Albuminuria: more than a renal risk marker?

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Early proteinuria lowering by ACE inhibition predicts renal survival in children with chronic kidney disease

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Submitted

Abstract

Background

Proteinuria predicts progression of renal failure in chronic kidney disease (CKD). While pharmacotherapeutic proteinuria lowering was found nephroprotective in adults, the predictive value of early drug-induced proteinuria reduction for long-term renal survival in pediatric CKD is unknown. We analysed data from the ESCAPE Trial for a potential association between the initial antiproteinuric effect of standardized ACE inhibition and subsequent renal disease progression in children with CKD.

Methods

280 eligible children with CKD stage II-IV (mean age 11.7 years, mean eGFR 43 ml/min/1.73m^2, 71% congenital renal malformations) received a fixed dose of ramipril (6 mg/m^2/day) and were subsequently randomized to conventional or intensified blood pressure control. Initial proteinuria reduction was assessed from baseline to first measurement on ramipril (at 2.5±1.3 months). Multivariable Cox modelling was used to estimate the association between initial proteinuria reduction and the risk of reaching a renal end point (50% eGFR decline or end-stage renal disease), which occurred in 80 patients during 5 years observation.

Results

Ramipril therapy lowered proteinuria by a mean of 43.5% (95% CI 36.3-49.9%). Relative to proteinuria reduction <30%, 30-60% reduction resulted in a HR of 0.70 (95% CI 0.40-1.22) and >60% reduction in HR of 0.42 (0.22-0.79). This association was independent of age, gender, CKD diagnosis, baseline eGFR, baseline proteinuria, initial blood pressure, and concomitant blood pressure reduction.

Conclusions

The early antiproteinuric effect of ACE inhibition is associated with long-term preservation of renal function in children with CKD. Proteinuria lowering should be considered an important target in the management of pediatric CKD.

Introduction

In the general adult population, increased levels of urinary albumin are present in approximately 7% of individuals and are associated with a higher risk of renal and cardiovascular disease.[1-3] We recently showed that in the general toddler population, increased albuminuria is present in approximately 7% of the children, in analogy to the adult population.[4] Also in children with chronic kidney disease, higher proteinuria levels are associated with an increased risk of cardiovascular and renal disease progression.[5-7]

Antagonists of the renin-angiotensin system (RAS) efficiently lower proteinuria. Studies with angiotensin converting enzyme (ACE) inhibitors and angiotensin II type I receptor blockers (ARBs) in adults with chronic kidney disease (CKD) due to glomerular disorders have shown that the larger the reduction in albuminuria induced by these agents during the first months of treatment, the larger the reduction in renal and cardiovascular risk during subsequent follow-up.[8-10] Also in children, in whom CKD is most often caused by a congenital nephron deficit due to kidney maldevelopment, ACE inhibitors and ARBs have been shown to reduce albuminuria.[11,12] However, the effect of proteinuria lowering on long-term renal survival has not been established in the pediatric CKD population.

Here, we made use of the largest pharmacological nephroprotection trial performed to date in children to investigate a possible quantitative association between the initial antiproteinuric effect of ACE inhibition and subsequent CKD progression. We also determined whether residual proteinuria (i.e. the proteinuria level during ACE inhibition) is associated with a higher renal risk, arguing that positive findings for these two associations would strengthen the hypothesis that albuminuria is an important modifiable determinant of renal disease progression also in pediatric CKD.

Materials and methods

Study design and patients

For this study we used data from the Effect of Strict Blood Pressure Control and ACE inhibition on the Progression of CRF in Pediatric Patients (ESCAPE) trial. Rationale, study design and results of this study have been published elsewhere.[11] In short, the ESCAPE trial was an investigator-initiated, randomized, controlled trial investigating whether intensified blood pressure control (<50th percentile for age) would delay the progression of renal disease in children with CKD who were receiving a fixed dose of ACE inhibition. In this study, 385 children with CKD (aged 3-18 years, eGFR of 15-80 ml/min/1.73m^2 body-surface area), whose 24-hour mean arterial pressure (MAP) was either elevated (>95th percentile) or controlled with antihypertensive medication, were included. Exclusion criteria were renal-artery stenosis, a history of kidney transplantation, an unstable clinical condition, treatment with immunosuppressive agents (including glucocorticoids) and major primary cardiac, hepatic or gastrointestinal disorders. The study protocol was

approved by the central ethics committee of the medical faculty of the University of Heidelberg and by the local institution review board of each site. Parents of all children provided written informed consent.

At screening, eligible patients underwent an ambulatory blood pressure monitoring. Eligible patients started a run-in period of six months, during which they attended clinic visits every two months. At least two months before the end of the run-in period, any treatment with an inhibitor of the renin-angiotensin system was discontinued. After the run-in period, all children received the same dose of the ACE inhibitor ramipril (6mg/m^2 body-surface area per day, equivalent to the maximum approved dose of 10mg/day in adults). The dosage was gradually uptitrated over the course of two months. Subsequently, patients were stratified to either a conventional blood-pressure target (50^{th}-95^{th} percentile of 24-hour mean arterial pressure (MAP)) or an intensified blood-pressure target (<50^{th} percentile of 24-hour MAP). To reach the blood-pressure target, any antihypertensive agent could be prescribed except for other inhibitors of the renin-angiotensin system.

During the 5-year study period, blood-pressure, proteinuria and eGFR were assessed every two months, and 24-hour ambulatory blood pressure measurements were performed every six months. eGFR was assessed by means of the Schwartz formula, with the use of measurements of serum creatinine and height and a k constant of 0.55.[13] ACE I/D genotype was measured in blood collected during the run-in period, using the method that has been extensively described previously.[14]

Proteinuria measurements

Urine collections (where possible a 24-hour urine collection), were performed every two months. If collection of a 24-hour urine sample was not possible due to young age or enuresis, a random urine sample was collected during the clinical visit. At the baseline visit, a random sample instead of a 24-hour urine sample was collected in 43 individuals. Total protein and creatinine concentration were measured in the samples with the use of Coomassie blue staining and modified Jaffe reaction, respectively. Proteinuria was measured as the urinary protein-to-creatinine ratio (PCR) in mg/mg. Throughout the article we use the term proteinuria.

The initial proteinuria reduction was defined as the natural logarithm of the reduction in proteinuria from baseline measurement to the first proteinuria measurement after attainment of the full dose of ramipril, calculated as follows: ln(first measurement after full dose of ramipril / baseline measurement). We defined residual proteinuria as the level of proteinuria present during treatment with 6mg/m^2 ramipril. Proteinuria exposure over time was calculated as the area under the curve (AUC) of all proteinuria measurements from baseline until either reaching the end point or end of study. Median number of proteinuria measurements to calculate the AUC was 15 (25^{th}-75^{th} percentile 8 to 24 measurements).

In this study, we included 280 children of the initial ESCAPE study population. Children with a missing proteinuria level at baseline (n=43), no follow-up measurement within 6 months after starting ramipril (n=29), a missing ambulatory blood pressure measurement at baseline (n=3) or after 6 months (n=21), or who were lost to follow up (n=9) were excluded.

Outcomes

The pre-specified primary efficacy measure of ESCAPE study was time from attainment of the full dose of ramipril until the first event of the composite end point, which was defined as a sustained 50% reduction of eGFR or progression to end-stage renal disease (eGFR <10 ml/min/1.73m^2 or start of renal replacement therapy). In this study, the same composite end point was used.

Statistical analyses

The cumulative event rate for the composite renal end point in subgroups of proteinuria reduction was assessed using the Kaplan-Meier procedure. Proteinuria reduction was stratified into three subgroups; >60% reduction, 30-60% reduction and <30% reduction. These groups were chosen post hoc, in order to provide easily understandable thresholds, whereas the number of patients within the groups remains similar. Differences in population characteristics between three groups of proteinuria reduction were tested with Chi^2 test, ANOVA or Spearman rank correlation test, where appropriate. A Cox proportional hazards model was used to estimate the renal risk difference among the three subgroups of proteinuria reduction. The Cox model was adjusted for the following covariates: age, gender, CKD diagnosis (glomerulopathy, Congenital Anomalies of the Kidney and Urinary Tract (CAKUT), or other diagnosis), baseline eGFR, baseline proteinuria, baseline blood pressure, and blood pressure reduction from baseline to month 6. Multivariable linear regression was performed to assess which baseline variables were associated with proteinuria reduction. In order to ascertain that the effect of proteinuria reduction on the composite renal endpoint was not modified by either baseline proteinuria or blood pressure reduction, we performed two separate multivariable Cox models in which an interaction term between either baseline proteinuria and proteinuria reduction or blood pressure reduction and proteinuria reduction was included.

The association between residual proteinuria and the renal end point was estimated using the Kaplan-Meier procedure, with residual proteinuria categorized into three subgroups; <0.2 mg/mg, 0.2 - 1.0 mg/mg and >1.0 mg/mg. In order to assess the effect of residual proteinuria on the renal end point, a multivariable Cox proportional hazards model with the three group of residual proteinuria was performed, adjusted for the covariates mentioned earlier. As proteinuria may change over time during prolonged exposure to RAAS blockade, we also assessed the association between subgroups of exposure to proteinuria over time and renal risk using both the Kaplan-Meier analysis and

a multivariable Cox proportional hazards model, adjusted for the covariates mentioned above.[15] Exposure to proteinuria was stratified into tertiles.

In order to assess whether the findings of the association between proteinuria reduction and the composite renal endpoint were robust and not dependent of the selection of the thresholds, we analysed the association between proteinuria reduction as a continuous measure and the composite renal endpoint in a sensitivity analysis. Sensitivity of the proteinuria assay in the low-normal proteinuria range is low and measurements below the limit of detection may introduce misclassifications in proteinuria reduction. Therefore, a sensitivity analysis was performed, in which children with a baseline proteinuria <0.1 mg/mg were excluded. In this sensitivity analysis we used a Cox proportional hazards model with initial proteinuria reduction and the same covariates as described earlier. In order to ascertain that the results are not driven by the individuals with the highest baseline proteinuria, we performed a sensitivity analysis in which patients with a baseline proteinuria >90th percentile were excluded. A final sensitivity analysis was performed, in which children who started additional antihypertensive medication to reach the blood pressure target were excluded to avoid interference of other antihypertensive therapy on the association between proteinuria change and renal outcome. In this analysis, proteinuria reduction was analysed as a continuous measure as we did not have enough power to use three proteinuria reduction groups.

Data are expressed as either mean and standard deviation or median and interquartile range for continuous variables and percentages and count for categorical variables. All analyses were performed using STATA version 14 (Statacorp LP).

Results

Mean patient age was 11.7 years (standard deviation (SD) 3.9) and 60% were male. The mean time interval between baseline proteinuria measurement and first measurement on full-dose ramipril was 2.5 months (SD 1.3 months). The characteristics of the population included in the current study were similar to those of the overall ESCAPE trial population (Table 1).

Initial proteinuria reduction within the study population

The mean initial proteinuria change was –40.2% (95% confidence interval [CI] -49.1 to -29.6%) in the conventional blood pressure control group and -46.7% (95% CI -55.5% to -36.2%) in the intensified blood pressure control group (p=0.35 for the between group difference) (Figure 1). Due to the similar initial proteinuria change in the two study arms the groups were combined for further analysis. Initial proteinuria change was similar between the different renal diagnoses, with a mean initial proteinuria change of -48.7% (95% CI -61.1% to -32.1%) in the children with glomerulopathies, -39.9% (95% CI -47.7% to -30.9%) in the children with CAKUT and -53.6% (95% CI -68.3% to -32.2%) in the children

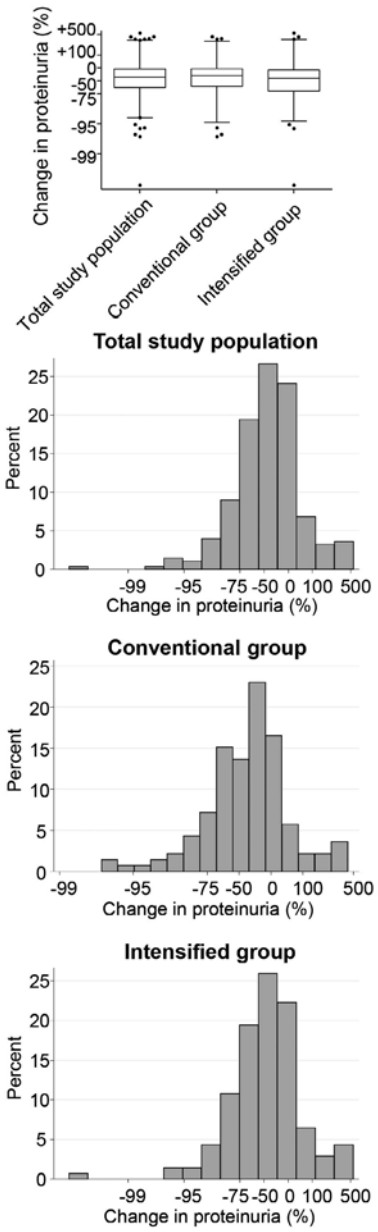

Figure 1. Distribution of initial proteinuria change in the total study population. Left panel: box-whisker plots of proteinuria change. Whiskers represent 2.5th-97.5th percentile. Right panel: distribution of intraindividual proteinuria change in total study population, conventional blood pressure control group and intensified blood pressure control group.

with other diagnoses (p=0.26). In the total study population, initial proteinuria was reduced by a mean of 43.5%, with a large inter-individual variation (range -99.8% to +547%; Figure 1). An initial proteinuria reduction by more than 60% was observed in 33%, 30 to 60% reduction in 27% and less than 30% reduction in 40% of the patients. Baseline proteinuria was lower in the group with the least proteinuria reduction, and age was different between the three groups of proteinuria reduction. Other population characteristics were similar among the groups (Table 1). By multivariable linear regression analysis, higher proteinuria (β=0.14 per 1 mg/mg; p<0.001) was independently associated with a larger proteinuria reduction, whereas sex, age, treatment assignment, primary renal diagnosis, baseline eGFR, baseline blood pressure, baseline serum urea and ACE I/D genotype were not independently associated with proteinuria lowering (Supplementary table 1).

Initial proteinuria reduction as a predictor of renal outcomes

Larger initial proteinuria reduction was associated with a larger risk reduction for the primary renal end point (Figure 2A). Taking the differences in baseline characteristics into account in a multivariable Cox model, the subgroup with the largest initial proteinuria reduction (>60%) remained at lowest risk (hazard ratio 0.42 (95% CI 0.22 – 0.79) relative to the patients with <30% reduction. The intermediate proteinuria responders (30-60% reduction) showed an insignificant relative risk reduction (hazard ratio 0.70 (95% CI 0.40 – 1.22) (Figure 2A and Table 2). The effect of proteinuria reduction was not modified by either baseline proteinuria or blood pressure reduction as evidenced by insignificant interaction terms represented in Supplementary table 2 and 3. Results were similar when proteinuria reduction was analysed as a continuous variable (Supplementary table 4).

A sensitivity analysis that excluded 26 individuals with baseline proteinuria below 0.1 mg/mg showed a similar pattern in that patients with a larger initial proteinuria reduction had a lower risk of the composite end point with HR's of 0.43 (95% CI 0.23 to 0.83) for the >60% reduction group and 0.75 (95% CI 0.43 to 1.33) for the 30-60% reduction group compared to the <30% reduction group (Supplementary table 5). The same results were seen when patients with a baseline proteinuria >90th percentile were excluded (Supplementary table 6). Results were also confirmed when 138 patients with additional antihypertensive medication during the study were excluded, with larger initial proteinuria reduction remaining associated with a lower renal risk, with a hazard ratio of 0.41 (95% CI 0.22 to 0.77) (Supplementary table 7).

Residual proteinuria as a predictor of renal outcomes

After attaining the full dose of ramipril, the median residual proteinuria was 0.44 mg/mg (25th-75th percentile 0.14 – 1.04 mg/mg). Residual proteinuria was <0.2 mg/mg in 32%, between 0.2 and 1.0 mg/mg in 42% and >1.0 mg/mg in 26% of patients. Kaplan-Meier analysis and Cox modelling revealed that children with a higher residual proteinuria level carry a higher risk of reaching the composite renal end point (Figure 2B), with HR's calculated with the multivariable Cox model of 3.91 (95% confidence interval (CI) 1.64 – 9.33) for the residual proteinuria >2.0 mg/mg group and 1.63 (95% CI 0.70 – 3.81) for the residual proteinuria 0.2 – 2.0 mg/mg group compared to the residual proteinuria <0.2 mg/mg group

The median exposure to proteinuria over time during the entire study period as calculated with the AUC of all proteinuria measurements from baseline until either reaching the end point or end of study was 0.1 (25th-75th percentile 0.1 – 0.2) mg/mg in the group with the lowest exposure, 0.6 (0.4 – 0.9) mg/mg in the medium proteinuria exposure group, and 2.1 (1.5 – 3.2) mg/mg in the highest exposure group. Higher proteinuria exposure over time was an independent predictor for reaching the renal end point (Figure 2C; Supplementary table 8).

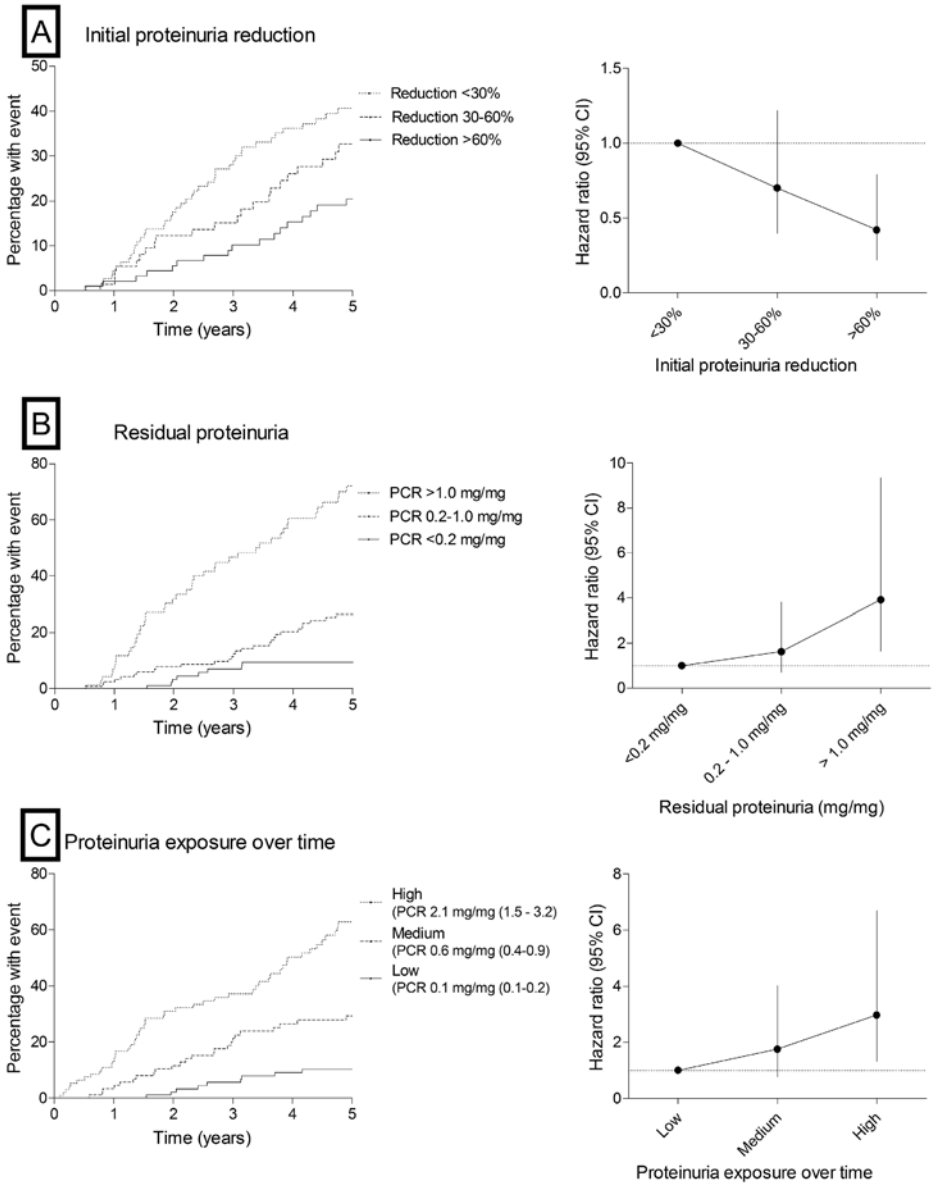

Figure 2. Risk on composite renal end point with Kaplan Meier analysis and hazard ratios calculated with cox proportional hazard model[1] for initial proteinuria reduction (A), residual proteinuria (B) and exposure to proteinuria over time (C).

[1]*Initial proteinuria reduction adjusted for:* age, gender, CKD diagnosis, baseline ambulatory MAP, baseline eGFR, baseline proteinuria, change in ambulatory MAP

Residual proteinuria adjusted for: age, gender, CKD diagnosis, baseline ambulatory MAP, baseline eGFR, change in ambulatory MAP

Long term exposure to proteinuria adjusted for: age, gender, CKD diagnosis, baseline ambulatory MAP, baseline eGFR, change in ambulatory MAP

Table 1. Population characteristics (based on proteinuria reduction divided into three categories)

	Total ESCAPE population (n=385)	**Population selected for current analysis (n=280)**				
		Total study population (n=280)	*Proteinuria reduction >60% (n=92)*	*Proteinuria reduction 30-60% (n=76)*	*Proteinuria reduction <30% (n=112)*	*P-value*[1]
Male sex, n	230 (60)	167 (60)	54 (59)	49 (64)	64 (57)	0.588
Age, years	11.6 (4.0)	11.7 (3.9)	10.9 (3.8)	12.4 (3.9)	11.5 (3.8)	0.042
Conventional treatment arm, n	195 (51)	140 (50)	41 (45)	40 (53)	59 (53)	0.445
Renal diagnosis						0.437
- Glomerulopathies, n	51 (13)	36 (13)	14 (15)	10 (13)	12 (11)	
- CAKUT, n	267 (70)	199 (71)	60 (65)	58 (76)	81 (72)	
- Other, n	66 (17)	45 (16)	18 (20)	8 (11)	19 (17)	
ACE polymorphism						0.289
- II genotype, n	70 (20)	52 (19)	23 (25)	12 (16)	17 (16)	
- ID genotype, n	184 (59)	139 (52)	44 (48)	43 (58)	52 (55)	
- DD genotype, n	103 (29)	79 (29)	25 (27)	19 (26)	35 (34)	
Reached end point, n	133 (36)	80 (29)	17 (18)	22 (29)	41 (37)	0.267
Baseline eGFR, ml/min/1.73m2	44 (29 – 59)	46 (33–59)	50 (37–61)	43 (28–55)	45 (31–60)	0.171
Baseline urinary protein/ creatinine ratio, mg/mg	0.9 (0.3 – 2.0)	0.8 (0.3 – 1.8)	1.0 (0.4 – 2.3)	1.0 (0.4 – 1.8)	0.6 (0.2 – 1.5)	0.001
Baseline serum urea, mmol/L	13.1 (6.5)	12.8 (6.1)	12.1 (5.7)	13.5 (6.1)	13.0 (6.5)	0.443
Baseline ambulatory MAP, SDS	1.2 (0.2 – 2.3)	1.2 (0.2 – 2.3)	1.3 (0.4 – 2.1)	1.0 (0.2 – 2.2)	1.1 (0.2 – 2.4)	0.757
Ambulatory MAP reduction, SDS	1.2 (0.3 – 2.1)	1.2 (0.4 – 2.1)	1.4 (0.5 – 2.2)	1.2 (0.6 – 2.0)	1.1 (0.1 – 2.1)	0.007

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

[1]P-value for difference among the three strata of proteinuria reduction.

Table 2. Adjusted cox proportional hazards model with association between initial proteinuria reduction and composite renal end point

	Hazard ratio	95% confidence interval	P-value
Proteinuria reduction			
- <30%	1.00 (reference group)		
- 30-60%	0.70	0.40 – 1.22	0.206
- >60%	0.42	0.22 – 0.79	0.007
Male sex	0.77	0.47 – 1.25	0.290
Age, years	1.08	1.02 – 1.15	0.014
Baseline ambulatory MAP, SDS	1.18	1.00 – 1.38	0.049
Diagnosis group			
- Glomerulopathies	1.00 (reference group)		
- CAKUT	0.57	0.31 – 1.05	0.070
- Other	0.85	0.38 – 1.89	0.692
Baseline eGFR, ml/min/1.73m^2	0.93	0.91 – 0.94	<0.001
Baseline Urinary protein/ creatinine ratio, mg/mg	1.21	1.09 – 1.34	<0.001
Ambulatory MAP reduction, SDS	0.92	0.77 – 1.10	0.385

No interaction was detected between proteinuria reduction and baseline proteinuria when added to the model (p=0.115). All model parameters are shown in Supplementary table 2.

No interaction was detected between proteinuria reduction and blood pressure reduction when added to the model (p=0.104). All model parameters are shown in Supplementary table 3.

Discussion

In this post-hoc analysis of a large interventional trial, we have studied the effect of proteinuria-lowering with standardized ACE inhibition on renal survival in children with CKD. A higher degree of proteinuria lowering during the first months of treatment was independently associated with a lower risk of CKD progression. In addition, both a higher residual proteinuria level after attaining the full dose of ramipril and the total exposure to proteinuria during follow-up accounted for a higher risk of CKD progression. These findings were independent of the underlying disease, baseline proteinuria and blood pressure control. Collectively, these data extend previous studies in adult populations and highlight the importance of proteinuria as a risk factor for renal disease progression in children with CKD.

Whereas the degree of proteinuria has been described as a risk factor for progression of renal disease in children, the long-term effect of drug induced proteinuria lowering on renal survival has not been well established in children. In adults, several post-hoc trial analyses have shown a positive association between initial reduction of proteinuria or albuminuria and renal disease progression. These studies have been performed in different patient populations with different disorders (e.g., diabetic nephropathies, non-

diabetic hypertensive kidney disease, and proteinuric chronic nephropathy) and have used drugs intervening on the renin-angiotensin system.[8-10,16,17] One observational study in 20 children with chronic nephropathies investigated the effect of combined treatment of ramipril and losartan on eGFR slopes. Children who achieved remission of proteinuria (defined as >50% reduction in proteinuria to <200 mg per day) had improved eGFR slopes compared to children who did not achieve remission.[12] However, that study did not assess the effect of proteinuria reduction during RAAS blockade on clinical outcomes. Here, we demonstrate in a large prospectively followed pediatric cohort that more efficient proteinuria lowering during the first few months of ACE inhibitor therapy is associated with a reduced risk of renal failure progression. In keeping with previous findings in adults, our results emphasize the potential importance of proteinuria as a therapeutic target in children with CKD.

The initial proteinuria lowering effect varied widely between individuals, in keeping with observations in adults.[18,19] We found no clear indicators that could explain the large variation of proteinuria response to a defined ACE inhibitor dose. In adults, determinants of the individual response to an ACE inhibitor include dietary consumption of salt and proteins and the ACE I/D polymorphism.[20-23] In this study, the ACE I/D genotype did not explain the variability of the proteinuria response to ramipril.

In order to further investigate the role of proteinuria as a risk predictor of renal outcomes during continued ACE inhibition, we also assessed the association between residual proteinuria and renal outcome. Several adult studies have shown that exposure to proteinuria over time is a very important, if not the most important, predictor of renal outcomes in adults.[24-26] To our knowledge, no study in children has investigated the predictive value of long term exposure to proteinuria. Both higher residual proteinuria and higher proteinuria exposure over time accounted for a higher renal risk in this study population, further suggesting that proteinuria might be a very important parameter in renal disease progression in children with CKD. It should be emphasized though that the early proteinuria reduction predicted renal survival as well as the long-term evolution of proteinuria, highlighting the true predictive value of this early effect.

The observation that patients with the least proteinuria reduction were at highest risk of CKD progression warrants additional strategies to further lower proteinuria in these patients. These include the addition of hydrochlorothiazide to the treatment protocols, dietary interventions such as a moderation of dietary sodium or protein intake, or possibly novel proteinuria lowering therapies other than RAS inhibition (e.g. SGLT-2 inhibitors)[6,27-31]. Finally, monitoring blood pressure and treating hypertension is also important in these patients, as blood pressure control is the only other intervention that has been proven to be nephroprotective in children with CKD.[11]

We recognize several limitations to our study. First, it should be noted that this study is a post-hoc analysis of a clinical trial that was not designed to investigate the association between ACE inhibition induced proteinuria lowering and renal end points and that

results must be interpreted accordingly. A prospective study aimed at investigating the effect of proteinuria lowering on renal survival in children with CKD would be required to unequivocally confirm the findings described in this paper. Furthermore, additional antihypertensive medication initiated during the trial in approximately half of the study population to reach the blood pressure target could have interfered with CKD progression. A sensitivity analysis that excluded patients who received additional antihypertensive medication showed similar results as our main analyses, suggesting minimal impact of additional antihypertensive medication use on our findings. A final caveat relates to the difficulty of separating out the relative benefits of proteinuria and blood pressure reduction. However, as blood pressure lowering was taken into account as a covariate in the multivariable Cox models, it is suggested that the effect of proteinuria reduction was largely independent of the effect of blood pressure lowering. Moreover, the statistically non-significant interaction between blood pressure reduction and proteinuria reduction suggests that the effect of proteinuria reduction is not modified by blood pressure reduction.

In conclusion, this post-hoc analysis shows that the early antiproteinuric effect of ACE inhibition independently predicts long-term preservation of renal function in children with CKD. Moreover, higher residual proteinuria and higher long term proteinuria exposure account for worse renal survival. These findings indicate that proteinuria lowering is an important target in the management of children with CKD.

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Supplementary table 1. Multivariable linear regression analysis of association between proteinuria reduction and baseline variables.

	Coefficient	P-value
Male sex	-0.24	0.086
Age, years	0.03	0.078
Conventional blood pressure control	0.06	0.618
Diagnosis group		
- Glomerulopathies	0.00 (reference group)	
- CAKUT	0.00	0.990
- Other	-0.28	0.307
Baseline eGFR, 10 ml/min/1.73m^2	-0.05	0.407
Baseline ambulatory MAP, SDS	0.04	0.323
Baseline urinary protein:creatinine ratio, mg/mg	-0.14	<0.001
Baseline serum urea, mmol/L	0.01	0.457
ACE I/D genotype		
- II genotype	0.00 (reference group)	
- ID genotype	0.15	0.375
- DD genotype	0.22	0.262

Supplementary table 2. Multivariable Cox proportional hazards model with association between interaction between proteinuria reduction and baseline proteinuria and the composite renal endpoint

	Hazard ratio	95% confidence interval	P-value
Proteinuria reduction, per 10% reduction	0.93	0.88 – 0.98	0.012
Baseline Urinary protein/ creatinine ratio, mg/mg	1.35	1.19 – 1.54	<0.001
Proteinuria reduction * baseline proteinuria	1.15	0.97 – 1.38	0.115
Male sex	0.91	0.55 – 1.51	0.708
Age, years	1.08	1.01 – 1.15	0.019
Baseline ambulatory MAP, SDS	1.21	1.03 – 1.41	0.018
Diagnosis group			
- Glomerulopathies	1.00 (reference group)		
- CAKUT	0.58	0.31 – 1.05	0.074
- Other	0.85	0.38 – 1.88	0.690
Baseline eGFR, ml/min/1.73m^2	0.93	0.91 – 0.94	<0.001
Ambulatory MAP reduction, SDS	0.89	0.74 – 1.06	0.185

Supplementary table 3. Multivariable Cox proportional hazards model with association between interaction between proteinuria reduction and blood pressure reduction and the composite renal endpoint

	Hazard ratio	95% confidence interval	P-value
Proteinuria reduction, per 10% reduction	0.90	0.86 – 0.95	<0.001
Ambulatory MAP reduction, SDS	0.84	0.70 – 1.01	0.064
Proteinuria reduction * MAP reduction	0.83	0.66 – 1.04	0.104
Male sex	0.90	0.54 – 1.49	0.684
Age, years	1.08	1.01 – 1.15	0.025
Baseline ambulatory MAP, SDS	1.20	1.02 – 1.40	0.024
Diagnosis group			
- Glomerulopathies	1.00 (reference group)		
- CAKUT	0.56	0.30 – 1.02	0.057
- Other	0.80	0.36 – 1.77	0.580
Baseline eGFR, ml/min/1.73m^2	0.92	0.91 – 0.94	<0.001
Baseline urinary protein:creatinine ratio, mg/mg	1.24	1.12 – 1.38	<0.001

Supplementary table 4. Sensitivity analysis: Adjusted cox proportional hazards model with association between initial proteinuria reduction and composite renal end point (proteinuria reduction analysed as continuous measure)

	Hazard ratio	95% confidence interval	P-value
Proteinuria reduction, per 10% reduction	0.93	0.90 – 0.96	<0.001
Male sex	0.89	0.54 – 1.47	0.649
Age, years	1.07	1.00 – 1.14	0.040
Baseline ambulatory MAP, SDS	1.22	1.04 – 1.42	0.014
Diagnosis group			
- Glomerulopathies	1.00 (reference group)		
- CAKUT	0.58	0.32 – 1.05	0.072
- Other	0.82	0.37 – 1.79	0.614
Baseline eGFR, ml/min/1.73m^2	0.93	0.91 – 0.94	<0.001
Baseline urinary protein/ creatinine ratio, mg/mg	1.24	1.12 – 1.37	<0.001
Ambulatory MAP reduction, SDS	0.89	0.74 – 1.06	0.182

Supplementary table 5. Sensitivity analysis: Adjusted cox proportional hazards model with association between initial proteinuria reduction and composite renal end point (subjects with baseline proteinuria < 0.1 mg/mg excluded). n=254

	Hazard ratio	95% confidence interval	P-value
Proteinuria reduction			
- <30%	1.00 (reference group)		
- 30-60%	0.75	0.43 – 1.33	0.324
- >60%	0.43	0.23 – 0.83	0.011
Male sex	0.78	0.47 – 1.30	0.347
Age, years	1.07	1.00 – 1.14	0.057
Baseline ambulatory MAP, SDS	1.18	1.00 – 1.39	0.051
Diagnosis group			
- Glomerulopathies	1.00 (reference group)		
- CAKUT	0.56	0.30 – 1.03	0.063
- Other	0.71	0.31 – 1.63	0.413
Baseline eGFR, ml/min/1.73m^2	0.93	0.91 – 0.95	<0.001
Baseline urinary protein/ creatinine ratio, mg/mg	1.22	1.10 – 1.35	<0.001
Ambulatory MAP reduction, SDS	0.90	0.75 – 1.08	0.271

Supplementary table 6. Sensitivity analysis: Adjusted cox proportional hazards model with association between initial proteinuria reduction and composite renal end point (subjects with baseline proteinuria >90th percentile (3.2 mg/mg) excluded). n=254

	Hazard ratio	95% confidence interval	P-value
Proteinuria reduction, per 10% reduction	0.93	0.89 – 0.96	<0.001
Male sex	0.78	0.44 – 1.37	0.396
Age, years	1.06	0.99 – 1.14	0.086
Baseline ambulatory MAP, SDS	1.11	0.91 – 1.36	0.284
Diagnosis group			
- Glomerulopathies	1.00 (reference group)		
- CAKUT	0.67	0.29 – 1.52	0.336
- Other	1.23	0.47 – 3.22	0.675
Baseline eGFR, ml/min/1.73m^2	1.92	1.34 – 2.76	<0.001
Baseline urinary protein/ creatinine ratio, mg/mg	0.92	0.90 – 0.94	<0.001
Ambulatory MAP reduction, SDS	0.94	0.74 – 1.18	0.581

Supplementary table 7. Sensitivity analysis: Adjusted cox proportional hazards model with association between initial proteinuria reduction and composite renal end point (subjects with additional antihypertensive therapy excluded). n=142

	Hazard ratio	95% confidence interval	P-value
Proteinuria reduction, per 10% reduction	0.92	0.87 – 0.98	0.006
Male sex	0.59	0.26 – 1.33	0.209
Age, years	1.05	0.93 – 1.17	0.444
Baseline ambulatory MAP, SDS	1.46	1.04 – 2.03	0.027
Diagnosis group			
- Glomerulopathies	1.00 (reference group)		
- CAKUT	0.30	0.10 – 0.91	0.032
- Other	0.41	0.10 – 1.75	0.226
Baseline eGFR, ml/min/1.73m^2	0.91	0.87 – 0.94	<0.001
Baseline urinary protein/ creatinine ratio, mg/mg	1.08	0.89 – 1.32	0.437
Ambulatory MAP reduction, SDS	0.56	0.34 – 0.93	0.024

Supplementary table 8. Sensitivity analysis: Adjusted cox proportional hazards model with association between proteinuria exposure over time and composite renal end point.

	Hazard ratio	95% confidence interval	P-value
Proteinuria exposure over time:			
- Low	1.00 (reference group)		
- Medium	1.76	0.77 – 4.03	0.179
- High	2.97	1.31 – 6.70	0.009
Male sex	0.72	0.43 – 1.22	0.227
Age, years	1.06	0.99 – 1.14	0.076
Baseline ambulatory MAP, SDS	1.19	1.01 – 1.41	0.037
Diagnosis group			
- Glomerulopathies	1.00 (reference group)		
- CAKUT	0.44	0.24 – 0.80	0.008
- Other	0.83	0.37 – 1.88	0.663
Baseline eGFR, ml/min/1.73m^2	0.93	0.91 – 0.95	<0.001
Ambulatory MAP reduction, SDS	0.91	0.76 – 1.09	0.316