Newer Diabetes Medications and Combinations

Update #3 Final Report

Executive Summary

October 2017

This report is intended only for state employees in states participating in the Drug Effectiveness Review Project (DERP). Do not distribute outside your state Medicaid agency and public agency partners.

Shading indicates new information for this update.
Background
Diabetes mellitus (diabetes) is a chronic disease associated with significant morbidity and health care costs. The prevalence of diabetes among adults in the United States has increased substantially over the past 2 decades, raising from 9.8% in the 1988 to 1994 period to 12.4% in the 2011 to 2012 period. The 2017 American Diabetes Association treatment guidelines recommend an HbA1C goal of <7% for most nonpregnant adults in order to prevent adverse microvascular and macrovascular outcomes. Pharmacologic options for type 2 diabetes include sulfonylureas, biguanides, thiazolidinediones, meglitinide, 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.

Within recent years, several new antihyperglycemic agents have been approved. 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). For the purposes of this report, we consider the following to be “newer diabetes medications”: DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors.

Scope and 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?
   1. Does the effect differ when used as monotherapy versus combination therapy?
   2. Does the effect differ in patients with and without prior cardiovascular disease?
   3. 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?
   1. How does the efficacy and effectiveness of newer diabetes medications compare with each other within and across classes?
   2. How does the efficacy and effectiveness of newer diabetes medications compare between monotherapy and combination (add-on) therapy of newer diabetes medication?
3. What are the comparative harms of newer diabetes medications for adults with type 2 diabetes mellitus?
   1. How do adverse event outcomes of newer diabetes medications compare with each other within and across classes?
   2. 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?
Methods Summary
We followed systematic review methodology and procedures developed specifically for the Drug Effectiveness Review Project (DERP) and that are in accordance with current guidance for systematic reviews; for example, using dual review for study inclusion, quality assessments, and data abstraction. Detailed methods are available upon request.

Inclusion Criteria
Populations
- Adults with type 2 diabetes

Table 1. Included drugs

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Shading indicates drugs new to this update report.
Comparators
• Other newer diabetes medications (head-to-head comparisons), including fixed-dose or fixed-ratio combinations or add-on therapy versus monotherapy.
• Metformin (versus mono- or dual therapy with at least one newer diabetes medication).
• For Key Question (KQ) 1, placebo comparisons are also eligible.

Literature Search
Searches were conducted from February 2016 through July 2017.

Results
Overview
Through comprehensive searching and receipt of dossiers from 5 pharmaceutical manufacturers, we identified and screened for inclusion a total of 1,120 publications for this update review. By applying eligibility and exclusion criteria to these publications, we ultimately included 33 studies in 41 publications in this update, including 26 trials (in 32 publications), 3 observational studies, and 4 systematic reviews.

Applicability
Most studies in this report represented a selected population: primarily white, middle-aged, obese adults with moderately elevated baseline HbA1C (8% to 9%) and with diabetes for less than 10 years. Many trials included narrowly-defined populations of patients who had to undergo placebo run-in periods prior to randomization. The majority of studies enrolled patients who were treatment-experienced. Minorities and patients with comorbidities were generally underrepresented.

Key Findings
Key Question 1: Evidence on newer diabetes medications and cardiovascular events

SGLT2 Inhibitors
Empagliflozin
• The composite outcome of major adverse cardiovascular events (MACE; cardiovascular death, nonfatal myocardial infarction, or stroke) occurred less often with empagliflozin than placebo (10.5% vs. 12.1%; HR 0.86, 95% CI 0.74 to 0.99), as did cardiovascular death (3.7% vs. 5.9%, HR 0.62, 95% CI 0.49 to 0.77) and hospitalization for heart failure (2.7% vs. 4.1%, HR 0.65, 95% CI 0.50 to 0.85) (moderate strength). There was no difference in myocardial infarctions (MIs) or stroke (low strength), but all-cause mortality was lower with empagliflozin.
• Subgroup analysis showed that obesity reduced the benefit of empagliflozin. Age also affected outcomes, with patients 65 years or older showing lower MACE rates (11.4% vs. 15.5%, HR 0.71, 95% CI 0.59 to 0.87) and younger patients no benefit. Younger patients had a higher stroke risk with empagliflozin than with placebo (3.2% vs. 2.0%), while treatment did not affect stroke risk for patients 65 years or older. Cardiovascular history did not alter the effect of treatment on outcomes (KQ1.2).
• Dapagliflozin: observational evidence suggests lower **all-cause mortality** with dapagliflozin than placebo (8.4 vs. 17.2 deaths per 1,000 person-years, **adjusted incidence rate ratio 0.50, 95% CI 0.33 to 0.75**).

**Canagliflozin**

• Canagliflozin was associated with lower **MACE** rates than placebo (HR 0.86, 95% CI 0.75 to 0.97; 14.7% vs. 16.1% in CANVAS, 5.5% vs. 6.6% in CANVAS-R), and fewer hospitalizations for **heart failure** (2.1% vs. 2.8%, HR 0.67, 95% CI 0.52 to 0.87) (moderate strength). Differences in cardiovascular death, nonfatal MI, and nonfatal stroke were not statistically significant (low strength).

• Canagliflozin had higher rates of extremity **amputation** (6.3 vs. 3.4 participants per 1,000 patient-years, HR 1.97, 95% CI 1.41 to 2.75).

• Use of other medications affected outcomes of canagliflozin treatment, with patients given beta-blockers or diuretics benefitting from canagliflozin treatment; those not taking beta-blockers or diuretics did not benefit from SGLT2 treatment. Outcomes did not change based on history of cardiovascular disease (KQ1.2).

**DPP-4 Inhibitors**

**Alogliptin**

• In patients with recent acute coronary syndrome, there was no difference between alogliptin and placebo in cardiovascular outcomes including MACE (11.3% vs. 11.8%, P=0.32, moderate strength), cardiovascular (CV) death, nonfatal MI, and hospitalization for heart failure (low strength).

• In subgroup analyses, use of other medications changed the effect of alogliptin on MACE; patients who were insulin-naïve at baseline, as well as those treated with biguanides, benefitted more from alogliptin. Patients with better renal function also saw more benefit from alogliptin treatment. Baseline cardiovascular disease did not change the effect of treatment on outcomes (KQ1.2).

**Saxagliptin**

• Saxagliptin treatment compared with placebo did not change the MACE composite outcome (7.3% vs. 7.2%), cardiovascular death, or MI. However, treatment with saxagliptin was associated with an **increase in hospitalizations for heart failure** (3.5% vs. 2.8%, HR 1.27, 95% CI 1.07 to 1.51) (moderate strength for 4 outcomes). Saxagliptin did not change stroke rates (low strength).

• Patients treated with saxagliptin were less likely to have worsening microalbuminuria and more likely to see improvement than those given placebo (P<0.01 for all time periods).

• Subgroup analysis included history of heart failure, which did not change the effect of treatment on cardiovascular outcomes (KQ1.2).

**Sitagliptin**

• There was no difference in any cardiovascular outcome for patients treated with sitagliptin compared with placebo (moderate strength for MACE, CV death, any MI, any stroke, and heart failure hospitalization).
Sitagliptin was associated with higher retinopathy rates than placebo (2.8% vs. 2.2%, EPC-calculated RR 1.30, 95% CI 1.06 to 1.59). Obese patients benefitted more from sitagliptin than non-obese patients, the reverse of the finding with empagliflozin. Prior heart failure and hypertension did not change the effect of treatment on outcomes (KQ1.2).

Saxagliptin compared with Sitagliptin
- There was no difference in the risk of hospitalization for heart failure between saxagliptin and sitagliptin in patients with a history of CV disease (moderate strength).

GLP-1 Analogs
Semaglutide
- Fewer patients treated with semaglutide experienced a major CV event (6.6% vs. 8.9% for placebo, HR 0.74, 95% CI 0.58 to 0.95) (moderate strength). Nonfatal stroke rates were lower with semaglutide than placebo (1.6% vs. 2.7%, HR 0.61, 95% CI 0.38 to 0.99), but there was no significant difference in nonfatal MI (2.9% vs. 3.9%) or hospitalization for heart failure (3.6% vs. 3.3%) (low strength for 3 outcomes).
- Retinopathy complications were more likely with semaglutide than placebo (3.0% vs. 1.8%, HR 1.76, 95% CI 1.11 to 2.78), while nephropathy (3.8% vs. 6.1%. HR 0.64, 95% CI 0.46 to 0.88) and revascularization (5.0% vs. 7.6%, HR 0.65, 95% CI 0.50 to 0.86) were less likely.
- Subgroups including cardiovascular history (KQ1.2) did not change the effect of semaglutide on MACE.

Lixisenatide
- In patients with recent acute coronary syndrome, lixisenatide treatment had no effect on an alternate CV outcome (CV death, nonfatal MI, nonfatal stroke, or unstable angina), and no differences in treatment effect were seen across subgroups including prior cardiovascular disease (KQ1.2). Lixisenatide treatment did not affect rates of CV death, any MI, or hospitalization for heart failure (moderate strength), or rates of any stroke (low strength).

Liraglutide
- Rates of MACE (13.0% vs. 14.9%, HR 0.87, 95% CI 0.78 to 0.97) and of cardiovascular death (4.7% vs. 6.0%, HR 0.66 to 0.93) were lower in patients treated with liraglutide than those given placebo (moderate strength). Effects on any MI, any stroke, and hospitalization for heart failure were not statistically significant.
- Subgroup analysis showed that baseline cardiovascular history changed the effectiveness of liraglutide. Patients with established cardiovascular disease benefitted from liraglutide (14.0% vs. 16.7% for placebo, HR 0.83, 95% CI 0.74 to 0.93 for MACE outcome), while those with CV risk factors but no established disease did not. Patients with lower baseline renal function also saw more benefit from liraglutide.
Cardiovascular Outcomes by Drug Class (KQ1.3)

- Compared with placebo, addition of SGLT2 inhibitors and 2 of the 3 GLP-1 agonists to standard care decreased the risk of cardiovascular events (MACE; CV deaths, nonfatal MI, or nonfatal stroke). No head-to-head comparisons were available, and indirect meta-analyses did not show statistically significant differences between individual drugs or drug classes for either MACE or CV deaths. Some differences were close to statistical significance, and suggested that CV event rates may be lower with SGLT2 inhibitors than with DPP-4 inhibitors, and higher with DPP-4 inhibitors than with some GLP-1 agonists.

Key Questions 2 & 3: Comparative efficacy and harms of newer diabetes medications

I. Intra-class Comparisons (within a class)

**DPP-4 Inhibitors**

- Saxagliptin and sitagliptin had similar outcomes over 18 to 24 weeks.

**GLP-1 Analogs**

**Comparisons with Liraglutide**

- There were no differences in HbA1c outcomes, withdrawal due to adverse events, or serious adverse events at 26 weeks, but **weight loss was greater with liraglutide 1.8 mg daily than dulaglutide 1.5 mg weekly (-2.90 kg vs. -3.61 kg; difference, 0.71 kg; P=0.011).** In Japanese patients the only difference was that **appetite was decreased in more patients with liraglutide 0.9 mg than with dulaglutide 0.75 mg weekly (5.8% vs. 0.7%; P=0.003).**

- **Liraglutide 0.6 to 1.8 mg daily resulted in greater improvement in HbA1c (≤7%: 52% vs. 42%; RR 1.23, 95% CI 1.06 to 1.42) and weight loss (-2.19 kg vs. -0.64 kg; difference 1.55 kg, 95% CI 1.05 to 2.06 kg) than albiglutide 30 and 50 mg at 32 weeks, with no difference in adverse event outcomes.**

- **Lixisenatide 20 ug daily reduced HbA1c more than liraglutide 1.8 mg daily at 26 weeks (≤7%: 74.2% versus 45.5%; P< 0.0001, a moderate-strength finding), with no difference in weight change. While withdrawals due to adverse events did not differ significantly, more patients on liraglutide had serious adverse events (5.9% vs. 3.5%) and decreased appetite (6.4% vs. 2.5%).**

- **Reduction in HbA1c was significantly greater with semaglutide 1.6 mg weekly than liraglutide 1.2 mg or 1.8 mg daily (-1.7% vs. -1.2% and -1.3%), but the difference in the proportion achieving HbA1c ≤7% was not statistically significant (81% vs. 59% and 57%). Change in body weight was greater with semaglutide than with liraglutide (1.2 mg daily; difference -3.0 kg, 95% CI -4.0 to -2.0 and 1.8 mg daily; difference -2.2 kg, 95% CI -3.2 to -1.3). However, more patients on semaglutide withdrew due to adverse events (29.8% vs. 4.4% and 10%) and reported GI adverse events (74.5% vs. 33.3% and 30.0%).**
**Comparisons with Exenatide**

- Dulaglutide 0.75 mg or 1.5 mg once weekly improved HbA1c more than exenatide 5 to 10 µg twice daily at 26 weeks (<7%: 78% and 66% vs. 52%; P<0.001) at 26 weeks. Change in weight and adverse event outcomes were not significantly different between groups.
- There were no differences between albiglutide 30 mg weekly and exenatide 10 mg twice daily at 16 weeks in HbA1c outcome, weight change or adverse event outcomes.
- Based on 3 trials, there were no significant differences between exenatide XR 2 mg once weekly and exenatide 10 ug twice daily on HbA1c outcomes, weight change or adverse event outcomes (moderate strength).
- Liraglutide 1.8 mg once daily improved HbA1c more than exenatide 10 µg twice daily (-1.12% vs. -0.79%; difference -0.33%; 95% CI -0.47 to -0.18; P<0.0001). There was no difference in weight loss (-3.24 kg vs. -2.87 kg; P=0.2235), or withdrawal due to adverse events (10% vs. 13%), although nausea was reported to persist longer with exenatide.

**SGLT-2 Inhibitors**

- No evidence.

**II. Between-Class Comparisons**

**DPP-4 Inhibitors compared with GLP-1 Analogs**

- **Sitagliptin compared with Exenatide XR**
  - Based on two 26-week trials, exenatide XR was more efficacious than sitagliptin in reducing HbA1c (WMD −0.48; 95% CI, −0.69 to −0.26) and resulted in a greater proportion of patients achieving HbA1c <7% (62% vs. 39%; RR 1.57, 95% CI 1.34 to 1.83, I²=0); weight loss was also greater with exenatide XR than sitagliptin (WMD −1.32 kg; 95% CI −1.87 to −0.76 kg).
  - Exenatide XR resulted in more withdrawals due to adverse events (4% vs. 2%, RR 2.61; 95% CI 1.03 to 6.61) and more gastrointestinal side effects.

- **Sitagliptin compared with Liraglutide**
  - Liraglutide reduced HbA1c (liraglutide 1.2 mg −1.24%; liraglutide 1.8 mg −1.5%; sitagliptin −0.9%; P<0.0001 for both doses of liraglutide compared with sitagliptin) and weight (liraglutide 1.2 mg, −2.86 kg; liraglutide 1.8 mg, −3.38 kg; sitagliptin, −0.96 kg; P<0.0001 for both comparisons) compared to sitagliptin, and resulted in a greater proportion of patients achieving HbA1c <7% (OR 4.5; 95% CI 2.90 to 6.97 and OR 2.75; 95% CI 1.78 to 4.25 for liraglutide 1.2 and 1.8 mg vs. sitagliptin, respectively).
  - Liraglutide 0.9 mg, 1.2 mg, and 1.8 mg doses caused more withdrawal due to adverse events (59% vs. 48%, RR 1.16; 1.05 to 1.28; 7% vs. 2%, RR 3.28; 95% CI 1.81 to 5.93, respectively) and gastrointestinal adverse events than sitagliptin.
Sitagliptin compared with Albiglutide
- One trial found that albiglutide reduced mean HbA1c more than sitagliptin over 104 weeks (−0.63% vs. −0.28%, \(P<0.001\)), though there were no differences in the proportion of patients achieving HbA1c <7% (39% vs. 32%; RR 1.22, 95% CI 0.98 to 1.52) or in weight loss.
- There were no differences in withdrawals due to adverse events, but gastrointestinal adverse events were more common with albiglutide than sitagliptin.

Sitagliptin compared with Dulaglutide
- Dulaglutide 0.75 mg and 1.5 mg resulted in a greater proportion of patients achieving HbA1c <7% than sitagliptin (55% and 61% vs. 38%, \(P<0.001\) for comparisons with sitagliptin) and greater reductions in body weight at 26 weeks based on 1 trial.
- Withdrawals due to adverse events were similar between the drugs, though gastrointestinal adverse events were more common with dulaglutide at 26 weeks (RR 1.84, 95% CI 1.38 to 2.46) and at 104 weeks (RR 1.44, 95% CI 1.19 to 1.74).

Sitagliptin compared with Semaglutide
- Based on 1 trial, semaglutide 0.5 and 1.0 mg doses reduced HbA1c (mean difference -0.77%; 95% CI -0.92 to -0.62 and mean difference -1.06; 95% CI -1.21 to -0.91, respectively) and weight (mean difference -2.35 kg; 95% CI -3.06 to -1.63 kg and -4.20 kg; 95% CI -4.91 to -3.49 kg, respectively) than sitagliptin.
- Withdrawals due to adverse events were more common with semaglutide 0.5 mg (OR 2.74; 95% CI, 1.43 to 5.22) and semaglutide 1.0 mg (OR 3.23; 95% CI 1.72 to 6.09) than sitagliptin.

Saxagliptin compared with Liraglutide
- Liraglutide reduced HbA1c more than saxagliptin (−1.50%, 95% CI −1.67 to −1.34 vs. −1.23%, 95% CI −1.36 to −1.11; \(P<0.01\)), but there were no differences in the proportion of patients achieving HbA1c <7% (51% vs 39%; RR 1.45, 95% CI 0.95 to 2.22) at 24 weeks; weight loss was also greater with liraglutide (−6.0 kg; 95% CI −6.8 to −5.3 vs. −0.9 kg; 95% CI −1.5 to −0.4).
- Liraglutide resulted in more nausea than sitagliptin (27% vs. 3%; RR 8.37, 95% CI 2.02 to 35), but there was no difference in withdrawals due to adverse events.

DPP-4 Inhibitors compared with SGLT2 Inhibitors
Sitagliptin compared with Canagliflozin
- Based on a review of 5 trials, canagliflozin 300 mg resulted in greater decrease in HbA1c than sitagliptin (mean difference −0.16% (95% CI −0.29 to −0.02), as well as a greater proportion of patients achieving HbA1c <7% (RR 1.20, 95% CI 1.07 to 1.33) (strength of evidence: moderate); Canagliflozin 100 mg may reduce HbA1c more than sitagliptin (strength of evidence: low).
- Weight loss was greater with canagliflozin 300 mg than sitagliptin (mean difference -2.91 kg, 95% CI -3.50 to -2.33 kg) (strength of evidence: moderate).
• There were no differences in withdrawals due to adverse events between canagliflozin and sitagliptin (strength of evidence: low).
• Genital mycotic infections were much more common with canagliflozin 300 mg than sitagliptin (RR 11.96, 95% CI 2.84 to 50.41 in men and RR 3.99, 95% CI 2.15 to 7.40 in women) (strength of evidence: high).

**Sitagliptin compared with Empagliflozin**
- Two trials (n=883) provided evidence of improved weight loss with empagliflozin compared with sitagliptin but no difference between drugs in lowering HbA1c or in proportions who achieved a HbA1c <7% with empagliflozin 25 mg and sitagliptin (44% vs. 38%; RR 1.17, 95% CI 0.96 to 1.43) or between empagliflozin 10 mg and sitagliptin (32% vs. 38%; RR 0.88, 95% CI 0.70 to 1.10) (strength of evidence: moderate); rates of hypoglycemia did not differ between the groups (strength of evidence: low).

**Sitagliptin compared with Dapagliflozin**
- Dapagliflozin was similar to sitagliptin in reducing HbA1c and resulted in greater weight change in one small study (n=80) (strength of evidence: low).

**Linagliptin compared with Empagliflozin**
- Two trials provided evidence that treatment with empagliflozin 25 mg improves the likelihood of achieving a HbA1c <7% more than treatment with linagliptin 5 mg (OR 3.3, 95% CI 1.9 to 4.6) as does treatment with empagliflozin 10 mg versus linagliptin (OR 3.3, 95% CI 1.9 to 4.7); overall HbA1c was reduced more with either dose of empagliflozin compared with linagliptin and patients also lost more weight with empagliflozin (mean weight loss 2 to 3 kg with empagliflozin vs. 0.7 to 0.8 kg with linagliptin) (strength of evidence: moderate).
- Linagliptin and empagliflozin resulted in comparable rates of withdrawal due to adverse events and hypoglycemia, but empagliflozin caused more cases of genital mycotic infections (RR 3.99, 95% CI 1.08 to 14.00) (strength of evidence: moderate).

**Saxagliptin compared with Dapagliflozin**
- Treatment with dapagliflozin 10 mg increased weight loss when compared with saxagliptin 5 mg in patients poorly controlled on metformin (2.4 kg, 95% CI 2.9 kg to 1.9 kg vs. 0 kg, 95% CI −0.5 to 0.5) but there was no difference in proportions of patients who achieved an HbA1c < 7% based on a single trial (strength of evidence: low).

**GLP-1 Inhibitors compared with SGLT2 Inhibitors**

**Exenatide compared with Dapagliflozin**
- A single trial (n=685) reported no differences in HbA1c, weight change, or withdrawal due to adverse events between exenatide and dapagliflozin (strength of evidence: low).
III. Fixed-dose or Fixed-ratio Combination Products (FDCPs) or Dual Therapy

**GLP-1 Analogs and Long-acting Insulins**

**Lixisenatide plus Glargine Insulin**
- Evidence from 3 (N = 323 to 1,170) 26 to 30 week trials of lixisenatide 5-20 mcg/glargine 10-40 units daily found the combination superior to glargine alone in HbA1c outcomes (mean change -0.17% to -0.5%; % HbA1c <7% differences 14% and 26%) (strength of evidence: moderate). The combination was also superior to lixisenatide alone (differences: %HbA1c <7 40.6%, 95% CI 33.6 to 47.6; mean change in HbA1c -0.8, 95% CI -0.9 to -0.7). Weight change was better with the combination than glargine alone, but lixisenatide alone was better than the combination (differences were small; <1 to 2 kg). Withdrawals due to adverse events were highest with lixisenatide alone and lowest with glargine alone (strength of evidence: low).

**Liraglutide plus Degludec**
- Evidence from 3 (N = 413, 557, and 1663) 26-week trials of liraglutide/degludec daily found that in comparison to degludec, glargine, or liraglutide alone, the combination resulted in significantly better HbA1c outcomes (% HbA1c <7%: ORs 2.33 to 5.44). Weight change favored the combination compared with glargine or degludec alone (differences of 2.2 kg to 3.2 kg; P<0.0001), but liraglutide alone was better than the combination (difference 2.44 kg; P<0.0001). Hypoglycemia occurred less frequently with the combination than glargine (2.23 vs. 5.05 events/patient year; P<0.0001), more frequently than liraglutide (32% vs. 7%; relative risk 7.61, 95% CI 5.17 vs. 11.21), and had conflicting evidence compared with degludec alone. Withdrawal due to adverse events was similar between the combination and degludec alone, but higher than glargine (3.24% vs. 0.36%), and lower than liraglutide. Nausea was more common with the combination than either insulin alone (9 and 9.4% vs 4 and 1.1%), but less than liraglutide alone (5.8% vs 1.2%).

**SGLT2 Inhibitors with DPP-4 Inhibitors**
- Two trials found empagliflozin plus linagliptin to be superior to component monotherapy in mean reduction in HbA1c, the proportion of patients achieving HbA1c <7%, and mean weight reduction in drug-naïve patients and patients on background metformin therapy (strength of evidence: moderate).
- Three trials found triple therapy with dapagliflozin plus saxagliptin (similar to QTERN® FDCP) plus metformin to be superior to dual therapy with metformin and either dapagliflozin or saxagliptin on HbA1c outcomes. The range in differences in mean change in HbA1c was -0.35% to -0.91% and the difference in the proportion with HbA1c <7% ranged from 12.2% to 25.6% at 24 weeks. Weight loss was greatest (1.8 kg to 2.4 kg more), and incidence of genital infections (was highest in dapagliflozin-containing regimens (2.5% to 6%). There were no other important differences (strength of evidence: moderate for mean change in HbA1c and weight change, low for others).
**SGLT2 inhibitors with DPP-4 Inhibitors**

**Dapagliflozin plus Saxagliptin and Metformin**
- Three trials compared triple therapy with dapagliflozin plus saxagliptin (same components as QTERN®) and metformin with dual therapy of metformin with one of the other component drugs. Triple therapy resulted in significantly better HbA1c outcomes than dual therapy, and differences seen at 24 weeks were consistent at 52 weeks. **Dual therapy using saxagliptin had significantly less weight loss than triple therapy with saxagliptin or dapagliflozin (-1.8 kg to -2.4 kg).** Genital infection incidence was greatest with dual therapy of dapagliflozin with metformin (2.5% and 6%) and lowest with metformin with saxagliptin (0.6% in 2 trials).

**DPP-4 Inhibitors with Other Oral Diabetes Medicines**
- Alogliptin plus metformin (Kazano®) resulted in better HbA1c reductions than monotherapy for all dose comparisons; between-group differences ranged from −0.44% to −0.99%, P<0.001. Greater reduction in weight was seen with alogliptin/metformin 12.5 mg/1,000 mg twice daily than alogliptin 12.5 mg twice daily (−1.16 kg; P<0.003). (strength of evidence: moderate).
- Two trials (N=287 and 316) found greater reduction in HbA1c with linagliptin plus metformin (Jentadueto®) than with component monotherapy over 24 weeks (−0.70%, 95% CI −0.98% to −0.42% for 1,000 mg metformin and −1.10%; 95% CI −1.38% to −0.82% for 2,000 mg metformin in 1 study and −0.8%, 95% CI −1.1% to −0.5% for 1,500 mg to 2,000 mg metformin in the other) (strength of evidence: moderate). Weight loss findings were inconsistent (strength of evidence: low).
- Meta-analysis of 2 trials of sitagliptin plus metformin (Janumet®) (N=1,478) indicates greater reduction in HbA1c with sitagliptin 100 mg plus metformin 2,000 mg over 18 to 24 weeks compared with metformin monotherapy (WMD −0.60%, 95% CI −0.75 to −0.45) (strength of evidence: moderate). Differences in weight change were inconsistent across the trials, with no significant differences in the trial with longer follow-up (strength of evidence: low).
- A trial (n=654) of alogliptin plus pioglitazone (Osen®) found greater reduction in HbA1c and greater proportion of patients achieving an HbA1c <7% with combination therapy compared to component monotherapy over 26 weeks. Patients gained weight with higher-dose combination therapy (strength of evidence: low).

**SGLT2 Inhibitors with Other Oral Diabetes Medications**
- Evidence from 1 trial indicates that canagliflozin (100 mg or 300 mg) plus metformin (Invokamet®) was better in reducing HbA1c than either drug alone, although the differences was small (0.36% to 0.46% more). Compared with metformin alone, more patients achieved HbA1c <7% with only the higher dose of the combination (56.8% vs. 43.0%; RR 1.32, 95% CI 1.10 to 1.59), but both dose comparisons were superior to canagliflozin alone (100mg: 49.6% vs. 38.8%; RR 1.28, 95% CI 1.05 to 1.57 and 300 mg: 56.8% vs. 42.8%; RR 1.32, 95% CI 1.11 to 1.60). Weight loss was also greater with dual therapy compared to monotherapy (canagliflozin 100 mg: difference −1.2 kg, 95% CI
–1.9 kg to –0.6 kg; canagliflozin 300 mg: difference –2.0 kg, 95% CI –2.4 kg to –1.3 kg) (strength of evidence: low).

**Dual Therapy (not in FDCP)**
**Exenatide compared with Dapagliflozin**
- The combination was superior to the components alone on HbA1c and weight outcomes (mean change in HbA1c -1.4% to -2.0%, difference vs. exenatide -0.4%, 95% CI -0.6 to -0.1 and vs. dapagliflozin -0.6, 95% CI -0.8 to -0.3; % HbA1c 7% 45% vs 27% with exenatide, p<0.001, and 19% with dapagliflozin, p<0.001; Weight change -3.41 kg vs. -1.54 kg with exenatide, difference -1.87 kg, 95% CI -2.66 to -1.08 kg and -2.19 kg with dapagliflozin. difference -1.22 kg, 95% CI -2.00 to -0.44 kg).

**Linagliptin plus Low-dose Metformin compared with High-dose Metformin**
- There were no differences in HbA1c outcomes, slightly more weight loss in the high-dose metformin group, and no differences in adverse event outcomes.

**IV. Comparisons with Metformin**

**DPP-4 Inhibitors compared with Metformin**
**Linagliptin compared with Metformin**
- Linagliptin resulted in less reduction in HbA1c than high-dose metformin in 2 of 3 trials, while there were no differences between linagliptin and low-dose metformin (strength of evidence: low).
- There was no difference between linagliptin and metformin in withdrawals due to adverse events (strength of evidence: low).

**Sitagliptin compared with Metformin**
- A meta-analysis of 3 trials found that high-dose metformin was more efficacious than sitagliptin (WMD -0.30%, 95% CI, -0.52 to -0.09, I2 84.7%); a subsequently published trial (that could not be combined with the others) reported consistent findings (-0.57%) (strength of evidence: moderate).
- Metformin resulted in greater reductions in body weight, with between-group differences ranging from -1.2 kg to -1.7 kg (strength of evidence: moderate).
- There were no differences between sitagliptin and metformin in withdrawals due to adverse events or hypoglycemia (strength of evidence: moderate).

**Saxagliptin compared with Uptitrated Metformin**
- Our meta-analysis (2 trials; n=1677) found no difference in HbA1c with the addition of saxagliptin 5 mg compared with uptitration of metformin in patients not at goal on submaximal doses of metformin (WMD –0.31, 95% CI –0.74 to 0.13) (strength of evidence: low due to heterogeneity).
• In 1 trial (n=282), the uptitration of metformin was associated with a greater reduction in weight compared with adding saxagliptin 5 mg, between-group difference: −0.9 kg (95% CI −0.24 to −1.56) (strength of evidence: low).

**GLP-1 Analogs compared with Metformin**

**Exenatide XR compared with Metformin**
• One study (n=494) reported no differences between exenatide XR and metformin in HbA1c or weight change, though estimates were imprecise (strength of evidence: low).

**Dulaglutide compared with Metformin**
• One trial (n=807) found greater mean reduction in HbA1c and proportion of patients achieving HbA1c <7% with dulaglutide than metformin (RR 1.16, 95% CI 1.01 to 1.34). Weight change was less with dulaglutide 0.75 mg than metformin, while there was no difference in weight change between dulaglutide 1.5 mg and metformin (strength of evidence: low).

**SGLT2 Inhibitors compared with Metformin**

**Dapagliflozin compared with Metformin**
• Dapagliflozin 10 mg reduced HbA1c more than metformin 1,500 mg to 2,000 mg daily (meta-analysis of 2 trials; N=522; WMD −0.11%, 95% CI −0.11 to −0.05). This difference is very small, and not considered clinically important. There was no difference between dapagliflozin 5 mg and metformin
• Dapagliflozin reduced weight more than metformin at 24 weeks (meta-analysis of 2 trials, N=505, WMD −1.18 kg, 95% CI −1.86 to −0.26 for 5 mg dapagliflozin and WMD −1.3 kg, 95% CI −1.8 to −0.7 for 10 mg) (strength of evidence: low).

**Empagliflozin compared with Metformin**
• There were no differences in mean reduction in HbA1c or the proportion of patients achieving an HbA1c <7% (strength of evidence: moderate).
• Empagliflozin resulted in more weight loss than metformin, and no difference in withdrawals due to adverse events (strength of evidence: low).

**Canagliflozin compared with Metformin**
• One trial (n=1,186) of canagliflozin compared with metformin found no differences in mean HbA1c reduction or in the proportion of patients achieving HbA1c <7%. Weight reduction was greater with canagliflozin 100 mg (−3.0 kg; treatment difference −0.9 kg, 95% CI −1.6 to −0.2 kg) and 300 mg (−3.9 kg; treatment difference −1.8 kg, 95% CI −2.6 to −1.1 kg) compared to metformin (−2.1 kg) (strength of evidence: low).
Key Question 4: Subgroups

- Gender. There was no evidence of a difference between treatment with SGLT2 inhibitors and DPP-4 inhibitors on genital infections based on gender.
- Renal impairment. Albiglutide resulted in greater reduction in HbA1c than sitagliptin (0.83% vs. 0.52%) with similar risk of experiencing hypoglycemia, any adverse event, withdrawing from the study due to adverse events, and gastrointestinal adverse events.

Summary

This report synthesizes the evidence on newer diabetes medication, updating the prior report. Key findings include the superiority of SGLT-2 inhibitors and some GLP-1 agonists over placebo in preventing cardiovascular events. DPP-4 inhibitors and the GLP-1 agonist lixisenatide were not different to placebo. Other key findings are that there are small but statistically significant differences on a drug-by-drug basis in HbA1c, weight, or adverse event outcomes depending on the comparison. SGLT-2 inhibitors cause more weight loss than other classes, but also cause more genital infections. Combination products generally have better HbA1c outcomes than monotherapy with components (triple therapy is also better than dual therapy) but weight and adverse event outcomes vary by comparison. In comparison with metformin alone, outcomes were similar with DPP-4 inhibitors, mixed results in comparison with GLP-1 agonists, and SGLT-2 inhibitors caused more weight loss.

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Suggested Citation:

Conflict of Interest Disclosures:
No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.