



(RESEARCH ARTICLE)



## RETROSPECTIVE STUDY OF EFFICACY AND SAFETY OF THE COMBINATION LINAGLIPTIN, EMPAGLIFLOZIN, METFORMIN IN THE MANAGEMENT OF TYPE 2 DIABETES IN INDIA IN THE REAL-WORLD SETTING

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### ABSTRACT

**Background:** Type 2 diabetes mellitus (T2DM) is a progressive disorder with high cardiovascular (CV) risk, often inadequately controlled on monotherapy. This study aimed to evaluate real-world efficacy, safety, CV outcomes, tolerability and adherence of the empagliflozin, sitagliptin and metformin fixed-dose combination (FDC) in Indian patients.

**Methods:** This questionnaire-based study collected responses from healthcare practitioners (HCPs) in India regarding their last 10 patients with T2DM who received the linagliptin, empagliflozin and metformin combination. The study assessed the data on baseline glycemia, prior therapy, HbA1c (glycated hemoglobin) thresholds, glycemic target achievement, CV risk, adverse events, and adherence to the combination.

**Results:** A total of 571 HCPs were involved in the study. In real-world practice, 30.82% of HCPs reported that all of their last 10 patients on two-drug therapy had HbA1c >7.0%. At HbA1c levels of 7.6-8.0%, 33.27% of HCPs initiated the triple combination of linagliptin, empagliflozin, and metformin. The most common CV risk factors observed were uncontrolled blood glucose (40.11%) and hypertension (32.75%). After 6 months of therapy, 34.15% of patients achieved target HbA1c, with 38.35% of HCPs reporting a 1.25-1.5% reduction and 31.00% reporting 0.75-1.0% reduction after 4 months in newly diagnosed patients. Weight loss was noted in 63.92% of patients, while hypoglycemia was reported in 38.18%. The triple FDC was rated excellent by HCPs for efficacy (50.96%), safety (47.81%), and patient adherence (50.79%).

**Conclusion:** The fixed-dose combination of empagliflozin, linagliptin, and metformin demonstrated effective glycemic control, favorable weight outcomes, and good tolerability, while addressing key cardiovascular and renal risk factors in routine clinical practice.

**Keywords:** Cardiovascular, Adherence, Glycemic control, Hypoglycemia.

## 1 INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a heterogeneous, non-autoimmune condition characterized by progressive  $\beta$ -cell failure and impaired insulin secretion, leading to insulin resistance [1]. The International Diabetes Federation estimates that 589 million adults aged 20–79 years were living with T2DM in 2025, with projections indicating an increase to 853 million by 2050 [2]. India contributes significantly to the global diabetes burden, with approximately 101 million individuals currently affected by T2DM, a figure that continues to rise steadily [3]. India has become a major contributor, driven by rising diabetes rates in both rural and urban areas, compounded by increasing hypertension, dyslipidemia, obesity, and lifestyle changes [4].

Long-term glycemic control remains difficult to achieve and sustain, particularly in patients with elevated cardiovascular (CV) risk or established CV disease, despite the growing arsenal of glucose-lowering options. Metformin monotherapy has been shown to significantly reduce HbA1c and fasting plasma glucose compared with placebo in drug-naïve patients with type 2 diabetes mellitus, supporting its use as effective first-line therapy [5]. As clinical experience and evidence evolve, the early and strategic use of combination therapies is increasingly encouraged to overcome therapeutic inertia, slow progression, and significantly lower the likelihood of serious complications [6]. Combining sodium-glucose cotransporter-2 inhibitors (SGLT2i) with dipeptidyl peptidase-4 inhibitors (DPP-4i) on a metformin background has been shown to significantly improve glycemic control, with additional benefits on weight and a favorable safety profile [7].

The triple fixed-dose combination (FDC) of dapagliflozin, sitagliptin, and metformin achieved significantly better glycemic control while maintaining a comparable tolerability and safety profile. This FDC may serve as an effective treatment intensification option for patients with T2DM who remain inadequately controlled on metformin monotherapy [8]. The SGLT2i demonstrate a clinically meaningful reduction in CV risk in real-world practice, with consistent protective effects observed across individual agents within the class [9]. Additionally, DPP-4 inhibitors represent a well-established, effective, and safe glucose-lowering class with consistent glycemic benefits, metabolic neutrality, and a low risk of hypoglycemia across diverse patient populations with T2DM [10].

Understanding real-world prescribing patterns, clinical outcomes, safety, and physician experiences is essential to bridging the gap between controlled trial evidence and everyday clinical care. Therefore, this questionnaire-based study was conducted to evaluate the real-world efficacy and safety associated with the FDC of empagliflozin, sitagliptin, and metformin in the management of T2DM in India.

## 2 METHODS

### 2.1 Study design

This questionnaire-based study was conducted among Indian healthcare professionals (HCPs). Participation in the study was entirely voluntary, and both the study procedures and data analysis were designed to maintain the confidentiality and anonymity of all participating HCPs.

### 2.2 Study questionnaire

The study questionnaire was developed based on existing literature, clinical guidelines, and expert opinions. It included a total of 25 questions that focused on HCPs' experiences with the combination of empagliflozin, linagliptin, and metformin in patients with T2DM. These questions captured and collected information on baseline glycaemia, prior therapy, HbA1c (glycated hemoglobin) thresholds for initiating triple therapy, glycemic outcomes, insulin refusal, CV risk and complications, heart failure status, dietary compliance, HbA1c reduction, weight and safety outcomes, need for add-on therapy, and physicians' overall assessment of efficacy, safety, and adherence.

### 2.3 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 reviewed and approved by an Independent Ethics Committee (ACEAS - Independent Ethics Committee; Date of approval: 11<sup>th</sup> Feb, 2025). Written informed consent was obtained from all participating HCP before completion of the surveillance questionnaire.

### 2.4 Data analysis

The responses of HCPs were entered into Microsoft excel and descriptive statistics, such as frequencies and percentages, were used to present data.

### 3 RESULTS

A total of 571 HCPs were involved in this study, wherein the response noted was based on the experience with last 10 patients. According to 30.82% of HCPs, all patients treated with two-drug therapy had HbA1c >7.0% and these patients were treated by nearly half (48.86%) of HCPs with a combination of sitagliptin and metformin, followed by glimepiride and metformin (33.63%). At HbA1c levels of 7.6-8.0%, 33.27% of HCPs initiated combination therapy with linagliptin, empagliflozin, and metformin. Uncontrolled blood glucose (40.11%) and hypertension (32.75%) were the most commonly observed CV risk factors among patients with T2DM. Almost 37.30% of HCPs reported that two patients were newly diagnosed treatment-naïve T2DM patients with high CV risk. Similarly, 39.58% of HCPs reported that two patients had a diabetes duration of less than 3 years.

Diabetic kidney disease (DKD) or CKD was the most commonly (43.26%) observed diabetes-related complication, followed by diabetic neuropathy (25.92%). A substantial proportion of HCPs (46.23%) reported observing grade 2 heart failure, while 42.91% noted that two patients had either grade 1 or grade 2 heart failure. Approximately 35.03% of HCPs reported that four patients were non-compliant with dietary recommendations and continued to consume a high-carbohydrate diet (Table 1).

**Table 1: Patient profile, baseline characteristics, and treatment initiation**

| Questions                                                                                                             | Options                    | Response (N=571) |
|-----------------------------------------------------------------------------------------------------------------------|----------------------------|------------------|
| How many of these 10 patients had been treated with two-drug therapy had uncontrolled diabetes with HbA1c>7.0%?       | <8/10                      | 87 (15.24)       |
|                                                                                                                       | 8/10                       | 161 (28.20)      |
|                                                                                                                       | 9/10                       | 147 (25.74)      |
|                                                                                                                       | All                        | 176 (30.82)      |
| Which of these were the 2 drugs the patients had been treated with?                                                   | Sitagliptin + Metformin    | 279 (48.86)      |
|                                                                                                                       | Glimepiride + Metformin    | 192 (33.63)      |
|                                                                                                                       | Teneligliptin + Metformin  | 61 (10.68)       |
|                                                                                                                       | Others                     | 39 (6.83)        |
| At what HbA1c level did you initiate treatment with combination therapy with Linagliptin + Empagliflozin + Metformin? | 7.0-7.5                    | 118 (20.67)      |
|                                                                                                                       | 7.6-8.0                    | 190 (33.27)      |
|                                                                                                                       | 8.1-8.5                    | 168 (29.42)      |
|                                                                                                                       | >8.5                       | 95 (16.64)       |
| What were the CV risk factors observed in these 10 patients?                                                          | Uncontrolled blood glucose | 229 (40.11)      |
|                                                                                                                       | Hypertension               | 187 (32.75)      |
|                                                                                                                       | Dyslipidemia               | 66 (11.56)       |
|                                                                                                                       | Family history of CVD      | 49 (8.58)        |
|                                                                                                                       | Obesity                    | 11 (1.93)        |
|                                                                                                                       | CKD                        | 14 (2.45)        |
|                                                                                                                       | Age                        | 15 (2.63)        |
| How many of these 10 patients were newly diagnosed treatment-naïve T2DM patients with high CV risk?                   | 1/10                       | 113 (19.79)      |
|                                                                                                                       | 2/10                       | 213 (37.30)      |
|                                                                                                                       | 3/10                       | 161 (28.20)      |
|                                                                                                                       | >3                         | 84 (14.71)       |
| How many of these 10 patients had a duration of diabetes < 3 years, which would make it essential                     | 1/10                       | 111 (19.44)      |
|                                                                                                                       | 2/10                       | 226 (39.58)      |

|                                                                                                                                                                                                                    |                                |             |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|-------------|
| to give them CV protective OHAs, considering the need to prevent CV complications in their life ahead?                                                                                                             | 3/10                           | 150 (26.27) |
|                                                                                                                                                                                                                    | >3                             | 84 (14.71)  |
| Which of these complications of diabetes did you observe in these 10 patients                                                                                                                                      | Diabetic kidney disease or CKD | 247 (43.26) |
|                                                                                                                                                                                                                    | Diabetic neuropathy            | 148 (25.92) |
|                                                                                                                                                                                                                    | Diabetic retinopathy           | 83 (14.54)  |
|                                                                                                                                                                                                                    | Myocardial infarction / Angina | 62 (10.86)  |
|                                                                                                                                                                                                                    | Heart failure                  | 31 (5.43)   |
| What grade of heart failure did you observe in these patients?                                                                                                                                                     | Grade 1                        | 176 (30.82) |
|                                                                                                                                                                                                                    | Grade 2                        | 264 (46.23) |
|                                                                                                                                                                                                                    | Grade 3                        | 103 (18.04) |
|                                                                                                                                                                                                                    | Grade 4                        | 28 (4.90)   |
| How many of these 10 patients had Grade 1 or Grade 2?                                                                                                                                                              | 1/10                           | 102 (17.86) |
|                                                                                                                                                                                                                    | 2/10                           | 245 (42.91) |
|                                                                                                                                                                                                                    | 3/10                           | 176 (30.82) |
|                                                                                                                                                                                                                    | >3                             | 48 (8.41)   |
| How many of these 10 patients were diet non-compliant and continued to take a high-carbohydrate diet, which could lead to glycemic excursions (MAGE) and increase the risk of heart disease?                       | 3/10                           | 175 (30.65) |
|                                                                                                                                                                                                                    | 4/10                           | 200 (35.03) |
|                                                                                                                                                                                                                    | 5/10                           | 124 (21.72) |
|                                                                                                                                                                                                                    | >5                             | 72 (12.61)  |
| Data presented as n (%).; CV, cardiovascular; CVD, cardiovascular disease; HbA1C, glycated hemoglobin; MAGE, mean amplitude of glycemic excursions; OHAs, oral hypoglycemic agent; T2DM, type 2 diabetes mellitus. |                                |             |

Out of 10 patients, five (34.15%) achieved the target HbA1c after 6 months of treatment. According to 38.35% of HCPs, HbA1c reduction of approximately 1.25-1.5% was observed with the combination of linagliptin, empagliflozin, and metformin in newly diagnosed T2DM patients after 4 months of treatment, followed by a reduction of 0.75-1.0% as reported by 31.00% of HCPs. The majority of HCPs (63.92%) reported weight loss in patients receiving the triple combination therapy, indicating a potential beneficial metabolic effect. In contrast, hypoglycemia was the most common adverse effect observed 38.18% of HCPs. Regarding long-term glycemic control, most of the HCPs (83.89%) observed sustained control at each follow-up visit. Additionally, 83.36% of HCPs preferred triple combination therapy for patients who refused insulin therapy.

Over the 6-month treatment period, 35.20% of HCPs reported hospitalization of two patients for CV events, while 29.77% indicated that none of their patients experienced hypoglycemic episodes. As reported by 33.27% of HCPs, two patients required the addition of another OHA while on dual therapy. Patients with heart failure, high CV risk, HbA1c levels >8.5%, and those not responding adequately to dual OHA therapy were considered appropriate candidates (all; 32.05%) for the FDC of linagliptin, empagliflozin, and metformin (Table 2).

**Table 2: Treatment outcomes, safety, and clinical impact of triple combination therapy**

| Questions                                                                                                                                                    | Options                                  | Response (N=571) |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|------------------|
| How many out of these 10 patients reached target HbA1c after 6 months of treatment?                                                                          | 4/10                                     | 114 (19.96)      |
|                                                                                                                                                              | 5/10                                     | 195 (34.15)      |
|                                                                                                                                                              | 6/10                                     | 153 (26.80)      |
|                                                                                                                                                              | >6/10                                    | 109 (19.09)      |
| How much was the reduction in HbA1c with Linagliptin + Empagliflozin + Metformin in newly diagnosed T2DM patients after 4 months of treatment?               | 0.25 -0.5%                               | 84 (14.71)       |
|                                                                                                                                                              | 0.75-1.0%                                | 177 (31.00)      |
|                                                                                                                                                              | 1.25-1.5%                                | 219 (38.35)      |
|                                                                                                                                                              | >1.5%                                    | 91 (15.94)       |
| What was the impact on weight of these 10 patients?                                                                                                          | Weight loss                              | 365 (63.92)      |
|                                                                                                                                                              | Weight gain                              | 102 (17.86)      |
|                                                                                                                                                              | No change in weight                      | 104 (18.21)      |
| What were the adverse effects you observed in these 10 patients treated with the FDC of Linagliptin + Empagliflozin + Metformin?                             | Rarely Hypoglycemia                      | 218 (38.18)      |
|                                                                                                                                                              | Rarely Genital mycosis                   | 205 (35.90)      |
|                                                                                                                                                              | Urinary tract infections                 | 148 (25.92)      |
| Did you observe long term glycemic control in these 10 patients over the per of follow up?                                                                   | Yes                                      | 479 (83.89)      |
|                                                                                                                                                              | No                                       | 92 (16.11)       |
| Did you use the triple combination in patients who refused insulin therapy?                                                                                  | Yes                                      | 476 (83.36)      |
|                                                                                                                                                              | No                                       | 95 (16.64)       |
| Over the treatment period of 6 months with Linagliptin + Empagliflozin + Metformin, how many out of these 10 T2DM patients were hospitalized for a CV event? | 1/10                                     | 165 (28.90)      |
|                                                                                                                                                              | 2/10                                     | 201 (35.20)      |
|                                                                                                                                                              | 3/10                                     | 145 (25.39)      |
|                                                                                                                                                              | >3                                       | 60 (10.51)       |
| Over the treatment period of 6 months with Linagliptin + Empagliflozin, many of the 10 T2DM patients had hypoglycemic episodes?                              | 1/10                                     | 98 (17.16)       |
|                                                                                                                                                              | 2/10                                     | 166 (29.07)      |
|                                                                                                                                                              | 3/10                                     | 87 (15.24)       |
|                                                                                                                                                              | >3                                       | 50 (8.76)        |
|                                                                                                                                                              | None                                     | 170 (29.77)      |
| How many out of these 10 patients needed another OHA to be added?                                                                                            | 1/10                                     | 148 (25.92)      |
|                                                                                                                                                              | 2/10                                     | 190 (33.27)      |
|                                                                                                                                                              | 3/10                                     | 87 (15.24)       |
|                                                                                                                                                              | >3                                       | 42 (7.36)        |
|                                                                                                                                                              | None                                     | 104 (18.21)      |
| In which of these patient profiles would you consider the FDC of Linagliptin + Empagliflozin + Metformin?                                                    | Patients not responding to 2 OHA therapy | 134 (23.47)      |
|                                                                                                                                                              | Patients with HbA1c >8.5%                | 162 (28.37)      |
|                                                                                                                                                              | Patients with CV risk                    | 79 (13.84)       |
|                                                                                                                                                              | Patients with heart failure              | 13 (2.28)        |

|                                                                                                                                          |                  |             |
|------------------------------------------------------------------------------------------------------------------------------------------|------------------|-------------|
|                                                                                                                                          | All of the above | 183 (32.05) |
| Data presented as n (%).; CV, cardiovascular; HbA1C, glycated hemoglobin; OHAs, oral hypoglycemic agent; T2DM, type 2 diabetes mellitus. |                  |             |

Nearly half of HCPs (40.28%) reported that two patients had a history of ischemic heart disease (IHD), while 32.40% indicated that two patients had a prior hospitalization for heart failure (Figure 1). HCPs rated the triple FDC of empagliflozin, linagliptin, and metformin as excellent in terms of efficacy (50.96%), safety (47.81%), and patient adherence (50.79%). Additionally, the FDC was rated as good by 34.15% for efficacy, 39.58% for safety, and 35.90% for patient adherence (Figure 2).

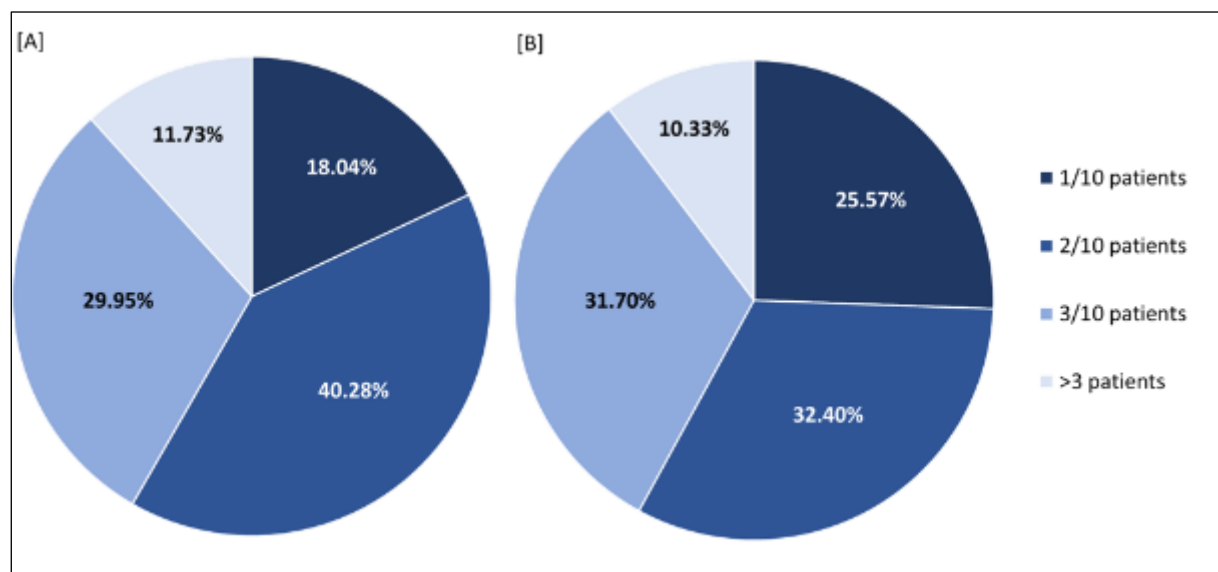


**Figure 1: T2DM patients with history of [A] IHD and [B] hospitalization for heart failure T2DM, type 2 diabetes mellitus; IHD, ischemic heart disease.**

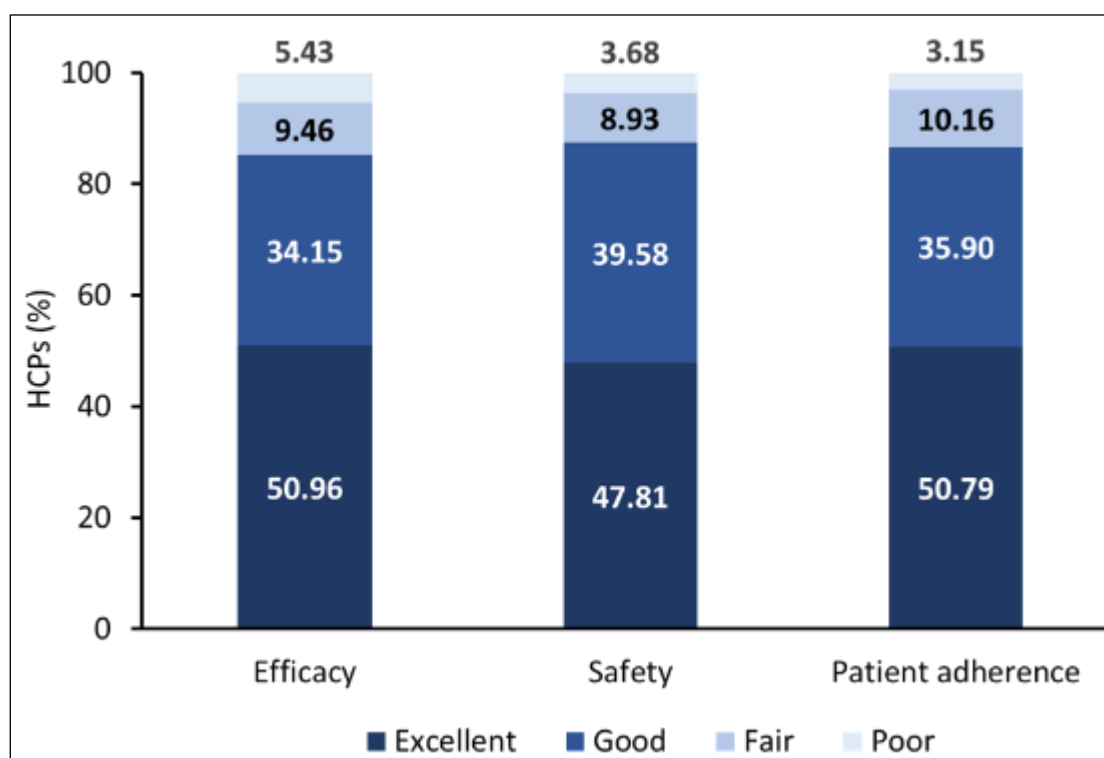


**Figure 2: HCPs global assessment of triple FDC therapy FDC, fixed drug combination.**

## 4 DISCUSSION

Type 2 diabetes mellitus is a chronic metabolic condition characterized by progressive insulin resistance and declining  $\beta$ -cell function, leading to sustained hyperglycemia and an elevated risk of CV and renal complications. Early and effective glycemic management is crucial, particularly in patients at high cardiometabolic risk, where treatment delays may accelerate disease progression and long-term morbidity. Early and sustained glycemic control, supported by individualized therapy and comprehensive management of cardiovascular and metabolic risk factors, is fundamental to improving long-term outcomes in people with type 2 diabetes. Combination therapies targeting multiple pathophysiological defects, such as metformin, dapagliflozin, and sitagliptin, have emerged as a practical approach for improving glycemic control and addressing residual CV risk.

In the current study, HCPs reported that patients receiving dual therapy remained inadequately controlled, with HbA1c levels exceeding 7%. Nearly half of these patients were treated with a sitagliptin-metformin combination, followed by glimepiride-metformin, reflecting real-world prescribing patterns that favor incretin-based regimens for patients with suboptimal glycemic control [11]. At HbA1c level of 7.6-8.0%, HCPs preferred early treatment intensification with a triple combination of linagliptin, empagliflozin, and metformin, reflecting a clinical preference for early intensification. This approach suggests a shift away from traditional stepwise escalation toward earlier use of combination therapy in patients at higher risk [12].

Uncontrolled blood glucose and hypertension were the most common CV risk factors which underscore the critical need for integrated management of glycaemia and blood pressure in patients with T2DM. Many HCPs encountered newly diagnosed high-risk patients as well as patients with a diabetes duration of less than 3 years. These findings are consistent with current evidence emphasizing early comprehensive risk reduction strategies [13].

Diabetic kidney disease was the most frequently observed complication, followed by diabetic neuropathy, reflecting the high real-world burden of renal and nerve involvement in T2DM and the need for comprehensive complication screening and management [14]. In addition, heart failure (Grade 1-2) was frequently observed among T2DM patients. This finding aligns with existing literature demonstrating a higher prevalence and risk of heart failure among individuals with T2DM compared with those without diabetes [15]. Here you can add what it indicates something like together, these observations emphasize the importance of routine screening and early management of both microvascular and macrovascular complications in clinical practice.

With respect to glycemic outcomes, HCPs reported that four patients were diet non-compliant and continued high-carbohydrate intake, which may exacerbate glycemic excursions and CV risk, consistent with evidence that diets high in glycemic load are linked to poorer glycemic control and elevated cardiometabolic risk in T2DM [16]. The current study reported that, in newly diagnosed patients with T2DM, the combination of linagliptin, empagliflozin, and metformin reduced HbA1c levels by 1.25-1.5%. These findings are supported by a study conducted by Lv Q et al., which demonstrated that early initiation of linagliptin and metformin helps achieve effective glycemic control without increasing the risk of hypoglycemia [17].

The majority of HCPs reported that weight loss in patients receiving the triple combination therapy. Evidence suggests that triple combination therapy promotes weight loss and improves treatment adherence, while also reducing the risk of hypoglycemia; however, this differs from the findings of the current study [18]. Most of the HCPs preferred triple combination therapy for patients who refused insulin treatment. Recent evidence supports triple therapy with metformin, empagliflozin, and linagliptin as a safe, well-tolerated alternative to insulin with improved glycemic control in patients inadequately controlled on dual therapy [19]. Over the 6-month treatment period, HCPs reported hospitalization of two patients for CV events. This finding aligns with the evidence indicating that, despite advances in glucose-lowering therapies, patients with T2DM remain at significant risk of CV complications [20]. Patients with heart failure, high CV risk, HbA1c levels > 8.5%, and inadequate response to dual oral therapy were considered suitable candidates for fixed-dose combination therapy with linagliptin, empagliflozin, and metformin. This is consistent with expert consensus that triple oral combination therapy demonstrated strong and durable glycemic-lowering efficacy [19].

Patients with T2DM frequently have CV comorbidities, such as IHD and heart failure, indicating a high burden of macrovascular disease. The current findings, reflecting prior IHD and heart failure-related hospitalizations, reinforce the need for integrated CV risk management alongside glycemic control in routine clinical practice [21]. Half of the HCPs rated the triple FDC of empagliflozin, linagliptin, and metformin as excellent in terms of efficacy, safety, and patient adherence. Clinical evidence indicates that triple FDC therapy combining metformin with empagliflozin and linagliptin demonstrates strong efficacy and safety, along with improved tolerability and adherence compared with dual therapies [19]. Early use of the empagliflozin, linagliptin, and metformin triple FDC was favored for patients with uncontrolled

T2DM and high cardiometabolic risk, offering effective glycemic control, good tolerability, and improved patient adherence.

The study has certain limitations. The relatively small sample size may limit the generalizability of the findings, as the responses might not fully reflect the wider HCP population. Moreover, reliance on self-reported questionnaire data introduces the potential for response bias. These factors should be taken into account when interpreting the results.

## 5 CONCLUSION

The fixed-dose combination of empagliflozin, linagliptin, and metformin led to meaningful improvements in blood glucose control, helped achieve favorable weight outcomes, and was generally well tolerated. Importantly, this combination also addressed common cardiovascular and kidney-related risk factors seen in routine clinical practice. These results support the early use of mechanism-based, cardioprotective combination therapy as a practical option instead of gradual step-by-step treatment escalation or early insulin initiation in selected patients with type 2 diabetes. However, larger prospective studies are needed to confirm these findings and to understand the long-term cardiovascular and renal benefits.

## STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

### *Funding Source*

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### *Disclosure of conflict of interest*

All authors have no conflicts of interest to declare.

### *Statement of ethical approval*

The study protocol were approved by an Independent Ethics Committee (ACEAS - Independent Ethics Committee; Date of approval: 11th Feb, 2025).

### *Statement of informed consent*

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

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