Introduction

Metabolism refers to how the body converts the energy supplied by food into energy the body can use. Diabetes is a disease of the metabolic system. Diabetes involves production of and response to insulin. Insulin is a hormone produced by certain cells in the pancreas called beta cells. These cells regulate the amount of glucose (sugar) in the blood. There are two types of diabetes: type I and type II. In type I diabetes, the pancreas no longer makes insulin. The beta cells of the pancreas have been destroyed. The body needs an external supply of insulin in order to use glucose. Type I diabetes is usually diagnosed in children and young adults. In type II diabetes, people can still make insulin, but their bodies don’t respond well to it. This is known as insulin resistance. Type II diabetes can be diagnosed at any age and can be affected and modified by a number of factors, such diet and exercise and other health conditions. It can also be a side-effect of certain drugs. Type II diabetes can be treated with oral or injectable noninsulin agents, as well as insulin injections.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Policy Coverage Criteria

Documentation in the form of clinical chart notes is required for a review of all non-preferred agents.

Note: The following insulin products are NOT affected by this policy:

- Levemir® (detemir)
- Lantus® (glargine)
- Tresiba® (degludec)
- Ryzodeg® (degludec and aspart combination)

- Humulin® R U-500 and Humulin® R U-500 KwikPen
- Toujeo® (glargine) U-300
  - For details on Toujeo® (glargine U-300) for Closed Formulary Benefits, see Related Policies.
Select the link below to view coverage criteria for non-preferred products:

Insulin Products (Vials and Prefilled Pens)

Coverage Criteria: Non-preferred insulin products used for the treatment of type I and type II diabetes mellitus may be considered **medically necessary** when patient has a contraindication or intolerance to the preferred agent **OR** this insulin product was ineffective in reducing A1C to goal after three months of therapy. For preferred and non-preferred products, see table below.

<table>
<thead>
<tr>
<th>Preferred Insulin</th>
<th>Non-preferred Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-Acting Insulin</strong></td>
<td></td>
</tr>
<tr>
<td>• Novolog® (aspart)</td>
<td>• Humalog® (lispro)</td>
</tr>
<tr>
<td>• Apidra® (glulisine)</td>
<td>• Admelog® (lispro)</td>
</tr>
<tr>
<td>• Admelog Solostar® (lispro)</td>
<td></td>
</tr>
<tr>
<td><strong>Regular-Acting/Short-acting Insulin</strong></td>
<td></td>
</tr>
<tr>
<td>• Novolin R</td>
<td>• Humulin® R</td>
</tr>
<tr>
<td><strong>Intermediate-Acting NPH Insulin</strong></td>
<td></td>
</tr>
<tr>
<td>• Novolin N</td>
<td>• Humulin® N</td>
</tr>
<tr>
<td><strong>Mix of Intermediate-Acting NPH and Regular (Short-Acting) Insulin</strong></td>
<td></td>
</tr>
<tr>
<td>• Novolin Mix 70/30</td>
<td>• Humulin® Mix 70/30</td>
</tr>
<tr>
<td><strong>Mix of Intermediate Insulin Lispro Protamine + Rapid-acting Insulin Lispro and Mix of Intermediate-acting Insulin Aspart Protamine + Rapid-acting Insulin Aspart</strong></td>
<td></td>
</tr>
<tr>
<td>• Novolog® Mix 70/30</td>
<td>• Humalog® Mix 75/25</td>
</tr>
<tr>
<td>• Humalog® Mix 50/50</td>
<td></td>
</tr>
</tbody>
</table>

Note: Documentation in the form of clinical chart notes is required for a review of all below-mentioned agents.
Insulin and Injectable Noninsulin Combination Products

<table>
<thead>
<tr>
<th>Preferred Injectable</th>
<th>Non-preferred Injectable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin and Glucagon-like Peptide-1 (GLP-1) Receptor Agonists</strong></td>
<td></td>
</tr>
<tr>
<td>• Xultophy® (insulin degludec+liraglutide)</td>
<td>• Soliqua® (insulin glargine+lixisenatide)</td>
</tr>
</tbody>
</table>

**Coverage Criteria:** For the above drugs to be considered *medically necessary*, the patient needs to have a diagnosis of type II diabetes, and have an adequate trial of:
- Metformin(unless contraindicated)

**Coverage Criteria:** For the above drug to be considered *medically necessary*, the patient needs to have a diagnosis of type II diabetes, and have an adequate trial of:
- Metformin(unless contraindicated)

Injectable Noninsulin Products

<table>
<thead>
<tr>
<th>Preferred Injectable</th>
<th>Non-preferred Injectable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucagon-like Peptide-1 (GLP-1) Receptor Agonists</strong></td>
<td></td>
</tr>
<tr>
<td>• Bydureon® and Byetta® (exenatide)</td>
<td>• Tanzeum® (albiglutide)</td>
</tr>
<tr>
<td>• Victoza® (liraglutide)</td>
<td>• Trulicity® (dulaglutide)</td>
</tr>
<tr>
<td>• Ozempic® (semaglutide)</td>
<td>• Adlyxin® (lixisenatide)</td>
</tr>
</tbody>
</table>

**Coverage Criteria:** For the above drugs to be considered *medically necessary*, patient needs to have a diagnosis of type II diabetes, and have an adequate trial of:
- Metformin(unless contraindicated)

**Coverage Criteria:** For the above drugs to be considered *medically necessary*, the patient needs to have a diagnosis of type II diabetes, and have an adequate trial of:
- Metformin(unless contraindicated)
  AND
- Victoza® (liraglutide)
  AND
- Bydureon® or Byetta® (exenatide)

**Amylin Mimetics**

<table>
<thead>
<tr>
<th>Preferred Injectable</th>
<th>Non-preferred Injectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Symlin® (pramlintide)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Coverage Criteria:** For the above drug to be considered *medically necessary*, patient needs:
- To have a diagnosis of type I or type II diabetes,
  AND
### Preferred Injectable

- Be concurrently receiving insulin therapy.

### Non-preferred Injectable

All other uses of pramlintide are considered investigational.

### Oral Products

#### Preferred Oral Drug

<table>
<thead>
<tr>
<th>Preferred Oral Drug</th>
<th>Non-preferred Oral Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Januvia® (sitagliptin)</td>
<td>Nesina (alogliptin)</td>
</tr>
<tr>
<td>Onglyza® (saxagliptin)</td>
<td>alogliptin</td>
</tr>
<tr>
<td></td>
<td>Oseni (alogliptin/pioglitazone)</td>
</tr>
<tr>
<td></td>
<td>alogliptin/pioglitazone</td>
</tr>
<tr>
<td></td>
<td>Tradjenta® (linagliptin)</td>
</tr>
</tbody>
</table>

**Coverage Criteria:** For the above drugs to be considered *medically necessary*, patient needs to have an adequate trial of:
- Metformin (unless contraindicated)

### Non-preferred Oral Drug

- Nesina (alogliptin)
- alogliptin
- Oseni (alogliptin/pioglitazone)
- alogliptin/pioglitazone
- Tradjenta® (linagliptin)

**Coverage Criteria:** For the above drugs to be considered *medically necessary*, patient needs to have an adequate trial of:
- Metformin (unless contraindicated)
  
  **AND**
  - Onglyza® OR Kombiglyze®
  
  **AND**
  - Januvia® OR Janumet®

#### Biguanide and DPP-4 Combination

<table>
<thead>
<tr>
<th>Preferred Oral Drug</th>
<th>Non-preferred Oral Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janumet® (sitagliptin + metformin)</td>
<td>Kazano (alogliptin + metformin)</td>
</tr>
<tr>
<td>Janumet® XR (sitagliptin + metformin extended release)</td>
<td>Jentadueto (linagliptin + metformin)</td>
</tr>
<tr>
<td>Kombiglyze® (saxagliptin + metformin)</td>
<td>Jentadueto XR (linagliptin + metformin extended release)</td>
</tr>
<tr>
<td>Kombiglyze® XR (saxagliptin + metformin extended release)</td>
<td>alogliptin/metformin</td>
</tr>
</tbody>
</table>

**Coverage Criteria:** No Prior Authorization Required.

**Coverage Criteria:** For the above drugs to be considered *medically necessary*, patient needs to have an adequate trial of:
- Onglyza® OR Kombiglyze®
<table>
<thead>
<tr>
<th>Preferred Oral Drug</th>
<th>Non-preferred Oral Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AND</strong></td>
<td></td>
</tr>
<tr>
<td>• Januvia® OR Janumet®</td>
<td></td>
</tr>
</tbody>
</table>

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

- Invokana® (canagliflozin)
- Jardiance® (empagliflozin)
- Farxiga® (dapagliflozin)
- Steglatro® (ertugliflozin)

**Coverage Criteria:** For the above drugs to be considered *medically necessary*, patient needs to have an adequate trial of:
- Metformin (unless contraindicated)

<table>
<thead>
<tr>
<th><strong>Coding</strong></th>
<th>N/A</th>
</tr>
</thead>
</table>

### Dipeptidyl Peptidase IV Inhibitor (DPP-4) and Sodium-Glucose Cotransporter 2 Inhibitor

- Steglujan™ (ertugliflozin and sitagliptin)
- Qtern® (dapagliflozin and saxagliptin)
- Glyxambi® (empagliflozin and linagliptin)

**Coverage Criteria:** For the above drugs to be considered *medically necessary*, patient needs to have an adequate trial of:
- Metformin (unless contraindicated)

**AND**

- Onglyza® OR Kombiglyze®

**Coding**

N/A
Benefit Application

This benefit is managed through Pharmacy.

Evidence Review

Insulin Agents

Types and Characteristics of Commonly Used Insulin Products

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Brand Name</th>
<th>Onset of Action</th>
<th>Peak Effect</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting Insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro</td>
<td>Humalog</td>
<td>&lt; 15 minutes</td>
<td>30 to 90 minutes</td>
<td>3 to 5 hours</td>
</tr>
<tr>
<td>Aspart</td>
<td>Novolog</td>
<td>&lt; 15 minutes</td>
<td>30 to 90 minutes</td>
<td>3 to 5 hours</td>
</tr>
<tr>
<td>Glulisine</td>
<td>Apidra</td>
<td>&lt; 15 minutes</td>
<td>30 to 90 minutes</td>
<td>3 to 5 hours</td>
</tr>
<tr>
<td>Short-acting Insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>Humulin R</td>
<td>0.5 to 1 hour</td>
<td>2 to 4 hours</td>
<td>4 to 8 hours</td>
</tr>
<tr>
<td></td>
<td>Novolin R</td>
<td>0.5 to 1 hour</td>
<td>2 to 4 hours</td>
<td>4 to 8 hours</td>
</tr>
<tr>
<td>Intermediate-acting Insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>Humulin N</td>
<td>1 to 2 hours</td>
<td>4 to 10 hours</td>
<td>10 to 18 hours</td>
</tr>
<tr>
<td></td>
<td>NovolinN</td>
<td>1 to 2 hours</td>
<td>4 to 10 hours</td>
<td>10 to 18 hours</td>
</tr>
<tr>
<td>Long-acting Insulins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine</td>
<td>Lantus</td>
<td>1 to 2 hours</td>
<td>No peak</td>
<td>20 to 24 hours</td>
</tr>
<tr>
<td>Detemir</td>
<td>Levemir</td>
<td>1 to 2 hours</td>
<td>3 to 9 hours</td>
<td>6 to 24 hours *</td>
</tr>
<tr>
<td>Combination Insulins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mix of intermediate insulin lispro protamine and rapid-acting insulin lispro</td>
<td>Humulin 70/30 and Novolin 70/30</td>
<td>0.5 to 1 hour</td>
<td>2 to 10 hours</td>
<td>10 to 18 hours</td>
</tr>
<tr>
<td>Insulin</td>
<td>Brand Name</td>
<td>Onset of Action</td>
<td>Peak Effect</td>
<td>Duration of Action</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>------------------------------------------------</td>
<td>----------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Mix of intermediate-acting insulin aspart</td>
<td>Humalog 75/25 and Novolog 70/30</td>
<td>&lt;15 minutes</td>
<td>1 to 2 hours</td>
<td>10 to 19 hours</td>
</tr>
</tbody>
</table>

*Duration of action for detemir is dose-dependent.

**Insulin Interchangeability**

As shown in the table above, two brands of insulin products have similar pharmacokinetic profiles. Currently, there is no scientific literature or evidence to suggest that one insulin brand is superior over the other. Switching between insulin brands should be done in consultation with a physician and requires medical supervision (close monitoring of blood glucose) during the initial phase.

**Injectable Noninsulin Agents**

**GLucagon-Like Peptide-1 (GLP-1) Receptor Agonists**

GLP-1 agonists are indicated as an adjunct to diet and exercise for glycemic control in adults with T2DM. All are available as SQ injections with exenatide (Byetta) administered twice daily, liraglutide (Victoza) once daily and all others administered once weekly. GLP-1 agonists act to enhance glucose-dependent insulin secretion, suppress glucagon secretion, and slow gastric emptying. GLP-1 agonists also decrease body weight and systolic blood pressure. GLP-1 agonists are currently recommended as dual or triple therapy with metformin by the ADA.

Most significantly, a large, well-designed head-to-head trial with liraglutide and exenatide ER found liraglutide significantly more effective in decreasing HbA1c. Additional data indicates exenatide twice daily (Byetta) and albiglutide (Tanzeum) are associated with less reduction in HbA1c than other GLP-1 agonists. Efficacy and safety data is now available to 5 years with exenatide ER. Common AE include nausea, vomiting, and diarrhea as well as injection site reactions with exenatide ER and albiglutide. The class carries a black box warning for use in patients with a history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. While cardiovascular outcomes studies are on-going, available data with short-term trials does not indicate increased risk. Cost-effectiveness analyses have found GLP-1 agonists cost effective in comparison to other brand agents for T2DM and liraglutide cost.
effective in comparison to exenatide ER. Cost effectiveness comparisons with generic agents are not available.

A newer agent in this class is called lixisenatide is a GLP-1 receptor agonist that has been shown to have significant effect on reducing HbA1c%, 2-h PPG, and modest weight loss benefit from 9 DB placebo-controlled RCTs and 5 meta-analysis. From the perspective of safety, it is considered generally well tolerated. The most common side effect is GI disorders (N/V/D) and the occurrence is more frequent than insulin and OADs. Of note, it has significantly less hypoglycemia than insulin. Based on the results from four phase 3 or phase 4 active-controlled RCTs, compared to other GLP-1 receptor agonists in the same drug class, lixisenatide does not appear to be relatively more efficacious or safer. Currently, there is no cost-effectiveness analysis conducted in a US setting.

**Amylin Mimetics (pramlintide)**

Pramlintide is an amylin analog designed for patients with type 1 or type 2 diabetes who use mealtime insulin and have failed to achieve desired glycemic control despite optimal insulin therapy. Amylin is a 37-amino acid peptide that is stored in pancreatic beta cells and is co-secreted with insulin and has a similar plasma kinetic profile. It affects glucose control through several mechanisms, including slowed gastric emptying, regulation of postprandial glucagon, and reduction of food intake. Glucose influx is better regulated, allowing exogenous insulin therapy to more easily match physiologic needs. Pramlintide is dosed before major meals and titrated as tolerated. Pramlintide has an anorexic effect and carries a black box warning for risk of severe hypoglycemia. This risk may be reduced by careful patient selection and instruction, and by insulin dose reduction.

Pramlintide has been studied in randomized controlled trials in both type 1 and type 2 diabetes. In type 1 diabetes, 30 to 60 mcg of pramlintide administered subcutaneously with meals resulted in sustained, albeit modest (<1 percentage point) reductions in glycated HbA1c over the 52-week trial. More than twice as many patients (25 versus 11.3 percent) achieved an A1c of less than 7% in the treatment group vs. placebo, with no increase in insulin dose or incidence of severe hypoglycemia. Modest reductions in body weight (mean of 0.5 kg) were seen in the treatment group, compared with weight gain in patients receiving insulin only.

In a 24-week trial of patients with inadequately controlled type 2 diabetes, the addition of preprandial pramlintide to basal insulin with or without oral agents had similar glycemic efficacy as the addition of premeal rapid acting insulin analogs (A1c reduction of approximately 1%). Patients randomly assigned to pramlintide maintained their weight, whereas those assigned to
rapid acting insulin gained weight (mean 4.7 kg). Pramlintide was associated with fewer hypoglycemic events compared with prandial insulin. In addition to modest reductions in A1c and weight, pramlintide has been associated with reductions in postprandial glucose excursions and in surrogate markers of cardiovascular risk and oxidative stress. The clinical implications of these findings are unknown.

A recent meta-analysis included ten RCTs that evaluated the use to pramlintide as adjunct treatment with insulin in patients with type I diabetes. Pramlintide was found to reduce HbA1c by a mean of 0.41%, reduce TDD of insulin, and reduce body weight. With regard to safety, pramlintide had significantly more reported incidence of hypoglycemia, nausea, vomiting, and anorexia.

**Insulin and Injectable Noninsulin Combination Products**

**Insulin and Glucagon-Like Peptide-1 Receptor Agonists**

**Xultophy® (insulin degludec and liraglutide)**

Xultophy® (insulin degludec/liraglutide) combines two complementary mechanisms of action into a once daily self-injection. Six trials have been published, all of which have shown equal or improved efficacy to active comparators in patients above HbA1c goal. IDegLira has received a narrow indication for patients inadequately controlled on liraglutide (less than 1.8 mg daily) or basal insulin (less than 50 units daily). This patient population can better reach goal using the combination product without negatively affecting adherence rates. The combination product offers benefits in terms of efficacy, safety and cost compared to alternative strategies such as basal-bolus dosing, using the separate products in multiple doses, and uptitrating a basal insulin. While the trials largely excluded those with a BMI above 40 kg/m², the consistent positive results in disparate treatment groups suggests strong Phase III evidence for insulin degludec/liraglutide.

**Soliqua® (insulin glargine and lixisenatide)**

Soliqua® (insulin glargine and lixisenatide) like Xultophy® combines two complementary mechanisms of action into a once daily self-injection. iGlarLixi was studied in two clinical trials: 1. LixiLan-L: in patients uncontrolled on basal insulin, with or without previous exposure to metformin, with insulin glargine alone as comparator; and 2. LixiLan-O: in patients uncontrolled on 2 or more oral anti-diabetic drugs, with insulin glargine alone, and lixisenatide alone as
comparators. In study 1, Soliqua showed superiority to insulin glargine alone in terms of hemoglobin A1C reduction, with no increase in hypoglycemia or weight. Fasting plasma glucose (FPG) reduction with Soliqua was comparable to that of insulin glargine alone. Post prandial glucose (PPG) reduction with Soliqua was greater than that of insulin glargine alone. In study 2, Soliqua showed superiority to insulin glargine alone and lixisenatide alone with regard to hemoglobin A1C reduction with no increases in hypoglycemia (as compared to glargine). FPG reduction with Soliqua was comparable to that of insulin alone and greater than that of lixisenatide alone. Reduction in 2-h PPG with Soliqua was greater than that of insulin glargine alone and lixisenatide alone. Study also showed that Soliqua resulted in significantly greater weight loss compared with insulin glargine alone, but demonstrated less weight loss compared with lixisenatide alone. For full description of the clinical trials, please refer to the package insert.

Oral Agents

*Dipeptidyl Peptidase IV Inhibitors (DPP-4 inhibitors)*

Comparisons with DPP-4 inhibitors and placebo have found the class decreases HbA1c approximately -0.56% to -0.8%. Trials assessing these agents as add-on therapy have found similar HbA1c decreases. No difference in efficacy has been found between DPP-4 inhibitors and other add-on therapy for diabetes including sulfonylureas and TZDs; however, DPP-4 inhibitors are less effective than metformin. Head-to head-trials with saxagliptin and sitagliptin have found no difference between agents; however, no comparative data is available to date with newer agents (linagliptin and alogliptin). Long-term trial data is available for all agents. The ADA guidelines recommend the class as an option along with sulfonylureas, TZDs, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin for add-on therapy with metformin.

The agents are generally well tolerated with little hypoglycemia unless given with insulin or sulfonylureas. The DPP-4 inhibitors appear weight neutral. Reports of pancreatitis have led to an FDA warning; however, trial data does not consistently support this and further study is needed. Several recent randomized controlled trials have indicated that DPP-4 inhibitors did not increase the risk of adverse cardiovascular outcomes. However, the SAVOR-TIMI 53 study found an increase rate of heart failure hospitalization. Further study is ongoing.
**Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors**

SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) are oral agents indicated to improve glycemic control in adults with T2DM as an adjunct to diet and exercise. SGLT2 inhibitors decrease glucose reabsorption in the proximal nephron and increase urinary glucose excretion. The mechanism of action of SGLT2 inhibitors is not dependent on insulin.

Large, well-designed, long-term trials and meta-analyses have shown SGLT2 inhibitors decrease HbA1c in comparison to placebo (-0.7 to -1.1%). SGLT2 inhibitors have been extensively studied in dual and triple therapy regimens, typically as add-on agents to metformin, SUs, DPP4s, and TZDs. Since the last review, new data has become available supporting the use of dapagliflozin in triple therapy regimens. Additionally, longer duration trials to 104 weeks have been published indicating continued effectiveness. Trials comparing SGLT2 inhibitors to other classes of agents have found no difference in effectiveness in comparison with metformin. However, available data conflicts about the efficacy of SGLT2 inhibitors in comparison to other classes (SU, TZDs, and DPP4s) with some data indicating superiority and others non-inferiority. In addition, trials with SGLT2 inhibitors are associated with decreased body weight and BP. Adverse events with SGLT2 inhibitors include genital mycotic infections, UTIs, and, less commonly, volume depletion and renal-related effects. The FDA has recently issued two safety warnings for the class, concerning an increased risk of DKA across the class as well as increased incidence of upper extremity, low-trauma fractures with canagliflozin. Further research is needed to fully define these effects as well as the CV effects of the class. Cost effectiveness studies in the US setting comparing SGLT2 inhibitors to other classes of agents for T2DM are not available and drug costs remain high.

**EMPA-REG: CV Outcomes Trial Summary**

The goal of the trial was to examine the long-term effects of empagliflozin versus placebo, in addition to standard of care (such as, lifestyle, risk reduction with antihypertensive treatment, statins, aspirin, and metformin), on cardiovascular (CV) morbidity and mortality in patients with T2DM and high risk of CV events. This was a randomized (1:1:1 to empagliflozin 10mg, 25mg, and placebo), double-blind, placebo-controlled, international CV outcomes trial. Total number of participants was 7,028. This was an industry-sponsored trial.

Key findings included:
The primary outcome, CV death, nonfatal MI, or stroke for empagliflozin vs. placebo: 10.5% vs. 12.1%, hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.74 to 0.99, p<0.001 for non-inferiority; p=0.04 for superiority.

- For CV death: 3.7% vs. 5.9%, p<0.001
- All MI: 4.8% vs. 5.4%, p=0.23
- All stroke: 3.5% vs. 3.0, p=0.26

Reduced risk of composite cardiovascular events (NNT=63/3 years) and all cause death (NNT=38/3 years). The 10mg daily dose provided almost the same benefit as the 25mg dose. Benefit realized despite A1C not reaching target (A1C=7.8%). Mean change was about ≤0.6%.

- Increased risk of genital infections in both males (NNH=29/3 years) and females (NNH=14/3 years). Urosepsis, although rare, was also increased with empagliflozin (~0.4% vs. 0.1%). Serious Adverse Events (SAE) were less with empagliflozin than placebo (NNT=24). A

- Empagliflozin also lowered systolic blood pressure (SBP) by 3 to 4 mm Hg, and diastolic blood pressure (DBP) by 1 to 2 mm Hg.

- Weight was also noted to decrease by about 1 to 2 kg, which was more than in the placebo group.

- Average A1C achieved in the empagliflozin group was 7.8%.

For details on secondary outcomes (all-cause mortality, congestive heart failure (CHF) hospitalization, CV death, all cause hospitalization, coronary revascularization, A1C at 12 weeks for 10mg dose, A1C at 12 weeks for 25mg dose, confirmed hypoglycemic event, and urinary tract infection rates), and for renal outcomes (incident or worsening nephropathy, doubling of serum creatinine, progression to macroalbuminuria, and initiation of renal replacement therapy), please refer to the American College of Cardiology article, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients- EMPA-REG Outcome. Available at: https://www.acc.org/latest-in-cardiology/clinical-trials/2015/09/17/10/11/empa-reg-outcome.

The results of this trial demonstrate that empagliflozin is superior to placebo in improving glycemic control, and reducing CV events in patients with type 2 diabetes and established cardiovascular disease. The fact that CV safety is thought to be established in this trial is an important factor in light of the prior serious safety concerns involving rosiglitazone. However,
the mechanism for this benefit is still unknown (and may be due to non-glucose related mechanism).

**Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes Results (LEADER) Trial**

The goal of this trial was to examine the long-term effects of liraglutide on cardiovascular outcomes and other clinically important events. This was a multicenter, double-blind, randomized (1:1), placebo-controlled trial at 410 sites in 32 countries, and included a total of 9,340 participants. Trial follow-up was about 3.8 years (+/- 3 months). Selected patients had established cardiovascular disease, chronic kidney disease of stage 3 or greater, or both (in addition to having diabetes). This trial was supported by Novo Nordisk and by grants from the National Institutes of Health.

Key findings for the primary outcomes included:

- The primary composite outcome (the first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke) occurred fewer in patients in the liraglutide group, 608 of 4668 (13.0%) than in the placebo group, 694 of 4672 (14.9%); HR 0.87 with 95% CI; 0.78 to 0.97, p<0.001 for non-inferiority; p=0.01 for superiority.
- Death from CV causes occurred in fewer patients in liraglutide group, 219 patients (4.7%) than in the placebo group, 278 (6.0%); HR 0.78; with 95% CI, 0.66 to 0.93; p=0.007.
- Rate of death from any cause was lower in liraglutide group, 981 patients (8.2%) than in the placebo group, 447 (9.6%); HR 0.85; 95 CI, 0.74 to 0.97; p=0.02.
- Nonfatal MIs were fewer in the liraglutide group than in the placebo group, but not significant
- Nonfatal stroke events were fewer in the liraglutide group than in the placebo group, but not significant
- Glycemic control analysis showed a mean difference in A1C between the liraglutide group and placebo of -0.40 percentage points (95% CI, -0.45 to -0.34)
- Weight loss was 2.3 kg (95%CI, 2.5 to 2.0) higher in the liraglutide group
Systolic blood pressure was 1.2 mm Hg (95% CI, 1.9 to 0.5) lower in the liraglutide group, however, the diastolic blood pressure was 0.6 mm Hg (95% CI, 0.2 to 1.0) higher in liraglutide group (and so was the heart rate at 3.0 beats per minute 95% CI, 2.5 to 3.4).

For details on the secondary outcomes (transient ischemic attack, coronary revascularization, hospitalization for unstable angina pectoris, hospitalization for heart failure, microvascular events, such as retinopathy and nephropathy, and safety and adverse events information, please refer to The New England Journal of Medicine article available at: http://www.nejm.org/doi/full/10.1056/NEJMoa1603827.

The results of this trial suggest that liraglutide has lower rates of CV events and death from any cause when compared to placebo, however, this study has a few limitations, such as relatively short period of follow-up, and the fact that participants in the study already had high risk for CV events, and had a mean baseline A1C of 8.7%, which makes it challenging to apply these findings to patients with milder forms of the disease. It is important to recognize that the findings of CV benefits in this trial are different from the ones described in EMPA-REG trial, particularly the time to benefit was seen earlier in EMPA-REG than in the current study.

Practice Guidelines and Position Statements

**American Association of Clinical Endocrinologists and American College of Endocrinologists (AACE/ACE) Comprehensive Diabetes Management Algorithm (2019)**

<table>
<thead>
<tr>
<th>Goals for Glycemic Control of Type 1 and Type 2 Diabetes Mellitus</th>
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<tbody>
<tr>
<td><strong>A1C</strong></td>
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<tr>
<td><strong>Pre-Prandial Plasma Glucose</strong></td>
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<tr>
<td><strong>Peak Post-Prandial Glucose</strong></td>
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*Considerations should include residual life expectancy; duration of diabetes; presence or absence of microvascular (renal and retinal) and macrovascular (CV) complications; CVD risk factors; comorbid conditions; risk for severe hypoglycemia (especially in older adults); and psychological, social, and economic status (affordability of treatment choice can have impact on compliance). Adapted from AACE Diabetes Resource Center.
Type 1 and Type 2 Diabetes Mellitus Management

Current and complete list of recommendations from AACE/ACE can be found at:

- For Type 1: http://outpatient.aace.com/type1-diabetes/treatment
- For Type 2: https://www.aace.com/publications/algorithm

U.S. Preventive Services Task Force Recommendations

Published recommendations include:

- AbnormLelandhenry8

- Al Blood Glucose and Type 2 Diabetes Mellitus Screening for adults aged 40 to 70 years who are overweight or obese.

- Gestational Diabetes Mellitus Screening for asymptomatic pregnant women after 24 weeks of gestation.

References


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