



*Review*

## SAFETY PROFILE OF DIPEPTIDYL PEPTIDASE-4 INHIBITORS

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### ABSTRACT

Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) are oral antidiabetic agents commonly used for the treatment of type 2 diabetes mellitus. More than ten years of clinical experience with this group of drugs provides evidence of their efficacy and good tolerability especially in patients at risk of hypoglycemia. DPP-4 inhibitors act by increasing the levels of the incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) and thus augmenting glucose-induced insulin secretion. The enzyme DPP-4 degrades plenty of substrates including chemokines, cytokines, and neuropeptides. Thus the inhibition of DPP-4 may affect many biological and pathological processes. Although rarely DPP-4 inhibitors have been reported to induce the development of infections, heart failure, liver injury and pancreatitis. The long-term effects of DPP-4 inhibition on the immune function are still not clarified. The close monitoring of polymorbid patients using DPP-4 inhibitors, and the reporting of possible adverse reactions associated with these drugs is warranted.

**Key words:** dipeptidyl peptidase-4 inhibitors, diabetes mellitus, adverse reaction

### INTRODUCTION

Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) or gliptins are oral antihyperglycaemic agents for the treatment of type 2 diabetes mellitus (T2DM). The first DPP-4 inhibitor sitagliptin was approved in 2006 (1). Ever since many new members of this drug group were marketed. Currently, there are more than nine DPP-4 inhibitors commercially available. Sitagliptin, saxagliptin, linagliptin, and alogliptin are approved by the Food and Drug Administration (FDA) in the USA and the European Medicines Agency (EMA). Vildagliptin has approval from the EMA, but it is not authorized for use in the USA. Anagliptin, teneligliptin, gemigliptin, and omarigliptin are marketed mainly in Asian countries.

Due to the rising incidences of diabetes particularly type T2DM worldwide, the global DPP-4 inhibitors market is forecasted to grow during the period 2020-2026 (2).

### PHARMACOLOGY

DPP-4 inhibitors belong to a relatively new group of antidiabetic drugs that mimic the incretin effect or prolong incretin action. Incretins are gut hormones that are secreted from enteroendocrine cells within minutes after food intake. Thus oral glucose load causes a release of incretins, principally glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) that amplify the glucose-induced insulin secretion (3). The effect of GLP-1 on insulin is more pronounced when glucose levels are high and less when glucose levels are normal. This explains the lower risk for hypoglycemia with GLP-1-affecting drugs as compared with sulfonylureas. GLP-1 is produced in enteroendocrine L cells that are found among the enterocytes in the small intestine and ascending

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colon (4). GIP is released in response to nutrients from enteroendocrine cells (called K cells) located primarily in the duodenum and jejunum. Both GLP-1 and GIP act by binding to their specific receptors (GLP-1R and GIPR). These receptors are coupled to an increase in intracellular cAMP and Ca<sup>2+</sup> levels in β cells.

In addition to its insulin-stimulatory effect, GLP-1 has several other biologic effects. It suppresses glucagon secretion (5), delays gastric emptying, and decreases food intake (6). GIP is also involved in fat metabolism in adipocytes: it acts by enhancing insulin-stimulated incorporation of fatty acids into triglycerides, stimulates lipoprotein lipase activity, and modulates fatty acid synthesis (7). Both incretins have a very short half-life being rapidly degraded by the enzyme dipeptidyl peptidase 4 (DPP-4).

Inhibitors of DPP-4 prolong the action of endogenous GLP-1 and GIP. Alogliptin, linagliptin, and sitagliptin are competitive inhibitors of the DPP-4 enzyme while saxagliptin and vildagliptin inhibit DPP-4 through the

formation of a covalent enzyme-inhibitor complex (8).

DPP-4, identical to CD26, a T-cell activation molecule is a transmembrane glycoprotein functioning as a serine protease, selectively cleaving dipeptides from peptides and proteins (9, 10). DPP-4/CD26 is expressed in many tissues such as the lung, spleen, pancreas, kidney, liver, gut, and bone marrow, but also on immune cells such as T helper cells type 17 (Th17), B cells, activated natural killer cells, macrophages, and myeloid cells (9, 11-13). The substrates of DPP-4 are incretin peptides, chemokines, cytokines, and neuropeptides. They are involved in the neuroendocrine system, nociception, metabolism, cardiovascular functions, and immune regulation (13). DPP-4/CD26 exists also in soluble form in plasma maintaining its enzymatic activity (9).

The main pharmacokinetic features of the DPP-4 inhibitors used in Europe are shown in **Table 1**.

Most of the drugs are administered orally once daily but some require once weekly regimen (e.g. omarigliptin).

**Table 1. Pharmacokinetics of DPP-4 inhibitors**

Pharmacokinetic parameter	sitagliptin	vildagliptin	saxagliptin	linagliptin	alogliptin
Oral bioavailability	87%	85%	75%	30%	63%
Half-life (hrs)	12	2	3	113-130	21
Metabolism	20% CYP3A4	2%	50% CYP3A4/5 active metabolite	10%	10%
Excretion	Renal	Renal and hepatic	Renal and hepatic	Hepatic	Renal
Dose regimen in renal failure	Adjusted	Adjusted	Adjusted	No dosage adjustment	Adjusted

\*adapted from Golightly et al., 2012 and Nolte Kennedy & Masharani, 2018.

Except for saxagliptin, which is primarily metabolized by hepatic cytochrome P450 (CYP) 3A4 and 3A5, DPP-4 inhibitors are not substrates for CYP enzymes. Thus, they neither induce nor inhibit hepatic enzymes and their potential for drug interactions with other medications is minimal. Coadministration of saxagliptin with

strong CYP3A4/5 inhibitors (antivirals, antifungal agents) significantly affects the concentrations of saxagliptin and its active metabolite 5-hydroxy-saxagliptin. In these cases, dosage adjustment is necessary (8).

### Therapeutic Uses

DPP-4 inhibitors are indicated for the treatment of T2DM. They can be applied as monotherapy or as add-on therapy with metformin, sulfonylureas, thiazolidinediones, or sodium-glucose cotransporter-2 (SGLT2) inhibitors (14). Administered in doses that lower the activity of DPP-4 by more than 95% DPP-4 inhibitors can cause a greater than the 2-fold elevation of plasma concentrations of GIP and GLP-1 leading to increased insulin secretion and improvement in fasting and postprandial hyperglycemia (15). DPP-4 inhibitors have modest glucose-reducing potential. Used as monotherapy in T2DM, they reduce A1c levels by an average of 0.8% but when added to metformin, thiazolidinediones, sulfonylureas, and insulin, a further reduction of A1c by about 0.5% can be expected (15). The risk of hypoglycaemia is minimal. Treatment with a DPP-4 inhibitor does not affect body weight. Clinical trials have demonstrated the cardiovascular safety of saxagliptin, alogliptin, sitagliptin, and linagliptin (16). Generally, DPP-4 inhibitors are characterized by intermediate glucose-lowering potential, low risk of hypoglycemia, neutral effect on body weight, and low incidence of adverse effects.

Certain differences exist between various DPP-4 inhibitors regarding their potency and target selectivity, as well as the need for dosage adjustment in patients with renal and liver failure.

### ADVERSE REACTIONS

DPP-4 inhibitors are well-tolerated drugs. Results from studies performed in the first decade after their approval confirms the safety and tolerability of this group of drugs (17). DPP-4 inhibitors are considered to be weight neutral and to have a low risk of hypoglycemia compared with sulfonylureas and insulin (18, 19). Due to their good safety profile, DPP-4 inhibitors can be used in the elderly population, in patients with mild renal impairment, and in patients at risk of hypoglycemia.

The summary of product characteristics for most DPP-4 inhibitors includes as contraindications hypersensitivity reactions and warning not to use these medications during pregnancy and lactation, as well as precautions in cases of

concomitant hepatic disease, renal impairment, heart failure, and pancreatic disorders.

### 1. Infection and Immunity

Common adverse effects include nasopharyngitis, upper respiratory infections, and headaches. An increased reporting of upper respiratory tract infections for diabetic patients using DPP-4 inhibitors compared with patients using other antidiabetic drugs has been detected (20, 21). Meta-analyses confirmed a slightly increased risk of nasopharyngitis, especially for sitagliptin (22). It is hypothesized that the effects of DPP-4 inhibitors cause a slight disbalance of the immune system and consequent increased risk of common, but not severe infections such as upper respiratory tract infections (20). The mechanisms for the risk of infections in DPP-4 inhibitor use are not clear. The cleavage of immunoregulating substrates by DPP4/CD26 might influence immune activity or function (23). CD26 may also affect immune responses by directly regulating T lymphocytes (24). The potential of DPP-4 inhibitors to alter immune function present a source of safety concerns for researchers and clinicians.

### Autoimmune Diseases

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder characterized by the destruction of pancreatic  $\beta$  cells. In some clinical studies, higher DPP-4 levels in patients with T1DM were found (25). Experimental investigations have shown that inhibition of DPP-4 activity stimulated  $\beta$ -cell proliferation (26). Although some studies have provided evidence for the therapeutic effect of DPP-4 inhibitors in patients with T1DM a systematic review and meta-analysis of existing data does not support these positive results (27).

Inflammatory bowel disease (IBD) is an autoimmune disease characterized by chronic progressive inflammation affecting the gastrointestinal tract. Some studies disclose a potential association of DPP-4 inhibition with the risk of IBD in patients with T2DM (28, 29). However, the clinical evidence about the effect of DPP-4 inhibitors on IBD is generally considered to be limited and inconsistent (30).

The role of DPP-4 inhibitors in rheumatoid arthritis remains unclear (31). DPP-4 inhibitors

can increase the risk of nonspecific arthritis and severe arthralgia (31, 32). Joint pain occurs from days to months after the start of therapy with a DPP-4 inhibitor and typically resolves after discontinuation of therapy. These adverse events have been attributed to cytokine-induced inflammation (19). The US FDA published a safety announcement regarding the entire drug class based on 33 case reports of severe joint pain in 2015 (33). The risk of severe joint pain or nonspecific arthropathies in patients with T2DM using DPP-4 inhibitors was not verified in population-based cohort studies (34, 35). Considering systemic lupus erythematosus (SLE) recent population-cohort studies from Taiwan and Korea showed that DPP-4 inhibitor use was associated with a reduced risk of SLE (35, 36).

### **Dermatologic Reactions (hypersensitivity and autoimmune disorders)**

Reports of hypersensitivity reactions such as anaphylaxis and angioedema, occurring after the first dose or up to 3 months of drug initiation, have been reported with DPP-4 inhibitors. Angioedema as an adverse reaction is typical for angiotensin-converting enzyme (ACE) inhibitors and is attributed to the accumulation of vasoactive kinins normally degraded by ACE. DPP-IV inhibitors block the degradation not only of incretins but of other peptides (e.g. substance P). Substance P is also involved in the development of angioedema induced by ACE inhibitors. Substance P is normally degraded by ACE but when this enzyme is inhibited, it is inactivated by DPP-IV. Thus the inhibition of DPP-IV could increase the risk of angioedema in patients taking ACE inhibitors as concurrent medication (37).

Serious skin reactions including Stevens-Johnson syndrome, bullous pemphigoid (BP), pemphigus, urticaria, vasculitis, as well as stomatitis and mouth ulceration have also been reported. Bullous pemphigoid is a rare chronic, autoimmune, blistering disease in elderly patients (38) with a poor prognosis (39). The first cases of BP induced by vildagliptin in combination with metformin were reported by Pasmazi et al. in 2011 (40). Since then many types of studies including case reports, case series, observational studies, and pharmacovigilance database analysis continue to report the probable association

between DPP-4 inhibitor use and the development of BP (41). BP can be triggered by various groups of drugs but the gliptins seem to be associated with the highest risk of drug-induced BP (41, 42).

### **2. Cardiovascular Function**

T2DM is associated with a higher risk of cardiovascular disease but this risk can be reduced by maintaining glucose control as data from randomized controlled trials (RCTs) show (43). A meta-analysis of 182 clinical trials revealed that DPP-4 inhibitors are not associated with any increase or reduction of major adverse cardiovascular events, all-cause mortality, and heart failure but saxagliptin seems to be associated with an increased risk of hospitalization for heart failure (44). A meta-analysis of RCTs and observational cohort studies including 157,478 participants with T2DM showed that cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke were not significantly different in T2DM patients treated with DPP-4 inhibitors versus patients treated with no DPP-4 inhibitors and that those drugs might be safely used considering potential cardiovascular events (45).

Several clinical trials have demonstrated cardiovascular safety with no reduction of the cardiovascular risk for saxagliptin, alogliptin, sitagliptin, and linagliptin (16). Unlike GLP-1 receptor agonists, DPP-4 inhibitors display no superiority over placebo concerning major acute cardiovascular events (46). At present, there is limited data to suggest that DPP-4 inhibitors may trigger heart failure. Evidence from some clinical trials and observational studies is consistent with increased risk even in patients without a history of heart failure (47). Thus DPP-4 inhibitors are not recommended for patients with pre-existing cardiovascular disease until more RCTs of DPP-4 inhibitors in patients with established heart failure are carried out.

### **3. Pancreatitis**

A slight risk of acute pancreatitis with DPP-4 inhibitors has been reported in a meta-analysis of the 3 cardiovascular outcome trials - EXAMINE, SAVOR, and TECOS (48). These data were confirmed in a recent meta-analysis of 36 RCTs, which showed an increased risk of acute

pancreatitis but not of pancreatic cancer with the use of DPP-4 inhibitors (49). Observational studies performed in various countries could not verify these results. The FDA and EMA announced that available data do not support an increased risk of pancreatitis in patients receiving DPP-4 inhibitors but more data are needed to suspect a causal relationship. Pancreatitis during DPP-4 inhibition may be due to the chronic stimulation of pancreatic acinar and duct cells by GLP-1. These cells express GLP-1 receptors and proliferate in response to chronic stimulation by GLP-1 in experimental studies (50). Because of uncertainty regarding the association between the risk of acute pancreatitis and DPP-4 inhibitor use EMA and FDA state that pancreatic events will be considered a risk associated with DPP-4 inhibitors until more data are available (51).

#### 4. Renal Function

DPP-4 inhibitors have been used safely in patients with chronic kidney disease (CKD), but their effects on renal outcomes are uncertain (52). Saxagliptin is reported to decrease urine albumin-to-creatinine ratio (UACR) in diabetic patients with cardiovascular disease without affecting renal function (53). Linagliptin reduced albuminuria progression in patients with CKD (54). DPP-4 inhibitors could reduce albuminuria through antioxidant, anti-inflammatory, and anti-fibrotic effects (52). However, in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) trial, this drug showed a small but early decline in estimated glomerular filtration rate (eGFR) with no changes of UACR (55).

A meta-analysis of 23 RCTs involving 41,359 patients comparing DPP-4 inhibitors with placebo or other antidiabetic agents in patients with T2DM showed that DPP-4 inhibitors had beneficial effects on renal function mainly by reducing albuminuria but DPP-4 inhibitors treatment was associated with a small decline in eGFR compared with controls (52). Significant effects on eGFR have been rarely reported in clinical studies of DPP-4 inhibitors, and albuminuria is affected variably. The long-term effects of DPP-4 inhibitors on renal function and the development of end-stage renal disease are still unknown.

Monitoring of renal function is recommended in diabetic patients on DPP-4 inhibitor therapy especially elderly patients with cardiovascular risk factors and chronic kidney disease.

#### 5. Liver Function

Postmarketing surveillance has provided data on elevated liver enzymes and hepatic failure possibly associated with alogliptin, sitagliptin, and saxagliptin. The latency period ranged from 2 to 12 weeks of starting therapy and the pattern of liver injury was usually hepatocellular. Discontinuation of the medication resulted in the reversal of liver abnormalities (56). In a recent population-based study of DPP-4 inhibitors and SGLT-2 inhibitors in patients with type 2 diabetes DPP-4 inhibitors were associated with an increased risk of acute liver injury compared with SGLT-2 inhibitors (57).

Regarding linagliptin which is the only DPP-4 inhibitor primarily excreted by the liver and bile analysis of data from 17 placebo-controlled RCTs of linagliptin including patients with a history of hepatic disorders, showed that linagliptin is well tolerated in this patient population (58). According to the conducted studies, there is no concern for hepatotoxicity for alogliptin, saxagliptin, vildagliptin, and linagliptin (59). It is however recommended to discontinue a DPP-4 inhibitor in case of clinical and laboratory symptoms suggestive of liver impairment.

#### CONCLUSION

DPP-4 inhibitors have evolved as a well-established group of oral antidiabetic drugs in the management of T2DM in patients with no pre-existing cardiovascular disorders. They are mainly used as second or third-line therapy in patients with high risk for hypoglycemia. DPP-4 inhibitors can be used as monotherapy or in double or triple combinations with other antidiabetic drugs. Due to their favorable safety profile, DPP-4 inhibitors remain a therapeutic option for elderly diabetic patients and those with mild chronic kidney disease although they lack the beneficial effects of SGLT-2 inhibitors and GLP-1 receptor agonists on cardiovascular outcomes.

Monitoring of patients using DPP-4 inhibitors is mandatory considering the pleiotropic effects of DPP-4 inhibition. Experimental and clinical

research focused on the action of incretins and other substrates of DPP-4 on cardiovascular function, immunity, infection, and cancer will enlarge the current knowledge of the beneficial and adverse effects of DPP-4 inhibitors.

## REFERENCES

- Nathan, D.M., Finding new treatments for diabetes—how many, how fast... How good? *NEJM*, 356,(5): 437–440, 2007.
- Dipeptidyl Peptidase-4 (DPP-4) Inhibitors Market 2022 to Eyewitness Massive Growth by 2028  
<https://www.marketwatch.com/press-release/dipeptidyl-peptidase-4-dpp-4-inhibitors-market-2022-to-eyewitness-massive-growth-by-2028-2022-10-21>
- Nolte Kennedy, M.S. and Masharani, U, Pancreatic Hormones and Antidiabetic Drugs. In: Katzung, B.G. (ed) Basic & Clinical Pharmacology, 14th ed., McGraw-Hill Companies, Inc., pp 747-771, 2018.
- Doyle, M.E and Egan, J.M., Mechanisms of action of glucagon-like peptide 1 in the pancreas. *Pharmacol Ther*, 113:546-593, 2007.
- Komatsu, R., Matsuyama, T., Namba, M., Watanabe, N., Itoh, H., Kono, N., Tarui, S., Glucagonostatic and insulinotropic action of glucagonlike peptide I-(7–36)-amide. *Diabetes*, 38:902-905, 1989.
- Willms, B., Werner, J., Holst, J.J., Orskov, C., Creutzfeldt, W., Nauck, M.A., Gastric emptying, glucose responses, and insulin secretion after a liquid test meal: effects of exogenous glucagon-like peptide-1 (GLP-1)-(7–36) amide in type 2 (non-insulin-dependent) diabetic patients. *J Clin Endocrinol Metab*, 81:327-332, 1996.
- Yip, R.G. and Wolfe, M.M., GIP biology and fat metabolism. *Life Sci*, 2000;66:91-103, 2000.
- Golightly, L.K., Drayna, C.C., McDermott, M.T., Comparative Clinical Pharmacokinetics of Dipeptidyl Peptidase-4 Inhibitors. *Clin Pharmacokinet*, 51(8): 501-514, 2012.
- Gorrell, M.D., Gysbers, V., McCaughan, G.W. CD26: a multifunctional integral membrane and secreted protein of activated lymphocytes. *Scand J Immunol*, 54,(3): 249–264, 2001.
- Kirby, M., Yu, D.M.T., O'Connor, S.P., Gorrell, M.D., Inhibitor selectivity in the clinical application of dipeptidyl peptidase-4 inhibition. *Clin Sci*, 118(1): 31–41, 2010.
- Mentlein, R., Dipeptidyl-peptidase IV (CD26)-role in the inactivation of regulatory peptides. *Regul Peptides*, 85(1): 9–24, 1999.
- Abbott, C.A., Baker, E., Sutherland, G.R., McCaughan, G.W., Genomic organization, exact localization, and tissue expression of the human CD26 (dipeptidyl peptidase IV) gene. *Immunogenetics*, 40:331-8,994.
- Klemann, C., Wagner, L., Stephan, M., von Hörsten, S., Cut to the chase: a review of CD26/dipeptidyl peptidase-4's (DPP4) entanglement in the immune system. *Clin Exp Immunol*, 185:1-21, 2016.
- Eligar, V.S., Dipeptidyl peptidase-4 inhibitors in management of type 2 diabetes mellitus. In: Tripathi K, Saboo B (eds), Sadikot's International Textbook of Diabetes, 1st ed., Jaypee Brothers Medical Publishers, New Delhi, pp 303-308, 2019.
- Powers, A.C., and D'Alessio, D. Endocrine Pancreas and Pharmacotherapy of Diabetes Mellitus and Hypoglycemia In: Brunton LL, Hilal-Dandan R, Knollmann BC, (eds), Goodman and Gilman's The pharmacological basis of therapeutics, 13th ed., McGraw-Hill Education pp 863-886, 2018.
- American Diabetes Association Professional Practice Committee (2022) 10. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes-2022. *Diabetes Care* 45(Suppl 1):S144-S174. <https://doi.org/10.2337/dc22-S010>
- Sesti, G., Avogaro, A., Belcastro, S., Bonora, B.M., Croci, M., Daniele, G., Dauriz, M., Dotta, F., Formichi, C., Frontoni, S., Invitti, C., Orsi, E., Picconi, F., Resi, V., Bonora, E., Purrello, F., Ten years of experience with DPP-4 inhibitors for the treatment of type 2 diabetes mellitus. *Acta Diabetol*, 56(6):605-617, 2019 doi: 10.1007/s00592-018-1271-3
- Deacon, C.F., A review of dipeptidyl peptidase-4 inhibitors Hot topics from randomized controlled trials, *Diabetes Obes Metab*, Suppl 1:34-46, 2018 doi: 10.1111/dom.13135. 2018.
- Scheen, A.J., The safety of gliptins: updated data in 2018. *Expert Opin Drug Saf*,

- 17(4):387-405, 2018. doi: 10.1080/14740338.2018.1444027.
20. Willemsen, M.J., Mantel-Teeuwisse, A.K., Straus, S.M., Meyboom, R.H., Egberts, T.C., Leufkens, H.G., Use of dipeptidyl peptidase-4 inhibitors and the reporting of infections: a disproportionality analysis in the World Health Organization VigiBase. *Diabetes Care*, 34(2):369-374 2011 doi: 10.2337/dc10-1771.
21. Scheen, A.J., A review of gliptins in 2011. *Expert Opin Pharmacother*, 1:81–99, 2012
22. Makrilakis, K., The Role of DPP-4 Inhibitors in the Treatment Algorithm of Type 2 Diabetes Mellitus: When to Select, What to Expect. *Int J Environ Res Public Health*, 16(15):2720, 2019 doi: 10.3390/ijerph16152720.
23. De Meester, I., Korom, S., Van Damme, J., Scharpé, S., CD26, let it cut or cut it down. *Immunol Today* 20: 367-375). 1999.
24. Ishii, T., Ohnuma, K., Murakami, A., Takasawa, N., Kobayashi, S., Dang, N.H., Schlossman, S.F., Morimoto, C., CD26-mediated signaling for T cell activation occurs in lipid rafts through its association with CD45RO. *Proc Natl Acad Sci USA*, 98: 12138-43, 2001.
25. Osawa, S., Kawamori, D., Katakami N., Takahara, M., Sakamoto, F., Katsura, T. et al. Significant elevation of serum dipeptidyl peptidase-4 activity in young-adult type 1 diabetes. *Diab Res Clin Pract*, 113:135–142, 2016. doi: 10.1016/j.diabres.2015.12.022
26. Holst, J. J., The physiology of glucagon-like peptide 1. *Physiol Rev* 87(4):1409–1439, 2007. doi: 10.1152/physrev.00034.2006.
27. Wang, Q., Long, M., Qu, H., Shen, R., Zhang, R., Xu, J., Xiong, X., Wang, H., Zheng, H., DPP-4 Inhibitors as Treatments for Type 1 Diabetes Mellitus: A Systematic Review and Meta-Analysis. *J Diabetes Res*. 2018:5308582, 2018. doi: 10.1155/2018/5308582).
28. Abrahami, D., Douros, A., Yin, H., Yu, O.H.Y., Renoux, C., Bitton, A., Azoulay, L., Dipeptidyl peptidase-4 inhibitors and incidence of inflammatory bowel disease among patients with type 2 diabetes: population based cohort study. *BMJ*, 360:k872, 2018.
29. Wang, T., Lu, W., Li, D., Tang, H., Yang, J.Y., Buse, J.B., Sturmer, T., Assessing the association between dipeptidyl peptidase 4 inhibitor use and inflammatory bowel disease through drug adverse event reporting. *Diabetes Care*, 42:e89–e91, 2019.
30. Huang, J., Liu, X., Wei, Y., Li, X., Gao, S., Dong, L., Rao, X., Zhong, J., Emerging Role of Dipeptidyl Peptidase-4 in Autoimmune Disease. *Front. Immunol*, 13:830863, 2022. doi: 10.3389/fimmu.2022.830863
31. Roy, A., Sahoo, J., Narayanan, N., Merugu, C., Kamalanathan, S., Naik, D., Dipeptidyl peptidase-4 inhibitor-induced autoimmune diseases: Current evidence. *World J Diabetes*, 12(9):1426-1441, 2021. DOI: 10.4239/wjd.v12.i9.1426
32. Mascolo, A., Rafaniello, C., Sportiello, L., Sessa, M., Cimmaruta, D., Rossi, F., Capuano, A., Dipeptidyl peptidase (DPP)-4 inhibitor-induced arthritis/arthralgia: a review of clinical cases. *Drug Saf*, 39:401–407, 2016.
33. Food and Drug Administration (US FDA) MedWatch. Drug safety communication: FDA warns that DPP-4 inhibitors for type 2 diabetes may cause severe joint pain. Retrieved August 28, 2015. Available on the World Wide Web at: <http://www.fda.gov/Drugs/DrugSafety/ucm459579.htm>
34. Hou, W.H., Chang, K.C., Li, C.Y., Ou, H.T., Dipeptidyl peptidase-4 inhibitor use is not associated with elevated risk of severe joint pain in patients with type 2 diabetes mellitus: a population-based cohort study. *Pain*, 157(9):1954-1959, 2016.
35. Seong, J-M., Yee, J., Gwak, H.S., Dipeptidyl peptidase-4 inhibitors lower the risk of autoimmune disease in patients with type 2 diabetes mellitus: A nationwide population-based cohort study, *Br J Clin Pharmacol*, 85:1719-1727, 2019. <https://doi.org/10.1111/bcp.13955>
36. Chen, Y.C., Chen, T.H., Sun, C.C., Chen, J.Y., Chang, S.S., Yeung, L., et al. Dipeptidyl Peptidase-4 Inhibitors and the Risks of Autoimmune Diseases in Type 2 Diabetes Mellitus Patients in Taiwan: A Nationwide Population-Based Cohort Study. *Acta Diabetol*, 57(10):1181–1192, 2020. doi: 10.1007/s00592-020-01533-5

37. Brown, N.J., Byiers, S., Carr, D., Maldonado, M., Warner, B.A., Dipeptidyl peptidase-IV inhibitor use associated with increased risk of ACE inhibitor-associated angioedema. *Hypertension*, 54(3):516-23, 2009 doi: 10.1161/HYPERTENSIONAHA.109.134197
38. Roujeau, J.C., Lok, C., Bastuji-Garin, S., Mhalla, S., Enginger, V., Bernard, P., High risk of death in elderly patients with extensive bullous pemphigoid. *Arch Dermatol*, 134(4):465-469, 1998.
39. Joly, P., Benichou, J., Lok, C., Hellot, M.F., Saiag, P., Tancrede-Bohin, E., Sassolas, B., Labeille, B., Doutre, M.S., Gorin, I., Pauwels, C., et al. Prediction of Survival for Patients With Bullous Pemphigoid: A Prospective Study. *Arch Dermatol*, 141(6):691–698, 2005. doi:10.1001/archderm.141.6.691
40. Pasmatzi, E., Monastirli, A., Habeos, J., Georgiou, S., Tsambaos, D., Dipeptidyl peptidase-4 inhibitors cause bullous pemphigoid in diabetic patients: report of two cases. *Diabetes Care*, 34(8):e133, 2011. doi: 10.2337/dc11-0804.
41. Chouchane, K., Di Zenzo, G., Pitocco, D., Calabrese, L., De Simone, C., Bullous pemphigoid in diabetic patients treated by gliptins: the other side of the coin. *J Transl Med*, 19(1):520, 202. doi: 10.1186/s12967-021-03192-8.
42. Tasanen, K., Varpuluoma, O., Nishie, W., Dipeptidyl peptidase-4 inhibitor-associated bullous pemphigoid, *Front Immunol*, 10:1238 2019. <https://doi.org/10.3389/fimmu.2019.01238>
43. Mannucci, E., Monami, M., Lamanna, C., Gori, F., Marchionni, N., Prevention of cardiovascular disease through glycemic control in type 2 diabetes: a meta-analysis of randomized clinical trials. *Nutr Metab Cardiovasc Dis*, 19:604-612, 2009.
44. Mannucci, E., Nreu, B., Monterecci, C., Ragghianti, B., Gallo, M., Giaccari, A., Monami, M., Cardiovascular events and all-cause mortality in patients with type 2 diabetes treated with dipeptidyl peptidase-4 inhibitors: An extensive meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis*, 31(10): 2745-2755, 2021.
45. Liu, D., Jin, B., Chen, W., Yun, P., Dipeptidyl peptidase 4 (DPP-4) inhibitors and cardiovascular outcomes in patients with type 2 diabetes mellitus (T2DM): a systematic review and meta-analysis. *BMC Pharmacol Toxicol*, 20(1): 15, 2019. <https://doi.org/10.1186/s40360-019-0293-y>
46. Ahrén, B., DPP-4 Inhibition and the Path to Clinical Proof, *Front Endocrinol (Lausanne)*, 19;10:376, 2019. doi: 10.3389/fendo.2019.00376.
47. Packer, M., Worsening Heart Failure During the Use of DPP-4 Inhibitors: Pathophysiological Mechanisms, Clinical Risks, and Potential Influence of Concomitant Antidiabetic Medications, *JACC: Heart Fail*, 6(6):445-451, 2018.
48. Tkac, I. and Raz, I., Combined analysis of three large interventional trials with gliptins indicates increased incidence of acute pancreatitis in patients with type 2 diabetes. *Diabetes Care*, 40:284–286, 2017.
49. Rehman, M.B., Tudrej, B.V., Soustre, J., Buisson, M., Archambault, P., Pouchain, D., Vaillant-Roussel, H., Gueyffier, F., Faillie, J.L., Perault-Pochat, M.C., Cornu, C., Boussageon, R., Efficacy and safety of DPP-4 inhibitors in patients with type 2 diabetes: meta-analysis of placebo-controlled randomized clinical trials. *Diabetes Metab*, 43:48-58, 2017.
50. Perfetti, R., Zhou, J., Doyle, M.E., Ean, J.M., Glucagon-like peptide-1 induces cell proliferation and pancreatic-duodenum homeobox-1 expression and increases endocrine cell mass in the pancreas of old glucose-intolerant rats. *Endocrinology*, 141:4600-4605, 2000. doi: 10.1210/endo.141.12.7806
51. Egan, A.G., Blind, E., Dunder, K., de Graeff, P.A., Hummer, B.T., Bourcier, T., Rosebraugh, C., Pancreatic safety of incretin-based drugs-FDA and EMA assessment. *NEJM*, 27;370(9):794-797, 2014. doi: 10.1056/NEJMp1314078.
52. Bae, J.H., Kim, S., Park, E.G., Kim, S.G., Hahn, S., Kim, N.H., Effects of Dipeptidyl Peptidase-4 Inhibitors on Renal Outcomes in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. *Endocrinol Metab (Seoul)*, 34(1):80-92, 2019. doi: 10.3803/EnM.2019.34.1.80.
53. Mosenzon, O., Leibowitz, G., Bhatt, D.L., Cahn, A., Hirshberg, B., Wei, C., et al. Effect of saxagliptin on renal outcomes in the



- SAVOR-TIMI 53 trial. *Diabetes Care*, 40:69-76, 2017.
54. Rosenstock, J., Perkovic, V., Johansen, O.E., Cooper, M.E., Kahn, S.E., Marx, N., et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *JAMA*, 321:69-79, 2019.
55. Cornel, J.H., Bakris, G.L., Stevens, S.R., Alvarsson, M., Bax, W.A., Chuang, L.M., et al. Effect of sitagliptin on kidney function and respective cardiovascular outcomes in type 2 diabetes: outcomes from TECOS. *Diabetes Care*, 39:2304-2310, 2016.
56. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. <https://www.ncbi.nlm.nih.gov/books/NBK548275>
57. Pradhan, R., Yin, H., Yu, O. H.Y., Azoulay, L., Incretin-Based Drugs and the Risk of Acute Liver Injury Among Patients With Type 2 Diabetes. *Diabetes Care*, 2022; 45 (10): 2289–2298, 2022.
58. Inagaki, N., Sheu, W.H., Owens, D.R., et al. Efficacy and safety of linagliptin in type 2 diabetes patients with self-reported hepatic disorders: a retrospective pooled analysis of 17 randomized, doubleblind, placebo-controlled clinical trials. *J Diabetes Complications*, 30:1622-1630, 2016.
59. Papazafiropoulou, A., Melidonis, A., Antidiabetic agents in patients with hepatic impairment. *World J Meta-Anal*, 7(8): 380-388, 2019. DOI: 10.13105/wjma.v7.i8.380