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A double-blind, Randomized controlled trial on glucose-lowering EFfects and safety of adding 0.25 or 0.5 mg lobeglitazone in type 2 diabetes patients with INadequate control on metformin and dipeptidyl peptidase-4 inhibitor therapy: REFIND study

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Abstract

Aims: To compare the efficacy and safety of adding low-dose lobeglitazone (0.25 mg/day) or standard-dose lobeglitazone (0.5 mg/day) to patients with type 2 diabetes mellitus (T2DM) with inadequate glucose control on metformin and dipeptidyl peptidase (DPP4) inhibitor therapy.

Materials and Methods: In this phase 4, multicentre, double-blind, randomized controlled, non-inferiority trial, patients with T2DM insufficiently controlled by metformin and DPP4 inhibitor combination therapy were randomized to receive either low-dose or standard-dose lobeglitazone. The primary endpoint was non-inferiority of low-dose lobeglitazone in terms of glycaemic control, expressed as the difference in mean glycated haemoglobin levels at week 24 relative to baseline values and compared with standard-dose lobeglitazone, using 0.5% non-inferiority margin.

Results: At week 24, the mean glycated haemoglobin levels were 6.87 ± 0.54% and 6.68 ± 0.46% in low-dose and standard-dose lobeglitazone groups, respectively ($p = .031$). The between-group difference was 0.18% (95% confidence interval 0.017-0.345), showing non-inferiority of the low-dose lobeglitazone. Mean body weight changes were significantly greater in the standard-dose group (1.36 ± 2.23 kg) than in the low-dose group (0.50 ± 1.85 kg) at week 24. The changes in HOMA-IR, lipid profile and liver enzyme levels showed no significant difference between the groups. Overall treatment-emergent adverse events (including weight gain, oedema and hypoglycaemia) occurred more frequently in the standard-dose group.

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Conclusions: Adding low-dose lobeglitazone to metformin and DPP4 inhibitor combination resulted in a non-inferior glucose-lowering outcome and fewer adverse events compared with standard-dose lobeglitazone. Therefore, low-dose lobeglitazone might be one option for individualized strategy in patients with T2DM.

KEYWORDS
antidiabetic drugs, beta-cell function, glycaemic control, thiazolidinediones, type 2 diabetes

1 | INTRODUCTION

According to the International Diabetes Federation (IDF), type 2 diabetes mellitus (T2DM) has reached epidemic proportions globally, including South Korea.[1-3] For some patients, the choice of glucose-lowering medication in treating T2DM is challenging. According to most guidelines, metformin is the recommended initial drug of choice. When blood glucose levels are not adequately controlled with metformin monotherapy, combination therapy might be considered as a next step.[4,5] Dipeptidyl peptidase-4 (DPP4) inhibitors with metformin are commonly prescribed as dual combination therapy in many countries.[6] Despite the introduction of these combination therapies, the proportion of patients whose blood glucose levels are not well controlled remains high.[7,8]

Technically, thiazolidinediones (TZDs) are the only insulin sensitizers among various antidiabetic agents. They activate peroxisome proliferator-activated receptor gamma and simultaneously improve insulin resistance in adipose cells, upregulate glucose uptake and utilization by the muscles, and reduce hepatic glucose production.[9-12] Considering the pathophysiology of T2DM, which includes insulin resistance and beta-cell dysfunction, the frequency of TZD usage will probably increase.[13] After the United States Food and Drug Administration approved pioglitazone and rosiglitazone in 1999, the adoption of TZDs has markedly increased. However, in clinical practice, the proportion of patients taking TZDs is lower than expected.[14] In fact, the use of TZDs had declined drastically since 2007, when Nissen and Wolski reported the cardiovascular risk of rosiglitazone.[15] Despite evidence of rosiglitazone's neutral effects on cardiovascular outcomes, safety concerns such as heart failure, oedema, as well as weight gain and fractures have reduced TZD use.[16-20]

Reducing adverse effect risks associated with TZDs use may improve their accessibility for diverse cases in clinical practice. The risk of adverse effects may be reduced by using low doses at treatment initiation. In previous studies, low-dose pioglitazone (7.5 mg/day) showed fewer adverse effects than standard-dose pioglitazone (15 mg/day), while low-dose pioglitazone showed non-inferiority for similar outcomes.[21-23]

Lobeglitazone (Chong Kun Dang Pharmaceutical Corporation, Seoul, Korea) is a TZD widely adopted in Korea. Along with its glucose-lowering and lipid-modifying effects, lobeglitazone has beneficial effects on beta-cell function and survival.[24-26] A recent study has shown that lobeglitazone may improve albuminuria in patients with T2DM.[27] Similar to other oral antidiabetic agents, lobeglitazone is effective as monotherapy and combination therapy.[25,28,29]

In this study, we aimed to evaluate the efficacy and safety of low-dose (0.25 mg/day) lobeglitazone compared with standard-dose (0.5 mg/day) lobeglitazone in patients with T2DM and poor glucose control despite combination treatment with metformin and DPP4 inhibitor we often encounter in clinical practice.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a randomized, double-blind, multicentre, phase 4 study conducted at seven centres between October 2018 and September 2021 (ClinicalTrials.gov: NCT03770052). The study comprised a 2-week screening, 24 weeks of treatment and a 30-day follow-up period.

The study protocol and other relevant documents were approved by the Institutional Review Board (IRB no. 1712-003-072) of each centre. Written informed consent was obtained from eligible patients before enrolment. This study complied with the Declaration of Helsinki, Guidelines for Good Clinical Practice, and applicable local laws and regulations.

2.2 | Study population

The study included Korean patients with confirmed diagnosis of T2DM aged 19-80 years. Eligible patients were previously treated with metformin plus DPP4 inhibitor for at least 3 months without any DPP4 inhibitor or metformin dose titration (≥500 mg/day) for over 8 weeks before screening. Other inclusion criteria were body mass index (BMI) between 20 and 45 kg/m^2 and glycated haemoglobin (HbA1c) levels of 7.0%-9.0%.

The key exclusion criteria were any history of severe heart failure (New York Heart Association Class III or IV), major cardiovascular or cerebrovascular event in the last 6 months, use of medications affecting blood glucose level, renal or hepatic dysfunction [estimated glomerular filtration rate <45 $ml/min/1.73m^2$, or levels of aspartate

aminotransferase (AST) or alanine aminotransferase (ALT) 2.5 times higher than the upper normal limit], abnormal lipid profile [triglycerides levels of >500 mg/dl or low-density lipoprotein (LDL) cholesterol of >160 mg/dl], use of insulin or any TZDs in the previous 8 weeks, and history of bladder malignancy.

2.3 | Data collection

Initial screening collected data on medical history, anthropometric measurements, physical examination and laboratory test findings. Biochemical tests included complete blood count, fasting blood glucose, fasting insulin, fasting C-peptide, HbA1c, creatinine, lipid profiles, liver enzymes, thyroid stimulating hormone, high sensitivity C-reactive protein (hs-CRP) and serum adiponectin level assessments. The participants underwent follow-up blood tests (except blood count levels) and physical measurements at week 24 for comparisons with baseline values.

2.4 | Sample size

To show the non-inferiority of Arm B (lobeglitazone 0.25 mg) compared with Arm A (lobeglitazone 0.5 mg), between group difference in HbA1c was evaluated with a non-inferiority limit of $\delta = 0.5\%$. Based on a 5% significance level and a statistical power of 90%, a sample size of 69 patients per treatment group was required. Considering a 20% drop-out rate, we aimed to enrol a total of 174 patients ($n = 87$ per group).

2.5 | Treatments

Eligible patients were randomly assigned to receive low-dose (0.25 mg) or standard-dose (0.5 mg) lobeglitazone once daily as an add-on therapy to metformin and DPP4 inhibitors (low-dose group vs. standard-dose group). In each group, the treatment continued for 24 weeks. The doses of metformin (≥500 mg) and DPP4 inhibitors were as before the initiation of the trial. Each patient visited the centre three times for safety and efficacy evaluation. Stratified block randomization was performed at each site using SAS version 9.3. This clinical trial used a double-blind protocol.

2.6 | Outcomes

The primary endpoint was defined as HbA1c levels at 24 weeks. Secondary endpoints included changes in HbA1c levels and body weight at 24 weeks relative to baseline values, the proportion of patients achieved HbA1c <7%, adverse event incidence, 24-week changes in homeostatic model assessment of insulin resistance (HOMA-IR), serum lipid profiles, hs-CRP, liver enzymes and adiponectin levels.

2.7 | Statistical analyses

The main efficacy analysis was based on a full-analysis (FA) set population that received medication at least once after

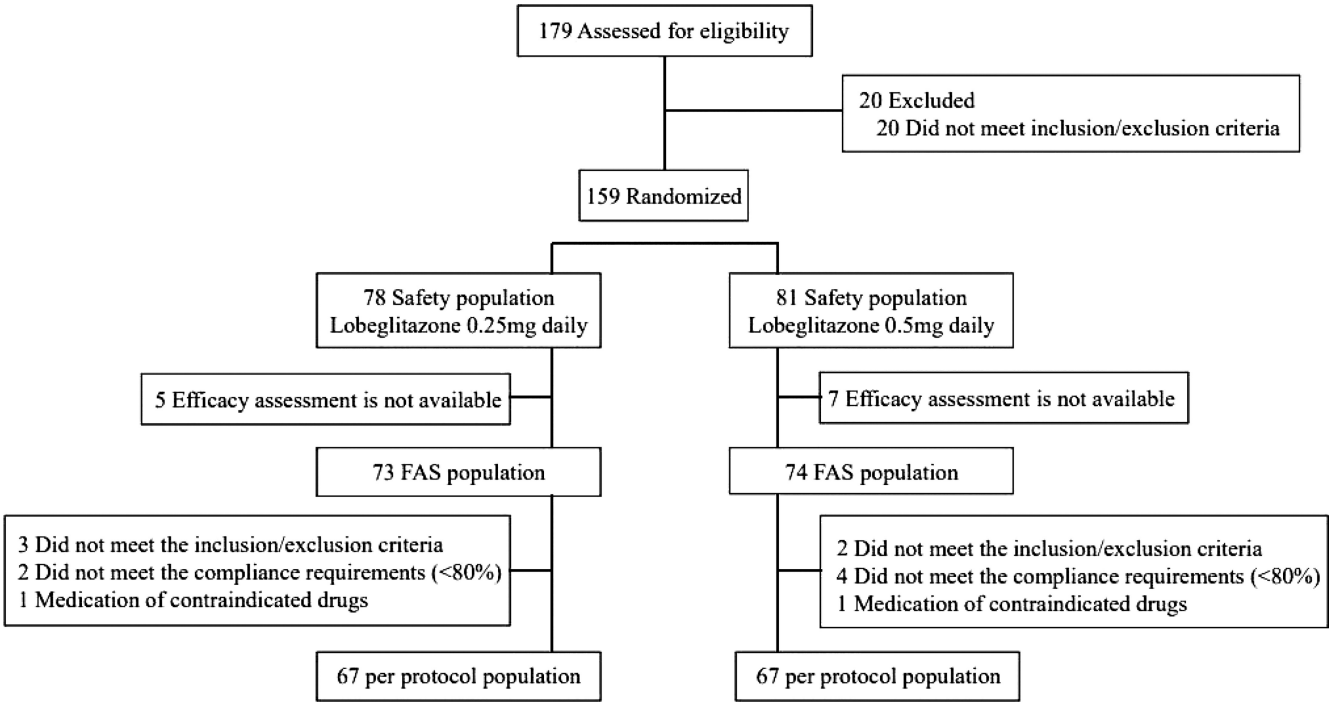

FIGURE 1 Patient allocation. FAS, full analysis set

randomization and underwent efficacy evaluation. The per-protocol (PP) set population was defined as patients who finished the trial and fulfilled all study protocol criteria. We used the PP group for minor efficacy analysis.

For primary efficacy evaluation, non-inferiority was confirmed if the upper limit of the 95% confidence interval was ≤0.5% of the difference in the mean HbA1c value at week 24. The independent sample t-test was used to evaluate the differences in HbA1c, body weight, HOMA-IR, LDL-cholesterol, high-density lipoprotein-cholesterol, hs-CRP, adiponectin, AST and ALT values at 24 weeks. Status comparisons before and after lobeglitazone administration were performed using the paired sample t-test. Frequencies and percentages were presented to evaluate the achievement rate of HbA1c <7% at 24 weeks and the chi-squared and Fisher exact tests were used to confirm the results.

Safety evaluation was performed in the safety set population, defined as participants who were exposed to at least a single dose of the trial medication after randomization. Data on adverse events that occurred throughout the study period were analysed using MedDRA version 21.1.

The chi-squared test or Fisher exact test and independent-sample t-test were used to compare variables between the two groups. The paired-samples t-test or McNemar test was used for variance analysis before and after the intervention. Statistical analyses were performed using SAS software version 9.4. All results were considered statistically significant at $p < .05$.

3 | RESULTS

3.1 | Baseline characteristics

The study flowchart is presented in Figure 1. Among the 179 patients screened for study eligibility, 20 were excluded because they could not meet the inclusion and exclusion criteria. In total, 159 eligible patients were randomized and defined as the safety set (78 in the

TABLE 1 Baseline demographic and clinical characteristics (FA set population)

Characteristics	Lobeglitazone 0.25 mg (N = 73)	Lobeglitazone 0.5 mg (N = 74)	*p*-value
Age (years)	61.7 ± 8.8	61.2 ± 8.5	.749
Sex, male (%)	35 (48.0)	36 (48.7)	.932
Body weight (kg)	66.8 ± 10.8	67.8 ± 12.8	.609
BMI (kg/m^2)	25.3 ± 3.2	25.5 ± 3.2	.751
Disease duration (years)	10.0 ± 6.4	9.5 ± 5.8	.586
Metformin dose (mg/day)	1035 ± 511	1141 ± 521	.217
HbA1c (%)	7.62 ± 0.48	7.70 ± 0.58	.401
Fasting plasma glucose (mg/dl)	151.2 ± 22.7	152.2 ± 28.4	.805
SBP (mmHg)	126.3 ± 12.3	126.1 ± 13.3	.953
DBP (mmHg)	74.3 ± 9.6	74.9 ± 10.4	.720
Creatinine (mg/dl)	0.79 ± 0.18	0.78 ± 0.18	.821
Total cholesterol (mg/dl)	144.0 ± 26.1	144.8 ± 26.0	.848
Triglyceride (mg/dl)	127.8 ± 53.3	133.1 ± 65.3	.590
LDL cholesterol (mg/dl)	81.6 ± 23.0	82.7 ± 24.5	.772
HDL cholesterol (mg/dl)	50.4 ± 11.5	48.8 ± 12.2	.405
HOMA-IR	4.4 ± 6.2	3.7 ± 2.7	.443
TSH (μIU/ml)	2.4 ± 1.6	2.2 ± 1.5	.302
Fasting plasma insulin (μIU/ml)	11.8 ± 18.7	9.9 ± 7.3	.431
C-peptide (ng/ml)	2.7 ± 2.7	2.6 ± 1.6	.793
Adiponectin (μg/ml)	7.2 ± 4.9	6.3 ± 3.4	.212
AST (U/L)	27.4 ± 10.6	25.3 ± 9.8	.217
ALT (U/L)	32.0 ± 18.0	30.2 ± 18.0	.542
hs-CRP (mg/dl)	0.2 ± 0.3	0.2 ± 0.4	.914

Note: Data are means ± standard deviation, for continuous variables and frequencies (percentage) for categorical variables.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TSH, thyroid stimulating hormone.

low-dose group and 81 in the standard-dose group). For the main analysis, we excluded 12 patients who were not available for the efficacy assessment (five in the low-dose group and seven in the standard dose-group), and 147 patients (73 in the low-dose group and 74 in the standard-dose group) were included in the FA set. We further excluded 13 patients; six patients (three did not meet the inclusion/exclusion criteria, two did not meet the compliance requirements and one had contraindicated drugs) in the low-dose group and seven (two did not meet the inclusion/exclusion criteria, four did not meet the compliance requirements and one had contraindicated drugs) in the standard-dose group. In total, 134 patients (67 patients in each group) were assigned to the PP set for minor analysis.

Table 1 summarizes the baseline demographic and clinical characteristics of the FA set population. Baseline characteristics were comparable between the two groups in terms of age, sex, BMI, disease duration, mean HbA1c values and other biochemical parameters.

3.2 | Primary efficacy outcome

In the FA set, the HbA1c level at 24 weeks decreased from 7.62 ± 0.48 to 6.87 ± 0.54% in the low-dose lobeglitazone (0.25 mg) group and from 7.70 ± 0.58 to 6.68 ± 0.46% in the standard-dose lobeglitazone (0.5 mg) group. HbA1c levels were significantly different between the groups ($p = .031$) (Figure 2A). However, the upper limit of the 95% confidence interval was 0.345%, which satisfied the non-inferiority limit of 0.5%, showing that the low-dose treatment was non-inferior to the standard-dose treatment in terms of the mean HbA1c level after 24 weeks. Similarly, in the PP set, a significant difference was observed between the groups at week 24 ($p = .040$); non-inferiority of the low-dose treatment to the standard-dose treatment was also observed.

3.3 | Secondary efficacy outcomes

At the end of 24 weeks, changes in HbA1c levels from baseline were significantly greater in the standard-dose group than in the low-dose group (−1.01 ± 0.66% vs. −0.76 ± 0.61%, $p = .016$) (Figure 2B).

Changes in body weight were significantly lower in the low-dose group than in the standard-dose group (low-dose group: 0.50 ± 1.85 kg vs. standard-dose group: 1.36 ± 2.23 kg, $p = .012$). Meanwhile, changes in serum adiponectin levels were significantly higher in the standard-dose group than in the low-dose group (low-dose group: 6.6 ± 8.5 μg/ml vs. standard-dose group: 14.1 ± 14.9 μg/ml, $p < .001$) (Figure 2C,D). A similar tendency was observed in the PP set.

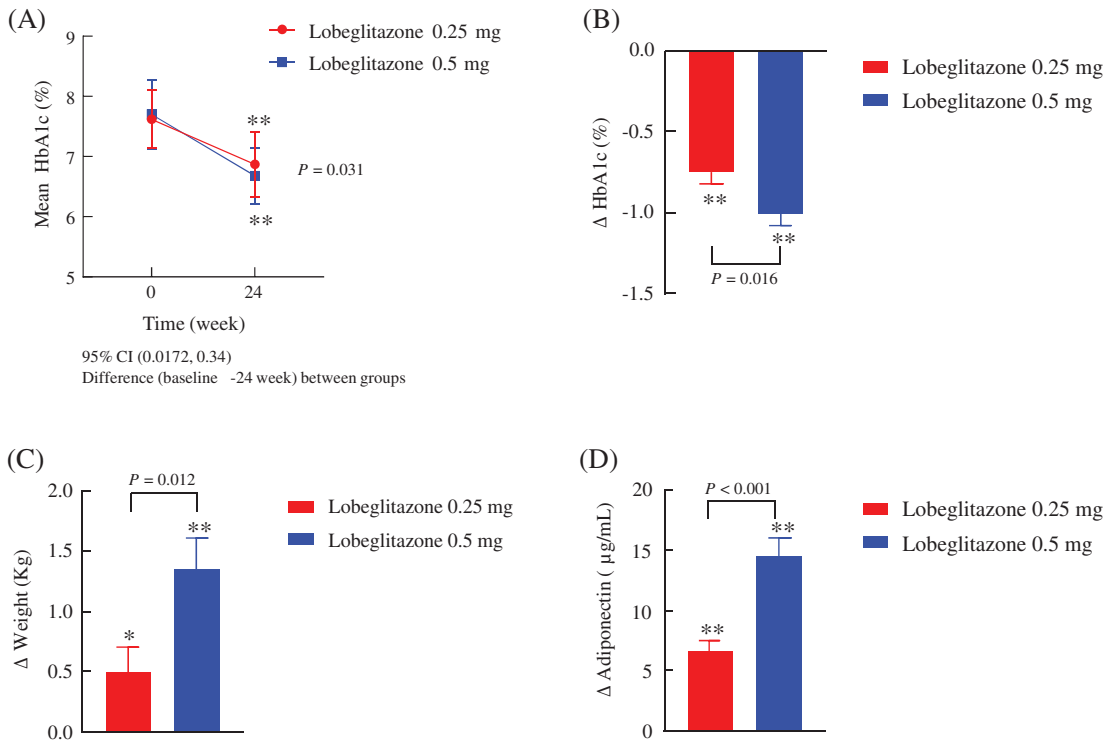

FIGURE 2 Comparing efficacy outcomes between the low-dose and the standard-dose group after 24 weeks from baseline. A, Mean HbA1c level (%). B, Changes to HbA1c level (%). C, Changes to body weight (kg). D, Changes to serum adiponectin level (μg/ml). *$p < .05$, **$p < .001$; 24 weeks versus baseline. HbA1c, glycated haemoglobin

Target achievement rate of HbA1c <7% after 24 weeks from baseline was comparable in both groups (low-dose group: 64.4% vs. standard-dose group: 75.7%, $p = .135$) (Figure 3A). Changes in HOMA-IR (low-dose group: −1.8 ± 6.0 vs. standard-dose group: −1.6 ± 2.8, $p = .791$), LDL (low-dose group: −2.6 ± 21.1 mg/dl vs. standard-dose group: −0.3 ± 18.3 mg/dl, $p = .486$) and high-density lipoprotein (low-dose group: 4.3 ± 7.9 mg/dl vs. standard-dose group: 4.7 ± 7.6 mg/dl, $p = .791$) values were comparable between the two groups (Figure 3B,C). AST (low-dose group: −0.8 ± 10.9U/L vs. standard-dose group: −2.0 ± 9.0 U/L, $p = .451$) and ALT (low-dose group: −5.3 ± 18.3 U/L vs. standard-dose group: −7.5 ±13.5 U/L, $p = .421$) values decreased significantly after 24 weeks and were comparable in both groups (Figure 3D).

3.4 | Safety outcomes

Table 2 shows safety outcomes in each treatment group. Seventy of 159 (44.0%) patients in the safety set experienced at least one treatment-emergent adverse event. Although the incidence of total treatment-emergent adverse events was comparable between the groups [low-dose: 30 of 78 (38.5%) vs. standard-dose: 40 of 81 (49.4%), $p = .220$], oedema, weight gain and hypoglycaemia would probably to occur in the standard-dose group than in the low-dose group. The rate of adverse drug reactions was higher in the standard-dose group (16.1%, n = 13) than in the low-dose group (3.9%, n = 3) ($p = .022$). The most frequently reported adverse reaction was oedema. Severe adverse events, such as pneumonia, ileus, atrial

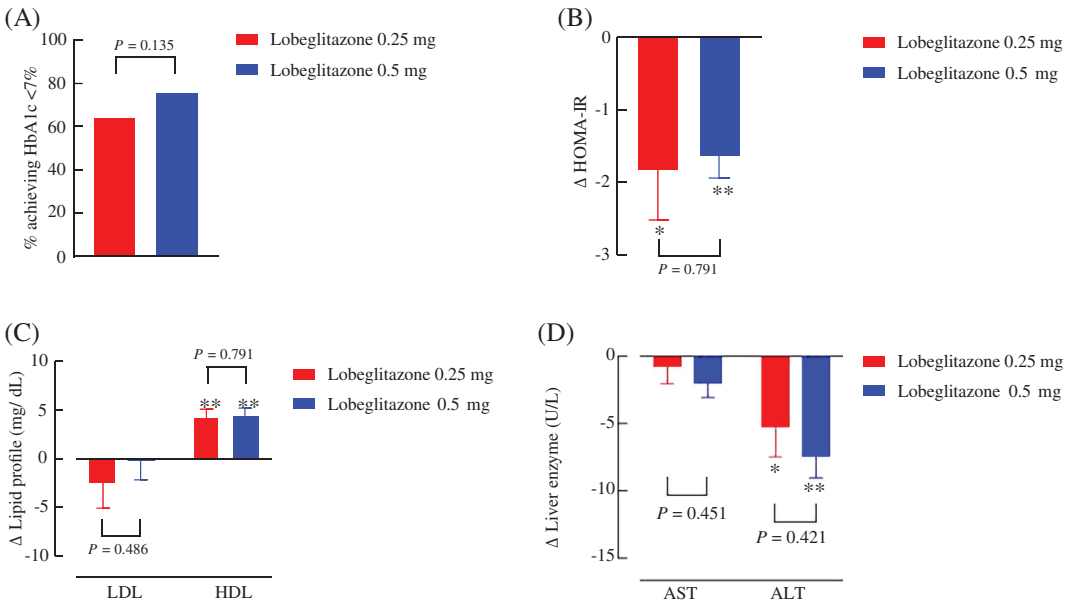

FIGURE 3 Comparison of efficacy outcomes between the low-dose and the standard-dose groups after 24 weeks from baseline (continued). A, Proportion of patients achieving target HbA1c <7%. B, Changes to HOMA-IR. C, Changes to lipid profiles (mg/dl). D, Changes to Liver enzyme level (U/L). *$p < .05$, **$p < .001$; 24 weeks versus baseline. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein

TABLE 2 Summary of adverse events

	Lobeglitazone 0.25 mg (N = 78) n (%)	Lobeglitazone 0.5 mg (N = 81) n (%)	*p*-value n (%)
Treatment-emergent adverse effects	30 (38.5)	40 (49.4)	.220
Oedema	3 (3.9)	10 (12.4)	.080
Weight gain	3 (3.9)	5 (6.2)	.719
Hypoglycaemia	–	2 (2.5)	.497
Adverse drug reactions	3 (3.9)	13 (16.1)	.022
Severe adverse events	6 (7.7)	6 (7.4)	1.000

Note: Present data show number of events, n (proportion from total number, %).
$p < .05$ was considered significant.

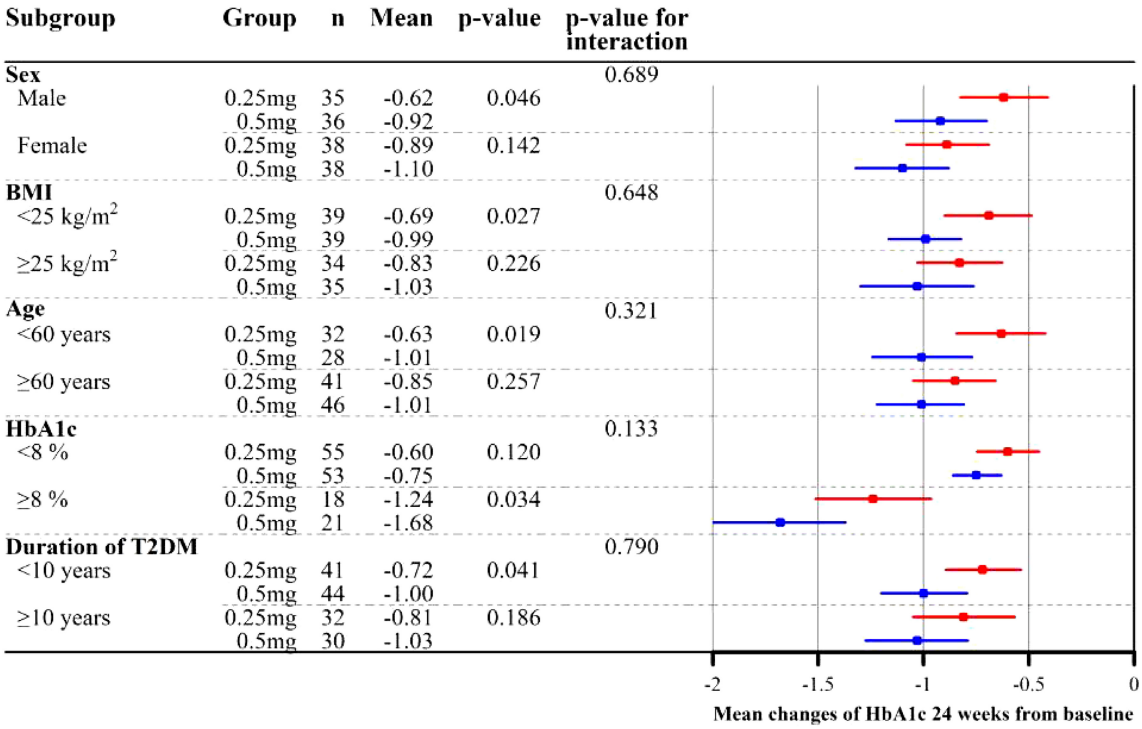

FIGURE 4 Subgroup analysis. Mean changes of HbA1c (%) from baseline to the end of treatment (24 weeks) in patient subgroups defined by sex, BMI (<25 or ≥25 kg/m^2), age (<60 or ≥ 60 years), baseline HbA1c values (<8 or ≥8 %) and duration of T2DM (<10 or ≥ 10 years). BMI, body mass index; HbA1c, glycated haemoglobin; T2DM, type 2 diabetes mellitus.

fibrillation and transient ischaemic attack were reported. The incidence of these adverse events was comparable in both groups; all cases recovered ($p = 1.000$).

3.5 | Subgroup analysis

In the FA set population, we performed a subgroup analysis for the change in HbA1c level at 24 weeks relative to baseline values. Figure 4 presents a forest plot of the changes in HbA1c levels from baseline. Patients were stratified by sex, BMI (<25 or ≥25 kg/m^2), age (<60 or ≥60 years), baseline HbA1c (<8 or ≥8%) and duration of T2DM (<10 or ≥10 years). Overall, the mean changes in HbA1c at week 24 from baseline tended to be greater in the 0.5 mg standard doses in each subgroup. The mean change in HbA1c between the two doses of lobeglitazone (0.25 vs. 0.5 mg) was statistically significant in the subgroup of men ($p = .046$), and patients with BMI of <25 kg/m^2 ($p = .027$), aged <60 years ($p = .019$), with baseline HbA1c ≥8% ($p = .034$), and T2DM duration of <10 years ($p = .041$). No significant difference was observed between the two lobeglitazone doses in the remaining subgroups.

4 | DISCUSSION

In this randomized trial of Korean patients with T2DM inadequately controlled by metformin and DPP4 inhibitors, adding low-dose lobeglitazone (0.25 mg) showed non-inferiority compared with standard-dose lobeglitazone (0.5 mg) in terms of improving HbA1c levels after 24 weeks of treatment.

To our knowledge, this study is the first randomized controlled trial to compare the efficacy and safety of low- and standard-dose lobeglitazone as an add-on therapy to metformin plus DPP4 inhibitors. The combination of metformin plus DPP4 inhibitor is a common dual antidiabetic therapy in Korea.[2] A previous retrospective study revealed that the combination of lobeglitazone and DPP4 inhibitor might be more potent than other lobeglitazone-combined regimens.[12] In this respect, our study might be an option when considering adding one more drug in common combination.

In Western patients, the main pathophysiology of diabetes has been considered insulin resistance, whereas in Korean patients, decreased insulin secretion capacity has traditionally been recognized as the main cause. However, as Korean diets are becoming westernized, the association between the pathophysiology of T2DM and beta-cell function defects has become more controversial.[23] Emerging evidence suggests that insulin resistance is the leading pathophysiology involved in the T2DM of Korean patients.[23,30,31] Therefore, TZD treatment may benefit Korean patients.

From some point of view, TZDs are yet to be underestimated. The pathophysiology of T2DM is complex and often comorbid with metabolic syndrome. TZDs may affect various aspects of diabetes treatment, including improving insulin sensitivity and reducing beta-cell burden. Previously, TZDs such as rosiglitazone and pioglitazone have shown beneficial effects in preserving pancreatic beta-cells.[32-34] In another study, lobeglitazone has shown favourable outcomes on beta-cell function in mice.[26] TZDs are the only direct insulin

sensitizers approved for the treatment of T2DM. The potential pleiotropic effects are another advantage of TZDs. A recent study has shown that long-term use of pioglitazone was associated with reduced dementia incidence.[35] Nevertheless, the use of TZDs has been limited by safety concerns, including fluid retention, weight gain, heart failure and fracture risk.[16,36,37] The use TZDs may increase if the risk of side effects is reduced. This study aimed to show the benefits of low-dose lobeglitazone in reducing side effect risk while maintaining treatment efficacy. In the present randomized controlled trial, low-dose lobeglitazone showed non-inferiority at lowering mean HbA1c levels after 24 weeks of administration compared with standard-dose lobeglitazone. Low-dose lobeglitazone resulted in lower weight gain than the standard-dose. For safety aspects, low-dose lobeglitazone was associated with lower rates of weight gain, oedema and hypoglycaemia than standard-dose lobeglitazone. Neither the low-dose nor the standard-dose lobeglitazone groups were associated with severe adverse drug reactions.

Several studies have evaluated the efficacy and safety of low-dose pioglitazone compared with standard- and high-dose pioglitazones.[21,22,38,39] In these studies, low-dose pioglitazone showed comparable glucose-lowering efficacy and better safety outcomes than standard- and high-dose pioglitazones.[38] This study compared the efficacy and safety of two doses of lobeglitazones. Lobeglitazone has shown similar glucose-lowering outcomes as pioglitazone.[28] Lobeglitazone has a strong affinity for peroxisome proliferator-activated receptor-γ,[40] which means it has excellent efficacy at lower doses per kilogram. In addition, compared with other TZDs and placebo, lobeglitazone showed no harmful effects on bone mineral density over 52 weeks of administration.[41] In this context, the present findings on lobeglitazone are meaningful.

In this randomized controlled trial, standard-dose lobeglitazone showed better efficacy than low-dose lobeglitazone at improving HbA1c levels after 24 weeks. Furthermore, increased serum adiponectin levels, which contribute to improved insulin sensitivity, were significantly higher in the standard-dose than in the low-dose lobeglitazone group. Standard-dose lobeglitazone is more effective at lowering glucose levels and reducing insulin resistance than low-dose lobeglitazone. However, in this study, low-dose lobeglitazone was non-inferior to standard-dose lobeglitazone in glucose-lowering outcome, and showed an improved safety profile.

Effective disease management requires understanding the effects of individual factors on treatment effectiveness. When exposed to TZD, obese women had a greater HbA1c reduction, increased weight gain and higher oedema risk than their counterparts did.[42] In this study, females and obese individuals achieved greater glycaemic control but showed no difference in glycaemic control according to the dose of lobeglitazone. Therefore, in these subgroups, it might be reasonable to initiate therapy with a low-dose lobeglitazone in terms of effectiveness against side effects. In addition, older adults, patients with relatively good glycaemic control or longer duration of diabetes also experienced similar outcomes independent of the treatment dose.

This study had some limitations. First, it was conducted in Korea, and the findings might not be generalized to other populations or ethnicities. Second, our study adopted a non-inferiority margin of 0.5%, which was relatively high, based on precedent studies of pioglitazone.[21,22,43] In these previous studies, the difference in mean HbA1c after 3-6 months from the baseline according to each dose of pioglitazone was between 0% and 0.6%. However, previous randomized controlled trials generally used a non-inferiority margin of 0.3-0.4%,[44-46] and the upper limit of the confidence interval in our study, 0.345%, still falls within this range. Therefore, we could say that low-dose lobeglitazone is non-inferior to standard-dose lobeglitazone even in the lower margin settings that are commonly used. Third, this study involved a small sample size and short follow-up period. Long-term safety outcomes and adverse effects, including heart failure rates, were not evaluated in this study.

This study has several strengths. First, this is the first trial to evaluate the effectiveness and safety of low-dose TZD as a third-line therapy. Second, lobeglitazone previously had only one dose, but by suggesting another option, it can reduce the side effect even a little. In addition, by comparing the two doses in various subgroups of patients, we could infer in which group low-dose lobeglitazone was more applicable.

In conclusion, considering its non-inferior glucose-lowering effects and favourable safety outcomes, 0.25 mg lobeglitazone might be an optional dose in some patients who are concerned about side effects. By adding this dosage, we will be able to expand the opportunity to provide precision medicine to patients with T2DM.

AUTHOR CONTRIBUTIONS

SR, SSK, IJK, JMH, SKK, ESK, M-kK, CWL, GK and JHP contributed to the design of the study. All authors recruited participants. JCB, YIK, ISN-G, SY and MJK contributed to data analysis and interpretation. SR, SSK and IJK wrote the initial draft of the manuscript, and all the authors critically reviewed and approved the final version. SSK and IJK are the guarantors of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST

This study was supported by a research grant from Chong Kun Dang Pharmaceutical Corporation, Seoul, Republic of Korea. The authors declare that they have no competing interests.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Aschner P, Karuranga S, James S, et al. The international diabetes Federation's guide for diabetes epidemiological studies. *Diabetes Res Clin Pract*. 2021;172:108630.
2. Jung C-H, Son JW, Kang S, et al. Diabetes fact sheets in Korea, 2020: an appraisal of current status. *Diabetes Metab J*. 2021;45(1):1-10.
3. Oh MY, Kim SS, Kim IJ, et al. Clinical characteristics of diabetic patients transferred to Korean referral hospitals. *Diabetes Metab J*. 2014;38(5):388-394.
4. Committee of Clinical Practice Guidelines KDA. 2021 clinical practice guidelines for diabetes mellitus in Korea. *Diabetes Metab J*. 2021;45(4):461-481.
5. Moon JS, Suh S, Kim SS, et al. Efficacy and safety of treatment with quadruple oral hypoglycemic agents in uncontrolled type 2 diabetes mellitus: a multi-center, retrospective, observational study. *Diabetes Metab J*. 2020;45(5):675-683.
6. Lee KA, Jin HY, Kim YJ, Im YJ, Kim EY, Park TS. Treatment patterns of type 2 diabetes assessed using a common data model based on electronic health records of 2000-2019. *J Korean Med Sci*. 2021;36(36):e230.
7. Kim BY, Won JC, Lee JH, et al. Diabetes fact sheets in Korea, 2018: an appraisal of current status. *Diabetes Metab J*. 2019;43(4):487-494.
8. Fang M, Wang D, Coresh J, Selvin E. Trends in diabetes treatment and control in U.S. adults, 1999-2018. *N Engl J Med*. 2021;384(23):2219-2228.
9. Kim H, Haluzik M, Gavrilova O, et al. Thiazolidinediones improve insulin sensitivity in adipose tissue and reduce the hyperlipidaemia without affecting the hyperglycaemia in a transgenic model of type 2 diabetes. *Diabetologia*. 2004;47(12):2215-2225.
10. Kim WJ. Recent perspective on thiazolidinedione. *J Korean Diabetes*. 2021;22(2):97-104.
11. Babar T, Skugor M. Diabetes mellitus treatment. In: Cleveland C, ed. *Current Clinical Medicine*. 2nd ed. Philadelphia: W.B. Saunders; 2010:358-363.e351.
12. Bae J, Park T, Kim H, Lee M, Cha B-S. Lobeglitazone: a novel thiazolidinedione for the management of type 2 diabetes mellitus. *Diabetes Metab J*. 2021;45(3):326-336.
13. Davidson MA, Mattison DR, Azoulay L, Krewski D. Thiazolidinedione drugs in the treatment of type 2 diabetes mellitus: past, present and future. *Crit Rev Toxicol*. 2018;48(1):52-108.
14. Suk JH, Lee CW, Son SP, et al. Current status of prescription in type 2 diabetic patients from general hospitals in busan. *Diabetes Metab J*. 2014;38(3):230-239.
15. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007;356(24):2457-2471.
16. Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. *Circulation*. 2003;108(23):2941-2948.
17. Hernandez AV, Usmani A, Rajamanickam A, Moheet A. Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus. *Am J Cardiovasc Drugs*. 2011;11(2):115-128.
18. Meier C, Kraenzlin ME, Bodmer M, Jick SS, Jick H, Meier CR. Use of thiazolidinediones and fracture risk. *Arch Intern Med*. 2008;168(8):820-825.
19. Yanai H, Adachi H. The low-dose (7.5 mg/day) pioglitazone therapy. *J Clin Med Res*. 2017;9(10):821-825.
20. Kim JH, Kim SS, Baek HS, et al. Comparison of vildagliptin and pioglitazone in Korean patients with type 2 diabetes inadequately controlled with metformin. *Diabetes Metab J*. 2016;40(3):230-239.
21. Majima T, Komatsu Y, Doi K, et al. Safety and efficacy of low-dose pioglitazone (7.5 mg/day) vs standard-dose pioglitazone (15 mg/day) in Japanese women with type 2 diabetes mellitus. *Endocr J*. 2006;53(3):325-330.
22. Rajagopalan S, Dutta P, Hota D, Bhansali A, Srinivasan A, Chakrabarti A. Effect of low dose pioglitazone on glycemic control and insulin resistance in type 2 diabetes: a randomized, double blind, clinical trial. *Diabetes Res Clin Pract*. 2015;109(3):e32-e35.
23. Kim J-D, Lee W-Y. Insulin secretory capacity and insulin resistance in Korean type 2 diabetes mellitus patients. *Endocrinol Metab*. 2016;31(3):354-360.
24. Kim SG, Kim DM, Woo J-T, et al. Efficacy and safety of lobeglitazone monotherapy in patients with type 2 diabetes mellitus over 24-weeks: a multicenter, randomized, double-blind, parallel-group, placebo controlled trial. *PLoS One*. 2014;9(4):e92843.
25. Kim SH, Kim SG, Kim DM, et al. Safety and efficacy of lobeglitazone monotherapy in patients with type 2 diabetes mellitus over 52 weeks: an open-label extension study. *Diabetes Res Clin Pract*. 2015;110(3):e27-e30.
26. Kwon MJ, Lee YJ, Jung HS, et al. The direct effect of lobeglitazone, a new thiazolidinedione, on pancreatic beta cells: a comparison with other thiazolidinediones. *Diabetes Res Clin Pract*. 2019;151:209-223.
27. Kim K-S, Hong S, Ahn H-Y, Park C-Y. Comparative efficacy of Lobeglitazone versus pioglitazone on albuminuria in patients with type 2 diabetes mellitus. *Diabetes Ther*. 2021;12(1):171-181.
28. Jin SM, Park CY, Cho Y, et al. Lobeglitazone and pioglitazone as add-ons to metformin for patients with type 2 diabetes: a 24-week, multicentre, randomized, double-blind, parallel-group, active-controlled, phase III clinical trial with a 28-week extension. *Diabetes Obes Metab*. 2015;17(6):599-602.
29. Lim S, Ku EJ, Lee SY, et al. Therapeutic efficacy and safety of initial triple combination of metformin, sitagliptin, and lobeglitazone in drug-naïve patients with type 2 diabetes: initial triple study. *BMJ Open Diabetes Res Care*. 2020;8(1):e000807.
30. Ha KH, Park CY, Jeong IK, et al. Clinical characteristics of people with newly diagnosed type 2 diabetes between 2015 and 2016: difference by age and body mass index. *Diabetes Metab J*. 2018;42(2):137-146.

31. Kim M-k. Insulin resistance versus β-cell failure: is it changing in Koreans? *Diabetes Metab J*. 2018;42(2):128-129.
32. Viberti G, Freed M, Holman R, Lachin J, Heise M. Prevalence of microalbuminuria in recently diagnosed type 2 diabetes mellitus and its relationship to non-traditional risk factors: observations from the ADOPT study. *Diabetes Care*. 2002;25(10):1737-1743.
33. Gerstein HC, Yusuf S, Bosch J. The DREAM trial–Authors' reply. *Lancet*. 2006;368(9552):2050-2051.
34. DeFronzo RA, Tripathy D, Schwenke DC, et al. Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med*. 2011;364(12):1104-1115.
35. Heneka MT, Fink A, Doblhammer G. Effect of pioglitazone medication on the incidence of dementia. *Ann Neurol*. 2015;78(2):284-294.
36. Fu Y, Gerasimova M, Batz F, et al. PPARγ agonist-induced fluid retention depends on αENaC expression in connecting tubules. *Nephron*. 2015;129(1):68-74.
37. Kahn SE, Zinman B, Lachin JM, et al. Rosiglitazone-associated fractures in type 2 diabetes: an analysis from a diabetes outcome progression trial (ADOPT). *Diabetes Care*. 2008;31(5):845-851.
38. Adachi H, Katsuyama H, Yanai H. The low dose (7.5 mg/day) pioglitazone is beneficial to the improvement in metabolic parameters without weight gain and an increase of risk for heart failure. *Int J Cardiol*. 2017;227:247-248.
39. Panikar V, Kale NJ, Hoskote SS, Deogaonkar N, Joshi SR. Effect of low (7.5 mg/day), standard (15 mg/day) and high (30 mg/day) dose pioglitazone therapy on glycemic control and weight gain in recently-diagnosed type 2 diabetes patients. *J Assoc Physicians India*. 2015;63(11):36-39.
40. Lee MA, Tan L, Yang H, Im Y-G, Im YJ. Structures of PPARγ complexed with lobeglitazone and pioglitazone reveal key determinants for the recognition of antidiabetic drugs. *Sci Rep*. 2017;7(1):1-11.
41. Lim S, Kim KM, Kim SG, et al. Effects of lobeglitazone, a novel thiazolidinedione, on bone mineral density in patients with type 2 diabetes mellitus over 52 weeks. *Diabetes Metab J*. 2017;41(5):377-385.
42. Dennis JM, Henley WE, Weedon MN, et al. Sex and BMI alter the benefits and risks of sulfonylureas and thiazolidinediones in type 2 diabetes: a framework for evaluating stratification using routine clinical and individual trial data. *Diabetes Care*. 2018;41(9):1844-1853.
43. Panomvana EA. Comparisons of effectiveness, safety, and pharmacokinetic parameters between low and high doses of pioglitazone in yype 2 diabetic patients. *Int J Pharm*. 2012;2(1):8-14.
44. McCrimmon RJ, Al Sifri S, Emral R, et al. Advancing therapy with iGlarLixi versus premix BIAsp 30 in basal insulin-treated type 2 diabetes: design and baseline characteristics of the SoliMix randomized controlled trial. *Diabetes Obes Metab*. 2021;23(6):1221-1231.
45. Hong SM, Park CY, Hwang DM, et al. Efficacy and safety of adding evogliptin versus sitagliptin for metformin-treated patients with type 2 diabetes: a 24-week randomized, controlled trial with open label extension. *Diabetes Obes Metab*. 2017;19(5):654-663.
46. Ji L, Kang ES, Dong X, et al. Efficacy and safety of insulin glargine 300 U/mL versus insulin glargine 100 U/mL in Asia Pacific insulin-naïve people with type 2 diabetes: the EDITION AP randomized controlled trial. *Diabetes Obes Metab*. 2020;22(4):612-621.

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