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Drug Class Update with New Drug Evaluation: GLP-1 Receptor Agonists and SGLT-2 Inhibitors

Date of Review: October 2022

Date of Last Review: GLP-1 receptor agonists (August 2020)
SGLT-2 inhibitors (August 2021)

Dates of Literature Search: 08/01/2020 - 08/08/2022

Generic Name: tirzepatide

Brand Name (Manufacturer): Mounjaro (Eli Lilly and Company)

Dossier Received: yes

Plain Language Summary:

- Drugs used to treat diabetes lower sugar levels in the blood. Drugs work to lower sugar levels in different ways. Diabetes drugs are divided into classes based on how they work. Drugs that lower sugars the same way are put into the same class. This report is reviewing two classes of drugs. The first class is called sodium-glucose cotransporter 2 (SGLT2) inhibitors and the second class is called glucagon-like peptide-1 receptor agonist (GLP-1 RA). A new drug will also be reviewed that is part of new class called GLP1 RAs / glucose-dependent insulinotropic polypeptide (GIP) agonists.
- A review was done that looked at SGLT2 inhibitors in people that had type 2 diabetes (T2D) and heart disease or had a high chance of getting heart disease. The review found SGLT2 drugs, when compared to treatment with a sugar pill, was more effective at reducing the risk dying from heart disease or having to go into the hospital because of a failing heart, dying due to any cause, or having any major heart related issue (such as a heart attack or stroke). The results were the same for different ages of people, men and women and for those of different races.
- A report found using GLP-1 RAs, compared to other drugs used to lower sugar levels, may cause an increased risk of gallbladder or biliary diseases. Biliary diseases are diseases that affect the bile ducts, gallbladder and other structures involved in the production and transportation of bile.
- A respected organization that produces guidelines for managing diabetes recommends that most people needing medication to lower sugars for the first time should try metformin. People that also have heart issues should consider using a SGLT2 inhibitor with metformin.
- A respected organization that produces guidelines for managing diabetes recommends that adults who have kidney disease, even if they don't have diabetes, should consider using the drug dapagliflozin, which is a type of SGLT2 inhibitor.
- A medication which is part of the GLP-1 RA class is called semaglutide. It was previously available just as a weekly injectable but is now formulated as an oral tablet that is taken once a day to reduce sugars in the blood.
- The Food and Drug Administration (FDA) reviews the proper uses of drugs and they recently evaluated dapagliflozin, which is part of the SGLT2 inhibitor class. They have authorized dapagliflozin to be used to reduce the risk of worsening kidney disease and death from heart disease and reduce the chance of going to the hospital for heart disease.
- The FDA reviewed exenatide, which is part of the GLP-1 RA class, and found that it is effective in lowering sugar concentrations in children with diabetes who are 10 years and older.

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- Empagliflozin, which is part of the SGLT2 inhibitor class, was reviewed by the FDA. They evaluated the use of empagliflozin in people with heart failure and decreased ability for the heart to pump blood well and in those with heart failure and normal ability to pump blood. Empagliflozin was found to reduce the chance of dying from heart disease or getting hospitalized for heart failure in both of these type of people.
- A combination of 2 products used to treat T2M containing dapagliflozin and metformin was approved by the FDA to be used to decrease the risk of death from heart disease and for going to the hospital for heart failure in people with heart disease and reduced ability to pump blood. This combination was also approved for reducing the risk of worsening kidney disease and dying from heart disease and going to the hospital for heart failure in people with kidney disease they is likely to get worse.
- Harmful effects of drugs are also tracked by the FDA. There are 3 new warnings for drugs that are used for diabetes. The drugs in the GLP-1 RA class have been shown to possibly increase the risk of gallbladder diseases. Exenatide extended release, which is a GLP-1 RA type drug, has shown to interfere with the ability of a component in the blood. A combination product, dapagliflozin and metformin, has shown a risk of possibly increasing the chance of kidney problems in some people.
- A new drug called tirzepatide was approved by the FDA. Tirzepatide was compared to other drugs for T2D and compared to sugar pills. Tirzepatide was found to lower sugars in the blood better than a sugar pill and the drugs it was compared to. Tirzepatide was also shown to cause weight loss of about 4 pounds to 33 pounds more than placebo or other drugs for diabetes.
- The data we have for drugs to treat T2D is most often studied in White people around 50 to 60 years of age, that are overweight, have had diabetes for around 5 years and have tried other drugs for to lower sugars in the blood.

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

- **Purpose for Class Update:** To identify new evidence for the glucagon-like peptide-1 receptor agonist (GLP-1 RA) and sodium-glucose cotransporter 2 (SGLT2) inhibitor classes since the last reviews and to evaluate the evidence for the newly approved drug, tirzepatide, to determine place in therapy. The focus of this review is for the use of SGLT2 inhibitors and GLP-1 RAs for people with T2D. There is evidence that the use of GLP-1 RAs when used in people, with and without T2D, results in weight reduction. The use of drugs that are indicated for weight loss alone are not covered in this review and evidence for this purpose will be presented in future reviews.

Research Questions:
1. In patients with type 2 diabetes (T2D), what is the comparative evidence for efficacy or harms of GLP-1 RA and SGLT2 inhibitors for important outcomes (e.g., hemoglobin A1c [HbA1C], microvascular outcomes, macrovascular outcomes and mortality)?
2. Are there subpopulations of patients with T2D for which GLP-1 RAs and SGLT2 inhibitors may be more effective or associated with less harm?
3. What is the evidence for the effectiveness and harms of tirzepatide in patients with T2DM?
4. Are there specific subpopulations for which tirzepatide may be specifically indicated, more effective, or associated with less harm?

Conclusions:
- Two high quality systematic review and meta-analyses, 2 high quality guidelines, one new formulation, 5 new indications, 3 new safety warnings, 4 randomized controlled trials (RCTs) and one new drug evaluation are included in this update.

- A systematic review and meta-analysis found moderate quality evidence that SGLT2 inhibitors were more effective than placebo in people with T2DM and atherosclerotic cardiovascular disease (ASCVD) or at high risk of ASCVD for the following outcomes: cardiovascular (CV) death or hospitalization for heart failure (HF), all-cause mortality, major adverse cardiovascular events (MACE), and hospitalizations for HF or emergency department visits for HF.[1] Subgroup analyses found results of findings for SGLT2 inhibitors to be consistent across sex, ethnicities and age.[1]
- A 2022 systematic review and meta-analysis identified GLP-1 RAs were associated with an increased risk of a composite assessment of gallbladder or biliary diseases compared to active treatments or placebo in adult patients (with or without diabetes) (relative risk [RR] 1.37; 95% confidence interval [CI], 1.23 to 1.52; I^2 = 0%; high quality evidence).[2] Other adverse outcomes associated with the use of GLP-1 RAs more than controls were cholelithiasis, cholecystitis, biliary disease, and cholecystectomy.
- The National Institute for Health and Care Excellence (NICE) updated guidance on managing patients with diabetes with an emphasis on the evidence for clinical data related to SGLT2 inhibitors in people with CV disease or at high risk of developing CV disease. In people without comorbidities, metformin is recommended as first-line therapy.[3] Those that have chronic HF or established atherosclerotic CV disease should be offered a SGLT2 inhibitor with proven CV benefit in addition to metformin (e.g., empagliflozin, canagliflozin, and dapagliflozin).[3]
- In adults with or without diabetes, NICE guidance recommends dapagliflozin as an option for adults with chronic kidney disease (CKD) and who meet additional criteria such as T2D, receiving standard of care for CKD and an estimated glomerular filtration rate (eGFR) is between 25 ml/min/1.73 m^2 and 75 ml/min/1.73 m^2 .[4]
- There was one new formulation of semaglutide (Rybelsus®) FDA-approved since the last update.[5] Five drugs have new indications and/or labeling changes: dapagliflozin (Farxiga®), exenatide (Bydureon®), empagliflozin (Jardiance®), dapagliflozin/metformin (Xigduo XR®) and lixisenatide (Adlyxin®).[6, 7, 8, 9, 10]
- Four good quality RCTs provided evidence for use of the following medications: empagliflozin, ertugliflozin, and dapagliflozin.[11–14]
    - There was moderate quality evidence that empagliflozin was more effective than placebo at preventing CV death or hospitalizations for HF in patients with reduced or preserved ejection fraction, with or without diabetes.[11,14]
    - Ertugliflozin was non-inferior to placebo for the risk of major adverse CV outcomes based on moderate evidence.[12]
    - There was moderate quality of evidence that dapagliflozin was more effective than placebo for reduction in the sustained decline of eGFR of at least 50%, end-stage kidney disease, death from renal or CV causes, and the composite outcome of death from CV causes or hospitalization for HF.[15]
- There were 3 new safety alerts pertaining to the following products: GLP-1 RAs, Bydureon® and Qtern®. There is evidence of an increased risk of acute gallbladder disease related to GLP-1 RAs. Exenatide extended release (Bydureon®) may cause drug induced thrombocytopenia. Dapagliflozin/metformin (Qtern®) may cause intravascular volume depletion and hypotension with case reports of acute kidney injury.
- Tirzepatide is a GLP-1 RA and glucose-dependent insulinotropic polypeptide (GIP) approved in May of 2022 for adult patients with T2D.[16] Five phase 3 RCTs were evaluated for approval comparing tirzepatide to placebo or semaglutide, insulin degludec, or insulin glargine. Tirzepatide demonstrated HbA1c lowering of -1.87% to -2.58% ($P<0.05$ for all comparisons; high quality evidence).[17–21] The number of patients obtaining an HbA1c of 7% or less, was more common with tirzepatide versus comparators (placebo and active controls) with number needed to treat (NNT) of 2 to 34 over 40-52 weeks.[17–21] Tirzepatide was associated with weight loss more than placebo, semaglutide, insulin degludec and insulin glargine with differences ranging from -1.9 kg to -15.2 kg. Cardiovascular outcome trials are ongoing.
- A majority of the evidence for SGLT2 inhibitors and GLP-1 RAs comes from trials enrolling predominately people of White ethnicity, people who are overweight and people 50-60 years of age.

Recommendations:

- Include the glucose-dependent insulinotropic polypeptide (GIP) therapies in the prior authorization (PA) criteria with GLP-1 RAs.
- Update the GLP-1 RA PA criteria to remove concomitant prandial insulin restriction.
- Maintain clinical PA criteria for the preferred SGLT2 inhibitors as second line therapy after metformin in patients with diabetes and update PA to clarify that renal function should be evaluated on an annual basis.
- Maintain tirzepatide as non-preferred on the preferred drug list (PDL) and subject to the GLP-1 RA and GLP + GIP agonist PA criteria.
- No changes are recommended to the preferred drug list (PDL) after review of the current literature or after evaluation of drug costs in executive session.

Summary of Prior Reviews and Current Policy

- The last review of SGLT2 inhibitors was in 2021. Evidence from systematic reviews and meta-analyses found that SGLT2 inhibitors reduced the risk of all-cause mortality, CV mortality and hospitalizations for HF in patients with and without diabetes. Canagliflozin, dapagliflozin and empagliflozin are preferred therapies in this class.
- A review of newer diabetic agents in August of 2020 identified literature that SGLT-2 inhibitors (e.g., canagliflozin, dapagliflozin, empagliflozin) reduce the risk of hospitalizations due to HF. The requirement for step therapy, other than metformin, was removed for the SGLT2 class. Currently step therapy with metformin only applies to non-preferred treatments.
- The GLP-1 RAs were part of a review of the newer diabetes drugs report in August of 2020. Evidence found GLP-1 RAs (e.g. exenatide extended-release, liraglutide, and semaglutide) reduce the risk of all-cause mortality in people with T2D. The evidence for HF outcomes was neutral with no benefits or harms demonstrated. The requirement for step therapy, other than metformin, was removed for GLP-1 RAs. After executive session dulaglutide was designated a preferred therapy on the PDL. Dulaglutide, exenatide and liraglutide are preferred therapies in this class.

Background:

Approximately 287,000 adult Oregonians have T2D.[22] It is estimated that over 38,000 of these patients are Oregon Health Plan (OHP) members.[22] The Oregon Health Plan paid $106 million in direct medical claims for diabetes and diabetes-related complications in 2012.[22] The overall cost to the state is estimated at $3 billion a year.[22] According to the Centers for Disease Control and Prevention (CDC), as many as 1 in every 3 adults will have T2D by 2050.[23] Despite a variety of treatment options, a significant number of patients fail to meet HbA1c goals within 3 years of being diagnosed and 50% of patients require combination therapy to control their diabetes.[24,25]

Underlying characteristics that lead to hyperglycemia and T2D are insulin resistance and impaired insulin secretion. While evidence has shown the importance of lifestyle modifications, such as diet and exercise changes, antidiabetic treatments are necessary to reduce glucose levels in most patients with T2D.[26] Pharmacotherapy improves hyperglycemia by increasing glucose uptake, increasing glucose secretion and/or increasing insulin sensitivity. Goal glucose levels are dependent upon patient characteristics, such as age and comorbidities; however, guidelines recommend a goal HbA1c of less than 7% for most patients but a range of less than 6.5% to less than 8% may be appropriate.[27] Classes of non-insulin antidiabetic agents currently available are: alpha-glucosidase inhibitors, biguanides, DPP-4 inhibitors, GLP-1 RAs, insulins, meglitinides, SGLT2 inhibitors, sulfonylureas, thiazolidinediones, bile acid sequestrants, dopamine-2 agonists and amylin mimetics. Current evidence and guidelines recommend metformin as a first-line treatment in most patients with T2D due to its safety profile, low risk of hypoglycemia and potential CV benefit.[3,27,28] There is no consensus on a universally recognized second-line treatment, and therefore, selection should be dependent on degree of glucose lowering required to assist in obtaining goal HbA1c levels, patient specific characteristics including comorbidities, and harms of

therapy.[3] Therapies that have demonstrated renal and CV benefits are outlined in **Table 1.** People that may benefit from weight loss should consider SGLT2 inhibitors or GLP-1 RAs, which have high quality evidence demonstrating weight reductions with use.[27] This update will focus on new evidence for the use of SGLT2 inhibitors and GLP-1 RAs.

In 2008, the Food and Drug Administration (FDA) started requiring evaluation of CV risk for antidiabetic therapies. Cardiovascular studies have been published for each of the newer classes of antidiabetic therapies. These studies are most applicable to patients with CV disease or at high risk of CV disease (e.g., 55 years or older with coronary, carotid, or lower-extremity artery stenosis greater than 50% or left ventricular hypertrophy). A comparison table of effectiveness and harms can be found in **Table 1**. Both the SGLT2 inhibitors and GLP-1 RAs have demonstrated CV benefits. Guidelines have identified the following drugs as having an CV advantage compared to other therapies: canagliflozin, empagliflozin and liraglutide.[29] There is also evidence that SGLT2 inhibitors slow progression of CKD in people with CKD and albuminuria (200 mg/g creatinine or more).[30] For people with T2D and CKD without albuminuria, both SGLT2 inhibitors or GLP-1 RAs are recommended to decrease CV risk.[27]

Table 1. Cardiovascular Outcomes for Newer Diabetes Medications Vs. Placebo[27,30]

Outcome	All-Cause Mortality	Stroke	CV Death/ CV Events	Myocardial Infarction	Hospitalization for Heart Failure	Serious Adverse Events	Chronic Kidney Disease
Drug Class							
GLP-1 RA	*Small risk reduction (moderate quality evidence)* Benefit: Exenatide ER Liraglutide Semaglutide oral Neutral: Albiglutide Dulaglutide Lixisenatide Semaglutide inj	*No effect (low quality evidence)* Benefit: Dulaglutide Neutral: Albiglutide Exenatide ER Liraglutide Lixisenatide Semaglutide oral No evidence: Semaglutide inj	*Reduced risk (moderate quality evidence)* Benefit: Dulaglutide* Liraglutide* Semaglutide inj*	*No conclusion (very low quality evidence)* Benefit: Albiglutide Liraglutide Neutral: Dulaglutide Exenatide ER Lixisenatide Semaglutide oral No evidence: Semaglutide inj	*No effect (moderate quality evidence)* Neutral: Dulaglutide Exenatide ER Liraglutide Lixisenatide Semaglutide (oral and inj) No evidence: Albiglutide	*Reduced risk (low quality evidence)* Benefit: Albiglutide Dulaglutide Semaglutide (oral and inj) No evidence: Exenatide ER Liraglutide Lixisenatide	*Reduced risk of eGFR decline (low quality evidence)* Benefit: Liraglutide
SGLT-2 Inhibitors	*No effect (moderate quality evidence)* Benefit: Empagliflozin Neutral:	*No effect (low quality evidence)* Neutral: Canagliflozin Dapagliflozin Empagliflozin	*Reduced Risk (moderate quality evidence)* Benefit: Canagliflozin* Dapagliflozin* Empagliflozin∞*	*No effect (moderate quality evidence)* Neutral: Canagliflozin Dapagliflozin Empagliflozin	*Significant risk reduction (moderate quality evidence)* Benefit: Canagliflozin Dapagliflozin*	*Significant risk reduction (moderate quality evidence)* Benefit: Dapagliflozin Empagliflozin	*Reduced risk of eGFR decline, end stage kidney disease CV death and hospitalization for HF in adults with* CKD *(moderate quality evidence)*

	Canagliflozin Dapagliflozin				Empagliflozin*	Neutral or benefit: (conflicting results) Canagliflozin	Benefit: Dapagliflozin* Canagliflozin*

Key: ∞ For patients with preserved and reduced ejection fraction
* FDA indicated for this outcome
Abbreviations: CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ER = extended release; GLP-1 = glucagon-like peptide 1; HR = heart failure; inj = injection; SGLT-2 = sodium-glucose cotransporter-2

Important outcomes in patients with diabetes are microvascular and macrovascular complications, mortality, HbA1c reduction, severe adverse events and hypoglycemia. Hemoglobin A1C reduction is often used as a surrogate marker to assess comparative efficacy of different antidiabetic therapies, as hyperglycemia is associated with increased microvascular complications, and possibly macrovascular outcomes as well. A clinically relevant change in HbA1c is considered to be 0.3% or more.[31] Available data for most new drugs are limited to short-term studies, which prevents the assessment of the durability of most antidiabetic treatments to control glucose levels long-term.

Abbreviated Drug Utilization Evaluation:
The quarterly costs paid to pharmacies for SGLT2 inhibitors and GLP-1 RAs are substantial. Utilization of preferred agents was 89% for SGLT2 inhibitors and 78% for GLP-1 RAs.

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, 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, and the Canadian Agency for Drugs and Technologies in Health (CADTH) 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.

Systematic Reviews:
Bhattarai, et al – Association of Sodium-Glucose Cotransporter 2 Inhibitors with Cardiovascular Outcomes in Patients with Type 2 Diabetes and Other Risk Factors for Cardiovascular Disease
A 2022 systematic review and meta-analysis evaluated the CV benefit of SGLT2 inhibitors. Randomized controlled trials compared SGLT2 inhibitors to placebo in patients with ASCVD or risk factors for ASCVD, diabetes or HF.[1] Trials studied the following drugs: empagliflozin, canagliflozin, dapagliflozin and sotagliflozin (not approved in the US). Ten trials were identified with 71,553 participants. The mean age was 65 years old, 79.43% were White, 25.57% were Asian, 19% were Black and 69.4% had established CVD. The mean follow-up was 2.3 years.[1] All of the trials were considered high-quality with a Jadad score of 8. Authors reported no

conflicts of interest. Funding source was not disclosed. The primary outcome of interest was CV death and hospitalization for HF. Key secondary outcomes were MACE, hospitalization for heart failure, CV death, acute MI, and all-cause mortality.

SGLT2 inhibitors were associated with a reduced risk of CV death and hospitalization for HF compared to placebo (odds ratio [OR] 0.67; 95% CI, 0.55 to 0.80; P<0.001; I^2= 92%).[1] Major CV adverse events were reduced in those taking SGLT2 inhibitors compared to placebo, 9.82% versus 10.22% (OR 0.90; 95% CI, 0.81 to 0.99; P=0.03; I^2=66%).[1] Participants taking SGLT2 inhibitors demonstrated a decreased risk of hospitalizations for HF and emergency department visits for HF (OR 0.67; 95% CI, 0.62 to 0.72), CV death (OR 0.87; 95% CI, 0.79 to 0.97; P=0.09; I^2=52%) and all-cause mortality (OR 0.87; 95% CI, 0.80 to 0.9; P=0.004; I^2=59%).[1] There was no difference in the incidence of myocardial infarction (MI) between groups. Subgroup analyses found no difference in treatment effect based on sex; however, men were associated with a higher incidence of CV death or HF hospitalization compared to women. Results were similar in groups younger than 65 years of age and those 65 years and older.

Limitations to the analysis include high heterogeneity in outcomes between the study comparisons. The results are most applicable to people who are White with a history of ASCVD or who have high risk of ASCVD.

He, et al – Association of Glucagon-like Peptide-1 Receptor Agonist Use with Risk of Gallbladder and Biliary Diseases

A 2022 systematic review and meta-analysis evaluated the use of GLP-1 RAs and the risk of gallbladder and biliary disease.[2] Seventy-six RCTs (n=103,371) evaluating the use of GLP-1 RAs compared to placebo or active treatment (e.g., rosiglitazone, glimepiride, sitagliptin, orlistat, insulin glargine, canagliflozin, empagliflozin, metformin, insulin lispro, dapagliflozin, and glibenclamide, (not available in the US) in adult patients were included. Included patients had a mean age of 57.8 years, mean HbA1c of 7.8%, mean body mass index (BMI) of 32.6 kg/m^2.[2] Eighty-four percent of participants had T2D and 40.5% were women. Sixty trials evaluated treatment for diabetes, 13 trials evaluated weight loss and 3 evaluated nonalcoholic steatohepatitis, polycystic ovary syndrome and schizophrenia. Trial durations lasted from 26-104 weeks. Trials were considered to be moderate to high quality. There was no publication bias based on the Egger test and funnel plot analysis. The primary outcome was the composite of gallbladder or biliary diseases, and key secondary outcomes included biliary diseases, biliary cancer, cholecystectomy, cholecystitis, and cholelithiasis.

Treatment with GLP-1 RAs resulted in an increased risk of a composite assessment of gallbladder or biliary diseases compared to controls (RR 1.37; 95% CI, 1.23 to 1.52; I^2 = 0%).[2] There were an additional 27 events per 10,000 patients treated per year compared to controls. Randomization to GLP-1 RAs was also associated with an increased risk of the following outcomes compared to control: cholelithiasis (RR 1.27; 95% CI, 1.10 to 1.47), cholecystitis (RR 1.36; 95% CI, 1.14 to 1.62), biliary disease (RR 1.55; 95% CI, 1.08 to 2.22), and cholecystectomy (RR 1.70; 95% CI, 1.25 to 2.32).[2] There was no evidence of an increased risk of biliary tract cancer. Analysis of individual GLP-1 RAs agents found an increased risk for liraglutide, dulaglutide, subcutaneous semaglutide and exenatide; however, the risk was not statistically significant for subcutaneous semaglutide and exenatide. There was no increased risk with albiglutide, oral semaglutide, and lixisenatide. GLP-1 RA use beyond 26 weeks was associated with increased risk of gallbladder disease or biliary diseases (RR 1.40; 95% CI, 1.26 to 1.56) but shorter treatment durations did not have the associated risk.[2] Trials in which GLP-1 RAs were used for weight loss had a higher risk of the primary outcome compared to use in other populations (e.g. diabetes) which may be a result of higher doses and longer treatment durations used in trials evaluating weight loss.

Limitations to the review include potential for under reporting of biliary events. In many included trials, biliary events were not a predefined safety endpoint, and only a small number of events were reported. Many outcomes or subgroups, may not have sufficient power to detect differences between groups.

After review, 31 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). [32–44, 45–61]

New Guidelines:

High Quality Guidelines:

NICE – Type 2 Diabetes Management in Adults: 2022 Update

The National Institute for Health and Care Excellence updated the original 2015 publication on managing adults with diabetes with new evidence and guidance. Drug treatment included in the review were: dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP-1 RAs, SGLT2 inhibitors, sulfonylureas and metformin.[3] The main focus of the update was the evidence for clinical and cost-effectiveness of the SGLT2 inhibitor class in people with CV disease or at high risk of developing CV disease. Recommendations are for people with T2DM, and use of these therapies in people without T2DM was not discussed.[3]

The guidance maintains the recommendation for standard-release metformin as first-line therapy in people without comorbidities. People should be assessed for CV risk.

- In people with chronic HF, established atherosclerotic CV disease or high risk of developing CV disease, a SGLT2 inhibitor with proven CV benefit is recommended in addition to metformin.[3] If combination therapy is initiated with metformin and a SGLT2 inhibitor, the medications should be started sequentially to ensure metformin is tolerated. If metformin is contraindications or not tolerated, then a SGLT2 inhibitor should be offered in this population.[3]
- For people that are unable to take metformin and who don't have a CV indication, then a DPP-4 inhibitor, pioglitazone, or sulfonylurea is recommended. SGLT2 inhibitors may also be considered in patients without CV indications.[3]
- An SGLT2 inhibitor should be added at any stage after the first-line treatment has been initiated if the person has or develops chronic HF or established atherosclerotic CV disease. The SGLT2 inhibitor can be added to the current treatment or replace the existing treatment. Using ertugliflozin for CV risk reduction is considered off-label if serum glucose is controlled.[3]
- There was insufficient evidence to justify recommending SGLT2 inhibitors for people with T2DM at lower risk of CV disease. SGLT-2 inhibitors demonstrated differences in CV benefits so recommendations for use of a specific SGLT2 inhibitors state that drugs with proven benefit should be used (there was greater uncertainty about the benefits of ertugliflozin).[3]

People who are not meeting glucose targets with monotherapy may be considered for treatment with a DPP-4 inhibitor, pioglitazone, sulfonylurea or SGLT2 inhibitor (if they meet the previous outlined specifications as noted above).[3] If a combination therapy with metformin and an additional oral agent has not succeeded in lowering glucose levels to the desired level, then triple oral therapy with a DPP-4 inhibitor, pioglitazone, sulfonylurea, or SGLT-2 inhibitor can be added. In people who are unable to take metformin and combination therapy with 2 oral drugs does not allow obtainment of goal glucose levels, insulin should be considered.[3]

The clinical effectiveness of GLP-RAs to lower glucose was not included in this review, and therefore, specific recommendations related to GLP-1 RAs were not updated. GLP-1 RAs when used for CV benefit were not cost-effective, and they are only recommended as an alternate treatment option. GLP-1 RAs should be continued if HbA1c has been reduced by at least 1% and weight loss has improved by at least 3% at 6 months (2015 recommendation).[3]

GLP-1 RA therapy should be considered in people who have:

- Inadequate glycemic control while taking triple oral therapy with metformin and 2 other drugs[3]

- BMI of 35 kg/m^2 or higher and specific psychological or other medical problems related to obesity[3]
- BMI of lower than 35 kg/m^2 and which insulin has significant occupational implications or weight loss would benefit other obesity-related comorbidities

SGLT2 inhibitors may also be considered for people with T2DM and CKD taking an ARB or ACE inhibitor if they have an albumin to creatinine ratio (ACR) between 3 and 30 mg/mmol and they meet the eGFR thresholds outlined in the drug labeling.[3] People who are starting SGLT2 inhibitors should be evaluated for risk of diabetic ketoacidosis (DKA). The presence of the following factors may increase risk of DKA: previous episodes of DKA, a current illness, or a very low carbohydrate or ketogenic diet. Risk factors should be modified if possible.

NICE – Dapagliflozin for Chronic Kidney Disease

A Technology Appraisal Guidance was published in March of 2022 on the use of dapagliflozin in treating CKD in adults, with and without diabetes.[4] Recommendations were based on the DAPA-CKD trial (**Table 2**). NICE recommends the use of dapagliflozin as an option for adults with CKD if the following criteria are met:

- Dapagliflozin is added as an adjunct to standard care (e.g., highest tolerated licensed ACE inhibitor or ARB unless contraindicated)[4] AND
- The person's eGFR is between 25 ml/min/1.73 m^2 and 75 ml/min/1.73 m^2 AND
- The person has T2DM OR the person has a urine albumin-to-creatinine ratio (uACR) or 22.6 mg/mmol or greater

Additional Guidelines for Clinical Context:

ADA – Pharmacological Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes 2022

The American Diabetes Association (ADA) updated pharmacological treatment recommendations for managing patients with type 1 diabetes (T1D) and T2D. For the purpose of this review we will focus on the treatment of people with T2D, with a focus on SGLT2 inhibitors and GLP-1 RA.[27] Choice of antidiabetic therapy should be determined by a person's specific preferences, including: comorbidities, hypoglycemia risk, impact on weight, cost, access, and risk for adverse reactions. Antidiabetic treatment should be re-evaluated every 3-6 months and intensification of therapy should not be delayed if glucose goals are not met.[27]

Specific treatment recommendations are as follows[27]:

- Metformin is recommended first-line in combination with lifestyle changes.
- Persons with T2D with or at high risk of atherosclerotic CV disease, HF, and/or CKD should be considered candidates for GLP-1 RAs or SGLT2s with or without metformin.
- Metformin should be continued, if tolerated and not contraindicated, if insulin is started due to the metabolic benefits of metformin.
- Combination therapy at treatment initiation may be considered to extend the time to treatment failure.
- GLP-1 RAs are recommended over insulin for people with T2D if possible.
- If insulin is used in people with T2D, GLP-1 RAs are recommended in combination for greater durability of treatment effect.
- People receiving high doses of basal insulin (0.5 IU/kg/day or more) should be evaluated for additional therapies (not specifically describied).

ADA – Chronic Kidney Disease and Risk Management: Standards of Medical Care in Diabetes 2022

The management of people with diabetes and CKD was updated in the 2022 recommendations by the ADA.[30] The use of SGLT2 inhibitors is recommended for people with T2D, diabetic kidney disease, eGFR of 25 mL/min/1.73 m^2 or greater, and urinary albumin creatinine of 300 mg/g or greater. Evidence has demonstrated a reduction in progression of CKD and CV events.[30]

ADA – Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes 2022

The ADA provided guidance for the management of people with diabetes in regards to CV risk reduction.[62] As mentioned above, SGLT2 inhibitor or GLP-1 RAs with demonstrated CV benefit are recommended for people with T2D who have established atherosclerotic CV disease or established kidney disease to reduce the risk of adverse CV outcomes. SGLT2 inhibitors with demonstrated CV benefit are also recommended for people with T2D and multiple atherosclerotic CV risk factors.[62] Reduction in HF hospitalizations and/or reduction in major CV events have been demonstrated with SGLT2 inhibitors in this population. GLP-1 RAs with demonstrated CV benefit have been shown to reduce the risk of major CV events in people with T2D and established atherosclerotic CV disease or multiple atherosclerotic CV risk factors. In people with T2D and established atherosclerotic CV disease or multiple atherosclerotic CV risk factors, combination therapy with SGLT2 inhibitors and GLP-1 RAs with demonstrated CV benefit may be considered to lower the risk of adverse CV and kidney events. In people with T2DM and established HF with reduced ejection fraction, treatment with a SGLT2 is recommended to reduce the risk of HF and CV death. People with T2D and HF can continue with metformin if eGFR is 30 mL/min/1.73m^2 or above; however, metformin should be discontinued/avoided patients who are unstable or hospitalized.[62]

After review, 2 guidelines were excluded due to poor quality.[63,64]

New Formulations or Indications:

New Formulations:

Semaglutide (Rybelsus®): Semaglutide oral tablets was approved for use in January 2020 as an adjunct to diet and exercise to improve glycemic control in adults with T2D.[5] Semaglutide tablets are given once daily instead of once weekly like the semaglutide injection. Currently, semaglutide oral tablets do not have the same indication for CV disease reduction in adults with T2D as the injectable formulation. There is a boxed warning for the risk of thyroid c-cell tumors with oral semaglutide as with other GLP-1 RA products.[5]

New Indications:

Dapagliflozin (Farxiga®): In April of 2021, dapagliflozin received an expanded to indication for risk reduction of sustained eGFR decline, end stage kidney disease, CV death, and hospitalization for HF in adults with CKD at risk of progression.[6] Details on the evidence used for the expanded indication are provided in **Table 3**.

Exenatide (Bydureon®): The FDA approved an expanded indication for exenatide in pediatric patients 10 years of age and older with T2D in July of 2021.[7] Evidence for the approval was based on one 24-week, double-blind, placebo-controlled RCT in which exenatide was more effective than placebo with an HbA1c reduction of -0.71% (95% CI, -1.42 to 0: $p<0.05$).[7]

Empagliflozin (Jardiance®): In 2021, empagliflozin received an expanded indication to reduce the risk of CV death and hospitalization for HF in adults with HF and reduced ejection fraction (**Table 3**). Empagliflozin has also been shown to be effective in those with preserved ejection fraction; therefore, labeling as of 2/2022 includes an indication for HF, without delineation of ejection fraction.

Dapagliflozin and metformin (Xigduo XR®): The combination product of dapagliflozin and metformin received an expanded indication for reduced risk of CV death and hospitalization for HF in adults with HF (New York Heart Association [NYHA]class II-IV) with reduced ejection fraction in February of 2022.[9] An additional indication was approved in April of 2022 is to reduce the risk of sustained eGFR decline, end-stage kidney disease [ESKD], CV death and hospitalization for HF in adults with CKD at risk of progression (**Table 3**).[9] Both new indications apply to people with and without diabetes.

Lixisenatide (Adlyxin®): The FDA removed the statement that "lixisenatide has not been studied in combination with short acting insulin" from the limitations of use section in the labeling.[10]

New FDA Safety Alerts:

Table 2. 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)
GLP-1 RAs[65]	Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	June 2022	Warnings	Due to the risk of acute gallbladder disease, if cholelithiasis or cholecystitis are suspected then gallbladder studies should be performed.
Exenatide ER[7]	Bydureon	February 2020	Warnings	Risk of drug induced thrombocytopenia has been reported, including serious bleeding which may be fatal. Discontinue exenatide promptly if this occurs.
Dapagliflozin and saxagliptin[66]	Qtern	March 2022	Warnings	Dapagliflozin may cause intravascular volume depletion and hypotension with case reports of acute kidney injury. Monitor for hypotension and renal function after initiating therapy.

Randomized Controlled Trials:
A total of 263 citations were manually reviewed from the initial literature search. After further review, 258 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 5 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Anker, et al[11] EMPEROR-Preserved DB, PC, MC, NI, RCT	1. Empagliflozin 10 mg orally once daily 2. Placebo Median duration: 26.2 months	Adult patients with class II-IV HF and an ejection fraction of more than 40% (with or without diabetes) N=5988	Composite of CV death or hospitalization for HF	1. Empagliflozin: 415 (13.8%) 2. Placebo: 511 (17.1%) HR 0.79 (95% CI, 0.69 to 0.90) P<0.001	Patients were on background standard of care medications for HF. Results were similar in patients with and without diabetes. Empagliflozin was more effective than placebo at preventing CV death or hospitalizations for HF.
Cannon, et al[12] VERTIS CV DB, PC, MC, NI, RCT	1. Ertugliflozin 5 mg orally once daily 2. Ertugliflozin 15 mg orally once daily 3. Placebo Mean duration: 3.5 years	Adult patients (at least 40 years old) with T2DM and atherosclerotic CV disease N=8238	Incidence of major adverse CV events (a composite of death from CV causes nonfatal MI, or nonfatal stroke)	1. Ertugliflozin (pooled doses): 653 (11.9%) 2. Placebo: 327 (11.9%) HR 0.97 (95% CI, 0.85 to 1.11) P<0.001 for non-inferiority	Ertugliflozin was non-inferior to placebo for the risk of major adverse CV outcomes.
Heerspink, et al[13] DAPA-CKD DB, PC, MC, RCT, Phase 3	1. Dapagliflozin 10 mg orally once daily 2. 2. Placebo Median duration: 2.4 years	Adult patients (with or without diabetes) with eGFR of 25 to 75 ml/min/1.73 m2 and urinary albumin-to-creatinine ratio of 200 to 5000 N = 4304	Sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or CV causes	1. Dapagliflozin: 197 (9.2%) 2. Placebo: 312 (14.5%) HR 0.61 (95% CI, 0.51 to 0.72) P<0.001	Results were similar for those with and without diabetes. Trial was stopped early due to efficacy. All patients were on a background ACE or ARB. Dapagliflozin was more effective than placebo for the primary outcome and for the composite outcome of death from CV causes or hospitalization for heart failure.

Packer, et al[14] EMPEROR-Reduced DB, PC, PG, RCT, Phase 3	1. Empagliflozin 10 mg orally once daily 2. 2. Placebo Median duration: 16 months	Adult patients with class II-IV HF and an ejection fraction of 40% or less (with or without diabetes) N=3730	Composite of CV death or hospitalization for worsening HF	1. Empagliflozin: 361 (19.4%) 2. Placebo: 462 (24.7%) HR 0.75 (95% CI, 0.65 to 0.86) P<0.001	Results were similar in patients with or without diabetes. All patients were on standard of care HF treatments (e.g., diuretics, ACE or ARBs, neprilysin, beta-blockers, and mineralocorticoid receptor antagonists) Empagliflozin was more effective than placebo for reducing CV death or hospitalization for HF

Abbreviations: ACE – angiotensin converting enzyme; ARB – angiotensin receptor blocker; CV – cardiovascular; DB – double-blind: eGFR – estimated glomerular filtration; HF – heart failure; HR – hazard ratio; MC – multi-center; NI – non-inferiority trial; PC – placebo controlled; PG – parallel group; RCT – randomized controlled trial; T2DM – type 2 diabetes mellitus

NEW DRUG EVALUATION:

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Tirzepatide is a dual GIP and GLP-1 RA therapy approved as an adjunct to diet and exercise to improve glycemic control in adult patients with T2D. Approval of tirzepatide was based on 5 phase 3 trials.[17–21] All trials were multi-center, randomized, parallel-group design in patients with T2D. Tirzepatide was compared to placebo in 2 trials and compared to active treatment in the remaining 3 trials (SURPASS trials 1-5). Comparators were insulin glargine, insulin degludec and semaglutide 1 mg. Tirzepatide was studied with stable dose background therapy of insulin glargine (with or without metformin), metformin alone, or combination treatment with metformin, sulfonylurea, and SGLT2 inhibitors. Dosing titration of tirzepatide and comparators are outlined in **Table 4**. Patients from 24 countries, 23.1% from North America, were included. Participants were predominantly White (80%), 55% were male with a mean age of 58 years. The mean BMI across the trials was 33 kg/m^2.[17–21] Most participants did not have significant comorbidities with the exception of SURPASS-4 which enrolled patients at increased CV risk. Baseline HbA1c values ranged from 7 to 10.5%. To meet inclusion criteria, patients had to have an eGFR of at least 30 mL/min/1.73 m^2. There were small protocol amendments to all 5 trials but the FDA concluded that it would have only affected 0.2-0.9% of primary endpoint data so it would be unlikely that it would have made a significant difference in the results.[67] Detailed trial information is available in **Table 5**.

Table 4. Titration and Dosing of Tirzepatide and other Diabetes Medications.

Study	Tirzepatide Titration	Other Diabetes Medications
SURPASS-1[17]	- Tirzepatide initiated at 2.5 mg/week and increased by 2.5 mg every 4 weeks until the assigned dose was reached	- Not applicable
SURPASS-2[18]	- Same as above	- Semaglutide was initiated at a starting dose of 0.25 mg once weekly and the dose was doubled every 4 weeks until 1 mg was reached (dose for diabetes up to 2 mg/week) - Only insulin was allowed for acute therapy if needed - Background therapy with metformin
SURPASS-3[19]	- Same as above	- Insulin degludec was initiated at 10 U/day and titrated once weekly to a fasting self-monitored blood glucose of less than 90 mg /dL - Background therapy with stable dose of metformin +/- a SGLT-2 inhibitor
SURPASS-4[20]	- Same as above	- Insulin glargine was initiated at 10 units/day and adjusted weekly to a treat to target fasting blood glucose of less than 100 mg/dL - Background therapy: stable dose of metformin, SGLT2 inhibitor, and/or SU
SURPASS-5[21]	- Same as above	- Initial 4-week insulin glargine stabilization period followed by a 36-week insulin titration period* - Metformin 1500 mg/day (if taking at baseline)

* Between weeks 5 and 40 patients self-adjusted insulin glargine dose to target fasting blood glucose of less than 100 mg/dL.

Tirzepatide demonstrated improved efficacy over all comparators studied. HbA1c changes from baseline ranged from -1.87% to -2.58% ($P<0.05$ for all comparisons) (**Table 6**).[17–21] The magnitude of HbA1c lowering was considered clinically meaningful (difference to comparator reductions of -0.4% to -1.6%), with exception of the tirzepatide 5 mg compared to sitagliptin 1 mg which demonstrated a difference of -0.2% (95% CI, -0.3 to -0.0).[18] Glucose lowering was sustained in all trials and all doses reached near normal blood glucose levels suggesting there is no dose-response effect of tirzepatide.[68] Patients receiving tirzepatide achieved HbA1c less than 7% more than comparators ranging from 75.1% to 89.6% of the population studied ($P<0.05$ for all comparisons).[67] Weight loss was more significant in the tirzepatide groups versus comparators with losses of -5.3 kg to -11.3 kg. Hierarchical testing was not performed for the effect of tirzepatide on blood pressure and lipids; however a beneficial effect was demonstrated with tirzepatide. Tirzepatide lowered systolic blood pressures 6-9 mmHg and diastolic blood pressure 3-4 mmHg compared to changes of 2 mmHg in diastolic and systolic blood pressures with placebo.[67] Small reductions in triglyceride (TG), total cholesterol (TC) and very-low-density lipoprotein-C (VLDL-C) and increases in HDL-C were demonstrated with tirzepatide.

There is insufficient evidence on the effect of tirzepatide on cardiovascular outcomes in patients with T2DM. There is an ongoing trial (SURPASS-CVOT) which should delineate the CV impact. Until trial results are available, tirzepatide is not recommended to reduce CV events in adults with CV disease or CV risk factors as demonstrated with other GLP-1 RAs and SGLT-2 inhibitors. There is insufficient evidence for the use of tirzepatide to reduce the risk of HF or CKD progression. There was limited evidence for non-White populations (12% of the population studied) and those 75 years and older. There is insufficient data in patients with an eGFR of 30 mL/min/1.73 m^2 or less.

Clinical Safety:

Tirzepatide safety data comes from the analysis of 5119 patients, with a mean treatment exposure of approximately 43 weeks. The most common adverse reactions seen with tirzepatide occurring in 5% or more of patients were: nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain.[16] Serious adverse events occurred in 5.5% of patients in the placebo arm compared to 5.4% with tirzepatide.[67] Tirzepatide has been associated with pancreatitis (less than 0.1%), hypoglycemia with concomitant use of insulin secretagogues or insulin, hypersensitivity reactions, acute kidney injury (less than 0.1%), severe gastrointestinal disease (less than 0.1%), diabetic retinopathy complications in patients with a history of diabetic retinopathy, and acute gallbladder disease.[16] There is a boxed warning for the risk of thyroid c-cell tumors, and tirzepatide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma.[16] In placebo comparisons, tirzepatide had a higher rate of discontinuations, 86.6% versus 91.1%, that were dose-related.[67] Tirzepatide may reduce the effectiveness of oral hormonal contraceptives and patients should be advised to switch to non-oral contraceptive method.[16] Long-term treatment with tirzepatide will assist in informing safety profile in patients who likely will require chronic use over many years. Discontinuation rates across the trials ranged from 9 to 15% across all 5 trials.[67]

Table 5. Adverse Reactions in 5% or More of Patients Treated with Tirzepatide in Placebo-Controlled Trials

Adverse Reaction	Placebo (n=235) %	Tirzepatide 5 mg (n=237) %	Tirzepatide 10 mg (n=240) %	Tirzepatide 15 mg (n=241) %
Nausea	4	12	15	18
Diarrhea	9	12	13	17
Decreased Appetite	1	5	10	11
Vomiting	2	5	5	9
Constipation	1	6	6	7
Dyspepsia	3	8	8	5
Abdominal Pain	4	6	5	5

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Mortality
2) Cardiovascular events
3) Reduction in A1C
4) Reductions in weight
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Changes in A1C from baseline

Table 5. Pharmacology and Pharmacokinetic Properties[16]

Parameter	
Mechanism of Action	Glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist
Oral Bioavailability	NA
Distribution and Protein Binding	10.3 Liters Highly bound to plasma albumin (99%)
Elimination	0.061 Liters/hour
Half-Life	5 days
Metabolism	Proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid moiety and amide hydrolysis

Table 6. Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Rosenstock, et al [17] SURPASS-1 Phase 3, DB, MC, PG, RCT	1. Tirzepatide 5 mg SC once weekly 2. Tirzepatide 10 mg SC once weekly 3. Tirzepatide 15 mg SC once weekly 4. Placebo SC once weekly Duration: 40 weeks	Demographics: Female: 48% Age: 54.1 years White: 36% Asian: 35% American Indian or Alaska Native: 25% Baseline A1C: 7.94% Weight: 85.9 kg Previous diabetes medication use: 46% Key Inclusion Criteria: - Age ≥18 years - T2DM inadequately controlled with diet and exercise - A1C of 7.0 to 9.5% - BMI ≥23 kg/m^2 (stable for the previous 3 months) Key Exclusion Criteria: - T1DM - Use of antidiabetic medication within previous 3 months - eGFR of ≤30 mL/min/1.73 m^2 - history of pancreatitis - diabetic retinopathy requiring urgent treatment or diabetic maculopathy	mITT: 1. 121 2. 121 3. 121 4. 115 PP: 1. 110 2. 109 3. 95 4. 98 Attrition: 1. 11 (9.1%) 2. 12 (9.9%) 3. 26 (21.5%) 4. 17 (14.8%)	Primary Endpoint: Change in A1C level from baseline at 40 weeks: 1. -1.87% 2. -1.89% 3. -2.07% 4. 0.04% Tirzepatide 5 mg vs. placebo: ETD -1.91 (95% CI, -2.18 to -1.63); P<0.0001 Tirzepatide 10 mg vs. placebo: ETD -1.93 (95% CI, -2.21 to -1.65); P<0.0001 Tirzepatide 15 mg vs. placebo: ETD -2.11 (95% CI, -2.39 to -1.83); P<0.0001 Secondary Endpoints: Number of patients with an A1c <7%: 1. 105 (87%) 2. 108 (92%) 3. 102 (88%) 4. 22 (19%) Tirzepatide 5 mg vs. placebo: OR 49.0 (95% CI, 21.1 to 113.7); P<0.0001 Tirzepatide 10 mg vs. placebo: OR 80.4 (95% CI, 31.8 to 203.2); P<0.0001 Tirzepatide 15 mg vs. placebo: OR 52.9 (95% CI, 22.3 to 125.7); P<0.0001 Changes in body weight from baseline to week 40 1. -7.0 kg 2. -7.8 kg 3. -9.5 kg 4. -0.7 kg Tirzepatide 5 mg vs. placebo: MD -6.3 kg (95% CI, -7.8 to -4.7); P<0.0001 Tirzepatide 10 mg vs. placebo: MD -7.1 kg (95% CI, -8.6 to -5.5); P<0.0001 Tirzepatide 15 mg vs. degludec: MD -8.8 kg (95% CI, -10.3 to -7.2); P<0.0001	NA NA NA ARR 68 NNT 2 ARR 73 NNT 2 ARR 69 NNT 2 NA NA NA	Nausea: 1. 14 (12%) 2. 16 (13%) 3. 22 (18%) 4. 7 (6%) Diarrhea: 1. 14 (12%) 2. 17 (14%) 3. 14 (12%) 4. 9 (8%) Vomiting: 1. 4 (3%) 2. 3 (2%) 3. 7 (6%) 4. 2 (2%) Hypoglycemia: 1. 7 (6%) 2. 8 (7%) 3. 8 (7%) 4. 1 (1%) DC due to adverse events: 1. 4 (3%) 2. 6 (5%) 3. 8 (7%) 4. 3 (3%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized 1:1:1:1 via computer generated random sequence. Baseline characteristics were well matched. Performance Bias: (Low) All patients, investigators, and sponsor were blinded to treatment assignment. All pens were similar in appearance. Detection Bias: (Unclear) No details on the outcome assessment were reported. Attrition Bias: (High) Attrition was high in two of the four groups which could bias results. Missing values imputed by mixed model and repeated measures. Reporting Bias: (Low) Trial was conducted according to protocol and outcomes reported as pre-specified. Other Bias: (High) The study was funded by the manufacturer. **Applicability**: Patient: Studied in patients with T2DM inadequately controlled with diet and exercise. Results are most applicable to White, Asian and American Indian with early T2DM as demonstrated by less than half of participants on antihyperglycemic therapy. Intervention: Dose of tirzepatide was appropriate based on efficacy and safety studies done in phase 1 and 2 trials. Comparator: Placebo. Outcomes: Lowering of HbA1c, obtainment of HbA1c goals and weight reduction are appropriate surrogate outcomes. Setting: 52 medical centers in India, Japan, Mexico, and the U.S. (number of sites not provided).

2. Frias, et al[68] SURPASS-2 Phase 3, MC, OL, PG, RCT	1. Tirzepatide 5 mg† SC once weekly 2. Tirzepatide 10 mg† SC once weekly 3. Tirzepatide 15 mg† SC once weekly 4. Semaglutide 1 mg SC once weekly Duration: 40 weeks Background therapy: metformin † Doses of tirzepatide were blinded, other assessments were open-label	Demographics: Female: 53% Age: 56.6 years White: 82.6% Baseline A1C: 8.28% Weight: 93.7 kg Metformin use: 100% Key Inclusion Criteria: - Age ≥18 years - T2DM that was inadequately controlled with metformin (≥1500 mg/day) - A1C 7.0 to 10.5% - BMI ≥25 kg/m^2 (stable for the previous 3 months) Key Exclusion Criteria: - T1DM - eGFR ≤45 mL/min/1.73 m^2 - history of pancreatitis - diabetic retinopathy requiring urgent treatment or diabetic maculopathy	mITT: 1. 471 2. 469 3. 470 4. 469 PP: 1. 431 2. 411 3. 408 4. 428 Attrition: 1. 40 (8.5%) 2. 58 (12.4%) 3. 62 (13.2%) 4. 41 (8.7%)	Primary Endpoint: Change in HbA1C level from baseline at 40 weeks: 1. -2.01% 2. -2.24% 3. -2.30% 4. -1.86% Tirzepatide 5 mg vs. semaglutide: ETD -0.15 (95% CI, -0.28 to -0.03); P=0.02 Tirzepatide 10 mg vs. semaglutide: ETD -0.39 (95% CI, -0.51 to -0.26); P<0.001 Tirzepatide 15 mg vs. semaglutide: ETD -0.45 (95% CI, -0.57 to -0.32); P<0.001 Secondary Endpoints: Number of patients with an A1c <7%: 1. 386 (82%) 2. 404 (86%) 3. 404 (86%) 4. 371 (79%) Tirzepatide 5 mg vs. semaglutide*: P<0.05 Tirzepatide 10 mg vs. semaglutide*: P<0.05 Tirzepatide 15 mg vs. semaglutide*: P<0.001 Changes in body weight from baseline to week 40 1. -7.6 kg 2. -9.3 kg 3. -11.2 kg 4. -5.7 kg Tirzepatide 5 mg vs. semaglutide: ETD -1.9 kg (95% CI, -0.28 to -1.0); P<0.001 Tirzepatide 10 mg vs. semaglutide: ETD -3.6 kg (95% CI, -4.5 to -2.7); P<0.001 Tirzepatide 15 mg vs. semaglutide: ETD -5.5 kg (95% CI, -6.4 to -4.6); P<0.001	NA NA NA ARR 3/ NNT 34 ARR 7/ NNT 15 ARR 7/ NNT 15 NA NA NA	Nausea: 1. 6 (1.3%) 2. 7 (1.5%) 3. 4 (0.9%) 4. 4 (0.9%) Diarrhea: 1. 1 (0.2%) 2. 3 (0.6%) 3. 6 (1.3%) 4. 1 (0.2%) Vomiting: 1. 1 (0.2%) 2. 4 (0.9%) 3. 4 (0.9%) 4. 3 (0.6%) Hypoglycemia: 1. 29 (0.6%) 2. 10 (0.2%) 3. 80 (1.7%) 4. 19 (0.4%) DC due to adverse events: 1. 28 (6%) 2. 40 (8.5%) 3. 40 (8.5%) 4. 19 (4.1%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Unclear) Baseline characteristics were well matched. Patients were randomized 1:1:1:1 and stratified by country and baseline A1C (> 8.5% or ≤ 8.5%); however details on randomization process were not provided. Performance Bias: (High). Open-label study design lends itself to potential bias towards study treatment. Detection Bias: (Unclear) Blinding of outcome assessors was not described. Attrition Bias: (High) Attrition rates exceeded 10% in the tirzepatide 10 mg and 15 mg groups. Conservative multiple imputation method used for missing data. Reporting Bias: (Low) Study was performed as described in the protocol. Other Bias: (High) Study funded by the manufacturer. **Applicability**: Patient: Studied in patients not previously controlled on metformin. The gender demographics are similar to the Medicaid FFS population in Oregon. American Indians, African American and Hispanics were under represented compared to Oregon and National statistics. Patients were overweight with a BMI of at least 25 and predominantly white. Intervention: Dose of tirzepatide was appropriate based on efficacy and safety studies done in phase 1 and 2 trials. Comparator: Semaglutide is an appropriate comparator; however, the maximum dose is 2 mg once weekly which would provide additional glucose lowering and weight loss. Outcomes: Lowering of HbA1c, obtainment of HbA1c goals and weight reduction are appropriate outcomes. Setting: Study sites included 128 locations in the United States, Argentina, Australia, Brazil, Canada, Israel, Mexico and the

								United Kingdom. Twenty-five percent were from the U.S.
3. Ludvik, et al SURPASS-3[19] Phase 3, MC, NI, OL, PG, RCT Non-inferiority boundary set at 0.3%	1. Tirzepatide 5 mg SC once weekly 2. Tirzepatide 10 mg SC once weekly 3. Tirzepatide 15 mg SC once weekly 4. Insulin degludec SC once daily Duration: 52 weeks Background therapy: stable dose of metformin +/- a SGLT-2 inhibitor	Demographics: Female: 44% Age: 57 years White: 91% Baseline A1C: 8.17% Bodyweight: 94.3 kg Metformin use: 68% Metformin and SGLT-2 use: 32% Key Inclusion Criteria: - Age ≥18 years - T2DM - A1C 7.0% to 10.5% - Insulin naïve - Metformin alone or in combination with an SGLT-2 inhibitor - BMI ≥25 kg/m^2 Key Exclusion Criteria: - T1DM - eGFR ≤30 mL/min/1.73 m^2 or <45 mL/min/1.73 m^2 for patients taking metformin - history of pancreatitis - hepatitis - proliferative diabetic retinopathy requiring urgent treatment or diabetic maculopathy - use of other antihyperglycemic medications in 3 months prior to screening	mITT: 1. 358 2. 360 3. 359 4. 360 PP: 1. 431 2. 411 3. 408 4. 428 Attrition: 1. 40 (8.5%) 2. 58 (12.4%) 3. 62 (13.2%) 4. 41 (8.7%)	Primary Endpoint: Change in A1C level from baseline at week 52: 1. -1.93% 2. -2.20% 3. -2.37% 4. -1.34% Tirzepatide 5 mg vs. degludec: ETD -0.59% (95% CI, -0.73 to -0.45);P<0.0001 Tirzepatide 10 mg vs. degludec: ETD -0.86% (95% CI, -1.00 to -0.72); P<0.001 Tirzepatide 15 mg vs. degludec: ETD -1.04% (95% CI, -1.17 to -0.90); P<0.001 Secondary Endpoints: Number of patients with an A1c <7%: 1. 291 (82%) 2. 314 (90%) 3. 327 (93%) 4. 215 (61%) Tirzepatide 5 mg vs. degludec: OR 3.45 (95% CI, 2.38 to 5.01); P<0.0001 Tirzepatide 10 mg vs. degludec: OR 7.02 (95% CI, 4.55 to 10.84); P<0.001 Tirzepatide 15 mg vs. degludec: OR 10.79 (95% CI, 6.65 to 17.48); P<0.0001 Changes in body weight from baseline to week 52 1. -7.5 kg 2. -10.7 kg 3. -12.9 kg 4. 2.3 kg Tirzepatide 5 mg vs. degludec: ETD -9.8 kg (95% CI, -10.8 to -8.8); P<0.001 Tirzepatide 10 mg vs. degludec: ETD -13.0 kg (95% CI, -14.0 to -11.9); P<0.0001 Tirzepatide 15 mg vs. degludec: ETD -15.2 kg (95% CI, -16.2 to -14.2); P<0.0001	NA NA NA ARR 21 NNT 5 ARR 29 NNT 4 ARR 32 NNT 4 NA NA NA	Nausea: 1. 3 (1%) 2. 7 (2.0%) 3. 9 (3%) 4. 1 (<1%) Diarrhea: 1. 4 (1%) 2. 1 (<1%) 3. 3 (1%) 4. 0 Vomiting: 1. 3 (1%) 2. 6 (2%) 3. 3 (1%) 4. 0 Hypoglycemia (less than or equal to 70 mg/dL): 1. 30 (8%) 2. 49 (14%) 3. 51 (14%) 4. 170 (48%) DC due to adverse events: 1. 25 (7%) 2. 37 (10%) 3. 39 (11%) 4. 5 (1%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized 1:1:1:1 by a computer generated random sequence interactive web-response system. Baseline characteristics were well matched. Performance Bias: (High) Open-label study design lends itself to potential bias towards study treatment. Detection Bias: (Unclear) Blinding of outcome assessors was not described Attrition Bias: (High) Analysis was done on mITT population. High attrition rates (greater than 10%) may bias results. Missing values were imputed using the predicted value from primary endpoint mixed model for repeated measures analysis and then dichotomised. Reporting Bias: (Low) Trial was conducted as outlined in methods. Other Bias: (High) Manufacturer was involved in funding, study design, data collection, data review, data analysis, and drafting of report. **Applicability**: Patient: The gender demographics are similar to the Medicaid FFS population in Oregon. American Indians, African American and Hispanics were under represented compared to Oregon and National statistics. Patients were overweight with a BMI of at least 25 and predominantly white. Intervention: Dose of tirzepatide was appropriate based on efficacy and safety studies done in phase 1 and 2 trials. Comparator: Insulin degludec is an appropriate comparator and titration was appropriate. Outcomes: Lowering of HbA1c, obtainment of HbA1c goals and weight reduction are appropriate outcomes.

								Setting: One hundred twenty-two sites and 13 countries (description of sites not provided).
4. Del Prato, et al[20] SURPASSS- 4 Phase 3, OL, MC, NI, PG, RCT	1. Tirzepatide 5 mg SC once weekly 2. Tirzepatide 10 mg SC once weekly 3. Tirzepatide 15 mg SC once weekly 4. Insulin glargine SC once weekly Duration: 52 weeks and variable treatment period of up to an additional 52 weeks to collect additional CV outcome data Background therapy: stable dose of metformin, SGLT2 inhibitor, and/or SU	Demographics: Female: 38% Age: 63.6 years White: 82% Baseline A1C: 8.52% Bodyweight: 90.3 kg History of CV disease‡: 87% Metformin use: 95% SGLT-2 use: 25% SU use: 54% Key Inclusion Criteria: - Age ≥18 years - T2DM - A1C 7.0% to 10.5% - Stable doses of AHA (metformin, SGLT2i, and/or SU) for ≥3 months - BMI ≥25 kg/m^2 - Increased CV risk (peripheral arterial or cerebrovascular disease or 50 or older with a history of CKD and eGFR <60 mL/min/1.73 m^2 or history of CHF [NYHA II-III]) Key Exclusion Criteria: - T1DM - pancreatitis - proliferative diabetic retinopathy or diabetic maculopathy - cancer - NYHA IV heart failure	mITT: 1. 329 2. 330 3. 338 4. 1005 PP: 1. 294 2. 312 3. 313 4. 882 Attrition: 1. 35 (10.6%) 2. 18 (5.4%) 3. 25 (7.4%) 4. 123 (12.2%)	Primary Endpoint: Change in A1C level from baseline at week 52: 1. -2.24% 2. -2.43% 3. -2.58% 4. -1.44% Non-inferiority margin: 0.3% Tirzepatide 5 mg vs. degludec: ETD -0.80% (95% CI, -0.92 to -0.68);P<0.0001 Tirzepatide 10 mg vs. degludec: ETD -0.99% (95% CI, -1.11 to -0.87);P<0.0001 Tirzepatide 15 mg vs. degludec: ETD -1.14% (95% CI, -1.26 to -1.02); P<0.0001 Secondary Endpoints: Number of patients with an A1c <7%: 1. 264 (81%) 2. 283 (88%) 3. 303 (91%) 4. 496 (51%) Tirzepatide 5 mg vs. degludec: OR 4.78 (95% CI, 3.47 to 6.58); P<0.0001 Tirzepatide 10 mg vs. degludec: OR 9.23 (95% CI, 6.31 to 13.49); P<0.0001 Tirzepatide 15 mg vs. degludec: OR 11.87 (95% CI, 7.88 to 17.89); P<0.0001 Changes in body weight from baseline to week 52 1. -7.1 kg 2. -9.5 kg 3. -11.7 kg 4. 1.9 kg Tirzepatide 5 mg vs. degludec: ETD -9.0 kg (95% CI, -9.8 to -8.3); P<0.0001	NA NA NA ARR 30 NNT 4 ARR 37 NNT 3 ARR 40 NNT 3 NA	Nausea: 1. 39 (12%) 2. 53 (16%) 3. 76 (23%) 4. 23 (2%) Diarrhea: 1. 41 (13%) 2. 65 (20%) 3. 74 (22%) 4. 44 (4%) Vomiting: 1. 16 (5%) 2. 27 (8%) 3. 29 (9%) 4. 16 (2%) Hypoglycemia (less than or equal to 70 mg/dL): 1. 30 (8%) 2. 49 (14%) 3. 51 (14%) 4. 170 (48%) DC due to adverse events: 1. 37 (11%) 2. 28 (9%) 3. 36 (11%) 4. 54 (5%)		**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Patients were randomized 1:1:1:3 using an interactive web-response system to receive tirzepatide or glargine. Baseline characteristics were well matched. Performance Bias: (High) Study was open-label due to different medication dosing frequencies which predisposes results to bias. Detection Bias: (Low) Data was stored via locked database. Analysis was done by manufacturer. Attrition Bias: (High) Attrition was high in 2 of the 4 groups. Missing data was handled by the mixed model for repeated measures. Reporting Bias: (Low) There were changes to the protocol to allow for in-home visits due to COVID and primary endpoint window was widened to 50 to 60 weeks if needed. Other Bias: Manufacturer was involved in funding, study design, data collection, data review, data analysis, and drafting of report. **Applicability**: Patient: Studied in patients with increased CV risk and a history of multiple AHA use. Intervention: Dose of tirzepatide was appropriate based on efficacy and safety studies done in phase 1 and 2 trials. Comparator: Insulin glargine is an appropriate comparator (see dosing above in Table 4). Outcomes: Lowering of HbA1c, obtainment of HbA1c goals and weight reduction are appropriate outcomes. Setting: 187 sites and 14 countries: Argentina, Australia, Brazil, Canada, Greece, Israel, Mexico, Poland, Romania,

		- history of ketoacidosis - eGFR ≤30 mL/min/1.73 m^2 or <45 mL/min/1.73 m^2 for patients taking metformin - history of pancreatitis - hepatitis - - use of other antihyperglycemic medications in 3 months prior to screening		Tirzepatide 10 mg vs. degludec: ETD -11.4 kg (95% CI, -12.1 to -10.6); P<0.0001 Tirzepatide 15 mg vs. degludec: ETD -13.5 kg (95% CI, -14.3 to -12.8); P<0.0001	NA NA			Russia, Slovakia, Spain, Taiwan, and the U.S. (number of sites not described).
5. Dahl, et al[21] SURPASS-5 Phase 3, DB, MC, PG, RCT	1. Tirzepatide 5 mg* SC once weekly 2. Tirzepatide 10 mg* SC once weekly 3. Tirzepatide 15 mg * SC once weekly 4. Placebo SC once weekly Duration: 40 weeks Background therapy: basal insulin glargine with or without metformin	Demographics: Female: 44% Age: 61 years White: 80.4% Baseline A1C: 8.3% Weight: 95.2 kg Metformin use: 83% Key Inclusion Criteria: - Age ≥18 years - T2DM - A1C 7.0% to 10.5% - Receiving insulin glargine (>20 units/day or >0.25IU/kg/day) - Metformin (minimum dose of 1500 mg/day) - BMI ≥23 kg/m^2 Key Exclusion Criteria: - T1DM - eGFR ≤30 mL/min/1.73 m^2 or <45 mL/min/1.73	mITT: 1. 116 2. 119 3. 120 4. 120 PP: 1. 109 2. 115 3. 110 4. 117 Attrition: 1. 7 (6%) 2. 4 (3%) 3. 10 (8.3%) 4. 3 (2.5%)	Primary Endpoint: Change in A1C level from baseline at 40 weeks: 1. -2.11% 2. -2.40% 3. -2.34% 4. -0.86 Tirzepatide 5 mg vs. placebo: MTD -1.24% (95% CI, -1.48 to -1.01); P<0.001 Tirzepatide 10 mg vs. placebo: MTD -1.53% (95% CI, -1.77 to -1.30); P<0.001 Tirzepatide 15 mg vs. placebo: MTD -1.47% (95% CI, -1.7 to -1.23); P<0.001 Secondary Endpoints: Patient met A1C target of <7%: 1. 101 (87%) 2. 106 (90%) 3. 100 (85%) 4. 41 (35%) Tirzepatide 5 mg vs. placebo: OR 14.7 (95% CI, 7.0 to 30.6); P<0.001 Tirzepatide 10 mg vs. placebo: OR 19.5 (95% CI, 9.2 to 41.3); P<0.001	NA NA NA ARR 52 NNT 2 ARR 55 NNT 2	Nausea: 1. 1 (0.9%) 2. 2 (1.7%) 3. 4 (3.3%) 4. 0 (0%) Diarrhea: 1. 1 (0.9%) 2. 2 (1.7%) 3. 4 (3.3%) 4. 0 (0%) Vomiting: 1. 1 (0.9%) 2. 2 (1.7%) 3. 4 (3.3%) 4. 0 (0.6%) Hypoglycemia (blood glucose less than 70 mg/dL): 1. 70 (60.3%) 2. 75 (63.0%) 3. 72 (60.0%) 4. 73 (60.8%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Patients were randomized 1:1:1:1 via a computer-generated random sequence using an interactive web response system. There were more women randomized to the tirzepatide 10 mg group. Performance Bias: (Low) All patients, providers and sponsors blinded to treatment assignment. Detection Bias: (Low) External independent adjudication committee members blinded to treatment. Attrition Bias: (Low) Assessment was done on FAS population and missing values were imputed using the method of multiple imputation. Attrition was low (less than 10%). Reporting Bias: (Low) Study protocol was followed as detailed in the methods. Other Bias: (High) Study was funded by manufacturer. **Applicability**: Patient: Studied in patients with T2DM inadequately controlled with insulin glargine with or without metformin. Results most applicable to patients who

		m^2 for patients taking metformin - history of pancreatitis - hepatitis - proliferative diabetic retinopathy requiring urgent treatment or diabetic maculopathy - use of other antihyperglycemic medications in 3 months prior to screening		Tirzepatide 15 mg vs. placebo: OR 11.5 (95% CI, 5.6 to 23.3); P<0.001 <u>Changes in body weight from baseline to week 40</u> 1. -5.4 kg 2. -7.5 kg 3. -8.8 kg 4. 1.6 kg Tirzepatide 5 mg vs. placebo: -7.1 kg (95% CI, -8.7 to -5.4); P<0.001 Tirzepatide 10 mg vs. placebo: -9.1 kg (95% CI, -10.7 to -7.5); P<0.001 Tirzepatide 15 mg vs. placebo: -10.5 kg (95% CI, -12.1 to -8.8); P<0.001	ARR 50 NNT 2 NA NA NA	<u>DC due to adverse events:</u> 1. 7 (6%) 2. 10 (8.4%) 3. 13 (10.8%) 4. 3 (2.5%)		are white with a history of AHA use. Other ethnicities were under represented compared to Oregon and National statistics. <u>Intervention</u>: Dose of tirzepatide was appropriate based on efficacy and safety studies done in phase 1 and 2 trials. <u>Comparator</u>: Placebo appropriate to determine efficacy. <u>Outcomes</u>: Lowering of HbA1c, obtainment of HbA1c goals and weight reduction are appropriate outcomes. <u>Setting</u>: Forty-five treatment centers in 7 countries: Czech Republic, Germany, Japan, Poland, Slovakia, Spain, and U.S.

<u>Key:</u> * CI not reported, ‡ Defined as known coronary, peripheral arterial or cerebrovascular disease or aged 50 years or older with either a history of chronic kidney disease and an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m^2 or history of congestive heart failure (New York Heart Association Class II or III).
<u>Abbreviations</u>: A1C = glycated hemoglobin level; AHA = antihyperglycemic agent; ARR = absolute risk reduction; BMI = body-mass index; CI = confidence interval; CV = cardiovascular risk; DC = discontinuation; eGFR = estimated glomerular filtration rate; ETD = estimated treatment difference; TT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NI = non-inferiority; NNH = number needed to harm; NNT = number needed to treat; NYHA = New York Heart Association; OL – open label; OR = odds ratio; PG = parallel group; PP = per protocol; RCT = randomized controlled trial; SC = subcutaneous; SGLT-2 = sodium glucose cotransporter; SU = sulfonylurea; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; U.S. = United States

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Appendix 1: Current Preferred Drug List

GLP-1 Receptor Agonists

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

SGLT-2 Inhibitors

Generic	Brand	Form	PDL
canagliflozin	INVOKANA	TABLET	Y
dapagliflozin propanediol	FARXIGA	TABLET	Y
empagliflozin	JARDIANCE	TABLET	Y
canagliflozin/metformin HCl	INVOKAMET XR	TAB BP 24H	N
canagliflozin/metformin HCl	INVOKAMET	TABLET	N
dapagliflozin/metformin HCl	XIGDUO XR	TAB BP 24H	N
dapagliflozin/saxagliptin HCl	QTERN	TABLET	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	STEGLUJAN	TABLET	N

Appendix 2: Abstracts of Comparative Clinical Trials

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Anker SD, Gerasimos Filippatos, João P Ferreira, Edimar Bocchi, Michael Böhm, Hans-Peter Brunner-La Rocca, Dong-Ju Choi, Vijay Chopra, Eduardo Chuquiure-Valenzuela, Nadia Giannetti, Juan Esteban Gomez-Mesa, Stefan Janssens, James L Januzzi, Jose R Gonzalez-Juanatey, Bela Merkely, Stephen J Nicholls, Sergio V Perrone, Ileana L Piña, Piotr Ponikowski, Michele Senni, David Sim, Jindrich Spinar, Iain Squire, Stefano Taddei, Hiroyuki Tsutsui, Subodh Verma, Dragos Vinereanu, Jian Zhang, Peter Carson, Carolyn Su Ping Lam, Nikolaus Marx, Cordula Zeller, Naveed Sattar, Waheed Jamal, Sven Schnaidt, Janet M Schnee, Martina Brueckmann, Stuart J Pocock, Faiez Zannad, Milton Packer, EMPEROR-Preserved Trial Investigators

Abstract

Background: Sodium-glucose cotransporter 2 inhibitors reduce the risk of hospitalization for heart failure in patients with heart failure and a reduced ejection fraction, but their effects in patients with heart failure and a preserved ejection fraction are uncertain.

Methods: In this double-blind trial, we randomly assigned 5988 patients with class II-IV heart failure and an ejection fraction of more than 40% to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure.

Results: Over a median of 26.2 months, a primary outcome event occurred in 415 of 2997 patients (13.8%) in the empagliflozin group and in 511 of 2991 patients (17.1%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.69 to 0.90; P<0.001). This effect was mainly related to a lower risk of hospitalization for heart failure in the empagliflozin group. The effects of empagliflozin appeared consistent in patients with or without diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (407 with empagliflozin and 541 with placebo; hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P<0.001). Uncomplicated genital and urinary tract infections and hypotension were reported more frequently with empagliflozin.

Conclusions: Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Preserved ClinicalTrials.gov number, NCT03057951).

Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes

Christopher P Cannon, Richard Pratley, Samuel Dagogo-Jack, James Mancuso, Susan Huyck, Urszula Masiukiewicz, Bernard Charbonnel, Robert Frederich, Silvina Gallo, Francesco Cosentino, Weichung J Shih, Ira Gantz, Steven G Terra, David Z I Cherney, Darren K McGuire, VERTIS CV Investigators

Abstract

Background: The cardiovascular effects of ertugliflozin, an inhibitor of sodium-glucose cotransporter 2, have not been established.

Methods: In a multicenter, double-blind trial, we randomly assigned patients with type 2 diabetes and atherosclerotic cardiovascular disease to receive 5 mg or 15 mg of ertugliflozin or placebo once daily. With the data from the two ertugliflozin dose groups pooled for analysis, the primary objective was to show the noninferiority of ertugliflozin to placebo with respect to the primary outcome, major adverse cardiovascular events (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). The noninferiority margin was 1.3 (upper boundary of a 95.6% confidence interval for the hazard ratio [ertugliflozin vs. placebo] for major adverse cardiovascular events). The first key secondary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure.

Results: A total of 8246 patients underwent randomization and were followed for a mean of 3.5 years. Among 8238 patients who received at least one dose of ertugliflozin or placebo, a major adverse cardiovascular event occurred in 653 of 5493 patients (11.9%) in the ertugliflozin group and in 327 of 2745 patients

(11.9%) in the placebo group (hazard ratio, 0.97; 95.6% confidence interval [CI], 0.85 to 1.11; P<0.001 for noninferiority). Death from cardiovascular causes or hospitalization for heart failure occurred in 444 of 5499 patients (8.1%) in the ertugliflozin group and in 250 of 2747 patients (9.1%) in the placebo group (hazard ratio, 0.88; 95.8% CI, 0.75 to 1.03; P = 0.11 for superiority). The hazard ratio for death from cardiovascular causes was 0.92 (95.8% CI, 0.77 to 1.11), and the hazard ratio for death from renal causes, renal replacement therapy, or doubling of the serum creatinine level was 0.81 (95.8% CI, 0.63 to 1.04). Amputations were performed in 54 patients (2.0%) who received the 5-mg dose of ertugliflozin and in 57 patients (2.1%) who received the 15-mg dose, as compared with 45 patients (1.6%) who received placebo.

Conclusions: Among patients with type 2 diabetes and atherosclerotic cardiovascular disease, ertugliflozin was noninferior to placebo with respect to major adverse cardiovascular events. (Funded by Merck Sharp & Dohme and Pfizer; VERTIS CV ClinicalTrials.gov number, NCT01986881.).

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J L Heerspink [1], Bergur V Stefánsson [1], Ricardo Correa-Rotter [1], Glenn M Chertow [1], Tom Greene [1], Fan-Fan Hou [1], Johannes F E Mann [1], John J V McMurray [1], Magnus Lindberg [1], Peter Rossing [1], C David Sjöström [1], Roberto D Toto [1], Anna-Maria Langkilde [1], David C Wheeler [1], DAPA-CKD Trial Committees and Investigators

Abstract

Background: Patients with chronic kidney disease have a high risk of adverse kidney and cardiovascular outcomes. The effect of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes, is not known.

Methods: We randomly assigned 4304 participants with an estimated glomerular filtration rate (GFR) of 25 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 200 to 5000 to receive dapagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.

Results: The independent data monitoring committee recommended stopping the trial because of efficacy. Over a median of 2.4 years, a primary outcome event occurred in 197 of 2152 participants (9.2%) in the dapagliflozin group and 312 of 2152 participants (14.5%) in the placebo group (hazard ratio, 0.61; 95% confidence interval [CI], 0.51 to 0.72; P<0.001; number needed to treat to prevent one primary outcome event, 19 [95% CI, 15 to 27]). The hazard ratio for the composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI, 0.45 to 0.68; P<0.001), and the hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI, 0.55 to 0.92; P = 0.009). Death occurred in 101 participants (4.7%) in the dapagliflozin group and 146 participants (6.8%) in the placebo group (hazard ratio, 0.69; 95% CI, 0.53 to 0.88; P = 0.004). The effects of dapagliflozin were similar in participants with type 2 diabetes and in those without type 2 diabetes. The known safety profile of dapagliflozin was confirmed.

Conclusions: Among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo. (Funded by AstraZeneca; DAPA-CKD ClinicalTrials.gov number, NCT03036150.).

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

Milton Packer [1], Stefan D Anker [1], Javed Butler [1], Gerasimos Filippatos [1], Stuart J Pocock [1], Peter Carson [1], James Januzzi [1], Subodh Verma [1], Hiroyuki Tsutsui [1], Martina Brueckmann [1], Waheed Jamal [1], Karen Kimura [1], Janet Schnee [1], Cordula Zeller [1], Daniel Cotton [1], Edimar Bocchi [1], Michael Böhm [1], Dong-Ju Choi [1], Vijay Chopra [1], Eduardo Chuquiure [1], Nadia Giannetti [1], Stefan Janssens [1], Jian Zhang [1], Jose R Gonzalez Juanatey [1], Sanjay Kaul [1], Hans-Peter Brunner-La Rocca [1], Bela Merkely [1], Stephen J Nicholls [1], Sergio Perrone [1], Ileana Pina [1], Piotr Ponikowski [1], Naveed Sattar [1], Michele Senni [1], Marie-France Seronde [1], Jindrich Spinar [1], Iain Squire [1], Stefano Taddei [1], Christoph Wanner [1], Faiez Zannad [1], EMPEROR-Reduced Trial Investigators

Abstract

Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure in patients regardless of the presence or absence of diabetes. More evidence is needed regarding the effects of these drugs in patients across the broad spectrum of heart failure, including those with a markedly reduced ejection fraction.

Methods: In this double-blind trial, we randomly assigned 3730 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of cardiovascular death or hospitalization for worsening heart failure.

Results: During a median of 16 months, a primary outcome event occurred in 361 of 1863 patients (19.4%) in the empagliflozin group and in 462 of 1867 patients (24.7%) in the placebo group (hazard ratio for cardiovascular death or hospitalization for heart failure, 0.75; 95% confidence interval [CI], 0.65 to 0.86; P<0.001). The effect of empagliflozin on the primary outcome was consistent in patients regardless of the presence or absence of diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (hazard ratio, 0.70; 95% CI, 0.58 to 0.85; P<0.001). The annual rate of decline in the estimated glomerular filtration rate was slower in the empagliflozin group than in the placebo group (-0.55 vs. -2.28 ml per minute per 1.73 m^2 of body-surface area per year, P<0.001), and empagliflozin-treated patients had a lower risk of serious renal outcomes. Uncomplicated genital tract infection was reported more frequently with empagliflozin.

Conclusions: Among patients receiving recommended therapy for heart failure, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Reduced ClinicalTrials.gov number, NCT03057977.).

Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial

Rosenstock J , Carol Wysham, Juan P Frías, Shizuka Kaneko, Clare J Lee, Laura Fernández Landó, Huzhang Mao, Xuewei Cui, Chrisanthi A Karanikas, Vivian T Thieu

Background: Despite advancements in care, many people with type 2 diabetes do not meet treatment goals; thus, development of new therapies is needed. We aimed to assess efficacy, safety, and tolerability of novel dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist tirzepatide monotherapy versus placebo in people with type 2 diabetes inadequately controlled by diet and exercise alone.

Methods: We did a 40-week, double-blind, randomised, placebo-controlled, phase 3 trial (SURPASS-1), at 52 medical research centres and hospitals in India, Japan, Mexico, and the USA. Adult participants (≥18 years) were included if they had type 2 diabetes inadequately controlled by diet and exercise alone and if they were naive to injectable diabetes therapy. Participants were randomly assigned (1:1:1:1) via computer-generated random sequence to once a week tirzepatide (5, 10, or 15 mg), or placebo. All participants, investigators, and the sponsor were masked to treatment assignment. The primary endpoint was the mean change in glycated haemoglobin (HbA_{1c}) from baseline at 40 weeks. This study is registered with ClinicalTrials.gov, NCT03954834.

Findings: From June 3, 2019, to Oct 28, 2020, of 705 individuals assessed for eligibility, 478 (mean baseline HbA_{1c} 7·9% [63 mmol/mol], age 54·1 years [SD 11·9], 231 [48%] women, diabetes duration 4·7 years, and body-mass index 31·9 kg/m^2) were randomly assigned to tirzepatide 5 mg (n=121 [25%]), tirzepatide 10 mg (n=121 [25%]), tirzepatide 15 mg (n=121 [25%]), or placebo (n=115 [24%]). 66 (14%) participants discontinued the study drug and 50 (10%) discontinued the study prematurely. At 40 weeks, all tirzepatide doses were superior to placebo for changes from baseline in HbA_{1c}, fasting serum glucose, bodyweight, and HbA_{1c} targets of less than 7·0% (<53 mmol/mol) and less than 5·7% (<39 mmol/mol). Mean HbA_{1c} decreased from baseline by 1·87% (20 mmol/mol) with tirzepatide 5 mg, 1·89% (21 mmol/mol) with tirzepatide 10 mg, and 2·07% (23 mmol/mol) with tirzepatide 15 mg versus +0·04% with placebo (+0·4 mmol/mol), resulting in estimated treatment differences versus placebo of -1·91% (-21 mmol/mol) with tirzepatide 5 mg, -1·93% (-21 mmol/mol) with tirzepatide 10 mg, and -2·11% (-23 mmol/mol) with tirzepatide 15 mg (all p<0·0001). More participants on tirzepatide than on placebo met HbA_{1c} targets of less than 7·0% (<53

mmol/mol; 87-92% vs 20%) and 6·5% or less (≤48 mmol/mol; 81-86% vs 10%) and 31-52% of patients on tirzepatide versus 1% on placebo reached an HbA_{1c} of less than 5·7% (<39 mmol/mol). Tirzepatide induced a dose-dependent bodyweight loss ranging from 7·0 to 9·5 kg. The most frequent adverse events with tirzepatide were mild to moderate and transient gastrointestinal events, including nausea (12-18% vs 6%), diarrhoea (12-14% vs 8%), and vomiting (2-6% vs 2%). No clinically significant (<54 mg/dL [<3 mmol/L]) or severe hypoglycaemia were reported with tirzepatide. One death occurred in the placebo group.
Interpretation: Tirzepatide showed robust improvements in glycaemic control and bodyweight, without increased risk of hypoglycaemia. The safety profile was consistent with GLP-1 receptor agonists, indicating a potential monotherapy use of tirzepatide for type 2 diabetes treatment.

Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes
Juan P Frías, Melanie J Davies , Julio Rosenstock, Federico C Pérez Manghi, Laura Fernández Landó, Brandon K Bergman, Bing Liu, Xuewei Cui, Katelyn Brown, SURPASS-2 Investigators
Background: Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist that is under development for the treatment of type 2 diabetes. The efficacy and safety of once-weekly tirzepatide as compared with semaglutide, a selective GLP-1 receptor agonist, are unknown.
Methods: In an open-label, 40-week, phase 3 trial, we randomly assigned 1879 patients, in a 1:1:1:1 ratio, to receive tirzepatide at a dose of 5 mg, 10 mg, or 15 mg or semaglutide at a dose of 1 mg. At baseline, the mean glycated hemoglobin level was 8.28%, the mean age 56.6 years, and the mean weight 93.7 kg. The primary end point was the change in the glycated hemoglobin level from baseline to 40 weeks.
Results: The estimated mean change from baseline in the glycated hemoglobin level was -2.01 percentage points, -2.24 percentage points, and -2.30 percentage points with 5 mg, 10 mg, and 15 mg of tirzepatide, respectively, and -1.86 percentage points with semaglutide; the estimated differences between the 5-mg, 10-mg, and 15-mg tirzepatide groups and the semaglutide group were -0.15 percentage points (95% confidence interval [CI], -0.28 to -0.03; P = 0.02), -0.39 percentage points (95% CI, -0.51 to -0.26; P<0.001), and -0.45 percentage points (95% CI, -0.57 to -0.32; P<0.001), respectively. Tirzepatide at all doses was noninferior and superior to semaglutide. Reductions in body weight were greater with tirzepatide than with semaglutide (least-squares mean estimated treatment difference, -1.9 kg, -3.6 kg, and -5.5 kg, respectively; P<0.001 for all comparisons). The most common adverse events were gastrointestinal and were primarily mild to moderate in severity in the tirzepatide and semaglutide groups (nausea, 17 to 22% and 18%; diarrhea, 13 to 16% and 12%; and vomiting, 6 to 10% and 8%, respectively). Of the patients who received tirzepatide, hypoglycemia (blood glucose level, <54 mg per deciliter) was reported in 0.6% (5-mg group), 0.2% (10-mg group), and 1.7% (15-mg group); hypoglycemia was reported in 0.4% of those who received semaglutide. Serious adverse events were reported in 5 to 7% of the patients who received tirzepatide and in 3% of those who received semaglutide.
Conclusions: In patients with type 2 diabetes, tirzepatide was noninferior and superior to semaglutide with respect to the mean change in the glycated hemoglobin level from baseline to 40 weeks. (Funded by Eli Lilly; SURPASS-2 ClinicalTrials.gov number, NCT03987919.).

Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial
Bernhard Ludvik, Francesco Giorgino, Esteban Jódar, Juan P Frias, Laura Fernández Landó, Katelyn Brown, Ross Bray, Ángel Rodríguez
Background: Tirzepatide is a novel dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist under development for the treatment of type 2 diabetes. We aimed to assess the efficacy and safety of tirzepatide versus titrated insulin degludec in people with type 2 diabetes inadequately controlled by metformin with or without SGLT2 inhibitors.
Methods: In this open-label, parallel-group, multicentre (122 sites), multinational (13 countries), phase 3 study, eligible participants (aged ≥18 years) had a baseline glycated haemoglobin (HbA_{1c}) of 7·0-10·5%, body-mass index of at least 25 kg/m^2, stable weight, and were insulin-naive and treated with metformin alone or in combination with an SGLT2 inhibitor for at least 3 months before screening. Participants were randomly assigned (1:1:1:1), using an interactive web-

response system, to once-weekly subcutaneous injection of tirzepatide (5, 10, or 15 mg) or once-daily subcutaneous injection of titrated insulin degludec, and were stratified by country, HbA_{1c}, and concomitant use of oral antihyperglycaemic medications. Tirzepatide was initially given at 2·5 mg and the dose was escalated by 2·5 mg every 4 weeks until the assigned dose was reached. Insulin degludec was initially given at 10 U per day and was titrated once weekly to a fasting self-monitored blood glucose of less than 5·0 mmol/L (<90 mg/dL), following a treat-to-target algorithm, for 52 weeks. The primary efficacy endpoint was non-inferiority of tirzepatide 10 mg or 15 mg, or both, versus insulin degludec in mean change from baseline in HbA_{1c} at week 52. Key secondary efficacy endpoints were non-inferiority of tirzepatide 5 mg versus insulin degludec in mean change from baseline in HbA_{1c} at week 52, superiority of all doses of tirzepatide versus insulin degludec in mean change from baseline in HbA_{1c} and bodyweight, and the proportion of participants achieving HbA_{1c} of less than 7·0% (<53 mmol/mol) at week 52. We used a boundary of 0·3% to establish non-inferiority in HbA_{1c} difference between treatments. Efficacy and safety analyses were assessed in the modified intention-to-treat population (all participants who received at least one dose of study drug). This trial is registered with ClinicalTrials.gov, number NCT03882970, and is complete.

Findings: Between April 1 and Nov 15, 2019, we assessed 1947 participants for eligibility, 1444 of whom were randomly assigned to treatment. The modified intention-to-treat population was 1437 participants from the tirzepatide 5 mg (n=358), tirzepatide 10 mg (n=360), tirzepatide 15 mg (n=359), and insulin degludec (n=360) groups. From a mean baseline HbA_{1c} of 8·17% (SD 0·91), the reductions in HbA_{1c} at week 52 were 1·93% (SE 0·05) for tirzepatide 5 mg, 2·20% (0·05) for tirzepatide 10 mg, and 2·37% (0·05) for tirzepatide 15 mg, and 1·34% (0·05) for insulin degludec. The non-inferiority margin of 0·3% was met. The estimated treatment difference (ETD) versus insulin degludec ranged from -0·59% to -1·04% for tirzepatide ($p<0·0001$ for all tirzepatide doses). The proportion of participants achieving a HbA_{1c} of less than 7·0% (<53 mmol/mol) at week 52 was greater ($p<0·0001$) in all three tirzepatide groups (82%-93%) versus insulin degludec (61%). At week 52, from a baseline of 94·3 kg (SD 20·1), all three tirzepatide doses decreased bodyweight (-7·5 kg to -12·9 kg), whereas insulin degludec increased bodyweight by 2·3 kg. The ETD versus insulin degludec ranged from -9·8 kg to -15·2 kg for tirzepatide ($p<0·0001$ for all tirzepatide doses). The most common adverse events in tirzepatide-treated participants were mild to moderate gastrointestinal events that decreased over time. A higher incidence of nausea (12-24%), diarrhoea (15-17%), decreased appetite (6-12%), and vomiting (6-10%) was reported in participants treated with tirzepatide than in those treated with insulin degludec (2%, 4%, 1%, and 1%, respectively). Hypoglycaemia (<54 mg/dL or severe) was reported in five (1%), four (1%), and eight (2%) participants on tirzepatide 5, 10, and 15 mg, respectively, versus 26 (7%) on insulin degludec. Treatment discontinuation due to an adverse event was more common in the tirzepatide groups than in the insulin degludec group. Five participants died during the study; none of the deaths were considered by the investigators to be related to the study treatment.

Interpretation: In patients with type 2 diabetes, tirzepatide (5, 10, and 15 mg) was superior to titrated insulin degludec, with greater reductions in HbA_{1c} and bodyweight at week 52 and a lower risk of hypoglycaemia. Tirzepatide showed a similar safety profile to that of GLP-1 receptor agonists.

Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial

Stefano Del Prato, Steven E Kahn, Imre Pavo, Govinda J Weerakkody, Zhengyu Yang, John Doupis, Diego Aizenberg, Alan G Wynne, Jeffrey S Riesmeyer, Robert J Heine, Russell J Wiese, SURPASS-4 Investigators

Background: We aimed to assess efficacy and safety, with a special focus on cardiovascular safety, of the novel dual GIP and GLP-1 receptor agonist tirzepatide versus insulin glargine in adults with type 2 diabetes and high cardiovascular risk inadequately controlled on oral glucose-lowering medications.

Methods: This open-label, parallel-group, phase 3 study was done in 187 sites in 14 countries on five continents. Eligible participants, aged 18 years or older, had type 2 diabetes treated with any combination of metformin, sulfonylurea, or sodium-glucose co-transporter-2 inhibitor, a baseline glycated haemoglobin (HbA_{1c}) of 7·5-10·5% (58-91 mmol/mol), body-mass index of 25 kg/m^2 or greater, and established cardiovascular disease or a high risk of cardiovascular events. Participants were randomly assigned (1:1:1:3) via an interactive web-response system to subcutaneous injection of either once-per-week tirzepatide (5 mg, 10 mg, or 15 mg) or glargine (100 U/mL), titrated to reach fasting blood glucose of less than 100 mg/dL. The primary endpoint was non-inferiority (0·3% non-

inferiority boundary) of tirzepatide 10 mg or 15 mg, or both, versus glargine in HbA_{1c} change from baseline to 52 weeks. All participants were treated for at least 52 weeks, with treatment continued for a maximum of 104 weeks or until study completion to collect and adjudicate major adverse cardiovascular events (MACE). Safety measures were assessed over the full study period. This study was registered with ClinicalTrials.gov, NCT03730662.
Findings: Patients were recruited between Nov 20, 2018, and Dec 30, 2019. 3045 participants were screened, with 2002 participants randomly assigned to tirzepatide or glargine. 1995 received at least one dose of tirzepatide 5 mg (n=329, 17%), 10 mg (n=328, 16%), or 15 mg (n=338, 17%), or glargine (n=1000, 50%), and were included in the modified intention-to-treat population. At 52 weeks, mean HbA_{1c} changes with tirzepatide were -2·43% (SD 0·05) with 10 mg and -2·58% (0·05) with 15 mg, versus -1·44% (0·03) with glargine. The estimated treatment difference versus glargine was -0·99% (multiplicity adjusted 97·5% CI -1·13 to -0·86) for tirzepatide 10 mg and -1·14% (-1·28 to -1·00) for 15 mg, and the non-inferiority margin of 0·3% was met for both doses. Nausea (12-23%), diarrhoea (13-22%), decreased appetite (9-11%), and vomiting (5-9%) were more frequent with tirzepatide than glargine (nausea 2%, diarrhoea 4%, decreased appetite <1%, and vomiting 2%, respectively); most cases were mild to moderate and occurred during the dose-escalation phase. The percentage of participants with hypoglycaemia (glucose <54 mg/dL or severe) was lower with tirzepatide (6-9%) versus glargine (19%), particularly in participants not on sulfonylureas (tirzepatide 1-3% vs glargine 16%). Adjudicated MACE-4 events (cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina) occurred in 109 participants and were not increased on tirzepatide compared with glargine (hazard ratio 0·74, 95% CI 0·51-1·08). 60 deaths (n=25 [3%] tirzepatide; n=35 [4%] glargine) occurred during the study.
Interpretation: In people with type 2 diabetes and elevated cardiovascular risk, tirzepatide, compared with glargine, demonstrated greater and clinically meaningful HbA_{1c} reduction with a lower incidence of hypoglycaemia at week 52. Tirzepatide treatment was not associated with excess cardiovascular risk.

Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control in Patients With Type 2 Diabetes: The SURPASS-5 Randomized Clinical Trial
Dominik Dahl, Yukiko Onishi, Paul Norwood, Ruth Huh, Ross Bray, Hiren Patel, Ángel Rodríguez

Importance: The effects of tirzepatide, a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, as an addition to insulin glargine for treatment of type 2 diabetes have not been described.
Objective: To assess the efficacy and safety of tirzepatide added to insulin glargine in patients with type 2 diabetes with inadequate glycemic control.
Design, setting, and participants: Randomized phase 3 clinical trial conducted at 45 medical research centers and hospitals in 8 countries (enrollment from August 30, 2019, to March 20, 2020; follow-up completed January 13, 2021) in 475 adults with type 2 diabetes and inadequate glycemic control while treated with once-daily insulin glargine with or without metformin.
Interventions: Patients were randomized in a 1:1:1:1 ratio to receive once-weekly subcutaneous injections of 5-mg (n = 116), 10-mg (n = 119), or 15-mg (n = 120) tirzepatide or volume-matched placebo (n = 120) over 40 weeks. Tirzepatide was initiated at 2.5 mg/week and escalated by 2.5 mg every 4 weeks until the assigned dose was achieved.
Main outcomes and measures: The primary end point was mean change from baseline in glycated hemoglobin A1c (HbA1c) at week 40. The 5 key secondary end points included mean change in body weight and percentage of patients achieving prespecified HbA1c levels.
Results: Among 475 randomized participants (211 [44%] women; mean [SD] age, 60.6 [9.9] years; mean [SD] HbA1c, 8.31% [0.85%]), 451 (94.9%) completed the trial. Treatment was prematurely discontinued by 10% of participants in the 5-mg tirzepatide group, 12% in the 10-mg tirzepatide group, 18% in the 15-mg tirzepatide group, and 3% in the placebo group. At week 40, mean HbA1c change from baseline was -2.40% with 10-mg tirzepatide and -2.34% with 15-mg tirzepatide vs -0.86% with placebo (10 mg: difference vs placebo, -1.53% [97.5% CI, -1.80% to -1.27%]; 15 mg: difference vs placebo, -1.47% [97.5% CI, -1.75% to -1.20%]; P < .001 for both). Mean HbA1c change from baseline was -2.11% with 5-mg tirzepatide (difference vs placebo, -1.24% [95% CI, -1.48% to -1.01%]; P < .001]). Mean body weight change from baseline was -5.4 kg with 5-mg tirzepatide, -7.5 kg with 10-mg tirzepatide, -8.8 kg with 15-mg tirzepatide and 1.6 kg with

placebo (5 mg: difference, -7.1 kg [95% CI, -8.7 to -5.4]; 10 mg: difference, -9.1 kg [95% CI, -10.7 to -7.5]; 15 mg: difference, -10.5 kg [95% CI, -12.1 to -8.8]; P < .001 for all). Higher percentages of patients treated with tirzepatide vs those treated with placebo had HbA1c less than 7% (85%-90% vs 34%; P < .001 for all). The most common treatment-emergent adverse events in the tirzepatide groups vs placebo group were diarrhea (12%-21% vs 10%) and nausea (13%-18% vs 3%).

Conclusions and relevance: Among patients with type 2 diabetes and inadequate glycemic control despite treatment with insulin glargine, the addition of subcutaneous tirzepatide, compared with placebo, to titrated insulin glargine resulted in statistically significant improvements in glycemic control after 40 weeks.

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to August 08, 2022
Search Strategy:

#	Searches	Results
1	dulaglutide.mp.	605
2	exenatide.mp. or Exenatide/	3671
3	liraglutide.mp. or Liraglutide/	3702
4	lixisenatide.mp.	542
5	semaglutide.mp.	886
6	tirzepatide.mp.	106
7	dapagliflozin.mp.	2191
8	canagliflozin.mp. or Canagliflozin/	1592
9	empagliflozin.mp.	2279
10	ertugliflozin.mp.	221
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	12176
12	limit 11 to (english language and humans)	7486
13	limit 12 to (yr="2020 -Current" and (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review"))	263

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MOUNJARO safely and effectively. See full prescribing information for MOUNJARO.

MOUNJARO™ (tirzepatide) Injection, for subcutaneous use
Initial U.S. Approval: 2022

WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- **Tirzepatide causes thyroid C-cell tumors in rats. It is unknown whether MOUNJARO causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).**
- **MOUNJARO is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).**

---------- INDICATIONS AND USAGE ----------

MOUNJARO™ is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Limitations of Use:

- Has not been studied in patients with a history of pancreatitis (1, 5.2)
- Is not indicated for use in patients with type 1 diabetes mellitus (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended starting dosage is 2.5 mg injected subcutaneously once weekly (2.1)
- After 4 weeks, increase to 5 mg injected subcutaneously once weekly (2.1)
- If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose.
- The maximum dosage is 15 mg subcutaneously once weekly (2.1).
- Administer once weekly at any time of day, with or without meals. (2.2)
- Inject subcutaneously in the abdomen, thigh, or upper arm. (2.2)
- Rotate injection sites with each dose.

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL in single-dose pen (3)

---------- CONTRAINDICATIONS ----------

- Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4, 5.1)
- Known serious hypersensitivity to tirzepatide or any of the excipients in MOUNJARO (4, 5.4)

----------WARNINGS AND PRECAUTIONS----------

- *Pancreatitis:* Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. (5.2)
- *Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin:* Concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing dose of insulin secretagogue or insulin may be necessary. (5.3)
- *Hypersensitivity Reactions:* Hypersensitivity reactions have been reported. Discontinue MOUNJARO if suspected. (5.4)
- *Acute Kidney Injury:* Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions. (5.5)
- *Severe Gastrointestinal Disease:* Use may be associated with gastrointestinal adverse reactions, sometimes severe. Has not been studied in patients with severe gastrointestinal disease and is not recommended in these patients. (5.6)
- *Diabetic Retinopathy Complications in Patients with a History of Diabetic Retinopathy:* Has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Monitor patients with a history of diabetic retinopathy for progression. (5.7)
- *Acute Gallbladder Disease:* Has occurred in clinical trials. If cholelithiasis is suspected, gallbladder studies and clinical follow-up are indicated. (5.8)

----------ADVERSE REACTIONS----------

The most common adverse reactions, reported in ≥5% of patients treated with MOUNJARO are: nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

MOUNJARO delays gastric emptying and has the potential to impact the absorption of concomitantly administered oral medications. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy:* Based on animal study, may cause fetal harm. (8.1)
- *Females of Reproductive Potential:* Advise females using oral contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation. (7.2, 8.3, 12.3)

Appendix 5: Key Inclusion Criteria

Population	Patients with type 2 diabetes mellitus
Intervention	GLP-1 RAs, SGLT-2 inhibitors or tirzepatide
Comparator	Placebo or active control (e.g., antihyperglycemic medications)
Outcomes	HbA1c lowering, cardiovascular events, death, hospitalization
Setting	Outpatient

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.
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

Approval Criteria		
4. Has the patient tried and failed 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

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 Review: *10/22 (KS), 8/20 (KS), 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: *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 SGLT-2 inhibitors

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. Approved Indications for SGLT2 Inhibitors (in addition to glucose lowering)

Drug Name	CV risk reduction in patients with T2D and established CV disease	Reduction in risk of end-stage kidney disease in patients with T2D and diabetic nephropathy with albuminuria >300 mg/day	Reduction in risk of eGFR decline and end-stage kidney disease CV death and hospitalization for HF in patients with CKD at risk of progression	HF risk reduction in patients with T2D and established CV disease or multiple CV risk factors	HF risk reduction in patients with HF and HFrEF
Canagliflozin	X	X			
Dapagliflozin			X	X	X
Empagliflozin	X				X
Ertugliflozin					

Abbreviations: CKD – chronic kidney disease; CV – cardiovascular; eGFR – estimated glomerular filtration rate; HF – heart failure; HFrEF – heart failure with reduced ejection fraction; T2D – type 2 diabetes

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization?	**Yes:** Go the **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code	
3. Does the patient qualify for the requested therapy based on diagnoses and requirements in Table 1?	**Yes:** Go to #5	**No:** Go to #4
4. Does the patient have T2D and failed, or have contraindications to, metformin or is requesting a SGLT2 inhibitor to be used in combination with metformin? (document contraindication, if any)	**Yes:** Go to #5	**No:** Pass to RPh. Deny and recommend trial of metformin. See below for metformin titration schedule.

Approval Criteria		
5. Is the request for a SGLT2 inhibitor (including combination products) and there is a documented estimated glomerular filtration rate (eGFR) within the last 12 months showing the product is not contraindicated? Products listed below should not be used in the following patients: • Canagliflozin and on dialysis, or • Empagliflozin and on dialysis , or • Dapagliflozin and eGFR on dialysis, or • Ertugliflozin and eGFR <30 mL/min/ 1.73 m^2?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the request for the renewal of a SGLT2 inhibitor (including combination products) and there is a documented eGFR within the last 12 months showing the product is not contraindicated? : Products listed below should not be used in the following patients: • Canagliflozin and on dialysis, or • Empagliflozin and on dialysis, or • Dapagliflozin and on dialysis, or • Ertugliflozin and eGFR <30 mL/min/ 1.73 m^2?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

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 but is often 850 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.