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DERP VI Update #3 Scan #1: Newer Diabetes Medications and Combinations

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Objectives

The purpose of this literature scan is to preview the volume and nature of new research that has emerged since the last full review on newer diabetes medications and combinations. The literature search for this scan focuses on new randomized controlled trials (RCTs) and systematic reviews, as well as actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Comprehensive searches, quality assessment, and synthesis of evidence would follow only if DERP participating organizations agreed to proceed with an update of either the full report or another research product.

Topic History

Update #3: October 2017, searches through May 12, 2017

Update Report #2: July 2016

Streamlined Update Report #1: June 2014

Original Report: February 2011

Background and Context

The 2018 American Diabetes Association treatment guidelines recommend a hemoglobin A1c (HbA1c) goal of less than 7% for most nonpregnant adults to prevent adverse microvascular and macrovascular outcomes.¹ The guidelines acknowledge that less stringent (HbA1c < 8%) or more stringent (HbA1c < 6.5%) goals could be appropriate for certain populations.¹

Pharmacological options for type 2 diabetes include sulfonylureas, biguanides, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin.² Because of the progressive nature of diabetes, practitioners and patients often experience challenges in reaching and sustaining treatment goals.² Patients with type 2 diabetes often require more than 1 type of diabetes medication to achieve glycemic control. Within recent years, several new antihyperglycemic agents have been approved.² These agents offer mechanisms of glycemic control beyond that of traditional oral agents and insulin by targeting alternate gluco-regulatory receptors and hormones such as amylin, GLP-1, glucose-dependent insulinotropic peptide (GIP), DPP-4, and sodium-glucose cotransporter 2 (SGLT2).²

Key Questions

1. What is the evidence from randomized controlled trials that newer diabetes medications reduce the risk of cardiovascular events, including mortality, in adults with type 2 diabetes mellitus?
 - a. Does the effect differ when used as monotherapy versus combination therapy?
 - b. Does the effect differ in patients with and without prior cardiovascular disease?

- c. Is there evidence of a class effect?
2. What is the comparative efficacy and effectiveness of newer diabetes medications used as monotherapy and drug combinations (administered as fixed-dose combination products or dual therapy) for adults with type 2 diabetes mellitus?
 - a. What is the comparative efficacy and effectiveness of newer diabetes medications within and across classes?
 - b. How does the efficacy and effectiveness of newer diabetes medications compare between monotherapy and combination (add-on) therapy of newer diabetes medications?
3. What are the comparative harms of newer diabetes medications for adults with type 2 diabetes mellitus?
 - a. How do adverse event outcomes of newer diabetes medications compare with each other within and across classes?
 - b. How do adverse event outcomes of newer diabetes medications compare to monotherapy and combination (add-on) therapy with newer diabetes medications?
4. Are there subgroups of patients based on demographics (e.g., age, racial groups, gender), comorbidities (e.g., drug-disease interactions, obesity), or other medications (drug-drug interactions) for which newer diabetes medications and drug combinations (administered as fixed-dose combination products or dual therapy) differ in efficacy/effectiveness or tolerability and frequency of adverse events?

Inclusion Criteria

Using the PICO outlined below, we screened our search results for eligible systematic reviews and meta-analyses and RCTs published since the execution of the search strategy in the most recent update review, which occurred on May 12, 2017. We only included systematic reviews that had search strategies and eligible RCTs published after May 12, 2017.

Population

Adults with type 2 diabetes

Interventions

Table 1. Included Interventions

Class	Generic Names	Brand Names	FDA Approval Date
Oral Drugs			
SGLT2 Inhibitors	Empagliflozin	Jardiance	8/1/14
	Dapagliflozin	Farxiga	1/8/14
	Canagliflozin	Invokana	3/29/13

Class	Generic Names	Brand Names	FDA Approval Date
DPP-4 Inhibitors	Alogliptin	Nesina	1/25/13
	Linagliptin	Tradjenta	5/2/11
	Saxagliptin	Onglyza	7/31/09
	Sitagliptin	Januvia	10/16/06
Fixed-Dose Combination Products of Oral Drugs			
SGLT2 Inhibitor with DPP-4 Inhibitor	Dapagliflozin-saxagliptin	Qtern	2/27/17
	Empagliflozin-linagliptin	Glyxambi	1/30/15
SGLT2 Inhibitor with Metformin	Empagliflozin-metformin ER	Synjardy XR	12/9/16
	Canagliflozin-metformin ER	Invokamet XR	9/20/16
	Empagliflozin-metformin	Synjardy	8/26/15
	Dapagliflozin-metformin ER	Xigduo XR	10/29/14
	Canagliflozin-metformin	Invokamet	8/8/14
DPP-4 Inhibitor with TZD	Alogliptin-pioglitazone	Oseni	1/25/13
DPP-4 Inhibitor with Metformin	Linagliptin-metformin ER	Jentadueto XR	5/27/16
	Alogliptin-metformin	Kazano	1/25/13
	Sitagliptin XR-metformin	Janumet XR	2/2/12
	Linagliptin-metformin	Jentadueto	1/30/12
	Saxagliptin-metformin ER	Kombiglyze XR	11/5/10
	Sitagliptin-metformin	Janumet	3/30/07
Subcutaneous Injection Drugs			
GLP-1 Agonists	Lixisenatide	Adlyxin	7/27/16
	Dulaglutide	Trulicity	9/18/14
	Albiglutide	Tanzeum	4/15/14
	Exenatide XR	Bydureon	1/27/12
	Liraglutide	Victoza	1/25/10
	Exenatide	Byetta	4/28/05
GLP-1 Agonist with Long-acting Insulin	Liraglutide-insulin degludec U100/3.6mg	Xultophy	11/21/16
	Lixisenatide-insulin glargine U100/33mg	Soliqua	11/21/16

Comparators

- Other newer diabetes medications (head-to-head comparisons)
- Head-to-head comparisons of combinations or add-on therapy versus monotherapy
- Metformin (versus mono- or dual therapy with at least 1 newer diabetes medication)
- Included drug versus long-acting insulin monotherapy (add-on treatment) using fixed-ratio combination product
- For Key Question 1, placebo comparisons are also eligible

Outcomes

Efficacy and Effectiveness

- Mortality (all-cause and cardiovascular-related)
- Cardiovascular outcomes (fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, hospitalization for heart failure)
- HbA1c
- Body weight

Harms

- Adverse events (adverse drug reactions, hypoglycemia, other)
- Serious adverse events
- Withdrawals due to adverse events

Methods

We searched the FDA website to identify newly approved drugs, new indications, and new serious harms (e.g., boxed warnings) for included interventions. To identify new drugs, we also searched CenterWatch, a privately owned database of clinical trials information, and conducted an internet search using Google. To identify relevant literature, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from July 12, 2017, to August 15, 2018, using terms for included drugs and limits for English language and humans. We also conducted an internet search using Google and Google Scholar with key words for included drugs.

Findings

New Drugs or Formulations

Table 2. Newly Approved Drugs and Formulations

Class Route of Administration	Generic Name (Brand Name)	FDA Approval Date Indications
SGLT2 inhibitor Oral	Ertugliflozin (Steglatro)	12/19/17 Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
SGLT2 inhibitor + metformin Oral, fixed-dose combination product	Ertugliflozin- metformin (Segluromet)	12/19/17 Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus that is not adequately controlled on a regimen containing ertugliflozin or metformin, or in patients who are already treated with both ertugliflozin and metformin

Class Route of Administration	Generic Name (Brand Name)	FDA Approval Date Indications
GLP-1 agonists Subcutaneous injection	Semaglutide (Ozempic)	12/5/17 Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

New Indications

In August 2017, the FDA approved an update to the liraglutide product label to include an indication to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease.³

New Serious Harms

In May 2017, the FDA began requiring a boxed warning to be added to the canagliflozin drug label to describe the increased risk of leg and foot amputations.⁴

Systematic Reviews

We identified 12 new systematic reviews with searches conducted after May 12, 2017.⁵⁻¹⁶ Only 4 of these included RCTs published after that date (Table 3).¹⁷⁻²⁰ One review focused on cardiovascular outcomes,¹⁷ and the others focused on other efficacy and safety outcomes.¹⁸⁻²⁰

Table 3. New Systematic Reviews of Newer Diabetes Drugs

Author, Year	Included Studies	Comparisons	Primary Outcomes
Bethel et al., 2018 ¹⁷	4 RCTs	GLP-1 receptor agonists compared with placebo	Cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke
Palanisamy et al., 2018 ¹⁸	72 RCTs	Oral antidiabetic agents approved by the FDA from 2013 to 2017	HbA1c, weight, and adverse events
Shi et al., 2018 ¹⁹	9 RCTs	Semaglutide compared to placebo or other therapies	HbA1c, weight, and adverse events
Witkowski et al., 2018 ²⁰	75 RCTs (network meta-analysis)	Semaglutide compared to other GLP-1 agonists	HbA1c, weight, and adverse events

RCTs

We identified 5 RCTs published after May 12, 2017 (Table 4).²¹⁻²⁵ Only 1 of these reported cardiovascular outcomes.²² In this study, 14,752 participants with type 2 diabetes, of whom 73.1% had previous cardiovascular disease, were randomized to extended-release exenatide injection 2 mg once per week or a weekly placebo injection.²² The primary outcome was the first occurrence of any component of the composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.²²

Table 4. New RCTs of Newer Diabetes Drugs

Author, Year Study Name	Population Sample Size (N)	Intervention and Comparators	Outcomes Follow-up Duration
Ahmann et al., 2018 ²¹ SUSTAIN 3 NCT01885208	Adults with type 2 diabetes N = 813	Semaglutide 1.0 mg Extended-release exenatide 2.0 mg	Change from baseline in HbA1c, body weight, and adverse effects after 56 weeks
Holman et al., 2017 ²² EXSCEL NCT01144338	Adults with type 2 diabetes (73% had previous cardiovascular disease) N = 14,752	Extended-release exenatide 2 mg Placebo	Composite of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke after 56 weeks
Seino et al., 2017 ²⁵ NCT02254291	Japanese adults with type 2 diabetes treated with diet and exercise only or oral antidiabetic drug monotherapy (washed out during the run-in period) N = 308	Semaglutide .5 mg or 1.0 mg once weekly Sitagliptin 100 mg once daily	Treatment-emergent adverse events after 30 weeks
Pratley et al., 2018a ²⁴ NCT02099110	Adults with type 2 diabetes on metformin monotherapy N = 1232	Ertugliflozin 5 or 15 mg per day Sitagliptin 100 mg per day Ertugliflozin plus sitagliptin	Change from baseline in HbA1c after 26 weeks
Pratley et al., 2018b ²³ SUSTAIN 7 NCT02648204	Adults with type 2 diabetes on metformin monotherapy N = 1201	Semaglutide .5 mg Dulaglutide .75 mg Semaglutide 1 mg Dulaglutide 1.5 mg Once weekly	Change from baseline in HbA1c and change in body weight after 40 weeks

We also identified 1 new subgroup analysis from the EMPA-REG OUTCOME trial, a placebo-controlled trial of empagliflozin that was previously included.²⁶ The analysis compared the relative effects of empagliflozin on cardiovascular outcomes in women compared to men.²⁶

Summary

Since the last update report on this topic, we have identified:

- 3 new products
 - Ertugliflozin (Steglatro)
 - Ertugliflozin-metformin (Segluromet)
 - Semaglutide (Ozempic)
- 1 new indication for an existing product (Victoza [liraglutide])
- 1 new FDA boxed warning
- 4 new systematic reviews, 1 with cardiovascular outcomes
- 5 new RCTs, 1 with cardiovascular outcomes (exenatide vs. placebo)
- 1 new subgroup analyses of an RCT previously included

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Appendix A. Abstracts of Relevant Studies

Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. *Diabetes Care*. 2018;41(2):258-266.

OBJECTIVE: To compare the efficacy and safety of once-weekly semaglutide 1.0 mg s.c. with exenatide extended release (ER) 2.0 mg s.c. in subjects with type 2 diabetes. **RESEARCH DESIGN AND METHODS:** In this phase 3a, open-label, parallel-group, randomized controlled trial, 813 subjects with type 2 diabetes taking oral antidiabetic drugs were randomized (1:1) to semaglutide 1.0 mg or exenatide ER 2.0 mg for 56 weeks. The primary end point was change from baseline in HbA1c at week 56. **RESULTS:** Mean HbA1c (8.3% [67.7 mmol/mol] at baseline) was reduced by 1.5% (16.8 mmol/mol) with semaglutide and 0.9% (10.0 mmol/mol) with exenatide ER (estimated treatment difference vs. exenatide ER [ETD] -0.62% [95% CI -0.80, -0.44] [-6.78 mmol/mol (95% CI -8.70, -4.86)]; $P < 0.0001$ for noninferiority and superiority). Mean body weight (95.8 kg at baseline) was reduced by 5.6 kg with semaglutide and 1.9 kg with exenatide ER (ETD -3.78 kg [95% CI -4.58, -2.98]; $P < 0.0001$). Significantly more subjects treated with semaglutide (67%) achieved HbA1c $<7.0\%$ (<53 mmol/mol) versus those taking exenatide ER (40%). Both treatments had similar safety profiles, but gastrointestinal adverse events were more common in semaglutide-treated subjects (41.8%) than in exenatide ER-treated subjects (33.3%); injection-site reactions were more frequent with exenatide ER (22.0%) than with semaglutide (1.2%). **CONCLUSIONS:** Semaglutide 1.0 mg was superior to exenatide ER 2.0 mg in improving glycemic control and reducing body weight after 56 weeks of treatment; the drugs had comparable safety profiles. These results indicate that semaglutide treatment is highly effective for subjects with type 2 diabetes who are inadequately controlled on oral antidiabetic drugs.

Bethel MA, Patel RA, Merrill P, et al. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. *Lancet Diabetes Endocrinol*. 2018;6(2):105-113.

BACKGROUND: Glucagon-like peptide-1 (GLP-1) receptor agonists are effective glucose-lowering drugs. Findings from cardiovascular outcome trials showed cardiovascular safety of GLP-1 receptor agonists, but results for cardiovascular efficacy were varied. We aimed to examine overall cardiovascular efficacy for lixisenatide, liraglutide, semaglutide, and extended-release exenatide.

METHODS: In this systematic review and meta-analysis, we analysed data from eligible trials that assessed the safety and efficacy of GLP-1 receptor agonists compared with placebo in adult patients (aged 18 years or older) with type 2 diabetes and had a primary outcome including, but not limited to, cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke. We searched PubMed and MEDLINE without language restrictions up to Sept 18, 2017, for eligible trials. We did a meta-analysis of available trial data using a random-effects model to calculate

overall hazard ratios (HRs) for cardiovascular efficacy outcomes and odds ratios for key safety outcomes.

FINDINGS: Of 12 articles identified in our search and screened for eligibility, four trials of cardiovascular outcomes of GLP-1 receptor agonists were identified: ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN 6 (semaglutide), and EXSCEL (extended-release exenatide). Compared with placebo, GLP-1 receptor agonist treatment showed a significant 10% relative risk reduction in the three-point major adverse cardiovascular event primary outcome (cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke; HR 0.90, 95% CI 0.82-0.99; $p=0.033$), a 13% RRR in cardiovascular mortality (0.87, 0.79-0.96; $p=0.007$), and a 12% relative risk reduction in all-cause mortality (0.88, 0.81-0.95; $p=0.002$), with low-to-moderate between-trial statistical heterogeneity. No significant effect of GLP-1 receptor agonists was identified on fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, hospital admission for unstable angina, or hospital admission for heart failure. Overall, no significant differences were seen in severe hypoglycaemia, pancreatitis, pancreatic cancer, or medullary thyroid cancer reported between GLP-1 receptor agonist treatment and placebo.

INTERPRETATION: Our findings show cardiovascular safety across all GLP-1 receptor agonist cardiovascular outcome trials and suggest that drugs in this class can reduce three-point major adverse cardiovascular events, cardiovascular mortality, and all-cause mortality risk, albeit to varying degrees for individual drugs, without significant safety concerns. GLP-1 receptor agonists have a favourable risk-benefit balance overall, which should allow the choice of drug to be individualised to each patient's needs.

FUNDING: Amylin Pharmaceuticals (AstraZeneca).

Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2017;377(13):1228-1239.

BACKGROUND: The cardiovascular effects of adding once-weekly treatment with exenatide to usual care in patients with type 2 diabetes are unknown.

METHODS: We randomly assigned patients with type 2 diabetes, with or without previous cardiovascular disease, to receive subcutaneous injections of extended-release exenatide at a dose of 2 mg or matching placebo once weekly. The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The coprimary hypotheses were that exenatide, administered once weekly, would be noninferior to placebo with respect to safety and superior to placebo with respect to efficacy.

RESULTS: In all, 14,752 patients (of whom 10,782 [73.1%] had previous cardiovascular disease) were followed for a median of 3.2 years (interquartile range, 2.2 to 4.4). A primary composite outcome event occurred in 839 of 7356 patients (11.4%; 3.7 events per 100 person-years) in the exenatide group and in 905 of 7396 patients (12.2%; 4.0 events per 100 person-years) in the

placebo group (hazard ratio, 0.91; 95% confidence interval [CI], 0.83 to 1.00), with the intention-to-treat analysis indicating that exenatide, administered once weekly, was noninferior to placebo with respect to safety ($P < 0.001$ for noninferiority) but was not superior to placebo with respect to efficacy ($P = 0.06$ for superiority). The rates of death from cardiovascular causes, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, hospitalization for heart failure, and hospitalization for acute coronary syndrome, and the incidence of acute pancreatitis, pancreatic cancer, medullary thyroid carcinoma, and serious adverse events did not differ significantly between the two groups.

CONCLUSIONS: Among patients with type 2 diabetes with or without previous cardiovascular disease, the incidence of major adverse cardiovascular events did not differ significantly between patients who received exenatide and those who received placebo. (Funded by Amylin Pharmaceuticals; EXSCEL ClinicalTrials.gov number, NCT01144338 .).

Palanisamy S, Yien ELH, Shi LW, et al. Systematic review of efficacy and safety of newer antidiabetic drugs approved from 2013 to 2017 in controlling HbA1c in diabetes patients. *Pharmacy*. 2018;6(3):27.

Type 2 Diabetes Mellitus (T2DM) is the most common form of diabetes mellitus and accounts for about 95% of all diabetes cases. Many newer oral as well as parenteral antidiabetic drugs have been introduced in to the market in recent years to control hyperglycemic conditions in diabetes patients and many of these drugs produce potential side effects in diabetes patients. Hence, this systematic review was aimed to analyze and compare the efficacy and safety of oral antidiabetic agents in controlling HbA1c in T2DM patients, that were approved by the United States-Food and Drug Administration (US-FDA) from 2013 to 2017. All randomized controlled, double-blind trials published in English during the search period involving the newer antidiabetic agents were selected. In the outcome assessment comparison, semaglutide demonstrated the highest efficacy in lowering HbA1c, with a 1.6% reduction ($p < 0.0001$) when given at a dose of 1.0 mg. The safety profile of all the agents as compared to placebo or control were similar, with no or slight increase in the occurrence of adverse events (AEs) but no fatal reaction was reported. The most common AEs of all the antidiabetic agents were gastrointestinal in nature, with several cases of hypoglycemic events. However, among all these agents, semaglutide seems to be the most efficacious drug to improve glycemic control in terms of HbA1c. Alogliptin has the least overall frequency of AEs compared to other treatment groups.

Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol*. 2018;6(4):275-286.

BACKGROUND: Despite common mechanisms of actions, glucagon-like peptide-1 receptor agonists differ in structure, pharmacokinetic profile, and clinical effects. This head-to-head trial compared semaglutide with dulaglutide in patients with inadequately controlled type 2

diabetes. **METHODS:** This was an open-label, parallel-group, phase 3b trial done at 194 hospitals, clinical institutions or private practices in 16 countries. Eligible patients were aged 18 years or older and had type 2 diabetes with HbA1c 7.0-10.5% (53.0-91.0 mmol/mol) on metformin monotherapy. Patients were randomly assigned (1:1:1) by use of an interactive web-response system to once a week treatment with either semaglutide 0.5 mg, dulaglutide 0.75 mg, semaglutide 1.0 mg, or dulaglutide 1.5 mg subcutaneously. The primary endpoint was change from baseline in percentage HbA1c; the confirmatory secondary endpoint was change in bodyweight, both at week 40. The primary analysis population included all randomly assigned patients exposed to at least one dose of trial product obtained while on treatment and before the onset of rescue medication. The safety population included all randomly assigned patients exposed to at least one dose of trial product obtained while on treatment. The trial was powered for HbA1c non-inferiority (margin 0.4%) and bodyweight superiority. This trial is registered with ClinicalTrials.gov, number NCT02648204. **FINDINGS:** Between Jan 6, 2016, and June 22, 2016, 1201 patients were randomly assigned to treatment; of these, 301 were exposed to semaglutide 0.5 mg, 299 to dulaglutide 0.75 mg, 300 to semaglutide 1.0 mg, and 299 to dulaglutide 1.5 mg. 72 (6%) patients withdrew from the trial (22 receiving semaglutide 0.5 mg, 13 receiving dulaglutide 0.75 mg, 21 receiving semaglutide 1.0 mg, and 16 receiving dulaglutide 1.5 mg). From overall baseline mean, mean percentage HbA1c was reduced by 1.5 (SE 0.06) percentage points with semaglutide 0.5 mg versus 1.1 (0.05) percentage points with dulaglutide 0.75 mg (estimated treatment difference [ETD] -0.40 percentage points [95% CI -0.55 to -0.25]; $p < 0.0001$) and by 1.8 (0.06) percentage points with semaglutide 1.0 mg versus 1.4 (0.06) percentage points with dulaglutide 1.5 mg (ETD -0.41 percentage points [-0.57 to -0.25]; $p < 0.0001$). From overall baseline mean, mean bodyweight was reduced by 4.6 kg (SE 0.28) with semaglutide 0.5 mg compared with 2.3 kg (0.27) with dulaglutide 0.75 mg (ETD -2.26 kg [-3.02 to -1.51]; $p < 0.0001$) and by 6.5 kg (0.28) with semaglutide 1.0 mg compared with 3.0 kg (0.27) with dulaglutide 1.5 mg (ETD -3.55 kg [-4.32 to -2.78]; $p < 0.0001$). Gastrointestinal disorders were the most frequently reported adverse event, occurring in 129 (43%) of 301 patients receiving semaglutide 0.5 mg, 133 (44%) of 300 patients receiving semaglutide 1.0 mg, 100 (33%) of 299 patients receiving dulaglutide 0.75 mg, and in 143 (48%) of 299 patients receiving dulaglutide 1.5 mg. Gastrointestinal disorders were also the most common reason for discontinuing treatment with semaglutide and dulaglutide. There were six fatalities: one in each semaglutide group and two in each dulaglutide group. **INTERPRETATION:** At low and high doses, semaglutide was superior to dulaglutide in improving glycaemic control and reducing bodyweight, enabling a significantly greater number of patients with type 2 diabetes to achieve clinically meaningful glycaemic targets and weight loss, with a similar safety profile. **FUNDING:** Novo Nordisk.

Pratley RE, Eldor R, Raji A, et al. Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with type 2 diabetes mellitus inadequately controlled with metformin: the VERTIS FACTORIAL randomized trial. *Diabetes Obes Metab.* 2018;20(5):1111-1120.

AIM: To evaluate the efficacy and safety of ertugliflozin and sitagliptin co-administration vs the individual agents in patients with type 2 diabetes who are inadequately controlled with metformin.

METHODS: In this study (Clinicaltrials.gov NCT02099110), patients with glycated haemoglobin (HbA1c) $\geq 7.5\%$ and $\leq 11.0\%$ (≥ 58 and ≤ 97 mmol/mol) with metformin ≥ 1500 mg/d (n = 1233) were randomized to ertugliflozin 5 (E5) or 15 (E15) mg/d, sitagliptin 100 mg/d (S100) or to co-administration of E5/S100 or E15/S100. The primary endpoint was change from baseline in HbA1c at Week 26.

RESULTS: At Week 26, least squares mean HbA1c reductions from baseline were greater with E5/S100 (-1.5%) and E15/S100 (-1.5%) than with individual agents (-1.0%, -1.1% and -1.1% for E5, E15 and S100, respectively; $P < .001$ for all comparisons). HbA1c $< 7.0\%$ (< 53 mmol/mol) was achieved by 26.4%, 31.9%, 32.8%, 52.3% and 49.2% of patients in the E5, E15, S100, E5/S100 and E15/S100 groups, respectively. Fasting plasma glucose reductions were significantly greater with E5/S100 and E15/S100 compared with individual agents. Body weight and systolic blood pressure (SBP) significantly decreased with E5/S100 and E15/S100 vs S100 alone. Glycaemic control, body weight and SBP effects of ertugliflozin were maintained to Week 52. Genital mycotic infections were more common among ertugliflozin-treated patients compared with those treated with S100. Incidences of symptomatic hypoglycaemia and adverse events related to hypovolaemia or urinary tract infection were similar among groups.

CONCLUSIONS: In patients with uncontrolled type 2 diabetes while using metformin, co-administration of ertugliflozin and sitagliptin provided more effective glycaemic control through 52 weeks compared with the individual agents.

Seino Y, Terauchi Y, Osonoi T, et al. Safety and efficacy of semaglutide once weekly vs sitagliptin once daily, both as monotherapy in Japanese people with type 2 diabetes. *Diabetes Obes Metab.* 2018;20(2):378-388.

AIMS: To assess the safety and efficacy of monotherapy with once-weekly subcutaneous (s.c.) semaglutide vs sitagliptin in Japanese people with type 2 diabetes (T2D). METHODS: In this phase IIIa randomized, open-label, parallel-group, active-controlled, multicentre trial, Japanese adults with T2D treated with diet and exercise only or oral antidiabetic drug monotherapy (washed out during the run-in period) received once-weekly s.c. semaglutide (0.5 or 1.0 mg) or once-daily oral sitagliptin 100 mg. The primary endpoint was number of treatment-emergent adverse events (TEAEs) after 30 weeks. RESULTS: Overall, 308 participants were randomized and exposed to treatment, with similar baseline characteristics across the groups. In total, 2.9% of

participants in both the semaglutide 0.5 mg and the sitagliptin group prematurely discontinued treatment, compared with 14.7% in the semaglutide 1.0 mg group. The majority of discontinuations in the semaglutide 0.5 and 1.0 mg groups were attributable to adverse events (AEs). More TEAEs were reported in semaglutide- vs sitagliptin-treated participants (74.8%, 71.6% and 66.0% in the semaglutide 0.5 mg, semaglutide 1.0 mg and sitagliptin groups, respectively). AEs were mainly mild to moderate. Gastrointestinal AEs, most frequently reported with semaglutide, diminished in frequency over time. The mean glycated haemoglobin (HbA1c [baseline 8.1%]) decreased by 1.9% and 2.2% with semaglutide 0.5 and 1.0 mg, respectively, vs 0.7% with sitagliptin (estimated treatment difference [ETD] vs sitagliptin -1.13%, 95% confidence interval [CI] -1.32; -0.94, and -1.44%, 95% CI -1.63; -1.24; both $P < .0001$). Body weight (baseline 69.3 kg) was reduced by 2.2 and 3.9 kg with semaglutide 0.5 and 1.0 mg, respectively (ETD -2.22 kg, 95% CI -3.02; -1.42 and -3.88 kg, 95% CI -4.70; -3.07; both $P < .0001$). **CONCLUSIONS:** In Japanese people with T2D, more TEAEs were reported with semaglutide than with sitagliptin; however, the semaglutide safety profile was similar to that of other glucagon-like peptide-1 receptor agonists. Semaglutide significantly reduced HbA1c and body weight compared with sitagliptin.

Shi FH, Li H, Cui M, Zhang ZL, Gu ZC, Liu XY. Efficacy and safety of once-weekly semaglutide for the treatment of type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Front Pharmacol.* 2018;9:576.

Background: Semaglutide, a newly once-weekly glucagon like peptide-1 (GLP-1) receptor agonist, has showed a favorable effect on glycaemic control and weight reduction in type 2 diabetes mellitus (T2DM). This meta-analysis was conducted to evaluate the clinical efficacy and safety of semaglutide in T2DM. Methods: A comprehensive searching was performed for Phase III randomized controlled trials (RCTs) which reported the efficacy and safety data of semaglutide and other therapies. The efficacy data expressed as weight mean difference (WMD) and the safety data expressed as risk ratios (RRs) were calculated by employing random-effects model. Heterogeneity was assessed through I^2 test, and subgroup analyses were performed by different control groups, dosage of semaglutide, and durations of follow up. Results: 9 RCTs including 9,773 subjects met the inclusion criteria. For efficacy, compared with other therapies, semaglutide resulted in a significant reduction in glycosylated hemoglobin (weight mean difference, WMD: -0.93%, 95% CI: -1.24 to -0.62, $P < 0.001$), fasting plasma glucose (WMD: -1.15 mmol/L, 95% CI: -1.67 to -0.63, $P < 0.001$), mean self-monitoring of plasma glucose (WMD: -1.19 mmol/L, 95% CI: -1.68 to -0.70, $P < 0.001$), body weight (WMD: -3.47 kg, 95% CI: -3.96 to -2.98, $P < 0.001$), body mass index (WMD: -1.25 kg/m², 95% CI: -1.45 to -1.04, $P < 0.001$), systolic blood pressure (WMD: -2.55 mmHg, 95% CI: -3.22 to -1.88, $P < 0.001$), with the exception of negative result of diastolic blood pressure (WMD: -0.29 mmHg, 95% CI: -0.65 to 0.07, $P = 0.113$) and increased impact on pulse rate (WMD: -2.21, 95% CI: 1.54 to 2.88, $P < 0.001$). The results were consistent across the key subgroups. For safety, semaglutide did not increase the risk of any adverse events, hypoglycemia and pancreatitis, but induced a higher risk

of gastrointestinal disorders when compared with other therapies (RR: 1.98, 95%CI: 1.49 to 2.62, P < 0.001). Conclusion: Semaglutide was effective and acceptable in patients with T2DM except for a high risk of gastrointestinal disorders. The capacity of glycaemic and body weight control of semaglutide appeared more effective than other add-on therapies including other GLP-1 receptor agonists of exenatide release and dulaglutide.

Witkowski M, Wilkinson L, Webb N, Weids A, Glah D, Vrazic H. A systematic literature review and network meta-analysis comparing once-weekly semaglutide with other GLP-1 receptor agonists in patients with type 2 diabetes previously receiving 1-2 oral anti-diabetic drugs. *Diabetes Ther.* 2018;9(3):1149-1167.

INTRODUCTION: Once-weekly semaglutide is a new glucagon-like peptide-1 (GLP-1) analogue administered at a 1.0 or 0.5 mg dose. As head-to-head trials assessing once-weekly semaglutide as an add-on to 1-2 oral anti-diabetic drugs (OADs) vs other GLP-1 receptor agonists (GLP-1 RAs) are limited, a network meta-analysis (NMA) was performed. The objective was to assess the relative efficacy and safety of once-weekly semaglutide vs GLP-1 RAs in patients with type 2 diabetes (T2D) inadequately controlled on 1-2 OADs.

METHODS: A systematic literature review (SLR) was conducted in order to identify trials of GLP-1 RAs in patients inadequately controlled on 1-2 OADs. Data at 24+/-4 weeks were extracted for efficacy and safety outcomes (feasible for analysis in a NMA), which included the key outcomes of change from baseline in glycated hemoglobin (HbA_{1c}), systolic blood pressure (SBP), and weight, as well as discontinuation due to adverse events (AEs). Data were synthesized using a NMA and a Bayesian framework.

RESULTS: In total, 26 studies were included across the base case analyses. Once-weekly semaglutide 1.0 mg was associated with significantly greater reductions in HbA_{1c} and weight vs all GLP-1 RA comparators. Once-weekly semaglutide 0.5 mg also achieved significantly greater reductions in HbA_{1c} and weight compared with the majority of other GLP-1 RAs. Both doses of once-weekly semaglutide were associated with similar odds of discontinuation due to AEs compared with other GLP-1 RAs.

CONCLUSION: Overall, once-weekly semaglutide 1.0 mg as an add-on to 1-2 OADs is the most efficacious GLP-1 RA in terms of the reduction of HbA_{1c} and weight from baseline after 6 months of treatment. In addition, the analysis suggests that once-weekly semaglutide is well tolerated and not associated with an increase in discontinuations due to AEs compared with other GLP-1 RAs.

FUNDING: Novo Nordisk.

Zinman B, Inzucchi SE, Wanner C, et al. Empagliflozin in women with type 2 diabetes and cardiovascular disease - an analysis of EMPA-REG OUTCOME. *Diabetologia*. 2018;61(7):1522-1527.

AIMS/HYPOTHESIS: The global epidemic of type 2 diabetes affects women and men equally; however, the relative impact on the cardiovascular (CV) system appears greater for women than men when compared with peers without diabetes. Furthermore, women are often under-represented in CV outcome trials, resulting in less certainty about the impact of CV prevention therapies across the sexes. The EMPA-REG OUTCOME trial, which included 28.5% women, found that empagliflozin, given in addition to standard of care, reduced the risk of CV death by 38%, heart failure (HF) hospitalisation by 35% and a composite endpoint for incident or worsening nephropathy by 39%. Here we report a secondary analysis of the trial to determine the relative effects of empagliflozin in women vs men.

METHODS: The population studied were individuals with type 2 diabetes ($HbA_{1c} > 53-86$ mmol/mol [7-10%] and $eGFR > 30$ ml min⁻¹ [1.73 m]⁻²), with established atherosclerotic CV disease. Individuals were randomised to receive empagliflozin 10 mg or 25 mg, or placebo once daily in addition to standard of care, and followed. The trial continued until ≥ 691 individuals had experienced an adjudicated event included in the primary outcome. All CV outcome events, including HF hospitalisations and deaths were prospectively adjudicated by blinded clinical events committees.

RESULTS: At baseline, the demographic profile of the 2004 women (age +/- standard deviation 63.6+/-8.8 years) compared with the 5016 men (age 63.0+/-8.6 years) in the trial was largely similar, with the exception that LDL-cholesterol was numerically higher in women (2.5+/-1.0 vs 2.1+/-0.9 mmol/l), consistent with lower rates of lipid-lowering therapies (75.4% vs 83.2%). Women were also less likely to have smoked (31.5% vs 69.9%). The annualised incidence rate for women in the placebo group was numerically lower than in men for CV death (1.58% vs 2.19%), numerically higher for HF hospitalisation (1.75% vs 1.33%) and similar for renal events (7.22% vs 7.75%). We did not detect any effect modification by sex within the statistical power restrictions of the analysis for CV death, HF hospitalisation and incident or worsening nephropathy (interaction p values 0.32, 0.20 and 0.85, respectively). Compared with placebo, empagliflozin increased the rates of genital infections in both women (2.5% vs 10.0%) and men (1.5% vs 2.6%).

CONCLUSIONS/INTERPRETATION: CV death, HF hospitalisation and incident or worsening nephropathy rate reductions induced by empagliflozin were not different between women and men.