



**TITLE: Combination Use of Insulin and Dipeptidyl Peptidase-4 (DPP-4) Inhibitors in Type 2 Diabetes: Clinical Effectiveness**

**DATE:** 8 July 2014

**RESEARCH QUESTION**

What is the clinical efficacy and safety of dipeptidyl peptidase-4 (DPP-4) inhibitors used in combination with insulin for patients with inadequate glycemic control on a basal or biphasic insulin regimen?

**KEY MESSAGE**

Four systematic reviews and seven randomized controlled trials were identified regarding the clinical efficacy and safety of DPP-4 inhibitors used in combination with insulin for patients with inadequate glycemic control on a basal or biphasic insulin regimen.

**METHODS**

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 5), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between Jan 1, 2012 and Jun 24, 2014. Internet links were provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.

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## RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials.

Four systematic reviews and seven randomized controlled trials were identified regarding the clinical efficacy and safety of DPP-4 inhibitors used in combination with insulin for patients with inadequate glycemic control on a basal or biphasic insulin regimen.

Additional references of potential interest are provided in the appendix.

## OVERALL SUMMARY OF FINDINGS

This is an update to a previously published CADTH Optimal Use report, published in July 2013 ([Combination Use of Insulin and Incretins in Type 2 Diabetes](#)).

Four systematic reviews<sup>1-4</sup> were identified examining the addition of dipeptidyl peptidase-4 (DPP-4) inhibitors to insulin therapy in patients with type 2 diabetes. In one review,<sup>1</sup> the effectiveness of five DPP-4 inhibitors used as monotherapy, dual therapy (including insulin), or triple therapy for glycemic control was compared through meta-analysis. The results specific to DPP-4 plus insulin treatment were not presented in the abstract; however, overall, the comparisons found the five DPP-4 inhibitors to be similar in terms of mean change from baseline of HbA1c and body weight.<sup>1</sup> One review<sup>2</sup> compared the effectiveness of the DPP-4 agents available in Canada. The authors found that the addition of DPP-4 therapy to insulin resulted in modest HbA1c lowering while maintaining body weight.<sup>2</sup> In a third review,<sup>3</sup> DPP-4 inhibitors reduced HbA1c by less than 1% while having no significant impact on body weight when combined with basal insulin. A fourth review<sup>4</sup> sought to examine the longer term safety of treatment with DPP-4 inhibitors. Studies were included in the review if they were 18 weeks or longer in duration. Adverse event rates associated with DPP-4 treatment were similar to the rates observed with placebo treatment. The risk of hypoglycemia was significantly elevated with combination therapy of sitagliptin or linagliptin with insulin or sulphonylurea when compared with placebo.

The results of the identified randomized controlled trials are summarized in Table 1. DPP-4 inhibitors were generally well tolerated and reported to be effective for the management of patients with type 2 diabetes. There may be overlap between these randomized controlled trials and those included in the systematic reviews summarized previously.

**Table 1: Summary of Included Randomized Controlled Trials**

Author and Year	Intervention(s) and Comparator(s)	Results and Conclusions
Derosa et al. (2014) <sup>5</sup>	Sitagliptin versus placebo as add-on to existing antidiabetic therapy	HbA1c, fasting plasma glucose, and postprandial plasma glucose were reduced in the sitagliptin group. Sitagliptin also had a positive effect on lipid profile.

**Table 1: Summary of Included Randomized Controlled Trials**

Author and Year	Intervention(s) and Comparator(s)	Results and Conclusions
Barnett et al. (2013) <sup>6</sup>	Saxagliptin versus placebo as add-on therapy for patients inadequately controlled with insulin alone or insulin plus metformin	Mean change in HbA1c was greater in the saxagliptin group. Increase from baseline in mean total daily insulin dose was smaller in the saxagliptin group. The incidence of AEs was similar between groups.
Giampietro et al.(2013) <sup>7</sup>	Fixed-dose sitagliptin plus metformin versus sitagliptin as add-on to insulin	Combination therapy resulted in significant improvements in metabolic control, lipid profile, and decreased insulin requirements.
McGill et al. (2013) <sup>8</sup>	Linagliptin versus placebo as add-on to existing background therapy	Mean HbA1c was significantly lower in the linagliptin group. Mean insulin requirements were lower in the linagliptin group. Adverse event rates were similar between groups.
Yki-Jarvinen et al. (2013) <sup>9</sup>	Linagliptin versus placebo as add-on to existing background therapy	Change in HbA1c was significantly greater in the linagliptin group. Adverse event rates and hypoglycemia were similar between groups. Mean body weight remained the same.
Barnett et al. (2012) <sup>10</sup>	Saxagliptin versus placebo as add-on to insulin or insulin plus metformin	Reductions in HbA1c and postprandial glucose were significantly greater in the saxagliptin group. Adverse event rates and hypoglycemia were similar between groups.
Hong et al. (2012) <sup>11</sup>	Sitagliptin plus insulin versus increased insulin dose	Decrease in HbA1c was significantly greater in the sitagliptin group. Hypoglycemic events were less common and less severe in the sitagliptin group. Adverse event rates were similar between both groups.

## REFERENCES SUMMARIZED

## Health Technology Assessments

No literature identified.

## Systematic Reviews and Meta-analyses

1. Craddy P, Palin HJ, Johnson KI. Comparative effectiveness of dipeptidylpeptidase-4 inhibitors in type 2 diabetes: a systematic review and mixed treatment comparison. *Diabetes Ther.* 2014 Jun;5(1):1-41.  
[PubMed: PM24664619](#)

**OBJECTIVE: To compare the safety and efficacy of the dipeptidylpeptidase-4 (DPP-4) inhibitors in patients with type 2 diabetes and inadequate glycemic control.**

**DESIGN:** 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.

**DATA SOURCES:** MEDLINE, MEDLINE In-Process, EMBASE, and BIOSIS via Dialog ProQuest; Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews via EBSCO; four diabetes and two technical congress abstracts; and health technology assessment organization websites. **ELIGIBILITY CRITERIA: Patients with type 2 diabetes and inadequate glycemic control receiving any pharmacological anti-diabetic treatment.**

**DATA EXTRACTION AND ANALYSIS:** Title/abstracts were reviewed for eligibility, followed by full-text review of publications remaining after first pass. A three-person team filtered articles and an independent reviewer checked a random selection (10%) of filtered articles. Data extraction and quality assessment of studies were also independently reviewed. **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).** **RESULTS:** 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 (HbA1c) or body weight, or the proportions of patients achieving HbA1c <7% or experiencing a hypoglycemic event, apart from in patients on alogliptin plus metformin, who achieved HbA1c <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)].**

**CONCLUSIONS: 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.**

2. Goldenberg R. Insulin plus incretin agent combination therapy in type 2 diabetes: a systematic review. *Curr Med Res Opin.* 2014 Mar;30(3):431-45.  
[PubMed: PM24106875](#)

**BACKGROUND:** Insulin and incretin agents (dipeptidyl peptidase-4 inhibitors [DPP4is] and glucagon-like peptide-1 receptor agonists [GLP1 RAs]) are second-line treatment

options in patients with type 2 diabetes (T2D) not achieving glycemic targets with metformin. Combinations of insulin with incretin agents have been explored in randomized controlled trials (RCTs) and retrospective studies. However, the optimal approach is still elusive; numerous combination regimens can be envisioned, differing in composition and in order of addition. **SCOPE: A systematic survey was conducted of RCTs testing insulin/DPP4i or insulin/GLP1 RA regimens. PubMed and other online databases were queried using 'insulin' and the names of all incretin agents available in Canada, along with 'combination', 'concomitant', 'concurrent', and 'add-on'. Web of Science and clinicaltrials.gov were searched to identify unpublished trials. FINDINGS: Fifteen placebo-controlled or active-comparator RCTs were identified, reporting outcomes for regimens combining insulins and incretin agents available in Canada. DPP4i add-on to insulin therapy (six trials) leads to modest A1c lowering, with weight neutrality. GLP1 RA and insulin combination therapy (GLP1 RA add-on, five trials; insulin add-on, two trials) is associated with significant A1c lowering, with beneficial effects on body weight. A single proof-of-concept trial compared GLP1 RA to DPP4i add-on to insulin, and only one RCT examined simultaneous introduction of an incretin agent with insulin. Adding an incretin agent to established basal insulin therapy may represent a useful alternative to insulin intensification with prandial or premixed insulin. Initial introduction of an incretin agent, with subsequent introduction of insulin, offers potential practical advantages. No study directly comparing order of addition has yet been reported. CONCLUSIONS: Insulin/incretin combination therapy comprises a variety of efficacious, weight-sparing regimens and may be considered for many patients who do not achieve glycemic targets when treated with insulin or an incretin agent.**

3. Rizos EC, Ntzani EE, Papanas N, Tsimihodimos V, Mitrogianni Z, Maltezos E, et al. Combination therapies of DPP4 inhibitors and GLP1 analogues with insulin in type 2 diabetic patients: a systematic review. *Curr Vasc Pharmacol*. 2013 Nov;11(6):992-1000. [PubMed: PM22724475](#)

**OBJECTIVE:** The use of dipeptidyl-peptidase 4 (DPP4) inhibitors and glucagon like peptide 1 (GLP1) analogues for the treatment of diabetic mellitus (DM) type 2 is growing. Currently some of these agents have been approved in combination with insulin.

**METHODS:** We considered randomised controlled trials (RCTs) evaluating GLP1 analogues or DPP4 inhibitors combined with basal insulin in diabetic patients. We were limited to trials published in English language. **RESULTS:** PubMed search retrieved 207 items. After excluding irrelevant items we ended with **7 eligible studies with 1808 participants**. Mean baseline HbA1c was 8.5% and median follow up was 24 weeks. Exenatide combined with insulin was used in 2 studies; **DPP4 inhibitors were used in 5 studies (2 with sitagliptin, 1 with saxagliptin, 1 with vildagliptin and 1 with alogliptin)**. **CONCLUSION: Incretin-based therapies combined with basal insulin are able to reduce HbA1c by 0.5-0.7%. DPP4 inhibitors have no significant effect on weight, whereas GLP1 analogues reduced weight by 1-2 kg. Hypoglycaemia rates were generally comparable in all treatment groups.** These are promising results, but the available evidence is limited. This is a poorly investigated field with few RCTs. New studies focusing on head-to-head comparisons with short-acting insulin on top of basal insulin are needed.

4. Goossen K, Graber S. Longer term safety of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus: systematic review and meta-analysis. *Diabetes Obes Metab*. 2012 Dec;14(12):1061-72.

[PubMed: PM22519906](#)

Dipeptidyl peptidase-4 (DPP-4) inhibitors are oral antidiabetic agents that hold the potential of slowing the progress of type 2 diabetes mellitus. Their long-term safety is still a subject of debate. **A systematic review of randomized, controlled trials was undertaken to comprehensively profile the safety of chronic treatment of type 2 diabetes mellitus with DPP-4 inhibitors.** We searched data sources including MEDLINE, CENTRAL, publishers' and manufacturers' databases. **Eligible trials were double-blind, randomized, placebo or active-controlled trials with  $\geq 18$  weeks duration in patients with type 2 diabetes reporting safety outcomes.** Meta-analysis was performed separately for trials in which the control group received placebo (44 studies), another gliptin (3 studies) and any other antidiabetic drug (20 studies). Risk ratios with 95% confidence intervals were computed using a Mantel-Haenszel fixed-effect model for general safety outcomes, hypoglycaemia and adverse events by system organ class. Of 307 publications retrieved, **67 randomized, controlled trials met the eligibility criteria and were included in this review (4 alogliptin, 8 linagliptin, 8 saxagliptin, 20 sitagliptin, and 27 vildagliptin trials).** **Adverse events with gliptin treatment were at placebo level** (relative risk (RR) 1.02 [0.99, 1.04]). No increased risk of infections was detectable (RR 0.98 [0.93, 1.05] compared to placebo and 1.02 [0.97, 1.07] compared to other antidiabetic drugs). Asthenia (RR 1.57 [1.09, 2.27]) as well as cardiac (RR 1.37 [1.00, 1.89]) and vascular disorders (RR 1.74 [1.05, 2.86] for linagliptin) emerged as adverse events associated with DPP-4 inhibitor treatment. **The risk of hypoglycaemia was low with DPP-4 inhibitor treatment (RR 0.92 [0.74, 1.15] compared to placebo, RR 0.20 [0.17, 0.24] compared to sulphonylureas) in the absence of sulphonylurea or insulin co-therapy, but significantly elevated for combination therapy of sulphonylurea or insulin with sitagliptin or linagliptin (RR 1.86 [1.46, 2.37] compared to placebo).** **A large body of data supports the long-term safety of gliptin treatment and refutes an increased risk of infections.** Further research is needed to clarify a possible link to asthenia, cardiac and vascular events. For combination therapy with insulin or insulin secretagogues, a careful choice of the agent used may limit the risk of hypoglycaemia.

#### Randomized Controlled Trials

5. Derosa G, Ragonesi PD, Fogari E, Cicero AF, Bianchi L, Bonaventura A, et al. Sitagliptin added to previously taken antidiabetic agents on insulin resistance and lipid profile: a 2-year study evaluation. *Fundam Clin Pharmacol*. 2014 Apr;28(2):221-9.

[PubMed: PM23039403](#)

**The aim of this study was to evaluate whether the positive effects of sitagliptin on glycemic control and insulin resistance were maintained also after 2 years of therapy and whether sitagliptin could be effective also in improving lipid profile.** In this randomized, double-blind, placebo-controlled trial, 205 patients with type 2 diabetes in therapy with different antidiabetic drugs were randomized to add sitagliptin 100 mg once a day or placebo to their current therapy. We evaluated at the baseline and after 6, 12, 18, and 24 months the following parameters: body mass index, glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), postprandial plasma glucose (PPG), fasting plasma

insulin (FPI), homeostasis model assessment insulin resistance index (HOMA-IR), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (Tg). **Sitagliptin, added to previously taken antidiabetic agents, proved to be effective in improving glycemic profile, reducing HbA1c by -17.5%, FPG by -12.7%, PPG by -20.5%.** Regarding insulin resistance, sitagliptin decreased FPI by -8.3% and HOMA-IR by -20.0%, confirming that what have been already reported in short-term studies can be applied also after 2 years of treatment. Sitagliptin also reduced body weight by -4.3%. **Our study also showed the positive effect of sitagliptin on lipid profile; in particular, sitagliptin decreased TC by -13.3%, LDL-C by -20.4%, and Tg by -32.3%, and also increased HDL-C by + 13.6%.** Sitagliptin proved to be effective on glycemic profile and insulin resistance even after 2 years of therapy and to be effective in improving body weight and lipid profile.

6. Barnett AH, Charbonnel B, Li J, Donovan M, Fleming D, Iqbal N. Saxagliptin add-on therapy to insulin with or without metformin for type 2 diabetes mellitus: 52-week safety and efficacy. *Clin Drug Investig.* 2013 Oct;33(10):707-17.  
[PubMed: PM23949898](#)

**BACKGROUND:** Achievement of glycemic control is an important objective in the management of type 2 diabetes mellitus (T2DM). **OBJECTIVE:** **The objective of this study was to evaluate the safety and efficacy of the dipeptidyl peptidase-4 inhibitor saxagliptin versus placebo as add-on therapy in patients with T2DM inadequately controlled with insulin alone or insulin plus metformin.** **METHODS:** This was a long-term (28-week) extension of a short-term (24-week), randomized, double-blind, parallel-group trial of saxagliptin 5 mg once daily versus placebo as add-on therapy to open-label insulin or insulin plus metformin therapy totaling 52 weeks of treatment. In contrast with the goal of maintaining a stable insulin dosage during the short-term phase, **during the extension phase the insulin dosage was flexible and adjusted as deemed appropriate by the investigator.** The study was conducted in a clinical practice setting, including family practice and hospital sites. Patients with T2DM aged 18-78 years with glycated hemoglobin (HbA1c) 7.5-11 % on a stable insulin regimen (30-150 U/day with or without metformin) for  $\geq 8$  weeks at screening were included in the study. **Patients were stratified by metformin use and randomly assigned 2:1 to oral saxagliptin 5 mg (n = 304) or placebo (n = 151) once daily. All patients who completed the initial 24 weeks of treatment were eligible to participate in the 28-week extension, regardless of whether they had required rescue treatment. The main outcome measure was change in HbA1c from baseline to week 52.** **RESULTS:** **In general, the outcomes achieved at week 24 were sustained to week 52.** Adjusted mean change from baseline HbA1c at week 52 was greater with saxagliptin (-0.75 %) versus placebo (-0.38 %); the adjusted between-group difference was -0.37 % (95 % CI -0.55 to -0.19); between-group differences were similar in patients treated with metformin (-0.37 % [95 % CI -0.59 to -0.15]) and without metformin (-0.37 % [95 % CI -0.69 to -0.04]). **At week 52, a greater proportion of patients receiving saxagliptin achieved HbA1c <7 % than those receiving placebo (21.3 vs. 8.7 %; between-group difference 12.6 % [95 % CI 6.1-19.1]). The increase from baseline in mean total daily insulin dose at week 52 was numerically smaller with saxagliptin (5.67 vs 6.67 U with placebo; difference, -1.01 U [95 % CI -3.24 to 1.22]).** During the 52-week study period, the proportion of patients reporting  $\geq 1$  adverse event (AE) was 66.4 % with saxagliptin and 71.5 % with placebo, the majority being mild or moderate in intensity. The most common AEs ( $\geq 5$  % with saxagliptin or placebo) were urinary tract infection, nasopharyngitis, upper respiratory tract

infection, headache, influenza, and pain in extremity; the incidence of each AE was similar between treatment groups. **In the saxagliptin and placebo groups, the incidence of reported hypoglycemia was 22.7 and 26.5 %, respectively; the incidence of confirmed hypoglycemia (fingerstick glucose  $\leq$ 50 mg/dL [ $\leq$ 2.77 mmol/L] with characteristic symptoms) was 7.6 and 6.6 %, respectively.** Adjusted mean change from baseline body weight was +0.8 kg with saxagliptin and +0.5 kg with placebo. CONCLUSION: Saxagliptin 5 mg once daily as add-on to insulin, with or without concomitant metformin, produced a durable improvement in glycemetic control and was well tolerated over 52 weeks of treatment.

7. Giampietro O, Giampietro C, Bartola LD, Masoni MC, Matteucci E. Sitagliptin as add-on therapy in insulin deficiency: biomarkers of therapeutic efficacy respond differently in type 1 and type 2 diabetes. *Drug Des Devel Ther* [Internet]. 2013 [cited 2014 Jul 7] ;7:99-104. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3576885>  
[PubMed: PM23439744](#)

BACKGROUND: Sitagliptin has been proven to be effective and safe as add-on to insulin in adult patients with type 2 diabetes and absolute insulin deficiency. Recently, it has been suggested to extend the use of dipeptidyl-peptidase-4 inhibitors to type 1 diabetes. **The aim of this study was to evaluate and compare the effects of a long-term, fixed-dose combination of sitagliptin and metformin as add-on to insulin on body mass index, fasting plasma glucose, fructosamine, HbA(1c), lipids, and daily dose of insulin in both type 1 diabetes and insulin-treated type 2 diabetes.** METHODS: We recruited 25 patients with type 1 diabetes (mean age 51 +/- 10 years, mean disease duration 26 +/- 13 years) and **31 insulin-treated type 2 diabetic patients (mean age 66 +/- 8 years, mean disease duration 19 +/- 9 years), who received sitagliptin with metformin as a fixed-dose combination (50/1000 mg once or twice daily) or sitagliptin (100 mg once daily, if intolerant to metformin) in addition to ongoing insulin therapy for 46 +/- 19 weeks and 56 +/- 14 weeks, respectively.** RESULTS: After 21 +/- 9 weeks, patients with type 1 diabetes had a significantly lower body mass index, fasting plasma glucose, fructosamine, HbA(1c), and daily insulin requirement. After 49 +/- 17 weeks, they maintained their weight loss and total daily insulin dose and showed a significant reduction in low-density lipoprotein cholesterol levels, whereas their HbA(1c) had returned to baseline values. **In patients with type 2 diabetes, long-term treatment remained weight-neutral but had persistent beneficial effects on short-term, intermediate-term, and long-term biomarkers of metabolic control, as well as on low-density lipoprotein cholesterol levels and insulin requirement.** CONCLUSION: Clinical outcomes differed according to type of diabetes in terms of quality and over time. **In type 2 diabetes, the combination therapy significantly improved metabolic control and the lipid profile, and decreased insulin requirements, even in the absence of clinically significant weight loss.** In type 1 diabetes, the combined therapy only temporarily improved metabolic control, but significantly decreased body weight, low-density lipoprotein cholesterol levels, and insulin requirements.

8. McGill JB, Sloan L, Newman J, Patel S, Sauce C, von Eynatten M, et al. Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment: a 1-year, randomized, double-blind, placebo-controlled study. *Diabetes Care* [Internet]. 2013 Feb [cited 2014 Jul 7];36(2):237-44. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3554278>  
[PubMed: PM23033241](#)

**OBJECTIVE:** This placebo-controlled study assessed long-term efficacy and safety of the dipeptidyl peptidase-4 inhibitor linagliptin in patients with type 2 diabetes and severe renal impairment (RI). **RESEARCH DESIGN AND METHODS:** In this 1-year, double-blind study, 133 patients with type 2 diabetes (HbA(1c) 7.0-10.0%) and severe RI (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m(2)) at screening were randomized to linagliptin 5 mg (n = 68) or placebo (n = 65) once daily, added to existing background therapy. The primary efficacy end point was HbA(1c) change from baseline to week 12. Efficacy and safety end points were assessed after 1 year. **RESULTS:** At week 12, adjusted mean HbA(1c) decreased by -0.76% with linagliptin and -0.15% with placebo (treatment difference, -0.60%; 95% CI -0.89 to -0.31; P < 0.0001). HbA(1c) improvements were sustained with linagliptin (-0.71% over placebo (0.01%) at 1 year (treatment difference -0.72%, -1.03 to -0.41; P < 0.0001). Mean insulin doses decreased by -6.2 units with linagliptin and -0.3 units with placebo. Overall adverse event incidence was similar over 1 year (94.1 vs. 92.3%). Incidence of severe hypoglycemia with linagliptin and placebo was comparably low (three patients per group). Linagliptin and placebo had little effect on renal function (median change in eGFR, -0.8 vs. -2.2 mL/min/1.73 m(2)), and no drug-related renal failure occurred. **CONCLUSIONS:** In patients with type 2 diabetes and severe RI, linagliptin provided clinically meaningful improvements in glycemic control with very low risk of severe hypoglycemia, stable body weight, and no cases of drug-related renal failure. The potential for linagliptin to spare insulin and provide long-term renal safety warrants further investigations.

9. Yki-Jarvinen H, Rosenstock J, Duran-Garcia S, Pinnett S, Bhattacharya S, Thiemann S, et al. Effects of adding linagliptin to basal insulin regimen for inadequately controlled type 2 diabetes: a  $\geq$ 52-week randomized, double-blind study. *Diabetes Care* [Internet]. 2013 Dec [cited 2014 Jul 7];36(12):3875-81. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3836100>  
[PubMed: PM24062327](#)

**OBJECTIVE:** To evaluate the efficacy and long-term safety of linagliptin added to basal insulins in type 2 diabetes inadequately controlled on basal insulin with or without oral agents. **RESEARCH DESIGN AND METHODS:** A total of 1,261 patients (HbA1c  $\geq$ 7.0% [53 mmol/mol] to  $\leq$ 10.0% [86 mmol/mol]) on basal insulin alone or combined with metformin and/or pioglitazone were randomized (1:1) to double-blind treatment with linagliptin 5 mg once daily or placebo for  $\geq$ 52 weeks. The basal insulin dose was kept unchanged for 24 weeks but could thereafter be titrated according to fasting plasma glucose levels at the investigators' discretion. The primary end point was the mean change in HbA1c from baseline to week 24. The safety analysis incorporated data up to a maximum of 110 weeks. **RESULTS:** At week 24, HbA1c changed from a baseline of 8.3% (67 mmol/mol) by -0.6% (-6.6 mmol/mol) and by 0.1% (1.1 mmol/mol) with linagliptin and placebo, respectively (treatment difference -0.65% [95% CI -0.74 to -0.55] [-7.1 mmol/mol]; P < 0.0001). Despite the option

to uptitrate basal insulin, it was adjusted only slightly upward (week 52, linagliptin 2.6 IU/day, placebo 4.2 IU/day;  $P < 0.003$ ), resulting in no further HbA1c improvements. **Frequencies of hypoglycemia (week 24, linagliptin 22.0%, placebo 23.2%; treatment end, linagliptin 31.4%, placebo 32.9%) and adverse events (linagliptin 78.4%, placebo 81.4%) were similar between groups.** Mean body weight remained unchanged (week 52, linagliptin -0.30 kg, placebo -0.04 kg). **CONCLUSIONS: Linagliptin added to basal insulin therapy significantly improved glycaemic control relative to placebo without increasing hypoglycemia or body weight.**

10. Barnett AH, Charbonnel B, Donovan M, Fleming D, Chen R. Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin. *Curr Med Res Opin.* 2012 Apr;28(4):513-23.  
[PubMed: PM22313154](#)

**OBJECTIVE: To evaluate efficacy and safety of saxagliptin as add-on therapy in patients with type 2 diabetes (T2D) with inadequate glycaemic control on insulin alone or combined with metformin.** **METHODS: Adults (n = 455) with HbA(1c) 7.5-11% on stable insulin therapy (30-150 U/day +/- metformin) for at least 8 weeks were stratified by metformin use and randomly assigned 2:1 to receive saxagliptin 5 mg or placebo once daily for 24 weeks.** Patients were to maintain stable insulin doses but these could be decreased to reduce risk of hypoglycemia. Patients with hyperglycemia or substantially increased insulin use were rescued with a flexible insulin regimen and remained in the study. Metformin doses were kept stable. The primary efficacy endpoint was change in HbA(1c) from baseline to week 24 (or rescue). **RESULTS: Patients treated with saxagliptin versus placebo had significantly greater reductions in adjusted mean HbA(1c) (difference: -0.41%,  $p < 0.0001$ ), postprandial glucose (PPG) 180-minute area under the curve (-3829.8 mg.min/dL,  $p = 0.0011$ ), and 120-minute PPG (-23.0 mg/dL,  $p = 0.0016$ ) at 24 weeks. Treatment with saxagliptin resulted in similar reductions in HbA(1c) relative to placebo, irrespective of metformin treatment.** At 24 weeks, difference in adjusted mean fasting plasma glucose for saxagliptin versus placebo was -4.02 mg/dL ( $p = 0.3958$ ); 17.3% and 6.7% of patients in the saxagliptin and placebo groups, respectively, achieved HbA(1c)  $< 7\%$ . **Mean change from baseline in body weight at week 24 was 0.39 kg for saxagliptin and 0.18 kg for placebo. Hypoglycemia was reported in 18.4% and 19.9% of patients in the saxagliptin and placebo groups, respectively (confirmed hypoglycemia: 5.3%, 3.3%).** Other adverse events reported in at least 5% of patients were urinary tract infection (saxagliptin, placebo: 5.9%, 6.0%), influenza (3.0%, 6.6%), and pain in extremity (1.6%, 6.0%). **CONCLUSIONS: Saxagliptin 5-mg once-daily add-on therapy improves glycaemic control in T2D patients on insulin alone or combined with metformin and is generally well-tolerated.** NCT00757588

11. Hong ES, Khang AR, Yoon JW, Kang SM, Choi SH, Park KS, et al. Comparison between sitagliptin as add-on therapy to insulin and insulin dose-increase therapy in uncontrolled Korean type 2 diabetes: CSI study. *Diabetes Obes Metab.* 2012 Sep;14(9):795-802.  
[PubMed: PM22443183](#)

**AIM:** Individuals requiring insulin therapy for type 2 diabetes often require escalation of their regimen to achieve glycaemic control. Optimal management strategies for uncontrolled type 2 diabetes would improve glycaemic control without hypoglycaemia and weight gain. This study compared the efficacy and tolerability of adding sitagliptin, an oral

dipeptidyl peptidase-4 inhibitor, and an up to 20% increase in insulin dose in patients with uncontrolled type 2 diabetes on insulin therapy. **METHODS: We conducted a 24-week, randomized, active-competitor, parallel-group study in subjects with uncontrolled type 2 diabetes [haemoglobin A1c (HbA1c) = 7.5-11%] currently using insulin therapy. Subjects were randomly assigned to either the sitagliptin adding (100 mg daily, n = 70) or an insulin-increasing arm ( $\geq 10\%$  at week 12 and  $\geq 10\%$  at week 24, n = 70) while continuing other medications. RESULTS: Average baseline HbA1c was 9.2% in both groups. HbA1c decreased more at 24 weeks in the sitagliptin adding than the insulin-increasing arm ( $-0.6 \pm 0.1\%$  vs.  $-0.2 \pm 0.1\%$ ,  $p < 0.01$ ). Insulin was increased by 25% at 24 weeks in the insulin-increasing group. Hypoglycaemic events were less common and less severe in sitagliptin adding arm than insulin-increasing arm (7.0 vs. 14.3 events per patient-year,  $p < 0.05$ ). Weight was stable in the sitagliptin adding subjects ( $68.6 \pm 11.6$  vs.  $68.1 \pm 11.4$  kg) but increased in the insulin-increasing subjects ( $66.2 \pm 10.6$  vs.  $67.4 \pm 9.7$  kg,  $p < 0.05$ ). Other adverse events occurred at similar rates in both arms. CONCLUSIONS: Compared to a 25% increase in insulin dose, adding sitagliptin to an insulin-based regimen was more effective at lowering HbA1c and associated with less hypoglycaemia and weight gain over 24 weeks. Clinical trial number: NCT01100125**

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**APPENDIX – FURTHER INFORMATION:****Review Articles**

12. Ahren B. Insulin plus incretin: A glucose-lowering strategy for type 2-diabetes. *World J Diabetes* [Internet]. 2014 Feb 15 [cited 2014 Jul 7];5(1):40-51. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3932426>  
[PubMed: PM24567800](#)

There are many advantages of combining incretin therapy [glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors] with insulin therapy as a glucose-lowering strategy in type 2 diabetes. One important advantage is the complementary mode of the mechanistic action of incretin and insulin therapy. Another advantage is the reduction in risk of hypoglycemia and weight gain when adding incretin therapy to insulin. Several clinical trials have studied the addition of GLP-1 receptor agonists [exenatide BID (twice daily), lixisenatide, albiglutide] or DPP-4 inhibitors (vildagliptin, sitagliptin, saxagliptin, alogliptin, linagliptin) to ongoing insulin therapy or adding insulin to ongoing therapy with a GLP-1 receptor agonist (liraglutide). These studies show improved glycemia in the presence of limited risk for hypoglycemia and weight gain with the combination of incretin therapy with insulin. This article reviews the background and clinical studies on this combination.

13. Khachikian D. Drug class review: dipeptidyl-peptidase 4 (DPP-4) inhibitors [Internet]. Washington (DC): U.S. Department of Veterans Affairs; 2014 [cited 2014 Jul 7]. Available from: [http://www.pbm.va.gov/PBM/clinicalguidance/drugclassreviews/DPP4\\_inhibitor\\_Drug\\_Class\\_Review.docx](http://www.pbm.va.gov/PBM/clinicalguidance/drugclassreviews/DPP4_inhibitor_Drug_Class_Review.docx)  
-click on cancel when prompted for password  
See: *Combination with Insulin, page 5*
14. Meece JD, Pearson TL, Siminerio LM. Complementary Approaches to Improving Glucose Control-Insulin and Incretins: Patient Case Studies in Action. *Diabetes Educ*. 2014 May 19;40(1 suppl):4S-26S.  
[PubMed: PM24841710](#)

**PURPOSE:** The use of insulin and incretin-based therapies together has recently emerged as a new therapeutic option for patients with type 2 diabetes. This approach can be used across the continuum of diabetes and is supported by clinical trial evidence. To illustrate how these data may apply to clinical care, this supplement uses patient case studies to provide clinical context for diabetes educators. Relevant medical literature was searched and cited. Search terms included insulin, DPP-4 inhibitors, GLP-1 receptor agonists, hypoglycemia, and weight gain. **CONCLUSION:** Insulin remains the most potent glucose-lowering agent available for the treatment of type 2 diabetes but has limitations, primarily of hypoglycemia and secondarily of weight gain. The addition of incretin-based therapies complements the glucose-lowering potential of basal insulin, without increasing the risk of hypoglycemia, potentially allowing for lower doses of insulin and without increasing weight gain (DPP-4 inhibitors) or possibly with weight loss (GLP-1 receptor agonists). Incretin-based therapies offer advantages over prandial insulin to address postprandial hyperglycemia.

15. Maxwell LG, McFarland MS. Clinical utility and tolerability of linagliptin in diabetic patients. *Drug Healthc Patient Saf* [Internet]. 2013 [cited 2014 Jul 7];5:67-78. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3617918>  
[PubMed: PM23576884](#)

**BACKGROUND:** The purpose of this paper is to review the efficacy, safety, and tolerability of linagliptin in the management of hyperglycemia in adults with type 2 diabetes mellitus. **METHODS:** A Medline search was performed using the keywords "linagliptin" and "type 2 diabetes" for articles published September 2010 through July 2012. The literature search was limited by the following criteria: articles' publication in the English language, clinical trials, randomized controlled trials, and research conducted in humans. **RESULTS:** A review of the data for linagliptin in the treatment of type 2 diabetes as monotherapy or in combination with other antidiabetic therapies suggests clinical efficacy in terms of reductions in glycosylated hemoglobin, fasting plasma glucose, and postprandial glucose. Most adverse events with linagliptin are considered to be mild to moderate in nature. Although linagliptin therapy may offer a low risk of hypoglycemia, the risk increases when it is used in combination with insulin secretagogues. Linagliptin can generally be considered weight neutral, but a weight increase was observed when linagliptin was used in combination with a thiazolidinedione. **CONCLUSION:** Linagliptin is a once-daily oral medication used for the treatment of type 2 diabetes. The use of linagliptin as monotherapy or in combination with metformin, sulfonylureas, or pioglitazone led to improvement in glycemic control and was well tolerated by most patients.

16. Scheen AJ. DPP-4 inhibitors in the management of type 2 diabetes: a critical review of head-to-head trials. *Diabetes Metab*. 2012 Apr;38(2):89-101.  
[PubMed: PM22197148](#)

Dipeptidyl peptidase-4 (DPP-4) inhibitors offer new options for the management of type 2 diabetes. Direct comparisons with active glucose-lowering comparators in drug-naïve patients have demonstrated that DPP-4 inhibitors exert slightly less pronounced HbA(1c) reduction than metformin (with the advantage of better gastrointestinal tolerability) and similar glucose-lowering effects as with a thiazolidinedione (TZD; with the advantage of no weight gain). In metformin-treated patients, gliptins were associated with similar HbA(1c) reductions compared with a sulphonylurea (SU; with the advantage of no weight gain, considerably fewer hypoglycaemic episodes and no need for titration) and a TZD (with the advantage of no weight gain and better overall tolerability). DPP-4 inhibitors also exert clinically relevant glucose-lowering effects compared with a placebo in patients treated with SU or TZD (of potential interest when metformin is either not tolerated or contraindicated), and as oral triple therapy with a good tolerability profile when added to a metformin-SU or pioglitazone-SU combination. Several clinical trials also showed a consistent reduction in HbA(1c) when DPP-4 inhibitors were added to basal insulin therapy, with no increased risk of hypoglycaemia. Because of the complex pathophysiology of type 2 diabetes and the complementary actions of glucose-lowering agents, initial combination of a DPP-4 inhibitor with either metformin or a glitazone may be applied in drug-naïve patients, resulting in greater efficacy and similar safety compared with either drug as monotherapy. However, DPP-4 inhibitors were less effective than GLP-1 receptor agonists for reducing HbA(1c) and body weight, but offer the advantage of being easier to use (oral instead of injected administration) and lower in cost. Only one head-to-head trial demonstrated the non-inferiority of saxagliptin vs sitagliptin. Clearly, more trials of direct comparisons between different incretin-based therapies are needed.

Because of their pharmacokinetic characteristics, pharmacodynamic properties (glucose-dependent glucose-lowering effect) and good overall tolerability profile, DPP-4 inhibitors may have a key role to play in patients with renal impairment and in the elderly. The role of DPP-4 inhibitors in the therapeutic armamentarium of type 2 diabetes is rapidly evolving as their potential strengths and weaknesses become better defined mainly through controlled clinical trials.

17. Yang LP. Saxagliptin: a review of its use as combination therapy in the management of type 2 diabetes mellitus in the EU. *Drugs*. 2012 Jan 22;72(2):229-48.  
[PubMed: PM22221000](#)

Saxagliptin (Onglyza) is a dipeptidyl peptidase 4 inhibitor widely approved for the treatment of type 2 diabetes mellitus. In the EU, saxagliptin is indicated as combination therapy with metformin, a sulfonylurea, a thiazolidinedione, or insulin (with or without metformin) for the treatment of adult patients with type 2 diabetes, including those with mild to severe renal impairment. This article reviews the clinical efficacy and tolerability of add-on saxagliptin therapy in patients with type 2 diabetes, in line with its approved indications in the EU, and summarizes the drug's pharmacological properties. The clinical efficacy of saxagliptin 5 mg/day in combination with metformin, glibenclamide (glyburide), a thiazolidinedione, or insulin (with or without metformin) has been demonstrated in several randomized, double-blind, placebo-controlled, multicentre, phase III trials (18-104 weeks in duration) in patients with type 2 diabetes. In these trials, glycosylated haemoglobin (HbA(1c)) was changed from baseline (primary endpoint) by a greater extent with add-on saxagliptin 5 mg/day (-1.09% to +0.03%) than with comparator regimens (-0.44% to +0.69%). Two other randomized, double-blind trials showed that saxagliptin 5 mg/day as add-on therapy to metformin was noninferior to uptitrated glipizide in terms of lowering HbA(1c) (-0.74% vs -0.80%) at 52 weeks, or sitagliptin (-0.52% vs -0.62%) at 18 weeks. Saxagliptin 2.5 mg/day as add-on to existing anti-diabetic therapy was also effective for up to 52 weeks in a randomized, double-blind, placebo-controlled, multicentre trial in patients with type 2 diabetes and renal impairment (HbA(1c) was reduced by 1.08% vs 0.36%;  $p \leq 0.007$ ). Saxagliptin as add-on therapy for up to 4 years was generally well tolerated in clinical trials. Treatment with saxagliptin did not increase the risk of hypoglycaemia or cardiovascular outcomes relative to placebo or active comparators, and was generally weight neutral. In conclusion, saxagliptin is a useful option as add-on therapy to metformin, a sulfonylurea, a thiazolidinedione, or insulin (with or without metformin) in patients with type 2 diabetes who require combination therapy.