ORIGINAL ARTICLE

Effects of Allopurinol on the Progression of Chronic Kidney Disease

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ABSTRACT

BACKGROUND

Elevated serum urate levels are associated with progression of chronic kidney disease. Whether urate-lowering treatment with allopurinol can attenuate the decline of the estimated glomerular filtration rate (eGFR) in patients with chronic kidney disease who are at risk for progression is not known.

METHODS

In this randomized, controlled trial, we randomly assigned adults with stage 3 or 4 chronic kidney disease and no history of gout who had a urinary albumin:creatinine ratio of 265 or higher (with albumin measured in milligrams and creatinine in grams) or an eGFR decrease of at least 3.0 ml per minute per 1.73 m^2 of body-surface area in the preceding year to receive allopurinol (100 to 300 mg daily) or placebo. The primary outcome was the change in eGFR from randomization to week 104, calculated with the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.

RESULTS

Enrollment was stopped because of slow recruitment after 369 of 620 intended patients were randomly assigned to receive allopurinol (185 patients) or placebo (184 patients). Three patients per group withdrew immediately after randomization. The remaining 363 patients (mean eGFR, 31.7 ml per minute per 1.73 m^2; median urine albumin:creatinine ratio, 716.9; mean serum urate level, 8.2 mg per deciliter) were included in the assessment of the primary outcome. The change in eGFR did not differ significantly between the allopurinol group and the placebo group (–3.33 ml per minute per 1.73 m^2 per year [95% confidence interval {CI}, –4.11 to –2.55] and –3.23 ml per minute per 1.73 m^2 per year [95% CI, –3.98 to –2.47], respectively; mean difference, –0.10 ml per minute per 1.73 m^2 per year [95% CI, –1.18 to 0.97]; P=0.85). Serious adverse events were reported in 84 of 182 patients (46%) in the allopurinol group and in 79 of 181 patients (44%) in the placebo group.

CONCLUSIONS

In patients with chronic kidney disease and a high risk of progression, urate-lowering treatment with allopurinol did not slow the decline in eGFR as compared with placebo. (Funded by the National Health and Medical Research Council of Australia and the Health Research Council of New Zealand; CKD-FIX Australian New Zealand Clinical Trials Registry number, ACTRN12611000791932.)

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Elevated serum urate levels are associated with increased risks of onset and progression of chronic kidney disease and end-stage kidney disease.[1,2] Observational studies have shown a linear association between serum urate levels and various outcomes, including albuminuria,[3] onset of chronic kidney disease,[4,5] progression to end-stage kidney disease,[6] cardiovascular events, and death.[7] The serum urate level increases linearly with decreasing glomerular filtration rate as a result of reduced excretion.[8] Thus, it is unclear whether elevated serum urate levels play a causative role in the progression of kidney disease, are an indirect marker of decreased kidney function, or both.

Single-center trials have shown that urate-lowering treatment with allopurinol or febuxostat could slow the progression of chronic kidney disease over a short follow-up period of 6 to 12 months.[9-11] Our systematic review and meta-analysis evaluating the effect of allopurinol on kidney outcomes included eight randomized, controlled trials (involving 476 participants).[12] Allopurinol was compared with placebo in two trials, and there was no study medication in the control group of the remaining six trials. The mean difference in the change in glomerular filtration rate from baseline to trial completion between the allopurinol groups and the control groups was 3.1 ml per minute per 1.73 m^2 of body-surface area (95% confidence interval [CI], −0.9 to 7.0). However, that review was limited by its small size (eight trials, with a median of 57 participants per trial) and a median follow-up period of 11 months; in addition, only two of the trials were placebo-controlled. A scientific workshop organized by the National Kidney Foundation of the United States in September 2016 reviewed and reported the contemporary evidence and suggested that further trials of allopurinol or febuxostat both in the general population and in patients with chronic kidney disease were indicated.[13]

The present trial, the Controlled Trial of Slowing of Kidney Disease Progression from the Inhibition of Xanthine Oxidase (CKD-FIX), was designed to test the hypothesis that urate-lowering therapy with allopurinol would attenuate the decline in the estimated glomerular filtration rate (eGFR) over a period of 104 weeks in patients with chronic kidney disease.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this investigator-initiated, randomized, double-blind, placebo-controlled trial at 31 centers in Australia and New Zealand. The trial protocol was approved by ethics committees at all participating sites in Australia and by the Northern Region A Health and Disability Ethics Committee for sites in New Zealand and is available with the full text of this article at NEJM.org. The funders of the trial — the National Health and Medical Research Council of Australia and the Health Research Council of New Zealand — had no role in trial design, data collection, data analysis, data interpretation, or the writing of the manuscript that was submitted. The Australasian Kidney Trials Network (University of Queensland) coordinated the trial and conducted all statistical analyses. The authors (who made up the trial steering committee) designed and supervised the trial. Site investigators and trial coordinators collected data on patients at each site. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

PATIENTS

Adults with stage 3 or 4 chronic kidney disease (eGFR, 15 to 59 ml per minute per 1.73 m^2) who were deemed to be at increased risk for progression of chronic kidney disease were eligible. An increased risk of progression of chronic kidney disease was defined as a urinary albumin:creatinine ratio of 265 or higher (with albumin measured in milligrams and creatinine in grams) (≥30 with albumin measured in milligrams and creatinine in millimoles) or a decrease in eGFR of at least 3.0 ml per minute per 1.73 m^2 in the preceding 12 months (calculated as the difference between the first and last of at least three measurements of eGFR, with each test performed at least 4 weeks apart). Key exclusion criteria were a history of gout, allopurinol hypersensitivity, clinical indication for allopurinol, and unresolved acute kidney injury in the previous 3 months. (Table S1 in the Supplementary Appendix, available at NEJM.org). All the patients provided written informed consent before participation in the trial.

TRIAL PROCEDURES

Eligible patients were randomly assigned to receive allopurinol or placebo in a 1:1 ratio with an adaptive allocation algorithm designed to minimize imbalance between the treatment groups in the following variables: trial center, stage of chronic kidney disease (stage 3 or stage 4), albuminuria (urinary albumin:creatinine ratio, ≥530 or <530 with albumin measured in milligrams and creatinine in grams [≥60 or <60 with albumin measured in milligrams and creatinine in millimoles]), and diabetes mellitus status (present or absent). Randomization was performed with a Web-based system through a password-protected encrypted website interface.

Allopurinol 100-mg tablets (Zyloprim, Aspen Pharma) and placebo tablets were purchased from Aspen Pharma. The total trial follow-up period of 104 weeks (2 years) included the initial dose-escalation phase of 12 weeks and the subsequent 92-week follow-up phase. During the dose-escalation phase, the starting dose of allopurinol (100 mg) or placebo was one tablet by mouth daily and could be increased every 4 weeks to a maximum of three tablets daily if all the criteria for dose adjustment were met (Table S2). Dose adjustment on the basis of serum urate level was not permitted at any time during the trial. During the follow-up phase, patients underwent assessment in the clinic every 16 weeks. Patients were withdrawn from the trial earlier than 104 weeks if they received dialysis for more than 30 days or underwent kidney transplantation.

OUTCOMES

The primary outcome was the change in the eGFR from baseline (i.e., randomization) to 104 weeks, determined with the Chronic Kidney Disease Epidemiology (CKD-EPI) creatinine equation.[14] Sensitivity analyses were conducted with the use of the CKD-EPI equation, based on cystatin C alone and in combination with creatinine, and the Modification of Diet in Renal Disease equation.

The secondary outcomes were a composite of a 40% reduction from baseline in eGFR (confirmed by a second measurement at the next scheduled study visit, with the exception of the last study visit), end-stage kidney disease (dialysis for ≥30 days or kidney transplantation), or death from any cause; a composite of a 30% reduction from baseline in eGFR, end-stage kidney disease, or death from any cause; individual components of the composite kidney outcomes; blood pressure, albuminuria, and serum urate level; cardiovascular events; hospitalization for any cause; and quality-of-life summary scores on the 36-Item Short-Form Health Survey. Safety outcomes included all serious adverse events and drug reactions. Specific safety outcomes of interest were erythema multiforme, the Stevens–Johnson syndrome, toxic epidermal necrolysis, minor rash, hypersensitivity syndrome, aplastic anemia, and thrombocytopenia.

STATISTICAL ANALYSIS

Under the assumption of an annual decline in eGFR of 3 ml per minute per 1.73 m^2,[15] loss to follow-up of 5%, and drop-in and drop-out rates of 5%, enrollment of 620 patients (310 in each group) would provide 90% power to detect a 20% attenuation in the decline in eGFR after 2 years of follow-up. This difference (0.6 ml per minute per 1.73 m^2 per year) is at the lower end of the range of a reduction in the eGFR slope by 0.5 to 1.0 ml per minute per 1.73 m^2 per year over a period of 2 to 3 years, which was associated with a hazard ratio of approximately 0.7 for the clinical outcome of end-stage kidney disease during subsequent years in cohort studies and randomized trials.[16-18]

The primary outcome was analyzed jointly with the time to trial discontinuation to accommodate data on informative discontinuations (missing not at random) resulting from death or end-stage kidney disease before completion of the 104-week follow-up visit. Measurements of eGFR over time were analyzed with a linear mixed model with fixed effects for treatment, continuous time, the interaction of treatment with continuous time, and centered baseline eGFR and random intercepts and random slopes. The estimate of treatment effect was the difference between the allopurinol group and the placebo group in the annual change in eGFR. This estimate included the time to discontinuation for informative reasons (death or end-stage kidney disease), analyzed with a Weibull parametric survival model with random effects. Prespecified subgroup analyses were performed by including as a fixed effect in the linear mixed model the interaction of treatment, time as a continuous variable, and subgroup.

Analyses of secondary outcomes were not adjusted for multiplicity. Repeatedly measured continuous secondary outcomes were analyzed with the use of the same joint modeling approach. Binary secondary outcomes were analyzed with log binomial regression models to obtain estimates of risk ratios and 95% confidence intervals. Participants who could not be assessed for categorical secondary outcomes for missing-not-at-random reasons were not included in the analysis for that outcome. We also conducted post hoc analyses of binary secondary outcomes by using Cox regression models to obtain estimates of hazard ratios and 95% confidence intervals. The relationship of serious adverse events and adverse drug reactions to allopurinol or placebo was analyzed with chi-square tests. Statistical analyses were performed with SAS software, version 9.4 (SAS Institute), with joint models implemented with the use of the %JM macro.[19]

RESULTS

PATIENT ENROLLMENT AND BASELINE CHARACTERISTICS

From March 2014 through December 2016, a total of 369 patients (60% of the target number) were randomly assigned to the allopurinol group (185 patients) or the placebo group (184 patients) (Fig. S1). A decision was made by the trial steering committee to stop further recruitment because of a slower-than-anticipated recruitment rate that rendered the number of participants unlikely to reach the projected target within a reasonable time frame. This was a pragmatic decision based on trial logistics and funding; no interim efficacy or futility analyses were conducted before this decision was made. Six patients (3 in each group) withdrew consent immediately after randomization. The remaining 363 patients received at least one dose of the randomly assigned treatment and were included in the assessment of the primary outcome.

At the end of the 12-week dose-escalation phase, 126 (69%), 17 (9%), and 9 (5%) of the 182 patients in the allopurinol group were taking three tablets, two tablets, and one tablet of allopurinol once daily, respectively; the corresponding numbers in the placebo group were 126 (70%), 27 (15%), and 10 (6%) of 181 patients. During the 104-week follow-up period, 54 patients (30%) in the allopurinol group and 45 patients (25%) in the placebo group discontinued the assigned regimen (Table S3). In total, 132 patients (73%) in the allopurinol group and 144 patients (80%) in the placebo group completed the 104-week follow-up period. The patients who had been assigned to the allopurinol group took allopurinol for a mean of 75.8 weeks (83% of 91.5 weeks of follow-up), and the patients who had been assigned to the placebo group took placebo for a mean of 83.0 weeks (88% of 94.2 weeks of follow-up).

The patients' baseline characteristics, with the exception of the primary cause of kidney disease, were balanced between the assigned treatment groups (Table 1 and Table S4). The mean (±SD) eGFR was 31.7±12.0 ml per minute per 1.73 m^2, and the median urinary albumin:creatinine ratio was 716.9 (interquartile range, 244.3 to 1857) (with albumin measured in milligrams and creatinine in grams). The mean serum urate level was 8.2±1.8 mg per deciliter (490±110 μmol per liter).

PRIMARY OUTCOME

The change in the eGFR did not differ significantly between the allopurinol group and the placebo group (–3.33 ml per minute per 1.73 m^2 per year [95% CI, –4.11 to –2.55] and –3.23 ml per minute per 1.73 m^2 per year [95% CI, –3.98 to –2.47], respectively; mean difference, –0.10 ml per minute per 1.73 m^2 per year [95% CI, –1.18 to 0.97]; P=0.85) (Fig. 1). Additional analyses and sensitivity analyses showed similar results (Table S5). The results for the primary outcome were consistent across a wide range of prespecified subgroups (Fig. S2). A post hoc futility analysis revealed that had the target enrollment of 620 patients been met, the conditional power to detect the prespecified clinically meaningful difference of 0.6 ml per minute per 1.73 m^2 per year would have been only 1 in 1000. A post hoc power calculation showed that the sample required to accommodate the discontinuation rate of 30% was 1006 patients. The conditional power for the sample size of 1006 patients was 17% (futility index, 83%).

SECONDARY OUTCOMES

The secondary composite outcome of a 40% decrease in eGFR, end-stage kidney disease, or death

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

Characteristic	Allopurinol (N=182)	Placebo (N=181)	Total (N=363)
Age — yr	62.3±12.6	62.6±12.9	62.4±12.7
Female sex — no. (%)	70 (38)	65 (36)	135 (37)
Race or ethnic group — no. (%)†			
White	143 (79)	129 (71)	272 (75)
Australian Aboriginal or Torres Strait Islander	2 (1)	2 (1)	4 (1)
New Zealand Maori	13 (7)	15 (8)	28 (8)
Asian	8 (4)	11 (6)	19 (5)
Other	16 (9)	24 (13)	40 (11)
Median body-mass index (IQR)‡	30 (26–36)	31 (27–35)	30 (26–36)
Blood pressure — mm Hg§			
Systolic	138.4±18.2	140.2±20.0	139.3±19.1
Diastolic	76.8±11.1	76.5±12.2	76.7±11.6
Primary cause of kidney disease — no. (%)			
Diabetic kidney disease	75 (41)	90 (50)	165 (45)
Nondiabetic kidney disease	107 (59)	91 (50)	198 (55)
Diabetes mellitus — no. (%)	104 (57)	106 (59)	210 (58)
Hypertension — no. (%)	171 (94)	173 (96)	344 (95)
Cardiovascular disease — no. (%)	58 (32)	64 (35)	122 (34)
SF-36 quality-of-life summary score¶	68.8±18.7	68.2±18.8	68.5±18.8
Receiving ACE inhibitor — no. (%)	71 (39)	75 (41)	146 (40)
Receiving ARB — no. (%)	63 (35)	67 (37)	130 (36)
eGFR — ml/min/1.73 m^2	31.6±11.7	31.9±12.4	31.7±12.0
Median urinary albumin:creatinine ratio (IQR)‖	716.9 (237.2–1947)	716.9 (246.0–1857)	716.9 (244.3–1857)
Serum urate — mg/dl**	8.2±1.8	8.2±1.7	8.2±1.8

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. To convert the values for serum urate to micromoles per liter, multiply by 59.48. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, eGFR estimated glomerular filtration rate, and IQR interquartile range.
† Race and ethnic group were reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 1 patient in the allopurinol group and 4 patients in the placebo group.
§ Data were missing for 1 patient in the placebo group.
¶ Scores on the 36-Item Short-Form Health Survey (SF-36) quality-of-life summary score range from 0 to 100, with higher scores indicating better quality of life. Data were missing for 1 patient in the allopurinol group.
‖ Albumin was measured in milligrams, and creatinine in grams. Data were missing for 3 patients in the allopurinol group and 2 patients in the placebo group.
** Data were missing for 9 patients in the allopurinol group and 2 patients in the placebo group.

from any cause occurred in 63 patients (35%) in the allopurinol group and 51 patients (28%) in the placebo group (risk ratio, 1.23; 95% CI, 0.90 to 1.67; hazard ratio, 1.34; 95% CI, 0.92 to 1.93) (Table 2). Similar results were observed for the composite outcome of a 30% decrease in the eGFR, end-stage kidney disease, or death from any cause (risk ratio, 1.13; 95% CI, 0.89 to 1.44; hazard ratio, 1.23; 95% CI, 0.90 to 1.69).

The mean serum urate level in the allopurinol group decreased to 5.1 mg per deciliter (95% CI, 4.8 to 5.3) (300 μmol per liter [95% CI, 290 to 320]) at 12 weeks and remained at 5.3 mg per deciliter (95% CI, 5.1 to 5.6) (320 μmol per liter

Table 2. Effects of Allopurinol on Secondary Outcomes.

Outcome*	Allopurinol	Placebo	Risk Ratio (95% CI)†	Hazard Ratio (95% CI)‡
	no./total no. (%)			
40% decrease in eGFR, end-stage kidney disease, or death	63/182 (35)	51/181 (28)	1.23 (0.90–1.67)	1.34 (0.92–1.93)
30% decrease in eGFR, end-stage kidney disease, or death	82/182 (45)	72/181 (40)	1.13 (0.89–1.44)	1.23 (0.90–1.69)
40% decrease in eGFR	47/166 (28)	37/167 (22)	1.28 (0.88–1.86)	1.39 (0.90–2.13)
30% decrease in eGFR	70/170 (41)	63/172 (37)	1.12 (0.86–1.47)	1.21 (0.86–1.70)
End-stage kidney disease	25/171 (15)	19/175 (11)	1.35 (0.77–2.35)	1.38 (0.76–2.50)
Death from any cause	11/157 (7)	6/162 (4)	1.89 (0.72–4.99)	1.89 (0.70–5.11)
Fatal or nonfatal cardiovascular event	22/152 (14)	30/163 (18)	0.79 (0.48–1.30)	0.74 (0.43–1.29)
Hospitalization for any cause	83/171 (49)	77/172 (45)	1.08 (0.86–1.36)	1.17 (0.86–1.60)

* End-stage kidney disease was defined as receipt of dialysis for at least 30 days or kidney transplantation.
† Results were estimated from a prespecified analysis of log binomial regression models. Confidence intervals have not been adjusted for multiplicity, and inferences drawn from the intervals may not be reproducible.
‡ Results were estimated from a post hoc analysis of Cox regression models. Confidence intervals have not been adjusted for multiplicity, and inferences drawn from the intervals may not be reproducible.

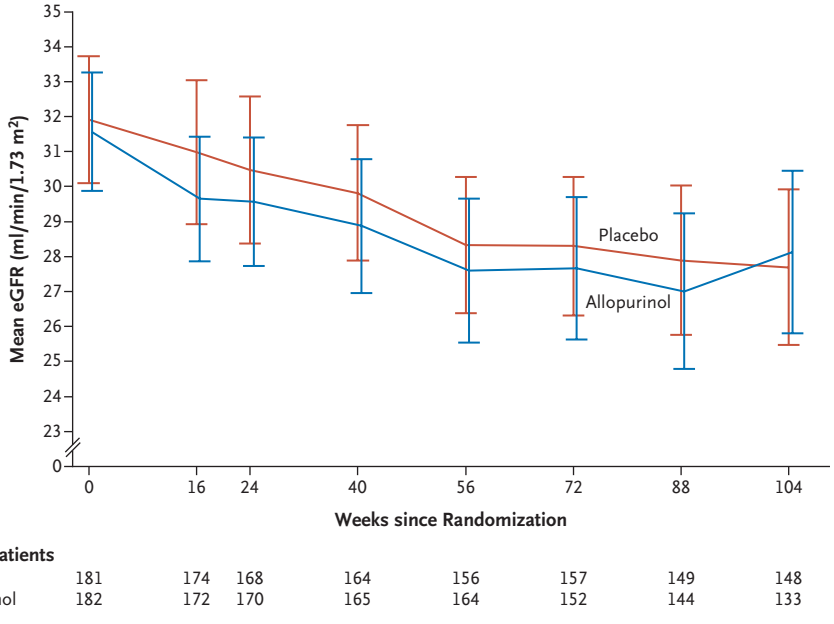

Figure 1. Effect of Allopurinol on Estimated Glomerular Filtration Rate (eGFR).
The effects of allopurinol and placebo on the eGFR are shown. I bars indicate 95% confidence intervals.

[95% CI, 300 to 330]) up to 104 weeks. The mean serum urate level in the placebo group at 12 weeks was 8.2 mg per deciliter (95% CI, 7.9 to 8.5) (490 μmol per liter [95% CI, 470 to 510]) and remained at 8.2 mg per deciliter (95% CI, 7.9 to 8.4) (490 μmol per liter [95% CI, 470 to 500]) for the duration of follow-up.

Overall, the mean difference in the serum urate level, with adjustment for baseline values, was –2.7 mg per deciliter (95% CI, –3.0 to –2.5)

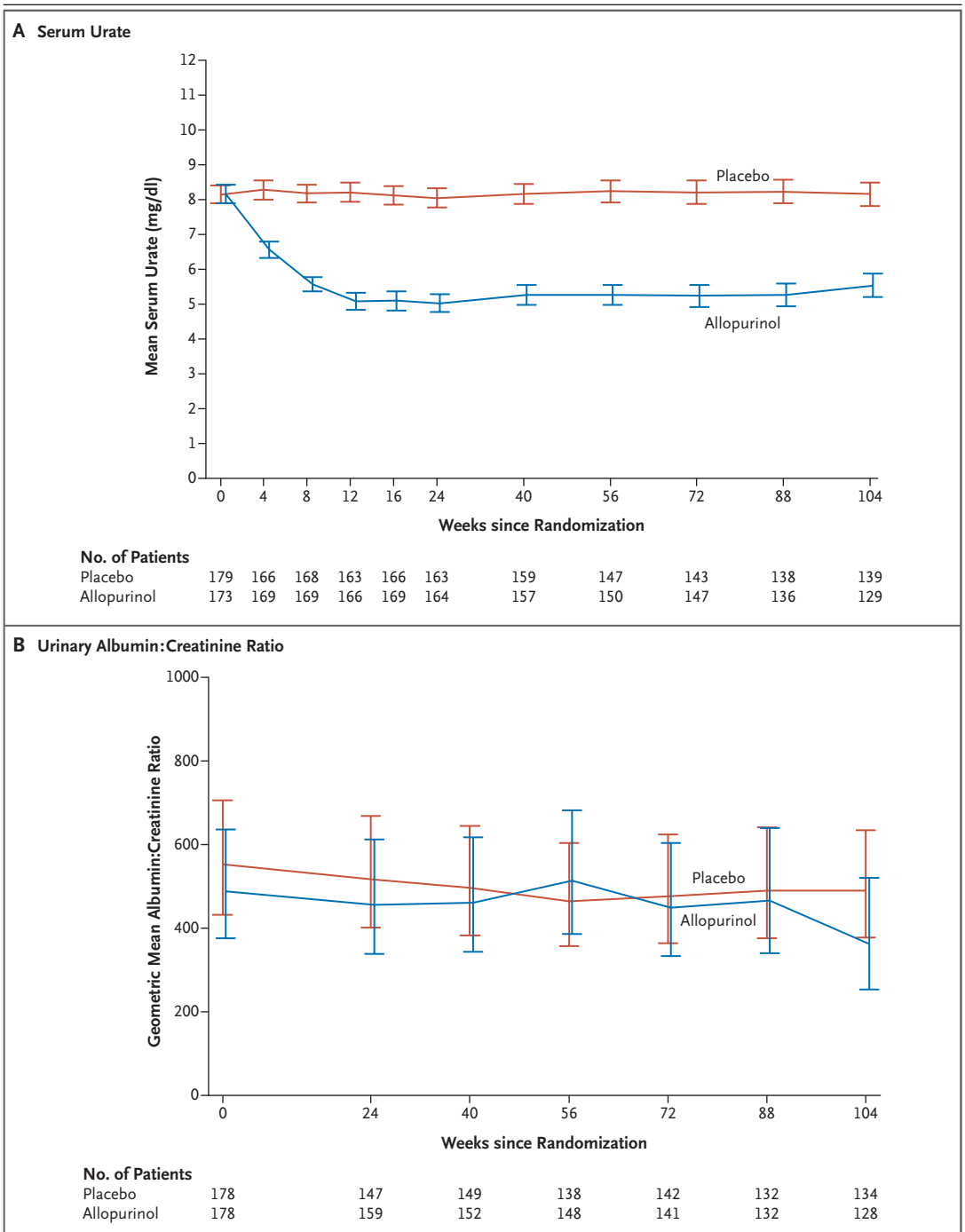

Figure 2. Effect of Allopurinol on Serum Urate and Albuminuria.

The effects of allopurinol and placebo on serum urate levels (Panel A) and the urinary albumin:creatinine ratio (Panel B) are shown. Albumin was measured in milligrams, and creatinine in grams. To convert the values for serum urate to micromoles per liter, multiply by 59.48. I bars indicate 95% confidence intervals.

Table 3. Serious Adverse Events.*

Event	Allopurinol (N=182)	Placebo (N=181)	Total (N=363)
Serious adverse events			
No. of patients (%)†	84 (46)	79 (44)	163 (45)
Total no. of events	170	167	337
No. of events per patient	0.93	0.92	0.93
Serious adverse events according to body system — no. of events/total no. (%)			
Cardiovascular event	33/170 (19)	44/167 (26)	77/337 (23)
Respiratory event	15/170 (9)	18/167 (11)	33/337 (10)
Gastrointestinal event	19/170 (11)	21/167 (13)	40/337 (12)
Renal event	39/170 (23)	30/167 (18)	69/337 (20)
Neurologic event	11/170 (6)	6/167 (4)	17/337 (5)
Musculoskeletal event	11/170 (6)	17/167 (10)	28/337 (8)
Endocrine event	6/170 (4)	3/167 (2)	9/337 (3)
Cancer or neoplasm	6/170 (4)	7/167 (4)	13/337 (4)
Hematologic event	4/170 (2)	2/167 (1)	6/337 (2)
Skin-related event	10/170 (6)	10/167 (6)	20/337 (6)
Other event	16/170 (9)	9/167 (5)	25/337 (7)

* Percentages may not total 100 because of rounding. Detailed data on serious adverse events according to body system are provided in Table S6.
† The difference between the groups was not significant (P=0.63 by chi-square test).

(–160 μmol per liter; 95% CI, –180 to –150) (Fig. 2A). There were no significant between-group differences in the urinary albumin:creatinine ratio (geometric mean difference, –9%; 95% CI, –24 to 10) (Fig. 2B), systolic blood pressure (mean difference, –1.79 mm Hg; 95% CI, –4.69 to 1.11) or diastolic blood pressure (mean difference, –3.21 mm Hg; 95% CI, –6.82 to 3.40) (Figs. S3 and S4), or health-related quality of life (mean difference in 36-Item Short-Form Health Survey quality-of-life summary score, –4.4; 95% CI, –10.5 to 1.6).

ADVERSE EVENTS

Serious adverse events occurred at similar frequencies in the two groups (170 events among 84 participants [46%] in the allopurinol group and 167 events among 79 participants [44%] in the placebo group) (Table 3 and Table S6). Eleven participants (6%) in the allopurinol group and 6 (3%) in the placebo group died. There were no significant differences in the risks of nonserious adverse drug reactions, including rash (Table S7).

DISCUSSION

In patients with stage 3 or 4 chronic kidney disease and an elevated risk of disease progression, we did not observe that treatment with allopurinol resulted in slower eGFR decline than did placebo over the 104-week follow-up period, despite a sustained mean reduction of 35% in serum urate levels in the allopurinol group. Furthermore, we did not observe a greater decrease in proteinuria, blood pressure, or the risk of the composite kidney outcome of a decline in the eGFR (when either a 40% or a 30% decline from baseline was used), end-stage kidney disease, or death in association with allopurinol.

Our results are consistent with those of the FEATHER (Febuxostat versus Placebo Randomized Controlled Trial Regarding Reduced Kidney

Function in Patients with Hyperuricemia Complicated by Chronic Kidney Disease Stage 3) and PERL (Preventing Early Renal Loss in Diabetes) trials[20,21] and those in adequately powered mendelian randomization studies.[22,23] Our results do not appear to support the view that circulating urate levels play a causal role in the progression of chronic kidney disease. Evidence from observational studies shows only an association between urate levels and progression of chronic kidney disease, not a cause-and-effect relationship.

The lack of effect of allopurinol treatment on the progression of chronic kidney disease in the present trial has a few possible alternative explanations. First, the enrollment of patients with at least moderately advanced chronic kidney disease could have limited the ability of allopurinol to prevent further decline in the eGFR. The epidemiologic association between serum urate levels and the onset of chronic kidney disease or progression to end-stage kidney disease has been described in cohort studies involving participants who did not have chronic kidney disease at baseline.[1,2] Second, the trial did not have a serum urate level–based inclusion criterion, and therefore some participants had normal serum urate levels and others had elevated serum urate levels at enrollment. However, our trial population had a markedly elevated mean baseline serum urate level of 8.2 mg per deciliter. Third, we did not adjust doses against serum urate levels, in order to avoid inadvertent unmasking of the randomly assigned intervention. However, a sustained mean reduction of 35% in serum urate levels was attained with allopurinol. Fourth, 76% of the patients in the trial were taking a renin–angiotensin system inhibitor at baseline, which could have attenuated the potential effects of allopurinol on the activity of the renin–angiotensin system in this trial population. However, this seems unlikely, since available trial-based evidence shows that urate lowering with allopurinol or probenecid has no effect on kidney-specific or systemic activity of the renin–angiotensin system.[24] Fifth, a higher-than-anticipated percentage of patients (30%) discontinued allopurinol. Despite this, only 17% of person-years of treatment time was lost, and the difference in serum urate levels between the allopurinol and placebo groups was maintained throughout follow-up. A second post hoc futility analysis showed that had we enrolled the 1006 patients needed to maintain sufficient power to accommodate this percentage of patients having discontinued allopurinol, we still would have had a relatively low probability of finding a significant effect of the drug.

The lack of benefit of allopurinol in slowing the progression of chronic kidney disease in our trial is noteworthy because we specifically enrolled patients who had an elevated risk of progression in order to maximize the potential to show an effect of allopurinol on the decline in eGFR. Other strengths of the present trial included the markedly elevated baseline serum urate levels, a large sustained reduction in serum urate levels, and an analysis involving the shared-parameter joint modeling approach, which makes the most conservative assumption that data are missing not at random.

Our trial also had some major limitations, including insufficient power as a result of incomplete enrollment, a high percentage of patients who discontinued the trial regimen, the use of a serum creatinine–based equation for the calculation of eGFR,[25] and the use of a surrogate outcome. The fact that we did not use a measurement of glomerular filtration rate with plasma clearance of an exogenous glomerular filtration marker, such as iohexol, was also a limitation.

In the present trial, which was stopped early, we did not find that allopurinol was more effective than placebo in slowing the decline in eGFR over a period of 104 weeks in patients with stage 3 or 4 chronic kidney disease and an elevated risk of disease progression.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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