Annals of Pharmacy Practice and Pharmacotherapy
ISSN: 3062-4436
2025, Volume 5, Issue 2, Page No: 197-211

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Impact of Dotinurad on Uric Acid Control and Kidney Function in Patients with Stage G3–G5 CKD: A Propensity-Matched Analysis

Oliver Grant[1], David Clark[1]*, Sophia Nguyen[2]

[1]Department of Pharmacy Practice and Patient Care, Faculty of Pharmacy, University of Glasgow, Glasgow, United Kingdom.
[2]Department of Clinical Pharmacotherapy and Drug Management, Faculty of Pharmaceutical Sciences, National University of Singapore, Singapore.

***E-mail** ✉ david.clark@gmail.com

Received: 04 November 2025; **Revised:** 20 December 2025; **Accepted:** 22 December 2026

ABSTRACT

We explored the therapeutic efficacy and tolerability of dotinurad, a selective inhibitor of urate reabsorption, among hyperuricemic subjects suffering from advanced chronic kidney disease (CKD) (classified as stage G3-5). A retrospective evaluation was performed on the records of 34 individuals (mean age, 68.6 ± 13.3 years; 17 male and 17 female) after a 12-month course of dotinurad, focusing on alterations in uric acid (UA) and the urine protein-to-creatinine ratio (UPCR), alongside the yearly rate of change in estimated glomerular filtration rate (eGFR). Each patient presented with hyperuricemia (UA ≥ 6.0 mg/dL) and advanced CKD (average eGFR: 32.0 ± 13.3 mL/min/1.73m²; stage G3, n = 17; G4, n = 13; G5, n = 4). A comparator arm was formed from the records of 34 propensity-score-matched counterparts who were not prescribed dotinurad. Serum UA concentrations fell markedly within the dotinurad-treated group (7.1 ± 0.8 mg/dL to 5.9 ± 1.0 mg/dL, P < 0.05), while remaining static in the matched controls. The UPCR did not vary appreciably between the two cohorts. A substantial reduction in low-density lipoprotein cholesterol was also registered in the dotinurad arm (98.8 ± 43.4 mg/dL to 82.9 ± 33.1 mg/dL, P < 0.05). After 12 months of dotinurad administration, the yearly eGFR slope improved significantly, from −6.0 ± 12.9 mL/min/1.73 m²/year to −0.9 ± 4.6 mL/min/1.73 m²/year (P < 0.05); the control group showed no comparable shift. Dotinurad is capable of diminishing UA levels and could mitigate the loss of kidney function in patients burdened by both hyperuricemia and advanced CKD.

Keywords: Chronic kidney disease, Dotinurad, Hyperuricemia, Uric acid, Renal function

How to Cite This Article: Grant O, Clark D, Nguyen S. Impact of Dotinurad on Uric Acid Control and Kidney Function in Patients with Stage G3–G5 CKD: A Propensity-Matched Analysis. Ann Pharm Pract Pharmacother. 2025;5(2):197-211. https://doi.org/10.51847/9quTB0jYLs

Introduction

Hyperuricemia constitutes a serious, potential sequela of chronic kidney disease (CKD) and is recognized worldwide as being linked to the advancement toward end-stage renal disease [1, 2]. It has been theorized that the precipitation of uric acid (UA) crystals within renal tubules and the interstitium, triggered by hyperuricemia—a process termed urate nephropathy—is responsible for the deterioration of CKD associated with elevated UA [3]. Pharmacotherapies that lower UA have been observed to cut UA levels and to slow the deterioration of renal performance in asymptomatic hyperuricemic individuals with CKD [4-6]. Accordingly, a considerable number of CKD patients presenting with gout or asymptomatic hyperuricemia are managed with UA-lowering agents [7].
Dotinurad, an agent indicated for gout and hyperuricemia, lowers serum UA levels by selectively blocking urate transporter 1 [8]. Evidence from a Phase III randomized controlled trial demonstrated that dotinurad lowered UA levels in hyperuricemic individuals, with or without gout, who had preserved renal function [9]; nonetheless, the capacity of dotinurad to lower UA and safeguard the kidneys has yet to be clarified in hyperuricemic subjects with

advanced CKD (stages G3-5). The present analysis was performed to gauge the drug's influence on UA handling and renal performance in individuals concurrently exhibiting hyperuricemia and advanced-stage CKD.

Materials and Methods

Ethical approval

The Institutional Review Board of Saitama Medical Center, Jichi Medical University, granted permission for this analysis (S18-114), which was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Because the work used a retrospective framework, the requirement to secure patients' informed consent was set aside. All persons whose data were included received notification of their ability to opt out. Study-related information was additionally displayed on the institutional noticeboards situated in the Medical Center's waiting rooms.

Patients

We undertook a retrospective appraisal of cases of patients cared for at Jichi Medical University's Saitama Medical Center during the period from September 1, 2019, to December 31, 2021. Enrollment necessitated satisfying the following criteria: (1) age older than 20 years; (2) an established diagnosis of hyperuricemia (UA ≥ 6.0 mg/dL), together with an estimated glomerular filtration rate (eGFR) no greater than 60 mL/min/1.73 m²; (3) continuous dotinurad intake for no less than 12 months; (4) first prescription of dotinurad between September 1, 2020, and December 31, 2020. Grounds for exclusion comprised: (1) concurrent use of uricosuric medications apart from dotinurad; (2) presence of malignant disease; or (3) current or prior receipt of renal replacement interventions such as hemodialysis, peritoneal dialysis, or kidney transplantation. Past reports indicate that a serum uric acid level surpassing 6.0 mg/dL correlates with a heightened probability of cardiovascular illness and progression to end-stage renal disease [10, 11]. Several contemporary studies have adopted a threshold of UA ≥ 6.0 mg/dL to demarcate hyperuricemia [12, 13]. For that reason, hyperuricemia in the present investigation was set at UA ≥ 6.0 mg/dL. The control cohort was assembled from the records of Medical Center attendees who were not exposed to dotinurad during the September 1, 2019–December 31, 2021 window, who met the enrollment and exclusion criteria except for dotinurad use, and who were matched to the treated patients via propensity score matching.

Study design

We conducted a retrospective, single-center pilot comparison study. The study's layout is depicted in **Figure 1.** Information from the 34 individuals who received dotinurad was matched to data from a reference cohort of 34 subjects whose initial profiles aligned with those of the dotinurad-treated set. The starting-point data for the treated individuals were logged on the dates on which intravenous therapy was commenced (September 1, 2020, through December 31 2020). Similarly, baseline measurements for the reference arm were recorded across that exact date range (September 1, 2020, through December 31, 2020), coinciding with the subjects' appointments at Saitama Medical Center.

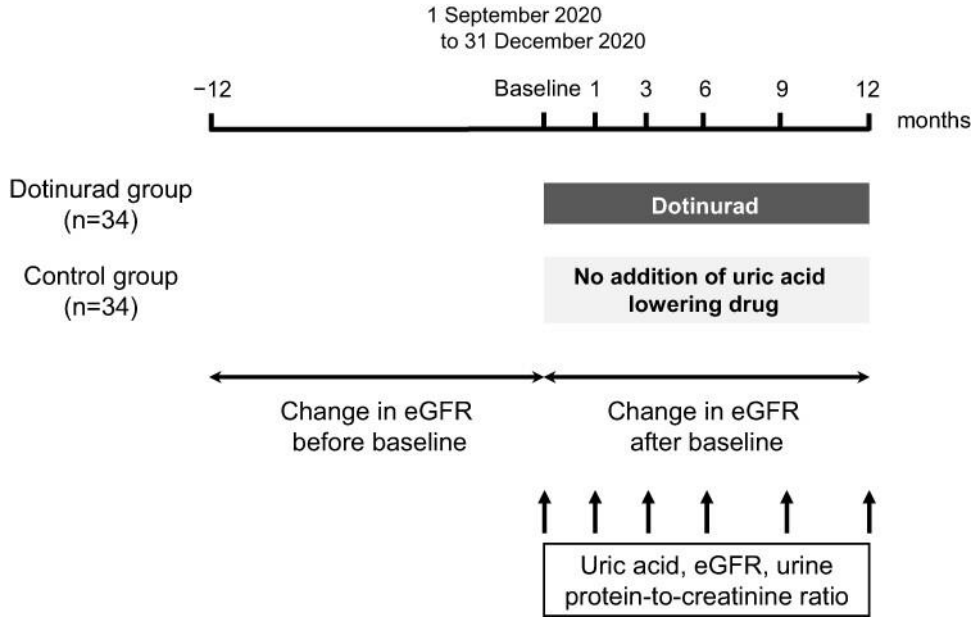

Figure 1. Study design. Abbreviation: eGFR = estimated glomerular filtration rate.

Dotinurad was administered orally once daily. Therapy was initiated at a strength of 0.5 mg/day. The dose was increased when hyperuricemia remained uncontrolled. At the conclusion of the 12-month observation, the dose strengths were as follows: 0.5 mg/day for 24 individuals, 1.0 mg/day for 8 individuals, 2.0 mg/day for 1 individual, and 4.0 mg/day for 1 individual **(Figure 2).** We tracked fluctuations in serum UA, the urine protein-to-creatinine ratio (UPCR), and eGFR at months 1, 3, 6, 9, and 12, and compared them with baseline values for both the treated and reference arms. The yearly trajectories of eGFR (mL/min/1.73 m²/year) were determined for each group across the 12 months leading up to baseline and the 12 months following baseline. To identify variables independently associated with changes in eGFR, UA, and time-averaged UA during the dotinurad therapy window, we conducted a multiple linear regression analysis.

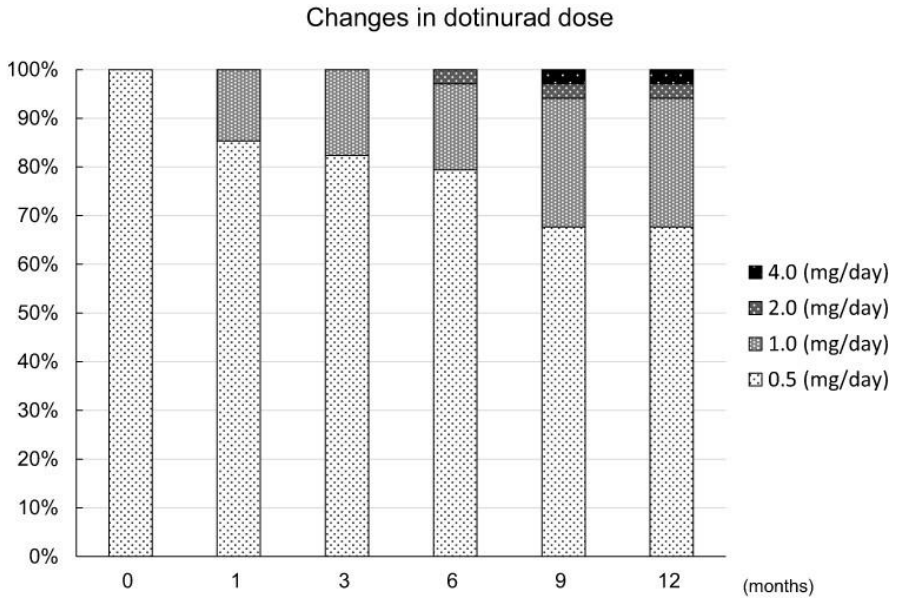

Figure 2. Changes in the distribution of dotinurad doses administered to patients.

Laboratory methods

The Clinical Laboratory facility at Saitama Medical Center measured hematological and urinary parameters. Each individual's eGFR was calculated by applying the modified version of the Modification of Diet in Renal Disease equation issued by the Japanese Society of Nephrology: eGFR (mL/min/1.73 m²) = 194 × age$^{-0.287}$ × serum

creatinine$^{-1.094}$ (applying a multiplication factor of 0.739 for female individuals) [14]. The hemoglobin A1c (HbA1c) results are expressed in terms aligned with the National Glycohemoglobin Standardization Program.
Hypertension was characterized by a mean systolic blood pressure ≥140 mmHg and/or a mean diastolic blood pressure ≥ 90 mmHg, or by concurrent use of antihypertensive therapy. Diabetes mellitus was identified based on an HbA1c value ≥ 6.5% or the administration of hypoglycemic agents and/or insulin. To quantify yearly eGFR shifts, we used linear regression, yielding a monthly slope for each individual within the pre-baseline and post-baseline windows. Blood pressure was measured with an automated arm cuff while each individual was seated; a pair of determinations was performed with a 1- to 2-minute pause in between, and the average of the two was used in the analyses.
Serial UA levels were assembled for all individuals, spanning the point of dotinurad initiation out to the 12-month mark, and these time-series measurements were utilized to derive a time-averaged figure for each individual, in accordance with the equation below:

$$\text{Time averaged } UA = \frac{1}{2(t_n - t_0)} \sum_{i=1}^{n} (UA_i + UA_{i-1})\,(t_i - t_{i-1}) \quad (1)$$

where the UA values UA_0, UA_1, … UA_n were obtained at time points t_0, t_1, … t_n.

Statistical analyses
Propensity score matching was applied to assemble a control group whose baseline characteristics closely matched those of the dotinurad-treated individuals. The propensity model incorporated age, sex, UA, and eGFR as independent covariates. The one-to-one pairing was achieved by selecting, for each dotinurad recipient, the control with the most proximate logit-transformed propensity score (within a caliper of 0.25); all subsequent analytical steps were performed on the resulting matched pairs. UPCR, triglyceride, and β_2-microglobulin departed from a Gaussian distribution; even so, drawing on the central limit theorem, they were treated as conforming to a normal distribution because each group comprised in excess of 30 observations [15]. Findings are reported as means ± standard deviations. Student's t-test was brought to bear to contrast clinical variables between the treated and control arms.
In contrast, a repeated-measures analysis of variance augmented by Tukey's test was used to compare clinical variables within each arm at baseline and at months 1, 3, 6, 9, and 12. Paired t-tests served to contrast the yearly eGFR shifts before and after baseline in both arms. Yearly eGFR changes were probed by linear regression and expressed as the slope per month for each individual. Linear regression was also used to examine pairwise relationships among variables. Candidate variables that simple linear regression assessments flagged as bearing a meaningful relationship to the changes in eGFR, UA, and time-averaged UA over the course of dotinurad therapy (at $P < 0.10$) were bundled into the present multiple linear regression model to isolate those covariates that bore an independent relationship to the changes in eGFR, UA, and time-averaged UA during the dotinurad treatment block. Statistical results yielding a probability (p) value below 0.05 were interpreted as significant. Data processing was performed using JMP 11 software (SAS, Cary, NC, USA).

Results and Discussion

The patients' characteristics
We screened a pool of 250 individuals with hyperuricemia and an eGFR of less than 60 mL/min/1.73 m²; within this group, 44 were on dotinurad, and 206 were not. Of those 44 candidates under dotinurad care, 10 fell short of meeting the full set of entry requirements, yielding a final treated cohort of 34. Using one-to-one propensity score matching, 34 subjects who had not been exposed to dotinurad were paired with treated individuals, forming the comparator arm **(Figure 3)**. Overall, the analysis therefore drew upon the records of 68 patients (an equal split of 34 men and 34 women, averaging 68.7 ± 13.8 years of age).

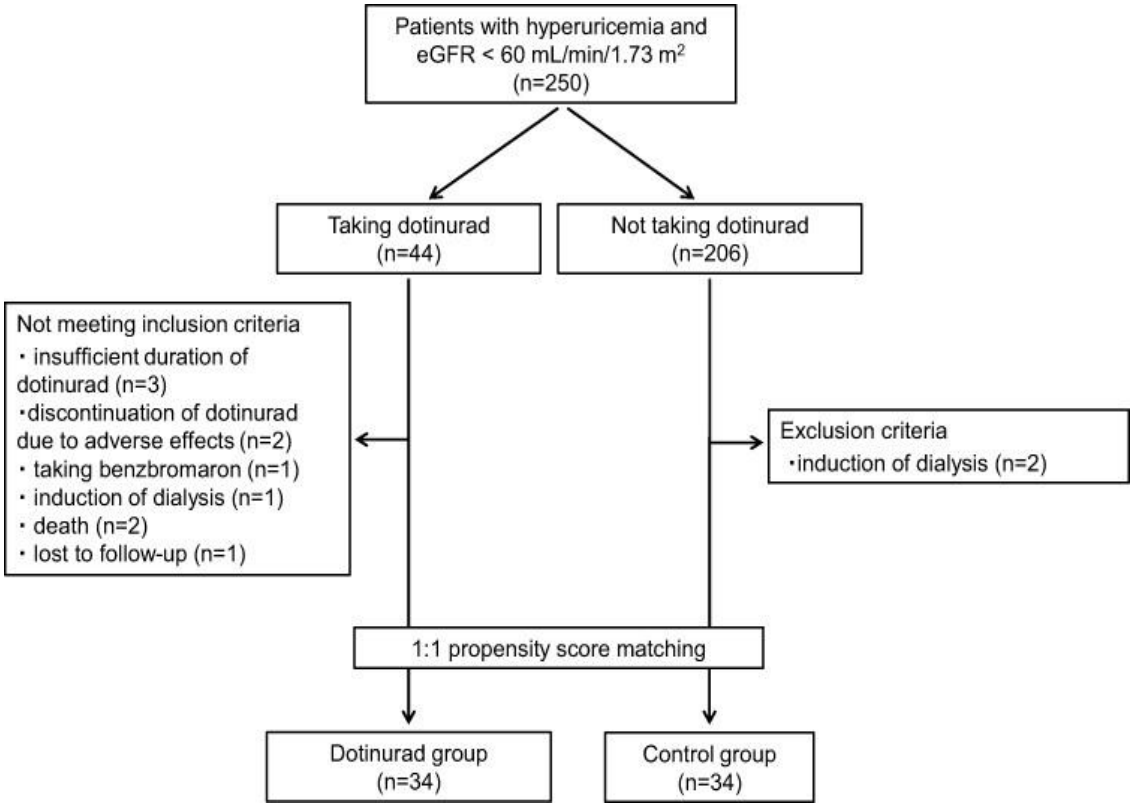

Figure 3. Patient flow diagram.

The mean eGFR documented at baseline for the complete set of 68 individuals was 32.3 ± 14.2 mL/min/1.73 m². When classified by CKD severity, the distribution was as follows: stage G3a, 14 subjects (20.6%); stage G3b, 23 subjects (33.8%); stage G4, 21 subjects (30.9%); and stage G5, 10 subjects (14.7%). No participant required renal replacement modalities during the observation window. A comprehensive overview of the baseline characteristics of the entire sample, along with the medication profiles of the dotinurad and comparator arms, is presented in **Table 1**. The two arms were well matched across their clinical attributes, with the sole exceptions of high-density lipoprotein (HDL) cholesterol values and the share of individuals on a statin, eicosapentaenoic acid, or a dipeptidyl peptidase-4 (DPP-4) inhibitor. Diabetes mellitus was present in 36.8% of the study population, while hypertension was documented in 86.8%. Over the entire duration of the treatment interval, there was no adjustment to the type or dosing strength of any background UA-lowering agent in either arm. Among those allocated to the dotinurad arm, the agents newly prescribed during the 12 months immediately before baseline included: blood-pressure-lowering drugs in 4 subjects, cholesterol-lowering drugs in 4 subjects, diuretic compounds in 3 subjects, and a UA-lowering compound in 1 subject. Within the control arm during that same pre-baseline stretch, the following were introduced: blood-pressure-lowering drugs in four subjects, cholesterol-lowering drugs in two subjects, and a diuretic in a single subject. Once the dotinurad treatment phase was underway, blood-pressure-lowering pharmacotherapy was commenced in four dotinurad-treated subjects and discontinued in two. In contrast, in the control arm, it was initiated in two subjects.

Table 1. Participants' characteristics and medications at baseline.

Baseline characteristics	P-value	Control group (n = 34)	Dotinurad group (n = 34)
Age (years)	0.93	68.9 ± 14.4	68.6 ± 13.3
Male sex, n (%)	1.00	17 (50.0)	17 (50.0)
BMI (kg/m²)	0.70	25.0 ± 4.4	24.4 ± 4.4
Systolic BP (mmHg)	0.07	125.6 ± 16.0	136.3 ± 19.9
Diastolic BP (mmHg)	0.46	74.9 ± 8.5	78.0 ± 15.2
Diabetes mellitus, n (%)	0.08	9 (26.5)	16 (47.1)
Hypertension, n (%)	0.73	29 (85.3)	30 (88.2)

Gout, n (%)	1.00	0 (0.0)	0 (0.0)
Antiplatelet use, n (%)	0.59	10 (29.4)	8 (23.5)
Statin use, n (%)	0.002*	10 (29.4)	25 (73.5)
Eicosapentaenoic acid use, n (%)	0.024*	1 (2.9)	7 (20.6)
Other urate-lowering agents, n (%)	0.46	12 (35.3)	15 (44.1)
Febuxostat, n (%) (overall)	0.17	6 (17.6)	12 (35.3)
• 10 mg/day	0.34	3 (8.8)	2 (5.9)
• 20 mg/day	—	3 (8.8)	8 (23.5)
• 40 mg/day	—	0 (0.0)	2 (5.9)
• 60 mg/day	—	0 (0.0)	0 (0.0)
Allopurinol, n (%) (overall)	0.71	5 (14.7)	3 (8.8)
• 50 mg/day	0.64	2 (5.9)	0 (0.0)
• 100 mg/day	—	3 (8.8)	2 (5.9)
• 200 mg/day	—	0 (0.0)	1 (2.9)
Topiroxostat, n (%) (overall)	1.00	1 (2.9)	0 (0.0)
• 40 mg/day	1.00	1 (2.9)	0 (0.0)
• 80 mg/day	—	0 (0.0)	0 (0.0)
Alkali supplementation, n (%)	0.65	2 (5.9)	3 (8.8)
DPP-4 inhibitor, n (%)	0.040*	4 (11.8)	11 (32.4)
SGLT-2 inhibitor, n (%)	0.08	0 (0.0)	3 (8.8)
GLP-1 receptor agonist, n (%)	0.65	2 (5.9)	3 (8.8)
Insulin therapy, n (%)	0.56	2 (5.9)	1 (2.9)
Diuretics, n (%)	0.32	10 (29.4)	14 (41.2)
β-blockers, n (%)	0.17	6 (17.6)	11 (32.4)
Calcium channel blockers, n (%)	1.00	22 (64.7)	22 (64.7)
RAAS inhibitors, n (%)	0.81	21 (61.8)	22 (64.7)
BUN (mg/dL)	0.61	31.8 ± 18.7	29.8 ± 12.7
Serum creatinine (mg/dL)	0.85	1.9 ± 0.9	1.8 ± 0.8
eGFR (mL/min/1.73m²)	0.88	32.6 ± 15.2	32.0 ± 13.3
Primary CKD cause	0.20		
• Hypertensive nephrosclerosis		13 (38.2)	13 (38.2)
• Diabetic kidney disease		5 (14.7)	8 (23.5)
• Chronic glomerulonephritis		4 (11.8)	5 (14.7)
• Other causes		12 (35.3)	8 (23.5)
CKD stage distribution	0.92		
• G3a		7 (20.6)	7 (20.6)
• G3b		13 (38.2)	10 (29.4)
• G4		8 (23.5)	13 (38.2)
• G5		6 (17.6)	4 (11.8)
HbA1c (%)	0.85	6.2 ± 0.9	6.2 ± 0.6
Serum albumin (g/dL)	0.72	3.8 ± 0.4	4.1 ± 0.5
LDL cholesterol (mg/dL)	0.47	105.7 ± 33.2	98.8 ± 43.4
HDL cholesterol (mg/dL)	0.020*	60.1 ± 20.1	50.4 ± 12.9
Triglycerides (mg/dL), median (IQR)	0.17	116.0 (89.0–184.0)	143.0 (96.5–226.0)
Uric acid (mg/dL)	0.78	7.1 ± 0.8	7.1 ± 0.8
Hemoglobin (g/dL)	0.77	12.0 ± 2.0	12.1 ± 1.7
Urinary protein excretion (g/gCr), median (IQR)	0.73	0.32 (0.03–1.20)	0.56 (0.04–1.54)
Urinary NAG (IU/L)	0.36	8.2 ± 4.2	9.5 ± 5.4
Urinary β2-microglobulin (μg/L), median (IQR)	0.26	243.0 (111.0–1125.0)	648.0 (149.6–4085.0)

Note: P-values are statistically significant. Abbreviations: BMI = body mass index; BUN = blood urea nitrogen; CCB = calcium channel blocker; CKD = chronic kidney disease; DBP = diastolic blood pressure; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NAG = N-acetyl-β-glucosaminidase; RAS = renin angiotensin system; SBP = systolic blood pressure; SGLT-2 = sodium glucose cotransporter-2.

Effects of dotinurad on UA control

In the cohort receiving dotinurad, the serum UA concentration underwent a marked descent, moving from a baseline of 7.1 ± 0.8 mg/dL to 6.1 ± 1.0 mg/dL by the first monthly assessment ($P < 0.05$), and this reduction endured through subsequent visits, registering 6.0 ± 1.0 mg/dL at month 3 ($P < 0.05$), 5.9 ± 1.2 mg/dL at month 6 ($P < 0.05$), 6.1 ± 1.1 mg/dL at month 9 ($P < 0.05$), and 5.9 ± 1.0 mg/dL once 12 months had been completed ($P < 0.05$). The picture was entirely different for the comparator group, whose UA figures at months 1, 3, 6, 9, and 12 did not depart in any statistically meaningful manner from the starting levels **(Figure 4).**

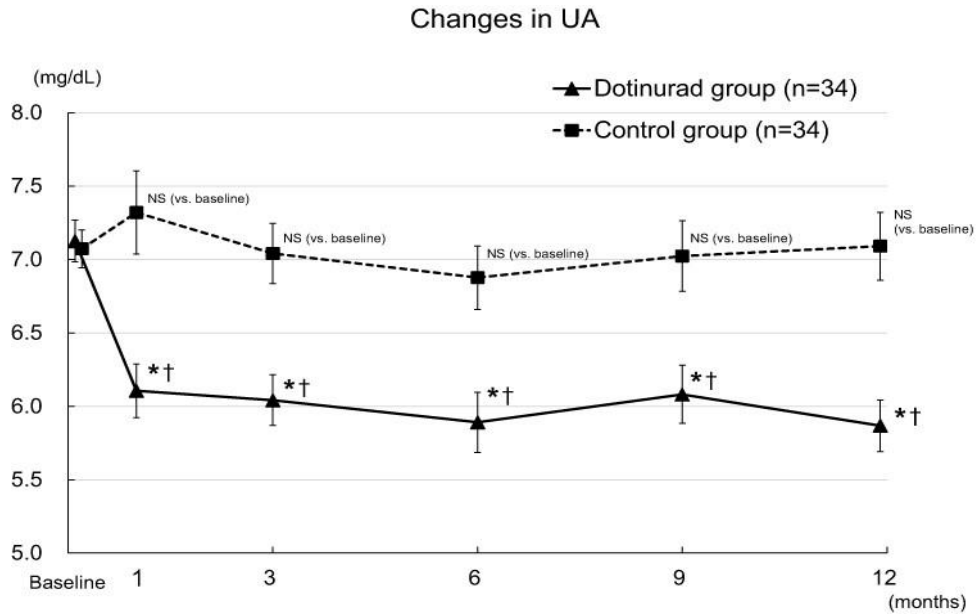

Figure 4. Changes in uric acid (UA) values in the dotinurad and control groups. Vertical bars: standard error of the mean. $P < 0.05$ vs baseline; †$P < 0.05$ vs the control group. Abbreviations: NS = not significant; UA = uric acid.

Effects of dotinurad on the UPCR and the eGFR's annual change

Neither the treated patients nor the comparator subjects exhibited a discernible shift in UPCR from their respective baselines at months 1, 3, 6, 9, or 12, as shown in **Figure 5**. As for the yearly rate of renal function change, dotinurad-treated individuals showed a significant improvement, advancing from a pre-baseline slope of −6.0 ± 12.9 to −0.9 ± 4.6 mL/min/1.73 m²/year during the subsequent 12-month phase ($P < 0.05$) **(Figures 6 and 7)**. The scenario in the reference arm was the opposite: they experienced a significant acceleration in kidney function loss, moving from a pre-baseline rate of 0.9 ± 4.7 to −3.4 ± 6.7 mL/min/1.73 m²/year over the corresponding post-baseline interval ($P < 0.05$) **(Figures 6 and 7).**

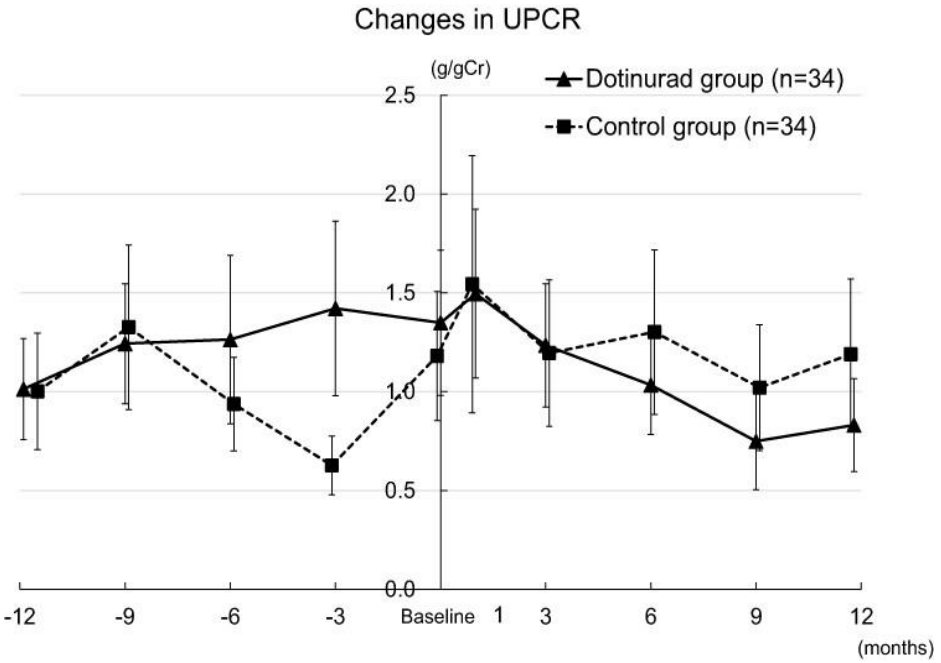

Figure 5. Changes in the urine protein-to-creatinine ratio (UPCR) in the dotinurad and control groups. Vertical bars: standard error of the mean.

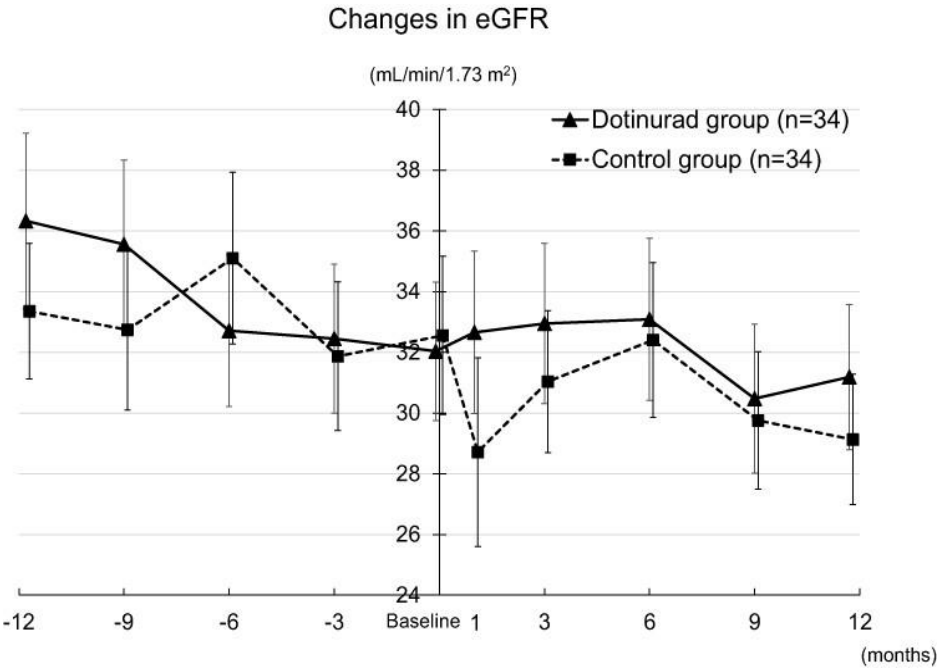

Figure 6. Changes in estimated glomerular filtration rate (eGFR) in the dotinurad-treated and control patients. Vertical bars: standard error of the mean.

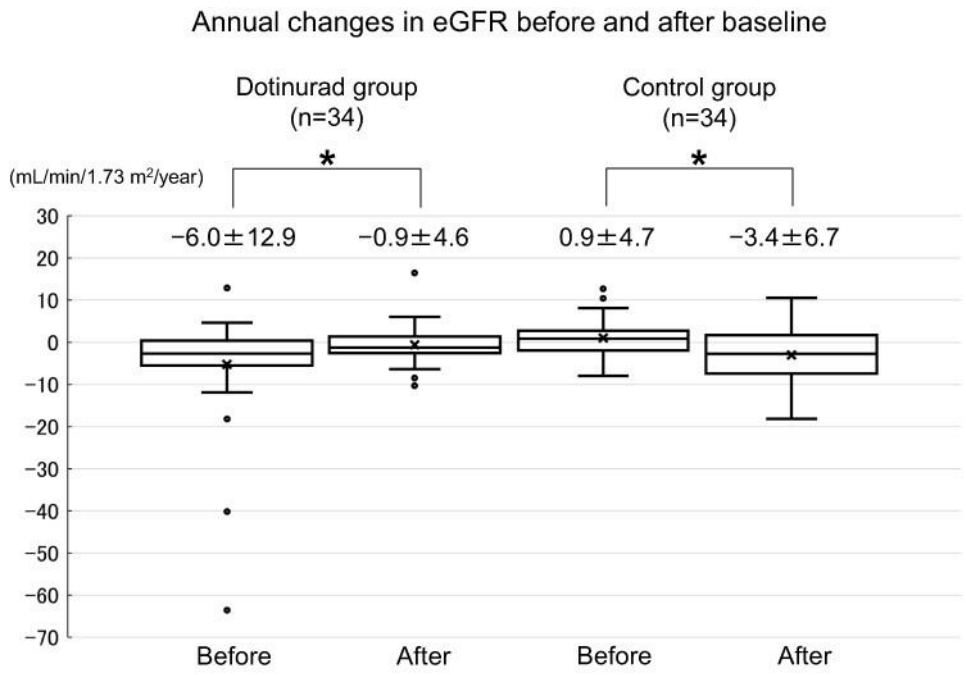

Figure 7. Annual eGFR change from pre- to post-baseline in the dotinurad and control groups ($P < 0.05$).

Factors associated with the change in eGFR during the dotinurad treatment

As summarised in **Table 2**, univariate linear regression investigations brought to light a marginal or statistically meaningful connection linking the variation in eGFR throughout the dotinurad treatment course with each of the following: HDL cholesterol concentration, the coadministration of a DPP-4 inhibitor, the coadministration of a β-blocker, the mean daily quantity of dotinurad taken over the 12 months, and the time-averaged UA concentration. A multivariate linear regression model was then built, incorporating all covariates that the univariate assessments had flagged as marginally or significantly ($P < 0.10$) associated with eGFR variation during dotinurad treatment. From this model, it emerged that DPP-4 inhibitor coadministration (standard coefficient [β] = 0.291, $P = 0.046$) and time-averaged UA (β = −0.520, $P = 0.004$) each independently associated with the degree of eGFR modification recorded during the dotinurad therapy window.

Table 2. Simple and multiple linear regression analyses of variables associated with the change in estimated glomerular filtration rate during the administration of dotinurad.

Variable	Multivariable linear regression		Univariate linear regression	
	Standardized coefficient	P-value	Standardized coefficient	P-value
Age (years)			−0.101	0.57
Male sex (yes vs no)			0.063	0.72
Baseline BMI (kg/m²)			−0.048	0.80
Baseline systolic BP (mmHg)			−0.272	0.12
Baseline diastolic BP (mmHg)			−0.196	0.27
Baseline HbA1c (%)			−0.195	0.35
Baseline albumin (g/dL)			0.205	0.25
Baseline BUN (mg/dL)			0.102	0.57
Baseline eGFR (mL/min/1.73 m²)			−0.031	0.86
Baseline uric acid (mg/dL)			0.051	0.78
Baseline HDL cholesterol (mg/dL)	0.237	0.13	0.295	0.095*
Baseline LDL cholesterol (mg/dL)			−0.025	0.89
Baseline triglycerides (mg/dL)			−0.189	0.29
Baseline hemoglobin (g/dL)			−0.153	0.39
Baseline urinary protein excretion (g/gCr)			−0.238	0.18

Baseline NAG (IU/L)			−0.176	0.32
Baseline β2-microglobulin (μg/L)			−0.183	0.33
Hypertension (yes vs no)			−0.018	0.92
Diabetes mellitus (yes vs no)			0.101	0.57
Antiplatelet therapy (yes vs no)			−0.206	0.24
Statin use (yes vs no)			−0.046	0.80
Eicosapentaenoic acid use (yes vs no)			−0.180	0.31
Other urate-lowering therapy (yes vs no)			−0.275	0.12
Alkali supplementation (yes vs no)			−0.001	1.00
DPP-4 inhibitor use (yes vs no)	0.291	0.046*	0.353	0.041*
Diuretic use (yes vs no)			−0.086	0.63
β-blocker use (yes vs no)	−0.118	0.45	−0.450	0.008*
Calcium channel blocker use (yes vs no)			0.073	0.68
RAS inhibitor use (yes vs no)			0.149	0.40
Mean dotinurad dose over 12 months (mg/day)	−0.019	0.91	−0.404	0.018*
Time-averaged uric acid (mg/dL)	−0.520	0.004*	−0.627	<0.001*
Initial dotinurad dose (mg/day)			0.000	–

Notes: Abbreviations are explained in the **Table 1** footnote. P-values are marginally or statistically significant.

Factors associated with the change in UA during the first 1 month of dotinurad treatment

Univariate regression analyses pinpointed a marginal or statistically significant association between the UA decline measured over the opening month of dotinurad therapy and the following collection of predictors **(Table 3):** blood urea nitrogen (BUN), eGFR, UA, hemoglobin, a prior history of diabetes mellitus, a prior history of myocardial infarction, the concurrent ingestion of another UA-lowering drug, the concurrent ingestion of an alkali supplement, and the concurrent ingestion of a calcium channel blocker. Upon fitting a multiple linear regression equation that encompassed those variables, the univariate analyses had shown to be marginally or significantly tied ($P < 0.10$) to the UA shift during that inaugural month, it became evident that the UA concentration measured at baseline bore an independent relationship with the magnitude of the UA decrease achieved throughout the first month of dotinurad administration ($\beta = -0.436$, $P = 0.005$).

Table 3. Simple and multiple linear regression analyses of variables associated with the change in uric acid during the first 1 month of dotinurad administration.

Variable	**Multivariable linear regression**		**Univariate loinear regression**	
	Standardized coefficient	**P-value**	**Standardized coefficient**	**P-value**
Age (years)			0.097	0.60
Male sex (yes vs no)			−0.173	0.34
Baseline BMI (kg/m²)			−0.197	0.31
Baseline systolic BP (mmHg)			0.073	0.69
Baseline diastolic BP (mmHg)			−0.011	0.95
Baseline HbA1c (%)			0.132	0.55
Baseline albumin (g/dL)			−0.076	0.68
Baseline BUN (mg/dL)	0.254	0.36	0.536	0.002*
Baseline eGFR (mL/min/1.73 m²)	−0.136	0.56	−0.586	<0.001*
Baseline uric acid (mg/dL)	−0.436	0.005*	−0.305	0.089*
Baseline HDL cholesterol (mg/dL)			−0.093	0.62
Baseline LDL cholesterol (mg/dL)			−0.223	0.22
Baseline triglycerides (mg/dL)			−0.007	0.97
Baseline hemoglobin (g/dL)	−0.127	0.47	−0.340	0.057*
Baseline urinary protein excretion (g/gCr)			0.169	0.36

Baseline NAG (IU/L)			0.306	0.46
Baseline β2-microglobulin (μg/L)			0.250	0.20
Hypertension (yes vs no)			0.154	0.40
Diabetes mellitus (yes vs no)	0.188	0.18	0.346	0.053*
History of myocardial infarction (yes vs no)	0.132	0.32	0.313	0.082*
History of stroke (yes vs no)			−0.182	0.32
Antiplatelet therapy (yes vs no)			0.176	0.33
Statin use (yes vs no)			0.057	0.76
Eicosapentaenoic acid use (yes vs no)			−0.070	0.70
Other urate-lowering therapy (yes vs no)	0.201	0.18	0.343	0.055*
Alkali supplementation (yes vs no)	0.088	0.55	0.378	0.033*
DPP-4 inhibitor use (yes vs no)			0.111	0.55
Diuretic use (yes vs no)			0.253	0.16
β-blocker use (yes vs no)			0.046	0.80
Calcium channel blocker use (yes vs no)	0.173	0.22	0.389	0.028*
RAS inhibitor use (yes vs no)			−0.103	0.57
Initial dotinurad dose (mg/day)			0.000	–

Notes: Abbreviations are explained in the **Table 1** footnote. P-values are marginally or statistically significant.

Factors associated with the time-Averaged UA during dotinurad treatment

As detailed in **Table 4,** univariate linear regression scans brought to light a marginal or statistically discernible connection between the time-averaged UA readings logged across the dotinurad treatment interval and the following set of variables: HbA1c percentage, eGFR, triglyceride concentration, β2-microglobulin level, a prior diagnosis of diabetes mellitus, concurrent prescription of other UA-lowering preparations, concurrent prescription of a diuretic, concurrent prescription of a β-blocker, and the mean quantity of dotinurad administered per day throughout the 12 months. Using the covariates identified by the univariate regression tests as bearing a marginal or significant association ($P < 0.10$) with the time-averaged UA figures, we fit a multivariable linear regression equation. The output of that multivariable analysis revealed a singular independent relationship: the co-ingestion of a β-blocker was independently associated with the time-averaged UA levels sustained during dotinurad therapy ($\beta = 0.798$, $P = 0.017$).

Table 4. Simple and multiple linear regression analyses of variables associated with the time average of uric acid during the administration of dotinurad.

Variable	**Multivariable linear regression**		**Univariate linear regression**	
	Standardized coefficient	**P-value**	**Standardized coefficient**	**P-value**
Age (years)			−0.046	0.79
Male sex (yes vs no)			0.165	0.35
Baseline BMI (kg/m²)			0.228	0.23
Baseline systolic BP (mmHg)			0.134	0.45
Baseline diastolic BP (mmHg)			0.136	0.44
Baseline HbA1c (%)	0.181	0.60	0.367	0.071*
Baseline albumin (g/dL)			−0.134	0.45
Baseline eGFR (mL/min/1.73 m²)	−0.427	0.33	−0.329	0.057*
Baseline uric acid (mg/dL)			0.175	0.32
Baseline HDL cholesterol (mg/dL)			−0.202	0.26
Baseline LDL cholesterol (mg/dL)			−0.113	0.52
Baseline triglycerides (mg/dL)	−0.076	0.79	0.307	0.078*
Baseline hemoglobin (g/dL)			−0.112	0.53
Baseline urinary protein excretion (g/gCr)	0.460	0.15	0.231	0.20
Baseline NAG (IU/L)			0.163	0.39

Baseline β2-microglobulin (μg/L)	−0.238	0.59	0.361	0.050*
Hypertension (yes vs no)			0.010	0.95
Diabetes mellitus (yes vs no)	0.222	0.40	0.293	0.093*
Antiplatelet therapy (yes vs no)			−0.020	0.91
Statin use (yes vs no)			−0.060	0.74
Eicosapentaenoic acid use (yes vs no)			0.165	0.35
Other urate-lowering therapy (yes vs no)	−0.384	0.19	0.391	0.022*
Alkali supplementation (yes vs no)			0.117	0.51
DPP-4 inhibitor use (yes vs no)			−0.060	0.74
Diuretic use (yes vs no)	0.182	0.62	0.497	0.003*
β-blocker use (yes vs no)	0.798	0.017*	0.500	0.003*
Calcium channel blocker use (yes vs no)			0.106	0.55
RAS inhibitor use (yes vs no)			−0.152	0.39
Mean dotinurad dose over 12 months (mg/day)	−0.093	0.81	0.555	0.001*
Initial dotinurad dose (mg/day)			0.000	–

Notes: Abbreviations are explained in the **Table 1** footnote. P-values are marginally or statistically significant.

Other clinical parameters' changes, and adverse effects

A significant decrease in low-density lipoprotein (LDL) cholesterol was observed among dotinurad recipients, from a baseline of 98.8 ± 43.4 mg/dL to 82.6 ± 30.1 mg/dL at the 9-month evaluation ($P < 0.05$). This improvement persisted through month 12, with a reading of 82.9 ± 33.1 mg/dL ($P < 0.05$) **(Figure 8).** In addition, as **Figure 8** depicts, the LDL cholesterol figures in the dotinurad arm stood apart in a statistically meaningful manner from those in the comparator cohort at the 6-, 9-, and 12-month time points **(Figure 8).** An examination of the remaining clinical and laboratory indices—among them body mass index, systolic blood pressure, HbA1c, HDL cholesterol, triglyceride, albumin, C-reactive protein, and hemoglobin—yielded no significant divergences between the starting figures and those captured at months 1, 3, 6, 9, or 12 within either the dotinurad group or the reference group (data suppressed). Episodes of acute gouty arthritis were not witnessed in either arm at any point throughout the study timeframe. That said, untoward reactions arose in two dotinurad-exposed individuals (manifesting as pyrexia and nausea), necessitating the cessation of their dotinurad regimens.

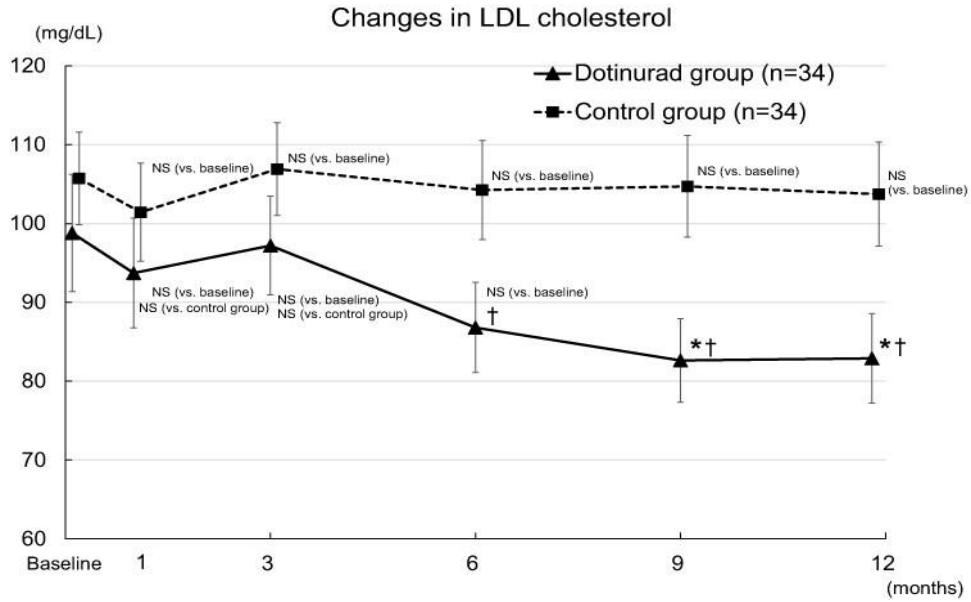

Figure 8. Changes in low-density lipoprotein (LDL) cholesterol in the dotinurad and control groups. Vertical bars: standard error of the mean. $P < 0.05$ vs baseline; †$P < 0.05$ vs the control group.

The data emerging from our analyses establish that the introduction of the selective urate reabsorption blocker dotinurad in subjects carrying a dual burden of hyperuricemia and advanced CKD achieved a meaningful

reduction in circulating UA and a braking of kidney function deterioration, while being free of any major safety signals. The results of our multivariable linear regression modeling further illuminated three key observations: (1) co-prescription of a DPP-4 inhibitor and the average UA exposure over time each carried an independent association with the shift in eGFR observed across the dotinurad treatment period; (2) the UA value recorded at study entry was independently related to the extent of UA lowering accomplished within the inaugural month of dotinurad therapy; and (3) background β-blocker intake proved to be an independent correlate of the time-averaged UA concentration maintained while on dotinurad. Taken together, these patterns imply that dotinurad delivers beneficial impacts on UA handling and kidney performance in hyperuricemic individuals living with advanced CKD, and they point toward a satisfactory tolerability profile for this therapeutic within that demographic.

A body of literature has previously linked UA-lowering agents with an attenuation of renal function decline in CKD cohorts [4-6]. Nonetheless, dotinurad did not produce a detectable antiproteinuric effect in this investigation. It may well be that UA-lowering pharmacotherapies lose their ability to curb urinary protein excretion once CKD has advanced. Dedicated studies focused on the antiproteinuric potential of these drugs in advanced CKD populations are therefore still required.

In the present study, the yearly trajectory of eGFR shifted significantly in a favorable direction among dotinurad recipients, whereas no such shift occurred in the comparator arm. A protective effect on kidney tissue has been hypothesized, as uricosuric compounds may delay the progression of glomerulosclerosis [16]. Elsewhere, it has been shown that lowering UA suppresses RAS activity, thereby reducing intraglomerular pressure and potentially helping preserve eGFR [17]. As **Table 2** makes clear, however, the renal functional changes we tracked were unrelated to urinary protein excretion or blood pressure. This raises the possibility that any renoprotective mechanism attributable to dotinurad operates through channels distinct from proteinuria and systemic hemodynamics.

Also apparent from **Table 2** is the finding that the rate of kidney function loss from baseline through to month 12 was significantly tied to concurrent DPP-4 inhibitor use. A conceivable biological underpinning lies in the capacity of DPP-4 blockade to augment renal synthesis of cyclic adenosine monophosphate (cAMP) by raising circulating levels of stromal cell-derived factor-1α [18]. Higher cAMP concentrations are known to trigger antioxidant defenses and to dampen reactive oxygen species, which are considered a key culprit in the worsening of CKD. It is further speculated that DPP-4 inhibitors increase the availability of active glucagon-like peptide-1, which, in turn, elevates cAMP and reduces oxidative burden [18].

Turning to **Table 3,** the magnitude of the UA drop from baseline to the one-month assessment was tied to the initial UA reading. A recent study found that individuals with higher baseline serum UA showed a sharper decline in serum UA during the first 4 weeks of UA-lowering pharmacotherapy [19]. Our findings align closely with that report, indicating that the degree of early UA reduction is intimately linked to the pretreatment UA level [19].

We also documented a relationship between the time-averaged UA level and concurrent β-blocker therapy **(Table 4),** an observation that aligns with prior research [20-22]. Among the mechanisms put forward is the notion that β-blockers stimulate the pentose phosphate pathway, thereby accelerating UA biosynthesis [21]. That said, a definitive verdict on whether β-blockers represent an independent driver of hyperuricemia has yet to be reached [20].

As illustrated in **Figure 8**, dotinurad therapy was associated with a decrease in LDL cholesterol concentrations. Reports in the literature indicate that compounds that reduce UA can also lower serum LDL cholesterol in individuals with hyperlipidemia [23-25]. The biological pathways connecting UA reduction to LDL cholesterol regulation remain to be elucidated, though a proposed explanation centers on the capacity of reduced UA to temper oxidative stress and inflammation, both of which intersect with LDL cholesterol metabolism [23]. It warrants mention, however, that close to 70% of the dotinurad-treated patients in our series were also on statin therapy, a factor that could have influenced the results. Future studies specifically designed to examine the LDL cholesterol-modulating properties of dotinurad in hyperuricemic patients with advanced CKD are therefore necessary.

An earlier observational investigation reported that serum uric acid exceeding 6.0 mg/dL conferred an elevated risk of advancement to end-stage kidney disease among patients with moderate to severe CKD [11]. Our present findings demonstrate that dotinurad blunted the decline in renal function in subjects with UA levels meeting or exceeding the 6.0 mg/dL threshold in advanced CKD. These results lend weight to the view that UA-lowering intervention could yield renoprotective dividends in hyperuricemic (UA ≥6.0 mg/dL) individuals with advanced CKD. Broader, longer trials will be indispensable to more fully define the kidney-sparing properties of dotinurad

in this population. The current report constitutes the first evidence linking dotinurad to renoprotection in hyperuricemic patients grappling with advanced CKD, and the data it contributes may prove valuable in shaping subsequent explorations of dotinurad treatment in this clinical context.

Several limitations inherent to this investigation warrant acknowledgment. Given its single-center, retrospective, observational design, the potential for patient selection bias cannot be entirely ruled out; however, propensity score matching was employed to mitigate this bias within the control arm. The modest size of the study cohort (n=68) and the fact that enrolment was confined to a single medical facility limit the generalizability of the findings. The dotinurad group exhibited higher systolic blood pressure readings and a greater prevalence of diabetes compared with the control arm. This discrepancy may well have influenced the course of kidney function over time. An additional consideration is that pharmacotherapies initiated before the commencement of dotinurad administration may have affected renal function and urinary protein excretion. Nearly half of the study participants were concurrently receiving alternative UA-lowering agents such as allopurinol or febuxostat; however, it seems improbable that these medications materially swayed our observations, as the propensity-score matching procedure yielded no appreciable imbalances between the two groups with respect to baseline characteristics—the usage of UA-lowering drugs being no exception—and throughout the treatment period there were no alterations to either the type or the dosage of any UA-lowering medication being taken. Robust confirmation of dotinurad's capacity to afford renoprotection in patients with advanced CKD will require conducting long-term, larger-scale randomized clinical trials. The possibility of confounding by other UA-lowering therapies cannot be ruled out entirely, even though the two groups did not differ in the proportion of patients prescribed such agents. Accordingly, additional prospective, multicentre, large-scale studies that set dotinurad head-to-head against alternative UA-lowering compounds are called for to substantiate the findings reported here.

Conclusion

In summary, dotinurad, an agent that selectively blocks urate reabsorption, can lower UA levels and may help slow the worsening of kidney function in individuals with both hyperuricemia and advanced CKD, while exhibiting an acceptable safety profile with no serious untoward events.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: The present study received approval from the Saitama Medical Center Institutional Review Board, Jichi Medical University (no. S18-114). It was conducted in accordance with the ethical principles of the Declaration of Helsinki.

References

1. Jalal DI, Chonchol M, Chen W, Targher G. Uric acid as a target of therapy in CKD. Am J Kidney Dis. 2013;61(1):134-46.
2. Mallat SG, Al Kattar S, Tanios BY, Jurjus A. Hyperuricemia, hypertension, and chronic kidney disease: an emerging association. Curr Hypertens Rep. 2016;18(10):74.
3. Abbasi MT, Asghar MR, Bashir K, Hashmi MN. Hyperuricemia in renal patients: treat or not to treat. Arch Clin Nephrol. 2021;7(1):50-6.
4. Chou HW, Chiu HT, Tsai CW, Lee MH, Yang LY, Kuo CC, et al. Comparative effectiveness of allopurinol, febuxostat and benzbromarone on renal function in chronic kidney disease patients with hyperuricemia: a 13-year inception cohort study. Nephrol Dial Transplant. 2018;33(9):1620-7.
5. Fujimori S, Ooyama K, Ooyama H, Moromizato H. Efficacy of benzbromarone in hyperuricemic patients associated with chronic kidney disease. Nucleosides Nucleotides Nucleic Acids. 2011;30(12):1035-8.
6. Yu H, Liu X, Song Y, Li X, Ma L, Lu J, et al. Safety and efficacy of benzbromarone and febuxostat in hyperuricemia patients with chronic kidney disease: a prospective pilot study. Clin Exp Nephrol. 2018;22(6):1324-30.

7. Jeyaruban A, Hoy W, Cameron A, Lynch B, Wang Z, Shaw J, et al. Hyperuricaemia, gout and allopurinol in the CKD Queensland registry. J Nephrol. 2021;34(3):753-62.
8. Hosoya T, Sano T, Sasaki T, Fushimi M, Ohashi T. Clinical efficacy and safety of dotinurad, a novel selective urate reabsorption inhibitor, in Japanese hyperuricemic patients with or without gout: an exploratory, randomized, multicenter, double-blind, placebo-controlled, parallel-group early phase 2 study. Clin Exp Nephrol. 2020;24(Suppl 1):44-52.
9. Hosoya T, Sano T, Sasaki T, Fushimi M, Ohashi T. Dotinurad versus benzbromarone in Japanese hyperuricemic patients with or without gout: a randomized, double-blind, parallel-group, phase 3 study. Clin Exp Nephrol. 2020;24(Suppl 1):62-70.
10. Bos MJ, Koudstaal PJ, Hofman A, Witteman JCM, Breteler MMB. Uric acid is a risk factor for myocardial infarction and stroke: the Rotterdam study. Stroke. 2006;37(6):1503-7.
11. Uchida S, Chang WX, Ota T, Tamura Y, Shiraishi T, Kumagai T, et al. Targeting uric acid and the inhibition of progression to end-stage renal disease—a propensity score analysis. PLoS One. 2015;10(12):e0145506.
12. Remedios C, Shah M, Bhasker AG, Lakdawala M. Hyperuricemia: a reality in the Indian obese. Obes Surg. 2012;22(6):945-8.
13. Trifirò G, Morabito P, Cavagna L, Ferrajolo C, Pecchioli S, Simonetti M, et al. Epidemiology of gout and hyperuricaemia in Italy during the years 2005-2009: a nationwide population-based study. Ann Rheum Dis. 2013;72(5):694-700.
14. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53(6):982-92.
15. Vrbin CM. Parametric or nonparametric statistical tests: considerations when choosing the most appropriate option for your data. Cytopathology. 2022;33(6):663-7.
16. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, et al. A role for uric acid in the progression of renal disease. J Am Soc Nephrol. 2002;13(12):2888-97.
17. Shibagaki Y, Ohno I, Hosoya T, Kimura K. Safety, efficacy and renal effect of febuxostat in patients with moderate-to-severe kidney dysfunction. Hypertens Res. 2014;37(10):919-25.
18. Kim YG, Byun J, Yoon D, Shin D, Cho Y, Kim JH, et al. Renal protective effect of DPP-4 inhibitors in type 2 diabetes mellitus patients: a cohort study. J Diabetes Res. 2016;2016:1423191.
19. Pang L, Xue X, He Y, Wang J, Zhang Y, Li C, et al. The effect of decrease in serum urate for the risk of gout flares during urate-lowering therapy initiation among Chinese male gout patients: a prospective cohort study. J Inflamm Res. 2023;16:3937-47.
20. Ueno S, Hamada T, Taniguchi S, Ohtani N, Miyazaki S, Mizuta E, et al. Effect of antihypertensive drugs on uric acid metabolism in patients with hypertension: cross-sectional cohort study. Drug Res (Stuttg). 2016;66(12):628-32.
21. Juraschek SP, Appel LJ, Miller ER III. Metoprolol increases uric acid and risk of gout in African Americans with chronic kidney disease attributed to hypertension. Am J Hypertens. 2017;30(9):871-5.
22. Medical Research Council Working Party on Mild to Moderate Hypertension. Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension. Lancet. 1981;2(8246):539-43.
23. Wu J, Zhang YP, Qu Y, Jie LG, Deng JX, Yu QH. Efficacy of uric acid-lowering therapy on hypercholesterolemia and hypertriglyceridemia in gouty patients. Int J Rheum Dis. 2019;22(8):1445-51.
24. Heikal MM, Shaaban AA, Elkashef WF, Ibrahim TM. Effect of febuxostat on biochemical parameters of hyperlipidemia induced by a high-fat diet in rabbits. Can J Physiol Pharmacol. 2019;97(7):611-22.
25. Marinchev L, Kunev K. The effect of benzbromarone on hyperlipidemia in gout. Vutr Boles. 1990;29(5):99-102.