data not shown) as other patients. This contrasts with the unfavorable results of ACEI-ARB therapy in the ONTARGET trial [23], presumably reflecting different patient cohorts – the ONTARGET cohort did not have CKD or significant proteinuria. However, this study does not allow conclusions or recommendations about dual ACE-ARB or any specific treatment regimen. The protocol was based on the hypothesis that no single drug combination would be optimal for all patients. Instead, it utilized multiple drugs thought to provide specific renal protection beyond BP control, in a flexible, individualized manner based on clinical characteristics. The emphasis of treatment was achieving target goals rather than on using specific combinations, and resulted in many variations in drug combinations and dosing, rendering comparisons impossible. The flexible, individualized approach contrasts with the more linear approach often used in CKD studies, in which certain combinations of medicines are prescribed for all patients or added in a specific sequence per protocol. The success of the individualized approach in this study should interest both practicing clinicians and investigators.

We observed a low incidence of hyperkalemia, similar to previous reports of RASI (including triple RASI [24]), but achieving this required considerable clinical effort. A low potassium diet was prescribed at the initial visit and reviewed at every subsequent visit. Changes in RASI were prescribed only incrementally and with careful follow-up of electrolytes, generally within several weeks. Relatively high doses of furosemide were used. This level of vigilance may be necessary to minimize hyperkalemia with aggressive RASI.

Serum creatinine increased more than 30% (median of 57.5%) in 41% of the cohort, indicating that this is a common feature of dual goal therapy with aggressive RASI and furosemide. These patients had a higher initial BP than the UT cohort. This suggests that the extent of

decline in GFR following therapy reflects, at least in part, the amount of BP reduction needed to achieve the goal.

The observed increases in serum creatinine could have variably derived from increased RASI, increased diuretics, or lower BP. We cannot characterize the relative contributions of these components as almost all patients received significant increases in both RASI and furosemide, often simultaneously or in rapid succession.

If the 30% rule was applied to all the patients in this study, medication dosages would often have been decreased or medications discontinued, presumably resulting in increased BP and/or urine protein. This would likely have adversely affected the course of the patients' CKD. Although the reported data do not constitute proof, long-term follow-up of the patients maintained on RASI after serum creatinine increased over 30% showed a remarkably stable eGFR, with minimal progression to ESRD or death. This supports the hypothesis that the primary aim of therapy should be achieving and maintaining target BP and proteinuria goals, and not focusing on the magnitude of the initial serum creatinine increase.

Previous studies [1–6] suggested that an initial fall in GFR less than 30% following RASI or BP control was subsequently associated with improved GFR as compared to patients without an initial fall. However, follow-up did not always demonstrate favorable hard renal outcomes [3]. In the current study, long-term follow-up demonstrated similar eGFR and incidence of ESRD/death in the OT and UT groups.

This retrospective report has several limitations. Only hypotheses can be generated about the value of this treatment approach. The patients were largely African-American and results may not be applicable to other patient

populations. Urine protein, per common community practice, was not routinely quantified. Information about clinical characteristics before presentation to the CKD clinic was not uniformly available and is not presented. The study does not resolve issues regarding treatment of non-proteinuric patients in whom the role of both aggressive BP control [25] and dual RASI (the ONTARGET trial) [23] has been challenged. There were only 20 such patients in this study and we do not know how many had intrinsically non-proteinuric renal disease versus proteinuric renal disease that had responded to RASI started prior to presentation to our clinic. Nevertheless, more aggressive RASI with subsequent SBPs of about 130 mm Hg was well tolerated by our minimally proteinuric patients and the decline in eGFR equally slow.

In conclusion, 41% of CKD patients treated with an aggressive RASI and furosemide regimen, targeting SBP of 125 mm Hg and reduction of urine protein, had an initial increase in serum creatinine greater than 30%, a level for which current clinical guidelines advise reduction or discontinuation of RASIs. However, in this study, treatment was continued without alteration. These patients subsequently had stable eGFR over long-term follow-up with relatively low progression to ESRD or death. It appears that achieving the target BP and urine protein via RASI and diuretics should not be compromised by an effort to limit the initial increase in the serum creatinine to less than 30%.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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