

DIABETES MELLITUS



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BCPS

Therapeutic Management of T2D

1. Given the progressive nature of T2D, a stepwise approach is usually needed.
2. ADA treatment recommendations for hyperglycemia emphasize a patient-centered approach to care, considering patient preferences, needs, and values.
3. Metformin remains the initial drug of choice, unless contraindicated or adverse effects preclude its use or if improvements in exercise and diet early after diagnosis fail to control hyperglycemia. (Consider combination therapy of metformin with the medications listed in the text that follows if baseline A1C is 1.5% or greater above personal goal A1C.)
4. If metformin monotherapy fails to allow the patient to attain or maintain glycemic control, adding other agents is based on several criteria and weighs the advantages and disadvantages of the various oral and injectable agents.
 - a. Efficacy in lowering A1C (also focus on ability to lower fasting or postprandial glucose concentrations or both)
 - b. Existing comorbidities
 - i. Cardiovascular disease: Consider GLP-1 agonist or SGLT-2 inhibitor
 - ii. Heart failure or chronic kidney disease: Consider SGLT-2 inhibitor
 - c. Risk of hypoglycemia
 - d. Effects on weight
 - e. Adverse effect profile
 - f. Cost
 - g. Oral or injection patient preference

Biguanides (A1C↓1.5% to 2.0%)

Metformin is the only biguanide available in the United States. It is oral and available as an immediate-release formulation that is dosed twice daily or an extended-release (XR) formulation that is dosed once or twice daily. Its benefits in relation to glucose lowering are complex and not yet fully understood.

1-At the cellular level, metformin activates AMP kinase.

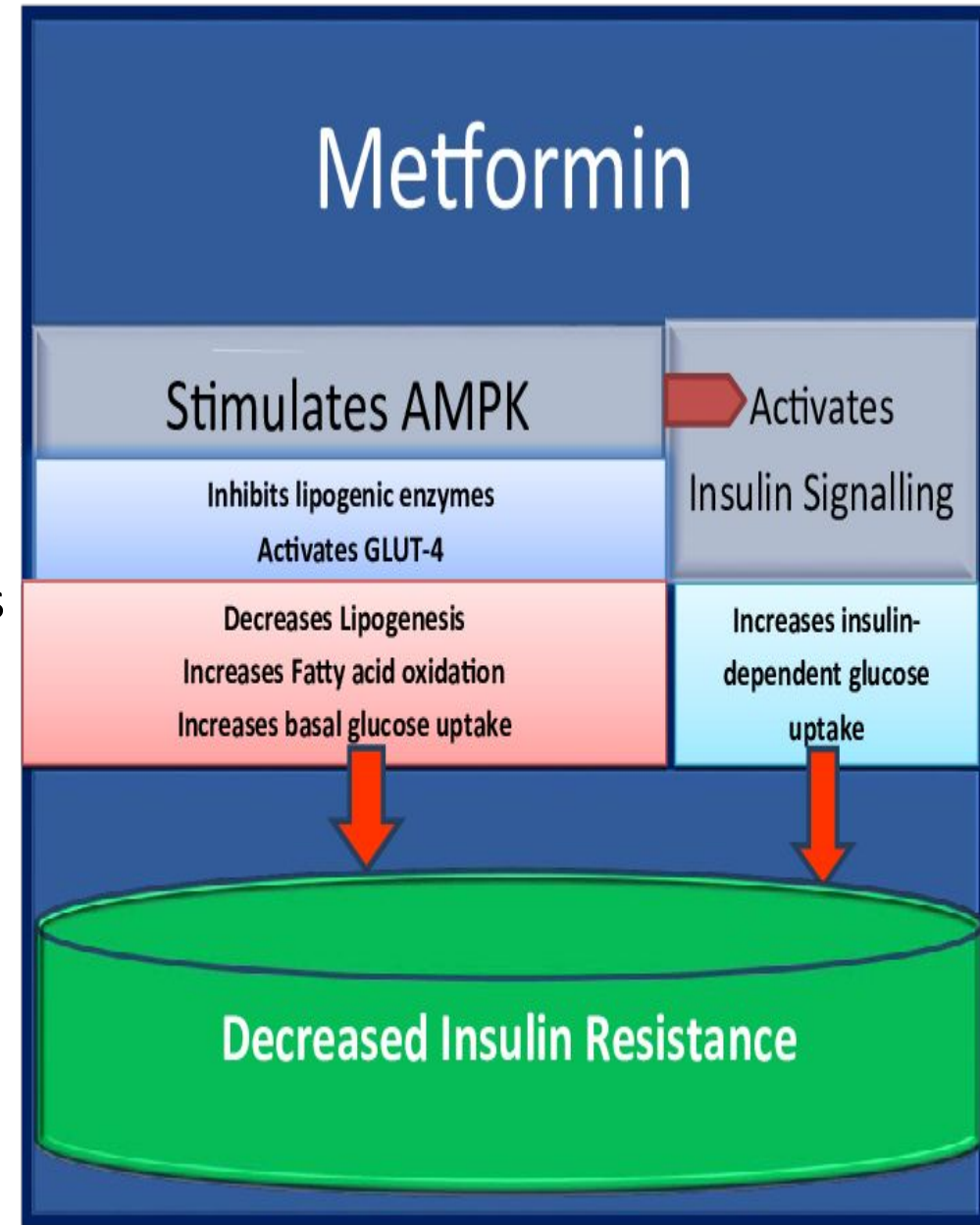
2- Metformin has been shown to decrease hepatic glucose production, yet not all of its effects can be explained by that mechanism

3-There is increasing evidence of mechanisms in the gut.

4-metformin's effects may be partially related to enhanced insulin sensitivity in peripheral (muscle) tissues, which allows for an increased uptake of glucose into muscle cells.

5- Metformin has no direct effect on the β -cell, but insulin concentrations are reduced due to improved insulin sensitivity

The main effect of Metformin appears to be decreasing hepatic glucose production through a mild inhibition of the mitochondrial respiratory-chain complex. This transient decrease in cellular energy status promotes activation of adenosine monophosphate-activated protein (AMPK), a well-known cellular energetic sensor. AMPK is a protein kinase ubiquitously expressed in mammalian tissues and involved in regulating energy balance. Activation of AMPK stimulates adenosine triphosphate (ATP)-producing catabolic pathways, while inhibiting ATP-consuming anabolic pathways, thereby, maintaining cellular energy stores. In skeletal muscle, activation of AMPK increases glucose uptake and lipid oxidation. In adipose tissue, activation of AMPK reduces both lipolysis and lipogenesis. Metformin regulates glucose transporter 4 (GLUT4) translocation through AMP activated Protein Kinase (AMPK)-mediated Cbl/CAP Signaling. In the liver, activation of AMPK inhibits gluconeogenesis and lipid synthesis but increases lipid oxidation. The activated AMPK decreases flux of free fatty acids and inhibits lipolysis, which may indirectly improve insulin sensitivity through reduced lipotoxicity (reduces hepatic lipogenesis) and exert an indirect effect on hepatic insulin sensitivity to control hepatic glucose output. In the heart, Metformin increases fatty acids uptake and oxidation, and increases glucose uptake and glycolysis. Metformin can also antagonize the action of glucagon, thus reducing fasting glucose levels. In summary, activation of AMPK in skeletal muscle, liver and adipose tissue decreases circulating glucose, lipids, reduces fat accumulation and enhances insulin sensitivity.



Metformin enhances insulin signaling in insulin-dependent and -independent pathways.

Metformin is the drug of choice in patients with type 2 DM due to extensive experience, high efficacy, minimal hypoglycemia risk, positive or neutral effects on weight, potential positive impact on CV risk, manageable side-effect profile, and low cost. **Current treatment guidelines recommend initiating metformin as first-line pharmacotherapy unless a contraindication or intolerability exists.**

Absorption, Excretion, and Dosing. Metformin is absorbed mainly from the small intestine. The drug is stable, does not bind to plasma proteins, and is excreted unchanged in the urine. It has a half life of about 2 hours. The maximum recommended daily dose of metformin in the United States is 2.5 g given in three doses with meals.

Metformin does not cause weight gain, and may actually lead to a modest (2-3 kg) **weight loss**. Since metformin does not directly increase insulin secretion from the pancreas, it has a **low risk of hypoglycemia**.

Metformin also has positive effects on several components of the insulin **resistance syndrome**. Metformin decreases plasma triglycerides **TG** and low-density lipoprotein cholesterol (**LDL-C**) by approximately 8% to 15% and modestly increases high density lipoprotein cholesterol (**HDL-C**) by 2%.

Adverse effects

Metformin frequently **causes GI side effects**, including diarrhea, abdominal discomfort, and/or stomach upset. These side effects are usually dose dependent, transient, mild in nature, and can be minimized with slow dose titration. Patients should take metformin with or immediately after meals. When initiating therapy, it is important to use a low dose, typically 500 mg given with the largest meal, to minimize GI adverse effects. The dose is then increased in 500 mg increments over several weeks. Approximately 5% to 10% of patients cannot tolerate metformin despite the slow dose titration.

Metformin may cause **a metallic taste**, due to metformin in salivary secretions and may lower **vitamin B12** concentrations. Therefore, B12 levels or ethylmalonic acid should be measured annually or if a deficiency is suspected. Peripheral neuropathy, a microvascular complication that is common in diabetes, could manifest or worsen with B12 deficiency.

Rare cases of **lactic acidosis** have been reported with metformin, usually in the setting of severe illness or acute kidney injury. The risk appears to be exceedingly small but may increase in patients with moderate-to-severe renal insufficiency or tissue hypoperfusion states such as acute congestive heart failure, excessive alcohol intake, and hepatic impairment.

Contraindications and precautions (because of risk of lactic acidosis)

i. Renal impairment (contraindicated because of increased risk of lactic acidosis)

(a) Historically contraindicated if SCr 1.5 mg/dL or greater in men and 1.4 mg/dL or greater in women or reduced creatinine clearance (CrCl)

(b) In 2016, the FDA suggested that eGFR be used as a measure of kidney function rather than creatinine alone. Discontinue if eGFR is less than 30 mL/minute/1.73 m², and initiating if eGFR is 30–45 mL/minute/1.73 m² is not recommended.

(c) Monitor renal function every 3–6 months in patients with eGFR of 45–60 mL/minute/1.73 m² and every 3 months if 30–45 mL/minute/1.73 m².

ii. Age 80 or older (use caution and carefully assess renal function)

iii. High risk of cardiovascular event or hypoxic state.

iv. Hepatic impairment.

v. Congestive heart failure (especially if prone to exacerbations)

vi. Interrupt therapy in patients with eGFR of 30–60 mL/minute/1.73 m² if undergoing procedures using iodinated contrast dye because of risk of nephrotoxicity. Reinitiate after 48 hours and after normal SCr concentrations are achieved.

Synthetic Amylin Analog (A 1c ↓ 0.5-1%)

Amylin is a hormone that is cosecreted with insulin from β cells following food intake. It delays gastric emptying, decreases postprandial glucagon secretion, and improves satiety. ***Pramlintide*** is a synthetic amylin analog that is indicated as an adjunct to mealtime insulin therapy in patients with type **1 and type 2 diabetes**.

Pramlintide is administered by subcutaneous injection immediately before meals. When *pramlintide* is initiated, the dose of mealtime insulin should be decreased by 50% to avoid a risk of severe hypoglycemia.

Other adverse effects include nausea, anorexia, and vomiting.

Pramlintide may not be mixed in the same syringe with insulin, and it should be avoided in patients with diabetic **gastroparesis (delayed stomach emptying)**, **cresol hypersensitivity**, or **hypoglycemic unawareness and A1c greater than 9%**.



Sulfonylureas (A 1C 1.5-2↓)

Sulfonylureas are oral agents, available in either immediate-release or extended release formulations, typically dosed once or twice daily. They enhance insulin secretion by binding to a specific sulfonylurea receptor (SUR1) on pancreatic β -cells. Binding closes an adenosine triphosphate-dependent K^+ channel, leading to decreased potassium efflux and subsequent depolarization of the membrane. Voltage-dependent Ca^{+2} channels open and allow an inward flux of Ca^{+2} . Increases in intracellular Ca^{+2} bind to calmodulin on insulin secretory granules, causing translocation of secretory granules of insulin to the cell surface and resultant exocytosis of the granule of insulin.

Sulfonylureas are classified as first-generation and second-generation agents. The classification schemes are based on relative potency. First-generation agents (chlorpropamide, tolazamide, and tolbutamide) are lower in potency relative to the second-generation drugs (glyburide, glipizide, and glimepiride)

Drug	Initial Dosage	Maximum Daily Dosage (mg)
Glyburide (not micronized)	2.5–5.0 mg once or twice daily	20
Glyburide (micronized)	1.5–3 mg once or twice daily	12
Glipizide	5 mg once or twice daily (once daily with extended release)	40 (little improved efficacy > 20 mg/day)
Glimepiride	1–2 mg once daily	8

Absorption, Fate, and Excretion. The sulfonylureas have similar spectra of activities; thus their pharmacokinetic properties are their most distinctive characteristics. Although the rates of absorption of the different sulfonylureas vary, all are effectively absorbed from the gastrointestinal tract. However, food and hyperglycemia can reduce the absorption of sulfonylureas. **Hyperglycemia *per se* inhibits gastric and intestinal motility and thus can retard the absorption of many drugs.** In view of the time required to reach an optimal concentration in plasma, sulfonylureas with short half-lives may be more effective when given 30 minutes before eating. Sulfonylureas in plasma are largely (90% to 99%) bound to protein, especially albumin; plasma protein binding is least for chlorpropamide and greatest for glyburide. The volumes of distribution of most of the sulfonylureas are about 0.2 L/kg. All the sulfonylureas are metabolized by the liver, and the metabolites are excreted in the urine. Metabolism of chlorpropamide is incomplete, and about 20% of the drug is excreted unchanged. Thus sulfonylureas should be administered with caution to patients with either renal or hepatic insufficiency.

ADVERSE EFFECTS

The most common side effect of sulfonylureas is **hypoglycemia**. Due to its **active metabolite, glyburide** has a higher risk of hypoglycemia compared to other sulfonylureas while glipizide and glimepiride have lower risks. Those who skip meals, exercise vigorously, or lose substantial amounts of weight are more prone to experiencing hypoglycemia. A lower dose should initially be used in high-risk patients. Severe hypoglycemia in the elderly can present as an acute neurological emergency that may mimic a cerebrovascular accident. Thus, it is important to check the plasma glucose level of any elderly patient presenting with acute neurological symptoms. Because of the long half-life of some sulfonylureas, it may be necessary to treat elderly hypoglycemic patients for 24 to 48 hours with an intravenous glucose infusion.

Weight gain is common with sulfonylureas—typically 1 to 2 kg. Whenever possible, clinicians should avoid the use of medications that cause weight gain in patients who are overweight or obese. Other side effects of sulfonylureas include nausea and vomiting, **cholestatic jaundice, agranulocytosis, aplastic and hemolytic anemias, generalized** hypersensitivity reactions, and dermatological reactions

Daonil[®] 5mg

(Glibenclamide)

Oral Antidiabetic

60 Tablets

SANOFI 



Amaryl[®]

glimepiride

Oral use

30 tablets

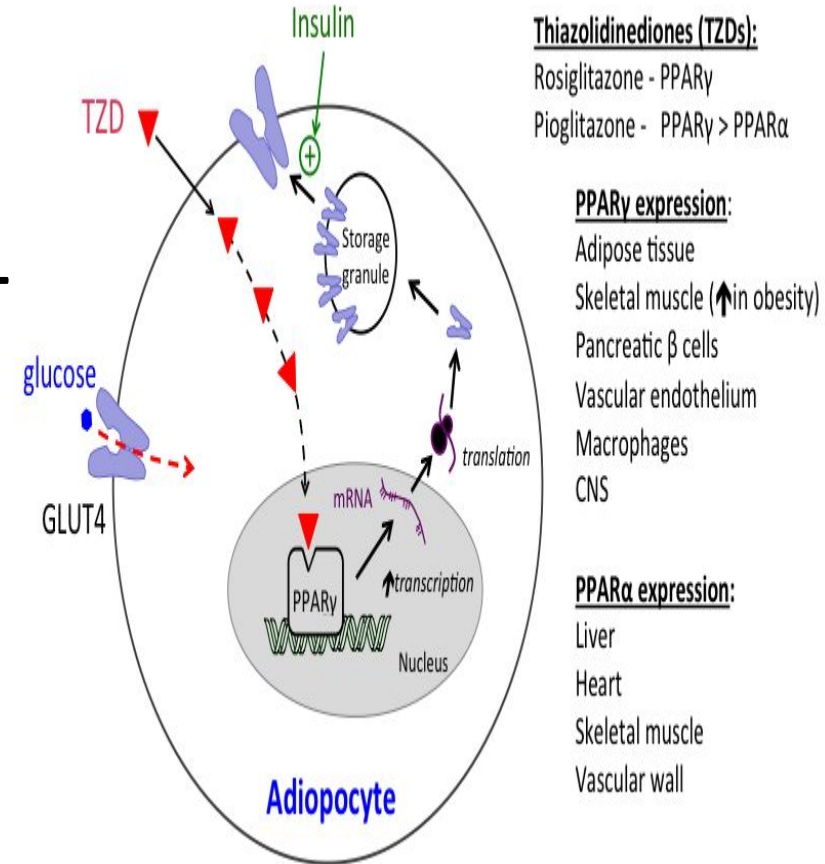
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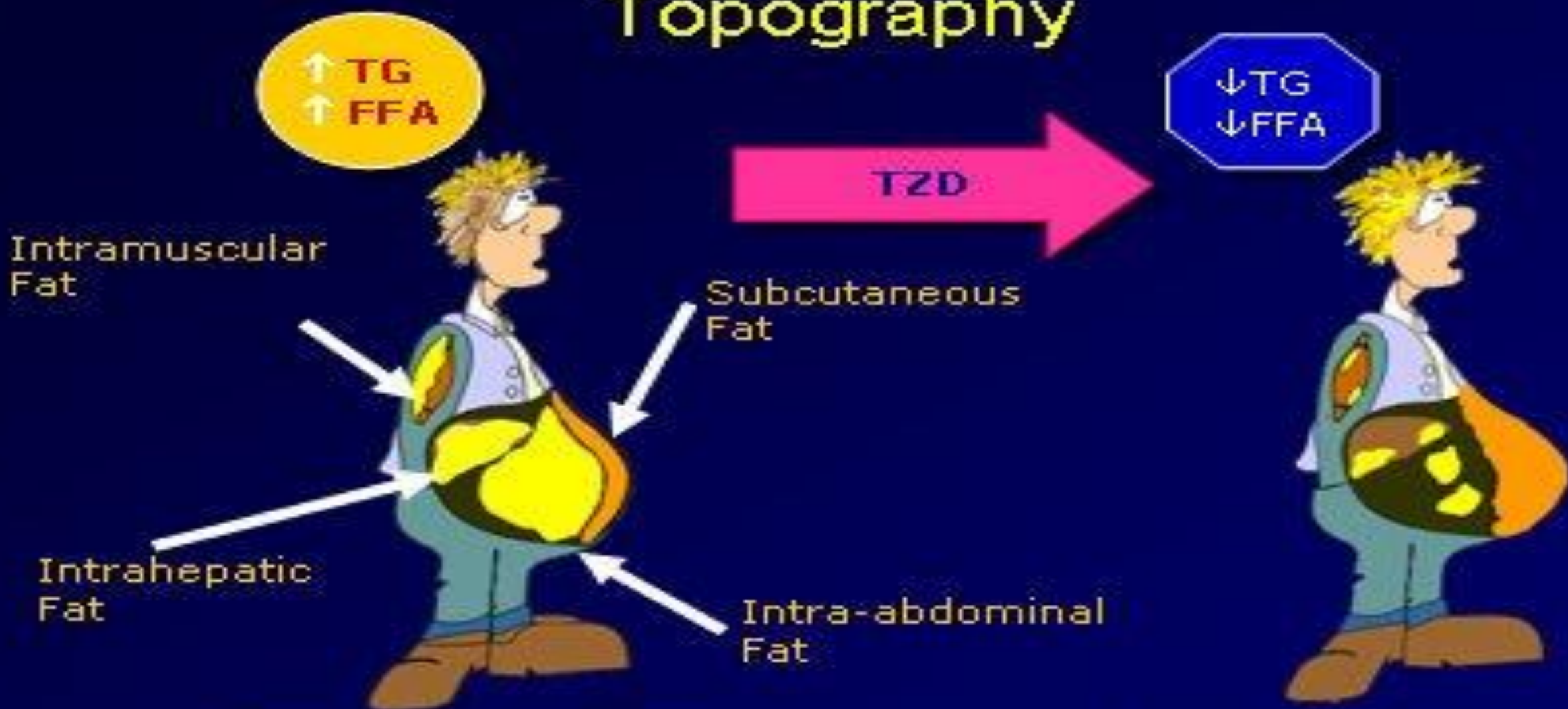


Thiazolidinediones TZDs (glitazones) (A 1C 0,5-1.4)

Pioglitazone and **rosiglitazone** are the two currently FDA-approved thiazolidinediones (TZDs) for the treatment of type 2 DM. They are oral agents, dosed once daily. TZDs work by binding to the **peroxisome proliferator activator receptor- γ (PPAR- γ)**, a nuclear receptor that is predominantly located on fat cells and vascular cells. Activation of PPAR- γ alters the transcription of several genes involved in glucose and lipid metabolism and energy balance. TZDs enhance insulin sensitivity at muscle, liver, and fat tissues. TZDs cause **preadipocytes** to differentiate into mature fat cells in subcutaneous fat stores. Small fat cells are more sensitive to insulin and more able to store FFAs. This allows a flux of FFAs out of the plasma, visceral fat, and liver into subcutaneous fat, a less insulin-resistant storage tissue. Muscle intracellular fat products, which contribute to insulin resistance, also decline.



Effect of Thiazolidinediones on Fat Topography



TZDs, but not MET, reduce macrophage infiltration into adipose tissue

The ADA algorithm recommends TZDs as a potential **second-line treatment** choice for type 2 DM, particularly when medication cost is a major concern or for those with a compelling need to avoid hypoglycemia. They can be used in combination with metformin and other second-line options.

A meta-analysis published in 2007 reported higher rates of **myocardial infarction** (MI) with rosiglitazone compared to placebo or other diabetes medications. This prompted a safety communication from the FDA and prescribing restrictions for the drug. **These restrictions were later removed after re-evaluation of the data determined no increased risk.** The prospective, multicenter, open-label trial found that rosiglitazone was noninferior to the metformin/sulfonylurea comparator for all CV outcomes except heart failure. Alternatively, pioglitazone has been associated with benefits related to **macrovascular outcomes**. In the PROactive study, three years of pioglitazone 45 mg resulted in a significant reduction of the composite of all-cause **mortality, nonfatal myocardial infarction, or stroke** by 16% in patients with type 2 DM who had previous macrovascular events.

Adverse effects

i. Weight gain

ii. **Fluid retention** (particularly peripheral edema) is worse with insulin use and is dose dependent.

Edema is less responsive to diuretic therapy. **Macular edema** can result.

iii. Risk of proximal **bone fractures**; use caution in patients with existing osteopenia or osteoporosis

(discontinuation reduces risk)

iv. Possible risk of **bladder cancer** with pioglitazone (dosage and duration of use dependent). Data are contradictory.

v. Increased risk of heart failure

(a) Boxed warning

(b) More than a 2-fold higher relative risk, although absolute risk is quite small

Both agents have been withdrawn from some countries in Europe.

Contraindications and precautions

i. Hepatic impairment

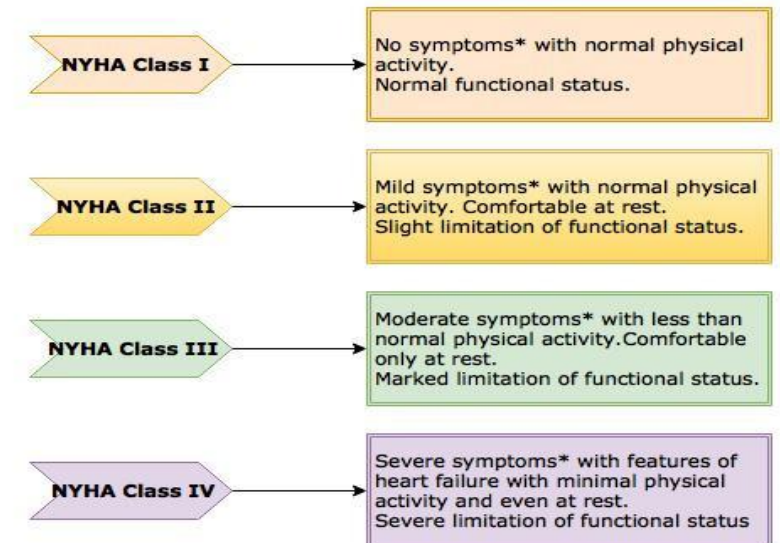
ii. Class III/IV heart failure (symptomatic heart failure)

iii. Existing fluid retention

Absorption, Excretion, and Dosing.

Rosiglitazone and pioglitazone are taken once a day. Both agents are absorbed within about 2 hours, but the maximum clinical effect is not observed for 6 to 12 weeks. The thiazolidinediones are metabolized by the liver and may be administered to patients with renal insufficiency but should not be used if there is active hepatic disease or significant elevations of serum liver transaminases.

New York Heart Association (NYHA) Classification of severity of Heart Failure



Symptoms - Fatigue, palpitations, chest pain, dyspnea, syncope

Glucagon-Like Peptide-1 Receptor Agonists(0.5%–1.5% A1C)

Mechanism of action: Synthetic analog of human GLP-1 that binds to GLP-1 receptors, resulting in glucose-dependent insulin secretion, reduction in glucagon secretion, and reduced gastric emptying; promotes satiety

Approved agents: Exenatide, liraglutide, dulaglutide, lixisenatide, and semaglutide

Six of these are delivered subcutaneously with dosing schedules ranging from twice daily (Exenatide) to once weekly and one is delivered orally once daily(semaglutide)

Adverse effects

- i. Nausea, vomiting, diarrhea common, but can subside or cease over time
- ii. **Hypoglycemia** common with concurrent sulfonylurea (consider reduction in sulfonylurea dose)
- iii. Postmarketing reports of pancreatitis and **acute renal failure** or impairment

Contraindications and precautions

- i. Impaired renal function: CrCl less than 30 mL/minute/1.73 m² for either exenatide formulation; less specific for liraglutide. No dose adjustment necessary with semaglutide
- ii. History of severe GI tract disorder, particularly **gastroparesis**
- iii. History of **pancreatitis**
- iv. For liraglutide, semaglutide, dulaglutide, once-weekly exenatide:
Contraindicated in patients with a personal or family history of medullary **thyroid carcinoma** (adverse effect found in rodent studies but not in humans)

HP8796

1 Prefilled Pen. Each Pen will deliver 60 doses, 10 µg per dose.

Byetta™ 10 µg, solution for injection

Exenatide 0.25mg/ml, 2.4ml

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Each prefilled pen contains **Exenatide 0.25 mg** (2.4 ml) (NADA 141-293)
Store at 2°C-8°C (36°F-46°F) in a refrigerator. Protect from light. Do not freeze.
Do not use if the solution is cloudy or contains a precipitate.



Dipeptidyl Peptidase-4 Inhibitors DPP-4 inhibitors (gliptin)(0.5%–0.8% A1C)

Four DPP-4 inhibitors are approved by the FDA: sitagliptin, saxagliptin, linagliptin, and alogliptin, all of which are oral, once daily products. These agents inhibit the DPP-4 enzyme responsible for the rapid degradation of GLP-1 which in turn increases pancreatic insulin secretion, limits glucagon secretion, slows gastric emptying, and promotes satiety

Adverse effects

- i. Upper respiratory and urinary tract infections, headache, severe joint pain
- ii. **Hypoglycemia** with monotherapy is minimal, but frequency is increased with concurrent sulfonylurea therapy (can lower dosage of sulfonylurea when initiating).
- iii. Sitagliptin has had some postmarketing reports of **acute pancreatitis, angioedema, Stevens- Johnson syndrome**, and anaphylaxis.

iv. Safety studies of saxagliptin and, to a lesser extent, alogliptin (but not sitagliptin and linagliptin) have shown an increased risk of heart failure hospitalization. In 2017, the FDA recommended warnings to package labeling of all DPP-4 inhibitors.

Contraindications and precautions

- i. Previous hypersensitivity to the agents
- ii. History of pancreatitis

considered weight neutral

Sodium-Glucose Cotransporter-2 Inhibitors SGLT-2(gliflozin) inhibitor(0.3%–1.0%A1C)

Four SGLT-2 inhibitors have been approved by the FDA including canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, all of which are oral, once daily products. SGLT-2 inhibitors reduce plasma glucose by preventing the kidneys **from reabsorbing glucose back into the bloodstream, leading to increased glucose excretion in the urine.** By inhibiting SGLT-2, the renal tubular threshold for glucose reabsorption is lowered and **glucosuria** occurs at lower levels of plasma glucose concentrations. SGLT-2 inhibition lowers BG through an insulin independent mechanism and exerts its glucose-lowering effect whenever the plasma glucose is elevated. Thus, **SGLT-2 inhibitors can lower both FPG and PPG and are effective even in the absolute absence of insulin.**

Empagliflozin, dapagliflozin, and canagliflozin can reduce cardiovascular morbidity in patients with T2D and established cardiovascular disease and may improve renal outcomes.

Canagliflozin or dapagliflozin in patients with significant urine albumin excretion and renal insufficiency reduces the risk of end-stage renal disease, doubling of SCr, or renal death.

- **Mild weight loss**

- **Adverse effects**

- i. Increased urination

- ii. Urinary tract infections

- iii. Genital mycotic infections (more common in females)

- iv. Hypotension

- v. Increased hypoglycemia risk with concomitant insulin or insulin secretagogue

- vi. Class is linked with rare cases of **euglycemic DKA and Fournier gangrene.**

- vii. Possible increased **bone fracture risk**, decreased bone mineral density, and foot or leg amputation with canagliflozin

Meglitinides(0.5%–1.5% A1C ↓)

- Meglitinides are similar to **sulfonylureas**, except they have a faster onset and shorter duration of action. By binding to a site adjacent to the sulfonylurea receptor, **nateglinide and repaglinide** stimulate insulin secretion from the β -cells of the pancreas.
- Adverse effects: **Hypoglycemia** (though less than with sulfonylureas), **weight gain, upper respiratory infection**

α -Glucosidase Inhibitors(0.5%–0.8% A1C)

Mechanism of action: Slows the absorption of glucose from the intestine to the bloodstream by slowing the breakdown of large carbohydrates into smaller absorbable sugars

Two agents available: Acarbose and miglitol

Adverse effects

- i. Flatulence, diarrhea, abdominal pain
- ii. Increased liver enzymes with high doses of acarbose

Contraindications and precautions: Inflammatory bowel disease, colonic ulcerations, intestinal obstruction

Treatment of Inpatient DM (non–critically ill population)

1. Joint guidelines from the ADA and AACE. The Endocrine Society also has guidelines (2016 ADA recommendations added new subsection dedicated to the issue).
2. Strong association between admission hyperglycemia and worse inpatient outcomes and length of stay. Outcomes are worse in those who have stress-related hyperglycemia or are not known to have diabetes previously.
3. Glycemic goals
 - a. Less than 140 mg/dL fasting or premeal
 - b. Less than 180 mg/dL random glucose
4. Treatment
 - a. Assess glucose concentrations before meals and at bedtime, if eating (every 4–6 hours if taking nothing by mouth [NPO]).
 - b. Threshold for initiating therapy is 180 mg/dL or greater.
 - c. According to the guidelines, subcutaneous insulin administration is the most practical way to improve hyperglycemia.
 - d. Oral diabetes agents are generally not recommended unless the patient is clinically stable and eating regularly, and no significant precautions or contraindications for their use exist.
 - e. Use of sliding-scale insulin alone is not recommended.
 - f. Basal-bolus insulin therapy as described earlier in the treatment of T1D is recommended unless the patient is NPO. If NPO, use basal insulin alone

Comparison of Therapies for Type 2 Diabetes Hyperglycemia Added to Metformin

Agent or Class	Primary Glycemic Effect	Benefits	Limitations and Precautions
Sulfonylurea	Fasting and prandial	Efficacy Cost	Weight gain Hypoglycemia risk Hastens β cell dysfunction
Meglitinide	Prandial	Prandial focus Use in kidney impairment	Hypoglycemia risk Weight gain Mealtime dosing
Pioglitazone	Fasting and prandial	Improved insulin sensitivity and pancreatic function Low risk of hypoglycemia Possible cardiovascular benefit Cost	Weight gain and edema Risk of heart failure Risk of osteoporosis Possible bladder cancer risk?
α -Glucosidase inhibitor	Prandial	No systemic absorption Prandial focus Weight loss	GI adverse effect profile Mealtime dosing Modest A1C effect
DPP-4 inhibitor	Prandial	Well tolerated Weight neutral	Possible pancreatitis risk? Modest A1C effect Possible increased heart failure risk (saxagliptin)

Agent or Class	Primary Glycemic Effect	Benefits	Limitations and Precautions
GLP-1 agonist	Once- or twice-daily formulations have prandial focus Once-weekly formulations affect both fasting and prandial	Greater effect on prandial glucose Weight loss Efficacy Improves pancreatic function? Cardiovascular benefit (liraglutide, semaglutide, dulaglutide)	Nausea and vomiting Injection-site effects Questionable pancreatitis or thyroid cancer risk? Cost
SGLT-2 inhibitors	Fasting and prandial	Low risk of hypoglycemia Efficacy Weight loss Possible heart failure and renal benefit	Urinary tract and genital infections Diuresis Euglycemic DKA?
Amylin agonist	Prandial	Modest weight loss Efficacy on postprandial glucose	High risk of hypoglycemia Must be taken with insulin Frequent injections Injection-site effects GI adverse effects
Insulin	Basal: Fasting Bolus: Prandial	Significant A1C reduction Flexibility in dosing strategies and titration	Hypoglycemia Weight gain Injection-site effects

Generic Name	Starting Dose	Usual Recommended Dose	Maximal dose (mg/day)	Dosing/Use in Renal Insufficiency ^a
Biguanides				
Metformin	500 mg once or twice daily or 850 mg once daily, titrate to target dose as tolerated	1,000 mg twice daily	2,550	Do not initiate if eGFR 30-45; Do not use if eGFR<30
Metformin XR	500 mg to 1,000 mg once daily, titrate to target dose as tolerated	2,000 mg once daily	2,500	Do not initiate if eGFR 30-45; Do not use if eGFR<30
Sulfonylureas (first generation)				
Chlorpropamide	250 mg once daily (100 mg once daily in older adults)	100-500 mg once daily	750	Consider alternative agent or initiate conservatively at 100 mg in renal insufficiency to avoid hypoglycemia
Tolazamide	250 mg once daily (100 mg once daily in older adults or if FPG<200 mg/dL [11.1 mmol/L])	250-500 mg once daily	1,000	Consider alternative agent or initiate conservatively at 100 mg in renal insufficiency to avoid hypoglycemia
Tolbutamide	1,000-2,000 mg once daily (250-500 mg once daily in older adults)	1,000-2,000 mg once daily	3,000	Consider alternative agent or initiate conservatively in renal insufficiency to avoid hypoglycemia
Sulfonylureas (second generation)				
Glimepiride	1-2 mg once daily (1 mg once daily in older adults)	4 mg once daily	8	Initiate conservatively at 1 mg in renal insufficiency to avoid hypoglycemia
Glipizide	5 mg once daily (2.5 mg daily in older adults)	5-10 mg once daily	40	Initiate conservatively at 2.5 mg in renal insufficiency to avoid hypoglycemia
Glipizide XL	5 mg once daily (2.5 mg once daily in older adults)	5-10 mg once daily	20	Initiate conservatively at 2.5 mg in renal insufficiency to avoid hypoglycemia
Glyburide	2.5-5 mg once daily (1.25 mg once daily in older adults)	5-10 mg once daily	20	Consider alternative agent or initiate conservatively at 1.25 mg in renal insufficiency to avoid hypoglycemia
Glyburide micronized	1.5-3 mg once daily (0.75 mg once daily in older adults)	3-6 mg once daily	12	Consider alternative agent or initiate conservatively at 0.75 mg in renal insufficiency to avoid hypoglycemia
Meglitinides				
Nateglinide	120 mg three times daily before meals	120 mg three times daily before meals	360	No adjustment required
Repaglinide	1-2 mg three times daily before meals (0.5 mg before meals if A1C<8% [0.08; 64 mmol/mol Hb])	2-4 mg three times daily before meals	16	Initiate conservatively at 0.5 mg before meals if CrCl 20-40 mL/min (0.33 to 0.67 mL/s)

Thiazolidinediones				
Pioglitazone	15 mg once daily	30 mg once daily	45	No dose adjustment required
Rosiglitazone	4 mg once daily or in two divided doses	4 mg once daily or in two divided doses	8	No dose adjustment required
α-Glucosidase inhibitors				
Acarbose	25 mg once to three times daily with meals	50 mg once to three times daily with meals	300	Avoid if CrCl < 25 mL/min (0.42 mL/s)
Miglitol	25 mg once to three times daily with meals	50 mg once to three times daily with meals	300	Avoid if CrCl < 25 mL/min (0.42 mL/s)
Sodium-glucose transporter (SGLT)-2 inhibitors				
Canagliflozin	100 mg once daily	100-300 mg once daily	300	100 mg once daily if eGFR 45-60; avoid if eGFR < 30
Dapagliflozin	5 mg once daily	5-10 mg once daily	10	Not recommended if eGFR < 45; avoid if eGFR < 30
Empagliflozin	10 mg once daily	10-25 mg once daily	25	Not recommended if eGFR < 45; avoid if eGFR < 30
Ertugliflozin	5 mg once daily	5-15 mg once daily	15	Avoid if eGFR < 60
Dipeptidyl peptidase (DPP)-4 inhibitors				
Alogliptin	25 mg once daily	25 mg once daily	25	12.5 mg once daily if CrCl 30-60 mL/min (0.5-1.0 mL/s); 6.25 mg once daily if CrCl < 30 mL/min (0.5 mL/s)
Linagliptin	5 mg once daily	5 mg once daily	5	No dose adjustment needed
Saxagliptin	2.5-5 mg once daily	5 mg once daily	5	2.5 mg once daily if eGFR $\leq$ 50
Sitagliptin	100 mg once daily	100 mg once daily	100	50 mg once daily if eGFR 30-50 25 mg once daily if eGFR < 30
Bile acid sequestrants				
Colestevlam	1.875 g twice daily or 3.75 g once daily	1.875 g twice daily or 3.75 g once daily	3.75 g/day	No dose adjustment needed
Dopamine agonists				
Bromocriptine	0.8 mg once daily	1.6-4.8 mg once daily	4.8	No dose adjustment needed