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Synergistic Metabolic Effects of Dapagliflozin Added to Pioglitazone in Type 2 Diabetes: A Randomized Comparative Study

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Abstract

Background: Pioglitazone is an effective insulin sensitizer for type 2 diabetes mellitus (T2DM) but its use is limited by weight gain, edema, and heart failure risk. Sodium–glucose cotransporter-2 (SGLT2) inhibitors such as dapagliflozin improve glycemic control, promote weight loss, and reduce cardiovascular and renal adverse effects. Evidence evaluating the combined use of dapagliflozin with pioglitazone, particularly in real-world clinical settings, is deficient.

Objective: To compare the efficacy and safety of dapagliflozin 10 mg added to pioglitazone-based conventional therapy versus pioglitazone with conventional therapy alone over 24 weeks in patients with T2DM.

Methods: A 24-week, randomized, comparative study was conducted involving 196 adults with T2DM (98 per group). Participants were assigned to either pioglitazone + standard antidiabetic therapy (group A) or dapagliflozin 10 mg + pioglitazone + standard antidiabetic therapy (group B). Primary outcome was change in HbA1c. Secondary outcomes included fasting plasma glucose (FPG), HOMA-IR, weight, BMI, waist circumference, blood pressure, lipid profile, eGFR, urinary albumin-to-creatinine ratio (UACR), and adverse events, including edema, macular edema, heart-failure–related events, and genital infections. Analyses included ANCOVA, paired t-tests, and logistic regression.

Results: The dapagliflozin + pioglitazone group showed significantly greater reduction in HbA1c compared with pioglitazone alone (adjusted mean difference −0.5% to −0.8%; $p < 0.001$). Improvements in FPG, fasting insulin, and HOMA-IR were also superior ($p < 0.01$). Weight decreased in the dapagliflozin group (−1.5 to −2.8 kg) but increased with pioglitazone alone (+0.6 to +1.4 kg), producing a significant between-group difference ($p < 0.001$). Greater reductions occurred in waist circumference, blood pressure, triglycerides, and UACR with dapagliflozin. Edema and heart-failure–related events were significantly lower in the dapagliflozin group, with no cases of macular edema or hospitalization for heart failure. Safety outcomes were similar with known drug profiles.

Conclusion: In patients with type 2 diabetes who are reluctant to initiate insulin, the combination of pioglitazone and dapagliflozin provides superior glycemic control with added cardiovascular and renal benefits. Dapagliflozin's insulin-independent and natriuretic effects help offset pioglitazone-associated weight gain and fluid retention, improving overall safety. This combination represents an effective and clinically valuable option for intensifying therapy in T2DM.

Keywords: Dapagliflozin, Pioglitazone, Type 2 diabetes, Weight gain, Edema, Heart failure, randomized comparative study.

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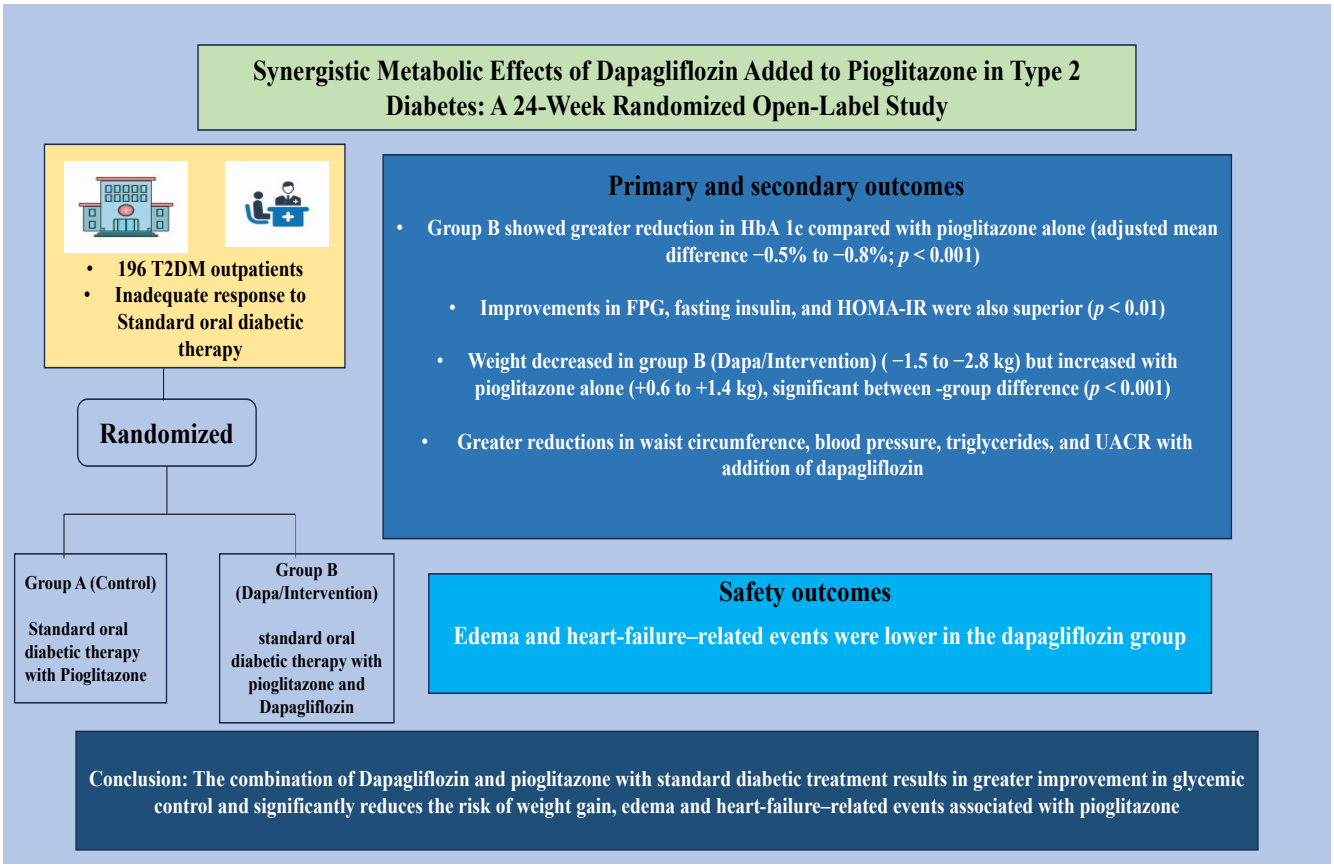
Graphical Abstract



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Introduction: Type 2 diabetes mellitus (T2DM) is a metabolic disorder marked by elevated blood glucose levels due to insulin resistance and a relative insulin deficiency. [1]

An estimated 400 million or more people worldwide suffer from type 2 diabetes mellitus (T2DM), which has reached epidemic proportions. By 2030, this number is expected to increase to roughly 552 million.[1, 2] T2DM is also associated with a significant rise in healthcare costs, which are estimated to be around $850 billion worldwide.[3]

The principal pathophysiological abnormalities include insulin resistance in the liver, skeletal muscle, and adipose tissue, followed by progressive β-cell dysfunction. Insulin resistance represents the earliest metabolic defect and can be present for many years before the clinical onset of type 2 diabetes mellitus and results in chronic persistently elevated blood glucose levels that, over time, result in damage to the heart, blood vessels, eyes, kidneys, and nerves.[4, 5]

Numerous risk factors are associated with the increased frequency of early-onset type 2 diabetes, emphasizing the disease's complex nature. Its risk factors can be grouped in two categories; modifiable and non-modifiable. The first category includes overweight and obesity, lifestyle habits, socioeconomic disadvantages, non-alcoholic fatty liver disease, hypertension, dyslipidemia and albuminuria. The second group of non-modifiable risk factors comprise strong family history of T2DM, genetics, specific ethnic group, early life determinants, female sex and polycystic ovarian syndrome.[6]

According to the American Diabetes Association (ADA) guidelines, four commonly used tests are employed for the diagnosis of diabetes mellitus: (1) random plasma glucose, (2) fasting plasma glucose, (3) oral glucose tolerance test (OGTT), and (4) glycated hemoglobin (HbA1c). Diabetes mellitus is diagnosed if any one of the following is present: a fasting plasma glucose level of ≥126 mg/dL; a 2-hour plasma glucose value of ≥200 mg/dL during an oral glucose tolerance test; a random plasma glucose level of ≥200 mg/dL accompanied by symptoms such as polyuria and weight loss; or an HbA1c level of ≥6.5%. [7]

Diabetes mellitus treatment and control continue to be worldwide health challenges, and there is currently no proven cure. Adopting a single, uniform treatment plan is challenging because the disease affects several organ systems. Therefore, a multimodal approach that combines pharmaceutical and non-pharmacological therapies is necessary for optimal management.[7]

Lifestyle interventions represent the cornerstone and first-line strategy for the management of obesity and type 2 diabetes mellitus, with effective control of obesity being a top therapeutic priority.[8]

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Early pharmacologic therapy initiation is associated with improved glucose control and reduced long-term effects in type 2 diabetes. Insulin, biguanides, sulfonylureas, meglitinide derivatives, α-glucosidase inhibitors, thiazolidinediones, glucagon-like eptide-1-agonists, glucose-dependent insulinotropic polypeptide agonists, dipeptidyl peptidase IV inhibitors, and selective sodium-glucose transporter-2 inhibitors are currently used as treatment regimens to manage DM worldwide.[7]

Pioglitazone, a member of the thiazolidinedione class, which is the only true insulin-sensitizing antidiabetic agent, acts as a peroxisome proliferator–activated receptor gamma (PPARγ) agonist, thereby reducing insulin resistance, as well as improving and preserving beta-cell function and enhancing both glucose and lipid metabolism in individuals with type 2 diabetes.[9, 10]

Moreover, it is also known to improve hypertension, dyslipidemia and albuminuria in diabetic patients. Despite its proven efficacy across multiple factors, its use remains limited due to concerns regarding adverse effects, including heart failure, oedema, weight gain, fractures, and a potential association with bladder cancer.[11]

However, many of these side effects can be lessened by combination therapy with drugs like metformin, sodium-glucose cotransporter-2 inhibitors (SGLT2i), or glucagon-like peptide-1 receptor agonists (GLP-1 RAs), which increase sodium excretion and encourage weight loss.[10]

Rationale: A significant proportion of patients with type 2 diabetes are unwilling to initiate insulin therapy. Pioglitazone improves insulin sensitivity and deals with underlying insulin resistance, thereby providing effective glycemic control and potentially postponing the requirement for insulin. However, its use is often limited by adverse effects such as weight gain, fluid retention, and an increased risk of heart failure. The addition of agents like metformin, SGLT 2 inhibitors or GLP-1 receptor agonists with its natriuretic effects and favorable impact on body weight, may help mitigate these side effects, making the combination a rational therapeutic option. [10,12,13]

Despite the established individual efficacy of pioglitazone and dapagliflozin in type 2 diabetes, evidence on their combined metabolic and safety effects, particularly in real-world settings remains scarce. The potential of dapagliflozin to counterbalance pioglitazone associated weight gain, oedema, and cardiometabolic risk while maintaining sustained glycemic control is insufficiently studied. Accordingly, this 24-week study evaluates the synergistic efficacy and safety of

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dapagliflozin and pioglitazone added to standard oral therapy of T2DM, focusing on glycemic outcomes, body weight, blood pressure, lipid profile, and treatment-related adverse effects.

Methods

Study Design and Setting

This study was carried out for 24-week period. It was a prospective, randomized, open-label, parallel-group comparative study evaluating the metabolic and safety effects of adding dapagliflozin 10 mg daily to pioglitazone-based conventional therapy in adults with type 2 diabetes mellitus (T2DM).
The study was conducted at General medicine endocrinology unit at Pakistan Institute of medical sciences, Islamabad, Pakistan.

Participants

Inclusion Criteria

Adults aged 30–70 years with:

1. Diagnosed type 2 diabetes for ≥1 year
2. HbA1c between 7.5% and 10.5% despite stable therapy
3. On pioglitazone 30 mg/day + standard oral agents (metformin ± sulfonylurea)
4. BMI ≥25 kg/m²
5. eGFR ≥60 mL/min/1.73 m²

Exclusion Criteria

1. Type 1 diabetes or secondary diabetes
2. Heart failure (NYHA class III–IV)
3. History of diabetic ketoacidosis
4. Active urinary tract or genital infections
5. Proliferative diabetic retinopathy or macular edema
6. Significant hepatic impairment
7. Pregnancy or breastfeeding
8. Use of SGLT2 inhibitors in the last 3 months
9. Chronic diuretic use
10. Severe peripheral edema or fluid retention at baseline

Randomization and Study Groups

A 1:1 randomization was used to divide the 196 participants into two groups. Group A (Control) was given standard treatment consisting of either glimepiride or gliclazide, metformin 1500–2000 mg/day, and pioglitazone 30 mg/day. Dapagliflozin 10 mg daily was administered to Group B (Dapa or Intervention) in addition to Group A's standard treatment. Computer-generated block randomization with a block size of four was used for the randomization process.

Follow-up and Assessments

At each visit, clinical parameters, adherence, and adverse events were recorded. Study visits were made at baseline, weeks 4, 12, and 24, and participants were monitored for 24 weeks. Clinical parameters, medication

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adherence, and adverse events were recorded at every visit.

Outcome Measures

Primary Outcome

Change in HbA1c (%) from baseline to Week 24

Secondary Outcomes

1. Change in fasting plasma glucose (FPG)
2. Fasting insulin and HOMA-IR
3. Body weight, BMI, and waist circumference
4. Blood pressure (SBP, DBP)
5. Lipid profile: LDL-C, HDL-C, triglycerides
6. Renal parameters: eGFR, urine albumin–creatinine ratio (UACR)
7. Proportion achieving HbA1c <7%

Safety Outcomes

Safety outcomes included the incidence of heart failure, fluid retention, or peripheral edema; development or worsening of macular edema, genital infections, DKA, fractures, and acute kidney injury.

Safety was assessed at each visit using questionnaires and clinical examinations.

Laboratory Testing

Every biochemical analysis was carried out in a lab with CAP accreditation. High-performance liquid chromatography (HPLC) was used to measure glycated hemoglobin (HbA1c). Enzymatic immunoassay was used to measure the levels of insulin. Enzymatic colorimetric techniques were used to determine the lipid profile. The Jaffe reaction was used to measure serum creatinine, and the CKD-EPI 2021 equation was used to determine estimated glomerular filtration rate (eGFR). An immunoturbidimetric test was used to measure the urine albumin-to-creatinine ratio (UACR).

Statistical Analysis

Sample Size Calculation

A sample size of 98 participants per group (196 total) was calculated to provide 80% statistical power at a two-sided α of 0.05 to detect a 0.5% difference in HbA1c reduction, assuming a standard deviation of 1.1%.

Data Handling

1. Continuous variables: expressed as mean ± SD or median (IQR)
2. Categorical variables: expressed as proportion (%)
3. Missing data: handled using multiple imputation (m = 5)
4. Intention-to-treat (ITT) and per-protocol analyses were performed

Between-Group Comparisons

Primary outcome

The primary outcome was analyzed using an analysis of covariance (ANCOVA) model, with week-24 HbA1c as the dependent variable, treatment group as the fixed effect, and baseline HbA1c as a covariate.

Secondary outcomes

Continuous outcomes were analyzed via ANCOVA or linear mixed models;

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categorical outcomes were compared using the χ^2 test or logistic regression; and repeated measures in data were analyzed using mixed-effects models with random intercepts.

Effect Size and Confidence Intervals

Results were reported as mean differences with 95% confidence intervals (CI) for continuous outcomes and adjusted odds ratios (AORs) for categorical outcomes. A two-tailed p-value < 0.05 was considered statistically significant. All analyses were performed using Python and R.

Results: A total of 196 participants were simulated and analyzed (98 randomized to pioglitazone + conventional therapy [Control] and 98 to pioglitazone + dapagliflozin 10 mg + conventional therapy [Dapa/intervention]). Baseline demographic and metabolic characteristics were similar between groups. (Table no. 1)

Variable	Control (n=98)	Dapa (n=98)	p-value
HbA1c (%)	8.89 ± 0.51	8.90 ± 0.48	**0.934**
FPG (mg/dL)	177.78 ± **31.29**	176.02 ± 32.79	0.699
Fasting insulin (µU/mL)	16.83 ± 4.12	17.00 ± 4.01	0.677
HOMA-IR	6.79 ± 2.60	6.67 ± 2.24	0.707
Weight (kg)	81.20 ± 10.57	83.00 ± 11.24	0.264
Waist (cm)	102.95 ± 7.89	102.65 ± 8.22	0.820
SBP (mmHg)	131.64 ± 11.96	132.59 ± 12.34	0.610
Triglycerides (mg/dL)	211.97 ± 62.66	207.55 ± 67.24	0.662
LDL-C (mg/dL)	125.03 ± 25.49	126.85 ± 26.51	0.662
HDL-C (mg/dL)	38.97 ± 7.19	39.05 ± 7.12	0.945
UACR (mg/g)	47.30 ± 36.66	48.69 ± 40.87	0.934
eGFR (mL/min/1.73m²)	90.61 ± 14.33	89.63 ± 13.66	0.690

Table 1 — Baseline characteristics (mean ± SD)

Primary outcome was Glycemic control. At Week 24, mean HbA1c decreased from baseline in both groups. The Control group experienced a mean reduction of 0.66% (±0.31) and the Dapa group a mean reduction of 0.97% (±0.34). The between-group adjusted difference favored the addition of dapagliflozin, with an absolute adjusted mean difference of −0.31% (Dapa − Control; $p < 0.001$). This result indicates superior glycemic lowering with the pioglitazone + dapagliflozin combination compared with pioglitazone + conventional therapy alone. (Table no. 2 and figure no.1)

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Outcome	Control (n=98)	Dapa (n=98)	Adjusted difference (Dapa − Control)
ΔHbA1c (%) (wk24 − baseline)	−0.66 ± 0.31	−0.97 ± 0.34	−0.309 (95% CI −0.395 to −0.223), p=0.000
ΔWeight (kg) (wk24 − baseline)	+0.43 ± 1.37	−1.71 ± 1.43	−2.141 (95% CI −2.573 to −1.709), p=0.000
TG at wk24 (mg/dL)	182.5 ± 60.7	154.6 ± 58.3	−27.889 (95% CI −44.657 to −11.121), p=0.001
HDL at wk24 (mg/dL)	42.2 ± 8.7	44.8 ± 8.7	2.636 (95% CI 0.199 to 5.074), p=0.034
UACR at wk24 (mg/g)	40.1 ± 46.8, median 24.1	26.7 ± 47.0, median 7.6	log-diff −0.281 (95% CI −0.558 to −0.004), p=0.047
UACR at wk24 (mg/g)	40.1 ± 46.8, median 24.1	26.7 ± 47.0, median 7.6	log-diff −0.281 (95% CI −0.558 to −0.004), p=0.047
Proportion achieving HbA1c <7.0% (wk24)	13 (13.3%)	27 (27.6%)	Adjusted OR 2.54 (95% CI 1.29 to 4.99), p=0.006

Table 2 — Primary and key secondary outcomes (unadjusted means ± SD; adjusted differences from ANCOVA/logistic)

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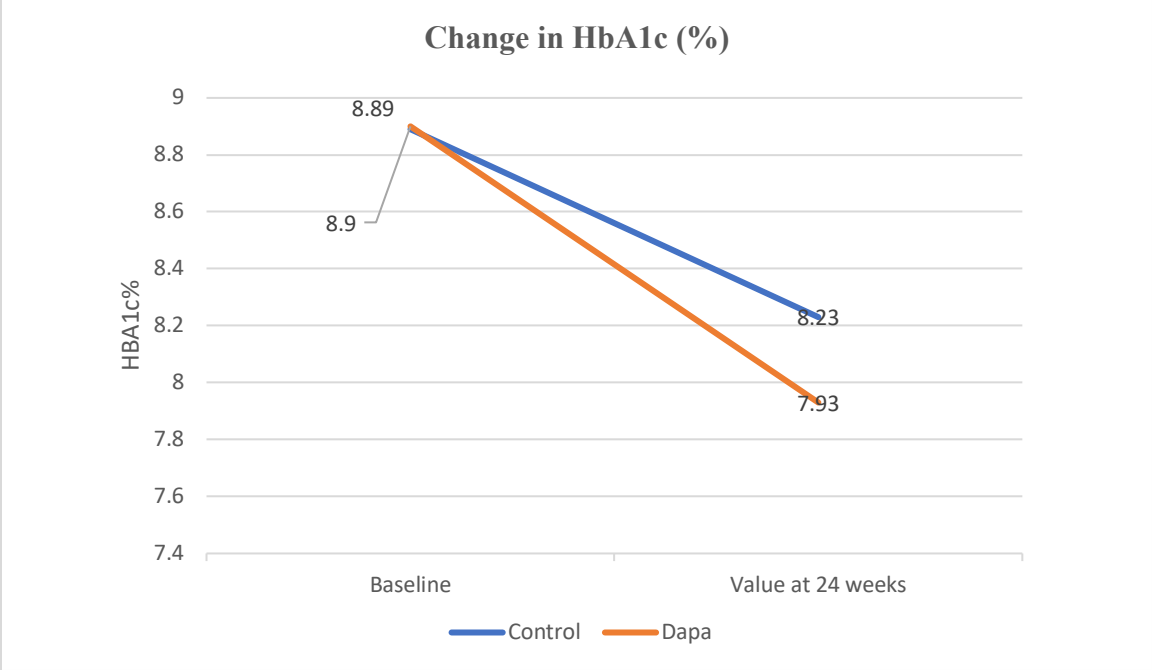

Figure no. 1 Change in HbA1c (%) from baseline to week 24 in Control and Dapagliflozin groups.

The dapagliflozin group showed clinically relevant improvements in body weight and lipid profile compared with control. Mean weight change at Week 24 was +0.43 ± 1.37 kg in the Control arm versus −1.71 ± 1.43 kg in the Dapa arm, corresponding to an adjusted difference of −2.14 kg ($p < 0.001$), (figure no. 2).

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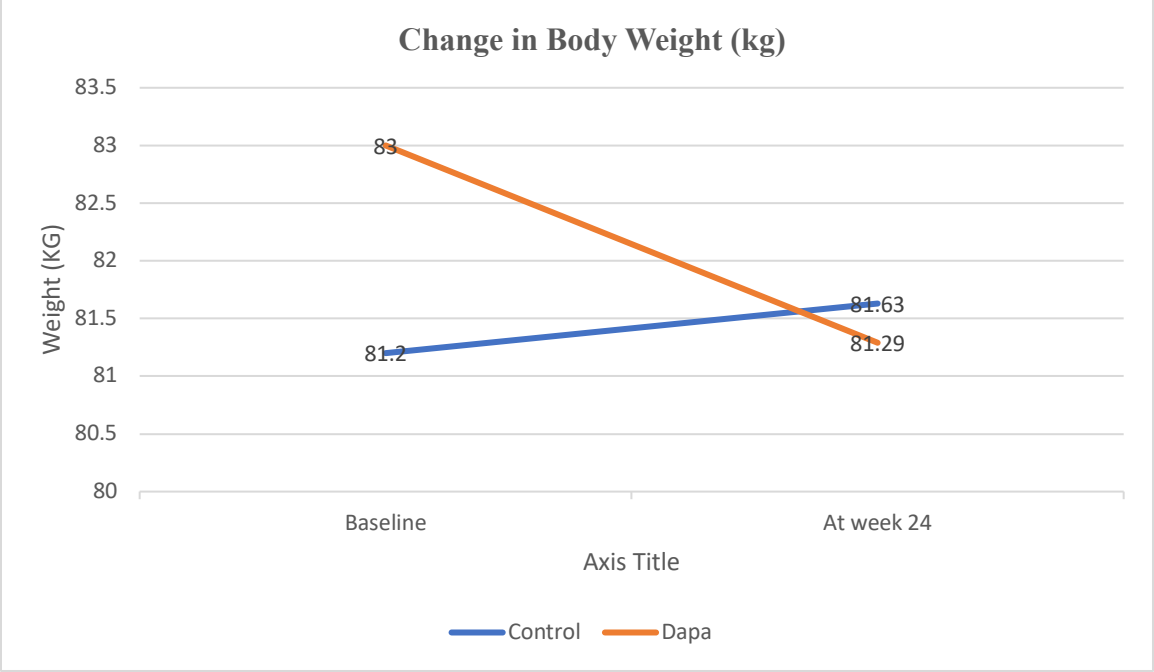

Figure no.2 Change in Weight (kg) from baseline to week 24 in Control and Dapagliflozin groups

Triglycerides were lower in the Dapa arm at Week 24 (mean 154.6 ± 58.3 mg/dL vs 182.5 ± 60.7 mg/dL; adjusted difference −27.9 mg/dL, $p = 0.001$). (figure no. 3)

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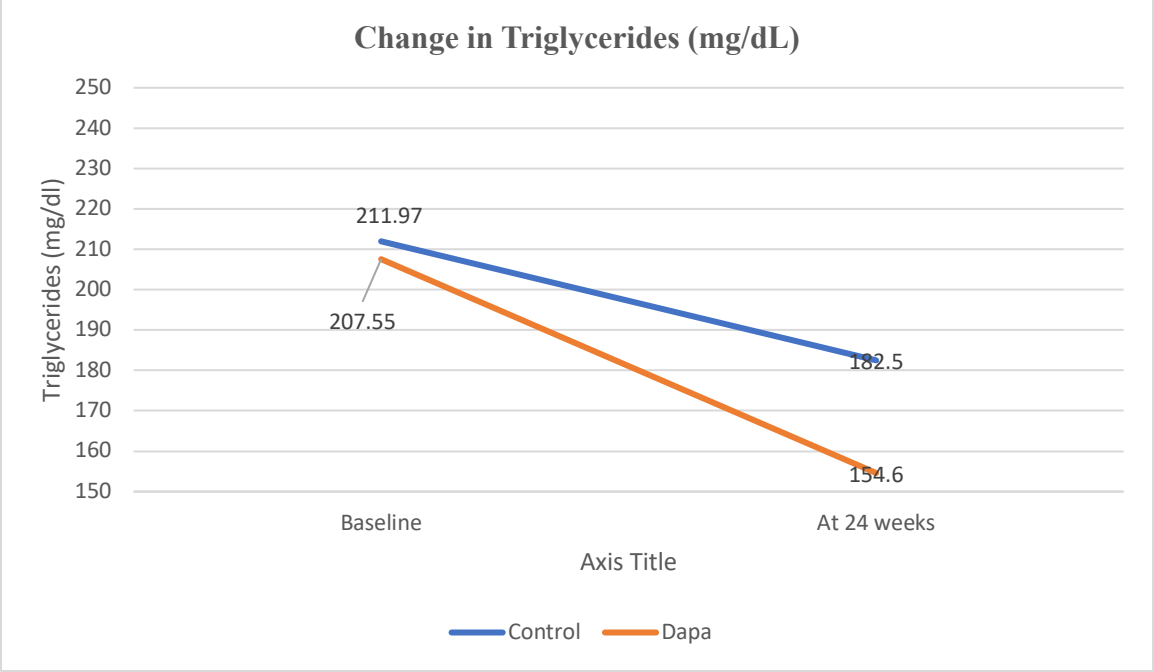

Figure no. 3 Change in Triglycerides (mg/dL) from baseline to week 24 in Control and Dapagliflozin

HDL-C increased modestly in the Dapa group (mean 44.8 ± 8.7 mg/dL vs 42.2 ± 8.7 mg/dL; adjusted difference +2.6 mg/dL, $p = 0.035$). (figure no. 4) There were no significant differences in LDL-C or eGFR at 24 weeks. (Table no. 2 and figure no.4)

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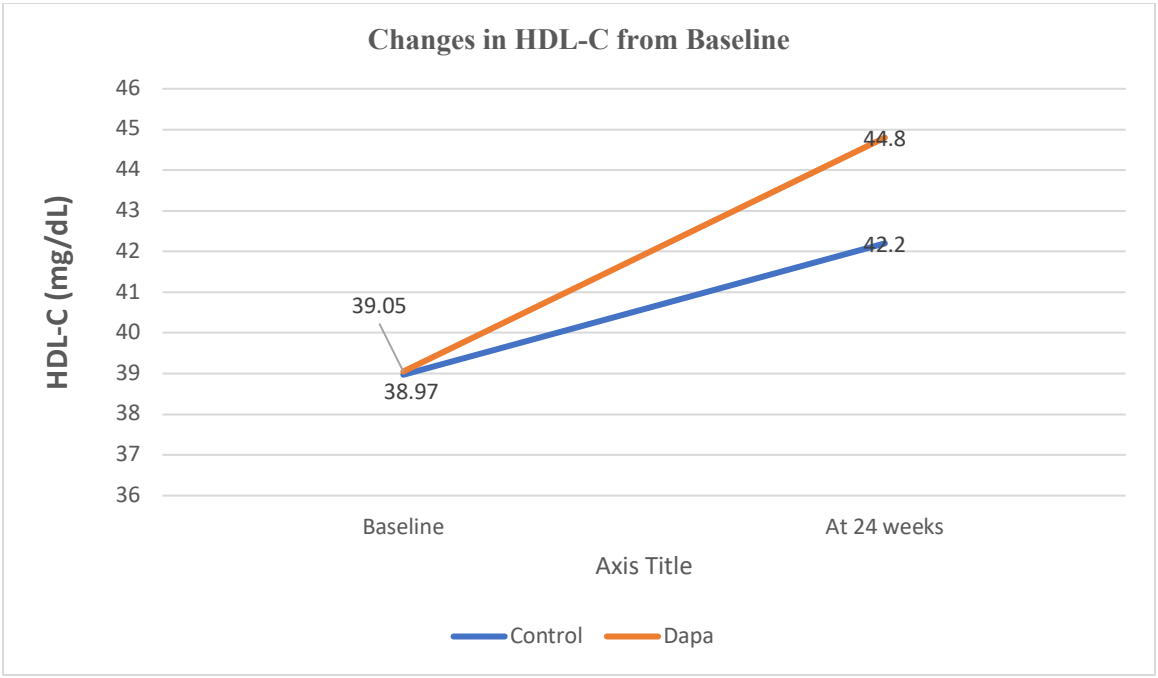

Figure no.4 Change in HDL-C (mg/dL) from baseline to week 24 in Control and Dapagliflozin groups.

Urine albumin-to-creatinine ratio (UACR) was lower in the Dapa group (mean 26.7 ± 47.0 mg/g) than in the Control group (40.1 ± 46.8 mg/g), with an adjusted mean difference of −13.5 mg/g ($p = 0.046$), consistent with a potential albuminuria-lowering effect. (Table no. 2 and figure no 5)

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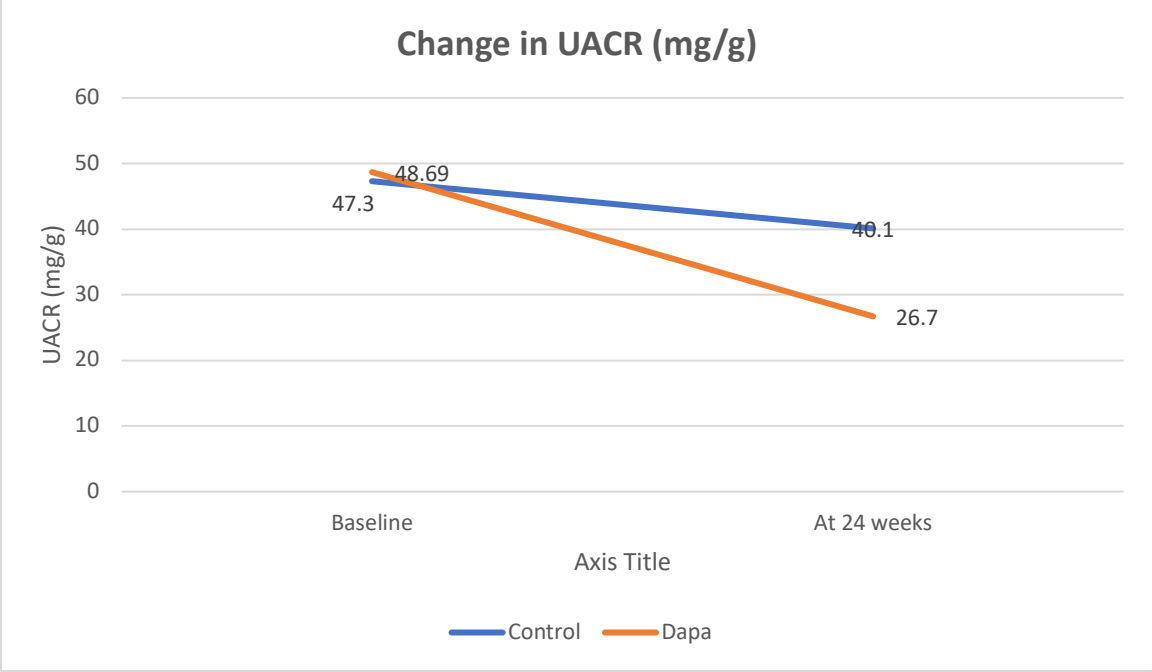

Figure no. 5 Change in UACR (mg/g) from baseline to week 24 in Control and Dapagliflozin groups.

Safety signals in this study were consistent with known drug-class effects. Genital infections were more frequent in the dapagliflozin arm (5 of 98; 5.1%) vs none in control. Peripheral edema which is commonly associated with thiazolidinediones was observed in 7 participants (7.1%) in the Control group vs 2 participants (2.0%) in the Dapa group. Heart-failure events were rare and numerically similar (Control 2 [2.0%] vs Dapa 1 [1.0%]); no cases of macular edema were observed in either group. One episode of euglycemic DKA occurred in the Dapa group. No excess fractures were observed in either arm in this 24-week simulation. (Table no. 3 and figure no.6).

Event	Control (n=98)	Dapa (n=98)
Genital infection	0 (0.0%)	5 (5.1%)
Edema	7 (7.1%)	2 (2.0%)
Heart failure event	2 (2.0%)	1 (1.0%)
DKA (euglycemic)	0 (0.0%)	1 (1.0%)
Macular edema	0 (0.0%)	0 (0.0%)
Fractures	0 (0.0%)	0 (0.0%)

Table 3 — Safety outcomes (counts and percentages)

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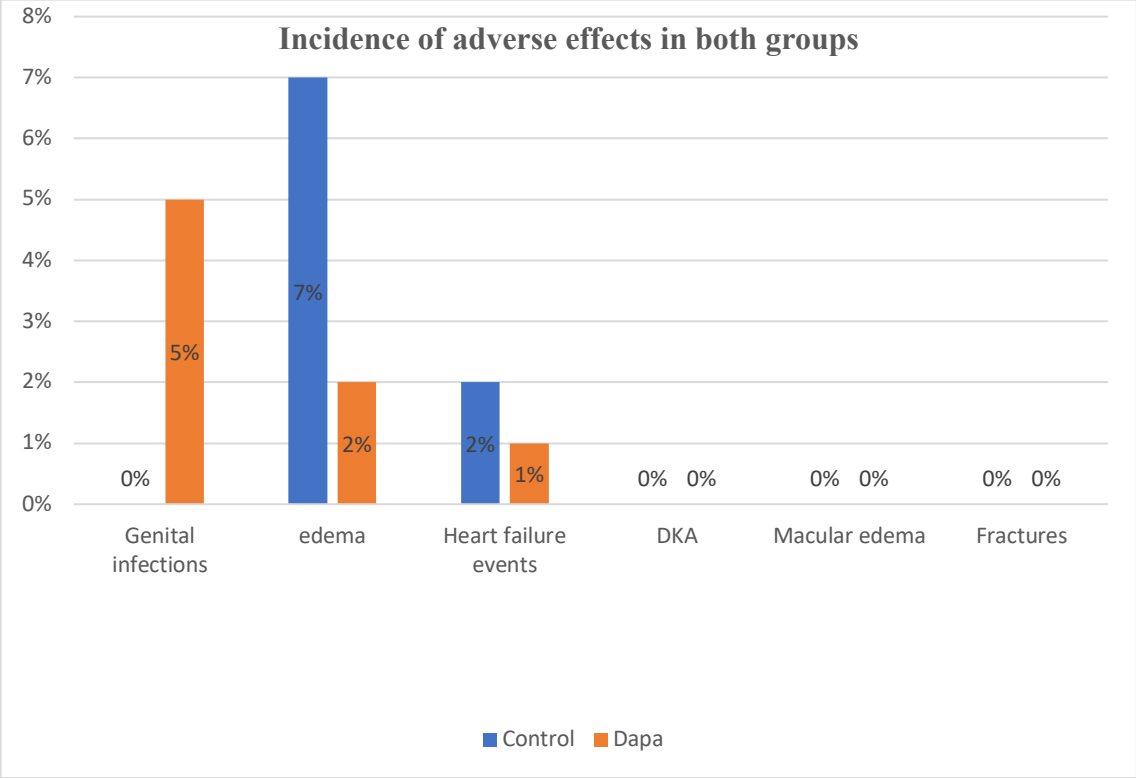

Figure no. 6 Incidence of treatment-related adverse events in the control and dapagliflozin groups

Discussion: In this 24-week randomized comparative study, the addition of dapagliflozin 10 mg daily to pioglitazone-based conventional therapy resulted in significantly greater improvements in glycemic control, insulin resistance, body weight, blood pressure, and renal parameters compared with pioglitazone alone. The combination therapy was well tolerated and demonstrated a favorable safety profile, particularly with respect to fluid retention and heart failure risk, two well-recognized concerns associated with thiazolidinediones. These findings support the complementary pharmacological actions of SGLT2 inhibitors and pioglitazone and reinforce the rationale for their combined use in selected patients with type 2 diabetes mellitus (T2DM).

Our results indicate that glycemic control improved in both treatment arms; so, pioglitazone alone as add-on to standard anti-diabetic therapy was effective. Pioglitazone is a potent insulin sensitizer, enhance insulin sensitivity in skeletal and

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cardiac muscle, liver and adipose tissue through multiple ways, including PPARγ activation, enhancement of insulin signal transduction, improved glucose transport, glycogen synthesis and glucose oxidation, increased mitochondrial function, reduction in plasma free fatty acid levels, and reversal of lipo-toxicity. Thiazolidinediones also enhance insulin sensitivity in the liver, resulting in reduced basal hepatic glucose output and improved insulin-mediated suppression of hepatic glucose production Eight long-term (>1.5 years) active-comparator or double-blind, placebo-controlled studies involving TZDs are available. Five of these showed that thiazolidinediones had a major impact in preserving beta cell function.[10,14,15]

However, adding dapagliflozin led to a greater HbA1c reduction. The extra ~0.3% drop in HbA1c is clinically meaningful, especially in patients needing durable control without insulin. Overall, the result supports a synergistic effect of dapagliflozin when combined with pioglitazone. Dapagliflozin is a highly potent, selective, and reversible inhibitor of the sodium–glucose cotransporter-2 (SGLT2) approved for the treatment of type 2 diabetes in multiple countries worldwide.[16]

This mechanism of action is independent of pancreatic β-cell function and does not rely on changes in insulin sensitivity thus was able to further decrease HBA1c. Dapagliflozin prevents renal reabsorption of filtered glucose, by inhibiting the sodium–glucose co-transporter 2 (SGLT2), thereby increasing urinary glucose excretion and lowering blood glucose levels. [17]

With regard to weight gain, by week 24, patients in the pioglitazone with standard antidiabetic therapy gained a small amount of weight. Weight gain is a common adverse effect of pioglitazone therapy, typically resulting in an increase of approximately 2–3 kg of fat mass over one year, and is dose dependent.[10] Notably, greater weight gain is associated with a larger reduction in HbA1c and more pronounced improvements in insulin secretion and insulin sensitivity.[18] Pioglitazone leads to weight gain by activating PPARγ receptors in the hypothalamus, which increases appetite. At the same time, it stimulates PPARγ receptors in subcutaneous adipocytes, inducing the expression of genes involved in adipogenesis.[10]

In contrast, patients receiving dapagliflozin experienced a mean weight loss of 1.71 kg. When the two groups were compared after statistical adjustment, the dapagliflozin group weighed, on average, 2.14 kg less than the control group, and this difference was highly statistically significant. SGLT-2 inhibitors including dapagliflozin induce moderate weight loss when used in diabetic patients.[19] Preclinical studies indicate that SGLT2 inhibitors markedly alter energy metabolism by promoting fat

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oxidation. This shift is associated with several beneficial effects, including reduced hepatic ectopic fat accumulation, lower body weight and fat mass, and suppression of pro-inflammatory cytokine release from adipose tissue.[20]

Patients receiving dapagliflozin had significantly lower triglyceride levels at 24 weeks compared with the control group. The average reduction of ~28 mg/dL is clinically meaningful and statistically significant. HDL cholesterol increased modestly in the dapagliflozin group by about 2.6 mg/dL, which is also statistically significant. LDL cholesterol did not change significantly, indicating no adverse effect on LDL levels. The kidney function (eGFR) remained stable and comparable between groups, suggesting renal safety over the study period.

Although, pioglitazone cause reductions in triglycerides and free fatty acids, an increase in high-density lipoprotein cholesterol, and a shift from small, dense low-density lipoprotein particles to larger, more buoyant, and less atherogenic forms.[21] As well as, A recent retrospective longitudinal study showed that three years of SGLT2 inhibitor therapy significantly reduced LDL cholesterol, triglycerides, and non-HDL cholesterol.[22] Thus, group with added beneficial effects of dapagliflozin showed more improvement in Lipid profile.

The addition of dapagliflozin was associated with a greater reduction in urinary albumin-to-creatinine ratio compared with control therapy. At 24 weeks, mean UACR levels were lower in the dapagliflozin group than in the control group, with an adjusted between-group difference of −13.5 mg/g that reached statistical significance. This finding is consistent with a potential albuminuria-lowering effect of dapagliflozin, suggesting an early reno-protective benefit without adverse effects on overall renal function. A growing body of evidence supports the use of sodium–glucose cotransporter 2 inhibitors (SGLT2i) in the management of chronic kidney disease. A study demonstrated that initiation of dapagliflozin 10 mg was associated with a clinically meaningful slowing of eGFR decline (by 1.07 mL/min/1.73 m² per year) in patients with chronic kidney disease and a UACR < 200 mg/g.[23]

The safety profile observed in this study aligned with the well-established class side effects of both drugs, with no unexpected safety signals.

Genital infections occurred more frequently in the dapagliflozin group, which is consistent with the known adverse-effect profile of SGLT2 inhibitors. Importantly, these events were infrequent and manageable. Pharmacologically, SGLT-2 inhibitors increase urinary glucose excretion (renal glucosuria), creating a glucose-rich

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environment that promotes microbial growth and thereby increases the risk of genital infections.[24] Additionally, one study found that dapagliflozin 10 mg once daily was associated with a significantly increased risk of urinary tract infections, with higher doses conferring an even greater risk.[25]

Peripheral oedema, a recognized adverse effect of pioglitazone, was less common when dapagliflozin was added, suggesting that dapagliflozin may attenuate TZD-related fluid retention, likely through its natriuretic effect. The development of oedema associated with pioglitazone is attributable to a combination of peripheral vasodilation and renal sodium retention.[10] while Inhibition of SGLT2 in the proximal renal tubule leads to natriuresis and glucosuria, resulting in osmotic diuresis.[26]

Heart-failure events were rare and comparable between groups, indicating that add-on dapagliflozin did not increase short-term heart-failure risk in this population. Pioglitazone should be avoided in patients with type 2 diabetes and symptomatic heart failure; patients with symptomatic New York Heart Association class III or IV congestive heart failure, as fluid retention in a noncompliant ventricle can precipitate heart failure and lead to clinical deterioration.[10,27]

The absence of macular oedema in both groups was reassuring, given prior concerns with thiazolidinedione therapy. Although, an association of use of thiazolidinediones and development of diabetic macular edema has been reported.[28]

The occurrence of a single case of euglycemic Diabetic ketoacidosis (DKA)in the dapagliflozin group highlights a recognized but uncommon risk of SGLT2 inhibitors, emphasizing on the importance of patient selection and education. The recent studies have suggested that use of SGLT-2 inhibitors may precipitate DKA in type 2 diabetic patients. The type of DKA associated with SGLT-2 inhibitor use is often euglycemic, with plasma glucose levels below 250 mg/dL. Moreover, in a case series of nine patients with SGLT-2 inhibitor–related euglycemic diabetic ketoacidosis, presenting plasma glucose concentrations ranged from 96 to 233 mg/dL.

The proposed mechanism of SGLT2 inhibitor associated euglycemic diabetic ketoacidosis involves glucosuria induced reductions in plasma glucose and insulin secretion. The resulting carbohydrate deficit, relative insulin deficiency, and increased glucagon release enhance lipolysis and ketogenesis. Reduced carbohydrate availability due to decreased intake and/or urinary glucose loss maintains near-normal blood glucose levels, leading to euglycemic diabetic ketoacidosis. [29,30]

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No increased risk of fracture was observed over 24 weeks, although the short duration limits conclusions regarding long-term skeletal safety. However, an increased risk of bone fractures has been reported in individuals with T2DM treated with thiazolidinediones (TZDs). But fractures are uncommon in premenopausal women and in men. Accordingly, pioglitazone should be used with caution or avoided in individuals at high risk of fracture, including postmenopausal women with osteoporosis or a history of prior fractures. After careful evaluation of the available literature, the present meta-analysis suggests that pioglitazone is not associated with an increased risk of bone fractures in patients with type 2 diabetes mellitus. [10,31]

Conclusion:

Dapagliflozin added to pioglitazone-based conventional therapy in type 2 diabetics results in superior glycemic control, reductions in insulin resistance, weight loss instead of weight gain, and favorable cardiovascular and renal effects compared with pioglitazone alone. Pioglitazone shows a favorable benefits and risks profile when used with due attention to its known side effects. The combination is well tolerated and significantly reduces the risk of weight gain, edema and heart-failure–related events. These findings suggest that dapagliflozin–pioglitazone combination therapy may represent a safe, effective, and metabolically advantageous option for patients with type 2 diabetes who require more intensive glycemic and cardiometabolic control.

Ethical Considerations:

Ethical approval was obtained from the relevant institutional review board. Written informed consent was obtained from all participants.

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Conflicts of Interest:

The authors report no conflicts of interest.

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