Simplifying Type 2 DM Care with Linagliptin: A Position Paper

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the prevalent forms of diabetes worldwide, contributing to approximately 90% of all cases. It occurs when the pancreas cannot produce sufficient insulin, and the body is unable to effectively utilize the insulin produced. Diabetes has a global incidence of 10.8% in urban settings and a slightly lower prevalence of 7.2% in rural regions. Over the years, the number of individuals living with diabetes has continuously increased. In 2000, the estimated global count was 151 million, which rose by 88% to 285 million in 2009. As per the International Diabetes Federation (IDF) estimates, in 2021, approximately 537 million adults aged 20–79 years are living with diabetes. Projections indicate that this number will rise to 643 million by 2030 and further to 783 million by 2045. Unfortunately, diabetes and its complexities have a significant impact on mortality rates. In 2021 alone, an estimated 6.7 million deaths were attributed to diabetes-related causes. India is the second leading country in the global diabetes epidemic. Based on the epidemiological studies that were conducted in India, the IDF Diabetes Atlas 2021 reported 74.2 million adults (20–79 years) with diabetes. From 32.7 million in the year 2000, the number of people with diabetes in the year 2015 had risen to 69.2 million. In India, district level household survey data showed a rise to 7.7% in 2016 from 5.5% in 1990 in diabetes prevalence in individuals aged 20 years or more. It is predicted that in the year 2040, the prevalence will rise to 123.5 million people.

First-line therapy in T2DM depends on comorbidities, patient-centered treatment factors, and management needs but will generally include metformin and comprehensive lifestyle modification. While metformin therapy offers numerous benefits, it is important to acknowledge that it can be accompanied by gastrointestinal adverse effects. These effects may hinder or restrict its usage in certain patients. Sulphonylurea (SU) has been a preferred second-line glucose-lowering therapy in T2DM patients. SU are commonly used to effectively reduce plasma glucose levels, but they can also lead to varying degrees of hypoglycemia, β-cell death, weight gain, and potentially adverse cardiac outcomes. On the other hand, gliptins are newer incretin-based therapies for treating T2DM. They possess antihyperglycemic properties with a relatively safe adverse effect profile. Gliptins carry a low risk of hypoglycemia and are weight neutral. The selection of pharmacologic agents should be guided by a patient-centered approach, as stated in the 2022 American Diabetes Association guidelines. They should be evaluated for their effectiveness, risk of hypoglycemia, impact on weight, cardiovascular (CV) and renal comorbidities, cost and accessibility, potential adverse effects, and patient preferences. Pharmacotherapy should be started at the time T2DM is diagnosed unless there are contraindications; for many patients, this will be metformin monotherapy in combination with lifestyle modification. However, medication(s) from other antidiabetic classes should be provided for the ones intolerant to or have contraindications to using metformin. Among individuals with T2DM who have established atherosclerotic CV disease or indicators of high CV risk, established kidney disease, or heart failure (HF), a sodium-glucose cotransporter 2 inhibitor (SGLT2i) and/or glucagon-like peptide 1 receptor agonist (GLP-1) with demonstrated CV disease benefit is recommended as part of the glucose-lowering regimen and comprehensive CV risk reduction, independent of A1C and in consideration of patient-specific factors. If the A1C levels are above the individualized target and there is a compelling need to reduce hypoglycemia, GLP-1 RA, SGLT2i, dipeptidyl peptidase 4 (DPP-4) inhibitor, or thiazolidinedione class of drugs may be administered. If the A1C levels remain still beyond the target, the patient therapy can be continued in combination with...
the other antidiabetic agents from the category of drugs mentioned. If the glycemic target is still not achieved, SU or basal insulin can be added to the therapy. DPP-4 inhibitors, as a class of antidiabetic agents, are effective in the treatment of diabetes. The most widely used DPP-4 inhibitors are saxagliptin, alogliptin, sitagliptin, vildagliptin, and linagliptin. Linagliptin is a DPP-4 inhibitor that has shown high efficacy by inhibiting 80–90% of DPP-4 but not all DPP-4 inhibitors are administered as once-daily dosing. DPP-4 inhibitors have an oral route of administration and a mechanism of action based on the inhibition of the DPP-4 enzyme, thus preventing the breakdown of both GLP-1 and glucose-dependent insulino-tropic polypeptide (GIP), thereby prolonging their activity and glucose-stimulated insulin secretion, thereby resulting in a low risk of hypoglycemia. DPP-4 inhibitors are weight neutral with an acceptable safety profile.

The objective of this position paper is to understand the role of linagliptin in simplifying the management of T2DM with good efficacy, robust CV, and renal safety evidence and its use across broad patients without any dose modification.

**Materials and Methods**

To understand the simplicity aspect of linagliptin therapy in T2DM patients, multiple Advisory Board Meetings were conducted with 87 leading key opinion leaders (KOLs) from diabetes specialty PAN India. For the Advisory Board, 16 statements on simplicity aspects of linagliptin were drafted and supported with data from the scientific literature. These statements were presented to a small group of expert panels for validation. After the validation of these statements by the expert panel, the statements were presented as poll questions to 87 KOLs from the diabetes specialty in five zonal advisory board meetings, which were executed on a virtual platform. During the Advisory board meetings, the opinions of these thought leaders were gathered to determine the areas of agreement, neutrality, and disagreement. The statements were considered valid only if 30% of KOLs had responded during poll questions in the advisory board meetings. The results of the poll questions were collected, analyzed, and presented to a group of seven experts from the diabetes specialty, along with supportive scientific data to a respective statement during the national advisory board meeting to form expert opinions. A >50% agreement on a statement was taken into consideration to form an expert opinion (Fig. 1). The statements are listed in Table 1 and addressed in the sections mentioned below:

- Clinical efficacy of a DPP-4 inhibitor.
- Clinical efficacy of linagliptin in T2DM.
- Cardiovascular (CV) and HF safety evidence of linagliptin from (CV outcome trial) CVOTs.
- Clinical evidence of linagliptin in T2DM with renal impairment (RI).
- Convenience and adherence with linagliptin in T2DM.
- Safety of linagliptin across a broad range of T2DM patients.

**Results from the Expert Panel Discussion**

**Clinical Efficacy of a DPP-4 Inhibitor**

Dipeptidyl peptidase 4 (DPP-4) inhibitors possess a unique mode of action by inhibiting the DPP-4 enzyme, which plays a role in the rapid degradation of two important incretin hormones: GLP-1 and GIP. The clinical efficacy of several DPP-4 inhibitors, such as saxagliptin, alogliptin, vildagliptin, linagliptin, and sitagliptin, has been demonstrated in numerous studies. A decrease in hemoglobin A1C (HbA1C) and improvement in parameters like fasting plasma glucose (FPG) and postprandial glucose (PPG) are characteristic changes associated with the DPP-4 inhibitors treatment. Table 2, given below, lists the clinical trials which prove these results. Craddy et al. did a comprehensive study to compare the efficacy of DPP-4 inhibitors in T2DM. The review found no significant differences in the average change from baseline in body weight or glycosylated HbA1C, nor in the proportions of patients achieving HbA1C levels below 7% or experiencing hypoglycemic events (0.7–0.8%).

In linagliptin-treated patients, no significant hypoglycemic episodes were seen, and there were no significant hypoglycemic episodes. Studies by Taskinen et al. and Groop et al. that were conducted to evaluate the efficacy and safety of linagliptin administered as an add-on therapy to metformin in patients with T2DM with inadequate glycemic control (n = 701), significant reductions were observed from baseline in HbA1C (−0.49 vs 0.15%), FPG (−0.59 vs 0.58 mmol/L), and PPG (−2.7 vs 1.0 mmol/L); p < 0.0001 in linagliptin patients. Hypoglycemic events were also rare (0.6%) in linagliptin-treated patients.

**Preparation of manuscript—Final approval from the experts (n = 7)**

![Fig. 1: Summary of the process](image)

**Clinical Efficacy of Linagliptin in T2DM**

**Efficacy of Linagliptin in Drug Naïve Patients and as an Add-on Therapy to Metformin**

As per the experts, achieving good glycemic control with linagliptin is the reason for its growing use in therapy. A reduction in HbA1C and PPG and an improvement in FPG levels make linagliptin a suitable choice of treatment. Mentioned below are some studies which testify to the positive impact of linagliptin on glycemic control. Del Prato et al. conducted a study to assess the safety and efficacy of linagliptin. It demonstrated that linagliptin treatment caused a placebo-corrected change in HbA1C from a baseline of approximately—0.69% (p < 0.0001) after the treatment period of 24 weeks. The adjusted HbA1C reduction in patients with baseline HbA1C of 9.0% was 1.01% (p < 0.0001). Improvements in FPG (p < 0.0001) and PPG (p < 0.0001) were seen, and there were no significant hypoglycemic episodes.

![Fig. 2: Comparative efficacy of DPP4 inhibitors](image)
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Table 1: The questionnaire to rate each item using a 9-point scale (1–5, disagreement; 5, neutral; 6–9, agreement)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Question</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The efficacy of linagliptin is comparable to other gliptins (n = 65)</td>
<td>4.60%</td>
<td>3.10%</td>
<td>92.30%</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>Linagliptin can be administered as a single agent in drug naive patients when contraindicated/inefficient to metformin (n = 61)</td>
<td>0.00%</td>
<td>4.90%</td>
<td>95.10%</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td>Linagliptin can be considered a viable option for second-line treatment after metformin failure (n = 61)</td>
<td>1.60%</td>
<td>4.90%</td>
<td>93.50%</td>
<td>100%</td>
</tr>
<tr>
<td>4</td>
<td>Linagliptin-metformin FDC as a 1st line shows better efficacy as compared to metformin monotherapy (n = 61)</td>
<td>0.00%</td>
<td>4.90%</td>
<td>95.10%</td>
<td>100%</td>
</tr>
<tr>
<td>5</td>
<td>Linagliptin has comparable efficacy with relatively better durability and safety compared to SU (n = 65)</td>
<td>7.70%</td>
<td>27.70%</td>
<td>64.60%</td>
<td>100%</td>
</tr>
<tr>
<td>6</td>
<td>Linagliptin has better efficacy across the Asian population compared to Caucasians (n = 65)</td>
<td>0.00%</td>
<td>21.50%</td>
<td>78.50%</td>
<td>100%</td>
</tr>
<tr>
<td>7</td>
<td>Linagliptin can be an effective oral antidiabetic drug (OAD) as an add-on to insulin (n = 64)</td>
<td>0.00%</td>
<td>14.10%</td>
<td>85.90%</td>
<td>100%</td>
</tr>
<tr>
<td>8</td>
<td>Linagliptin has a reassuring safety profile with robust evidence across the cardiac and renal comorbidities with CARMELINA (n = 69)</td>
<td>0.00%</td>
<td>2.90%</td>
<td>97.10%</td>
<td>100%</td>
</tr>
<tr>
<td>9</td>
<td>Linagliptin has been shown to have a favorable effect on hHF and may be considered in T2DM with a risk of HF (n = 69)</td>
<td>1.50%</td>
<td>15.90%</td>
<td>82.60%</td>
<td>100%</td>
</tr>
<tr>
<td>10</td>
<td>Linagliptin has the best renal safety evidence among the gliptins (n = 70)</td>
<td>2.90%</td>
<td>12.80%</td>
<td>84.30%</td>
<td>100%</td>
</tr>
<tr>
<td>11</td>
<td>Linagliptin has proven safety and effectiveness across the spectrum of CKD in T2DM (n = 70)</td>
<td>1.40%</td>
<td>4.30%</td>
<td>94.30%</td>
<td>100%</td>
</tr>
<tr>
<td>12</td>
<td>The use of a single 5mg once-daily dose of linagliptin simplifies the management of T2DM across a wide patient profile, regardless of cardiac, renal, or hepatic comorbidities (n = 70)</td>
<td>1.40%</td>
<td>4.30%</td>
<td>94.30%</td>
<td>100%</td>
</tr>
<tr>
<td>13</td>
<td>The ease of use and simplicity aspect of linagliptin make it a preferred choice in teleconsultation among the gliptins (n = 70)</td>
<td>2.90%</td>
<td>21.40%</td>
<td>75.70%</td>
<td>100%</td>
</tr>
<tr>
<td>14</td>
<td>Patients with T2DM who have mild-moderate liver dysfunction can utilize linagliptin without risk (n = 61)</td>
<td>1.60%</td>
<td>11.50%</td>
<td>86.90%</td>
<td>100%</td>
</tr>
<tr>
<td>15</td>
<td>Linagliptin can be safely considered in the broad patient profile, including elderly patients with T2DM (n = 60)</td>
<td>0.00%</td>
<td>1.70%</td>
<td>98.30%</td>
<td>100%</td>
</tr>
<tr>
<td>16</td>
<td>Compared to glimepiride, linagliptin offers the benefit of weight neutrality and a lower risk of hypoglycemia which helps alleviate concerns related to weight gain and hypoglycemia in patients with T2DM (n = 60)</td>
<td>0.00%</td>
<td>3.30%</td>
<td>96.70%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 2: Due to variations in study design, methodology, and populations, comparison of studies should be evaluated cautiously.10–45

<table>
<thead>
<tr>
<th>Condition</th>
<th>SAVOR TIMI 53 (saxagliptin)</th>
<th>TECOS (sitagliptin)</th>
<th>CARMELINA (linagliptin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHF</td>
<td>HR 1.27† (95% CI 1.07–1.51)</td>
<td>HR 1.00† (95% CI 0.83–1.20)</td>
<td>HR 0.90† (95% CI 0.74–1.08)</td>
</tr>
<tr>
<td>CV death</td>
<td>HR 1.03 (95% CI 0.87–1.22)</td>
<td>HR 1.03 (95% CI 0.89–1.19)</td>
<td>HR 0.96 (95% CI 0.81–1.14)</td>
</tr>
<tr>
<td>3P-MACE</td>
<td>HR 1.00† (95% CI 0.89–1.12)</td>
<td>HR 0.99† (95% CI 0.89–1.10)</td>
<td>HR 1.02† (95% CI 0.89–1.17)</td>
</tr>
</tbody>
</table>

†Testing for superiority for 3P-MACE was the primary endpoint (4P-MACE for sitagliptin); †exploratory outcome; 3P-MACE, 3-point major adverse CV events; CI, confidence interval; HR, hazard ratio.

change in body weight was observed in both groups.310

Lv et al. investigated the possibility that the initial combination therapy with metformin and linagliptin could offer better glycemic control (HbA1C ≤ 6.5%) than metformin alone without aggravating hypoglycemia. In comparison to metformin alone, combination therapy increased the proportion of patients who achieved HbA1C ≤ 6.5%, both for metformin doses of 1000 mg (49.5 vs 35.4%, respectively) and 500 mg (40.1 vs 22.9%, respectively). Early combination therapy with metformin and linagliptin increases the likelihood of obtaining tight glycemic control (HbA1C of ≤6.5%) without raising the risk of hypoglycemia or other side effects.11

Efficacy of Linagliptin vs Sulfonylureas (SU) in T2DM

The usage of SU is linked to a higher risk of weight gain and hypoglycemia. SU has reliable efficacy, particularly in patients with recently diagnosed diabetes.12 They are the most extensively used antihyperglycemic medications that act by lowering glucose levels by exhibiting their effect on β-cells and inducing an insulinotropic response.13 Outpatients suffering from T2DM to HbA1C readings of 6.5–10.0% participated in a 2-year parallel-group, noninferiority double-blind experiment conducted by Gallwitz et al. in 2012. Then, these patients were randomly assigned to receive either oral linagliptin (5 mg) or oral glimepiride (1–4 mg) once
In the linagliptin [−0.16% (standard error 0.03)] and glimepiride [−0.36% (0.03)] groups, comparable patterns of declines in adjusted mean HbA1C were observed [difference 0.20%, 97.5% confidence interval (CI): 0.09–0.30]. Consequently, the trial’s predetermined noninferiority threshold of 0.35% was achieved. When compared to the glimepiride group, the incidence of hypoglycemia and severe hypoglycemia was lower in the linagliptin group [one (1%) vs 12 (2%) patients]. When compared to the glimepiride group, the linagliptin group’s patients reported considerably fewer CV events (12 vs 26 patients). According to the study’s findings, linagliptin is noninferior to glimepiride in terms of efficacy and has a reduced risk of adverse events than glimepiride.14

**Opinions from experts on the efficacy of linagliptin in T2DM**

Linagliptin can be used as monotherapy in drug naive patients when contraindicated/ intolerant to metformin (95.1%).

Linagliptin can be considered a second-line therapy after metformin failure (93.5%).

Linagliptin-metformin fixed dose combination (FDC) as a 1st line shows better efficacy as compared to metformin monotherapy (95.1%).

**Efficacy of Linagliptin in Asians with T2DM**

In a study conducted by Sarashina et al., the impact of race on the pharmacodynamics, pharmacokinetics, safety and efficacy of linagliptin monotherapy was assessed in patients with T2DM. It consisted of two studies: study 1 consisted of Japanese patients exclusively, and study 2 enrolled both White and Asian patients. The results showed that linagliptin effectively inhibited DPP-4 activity in plasma, with concentrations more than half-maximal inhibitory concentration and DPP-4 inhibition of >80% at the trough. This inhibition was consistent in study 1 and study 2, indicating similar pharmacokinetics and pharmacodynamics across the different racial groups. Furthermore, the reduction in FPG concentrations was similar in magnitude across all groups. However, there was a greater decrease in HbA1C levels observed in study 1 (Japanese) and the Asian (non-Japanese) patients in study 2. The safety profile of linagliptin was favorable in each racial group, indicating the medication can be safely used in patients of different races. Based on these findings, the study concluded that a daily dose of 5 mg of linagliptin is appropriate for use in various racial groups.15

**Opinions from experts on the efficacy of linagliptin compared to SUs in Asians, an add-on to insulin therapy**

Linagliptin has comparable efficacy with relatively better durability and safety compared to glimepiride (64.6%).

Linagliptin has better efficacy across the Asian population compared to Caucasians (78.5%).

Linagliptin can be an effective OAD as an add-on to insulin (85.9%).

**Cardiovascular (CV) and HF Safety Evidence of Linagliptin from CVOTS**

As various glucose-lowering medications are associated with many CV safety issues, CV disease is the primary cause of mortality among diabetic individuals. The effects of linagliptin on CV safety have been examined in significant, large landmark trials like CAROLINA and CARMELINA. Participants with T2DM who were at high CV risk (history of vascular disease and urine-albumin creatinine ratio [UACR] 30 mg/gm) and high renal risk were examined for their reactions to linagliptin in the CARMELINA randomized clinical investigation performed by Rosenstock et al. Randomly assigned patients were given linagliptin (n = 3494) or a placebo (n = 3485). Major adverse CV events (MACE) with a 3-point outcome occurred in 434 of 3,494 subjects (12.4%) receiving linagliptin and 420 of 3,485 subjects (12.1%) receiving a placebo [hazard ratio (HR), 1.02; 95% CI, 0.89–1.17; p < 0.001 for noninferiority; p < 0.74 for superiority]. Hospitalization for HF (hHF) was noted in 209 (6.0%) linagliptin patients compared to 226 (6.5%) placebo patients. Linagliptin did not increase the probability of a composite CV outcome over a median of 2.2 years compared to placebo in T2DM patients with high CV and/or renal risk when added to usual therapy.17

Similarly, patients with relatively early T2DM and risk factors for established evidence of atherosclerotic CV disease were included in the CAROLINA study to compare the linagliptin (n = 3,203) and glimepiride (n = 3,010) CV outcomes. In the linagliptin group, 356 out of 3,023 participants (11.8%) and, in the glimepiride group, 362 out of 3,010 (12.0%) experienced the primary endpoint, 3-point MACE. The noninferiority requirement (p < 0.001 for noninferiority) was therefore satisfied, but not the superiority criterion (p = 0.76).18

The European Society of Cardiology: European Association for the Study of Diabetes guideline 2019 also states that among the available DPP-4 inhibitor, linagliptin and sitagliptin have neutral effects on the risk of hHF and may be considered for T2DM treatment in patients with HF.19

**Clinical Evidence of Linagliptin in T2DM with RI**

One of the most prevalent comorbidities among people with T2DM is RI. The choice of glucose-lowering medications in T2DM is significantly influenced by impaired renal function. Linagliptin may offer a novel therapy option for T2DM patients with RI because it is primarily eliminated through the hepatobiliary route, and only 5% is eliminated through the renal route.20 According to a pooled study of three clinical trials examining the impact of renal function on the efficacy and safety of linagliptin concluded that renal function was unaffected after 24 weeks of linagliptin treatment in all normal, mild, and moderate renal function groups. Linagliptin has a favorable efficacy and safety profile in T2DM patients with more severe renal complications. Linagliptin showed consistent efficacy in all stages of RI with mean change in HbA1C: normal renal function (−0.63%),
mild RI (−0.69%), moderate RI (−0.69%), and severe RI (−0.72%). Linagliptin is generally well-tolerated in all stages of RI.21

In solid organ transplants like kidneys, new-onset diabetes after transplantation (NODAT) is a significant and common metabolic complication.22 In a retrospective analysis by Sanyal et al., a total of 21 subjects with NODAT received linagliptin. A decrease in PPG, FPG, and HbAIC was observed after 24 weeks. No significant change in tacrolimus level and dose of tacrolimus remained unchanged over the study period. There were no changes in the estimated glomerular filtration rate (eGFR) with linagliptin. Minimal weight gain and only a single minor hypoglycemic episode were reported.23

Patients with kidney disease have been appropriately investigated for linagliptin’s safety and efficacy in CARMELINA CVOT, where 74% of the trial population had prevalent kidney disease. Time to the first adjudicated mortality owing to renal failure, end-stage renal disease (ESRD), or a persistent 40% or more drop in eGFR from baseline were the kidney-related outcomes. The occurrence of kidney outcomes was noted for 9.4% of those taking linagliptin vs 8.8% in the placebo (p = 0.62). Death due to renal failure and an exploratory composite of prolonged ESRD were recorded in similar patients with linagliptin vs placebo (3.9 vs 4.4%, respectively). Progression of albuminuria was less frequent in the linagliptin group (763/2162 [35.3%]; 21.4 per 100 person-years) as compared to the placebo group (819/2129 [38.5%]; p = 0.003).17

A study by Wanner et al. reported nephrotic range proteinuria (NRP) in a total of 646/6979 patients (9.3% [linagliptin]/placebo n = 317/n = 329). The median UACR in NRP participants was 3486 (Q1; 2746/Q3; 4941) mg/g and had a lower eGFR (39.9/56.1 mL/minute/1.73 m²). Regardless of the NRP status, the linagliptin group showed a neutral effect. The occurrence rate of parameters like a mild RI (−0.72%), moderate RI (−0.69%), and severe RI (−0.72%). Linagliptin is generally well-tolerated in all stages of RI.21

Opinions from experts on renal evidence with linagliptin
Linagliptin has the best renal safety evidence among the gliptins (84.3%). Linagliptin has proven safety and effectiveness across the spectrum of chronic kidney disease (CKD) in T2DM (94.3%).

Convenience and Adherence with Linagliptin in T2DM
Inappropriate Renal Dose Adjustment of DPP-4 inhibitor is Associated with Poor Clinical Outcomes in T2DM
Glitins have similar efficacy profiles but distinct pharmacokinetic characteristics. Patients with T2DM and CKD were studied in a retrospective observational cohort study (N = 82,332). The cohort was separated based on the daily dose of DPP-4 inhibitor (with or without dosage modifying them based on eGFR). The suitable or incorrect dosage of DPP-4 inhibitors was determined based on the daily dose of DPP-4 inhibitor, the patient’s eGFR, and the manufacturer’s guidelines. Between 2009 and 2012, over 40% of patients with T2DM and CKD received incorrect DPP-4 inhibitor dosages, which decreased to 24.4% in 2015. In individuals with T2DM and CKD stage 3 or 4, inappropriate DPP-4 inhibitor dosing was associated with a 15% higher risk of death from any cause, a 7.6% higher risk of emergency department visits, and a 19.9% higher risk of serious hypoglycemia compared to individuals given an appropriate dose.26 In the case of mild RI, sitagliptin, saxagliptin, and vildagliptin are given in the following doses: 100 mg once a day (OD), 5 mg OD and 50 mg twice a day, respectively. However, for moderate to severe RI, dosage adjustment is clinically necessary. Saxagliptin is adjusted at 2.5 mg OD dosage for moderate/severe RI, whereas vildagliptin is changed at 50 mg OD dose. In the case of sitagliptin, 50 mg OD is prescribed for moderate RI and 25 mg OD for severe RI. Linagliptin, on the other hand, does not require dosage change in RI.20,27–30 Instances of a necessity to modify the DPP-4 inhibitor dosage for diabetic patients suffering from RI have been reported for therapies that involve the use of sitagliptin, vildagliptin, saxagliptin, and teneligliptin. Tmax of linagliptin occurred approximately 1.5 hours after oral administration of a 5 mg OD dosage to healthy participants; the mean plasma area under the curve (AUC) was 139 nmol*hour/L, and Cmax was 8.9 nmol/L. Following oral treatment, the bulk of linagliptin (about 90%) is excreted unaltered, showing that metabolism is a minor elimination mechanism. Renal clearance at a steady state was approximately 70 mL/minute. Treatment with 5 mg OD linagliptin has shown efficacy and safety in all stages of RI, including hemodialysis. The adjustment of dose can be a major challenge in diabetic patients with RI, and therefore linagliptin may be an ideal choice of treatment in such instances.22,27–31 Hence, a single 5 mg OD dosing without dose adjustment with linagliptin is convenient for the management of T2DM and increases patient adherence to the dosing regimen across the broad patient profiles, as per the experts’ opinion.

Opinions from experts on convenience and adherence of linagliptin in T2DM
A single 5 mg OD dosing of linagliptin across the T2DM patient profile, irrespective of cardiac, renal, or hepatic comorbidities, eases up management of T2DM (94.3%). The ease of use and simplicity aspect of linagliptin makes it a preferred choice in teleconsultation among gliptins (75.7%).

Safety of Linagliptin across a Broad Range of T2DM Patients
Linagliptin’s clinical safety has been evaluated in more than 14,000 T2DM patients.20 Among the DDP-4 inhibitors available in the market, linagliptin has some data which demonstrate that dose modification is not essential for any mild/moderate, or severe hepatic impairment.20,27–31 Graefe-Mody et al. investigated the effect of hepatic impairment on the pharmacodynamics, pharmacokinetics, and tolerability of linagliptin. An open-label, parallel-group, single-center study was conducted that enrolled healthy subjects (n = 8) and patients with severe (n = 8), moderate (n = 9), and mild (n = 8) hepatic impairment. Renal excretion of unaltered linagliptin (s7%) and accumulation determined by AUC or Cmax were comparable between groups. At steady-state trough levels, median plasma DPP-4 inhibition was similar in healthy (91%), mild (90%), and moderate (89%) hepatic impairment patients, as well as in patients with severe hepatic impairment receiving a single dosage 24 hours later (84%). Since linagliptin was well tolerated, the patient...
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with liver impairment does not require dose adjustment for linagliptin. A pooled analysis was conducted by Inagaki et al. in 2016 to assess the effectiveness of linagliptin in patients with T2DM and hepatic difficulties. Between participants with and without baseline hepatic problems, there was no discernible difference in HbA1C reduction ($p = 0.4042$). In patients taking linagliptin, acute pancreatitis and biliary psephomiphic have been reported. In the CARMELINA experiment, adjudicated acute pancreatitis was recorded in 0.3% of linagliptin-treated patients and 0.1% of placebo-treated patients, while biliary psephomiphic was documented in 0.2% of linagliptin-treated patients, but not in any placebo-treated patients. In such cases, linagliptin should be discontinued.

Hypoglycemia in patients with T2DM often results in a series of physiologic effects that may lead to cardiac arrhythmias and can cause oxidative stress. These consequences could result in ischemic cerebral damage and may cause sudden cardiac death. Thus acute and chronic episodes of hypoglycemia may initiate several potential mechanisms that raise the possibility of CV complications. A study conducted by Greco et al. concluded that, among elderly T2DM patients, severe hypoglycemia is a significant and frequent metabolic emergency. The glucose-lowering mechanisms of many pharmacological agents also contribute directly to weight gain. The CAROLINA study found that across all specified hypoglycemia severity categories, the incidence of hypoglycemic episodes (as assessed by the investigator) was lower in the linagliptin group than in the glimepiride group. Lower hypoglycemia risk in the analyzed subgroups was consistently observed in the linagliptin group vs the glimepiride group.

A study by Barnett et al. assessed the safety and efficacy of linagliptin in elderly patients. HbA1C was $-0.61$ vs $-0.04\%$, placebo, $p < 0.0001$. A 0.64% placebo-corrected reduction was observed. Both the linagliptin and placebo groups had roughly comparable levels of overall safety and tolerability; 75.9% of patients in each group experienced a negative side effect (placebo $n = 60$, linagliptin $n = 123$). There was no mortality. The study drug was not deemed to be responsible for any of the severe adverse events that occurred, but it did impact 6.3% (five) of the patients in the placebo group and 8.6% (14) of patients in the linagliptin group. The most frequent adverse event was hypoglycemia, which occurred in both groups but at similar rates, 16.5% (13) in the placebo group and 24% (39) in the linagliptin group; odds ratio 1.58, 95% CI: 0.78–3.78, $p = 0.2083$.

Therefore, it can be suggested that linagliptin is effective in lowering glucose with a safety profile similar to placebo. Espeland et al. conducted a study to compare the CV safety of linagliptin with glimepiride in older and younger participants in the CAROLINA trial. Moderate-to-severe hypoglycemia was markedly reduced with linagliptin, with no differences among age groups ($p = 0.23$). The mean weight was $-1.54$ kg (95% CI: $-1.80$–$-1.28$), lower for linagliptin versus glimepiride. A relative risk reduction of 83% in hypoglycemia was reported in older patients over 75 years with linagliptin.

Weight neutrality across age groups was a vital observation with linagliptin. Linagliptin-basal insulin regimens are also an effective alternative to intensive basal-bolus insulin in very old T2DM patients. In the CARMELINA study, it was concluded that treatment based on linagliptin does not elevate the risk of cardioevents in older patients.

**Opinions from experts on the safety of linagliptin across a broad range of T2DM patients**

- Linagliptin can be safely used in T2DM patients with mild to moderate liver dysfunction (86.9%).
- Linagliptin can be safely considered in broad patient profiles, including elderly patients with T2DM (98.3%).
- Linagliptin, with a lower risk of hypoglycemia and weight neutrality as compared to glimepiride, alleviates the fear of hypoglycemia and weight gain in T2DM (96.7%).

**CONCLUSION**

The current position paper has been developed based on expert opinions, experience, and common therapy practices in India while providing relevant clinical evidence to support the guidance that has been developed for the use of linagliptin. To effectively treat a patient with T2DM, healthcare professionals must take into account a number of factors when choosing a regimen for drug treatment, including the patient’s preferences, age, reduction of CV risk, individualized glycemic targets, avoidance of hypoglycemia, renal protection, comorbidities, cost, weight gain, and other side effects of the medication. The expert opinions documented in this paper help justify the clinical role of linagliptin in managing T2DM. It is an efficacious and well-tolerated drug for the management of T2DM. It reduces the risk of hypoglycemia, is weight neutral, and does not require dose adjustment across the broad patient profile regardless of hepatic or renal status. It can be utilized as a single agent for drug naive patients when metformin is contraindicated/patients who are intolerant to metformin or as second-line therapy after metformin failure, or as an effective OAD add-on to insulin.

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