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

Therapeutic Class

- **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, one single-entity agent in this drug class has been approved by the FDA and is commercially available in the United States. Canagliflozin (Invokana®) is an oral once daily tablet, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Overall, canagliflozin is 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, or insulin consistently demonstrates improved benefits in glycemic control over placebo. With one agent approved and several in development, to date there have been no within class head-to-head trials published. Currently, none of the SGLT2 inhibitors are available generically.[1, 4-12]

  Though clinical experience is limited, the SGLT2 inhibitors are associated with weight loss compared to other antidiabetic agents commonly used in the management of type 2 diabetes. 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. During clinical trials, common adverse side effects associated with canagliflozin use included increased incidence of female genital mycotic infections, urinary tract infection, and increased urination.[1-12]

  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. 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.[11-18]

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

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Canagliflozin (Invokana®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 100 mg 300 mg	-

Evidence-based Medicine

- The only medication in the therapeutic class, canagliflozin, has been studied in the treatment of type 2 diabetes in nine phase III, double-blind, randomized, controlled, multinational studies (n=10,300). These trials included this agent as monotherapy, in combination with metformin, sulfonylurea, metformin and sulfonylurea, metformin and a thiazolidinedione and in combination with insulin (with or without other antihyperglycemic agents). In addition, the efficacy of this agent was compared to a dipeptidyl peptidase-4 (DPP-4) inhibitor and a sulfonylurea. Several of the results summarized within this section were presented in abstract or as poster form at professional medical conferences and were not published within medical journals at the time of this review, but were included within this review due to their inclusion within the product package insert and importance in defining the place in therapy of this agent.[3-12]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Metformin remains the cornerstone of most antidiabetic treatment regimens.
  - Patients with a 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.
- Other Key Facts:
  - Currently, canagliflozin (Invokana®) is the only one single-entity agent in this novel drug class that has been approved by the Food and Drug Administration (FDA) and is commercially available in the United States.
  - Canagliflozin is available in an once oral once daily tablet dosed 100 and 300 mg daily.
  - Overall, canagliflozin is significantly more effective compared to placebo in reducing 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.
  - Other effects observed in trials include weight loss and small decreases in systolic and diastolic blood pressure.
  - Common adverse side effects associated with canagliflozin use included increased incidence of female genital mycotic infections, urinary tract infection, and increased urination.

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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]

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Though clinical experience is limited, the SGLT2 inhibitors are associated with weight loss compared to other antidiabetic agents commonly used in the management of type 2 diabetes. 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. During clinical trials, common adverse side effects associated with canagliflozin use included increased incidence of female genital mycotic infections, urinary tract infection, and increased urination.[1-12]

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. 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.[11-18]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Canagliflozin (Invokana®)	Sodium-glucose co-transporter 2 inhibitor	-

Indications

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

Generic Name	Adjunct to Diet and Exercise to Improve Glycemic Control in Adults With Type 2 Diabetes
Canagliflozin	✔

Pharmacokinetics

Table 3. Pharmacokinetics[3, 19]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Canagliflozin	65	33	None	10.6 to 13.1

*Active metabolite.

Clinical Trials

The only medication in the therapeutic class, canagliflozin, has been studied in the treatment of type 2 diabetes in nine phase III, double-blind, randomized, controlled, multinational studies (n=10,300). These trials included this agent as monotherapy, in combination with metformin, sulfonylurea, metformin and a sulfonylurea, metformin and a thiazolidinedione and in combination with insulin (with or without other antihyperglycemic agents). In addition, the efficacy of this agent was compared to a dipeptidyl peptidase-4 (DPP-4) inhibitor and a sulfonylurea. Several of the results summarized within this section were presented in abstract or as poster form at professional medical conferences and were not published within medical journals at the time of this review, but were included within this review due to their inclusion within the product package insert and importance in defining the place in therapy of this agent.[3-12]

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).[4-12]

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.[4]

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.[5]

A non-inferiority study comparing canagliflozin to sitagliptin found that when added to patients not adequately controlled with metformin 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).[7]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Monotherapy				
Stenlof et al[4] 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 type 2 diabetes mellitus, 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 extension study 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.
Add-on Therapy				
Rosenstock et al[5] Canagliflozin 50 mg QD vs canagliflozin 100 mg QD vs canagliflozin 200 mg QD vs canagliflozin 300 mg QD vs canagliflozin 300 mg BID vs sitagliptin 100 mg QD vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age with type 2 diabetes mellitus, an HbA_{1c} level ≥7.0 and <10.5%, were on 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	N=451 12 weeks	Primary: Change in HbA_{1c} level from baseline to week 12 Secondary: Change in FPG, change in body weight, and overnight urinary glucose -to-creatinine ratio	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 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).
Bode et al[6] (abstract)	DB, MC, PC, RCT Patients 55 to 80	N=716 26 weeks	Primary: Change in HbA_{1c} level from	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Canagliflozin 100 mg QD vs canagliflozin 300 mg QD vs placebo	years of age with type 2 diabetes mellitus, an HbA_{1c} ≥7.0 and <10% despite treatment with blood glucose lowering therapy		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	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).
Triple Combination Therapy				
Schernthaner et al[7] (abstract) Canagliflozin 300 mg QD vs sitagliptin 100 mg QD vs placebo	AC, DB, RCT Patients with type 2 diabetes mellitus, 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).

Drug regimen abbreviations: BID=two times a day, QD=once-daily
Study abbreviations: AC=active-controlled, DB=double-blind, MC=multicenter, PC=placebo-controlled, RCT=randomized controlled trial
Miscellaneous: FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin, HDL-C= high density lipoprotein cholesterol, PPG=postprandial glucose

Special Populations

Table 5. Special Populations[3,19]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Canagliflozin	Use with caution as elderly patients are more likely to have reduced intravascular volume. Safety and efficacy in children have not been established.	Renal dose adjustment is required in patients with moderate dysfunction, lower doses are recommended. Safety and efficacy in patients with severe renal dysfunction have not been established; not expected to be effective in these patient populations.	No dose adjustments are required in patients with mild to moderate hepatic impairment. Not studied with severe hepatic dysfunction.	C	Unknown; use with caution.

Adverse Drug Events

Table 6. Adverse Drug Events[3]

Adverse Event	Canagliflozin
Constipation	1.8 to 2.3
Female genital mycotic infections*	10.4 to 11.4
Increased urination†	4.6 to 5.3
Male genital mycotic infections‡	3.7 to 4.2
Nausea	2.2 to 2.3
Thirst§	2.3 to 2.8
Urinary tract infections§§	4.3 to 5.9
Vulvovaginal pruritus	1.6 to 3.0

*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.

Contraindications/Precautions

Table 7. Contraindications[3]

Contraindication(s)	Canagliflozin
Hypersensitivity	✔
Renal impairment, severe	✔

Table 8. Warnings and Precautions[3]

Warning(s)/Precaution(s)	Canagliflozin
Genital mycotic infections; patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections	✔
Hyperkalemia: Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin angiotensin-aldosterone system are more likely to develop hyperkalemia	✔
Hypersensitivity reactions; there have been reports of serious hypersensitivity reactions with therapy	✔
Hypotension; symptomatic hypotension due to intravascular volume contraction can occur particularly in patients with impaired renal function.	✔
Impairment in Renal Function; increases serum creatinine and decreases in glomerular filtration rate. Patients with hypovolemia may be more susceptible to these changes. More frequent renal function monitoring is recommended in patients with moderate-severe renal impairment.	✔
Increased low density lipoprotein (LDL-C); Dose-related increases in LDL‑C occur with therapy. Monitor LDL-C and treat per standard of care	✔
Use of medications known to cause hypoglycemia; patients receiving therapy in combination with an insulin secretagogue or insulin may have an increased risk of hypoglycemia	✔

Drug Interactions

There are no documented contraindicated drug interactions associated with the SGLT2 inhibitors. Major drug interactions are outlined in Table 9.[73]

Table 9. Drug Interactions[18,19]

Generic Name	Interacting Medication or Disease	Potential Result
Sodium-glucose co-transporter 2 (SGLT2) inhibitors (canagliflozin)	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.
SGLT2 Inhibitors (canagliflozin)	UGT enzyme inducers (e.g., rifampin)	Co-administration with inducers of UGT1A9 and UGT2B4, caused decreased plasma concentrations of the SGLT2 inhibitor and may decrease efficacy. Consider increasing the dose if patients are currently tolerating lowering doses, require additional glycemic control and have adequate renal function.

UGT= UDP-Glucuronosyltransferase

Dosage and Administration

Table 10. Dosing and Administration[3]

Generic Name	Adult Dose	Pediatric Dose	Availability
Canagliflozin	Type 2 diabetes mellitus: Tablet: initial, 100 mg QD; maintenance, 300 mg QD; maximum, 300 mg QD; dose may be increased from 100 to 300 mg QD if the patient has an glomerular filtration rate >60 mL/min/ 1.73m^2 and requires additional glycemic control	Safety and efficacy in children have not been established.	Tablet: 100 mg 300 mg

QD=once daily

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
American Diabetes Association: **Standards of Medical Care in Diabetes (2013)**[13]	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 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

Clinical Guideline	Recommendations
	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 Patient-Centered Approach (2012)**[14]	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 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. Initial drug therapy • 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

Clinical Guideline	Recommendations

selection.

Advancing to dual combination therapy

- 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.
- 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	Rare	Gastro-intestinal	Hypo-glycemia

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
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<tr><td colspan="6">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)</td></tr>
<tr><td>Three Drug Combin-ations</td><td>Metformin + sulfonylurea +</td><td>Metformin + TZD +</td><td>Metformin + DPP-4 inhibitor +</td><td>Metformin + GLP-1 receptor agonist +</td><td>Metformin + insulin therapy +</td></tr>
<tr><td></td><td>TZD, DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>TZD, DPP-4 inhibitor, or GLP-1 receptor agonist</td></tr>
<tr><td colspan="6">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</td></tr>
<tr><td>More Complex Insulin Strategies</td><td colspan="5">Insulin (multiple daily doses)</td></tr>
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<tr><td>American College of Physicians: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012)[15]</td><td>

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.

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<tr><td>American Association of Clinical Endocrinologists: Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan (2011)[16]</td><td>
<u>Antihyperglycemic pharmacotherapy</u>

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 (NPH) 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 α-glucosidase

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Clinical Guideline	Recommendations
	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. • 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)** [17]	<u>Principles underlying the algorithm</u> • 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 (NPH) 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. <u>Monotherapy</u> • 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

Clinical Guideline	Recommendations
	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. <u>Combination therapy</u> • 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. • 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 Sulfoureas and glinides. <u>Three-drug combination therapy</u> • 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.

Clinical Guideline	Recommendations
	o Basal insulin. o DPP-4 inhibitors. o Colesevelam. o Bromocriptine quick release. o Alpha-glucosidase inhibitors. o Sulfoureas 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 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 NPH 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

Clinical Guideline	Recommendations
	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)**[18]	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. 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

Clinical Guideline	Recommendations
	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. <u>Clinical support-clinical considerations in patients with type 1 diabetes</u> • 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. <u>Clinical support-clinical considerations in patients with type 2 diabetes</u> • Combining therapeutic agents with different modes of action may be advantageous. • Use insulin sensitizers, such as metformin or TZDs, as part of the

Clinical Guideline	Recommendations
	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 NPH 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, one single-entity agent, canagliflozin (Invokana®), in this drug class has been approved by the Food and Drug Administration (FDA) and is commercially available in the United States. Canagliflozin is available as an oral once daily tablet and has 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. With one agent approved and several in development, to date there have been no within class head-to-head trials published. Currently, there is no agent available generically in the class.[3-12]

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.[1-3] During clinical trials, common adverse side effects associated with canagliflozin use included increased incidence of female genital mycotic infections, urinary tract infection, and increased urination.[3]

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens.[13-18] 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.[17] 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.

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