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Product Monograph

Taking one step forward, to help more patients to

Live well with Diabetes in India

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Sitagliptin Phosphate tablets IP 25mg, 50mg and 100mg

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Real World experience in **India** for over **11 years**[1]

> 3L[2] Indian patients Living well with Diabetes

Available at **> 10 L chemists**[3] across India

Best-in-class Efficacy, Safety & Hassle-free experience[4,5,6,7,8,9]

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1. Source: ORG IMS, Launched in August 2011, 2. As per ORG IMS MAT Mar'22 C. Units. 3. https://business.mapsofindia.com/chemists. 4. Craddy Paul et al. Diabetes Ther 2014; 5: 1 – 41. 5. Green J B et al. N Engl J Med. 2015 Jul; 373: 232 – 242. 6. Engel SS, Suryawanshi S, et al. TECOS Study Group. Diabetes, Obesity & Metabolism 2017 Nov; 19 (11): 1587 – 1593. 7. Korbot KJ, Ferrante SA, et al. Curr. Med. Res. Opin. 2012 Aug; 28 (8): 1281-7. 8. Nauck MA et al. Diabetes, Obesity & Metabolism 2007; 9 (2): 194 – 205. 9. Mishriky BM, et al. Diabetes, Obesity & Metabolism 2018 Mar; 44 (2): 112 – 120.

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Preface

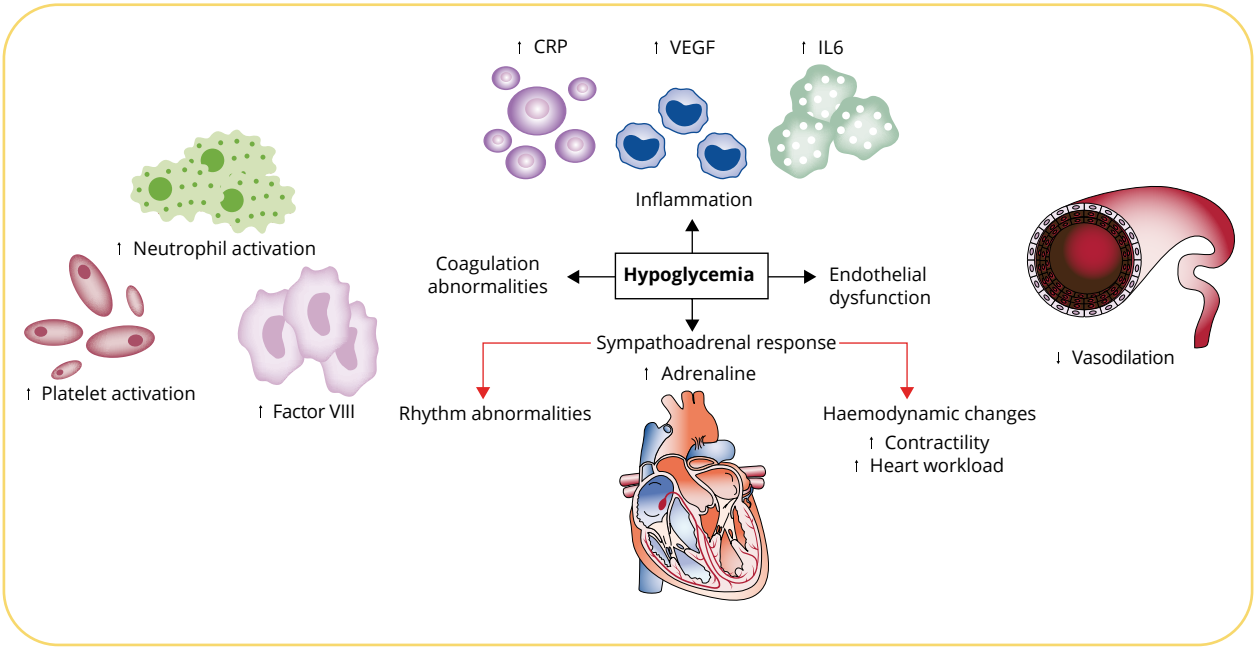
Despite the availability of numerous pharmacotherapies, diabetes remains a major global health issue and is amongst the four most common noncommunicable diseases, assuming epidemic proportions in India. Poor glycaemic control increases the risk of developing microvascular and macrovascular complications associated with T2D. A major focus of the multifactorial approach recommended in current treatment guidelines for the management of T2D is attainment of good glycaemic control, with the primary goal being prevention of the onset and/or progression of microvascular and macrovascular complications. Although dietary and lifestyle modifications are important cornerstones in the management of T2D, given the progressive nature of the disease, it invariably requires pharmacological intervention to achieve and maintain good glycaemic control. In addition to targeting glycaemic control, the choice of antihyperglycaemic drug should also prioritize minimizing the risk of adverse effects such as bodyweight gain and hypoglycaemia (both severe and non-severe), with both of these adverse effects considered CV risk factors. Dipeptidyl peptidase-4 (DPP-4) inhibitors are a relatively new class of oral diabetes drugs, which act by inhibiting the DPP4 enzyme. Sitagliptin was the first DPP4i approved for treatment of T2DM.

Extensive experience in the clinical trial and real-world settings has firmly established the glycaemic efficacy of sitagliptin, as monotherapy, initial combination therapy or add-on combination therapy with other antihyperglycaemic drugs (including insulin), in adult patients with T2D. Sitagliptin monotherapy or add-on therapy also provided effective glycaemic control in high-risk patients with T2D, including obese patients, elderly patients, patients with varying degrees of renal impairment and patients with established CVD.

This monograph provides a detailed description of Sitagliptin and its place in therapy.

Hypoglycemia and Weight gain in Diabetes

Diabetes mellitus is associated with significant morbidity and mortality derived from long-term microvascular and macrovascular complications of chronic hyperglycaemia. The Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) have clearly shown the benefits of intensive glycaemic control for preventing or delaying the development and progression of long-term complications. However, intensive glycemic control, is associated with an increased incidence of hypoglycemia, which is the major barrier to the implementation of intensive treatment from the physician's and patient's perspective[1]. Hypoglycemia has long been recognized as a dangerous side-effect of treatment of diabetes with insulin or insulin secretagogues. Study findings have suggested that hypoglycemia is associated with an increased risk of cardiovascular events and mortality. The mechanisms by which hypoglycemia might provoke cardiovascular events have been identified in experimental studies, and in clinical studies cardiac arrhythmias have been reported to be induced by hypoglycemia, with one report describing sudden death during a severe episode. Emerging evidence suggests that the association between hypoglycemia and cardiovascular events and mortality is likely to be multifactorial[2].



Mechanisms by which hypoglycaemia may affect cardiovascular events[3].

Many patients with diabetes suffer from impaired defense mechanisms against hypoglycemia and/or lack of hypoglycemia awareness; therefore, plasma glucose concentrations <70 mg/dL are defined as clinically significant in diabetes and require intervention irrespective of symptom severity[4].

The current classification of hypoglycemic episodes in diabetes includes three levels corresponding to the severity of hypoglycemia[5]

- **Level 1** hypoglycemia: defined as plasma glucose concentration <70 mg/dL but >54 mg/dL
- **Level 2** hypoglycemia: defined as plasma glucose concentration below 54 mg/dL requiring immediate intervention to correct the hypoglycemia
- **Level 3** hypoglycemia: defined as a serious event characterized by a change in the mental status or impairment in the patient's physical ability to function that requires intervention by another person to correct the glucose concentration

Following are common reasons for hypoglycemia seen in diabetic patients[6]

- Treatment with Insulin, SU or Repaglinides at high dose or with incorrect timing related to meals
- Eating a very low carbohydrate food portion
- Prolonged fasting
- Drinking alcohol – causes lack of endogenic glucose production
- Unplanned physical exercise
- Consumption of sweets during festivals
- Comorbid conditions like renal failure, hepatic failure, and hypothyroidism causing drop in insulin excretion

The frequency and severity of hypoglycemia negatively impact on quality of life and promote fear of future hypoglycemia. This fear results in reduced self-care, compliance and poor glucose control. Thus, it is important to prevent, recognize and treat hypoglycemic episodes due to the use of insulin or insulin secretagogues[7].

Approximately half of patients with type 2 diabetes (T2D) do not achieve globally recognized blood glucose targets, despite the availability of a wide range of effective glucose-lowering therapies. Failure to maintain good glycemic control increases the risk of diabetes-related complications and long-term health care costs[8].

In patients with T2D, prevention of weight gain, and modest weight reduction of as little as 5%, can reduce diabetes-associated complications and significantly improve cardiovascular risk factors. However, weight gain during anti diabetes therapy is common and has been cited as a reason for delaying treatment intensification—particularly with insulin-based regimens[9].

Achieving the individual glycemic target remains even more challenging for overweight and obese patients, as there are data that suggest that people with T2D experience more difficulty in trying to lose excess weight and maintain a healthy weight. A popular misconception among physicians' is that obesity is failure of healthy lifestyle and a temporary change to better diet and more physical activity will reverse obesity[10].

While reduction of hyperglycemia remains the foremost goal in the treatment of patients with type 2 diabetes, the avoidance of weight gain may be a clinically important secondary goal. The traditional pharmacotherapies for type 2 diabetes can further increase weight and this may undermine the benefits of improved glycemic control, thus there is still a large unmet medical need in patients with T2D who miss their individualized glycemic and weight-loss targets[11].

Limitation of existing therapies (SU, Meglitinides, TZDs, and Insulins).
Sulfonylureas show high efficacy in lowering A1C (reductions of ~1.25% versus placebo), but are associated with weight gain and hypoglycemia. Sulfonylureas are considered to have the highest risk of severe hypoglycemia of the available T2D therapies. Meta-analyses have demonstrated that when added to other agents, sulfonylureas are associated with weight gain ranging between 2.01 and 2.3 kg versus placebo. Due to associated hypoglycemia, weight gain, and possible cardiovascular risk, together with their diminished efficacy over time, sulfonylureas should be avoided in patients with obesity.

Thiazolidinediones (TZDs) show relatively high efficacy in reducing A1C (reductions of ~1.25% versus placebo), are associated with weight gain and a low risk of hypoglycemia, and induce durable antihyperglycemic effects. Weight gain seen with TZDs ranges from 2.30 to 4.25 kg.

Meglitinides (glinides) Glinides have A1C-lowering properties (reductions of ~0.75% versus placebo), a shorter half-life, and a similar side effect profile, but with a lower risk of hypoglycemia, compared with sulfonylureas. In addition, their relatively short half-life means they must be administered frequently. Weight gain is similar to that seen with sulfonylureas (0.91 to 2.67 kg), which suggests glinides should also be avoided in patients with obesity.

Insulin and Insulin Analogs Compared with most other antihyperglycemic therapies, there is a substantial risk of hypoglycemia with insulin—especially with regimens that include prandial insulin. Weight gain with insulin ranges between 1.56 and 5.75 kg, which is substantially greater than with other agents.

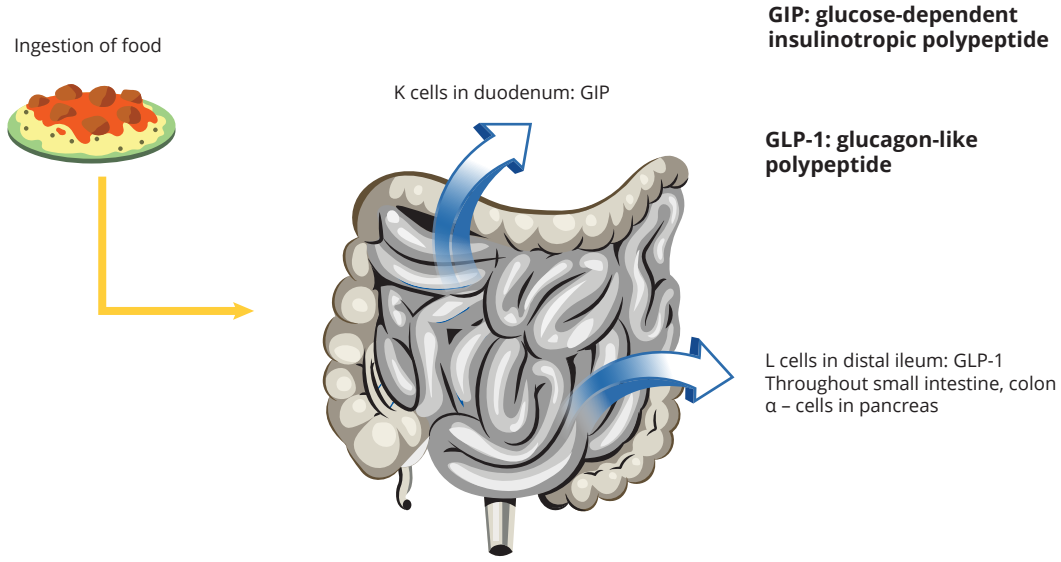
Thus, with the proven benefits of weight-loss and the potential risks of weight gain in patients with T2D, the effect of antihyperglycemic agents on body weight is an important factor to consider when individualizing patient therapy[8]. The consensus statement of ADA in 2018 has recommend that when choosing antihyperglycemic treatments for patients who are overweight or have obesity, wherever possible, consideration should be given to medications that promote weight-loss or that are weight-neutral[12].

Physiology of Incretin hormones

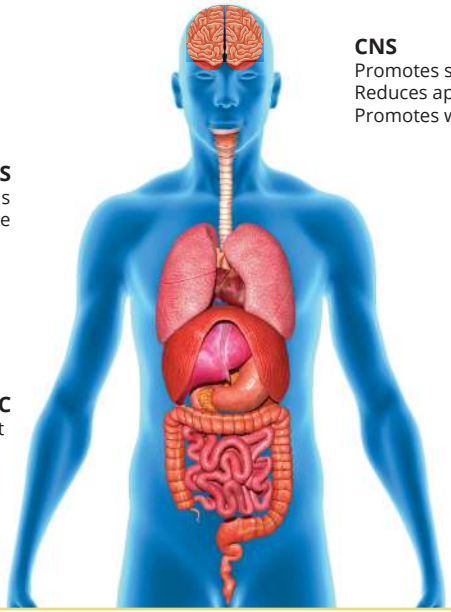
Incretin hormones are gut peptides that are secreted after nutrient intake and stimulate insulin secretion together with hyperglycemia. GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1) are the known incretin hormones from the upper (GIP, K cells) and lower (GLP-1, L cells) gut. Together, they are responsible for the incretin effect: a two- to three-fold higher insulin secretory response to oral as compared to intravenous glucose administration. In subjects with type 2 diabetes, this incretin effect is diminished or no longer present[13].

GLP-1 and GIP secretion is stimulated very rapidly, probably at the first emptying of gastric contents into the small intestine, and then continues at a rate which is proportional with the graded emptying of the stomach contents. The two incretin hormones have specific receptors (a single type for each) that are expressed in high numbers on the beta cells explaining that elevated plasma concentrations may result in stimulated insulin secretions. GLP-1 seems to be more potent than GIP, but the major difference lies in the effectiveness of the two hormones in type 2 diabetes, where GLP-1 retains it stimulatory activity, whereas that of GIP is almost completely lost. The deficiency of incretin hormones develops very early in course of T2DM and a similar deficiency occurs during the development of insulin resistance[14].

Major Incretin Hormones



Incretin actions



CNS
Promotes satiety
Reduces appetite
Promotes weight loss

GI
Slows gastric emptying
Promotes weight loss

ENDOCRINE
↑ insulin secretion
↓ glucagon release
Actions are glucose-dependent
Corrects β and α-cell dysfunction

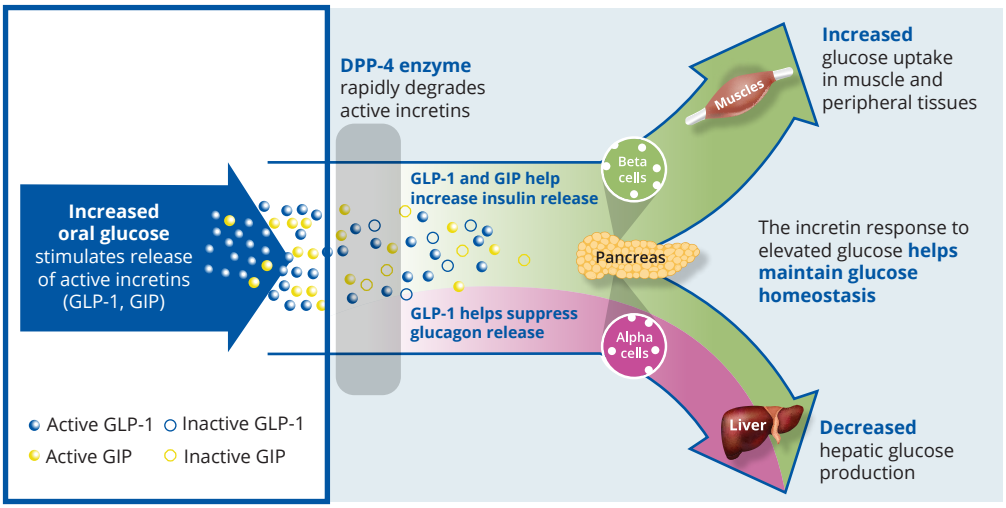
↑ β cell proliferation*
↓ β cell apoptosis*

OTHERS
↓ lipolysis
cardioprotective

HEPATIC
↓ hepatic glucose output

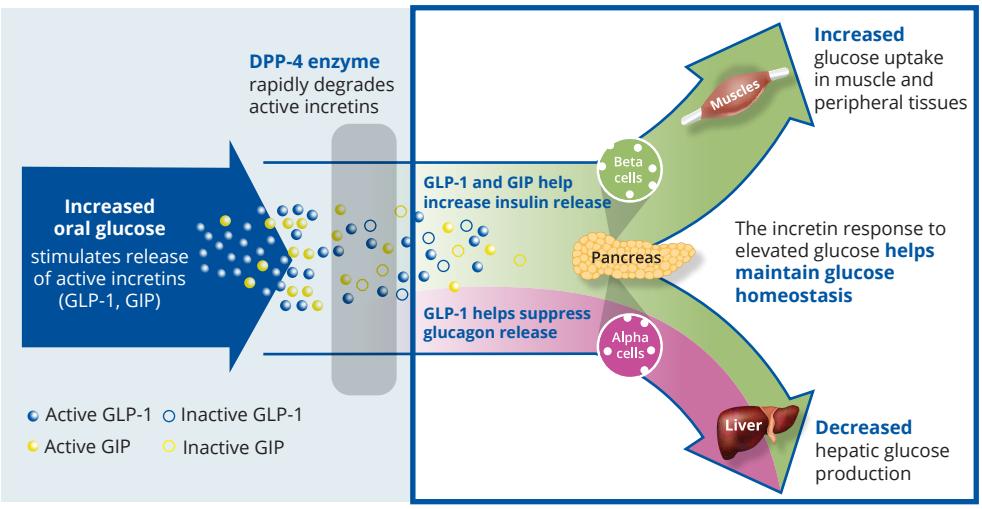
Release of incretin hormones

Incretins are naturally occurring hormones that the gut releases throughout the day; level of active incretins increases significantly when food is ingested



Action of incretin hormones

When glucose levels are elevated, both GLP-1 and GIP signal β-cells to increase insulin release and GLP-1 signals α-cells to suppress glucagon release



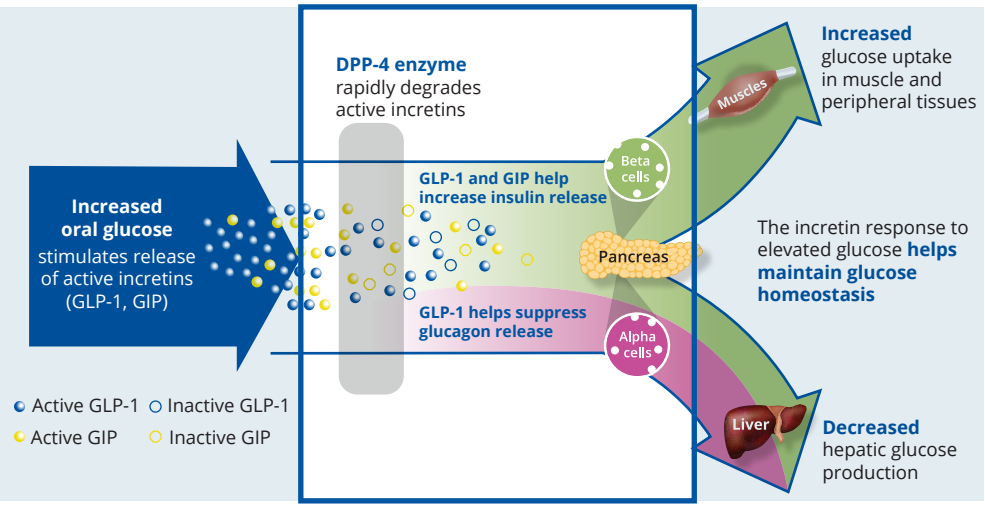
DPP4 enzymes & its inhibitors

The incretin hormones are substrates for the almost ubiquitous enzyme, dipeptidyl peptidase 4, which is circulating, but also bound to cell membranes in the liver, the kidneys and to the luminal surface of endothelial cells. The enzyme cleaves off the two N-terminal amino acids, leaving behind truncated peptides, which have lost their insulinotropic properties and actually may act as, rather weak, receptor antagonists[13].

The DPP-4 mediated degradation leaves GIP with a half-life in the circulation of 7 min. GLP-1 is exquisitely sensitive to DPP-4 and most of the newly secreted GLP-1 is broken down already in the capillaries of the gut, so that only about 2/3 or 1/4 of what arrives to the liver remains intact. In the liver, 50% of what is presented is broken down so that in total about 12% of what was secreted arrives to the systemic circulation in the intact form. And, because of the soluble DPP-4, it has been found that only about 8% of what was released arrives at the peripheral targets (e. g. the endocrine pancreas) in the intact form, this the half-life observed in infusion studies is around 1–2 min[13].

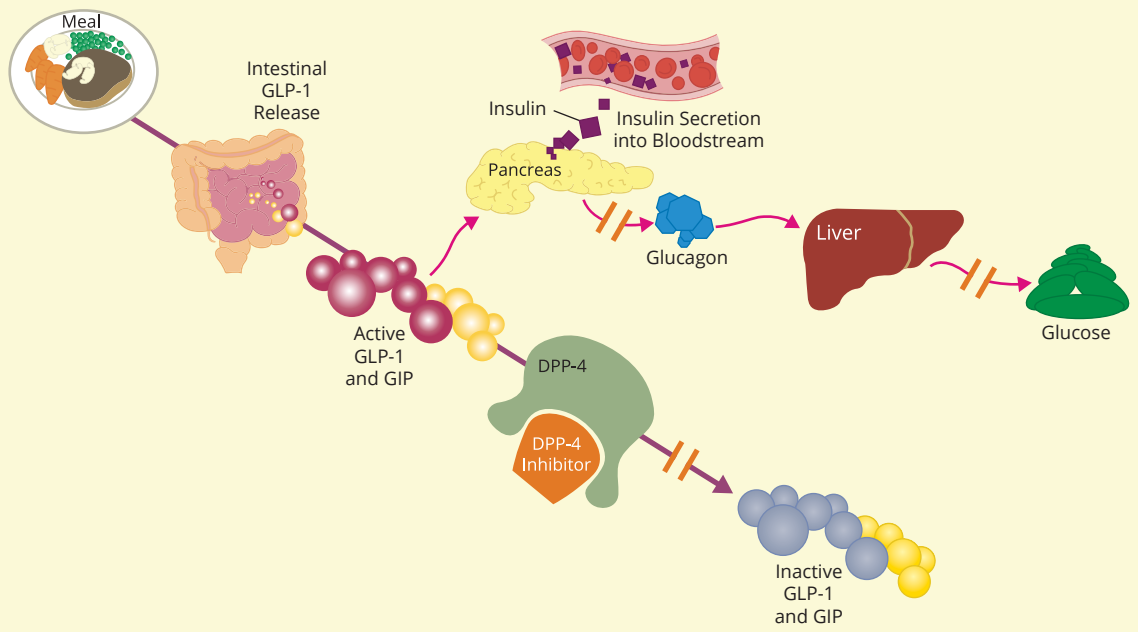
Degradation of incretin hormones

Physiologic activity of incretins is limited by the enzyme dipeptidyl-peptidase 4 (DPP-4), which rapidly degrades active incretins after their release



Dipeptidyl-peptidase 4 inhibitors lower DPP4 activity by 70–90%, they do not pass the blood–brain barrier and have no direct effect on satiety or on altering gastric emptying. The inhibitors have been classified into three classes depending on their different binding modes in the DPP4 active center.

DPP-4 inhibitors delay the degradation of GLP-1

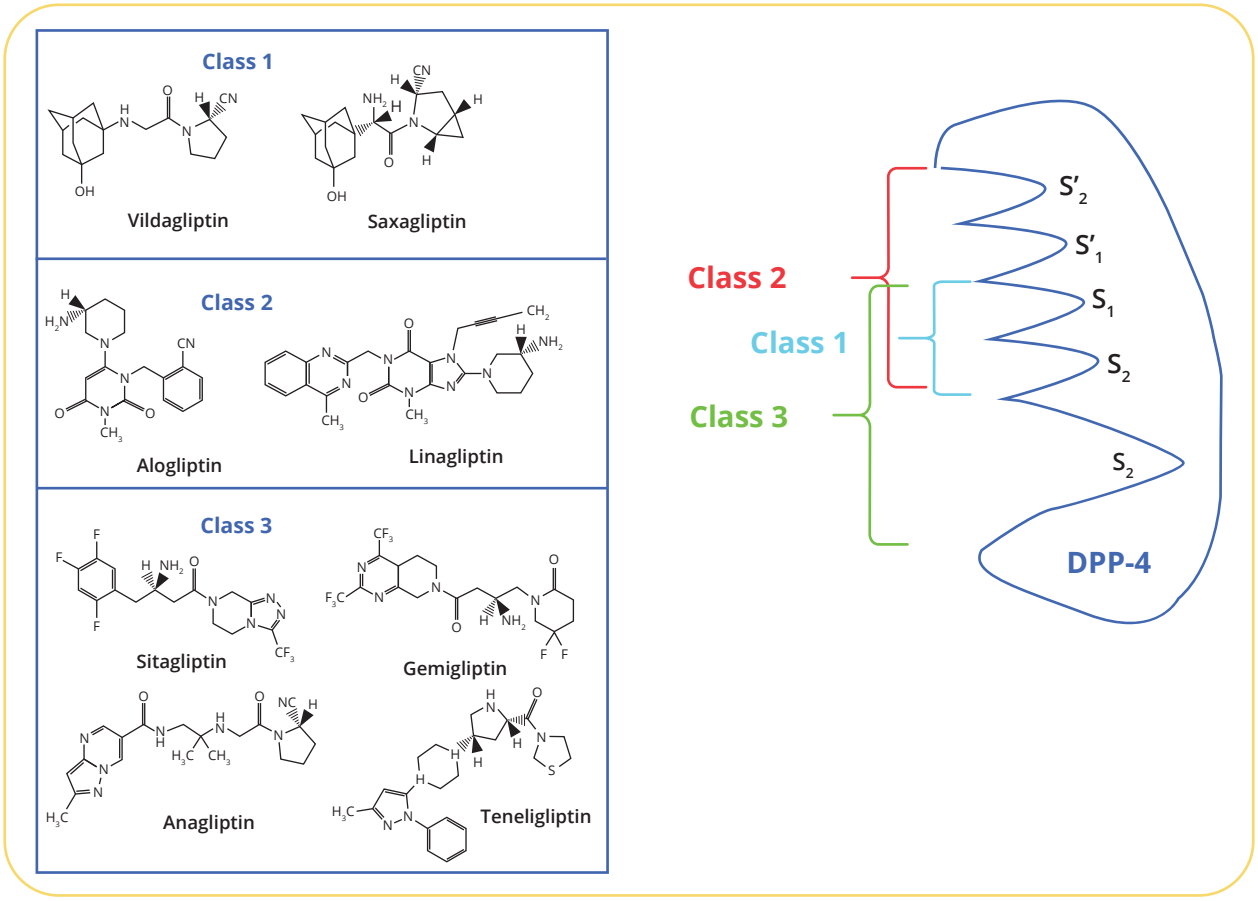


Class 1 contains vilda- and saxagliptin, which only bind to the S1 and S2 subsites and form a covalent bond with the nitrile group of their cyanopyrrolidine moiety and Ser630 of DPP4.

Class 2 contains alo- and linagliptin, which also interact with the S1' subsite or even in case of linagliptin with the S2' subsite.

Class 3 has the highest inhibitory function toward DPP4, because both sita- and teneligliptin interact with the S2-extensive subsite of the DPP4 active center, and an increasing number of interactions seems to increase the potency of the gliptin. The binding of the DPP4 S2-extensive subsite also guarantees a high specificity toward DPP4 since other close-related peptidases like DPP8, DPP9, and FAP lack this subsite.

Additionally, Sitagliptin, is also known to lower the level of free fatty acids (FFA) and thereby its insulin-sensitizing properties. Furthermore, sitagliptin was shown to have potent anti-inflammatory properties by suppressing expression of pro-inflammatory genes in mouse and humans[15].



Classes of DPP-4 inhibitors with the various commonly used DPP-4 inhibitors (left side) and the binding domains of the various classes to specific areas of the DPP-4 molecule (right side).

Pharmacology of Sitagliptin

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor which slows the inactivation of endogenous incretin hormones. Incretin hormones including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme, DPP-4. Sitagliptin exerts its action by inhibiting the enzyme DPP-4 and this activity lasts for a 24-hours[16].

Indications

Sitagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus[16].

Clinical Pharmacology (PK, PD, MOA)

Pharmacokinetics.

Following a single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 μM•hr, Cmax was 950 nM, and apparent terminal half-life (t1/2) was 12.4 hours. Plasma AUC of sitagliptin increased in a dose-proportional manner and increased approximately 14% following 100 mg doses at steady-state compared to the first dose[16].

Absorption: The absolute bioavailability is approximately 87%. Oral administration of sitagliptin 100 mg is rapidly absorbed with a peak plasma concentration (T max) occurring 1 to 4 hours post dose[16].

Distribution: 38% reversibly bound to plasma proteins. The Vd of 100 mg IV sitagliptin is 198 L[16].

Metabolism: Approximately 16% of an oral dose is excreted as metabolites. Six metabolites were detected at trace levels and not expected to contribute to the activity of sitagliptin. The primary enzyme responsible for metabolism is CYP3A4 with contribution from CYP2C8[16].

Excretion: 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. The terminal t1/2 following a 100 mg oral dose is approximately 12.4 hours and renal clearance is 350 mL/min.

Coadministration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics of sitagliptin[16].

The pharmacokinetics of sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes mellitus.

Pharmacodynamics.
In patients with type 2 diabetes mellitus, administration of sitagliptin led to inhibition of DPP4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycaemia.

In patients with type 2 diabetes mellitus administered sitagliptin 100 mg (N = 81) or sitagliptin 200 mg (N = 63) daily, there were no meaningful changes in QTc interval based on ECG data obtained at the time of expected peak plasma concentration[16].

Mechanism of Action.
Sitagliptin is a DPP-4 inhibitor, which is believed to exert its action in patients with type 2 diabetes mellitus by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme, DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signalling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses[16].

Dosage & Administration

Recommended Dosing: The recommended dose of Sitagliptin is 100 mg once daily. It can be taken with or without food[16].

Recommendations for Use in Renal Impairment: Assess renal function prior to initiation of Sitagliptin and periodically thereafter. For patients with an estimated glomerular filtration rate [eGFR] greater than or equal to 45 mL/min/1.73 m^2 to less than 90 mL/min/1.73 m^2 , no dosage adjustment for Sitagliptin is required. For patients with moderate renal impairment (eGFR greater than or equal to 30 mL/min/1.73 m^2 to less than 45 mL/min/1.73 m^2), the dose of Sitagliptin is 50 mg once daily. For patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or with end-stage renal disease (ESRD) requiring haemodialysis or peritoneal dialysis, the dose of Sitagliptin is 25 mg once daily. Sitagliptin may be administered without regard to the timing of dialysis[16].

Use in special populations

Pregnancy: Limited data available in pregnant women and not sufficient to inform a drug-associated risk for major birth defects and miscarriage. There are risks to mother and foetus associated with poorly controlled diabetes in pregnancy[16].

Lactation: There is no information regarding the presence of sitagliptin in human milk, the effects on the breastfed infant, or the effects on milk production[16].

Pediatrics: The safety and effectiveness of sitagliptin have not been established in pediatric patients[16].

Geriatrics: No overall differences in safety or effectiveness were observed between subjects of 65 years and over and younger subjects. sitagliptin is substantially excreted by the kidney, and because aging can be associated with reduced renal function, renal function should be assessed more frequently in elderly patients[16].

Renal Impairment: Sitagliptin is excreted by the kidney, and sitagliptin exposure is increased in patients with renal impairment. Lower dosages are recommended in patients with eGFR less than 45 mL/min/1.73m^2. An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal impairment with eGFR of 30 to less than 45 mL/min/1.73 m^2 and an approximately 4-fold increase was observed in patients with severe renal impairment, including patients with ESRD on haemodialysis, as compared to normal healthy control subjects[16].

Hepatic Impairment: In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and Cmax of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls 11 following administration of a single 100-mg dose of sitagliptin. These differences are not considered to be clinically meaningful. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score >9)[16].

Contraindications

History of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema[16].

Precautions

- **Pancreatitis:** Post marketing reports of hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue[16]
- **Heart failure:** Heart failure has been reported with two other members of the DPP-4 inhibitor class. Consider risk vs. benefit for those with risk factors for heart failure and monitor patients for signs and symptoms[16]
- **Acute Renal Failure:** Post marketing reports of acute renal failure. Assess renal function prior to initiation and periodically thereafter[16]
- Increased risk of Hypoglycemia when sitagliptin added to insulin secretagogue (e.g. sulfonylurea) or insulin therapy. Consider lowering dose if sitagliptin is added to these therapies[16]
- Hypersensitivity reactions have been reported in post marketing reports including anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome[16]
- Arthralgia and severe joint pain reported in patients taking DPP-4 inhibitors[16]
- Bullous pemphigoid noted in post marketing reports. Tell patients to report the development of blisters or erosions[16]

Adverse Reactions

Adverse reactions reported in ≥5% of patients treated with and more commonly than in patients treated with placebo are: upper respiratory tract infection, nasopharyngitis and headache. In the add-on to sulfonylurea and add-on to insulin studies, hypoglycaemia was also more commonly reported in patients treated with Sitagliptin compared to placebo[16].

Drug interactions

Effects of Sitagliptin on Other Drugs

In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, digoxin, warfarin, or an oral contraceptive (ethinyl estradiol and norethindrone), providing in vivo evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, P-gp, and organic cationic transporter (OCT)[16].

Coadministered Drug	Dose of Coadministered Drug*	Dose of Sitagliptin*	Geometric Mean Ratio (ratio with/without sitagliptin) No Effect = 1.00		
				AUC†	C_{max}
Digoxin	0.25 mg‡ once daily for 10 days	100 mg‡ once daily for 10 days	Digoxin	1.11§	1.18
Glyburide	1.25 mg	200 mg‡ once daily for 6 days	Glyburide	1.09	1.01
Simvastatin	20 mg	200 mg‡ once daily for 5 days	Simvastatin	0.85¶	0.80
			Simvastatin Acid	1.12¶	1.06
Rosiglitazone	4 mg	200 mg‡ once daily for 5 days	Rosiglitazone	0.98	0.99
Warfarin	30 mg single dose on day 5	200 mg‡ once daily for 11 days	S(-) Warfarin	0.95	0.89
			R (+) Warfarin	0.99	0.89
Ethinyl estradiol and norethindrone	21 days once daily of 35 µg ethinly estradiol with norethindrone 0.5 mg x 7 days, 0.75 mg x 7 days. 1.0 mg x 7 days	200 mg‡ once daily for 21 days	Ethinyl estradiol	0.99	0.97
			Norethindrone	1.03	0.98
Metformin HCl	1000 mg‡ twice daily for 14 days	50 mg‡ twice daily for 7 days	Metformin	1.02#	0.97

* All doses administered as single dose unless otherwise specified.

† AUC is reported as $AUC_{0-\infty}$ unless otherwise specified.

‡ Multiple dose.

§ AUC_{0-24hr}.

¶ AUC_{0-last}.

AUC_{0-12hr}.

Effects of Other Drugs on Sitagliptin

Clinical data described below suggest that sitagliptin is not susceptible to clinically meaningful interactions by co-administered medications[16].

Coadministered Drug	Dose of Coadministered Drug*	Dose of Sitagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC†	C_{max}
Cyclosporine	600 mg once daily	100 mg once daily	Sitagliptin	1.29	1.68
Metformin HCl	1000 mg‡ twice daily for 14 days	50 mg‡ twice daily for 7 days	Sitagliptin	1.02§	1.05

* All doses administered as single dose unless otherwise specified.

† AUC is reported as $AUC_{0-\infty}$ unless otherwise specified.

‡ Multiple dose.

§ AUC_{0-12hr}.

Concomitant Use with Insulin or Insulin Secretagogues

When Sitagliptin was used in combination with insulin or insulin secretagogues (e.g.,sulfonylurea), medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycaemia[16].

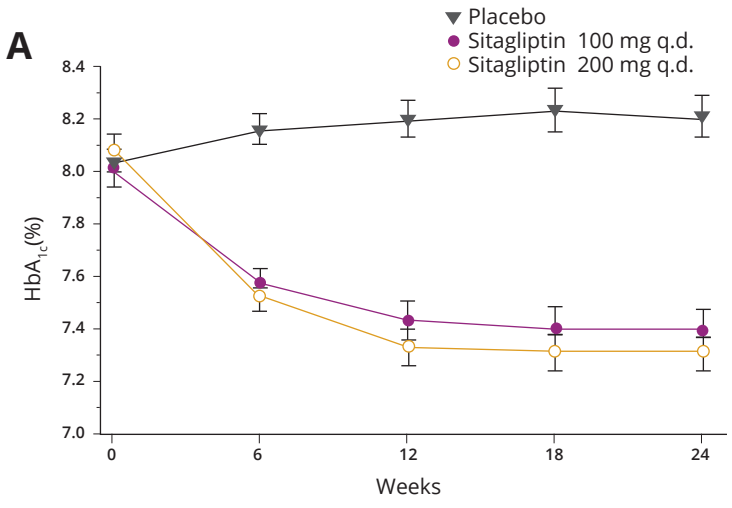
Monotherapy

1. Effect of the Dipeptidyl Peptidase-4 Inhibitor Sitagliptin as Monotherapy on Glycemic Control in Patients with Type 2 Diabetes[17].

Sitagliptin 100 mg q.d. was the most effective dose and was selected for continued development. Hence a 24 weeks randomized, double-blind, placebo-controlled study was conducted to explore tolerability and potential dose-dependent efficacy of once-daily sitagliptin 100 and 200 mg as monotherapy in patients with inadequately controlled type 2 diabetes. 741 patients (baseline HbA_{1c}- 8.0%) were randomized to sitagliptin 100 or 200 mg or placebo for 24 weeks. Sitagliptin 100 and 200 mg produced significant (p <0.001) placebo subtracted reductions in A1C (-0.79 and -0.94%, respectively) and fasting plasma glucose (-1.0 mmol/l [-17.1 mg/dl] and -1.2 mmol/l [-21.3 mg/dl], respectively). Patients with baseline A1C 9% had greater reductions in placebo-subtracted A1C with sitagliptin 100 and 200 mg (-1.52 and -1.50%, respectively) than those with baseline A1C 8% (-0.57 and -0.65%) or 8 to 9.0% (-0.80 and -1.13%, respectively) **(Figure 1)**. In a meal tolerance test, sitagliptin 100 and 200 mg significantly decreased 2-h postprandial glucose (PPG) (placebo-subtracted PPG -2.6 mmol/l [-46.7 mg/dl] and -3.0 mmol/l [-54.1 mg/dl], respectively) **(Figure 2)**. Results for the above key efficacy parameters were not significantly different between sitagliptin doses. Homeostasis model assessment of beta-cell function and proinsulin-to-insulin ratio improved with sitagliptin. The incidence of hypoglycaemia was similar, and overall gastrointestinal adverse experiences were slightly higher with sitagliptin. No meaningful body weight changes from baseline were observed with sitagliptin 100 (-0.2 kg) or 200 mg (-0.1 kg). The body weight change with placebo (-1.1 kg) was significantly (p <0.01) different from that observed with sitagliptin.

Key Highlights

- In this 24-week study, once-daily sitagliptin monotherapy improved glycaemic control in the fasting and postprandial states, improved measures of beta-cell function, and was well tolerated in patients with type 2 diabetes
- Results for the above key efficacy parameters were not significantly different between sitagliptin doses
- There were no meaningful differences between groups in incidences of overall clinical adverse experiences or of those assessed as serious, drug-related, or leading to discontinuation



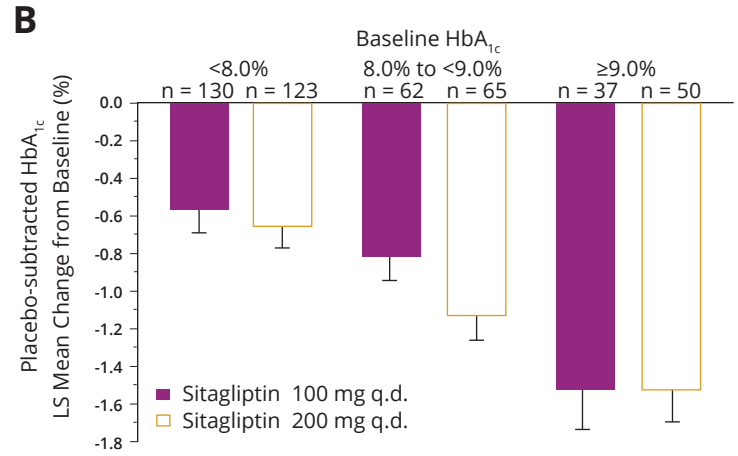


Figure 1 – *A: A1C (means ± SE) over time during the 24-week treatment period for patients treated with sitagliptin 100 or 200 mg q.d or with placebo. B: Placebo-subtracted least-squares (LS) mean change in A1C from baseline (±SE) by baseline A1C at study end point.*

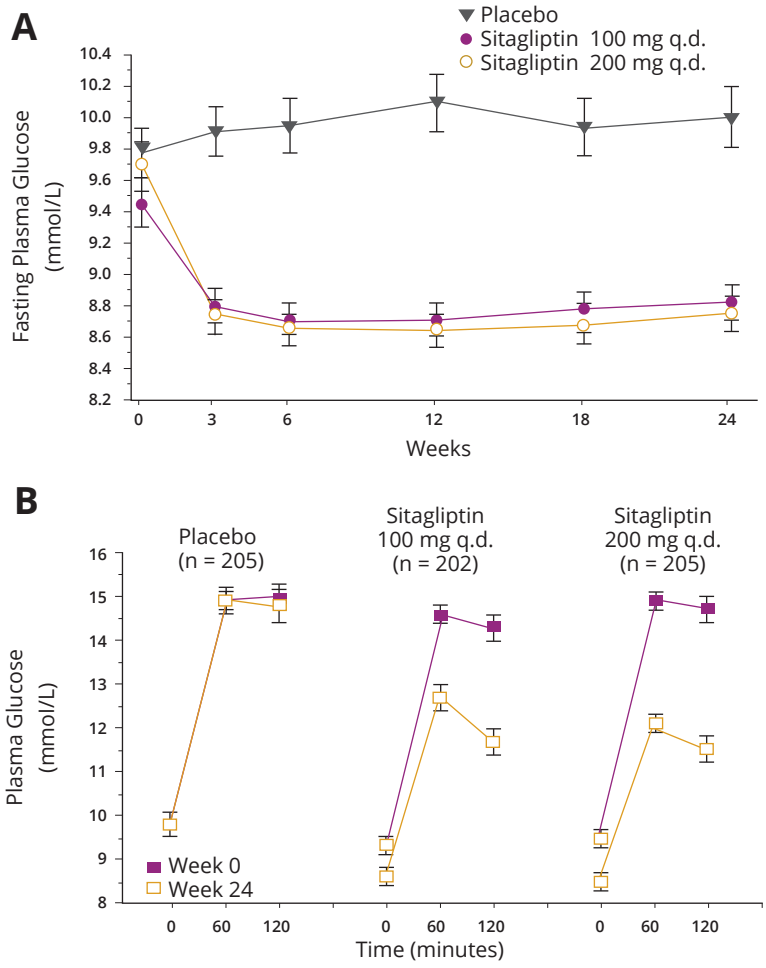


Figure 2 – *Change in plasma glucose with treatment. A: Fasting plasma glucose (means ± SE) over time during the 24-week treatment period for patients treated with sitagliptin 100 or 200 mg q.d. or placebo. B: Plasma glucose response during a meal tolerance test at baseline and week 24 by treatment group (means ± SE).*

2. Sitagliptin: A Review of Its Use as monotherapy in Patients with Type 2 Diabetes Mellitus[18].

Numerous clinical trials have evaluated the efficacy of sitagliptin on glycaemic control in patients with type 2 diabetes, including its use as monotherapy. This section focuses on larger randomized studies in which sitagliptin was administered at clinically relevant dosages. The primary efficacy endpoint of the trials was the change from baseline in HbA_{1c} levels, although various secondary outcomes, such as the change from baseline in fasting plasma glucose (FPG) levels and the proportion of patients achieving target HbA_{1c} levels, were also evaluated.

The main efficacy outcomes from randomized, double blind, placebo-controlled trials with sitagliptin as monotherapy in patients with type 2 diabetes are presented in Table 1. Eligibility criteria were generally similar between trials in that the studies included adults (typically 18–75 years) with inadequate glycaemic control (HbA_{1c} typically 7–10 %). One study included only elderly patients (mean age-72 years), one trial was in Japanese patients and another was in Chinese, Indian and Korean patients. In all of the studies, patients were randomized to receive sitagliptin 100 mg/day or placebo for 12–24 weeks, although in the study in elderly patients the sitagliptin dosage was 50 or 100 mg/ day depending on renal function **(Table 1)**.

Key Highlights

- Oral sitagliptin 100 mg once daily as monotherapy significantly improved glycaemic control relative to placebo in adult patients with inadequately controlled type 2 diabetes
- After 12–24 weeks of therapy, HbA_{1c}, FPG and 2-hour PPG (assessed during a meal tolerance test) levels were significantly reduced with sitagliptin 100 mg once daily relative to placebo
- In addition, more sitagliptin than placebo recipients achieved target HbA_{1c} levels of <7% or target levels of <6.5% (35% vs 6% [p <0.001])

Table 1 - Efficacy of sitagliptin as monotherapy in adults (aged ≥18 years) with inadequately controlled type 2 diabetes in randomized, double-blind, placebo-controlled trials

Study (duration)	Treatment (mg once daily) [no. of pts][a]	HbA_{1c} levels (%)		FPG (mmol/L)		Pts at target HbA_{1c} (%)[b]
		Change from BL [BL]	Diff. from PL	Change from BL [BL]	Diff. from PL	
Aschner et al. [38] (24 weeks)	SIT 100 [229] PL [244]	-0.61 [8.0] +0.18 [8.0]	-0.79*	-0.7 [9.5] +0.3 [9.8]	-1.0*	41* 17
Barzilai et al. [39][c] (24 weeks)	SIT 50 or 100 [101] PL [91]	-0.5 [7.8] +0.2 [7.7]	-0.7*	-0.9 [9.7] +0.6 [9.2]	-1.5*	35* 15
Mohan et al. [40][d] (18 weeks)	SIT 100 [339] PL [169]	-0.7 [8.7] +0.3 [8.7]	-1.0*	-1.4 [10.5] +0.3 [10.5]	-1.7*	21* 5
Nonaka et al. [41][e] (12 weeks)	SIT 100 [75] PL [75]	-0.65 [7.5] +0.41 [7.7]	-1.05*	-1.2 [9.1] +0.5 [9.1]	-1.8*	58* 15
Raz et al. [42] (18 weeks)	SIT 100 [193] PL [103]	-0.48 [8.0] +0.12 [8.1]	-0.60*	-0.7 [10.0] +0.4 [10.2]	-1.1*	36* 16

Least squares mean changes from BL are presented (mean values are reported for BL); any discrepancies in values due to conversion (from mg/dL to mmol/L for FPG) and/or rounding

BL baseline, *Diff.* difference, *FPG* fasting plasma glucose, *HbA_{1c}* glycosylated haemoglobin, *PL* placebo, *pts* patients, *SIT* sitagliptin, **p* ≤0.001 vs. PL

a No. of pts is for HbA_{1c} analyses (and varied for other parameters)

b Target HbA_{1c} was <7.0 %

c In elderly pts ≥65 years of age; SIT dosage based on renal function

d In Chinese, Indian and Korean pts

e In Japanese pts

Initial Combination Therapy

1. Sitagliptin: a review of its use as initial combination therapy in the management of type 2 diabetes mellitus[19].

The efficacy of sitagliptin as initial combination therapy with metformin or pioglitazone was evaluated in two 24-week, randomized, double-blind, placebo or active comparator controlled trials and a double blind 30-week, followed by a 50-week extension of one study in patients with inadequately controlled type 2 diabetes. In sitagliptin+metformin study, patients (mean disease duration of 4.5 years) were included regardless of whether they had received previous oral antihyperglycaemic therapy; at baseline 50% of these patients were not receiving oral antihyperglycaemic therapy. The sitagliptin+pioglitazone study included treatment-naive patients (»97% of patients had no prior treatment with oral antihyperglycaemic agents at baseline) with a mean disease duration of »2 years. Oral sitagliptin as initial combination therapy with metformin or pioglitazone significantly improved glycaemic control in adult patients with inadequately controlled type 2 diabetes. After 24 weeks of treatment, HbA_{1c}, FPG and 2-hour PPG levels were significantly reduced with sitagliptin plus metformin compared with sitagliptin or metformin monotherapy or placebo, or with sitagliptin plus pioglitazone compared with pioglitazone monotherapy **(Table 1)**. In addition, more patients receiving sitagliptin plus metformin or sitagliptin plus pioglitazone achieved target HbA_{1c} levels of <7% or <6.5% than those receiving monotherapy or placebo. Furthermore, the improvement in glycaemic control observed with sitagliptin plus metformin was maintained during long-term therapy in double-blind extension of the 24-week trial with reductions in glycaemic parameters being observed at week 54 **(Table 1)**.

Key Highlights

- Initial therapy with the combination of sitagliptin and metformin/pioglitazone provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo, to metformin alone, and to sitagliptin alone
- Mean reductions from baseline in A1C were generally greater for patients with higher baseline A1C values
- The decrease in body weight in the groups given sitagliptin in combination with metformin was similar to that in the groups given metformin alone or placebo
- Initial combination therapy or maintenance of combination therapy may not be appropriate for all patients. These management options are left to the discretion of the health care provider

Table 1- Efficacy of oral sitagliptin (SIT) as initial combination therapy with metformin (MET) or pioglitazone (PIO) in patients (pts) aged ‡18 y with inadequately controlled type 2 diabetes mellitus.

Study (duration of treatment)	Treatment (mg)[a] [no. of pts]	HbA_{1c} levels (%)		FPG (mg/dL)		2-h PPG (mg/dL)		Pts at target HbA_{1c}[b] (%)	
		change from BL [BL[c]]	btwn-grp diff.[d]	change from BL [BL[c]]	btwn-grp diff.[d]	change from BL [BL[c]]	btwn-grp diff.[d]	<7%	<6.5%
With MET									
Goldsteinetal.[39] (24 wk)	SIT 50 bid + MET 500 bid [147 – 183]	-1.40[e] [8.8]	-1.57**††	-47.1 [204]	-52.9**††	-92.5 [292]	-92.8**††	43**†	22*†
	SIT 50 bid + MET 1000 bid [152 – 180]	-1.90[e] [8.8]	-2.07**††	-63.9 [197]	-69.7**††	-116.6 [287]	-116.9**††	66**†	44*†
	SIT 100 od [136 - 178]	-0.66[e] [8.9]	-0.83**	-17.5 [201]	-23.3**	-51.9 [285]	-52.2**	20**	10*
	MET 500 bid [141 -179]	-0.82[e] [8.9]	-0.99**	-27.3 [205]	-33.1**	-53.4 [293]	-53.7**	23**	9*
	MET 1000 bid [138 -179]	-1.13[e] [8.7]	-1.30**	-29.3 [197]	-35.1**	-78.0 [283]	-78.3**	38**	20*
	PL [129 - 169]	0.17[e] [8.7]		5.8 [196]		0.3 [277]		9	2*
Continuation phase									
Williams-Herman et al.[53] (54 wk)	SIT 50 bid + MET 500 bid [121 - 147]	-1.4 [8.8]		-42.5 [197]		-89.6 [282]		48	
	SIT 50 bid + MET 1000 bid [132 - 153]	-1.8 [8.7]		-55.6 [195]		-107.9 [280]		67	
	SIT 100 od [87 - 106]	-0.8 [8.7]		-16.0 [183]		-45.9 [260]		23	
	MET 500 bid [92 - 117]	-1.0 [8.7]		-29.0 [188]		-58.6 [269]		25	
	MET 1000 bid [116 - 134]	-1.3 [8.5]		-39.6 [188]		-76.3 [277]		44	
With PIO									
Yoon et al.[40][f] (24 wk)	SIT 100 od + PIO 30 od [216 - 256]	-2.4[e] [9.5]	-0.9‡	-63.0 [204]	-22.8‡	-113.6	-44.7‡	60‡	38‡
	PIO 30 od [211 - 253]	-1.5[e] [9.5]		-40.2 [202]		-68.9		28	14

a Treatment naive pts with inadequate glycaemic control (HbA_{1c} levels of 8–12%) directly entered a 2-wk, single-blind, PL run-in period.[40] Pts who were or were not receiving OHA therapy at screening entered a 2-wk, single-blind, PL run-in period (directly or after a drug wash-out and/or a diet and exercise lead-in period) if they had inadequate glycaemic control (HbA_{1c} levels of 7.5–11%).[39]

b Target levels of <7% according to the American Diabetes Association guidelines[60] or <6.5% according to the International Diabetes Federation.[61]

c Mean values reported.

d Difference from the PL[39,53] or PIO[40] groups.

e Primary endpoint.

f Abstract plus poster presentation. Pt numbers for this study are available from other sources.[63]

2. Four-Year Durability of Initial Combination Therapy with Sitagliptin and Metformin in Patients with Type 2 Diabetes in Clinical Practice; COSMIC Study[20].

Previous randomized clinical studies have shown that sitagliptin monotherapy reduced the glycosylated haemoglobin (HbA_{1c}) level by 0.4–0.6%, and sitagliptin combination therapy with metformin or thiazolidinedione decreased HbA_{1c} by 0.4–1.4% over 18–52 weeks of treatment in patients with type 2 diabetes. More specifically, the clinical trials with sitagliptin and metformin as initial combination therapy have shown an average reduction of HbA_{1c} by 0.8%. Previous studies have only reported the efficacy and safety of sitagliptin with or without metformin over a 2-year time frame. In recent years, a combination of a DPP-4 inhibitor and metformin has commonly been used, demonstrating the additive effects resulting from complementary mechanisms of action. However, there have been few studies of the long-term durability and safety of combination therapy, particularly in the real-world clinical setting. Hence the long-term durability and safety of initial combination therapy with sitagliptin and metformin in patients with T2D in clinical practice was conducted along with evaluation of the predictive markers for therapeutic efficacy of the co-administration of sitagliptin and metformin. 1,178 patients with type 2 diabetes (HbA_{1c}- 7.5% or 58 mmol/mol) were prescribed initial combination therapy with sitagliptin and metformin. 890 individuals (age, 58.0 ±12.5 years; BMI, 25.4 ± 3.5 kg/m2; HbA_{1c}, 8.6 ± 1.1%) were followed up with every 3–6 months for 4 years. Homeostasis model assessments for insulin resistance and β-cell function (HOMA-β) were recorded at baseline. At the end of every year of treatment, changes in HbA_{1c} from the baseline were assessed. After 1 year, 72.2% of patients with initial combination therapy had responded, defined as HbA_{1c} reduction 0.8% or attainment of the target HbA_{1c}-7.0%. After 4 years, 35.4% of the patients still showed a response, with an HbA_{1c} level of 7.0 ± 0.9%. A high HbA_{1c} level at baseline was the most significant independent predictor of the long-term response (P <0.001). In addition, low HOMA-β was a significant predictor of a greater reduction in HbA_{1c} (Figure 2,3,4).This treatment was generally well tolerated over the 4-year follow-up period, without any serious adverse event.

Key Highlights

- This real-world follow-up study shows a persistent glucose-reducing effect of initial combination therapy with sitagliptin and metformin for up to 4 years

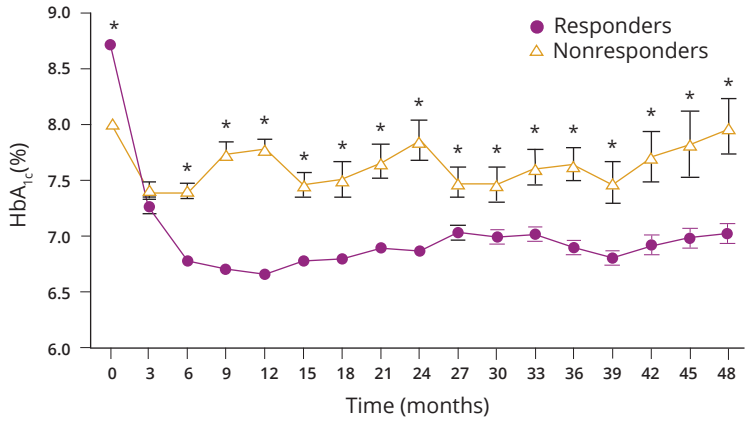


Figure 2 - Comparison of HbA_{1c} levels for 48 months between responders (n=315) and nonresponders (n=42) when response was defined as ≥0.8% of HbA_{1c} reduction from baseline or attainment of target HbA_{1c} (≤ 7.0%) at the end of 4 years' follow-up. *P<0.001 for responder vs. nonresponder group.

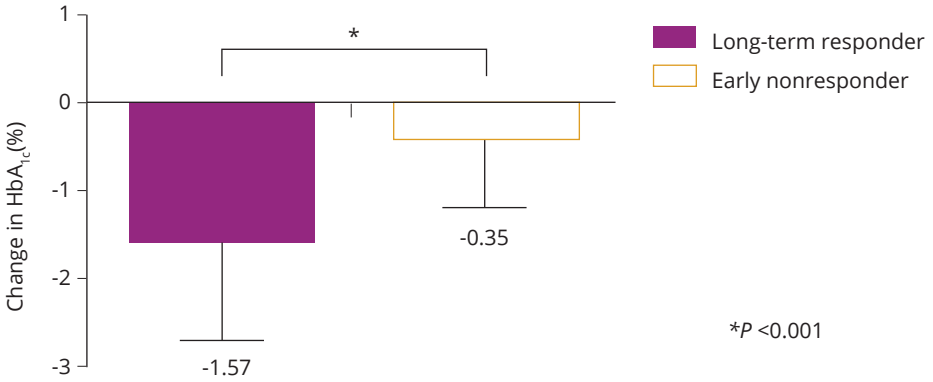


Figure 3 - Reduction in HbA_{1c}(%) after 3 months in long-term responders and early nonresponders.

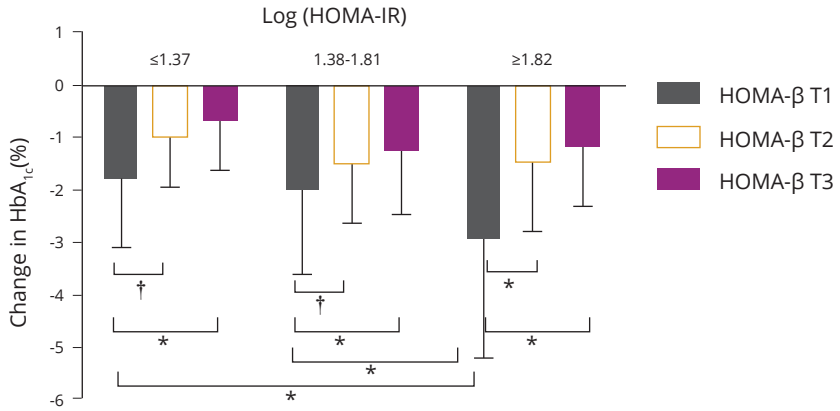


Figure 4 - Changes in HbA_{1c}(%) after initial combination therapy with sitagliptin and metformin according to the tertiles (T) of HOMA-IR and HOMA-β at baseline. HOMA-IR and HOMA-β; homeostasis model assessment of insulin resistance and β-cell function. Logarithmically transformed values of HOMA-IR and HOMA-β were used for analysis. Log (HOMA-β) tertiles; T1 ≤3.65, 3.66 ≤T2 ≤4.17, T3 ≥4.18. *P <0.001, †P <0.05

Combination Therapy (Double and Triple combination)

1. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin added to ongoing metformin therapy in patients with Type 2 Diabetes inadequately controlled with metformin alone[21].

Treatment with a single antihyperglycemic agent is often unsuccessful in achieving and/or maintaining glycaemic control in patients with type 2 diabetes, and many patients require combinations of antihyperglycemic agents. Metformin, a biguanide, is one of the most commonly used first-line antihyperglycemic agents in the treatment of type 2 diabetes, which acts primarily by lowering hepatic glucose production and may also improve insulin resistance. Because sitagliptin and metformin target potentially complementary pathways, the addition of sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin monotherapy may provide improved glycemic control. Hence, the efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, added to ongoing metformin therapy, were assessed in patients with type 2 diabetes who had inadequate glycemic control (HbA_{1c} [A1C] >7 and <10%) with metformin alone. After a screening diet/exercise run-in period, a metformin dose titration/stabilization period, and a 2-week, single-blind, placebo run-in period, 701 patients, aged 19–78 years, with mild to moderate hyperglycaemia (mean A1C 8.0%) receiving ongoing metformin (>1,500 mg/day) were randomly assigned to receive the addition of placebo or sitagliptin 100 mg once-daily in a 1:2 ratio for 24 weeks. Patients exceeding specific glycemic limits were provided rescue therapy (pioglitazone) until the end of the study. The primary efficacy end point was change from baseline at week 24 in A1C. Secondary efficacy end points included change from baseline at week 24 in FPG as well as in glucose, insulin, and C-peptide concentrations, measured immediately before and at 60 and 120 min after a standard meal, and a lipid panel (total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and triglyceride-to-HDL cholesterol ratio). Exploratory end points included mean glucose, insulin, and C-peptide concentrations, as well as area under the curve (AUC) for glucose, insulin, and C-peptide, and insulin AUC–to–glucose AUC ratio, after a standardized morning meal. Safety and tolerability were assessed throughout the study. The efficacy analyses were based on an all-patients-treated population using an ANCOVA and excluded data obtained after glycemic rescue.

At week 24, sitagliptin treatment led to significant reductions compared with placebo in A1C (-0.65%), fasting plasma glucose, and 2-h postmeal glucose. Fasting insulin, fasting C-peptide, fasting proinsulin-to-insulin ratio, postmeal insulin and C-peptide areas under the curve (AUCs), postmeal insulin AUC–to–glucose AUC ratio, homeostasis model assessment of beta-cell function, and quantitative insulin sensitivity check index were significantly improved with sitagliptin relative to placebo. A significantly greater proportion of patients achieved an A1C <7% with sitagliptin (47.0%) than with placebo (18.3%) **(Table 1)**. There was no increased risk of hypoglycemia or gastrointestinal adverse experiences with sitagliptin compared with placebo. Body weight decreased similarly with sitagliptin and placebo.

Key Highlights

- Sitagliptin 100 mg once-daily added to ongoing metformin therapy was efficacious and well tolerated in patients with type 2 diabetes who had inadequate glycemic control with metformin alone
- In patients with type 2 diabetes who had inadequate glycemic control with metformin alone, the addition of sitagliptin 100 mg once-daily provided effective and sustained improvement in A1C, FPG, and 2-h postmeal glucose, as well as significant improvements in indexes of insulin secretion and Beta-cell function, including HOMA-A and the fasting proinsulin-to-insulin ratio
- Treatment with sitagliptin was associated with a low rate of hypoglycaemia that was similar to that seen with placebo, as well as a neutral effect on body weight

Table 1—Glycemic efficacy end points

Parameter	*n*	Baseline	Week 24	Least-squares change from baseline
A1C (%)				
Placebo	224	8.03 ± 0.82	7.95 ± 1.10	-0.02 (-0.15 to 0.10)
Sitagliptin 100 mg q.d.	453	7.96 ± 0.81	7.26 ± 0.97	-0.67 (-0.77 to -0.57)*
FPG (mmol/l)				
Placebo	226	9.6 ± 2.3	9.9 ± 2.8	0.5 (0.2 to 0.8)
Sitagliptin 100 mg q.d.	454	9.4 ± 2.3	8.4 ± 2.2	-0.9 (-1.2 to -0.7)*
Insulin (pmol/l)				
Placebo	197	72.0 ± 45.6	72.0 ± 40.8	-1.2 (-10.2 to 8.4)
Sitagliptin 100 mg q.d.	419	72.6 ± 58.2	81.6 ± 76.2	7.8 (0.6 - 15.0)†
Proinsulin-to-insulin ratio				
Placebo	169	0.37 ± 0.20	0.37 ± 0.21	0.02 (- 0.02 to 0.05)
Sitagliptin 100 mg q.d.	397	0.36 ± 0.21	0.33 ± 0.21	-0.03 (- 0.05 to 0.00)‡
C-peptide (nmol/l)				
Placebo	186	0.83 ± 0.40	0.87 ± 0.40	0.03 (-0.03 to 0.01)
Sitagliptin 100mg q.d.	390	0.83 ± 0.43	0.93 ± 0.43	0.10 (0.03 - 0.13)‡
HOMA- β				
Placebo	196	45.1 ± 34.2	47.6 ± 37.5	3.5 (-4.9 to 11.8)
Sitagliptin 100 mg q.d.	418	46.4 ± 38.9	65.2 ± 68.9	19.5 (12.9 - 26.2)*
QUICKI				
Placebo	196	0.314 ± 0.031	0.312 ± 0.028	-0.002 (-0.007 to 0.003)
Sitagliptin 100 mg q.d.	418	0.315 ± 0.032	0.318 ± 0.036	0.003 (-0.000 to 0.007)†

Data are means ± SD or mean (95% CI). To convert glucose from millimoles per liter to milligrams per deciliter, divide by 0.05551. *P <0.001 vs. placebo; †P <0.050 vs.placebo; ‡P <0.010 vs. placebo.

2. Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study[22].

Many patients with type 2 diabetes do not achieve or maintain glycaemic goals with a single antihyperglycemic agent and require additional therapy. Metformin is recommended as the first-line therapy for most patients with type 2 diabetes. Sulphonylureas are the most commonly prescribed second-line therapy, but are associated with weight gain and an increased risk of hypoglycaemia. Sitagliptin, a DPP-4 inhibitor, is a newer antihyperglycemic therapy that has been shown to be weight neutral and to have a low risk of hypoglycaemia when co-administered with metformin.

The present study assessed the 2-year efficacy and safety for sitagliptin compared with glipizide, a sulphonylurea, when added to ongoing metformin therapy. Patients who were on a stable dose of metformin (‡ 1500 mg / day) for at least 8 weeks were randomised in a double-blind manner to receive either sitagliptin 100 mg q.d. (N = 588) or glipizide 5 mg/day (up-titrated up to 20 mg / day based upon prespecified glycaemic criteria) (N = 584). The efficacy analysis assessed the change in HbA_{1c} from baseline using the per-protocol (PP) population.

For the PP cohort, mean baseline HbA_{1c} was 7.3% in both groups. After 2 years, the least squares (LS) mean change in HbA_{1c} from baseline [95% confidence interval (CI)] was -0.54% (-0.64, -0.45) with sitagliptin (n = 248) and -0.51% (-0.60, -0.42) with glipizide (n = 256). The rise in HbA_{1c} from week 24 to week 104 [i.e. coefficient of durability (COD)] was smaller with sitagliptin [COD (95% CI) 0.16%/year (0.10, 0.21)] compared with glipizide [0.26%/year (0.21, 0.31)]. The proportion of patients with an HbA_{1c}<7% was 63% and 59% with sitagliptin and glipizide, respectively. The beta-cell responsiveness to a meal challenge was maintained with sitagliptin and decreased with glipizide **(Table 1)**. The proportion of patients who reported hypoglycaemia was 5% with sitagliptin and 34% with glipizide [difference in proportions (95% CI) = -29% (-33, -25)] **(Figure 1)**. Relative to baseline, sitagliptin was associated with weight loss (-1.6 kg) compared with weight gain (+0.7 kg) with glipizide **(Figure 2)**.

Key Highlights

- In patients with type 2 diabetes, adding sitagliptin to metformin monotherapy improved glycaemic control over 2 years, similar to the glucose-lowering efficacy observed with adding glipizide, but with greater durability and generally better maintenance of beta-cell function
- Sitagliptin was generally well tolerated with a lower risk of hypoglycaemia and weight loss compared with weight gain observed with glipizide

Table 1: Key efficacy results in the per-protocol cohort after 2 years of treatment

	n	Week 0 (Baseline) mean (SD)	Week 104 mean (SD)	LS mean change from baseline (95% CI)	Difference in LS mean change (95% CI)
HbA_{1c}, %					
Glipizide + Metformin	256	7.31 (0.74)	6.80 (0.59)	-0.51 (- 0.60, - 0.42)	-0.03 (- 0.13, 0.07)
Sitagliptin + Metformin	248	7.30 (0.64)	6.77 (0.58)	- 0.54 (-0.64, -0.45)	
Fasting plasma glucose, mmol/l					
Glipizide + Metformin	251	8.5 (1.9)	7.7 (1.7)	-1.0 (-1.3, -0.7)	-0.1 (0.4, 0.2)
Sitagliptin + Metformin	249	8.4 (1.7)	7.6 (1.7)	-1.1 (-1.4, -0.8)	
Fasting serum insulin, pmol/l					
Glipizide + Metformin	241	78.0 (50.4)	94.8 (69.0)	12.6 (4.2, 20.4)	-18.0 (-26.4, - 9.0)
Sitagliptin + Metformin	237	78.6 (56.4)	76.8 (43.8)	-5.4 (-13.8, 3.0)	
Fasting serum proinsulin, pmol/l					
Glipizide + Metformin	249	22.9 (18.0)	26.5 (20.1)	2.1 (-0.7, 4.8)	-6.9 (-9.7, - 4.0)
Sitagliptin + Metformin	242	23.9 (20.7)	20.0 (18.3)	-4.8 (-7.6, -2.0)	
Proinsulin/insulin ratio					
Glipizide + Metformin	240	0.31 (0.16)	0.30 (0.18)	-0.01 (-0.03, 0.02)	-0.04 (-0.07, -0.01)
Sitagliptin + Metformin	235	0.32 (0.17)	0.26 (0.16)	-0.05 (- 0.08, - 0.02)	
HOMA-β (%)					
Glipizide + Metformin	234	59.2 (48.2)	77.5 (107.9)	19.2 (5.7, 32.7)	- 6.3 (-20.3, 7.6)
Sitagliptin + Metformin	232	59.8 (50.7)	71.2 (58.0)	12.9 (- 0.7, 26.5)	
HOMA-IR					
Glipizide + Metformin	234	5.0 (3.4)	5.6 (5.1)	0.2 (-0.5, 0.9)	-1.1 (-1.8, -0.4)
Sitagliptin + Metformin	232	4.9 (3.8)	4.4 (3.2)	-0.9(-1.6, -0.2)	
QUICKI					
Glipizide + Metformin	234	0.314 (0.033)	0.311 (0.029)	-0.001 (-0.005, 0.003)	0.008 (0.003, 0.012)
Sitagliptin + Metformin	232	0.315 (0.029)	0.319 (0.029)	0.006 (0.002, 0.010)	

SD, standard deviation; LS, least squares; CI, confidence interval.

Figure 1 - Proportion of patients with 0, 1, 2, 3, 4, 5, 6, or more than 6 hypoglycaemic episodes in the sitagliptin group (purple bars) and glipizide group (yellow bars) during the 2-year study.

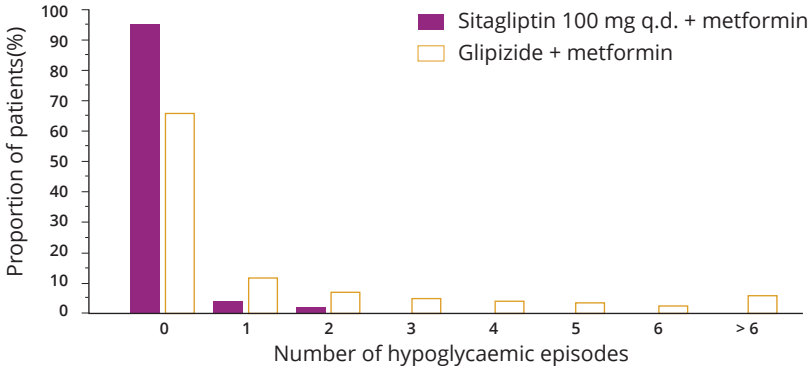
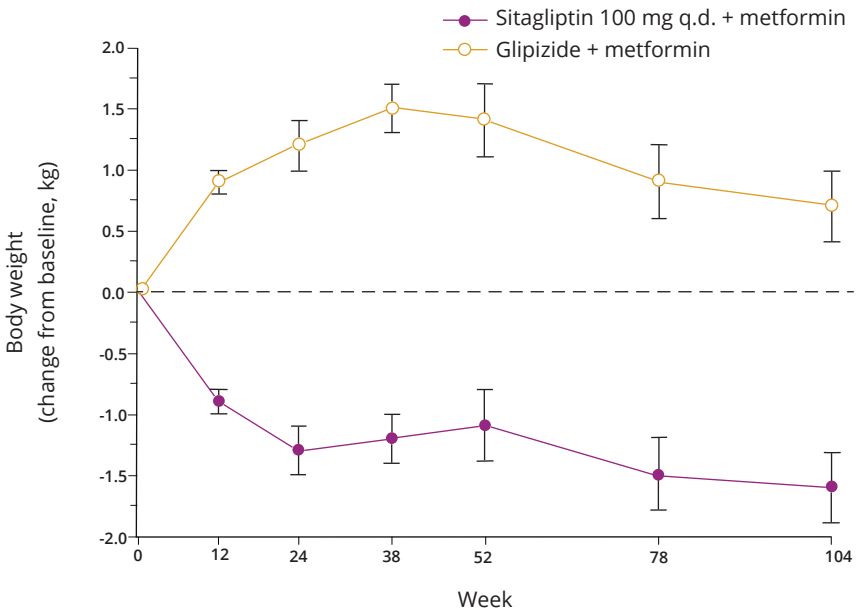


Figure 2 - Body weight change (LS mean change from baseline ± SE) over 2 years in patients on ongoing metformin therapy treated with sitagliptin 100 mg q.d. or glipizide.



3. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial[23].

A prior study showed that the glycaemic efficacy of the addition of sitagliptin to ongoing metformin monotherapy was non-inferior to the addition of glipizide. To provide an additional comparison to another commonly used sulfonylurea, this study assessed the efficacy and safety of sitagliptin compared with glimepiride in patients with type 2 diabetes mellitus and inadequate glycaemic control on metformin monotherapy. Patients with type 2 diabetes and an HbA_{1c} of 6.5–9.0% while on a stable dose of metformin (≥1500 mg/day) combined with diet and exercise for at least 12 weeks were randomized in a double-blind manner to receive either sitagliptin 100 mg daily (N = 516) or glimepiride (starting dose 1 mg/day and up-titrated, based upon patient's self-monitoring of blood glucose results, to a maximum dose of up to 6 mg/day) (N = 519) for 30 weeks. The primary analysis assessed whether sitagliptin is non-inferior to glimepiride in reducing HbA_{1c} at week 30 (based on the criterion of having an upper bound of the 95% CI less than the prespecified non-inferiority bound of 0.4%). The primary efficacy outcome was changed from baseline in HbA_{1c} at week 30. Secondary efficacy endpoints included the percentages of patients with HbA_{1c} values at goals of <7.0 and <6.5%, change from baseline in FPG and mean or median percent change from baseline in fasting lipid parameters.

The mean baseline HbA_{1c} was 7.5% in both the sitagliptin group (n = 443) and the glimepiride group (n = 436). After 30 weeks, the least squares (LS) mean change in HbA_{1c} from baseline was −0.47% with sitagliptin and −0.54% with glimepiride, with a between-group difference (95% CI) of 0.07% (−0.03, 0.16). This result met the prespecified criterion for declaring non-inferiority. The percentages of patients with an HbA_{1c} <7.0% at week 30 were 52 and 60% in the sitagliptin and glimepiride groups, respectively **(Figure 1)**. The LS mean change in fasting plasma glucose from baseline (95% CI) was −0.8 mmol/l (−1.0, −0.6) with sitagliptin and −1.0 mmol/l (−1.2, −0.8) with glimepiride, for a between-group difference (95% CI) of 0.2 mmol/l (−0.1, 0.4). Relative to baseline, sitagliptin was associated with a mean weight loss (−0.8 kg), whereas glimepiride was associated with a mean weight gain (1.2 kg), yielding a between-group difference of −2.0 kg (p <0.001) **(Figure 2)**. The percentages of patients for whom hypoglycaemia was reported were 7% in the sitagliptin group and 22% in the glimepiride group (percentage-point difference = −15, p <0.001) **(Figure 3)**.

Key Highlights

- In patients with type 2 diabetes and inadequate glycaemic control on metformin monotherapy, the addition of sitagliptin or glimepiride led to similar improvement in glycaemic control after 30 weeks
- Sitagliptin was generally well tolerated. Compared to treatment with glimepiride, treatment with sitagliptin was associated with a lower risk of hypoglycaemia and with weight loss versus weight gain

Figure 1 - HbA_{1c} (mean ± s.e.), per-protocol (PP) population.

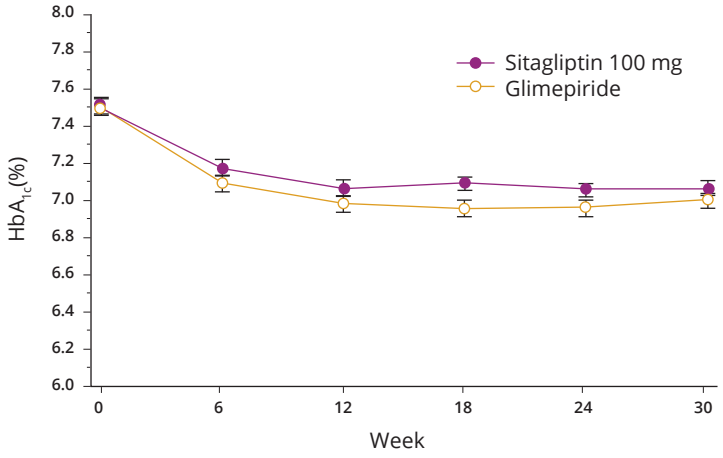
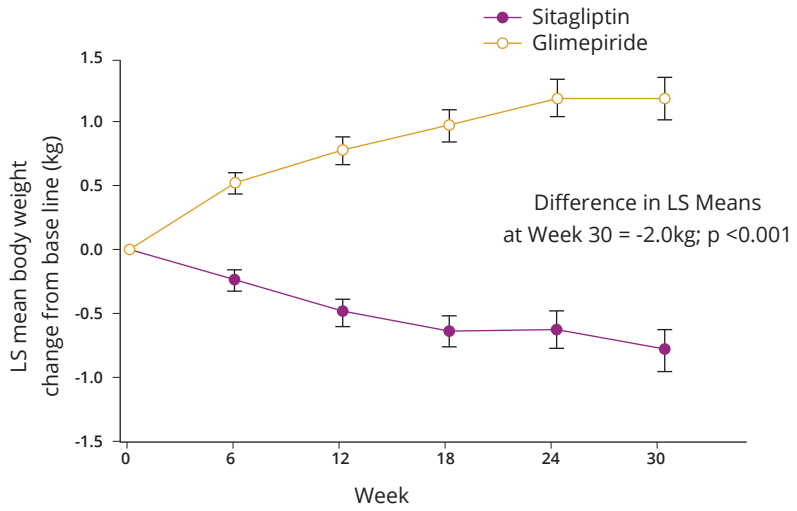


Figure 2 - Body weight change from baseline [least squares (LS) mean ± s.e.] over time.



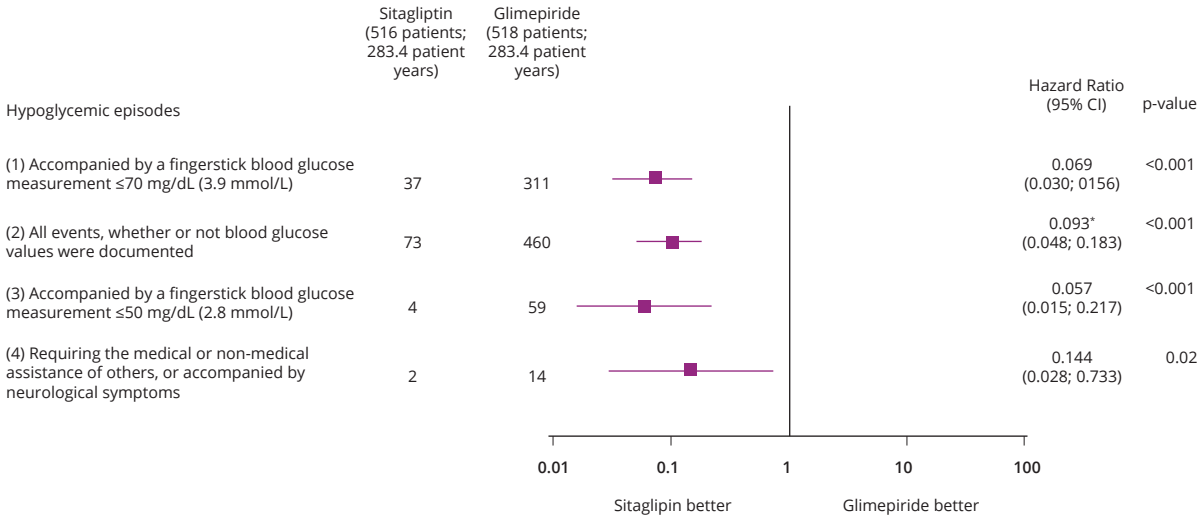


Figure 3 - Hazard ratios for hypoglycaemic events. Model terms: Treatment, most recent HbA_{1c} value prior to the event, time from randomization to the event, gender, age group (< or ≥65 years), most recent squared HbA_{1c} value prior to the event (model 1 only), and treatment-by-most recent HbA_{1c} interaction (model 2 only). *Hazard ratio at a HbA_{1c} value of 6.5%. Fixed-sequence testing procedure (model 1 through model 4). Variances relaxed to account for clustering by patient; Cl = confidence intervals.

4. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin[24].

Treatment with a single antihyperglycaemic agent is often unsuccessful at achieving and/or maintaining long-term glycaemic control in patients with type 2 diabetes, so many patients require combination therapies [1]. Monotherapy with metformin or a sulphonylurea is the most commonly used initial oral hypoglycaemic agent (OHA) regimen to treat patients with type 2 diabetes. As with all OHAs, monotherapy with a sulphonylurea may not achieve or maintain glycaemic control; therefore novel, efficacious and well-tolerated therapies that can be added to a sulphonylurea agent are needed. Similarly, dual combination therapy with a sulphonylurea agent and metformin also may not achieve or maintain glycaemic control. In this setting, use of insulin is often the next therapeutic step. Insulin requires parenteral administration, which many patients find undesirable, and the addition of a thiazolidinedione can lead to oedema and an increase in body weight. Hence, there is a need for additional OHA options that can be added to the dual combination of sulphonylurea and metformin to avoid the need to switch to insulin. Given the different mechanisms of action of sitagliptin and sulphonylurea agents, combination therapy with these two agents would seem a rational approach to improving glycaemic control. Previous studies have shown that sitagliptin provides effective add-on combination treatment with metformin. If sitagliptin is effective in combination with a sulphonylurea agent, then triple combination therapy with metformin and a sulphonylurea agent would likely be effective as well.

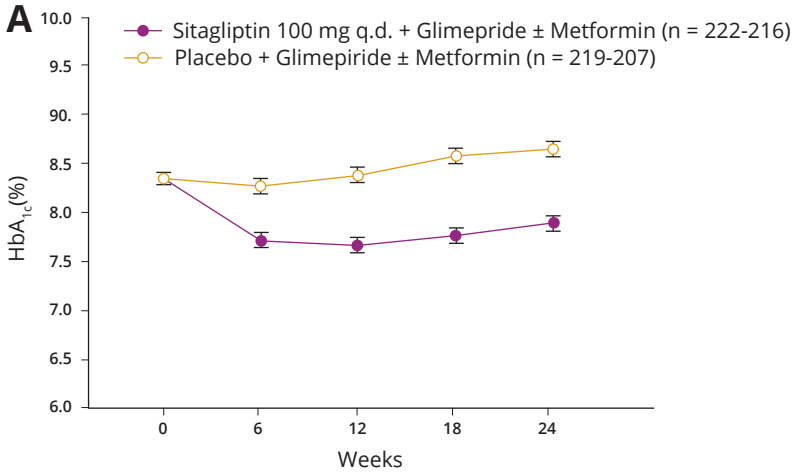
In this study, the efficacy and tolerability profile of adding sitagliptin 100 mg or placebo to ongoing treatment with glimepiride alone or glimepiride in combination with metformin was assessed in patients with type 2 diabetes who had inadequate glycaemic control [glycosylated haemoglobin (HbA_{1c}) >7.5% and <10.5%] over a 24-week period. In addition to assessment in the overall study population, the efficacy and tolerability of sitagliptin relative to placebo in the individual subpopulations of patients on glimepiride alone or on glimepiride and metformin were examined separately. After a screening, diet/exercise run-in and drug wash-off period, a glimepiride +/- metformin dose titration/ stabilization period and a 2-week, single-blind placebo run-in, 441 patients (of ages 18–75 years) were randomized to receive the addition of sitagliptin 100 mg once daily or placebo in a 1:1 ratio for 24 weeks. Of these patients, 212 were on glimepiride (≥4 mg/day) monotherapy and 229 were on glimepiride (≥4 mg/day) plus metformin (≥1500 mg/day) combination therapy. Patients exceeding pre-specified glycaemic thresholds during the double-blind treatment period were provided open-label rescue therapy (pioglitazone) until study end. The primary efficacy analysis evaluated the change in HbA_{1c} from baseline to Week 24. Secondary efficacy endpoints included fasting plasma glucose (FPG), 2-h post-meal glucose and lipid measurements.

Mean baseline HbA_{1c} was 8.34% in the sitagliptin and placebo groups. After 24 weeks, sitagliptin reduced HbA_{1c} by 0.74% (p <0.001) relative to placebo. In the subset of patients on glimepiride plus metformin, sitagliptin reduced HbA_{1c} by 0.89% relative to placebo, compared with a reduction of 0.57% in the subset of patients on glimepiride alone **(Figure 1)**. The addition of sitagliptin reduced FPG by 20.1 mg/dl (p <0.001) and increased homeostasis model assessment-b, a marker of b-cell function, by 12% (p <0.05) relative to placebo. In patients who underwent a meal tolerance test (n = 134), sitagliptin decreased 2-h post-prandial glucose (PPG) by 36.1 mg/dl (p <0.001) relative to placebo **(Table 1)**. The addition of sitagliptin was generally well tolerated, although there was a higher incidence of overall (60 vs. 47%) and drug-related adverse experiences (AEs) (15 vs. 7%) in the sitagliptin group than in the placebo group **(Table 2)**. This was largely because of a higher incidence of hypoglycaemia AEs (12 vs. 2%, respectively) in the sitagliptin group compared with the placebo group. Body weight modestly increased with sitagliptin relative to placebo (+0.8 vs. -0.4 kg; p <0.001).

Key Highlights

- Sitagliptin 100 mg once daily significantly improved glycaemic control and b-cell function in patients with type 2 diabetes who had inadequate glycaemic control with glimepiride or glimepiride plus metformin therapy
- The addition of sitagliptin was generally well tolerated, with a modest increase in hypoglycaemia and body weight, consistent with glimepiride therapy and the observed degree of glycaemic improvement

Figure 1 - Mean (SE) HbA_{1c} over time for sitagliptin 100 mg once daily vs. placebo in the entire study cohort (A) and in the subset of patients taking glimepiride monotherapy (Stratum 1) or glimepiride plus metformin combination therapy (Stratum 2) (B). HbA_{1c}, glycosylated haemoglobin.



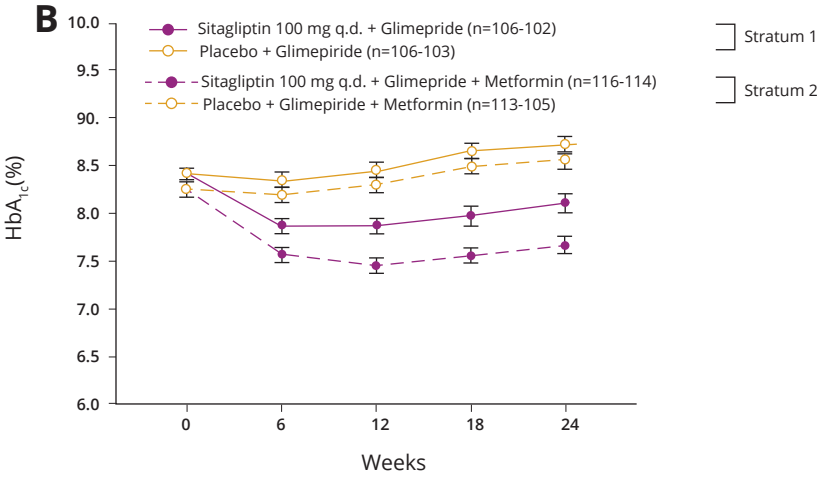


Table 1: LS mean change from baseline to Week 24 in glycaemic and meal tolerance test

	n	Week 0 (Baseline) mean (s.d)	Week 24 mean (s.d)	LS mean change from baseline (95% CI)	Difference in LS mean change (95% CI)
Glycaemic parameters Fasting serum insulin, µIU/ml					
Sitagliptin + G ± M	188	14.8 (13.8)	16.2 (12.9)	1.8 (0.8 to 2.9)*	1.8 (0.2 to 3.4)†
Placebo + G ± M	162	12.4 (10.4)	12.9 (9.1)	0.1 (-1.1 to 1.2)	
HOMA-β (%)					
Sitagliptin + G ± M	186	50.7 (47.8)	61.4 (57.3)	11.3 (4.4 to 18.1)*	12.0 (1.8 to 22.1)†
Placebo + G ± M	156	47.4 (47.7)	47.4 (55.2)	-0.7 (-8.2 to 6.8)	
Proinsulin/insulin ratio					
Sitagliptin + G ± M	180	0.517 (0.363)	0.452 (0.271)	-0.057 (-0.091 to -0.022)‡	-0.028 (-0.080 to 0.025)
Placebo + G ± M	144	0.491 (0.286)	0.473 (0.269)	-0.029 (-0.068 to 0.010)	
Meal tolerance test parameters 2-hr post-meal insulin, µIU/ml					
Sitagliptin + G ± M	63	55.6 (46.7)	65.7 (53.5)	10.6 (3.4 to 17.9)‡	14.4 (3.9 to 24.9)†
Placebo + G ± M	59	46.3 (27.1)	43.3 (32.1)	-3.8 (-11.3 to 3.7)	
2-hr post-meal C-peptide, ng/ml					
Sitagliptin + G ± M	70	7.1 (3.2)	7.6 (2.7)	0.6 (0.2 to 0.9)*	1.1 (0.6 to 1.6)§
Placebo + G ± M	65	6.5 (2.9)	6.1 (2.5)	-0.5 (-0.9 to -0.2)‡	
Glucose total AUC, mg x h/dl					
Sitagliptin + G ± M	67	497.1 (84.1)	465.1 (95.6)	-33.4 (-54.5 to -12.2)‡	-61.2 (-91.5 to -30.8)§
Placebo + G ± M	64	499.9 (97.9)	526.3 (103.8)	27.8 (6.2 to 49.4)‡	
Insulin total AUC, µIU x h/ml					
Sitagliptin + G ± M	51	92.8 (68.6)	98.9 (73.7)	6.5 (-3.1 to 16.2)	7.6 (-6.3 to 21.4)
Placebo + G ± M	50	69.4 (39.0)	68.8 (50.9)	-1.0 (-10.8 to 8.7)	
C-peptide total AUC, ng x h/ml					
Sitagliptin + G ± M	68	10.9 (4.7)	11.5 (4.6)	0.7 (0.2 to 1.1)‡	1.0 (0.3 to 1.7)†
Placebo + G ± M	65	9.7 (3.9)	9.5 (3.5)	-0.4 (-0.9 to 0.1)	
Insulin total AUC/glucose total AUC ratio					
Sitagliptin + G ± M	47	0.200 (0.150)	0.226 (0.164)	0.029 (0.003 to 0.054)‡	0.045 (0.010 to 0.081)†
Placebo + G ± M	48	0.151 (0.103)	0.137 (0.114)	-0.017 (-0.041 to 0.008)	

LS, least squares; s.d., standard deviation; CI, confidence interval; G, glimepiride; M, metformin; HOMA–b, homeostasis model assessment–b; AUC, area under curve.

Table 2: Summary of clinical Adverse events*

n (%)	Entire cohort (n = 222)	Glimepiride (n = 106)	Glimepiride + metformin (n = 116)	Entire cohort (n = 219)	Glimepiride (n = 106)	Glimepiride + metformin (n = 113)
One or more AEs	132 (59.5)	59 (55.7)	3 (62.9)	103 (47.0)	43 (40.6)	60 (53.1)
Drug-related AEs†	33 (14.9)	12 (11.3)	21 (18.1)	15 (6.8)	7 (6.6)	8 (7.1)
Serious AEs (SAEs)	12 (5.4)	5 (4.7)	7 (6.0)	8 (3.7)	6 (5.7)	2 (1.8)
Drug-related SAEs†	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	1(0.5)‡	0 (0.0)	1 (0.9)‡	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuations because of AEs	5 (2.3)	3 (2.8)	2 (1.7)	3 (1.4)	1 (0.9)	2 (1.8)
Discontinuations because of drug-related AEs†	1 (0.5)	1 (0.9)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.9)
Discontinuations because of SAEs	3 (1.4)	2 (1.9)	1 (0.9)	1 (0.5)	1 (0.9)	0 (0.0)
Discontinuations because of drug-related SAEs†	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Clinical AEs of special interest Hypoglycaemia	27 (12.2)	8 (7.5)	19 (16.4)	4 (1.8)	3 (2.8)	1 (0.9)
Overall gastrointestinal AEs Selected gastrointestinal AEs	11 (5.0)	6 (5.7)	5 (4.3)	10 (4.6)	2 (1.9)	8 (7.1)
Abdominal pain	5 (2.3)	3 (2.8)	2 (1.7)	2 (0.9)	0 (0.0)	2 (1.8)
Diarrhoea	3 (1.4)	2 (1.9)	1 (0.9)	6 (2.7)	2 (1.9)	4 (3.5)
Nausea	1 (0.5)	0 (0.0)	1 (0.9)	1 (0.5)	0 (0.0)	1 (0.9)
Vomiting	3 (1.4)	1 (0.9)	2 (1.7)	1 (0.5)	0 (0.0)	1 (0.9)

AE, adverse experience.

* Excludes AEs after initiating glycaemic rescue therapy (pioglitazone).

† Considered by the investigator as possibly, probably or definitely related to study drug.

‡ One patient receiving triple-combination therapy died from interstitial lung disease during the course of the study.

5. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study[25].

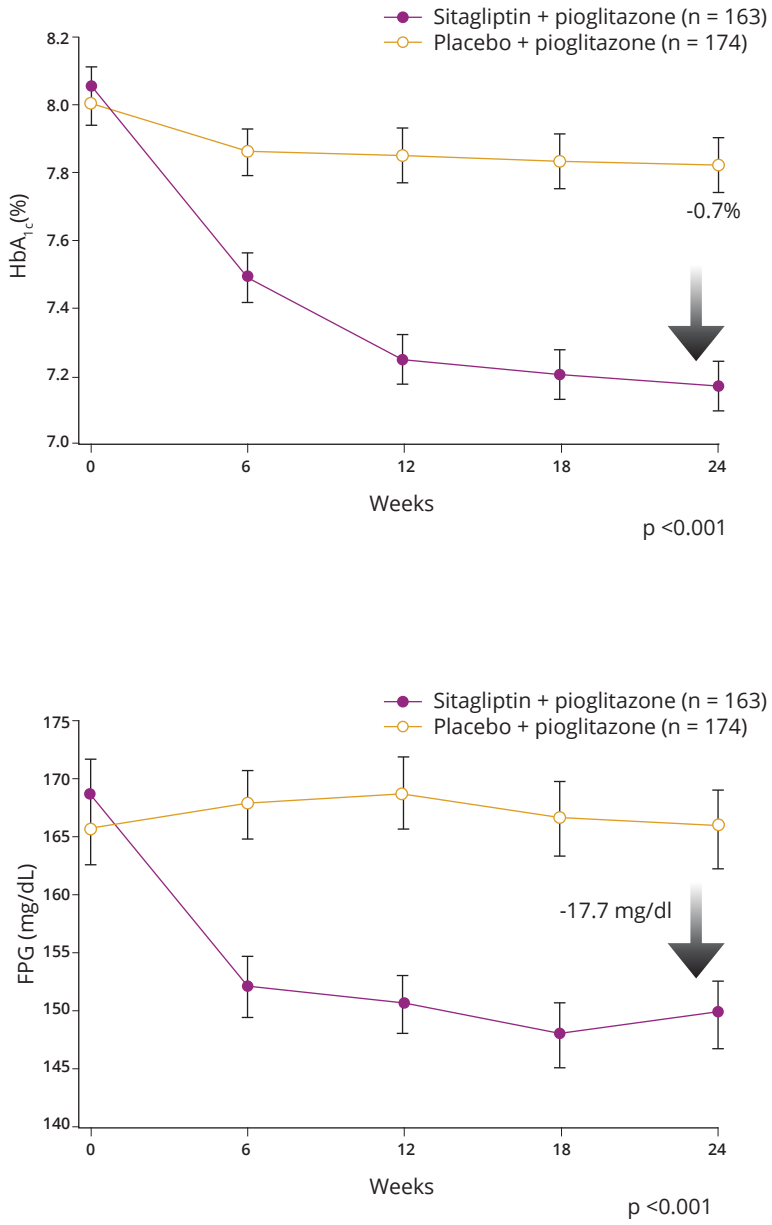
The efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy were assessed in patients with type 2 diabetes and inadequate glycemic control (glycosylated hemoglobin [HbA(1c)] > or = 7% and < or = 10%) while receiving a stable dose of pioglitazone. This was a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel group study in patients aged > or = 18 years. At screening, all patients began a diet/exercise program that continued throughout the study period. Patients taking antihyperglycemic therapy other than pioglitazone underwent a washout of this therapy and entered an 8- to 14-week open-label pioglitazone dose-titration/stabilization period. Patients with an HbA(1c) > or = 7% and < or = 10% at the end of this period entered a 2-week, single-blind, placebo run-in period (total duration of run-in period, up to 21 weeks). Patients who had been receiving pioglitazone monotherapy (30 or 45 mg/d) and had an HbA(1c) > or = 7% and < or = 10% entered the 2-week, single-blind, placebo run-in period directly. Thus, at the time of randomization, all patients were receiving ongoing pioglitazone (30 or 45 mg/d). Patients were randomized in a 1:1 ratio to receive sitagliptin 100 mg once daily or placebo for 24 weeks. The primary efficacy end point was the change from baseline in HbA(1c) at week 24. Secondary efficacy end points included the change from baseline in fasting plasma glucose (FPG), insulin, and proinsulin; the Homeostasis Model Assessment beta-cell function and insulin-resistance indexes; the proinsulin/ insulin ratio; the Quantitative Insulin Sensitivity Check Index; the percent changes from baseline in selected lipid parameters; the proportion of patients meeting the American Diabetes Association HbA(1c), goal of <7.0%; the proportion of patients requiring metformin rescue therapy; and the time to the initiation of rescue therapy.

One hundred seventy-five patients were randomized to receive sitagliptin, and 178 were randomized to receive placebo. The mean (SD) baseline HbA_{1c} value was 8.1% (0.8) in the sitagliptin group and 8.0% (0.8) in the placebo group. After 24 weeks, sitagliptin added to pioglitazone therapy was associated with significant reductions compared with placebo in HbA(1c) (between-treatment difference in least squares [LS] mean change from baseline. -0.70 %; 95 % CI, -0.85 to -0.54; P <0.001) and FPG (-17.7 mg/dL; 95% CI, -24.3 to -11.0; P <0.001). Mean HbA(1c) values at end point were 7.2% (0.9) and 7.8% (1.1) in the respective treatment groups, and the proportions of patients reaching a target HbA(1c) of <7.0% were 45.4% and 23.0% (P <0.001) **(Figure 1)**. Significant reductions in fasting serum proinsulin levels and the proinsulin/insulin ratio were seen with sitagliptin treatment compared with placebo (both, P <0.01). Sitagliptin was generally well tolerated, with no increased risk of hypoglycemia compared with placebo (2 vs 0 patients, respectively).

Key Highlights

- The addition of sitagliptin to pioglitazone gave statistically significant reduction of HbA_{1c} and FPG as compared to placebo- pioglitazone group
- Sitagliptin produced a better protection of β-cell function which was indicated by reduction in proinsulin: insulin levels and increase in HOMA-beta parameters

Figure 1 - Change in A1C and FPG at 24 weeks when sitagliptin was added to pioglitazone.



6. Sitagliptin: A Review of its use as add on in insulin-naive and insulin treated Patients with Type 2 Diabetes Mellitus[26].

In insulin-naive patients, adding sitagliptin to background metformin therapy was not as effective as adding insulin glargine (titrated to target FPG levels) in terms of reductions in HbA_{1c} levels at 24 weeks **(Table 1)**, with an adjusted mean BGD of -0.59% (95% CI -0.77 to -0.42; p <0.0001). Improvements from baseline in other glycaemic parameters at 24 weeks also significantly favoured add-on insulin glargine, including LSM changes in FPG and in self-monitored FPG (p <0.0001) and 7-point plasma glucose profiles (p <0.0012). There was no significant BGD in the proportion of patients achieving a target HbA_{1c} level of 7% **(Table 1)**. In patients receiving stable dosages of insulin (±metformin), add-on sitagliptin was significantly more effective than add-on placebo in terms of improvements in glycaemic control at 24 weeks, as reflected in the significantly higher proportion of patients in the sitagliptin group attaining a target HbA_{1c} level of <7%. In patients who were intensively titrating basal insulin to target FPG levels, add-on sitagliptin significantly reduced the daily insulin dose compared with add-on placebo after 24 weeks treatment. Glycaemic control also improved to a greater extent with add-on sitagliptin than with add-on placebo, with significantly more patients in the sitagliptin group attaining a target HbA_{1c} level of <7% **(Table 1)**.

Key Highlights

- In insulin-naive patients, adding sitagliptin to background metformin therapy was not as effective as adding insulin glargine
- In patients receiving stable dosages of insulin (±metformin), add-on sitagliptin was significantly more effective than add-on placebo in terms of improvements in glycaemic control at 24 weeks

Table 1 - Efficacy of add-on sitagliptin therapy in insulin-naive [16] or insulin-treated [17, 31] adults (aged ≥18 years) with inadequately controlled type 2 diabetes in large (n >450), randomized, double-blind [17, 31] or open-label [16], multicentre, phase 3 trials

Study (primary timepoint; weeks)	Treatment (mg/day) [no. of pts]	LSM change in HbA_{1c} level (%) from BL (mean BL)	Mean change in daily Ins dose (IU) from BL (BL)	Mean change in daily Ins dose (IU) from BL (BL)	% pts at a target HbA_{1c} of < 7%
Aschner et al. [16] (24)	SIT 100 + MET [253] InsG[b] + MET [227]	-1.13[a] (8.5) -1.72**[a] (8.5)		NR (9.5) NR**[c] (9.1)	63 59
Mathieu et al. [17] (24)	SIT 100 + InsG[b] ± MET [329] PL + InsG[b] ± MET [329]	-1.3** (8.7) -0.9 (8.8)	+19.0*[a] (37.3) +23.8[a] (36.6)	-3.1**[d] (9.8) -2.5[d] (9.8)	38**[e] 21
Vilsbøll et al. [31] (24)	SIT 100 + Ins[f] ± MET [312] PL + Ins[f] ± MET [305]	-0.06**[a] (8.7) 0[a] (8.6)		-1.0** (9.8) -0.2 (9.9)	13** 5

Subcutaneous insulin, with other study drugs administered orally

BL baseline, *FPG* fasting plasma glucose, *HbA_{1c}* glycated haemoglobin, *Ins* insulin, *InsG* insulin glargine, *LSM* least-square mean, *MET* metformin, *NR* not reported, *PL* placebo, *pts* patients, *SIT* sitagliptin

* p <0.01, ** p ≤0.001 vs. comparator group

a Primary endpoint

b Titrated to attain an FPG of 4–5.5 [16] or 4–5.6 [17] mmol/L

c Between-group difference of -2.3 mmol/L in favour of InsG + MET

d Mean value

e Post-hoc analysis of pts with an HbA_{1c} of <7% at week 24 or the last visit prior to discontinuation

f Stable dosages (≥15 IU/day); long- or intermediate-acting or premixed insulin

Comparative Studies

1. Comparative effectiveness of Dipeptidylpeptidase-4 Inhibitors in Type 2 Diabetes: A systematic review and mixed treatment comparison[27].

To compare the safety and efficacy of the dipeptidylpeptidase-4 (DPP-4) inhibitors in patients with type 2 diabetes and inadequate glycemic control. Systematic review of randomized controlled trials (RCTs), health economic evaluation studies, systematic reviews, and meta-analyses, followed by primary Bayesian mixed treatment comparison meta-analyses (MTCs), and secondary frequentist direct comparison meta-analyses using a random effects model. Outcomes were reported as weighted mean change from baseline, or odds ratio (OR) with 95% credible interval. Patients with type 2 diabetes and inadequate glycemic control receiving any pharmacological anti-diabetic treatment were eligible. Five DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin) were compared via meta-analysis (where data were available) as monotherapy, dual therapy (plus metformin, sulfonylurea, pioglitazone, or insulin), and triple therapy (plus metformin/sulfonylurea).

The review identified 6,601 articles; 163 met inclusion criteria and 85 publications from 83 RCTs contained sufficient or appropriate data for analysis. MTCs demonstrated no differences between DPP-4 inhibitors in mean change from baseline in glycosylated hemoglobin (HbA_{1c}) or body weight, or the proportions of patients achieving HbA_{1c}<7% or experiencing a hypoglycemic event, apart from in patients on alogliptin plus metformin, who achieved HbA_{1c} <7% more frequently than those treated with saxagliptin plus metformin [OR 6.41 (95% CI 3.15–11.98) versus 2.17 (95% CI 1.56–2.95)] **(Table 1)**.

Key Highlights

- This systematic review and MTC showed similar efficacy and safety for DPP-4 inhibitors as treatment for type 2 diabetes, either as monotherapy or combination therapy
- This systematic review and MTC of DPP-4 inhibitors confirmed no difference between alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin, either as monotherapy, or as dual therapy (plus metformin or SU); alogliptin, linagliptin, sitagliptin, and vildagliptin as dual therapy (plus pioglitazone); sitagliptin and vildagliptin as dual therapy (plus insulin), or linagliptin, sitagliptin, and vildagliptin as triple therapy (plus metformin and SU)
- The study showed that the DPP-4 inhibitors have similar efficacy in terms of mean reduction (i.e., improvement) in HbA_{1c} from baseline, increased proportion of patients achieving HbA_{1c} <7%, mean change in body weight from baseline, and number of patients experiencing a hypoglycemic event

Table 1: Absolute treatment effect mixed treatment comparisons

	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin
Monotherapy					
Weighted absolute HbA_{1c} change from baseline (95% CrI)	-0.58 (-0.83 to -0.33)	-0.58 (-0.81 to -0.35)	-0.45 (-0.75 to -0.15)	-0.59 (-0.75 to -0.43)	-0.52 (-0.71 to -0.31)
Absolute probability of achieving HbA_{1c} <7% (95% CrI)	0.40 (0.34 to 0.59)	0.34 (0.19 to 0.53)	0.25 (0.11 to 0.44)	0.37 (0.24 to 0.51)	0.39 (0.24 to 0.55)
Absolute mean weight change from baseline, kg (95% CrI)	-0.17 (-0.60 to 0.23)	-0.12 (-0.62 to 0.38)	–	0.20 (-0.18 to 0.60)	0.33 (-0.12 to 0.80)
Absolute probability of having a hypoglycemic event (95% CrI)	0.0013 (0.000032 to 0.0071)	0.008 (0.000028 to 0.0042)	0.0088 (0.00062 to 0.038)	0.0029 (0.00046 to 0.0097)	0.0037 (0.00043 to 0.014)
DPP-4 inhibitor + metformin					
Weighted absolute HbA_{1c} change from baseline (95% CrI)	-1.10 (-1.38 to -0.82)	-0.99 (-1.17 to -0.82)	-1.03 (-1.21 to -0.85)	-1.06 (-1.22 to -0.91)	-1.02 (-1.18 to -0.86)
Absolute probability of achieving HbA_{1c} <7% (95% CrI)	0.56 (0.32 to 0.78)	0.41 (0.22 to 0.63)	0.31 (0.17 to 0.50)	0.38 (0.22 to 0.57)	0.35 (0.18 to 0.54)
Absolute mean weight change from baseline, kg (95% CrI)	-0.45 (-2.22 to 1.31)	-0.54 (-6.31 to 5.09)	–	-0.99 (-2.38 to 0.35)	0.15 (-0.99 to 1.28)
Absolute probability of having a hypoglycemic event (95% CrI)	0.0039 (0.00028 to 0.017)	0.012 (0.0036 to 0.028)	0.013 (0.0045 to 0.030)	0.021 (0.0074 to 0.047)	0.012 (0.0037 to 0.031)
DPP-4 inhibitor + sulfonylurea					
Weighted absolute HbA_{1c} change from baseline (95% CrI)	-0.40 (-0.81 to -0.01)	-0.40 (-0.84 to 0.04)	-0.60 (-1.11 to -0.08)	-0.61 (-0.94 to -0.29)	-0.75 (-1.02 to -0.44)
Absolute probability of achieving HbA_{1c} <7% (95% CrI)	0.21 (0.04 to 0.53)	0.34 (0.05 to 0.77)	0.26 (0.06 to 0.60)	0.15 (0.022 to 0.48)	0.36 (0.12 to 0.66)
Absolute mean weight change from baseline, kg (95% CrI)	0.87 (-0.58 to 2.30)	0.47 (-1.22 to 2.18)	–	0.72 (-0.39 to 1.96)	–
Absolute probability of having a hypoglycemic event (95% CrI)	0.043 (0.0035 to 0.18)	0.05 (0.0026 to 0.23)	0.05 (0.0045 to 0.20)	0.11 (0.0096 to 0.44)	0.093 (0.0068 to 0.38)
DPP-4 inhibitor + metformin + sulfonylurea					
Weighted absolute HbA_{1c} change from baseline (95% CrI)	–	-0.65 (-6.87 to 5.60)	–	-0.94 (-7.34 to 5.40)	-0.80 (-7.00 to 5.43)
Absolute probability of achieving HbA_{1c} <7% (95% CrI)	–	–	–	–	–
Absolute mean weight change from baseline, kg (95% CrI)	–	0.14 (-6.11 to 6.39)	–	1.60 (-4.73 to 7.89)	–
Absolute probability of having a hypoglycemic event (95% CrI)	–	0.13 (0.00057 to 0.76)	–	0.21 (0.0011 to 0.89)	0.17 (0.00071 to 0.84)
DPP-4 inhibitor + pioglitazone					
Weighted absolute HbA_{1c} change from baseline (95% CrI)	-1.29 (-1.52 to -1.05)	-1.16 (-1.56 to -0.76)	–	-1.53 (-1.95 to -1.11)	-1.17 (-1.43 to -0.91)
Absolute probability of achieving HbA_{1c} <7% (95% CrI)	0.54 (0.34 to 0.73)	0.40 (0.18 to 0.65)	–	0.59 (0.34 to 0.80)	0.47 (0.27 to 0.67)
Absolute mean weight change from baseline, kg (95% CrI)	1.59 (0.84 to 2.37)	2.24 (1.10 to 3.38)	–	2.14 (0.63 to 3.65)	1.28 (0.11 to 2.44)
Absolute probability of having a hypoglycemic event (95% CrI)	0.059 (0.00021 to 0.47)	0.036 (0.00055 to 0.33)	–	0.014 (0.000031 to 0.11)	0.0030 (0.0000084 to 0.021)
DPP-4 inhibitor + insulin					
Weighted absolute HbA_{1c} change from baseline (95% CrI)	–	–	–	-0.56 (-5.22 to 4.09)	-0.70 (-4.03 to 2.56)
Absolute probability of achieving HbA_{1c} <7% (95% CrI)	–	–	–	–	–
Absolute mean weight change from baseline, kg (95% CrI)	–	–	–	-1.03 (-7.31 to 5.32)	1.48 (-4.86 to 7.82)
Absolute probability of having a hypoglycemic event (95% CrI)	–	–	–	0.22 (0.0086 to 0.7903)	0.30 (0.007 to 0.891)

CrI credible interval, DPP-4 dipeptidylpeptidase-4, HbA_{1c} glycosylated hemoglobin, SU sulfonylurea

* Statistically significant versus comparator: monotherapy versus placebo, DPP-4 + metformin versus metformin, DPP-4 + SU versus SU, DPP-4 + metformin + SU versus metformin + SU, DPP-4 + pioglitazone versus pioglitazone, DPP-4 + insulin versus insulin

Statistically significant difference between alogliptin + metformin and saxagliptin + metformin

Studies in Special Population

1. Elderly population

Two-year assessment of the efficacy and safety of sitagliptin in elderly patients with type 2 diabetes: Post hoc analysis of the ASSET-K study[28].

There have only been a few reports about use of dipeptidyl peptidase 4 (DPP-4) inhibitors in elderly patients with type 2 diabetes mellitus (T2DM), suggesting that the safety of these agents has not been sufficiently demonstrated. Hence a comparative review of the efficacy and safety of sitagliptin for Japanese patients with T2DM managed in the real-world clinical setting was conducted. An age-stratified analysis was performed of 831 patients who were treated with sitagliptin for 2 years. Parameters assessed included the haemoglobin A1C (HbA_{1c}), body weight, serum creatinine, and adverse events. HbA_{1c} and the incidence of hypoglycaemia were also evaluated in patients treated with sitagliptin and a sulfonylurea (SU), who were divided into three age groups (<65 years, 65–74 years, and ≥75 years).

In patients aged <65 years, HbA_{1c} showed a significant decrease ($p< 0.05$) from 8.1 ± 1.2 % at the start of add-on treatment with sitagliptin to 7.4 ± 1.0 % at 12 months and 7.3 ± 0.9 % at 24 months. There was also a significant decrease ($p < 0.05$) in HbA_{1c} in patients aged 65–74 years (7.6 ± 0.9 %, 7.0 ± 0.7 %, and 7.0 ± 0.7 %, respectively). Furthermore, HbA_{1c} decreased significantly ($p <0.05$) in patients aged ≥75 years (7.7 ± 0.9 %, 7.1 ± 0.7 %, and 7.1 ± 1.1 %, respectively) **(Fig.1)**. There was no significant change in body weight in any of the age groups **(Fig. 2)**. Fasting and casual postprandial glucose levels showed a significant decrease at 12 and 24 months compared with the start of add-on sitagliptin therapy in all age groups ($p <0.05$) **(Figs. 3 and 4)**. Assessment of renal function showed that serum creatinine was significantly increased at 24 months in all age groups **(Fig. 5)**. Hypoglycaemia only occurred in patients who received combined treatment with an SU and sitagliptin, and there was no age-related difference in its incidence **(Fig 6)**.

Key Highlights

- Comparison of glycaemic control parameters, laboratory values, and adverse events revealed significant improvement of HbA_{1c}, casual postprandial plasma glucose, and fasting plasma glucose in each age group with no change in body weight
- HbA_{1c} was improved by 2 years of sitagliptin therapy in all three age groups, and age did not seem to influence the incidence of hypoglycaemic events.
- These results confirm the efficacy and safety of sitagliptin in patient's ≥75 years old, suggesting that it is also useful for treating elderly patients with T2DM

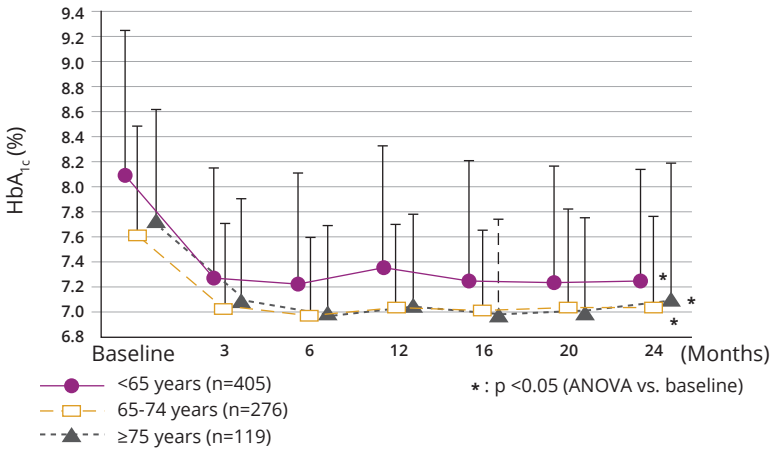


Figure 1 - Changes in HbA_{1c} over the 2-year observation period. ANOVA, analysis of variance; HbA_{1c}, hemoglobin A_{1c}.

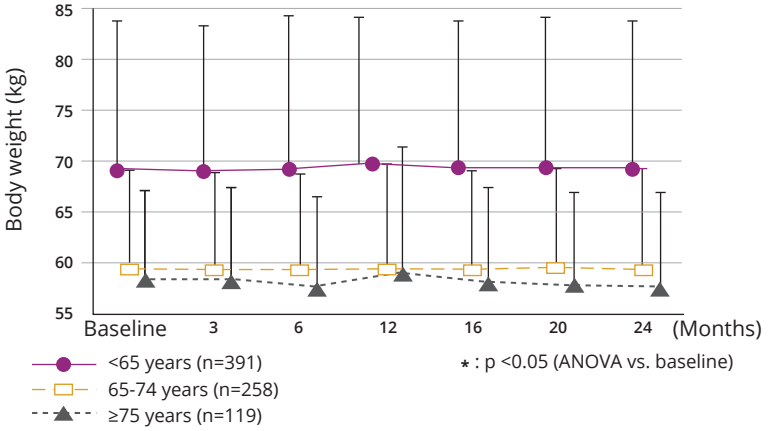


Figure 2 - Changes in body weight over the 2-year observation period. ANOVA, analysis of variance.

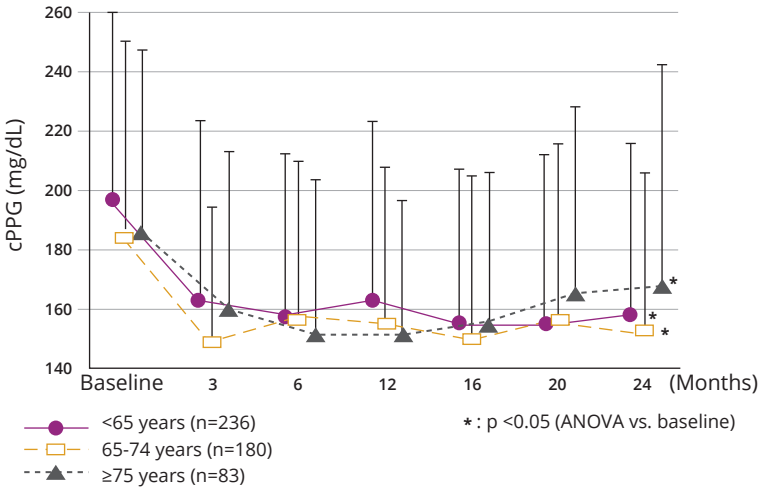


Figure 3 - Changes in casual postprandial plasma glucose over the 2-year observation period. ANOVA, analysis of variance; cPPG, casual postprandial plasma glucose.

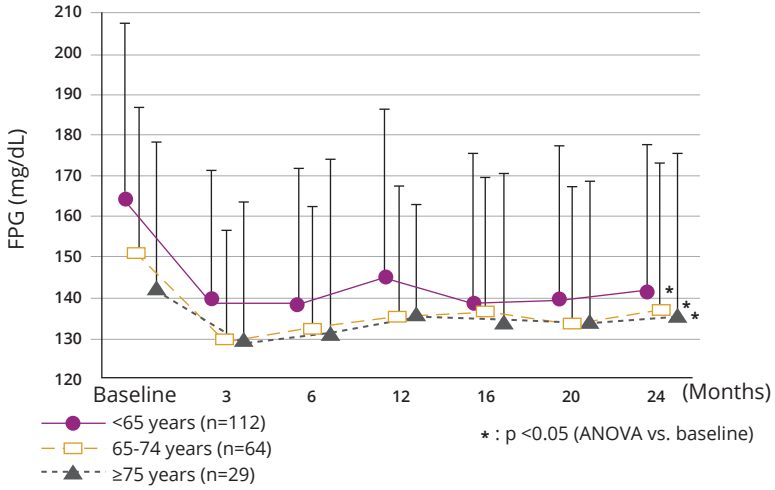


Figure 4 - Changes in fasting plasma glucose over the 2-year observation period. ANOVA, analysis of variance; FPG, fasting plasma glucose.

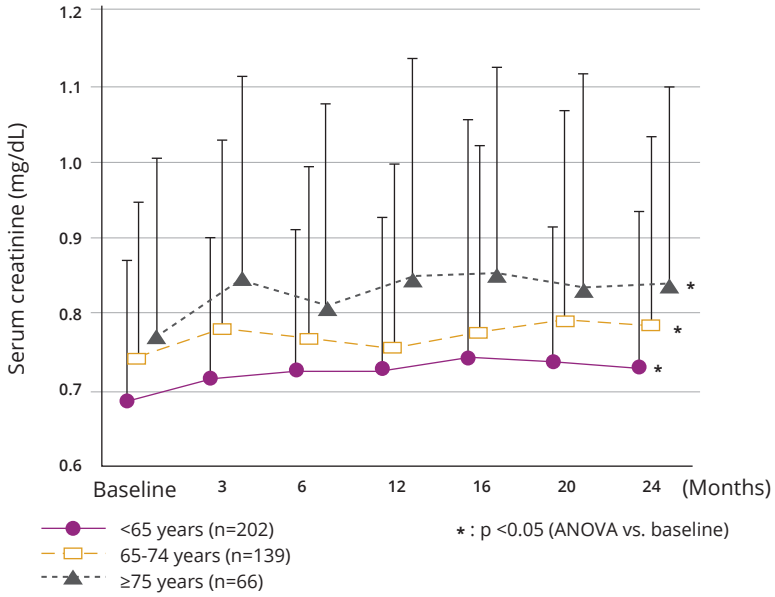


Figure 5 - Changes in serum creatinine over the 2-year observation period. ANOVA, analysis of variance.

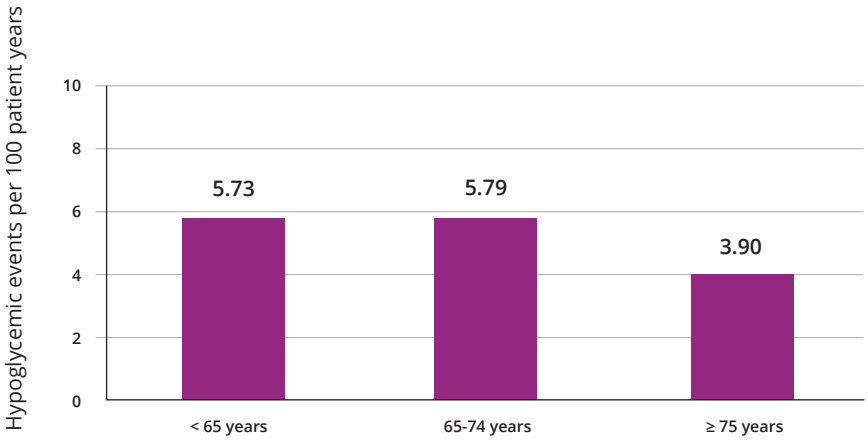


Figure 6 - Hypoglycemia in patients receiving sitagliptin plus SU therapy during the 2-year observation period.

Anti-atherosclerotic effects of sitagliptin

Anti-atherosclerotic effects of sitagliptin in patients with type 2 diabetes mellitus[29].

Advanced glycation end products, selectins, and adiponectin play important roles in the development of atherosclerosis in individuals with diabetes. Sitagliptin has been shown to reduce the concentration of glycated haemoglobin in diabetic patients. However, its effects on soluble receptor for advanced glycation end products (sRAGEs), selectins, and adiponectin in these patients are poorly understood. This study was conducted to assess the effects of sitagliptin on the circulating levels of sRAGEs, monocyte chemoattractant protein-1 (MCP-1), selectins, and adiponectin in patients with type 2 diabetes. The study cohort included 72 nondiabetic and 113 diabetic patients, selected from among those admitted for the treatment of hypertension, hyperlipidemia, and diabetes. Diabetic patients eligible for sitagliptin monotherapy or combination therapy (eg, sitagliptin plus a sulfonylurea) were administered sitagliptin (50 mg/day) for 6 months. Levels of soluble P-selectin (sP-selectin), soluble E-selectin (sE-selectin), soluble vascular cell adhesion molecule-1 (sVCAM-1), MCP-1, sRAGEs, and adiponectin were measured by ELISA at baseline and after 3 and 6 months of treatment. At baseline, the levels of MCP-1, sP-selectin, sE-selectin, and sVCAM-1 were higher and the level of adiponectin was lower in diabetic patients than in nondiabetic patients. Renal function was almost normal (S-CRTN -2.0 mg/dL) in 65 of the 113 diabetic patients. Administration of sitagliptin to these 65 patients for 3 months significantly reduced fasting blood glucose and HbA_{1c} (data not shown), and administration for 6 months significantly reduced plasma concentrations of sP-selectin, sE-selectin, sVCAM-1, and MCP-1 relative to baseline (P,0.05 each; **Figure 1A–D)**. Sitagliptin treatment significantly increased adiponectin concentrations after 3 ($P < 0.05$) and 6 ($P < 0.01$) months relative to baseline **(Figure 1F)**. Sitagliptin also increased sRAGE concentration relative to baseline, although the differences were not statistically significant **(Figure 1E)**. Diabetic patients were divided into two subgroups according to their adiponectin response to sitagliptin treatment. Responders showed significant reductions in plasma concentrations of sP-selectin, sE-selectin, sVCAM-1, and MCP-1 relative to baseline ($P < 0.01$ for each; **Figure 2A–D**), and all the four concentrations were significantly lower in responders than in nonresponders after 6 months of sitagliptin treatment (two-factor ANOVA; $P < 0.05$ each). However, responders showed a significant increase in plasma concentration of sRAGE and adiponectin **(Figure 2E and F)**.

Key Highlights

- Sitagliptin therapy for 3 and 6 months significantly reduced plasma levels of sP-selectin, sE-selectin, sVCAM-1, and MCP-1 relative to baseline, while significantly increasing adiponectin levels
- sRAGEs did not exhibit a statistical significance, although there was an increasing tendency
- Sitagliptin shows an adiponectin-dependent anti-atherothrombotic effect, which may be beneficial for primary prevention of atherothrombosis, in patients with type 2 diabetes

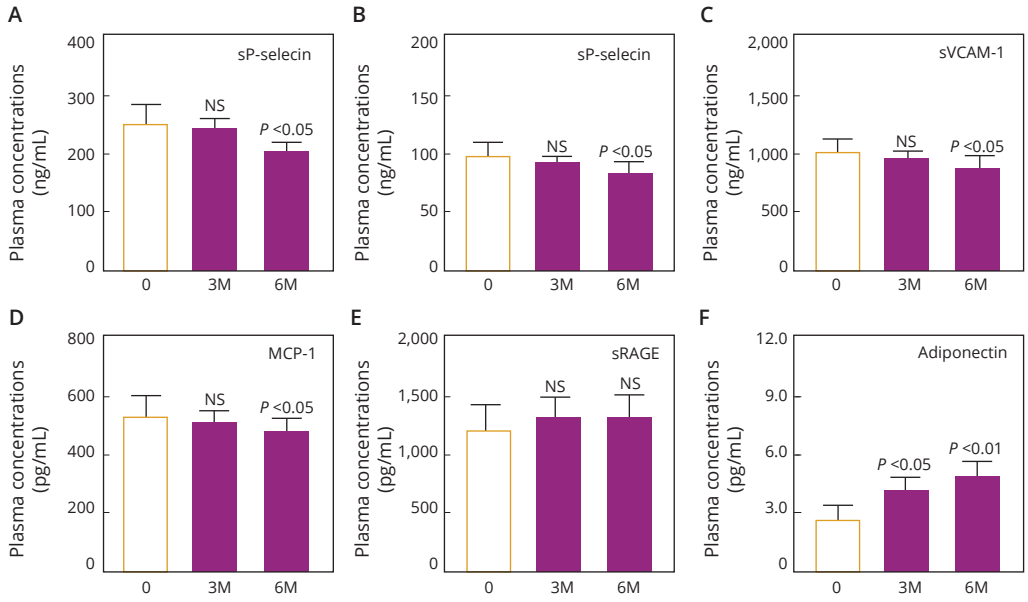


Figure 1 - Plasma concentrations of sP-selectin (**A**), sE-selectin (**B**), sVCAM-1 (**C**), MCP-I (**D**), sRAGE (**E**), and adiponectin (**F**) before and after sitagliptin treatment in diabetic patients.

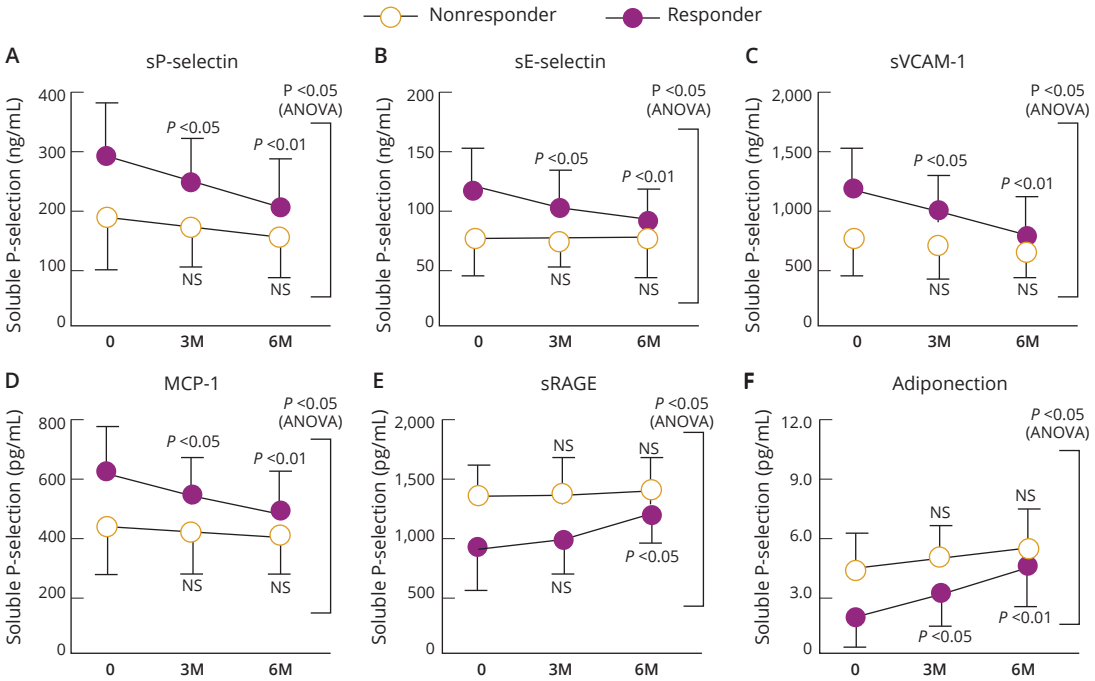


Figure 2 - Changes in sP-selectin **(A)**, sE-selectin **(B)**, sVCAM-1 **(C)**, MCP-I **(D)**, sRAGE **(E)**, and adiponectin **(F)** in response to treatment with sitagliptin of patients with type 2 diabetes with and without significant improvements in adiponectin.

Safety and efficacy of Sitagliptin in patients with hepatic impairment

➤ Efficacy and safety of sitagliptin for the treatment of diabetes mellitus complicated by chronic liver injury[30].

Patients with type 2 diabetes mellitus (T2DM) patients often also present with chronic liver injury, and a previous study showed that approximately 80% of T2DM patients have a fatty liver (Browning et al. 2004). In particular, non-alcoholic fatty liver disease (NAFLD) is a frequent complication of T2DM (Arase et al. 2009), and is the most common form of chronic liver injury in many countries around the world (Angulo 2002). On the other hand, since most oral hypoglycemic agents are metabolized in the liver and may induce liver damage, the treatment of T2DM patients with chronic liver injury is often difficult (Nauck et al. 2007). Since the DPP-4 inhibitor sitagliptin is minimally metabolized in the liver and over 80% is excreted in an unaltered state in the urine (Drucker and Nauck 2006), it is expected that the pharmacokinetic of sitagliptin will have few negative effects even in patients with chronic liver injury. Hence this study was conducted to investigate the efficacy and safety of a dipeptidyl peptidase-4 inhibitor, sitagliptin, for treating diabetes mellitus complicated by chronic liver injury. Sitagliptin was administered for 13.7 ± 10.1 months to 122 patients with DM complicated by chronic liver injury (including 19 patients with liver cirrhosis), and changes in hemoglobin A1C (HbA_{1c}) and liver enzymes (transaminases, etc.) were evaluated.

HbA_{1c} was reduced from 8.48 ± 1.43% to 7.87 ± 1.35% (P <0.001). Among liver enzymes, alanine aminotransferase (ALT) levels improved from 75.1 ± 45.2 to 65.8 ± 35.8 IU/L (P = 0.012) and gamma-glut amyl-trans peptidase from 155.2 ± 161.1 to 133.2 ± 127.4 IU/L (P = 0.044) **(Table 2)**. An analysis of 19 patients with liver cirrhosis also showed reductions in HbA_{1c} with no deterioration of liver enzymes **(Table 1)**.

Key Highlights

- Among the causes of liver injury, non-alcoholic fatty liver disease and alcoholic liver disease both showed the reductions in HbA_{1c} with no deterioration of liver enzymes
- Sitagliptin can be administered effectively and safely to patients with diabetes mellitus complicated by chronic liver injury, including liver cirrhosis

Table 1: Changes in clinical data of diabetes mellitus complicated by liver cirrhosis

	LC group (n = 19)		
	Pre-treatment	Post-treatment	P value
HbA_{1c} (%)	8.12 ± 1.29	7.38 ± 1.24	0.006
AST (IU/L)	60.4 ± 30.9	64.5 ± 33.3	0.628
ALT (IU/L)	49.5 ± 28.4	44.5 ± 24.3	0.483
YGT (IU/L)	277.6 ± 310.4	212.7 ± 277.5	0.237

Table 2: Changes in clinical data of diabetes mellitus complicated by chronic liver injury (NAFLD and ALD)

	NAFLD group (n=62)				ALD group (n=17)		
	Pre-treatment	Post-treatment	P value		Pre-treatment	Post-treatment	P value
HbA_{1c} (%)	8.57 ± 1.23	7.99 ± 1.22	<0.001	HbA_{1c} (%)	8.29 ± 1.77	7.79 ± 1.42	0.099
AST (IU/L)	52.7 ± 25.3	55.5 ± 29.4	0.491	AST (IU/L)	66.5 ± 28.3	63.1 ± 22.0	0.563
ALT (IU/L)	79.2 ± 45.4	74.7 ± 41.5	0.398	ALT (IU/L)	88.0 ± 67.4	63.0 ± 26.1	0.083
YGT (IU/L)	112.0 ± 80.4	115.4 ± 95.7	0.713	YGT (IU/L)	232.8 ± 144.7	163.8 ± 102.3	0.023

➤ Efficacy and safety in sitagliptin therapy for diabetes complicated by chronic liver disease caused by hepatitis C virus[31].

Diabetes is present in patients with chronic liver disease caused by hepatitis C virus (HCV). In addition, Diabetes mellitus has been suggested to enhance the development of hepatocellular carcinoma in patients with chronic hepatitis C (Kawamura et al. 2008; Veldt et al. 2008). The aim of this case–control study is to assess the efficacy and safety of dipeptidyl peptidase-4 inhibitor (sitagliptin) for type 2 diabetes mellitus (T2DM) with chronic liver disease caused by HCV. Sixteen HCV positive patients with T2DM treated by sitagliptin were retrospectively enrolled. These patients were given sitagliptin between December 2009 and January 2010. Another 16 HCV patients with T2DM treated only with diet and excise for 48 weeks were selected as the control group. Serum levels of fasting plasma glucose (FPG), haemoglobin A1C (HbA_{1C}), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured before and 12, 24, 36 and 48 weeks after the initiation of treatment.

In the sitagliptin group, the average HbA_{1c} level decreased approximately 0.8% at 48 weeks after the initiation of sitagliptin **(Figure 1)**. Next, the average FPG level decreased approximately 20 mg/dL during follow up after the initiation of sitagliptin **(Figure 2)**. All the patients were able to take sitagliptin of 50 mg/day without reduction because of sitagliptin-related side-effects. On the other hand, in the control group, the average HbA_{1c} and FPG level did not change with statistical significance during follow up of 48 weeks. Regarding aminotransferase, there were no significant changes of average AST and ALT level during follow up of 48 weeks in both the sitagliptin group and control group **(Figure 3)**.

Key Highlights

- Sitagliptin is effective and safe for the treatment of T2DM complicated with HCV positive chronic liver disease
- In the present study, none of the patients treated with DDP-4 inhibitor had sitagliptin-related episodes severe enough to stop the sitagliptin therapy. Thus, all the patients could take sitagliptin of 50 mg/day over 48 weeks without reduction or stopping

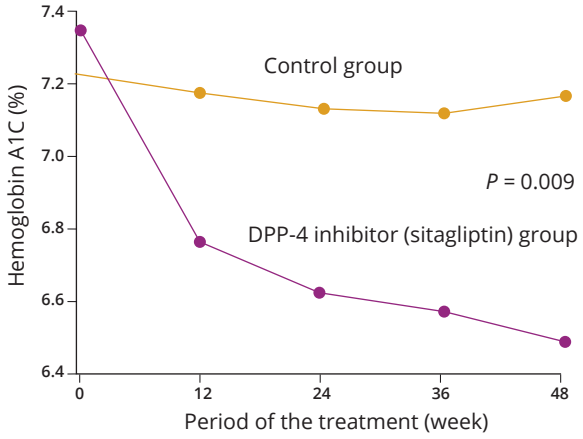


Figure 1 - Change of average hemoglobin A1C (HbA_{1c}) level during follow up was plotted in both the dipeptidyl peptidase-4 (DPP-4) inhibitor group and control group.

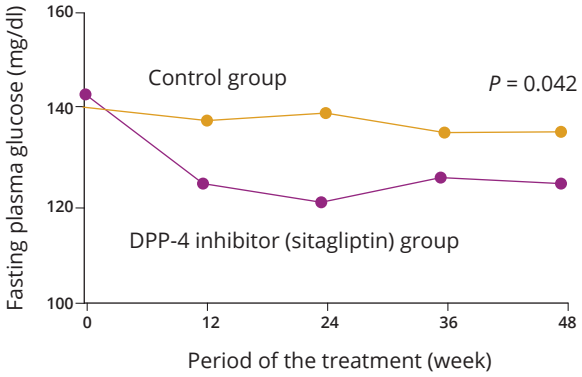


Figure 2 - Change of average fasting plasma glucose during follow up was plotted in both thedipeptidyl peptidase-4 (DPP-4) inhibitor group and control group.

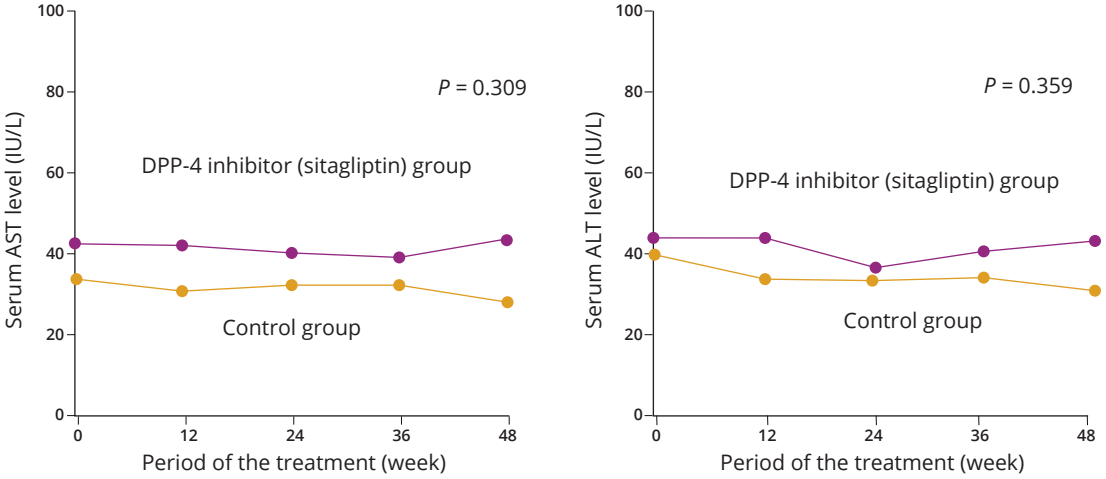


Figure 3 - Change of average aminotransferase level during follow up was plotted in both the dipeptidyl peptidase-4 (DPP-4) inhibitor group and control group. (a) Change of average aspartate aminotransferase (AST) level during follow up was plotted in both the DPP-4 inhibitor group and control group. (b) Change of average alanine aminotransferase (ALT) level during follow up was plotted in both the DPP-4 inhibitor group and control group.

Safety and efficacy of Sitagliptin in patients with renal impairment

OADs in CKD#

	Metformin	SUs	Pioglitazone	Gliptins	SGLT2is
Efficacy Considerations	Efficacy not majorly dependent on renal function	Hypoglycemia properly of SUs increases with reducing renal function	Efficacy not majorly dependent on renal function	Effective across the spectrum of CKD	Efficacy reduced with increasing renal insufficiency
Safety Considerations	Increased risk of lactic acidosis in CKD	Increased risk of hypoglycemia in CKD	increased risk of fluid retention/ edema and CHF in CKD	None*	Increased AEs related to reduced intravascular volume and renal function
Usage restriction	**eGFR <60:** Can be used **eGFR 30-45:** Don't initiate **eGFR <30:** contraindicated	Start with lower dose and titrate slowly in CKD	No dose adjustment required based on renal function alone	Can be used in all stages of CKD**	Initiation/Use not recommended in eGFR <45

*A reduced dose is recommended for giliptins which are excreted renally (to maintain same drug concentration)
** except Teneligliptin

 # Prescribing information of the mentioned OADs

➤ **Safety of sitagliptin in patients with type 2 diabetes and chronic kidney disease: outcomes from TECOS[32].**

Key highlights

- CKD was present in 3324 (23%) participants at entry into TECOS
- The mean (SD) age for this CKD cohort was 68.8 (7.9) years, mean diabetes duration was 13.7 (9.0) years
- Treatment with sitagliptin was generally well tolerated, with no meaningful differences in safety outcomes observed between those with CKD assigned to sitagliptin or placebo
- Sitagliptin has no clinically significant impact on cardiovascular or CKD outcomes, irrespective of baseline eGFR
- With appropriate reduction of dose [Sitagliptin (25–50 mg/day)], it has been shown to be safe and effective in achieving reduction in HbA_{1c} when compared with other DPP4 inhibitors in renal disease in type 2 diabetes across major CVOTs **(Table 1)**

Table 1: Dose adjustments according to eGFR in the major clinical trials[33]

Trial	Compound evaluated	Renal exclusion criteria	Dose adjustments
EXAMINE	Alogliptin	Requiring dialysis 14 days prior to screening	60 mL/min per 1.73 m^2: 25 mg 30–60 mL/min per 1.73 m^2: 12.5 mg <30 mL/min per 1.73 m^2: 6.25 mg
SAVOR-TIMI 53	Saxagliptin	ESRF requiring dialysis, transplantation or serum creatinine >6.0 mg per decilitre (530 µmol per litre)	>50 mL/min per 1.73 m^2: 5 mg <50 mL/min per 1.73 m^2: 2.5 mg
TECOS	Sitagliptin	eGFR <30 mL/min per 1.73 m^2 or requiring dialysis	>50 mL/min per 1.73 m^2: 100 mg <50 mL/min per 1.73 m^2: 50 mg
CARMELINA	Linagliptin	eGFR <15 mL/min per 1.73 m^2 or requiring dialysis	None

➤ **The renoprotective effect and safety of a DPP-4 inhibitor, sitagliptin, at a small dose in type 2 diabetic patients with a renal dysfunction when changed from other DPP-4 inhibitors: REAL trial[34].**

The multicenter, prospective, open-label study was conducted in type 2 diabetic (T2DM) patients with renal dysfunction, to clarify the efficacy and the safety in relation to renal function and glycemic control, and the economic effect when other dipeptidyl peptidase-4 (DPP-4) inhibitors were switched to a small dose of sitagliptin depending on their renal function. Vildagliptin, alogliptin, or linagliptin received for more than 2 months were changed to sitagliptin at 25 or 12.5 mg/ day depending on their renal function in 49 T2DMs. Renal function and glycemic control, and the drug cost were assessed during 6 months.

Estimated glomerular filtration rate was not changed in patients not on hemodialysis (n = 29) **(Table 2)**. The HbA_{1c} levels were not altered in all of the patients including those on hemodialysis (n = 20) **(Table 1)**. The active glucagon-like peptide-1 levels or other renal parameters were not altered significantly. There were no adverse events to be related to the drugs. The daily drug expense was reduced by 88.1 yen per patient **(Figure 1)**.

Key Highlights

- Switching to a small dose of sitagliptin according to the renal function in T2DM patients with renal dysfunction demonstrated the same efficacy and safety as those with other full-dose DPP-4 inhibitors, indicating a therapeutic option with a high cost performance

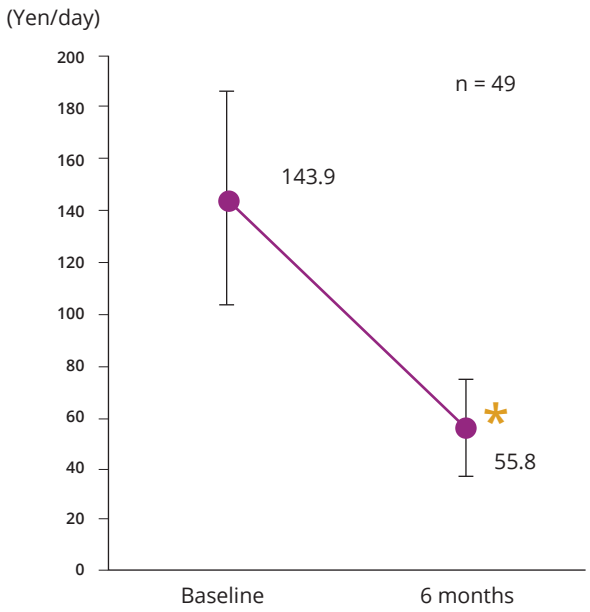
Table 1: Vital and serum parameters determined before and during the study

Parameters	All patients (n = 49)		
	0M	3M	6M
SBP(mmHg)	138.9 ± 20.2	143.4 ± 21.1	138.4 ± 21.5
DBP (mmHg)	75.9 ± 12.8	77.6 ± 15.0	76.1 ± 13.6
Pulse rate (betas/min)	73.1 ± 10.6	74.9 ± 10.9	74.7 ± 11.6
Body weight (kg)	61.5 ± 10.6	61.6 ± 10.6	61.8 ± 10.6
BMI (kg/m^2)	23.9 ± 3.2	23.9 ± 3.2	24.0 ± 3.3
HbA_{1c} (%)	6.30 ± 0.75	6.44 ± 0.90	6.40 ± 0.81
Plasma glucose (mg/dL)	152.6 ± 46.9	150.3 ± 47.0	153.4 ± 49.8
C -peptide (ng/mL)	5.89 (4,7.82)	6.42 (4.01,8.72)	6.17 (4.28, 8.45)
aGLP-1 (pmol/L)	7.3 (4.88, 10.15)	5.7 (3.5, 11.65)	6.75 (3.73, 10)

Table 2: Renal parameters in patients not on haemodialysis (n = 29)

Parameters	0M	3M	6M
eGFR (mL/min/1.73 m²)	43.5 ± 14.9	43.8 ± 16.6	42.6 ± 14.4
eGFRcys (mL/min/1.73 m²)	60.5 ± 24.6	60.6 ± 24.2	61.3 ± 25.5
UACR (mg/gCr)	17.4 (4.8, 62.4)	22.9 (8.8, 51.7)	21.2 (9.2, 118.5)
Urinary β²-microglobulin (μg/gCr)	166 (58.8, 580.5)	228.5 (84, 1217.3)	505 (71, 1550)
Urinary collagen IV (μg/gCr)	4.5 (3.03, 9.85)	5.55 (3.23, 11.25)	6.5 (2.68, 9.85)
L-FABP (μg/gCr)	5.2 (3.4, 24.3)	5.5 (2.7, 14.7)	5.1 (2.8, 16.8)
U-8 isoprotane (pg/mgCr)	208 (125, 279.8)	160.5 (126.5, 214)	193.5 (114.5, 268.5)

Figure 1 - Daily drug cost. * *p* <0.05 vs 0M.



➤ **Efficacy and Safety of Sitagliptin in Patients with Type 2 Diabetes and ESRD Receiving Dialysis: A 54-Week Randomized Trial[35].**

Treatment with oral antihyperglycemic agents has not been well characterized in patients with type 2 diabetes and end-stage renal disease (ESRD). The efficacy and safety of sitagliptin and glipizide monotherapy in patients with type 2 diabetes and ESRD on dialysis therapy were assessed in this study. It is a 54-week, randomized, double-blind, parallel-arm study. From 31 clinical sites in 12 countries, 129 patients 30 years or older with type 2 diabetes and ESRD who were on dialysis therapy and had a hemoglobin A1C (HbA_{1c}) level of 7%-9% were randomly assigned 1:1 to treatment. Monotherapy with sitagliptin, 25 mg daily or glipizide (initiated with 2.5 mg daily and titrated up to a potential maximum dose of 10 mg twice daily or down to avoid hypoglycemia). Primary end points were 54-week change in HbA_{1c} level from baseline and tolerability with sitagliptin. A secondary end point was the comparison of sitagliptin versus glipizide on the incidence of symptomatic hypoglycemia.

Of 129 patients randomly assigned, 64 were in the sitagliptin group (mean baseline age, 61 years; HbA_{1c}, 7.9%) and 65 were in the glipizide group (mean baseline age, 59 years; HbA_{1c}, 7.8%). After 54 weeks, the least squares mean change from baseline in HbA_{1c} level was -0.72% (95% CI, -0.95% to -0.48%) with sitagliptin and -0.87% (95% CI, -1.11% to -0.63%) with glipizide, for a difference of 0.15% (95% CI, -0.18% to -0.49%) **(Table 2)**. The incidences of symptomatic hypoglycemia and severe hypoglycemia were 6.3% versus 10.8% (between-group difference, -4.8% [95% CI, -15.7% to -5.6%]) and 0% versus 7.7% (between-group difference, -7.8% [95% CI, -17.1% to -1.9%]) in the sitagliptin and glipizide groups, respectively **(Table 1)**. Higher incidences (i.e, 95% CI around between-treatment difference excluded 0) of cellulitis and headache were found with sitagliptin compared to glipizide (6.3% vs 0%, respectively, for both).

Key Highlights

- Treatment with sitagliptin or glipizide monotherapy was effective and well tolerated over 54 weeks in patients with type 2 diabetes and ESRD who were receiving dialysis
- Treatment with dose-adjusted sitagliptin provided clinically meaningful reductions from baseline in HbA_{1c} and FPG levels similar to those observed with glipizide over 54 weeks in patients with type 2 diabetes mellitus and ESRD on dialysis therapy
- Sitagliptin generally was well tolerated, with weight neutrality, a numerically lower incidence of symptomatic hypoglycaemia, and of severe hypoglycaemia compared to glipizide

Table 1: Adverse Events of Symptomatic and Severe Hypoglycaemia

	Sitagliptin (n = 64)	Glipizide (n = 65)	Difference (%)[a]
Symptomatic hypoglycemia Total no. of episodes Proportion of patients	 7 4 (6.3)	 16 7 (10.8)	 -4.5 (-15.3 to 5.6)[b]
Severe hypoglycemia Total no. of episodes Proportion of patients	 0 0 (0)	 5 5 (7.7)	 -7.8 (-17.1 to -1.9)

Note: Data for treatment groups are given as number (percentage); difference data, as mean (95% confidence interval).

[a]Based on Miettinen and Nurminen method[11] calculated for an adverse event when at least 4 patients experienced the event in atleast one treatment group. A patient with multiple adverse events within a system organ class is counted a single time for that system organ class.

Table 2: Efficacy End Points

	Sitagliptin[a]	Glipizide[a]	Difference
Hemoglobin A_{1c} (%)	-0.72 (-0.95 to -0.48)	-0.87 (-1.11 to -0.63)	0.15 (-0.18 to 0.49)
FPG (mg/dL)	-26.6 (-38.0 to -15.3)	-31.2 (-42.6 to -19.9)	4.6 (-11.5 to 20.7)
Fasting insulin (µIU/mL)	1.0 (-1.2 to 3.2)	0.2 (-2.1 to 2.5)	0.8 (-2.4 to 4.0)
Fasting proinsulin (pmol/L)	5.1 (-3.5 to 13.7)	2.1 (-7.1 to 11.3)	3.0 (-9.6 to 15.5)
Proinsulin to insulin ratio	0.21 (-0.29 to 0.71)	0.11 (-0.43 to 0.64)	0.10 (-0.63 to 0.83)
HOMA-β	36.0 (7.8 to 64.2)	34.4 (4.7 to 64.2)	1.6 (-39.3 to 42.5)
HOMA-IR	-0.3 (-1.2 to 0.6)	-0.3 to (-1.2 to 0.7)	-0.0 (-1.3 to 1.3)

Note: Data for treatment groups and difference are presented as least squares mean change (95% confidence interval). The value -0.0 reflects a number less than 0 that rounded to 0. Conversion factor for glucose in mg/dL to mmol/L, x0.05551.

Abbreviations: FPG, fasting plasma glucose; HOMA-β, homeostasis model assessment of □-cell function; HOMA-IR, HOMA of insulin resistance.

[a] For analyses, treatment/n = 59/62 for hemoglobin A_{1c}, 59/60 for FPG, 42/46 for fasting insulin, 41/46 for fasting proinsulin and proinsulin to insulin ratio, and 40/44 for HOMA-β and HOMA-IR measurements, respectively.

➤ **Higher-Dose Sitagliptin and the Risk of Congestive Heart Failure in Older Adults with CKD[36].**

Sitagliptin, a dipeptidyl peptidase-4 inhibitor, is commonly prescribed to patients with type 2 diabetes. As this drug is primarily eliminated by the kidney, a reduced dose is recommended for patients with CKD. Some evidence suggests that sitagliptin is associated with a higher risk of congestive heart failure, particularly at higher doses. In this study, assessment of 1-year risk of death or hospitalization with congestive heart failure in patients with CKD was done for those who were newly prescribed sitagliptin at >50 versus <0 mg/d. This population-based cohort study included older adults (>66 years) with type 2 diabetes and an eGFR <45 ml/min per 1.73 m2 (but not receiving dialysis) who were newly prescribed sitagliptin between 2010 and 2017 in Ontario, Canada. The primary composite outcome was death or hospitalization with congestive heart failure. Secondary outcomes included hospitalization with pancreatitis or hypoglycemia, all-cause hospitalization, and glycemic control.

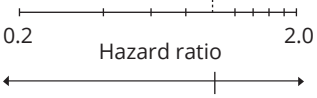
Of 9215 patients, 6518 started sitagliptin at >50 mg/d, and 2697 started sitagliptin at <50 mg/d. The 1-year risk of death or hospitalization with congestive heart failure did not differ significantly between groups (79 versus 126 events per 1000 person-years; weighted hazard ratio, 0.88; 95% confidence interval, 0.67 to 1.14); hospitalization with pancreatitis (weighted hazard ratio, 0.98; 95% confidence interval, 0.32 to 3.03) and hypoglycemia (weighted hazard ratio, 1.10; 95% confidence interval, 0.64 to 1.90) also did not differ significantly between groups. Patients starting sitagliptin at >50 mg/d had lower mean glycated hemoglobin concentrations (weighted between-group difference, -0.12%; 95% confidence interval, -0.19 to -0.06) and a lower risk of all cause hospitalization (weighted hazard ratio, -0.81; 95% confidence interval, -0.66 to -0.98). Neither baseline eGFR category or history of congestive heart significantly modified the association between starting sitagliptin at >50 versus <50 mg/day and the risk of death or hospitalization with congestive heart failure **(Figure 1).**

Key Highlights

- The risk of death or congestive heart failure was not higher in older adults with CKD starting sitagliptin at >50 versus <50 mg/d

Figure 1 - Subgroup analysis for risk of death of heart failure by eGFR category and by history of heart failure.

Subgroup	*Number of events / Number of individuals*		*Event rate per 1000 person-years*		*Hazard Ratio (95% CI)*	*P-value for interaction*
	>50 mg/day	**≤50 mg/day**	**>50 mg/day**	**≤50 mg/day**		
Baseline eGFR (mL/min per 1.73 m²)						
30-44	361/5254	354/5076	71.3	72.5	0.99 (0.70-1.38)	0.14
<30	134/1264	189/1234	112.9	170.1	0.67 (0.42-1.06)	
History of heart failure						
No	250/5079	265/5011	50.5	54.5	0.93 (0.64-1.36)	0.25
Yes	245/1439	278/1299	188.3	245.5	0.77 (0.51-1.16)	



Lower risk with sitagliptin use at dose **>50 mg/day**

Higher risk with sitagliptin use at dose **>50 mg/day**

➤ **Efficacy of different dipeptidyl peptidase-4 (DPP-4) inhibitors on metabolic parameters in patients with type 2 diabetes undergoing dialysis[37].**

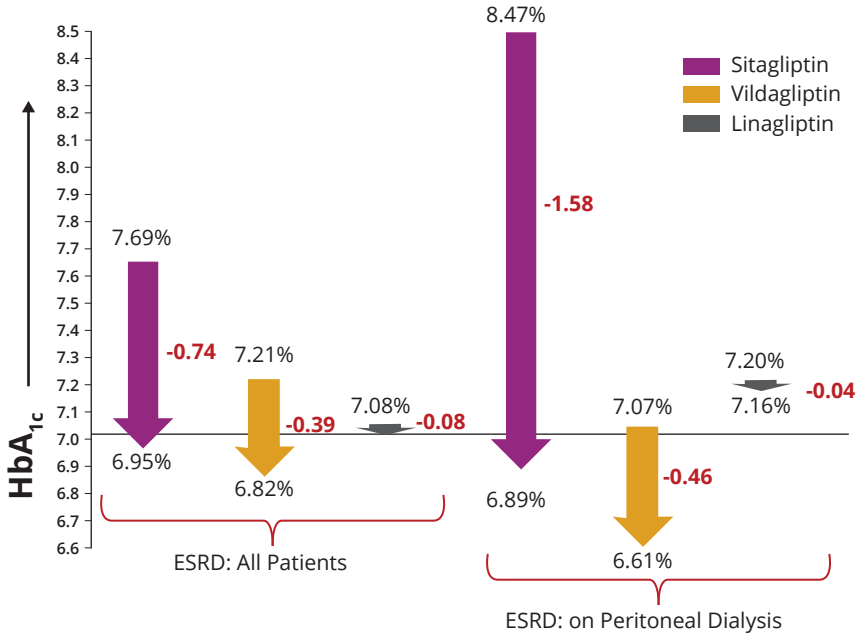
Hyperglycaemia is associated with increased mortality and morbidity in patients with type 2 diabetes mellitus (T2DM) who are undergoing dialysis. Although dipeptidyl peptidase-4 (DPP-4) inhibitors have been widely used in end-stage renal disease (ESRD) patients with T2DM, there are few studies on their efficacy in this population. Hence the effect of 3 different DPP-4 inhibitors on metabolic parameters in ESRD patients with T2DM was assessed. 200 ESRD patients with T2DM who were treated with DPP-4 inhibitors (sitagliptin, vildagliptin, or linagliptin) were enrolled and analyzed retrospectively. The changes in glycated hemoglobin (HbA_{1c}), fasting plasma glucose, and lipid profiles were assessed before and after 3 months of treatment with DPP-4 inhibitors. Subgroup analysis was done for each hemodialysis (HD) and peritoneal dialysis (PD) group.

There was no significant difference in the decrease in the HbA_{1c} level among sitagliptin, vildagliptin, and linagliptin treatment groups (-0.74±1.57, -0.39±1.45, and -0.08±1.40, respectively, P = 0.076). The changes in fasting blood glucose and lipid profiles were also not significantly different. In HD patients (n = 115), there was no difference in the HbA_{1c} level among the 3 groups. In contrast, in PD patients (n = 85), HbA_{1c} was reduced more after 3 months of treatment with sitagliptin compared with vildagliptin and linagliptin (-1.58±0.95, -0.46±0.98, -0.04±1.22, respectively, P = 0.001) **(Figure 1)**.

Key Highlights

- There was no significant difference in the glucose-lowering effect between the different DPP-4 inhibitors tested in ESRD patients. The glucose-lowering efficacy of the 3 DPP-4 inhibitors was comparable in ESRD patients
- In peritoneal dialysis patients, sitagliptin tends to lower the HbA_{1c} level more than the other inhibitors

Figure 1 - Efficacy of gliptins in HbA_{1c} levels in ESRD and PD patients.



Safety Analysis of Sitagliptin

1. Research article Safety and tolerability of sitagliptin in clinical studies: a pooled analysis of data from 10,246 patients with type 2 diabetes[38].

In a previous pooled analysis of 12 double-blind clinical studies that included data on 6,139 patients with type 2 diabetes, treatment with sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, was shown to be generally well tolerated compared with treatment with control agents. As clinical development of sitagliptin continues, additional studies have been completed, and more patients have been exposed to sitagliptin. The purpose of the present analysis is to update the safety and tolerability assessment of sitagliptin by pooling data from 19 double-blind clinical studies. The present analysis included data from 10,246 patients with type 2 diabetes who received either sitagliptin 100 mg/day (N = 5,429; sitagliptin group) or a comparator agent (placebo or an active comparator) (N = 4,817; nonexposed group). The 19 studies from which this pooled population was drawn represent the double-blind, randomized studies that included patients treated with the usual clinical dose of sitagliptin (100 mg/day) for between 12 weeks and 2 years and for which results were available as of July 2009. These 19 studies assessed sitagliptin taken as monotherapy, initial combination therapy with metformin or pioglitazone, or as add-on combination therapy with other antihyperglycemic agents (metformin, pioglitazone, a sulfonylurea ± metformin, insulin ± metformin, or rosiglitazone + metformin). Patients in the non-exposed group were taking placebo, metformin, pioglitazone, a sulfonylurea ± metformin, insulin ± metformin, or rosiglitazone + metformin. The analysis used patient-level data from each study to evaluate between-group differences in the exposure-adjusted incidence rates of adverse events.

Summary measures of overall adverse events were similar in the sitagliptin and non-exposed groups, except for an increased incidence of drug-related adverse events in the non-exposed group **(Table 1)**. Incidence rates of specific adverse events were also generally similar between the two groups, except for increased incidence rates of hypoglycemia, related to the greater use of a sulfonylurea, and diarrhea, related to the greater use of metformin, in the non-exposed group and constipation in the sitagliptin group **(Table 2)**. Treatment with sitagliptin was not associated with an increased risk of major adverse cardiovascular events.

Key Highlights

- In this updated pooled safety analysis of data from 10,246 patients with type 2 diabetes, sitagliptin 100 mg/day was generally well tolerated in clinical trials of up to 2 years in duration

Table 1: Adverse events summary

	Incidence Rate per 100 Patient-years†		
	Sitagliptin 100 mg	Non-exposed	Difference between Sitagliptin and Non-exposed (95% CI)*
With one or more adverse events	153.5	162.6	-7.6 (-15.6, 0.3)
With drug-related‡ adverse events	20.0	26.8	-6.4 (-8.7, -4.1)
With serious adverse events	7.8	7.9	-0.1 (-1.3, 1.1)
With serious drug-related‡ adverse events	0.4	0.3	0.1 (-0.1, 0.4)
Who died	0.3	0.5	-0.2 (-0.5, 0.1)
Discontinued due to adverse events	4.8	5.2	-0.5 (-1.5, 0.4)
Discontinued due to drug-related‡ adverse events	1.7	2.3	-0.5 (-1.1, 0.1)
Discontinued due to serious adverse events	1.7	1.7	-0.0 (-0.6,0.5)
Discontinued due to serious drug-related‡ adverse events	0.2	0.1	0.1 (-0.1, 0.3)

Table 2: Gastrointestinal and hypoglycaemia adverse events

Adverse Event	Incidence Rate per 100 Patient-years†		
	Sitagliptin 100 mg	Non-exposed	Difference between Sitagliptin and Non-exposed (95% CI)*
Gastrointestinal disorders SOC			
One or more select event (abdominal pain‡ ,diarrhea, nausea,vomiting)	14.0	17.2	-2.9 (-4.8, -1.1)
Abdominal pain‡	4.1	4.7	-0.7 (-1.7, 0.3)
Diarrhea	7.1	10.0	-2.5 (-3.9, -1.1)
Nausea	3.1	4.0	-0.7 (-1.6, 0.2)
Vomiting	1.9	1.9	0.0 (-0.6, 0.6)
Metabolism and nutrition disorders SOC			
Hypoglycemia	4.9	11.7	-6.7 (-8.2, -5.3)

Importance of Cardiovascular Outcome Trials (CVOTs)

- The CV mortality with Tolbutamide was noted in UGDP study in 1961
- The Rosigliatzone induced increased CV death data came in 2007 which led to the withdrawal of Rosiglitazone in EU and restricted use in US
- In ACCORD study the increased mortality observed in intense glucose lowering arm also raised concerns
- Hence in 2008 USFDA mandated the CV Safety requirement of all new diabetes drugs

Guidelines issued by USFDA for CVOTs

- If the HR of the Meta-analysis of the investigational drug vs placebo is <1.3 with 95% C.I Post marketing CVOT generally not necessary
- If the HR of the Meta-analysis of the investigational drug vs placebo is >1.3 with 95% C.I, post marketing CVOT trials needed to prove HR <1.3
- If the HR is >1.8 Inadequate data and hence not approved for marketing

TECOS Study

➤ **Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes- TECOS study[32].**

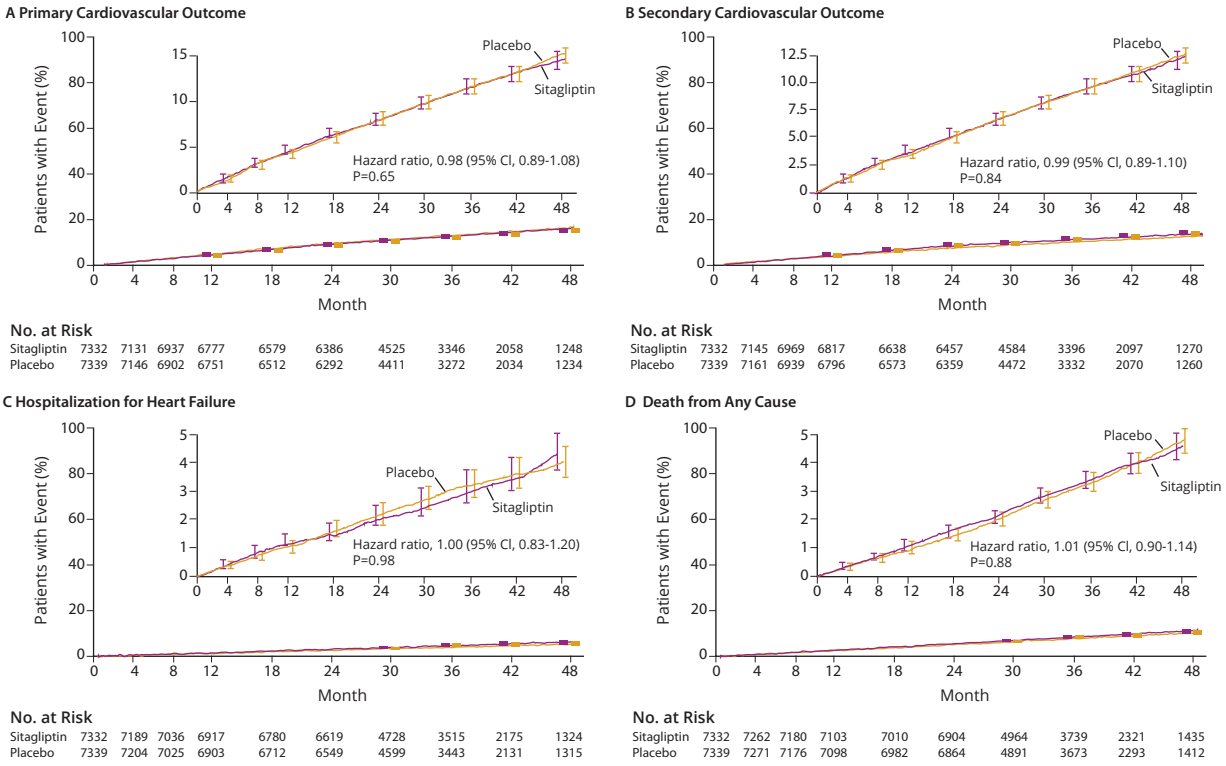
Data are lacking on the long-term effect on cardiovascular events of adding sitagliptin, a dipeptidyl peptidase 4 inhibitor, to usual care in patients with type 2 diabetes and cardiovascular disease. In the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), the long-term cardiovascular safety of adding sitagliptin to usual care, as compared with usual care alone was assessed, in patients with type 2 diabetes and established cardiovascular disease. In this randomized, double-blind study, 14,671 patients were assigned to add either sitagliptin or placebo to their existing therapy. Open-label use of antihyperglycemic therapy was encouraged as required, aimed at reaching individually appropriate glycemic targets in all patients. To determine whether sitagliptin was noninferior to placebo, a relative risk of 1.3 was used as the marginal upper boundary. The primary cardiovascular outcome was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina.

During a median follow-up of 3.0 years, there was a small difference in glycated hemoglobin levels (least-squares mean difference for sitagliptin vs. placebo, −0.29 percentage points; 95% confidence interval [CI], −0.32 to −0.27). Overall, the primary outcome occurred in 839 patients in the sitagliptin group (11.4%; 4.06 per 100 person-years) and 851 patients in the placebo group (11.6%; 4.17 per 100 person-years). Sitagliptin was noninferior to placebo for the primary composite cardiovascular outcome (hazard ratio, 0.98; 95% CI, 0.88 to 1.09; P <0.001). Rates of hospitalization for heart failure did not differ between the two groups (hazard ratio, 1.00; 95% CI, 0.83 to 1.20; P = 0.98). There were no significant between-group differences in rates of acute pancreatitis (P = 0.07) or pancreatic cancer (P = 0.32). **(Figure 1).**

Key Highlights

- Among patients with type 2 diabetes and established cardiovascular disease, adding sitagliptin to usual care did not appear to increase the risk of major adverse cardiovascular events, hospitalization for heart failure, or other adverse events

Figure 1 - Primary and secondary cardiovascular outcome.



Kaplan-Meier Curves for Primary and Secondary Outcomes (Intention-to Treat Population).
Shown are the rates of the primary cardiovascular outcome (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) (Panel B), hospitalization for heart failure (Panel C), and death from any cause (Panel D) in the sitagliptin and placebo groups.The inset graph in each panel shows the same curves on a larger scale. The I bars indicate 95% confidence intervals.

TECOS versus other CVOTs

➤ Comparing the main CVOTs OF GLIPTINS[39].

Table 1. The major clinical trials evaluating the cardiovascular safety of DPP4i in type 2 diabetes.

Trial	Compound evaluated	Year published	Participants randomized	Median follow-up time (years)	MACE definition	Main inclusion criteria at baseline
EXAMINE	Alogliptin	2013	5380	1.5	3P: cardiovascular death, non-fatal MI or stroke	Recent myocardial infarction or unstable angina requiring hospitalization HbA_{1c}: 6.5%–11.0% (7%–11.0% when on insulin)
SAVOR-TIMI 53	Saxagliptin	2013	16,492	2.1	3P: cardiovascular death, non-fatal MI or stroke	History of, or high risk for, cardiovascular disease >40 years old HbA_{1c}: 6.5%–12.0%
TECOS	Sitagliptin	2015	14,735	3.0	4P: cardiovascular death, non-fatal MI or stroke, or hosp. unstable angina	Established cardiovascular disease >50 years old HbA_{1c}: 6.5%–8%
CARMELINA	Linagliptin	2018	6991	2.2	3P: cardiovascular death, non-fatal MI or stroke	High cardiovascular (prior CVD or albuminuria) and renal risk HbA_{1c}: 6.5%–10.0%

EXAMINE[3]: Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; SAVOR-TIMI 53[5]: Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction; TECOS[4]: Trial Evaluating Cardiovascular Outcomes with Sitagliptin; CARMELINA[7,8]: Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus; MACE: major adverse cardiovascular events, MI: myocardial infarction; 3P: 3-point; 4P: 4-point; HbA_{1c}: glycated haemoglobin; CVD: cardiovascular disease.

The only CVOT which had evaluated 4P MACE as primary endpoint is TECOS.

Table 1. summary of CVOTs of DPP4 inhibitors in patients with T2DM

CVOT	Comparators	Participants randomized (N)	Characteristics of study population	Median duration of follow up (years)	Primary outcomes	CV outcomes	HF outcomes	Kidney outcomes
SAVOR-TIMI 53 [8]	Saxagliptin versus placebo	16,492	History of or at risk for CV events	2.1	CV death, MI, or stroke	No increased risk of ischemic events	Increased risk of HHF with saxagliptin (HR 1.27; 95% CI, 1.07 to 1.51)	Not designed to study kidney outcomes
EXAMINE [9,34]	Alogliptin versus placebo	5,380	Recent acute coronary syndrome	1.5	CV death, MI, or stroke	No increased risk of MACE	No significant difference (HR 1.07; 95% CI, 0.79 to 1.46)	Not designed to study kidney outcomes
TECOS [10]	Sitagliptin versus placebo	14,671	Existing CVD	3.0	CV death, MI, UA, or stroke	No increased risk of MACE	No increase in risk of HHF	Not designed to study kidney outcomes
CAROLINA [16]	Linagliptin versus glimepiride	6,042	Early T2DM and risk factors for or established atherosclerotic disease	6.3	CV death, MI, or stroke	No increase in risk of composite CV outcome	No significant difference (HR 0.90; 95% CI, 0.74 to 1.08)	Not designed to study kidney outcomes
CARMELINE [12,13]	Linagliptin versus placebo	6,979	High risk of CV and kidney events	2.2	CV death, MI, or stroke	No increase in risk of composite CV outcome	No increase in risk of HHF	No increased risk of composite kidney endpoint*; significant reduction in albuminunia progression

*Composite kidney endpoint of time to first occurrence of sustained end-stage kidney disease, renal death (adjudicated death due to kidney disease), or a sustained decrease of ≥40% in estimated glomerular filtration rate from baseline.

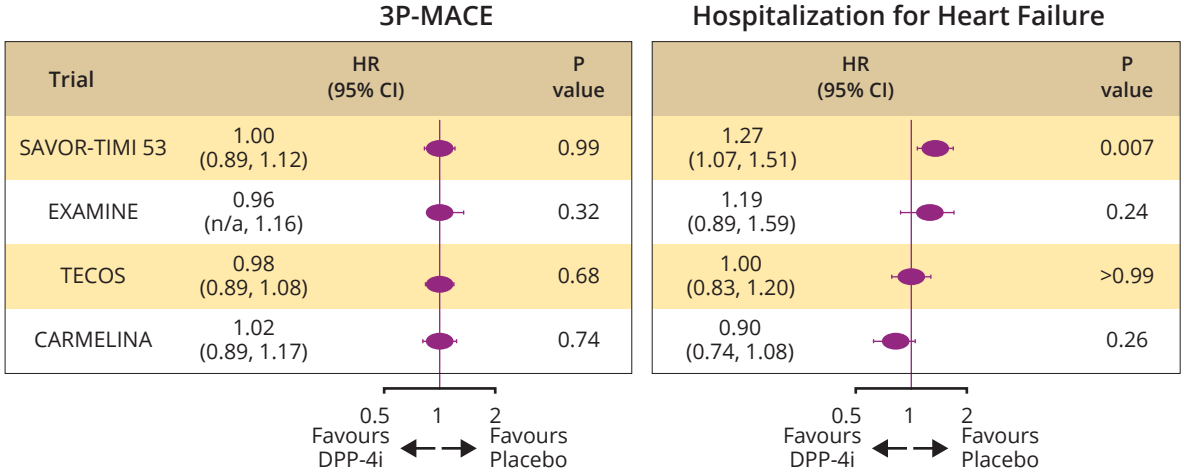
CI, confidence interval; CV, cardiovascular, CVD, cardiobascular disease, T2DM, type 2 diabetes mellitus, HF, heart failure, HHF, hospitalization for heart failure, HR, hazard ratio; MACE , major adverse cardiovascular events; MI, myocardial infarction, UA, unstable angine.

Table 3. Statistical signals for the major safety concerns in the large clinical trials evaluating DPP4i

Concern	Alogliptin (EXAMINE)	Saxagliptin (SAVOR TIMI 53)	Sitagliptin (TECOS)	Linagliptin (CARMELINA)
Heart failure	No	Yes	No	No
Pancreatitis	No	No	Borderline	Yes
Pancreatic cancer	No	No	No	No

EXAMINE[3]: Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; SAVOR-TIMI 53[5]: Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction; TECOS[4]: Trial Evaluating Cardiovascular Outcomes with Sitagliptin; CARMELINA[8]: Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus. Data were derived from the literature.[3–5,8]

The only CVOT which had the safety signals like Heart failure- SAVOR TIMI 53.
DPP-4 Inhibitor CVOT Overview



Adapted from Rosenstock J et al. Cardiovascular and renal microvascular outcome study with linagliptin patients with type 2 diabetes mellitus (CARMELINA). EASD 2018. Oct 4th, 2018. Berlin, Germany.

Key Highlights

- Among DPP4i's, Sitagliptin and Linagliptin has shown CV safety and no increased risk of Hospitalization for Heart Failure
- Saxagliptin & Alogliptin showed increased risk of hHF
- hHF risk is a molecule attribute & not a class attribute as believed earlier. TECOS demystifying this perception

Guideline Recommendations

According to ADA 2022, Metformin should be started at the time type 2 diabetes is diagnosed unless there are contraindications; for many patients this will be monotherapy in combination with lifestyle modifications. Additional and/or alternative agents may be considered in special circumstances, such as in individuals with established or increased risk of cardiovascular or renal complications. If the A1C target is not achieved after approximately 3 months, metformin can be combined with any one of the preferred six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 RA, or basal insulin; the choice of which agent to add is based on drug-specific effects and patient factors.

Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy (60)	Hypoglycemia	Weight change (109)	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential Benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30 mL/min/ 1.73m²	▪ Gastrointestinal side effects common (diarrhoea,nausea) ▪ Potential for B12 deficiency
DPP-4 Inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin): can be used in renal impairment ▪ No dose adjustment required for Linagliptin	▪ Pancreatititis has been reported in clinical trials but casually has not been established. Discontinue if pancreatitis is suspected. ▪ Joint pain

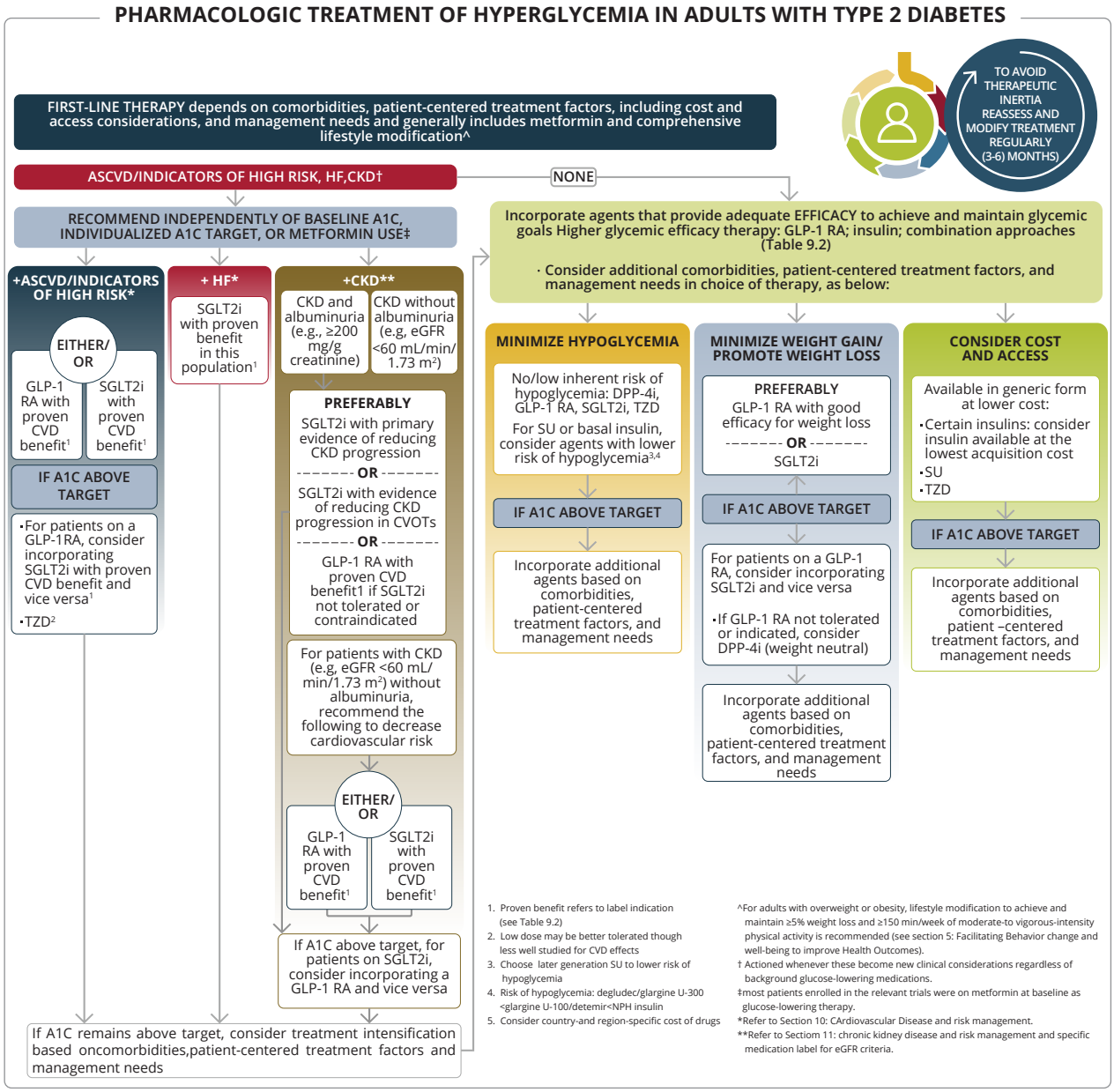


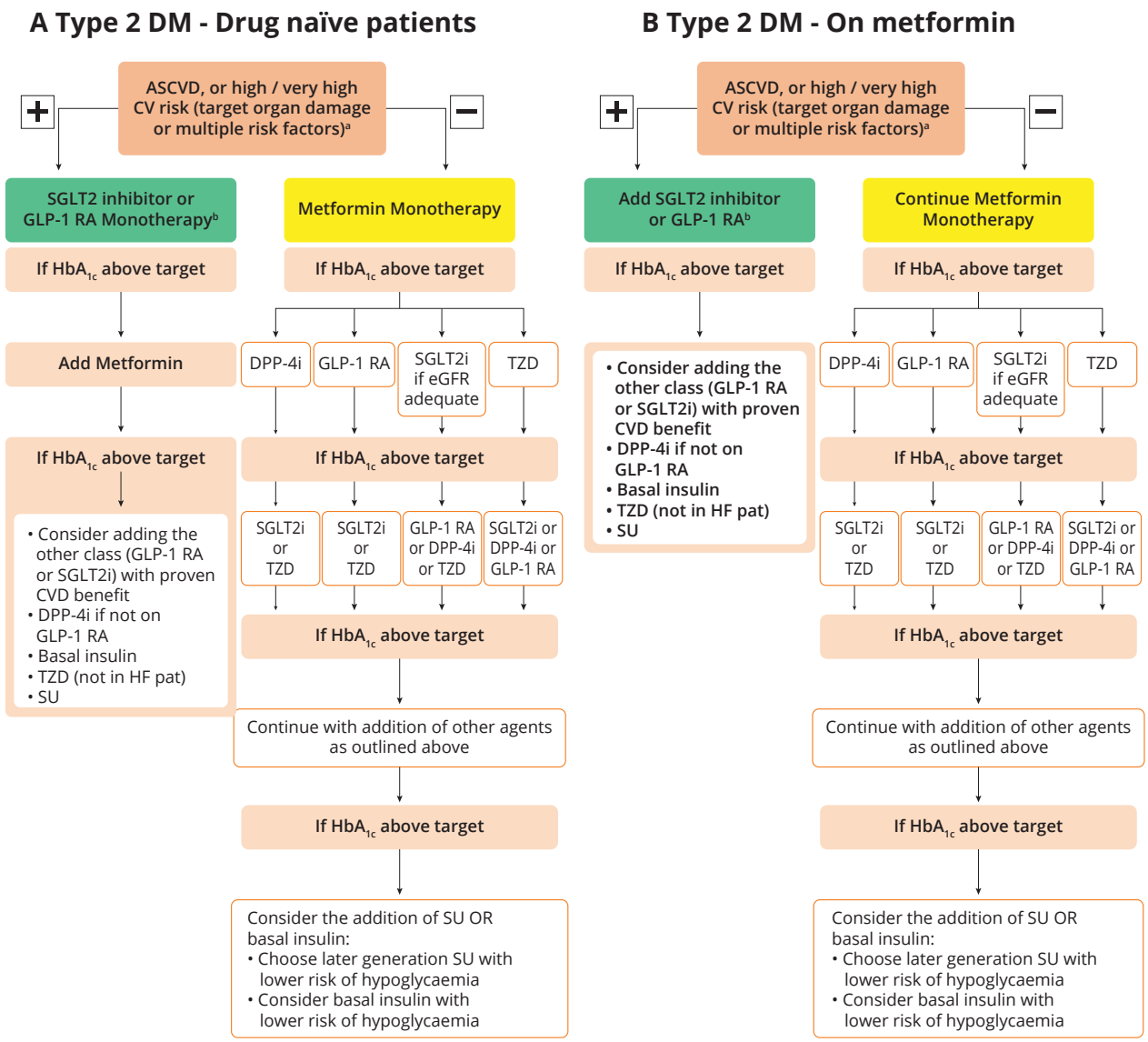
Figure 9.3—Pharmacologic treatment of hyperglycemia in adults with type 2 diabetes. 2022 ADA Professional Practice Committee (PPC) adapt tion of Davies et al. (43) and Buse et al. (44). For appropriate context, see Fig. 4.1. The 2022 ADA PPC adaptation emphasizes incorporation of therapy rather than sequential add-on, which may require adjustment of current therapies. Therapeutic regimen should be tailored to comorbidities, patient-centered treatment factors, and management needs. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.

For patients without established ASCVD, indicators of high ASCVD risk, HF, or CKD, the choice of a second agent to add to metformin is not yet guided by empiric evidence comparing across multiple classes. Rather, drug choice is based on efficacy, avoidance of side effects (particularly hypoglycaemia and weight gain), cost, and patient preferences[40].

In ESC-EASD 2019, Sitagliptin can be given in HF in view of neutral outcomes form TECOS study[41].

DM treatment to reduce HF risk
SGLT2 inhibitors (empagliflozin, canagliflozin, or dapagliflozin) are recommended to lower risk of HF hospitalization
Metformin should be considered in patients with DM and HF if eGFR >30 mL/min/1.73 m^2
GLP1-RAs and DPP4 inhibitors sitagliptin and linagliptin have a neutral effect on risk of HF and may be considered
Insulin treatment in HF may be considered
DPP4 inhibitor saxagliptin in HF is not recommended
Thiazolidinediones (pioglitazone and rosiglitazone) in HF are not recommended

Recommendations	Class[a]	Class[b]
SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) are recommended to lower risk of HF hospitalization in patients with DM.[306,311,496]	I	A
Metformin should be considered for DM treatment in patients with HF, if the eGFR is stable and >30 mL/min/1.73 m^2.[484,485]	IIa	C
GLP1-RAs (lixisenatide, liraglutide, semaglutide, exenatide, and dulaglutide) have a neutral effect on the risk of HF hospitalization, and may be considered for DM treatment in patients with HF.[158,176,297,299,300,303,498,499]	IIb	A
The DPP4 inhibitors sitagliptin and linagliptin have a neutral effect on the risk of HF hospitalization, and may be considered for DM treatment in patients with HF.[293,294]	IIb	B



Treatment algorithm in patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease, or high/very high CV risk

Comparison between DPP-4 inhibitors

The DPP-4 inhibitors based on their structure can be divided into those that mimic the DPP-4 molecule (peptidomimetics, vildagliptin and saxagliptin) and those that do not (non-peptidomimetics, sitagliptin, alogliptin, linagliptin).

In general, the peptidomimetics have lesser selectivity toward DPP-4 compared to DPP8/9. Lesser the relative selectivity toward DPP-4 and greater the relative inhibition of DPP8/9 greater is the possibility of side effects.

Table 1: Pharmacokinetic profile of DPP-4 inhibitors/gliptins[14-18,28-34,40-43]

	Chemistry	Metabolism	Elimination route
Sitagliptin (US, FDA approved)	Non-peptidomimetic (β-amino acid-based)	Not appreciably metabolized	Renal (~80% unchanged as parent)
Vildagliptin (EU, approved)	Peptide-like	Hepatically hydrolyzed to inactive metabolite	Renal (22% as parent, 55% as metabolite)
Alogliptin (Japan, approved)	Non-peptidomimeti (modified pyrimidinedione)	Not appreciably metabolized	Renal (>70% unchanged as parent)
Saxagliptin (US FDA approved)	Peptide-like	Some metabolism to active metabolite	Renal (12-29% as parent, 21-52% as metabolite)
Linagliptin (US, FDA approved)	Non-peptidomimetic (xanthine)	Not appreciably metabolized	Biliary (unchanged as parent); <6% via kidney

Table 2: Pharmacokinetic profile continued[14-18,28-34,40-43]

	Dosing	Compound t½ (half-life)	DPP-4 inhibition	Drug interactions
Sitagliptin (launched)	100 mg qd	8-24 h	Max ~97%; >80% 24 h post-dose	None known
Vildagliptin (launched)	50 mg bid	1½-4½ h	Max ~95%; >80% 12 h post dose	None known
Alogliptin (launched, Japan)	25 mg qd (anticipated)	12-21 h	Max ~90%; ~75% 24 h post-dose	None known
Saxagliptin (launched)	5 mg qd	2-4 h (parent) 3-7 h (metabolite)	Max ~80%; ~70% 24 h post-dose	Caution – with drugs metabolized by CYP3A4/5 system (atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefaz odone, nelfinavir, ritonavir, saquinavir, and telithromycin)
Linagliptin (phase 3)	5 mg qd (anticipated)	10 – 40 h	Max ~80%; ~70% 24 h post-dose	

DPP-4: Dipeptidyl peptidase-4

Table 3: DPP-4 inhibitor in vitro selectivity, (fold selectivity for DPP-4 vs. other enzymes)[14-18,28-34,40-43]

	FAPα	DPP-8	DPP-9
Vildagliptin	285	270	32
Sitagliptin (highly selective)	>5 550	>2 660	>5 550
Saxagliptin	?	390	77
Alogliptin Highly selective)	>14 000	>14 000	>14 000
Linagliptin (highly selective)	89	40000	>100 000

FAP: Fibroblast activating protein; DPP-8: Dipeptidyl peptidase-8; DPP-9: Dipeptidyl peptidase-9

In hepatic insufficiency patients, only Vildagliptin has not been recommended for patients with alanine aminotransferase or aspartate aminotransferase more than three times the upper limit of normal. Similarly, in Renal insufficiency, sitagliptin, vildagliptin, and saxagliptin can be used in patients with mild renal insufficiency without dose adjustment; however only sitagliptin and saxagliptin can be used in patients with moderate or severe renal insufficiency.

A meta-analysis comparing the efficacy of sitagliptin versus vildagliptin showed that the overall HbA_{1c} reduction was ~0.74% and 0.73%, respectively. The glycemic outcomes were better if the initial HbA_{1c} was higher >9% versus <8%[42] .

After that other gliptins like vildagliptin, saxagliptin etc were also available for the management of T2DM. The systematic review and MTC by Craddy *et al* showed similar efficacy and safety for DPP-4 inhibitors as treatment for type 2 diabetes, either as monotherapy or combination therapy. This systematic review and MTC of DPP-4 inhibitors confirmed no difference between alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin, either as monotherapy, or as dual therapy (plus metformin or SU); alogliptin, linagliptin, sitagliptin, and vildagliptin as dual therapy (plus pioglitazone); sitagliptin and vildagliptin as dual therapy (plus insulin), or linagliptin, sitagliptin, and vildagliptin as triple therapy (plus metformin and SU).

The study showed that the DPP-4 inhibitors have similar efficacy in terms of mean reduction (i.e., improvement) in HbA_{1c} from baseline, increased proportion of patients achieving HbA_{1c} <7%, mean change in body weight from baseline, and number of patients experiencing a hypoglycaemic event[27].

Sitagliptin was the first DPP4i approved for treatment of T2DM. Extensive experience in the clinical trial and real-world settings has firmly established the glycaemic efficacy of sitagliptin, as monotherapy, initial combination therapy or add-on combination therapy with other antihyperglycemic drugs (including insulin), in adult patients with T2DM. Sitagliptin monotherapy or add-on therapy also provided effective glycaemic control in high-risk patients with T2D, including obese patients, elderly patients, patients with varying degrees of renal impairment and patients with established CVD.

Highlights

1. DPP-4 inhibitors may be considered for the treatment of type 2 diabetes in those who are intolerant or have contraindications to the first-line treatment, metformin, such as those with severe renal impairment.
2. Since DPP-4 inhibitor monotherapy has a low risk for hypoglycemia, it may be considered for those at high risk for hypoglycemia.
3. DPP-4 inhibitors can be prescribed as an add-on drug therapy for those inadequately controlled on metformin, TZD or sulfonylurea, although the risk for hypoglycemia is greater when combined with a sulfonylurea.

4. Combination of a DPP-4 inhibitor with a GLP-1 receptor agonist does not provide additive glucose-lowering effects.
5. CVOT trials of Sitagliptin have proven its neutrality and thus ESC-EASD had recommended it for the treatment of Diabetes patients with Heart Failure.
6. Sitagliptin, as monotherapy or combination therapy, is generally well tolerated and improves glycaemic control, which was demonstrated in well-designed clinical trials in patients with type 2 diabetes. It had a low risk of hypoglycaemia and was generally weight-neutral. Sitagliptin, along with an established glycaemic efficacy, will help to overcome the important barriers of hypoglycaemia and obesity which are established obstacles to optimum glycaemic control.

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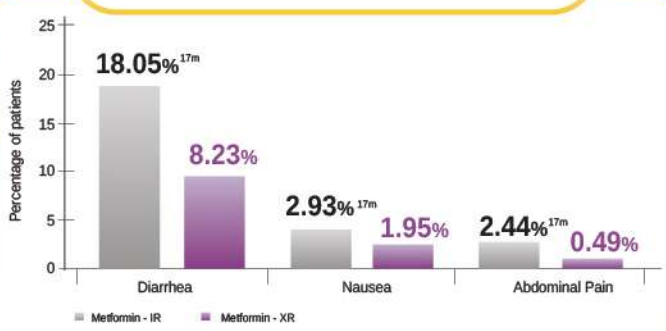

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