

## ORIGINAL ARTICLE

# Strict Blood-Pressure Control and Progression of Renal Failure in Children

The ESCAPE Trial Group\*

## ABSTRACT

**BACKGROUND**

Although inhibition of the renin–angiotensin system delays the progression of renal failure in adults with chronic kidney disease, the blood-pressure target for optimal renal protection is controversial. We assessed the long-term renoprotective effect of intensified blood-pressure control among children who were receiving a fixed high dose of an angiotensin-converting–enzyme (ACE) inhibitor.

**METHODS**

After a 6-month run-in period, 385 children, 3 to 18 years of age, with chronic kidney disease (glomerular filtration rate of 15 to 80 ml per minute per 1.73 m<sup>2</sup> of body-surface area) received ramipril at a dose of 6 mg per square meter of body-surface area per day. Patients were randomly assigned to intensified blood-pressure control (with a target 24-hour mean arterial pressure below the 50th percentile) or conventional blood-pressure control (mean arterial pressure in the 50th to 95th percentile), achieved by the addition of antihypertensive therapy that does not target the renin–angiotensin system; patients were followed for 5 years. The primary end point was the time to a decline of 50% in the glomerular filtration rate or progression to end-stage renal disease. Secondary end points included changes in blood pressure, glomerular filtration rate, and urinary protein excretion.

**RESULTS**

A total of 29.9% of the patients in the group that received intensified blood-pressure control reached the primary end point, as assessed by means of a Kaplan–Meier analysis, as compared with 41.7% in the group that received conventional blood-pressure control (hazard ratio, 0.65; confidence interval, 0.44 to 0.94;  $P=0.02$ ). The two groups did not differ significantly with respect to the type or incidence of adverse events or the cumulative rates of withdrawal from the study (28.0% vs. 26.5%). Proteinuria gradually rebounded during ongoing ACE inhibition after an initial 50% decrease, despite persistently good blood-pressure control. Achievement of blood-pressure targets and a decrease in proteinuria were significant independent predictors of delayed progression of renal disease.

**CONCLUSIONS**

Intensified blood-pressure control, with target 24-hour blood-pressure levels in the low range of normal, confers a substantial benefit with respect to renal function among children with chronic kidney disease. Reappearance of proteinuria after initial successful pharmacologic blood-pressure control is common among children who are receiving long-term ACE inhibition. (ClinicalTrials.gov number, NCT00221845.)

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**A**MONG BOTH ADULTS AND CHILDREN, chronic kidney disease tends to progress to end-stage renal failure, which is a major clinical problem. Systemic hypertension and glomerular hyperfiltration lead to progressive nephron damage.<sup>1-3</sup> Effective blood-pressure control delays the progression of renal disease in adults with chronic kidney disease, and antihypertensive agents that inhibit the renin-angiotensin system provide superior renoprotection, owing to their additional antiproteinuric, antiinflammatory, and antifibrotic properties.<sup>4-7</sup>

Children comprise less than 1% of the total population with chronic kidney disease and often have congenital kidney malformations, urinary tract disorders, or genetic disorders that affect nephron formation or function. Hypertension is present in approximately 50% of children with chronic kidney disease.<sup>8,9</sup> Both high blood pressure and increased proteinuria are predictors of the progression of renal disease among children with chronic kidney disease,<sup>10</sup> providing a rationale for pharmacologic therapy to control blood pressure and reduce proteinuria. We conducted an international, multicenter, multiyear trial that examined the efficacy of intensified blood-pressure control, in addition to fixed high-dose therapy with an angiotensin-converting-enzyme (ACE) inhibitor, in delaying the progression of renal disease among children with various types of underlying kidney disorders.

## METHODS

### STUDY DESIGN

The Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients (ESCAPE) trial was an investigator-initiated, randomized, controlled clinical trial. We investigated whether intensified blood-pressure control aimed at achieving 24-hour blood-pressure levels in the low range of normal would slow the progression of renal disease among children with chronic renal disease who were receiving fixed-dose ACE-inhibition therapy. Thirty-three pediatric nephrology units in Europe collaborated in the trial.

The study was originally planned as a 3-year study, with a single interim analysis after 2 years. The prespecified stopping criteria were a significant difference in the incidence of progression to

the end point between the two groups at the interim analysis ( $P < 0.05$  by Kaplan-Meier analysis with the use of a log-rank test), significantly accelerated progression of renal failure as compared with the progression rate before the start of the study, and an increased incidence of adverse events either in the total cohort or in either study group. When the interim analysis revealed a slower overall rate of progression than that anticipated, the study period was extended to 5 years. A protocol amendment was filed and was accepted by the ethics committee at each site.

The study was initiated and designed exclusively by the investigators. The study protocol was approved by the central ethics committee of the medical faculty of the University of Heidelberg and by the local institutional review board at each site. Parents of all children provided written informed consent, and the patients provided assent. Data were collected by the local investigators and were analyzed at a central location by the trial coordinators, who vouch for the accuracy and completeness of the data and the analysis. Onsite monitoring of study-data collection was performed by an independent clinical research organization (Omnicare Clinical Research). Aventis Pharmaceuticals (now Sanofi-Aventis) supplied the ramipril and financed the audit of Good Clinical Practices but had no other role in the design of the study, the accrual or analysis of the data, the preparation of the manuscript, or the decision to submit the manuscript for publication.

### PATIENTS

From April 1998 through December 2001, we enrolled 468 children 3 to 18 years of age with stage II to IV chronic kidney disease (i.e., a glomerular filtration rate of 15 to 80 ml per minute per 1.73 m<sup>2</sup> of body-surface area) whose 24-hour mean arterial pressure was either elevated (i.e., >95th percentile) or controlled by antihypertensive medication. Patients were excluded if they had renal-artery stenosis, had undergone kidney transplantation, were in an unstable clinical condition, were receiving immunosuppressive treatment including glucocorticoids, or had major primary cardiac, hepatic, or gastrointestinal disorders. Patients were withdrawn from the study if severe adverse events occurred, if a major concomitant disease developed, if they were obviously noncompliant with the protocol, or if they requested to be withdrawn.

**RUN-IN PERIOD**

Eligible patients underwent ambulatory blood-pressure monitoring at screening, after which they attended clinic visits every 2 months for 6 months. Any treatment with an antagonist of the renin-angiotensin system was discontinued at least 2 months before the end of the run-in period. At the end of the run-in period, 385 patients met the eligibility criteria, underwent baseline examinations, and were randomly assigned to conventional or intensified blood-pressure control (Fig. 1 and Table 1; for additional details, see the Supplementary Appendix, available with the full text of this article at NEJM.org).

**RANDOM ASSIGNMENT AND ADJUSTMENT OF BLOOD PRESSURE**

All children received the same dose of the ACE inhibitor ramipril (Delix, Aventis Pharmaceuticals) at the highest antihypertensive dose approved in adults (10 mg per day) adapted for body size — 6 mg per square meter of body-surface area per day. The dose was increased gradually over the course of the first 2 months from 1.25 mg per square meter per day to 6 mg per square meter per day and was continuously adjusted for the patient's growth during the course of the study.

Patients were centrally stratified according to the underlying-disease group and the annualized decrease in the glomerular filtration rate during the run-in period (fast decrease,  $\geq 3$  ml per minute per  $1.73 \text{ m}^2$  per year; slow decrease,  $< 3$  ml per minute per  $1.73 \text{ m}^2$  per year) and were randomly assigned to either a conventional blood-pressure target (50th to 90th percentile of 24-hour mean arterial pressure) or an intensified blood-pressure target (below the 50th percentile).<sup>11</sup> A blocked randomization scheme, with a block size of four, was used for each center.

During the 5-year study period, blood pressure measured in the outpatient clinic with the use of auscultatory or oscillometric techniques, glomerular filtration rate, and urinary protein excretion were assessed every 2 months, and ambulatory blood-pressure monitoring was performed every 6 months. Antihypertensive therapy was adjusted according to levels of 24-hour mean arterial pressure to achieve the target blood-pressure levels. Any antihypertensive agents except for other antagonists of the renin-angiotensin system were allowed to be added to the patient's drug regimen. A standardized antihypertensive drug-escalation

protocol was suggested but was not compulsory (see the Supplementary Appendix).

**BLOOD-PRESSURE MONITORING**

Ambulatory blood-pressure monitoring was performed with the use of Spacelabs 90207 oscillometric devices (Spacelabs Healthcare) at screening, immediately before randomization, and every 6 months during the study period, as described previously (see the Supplementary Appendix).<sup>11,12</sup>

**OUTCOME MEASURES**

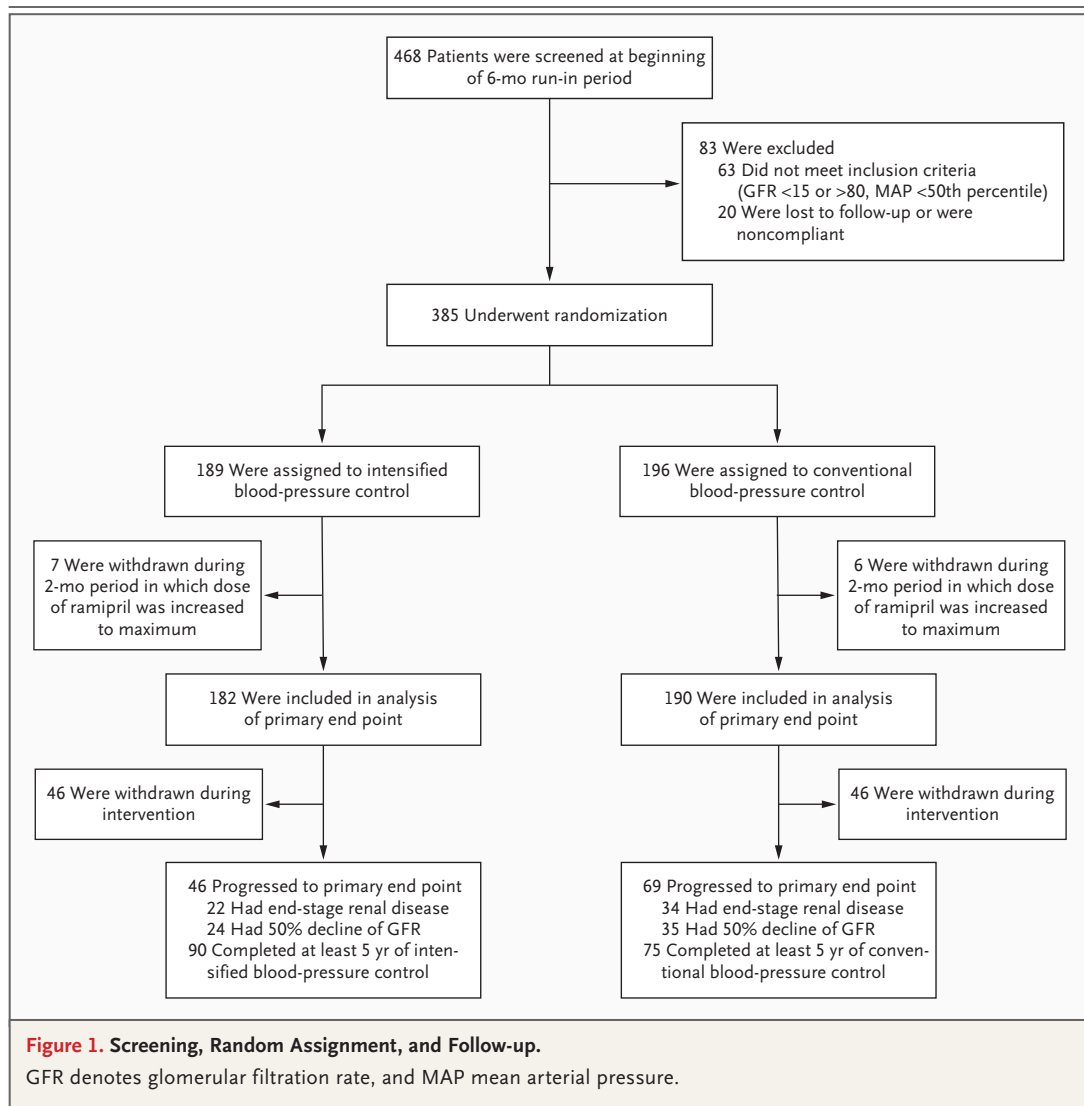
The primary efficacy measure was the time from attainment of the full dose of the ACE inhibitor (month 2) to the first event of the composite end point, which was defined as a 50% reduction in the glomerular filtration rate or progression to end-stage renal disease (glomerular filtration rate  $< 10$  ml per minute per  $1.73 \text{ m}^2$  or start of renal-replacement therapy). Since an acute decrease in the glomerular filtration rate ( $< 25\%$  decrease) is expected after the start of ACE-inhibitor therapy,<sup>13</sup> the glomerular filtration rate that was recorded 2 months after the initiation of ramipril was used as a baseline for the analysis of the reduction in the glomerular filtration rate over time. Secondary end points included changes in blood pressure, glomerular filtration rate, and urinary protein excretion.

**LABORATORY ASSESSMENTS**

Serum and urinary creatinine concentrations and urinary protein concentration were measured at a central location, with the use of Coomassie blue staining for the measurement of protein levels and a modified Jaffé reaction for creatinine measurements. The glomerular filtration rate was estimated by means of the Schwartz formula,<sup>14</sup> with the use of measurements of serum creatinine and height and a  $k$  constant of 0.55; this constant was validated in the central laboratory and was used throughout the study. Proteinuria was expressed as the ratio of protein to creatinine, as determined in 24-hour urine samples. If collection of urine samples was not feasible owing to the patient's age or to enuresis, the protein-to-creatinine ratio was determined in a spot urine sample (14% of samples).

**STATISTICAL ANALYSIS**

We estimated that with 183 subjects in each group, the study would have 80% power to show a clini-



cally relevant difference of 12.5 percentage points in the delay of the progression of renal disease (estimated rate of 85.0% in the group receiving intensified blood-pressure control vs. 72.5% in the group receiving conventional blood-pressure control), at an alpha level of 5%. Anticipating a 30% cumulative dropout rate, we aimed to screen 475 patients.

The following baseline variables were predefined as cofactors that could potentially affect the primary study outcome: progression rate before the start of the study; baseline glomerular filtration rate, blood pressure, and urinary protein excretion; age; sex; and underlying renal disease.

Primary outcomes were analyzed on a time-to-event basis according to the intention-to-treat principle by means of the Kaplan–Meier technique, with the use of log-rank statistics to test for differences in the rates of the end points and Cox proportional-hazard modeling to assess the effects of potential risk factors. Longitudinal changes in proteinuria and blood pressure were evaluated with the use of repeated-measure analysis of variance.

Height, body-mass index, and mean arterial pressure were normalized to standard deviation scores with the use of European reference data sets.<sup>11,15,16</sup> Results are expressed as means  $\pm$  SD, unless otherwise stated.

**Table 1. Baseline Demographic and Clinical Characteristics of the Patients.\***

Characteristic	Intensified Blood-Pressure Control (N=189)	Conventional Blood-Pressure Control (N=196)	P Value
Age (yr)	11.5±4.1	11.5±4.0	0.91
Male sex (%)	56.6	62.2	0.20
Underlying renal disorder (% of patients)			0.71
Glomerulopathies	14	12	
Hypoplasia–dysplasia	66	71	
Other	20	17	
Duration of chronic kidney disease (yr)	6.4±4.4	6.7±4.5	0.69
24-hour mean arterial pressure			
mm Hg	89.5±10.3	89.5±9.5	0.46
Standard-deviation score	1.53±2.15	1.45±1.61	0.93
>95th percentile of mean arterial pressure (%)	37.6	40.8	0.47
ACE-inhibitor washout required (%)	32.8	35.5	0.63
Antihypertensive treatment other than ramipril (% of patients)			
No. of medications			0.21
None	67	67	
1	19	23	
≥2	14	10	
Type of medication			0.65
Diuretic	9	11	
Calcium-channel blocker	18	15	
Beta-blocker	24	21	
Estimated GFR (ml/min/1.73 m <sup>2</sup> )	46.4±19.1	45.4±19.9	0.57
Median change in GFR (ml/min/1.73 m <sup>2</sup> /yr)	−3.8	−4.5	0.50
GFR reduction >3 ml/yr (%)	48.7	52.0	0.47
24-Hr urinary protein excretion (mg/m <sup>2</sup> /day)	978±1603	804±1250	0.33
Urinary protein-to-creatinine ratio†			
Mean	1.40±1.45	1.16±1.32	0.12
Distribution (% of patients)			0.11
<0.5	33	41	
0.5–1.5	18	21	
>1.5	49	38	

\* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, and GFR glomerular filtration rate.

† Both protein and creatinine were measured in milligrams.

## RESULTS

### PATIENTS

A total of 83 of the 468 patients who entered the run-in period did not meet the inclusion criteria (Fig. 1, and the Supplementary Appendix). The remaining 385 patients were randomly assigned to intensified blood-pressure control (189 patients) or conventional blood-pressure control (196). The

groups did not differ significantly with respect to baseline characteristics (Table 1). Underlying renal disorders included renal hypoplasia–dysplasia with or without obstructive or reflux uropathies (264 patients), glomerulopathies (52), and other congenital or hereditary nephropathies (69).

A total of 13 patients (7 in the group that received intensified blood-pressure control and 6 in the group that received conventional blood-pres-



sure control) were withdrawn from the study during the 2-month period in which the dose of ramipril was increased to the maximum dose. The reasons for withdrawal included request by the patient, loss to follow-up, or noncompliance (nine patients), hyperkalemia (two), and acute deterioration of the glomerular filtration rate (two). After withdrawal of these patients, 372 patients — 182 in the group that received intensified blood-pressure control and 190 in the group that received conventional blood-pressure control — remained and were included in the analysis of the primary end point. During the course of the study, 92 patients (46 in each group) were withdrawn before reaching the primary end point; the reasons for withdrawal included transition to adult units (49 patients), patient's request (12), nonadherence with taking the study medication (12), hyperkalemia (7), hypotension (2), and other adverse events (10). The rate of withdrawal for reasons other than reaching the primary end point was 5.5% per year, as compared with rates of 10 to 21% per year that have been reported in trials of renoprotection in adults.<sup>4,5,17,18</sup> The types and incidences of adverse events did not differ significantly between the two groups (Table 2).

#### PRIMARY COMPOSITE END POINT

A total of 46 of 182 patients in the intensified-control group, as compared with 69 of 190 in the conventional-control group, progressed to the primary end point, corresponding to an actuarial 5-year rate of delay in the progression of renal disease of 70.1% versus 58.3% ( $P=0.02$  with the use of the log-rank test) (Fig. 2A). The hazard ratio for progression to the end point with intensified blood-pressure control was 0.65 (95% confidence interval [CI], 0.44 to 0.94;  $P=0.02$ ).

Several covariates were associated with an increased overall risk of reaching the primary end point. These included a low baseline glomerular filtration rate (hazard ratio for high glomerular filtration rate, 0.92; 95% CI, 0.91 to 0.94;  $P<0.001$ ), greater degree of proteinuria (hazard ratio, 1.46; 95% CI, 1.35 to 1.59;  $P<0.001$ ), higher 24-hour mean arterial pressure (hazard ratio, 1.23; 95% CI, 1.13 to 1.33;  $P<0.001$ ), and older age (hazard ratio, 1.07; 95% CI, 1.02 to 1.12;  $P=0.002$ ). The reduction in risk achieved with intensified blood-pressure control remained significant after adjustment for these covariates.

An initial 50% reduction in proteinuria within the first 2 months after the initiation of ramipril

therapy was highly predictive of a delay in the progression of renal disease (hazard ratio, 0.46; 95% CI, 0.27 to 0.79;  $P=0.005$ ). ACE-inhibitor therapy before the start of the study did not influence the effect of the intervention on delay in the progression of renal disease. The results of additional subgroup analyses are shown in Figure 3 and in the Supplementary Appendix.

#### SECONDARY OUTCOMES

##### Blood Pressure

Within 2 months after the start of ramipril therapy, the mean ( $\pm$ SD) systolic and diastolic blood pressures as measured in the outpatient clinic were reduced in the study cohort as a whole; mean systolic pressure decreased from  $118.3\pm 14.3$  mm Hg to  $109.4\pm 14.4$  mm Hg ( $P<0.001$ ) in the study cohort as a whole, with a mean level after 2 months of  $108.2\pm 14.7$  mm Hg in the intensified-control group and  $110.2\pm 14.5$  in the conventional-control group ( $P=0.22$ ), and mean diastolic pressure decreased from  $73.0\pm 12.3$  mm Hg to  $65.0\pm 12.5$  mm Hg in the study cohort as a whole ( $P<0.001$ ), with a mean level after 2 months of  $63.8\pm 14.0$  mm Hg in the intensified-control group and  $64.8\pm 12.5$  mm Hg in the conventional-control group ( $P=0.50$ ). Ambulatory blood-pressure monitoring confirmed that there was a marked reduction in 24-hour blood-pressure levels in the first 6 months of the study. At the 6-month examination, 24-hour systolic and diastolic blood pressures and mean arterial pressure had decreased from  $119.2\pm 11.9$ ,  $73.4\pm 9.8$ , and  $89.3\pm 9.9$  mm Hg, respectively (i.e., standard-deviation scores of  $0.9\pm 1.4$ ,  $1.2\pm 1.8$ , and  $1.5\pm 1.9$ ), to  $111.4\pm 10.5$ ,  $66.1\pm 8$ , and  $81.9\pm 8.2$  mm Hg (i.e., standard-deviation scores of  $0.1\pm 1.3$ ,  $-0.2\pm 1.5$ , and  $0.1\pm 1.5$ ) ( $P<0.001$  for all comparisons). In the cohort as a whole, 24-hour mean arterial pressure continued to be reduced during the 5-year study period, at a time-integrated mean of  $81.8\pm 7.5$  mm Hg (standard-deviation score of  $0.02\pm 1.3$ ) ( $P<0.001$ ) (Fig. 4).

The mean dose of ramipril was  $5.2\pm 1.3$  mg per square meter per day in the intensified-control group and  $5.1\pm 1.4$  mg per square meter per day in the conventional-control group ( $P=0.50$ ). Adherence to the medication regimen was assessed by repetitive assessments of plasma ACE activity, which decreased from  $58\pm 29$  IU per liter at baseline to  $13\pm 10$  IU per liter during treatment, indicating excellent compliance with the drug regimen.

After the 6-month examination, at which ambulatory blood-pressure monitoring was per-

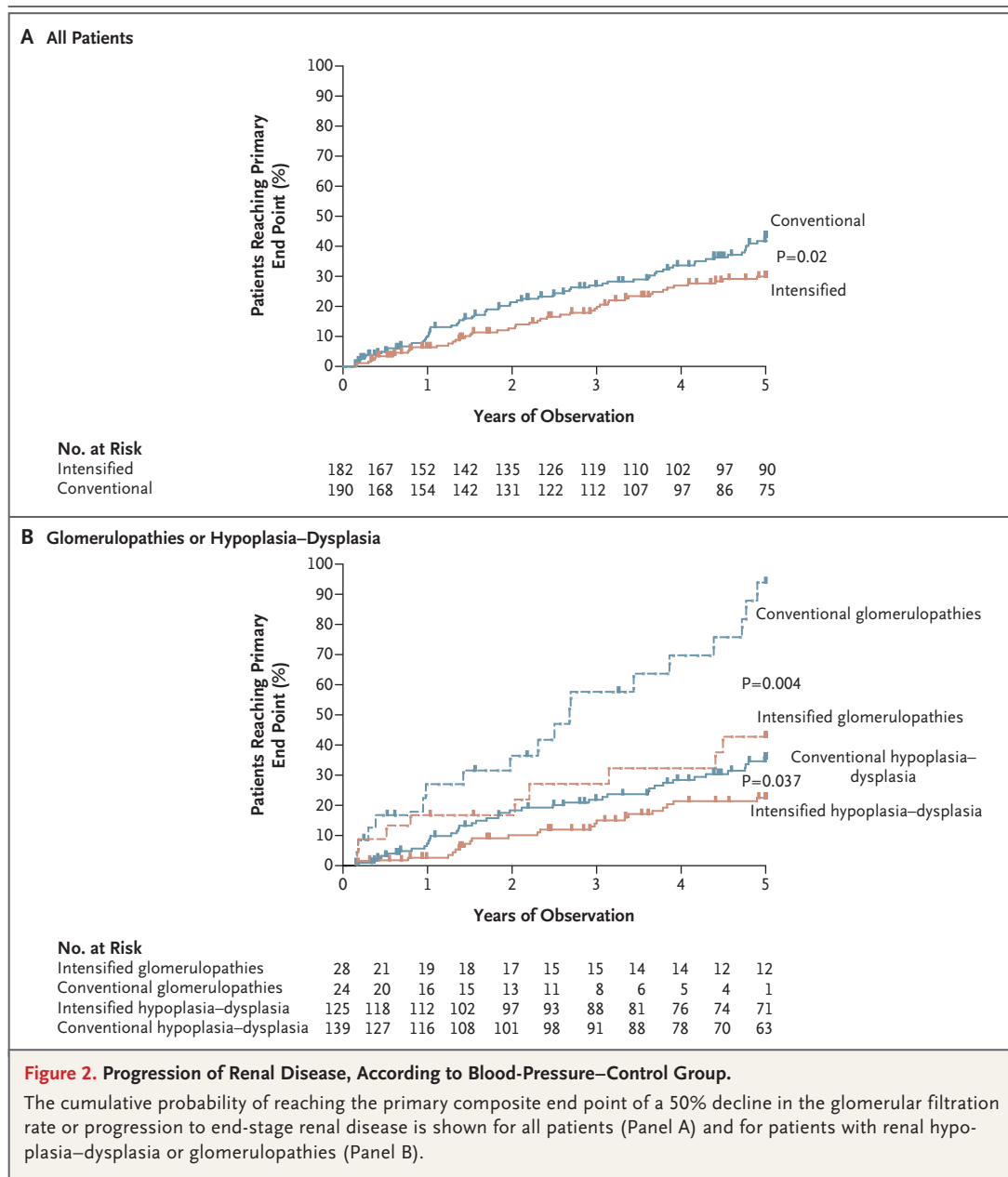
**Table 2. Reported Adverse and Serious Adverse Events.\***

Event	Intensified Blood-Pressure Control (N=189)	Conventional Blood-Pressure Control (N=196)
	<i>no. of events</i>	
Any adverse event	42	48
Any serious adverse event	48	62
Discontinuation of study medication		
Due to adverse event	20	30
Due to serious adverse event	36	42
Type of adverse event		
Decreased glomerular filtration rate	21	29
Hyperkalemia	8	10
Hypotension	2	0
Dizziness	1	0
Cough	0	4
Stomatitis	1	0
Tonsillitis	2	0
Urinary tract infection	0	1
Nocturnal enuresis	0	1
Gastrointestinal symptoms	1	0
Fatigue	0	1
Hair loss	2	0
Increase in liver enzymes	2	1
Leukocytopenia	2	1
Type of serious adverse events		
Death	0	1
Need for renal-replacement therapy	30	39
Decreased glomerular filtration rate	1	1
Hyperkalemia	3	4
Hypotension	0	2
Dizziness	0	1
Respiratory tract infection	2	3
Pyelonephritis	2	0
Enteritis or diarrhea	3	0
Weight loss	0	2
Headache	1	0
Pericarditis	0	1
Anemia	1	0
Skin infection after insect bite	1	0
Pregnancy†	0	1
Urologic surgery	1	0
Planned diagnostic procedure (inpatient)	3	2
Esophageal varicose vein bleeding‡	0	4
Dislocation of knee (accident)	0	1

\* Adverse event refers to any adverse event other than a serious adverse event. Adverse events and serious adverse events were defined according to the Good Clinical Practices guidelines. An event was considered to be a serious adverse event if it led to hospitalization or resulted in persistent or significant disability or incapacity.

† Pregnancy was considered to be a serious adverse event because angiotensin-converting–enzyme inhibitor therapy can be detrimental to the fetus.

‡ All four of these events occurred in one patient with autosomal recessive polycystic kidney disease.

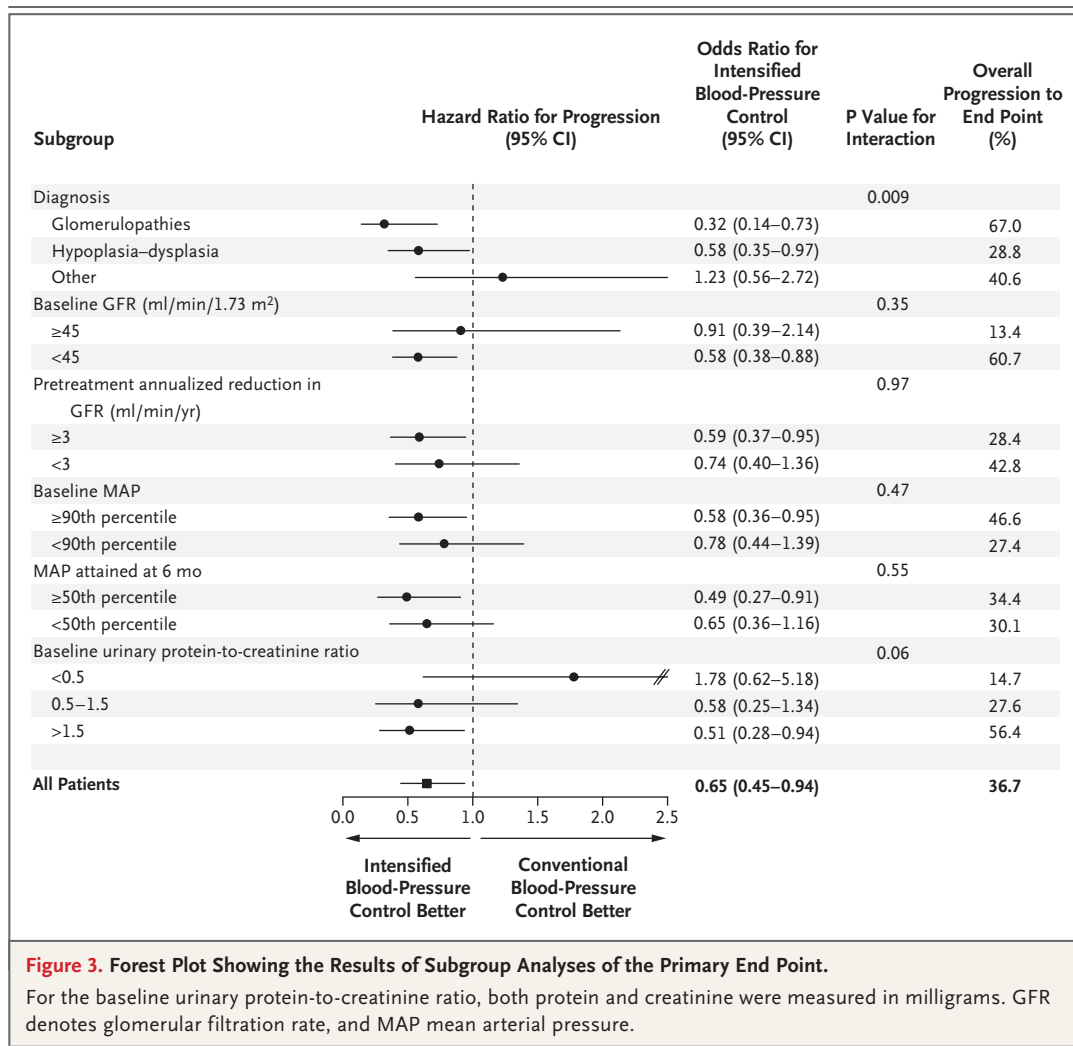


formed, antihypertensive medication other than ramipril was adjusted to reach the blood-pressure target for each group. The mean number of antihypertensive drugs prescribed per patient in addition to ramipril was  $0.9 \pm 1.1$  in the intensified-control group, as compared with  $0.5 \pm 0.9$  in the conventional-control group ( $P=0.003$ ).

In the intensified-control group, the target 24-hour mean arterial pressure (<50th percentile) was reached by 60% of the patients at 12 months, 73% at 24 months, 71% at 36 months,

72% at 48 months, and 74% at 60 months. In the conventional-control group, 24-hour mean arterial pressure dropped below the 50th percentile even with ramipril monotherapy in more than 50% of the patients. The groups differed in 24-hour mean arterial pressure by 3.8 mm Hg at 12 months, 3.1 mm Hg at 24 months, 2.7 mm Hg at 36 months, 3.9 mm Hg at 48 months, and 2.9 mm Hg at 60 months ( $P=0.002$  to  $0.03$ ). A time-integrated mean arterial pressure within the target range was attained by 63.8% of the patients





in the intensified-control group and by 49.1% in the conventional-control group.

#### Reduction in the Glomerular Filtration Rate

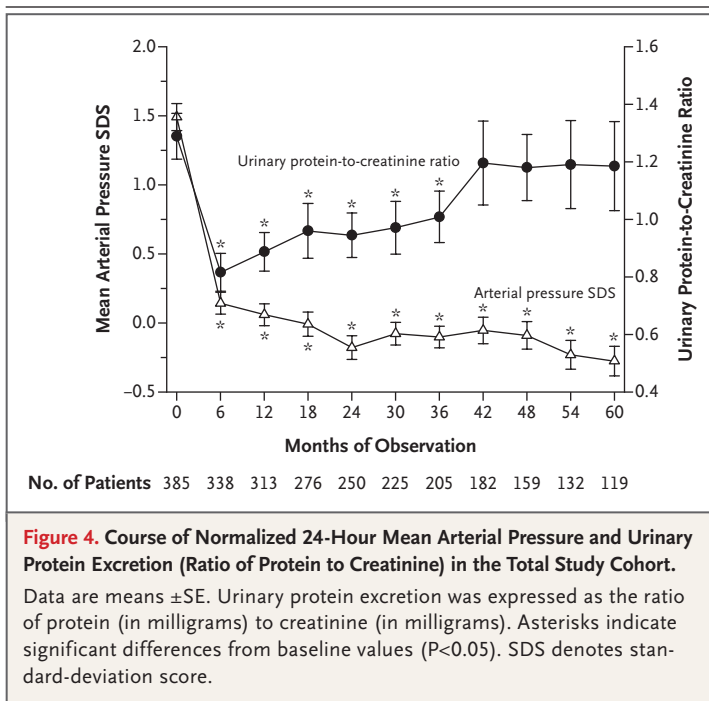
The annualized reduction in the glomerular filtration rate changed from  $3.3 \pm 9.7$  ml per minute per  $1.73 \text{ m}^2$  per year during the 6-month run-in period to  $2.4 \pm 7.6$  ml per minute per  $1.73 \text{ m}^2$  per year between month 2 and the last observation ( $P=0.11$ ). The acute change in the glomerular filtration rate during the initiation of ramipril therapy (months 0 to 2) was  $-2.1 \pm 6.9$  ml per minute per  $1.73 \text{ m}^2$ , and there was no significant difference between the two groups (a change of  $-1.6 \pm 7.2$  in the intensified-control group and of  $-2.6 \pm 6.5$  in the conventional-control group,  $P=0.22$ ). The annual reduction in the glomerular filtration rate was  $1.1 \pm 7.8$  ml per minute per  $1.73 \text{ m}^2$  in the intensi-

fied-control group and  $2.5 \pm 5.9$  in the conventional-control group ( $P=0.29$ ).

The slope of the glomerular filtration rate from month 2 to the end of the intervention period was significantly associated with age ( $r=-0.27$ ,  $P<0.001$ ), baseline urinary protein excretion ( $r=-0.29$ ,  $P<0.001$ ), 24-hour mean arterial pressure ( $r=-0.24$ ,  $P<0.001$ ), and glomerular filtration rate ( $r=0.41$ ,  $P<0.001$ ). The mean glomerular filtration rate (positive association, partial  $r^2=0.16$ ), 24-hour mean arterial pressure (negative association, partial  $r^2=0.10$ ), and age (negative association, partial  $r^2=0.02$ ) were independent predictors of the slope of the glomerular filtration rate.

#### Proteinuria

Median urinary protein excretion was reduced from 0.82 g of protein per gram of creatinine (in-



terquartile range, 0.27 to 1.74) to 0.36 g of protein per gram of creatinine (interquartile range, 0.11 to 0.95) during the first 6 months ( $P < 0.001$ ). In contrast to the persistently excellent blood-pressure control, proteinuria gradually increased again over time, resulting in a level of proteinuria after 36 months that did not differ significantly from that at baseline (Fig. 4).

## DISCUSSION

The results of this trial show that intensified blood-pressure control delays the progression of renal disease in children with chronic kidney disease who receive a fixed high dose of an ACE inhibitor. Despite the relatively modest additional reduction in blood pressure achieved with intensified antihypertensive treatment, the progression of renal disease was significantly delayed with the intensified-intervention protocol. In the cohort as a whole, a target blood pressure in the low range of normal was associated with a 35% reduction in the relative risk of losing 50% of renal function or progression to end-stage renal disease within 5 years after the initiation of ramipril therapy. Intensified blood-pressure control effectively delayed the progression of renal disease among children with an underlying glomerulopathy or renal hypoplasia or dysplasia, but not among children

with other congenital or hereditary nephropathies.

When the present trial was designed in the late 1990s, several prospective, randomized trials involving adults with kidney disease, whether it was associated with diabetes or not, had established the renoprotective advantage of ACE inhibitors over other antihypertensive drug classes,<sup>4-7</sup> and it seemed to us to be unethical in a long-term, randomized, controlled trial to expose children with chronic kidney disease to an antihypertensive protocol that did not include an ACE inhibitor. Hence, we decided to treat all patients with a fixed high dose of an ACE inhibitor and to add antihypertensive agents that do not target the renin-angiotensin system, if required, to achieve the target blood pressure in the low range of normal.

The dose of ramipril that we used (6 mg per square meter per day) was the highest antihypertensive dose approved in adults, adapted for body size, and was higher by a factor of four than that previously used in children.<sup>19</sup> Thus, we hoped that any renoprotective effect of intensified blood-pressure control would be independent of and additive to that of inhibition of the renin-angiotensin system.

Within the first 6 months after the initiation of ramipril therapy, the addition of ramipril alone was associated with a decreased 24-hour mean arterial pressure in both groups — to approximately the 50th percentile, on average. Given this marked initial response, considerable overlap between the treatment groups emerged. More than 50% of the patients in the conventional-control group attained blood-pressure levels in the low range of normal, and relatively little additional antihypertensive medication was required in the intensified-control group to achieve the low-normal blood-pressure target. We speculate that the excellent antihypertensive efficacy of the ACE inhibitor might be related to the high proportion of patients with relatively mild hypertension at baseline — mainly those with renal dysplasia. Notwithstanding the marked background effect of ramipril, a consistent difference of approximately 3 to 4 mm Hg in 24-hour mean arterial pressure was achieved with the intensified intervention from the end of the first year to the end of the 5-year study period.

The consistent benefit with respect to the delay in the progression of renal disease that we observed with intensified blood-pressure control is

consistent with the results of the Modification of Diet in Renal Disease (MDRD) trial involving patients with chronic kidney disease and proteinuria<sup>20,21</sup> but differs in part from the findings of other studies involving adults with low-normal blood-pressure targets.<sup>22-24</sup> The variable findings in blood-pressure intervention trials may be explained by differences in the underlying kidney disorders or the racial or ethnic backgrounds of the subjects or by the use in our study of ambulatory blood-pressure monitoring, which may have allowed more efficient monitoring of achieved blood pressure than was performed in other studies. Moreover, our mean follow-up period was longer than that of previous trials involving adults; no significant difference between the treatment groups would have been detected if this trial had been stopped after 3 years.

Within the first 6 months, treatment with ramipril was associated with decreased proteinuria (an average decrease of 50%). The early anti-proteinuric response was predictive of long-term benefit with respect to kidney function, confirming previous findings in studies involving adults.<sup>5,25,26</sup> However, proteinuria gradually increased during ongoing ACE-inhibitor therapy to levels that were no different after the third year of follow-up from those at baseline. This increase in proteinuria was independent of continuously excellent blood-pressure control. We speculate that the late increase in proteinuria may be related to the “aldosterone breakthrough” phenomenon, a condition that was recently reported to occur in up to 40% of adults receiving long-term ACE-inhibitor therapy<sup>27</sup> and that is thought to be due to up-regulation of other enzymes such as

chymase. Alternatively, intrarenal vasoactive mediators may be up-regulated over time to compensate for the reduced angiotensin tone. Preliminary results among our participants suggest that there is an up-regulation of urinary excretion of endothelin-1 that parallels the rise in proteinuria.<sup>28</sup> Finally, it is possible that the late increase in proteinuria reflected the natural course of the underlying kidney disorders. Proteinuria during treatment was clearly inversely associated with preservation of kidney function and the rate of decline in the glomerular filtration rate. Thus, follow-up strategies are needed to treat patients in whom secondary proteinuria that is resistant to ACE-inhibitor therapy develops. Such strategies might include increasing the dose of ACE inhibitors, switching to treatment with angiotensin type 1–receptor blockers or renin inhibitors, or administering combination therapies.

In conclusion, targeting blood-pressure control to the low range of normal is associated with slowing the progression of renal disease among children with progressive chronic kidney disease due to primary glomerulopathies or renal hypoplasia–dysplasia. The renoprotective effect of intensified blood-pressure control is additive to the potential benefit conferred by high-dose ACE inhibition.

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#### APPENDIX

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