Drugs for Diabetes

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I. Overview

- The pancreas produces the peptide hormones **insulin, glucagon, and somatostatin.** The peptide hormones are secreted from cells in the islets of Langerhans (***β-cells produce insulin, α cells produce glucagon, and δ cells produce somatostatin)***.
- These hormones play an important role in regulating metabolic activities of the body, particularly glucose homeostasis.
- A relative or absolute lack of insulin, as seen in diabetes mellitus, can cause serious hyperglycemia. Left untreated, **retinopathy, nephropathy, neuropathy, and cardiovascular complications may result**.
  Administration of insulin preparations or other glucose-lowering agents (Figure 24.1) can reduce morbidity and mortality associated with diabetes.

INSULIN

Inhaled insulin AFREZZA
Insulin aspart NOVOLOG
Insulin degludec TRESIBA
Insulin detemir LEVEMIR
Insulin glargine BASAGLAR, LANTUS, TOUJEO
Insulin glulisine APIDRA
Insulin lispro HUMALOG
NPH insulin suspension HUMULIN N, NOVOLIN N
Regular insulin HUMULIN R, NOVOLIN R

AMYLIN ANALOG

Pramlintide SYMLIN

ORAL AGENTS

Acarbose PRECOSE
Alogliptin NESINA
Bromocriptine CYCLOSET
Canagliflozin INVOKANA
Colesevelam WELCHOL
Dapagliflozin FARXIGA
Empagliflozin JARDIANCE
Ertugliflozin STEGLATRO
Glimepiride AMARYL
Glipizide GLUCOTROL
Glyburide DIABETA, GLYNASE PRESTAB
Linagliptin TRADJENTA
Metformin FORTAMET, GLUCOPHAGE
Miglitol GLYSET
Nateglinide STARLIX
Pioglitazone ACTOS
Repaglinide PRANDIN
Rosiglitazone AVANDIA
Saxagliptin ONGLYZA
Sitagliptin JANUVIA
Tolbutamide GENERIC ONLY

GLP-1 RECEPTOR AGONISTS

Albiglutide TANZEUM
Dulaglutide TRULICITY
Exenatide BYETTA, BYDUREON
Liraglutide VICTOZA
Lixisenatide ADLYXIN
Semaglutide OZEMPIC

II. Diabetes Mellitus

- Diabetes is not a single disease. Rather, it is a heterogeneous group of syndromes characterized by elevated blood glucose attributed to a ***relative or absolute deficiency of insulin.***
- The American Diabetes Association (ADA) recognizes four clinical **classifications of diabetes: type 1 diabetes, type 2 diabetes, gestational diabetes, and diabetes due to other causes such as genetic defects or medications.** Figure 24.2 summarizes the characteristics of type 1 and type 2 diabetes.
- Gestational diabetes is defined as carbohydrate intolerance with onset or first recognition during pregnancy.

	Type 1	Type 2
Age at onset	Usually during childhood or puberty	Commonly over age 35
Nutritional status at time of onset	Commonly undernourished	Obesity usually present
Prevalence among diagnosed diabetics	5%–10%	90%–95%
Genetic predisposition	Moderate	Very strong
Defect or deficiency	β Cells are destroyed, eliminating the production of insulin	Inability of β cells to produce appropriate quantities of insulin; insulin resistance; other defects

igure 24.2 Comparison of type 1 and type 2 diabetes.

A. Type 1 diabetes

Type 1 diabetes most commonly afflicts children, adolescents, or young adults, but some latent forms occur later in life. The disease is characterized by an absolute deficiency of insulin due to destruction of β cells.

Without functional β cells, the pancreas fails to respond to glucose, and a person with type 1 diabetes shows classic symptoms of insulin deficiency (polydipsia, polyphagia, polyuria, and weight loss).

- **1. Cause**
  Loss of β-cell function in type 1 diabetes results from **autoimmune-mediated processes** that may be triggered by viruses or other environmental toxins.
- In patients without diabetes, constant β-cell secretion maintains low **basal levels of circulating insulin**. This suppresses lipolysis, proteolysis, and glycogenolysis. A burst of insulin secretion occurs within 2 minutes after ingesting a meal, in response to transient increases in circulating glucose and amino acids. This lasts for up to 15 minutes, followed by the postprandial secretion of insulin. However, ***without functional β cells, those with type 1 diabetes can neither maintain basal secretion of insulin nor respond to variations in circulating glucose*** (Figure 24.3).

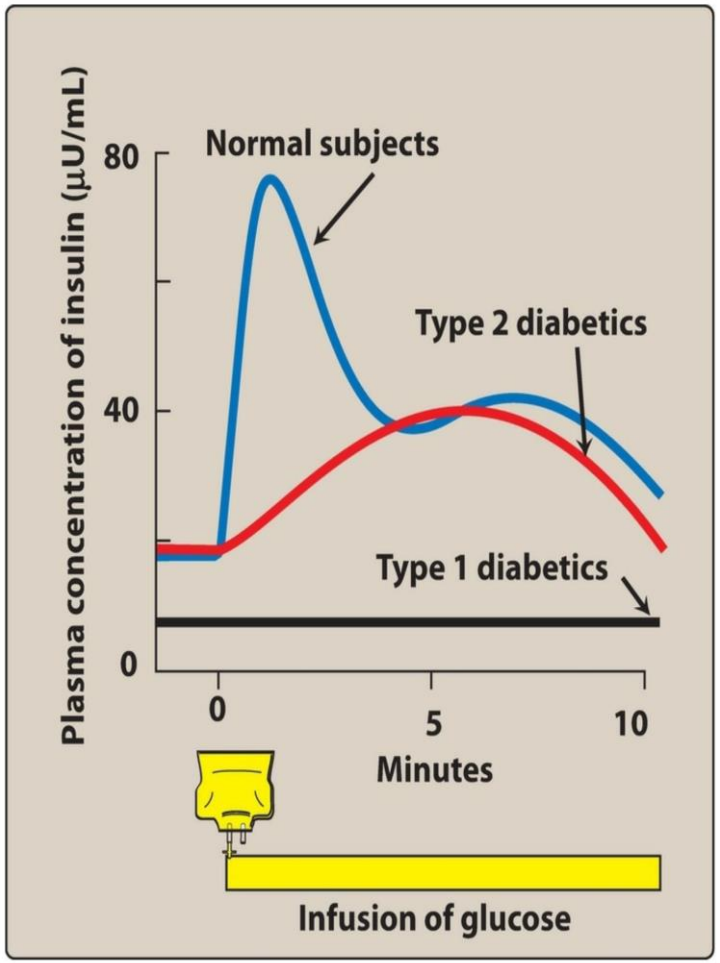


Figure 24.3 Release of insulin that occurs in response to an IV glucose load in normal subjects and diabetic patients.

- **2. Treatment**
  A person with type 1 diabetes must **rely on exogenous insulin** to ***control hyperglycemia, avoid ketoacidosis, and maintain acceptable levels of glycosylated hemoglobin (HbA1c).***
- [Note: HbA1c is a marker of overall glucose control and is used to monitor diabetes in clinical practice. The rate of formation of HbA1c is proportional to the average blood glucose concentration over the previous 3 months. A higher average glucose results in a higher HbA1c.]
- ***The goal of insulin therapy in type 1 diabetes is to maintain blood glucose as close to normal as possible and to avoid wide fluctuations in glucose***. The use of home blood glucose monitors facilitates frequent self-monitoring and treatment with insulin.

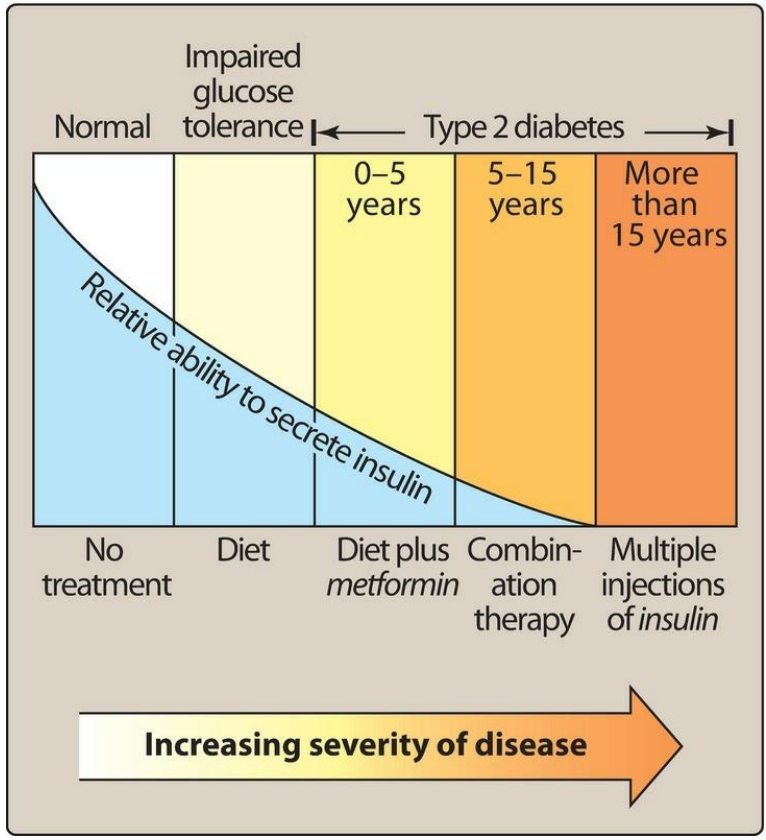
B. Type 2 diabetes

- Type 2 diabetes accounts for greater **than 90% of cases**.
- Type 2 diabetes is influenced by genetic factors, aging, obesity, and peripheral insulin resistance, rather than autoimmune processes.
- The metabolic alterations are generally milder than those observed with type 1 diabetes (for example, patients with type 2 diabetes typically are **not ketotic**), but the long-term clinical consequences are similar.

1. Cause

Type 2 diabetes is ***characterized by a lack of sensitivity of target organs to insulin*** (Figure 24.4). In type 2 diabetes, the pancreas retains some β-cell function, but ***insulin secretion is insufficient*** to maintain glucose homeostasis (Figure 24.3)

- in the face of increasing peripheral insulin resistance. The β-cell mass may gradually decline over time in type 2 diabetes. In contrast to patients with type 1 diabetes, those with type 2 diabetes are often obese. **Obesity** contributes to insulin resistance, which is considered the major underlying defect of type 2 diabetes.



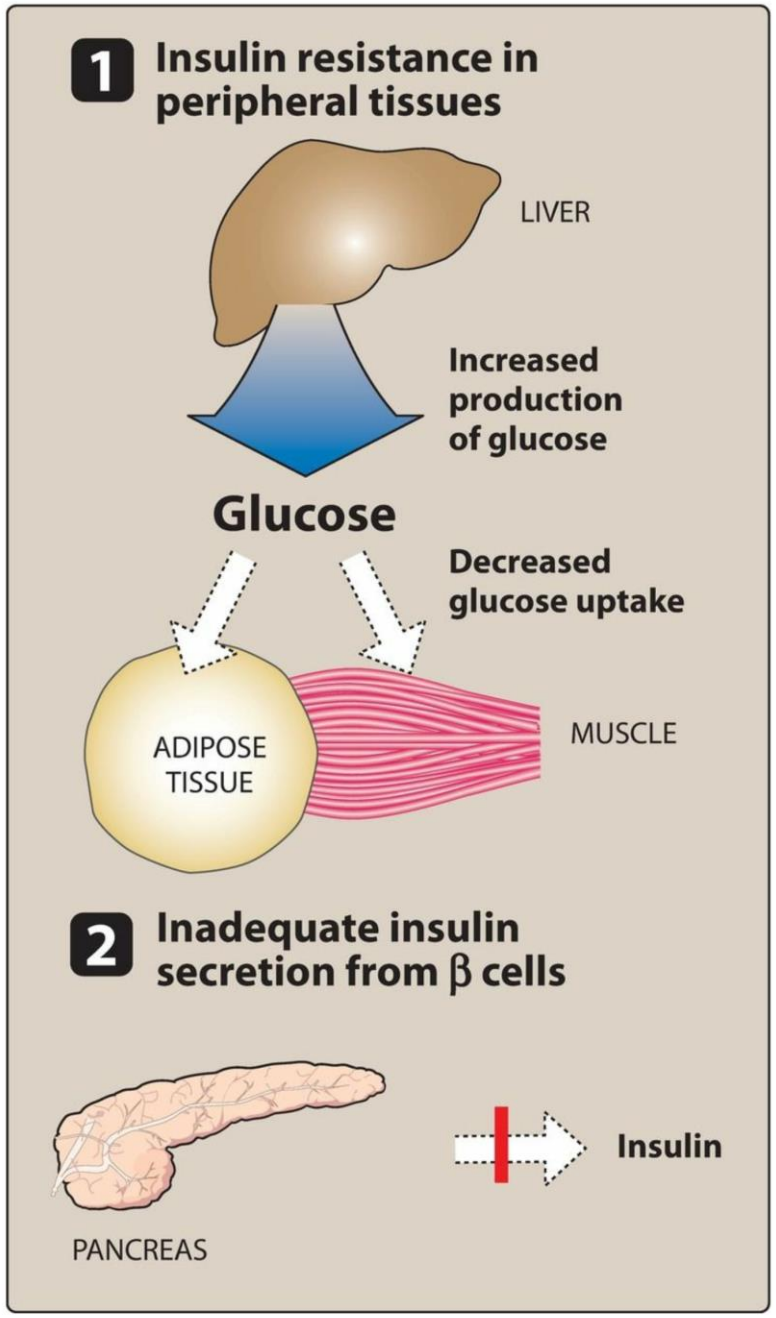


Figure 24.4 Major factors contributing to hyperglycemia observed in type 2 diabetes.

2. Treatment

The **goal** in treating type 2 diabetes is to ***maintain blood glucose within normal limits and to prevent the development of long-term complications***. Weight reduction, exercise, and dietary modification decrease insulin resistance and correct hyperglycemia in some patients with type 2 diabetes. However, most patients require pharmacologic intervention with oral glucose-lowering agents. As the disease progresses, β-cell function declines, and insulin therapy is often needed to achieve satisfactory glucose levels (Figure 24.5).

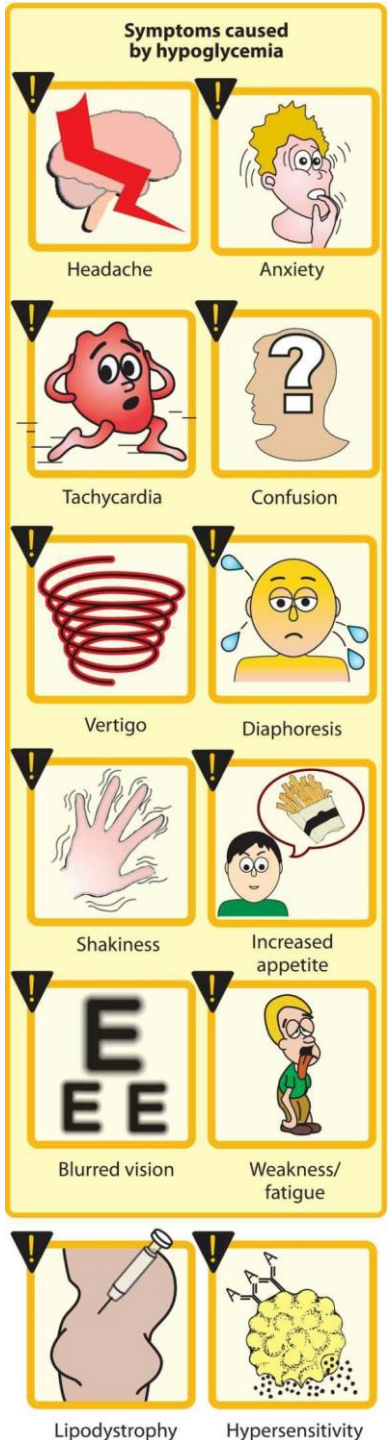
III. Insulin and Insulin Analogs

- Insulin [IN-su-lin] is a **polypeptide** hormone consisting of two peptide chains that are connected by disulfide bonds. It is synthesized as a precursor (**proinsulin**) that undergoes proteolytic cleavage to ***form insulin and C-peptide***, both of which are secreted by the β cells of the pancreas. [Note: Because insulin undergoes significant hepatic and renal extraction, plasma insulin levels may not accurately reflect insulin production. Thus, ***measurement of C-peptide provides a better index of insulin levels***.]
- Insulin secretion is regulated by blood glucose levels, certain amino acids, other hormones, and autonomic mediators. Secretion is most often triggered by increased blood glucose, which is
  taken up by the glucose transporter into the β cells of the pancreas. There, it is phosphorylated by glucokinase, which acts as a glucose sensor. The products of glucose metabolism enter the mitochondrial respiratory chain and generate adenosine triphosphate (ATP). The rise in ATP levels causes a blockade of K+ channels, leading to membrane depolarization and an influx of Ca2+. The increase in intracellular Ca2+ causes pulsatile insulin exocytosis.

- **A. Mechanism of action**
  Exogenous insulin is administered to replace absent insulin secretion in type 1 diabetes or to supplement insufficient insulin secretion in type 2 diabetes.
- **B. Pharmacokinetics**
  Human insulin is produced by recombinant DNA technology using strains of **Escherichia coli or yeast** that are
  genetically altered to contain the gene for human insulin. Modification of the amino acid sequence of human insulin produces insulins with different pharmacokinetic properties.
- ***Insulin preparations vary primarily in their onset and duration of activity. Dose, injection site, blood supply, temperature, and physical activity can also affect the onset and duration of various insulin preparations.*** Because insulin is a polypeptide, it is degraded in the gastrointestinal tract if taken orally. Therefore, it is generally administered by **subcutaneous** injection, although an **inhaled** insulin
  formulation is also available. [Note: In a hyperglycemic emergency, *regular insulin* is administered intravenously (**IV**).]

- Continuous subcutaneous insulin infusion (also called the **insulin pump**) is another method of insulin delivery.
  This method of administration may be more convenient for some patients, eliminating multiple daily injections of insulin. The pump is programmed to deliver a basal rate of insulin. In addition, it allows the patient to deliver a bolus of insulin to cover mealtime carbohydrate intake and compensate for high blood glucose

- **C. Adverse effects**
  Hypoglycemia is the most serious and common adverse reaction to insulin (Figure 24.6). Other adverse effects include **weight gain, local injection site reactions, and lipodystrophy**. Lipodystrophy can be minimized by rotation of injection sites. Diabetics with renal insufficiency may require a decrease in insulin dose. Due to the potential for bronchospasm with inhaled insulin, patients with asthma, chronic obstructive pulmonary disease, and smokers should not use this formulation.



- **IV. Insulin Preparations and Treatment**
  Insulin preparations are classified as **rapid-**, **short-**, **intermediate-**, or **long-acting**. Figure 24.7 summarizes onset of action, timing of peak level, and duration of action for the various types of insulin. It is important that clinicians exercise caution when adjusting insulin treatment, paying strict attention to the dose and type of insulin.

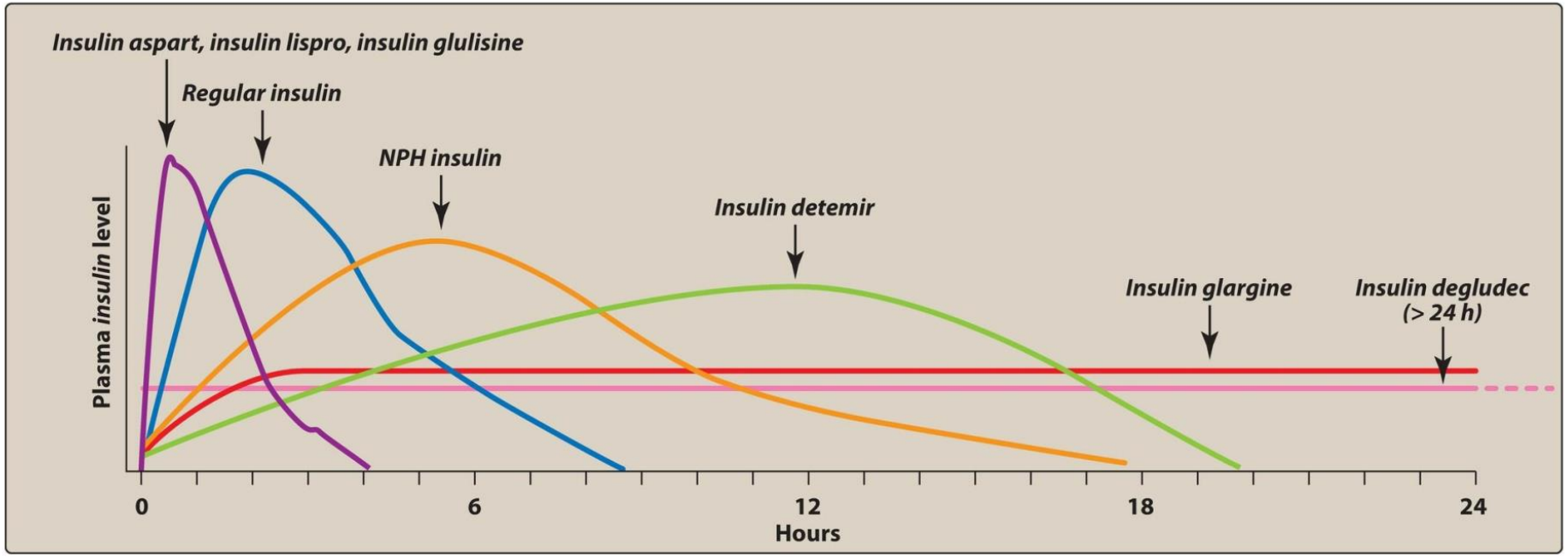
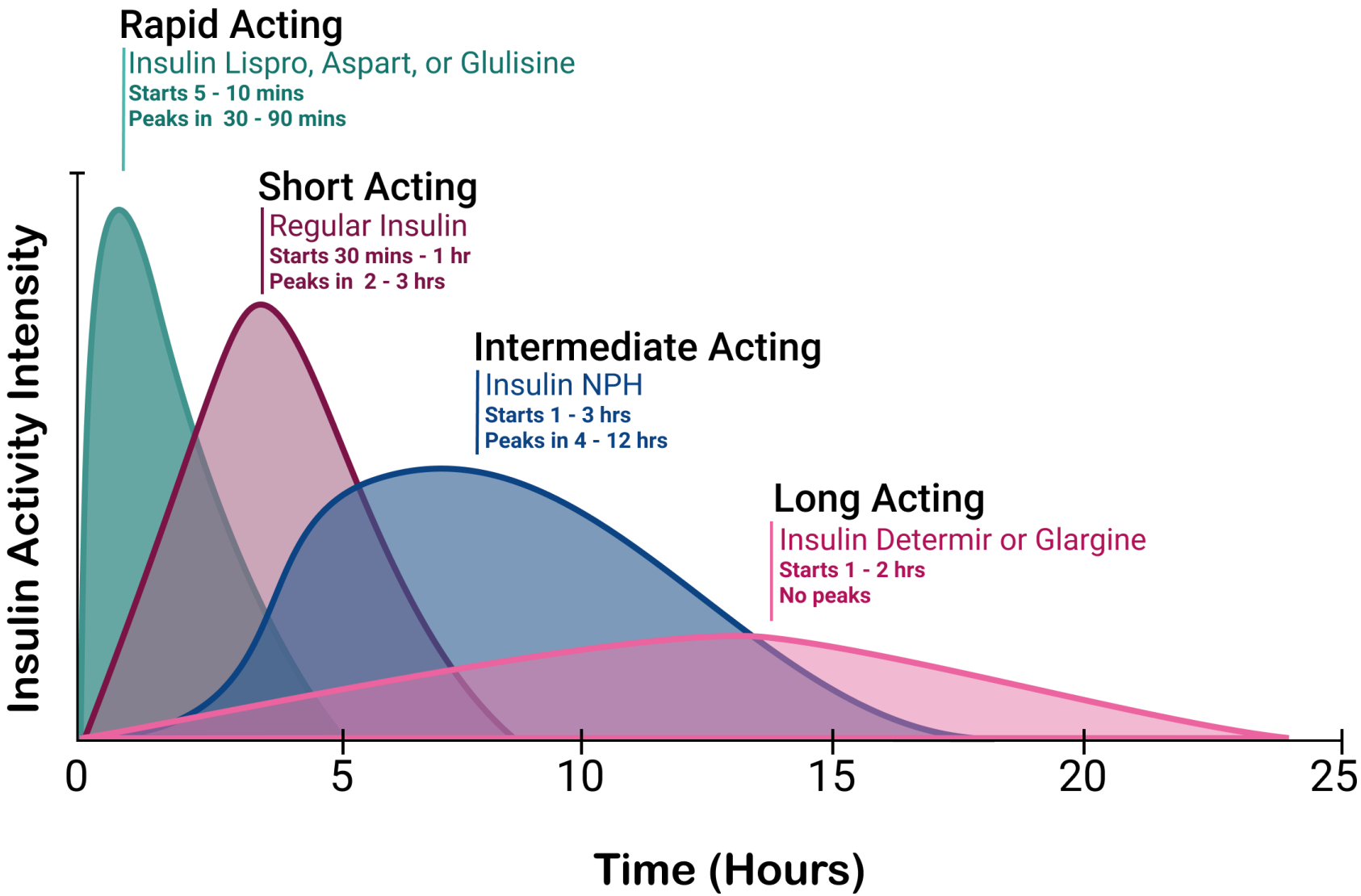


Figure 24.7 Onset and duration of action of human insulin and insulin analogs. NPH = neutral protamine Hagedorn.

Types of Insulin



- **A. Rapid-acting and short-acting insulin preparations**
  Five preparations fall into this category: ***regular insulin, insulin lispro [LIS-proe], insulin aspart [AS-part], insulin glulisine [gloo-LYSE-een], and inhaled insulin.***

- ***Regular insulin*** is a *short-acting, soluble, crystalline zinc insulin*.
  Insulin lispro, aspart*, and *glulisine are classified as **rapid-acting** insulins.
  Modification of the amino acid sequence of *regular insulin* produces analogs that are rapid-acting insulins. This modification results in more rapid absorption, a quicker onset, and a shorter duration of action after subcutaneous injection. Peak levels of *insulin* ***lispro*** are seen at **30 to 90 minutes**, as compared with **50 to 120 minutes** for ***regular*** *insulin*.
  Insulin aspart and *insulin glulisine* have pharmacokinetic and pharmacodynamic properties similar to those of *insulin lispro*. ***Inhaled insulin*** is also considered ***rapid-acting.***


NovoLog®
(insulin aspart) injection
100 units/mL (U-100)
For intravenous or subcutaneo
Rx only
Use only with a U-100 syringe.
10 mL multiple-dose vial
ONLY FOR RETAIL SALE BY
WALMART AND ITS AFFILIATES
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NovoLog®
(insulin aspart) injection
100 units/mL (U-100)
For intravenous or
subcutaneous use
10 mL multiple-dose vial
Manufactured by: Novo Nordisk
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℞ 100 U/ml 5×3 ml
Solution for injection, for s.c. use
Insulin aspart
NovoRapid®
FlexPen®
Insulin aspart,
biosynthetic (r-DNA origin)
NovoRapid® FlexPen®
is designed to be used
with NovoFine® needles
NovoFine® needles
are not included
Ask for NovoFine® needles
Destroy FlexPen® after use.
NovoRapid®
FlexPen®
novo nordisk®

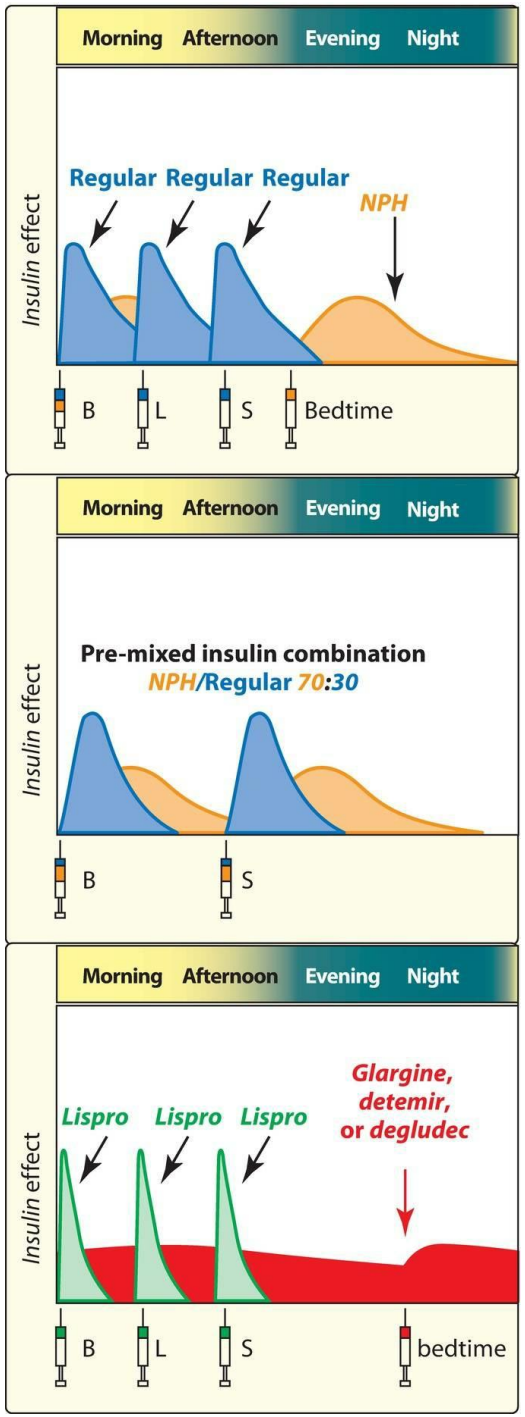

NDC 0002-8799-59
Humalog
KwikPen®
insulin lispro injection, USP (rDNA origin)
For Single Patient Use Only
HP-8799
U-100
100 units per mL
Rx only
Needles not included
This device is recommended for use with
Becton, Dickinson and Company's insulin pen needles
prefilled insulin delivery device
5 x 3 mL Prefilled Pens
Read Insulin Delivery Device Instructions for Use


Apidra® SoloStar®
Insulin glulisine
100 IU/mL
Injection solution for s.c. use
SANOFI
5 SOLOSTAR injection pens with cartridges
Apidra®
SoloStar®
Insulin glulisine


NDC 0002-8215-01
10 mL
HI-210
100 units per mL
Humulin® R
REGULAR
insulin human injection
U-100
Lilly

- This dry powder formulation is inhaled and absorbed through pulmonary tissue, with peak levels achieved within **45 to 60 minutes**.
- Rapid- or short-acting insulins are ***administered to mimic the prandial (mealtime) release of insulins and to control postprandial glucose***. They may also be used in cases where swift correction of elevated glucose is needed. **Rapid-** and **short-acting** insulins are usually used in conjunction with **alonger-actin**g basal insulin that provides control of fasting glucose. *Regular insulin* should be injected subcutaneously ***30 minutes before*** a meal, whereas rapid-acting insulins are administered in the 15 minutes preceding a meal or ***within 15 to 20 minutes after starting a meal***. Rapid-acting insulin suspensions are commonly used in external insulin pumps, and they are suitable for IV administration, although *regular insulin* is most commonly used when the IV route is needed.

- **B. Intermediate-acting insulin**
- **Neutral protamine Hagedorn (NPH)** insulin is an intermediate-acting insulin formed by the addition of **zinc and protamine** to regular insulin. [Note: Another name for this preparation is insulin isophane.] The combination with protamine forms a complex that is less soluble, resulting in delayed absorption and a longer duration of action. NPH insulin is used for basal (fasting) control in type 1 or 2 diabetes and is usually given along with rapid- or short-acting insulin for mealtime control. NPH insulin should be given only subcutaneously (never IV), and it should not be used when rapid glucose lowering is needed (for example, diabetic ketoacidosis).



c. Long-acting insulin preparations

The isoelectric point of *insulin* ***glargine*** [GLAR-geen] is lower than that of human insulin, leading to formation of a
precipitate at the injection site that releases insulin over an extended period. It has a slower onset than *NPH insulin*
and a flat, prolonged hypoglycemic effect with no peak (Figure 24.7). *Insulin* ***detemir*** [deh-TEE-meer] has a fatty acid side chain that enhances association to albumin. Slow dissociation from albumin results in long-acting properties similar to those of *insulin glargine*. ***Insulin degludec*** [de-GLOO-dek] remains in solution at physiologic
pH, with a slow release over an extended period.

- It has the longest half-life of the long-acting insulins. As with *NPH insulin*, *insulin glargine*, *insulin detemir*, and *insulin degludec* are used for basal control and should only be administered subcutaneously.
- *Long-acting insulins should not be mixed in the same syringe with other insulins, because doing so may alter the pharmacodynamic profile.*


NDC 0088-2219-05
Lantus® SoloStar®
insulin glargine injection
For Single Patient Use Only
100 units/mL (U-100)
Five 3 mL Prefilled Pens
Solution for injection in a disposable insulin delivery device
Do not mix with other insulins
For subcutaneous injection only
Use only if solution is clear and colorless with no particles visible
Use within 28 days after initial use
*Needles not included (see back panel)
℞ ONLY
SANOFI


5×3 ml
Levemir®
FlexPen®
100 U/ml
100 U/ml
Solution for injection in pre-filled pen
Insulin detemir
Subcutaneous use
Designed to be used with NovoFine®
or NovoTwist® disposable needles up
to a length of 8 mm
Needles are not included
novo nordisk®


5 x 3 ml
Cartouches/Patronen
HI 0719
Humuline®
100 IU/mL
70/30
Suspension for Injection in Cartridges
Human Insulin
30% Soluble Insulin
70% Isophane Insulin
Subcutaneous (or
intramuscular) injection only
Lilly

- **D. Insulin combinations**
  Various premixed combinations of human insulins, such as 70% *NPH insulin* plus 30% *regular insulin* (Figure 24.8)
  or 50% of each of these, are also available. Use of premixed combinations decreases the number of daily injections but makes it more difficult to adjust individual components of the insulin regimen.

- **E. Standard treatment versus intensive treatment**
- **Standard** insulin therapy involves **twice daily injections**. In contrast, **intensive** treatment utilizes **three or more** injections daily with frequent monitoring of blood glucose levels.
- The ADA recommends a **target** mean blood glucose level of ***154 mg/dL or less (HbA1c ≤ 7%)*** for most patients, and intensive treatment is more likely to achieve this goal. ***The frequency of hypoglycemic episodes, coma, and seizures is higher with intensive insulin regimens*** (Figure 24.9A). However, patients on intensive therapy show a significant reduction in microvascular complications of diabetes such as **retinopathy**, **nephropathy, and neuropathy** compared to patients receiving standard care (Figure 24.9B). Intensive therapy should not be recommended for patients with long-standing diabetes, significant microvascular complications, advanced age, and those with hypoglycemic unawareness.

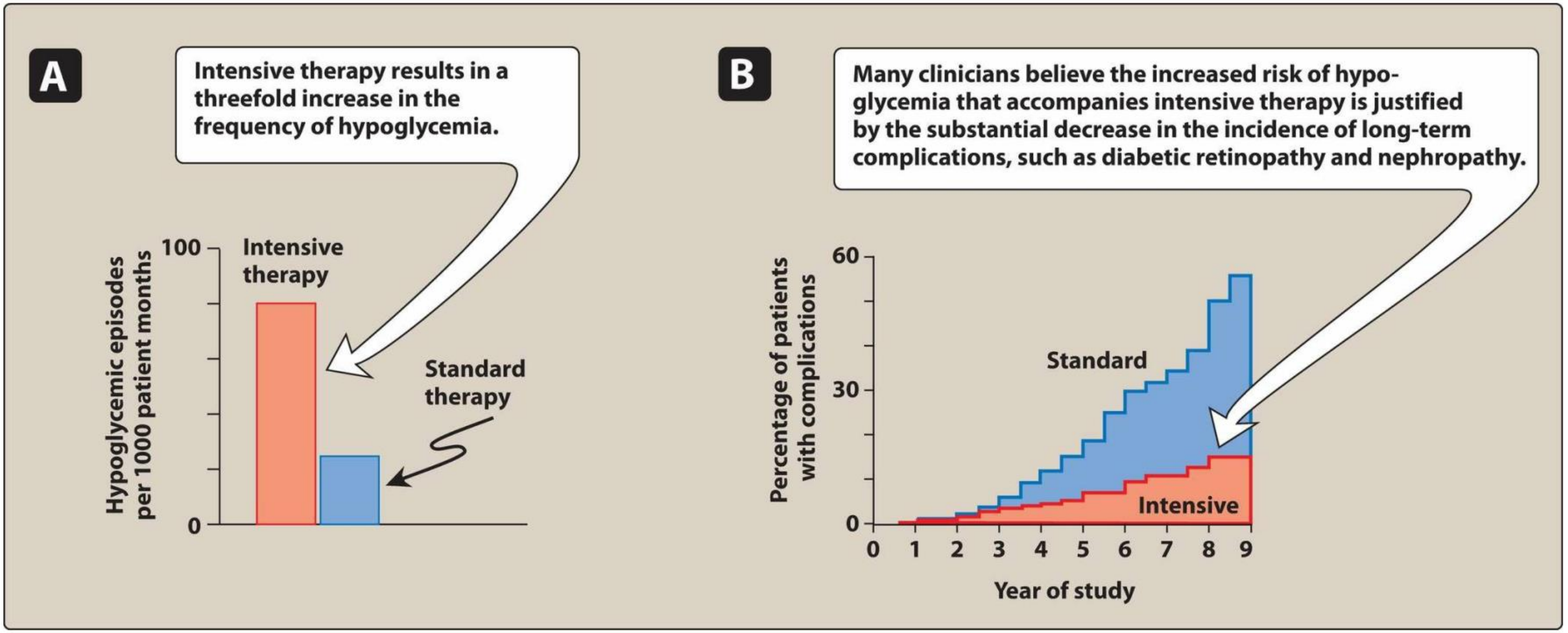


Figure 24.9 A. Effect of tight glucose control on hypoglycemic episodes in a population of patients with type 1 diabetes receiving intensive or standard therapy. **B.** Effect of standard and intensive care on the long-term complications of diabetes.

- **V. Synthetic Amylin Analog**
  Amylin is a hormone that is co-secreted with insulin from β cells following food intake.
- ***It delays gastric emptying, decreases postprandial glucagon secretion, and improves satiety.*** ***Pramlintide*** [PRAM-lin-tide] 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.

- **VI. Glucagon-like Peptide Receptor Agonists**
- Oral intake of glucose results in a higher secretion of insulin than occurs when an equal load of glucose is given IV. This effect is referred to as the “incretin effect” and is markedly reduced in type 2 diabetes. The incretin effect occurs because the gut releases incretin hormones, notably glucagon-like peptide-1 (GLP-1) and glucose-dependent
insulinotropic polypeptide (GIP), in response to a meal. Incretin hormones are responsible for 60% to 70% of postprandial insulin secretion. ***Albiglutide*** [al-bi-GLOO-tide], ***dulaglutide*** [doo-la-GLOO-tide], ***exenatide*** [EX-enah-tide], ***liraglutide*** [LIR-a-GLOO-tide], ***lixisenatide*** [lix-i-SEN-a-tide], and *semaglutide* [sem-a-GLOO-tide] are injectable GLP-1 receptor agonists used for the treatment of type 2 diabetes.
-

- *Liraglutide* is also approved to reduce the risk of cardiovascular events and cardiovascular mortality in patients with type 2 diabetes and cardiovascular disease. Two premixed preparations of long-acting insulins and GLP-1 receptor agonists are available: *insulin glargine* plus *lixisenatide* and *insulin degludec* plus *liraglutide*. Use of these combinations may decrease daily insulin requirements and the number of daily injections.
- **A. Mechanism of action**
  These agents are analogs of GLP-1 that exert their activity by improving glucose-dependent insulin secretion, slowing gastric emptying time, reducing food intake by enhancing satiety (a feeling of fullness), decreasing postprandial glucagon secretion, and promoting β-cell proliferation. Consequently, postprandial hyperglycemia is reduced, HbA1c levels decline, and weight loss may occur.

- **B. Pharmacokinetics**

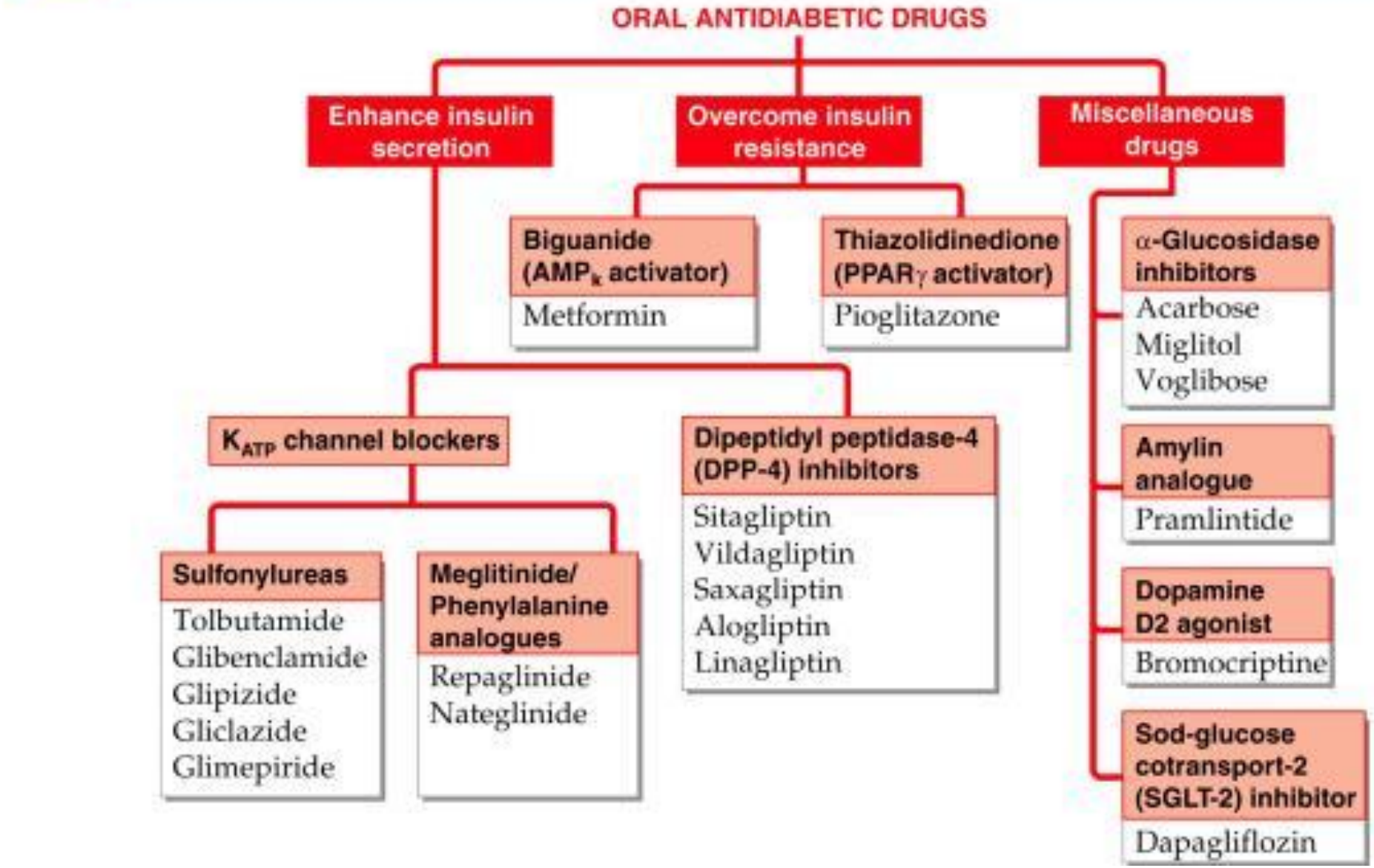
  GLP-1 receptor agonists are administered subcutaneously, since they are polypeptides. *Albiglutide*, *dulaglutide*, *liraglutide*, and *semaglutide* are considered long-acting GLP-1 receptor agonists. *Albiglutide*, *dulaglutide*, and *semaglutide* are dosed once weekly, while *liraglutide* is available as a once-daily injection. *Lixisenatide* is a shortacting GLP-1 receptor agonist that is dosed once daily. *Exenatide* is available as both a short-acting (dosed twice daily) and extended-release preparation (dosed once weekly). *Exenatide* should be avoided in patients with severe renal impairment.

- **C. Adverse effects**

  The main adverse effects of the incretin mimetics consist of nausea, vomiting, diarrhea, and constipation. GLP-1 receptor agonists have been associated with pancreatitis and should be avoided in patients with chronic pancreatitis. Longer-acting agents have been associated with thyroid C-cell tumors in rodents. It is unknown if GLP-1 receptor agonists cause these tumors or thyroid carcinoma in humans, although they are contraindicated in patients with a history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2.

VII. Oral Agents

- Oral agents are **useful** in the treatment of **patients** who have type 2 diabetes that **is not controlled with diet.**
- Patients who developed diabetes **after age 40** and have **had diabetes less than 5 years** are most likely to respond well to oral glucose-lowering agents. Patients with **long-standing disease** may require a combination of **oral agents with or without insulin** to control hyperglycemia. Figure 24.10 summarizes the duration of action of some of the oral glucose-lowering drugs, and Figure 24.11 illustrates some of the common adverse effects.


ORAL ANTIDIABETIC DRUGS
Enhance insulin secretion
Overcome insulin resistance
Miscellaneous drugs
Biguanide (AMPK activator)
Metformin
Thiazolidinedione (PPARγ activator)
Pioglitazone
α-Glucosidase inhibitors
Acarbose
Miglitol
Voglibose
KATP channel blockers
Dipeptidyl peptidase-4 (DPP-4) inhibitors
Sitagliptin
Vildagliptin
Saxagliptin
Alogliptin
Linagliptin
Amylin analogue
Pramlintide
Sulfonylureas
Tolbutamide
Glibenclamide
Glipizide
Gliclazide
Glimepiride
Meglitinide/ Phenylalanine analogues
Repaglinide
Nateglinide
Dopamine D2 agonist
Bromocriptine
Sod-glucose cotransport-2 (SGLT-2) inhibitor
Dapagliflozin

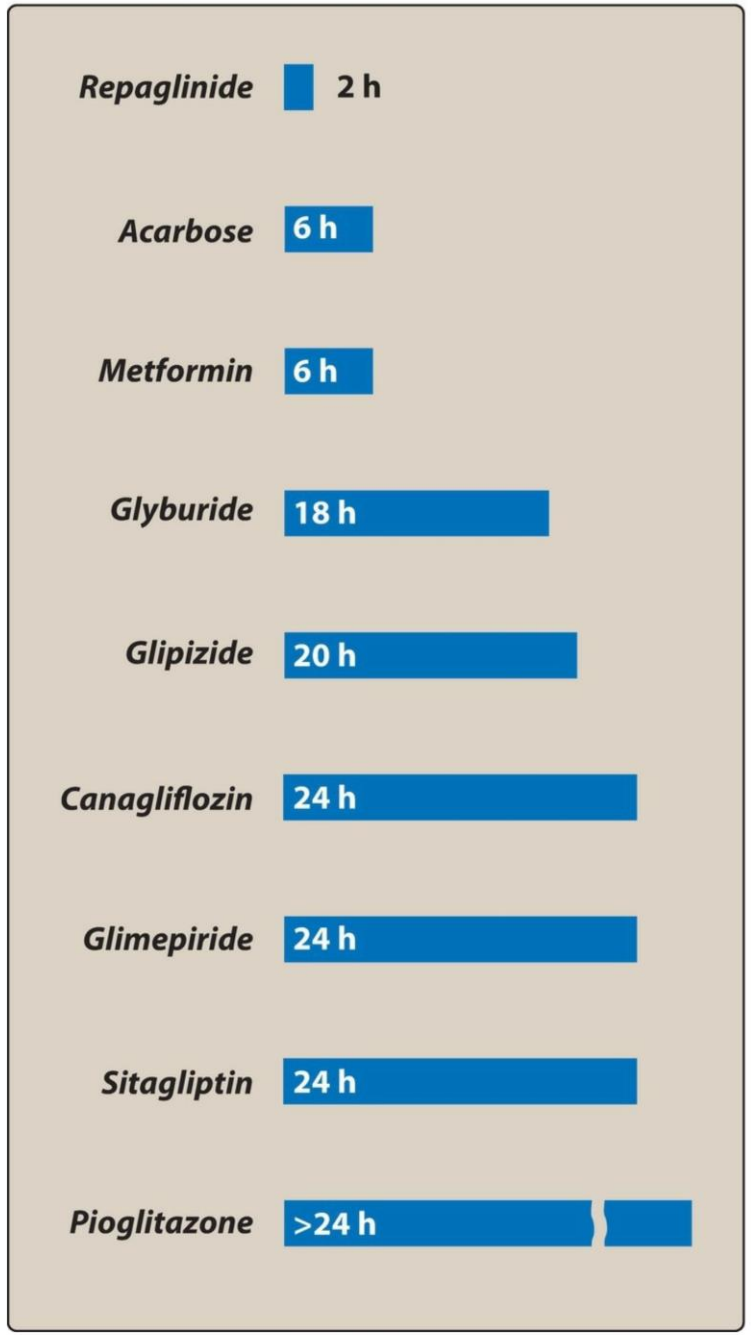


Figure 24.10 Duration of action of some oral hypoglycemic agents.

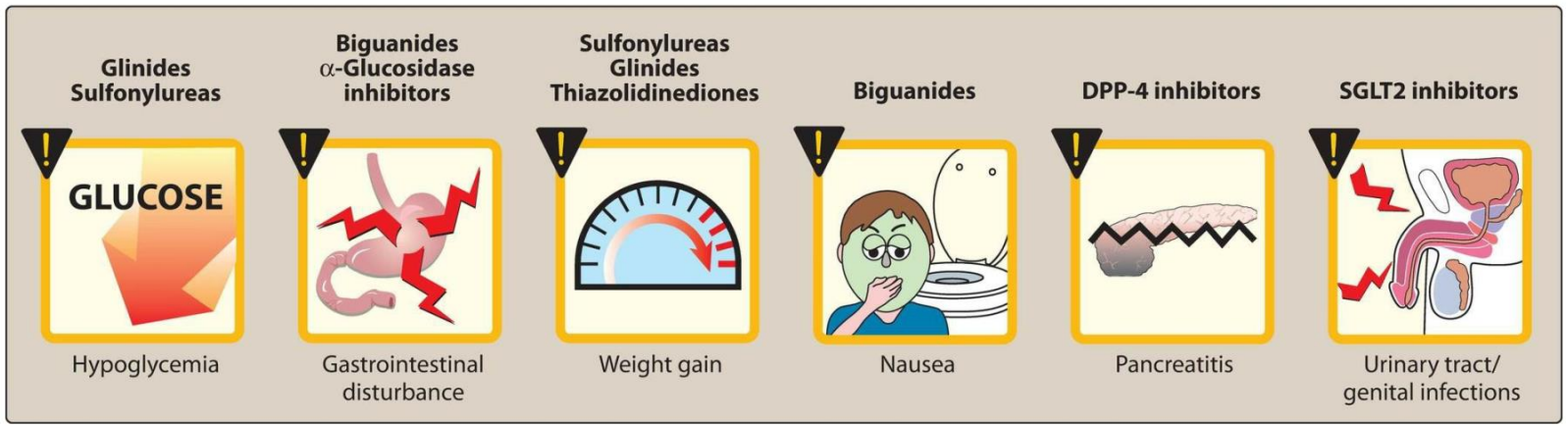


Figure 24.11 Some adverse effects observed with oral hypoglycemic agents.

A. Sulfonylureas

- These agents are classified as insulin **secretagogues**, *because they promote insulin release from the β cells of the pancreas*. The sulfonylureas most used in clinical practice are the second-generation drugs *glyburide* [GLYE-byooride], *glipizide* [GLIP-ih-zide], and *glimepiride* [GLYE-me-pih-ride].

1. Mechanism of action

These agents *stimulate insulin release* from the β cells of the pancreas. Sulfonylureas *block ATP-sensitive K+ channels*, resulting in depolarization, Ca2+ influx, and insulin exocytosis. In addition, sulfonylureas may *reduce hepatic glucose production* and *increase peripheral insulin sensitivity.*

2. Pharmacokinetics

Given orally, these drugs bind to serum proteins, are metabolized by the liver, and are excreted in the urine and feces. The **duration of action** ranges from **12 to 24 hours**.

- **3. Adverse effects**
  Adverse effects of the sulfonylureas include **hypoglycemia**, **hyperinsulinemia, and weight gain**.
- They should be used with **caution** in **hepatic or renal insufficiency,** since accumulation of sulfonylureas may cause hypoglycemia. Renal impairment is a particular problem for *glyburide*, as it may increase the duration of action and increase the risk of hypoglycemia significantly.
- ***Glipizide or glimepiride are safer options in renal dysfunction and in elderly patients.***
- Figure 24.12 summarizes some drug interactions with sulfonylureas.

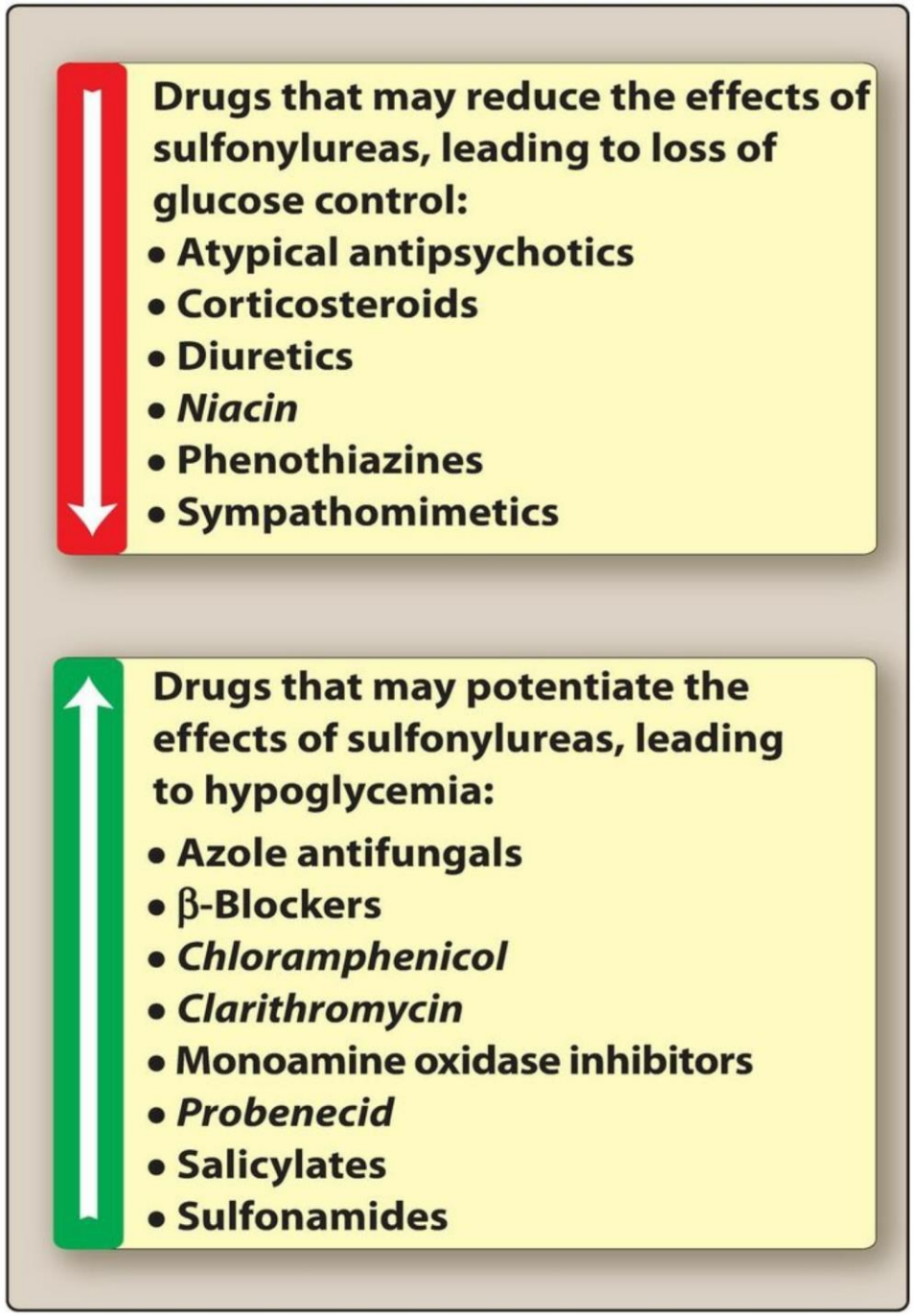
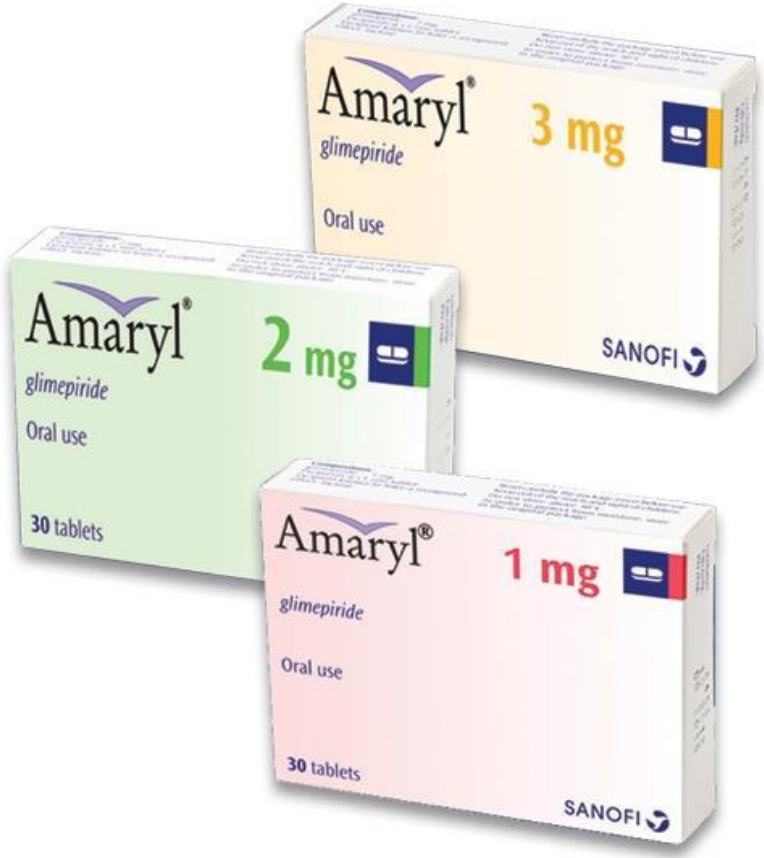


Figure 24.12 Drugs interacting with sulfonylureas.

Table 1: Classification of SUs[3,4]

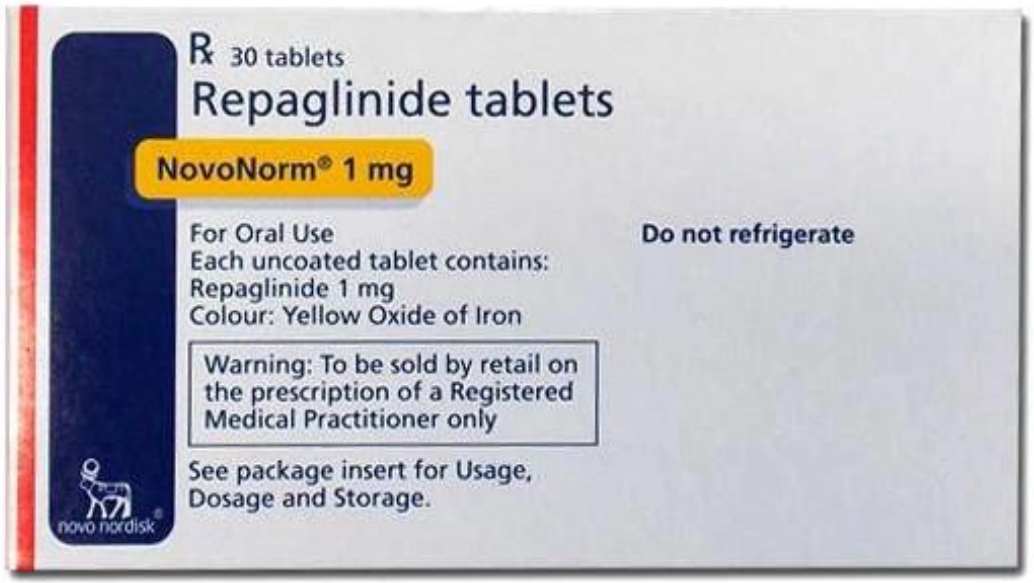
Classification based on generation	**Molecules**
First-generation	Tolbutamide, chlorpropamide
Second-generation	Glipizide, glibenclamide, gliclazide
Third-generation	Glimepiride
Classification based on hierarchy of development	
Conventional	Tolbutamide, glibenclamide
Modern	Glimepiride, gliclazide MR, glipizide MR
Classification based on mechanism of action	
Short-acting	Tolbutamide
Intermediate-acting	Glipizide, gliclazide
Long-acting	Glibenclamide, glimepiride, glipizide MR, gliclazide MR

SUs: Sulfonylureas



- **B. Glinides**
  This class of agents includes ***repaglinide*** [re-PAG-lin-ide] and ***nateglinide*** [nuh-TAY-gli-nide]. Glinides are also considered ***insulin secretagogues.***
- **1. Mechanism of action**
  Like the sulfonylureas, the glinides **stimulate insulin secretion**. In contrast to the sulfonylureas, the glinides ***have a rapid onset and a short duration of action***. They are particularly effective in the early release of insulin that occurs after a meal and are categorized as ***postprandial glucose regulators.***
- Glinides should ***not be used in combination with sulfonylureas*** due to overlapping mechanisms of action and increased risk of serious hypoglycemia.
- **2. Pharmacokinetics**
  Glinides should be taken prior to a meal and are well absorbed after oral administration. Both glinides are metabolized to inactive products by cytochrome P450 3A4 (CYP3A4; see Chapter 1) in the liver and are excreted through the bile.
- **3. Adverse effects**
  Although glinides cause **hypoglycemia** and **weight gain**, the incidence is lower than that with sulfonylureas. By inhibiting hepatic metabolism, the lipid-lowering drug *gemfibrozil* may significantly increase the effects of *repaglinide*, and concurrent use is contraindicated.

  These agents should be used with **caution in patients with hepatic impairment**.


℞ 30 tablets
Repaglinide tablets
NovoNorm® 1 mg
For Oral Use
Each uncoated tablet contains:
Repaglinide 1 mg
Colour: Yellow Oxide of Iron
Do not refrigerate
Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only
See package insert for Usage, Dosage and Storage.
novo nordisk


NOVARTIS
STARLIX
nateglinid
120 mg

C. Biguanides

- ***Metformin*** [met-FOR-min], 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, the risk of hypoglycemia is far less than that with sulfonylureas. *Metformin* is also ***useful in the treatment of polycystic ovary syndrome***, as it reduces insulin resistance seen in this disorder.
-

  1. Mechanism of action
  The main mechanism of action of *metformin* is **reduction of hepatic gluconeogenesis**. [Note: Excess glucose produced by the liver is a major source of high blood glucose in type 2 diabetes, accounting for high fasting blood glucose.] *Metformin* also **slows intestinal absorption of sugars** and **improves peripheral glucose uptake and utilization.**

- ***Weight loss may occur because metformin causes loss of appetite***.
- The ADA recommends *metformin* ***as the initial drug of choice for type 2 diabetes***. *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.
- **2. Pharmacokinetics**
  Metformin is well absorbed after oral administration, is **not bound** to serum proteins, and is **not metabolized**. Excretion is via the urine.

3. Adverse effects

These are largely **gastrointestinal**, including diarrhea, nausea, and vomiting. These effects can be alleviated by titrating the dose of *metformin* slowly and administering doses with meals.

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 be associated with vitamin B12 deficiency***, and periodic measurement of vitamin B12 levels is recommended, especially in patients with anemia or

peripheral neuropathy.

D. Thiazolidinediones

- The thiazolidinediones (TZDs) are also **insulin sensitizers**. The two agents in this class are ***pioglitazone*** [pye-ohGLI-ta-zone] and ***rosiglitazone*** [roe-si-GLIH-ta-zone].
- Although insulin is required for their action, the TZDs do not promote its release from the β cells, so hyperinsulinemia is not a risk.
- **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.***
- The TZDs can be used as monotherapy or in combination with other glucose-lowering agents or insulin. The dose of insulin may have to be lowered when used in combination with these agents. The ADA recommends ***pioglitazone as a second- or third-line agent for type 2 diabetes***. ***Rosiglitazone*** is less utilized due to concerns regarding ***cardiovascular adverse effects.***

2. Pharmacokinetics

Pioglitazone and *rosiglitazone* are well absorbed after oral administration and are ***extensively bound to serum albumin***. Both undergo extensive metabolism by different CYP450 isozymes (see Chapter 1). 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.

- **3. Adverse effects**
  Liver toxicity has occasionally been reported with these drugs, and baseline and periodic monitoring of liver function is recommended. **Weight gain** can ***occur because TZDs may increase subcutaneous fat and cause fluid retention.***
  [Note: 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 in women**.
  Pioglitazone may also **increase the risk of bladder cancer**. Additionally, *rosiglitazone* carries a boxed warning about the potential **increased risk of myocardial infarction and angina with the use of this agent.**

E. alpha-Glucosidase inhibitors

- ***Acarbose*** [AY-car-bose] and ***miglitol*** [MIG-li-tol] are oral agents used for the treatment of type 2 diabetes.
- **1. Mechanism of action**
  Located in the intestinal brush border, α-glucosidase enzymes break 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.
- ***[Note: It is important that hypoglycemia in this context be treated with glucose rather than sucrose, because sucrase is also inhibited by these drugs.]***

- **2. Pharmacokinetics**
  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.
-
  3. Adverse effects
  The ***most common adverse 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*** [al-oh-GLIP-tin], ***linagliptin*** [lin-a-GLIP-tin], ***saxagliptin*** [sax-a-GLIP-tin], and ***sitagliptin*** [si-ta-GLIPtin] are ***oral dipeptidyl peptidase-4 (DPP-4) inhibitors*** used for the treatment of type 2 diabetes.
- **1. Mechanism of action**
  These drugs inhibit the enzyme DPP-4, which is responsible for the inactivation of incretin hormones such as GLP-1 (Figure 24.13). Prolonging the activity of incretin hormones increases release of insulin 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.

- Treatment guidelines do not recommend the combination of DPP-4 inhibitors with GLP-1 receptor agonists for management of diabetes due to overlapping mechanisms and toxicity.
  Unlike GLP-1 receptor agonists, these drugs ***do not cause satiety or fullness and are weight neutral.***
-

  2. Pharmacokinetics
  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.

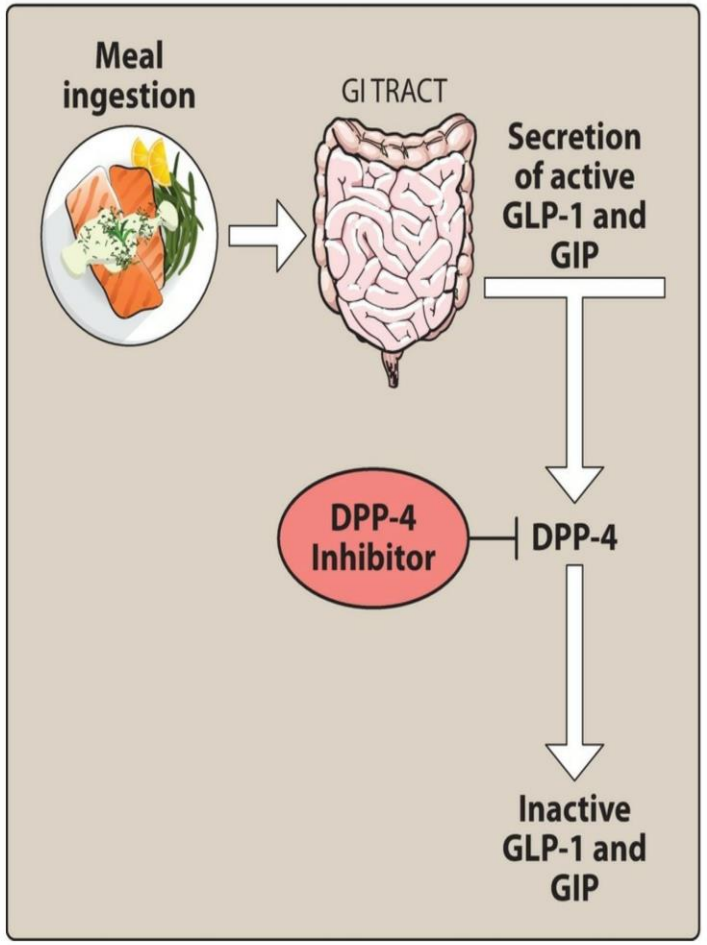


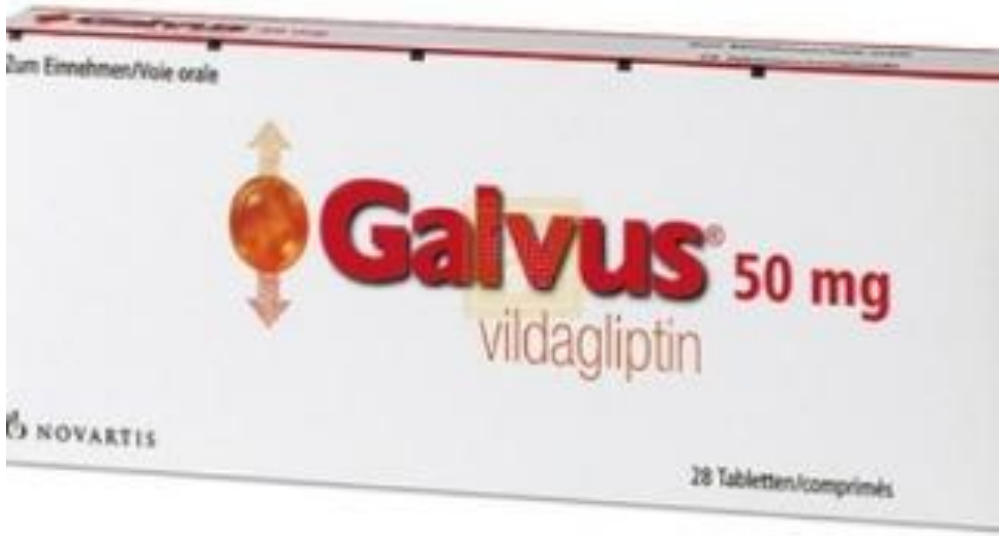
Figure 24.13 Mechanism of action of DPP-4 inhibitors. DPP-4 = dipeptidyl peptidase-4. GIP = glucose-dependent insulinotropic peptide; GLP-1 = glucagon-like peptide-1.

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 the use of DPP-4 inhibitors. Agents in this class may also increase the risk of severe, disabling ***joint pain***. *Alogliptin* and *saxagliptin* have also been shown to ***increase the risk of heart failure hospitalizations*** and should be used with caution in patients with

or at risk for heart failure.


Zum Einnehmen/Voie orale
Galvus 50 mg
vildagliptin
NOVARTIS
28 Tabletten/comprimés


MSD
Januvia 100 mg
(Sitagliptin)
28 Filmtabletten


28 film kaplı tablet
Oral antidiyabetik
onglyza 5 mg
Film Kaplı Tablet
(saksagliptin)
AstraZeneca
Bristol-Myers Squibb

G. Sodium–glucose cotransporter 2 inhibitors

- ***Canagliflozin*** [kan-a-gli-FLOE-zin], ***dapagliflozin*** [dap-a-gli-FLOE- zin], ***empagliflozin*** [em-pa-gli-FLOE-zin], and ***ertugliflozin*** [er-too-gli-FLOE-zin] are oral agents for the treatment of type 2 diabetes. ***Empagliflozin*** is also ***indicated to reduce the risk of cardiovascular death in patients with type 2 diabetes and cardiovascular disease.***
- **1. Mechanism of action**
  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.

- **2. Pharmacokinetics**
  These agents are ***given once daily in the morning***. *Canagliflozin* should be taken before the first meal of the day. All drugs are mainly metabolized by glucuronidation to inactive metabolites. ***These agents should be avoided in patients with renal dysfunction.***
- **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.***

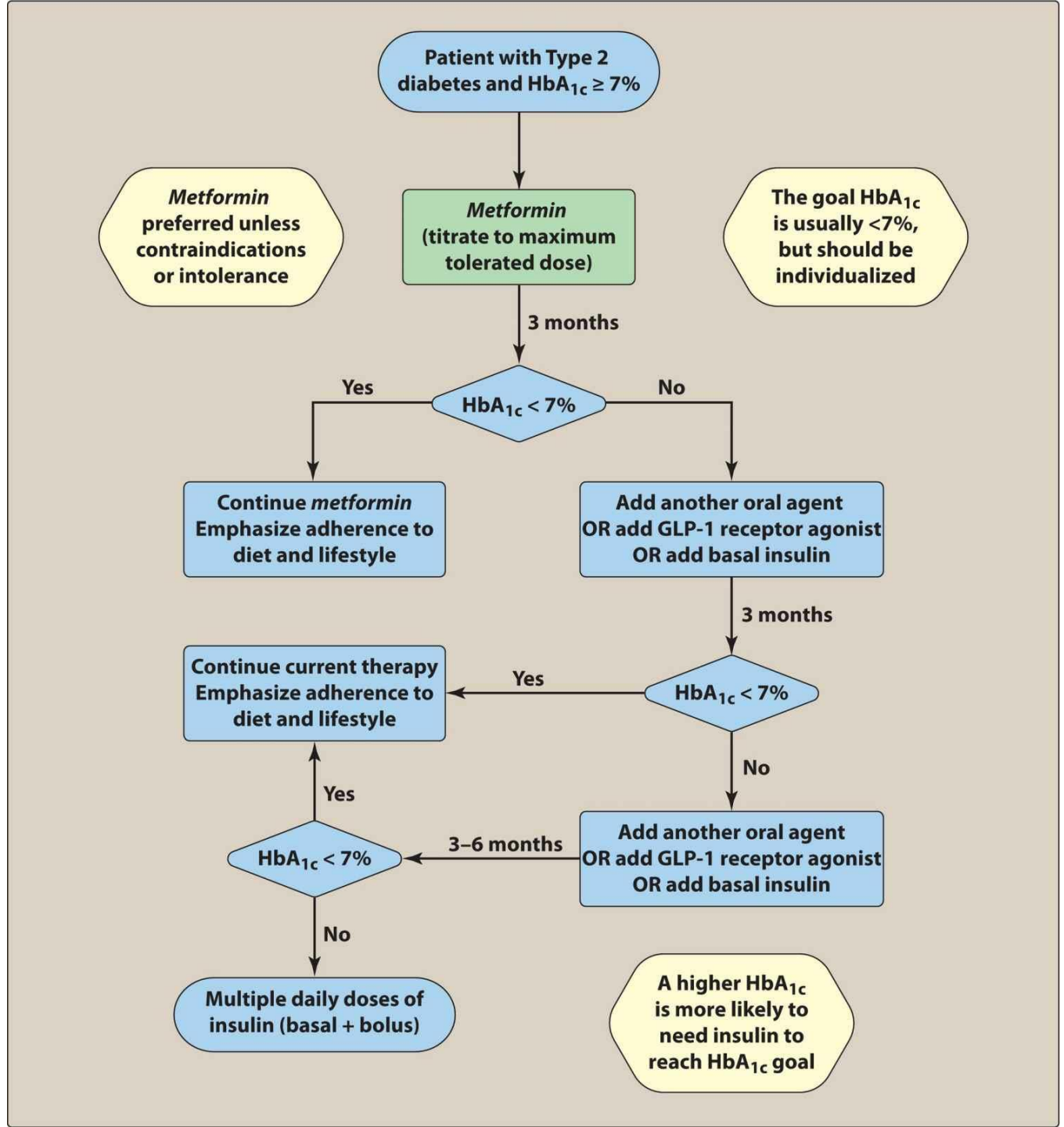
- **Hypotension** has also occurred, particularly in the elderly or patients on diuretics. Thus, volume status should be evaluated prior to starting these agents.
- **Ketoacidosis** has been reported with use of SGLT2 inhibitors, and these agents should be used with **caution** in patients with risk factors that predispose to ketoacidosis (for example, alcohol abuse and caloric restriction related to surgery or illness).

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 and vitamin B_{12} levels.
Thiazolidinediones *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. Not a preferred therapy. Reserve for patients unable to tolerate other agents.

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.
SGLT2 inhibitors *Canagliflozin* *Dapaglifozin* *Empagliflozin* *Ertugliflozin*	Increases urinary glucose excretion		No	Once-daily dosing in the morning. Risk of hypotension, genitourinary infections. Avoid in severe renal impairment. *Empagliflozin* is approved to reduce cardiovascular events in patients with type 2 diabetes.
GLP-1 receptor agonists *Albiglutide* *Dulaglutide* *Exenatide* *Liraglutide* *Lixisenatide* *Semaglutide*	Increases glucose-dependent insulin release; decreases secretion of glucagon; slows gastric emptying; increases satiety		No	Injection formulation. *Liraglutide* and *lixisenatide* are dosed once daily. *Albiglutide*, *dulaglutide*, and *semaglutide* are dosed once weekly. *Exenatide* is dosed twice daily and extended-release *exenatide* is dosed once weekly. *Liraglutide* is approved to reduce cardiovascular events in patients with type 2 diabetes. Weight loss may occur. Risk of pancreatitis. Contraindicated in patients with a history of medullary thyroid carcinoma.


Patient with Type 2 diabetes and HbA1c ≥ 7%
Metformin preferred unless contraindications or intolerance
Metformin (titrate to maximum tolerated dose)
The goal HbA1c is usually <7%, but should be individualized
3 months
Yes
HbA1c < 7%
No
Continue metformin Emphasize adherence to diet and lifestyle
Add another oral agent OR add GLP-1 receptor agonist OR add basal insulin
3 months
Continue current therapy Emphasize adherence to diet and lifestyle
Yes
HbA1c < 7%
No
Yes
HbA1c < 7%
3–6 months
Add another oral agent OR add GLP-1 receptor agonist OR add basal insulin
No
Multiple daily doses of insulin (basal + bolus)
A higher HbA1c is more likely to need insulin to reach HbA1c goal


THANK YOU :)