



Comparative Efficacy of Lobeglitazone Versus Pioglitazone on Albuminuria in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: The aim of this analysis was to evaluate the efficacy of lobeglitazone on albuminuria at 24 weeks of follow-up in patients with type 2 diabetes mellitus (T2DM) compared with pioglitazone using data from a randomized, double-blinded phase III trial.

Methods: In the phase III trial, patients who were inadequately controlled with metformin

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received 0.5 mg of lobeglitazone or 15 mg of pioglitazone for 24 weeks. Post hoc, exploratory analysis was used to investigate mean changes from baseline in the urine albumin–creatinine ratio (UACR) between the lobeglitazone ($N = 104$) and pioglitazone ($N = 101$) treatment groups.

Results: After 24 weeks of treatment, UACR was slightly decreased in the lobeglitazone group (-4.3 mg/g creatinine [Cr]) compared to baseline and slightly increased in the pioglitazone group (5.2 mg/g Cr), with no change in the estimated glomerular filtration rate in either group; this difference was not statistically significant ($P = 0.476$). The incidence of new-onset microalbuminuria (2.4%) and the progression of albuminuria by >1 stage (2.9%) in the lobeglitazone group were lower than the respective values in the pioglitazone group (6.8 and 6.1%, respectively). Of the patients in the lobeglitazone group, 50% exhibited regression to normoalbuminuria, compared to 39.3% of the patients in the pioglitazone. In subjects in the lobeglitazone group with micro- and macroalbuminuria, UACR tended to be more decreased and HbA1c was more reduced compared to those with normoalbuminuria ($P = 0.014$).

Conclusion: Lobeglitazone had a tendency to improve albuminuria in patients with T2DM and had comparable effects on albuminuria as pioglitazone which has demonstrated beneficial effects.

Trial Registration: ClinicalTrials.gov identifier, NCT01106131.

Keywords: Albuminuria; Diabetes mellitus, type 2; Pioglitazone; Thiazolidinediones

Key Summary Points

Why carry out this study?

Thiazolidinediones (TZDs) decrease urinary albumin excretion and improve albuminuria values in patients with type 2 diabetes mellitus (T2DM).

Lobeglitazone, a novel TZD developed in Korea, has been used in patients with T2DM.

To date, no study has assessed the efficacy of lobeglitazone on albuminuria

What was learned from the study?

This is the first study to evaluate the efficacy of lobeglitazone on albuminuria for 24 weeks in patients with T2DM, in comparison to pioglitazone.

Lobeglitazone was shown to have a tendency to improve albuminuria in patients with T2DM and had comparable effects on albuminuria as pioglitazone which has demonstrated beneficial effects.

decrease in kidney function in persons with diabetes, is an important risk factor for various cardiovascular diseases and is the most common cause of end-stage renal disease worldwide [4–8]. Many drugs are excreted through the kidneys, and when kidney function is poor, the metabolites of these drugs accumulate in the body. In patients with T2DM, reduced renal function can result in limitations in the use of anti-diabetic medications and increased risk of complications [9, 10]. The diagnosis of DKD is based on the presence of albuminuria and/or a reduced estimated glomerular filtration rate (eGFR) without other primary causes of kidney damage [5]. In particular, albuminuria, a marker for DKD, is an independent predictor of cardiovascular diseases and its appropriate management is of great importance [11–13].

Thiazolidinediones (TZDs) are a class of oral anti-diabetic drugs that decrease insulin resistance through their activation of peroxisome proliferator-activated receptor gamma (PPAR γ) [14]. Although fluid retention, weight gain, and an elevated risk for bone fractures are known side effects of TZDs, these drugs also have many beneficial effects on cardiovascular disease, nonalcoholic fatty liver disease (NAFLD), and inflammation [15, 16]. Recently, anti-diabetic drugs have attracted increased interest for their renoprotective effects, such as improvement of albuminuria, in addition to their glucose-lowering effects. TZDs have neutral effects on DKD progression and do not require dose adjustments based on renal function [9, 16]. Several studies have shown that TZDs improve albuminuria values in patients with T2DM [17–20].

Lobeglitazone is a novel TZD developed in Korea that has been used in several countries to treat patients with T2DM [21]. However, to date, the efficacy of lobeglitazone for reducing albuminuria has not been studied. The aim of this analysis was to evaluate the efficacy of lobeglitazone versus pioglitazone on albuminuria in patients with T2DM in a 24-week clinical trial.

DIGITAL FEATURES

This article is published with digital features, including a summary slide and video abstract, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13073183>.

INTRODUCTION

Good renal function is important in patients with type 2 diabetes mellitus (T2DM) [1–3]. Diabetic kidney disease (DKD), defined as a

METHODS

Study Design

This was post hoc analysis of the 24-week, multicenter, randomized, double-blind, parallel group, active-controlled phase III clinical trial and had the aim to investigate the effect of lobeglitazone on albuminuria (Clinical Trials registration number: NCT01106131). The original study was conducted from June 2010 to April 2012 in South Korea [22] and included 253 participants who were randomized (1:1 ratio) into two treatment groups, one receiving lobeglitazone 0.5 mg once daily (128 patients) and one receiving pioglitazone 15 mg once daily (125 patients) as an add-on therapy to metformin for 24 weeks. The results of the original study showed that the glucose-lowering efficacy and safety of lobeglitazone were not inferior to those of pioglitazone. Ultimately, only 205 participants (104 in the lobeglitazone group and 101 in the pioglitazone group) were included in the present analysis because the urine albumin–creatinine ratio (UACR) values were missing for 48 participants. The primary outcome of this analysis was change in UACR between the baseline and week 24; the secondary outcomes were change in new-onset microalbuminuria, progression or regression of albuminuria, regression to normoalbuminuria, and glycated hemoglobin (HbA1c) at week 24.

The study was approved by the Institutional Review Board of CHA Bundang Medical Center (2019-10-064) and complied with the Declaration of Helsinki of 1964 and its later amendments and with Korea Good Clinical Practice guidelines. Written informed consent was obtained from all individual participants in the original study [22].

Study Patients

Patients aged 18–80 years with T2DM who had HbA1c 7.0–10.0% despite a stable regimen of metformin (\geq metformin 1000 mg/day) were enrolled. Exclusion criteria for this analysis included: type 1 diabetes or a secondary form of diabetes; the use of insulin or TZDs within

60 days prior to consent; a known hypersensitivity to or serious adverse events (AEs) associated with TZD; the presence of proliferative diabetic retinopathy; active infection and trauma; congestive heart failure (New York Heart Association Class III or IV); ischemic stroke or cerebral hemorrhage within the past 6 months.

Measurements and Definitions

Subjects wore minimal clothing and no shoes during the weight and height measurements. Blood pressure was measured by trained nurses using an automatic blood pressure monitor after the patients had been seated for 10 min. Plasma glucose, HbA1c, insulin, and the lipid profile were measured after an overnight fast. UACR was measured in a single random urine sample. Albuminuria was based on the UACR measurement and defined as microalbuminuria (30–300 mg/g creatinine [Cr]) or macroalbuminuria (> 300 mg/g Cr).

Statistical Analysis

Data for categorical factors are reported as percentages, and continuous variables are presented as the mean \pm standard deviation. The progression of albuminuria by > 1 stage was defined as the albuminuria category changing from normoalbuminuria to either microalbuminuria or macroalbuminuria, or from microalbuminuria to macroalbuminuria. The regression of albuminuria by > 1 stage was defined as the change in albuminuria category from macroalbuminuria or microalbuminuria to normoalbuminuria, or from macroalbuminuria to microalbuminuria. All statistical analyses were performed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria; <http://www.rproject.org>).

RESULTS

The baseline characteristics of the participants are shown in Table 1. Demographic, anthropometric, and clinical characteristics were

Table 1 Baseline characteristics of the study participants

Baseline patient characteristics	Lobeglitazone group (<i>N</i> = 104)			Pioglitazone group (<i>N</i> = 101)			<i>P</i> value**
	Nor moalbu minuria	Micro-/macroal buminuria	<i>P</i> value*	Nor moalbu minuria	Micro-/macroal buminuria	<i>P</i> value*	
Age (years)	55.9 ± 10.8	57.0 ± 8.9	0.704	56.3 ± 12.8	59.0 ± 8.7	0.302	0.274
Male	35 (41.7)	8 (40.0)	1.000	31 (42.5)	19 (67.9)	0.039	0.302
Height (cm)	162.3 ± 7.6	160.3 ± 8.6	0.313	163.3 ± 10.7	160.3 ± 7.6	0.181	0.700
Weight (kg)	72.8 ± 13.7	65.2 ± 10.0	0.028	67.6 ± 16.1	64.4 ± 9.0	0.342	0.374
Body mass index (kg/m ²)	27.6 ± 4.8	25.3 ± 3.0	0.052	25.0 ± 3.7	25.0 ± 2.8	0.957	0.112
Systolic blood pressure (mmHg)	130.0 ± 12.9	124.9 ± 13.7	0.132	128.3 ± 13.1	122.4 ± 15.7	0.064	0.363
Diastolic blood pressure (mmHg)	85.9 ± 8.7	80.4 ± 9.9	0.018	80.5 ± 10.0	77.1 ± 9.4	0.129	0.014
Diabetes duration (year)	6.6 ± 4.7	7.2 ± 5.2	0.599	7.3 ± 5.5	8.1 ± 6.1	0.523	0.328
Fasting plasma glucose (mg/dL)	163.9 ± 43.8	147.2 ± 37.2	0.128	167.2 ± 45.4	148.8 ± 30.2	0.055	0.514
HbA1c (%)	8.05 ± 0.54	7.81 ± 0.73	0.107	8.00 ± 0.67	7.89 ± 0.71	0.469	0.530
Total cholesterol (mg/dL)	165.6 ± 37.2	158.2 ± 34.5	0.428	174.3 ± 35.7	163.1 ± 35.7	0.166	0.197
Triglyceride (mg/dL)	152.1 ± 50.2	134.8 ± 74.7	0.224	199.5 ± 139.6	130.5 ± 63.1	0.017	0.333
HDL-cholesterol (mg/dL)	47.4 ± 9.0	49.8 ± 11.7	0.311	44.6 ± 11.2	48.9 ± 11.3	0.090	0.312
Creatinine (mg/dL)	0.74 ± 0.22	0.71 ± 0.20	0.485	0.80 ± 0.17	0.71 ± 0.16	0.021	0.375
eGFR (mL/min/1.73 m ²)	95.7 ± 16.1	98.6 ± 13.9	0.463	94.6 ± 17.6	96.7 ± 12.3	0.558	0.331
UACR (mg/g Cr)	8.0 ± 5.9	115.1 ± 129.2	0.001	8.7 ± 6.8	209.4 ± 542.3	0.041	0.209
Normoalbuminuria	84 (100.0)	0 (0.0)	< 0.001	73 (100.0)	0 (0.0)	< 0.001	0.341
Microalbuminuria	0 (0.0)	19 (95.0)		0 (0.0)	26 (92.9)		
Macroalbuminuria	0 (0.0)	1 (5.0)		0 (0.0)	2 (7.1)		

Data are expressed as the mean ± standard deviation (SD) or as a number with the percentage in parentheses
Cr Creatinine, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *HDL* high-density lipoprotein, *UACR* urine albumin-to-creatinine ratio

*Significant difference at *P* < 0.05 (normoalbuminuria vs. micro-/macroalbuminuria); **significant difference at *P* < 0.05 (lobeglitazone vs. pioglitazone)

Table 2 Changes in the efficacy parameters at end of the follow-up period (week 24)

Efficacy parameters	Change in lobeglitazone group at 24 weeks			Change in pioglitazone group at 24 weeks		
	Nor moalbu minuria	Micro-/macroal buminuria	<i>P</i> value*	Nor moalbu minuria	Micro-/macroal buminuria	<i>P</i> value*
HbA1c (%)	− 0.71 ± 0.61**	− 1.11 ± 0.54**	0.008	− 0.79 ± 0.60**	− 0.74 ± 0.84**	0.778
Creatinine (mg/dL)	0.01 ± 0.09	− 0.01 ± 0.11	0.418	0.02 ± 0.07	0.00 ± 0.09	0.447
eGFR (mL/min/1.73 m ²)	− 1.4 ± 6.9	0.9 ± 10.4	0.358	− 1.5 ± 5.6	0.2 ± 8.6	0.358
UACR (mg/g Cr)	0.7 ± 9.4	− 25.4 ± 174.3	0.511	1.3 ± 11.9	15.3 ± 209.9	0.726
Weight (kg)	1.1 ± 1.7**	0.5 ± 3.0	0.399	0.8 ± 2.2**	1.3 ± 2.6**	0.320
Systolic blood pressure (mmHg)	1.3 ± 13.8	− 2.4 ± 14.8	0.322	2.3 ± 13.2	− 0.6 ± 13.1	0.328
Diastolic blood pressure (mmHg)	− 1.7 ± 9.0	− 3.8 ± 12.8	0.502	1.1 ± 9.2	− 2.3 ± 10.9	0.153
Total cholesterol (mg/dL)	9.4 ± 24.4**	4.8 ± 23.4	0.443	10.5 ± 22.7**	12.4 ± 28.1**	0.754
Triglyceride (mg/dL)	− 14.9 ± 62.2**	− 10.6 ± 57.9	0.771	− 19.0 ± 60.6**	− 10.3 ± 106.5	0.686
HDL-cholesterol (mg/dL)	4.9 ± 7.9**	3.3 ± 7.8	0.404	7.3 ± 9.4**	5.6 ± 10.2**	0.448

Data are expressed as the mean ± SD

*Significant difference at $P < 0.05$ (normoalbuminuria vs. micro-/macroalbuminuria); **significant difference at $P < 0.05$ vs. baseline

comparable between the lobeglitazone and pioglitazone groups. There were also no significant between-group differences in serum Cr, eGFR, and UACR values nor in medication history, including use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker that was not reported previously (Table 1; Electronic Supplementary Material [ESM] Table S1).

The reduction in HbA1c levels between baseline and week 24 of treatment was statistically significant in both groups (Table 2). Serum Cr and eGFR were not altered at 24 weeks compared with baseline. Baseline UACR did not differ between the two groups (lobeglitazone group 25.1 mg/g Cr; pioglitazone group 66.7 mg/g Cr). At 24 weeks, the UACR had

decreased in the lobeglitazone group relative to baseline (− 4.3 mg/g Cr) and increased in the pioglitazone group (5.2 mg/g Cr), although the difference in either group was not statistically significant ($P = 0.476$) (Fig. 1). These trends appeared more apparent in patients with micro- and macroalbuminuria than in those with normoalbuminuria (lobeglitazone group − 25.4 mg/g Cr; pioglitazone group 15.3 mg/g Cr), although the difference was not statistically significant ($P = 0.467$).

The proportion of patients with normoalbuminuria did not differ between the two groups at baseline (81.2 vs. 73.6%, lobeglitazone vs. pioglitazone group) (Table 3). At 24 weeks, the incidence of new-onset microalbuminuria (2.4% [2/84] vs. 6.8% (5/73), lobeglitazone vs.

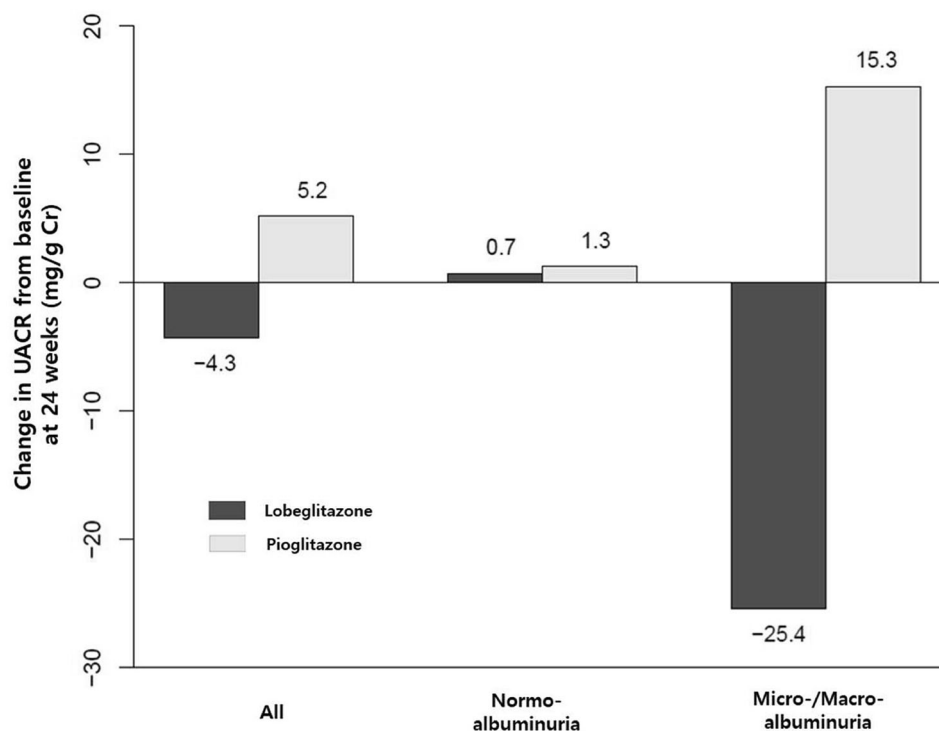


Fig. 1 Mean changes from baseline in the urine albumin-creatinine ratio (*UACR*) at end of the follow-up period (week 24). *Cr* Creatinine

Table 3 Transitions in albuminuria categories from baseline to the end of the follow-up period (week 24)

Transition from:	Lobeglitazone group				Pioglitazone group			
	Transition to:				Transition to:			
	Normoal- buminuria	Microal- buminuria	Macroal- buminuria	Total	Normoal- buminuria	Microal- buminuria	Macroal- buminuria	Total
Normoalbuminuria	82	2	0	84	68	5	0	73
Microalbuminuria	10	8	1	19	11	14	1	26
Macroalbuminuria	0	1	0	1	0	0	2	2
Total	92	11	1	104	79	19	3	101

pioglitazone group) and the progression of albuminuria by > 1 stage in the lobeglitazone group (2.9% [3/103] vs. 6.1% [6/99], lobeglitazone vs. pioglitazone group) was lower in the lobeglitazone than in the pioglitazone group. However, 50.0% (10/20) of the patients in the lobeglitazone group had regressed to normoalbuminuria compared to 39.3% (11/28) in the pioglitazone group.

A 73% reduction of risk for new-onset microalbuminuria and a 52% reduction of risk for the progression of albuminuria by > 1 stage was observed in the lobeglitazone group after adjustment for age, sex, body mass index, systolic blood pressure, and HbA1c (ESM Table S2); however, these reductions were not significantly different from those observed in the pioglitazone group. In addition, compared to

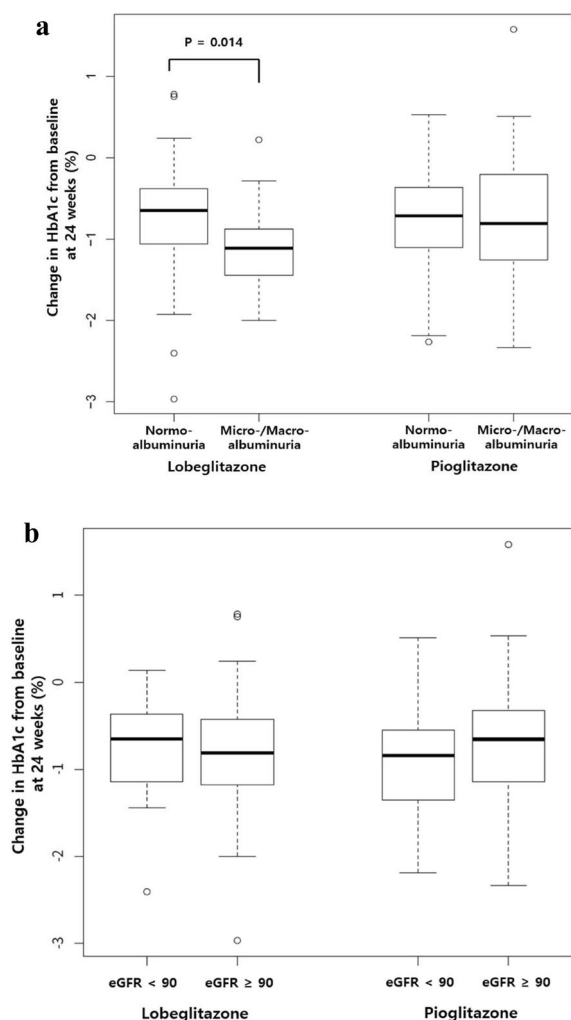


Fig. 2 Boxplot of mean changes in glycated hemoglobin (*HbA1c*) at end of the follow-up period (week 24) according to albuminuria categories (a) and estimated glomerular filtration rate (eGFR) (b)

pioglitazone group, more patients in the lobeglitazone group showed an improvement in albuminuria, as estimated by the regression of albuminuria by > 1 stage (odds ratio [OR] 1.56, 95% confidence interval [CI] 0.43–5.79) and regression to normoalbuminuria (OR 1.24, 95% CI 0.34–4.51).

In the lobeglitazone group, patients with micro- and macroalbuminuria showed a greater reduction in HbA1c than did patients with normoalbuminuria ($P = 0.014$); however, no similar difference was observed in the pioglitazone group (Fig. 2a). In addition, there was no

difference in the level of HbA1c reduction according to albuminuria categories in patients with $eGFR < 90$ mL/min/1.73 m² and those with $eGFR \geq 90$ mL/min/1.73 m² ($P = 0.697$) (Fig. 2b). The association between UACR and change of HbA1c was not statistically meaningful in either treatment group (data not shown).

DISCUSSION

The results of our study show that in patients with T2DM, lobeglitazone (0.5 mg/day) tended to improve albuminuria and was not inferior to pioglitazone (15 mg/day) in this respect. During the study period, the UACR decreased slightly in the lobeglitazone group and increased in the pioglitazone group, with no change in the eGFR in either group. Compared to the pioglitazone group, the progression of albuminuria in the lobeglitazone group tended to be low and the regression tended to be high. None of these results were statistically significant, but they suggest that lobeglitazone has similar effects on albuminuria as pioglitazone, with demonstrated beneficial effects. To the best of our knowledge, this is the first study to evaluate the efficacy of treatment with lobeglitazone versus pioglitazone on albuminuria for 24 weeks in patients with T2DM.

TZDs are PPAR γ agonists and are important anti-diabetic drugs that improve insulin resistance [14]. They have beneficial effects on cardiovascular disease, NAFLD, and inflammation, but are associated with side effects of fluid retention, weight gain, and an elevated risk of bone fracture [14–16]. Renal outcomes in patients with T2DM treated with TZDs have recently been gaining interest, with several studies showing that TZDs have protective effects on renal function [17–20]. A meta-analysis of 15 studies involving 2860 patients with T2DM found that treatment with TZDs significantly decreased urinary albumin and protein excretion [23]. In studies with pioglitazone, the weighted mean difference of proportional change between the pioglitazone and control groups was -16.2% (95% CI -20.8 to -11.6) of UACR [23]. In the present study, treatment

with lobeglitazone decreased the UACR, but treatment with pioglitazone had the opposite effect. In addition, new-onset microalbuminuria and the progression of albuminuria by > 1 stage was lower in the lobeglitazone group than in the pioglitazone group, while the regression of albuminuria by > 1 stage and regression to normoalbuminuria was higher in the lobeglitazone, although these differences were not statistically significant. No differences were observed between the two groups regarding the incidence of AEs, severe AEs, or drug-related AEs in the original study [22] and this study (data not shown). While these results do not allow the conclusion to be drawn that lobeglitazone is superior to pioglitazone, they do demonstrate that lobeglitazone tended to improve albuminuria in patients with T2DM with negligible differences compared to pioglitazone.

Lobeglitazone is a new PPAR γ agonist and has been used in patients with T2DM. In one study, lobeglitazone administered 0.5 mg per day achieved a HbA1c reduction of approximately 0.6% versus placebo [21] and approximately 0.88% in patients taking triple therapy [24]. It has been shown that the efficacy of lobeglitazone (0.5 mg/day) is not inferior to pioglitazone (15 mg/day) as an add-on to metformin in terms of reducing the HbA1c level after 24 weeks (-0.74 vs. -0.74% , lobeglitazone vs. pioglitazone) [22], with both drugs exhibiting similar effects on weight, edema, and lipid profiles [21, 22]. Like pioglitazone, treatment with lobeglitazone resulted in significantly improved hepatic steatosis in patients with T2DM with NAFLD [25, 26] and exhibited anti-atherosclerotic properties [27]. However, in terms of bone metabolism, lobeglitazone has been reported to have no detrimental effect on bone mineral density while pioglitazone exhibits negative effects [28, 29]. In an *in vivo* study of db/db (diabetic) mice, lobeglitazone showed beneficial effects on beta cell survival and function and was comparable to other TZDs [30]. Several studies have evaluated the efficacy of pioglitazone on the UACR. In one study that compared pioglitazone and metformin for 52 weeks, the UACR was reduced by 19% following pioglitazone treatment in 597 drug-naive patients with T2DM [19]. The authors of

another study reported that the UACR was reduced by 10% in the metformin + pioglitazone (15 mg/day) treatment group compared to an increase of 6% in the metformin + gliclazide (80 mg/day) treatment group [31]. In the present study, the UACR was reduced by 15.6% in the lobeglitazone group compared to an increase of 8.4% in the pioglitazone group over the course of 24 weeks. One possible explanation for the increase of the UACR in the pioglitazone group may be the relatively short duration of the study and the low number of participants. In addition, although the renal benefit of pioglitazone was generally positive when administered at a dose of 30–45 mg, the dose of pioglitazone used in the present study was 15 mg/day because this was the highest dose covered by the Korean national health insurance system during the study period. Thus, the results of this study alone cannot determine whether pioglitazone has negative effects on UACR. More importantly, these results do suggest that lobeglitazone has beneficial effects on albuminuria and is that it is comparable to pioglitazone in this respect. Further studies comparing higher doses of lobeglitazone and pioglitazone are needed because lobeglitazone has been shown to be well tolerated at doses of up to 4 mg for 7 days in a short-term study conducted in healthy volunteers [32].

TZDs reduce renal damage by improving hyperglycemia as well as modifying several mechanisms that are independent of hyperglycemia [33–39]. The anti-inflammatory and anti-oxidative effects of TZDs are well known and could be a possible mechanism of renal protection [33–35]. In addition, TZDs have been shown to downregulate the activity of the renin–angiotensin system and found to improve renal microcirculation and endothelial function [33, 36, 37]. Several studies have demonstrated that TZDs can protect against renal injury through a direct action on PPAR γ receptors at the level of the renal glomerular and tubular segments [33, 38, 39]. Lobeglitazone shares many properties with other TZDs, which may explain its renal protective effect. In animal studies, lobeglitazone has shown a renoprotective effect on renal fibrosis through inhibition of the transforming growth factor β /

Smad3 pathway [40]. In the present study, there was a greater decrease in UACR and a greater reduction in HbA1c in subjects in the lobeglitazone group who had micro- and macroalbuminuria than in those with normoalbuminuria. These results may support the theory that lobeglitazone is able to be safely used by patients with reduced renal function even though its renoprotective mechanism has yet to be identified.

Several limitations should be considered in the interpretation of our findings. First, the sample size was calculated based on the primary outcome of the original study. Therefore, it may not have been appropriate to evaluate the effect on albuminuria. Second, this study was not designed primarily to investigate the renoprotective effect of lobeglitazone. As a result, many renal parameters that would be helpful to test the efficacy of the drug were not included in the study. Third, a single random urine sample was used to calculate the UACR without adjusting for day-to-day biological variability. Finally, the relatively short study duration did not provide enough time to evaluate the long-term renal outcomes of lobeglitazone.

CONCLUSION

The results of this post hoc analysis of the 24-week, randomized, double-blind study showed that lobeglitazone tended to improve albuminuria values in patients with T2DM. The UACR was slightly decreased in the lobeglitazone group with no change in eGFR. In addition, lobeglitazone exhibited similar effects on albuminuria compared with pioglitazone with its proven beneficial effects. Large-scale, longer-term mechanistic studies are warranted to confirm these findings.

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Disclosures. Kyung-Soo Kim, Sangmo Hong, Hong-Yup Ahn, and Cheol-Young Park have nothing to disclose.

Compliance with Ethics Guidelines. The study was approved by the Institutional Review Board of CHA Bundang Medical Center (2019-10-064) and complied with the Declaration of Helsinki of 1964 and its later amendments and with Korea Good Clinical Practice guidelines. Written informed consent was obtained from all individual participants in the original study [22]

Data Availability. The ChongKunDang Pharmaceutical Corp. provides access to all individual participant data collected during the trial, after anonymization. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report and blank or annotated case report forms, will be provided in a secure data-sharing environment.

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