Therapeutic Class Overview
Incretin Mimetics & Amylinomimetics

INTRODUCTION

- Diabetes mellitus affects more than 30 million people in the United States (U.S.) (*Centers for Disease Control and Prevention [CDC] 2020*).
- Diabetes mellitus is defined as a group of metabolic disorders characterized by hyperglycemia that result from defects in the secretion and action of insulin (*American Diabetes Association [ADA] Diabetes Basics 2021*).
- The classification of diabetes includes 4 clinical classes: 1) type 1 diabetes mellitus (T1DM), which results from beta-cell (β-cell) destruction, usually leading to absolute insulin deficiency, 2) type 2 diabetes mellitus (T2DM) which results from a progressive insulin secretory defect on the background of insulin resistance, 3) other specific types of diabetes due to other causes, eg, genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of human immunodeficiency virus/acquired immunodeficiency syndrome or after organ transplantation), and 4) gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy that is not clearly overt diabetes) (*ADA 2021*).
- Insulin is the standard treatment for T1DM. Pharmacologic options for T2DM include sulfonylureas (SFUs), biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin.
- The GLP-1 receptor agonists (albiglutide, dulaglutide, exenatide, exenatide extended-release [ER], liraglutide, lixisenatide, and semaglutide) were developed to mimic the effects of endogenous GLP-1 and are Food and Drug Administration (FDA)-approved as adjunctive therapy to diet and exercise to improve glycemic control in adults with T2DM. All GLP-1 receptor agonists are administered via subcutaneous injection, with the exception of Rybelsus (semaglutide) tablets, which are administered orally. As of 2018, albiglutide was discontinued by the manufacturer due to limited prescribing of the drug and not because of safety concerns (*DRUGS@FDA 2021*). Bydureon pen is being phased out and replaced with Bydureon BCise, an autoinjector device that allows for more convenient administration (*AstraZeneca 2021).*
- Pramlintide is the only amylin analog, or amylinomimetic, in the class, and is FDA-approved as an adjunctive treatment with insulin in patients with T1DM or T2DM who have failed to achieve desired glucose control despite optimal insulin therapy. It is a synthetic analog of human amylin, a naturally occurring neuroendocrine hormone synthesized by pancreatic β-cells that contributes to glucose control during the post-prandial period.
- This review will focus on the GLP-1 receptor agonists and pramlintide and their respective FDA-approved indications for treatment of diabetes. Liraglutide (Saxenda) and semaglutide (Wegovy) are also indicated as adjunctive therapy for chronic weight management; however, the use of liraglutide and semaglutide for this indication will not be included in this review.
- Medispan class: Endocrine and Metabolic Drugs; Incretin Mimetic Agents (GLP-1 Receptor Agonists) and Amylin Analogs

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Adlyxin (lixisenatide)	-
Bydureon BCise (exenatide ER)*	-
Byetta (exenatide)	
Ozempic (semaglutide)	-
Rybelsus (semaglutide)	-
Symlin (pramlintide)	-
Trulicity (dulaglutide)	-
Victoza (liraglutide)	-

*Bydureon pen has been discontinued by the manufacturer and has been replaced by the BCise autoinjector device.

(*DRUGS@FDA 2021*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. FDA Approved Indications

Indication	Adlyxin (lixisenatide)	Byetta (exenatide)	Bydureon BCise (exenatide ER)	Ozempic (semaglutide)	Rybelsus (semaglutide)	Symlin (pramlintide)	Trulicity (dulaglutide)	Victoza (liraglutide)
Indications								
T1DM, as an adjunctive treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy						✔		
T2DM, as an adjunctive treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy						✔		
Adjunct to diet and exercise to improve glycemic control in adults with T2DM	✔	✔	✔	✔	✔		✔	✔
Adjunct to diet and exercise to improve glycemic control in patients 10 years and older with T2DM								✔
Reduce the risk of major adverse cardiovascular (CV) events (MACE; CV death, non-fatal myocardial infarction [MI], or non-fatal stroke) in adults with T2DM and established CV disease (CVD)				✔				✔
Reduce the risk of MACE (CV death, non-fatal MI, or non-fatal stroke) in adults with T2DM who have established CVD or multiple CV risk factors							✔	
Limitations of Use								
Not recommended as first-line therapy for patients inadequately controlled on diet and exercise because of the uncertain relevance of the rodent C-cell tumor findings to humans. Prescribe only to patients for whom the potential benefits are considered to outweigh the potential risk.			✔		✔		✔	
Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in these patients.	✔	✔	✔	✔	✔		✔	

Indication	Adlyxin (lixisenatide)	Byetta (exenatide)	Bydureon BCise (exenatide ER)	Ozempic (semaglutide)	Rybelsus (semaglutide)	Symlin (pramlintide)	Trulicity (dulaglutide)	Victoza (liraglutide)
Not indicated in treatment of patients with T1DM or for treatment of patients with diabetic ketoacidosis. Not a substitute for insulin in these patients.	✔							
Not indicated in treatment of patients with T1DM.		✔	✔	✔	✔		✔	✔
Has not been studied in patients with severe gastrointestinal (GI) disease, including severe gastroparesis. Not recommended in patients with pre-existing severe GI disease.							✔	
Has not been studied in patients with gastroparesis. Not recommended in patients with gastroparesis.	✔							
Not studied in combination with prandial/short-acting insulin.	✔							
Should not be used with other products containing the active ingredient.		✔	✔					✔

(Prescribing information: *Adlyxin 2019*, *Bydureon BCise 2020, Byetta 2021, Ozempic 2021, Rybelsus 2021, Symlin 2019, Trulicity 2021, Victoza 2020*)

NOTE: Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Dulaglutide

- The approval of dulaglutide was based on 6 pivotal trials enrolling over 3,000 patients as a part of the AWARD phase 3 program. Trials evaluated the use of dulaglutide 0.75 mg and 1.5 mg strengths. The primary outcome in each trial was the change in hemoglobin A1c (HbA1c) from baseline to 26 through 52 weeks.
  - AWARD-1 demonstrated that once weekly dulaglutide resulted in significantly larger improvements in HbA1c at 26 weeks compared to placebo and exenatide in patients taking maximally tolerated doses of metformin and pioglitazone (*Wysham et al 2014*).
  - AWARD-2 was an open-label (OL) study that demonstrated superiority of dulaglutide 1.5 mg once weekly and noninferiority of dulaglutide 0.75 mg once weekly compared to daily insulin glargine in terms of HbA1c reduction from baseline to week 52 (*Giorgino et al 2015*).
  - AWARD-3 was a double-blind (DB) study that demonstrated superiority of dulaglutide 0.75 mg and 1.5 mg once weekly to metformin in patients inadequately treated with diet and exercise with or without submaximal dosing of at least 1 oral antidiabetic drug (OAD). At 26 weeks, changes from baseline HbA1c were 0.78%, 0.71%, and 0.56% for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and metformin, respectively (*Umpierrez et al 2014*).
  - AWARD-4 was an OL, 52-week, noninferiority study which found that dulaglutide once-weekly (both 1.5 mg and 0.75 mg strengths) in combination with insulin lispro resulted in significantly greater improvement in glycemic control than insulin glargine in combination with insulin lispro ($p = 0.005$ and $p = 0.015$ for dulaglutide 1.5 mg and 0.75 mg, respectively) (*Blonde et al 2015*).

- AWARD-5 was a DB trial that compared placebo, once-weekly dulaglutide (0.75 mg and 1.5 mg), and sitagliptin 100 mg once daily in uncontrolled metformin-treated patients. At weeks 52 and 104, both dulaglutide strengths were superior to sitagliptin in terms of HbA1c reduction from baseline ($p < 0.001$ for all comparisons) (*Nauck et al 2014, Weinstock et al 2015*).
- AWARD-6 was an OL trial which demonstrated that, in patients taking concurrent metformin, dulaglutide 1.5 mg once weekly was noninferior to liraglutide once daily in HbA1c reduction from baseline to week 26 (*Dungan et al 2014*).
- The AWARD-7 trial was an OL, non-inferiority study that enrolled patients with T2DM and moderate-to-severe chronic kidney disease (CKD) who were currently on insulin therapy. Patients were randomized to once-weekly dulaglutide (0.75 mg or 1.5 mg) or daily insulin glargine, all in combination with insulin lispro. At week 26, the change in HbA1c with dulaglutide 1.5 mg and 0.75 mg was non-inferior to insulin glargine ($p \leq 0.0001$ for both comparisons) (*Tuttle et al 2018*).

Exenatide

- The efficacy of exenatide as add-on therapy to metformin alone, an SFU alone, or metformin in combination with an SFU was evaluated in 3 placebo-controlled (PC), 30-week, randomized controlled trials (RCTs). In all trials, there were significant decreases in HbA1c with exenatide compared to placebo ($p < 0.001$, $p < 0.002$, and $p < 0.0001$, respectively) (*Buse et al 2004, DeFronzo et al 2005, Kendall et al 2005*). Extensions of these 30-week trials demonstrated that the benefits of exenatide are sustained (*Blonde et al 2006, Buse et al 2007, Klonoff et al 2008, Ratner et al 2006, Riddle et al 2006*).
- A trial evaluating exenatide as add-on therapy in patients currently taking a TZD found that at week 16, exenatide significantly decreased HbA1c ($p < 0.001$), fasting plasma glucose (FPG) ($p < 0.001$), and body weight ($p < 0.001$) compared to placebo (*Zinman et al 2007*).
- When exenatide was compared to glyburide as add-on therapy to metformin, exenatide significantly decreased body weight and body mass index (BMI) ($p < 0.001$ for both), whereas the SFU caused significant increases in both ($p < 0.05$ for both). Both treatments significantly decreased HbA1c, FPG, and postprandial plasma glucose (PPG) (exenatide; $p < 0.001$ for all; glyburide; $p < 0.001$ for all). Only exenatide significantly improved insulin resistance ($p < 0.01$) and β-cell function ($p < 0.05$) (*Derosa et al 2010*).
- The EUREXA study compared the efficacy of exenatide and glimepiride as add-on therapy to metformin. Patients receiving exenatide exhibited greater reductions in HbA1c from baseline (-0.36%), compared to those receiving glimepiride (-0.21%; $p = 0.002$) (*Gallwitz et al 2012*).
- Several trials have compared exenatide to insulin therapy as add-on therapy to metformin and/or an SFU (*Bunck et al 2009, Bunck et al 2010, Davies et al 2009, Heine et al 2005, Nauck et al 2007, Secnik et al 2006*). Similar improvements in HbA1c between treatments were observed in 3 of the trials while mixed results were observed for decreases in FPG. Specifically, in 2 trials, insulin therapy was “superior” in decreasing FPG (p value not reported and $p < 0.0001$), while in another trial there was no difference between the 2 treatments ($p = 0.689$). Insulin therapy was associated with an increase in body weight compared to a decrease with exenatide (*Bunck et al 2009, Heine et al 2005, Nauck et al 2007*). Patient-reported health outcome measures demonstrated no differences between exenatide or insulin therapy; both achieved significant improvements from baseline. However, neither treatment improved Diabetes Treatment Flexibility Scores ($p = 0.93$ for both) (*Secnik et al 2006*).
- Exenatide once weekly was also compared to daily insulin glargine in diabetic patients inadequately controlled with OADs. Following 26 weeks of therapy, exenatide was found to be statistically noninferior to insulin glargine for the change in HbA1c from baseline to endpoint (*Inagaki et al 2012*).

Exenatide ER

- Approval of exenatide ER in the management of T2DM was based on the clinical evidence for safety and efficacy derived from the DURATION trials (1 through 5). Exenatide ER was added to existing antidiabetic regimens in 4 of the 5 trials (1, 2, 3, and 5). In contrast, DURATION-4 compared exenatide ER, metformin, pioglitazone, and sitagliptin all as monotherapy (*Bergenstal et al 2010, Blevins et al 2011, Diamant et al 2010, Drucker et al 2008, Russell-Jones et al 2012*).
  - Overall, exenatide ER as add-on therapy to existing antidiabetic regimens significantly decreased HbA1c compared to exenatide ($p < 0.005$), sitagliptin ($p < 0.0001$), pioglitazone ($p = 0.0165$), and insulin therapy ($p = 0.017$), with no increased risk of hypoglycemia. In terms of decreases in body weight, exenatide ER was superior compared to sitagliptin ($p = 0.0002$) and pioglitazone ($p < 0.0001$), and similar compared to exenatide ($p = 0.89$) (*Bergenstal et al 2010, Blevins et al 2011, Drucker et al 2008*).

- As expected, gastrointestinal (GI)-related adverse events (AEs) were reported more commonly with the incretin-based therapies. When compared to exenatide, exenatide ER was associated with lower incidences of nausea (14.0% vs 35.0%) and vomiting (4.7% vs 8.9%), and higher incidences of diarrhea (9.3% vs 4.1%) and injection site-related AEs (13% vs 10%) (*Blevins et al 2011*).
- In the DURATION-4 trial, the decrease in HbA1c achieved with exenatide ER monotherapy was superior compared to sitagliptin ($p < 0.001$) and similar compared to metformin ($p = 0.62$) and pioglitazone ($p = 0.328$). Exenatide ER and metformin were similar in terms of associated decreases in body weight, with exenatide ER achieving superiority compared to sitagliptin and pioglitazone. Overall, exenatide ER was associated with more GI-related AEs, with the exception of diarrhea which occurred at the highest frequency in patients receiving metformin (*Diamant et al 2010*).
- An OL extension of the DURATION-1 trial demonstrated that treatment with exenatide ER was associated with sustained improvements in glycemic control over a 7-year period with no unexpected safety findings (*Philis-Tsimikas et al 2019*).

- In a post-hoc analysis of 4 clinical trials, patients were treated with weekly exenatide for 52 weeks. Patients had significant lowering of HbA1c, blood pressure and low-density lipoprotein (LDL) levels without an increase in weight or hypoglycemia (*Bergenstal et al 2013*).
- The DURATION-6 trial compared HbA1c reductions between liraglutide once daily and exenatide once weekly in patients with T2DM previously treated with lifestyle modifications and oral agents. Both therapies resulted in improvements in glycemic control; however, greater reductions were noted with liraglutide (*Buse et al 2013*).
- Bydureon BCise is a formulation of Bydureon that is administered via an autoinjector device. It was approved based on the results of two 28-week, OL, AC trials. In the DURATION-NEO-1 trial, Bydureon BCise 2 mg once weekly achieved a statistically significant HbA1c reduction vs Byetta 10 mcg twice daily ($p < 0.05$) in patients with T2DM inadequately controlled with diet and exercise alone or with a stable regimen of metformin, an SFU, a TZD, or a combination of any 2 of these agents. In the DURATION-NEO-2 trial, Bydureon BCise 2 mg once weekly achieved a statistically significant HbA1c reduction vs placebo ($p < 0.05$) in patients with T2DM on metformin. The difference vs sitagliptin was -0.28% (95% confidence interval [CI], -0.62% to -0.02%) (*Bydureon BCise Prescribing Information 2020, Gadde et al 2017, Wysham et al 2017*).

Liraglutide

- Approval of liraglutide in the management of T2DM was based on the clinical evidence for safety and efficacy derived from the LEAD trials (1 through 6). The LEAD trials evaluated liraglutide monotherapy (LEAD-3); add-on therapy to an SFU (LEAD-1), metformin (LEAD-2), metformin plus a TZD (LEAD-4), metformin plus an SFU (LEAD-5); and monotherapy head-to-head with exenatide (LEAD-6).
  - In LEAD-1, liraglutide was compared to placebo or rosiglitazone as add-on therapy to an SFU. After 26 weeks, liraglutide (0.6, 1.2, and 1.8 mg per day) significantly decreased HbA1c compared to placebo ($p < 0.0001$ for all), with only higher doses achieving superiority compared to rosiglitazone ($p < 0.001$ for both) (*Marre et al 2009*).
  - In LEAD-2, liraglutide was compared to placebo and an SFU as add-on therapy to metformin. Liraglutide significantly decreased HbA1c compared to placebo; however, similar decreases were observed with liraglutide compared to the SFU. Liraglutide was associated with significant decreases in body weight compared to placebo ($p < 0.01$) and the SFU ($p < 0.001$) (*Nauck et al 2009*). Results of an 18-month OL extension trial were consistent with the DB study (*Nauck et al 2013*).
  - In LEAD-3, liraglutide was compared to an SFU as monotherapy, and liraglutide was superior in decreasing HbA1c ($p = 0.0014$ and $p < 0.0001$ for liraglutide 1.2 mg and 1.8 mg, respectively). In addition, increases in body weight were reported with the SFU, while liraglutide significantly decreased body weight ($p = 0.027$) (*Garber et al 2009*). In a 1-year extension trial, patients continuing liraglutide for a total of 2 years maintained significant improvements in HbA1c compared to the SFU (*Garber et al 2011*).
  - In LEAD-4 and LEAD-5, liraglutide was compared to placebo as add-on therapy to metformin plus an SFU and to a TZD. LEAD-5 also had an OL arm of insulin therapy. Results achieved with liraglutide in terms of decreases in HbA1c, body weight, and FPG compared to placebo were similar to those observed in the other LEAD trials (*Russell-Jones et al 2009; Zinman et al 2009*). When compared to insulin therapy, decreases in HbA1c ($p = 0.0015$) and body weight ($p < 0.001$) and improvements in β-cell function ($p = 0.0019$) were significantly greater with liraglutide. It was noted that decreases in PPG were not different between the 2 treatments, and the likelihood of patients achieving FPG goals were also similar (*Russell-Jones et al 2009*).
  - LEAD-6 was a head-to-head trial comparing liraglutide to exenatide as add-on therapy to existing antidiabetic treatment regimens. Liraglutide significantly decreased HbA1c compared to exenatide (1.12% vs 0.79%; $p < 0.0001$),

and a significantly greater proportion of patients receiving liraglutide achieved HbA1c goals of < 7%. Significant decreases in FPG were also achieved with liraglutide ($p < 0.0001$); however, exenatide significantly decreased PPG after breakfast and dinner ($p < 0.0001$ and $p = 0.0005$) (*Buse et al 2009*). A 14-week, extension trial revealed that patients who were switched from exenatide to liraglutide achieved additional glycemic control and cardiometabolic benefits (*Buse et al 2010*).

- Liraglutide was studied in children and adolescents aged 10 to less than 17 years with T2DM in the PC Ellipse trial (*Tamborlane et al 2019*). After 26 weeks of DB treatment, liraglutide was associated with a significantly greater decrease in HbA1c vs placebo (mean difference [MD], -1.06%; 95% CI, -1.65 to -0.46; $p < 0.001$), which was maintained over an additional 26-week OL extension (MD, -1.30%; 95% CI, -1.89 to -0.70).

Lixisenatide

- The approval of lixisenatide was based on several phase 3 trials as part of the GetGoal clinical trial program. Lixisenatide 20 mcg once daily was evaluated as monotherapy, in combination with OADs, and in combination with basal insulin (with or without OADs). Its efficacy was compared with placebo, exenatide, and insulin glulisine. The primary endpoint, the difference in change in HbA1c from baseline to trial end between the lixisenatide and comparator groups, was assessed at varying time points ranging between 12 and 26 weeks.
  - GetGoal-Mono found that lixisenatide 20 mcg once daily as monotherapy resulted in significantly larger improvements in HbA1c at 12 weeks compared to placebo in patients with T2DM inadequately controlled on diet and exercise ($p < 0.0001$) (*Fonseca et al 2012*).
  - GetGoal-F1 was a DB study which found that lixisenatide 20 mcg once daily as add-on therapy to metformin was superior vs placebo in terms of HbA1c reduction from baseline to week 24. The least squares mean change from baseline was -0.26% for the placebo group vs -0.72% for the lixisenatide group. The difference vs placebo was -0.46% ($p < 0.0001$) (*Adlyxin Prescribing Information 2019, Bolli et al 2014*).
  - GetGoal-M-Asia demonstrated superiority of lixisenatide 20 mcg once daily as add-on therapy to metformin with or without an SFU compared to placebo in terms of HbA1c reduction from baseline to week 24 (*Yu et al 2014*).
  - GetGoal-S was a 24-week, DB study which found that lixisenatide 20 mcg once daily in combination with an SFU with or without metformin resulted in significantly greater improvement in glycemic control than placebo; the difference from placebo in change in HbA1c was -0.58% ($p < 0.0001$) (*Adlyxin Prescribing Information 2019, Rosenstock et al 2014*).
  - GetGoal-P was a 24-week, DB study which found that lixisenatide 20 mcg once daily in combination with pioglitazone with or without metformin resulted in significantly greater improvement in glycemic control than placebo; the difference from placebo in change in HbA1c was -0.48% ($p < 0.0001$) (*Adlyxin Prescribing Information 2019, Pinget al 2013*).
  - In GetGoal-Duo 1, lixisenatide was compared to placebo as add-on therapy to basal insulin and metformin with or without a TZD. Treatment with lixisenatide resulted in a significant reduction in HbA1c at week 24 vs placebo (*Riddle et al 2013a*).
  - In GetGoal-L, lixisenatide was compared to placebo as add-on therapy to basal insulin with or without metformin while in Get-Goal-L-Asia, lixisenatide was compared to placebo as add-on therapy to basal insulin with or without an SFU. Both studies found that lixisenatide was superior to placebo in terms of HbA1c reduction from baseline to week 24 (*Riddle et al 2013b, Seino et al 2012*).
  - GetGoal-Duo 2 was a 26-week, OL trial that compared lixisenatide to insulin glulisine once daily or 3 times daily for intensification of optimized insulin glargine ± metformin in patients with T2DM uncontrolled on basal insulin ± OADs (ie, an SFU and/or a DPP-4 inhibitor, and/or a glinide). Lixisenatide was found to be noninferior to both insulin glulisine regimens in terms of HbA1c reduction from baseline to week 26. However, lixisenatide provided less HbA1c reduction than insulin glulisine 3 times daily and the difference was statistically significant; the least squares MD of lixisenatide vs insulin glulisine 3 times daily was 0.23 ($p = 0.0002$) (*Adlyxin Prescribing Information 2019, Rosenstock et al 2016*).
  - GetGoal-X was a 24-week, OL trial that evaluated lixisenatide vs exenatide twice daily as add-on therapy to metformin. Lixisenatide met the pre-specified noninferiority margin vs exenatide twice daily for the difference in HbA1c reduction from baseline to week 24. However, lixisenatide provided less HbA1c reduction than exenatide and the difference was statistically significant; the least squares MD vs exenatide was 0.17% ($p = 0.0175$) (*Adlyxin Prescribing Information 2019, Rosenstock et al 2013*).
  - A meta-analysis (MA) of 76-week data from 5 trials in the GetGoal clinical trial program (GetGoal-M, GetGoal-F1, GetGoal-S, GetGoal-P, and GetGoal-L) supported the sustained efficacy and tolerability of lixisenatide (*Broglio et al 2017*).

Semaglutide

- The approval of semaglutide was based on several phase 3 trials as part of the SUSTAIN clinical trial program. Semaglutide was evaluated as monotherapy, in combination with OADs, and in combination with basal insulin. Its efficacy was compared with placebo, sitagliptin, exenatide ER, insulin glargine, and dulaglutide. The primary endpoint, the difference in change in HbA1c from baseline to trial end between the semaglutide and comparator groups, was assessed at varying time points ranging between 30 and 56 weeks.
  - SUSTAIN 1 was a 30-week, PC trial which found that semaglutide 0.5 mg and 1 mg weekly significantly improved HbA1c vs placebo ($p < 0.0001$) (*Sorli et al 2017)*.
  - SUSTAIN 2 was a 56-week, OL trial that compared semaglutide 0.5 mg and 1 mg weekly to sitagliptin 100 mg daily in patients on metformin and/or TZDs. Compared with sitagliptin, treatment with semaglutide resulted in statistically significant reductions in HbA1c from baseline to week 56. The mean change from baseline was -1.3% for semaglutide 0.5 mg, -1.5% for semaglutide 1 mg, and -0.7% for sitagliptin. The difference vs sitagliptin was -0.6% ($p < 0.0001$) for semaglutide 0.5 mg and -0.8% ($p < 0.0001$) for semaglutide 1 mg (*Ahrén et al 2017, Ozempic Prescribing Information 2021*).
  - SUSTAIN 3 was a 56-week, OL trial that compared semaglutide 1 mg to exenatide ER 2 mg once weekly. At week 56, mean change from baseline in HbA1c was -1.4% in the semaglutide group vs -0.9% in the exenatide ER group (difference: -0.5%, $p < 0.0001$) (*Ahmann et al 2018, Ozempic Prescribing Information 2021*).
  - SUSTAIN 4 was a 30-week OL, AC trial in patients on metformin with or without an SFU that compared semaglutide 0.5 mg and 1 mg to insulin glargine initiated at 10 units once daily. Compared with insulin glargine, treatment with semaglutide resulted in statistically significant reductions in HbA1c from baseline to week 30. The mean change from baseline was -1.2% for semaglutide 0.5 mg, -1.5% for semaglutide 1 mg, and -0.9% for insulin glargine. The difference vs insulin glargine was -0.3% ($p < 0.0001$) for semaglutide 0.5 mg and -0.6% ($p < 0.0001$) for semaglutide 1 mg (*Aroda et al 2017*, *Ozempic Prescribing Information 2021*).
  - SUSTAIN 5 was a 30-week, DB, PC trial in patients inadequately controlled with basal insulin, with or without metformin, which found that semaglutide 0.5 mg and 1 mg significantly reduced HbA1c vs placebo ($p < 0.0001$) (*Rodbard et al 2018).*
  - SUSTAIN 7 was a 40-week, OL trial that compared semaglutide to dulaglutide once weekly in patients on metformin monotherapy. From a mean baseline HbA1c of 8.2%, semaglutide 0.5 mg achieved a statistically significant reduction of 1.5% vs a reduction of 1.1% with dulaglutide 0.75 mg at week 40, while semaglutide 1.0 mg achieved a statistically significant reduction of 1.8% vs a reduction of 1.4% with dulaglutide 1.5 mg (both $p < 0.0001$ for noninferiority and superiority) *(Pratley et al 2018).*

Oral Semaglutide

- The Peptide Innovation for Early Diabetes Treatment (PIONEER) clinical development program for oral semaglutide consisted of 10 clinical trials that enrolled a total of 9543 adult patients with T2DM *(Novo Nordisk news release 2019).*
- PIONEER 1, 5, and 8 were Phase 3a, DB, PC, multicenter (MC), RCTs that evaluated the glycemic efficacy of Rybelsus compared to placebo in various settings. The primary endpoint was the change from baseline to Week 26 in HbA1c. Secondary endpoints included body weight, FPG, and the proportion of patients achieving HbA1c < 7.0%. Overall, Rybelsus improved HbA1c, FPG, and body weight (at higher doses) with a similar safety profile to other GLP-1 receptor agonists *(Buse et al 2019, Novo Nordisk medical information 2019)*.
  - PIONEER 1 (N = 703) compared 3 doses of Rybelsus to placebo as monotherapy for 26 weeks in treatment-naïve patients managed by diet and exercise alone *(Aroda et al 2019)*.
  - PIONEER 5 (N = 324) evaluated the effect of Rybelsus 14 mg compared to placebo for 26 weeks in patients with moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥ 30 and < 60 mL/min/1.73 m^2) receiving a stable dose of metformin, SU, and/or basal insulin *(Mosenzon et al 2019).*
  - PIONEER 8 (N = 731) assessed the safety and efficacy of 3 doses of Rybelsus compared to placebo for 52 weeks as add-on therapy in patients with T2DM inadequately controlled on insulin with or without metformin *(Zinman et al 2019)*.
- PIONEER 2, 3, 4, and 7 evaluated the glycemic efficacy of Rybelsus compared to other antidiabetic agents *(Pieber et al 2019, Pratley et al 2019, Rodbard et al 2019, Rosenstock et al 2019)*. For HbA1c reduction, Rybelsus was superior to empagliflozin 25 mg and sitagliptin 100 mg, and noninferior to liraglutide 1.8 mg. For body weight reduction, Rybelsus was superior to sitagliptin and liraglutide, but not significantly different from empagliflozin *(Buse et al 2019)*. The incidences of AEs were similar for Rybelsus compared to empagliflozin, sitagliptin, and liraglutide. The hypoglycemia

risk was low with Rybelsus, empagliflozin, sitagliptin, and liraglutide. Rates of GI AEs were consistent with the GLP-1 receptor agonists class and higher than those observed with empagliflozin and sitagliptin *(Buse et al 2019).*
  - PIONEER 2 (N = 822) was a 52-week, Phase 3a, OL, MC RCT that compared Rybelsus 14 mg (n = 412) to the SGLT2 inhibitor empagliflozin 25 mg (n = 410) as add-on therapy in patients with T2DM inadequately controlled by metformin *(Rodbard et al 2019).*
  - PIONEER 3 (N = 1864) was a 78-week, Phase 3a, DB, double dummy (DD), parallel-group (PG), MC RCT that compared Rybelsus 3 mg (n = 466), 7 mg (n = 466), or 14 mg (n = 465) to the DPP-4i sitagliptin 100 mg (n = 467) as add-on therapy in patients with T2DM inadequately controlled by metformin with or without an SU *(Rosenstock et al 2019).*
  - PIONEER 4 (N = 711) was a 52-week, Phase 3a, DB, DD, PG, MC RCT that evaluated the effect of Rybelsus 14 mg (n = 285), the injectable GLP-1 receptor agonist liraglutide 1.8 mg (n = 284), or placebo (n = 142) as add-on therapy in patients with T2DM inadequately controlled by metformin with or without an SGLT2 inhibitor *(Pratley et al 2019).*
  - PIONEER 7 (N = 504) was a 52-week, Phase 3a, OL, MC RCT that compared flexible dose adjustments of daily Rybelsus (n = 253) to a fixed dose of daily sitagliptin 100 mg (n = 251) in patients with T2DM inadequately controlled on stable daily doses of 1 or 2 OADs *(Pieber et al 2019).*

Cardiovascular (CV) outcomes

- A MC, DB, PC, RCT (REWIND trial; N = 9901) evaluated the long-term effects of dulaglutide vs placebo in patients with T2DM who had either a previous CV event or CV risk factors. A total of 31.5% of patients reported previous CV disease and 22.2% had baseline eGFR < 60 mL/min per 1.73 m^2. The median follow-up was 5.4 years. The primary composite outcome (CV death, non-fatal MI, or non-fatal stroke) occurred 12.0% of patients in the dulaglutide group vs 13.4% in the placebo group (hazard ratio [HR], 0.88; 95% CI, 0.79 to 0.99; p = 0.026). All-cause mortality did not differ between groups (10.8% in the dulaglutide group vs 12.0% in the placebo group (HR, 0.90; 95% CI, 0.80 to 1.01; p = 0.067). The rates of death from CV causes, nonfatal MI, and hospitalization for heart failure (HF) did not differ significantly between groups, while non-fatal MI was statistically significantly different in favor of dulaglutide (*Gerstein et al 2019*).
- A MC, DB, PC, RCT (EXSCEL trial; N = 14,752) was conducted to evaluate the long-term effects of exenatide ER vs placebo, as added to usual care, on CV outcomes in patients with T2DM with or without previous CV disease. A total of 73.1% of patients had previous CV disease, and the median follow-up was 3.2 years. A primary composite outcome event (CV death, non-fatal MI, or non-fatal stroke) occurred in 11.4% of patients in the exenatide ER group vs 12.2% in the placebo group (HR, 0.91; 95% CI, 0.83 to 1.00). Thus, exenatide ER was found to be noninferior to placebo with respect to safety (p < 0.001), but not superior to placebo with respect to efficacy (p = 0.06). The risk of death from any cause was 6.9% vs 7.9% in the exenatide ER and placebo groups, respectively (HR, 0.86; 95% CI, 0.77 to 0.97); the difference was not statistically significant on the basis of the hierarchical testing plan. The rates of death from CV causes, nonfatal MI, nonfatal stroke, and hospitalization for HF did not differ significantly between groups (*Holman et al 2017*).
- A MC, DB, PC, RCT (LEADER trial; N = 9340) was conducted to evaluate the long-term effects of liraglutide vs placebo on CV outcomes in patients with T2DM and high CV risk. The median follow-up was 3.8 years. It was found that the primary composite outcome (CV death, non-fatal MI, or non-fatal stroke) occurred in fewer patients in the liraglutide group (13.0%) vs the placebo group (14.9%) (HR, 0.87; 95% CI, 0.78 to 0.97; p < 0.001 for noninferiority; p = 0.01 for superiority). Fewer patients died from CV causes in the liraglutide group (4.7%) vs the placebo group (6.0%) (HR, 0.78; 95% CI, 0.66 to 0.93; p = 0.007). The rate of death from any cause was lower in the liraglutide group (8.2%) vs the placebo group (9.6%) (HR, 0.85; 95% CI, 0.74 to 0.97; p = 0.02). The rates of nonfatal MI, nonfatal stroke, and hospitalization for HF were non-significantly lower in the liraglutide group than in the placebo group (*Marso et al 2016a*).
  - A prespecified secondary analysis found that the composite renal outcome (new-onset persistent macro albuminuria, persistent doubling of serum creatinine level, end-stage renal disease, and death due to renal disease) occurred in fewer patients in the liraglutide group vs the placebo group (5.7% vs 7.2%; HR, 0.78; 95% CI, 0.67 to 0.92; p = 0.003) (*Mann et al 2017*).
  - Post-hoc analyses of the LEADER trial have reported that the risk reduction in the primary outcome was consistent in patients with CKD (HR, 0.69; 95% CI, 0.57 to 0.85), a history of a MI or stroke (HR, 0.85; 95% CI, 0.73 to 0.99), and established atherosclerotic CVD (ASCVD) (without a MI/stroke) (HR, 0.76; 95% CI, 0.62 to 0.94) (*Mann et al 2018, Verma et al 2018*).
  - The risk of acute gallbladder or biliary disease was increased with liraglutide vs placebo (HR, 1.60; 95% CI, 1.23 to 2.09) *(Nauck et al 2019)*.

- A MC, DB, PC, RCT (ELIXA trial; N = 6068) evaluated the long-term effects of lixisenatide vs placebo on CV outcomes in patients with T2DM who had a recent acute coronary syndrome (ACS) event within 180 days of screening. The median follow-up was 25 months. It was found that the primary endpoint event (a composite of the first occurrence of any of the following: death from CV causes, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina) occurred in 13.4% of patients in the lixisenatide group and 13.2% in the placebo group (HR, 1.02; 95% CI, 0.89 to 1.17), which demonstrated noninferiority of lixisenatide to placebo ($p < 0.001$), but did not demonstrate superiority ($p = 0.81$). The rates of the individual CV components of the primary endpoint were similar between the lixisenatide and placebo groups (*Pfeffer et al 2015*).
- *Marso et al 2016b* conducted a MC, DB, PC, RCT (SUSTAIN 6 trial; N = 3297) to assess the noninferiority of semaglutide as compared to placebo in terms of CV safety in patients with T2DM, 83.0% of whom had CV disease. Patients were randomized to semaglutide 0.5 mg or 1.0 mg once weekly or placebo. The median observation time was 2.1 years. The primary composite outcome was the first occurrence of CV death, nonfatal MI, or nonfatal stroke. The noninferiority margin was 1.8 for the upper boundary of the 95% CI of the HR.
  - The primary composite outcome occurred in 6.6% of the semaglutide group vs 8.9% of the placebo group (HR, 0.74 [95%CI, 0.58 to 0.95]; $p < 0.001$ for noninferiority). Although a p value of 0.02 for superiority was calculated; testing for superiority was not prespecified. Nonfatal stroke occurred in 1.6% in the semaglutide group vs 2.7% in the placebo group (HR, 0.61; 95% CI, 0.38 to 0.99; $p = 0.04$). Rates of nonfatal MI, CV death, and all-cause death were not statistically significantly different between groups.
  - Rates of new or worsening nephropathy were lower in the semaglutide group, but rates of retinopathy complications were significantly higher (3.0% for semaglutide vs 1.8% for placebo, HR, 1.76; 95% CI, 1.11 to 2.78]; $p = 0.02$).
- A MC, DB, PC, RCT (Harmony Outcomes trial; N=9463) evaluated the long-term effects of the previously available GLP-1 receptor agonist, albiglutide, vs placebo on CV outcomes in patients with T2DM and established CV disease. The median follow-up was 1.6 years. The primary endpoint (a composite of the first occurrence of any of the following: death from CV causes, MI, or stroke) occurred in 7% of patients in the albiglutide group and 9% in the placebo group (HR, 0.78; 95% CI, 0.68 to 0.90), which demonstrated noninferiority and superiority of albiglutide to placebo ($p < 0.0001$ for noninferiority; $p = 0.0006$ for superiority). The rate of fatal or non-fatal stroke was significantly improved in the albiglutide group, but other individual CV components of the primary endpoint were nonsignificantly lower in the albiglutide group than in the placebo group (*Hernandez et al 2018*).
- PIONEER 6 (N = 3183) was an event-driven, Phase 3a, DB, PC, MC RCT designed to confirm the CV safety of Rybelsus (n = 1591) vs placebo (n = 1592) as add-on therapy to standard of care in T2DM patients ≥ 50 years of age with established CVD/CKD or ≥ 60 years of age with CV risk factors (CVRFs) *(Husain et al 2019)*. After a median follow-up of 15.9 months (range, 0.4 to 20.0), Rybelsus demonstrated noninferiority to placebo with respect to 3-point major adverse cardiovascular event (MACE). A primary outcome event (CV death, nonfatal MI, or nonfatal stroke) occurred in 3.8% of patients in the Rybelsus group vs 4.8% in the placebo group (HR, 0.79; 95% CI, 0.57 to 1.11; $p < 0.001$ for noninferiority; $p = 0.17$ for superiority).
  - The ongoing SOUL CVOT will evaluate > 9000 patients for 3.5 to 5 years to determine whether Rybelsus provides a CV benefit. The estimated study completion date is in 2024 *(ClinicalTrials.gov 2021)*.

Meta-analyses

- Meta-analyses and Cochrane Reviews evaluating GLP-1 receptor agonists have found that they lead to decreases in HbA1c of ~1%, with greater decreases in body weight and systolic blood pressure compared to placebo and other antidiabetic agents (*Avgerinos et al 2020*, *Wang et al 2013, Shyangdan et al 2011, Sun et al 2015*).
- A systematic review and mixed-treatment comparison analysis of GLP-1 receptor agonists found that there were no differences in efficacy within the short-acting (exenatide or lixisenatide) or long-acting (albiglutide, dulaglutide, exenatide ER, liraglutide) groups. However, dulaglutide, liraglutide, and exenatide ER were superior to exenatide and lixisenatide at lowering HbA1c and FPG. There were no clinically meaningful differences between agents in weight loss or hypoglycemia. Albiglutide had the lowest risk of nausea and diarrhea, while exenatide ER had the lowest risk of vomiting (*Htike et al 2016*).
- A systematic review and network meta-analysis sponsored by the manufacturer of semaglutide (Novo Nordisk) found that in patients with T2DM who were inadequately controlled on 1 to 2 OADs, semaglutide 1.0 mg was associated with significantly greater reductions in HbA1c and weight vs all GLP-1 receptor agonist comparators after 6 months of treatment, while the 0.5 mg dose achieved statistically significant reductions in HbA1c and weight vs the majority of other GLP-1 receptor agonists (*Witkowski et al 2018a*). Similar results were found in another Novo Nordisk-sponsored systematic review of trials in patients previously receiving basal insulin (*Witkowski et al 2018b*).

- Meta-analyses have revealed that incretin-based therapies are not associated with an increased risk of pancreatitis and appear to reduce all-cause mortality, CV mortality, and the incidence of MI compared to placebo or other antidiabetic agents. However, treatment with GLP-1 receptor agonists was associated with a significant increase in the incidence of cholelithiasis (*Monami et al 2017a*, *Monami et al 2017b)*.
- A meta-analysis found that overall, GLP-1 receptor agonists did not appear to be associated with an increase in the incidence of retinopathy, and there was a reduction in the incidence of nephropathy vs comparators (*Dicembrini et al 2017*).
- A meta-analysis found that treatment with exenatide ER did not increase the risk of CV events compared with placebo or active comparators, and may reduce the risk of all-cause mortality *(Bonora et al 2019)*.
- A systematic review and meta-analysis of 16 observational cohort studies in patients with T2DM (N = 285,436) found that overall, the results favored GLP-1 receptor agonists for all-cause mortality (HR, 0.63; 95% CI, 0.44 to 0.89) and CV events (HR, 0.84; 95% CI, 0.75 to 0.94) vs other antidiabetic treatment regimens (including OADs and insulin); results for hospitalization for HF were neutral (HR, 0.94; 95% CI, 0.78 to 1.14) (*Herrera Comoglio et al 2020*).
- A systematic review and network meta-analysis comparing treatments for T2DM found that patients at increased CV risk receiving background metformin (N = 145,694) had a reduced risk of all-cause mortality and CV death with the addition of oral semaglutide (odds ratio [OR], 0.50; 95% CI, 0.31 to 0.83 and OR, 0.51; 95% CI, 0.28 to 0.94, respectively) or liraglutide (OR, 0.84; 95% CI, 0.73 to 0.97 and OR, 0.78; 95% CI, 0.65 to 0.93) vs placebo. The addition of exenatide ER only reduced all-cause mortality vs placebo (OR, 0.86; 95% CI, 0.76 to 0.98). The odds of stroke were lowered with both dulaglutide (OR, 0.76; 95% CI, 0.62 to 0.94) and subcutaneous semaglutide (OR, 0.61; 95% CI, 0.37 to 0.99) (*Tsapas et al 2020*).
- A meta-analysis of the 10 PIONEER trials demonstrated that when compared to an active comparator, oral semaglutide significantly reduced HbA1c by 0.33% ($p < 0.00001$) and body weight by 1.52 kg ($p < 0.00001$), and significantly increased the number of patients who achieved an HbA1c < 7.0% by 47% ($p = 0.0006$).The clinical significance of the changes in HbA1c and body weight with oral semaglutide vs other antidiabetic agents is unclear (*Li et al 2021*).
- A network meta-analysis was performed to compare the effect of newer antidiabetic agents (SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors) on a composite kidney outcome (kidney death and clinical end-stage kidney disease). A total of 7 RCTs were included (N = 58,346) with patients being randomized to either placebo or canagliflozin (n = 14,543), dapagliflozin (n = 17,160), empagliflozin (n = 7018), linagliptin (n = 6979), liraglutide (n = 9340), and semaglutide (n = 3297). Dapagliflozin showed the highest reduction in the risk of the composite kidney outcome (HR, 0.53; 95% CI, 0.43 to 0.66), followed by empagliflozin (HR, 0.61; 95% CI, 0.53 to 0.70), canagliflozin (HR, 0.63; 95% CI, 0.54 to 0.74), semaglutide (HR, 0.64; 95% CI, 0.46 to 0.88), and liraglutide (HR, 0.78; 95% CI, 0.67 to 0.91) *(Cha et al 2021)*.

Pramlintide

- The safety and efficacy of pramlintide in patients with T1DM have been established in PC, RCTs when administered in addition to existing insulin regimens. In a 52-week, DB, MC, PC study, pramlintide significantly reduced HbA1c from baseline compared to placebo (-0.39% vs -0.12%; $p = 0.0071$) and was also associated with a significant weight loss compared to placebo ($p < 0.001$) (*Whitehouse et al 2002*). In a second 52-week study, patients experienced a significant reduction in HbA1c when receiving pramlintide 60 mcg 3 times daily (-0.41% vs -0.18%; $p = 0.012$) and pramlintide 60 mcg 4 times daily (-0.39% vs -0.18%; $p = 0.013$) at 26 weeks. Treatment with pramlintide 3 or 4 times daily continued to maintain reductions in HbA1c at 52 weeks compared to treatment with placebo ($p = 0.011$ and $p = 0.001$ for the 3- and 4 times daily dosing, respectively) (*Ratner et al 2004*).
- A systematic review and meta-analysis of 10 randomized, PC studies (N = 3297) evaluating the effect of pramlintide as adjunctive therapy to insulin in patients with T1DM found that, compared to placebo, pramlintide resulted in significant reductions in HbA1c ($p < 0.001$), total daily insulin dose ($p = 0.024$), mean mealtime insulin dose ($p < 0.001$), body weight ($p < 0.001$), and PPG ($p = 0.002$) (*Qiao et al 2017*).
- A systematic review and meta-analysis of 58 trials evaluated the efficacy and safety of glucose-lowering drugs used as an adjunct to insulin therapy in adults with type 1 diabetes (*Avgerinos et al 2021*). Relevant results from the network meta-analysis for pramlintide are as follows: pramlintide was superior to placebo for reduction in bolus insulin dose (MD, -4.36 units; 95% CI, -8.37 to -0.35); pramlintide was superior to rosiglitazone and placebo for change in body weight (MD, -2.78 kg [95% CI, -4.85 to -0.71] and MD, -1.73 kg [95% CI, -2.41 to -1.06], respectively); and pramlintide increased the risk of treatment discontinuation and nausea vs placebo (OR, 2.53 [95% CI, 1.61 to 3.97] and OR, 4.07 [95% CI, 2.57 to 6.42], respectively)

- A systematic review and meta-analysis of 8 PC, RCTs assessed the effect of pramlintide in patients with T2DM and in obese patients without diabetes. Four T2DM studies (N = 930; 16 to 52 weeks duration) and 4 obesity studies (N = 686; 6 to 24 weeks duration) were included. Of the T2DM studies, 3 studies used meal-time placebo as the comparator while 1 study used rapid-acting insulin as the comparator. When endpoint data from all T2DM studies were combined, pramlintide was associated with a small but significant reduction in HbA1c (MD, -0.33% [95% CI, -0.51 to -0.14]; p = 0.0004). In the meta-analysis of the T2DM studies, patients on pramlintide were 1.52 times more likely to reach the HbA1c goal ≤ 7% than patients in the control group; however, this difference was not significant (p = 0.18). Pramlintide was associated with a significant change in body weight in patients with T2DM compared to the control group (-2.57 kg [95% CI, -3.44 to -1.70]; p < 0.00001) (*Singh-Franco et al 2011*).

CLINICAL GUIDELINES

- Professional society guidelines emphasize individualized therapy based upon patient- and drug-specific factors such as comorbidities, weight, hypoglycemia risk, propensity for AEs, drug interactions, and patient preferences *(ADA 2021, Buse et al 2020, Das et al 2020, Garber et al 2020)*.
- Metformin is recommended for first-line pharmacologic therapy in treatment-naïve patients with T2DM, unless the patient has contraindications or intolerance. SGLT2 inhibitors or GLP-1 receptor agonists should be considered for patients with ASCVD, HF, or CKD, independent of HbA1c. Metformin is considered the drug of choice for children with T2DM *(ADA 2021, Buse et al 2020, Copeland et al 2013, Das et al 2020, Garber et al 2020, KDIGO 2020, Rangaswami et al 2020)*.

- **ADA: Standards of Medical Care in Diabetes: Pharmacological therapy for T2DM** *(ADA 2021)*
  - Metformin (if not contraindicated and if tolerated) is the preferred initial pharmacological agent for T2DM (level A).
  - Metformin should be continued when used in combination with other agents, including insulin, if not contraindicated and if tolerated (level A).
  - Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure (level A).
  - Early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when HbA1c levels (> 10%) or blood glucose levels (> 300 mg/dL) are very high (level E).
  - A patient-centered approach should be used to guide the choice of pharmacologic therapy. Considerations include comorbidities (ASCVD, HF, CKD), hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences (level E).
  - In patients with T2DM and established ASCVD or indicators of high risk, established kidney disease, or HF, SGLT2 inhibitors or GLP-1 receptor agonists with demonstrated CVD benefit are recommended as part of the antihyperglycemic regimen, independent of HbA1c (level A).
  - In patients with T2DM who need greater glucose lowering than can be obtained with oral agents, GLP-1 receptor agonists are preferred to insulin when possible (level B).
  - Intensification of treatment for patients with T2DM not meeting treatment goals should not be delayed (level B).
  - The medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3 to 6 months) and adjusted as needed to incorporate specific factors that impact treatment choice (level E).
  - choice of add-on therapy should be determined based on 1) whether the patient has indicators of high risk or established ASCVD, CKD, or HF; and 2) in patients without these conditions, whether there is a compelling need to minimize hypoglycemia or to minimize weight gain or promote weight loss.
    - If ASCVD predominates, recommendations are:
      - Preferably a GLP-1 receptor agonist with proven cardiovascular disease (CVD) benefit; or
      - An SGLT2 inhibitor with proven CVD benefit (if estimated glomerular filtration rate [eGFR] is adequate)
    - If HF predominates, recommendations are:
      - Preferably an SGLT2 inhibitor with proven benefit in this population (ie, dapagliflozin and empagliflozin)
    - If CKD predominates, recommendations are:
      - Preferably an SGLT2 inhibitor with evidence of reducing CKD progression in cardiovascular outcome trials if eGFR is adequate (ie, canagliflozin and dapagliflozin); or
      - If the SGLT2 inhibitor is not tolerated or is contraindicated, or if the eGFR is less than adequate, a GLP-1 receptor agonist with proven CVD benefit

- In patients with T2DM and CKD and thus at increased risk of cardiovascular events, either an SGLT2 inhibitor with proven CVD benefit or GLP-1 receptor agonist with proven CVD benefit.
- In patients without established ASCVD, CKD, or HF, recommendations are:
  - If there is a compelling need to minimize hypoglycemia: a DPP-4 inhibitor, a GLP-1 receptor agonist, an SGLT2 inhibitor, or a TZD; or
  - If there is a compelling need to minimize weight gain or promote weight loss: a GLP-1 receptor agonist with good efficacy for weight loss or an SGLT2 inhibitor.

Table 3. ADA Factors to Consider for Antihyperglycemic Therapies in T2DM

Class*	Efficacy	Hypoglycemia	Weight	ASCVD	CHF	Route	DKD Progression
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Oral	Neutral
SGLT2i	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin
GLP-1ra	High	No	Loss	Benefit: See labeled indication Neutral: lixisenatide	Neutral	SQ, oral	Benefit: liraglutide
DPP-4i	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	Oral	Neutral
TZD	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Oral	Neutral
SFU (2nd generation)	High	Yes	Gain	Neutral	Neutral	Oral	Neutral
Insulin	Highest	Yes	Gain	Neutral	Neutral	SQ	Neutral

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; DKD = diabetic kidney disease; DPP-4i = dipeptidyl peptidase 4 inhibitor; GLP-1ra = glucagon-like peptide-1 receptor agonist; SFU = sulfonylurea; SGLT2i = sodium-glucose cotransporter-2 inhibitor; SQ = subcutaneous; T2DM = type 2 diabetes mellitus; TZD = thiazolidinediones
* Other antidiabetic drugs not shown in above table (eg, inhaled insulin, alpha-glucosidase inhibitors (AGIs), colesevelam, bromocriptine, and pramlintide) may be tried in specific situations; however, considerations include modest efficacy in T2DM, frequency of administration, potential for drug interactions, cost, and/or side effects.
† FDA approved for CVD benefit
‡ FDA approved for HF indication
§ FDA approved for CKD indication

- **American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) - Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm** *(Garber et al 2020)*
  - The choice of diabetes therapies must be individualized based on attributes specific to both patients and the medications themselves. Medication attributes include antihyperglycemic efficacy, mechanism of action, risk of inducing hypoglycemia, risk of weight gain, other AEs, tolerability, ease of use, likely adherence, cost, and safety or risk reduction in heart, kidney, or liver disease. Patient-specific considerations include initial HbA1c, duration of T2DM, and obesity status.
    - The choice of therapy depends on the individual patient's cardiac, cerebrovascular, and renal status.
    - Combination therapy is usually required and should involve agents with complementary mechanisms of action.
    - The therapeutic regimen should be as simple as possible to optimize adherence.
  - For patients with recent-onset T2DM or mild hyperglycemia (HbA1c < 7.5%), lifestyle therapy plus antihyperglycemic monotherapy (preferably with metformin) is recommended.

- For patients with established or high ASCVD risk, stage 3 CKD, or HF with reduced ejection fraction, an SGLT2 inhibitor or long-acting GLP-1 receptor agonist with proven efficacy is recommended independent of glycemic control.
- Other acceptable alternatives to metformin as initial therapy include DPP-4 inhibitors and TZDs. Alpha-glucosidase inhibitors, SFUs, and meglitinides may also be appropriate as monotherapy for select patients.

○ GLP-1 receptor agonists have robust HbA1c-lowering properties, are usually associated with weight loss, lipid, and blood pressure reductions, and are available in several formulations. The risk of hypoglycemia with GLP-1 receptor agonists is low, and they reduce fluctuations in both fasting and postprandial glucose levels by stimulating glucose-dependent insulin secretion and suppressing glucagon secretion.

- In the LEADER trial, liraglutide significantly reduced the risk of nephropathy and of death from certain CV causes.
- Data from the SUSTAIN 6, REWIND and HARMONY trials with injectable semaglutide, dulaglutide, and albiglutide, respectively, suggest other GLP1 receptor agonists also have CV disease benefits.
- GLP-1 receptor agonists based on exendin-4 have been proven to be safe in CV disease, but they have not been shown to confer CV benefits.
- No studies have confirmed that incretin agents cause pancreatitis; however, GLP-1 receptor agonists should be used cautiously, if at all, in patients with a history of pancreatitis and discontinued if pancreatitis develops.

Table 4. 2020 AACE/ACE Profiles of Antidiabetic Medications

Drug Class	Hypoglycemia	Weight	Renal/GU	GI	Cardiac	Bone	Ketoacidosis
Metformin	Neutral	Slight loss	eGFR < 30: contraindicated	Moderate	Neutral	Neutral	Neutral
GLP-1ra	Neutral	Loss	Possible benefit: long-acting GLP-1ra Exenatide not indicated CrCl < 30	Moderate	Potential benefit of long-acting GLP-1ra in ASCVD Neutral for HF	Neutral	Neutral
SGLT2i	Neutral	Loss	Genital mycotic infections Not indicated eGFR < 45* Potential CKD benefit*	Neutral	Prevent HHF; Manage HFrEF† Empagliflozin FDA approved to reduce CV mortality Canagliflozin FDA approved to reduce MACE	Neutral	DKA can occur in various stress settings
DPP-4i	Neutral	Neutral	Dose adjustment necessary (except linagliptin) Albuminuria reduction	Neutral	Possible increased HHF with alogliptin and saxagliptin	Neutral	Neutral
AGI	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral
TZD	Neutral	Gain	Neutral	Neutral	Moderate CHF risk May reduce stroke risk	Moderate fracture risk	Neutral
SFU	Moderate/severe	Gain	More hypoglycemia risk	Neutral	Possible ASCVD risk Neutral for HF	Neutral	Neutral

Drug Class	Hypoglycemia	Weight	Renal/GU	GI	Cardiac	Bone	Ketoacidosis
Meglitinide	Mild	Gain	More hypoglycemia risk	Neutral	Possible ASCVD risk	Neutral	Neutral
Colesevelam	Neutral	Neutral	Neutral	Mild	Lowers LDL-C	Neutral	Neutral
Bromocriptine QR	Neutral	Neutral	Neutral	Moderate	Safe in ASCVD	Neutral	Neutral
Insulin	Moderate to severe	Gain	More hypoglycemia risk	Neutral	CHF risk Neutral for ASCVD	Neutral	Neutral
Pramlintide	Neutral	Loss	Neutral	Moderate	Neutral	Neutral	Neutral

Abbreviations: AGI = alpha-glucosidase inhibitor; ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CKD = chronic kidney disease; CrCl = creatinine clearance; CV = cardiovascular; DKA = diabetic ketoacidosis; DPP-4i = dipeptidyl peptidase 4 inhibitor; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; GI = gastrointestinal; GLP-1ra = glucagon-like peptide-1 receptor agonist; GU = genitourinary; HFrEF = heart failure reduced ejection fraction; HHF = hospitalization for heart failure; LDL-C = low density lipoprotein-cholesterol; MACE = major adverse cardiovascular events; QR = quick release; SFU = sulfonylurea; SGLT2i = sodium-glucose cotransporter-2 inhibitor; TZD = thiazolidinedione

* Canagliflozin indicated for eGFR ≥ 30 mL/min/1.73 m^2 in patients with CKD 3 and albuminuria.

† Dapagliflozin has a potential benefit in primary prevention of HHF and demonstrated efficacy in HFrEF.

- **Endocrine Society: Guideline for Treatment of Diabetes in Older Adults** (*LeRoith et al 2019*)
  - Glycemic management strategies must be adjusted to the individual needs of older patients. Specific factors regarding certain drug classes are particularly important for older patients with diabetes, especially those with CKD and heart disease.
    - In T2DM patients ≥ 65 years of age, metformin is recommended as the initial oral medication chosen for glycemic management in addition to lifestyle management (unless the patient has significantly impaired kidney function or gastrointestinal intolerance).
    - Patients who are not able to achieve glycemic targets with metformin and lifestyle changes can receive add-on therapy with oral or injectable agents and/or insulin.
      - GLP-1 receptor agonists and SGLT2 inhibitors should be prescribed early, given their beneficial CV outcomes.
      - SFUs and meglitinides should be avoided and insulin should be used sparingly to reduce the risk of hypoglycemia.
      - Glycemic treatment regimens should be kept as simple as possible.
  - GLP-1 receptor agonists increase insulin release, decrease glucagon secretion, delay gastric emptying, suppress appetite, and do not cause hypoglycemia. Nausea is a common side effect, and initial concern about an increased risk for pancreatitis has not been proven. Liraglutide and semaglutide have been found to improve CV outcomes.

- **American College of Cardiology (ACC)/American Heart Association (AHA): Guideline on the Primary Prevention of CV Disease** *(Arnett et al 2019)*
  - For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk.
  - For adults with T2DM and additional ASCVD risk factors who require glucose lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate an SGLT2 inhibitor or GLP-1 receptor agonist to improve glycemic control and reduce CVD risk.
    - SGLT2i act in the proximal tubule to increase urinary excretion of glucose and sodium, leading to a reduction in HbA1c, body weight, and blood pressure. Three RCTs have shown a significant reduction in ASCVD events and HF with use of an SGLT2i. Although most patients studied had established CVD at baseline, the reduction in HF has been shown to extend to primary prevention populations.
    - The GLP-1 receptor agonists increase insulin and glucagon production in the liver, increase glucose uptake in muscle and adipose tissue, and decrease hepatic glucose production. Three GLP-1 receptor agonists have been found to significantly reduce the risk of ASCVD in adults with T2DM who are at high ASCVD risk.

- **American College of Cardiology: Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients with Type 2 Diabetes** *(Das et al 2020)*

- Based on the CV benefits with GLP-1 receptor antagonists and SGLT2 inhibitors, a discussion of benefits should be initiated with patients who are at high risk for ASCVD, HF, or diabetic kidney disease (DKD).
  - A GLP-1 receptor antagonist with CV benefit is recommended in patients with established or very high risk for ASCVD. Albiglutide [discontinued in the US], dulaglutide, liraglutide, and injectable semaglutide have proven benefit in reducing CV events. Exenatide once weekly and oral semaglutide have demonstrated numerically favorable but not statistically significant reductions in CV events. Lixisenatide is not associated with a reduction in ASCVD event risk.
  - The ACC pathway considers dulaglutide, liraglutide, and injectable semaglutide as the preferred GLP-1 receptor agonists for patients with T2DM and ASCVD or at high risk for ASCVD.
  - Concomitant use of SGLT2 inhibitors or GLP-1 receptor antagonists with sulfonylurea, glinides, or insulin increases the risk of hypoglycemia.
    - When starting an SGLT2 inhibitor or GLP-1 receptor antagonist for CV benefit in patients with well-controlled baseline HbA1c, SFUs should be weaned or stopped, and insulin doses should be decreased by approximately 20%. Treatment with DPP-4 inhibitors should be discontinued prior to initiating a GLP-1 receptor antagonist.
    - Patients should monitor for hypoglycemia for the first 4 weeks of therapy. Consider discontinuing sulfonylurea agents and glinides or decreasing insulin based on glucose monitoring.

- **American Heart Association: Scientific Statement on Cardiorenal Protection with the Newer Antidiabetic Agents in Patients with Diabetes and Chronic Kidney Disease** *(Rangaswami et al 2020)*
  - Initiation of an SGLT2 inhibitor or GLP-1 receptor agonist is recommended in patients with T2DM and CKD, given their renoprotective benefits and reduction of CV AEs.
    - Given that the benefit appears to be a class wide effect, selection of a specific SGLT2 inhibitor or GLP-1 receptor antagonist should be based on affordability.
    - Phenotype of CVD may influence selection of SGLT2 inhibitor versus GLP-1 receptor agonists, as SGLT2 inhibitors display dominant benefits for HF and GLP-1 receptor agonists for ASCVD.
    - Severity of CKD may also be considered when selecting an agent, since GLP-1 receptor antagonists are better studied in severe CKD.

- **Kidney Disease Improving Global Outcomes (KDIGO): Clinical Practice Guideline for Management in Chronic Kidney Disease** *(KDIGO 2020)*
  - First line therapy for patients with T2DM and CKD with an eGFR ≥30 ml/min/1.73 m^2 includes metformin and an SGLT2 inhibitor, with additional therapy as needed to achieve glycemic control.
    - Preference should be given to SGLT2 inhibitors with CV and kidney benefits.
    - If HbA1c goals are not achieved with metformin and SGLT2 inhibitors, or a patient is unable to use either medication, a long-acting GLP-1 receptor agonist with cardiovascular benefits is recommended.
    - Insulin and SFU doses may need to be decreased or stopped in the setting of hypoglycemia when used with GLP-1 receptor agonists and SGLT2 inhibitors.
    - Medications within the following classes should be utilized if glycemic control is not achieved with first line or preferred second line agents: DPP-4 inhibitors, insulin, SFUs, TZDs, and alpha-glucosidase inhibitors.

SAFETY SUMMARY

- GLP-1 receptor agonists are contraindicated in patients with hypersensitivity to any component of the products. With the exception of exenatide twice daily injection and lixisenatide, they are also contraindicated in those with a personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome, type 2 (MEN 2). Exenatide and exenatide ER are also contraindicated in patients with a history of drug-induced immune-mediated thrombocytopenia from exenatide products.
- All GLP-1 receptor agonists, except exenatide twice daily injection and lixisenatide, carry a boxed warning for risk of thyroid C-cell tumors. Other safety risks include pancreatitis (including fatal and non-fatal hemorrhagic or necrotizing pancreatitis), serious hypersensitivity reactions, immunogenicity, serious hypoglycemia when used in combination with SFUs or insulin, and renal impairment. Liraglutide and exenatide ER have a warning for acute gallbladder disease. Dulaglutide, exenatide, and exenatide ER are not recommended for patients with severe gastrointestinal disease, including gastroparesis; lixisenatide is also not recommended for patients with gastroparesis. Semaglutide carries a warning for diabetic retinopathy complications due to the results of the SUSTAIN 6 trial, which found a higher rate of events in patients treated with semaglutide vs placebo; the absolute risk was larger among patients with a history of

diabetic retinopathy at baseline compared to those without. Dulaglutide also carries a warning for diabetic retinopathy complications based data from a CV outcomes trial. Common AEs with these drugs include: nausea, diarrhea, vomiting, headache, and injection site reactions.

- Pramlintide is contraindicated in patients with hypersensitivity to any component of the drug and in those with hypoglycemia unawareness and confirmed gastroparesis. It has a boxed warning for increased risk of hypoglycemia, particularly in patients with T1DM. Common AEs include nausea, headache, anorexia, and vomiting; the incidence of nausea tends to be higher at the beginning of treatment and decreases with time in most patients. Gradual titration of the dose minimizes the incidence and severity of nausea.
- The pregnancy risks for dulaglutide, exenatide, exenatide ER, liraglutide, pramlinitide, semaglutide, and lixisenatide are uncategorized in accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR).
  - There are no adequate and well-controlled studies in pregnant women. These drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether these drugs are excreted in human milk.

DOSING AND ADMINISTRATION

Table 5. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Adlyxin (lixisenatide)	Injection	SC	Once daily	Inject in the abdomen, thigh, or upper arm. Administer within 1 hour before the first meal of the day, preferably the same meal each day.
Bydureon BCise (exenatide ER)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food. Administer immediately after the autoinjector is prepared.
Byetta (exenatide)	Injection	SC	Twice daily	Inject in the thigh, abdomen, or upper arm. Inject within 60 minutes prior to the morning and evening meals (or before the 2 main meals of the day, approximately 6 hours or more apart).
Ozempic (semaglutide)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food.
Rybelsus (semaglutide)	Tablets	Oral	Once Daily	Must be taken at least 30 minutes before the first food, beverage or other oral medications of the day with no more than 4 ounces of plain water only. Swallow whole. Do not crush or chew tablets
Symlin (pramlintide)	Injection	SC	Prior to major meals	Inject in the thigh or abdomen. Administer immediately prior to each major meal. Reduce mealtime insulin doses by 50%. Adjust insulin doses to optimize glycemic control once the target dose of pramlintide is achieved and nausea (if experienced) has subsided. The dose should be decreased if significant nausea persists.
Trulicity (dulaglutide)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Victoza (liraglutide)	Injection	SC	Once daily	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food.

CONCLUSION

- The GLP-1 receptor agonists exenatide, exenatide ER, dulaglutide, lixisenatide, and semaglutide are incretin-based antidiabetic therapies that are FDA-approved as adjunctive therapy to diet and exercise in adult patients with T2DM; liraglutide is approved for patients 10 years and older. Additionally, liraglutide, dulaglutide, and subcutaneous semaglutide are indicated to reduce the risk of MACE in patients with established CV disease, and dulaglutide is also approved to reduce the risk of MACE in patients with multiple CV risk factors. Pramlintide is the only agent within the amylinomimetic medication class and is FDA-approved as adjunctive therapy in patients with T1DM or T2DM who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.
- The incretin mimetics are available as SC injections to be administered in the abdomen, thigh, or upper arm. Semaglutide is additionally available in an oral formulation. Exenatide is administered twice daily (60 minutes prior to meals); liraglutide is administered once daily (independent of meals); and lixisenatide is administered once daily (1 hour prior to the first meal of the day). Exenatide ER, dulaglutide, and semaglutide are administered once weekly. Bydureon pen is being phased out and replaced by Bydureon BCise, an autoinjector device that allows for more convenient administration (*AstraZeneca 2021).* Pramlintide is available as a SC injection to be administered immediately prior to each major meal.
- The incretin mimetics have been studied extensively in combination with, and in comparison to, a variety of antidiabetic therapies. The agents are significantly more effective than placebo in reducing HbA1c, FPG, PPG, and body weight. Efficacy data comparing treatment to an SFU, TZD, DPP-4 inhibitor or insulin is mixed, with the GLP-1 agonists achieving significantly greater or comparable benefits in glycemic outcomes.
- Several CV outcomes trials evaluating GLP-1 receptor agonists in patients with T2DM and high CV risk have been published. The LEADER, Harmony Outcomes, REWIND, and SUSTAIN 6 trials demonstrated a statistically significant CV risk reduction with liraglutide, albiglutide, dulaglutide, and subcutaneous semaglutide, respectively, vs placebo (*Gerstein et al 2019, Hernandez et al 2018, Marso et al 2016a, Marso et al 2016b*). The ELIXA, EXSCEL, and PIONEER 6 CV outcome trials did not demonstrate statistically significant reductions in MACE with lixisenatide, exenatide ER, or oral semaglutide, respectively, vs placebo (*Holman et al 2017, Husain et al 2019, Pfeffer et al 2015*).
- Overall, the AE profiles of the GLP-1 receptor agonists are similar. With the exception of lixisenatide and exenatide twice daily injection, all of the agents (including exenatide ER) have a boxed warning regarding the risk of thyroid C-cell tumors. Exenatide and exenatide ER are contraindicated in patients with a history of drug-induced immune-mediated thrombocytopenia from exenatide products. Other warnings include increased risks of pancreatitis (including fatal and non-fatal hemorrhagic or necrotizing pancreatitis), serious hypersensitivity reactions, immunogenicity, serious hypoglycemia when used in combination with SFUs or insulin, and renal impairment. Dulaglutide, exenatide and exenatide ER are not recommended for patients with severe gastrointestinal disease, including gastroparesis; lixisenatide is also not recommended for patients with gastroparesis. Liraglutide and exenatide ER also have a warning for acute gallbladder disease, while dulaglutide and semaglutide have a warning for diabetic retinopathy complications.
- According to current clinical guidelines for the management of T2DM, metformin is recommended first-line for the initial pharmacologic treatment of T2DM, and GLP-1 receptor agonists are among the second-line options. GLP-1 receptor agonists or SGLT2 inhibitors should be considered for patients with established ASCVD, high ASCVD risk, HF, or CKD, independent of HbA1c *(ADA 2021, Das et al 2020, Garber et al 2020, KDIGO 2020, Rangaswami et al 2020).* A 2020 AHA scientific statement and 2020 KDIGO guideline both note that GLP-1 receptor agonists are preferred over SGLT2 inhibitors for patients with severe CKD (*Rangaswami et al 2020, KDIGO 2020)*. A 2020 ACC expert consensus decision pathway for patients with T2DM and ASCVD or high risk for ASCVD recognizes dulaglutide, liraglutide, and injectable semaglutide as the preferred GLP-1 receptor agonists (*Das et al 2020)*.
- Current clinical guidelines do not support the use of amylinomimetics in the management of T2DM. Among T1DM patients, there is limited evidence available to support the routine use of adjunctive therapies, including pramlintide, to insulin therapy (*ADA 2021, Garber et al 2020*).

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