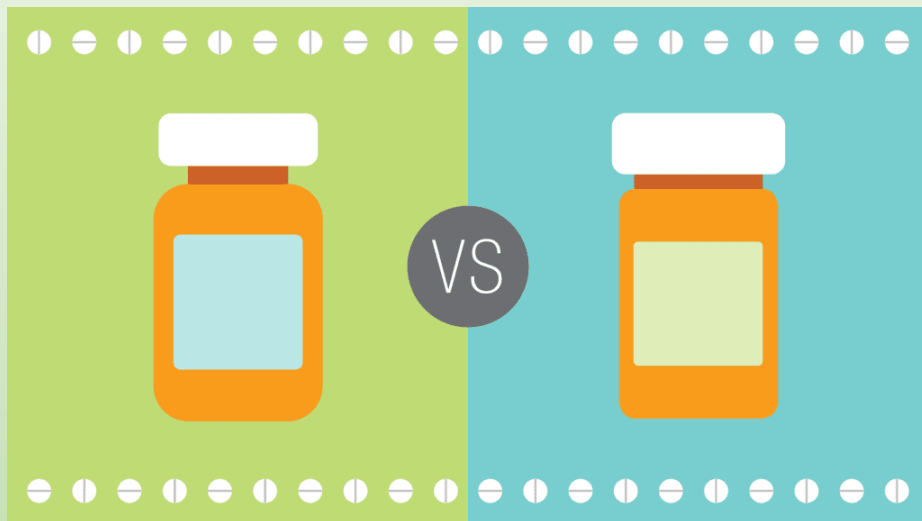




Antidiabetic Drugs (ORAL)

Ehsan Mohajeri

Pharm.D., Ph.D. of Pharmaceutics

Faculty of Pharmacy, Kerman University of Medical Sciences

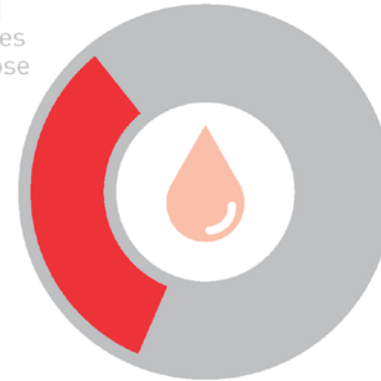
DIABETES IS ON THE RISE



422 MILLION
adults have diabetes

3.7 MILLION
deaths due to diabetes
and high blood glucose

1.5 MILLION
deaths caused
by diabetes



THAT'S **1** PERSON IN **11**



Main types of diabetes



TYPE 1 DIABETES

Body does not produce
enough insulin



TYPE 2 DIABETES

Body produces insulin
but can't use it well



GESTATIONAL DIABETES

A temporary condition in
pregnancy

Consequences

Diabetes can lead to complications in many parts of
the body and increase the risk of dying prematurely.

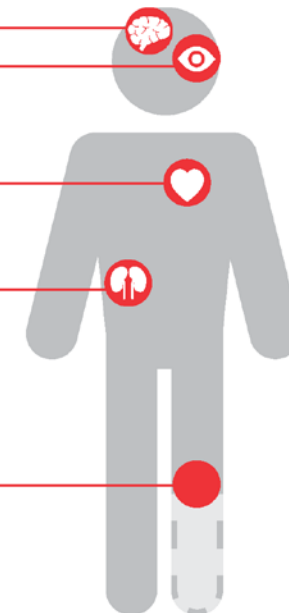
Stroke

Blindness

Heart attack

Kidney failure

Amputation



Risk factors for type 2 diabetes

Genetics, age and family history of diabetes can increase the likelihood of becoming diabetic and cannot be changed. But some behaviours that increase risk can:



Unhealthy diet



1 in 3 is overweight



Physical inactivity



1 in 10 is obese

KEY ACTIONS

FOR EVERYONE



Eat healthily



Be physically active



Avoid excessive weight gain



Check blood glucose if in doubt



Follow medical advice

FOR GOVERNMENTS



Healthy Environments

ENSURE



Better Diagnosis & Treatment



Better Data

Antidiabetic Drugs

- Antidiabetic drugs (AD) are all pharmacological agents that have been approved **for hyperglycemic treatment in T2DM**
- If lifestyle modifications (**Weight Loss, Dietary Modification, & Exercise**) do not sufficiently reduce A₁C levels (target level ~ 7%), pharmacological treatment with AD drugs should be initiated.

Antidiabetic Drugs

- AD drugs classified according to their mechanism of action as: **Insulinotropic** or **Non-Insulinotropic**
- They are available as **Monotherapy** or **Combination Therapies**, with the latter involving 2 (or, less commonly, 3) antidiabetic drugs and/or insulin

Antidiabetic Drugs

Insulinotropic agents

- stimulate the secretion of insulin from pancreatic β -cells

1. **Glucose-independent:** Insulin is secreted regardless of the BG level, even if BG levels are low $\rightarrow$ Risk of Hypoglycemia

Sulfonylureas & Meglitinides

2. **Glucose-dependent:** Insulin secretion is stimulated by elevated BG levels (postprandially) depend on residual β -cell function

GLP-1 Agonists & DPP-4 Inhibitors

Antidiabetic Drugs

Non-insulinotropic agents

- These agents do not depend on residual Insulin production
- Effective in patients with Nonfunctional Endocrine Pancreatic β -cells

Biguanides

SGLT-2 Inhibitors

Thiazolidinediones

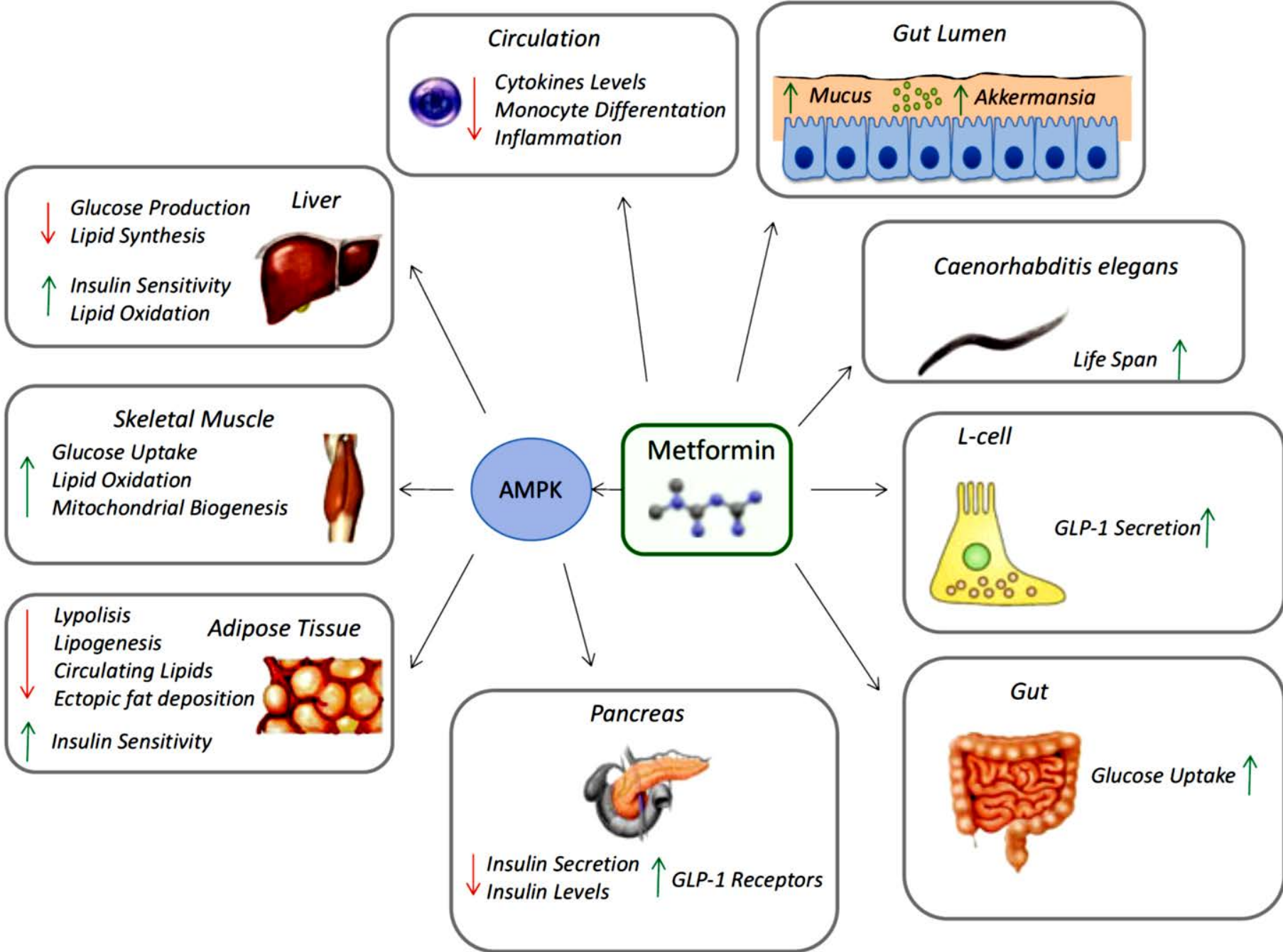
Alpha-Glucosidase Inhibitors

Antidiabetic Drugs

Biguanides (Metformin)

- Mechanism of action:

- ✓ Enhances effect of Insulin
- ✓ **Reduction in Insulin Resistance** (via modification of Glucose metabolic pathways)
- ✓ **Decreases Hepatic Gluconeogenesis & Intestinal Glucose Absorption**
- ✓ Increases **Peripheral** Insulin Sensitivity
- ✓ Lowers **Postprandial & Fasting BG levels**
- ✓ **↓ LDL & ↑ HDL**
- ✓ Inhibits Mitochondrial Glycerophosphate Dehydrogenase



AMP-activated protein kinase (AMPK)

Antidiabetic Drugs

Metformin

- Indication:

Drug of choice in all patients with T2DM

- Clinical Characteristics:

- **Glycemic Efficacy**: lowers HbA_{1c} by 1.2–2% over 3 months
- **Weight Loss** or weight stabilization
- **No Risk of Hypoglycemia**
- Beneficial Effect on **Dyslipidemia**
- Reduces Risk of **Macroangiopathic Complications**
- **Cost-effective**

Antidiabetic Drugs

Metformin

Important ADRs:

- **GI:** Nausea, Diarrhea, Flatulence
- **Vitamin B₁₂ deficiency**
- **Metallic taste in the mouth (Dysgeusia)**
- **Lactic Acidosis** (Incidence ~ 8 cases/100,000 patient years, GI Prodromal Symptoms: nausea, vomiting, diarrhea, abdominal pain and Severe symptoms: muscle cramps, hyperventilation, apathy, disorientation, coma)

Antidiabetic Drugs

Metformin

- **Contraindications**

- ❖ **Renal Failure** (if $CL_{cr} < 30$ mL/min)
- ❖ **Severe Liver Failure**
- ❖ Intravenous **Iodinated Contrast** Medium
- ❖ Chronic Pancreatitis, Starvation Ketosis, Ketoacidosis
- ❖ Heart Failure, Respiratory Failure, Shock, Sepsis
- ❖ Alcoholism

Antidiabetic Drugs

- If Metformin is **contraindicated, not tolerated**, or does not **sufficiently control** BG levels, another class of AD drug may be administered
- Most AD drugs are not recommended or should be used with caution in patients with moderate or severe **Renal Failure** or other significant comorbidities
- Oral AD drugs are not recommended during **pregnancy or breastfeeding**

Drug - Metformin interactions

- **Alcohol (Ethyl):** May enhance the adverse/toxic effect of Metformin. Specifically, alcohol may potentiate the risk of lactic acidosis **Risk X: Avoid combination**
- **Cimetidine:** May increase the serum concentration of Metformin. Management: Consider alternatives to cimetidine in patients receiving metformin due to a potential for increased metformin concentrations and toxicity (including lactic acidosis). **Risk D: Consider therapy modification**
- **Iodinated Contrast Agents:** May enhance the adverse/toxic effect of Metformin. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. **Exceptions:** Diatrizoate Meglumine; Diatrizoate Sodium; Ethiodized Oil. **Risk D: Consider therapy modification**
- **Androgens:** May enhance the hypoglycemic effect of BG Lowering Agents. **Exceptions:** Danazol. **Risk C: Monitor therapy**
- **Carbonic Anhydrase Inhibitors:** May enhance the adverse/toxic effect of Metformin. Specifically, the risk of developing lactic acidosis may be increased. **Exceptions:** Brinzolamide; Dorzolamide. **Risk C: Monitor therapy**
- **Cephalexin:** May increase the serum concentration of **Metformin**. **Risk C: Monitor therapy**
- **Lamotrigine:** May increase the serum concentration of Metformin. **Risk C: Monitor therapy**
- **MAO Inhibitors:** May enhance the hypoglycemic effect of BG Lowering Agents. **Risk C: Monitor therapy**
- **NSAIDs:** May enhance the adverse/toxic effect of Metformin. **Risk C: Monitor therapy**
- **Ondansetron:** May increase the serum concentration of Metformin. **Risk C: Monitor therapy**
- **SSRI:** May enhance the hypoglycemic effect of BG Lowering Agents. **Risk C: Monitor therapy**
- **Topiramate:** May enhance the adverse/toxic effect of Metformin. **Risk C: Monitor therapy**
- **Verapamil:** May diminish the therapeutic effect of Metformin. **Risk C: Monitor therapy**

Metformin HCL Tablet Oral Companies

500	750	1000
Apotex ,Hexal		Hexal
اسوه		اسوه
رازک، رها، اکتور		امین
ریحانه، سامی ساز		رازک
لقمان، شفا، ناژو، اکسیر		ماد
پور سینا، آتیه، زاگرس		شفا
آریا، تولید دارو، شاری		ریحانه، ثنمد
ماد، مهبان، فاخر، مینو		لقمان ، حکیم، شهردارو

Metformin HCl Tablet

- GLUCOPHAGE® 500, 1000 mg (Merck)
- METFORSAM® 500 mg (SamiSaz)
- NODIAX® 1000 mg (Senamed)
- GLOBETGUT® 500 mg (Kharazmi)
- METFORTEX® 500, 1000 mg (TC)
- METGLINDINE® 500 mg (IH)
- METOVER® 500 mg (Actover)
- RAHAMET® 500, 1000 mg
- GLUCODOR® 500 mg (Dorsa)
- METFORBET® 500 mg (Soha)
- VARIO-MET® 500 mg (Varian)
- CHEMFORMIN® 500 mg (CD)
- METFORBIOX® 500, 1000 mg (Bakhtar)
- GLUCOFF® 500 mg (Pars)
- GLUCANO® 500 mg (Nano Hayat)
- NILFORMIN® 500 mg (Nil Pharmed)

100 TABLETS

Warning and Precautions:

- Keep out of the reach of children.
- Prescription medicine only.
- Store below 30° C, protect from light and moisture.
- read the enclosed leaflet carefully.



Neal Pharmed Co.
Alborz IRAN

شرکت داروسازی نیل فارمد
تهران - ایران

100 قرص

Nilformin[®] 500

METFORMIN

نیل فورمین ۵۰۰

متفورمین

Each tablet contains:
Metformin HCl 500 mg



هشدارها و احتیاط ها:

- دارو را همراه یا بلافاصله بعد از غذا میل نمایید.
- دارو را دور از دسترس کودکان نگهداری نمایید.
- فروش بدون نسخه پزشک ممنوع است.
- دارو را دور از نور و رطوبت و حر دمای کمتر از ۳۰ درجه سانتیگراد نگهداری نمایید.
- قبل از مصرف برگه راهنمای دارو را به دقت مطالعه نمایید.
- مزاجه چاقب (رطوبه درون بسته بندی خوراک) نمی باشد.

دستور پزشک:



Metformin HCL Tablet

- Extended Release

500	750	1000
مرک (اکتور)	مرک (اکتور)	مرک (اکتور)
شاری	شاری	شاری
سپونین	کوشان فارمد	عبیدی
	تسینم	ابوریحان
		آرامیس
		سامی ساز
		الحاوی
		زوگر
		واریان

Metformin HCL Tablet

Extended Release

- ❖ GLOMET® 500, 1000 mg (Abidi)
- ❖ GLUCOPHAGE® XR 500, 750, 1000 mg (Merck)
- ❖ GLY-ONCE® 500, 750 mg (Koshan Pharmed)
- ❖ METELIN® ER 500 mg (Saponin)
- ❖ **MERICUM®** ER 500 mg (Abureyhan)
- ❖ METFORTEX® ER 500 mg (TC)
- ❖ **VARIO-MET®** ER 1000 mg (Varian)
- ❖ **ZUGER®** ER 500, 750, 1000 mg (Tasnim)
- ❖ **MERICUM®** 500, 1000 mg (Abureyhan)
- ❖ **METIXAR®** 500, 1000 mg (Alhavi)
- ❖ METFORSAM® 500, 1000 mg (SamiSaz)
- ❖ **SLOMET®** 500 mg (Aramis)
- ❖ METFOXIR® 500 mg (Exir)
- ❖ **METFIDEX®** 500 mg (TebMofid)



Extended Release Metformin

Received: 23 June 2017 | Revised: 15 August 2017 | Accepted: 24 August 2017

DOI: 10.1111/dom.13104

WILEY

BRIEF REPORT

Metformin extended-release versus immediate-release: An international, randomized, double-blind, head-to-head trial in pharmacotherapy-naïve patients with type 2 diabetes

Naresh Aggarwal MD¹  | Anuj Singla PhD¹ | Chantal Mathieu MD, PhD² |
Eduard Montanya MD, PhD³ | Andreas F. H. Pfeiffer MD⁴ | Eva Johnsson MD, PhD⁵ |
June Zhao MD, PhD⁶ | Nayyar Iqbal MD⁶ | Clifford Bailey PhD⁷

Adverse events were similar between groups and consistent with previous studies.

Overall, metformin XR demonstrated efficacy and safety similar to that of metformin IR over 24 weeks, with the **advantage of once-daily dosing**.

Extended Release Metformin

J Ayub Med Coll Abbottabad 2017;29(2)

ORIGINAL ARTICLE

DOSE COMPARISON AND SIDE EFFECT PROFILE OF METFORMIN EXTENDED RELEASE VERSUS METFORMIN IMMEDIATE RELEASE

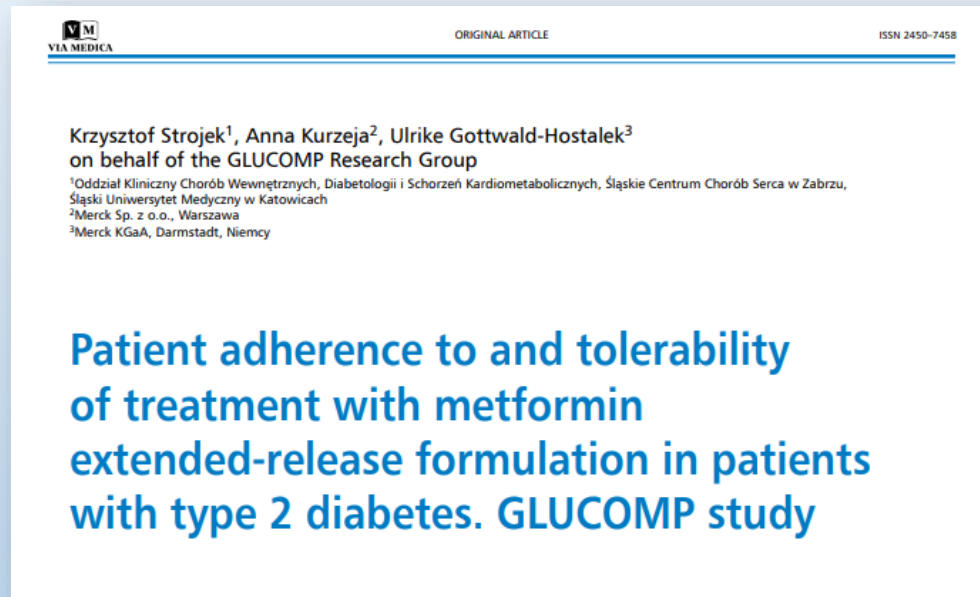
Maliha Hameed, Khurshid Khan, Sadia Salman, Nasir Mehmood

Endocrinology Department, Allama Iqbal Medical College, Jinnah Hospital, Lahore-Pakistan

Background: Diabetes Mellitus type 2 is very common worldwide, with majority of cases in Asia Pacific region. Metformin is the first line therapy, along with lifestyle modification for all type 2 diabetics as recommended by ADA. Metformin is available as conventional Metformin Immediate

All three Metformin groups were effective in reduction of HbA1C and glycemic control clinically and **there is no statistical difference in HbA1c reduction** among groups at three months.

Extended Release Metformin



After 3 months of treatment with metformin extended release formulation 96% of subjects demonstrated **excellent or good adherence**. Treatment adherence was significantly lower with 2 or 3 concomitant medications as compared to one ($p < 0.001$).

The occurrence **of adverse events significantly decreased** treatment adherence ($p < 0.001$)

Approximately 90% of patients declared they had preferred the use of metformin extended-release formulation.

Extended Release Metformin

DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

ORIGINAL ARTICLE

Comparative effectiveness of metformin monotherapy in extended release and immediate release formulations for the treatment of type 2 diabetes in treatment-naïve Chinese patients: Analysis of results from the CONSENT trial

Linong Ji MD , Jing Liu MD, Jing Yang MD, Yufeng Li MD, Li Liang BSc, Dalong Zhu MD, Quanmin Li MD, Tianrong Ma PhD, Haiyan Xu MSc, Yanlan Yang MD, Jiaoe Zeng MD, Bo Feng MD ... [See all authors](#) ✓

First published: 11 December 2017 | <https://doi.org/10.1111/dom.13190> | Citations: 2

Funding information The study was funded by Merck Serono China Co. Ltd., an affiliate of Merck KGaA, Darmstadt, Germany.

Metformin XR **was non-inferior to metformin IR** for the LSM change in HbA1c from baseline to week 16 and not superior to metformin IR for overall GI AE incidence during treatment of Chinese T2DM patients.

Extended Release Metformin



This population of type 2 diabetes patients managed in the usual care setting adhered well to an extended-release metformin regimen, with **strong preference overall** for this regimen over their previous immediate-release metformin regimen

Extended Release Metformin

METFORMIN EXTENDED VERSUS IMMEDIATE RELEASE IN SAUDI ARABIA: A COST-EFFECTIVENESS ANALYSIS

Alsultan M¹, Al-Omar H¹, Vandewalle B², Placido M², Afonso-Silva M², Mota M², Marques S², Félix J³

¹King Saud University, Riyadh, Saudi Arabia, ²Exigo Consultores, Lisbon, Portugal, ³Exigo

- Metformin XR represents **more lifetime savings** per patient comparing with IR formulation
- The **delay in more expensive advanced lines of therapy** in patients with metformin XR as first-line therapy
- **QALY are estimated to be higher** with XR formulation compared to IR
- **Diabetes complications** as renal failure were slight less prolonged
- **Diabetes complications also had lower costs** in patients with metformin

Conclusions: **Treating Saudi Arabia patients with metformin XR as first-line therapy, instead of IR formulation, is cost saving and improves health outcomes.**

Extended Release Metformin

Efficacy

Side effects

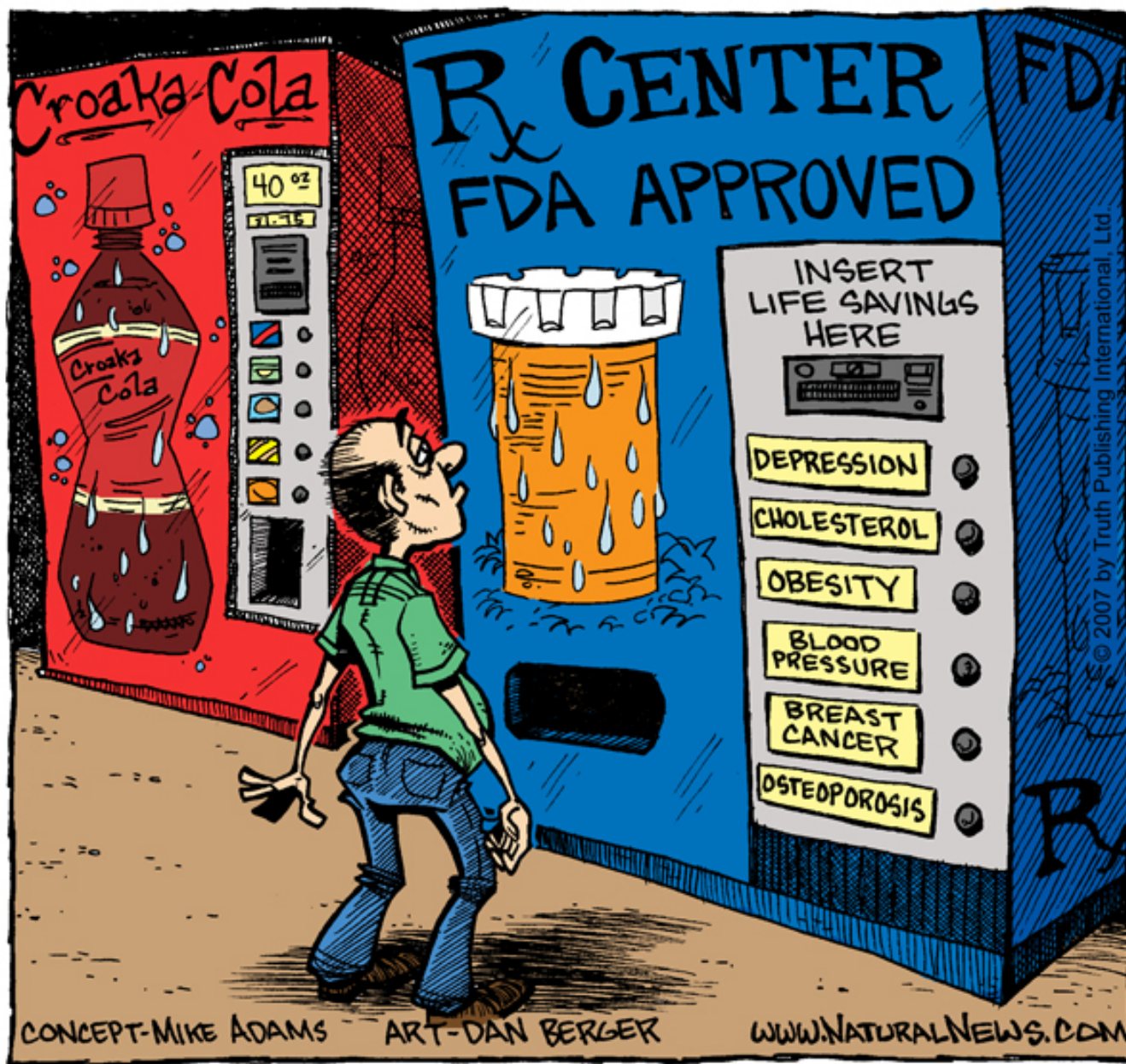
Adherence

Cost



COUNTERTHINK

WHAT THE DRUG COMPANIES REALLY WANT

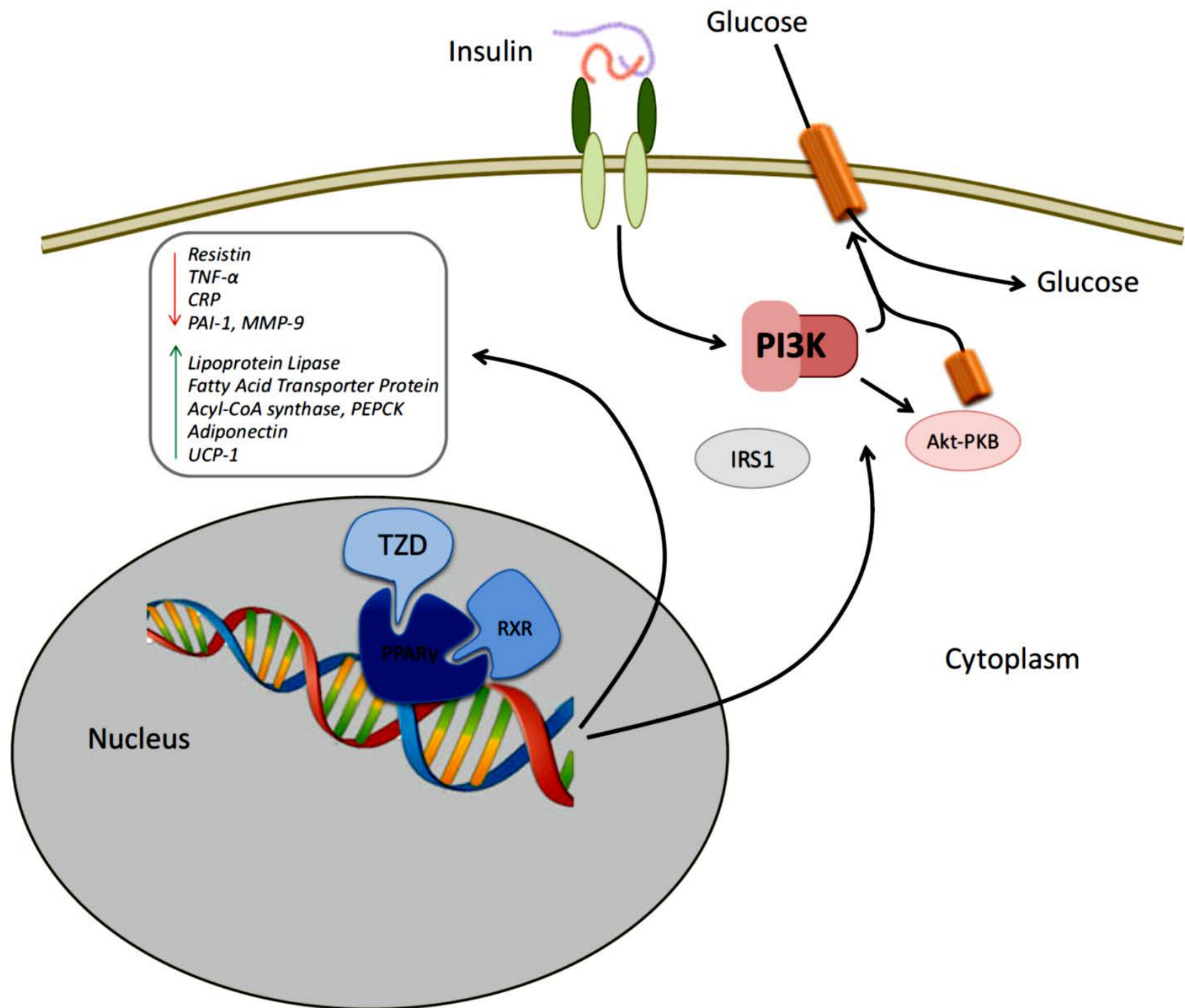


Antidiabetic Drugs

- **Thiazolidinediones (TZD, Glitazones, Insulin Sensitizers)**

Pioglitazone & Rosiglitazone

- **Mechanism of action:**
- Activation of **Transcription Factor PPAR γ** (Gamma Type Peroxisome Proliferator-activated Receptor)
- $\uparrow$ Transcription of Genes involved in Glucose & lipid metabolism
- $\uparrow$ **Levels of adipokines** such as adiponectin
- $\uparrow$ Storage of TG and subsequent reduction of products of lipid metabolism (FFA) that enhance Insulin resistance
- $\uparrow$ **Glucose utilization & hepatic Glucose production reduced**



Antidiabetic Drugs

Pioglitazone

- **Clinical characteristics**
- Glycemic efficacy: Lowers HbA1c by 1% in 3 Months
- Favorable Effect on Lipid metabolism: ↓ triglyceride, ↓ LDL, ↑ HDL
- No Risk of Hypoglycemia
- **Important side effects:**
 - Fluid Retention & Edema
 - Weight Gain
 - Increased Risk of Heart Failure
 - Increased Risk of Bone Fractures (Osteoporosis!)
- **Contraindications:**
- CHF, Liver Failure, History or active bladder cancer, Macrohematuria

Drug Interactions

- **CYP2C8 Inhibitors (Strong):** May increase the serum concentration of Pioglitazone. Management: Limit the pioglitazone dose to 15 mg daily and monitor for increased pioglitazone toxicities (eg, hypoglycemia) when used in combination with strong CYP2C8 inhibitors. **Risk D: Consider therapy modification**
- **Insulins:** Pioglitazone may enhance the adverse/toxic effect of Insulins. Specifically, the risk for hypoglycemia, fluid retention, and heart failure may be increased with this combination. Management: If insulin is combined with pioglitazone, dose reductions should be considered to reduce the risk of hypoglycemia. Monitor patients for fluid retention and signs/symptoms of heart failure. **Risk D: Consider therapy modification**
- **Sulfonylureas:** Thiazolidinediones may enhance the hypoglycemic effect of Sulfonylureas. Management: Consider sulfonylurea dose adjustments in patients taking thiazolidinediones and monitor for hypoglycemia. **Risk D: Consider therapy modification**
- **CYP2C8 Inducers (Moderate):** May decrease serum concentration of Pioglitazone. **Risk C: Monitor therapy**
- **MAO Inhibitors:** May enhance hypoglycemic effect of BG Lowering Agents. **Risk C: Monitor therapy**
- **Pregabalin:** May enhance the fluid-retaining effect of Thiazolidinediones. **Risk C: Monitor therapy**
- **SSRI:** May enhance the hypoglycemic effect of Blood Glucose Lowering Agents. **Risk C: Monitor therapy**
- **Thiazide Diuretics:** May diminish the therapeutic effect of Antidiabetic Agents. **Risk C: Monitor therapy**
- **Topiramate:** May decrease the serum concentration of Pioglitazone. **Risk C: Monitor therapy**

Montelukast, Clopidogrel, Gemfibrozil, Trimethoprim

کشور	صاحب نام تجاری	نام دارو	
	کارخانجات دارو پخش	پیوگلیتازون	۱
	کارخانجات دارو پخش	پیوگلیتازون	۲
	داروسازی سامی ساز	پی توز	۳
	داروسازی سامی ساز	پی توز	۴
	فن آوریهای نوین دارویی آتیه	پیوگلیتازون	۵
	پارس دارو	پیوگلیتازون	۶
	داروسازی جالینوس	پیوگلیتازون	۷
	دارو سازی اسوه	گلو تازون	۸
	سجاد داروی شرق	پیوسد	۹
	تولید مواد داروئی درسا دارو	دیدار	۱۰
	لابراتوارهای رازک	پیوگلیتازون	۱۱
	دارو سازی حکیم	پیوگلیتازون-حکیم	۱۲
	داروسازی تهران شیمی	هیپوتازون	۱۳
	داروسازی زهراوی	گلیتوز	۱۴

پیگلو فورمین® ۵۰۰/۱۵

متفورمین ۵۰۰ / پیوگلیتازون ۱۵

هر قرص حاوی :

متفورمین هیدروکلراید ۵۰۰ میلی گرم

پیوگلیتازون (به صورت هیدروکلراید) ۱۵ میلی گرم

فروش بدون نسخه پزشک ممنوع است.

**مصرف این دارو در دوران بارداری و شیردهی باید تحت نظر پزشک
متخصص انجام گیرد.**

قبل از مصرف برگه راهنمای درون جعبه را مطالعه نمایید.

دارو را همراه یا بعد از غذا میل نمایید.

در دمای کمتر از ۳۰ درجه سانتیگراد،

دوران دورو رطوبت نگهداری شود.

دور از دسترس اطفال نگهداری شود.



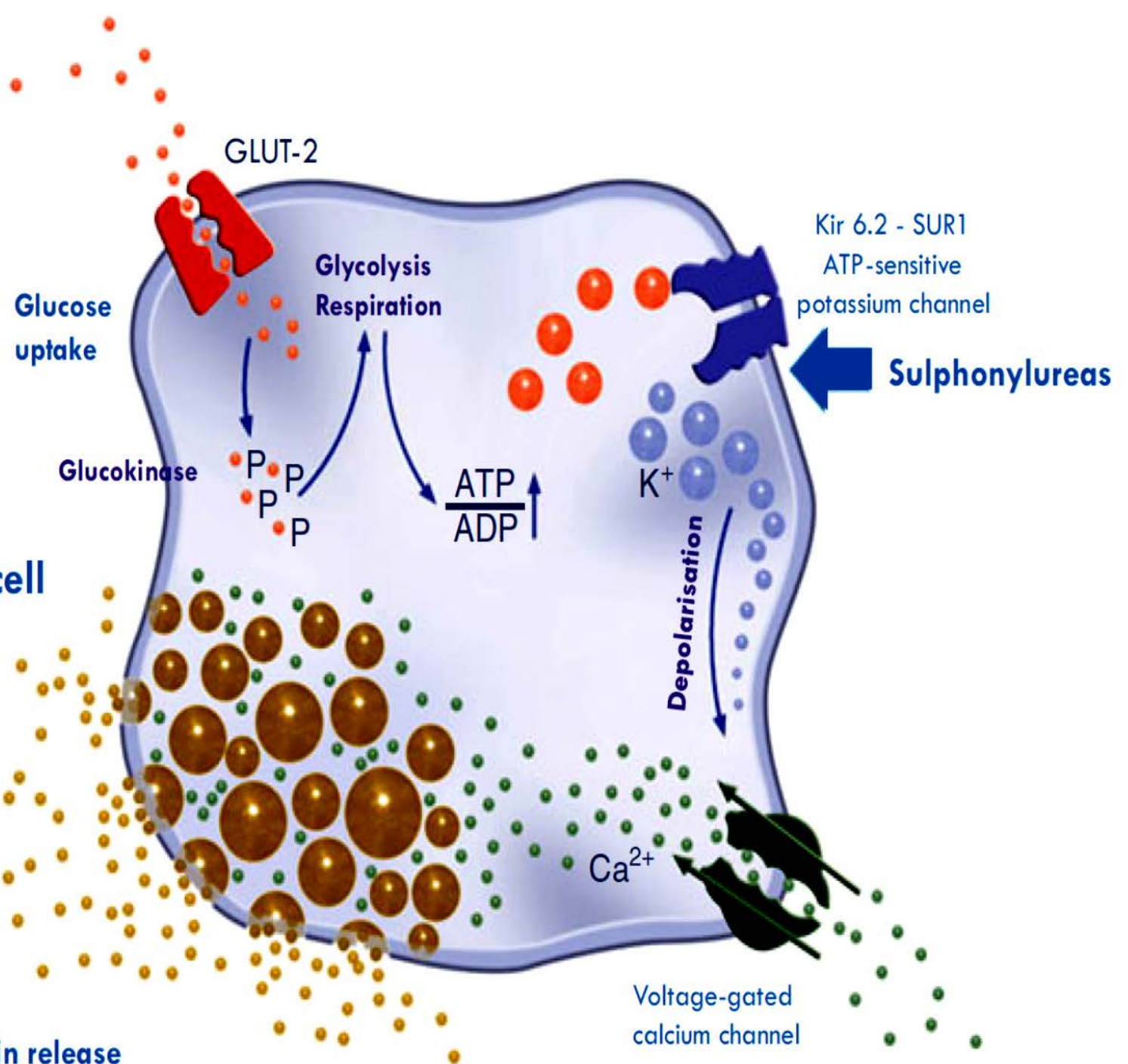
Antidiabetic Drugs

Sulfonylureas

- **Glyburide or Glibenclamide** (Relatively long Half-Life)
- **Gliclazide** (Short-acting agent)
- **Mechanism of action**
 - Block ATP-sensitive K Channels of Pancreatic B-cells
 - → Depolarization of cell membrane
 - → Ca influx
 - → Insulin secretion
- **Extra pancreatic effect:**
- Decreases hepatic gluconeogenesis & Increases Peripheral Insulin sensitivity
- **Indications:**
- Particularly suitable for patients **who are not overweight**, do not consume **alcohol**, and adhere to a consistent dietary routine

Pancreatic β -cell

Insulin release



Sulfonylureas

- **Clinical characteristics**
 - Glycemic efficacy: lowers HbA_{1c} by **1.2% over 3 months**
 - Long-term experience
 - Low-cost
 - **Important side effects:**
 - Life-threatening Hypoglycemia
 - Increased Risk In Patients With RF
 - Weight Gain
 - Hematological Changes: Granulocytopenia, Hemolytic Anemia
 - Allergic Skin Reactions
 - Alcohol Intolerance
- Compared to metformin, sulfonylureas are associated with more cardiovascular (macrovascular) complications.**

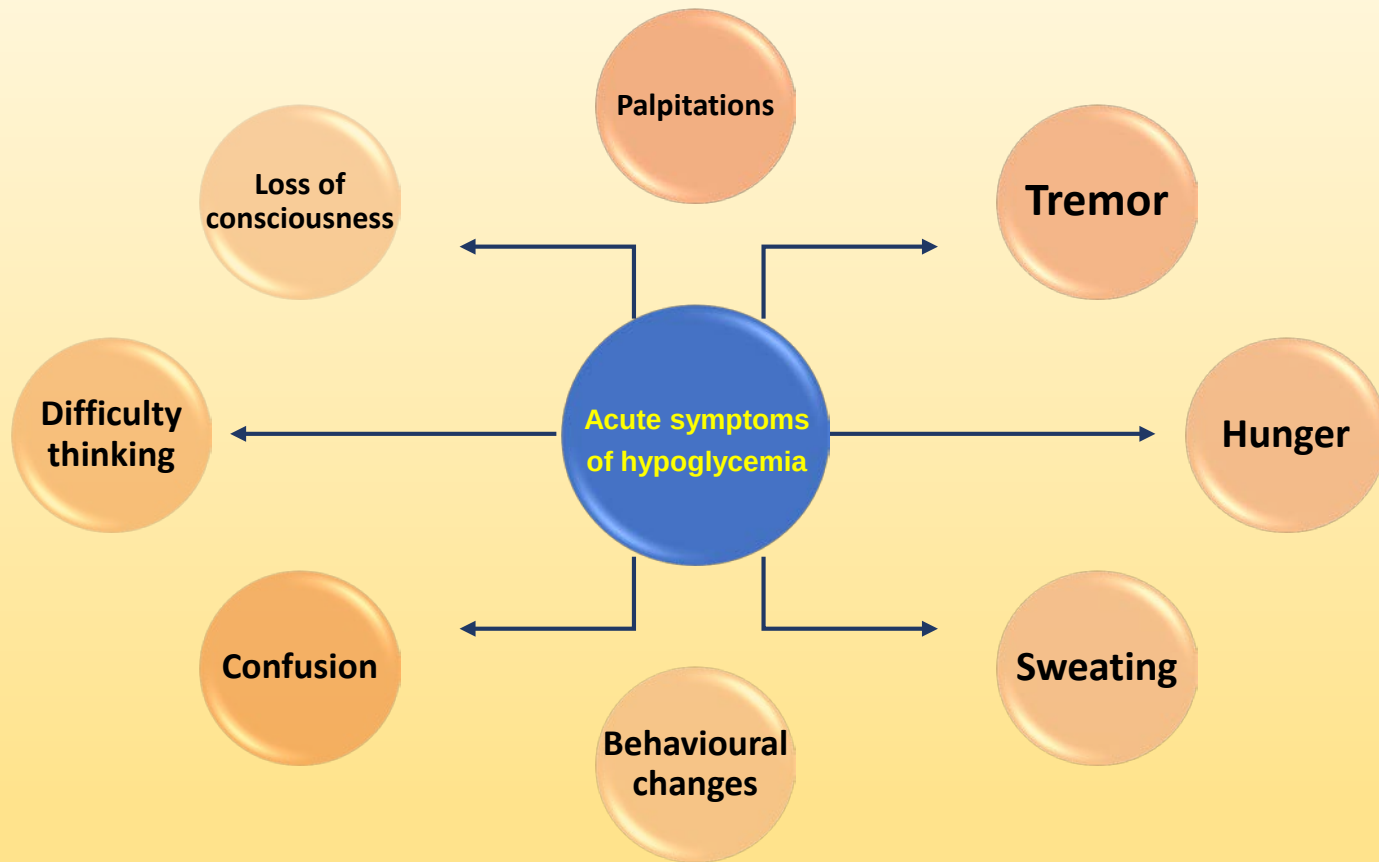
Sulfonylureas

- **Contraindications:**
 - Severe Cardiovascular Comorbidity
 - Obesity
 - Sulfonamide Allergy
 - Severe Liver Failure
 - Severe Kidney Failure

Beta-blockers may mask the warning signs of **hypoglycemia** (e.g., tachycardia).

Since sulfonylureas also increase the risk of hypoglycemia, the combination of these two substances should be avoided!

Hypoglycemia Main Symptoms



Drug-Glyburide Interactions

- **DPP4 Inhibitors:** May **enhance the hypoglycemic effect** of Sulfonylureas. Management: Consider a **decrease in sulfonylurea** dose when initiating therapy with a DPP₄ Inhibitors and monitor patients for hypoglycemia. **Risk D: Consider therapy modification**
- **Fluconazole:** May **increase the serum concentration** of Sulfonylureas. Management: Seek alternatives when possible. If used together, monitor closely for increased effects of sulfonylureas if fluconazole is initiated/dose increased, or decreased effects if fluconazole is discontinued/dose decreased. **Risk D: Consider therapy modification**
- **GLP₁ Agonists:** May enhance the hypoglycemic effect of Sulfonylureas. Management: Consider sulfonylurea dose reductions when used in combination with GLP₁ agonists. **Risk D: Consider therapy modification**

Drug-Gliclazide Interactions

- **DPP₄ Inhibitors:** May enhance the hypoglycemic effect of Sulfonylureas. Management: Consider a decrease in sulfonylurea dose when initiating therapy with a DPP₄ Inhibitors and monitor patients for hypoglycemia. **Risk D: Consider therapy modification**
- **Fluconazole:** May increase the serum concentration of Sulfonylureas. Management: Seek alternatives when possible. If used together, monitor closely for increased effects of sulfonylureas if fluconazole is initiated/dose increased, or decreased effects if fluconazole is discontinued/dose decreased. **Risk D: Consider therapy modification**
- **GLP₁ Agonists:** May enhance the hypoglycemic effect of Sulfonylureas. Management: Consider sulfonylurea dose reductions when used in combination with GLP₁ agonists. **Risk D: Consider therapy modification**
- **Rifampin:** May decrease the serum concentration of Sulfonylureas. Management: Seek alternatives to these combinations when possible. Monitor closely for diminished therapeutic effects of sulfonylureas if rifampin is initiated/dose increased, or enhanced effects if rifampin is discontinued/dose decreased. **Risk D: Consider therapy modification**
- **SGLT₂ Inhibitors:** May enhance the hypoglycemic effect of Sulfonylureas. Management: Consider a decrease in sulfonylurea dose when initiating therapy with a SGLT2 inhibitor and monitor patients for hypoglycemia. **Risk D: Consider therapy modification**

کشور	صاحب نام تجاری	نام دارو	
	داروسازی تهران شیمی	گلیبوتکس	۱
	داروسازی تهران شیمی	گلیبوتکس	۲
	ایران ناژو	گلی بنکلامید-ناژو	۳
	داروئی ارایشی و بهداشتی مینو	گلی بنکلامید مینو	۴
	داروسازی سامی ساز	گلی بنکلامید	۵
	پور سینا	گلی بنکلامید	۶
	دارو سازی حکیم	گلی بنکلامید-حکیم	۷
	لابراتوار داروسازی و بهداشتی شفا	گلی بنکلامید-شفا	۸
	Lagap	ملیکس	۹
	Lagap	ملیکس	۱۰
	Apotex	آپو-گلیبوراید	۱۱
	لابراتوارهای شهر دارو	گلی بنکلامید	۱۲
	لابراتوارهای شهر دارو	گلی بنکلامید	۱۳
	پارس دارو	گلونیل	۱۴

500/5 & 500/2.5

کشور	صاحب نام تجاری	نام دارو	
	داروسازی تهران شیمی	گلیکومین	۱
	باختر بیوشیمی	گلیفورمین	۲
	داروسازی فاتک شیمی پارس	متفورمین / گلی بنکلامید	۳
	داروسازی فاتک شیمی پارس	متفورمین / گلی بنکلامید	۴
	داروئی و بهداشتی لقمان (سهام عام)	متفورمین / گلی بنکلامید	۵
	داروئی و بهداشتی لقمان (سهام عام)	متفورمین / گلی بنکلامید	۶
	لابراتوار دارو سازی آرایشی و بهداشتی مینا سهامی	گلوکودکس	۷
	Hexal	متفورمین کامپ هگزال	۸
	Merck Sante	گلوکوونس	۹

80 mg

کشور	صاحب نام تجاری	نام دارو	
	داروسازی دکتر عبیدی	دیابزید	۱
	داروسازی دکتر عبیدی	دیابزید	۲
	صنعتی کیمیدارو	گلی کلایزید	۳
	صنعتی کیمیدارو	گلی کلایزید	۴
	ایران هورمون	کلایزکس	۵
	ایران هورمون	کلایزکس	۶
	داروسازی آریا	گلی کلایزید آریا	۷
	پور سینا	گلی کلایزید	۸
	داروسازی تهران دارو	گلی کلایزید	۹
	داروسازی تهران شیمی	گلی زیتکس	۱۰
	لابراتوارهای رازک	گلی کلایزید	۱۱
	لابراتوارهای رازک	گلی کلایزید	۱۲
	البرز دارو	گلیکلایزید	۱۳

30,60 mg ER

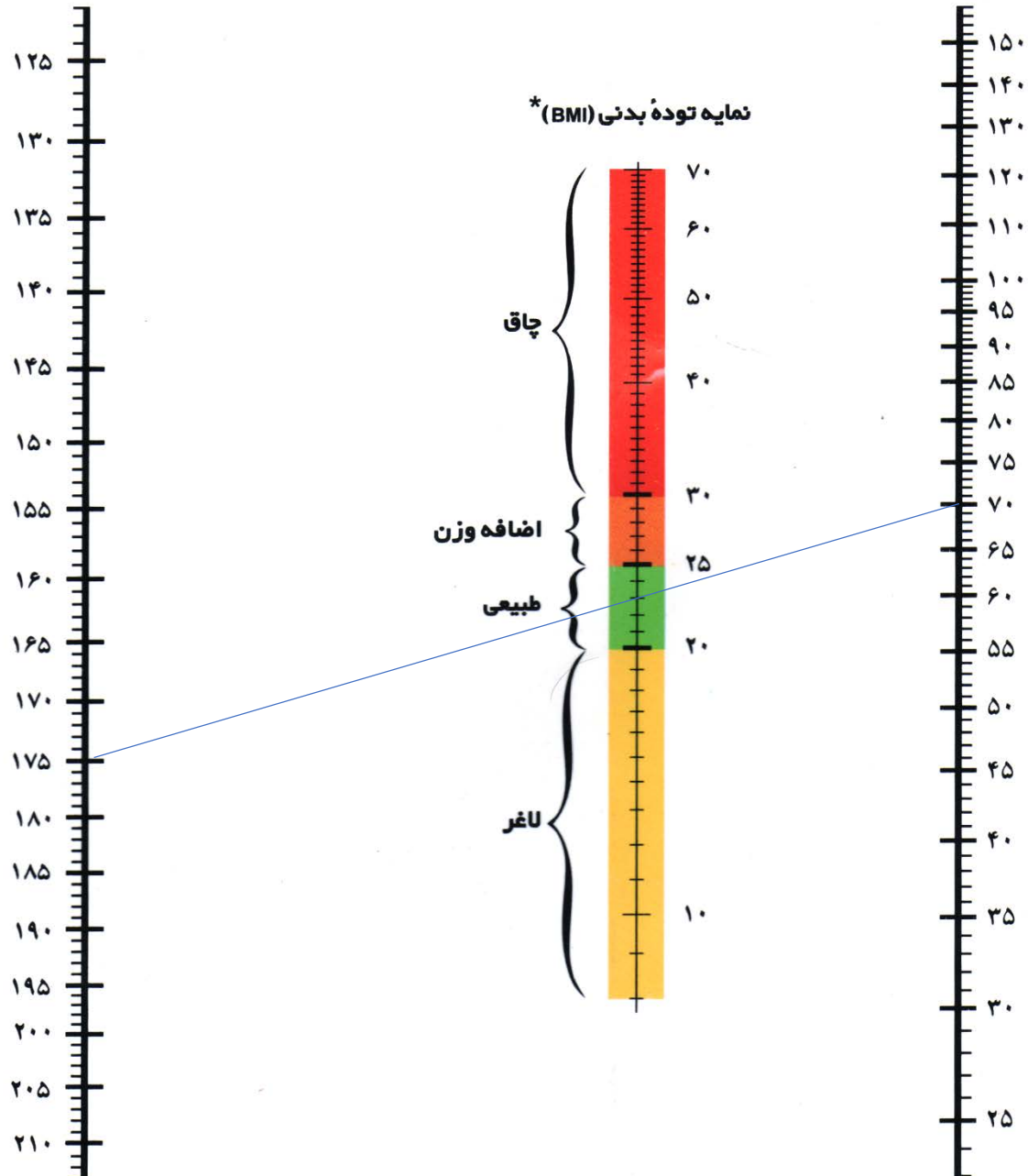
کشور	صاحب نام تجاری	نام دارو	
	داروسازی دکتر عبیدی	دیابزید	۱
	داروسازی دکتر عبیدی	دیابزید	۲
	کوشان فارمد	زیدامد	۳
	کوشان فارمد	زیدامد	۴
	داروسازی تهران شیمی	گلی زیتکس	۵
	داروسازی تهران دارو	گلی کلایزید	۶
	داروسازی تهران دارو	گلی کلایزید	۷
	دارو درمان آریا سپاهان	گلی زیداس	۸
	دارو سازی تسنیم	گلایزان	۹



وزن (کیلوگرم)

قد (سانتیمتر)

نمایه توده بدنی (BMI) *



Antidiabetic Drugs

Meglitinides (Sulfonylurea Analogue)

- Repaglinide, Nateglinide
- **Mechanism of action:**
- Enhances Insulin Secretion (similar mechanism of action to SU)
- **Indications:**
 - Particularly suitable for patients with **postprandial peaks** in BG levels
 - Repaglinide should be taken shortly **Before Meals**
 - Glycemic efficacy: lowers HbA_{1c} by **0.75% over 3 months**
 - More **expensive** than SU
 - well tolerated by patients with CKD
- **Important side effects:**
 - Life-threatening **hypoglycemia** (less risky than SU)
 - Increased Risk in RF patients
 - Weight Gain
 - Hepatotoxicity (Rare)
- **Contraindications:** Severe Liver & Renal Failure

Drug-Repaglinide Interactions

- **CYP2C8 Inhibitors (Strong):** May increase the serum concentration of Repaglinide. **Risk X: Avoid combination** Gemfibrozil & Trimethoprim
- **Clonidogrel:** May increase concentration of Repaglinide. Management: Avoid use of clonidogrel and repaglinide if possible; if the combination must be used, limit total repaglinide daily dose to no more than 4 mg. This is contraindicated in some non-US labeling. **Risk D: Consider therapy modification**
- **Cyclosporine (Systemic):** May increase the serum concentration of Repaglinide. Management: Limit the daily repaglinide dose to a maximum of 6 mg with concurrent use of cyclosporine, and monitor closely for increased repaglinide effects. **Risk D: Consider therapy modification**
- **CYP3A4 Inducers (Strong):** May increase the metabolism of CYP3A4 Substrates (High risk with Inducers). Management: Consider an alternative for one of the interacting drugs. Some combinations may be specifically contraindicated. Consult appropriate manufacturer labeling. **Risk D: Consider therapy modification**

Tablet 0.5, 1, 2 mg

کشور	صاحب نام تجاری	نام دارو	
	صنعتی کیمیدارو	رپاگین	۱
	کارخانجات دارو پخش	رپاگلیناید	۲
	کارخانجات دارو پخش	رپاگلیناید	۳
	دارو سازی تسنیم	گلیرز	۴
	داروسازی سامی ساز	پراگلیناید	۵
	داروسازی سامی ساز	پراگلیناید	۶
	داروسازی ابوریحان	نیوبت	۷
	Novonordisk	نوونورم	۸
	داروئی و بهداشتی لقمان (سهام عام)	رپاگلیناید	۹
	مهردارو	رپاگلیناید	۱۰
	رامو فارمین	رپاگلیناید	۱۱
	دارو سازی فارابی	رپاگلیناید	۱۲
	سجاد داروی شرق	رپاسد	۱۳
	داروسازی جالینوس	رپاگلیناید	۱۴



Antidiabetic Drugs

Alpha-Glucosidase Inhibitors

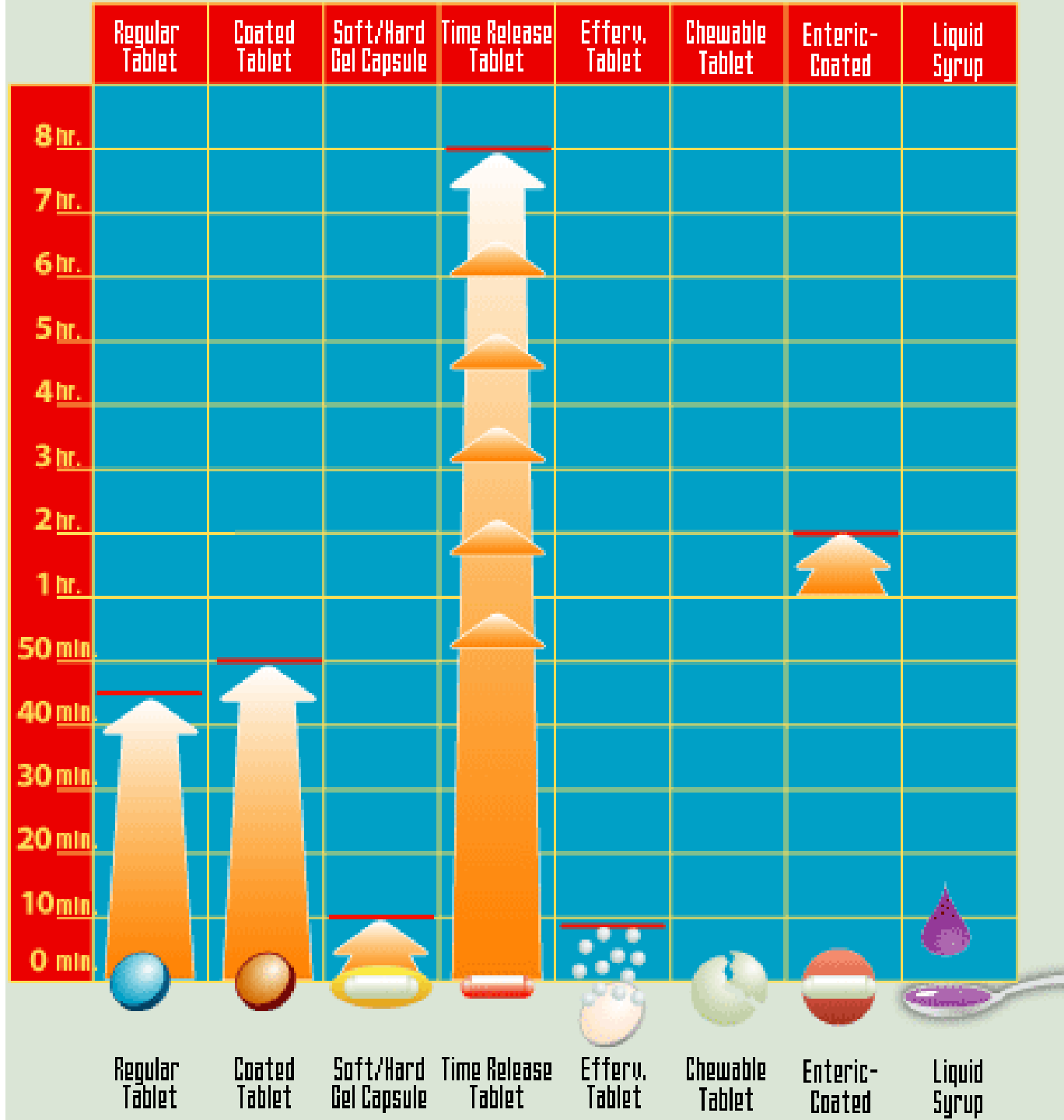
- **Acarbose, Miglitol**
- **Mechanism of action:**
 - Inhibits Alpha-Glucosidase → Decreased Intestinal Glucose Absorption
- **Clinical characteristics:**
 - Glycemic efficacy: Lowers HbA₁C by **0.8%** over 3 Months
 - **No Risk of Hypoglycemia**
 - Effective in controlling **Postprandial BG** levels
- **Important side effects:** GI (flatulence, abdominal discomfort, diarrhea)
- **Contraindications:** IBD, Malabsorption, Severe RF

Drug-Acarbose Interactions

- **Digoxin**: Acarbose may decrease the serum concentration of Digoxin. **Risk C**: Monitor therapy
- **MAO Inhibitors**: May enhance the hypoglycemic effect of BG Lowering Agents. **Risk C**: Monitor therapy
- **Neomycin**: May enhance the adverse/toxic effect of Acarbose. Neomycin may decrease the metabolism of Acarbose. **Risk C**: Monitor therapy
- **SSRIs**: May enhance the hypoglycemic effect of BG Lowering Agents. **Risk C**: Monitor therapy
- **Thiazide Diuretics**: May diminish the therapeutic effect of Antidiabetic Agents. **Risk C**: Monitor therapy

Tablet 50, 100 mg

کشور	صاحب نام تجاری	نام دارو	
	داروسازی امین	آکاربوز	۱
	داروسازی اکسیر	آکاربکس	۲
	داروسازی تهران شیمی	آکارماکس	۳
	داروسازی آریا	آکاربوز آریا	۴
	داروسازی حکیم	آکاربوز-حکیم	۵
	لابراتوار داروسازی و بهداشتی شفا	آکاربوز-شفا	۶
	پور سینا	آکاربوز	۷
	کیش مدیفارم	گلوکونورم	۸
	داروسازی طب مفید نیکان	آکاربوز	۹

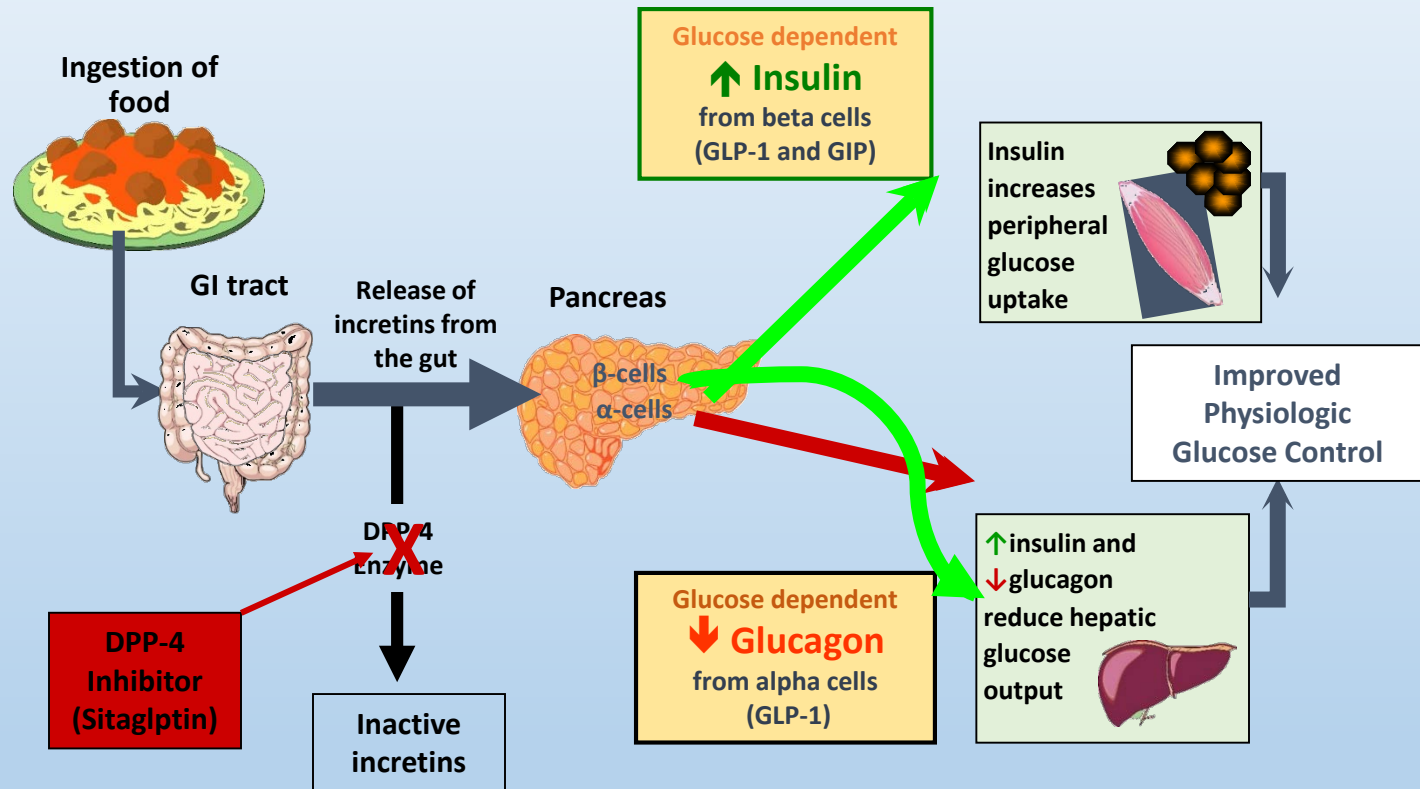


Antidiabetic Drugs

Dipeptidyl Peptidase-4 Inhibitors (Gliptins, DPP4I)

- Sitagliptin, Linagliptin, Saxagliptin
- Mechanism of action:
- Gliptins Indirectly **Increase Endogenous Incretin effect** by inhibiting DPP4 that breaks down GLP₁ →
 - ↑ Insulin Secretion
 - ↓ Glucagon Secretion
 - Delayed Gastric Emptying
- Clinical characteristics
- Glycemic Efficacy: Lowers HbA_{1c} by **0.5–0.75%** over 3 months
- **No Risk of Hypoglycemia** (unless Insulin and/or Insulinotropic Drugs are used simultaneously)

DPP4 Inhibitors Improve Glucose Control by Increasing Incretin Levels in Type 2 Diabetes

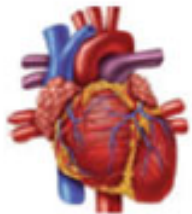


Cytoprotective Effects Of Dipeptidyl Peptidase-4 Inhibitors On Organs

Cytoprotective effects on organs target of diabetes

Anti-inflammatory, antiapoptotic and antioxidant properties

Promotion of cytoprotection



Heart

Cardioprotection



Vessels

Atheroprotection



Kidney

Renoprotection



Retina

Retinal protection

Control of micro-and macrovascular complications

Prevention of CV events, ESRD blindness

Dipeptidyl Peptidase-4 Inhibitors

- **Important side effects**
 - **GI complaints:** diarrhea, constipation
 - Nasopharyngitis and Upper Respiratory Tract Infection
 - **Arthralgia**
 - Headaches, Dizziness
 - UTI (mild)
 - Increased Risk of Pancreatitis
 - ARF
- **Contraindications:**
 - Hypersensitivity
 - Liver Failure

Sitagliptin: Once-Daily Dosing Administration

Usual Dosing for Sitagliptin

The recommended dose of Sitagliptin is **100 mg once daily** as monotherapy or as combination therapy with metformin or a PPAR γ agonist.

Patients With Renal Insufficiency

A dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with end-stage renal disease requiring hemodialysis or peritoneal dialysis.

50 mg once daily	25 mg once daily
<u>Moderate</u> eGFR greater than or equal to 30 mL/min/1.73 m ² to less than 45 mL/min/1.73 m ²	<u>Severe and ESRD</u> eGFR less than 30 mL/min/1.73 m ² (including patients with end stage renal disease [ESRD] on dialysis)

Assessment of renal function is recommended prior to Sitagliptin initiation and periodically thereafter.





Linagliptin has the broadest clinical evidence in the DPP-4I class

	Monotherapy	Dual therapy	Triple therapy		High CV risk	Heart failure	High kidney risk
Vildagliptin	✓	✓	✓		Limited evidence [†]	Limited evidence	Limited evidence
Saxagliptin	✓	✓	✓ [*]		Proven safety	Safety signal	Limited evidence
Alogliptin	✓	✓	✓ [†]		Proven safety	Uncertain [§]	Limited evidence
Sitagliptin	✓	✓	✓		Proven safety	Proven safety	Limited evidence
Linagliptin	✓	✓	✓		Proven safety	Proven safety	Proven safety

Drug-Linagliptin Interactions

- **CYP3A4 Inducers (Strong):** May decrease the serum concentration of Linagliptin. Management: Strongly consider using an alternative to any strong CYP3A4 inducer in patients who are being treated with linagliptin. If this combination is used, monitor patients closely for evidence of reduced linagliptin effectiveness. **Risk D:** Consider therapy modification
- **Insulins:** DDP4 Inhibitors may enhance the hypoglycemic effect of Insulins. Management: Consider a decrease in insulin dose when initiating therapy with a DDP4 inhibitor and monitor patients for hypoglycemia. **Risk D:** Consider therapy modification
- **P-glycoprotein/ABCB1 Inducers:** May decrease the serum concentration of Linagliptin. Management: Strongly consider using an alternative to any strong P-glycoprotein inducer in patients who are being treated with linagliptin. If this combination is used, monitor patients closely for evidence of reduced linagliptin effectiveness. **Risk D:** Consider therapy modification

Carbamazepine, Dexamethasone, Doxorubicin, Phenobarbital, Phenytoin, Prazosin, Rifampicin, St. John's Wort, Tenofovir, Trazodone, & Vinblastine

Drug-Linagliptin Interactions

- **Insulins:** DPP4 Inhibitors may enhance the hypoglycemic effect of Insulins. Management: Consider a decrease in insulin dose when initiating therapy with a DPP4 inhibitor and monitor patients for hypoglycemia. **Risk D:** Consider therapy modification
- **Sulfonylureas:** DPP4 Inhibitors may enhance the hypoglycemic effect of Sulfonylureas. Management: Consider a decrease in sulfonylurea dose when initiating therapy with a DPP4inhibitor and monitor patients for hypoglycemia. **Risk D:** Consider therapy modification



Tablet 5 mg

کشور	صاحب نام تجاری	نام دارو	
	الحاوی	ملیجنت	۱
	Boehringer Ingelheim GmbH	تراجنتا	۲
	داروسازی ابوریحان	لیناگلیپتین	۳
	داروسازی دکتر عبیدی	لیرنتا	۴
	داروسازی سامی ساز	لیناگلیپتین	۵
	واریان فارمد	لینوگلوکو	۶
	دارو سازی طب مفید نیکان	لیجنتین	۷

Linagliptin-Metformin

2.5-500, 2.5-1000 mg

کشور	صاحب نام تجاری	نام دارو	
	الحاوی	ملیجنت-ام	۱
	داروسازی سامی ساز	لیناگلیپتین / متفورمین	۲
	داروسازی دکتر عبیدی	ایروپریم	۳



Tablet 25, 50, 100 mg



زیپتین® 50 (سیتاگلیپتین 50 میلی گرم بصورت فسفات منوهیدرات)



زیپتین® 100 (سیتاگلیپتین 100 میلی گرم بصورت فسفات منوهیدرات)



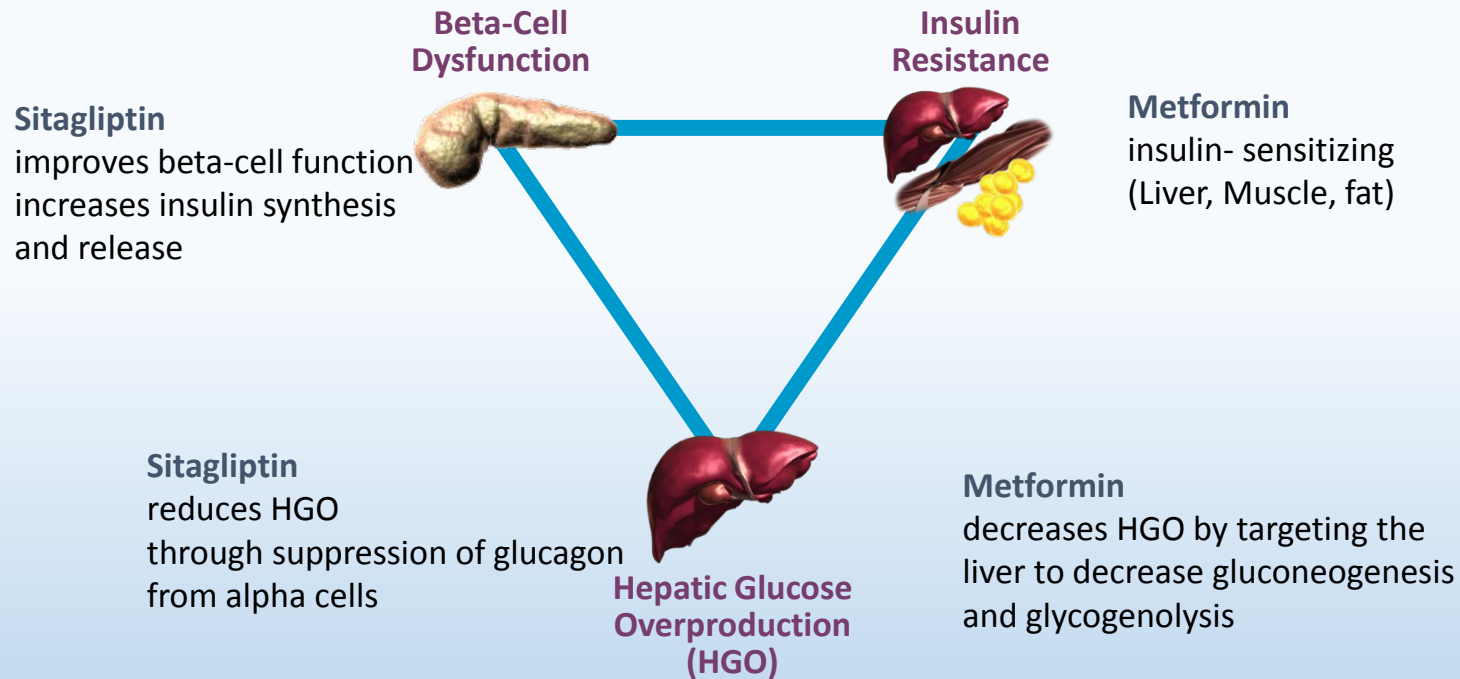
Tablet 25, 50, 100 mg

کشور	صاحب نام تجاری	نام دارو	
	سبحان دارو	ژانوپتین	۱
	داروسازی دکتر عبیدی	زیپتین	۲
	داروسازی دکتر عبیدی	زیپتین	۳
	Merck Sharp & Dohme	ژانوویا	۴
	داروسازی تهران شیمی	ژانووکس	۵
	لابراتوارهای شهر دارو	سیتاگلیپتین	۶
	داروسازی ابوریحان	سیتاگلیپتین	۷
	دارو سازی اسوه	سیتاویکس	۸
	داروسازی اکسیر	دیابتوز	۹
	الحاوی	سیتال	۱۰
	داروسازی تولید دارو	سیتاگلیپتین	۱۱
	باختر بیوشیمی	بایوسیتال	۱۲
	کیش مدیفارم	سیتانورم	۱۳
	داروسازی امین	سیتاگمین	۱۴

Tablet 25, 50, 100 mg

	داروسازی خوارزمی	سیتاگلیپتین	۱۵
	آرنا حیات دانش	دیپتین	۱۶
	سجاد داروی شرق	جانوسد	۱۷
	البرز دارو	سیتاگلیپتین	۱۸
	ایران دارو	سیتاگلیپتین	۱۹
	لابراتوارهای رازک	سیتاگلیپتین	۲۰
	لابراتوارهای رازک	سیتاگلیپتین	۲۱
	کوشان فارمد	سانوپتین	۲۲
	داروسازی تهران دارو	گلیپ لس	۲۳
	داروسازی جابر ابن حیان	سیتاگلیپتین	۲۴
	داروسازی اوه سینا	سیتاگلیپتین	۲۵
	پارس دارو	سیتابت	۲۶
	داروسازی جالینوس	سیتاگلیپتین	۲۷
	داروسازی سامی ساز	سیتاگلیپتین	۲۸
	دارو سازی سبا	سیتاگلیکس	۲۹

Sitagliptin and Metformin Target the Core Metabolic Defects of Type 2 Diabetes



Sitagliptin / Metformin Tablet





Sitagliptin / Metformin Tablet 50/1000 mg

کشور	صاحب نام تجاری	نام دارو	
	داروسازی دکتر عبیدی	زیپمت	۱
	الحاوی	سیتال	۲
	داروسازی تهران شیمی	ژانومیکس	۳
	کیش مدیفارم	سیتاپلاس	۴
	واریان فارمد	متژان	۵
	داروسازی سامی ساز	متگلیپت	۶



Sitagliptin / Metformin Tablet 50/500 mg

کشور	نام دارو	صاحب نام تجاری
	۱ سیتافورمین	دارو سازی اسوه
	۲ زیپمت	دارو سازی دکتر عبیدی
	۳ زیپمت	دارو سازی دکتر عبیدی
	۴ سیتاپلاس	کیش مدیفارم
	۵ سیتاپلاس	کیش مدیفارم
	۶ سیتاگلیپتین / متفورمین	دارو سازی تولید دارو
	۷ بایوسیتال-ام	باختر بیوشیمی
	۸ سیتال	الحاوی
	۹ سیتال	الحاوی
	۱۰ گلیبرا	کارخانجات دارو پخش
	۱۱ آراسیمت	دارو سازی آرامیس فارمد



Sitagliptin / Metformin Tablet 50/500 mg



	دارو سازی سبا	سیتافوربت	۱۲
	لابراتوار های رازک	سیتاگلیپتین / متفورمین	۱۳
	لابراتوار های رازک	سیتاگلیپتین / متفورمین	۱۴
	دارو سازی تهران شیمی	ژانومیکس	۱۵
	سجاد داروی شرق	سیتاگلیپتین / متفورمین	۱۶
	پارس دارو	سیتاگلیپتین / متفورمین	۱۷
	دارو سازی تهران دارو	سیتاگلیپتین / متفورمین	۱۸
	واریان فارمد	متزان	۱۹
	دارو سازی جابر ابن حیان	سیتاگلیپتین / متفورمین	۲۰
	دارو سازی سامی ساز	متگلیپت	۲۱
	پارس دارو	سیتابت-پلاس	۲۲

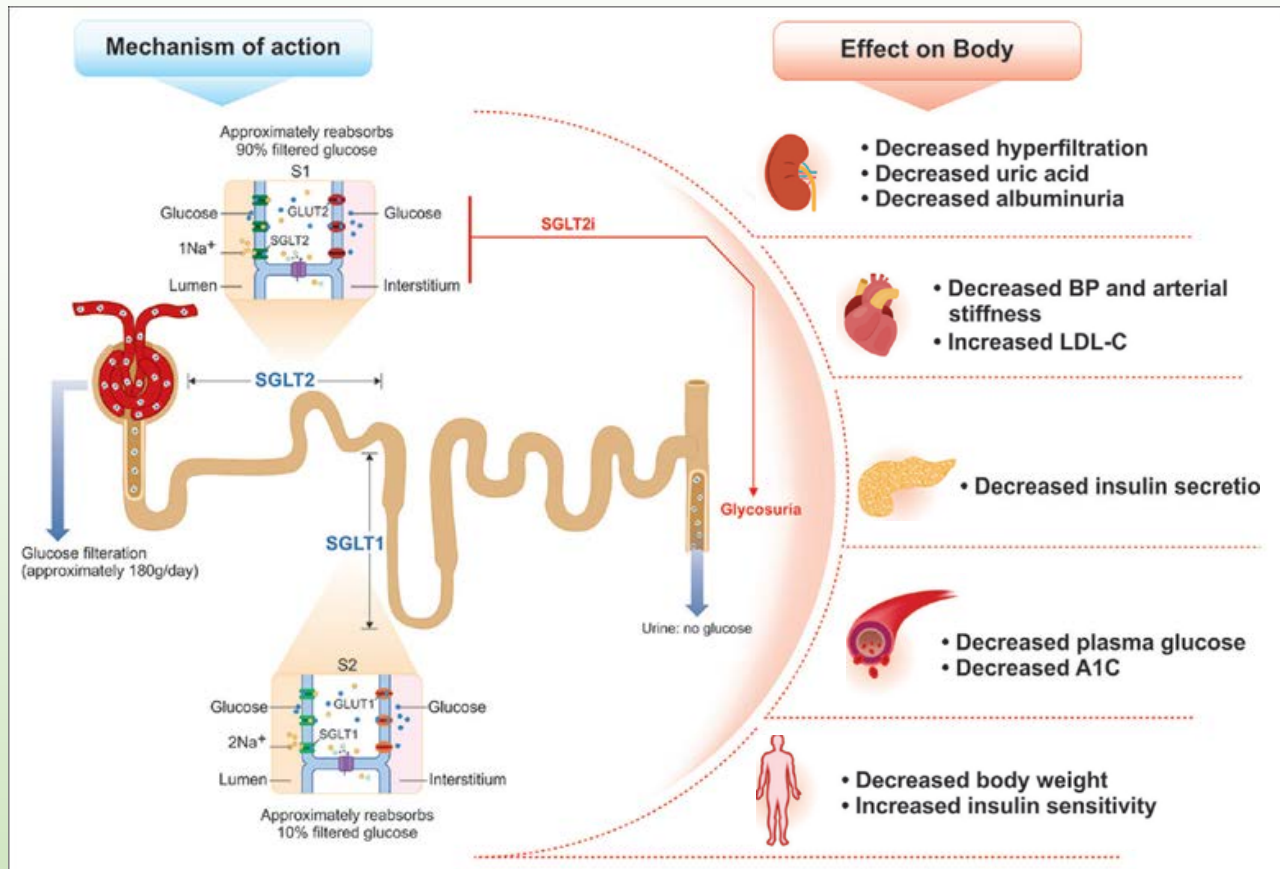


Antidiabetic Drugs

SGLT-2 inhibitors (Gliflozins)

- **Empagliflozin**, Dapagliflozin, Canagliflozin
- **Mechanism of action:**
- Reversible Inhibition of the **Na-dependent Glucose co-transporter (SGLT-2)** in kidney proximal tubule → Reduced Glucose reabsorption → Glycosuria
- **Indications:**
- Treatment option used especially in **young patients** with treatment-compliant T2DM without significant RF
- Glycemic efficacy: lowers HbA_{1c} by **0.6%** over 3 months
- Promotes **Weight Loss**
- Reduces **BP**
- **Important side effects:**
 - **UTI**, Genital Infections (vulvovaginitis, balanitis)
 - Dehydration as a result of Polyuria
 - Severe Diabetic Ketoacidosis
- **Contraindications: CKD, Recurrent UTI**

Mechanism of action and effects of SGLT-2 inhibitors on the body

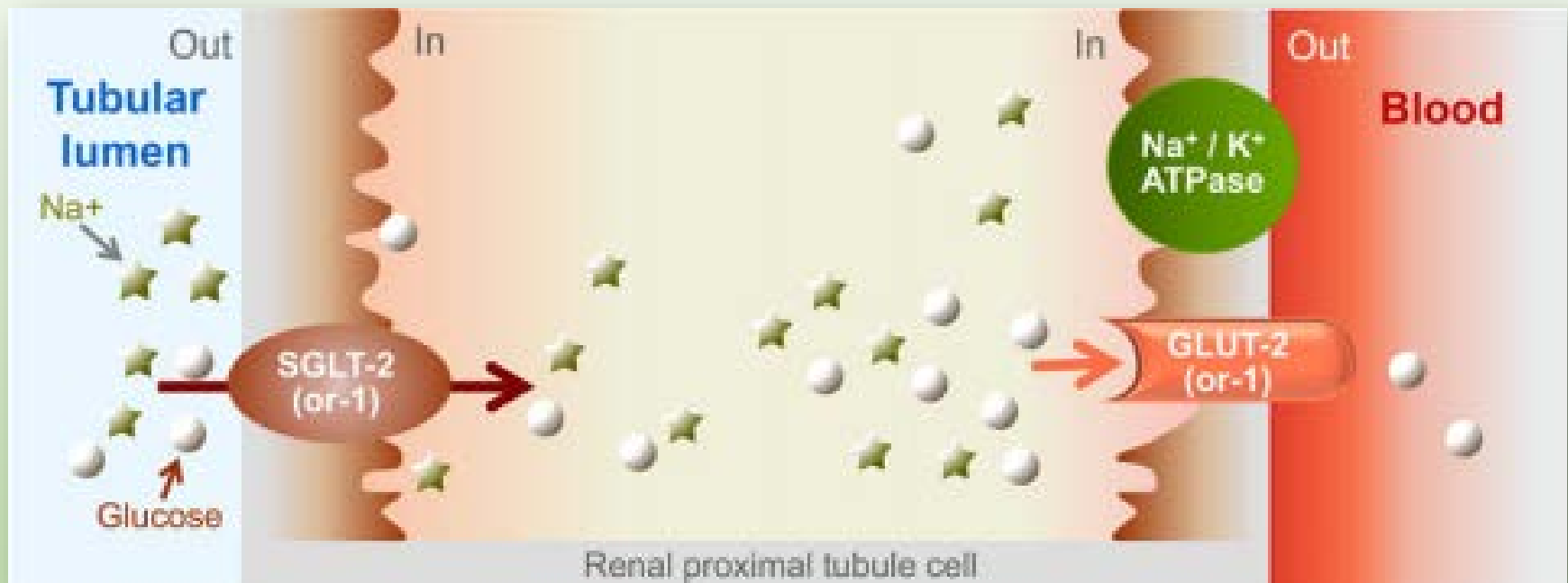


Glucose Transporters

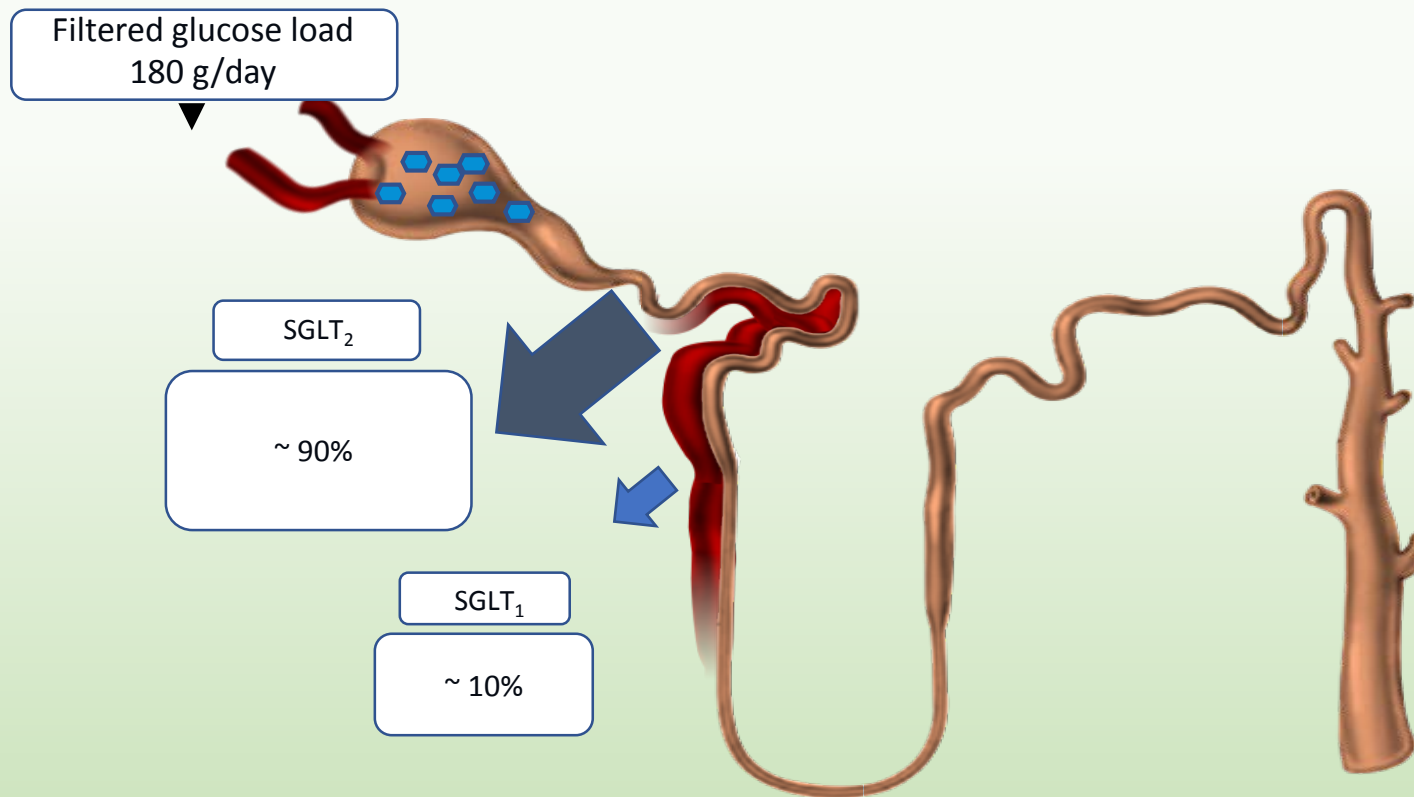
They are classified into two families:

- 1- *facilitative glucose transporters (GLUTs)*
- 2- *sodium-dependent glucose transporters (SGLTs)*

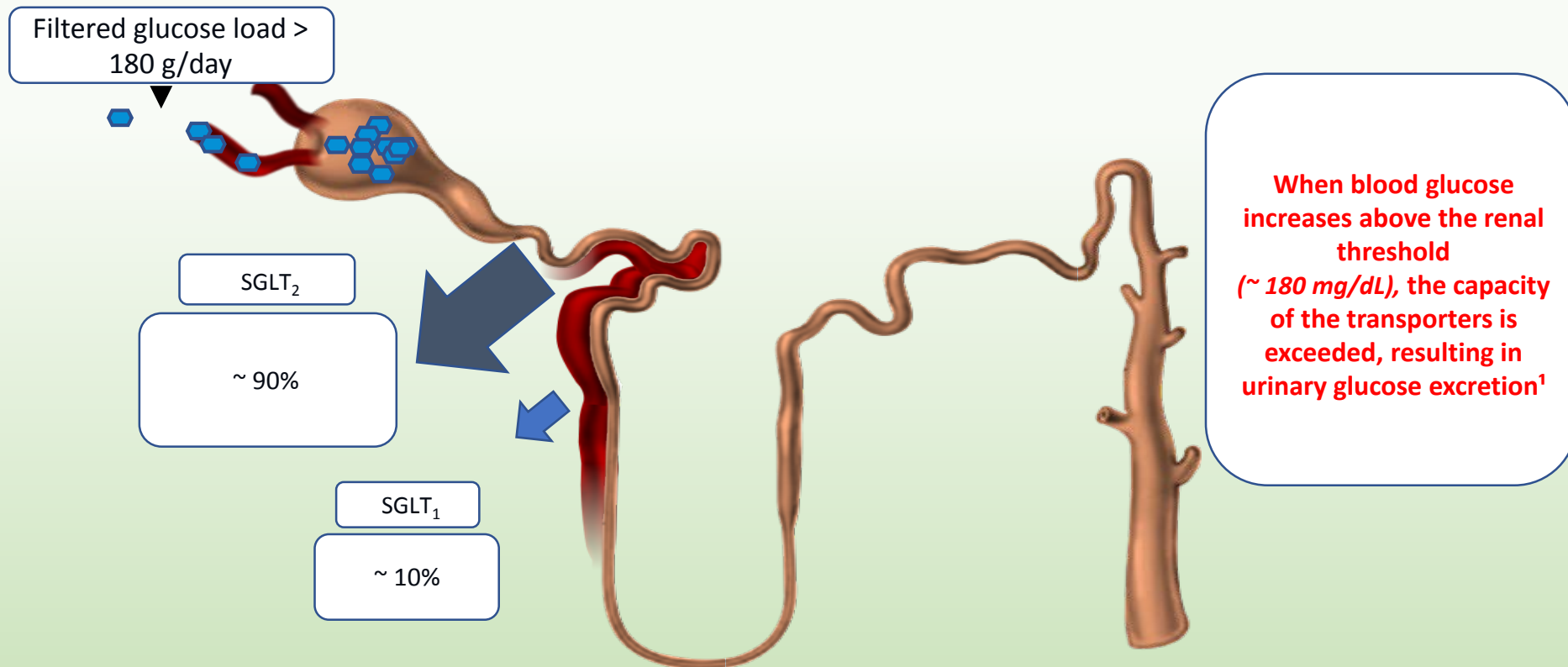
- *$SGLT_1$: low capacity, high affinity, mostly in intestine*
- *$SGLT_2$: high capacity, low affinity, mostly in kidney*



Renal glucose re-absorption in healthy individuals

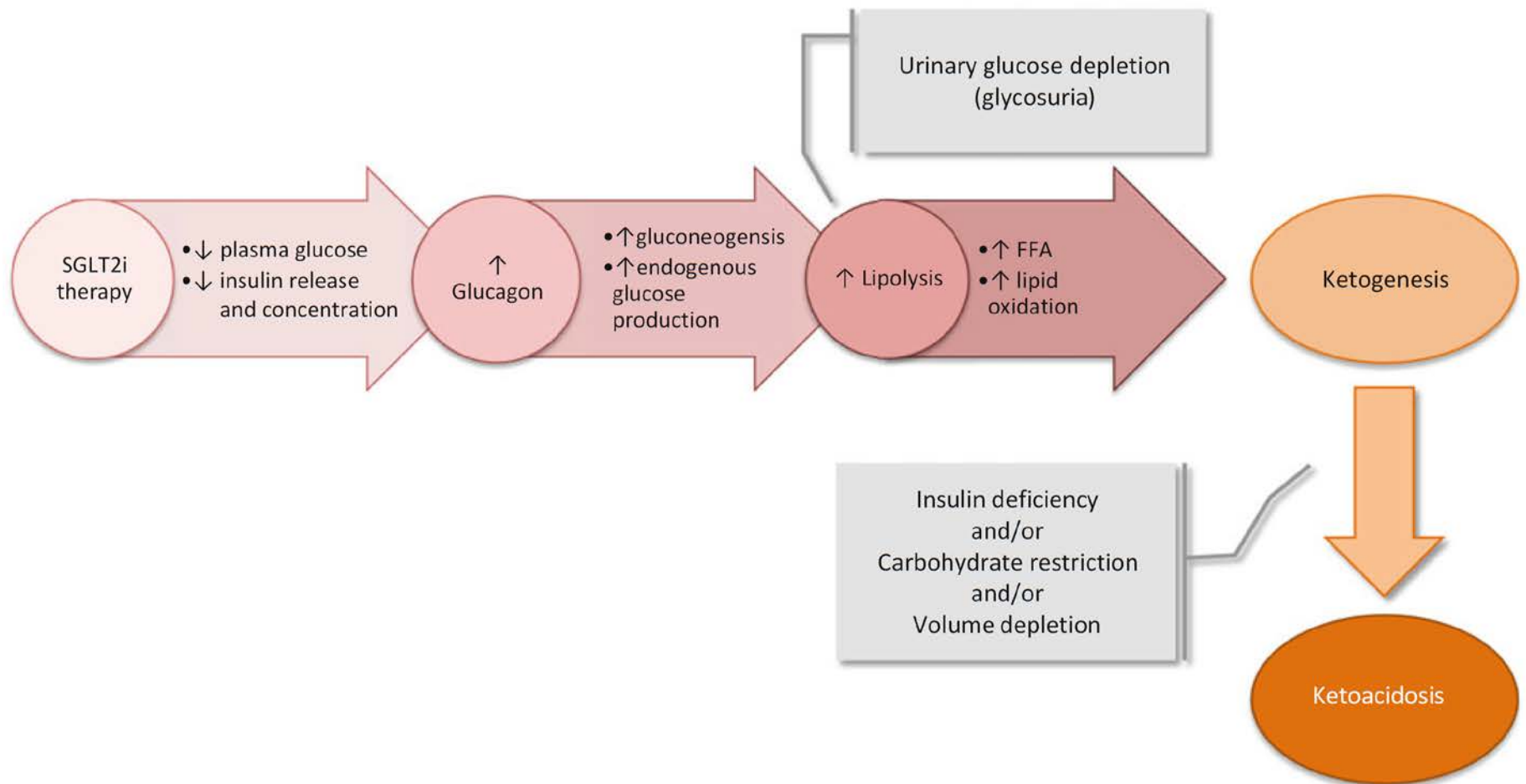


Renal glucose re-absorption in healthy individuals



Expected Clinical Effects of SGLT2 Inhibition





SGLT2 Inhibitors Drug Interactions

- **Insulins:** SGLT2 Inhibitors may enhance the hypoglycemic effect of Insulins. Management: Consider a decrease in insulin dose when initiating therapy with a SGLT2 inhibitor and monitor patients for hypoglycemia. **Risk D:** Consider therapy modification
- **Sulfonylureas:** SGLT2 Inhibitors may enhance the hypoglycemic effect of Sulfonylureas. Management: Consider a decrease in sulfonylurea dose when initiating therapy with a SGLT2 inhibitor and monitor patients for hypoglycemia. **Risk D:** Consider therapy modification
- **Loop Diuretics:** Empagliflozin may enhance the hypotensive effect of Loop Diuretics. **Risk C:** Monitor therapy

Empagliflozin 10,25 mg Tablet



گلورپیا 10 (امپاگلیفلوزین 10 میلی گرم)



گلورپیا 25 (امپاگلیفلوزین 25 میلی گرم)

Empagliflozin 10,25 mg Tablet

کشور	صاحب نام تجاری	نام دارو	
	داروسازی دکتر عبیدی	گلورپیا	۱
	داروسازی دکتر عبیدی	گلورپیا	۲
	الحاوی	امپادیانس	۳
	نانو حیات دارو	پگلینو	۴
	Boehringer Ingelheim	جاردیانس	۵
	داروسازی ابوریحان	امابت	۶
	داروسازی تهران شیمی	جاردیپا	۷
	پارس دارو	امپاتوس	۸
	واریان فارمد	امپاگلوکو	۹
	لابراتوار داروسازی و بهداشتی شفا	امپاگلیفلوزین	۱۰

Empagliflozin-Metformin Tablet

12.5-500 & 5-500 Mg

12.5-1000 & 5-1000 Mg



Empagliflozin-Metformin Tablet

12.5-500 & 5-500 Mg

12.5-1000 & 5-1000 Mg

کشور	صاحب نام تجاری	نام دارو	
	داروسازی دکتر عبیدی	سینورپا	۱
	الحاوی	امپا دیانس-ام	۲
	پارس دارو	امپاتوس-پلاس	۳

EMPAGLIFLOZIN-LINAGLIPTIN 10-5 & 25-5 mg Tablet



گلورنتا ۱۰/۵ (امپاگلیفلوزین + لیناگلیپتین)



گلورنتا ۲۵/۵ (امپاگلیفلوزین + لیناگلیپتین)

کشور	صاحب نام تجاری	نام دارو	
	الحاوی	امپاچنت	۱
	داروسازی دکتر عبیدی	گلورنتا	۲
	Boehringer Ingelheim	گلایزامبی	۳

نام عمومی : DAPAGLIFLOZIN (AS PROPANEDIOL) TABLET ORAL 10 mg

نحوه مصرف : ORAL

صاحب برند :  AstraZeneca Ab

تاریخ اعتبار پروانه : ۱۴۰۱/۰۸/۰۱

قیمت واحد : - ریال

IRC : ۳۶۷۰۸۰۴۴۷۶۶۵۰۱۵۰

نام : FORXIGA

شکل دارویی : TABLET

صاحب پروانه : کوپل دارو

تولید کننده : AstraZeneca Ab

قیمت مصرف کننده هر بسته : - ریال

GTIN : ۰۵۰۰۰۴۵۶۰۲۷۶۶۳

تعداد در بسته : 28 TABLET in 2 BLISTER PACK in 1 BOX



Pancreas



**Impaired
Insulin
Secretion**

- Sulfonylureas
- Glinides
- DPP4-I
- GLP-1 agonists
- GK agonists
- GPRs, IL-receptor antagonists

**Increased
Glucagon
Secretion**

- DPP4-I
- GLP-1 agonists
- Glucagon receptor antagonist

Liver



**Increased
Glucose
Production**

- Metformin
- GK agonists
- Glucagon receptor antagonists

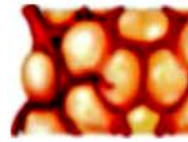
Muscle



**Decreased
Glucose
Uptake**

- TZDs
- Metformin
- Dual/Pan PPARs

Adipose Tissue



**Increased
Lipolysis**

- TZDs
- Metformin
- Dual/Pan PPARs
- 11 β HSD-I

Gut



**Decreased
Incretin Effect**

- DPP4-I
- GLP-1 agonists
- Bile acid sequestrants

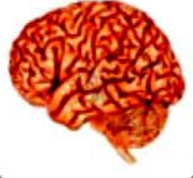
Kidney



**Increased
Glucose
Reabsorption**

- SGLT2-I

Brain



**Neurotransmitter
Dysfunction**

- Bromocriptin

A fourth class of dual PPAR agonists, so-called *glitazars*, which bind to both the α and γ PPAR isoforms, are currently under active investigation for treatment of a larger subset of the symptoms of the metabolic syndrome. In June 2013, saroglitazar was the first glitazar to be approved for clinical use

The glucose-phosphorylating enzyme glucokinase (GK) was identified as an outstanding drug target for developing antidiabetic medicines because it has an exceptionally high impact on glucose homeostasis because of its glucose sensor role in pancreatic β -cells and as a rate-controlling enzyme for hepatic glucose clearance and glycogen synthesis, both processes that are impaired in type 2 diabetes

Algorithm for T2DM

- **HbA₁C target for adults: < 7% (53 mmol/mol)**
- The guidelines for treatment of DM recommend an **individualized** treatment strategy.
- If target A₁C is not reached within **3 months with conservative measures** (e.g., diet, exercise), the next step in the therapeutic algorithm should be initiated.

Treatment algorithm	Description
General measures	Weight reduction, exercise , medical nutrition therapy, self-management education 
Monotherapy 	The drug of choice is <u>metformin</u> . 
Dual therapy 	- Metformin + - A second oral antidiabetic drug: <u>dipeptidyl peptidase-4 inhibitor</u>, <u>sulfonylureas</u>, <u>thiazolidinedione</u>, <u>meglitinides</u>, <u>SGLT-2 inhibitors</u>, <u>alpha-glucosidase inhibitors</u>, <u>amylin analogs</u>  <u>GLP-1 receptor agonists (incretin mimetics)</u>  - Basal <u>insulin</u> 
Triple therapy 	Add a third oral antidiabetic drug, nightly basal <u>insulin</u> , or injectable <u>GLP-1 receptor agonist</u>
Combination injectable therapy 	<u>Metformin</u> + basal <u>insulin</u> + mealtime <u>insulin</u> or <u>GLP-1 receptor agonist</u>

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†

NO

CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET

ASCVD PREDOMINATES

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)

PREFERABLY

GLP-1 RA with proven CVD benefit¹

OR

SGLT2i with proven CVD benefit¹ if eGFR adequate²

If A1C above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit¹
- DPP-4i if not on GLP-1 RA
- Basal insulin⁴
- TZD⁵
- SU⁶

HF OR CKD PREDOMINATES

- Particularly HFREF (LVEF <45%)
- CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >30 mg/g, particularly UACR >300 mg/g

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate³

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate³ add GLP-1 RA with proven CVD benefit¹

If A1C above target

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:

- For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit¹
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin⁴
- SU⁶

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i

GLP-1 RA

SGLT2i²

TZD

If A1C above target

If A1C above target

If A1C above target

If A1C above target

SGLT2i²

SGLT2i²

GLP-1 RA

SGLT2i²

OR

DPP-4i

OR

DPP-4i

OR

GLP-1 RA

TZD

TZD

TZD

GLP-1 RA

If A1C above target

Continue with addition of other agents as outlined above

If A1C above target

Consider the addition of SU⁶ OR basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia⁷

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

EITHER/ OR

GLP-1 RA with good efficacy for weight loss⁸

SGLT2i²

If A1C above target

SGLT2i²

GLP-1 RA with good efficacy for weight loss⁸

If A1C above target

If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

- SU⁶ • TZD⁵ • Basal insulin

COST IS A MAJOR ISSUE⁹⁻¹⁰

SU⁶

TZD¹⁰

If A1C above target

TZD¹⁰

SU⁶

If A1C above target

- Insulin therapy basal insulin with lowest acquisition cost
- OR
- Consider DPP-4i OR SGLT2i with lowest acquisition cost¹⁰



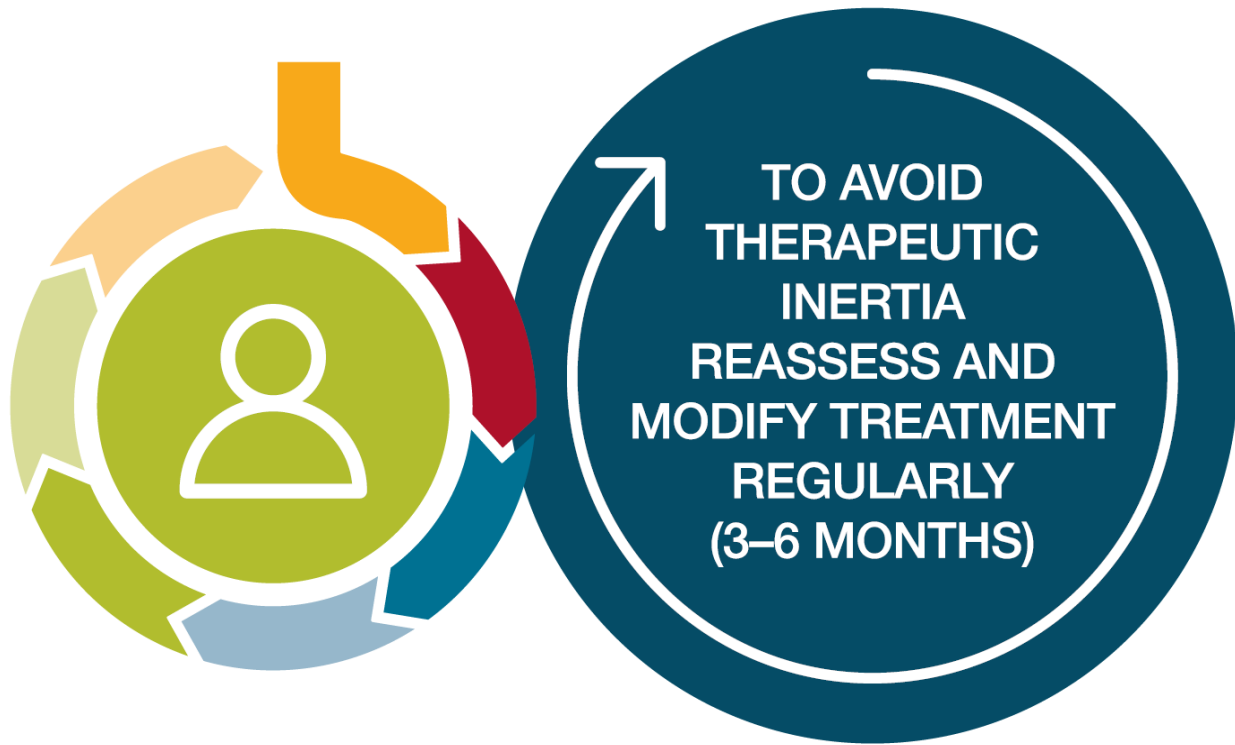
1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDECE. Dapagliflozin has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects

6. Choose later generation SU to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

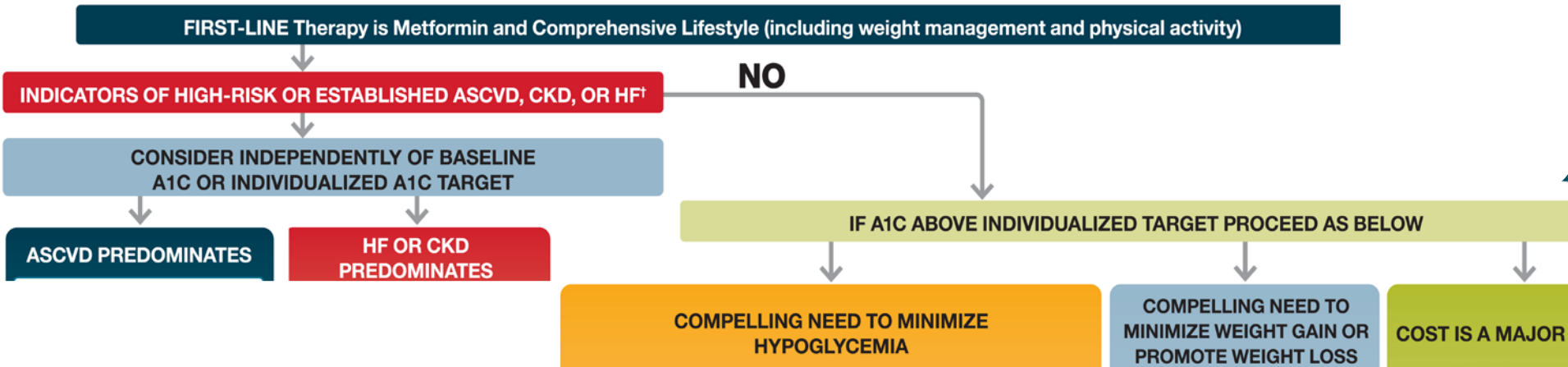
LVH = Left Ventricular Hypertrophy; HFREF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

Antidiabetic drugs



Antidiabetic drugs



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- DPP-4i if not on GLP-1 RA
- Basal insulin⁴
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- SU⁶

HF OR CKD PREDOMINATES

- Particularly HFrEF (LVEF $<45\%$)
- CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >30 mg/g, particularly UACR >300 mg/g

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate³

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate² add GLP-1 RA with proven CVD benefit¹

If A1C above target

▪ Avoid TZD in the setting of HF
Choose agents demonstrating CV safety:

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- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
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HYPOGLYCEMIA**

DPP-4i

GLP-1 RA

SGLT2i²

TZD

If A1C
above target

If A1C
above target

If A1C
above target

If A1C
above target

SGLT2i²

SGLT2i²

GLP-1 RA
OR
DPP-4i
OR
TZD

SGLT2i²
OR
DPP-4i
OR
GLP-1 RA

OR
TZD

OR
TZD

If A1C above target

Continue with addition of other agents as outlined above

If A1C above target

Consider the addition of SU⁶ **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia⁷

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)



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NO



IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW



COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

**EITHER/
OR**

GLP-1 RA with
good efficacy
for weight
loss[§]

SGLT2i[‡]



If A1C above target



SGLT2i[‡]

GLP-1 RA with
good efficacy
for weight
loss[§]



If A1C above target



If quadruple therapy required,
or SGLT2i and/or GLP-1 RA not
tolerated or contraindicated, use
regimen with lowest risk of
weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA)
based on weight neutrality



If DPP-4i not tolerated or
contraindicated or patient already
on GLP-1 RA, cautious addition of:

• SU[¶] • TZD[§] • Basal insulin

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SU⁶

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If A1C above target

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If A1C above target

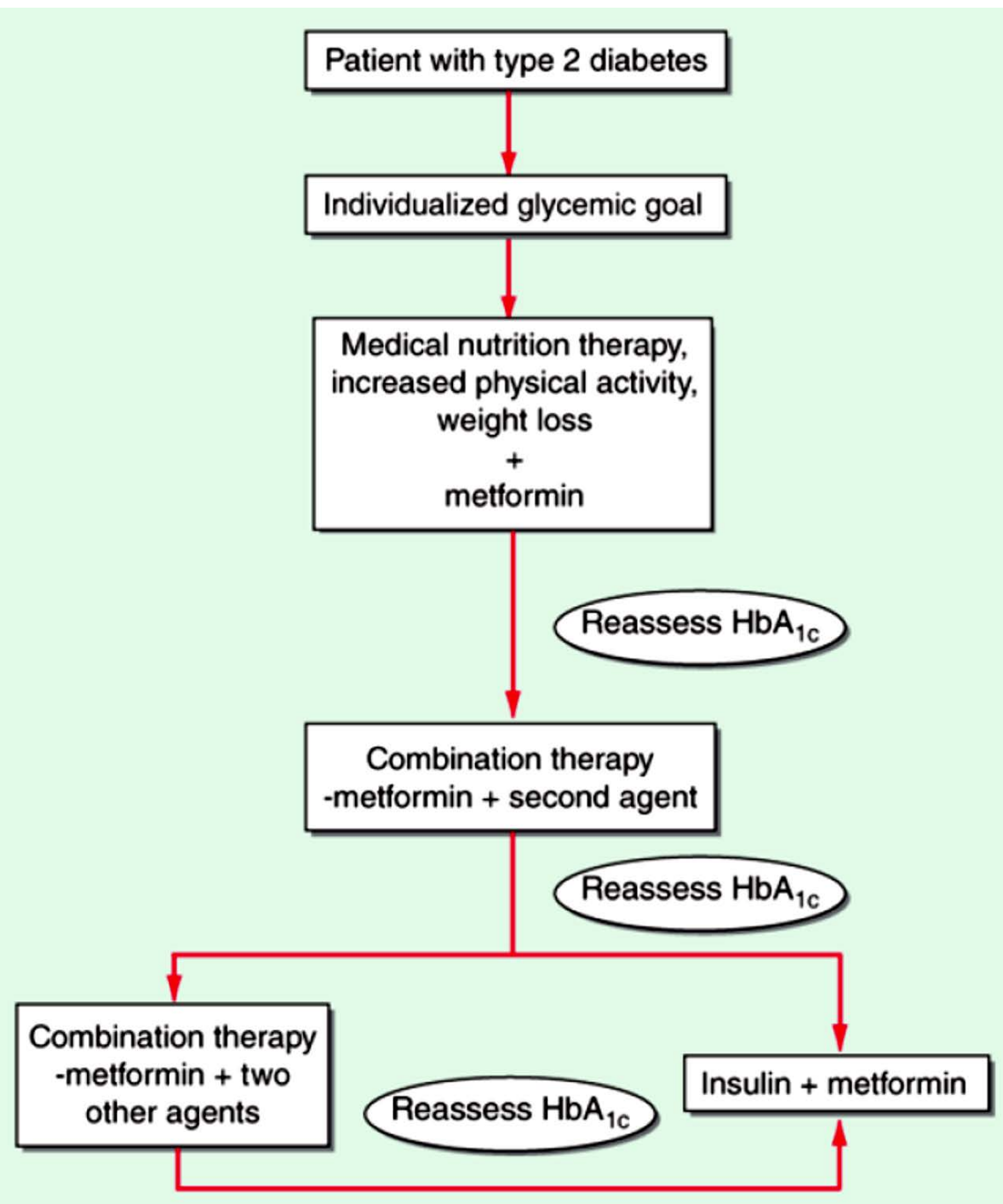
- Insulin therapy basal insulin with lowest acquisition cost
- OR
- Consider DPP-4i OR SGLT2i with lowest acquisition cost¹⁰

Antidiabetic drugs

		Efficacy*	Hypoglycemia	Weight Change	CV Effects	
					ASCVD	CHF
Metformin		High	No	Neutral (Potential for Modest Loss)	Potential Benefit	Neutral
SGLT-2 Inhibitors		Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin [†]	Benefit: canagliflozin, empagliflozin
GLP-1 RAs		High	No	Loss	Neutral: lixisenatide, exenatide extended release	Neutral
					Benefit: liraglutide [†]	
DPP-4 Inhibitors		Intermediate	No	Neutral	Neutral	Potential Risk: saxagliptin, alogliptin
Thiazolidinediones		High	No	Gain	Potential Benefit: pioglitazone	Increased Risk
Sulfonylureas (2nd Generation)		High	Yes	Gain	Neutral	Neutral
Insulin	Human Insulin	Highest	Yes	Gain	Neutral	Neutral
	Analogues					

	Cost	Oral/SQ	Renal effects	
			Progression of DKD	Dosing/use considerations*
Metformin	Low	Oral	Neutral	Contraindicated with eGFR <30 mL/min/1.73 m²
SGLT-2 Inhibitors	High	Oral	Benefit: canagliflozin, empagliflozin, dapagliflozin	Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)
GLP-1 RAs	High	SQ; oral (semaglutide)	Benefit: liraglutide	- Renal dose adjustment required (exenatide, lixisenatide) - Caution when initiating or increasing dose due to potential risk of acute kidney injury

DPP-4 inhibitors		High	Oral	Neutral	- Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment - No dose adjustment required for linagliptin
Thiazolidinediones		Low	Oral	Neutral	- No dose adjustment required - Generally not recommended in renal impairment due to potential for fluid retention
Sulfonylureas (2nd generation)		Low	Oral	Neutral	- Glyburide: not recommended - Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia
Insulin	Human insulin	Low	SQ; inhaled	Neutral	Lower insulin doses required with a decrease in eGFR; titrate per clinical response
	Analogs	High	SQ		



Antidiabetic drugs

- **Common contraindications of antidiabetic agents**
- **Type 1 diabetes mellitus**: Patients require insulin therapy
- **Pregnancy and breastfeeding.**
- **Renal failure** : Antidiabetic drugs that may be administered if $\text{GFR} < 30 \text{ mL/min}$ include **DPP-4 inhibitors, incretin mimetic drugs, meglitinides, and thiazolidinediones.**
- **Pause antidiabetic treatment in the following cases:**
 - Major surgery performed under general anesthesia
 - Acute conditions requiring hospitalization (infections, organ failure)
 - Elective procedures associated with an increased risk of hypoglycemia (periods of fasting, irregular food intake)

Interactions



Drug interactions with diabetes

- Which medications can worsen glycemic control?
- The theorized mechanisms for interactions include:
 - 1.Decreased Peripheral Insulin Sensitivity**
 - 2.Decreased Insulin Secretion**
 - 3.Increased Gluconeogenesis**

Drug interactions with diabetes

Corticosteroids

- The **route of administration** and the **dose** are factors that determine the impact of this class on blood glucose.
- Lower risk is associated with inhaled and topical formulations vs. oral formulations.
- The effect on BG may be dramatic and **prolonged**, requiring dose increases in diabetes medications to achieve glycemic control during concomitant therapy.

Drug interactions with diabetes

Atypical antipsychotics

- These medications have been frequently reported to be associated with significant **increases in weight**, diabetes (even diabetic ketoacidosis) and may have an adverse effect on lipids.
- The weight gain appears to be rapid, within the first few months of therapy, but may not plateau for as long as one year after treatment initiation.
- The increase in weight is widely variable (2 to 10 kg), and is reportedly due to an increase in body fat, suggesting insulin resistance as the mechanism. The relative risk of hyperglycemia and weight gain varies between agents within this class.
- **Clozapine & Olanzapine** appear to be ranked highest.
- Switching patients to the lowest risk agents **Aripiprazole** or intermediate risk agents **Risperidone** or **Quetiapine** is one option.

Drug interactions with diabetes

Niacin

- This agent is commonly used in patients with diabetes who are not meeting optimal **HDL** targets.
- Its effect on blood glucose is dose dependent and was reported more frequently when **large doses** (2 to 3 g/day) were used.
- When concomitant use is required, providers should use therapeutic approaches to compensate for mild increases in BG caused by this medication.

Drug interactions with diabetes

Fluoroquinolone antibiotics

- This class has been associated with glucose and insulin dysregulation. One theory related to fluoroquinolone-associated hyperglycemia suggests that the fluoroquinolones directly inhibit insulin release.
- An agent in this class, **Gatifloxacin** appeared to have the highest association with hyperglycemia and DKA.
- The fluoroquinolone class is also associated with hypoglycemia, theorized to be related to blockade of ATP-sensitive K⁺ channels.
- Careful monitoring is required for all the fluoroquinolones in view of their shared potential for delayed hyperglycemia, and perhaps early hypoglycemia, that may be dose related.

Drug interactions with diabetes

Diuretics

- The **thiazide** diuretics have long been known to contribute to hyperglycemia.
- The effects appear to be dose dependent and the extent of the effect may vary between patients.
- When starting patients on medications in this class, providers should inform patients to closely monitor their blood glucose to determine if adjustments will be needed in their diabetes medications.

Drug interactions with diabetes

Beta-blockers

- This class may cause either **hyperglycemia** or **hypoglycemia**, even potentiating insulin-induced hypoglycemia.
- In addition, these agents may **mask the sympathetically** mediated symptoms of hypoglycemia.
- Patients should be forewarned of this information and closely monitor their BG in the presence of new or worsened sweating.

Drug interactions with diabetes

OTC products, other drugs

- “Sugar-free” liquids include various cough and cold remedies, treatments for various gastrointestinal disorders, and many others.
- Products that contain sugar alcohols can raise glucose, especially with excessive or regular use.
- Providers should encourage patients to read the ingredient list on all OTC liquids and avoid or minimize use of those containing any type of nutritive sweetener.
- Patients may also bring in all their OTC and herbal medications for a comprehensive review and to receive recommendations about avoiding interactions with their diabetes.

Drug interactions with diabetes

OTC products, other drugs

- **Sympathomimetics** consist of ingredients such as pseudoephedrine and phenylephrine, which may increase blood glucose in a dose-dependent fashion.
- These drugs can also increase blood pressure and are best avoided in the presence of cardiovascular disease.
- Providing a “Safe OTC List” as a proactive measure may assist patients in the best product selection.
- A useful rule of thumb is to advise patients to take the lowest dose for the shortest period of time.
- Tertiary references list other medications associated with hyperglycemia including **pentamidine, exogenous thyroid hormone, oral contraceptives, phenytoin, α -interferon and protease inhibitors**.
- In summary, it is imperative that patients are asked about all the medications they are taking at the beginning of each provider visit.
- This will enable us to determine if there are any actual or potential interactions between their current medications and their diabetes control.

Drug interactions

- Table 1 lists the current oral hypoglycemic agents and their pathways of elimination.
- Notice that all of the agents, except metformin, are metabolized by the cytochrome P-450 system.
- The majority of the agents are substrates for CYP2C9, with CYP3A4 or CYP2C8 metabolizing the remaining agents.

Elimination Pathways for Oral Hypoglycemic Agents

Oral Hypoglycemic Agent	Substrate of CYP-450 Enzymes
Chlorpropamide (Diabinese)	2C9
Glipizide (Glucotrol)	2C9
Glimepiride (Amaryl)	2C9
Glyburide (DiaBeta)	2C9
Metformin (Glucophage)	Renal elimination
Nateglinide (Starlix)	2C9 / 3A4
Pioglitazone (Actos)	3A4 / 2C8
Repaglinide (Prandin)	3A4 / 2C8
Rosiglitazone (Avandia)	2C8 / 2C9
Tolbutamide (Orinase)	2C9

Adapted from Hansten PD, Horn JR. *The Top 100 Drug Interactions: A Guide to Patient Management*. Edmonds, WA: H&H Publications; 2004:157-169.

Drug interactions

- Table 2 lists common drugs that are known CYP2C9, CYP3A4, or CYP2C8 inhibitors.
- The combination of an oral hypoglycemic drug with a drug known to inhibit its metabolism is likely to result in a drug interaction.
- The plasma concentration of the hypoglycemic agent will increase, leading to an enhanced hypoglycemic response.
- The magnitude of each interaction and the ultimate effect on the patient's blood glucose concentrations will be difficult to predict.

Common Inhibitors of CYP2C8, CYP2C9, and CYP3A4

Drug	CYP-450 Enzymes Inhibited
Atazanavir (Reyataz)	3A4, 2C9
Clarithromycin (Biaxin)	3A4
Erythromycin	3A4
Fluconazole (Diflucan)	2C9, 3A4
Fluoxetine (Prozac)	2C9
Fluvastatin (Lescol)	2C9
Fluvoxamine (Luvox)	2C9, 3A4
Gemfibrozil (Lopid)	2C8
Grapefruit (large doses)	3A4
Indinavir (Crixivan)	3A4
Isoniazid (INH)	2C9
Itraconazole (Sporanox)	3A4
Ketoconazole (Nizoral)	3A4
Metronidazole (Flagyl)	2C9
Ritonavir (Norvir)	3A4
Sulfamethoxazole	2C9
Voriconazole (Vfend)	3A4, 2C9

Adapted from Hansten PD, Horn JR. *The Top 100 Drug Interactions: A Guide to Patient Management*. Edmonds, WA: H&H Publications; 2004:157-169.

