

Linagliptin: Cardiovascular and Renal Safety beyond Doubt at a Steep Price

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Abstract

Dipeptidyl peptidase-IV inhibitors or “gliptins” are commonly used oral anti-diabetic drugs for Type 2 diabetes mellitus, preferred as add-on therapy after metformin. Various cardiovascular outcome trials (CVOTs) have established their cardiovascular safety. Approved later than other gliptins, linagliptin has unique pharmacokinetic profile. A literature review was performed by searching science databases, in addition to the Medline database via PubMed, for relevant articles. The search included meta-analyses, systematic reviews, review articles, and randomized and nonrandomized trials. Related publications in the English language were reviewed, and the most relevant papers were summarized. This review explores the potential of clinical use of this drug in light of the two recently reported CVOTs, and cost of therapy. Results of CAROLINA and CARMELINA, published in 2019 and 2018, respectively, provide robust proof of long-term CV and renal safety of linagliptin. Both trials are first of their kinds for including diabetes population with renal compromise and use of an active comparator, respectively. Physicians can confidently choose in subsets of adults with diabetes who have compromised renal or cardiac functions or who are at high risk without any dose adjustments. However, the price of the drug is very high, costlier than other oral drugs. Cost remains the biggest hurdle and is likely to remain so with the drug being patent protected for a considerable time in future. Thus, despite the promise of CV and renal safety, linagliptin is likely to remain out of reach for majority of the Indian population with diabetes.

Keywords: Cardiovascular outcome trials, cardiovascular, linagliptin, renal, safety

INTRODUCTION

Dipeptidyl peptidase-IV inhibitors (DPP-IV i's) or “gliptins” are an established class of oral antidiabetic drugs for Type 2 diabetes mellitus (T2DM). Sitagliptin was the first agent approved by U.S. Food and Drug Administration (US FDA) in this class in 2006, followed by approvals of vildagliptin, saxagliptin, linagliptin, alogliptin, and teneligliptin across the world. These drugs inhibit the degradation of glucagon-like peptide-1 (GLP-1) by inhibiting the DPP-IV enzyme, thereby amplifying the incretin effect – enhancing glucose-dependent insulin secretion, slowing gastric emptying, reducing postprandial glucagon secretion and food intake.^[1] Gliptins are commonly used as add-on drugs in T2DM as part of dual- or triple-drug regimens, usually administered as single daily dose except vildagliptin which is used twice a day.

The latest American (American Diabetes Association [ADA] 2019), European (ADA-EASD, European Association for the Study of Diabetes, consensus report 2018), and Indian (Indian Council of Medical Research [ICMR], 2018)

guidelines for the management of T2DM recommend gliptins as one of the first choice add-on drugs after metformin, with advantages of weight neutrality, minimal risk of hypoglycemia, good gastrointestinal tolerability, along with improvement in beta cell function.^[2-5] They may also be considered as the initial drug where metformin is contraindicated or not tolerated.^[6] Although gliptins differ in pharmacokinetic and pharmacodynamic properties, their anti-hyperglycemic effects are remarkably similar; HbA1c reduction of approximately 0.75%, fasting glucose reduction of approximately 18 mg/dL has been reported.^[5] These drugs, as a class, are associated with mild adverse effects such as nasopharyngitis, headache, and

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skins reactions. Concerns have been raised though for severe joint pains and pancreatitis.^[7] Cost considerations are however needed in the setting of developing countries – prescribing based on patient affordability, where sulfonylureas (SU's) definitely score despite proven problems of weight gain, hypoglycemia, lack of sustainability of glycemic control, and questionable cardiovascular safety. Availability of teneligliptin at significantly lower prices, and as a generic formulation in the government's mass generic drug scheme (Pradhan Mantri Bhartiya Janaushadhi Pariyojna) has made it relatively preferred over other costlier gliptins.^[8,9]

Search strategy

To find evidence and data for reviewing potential of clinical utility of linagliptin in India in light of the recent publication of cardiovascular outcome trials (CVOT) results, and costing of drugs for diabetes in India, a search was carried out using PubMed (Medline), Cochrane Library, Medscape and Google Scholar search engines from 2000 to 2019. The search terms identified and used were “linagliptin,” “DPP-IV inhibitor,” “CVOT,” “diabetes,” “cost” as the key terms extracted from the titles and abstracts of the relevant studies for different sections of the review. While Searching with PubMed search engine, medical subject headings (MeSH terms), subheadings and “All Fields” were combined with Key Boolean operators “AND,” “OR,” and “NOT” to get the relevant studies and exclude studies which do not match the requirements. Additionally hand searching – bibliography searching were performed along with accessing cost-related data from commercial drug directories and web resources as well as published treatment guidelines.

Research articles, review articles, and editorials were identified and reviewed. Both abstracts and full text articles in English language were included. The identified articles focused on linagliptin and other DPP-IV inhibitors, CVOTs for diabetes, and cost of therapy for diabetes in the Indian scenario.

NEED AND OUTCOMES OF GLIPTIN CARDIOVASCULAR OUTCOME TRIALS FOCUS ON LINAGLIPTIN

Globally cardiovascular disease (CVD) affects approximately 32.2% of all individuals with T2DM.^[10] CVD is a major cause of mortality among individuals, with T2DM with coronary artery disease and stroke being the major contributors.^[10] Individuals with T2DM are disproportionately affected by CVD compared with individuals without diabetes; death rates have been estimated to be higher among individuals with T2DM without prior myocardial infarction (MI) compared to those who do not have diabetes. The death rates among those with a prior MI increased from 15.9% among those without diabetes to 42% in those with T2DM.^[11] Prevalence data for CAD among individuals with diabetes in India are limited, available mostly through small-scale studies. The CUPS (Chennai Urban Population Study) study showed the prevalence of CAD among individuals with diabetes was 21.4% (25.3% in known diabetes, 13.1% in newly diagnosed

diabetes).^[12] The A1chieve study showed that cardiovascular complications (23.6%) were the second most common complication in T2DM following neuropathy (24.6%).^[13] In the CINDI study, risk factors for CVD, such as hypertension, obesity, and dyslipidemia were observed in 23.3%, 26%, and 27%, respectively, among individuals with newly- diagnosed T2DM.^[14]

Intensive glycemic control reduces the risk of microvascular complications in patients with T2DM, but several clinical trials have shown no benefits on macrovascular risks especially among those at high risk for cardiovascular events.^[15-19] There have been growing concerns for adverse cardiovascular outcomes of certain glucose lowering agents and their combinations used to control hyperglycemia. A meta-analysis of randomized controlled trials of rosiglitazone concluded that there is an increased risk of MI and death in patients on rosiglitazone.^[20] This triggered a series of discussions on the need to evaluate therapies for diabetes more closely from a cardiovascular perspective. In 2008, the FDA issued guidance to pharmaceutical industry on the conduct of clinical studies to prove that the new drugs for diabetes confer to acceptable levels of CV safety.^[21] In addition to safety, the importance of preventing cardiovascular complications (CV benefit) while managing T2DM has been emphasized upon in the latest position statement issued by the ADA and EASD.^[3]

Based on postapproval commitment, large prospective CVOTs were initiated to assess the CV safety and efficacy of gliptins in patients with T2DM and established CV disease. Single CVOTs have been reported for each of the three gliptins: saxagliptin (SAVOR TIMI 53), alogliptin (EXAMINE) and sitagliptin (TECOS).^[22-24] No dedicated CVOT has been conducted for vildagliptin but its safety was specifically evaluated in individuals with T2DM with reduced LVEF, NYHA class I – III heart failure (VIVID).^[25] Safety was uniformly demonstrated across the class for atherosclerotic CV outcomes, with a neutral effect on major adverse CV event (MACE) outcomes in the CVOTs of saxagliptin, alogliptin, and sitagliptin. These studies were relatively short in duration (median follow-up of 2.1 and 1.5 years respectively) and included individuals with T2DM, predominantly or exclusively with symptomatic CV complications.^[22-24] However, trials for saxagliptin and alogliptin showed an unexpected finding in the form of an increased risk for hospitalization for heart failure (hHF) which was statistically significant in SAVOR TIMI 53 (saxagliptin). Consequently, a warning has been included in the product labels for these agents.^[26] The safety of the class for hospitalization for HF risk came under the scanner, which has added to concerns that some agents for T2DM that stimulate insulin signaling might increase heart failure risk.^[27] Subsequent meta-analysis have however shown inconclusive evidence regarding risk of HF with gliptins as a class.^[28] In this review, we focus on analyzing the cardiovascular and renal safety of linagliptin and cost considerations with its use in an Indian context.

LINAGLIPTIN: A UNIQUE DIPEPTIDYL PEPTIDASE-IV INHIBITOR

Linagliptin, a xanthine-based DPP-IV inhibitor with a molecular mass of 472.5 Da, was developed by Boehringer Ingelheim Pharmaceuticals, Germany. It was approved by the US FDA and the European medicines agency (EMA) in 2011, followed by many countries worldwide including India (2012), for use at an oral dose of 5 mg once daily. Developed later than other gliptins, linagliptin is unique with regard to its pharmacokinetic profile within this class. It has relatively greater interaction with and superior inhibitory activity (>80%) on DPP-IV enzyme, and has a long elimination half-life (terminal $t_{1/2}$ > 100 h).^[29] It is one of the nonpeptidomimetic inhibitors which generally have greater selectivity, higher potency, faster activity and lesser chances of side effects.^[5] So far, linagliptin is the only gliptin with a non-renal route of excretion, through feces (>80%), allowing its safe use in patients with reduced renal function without dose adjustment. The biliary excretion is related to its chemical structure and the high degree of protein-binding in plasma and tissues. Hepatic metabolism is minor through CYP3A4; does not necessitate dose adjustment in patients with hepatic failure, or cause clinically significant drug interactions.^[30] Studies with linagliptin have shown substantial glycemic reductions, good tolerability without risk of hypoglycemia.^[31]

For evaluating CV safety of linagliptin, two well-designed, randomized double-blinded CVOTs – CARMELINA (CARdiovascular Safety and Clinical outcoME with LINagliptin) and CAROLINA (CARDiovascular Outcome study of LINagliptin versus glimepiride in patients with type 2 diabetes) were initiated and their complete results have been announced recently – CAROLINA in June 2019, CARMELINA in October 2018.^[32,33] In contrast to the other CVOTs for gliptins, these two trials included a substantial number of individuals with T2DM with varying clinical characteristics, and have provided a wide and comprehensive dataset on the long-term safety of this drug. Table 1 displays study characteristics and major findings of CARMELINA and CAROLINA trials.^[34,35]

CARMELINA: A FIRST AMONG CARDIOVASCULAR OUTCOME TRIALS

Full results of CARMELINA, the first CVOT for linagliptin, were first reported in October 2018, and have been published since.^[34] This trial comprised of individuals with established T2DM and CVD and/or chronic kidney disease (CKD); a population practically seen in clinical practice, yet underrepresented in CVOTs. It is the first gliptin CVOT to have a substantial proportion of patients (74%) with renal impairment and/or characterized macroalbuminuria at baseline. A limitation of the earlier CVOTs has been that only a minority of individuals in the study cohorts had reduced renal function at baseline, while renal outcomes were usually only assessed as exploratory or *post hoc* analyses.^[36] Heart

failure risk may be of particular concern in these individuals; heart failure and CKD being driven by diverse cardio-renal interactions including hemodynamic and neurohormonal mechanisms, such as activation of the renin–angiotensin–aldosterone system, in addition to inflammatory processes that are common to CKD, CVD, and diabetes.^[37]

The proportion of individuals with T2DM with reduced renal function at baseline was more than two-fold higher in CARMELINA than other DPP-4 inhibitor CVOTs, five-fold higher for severely reduced renal function (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m²), and between 4 and 8 folds higher for macroalbuminuria (urinary albumin-to-creatinine ratio >300 mg/g).^[34] According to Kidney Disease–Improving Global Outcomes, 93% of trial subjects in CARMELINA had at least moderate renal risk at baseline. Although CARMELINA was primarily a CV safety study, a renal composite was a key secondary outcome, providing a confident assessment of long-term renal safety of a gliptin for the 1st time in T2DM.

The trial demonstrated non-inferiority to placebo for the primary outcome of time to first occurrence of 3 point MACE (hazard ratio [HR] 1.02, 95% confidence interval [CI] 0.89, 1.17, $P < 0.001$), thus reassuring the CV safety of linagliptin in this high-risk population.^[34] It also demonstrated no increase in risk of hHF (HR 0.90, 95% CI 0.74, 1.08, $P = 0.26$), which was an exploratory outcome.^[34] The key secondary renal endpoint was a composite of time to first occurrence of end-stage renal disease, death due to renal failure, or a sustained decrease of at least 40% in eGFR from baseline. CARMELINA demonstrated a neutral effect with linagliptin for this renal end point (HR 1.04, 95% CI 0.89, 1.22, $P = 0.62$), including prespecified sensitivity analyses and subgroup analyses stratified by baseline renal risk.^[34] The study also demonstrated a neutral effect of linagliptin in several exploratory analyses for renal and other microvascular outcomes, except for progression of albuminuria, where linagliptin in fact showed a positive effect.^[34] The additional renal analyses further endorsed the robust and wide-ranging safety profile of linagliptin. Glycemic control was improved versus placebo with a less frequent initiation or intensification of insulin therapy, in a study design that permitted additional glucose lowering therapy where required. This is a particularly relevant finding in a population of T2DM with renal impairment for whom therapeutic options for glucose lowering can be rather limited.

Similar to other CVOTs for the gliptins, no significant benefit in reducing CV or renal risk was observed from CARMELINA. Unfortunately the high event rate in the trial across both study arms, which may have been due to the substantial burden of cardiorenal risk at baseline, led to early cessation of the study. Therefore, follow-up was available for a median of only 2.2 years, and thus any speculated long-term benefit that might have occurred with continued linagliptin therapy could not be revealed. Even so, it should not diminish the important safety findings from CARMELINA.

Table 1: Study characteristics and findings of CARdiovascular Safety and Clinical outcoME with LINAgliptin and CAROLINA trials^[34,37]

Trial features	CARMELINA	CAROLINA
Announcement of results	October 2018 (EASD meet)	June 2019 (ADA meet)
Type of trial	Randomised, double-blind, placebo-controlled trial	Randomised, double-blind, active-controlled trial
Purpose of trial	To assess the long-term CV and kidney safety profile of linagliptin versus placebo, in addition to background standard care	To assess the long-term CV safety profile of linagliptin versus active comparator, in addition to background standard care
Study drug	Oral linagliptin 5 mg/day	Oral linagliptin 5 mg/day
Comparator	Placebo	Glimepiride 1-4 mg/day
Trial population	Adults with T2DM including cardiovascular disease and/or kidney disease	Adults with early T2DM and increased cardiovascular risk or established cardiovascular disease
Number of countries and centers	27 and >600	43 and >600
Number of participants	6979	6033
Duration of follow-up (median)	2.2 years	6.2 years
Duration of diabetes (mean)	14.8 years	6.2 years
Background therapies	55% metformin 57% insulin	83% metformin 9% treatment naïve (insulin - excluded)
Primary end point	3P - MACE: Time to first occurrence of CV death, nonfatal MI or nonfatal stroke	3P - MACE: time to first occurrence of CV death, nonfatal MI or nonfatal stroke
Secondary end points	Renal safety: time to first occurrence of any of - sustained eGFR reduction, progression to sustained ESKD, death due to kidney disease	4P MACE: Composite of 3P-MACE plus time to first occurrence of hospitalization for unstable angina Proportion of patients on treatment and maintaining HbA1c ≤7.0% at final visit
Key results	Linagliptin versus placebo group CV safety: HR 1.02 (0.89-1.17, 95% CI) Renal safety: HR 1.04 (0.89-1.22) Risk of hospitalization due to HF: HR 0.90 (0.74-1.08)	Linagliptin versus glimepiride CV safety: HR 0.98 (0.84-1.14, 95% CI) Risk of hospitalization unstable angina (4P MACE): 13.2% versus 13.3%

CARMELINA=CARdiovascular Safety and Clinical outcoME with LINAgliptin, CAROLINA=CARdiovascular Outcome study of LINAgliptin, EASD=European Association for the Study of Diabetes, ADA=American Diabetes Association, CV=Cardiovascular, T2DM=Type 2 diabetes mellitus, MACE=Major adverse CV event, MI=Myocardial infarction, eGFR=Estimated glomerular filtration rate, ESKD=End-stage renal disease, HbA1c=Glycated hemoglobin, HF=Heart failure, HR=Hazard ratio

CAROLINA: THE FIRST HEAD TO HEAD CARDIOVASCULAR OUTCOME TRIALS

CAROLINA is the latest gliptin CVOT, whose results have been announced in June 2019.^[35] It compared a gliptin to an active comparator for the 1st time – linagliptin 5 mg/day with glimepiride 1–4 mg/day, with respect to long term CV safety in adults with relatively early T2DM at increased risk of CV events, and with less optimized glycemic control.^[38] It has provided the first head-to-head comparison of a gliptin with another class of oral glucose-lowering agent, and provides valuable information about both linagliptin and glimepiride. The study population was a cohort of adults with early T2DM (median duration 6.2 years) and a mean baseline HbA1c of 7.2%. Study medications were added to stable background glucose-lowering medication and cardiovascular standard of care. More than three fourth of participants (>80%) were on monotherapy predominantly with metformin, 34.5% had established CV complications with 13.8% having a previous MI and >35% were at increased CV risk at study entry. This study reaffirms the cardiovascular safety of linagliptin demonstrated in CARMELINA in a wider and different population of individuals with T2DM. The primary endpoint, defined as time to first occurrence of 3P-MACE, occurred in 11.8% of the linagliptin group compared to 12.0%

of the glimepiride group after a median follow-up of >6 years, the longest for a gliptin CVOT. Non inferiority of linagliptin versus glimepiride was thus established (HR 0.98, 95% CI 0.84–1.14). No new safety signal was generated, showing consistency with previously available overall safety data. Linagliptin was similar to glimepiride in the secondary end point of 3P-MACE plus hospitalization for unstable angina, i.e., 4P-MACE.^[35]

Additionally, a higher proportion of participants within the linagliptin group (16.0%) achieved the secondary composite efficacy end point which comprised of HbA1c ≤7% at the final visit without rescue medication, moderate or severe hypoglycemia or a 2% or greater weight gain, versus the glimepiride group (10.2%). Linagliptin demonstrated similar overall effects on HbA1c, but significantly reduced the relative risk for hypoglycemia by 77%, seen across all categories of hypoglycemia including those requiring hospitalization. A weight reduction benefit of -1.5 kg compared to glimepiride (95% CI -1.8, -1.3) was also seen with linagliptin.^[35] The CAROLINA trial additionally provides reassurance about the long-debated cardiovascular safety of SU's, while illustrating the well-known risks of hypoglycemia and weight gain seen with this drug class at the same time.

CHOOSING A GLIPTIN – INDIAN PERSPECTIVE AND IMPLICATIONS OF THE LINAGLIPTIN CARDIOVASCULAR OUTCOME TRIALS

The IDF reported in 2017 that approximately 73 million adult individuals with diabetes live in India, second highest in the world, and has anticipated this number to reach 135 million by 2045.^[39] High cost of care and loss of productivity have made diabetes an expensive disease. WHO has already raised concerns about the financial burden of diabetes as it indicated that in low income Indian families with an adult having diabetes, as much as 25% of family income was spent on diabetic care.^[40] The additional costs associated with managing downstream complications can be very substantial.

Recent treatment guidelines recommend SGLT2 inhibitors such as empagliflozin or the GLP-1 receptor agonist, liraglutide, as preferred second-line therapies in patients with CVD who have failed to achieve glycemic control while on monotherapy.^[2-4] This paradigm shift in the management of T2DM is largely supported by evidence from recent landmark clinical trials - EMPA-REG OUTCOME, CANVAS, LEADER and SUSTAIN-6.^[41-45] A recently published Indian Guidance on Cardiovascular and Renal Comorbidity Management in T2DM also recommends similar approach to reduce both CVD and all-cause mortality, and also improve renal outcomes.^[46] However, considering the potential adverse effects or patient convenience (non-preference for injectable therapy) or the high expenses, it is difficult to see an increase in prescription of SGLT 2 inhibitors and GLP-1 agonists in India.

Despite not being accurately representative of Indian population, several epidemiological studies collectively reflect a significant existing burden of cardiovascular and renal complications in Indian diabetics, a 2.35-fold higher risk of coronary artery disease (CAD) and a nearly 2-fold increased risk of CKD, in presence of diabetes.^[12-14,47-50] Strikingly, India ranked highest in the prevalence of CKD (39.8%), and second highest in the prevalence of albuminuria (8.56%) in the “Joint Asia Diabetes Evaluation” registry, which assessed the diabetes care standards across seven Asian countries.^[49] Thus, in the substantial subset of Indians with diabetes, having high risk of or established CVD with declining renal functions, it is important to consider gliptins with proven CV and renal safety. Currently available gliptins in India are sitagliptin, vildagliptin, saxagliptin, linagliptin, and teneligliptin. Teneligliptin has become available relatively recently in Japan, Argentina and India. It is currently undergoing Phase 1 trials in the US and Phase 2 trials in Europe, progress of which is not verifiable.^[51,52]

All gliptins have the similar (modest) glycemic efficacy and safety profile.^[53] With sitagliptin, saxagliptin and vildagliptin, dose reduction is required with declining renal function status. Despite lack of concrete evidence, general recommendations are to avoid saxagliptin and alogliptin in compromised cardiac status. No CVOT has been conducted for Vildagliptin as it's not approved in the U.S. The VIVIDDD demonstrated safety in diabetics with

reduced ejection fraction. In this scenario, linagliptin with the cardiovascular safety and renal safety being ably supported by CAROLINA and CARMELINA becomes a very viable option.

However, the biggest barrier to use of linagliptin is its high cost; presently costliest among the available gliptins with only two brands available in the Indian market at almost INR 50/tab (USD 0.67/tab). In comparison, sitagliptin is available at approximately INR 30–40/tab (USD 0.40–0.53/tab), saxagliptin at approximately INR 40/tab (USD 0.53/tab) and vildagliptin at approximately INR 9/tab (USD 0.12/tab). All these drugs are also available as fixed-dose combinations with metformin at slightly higher costs as listed in commercial drug directories and online pharmacies. These prices are a significant burden for an average Indian diabetic, proving to be a significant hindrance to prescription of these drugs and subsequent adherence to them. Teneligliptin was introduced in India in May 2015, and along with vildagliptin, is available at almost one quarter to one-fifth of the cost of other gliptins at INR 5–10/tablet (USD 0.067–0.13/tablet) as a branded formulation. It is the only gliptin available under the generic drug scheme of the government priced at INR 4.95 (USD 0.066) per tablet.^[9] This is a positive step in a developing country like India, where the cost of medicines is largely an out-of-pocket expenditure and a huge limiting factor in health care especially with regards to treatment adherence. In a short span of time, teneligliptin has thus becoming one of the most widely prescribed gliptins in India including at tertiary care government centers such as AIIMS Bhopal. However, long-term safety studies including cardiovascular and renal safety studies are still awaited and required; current data available for teneligliptin does not point toward any signal for serious adverse effect.^[54,55] It can be used in individuals having T2DM with renal impairment, including those on hemodialysis, without the need for dose adjustment. The efficacy and safety of teneligliptin in CKD requiring hemodialysis is based on findings of small observational studies.^[56-60] No dedicated CVOT has been conducted for teneligliptin, such a trial is much needed to establish its cardiovascular safety. There have been reports of QTc prolongation with teneligliptin at high doses especially with other QT prolonging drugs.^[51] One trial – the Teneligliptin On the Progressive Left Ventricular Diastolic Dysfunction With T2DM study is currently ongoing and is designed to assess effect of long term treatment with teneligliptin on cardiac diastolic function in patients with T2DM. It is recruiting patients of age 20–85 years with ejection fraction of >40%, and is expected to be completed in June 2021.^[61,62] Rather than being a proper CVOT, it appears similar to the VIVIDDD trial of vildagliptin.

Similar to teneligliptin, vildagliptin is also now available at significantly cheaper price since it has gone off patent recently (December 2019) and cheaper generic versions of this popular drug are available in the Indian market.^[63] But properly designed, large, global, long-term safety studies especially focused on CV and/or renal outcomes are lacking for both these drugs. Moreover, neither of these drugs are approved by the US FDA; teneligliptin is not approved in the EU also.

On the other hand, the two linagliptin CVOTs provide robust clinical evidence for a T2DM population that is highly relevant to clinical practice – reassurance of renal safety with reduced progression of albuminuria, and safety even in patients at high risk of heart failure. CARMELINA and CAROLINA, together, have demonstrated long-term cardiovascular safety compared with placebo as well as an active comparator in a broad range of adults with T2DM including those having CVD, renal disease, or both, or those at high risk. The durability of glycemic management was demonstrated too. In overcoming the crucial high price barrier in India, patent protection seems to be the biggest hurdle at present with linagliptin covered until at least August 2023 with the innovator modifying the patent to extend the use in routine treatment of T2DM in combination with other oral drugs and insulin.^[64,65] With further multiple patents, this has been extended to 2029 for the specific indication of treatment of T2DM in individuals with renal impairment and for whom metformin therapy is inappropriate by administering linagliptin without dose adjustment.^[65] This directly translates into the lack of any chance that linagliptin prices would come down in the near future or even considerably foreseeable times

unless the innovator company decides to reduce prices, which is highly unlikely. The branded generic versions of the drug cannot be launched for years to come; this was something which brought down prices tremendously for teneligliptin and vildagliptin, making these drugs affordable.

In India, where recent studies analyzing diabetes expenditure have shown that even in government facilities, individuals with diabetes have to spend up to INR 750/month (USD 10.02/month), and monthly drug costs can range from INR 300 to 3000 (USD 4.01–40.07), a single tablet costing INR 50 (USD 0.67), INR 1500/month (USD 20.03/month) is a significant cost burden which majority of the population would not be able to bear. To put this drug price impact into perspective, we need to bear in mind we have a per capita income of <INR 10,000 (USD 133.55)/month.^[66-68] If we go by World Bank definition, >30% population is below poverty line defined as monthly income of less than approximately INR 2200 (USD 29.38).^[69]

Table 2 displays a per unit out-of-pocket expense (median brand price), expected HbA1c reduction with monotherapy, CV and renal benefit/safety potential of the commonly used oral

Table 2: Effects, safety and expenses with oral drugs for diabetes

Class and Compounds	Expected HbA1c reduction (%)	Cardiovascular effects		Renal effects		Out of pocket expense (INR)
		ASCVD	CHF	Progression of CKD	Dose consideration	
Biguanides: Metformin	1.0-2.0	Potential benefit	Neutral	Neutral	C/I in severe and modification in moderately severe CKD*	500 mg: INR 1.5 (USD 0.021) 1000 mg: INR 3.3 (USD 0.046)
Sulfonylureas: Glipizide Glimipiride Gliclazide Glibenclamide	1.0-2.0	Neutral (no CVOTs done)	Neutral (no CVOTs)	Neutral	Glipizide: No adjustment Glimipiride: Avoid in moderate CKD* Gliclazide: Reduce dose in severe CKD* Glibenclamide: Avoid in moderate CKD*	Glipizide 5 mg - INR 0.85 (USD 0.012) Glimipiride 1 mg - INR 2.6 (USD 0.036) 2 mg - INR 4.5 (USD 0.063) Gliclazide 5 mg - INR 0.86 (USD 0.012) Glibenclamide 5 mg - INR 0.73 (USD 0.010) 15 mg - INR 3.2 (USD 0.045)
Thioazolidinediones: Pioglitazone	0.5-1.4	Potential benefit	Increased risk	Neutral	Not recommended in CKD*	Vildagliptin 50 mg - INR 9.03 (USD 0.12)
DPP 4 inhibitors: Saxagliptin Alogliptin Sitagliptin Linagliptin Teneligliptin Vildagliptin	0.5-0.8	Neutral (CVOTs data available)	Potential increase in risk: saxagliptin, alogliptin	Neutral	Saxagliptin, alogliptin, sitagliptin, vildagliptin: Dose reduction in moderate CKD Linagliptin, teneligliptin: No adjustment required	Sitagliptin 100 mg - INR 45 (USD 0.60) Teneligliptin 20 mg - INR 9.9 (USD 0.13) Linagliptin 5 mg - INR 46.8 (USD 0.63)
SGLT 2 inhibitors: Empagliflozin Canagliflozin Dapagliflozin	0.5-1.0	Benefit: empagliflozin, canagliflozin (CVOTs data available)	Benefit: empagliflozin, canagliflozin	Benefit: empagliflozin, canagliflozin	All molecules: Monitoring required in moderately severe and contra-indicated in severe CKD*	Dapagliflozin 10 mg - INR 47.5 (USD 0.67) Empagliflozin 25 mg - INR 57 (USD 0.80) 10 mg - INR 47 (USD 0.66) Canagliflozin 100 mg - INR 54.7 (USD 0.77)

*GFR (mL/min/1.73m²) categories in CKD - Normal or high (Grade 1) ≥ 90, mild (Grade 2) 60-89, mild to moderate (Grade 3a) 45-59, moderate to severe (Grade 3b) 30-44, severe (Grade 4) 15-29, kidney failure (Grade 5) <15. CKD=Chronic kidney disease, CVOTs=Cardiovascular Outcome Trials, INR=International normalized ratio, HbA1c=Glycated haemoglobin

drugs for diabetes used as first line or second line according to all accepted treatment guidelines.^[2,70,71]

It is clearly visible that drug costs, considering median branded prices from formulations available in the market, increase exponentially when moving from older molecules such as metformin and SU's to the relatively newer molecules such as DPP 4 inhibitors and SGLT 2 inhibitors. Per unit out-of-pocket expenses for the latter group of molecules are as high as fifty times, what the newer molecules offer at these high costs are proven cardiovascular and/or renal benefits/safety. Hence, it comes down to the discretion of the physician as well as the affording capacity of the individuals with diabetes as to which drugs to use as add-on therapies. Based on CAROLINA data, if we compare estimated cost in the two arms over a 6-year follow-up period, linagliptin would cost INR 1,02,492 (USD 1,368.82) taking a median price of INR 46.8 (USD 0.63) for a dose of 5 mg/day whereas the cost of therapy with glimepiride 4 mg/day would be INR 19,710 (USD 263.24) at a median branded price of INR 4.5 (USD 0.06) for 2 mg tablets. Hence, treatment with linagliptin would be more than five times costlier than glimepiride over same follow-up period of 6 years. It is to be noted that this difference in therapy costs would provide a lesser incidence of 3P MACE by 0.2% as per CAROLINA data.^[35] Thus, using linagliptin for cardiovascular safety per se is definitely an expensive proposition compared to glimepiride. Moreover, the cost of linagliptin puts it beyond reach of majority of the population with diabetes in India, especially with very little scope of medical reimbursements or insurance payouts as in countries like the USA. For those who can afford though, it should definitely be offered by treating physicians especially to those who are at high risk or already have compromised cardiac functions or have renal impairment or CKD (eGFR <30 mL/min/1.73 m²). For now, it is very likely that prescribers in India will prefer to write drugs like teneligliptin and vildagliptin when it comes to choosing among the gliptins, chiefly because they would be affordable.

CONCLUSION

DPP IV inhibitors like linagliptin achieve an overall modest reduction of HbA1c, have a good safety profile in more fragile subsets of T2DM population having been thoroughly evaluated in the elderly and those with cardiac and/or renal impairment. They offer a safer profile compared to SGLT-2 inhibitors for whom expected adverse events like urogenital infections, volume depletion, and warnings for unexpected adverse events such as ketoacidosis, bone fractures and risk of amputation, from the FDA and the EMA reduce acceptability. When compared to SGLT 2 inhibitors or GLP1 agonists, gliptins do not confer similar short-term benefits of cardiovascular or renal protection, but are still preferred as add-on therapy after metformin.

CAROLINA, in succession to CARMELINA, is a welcome attempt that has provided robust proof of long term CV and renal safety regarding use of linagliptin. Barring the important cost considerations, these CVOTs credibly support the use

of linagliptin before a sulfonylurea and other gliptins in subsets of adults with diabetes who have compromised renal or cardiac functions or who are at high risk for the same. Physicians can have ample confidence in using this drug with safety in individuals with CKD and CVD, without any dose adjustments. But the significantly high drug acquisition cost remains the biggest hurdle with the drug being patent protected, and priced at a premium – costlier than all other gliptins and even the SGLT 2 inhibitors. Therefore, at present linagliptin remains perhaps out of reach of majority of Indians with diabetes, but could be one of the first choices among those with cardiovascular and renal complications or high risk.

Work done by authors

The authors are part of a diabetes research team working at AIIMS, Bhopal, with collaboration of the departments of pharmacology and medicine for the last 2 years. We have been carrying various cross sectional and cohort studies on therapeutics of diabetes covering clinical utility of different classes of drugs. The authors have independently also carried out and published substantial preclinical and clinical research on diabetes and other non-communicable diseases as well as pharmacoeconomics. Senior authors in the study have a cumulative academic and clinical experience of almost 40 years.

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Conflicts of interest

There are no conflicts of interest.

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