Therapeutic Class Overview
Sodium-glucose co-transporter 2 (SGLT2) Inhibitors

Therapeutic Class

- **Overview/Summary:** Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a class of oral antidiabetic agents approved by the Food and Drug Association (FDA) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.[1-7] The kidneys play a pivotal role in controlling plasma glucose concentration; reabsorbing nearly all plasma glucose in the proximal tubules and preventing glucose excretion in patients with normal glucose-tolerance. Approximately 90% of the filtered renal glucose is done in the early convoluted segment of the proximal tubule and is facilitated by the SGLT2 transporter. The remaining 10% of filtered glucose is reabsorbed in the distal straight segment of the proximal tube by the SGLT1 transporter. In diabetic patients, the SGLT transporter system is often overwhelmed and unable to reabsorb all filtered plasma glucose due to hyperglycemic conditions. Once this threshold capacity is reached and surpassed, excess glucose that is not reabsorbed is excreted into the urine. In addition, a chronic elevated plasma glucose concentration provides the stimulus that ultimately leads to increased SGLT2 expression by the renal proximal tubular cells, resulting in an undesirable increase in renal capacity and threshold to reabsorb filtered glucose in both type 1 and type 2 diabetic patients.[1,2] SGLT2 inhibitors improve glycemic control by producing glucosuria. This is accomplished by inhibiting SGLT2 and increasing urinary glucose excretion. The net effect is an increase excretion of glucose from the body and normalizing plasma glucose levels. At this time, it is unknown if this mechanism of action serves to reduce the kidney's threshold capacity to reabsorb glucose, thus causing glucose excretion at lower plasma concentrations, or if the mechanism of action serves to prevent reabsorption of glucose load at all plasma glucose concentrations. SGLT2 inhibitors also have beneficial nonglycemic effects, such as weight loss observed during clinical trials and small decreases in systolic and diastolic blood pressure.[1,2]

Table 1. Current Medications Available in Therapeutic Class[3-8]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Agent Products			
Canagliflozin (Invokana®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 100 mg 300 mg	-
Dapagliflozin (Farxiga®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 5 mg 10 mg	-
Empagliflozin (Jardiance®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 10 mg 25 mg	-
Combination Products			
Canagliflozin/ metformin (Invokamet®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes*	Tablet: 50/500 mg 50/1,000 mg 150/500 mg 150/1,000 mg	-
Dapagliflozin/ metformin ER (Xigduo XR®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes†	Tablet: 5/500 mg 5/1000 mg 10/500 mg 10/1000 mg	-
Empagliflozin/ linagliptin (Glyxambi®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes‡		

ER=extended-release

*For patients who are not adequately controlled on a regimen containing metformin or canagliflozin or in patients already being treated with both canagliflozin and metformin.
†When treatment with both dapagliflozin and metformin is appropriate.
‡When treatment with both empagliflozin and linagliptin is appropriate.

Evidence-based Medicine

- Each agent has been studied as monotherapy and dual and triple therapy compared to placebo and active controls and combinations of placebo and active controls.
- As monotherapy, patients randomized to canagliflozin 100 or 300 mg daily compared to patients randomized to placebo had a statistically significant improvement in HbA_{1c}. Both doses also resulted in a greater proportion of patients achieving an HbA_{1c} <7.0%, significant reductions in FPG and post prandial glucose (PPG), and in percent body weight reduction compared to placebo. There were also small decreases from baseline in systolic blood pressure relative to placebo (P values not reported).[9]
- As monotherapy in treatment-naïve patients, dapagliflozin was evaluated in two placebo-controlled trials. The first trial included 274 patients randomized to treatment with 2.5, 5 and 10 mg or placebo. At week 24, treatment with dapagliflozin 5 and 10 mg resulted in significant improvements in HbA_{1c} compared to placebo (-0.6, -0.8, -0.9 vs -0.2%, respectively; P<0.05 for 5 and 10 mg comparisons). Change in FPG (-24.1 and -28.8 vs -4.1 mg/dL, respectively) from baseline was also significantly greater in the 5 and 10 mg groups compared to placebo (P<0.05 for both comparisons).[11]
- There have been no clinical efficacy studies conducted with Xigduo XR® (dapagliflozin/metformin) combination tablets. FDA-approval of dapagliflozin/metformin ER was based on previous studies conducted with the bioequivalent single-entity agents.[7] Combination therapy with metformin extended-release in patients who were treatment-naïve led to significantly greater reductions in HbA_{1c} compared to either monotherapy (dapagliflozin or metformin) in the first study (-2.0 vs -1.2 and -1.4%, respectively; P<0.0001) and second study (-2.0 vs -1.5 and -1.4%, respectively; P<0.0001). In the second study, treatment with 10 mg strength (as monotherapy) was also non-inferior to metformin (as monotherapy) for reduction of HbA_{1c}.[13]
- The safety and efficacy of empagliflozin monotherapy was evaluated in a double-blind, placebo-controlled study of patients with type 2 DM (N=986). At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons), FPG (-19 mg/dL and -25 mg/dL vs. 12 mg/dL, respectively; P values not reported) and body weight (-2.8 kg and -3.2 kg vs. -0.4 kg, respectively; P values not reported) compared with placebo.[14]
- Similar results were observed when comparing sodium glucose co-transport 2 agents in combination for the treatment of diabetes mellitus.[16-30]
- The safety and efficacy of empagliflozin added to linagliptin was evaluated in a 52 week double-blind, active-control, randomized trial. Change from baseline in HbA_{1c} at week 24 was significantly improved in the combination groups compared with the individual component groups (P<0.001).[31] When started as initial therapy, empagliflozin/linagliptin reduced HbA_{1c} from baseline significantly greater when compared with individual linagliptin and empagliflozin 10 mg. Empagliflozin 25 mg/linagliptin 5 mg, however, did not show a statistically significant difference compared with empagliflozin alone (P=0.179).[32]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[33-38]
  - Metformin remains the cornerstone of most antidiabetic treatment regimens.
  - Patients with high glycosylated hemoglobin (HbA_{1c}) will likely require combination or triple therapy in order to achieve glycemic goals.
    - Uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
    - The role of sodium-glucose co-transporter 2 (SGLT2) inhibitors are addressed in only one treatment guideline and are recommended as a potential second-line treatment option to be added in combination with metformin in patients not achieving glycemic goals.[37]

- Other Key Facts:
  - Canagliflozin is formulated with metformin in a single tablet (Invokamet®). Empagliflozin is formulated with linagliptin in a single tablet (Glyxambi®). Dapagliflozin is formulated with metformin as a single extended-release tablet (Xigduo XR®).[6-8]
  - All products are dosed once daily, with the exception of canagliflozin/metformin, which is dosed twice dialy.[3-8]
  - Other effects observed in trials include weight loss and small decreases in systolic and diastolic blood pressure.
  - Common adverse side effects associated with SGLT2 inhibitor use included increased incidence of female genital mycotic infections, urinary tract infection, and increased urination.

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Therapeutic Class Review
Sodium-glucose co-transporter 2 (SGLT2) Inhibitors

Overview/Summary

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a novel class of oral antidiabetic agents recently approved by the Food and Drug Association (FDA). The kidneys play a pivotal role in controlling plasma glucose concentration; reabsorbing nearly all plasma glucose in the proximal tubules and preventing glucose excretion in patients with normal glucose-tolerance. Approximately 90% of the filtered renal glucose is done in the early convoluted segment of the proximal tubule and is facilitated by the SGLT2 transporter. The remaining 10% of filtered glucose is reabsorbed in the distal straight segment of the proximal tube by the SGLT1 transporter. In diabetic patients, the SGLT transporter system is often overwhelmed and unable to reabsorb all filtered plasma glucose due to hyperglycemic conditions. Once this threshold capacity is reached and surpassed, excess glucose that is not reabsorbed is excreted into the urine. In addition, a chronic elevated plasma glucose concentration provides the stimulus that ultimately leads to increased SGLT2 expression by the renal proximal tubular cells, resulting in an undesirable increase in renal capacity and threshold to reabsorb filtered glucose in both type 1 and type 2 diabetic patients.[1,2]

SGLT2 inhibitors improve glycemic control by producing glucosuria. This is accomplished by inhibiting SGLT2 and increasing urinary glucose excretion. The net effect is an increase excretion of glucose from the body and normalizing plasma glucose levels. At this time, it is unknown if this mechanism of action serves to reduce the kidney's threshold capacity to reabsorb glucose, thus causing glucose excretion at lower plasma concentrations, or if the mechanism of action serves to prevent reabsorption of glucose load at all plasma glucose concentrations. SGLT2 inhibitors also have beneficial nonglycemic effects, such as weight loss observed during clinical trials and small decreases in systolic and diastolic blood pressure.[1,2]

Currently, three single-entity agents, and three combination products in this drug class have been approved by the FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and are commercially available in the United States. Canagliflozin (Invokana®), dapagliflozin (Farxiga®) and empagliflozin (Jardiance®) are oral once daily tablets. The combination products include canagliflozin/metformin (Invokamet®), which is a twice-daily tablet, dapagliflozin/metformin (Xigduo XR®), which is a once-daily extended-release (ER) tablet and empagliflozin/linagliptin (Glyxambi®), which is also a once-daily tablet.[3-8]

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens. Additionally, patients with a high HbA_{1c} will likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. The role of SGLT2 inhibitors are currently addressed in only one treatment guideline, and are recommended as a potential second-line treatment option to be added in combination with metformin in patients not achieving glycemic goals.[37] Patients who are not appropriate for initial therapy with metformin, may be initiated on another oral antidiabetic agent, such as a sulfonylurea/glinide, thiazolidinedione, or a dipeptidyl pepetidase-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful.[33-38]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Agent Products		
Canagliflozin (Invokana®)	SGLT2 inhibitor	-
Dapagliflozin (Farxiga®)	SGLT2 inhibitor	-
Empagliflozin (Jardiance®)	SGLT2 inhibitor	-
Combination Products		
Canagliflozin/metformin (Invokamet®)	SGLT2 inhibitor/biguanide	-
Dapagliflozin/metformin ER (Xigduo XR®)	SGLT2 inhibitor/biguanide	-
Empagliflozin/linagliptin (Glyxambi®)	SGLT2 inhibitor/DPP-4 inhibitor	-

DPP-4= dipeptidyl peptidase-4, ER=extended-release, SGLT2=Sodium-glucose co-transporter 2

Indications

Table 2. Food and Drug Administration-Approved Indications[3-8]

Generic Name	Adjunct to Diet and Exercise to Improve Glycemic Control in Adults With Type 2 Diabetes
Single Agent Products	
Canagliflozin	a
Dapagliflozin	a
Empagliflozin	a
Combination Products	
Canagliflozin/metformin	a *
Dapagliflozin/metformin	a †
Empagliflozin/linagliptin	a ‡

*For patients who are not adequately controlled on a regimen containing metformin or canagliflozin or in patients already being treated with both canagliflozin and metformin.
†When treatment with both dapagliflozin and metformin is appropriate.
‡When treatment with both empagliflozin and linagliptin is appropriate.

Pharmacokinetics

Table 3. Pharmacokinetics[3-8]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single Agent Products				
Canagliflozin	65	33	None	10.6 to 13.1
Dapagliflozin	78	75	None	12.9
Empagliflozin	Not reported	54.4	None	12.4
Combination Products				
Canagliflozin/ metformin	65/ 50 to 60	33/ Not reported	None	10.6 to 13.1/ 17.6
Dapagliflozin/ metformin ER	78/ 50	75/ 90	None	12.9/ 17.6
Empagliflozin/ linagliptin	Not reported/ 30	54.4/ 5	None	12.4/ Not reported

ER=extended-release

Clinical Trials

Canagliflozin has been studied as monotherapy in the treatment of type 2 diabetes in several clinical trials.[3,9,10] As monotherapy, patients randomized to canagliflozin 100 or 300 mg daily compared to patients randomized to placebo had a statistically significant improvement in HbA_{1c}. Both doses also resulted in a greater proportion of patients achieving an HbA_{1c} <7.0%, significant reductions in fasting plasma glucose (FPG) and post prandial glucose (PPG), and in percent body weight reduction compared to placebo. There were also small decreases from baseline in systolic blood pressure relative to placebo.[9] The safety and efficacy of canagliflozin added to pioglitazone with or without metformin was evaluated in a double-blind, placebo-controlled, study of patients with type 2 DM in combination with pioglitazone 30 mg per day, with or without metformin ≥1,500 mg per day (N=498). At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (-0.6% and -0.7% vs. -0.1%, respectively; P<0.0001 for both comparisons), FPG (-17 mg/dL and -22 mg/dL vs. 7 mg/dL, respectively; P values not reported) and body weight (-2.0 kg and -1.8 kg vs. -0.6 kg, respectively; P values not reported) compared with placebo.[10] Across all studies, treatment was generally associated with a 0.7 to 1.1% decrease in glycosylated hemoglobin (HbA_{1c}) from baseline. Secondary endpoints generally favored or were similar when comparing canagliflozin to placebo and active-control, sitagliptin. Common adverse events included urinary tract infections, genital mycotic infections, and adverse events related to osmotic diuresis (e.g., decreased intravascular volume).[9,10]

As monotherapy in treatment-naïve patients, dapagliflozin was evaluated in two placebo-controlled trials. The first trial included 274 patients randomized to treatment with 2.5, 5 and 10 mg or placebo. At week 24, treatment with dapagliflozin 5 and 10 mg resulted in significant improvements in HbA_{1c} compared to placebo (-0.6, -0.8, -0.9 vs -0.2%, respectively; P<0.05 for 5 and 10 mg comparisons). Change in FPG (-24.1 and -28.8 vs -4.1 mg/dL, respectively) from baseline was also significantly greater in the 5 and 10 mg groups compared to placebo (P<0.05 for both comparisons). Changes in HbA_{1c} and FPG for the 2.5 mg arm and changes in weight for all three comparisons also favored the treatment arm; however differences were not considered significant.[11] The second trial included 282 patients randomized to treatment with 1, 2.5 and 5 mg or placebo. Results mirrored the first trial in that patients randomized to treatment with dapagliflozin experienced significantly greater decreases in HbA_{1c}, FPG and body weight.[12]

There have been no clinical efficacy studies conducted with Xigduo XR® (dapagliflozin/metformin) combination tablets. FDA-approval of dapagliflozin/metformin ER was based on previous studies conducted with the bioequivalent single-entity agents.[7] Combination therapy with metformin extended-release in patients who were treatment-naïve led to significantly greater reductions in HbA_{1c} compared to either monotherapy (dapagliflozin or metformin) in the first study (-2.0 vs -1.2 and -1.4%, respectively; P<0.0001) and second study (-2.0 vs -1.5 and -1.4%, respectively; P<0.0001). In the second study, treatment with 10 mg strength (as monotherapy) was also non-inferior to metformin (as monotherapy) for reduction of HbA_{1c}.[13]

The safety and efficacy of empagliflozin monotherapy was evaluated in a double-blind, placebo-controlled study of patients with type 2 DM (N=986). At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons), fasting plasma glucose (FPG) (-19 mg/dL and -25 mg/dL vs. 12 mg/dL, respectively; P values not reported) and body weight (-2.8 kg and -3.2 kg vs. -0.4 kg, respectively; P values not reported) compared with placebo. Systolic blood pressure (SBP) was significantly reduced compared to placebo by -2.6 mmHg (placebo-adjusted, P=0.0231) in patients randomized to 10 mg of empagliflozin and by -3.4 mmHg (placebo-corrected, P=0.0028) in patients randomized to 25 mg of empagliflozin. Sitagliptin was evaluated as an active comparator in this trial and demonstrated similar reduction in HbA1c.[14] The safety and efficacy of empagliflozin in renal disease was evaluated in a double-blind, placebo-controlled, parallel group study of patients with type 2 DM and a baseline estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2 (N=738; 290 with mild renal impairment [eGFR ≥60 to <90 mL/min/1.73 m^2], 374 with moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m^2], and 74 with severe renal impairment [eGFR <30 mL/min/1.73 m^2]). At week 24, empagliflozin 25 mg provided statistically significant reduction in HbA1c relative to placebo in patients with mild to moderate renal impairment (-0.5% placebo-corrected comparison; P<0.0001). The glucose lowering efficacy decreased with decreasing level of renal function

in the mild to moderate range. For patients with severe renal impairment, the analyses of changes in HbA_{1c} and FPG showed no discernible treatment effect compared to placebo.[15]

As an add-on therapy in patients not adequately controlled with metformin, canagliflozin 100 and 300 mg once daily resulted in a significant improvement in HbA_{1c} compared to placebo. Compared to placebo both doses also resulted in a greater proportion of patients achieving an HbA_{1c} <7.0%, having a significant reduction in FPG, having an improved PPG and percent body weight reduction. As in the monotherapy studies, statistically significant mean changes from baseline in systolic blood pressure relative to placebo were also observed.[16]

Several trails showed dapagliflozin was effective at reducing HbA_{1c} and fasting blood glucose.[16-21] One trial evaluated dapagliflozin, as an add-on therapy to metformin, compared to glipizide in treatment-experienced patients. At week 52, dapagliflozin plus metformin and glipizide plus metformin had identical HbA1c reductions of 0.52% which met the criteria for non-inferiority. The dapagliflozin arm also had significantly greater weight loss, improvements in systolic blood pressure and fewer episodes of hypoglycemia.[17] The clinical trial program for dapagliflozin also included trials in patients with a history of cardiovascular disease, as well as overweight and obese patients. The results suggested that the drug was safe and effective.[17-22]

The safety and efficacy of empagliflozin added to metformin was evaluated in a double-blind, placebo-controlled study of patients with type 2 DM inadequately controlled on at least 1,500 mg of metformin per day (N=637). At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons), FPG (-20 mg/dL and -22 mg/dL vs. 6 mg/dL, respectively; P values not reported) and body weight (-2.5 kg and -2.9 kg vs. -0.5 kg, respectively; P<0.001 for both comparisons) compared with placebo. SBP was statistically significantly reduced compared to placebo by -4.1 mmHg (placebo-adjusted, P=0.0231) in patients randomized to 10 mg of empagliflozin and by -4.8 mmHg (placebo-corrected, P=0.0028) in patients randomized to 25 mg of empagliflozin.[23] The safety and efficacy of empagliflozin was evaluated in an active-control study versus glimepiride (in combination with metformin). The study was a double-blind, active-controlled, non-inferiority design of patients with type 2 DM inadequately controlled on metformin monotherapy (N=1,545). At week 52, empagliflozin 25 mg daily meet the non-inferiority criteria for lowering HbA_{1c} compared to glimepiride (-0.7% vs. -0.7%). There was a greater reduction in FPG and body weight with empagliflozin 25 mg compared to glimepiride; however the significance was not reported (-19 mg/dL vs. -9 mg/dL and -3.9 kg vs. 2 kg; P values not reported). SBP at week 52 was also statistically significantly reduced compared to glimepiride (-3.6 mmHg vs. 2.2 mmHg; P<0.0001).[24]

A non-inferiority study comparing canagliflozin to sitagliptin found that when added to patients not adequately controlled with metformin and a sulfonylurea the 100 mg dose of canagliflozin was non-inferior to sitagliptin 100 mg in HbA_{1c} decrease from baseline. The canagliflozin 300 mg dose was found to a have a significantly greater decrease in HbA_{1c} from baseline. Select secondary endpoints including decreases in FPG, systolic blood pressure and weight also favored both canagliflozin doses. However, there were no significant differences documented between the groups in other secondary endpoints (proportion of patients achieving HbA_{1c} goals, triglycerides).[25]

Treatment with dapagliflozin plus sitagliptin resulted in a significantly greater reduction in HbA_{1c} from baseline to week 24 compared to placebo plus sitagliptin (-0.5 vs 0.1; P<0.0001). Similarly, treatment with dapagliflozin, sitagliptin and metformin combination therapy resulted in a significantly greater reduction in HbA_{1c} compared to the placebo, sitagliptin and metformin group (-0.4 vs -0.0; P<0.0001).[26] When combined with insulin ± another oral antidiabetic, dapagliflozin resulted in a significant decrease from baseline to week 24 in HbA1c across all doses compared to placebo plus insulin (-0.79, -0.89 and -0.96 for dapagliflozin 2.5, 5 and 10 mg, respectively, compared to -0.39 for placebo; P<0.001 for all).[27]

The safety and efficacy of empagliflozin added to metformin and a sulfonylurea was evaluated in a double-blind, placebo-controlled study of patients with type 2 DM inadequately controlled on at least 1,500 mg of metformin per day and a sulfonylurea (N=666). At week 24, empagliflozin 10 mg or 25 mg

daily provided statistically significant reductions in HbA_{1c} (-0.8% and -0.8% vs. -0.2%, respectively; P<0.0001 for both comparisons), FPG (-23 mg/dL and -23 mg/dL vs. 6 mg/dL, respectively; P values not reported) and body weight (-2.9 kg and -3.2 kg vs. -0.5 kg, respectively; P<0.001 for both comparisons) compared with placebo.[28] At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in HbA_{1c} compared to placebo (-0.6% and -0.7% vs. -0.1%, respectively; P<0.0001 for both comparisons) when used in conjunction with pioglitazone ± metformin.[29] The safety and efficacy of empagliflozin added to insulin with or without metformin and/or sulfonylureas was evaluated in an unpublished double-blind, placebo-controlled, study of patients with type 2 DM in inadequately controlled with basal insulin (e.g., insulin glargine, insulin detemir, NPH), with or without metformin and/or sulfonylureas. Insulin dose was fixed through the first 18 weeks of the study; however, it could be adjusted through the remaining 60 weeks (N=494). At weeks 18 and 78, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} (-0.6% and -0.7% vs. 0%, respectively for the week 18 endpoint and -0.4% and -0.6% vs. 0.1%, respectively for the week 78 endpoint; P<0.0001 for all comparisons), FPG (-17.9 mg/dL and -19.1 mg/dL vs. 10.4 mg/dL, respectively; P<0.001, for the week 18 endpoint, and -10.1 mg/dL and -15.2 mg/dL vs. 2.8 mg/dL, respectively; P=0.049 and P<0.001, respectively, for the week 78 endpoint) and body weight (-1.8 kg and -1.4 kg vs. -0.1 kg, respectively; P=0.0052 and P=0.0463 for the week 18 endpoint, and -2.4 kg and -2.4 kg vs. 0.7 kg; P<0.001 for both comparisons for the week 78 endpoint) compared with placebo.[30]

The safety and efficacy of empagliflozin added to linagliptin was evaluated in a 52 week double-blind, active-control, randomized trial. A total of 686 patients with type 2 diabetes who were on a stable dose of metformin were randomized 1:1:1:1:1 to receive empagliflozin/linagliptin (10/5 mg or 25/5 mg) or one of the individual components (empagliflozin 10 or 25 mg or linagliptin 5 mg). The primary endpoint, change from baseline in HbA_{1c} at week 24 was significantly improved in the combination groups compared with the individual component groups (P<0.001). Treatment with the combination product also provided a significant improvement in body weight (P<0.0001) compared to linagliptin alone. There was no difference in body weight when the combination products were compared to empagliflozin alone.[31] Another study evaluated empagliflozin added to linagliptin as initial therapy. The design was similar to the metformin add-on study where the combination was compared to the individual components. This study concluded that reductions from baseline in HbA_{1c} was significantly greater when compared with individual linagliptin and empagliflozin 10 mg, but empagliflozin 25 mg/linagliptin 5 mg did not show a statistically significant difference compared with empagliflozin alone (P=0.179).[32]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Monotherapy				
Stenlof et al[9] DIA3005 Canagliflozin 100 mg QD vs canagliflozin 300 mg QD vs placebo Patients received metformin rescue if FPG was >270 mg/dL after day 1 to week 6; >240 mg/dL after week 6 to week 12; or >200 mg/dL after week 12 to week 26. A substudy was conducted for patients with hyperglycemia. These patients were not allowed to receive placebo. Following completion of the study, patients randomized to receive placebo were transitioned	AC, DB, MC, PC, RCT Patients ≥18 and <80 years of age with T2DM, FPG <270 mg/dL and no antihyperglycemic therapy and an HbA_{1c} ≥7.0 and <10.0% or prior metformin plus sulfonylurea combination therapy and an HbA_{1c} ≥6.5 and <9.5%	N=584 (N=91 enrolled in the hyper-glycemic substudy) 26 weeks followed by a 26 week ES using active control (sitagliptin)	Primary: Change in HbA_{1c} level from baseline to week 26 Secondary: Proportion of patients with HbA_{1c} <7.0%, change in FPG, PPG and systolic blood pressure, percent change in body weight, triglyceride level, HDL-C, apolipoprotein B and safety endpoints	Primary: At the end of treatment, the 100 and 300 mg QD doses resulted in a statistically significant improvement in HbA_{1c} (-1.03 and -0.77 vs 0.14%, respectively; P<0.001 for both doses) compared to placebo. Secondary: Both doses also resulted in a greater proportion of patients achieving an HbA_{1c} <7.0% (45 and 62 vs 21%, respectively; P<0.01), significant reductions of FPG (-27 and -35 vs 8 mg/dL, respectively; P<0.01), significant reductions of PPG (-43 and -59 vs 5 mg/dL, respectively; P<0.01), and in percent body weight reduction compared to placebo (-2.8 and -3.9 kg, respectively; P<0.01). From baseline, with the 100 and 300 mg doses, there were decreases in systolic blood pressure (-3.7 and -5.4 mm Hg, respectively) and increases in HDL-C (11.2 and 10.6 vs 4.5 mg/dL, respectively; P<0.01) relative to placebo. There was also a significantly smaller increase from baseline in triglycerides, including a decrease with the 300 mg dose (2.5 and -2.3 vs 7.9 mg/dL, respectively; P<0.01). In a subset of patients with samples sufficient for analysis (n=349), greater increases in apolipoprotein B levels were seen with canagliflozin 100 (1.2%) and 300 mg (3.5%) than with placebo (0.9%). Urinary tract infections, genital mycotic infections, and adverse events related to osmotic diuresis and reduced intravascular volume occurred at higher rates with both doses of canagliflozin than with placebo. The incidence of documented hypoglycemic episodes prior to rescue therapy was similar between the treatment groups (canagliflozin 100 mg, 3.6%; canagliflozin 300 mg, 3.0%; placebo, 2.6%), and no severe hypoglycemic episodes were reported. Efficacy was maintained throughout the 52 week study period and the adverse

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
to therapy with sitagliptin.				event profile was similar through the 26 week extension period of the study.
Bode et al[10] (abstract) Canagliflozin 100 mg QD vs canagliflozin 300 mg QD vs placebo	DB, MC, PC, RCT Patients 55 to 80 years of age with T2DM, an HbA_{1c} ≥7.0 and <10% despite treatment with blood glucose lowering therapy	N=716 26 weeks	Primary: Change in HbA_{1c} level from baseline to week 26 Secondary: Proportion of patients with HbA_{1c} <7.0%, change in FPG, and systolic blood pressure, percent change in body weight, triglyceride level, and HDL-C	Primary: At 26 weeks, significant reductions in HbA_{1c} were observed in all canagliflozin treatment groups compared placebo (-0.60 and -0.73% for canagliflozin 100 and 300 mg QD respectively vs -0.03% for placebo; P<0.001 for all doses). Secondary: At 26 weeks, a greater proportion of patients achieved an HbA_{1c} <7.0% with canagliflozin compared to placebo (percent not reported; P<0.001) At week 26, greater reductions in FPG, systolic blood pressure, and increased HDL-C levels were observed with canagliflozin vs placebo (P< 0.001).
Ferranini et al[11] Dapagliflozin 2.5 mg QD vs dapagliflozin 5 mg QD vs dapagliflozin 10 mg QD vs placebo Patients were divided into	DB, MC, PC, PG, RCT Patients with T2DM, 18 to 77 years of age, who were treatment naïve with inadequately controlled blood sugar, BMI ≤45 kg/m^2 and fasting C-peptide ≥1.0 ng/mL	N=485 24 weeks	Primary: Change from baseline in HBA_{1c} Secondary: Change from baseline in FPG and body weight and safety assessments	Primary: At week 24, dapagliflozin 5 and 10 mg QAM provided significant improvements in HbA_{1c} compared to placebo (0.8%, -0.9% vs -0.2%, respectively; P<0.05 for 5 and 10 mg comparisons). Secondary: Change in FPG (-24.1 and -28.8 vs -4.1 mg/dL, respectively) from baseline was also significantly greater in the 5 and 10 mg QAM comparison compared to placebo (P<0.05 for both comparisons). Changes in HbA_{1c} and FPG for the 2.5 mg arm and changes in weight for all three comparisons also favored the treatment arm; however differences were not considered significant. In both exploratory cohorts (QAM dosing and high HbA_{1c}), dapagliflozin had greater reductions in primary and secondary analyses compared to placebo. However, in the high HbA_{1c} cohort the reduction compared to placebo was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QAM and QPM dosing cohorts. In addition, those with HbA_{1c} >10.0 and ≤12.0% were evaluated separately in a high HBA1c cohort. The QAM dosing cohort was used for evaluation of primary and secondary endpoints.				considered numerically greater. Treatment with dapagliflozin did not result in any clinically meaningful changes from baseline in serum electrolytes, serum albumin or renal function. Signs, symptoms, and other reports suggestive of urinary tract infections and genital infection were more frequently noted in the dapagliflozin arms. There were no major episodes of hypoglycemia.
Bailey et al[12] Dapagliflozin 1 mg QD vs dapagliflozin 2.5 mg QD vs dapagliflozin 5 mg QD vs placebo	DB, MC, PC, PG, RCT Patients with T2DM, 18 to 77 years of age, who were treatment naïve with inadequately controlled blood sugar, BMI ≤45 kg/m^2 and fasting C-peptide ≥0.34 ng/mL	N=282 24 weeks	Primary: Change from baseline in HbA_{1c} Secondary: Change from baseline in FPG and body weight, glucose after two hour liquid meal, percentage of patients with HbA_{1c} <7.0% and safety assessments	Primary: At week 24, dapagliflozin 1, 2.5 and 5 mg QD provided significant improvements in HbA_{1c} compared to placebo (-0.7%, -0.7%, -0.8% vs 0.2%, respectively; P<0.05 for all comparisons). Secondary: Changes in FPG and body weight and glucose after two hour liquid meal were significantly lower in the dapagliflozin arms compared to placebo (P<0.05 for all comparisons). The change in percentage of patients with HbA_{1c} <7.0% was greater in the dapagliflozin arms; however only the 1 mg QD arm was considered significantly greater than placebo (53.6 vs 24.6%, respectively; P<0.05). No major episodes of hypoglycemia were reported during the study, and frequency of minor episodes was similar for dapagliflozin and placebo groups. No clinically meaningful changes were observed in serum electrolytes, serum albumin, or renal function parameters.
Henry et al[13] Dapagliflozin 5 or 10 mg QD vs metformin extended-release titrated to 2,000	AC, DB, MC, PG, RCT Patients with T2DM, 18 to 77 years of age, who were treatment naïve with inadequately	N=598 for Study 1, N=638 for Study 2 2 trials each 24 weeks in duration	Primary: Change from baseline in HbA_{1c} Secondary: Change from baseline in FPG and body weight, glucose after two	Primary: Combination therapy led to significantly greater reductions in HbA_{1c} compared to either monotherapy (dapagliflozin and metformin) in the first study (-2.0 vs -1.2 and -1.4%, respectively; P<0.0001) and second study (-2.0 vs -1.5 and -1.4%, respectively; P<0.0001). In Study 2, treatment with dapagliflozin 10 mg (as monotherapy) was also non-inferior to metformin (as monotherapy) for reduction of HbA_{1c}.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg daily vs dapagliflozin 5 or 10 mg QD and metformin titrated to 2,000 mg daily Dapagliflozin was dosed at 5 mg QD and 10 mg QD in the first and second trials, respectively.	controlled blood sugar, BMI ≤45 kg/m^2 and fasting C-peptide ≥0.34 ng/mL		hour liquid meal, percentage of patients with HbA_{1c} <7.0% and safety assessments	Secondary: Combination therapy was statistically superior to monotherapy in reduction of FPG (P<0.0001 for both studies); combination therapy was more effective than metformin for weight reduction (P<0.0001). Events suggestive of genital infection were reported in 6.7, 6.9 and 2.0% (Study 1) and 8.5, 12.8 and 2.4% (Study 2) of patients in combination, dapagliflozin and metformin groups; events suggestive of urinary tract infection were reported in 7.7, 7.9 and 7.5% (Study 1) and 7.6, 11.0 and 4.3% (Study 2) of patients in the respective groups. No major hypoglycemia was reported.
Roden et al[14] Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs sitagliptin 100 mg QD vs placebo	AC, DB, MC, PC, RCT Patients with type 2 DM and HbA_{1c} of ≥7% to <10%,	N=986 24 weeks	Primary: HbA_{1c} Secondary: FPG, body weight, SBP and safety evaluations	Primary: At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} compared to placebo (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons) . In the active comparator analysis, adjusted mean differences in change from baseline HbA_{1c} at week 24 was -0.73% (-0.88 to -0.59; P<0.0001) for sitagliptin compared to placebo. Secondary: At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in FPG (-19 mg/dL and -25 mg/dL vs. 12 mg/dL, respectively; P values not reported) and body weight (-2.8 kg and -3.2 kg vs. -0.4 kg, respectively; P values not reported) compared with placebo. SBP was statistically significantly reduced compared to placebo by -2.6 mmHg (placebo-adjusted, P=0.0231) in patients randomized to 10 mg of empagliflozin and by -3.4 mmHg (placebo-corrected, P=0.0028) in patients randomized to 25 mg of empagliflozin. There were 140 (61%) patients in the placebo group that reported adverse events (four [2%] severe and six [3%] serious), as did 123 (55%) patients in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				empagliflozin 10 mg group (eight [4%] severe and eight [4%] serious), 135 (60%) patients in the empagliflozin 25 mg group (seven [3%] severe and five [2%] serious), and 119 (53%) patients in the sitagliptin group (five [2%] severe and six [3%] serious).
Barnett et al[15] Empagliflozin 10 mg QD vs. empagliflozin 25 mg QD vs placebo Patients with Stage III chronic kidney disease (eGFR ≥ <60 mL/min/1.73 m2] were only assigned to the empagliflozin 25 mg QD arm.	DB, MC, PC, PG, RCT Patients with type 2 DM, HbA_{1c} of ≥7% to <10%, BMI ≤45 kg/m^2 and a baseline eGFR <90 mL/min/1.73 m^2	N=738; 290 with mild renal impairment [eGFR ≥60 to <90 mL/min/1.73 m^2], 374 with moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m^2], and 74 with severe renal impairment [eGFR <30 mL/min/1.73 m^2]). 52 weeks	Primary: HbA_{1c} Secondary: FPG, body weight, SBP and safety evaluations	Primary: At week 24, empagliflozin 25 mg provided statistically significant reduction in HbA_{1c} relative to placebo in patients with mild to moderate renal impairment (-0.5% placebo-corrected comparison; P<0.0001). The glucose lowering efficacy decreased with decreasing level of renal function in the mild to moderate range. For patients with severe renal impairment, the analyses of changes in HbA_{1c} and FPG showed no discernible treatment effect compared to placebo. Secondary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG in the mild renal impairment group (-13.86 mg/dL and –18 mg/dL vs. 5.58 mg/dL, respectively; P<0.0001) and moderate renal impairment group (-9 mg/dL vs. 10.8 mg/dL, respectively; P<0.0001). Significant body weight and SBP decreases were noted in most treatment comparisons. Adverse events included UTI and genital mycotic infections.
Add-on Therapy				
Rosenstock et al[16] Canagliflozin 50 mg QD vs canagliflozin 100 mg QD	DB, MC, PC, RCT Patients 18 to 65 years of age with T2DM, an HbA_{1c} ≥7.0 and <10.5%, were on	N=451 12 weeks	Primary: Change in HbA_{1c} level from baseline to week 12 Secondary:	Primary: At 12 weeks, significant reductions in HbA_{1c} were observed in all canagliflozin treatment groups compared placebo (-0.79, -0.76, -0.70, -0.92, -0, and -0.95% for canagliflozin 50, 100, 200, and 300 mg QD and 300 mg BID, respectively, vs -0.22% for placebo; P<0.001 for all doses). At 12 weeks, significant reductions in HbA_{1c} were observed with sitagliptin 100

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs canagliflozin 200 mg QD vs canagliflozin 300 mg QD vs canagliflozin 300 mg BID vs sitagliptin 100 mg QD vs placebo	metformin monotherapy at a stable (≥3 months) dose of ≥1,500 mg/day, had a stable body weight and BMI 25 to 45 kg/m^2 (24 to 45 kg/m^2 for those of Asian descent), and had serum creatinine <1.5 mg/dL for men and <1.4 mg/dL for women		Change in FPG, change in body weight, and overnight urinary glucose -to-creatinine ratio	mg compared to placebo (-0.74 vs -0.22%; P<0.001). Secondary: At 12 weeks, a greater proportion of patients achieved the target HbA_{1c} <7.0% with canagliflozin doses of 100 mg QD and above (53 to 72%) and with sitagliptin (65%) compared to placebo (34%; P<0.05 for canagliflozin and sitagliptin). Significantly greater reductions in FPG were observed at 12 weeks with all canagliflozin doses (-16.2 to -27.0 mg/dL) compared to an increase observed with placebo (3.6 mg/dL; P<0.001 for all doses). FPG reductions were maximized with the 200 mg QD dose. Sitagliptin reduced FPG -12.6 mg/dL (P value compared to placebo not reported). Significant weight reductions were observed in canagliflozin groups relative to placebo, -2.3 to -3.4% (-2.0 to -2.9 kg; P<0.001 for all doses) at week 12. Reductions observed in the placebo and sitagliptin treatment groups were -1.1% (-0.8 kg) and -0.6% (-0.4 kg) from baseline, respectively. All doses of canagliflozin increased the overnight urinary glucose-to-urinary creatinine ratio (35.4 to 61.6 mg/mg) as compared to placebo (1.9 mg/mg; P<0.001 for all doses). Sitagliptin reduced urinary glucose-to-urinary creatinine ratio -1.9 mg/mg (P value compared to placebo not reported).
Nauck et al[17] Dapagliflozin 10 mg QD vs glipizide 10 mg BID Studied agent added on to OL dosed metformin.	AC, DB, MC, PG, RCT Patients with T2DM, ≥18 years of age, who were previously treated with oral anti-diabetic agents, inadequately controlled blood sugar, BMI ≤45	N=801 52 weeks	Primary: Change from baseline in HbA_{1c} Secondary: Change from baseline in body weight, percentage of patients who lost >5% of body weight,	Primary: At week 52, both dapagliflozin plus metformin and glipizide plus metformin therapies had identical $HbA1_c$ reductions of 0.52% which met the criteria for non-inferiority. Secondary: Treatment with dapagliflozin resulted in weight loss of -3.22 kg vs weight gain of 1.44 kg with glipizide. Other secondary endpoints including percentage of patients who lost >5% of body weight and percentage of patients with ≥1 hypoglycemic event also favored dapagliflozin (P<0.001). Mean systolic blood pressure was reduced with dapagliflozin but not with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	kg/m^2 and fasting C-peptide ≥0.34 ng/mL		percentage of patients with ≥1 hypoglycemic event and systolic blood pressure changes	glipizide at 208 weeks (in an extension cohort): difference, −3.67 mmHg (95% CI, −5.92 to −1.41).
Bailey et al[18] Dapagliflozin 2.5 mg QD vs dapagliflozin 5 mg QD vs dapagliflozin 10 mg QD vs placebo	DB, MC, PC, PG, RCT Patients 18 to 77 years of age with T2DM with a HbA_{1c} of 7.0 to 10.0% who have been on a stable dose of metformin (≥1,500 mg/day) for ≥8 weeks	N=546 24 weeks	Primary: Change in HbA_{1c} from baseline at week 24 Secondary: Change in fasting blood glucose and weight from baseline at week 24	Primary: Treatment with dapagliflozin 2.5, 5 or 10 mg plus metformin resulted in a significantly greater reduction from baseline to week 24 in HbA_{1c} compared to placebo plus metformin (-0.67, -0.70 and -0.84 for dapagliflozin 2.5, 5 and 10 mg, respectively, compared to -0.30 for placebo; P<0.05 for all). Secondary: Treatment with dapagliflozin 2.5, 5 or 10 mg plus metformin resulted in significantly greater reductions from baseline to week 24 in fasting blood glucose and weight compared to the placebo group (P<0.05 for all).
Bailey et al[19] Dapagliflozin 2.5 mg QD vs dapagliflozin 5 mg QD vs dapagliflozin 10 mg QD vs	DB, ES, MC, PC, PG, RCT Patients 18 to 77 years of age with T2DM with a HbA_{1c} of 7.0 to 10.0% who have been on a stable dose of metformin (≥1,500 mg/day) for ≥8 weeks	N=546 102 weeks	Primary: Change in HbA_{1c} from baseline at week 102 Secondary: Change in fasting blood glucose and weight from baseline at week 102	Primary: Treatment with dapagliflozin 2.5, 5 or 10 mg plus metformin resulted in significantly greater reductions from baseline to week 102 in HbA_{1c} compared to placebo (-0.48, -0.58 and -0.78 for dapagliflozin 2.5, 5 and 10 mg, respectively, compared to 0.02 for placebo; P=0.008 for dapagliflozin 2.5 mg vs placebo and P<0.0001 for dapagliflozin 5 and 10 mg vs placebo). Secondary: Patients treated with all doses of dapagliflozin achieved sustained reductions in fasting blood glucose (-1.07 to -1.47) and weight (-1.10 to -1.74) at week 102 compared to increases in fasting blood glucose and weight in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				
Bolinder et al[20] Dapagliflozin 10 mg QD vs placebo	DB, MC, PC, PG, RCT Diabetic patients	N=182 24 weeks	Primary: Change in total body weight from baseline at week 24 Secondary: Change in waist circumference and dual-energy x-ray absorptiometry total-body fat mass from baseline at week 24, proportion of patients achieving body weight reduction of ≥5% at week 24	Primary: Treatment with dapagliflozin plus metformin resulted in a placebo-corrected reduction in total body weight of -2.08 kg at week 24 (95% CI, -2.84 to -1.31; P<0.0001). Secondary: Treatment with dapagliflozin plus metformin resulted in placebo-corrected reductions in waist circumference and dual-energy x-ray absorptiometry total-body fat mass of -1.52 cm (95% CI, -2.74 to -0.31; P=0.0143) and -1.48 kg (95% CI, -2.22 to -0.74; P=0.0001), respectively, at week 24. The placebo-corrected proportion of patients treated with dapagliflozin plus metformin who achieved ≥5% weight reduction was 26.2% (95% CI, 15.5 to 36.7; P<0.0001).
Strojek et al[21] Dapagliflozin 2.5 mg QD vs dapagliflozin 5 mg QD vs dapagliflozin 10 mg QD vs	DB, MC, PC, PG, RCT Patients ≥18 years of age with T2DM with a HbA_{1c} of 7.0 to 10.0% and a fasting blood glucose ≤15 mmol/L who were stabilized on a sulfonylurea monotherapy	N=596 24 weeks	Primary: Change in HbA_{1c} from baseline at week 24 Secondary: Change in fasting blood glucose and weight from baseline at week 24	Primary: Compared to placebo plus glimepiride, treatment with dapagliflozin in combination with glimepiride resulted in a significantly greater reduction in HbA_{1c} from baseline to week 24 across all dapagliflozin treatment arms (-0.58, -0.63 and -0.82 for dapagliflozin 2.5, 5 and 10 mg, respectively, compared to -0.13 for placebo; P<0.0001 for all). Secondary: Compared to placebo plus glimepiride, treatment with dapagliflozin 5 and 10 mg in combination with glimepiride resulted in a significantly greater reduction in fasting blood glucose from baseline to week 24 (-1.18 and -1.58 for dapagliflozin 5 and 10 mg, respectively, compared to -0.11 for placebo; P<0.0001 for both). Treatment with dapagliflozin 2.5 mg plus glimepiride did not result in a significantly greater reduction in fasting blood glucose compared

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	dose at least half the maximal recommended dose for ≥8 weeks			to placebo plus glimepiride. Patients treated with dapagliflozin 5 or 10 mg plus glimepiride achieved significantly greater reductions in weight from baseline to week 24 compared to placebo plus glimepiride (-1.56 and -2.26 for dapagliflozin 5 and 10 mg, respectively, compared to -0.72 for placebo; P<0.01 and P<0.0001, respectively). Treatment with dapagliflozin 2.5 mg plus glimepiride did not result in a significantly greater reduction in weight compared to placebo plus glimepiride.
Rosenstock et al[22] Dapagliflozin 5 mg QD vs dapagliflozin 10 mg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with T2DM with a HbA_{1c} of 7.0 to 10.5% who were treatment naïve or who had previously received metformin, a sulfonylurea or pioglitazone	N=420 24 weeks plus 24-week extension trial	Primary: Change in HbA_{1c} from baseline at week 24 Secondary: Change from baseline at week 24 in FPG, two-hour PPG and weight	Primary: Treatment with dapagliflozin plus pioglitazone resulted in significantly greater reductions in HbA_{1c} from baseline to week 24 compared to placebo plus pioglitazone (-0.82 and -0.97 for dapagliflozin 5 mg and 10 mg, respectively; P=0.0007 and P<0.0001, respectively). Secondary: Treatment with dapagliflozin 5 or 10 mg plus pioglitazone resulted in significantly greater reductions in FPG, two hour PPG and weight from baseline to week 24 (P<0.0001 for all).
Häring et al[23] Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs placebo	DB, MC, PC, RCT Patients with type 2 DM and HbA_{1c} of ≥7% to <10%,inade-quately controlled on ≥ 1,500 mg of metformin per day	N=637 24 weeks	Primary: HbA_{1c} Secondary: FPG, body weight, SBP and safety evaluations	Primary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in HbA_{1c} compared to placebo (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons). Secondary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG (-20 mg/dL and -22 mg/dL vs. 6 mg/dL, respectively; P values not reported) and body weight (-2.5 kg and -2.9 kg vs. -0.5 kg, respectively; P<0.001 for both comparisons) compared with placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients continued treatment with metformin.				SBP was statistically significantly reduced compared to placebo by -4.1 mmHg (placebo-adjusted, P=0.0231) in patients randomized to 10 mg of empagliflozin and by -4.8 mmHg (placebo-corrected, P=0.0028) in patients randomized to 25 mg of empagliflozin. Confirmed hypoglycemic adverse events were reported in 0.5%, 1.8%, and 1.4% of patients receiving placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Events consistent with urinary tract infections were reported in 4.9%, 5.1%, and 5.6% of patients, and events consistent with genital infections were reported in 0%, 3.7%, and 4.7% of patients, respectively.
Ridderstråle et al[24] empagliflozin 25 mg QD vs glimepiride 1 to 4 mg QD Patients continued treatment with metformin.	AC, DB, MC, RCT Patients with type 2 DM and HbA_{1c} of ≥7% to <10%, inadequately controlled on metformin monotherapy	N=1,545 104 weeks	Primary: HbA_{1c} (tested for non-inferiority at week 52, tested for superiority at week 104) Secondary: FPG, body weight, SBP and safety evaluations	Primary: At week 52, empagliflozin 25 mg meet the non-inferiority criteria for lowering HbA_{1c} compared to glimepiride (-0.7% vs -0.7%). Non-inferiority continued to be demonstrated at week 104. In addition, at week 104, adjusted mean difference in change from baseline in HbA1c with empagliflozin versus glimepiride was -0.11% (95% CI, -0.19 to -0.02; P=0.0153 for superiority). Secondary: At week 52, There was a greater reduction in FPG and body weight with empagliflozin 25 mg compared to glimepiride; however the significance was not reported (-19 mg/dL vs. -9 mg/dL and -3.9 kg vs 2 kg; P values not reported). SBP was also statistically significantly reduced compared to glimepiride (-3.6 mmHg vs. 2.2 mmHg; P<0.0001).[1,5] Adverse events were reported in 661 (86%) patients treated with empagliflozin and 673 (86%) patients treated with glimepiride. Severe adverse events were reported in 72 (9%) patients in the empagliflozin group and 68 (9%) in the glimepiride group. Serious adverse events were reported in 119 (16%) patients in the empagliflozin group and 89 (11%) in the glimepiride group. Confirmed hypoglycemic adverse events (plasma glucose ≤3·9 mmol/L or requiring assistance) at week 104 were reported in 19 (2%) patients treated with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				empagliflozin and 189 (24%) patients treated with glimepiride.
Triple Combination Therapy				
Schernthaner et al[25] (abstract) Canagliflozin 300 mg QD vs sitagliptin 100 mg QD vs placebo	AC, DB, RCT Patients with T2DM, receiving a stable dose of metformin and a sulfonylurea	N=755 52 weeks	Primary: Change in HbA_{1c} level from baseline to week 52 Secondary: Change in FPG, systolic blood pressure, body weight, triglycerides, and HDL-C	Primary: At the end of the 52 treatment period, canagliflozin 300 mg once daily was considered non-inferior to and produced significant reductions in HbA_{1c} compared to sitagliptin 100 mg QD (-1.03 and -0.66%; difference, 0.37%; 95% CI, -0.50 to -0.25). Secondary: At week 52, greater reductions in FPG, body weight, and systolic blood pressure were observed with canagliflozin vs sitagliptin (P<0.001).
Jabbour et al[26] Dapagliflozin 10 mg QD ± metformin vs placebo ± metformin Patients taking metformin received doses ≥1,500 mg/day.	DB, MC, PC, PG, RCT Patients aged ≥18 years with T2DM with a HbA1c of 7.0 to 10.5% who were treatment naïve or who had previously received metformin, sitagliptin, vitagliptin or a combination	N=432 24 weeks	Primary: Change in HbA_{1c} from baseline at week 24 Secondary: Change from baseline at week 24 in fasting blood glucose, two-hour PPG and weight	Primary: Treatment with dapagliflozin plus sitagliptin resulted in a significantly greater reduction in HbA_{1c} from baseline to week 24 compared to placebo plus sitagliptin (-0.5 vs 0.1; P<0.0001). Similarly, treatment with dapagliflozin, sitagliptin and metformin combination therapy resulted in a significantly greater reduction in HbA_{1c} compared to the placebo, sitagliptin and metformin group (-0.4 vs -0.0; P<0.0001). Secondary: Treatment with dapagliflozin plus sitagliptin and dapagliflozin, sitagliptin and metformin resulted in significantly greater reductions from baseline to week 24 in fasting blood glucose, two hour PPG and weight compared to their respectively placebo comparator groups (P<0.0001 for all).
Wilding et al[27] Dapagliflozin 2.5 mg QD ± oral antidiabetic agent	DB, MC, PC, PG, RCT Patients 18 to 80 years of age with	N=800 24 weeks plus 24-week extension	Primary: Change in HbA_{1c} from baseline at week 24	Primary: Treatment with dapagliflozin plus insulin resulted in a significant decrease from baseline to week 24 in HbA_{1c} across all doses compared to placebo plus insulin (-0.79, -0.89 and -0.96 for dapagliflozin 2.5, 5 and 10 mg, respectively, compared to -0.39 for placebo; P<0.001 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs dapagliflozin 5 mg QD ± oral antidiabetic agent vs dapagliflozin 10 mg QD ± oral antidiabetic agent vs placebo	T2DM, BMI ≤45 kg/m^2 and a HbA_{1c} of 7.5 to 10.5% who are stabilized on an insulin regimen of >30 IU/day for ≥8 weeks ± other oral antidiabetic agents	trial	Secondary: Change from baseline to week 24 in fasting blood glucose, insulin dose and weight	Secondary: Treatment with dapagliflozin 2.5, 5 or 10 mg plus insulin resulted in significantly greater reductions from baseline to week 24 in fasting blood glucose, insulin dose and weight compared to placebo (P<0.001 for all).
Häring et al[28] Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs placebo Patients continued treatment with metformin and sulfonylurea.	DB, MC, PC, RCT Patients aged ≥18 years with type 2 DM and HbA_{1c} of ≥7% to <10%, inadequately controlled on ≥ 1,500 mg of metformin per day and a sulfonylurea	N=666 24 weeks	Primary: HbA_{1c} Secondary: FPG, body weight, SBP and safety evaluations	Primary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in HbA_{1c} compared to placebo (-0.8% and -0.8% vs. -0.2%, respectively; P<0.0001 for both comparisons). Secondary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG (-23 mg/dL and -23 mg/dL vs. 6 mg/dL, respectively; P values not reported) and body weight (-2.9 kg and -3.2 kg vs. -0.5 kg, respectively; P<0.001 for both comparisons) compared with placebo. Decreases in SBP were also significantly greater with both empagliflozin doses than placebo. Adverse events were reported in 62.7, 67.9, and 64.1% of patients on placebo and empagliflozin 10 and 25 mg, respectively. Events consistent with urinary tract infection were reported in 8.0, 10.3, and 8.3% of patients on placebo and empagliflozin 10 and 25 mg, respectively (females: 13.3, 18.0, and 17.5%, respectively; males: 2.7, 2.7, and 0%, respectively). Events consistent with genital infection were reported in 0.9, 2.7, and 2.3% of patients on placebo and empagliflozin 10 and 25 mg, respectively (females: 0.9, 4.5, and 3.9%, respectively; males: 0.9% in each group).
Kovacs et al[29]	DB, MC, PC, RCT	N=498	Primary: HbA_{1c}	Primary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs placebo Patients continued treatment with pioglitazone with or without metformin.	Patients with type 2 DM and HbA_{1c} of ≥7% to <10%, inadequately controlled on pioglitazone 30 mg per day, with or without metformin ≥1,500 mg per day	24 weeks	Secondary: FPG, body weight, SBP and safety evaluations	reductions in HbA_{1c} compared to placebo (-0.6% and -0.7% vs. -0.1%, respectively; P<0.0001 for both comparisons). Secondary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG (-17 mg/dL and -22 mg/dL vs. 7 mg/dL, respectively; P<0.001) and body weight (-2.0 kg and -1.8 kg vs. -0.6 kg, respectively; P<0.001) compared with placebo. Adverse events were reported in 661 (86%) patients treated with empagliflozin and 673 (86%) patients treated with glimepiride. Severe adverse events were reported in 72 (9%) patients in the empagliflozin group and 68 (9%) in the glimepiride group. Serious adverse events were reported in 119 (16%) patients in the empagliflozin group and 89 (11%) in the glimepiride group. Confirmed hypoglycemic adverse events (plasma glucose ≤3·9 mmol/L or requiring assistance) at week 104 were reported in 19 (2%) patients treated with empagliflozin and 189 (24%) patients treated with glimepiride. Similar proportions of patients reported adverse events with empagliflozin (67.3-71.4%) and placebo (72.7%). Confirmed hypoglycemia was reported by 1.2-2.4% of patients on empagliflozin and 1.8% on placebo.
Rosenstock et al[30] Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs placebo Members used fixed insulin dosing through the	DB, MC, PC, RCT Patients with type 2 DM in inadequately controlled with basal insulin (e.g., insulin glargine, insulin detemir, NPH), with or without metformin and/or sulfonylureas.	N=494 78 weeks	Primary: HbA_{1c} Secondary: FPG, body weight, SBP and safety evaluations	Primary: At weeks 18 and 78, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} compared to placebo (-0.6% and -0.7% vs 0%, respectively for the week 18 endpoint and -0.4% and -0.6% vs. 0.1%, respectively for the week 78 endpoint; P<0.0001 for all comparisons). Secondary: At weeks 18 and 78, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in FPG (-17.9 mg/dL and -19.1 mg/dL vs 10.4 mg/dL, respectively; P<0.001, for the week 18 endpoint, and -10.1 mg/dL and -15.2 mg/dL vs 2.8 mg/dL, respectively; P=0.049 and P<0.001, respectively for the week 78 endpoint) and body weight (-1.8 kg and -1.4 kg vs -0.1 kg, respectively; P=0.0052 and P=0.0463 for the week 18 endpoint, and -2.4 kg and -2.4 kg vs 0.7 kg; P<0.001 for both comparisons for the week 78 endpoint) compared with placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
first 18 weeks of the study period; however this could be adjusted through the final 60 weeks.				SBP also decreased from baseline to week 78 with empagliflozin 10 mg or 25 mg QD compared to placebo (-4.1 mmHg and -2.4 mmHg vs 0.1 mmHg; P<0.01 for the 10 mg comparison, P value not significant for the 25 mg comparison). Confirmed hypoglycemic adverse events were reported in 33 patients (20%), 44 (28%), and 35 (21%) in the empagliflozin 10 mg, 25 mg and placebo groups, respectively. At week 78, confirmed hypoglycemic adverse events were reported in similar proportions of patients receiving placebo and empagliflozin. Events consistent with UTI or genital infection at week 78 were reported by more patients receiving empagliflozin than placebo.
DeFronzo et al[31] Empagliflozin/linagliptin 25 mg/5 mg vs empagliflozin/linagliptin 10 mg/5 mg vs empagliflozin 25 mg vs empagliflozin 10 mg vs linagliptin 5 mg All recipients received the	AC, DB, MC, PG, RCT Patients aged ≥18 years with a HbA_{1c} of >7% to <10.5% and treated with immediate-release metformin ≥1,500 mg per day at an unchanged dose for ≥12 weeks prior to initiation hesitant	N=686 52 weeks (primary endpoint at 24 weeks)	Primary: Change from baseline at week 24 in HbA_{1c} Secondary: Change from baseline in FPG, body weight, proportion of patients with baseline HbA_{1c} ≥7 who had HbA_{1c} <7 at week 24, subgroup analysis of HbA_{1c} based on baseline HbA_{1c} and change from baseline in HbA_{1c}, FPG, weight, and blood pressure at week 52 and the proportion of	Primary: At week 24, reductions from baseline in HbA_{1c} were significantly greater with empagliflozin/linagliptin compared with the individual components. Treatment differences in HbA_{1c} for empagliflozin 25 mg/linagliptin 5 mg when compared to individual empagliflozin 25 mg was -0.58% (P<0.001) and -0.50% when compared to linagliptin 5 mg (P<0.001). Treatment differences in HbA_{1c} for empagliflozin 10 mg/linagliptin 5 when compared to individual empagliflozin 10 mg was -0.42% (P<0.01) and -0.39% when compared to linagliptin 5 mg (P<0.001). Secondary: In subjects with HbA_{1c} ≥8.5% at baseline, reductions from baseline HbA_{1c} were significantly greater with empagliflozin 25 mg/linagliptin 5 mg compared with individual empagliflozin 25 mg and linagliptin 5 mg (P<0.01 for both). Reductions from baseline HbA_{1c} (subjects with HbA_{1c} ≥8.5% at baseline) were significantly greater with empagliflozin 10 mg/linagliptin 5 mg compared with individual linagliptin 5 mg (P=0.001), but not empagliflozin 10 mg (P=0.090). In subjects with baseline HbA_{1c} ≥7%, significantly more subjects in the empagliflozin/linagliptin groups reached HbA_{1c} <7% at week 24 compared with the respective individual components (P<0.001 for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
study agents in combination with metformin.			patients with baseline HbA_{1c} ≥7 who had HbA_{1c} <7 at week 52	Reductions from baseline in FPG at week 24 were significantly greater with empagliflozin/linagliptin compared with the individual components (P<0.001 for both empagliflozin 25 mg/linagliptin 5 mg comparisons and P=0.002 and P<0.001 for empagliflozin 10 mg/linagliptin 5 mg compared to the individual components, respectively. Reductions from baseline in weight at week 24 were significantly greater with both strengths of empagliflozin/linagliptin compared with linagliptin (P<0.001 for both comparisons), but were not significantly different compared with the respective empagliflozin components (P=0.668 for empagliflozin 25 and P=0.876 for empagliflozin 10 mg). Reductions from baseline in SBP at week 52 were significantly greater with both strengths of empagliflozin/linagliptin compared with individual linagliptin (P=0.005 and P=0.022), but not compared with the respective empagliflozin components (P=0.578 and P=0.609). Empagliflozin/linagliptin reduced diastolic blood pressure at week 52. The difference in change from baseline in empagliflozin 25 mg/linagliptin 5 mg compared with linagliptin 5 mg was of borderline significance (P=0.05) and not significant compared to empagliflozin 25 mg (P=0.703). For empagliflozin 10 mg/linagliptin 5, neither comparison to individual components were statistically significant (P=0.052 and P=0.620).
Lewin et al[32] Empagliflozin/linagliptin 25 mg/5 mg vs empagliflozin/linagliptin 10 mg/5 mg vs empagliflozin 25 mg vs	AC, DB, MC, PG, RCT Patients aged ≥18 years with a BMI ≤45 kg/m^2, HbA_{1c} of >7% to ≤10.5%, despite diet and exercise regimens not treated with oral antidiabetics, GLP-1 analogs or insulin for ≥12 months	N=667 52 weeks (primary endpoint at 24 weeks)	Primary: Change from baseline at week 24 in HbA_{1c} Secondary: Change from baseline in FPG, weight at week 24, proportion of subjects with baseline HbA_{1c} ≥7% who had HbA_{1c} <7% at week 24, changes from baseline in	Primary: At week 24, reductions from baseline in HbA_{1c} were significantly greater with both empagliflozin/linagliptin groups compared with the individual components (P=<0.001 for all comparisons), except for empagliflozin 25 mg/linagliptin 5 mg versus empagliflozin 25 mg (P=0.179). Secondary: Significantly more subjects with baseline HbA_{1c} ≥7% reached HbA_{1c} <7% at week 24 with either empagliflozin/linagliptin dose compared with the individual components (P=0.022 for empagliflozin 25 mg, P<0.001 for others). Reductions from baseline in FPG at week 24 were significantly greater with both doses of empagliflozin/linagliptin compared with linagliptin (P<0.001 for both), but were not significantly different compared with the respective empagliflozin components (P=0.161 and P=0.125 for empagliflozin 25 mg and 10 mg respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
empagliflozin 10 mg vs linagliptin 5 mg No antidiabetic agents may have been used in the previous 12 months for inclusion.			HbA_{1c} at week 24 in subgroups of subjects with HbA_{1c} ≥8.5% and <8.5% at baseline, changes from baseline in HbA_{1c}, FPG, weight, systolic and diastolic blood pressure at week 52, and the proportion of subjects with baseline HbA_{1c} ≥7% who had HbA_{1c} <7% at week 52.	Reductions from baseline in weight at week 24 were significantly greater with empagliflozin/linagliptin compared with linagliptin (P=0.018 and P<0.01) but not compared with the respective empagliflozin components (P=0.801 and P=0.362). Reductions in HbA1c with empagliflozin/linagliptin were sustained at week 52. Significantly greater proportions of subjects with baseline HbA_{1c} ≥7% had HbA_{1c} <7% at week 52 with empagliflozin/linagliptin compared with the individual components (P=0.004 for empagliflozin 10 mg/linagliptin 5 mg group compared to empagliflozin 10 mg; P<0.001 for others), except for empagliflozin 25 mg/linagliptin 5 mg compared with empagliflozin 25 mg (P=0.460). At week 52, reductions from baseline in FPG were significantly greater with either dose of empagliflozin/linagliptin compared with linagliptin (P<0.001 for both), but were not significantly different compared with the respective empagliflozin components (P=0.197 and P=0.096 for empagliflozin 25 mg and 10 mg respectively). Reductions from baseline in weight at week 52 were significantly greater with either dose of empagliflozin/linagliptin compared with linagliptin (P=0.002 and P=0.017), but were not significantly different compared with the respective empagliflozin components (P=0.532 and P=0.169). Changes from baseline in SBP and DBP at week 52 were not significantly different between empagliflozin/linagliptin and the individual components.

Drug regimen abbreviations: BID=two times a day, QAM=once every morning, QD=once-daily, QPM=once every evening
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, ES=extension study, OL=open label, MC=multicenter, PC=placebo-controlled, PG=parallel group, RCT=randomized controlled trial
Miscellaneous: BMI=body mass index, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin, HDL-C= high density lipoprotein cholesterol, PPG=postprandial glucose, T2DM=type 2 diabetes mellitus

Special Populations

Table 5. Special Populations[3-8,38]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Agent Products					
Canagliflozin	Use with caution as elderly patients are more likely to experience adverse reactions related to volume depletion and renal impairment or failure. Safety and efficacy in children have not been established.	Renal dose adjustment is required in patients with moderate dysfunction (eGFR of 45 to less than 60 mL/min/1.73 m^2) Safety and efficacy in patients with severe renal dysfunction have not been established; not expected to be effective.	No dose adjustments are required in patients with mild to moderate hepatic impairment. Not studied with severe hepatic dysfunction.	C	Unknown; use with caution.
Dapagliflozin	Use with caution as elderly patients are more likely to experience adverse reactions related to volume depletion and renal impairment or failure. Safety and efficacy in children have not been established.	Not recommended for use in patients with moderate to severe renal disease (eGFR<60ml/min/ 1.73m^2)	No dose adjustments are required in patients with mild to moderate hepatic impairment. Not studied with severe hepatic dysfunction.	C	Unknown; use with caution.
Empagliflozin	Use with caution as elderly patients are more likely to experience adverse reactions related to volume depletion and renal impairment or failure. Safety and efficacy in	No dose adjustment is required in patients with eGFR ≥45mL/min Do not use in patients with eGFR <45mL/min	Use caution in hepatic disease; AUC increased by 23%, 47%, and 75% with mild, moderate, and severe disfunction respectively.	C	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	children have not been established.				
Combination Products					
Canagliflozin/ metformin	Use with caution as elderly patients are more likely to experience adverse reactions related to volume depletion and renal impairment or failure. Safety and efficacy in children have not been established.	No dose adjustments are required in patients with mild renal impairment. For moderate impairment (eGFR 45-59), use 50 mg twice daily. Do not use for severe impairment (eGFR<45) or in patients who have serum creatinine <1.5 (males) or <1.4 (females) mg/dL.	No dose adjustments are required in patients with mild to moderate hepatic impairment. Do not use in patients with severe impairment.	C	Unknown; use with caution.
Dapagliflozin/ metformin ER	Use with caution as elderly patients are more likely to experience adverse reactions related to volume depletion and renal impairment or failure. Safety and efficacy in children have not been established.	No dose adjustments are required in patients with mild renal impairment (eGFR≥60). Contraindicated in patients with moderate to severe renal impairment or end-stage renal disease.	Avoid use in patients with clinical or laboratory evidence of hepatic disease as there is an increased risk of lactic acidosis secondary to the use of metformin.	C	Unknown; use with caution.
Empagliflozin/ linagliptin	Use with caution as elderly patients are more likely to experience adverse reactions related to volume depletion and renal impairment or failure. Safety and	No dose adjustments are required in patients with mild to moderate renal impairment (eGFR ≥45). Do not use in severe renal impairment (eGFR<45) or in	No dose adjustments are required for hepatic impairment.	C	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	efficacy in children have not been established.	patients who persistently have eGFR <45.			

eGFR=estimated glomerular filtration rate, ER=extended-release, min=minute

Adverse Drug Events

Table 6. Adverse Drug Events[3-8]

Adverse Event	Single Agent Products			Combination Products		
	Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin/ Metformin#	Dapagliflozin/ Metformin ER	Empagliflozin/ linagliptin
Arthralgia	-	-	2.3 to 2.4	-	-	2.3 to 3.4
Back pain	-	3.1 to 4.2	-	-	2.5 to 3.4	-
Constipation	1.8 to 2.3	1.9 to 2.2	-	1.8 to 2.3	1.9 to 2.9	-
Cough	-	-	-	-	1.4 to 3.2	1.4 to 2.1
Diarrhea	-	-	-	-	4.2 to 5.9	3.0 to 3.3
Discomfort with urination	-	1.6 to 2.1	-	-	1.6 to 2.2	-
Dizziness	-	-	-	-	1.8 to 3.2	-
Dyslipidemia	-	2.1 to 2.5	2.9 to 3.9	-	1.5 to 2.7	2.9 to 3.9
Female genital mycotic infections*	10.4 to 11.4	6.9 to 8.4	5.4 to 6.4	10.4 to 11.4	9.3 to 9.4	1.5 to 6.4
Headache	-	-	-	-	3.3 to 5.4	-
Increased urination†	4.6 to 5.3	2.9 to 3.8	3.2 to 3.4	4.6 to 5.3	2.4 to 2.6	1.0 to 3.4
Influenza	-	2.3 to 2.7	-	-	2.6 to 4.1	-
Male genital mycotic infections‡	3.7 to 4.2	2.7 to 2.8	1.6 to 3.1	3.7 to 4.2	3.6 to 4.3	1.6 to 3.1
Nasopharyngitis	-	6.3 to 6.6	-	-	5.2 to 6.3	5.9 to 6.6
Nausea	2.2 to 2.3	2.5 to 2.8	1.1 to 2.3	2.2 to 2.3	2.6 to 3.9	1.1 to 2.3
Pain in extremity	-	1.6 to 2.1	-	-	1.7 to 2.0	-
Pharyngitis	-	-	-	-	1.5 to 2.7	-
Thirst§	2.3 to 2.8	-	1.5 to 1.7	2.3 to 2.8	-	1.5 to 1.7
Upper respiratory tract infection	-	-	3.2 to 3.4	-	-	7.0
Urinary tract infections§§	4.3 to 5.9	4.3 to 5.7	7.6 to 9.3	4.3 to 5.9	5.5 to 6.1	11.4 to 12.5
Vulvovaginal pruritus	1.6 to 3.0	-	-	-	-	-

ER=extended-release

*Female genital mycotic infections included: vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis, vaginal infection, vulvitis, and genital infection fungal.

† Increased urination includes: polyuria, pollakiuria, urine output increased, micturition urgency, and nocturia.

‡ Male genital mycotic infections include: balanitis or balanoposthitis, balanitis candida, and genital infection fungal.

§ Thirst includes the following adverse reactions: thirst, dry mouth, and polydipsia.

§§Urinary tract infection includes: urinary tract infection, cystitis, kidney infection, and urosepsis.

The incidence and type of adverse reactions for the combination canagliflozin/metformin was similar to the adverse reactions of canagliflozin alone. There were no additional adverse reactions identified in the pooling of three additional placebo-controlled studies that included metformin relative to the four placebo-controlled studies used for canagliflozin alone.

As osmotic diuretics, sodium-glucose co-transporter 2 inhibitors may lead to reductions in intravascular volume was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). The three factors associated with the largest increase in volume depletion-related adverse reactions were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m2), and age 75 years and older. For canagliflozin, an increased incidence was observed in patients on the 300 mg dose. The proportions of volume-depletion-related adverse reactions are listed in Table 7.

Table 7. Proportion of Patients with at Least One Volume Depletion-Related Adverse Reaction[3-8]

Volume Depletion-Related Adverse Effects	Single Agent Products			Combination Products		
	Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin/ Metformin#	Dapagliflozin/ Metformin ER	Empagliflozin/ linagliptin†
Overall Population	2.3 to 3.4	0.3 to 0.5	0.7 to 1.1	2.3 to 3.4	0.6 to 1.1	-
65 years of age and older	4.9 to 8.7	2.3 to 4.4	0.8 to 1.7	4.9 to 8.7	0.5 to 1.7	-
75 years of age and older0	-	-	-	-	-	-
eGFR <60 mL/min/1.73 m^2	4.7 to 8.1	-	-	4.7 to 8.1	-	-
eGFR 35 to 59 mL/min/1.73 m^2	-	-	1.5 to 1.9	-	-	-
eGFR ≥30 and <60 mL/min/ 1.73 m^2	-	-	-	-	0.9 to 1.9	-
Use of loop diuretic	3.2 to 8.8	-	1.5 to 2.5	3.2 to 8.8	0 to 9.7	-

eGFR=estimated glomerular filtration rate, ER=extended-release, min=minute
-Not reported.
†No information reported for empagliflozin/linagliptin
The incidence and type of adverse reactions for the combination canagliflozin/metformin was similar to the adverse reactions of canagliflozin alone. There were no additional adverse reactions identified in the pooling of three additional placebo-controlled studies that included metformin relative to the four placebo-controlled studies used for canagliflozin alone.

Sodium-glucose co-transporter 2 inhibitors are associated with a dose-dependent increase in serum creatinine and a concomitant fall in estimated GFR. Patients with moderate renal impairment at baseline had larger mean changes. The changes in serum creatinine and eGFR are listed in Table 8.

Table 8. Changes in Serum Creatinine and eGFR[3-8]

Changes in Serum Creatinine and eGFR		Single Agent Products			Combination Products		
		Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin/ Metformin#	Dapagliflozin/ Metformin ER	Empagliflozin/ linagliptin†
Baseline	Creatinine (mg/dL)	0.82	0.85	0.85	0.82	0.847 to 0.860	-
	eGFR (mL/min/1.73 m^2)	88.3 to 88.8	87.8	87.1	88.3 to 88.8	85.3 to 86.7	-

Changes in Serum Creatinine and eGFR		Single Agent Products			Combination Products		
		Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin/ Metformin#	Dapagliflozin/ Metformin ER	Empagliflozin/ linagliptin†
Week 1	Creatinine (mg/dL)	-	-	-	-	0.029 to 0.041	-
	eGFR (mL/min/1.73 m^2)	-	-	-	-	-2.9 to -4.1	-
Week 6	Creatinine (mg/dL)	0.03 to 0.05	-	-	0.03 to 0.05	-	-
	eGFR (mL/min/1.73 m^2)	-3.8 to -5	-	-	-3.8 to -5	-	-
Week 12	Creatinine (mg/dL)	-	0.01 to 0.02	0.01 to 0.02	-	-	-
	eGFR (mL/min/1.73 m^2)	-	-1.3 to -1.4	-1.3 to -1.4	-	-	-
Week 24	Creatinine (mg/dL)	-	0.01	0.01	-	-0.001 to 0.001	-
	eGFR (mL/min/1.73 m^2)	-	-0.6 to -1.4	-0.6 to -1.4	-	0.3 to 0.8	-
End of treatment*	Creatinine (mg/dL)	0.02 to 0.03	-	-	0.02 to 0.03	-	-
	eGFR (mL/min/1.73 m^2)	-2.3 to 3.4	-	-	-2.3 to 3.4	-	-
Baseline	Creatinine (mg/dL)	1.62 to 1.63	1.46	1.46	1.62 to 1.63	1.52 to 1.53	-
	eGFR (mL/min/1.73 m^2)	38.5 to 39.7	45.4	45.4	38.5 to 39.7	43.9 to 44.2	-
Week 1	Creatinine (mg/dL)	-	-	-	-	0.13 to 0.18	-
	eGFR (mL/min/1.73 m^2)	-	-	-	-	-3.8 to -5.5	-
Week 3	Creatinine (mg/dL)	0.18 to 0.28	-	-	0.18 to 0.28	-	-
	eGFR (mL/min/1.73 m^2)	-4.6 to -6.2	-	-	-4.6 to -6.2	-	-
Week 12	Creatinine (mg/dL)	-	0.12	0.12	-	-	-
	eGFR (mL/min/1.73 m^2)	-	-3.8	-3.8	-	-	-
Week 24	Creatinine (mg/dL)	-	0.10	0.10	-	0.08 to 0.16	-
	eGFR (mL/min/1.73 m^2)	-	-3.2	-3.2	-	-4.0 to -7.4	-
Week 52	Creatinine (mg/dL)	-	0.11	0.11	-	0.06 to 0.15	-
	eGFR (mL/min/1.73 m^2)	-	-2.8	-2.8	-	-4.2 to -7.3	-
End of treatment*	Creatinine (mg/dL)	0.16 to 0.18	-	-	0.16 to 0.18	-	-
	eGFR (mL/min/1.73 m^2)	-3.6 to -4.0	-	-	-3.6 to -4.0	-	-

eGFR=estimated glomerular filtration rate, ER=extended-release, min=minute
-Not reported.
†No information reported for empagliflozin/linagliptin
*Week 26 for canagliflozin.

#The incidence and type of adverse reactions for the combination canagliflozin/metformin was similar to the adverse reactions of canagliflozin alone. There were no additional adverse reactions identified in the pooling of three additional placebo-controlled studies that included metformin relative to the four placebo-controlled studies used for canagliflozin alone.

Table 9. Incidence of Hypoglycemia[3-8]

Hypoglycemia	Single Agent Products			Combination Product		
	Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin/ metformin	Dapagliflozin/ metformin ER	Empagliflozin/ linagliptin+
Monotherapy						
Overall (%)	0.4	0.4	0	-	-	2.2 to 3.6
Severe (%)	0	0	0	-	-	0
Metformin Combination						
Overall (%)	1.4 to 1.8	1.4 to 1.8	0.7 to 1.5	3.2 to 4.6	0.7 to 1.5	-
Severe (%)	0	0	0	-	0	-
Metformin + Sulfonylurea Combination						
Overall (%)	11.5 to 16.1	11.5 to 16.1	5.5 to 6.0	27.4 to 30.1	1.7	-
Severe (%)	0	0	0	0.6	0	-
Pioglitazone ±Metformin Combination						
Overall (%)	1.2 to 2.4	1.2 to 2.4	2.1	2.7 to 5.3	-	-
Severe (%)	0		0	-	-	-
DDP4 Inhibitor Combination						
Overall (%)	-	-	1.8	-	2.22	-
Severe (%)	-	-	0.4	-	0.4	-
Insulin Combination						
Overall (%)	19.5 to 28.4	19.5 to 28.4	40.3 to 43.4	41.7 to 47.3	40.8	-
Severe (%)	1.8 to 2.7	1.3	0.5	0.7 to 2.0	0.5	-

ER=extended-release
-Not reported.

Contraindications

Table 10. Contraindications[3-8]

Contraindications	Single Agent Products			Combination Product		
	Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin/ metformin	Dapagliflozin/ metformin ER	Empagliflozin/ linagliptin+
Hypersensitivity to the drug or inactive components	a	a	a	a	a	a
Metabolic acidosis (acute or chronic) including diabetic ketoacidosis	-	-	-	a	a	-
Moderate to severe renal impairment, ESRD, or on dialysis	-	-	-	-	a	-
Severe renal impairment, ESRD, or on dialysis	a	a	a	a	-	a

ER=extended-release, ESRD=end stage renal disease

Warnings and Precautions

Table 11. Warnings and Precautions[3-8]

Warnings and Precautions	Single Agent Products			Combination Product		
	Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin/ metformin	Dapagliflozin/ metformin ER	Empagliflozin/ linagliptin[+]
Alcohol intake; increase risk of lactic acidosis	-	-	-	a	a	-
Bladder cancer: an imbalance in bladder cancers was observed in clinical trials. Use is not recommended in patients with active bladder cancer or a history of bladder cancer.	-	a	-	-	a	-
Genital mycotic infections; patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections.	a	a	a	a	a	a
Hyperkalemia can occur, use with caution in renal disease and with certain medications.	a	-	-	a	a	-
Hypersensitivity reactions have been reported.	a	a	a	a	a	a
Hypoglycemia increased with concurrent use of sulfonylurea or insulin	-	-	-	a	-	a
Hypotension; symptomatic hypotension due to intravascular volume contraction can occur particularly in patients with impaired renal function.	a	a	a	a	a	a
Hypoxic states; shock has been reported due to lactic acidosis	-	-	-	a	a	-
Iodinated Contrast Materials; temporarily suspend use if contrast materials to be used	-	-	-	-	a	-
Impairment in hepatic function; may increase risk of lactic acidosis	-	-	-	a	-	-
Impairment in renal function; increases serum creatinine and decreases in glomerular filtration rate.	a	a	a	a	a	a
Increased low density lipoprotein; dose-related	a	a	a	a	a	a
Lactic acidosis may occur	-	-	-	a	a	
Pancreatitis, acute has been reported	-	-	-	-	-	a
Surgical Procedures; temporarily suspend for any surgery (except minor procedures)	-	-	-	-	a	-
Urinary tract infections; increased risk for UTIs with use	-	-	a	-	-	a
Use of medications known to cause hypoglycemia; increased risk for hypoglycemia	a	a	a	-	a	a
Vitamin B12 levels decrease to subnormal; no clinical manifestation; monitor B12 every two to three years	-	-	-	a	a	-

ER=extended-release

Drug Interactions

There are no documented contraindicated drug interactions associated with the SGLT2 inhibitors. Major drug interactions are outlined in Table 12.

Table 12. Drug Interactions[3-8,39]

Generic Name	Interacting Medication or Disease	Potential Result
Canagliflozin, canagliflozin/ metformin, dapagliflozin/ metformin ER	Digoxin	Coadministration with digoxin may increase digoxin exposure. Use caution if concomitant use is required and monitor digoxin levels. Consider advising the patient to report signs or symptoms of digoxin toxicity.
Canagliflozin, canagliflozin/ metformin	UGT enzyme inducers (e.g., rifampin)	Co-administration with inducers of UGT1A9 and UGT2B4 caused decreased plasma concentrations of canagliflozin and may decrease efficacy. Consider increasing the dose if patients are currently tolerating lowering doses, require additional glycemic control and have adequate renal function.
Canagliflozin/ metformin	Topiramate	Decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis and may increase the risk of lactic acidosis. Monitor for signs and symptoms of acidosis when these drugs are used concomitantly.
Canagliflozin/ metformin	Carbonic anhydrase inhibitors	
Empagliflozin	Diuretics	Co-administration results in increased urine volume and frequency of voids, which might enhance the potential for volume depletion
Empagliflozin	Insulin or Insulin Secretagogues	Co-administration increases the risk for hypoglycemia
Empagliflozin/ linagliptin	CYP3A4 inducers and P-glycoprotein inducers	Reduced efficacy of linagliptin, use alternative treatments as needed.

ER=extended-release, UGT=UDP-glucuronosyltransferase

Dosage and Administration

Table 13. Dosing and Administration[3-8]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Agent Products			
Canagliflozin	Type 2 diabetes mellitus: Initial: 100 mg once daily Maintenance: 300 mg once daily Maximum: 300 mg once daily (may increase to 300 mg once daily if the patient has an eGFR rate >60 mL/min/ 1.73m^2 and requires additional glycemic control) It is recommended that volume depletion be corrected before initiating canagliflozin.	Safety and efficacy in children have not been established.	Tablet: 100 mg 300 mg
Dapagliflozin	Type 2 Diabetes Mellitus: Initial: 5 mg once daily Maintenance: 5 to 10 mg once daily	Safety and efficacy in children have	Tablet: 5 mg 10 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Maximum: 10 mg once daily It is recommended that volume depletion be corrected before initiating dapagliflozin.	not been established.	
Empagliflozin	Type 2 Diabetes Mellitus: Initial: 10 mg once daily Maintenance: 10 to 25 mg once daily Maximum: 25 mg once daily It is recommended that volume depletion be corrected before initiating canagliflozin.	Safety and efficacy in children have not been established.	Tablet: 10 mg 25 mg
Combination Products			
Canagliflozin/ metformin	Type 2 Diabetes Mellitus*: Initial: based on current regimen; start canagliflozin 50 mg and/or metformin 500 mg twice daily with meals Maximum: canagliflozin 300 mg and/or metformin 2,000 mg daily It is recommended that volume depletion be corrected before initiating canagliflozin.	Safety and efficacy in children have not been established.	Tablet: 50/500 mg 50/1,000 mg 150/500 mg 150/1,000 mg
Dapagliflozin/ metformin ER	Type 2 Diabetes Mellitus*: Initial: based on current regimen; start one tablet once daily in the morning with food Maximum: 10 mg/2,000 mg	Safety and efficacy in children have not been established.	Tablet: 5/500 mg 5/1000 mg 10/500 mg 10/1000 mg
Empagliflozin/ linagliptin	Type 2 Diabetes Mellitus*: Initial: 10 mg/5 mg QAM Maximum: 25 mg/5 mg QAM	Safety and efficacy in children have not been	Tablet: 10 mg/5 mg 25 mg/5 mg

ER=extended-release, QAM=every morning
*For patients who are not adequately controlled on a regimen containing metformin or canagliflozin or in patients already being treated with both canagliflozin and metformin

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
American Diabetes Association: **Standards of Medical Care in Diabetes (2014)**[33]	Current criteria for the diagnosis of diabetes · The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). Prevention/delay of type 2 diabetes · An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity, should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%. · Metformin therapy for prevention of type 2 diabetes may be considered in

Clinical Guideline	Recommendations
	patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%, especially for those with a body mass index >35 kg/m^2, age <60 years, and women with prior gestational diabetes mellitus. Glycemic goals in adults · Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%. · It may be reasonable for providers to suggest more stringent HbA_{1c} goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. · Conversely, less stringent HbA_{1c} goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. Pharmacologic and overall approaches to treatment-type 1 diabetes · Recommended therapy consists of the following components: o Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. o Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. o For many patients, use of insulin analogs to reduce hypoglycemic risk. Pharmacologic and overall approaches to treatment-type 2 diabetes · At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated. · In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the onset. · If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the HbA_{1c} target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin. · Because of the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes.
American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes: A**	Key points · Glycemic targets and glucose-lowering therapies must be individualized. · Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. · Unless there are prevalent contraindications, metformin is the optimal first line drug. · After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents

Clinical Guideline	Recommendations
Patient-Centered Approach (2012)[34]	is reasonable, aiming to minimize side effects where possible. · Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. · All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. · Comprehensive cardiovascular risk reduction must be a major focus of therapy. <u>Initial drug therapy</u> · It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. · Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. · Patients with high baseline HbA_{1c} (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance. · If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. · If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful. · Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates. · Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection. <u>Advancing to dual combination therapy</u> · If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required. · On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%. · If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted. · Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered. · It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration.

Clinical Guideline	Recommendations

- For all medications, consideration should also be given to overall tolerability.

Advancing to triple combination therapy

- Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin.
- Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} ≥8.5%) makes it unlikely that another drug will be of sufficient benefit.
- In using triple combinations the essential consideration is to use agents with complementary mechanisms of action.
- Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence.

Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations

Initial Drug Monotherapy	Metformin				
Efficacy (↓HbA_{1c})	High				
Hypoglycemia	Low risk				
Weight	Neutral/loss				
Side Effects	Gastrointestinal/lactic acidosis				
If needed to reach individualized HbA_{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)					
Two Drug Combin-ations	Metformin + sulfonylurea	Metformin + thia-zolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)
Efficacy (↓HbA_{1c})	High	High	Inter-mediate	High	Highest
Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	High risk
Weight	Gain	Gain	Neutral	Loss	Gain
Major Side Effects	Hypo-glycemia	Edema, heart failure, bone fracture	Rare	Gastro-intestinal	Hypo-glycemia
If needed to reach individualized HbA_{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)					
Three Drug Combin-ations	Metformin + sulfonylurea +	Metformin + TZD +	Metformin + DPP-4 inhibitor +	Metformin + GLP-1 receptor agonist +	Metformin + insulin therapy +
	TZD, DPP-4 inhibitor, GLP-1 receptor agonist, or insulin	Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin	Sulfonyl-urea, TZD, or insulin	Sulfonyl-urea, TZD, or insulin	TZD, DPP-4 inhibitor, or GLP-1 receptor agonist
If combination therapy that includes basal insulin has failed to achieve HbA_{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents					
Complex Insulin Strategies	Insulin (multiple daily doses)				

Clinical Guideline	Recommendations
American College of Physicians: **Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012)**[35]	· Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia. · Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes. · It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia.
American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan (2011)**[36]	Antihyperglycemic pharmacotherapy · The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2009 American Association of Clinical Endocrinologists/ American College of Endocrinology Diabetes Algorithm for Glycemic Control.[59] · Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia. · Antihyperglycemic agents may be broadly categorized by whether they predominantly target FPG or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making. · TZDs and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG. · When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn because they are associated with less hypoglycemia. · The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose. · When postprandial hyperglycemia is present, glinides and/or alpha-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. · When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia. · Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, HbA_{1c}, and weight. · Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy. · Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained.

Clinical Guideline	Recommendations
	· Most patients with an initial HbA_{1c} level >7.5% will require combination therapy using agents with complementary mechanisms of action.
American Association of Clinical Endocrinologists: American Association of Clinical Endocrinologists: **Comprehensive Diabetes Management Algorithm 2013 Consensus Statement (2013)**[37]	Principles underlying the algorithm · Lifestyle optimization is essential for all patients with diabetes; however, should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. · Achieving an HbA_{1c} ≤6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. · Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost. · For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. · Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). · Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain. · Rapid-acting insulin analogs are superior to regular insulin because they are more predictable. · Long-acting insulin analogs are superior to neutral protamine Hagedorn insulin because they provide a fairly flat response for approximately 24 hours and provide better reproducibility and consistency, both between and within patients, with a corresponding reduction in hypoglycemia risk. Monotherapy · Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} ≤7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day) and life-style modifications will achieve their glycemic goals in a majority of patients. · In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include: o GLP-1 receptor agonists. o DPP-4 inhibitors. o Alpha-glucosidase inhibitors. o Sodium glucose cotransporter 2 (SGLT-2) inhibitors. · TZD, sulfonylurea, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia. Combination therapy · Patients who present with an initial HbA_{1c} ≥7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin. · Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy.

Clinical Guideline	Recommendations
	· In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used. · Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus: o GLP-1 receptor agonists. o DPP-4 inhibitors. o TZD. o SGLT-2 inhibitors. o Basal insulin. o Colesevelam. o Bromocriptine quick release. o Alpha-glucosidase inhibitors. o Sulfonylureas and glinides. Three-drug combination therapy · Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent. · Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. · Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months has a high likelihood of reaching target with a third agent. · Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered. · Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfourea are used in conjunction with insulin. · Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus: o GLP-1 receptor agonists. o TZD. o SGLT-2 inhibitors. o Basal insulin. o DPP-4 inhibitors. o Colesevelam. o Bromocriptine quick release. o Alpha-glucosidase inhibitors. o Sulfonylureas and glinides Insulin therapy algorithm · Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. · Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and weight loss. · Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. · Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach

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	the recommended target by the addition of further oral antidiabetic drugs. Basal insulin · Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. · Titrate insulin dose every two to three days to reach glycemic goals. · Basal insulin analogues (glargine and detemir) are preferred over protamine Hagedorn insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. · Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia. Basal-bolus insulin regimens · Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin. · A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content. · Doses of insulin may be titrated every two to three days to reach glycemic goals. Basal insulin and incretin therapy regimens · Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. · The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.
American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (2007)**[38]	Glycemic management-all patients with diabetes · Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia. Glycemic targets include the following: o HbA_{1c} ≤6.5%. o FPG <100 mg/dL. o Two-hour PPG <140 mg/dL. · Refer patients for comprehensive, ongoing education in diabetes self-management skills and nutrition therapy. · Initiate self-monitoring blood glucose levels. Glycemic management-patients with type 2 diabetes · Aggressively implement all appropriate components of care at the time of diagnosis. · Persistently monitor and titrate pharmacologic therapy until all glycemic goals are achieved.

Clinical Guideline	Recommendations
	o First assess current HbA_{1c} level, fasting/pre-prandial glycemic profile, and two-hour PPG profile to evaluate the level of control and identify patterns. o After initiating pharmacologic therapy based on the patterns identified in the profile, persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved. o If glycemic goals are not achieved at the end of two to three months, initiate a more intensive regimen and persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved. o Recognize that patients currently treated with monotherapy or combination therapy who has not achieved glycemic goals will require either increased dosages of current medications or the addition of a second or third medication. o Consider insulin therapy in patients with HbA_{1c} >8.0% and symptomatic hyperglycemic, and in patients with elevated fasting blood glucose levels or exaggerated PPG excursions regardless of HbA_{1c} levels. o Initiate insulin therapy to control hyperglycemia and to reverse glucose toxicity when HbA_{1c} >10.0%. Insulin therapy can then be modified or discontinued once glucose toxicity is reversed. o Consider a continuous SC insulin infusion in insulin-treated patients. · Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least three times daily. Although monitoring glucose levels at least three times daily is recommended, there is no supporting evidence regarding optimal frequency of glucose monitoring with or without insulin pump therapy. · Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump. · Instruct patients whose glycemic levels are above target while being treated with oral agents alone, oral agents plus once-daily insulin, or once-daily insulin alone to monitor glucose levels at least two times daily. There is no supporting evidence regarding optimal frequency of glucose monitoring in these patients. · Instruct patients who are meeting target glycemic levels, including those treated non-pharmacologically, to monitor glucose levels at least once daily. · Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels. · Instruct patients to obtain comprehensive pre-prandial and two-hour PPG measurements to create a weekly profile periodically and before clinician visits to guide nutrition and physical activity, to detect post-prandial hyperglycemia, and to prevent hypoglycemia. · Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving. · Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is >250 mg/dL.

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	Clinical support-clinical considerations in patients with type 1 diabetes · Instruct patients to administer pre-prandial rapid-acting analog insulin 20 to 30 minutes before the meal when the pre-meal blood glucose levels is high and after the meal has begun when the pre-meal blood glucose level is below the reference range. · Measure 2:00 to 3:00 AM blood glucose periodically in all patients with diabetes to asses for nocturnal hypoglycemia, especially when the morning blood glucose level is elevated. · Consider using regular insulin instead of rapid-acting insulin analogs to obtain better control of post-prandial and pre-meal glucose levels in patients with gastroparesis. Insulin pump therapy may also be advantageous in these patients. · Some type 1 diabetics treated with basal insulin may require two daily injections of basal insulin for greater stability. · Carefully assess PPG levels when the HbA_{1c} level is elevated and pre-meal glucose measurements are at target levels. · Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the HbA_{1c} level is at or near target. · Arrange for continuous glucose monitoring for patients with unstable glucose control and for patients unable to achieve an acceptable HbA_{1c} level. Continuous glucose monitoring is particularly valuable in detecting both unrecognized nocturnal hypoglycemia and post-prandial hyperglycemia. · Some patients using pramlintide may achieve better post-prandial and pre-meal glucose control by combining it with regular insulin rather than rapid-acting analogs. · Individualize insulin regimens to accommodate patient exercise patterns. · Treat hypoglycemic reactions with simple carbohydrates. Clinical support-clinical considerations in patients with type 2 diabetes · Combining therapeutic agents with different modes of action may be advantageous. · Use insulin sensitizers, such as metformin or TZDs, as part of the therapeutic regimen in most patients unless contraindicated or intolerance has been demonstrated. · Insulin is the therapy of choice in patients with advanced chronic kidney disease. · Metformin, TZDs, and incretin mimetics do not cause hypoglycemia. However, when used in combination with secretagogues or insulin, these medications may need to be adjusted as blood glucose levels decline. · The weight gain associated with TZDs in some patients may be partly offset by combination therapy with metformin. · Carefully assess PPG levels if the HbA_{1c} level is elevated and pre-prandial glucose measurements are at target levels. · Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the HbA_{1c} level is at or near target. · Individualize treatment regimens to accommodate patient exercise patterns. · Administer basal insulin in the evening if fasting glucose is elevated. · Long-acting insulin analogs are associated with less hypoglycemia than

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	protamine Hagedorn insulin.

Conclusions

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a novel class of oral antidiabetic agents that improve glycemic control by increasing urinary glucose excretion and are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1,2]

Currently, three single-entity agents, and three combination products in this drug class have been approved by the FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and are commercially available in the United States. Canagliflozin (Invokana®), dapagliflozin (Farxiga®) and empagliflozin (Jardiance®) are oral once daily tablets. The combination products include canagliflozin/metformin (Invokamet®), which is a twice-daily tablet, dapagliflozin/metformin (Xigduo XR®), which is a once-daily extended-release (ER) tablet and empagliflozin/linagliptin (Glyxambi®), which is also a once-daily tablet.[3-8] Canagliflozin, dapagliflozin, and empagliflozin have demonstrated to be significantly more effective compared to placebo in reducing glycosylated hemoglobin (HbA_{1c}) and fasting plasma glucose. Combination and add-on therapy with SGLT2 inhibitors and metformin, a sulfonylurea, a thiazolidinedione, and insulin consistently demonstrates improved benefits in glycemic control over placebo. There are currently no head-to-head trials that have been published. Currently, there are no agents available generically in the class.[3-32]

Though clinical experience is limited, the SGLT2 inhibitors are associated with several favorable side effects compared to other antidiabetic agents such as weight loss. Compared to sulfonylureas, the risk of hypoglycemia associated with the SGLT2 inhibitors is low as it reduces plasma glucose concentrations without stimulating insulin release or inhibiting its counterregulatory response.[1-8] During clinical trials, common adverse side effects associated with the SGLT2 inhibitors included increased incidence of female genital mycotic infections, urinary tract infection, and increased urination.[3-8]

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens.[33-38] Additionally, patients with a high HbA_{1c} will likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. The role of SGLT2 inhibitors are addressed in only one treatment guideline and are recommended as a potential second-line treatment option to be added in combination with metformin in patients not achieving glycemic goals.[37] Patients who are not appropriate for initial therapy with metformin, may be initiated on another oral antidiabetic agent, such as a sulfonylurea/glinide, thiazolidinedione, or a dipeptidyl pepetidase-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful.[33-38]

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