Review Article

A Review on Cardiovascular Outcome Studies of Dipeptidyl Peptidase-4 Inhibitors

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Abstract

The U.S. Food and Drug Administration issued a guidance for pharmaceutical industry defining preapproval and postapproval requirements for the demonstration of cardiovascular (CV) safety for all new medications developed for glycemic management in type 2 diabetes. However, results published from the studies of dipeptidyl peptidase-4 (DPP-4) inhibitors are conflicting with regard to different CV endpoints. Upcoming CV outcome studies perhaps will be able to provide additional insights related to diabetes management and help to provide the answers to some of these concerns. This article provides a brief overview regarding how various CV safety evidence of DPP-4 inhibitor evolved over time that highlights possible implication in clinical practice and translates them into effective diabetes management.

Keywords: Cardiovascular outcome, cardiovascular safety, diabetes, dipeptidyl peptidase-4 inhibitors

Introduction

The progressive rise in the incidence of type 2 diabetes mellitus (T2DM) in the last few decades, which is on verge of becoming a pandemic disorder in Indian populations, is attributed to several reasons such as the aging of population, rapid urbanization resulting in sedentariness, physical inactivity, and consequently, greater occurrence of obesity.[1] Presence of chronic complication and comorbidities attributes to large proportion of medical costs for type 2 diabetes.

Patients with type 2 diabetes have a two-fold to six-fold higher incidence of cardiovascular disease (CVD) than nondiabetic population, making CVD as a leading cause of death in such patients.[2] Therefore, the primary aim of glycemic control is focused on to prevent death and morbidity due to CVD and microvascular diseases. Extensive data, however, suggest that role of intensive glycemic control on reducing cardiovascular (CV) complications in patients with type 2 diabetes is debatable, though one large randomized study reported its beneficial effect on microvascular complication in newly diagnosed patients with T2DM after 10 years posttrial follow-up.[3] In contradict, randomized interventional data exist to suggest an actual increased risk of CV mortality when overly stringent strategies are employed in high-risk T2DM patients.[4]

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Following a meta-analysis conducted on 42 trials to examine the effect of Rosiglitazone, Nissen and Wolski[5] reported that there is an association between an increased risk of myocardial infarction (MI) and death from CV causes in subjects with diabetes on Rosiglitazone. This initiated a series of discussion on the need to more closely evaluate antidiabetic therapies from a CV perspective. These concerns over the ambiguity related to the CV profile of antidiabetic agents[6] lead regulatory agencies in both Europe and the United States to issue a directive [FDA, 2008; CHMP, 2012] to ascertain CV safety of new antidiabetic medications and to confer to an acceptable level of CV safety in patients.[7,8]

The earlier antidiabetic agents such as biguanides, sulfonylureas (SU), thiazolidinediones have not been tried for CV safety in large outcome trials. Metformin did show a reduction in CV events when analyzed in an inadequately powered subgroup with a small number of patients in the UKPDS (The UK Prospective Diabetes Study) trial[9]; thus, at present, limited evidence to prove that existing antidiabetic agent is cardioprotective.

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Previous Evidence on CV Safety of Dipeptidyl Peptidase-4 Inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors emerged as new class of antidiabetic agents that mediate their glucose-lowering effect through the incretin pathway and soon they achieved a place in the treatment paradigm of type 2 diabetes management as second-line oral medications according to American Diabetes Association (ADA) 2016 guidelines.[10] Currently available DPP-4 inhibitors in India are sitagliptin (US approved 2006), vildagliptin (EU approved 2007), saxagliptin (US approved 2009), linagliptin (US approved 2011), gemigliptin (Director General of Health Services (DCGI) approved 2015), and teneligliptin (DCGI approved 2015).

Associated benefits with the use of DPP-4 inhibitors such as weight neutrality and negligible incidence of severe hypoglycemia events make these agents preferred choice in diabetes treatment. Additionally, cardioprotective actions suggested by experimental and preliminary studies on several surrogate endpoints provided confidence to generate more data on CV effects of antidiabetic agents in patients with type 2 diabetes.[11]

Post hoc analyses of phase II and III controlled trials showed no CV harm with gliptins compared with placebo or other antihyperglycemic agents, and possibly indicated a CV protective effect.[11] U.S. Food and Drug Administration (USFDA) guidance for risk assessment of associated CVDs with antidiabetic agents urged to develop an analytical system that comprised adjudicated and nonadjudicated CV outcomes from pooled data of phase II and III trials.[12] It was also proposed that the trials should be designed to facilitate further prospective independent adjudication in the randomized trials to strengthen validity as well. In view of these recommendations, CV safety was evaluated through the examination of reports of CV adverse events in phase II and III trials but that mostly lacked a formal event adjudication process. Majority of these studies are retrospective adjudication and have certain limitations such as *post hoc* nature, primary endpoints selected, or noninclusion of high-risk population for CV events, no identified randomization procedure, and no extensive study period, to name some [Table 1].

A meta-analysis by Patil *et al*. (2012)[18] comprising 18 randomized trials ($n = 8544$) where patients were randomized to DPP-4 inhibitors ($n = 4998$) and other antidiabetic agents such as metformin, SU, and/or placebo ($n = 3546$) showed that DPP-4 inhibitors were not only linked with lower risk of developing CV event [risk ratio (RR) 0.48, 95% confidence interval (CI) 0.31–0.75, $P < 0.001$] but also have reduced risk of causing nonfatal MI or acute coronary syndrome (RR 0.40, 95% CI 0.18–0.88, $P < 0.02$) compared to placebo or other oral hypoglycemic agents.

In another meta-analysis (2013), 70 randomized controlled trials ($n = 41,959$) with DPP-4 inhibitors versus other comparators (oral hypoglycemic agents, insulin, or both) were analyzed and revealed a statistically significant lower incidence of major CV events overall with DPP-4 inhibitors (0.71 [0.59; 0.86], $P = 0.01$).[19]

In a systematic review and meta-analysis to evaluate the CV safety of gliptins, 50 trials enrolling 55,141 participants were included with mean follow-up of 45.3 weeks. DPP-4 inhibitors compared with all comparators (placebo and active) showed no difference in all-cause mortality and CV mortality but signaled toward increase in heart failure outcome (RR = 1.16, 95% CI 1.01–1.33, $P = 0.04$).[20]

With all these reports, it was quite evident that DPP-4 inhibitors, unlikely to their predecessor antidiabetic agents, have an advantage of being overall cardiac safe while improving the glycemic profile in a diabetic patient.

Current Status on Cardiovascular Safety of DPP-4 Inhibitors

Based on postapproval commitment under the new guidance, in addition to prelaunch meta-analysis, the antidiabetic agents including gliptins are conducting the postlaunch trials with the objective of establishing CV safety trials such as Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53), Examination of CV Outcomes with Alogliptin versus Standard of Care (EXAMINE), Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes (TECOS), CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA), and CARdiovascular Safety & Clinical outcoME with LINAgliptin (CARMELINA). Among these, EXAMINE, SAVOR-TIMI 53, and TECOS studies are completed, while CAROLINA and CARMELINA are still underway. These trials will address some of the limitations of previously conducted meta-analyses, i.e., they incorporate prospective blinded adjudication of CV events, inclusion of patients at increased risk for CV events (e.g., advanced age, preexisting CVD, specific CV risk factors, renal disease), and long treatment duration. Similar to the meta-analyses, the primary major adverse cardiac event (MACE) endpoint includes CV death, nonfatal MI, and nonfatal stroke; the linagliptin and sitagliptin studies also include hospitalization for unstable angina as a part of primary MACE endpoint and CARMELINA has a renal endpoint. These trials are expected to provide a comprehensive, unequivocal profile of extent of cardiac risk involved with respective antidiabetic agents.

SAVOR-TIMI 53 was the first CV outcome study for DPP-4 inhibitors to be published after implementation of USFDA regulatory mandate (2008) for CV safety assessment of glucose lowering agents in patients with T2DM. The study reported that saxagliptin did not increase or decrease the rate of ischemic events compared to placebo arm. It was associated with significantly improved glycemic control and

Table 1: Pooled analysis of phase II and III trials of DPP-4 inhibitors

DPP-4 inhibitors	No. of patient	Adjudication and design	Primary endpoints	Comparator	Risk ratio (95% CI)
Sitagliptin[13]	*n*=10,246	No adjudication	Reported CV ischemic events	Compared with placebo or active comparator	0.68 (0.41-1.12)
Vildagliptin[14]	*n*=10,988*,^	Retrospective	Cerebro and cardiovascular, acute coronary syndrome, transient ischemic attack, stroke	Active comparator/placebo	0.84 (0.62-1.14)
Saxagliptin[15]	*n*=3356	Retrospective meta-analysis	CVD, nonfatal stroke, nonfatal MI	Control treatment (placebo, metformin, up titrated glyburide, or a thiazolidinedione	0.44 (0.24-0.82)
Alogliptin[16]	*n*=3489	Prospective	CVD, nonfatal stroke, nonfatal MI	Control treatment	0.63 (0.21-1.91)
Linagliptin[17]	*n*=9459*	Prospective	CVD, nonfatal stroke, nonfatal MI and UAP with hospitalization	Receiving comparators (placebo, glimepiride and voglibose)	0.78 (0.16-0.70)

*In this analysis, a blinded committee adjudicated all the events. ^Data from patients receiving vildagliptin 50 mg twice daily (for vildagliptin 50 mg once daily: RR 0.88, 95% CI 0.37-2.11). RR: Risk Ratio, CI: Confidence interval, RCT: Randomised controlled trial, MI: Myocardial infarction, UAP: Unstable angina pectoris

reduced the development and progression of microalbuminuria. Another interesting finding was higher hypoglycemic events in saxagliptin group compared to the placebo.[21]

Moreover, the risk of secondary event such as hospitalization due to heart failure (hHF) was augmented irrespective of age category, being highest among patients with elevated levels of NT-pro-brain natriuretic peptide (NT-pro-BNP), previous heart failure, or chronic kidney disease (glomerular filtration rate <60 ml/min). An independent review was presented as oral presentation at EASD 2013 by Dr. Naveed Sattar from University of Glasgow, where it was pointed out that the baseline blood levels of NT-pro-BNP were significantly higher in this subgroup (333 pg/ml). Also, 13% of the patients had been diagnosed with heart failure at baseline. It is therefore required to be further analyzed if only seen in patients with heart failure.

The result of EXAMINE trial showed that the rates of major composite events were not increased with alogliptin as compared with placebo in a follow-up to 40 months. Alogliptin neither increased CV morbidity or mortality, nor worsened preexisting heart failure, including in those patients with a very recent acute coronary syndrome, after a median duration treatment of 18 months. In the primary analysis of the study, only nonsignificant increase in heart failure was detected but when subjects were subgrouped according to prior congestive heart failure (CHF), the patients with absence of prior CHF had a significant increase in the risk of CHF. In addition, assessment of NT-pro-BNP concentration from baseline to 6 months did not reveal any significant changes. The incidences of acute and chronic pancreatitis were similar in the two groups; no cases were fatal. There were no reports of pancreatic cancer.[22]

Results of TECOS trial were no different from other published CV outcome studies of gliptins with regard to primary composite endpoints demonstrating noninferiority of sitagliptin to placebo in terms if risk of four-point MACE outcome, with no increased risk of hHF. As far as increased risk of pancreatitis and pancreatic cancer with incretin-based therapies is concerned, no causal link between incretin-based drugs and these events has been established to date.[23]

Vildagliptin in Ventricular Dysfunction Diabetes study reported that diabetic patients with heart failure receiving vildagliptin showed no adverse effect on ejection fraction compared to placebo. Though the primary endpoint indicated that vildagliptin did not have an unfavorable effect on left ventricular ejection fraction, there was in fact, an increase in left ventricular end-diastolic volume ($P = 0.007$) and a 14% decrease in BNP in the vildagliptin group, suggesting that the increased left ventricular (LV) volumes observed did not result in increased LV wall stress.[24]

Interventional, randomized, single-blind clinical trial TOPLEVEL (Teneligliptin on the progressive left ventricular diastolic dysfunction with T2DM study) is underway to assess long-term CV effect of teneligliptin in approximately 1000 patients with T2DM and expected to be completed in 2019.[25] When teneligliptin was used in various clinical studies as monotherapy or combination therapy with duration ranging from 4 weeks to 1 year, none of these trials have reported any drug-related CV adverse effects.[26] However, one randomized, double-blind study observed a significant QT/QTc prolongation with 160 mg dose of teneligliptin in 240 healthy adult subjects.[27] It is advisable to exercise the caution in patients with diabetic patients with concurrent diseases such as arrhythmia and ischemia, and patients co-administered with drugs known for QT prolongation such as class IA or class III antiarrhythmic drugs.[28]

Omarigliptin is a once-weekly oral agent approved for the treatment of patients with T2DM in Japan (2015) and USA (2016). A randomized, double-blind study including 4202 patients with T2DM and established CVD was conducted to assess CV safety. In this study, there was no increase in the risk of MACE or hHF with omarigliptin and was generally well tolerated. Incidences of adverse events related to alanine aminotransferase (ALT) was found to be significantly increased at Week 54, which prompted a detailed assessment of adverse events, but later no imbalance in these parameters were observed.[29]

A brief description of each major CV outcome trials is provided in Figure 1.

Current Evidence Related to Occurrence of Heart Failure of DPP-4

One recent observational study[30] was conducted to compare a risk of hospitalization for CVDs between gliptins with glimepiride using database of Korean National Health Insurance Service of 19,951 in cohort. This study reported that risk of hospitalization for CVDs was found to be decreased among patients with a history of visit for CVDs in the DPP-4 inhibitors versus glimepiride group.

Similarly, one real world data[31] using a US insurance claims database, including 218,556 patients, investigated the comparative safety of DPP-4 inhibitors with other agents and saxagliptin and sitagliptin for the first time. There was no association between treatment with a DPP-4 inhibitors and rate of hHF relative to SU for patients with baseline CVD and treatment with saxagliptin relative to sitagliptin.

Another study reviewed pooled data[32] from five trials and 12 observation studies, of which one cohort and nested case–control study showed that there is nonsignificant increased risk of hospital admission of heart failure in sitagliptin group compared to no use.

Likewise, in a meta-analysis of 94 trials, 31 treatments with DPP-4 inhibitors did not affect CV mortality and incidence of stroke. Interestingly though, the risk of myocardial infarction was reduced with DPP-4 inhibitors in the short, but not in the long term (duration of treatment ≥29 weeks).[33]

Finally, updated meta-analyses of individual DPP-4 inhibitors also support that neither vildagliptin (RR 0.82; 95% CI 0.61–1.11)[34] nor linagliptin (HR 0.78; 95% CI 0.55–1.12)[35] are associated with an increased risk for a composite outcome of adjudicated MACE relative to comparators. Moreover, the event rates for new onset of HF or hospitalization for its aggravation were relatively low (0.4%) and similar in both vildagliptin and its comparator groups.

A recent assessment on the results of the EXAMINE trial[36] points out that the rate of HF was increased in patients on alogliptin who had no previous history of this disorder [hazards ratio (HR) 1.76; 95% CI 1.07–2.90; $P = 0.026$].

While one analysis of pooled data from 20 clinical trials comprising over 9000 patients with T2DM confirmed that the saxagliptin arm was not associated with an increased risk for ischemic events,[37] other trials reported an increased rate of hHF. The risk of HF hospitalization was augmented irrespective of age category,[38] being highest among patients with elevated levels of natriuretic peptides, previous HF, or chronic kidney disease.[39]

What are the Concerns with CV Safety Data of DPP-4 Inhibitors?

Existing CV outcome data are derived as a part of regulatory requirement with inclusion of high risk or established CVD patients with diabetes. However, what is the clinical impact of gliptins on CV risk factors if introduced in newly diagnosed diabetes patients with less advanced comorbid condition in a long-term duration trial is still inconclusive. As far as CV safety of new-generation SU is concerned, there is no adequately powered formal head-to-head study to provide the definitive evidence. All of the CV outcome trials conducted on DPP-4 inhibitors to date are placebo-controlled added on standard of care therapy. Thus, it is difficult to address the clinically relevant question of whether a DPP-4 inhibitor is a more suitable second-line therapy than Sus, which are one of the most widely used glucose lowering agents in diabetes management.[40]

Multiple CV variables included in the major outcome studies appears to be heterogeneous and differing characteristics of the study population, which poses a major challenge to data interpretation [Table 2]. Finally, most of the trials were not long

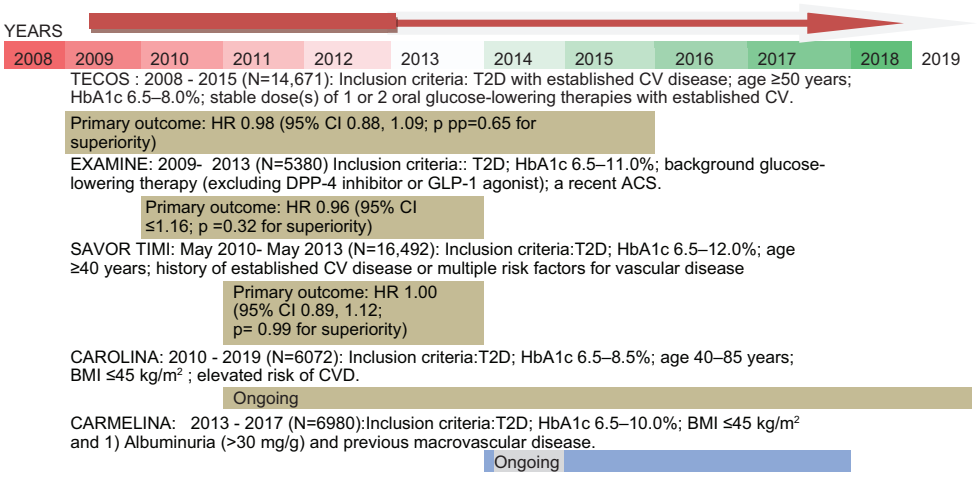

Figure 1: Study design and inclusion criteria of ongoing major CV outcome studies of DPP-4 inhibitor

Table 2: Baseline characteristic of study population in CV safety studies of DPP-4 inhibitors[21-23,40,47]

DPP-4 inhibitor (clinical study)	HbA1c (%)	Medication	Age and CV history	Diabetes duration years	Patients with established CVD%	Background medication	Result
Alogliptin (EXAMINE)[22]	6.5-11.0 7.0-10.0	Oral antidiabetic agents monotherapy or combination therapy insulin	≥18 years + ACS (past 15-90 days)	7.3	100	Metformin 67.4%, statin 90%, insulin 30%, RAAS blockers 81.5%	Primary outcome 11.3% versus 11.8% HR 0.96 95% CI <1.16; *P*=0.32
Linagliptin (CAROLINA)[40]	7.0-10.0 6.5-7.5	Glinide (±MET or AGI)	40-85 years CVD, diabetes-related end-organ damage ≥70 years, or ≥2 CV risk factors	6.2	34.5	Metformin 82.5%, statin 61%, insulin 0%, RAAS blockers 44.1%	Ongoing (estimated to complete in 2019)
Saxagliptin (SAVOR-TIMI 53)[21]	6.5-12.0	Treatment -naïve or antidiabetic treatment/insulin	≥40 years with CVD or ≥55 years (men) or ≥60 years (women) with ≥1 CVD risk factors	10.3	78.4	Metformin 69.9%, statin 78%, insulin 41%, RAAS blockers 81.8%	Primary outcome 7.3% versus 7.2%. HR 1.0 95% CI 0.89, 1.12, *P*=0.99
Sitagliptin (TECOS)[23]	6.5-8.0	Stable dose of anti-hyperglycemic agents including insulin	≥50 years Preexisting CVD	11.6	100	Metformin 81%, statin 80%, insulin 23%, RAAS blockers 78.3%	Primary outcome: 11.4% versus 11.6%. HR: 0.98 (95% CI 0.88-1.09) *P*<0.001
Linagliptin (CARMELINA)[47]	7.9%	Metformin, insulin, SU	65.8±9.1 established CVD	14.7±9.5 years	57	Metformin 54.8%, SU 34.9%, insulin 57.9%, beta-blockers 44.1%, blockers of the renin-angiotensin system (ACEi/ARBs) 81%	Ongoing

enough to comply with the FDA recommendations regarding CV outcomes.[41]

Several explanations have been hypothesized regarding discrepancies related to observation of hHF. Off-target effects of DPP-4 inhibition on substrates such as neuropeptide Y and substance *P* are linked to undesirable effects.[42] In SAVOR-TIMI 53, additional patients with established CVD recruited later during the study and increased rate of hypoglycemic events in saxagliptin arm are few explanations suggested for increased rate of hHF.[43]

Interestingly, the excess in hHF was observed only in the first months of the study, in some but not all subgroups considered (e.g., age, duration of disease, baseline HbA1c) and not in patients with a prior history of HF.[36,39] The authors concluded that these inconceivable findings can be result of chance alone as a false positive result of multiple subgroup testing.[44] Also, they state that these findings cannot be extrapolated to other drugs in the same class. Interaction with ACE inhibitors cannot be ruled out due to unclear mechanism but may relate to blockade of the peptides substance *P* and/or neuropeptide Y with DPP-4 inhibitors.[42]

Clinical Implications of CV Outcome Trials in Future Practice

The goal of a CV outcomes trial is to provide the evidence regarding safety and/or efficacy for regulatory and commercial acceptance. These insights can be used to tailor a treatment regimen according to a patient's disease characteristics and coexisting risk factor that will achieve optimal glycemic control with no adverse CV effect. The results from major CV safety studies not only provide some reassurance about the use of gliptins but also raise questions about the overall benefit of the drug class to suggest an alteration of the current risk/benefit profile of these agents. In a view of clinical finding of increase in the risk of hHF with saxagliptin and alogliptin in patients with existing heart or kidney disease, FDA recommended to add new information of potential increased risk of HF to labels of saxagliptin or alogliptin (2016). The definition of "higher CV risk" needs careful consideration and varies markedly between CV safety studies[45] [see Table 2]. The fact that most patients had severe CVD and were in an advanced stage of diabetes together with the short follow-up period and risk factor control are possible explanations for lack of demonstration

of CVD benefit and the failure to demonstrate clear clinical advantage, if any.[46]

What is Expected from Upcoming CVOT Trials?

CARMELINA[47] is unique in being the first single study to investigate both the CV and the renal safety of linagliptin prospectively to show the CV risk of glucose-lowering medicines. This trial is going beyond the FDA mandatory requirements by powering to measure CV endpoints and to measure a renal endpoint.

CAROLINA,[48] another CV outcome trial with linagliptin, incorporated all requirements mandated by FDA in outcome trials. The study includes more than 6000 patients with early T2DM and evidence of CVD or at high CV risk in 43 countries at more than 670 sites globally. These two trials will provide a definitive answer on CV safety profile of linagliptin. Moreover, inconsistent observations from retrospective trials on SUs indicated CV safety concerns will be addressed perhaps with relevant insights on CV safety of SUs in long-term therapy with comparison to DPP-4 inhibitor in patients predominantly on metformin (88.4% on metformin monotherapy). This would be the first in kind head-to-head comparison between a SU and a gliptin in high CV risk patients. Additionally, it would be helpful to clarify on various factors associated with increased rate of HF exacerbations in high-risk patients seen in previous trials. The study is expected to complete by March 2019. Further, substudies are planned to obtain additional insights in prevention of accelerated cognitive decline, glycemic variability, beta cell function, and latent autoimmune diabetes of adults.[49]

Another important study addressing this knowledge gap is a National Institutional Health, USA sponsored GRADE (Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness) study.[50] The GRADE trial is a pragmatic, parallel-group, unmasked clinical trial that will enroll 5000 patients who have been recently diagnosed with T2DM followed by a mean observation period of nearly 5 years. It is designed to provide a comprehensive comparative effectiveness study that will help to determine how to treat diabetes patients.

Because of complexity involved and variations in population of these CV outcome trials, recently a steering committee of the Academy for Cardiovascular Risk, Outcomes and Safety studies developed an information tool to provide resources for guidance, communication, and interpretation of clinical data that are aligned to the needs of treating physicians involved in the management of patients with T2DM.[51]

Conclusion

Based on current evidence to date, dedicated CV studies suggest a neutral effect of DPP-4 inhibitors on CV outcomes in patients with high risk or established CVD in diabetes, while the safety profile of linagliptin will be further illuminated through completion of relevant long-term studies. However, no robust conclusions can be drawn between individual DPP-4 inhibitors due to lack of head-to-head trials. An ongoing prospective study based on the comparison of linagliptin and glimepiride (CAROLINA) will provide further information on this issue. CV outcome studies appear to evolve in a major way from being a mere FDA regulatory requirement for CV safety assessment to informative trials that will help clinicians to derive some conclusive evidence related to diabetes treatment paradigm.

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Conflicts of Interest

Dr. Maneesha Khalse and Dr. Amit Bhargava are salaried employees of Lupin Limited Pharmaceutical Company, Mumbai, Maharashtra, India.

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