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# Antihypertensive and antiproteinuric efficacy of ramipril in children with chronic renal failure

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*Background.* While the antihypertensive and renoprotective potency of angiotensin-converting enzyme (ACE) inhibitors is well-established in adults with hypertension and/or chronic renal failure, little experience exists in pediatric chronic kidney disease.

*Methods.* As part of a prospective assessment of the renoprotective efficacy of ACE inhibition and intensified blood pressure (BP) control, 397 children (ages 3 to 18 years) with chronic renal failure [CRF; glomerular filtration rate (GFR) 11 to 80 mL/min/1.73 $m^2$] and elevated or high-normal BP received ramipril (6 mg/$m^2$) following a 6-month run-in period including a two-month washout of any previous ACE inhibitors. Drug efficacy was assessed by two monthly office BP and proteinuria assessments, and by ambulatory BP monitoring at start and after 6 months of treatment.

*Results.* In the 352 patients completing six months of treatment, 24-hour mean arterial pressure (MAP) had decreased by a mean of 11.5 mm Hg (−2.2 SDS) in initially hypertensive subjects, but only by 4.4 mm Hg (−0.8 SDS) in patients with initially normal BP. A linear correlation was found between MAP at baseline and the change of MAP during treatment ($r = 0.51$; $P < 0.0001$). The antihypertensive response was independent of changes in concomitant antihypertensive medication or underlying renal disease. BP was reduced with equal efficacy during day- and nighttime. Urinary protein excretion was reduced by 50% on average, with similar relative efficacy in patients with hypo/dysplastic nephropathies and glomerulopathies. The magnitude of proteinuria reduction depended on baseline proteinuria ($r = 0.32$, $P < 0.0001$), and was correlated with the antihypertensive efficacy of the drug ($r = 0.22$, $P < 0.001$). The incidence of rapid rises in serum creatinine and progression to end-stage CRF during treatment did not differ from the pretreatment observation period. Mean serum potassium increased by 0.3 mmol/L. Ramipril was discontinued in three patients due to symptomatic hypotension or hyperkalemia. Hemoglobin levels decreased by 0.6 g/dL in the first two treatment months and remained stable thereafter.

*Conclusion.* Ramipril appears to be an effective and safe antihypertensive and antiproteinuric agent in children with CRF-associated hypertension. The BP lowering and antiproteinuric effects are greatest in severely hypertensive and proteinuric children.

Most antihypertensive agents currently used in children are administered off label. Historically, explicit approval for pediatric use has usually not been applied for by the manufacturers because clinical studies in children are more demanding than trials in adult patients with respect to various ethical, biometrical, and practical issues. Only recently, the Best Drugs for Children Act in the U.S., and similar activities in Europe, have cleared the way for appropriate clinical trials to investigate the pharmacokinetic, dose-effect, and safety properties of individual drugs in children.

This development is particularly relevant to the field of pediatric hypertension, where long-term pharmacologic interventions with agents that combine excellent efficacy with a low side effect profile are required. In children, secondary hypertension is of renal origin in 85% of the cases [1]. Some degree of chronic renal failure (CRF) is often present in children with severe, persistent renal hypertension. In adults with CRF, renin-angiotensin system (RAS) antagonists have become pharmacotherapeutics of first choice, not only due to their excellent systemic antihypertensive properties, but also because of their unique renoprotective potential. Because of their preferential action on the efferent arteriolar tone, RAS antagonists reduce intraglomerular pressure and proteinuria. Moreover, angiotensin antagonism suppresses local growth factor, cytokine and chemokine release, with subsequent reduction of glomerular hypertrophy and sclerosis, as well as tubulointerstitial inflammation and fibrosis [2]. The renoprotective efficacy of RAS antagonists, which is in part independent of blood pressure, has been demonstrated in animal models and adults with various acquired nephropathies [3–9]. However, in children, the spectrum of renal disorders causing CRF

[1]Participants of the ESCAPE (Effect of Strict Blood Pressure Control and ACE Inhibition on CRF Progression in Pediatric Patients) Trial Group are listed in the **Appendix**.

**Key words:** ramipril, ACE inhibitor, hypertension, chronic renal failure, children.

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differs from adults, with a preponderance of hypo-/dysplastic and hereditary kidney disease.

In order to establish whether angiotensin-converting enzyme (ACE) inhibition and the level of blood pressure control affect the rate of CRF progression also in pediatric kidney disease, the ESCAPE trial, an international, randomized, five-year prospective study, has been launched in 33 European pediatric nephrology centers. As part of this trial, almost 400 children received a fixed dose of the ACE inhibitor ramipril for at least 6 months following a two-month washout period during which any RAS antagonist pretreatment was discontinued. The patients were followed bimonthly, and ambulatory blood pressure monitoring (ABPM) was performed before and after 6 months of treatment. This largest prospective assessment of an antihypertensive drug ever performed in children permits the assessment of the antihypertensive and antiproteinuric efficacy, as well as the safety of ramipril in children.

## METHODS

### Study protocol

Thirty-three pediatric nephrology units in 13 European countries collaborated in a prospective, investigator-initiated clinical trial to study the Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in PEdiatric Patients (ESCAPE trial).

The study protocol was developed exclusively by the participants, and data are collected and analyzed by the study coordinators. Monitoring of the collected data was performed by an independent clinical research organization (Omnicare Clinical Research). Industry sponsorship was confined to support of the investigator meetings.

Within this trial, children aged 3 to 18 years with CRF and high normal or elevated blood pressure (BP) received a fixed dose of the ACE inhibitor ramipril (6 mg/m$^2$ body surface area in tablets of 1.25, 2.5, or 5 mg as a single morning dose) and were randomized to either conventional or intensified BP targets, aiming for the 50th to 95th or below the 50th percentile of 24-hour mean arterial pressure (MAP) for height and gender [10], respectively. During five years of follow-up, office BP, glomerular filtration rate (GFR), and proteinuria are checked every two months, and ABPM is performed every six months. The study participants opted for open administration of ramipril because a comparative trial design using a control arm receiving placebo or non-RAS antagonist antihypertensive medication was considered unethical in the light of the established renoprotective efficacy of ACE inhibition in adult patients [7, 11]. The study protocol was approved by the local ethical committees, and written informed consent was obtained from the parents and assent from the patients.

During the first six months of the study, the effect of ramipril on BP and proteinuria was observed. Antihypertensive therapy was modified only if office BP was below the 5th or above the 95th percentile. Adaptation of treatment according to the randomized BP targets starts with the first ABPM profile after 6 months of ramipril therapy. Here, we present the results of the first six months of ramipril therapy, focusing on the antihypertensive and antiproteinuric efficacy, as well as on the safety of the drug in children.

### Patients

Four hundred and sixty-six children aged 3 to 18 years with mild to moderate CRF (initial GFR 15 to 80 mL/min/1.73m$^2$) and a 24-hour MAP greater than the 50th percentile for height and/or receiving antihypertensive medication were enrolled in a six-month run-in period. In all patients on prevalent ACE inhibitor therapy, this medication was discontinued at least two months before the end of the run-in period. During this wash-out period, blood pressure was controlled by home and casual BP measurements and, if necessary, antihypertensive medication was adjusted by adding non-RAS antagonists to maintain a blood pressure in the normal range.

At time of randomization 397 patients fulfilled the inclusion criteria and were started on ramipril, 352 of whom completed at least 6 months of treatment (Fig. 1, Table 1).

Renal hypo-/dysplasia was the underlying kidney disorder in 70%, acquired glomerulopathies in 13%, and hereditary or other kidney diseases in 17% of the patients.

Sixty-four percent of the patients had no antihypertensive medication at baseline, 22% were on antihypertensive monotherapy, and 14% were on two or more antihypertensive drugs. Antihypertensive therapy at baseline included calcium channel blockers (25%), beta- (17%) or alpha-adrenergic blockers (5%), diuretics (11%), centrally active and vasodilating agents (1% each). Mean 24-hour systolic BP at baseline was elevated to 118.8 mm Hg and diastolic BP to 73.3 mm Hg (+0.9 and +1.1 SDS, respectively). At baseline, 24-hour MAP was above the 95th percentile in 34%, between the 50th and 95th percentile in 39% and below the 50th percentile in 27% of patients. All patients with baseline 24-hour MAP below the 50th percentile were on prevalent antihypertensive medication.

Mean 24 hour heart rate was 83 bpm [i.e., in the mid-normal range (0.0 standard deviation scores)].

The decision whether concomitant antihypertensive medication was reduced, unchanged, or increased around the time of randomization and start of ramipril was at the discretion of the responsible physician. For the analysis of the BP lowering effect of ramipril, patients were classified post-hoc into four groups according to the change

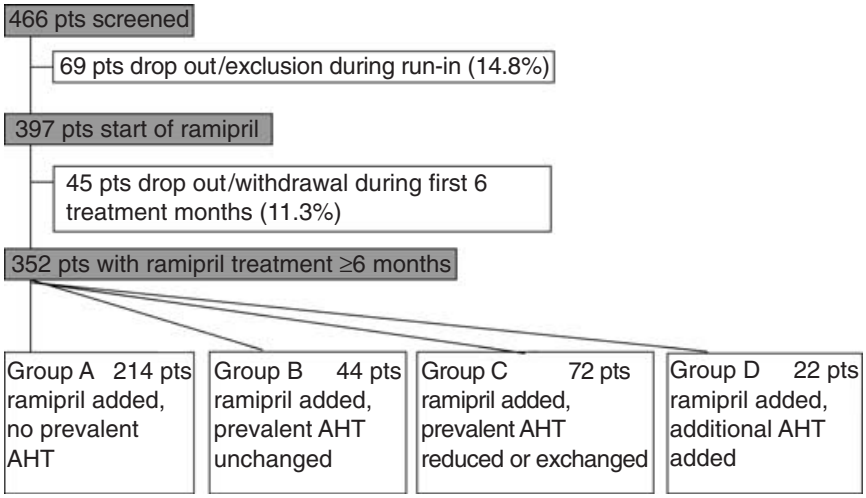


**Fig. 1. Study flow chart.** AHT, antihypertensive treatment; pts, patients.

in antihypertensive treatment regimen at introduction of ramipril. Ramipril was instituted as the first antihypertensive agent in group A ($N = 214$), or added to an unchanged preexisting antihypertensive medication in group B ($N = 44$). In group C ($N = 72$), the previous antihypertensive medication was discontinued or reduced at start of ramipril treatment. In group D ($N = 22$), additional antihypertensive medication was prescribed at or within two months after start of ramipril. Fifty-nine percent of patients in group B received one, 41% two or more antihypertensive agents at baseline. In group C, all patients were on antihypertensive medication at baseline, and 31% had at least two antihypertensive drugs. In group D, 50% were without antihypertensive treatment, 27% on monotherapy, and 23% on at least two antihypertensive drugs at baseline. A higher proportion of patients with glomerulopathies was present in group D (32%) than in groups A (9%), B (18%), or C (13%).

**Table 1.** Baseline clinical characteristics of study cohort prior to ramipril treatment ($N = 352$)

| | Mean ± SD | Range |
|---|---|---|
| Age *years* | 11.4 ± 4.0 | 3.5–18 |
| Height *cm* | 140.6 ± 22.4 | 89–190 |
| Height SDS | −0.9 ± 1.5 | −6.8–2.9 |
| Weight *kg* | 38.0 ± 17.4 | 9–102 |
| BMI $kg/m^2$ | 18.1 ± 3.7 | 11.3–33.3 |
| BMI SDS | −0.01 ± 1.3 | −4.6–3.2 |
| 24-hour systolic BP *mm Hg* | 118.8 ± 11.4 | 91–169 |
| 24-hour systolic BP SDS | 0.9 ± 1.4 | −3.3–7.9 |
| 24-hour diastolic BP *mm Hg* | 73.3 ± 9.3 | 57–119 |
| 24-hour diastolic BP SDS | 1.1 ± 1.7 | −2.2–9.8 |
| 24-hour MAP *mm Hg* | 89.1 ± 9.6 | 69–135 |
| 24-hour MAP SDS | 1.5 ± 1.9 | −2.0–16.2 |
| Urinary protein/creatinine ratio *mg/mg* | 1.38 ± 1.88 | 0.0–15.8 |
| Fractional sodium excretion % | 2.4 ± 2.0 | 0.3–11.3 |
| Creatinine clearance $mL/min/1.73m^2$ | 47.6 ± 18.4 | 10.2–80.0 |
| Patients in K/DOQI CKD [33] stage 1/2/3/4/5 % | –/28/52/18/2 | |

## Blood pressure monitoring

ABPM was performed with a Spacelabs 90207 automatic cuff-oscillometric device (Spacelabs Medical, Issaquah, WA, USA) at screening, at the start, and six months after start of ramipril. The cuff size was adjusted to the upper arm circumference. ABPM measurements were performed every 15 minutes during the daytime, and every 20 to 30 minutes at night. All ABPM profiles were analyzed centrally. ABPM profiles were divided into daytime (08.00 to 20.00 hours) and nighttime periods (24.00 to 06.00 hours).

Office BP measurements were obtained using auscultatory or oscillometric techniques at the bimonthly outpatient visits after sitting for 5 minutes in a relaxed position.

## Laboratory assessments

Serum and urinary creatinine and sodium, as well as urinary protein concentrations were measured centrally in parallel to local analyses. The central measurements of urinary protein excretion were performed using the Coumassie method, and those of serum and urinary creatinine by a modified Jaffé reaction. Serum and urinary electrolytes, serum protein, and liver enzymes, as well as blood cell counts were measured by standard laboratory techniques. In order to avoid artifacts due to sampling errors in 24-hour urine collections, proteinuria was expressed by the protein-creatinine ratio in the available urine samples (69% 24-hour urine collections, 31% morning spot urine samples). Sodium excretion was expressed by the fractional excretion rate. Creatinine clearance was estimated from serum creatinine and height was estimated using the published pediatric equations by Schwartz et al [12] as recommended by the K/DOQI CKD guidelines [13]. Estimated creatinine clearance was used to express GFR in the results section.

## Statistical analysis

ABPM data were analyzed using the Spacelabs ABPM Report Management System. All data was stored and

processed with the SAS software (SAS Institute, Cary, NC, USA). Blood pressure standard deviation scores (SDS) were calculated using European ABPM reference data [14]. Dipping was defined as a nocturnal decrease of BP by more than 10% compared with mean daytime BP.

The Shapiro-Wilk test was used to test for normal distribution. Urinary protein excretion parameters that were not normally distributed were log-transformed for further analysis. The longitudinal changes in blood pressure and safety parameters (bimonthly assessments) were evaluated by repeated-measure analysis of variance (ANOVA) including a within-subject factor (time) and a between-subject factor (e.g., different antihypertensive treatment groups). Pairwise comparisons between different time points and baseline were performed using the CONTRAST option of the general linear models procedure in the SAS software. For those parameters assessed only at start and after 6 months (ABPM data), paired Student *t* tests with a Bonferroni correction for multiple testing were applied.

For multivariate analysis the following variables were offered to the model: baseline creatinine clearance, baseline MAP SDS, age, gender, number of antihypertensive drugs at baseline, and underlying nephropathy (acquired vs. congenital). In addition, baseline proteinuria was offered to the model predicting the change of proteinuria.

Correlation coefficients were calculated using Spearman rank order correlation. *P* values of less than 0.05 were considered significant. All results are expressed as mean ± SD.

## RESULTS

### Blood pressure response

After six months of ramipril treatment, mean 24-hour MAP was reduced by 7.1 ± 8.0 mm Hg (i.e., by 1.3 ± 1.5 SDS) in the total cohort of 352 patients. The antihypertensive effect was equally marked for systolic and diastolic BP and for daytime and nighttime measurements (Table 2), with an unchanged fraction of nocturnal nondippers (at baseline 53 vs. 54% for systolic, 26 vs. 27% for diastolic BP at baseline and after 6 months, respectively). The bimonthly office BP assessments fully reflected the antihypertensive effect after two months of treatment (Table 3). Notably, whereas BP was significantly lower at baseline and after six months in group A compared with the other groups ($P < 0.05$), the BP response did not differ significantly between patients with no (group A), unchanged (group B), reduced (group C), or increased (group D) antihypertensive comedication (Table 2). The BP lowering effect of ramipril was independent of gender. Moreover, while baseline BP was significantly higher in patients with glomerulopathies compared with children with renal hypo-/dysplasia and hereditary or other kidney diseases, 24-hour MAP was

**Table 2.** Effect of ramipril on blood pressure

| | | Group A Ramipril added, no preexisting AHT ($N = 214$) | | | Group B Ramipril added, preexisting AHT unchanged ($N = 44$) | | | Group C Ramipril added, preexisting AHT reduced ($N = 72$) | | | Group D Ramipril added, preexisting AHT increased ($N = 22$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | 6 months | *P* value | Baseline | 6 months | *P* value | Baseline | 6 months | *P* value | Baseline | 6 months | *P* value |
| Office | Systolic BP *mm Hg* | 113.9 ± 12.9 | 106.5 ± 13.4 | [a] | 125.2 ± 13.8 | 116.8 ± 11.4 | [a] | 122.5 ± 12.2 | 113.1 ± 17.2 | [a] | 126 ± 13.2 | 118.1 ± 11.9 | [b] |
| | Diastolic BP *mm Hg* | 70.5 ± 11.2 | 62.6 ± 11.8 | [a] | 76.2 ± 10.3 | 70.6 ± 12.4 | [a] | 76.3 ± 12.9 | 69.8 ± 14.6 | [a] | 78.5 ± 10.1 | 72.4 ± 14.7 | [b] |
| ABPM | MAP 24-hour *mm Hg* | 86.1 ± 7.1 | 79.4 ± 6.3 | [a] | 93.5 ± 9.4 | 86.2 ± 8.1 | [a] | 94.3 ± 11.2 | 87.0 ± 9.7 | [a] | 94.7 ± 11.7 | 86.4 ± 7.5 | [b] |
| | MAP 24-hour SDS | 1.0 ± 1.3 | –0.3 ± 1.0 | [a] | 2.3 ± 1.8 | 0.9 ± 1.5 | [a] | 2.5 ± 2.7 | 1.1 ± 2.0 | [a] | 2.0 ± 1.9 | 0.6 ± 1.2 | [b] |
| | MAP daytime *mm Hg* | 89.7 ± 7.2 | 82.5 ± 6.8 | [a] | 96.9 ± 10.2 | 89.5 ± 8.8 | [a] | 98.2 ± 11.5 | 91.0 ± 9.8 | [a] | 98.6 ± 11.4 | 90.5 ± 9.1 | [c] |
| | MAP daytime SDS | 0.7 ± 1.2 | –0.5 ± 1.0 | [a] | 1.8 ± 1.7 | 0.6 ± 1.4 | [a] | 2.1 ± 2.3 | 0.7 ± 1.7 | [a] | 1.7 ± 1.7 | 0.5 ± 1.4 | [c] |
| | MAP nighttime *mm Hg* | 80.8 ± 8.3 | 74.2 ± 6.9 | [a] | 86.1 ± 10.1 | 80.6 ± 8.6 | [a] | 88.7 ± 12.1 | 81.2 ± 11.1 | [a] | 89.7 ± 10.8 | 80.0 ± 7.2 | [b] |
| | MAP nighttime SDS | 1.6 ± 1.3 | 0.6 ± 1.1 | [a] | 2.6 ± 1.8 | 1.6 ± 1.7 | [a] | 2.9 ± 2.3 | 1.8 ± 2.1 | [a] | 2.9 ± 1.6 | 1.3 ± 1 | [b] |

AHT, antihypertensive treatment. Mean ± SD. Significant difference between baseline and 6 months.
[a] $P < 0.0001$; [b] $P < 0.005$; [c] $P < 0.01$.

**Table 3.** Effect of ramipril on office BP, serum and urine biochemistry, and blood cell counts in the total study population

| | Baseline | 2 months | 4 months | 6 months |
|---|---|---|---|---|
| Office systolic BP *mm Hg* | 117.5 ± 14.0 | 109.8 ± 15.4[b] | 108.4 ± 15.6[b] | 109.7 ± 14.4[b] |
| Office diastolic BP *mm Hg* | 72.9 ± 11.8 | 65.1 ± 12.6[b] | 65.2 ± 12.6[b] | 65.4 ± 12.3[b] |
| Urinary protein/creatinine ratio *mg/mg* | 1.38 ± 1.88 | 0.88 ± 1.46[b] | 0.80 ± 1.19[b] | 0.77 ± 1.11[b] |
| 24-hour urinary protein excretion *mg/m²/day* | 1003 ± 1703 | 497 ± 869[b] | 506 ± 913[b] | 522 ± 902[b] |
| Estimated creatinine clearance *mL/min/1.73m²* | 47.6 ± 19.5 | 45.8 ± 19.8 | 44.8 ± 20.3[a] | 44.2 ± 20.0[b] |
| Fractional sodium excretion % | 2.4 ± 2.0 | 2.7 ± 2.3 | 3.0 ± 3.2 | 2.9 ± 2.9 |
| Serum potassium *mmol/L* | 4.3 ± 0.5 | 4.6 ± 0.6[b] | 4.6 ± 0.6[b] | 4.5 ± 0.8[a] |
| Hemoglobin level *g/dL* | 12.2 ± 1.6 | 11.6 ± 1.8[b] | 11.4 ± 1.8[b] | 11.6 ± 1.8[b] |
| Blood leukocyte count *T/μL* | 6.9 ± 1.8 | 6.8 ± 1.9 | 6.7 ± 2.0 | 6.8 ± 2.0 |
| Thrombocyte count *T/μL* | 260 ± 73 | 250 ± 76[b] | 254 ± 71[a] | 253 ± 73 |
| Albumin *g/L* | 42.0 ± 4.9 | – | – | 42.3 ± 5.7[a] |

Mean ± SD. Significant difference vs. baseline.
[a] $P < 0.05$; [b] $P < 0.005$.

reduced regardless of the underlying disease (Fig. 2). The BP response was also independent of individual variations of the ramipril dose administered (applied dose 5.2 ± 1.4 mg/m²/day).

Patients with baseline MAP greater than the 95th percentile ($N = 119$) had a significantly better response to ramipril [MAP change −11.5 ± 8.7 mm Hg (i.e., −2.2 ± 1.8 SDS)] compared to patients with MAP below the 95th percentile [ −4.4 ± 6.2 mm Hg (i.e. −0.8 ± 1.1 SDS), $P < 0.0001$]. After 6 months, 56% of all patients had achieved a MAP below the 50th percentile; in 29 patients (9.3%) 24-hour MAP dropped below the 5th percentile. Nevertheless in only 2 patients was symptomatic hypotension reported. In 12.7% of all patients blood pressure was still above the 95th percentile. No patient was withdrawn from the study due to non-response. In the initially hypertensive patients MAP was below the 95th percentile in 65%. Univariate regression analysis confirmed a linear relationship between baseline 24-hour MAP and its subsequent reduction during ramipril therapy ($r = -0.51$, $P < 0.0001$; Fig. 3). While no mean change in BP occurred when baseline MAP was below 80 mm Hg, MAP was reduced on average by 5.2 mm Hg with every 10 mm Hg baseline MAP above 80.

The change in 24-hour MAP was significantly greater in patients with a residual GFR <40 mL/min/1.73 m² (−1.7 ± 1.6 SDS) than in patients with better renal function (−1.1 ± 1.4 SDS, $P < 0.005$), and GFR was weakly inversely related to the blood pressure response ($r = -0.17$, $P < 0.01$). Furthermore, the change in 24-hour MAP SDS was positively correlated with the degree of proteinuria ($r = 0.25$; $P < 0.0001$) and fractional sodium excretion at baseline ($r = 0.20$, $P < 0.001$). The antihypertensive response was significantly greater in patients with gross proteinuria (urinary protein/creatinine ratio >1) (change in MAP −1.8 ± 1.8 SDS) than in children with mild or no proteinuria (−1.0 ± 1.4 SDS; $P < 0.0005$). Patient age was marginally inversely correlated with the antihypertensive response to ramipril ($r = -0.12$, $P < 0.05$).

Multivariate regression analysis revealed that the change in 24-hour MAP SDS in the total cohort was independently predicted by baseline MAP SDS (positive effect, partial $r^2 = 0.395$, $P < 0.0001$), the number of concomitant antihypertensive drugs at baseline (negative effect, partial $r^2 = 0.022$, $P < 0.005$), gender (male>female, partial $r^2 = 0.012$, $P < 0.05$), age (negative effect, partial $r^2 = 0.01$, $P < 0.05$), and baseline proteinuria (positive effect, partial $r^2 = 0.017$, $P < 0.01$). When only those patients were considered in whom the addition of ramipril was the only pharmacologic intervention during the study period (groups A and B), baseline MAP SDS (positive effect, partial $r^2 = 0.37$, $P < 0.0001$), GFR (negative effect, partial $r^2 = 0.044$, $P < 0.001$), age (negative effect, partial $r^2 = 0.023$, $P < 0.01$), gender (male>female, partial $r^2 = 0.014$, $P < 0.05$), and the number of concomitant antihypertensive drugs (negative effect, partial $r^2 = 0.014$, $P < 0.05$) emerged as independent predictors of the change in 24-hour MAP SDS.

In the subgroup of patients with manifest hypertension (MAP at baseline >95th percentile) baseline MAP

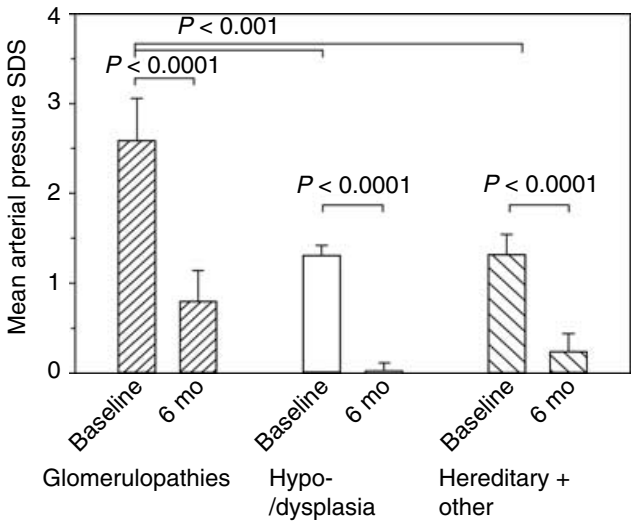


**Fig. 2. Change of 24-hour MAP SDS according to underlying renal disease.** Bars represent mean ± SEM.

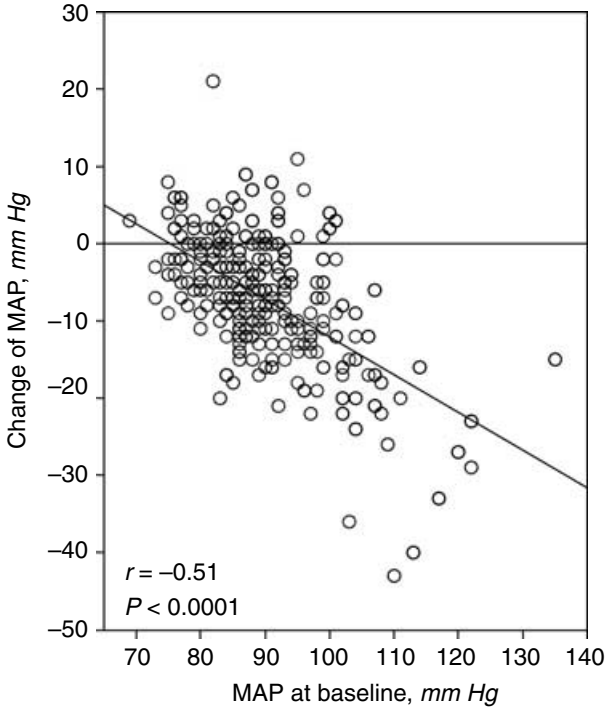


**Fig. 3. Correlation between baseline 24-hour MAP and change of 24-hour MAP during ramipril treatment**.

SDS ($r^2 = 0.37$, $P < 0.0001$) remained the only important predictor of the antihypertensive effect of ramipril.

### Antiproteinuric response

Ramipril reduced urinary protein excretion by approximately 50% within the first six treatment months (Table 3). The antiproteinuric effect of ramipril depended on baseline proteinuria ($r = 0.32$, $P < 0.0001$), and was weakly inversely correlated to age ($r = -0.12$, $P < 0.05$). Moreover, the antiproteinuric response to ramipril was associated with the blood pressure-lowering effect of the drug ($r = 0.22$, $P < 0.001$).

While patients with glomerulopathies had significantly greater proteinuria both at baseline ($2.93 \pm 3.53$ mg/mg) and after 6 treatment months ($1.66 \pm 2.80$ mg/mg) than children with renal hypo/dysplasia (baseline: $1.12 \pm 1.42$ mg/mg, 6 months: $0.67 \pm 0.91$ mg/mg) and hereditary or other kidney disorders (baseline: $1.07 \pm 1.71$ mg/mg, 6 months: $0.54 \pm 0.95$ mg/mg), the relative antiproteinuric effect of ramipril was independent of the underlying nephropathy. Also, the antiproteinuric response did not differ between patients who received additionally either a Ca-channel blocker, a β-blocker, or no antihypertensive medication.

In the total cohort, the change in protein excretion was independently predicted by baseline proteinuria (positive effect, partial $r^2 = 0.14$, $P < 0.0001$), baseline GFR (positive effect, partial $r^2 = 0.037$, $P < 0.0001$), gender (male>female, partial $r^2 = 0.027$, $P < 0.005$), and age (negative effect, partial $r^2 = 0.018$, $P < 0.05$).

As a possible effect of the antiproteinuric action of ramipril, serum albumin levels increased slightly but significantly within six months of ramipril treatment (Table 3).

**Table 4.** Reasons for withdrawal from the study during the run-in and the treatment period (duration 6 months each)

| | Pretreatment run-in period ($N = 466$) | Treatment period ($N = 397$) |
|---|---|---|
| Inclusion criteria not fulfilled | 32 (6.7%) | – |
| Increase of serum creatinine | 4 (0.9%) | 5 (1.3%) |
| Start of renal replacement therapy | 8 (1.7%) | 7 (1.8%) |
| Hypotension | – | 2 (0.5%) |
| Hyperkalemia | – | 1 (0.3%) |
| Cough | – | 1 (0.3%) |
| Noncompliance | 8 (1.7%) | 2 (0.5%) |
| Patient's request | 8 (1.7%) | 2 (0.5%) |
| Loss of follow-up | 8 (1.3%) | 25 (6.3%) |
| Others | 3 (0.6%) | – |
| Total | 69 (14.8%) | 45 (11.3%) |

### Adverse effects

Acute impairment of renal function has been reported in CRF patients receiving ACE inhibitors. A decline in calculated creatinine clearance by greater than 25% within any two-month interval was defined as the limit at which ramipril had to be discontinued. Ramipril was discontinued in five of 397 patients during the first six treatment months due to an acute GFR loss. Ramipril was successfully restarted in two of these five patients after several weeks. Seven patients started renal replacement therapy during the six-month observation period. An analysis of the rate of GFR loss before and after initiation of ramipril (linear regression analysis of GFR loss before and after start of treatment) indicated that in only one of these subjects was an accelerated deterioration of renal function associated with ramipril administration. The incidence of these events was similar to the six-month pretreatment run-in period (Table 4). In those patients who continued to receive ramipril for six months, GFR slowly decreased over time, becoming significantly different relative to baseline after four months (Table 3).

Serum potassium levels increased within two months of treatment by an average of 0.3 mmol/L ($P < 0.0001$, Table 3). A single patient was withdrawn from the study due to hyperkalemia (Table 4). The use of anion exchange resin did not change (3% of patients both before and during ramipril). Mean hemoglobin levels decreased by 0.6 g/dL within two months of treatment and remained stable thereafter (Table 3). In addition, the fraction of children requiring erythropoietin therapy increased from 6.1% to 10.5% within 6 months. This compared to stable hemoglobin levels in the pretreatment run-in period

(mean 12.1 ± 1.7 g/dL at screening, rate of change + 0.1 ± 1.2 g/dL during 6 months run-in period, fraction of EPO treated patients 5.5%). Platelet counts showed a transient slight decrease within the first four months of treatment but had recovered at six months. Leukocyte counts did not change significantly. No withdrawal from the study due to anemia, leukocytopenia, or thrombocytopenia was reported.

Notably, the changes in GFR, potassium, and hemoglobin levels were significantly correlated with the antihypertensive efficacy of ramipril. Those patients with a greater blood pressure response also tended to have a more marked drop of hemoglobin levels ($r = 0.25$, $P < 0.0001$), a greater increase of serum potassium ($r = -0.29$, $P < 0.0001$), and a marginally larger decline of GFR ($r = 0.11$, $P < 0.05$).

## DISCUSSION

This analysis describes the blood pressure–lowering, antiproteinuric, and adverse effects of a fixed dose of ramipril administered in almost 400 children with CRF and elevated or high normal blood pressure in the initial controlled intervention phase of the ESCAPE trial. The blood pressure response was strictly dependent on the prevailing blood pressure level, and the antiproteinuric response on the prevailing degree of proteinuria. The efficacy of ramipril was independent of the underlying renal disease, but slightly greater in patients with advanced CRF. Boys tended to respond better than girls and younger children better than older ones. Ramipril was well tolerated; in only 2.4% of patients was the drug withdrawn due to adverse effects.

In the children with manifest hypertension at start of treatment, MAP was lowered by an average of 11.6 mm Hg, shifting 65% of the initially hypertensive patients into the normal range. This level of antihypertensive efficacy was comparable to recent pediatric studies using ACE inhibitors [15, 16] or angiotensin II receptor antagonists [17–19], and superior to results reported with calcium channel blockers (amlodipine, felodipine) [20, 21] and β-blockers [22]. The relative inefficiency of non-RAS antagonists in controlling renal hypertension is underlined by the fact that 45% of the patients who entered the study with manifest hypertension were already receiving calcium channel blockers, and 20% were receiving beta blockers. Moreover, the overall blood pressure response in patients in whom concomitant antihypertensive medication was either reduced or increased around the start of ramipril (groups C and D) was not different from that observed when only ramipril was added (groups A and B), lending further support to the notion that angiotensin inhibition is a superior antihypertensive strategy in children with CRF.

Ramipril reduced blood pressure as efficiently in renal hypo-/dysplasia and hereditary kidney disorders as in acquired glomerulopathies, suggesting that children with CRF-associated hypertension will benefit from ACE inhibition regardless of their underlying disease.

Moreover, the use of ABPM permitted us to demonstrate that a single morning dose of ramipril provided equally good control of MAP during day- and nighttime.

However, blood pressure was not completely normalized in patients with very severe hypertension, particularly in children with glomerulopathies. A fixed ramipril dose (6 mg/m$^2$) was prescribed that was four times higher than the dose validated in the only clinical trial performed with ramipril in children to date [15]. We cannot exclude that an even higher dose might have yielded a still greater antihypertensive effect. A recent pediatric trial using the ACE inhibitor enalapril showed little dose dependency between 0.625 and 2.5 mg, but an almost doubled antihypertensive effect when the dose was increased from 2.5 to 20 mg [16]. Correspondingly, the full antihypertensive potential of ramipril may not have been exploited in individual patients in this trial.

The ESCAPE trial is not limited to hypertensive CRF patients, but also investigates the renoprotective efficacy of ACE inhibition and intensified blood pressure control in children with high normal blood pressure. This provided the opportunity to study the effect of ramipril in a wide range of baseline blood pressure. Interestingly, the blood pressure response to ramipril was closely related to the blood pressure level at baseline. Blood pressure was reduced on average by 20 mm Hg when baseline 24-hour MAP was 120 mm Hg, but did not change when the prevailing MAP was 80 mm Hg or less. Symptomatic hypotension was observed in only two out of almost 400 children. A lack of blood pressure lowering effect in normotensive patients has also been observed with other RAS antagonists in children [18, 19], and a relationship between baseline blood pressure and the blood pressure response has also been found with a beta-blocker/thiazide combination [22].

The change in 24-hour MAP tended to be more marked in patients with a GFR less than 40 mL/min/1.73 m$^2$. Albeit weak, this effect appeared independent of the prevailing degree of hypertension in the multivariate analysis. In addition, the degree of initial proteinuria was a positive predictor of the antihypertensive efficacy of ramipril, which is compatible with the interpretation that ramipril was most effective in children with a high intrarenal angiotensin tone and glomerular hypertension.

Because proteinuria is an important risk factor for disease progression, which is independent of blood pressure in adults [23] and children with CRF [24], we were particularly interested in the antiproteinuric efficacy of ramipril treatment. We observed an average reduction of proteinuria by approximately 50%, in keeping with other

pediatric trials using RAS antagonists [15, 17–19, 25, 26], and equivalent to the effect observed in adult nephropathies [27–29]. Notably, children with hypo/dysplastic renal disorders responded with a similar relative proteinuria reduction as patients with acquired glomerulopathies. Also, the degree of proteinuria at baseline was correlated with the relative antiproteinuric effect of ramipril, again suggesting that the drug was particularly efficacious in patients with a more marked renal disease activity. As for blood pressure, we do not know whether higher dosing of ramipril would have been more efficacious in lowering proteinuria; however, a study in 14 proteinuric children using only one quarter of the dose applied here reported a similar antiproteinuric effect [15].

Although ramipril was administered at a relatively high dose, remarkably few side effects occurred in the first six months of treatment. The observed mean increase of serum potassium by 0.3 mmol/L compared favorably with values reported in adults (0.3 to 0.6 mmol/L) [3, 4, 30]. Ramipril had to be discontinued because of persistent hyperkalemia only in a single patient (0.3%), compared with 1.2% to 1.6% in adult trials.

Five patients were withdrawn from the study due to an accelerated increase of serum creatinine, and seven patients reached the end point of renal replacement therapy. The incidence of these events was identical to the pretreatment period.

ACE inhibitors are known to interfere with hematopoiesis [31]. In our study, administration of ramipril was associated with a drop in mean hemoglobin levels by 0.6 g/dL within two months. Erythrocyte counts stabilized during further follow-up, but the fraction of patients requiring erythropoietin supplementation was nearly doubled compared to the pretreatment phase.

Dry cough is a frequently reported side effect of ACE inhibition in adults (5% to 39%) [32]. Remarkably, no increased incidence of cough was reported in our patients, and only a single patient was withdrawn due to persistent dry cough (0.3%).

## CONCLUSION

Ramipril appears to be an effective blood pressure lowering and antiproteinuric agent in children with CRF. The magnitude of the antihypertensive effect depends on the degree of blood pressure elevation at baseline, and the antiproteinuric effect on the prevailing level of proteinuria. The safety profile of the drug in children appears to be good. The continued trial will delineate the renoprotective efficacy of ACE inhibition in pediatric kidney diseases.

## APPENDIX

ESCAPE trial participants are as follows: A. Anarat (Adana); A. Bakkaloglu, F. Ozaltin (Ankara); A. Peco-Antic (Belgrade); U. Querfeld, J. Gellermann (Berlin); P. Sallay (Budapest); D. Drozdz (Cracow); K.-E. Bonzel, A.-M. Wingen (Essen); A. Zurowska, I. Balasz (Gdansk); F. Perfumo, A. Canepa (Genoa); D.E. Müller-Wiefel, K. Zepf (Hamburg); G. Offner, B. Enke (Hannover); O. Mehls, F. Schaefer, E. Wühl, C. Hadtstein (Heidelberg); U. Berg, G. Celsi (Huddinge); S. Emre, A. Sirin, I. Bilge (Istanbul); S. Çaliskan (Istanbul-Cerrahpasa); S. Mir, E. Serdaroglu (Izmir); C. Greiner, H. Eichstädt, S. Wygoda (Leipzig); K. Hohbach-Hohenfellner (Mainz); N. Jeck, G. Klaus (Marburg); A. Appiani, G. Ardissino, S. Testa (Milano); G. Montini (Padova); P. Niaudet, M. Charbit (Paris); J. Dusek (Prague); A. Caldas-Afonso, A. Teixeira (Porto); S. Picca, C. Matteucci (Rome); M. Wigger (Rostock); M. Fischbach, J. Terzic (Strasbourg); J. Fydryk, T. Urasinski (Szezecin); R. Coppo, L. Peruzzi (Torino); A. Jankauskiene (Vilnius); M. Litwin, M. Abuauba, R. Grenda (Warszawa); K. Arbeiter (Vienna); T.J. Neuhaus (Zurich).

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