



(RESEARCH ARTICLE)



EFFECTIVENESS OF EMPAGLIFLOZIN AND LINAGLIPTIN AS ADD-ON THERAPY TO METFORMIN IN TYPE 2 DIABETES: PHYSICIAN INSIGHTS FROM SOUTHERN INDIA

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World Journal of Advanced Research and Reviews, 2026, 32(01), 347–355

Publication history: Received on 11 August 2026; revised on 29 September 2026; accepted on 01 October 2026

Article DOI: <https://doi.org/10.30574/wjarr.2026.32.1.2448>

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a chronic global health burden associated with cardiovascular (CV) and renal complications. This study aimed to evaluate real-world efficacy, cardiometabolic outcomes, and long-term outcomes of the empagliflozin + linagliptin add-on therapy to metformin in T2DM patients.

Methods: This questionnaire-based study included physicians from southern India. A 17-item questionnaire assessed efficacy, cardiometabolic outcomes, and the long-term outcome of this combination add-on therapy, focusing on the last 10 patients.

Results: A total of 206 physicians from southern India participated. Physicians reported that 1-2 patients had pre-existing cardiovascular disease (37.86%). Additionally, most patients were previously on dual therapy before switching to this combination (32.04%). A significant reduction ($\geq 1\%$) in glycated haemoglobin (HbA1c) (47.09%) and improved glycaemic control (46.12%) were observed in most patients within 3 months. Compared with other regimens, this combination was more effective in HbA1c reduction (49.51%). Moderate improvements in postprandial glucose control (50.49%) and insulin sensitivity (42.23%) were also reported. Weight loss (> 2 kg) within 3 months (33.50%) and improved blood pressure (32.04%) were observed in some patients. In patients with T2DM and heart failure, 45.63% reported moderate symptom improvement, particularly for lipid profiles. Compared to similar regimens, this add-on therapy provided more or equal CV protection (40.78%). Renal function was monitored more frequently by 37.38% of physicians every 6 months. Moderate reductions were observed in long-term diabetes-related complications (43.69%) and associated hospitalisations (48.06%).

Conclusion: The empagliflozin + linagliptin add-on therapy to metformin was reported to improve glycaemic and cardiometabolic outcomes and reduce long-term diabetes related complications.

Keywords: Glycaemic efficacy, Cardiometabolic outcomes, Long-term impact, Type 2 diabetes mellitus, Therapy.

1 INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterised by inadequate insulin secretion and increasing insulin resistance [1]. According to the International Diabetes Federation, it accounts for over 90% of diabetes cases. The global diabetes burden is projected to increase by 46%, from 589 million in 2025 to 853 million by 2050 [2]. In India, diabetes affects 89.8 million individuals (10.5%), and the numbers are expected to rise to 156.7 million by 2050 [3]. Pooled estimates indicate a higher prevalence of diabetes in South India compared to North India, along with concomitant comorbidities [4].

Chronic hyperglycaemia leads to multi-organ damage, particularly causing microvascular (retinopathy, nephropathy, neuropathy), and macrovascular complications. These complications are associated with T2DM-associated mortality [5]. Optimal glycaemic control reduces the risk of micro and macrovascular complications and becomes the cornerstone of T2DM management [6].

The standard therapy for T2DM is typically metformin monotherapy or a combination, depending on the patient's tolerability and contraindications. In patients with a baseline glycated haemoglobin (HbA1c) $\geq 9\%$ and those unable to meet treatment goals with monotherapy alone, the American Diabetes Association and the European Association for the Study of Diabetes recommend initiating combination therapy [7]. Co-existing comorbidities and genetic factors in Indian patients with T2DM contribute to a reduced response to metformin. This significantly increases the risk of long-term diabetes complications, emphasising the need for fixed dose combinations (FDCs) [8].

Novel drug classes such as sodium–glucose cotransporter-2 (SGLT-2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors are gaining recognition for improving glycaemic control and cardiovascular (CV) outcomes. In clinical trials, empagliflozin has exhibited CV and renal protective properties [9]. Additionally, in patients with declining renal function, linagliptin may be an effective alternative for improving glycaemic control [10].

Several Indian studies have reported empagliflozin and linagliptin (empagliflozin + linagliptin) FDCs to be well-tolerated, effective in HbA1c reduction, and improve renal function when added to metformin. This reinforces the effectiveness of the add-on therapy in improving both glycaemic and non-glycaemic outcomes in the diverse Indian population with T2DM [11]. The present study aims to evaluate the efficacy, cardiometabolic outcomes, and long-term effects of empagliflozin + linagliptin as an add-on therapy to metformin in routine practice in Southern India. By evaluating the real-world efficacy and long-term outcomes, the study aims to contribute to individualised diabetes care and support clinical decision-making.

2 METHODS

2.1 Study design

This was a cross-sectional, digital, questionnaire-based study conducted among physicians involved in T2DM management to evaluate real-world physician insights on empagliflozin and linagliptin as an add-on therapy to metformin in their clinical practice in Southern India. Participation in the study was entirely voluntary, and the study procedures, along with the data analysis, ensured the anonymity and confidentiality of the respondents. The study protocol was approved by an independent ethics committee (IEC No: CIEC/2025/056).

2.2 Study questionnaire

The study questionnaire was designed based on clinical guidelines, existing literature and expert opinions. It consisted of 17 questions that focused on the real-world effectiveness of empagliflozin + linagliptin add-on therapy to metformin. The questionnaire further explored key areas such as patient demographics, glycaemic control, comparative insights with other glucose-lowering therapies and long-term outcomes. Physicians were asked to respond based on their experience with the last 10 patients treated with empagliflozin + linagliptin add-on therapy.

2.3 Inclusion criteria

The study included physicians from southern India with clinical experience in managing T2DM who had prescribed empagliflozin and linagliptin combination as an add-on therapy to metformin.

2.4 Data collection

The physicians, participating in the study, were provided with a concise overview of the study's nature and the process for completing the questionnaire. The questionnaire was given to physicians either in person or through online platforms, as per the physician's convenience.

2.5 Data analysis

Physician responses to the questions were entered in Microsoft Excel, and descriptive statistics like percentages were used to analyse the data.

3 RESULTS

A total of 206 physicians from southern India participated in the study. Physicians' responses were based on their experience with the last 10 patients. Most physicians (37.86%) reported that only 1-2 patients had pre-existing cardiovascular disease (CVD). A majority of physicians (54.85%) reported that none of the last 10 patients had a history of heart failure (HF). A higher number of physicians (32.04%) reported that most patients were on dual therapy before switching to this combination (Table 1).

Table 1: Demographics of T2DM patients on empagliflozin and linagliptin as an add-on therapy to metformin

Parameters	Response of physicians (N=206)
Pre-existing CVD	
1-2 patients	78 (37.86)
3-5 patients	71 (34.47)
6-10 patients	17 (8.25)
None	40 (19.42)
History of HF	
1-2 patients	61 (29.61)
3-5 patients	23 (11.17)
6-10 patients	9 (4.37)
None	113 (54.85)
Previously on dual therapy before switching to this combination	
1-2 patients	45 (21.84)
3-5 patients	61 (29.61)
6-10 patients	66 (32.04)
None	34 (16.50)
Data represented as n (%).	
CVD, cardiovascular disease; HF, heart failure; T2DM, type 2 diabetes mellitus.	

A majority of physicians (47.09%) reported significant HbA1c reduction ($\geq 1\%$) in 6-10 patients within 3 months, followed by 3-5 patients (34.47%), 1-2 patients (12.62%) and none (5.83%). After the initiation of the add-on therapy, most physicians (46.12%) observed improvement in glycaemic control within 3 months, followed by improvements within 1 month (34.47%) and 6 months (17.96%), while only 1.46% observed no significant improvement. Nearly half of the physicians (49.51%) reported more effective HbA1c reduction with empagliflozin + linagliptin as an add-on therapy to metformin compared with other oral antidiabetic regimens. A higher proportion of physicians (50.49%) observed moderate improvement in postprandial glucose (PPG) control, followed by 36.41% of physicians who observed significant improvement, while others observed no major impact (9.22%) or were not sure of the benefits (3.88%). The majority of physicians (57.28%) reported that the empagliflozin + linagliptin add-on therapy to metformin was moderately effective in T2DM management (Table 2). A considerable proportion of physicians (42.23%) observed improvement in insulin sensitivity in 3-5 patients (Figure 1)

Table 2: Efficacy outcomes of empagliflozin and linagliptin as add-on therapy to metformin

Parameter	Response of physicians (N=206)
Significant HbA1c reduction ($\geq 1\%$) within 3 months	
1-2 patients	26 (12.62)
3-5 patients	71 (34.47)
6-10 patients	97 (47.09)
None	12 (5.83)
Improvement in glycaemic control after initiating add-on therapy	
Within 1 month	71 (34.47)
Within 3 months	95 (46.12)
Within 6 months	37 (17.96)
No significant improvement observed	3 (1.46)
HbA1c reduction comparison to other oral antidiabetic regimens	
More effective	102 (49.51)
Equally effective	79 (38.35)
Less effective	17 (8.25)
Not sure	8 (3.88)
Benefits seen in postprandial glucose control	
Significant improvement	75 (36.41)
Moderate improvement	104 (50.49)
No major impact	19 (9.22)
Not sure	8 (3.88)
Overall effectiveness in T2DM management	
Highly effective	78 (37.86)
Moderately effective	118 (57.28)
Slightly effective	6 (2.91)
Not effective	4 (1.94)
Data represented as n (%). HbA1c, glycated haemoglobin; T2DM, type 2 diabetes mellitus.	

A notable proportion of physicians (33.50%) reported weight loss (>2 kg) within 3 months, and 32.04% observed improvement in blood pressure (BP) (Figure 2). In patients with both diabetes and HF receiving add-on therapy, 45.63% of physicians reported that the therapy was moderately effective in improving symptoms while 31.07% observed it to be very effective. A higher proportion of physicians (45.63%) reported moderate improvement in lipid profile. An equal proportion of physicians (40.78%) reported that the add-on therapy provided more or equal CV protection when compared with other SGLT-2/DDP-4/Metformin regimens. Most physicians (37.38%) monitored renal function every 6 months. A considerable proportion of physicians reported a moderate (43.69%) or significant (26.70%) reduction in long-term diabetes-related complications while 19.42% observed no significant impact and 10.19% were not sure (Table 3). Most physicians (48.06%) reported a moderate reduction in hospital admissions due to diabetes-related complications (Figure 3).

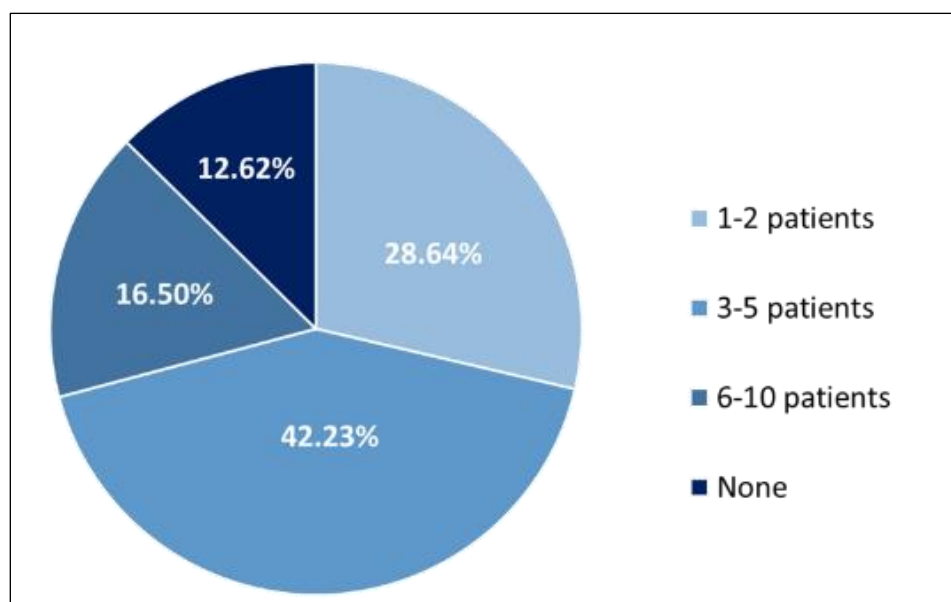


Figure 1: Improvements in insulin sensitivity with the combination add-on therapy

Table 3: Cardiometabolic outcomes and long-term impact of the combination add-on therapy to metformin

Parameters	Response of physicians (N=206)
Symptom improvement in patients with both diabetes and HF	
Very effective	64 (31.07)
Moderately effective	94 (45.63)
No noticeable improvement	17 (8.25)
Not sure	31 (15.05)
Impact on lipid profiles in patients with both diabetes and HF	
Significant improvement	21 (10.19)
Moderate improvement	94 (45.63)
No major impact	57 (27.67)
Not sure	34 (16.50)
CV protection compared with other SGLT-2/DPP-4/Metformin regimens	
More protective	84 (40.78)
Equally protective	84 (40.78)
Less protective	24 (11.65)
Not sure	14 (6.80)
Renal function monitoring compared to other diabetes medications	
Yes, every 3 months	61 (29.61)
Yes, every 6 months	77 (37.38)
No change in monitoring frequency	44 (21.36)
Not sure	24 (11.65)
Long-term diabetes-related complications	
Moderately reduces complications	90 (43.69)
Significantly reduces complications	55 (26.70)

No significant impact	40 (19.42)
Not sure	21 (10.19)

Data represented as n (%).

CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; HF, heart failure; SGLT-2, sodium-glucose cotransporter-2.

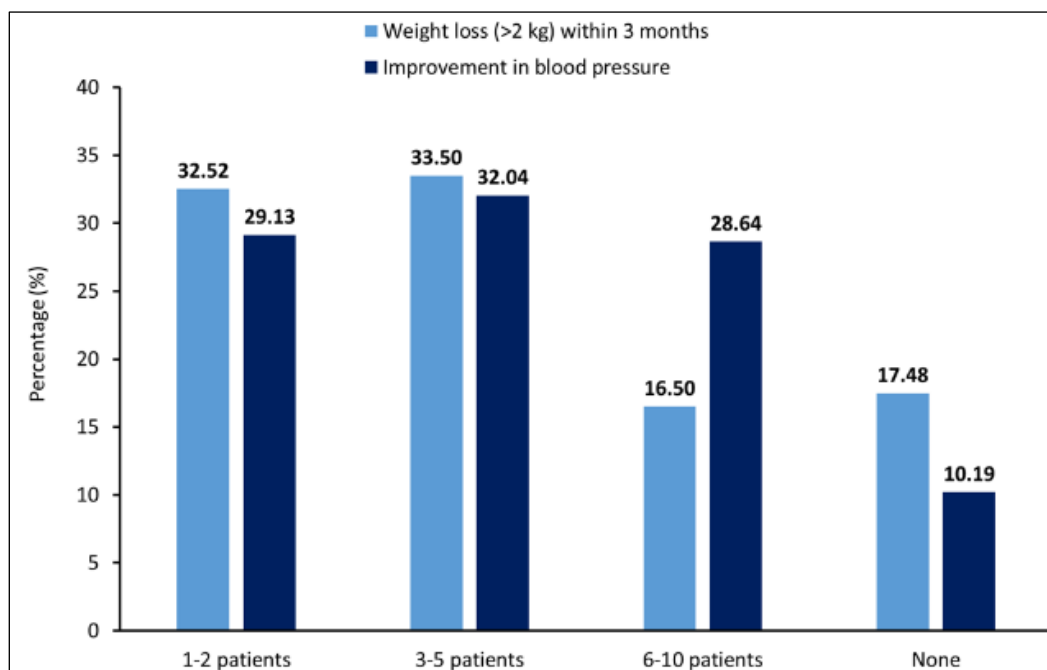


Figure 2: Weight loss (>2 kg) within 3 months and improvement in blood pressure in patients receiving the combination add-on therapy

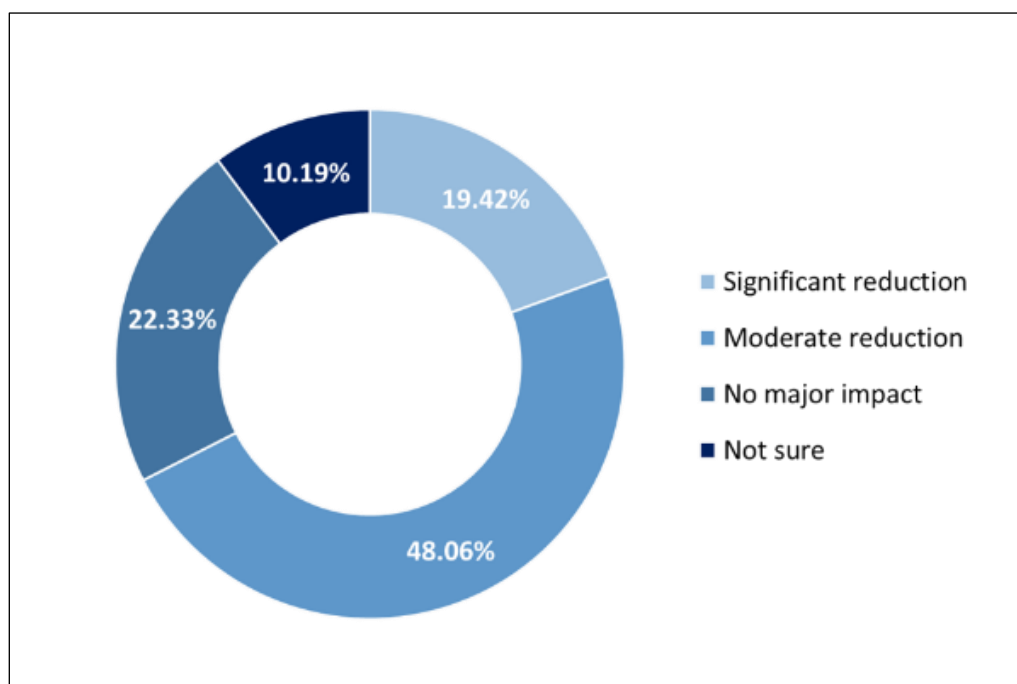


Figure 3: Impact of the combination add-on therapy on hospital admissions due to diabetes-related complications

4 DISCUSSION

The combination of empagliflozin and linagliptin offers benefits for patients unable to improve glycaemic control with metformin monotherapy and in comorbidities such as diabetic hypertension, congestive HF, atherosclerotic CVD, obesity, and impaired renal function [12]. This study aims to provide real-world insights from physicians of southern India regarding the efficacy, cardiometabolic outcomes, and long-term outcomes of empagliflozin + linagliptin add-on therapy to metformin in T2DM patients.

In the present study, most of the physicians reported that only a few patients had pre-existing CVD, and most physicians observed that none of their patients had a history of HF. These findings align with the REALISE study (Real-World Evaluation of Early Initiation of Dapagliflozin and Sitagliptin Combination Therapy in the Management of Type 2 Diabetes Mellitus) that reported co-existing CVDs in Indian patients with T2DM [8]. A majority of physicians reported that more than half of the patients on dual therapy switched to this combination therapy. Another retrospective analysis observed similar findings, where most of the Indian participants were on prior dual therapy for T2DM [11].

A large proportion of physicians reported a significant reduction in HbA1c ($\geq 1\%$) along with improved glycaemic control within 3 months of initiating this combination. A double-blind randomised parallel group trial also documented that linagliptin add-on to empagliflozin and metformin significantly improved HbA1c ($\geq 1\%$) ($P < 0.001$) [13]. According to a majority of physicians, this combination was more effective than other antidiabetic regimens in reducing HbA1c. This finding aligns with a retrospective analysis which depicts HbA1c reduction when empagliflozin and linagliptin combination was added to ongoing medications [11]. In the present study, most physicians documented moderate improvement in PPG control and moderate overall effectiveness of the combination in T2DM management. These findings are supported by a quasi-experimental study evaluating the efficacy of empagliflozin-linagliptin combination as an add-on therapy to metformin which reported sustained improvement in PPG control and long-term glycaemic control [14]. A large number of physicians reported improved insulin sensitivity in nearly half of their patients. Most physicians observed a weight loss of (> 2 kg) within 3 months and improvements in BP in a moderate proportion of patients. Similar findings were reported in a study which demonstrated a weight loss of ~ 5 kg and improved BP within 12 weeks of receiving this combination [14]. In the present study, most of the physicians reported moderate symptom improvement in patients with both T2DM and HF. The Empagliflozin Removal of Excess Glucose: Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) documented lower risk of CV morbidity and mortality in patients receiving empagliflozin [15]. Findings from the CARMELINA trial (Cardiovascular and Renal Microvascular Outcome Study with Linagliptin) confirmed the safety of linagliptin when added to usual care among T2DM adults with high CV and renal risk [16]. Most physicians reported moderate improvement in lipid profile in patients with T2DM and HF. A prospective observational study reported a decrease in lipid profile in patients receiving a fixed-dose combination of empagliflozin and linagliptin [7]. According to a higher proportion of physicians, empagliflozin + linagliptin add-on therapy demonstrated more or equal CV protection compared with other regimens, including SGLT-2 inhibitors, DPP-4 inhibitors, and metformin. Another prospective randomised controlled single centre study demonstrated similar findings, where the combination therapy improved BP and vascular function when compared with metformin and insulin glargine [17]. Most physicians in this study monitored renal function every 6 months for patients on the combination therapy, while others assessed renal function every 3 months. This is consistent with a retrospective analysis in which renal function was assessed at every visit up to 12 weeks [11]. Current study findings reported moderate reductions in hospital admissions due to long-term T2DM complications. Safety trials have shown cardioprotective and renoprotective benefits of empagliflozin, particularly in reducing hospitalisation for HF and kidney disease progression in T2DM patients. Additionally, another study reported that DPP-4i was associated with a lower risk of all-cause hospitalisations [18].

A key strength of this study is the ability to capture real-world perspectives from physicians based on their experience with empagliflozin + linagliptin add-on therapy to metformin in Indian T2DM patients. This study offers clinical insights into observed glycaemic and cardiometabolic outcomes along with the long-term impact of the combination therapy beyond the restrictions of controlled trial environments. However, the study has few limitations. The small sample size limits the generalizability of the results. Since the study was restricted to physicians from southern India, the findings may not reflect broader practice. Also, the findings are solely based on self-reported clinical perspectives, which may introduce response bias over time.

5 CONCLUSION

The physician responses from this study indicated that the empagliflozin + linagliptin add-on therapy to metformin is effective in improving glycaemic and cardiometabolic outcomes. Additionally, this combination therapy is associated with reduced long-term diabetes related complications.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Funding Source

The study was funded by Lloyd Healthcare Private Ltd., India.

Disclosure of conflict of interest

All authors have no conflicts of interest to declare.

Statement of ethical approval

The study protocol was approved by an Independent Ethics Committee (IEC No: CIEC/2025/056).

Statement of informed consent

Informed written consent was taken from all participants before enrollment in the study.

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