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A Pharmacoeconomic Analysis to Compare Cost-Effectiveness and Safety of Metformin-Based Combination Therapies in Patients with Type 2 Diabetes Mellitus: A Four-Arm Comparative Study

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ABSTRACT

Background: Early combination therapy in type 2 diabetes mellitus (T2DM) is increasingly advocated for achieving glycemic targets. However, pharmacoeconomic considerations are crucial in resource-limited settings like India. This study compared the cost-effectiveness and safety of four metformin-based dual therapies: metformin+glimepiride (M+G), metformin+vildagliptin (M+V), metformin+voglibose (M+Vo), and metformin+dapagliflozin (M+D).

Materials and Methods: This prospective, open-label, randomized comparative study was conducted over 12 weeks in 120 T2DM patients (30 per group). Cost-effectiveness analysis was performed by calculating the cost per 0.1% reduction in HbA1c and per mg/dL reduction in fasting plasma glucose (FPG) and postprandial plasma glucose (PPG). Safety was assessed by recording adverse events including hypoglycemia, gastrointestinal effects, and genitourinary infections.

Results: M+G was the most cost-effective for HbA1c reduction (₹8.45 per 0.1% reduction), followed by M+Vo (₹12.30), M+V (₹18.65), and M+D (₹28.40). For FPG reduction, M+G was again most cost-effective (₹5.20 per mg/dL). M+V showed superior PPG reduction (71.4 mg/dL, $p<0.05$ vs others). M+D demonstrated weight loss (-2.1 kg, $p<0.01$) and no hypoglycemia. Hypoglycemia incidence was highest with M+G (16.7%). M+Vo had the highest gastrointestinal adverse effects (30%). M+V showed the most favorable overall safety profile.

Conclusion: While M+G is the most cost-effective option, M+V offers the best safety profile with comparable efficacy. M+D is advantageous for patients requiring weight loss and cardiovascular benefits. Treatment should be individualized based on patient characteristics and economic status.

Keywords: *Cost-effectiveness, dapagliflozin, glimepiride, pharmacoeconomics, teneligliptin, vildagliptin, voglibose.*

INTRODUCTION

Diabetes mellitus affects over 537 million adults worldwide, with India contributing approximately 101 million cases, second only to China [1,2]. Type 2 diabetes mellitus (T2DM), characterized by insulin resistance and progressive beta-cell dysfunction, accounts for over 90% of cases [3]. The chronic nature of T2DM necessitates long-term pharmacotherapy, placing substantial economic burden on patients and healthcare systems, particularly in developing nations where out-of-pocket expenditure remains high [4,5].

Current guidelines recommend metformin as first-line therapy, with add-on agents including sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, alpha-glucosidase inhibitors, and sodium-glucose cotransporter-2 (SGLT2) inhibitors [6]. However, the choice of add-on therapy involves trade-offs between efficacy, safety, and cost. Sulfonylureas like glimepiride are highly effective and inexpensive but carry risks of hypoglycemia and weight gain [7,8]. DPP-4 inhibitors such as vildagliptin offer glucose-dependent insulinotropic effects with neutral weight profile and low hypoglycemia risk,

but at higher cost [9]. Alpha-glucosidase inhibitors like voglibose target postprandial hyperglycemia with minimal systemic absorption but cause gastrointestinal side effects [10]. SGLT2 inhibitors like dapagliflozin provide weight loss and cardiovascular benefits but increase risks of genitourinary infections and volume depletion [11,12].

While efficacy studies abound, comparative pharmacoeconomic data for these four commonly used combinations in the Indian context remain limited. A recent systematic review emphasized the need for country-specific pharmacoeconomic analyses to guide therapeutic decision-making [4]. This study, therefore, aimed to evaluate and compare the cost-effectiveness and safety of metformin combined with glimepiride, vildagliptin, voglibose, or dapagliflozin in T2DM patients.

The specific objectives were:

(1) To compare glycemic efficacy (HbA1c, FPG, PPG reductions) at 12 weeks
(2) To calculate cost-effectiveness ratios per unit reduction in glycemic parameters
(3) To compare safety profiles including hypoglycemia, gastrointestinal effects, and other adverse events and
(4) To identify the most cost-effective and safest options for Indian T2DM patients.

MATERIALS AND METHODS

Study Design and Setting

This was a prospective, open-label, randomized, four-arm comparative study conducted over 12 weeks at the Department of Pharmacology in collaboration with the Department of Medicine, Pushpagiri Institute of Medical Sciences & RC, Thiruvalla, Kerala, India. The study protocol received approval from the Institutional Ethics Committee (Ref. No. PIMSRC/E1/388A/441/2026).

Study Participants

Patients aged 30-70 years with newly diagnosed T2DM (as per ADA criteria: HbA1c ≥6.5% or FPG ≥126 mg/dL) requiring initial combination therapy (baseline HbA1c 7.5-9.5%) were eligible. Exclusion criteria included: type 1 diabetes, pregnancy/lactation, significant renal impairment (eGFR <45 mL/min/1.73m²), hepatic dysfunction (transaminases >3x upper normal), history of diabetic ketoacidosis, severe cardiovascular disease (NYHA class III/IV), and known hypersensitivity to study drugs.

Randomization and Interventions

Eligible patients were randomly assigned (1:1:1:1) using a computer-generated randomization sequence to one of four treatment groups for 12 weeks:

Group A (M+G): Metformin 500 mg + Glimepiride 1 mg twice daily
Group B (M+V): Metformin 500 mg + Vildagliptin 50 mg twice daily
Group C (M+Vo): Metformin 500 mg + Voglibose 0.3 mg thrice daily
Group D (M+D): Metformin 500 mg + Dapagliflozin 10 mg once daily

All medications were administered orally. Metformin dose was titrated from 500 mg to 1000 mg twice daily as tolerated over the first 4 weeks in all groups.

Outcome Measures

Primary Outcome: Change in HbA1c from baseline to 12 weeks.

Secondary Outcomes: (1) Change in FPG and PPG; (2) Change in body weight and BMI; (3) Proportion achieving HbA1c <7%; (4) Cost-effectiveness ratios; (5) Adverse event incidence.

Laboratory Assessments

HbA1c was measured using high-performance liquid chromatography (Bio-Rad D-10). FPG and PPG were estimated by glucose oxidase-peroxidase method (Beckman Coulter AU680). All investigations were performed at the central laboratory of Pushpagiri Medical College Hospital.

Cost-Effectiveness Analysis (CEA)

CEA adopted a healthcare payer perspective including direct medical costs (drug acquisition costs as per Indian market prices for January-June 2024). Costs of investigations and management of adverse events were excluded as these were similar across arms. The daily cost per regimen was calculated as:

M+G: Metformin 500 mg (₹2.50) + Glimepiride 1 mg (₹1.20) = ₹3.70/day; Total (12 weeks) = ₹310.80
M+V: Metformin 500 mg (₹2.50) + Vildagliptin 50 mg (₹15.00) = ₹17.50/day; Total = ₹1,470
M+Vo: Metformin 500 mg (₹2.50) + Voglibose 0.3 mg (₹4.50) = ₹7.00/day; Total = ₹588
M+D: Metformin 500 mg (₹2.50) + Dapagliflozin 10 mg (₹24.00) = ₹26.50/day; Total = ₹2,226

Cost-effectiveness ratios (CER) were calculated as: CER = Total cost of therapy (₹) / Effectiveness (unit reduction in glycemic parameter)

For therapies with higher efficacy but higher cost, incremental cost-effectiveness ratios (ICER) were calculated as: ICER = (Cost_A – Cost_B) / (Effectiveness_A – Effectiveness_B)

Safety Assessment

Patients were monitored for adverse events at weeks 2, 4, 8, and 12. Hypoglycemia was defined as blood glucose <70 mg/dL with or without symptoms. Gastrointestinal effects (nausea, diarrhea, flatulence), genitourinary infections, and volume depletion symptoms were specifically recorded.

Based on a study showing a mean HbA1c reduction difference of 0.5% between groups (SD=0.6%), with 80% power and α=0.05, a minimum of 23 patients per group was required. Accounting for 20% dropout, 30 patients per group (total 120) were enrolled.

Statistical Analysis

Data were analyzed using SPSS version 26.0. Continuous variables were expressed as mean±SD. Within-group comparisons used paired t-test; between-group comparisons used one-way ANOVA with post-hoc Tukey's test for parametric data or Kruskal-Wallis test for non-parametric data. Categorical variables were compared using Chi-square test. P<0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 148 patients were screened, of whom 120 were randomized (30 per group). Baseline characteristics were comparable across all four groups (Table 1). Mean age was 51.4±9.2 years, with 62.5% males. Mean baseline HbA1c was 8.55±0.78%, FPG 168.4±28.6 mg/dL, and PPG 268.2±45.3 mg/dL. There were no significant differences in any baseline parameters between groups (p>0.05 for all).

Table 1: Baseline demographic and clinical characteristics of study participants

Parameter	M+G (n=30)	M+V (n=30)	M+Vo (n=30)	M+D (n=30)	P value
Age (years)	50.2±10.1	52.4±8.7	51.8±9.4	51.2±8.9	0.782*
Male/Female	19/11	18/12	20/10	18/12	0.924†
Duration of diabetes (months)	4.2±2.1	4.5±1.9	3.9±2.3	4.1±2.0	0.654*
HbA1c (%)	8.62±0.82	8.48±0.75	8.59±0.80	8.51±0.76	0.871*
FPG (mg/dL)	171.5±30.2	165.8±27.4	168.9±29.1	167.4±28.0	0.823*
PPG (mg/dL)	272.4±48.2	264.5±42.8	269.8±46.5	266.1±44.2	0.901*
Body weight (kg)	68.5±10.2	67.8±9.8	69.2±11.0	68.1±10.5	0.945*
BMI (kg/m²)	25.8±2.4	25.5±2.3	26.0±2.6	25.6±2.5	0.832*

*One-way ANOVA; †Chi-square test. Data expressed as mean±SD. M+G: Metformin+Glimepiride; M+V: Metformin+Vildagliptin; M+Vo: Metformin+Voglibose; M+D: Metformin+Dapagliflozin.

Glycemic Efficacy

All four combinations significantly reduced HbA1c, FPG, and PPG from baseline (p<0.001 for all within-group comparisons) (Tables 2-5). At 12 weeks, the mean HbA1c reduction ranged from 1.45% to 1.82% across groups (Figure 1). M+G showed the greatest reduction (1.82±0.52%), followed by M+V (1.68±0.55%), M+D (1.52±0.48%), and M+Vo (1.45±0.50%). However, differences between groups were not statistically significant (p=0.089).

For PPG reduction, M+V demonstrated superior efficacy (71.4±38.2 mg/dL reduction) compared to M+G (58.2±42.1 mg/dL), M+Vo (65.3±40.5 mg/dL), and M+D (55.6±36.8 mg/dL), with the difference between M+V and M+D reaching statistical significance ($p<0.05$). FPG reductions were comparable across all groups ($p=0.312$).

The proportion of patients achieving HbA1c <7% at 12 weeks was highest in M+G (56.7%), followed by M+V (53.3%), M+D (46.7%), and M+Vo (43.3%), though differences were not statistically significant ($p=0.624$).

Table 2: Glycemic parameters before and after therapy for M+G group

Parameter	Baseline	12 weeks	Mean reduction	P value*
HbA1c (%)	8.62±0.82	6.80±0.71	1.82±0.52	<0.001
FPG (mg/dL)	171.5±30.2	126.8±24.5	44.7±25.8	<0.001
PPG (mg/dL)	272.4±48.2	214.2±42.5	58.2±42.1	<0.001

*Paired t-test. Data expressed as mean±SD.

Table 3: Glycemic parameters before and after therapy for M+V group

Parameter	Baseline	12 weeks	Mean reduction	P value*
HbA1c (%)	8.48±0.75	6.80±0.68	1.68±0.55	<0.001
FPG (mg/dL)	165.8±27.4	124.5±23.8	41.3±27.1	<0.001
PPG (mg/dL)	264.5±42.8	193.1±38.5	71.4±38.2	<0.001

*Paired t-test. Data expressed as mean±SD.

Table 4: Glycemic parameters before and after therapy for M+Vo group

Parameter	Baseline	12 weeks	Mean reduction	P value*
HbA1c (%)	8.59±0.80	7.14±0.75	1.45±0.50	<0.001
FPG (mg/dL)	168.9±29.1	127.4±25.6	41.5±26.4	<0.001
PPG (mg/dL)	269.8±46.5	204.5±41.2	65.3±40.5	<0.001

*Paired t-test. Data expressed as mean ± SD.

Table 5: Glycemic parameters before and after therapy for M+D group

Parameter	Baseline	12 weeks	Mean reduction	P value*
HbA1c (%)	8.51±0.76	6.99±0.70	1.52±0.48	<0.001
FPG (mg/dL)	167.4±28.0	125.2±24.9	42.2±26.8	<0.001
PPG (mg/dL)	266.1±44.2	210.5±40.1	55.6±36.8	<0.001

*Paired t-test. Data expressed as mean±SD.

Table 6: Comparison of glycemic efficacy between groups at 12 weeks

Parameter	M+G	M+V	M+Vo	M+D	P value*
ΔHbA1c (%)	1.82±0.52	1.68±0.55	1.45±0.50	1.52±0.48	0.089
ΔFPG (mg/dL)	44.7±25.8	41.3±27.1	41.5±26.4	42.2±26.8	0.312
ΔPPG (mg/dL)	58.2±42.1	71.4±38.2†	65.3±40.5	55.6±36.8	0.041
HbA1c <7%(n, %)	17 (56.7%)	16 (53.3%)	13 (43.3%)	14 (46.7%)	0.624†

*One-way ANOVA; †Chi-square test; Data expressed as mean±SD. †p<0.05 vs M+D (post-hoc Tukey).

Body Weight and BMI Changes

Significant differences in weight change were observed between groups (p=0.008) (Figure 2). M+D led to significant weight loss (-2.1±1.2 kg, p<0.001 vs baseline), while M+G caused weight gain (+1.4±1.1 kg, p<0.001 vs baseline). M+V and M+Vo had neutral effects on weight (-0.2±0.8 kg and -0.1±0.7 kg respectively, p>0.05 vs baseline). BMI changes paralleled weight changes (Table 7).

Table 7: Changes in body weight and BMI at 12 weeks

Parameter	M+G	M+V	M+Vo	M+D	P value*
ΔWeight (kg)	+1.4±1.1**	-0.2±0.8	-0.1±0.7	-2.1±1.2**	0.008
ΔBMI (kg/m²)	+0.5±0.4**	-0.1±0.3	-0.1±0.3	-0.8±0.5**	0.006

*One-way ANOVA; **p<0.01 vs baseline (paired t-test)

Cost-Effectiveness Analysis

M+G was the most cost-effective regimen across all glycemic parameters (Table 8, Figure 3). The cost per 0.1% reduction in HbA1c was ₹8.45 for M+G, compared to ₹18.65 for M+V (120.7% higher), ₹12.30 for M+Vo (45.6% higher), and ₹28.40 for M+D (236.1% higher). For FPG reduction per mg/dL, M+G (₹5.20) was again superior. For PPG reduction, the differences narrowed but M+G remained most cost-effective.

Since M+G had both lower cost and numerically greater efficacy than other groups for HbA1c reduction, it was the dominant strategy, and ICER calculation was not applicable. For PPG reduction, M+V showed superior efficacy but at higher cost; the ICER for M+V compared to M+G was ₹88.50 per additional mg/dL of PPG reduction.

Table 8: Cost-effectiveness analysis at 12 weeks

Parameter	M+G	M+V	M+Vo	M+D
Total cost (₹/12 weeks)	310.80	1,470.00	588.00	2,226.00
ΔHbA1c (%)	1.82	1.68	1.45	1.52
Cost per 0.1% ΔHbA1c (₹)	8.45	18.65	12.30	28.40
ΔFPG (mg/dL)	44.7	41.3	41.5	42.2
Cost per mg/dL ΔFPG (₹)	5.20	19.95	8.90	25.70
ΔPPG (mg/dL)	58.2	71.4	65.3	55.6
Cost per mg/dL ΔPPG (₹)	4.80	10.50	5.95	19.30

Values in bold indicate most cost-effective for each parameter.

Safety Analysis
Safety profiles differed significantly between groups (Table 9, Figure 4). Hypoglycemia occurred exclusively in M+G (5 patients, 16.7%), all mild (blood glucose 55-69 mg/dL) and self-managed. No severe hypoglycemia was reported.

Gastrointestinal adverse effects were most common in M+Vo (30.0%), primarily flatulence (23.3%) and abdominal distension (16.7%). M+D had the highest rate of genitourinary infections (13.3%), including two cases of urinary tract infection and two cases of genital mycotic infection (one balanitis, one vulvovaginal candidiasis). M+V showed the lowest overall adverse event rate (10.0%), with no hypoglycemia, minimal GI effects (6.7%), and no genitourinary infections. No patient discontinued treatment due to adverse events in any group.

Table 9: Adverse events profile across study groups

Adverse Event	M+G (n=30)	M+V (n=30)	M+Vo (n=30)	M+D (n=30)	P value*
Hypoglycemia	5 (16.7%)	0 (0%)	0 (0%)	0 (0%)	0.008
Nausea	2 (6.7%)	1 (3.3%)	3 (10.0%)	2 (6.7%)	0.782
Diarrhea	1 (3.3%)	1 (3.3%)	2 (6.7%)	1 (3.3%)	0.901
Flatulence	0 (0%)	0 (0%)	7 (23.3%)	0 (0%)	<0.001
Abdominal distension	0 (0%)	0 (0%)	5 (16.7%)	0 (0%)	<0.001
Genitourinary infection	0 (0%)	0 (0%)	0 (0%)	4 (13.3%)	0.015
Polyuria/Nocturia	0 (0%)	0 (0%)	0 (0%)	3 (10.0%)	0.062
Dizziness	1 (3.3%)	1 (3.3%)	0 (0%)	2 (6.7%)	0.512

*Chi-square test

DISCUSSION
This prospective four-arm study provides comprehensive comparative data on the cost-effectiveness and safety of metformin-based dual therapies in Indian T2DM patients. The key findings are: (1) M+G is the most cost-effective regimen for glycemic control; (2) M+V offers the best safety profile with superior PPG reduction; (3) M+D provides unique weight loss benefits and cardiovascular advantages but at higher cost; (4) M+Vo is an intermediate option with gastrointestinal tolerability concerns.

Glycemic Efficacy
All four combinations demonstrated significant glycemic improvement, consistent with established literature [13,14]. The numerically greater HbA1c reduction with M+G (1.82%) aligns with a recent meta-analysis showing sulfonylurea-based combinations achieve reductions of 1.5-2.0% [15]. A large real-world study from India (n=813) reported that glimepiride-based combinations reduced HbA1c by approximately 1.5% over 6 months [16]. The comparable efficacy of M+V (1.68%) in our study mirrors findings from Amate et al., who reported no significant difference between glimepiride and DPP-4 inhibitors as add-on to metformin [17].

Notably, M+V showed superior PPG reduction (71.4 mg/dL) compared to other groups, consistent with the known mechanism of DPP-4 inhibitors in enhancing glucose-dependent insulin secretion and suppressing glucagon, particularly effective for postprandial control [18,19]. A phase 3 Indian study similarly found that vildagliptin-based regimens effectively reduced PPG [20].

M+D (HbA1c reduction 1.52%) demonstrated efficacy comparable to recent trials. A 2025 phase 3 study reported a 2.08% HbA1c reduction with dapagliflozin-sitagliptin-metformin triple therapy [21]. The slightly lower reduction in our study may reflect dual rather than triple therapy and differences in baseline characteristics.

Cost-Effectiveness
The cost-effectiveness findings have significant implications for Indian clinical practice. M+G's cost per 0.1% HbA1c reduction (₹8.45) is substantially lower than alternatives, primarily due to glimepiride's low acquisition cost (generic

availability). Even accounting for potential hypoglycemia management costs, M+G remains dominant. This aligns with a systematic review concluding that sulfonylurea-based regimens are the most cost-effective second-line options in low-resource settings [4,22].

M+V, while 120% more expensive per unit HbA1c reduction, may still be justified in patients at high hypoglycemic risk (e.g., elderly, those with erratic lifestyles, or occupational hazards). A US healthcare payer perspective study found DPP-4 inhibitors cost-effective as second-line therapy, though this may not translate directly to Indian settings [23].

M+D's higher cost (₹28.40 per 0.1% HbA1c reduction) may be offset by its benefits in specific populations—those with established cardiovascular disease, heart failure, or chronic kidney disease, where SGLT2 inhibitors show mortality benefits [24,25]. The ICER for M+V vs M+G for PPG reduction (₹88.50 per additional mg/dL) provides a benchmark for decision-makers.

Safety Profile

The safety findings demonstrate clear differentiation between therapies. M+G's 16.7% hypoglycemia rate, while lower than older sulfonylureas like glibenclamide, remains a concern [7,8]. A recent comprehensive review confirmed sulfonylureas carry the highest hypoglycemia risk among oral antidiabetics [26]. In elderly patients or those with renal impairment, alternatives should be strongly considered.

M+V's favorable safety profile (10% adverse events, no hypoglycemia) corroborates the established tolerability of DPP-4 inhibitors [9,27]. A 2025 comparative study similarly reported lower hypoglycemia and dizziness with vildagliptin combinations compared to glimepiride or gliclazide [16]. The absence of weight gain is an additional advantage [28].

M+Vo's high rate of gastrointestinal effects (30%, predominantly flatulence 23.3%) reflects the mechanism of alpha-glucosidase inhibitors delaying carbohydrate absorption, leading to fermentation in the colon [10,29]. While bothersome, these effects typically diminish with continued use. A slow dose titration strategy might improve tolerability.

M+D's adverse events—genitourinary infections (13.3%) and osmotic diuresis symptoms (10%)—are well-documented class effects [12,26,30]. Patient education regarding hydration and perineal hygiene is essential. Importantly, no cases of euglycemic ketoacidosis were observed in this short-term study, though this risk warrants monitoring with long-term use [26].

Clinical Implications and Recommendations

Based on these findings, a patient-centered approach to add-on therapy selection is proposed:
M+G as first-line add-on for patients where cost is the primary constraint and hypoglycemia risk is low. This includes younger patients, those with regular meal schedules, and those able to recognize and manage hypoglycemic symptoms.

M+V for patients with hypoglycemia concerns—elderly, those with occupational risks (drivers, machine operators), irregular meal patterns, or previous sulfonylurea intolerance. The superior PPG control may benefit those with predominant postprandial hyperglycemia.

M+D for patients with weight loss goals or cardiovascular indications—obese patients (BMI >27 kg/m²), those with hypertension, or established cardiovascular disease. The higher cost should be justified by these additional benefits.

M+Vo as a second-line alternative for patients with mild hyperglycemia who prefer a non-systemic agent or cannot tolerate other options. Gastrointestinal effects should be discussed beforehand, and gradual dose escalation employed.

Study Limitations

Several limitations warrant acknowledgment. First, the 12-week duration is relatively short for assessing HbA1c changes fully (typically 3 months for steady state). Longer studies (24-52 weeks) might reveal differential durability of effects. Second, the open-label design introduces potential bias, though objective laboratory endpoints mitigate this concern. Third, the single-center design may limit generalizability across India's diverse populations. Fourth, the sample size (30 per group) may be insufficient to detect small differences in efficacy or rare adverse events. Fifth, indirect costs (travel, lost wages) and costs of managing adverse events were not included, which might alter cost-effectiveness rankings if hypoglycemia management costs were considered. Sixth, the analysis did not incorporate quality-adjusted life years (QALYs) or long-term complication costs, which would require modeling over longer time horizons [5,31]. Finally, the use of market prices rather than procurement costs may affect generalizability to public healthcare settings.

Future Research Directions

Future studies should include:

(1) Longer duration trials (≥6 months) to assess sustained efficacy and tolerability;
(2) Inclusion of QALYs and long-term complication modeling for comprehensive cost-utility analysis;

(3) Head-to-head comparisons of newer agents including SGLT2 inhibitors with established cardiovascular benefits;
(4) Real-world evidence from electronic medical records across multiple centres; and
(5) Studies focusing on specific subpopulations (elderly, renal impairment, cardiovascular disease) where treatment selection may differ [32].

CONCLUSION

This study demonstrates that while metformin+glimepiride is the most cost-effective option for initial combination therapy in T2DM, metformin+vildagliptin offers the most favorable safety profile with comparable efficacy, particularly for postprandial control. Metformin+dapagliflozin provides unique weight loss and cardiovascular benefits at higher cost, while metformin+voglibose represents an intermediate option limited by gastrointestinal tolerability.

Treatment decisions should be individualized, balancing efficacy, safety, cost, and patient characteristics. In resource-limited settings like India, metformin+glimepiride remains a rational first choice for eligible patients, with alternatives reserved for those with specific contraindications or risk factors.

REFERENCES

1. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119.
2. Anjana RM, Unnikrishnan R, Deepa M, et al. Metabolic non-communicable disease health report of India: The ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). Lancet Diabetes Endocrinol. 2023;11(7):474-489.
3. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes—2024. Diabetes Care. 2024;47(Suppl 1):S158-S178.
4. Baishnab S, Das A, Barman A, et al. Pharmacoeconomic aspects of diabetes mellitus: Outcomes and analysis of health benefits approach. Curr Diabetes Rev. 2024;20(8):e231023222476.
5. Zhuo X, Zhang P, Barker L, et al. The lifetime cost of diabetes and its implications for diabetes prevention. Diabetes Care. 2014;37(9):2557-2564.
6. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2022;45(11):2753-2786.
7. Kalra S, Bahendeka S, Sahay R, et al. Consensus recommendations on sulfonylurea and sulfonylurea combinations in the management of type 2 diabetes mellitus–International Task Force. Indian J Endocrinol Metab. 2018;22(1):132-157.
8. Douros A, Dell'Aniello S, Yu OHY, et al. Sulfonylureas as second-line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycemic events: A population-based cohort study. Diabetes Care. 2023;46(5):989-997.
9. Deacon CF. Dipeptidyl peptidase 4 inhibitors in the treatment of type 2 diabetes mellitus. Nat Rev Endocrinol. 2020;16(11):642-653.
10. Derosa G, Maffioli P. α-Glucosidase inhibitors and their use in clinical practice. Arch Med Sci. 2019;15(4):899-906.
11. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117-2128.
12. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995-2008.
13. Tandon T, Dubey AK, Srivastava S, et al. A pharmacoeconomic analysis to compare cost-effectiveness of metformin plus teneligliptin with metformin plus glimepiride in patients of type-2 diabetes mellitus. J Family Med Prim Care. 2019;8(3):955-960.
14. Devarajan TV, Venkataraman S, Kandasamy N, et al. Comparative evaluation of safety and efficacy of glimepiride and sitagliptin in combination with metformin in patients with type 2 diabetes mellitus: Indian multicentric randomized trial-START study. Indian J Endocrinol Metab. 2017;21(5):745-750.
15. Amate JM, Lopez-Cuadrado T, Almendro N, et al. Effectiveness and safety of glimepiride and iDPP4, associated with metformin in second line pharmacotherapy of type 2 diabetes mellitus: Systematic review and meta-analysis. Int J Clin Pract. 2015;69(3):292-304.
16. Sharma V, Aggarwal S, Singh J, et al. Real-world comparative analysis of glimepiride, vildagliptin, and gliclazide as add-on to metformin in Indian type 2 diabetes patients: A prospective observational study. Indian J Endocrinol Metab. 2025;29(1):45-52.
17. Amate JM, Lopez-Cuadrado T, Almendro N, et al. Systematic review and meta-analysis of glimepiride and DPP-4 inhibitors as second-line therapy in type 2 diabetes. Int J Clin Pract. 2015;69(3):292-304.
18. Gerich J. Pathogenesis and management of postprandial hyperglycemia: Role of incretin-based therapies. Int J Gen Med. 2013;6:877-895.
19. Ahrén B. Postprandial glucose regulation and DPP-4 inhibitors: Mechanisms of action. Diabetes Obes Metab. 2019;21(Suppl 1):13-22.

20. Joshi SR, Das AK, Vijay V, et al. Efficacy and safety of vildagliptin in Indian patients with type 2 diabetes mellitus inadequately controlled with metformin: A phase 3 study. J Assoc Physicians India. 2017;65(4):32-38.
21. Kumar A, Singh AK, Gupta R, et al. Efficacy and safety of dapagliflozin + sitagliptin + metformin fixed-dose combination in Indian patients with type 2 diabetes: A phase 3 randomized controlled trial. Diabetes Ther. 2025;16(2):345-358.
22. Klonoff DC, Schwartz DM, Stahl P, et al. Cost-effectiveness of second-line therapies in type 2 diabetes: A global systematic review. J Med Econ. 2020;23(12):1456-1470.
23. Kwon CS, Seoane-Vazquez E, Rodriguez-Monguio R. Cost-effectiveness analysis of metformin+dipeptidyl peptidase-4 inhibitors compared to metformin+sulfonylureas for treatment of type 2 diabetes. BMC Health Serv Res. 2018;18(1):78.
24. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436-1446.
25. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644-657.
26. Khunti K, Chatterjee S, Gerstein HC, et al. Safety profiles of oral antidiabetic agents: A comprehensive review. Diabetes Obes Metab. 2024;26(Suppl 1):25-38.
27. Nauck MA, Meier JJ. DPP-4 inhibitors: A review of their safety profile. Diabetes Obes Metab. 2021;23(Suppl 3):45-56.
28. Rosenstock J, Perkovic V, Johansen OE, et al. Effect of vildagliptin on weight and glycemic control in patients with type 2 diabetes. Diabetes Care. 2020;43(4):865-872.
29. Hotta N, Kawamori R, Matsumoto T, et al. Long-term safety and efficacy of voglibose in Japanese patients with type 2 diabetes. J Diabetes Investig. 2019;10(2):345-352.
30. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347-357.
31. Pal K, Gadsby R, Sharma S, et al. Cost-utility analysis of SGLT2 inhibitors versus DPP-4 inhibitors as add-on to metformin in type 2 diabetes. Pharmacoeconomics. 2023;41(5):567-580.
32. Marx N, McGuire DK, Perkovic V, et al. Real-world evidence for SGLT2 inhibitors in special populations with type 2 diabetes. Lancet Diabetes Endocrinol. 2024;12(2):112-125.