OPTIMAL DOSE ADJUSTMENT OF ORAL ANTIGLYCEMIC AGENTS IN DIABETIC NEPHROPATHY

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Introduction

CKD is the largest non-communicable cause of death globally,resulting in tens of millions of deaths annualy.

It is estimated that CKD affects 8–16% of the worldwide population, and in the US alone is projected to affect nearly 1 in 5 adults by 2050.

If allowed to progress, CKD will eventually transition to end-stage renal disease (ESRD), requiring dialysis or transplant for survival.

Diabetic nephropathy (DN) is the most common cause of endstagerenal disease (ESRD) in most of the countries worldwide.

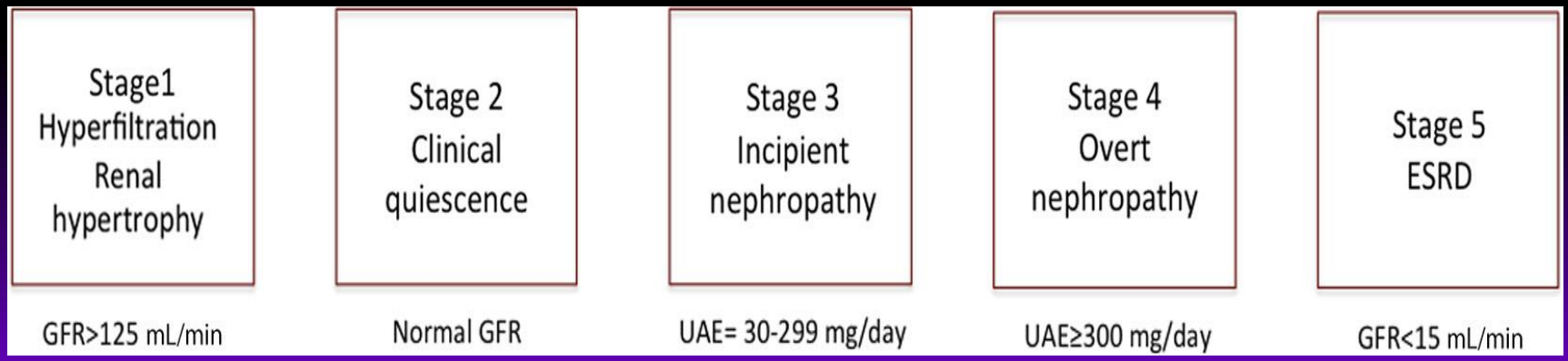
Bioorganic & Medicinal Chemistry Letters 26 (2016)

Diabetic Nephropathy

One third of type 1 diabetes mellitus (T1DM) patients develop ESRD, while **only 10–20%** of type 2 diabetes mellitus (T2DM) patients progress to ESRD .

DN increases the overall 10-year mortality among diabetic patients at least 6 folds compared to healthy age matched non-diabetic individuals.

The classical description of *diabetic nephropathy* is a slow and progressive increase in albuminuria, followed later by a decrease in (eGFR) below 60 mL/min/1.73 m2, which can, eventually, lead to (ESRD)



Journal of Advanced Research 8 (2017)

AJKD

Glycemic Management in ESRD and Earlier Stages of CKD

Mark E. Williams, MD,1 and Rajesh Garg, MD2

The management of hyperglycemia in patients with kidney failure **is complex**, and the goals and methods regarding glycemic control in chronic kidney disease (CKD) are not clearly defined.

Although aggressive glycemic control seems to be advantageous in early diabetic nephropathy, outcome data supporting tight glycemic control in patients with advanced CKD (including end-stage renal disease [ESRD]) are lacking.(**Am J Kidney Dis. 2014**)

Complexities in management of DM in CKD

1.Diagnostic problems

2.Glycemic Goal

3.A1C accuracy

4.Alterations in Glu homeostasis

5.Insulin resistance

6.Cr or eGFR?

7.Interindividual pharmacokinetic changes

8.Effects beyond glycemic control

Oral antiglycemic agents

1. Biguanides
2. Sulfonylureas
3. Thiazolidinediones
4. Dipeptidyl peptidase -4 inhibitors
5. SGLT2 inhibitors
6. Meglitinides (Glinides)
7. Alpha glucosidase inhibitors

Pharmacokinetics

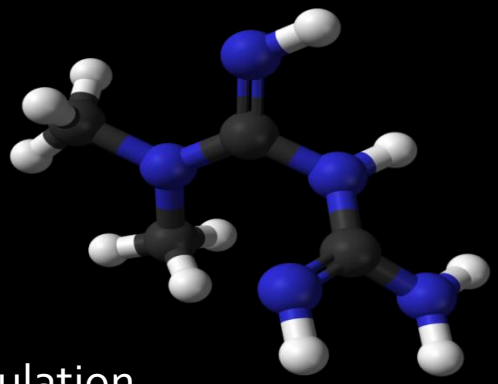
Renal dose adjustment

Renoprotective effects

Metformin (belonging to Biguanides)

- is globally accepted as the first choice in practically all therapeutic algorithms for diabetic subjects
- Metformin is an insulin sensitizer
- ***Low risk of hypoglycaemia***,modest weight loss, effectiveness and low cost
- The bioavailability of the drug is low (50%-60%).
- lower incidence of macro-vascular complications
- It reduces A1c by 1.0–2.0 %
- The most common side effects are diarrhea, bloating and cramping. (Vitamin B12 deficiency)
- In normal pH metformin remains as hydrophilic cation.

Metformin ……continued



Metformin is actively excreted by the urinary tube and
found unchanged in the urine

Metformin enters renal cells of the renal tubule from circulation.
This procedure takes place on the basolateral membrane of the cells and is mediated by **OCT2**.
Then, metformin is excreted into the lumen by **MATE** (1 and 2-K) in apical membrane

United States FDA label states, "do not use if SCr> 1.5 mg/dL in men, >1.4 mg/dL in women"
British National Formulary and the Japanese Society of Nephrology recommend cessation if eGFR < 30 mL/min/1.73 m2

Metformin-associated lactic acidosis (MALA)

Metformin inhibits complex I of the mitochondrial respiratory chain. This inhibition, leads to an incretion ofAMP:ATP ratio, which **activate AMPK**.
This inhibition leads also to increased anaerobic metabolism of glucose
In cytoplasm and the production of lactic acid.

The risk of lactic acidosis is also increased in patients with tissue hypoxia (shock, severe heart failure, sepsis, surgery related hypotension)

The incidence of lactic acidosis per 100000 patient-years : 4.3 cases

Nephrol Dial Transplant (2014)

Table 4—Recommended dose adjustments for metformin based on eGFR

eGFR (mL/min/1.73 m^2)	Proposed action
≥60	No contraindication to metformin Monitor kidney function annually
<60 and ≥45	Continue use Increase monitoring of renal function (every 3–6 months)
<45 and ≥30	Prescribe metformin with caution Use lower dose (e.g., 50%, or half-maximal dose) Closely monitor renal function (every 3 months) Do not start new patients on metformin
<30	Stop metformin

Adapted with permission from ADA (83).

Diabetes Care 2014 (A Report From an ADA Consensus Conference)

Data of **UKPDS** indicate that **treatment based on metformin** results in less total as well cardiovascular mortality.

Metformin is able to inhibit mTOR both dependent & independent of AMPK

Metformin inhibits hyperglycemia-induced **podocyte apoptosis** & (restoration of nephrin)

Metformin can *promote mesenchymal to epithelial transition (MET),* a consequence of upregulation of the epithelial marker cadherin.

Metformin suppresses inflammatory, oxidative and profibrotic renal damage markers and thus improves renal damage.

Metformin also blocks tumorogenesis via direct & indirect mechanisms.

Benefits beyond antiglycemic effects

Sulfonylureas

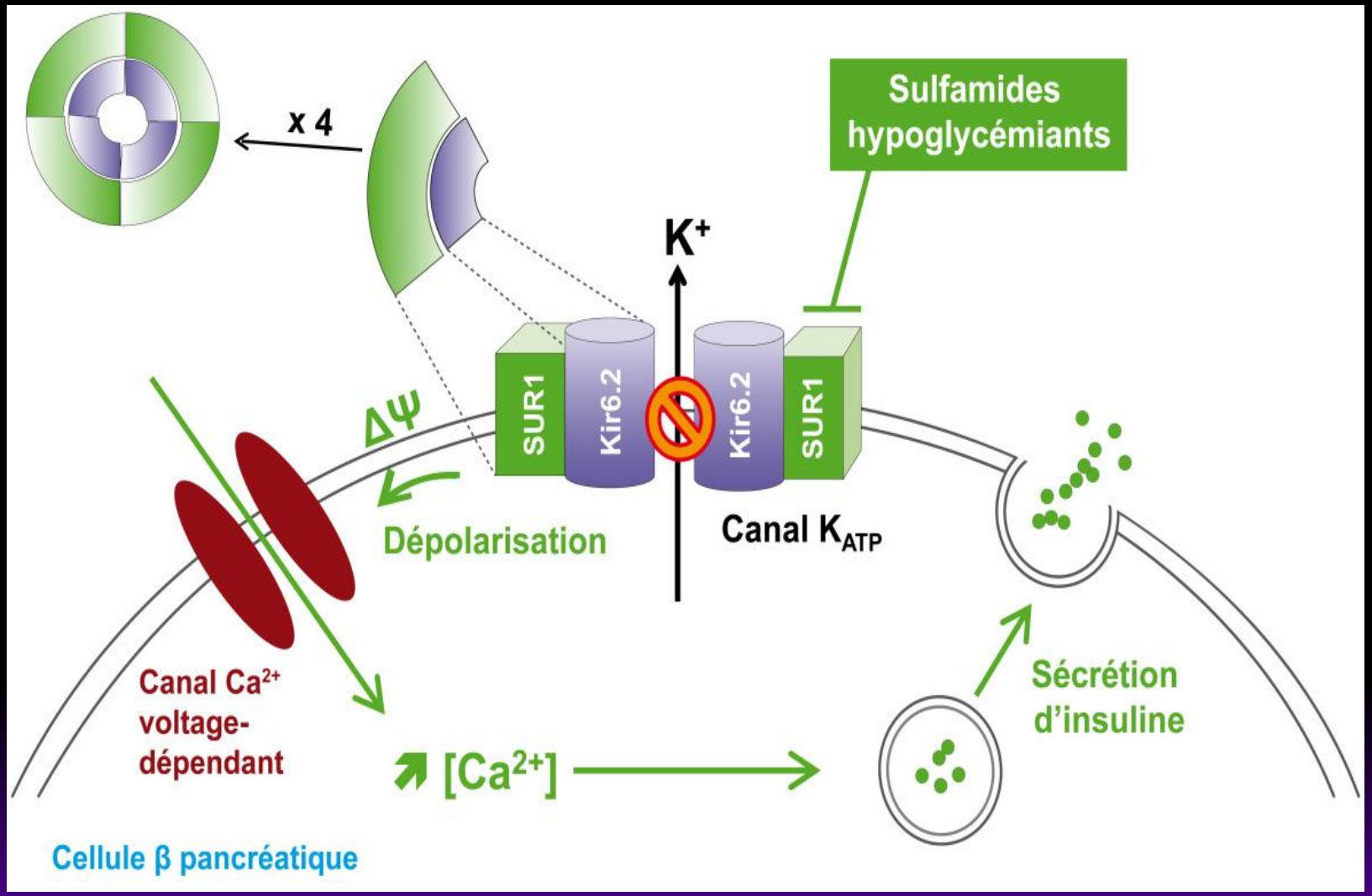
Lower blood glucose levels by releasing insulin from the pancreatic beta cells

Acting through sulfonylurea receptors, ***they close the (ATP)-sensitive potassium channels*** and depolarize the plasma membrane. Depolarization leads to degranulation of cells and insulin secretion.

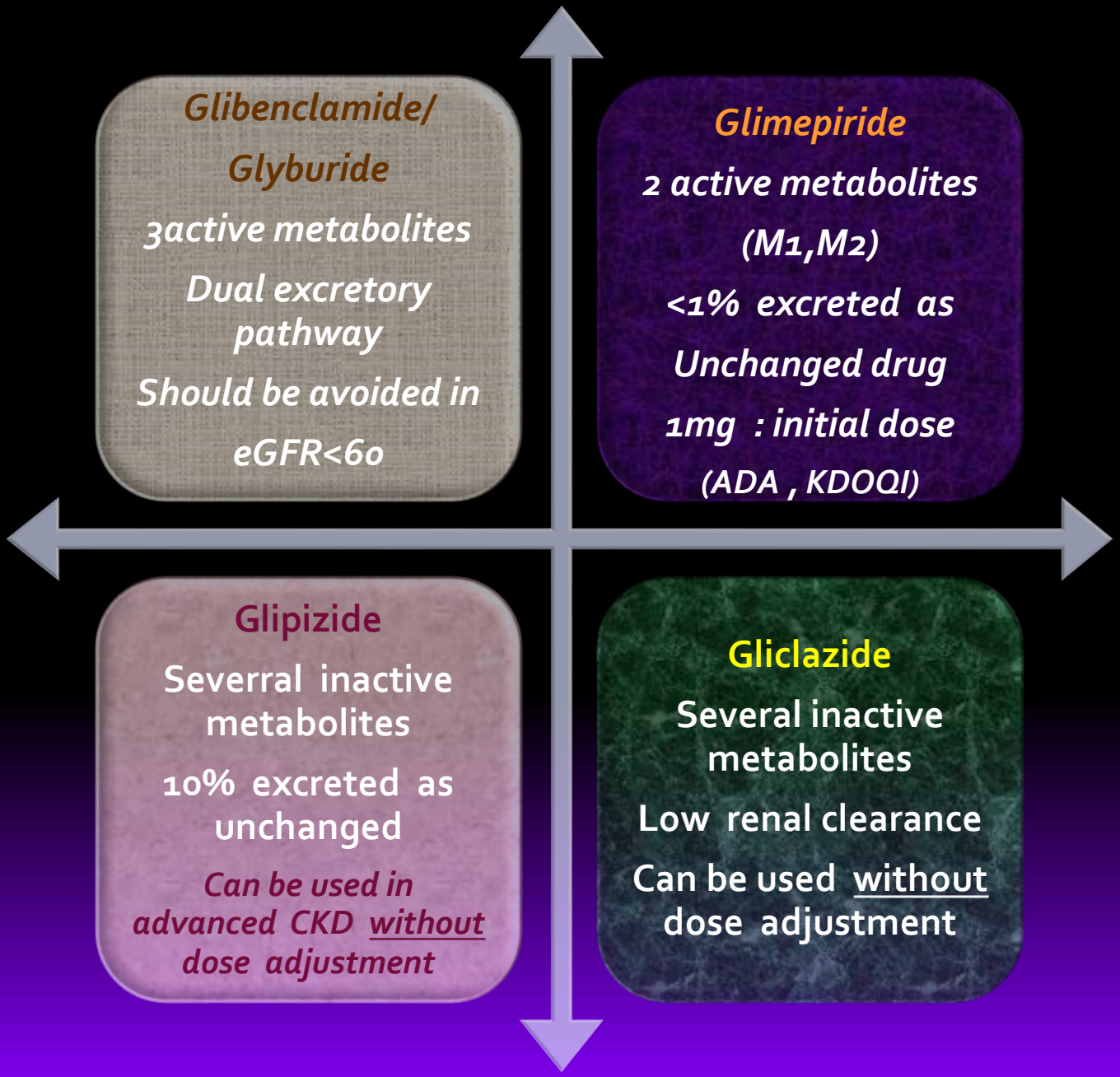
Effectiveness *of sulfonylureas is* *dependent on* *beta-cell reserves*

The glucose lowering effect of these drugs is not dependent on ambient glucose levels. (unregulated insulin release & risk of severe hypoglycemia)

They typically lower A1c by 1.5–2 %


x 4
Sulfamides hypoglycémiants
K+
SUR1
Kir6.2
Kir6.2
SUR1
ΔΨ
Dépolarisation
Canal KATP
Canal Ca2+ voltage-dépendant
[Ca2+]
Sécrétion d'insuline
Cellule β pancréatique

Sulfonylureas……..continued



THIAZOLIDINEDIONES (GLITAZONES)

Are insulin sensitizers (reduce insulin resistance)

Glitazones target specific *peroxisome proliferator-activated receptors* (PPARs). When activated, these receptors bind to DNA and, in complex with the retinoid X receptor, modulate genic transcription.

Glitazones ***preserve pancreatic ß-cell function***,

Because of the high molecular weight, high proteinbinding capacity and hepatic metabolism, the pharmacokinetic profile of pioglitazone, is similar in subjects with normal or impaired renal function, remaining unaffected even by hemodialysis.

No dose adjustment is usually required in the presence of CKD.

Glitazones……. continued

They do not cause hypoglycemia.

Pioglitazone is related with fluid retention, anemia and osteoporosis.

Thiazolidinediones have beneficial effects on other components of metabolic syndrome and cardiovascular risk factors.

(PPARγ) is
expressed in different renal cells that include MCs, tubular cells, and renal medullary interstitial cells.

Antiproteinuric effect in animal models of T1DM and T2DM through amelioration of glucose-induced oxidative stress, and downregulation of MCP1, ICAM1, NF-κB, and TGF β. (increament of Adipokines)

↓ Hb A1C ……0.5 - 1.4 %

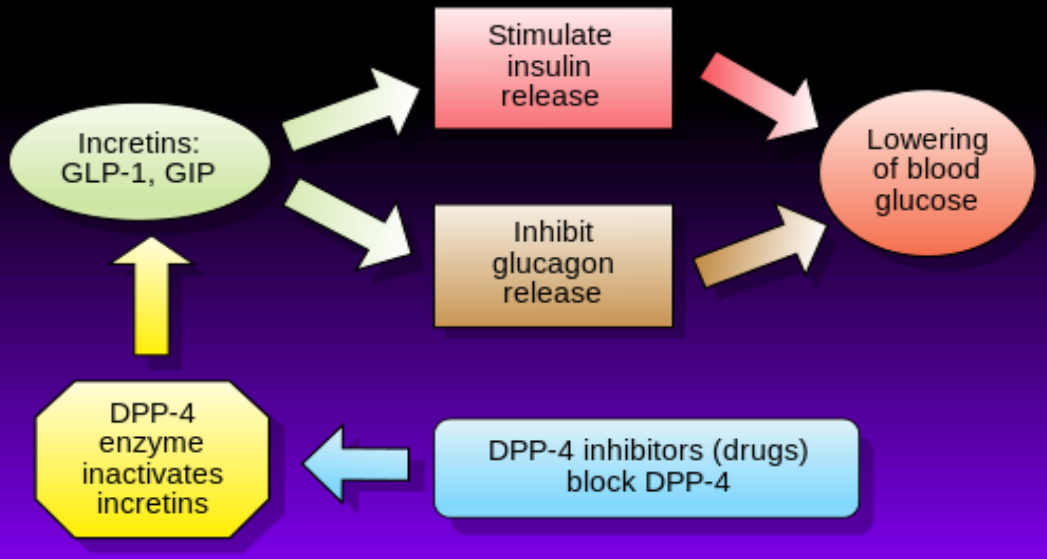
Whether the benefit of using pioglitazone outweighs the risks ?

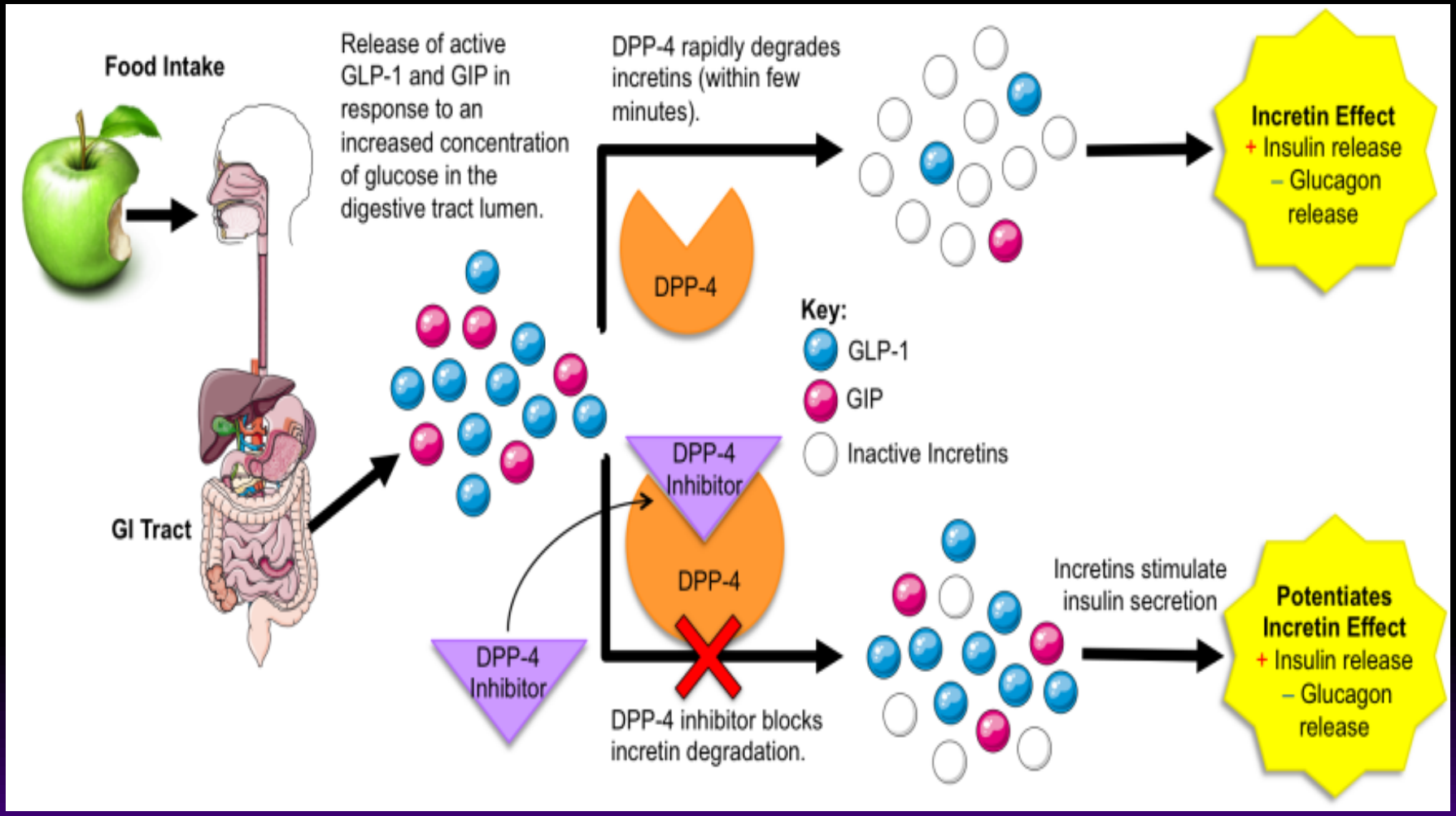
DPP4-inhibitors (incretin enhancers)

Selective DPP4 inhibitors
Limit the degradation of GDIP and GLP-1, producing a consequent increase in insulin release and decrease in glucagon concentration.
This reduces fasting glucose levels and glucose excursions following an oral glucose load or a meal.

This class of medication decreases A1c by 0.5–0.8 %

antidiabetic drugs with a very favorable profile:
safety, efficacy, and low risk of hypoglycemia and weight neutrality, possible beneficial effects on beta cells




Food Intake
Release of active GLP-1 and GIP in response to an increased concentration of glucose in the digestive tract lumen.
DPP-4 rapidly degrades incretins (within few minutes).
Incretin Effect
+ Insulin release
– Glucagon release
DPP-4
Key:
GLP-1
GIP
Inactive Incretins
GI Tract
DPP-4 Inhibitor
DPP-4
DPP-4 Inhibitor
Incretins stimulate insulin secretion
Potentiates Incretin Effect
+ Insulin release
– Glucagon release
DPP-4 inhibitor blocks incretin degradation.

Pharmacokinetic & renal dose adjustment

1.***Sitagliptin*** : is a highly selective DPP-4 inhibitor, orally administered once daily at the therapeutic dose of 100 mg.

very good bioavailability (87%), long half-life (t1/2: 12.4 h) .
does not produce active metabolites
excreted mostly unchanged in urine (87%)

Predominantly eliminated by the kidney through both glomerular filtration and tubular secretion , (high clearance)

The drug can be administered irrespective of HD timing.

If eGFR = 30-50 cc/min/1.73m2 . . . . .50 mg once daily
If eGFR < 30 cc/min/1.73m2 . . . . . 25 mg once daily

2.Linagliptin : *relatively low absorption and bioavailability (~30%) highly protein bound (>80%) .....long half-life ... several inactive metabolites.*

Nearly 85% ..... faecal excretion .....via the entero-hepatic system

no dose adjustments are required

Another DPP4 inhibitors (Gliptins)

3. **Vildagliptin** :

Absorption and bioavailability are both very high (>85%), half-life is low

The main routes of clearance
are hydrolysis by multiple tissues/organs and the kidneys

GFR >= 50 mL/min/1.73 m2: 50 mg twice daily
GFR < 50 mL/min/1.73 m2: 50 mg daily (KDOQI)

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4. **Saxagliptin** is a long-acting DPP-4 inhibitor

GFR >=50 mL/min/1.73 m2: 5 mg daily
GFR < 50 mL/min/1.73 m2: 2.5 mg daily

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5. **Alogliptin** is a highly selective DPP-4 inhibitor (100 % bioavailability)

25 mg daily if eGFR >=60 mL/min/1.73 m2
12.5 mg daily if eGFR : 30–60 mL/min/1.73 m2
6.25 mg daily if eGFR < 30 mL/min/1.73 m2

Table 2 Dose adjustment of dipeptidyl peptidase 4 inhibitors in chronic kidney disease

	CKD			
	CKD 1, 2 and 3a (Cl_{cr} > 50 mL/min)	CKD 3b (Cl_{cr} 30-50 mL/min)	CKD stage 4 (Cl_{cr} 15-30 mL/min)	CKD stage 5 (ESRD)
Sitagliptin (Januvia)	√ (100 mg × 1)	1/2 dose (50 mg × 1)	1/4 dose (25 mg × 1)	1/4 dose (25 mg × 1)
Vildagliptin (Galvus)	√ (50 mg × 2)	50 mg × 1		50 mg (no experience)
Saxagliptin (Onglyza)	√ (5 mg × 1)	1/2 dose (2.5 mg × 1)	1/2 dose (2.5 mg × 1)	1/2 dose (2.5 mg × 1)
Linagliptin (Trajenta)	√ (5 mg × 1)	√ (5 mg × 1)	√ (5 mg × 1)	P (5 mg × 1)
Alogliptin (Nesina)	√ (25 mg × 1)	1/2 dose (12.5 mg × 1)	1/4 dose (6.25 mg × 1)	1/4 dose (6.25 mg × 1)

Renoprotective effects of DPP4-inhibitors

Urinary **microvesicle-bound DPP-4** may be an early marker of renal damage before the onset of albuminuria.

DPP-4 is also expressed at the apical brush border surface of renal proximal tubular cells and also has
GLP-1 independent **renal** and **cardiovascular** actions

Can cause diuresis,natriuresis & lower BP (pleotropic effects via GLP1 or other substrates like BNP, stromal derived factor 1)

Vildagliptin treatment significantly
decreased UAE,
improved GFR,
dose-dependently inhibited interstitial expansion, glomerulosclerosis, and the thickening of the GBM and
significantly decreased expression of T GF- β1
(renoprotective effects in both type1 and type 2 DM)

J clinical & experimental nephrol,2017

Recent Advances in Management of Diabetic Nephropathy ,J clinical & experimental nephrol,2017

In comparison to other oral hypoglycemic agents that achieved a comparable decrease in HbA1c, sitagliptin significantly reduced UAE in an open-labeled, prospective, randomized study in T2DM ....?

Linagliptin directly inhibits DPP-4- integrin- β1 interaction, and thus blunts pathological TGF- β signaling and restores the physiological balance of VEGF receptors.
Consequently, EndMT and subsequent renal fibrosis are inhibited.

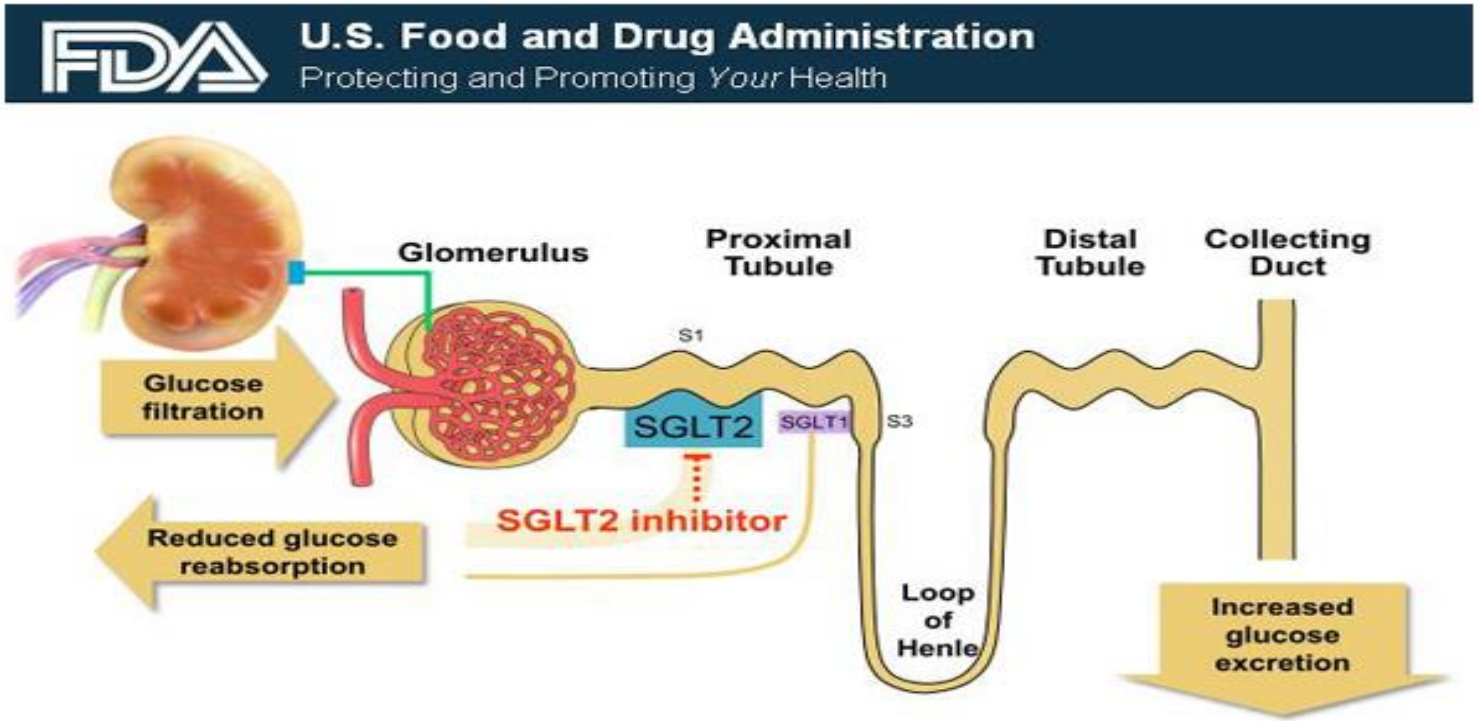
Saxagliptin in a rat model of T1DM has limited renal hypertrophy, TGF-β upregulation, NF-κB mediated macrophage infiltration, tubulointerstitial fibrosis in spite of the lack of change in UAE.

In SAVOR-TIMI 53

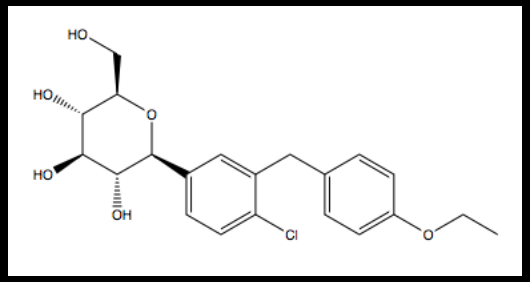
Saxagliptin decreased UAE but had no effect on eGFR in T2DM

Alogliptin reduces oxidative stress.

SGLT2 inhibitors



SGLT2 inhibitors



- Block the activation of the sodium–glucose transport proteins subtype 2, a tubular carrier which reabsorbs 90% of the glucose filtered in the glomerulus,
- leading to an increased loss of blood glucose through the urine
- low risk of hypoglycaemia
- several pleiotropic effects, including weight loss, the potential of lowering of blood pressure and an improvement in the metabolic milieu (e.g. triglycerides, uric acid and HDL levels)
- Adverse effects : tiredness, dehydration and appearing/worsening of urogenital infections
- Dapagliflozin received marketing authorization by the European Medicines Agency, while canagliflozin has been authorized more recently by the (FDA).
- reduction in A1c about 0.9–1.0 %

SGLT2 inhibition
increases distal sodium delivery,
increased distal tubular sodium absorption and hence
increases adenosine production,
causing afferent arteriolar vasoconstriction with
fall in renal blood flow, decreased hyperfiltration and
reduced renal injury (not related to RAAS blockade)

The incidence of cardiovascular events was observed to increased in the first 30 days post-initiation of treatment
probably due to volume depletion and hypotensive episodes .
Similarly, stroke may occur more often in patients undergoing hypotensive episodes.

EMPA-REG OUTCOMES :

This study supports a strong evidence for a reduction in cardiovascular risk with the use of a SGLT2 inhibitor (empaglifllozin). *J. Clin. Med.* ***2015***

Based on Empe-Reg trial:

Empagliflozin was also associated with a

Significant reduction in :

incident or worsening nephropathy by 39%,
progression to overt albuminuria by 38%
and doubling of serum creatinine by 44%

The significant favorable outcome of SGLT2 inhibitors is attributed to:

1.Direct effects : decrease in (hyperfiltration,tubular hypertrophy,Glu-induced tubular toxicity)

2.Indirect effects : improvement in metabolic milieu

SGLT2 inhibition decreases:
expression of TLR4,NFkB,MCP1,TGFß,IL6,collagen IV,
&
Macrophage infiltration,oxidative stress & Apoptosis

Warning !

In some cases, volume depletion and blood pressure lowering associated with SGLT2 inhibitors has been associated with acute-on-chronic renal impairment

Diabetic nephropathy is associated with *impaired autoregulation*

Monitoring of renal function is currently justified when using RAAS blockade or loop diuretics is recommended.

Canagliflozin
No dose adjustment required if eGFR > 60 mL/min/1.73 m2
100 mg daily if eGFR 45–59 mL/min/1.73 m2
Avoid use and discontinue in patients with eGFR < 45 mL/min/1.73 m2

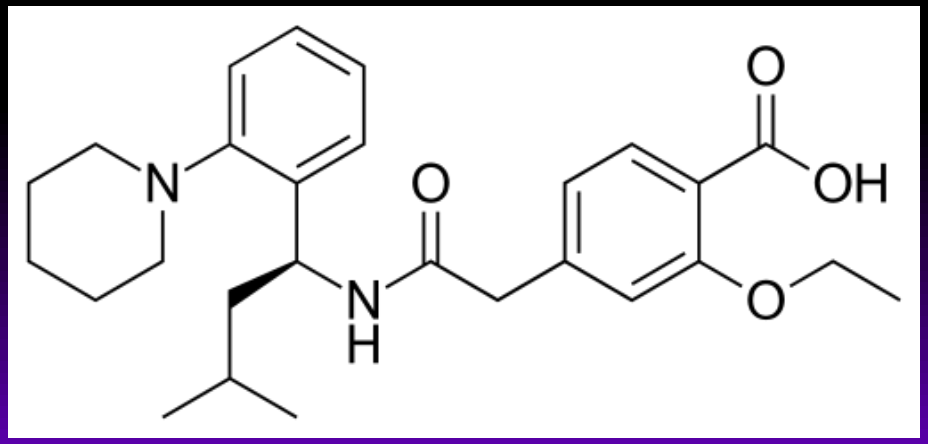
Dapagliflozin : Avoid use if eGFR <60 mL/min/1.73 m2
Empagliflozin : Avoid use in eGFR< 45 mL/min/1.73m2

MEGLITINIDES (Glinides)

Meglinitides (repaglinide, nateglinide) stimulate pancreatic insulin secretion by closing K-ATP channels on β-cell plasma membranes, in a similar manner to sulfonylureas but at a separate binding site.

Common side-effects of meglitinides are hypoglycaemia and weight gain. The disadvantage of the need for frequent dosing schedule.

Much shorter acting and their effects are more glucose-level dependent. Therefore,
The risk of hypoglycemia is lower with meglitinides than with sulfonylureas.



They are more effective for postprandial hyperglycemia.

The glinides reduce A1c on average by 0.5–1.5 %

KDOQI

Repaglinide

If GFR < 30 mL/min/1.73 m2 start conservatively at 0.5 mg with meals

Nateglinide

If GFR< 30 mL/min/1.73 m2 start conservatively at 60 mg with meals

α-Glucosidase inhibitors

Block the action of the enzyme located in the brush border of the small intestine,

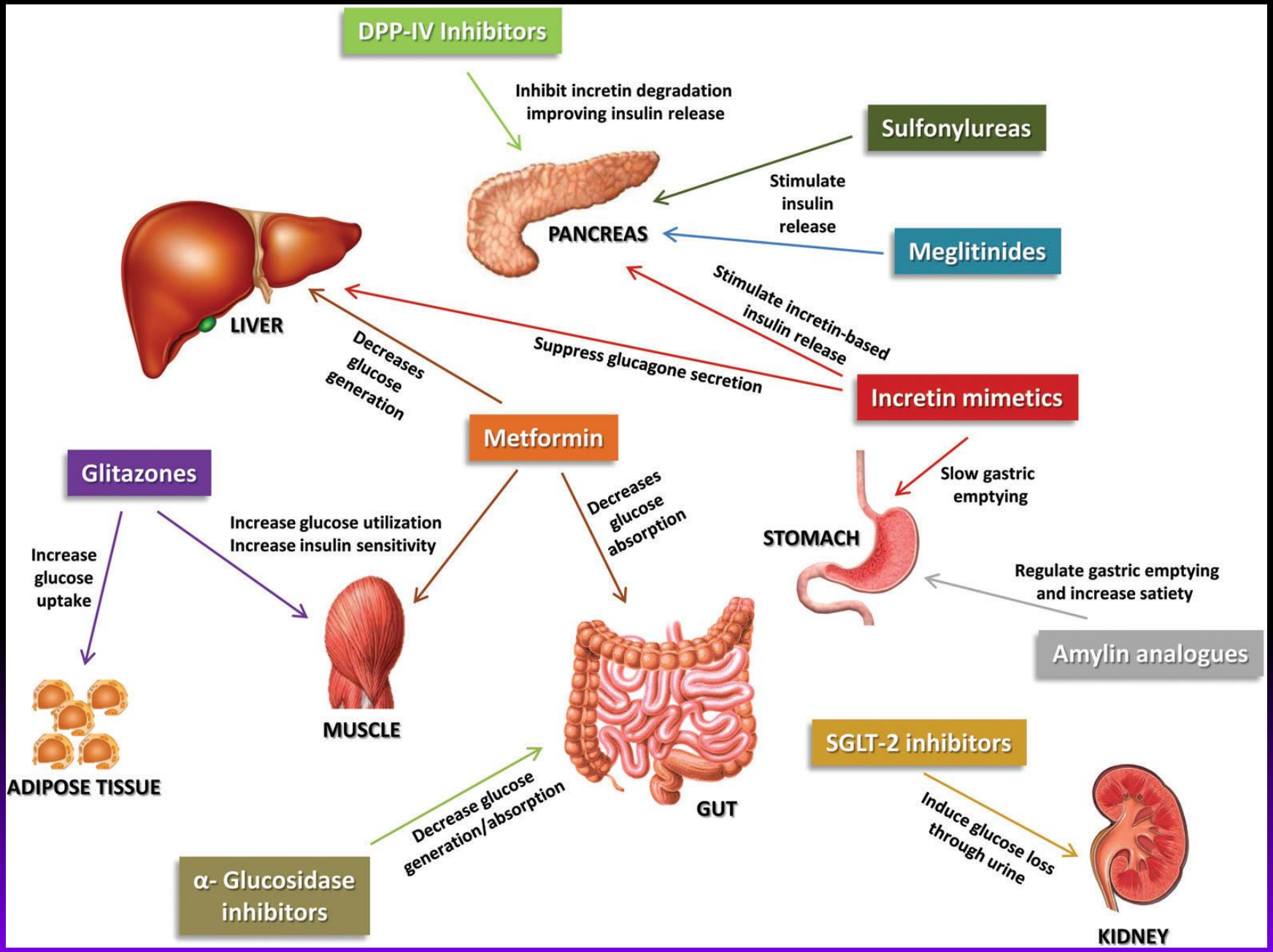
which is involved in the hydrolysis of oligosaccharides, trisaccharides and disaccharides into glucose and other monosaccharides

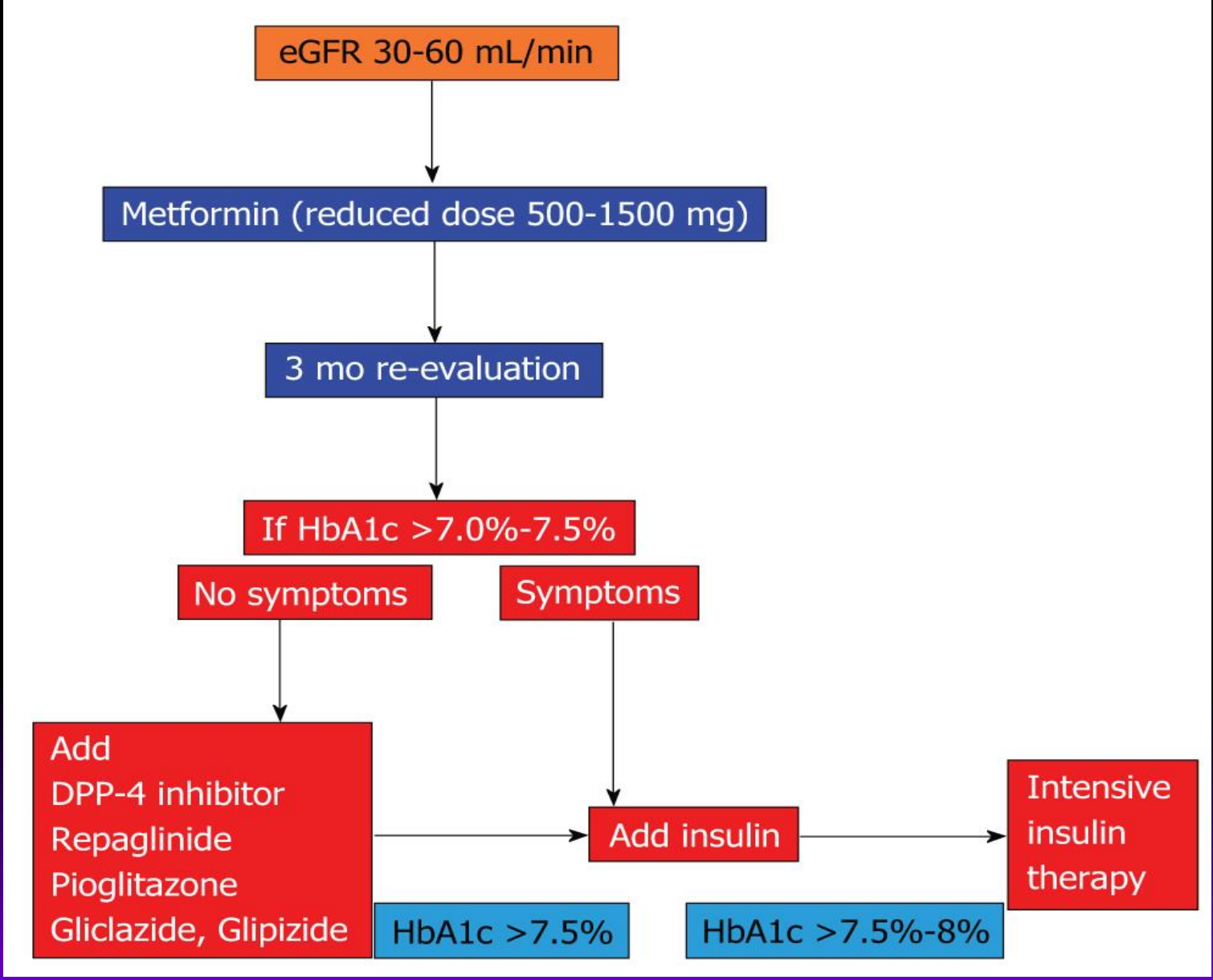
Slowing ingestion of carbohydrates and delaying absorption of glucose after a meal. (reducing postprandial glucose variations)

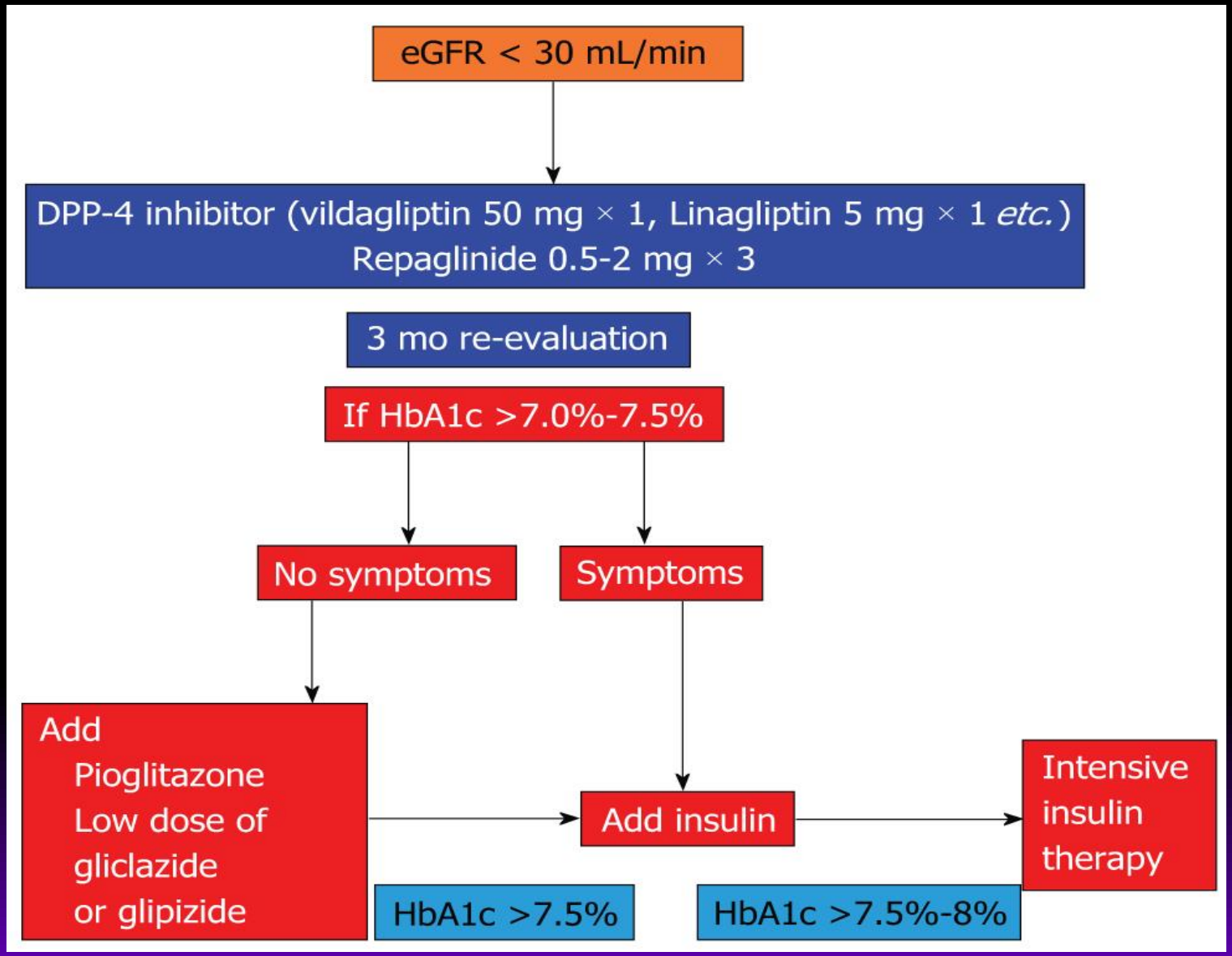
They typically lower A1c by 0.5–0.8 %
and usually do not lead to weight gain or loss

Their main limitations : frequent dosing - gastrointestinal side effects, mainly flatulence

Acarbose	Avoid if GFR <30 mL/min/1.73 m2
Miglitol	Avoid if GFR <25 mL/min/1.73 m2


DPP-IV Inhibitors
Inhibit incretin degradation improving insulin release
Sulfonylureas
Stimulate insulin release
PANCREAS
Meglitinides
LIVER
Stimulate incretin-based insulin release
Decreases glucose generation
Suppress glucagone secretion
Incretin mimetics
Metformin
Glitazones
Slow gastric emptying
Increase glucose utilization
Increase insulin sensitivity
Decreases glucose absorption
STOMACH
Increase glucose uptake
Regulate gastric emptying and increase satiety
Amylin analogues
MUSCLE
ADIPOSE TISSUE
GUT
SGLT-2 inhibitors
Decrease glucose generation/absorption
Induce glucose loss through urine
α- Glucosidase inhibitors
KIDNEY


eGFR 30-60 mL/min
Metformin (reduced dose 500-1500 mg)
3 mo re-evaluation
If HbA1c >7.0%-7.5%
No symptoms
Symptoms
Add
DPP-4 inhibitor
Repaglinide
Pioglitazone
Gliclazide, Glipizide
HbA1c >7.5%
Add insulin
HbA1c >7.5%-8%
Intensive insulin therapy



World J Diabetes 2014

THANKS