Stopping Renin-Angiotensin System Inhibitors in Chronic Kidney Disease: Predictors of Response

Anderson Roman Gonçalves^a Arif Khwaja^b Aimun K. Ahmed^b
Mohsen El Kossi^b Meguid El Nahas^b

^aDepartment of Medicine, University of Joinville Region – Univille, Joinville, Brazil; ^bSheffield Kidney Institute, Northern General Hospital, Sheffield, UK

Key Words

Chronic kidney disease • Renin-angiotensin system inhibitors • Predictors

Abstract

Background/Aims: Renin-angiotensin system (RAS) inhibitors are considered first-line agents for hypertensive patients with progressive chronic kidney disease (CKD). In a previous study, we showed that stopping RAS inhibitors increased estimated glomerular filtration rate (eGFR) in a significant number of advanced CKD patients. The present study tries to address who would benefit and whether this benefit is predictable. **Methods:** Forty-three CKD stage 4 patients had RAS inhibitors stopped and were followed for at least 24 months. Compared outcome groups were 'alive', 'renal replacement therapy (RRT)' or 'died'. Improvement in eGFR was used in a receiver-operating characteristic curve and finds the best predictor for surviving without RRT. **Results:** Patients who survived without RRT were all hypertensive and had a higher eGFR increment after stopping the drugs. Those with eGFR improvement ≥ 5 ml/min/1.73 m² were the most likely to survive long term without RRT (log-rank test, $p = 0.03$). They had a significant increment in blood pressure that correlated with eGFR improvement ($r = 0.403$,

$p = 0.013$). **Conclusion:** A significant increase in eGFR after stopping RAS inhibitors suggests that long-term survival without RRT is more likely. Our findings question the universal preemptive indication of RAS inhibitors in advanced CKD and suggest that they can be safely stopped, at least in some patients.

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Introduction

Use of renin-angiotensin system (RAS) inhibitors is perceived as the cornerstone of treatment of progressive and proteinuric nephropathies including diabetic nephropathy. RAS inhibitors are considered the first line of treatment for hypertension in the presence of chronic kidney disease (CKD) in most guidelines [1, 2]. A small number of studies in advanced CKD (stage 4) show some persistent protective effect of these agents in avoiding renal replacement therapy (RRT) [3–6], but the results are only consistent when the reduced estimated glomerular filtration rate (eGFR) is associated with significant proteinuria [7–9]. There is little doubt that overall angiotensin-converting enzyme (ACE) inhibitors and angiotensin T1 receptor blockers (ARBs) have some protective effect

on declining kidney function as shown in a number of studies over the last 25 years. However, critical analysis of some of the major studies cast some doubt on the validity of the generalization of this concept. For instance, a careful analysis of the data presented by the Ramipril Efficacy In Nephropathy (REIN) study of chronic non-diabetic nephropathies fail to show an overall effect of ramipril on the rate of decline of GFR [10]. Only subsequent subgroup analyses showed some benefit [5]. Also, a higher incidence of end-stage renal disease (ESRD) has been reported in diabetic patients persistently treated with ACE inhibitors [11]. Recently a post hoc analysis of the RENAAL trial showed that losartan was associated with a high risk of increased serum potassium levels, that in turn was associated with an increased risk of renal outcomes in patients with diabetes and nephropathy [12]. This may reflect the concern of using these agents in older patients with underlying cardiovascular disease (CVD) [13–15]. Consequently, in the majority of elderly CKD patients who are likely to have associated CVD, the renal benefit of RAS inhibitors, beyond cardiovascular protection, is a matter of debate [11, 13–16]. Further, there are some emerging reports showing that some patients with advanced renal insufficiency could benefit from stopping these agents and postponing RRT [17, 18].

In a small pilot observation, we recently noted that stopping RAS inhibitors increased eGFR in a significant number of patients [17]. This small study raised critical questions about who would benefit from stopping RAS inhibitors and whether this benefit is predictable. In order to answer these questions, we analyzed this database to look for predictors of improvement in the eGFR and risk of RRT or death.

Patients and Methods

This is an extension and analysis to a previously published pilot observational study [17]. The cohort represented 52 consecutive patients who were on RAS inhibitors and referred to the advanced kidney care clinic of the Sheffield Kidney Institute. We studied data for 43 patients as long-term follow-up data was missing for 9 patients. In summary, this is an observational report of 43 patients who were on inhibitors of RAS (17 females and 26 males), mean age 69.9 ± 13.0 years, who were referred to the advanced kidney care clinic of the Sheffield Kidney Institute in 2005–2006 in anticipation of starting RRT. The average eGFR was 19.3 ± 8.1 ml/min/1.73 m² at presentation to the clinic. Proteinuric kidney disease was defined as presence of urine protein:creatinine ratio ≥ 100 mg/mmol. Associated CVD was considered as a presence of history or signs of ischemic heart disease, cerebral or peripheral vascular disease or congestive cardiac failure.

Patients included for analysis were those who had stopped RAS inhibitors and were followed for at least 24 months, up to discharge (censored), start of RRT or death. Some patients were followed for a longer period (median follow-up 24 months). For the purpose of analysis, patients were divided into three groups based on the outcomes: *Survivors*, those who survived without RRT; *RRT*, those who started RRT, and *Died*, those who died before RRT. For clarity, blood pressure and eGFR data were named as *before* if they were obtained 1–3 months before stopping RAS inhibitors; as *baseline*, if obtained at the time of stopping, and as *after*, if obtained 1–3 months after baseline. The clinical management of the patients as RAS inhibitors were stopped is described in a previous study [17].

Serum creatinine was measured by the standard autoanalyzer technique. The four-variable MDRD formula was used to obtain eGFR. Blood pressure measurements were performed routinely according to standard procedures in all patients with an automatic Dinamap XL Model 9300 series device (Johnson & Johnson Medical, Tampa, Fla., USA).

Statistical Analysis

Categorical variables were compared by χ^2 test. One-way ANOVA with Tukey honest significance test or Dunnett's T3 post hoc analyses was used to compare between-group characteristics, according to variance. A paired t test was conducted to assess within-group differences between periods. A multinomial logistic regression was conducted including baseline variables with significant differences between outcome groups. A receiver-operating characteristic (ROC) curve was used to analyze the *after* eGFR improvement from *baseline* and find the best predictor point to the outcome 'survival without RRT' [19]. To evaluate the time-to-event effect, a Kaplan-Meier curve was built with the predicted eGFR change as grouping variable. $p < 0.05$ was considered statistically significant.

Results

The characteristics of each outcome group are shown in table 1. Survivors had higher *before* and *baseline* eGFR than RRT, were mostly non-proteinuric and were all hypertensive. RRT had a lower *before* and *baseline* eGFR and were mostly proteinuric. Died were older, had a higher *before* and *baseline* eGFR than RRT and only a small percentage had proteinuria. Survivors and Died had a significant decrease in *before* to *baseline* eGFR, but only Survivors had a significant increase in the *after* eGFR ($p < 0.05$). Functional improvement was absent in RRT and Died (fig. 1). The multinomial logistic regression analysis using age, gender, *before* and *baseline* eGFR, presence of hypertension and proteinuria, was unable to predict any of the three outcome groups.

For the question 'who would benefit from stopping RAS inhibitors', we analyzed the area under the ROC curve (AUC) for eGFR improvement as absolute (ml/

Table 1. Baseline and follow-up characteristics according to outcome group

Characteristics	Survivors (n = 21)	RRT (n = 13)	Died (n = 9)
Age, years	73 ± 8	60 ± 18	77 ± 5 ^{*,†}
Male, %	42.9	84.6 [*]	66.7
Median follow-up (range), months	32 (4–71)	12 (1–39)	17 (1–60)
eGFR, ml/min/1.73 m ²			
Before	23 ± 8 [†]	13 ± 6	22 ± 8 [†]
Baseline	18 ± 6 ^{†,§}	11 ± 3	17 ± 7 ^{†,§}
After	26 ± 8 [‡]	13 ± 4 [*]	20 ± 6
SBP, mm Hg			
Baseline	133 ± 16	132 ± 19	132 ± 30
After	150 ± 20 [‡]	149 ± 18 [‡]	127 ± 16 ^{*,†}
Δ (after – baseline)	16.6 ± 15	14.2 ± 17.8	–1.6 ± 19.6
DBP			
Baseline	68 ± 9	70 ± 11	75 ± 16
After	76 ± 9	83 ± 13	67 ± 4 ^{*,†}
Δ (after – baseline)	8.2 ± 8.6	10.9 ± 10.2	–4.2 ± 11.8 ^{*,†}
MAP			
Baseline	93 ± 9	96 ± 11	92 ± 17
After	99 ± 6	104 ± 9	90 ± 7 ^{*,†}
Proteinuria, %	28.6 [†]	76.9	16.7 [†]
Diabetes, %	61.9	55.6	38.5
Hypertension, %	100	66.7 [*]	76.9 [*]
Previous CVD, %	42.9	55.6	61.5

* p < 0.05 vs. survivors; † p < 0.05 vs. RRT; ‡ p < 0.05 vs. baseline; § p < 0.05 vs. before.

Fig. 1. eGFR variation according to group outcome. Mean eGFR values are *before*, *baseline* and *after* according to the period when RAS inhibitors were stopped. The values are mean ± SD. * p < 0.05 vs. *before*; † p < 0.05 vs. *baseline*.

min/1.73 m²) or percentage (%) changes from *baseline* to *after* periods in order to discriminate the outcome 'surviving without RRT'. The absolute eGFR improvement performed better than percentage eGFR improvement with an AUC of 0.720 (p = 0.014) and 0.667 (p = 0.061),

respectively. The best predictor point was between 4.5 and 5.5 ml/min/1.73 m² of improvement. Therefore, an increase in the *after* eGFR from *baseline* of ≥5 ml/min/1.73 m² was associated with survival without RRT in a time-to-event Kaplan-Meier analysis (log-rank test, p = 0.03), as shown in figure 2.

The second question about predictability of the benefit (eGFR increment of at least 5 ml/min/1.73 m² 1–3 months after stopping RAS inhibitors) was addressed by searching variables that differentiate the two resulting groups: ΔeGFR <5, those with eGFR increment <5 ml/min/1.73 m², and ΔeGFR ≥5, with eGFR increment ≥5 ml/min/1.73 m² (table 2). The variation in systolic blood pressure (SBP) and diastolic blood pressure (DBP) during the first 3 months after stopping RAS inhibitors were significantly higher in those in ΔeGFR ≥5. The eGFR increment was correlated with SBP increment (r = 0.403, p = 0.013) (fig. 3). Of note, both groups had a significant decrease in eGFR from the previous 3 months to baseline (21 ± 8 to 17 ± 6 ml/min/1.73 m² in ΔeGFR <5; 21 ± 9 to 14 ± 6 ml/min/1.73 m² in ΔeGFR ≥5). As expected, it was only in ΔeGFR ≥5 that the eGFR increased in the *after* period (25 ± 9 ml/min/1.73 m², p < 0.001). Com-

Fig. 2. Kaplan-Meier estimates of patients surviving without RRT. Time zero is when RAS inhibitors were stopped. Events were RRT or death. Solid line: patients with *baseline* to *after* eGFR increment ≥ 5 ml/min/1.73 m² (Δ eGFR ≥ 5); dashed line: those with eGFR increment < 5 ml/min/1.73 m² (Δ eGFR < 5). log-rank test, $p = 0.03$.

Fig. 3. Relationship between variation from *baseline* to *after* periods in eGFR (Δ eGFR) and systolic blood pressure (Δ SBP). *Baseline* values were obtained when the RAS inhibitors were stopped; *after* values were obtained 1–3 months after stopping RAS inhibitors; variation (Δ) is *after* minus *baseline* value.

pared with baseline values, the eGFR increment and blood pressure (SBP, DBP and MAP) were significantly higher in the Δ eGFR ≥ 5 group.

Discussion

This study builds on, and is derived from, our pilot study showing that stopping RAS inhibitors in advanced renal insufficiency leads to an overall improvement in renal function and delay in the initiation of RRT [17]. In that study we clearly demonstrated an improvement or stabilization of GFR in most patients after stopping RAS inhibitors [17]. Here we attempt to identify those most likely to benefit from such an intervention. Thus the data presented here is quite distinct from the data in our pilot study. In particular, a significant increment of blood pressure after stopping RAS inhibitors correlates with a significant improvement in eGFR, suggesting that a significant number of the cohort on RAS inhibitors had hemodynamically significant renovascular disease. The baseline characteristics were not discriminative, but a short follow-up after stopping RAS inhibitors provided enough data. It appears that whilst the majority of patients have an increment in eGFR of more than 20%, only those whose eGFR improves by at least 5 ml/min/1.73 m² during the first 3 months after stopping RAS inhibitors had a higher probability of surviving without RRT over

Table 2. Variables values according to eGFR increment group

Characteristics	Δ eGFR < 5	Δ eGFR ≥ 5
Age, years	71 $\pm$ 12	69 $\pm$ 14
Male, %	73.9	45.0
Outcome		
Alive/non-RRT	8	13
RRT	8	5
Death	7	2
eGFR, ml/min/1.73 m ²		
Before	21 $\pm$ 8	21 $\pm$ 9
Baseline	17 $\pm$ 6 [†]	14 $\pm$ 6 [†]
After	17 $\pm$ 7 [†]	25 $\pm$ 9 ^{*, †}
SBP, mm Hg		
Baseline	135 $\pm$ 21	130 $\pm$ 17
After	140 $\pm$ 20	151 $\pm$ 19 [†]
Δ (after – baseline)	6.5 $\pm$ 17.1	19.4 $\pm$ 15.8 [*]
DBP, mm Hg		
Baseline	71 $\pm$ 11	69 $\pm$ 11
After	73 $\pm$ 9	81 $\pm$ 12 ^{*, †}
Δ (after – baseline)	2.1 $\pm$ 11.2	10.9 $\pm$ 9.2 [*]
MAP, mm Hg		
Baseline	95 $\pm$ 12	92 $\pm$ 11
After	97 $\pm$ 9	102 $\pm$ 8 [†]
Proteinuria, %	34.8	45.0
Diabetes, %	60.9	45.0
Hypertension, %	78.3	95.0
Previous CVD, %	60.9	40.0

* $p < 0.05$ vs. Δ eGFR < 5 ; [†] $p < 0.05$ vs. *before*; [‡] $p < 0.05$ vs. *baseline*.

a 2-year period. Improved outcome in the group whose eGFR increased by more than 5 ml/min/1.73 m² coincided with a significant increase in blood pressure after stopping the RAS inhibitor.

Patients who proceeded to RRT (*RRT*) were different from those whose renal function improved in that they had lower eGFR at the time of discontinuation of the RAS inhibitor and failed to significantly increase their eGFR in response to this intervention. The more advanced stage of renal dysfunction in this subgroup may imply that there is a functional threshold beyond which functional recovery is less likely; CKD stage 5 rather than stage 4. In fact, the evidence for an advantageous effect of ACE inhibitors in the late stages of CKD is weak.

For those who responded, the rapid decline in eGFR *before* discontinuation of the RAS inhibitor raises questions about the possibility of an acute on chronic additional insult such as hypovolemia, decompensated congestive cardiac failure, use of iodinated radiocontrast agents or nephrotoxic drugs, among others [20]. Whilst such an event has been ruled out in our careful analysis, it cannot be categorically excluded in a retrospective observational study. It is well documented that AKI can precipitate ESRD in patients with CKD and the use of ACE inhibitors in these mostly elderly patients can only exacerbate such an insult [21] – another reason to use inhibitors of RAS with caution in advanced stages of CKD in the elderly.

With the above in mind, Suissa et al. [11] have related long-term use of inhibitors of RAS with an increasing incidence of ESRD in diabetic patients. This was particularly true in those who remained on these agents to the bitter end; reduced, almost halving, of the risk was reported in those who stopped these agents after a while [11]. Of note a large percentage of our patients were older diabetic patients.

The adverse effects of RAS inhibitors on glomerular hemodynamics are well recognized and the improvement seen in GFR associated with stopping these drugs may simply reflect altered glomerular hemodynamics. This suggests that glomerular autoregulation is preserved and that restoration of angiotensin II mediated efferent arteriolar vasoconstriction improves renal function. It is known that long-term hypertension, advanced CKD and aging are followed by a progressive loss of autoregulation [22, 23]. This may be compounded by the use of ACE inhibitors late in the course of CKD when residual renal function and avoidance of RRT depends on a small number of hyperfunctioning nephrons. In CKD, it is generally accepted that eGFR could be re-

duced by as much as 20–30% after starting RAS inhibitors, but information is lacking about the magnitude of functional recovery when these agents are discontinued. One would expect functional improvement to be more significant early in the course of CKD; this is what we seem to have observed albeit in a small sample size. When RAS inhibitors were stopped, calcium channel blockers (CCBs) were often used to control blood pressure. Whilst there is animal data, there is no human data to demonstrate that CCBs result in improvement in GFR. Therefore the observed increase in GFR is more likely to be due to stopping the RAS inhibitors and it is unlikely that starting CCBs *per se* would have improved GFR.

Our observation that those who improved are those whose blood pressure rose the most after stopping the RAS inhibitor is of considerable interest. Firstly, it may suggest that the beneficial effect of stopping the ACE inhibitor/ARB on renal function is not an agent-specific effect, but the consequence of increased blood pressure and consequent rise in perfusion pressure. Secondly, it suggests that perhaps current target blood pressure levels in CKD are too low for the aging CKD population. The majority of our patients were elderly and no distinction was made in our practice, based on applied guidelines, between target BP levels for younger and older CKD patients. Recent attention has been drawn to this important issue in CKD patients where the advantage of aggressive lowering of blood pressure has been questioned [24] and in ESRD patients where age, diabetes and lower blood pressure seemed to be detrimental [25].

Unsurprisingly proteinuric patients were more likely to require RRT. Of note, stopping ACE inhibitors in this group did not accelerate the rate of decline in eGFR nor did it increase the level of proteinuria [17]. It is well recognized that not all proteinuric CKD patients respond to these agents and that perhaps more attention should be paid to those who do not respond as increasing their inhibitors of RAS may seriously compromise their residual renal function with little or no benefit on proteinuria. Further, one wonders if such aggressive inhibition of RAS may underlie reports of hyperkalemia related to worsening of renal outcomes [12]. The concept that reduction of proteinuria is invariably protective of renal function may not always hold true as some studies showed that treating elderly and susceptible CKD patients with these agents can improve proteinuria while accelerating the decline of eGFR [26].

Our study has a number of serious limitations. It is a retrospective study, thus some data could be imprecise or

missing. A significant number of patients whose renal function improved back to CKD stage 3A or B were discharged, after a while, back to primary care thus limiting their follow-up data. We have conducted an observational study without a control group and therefore any interpretation of the data should be done with caution. It is not possible from the small number of patients studied and followed up to make sweeping conclusions about stopping RAS inhibitors and remission, ESRD or death. Some may argue that removing RAS inhibitors in patients with even advanced kidney disease is denying them 'renoprotection'. Whilst this may be theoretically true, the reality is that in this observational study, stopping these agents actually delayed the onset of RRT. Furthermore, the renoprotective effects of RAS inhibitors has predominantly been demonstrated in proteinuric kidney disease and whilst most of our patient group had non-proteinuric kidney disease and therefore may not derive 'renoprotection' from RAS inhibitors, particularly in advanced CKD.

Our findings question the universal preemptive indication of RAS inhibitors in advanced CKD and suggest

that they can be safely stopped, at least in some patients. This observation should draw more attention and caution to the use of these agents in older patients with advanced CKD. Also to draw attention to those who fail to respond in terms of proteinuria and the risks associated with their exposure to higher doses of these agents alone or in combination including that of hyperkalemia. We hope that our observation will trigger larger and randomized studies to answer the question of the utility and risk-benefit associated with inhibitors of RAS in advanced CKD proteinuric and otherwise. In particular, such trials will need to address whether any benefits in delaying dialysis with stopping RAS inhibitors are offset by adverse cardiovascular outcomes. It is important to recognize that most clinical trials showing the benefit of RAS inhibitors on cardiovascular outcomes excluded patients with advanced CKD [27, 28].

Disclosure Statement

The authors have no competing interests to declare.

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