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Drug Class Literature Scan: Non-Insulin Diabetes Drugs

Date of Review: August 2026

Literature Search: 07/01/18 – 05/15/26
Date of Last Review: GLP-1 Receptor Agonists and dual GLP-1 RA/GIP therapies (April 2024)
DPP-4 inhibitors (August 2020)
SGLT-2 Inhibitors (February 2025)
Sulfonylureas (July 2018)
Thiazolidinediones (July 2018)
Miscellaneous Antidiabetic Agents (July 2018)

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- New evidence for diabetic medicines is evaluated and included in this review.
- There are 7 classes of medicines, not including insulins, used for the treatment of diabetes, mostly type 2 diabetes (T2D),included in this review. The classes are glucagon-like peptide-1 receptor agonist (GLP-1 RAs), dual GLP-1 RA/glucagon-dependent insulinotropic polypeptide (GIP), dipeptidyl peptidase-4 inhibitors (DPP-4s), sodium-glucose cotransporter 2 (SGLT-2) inhibitors, sulfonylureas (SU), thiazolidinediones (TZD), and miscellaneous agents (such as metformin).
- Therapies initially approved to lower blood glucose for people with diabetes have been shown to have benefits in other diseases. Diabetes medicines have shown to improve kidney disease, heart failure, obstructive sleep apnea, polyendocrine metabolic ovary syndrome (PMOS), previously called polycystic ovary syndrome (PCOS), liver disease and cause weight loss.
- For people with chronic kidney disease the evidence found:
  - Older diabetes medicines called TZDs did not clearly lower the risk of dying from heart disease in people with T2D and kidney disease.
  - Metformin may slightly slow the loss of kidney function, but the benefit appears small.
  - GLP-1 medicines may lower the risk of death from any cause in people with diabetes and kidney disease.
  - DPP-4 medicines appear to provide little or no important benefit for people with diabetes and kidney disease.
- For heart disease (also called cardiovascular disease), GLP-1 medicines and SGLT2 inhibitors help lower the risk of death, heart problems, and hospitalization for heart failure in people with heart disease.
- For PMOS, metformin may improve the chances of pregnancy in women with PMOS undergoing fertility treatment, however; it has not clearly been shown to increase live birth rates. Guidelines recommend that metformin can be used to help manage PMOS, depending on a woman's symptoms and health goals.
- Evidence for the use of diabetic therapy for weight management has shown the following:

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    - Metformin may help reduce weight gain caused by antipsychotic medicines that are used to treat some mental health conditions, but the evidence is limited.
    - Tirzepatide leads to greater weight loss than placebo and semaglutide.
    - Semaglutide causes meaningful weight loss, considered to be 5% or more, compared with placebo and liraglutide, but usually less than tirzepatide.
    - Liraglutide helps more people lose at least 5% of their body weight compared with placebo.
    - Several weight-loss medicines can reduce body weight in children and teenagers with obesity, but the quality of evidence is low.
    - The United States (US) Preventive Services Task Force found limited evidence supporting the use of weight-loss medicines in children and adolescents with obesity.
    - Major obesity guidelines strongly recommend semaglutide and tirzepatide for treating overweight people with obesity.
- Some diabetes medicines, including metformin, TZDs, and alpha-glucosidase inhibitors, may help prevent or delay the development of T2D in high-risk people, such as those with prediabetes or have overweight or obesity.
- Several new diabetes treatment guidelines have been recently published. Recommendations include:
    - Metformin is the first treatment recommended for most adults with T2D.
    - Other diabetes medicines can be added if blood sugar goals are not reached.
    - Some newer guidelines recommend starting metformin together with an SGLT-2 inhibitor in certain patients, such as those with other health conditions, because this combination can improve blood sugar control, weight loss, and heart health.
- Recommendations from recent guidelines on the management of chronic kidney disease are the following:
    - For people with T2D and chronic kidney disease, SGLT-2 inhibitors and metformin are recommended as the main starting treatments.
    - SGLT2 inhibitors and GLP-1 medicines are strongly recommended because they reduce the risk of heart problems and death.
- Guidelines recommend that women who are pregnant with diabetes or develop gestational diabetes should be treated with insulin and/or metformin.
- There is limited evidence that suggest SGLT-2 inhibitors may help certain patients with lupus-related kidney disease, but the evidence is very weak and more research is needed.
- To summarize the new evidence:
    - Metformin remains the foundation of treatment for most people with type 2 diabetes.
    - SGLT-2 inhibitors and GLP-1 medications provide the strongest evidence for protecting the heart and kidneys from damage due to high blood sugar.
    - In people with obesity, tirzepatide produces the greatest weight loss, followed by semaglutide and liraglutide.
    - Many newer guidelines now emphasize not just lowering blood sugar, but also protecting the heart, kidneys, and reducing the risk of death.
- The Oregon Health Plan (OHP) pays for medications to treat T2D. Some of the diabetes medicines, especially when used for treatment of conditions other than diabetes, require that certain criteria are met through a process called prior authorization. After review of new evidence, the Drug Use Research and Management group recommends no changes to the current policy.

Conclusions:

- New evidence identified in this review includes: 13 high quality systematic reviews and meta-analyses, 14 high quality guidelines, 5 new formulations, 6 new indications, 4 safety warnings, and 8 randomized controlled trials (RCTs).

SYSTEMATIC REVIEWS

Chronic Kidney Disease

- A Cochrane review evaluating the use of thiazolidinediones (TZDs) in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD) found that they had little to no effect on risk of cardiovascular (CV) death compared to placebo or standard of care based on low quality of evidence. There was insufficient evidence for other outcomes.[1]
- A 2024 Cochrane Review found metformin use in patients with and without diabetes, compared to placebo or other diabetes treatments, may slightly decrease the decline in kidney function (i.e. estimated glomerular filtration rate [eGFR]) based on low quality evidence from 3 studies (mean difference [MD] 1.92 mL/min; 95% confidence interval [CI], 0.33 to 3.51).[2]
- A Cochrane Review evaluated to evidence for the use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in adult patients with CKD and T2D in a 2025 publication.[3] The use of GLP-1 RAs was found to decrease all-cause death (relative risk [RR] 0.85, 95% CI 0.74 to 0.98; moderate-quality of evidence) but had a minimal effect on CV death (RR 0.84, 95% CI 0.68 to 1.05; low-certainty evidence).
- The benefits and harms for the use of dipeptidyl peptidase-4 (DPP-4) inhibitors in individuals with T2D and CKD was assessed in a 2025 Cochrane review.[4] DPP-4 inhibitors were found to offer little benefit over standard of care or placebo in patients with T2D and CKD based on very-low to low quality of evidence.

Cardiovascular Disease

- A Cochrane review evaluated the effects using DPP-4 inhibitors, GLP-1 RAs or sodium-glucose cotransporter 2 (SGLT-2) inhibitors in people with established cardiovascular disease (CVD), with or without diabetes.[5] There was moderate to high strength of evidence that the use of GLP-1 RAs and SGLT-2 inhibitors reduced the risk of CV mortality, all-cause mortality and hospitalizations for heart failure (HF).

Polycystic Ovary Syndrome

- A Cochrane review published in 2020 found that metformin, compared to placebo or no treatment, may increase pregnancy rates in women with polyendocrine metabolic ovary syndrome (PMOS) undergoing in vitro fertilization (IVF) or intracytoplasmic sperm injection (ISI). There were no clear increases in live birth rates with metformin.[6]

Weight Management

- A 2022 Cochrane review found low-quality evidence that metformin, compared to placebo or no treatment, may be effective in preventing antipsychotic associated weight gain in people with schizophrenia.[7]
- A Cochrane review evaluated the effects of tirzepatide in weight loss in adults with other comorbidities such as diabetes or hypertension. Tirzepatide was found to result in more weight loss compared to placebo and semaglutide based on moderate strength of evidence.[8]
- Semaglutide was studied in a 2025 Cochrane review and demonstrated meaningful weight loss compared to placebo and liraglutide but less than tirzepatide (moderate quality of evidence for placebo studies and low quality of evidence for active treatment comparisons).[9]
- A Cochrane review found that the use of liraglutide for weight loss resulted in more patients obtaining a 5% weight decrease compared to those receiving placebo based on moderate evidence. Evidence on long term health outcome such as major adverse cardiovascular events (MACE) and mortality did not demonstrate a benefit with the use of liraglutide over placebo.[10]
- Pharmacotherapy (e.g., GLP-1 RAs, metformin, orlistat, sibutramine, topiramate, phentermine plus topiramate) was found to reduce body mass index (BMI) and decrease weight in children and adolescents with obesity based on low-quality evidence from a 2026 Cochrane Review.[11]
- Interventions for weight management in children and adolescents was published by the U.S. Preventive Services Task Force.[12] The use of liraglutide, semaglutide, orlistat and phentermine/topiramate were found to have limited evidence of BMI and weight reduction based on low strength of evidence.

Diabetes Screening

- The U.S. Preventive Services Task Force Screening for Prediabetes and Type 2 Diabetes Mellitus report was published in 2021.[13] There was no recommendation regarding preventative antidiabetic therapy; however, metformin, TZDs and alpha glucosidase inhibitors (AGIs) were found to reduce the incidence of diabetes.

GUIDELINES

Diabetes Prevention

- Guidance published in 2025 by the Scottish Intercollegiate Guideline Network (SIGN) recommends anti-diabetic and weight management pharmacotherapy to reduce the progression to T2D and to cause remission in certain people that are high risk due to comorbidities (e.g., CKD, CVD, overweight or obesity) and rising glucose levels.[14]

Glucose Management

- A guideline by SIGN on the pharmacological management of glycemia control in people with T2D was published in 2024.[15] Metformin is recommended first-line. Other treatments are recommended as second- or third-line therapies as needed for obtaining target glucose levels.
- The National Institute for Health and Care Excellence (NICE) updated guidance on the management of T2D in 2026.[16] One updated recommendation is for the use of metformin and an SGLT2 inhibitor in combination as initial management based on improved outcomes for glucose reduction, weight management and CV events.[16]
- The annual update to the Standards of Care in diabetes were published by the American Diabetes Association in 2026.[17] Recommendations for glucose management and pharmacotherapies to manage comorbidities are outlined below and align with fee-for-service (FFS) policy.
- Guidelines on the management of T2D were published in 2023 by the Veterans Administration/Department of Defense (VA/DoD).[18] Recommendations for pharmacotherapy are consistent with other guidelines.
- American College of Physicians (ACP) published guidance on the use of newer pharmacological treatment in patients with T2D. Recommendations support current FFS policy with metformin as the preferred first line therapy.[19]
- Guidelines for the management of type 1 diabetes (T1D) and T2D in children and young people was the focus of the 2023 guidance from NICE.[20] Metformin is recommended first line in children with T2D requiring pharmacotherapy.

Chronic Kidney Disease

- In 2022 Kidney Disease Improving Global Outcomes (KIDGO) published guidance on the management of T2D in patient with CKD.[21] The use of SGLT-2 inhibitors and metformin are recommended first line for most patients.
- The Department of Veterans Affairs (VA)/Department of Defense (DOD) published recommendations for the management CKD in the primary care setting. Both SGLT-2 inhibitors and GLP-1 RAs are strongly recommended in adults with CKD to reduce major adverse CV events and all-cause mortality.[22]

Weight Management

- Recommendations from The Obesity Society (TOS), the Obesity Medicine Association (OMA), and the Obesity Action Coalition (OAC) include strong recommendations for the use of semaglutide and tirzepatide for overweight and obesity based on moderate-quality evidence.[23]

Pregnancy

- A 2024 guideline from SIGN recommends the use of insulin and/or metformin for women who are pregnant and were diagnosed with diabetes before pregnancy or developed gestational diabetes.[24]
- A guideline by the Endocrine Society (ES) and European Society of Endocrinology (ESE) published guidance on the management of individuals who are pregnant with preexisting T1D or T2D.[25] Recommendations are consistent with other guideline recommendations for pharmacotherapy for pregnant women consisting of insulin and/or metformin.

Polycystic Ovary Syndrome

- An International evidence-based guideline for the assessment and management of PCOS was published in 2023.[26] The use of metformin is recommended for the management of PCOS dependent upon clinical variables.

Systemic Lupus Erythematosus

- Updated guidance from European Alliance of Associations for Rheumatology (EULAR) on the management of patients systemic lupus erythematosus (SLE) with kidney involvement recommends the use of SGLT-2 inhibitors in stable patients with SLE and lupus nephritis (LN) based on very low quality evidence.[27]

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on the evidence review.
- Review medication costs in executive session.

Summary of Prior Reviews and Current Policy

- Most recently the SGLT-2 inhibitors were reviewed at the February 2025 Pharmacy and Therapeutics (P &T) Committee meeting. Canagliflozin was made non-preferred based on cost.
- The GLP-1 RAs were reviewed at the April 2024 P & T Committee meeting and no changes were made after review of the clinical evidence and costs.
- In August 2024, drugs were reviewed for the treatment of Non-alcoholic Steatohepatitis (NASH) and weight management drugs for NAS and CV disease. The criteria for GLP-1 RAs were updated to include coverage of GLP-1 RAs that had compendial-support for the treatment of NASH in adults with overweight and obesity. The PA criteria for the use of semaglutide was updated to remove the age requirement in people with established CV disease with overweight or obesity because this population is at increased risk independent of age.
- Newer diabetes drugs were reviewed at the August 2020 P & T Committee meeting. The Committee recommended removal of requirement for step therapy, except for metformin. After comparative cost consideration in executive session, the Committee recommended making ONGLYZA, Trulicity, FARXIGA, JARDIANCE and INVOKANA preferred.
- Other antidiabetic therapies, classified as miscellaneous drugs, were reviewed in July 2018. The P & T Committee recommended amending the SGLT-2 PA) criteria to remove the amylin analogs from question #6 from the PA criteria. After comparative cost consideration in executive session, the Committee recommended making no changes to the PDL.
- Antidiabetic therapies account for significant quarterly costs in the Fee-For-Service (FFS) population. The most expensive classes are GLP-1 RAs and SGLT-2 inhibitors accounting for approximately $488,000 for 658 claims. The other classes consist of 1,143 claims and cost approximately $8,400 per quarter.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon the Scottish Intercollegiate Guidelines Network (SIGN), and the Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Chronic Kidney Disease

Cochrane – Thiazolidinediones for People with Chronic Kidney Disease and Diabetes

A 2025 Cochrane review evaluated the effect of TZD use in patients with T2D. There were 3,044 participants in 85 studies included in the review.[1] The median age was 62 years, with one study enrolling children. Studies evaluated patients on dialysis (7 studies), CKD 1 and 2 (5 studies), CKD 3-5 (6 studies), and the remaining studies included people with CKD 1-5.[1] Main endpoints of interest were CV death, severe hypoglycemia, MACE, non-fata myocardial infarction (MI) and kidney failure requiring kidney replacement therapy (KRT). Risk of bias was considered high for all outcomes due to blinding issues.

In the meta-analysis the control group was either placebo or standard of care.[1] There was low-quality evidence that the risk of CV death was not different between TZDs and control (RR 2.0; 95% CI, 0.01 to 3.97; 4 studies).[1] There was insufficient evidence to determine hypoglycemia risk with TZDs. Other important outcomes were not studied. In a comparison between TZDs and sulfonylureas there was no difference in CV death (RR 2.78; 95% CI, 0.11 to 67.92; 4 studies) based on low-quality evidence in patients with CKD stage 1 or 2.[1] No other outcomes were evaluated.

Overall, there was no benefit found for the use of TZDs in people with T2D with existing kidney disease for a reduction in the risk of CV death.[1]

Cochrane – Metformin for Preventing the Progression of Chronic Kidney Disease

Metformin was studied for the prevention of CKD progression in a 2024 Cochrane review.[2] Eleven studies (n=8,449) met inclusion criteria. Participants had Autosomal Dominant Polycystic Kidney Disease (ADPKD) (4 studies) or diabetes (7 studies). Metformin was compared to placebo or no treatment in 6 studies, active control (i.e., rosiglitazone, glyburide, pioglitazone, or glipizide) in 4 studies and one study compared diet and lifestyle modifications or other antidiabetic therapies.[2] Most of the included trials were considered to have a low risk of bias across most domains.

Compared to placebo, metformin may slightly decrease the decline in kidney function (i.e., eGFR) based on low-quality evidence from 3 studies (MD 1.92 mL/min; 95% CI, 0.33 to 3.51).[2] There was no difference in the risk of death between groups based on very low quality of evidence (RR 1.00; 95% CI, 0.76 to 1.32).[2] Withdrawals due to intolerance were higher with metformin compared to placebo (RR 2.19; 95% CI,1.46 to 3.27) (moderate quality of evidence).[2] Evidence for the outcomes for kidney failure were uncertain.

Comparisons of metformin to active treatment controls found little or no difference between the groups for the following outcomes: kidney function decline, all-cause death, study withdrawals and incidence of serious AE. Metformin may increase the urine albumin-creatinine ratio, compared to other active treatments, based on low-quality evidence (MD 14.61; 95% CI, 8.17 to 21.05; two studies).[2]

Cochrane – Glucagon-like Peptide-1 Receptor Agonists for People with Chronic Kidney Disease and Diabetes

A Cochrane review evaluated the evidence for the use of GLP-1 RAs in people with CKD.[3] There were 42 studies included (n = 48,148). All participants were adults with T2D and a median duration of 26 weeks. Participants with CKD stages 1-5 and dialysis were included.

GLP-1 RAs were compared to placebo and found to reduce all-cause death (RR 0.85; 95% CI, 0.74 to 0.98) (moderate-quality evidence).[3] There was low-quality evidence that CV death was similar with GLP-1 RAs compared to placebo with an incidence of 47 per 100 patients treated with GLP-1 RAs compared to placebo 56 per 1000 patients treated (RR 0.84; 95% CI, 0.68 to 1.05).[3] For the outcome of 3-point MACE (e.g., CV death, nonfatal MI or nonfatal stroke), at 137 weeks follow up, GLP-1 RA decreased the incidence more than placebo (RR 0.84; 95% CI, 0.73 to 0.98) based on moderate-quality evidence.[3] GLP-1 RAs reduced the incidence of 4-point MACE (e.g., CV death, nonfatal MI, nonfatal stroke, and coronary revascularization or hospitalization for unstable angina or HF) more than placebo (RR 0.77; 95% CI, 0.67 to 0.89).[3] At 610 weeks follow up, the risk of kidney failure (e.g., starting dialysis or kidney transplant) was not significantly different between GLP-1 RAs and placebo (RR 0.86; 95% CI, 0.66 to 1.13) (moderate-quality evidence).[3] There was moderate-quality evidence of no effect of GLP-1 RAs compared to placebo on the composite kidney outcomes (RR 0.89; 95% CI, 0.78 to 1.02). There were no significant differences in hypoglycemia rates between the two groups (low quality of evidence).[3]

There was insufficient evidence to determine the effect of GLP-1 RAs to other antidiabetic drugs or standard of care.

The risk of bias was considered low in most studies for all the primary outcomes that were placebo comparisons. In comparisons of GLP-1 RAs to DPP-4 inhibitors, SGLT-2 inhibitors, insulin, other GLP-1 RAs or standard of care there was unclear or high risk of bias due to missing data for the outcomes of all cause and CV death.[3] Overall, GLP-1 RAs have a demonstrated benefit, over placebo, in reducing all-cause death in patients with T2D and CKD.

Cochrane - Dipeptidyl peptidase 4 Inhibitors for People with Chronic Kidney Disease and Diabetes

A 2025 Cochrane review assessed the benefits and harms of DPP-4 inhibitors in people with CKD and diabetes.[4] There were 59 studies, enrolling 27,893 adults, included in the review. The DPP-4 inhibitors that were studied included: alogliptin, gemigliptin (not available in the US), linagliptin, omarigliptin (not available in the US), saxagliptin, sitagliptin, trelagliptin (not available in the US) and vildagliptin (not available in the US). DPP-4s were compared to placebo, standard medical care, SGLT-2 inhibitors, GLP-1 RAs, sulfonylureas, other DPP-4 inhibitors, insulin, or alpha-glucosidase inhibitors.[4] The primary outcomes were CV death and hypoglycemia requiring third-party assistance.

The use of DPP-4s was not found to provide benefit, compared to placebo or standard medical care, for the outcomes studied. There was low quality of evidence that there was little to no effect of DPP-4 inhibitors, compared to placebo or standard medical care, for CV death (RR 0.96; 95% CI, 0.82 to 1.14) and hypoglycemia requiring third-party assistance (RR 0.97; 95% CI, 0.76 to 1.25).[4] For the outcomes of 3-point MACE and kidney failure there was moderate-quality evidence that there was little or no effect of DPP-4 inhibitors, RR 1.03 (95% CI, 0.91 to 1.17) and RR 1.09 (95% CI, 0.78 to 1.53), respectively.[4] There was very-low quality evidence for 4-point MACE, nonfatal stroke and nonfatal MI that demonstrated that there was little effect of DPP-4 inhibitors compared to placebo. The risk of bias was low for most domains.

The evidence was uncertain to determine the effects of DPP-4 inhibitors compared to other anti-diabetic treatments. Overall, DPP-4 inhibitors offer little benefit over standard of care or placebo in patients with T2D and CKD.

Polyendocrine Metabolic Ovary Syndrome

Cochrane -Metformin Treatment in Women with Polyendocrine Metabolic Ovary Sydrome

A 2020 review evaluated the use of metformin for women with PMOS undergoing IVF or ICSI.[6] Metformin was compared to placebo or no treatment in 13 studies (n=1132). Results were divided based on the protocol used for IVF treatment, long GnRH-agonist or short GnRH-antagonist. Important outcomes were live birth rate, clinical pregnancy rates and a reduction in ovarian hyperstimulation syndrome (OHSS).[6]

Live birth rates per women using the long GnRH agonist protocol found no difference between metformin and placebo or no treatment (RR 1.30; 95% CI, 0.94 to 1.79) (low-quality evidence).[6] Live birth rates for the short protocol using GnRH-antagonists found that metformin may reduce live birth rates (RR 0.48; 95% CI,0.29 to 0.79) based on low-quality evidence.[6] There was low quality of evidence that the risk for OHSS was reduced with metformin compared to placebo or no treatment (RR 0.46; 95% CI,0.29 to 0.72). Clinical pregnancy rates per women was increased with the use of metformin in women who used the long protocol GnRH-agonist (low-quality evidence); however, the evidence is uncertain in women who used the short protocol GnRH-antagonist (RR 1.38; 95% CI, 0.21 to 9.14)(very low quality of evidence).[6] The rate of miscarriage was not statistically significantly different between groups (RR 0.86; 95% CI, 0.56 to 1.32) based on low quality of evidence. Metformin was associated with a higher risk of adverse reactions with a RR of 3.35 (95% CI, 2.34 to 4.79) (low quality of evidence).[6]

Overall, there was not compelling evidence that metformin increases live birth rates; however, metformin may increase pregnancy rates in women who used a long GnRH-agonist long protocol. Metformin may also decrease the risk of OHSS.

Diabetes and Weight Management

Cochrane – Pharmacological Interventions for Prevention of Weight Gain in People with Schizophrenia

A 2022 Cochrane review evaluated medication used as preventative therapy for antipsychotic-induced weight gain in people with schizophrenia.[7] Seventeen trials were included, five of which evaluated metformin. The comparator in all trials was placebo or no treatment.

Small sample sizes, allocation concealment and blinding of investigators and participants reduced the certainty of evidence.[7] Metformin was found to decrease the average change in weight compared to no treatment by -4.03 kg (95% CI, -5.78 to -2.28; 4 RCT) based on low quality of evidence.[7] Average reduction in BMI was found to be higher in patients treated with metformin (MD -1.63; 95% CI, -2.96 to 0.29; 5 trials) (low quality of evidence).[7] Early study discontinuation and nausea were not statistically significantly different between groups.

Other therapies that were studied, that will be presented elsewhere, are topiramate, H2 antagonists, and monoamine modulators. Metformin had the most evidence for use but strong conclusions were limited by short study durations, small sample sizes and a limited number of studies.

Cochrane – Tirzepatide for Adults with Obesity

A 2025 review evaluated the use of tirzepatide in adults with obesity.[8] There were 9 RCTs (n=7111) that were identified. Tirzepatide, given once weekly at 5 mg to 15 mg, was compared to placebo and in one study compared to semaglutide. Patients were 36.1 years to 65.25 years old. All participants had a weight-related comorbidity, such as diabetes, prediabetes, HF, or obstructive sleep apnea (OSA).

In trials lasting 12 to 18 months, tirzepatide resulted in more weight loss compared to placebo (MD -16.03%; 95% CI, -18.91 to -13.14) and more people lost at least 5% of weight (RR 3.60; 95% CI, 2.44 to 5.30) (both based on moderate strength of evidence).[8] There was an increase in non-serious adverse events (AE) with tirzepatide compared to placebo (RR 1.33; 95% CI, 1.03 to 1.71). Tirzepatide increased quality of life scores, based on IWQoL-Lite-CT (Impact of Weight on Quality of Life-Lite Clinical Trials) by 2.35 points (0-100 scale) compared to baseline, which is unlikely to be clinically significant.[8] For the outcomes of serious AE, AE leading to withdrawal, MACE and mortality there was no statistical difference between groups.

For trials with a mean follow-up of 176 weeks, the percent weight loss was higher with tirzepatide compared to placebo from evidence from one study (MD -15.6%; 95% -19.14 to -12.18) (moderate quality of evidence).[8] There was moderate quality of evidence that the percent of people with at least a 5% weight

reduction was higher with tirzepatide (RR 2.81; 95% CI, 2.33 to 3.38). [8] Nonserious AE were higher with tirzepatide compared to placebo (RR 1.05; 95% CI, 0.98 to 1.11). There was no difference found between serious AE, AE leading to withdrawal, MACE, mortality and quality of life as measured by SF-36.[8]

In one trial comparing tirzepatide to semaglutide for up to 72 weeks found tirzepatide resulted in more weight loss than semaglutide (MD -6.5%; 95% CI, -8.13 to - 4.87) based on moderate quality of evidence.[8] There was no statistically significant difference in non-serious AE between tirzepatide and semaglutide, 766 per 1000 vs. 790 per 1000, respectively (RR 0.97; 95% CI, 0.90 to 1.05) (low quality of evidence). There was moderate quality of evidence that there was no statistically significant difference in the AE leading to withdrawal between tirzepatide and semaglutide, 61 per 1000 vs, 80 per 1000 (RR 0.77; 95% CI, 0.46 to 1.30).[8]

In summary, tirzepatide is effective in causing weight reductions more than placebo and semaglutide. The certainty of evidence for other important outcomes was low and the sustainability of weight loss for more than 176 weeks is unknown.

Cochrane – Semaglutide for Adults with Obesity

A systematic review and meta-analysis were assessed in adults living with obesity taking semaglutide.[9] Eighteen RCTs, including 27,949 participants, were evaluated. The mean age ranged from 41 to 70 years. Participants had a BMI of 31.9 kg/m2 to 40.3 kg/m2.[9] Comparisons were between placebo, tirzepatide and liraglutide. Main outcomes were weight loss, AE, MACE, quality of life and mortality.

In trials lasting 6 months to 17 months, semaglutide decreased percent body weight lost more than placebo by a MD of -10.73% (95% CI, -12.24 to -9.21) and more people taking semaglutide lost 5% of weight (RR 2.68; 95% CI, 2.30 to 3.12)(both high quality of evidence).[9] Semaglutide was associated with more nonserious AE compared to placebo (RR 1.11; 95% CI, 1.01 to 1.22) based on low quality of evidence. Adverse events leading to withdrawal was higher with semaglutide (RR 1.84; 95% CI, 1.53 to 2.21) (moderate strength of evidence).[9] Low quality of evidence found the difference in MACE between semaglutide and placebo was 58 per 1000 versus 92 per 1000, respectively (RR 0.63; 95% CI, 0.44 to 0.90). Mortality was 4 per 1000 for semaglutide and 5 per 1000 for placebo so unlikely to be clinically significant in the short term but was statistically significant (RR 0.69; 95% CI, 0.48 to 0.98).[9] There was moderate quality of evidence that there was not a difference in quality of life based on the SF-36.

Longer term studies up to 104 weeks found more weight loss with semaglutide compared to placebo MD of -11.11% (95% CI, -16.47 to -5.75) and more people taking semaglutide lost 5% of weight (RR 2.74; 95% CI, 1.95 to 3.84)(both moderate quality of evidence).[9] Adverse events leading to withdrawal were higher in patients treated with semaglutide compared to placebo (RR 2.03; 95% CI, 1.86 to 2.20) based on moderate evidence but no difference was found for nonserious AE (very low quality of evidence).[9] In follow up to 240 weeks the difference in MACE favored semaglutide compared to placebo, 64 per 1000 compared to 78 per 1000, respectively (RR 0.81; 95% CI, 0.73 to 0.90) based on moderate quality of evidence.[9] Quality of life was not statistically significantly different between groups. There was moderate quality of evidence that the difference in mortality was small and favored semaglutide more than placebo (RR 0.82; 95% CI, 0.72 to 0.94).

There were 2 trials that compared semaglutide to liraglutide and found the percent of weight change was higher with semaglutide compared to liraglutide (MD -6.75%; 95% CI, -13.03% to 0.-46%) and more people taking semaglutide lost at least 5% of weight (RR 1.30; 95% CI, 0.99 to 1.71) but it was not statistically significant (both low quality of evidence).[9] There were no statistically significant differences in the outcomes of nonserious AE, serious AE, withdrawals due to AE, mortality or quality of life based on SF-36 scores.

Semaglutide was compared to tirzepatide and was associated with less weight loss based in 1 trial (MD 6.5%; 95% CI, 4.87% to 8.13%) and more people obtained a 10% or more weight loss with tirzepatide compared to semaglutide, 813 per 1000 versus 601 per 1000, respectively (low quality of evidence for both).[9] There were no statistically significant differences in nonserious AE, serious AE, and AE leading to withdrawals.

There was clinically significant weight loss demonstrated by semaglutide in medium and long-term studies. All but one study was funded by the manufacturer which may present conflict of interest concerns.

Cochrane – Liraglutide for Adults with Obesity

Liraglutide was studied in adults with obesity in a 2025 Cochrane review.[10] There were 24 studies included which compared liraglutide to placebo and with an active comparator arm in 2 studies. Patients (n=9,937) ranged from 31 years to 65 years. All patients had weight related comorbidities, such as diabetes, non-alcoholic fatty liver disease, POS, and OSA.[10] All but 2 studies were funded by the manufacturer.

In studies lasting 26-68 weeks liraglutide was associated with a larger percent of weight loss compared to placebo (MD -4.72%; 95% CI, -5.32 to -4.12); 16 trials) but the evidence was considered very low.[10] The number of people achieving a 5% or more weight reduction was higher in those receiving liraglutide (RR 2.10; 95% CI, 1.80 to 2.45; 18 trials) (moderate level of evidence).[10] The risk of any AE was higher with liraglutide compared to placebo (RR 1.07; 95% CI, 1.04 to 1.11) added on low quality of evidence and serious AE was also higher RR 1.20 (95% CI, 1.00 to 1.43). The evidence was uncertain on the risk of nonserious AE and withdrawals due to AE based on very low quality of evidence. The risk of MACE was not statistically significantly different between liraglutide and placebo (RR 0.86; 95% CI, 0.66 to 1.10) based on moderate quality of evidence.[10] There was low quality evidence that quality of life scores, based on IWQoL-Lite-CT, was 2.9 points higher than placebo, which was not statistically or clinically significant. The evidence for mortality was very uncertain (RR 0.44; 95% CI, 0.08 to 2.25).[10]

Two trials studied long-term use of liraglutide, 104 to 160 weeks, and found liraglutide compared to placebo demonstrated a higher percent of weight loss from baseline with a MD of -4.34% (95% CI, -5.2% to -3.43%) (low quality of evidence).[10] Moderate quality of evidence found the number of people achieving a 5% or more weight loss was higher in patients treated with liraglutide compared to placebo (RR 1.78; 95% CI, 1.51 to 2.09). The risk of withdrawal due to AE was higher with liraglutide compared to placebo (RR 2.16; 96% CI, 1.59 to 2.93). The difference in quality of life scores, as measured by the IWQoL-Lite-CT, was statistically significantly different, but unlikely clinically significantly different from placebo (MD 3.81; 95% CI, 1.03 to 6.59) (moderate quality of evidence).[10] The evidence for any AE, nonserious AE, serious AE, MACE and mortality was of low to very low quality and was not statistically significantly different from placebo.

In summary, liraglutide use resulted in more weight loss than placebo in the short and long term with the most evidence for outcome for the number of patients achieving a 5% or more weight loss.

Cochrane - Pharmacological Interventions for the Treatment of Obesity in Children and Adolescents

A 2026 Cochrane review evaluated the evidence for the treatment obesity in children and adolescents with pharmacotherapy.[11] Trial participants that ranged from 0-19 years of age with essential obesity were included. Treatments were given for at least 3 months. Therapies studied were: GLP-1 RAs, metformin, orlistat, sibutramine, topiramate, phentermine plus topiramate.[11] All treatments were in conjunction with a behavioral or lifestyle approaches. Thirty-seven RCTs were included (n=4,218). Eleven studies included both children and adolescents, 25 studies included adolescents only and one study evaluated only children. Median duration of follow-up was 11-13.5 months.[11]

For the comparison of pharmacological interventions (e.g., GLP-1 RAs, metformin, orlistat, sibutramine, topiramate, phentermine plus topiramate) to placebo, there was a larger reduction in BMI with pharmacological therapy (MD -1.8 kg/m^2; 95% CI, -2.36 to -1.24) and weight change (MD -5.47 kg; 95% CI, -7.45 kg to -3.5 kg)(low quality of evidence).[11] There was moderate-quality evidence that there were more AEs with pharmacotherapy compared to placebo (RR 1.03; 95% CI, 1.00 to 1.07). There was low-quality evidence that discontinuations due to AEs were not statistically different between groups (RR 1.50; 95% CI, 0.82 to 2.75).[11] Quality of life scores were higher in patients treated with pharmacotherapy (e.g., GLP-1 RAs, phentermine plus topiramate) compared to placebo by a small amount that is unlikely to be clinically significant (MD 1.02 points [total score 0-100]; 95% CI, 1.94 to 3.98) (moderate quality of evidence).[11]

Comparisons of pharmacotherapy (e.g., metformin) to no intervention found very low-quality evidence for a reduction in BMI (MD -1.51 kg/m^2; 95% CI, -2.29 to -0.73) and weight change (MD -3.2 kg; 95% CI, -6.12 kg to -0.28 kg).[11] Other outcomes were not reported.

Overall, pharmacotherapy may result in small, but potentially clinically significant (i.e., 5% or more weight loss from baseline), weight reductions in adolescents with obesity.

U.S. Preventive Services Task Force - Interventions for Weight Management in Children and Adolescents

The U.S. Preventative Services Task Force evaluated weight management interventions for children and adolescents with high BMI.[12] Evidence was searched through January 2024. Behavioral interventions and medications were evaluated. Fifty-eight RCTs (n=10,143) were included.

Behavioral interventions were associated with small decreases in BMI compared to no intervention (MD -0.7; 95% CI, -1.0 to -0.3) (high strength of evidence).[12] Some medications had a more substantial reduction in weight, compared to placebo, as described in **Table 1**.

Table 1. Recommendations for Weight Management for Children and Adolescents[12]

Recommendation	Strength of Evidence	Results Summary	Notes
Health Outcomes			
Liraglutide	Insufficient	QoL: MD 1.3; 95% CI, -1.6 to 4.2; p>0.05	- Evidence from 1 RCT - No group differences in weight change
Semaglutide	Insufficient	QoL: MD 4.3; 95% CI, 0.2 to 8.3; P<0.05	- Evidence from only 1 RCT - Small improvement in weight-related quality of life
Orlistat	Insufficient	Not reported	- Evidence from 2 RCTs - No group differences in weight change
Phentermine/topiramate	Insufficient	Not reported	- Evidence from 1 RCT
Intermediate Outcomes			
Liraglutide	Low for BMI and weight reduction Low for lipid and blood pressure changes	BMI: MD -1.6; 95% CI, -2.5 to -0.7; p<0.05 Weight: MD -4.5 kg; 95% CI, -7.2 to -1.8; p<0.05	- Evidence from 1 RCT

Semaglutide	Low for BMI and weight reduction	BMI: MD -6.0; 95% CI, -7.3 to -4.6; p<0.05 Weight: MD -17.7 kg; 95% CI, -21.8 to -13.7; p<0.05	- Evidence from 1 RCT
Orlistat	Low for BMI and weight reduction	BMI: MD -0.9; 95% CI NR; p=0.001 Weight: MD -2.6 kg; 95% CI NR; p-value NR	- Evidence from 2 RCTs
Phentermine/topiramate (15/92 mg dose)	Low for BMI and weight reduction	BMI: MD -5.4; 95% CI, -6.4 to -4.3; p<0.05 Weight: MD -15.8 kg; 95% CI, -18.8 to -12.8; p<0.05	- Evidence from 1 RCT
Harms			
Liraglutide	Insufficient for serious adverse events Low for increased adverse events	Harms may have been rare and underpowered to detect	- Evidence from 3 RCTs
Semaglutide	Insufficient for serious adverse events High for increased adverse events	Harms may have been rare and underpowered to detect	- Evidence from 1 RCT
Orlistat	Insufficient for serious adverse events Low for increased adverse events	Harms may have been rare and underpowered to detect	- Evidence from 2 RCTs
Phentermine/topiramate	Insufficient for serious adverse events Low for increased adverse events	Harms may have been rare and underpowered to detect	- Evidence from 2 RCTs
Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; NR = not reported; QoL = quality of life; RCTs = randomized controlled trials.			

Screening and Prevention

U.S. Preventive Services Task Force Screening for Prediabetes and Type 2 Diabetes Mellitus: An Evidence Review

A 2021 review done by the Agency for Healthcare Research and Quality (AHRQ) evaluated the benefits and harms of screening for abnormal glucose levels in primary care to inform guidance by the U.S. Preventative Task Force.[28] Literature was searched through September 10, 2019 . No specific recommendation regarding preventative drug therapy were made; however, evidence suggested benefit of antidiabetic medications.

For recently diagnosed individuals with T2D, long-term health outcomes were improved with intensive glucose control with insulin and sulfonylureas. Over a period of 20 years, there was a decreased risk of all-cause mortality (RR 0.87; 95% CI, 0.79 to 0.96), diabetes-related mortality (RR 0.83; 95% CI, 0.73 to 0.96), and MI (RR 0.85; RR 0.85; 95% CI, 0.74 to 0.97) with insulin and sulfonylurea use.[28] Metformin decreased risk for all-cause mortality (RR 0.64; 95% CI, 0.45 to 0.91), diabetes-related mortality (RR 0.58; 95% CI, 0.37 to 0.91) and MI (RR 0.61; 95% CI, 0.41 to 0.89) for follow-up at 10 years.[28]

In patient with pre-diabetes, the incidence of diabetes was reduced with metformin (RR 0.73; 95% CI, 0.64 to 0.83), TZDs (RR 0.50; 95% CI, 0.28 to 0.92), and alpha glucosidase inhibitors (AGIs) (RR 0.64; 95% CI, 0.43 to 0.96).[28]

Cardiovascular

Cochrane - Dipeptidyl Peptidase-4 Inhibitors, Glucagon-Like Peptide 1 Receptor Agonists and Sodium-Glucose Co-Transporter-2 Inhibitors for People with Cardiovascular Disease

A 2021 Cochrane review assessed the benefits and harms of using DPP-4 inhibitors, GLP-1 RAs and SGLT-2 inhibitors in people with CVD, with or without diabetes.[5] Thirty-one studies were included and considered to have an overall low risk of bias by the authors. All comparisons were to placebo. The DPP-4 inhibitors included the following medications: linagliptin, saxagliptin, alogliptin, sitagliptin, vildagliptin, and omarigliptin (not available in the US).[5] The GLP-1 RAs included trial of lixisenatide (discontinued), exenatide, albiglutide (discontinued) and semaglutide. SGLT-2 inhibitors included in the analysis were canagliflozin, dapagliflozin, empagliflozin, ertugliflozin and sotaglifozin.[5] Outcomes studied were CVD mortality, fatal and non-fatal MI, fatal and non-fatal stroke, all-cause mortality, hospitalizations for HF and safety.

Overall evidence suggests that there was no benefit for the major outcomes studied with the DPP-4 inhibitors.[5] There was high strength of evidence that DPP-4 inhibitors did not reduce the risk of CVD mortality, MI, stroke, and all-cause mortality. There was moderate strength of evidence that hospitalizations for HF were not reduced. There was moderate strength of evidence that the risk of pancreatitis may be increased with DPP-4 inhibitors (OR 1.63; 95% CI, 1.12 to 2.37).[5]

The use of GLP-1 RAs was found to reduce several efficacy endpoints (**Table 2**). There was low quality strength of evidence that GLP-1 RAs may reduce worsening renal function (OR 0.61; 95% CI, 0.44 to 0.84).[5]

There was evidence of an efficacy benefit for the use of SGLT-2 inhibitors compared to placebo (**Table 2).** There was no evidence that SGLT-2 inhibitors reduced the risk of MI or stroke. There was evidence that SGLT-2 inhibitors reduced the risk of worsening renal function (OR 0.59; 95% CI, 0.43 to 0.82).[5]

Table 2. Cochrane Systematic Review of DDP-4s, GLP-1 RAs and SGLT-2 inhibitors with Evidence of Benefit in Patients with Established CVD[5]

Outcome	Result	Strength of Evidence
GLP-1 RAs		
CV mortality	OR 0.87; 95% CI, 0.79 to 0.95	High
Stroke	OR 0.87; 95% CI, 0.77 to 0.98	High
All-cause mortality	OR 0.88; 95% CI, 0.82 to 0.95	High
Hospitalization for HF	OR 0.95; 95% CI, 0.85 to 1.06	High
SGLT-2 inhibitors		
CV mortality	OR 0.82; 95% CI, 0.70 to 0.95	Moderate
All-cause mortality	OR 0.84; 95% CI, 0.74 to 0.96	Moderate
Hospitalization for HF	OR 0.65: 95% CI, 0.59 to 0.71	High
Abbreviations: CI = confidence interval; CV = cardiovascular; HF = heart failure; GLP-1 RA = glucagon-like peptide-1 receptor agonists; OR = odds ratio; SGLT-2 = sodium-glucose cotransporter-2.		

In patients with established CV disease there is moderate- to high-quality evidence that the use of GLP-1 RAs and SGLT-2 inhibitors reduce the risk of CVD mortality and all-cause mortality. There was no evidence of benefit in these patients for the use of DPP-4 inhibitors.

After review, 110 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
High Quality Guidelines:

Diabetes Prevention

SIGN – Prevention and Remission of Diabetes

In 2025 SIGN published recommendations on preventing and remission of T2D. Recent advances in T2D demonstrate that clinically effective interventions are available to slow the progression to diabetes or even provide remission.[14] People at high risk of developing T2D, such as those with CVD, HTN, obesity, stroke, non-alcoholic fatty liver disease, PCOS, history of gestational diabetes, mental health conditions and those with learning disabilities, should be identified. Prediabetes is defined as a hemoglobin A1c (HbA1c) of 6.0-6.4% or a fasting plasma glucose (FPG) of 110 mg/dL to 125 m/dL and is associated with an increased risk of all-cause death.[14] Non-pharmacological interventions designed to improve diet, exercise and reduce body weight and ectopic fat should be employed to reduce T2D risk. Some patients may be candidates for treatment of prediabetes with medication (**Table 3**).[14] All patients considered for pharmacotherapy should be treated in a specialist weight management service. Non-pharmacological approaches may also be considered such as low-calorie diet and increased physical activity.

Table 3. Recommendations for Pharmacotherapy for People with Prediabetes[14]

Medication	Recommendation
Liraglutide	- Should be considered as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adults with a BMI ≥35 kg/m^2 with prediabetes (or lower for people from minority ethnic groups at increased risk of diabetes)
Semaglutide	- Should be considered as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adults with a BMI 30 kg/m^2 with prediabetes (or lower for people from minority ethnic groups at increased risk of diabetes)
Tirzepatide	- Should be considered as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adults with prediabetes or type 2 diabetes with a BMI ≥30 kg/m^2 (or lower for people from minority ethnic groups at increased risk of diabetes)
Metformin*	- Metformin may be offered to support lifestyle change for people whose HbA1c or fasting plasma glucose blood test results have deteriorated while participating in a lifestyle modification program or unable to participate in these types of programs and particularly if they have a BMI greater than 35 kg/m^2 - Start metformin with a low dose (for example, 500 mg once daily) and then increase gradually as tolerated, to 1,500 to 2,000 mg daily. If the person is intolerant of standard metformin consider using modified-release metformin - Metformin may cause vitamin B12 deficiency with long-term use; consider annual review of vitamin B12 levels, especially in those with anemia or peripheral neuropathy
Orlistat	- Can be considered if BMI is 28 kg/m^2 or more to manage obesity - Recommend that it be discontinued if at 3 months there has not been at least a 5% weight loss
Key: *Not indicated for weight management but has been shown to prevent progression from prediabetes to T2D Abbreviations: BMI = body mass index.	

Glucose Management

SIGN – Pharmacological Management of Glycemia Control in People with T2DM

A revised edition of the SIGN recommendations for glucose lowering treatments for people with T2DM were issued in 2024 and originally published in 2017.[15] Accreditation of the guideline process used by SIGN is endorsed by NICE. Recommendations pertaining to non-insulin therapies will be presented. All recommendations are in addition to lifestyle measures.

Key Recommendations for people with T2DM:[15]

- Metformin should be considered first-line oral treatment
- Patients with CV disease:
    - For patients with CV disease, a SGLT-2 inhibitor with proven CV benefit should be considered (empagliflozin and canagliflozin at GL publication)
    - GLP-1 RAs with proven CV benefit (liraglutide at GL publication), should be considered in people with established CV disease
- Sulfonylureas
    - For patients who are intolerant or have contraindications to metformin, a sulfonylurea should be considered as a first-line oral option
    - The use of sulfonylurea should be considered as an add-on second-line option to add to other oral therapies and may be useful in triple therapy
    - The use of sulfonylurea is associated with hypoglycemia and weigh gain
- Pioglitazone
    - For patients requiring dual and triple therapy, pioglitazone should be considered for lowering HbA1c
    - Pioglitazone should not be used in patients with heart failure
    - The long-term use of pioglitazone is associated with a risk of fracture
    - Pioglitazone is associated with the increased risk of peripheral edema, heart failure, weight gain, bladder cancer and fractures
- Dipeptidyl peptidase-4 inhibitors
    - The use of DPP-4s inhibitors should be considered, as dual or triple therapy, for lowering HbA1c
- Sodium glucose co-transporter 2 inhibitors
    - The use of SGLT-2 inhibitors should be considered as add-on therapy to metformin
    - See CV recommendation above
- Glucagon-like peptide-1 receptor agonists
    - GLP-1 RA therapy should be considered in individuals with a body mass index of $\geq$30 kg/m^2 (or ethnicity-adjusted equivalent) in combination with oral glucose lowering drugs or basil insulin (or both therapies) as a third or fourth option, when target glucose levels have not been achieved with other therapies.
    - In patients where combinations of oral glucose lowering therapies have been inadequate, GLP1 RAs should be considered as an alternative to insulin
    - See CV recommendations above
- Continuing oral therapies when adding basal insulin
    - Oral metformin should be continued with insulin therapy initiation to maintain or improve blood glucose control.
    - Consideration into stopping or reducing sulfonylureas when insulin is started while considering the benefits and risk of continuing other glucose-lowering therapies

NICE – Type 2 Diabetes Management

Guidelines for T2D management from NICE was updated February 2026.[16] Classes included in the update are: DPP-4 inhibitors, GLP-1 RAs (only liraglutide, dulaglutide and semaglutide were included), sulfonylureas, and SGLT-2 inhibitors. Pharmacotherapy recommendations are provided below. For initial therapy metformin and SGLT-2 inhibitor combination therapy is recommended based on evidence demonstrating that they were more effective at reducing HbA1c, weight and CV events compared to any other one therapy combination with metformin and metformin alone. There is also evidence that canagliflozin and dapagliflozin decreased the risk of end-stage renal failure.

Recommendations

Initial Therapy[16]:

- Metformin extended-release and an SGLT-2 inhibitor if there are no relevant comorbidities.
- SGLT-2 monotherapy can be offered if metformin is contraindicated or not tolerated.

T2D and HF[16]:

- Metformin extended release and an SGLT-2 inhibitor.
- SGLT-2 monotherapy can be offered if metformin is contraindicated or not tolerated.
- If additional therapy is needed to obtain glucose goals offer to add a DPP-4 inhibitor to current regimen.
- If a DPP-4 inhibitor is contraindicated, not tolerated, or not effective offer a SU or insulin.

T2D and ACVD[16]:

- Metformin extended-release, an SGLT-2 inhibitor and semaglutide subcutaneously up to 1 mg weekly for CV, glycemic and renal benefits.
- If metformin is contraindicated or not tolerated offer an SGLT-2 inhibitor and semaglutide subcutaneously up to 1 mg weekly for CV, glycemic and renal benefits.
- If a patient with T2D develops ACVD offer the addition of semaglutide subcutaneously for CV and renal benefits.
- If additional therapy is needed to obtain glucose goals offer to add a sulfonylurea, pioglitazone or insulin.

Early onset T2D[16]:

- Offer metformin extended release and SGLT2 inhibitor and consider adding a GLP-1 RA for CV, glycemic and renal benefits or tirzepatide for its glycemic benefits.
- If metformin is contraindicated or not tolerated offer an SGLT-2 inhibitor and a GLP-1 RA for CV, glycemic and renal benefits or tirzepatide for its glycemic benefits.
- If additional therapy is needed to obtain glucose goals offer to add a GLP-1 RA or tirzepatide. If these are contraindicated, not tolerated or not appropriate, offer a DPP-4 inhibitor. If a DPP-4 is not an option offer a sulfonylurea, pioglitazone or insulin.
- If the patient is taking a GLP-1 RA or tirzepatide and not at goal offer a sulfonylurea, pioglitazone or insulin.

T2D and obesity[16]:

- Metformin extended release and an SGLT-2 inhibitor should be offered.
- SGLT-2 monotherapy can be offered if metformin is contraindicated or not tolerated.
- The addition of a GLP-1 RA or tirzepatide can be considered for patients with T2D living with obesity and they have been taking initial therapy for at least 3 months and additional medication is needed to reach glucose targets if they are not already taking a GLP-1 RA or tirzepatide.
- If these options are not tolerated, contraindicated or not appropriate offer a DPP-4 inhibitor to current regimen or sulfonylurea, pioglitazone or insulin if a DPP-4 inhibitor is not an option.
- If patients are not already taking a GLP-1 RA or tirzepatide and need additional glucose lowering, offer a sulfonylurea, pioglitazone or insulin.

T2D and CKD[16]:
- Metformin extended release and an SGLT-2 inhibitor is recommended if eGFR is above 30 ml/min/1.73 m^2.
- SGLT-2 monotherapy can be offered if metformin is contraindicated or not tolerated.
- If the eGFR is 20 ml/min/1.73 m^2 to 30 ml/min/1.73 m^2 offer either dapagliflozin or empagliflozin and a DPP-4 inhibitor.
- If the eGFR is below 20 ml/min/1.73 m^2 consider a DPP-4 inhibitor.
- If a DPP-4 inhibitor is contraindicated, not tolerated or not effective consider pioglitazone or an insulin-based treatment.
- If additional glucose lowering is needed offer a DPP-4 inhibitor or if this is already being used or not an option, consider pioglitazone, a sulfonylurea or insulin.

T2D and frailty[16]:
- Metformin extended release is recommended.
- Offer an SGLT-2 inhibitor if the frailty of the person does not increase the risk for AE such as volume depletion or hypotension.
- If metformin is contraindicated or not tolerated and the patient is a candidate for an SGLT-2 inhibitor then offer SGLT-2 monotherapy if they are not a candidate then offer a DPP-4 inhibitor.
- If additional therapy is needed consider adding a DPP-4 inhibitor or a sulfonylurea, pioglitazone or insulin if a DPP-4 inhibitor is not an option.

T2D and no comorbidities requiring additional medication[16]:
- Offer the addition of a DPP-4 inhibitor to current regimen.
- If a DPP-4 inhibitor is contraindicated or not tolerated offer a sulfonylurea, pioglitazone or insulin therapy.

The use of a SGLT-2 inhibitor should be considered for their CV and renal benefits, even if they do not help the patient obtain glucose targets. The use of GLP-1 RAs should be discontinued if a person becomes underweight (BMI less than 18.5 kg/m^2).[16] The use of GLP-1 RAs and tirzepatide should be discontinued is the person is not obtaining their glucose goal and they are not being taken for CV benefit. The combined use of both a GLP-1 RA or tirzepatide and a DPP-4 inhibitor is not recommended. The risk of hypoglycemia and falls can be increased with SU or insulin therapy.

ADA – Standards of Care in Diabetes 2026

The ADA updates recommendations for standards of care for the management of diabetes on an annual basis.[17] Recommendations are graded from A to E, with A having the highest quality of evidence for support. Recommendations regarding non-insulin drug treatment will be presented.

Non-insulin pharmacologic recommendations for the treatment of T2D are included in **Table 4**.[17] Metformin is the most commonly prescribed first-line therapy for T2D. Medications should be evaluated at regular intervals, every 3-6 months and adjusted to meet glucose goals (Grade E).[17] Glucose lowering medications should be chosen based on glucose and weight goals, presence of comorbidities (e.g., CV, kidney disease, liver disease and other metabolic abnormalities) and hypoglycemia risk (Grade A).[17] The combination of DPP-4 inhibitors and GLP-1 RAs or GIP/GLP-1 RAs is not recommended due to lack of additional benefit (Grade B).[17]

Table 4. ADA Recommendations for Pharmacotherapy Management

Recommendation	Grade of Evidence
General Management[17]	
- Consider combination therapy as initial therapy to improve quicker attainment of glucose goals	A

- In individuals with T2D without severe hyperglycemia or hyperglycemic crisis, GLP-1–based therapy is preferred to insulin for initial or add-on glucose-lowering therapy	A
- If insulin is used, combination therapy with a GLP-1 RA, including a dual GIP and GLP-1 RA, is recommended to improve glucose levels as well as beneficial effects on weight and hypoglycemia risk. Insulin dosing should be reassessed upon addition or dose escalation of a GLP-1 RA or dual GIP and GLP-1 RA.	A
Cardiovascular[29]	
- In individuals with established or at high risk of ACVD should receive medications with demonstrated benefit to reduce CV events, such as GLP-1 RAs and/or SGLT-2 inhibitors for glucose management and CV risk reduction (regardless of HbA1c)	A
- Individuals who have T2D and established ASCVD or CKD, a SGLT-2 inhibitor or GLP-1A RA with demonstrated CV benefit is recommended to reduce CV risk and lower glucose	A
- SGLT-2 inhibitors with demonstrated CV benefit are recommended for people with type 2 diabetes and established ASCVD or multiple ASCVD risk factors, or CKD	A
- In individuals with T2D with established ASCVD or multiple risk factors for ASCVD, or CKD, a GLP-1 RA with demonstrated cardiovascular benefit is recommended to reduce the risk of cardiovascular events	A
- Combination therapy with an SGLT-2 inhibitor with demonstrated CV benefit and a GLP-1 RA with demonstrated CV benefit may be considered In people with T2D and established ASCVD or multiple risk factors for ASCVD for additive reduction of the risk of adverse cardiovascular and kidney events	A
- A SGLT-2 inhibitor is recommended in individuals with HF (with reduced or preserved EF) for glucose management and prevention of HF hospitalization (regardless of HbA1c)	A
- In individuals with T2D, obesity and symptomatic HF with preserved ejection fraction should include a dual GIP and GLP-1 RA with demonstrated benefit for HF-related symptoms and reduction in HF events (regardless of HbA1c)	A
- In individuals with T2D, obesity and symptomatic HF with preserved ejection fraction should include a GLP-1 RA with demonstrated benefit for HF-related symptoms and/or reduction in HF events (regardless of HbA1c)	A
- In individuals with T2D and asymptomatic (stage B) HF or with high risk of or established CVD, treatment with an SGLT-2 inhibitor with evidence of HF prevention benefit or a GLP-1 RA with HF prevention benefit is recommended to reduce the risk of hospitalization for HF	A for SGLT-2 inhibitors B for GlP-1 RAs
- Guideline-directed medical therapy for MI and symptomatic stage CHF is recommended with ACE inhibitors or ARBs (including ARBs and neprilysin inhibitors), MRAs, β-blockers, and SGLT2 inhibitors	A
- In individuals with stable HF, metformin may be continued for glucose lowering if eGFR remains >30 mL/min/1.73 m^2 but should be avoided in unstable or hospitalized individuals with HF	B
Chronic Kidney Disease[30]	
- In individuals with T2D who have CKD, with a confirmed eGFR of 20-60 mL/min/1.73 m^2 and/or albuminuria, an SGLT-2 inhibitor with demonstrated benefit should be use for glucose management and for slowing progression of CKD and reduction in CV events (regardless of HbA1c)	A
- In individuals with T2D and advanced CKD (eGFR <30 mL/min/1.73 m^2), a GLP-1 RA is preferred for glucose management due to lower risk of hypoglycemia and for CV event reduction	B

- In individuals with T2D and CKD a GLP-1 RA with demonstrated benefit is recommended to reduce kidney disease progression and cardiovascular risk	A
MASH and MASLD[17]	
- In individuals with T2D, MASLD, and over-weight or obesity, consider using a GLP-1 RA with demonstrated benefits in MASH	A
- In individuals with T2D, MASLD, and over-weight or obesity, consider using a dual GIP and GLP-1 RA with potential benefits in MASH	B
- A GLP-1 RA is preferred for glucose management for individuals with T2D and biopsy-proven MASH or those at high risk for liver fibrosis	A
- In individuals with T2D and biopsy-proven MASH or those at high risk for liver fibrosis pioglitazone or a dual GIP and GLP-1 RA can be considered for glucose management due to potential MASH benefits	B
- In individuals with T2D with biopsy-proven MASH or those at high risk of liver fibrosis (identified with noninvasive tests) due to potential beneficial effects on MASH combination therapy with pioglitazone plus a GLP-1 RA can be considered for the treatment of hyperglycemia	B
Special Circumstances[17]	
- Metformin should be considered as first-line treatment of hyperglycemia due to mTOR inhibitors	E
- Consider metformin first-line for hyperglycemia due to PI3K inhibitors that affect the α isoform	E
- In individuals with post transplantation DM or preexisting T2D the use of a DPP-4 inhibitor can be considered for mild hyperglycemia if insulin is not an option	A
- In individuals with post transplantation DM or preexisting T2D a GLP-1 RA can be considered for long-term glucose management due to additional cardiometabolic benefits	C
Pregnancy[31]	
- Metformin and glyburide should not be used to manage glucose in individuals with DM and pregnancy	A
- If metformin is used for PCOS and ovulation induction, it should be discontinued by the end of the first trimester	A
- In individuals with a history of GDM is found to have prediabetes and have overweight or obesity should be provided intensive lifestyle interventions and/or metformin for diabetes prevention	A
Children and Adolescents[17]	
- For children and adolescents that are incidentally diagnosed with T2D, metformin is recommended as the initial choice unless contraindicated due to renal function	A
- If individualized glycemic goals are not achieved or maintained with metformin (with or without long-acting insulin), GLP-1 RA and/or SGLT-2 inhibitor should be considered in children and adolescents	A
Obesity[32]	
- Prioritize medications with a beneficial effect on weight when choosing a glucose-lowering medication for people with diabetes and overweight and obesity	B
- Lifestyle changes should be considered for people with diabetes and overweight or obesity considering benefits and risks	A
- GLP-1 RAs or dual GLP-1 RAs/GIPs (i.e., semaglutide or tirzepatide) are the preferred therapy for individuals with diabetes and overweight or obesity due to their added weight-independent benefits	A

- Pharmacotherapy for weight loss that is chronic should be continued beyond reaching weight loss goals to maintain health benefits due to discontinuation often leading to weight gain and worsening or reemergence of cardiometabolic risk factors	B
- Obesity pharmacotherapy should have the dose and dose titration individualized to balance effectiveness, health benefits and tolerability. Consideration that the optimal treatment dose may not be the maximum approved dose	B
- Treatment may be intensified with additional approaches, including lifestyle management programs, metabolic surgery and additional or alternative pharmacological agents in people with diabetes not reaching weight treatment goals	A for all except B for alternative pharmacological agents
- For individuals with T1D and obesity (BMI $\geq$ 30.0 kg/m^2 or $\geq$ 27.5 kg/m^2 in Asian American individuals) the same obesity management strategies used for the general adult population, including GLP-1 RA based therapy and metabolic surgery should be applied	B for GLP-1 RA and C for metabolic surgery
Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CKD = chronic kidney disease; CV = cardiovascular disease; CVD = cardiovascular disease; DM = diabetes; eGFR = estimated glomerular filtration rate; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 RA = glucagon-like peptide-1 receptor agonists; GDM = gestational diabetes; HbA1 = hemoglobin A1c; HF = heart failure; LVH = left ventricular hypertrophy; MASH = metabolic dysfunction–associated steatohepatitis; MASLD - metabolic dysfunction–associated steatotic liver disease; MI – myocardial infarction; MRA = mineralocorticoid receptor antagonist; mTOR = mechanistic target of rapamycin; PCOS = polycystic ovary syndrome; SGLT-2 = sodium-glucose cotransporter-2; T1D = type 1 diabetes; T2D = type 2 diabetes.	

VA/DoD – Guidelines for the Management of Type 2 Diabetes Mellitus

Recommendations were updated by the VA/DoD on managing patients with T2D.[18] Rigorous review of the evidence was performed and GRADE methodology was applied to the evidence, rating it from Strong (high or moderate strength of evidence) or Weak. Text representing the strength of the evidence is presented in **Table 5**.[18] Literature was searched through 2022. The use of dual GLP-1/GIP receptor agonists were not evaluated.

Table 5. Strength and Direction of Recommendations and General Corresponding Text[18]

Recommendation Strength and Direction	General Corresponding Text
Strong for	We recommend . . .
Weak for	We suggest . . .
Neither for nor against	There is insufficient evidence to recommend for or against . . .
Weak against	We suggest against . . .
Strong against	We recommend against . . .

The VA/DoD recommends the use of metformin as first line for patients with T2D when pharmacotherapy is indicated and there are no contraindications to its use.[18] If the patient has established ASCVD or high risk for ASCVD, diabetic nephropathy, or HF consider a GLP-1 RA or SGLT-2 inhibitor. An SGLT-2 inhibitor or GLP-1 RA should be considered for patients with diabetic nephropathy.[18] For specific pharmacotherapy recommendations see Table 6.

Table 6. Recommendations from the VA/DoD for Pharmacotherapy for the Management of T2D in Adults[18]

Recommendation	Strength of Evidence
Metformin or other select medications (not described) is suggested for those patients who have prediabetes and have participated in healthy lifestyle modification and remain at high risk of progression to T2D. Patients should be evaluated for specific patient characteristics (e.g., age, life expectancy, co-occurring conditions, BMI, other risk factors) when selecting a medication.	Weak
SGLT-2 inhibitors or GLP-1 RAs, with proven CV benefit to decrease the risk of major adverse CV events, are suggested therapy for patients with ASCVD (i.e., CKD, LVH, HF)	Strong
SGLT-2 inhibitors or GLP-1 RAs, with proven CV benefit to decrease the risk of major adverse CV events, are suggested therapy for patients at high risk of ASCVD (i.e., CKD, LVH, HF)	Weak
Patients with HF we recommend SGLT-2 inhibitors to prevent hospital admissions for HF	Strong
SGLT-2 inhibitors with proven renal protection to improve renal outcomes are recommended for patients with CKD	Strong
GLP-1 RAs with proven renal protection to improve macroalbuminuria for adults with T2DM who have CKD and are not able to take SGLT-2 inhibitors	Strong
Patients with CVD or renal disease we suggest that the addition of SGLT-2 or GLP-1 RA be considered even if the patient has obtained their target range for glycemic control	Weak
Classes of antidiabetic therapies besides insulin, sulfonylureas or meglitinides in adults, especially those 65 years and older, are suggested to reduce risk of hypoglycemia	Weak
Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; GLP-1 RA = glucagon-like peptide-1 receptor agonists; HF = heart failure; LVH = left ventricular hypertrophy; SGLT-2 = sodium-glucose cotransporter 2; T1D = type 1 diabetes; T2D = type 2 diabetes.	

ACP – Newer Pharmacological Treatment in Adults with Type 2 Diabetes

An update by ACP on the use of newer pharmacotherapies for T2D was published in 2024, updating a guideline published in 2017.[19] Newer pharmacotherapies included in the guideline are GLP-1 RAs (dulaglutide, exenatide, liraglutide, lixisenatide, and semaglutide), GLP-1RA/GIP (tirzepatide), SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin), DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, and sitagliptin), and long-acting insulins (insulin glargine and insulin degludec).[19] Recommendations are based on a systematic review and network meta-analysis done by ACP. Recommendations are based on the certainty of evidence, ranging from low to high, and strength of recommendation: strong (ACP recommends) and conditional (ACP suggests). Most of the included studies were in addition to usual care in adults requiring additional glucose lowering. Studies including hospitalized adults with T2D and adults with T2D with acute comorbid conditions, such as acute stroke or MI, were excluded.[19] Main outcomes of interest were risk for all-cause mortality, CV morbidity, and progression of CKD. Weight loss was also an important outcome but data was insufficient to perform a network meta-analysis on weight loss.

The ACP recommends metformin and lifestyle modifications first line for patients with T2D.[19] The addition of an SGLT-2 inhibitor or GLP-1 RA to metformin is recommended for adults who have suboptimal glucose control (strong recommendation; high certainty of evidence). The use of SGLT2 inhibitors should be prioritized for those with CHF or CKD.[19] The ACP found both SGLT-2 inhibitors and GLP-1 RAs to reduce all-cause mortality compared to placebo or usual care based on high quality evidence. There was no evidence to suggest superiority of one class over another based on efficacy and harms outcomes. However, SGLT-2 inhibitors probably reduce the risk of hospitalizations due to CHF more than GLP-1 RAs and GLP1-RAs probably reduce the risk for stroke more than SGLT2s. The addition of a DPP-4 inhibitor to metformin is recommended against for the reduction in morbidity and all-cause mortality (strong recommendation; high-certainty of evidence).[19]

NICE – Management of Type 1 and Type 2 Diabetes Mellitus in Children and Young People

In 2023, NICE updated guidance on the treatment of young people with T1DM and T2DM.[20] Literature was searched through February 2023. Recommendations include:

- Maintenance of an HbA1c of 6.5% or less minimizes long-term complications.[20]
- Metformin is recommended as a first-line agent in children who require medication for T2D, in addition to dietary support.[20]
- Basal-bolus insulin is recommended in children who present with ketosis without diabetic ketoacidosis (DKA).[20]
- Review glucose monitoring 4 weeks after treatment is started.[20]
- If a change in treatment is required for individuals 10 years and older with T2D taking metformin monotherapy, offer liraglutide or dulaglutide if the following are met:[20]
    - HbA1c remains at 6.5% or greater,
    - Plasma glucose greater than126 mg/dL (4 or more days a week when fasting or before meals), or
    - Plasma glucose greater than 162 mg/dL (on 4 or more days a week, 2 hours after meals)
- Empagliflozin may be added to metformin children 10 years or older with T2D who are not able to tolerate liraglutide or dulaglutide or have a clear preference for empagliflozin.[20]
- Insulin can be considered in young people with T2D who are taking metformin, with or without liraglutide, dulaglutide, or empagliflozin, if an HbA1c of 6.5% cannot be obtained on current therapy.[20]
- In children on metformin and insulin, the addition of liraglutide or dulaglutide can be considered for those who are already on insulin therapy, instead of increasing insulin, if their HbA1c or glucose levels do not meet criteria (e.g., HbA1c ≥6.5%, plasma glucose level >126 mg/dL [4 or more days a week when fasting or before meals] or plasma glucose >162 mg/dL [on 4 or more days a week, 2 hours after meals]).[20]
- The addition of empagliflozin is recommended, instead of increasing insulin, in children already on insulin if their HbA1c or glucose levels do not meet recommendations for reducing or stopping insulin (e.g., HbA1c ≥6.5%, plasma glucose level >126 mg/dL [4 or more days a week when fasting or before meals]) and they are not able to tolerate liraglutide or dulaglutide or if they specifically request empagliflozin.[20]
- The lowest dose of medications should be used that achieves target HbA1c and blood glucose levels.[20]

Diabetes and Chronic Kidney Disease

KIDGO - Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease

The KDIGO updated guidance in 2022 for management of individuals with diabetes mellitus with CKD.[21] The strength of the recommendation was either Level 1 (strong), which are recommendations, and Level 2 (weak) which are suggestions. The quality of evidence is graded from A (high) to D (low). The most important outcomes in the management of CKD are mortality, CV events (e.g., MI, stroke and HF) and kidney related outcomes (e.g., progression to kidney failure and acute kidney injury).[21] Recommendations which include antidiabetic therapies will be included:

- It is recommended to treat patients with T2D, CKD, and an eGFR ≥20 ml/min/1.73 m^2 with a SGLT-2 inhibitor (1A recommendation).[21] The choice of SGLT-2 inhibitor should prioritize therapies with documented kidney or CV benefit and consider eGFR.
- In patients with T2D, CKD and estimated glomerular filtration rate [EGFR] of >30 ml/min/1.73 m^2 metformin is recommended (1B recommendation).[21]
- In patients with T2D and CKD (without dialysis and estimated glomerular filtration rate [EGFR] of >30 ml/min/1.73 m^2), metformin with a SGLT-2 inhibitor is recommended (1A recommendation).[21]
- Long-acting GLP-1 RAs with CV benefit are recommended for patients requiring additional medications for glucose lowering or who cannot tolerate

metformin and/or SGLT-2 inhibitors (1B recommendation).[21]

- o GLP-1 RAs are also preferred for those patients desiring weight loss, have heart failure, high-risk of ASCVD and wish to avoid hypoglycemia.
- o The combined use of GLP-1 RAs and DDP-4 inhibitors should not be used.
- o If GLP-1 RAs are used with sulfonylureas or insulin, the dose of those products should be reduced to reduce the risk of hypoglycemia.

VA/DOD – Primary Care Chronic Kidney Disease Management

The VA/DOD updated guidance on the treatment of CKD in the primary care setting in adults who have, or are at risk for, CKD.[22] This comprehensive guideline provides recommendations for diagnosis, assessment, risk factors and treatment. Evidence is current through June 30, 2024.[22] For the purpose of this review, the role of antidiabetic therapies in CKD will be presented **(Table 7**).

Table 7. Antidiabetic Therapies in the Management of Chronic Kidney Disease[22]

Recommendation	Strength
Medications to decrease CV disease and kidney outcomes	
- To reduce the risk of major adverse CV events, HF, progression of kidney disease and mortality the addition of SGLT-2 inhibitors to maximally tolerated ACE inhibitor or ARB is recommended in patients with CKD disease who have one or more of the following: T2D, albuminuria (UACR >200 mg/g), HF (SGLT-2 inhibitor should be continued until dialysis)	Strong
- In patients with T2D and albuminuric CKD a GLP-1 RA is recommended to be added to an ACE or ARB to reduce the progression of CKD, major adverse CV events and all-cause mortality	Strong
Abbreviations: ACE = angiotensin converting enzyme Inhibitor; ARB = angiotensin II receptor blocker; CKD = chronic kidney disease; CV = cardiovascular; GLP-1 RA = glucagon-like peptide-1 receptor agonists; HF = heart failure; SGLT-2 = sodium-glucose cotransporter 2; T2D = type 2 diabetes; UACR = urine albumin-to-creatinine ratio.	

Diabetes and Weight Management

TOS/OMA/OAC – Pharmacological Management of Overweight or Obesity

A 2026 guideline on the management of adults with overweight or obesity was published by a multidisciplinary panel.[23] Methodology was well described and recommendations were graded using the Granding of Recommendations Assessment, Development and Evaluation (GRADE) approach. Medications included in the review are orlistat, bupropion-naltrexone, phentermine, phentermine-topiramate, liraglutide, semaglutide and tirzepatide. Obesity medications are FDA approved for adults with a BMI of $\geq$ 27 kg/m^2 with at least one complication or BMI $\geq$ 30 kg/m^2.[23] Pharmacotherapy recommendations are provided in **Table 8.** All treatments should be used in conjunction with lifestyle/behavioral interventions. Evidence for the use of GLP-1 RAs and GLP-1 RAs/GIPs in patients with T2D and overweight or obesity also demonstrate HbA1c lowering, MACE and mortality benefits.[23]

Table 8. Recommendation for Pharmacotherapy for Obesity[23]

Recommendation	Strength of Recommendation / Level of Evidence
Orlistat for adults aged 18 years or older with overweight or obesity	Conditional; low certainty of evidence
Bupropion- naltrexone in adults aged 18 years or older with overweight or obesity	Strong; moderate certainty of evidence
Phentermine for 3 months or more in adults aged 18 years or older with overweight or obesity	Conditional; low certainty evidence
Phentermine- topiramate in adults aged 18 years or older with overweight or obesity	Conditional; low certainty of evidence

Liraglutide in adults aged 18 years or older with overweight or obesity	Conditional; low certainty evidence
Semaglutide in adults aged 18 years or older with overweight or obesity	Strong; moderate certainty evidence
Tirzepatide in adults aged 18 years or older with overweight or obesity	Strong; moderate certainty evidence
Setmelanotide in adults aged 18 years or older with monogenic obesity syndromes (e.g., risk alleles for LEPR, POMC, PCSK1, and BBS)	Strong; moderate certainty evidence
Continue obesity medications in adults undergoing medical obesity treatment during the weight maintenance phase, compared with not continuing obesity medications	Strong; moderate certainty evidence
GLP- 1 receptor agonists or GLP- 1 RA/GIP receptor dual agonists in adults aged 18 years or older with OSA * Evidence examined included trials using liraglutide or tirzepatide; tirzepatide is FDA approved for moderate- to-severe OSA	Conditional; low certainty of evidence
GLP- 1 receptor agonists or GLP- 1 RA/GIP receptor dual agonists in adults aged 18 years or older with HFpEF * Evidence examined included trials using semaglutide or tirzepatide, in which treatment of HFpEF is considered off-label use	Conditional; low certainty of evidence
GLP- 1 receptor agonists or GLP- 1 RA/GIP receptor dual agonists in adults aged 18 years or older to reduce liver fat and treat MASH * Semaglutide is not FDA approved for treatment of MASLD without MASH	Conditional; low certainty of evidence
GLP- 1 receptor agonists compared to lifestyle interventions/placebo in adults aged 18 years or older with osteoarthritis	Conditional; low certainty of evidence
Semaglutide in adults aged 18 years or older with a history of myocardial infarction, stroke, or symptomatic peripheral vascular disease	Conditional; low certainty of evidence
FDA- approved obesity medications in adults aged 18 years or older with type 2 diabetes	Conditional; low certainty of evidence
Abbreviations: BBS = Bardet-Biedl syndrome; FDA = Food and Drug Administration; GIP = glucose-dependent insulinotropic polypeptide ; GLP-1 RA = glucagon-like peptide-1 receptor agonists; HFpEF = heart failure with preserved ejection fraction; LEPR = leptin receptor; MASH = metabolic dysfunction–associated steatohepatitis; MASLD = - metabolic dysfunction–associated steatotic liver disease; OSA = obstructive sleep apnea; PCSK1 = Proprotein Convertase Subtilisin/Kexin Type 1; POMC = pro-opiomelanocortin (POMC).	

Diabetes and Pregnancy

SIGN – Management of Diabetes in Pregnancy

A 2024 guideline was published by SIGN outlined treatment and management of women with T1D and T2D during pregnancy.[24] Recommendations were considered 'strong' by being described as 'should' be used while 'conditional' recommendations are described as 'considered'. Recommendations for drug therapy will be included.

For gestational diabetes the avoidance of DPP-4 inhibitors, GLP-1 RAs, SGLT-2 inhibitors and TZDs is recommended.[24] The use of sulfonylureas should be avoided due to risk of neonatal hypoglycemia. If the patient requires medication for glucose management the use of metformin or insulin should be used first line. In women who have diabetes before pregnancy the use of insulin and/or metformin are recommended.[24] The use of insulin and/or metformin during breastfeeding is also recommended.

Endocrine Society and European Society of Endocrinology – Preexisting Diabetes and Pregnancy

In 2025 a joint guideline was published by the ES and ESE for the management of patients with preexisting T1D and T2D.[25] Evidence was searched through and was graded using GRADE methodology, with certainty of evidence graded from very low to high. The strength of the recommendation was designated as a 1 (Strong recommendation) or 2 (Conditional recommendation).

Recommendations related to pharmacotherapy in individuals that are pregnant are:

- Discontinuation of GLP-1 RAs prior to conception, rather than between the start of pregnancy and end of the first trimester, is suggested in individuals who have T2D and are taking a GLP-1 RA (Grade 2 /very low-quality evidence).[25]
- In individuals with T2D taking insulin, the routine addition of metformin is recommended against (Grade 2 /very low-quality evidence).[25]
- The use of a hybrid closed-loop pump is suggested rather than an insulin pump with CGM (without an algorithm) or multiple daily insulin injections in individuals with T1D (Grade 2 /very low-quality evidence).[25]

Polyendocrine Metabolic Ovary Syndrome

International Evidence Based Guideline – Management of Polyendocrine Metabolic Ovary Syndrome

An International evidence-based guideline on the assessment and management of PMOS was published in 2023 as partnership with the American Society of Reproductive Medicine (ASRM), the ES, European Society of Endocrinology and the European Society of Human Reproduction and Embryology (ESHRE).[26] The guideline was developed via a process to align with the Appraisal of Guidelines for Research and Evaluation II (AGREE II) framework. Recommendations were based on GRADE methodology and are comprised of the following 3 categories: EBR (evidence-based recommendations), CR (consensus recommendation) and PP (practice points). The evidence for the use of diabetes drugs in the management of PMOS will be presented.

Recommendations include the following:

- Women with PMOS are at an increased risk of impaired fasting glucose, impaired glucose tolerance and T2D, irrespective of age and BMI and glucose measurements should be assessed in adults and adolescents with PMOS (strong recommendation and low-quality evidence).[26]
- A conditional recommendation based on very low-quality evidence for the use of metformin as monotherapy for adults with PMOS and a BMI $\geq$25 kg/m^2 for anthropometric and metabolic outcomes (i.e., insulin resistance, glucose and lipid profiles).
- Metformin can be considered for adolescents at risk of or with PMOS for cycle regulation (Conditional recommendation based on very low-quality evidence).[26]
- In adults with PMOS and a BMI <25 kg/m^2 may consider metformin (Conditional recommendation with limited evidence).
- Women should be informed that metformin and lifestyle interventions have similar efficacy (Practice Point).[26] The use of combined oral contraceptive pills (COCP) could be recommended over the use of metformin for management of hirsutism in irregular menstrual cycles in PMOS (Conditional recommendation based on very-low quality evidence).[26]
- Metformin could be used over COCP for metabolic indications in PMOS (Conditional recommendation based on very-low quality evidence).
- A conditional recommendation based on very-low quality evidence for the combination of COCP and metformin could be considered to offer little additional clinical benefit over monotherapy in adults with PCOS with a BMI $\leq$30 kg/m^2.[26]
- Metformin, when used in combination with COCP, may be most beneficial in high metabolic risk groups including those with a BMI > 30 kg/m^2, diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups according to a practice point recommendation.[26]
- Metformin may be considered for irregular menstrual cycles when COCP is contraindicated according to a practice point recommendation.

- Metformin should be considered over inositol for hirsutism and central adiposity; however, metformin has more gastrointestinal side-effects than inositol (Conditional recommendation based on very-low quality of evidence).[26]
- A conditional recommendation for the use of anti-obesity medications (e.g., liraglutide, semaglutide, and orlistat) could be considered, in addition to lifestyle interventions, could be considered in the management of higher weight adults with PCOS similar to recommendations for the general population.[26]
- A conditional recommendation against the use of anti-obesity agents for PCOS for reproductive outcomes.
- Metformin could be considered in some circumstances (e.g. risk for preterm birth), to reduce preterm delivery and limit excess gestational weight gain, in pregnant women with PCOS (Conditional recommendation based on moderate quality of evidence).[26]
- A conditional recommendation based on low quality evidence for the use of metformin in women with PMOS and anovulatory infertility and no other fertility factors, could be used alone to improve clinical pregnancy and live birth rates; however, there are more effective ovulation agents.
- Clomiphene citrate in conjunction with metformin could be used rather than clomiphene citrate alone in women with PMOS with anovulatory infertility and no other infertility factors to improve ovulation and clinical pregnancy rates (Conditional recommendation based on low quality evidence).[26]
- Clomiphene citrate combined with metformin could be used rather than metformin alone in women with PMOS with anovulatory infertility and no other infertility factors to improve live birth rates (Conditional recommendation based on low quality evidence).
- A conditional recommendation based on very low-quality evidence recommends adjunct metformin therapy as an option to be used before and/or during follicle stimulation hormone (FSH) ovarian stimulation in women with PMOS undergoing IVF/ICSI treatment with GnRH agonist long protocol, to reduce the risk of developing ovarian hyperstimulation syndrome and miscarriage.[26]

<u>EULAR – Management of Systemic Lupus Erythematosus with Kidney Involvement</u>

In 2025 EULAR updated recommendations for patients with SLE and kidney involvement.[27] A literature search was performed from January 2019 to March 2024 to update the 2019 recommendations. The level of evidence was graded from 1-4 and the recommendations from highest (A) to lowest (D). Thirteen recommendations were included but for the purpose of this review only antidiabetic therapies will be discussed.

The guidance recommends the use of nonimmune treatments, which are considered second pillar treatment of lupus nephritis (LN).[27] SGLT-2 inhibitors are included for use in this population for stable patients with persistent proteinuria or eGFR ≤ 60 ml/min/1.73 m^2, or other risk factors for progressive CKD (Level 5/D). Studies of SGLT-2 inhibitors in patients with autoimmune disease-related CKD demonstrated delayed progression of GFR decline. Initiation of SGLT-2 inhibitors is recommended to be delayed 6-12 months after stabilization of LN with immunosuppressive therapy. There is insufficient evidence for use in pediatric patients.

After review, 6 guidelines were excluded due to poor quality.

New Formulations:

<u>RYBELSUS to OZEMPIC (semaglutide):</u> Oral semaglutide is available in two types of formulations, R1 and R2.[33] The R1 formulation is the original tablet available as 3 mg, 7 mg, and 14 mg. The R2 formulation (newer) is available as 1.5 mg, 4 mg and 9 mg. The doses are not interchangeable and it is recommended to not switch between the R1 and R2 formulations in during the first 30 days of use.[33] The R2 formulation has increased absorption with lower doses of semaglutide in an effort to reduce GI AE. The R2 formulation was changed from brand name Rybelsus to Ozempic tablets in January 2026.[33]

BRYNOVIN (sitagliptin): BRYNOVIN is an oral sitagliptin solution approved in January 2025 as an adjunct to diet and exercise to improve glucose control in adults with T2D.[34] BRYNOVIN is dosed at 100 mg daily (4 mL) with or without food. Renal adjustment is recommended for patients with an eGFR of less than 45 mL/min/1.73m^2.[34]

ZITUVIMET (sitagliptin/metformin): ZITUVIMET is sitagliptin, a DPP-4 inhibitor, and metformin, a biguanide combination tablet approved as an adjunct to diet and exercise to improve glucose control for adult patients with T2D.[35] The tablet is available as sitagliptin 50 mg/metformin 500 mg or sitagliptin 100 mg/metformin 1000 mg to be given twice daily with meals.[35]

ZITUVIMET XR (metformin/sitagliptin extended-release tablets): An extended-release tablet formulation of sitagliptin and metformin was approved in July of 2024. It is approved to improve glucose control in adult patients with T2D.[36] The extended-release tablets should be taken once daily, even if the patient is taking two tablets they should be taken together. ZITUVIMET XR is available as sitagliptin 100 mg/metformin 1,000 mg extended-release, sitagliptin 50 mg/ metformin 500 mg extended-release and sitagliptin 50 mg/metformin 1000 mg extended-release.[36]

ZITUVIO (sitagliptin): In October 2023 sitagliptin tablets were approved for use as an adjunct to diet and exercise to improve glucose levels in adults with T2D.[37] ZITUVIO is given as 100 mg daily with or without food. Patients with renal impairment should receive as reduced dose based on eGFR. ZITUVIMET is available 25 mg, 50 mg and 100 mg tablets.[37]

New Indications:

MOUNJARO (tirzepatide): In December of 2025 tirzepatide received the approval for an expanded indication for pediatric patients aged 10 years and older with T2D.[38] The expanded indication was approved based off a double-blind, placebo-controlled, open-label trial in pediatric patients 10 years of age and older with T2D and inadequate glucose control on metformin, basal insulin or both.[38] Tirzepatide 5 mg, tirzepatide 10 mg or placebo was given as a once-weekly subcutaneous injection. Tirzepatide 5 mg reduced HbA1c by -1.7% (95% CI, -2.4 to -1.0) and tirzepatide 10 mg by 2.0% (95% CI, -2.7 to -1.3) compared to placebo at 30 weeks.[38]

RYBELSUS (semaglutide): Semaglutide tablets were approved in October 2025 for a new indication for the reduction of the risk of major adverse CV events (CV death, non-fatal MI or non-fatal stroke) in adults with T2D who are at risk for these events.[33] Supportive evidence for this indication is based off a double-blind, placebo-controlled, randomized controlled trial in 9,650 patients with T2D and established CVD and/or CKD. Patients received semaglutide 14 mg or placebo. The primary outcome was time to first occurrence of a 3-point MACE (CV death, non-fatal MI and non-fatal stroke).[33] Semaglutide was more effective than placebo, 12.0% versus 13.8% (HR 0.86; 95% CI, 0.77 to 0.96).[33]

OZEMPIC (semaglutide): In January of 2025 semaglutide injection received a new indication to reduce the risk of sustained eGFR decline, end-stage kidney disease and CV death in adults with T2D.[39] Evidence for this approval was based on the FLOW trial described in Table 10.[40]

SYNJARDY (empagliflozin/metformin) and SYNJARDY XR (empagliflozin/metformin extended-release tablets): In March of 2025 SYNJARDY and SYNJARDY XR received the expanded indication to reduce the risk of sustained decline in eGFR, end-stage kidney disease, CV death and hospitalization in adults with CKD at risk of progression.[41] The expanded indication was supported by evidence from a study in patients (n=6,609) with CKD and with or without T2D in a double-blind,

placebo-controlled, randomized controlled trial. The primary composite endpoint was reduced with empagliflozin, and background metformin therapy, compared to placebo (HR 0.72; 95% CI, 0.48 to 1.09).[41]

XIGDUO XR (dapagliflozin/metformin extended-release tablets): The dapagliflozin component of the combination tablet received the expanded indication for approved use in adults with T2D to reduce the risk of CV death, hospitalization for HF, and urgent HF visit in patients with HF.[42] Evidence for the indication was from two double-blind, placebo-controlled, randomized controlled trials (DAPA-HF and DELIVER). Trials included patients with and without diabetes. The primary composite outcome was CV death, hospitalization for HF or urgent HF visit. In both trials dapagliflozin reduced the primary endpoint more than placebo (DAPA-HF trial: HR 0.74; 95% CI, 0.65 to 0.85; p<0.0001) and (DELIVER trial: HR 0.82; 95% CI, 0.73 to 0.92; p=0.0008).[43,44]

New FDA Safety Alerts:

Table 9. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Saxagliptin[45]	ONGLYZA	October 2024	Use in specific populations	Safety and effectiveness of saxagliptin have not been demonstrated in pediatric patients ages 10 to 17 years with T2D
Dulaglutide[39], liraglutide[46], semaglutide[39]	TRULICITY, VICTOZA, OZEMPIC	March 2026	Warnings and Precautions	Severe gastrointestinal adverse reactions have been reported in postmarketing reports including intestinal obstruction, severe constipation, including fecal impaction
Dulaglutide[38], exenatide[47], liraglutide[46], semaglutide[39], tirzepatide[38]	TRULICITY BYETTA VICTOZA OZEMPIC MOUNJARO	October 2024	Warnings and Precautions	Risk of pulmonary aspiration for patients undergoing elective surgeries or procedures requiring general anesthesia or deep sedation
Tirzepatide[38]	MOUNJARO	January 2026	Warnings and Precautions	Never share Kwikpens between patients, even if the needle is changed. There is a risk of transmission of blood-borne pathogens.

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38. MOUNJARO (tirzepatide injection)[prescribing information]. Indianapolis, IN; Lilly USA, LLC. December 2025.

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Appendix 1: Current Preferred Drug List

DPP-4 Inhibitors

Generic	Brand	Form	PDL
saxagliptin HCl	ONGLYZA	TABLET	Y
saxagliptin HCl	SAXAGLIPTIN HCL	TABLET	Y
sitagliptin phos/metformin HCl	JANUMET	TABLET	Y
sitagliptin phosphate	JANUVIA	TABLET	Y
alogliptin benz/metformin HCl	ALOGLIPTIN-METFORMIN	TABLET	N
alogliptin benz/metformin HCl	KAZANO	TABLET	N
alogliptin benz/pioglitazone	ALOGLIPTIN-PIOGLITAZONE	TABLET	N
alogliptin benz/pioglitazone	OSENI	TABLET	N
alogliptin benzoate	ALOGLIPTIN	TABLET	N
alogliptin benzoate	NESINA	TABLET	N
linagliptin	TRADJENTA	TABLET	N
linagliptin/metformin HCl	JENTADUETO XR	TAB BP 24H	N
linagliptin/metformin HCl	JENTADUETO	TABLET	N
linagliptin/metformin HCl	LINAGLIPTIN-METFORMIN	TABLET	N
saxagliptin HCl/metformin HCl	SAXAGLIPTIN-METFORMIN ER	TBMP 24HR	N
sitagliptin	SITAGLIPTIN	TABLET	N
sitagliptin	ZITUVIO	TABLET	N
sitagliptin HCl	BRYNOVIN	SOLUTION	N
sitagliptin phos/metformin HCl	JANUMET XR	TBMP 24HR	N
sitagliptin/metformin HCl	SITAGLIPTIN-METFORMIN	TABLET	N
sitagliptin/metformin HCl	ZITUVIMET	TABLET	N
sitagliptin/metformin HCl	SITAGLIPTIN-METFORMIN ER	TBMP 24HR	N
sitagliptin/metformin HCl	ZITUVIMET XR	TBMP 24HR	N

GLP-1 Receptor Agonists and GIP Therapies

Generic	Brand	Form	PDL
dulaglutide	TRULICITY	PEN INJCTR	Y
exenatide	BYETTA	PEN INJCTR	Y
exenatide	EXENATIDE	PEN INJCTR	Y
liraglutide	LIRAGLUTIDE	PEN INJCTR	Y
liraglutide	VICTOZA 2-PAK	PEN INJCTR	Y
liraglutide	VICTOZA 3-PAK	PEN INJCTR	Y
exenatide microspheres	BYDUREON BCISE	AUTO INJCT	N
semaglutide	OZEMPIC	PEN INJCTR	N
semaglutide	RYBELSUS	TABLET	N
tirzepatide	MOUNJARO	PEN INJCTR	N

SGLT-2 Inhibitors

Generic	Brand	Form	PDL
dapagliflozin propanediol	DAPAGLIFLOZIN	TABLET	Y
dapagliflozin propanediol	FARXIGA	TABLET	Y
empagliflozin	JARDIANCE	TABLET	Y
canagliflozin	INVOKANA	TABLET	N
canagliflozin/metformin HCl	INVOKAMET XR	TAB BP 24H	N
canagliflozin/metformin HCl	INVOKAMET	TABLET	N
dapaglifloz propaned/metformin	DAPAGLIFLOZIN-METFORMIN ER	TAB BP 24H	N
dapaglifloz propaned/metformin	XIGDUO XR	TAB BP 24H	N
empaglifloz/linaglip/metformin	TRIJARDY XR	TAB BP 24H	N
empagliflozin/linagliptin	GLYXAMBI	TABLET	N
empagliflozin/metformin HCl	SYNJARDY XR	TAB BP 24H	N
empagliflozin/metformin HCl	SYNJARDY	TABLET	N
ertugliflozin pidolate	STEGLATRO	TABLET	N
ertugliflozin/metformin	SEGLUROMET	TABLET	N
ertugliflozin/sitagliptin phos	STEGLUJAN	TABLET	N
sotagliflozin	INPEFA	TABLET	N

Sulfonylureas

Generic	Brand	Form	PDL
glimepiride	GLIMEPIRIDE	TABLET	Y
glipizide	GLIPIZIDE	TABLET	Y
glyburide	GLYBURIDE	TABLET	Y
chlorpropamide	CHLORPROPAMIDE	TABLET	N
glimepiride	GLIMEPIRIDE	TABLET	N
glipizide	GLIPIZIDE ER	TAB ER 24	N
glipizide	GLUCOTROL XL	TAB ER 24	N
glipizide	GLIPIZIDE	TABLET	N
glyburide,micronized	GLYBURIDE MICRONIZED	TABLET	N

Thiazolidinediones

Generic	Brand	Form	PDL
pioglitazone HCl	ACTOS	TABLET	Y
pioglitazone HCl	PIOGLITAZONE HCL	TABLET	Y
pioglitazone HCl/glimepiride	DUETACT	TABLET	N
pioglitazone HCl/glimepiride	PIOGLITAZONE-GLIMEPIRIDE	TABLET	N
pioglitazone HCl/metformin HCl	ACTOPLUS MET	TABLET	N
pioglitazone HCl/metformin HCl	PIOGLITAZONE-METFORMIN	TABLET	N

Miscellaneous Antidiabetic Agents

Generic	Brand	Form	PDL
metformin HCl	METFORMIN HCL ER	TAB ER 24H	Y
metformin HCl	METFORMIN HCL	TABLET	Y
acarbose	ACARBOSE	TABLET	N
glipizide/metformin HCl	GLIPIZIDE-METFORMIN	TABLET	N
glyburide/metformin HCl	GLYBURIDE-METFORMIN HCL	TABLET	N
metformin HCl	METFORMIN HCL	SOLUTION	N
metformin HCl	METFORMIN ER OSMOTIC	TAB ER 24	N
metformin HCl	METFORMIN ER GASTRIC	TABERGR24H	N
metformin HCl	METFORMIN HCL	TABLET	N
miglitol	MIGLITOL	TABLET	N
nateglinide	NATEGLINIDE	TABLET	N
pramlintide acetate	SYMLINPEN 120	PEN INJCTR	N
pramlintide acetate	SYMLINPEN 60	PEN INJCTR	N
repaglinide	REPAGLINIDE	TABLET	N

Appendix 2: New Comparative Clinical Trials

A total of 1601 citations were manually reviewed from the initial literature search. After further review, 1593 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 8 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 10. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Bliddal, et al[48] (STEP 9) DB, PC, RCT	Semaglutide 2.4 mg subcutaneously weekly Vs. Placebo Follow-up: 68 weeks	Participants with obesity (BMI ≥30 kg/m^2) and a clinical and radiologic diagnosis of moderate knee osteoarthritis with at least moderate pain (n=407)	Percent body weight change and change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score†	Change in body weight: Semaglutide: 13.7% Placebo: 3.2% (ED -10.5%; 95% CI, -12.3 to -8.6; P<0.001) Change in WOMAC pain score: Semaglutide: -41.7 points Placebo: -27.5 points (ED -14.1 points; 95% CI, -20.0 to -8.3; P<0.001)	- Mean WOMAC score was 70.9 points and mean BMI was 40.3 kg/m^2 - The WOMAC pain score is subjective - Long-term safety for chronic use is unknown - Results most applicable to those with very high BMIs - Funded by the manufacturer

Fox, et al[49] (SCALE) Phase 3a, RCT	Liraglutide 3.0 mg subcutaneously daily Vs. Placebo Treatment: 56 weeks Follow-up: 26 weeks	Children ages 6 to < 12 years with obesity (n=82)	Percent change in BMI	Liraglutide: -5.8% Placebo: 1.6% (ED -7.4%; 95% CI, -11.6 to -3.1; P<0.001)	- Serious adverse events in 12% of liraglutide and 8% in placebo group - Small sample size - Funded by the manufacturer
Kosiborod, et al[50] DB, RCT	Semaglutide 2.4 mg subcutaneously weekly Vs. Placebo Follow-up: 52 weeks	Patients with HF with preserved ejection fraction, BMI of $\geq$30 kg/m^2, and T2D (n=616)	Change from baseline in Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS)* and change in body weight from baseline	Change in KCCQ-CSS: Semaglutide: 13.7 points Placebo: 6.4 points (ED 7.3 points; 95% CI, 4.1 to 10.4; P<0.001) Change in body weight: Semaglutide: -9.8% Placebo: -3.4% (ED -6.4%; 95% CI, -7.6 to -5.2; P<0.001)	- One of the primary outcomes is subjective and a surrogate endpoint - No important health outcomes such as CV or all-cause mortality were studied - Funded by the manufacturer
Malhotra, et al [51] DB, Phase 3, RCT	Tirzepatide (maximum tolerated dose subcutaneously 10 mg or 15 mg weekly) Vs. Placebo subcutaneously weekly (n=52 weeks)	Two studies in adults with moderate-to-severe obstructive sleep apnea and obesity. One group was not receiving treatment with positive airway pressure (PAP) (n=234) at baseline and the second trial enrolled those receiving PAP (n=235)	Change in the apnea-hypopnea index (AHI) from baseline	Study 1: Tirzepatide: -25.3 events/hr Placebo: -5.3 events/hr ETD -20.0 events/hr; 95% CI, -25.8 to -14.2; P<0.001) Study 2: Tirzepatide: -29.3 events/hr Placebo: -5.5 events/hr ETD -23.8 events/hr; 95% CI, -29.6 to -17.9; P<0.001)	- Mean BMI 39 kg/m^2 - Neither study had participants with T1D or T2M - Evidence on outcomes such as stroke, CV events and MI would be helpful - Funded by the manufacturer
McGuire, et al[52] (SOUL)	Semaglutide orally up to max dose of 14 mg	Patients 50 years and older, HbA1c of 6.5% to 10.0% and	Major adverse cardiovascular events (a composite of death from cardiovascular causes,	Semaglutide: 579 (12%) Placebo: 668 (13.8%) (HR 0.86; 95% CI, 0.77 to 0.96; P=0.006)	- Most applicable for secondary prevention in patients with ASCVD and/or CKD

DB, PC, RCT, time to first event analysis	Vs. Placebo Mean follow-up: 47.5 months	known ASCVD, CKD or both (n=9650)	nonfatal myocardial infarction, or nonfatal stroke)		- An active comparator would be more informative - Funded by the manufacturer
Nicholls, et al[53] (SURPASS-CVOT) DB, NI, Phase 3	Tirzepatide subcutaneously once weekly (up to 15 mg) Vs. Dulaglutide 1.5 mg	Patients with T2D and atherosclerotic cardiovascular disease (n=13,299)	Composite of death from CV causes, MI or stroke (NI margin upper limit of 1.05; <1.00 indicated superiority)	Tirzepatide: 12.2% Dulaglutide: 13.1% (HR 0.92; 95% CI, 0.83 to 1.01; P=0.003 for noninferiority and P=0.09 for superiority)	- Mean age 64.1 years, mean HbA1c 8.4 and mean BMI was 32 kg/m^2 - Most applicable to patients with CV disease and T2D - Funded by the manufacturer
Packer, et al[54] DB, PC, RCT	Tirzepatide up to 15 mg subcutaneously weekly Vs. Placebo subcutaneously weekly Duration: 52 weeks Follow-up: 104 weeks	Patients with HF, and EF of at least 50% and a BMI of 30 kg/m^2 (n=365)	Composite of adjudicated death from cardiovascular causes or a worsening heart-failure event (assessed in a time-to-first-event analysis) and the change from baseline to 52 weeks in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) (scores range from 0 to 100, with higher scores indicating better quality of life)	Death from CV causes or worsening HF Tirzepatide: 36 (9.9%) Placebo: 56 (15.3%) (HR 0.62; 95% CI, 041 to 0.95; P=0.026) Change in KCCQ-CSS: Tirzepatide: 19.5 points Placebo: 12.7 points (MD 6.9 95% CI, 3.3 to 10.6; P<0.001)	- Composite endpoint driven by decreased risk of worsening heart failure - Results most applicable to individuals who are also obese - Most patients had mild to moderate HFpEF - Funded by the manufacturer
Perkovic, et al[40] (FLOW) DB, PC, RCT	Semaglutide 1.0 mg subcutaneously weekly Vs Placebo Median follow-up: 3.4 years	Patients with T2D and CKD (n=3533)	Major kidney disease events (e.g., composite of the onset of kidney failure, at least 50% reduction in the eGFR from baseline or death from kidney-related or CV causes)	Semaglutide: 331 Placebo: 410 (HR 0.76; 95% CI, 0.66 to 0.88; P=0.0003)	- Most patients were receiving ARBs (60.2%) or ACE inhibitors (35.1%) and some were also taking SGLT-2 inhibitors (15.6%) - Mean eGFR was 47.0 ml/min/1.73 m^2 - Results are most applicable to patients with a significant amount of albuminuria

					- Trial was stopped early due to benefit but may exaggerate treatment effect - Funded by the manufacturer

Key: * The Kansas City Cardiomyopathy Questionnaire clinical summary score ranges from 0 to 100 with higher scores demonstrating fewer symptoms and physical limitations; † The Western Ontario and McMaster Universities Osteoarthritis Index is scored from 0 to 100 with higher scores indicative of worse outcomes
Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CKD = chronic kidney disease; CI = confidence interval; CV = cardiovascular; DB= double blind; ED = estimated difference; EF = ejection fraction; ETD = estimated treatment difference; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1C; HFpEF = heart failure with preserved ejection fraction; HR = hazard ratio; MD = mean difference; MI = myocardial infarction; NI = noninferiority; PC = placebo controlled; RCT = randomized clinical trial; SGLT2 = sodium-glucose cotransporter 2; T2D = type 2 diabetes.

Appendix 3: Abstracts of Comparative Clinical Trials

Once-Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis

Bliddal, Harold Bays, Sébastien Czernichow, et al

Background: Weight reduction has been shown to alleviate symptoms of osteoarthritis of the knee, including pain. The effect of glucagon-like peptide-1 receptor agonists on outcomes in knee osteoarthritis among persons with obesity has not been well studied.

Methods: We conducted a 68-week, double-blind, randomized, placebo-controlled trial at 61 sites in 11 countries. Participants with obesity (a body-mass index [BMI; the weight in kilograms divided by the square of the height in meters] of ≥30) and a clinical and radiologic diagnosis of moderate knee osteoarthritis with at least moderate pain were randomly assigned, in a 2:1 ratio, to receive once-weekly subcutaneous semaglutide (2.4 mg) or placebo, in addition to counseling on physical activity and a reduced-calorie diet. The primary end points were the percentage change in body weight and the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score (on a scale of 0 to 100, with higher scores reflecting worse outcomes) from baseline to week 68. A key confirmatory secondary end point was the physical-function score on the 36-Item Short Form Health Survey (SF-36), version 2 (on a scale of 0 to 100, with higher scores indicating greater well-being).

Results: A total of 407 participants were enrolled. The mean age was 56 years, the mean BMI 40.3, and the mean WOMAC pain score 70.9. A total of 81.6% of the participants were women. The mean change in body weight from baseline to week 68 was -13.7% with semaglutide and -3.2% with placebo (P<0.001). The mean change in the WOMAC pain score at week 68 was -41.7 points with semaglutide and -27.5 points with placebo (P<0.001). Participants in the semaglutide group had a greater improvement in SF-36 physical-function score than those in the placebo group (mean change, 12.0 points vs. 6.5 points; P<0.001). The incidence of serious adverse events was similar in the two groups. Adverse events that led to permanent discontinuation of the trial regimen occurred in 6.7% of the participants in the semaglutide group and in 3.0% in the placebo group, with gastrointestinal disorders being the most common reason for discontinuation.

Conclusions: Among participants with obesity and knee osteoarthritis with moderate-to-severe pain, treatment with once-weekly injectable semaglutide resulted in significantly greater reductions in body weight and pain related to knee osteoarthritis than placebo. (Funded by Novo Nordisk; STEP 9 ClinicalTrials.gov number, NCT05064735.).

Liraglutide for Children 6 to <12 Years of Age with Obesity — A Randomized Trial

Claudia K. Fox, M.D., Margarita Barrientos-Pérez, M.D., Eric M. Bomberg, M.D., et al

BACKGROUND

No medications are currently approved for the treatment of nonmonogenic, nonsyndromic obesity in children younger than 12 years of age. Although the use of liraglutide has been shown to induce weight loss in adults and adolescents with obesity, its safety and efficacy have not been established in children.

METHODS

In this phase 3a trial, which consisted of a 56-week treatment period and a 26-week follow-up period, we randomly assigned children (6 to <12 years of age) with obesity, in a 2:1 ratio, to receive either once-daily subcutaneous liraglutide at a dose of 3.0 mg (or the maximum tolerated dose) or placebo, plus lifestyle interventions. The primary end point was the percentage change in the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters). The confirmatory secondary end points were the percentage change in body weight and a reduction in BMI of at least 5%.

RESULTS

A total of 82 participants underwent randomization; 56 were assigned to the liraglutide group and 26 to the placebo group. At week 56, the mean percentage change from baseline in BMI was −5.8% with liraglutide and 1.6% with placebo, representing an estimated difference of −7.4 percentage

points (95% confidence interval [CI], −11.6 to −3.2; P<0.001). The mean percentage change in body weight was 1.6% with liraglutide and 10.0% with placebo, representing an estimated difference of −8.4 percentage points (95% CI, −13.4 to −3.3; P=0.001), and a reduction in BMI of at least 5% occurred in 46% of participants in the liraglutide group and in 9% of participants in the placebo group (adjusted odds ratio, 6.3 [95% CI, 1.4 to 28.8]; P=0.02). Adverse events occurred in 89% and 88% of participants in the liraglutide and placebo groups, respectively. Gastrointestinal adverse events were more common in the liraglutide group (80% vs. 54%); serious adverse events were reported in 12% and 8% of participants in the liraglutide and placebo groups, respectively.

CONCLUSIONS

Among children (6 to <12 years of age) with obesity, treatment with liraglutide for 56 weeks plus lifestyle interventions resulted in a greater reduction in BMI than placebo plus lifestyle interventions. (Funded by Novo Nordisk; SCALE Kids ClinicalTrials.gov number, NCT04775082.)

Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes

Mikhail N Kosiborod, Mark C Petrie, Barry A Borlaug, et al

Background: Obesity and type 2 diabetes are prevalent in patients with heart failure with preserved ejection fraction and are characterized by a high symptom burden. No approved therapies specifically target obesity-related heart failure with preserved ejection fraction in persons with type 2 diabetes.

Methods: We randomly assigned patients who had heart failure with preserved ejection fraction, a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or more, and type 2 diabetes to receive once-weekly semaglutide (2.4 mg) or placebo for 52 weeks. The primary end points were the change from baseline in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations) and the change in body weight. Confirmatory secondary end points included the change in 6-minute walk distance; a hierarchical composite end point that included death, heart failure events, and differences in the change in the KCCQ-CSS and 6-minute walk distance; and the change in the C-reactive protein (CRP) level.

Results: A total of 616 participants underwent randomization. The mean change in the KCCQ-CSS was 13.7 points with semaglutide and 6.4 points with placebo (estimated difference, 7.3 points; 95% confidence interval [CI], 4.1 to 10.4; P<0.001), and the mean percentage change in body weight was -9.8% with semaglutide and -3.4% with placebo (estimated difference, -6.4 percentage points; 95% CI, -7.6 to -5.2; P<0.001). The results for the confirmatory secondary end points favored semaglutide over placebo (estimated between-group difference in change in 6-minute walk distance, 14.3 m [95% CI, 3.7 to 24.9; P = 0.008]; win ratio for hierarchical composite end point, 1.58 [95% CI, 1.29 to 1.94; P<0.001]; and estimated treatment ratio for change in CRP level, 0.67 [95% CI, 0.55 to 0.80; P<0.001]). Serious adverse events were reported in 55 participants (17.7%) in the semaglutide group and 88 (28.8%) in the placebo group.

Conclusions: Among patients with obesity-related heart failure with preserved ejection fraction and type 2 diabetes, semaglutide led to larger reductions in heart failure-related symptoms and physical limitations and greater weight loss than placebo at 1 year. (Funded by Novo Nordisk; STEP-HFpEF DM ClinicalTrials.gov number, NCT04916470.).

Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity

Authors: Atul Malhotra, M.D., Ronald R. Grunstein, M.D., Ph.D., Ingo Fietze, M.D., et al

BACKGROUND

Obstructive sleep apnea is characterized by disordered breathing during sleep and is associated with major cardiovascular complications; excess adiposity is an etiologic risk factor. Tirzepatide may be a potential treatment.

METHODS

We conducted two phase 3, double-blind, randomized, controlled trials involving adults with moderate-to-severe obstructive sleep apnea and obesity. Participants who were not receiving treatment with positive airway pressure (PAP) at baseline were enrolled in trial 1, and those who were receiving PAP

therapy at baseline were enrolled in trial 2. The participants were assigned in a 1:1 ratio to receive either the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or placebo for 52 weeks. The primary end point was the change in the apnea–hypopnea index (AHI, the number of apneas and hypopneas during an hour of sleep) from baseline. Key multiplicity-controlled secondary end points included the percent change in AHI and body weight and changes in hypoxic burden, patient-reported sleep impairment and disturbance, high-sensitivity C-reactive protein (hsCRP) concentration, and systolic blood pressure.

RESULTS

At baseline, the mean AHI was 51.5 events per hour in trial 1 and 49.5 events per hour in trial 2, and the mean body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) was 39.1 and 38.7, respectively. In trial 1, the mean change in AHI at week 52 was −25.3 events per hour (95% confidence interval [CI], −29.3 to −21.2) with tirzepatide and −5.3 events per hour (95% CI, −9.4 to −1.1) with placebo, for an estimated treatment difference of −20.0 events per hour (95% CI, −25.8 to −14.2) (P<0.001). In trial 2, the mean change in AHI at week 52 was −29.3 events per hour (95% CI, −33.2 to −25.4) with tirzepatide and −5.5 events per hour (95% CI, −9.9 to −1.2) with placebo, for an estimated treatment difference of −23.8 events per hour (95% CI, −29.6 to −17.9) (P<0.001). Significant improvements in the measurements for all prespecified key secondary end points were observed with tirzepatide as compared with placebo. The most frequently reported adverse events with tirzepatide were gastrointestinal in nature and mostly mild to moderate in severity.

CONCLUSIONS

Among persons with moderate-to-severe obstructive sleep apnea and obesity, tirzepatide reduced the AHI, body weight, hypoxic burden, hsCRP concentration, and systolic blood pressure and improved sleep-related patient-reported outcomes. (Funded by Eli Lilly; SURMOUNT-OSA ClinicalTrials.gov number, NCT05412004.)

Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes

Darren K. McGuire, M.D., M.H.Sc., Nikolaus Marx, M.D., Sharon L. Mulvagh,

BACKGROUND

The cardiovascular safety of oral semaglutide, a glucagon-like peptide 1 receptor agonist, has been established in persons with type 2 diabetes and high cardiovascular risk. An assessment of the cardiovascular efficacy of oral semaglutide in persons with type 2 diabetes and atherosclerotic cardiovascular disease, chronic kidney disease, or both is needed.

METHODS

In this double-blind, placebo-controlled, event-driven, superiority trial, we randomly assigned participants who were 50 years of age or older, had type 2 diabetes with a glycated hemoglobin level of 6.5 to 10.0%, and had known atherosclerotic cardiovascular disease, chronic kidney disease, or both to receive either once-daily oral semaglutide (maximal dose, 14 mg) or placebo, in addition to standard care. The primary outcome was major adverse cardiovascular events (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke), assessed in a time-to-first-event analysis. The confirmatory secondary outcomes included major kidney disease events (a five-point composite outcome).

RESULTS

Among the 9650 participants who had undergone randomization, the mean (±SD) follow-up was 47.5±10.9 months, and the median follow-up was 49.5 months. A primary-outcome event occurred in 579 of the 4825 participants (12.0%; incidence, 3.1 events per 100 person-years) in the oral semaglutide group, as compared with 668 of the 4825 participants (13.8%; incidence, 3.7 events per 100 person-years) in the placebo group (hazard ratio, 0.86; 95% confidence interval, 0.77 to 0.96; P=0.006). The results for the confirmatory secondary outcomes did not differ significantly between the two groups. The incidence of serious adverse events was 47.9% in the oral semaglutide group and 50.3% in the placebo group; the incidence of gastrointestinal disorders was 5.0% and 4.4%, respectively.

CONCLUSIONS
Among persons with type 2 diabetes and atherosclerotic cardiovascular disease, chronic kidney disease, or both, the use of oral semaglutide was associated with a significantly lower risk of major adverse cardiovascular events than placebo, without an increase in the incidence of serious adverse events. (Funded by Novo Nordisk; SOUL ClinicalTrials.gov number, NCT03914326.)

Cardiovascular Outcomes with Tirzepatide versus Dulaglutide in Type 2 Diabetes
Stephen J Nicholls, Imre Pavo, Deepak L Bhatt, et al
Background: Tirzepatide, a dual incretin agonist of the glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide receptors, has favorable effects on glycemic control and body weight. The effects on cardiovascular outcomes are uncertain.
Methods: We conducted an active-comparator-controlled, double-blind, noninferiority trial in which patients with type 2 diabetes and atherosclerotic cardiovascular disease were randomly assigned in a 1:1 ratio to receive a weekly subcutaneous injection of tirzepatide (up to 15 mg) or dulaglutide (1.5 mg), an agent that has been shown to reduce the incidence of cardiovascular events. The primary end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke and was tested for noninferiority of tirzepatide to dulaglutide with a margin of 1.05 for the upper limit of the 95.3% confidence interval for the hazard ratio. An upper limit of less than 1.00 was considered to indicate superiority of tirzepatide to dulaglutide.
Results: A total of 13,299 patients underwent randomization; 134 were subsequently excluded because they did not meet inclusion criteria. The modified intention-to-treat population thus included 6586 patients in the tirzepatide group and 6579 in the dulaglutide group. The mean (±SD) age of the patients was 64.1±8.8 years, 29.0% were women, the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 32.6±5.5, the mean glycated hemoglobin level was 8.4±0.9%, and the mean duration of diabetes was 14.7±8.8 years. A primary end-point event occurred in 801 patients (12.2%) in the tirzepatide group and 862 (13.1%) in the dulaglutide group (hazard ratio, 0.92; 95.3% confidence interval, 0.83 to 1.01; P = 0.003 for noninferiority; P = 0.09 for superiority). The incidence of adverse events appeared to be similar in the two groups, although more gastrointestinal adverse events were observed in the tirzepatide group.
Conclusions: Among patients with type 2 diabetes and atherosclerotic cardiovascular disease, tirzepatide was noninferior to dulaglutide with respect to a composite of death from cardiovascular causes, myocardial infarction, or stroke. (Funded by Eli Lilly; SURPASS-CVOT ClinicalTrials.gov number, NCT04255433.).

Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity
Milton Packer, Michael R Zile, Christopher M Kramer, et al
Background: Obesity increases the risk of heart failure with preserved ejection fraction. Tirzepatide, a long-acting agonist of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors, causes considerable weight loss, but data are lacking with respect to its effects on cardiovascular outcomes.
Methods: In this international, double-blind, randomized, placebo-controlled trial, we randomly assigned, in a 1:1 ratio, 731 patients with heart failure, an ejection fraction of at least 50%, and a body-mass index (the weight in kilograms divided by the square of the height in meters) of at least 30 to receive tirzepatide (up to 15 mg subcutaneously once per week) or placebo for at least 52 weeks. The two primary end points were a composite of adjudicated death from cardiovascular causes or a worsening heart-failure event (assessed in a time-to-first-event analysis) and the change from baseline to 52 weeks in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; scores range from 0 to 100, with higher scores indicating better quality of life).
Results: A total of 364 patients were assigned to the tirzepatide group and 367 to the placebo group; the median duration of follow-up was 104 weeks. Adjudicated death from cardiovascular causes or a worsening heart-failure event occurred in 36 patients (9.9%) in the tirzepatide group and in 56 patients (15.3%) in the placebo group (hazard ratio, 0.62; 95% confidence interval [CI], 0.41 to 0.95; P = 0.026). Worsening heart-failure events occurred in 29 patients (8.0%) in the tirzepatide group and in 52 patients (14.2%) in the placebo group (hazard ratio, 0.54; 95% CI, 0.34 to 0.85), and adjudicated death from cardiovascular causes occurred in 8 patients (2.2%) and 5 patients (1.4%), respectively (hazard ratio, 1.58; 95% CI, 0.52 to 4.83). At 52 weeks, the mean (±SD)

change in the KCCQ-CSS was 19.5±1.2 in the tirzepatide group as compared with 12.7±1.3 in the placebo group (between-group difference, 6.9; 95% CI, 3.3 to 10.6; P<0.001). Adverse events (mainly gastrointestinal) leading to discontinuation of the trial drug occurred in 23 patients (6.3%) in the tirzepatide group and in 5 patients (1.4%) in the placebo group.
Conclusions: Treatment with tirzepatide led to a lower risk of a composite of death from cardiovascular causes or worsening heart failure than placebo and improved health status in patients with heart failure with preserved ejection fraction and obesity. (Funded by Eli Lilly; SUMMIT ClinicalTrials.gov number, NCT04847557.).

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes
Vlado Perkovic, Katherine R Tuttle, Peter Rossing, et al
Background: Patients with type 2 diabetes and chronic kidney disease are at high risk for kidney failure, cardiovascular events, and death. Whether treatment with semaglutide would mitigate these risks is unknown.
Methods: We randomly assigned patients with type 2 diabetes and chronic kidney disease (defined by an estimated glomerular filtration rate [eGFR] of 50 to 75 ml per minute per 1.73 m^2 of body-surface area and a urinary albumin-to-creatinine ratio [with albumin measured in milligrams and creatinine measured in grams] of >300 and <5000 or an eGFR of 25 to <50 ml per minute per 1.73 m^2 and a urinary albumin-to-creatinine ratio of >100 and <5000) to receive subcutaneous semaglutide at a dose of 1.0 mg weekly or placebo. The primary outcome was major kidney disease events, a composite of the onset of kidney failure (dialysis, transplantation, or an eGFR of <15 ml per minute per 1.73 m^2), at least a 50% reduction in the eGFR from baseline, or death from kidney-related or cardiovascular causes. Prespecified confirmatory secondary outcomes were tested hierarchically.
Results: Among the 3533 participants who underwent randomization (1767 in the semaglutide group and 1766 in the placebo group), median follow-up was 3.4 years, after early trial cessation was recommended at a prespecified interim analysis. The risk of a primary-outcome event was 24% lower in the semaglutide group than in the placebo group (331 vs. 410 first events; hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.88; P = 0.0003). Results were similar for a composite of the kidney-specific components of the primary outcome (hazard ratio, 0.79; 95% CI, 0.66 to 0.94) and for death from cardiovascular causes (hazard ratio, 0.71; 95% CI, 0.56 to 0.89). The results for all confirmatory secondary outcomes favored semaglutide: the mean annual eGFR slope was less steep (indicating a slower decrease) by 1.16 ml per minute per 1.73 m^2 in the semaglutide group (P<0.001), the risk of major cardiovascular events 18% lower (hazard ratio, 0.82; 95% CI, 0.68 to 0.98; P = 0.029), and the risk of death from any cause 20% lower (hazard ratio, 0.80; 95% CI, 0.67 to 0.95, P = 0.01). Serious adverse events were reported in a lower percentage of participants in the semaglutide group than in the placebo group (49.6% vs. 53.8%).
Conclusions: Semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes in patients with type 2 diabetes and chronic kidney disease. (Funded by Novo Nordisk; FLOW ClinicalTrials.gov number, NCT03819153.).

Appendix 4: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to May 15, 2026

Search Strategy:

#	Searches	Results
1	dulaglutide.mp.	1231
2	exenatide.mp. or Exenatide/	4378
3	liraglutide.mp. or Liraglutide/	5624
4	semaglutide.mp.	4681
5	Tirzepatide/ or tirzepatide.mp.	2009
6	dapagliflozin.mp.	4397
7	empagliflozin.mp.	4397
8	canagliflozin.mp. or Canagliflozin/	2319
9	ertugliflozin.mp.	377
10	sotagliflozin.mp.	303
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	22669
12	limit 11 to (english language and humans and yr="2024 -Current")	3943
13	limit 12 to (clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or "systematic review")	557
14	saxagliptin.mp.	966
15	alogliptin.mp.	677
16	linagliptin.mp. or Linagliptin/	1265
17	sitagliptin.mp. or Sitagliptin Phosphate/	3561
18	glimepiride.mp.	1847
19	glipizide.mp. or Glipizide/	1328
20	glyburide.mp. or Glyburide/	7328
21	Chlorpropamide/ or chlorpropamide.mp.	2112
22	pioglitazone.mp. or Pioglitazone/	7339
23	Metformin/ or metformin.mp.	37026
24	Acarbose/ or acarbose.mp.	4810
25	miglitol.mp.	426
26	Nateglinide/ or nateglinide.mp.	621
27	pramlintide.mp.	492
28	repaglinide.mp.	1003
29	teplizumab.mp.	244
30	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29	63000
31	limit 30 to (english language and humans)	34586
32	limit 31 to yr="2018 -Current"	14890
33	limit 32 to (clinical trial, phase iii or meta analysis or practice guideline or "systematic review")	1601

Appendix 5: Key Inclusion Criteria

Population	Individuals with T2D, overweight and obesity, CKD, CVD, PCOS, SLE, MASH, OSA
Intervention	Antidiabetic therapies
Comparator	Active comparators or placebo
Outcomes	HbA1c, mortality, CV mortality, HF, MI, worsening renal function, BMI, weight loss, fertility, liver function (e.g., MASH resolution, fibrosis regression)
Setting	Outpatient

Appendix 6: Prior Authorization Criteria

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All non-preferred DPP-4 Inhibitors. Preferred products do not require PA when prescribed as second-line therapy in conjunction with metformin.

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code

Approval Criteria		
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient tried and failed metformin, or have contraindications to metformin? (document contraindication, if any)	**Yes:** Go to #4	**No:** Pass to RPh; deny and recommend trial of metformin. See below for metformin titration schedule.
4. Will the prescriber consider a change to a preferred product? <u>Message</u>: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Approve for up to 12 months

Initiating Metformin

1.	Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2.	After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3.	If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
4.	The maximum effective dose can be up to 1,000 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T/DUR Review: *8/20 (KS), 7/18; 9/17; 9/16; 9/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *9/1/20; 10/13/16; 10/15; 1/15; 9/14; 1/14; 2/13*

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists and Glucose Dependent Insulinotropic Polypeptide (GIP) Receptor Agonist

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All non-preferred GLP-1 receptor agonists and GLP-1 receptor + GIP receptor agonists. Preferred products do not require PA when prescribed as second-line therapy in conjunction with metformin.

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness. For requests for non-alcoholic or metabolic dysfunction-associated steatohepatitis (NASH/MASH), cardiovascular risk reduction, or obstructive sleep apnea, see weight management PA criteria.

Approval Criteria		
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #4
4. Has the patient tried and failed to meet hemoglobin A1C goals with metformin or have contraindications to metformin? (document contraindication, if any)	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of metformin. See below for metformin titration schedule.

Initiating Metformin

5.	Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
6.	After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
7.	If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
8.	The maximum effective dose can be up to 1,000 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T Review: *8/26 (KS),8/24, 10/22 (KS), 8/20, 6/20), 3/19, 7/18, 9/17; 1/17; 11/16; 9/16; 9/15; 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *9/1//24; 1/1/23; 9/1/20; 5/1/19; 8/15/18; 4/1/17; 2/15; 1/14*

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2 Inhibitors)

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All non-preferred SGLT-2 inhibitors require a PA. Preferred products do not require PA.

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA Approved Indications of SGLT2 Inhibitors*

Indication	Bexagliflozin	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin	Sotagliflozin
Adults with Type 2 Diabetes Mellitus						
Glucose lowering	X	X	X	X	X	
Heart failure		X	X	X		X
Kidney disease		X	X	X		X
Children with Type 2 Diabetes Mellitus						
Patients 10 years and older		X	X	X		
Adults without Diabetes Mellitus						
Heart failure			X	X		X
Kidney disease			X	X		
* FDA indications are current as of June 2026 ~~November 2024~~						

Approval Criteria	
1. What is the diagnosis being treated?	Record ICD10 code

Approval Criteria		
2. Will the prescriber consider switching to a preferred product? Message: • Preferred products do not require a PA. Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Does the patient have type 2 diabetes?	**Yes:** Approve for up to 12 months	**No:** Go to #4
4. Does the patient have heart failure and is requesting an SGLT-2 inhibitor with demonstrated cardiovascular benefit (see Table 1 above)?	**Yes:** Approve for up to 12 months	**No:** Go to #5
5. Does the patient have chronic kidney disease and is requesting an SGLT-2 inhibitor with demonstrated renal and cardiovascular benefits (see Table 1 above)?	**Yes:** Approve for up to 12 months	**No: No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *8/26 (KS), 2/25 (KS), 10/23 (KS), 10/22 (KS), 8/21 (KS), 8/20 (KS), 6/20, 7/18, 9/17; 9/16; 3/16; 9/15; 1/15; 9/14; 9/13*
Implementation: *11/1/23; 1/1/23; 9/1/20; 8/15/18; 10/13/16; 2/3/15; 1/1/14*