



Real-world glycemic and cardiometabolic outcomes with Empagliflozin-Linagliptin add-on to Metformin: Insights from clinician experience

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Abstract

Background: Type 2 diabetes mellitus (T2DM) often requires combination therapy, and the empagliflozin-linagliptin combination provides complementary glycaemic and metabolic benefits. This study aimed to assess healthcare practitioners' (HCPs) perspectives on the glycaemic efficacy, cardiometabolic benefits, and overall clinical utility of empagliflozin-linagliptin added to metformin in Indian patients with T2DM.

Methods: This cross-sectional, questionnaire-based survey assessed HCP-reported clinical experience with empagliflozin-linagliptin added to metformin in routine T2DM management in India. A structured 16-item online questionnaire collected data on the last 10 patients treated, evaluating glycated haemoglobin (HbA1c), overall glycaemic improvement, postprandial glucose control, insulin sensitivity, cardiometabolic outcomes, and trends in diabetes-related hospitalisations. Data were analysed descriptively, with categorical variables summarised as frequencies and percentages.

Results: A total of 377 HCPs participated. Among HCPs, 45.36% reported that 6–10 of their last 10 treated patients achieved a $\geq 1\%$ HbA1c reduction within 3 months, while 42.44% reported improvement in glycaemic control within 3 months. Improvement in insulin sensitivity among 6–10 treated patients was reported by 42.97% of HCPs. Moderate and significant improvement in postprandial glucose control were reported by 48.01% and 36.34% of HCPs, respectively. Blood pressure improvement among 3–5 treated patients was reported by 35.01% of HCPs, while 45.36% reported moderate improvement in lipid profiles. Compared with other SGLT2 inhibitor/DPP-4 inhibitor/metformin regimens, 41.38% of HCPs considered the combination more protective for cardiovascular outcomes. Regarding diabetes-related hospitalisations, 46.42% of HCPs reported a moderate reduction.

Conclusion: Empagliflozin-linagliptin add-on to metformin is effective, well-tolerated, and improves glycaemic, metabolic, and cardiorenal outcomes in Indian T2DM patients, supporting its use as a valuable option in routine clinical practice.

Keywords: Type 2 diabetes mellitus, Empagliflozin, Linagliptin, Metformin, cardiorenal, glycated haemoglobin, healthcare practitioners

Introduction

Type 2 diabetes mellitus (T2DM) is a non-autoimmune heterogeneous disease characterised by insulin resistance and metabolic syndrome [1]. It represents a significant and growing public health challenge worldwide, with a particularly high burden in India. India is often called the “diabetes capital of the world,” currently hosting approximately 77 million people with diabetes, a number projected to rise to over 100 million by 2030 due to rapid urbanisation, lifestyle changes, and genetic predisposition [2, 3]. The prevalence of T2DM in India continues to increase, compounded by the early age of onset compared to Western populations and high rates of undiagnosed disease, which pose major challenges for timely diagnosis and management [4, 5]. This escalating epidemic substantially strains healthcare resources, exacerbates cardiovascular risk, and significantly contributes to morbidity and mortality nationwide [6].

Lifestyle interventions-including dietary modification, regular physical activity, and stress management-complement pharmacological therapy and contribute to more effective disease management [7]. Metformin remains the cornerstone of T2DM management due to its well-

established efficacy, favourable safety profile, and cost-effectiveness. However, despite initial glycaemic control, its long-term effectiveness may decline with progressive β -cell dysfunction and increasing insulin resistance, thereby necessitating escalation to combination therapy [8]. While metformin remains the preferred first-line agent, clinical guidelines recommend combining it with additional drug classes, including sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP4) inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and glucagon-like peptide-1 receptor agonists to achieve enhanced glycemic control and improved overall clinical outcomes [7, 9].

The combined use of SGLT2 inhibitors and DPP4 inhibitors has emerged as an attractive option due to their complementary mechanisms of action and favourable safety profiles [10]. Sodium-glucose cotransporter-2 inhibitors promote glycosuria, leading to glucose lowering and weight reduction, as well as cardiovascular and renal benefits demonstrated in clinical trials [10, 11]. Dipeptidyl peptidase-4 inhibitors enhance endogenous incretin levels, improving β -cell function and insulin secretion with minimal hypoglycaemia risk [10]. The empagliflozin-linagliptin fixed-dose combination with metformin has shown promising

efficacy in improving glycaemic control while reducing pill burden and improving adherence ^[12]. These agents target distinct yet complementary pathways, offering a mechanistic rationale for their combination in T2DM management ^[13].

Real-world evidence from Indian clinical practice demonstrates that the empagliflozin-linagliptin combination added to metformin offers significant glycaemic and cardiometabolic benefits with a favourable safety profile. Retrospective studies report reductions in glycated haemoglobin (HbA1c), weight loss, and improvements in blood pressure (BP), without increased risk of hypoglycaemia or genitourinary infections ^[14]. These findings align with global data and reinforce the combination's effectiveness and tolerability in diverse Indian populations facing unique disease characteristics and treatment challenges. The present study offers insights from healthcare practitioners (HCPs) on the glycaemic and cardiometabolic outcomes of empagliflozin-linagliptin as an add-on to metformin in Indian patients with T2DM, reflecting practical treatment responses and therapeutic effectiveness in routine clinical practice.

Methods

Study design

This was a cross-sectional, questionnaire-based survey of healthcare practitioners (HCPs) in India. The survey assessed HCP-reported clinical experience with empagliflozin-linagliptin added to metformin in routine T2DM management. All findings were derived from HCP responses to a structured questionnaire.

Study questionnaire

The study questionnaire was developed based on clinical guidelines, published literature, and expert opinion. It comprised a total of 35 questions, of which 16 specifically focused on HCPs' experiences regarding patient characteristics, efficacy outcomes, cardiometabolic benefits, renal effects, and weight and hospitalisation outcomes in patients with T2DM treated with the empagliflozin-linagliptin combination as an add-on to metformin. These areas included patient demographics; glycaemic control, including improvements in HbA1c and fasting blood glucose; cardiovascular and renal outcomes; weight changes; and diabetes-related hospitalisations. The questionnaire specifically focused on the last 10 patients treated by each HCP.

Study procedure

The study protocol, informed consent form, and digital questionnaire were shared with HCP via a secure online link. Participation was voluntary, and no patient-identifiable information was collected. Completed questionnaires were reviewed for completeness and consistency before being included in the final analysis. The study protocol was approved by an Independent Ethics Committee (IEC No: CIEC/2025/056). Written informed consent was obtained from all participating HCP before completion of the surveillance questionnaire.

Data analysis

Responses to questions were entered into Microsoft Excel. Descriptive analysis was performed, and the results were presented as frequencies and percentages.

Results

Clinical Efficacy outcomes of empagliflozin + linagliptin add-on therapy to metformin

A total of 377 HCPs participated in the study and reported their clinical experience based on the last 10 patients treated with empagliflozin and linagliptin as add-on therapy to metformin. Nearly half of the HCPs (45.36%) reported that 6-10 of their patients achieved a significant HbA1c reduction of $\geq 1\%$ within 3 months, while 6.10% of HCPs observed no reduction. Regarding the time to improvement in glycaemic control after initiation of empagliflozin + linagliptin add-on therapy to metformin, 42.44% of HCPs reported improvement within 3 months, while 33.16% reported improvement within 1 month and 22.81% within 6 months. Compared with other oral antidiabetic regimens, 50.66% of HCPs considered the combination more effective for HbA1c reduction, and 5.84% were unsure.

Improvements in insulin sensitivity were observed in 6-10 patients by 42.97% of HCPs, while 17.51% of HCPs reported improvements in 1-2 patients. Regarding postprandial glucose control, 48.01% of HCPs reported moderate improvement, followed by significant improvement reported by 36.34% of HCPs. Among the HCPs, 46.42% indicated that the hypoglycaemia risk with this combination appeared significantly lower, while 37.14% reported it to be moderately lower compared with other oral antidiabetic therapies. With respect to overall effectiveness in T2DM management, 57.29% of HCPs rated the therapy as moderately effective, whereas 36.34% rated it as highly effective (Table 1).

Table 1: Clinical efficacy outcomes of empagliflozin + linagliptin add-on therapy to metformin

Parameters	Response of HCPs (N=377)
Patients achieving $\geq 1\%$ HbA1c reduction within 3 months	
1-2 patients	47 (12.47)
3-5 patients	136 (36.07)
6-10 patients	171 (45.36)
None	23 (6.10)
Time to improvement in glycemic control after initiating empagliflozin + linagliptin add-on to metformin	
Within 1 month	125 (33.16)
Within 3 months	160 (42.44)
Within 6 months	86 (22.81)
No significant improvement observed	6 (1.59)
Comparative HbA1c reduction versus other oral antidiabetic regimens	
More effective	191 (50.66)
Equally effective	135 (35.81)

Less effective	29 (7.69)
Not sure	22 (5.84)
Number of patients showing improvement in insulin sensitivity	
1-2 patients	38 (10.08)
3-5 patients	111 (29.44)
6-10 patients	162 (42.97)
1-2 patients	66 (17.51)
Benefits of empagliflozin + linagliptin add-on to metformin in postprandial glucose control	
Significant improvement	137 (36.34)
Moderate improvement	181 (48.01)
No major impact	47 (12.47)
Not sure	12 (3.18)
Relative hypoglycaemia risk versus other oral antidiabetic therapies	
Significantly lower	175 (46.42)
Moderately lower	140 (37.14)
No difference	51 (13.53)
Higher risk	11 (2.92)
Overall effectiveness in the management of T2DM	
Highly effective	137 (36.34)
Moderately effective	216 (57.29)
Slightly effective	18 (4.77)
Not effective	6 (1.59)
Data represented as n (%).	
HbA1c, glycated haemoglobin; HCPs, healthcare professionals; T2DM, type 2 diabetes mellitus.	

Cardiovascular comorbidities and prior therapy patterns among patients on empagliflozin-linagliptin add-on to metformin

The majority of patients receiving empagliflozin and linagliptin as an add-on to metformin had pre-existing cardiovascular disease, with 39.52% of HCPs reporting 1-2 patients affected, followed by 32.36% reporting 3-5 patients. Regarding

heart failure (HF) history, 53.85% of physicians reported having no prior episodes, while 28.65% of HCPs reported 1-2 patients with a history of HF. With respect to prior therapy, 30.77% of HCPs reported that 3-5 patients had previously been on dual therapy before switching to empagliflozin and linagliptin, whereas 16.45% of HCPs indicated that none of their patients had prior dual therapy experience (Table 2).

Table 2: Cardiovascular profile and prior therapy patterns among patients receiving Empagliflozin + Linagliptin

Parameters	Response of HCPs (N=377)
The number of patients who had pre-existing cardiovascular disease.	
1-2 patients	149 (39.52)
3-5 patients	122 (32.36)
6-10 patients	35 (9.28)
None	71 (18.83)
The number of patients who had a history of heart failure.	
1-2 patients	108 (28.65)
3-5 patients	48 (12.73)
6-10 patients	18 (4.77)
None	203 (53.85)
Number of patients previously on dual therapy before initiation of empagliflozin + linagliptin as an add-on to metformin	
1-2 patients	85 (22.55)
3-5 patients	116 (30.77)
6-10 patients	114 (30.24)
None	62 (16.45)
Data represented as n (%).	
HCPs, healthcare professionals.	

Cardiometabolic outcomes and renal monitoring with empagliflozin + linagliptin add-on therapy

Improvement in BP was reported in 3-5 patients by 35.01% of HCPs, followed by 29.44% reporting improvement in 1-2 patients. In patients with both diabetes and HF, the combination was considered moderately effective by 49.87% of HCPs, while 31.03% rated it as very effective. Regarding lipid profiles, 45.36% of HCPs reported moderate improvement, with significant improvement reported

By 14.32% of HCPs. Compared with other SGLT2/DPP4/Metformin regimens for cardiovascular protection, 41.38% of HCPs found the combination more protective, and 40.85% considered it equally protective. For renal function monitoring, 37.14% of HCPs reported performing it every 6 months, whereas 31.83% monitored every 3 months. In terms of long-term impact on diabetes-related complications, comparable proportions of HCPs reported moderate reduction (29.89%), significant reduction (29.79%), and no significant impact (29.77%) (Table 3).

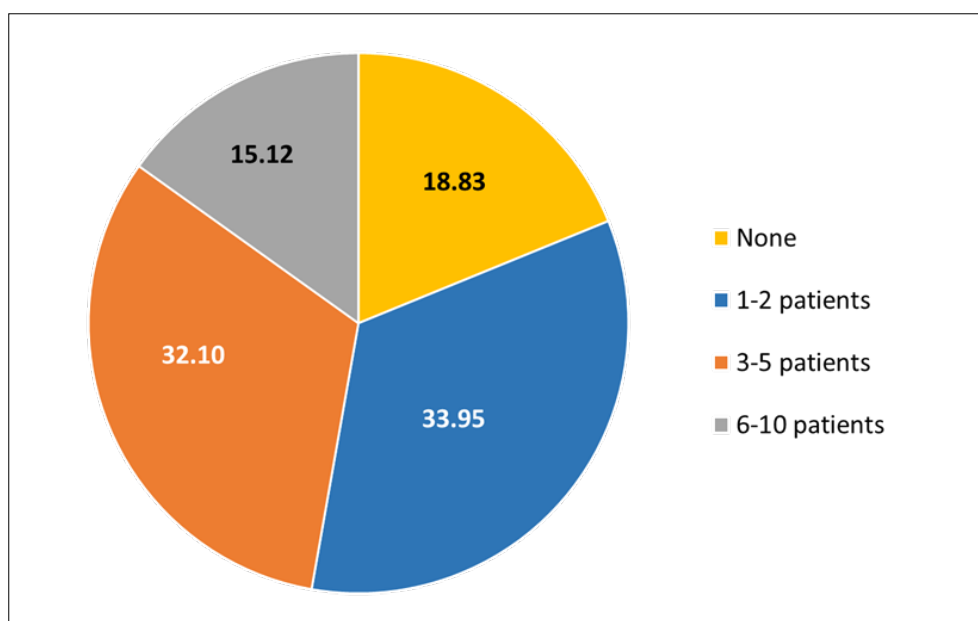
Table 3: Cardiometabolic outcomes and renal monitoring in patients receiving empagliflozin + linagliptin add-on to metformin

Parameters	Response of HCPs (N=377)
Improvement in blood pressure among the last 10 patients	
1-2 patients	111 (29.44)
3-5 patients	132 (35.01)
6-10 patients	100 (26.53)
None	34 (9.02)
Effectiveness in heart failure symptom improvement in patients with diabetes and heart failure	
Very effective	117 (31.03)
Moderately effective	188 (49.87)
No noticeable improvement	26 (6.90)
Not sure	46 (12.20)
Impact on lipid profiles	
Significant improvement	54 (14.32)
Moderate improvement	171 (45.36)
No major impact	98 (25.99)
Not sure	54 (14.32)
Cardiovascular protection vs other SGLT2/DPP4/Metformin regimens	
More protective	156 (41.38)
Equally protective	154 (40.85)
Less protective	37 (9.81)
Not sure	30 (7.96)
Frequency of renal function monitoring compared to other diabetes medications	
Yes, every 3 months	120 (31.83)
Yes, every 6 months	140 (37.14)
No change in monitoring frequency	73 (19.36)
Not sure	44 (11.67)
Long-term impact on diabetes-related complications	
Significantly reduces complications	101 (29.79)
Moderately reduces complications	173 (49.89)
No significant impact	67 (20.77)
Not sure	36 (10.55)
Data represented as n (%).	
DPP4, dipeptidyl peptidase 4; HCPs, healthcare professionals; SGLT2, sodium-glucose cotransporter 2.	

Impact of empagliflozin-linagliptin add-on therapy to metformin on weight loss and hospital admissions

Among the last 10 patients treated with the empagliflozin and linagliptin combination as an add-on to metformin, 33.95% of HCPs reported that 1-2 patients achieved a weight

Reduction of >2 kg within 3 months, whereas 18.83% indicated that none of their patients had significant weight loss (Figure 1). Furthermore, a moderate reduction in hospital admissions related to diabetes complications was observed by 46.42% of HCPs, while 22.28% reported no major impact (Figure 2).

**Fig 1:** Proportion of patients reporting ≥ 2 kg weight loss within 3 months on empagliflozin + linagliptin add-on to metformin

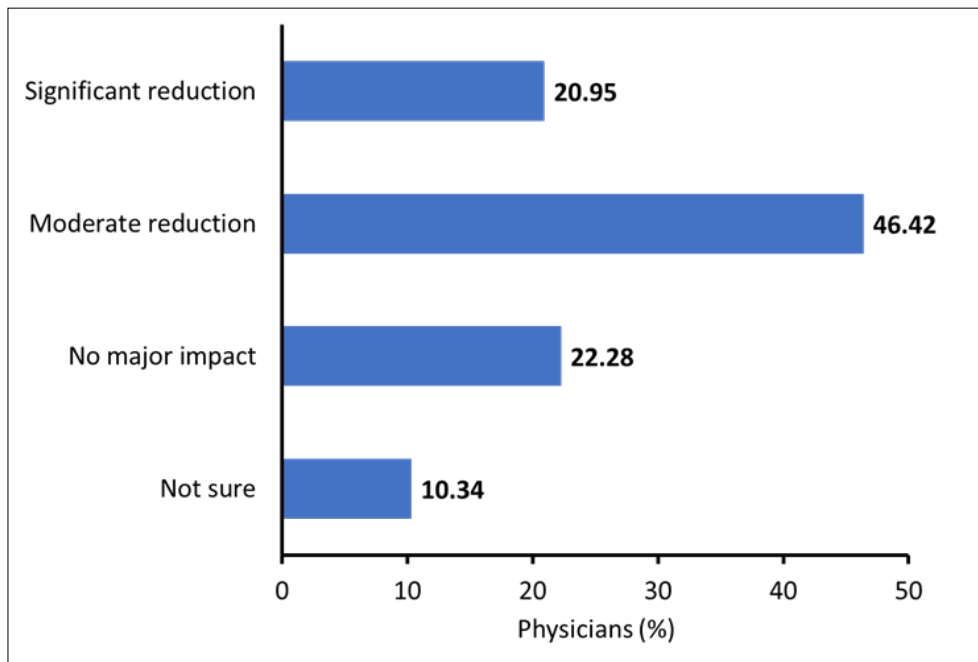


Fig 2: Impact of empagliflozin + linagliptin add-on to metformin on hospital admissions due to diabetes-related complications

Discussion

The present study offers insights into the clinical use of empagliflozin-linagliptin as an add-on to metformin, focusing on glycaemic responses, cardio-renal benefits, weight outcomes, and hospitalisation patterns as reported by HCPs managing Indian patients with T2DM. Of the 377 HCPs, nearly half reported that 6-10 patients achieved $\geq 1\%$ HbA1c reduction with improved glycemic control within 3 months of empagliflozin + linagliptin add-on therapy to metformin, and considered the combination more effective than other oral regimens for HbA1c lowering. These observations are supported by Phase III trial data where empagliflozin (10/25 mg)/linagliptin (5 mg) added to metformin produced greater HbA1c reductions (1.08-1.24%) versus individual components (0.68-0.81%) over 24 weeks, with 55-62% achieving HbA1c $< 7\%$ compared to 36-42% on monotherapy. This faster and superior glucose-lowering effect-visible by week 24, similar to the ~ 3 -month improvements reported by HCPs- reinforces the combination's enhanced HbA1c-reduction potential [15]. Improvements in insulin sensitivity were reported by HCPs, with most also noting moderate to significant enhancements in postprandial glucose control. These findings align with the prospective randomised controlled trial by Jung *et al.*, where empagliflozin (10-25 mg) + linagliptin (5 mg) add-on to metformin demonstrated improved vascular function and insulin sensitivity over 12 weeks, unlike metformin + insulin glargine. This supports HCP observations and reinforces the expected postprandial benefits arising from DPP-4i + SGLT2i synergy [16]. Among the HCP cohort, the majority perceived a lower risk of hypoglycaemia with this combination compared with other oral antidiabetic therapies, which is consistent with double-masked trial data where linagliptin 5 mg versus placebo added to empagliflozin (10 mg or 25 mg) plus metformin showed hypoglycaemia in $< 2\%$ of cases, similar to placebo, indicating tolerable glycaemic control without increased risk [17]. Additionally, most HCPs rated the regimen as moderately to highly effective in overall T2DM management, reflecting favourable clinical experience and acceptance in routine practice.

In the present study, patients receiving empagliflozin and linagliptin as add-on therapy to metformin predominantly had pre-existing cardiovascular disease. A similar finding was observed by Sharifuzzaman *et al.* in Bangladesh, where hypertension was the most common comorbidity among patients with diabetes, followed by dyslipidemia and chronic kidney disease [18]. With respect to HF history, more than half of the patients had no previous episodes, although a proportion were reported to have a known history of HF. This pattern is in line with an Indian meta-analysis that reported a pooled cardiovascular disease prevalence of 21.1% among individuals with T2DM [19]. About 30.77% of HCPs reported that 3-5 patients had previously been on dual therapy before switching to empagliflozin-linagliptin. This aligns with a real-world observational study by Inagaki *et al.*, where $\sim 25\%$ of patients transitioned from DPP-4 inhibitor-based dual therapy and experienced significant HbA1c reductions after the switch [20]. A study by Aufer *et al.* reported that patients receiving empagliflozin-linagliptin combination therapy for uncontrolled T2DM experienced reductions in systolic and diastolic BP of 11.09 mmHg and 4.41 mmHg, respectively ($p < 0.001$) [21]. Similarly, in the present study, HCPs observed improvements in BP among their patients, and the combination was rated as very to moderately effective in those with both diabetes and HF. Significant to moderate improvements in lipid profiles were observed in patients. Compared with other SGLT2i/DPP-4i/metformin regimens, HCPs considered the empagliflozin-linagliptin combination more or equally protective for cardiovascular outcomes. These findings are consistent with DeFronzo *et al.*, who reported that empagliflozin/linagliptin add-on to metformin led to moderate increases in HDL-C ($+3.1$ mg/dL vs. $+1.2$ mg/dL with linagliptin alone). At the same time, LDL-C and triglycerides remained largely unchanged [15].

In the current study, some HCPs reported monitoring renal function every 6 months, while others did so every 3 months. Regarding the long-term impact on diabetes-related complications, a comparable proportion of HCPs observed moderate to significant reductions (29.79%). These

outcomes correspond to pooled 52-week analyses, which demonstrated low hypoglycaemia rates (1.1-2.2%), stable eGFR, and reduced albuminuria, without HF or limb events, indicating moderate long-term microvascular and macrovascular benefits with approximately 30% relative risk reduction in relevant subsets ^[22]. Furthermore, HCPs observed a moderate reduction in hospital admissions related to diabetes complications. These findings align with prior evidence from a post-marketing surveillance study of empagliflozin/linagliptin FDC, which demonstrated moderate reductions in diabetes-related hospitalisations, with an approximate 46% relative risk decrease attributed to improved glycemic and BP control ^[20].

A key strength of this study is its ability to capture clinician experience with empagliflozin-linagliptin as an add-on to metformin in Indian patients with T2DM, offering meaningful insights into prescribing decisions, observed glycaemic and cardiometabolic response, and treatment tolerability beyond the limitations of controlled trial environments. The findings additionally provide a practical perspective on real-time therapeutic effectiveness and clinical utility in routine practice. However, the study is limited by its dependence on physician recall and lack of long-term follow-up, which restricts the ability to quantify the magnitude of clinical benefit or assess the durability of response over time. Larger, prospective studies with extended monitoring and objective metabolic endpoints are warranted to substantiate these early observations and strengthen evidence for broader application in real-world settings.

Conclusion

This study demonstrates that empagliflozin-linagliptin, when added to metformin, is effective and well-tolerated in routine clinical practice for Indian patients with T2DM. Healthcare practitioners reported improvements in HbA1c, postprandial control, BP, lipid profile, and overall cardiometabolic outcomes, with supportive renal safety and fewer diabetes-related hospitalisations. These insights reinforce the combination's clinical value and its role as a practical treatment option in diabetes management. However, larger long-term studies are needed to confirm these findings.

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