BMJ Open

Lobeglitazone and the risk of renal progression in Korean patients with type 2 diabetes mellitus: a retrospective cohort study

So-hyeon Hong ,[1] Hyejin Lee,[1] So-young Lee ,[2] Yeon-Ah Sung,[1] Young Sun Hong,[1] Do Kyeong Song,[1] Hyein Jung,[1] Min-ho Kim[2]

To cite: Hong S, Lee H, Lee S, *et al*. Lobeglitazone and the risk of renal progression in Korean patients with type 2 diabetes mellitus: a retrospective cohort study. *BMJ Open* 2026;**16**:e107482. doi:10.1136/bmjopen-2025-107482

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2025-107482).

Received 05 July 2025
Accepted 26 February 2026

Check for updates

© Author(s) (or their employer(s)) 2026. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ Group.

[1]Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, South Korea
[2]Ewha Medical Data Organization, Ewha Womans University Medical Center, Seoul, South Korea

Correspondence to
Dr So-hyeon Hong;
kicara@gmail.com

ABSTRACT

Objective To evaluate the effect of lobeglitazone on renal disease progression in patients with type 2 diabetes mellitus using longitudinal real-world data.

Design Retrospective cohort study.

Setting Hospital-based Common Data Model database.

Participants A total of 14 712 adults with type 2 diabetes mellitus who visited the Diabetes Center of Ewha Womans University Mokdong Hospital between 2013 and 2019 were identified. A 1:2 propensity score matching was performed to compare patients treated with lobeglitazone plus metformin with those receiving metformin monotherapy, sulfonylurea plus metformin, or a dipeptidyl peptidase-4 (DPP4) inhibitor plus metformin.

Interventions Treatment with lobeglitazone plus metformin compared with metformin monotherapy, sulfonylurea plus metformin or DPP4 inhibitor plus metformin.

Primary outcome measures Renal progression, defined as initiation of renal replacement therapy, a sustained ≥30% decline in estimated glomerular filtration rate (eGFR) from baseline, or doubling of serum creatinine with a concurrent eGFR ≤45 mL/min/1.73 m².

Results The HR of renal progression was 0.84 (95% CI 0.58 to 1.21) in the lobeglitazone plus metformin compared with metformin monotherapy, 1.00 (95% CI 0.79 to 1.27) compared with sulfonylurea plus metformin group, 1.10 (95% CI 0.84 to 1.44) compared with DPP4 inhibitor plus metformin group after adjusting for multiple variables. Subgroup analyses demonstrated significant interactions by sex in the comparison with metformin monotherapy (P for interaction=0.0179) and by glycaemic control in the comparisons with sulfonylurea plus metformin (P for interaction=0.0161) and DPP4 inhibitor plus metformin (P for interaction=0.0006), suggesting potential heterogeneity in treatment effects.

Conclusions Lobeglitazone showed renal outcomes comparable to those of other antidiabetic medications, with a possible heterogeneity in treatment effects according to sex and glycaemic control.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A longitudinal hospital-based Common Data Model database cohort of patients with type 2 diabetes mellitus in Korea with detailed electronic medical records providing comprehensive data on demographics, comorbidities, medications and laboratory results.
⇒ Propensity score matching minimised confounding in comparisons between treatment groups.
⇒ Lack of information on diabetes duration and lifestyle factors (diet, physical activity) limited adjustment for potential confounders.
⇒ Albuminuria data were missing in approximately one-third of patients, restricting inclusion in the primary outcome definition.

INTRODUCTION

Type 2 diabetes mellitus is one of the leading causes of chronic kidney disease (CKD) and end-stage renal disease (ESRD).[1] CKD develops in approximately 20%–40% of individuals with diabetes mellitus and progresses to ESRD, requiring dialysis or kidney transplantation.[2] Furthermore, the presence of CKD in patients with diabetes mellitus is associated with an increased risk of cardiovascular disease and mortality compared with those without CKD.[2] Therefore, it is important not only to achieve glycaemic control but also to consider antidiabetic medications with potential renoprotective effects to prevent CKD.

Thiazolidinediones (TZDs) are insulin sensitisers that act as peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists, a nuclear receptor involved in glucose and lipid metabolism.[3] They improve insulin sensitivity in the adipose tissue, muscle and liver, and suppress hepatic gluconeogenesis, leading to reduced blood glucose levels.[3 4] In addition to their metabolic effects, several studies have reported that TZDs have renoprotective effects. They found that the use of TZD reduced albuminuria and attenuated renal injury.[5 6] However, these findings have been inconsistent,[7] and most evidence is limited to rosiglitazone, which has been

BMJ Open: first published as 10.1136/bmjopen-2025-107482 on 19 March 2026. Downloaded from http://bmjopen.bmj.com/ on September 28, 2026 at Swets Subscription Service REF: 39804496 .
Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

withdrawn from clinical practice due to an increased risk of cardiovascular disease, or to pioglitazone.

Lobeglitazone is a TZD derivative that incorporates a pyrimidine substituent into the conventional TZD scaffold, resulting in a higher binding affinity for PPAR-γ.[8] It is currently prescribed in Korea as the second TZD following pioglitazone. Although several studies have demonstrated the renoprotective effects of lobeglitazone, epidemiological studies evaluating its effect on renal function remain limited.

Therefore, in this study, we investigated whether lobeglitazone is associated with a lower risk of renal progression in patients with type 2 diabetes mellitus. Using longitudinal real-world data from a tertiary care hospital, we compared the renal outcomes of patients treated with lobeglitazone with those receiving other antidiabetic medications, including metformin, sulfonylurea and dipeptidyl peptidase-4 (DPP4) inhibitors.

METHODS

Study design and population

This retrospective cohort study was conducted using the Common Data Model (CDM) database of Ewha Womans University Mokdong Hospital. The CDM was constructed from the hospital's electronic medical records (EMR), which include patient demographics, clinical measurements, laboratory results, medication records and diagnoses coded according to the International Classification of Diseases, 10th Revision (ICD-10). All data were anonymised and transformed into the Observational Medical Outcomes Partnership CDM version 5.0 using standardised analytical tools.[9]

We included patients with type 2 diabetes mellitus who visited the Diabetes Center of Ewha Womans University Mokdong Hospital between January 2014 and December 2019. Patients were excluded if they had a baseline estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, renal replacement therapy or a history of kidney transplantation. In addition, patients who had been prescribed pioglitazone, another TZD, were excluded. We next identified patients who had been prescribed metformin monotherapy or combination treatment with lobeglitazone plus metformin, sulfonylurea plus metformin, or a DPP4 inhibitor plus metformin for at least 3 months. To reduce potential confounding between the groups, 1:2 propensity score matching was performed separately for each comparison group. Matching was based on clinical variables including age, sex, body mass index (BMI), systolic and diastolic blood pressure, baseline eGFR, comorbidities and use of ACE inhibitors (ACEis) or angiotensin II receptor blockers (ARBs).

Measurements of variables and covariates

We collected patient information, including age, sex, BMI, systolic and diastolic blood pressure, use of antidiabetic medications, and ACEi and/or ARBs. In addition, we collected data on comorbidities including hypertension, hyperlipidaemia, cardiovascular disease, cerebrovascular disease and malignancy.

Patients underwent venous blood sampling after fasting for >8 hour. Haemoglobin A1C (HbA1C) levels were measured using high-performance liquid chromatography (HLC-723G7 and G8 instruments; Tosoh, Tokyo, Japan), and plasma creatinine, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride levels, and aspartate aminotransferase and alanine aminotransferase activities were measured using an enzymatic colourimetric procedure with an automated analyser (Hitachi 747 Automatic Chemistry Analyzer; Tokyo, Japan). The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration.[10] The urinary albumin-to-creatinine ratio (UACR) was assessed using a random spot urine sample and measured using radioimmunoassay (Immunotech; Prague, Czech Republic).

Hypertension was defined as having ICD-10 codes I10-I14, a prescription of antihypertensive medication for 30 days or more, or a measured blood pressure ≥140/90 mmHg. Hyperlipidaemia was defined as having ICD-10 code E78, a prescription of lipid-lowering agents for 30 days or more, or a total cholesterol level ≥240 mg/dL. Cardiovascular disease was defined using ICD-10 codes I20-25, cerebrovascular disease using ICD-10 codes I60–I69, and cancer using ICD-10 codes C00–C97.

Outcome

The primary outcome was renal progression. Renal progression was defined as the first occurrence of any of the following: ESRD requiring renal replacement therapy, a sustained decline in eGFR of ≥30% from baseline, or a persistent doubling of the serum creatinine level accompanied by an eGFR ≤45 mL/min/1.73 m^2.[11 12] Since UACR data were not available for a substantial proportion of the cohort, an additional analysis limited to patients with baseline UACR <30 mg/g creatinine was conducted to evaluate the development of albuminuria. The incidence of albuminuria was defined as the first occurrence of UACR ≥30 mg/g creatinine during follow-up.

Statistical analysis

The baseline characteristics of the study population are described using mean±SD for continuous variables and numbers (%) for categorical variables. Variable comparisons between groups were performed using Student's t-test for two-group comparisons and the χ^2 test for categorical variables.

A 1:2 propensity score matching was performed between the treatment groups using nearest-neighbour matching without replacement, with a calliper width set to 0.2 of the SD of the logit of the propensity score. Covariate balance before and after matching was assessed using standardised mean differences (SMD), and SMD <0.1 was considered adequate balance between groups.

BMJ Open: first published as 10.1136/bmjopen-2025-107482 on 19 March 2026. Downloaded from http://bmjopen.bmj.com/ on September 28, 2026 at Swets Subscription Service REF: 39804496 . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

The cumulative incidence of renal progression was assessed using Kaplan-Meier analysis with the log-rank test. Cox proportional hazards regression models were used to estimate the risk of renal progression by calculating the HRs and 95% CIs. Adjusted factors included age, sex, baseline eGFR and comorbidities such as hypertension, hyperlipidaemia, cardiovascular disease, cerebrovascular disease and cancer.

The proportional hazards assumption was assessed using Schoenfeld residuals. When the assumption was violated, a restricted mean survival time (RMST) analysis was additionally performed. All statistical analyses were performed using SAS V.9.4 (SAS Institute). Statistical significance was set at p<0.05.

RESULTS

Baseline characteristics

Of the 14712 patients, 5899 received lobeglitazone plus metformin for more than 3 months, 2027 received metformin monotherapy, 2622 received sulfonylurea plus metformin, and 1632 received DPP4 inhibitors plus metformin. After a 1:2 propensity score matching, 108 patients in the lobeglitazone plus metformin group were matched to 216 patients in the metformin monotherapy group, 186–372 patients in the sulfonylurea plus metformin group, and 154–308 patients in the DPP-4 inhibitor plus metformin group (online supplemental figure 1). All matched cohorts demonstrated a fair covariate balance, with SMDs of less than 0.1 across all variables (online supplemental table 1). HbA1c levels in the lobeglitazone plus metformin group were as follows when compared with each group: 7.3% vs 7.1% against metformin, 8.3% vs 8.0% against sulfonylurea plus metformin, 7.8% vs 7.9% against DPP4 inhibitor plus metformin.

Risk of renal progression of lobeglitazone compared with other antidiabetic medications

During a mean follow-up of 2.1±1.8 years, renal progression was observed in 141 of 324 patients (43.5%) in the lobeglitazone plus metformin versus metformin monotherapy group, 326 of 558 patients (58.4%) in the lobeglitazone plus metformin versus sulfonylurea plus metformin group, and 238 of 462 patients (51.5%) in the lobeglitazone plus metformin versus DPP4 inhibitor plus metformin group. Kaplan-Meier analysis revealed no statistically significant differences in renal progression between the groups (p=0.50, p=0.92 and p=0.30, respectively) (figure 1). The proportional hazards assumption was satisfied for the comparisons between the lobeglitazone plus metformin group and the metformin monotherapy group, and between the lobeglitazone plus metformin group and the DPP4 inhibitor plus metformin group. However, the assumption was violated for the comparison with the sulfonylurea plus metformin group; therefore, an additional RMST analysis was performed.

Patients with lobeglitazone plus metformin had a lower HR for renal progression compared with those treated with metformin monotherapy (HR, 0.89; 95% CI 0.62 to 1.27); however, it was not statistically significant. It remained unchanged after adjusting for age, sex, BMI, eGFR, the presence of hypertension and hyperlipidaemia, and the use of ACEi or ARBs (adjusted HR, 0.84; 95% CI 0.58 to 1.21). Similarly, no significant difference was observed in renal progression risk when comparing lobeglitazone plus metformin with sulfonylurea plus metformin (adjusted HR, 1.00; 95% CI 0.79 to 1.27) or with DPP-4 inhibitor plus metformin (adjusted HR, 1.10; 95% CI 0.84 to 1.44) (table 1).

Among patients with available UACR data, the risk of albuminuria showed similar trends to that observed for the primary outcome. The risk of incident albuminuria in the lobeglitazone plus metformin group was lower than that in the metformin monotherapy group, although the difference was not statistically significant (adjusted HR, 0.82; 95% CI 0.47 to 1.42), and was comparable to that in the sulfonylurea plus metformin group (adjusted HR, 1.05; 95% CI 0.76 to 1.47) and the DPP-4 inhibitor plus metformin group (adjusted HR, 1.08; 95% CI 0.76 to 1.56) (online supplemental table 2).

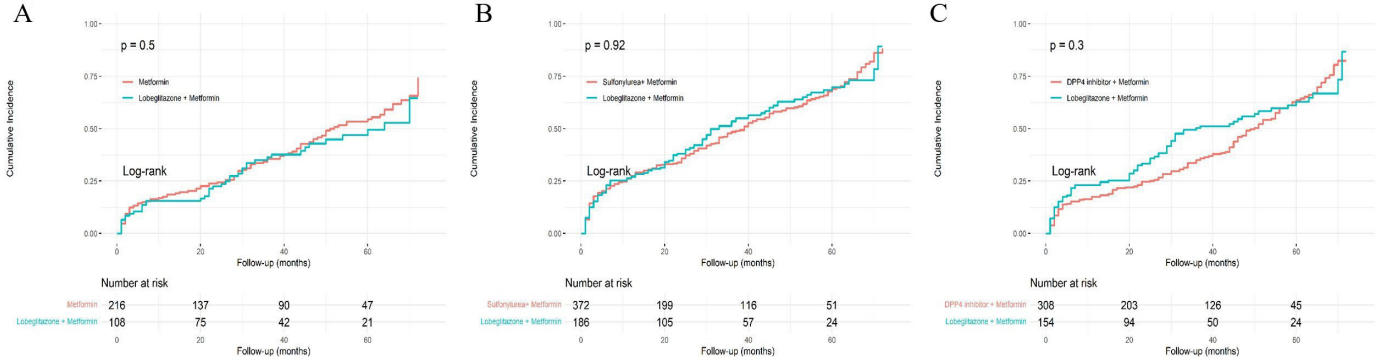


Figure 1 Cumulative incidence of renal progression in patients treated with lobeglitazone compared with other antidiabetic medications. (A) Lobeglitazone+metformin versus metformin. (B) Lobeglitazone+metformin versus sulfonylurea+metformin. (C) Lobeglitazone+metformin versus DPP4 inhibitor+metformin. DPP4, dipeptidyl peptidase-4.

BMJ Open: first published as 10.1136/bmjopen-2025-107482 on 19 March 2026. Downloaded from http://bmjopen.bmj.com/ on September 28, 2026 at Swets Subscription Service REF: 3980496 . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Table 1 HRs for renal progression in propensity-score-matched analysis

No	Lobeglitazone +metformin	Metformin	Lobeglitazone +metformin	Sulfonylurea +metformin	Lobeglitazone +metformin	DPP4 inhibitor +metformin
Number of patients	108	216	186	372	154	308
Mean (SD) follow-up, years	2.71 (1.91)	2.73 (2.04)	2.25 (1.86)	2.25 (1.95)	2.39 (1.92)	2.69 (1.90)
Events	42	99	108	218	81	157
Incidence rate/1000 person-years (95% CI)	143.59 (100.16 to 187.02)	168.01 (134.91 to 201.11)	257.50 (208.94 to 306.07)	260.87 (226.24 to 295.50)	220.31 (172.33 to 268.29)	189.44 (159.81 to 219.08)
HR (95% CI)						
Unadjusted	0.89 (0.62 to 1.27)		1.01 (0.80 to 1.27)		1.15 (0.88 to 1.50)	
Adjusted	0.84 (0.58 to 1.21)		1.00 (0.79 to 1.27)		1.10 (0.84 to 1.44)	

Adjusted for age, sex, BMI, eGFR, the presence of hypertension and hyperlipidaemia and the use of ACE inhibitors or ARBs.
ARB, angiotensin II receptor blocker; BMI, body mass index; DPP4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate.

Subgroup analysis

Subgroup analyses were performed stratified by age, sex, BMI, HbA1c, eGFR and the presence of hypertension and hyperlipidaemia. In the comparison between the lobeglitazone plus metformin group and the metformin monotherapy group, a significant interaction by sex was observed, suggesting potential heterogeneity in treatment effects (female subgroup: HR, 0.57; 95% CI 0.32 to 1.04; P for interaction=0.0179).

When compared with sulfonylurea plus metformin, a significant interaction by HbA1c level was observed (HbA1C<7%; HR, 0.71; 95% CI 0.44 to 1.16; P for interaction=0.0161). Compared with DPP4 inhibitor plus metformin, significant interactions were observed by BMI (BMI<25; HR, 0.96; 95% CI 0.67 to 1.37; P for interaction=0.0030) and HbA1C level (HbA1c<7%; HR, 0.85; 95% CI 0.51 to 1.40; P for interaction=0.0006), suggesting potential heterogeneity in treatment effects according to BMI and glycaemic control (table 2).

DISCUSSION

In this retrospective study, the risk of renal disease progression with lobeglitazone treatment was comparable to that observed with other antidiabetic medications in patients with type 2 diabetes mellitus. Subgroup analyses suggested possible heterogeneity in treatment effects, with potential renoprotective effects in female patients and those with HbA1C<7.0%. Considering the previously reported renoprotective properties of lobeglitazone in both animal and clinical studies, our findings suggest that these benefits may be more evident in specific subpopulations.

TZDs, synthetic agonists of the nuclear hormone receptor PPAR-γ, modulate the transcription of multiple genes involving glucose and lipid metabolism.[3] They improve insulin sensitivity by promoting glucose uptake and utilisation in adipose tissue and skeletal muscle and by suppressing hepatic gluconeogenesis.[3 4] Through these mechanisms, TZDs reduce blood glucose levels and have been widely used as therapeutic agents for type 2 diabetes mellitus. In addition to their metabolic effects, recent studies have reported that TZDs exert renoprotective effects. In patients with type 2 diabetes mellitus, treatment with pioglitazone for 6 months significantly reduced urinary albumin excretion and the number of podocytes in the urine, which are markers of glomerular podocyte injury.[5] A meta-analysis of 15 studies found that treatment with rosiglitazone and pioglitazone, two TZDs, significantly reduced urinary albumin excretion and the albumin–creatinine ratio in patients with type 2 diabetes, regardless of diabetic nephropathy status.[6] However, another study reported that patients receiving insulin-sensitisation therapy with metformin and TZDs exhibited a significant increase in the albumin–creatinine ratio compared with those receiving insulin-provision therapy with sulfonylurea and insulin.[7] Given conflicting evidence regarding the renoprotective effects of TZDs, studies investigating the renoprotective effects of lobeglitazone, a novel TZD, are limited.

Lobeglitazone is a member of the TZDs, incorporating a pyrimidine substituent into the conventional TZD scaffold, resulting in a high binding affinity for PPAR-γ.[8] It strongly inhibits Cdk5-mediated phosphorylation at Ser273, thereby providing therapeutic efficacy, even at low doses.[13] Kim *et al* evaluated the effect of lobeglitazone on albuminuria in patients with type 2 diabetes mellitus and found that, after 24 weeks of treatment, the incidence of microalbuminuria was lower in the lobeglitazone group than in the pioglitazone group.[14] Our analysis did not compare drugs within the TZDs; instead, we examined lobeglitazone in comparison with other antidiabetic agents, including metformin, sulfonylurea and DPP4 inhibitors. In addition, we applied propensity score matching to balance baseline characteristics across the treatment groups. In addition, the mean follow-up duration in our study exceeded 2 years, making a more robust assessment of long-term renal outcomes.

As a result, the lobeglitazone plus metformin group showed a lower risk of renal disease progression than

BMJ Open: first published as 10.1136/bmjopen-2025-107482 on 19 March 2026. Downloaded from http://bmjopen.bmj.com/ on September 28, 2026 at Swets Subscription Service REF: 3980496 . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Table 2 Subgroup analysis

	Lobeglitazone+metformin versus metformin		Lobeglitazone+metformin versus sulfonylurea+metformin		Lobeglitazone+metformin versus DPP4 inhibitor+metformin	
	HR (95% CI)	P for interaction	HR (95% CI)	P value	HR (95% CI)	P value
Age						
<50	1.27 (0.53 to 3.00)		1.42 (0.87 to 2.33)		1.90 (0.92 to 3.94)	
≥50	0.79 (0.53 to 1.18)	0.2536	0.91 (0.70 to 1.18)	0.1361	1.07 (0.80 to 1.44)	0.0360
Sex						
Male	1.25 (0.78 to 1.99)		1.11 (0.83 to 1.49)		1.24 (0.87 to 1.76)	
Female	0.57 (0.32 to 1.04)	0.0179	0.83 (0.56 to 1.22)	0.0771	1.01 (0.67 to 1.54)	0.0627
BMI						
<25	0.83 (0.51 to 1.36)		1.02 (0.75 to 1.39)		0.96 (0.67 to 1.37)	
≥25	0.94 (0.55 to 1.60)	0.0722	1.00 (0.71 to 1.42)	0.1281	1.56 (1.03 to 2.37)	0.0030
HbA1C						
<7.0%	0.93 (0.53 to 1.63)		0.71 (0.44 to 1.16)		0.85 (0.51 to 1.40)	
≥7.0%	0.89 (0.55 to 1.44)	0.1827	1.12 (0.86 to 1.46)	0.0161	1.34 (0.97 to 1.85)	0.0006
eGFR						
<60	0.90 (0.50 to 1.64)		0.95 (0.65 to 1.41)		1.10 (0.70 to 1.72)	
≥60	0.91 (0.58 to 1.45)	0.9191	1.02 (0.76 to 1.36)	0.5577	1.19 (0.85 to 1.68)	0.7809
Hypertension						
No	0.82 (0.45 to 1.50)		1.18 (0.84 to 1.66)		1.16 (0.78 to 1.73)	
Yes	0.90 (0.57 to 1.42)	0.5304	0.91 (0.66 to 1.25)	0.1986	1.16 (0.80 to 1.67)	0.4932
Hyperlipidaemia						
No	0.93 (0.58 to 1.47)		1.25 (0.92 to 1.69)		1.25 (0.89 to 1.75)	
Yes	0.86 (0.48 to 1.54)	0.8923	0.81 (0.56 to 1.17)	0.0649	1.06 (0.68 to 1.66)	0.2778

Adjusted for age, sex, BMI, eGFR, the presence of hypertension and hyperlipidemia and the use of ACE inhibitors or ARBs.
ARBs, angiotensin II receptor blockers; BMI, body mass index; DPP4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c.

the metformin monotherapy group, although the difference was not statistically significant. A similar trend was observed in the Kaplan-Meier analysis; the lobeglitazone plus metformin group exhibited a lower incidence of renal progression after 60 months than the sulfonylurea or DPP4 inhibitor plus metformin groups, with survival curves crossing beyond 60 months. These findings suggest the potential long-term benefit of lobeglitazone and highlight the need for further studies with larger cohorts to confirm its durability and renoprotective effects.

In the subgroup analysis, there was a statistically significant interaction by sex in the comparison between the lobeglitazone plus metformin group and metformin monotherapy, suggesting potential heterogeneity in treatment effects. A similar trend was observed in comparisons between the sulfonylurea and DPP4 inhibitor plus metformin groups, although statistical significance was not reached. The British Regional Heart Study and British Women's Heart Health Study reported that women experienced greater changes in visceral adiposity and insulin resistance than men during the transition to overt diabetes mellitus.[15 16] These metabolic differences may contribute not only to the development of diabetes mellitus but also to the progression of renal dysfunction. Another significant interaction was observed in the subgroup analysis based on HbA1c levels. The potential renoprotective effect of lobeglitazone plus metformin was more pronounced in patients with HbA1C<7.0% than in those with HbA1C≥7.0% in comparisons with both sulfonylurea and DPP4 inhibitor plus metformin groups, although the statistical significance was not reached. These findings should be interpreted cautiously, but it could be hypothesised that the renoprotective effect of lobeglitazone may be attenuated under chronic hyperglycaemic conditions by overwhelming its beneficial metabolic effects. Further studies are required to elucidate the underlying mechanisms.

The exact mechanism underlying the renoprotective effects of lobeglitazone is not fully understood. PPAR-γ is expressed in both the cortex and medulla of the kidneys and is known to be related to different metabolic processes.[17 18] Under hyperglycaemic status, SGLT-mediated glucose transport is impaired in the proximal convoluted tubule, leading to epithelial–mesenchymal transition (EMT) and subsequent renal fibrosis. PPAR-γ agonists have been reported to reverse this EMT process

BMJ Open: first published as 10.1136/bmjopen-2025-107482 on 19 March 2026. Downloaded from http://bmjopen.bmj.com/ on September 28, 2026 at Swets Subscription Service
REF: 3980449 .
Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

by reversing high-glucose-induced expression of phosphatidylinositol 3-kinase (PI3K)/Akt, glycogen synthase kinase- β, Snail 1 and beta-catenin.[19] In a mouse model of unilateral ureteral obstruction, which induces renal tubulointerstitial fibrosis and tubular atrophy, lobeglitazone suppressed extracellular matrix production by inhibiting the transforming growth factor-β (TGF-β)/Smad3 signalling pathway and downregulated the expression of fibrosis-related target genes, including plasminogen activator inhibitor-1, α-smooth muscle actin and type I collagen.[20]

The strength of this study is that it is the first retrospective longitudinal analysis to evaluate the impact of lobeglitazone on renal progression in patients with type 2 diabetes mellitus using different combinations of propensity score matching that accounted for various combinations of concomitant antidiabetic medications. The average follow-up duration exceeded 2 years across all comparison groups, which supports the long-term safety of lobeglitazone, as well as a significant renoprotective effect in specific subgroups. This study has certain limitations. First, it was an observational study using real-world data rather than a randomised controlled trial; therefore, potential confounding factors cannot be excluded, although adjustments for variables were performed. Second, changes in medication and HbA1c during follow-up were not assessed. Although patients were assigned to each treatment group based on receiving the same medication for at least 3 months at baseline, subsequent treatment changes and HbA1c trends were not reflected in the analysis. Third, SGLT2 inhibitors, which are well known for their renoprotective effects, were not included in this analysis. In Korea, SGLT2 inhibitors were reimbursed starting in 2014 but were limited to use with metformin or metformin plus sulfonylurea until 2019 (the study enrolment period). Therefore, their effect on this study was minimal. Fourth, information on the duration of diabetes mellitus, which may influence renal outcomes, was not available in the database and therefore could not be included in the analysis. Finally, the sample size was small. Nevertheless, certain subgroups with a small number of patients showed statistically significant results. Large-scale studies with more detailed consideration of clinical and metabolic factors are warranted to validate these findings.

CONCLUSIONS

In conclusion, the use of lobeglitazone in patients with type 2 diabetes mellitus was not associated with an increased risk of renal progression compared with other antidiabetic medications. Subgroup analyses suggest possible heterogeneity in treatment effects, with potential renoprotective effects in female patients and in those with HbA1c<7%. These results may help guide individualised treatment strategies in clinical practice. Further prospective studies are warranted to confirm these observations and to explore the underlying mechanisms of renoprotection.

Contributors Concept and design: S-hH and HL. Statistical analysis: S-yL and M-hK. Data interpretation: S-hH, HL, S-yL and M-hK. Data collection and management: S-yL and M-hK. Manuscript writing: S-hH. Supervision and critical review: HL, Y-AS, YSH, DKS and HJ. Guarantor: S-hH.

Funding This study was supported by Chong Kun Dang Pharmaceutical Corp, Seoul, Republic of Korea.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the institutional review board of Ewha Womans University (IRB no. 2022-05-020-011).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: https://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
So-hyeon Hong https://orcid.org/0000-0001-5194-8924
So-young Lee https://orcid.org/0009-0002-3561-200X

REFERENCES

1 de Boer IH, Khunti K, Sadusky T, *et al*. Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Diabetes Care* 2022;45:3075–90.
2 Fox CS, Matsushita K, Woodward M, *et al*. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* 2012;380:1662–73.
3 Yki-Järvinen H. Thiazolidinediones. *N Engl J Med* 2004;351:1106–18.
4 Sharma AM, Staels B. Review: Peroxisome proliferator-activated receptor gamma and adipose tissue--understanding obesity-related changes in regulation of lipid and glucose metabolism. *J Clin Endocrinol Metab* 2007;92:386–95.
5 Nakamura T, Ushiyama C, Osada S, *et al*. Pioglitazone reduces urinary podocyte excretion in type 2 diabetes patients with microalbuminuria. *Metab Clin Exp* 2001;50:1193–6.
6 Sarafidis PA, Stafylas PC, Georgianos PI, *et al*. Effect of thiazolidinediones on albuminuria and proteinuria in diabetes: a meta-analysis. *Am J Kidney Dis* 2010;55:835–47.
7 August P, Hardison RM, Hage FG, *et al*. Change in albuminuria and eGFR following insulin sensitization therapy versus insulin provision therapy in the BARI 2D study. *Clin J Am Soc Nephrol* 2014;9:64–71.
8 Jang JY, Bae H, Lee YJ, *et al*. Structural Basis for the Enhanced Anti-Diabetic Efficacy of Lobeglitazone on PPARγ. *Sci Rep* 2018;8:31.
9 Hripcsak G, Duke JD, Shah NH, *et al*. Observational Health Data Sciences and Informatics (OHDSI): Opportunities for Observational Researchers. *Stud Health Technol Inform* 2015;216:574–8.
10 Levey AS, Stevens LA, Schmid CH, *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–12.
11 Gerstein HC, Colhoun HM, Dagenais GR, *et al*. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *Lancet* 2019;394:131–8.

BMJ Open: first published as 10.1136/bmjopen-2025-107482 on 19 March 2026. Downloaded from http://bmjopen.bmj.com/ on September 28, 2026 at Swets Subscription Service REF: 3980496 . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

12 Persson F, Bain SC, Mosenzon O, *et al*. Changes in Albuminuria Predict Cardiovascular and Renal Outcomes in Type 2 Diabetes: A Post Hoc Analysis of the LEADER Trial. *Diabetes Care* 2021;44:1020–6.
13 Choi JH, Banks AS, Kamenecka TM, *et al*. Antidiabetic actions of a non-agonist PPARγ ligand blocking Cdk5-mediated phosphorylation. *Nature New Biol* 2011;477:477–81.
14 Kim K-S, Hong S, Ahn H-Y, *et al*. Comparative Efficacy of Lobeglitazone Versus Pioglitazone on Albuminuria in Patients with Type 2 Diabetes Mellitus. *Diabetes Ther* 2021;12:171–81.
15 Peters SAE, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. *Lancet* 2014;383:1973–80.
16 Wannamethee SG, Papacosta O, Lawlor DA, *et al*. Do women exhibit greater differences in established and novel risk factors between diabetes and non-diabetes than men? The British Regional Heart Study and British Women's Heart Health Study. *Diabetologia* 2012;55:80–7.
17 Yang T, Michele DE, Park J, *et al*. Expression of peroxisomal proliferator-activated receptors and retinoid X receptors in the kidney. *Am J Physiol* 1999;277:F966–73.
18 Corrales P, Izquierdo-Lahuerta A, Medina-Gómez G. Maintenance of Kidney Metabolic Homeostasis by PPAR Gamma. *Int J Mol Sci* 2018;19:2063. Available: https://www.semanticscholar.org/paper/Maintenance-of-Kidney-Metabolic-Homeostasis-by-PPAR-Corrales-Izquierdo-Lahuerta/b08aa2dc20b0111f3f4c4f2a32e8f768b450f40c
19 Lee YJ, Han HJ. Troglitazone ameliorates high glucose-induced EMT and dysfunction of SGLTs through PI3K/Akt, GSK-3β, Snail1, and β-catenin in renal proximal tubule cells. *Am J Physiol Renal Physiol* 2010;298:F1263–75.
20 Bae K-H, Seo JB, Jung Y-A, *et al*. Lobeglitazone, a Novel Peroxisome Proliferator-Activated Receptor γ Agonist, Attenuates Renal Fibrosis Caused by Unilateral Ureteral Obstruction in Mice. *Endocrinol Metab* 2017;32:115.

BMJ Open: first published as 10.1136/bmjopen-2025-107482 on 19 March 2026. Downloaded from http://bmjopen.bmj.com/ on September 28, 2026 at Swets Subscription Service REF: 39804496 .
Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.