A Randomized, Controlled Trial of Oral Intestinal Sorbent AST-120 on Renal Function Deterioration in Patients with Advanced Renal Dysfunction

Ran-hui Cha, Shin Wook Kang, Cheol Whee Park, Dae Ryong Cha, Ki Young Na, Sung Gyun Kim, Sun Ae Yoon, Sang Youb Han, Jae Hyun Chang, Sue K. Park, Chun Soo Lim, and Yon Su Kim

Abstract

Background and objectives The notion that oral intestinal sorbent AST-120 slows renal disease progression has not been evaluated thoroughly. In this study, we investigated the long-term effect of AST-120 on renal disease progression (doubling of serum creatinine, eGFR decrease >50%, or initiation of RRT) in patients with advanced CKD.

Design, setting, participants, & measurements We prospectively recruited 579 patients (CKD stage 3 or 4) from 11 medical centers in Korea from March 4, 2009 to August 31, 2010 and randomized them into an AST-120 arm and a control arm. Patients in the AST-120 arm were given 6 g AST-120 in three divided doses per day, and those in the control arm received only standard conventional treatment (open-label design) for 36 months or until the occurrence of primary outcomes.

Results Levels of serum and urine indoxyl sulfate and β2-microglobulin decreased throughout the study period in both treatment arms; however, there was not a significant difference in change in uremic toxins in the AST-120 and control arms. The two arms were not different in the occurrence of composite primary outcomes (100 events in 272 individuals in the AST-120 arm and 100 events in 266 individuals in the control arm; hazard ratio, 1.12; 95% confidence interval, 0.85 to 1.48; log-rank P=0.45). The decline in eGFR and change in proteinuria were similar in the two treatment arms over time ($P_{\text{randomization–time}}$=0.64 and $P_{\text{randomization–time}}$=0.16, respectively). There was no difference in mortality (nine deaths in the AST-120 arm and 11 deaths in the control arm; log-rank P=0.73) or unplanned hospitalizations (102 in the AST-120 arm and 109 in the control arm; log-rank P=0.76) in the two treatment arms. There was no significant difference of the health–related quality of life score between the two arms.

Conclusions Long-term use of AST-120 added to standard treatment did not change renal disease progression, proteinuria, mortality, and health–related quality of life in patients with advanced renal dysfunction.

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Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

Correspondence: Prof. Yon Su Kim, Department of Internal Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul, 110-799, Korea. Email: yonsukim@snu.ac.kr

Introduction

In Korea, approximately 1300 per 1 million of the population are receiving RRT, and the incidence of ESRD is increasing at a rate of ≥10% per year (1). The CKD prevalence in Korean adults was 7.2% in 2007 according to the Korean National Health and Nutrition Examination Survey (2). In clinical trials that have examined whether angiotensin–converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) slow CKD progression, both treatments were found to be effective in terms of serum creatinine (SCr) preservation, progression to ESRD, or death (3–5). However, many patients still progress to ESRD, despite the best medical management. Thus, new measures to alleviate renal progression are needed to improve clinical outcomes and lessen the socioeconomic burden of CKD.

Dietary proteins are usually hydrolyzed in the colon by bacteria, such as *Escherichia coli*. Protein-derived tryptophan is metabolized into indole, which is then absorbed into the bloodstream and oxidized into indoxyl sulfate (IS) in the liver (6). IS is normally excreted into the urine, but patients with CKD cannot effectively excrete IS because of reduced renal function (7,8). Elevated serum IS causes elevated expression of genes related to tubulointerstitial fibrosis, such as those coding for TGF-β1 and collagen (9,10).

AST-120 (Kremezin, Daiichi Sankyo, Japan and CJ HealthCare Corporation, Republic of Korea) adsorbs uremic toxins and precursors, including indole, and excretes them into the feces. AST-120 reduced glomerular sclerosis and SCr levels, increasing survival in CKD animal models (11–13), and it also alleviated uremic symptoms and slowed the rate of functional deterioration, even showing renal function recovery in patients with CKD (14–16). The renoprotective effects of AST-120 were related to the adsorption of uremic toxins, such as IS, and were not related to the adsorption or excretion of creatinine itself (17).

In the carbonaceous adsorbent used to prevent the progression of CKD (CAP-KD) Trial, researchers found no significant differences in primary composite outcomes, but the eGFR decreased less in the AST-120 arm (18). However, the study was limited by an insufficient number of enrolled patients (n=460) and a relatively short period of treatment.

Here, we investigated the long-term effects of AST-120 on renal disease progression in a large sample of patients with advanced CKD.

Materials and Methods

Study Design

The Kremezin Study against Renal Disease Progression in Korea was a prospective, 11–center, randomized, open–label, controlled study (Clinicaltrials.gov: NCT00860431). The participants were recruited from March 4, 2009 to August 31, 2010 and followed up for 36 months. The primary outcome was a composite of SCr doubling, 50% reduction in eGFR, or the initiation of RRT. Secondary outcomes were (*1*) eGFR changes (ΔeGFR per 3 months), (*2*) changes in urinary protein excretion, (*3*) all-cause mortality, (*4*) all-cause hospitalization other than planned surgeries and interventions, and (*5*) changes in health–related quality of life (QOL).

Eligibility

Patients eligible for this study (*1*) provided informed consent, (*2*) were ages ≥18 years old, (*3*) were followed over 6 months by nephrologists, (*4*) had CKD stage 3 or 4 with an eGFR estimated by the Cockcroft–Gault equation of 15–59 ml/min per 1.73 m^2 and an SCr of 2.0–5.0 mg/dl, (*5*) had a measured or expected eGFR decline of ≥2.5 ml/min per 1.73 m^2 over 6 months or ≥5 ml/min per 1.73 m^2 over 12 months (SCr values were measured two or more times at intervals of ≥4 weeks), (*6*) had controlled BP (systolic BP ≤160 mmHg and diastolic BP ≤100 mmHg measured three or more times at intervals of ≥4 weeks), and (*7*) had no significant changes in the medical treatment for CKD.

The study excluded patients who (*1*) had taken ketosteril or AST-120 within the last 2 months; (*2*) had a gastrointestinal disease, such as an active ulcer or inflammatory bowel disease; (*3*) had an obstructive uropathy or other reversible kidney disease; (*4*) had autosomal dominant polycystic kidney disease; (*5*) had proteinuria ≥10 g/d (spot urine protein-to-creatinine ratio ≥10.0 g/g creatinine); (*6*) had received a kidney transplantation; (*7*) had moderate to severe heart failure (New York Heart Association classes 3 and 4), uncontrolled arrhythmia, or unstable angina; (*8*) had active infections or uncontrolled inflammatory diseases; (*9*) had liver cirrhosis (Child–Turcotte–Pugh class B or C); (*10*) had a progressive malignancy; (*11*) had a cerebral infarction or hemorrhage within the last 6 months, with the exception of a transient ischemic attack; (*12*) showed an uncontrolled blood sugar level (hemoglobin A1c >10.0%); (*13*) had severe anemia (hemoglobin <7.0 g/dl); (*14*) had a life expectancy <12 months; (*15*) were pregnant, lactating, or planning to be

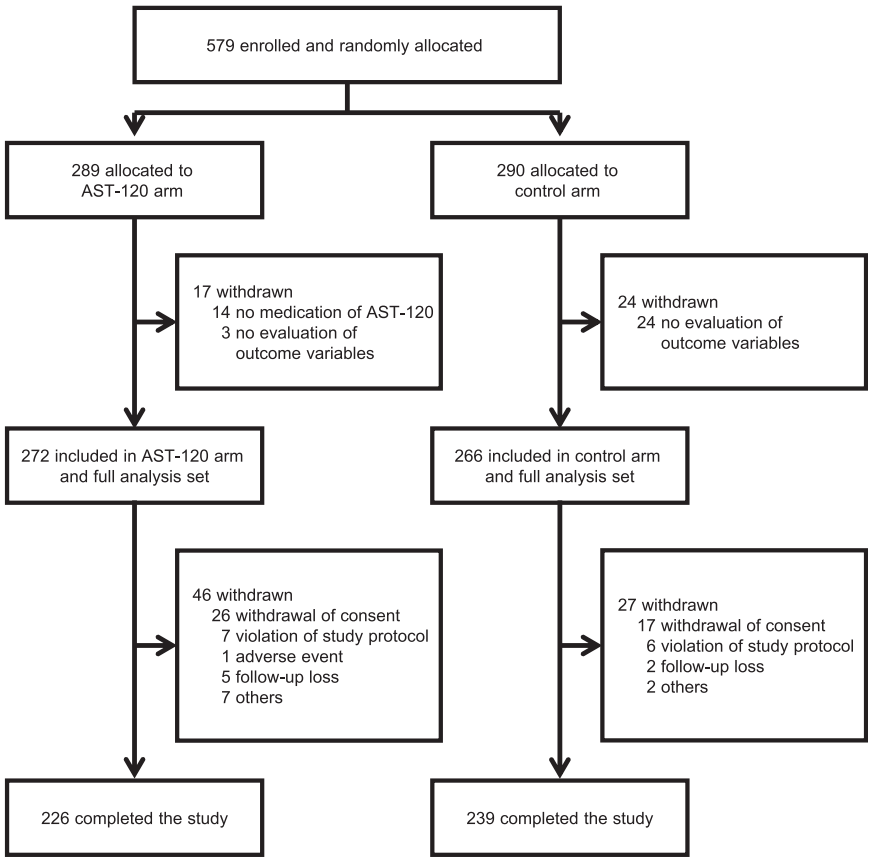

Figure 1. | **Diagram of participant enrollment and analysis in the Kremezin Study against Renal Disease Progression in Korea, 2009–2013.**

pregnant during the study period; and (*16*) were determined by the investigators to be inappropriate participants.

The protocol was approved by the institutional review boards of the participating centers. The results were evaluated by the Data and Safety Monitoring Board, which allowed for continuation of recruitment and interventions. We conducted this study in compliance with the principles of the Declaration of Helsinki.

Randomization

During the 2- to 6-month screening period, the SCr was measured three times at intervals of ≥4 weeks. The patients were enrolled and randomized 1:1 into the control and AST-120 arms. We performed mixed block randomization with blocks of four or six and statistical analytical software–generated random numbers. We stratified the patients by sex and cause of CKD (*i.e.*, diabetic versus nondiabetic nephropathy) and used web-based randomization with an algorithm managed by the Medical Research Collaborating Center in Seoul National University Hospital.

Interventions and Measurements

The participants received standard care, including ACE inhibitors and/or ARBs and lipid modifiers. In addition, physicians and nurses as well as dietitians intensively educated the participants about a low-salt and low-protein diet every time that they visited the clinics as scheduled. The participants in the AST-120 arm were instructed to self-administer the drug orally in three divided doses (three packs a day) for a total of 6 g/d. Those in the control arm received only standard conventional treatment (open-label design) for 36 months or until the occurrence of primary outcomes. The participants completed a daily record of AST-120 use, and the nurses compared those records with the residual packs of AST-120 every visit to assess compliance.

The participants visited the clinic every 3 months and underwent laboratory tests, including SCr, urinary protein excretion, serum β2-microglobulin (β2-MG), and serum and urine IS, and they completed health–related QOL questionnaires using the Medical Outcomes Study 36–Item Short–Form Health Survey (SF-36) as scheduled.

Measurement of IS

Serum and urine IS was measured with a high–performance liquid chromatography–fluorescence detector (Agilent 1100 Series; Agilent Technologies, Santa Clara, CA). Urine and serum (300 μl) were centrifuged at 13,000 rpm for 5 minutes, and a guard column (SG80; 5 μm; 4.6 × 150 mm; 40.0°C; CapcellPak MF, Shiseido, Japan) was used. The flow rate was 1.0 ml/min, and the total run time was 11.0 minutes. Eight standard samples of IS at concentrations from 0 to 10.0 mg/dl were prepared for calibration. The fluorescence intensity between 295 nm (excitation) and 390 nm (emission) was measured (reference range: serum, 0.05–1.00 mg/dl; urine, not established). The intra– and interassay

Table 1. Baseline characteristics of intention-to-treat participants

Variable	Control, *n*=266	AST-120, *n*=272	*P* Value
Age, yr	56.8±13.2	56.7±13.3	0.93
Sex, women/men (%)	88/178 (33.1/66.9)	87/185 (32.0/68.0)	0.79
ESRD cause, *n* (%)			>0.99
Diabetic	133 (50.0)	136 (50.0)	
Nondiabetic	133 (50.0)	136 (50.0)	
BMI, kg/m^2	24.5±3.5	24.7±3.9	0.97
BSA, m^2	1.73±0.18	1.73±0.17	0.97
SBP, mmHg	129.5±15.81	129.2±14.7	0.65
DBP, mmHg	75.8±10.2	75.8±9.9	0.85
Serum Cr, mg/dl	2.84±0.70	2.82±0.66	0.79
eGFR, ml/min per 1.73 m^2	26.6±7.3	26.9±7.7	0.79
CKD stage 3/4, *n* (%)	78/188 (29.3/70.7)	72/200 (26.5/73.5)	0.50
Urinary protein, g/g Cr	1.30 (0.41, 2.91)	1.18 (0.40, 2.89)	0.46
Hb, g/dl	11.3±1.7	11.4±1.9	0.67
Albumin, g/dl	4.0±0.5	4.0±0.4	0.46
Uric acid, mg/dl	8.1±1.7	8.3±2.1	0.30
LDL, mg/dl	95.3±38.2	92.1±28.9	0.84
CRP, mg/dl	0.12 (0.026, 0.49)	0.12 (0.027, 0.42)	0.40
Serum β2-MG, mg/L	6.73 (4.98, 8.39)	6.30 (4.89, 7.97)	0.28
Serum IS, mg/dl	0.53 (0.24, 0.93)	0.50 (0.26, 0.82)	0.87
Urine IS, mg/dl	5.52 (3.01, 9.58)	5.16 (2.94, 9.12)	0.60
RAS inhibitor, *n* (%)	238 (89.5)	249 (91.5)	0.46
β-Blocker, *n* (%)	141 (53.0)	144 (52.9)	>0.99
Calcium channel blocker, *n* (%)	180 (67.7)	177 (65.1)	0.58
Diuretics, *n* (%)	154 (57.9)	173 (63.6)	0.19
Lipid modifier, *n* (%)	179 (67.3)	185 (68.0)	0.92

Continuous variables: mean±SD or median (25%, 75%). BMI, body mass index; BSA, body surface area; SBP, systolic BP; DBP, diastolic BP; Cr, creatinine; Hb, hemoglobin; CRP, C-reactive protein; β2-MG, β2-microglobulin; IS, indoxyl sulfate; RAS, renin-angiotensin-aldosterone system.

Table 2. Uremic toxin levels over time: Intention-to-treat participants

Time	Serum IS, mg/dl			
	Control	Δ (95% CI)	AST-120	Δ (95% CI)
Enrollment	0.70±0.05	NA	0.64±0.03	NA
12 mo	0.89±0.05	0.18 (−1.61 to 1.90)	0.71±0.05	0.11 (−1.34 to 1.95)
24 mo	1.03±0.07	0.29 (−1.23 to 2.41)	0.65±0.05	0.12 (−1.15 to 1.95)
36 mo	0.98±0.08	0.26 (−1.51 to 2.95)	0.58±0.04	0.07 (−1.26 to 1.59)
P value (randomization)		<0.001		
P value (time)		<0.001		
P value (randomization × time)		0.29		

IS, indoxyl sulfate; β2-MG, β2-microglobulin; 95% CI, 95% confidence interval; NA, not applicable.

coefficients of variation were 5.54% and 3.42%, respectively, at the concentration of 0.5 mg/dl and 6.44% and 4.52%, respectively, at the concentration of 1.0 mg/dl.

Sample Size and Statistical Method

We estimated the sample size on the basis of the results of previous clinical trials. For the putative incidences of primary outcomes, we used 0.58 events per 3 years in the control arm and 0.45 events per 3 years in the AST-120 arm. We estimated the sample size required to detect a statistically significant difference between the two arms using the following equation (80% statistical power and 5% α-error [two sided]):

$$N_C = \left(\frac{Z_{\alpha/2}\sqrt{2\bar{p}(1-\bar{p})} + Z_{\beta}\sqrt{P_C(1-P_C)+P_T(1-P_T)}}{d} \right)^2$$

with P_C=0.58 and P_T=0.45.

Allowing for a 20% dropout or withdrawal rate, we calculated the required sample size as 289 patients per treatment arm.

We performed the primary analysis in intention-to-treat participants, who were defined as those who were randomized and evaluated regarding the study outcomes. We conducted all statistical analyses in the Medical Research Collaborating Center in Seoul National University Hospital using SAS, version 9.2 (SAS Institute Inc., Cary, NC). We used the *t* test to determine the means and SDs of the continuous variables, the chi-squared test for categorical variables, Kaplan–Meier survival analysis to determine cumulative survival probability, and the log-rank test to test the survival difference between the two arms. Multivariate Cox proportional hazards regression analysis was also used, and all of the variables were included in the model. The eGFR changes at each follow-up were calculated according to the following equation: $eGFR_{baseline} - eGFR_{each\ follow\text{-}up}$. We used a mixed model to test the within- and between-individual differences in the repeatedly measured eGFR changes between the two arms. Moreover, we selected the unstructured option for the covariance structure, because it is the most flexible model (19) and showed the smallest Akaike information criteria, Akaike information criteria with a correction for sample size, and Bayesian information criteria values in this analyses. A mixed model was also used to test the differences in the concentration changes of the uremic toxins and health-related QOL between the two arms. We considered $P<0.05$ (two sided) as statistically significant.

Results

The study enrolled 579 patients; 41 (24 in the control arm and 17 in the AST-120 arm) of these patients had never been followed up or taken any AST-120. Therefore, we evaluated 538 intention-to-treat participants (Figure 1). The AST-120 medication compliance was 90% (median of 94%).

Baseline Characteristics

The mean age of the analyzed patients was 57 years old, and 67.5% were men. Diabetic nephropathy was reported in 269 (50.0%) patients. The systolic and diastolic BPs were 129±15.2 and 76±10.0 mmHg, respectively. The mean SCr level was 2.83±0.68 mg/dl, and the mean eGFR was 26.7±7.5 ml/min per 1.73 m^2. The median urinary protein excretion rate was 1.24 (0.0–13.86) g/g creatinine. ACE inhibitors or ARBs were taken by 487 (90.5%) of the patients, β-blockers were taken by 285 (52.9%) of the patients, calcium channel blockers were taken by 357 (66.4%) of the patients, diuretics were taken by 327 (60.8%) of the patients, and lipid modifiers were taken by 364 (67.7%) of the patients. The baseline characteristics did not differ significantly between the two arms (Table 1).

Uremic Toxin Concentrations throughout the Study Period

At baseline, the two arms did not differ in uremic toxin levels, including the serum and urine IS and serum β2-MG. Also, there were no statistically significant differences in the changes in the uremic toxin levels over time between the two treatment arms (the *P* values for the randomization–time interaction of urine and serum IS and serum β2-MG were >0.05) (Table 2). Levels of the serum IS, urine IS, and β2-MG (mean; 95% confidence interval [95% CI]) between two treatment arms at the time of enrollment and 12, 24, and 36 months after the registration are as follows: serum IS: mean, 0.64; 95% CI, 0.57 to 0.71; mean, 0.71; 95% CI, 0.60 to 0.81; mean, 0.65; 95% CI, 0.55 to 0.75; and mean, 0.58; 95% CI, 0.49 to 0.66, respectively, in the AST-120 arm and mean, 0.70; 95% CI, 0.60 to 0.80; mean, 0.89; 95% CI, 0.79 to 0.10; mean, 1.03; 95% CI, 0.89 to 1.17; and mean, 0.98; 95% CI, 0.81 to 1.15, respectively, in the control arm; urine IS: mean, 6.70; 95% CI, 6.06 to 7.33; mean, 4.82; 95% CI, 4.25 to 5.39; mean, 5.22; 95% CI, 4.50 to 5.93; and mean, 5.50; 95% CI, 4.36 to 6.64, respectively, in the AST-120 arm

Table 2. (Continued)

Urine IS, mg/dl				β2-MG, mg/L			
Control	Δ (95% CI)	AST-120	Δ (95% CI)	Control	Δ (95% CI)	AST-120	Δ (95% CI)
7.71±0.48	NA	6.70±0.32	NA	6.91±0.16	NA	6.64±0.15	NA
7.14±0.37	−0.82 (−25.53 to 13.72)	4.82±0.03	−1.81 (−14.64 to 10.52)	7.63±0.27	1.19 (−2.91 to 8.37)	7.94±0.26	1.58 (−2.50 to 10.07)
7.90±0.40	0.17 (−24.97 to 15.38)	5.22±0.36	−1.17 (−12.69 to 10.59)	7.23±0.26	0.96 (−3.89 to 8.13)	7.39±0.29	1.35 (−2.14 to 9.33)
8.51±0.61	0.45 (−26.35 to 21.35)	5.50±0.58	−1.01 (−15.80 to 17.06)	7.16±0.28	1.17 (−3.77 to 6.95)	6.57±0.23	1.07 (−2.48 to 5.48)
		<0.001				0.58	
		0.04				<0.001	
		0.76				0.25	

and mean, 7.71; 95% CI, 6.76 to 8.66; mean, 7.14; 95% CI, 6.41 to 7.88; mean, 7.90; 95% CI, 7.11 to 8.69; and mean, 8.51; 95% CI, 7.32 to 9.71, respectively, in the control arm; and β2-MG: 6.64; 95% CI, 6.35 to 6.93; mean, 7.94; 95% CI, 7.42 to 8.45; mean, 7.39; 95% CI, 6.82 to 7.96; and mean, 6.57; 95% CI, 6.11 to 7.03, respectively, in the AST-120 arm and mean, 6.91; 95% CI, 6.58 to 7.23; mean, 7.62; 95% CI, 7.10 to 8.15; mean, 7.23; 95% CI, 6.72 to 7.75; and mean, 7.16; 95% CI, 6.60 to 7.71, respectively, in the control arm (Supplemental Figure 1).

Primary Outcome

By the end of the study period, 200 patients (37.2% of the analyzed participants) had reached a primary outcome. SCr doublings or >50% eGFR reductions were observed in 109 patients (52 in the control arm and 57 in the AST-120 arm), and RRT was initiated in 91 patients (48 in the control arm and 43 in the AST-120 arm) (Table 3). The two arms did not differ significantly in the cumulative rate of composite primary outcome occurrence (hazard ratio [HR], 1.12; 95% CI, 0.85 to 1.48; log-rank P=0.45) (Figure 2). Even after adjusting for diabetic nephropathy and the severity of kidney dysfunction, AST-120 was not a predictor of the occurrence of a primary outcome (HR, 1.15; 95% CI, 0.87 to 1.51; P=0.34).

Secondary Outcomes

The absolute loss of renal function was not delayed in the AST-120 arm (25%, median, and 75% change over 36 months: −8.8, −5.0, and −1.0, respectively, in the control arm and −8.0, −3.5, and 1.0, respectively, in the AST-120 arm; $P_{\text{randomization–time}}$=0.64) (Figure 3). Overall slope of eGFR progression in the AST-120 arm compared with the control arm was −1.47 (95% CI, −6.55 to 3.61; P=0.57).

The urinary protein excretion rate was also decreased during the study period (from 1.30 [0.00–9.00] to 1.09 [0.00–10.47] g/g creatinine in the control arm and from 1.18 [0.00–13.86] to 0.86 [0.00–5.43] g/g creatinine in the AST-120 arm). The changes in urine protein excretion were similar in the two treatment arms (25%, median, and 75% change over 36 months: −0.24, 0.12, and 0.89, respectively, in the control arm and −0.19, 0.08, and 0.57, respectively, in the AST-120 arm; $P_{\text{randomization–time}}$=0.16) (Table 4).

Twenty mortalities occurred during the study period (11 in the control arm and nine in the AST-120 arm; HR, 0.86; 95% CI, 0.36 to 2.08; log-rank P=0.73) (Table 3). Hospitalizations other than planned surgeries and interventions were observed in 211 patients (109 in the control arm and 102 in the AST-120 arm; log-rank P=0.76) (Table 3).

When we used a mixed model to test for differences in the repeatedly measured health–related QOL scores on the basis of the SF-36, we found no significant interaction between treatment and time (Table 5).

Safety

In total, 1378 and 1424 adverse events were observed throughout the study period in the control and AST-120 arms, respectively (P=0.03). The rates of severe adverse events were not different between two arms (100 in the control arm and 112 in the AST-120 arm; P=0.57). Gastrointestinal disorders, including constipation, nausea, and vomiting (204 in the control arm and 293 in the AST-120 arm), and nutritional problems, such as decreased appetite (56 in the control arm and 116 in the AST-120 arm), were more frequent in the AST-120 arm (P<0.001 and P<0.001, respectively). Among the patients who dropped out or withdrew, 27 discontinued the study because of AST-120–related complications. Adverse events according to body part or organs are listed in Supplemental Table 1.

Discussion

AST-120 did not delay the onset of composite primary outcomes. The AST-120 combination was not effective in lowering the concentrations of uremic toxins (*i.e.*, serum and urine IS and serum β2-MG) compared with the standard treatment alone and did not elicit greater protective effects on renal function (eGFR) or daily proteinuria. The all-cause mortalities and hospitalizations other than planned surgeries and interventions were not different between the two arms. The health–related QOL scores on the basis of the SF-36 showed no differences between two treatment arms.IS administration accelerates renal disease progression accompanied by increased expression of fibrogenic genes (12). IS is also associated with the impairment of antioxidative systems in both renal tubular cells and glomerular mesangial cells (20–22). In addition, IS downregulates Klotho expression in proximal tubular cells (23). AST-120 decreases urinary levels of IS and 8-hydroxydeoxyguanosine and ameliorates renal dysfunction in CKD rats (21,22). In some studies with patients with CKD, AST-120 decreased serum and urinary IS levels and the levels of advanced glycation end products (AGEs) (24,25). Also, AST-120 increased the renal expression of Klotho, which was decreased in uremic condition and inhibited cell senescence in the kidney of uremic rats, probably by alleviating IS overload on the kidney (26).

In this study, the lack of evidence on the beneficial effects of AST-120 on composite primary outcomes in patients with CKD may be attributable to several issues. Because

Table 3. Number of events, hazard ratios, and confidence intervals for the primary outcome, mortality, and hospitalizations: Intention-to-treat participants

Outcomes	Control (*n*=266)	AST-120 (*n*=272)	HR (95% CI)
Composite primary outcome			1.12 (0.85 to 1.48)
Events	100	100	
Censoring	166	172	
Mortality			0.86 (0.36 to 2.08)
Events	11	9	
Censoring	255	263	
Hospitalization			0.92 (0.84 to 1.24)
Events	109	102	
Censoring	157	170	

HR, hazard ratio; 95% CI, 95% confidence interval.

37.2% (200) of all of the analyzed participants reached a primary outcome, the disease may have been too far advanced (mean eGFR =26.7 ml/min per 1.73 m^2) for AST-120 to reverse its progression. In patients with CKD, AST-120 treatment decreased the serum and urinary levels of AGEs (24,25). The formation of AGEs increases in the presence of hyperglycemia and oxidative stress, such as that which occurs in uremic conditions. AGEs induce cellular responses, including the upregulation of profibrogenic and proinflammatory cytokines, which leads to progressive nephropathies. Renal dysfunction increases the level of circulating AGEs because of both reduced clearance and increased formation. Far advanced renal dysfunction of patients in this study and probably accompanying high levels of AGEs might be too much to be suppressed by AST-120.

As mentioned above, IS acts as a profibrotic, proinflammatory, and pro-oxidative factor, and the control of its concentration is associated with renal function preservation. The AST-120 combination failed to elicit significant differences in uremic toxins over the duration of the study period compared with the standard treatment alone, which may explain the negative result of this study.

Also, the detailed medical care was effective, because the eGFR declines were significantly slowed after randomization in both arms (Supplemental Figure 2). The Evaluating Prevention of Progression in CKD-1 and -2 Trials also revealed the same trend, and this trend was a potential cause

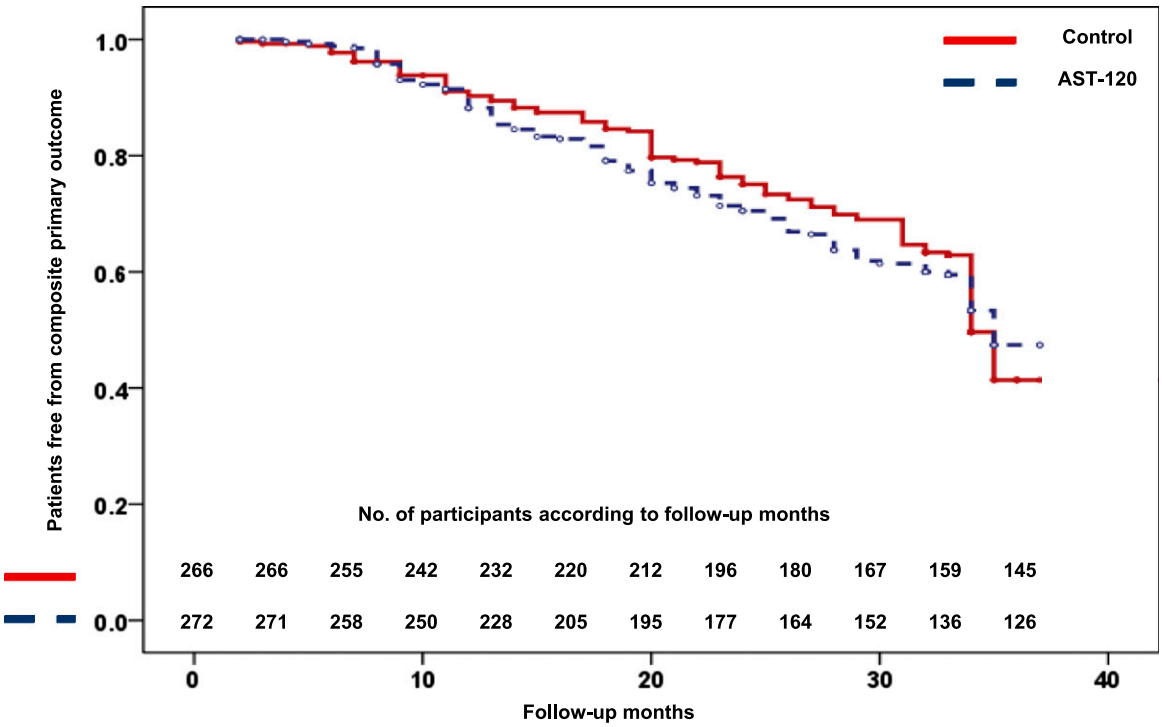

Figure 2. | Occurrence of composite primary outcomes in each treatment arm. Log-rank *P*=0.45.

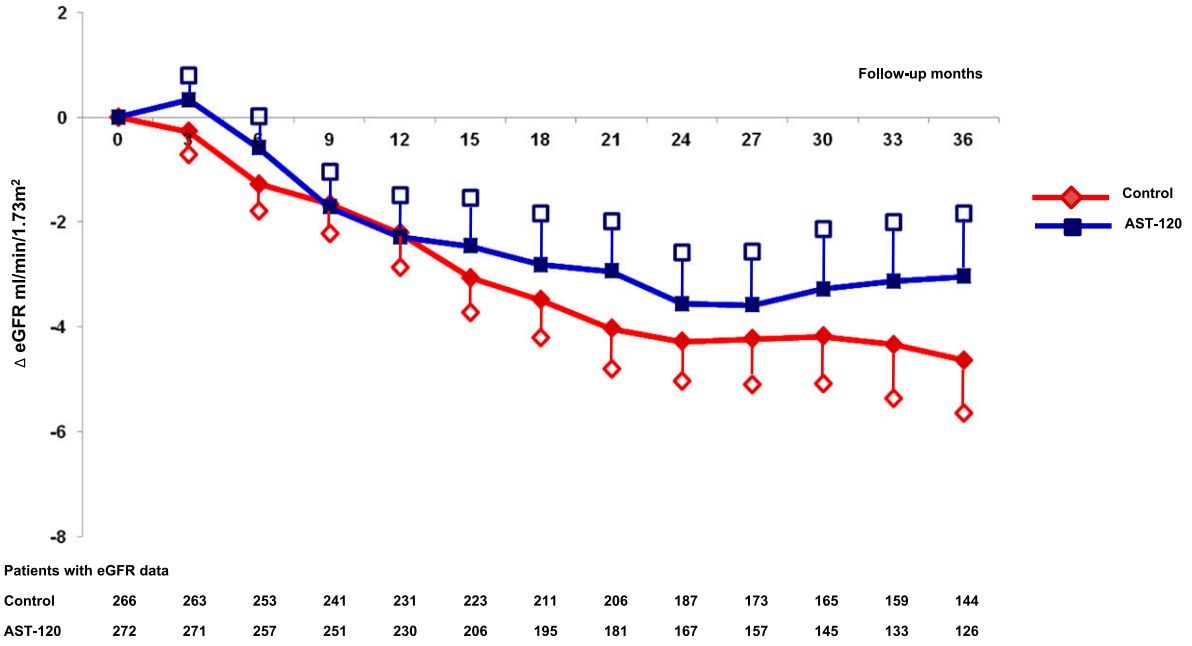

Figure 3. | Change of eGFR over time. Absolute change of eGFR from intention-to-treat participants ($P_{randomization}$=0.02; $P_{randomization–time}$=0.64). Vertical lines and white symbols indicate 95% confidence intervals.

of the negative results (27). In addition, the result of the CAP-KD Study was limited because of the infrequent primary end point events (18). During the study period, the attending physicians and nurses as well as dietitians advised the patients to consume a low-salt and low-protein diet. In uremic animals, low-protein diets delayed the progression of CKD by suppressing renal TGF-β1 expression and also, reduced serum IS levels (28,29). Likewise, adding AST-120 on the low-salt and low-protein diet did not improve renal outcomes in this study. In addition, most of the patients were also taking renin-angiotensin-aldosterone system blockers and lipid modifiers.

This study has some limitations. First, the run-in period before randomization was not included in the analysis; therefore, there might have been some misclassifications of the rates of renal function decline at the time of recruitment. A total of 367 (78.9%) patients had recorded eGFR levels at 12, 6, and 3 months before the randomization (33 [7.1%], 170 [36.6%], and 164 [35.3%] patients, respectively) and satisfied the inclusion criteria. These patients showed true progression according to the study protocol, and the remaining participants were recruited on the basis of the expected eGFR declines. Second, the exclusion of nearly 20% of the participants might have affected the analysis of the composite primary outcomes. Although we calculated the study sample size on the basis of the results from previous studies, the actual event rate was much lower than expected. A study with a larger sample size is needed

Table 4. Progression of urinary protein excretion rate over time

Time	Control	Δ (95% CI)	AST-120	Δ (95% CI)
Enrollment	1.30 (0.00, 0.41, 2.91, 9.00)	NA	1.18 (0.00, 0.40, 2.89, 13.86)	NA
12 mo	1.33 (0.00, 0.45, 2.30, 12.36)	0.10 (−3.55 to 5.13)	1.27 (0.00, 0.47, 2.71, 16.84)	0.35 (−2.81 to 5.14)
24 mo	1.06 (0.08, 0.43, 2.49, 9.22)	0.10 (−2.98 to 3.37)	0.92 (0.02, 0.38, 1.97, 13.05)	0.24 (−2.83 to 4.21)
36 mo	1.09 (0.00, 0.53, 2.17, 10.47)	0.42 (−2.92 to 5.86)	0.88 (0.00, 0.36, 1.63, 5.43)	0.15 (−2.98 to 2.87)
P value (randomization)			0.03	
P value (time)			<0.01	
P value (randomization × time)			0.16	

Median (minimum, 25%, 75%, maximum). *P* value (randomization, time, or randomization × time): a mixed model. 95% CI, 95% confidence interval; NA, not applicable.

Table 5. Absolute value of quality of life with the Medical Outcomes Study 36–Item Short–Form Health Survey: Intention-to-treat participants

Items	Absolute Value		*P* Value	
	AST-120	Control		
Physical function				
0 mo	24.64±4.66 (26 [10, 30])	24.16±4.94 (25 [10, 30])	Randomization	0.55
12 mo	24.48±4.84 (26 [11, 30])	24.01±5.03 (25 [10, 30])	Time	0.003
24 mo	24.34±5.19 (26 [10, 30])	23.86±5.27 (25 [10, 30])	Randomization × time	0.79
36 mo	23.99±5.31(25 [10, 30])	24.12±4.97 (25 [10, 30])		
Role: Physical				
0 mo	15.94±4.25 (17 [4, 20])	15.54±4.49 (16.5 [4, 20])	Randomization	0.40
12 mo	16.14±4.17 (17 [4, 20])	15.93±4.26 (17 [4, 20])	Time	0.18
24 mo	15.97±4.15 (17 [4, 20])	15.85±4.52 (17 [4, 20])	Randomization × time	0.85
36 mo	16.33±4.34 (17.5 [4, 20])	15.96±4.19 (17 [4, 20])		
Bodily pain				
0 mo	3.63±1.96 (3 [2, 11])	3.88±2.1 (3 [2, 11])	Randomization	0.91
12 mo	3.84±1.98 (3 [2, 10])	3.93±2.14 (3 [2, 11])	Time	0.76
24 mo	3.78±2.03 (3 [2, 10])	3.92±2.11 (3 [2, 10])	Randomization × time	0.06
36 mo	3.51±1.86 (3 [2, 10])	4±2.06 (4 [2, 10])		
General health				
0 mo	19.45±2.22 (19 [13, 27])	19.53±2.35 (20 [12, 26])	Randomization	0.65
12 mo	18.79±2.57 (19 [12, 25])	18.78±2.42 (19 [13, 28])	Time	0.06
24 mo	18.81±2.7 (19 [12, 25])	19.09±2.1 (19 [13, 24])	Randomization × time	0.65
36 mo	18.47±2.54 (19 [10, 25])	18.96±2.08 (19 [13, 24])		
Vitality				
0 mo	13.6±2.31 (13 [4, 20])	13.78±2.24 (14 [6, 20])	Randomization	0.11
12 mo	13.56±2.04 (13 [6, 20])	13.55±2.24 (14 [4, 20])	Time	0.60
24 mo	13.6±2.3 (13 [8, 20])	13.52±2.05 (13 [4, 20])	Randomization × time	0.66
36 mo	13.76±2.32 (14 [8, 20])	13.57±2.31 (14 [5, 20])		
Social functioning				
0 mo	6.01±1.19 (6 [2, 10])	5.97±1.04 (6 [2, 10])	Randomization	0.45
12 mo	5.98±1.06 (6 [2, 10])	5.9±0.97 (6 [2, 10])	Time	0.87
24 mo	6.01±1.05 (6 [3, 10])	5.88±1.17 (6 [2, 10])	Randomization × time	0.84
36 mo	5.96±1.21 (6 [2, 10])	5.89±1 (6 [3, 10])		
Role: Emotional				
0 mo	12.49±3.09 (14 [3, 15])	12.14±3.16 (13 [3, 15])	Randomization	0.69
12 mo	12.54±3.05 (14 [3, 15])	12.1±3.36 (13 [3, 15])	Time	0.74
24 mo	12.59±3.01 (14 [3, 15])	12.35±3.3 (14 [3, 15])	Randomization × time	0.69
36 mo	12.59±3.08 (14 [3, 15])	12.44±3.28 (14 [3, 15])		
Mental health				
0 mo	17.58±2.47 (18 [5, 23])	17.55±2.27 (18 [10, 23])	Randomization	0.26
12 mo	17.47±2.18 (18 [7, 22])	17.45±2.2 (17 [5, 23])	Time	0.22
24 mo	17.69±2.28 (18 [11, 25])	17.71±2.34 (18 [11, 24])	Randomization × time	0.12
36 mo	17.71±2.27 (18 [10, 23])	17.4±2.5 (17.5 [7, 24])		
Total score				
0 mo	113.35±10.83 (116 [66, 136])	112.56±10.79 (115 [72, 132])	Randomization	0.96
12 mo	112.79±10.78 (115 [72, 136])	111.66±10.99 (114 [69, 134])	Time	0.52
24 mo	112.79±11.2 (115 [73, 131])	112.19±12.24 (115 [67, 132])	Randomization × time	0.96
36 mo	112.33±11.98 (116 [76, 131])	112.35±11.7 (114 [68, 133])		

Mean±SD (median [minimum, maximum]).

to reach a conclusion about the effectiveness of AST-120. Third, we cannot confirm the actual compliance of the patients with their AST-120 regimens, because the compliance rates were on the basis of the counts of returned AST-120 packs and medication diaries.

In conclusion, adding AST-120 to standard therapy was not able to delay renal disease progression in terms of the composite primary outcomes (*i.e.*, SCr doubling, 50% reduction in eGFR, or the initiation of RRT). A longer clinical trial that recruits patients in earlier stages of kidney disease should be instituted to clarify the clinical usefulness of AST-120.

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Disclosures

None.

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