Impact of Dipeptidyl Peptidase-4 Inhibitors on Glycemic Control and Cardiovascular Safety with Adherence: An Overview

Keerthanaa Bhavadasan Ann Merry Davis Bharathi Kolanthavel

Department of Pharmacy Practice, KMCH College of Pharmacy, Dr. M.G.R. Medical University, Coimbatore, India

Keywords

Dipeptidyl peptidase-4 inhibitors · Biochemistry · Pharmacokinetics · Body weight · Safety and efficacy · Cardiovascular safety · Adherence

Abstract

Diabetes is a ubiquitous chronic disease worldwide. The prevalence is expected to increase further to 9.9% by the year 2045. Dipeptidyl peptidase-4 (DPP-4) inhibitors, also called as gliptins, act as incretin enhancers. They inhibit glucagon secretion and arouse postprandial insulin secretion, both in a glucose-dependent mode. In 2006, sitagliptin was approved as a first DPP-4 inhibitor in the treatment of diabetes concurrently with lifestyle modification. Sitagliptin has a high bioavailability, while linagliptin has a safety and tolerability profile similar to that of placebo, with a very low risk for hypoglycemia. DPP-4 inhibitors have a weight neutrality effect. One major benefit of gliptins is their excellent tolerability/safety profile compared with other glucose-lowering medications, including other new glucose-lowering agents such as sodium/glucose cotransporter 2 inhibitors. Compared with sulfonylureas, they have a smaller decline in HbA1c. The three gliptins showed excellent effect on glycemic control as an add-on therapy in treating type 2 diabetes. The major adverse cardiovascular events, malignancy and

pancreatitis, were not associated with the treatment with sitagliptin, a DPP-4 inhibitor. The objective of establishing cardiovascular safety trials such as SAVOR-TIMI 53, EXAMINE, TECOS, CAROLINA, and CARMELINA. DPP-4 inhibitors have higher rates of adherence and persistence compared with sulfonylureas and thiazolidinediones.

© 2020 The Author(s)

Published by S. Karger AG, Basel

Introduction

Diabetes is a ubiquitous chronic disease worldwide [1]. According to the International Diabetes Federation statistics, presently every 7 s someone is estimated to die from diabetes or its snags, with 50% of those deaths (4 million in total per year) occurring below the age of 60 [1]. This is not in favor of the background of a global diabetes prevalence of 8.8% of world inhabitants in 2017, which is standardized for the age group 20–79 years. The prevalence is expected to increase further to 9.9% in the next 20 years. Moreover, it was estimated that the number of adults with diabetes in humankind had increased from 108 million in 1980 to 422 million in 2014. Besides the growth and aging of the world population in general, the global obesity outbreak has turned out to be a key factor for the rise of diabetes events together with the immense

Fig. 1. Mechanism of action of DPP-4 inhibitors [24]. DPP-4, dipeptidyl peptidase-4; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1.

progress of multifactorial cardiovascular risk management and successful revascularization therapy of people with diabetes also contributing to the expansion of the worldwide diabetes population [2].

Current pharmacological agents particularly focus on many pathophysiological disturbances of diabetes aiming at increasing the available of insulin, slowing gastric emptying, and absorption of carbohydrates, reducing resistance to insulin or promoting urinary glucose excretion. Glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors improve glucose control through quite a few of these mechanisms [3] (Fig. 1).

DPP-4 inhibitors also known as gliptins, act as incretin enhancers. They inhibit glucagon secretion and arouse postprandial insulin secretion, both in a glucose-dependent mode. As monotherapy or add-on therapy, they improve glucose control in patients with type 2 diabetes (T2DM) without inducing hypoglycemia (except in combination with sulfonylureas or insulin). They are weight-neutral or may even induce slight weight loss. The good efficiency of DPP-4 inhibitors has been verified by head-to-head randomized controlled trials (RCTs) compared with other active glucose-lowering agents, especially sulfonylureas and clinical placebo-controlled studies [4].

Biochemistry

DPPs are a family of several complex proteases with similar chemical structure; the biological roles and identity of their endogenous substrates remain poorly understood for majority of them. Therefore, a vigilant evaluation of the selectivity and specificity of any pharmacological compound used to inhibit DPP-4 activity is obligatory.

Currently the most frequently used compounds are alogliptin, analogliptin, linagliptin, saxagliptin, sitagliptin, tengliptin, and vildagliptin [5]. In 2006, the first DPP-4 inhibitor, sitagliptin, was approved as a treatment for diabetes concurrently with lifestyle changes. All gliptins are idiosyncratic in their metabolism and excretion, and the suggested and daily dosage are required for an effective treatment. However, they are similar when comparing their efficacy regarding lowering HbA1c levels, patient tolerance, and safety profile [6].

Pharmacological Interactions

Clinically, gliptins were commonly prescribed together with other antidiabetic, antihyperlipidemic, and antihypertensive agents. Therefore, it is of greatest importance to establish whether potential detrimental interactions may be present. No adverse events (AEs) were disclosed in the coadministration with metformin, glibenclamide, glitazones, and simvastatin. The first DPP-4 inhibitor, sitagliptin, is currently available as monotherapy or in a fixed dose combination with other antidiabetic agents; it is a competitive and fully reversible DPP-4 inhibitor with a half maximal inhibitory concentration (IC_{50}) of 18 nM. The high selectivity ensures a beleaguered action on DPP-4 and prevents undesirable secondary effects or possible toxicities resulting from cross-inhibition of other DPP enzymes such as DPP8 or DPP9. A once daily dosage of 50 mg of sitagliptin in healthy subjects reduces DPP-4 activity by approximately 80% at 12 h, and administration of 100 mg once daily maintains inhibition at similar levels for 24 h. Moreover, sitagliptin is well tolerated, with these levels of inhibition being achieved in the absence of any overt increase in AE reporting or episodes of hypoglycemia, even at doses six times higher than the recommended 100 mg oral dose. In patients with T2DM, a dose of 100 mg once daily accomplished about 24 h mean DPP-4 inhibition of >80%, which resulted in a two-fold increase in active GLP-1 and gastric inhibitory polypeptide levels, leading to a near-maximal decrease in plasma glucose following an oral glucose tolerance test [5].

Table 1. Different types of gliptins and their structures with bioavailability, metabolism, and excretion [25, 26]

Drug	Structure	Bioavailability	Metabolism	Excretion
Alogliptin	Alogliptin	100%	hepatic	renal
Linagliptin		30%	hepatic	biliary
Saxagliptin	saxagliptin	75%	hepatic	renal
Sitagliptin		87%	hepatic	renal
Vildagliptin	vildagliptin	85%	hepatic	renal
Teneligliptin		63–85%	hepatic	renal

Pharmacokinetics (Table 1)

Sitagliptin has a high bioavailability, with around 80% of parent drug excreted unchanged in the urine. Renal clearance rates (~388 mL/min) are correspondingly independent of consequence, of ready glomerular filtration and active secretion of sitagliptin into the lumen of the nephron facilitated by the human organic anion transporter. Investigation into the effect of renal insufficiency on the pharmacokinetic profile of sitagliptin resulted in the recommendation that the dose be adjusted in patients with moderate or severe renal insufficiency or end-stage renal disease. No dose adjustment is needed for patients with mild renal insufficiency with a creatinine clearance >50 mL/min (i.e., 100 mg once daily). However, half the dose is recommended for patients with moderate renal insufficiency.

Similar to sitagliptin, vildagliptin is available either as monotherapy or in a fixed dose combination with metformin and is given at the same maximum daily dose of 100 mg (50 mg twice daily). Vildagliptin is effective both alone and in combination with other glucose-lowering agents for the treatment of T2DM. In contrast to sitagliptin, which is a competitive and dose-dependent DPP-4 inhibitor, vildagliptin is a “substrate blocker” demonstrating different enzyme kinetics. Vildagliptin has a lower selectivity for DPP-4 ($IC_{50} = 100 \text{ NM}$) than sitagliptin. Oral absorption of vildagliptin occurs within 3 h and the drug is swiftly and extensively metabolized, most likely in the liver. One-fourth of the oral dose is excreted unchanged in the urine.

Linagliptin was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency for the treatment of T2DM. In clinical trials, lina-

gliptin had a safety and tolerability profile similar to that of placebo, with a very low risk for hypoglycemia. A once daily dosage of 5 mg is recommended, whose effects mean reductions in DPP-4 activity of >80% that last for at least 24 h. Linagliptin binds tightly to plasma proteins and its pharmacokinetics is significantly influenced by storable high-affinity binding to DPP-4 in plasma and tissue. This leads to a long terminal half-life.

Saxagliptin is a potent, selective, and reversible DPP-4 inhibitor that is rapidly absorbed following oral administration. It differs from other gliptins in having an active metabolite (5-hydroxy saxagliptin) that is also a selective, reversible, and competitive DPP-4 inhibitor although the metabolite is only one-half as potent as saxagliptin; it is most likely responsible for the parent drug's extended pharmacodynamic activity. The metabolism of saxagliptin is mediated by enzyme cytochrome P450. However, there are no reported interactions between saxagliptin and three of the most frequently prescribed oral antidiabetic drugs: metformin, glyburide, and pioglitazone [7].

DPP-4 Inhibitors and Patient Weight

Overweight/obesity put patients to the risk of developing T2DM and maintain the glycemic control when the disease develops [6]. In first and foremost terms, the potential effects of various hyperglycemic classes of drugs on weight balance are well documented. Both insulin secretagogues (sulfonylurea's and glinides) and insulin promote weight gain, especially in regimens designed to achieve intensive glycemic control. Metformin is generally associated with weight neutrality or weight loss, while thiazolidinediones are associated with weight gain, and incretin-based therapies, including DPP-4 inhibitors and GLP-1 receptor agonists, are associated with weight neutrality or weight loss [8].

The extensively studied gliptins, using vildagliptin, enhance β - and α -cell sensitivity to glucose, resulting in an improved postprandial insulin response and blunted glucagon secretion as well as improved fasting glycemia. A low hypoglycemic risk in a wide range of settings and regimens is the mechanism action of vildagliptin, and presumably with a low risk for hypoglycemia-related defensive eating. The weight neutrality seen with vildagliptin appears to be an chief effect because the gliptins saxagliptin and sitagliptin have also been shown to produce improvements in glycemic control, both as monotherapy and as well as add-on therapy to other oral agents, with-

out significant change in body weight in most clinical trials [8].

Studies on the influence of DPP-4 inhibitors on patient weight demonstrated variable results but are generally considered to be neutral. Studies regarding treatment with sitagliptin showed variability between 3.306 pounds of weight loss in 13 months of therapy to 1.3 pounds of weight gain in 6 months of treatment. Studies regarding treatment with vildagliptin showed variability between 1.3 pounds of weight loss to 2.8 pounds of weight gain in 6 months of therapy. In a similar study saxagliptin showed variability from 1.3 pounds of weight loss to 1.54 pounds of weight gain in 6 months of therapy. In a meta-analysis of 13 studies regarding treatment with all three DPP-4 inhibitors, the effect of this group of drugs on weight was neutral [6].

On the other hand, the use of gliptins is not linked with weight gain: in SAVOR-TIMI 53, EXAMINE, and TECOS no significant weight changes were observed experimentally. The main reasons for this may be related to lesser degrees of serious hypoglycemic events, to a delay in gastric emptying, and to a sense of satiety secondary to a direct hypothalamic effect [9].

Safety and Efficacy

One major benefit of gliptins is their excellent tolerability/safety profile compared with other glucose-lowering medications, including other new glucose-lowering agents such as sodium/glucose cotransporter 2 inhibitors [4]. Compared with sulfonylureas, gliptins were associated with a smaller decline in HbA1c, and the weighted mean difference of HbA1c between the two groups was 0.08% (95% confidence interval [CI] 0.03–0.14, $p = 0.001$) [8].

This 12-week, randomized, open-label, parallel study evaluated the efficacy and safety of vildagliptin, sitagliptin, and linagliptin in patients with T2DM inadequately controlled on dual combination of a traditional oral hyperglycemic agent and insulin. All groups achieved a better glycemic control compared with baseline both at 6 and 12 weeks. After the treatment with vildagliptin, sitagliptin, and linagliptin, the fasting plasma glucose value decreased, but to a slightly different degree. At week 12, vildagliptin induced a significantly greater decrease in fasting plasma glucose than sitagliptin. Similarly, linagliptin and vildagliptin induced a significantly greater decline in postprandial glucose when compared with sitagliptin. At the week 12, the postprandial glucose levels of

patients treated with linagliptin revealed the most remarkable decrease, followed by vildagliptin. The three DPP-4 inhibitors showed excellent effect on glycemic control as add-on therapy in treating T2DM [10].

Sitagliptin

In an RCT the studies assessed sitagliptin taken as monotherapy in initial combination therapy with metformin or pioglitazone or as add-on combination therapy with other antihyperglycemic agents (metformin, pioglitazone, sulfonylurea $\pm$ metformin, metformin + pioglitazone or rosiglitazone, or insulin $\pm$ metformin). Compared with the sitagliptin group, the overall incidence rates of drug-related AEs and AEs were higher in the unexposed group. Treatment with sitagliptin was not associated with an increased risk of major adverse cardiovascular events, malignancy, or pancreatitis [11].

Linagliptin

The long-term effect of linagliptin as add-on therapy to insulin alone or in combination with other drugs such as metformin and/or pioglitazone was evaluated in a 52-week phase 3 randomized, placebo-controlled trial. The adjusted mean changes in HbA1c from baseline were significantly higher in the linagliptin than in the placebo group. Also, the proportion of patients with a reduction in HbA1c 0.5% was higher in the linagliptin group without an increase in hypoglycemia or body weight [3].

Saxagliptin

The efficacy and safety of saxagliptin as add-on therapy were evaluated in a randomized placebo-controlled study in which 455 patients with T2DM with inadequate glycemic control were on insulin alone. Patients were in 2:1 for receiving saxagliptin (5 mg/day) or placebo for 24 weeks. Compare to placebo, patients treated with saxagliptin had significantly greater reductions in HbA1c and postprandial glucose at 24 weeks. The difference in proportion of the patients achieving an HbA1c value of 7 was 17.3 and 6.7% of patients in the saxagliptin and placebo groups, respectively. Changes in body weight and confirmed hypoglycemia were similar in both groups. The favorable results associated with the combined use of saxagliptin and basal insulin were confirmed in a 28-week

extension analysis of the same trial [3]. In a meta-analysis of 30 RCTs comparing vildagliptin with comparators (placebo or other hypoglycemic agents: metformin, sulfonylureas, glitazones, α -glucosidase inhibitors), vildagliptin was not associated with an increase in overall risk of any AEs (RR = 0.97, 95% CI 0.94–0.99). The incidence of hypoglycemia was low with vildagliptin, and the risk with vildagliptin was not significantly different from the comparators (RR = 0.85, 95% CI 0.49–1.47). The use of vildagliptin did not display any increased risk of infection (RR = 1.03, 95% CI 0.94–1.13 for nasopharyngitis, and RR = 1.07, 95% CI 0.90–1.27 for upper respiratory tract infections). The safety and tolerance profile of vildagliptin with or without metformin has been confirmed in recent reviews [11].

Vildagliptin

In 2007, Fonseca et al. [12] published a study using vildagliptin in combination with insulin. In this 24-week randomized, double-blind, placebo-controlled trial, HbA1c levels decreased by 0.3% compared with placebo, without differences in body weight. Lower incidence and severity of hypoglycemia were reported in the vildagliptin compared with the placebo group. The American Diabetes Association's Standards of Medical Care in Diabetes recommend lowering HbA1c to 7.0% in most patients [9]. Noninsulin agents differ in potency and effective dosages, with a varied expected HbA1c improvement of 0.5–1.5% [13]. However, some patients failed to reach their HbA1c target due to hypoglycemia [14]. The most frequent AEs of vildagliptin were gastrointestinal AEs, hypoglycemia, headache, nasopharyngitis, influenza, cough, edema, and dizziness. Although the absolute occurrence was low, the incidence of AEs while taking vildagliptin varied in different trials when compared with placebo [14]. In T2DM adult patients in Turkey, the GALATA study was the first observational study that investigated the tolerability/safety and efficacy of vildagliptin as add-on to metformin [15]. Its findings revealed that vildagliptin and metformin therapy was associated with no significant tolerability or safety concerns, while it contributed to improved glycemic control irrespective of baseline HbA1c, age, or BMI. The results confirmed the tolerability/safety and efficacy of vildagliptin in both RCTs and real-life trials and provided additional information on the use of vildagliptin and metformin combination therapy in patients with T2DM.

Fig. 2. Clinical trials using various types of gliptins [9]. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium/glucose cotransporter 2.

Cardiovascular Events with Gliptins

Patients with T2DM have a two- to six-fold higher incidence of cardiovascular disease (CVD) than the non-diabetic population, making CVD as a leading cause of death in such patients. Therefore, the primary aim of glycemic control is focused on preventing death and morbidity due to CVD and microvascular diseases [16]. The earlier antidiabetic agents such as biguanides, sulfonylureas, and thiazolidinediones have not been tried for cardiovascular safety in large outcome trials. Metformin showed a reduction in cardiovascular events when analyzed in an inadequately powered subgroup with a small number of patients in the UK Prospective Diabetes Study trial; thus, at present there is limited evidence to prove that existing antidiabetic agents are cardioprotective [16].

Clinical Trials

Various clinical trials have been done in antidiabetic drugs for cardiovascular safety trials such as SAVOR-TIMI 53, EXAMINE, TECOS, CAROLINA, and CARMELINA (Fig. 2).

Savor-TIMI 53

SAVOR-TIMI 53 was the first cardiovascular outcome study for DPP-4 inhibitors to be published after the implementation of the FDA regulatory mandate (2008) for cardiovascular 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. It was as-

Table 2. Cardiovascular safety study done on alogliptin [18]

Endpoint	ALO (<i>n</i> = 2,701)	PL (<i>n</i> = 2,679)	HR for ALO (95% CI)
<i>Primary and secondary endpoints</i>			
Primary MACE composite	305 (11.3%)	316 (11.8%)	0.96 (≤ 1.16)
Cardiovascular death	89 (3.3%)	111 (4.1%)	0.79 (0.60, 1.04)
Nonfatal MI	187 (6.9%)	173 (6.5%)	1.08 (0.88, 1.33)
Nonfatal stroke	29 (1.1%)	32 (1.2%)	0.91 (0.55, 1.50)
Secondary MACE composite	344 (12.7%)	359 (13.4%)	0.95 (≤ 1.14)
<i>Exploratory endpoints</i>			
HbA1c, %	Baseline, mean (SD)	8.0 (1.1)	8.0 (1.1)
	Last visit, mean (SD)	7.7 (1.5) (<i>n</i> = 2,648)	8.1 (1.6) (<i>n</i> = 2,621)
	Change from baseline, LSM (SE)	−0.3 (0.03)	0.03 (0.03)
	Change from baseline, LSMD (95% CI) versus PL	−0.4 (−0.4 to −0.3)	NA
FPG, mmol/L	Baseline, mean (SD)	8.8 (3.2) (<i>n</i> = 2,680)	8.8 (3.1) (<i>n</i> = 2,655)
	Last visit, mean (SD)	8.9 (3.7)	9.3 (3.5)
	Change from baseline, LSM (SE)	0.1 (0.1)	0.5 (0.1)
	Change from baseline, LSMD (95% CI) versus PL	−0.3 (−0.5 to −0.1)	NA

ALO, alogliptin; CI, confidence interval; FPG, fasting plasma glucose; HR, hazard ratio; LSM, least squares mean; LSMD, least squares mean difference; MACE, major adverse cardiovascular events; MI, myocardial infarction; NA, not applicable; PL, placebo; SD, standard deviation; SE, standard error.

sociated with significantly improved glycemic control and reduced the development and progression of microalbuminuria. Another interesting finding was a higher number of hypoglycemic events in the saxagliptin group compared to the placebo group [16]. In a clinical trial SAVOR (Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus) a total of 16,492 patients were randomized. The 2.1-year median follow-up period was for the interquartile range 1.8–2.3 to the maximum follow-up time up to 2.9 years. A primary endpoint event of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke occurred in 613 patients in the saxagliptin group. A major secondary endpoint event of cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, hospitalization for unstable angina, coronary revascularization, or heart failure occurred in 1,059 patients in the saxagliptin group [17].

The EXAMINE trial showed that the rates of major composite events were not increased with alogliptin as compared with placebo in a follow-up period of 40 months. Alogliptin could neither increase cardiovascular morbidity or mortality nor worsen preexisting heart failure, including in patients with very recent acute coronary syndrome, after treatment of 18 months. The primary

analysis of the study not only showed significantly increased heart failure, but also patients who showed up with absence of congestive heart failure are at risk of developing congestive heart failure in the future. In addition, assessment of NT-pro-BNP concentration from baseline to 6 months did not reveal any significant changes. In the two groups of acute and chronic pancreatitis the incidence rates were similar [16].

A total of 8,033 patients were screened, and 5,380 patients were randomized to either alogliptin (*n* = 2,701) or placebo (*n* = 2,679). The length of study participation was variable, but the median duration of study drug treatment was 17.5 months and the maximum length of follow-up was 40.7 months. Patients were randomized to receive either alogliptin once daily or placebo once daily, in addition to standard of care for T2DM and to continuing current prophylaxis for cardiovascular comorbidities. The investigators were allowed to modify concomitant medications for T2DM and cardiovascular comorbidities throughout the duration of the study, with the exception of adding a DPP-4 inhibitor or a GLP-1 analog.

Alogliptin was not shown to be statistically superior to placebo with respect to cardiovascular outcomes. HbA1c levels in the alogliptin group were consistently significantly lower than in the placebo group over the course of

the study. There was a significant difference between the least squares mean difference values of the alogliptin and placebo groups for both HbA1c and fasting plasma glucose values at the last study visit [18] (Table 2).

The TECOS trial was no different from other published cardiovascular outcome studies of gliptins with regard to primary composite endpoints, demonstrating no inferiority of sitagliptin to placebo in terms of risk of four-point major adverse cardiovascular events outcome, with no increased risk of hypertensive heart failure. 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. TECOS evaluated the long-term effect on cardiovascular events of adding sitagliptin to patients with T2DM and any CVD.

In 2009–2012, 14,735 patients were enrolled in the randomized, placebo-controlled global clinical trial. TECOS was conducted in 38 countries which were coordinated jointly by the University of Oxford Diabetes Trials Unit and the Duke Clinical Research Institute. During a median follow-up of 36 months, there was a small difference in HbA1c levels (least squares mean difference for sitagliptin vs. placebo). Overall, the end result occurred in 839 patients of the sitagliptin group and in 851 patients of the placebo group. The first discovered gliptin-sitagliptin was not inferior to placebo for the primary composite cardiovascular outcome. Among patients with T2DM and established CVD, adding sitagliptin to usual care did not appear to increase the risk of major adverse cardiovascular events, hospitalization for heart failure, or other AEs. Our study results showed that sitagliptin may be used in a diverse group of patients with T2DM who are at high cardiovascular risk without increasing the rate of cardiovascular complications, but these results cannot exclude possible benefits or risks with longer durations of therapy or in patients with more complicated coexisting illnesses. In our trial involving patients with T2DM and established CVD, addition of sitagliptin to usual care did not have a significant effect on rates of major adverse cardiovascular events or hospitalization for heart failure [19].

The Vildagliptin in Ventricular Dysfunction Diabetes (VIVID) trial was a prospective, randomized, double-blind, parallel-group trial comparing vildagliptin with placebo added to standard therapy for 52 weeks in patients with T2DM and heart failure with reduced ejection fraction [20]. The primary goal of this safety study was to compare the effect of vildagliptin 50 mg twice daily with that of placebo, added to conventional treatment for dia-

betes, on left ventricular (LV) ejection fraction in patients with heart failure with reduced ejection fraction [20]. The VIVID trial reported that diabetic patients with heart failure receiving vildagliptin showed no adverse effect on ejection fraction compared to patients receiving placebo. Though the primary endpoint indicated that vildagliptin did not have an unfavorable effect on LV ejection fraction, there was in fact an increase in LV end-diastolic volume ($p = 0.007$) and a 14% decrease in brain natriuretic peptide in the vildagliptin group, suggesting that the increased LV volumes observed did not result in increased LV wall stress [16].

The TOPLEVEL study is designed as an open-label, marker-stratified, randomized multicenter study [21]. The purpose of the present study is to determine whether teneligliptin improves LV diastolic dysfunction and whether teneligliptin prevents progressive worsening of LV diastolic function in T2DM patients [21]. This is underway to assess the long-term cardiovascular effect of teneligliptin in approximately 1,000 patients with T2DM. During various clinical studies using teneligliptin as monotherapy or combination therapy with a duration ranging from 4 weeks to 1 year, there were no drug-related cardiovascular adverse effects [16]. In addition to effective glycemic control, the results of many clinical trials showed that teneligliptin, as monotherapy or add-on therapy, was well tolerated in patients with T2DM. It has apparently positive effects on cardiovascular safety markers, such as no clinically meaningful QT prolongation, small but significant improvement in LV function, improvement in adiponectin levels, and improvement in endothelial dysfunction. However, the impending results from the TOPLEVEL study will provide a perspective on the long-term impact of teneligliptin on various parameters of cardiovascular outcome, including the incidence of heart failure [22].

CARMELINA is unique in being the first single study to investigate both the cardiovascular and the renal safety of linagliptin prospectively to show the cardiovascular risk of glucose-lowering medicines. This trial is going beyond the FDA mandatory requirements by powering to measure cardiovascular and renal endpoint. Participants with end-stage renal disease were excluded. The final follow-up occurred on January 18, 2018. Linagliptin added to usual care compared with placebo added to usual care resulted in a noninferior risk of a composite cardiovascular outcome among adults with T2DM and high cardiovascular and renal risk over a median of 2.2 years [23].

Conclusion

The findings we present suggest that use of gliptins is not linked with weight gain. In SAVOR-TIMI 53, EXAMINE, and TECOS, no significant weight changes were observed experimentally. Gliptins have a weight-neutral effect in T2DM patients. Recent RCTs and meta-analyses, numerous observational studies conducted in many different countries, and the large clinical experience over the last 10 years with DPP-4 confirm the good safety profile of this pharmacological class, including in more fragile T2DM patients. Various studies, such as SAVOR-TIMI 53, EXAMINE, TECOS, CAROLINA, and CARMELINA, have been conducted for cardiovascular safety. While lack of adherence is one of the main problems in other oral hyperglycemic drugs, gliptins have a high rate of adherence among T2DM patients.

Acknowledgement

We acknowledge the contribution of KMCH College of Pharmacy for expertise in establishing, developing, and supporting the database. We thank the KMCH Hospital for providing the mortality data.

References

- Schott G, Martinez YV, Ediriweera de Silva RE, Renom-Guiteras A, Vögele A, Reeves D, et al. Effectiveness and safety of dipeptidyl peptidase 4 inhibitors in the management of type 2 diabetes in older adults: a systematic review and development of recommendations to reduce inappropriate prescribing. *BMC Geriatr*. 2017 Oct;17(Suppl 1):226.
- European Society of Cardiology. Global statistics on diabetes. Available from: www.escardio.org/Education/Diabetes-and-CVD/Recommended-Reading/global-statistics-on-diabetes [updated April 1, 2019; accessed August 27, 2019].
- Gomez-Peralta F, Abreu C, Gomez-Rodriguez S, Barranco RJ, Umpierrez GE. Safety and Efficacy of DPP4 Inhibitor and Basal Insulin in Type 2 Diabetes: An Updated Review and Challenging Clinical Scenarios. *Diabetes Ther*. 2018 Oct;9(5):1775–89.
- Scheen AJ. The safety of gliptins: updated data in 2018. *Expert Opin Drug Saf*. 2018 Apr;17(4):387–405.
- Fisman EZ, Tenenbaum A. Antidiabetic treatment with gliptins: focus on cardiovascular effects and outcomes. *Cardiovasc Diabetol*. 2015 Sep;14:129.
- Dicker D. DPP-4 inhibitors: impact on glycemic control and cardiovascular risk factors. *Diabetes Care*. 2011 May;34(Suppl 2):S276–8.
- Hocher B, Reichetzeder C, Alter ML. Renal and cardiac effects of DPP4 inhibitors – from preclinical development to clinical research. *Kidney Blood Press Res*. 2012;36(1):65–84.
- Foley JE, Jordan J. Weight neutrality with the DPP-4 inhibitor, vildagliptin: mechanistic basis and clinical experience. *Vasc Health Risk Manag*. 2010 Aug;6:541–8.
- Mannucci E, Mosenzon O, Avogaro A. Analyses of Results From Cardiovascular Safety Trials With DPP-4 Inhibitors: Cardiovascular Outcomes, Predefined Safety Outcomes, and Pooled Analysis and Meta-analysis. *Diabetes Care*. 2016 Aug;39(Suppl 2):S196–204.
- Tang YZ, Wang G, Jiang ZH, Yan TT, Chen YJ, Yang M, et al. Efficacy and safety of vildagliptin, sitagliptin, and linagliptin as add-on therapy in Chinese patients with T2DM inadequately controlled with dual combination of insulin and traditional oral hypoglycemic agent. *Diabetol Metab Syndr*. 2015 Oct;7(1):91.
- Scheen AJ. Safety of dipeptidyl peptidase-4 inhibitors for treating type 2 diabetes. *Expert Opin Drug Saf*. 2015 Apr;14(4):505–24.
- Fonseca V, Schweizer A, Albrecht D, Baron MA, Chang I, Dejager S. Addition of vildagliptin to insulin improves glycaemic control in type 2 diabetes. *Diabetologia*. 2007 Jun;50(6):1148–55.
- Spinar J, Smahelová A. SAVORTIMI 53 – saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *Vnitr Lek*. 2013 Nov;59(11):1003–7. Czech.
- Pan C, Wang X. Profile of vildagliptin in type 2 diabetes: efficacy, safety, and patient acceptability. *Ther Clin Risk Manag*. 2013;9:247–57.
- Ayvaz G, Keskin L, Akin F, Dokmetas HS, Tasan E, Ar IB, et al.; GALATA Study Group. Real-life safety and efficacy of vildagliptin as add-on to metformin in patients with type 2 diabetes in Turkey – GALATA study. *Curr Med Res Opin*. 2015 Apr;31(4):623–32.
- Khalse M, Bhargava A. A Review on Cardiovascular Outcome Studies of Dipeptidyl Peptidase-4 Inhibitors. *Indian J Endocrinol Metab*. 2018 Sep–Oct;22(5):689–95.
- Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013 Oct;369(14):1317–26.
- Canadian Agency for Drugs and Technologies in Health, Ottawa, ON. Available from: www.ncbi.nlm.nih.gov/books/NBK349194 [updated in August 2015; cited in August 2019].

Statement of Ethics

This project was reviewed in accordance with the Kovai Medical Center and Hospital Ethics Committee (Ref.: EC/AP/715/06/2019).

Disclosure Statement

The authors have nothing to disclose.

Funding Sources

None.

Author Contributions

K. Bhavadasan designed and directed the project. A.M. Davis and B. Kolanthavel contributed to the design and implementation of the review.

- 19 Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al.; TECOS Study Group. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2015 Jul;373(3):232–42.
- 20 McMurray JJ, Ponikowski P, Bolli GB, Lukashevich V, Kozlovski P, Kothny W, et al.; VIVID Trial Committees and Investigators. Effects of Vildagliptin on Ventricular Function in Patients With Type 2 Diabetes Mellitus and Heart Failure: A Randomized Placebo-Controlled Trial. *JACC Heart Fail*. 2018 Jan;6(1):8–17.
- 21 Imazu M, Nakano A, Ito S, Hamasaki T, Kitakaze M. Effects of teneligliptin on the progressive left ventricular diastolic dysfunction in patients with type 2 diabetes mellitus in open-label, marker-stratified randomized, parallel-group comparison, standard treatment-controlled multicenter trial (TOPLEVEL study): rationale and study design. *Cardiovasc Drugs Ther*. 2019 Jun;33(3):363–70.
- 22 Patel DK, Sharma RT, Patel HA, Barkate HV. Teneligliptin: a review on cardio-renal safety. *Int J Basic Clin Pharmacol*. 2016;5(2):232.
- 23 Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, et al.; CARMELINA Investigators. Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. *JAMA*. 2019 Jan;321(1):69–79.
- 24 Wikipedia contributors. Discovery and development of dipeptidyl peptidase-4 inhibitors. Available from: https://en.wikipedia.org/w/index.php?title=Discovery_and_development_of_dipeptidyl_peptidase-4_inhibitors&oldid=929873709 [December 8, 2019; retrieved April 10, 2020].
- 25 https://en.wikipedia.org/wiki/Discovery_and_development_of_dipeptidyl_peptidase-4_inhibitors.
- 26 Gupta V, Kalra S. Choosing a gliptin. *Indian J Endocrinol Metab*. 2011 Oct;15(4):298–308.