



# When should we start and stop ACEi/ARB in paediatric chronic kidney disease?

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## Abstract

Renin-angiotensin-aldosterone inhibitors (RAASi) are the mainstay therapy in both adult and paediatric chronic kidney disease (CKD). RAASi slow down the progression of kidney failure by optimization of blood pressure and reduction of proteinuria. Despite recommendations from published guidelines in adults, the evidence related to the use of RAASi is surprisingly scarce in children. Moreover, their role in advanced CKD remains controversial. Without much guidance from the literature, paediatric nephrologists may discontinue RAASi in patients with advanced CKD due to apparent worsening of kidney function, hyperkalaemia and hypotension. Current data suggest that this strategy may in fact lead to a more rapid decline in kidney function. The optimal approach in this clinical scenario is still not well defined and there are varying practices worldwide. We will in this review describe the existing evidence on the use of RAASi in CKD with particular focus on paediatric data. We will also address the use of RAASi in advanced CKD and discuss the potential benefits and harms. At the end, we will suggest a practical approach for the use of RAASi in children with CKD based on current state of knowledge.

**Keywords** Angiotensin-converting enzyme inhibitor · Angiotensin receptor blocker · RAAS inhibition · Blood pressure · Proteinuria · Chronic kidney disease · Children

## Introduction

Chronic kidney disease (CKD) in children is often characterized by gradual deterioration of kidney function, resulting in kidney failure and the need of kidney replacement therapy (KRT). Over the years, a number of strategies have been shown to slow CKD progression in children, including strict blood pressure control, reducing proteinuria, optimizing anaemia and achieving normal 25-hydroxyvitamin D levels [1–4]. Renin-angiotensin-aldosterone-system inhibitors (RAASi), consisting of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB), lower blood pressure and also urinary protein excretion by reducing intra-glomerular pressure and enhancing the barrier-size

selection function in the slit pore membrane [5]. To date, RAASi is the mainstay therapy to attenuate kidney progression in both adult and paediatric CKD by attaining desirable blood pressure and proteinuria control [6–15]. The anti-fibrotic and anti-inflammatory properties of RAASi provide additional benefits to preserve kidney function [6]. Despite an undisputed efficacy in delaying disease progression in multiple adult studies, evidence supporting the renoprotective effect of RAASi is less substantial in paediatric CKD. Their role in advanced CKD, defined as glomerular filtration rates (GFR) less than 30 ml/1.73 m<sup>2</sup>/min, also remains controversial [16]. With scant evidence from the literature, paediatric nephrologists may incline to discontinue RAASi due to worsening kidney function, hyperkalaemia and hypotension [17, 18]. While the intention of drug cessation is to restore kidney function and hopefully delay dialysis, discontinuation of RAASi in advanced CKD may accelerate the decline in GFR [19–21]. These controversies were highlighted in a recently published KDOQI survey in which 703 physicians' decisions on whether to consider RAASi discontinuation when patients' GFR fell below 20 ml/1.73 m<sup>2</sup>/min were examined [16]. Findings revealed that 46.2% would stop the drug while 53.8% would instead opt for continuation.

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Relevant data in the paediatric population are scarce, and this warrants careful extrapolation from the adult data. In this review, we describe the evidence related to the use of RAASi in reducing CKD progression in paediatric and adult populations. We carefully examine the available data on the efficacy and safety of RAASi therapy in advanced CKD. By the end of this review, we attempt to formulate an optimal approach to the use of RAASi in paediatric CKD and identify future research directions.

## RAASi in adult CKD: does one size fit all?

In adults, the control of blood pressure and proteinuria are the two main therapeutic targets to delay CKD progression. For decades, the use of RAASi has become an integral part of the standard management in diabetic nephropathy [22–26], which is a rare condition in children. Importantly, such beneficial effects in slowing down the progression of CKD appear to be independent of blood pressure control and extend to patients with microalbuminuria [27]. The renoprotective effect, however, is not confirmed in those who are non-albuminuric.

Clinical trials and meta-analysis have similarly demonstrated efficacy in the preservation of kidney function for non-diabetic CKD [9–11]. This effect was best illustrated by the benazepril trial, where 583 predominantly non-diabetic CKD patients were randomly assigned to benazepril or placebo, in addition to conventional antihypertensive therapies [10]. Fewer patients in the benazepril group experienced doubling of serum creatinine levels or progressed to dialysis, with an overall risk reduction of 53%. In a meta-analysis that reviewed 11 randomized controlled trials, including the aforementioned benazepril trial, ACEi therapy was found to be associated with a 30% relative risk reduction for reaching a doubled serum creatinine or kidney failure [9]. Importantly, multiple studies reported that a higher degree of proteinuria at baseline and reduction in urinary protein excretion following RAASi initiation were associated with better kidney outcomes [8, 9, 28–31]. The best renoprotective effects are indeed observed in those with proteinuria above 1000 mg per day [29, 30]. The treatment strategy with RAASi, however, is not universally efficacious in all types of CKD. In particular, the use of RAASi does not appear to confer clinical benefit in patients with polycystic kidney diseases and patients who have less severe proteinuria (less than 500–1000 mg protein per day) [9–11].

The Ramipril Efficacy in Nephropathy (REIN) trial examined the rates of GFR decline in adult patients (18–70 years) with chronic non-diabetic nephropathies and proteinuria who were randomly assigned to ramipril or placebo plus conventional anti-hypertensives to achieve a diastolic blood pressure less than 90 mmHg [8, 32, 33]. While both groups attained comparable blood pressure, ramipril effectively reduced the

rates of GFR decline and patients reaching kidney failure, suggesting an effect beyond hypertension control. With time, the tendency of GFR to decline could be effectively halted, and some patients even showed an improvement in GFR.

Results of the African American Study of Kidney Disease and Hypertension (AASK) showed that ACEi was better than beta blockers and calcium channel blockers in slowing the rate of CKD progression in African American (AA) patients with CKD secondary to hypertension [12, 34]. In this study, 1094 African Americans aged 18 to 70 years with hypertensive CKD (GFR 20–65 ml/1.73 m<sup>2</sup>/min) were recruited. The clinical composite endpoint comprised 50% drop in GFR, development of kidney failure or death. Compared with metoprolol and amlodipine, the ramipril group showed a risk reduction in reaching the clinical composite endpoint by 22% and 38% respectively. Of note, there was no difference on the composite outcome between the two blood pressure targets (102–107 mmHg versus 92 mmHg or less). This study supports the use of RAASi in an AA adult population and it also suggests a potential application in AA children who seem to have a faster decline in GFR and progression to kidney failure [35].

The ONTARGET trial evaluated the efficacy of monotherapy with ramipril or telmisartan, or both. There were 25,620 patients with atherosclerosis or diabetes recruited and the primary kidney outcomes were similar for ACEi or ARB monotherapy, but the outcome was worse in the group on combination therapy despite a higher degree of reduction in proteinuria [36, 37]. Concurring with these findings, in the VA NEPHRON-D study, combination therapy also led to a higher likelihood of adverse events, such as hospitalizations due to acute kidney injury or severe hyperkalaemia [36, 38].

The 2012 KDIGO guideline on CKD recommends either ACEi or ARB to be used in both diabetic and non-diabetic adults with CKD and urine albumin excretion over 300 mg per day [14]. Either agent can be used as monotherapy, while combination therapy is not advisable. Although there is substantial evidence to support RAASi in delaying progression of CKD, it is not clear how early these agents should be started. Nonetheless, collective findings from a few studies do suggest that maximal renoprotection is attained with earlier treatment and a higher basal GFR [10, 23].

## RAASi and paediatric CKD: what is the evidence?

CKD may arise from a number of kidney diseases which are associated with different degrees of nephron loss. Adult patients present with mainly glomerular disorders, while congenital anomalies of kidney and urinary tract (CAKUT) is the leading cause of chronic kidney diseases in children. CAKUT is associated with a substantially lower degree of proteinuria [39]. Progression of kidney disease is often

multifactorial and contributed to by multiple secondary factors [40]. After the initial loss of nephrons, compensatory glomerular hyperfiltration occurs in the remaining functional units of the kidney and this results in glomerular hypertension and hypertrophy in order to maintain GFR. With time, secondary glomerular injury ensues, which leads to the development of glomerulosclerosis, proteinuria and eventually progression of CKD. Therefore, children with CAKUT, even though it is a non-glomerular condition, may benefit from RAAS blockade through reduction of intra-glomerular pressure as well as optimization of blood pressure and proteinuria.

In contrast to the adult population, evidence of RAASi use in paediatric CKD is limited and is predominantly derived from the Chronic Kidney Disease Children (CKiD) study and Effect of Strict Blood Pressure Control and ACE inhibition on the Progression of CRF in Pediatric Patients (ESCAPE) trial. The efficacy of RAAS blockade has not been directly examined in most paediatric studies. Therefore, the beneficial effect of RAASi in children is mostly based on assumption and extrapolation to a certain extent.

The CKiD study prospectively enrolled patients aged 1 to 16 years, with an estimated GFR ranging from 30 to 90 ml/1.73 m<sup>2</sup>/min, from 54 participating centres in North America. Factors associated with CKD progression, defined as KRT initiation or 50% decline in GFR, were examined among 496 children [1]. Notably, nephrotic-range proteinuria (urinary protein-to-creatinine ratio > 2 mg/mg), hypoalbuminaemia and elevated blood pressure (systolic or diastolic blood pressure > 90th centile for age, sex and height) were the common risk factors for progression in both non-glomerular and glomerular CKD groups. The risk and rate of progression were more prominent in CKD of glomerular origin. In children with CKD of non-glomerular origin, a two-fold higher basal urine protein-to-creatinine ratio was associated with an accelerated GFR decline of 0.3 ml/1.73 m<sup>2</sup>/min per year, in addition to the 1.3 ml/1.73 m<sup>2</sup>/min per year average decline in the entire cohort [2]. This detrimental effect was observed even among normotensive children. Regarding blood pressure, the elevation of every unit of *z* score of the baseline systolic blood pressure was associated with an additional GFR decline of 0.4 ml/1.73 m<sup>2</sup>/min per year [2].

Based on these findings, hypertension and proteinuria are similarly considered as potential treatment targets in paediatric CKD, independent of the underlying disease. However, despite publication of relevant guidelines, hypertension remains prevalent in paediatric CKD, even at early stages, and is frequently under- or untreated [41–43]. RAASi is the preferred antihypertensive therapy as its use is associated with lower incidence of uncontrolled hypertension and a higher likelihood of normal ambulatory blood pressure results [41, 44]. RAASi also have an added benefit of reducing proteinuria, which may further improve blood pressure control [44, 45]. In another report by Abraham et al. from the CKiD study, 851

children (median GFR 52 ml/1.73 m<sup>2</sup>/min) were evaluated to test the effect of RAASi use on time to KRT [46]. Over a median of 4.1 years, 217 patients required initiation of KRT. In comparison to non-users, 472 (55%) RAASi users had a risk reduction of 21–37% for KRT with different statistical models. The authors concluded there was a substantial benefit of RAASi in paediatric CKD in delaying dialysis.

Another paediatric landmark study was the ESCAPE trial, which demonstrated that intensified blood pressure control successfully slowed the progression of CKD [4]. In this trial, 385 children with CKD (GFR 15–80 ml/1.73 m<sup>2</sup>/min) were recruited across the European Union. All children received ramipril at a dose of 6 mg per meter square body surface area per day, with additional antihypertensives as indicated to reach the target blood pressure. Children who underwent intensified blood pressure control with a target 24-h mean arterial blood pressure of less than the 50th percentile were less likely to develop 50% decline in GFR or kidney failure (30% vs. 41%, hazard ratio 0.65), compared to the group receiving conventional blood pressure control (50–95th percentile). An initial 50% reduction in protein excretion with ramipril also predicted a protective effect on CKD progression (hazard ratio 0.46). Notably, children with underlying glomerulopathy, a urine protein-to-creatinine ratio > 1.5 mg/mg, baseline GFR < 45 ml/1.73 m<sup>2</sup>/min and a decline of GFR > 3 ml/min per year benefited most from strict blood pressure control. The anti-proteinuric effect of ramipril was noted to wane over time and the protein excretion was similar to baseline values after three years. While the results of this trial support that intensified blood pressure control slows down the progression of CKD in children, it is important to be aware that both treatment and control groups received ACEi and therefore the effect of RAASi on kidney outcomes was not directly assessed. In a post hoc analysis of the ESCAPE trial, ramipril reduced proteinuria by 43.5% and a higher initial proteinuria reduction was associated with a lower risk of CKD progression [47].

In 2012, KDIGO recommended ACEi or ARB to be used in children with CKD in whom anti-hypertensive therapy is indicated, irrespective of proteinuria level [14]. The 2017 AAP Clinical Practice Guidelines for screening and management of high blood pressure in children and adolescents recommends ACEi or ARB as the preferred treatments for children with CKD who are hypertensive and proteinuric [15]. However, these recommendations are based on very limited evidence and there are no specifications from either guidelines under what circumstances RAASi would be indicated or not.

There are specific concerns regarding RAASi use in the paediatric population. While Snauwaert et al. reported favourable side effect profile in a systematic review, there were insufficient safety data in neonates and infants [48]. These young patients are susceptible to volume depletion and develop complications such as acute

kidney injury, hyperkalaemia and hypotension [49]. Profound hypotension is particularly prevalent in premature neonates receiving captopril, presumably due to a significant role of RAAS on blood pressure regulation and reduced drug clearance in this patient population [48, 50]. RAAS also regulates nephron development and there is concern that RAAS blockade during early stages of life may impair kidney maturation [51, 52]. The administration of RAASi to infants should be cautious until they have reached a corrected age of 44 weeks [53]. Besides, RAASi are potentially teratogenic and are contraindicated in young pregnant women [54]. In adolescents of child-bearing age, the use of these agents should be balanced with the risk of pregnancy. Appropriate patient education is essential. Finally, renoprotective is not a licensed indication and there is a limited choice of RAASi that are approved for use in children, especially for those younger than 6 years (Table 1). There is also a lack of long-term safety data of the RAASi on growth and maturation in children [48].

### RAASi in advanced CKD: what are the concerns?

The primary concerns regarding RAASi in advanced CKD are hyperkalaemia and an inadvertent decline in GFR, which would lead to earlier initiation of KRT. The Cardiovascular Comorbidity in Children with CKD (4C) study is an ongoing, multicentre, prospective observational study that enrolls children aged from 6 to 17 years with an estimated GFR (eGFR) of 10–60 ml/1.73 m<sup>2</sup>/min [60]. 298 (42%) and 82 (12%) of the 704 participants received RAASi at baseline and during the follow-up

phase of the study, respectively [17]. Seventy-three (19%) of these 380 children discontinued RAASi without reaching the composite kidney endpoint. The leading reasons to discontinue RAASi were worsening of kidney function (33%), hyperkalaemia (23%) and hypotension (17%). In the adult population, prospective trials showed that only a minority of patients required drug cessation due to a significant fall in kidney function and hyperkalaemia (Table 2) [19, 20].

Traditionally, an increase of less than 30% of the serum creatinine level following drug initiation has been generally expected [61]. However, this figure typically refers to earlier stages of CKD and it is uncertain if this limit is applicable to patients with advanced CKD. For instance, in a patient with baseline serum creatinine level of 300 µmol/L, a 30% increment will correspond to a significant and worrying increase of 100 µmol/L. The clinical significance of an acute change in serum creatinine associated with RAASi is also largely controversial [62, 63]. Schmidt et al. argued that the increase in creatinine following the initiation of RAASi would lead to adverse kidney outcomes in a graduated fashion, even when the increase was far less than 30% [64]. On the other hand, the GFR decline is caused by a fall in the intra-glomerular pressure, which may also be a modifiable factor for CKD progression. In a post hoc analysis of ONTARGET and TRANSCEND trials, a GFR decline of 15% or more at 2 and 8 weeks following drug initiation was observed in 16% and 7% of patients, respectively [62]. While the acute fluctuation in GFR was common, it did not predict subsequent kidney and cardiovascular outcomes. Furthermore, in a systemic review of 12 randomized clinical trials, a strong association was noted between preservation of kidney function and acute increase in serum creatinine

**Table 1** A summary of FDA-approved labeling for renin angiotensin aldosterone system inhibitors in the paediatric population [72]

Class	Drug	Paediatric labelling	Licensed age	Licensed indication (kidney-related)
ACEi	Benazepril	Yes	≥ 6 years	Hypertension
	Captopril	No	-	-
	Enalapril	Yes	≥ 1 month	Hypertension
	Fosinopril	Yes	≥ 6 years	Hypertension
	Lisinopril	Yes	≥ 6 years	Hypertension
	Ramipril	No	-	-
	Quinapril	No	-	-
ARB	Candesartan	Yes	≥ 1 year	Hypertension
	Eprosartan	No	-	-
	Irbesartan	No	-	-
	Losartan	Yes	≥ 6 years	Hypertension
	Olmesartan	Yes	≥ 6 years	Hypertension
	Telmisartan	No	-	-
	Valsartan	Yes	≥ 6 years	Hypertension

**Table 2** Effect of RAASi on kidney outcomes in patients with predominantly non-diabetic, advanced chronic kidney disease

Study/author	Study design	Study population	Age <sup>a</sup>	Number of patients with aCKD	GFR/sCr criteria for aCKD <sup>b</sup>	FU	Comparison	Primary endpoints	RAASi on Outcomes in aCKD	Adverse events
RAASi initiation (RAASi-naïve)										
AASK [34]	RCT	HTN-attributed CKD (N = 653)	18–70	~218	GFR < 40	36 m	Ramipril (N = 436) vs amlodipine (N = 217)	GFR ↓50% KF Death	BENEFIT	N/A
REIN [19]	RCT	Non-diabetic CKD (N = 322)	18–70	107	GFR 11–33	24 m	Ramipril (N = 52) vs placebo (N = 55)	ΔGFR KF	BENEFIT	K higher with ramipril, but never > 0.5 mmol/L Similar between two groups In Ramipril group, treatment terminated due to ↓GFR (N = 1), ↑K (N = 2) and Uncontrolled BP (N = 1) K higher with benazepril, but never > 0.5 mmol/L Similar between two groups In Benazepril group, 6 patients developed ↑K > 6 mmol/L and 2 required treatment cessation. 1 patient stopped due to ↓GFR
Hou et al. [20]	RCT	Non-diabetic CKD (N = 422)	18–70	224	sCr 3.1–5 mg/dL or 274–442 μmol/L	41 m	Benazepril (N = 112) vs Placebo (N = 122)	sCr dou- bled KF/death	BENEFIT	
RAASi users versus non-users (no specification on drug initiation or continuation)										
Hsu et al. [21]	Prospective cohort study	Predialysis CKD Stage 5 with renal anaemia	20–100	28497	sCr > 6 mg/dL or 530 μmol/L	7 m	ACEi/ ARB users (50%) vs Non-users (50%)	Dialysis Death	BENEFIT	↑ hospitalizations related to ↑K by 31%, but not in mortality N/A
HOST [55]	Retrospective cohort study	aCKD or KF on dialysis (N = 1753)	≥ 21	1099	GFR < 30	38 m	ACEi/ ARB users (53%) vs non-users (47%)	Dialysis Death	BENEFIT	↓ dialysis and death by 19%
Oh et al. [56]	Retrospective cohort study	CKD Stage 4–5	≥ 19	2076	GFR < 30	16 m	ACEi/ ARB users (n = 1237) vs non-users (n = 839)	Dialysis	HARMFUL	↑ dialysis by 38%



Table 2 (continued)

Study/author	Study design	Study population	Age <sup>a</sup>	Number of patients with aCKD	GFRe/sCr criteria for aCKD <sup>b</sup>	FU	Comparison	Primary endpoints	RAASi on Outcomes in aCKD	Adverse events
RAASi continuation versus discontinuation (patients already on treatments)										
4C study [17]	Prospective cohort study with Matched-controls	Paediatric CKD Stage 3–5	6–17	69	GFR < 27	14 m	Discontinue ACEi/ARB (N = 50) vs Continue (N = 50)	GFR ↓50% GFR < 10 Dialysis	BENEFIT	Reasons of discontinuation: GFR decline (N = 23, 33%) ↑K (N = 16, 23%) Hypotension (N = 12, 17%) Others (N = 18, 26%) N/A
Pita-fernandez et al. [57]	RCT	CKD Stage 3–5	≥ 50	46	GFR < 60	3 m	↓50% dose (N = 30) vs continue basal dose (N = 16)	ΔGFR	HARMFUL	Reducing ACEi dose led to: ↑GFR from 32.5 to 42.9 ml/1.73 m <sup>2</sup> /min N/A
Ahmed et al. [18]	Retrospective cohort study	CKD Stage 4–5	73 ± 2	52	GFR < 30	12–24 m	Discontinue ACEi/ARB	ΔGFR	HARMFUL	RAASi Discontinuation led to: ↑GFR from 16.38 ± 1 to 26.6 ± 2.2 ml/1.73 m <sup>2</sup> /min ↓ΔGFR decline from - 0.39 ± 0.07 to + 0.48 ± 0.1 ml/1.73 m <sup>2</sup> /min per year N/A
Onigbo et al. [58]	Prospective cohort study	CKD with RAS	75 (6–3–8–7)	26	GFR 24 ± 9	26.4	Discontinue ACEi/ARB	ΔGFR	HARMFUL	5 patients KF, 2 lost to FU In the remaining 19 patients, RAASi discontinuation led to: ↑GFR from 27.8 ± 9.5 to 39.7 ± 14.9 ml/1.73 m <sup>2</sup> /min N/A
STOP-ACEi [59]	RCT	CKD 4–5 on ACEi/ARB/both	≥ 18	410	eGFR < 30	36 m	Continuation vs discontinuation	ΔGFR	On-going (ISRCTN62869767)	
Ku et al.	RCT	CKD 4–5 on ACEi/ARB/both	≥ 18	60	GFR < 25	12 m	Continuation vs discontinuation	Dialysis	On-going (NCT03957161)	

AASK, African American Study of Kidney Disease and Hypertension; ACEi, angiotensin-converting enzyme inhibitor; aCKD, advanced chronic kidney disease; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FU, follow-up; GFR, glomerular filtration rate; HOST, Homocysteine in Kidney and End Stage Renal Disease; K, potassium levels; KF, kidney failure; N/A, not available; RAASi, renin-angiotensin-aldosterone inhibitors; RAS, renal artery stenosis; RCT, randomized controlled trial; REIN, Ramipril Efficacy in Nephrology; STOP-ACEi, Multi-centre Randomized Controlled Trial of ACE inhibitor/ARB withdrawal in Advanced Renal Disease; 4C, The Cardiovascular Comorbidity in Children with Chronic Kidney Disease; ΔGFR, change of GFR

<sup>a</sup>, <sup>b</sup> Inclusion criteria for age and GFR. Mean age and GFR of the study population are presented if the criterion was not specified in the studies

<sup>c</sup> GFR refers to either measured GFR or estimated GFR (ml/1.73 m<sup>2</sup>/min), as specified in the studies

up to 30% after ACEi therapy, although these patients had a milder degree of kidney impairment (serum creatinine > 124  $\mu\text{mol/L}$  or 1.4 mg/dL) [63]. In fact, an initial acute fall in GFR has been shown to predict a slower kidney function decline in the long term [65].

In our experience, the decline in GFR is usually modest and is rarely severe (> 30%). This decline usually occurs a few days after the start or modification of RAASi therapy and therefore close monitoring is warranted. Patients with bilateral renal artery stenosis and CKD patients with atherosclerosis are particularly at risk due to the pre-existing impaired intra-renal perfusion. Although these conditions are uncommon in the paediatric population, one should be extremely careful about using RAASi in young children who are susceptible to intravascular volume depletion. These patients would bear an increased risk of RAASi-related drug toxicity and mortality has also been reported [66].

Under normal circumstances, aldosterone is released in response to the elevation of serum potassium levels which, in turn, promotes urinary excretion of potassium. RAAS blockade reduces aldosterone secretion and action in the face of impaired potassium excretion related to CKD, leading to hyperkalaemia. Although the risk of hyperkalaemia is definite, most patients only present with mild hyperkalaemia which is amendable to nutritional and medical interventions [19, 20, 67]. Clinicians are advised to proactively prevent hyperkalaemia and balance the risk of hyperkalaemia against the potential benefit of RAASi. Besides, inhibition of RAAS reduces kidney net acid excretion in the cortical collecting tubule and can potentially result in metabolic acidosis [68].

In one observational study, up to 50% patients did not tolerate dual therapy with ACEi and ARB [69]. Combination therapy with ACEi and ARB should be avoided since this approach failed to show any added benefit in adult patients and was associated with an increased likelihood of adverse events, including hypotension, syncope and kidney dysfunction [70]. Finally, patients with advanced CKD are susceptible to acute kidney injury. The risk is particularly high in the presence of concomitant medication, such as diuretics.

### **RAASi in adult advanced CKD: should it be started?**

Although the available evidence supports the use of RAASi in early stages of CKD, there are very few studies addressing their efficacy in patients with a GFR less than 30 ml/1.73  $\text{m}^2/\text{min}$  [19, 20, 34]. Given the concerns of hyperkalaemia and worsening of kidney function, the clinical questions are whether the benefits would extend to advanced CKD. A summary of currently available data on kidney outcomes and adverse events is presented in Table 2.

In a post hoc analysis of the REIN trial, the benefit of ACEi in patients with advanced CKD was evaluated by comparing the change in GFR and the incidence of stage 5 CKD (CKD 5) in three different ranges of baseline kidney function [19]. In the group of lowest basal GFR (11 to 33 ml/min/1.73  $\text{m}^2$ ), ramipril reduced GFR decline by 22% and the CKD 5 incidence by 33%. Of the 52 patients in the lowest GFR group who received ramipril, only one had worsening of kidney function and two developed hyperkalaemia that required drug cessation. The adverse events for both treatment arms were also comparable across the three groups.

In one Chinese study, Hou et al. evaluated 422 non-diabetic CKD patients aged 18–70 years by assigning them into two groups according to serum creatinine levels (Group 1, 1.5 to 3 mg/dL (133 to 265  $\mu\text{mol/L}$ ); Group 2, 3.1 to 5 mg/dL (74 to 442  $\mu\text{mol/L}$ )) [20]. All patients initially received benazepril at 10 mg/day and increased to 20 mg/day if kidney function tolerated. Ninety-four patients who developed marked alteration in kidney function and severe hyperkalaemia were excluded from the study. After a 3-week wash-out period, the remaining 224 patients in Group 2 (GFR  $26 \pm 5$  ml/1.73  $\text{m}^2/\text{min}$ ) were randomly assigned to benazepril (10 mg twice daily) or placebo, alongside conventional antihypertensives. The primary outcome measure was the time to first composite kidney end point of a doubled creatinine level, CKD 5 or death. Over a mean follow-up of 3.4 years, fewer patients receiving benazepril reached the primary endpoint (41% versus 60%) with a 43% risk reduction, which was not attributable to blood pressure control. It was also associated with a 23% reduction in the rate of GFR decline (6.8 versus 8.8 ml/1.73  $\text{m}^2/\text{min}$  per year). The incidence of adverse events among the two arms was similar. While six patients developed hyperkalaemia and one developed acute decline of GFR out of the 112 patients in the benazepril group, only two patients were eventually withdrawn from the study due to persistent hyperkalaemia. It is, however, worth noting that this study was at risk of selection bias because a large proportion of patients did not tolerate ACEi and were excluded before study commencement [20].

In a controversies report presented by NKF-KDOQI, a careful review of available clinical data concluded that the decline in GFR and rise in serum potassium levels related to RAAS blockade in advanced CKD did not lead to adverse kidney outcomes [16]. ACEi or ARB monotherapy initiation appeared to be effective in slowing down the progression of CKD.

### **RAASi in adult advanced CKD: should it be stopped?**

The aforementioned trials focused on the initiation of RAASi in advanced CKD. However, there are even fewer data in

patients who are already receiving RAASi and have now reached CKD stage 4 or 5. To date, there are only a few studies addressing whether or not RAASi should be discontinued (or continued) in this setting [18, 57, 58].

In a small open randomized control trial, Pita-Fernandez et al. evaluated patients with  $\text{GFR} < 60 \text{ ml}/1.73 \text{ m}^2/\text{min}$  and heart failure treated with RAASi during hospitalization [57]. Patients were assigned to a 50% reduction of RAASi dose in the intervention group or standard basal dose in the control group. Following 1 to 3 months after discharge, the intervention group had an improved kidney function, with  $\text{GFR}$  increasing from 33 to 43  $\text{ml}/1.73 \text{ m}^2/\text{min}$ . The findings from this study are limited by very short-term patient outcomes. In an observational study, Ahmed et al. followed 52 elderly patients (mean age  $73.3 \pm 1.8$ ) with a baseline  $\text{GFR}$  of  $16.38 \pm 1 \text{ ml}/1.73 \text{ m}^2/\text{min}$  in whom ACEi or ARB were stopped [18]. After drug discontinuation for 12 months, 62% patients demonstrated  $\text{GFR}$  improvement of more than 25% and the overall  $\text{eGFR}$  was shown to be increased to  $26.6 \pm 2.2 \text{ ml}/1.73 \text{ m}^2/\text{min}$  from baseline. Hansen et al. reported a similar improvement of kidney function shortly after ACEi discontinuation in a group of patients with diabetic nephropathy ( $n = 42$ , mean age  $40 \pm 7$  years) [71]. The Mayo clinic group reported worsening of kidney function with RAASi in older CKD patients with renal artery stenosis [58]. These patients were generally older with different comorbidities, such as diabetes and renovascular disease, and are therefore at higher risk of vascular disease and impaired kidney perfusion. Withdrawal of ACEi or ARB may revert this phenomenon and explain the improvement observed in kidney function. It may however not be appropriate to extrapolate these findings to the paediatric population who have different pathophysiology of their primary kidney disease.

However, in a number of observational studies, where there was no specification regarding drug initiation or continuation, the use of RAASi appeared to have beneficial effect on kidney outcomes (Table 2) [21, 55]. Hsu et al. conducted a large-scale population-based longitudinal cohort study to investigate the role of RAASi in 28497 patients (20–100 years old) with pre-dialysis CKD 5 (serum creatinine  $> 6 \text{ mg}/\text{dL}$  or  $530 \mu\text{mol}/\text{L}$ ), hypertension and renal anaemia [21]. Although most patients progressed to long-term dialysis (71%) or died (20%) over a short period of 7 months, the use of ACEi/ARB amongst patients, compared to non-users, was associated with a small but significantly reduced risk for long-term dialysis and death by 6% (hazard ratio 0.94, 95% CI 0.92–0.97). This suggests the benefit of RAASi extends even to very advanced CKD and at least does not hasten the start of KRT.

To summarize, there is currently insufficient evidence to support continuation or cessation of RAASi in this clinical context. It is uncertain whether the outcomes will be different in subjects who are younger and at lower risk of vascular disease, as in those RAASi-naïve patients presented above

(predominantly less than 70 years) who attained promising results with drug initiation compared to those who are older and with more vascular disease. A multicentre, open-label, randomized controlled trial, the STOP-ACEi trial (trial registration number: ISRCTN62869767), is underway in the UK to examine the effect on progression of CKD following drug continuation versus discontinuation in 410 patients with stage 4 or 5 progressive CKD receiving ACEi or ARB [59]. The follow-up period is 3 years and the primary outcome is the difference in kidney function between the two groups. A similar randomized controlled trial is being conducted in the USA and is estimated to be completed by September 2020 (trial identifier: NCT03957161). Results of these trials will hopefully shed light on this controversial area in CKD management.

### RAASi in children with advanced CKD: what are the data?

To our knowledge, the only study that has specifically assessed the effect of RAASi (ACEi or ARB) continuation or withdrawal in advanced paediatric CKD is the recent 4C study [17]. The composite kidney endpoint in this study was defined as a sustained 50%  $\text{eGFR}$  decline or  $\text{eGFR} < 10 \text{ ml}/1.73 \text{ m}^2/\text{min}$  or KRT initiation. Sixty-nine children aged  $13.7 \pm 3.2$  years who discontinued RAASi ( $\text{eGFR} 27 \pm 12 \text{ ml}/1.73 \text{ m}^2/\text{min}$  prior to drug termination) were included. Congenital anomalies of kidney and urinary tract were the predominant primary kidney disease. The reasons for drug cessation were due to hyperkalaemia, symptomatic hypotension and raised creatinine. Upon drug withdrawal, blood pressure and albuminuria were increased by 2.8 mmHg and 115%, respectively, while potassium was only minimally decreased (0.17 meq/L).

More than a twofold decline in  $\text{eGFR}$  was reported following the discontinuation of RAASi ( $-1.5$  to  $-3.9 \text{ ml}/1.73 \text{ m}^2/\text{min}$  per year,  $p = 0.005$ ), over a median of 1.9 years and 1.2 years' follow-up before and after drug withdrawal, respectively. In order to confirm this change in  $\text{eGFR}$  to be independent of natural disease progression, a group of control patients who continued RAASi was selected for comparison by means of propensity score matching. The accelerated rate of decline in  $\text{eGFR}$  seen in the study cohort was not observed in the well-matched control cohort ( $-1.8$  to  $-1.2 \text{ ml}/1.73 \text{ m}^2/\text{min}$  per year,  $p = 0.30$ ). Of note, rebound albuminuria was significant (115%) and a more marked increase in urinary protein excretion was associated with worse subsequent kidney outcomes. Although the study is limited by its observational nature and selection bias, these findings demonstrated a strong anti-proteinuric effect of RAASi even in advanced paediatric CKD and that their withdrawal could accelerate the decline of kidney function.



While the continuation of RAASi appears to be promising in paediatric advanced CKD, randomized trials and separate studies on drug initiation in this group of patients are very much required to provide further guidance.

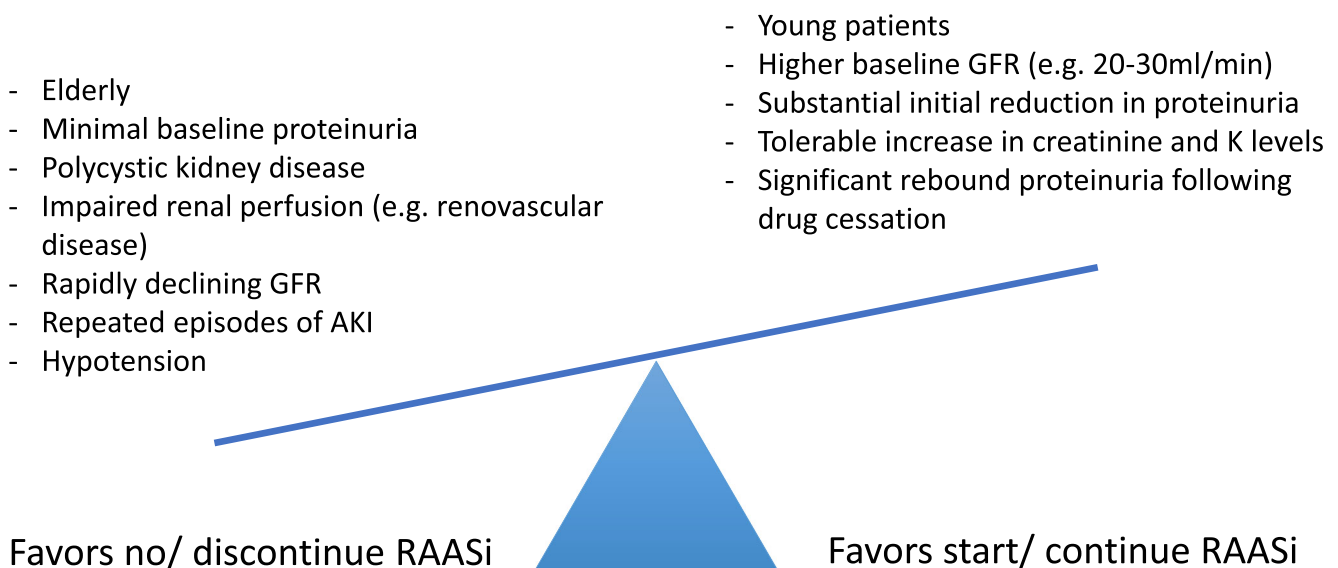
### Practical approach

The evidence related to the use of RAASi in children is much less substantial than in the adult population and this is particularly true in advanced CKD (GFR  $\leq 30$  ml/1.73 m<sup>2</sup>/min). There are many outstanding questions regarding the optimal approach and careful consideration is required when trying to extrapolate adult data to children. Moreover, different patients respond differently to RAASi and the potential benefits of reducing CKD progression have to be balanced against potential complications. Therefore, the decision on the use of RAASi in patients with advanced CKD should be individualized. Different factors including patient characteristics, treatment response such as changes in proteinuria and side effect profiles should be considered. These factors are presented in Fig. 1. Based on our clinical experience and limited existing data, we suggest an approach to RAASi therapy in paediatric CKD. A summary of these suggestions is presented in Table 3.

**Early CKD (stage I to III)** In children, there is more robust evidence to support strict blood pressure control (24-h mean arterial pressure less than 50 to 75th percentiles) than reduction of proteinuria in slowing kidney progression. We suggest early use of RAASi for renoprotection in all children with CKD I to III with high blood pressure ( $\geq 90$ th centile) and/or significant proteinuria/albuminuria (urinary protein-to-creatinine ratio  $\geq 0.5$  mg/mg or 50 mg/mmol; albumin-to-creatinine ratio  $\geq 0.3$  mg/mg or 30 mg/mmol). The administration of RAASi to young infants should be cautious, and contraindications include neonates, renal artery stenosis, pregnancy, hyperkalaemia despite treatment, history of angioedema and allergic reaction related to RAASi [53, 61]. Monotherapy with ACEi is the preferred option to ARB since more paediatric data are available on efficacy and safety of ACEi. It is important to monitor serum creatinine and potassium levels 3 to 5 days after drug initiation or adjustment. RAASi should be stopped in case of GFR decline  $> 30\%$ , persistent hyperkalaemia or hypotension. We also suggest RAASi to be temporarily withheld in acute situations with intravascular volume depletion related to dehydration, gastroenteritis, diuretic use or nephrotic state.

**Advanced CKD (stage IV and V, without KRT)** For children progressing to advanced stages of CKD, the limited paediatric data support continuation of RAASi to

## Factors to consider for use of RAASi in advanced CKD



**Fig. 1** Factors to consider for RAASi use in advanced chronic kidney disease. The decision on RAASi use in advanced CKD should be individualized and based on factors including baseline patient characteristics, treatment response and development of complications.

AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; K, potassium; RAASi, renin-angiotensin-aldosterone-system inhibitors

attenuate CKD progression. Therapy should be individualized, with careful monitoring to limit potential complications. Of note, worsening of kidney function can be difficult to interpret as it may simply reflect the natural course of the disease. We do, however, recommend cessation of RAASi if the patient develops hypotension, episodes of acute kidney injury or rapidly declining kidney function progressing to CKD 5. Hyperkalaemia should be actively prevented and managed before withdrawal of RAASi. Potential strategies include dietary restriction, acid-base correction, modification of concomitant medications associated with hyperkalaemia, judicious use of diuretics and potassium-binders. In the future, the availability of newer generation potassium-binding medications, such as patiromer, may potentially allow extended RAAS blockade in patients with advanced CKD.

There is currently no paediatric data to guide our decisions in RAASi-naïve children with advanced CKD. Judging from the adult data, it is reasonable to attempt RAAS blockade in

children without aforementioned contraindications. In those without significant proteinuria, we would suggest considering alternative antihypertensives for blood pressure control. Close monitoring of kidney function is mandatory following drug initiation or adjustment, and we suggest adopting a lower threshold to discontinue these agents in this vulnerable population. In line with the NKF-KDOQI controversies report, a GFR decline of > 20%, rather than 30%, can be adopted in this context [16]. If patients develop hypotension, uncontrolled hyperkalaemia, significant uraemia or GFR persistently falls more than 20% with dose adjustment, RAASi therapy should be terminated.

## Uncertainties and future research directions

The optimal use of RAASi in paediatric CKD remains controversial. Prospective investigations in children are very much needed to answer the outstanding questions related to the use of RAASi:

**Table 3** Summary of use of RAASi in paediatric chronic kidney disease

Summary of use of RAASi in paediatric CKD	
Indications	High blood pressure ( $\geq$ 90th centile) and/or Significant proteinuria/albuminuria - urinary protein-to-creatinine ratio $\geq$ 0.5 mg/mg or 50 mg/mmol - albumin-to-creatinine ratio $\geq$ 0.3 mg/mg or 30 mg/mmol
Suggested use specific to CKD stage	CKD I to III: early use and continued use CKD IV & V: - patients on RAASi: continue treatments if tolerate - patients not on RAASi: judicious initiation with close monitoring
Drug of choice	Monotherapy with ACEi ARB if ACEi not tolerated Avoid combination therapy
Intervention goal	24-h mean arterial pressure less than 50 to 75th centile Reduction of proteinuria/ albuminuria
Significant side effects	Decline in GFR, hyperkalaemia, metabolic acidosis, hypotension, angioedema, cough, teratogenicity, impair nephron development
Monitoring	Blood pressure, kidney function, potassium level 3 to 5 days following drug initiation or dose adjustment
Situations where dose reduction or drug cessation is required	GFR decline - CKD I to III: > 30%; CKD IV & V: > 20% Uncontrolled hyperkalaemia despite treatment Hypotension
Conditions in which RAASi are contraindicated or to be used with caution	Contraindicated in neonates, bilateral renal artery stenosis, pregnancy, hyperkalaemia despite treatment, history of angioedema and allergic reaction related to RAASi Cautious use in young infants

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; GFR, glomerular filtration rate; RAASi, renin-angiotensin-aldosterone inhibitors

1. To address the efficacy of RAAS blockade in delaying kidney progression in children with CKD, especially for those who are non-proteinuric
2. To identify the optimal timing and dosing of RAASi in children to attain the maximal effect in delaying disease progression
3. High-quality double-blinded randomized controlled trials testing RAASi initiation and its continuation versus cessation in advanced paediatric CKD
4. To identify the predictive factors of good response to RAASi in children with CKD
5. To develop and validate new potassium-binding agents in children to facilitate use of RAASi in those with hyperkalaemia
6. To investigate the relationship between kidney function changes from the use of RAASi and the long-term kidney outcome in children with CKD.

## Conclusion

RAAS blockade is an effective and important therapy in attenuating CKD progression by controlling blood pressure and reducing proteinuria. The evidence supporting its use in children is much less substantial than adults and its role in advanced CKD is also controversial. Despite a conventional concern that RAASi may worsen kidney function and potentially hasten the start of dialysis, recent findings suggest that the initiation or continuation ACEi or ARB monotherapy in paediatric and adult advanced CKD may improve kidney outcomes. Therefore, RAASi should be considered with close monitoring of blood pressure, serum creatinine and potassium levels. The degree of initial proteinuria reduction and rebound albuminuria upon drug cessation are both important predictors of worsening treatment outcomes. The use of RAASi should be individualized and based on factors including baseline patient characteristics, treatment response and side effect profiles. High-quality prospective randomized trials are very much needed to answer outstanding research questions and identify the optimal strategy for the use of RAASi in children.

## Key summary points

1. Although the evidence is much less substantial than adults, RAAS blockade is recommended in children with CKD with hypertension and/or proteinuria to delay CKD progression.

2. Monotherapy with ACEi or ARB is preferred to combination therapy, which is associated with higher risk of adverse events.
3. The degree of initial proteinuria reduction and rebound proteinuria after drug cessation are important predictors for treatment outcomes.
4. While the role of RAASi in advanced CKD is controversial, current data support its use with close monitoring of kidney function, blood pressure and potassium level.
5. Individualized approach is recommended, and one should consider factors including baseline patient characteristics, treatment response and side effect profiles.

## Multiple-choice questions (answers are provided following the reference list)

1. Which of the following is not predictive for kidney disease progression in both glomerular and non-glomerular CKD?
  - A. High blood pressure
  - B. Significant proteinuria
  - C. Age
  - D. Hypoalbuminaemia
2. Which of the following is not preferred in the management of paediatric CKD?
  - A. ACEi monotherapy
  - B. ACEi and ARB combination therapy
  - C. Normal protein intake
  - D. Attaining a normal vitamin D level
3. Which of the following predicts good kidney outcomes after RAAS blockade?
  - A. Significant initial reduction in proteinuria
  - B. Acute changes of GFR
  - C. Hyperkalaemia
  - D. Hypotension
4. What factors should be considered when one decides on the use of RAASi in advanced CKD?
  - A. Baseline patient characteristics e.g. underlying renal diagnosis
  - B. Treatment response, e.g. proteinuria reduction
  - C. Side effect profiles, e.g. hyperkalaemia
  - D. All of the above

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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#### Answers

1. C; 2. B; 3. A; 4.D

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