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Discontinuation of RAAS Inhibition in Children with Advanced CKD

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Abstract

Background and objectives Although renin-angiotensin-aldosterone system inhibition (RAASi) is a cornerstone in the treatment of children with CKD, it is sometimes discontinued when kidney function declines. We studied the reasons of RAASi discontinuation and associations between RAASi discontinuation and important risk markers of CKD progression and on eGFR decline in the Cardiovascular Comorbidity in Children with CKD study.

Design, setting, participants, & measurements In this study, 69 children with CKD (67% male, mean age 13.7 years, mean eGFR 27 ml/min per 1.73 m^2) who discontinued RAASi during prospective follow-up were included. Initial change in BP, 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 linear mixed effects modeling.

Results Physician-reported reasons for RAASi discontinuation were increase in serum creatinine, hyperkalemia, and symptomatic hypotension. After discontinuation of RAASi, BP and albuminuria increased, whereas potassium decreased. eGFR declined more rapidly after discontinuation of RAASi (−3.9 ml/min per 1.73 m^2 per year; 95% confidence interval, −5.1 to −2.6) compared with the slope during RAASi treatment (−1.5 ml/min per 1.73 m^2 per year; 95% confidence interval, −2.4 to −0.6; P=0.005). In contrast, no change in eGFR slope was observed in a matched control cohort of patients in whom RAASi was continued.

Conclusions Discontinuation of RAASi in children with CKD is associated with an acceleration of kidney function decline, even in advanced CKD.

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Introduction

Renin angiotensin aldosterone system inhibition (RAASi) with angiotensin-converting enzyme (ACE) inhibition or angiotensin receptor blockade (ARB) is a mainstay therapy for kidney and cardiovascular protection in adults and children with CKD (1). It has been shown that RAASi is renoprotective in early as well as advanced stages of CKD in patients with both diabetic and nondiabetic nephropathies (2–6).

Despite overwhelming randomized, controlled clinical trial evidence demonstrating that RAASi delays the progression of kidney function decline, clinicians frequently decide to discontinue RAASi in the course of kidney disease progression. Reasons for stopping include symptomatic side effects such as hypotension or cough (in the case of ACE inhibitor use), hyperkalemia, or to regain kidney 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 for CKD and possibly accelerate kidney 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 effect on kidney disease progression.

Materials and Methods

Study Design

For this study, data from the Cardiovascular Comorbidity in Children with CKD (4C) study were analyzed. The 4C study is an ongoing, multicenter, 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 6–17 years with an eGFR of 10–60 ml/min per 1.73 m^2 were included. Exclusion criteria were the presence of active systemic vasculitis, kidney vascular

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anomalies, and coexisting primary cardiovascular anomalies and anomalies of the limbs preventing diagnostic procedures. Study visits with measurements of eGFR, albuminuria, potassium, and BP were performed every 6 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. Switching between ACE inhibitors and ARB was defined as continuation of RAASi. Discontinuation of RAASi was defined as the removal of an ACE inhibitor or ARB from the recorded medications since the previous visit and the presence of a recorded discontinuation date in the database.

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 kidney end point, which was defined as a sustained 50% reduction in eGFR or progression to ESKD (eGFR<10 ml/min per 1.73 m^2 or start of KRT), 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 in the urine samples were measured centrally (Synlab Heidelberg) by turbidimetry and photometry, respectively. eGFR was assessed using the 2009 cystatin C/creatinine-based formula (11). Serum creatinine was measured enzymatically and serum cystatin C using the turbidimetric assay from Roche. Serum potassium was analyzed locally, to prevent falsely increased potassium levels owing to hemolysis. There were no specific recommendations in the 4C study protocol on how to measure BP. However, in general, official recommendations of the fourth report on the Diagnosis, Evaluation, and Treatment of High BP 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 BP, albuminuria, potassium, and eGFR after discontinuation of RAASi. Second, 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 kidney end point (a sustained 50% reduction in eGFR or progression to ESKD [eGFR<10 ml/min 1.73 m^2 or start of KRT]).

Statistical Analyses

The initial change in systolic BP, 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 because of its skewed distribution. *t* tests were used to test the difference in kidney 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 modeled to assess the difference in slope before and after discontinuation. eGFR slopes were represented as mean with 95% confidence interval (95% CI) and assessed for different subgroups. Differences in eGFR slopes before and after discontinuation were compared within the model using linear combinations of estimators. To define whether changes in eGFR slopes before and after RAASi discontinuation were not dependent on spontaneous kidney disease progression, eGFR slopes were also assessed in a control group of patients who continued RAASi therapy. Discontinued patients and continued controls were matched with one-to-one nearest-neighbor propensity score matching by eGFR, eGFR change compared with the previous visit, and follow-up time. The visit on which controls were matched to patients who discontinued a RAASi was defined as time point 0. eGFR slopes in the control group were assessed before and after time point 0 with a spline at time point 0. eGFR slopes in the control group were compared with RAASi-discontinuing patients that could be matched ($n=50$). To test whether eGFR slopes after time point 0 were different between RAASi discontinuers and patients who continued RAASi, we included all patients from the matched control analysis in one mixed linear model with random slope and intercept. We included a random effect for a matched pair cluster in the model. An interaction term for time and RAAS status was included, yielding two different slopes for the time after discontinuation (and nondiscontinuation in the synchronized controls).

Initial changes in BP 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 kidney end point, using a Cox proportional hazards model, adjusted for covariates at the last measurement before discontinuation (sex, age, eGFR, albuminuria, systolic BP).

Data are expressed as either mean and SD or median and interquartile range (IQR) for continuous variables, and percentages and counts (percent) for categorical variables. All analyses were performed using STATA version 14.2 (StataCorp).

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 without reaching the composite kidney end point or before reaching the composite kidney end point. Of these, 69 were eligible for this analysis, whereas four were excluded because of missing eGFR measurements before or after RAASi discontinuation (Supplemental Figure 1). During the last visit before discontinuation, mean age was 13.7 (SD 3.2) years and mean eGFR was

Table 1. Characteristics of participants in the Cardiovascular Comorbidity in Children with CKD (4C) study before discontinuation of RAASi

Characteristic	RAASi Use at Baseline or Start during Follow-Up (n=380)	Population Selected for Current Analysis (n=69[a])		Case-Control Study Cohorts	
	Characteristics at Enrollment in 4C Study	Characteristics at Enrollment in 4C Study	Characteristics at Last Visit before RAASi Discontinuation	Patients Who Discontinued RAASi (n=50)	Matched Controls on Continued RAASi (n=50)
Age, yr	12.5 (3.3)	11.5 (3.2)	13.7 (3.2)	14.3 (3.1)	14.4 (3.8)
Female, *n* (%)	132 (35)	23 (33)	23 (33)	15 (30)	17 (34)
Diagnosis, *n* (%)					
CAKUT	244 (64)	51 (74)	51 (74)	36 (72)	33 (66)
Other	136 (36)	18 (26)	18 (26)	14 (28)	17 (34)
Systolic BP, mm Hg	112 (15)	110 (14)	112 (16)	114 (16)	114 (13)
eGFR, ml/min per 1.73 m^2	30 (11)	30 (9)	27 (12)	28 (12)	28 (13)
eGFR slope, ml/min per 1.73 m^2 per yr[b]	N/A	N/A	−1.5 (3.7)	−1.5 (3.3)	−1.8 (2.5)
Albuminuria, mg/g	327 (84–1128)	395 (111–1184)	405 (151–1464)	360 (165–1544)	311 (63–962)
Serum potassium, meq/L	4.6 (0.6)	4.6 (0.5)	4.6 (0.6)	4.6 (0.6)	4.6 (0.5)
RAASi use, *n* (%)					
ACE inhibitor	268 (71)	63 (91)	63 (91)	45 (90)	49 (98)
ARB	55 (14)	6 (9)	6 (9)	5 (10)	1 (2)

Values for continuous variables are described as mean ± SD or median (interquartile range); values for categorical variables as number (percentage). RAASi, renin-angiotensin-aldosterone system inhibition; CAKUT, congenital anomalies of kidney and urinary tract; N/A, not applicable, no eGFR data were available before enrolment into the 4C study; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

[a]At enrolment in 4C study: eGFR n=65, albuminuria n=64. At last visit before RAASi discontinuation: eGFR n=65, potassium n=66. No missing values in other variables.

[b]eGFR slope is either the change in eGFR before RAASi discontinuation (in the patients who discontinued RAASi), or eGFR change before the matched visit (for patients in the matched control group).

Table 2. Physician-reported reasons for discontinuation of renin-angiotensin-aldosterone system inhibition in the study population

Reason	*N* (%)
Increase of serum creatinine	23 (33)
Hyperkalemia	16 (23)
Symptomatic side effects	
Hypotension	12 (17)
Cough	0 (0)
Other	2 (3)
Nonadherence	1 (1)
Patients wish	1 (1)
Other	6 (9)
Unknown	8 (12)

27 (SD 12) ml/min per 1.73 m^2. Most children (74%) had a congenital anomaly of the kidney or urinary tract as primary kidney diagnosis. The majority of the children discontinued an ACE inhibitor: 40 children discontinued enalapril, 22 children discontinued ramipril, and one child discontinued captopril. The other six children discontinued an ARB: four discontinued losartan and two discontinued candesartan. Fourteen (20%) children started other antihypertensive therapy directly after discontinuation of RAASi: a calcium channel blocker was started in eight children, a β-blocker in three children, a peripheral α-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 (IQR, 1.0–3.5 years) before discontinuation and 1.2 years (IQR, 0.6–2.3 years) after discontinuation of RAASi. During follow-up, there were a total of 22 hospitalizations before discontinuation and 117 hospitalizations after discontinuation of RAASi. In the study population, one event of AKI (eGFR loss of ≥50%) occurred. The characteristics of the control group patients on continued RAASi and the matched patients in whom RAASi was discontinued are also presented in Table 1.

Determinants for Discontinuation of RAASi

To establish why clinicians discontinued RAASi, the primary reasons for RAASi discontinuation were assessed by use of a questionnaire. The most important reasons stated were increase in serum creatinine, hyperkalemia, and symptomatic hypotension (Table 2). "Unknown" was listed when the reason for discontinuation could neither be reconstructed by the clinician in charge nor from the patient file. RAASi was discontinued during hospitalization in seven of the patients and outpatient in 62 of the patients.

At the time of RAASi discontinuation, mean eGFR was lower in those children who were discontinued because of an increase in serum creatinine (23 [SD 6] ml/min per 1.73 m^2) or hyperkalemia (25 [SD 10] ml/min per 1.73 m^2) compared with discontinuation because of symptomatic hypotension (39 [SD 16] ml/min per 1.73 m^2; $P<0.001$). The acceleration of eGFR decline after RAASi discontinuation occurred irrespectively of the reason for RAASi discontinuation (Table 3).

Associations between Discontinuation of RAASi and Kidney Parameters and Disease Progression

The median time between the last visit before and the first visit after discontinuation of RAASi was 6.4 (IQR, 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 BP by 2.8 mm Hg ($P=0.08$), whereas eGFR decreased by 1 ml/min per 1.73 m^2 ($P=0.08$) and potassium by 0.17 meq/L ($P=0.03$). For all parameters, large between-patient variability was observed (Figure 1, right panel).

We modeled the associations between discontinuation of RAASi and 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 per 1.73/m^2 per year after discontinuation, compared with −1.5 (95% CI, −2.4 to −0.6) ml/min per 1.73 m^2 per year before discontinuation ($P=0.005$). In the control group, eGFR slopes were similar before (−1.8 [95% CI, −2.6 to −1.1] ml/min per 1.73 m^2 per year) and after (−1.2 [95% CI, −2.0 to −0.4] ml/min per 1.73 m^2 per year) time point 0 ($P=0.30$), whereas eGFR decline in the matched patients who discontinued RAASi was significantly faster after discontinuation (eGFR slope −3.8 [95% CI, −5.4 to −2.3] ml/min per 1.73 m^2 per year) than before discontinuation (eGFR slope −1.5 [95% CI, −2.4 to −0.6] ml/min per 1.73 m^2 per year) ($P=0.02$; Figure 3). The comparison of slopes after time point 0 in the combined model showed a mean annual eGFR change of −3.6 (95% CI, −2.4 to −4.8) ml/min per 1.73 m^2 in the RAASi discontinuation group versus −1.4 (95% CI, −0.8 to −2.1) in the controls on continued RAASi (difference in slopes: $P<0.001$). Population characteristics between the

Table 3. eGFR slopes before and after discontinuation or renin-angiotensin-aldosterone system inhibitors

Population	*N*	eGFR Slope before Discontinuation	eGFR Slope after Discontinuation	*P* Value
Total study population	69	−1.5 (−2.4 to −0.6)	−3.9 (−5.1 to −2.6)	0.005
Study population with known reason of discontinuation	61	−1.6 (−2.5 to −0.7)	−4.0 (−5.2 to −2.7)	0.006
Reasons of discontinuation				
Increase in serum creatinine	23	−2.3 (−3.0 to −1.5)	−3.6 (−5.2 to −2.0)	0.18
Hyperkalemia	16	−1.3 (−2.5 to −0.0)	−3.8 (−6.4 to −1.2)	0.12
Symptomatic hypotension	12	−1.5 (−4.9 to 1.8)	−6.8 (−11.9 to −1.8)	0.11

Data are mean (95% confidence interval) eGFR slope (ml/min per 1.73 m^2 per yr).

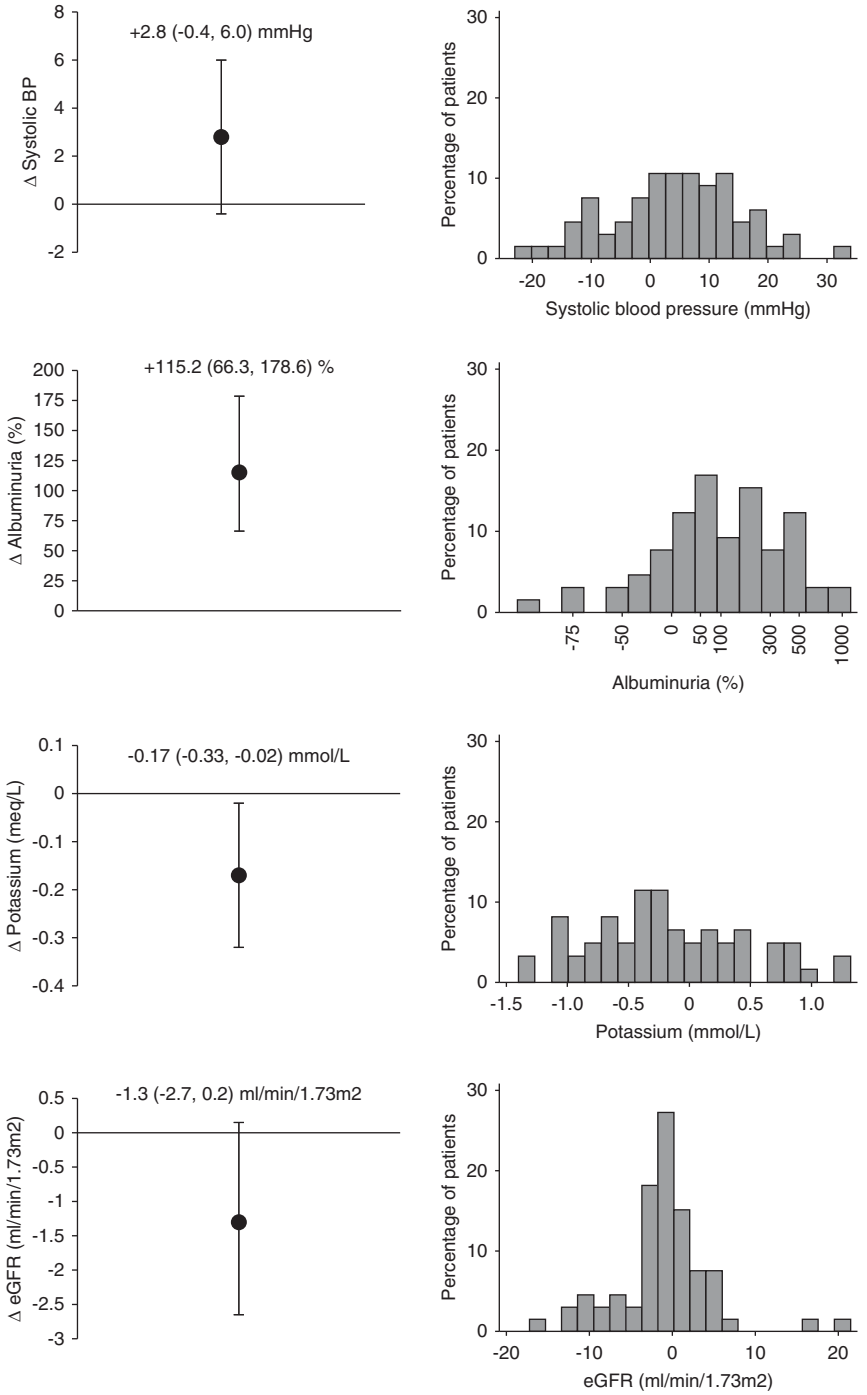

Figure 1. | Changes in BP, albuminuria, serum potassium, and eGFR associated with discontinuation of RAAS inhibitors. Initial changes observed in parameters of interest expressed as mean and 95% confidence intervals (left panel) and distribution of intraindividual change (right panel).

control group and matched patients who discontinued RAASi were similar as shown in Table 1.

Association between Initial Change in Albuminuria/BP and Kidney Disease Progression

After discontinuation, 33 patients started KRT or had a 50% decline in eGFR, with an incidence of 16.1 events per 100 patients per year. To determine whether changes in systolic BP and albuminuria after discontinuation of RAASi were associated with kidney outcomes, we tested the association between these parameters and the composite kidney end point with an adjusted Cox proportional hazards model (Supplemental Table 1). A larger increase in albuminuria after RAASi discontinuation was associated with a higher risk of attaining the composite kidney end

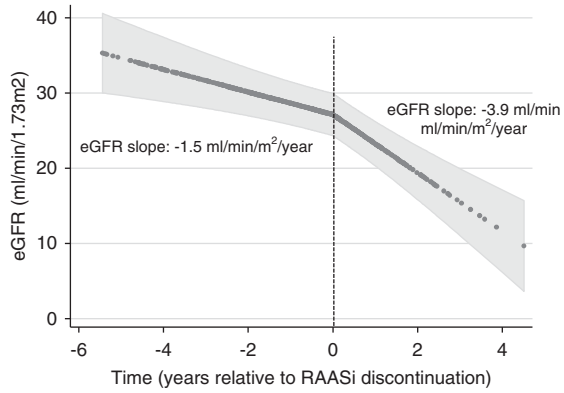

Figure 2. | Predicted eGFR values before and after discontinuation of RAASi in RAASi discontinuers, represented by dark gray dots. Light gray area represents 95% confidence interval. Dotted line at time point 0 represents time of discontinuation. RAASi, renin-angiotensin-aldosterone system inhibition.

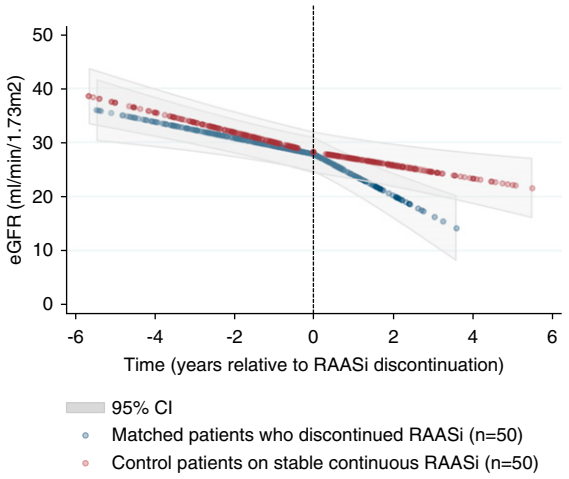

Figure 3. | Predicted eGFR values in control group on continuous RAASi (red dots) and matched patients who discontinued RAASi (blue dots). Light gray area represents 95% confidence interval (95% CI) per group. Dotted line at time point 0 represents either time of discontinuation (patients who discontinued RAASi) or time point of matched visit (control group on continuous RAASi).

point (hazard ratio, 2.15; 95% CI, 1.10 to 4.22). No association was observed between the magnitude of BP change after RAASi discontinuation and the composite kidney end point (Supplemental Table 1).

Discussion

This prospective study aimed to assess the effect of RAASi discontinuation on kidney 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 associations between RAASi withdrawal and kidney parameters, our study provides evidence for an adverse effect of RAASi discontinuation on the preservation of kidney function in children with CKD.

BP and albuminuria, the well established kidney (and cardiovascular) risk markers affected by RAASi, increased after stopping RAASi. The rise in albuminuria by 115% was highly significant and was associated with progression to the composite kidney end point. Our results contrast an adult study that reported no association between RAASi discontinuation and proteinuria (7). The substantial increase in albuminuria observed after RAASi discontinuation suggests strong and persistent albuminuria lowering upon RAASi initiation in this pediatric advanced CKD population. This notion is supported by data from the Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients (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 proteinuria lowering of RAASi in higher CKD stages might explain the large increase in albuminuria after discontinuation of the drug in this study.

The BP rise of approximately 3 mm Hg was modest, although even small changes in BP are considered to affect progression of kidney disease (18). 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 patients with CKD, a significant increase in mean arterial pressure of 4 mm Hg at 12 months after discontinuation of RAASi has been reported (7). Notably, the observed BP increase was of similar magnitude as achieved by intensified versus conventional antihypertensive management in the ESCAPE trial, where patients in the higher BP arm showed significantly faster long-term CKD progression (17). However, according to multivariable 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 BP after 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). Although 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 kidney function. Importantly, this acceleration in kidney function decline was not observed in a carefully matched control group of patients with the same current eGFR and eGFR slope and similar distribution of age, underlying disease spectrum, BP, and proteinuria, in whom RAASi administration was continued. The acceleration of long-term kidney disease progression is at variance to findings of a previous study in adult patients, where discontinuation of RAASi was followed by improvement of kidney function decline (7). The differences between our results and the earlier findings in adults may be related to differences in eGFR, proteinuria, and BP at time of RAASi discontinuation and/or in the underlying disease spectrum.

A total of 42% of the children participating in the 4C study used RAASi at inclusion in the study, a slightly lower

prevalence compared with the North American CKD in Children cohort, where 55% of 851 children used RAASi at time of enrolment (19,20). Treatment with RAASi is recommended in all children with CKD and either a consistently elevated BP (>90th percentile for age, sex, and height) or macroalbuminuria (1). 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 RAASi in a controlled trial would not have been ethically justified. Instead, we chose to use not only the patients as their own controls by analyzing extended, longitudinal, intraindividual eGFR data before and after RAASi discontinuation, but also included a well matched control group of 4C study patients on continued RAASi use that, in contrast to the patients who discontinued RAASi, showed no acceleration of kidney function decline. Another advantage of the observational study design of the 4C study was the possibility to assess the frequency and reasons of discontinuation. Limitations to this approach were given by the sample size and the variable follow-up time periods available to calculate the eGFR slopes.

In conclusion, in this study we assessed the frequency of, reasons for, and effect 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 kidney function decline. These results are consistent with the notion that RAASi is important for kidney protection in advanced pediatric CKD, and that clinicians should consider the possible adverse effect on long-term kidney function when discontinuing RAASi. The observational setting, with potential confounding by indication, is the major bias of this study.

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Dr. Melk, Dr. Querfeld, Dr. Schaefer, and Dr. Wühl contributed in design of the 4C study. Mr. Azukaitis, Dr. Bacchetta, Dr. Bayazit, Dr. Canpolat, Dr. Duzova, Dr. Erdogan, Dr. Fidan, Dr. Gellermann, Dr. Kaplan Bulut, Dr. Melk, Dr. Niemirska, Dr. Özçakar, Dr. Paripovic, Dr. Querfeld, Dr. Schaefer, Dr. Shroff, Dr. Thurn-Valsassina, and Dr. Wühl were involved in execution of the 4C study. Dr. de Zeeuw, Mrs. Gracchi, Dr. Heerspink, Dr. Schaefer, Dr. van den Belt, and Dr. Wühl designed the study. Dr. Kirchner and Dr. van den Belt analyzed the data. All authors drafted and/or revised the paper, and approved the final version of the manuscript.

Part of the work took place in the Biomedical Research Centre at Great Ormond Street Hospital for Children National Health Service Foundation Trust and University College London.

Disclosures

Dr. de Zeeuw reports other from AbbVie, other from Bayer, other from Boehringer Ingelheim, other from Fresenius, other from Janssen, other from Mitsubishi Tanabe, other from Mundipharma, outside the submitted work. Dr. Heerspink reports grants and other from AbbVie, grants and other from AstraZeneca, grants and other from Boehringer Ingelheim, other from Gilead, grants and other from Janssen, other from Merck, other from Mitsubishi Tanabe, and other from Retrophin, outside the submitted work. All remaining authors have nothing to disclose.

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Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.09750819/-/DCSupplemental.

Supplemental Table 1. Cox proportional hazards model in discontinuation population.

Supplemental Figure 1. Flow chart of inclusion of patients in study.

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Supplemental Material Table of Contents

*Supplemental Table 1***.** 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	0.76
Log-transformed albuminuria change, %	2.15	1.10 – 4.22	0.02
Female, n	1.00	0.41 – 2.40	0.99
Age, years	0.92	0.76 – 1.08	0.27
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	0.63

^composite endpoint: a sustained 50% reduction in eGFR or progression to end-stage kidney disease (eGFR < 10 ml/min/1.73m^2 or start of kidney replacement therapy)

†measurement at last visit before discontinuation

Supplemental Figure 1. Flow chart of inclusion of patients in study