Albuminuria: more than a renal risk marker?

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Should RAAS inhibition be discontinued in children with advanced chronic kidney disease? Results of the 4C study

Authors

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Abstract

Background

Although Renin Angiotensin Aldosterone System inhibition (RAASi) is a cornerstone in the treatment of renal complications in children with Chronic Kidney Disease (CKD), it is sometimes discontinued when renal function declines further. We studied the reasons and impact of discontinuation of RAASi on important risk markers of CKD progression and on eGFR decline in the observational Cardiovascular Comorbidity in Children with CKD (4C) study.

Methods

Children with CKD who discontinued RAASi during prospective follow-up were included. Initial change in blood pressure, albuminuria and potassium after discontinuation were assessed (median time 6 months). Rate of eGFR decline (eGFR slope) during a median of 1.9 years before and 1.2 years after discontinuation were estimated using a linear mixed effects model.

Results

69 children were included in the study (67% male, mean age 13.7 years, mean eGFR 27 ml/min/1.73m^2). Physician-reported reasons for RAASi discontinuation were increase in serum creatinine, hyperkalemia, and symptomatic hypotension. After discontinuation of RAASi, blood pressure and albuminuria increased whereas potassium decreased. eGFR declined more rapidly after discontinuation of RAASi (-3.9 ml/min/1.73m2/year (95% CI -5.1 to -2.6)) compared to the slope during RAASi treatment (-1.5 ml/min/1.73m^2/year (95% CI -2.4 to -0.6); P=0.005).

Conclusions

Discontinuation of RAASi in children with CKD is associated with an acceleration of renal function decline. These results indicate that RAASi is important for renal protection even in advanced CKD and that stopping this therapy, even for good clinical reasons, should be weighed against the negative impact on long term renal function.

Introduction

Renin Angiotensin Aldosterone System RAAS inhibition (RAASi) with Angiotensin Converting Enzyme (ACE) inhibition or Angiotensin Receptor Blockade (ARB) is a mainstay therapy for renal and cardiovascular protection in adults, and also in children, with chronic kidney disease (CKD).[1] RAASi has been shown to be renoprotective in early as well as in advanced stages of CKD in patients with both diabetic and non-diabetic nephropathies.[2-6]

Despite overwhelming randomized controlled clinical trial evidence demonstrating that RAASi delays the progression of renal function decline, clinicians frequently decide to discontinue RAASi in the course of renal disease progression. Reasons for stopping include symptomatic side effects such as hypotension or cough (in the case of ACE inhibitor use), hyperkalaemia, or to regain renal function and delay dialysis.[7-9]

Although the intention of the clinician is to prevent harm to the patient by discontinuing RAASi, it is unknown whether discontinuation of RAASi will affect risk markers and possibly accelerate renal function decline. Here, we studied the frequency of and reasons for RAASi discontinuation in a large cohort of pediatric patients with advanced CKD, and explored the impact on renal disease progression.

Materials and Methods

Study design

For this study, data from the Cardiovascular Comorbidity in Children with Chronic kidney disease (4C) study were analysed. The 4C study is an ongoing multicentre prospective observational study designed to explore the prevalence, degree and progression of cardiovascular comorbidity as well as its association with CKD progression during longitudinal follow-up. The detailed study design has been described elsewhere.[10] Children aged 6 to 17 years with an estimated GFR of 10-60 ml/min/1.73m^2 were included. Exclusion criteria were the presence of active systemic vasculitis, renal vascular anomalies, coexisting primary cardiovascular anomalies and anomalies of the limbs preventing diagnostic procedures. Study visits with measurements of eGFR, albuminuria, potassium and blood pressure were performed every six months. All prescribed medications, and the dates of any prescription changes since the previous visit were recorded at every study visit. In the absence of any changes in prescription, the use of ACE inhibitors and ARBs was assumed to be consistent between the visits. Discontinuation of RAASi was defined as the removal of an ACE inhibitor or ARB from the recorded medications since the previous visit.

Patient selection

Children who discontinued RAASi during follow-up in the 4C study, and who had at least one recorded eGFR measurement before and after discontinuation of therapy were included in the study population for this analysis. Children who discontinued RAASi after

reaching the composite renal endpoint were excluded from the analyses. Data of all available visits before and after discontinuation were included in the analyses, except for patients in the study population who had previously started RAASi during follow up of the 4C study. In this case, data of the visits before starting RAASi were excluded from the analyses.

Measurements

Spot urine samples were collected at every visit. Albumin and creatinine concentration of the urine samples were measured centrally (Synlab Heidelberg) by turbidimetry and photometry respectively. Estimated GFR was assessed using the 2009 cystatin C/creatinine-based formula.[11] Serum creatinine was measured enzymatically, and serum cystatin C using the turbidimetric assay of Roche. Serum potassium was analyzed locally, to prevent falsely increased potassium levels due to hemolysis. There were no specific recommendations in the 4C study protocol on how to measure blood pressure. However, in general, official recommendations of the 4th report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents were followed and oscillometric devices were used in most centers.[12]

Outcomes

We tested several efficacy measures in the study. First, we evaluated initial change in systolic blood pressure, albuminuria, potassium and eGFR after discontinuation of RAASi. Secondly, eGFR slopes before and after discontinuation of RAASi were assessed. Finally, we measured time from discontinuation of RAASi to the first event of a composite renal endpoint, which was defined as a sustained 50% reduction in eGFR or progression to end-stage renal disease (eGFR < 10 ml/min/1.73m^2 or start of renal replacement therapy).

Statistical analysis

The initial change in systolic blood pressure, potassium and eGFR was determined as the absolute difference between the first measurement after and last measurement before discontinuation of the RAASi. Albuminuria was log-transformed due to its skewed distribution. T-tests were used to test the difference in renal parameters before and after discontinuation of RAASi.

eGFR slopes before and after discontinuation were assessed using a linear mixed effects model with a random slope and random intercept. A spline at time of discontinuation was modelled to assess the difference in slope before and after discontinuation. eGFR slopes were represented as mean with 95% confidence interval (CI) and assessed for different subgroups. Differences in eGFR slopes before and after discontinuation were compared within the model using linear combinations of estimations.

Initial changes in blood pressure and albuminuria have been found to predict efficacy of RAASi in earlier studies.[13-16] We tested whether these changes during discontinuation

of RAASi are associated with the composite renal endpoint, using a Cox proportional hazards model, adjusted for covariates at the last measurement before discontinuation (gender, age, eGFR, albuminuria, systolic blood pressure).

Data are expressed as either mean and standard deviation (SD) or median and 25th-75th percentile for continuous variables and percentages and counts (%) for categorical variables. All analyses were performed using STATA version 14.2 (Statacorp LP).

Results

Of the 704 children that were included in the 4C cohort, 298 (42%) used any form of RAASi at entry into the study. An additional 82 (12%) started RAASi during follow-up of the study. Of these 380 children, 73 children (19%) discontinued RAASi before reaching the composite renal endpoint. Of these, 69 were eligible for this analysis, whereas 4 were excluded due to missing eGFR measurements before or after RAASi discontinuation. During the last visit before discontinuation, mean age was 13.7 (SD 3.2) years and mean eGFR was 27.3 (11.8) ml/min/1.73m2. Most children (74%) had a congenital anomaly of the kidney or urinary tract (CAKUT) as primary renal diagnosis. The majority of the children discontinued an ACE inhibitor: forty children discontinued enalapril, 22 children ramipril and one child captopril. The other six children discontinued an ARB: four discontinued losartan and two candesartan. Fourteen (20%) children started other antihypertensive therapy directly after discontinuation of RAASi: a calcium channel blocker was started in eight children, a beta blocker in three children, a peripheral alpha blocker in two children and one child started a diuretic. Additional characteristics of the study population at the last visit before discontinuation and at enrolment in the 4C study of RAASi are presented in Table 1. Median follow-up time was 1.9 years (1.0 – 3.5 years) before discontinuation and 1.2 years (0.6 – 2.3 years) after discontinuation of RAASi.

Table 1. Characteristics of the study population before discontinuation of RAAS inhibition

	RAASi use at baseline or start during follow-up (n=380)	**Selected population for current analysis (n=69)**	
	Characteristics at enrolment in 4C	*Characteristics at enrolment in 4C*	*Characteristics at last visit before RAASi discontinuation*
Age, years	12.5 (3.3)	11.5 (3.2)	13.7 (3.2)
Female, n	132 (35)	23 (33)	23 (33)
Diagnosis, n			
- CAKUT	244 (64)	51 (74)	51 (74)
- Other	136 (36)	18 (26)	18 (26)
Systolic blood pressure, mmHg	112 (15)	110 (14)	112 (16)
eGFR, ml/min/1.73m^2	30.4 (11.3)	30.2 (8.9)	27.3 (11.8)
eGFR slope, ml/min/1.73m^2/year	N/A	N/A	-1.5 (3.7)
Albuminuria, mg/g	327 (84 – 1128)	395 (111 – 1184)	405 (151 – 1464)
Serum potassium, mmol/L	4.6 (0.6)	4.6 (0.5)	4.6 (0.6)
RAAS inhibition use, n			
- ACE inhibitor	268 (71)	63 (91)	63 (91)
- ARB	55 (14)	6 (9)	6 (9)

Values for continuous variables are described as mean ± SD or median (25th-75th percentile); values for categorical variables as number (percentage).

N/A; not applicable - no eGFR data were available prior to enrolment into the 4C study

Determinants for discontinuation of RAAS inhibition

To establish why clinicians discontinued RAASi, the primary reasons for RAASi discontinuation were assessed. The most important reasons for RAASi discontinuation were increase in serum creatinine, hyperkalemia, and symptomatic hypotension (Table 2). No major differences in baseline characteristics between current and future RAASi users and RAASi discontinuers were observed (Table 1).

At the time of RAASi discontinuation mean eGFR was lower in those children who were discontinued due to an increase in serum creatinine (23.4 (5.6) ml/min/1.73m^2) or hyperkalemia (25.2 (10.2) ml/min/1.73m^2) compared to discontinuation due to symptomatic hypotension (38.6 (15.8) ml/min/1.73m^2; P<0.001). The acceleration of eGFR decline following RAASi discontinuation occurred irrespectively of the reason for RAASi discontinuation (Table 3).

Initial effect of discontinuation of RAASi on renal parameters and disease progression

The median time between the last visit before and the first visit after discontinuation of RAASi was 6.4 (5.7 – 7.0) months. The initial changes in CKD risk markers after RAASi

discontinuation are described in Figure 1. Albuminuria increased by 115% (P<0.001) and systolic blood pressure by 2.8 mmHg (P=0.08) whereas eGFR decreased by 1.3 ml/min/1.73m^2 (P=0.08) and potassium by 0.17 mmol/L (P=0.03). For all parameters, large between-patient variability was observed (Figure 1 right panel).

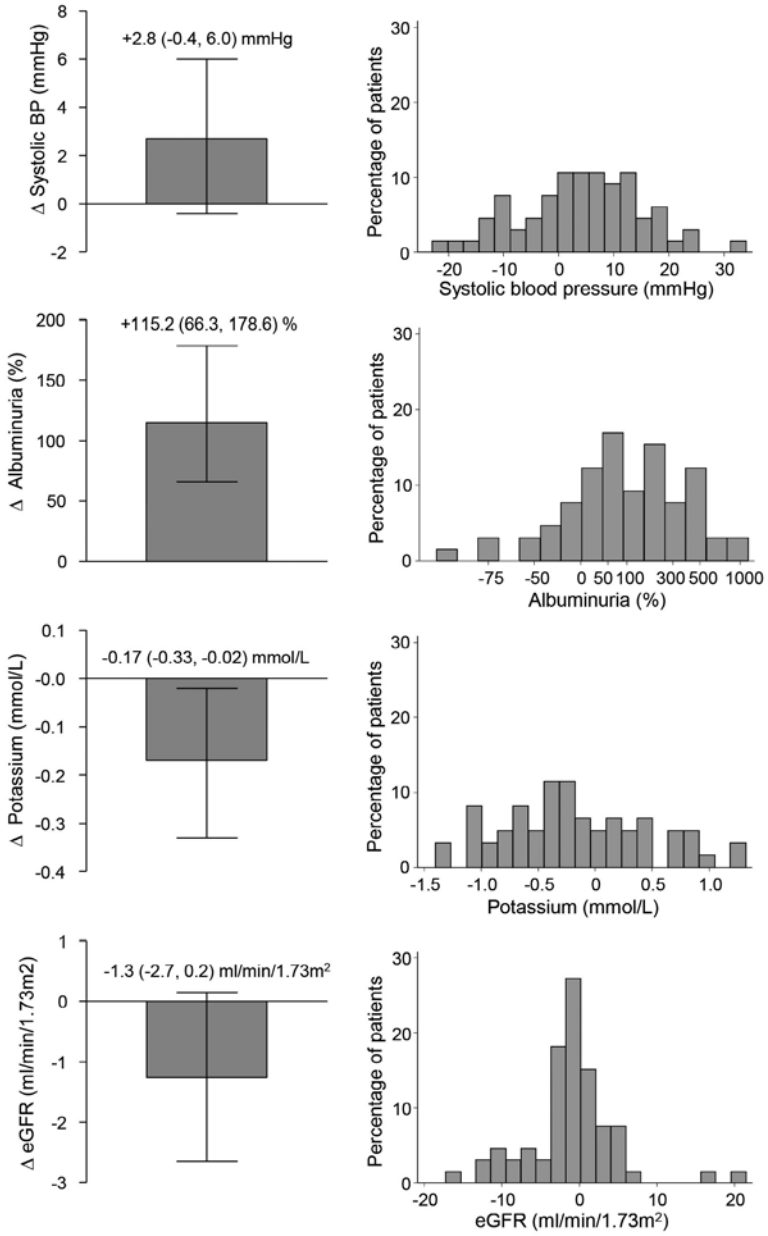
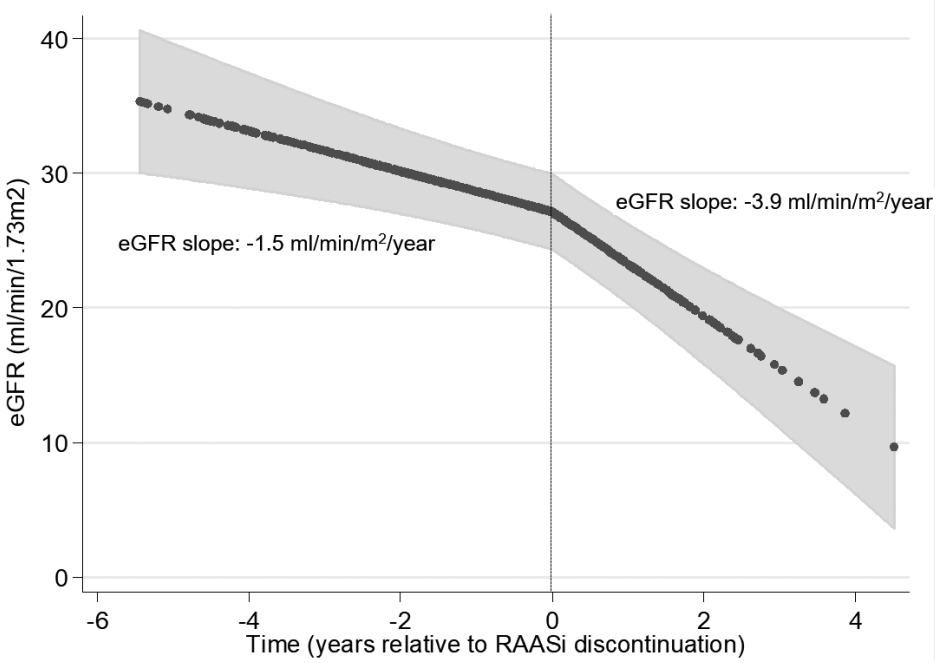


Figure 1. Initial changes observed in parameters of interest expressed as mean and 95% confidence intervals (left panel) and distribution of intraindividual change (right panel)

We modelled the effect of discontinuation of RAASi on eGFR slopes as shown in Figure 2. Discontinuation of RAASi was associated with a faster declining slope of -3.9 (95% CI -5.1 to -2.6) ml/min/1.73/m^2/year after discontinuation compared to -1.5 (95% CI -2.4 to -0.6) ml/min/1.73m^2/year before discontinuation (P=0.005).

Figure 2. Predicted eGFR values before and after discontinuation of RAAS inhibition, represented by dark grey dots. Light grey area represents 95% confidence interval. Dotted line at time=0 represents moment of discontinuation.



Association between initial change in albuminuria/blood pressure and renal disease progression

After discontinuation, 33 patients started renal replacement therapy or had a 50% decline in eGFR, with an incidence of 16.1 events per 100 patients/year. To determine whether changes in systolic blood pressure and albuminuria after discontinuation of RAASi were associated with renal outcomes, we tested the association between these parameters and the composite renal endpoint with an adjusted Cox proportional hazards model (Table 4). A larger increase in albuminuria after RAASi discontinuation was associated with a higher risk of attaining the composite renal endpoint (HR 2.15, 95% CI 1.10 - 4.22). No association was observed between the magnitude of blood pressure change after RAASi discontinuation and the composite renal endpoint (Table 4).

Table 2. Physician-reported reasons for discontinuation of RAAS inhibition in the study population

Reason	Number (%)
Increase of serum creatinine	23 (33)
Hyperkalemia	16 (23)
Dialysis/transplantation	0 (0)
Symptomatic side effects:	
- Hypotension	12 (17)
- Cough	0 (0)
- Other	2 (3)
Non-compliance	1 (1)
Patients wish	1 (1)
Other	6 (9)
Unknown	8 (12)

Table 3. eGFR slopes before and after discontinuation. Data are mean (95% CI) eGFR slope (ml/min/1.73m^2 per year).

Population	Number	eGFR slope before discontinuation	eGFR slope after discontinuation	P-value
Total study population	69	-1.5 (-2.4,-0.6)	-3.9 (-5.1,-2.6)	0.005
Study population with known reason of discontinuation	61	-1.6 (-2.5,-0.7)	-4.0 (-5.2,-2.7)	0.006
Reasons of discontinuation:				
- *Increase in serum creatinine*	23	-2.3 (-3.0,-1.5)	-3.6 (-5.2,-2.0)	0.176
- *Hyperkalemia*	16	-1.3 (-2.5,-0.0)	-3.8 (-6.4,-1.2)	0.116
- *Symptomatic hypotension*	12	-1.5 (-4.9, 1.8)	-6.8 (-11.9,-1.8)	0.109

Table 4. Cox proportional hazards model in discontinuation population

Variable	Hazard ratio	95% confidence interval	P-value
Systolic blood pressure change, mmHg	0.99	0.95 – 1.04	0.755
Log-transformed albuminuria change	2.15	1.10 – 4.22	0.025
Female, n	1.00	0.41 – 2.40	0.996
Age, years	0.92	0.76 – 1.08	0.268
eGFR, ml/min/1.73m^{2†}	0.92	0.86 – 0.98	0.009
Albuminuria, 100 mg/g†	1.11	1.04 – 1.18	0.001
Systolic blood pressure, mmHg†	1.00	0.97 – 1.05	0.625

†measurement at last visit before discontinuation

Discussion

This prospective study aimed to assess the impact of RAASi discontinuation on renal disease progression in children with CKD. To our knowledge no published studies have explored the causes and consequences of RAASi discontinuation in children in a clinical practice setting. In addition to describing the short-term effects of RAASi withdrawal, our study provides evidence for an adverse impact of RAASi discontinuation on the preservation of renal function in children with CKD.

Blood pressure and albuminuria, the well-established renal (and cardiovascular) risk markers impacted upon by RAAS inhibition, increased after stopping RAASi. The rise in albuminuria by 115% was highly significant and was associated with progression to the composite renal endpoint. Our results contrast an adult study that reported no effect of RAASi discontinuation on proteinuria.[7] The substantial increase in albuminuria observed after RAASi discontinuation suggests a strong and persistent albuminuria lowering effect upon RAASi initiation in this pediatric advanced CKD population. This notion is supported by data from the ESCAPE trial demonstrating a 50% reduction in proteinuria after start of an ACE inhibitor in a pediatric CKD population, with an even more profound albuminuria reduction observed in children with more advanced CKD stages.[17] Thus, the stronger effect of RAASi in higher CKD stages might explain the large increase in albuminuria after discontinuation of the drug in this study.

The blood pressure rise of approximately 3 mmHg was modest; however it must be taken into account that RAASi was immediately replaced by other antihypertensive medications in a subset of the children. In comparison, in adult CKD patients a significant increase in mean arterial pressure of 4 mmHg 12 months after discontinuation of RAASi has been reported.[7] Notably, the observed blood pressure increase was of similar magnitude as achieved by intensified vs. conventional antihypertensive management in the ESCAPE trial, where patients in the higher blood pressure arm showed significantly faster long-term CKD progression.[17] However, according to multivariate Cox regression analysis the risk of CKD progression of the patients in our study was predominantly associated with rebound albuminuria rather with the increase in blood pressure following RAASi discontinuation.

Earlier studies have described that discontinuation of RAASi is associated with an increase in eGFR.[7,8] This is a reason for clinicians to stop RAASi with the intent to delay the start of dialysis.[7] While an early increase in eGFR was not observed in our study, the time interval between eGFR measurements may have been too long, and any transient rise may have been masked by the progressive loss of renal function. The acceleration of long term renal disease progression is in contrast to findings of a previous study in adult patients, where discontinuation of RAASi was followed by improvement of renal function decline.[7] The differences between our results and the earlier findings may be related to differences in eGFR, proteinuria and blood pressure at time of RAASi discontinuation and/or in the underlying disease spectrum.

Forty-two percent of the children participating in the 4C study used RAASi at inclusion in the study, a slightly lower prevalence as compared to the North American Chronic Kidney Disease in Children (CKID) cohort where 55% of 851 children used RAASi at time of enrolment.[18,19] Treatment with RAASi is recommended in all children with CKD and either a consistently elevated blood pressure (>90th percentile for age, sex and height) or macroalbuminuria.[20] These criteria were met in 67% of the children, indicating significant underprescription of RAASi in European children with CKD.

The major limitation of our study was its observational design, with potential bias by indication that would not have been present in a randomized controlled trial. However, random discontinuation of nephroprotective RAAS inhibition in a controlled trial would not have been ethically justified. Moreover, extended longitudinal eGFR data before and after RAASi discontinuation were analyzed, using the patients as their own controls. Another advantage of the observational study design of the 4C study was the possibility to assess the frequency and reasons of discontinuation.

In conclusion, in this study we assessed the frequency and reasons as well as the impact of discontinuation of RAASi on eGFR decline in an observational cohort of children with CKD. Discontinuation of RAASi in children with CKD is associated with an acceleration of renal function decline. These results indicate that ACE inhibitor or ARB therapy is important for renal protection and that stopping this therapy even for good clinical reasons and even in advanced CKD should be weighed against the negative impact on long term renal function.

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