

- Biguanides

- Metformin (Glucophage, Fortamet, Riomet, Glumetza): preferred first medication. Promotes weight loss and improves insulin resistance. Dosage: 500 to 2,000 mg in divided doses or ER 1,000 to 2,000 mg every evening. Maximum effective dose 2,000 mg/day
- Avoid metformin and combination drugs containing metformin in renal insufficiency, prior to radiocontrast agent use, surgery, and severe acute illnesses (e.g., liver disease, cardiogenic shock, pancreatitis, hypoxia) due to increased risk of lactic acidosis.
- Caution with acute heart failure, alcohol abuse, elderly (can merge with previous bullet)
- Associated with GI side effects, vitamin B<sub>12</sub> deficiency (3)[A].

# contraindication

- glomerular filtration rate (eGFR) falls below 45 ml/min and avoided if it is less than 30 ml/min.
- contraindications include significant cardiac or respiratory insufficiency, or any other condition predisposing to major tissue hypoxia, e.g. hypotension, major infection, acute myocardial infarction.
- significant liver disease



### *Antihyperglycaemic action*

- *Suppresses hepatic glucose output*
- *Increases insulin-mediated glucose utilisation*
- *Decreases fatty acid oxidation*
- *Increases splanchnic glucose turnover*

### *Weight stabilisation or reduction*

#### *Improves lipid profile*

- *Reduces hypertriglyceridaemia*
- *Lowers plasma fatty acids and LDL-cholesterol; raises HDL-cholesterol in some patients*

### *No risk of serious hypoglycaemia*

#### *Counters insulin resistance*

- *Decreases endogenous or exogenous insulin requirements*
- *Reduces basal plasma insulin concentrations*

#### *Vascular effects*

- *Increased fibrinolysis*
- *Decreases plasminogen activator inhibitor 1 levels*
- *Improved endothelial function*

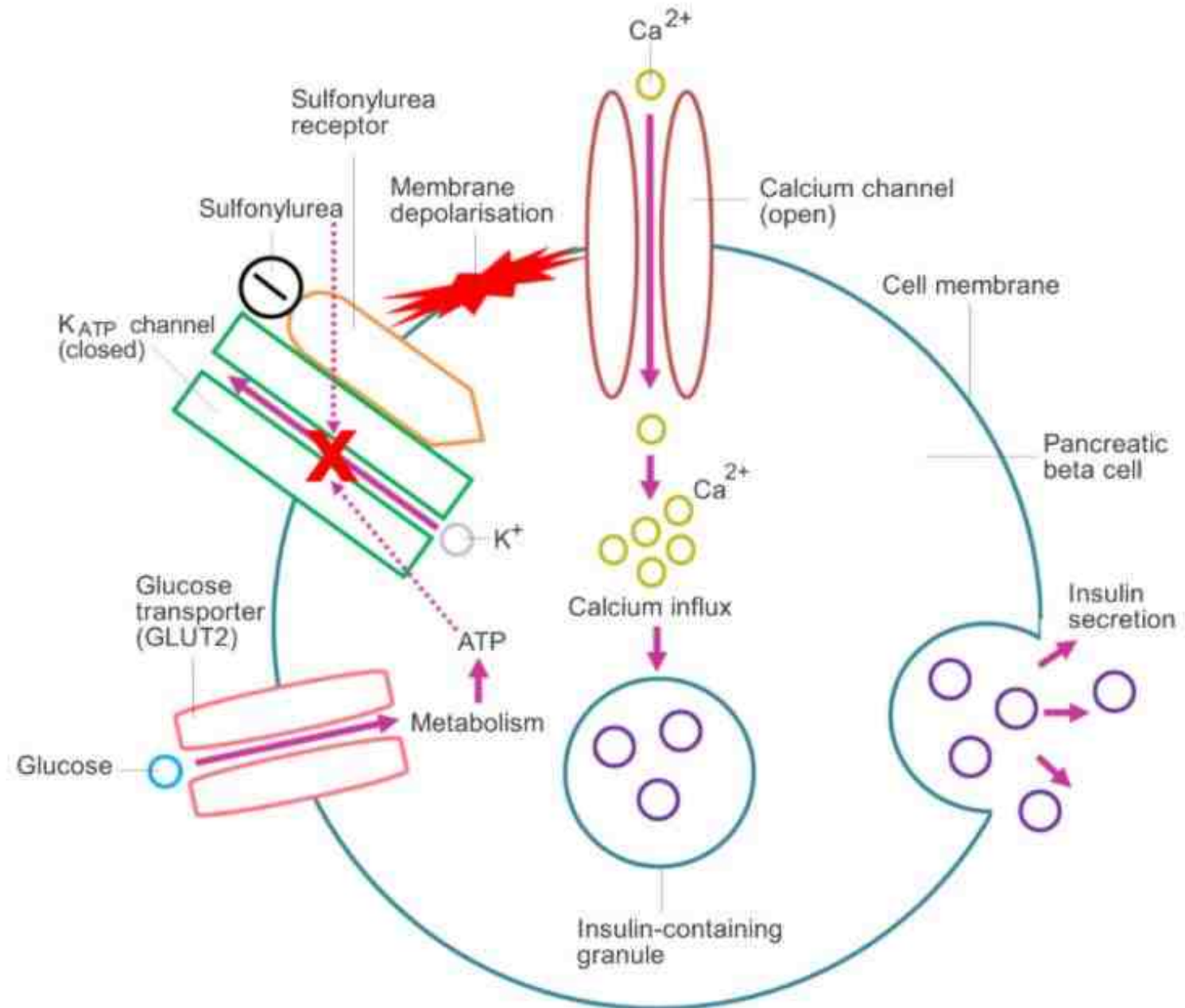




# SULFONYLUREAS

- Since their introduction in the 1950s, sulfonylureas have been used extensively for the treatment of type 2 diabetes. Modern examples include Glibanclamide (known as Glyburide in the USA and Canada), Gliclazide, Glipizide and Glimepiride

# SFU



- Sulfonylureas

- Caution with renal or liver disease, sulfa allergy, creatinine clearance <50 mL/min, elderly, pregnancy
- Glipizide (Glucotrol): 2.5 to 40 mg/day. Dosage >10 mg/day given BID 30 minutes before meals
- Glipizide extended-release: 5 to 20 mg/day
- Glyburide (DiaBeta, Glynase, Micronase): 1.25 to 20 mg/day, Glynase 0.75 to 12 mg/day
- Glimepiride (Amaryl): 1 to 8 mg/day (3)[A]
- Drugs that may potentiate effects of sulfonylureas: salicylates, clofibrate, warfarin (Coumadin), ethanol, and ACE inhibitors

**Table 4.** Second-Generation Sulfonylurea Dosing Strategies

<b>Drug</b>	<b>Initial Dosage</b>	<b>Maximal Daily Dosage (mg)</b>
Glyburide (nonmicronized)	2.5–5.0 mg once or twice daily	20
Glyburide (micronized)	1.5–3 mg once or twice daily	12
Glipizide	5 mg once or twice daily (once daily with extended release)	40 (little improved efficacy above 20 mg/day)
Glimepiride	1–2 mg once daily	8



**100 Scored Tablets**  
**Gliclazide Arya 80**  
Gliclazide

100 Scored Tablets

**Gliclazide Arya 80**

**Gliclazide**

Each Scored Tablet Contains:  
Gliclazide 80 mg

ARYA Pharmaceutical Co.  
Tehran - Iran



# Gliformin<sup>®</sup>

**No prior** treatment with sulfonylurea or metformin:  
maximum daily dose: 10 mg/2000 mg (limited experience with higher doses)

**Previously treated** with a sulfonylurea or metformin alone:  
Initial: 2.5 mg/500 mg or 5 mg/500 mg twice daily with meals;  
increase in increments no greater than 5 mg/500 mg; maximum daily dose: 20 mg/2000 mg



## Gliclazide decreases microthrombosis

- A partial inhibition of platelet aggregation and adhesion, with a decrease in the markers of platelet activation (beta thromboglobulin, **thromboxane B2**).
- An action on the vascular endothelium fibrinolytic activity with an increase in **tPA activity**.

- $\alpha$ -Glucosidase inhibitors
  - Acarbose (Precose): 25 to 100 mg TID
  - Miglitol (Glyset): 25 to 100 mg TID
  - Take at beginning of meals to decrease postprandial hyperglycemia.
  - Avoid in renal insufficiency and bowel diseases.
  - Drug binders, such as cholestyramine resin, should be taken at least 2 hours apart from  $\alpha$ -glucosidase inhibitors (3)[A].



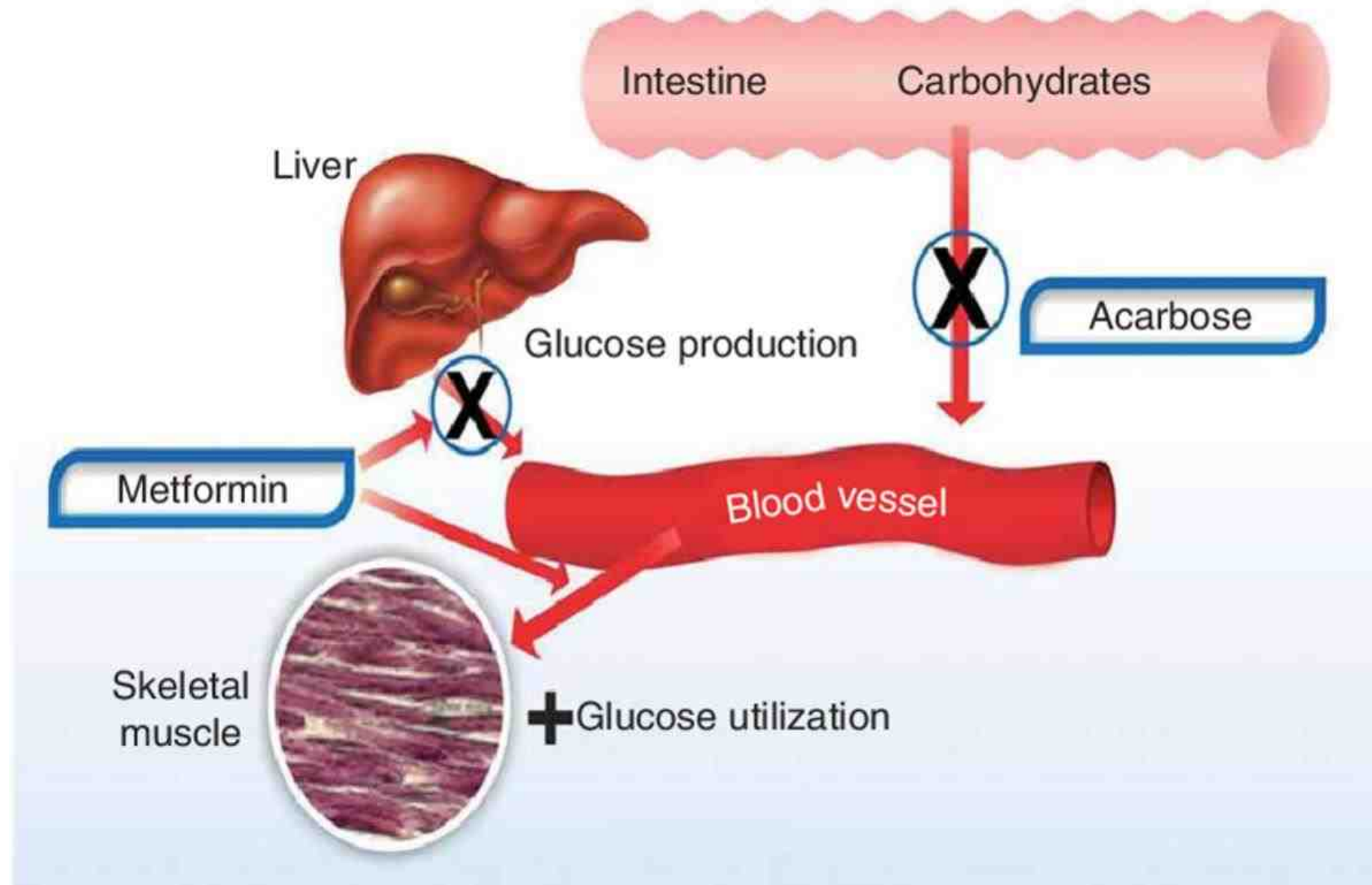
# Alpha-Glucosidase Inhibitors: Acarbose and Miglitol

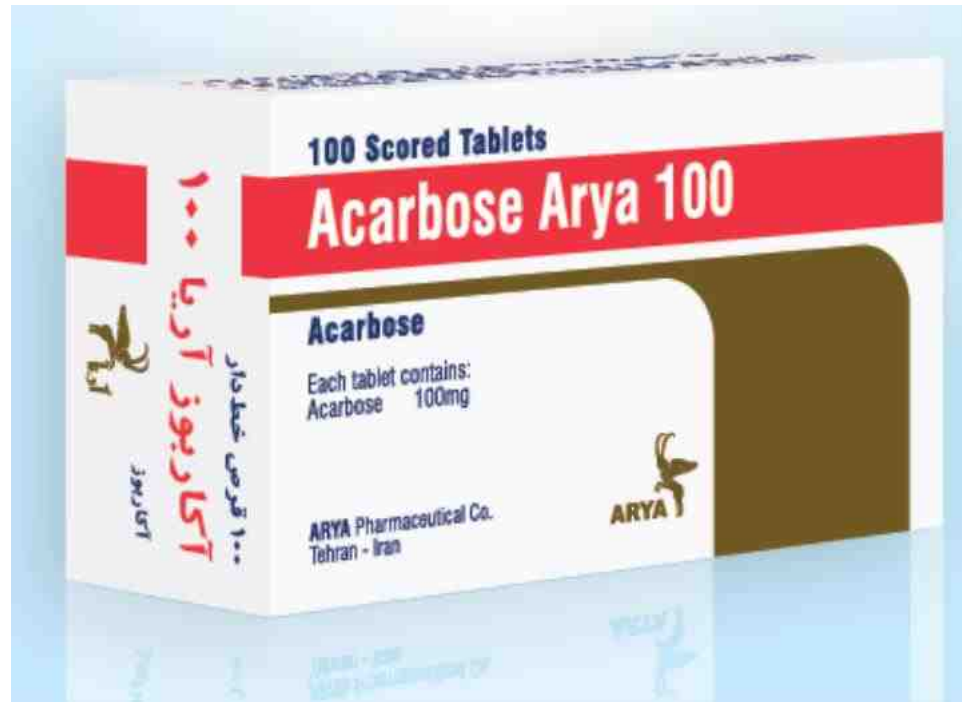
## ▶ Mechanism of Action

- Delay absorption of carbohydrates
- Depends on carbohydrate intake

## ▶ Safety and Efficacy

- Decrease A1C 0.5–1%
- Adverse events: **flatulence**; main risk: rare liver enzyme elevation



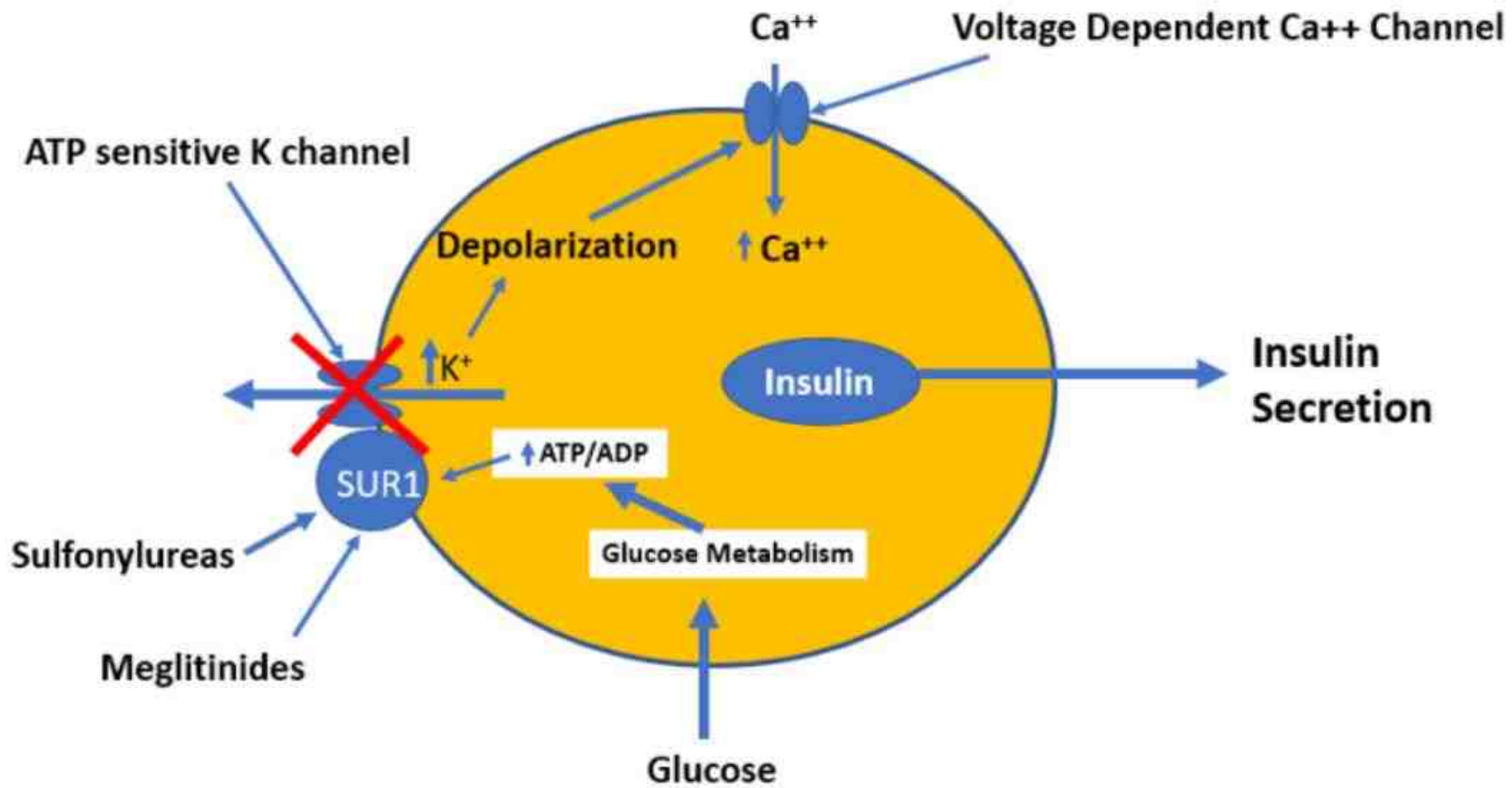


- Meglitinides

- Repaglinide (Prandin): 0.5 to 4 mg before meals; may be useful in patients with sulfa allergy or renal impairment

- Diphenylalanine derivatives

- Nateglinide (Starlix): 60 to 120 mg before meals TID (3)[A]





**Repaglinide**  
**0.5mg**  
tablets  
Repaglinide

Each tablet contains

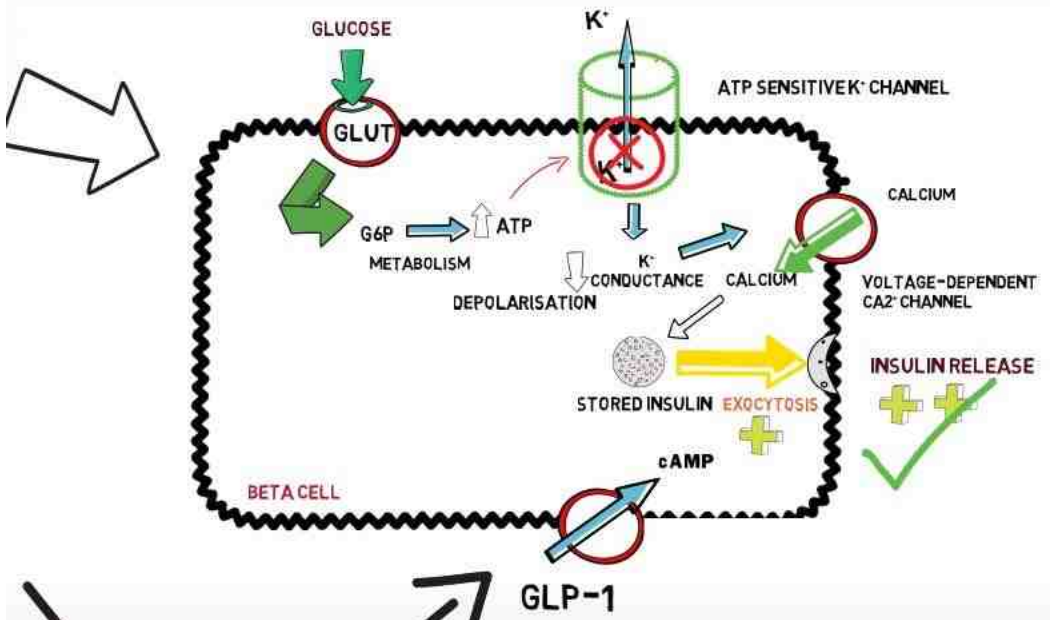
90 tablets

**Repaglinide**  
**1mg**  
tablets  
Repaglinide

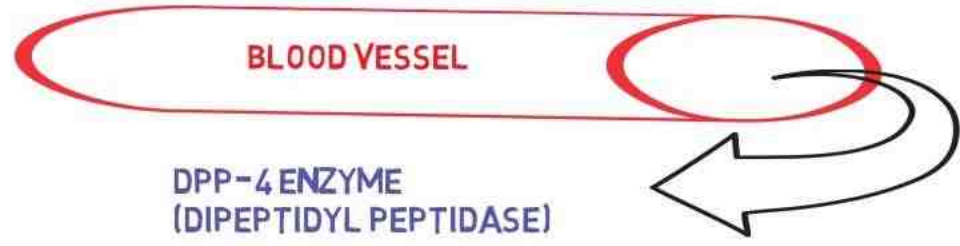
**Repaglinide**  
**2mg**  
tablets  
Repaglinide

Each tablet contains 2mg Repaglinide

90 tablets



ENDOTHELIUM OF THE BLOOD VESSEL SECRETES



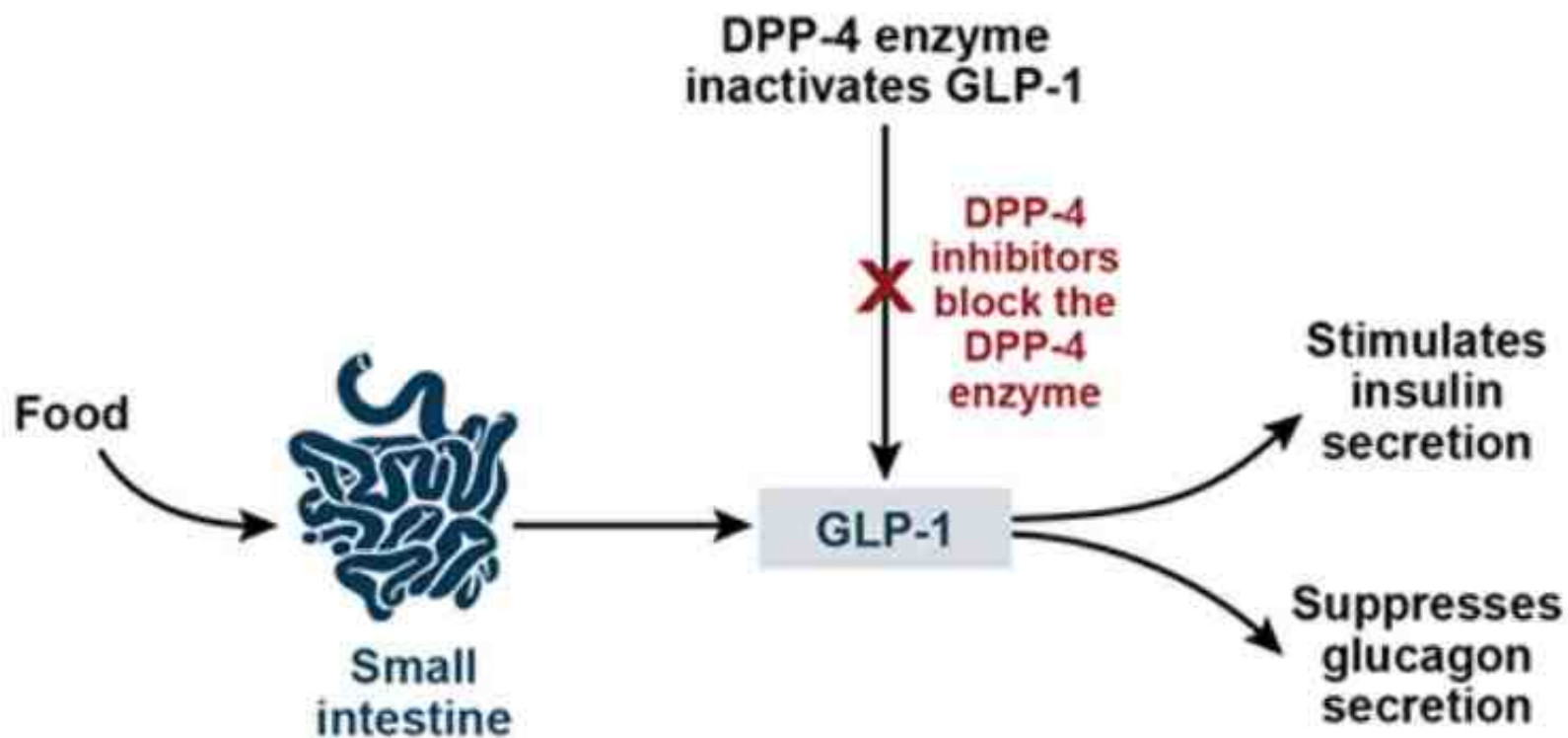
DPP-4 ENZYME

DPP-4 INHIBITORS



# DPP-4 Inhibitors

## *Mechanism of Action*





- Dipeptidyl peptidase-4 inhibitors
  - Weight neutral with minimal risk for hypoglycemia; dose adjustments in renal function decline with exception of linagliptin
  - Sitagliptin (Januvia): 100 mg/day
  - Saxagliptin (Onglyza): 2.5 mg/day, maximum 5 mg/day
  - Linagliptin (Tradjenta): 5 mg/day
  - Alogliptin (Nesina) 25 mg/day. Significant interactions with metformin (3)[A]
  - Linagliptin/metformin (Jentadueto): 2.5/500 mg PO BID, maximum 2.5/1,000 mg PO BID

# FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing **saxagliptin and alogliptin**

**Patients** taking these medicines should contact their health care professionals right away if they develop signs and symptoms of heart failure such as:

- Unusual shortness of breath during daily activities
- Trouble breathing when lying down
- Tiredness, weakness, or fatigue
- Weight gain with swelling in the ankles, feet, legs, or stomach

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## FDA Drug Safety Communication: FDA warns that DPP-4 inhibitors for type 2 diabetes may **cause severe joint pain**

The U.S. Food and Drug Administration (FDA) is warning that the type 2 diabetes medicines **sitagliptin, saxagliptin, linagliptin, and alogliptin may cause joint pain that can be severe and disabling**. We have added a new Warning and Precaution about this risk to the labels of all medicines in this drug class, called dipeptidyl peptidase-4 (DPP-4) inhibitors.




**Jentaduetto®**

**2.5 mg/850 mg**

**film-coated tablets**

Linagliptin/  
metformin hydrochloride

Oral use  
56 x 1 film-coated tablets

 Boehringer  
Ingelheim


**Jentaduetto®**

**2.5 mg/1,000 mg**

**film-coated tablets**

Linagliptin/  
metformin hydrochloride

Oral use  
56 x 1 film-coated tablets

 Boehringer  
Ingelheim

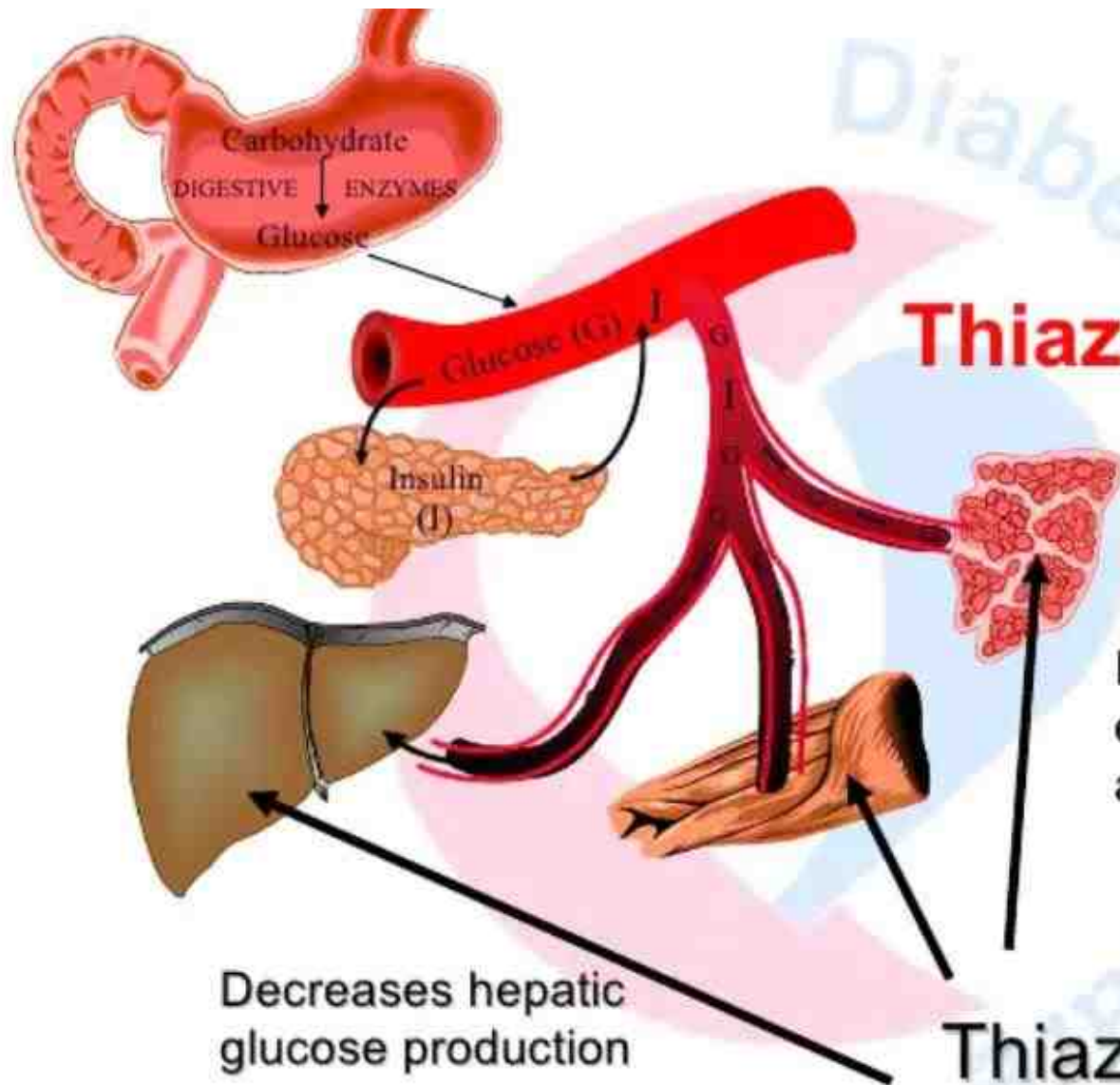
Sitagliptin (Januvia): 100 mg/day





- Thiazolidinediones

- Obtain baseline liver function tests: if abnormal, use with caution. Contraindicated in patients with NYHA Class III or IV heart failure.
- Pioglitazone (Actos): 15 to 45 mg/day
- Cumulative use of pioglitazone or rosiglitazone was not associated with the incidence of bladder cancer in a large, pooled multipopulation analysis (6)[A].
- Duetact (pioglitazone hydrochloride and glimepiride): 30/2 mg PO daily with meal
- Rosiglitazone (Avandia): 4 to 8 mg/day



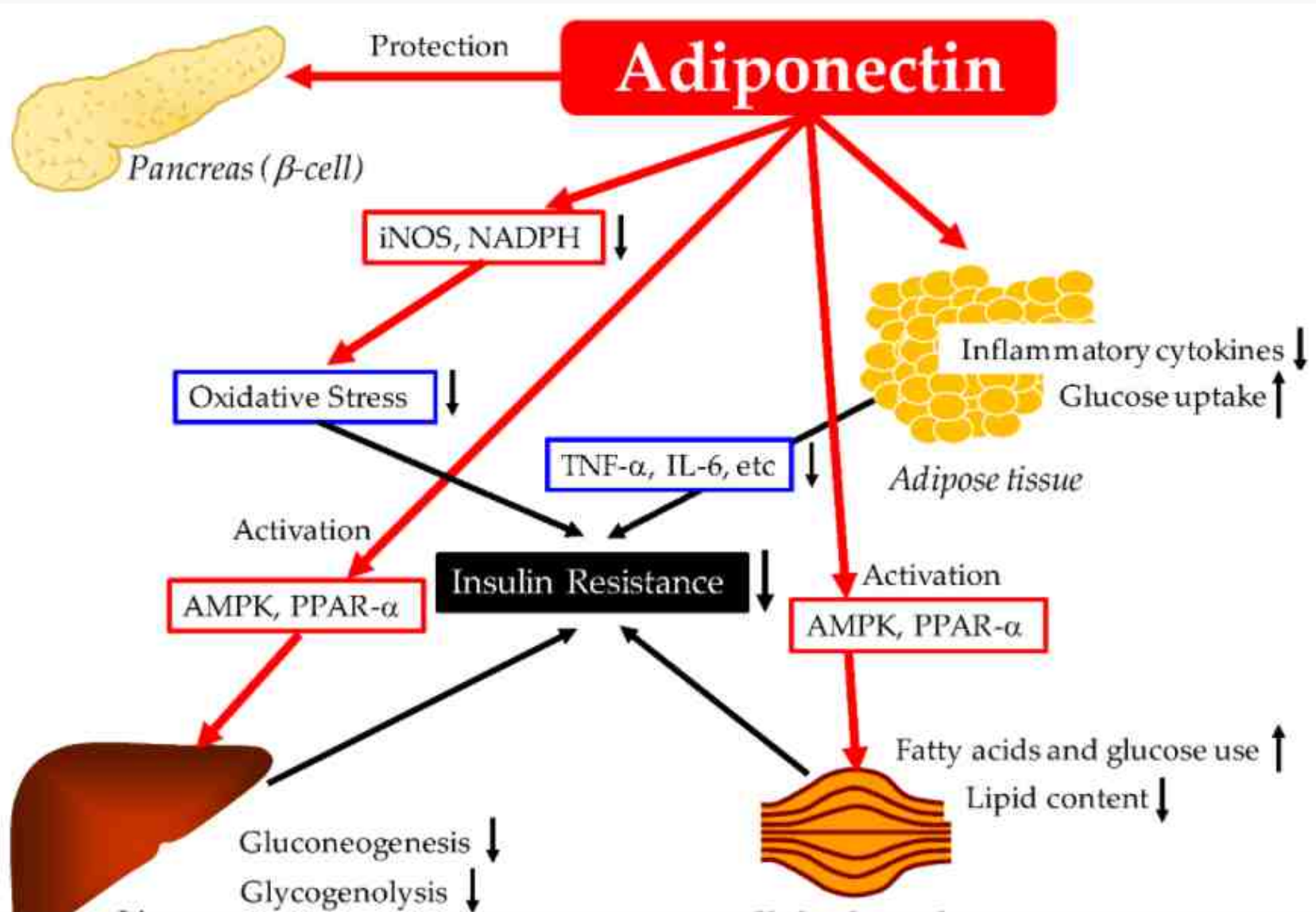
# Main Site of Action of Thiazolidinediones

Increases glucose entry into adipose and muscle tissue

Decreases hepatic glucose production

**Thiazolidinediones**  
Reduce Insulin Resistance







- GLP-1 (glucagonlike peptide-1) receptor agonist (incretins)
  - Exenatide (Byetta): 5 to 10 &mgr;g SC BID within 60 minutes before meals and at least 6 hours apart. Extended-release formulation (Bydureon): 2 mg SC weekly
  - Liraglutide (Victoza): 0.6 mg/day SC for 1 week, then increase to 1.2, maximum 1.8 mg/day. Less expensive and better tolerated than exenatide; contraindicated in patients with personal or family history of medullary thyroid cancer or (MEN) type 2 (black box warning).
  - Liraglutide (Saxenda): 3 mg SC daily approved for treatment of obesity.
  - Albiglutide (Tanzeum): 30 to 50 mg SC qwk in a single-dose pen
  - Dulaglutide (Trulicity) 0.75 to 1.5 mg weekly: 2 mg/wk Associated increased risk of acute pancreatitis with GLP-1 agonists and DPP4 inhibitors and caution with use in CKD <sup>3</sup> stage 4. GLP-1 analogs and Symlin require insulin adjustment and may exacerbate gastroparesis

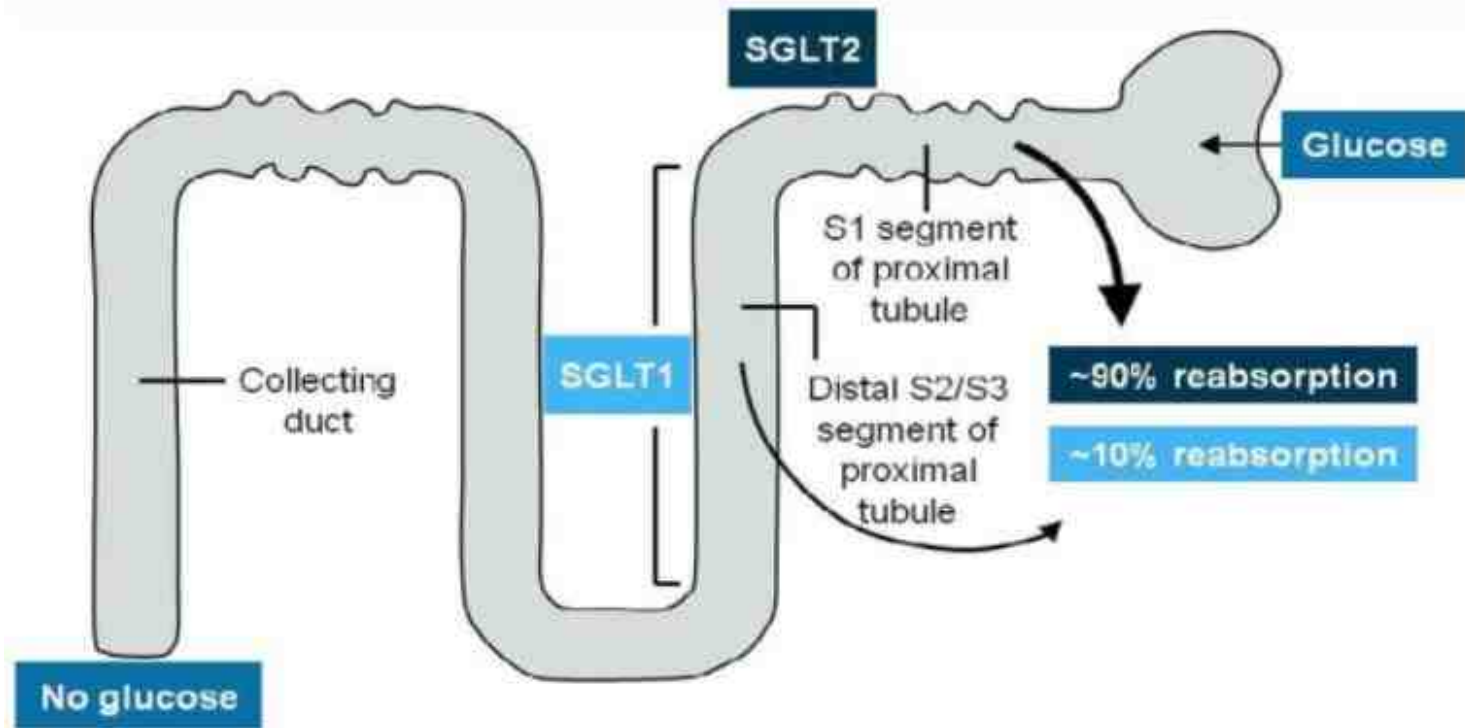


- Amylinomimetic

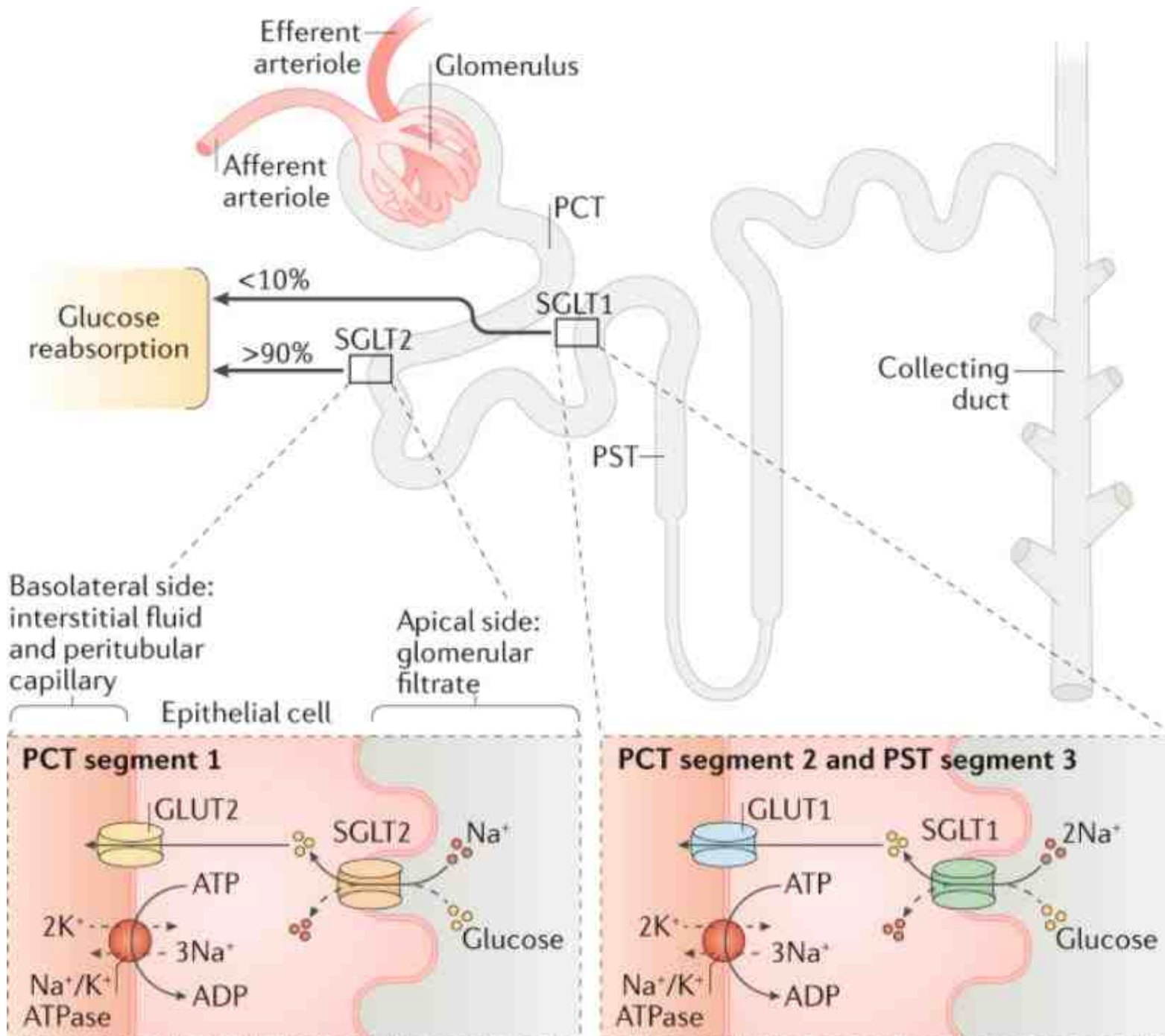
- Pramlintide (Symlin): 60 to 120 &mgr;g SC before every major meal
- Prandial insulins (short-acting/rapid-acting) should be reduced by 50% if pramlintide is initiated to avoid hypoglycemia.
- Avoid anticholinergics that slow intestinal absorption of nutrients (3)[A].



- SGLT2 inhibitors
  - Inhibits glucose reabsorption by sodium glucose cotransporter-2 inhibition
  - Canagliflozin (Invokana): 100 to 300 mg single dose before breakfast; adjust dose with renal function decline
  - Dapagliflozin (Farxiga): 5 to 10 mg daily; avoid use if eGFR <60
  - Empagliflozin (Jardiance): 10 to 25 mg daily; avoid use if eGFR <45
  - Xigduo (dapagliflozin-metformin): 5/100, 10/1,000 mg PO daily
  - May cause hypotension, genital mycotic infections, UTI, impairment of renal function, electrolyte abnormalities, elevated LDL, and DKA and increased fracture risk (canagliflozin)







- Sodium–glucose cotransporter 2 (SGLT2) inhibitors improve glycaemic control by blocking glucose reabsorption in the proximal convoluted tubule of the kidney and by increasing glycosuria.
- Large randomized trials of SGLT2 inhibitors report reductions in cardiovascular events (particularly hospitalization for heart failure) in patients with type 2 diabetes mellitus and in those with heart failure with reduced ejection fraction with or without diabetes.

- The cardiovascular benefits manifest rapidly and are unlikely to be related to the improvement in glycaemic control.
- Early natriuresis, reductions in plasma volume, improved vascular resistance, reduced blood pressure and changes in tissue sodium handling might underlie the rapid reduction in the risk of heart failure.

- A shift towards ketone body metabolism, reduced serum uric acid levels, reduced adipose tissue-mediated inflammation, decreased oxidative stress and suppression of damage mediated by advanced glycation end-products might also provide benefit.
- Ongoing outcome clinical trials in other groups of patients and more detailed mechanistic studies will shed further light on the mechanisms of cardiovascular benefit with SGLT2 inhibitors.



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**Jardiance**<sup>®</sup>

(empagliflozin)

Tablets

**10 mg**

Rx only

30 tablets



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NDC 0591-0153-30

**Jardiance**<sup>®</sup>

(empagliflozin)

Tablets

**25 mg**

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