Drugs for Diabetes

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VII. ORAL AGENTS/ C. Biguanides

Metformin, the only biguanide, is classified as an **insulin sensitizer**. It increases glucose uptake and use by target tissues, thereby decreasing insulin resistance.

Unlike sulfonylureas, metformin does **not promote insulin secretion**.

Therefore, **hyperinsulinemia** is not a problem, and the risk of **hypoglycemia** is far less than that with sulfonylureas.

VII. ORAL AGENTS/ C. Biguanides/ 1. Mechanism of action:

The main mechanism of action of metformin is **reduction of hepatic gluconeogenesis**.

Metformin also **slows intestinal absorption of sugars** and improves peripheral glucose **uptake and utilization**.

Weight loss may occur because metformin causes **loss of appetite**.

Metformin may be used alone or in combination with other oral agents or insulin.

Hypoglycemia may occur when metformin is taken in combination with insulin or insulin secretagogues, so adjustment in dosage may be required.

VII. ORAL AGENTS/ C. Biguanides/ 2. Pharmacokinetics and fate:

Metformin is well absorbed **orally**, is not bound to serum proteins, and is not metabolized. Excretion is via the urine.

VII. ORAL AGENTS/ C. Biguanides/ 3. Adverse effects:

These are largely **gastrointestinal**. Metformin is contraindicated in **renal dysfunction** due to the risk of lactic acidosis.

It should be discontinued in cases of acute myocardial infarction, exacerbation of heart failure, sepsis, or other disorders that can cause acute renal failure.

Metformin should be used with caution in patients older than 80 years and in those with heart failure or alcohol abuse.

It should be temporarily discontinued in patients undergoing procedures requiring IV radiographic contrast.

Rarely, potentially **fatal lactic acidosis** has occurred. Long-term use may interfere with **vitamin B12 absorption**.

VII. ORAL AGENTS/ D. Thiazolidinediones

The thiazolidinediones (**TZDs**) are also **insulin sensitizers**.

The two members of this class are **pioglitazone and rosiglitazone** .

Although insulin is required for their action, the TZDs do not promote its release from the β cells, so hyperinsulinemia is not a risk.

VII. ORAL AGENTS/ D. Thiazolidinediones/ 1. Mechanism of action:

The TZDs **lower insulin resistance** by acting as **agonists** for the peroxisome proliferator–activated receptor-γ (**PPARγ**), a nuclear hormone receptor.

Activation of PPARγ regulates the transcription of several insulin responsive **genes**, resulting in **increased insulin sensitivity in adipose tissue, liver, and skeletal muscle.**

Effects of these drugs on cholesterol levels are of interest. **Rosiglitazone increases LDL** cholesterol and triglycerides, whereas **pioglitazone decreases triglycerides**. Both drugs increase HDL cholesterol.

The TZDs can be used as monotherapy or in combination with other glucose-lowering agents or insulin.

VII. ORAL AGENTS/ D. Thiazolidinediones/ 2. Pharmacokinetics and fate:

Pioglitazone and rosiglitazone are well absorbed after **oral** administration and are extensively bound to serum albumin.

Both undergo **extensive metabolism** by different CYP450 isozymes.

Some metabolites of pioglitazone have activity.

Renal elimination of pioglitazone is negligible, with the majority of active drug and metabolites excreted in the bile and eliminated in the feces.

Metabolites of rosiglitazone are primarily excreted in the urine.

No dosage adjustment is required in renal impairment.

These agents should be avoided in nursing mothers.

VII. ORAL AGENTS/ D. Thiazolidinediones/ 3. Adverse effects:

A few cases of **liver toxicity** have been reported with these drugs, and periodic monitoring of liver function is recommended.

Weight gain can occur because TZDs **may increase subcutaneous fat and cause fluid retention.**

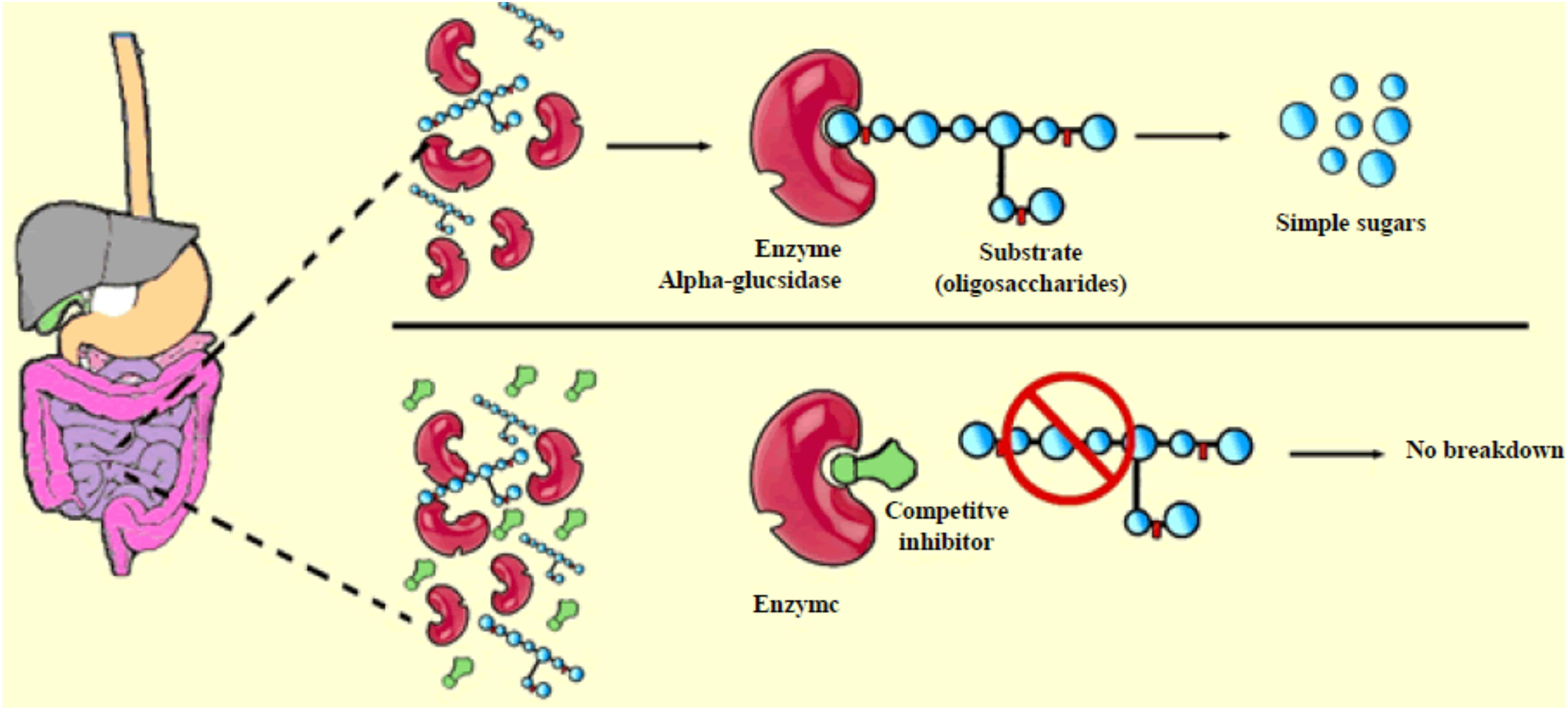
Fluid retention can worsen heart failure. These drugs should be avoided in patients with severe heart failure.

TZDs have been associated with **osteopenia and increased fracture risk**. Pioglitazone may also increase the risk of **bladder cancer**.

Several meta-analyses identified a potential increased risk of myocardial infarction and death from cardiovascular causes with rosiglitazone.

E. α-Glucosidase inhibitors/ 1. Mechanism of action:

Acarbose and miglitol are oral agents used for the treatment of type 2 diabetes.



E. α-Glucosidase inhibitors/ 1. Mechanism of action:

Acarbose and miglitol are oral agents used for the treatment of type 2 diabetes.

Located in the **intestinal brush border**, α-glucosidase enzymes b**reak down carbohydrates into glucose** and other simple sugars that can be absorbed.

Acarbose and miglitol reversibly inhibit α-glucosidase enzymes.

When taken at the start of a meal, these drugs delay the digestion of carbohydrates, resulting in lower postprandial glucose levels.

Since they do not stimulate insulin release or increase insulin sensitivity, these agents do not cause hypoglycemia when used as monotherapy.

However, when used with insulin secretagogues or insulin, hypoglycemia may develop.

E. α-Glucosidase inhibitors/ 2. Pharmacokinetics and fate:

Acarbose is poorly absorbed.

It is metabolized primarily by intestinal bacteria, and some of the metabolites are absorbed and excreted into the urine.

Miglitol is very well absorbed but has no systemic effects.

It is excreted unchanged by the kidney.

E. α-Glucosidase inhibitors/ 3. Adverse effects:

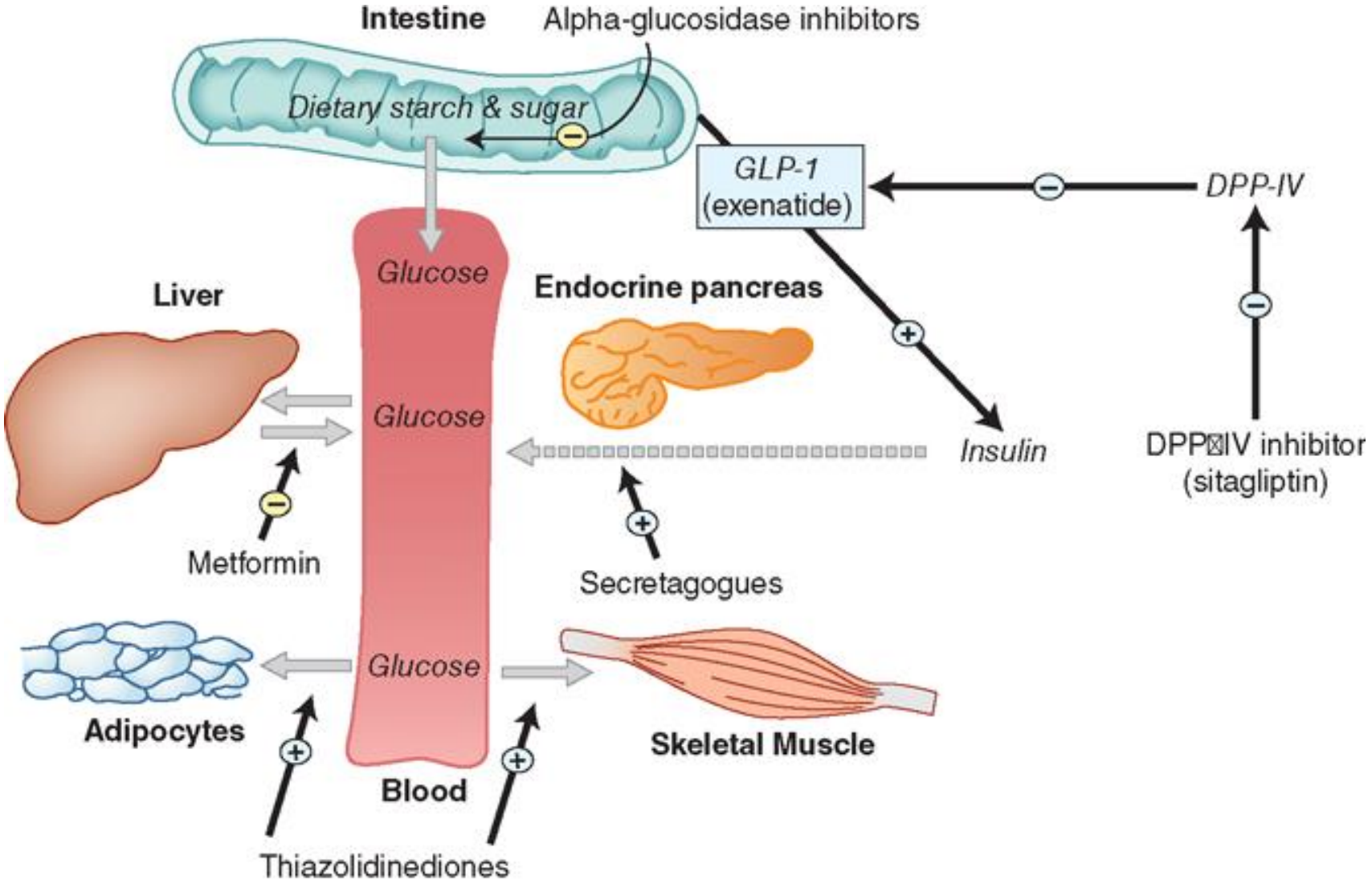
The major side effects are **flatulence, diarrhea, and abdominal cramping**.

Adverse effects limit the use of these agents in clinical practice.

Patients with inflammatory bowel disease, colonic ulceration, or intestinal obstruction should not use these drugs.

F. Dipeptidyl peptidase-4 inhibitors

Alogliptin, linagliptin, saxagliptin, and sitagliptin are orally active dipeptidyl peptidase-4 (**DPP-4) inhibitors** used for the treatment of type 2 diabetes.



F. Dipeptidyl peptidase-4 inhibitors/ 1. Mechanism of action:

These drugs **inhibit the enzyme DPP-4**, which is responsible for the **inactivation of incretin** hormones such as **GLP-1**.

Prolonging the activity of incretin hormones increases insulin release in response to meals and reduces inappropriate secretion of glucagon.

DPP-4 inhibitors may be used as monotherapy or in combination with sulfonylureas, metformin, TZDs, or insulin. Unlike incretin mimetics, these drugs do not cause satiety, or fullness, and are weight neutral.

F. Dipeptidyl peptidase-4 inhibitors/ 2. Pharmacokinetics and fate:

The DPP-4 inhibitors are well absorbed after **oral** administration.

Food does not affect the extent of absorption.

Alogliptin and sitagliptin are mostly excreted unchanged in the urine. Saxagliptin is metabolized via CYP450 3A4/5 to an active metabolite.

The primary route of elimination for **saxagliptin** and the metabolite is **renal**.

Linagliptin is primarily eliminated via the **enterohepatic** system.

All DPP-4 inhibitors except linagliptin require dosage adjustments in renal dysfunction.

F. Dipeptidyl peptidase-4 inhibitors/ 3. Adverse effects:

In general, DPP-4 inhibitors are well tolerated, with the most common adverse effects being **nasopharyngitis and headache**.

Although infrequent, **pancreatitis** has occurred with use of all DPP-4 inhibitors. Strong inhibitors of CYP450 3A4/5, such as ritonavir, atazanavir, itraconazole, and clarithromycin, may increase levels of saxagliptin. Therefore, reduced doses of saxagliptin should be used.

G. Sodium–glucose cotransporter 2 inhibitors/ 1. Mechanism of action:

Canagliflozin and dapagliflozin are the agents in this category of drugs for type 2 diabetes.

The sodium–glucose cotransporter 2 (SGLT2) is responsible for reabsorbing filtered glucose in the tubular lumen of the kidney.

By inhibiting SGLT2, these agents **decrease reabsorption of glucose**, increase urinary glucose excretion, and lower blood glucose.

Inhibition of SGLT2 also decreases reabsorption of sodium and causes **osmotic diuresis**.

Therefore, SGLT2 inhibitors **may reduce systolic blood pressure**. However, they are not indicated for the treatment of hypertension.

G. Sodium–glucose cotransporter 2 inhibitors/ 2. Pharmacokinetics and fate:

These agents are given **once daily** in the morning.

Canagliflozin should be taken before the first meal of the day. Both drugs are mainly **metabolized** by glucuronidation to inactive metabolites.

While the primary route of excretion for canagliflozin is via the feces, about one-third of a dose is renally eliminated.

These agents should be **avoided in patients with renal dysfunction**.

G. Sodium–glucose cotransporter 2 inhibitors/ 3. Adverse effects:

The most common adverse effects with SGLT2 inhibitors are **female genital mycotic infections** (for example, vulvovaginal candidiasis), **urinary tract infections**, and **urinary frequency.**

Hypotension has also occurred, particularly in the elderly or patients on diuretics. Thus, volume status should be evaluated prior to starting these agents.

H. Other agents

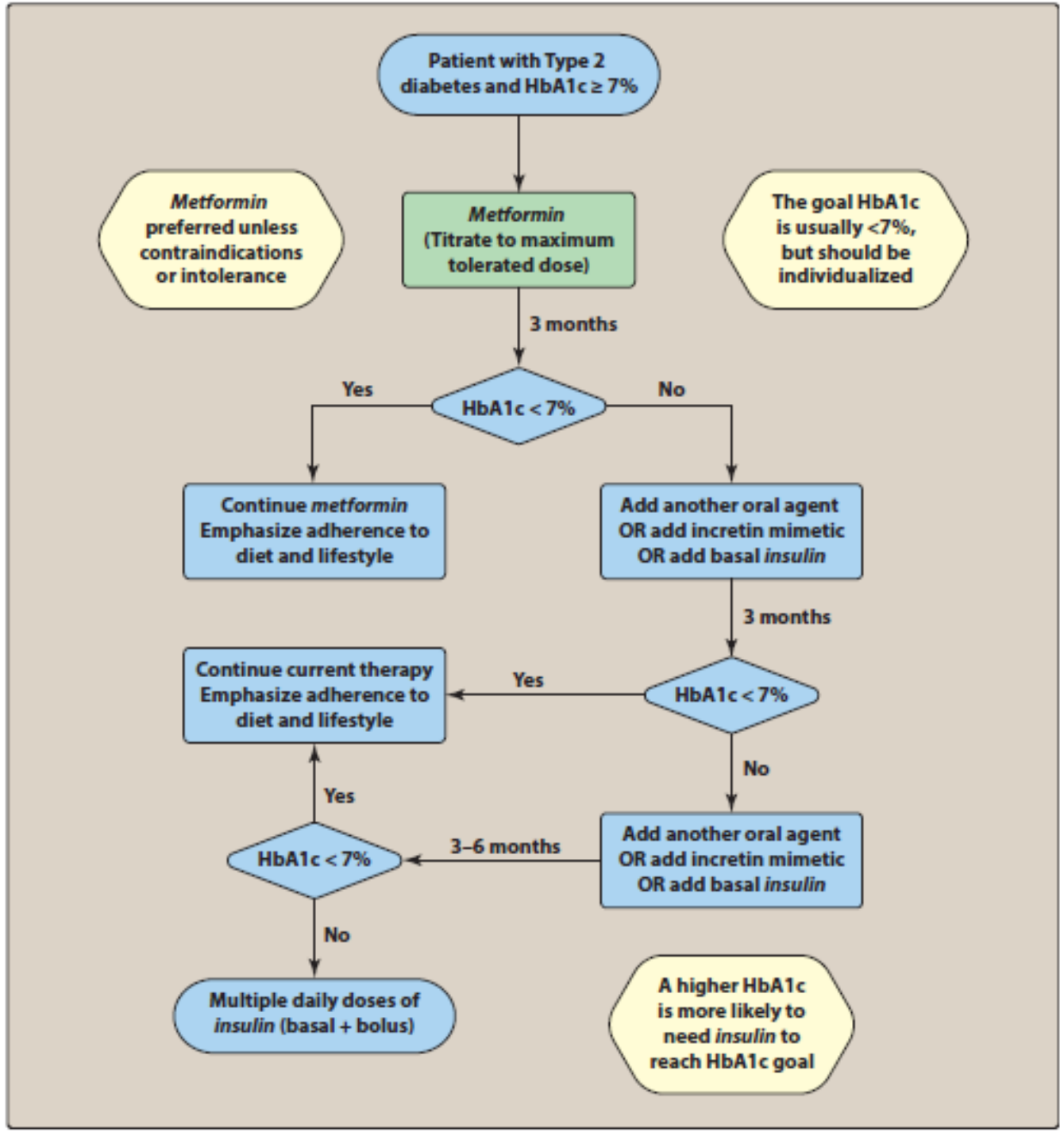
Both the dopamine agonist **bromocriptine** and the bile acid sequestrant **colesevelam** produce modest reductions in HbA1c.

The mechanism of action of glucose lowering is unknown for both of these drugs.

Although bromocriptine and colesevelam are indicated for the treatment of type 2 diabetes, their **modest efficacy, adverse effects**, and pill burden limit their use in clinical practice.

DRUG CLASS	MECHANISM OF ACTION	EFFECT ON PLASMA INSULIN	RISK OF HYPO-GLYCEMIA	COMMENTS
Sulfonylureas *Glimepiride* *Glipizide* *Glyburide*	Stimulates insulin secretion	↑	Yes	Well-established history of effectiveness. Weight gain can occur. Hypoglycemia most common with this class of oral agents.
Glinides *Nateglinide* *Repaglinide*	Stimulates insulin secretion	↑	Yes (rarely)	Taken with meals. Short action with less hypoglycemia. Postprandial effect.
Biguanides *Metformin*	Decreases hepatic production of glucose	↓	No	Preferred agent for type 2 diabetes. Well-established history of effectiveness. Weight loss may occur. Monitor renal function.
Thiazolidinediones (glitazones) *Pioglitazone* *Rosiglitazone*	Binds to peroxisome proliferator–activated receptor-γ in muscle, fat and liver to decrease insulin resistance	↓↓	No	Effective in highly insulin-resistant patients. Once-daily dosing for *pioglitazone*. Check liver function before initiation. Avoid in liver disease or heart failure.
α-Glucosidase inhibitors *Acarbose* *Miglitol*	Decreases glucose absorption	⇔	No	Taken with meals. Adverse gastro-intestinal effects.
DPP-4 inhibitors *Alogliptin* *Linagliptin* *Sitagliptin* *Saxagliptin*	Increases glucose-dependent insulin release; decreases secretion of glucagon	↑	No	Once-daily dosing. May be taken with or without food. Well tolerated. Risk of pancreatitis.
Incretin mimetics *Exenatide* *Liraglutide*	Increases glucose-dependent insulin release; decreases secretion of glucagon; slows gastric emptying; increases satiety	↑	No	Injection formulation. *Exenatide* should be injected twice daily within 60 minutes prior to morning and evening meals. Extended-release *exenatide* is given once weekly. *Liraglutide* is dosed once-daily without regard to meals. Weight loss may occur. Risk of pancreatitis.
SGLT2 inhibitors *Canagliflozin* *Dapagliflozin*	Increases urinary glucose excretion	⇔	No	Once-daily dosing in the morning. Risk of hypotension, hyperkalemia. Avoid in severe renal impairment.

Summary of oral agents used to treat diabetes. ⇔ = little or no change. DPP-4 = dipeptidyl peptidase-4.



Treatment guidelines for type 2 diabetes.