
بسم الله الرحمن الرحيم

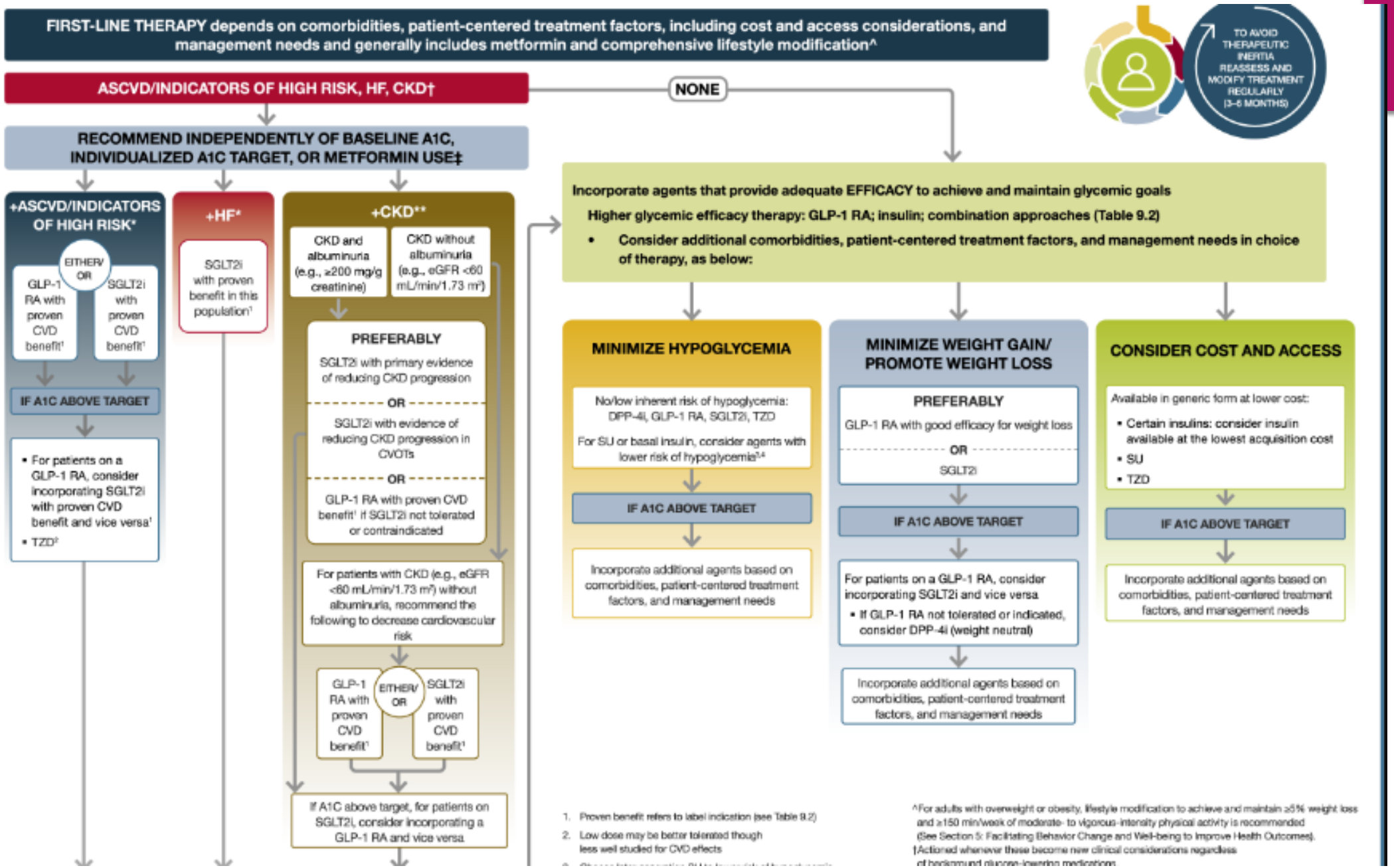
Pharmacologic Approaches to Glycemic Treatment

DR NEDA MEFTAH

- Advances in the therapy of type 2 DM have generated oral glucose-lowering agents that target different pathophysiologic processes in type 2 DM.

- Based on their mechanisms of action, glucose-lowering agents are subdivided into agents that increase insulin secretion, reduce glucose production, increase insulin sensitivity, enhance GLP-1 action, or promote urinary excretion of glucose.

Glucose-lowering Medication in Type 2 Diabetes:


FIRST-LINE THERAPY depends on comorbidities, patient-centered treatment factors, including cost and access considerations, and management needs and generally includes metformin and comprehensive lifestyle modification^
ASCVD/INDICATORS OF HIGH RISK, HF, CKD†
NONE
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
RECOMMEND INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE‡
+ASCVD/INDICATORS OF HIGH RISK*
EITHER/ OR
GLP-1 RA with proven CVD benefit¹
SGLT2i with proven CVD benefit¹
IF A1C ABOVE TARGET
• For patients on a GLP-1 RA, consider incorporating SGLT2i with proven CVD benefit and vice versa¹
• TZD²
+HF*
SGLT2i with proven benefit in this population¹
+CKD**
CKD and albuminuria (e.g., ≥200 mg/g creatinine)
CKD without albuminuria (e.g., eGFR <60 mL/min/1.73 m²)
PREFERABLY
SGLT2i with primary evidence of reducing CKD progression
OR
SGLT2i with evidence of reducing CKD progression in CVOTs
OR
GLP-1 RA with proven CVD benefit¹ if SGLT2i not tolerated or contraindicated
For patients with CKD (e.g., eGFR <60 mL/min/1.73 m²) without albuminuria, recommend the following to decrease cardiovascular risk
GLP-1 RA with proven CVD benefit¹
EITHER/ OR
SGLT2i with proven CVD benefit¹
If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA and vice versa
Incorporate agents that provide adequate EFFICACY to achieve and maintain glycemic goals
Higher glycemic efficacy therapy: GLP-1 RA; insulin; combination approaches (Table 9.2)
• Consider additional comorbidities, patient-centered treatment factors, and management needs in choice of therapy, as below:
MINIMIZE HYPOGLYCEMIA
No/low inherent risk of hypoglycemia: DPP-4i, GLP-1 RA, SGLT2i, TZD
For SU or basal insulin, consider agents with lower risk of hypoglycemia¹,⁴
IF A1C ABOVE TARGET
Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs
MINIMIZE WEIGHT GAIN/ PROMOTE WEIGHT LOSS
PREFERABLY
GLP-1 RA with good efficacy for weight loss
OR
SGLT2i
IF A1C ABOVE TARGET
For patients on a GLP-1 RA, consider incorporating SGLT2i and vice versa
• If GLP-1 RA not tolerated or indicated, consider DPP-4i (weight neutral)
Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs
CONSIDER COST AND ACCESS
Available in generic form at lower cost:
• Certain insulins: consider insulin available at the lowest acquisition cost
• SU
• TZD
IF A1C ABOVE TARGET
Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs
1. Proven benefit refers to label indication (see Table 9.2)
2. Low dose may be better tolerated though less well studied for CVD effects
^For adults with overweight or obesity, lifestyle modification to achieve and maintain ≥5% weight loss and ≥150 min/week of moderate- to vigorous-intensity physical activity is recommended (See Section 5: Facilitating Behavior Change and Well-being to Improve Health Outcomes).
†Actioned whenever these become new clinical considerations regardless

biguanide

- Metformin the only currently available biguanide.
- It increases glucose uptake and utilization by target tissues, thereby decreasing insulin resistance.
- It does not promote insulin secretion. Hyper insulinemia is not a problem. Thus, the risk of hypoglycemia is far less than that with sulfonylureas.

- Metformin is usually the first-line medication used for treatment of type 2 diabetes.
- In general,it is prescribed at initial diagnosis in conjunction with exercise and weight loss, as opposed to in the past, where it was prescribed after diet and exercise had failed.

Adverse effects:

- The most common adverse events are gastrointestinal: nausea, diarrhea, crampy abdominal pain.
- About one third of patients have some gastrointestinal distress, particularly early in their course of treatment.
- This distress can be minimized by starting with a low dose once daily with meals and titrating upward slowly (over weeks) to effective doses.
- Sustained-release metformin is associated with less frequent and less severe upper gastrointestinal symptoms,

- metformin can be used safely in patients with eGFRmore than 30 mL/ minute per 1.73 m2, with dose reduction to a maximm daily dose of 1000 mg when the eGFR falls below about 50 mL/minute per 1.73 m2 and avoidance when the eGFR is less than 30 mL/minute per 1.73 m2.

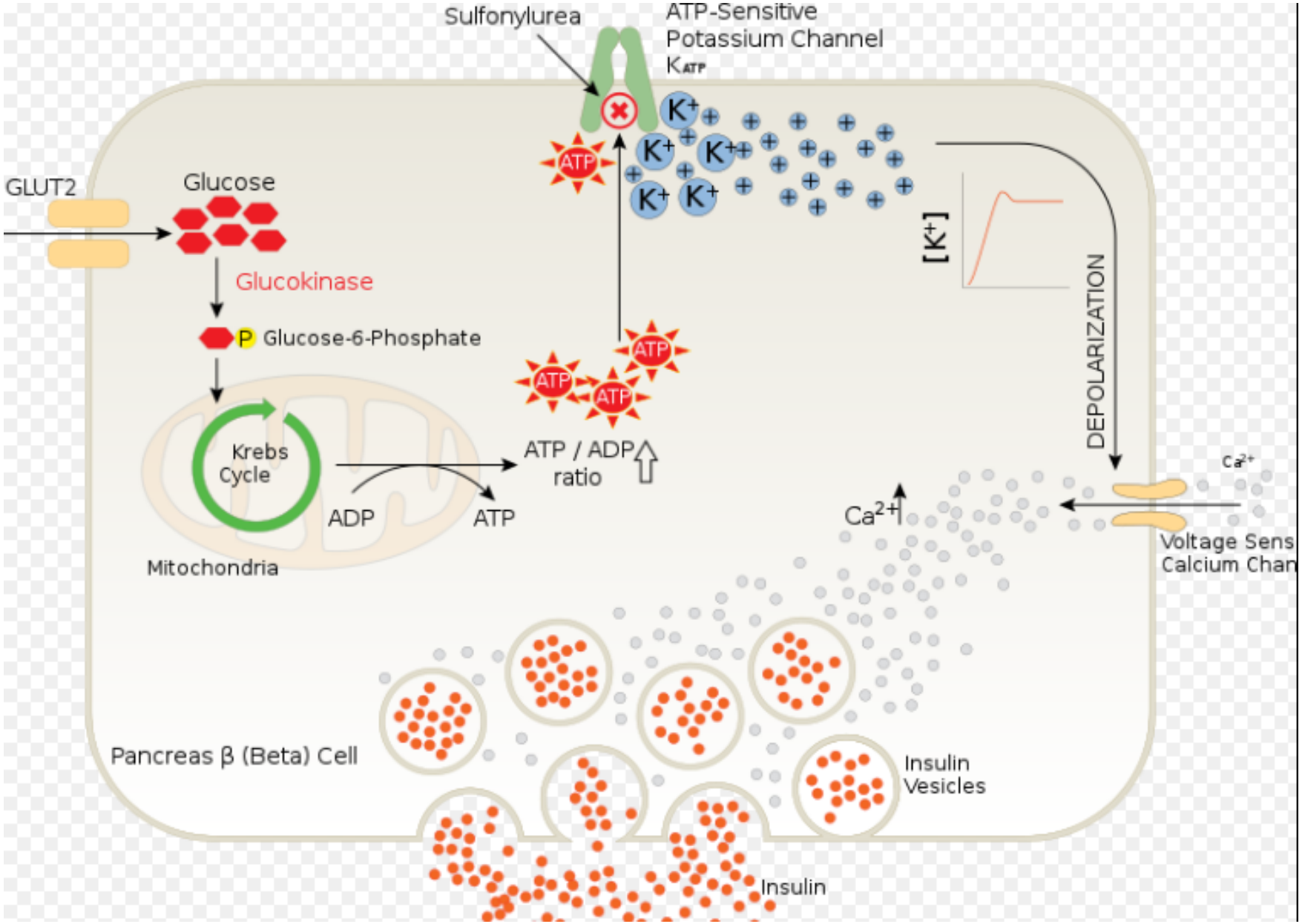
Furthermore, metformin effectively lowers HbA1c concentration by about 1–2%, is weight neutral, does not cause hypoglycaemia, and can have modest beneficial effects on blood pressure and lipid profile.

Sulfonylureas

Sulfonylureas :

- First-generation sulfonylurea (chlorpropamide, tolazamide, tolbutamide); have a longer half-life, a greater incidence of hypoglycemia, more frequent drug interactions' and are now rarely used.
- Second-generation sulfonylureas have a more rapid onset of action and better coverage of the glucose rise, but the shorter half-life of some agents may require more than once-a-day dosing .(Glipizide, Glyburide)

- These drugs exert their hypo glycemic effects by stimulating insulin secretion from the pancreatic beta-cell.
- Their primary mechanism of action is to close ATP-sensitive K-channels in the beta-cell plasma membrane, and so initiate a chain of events which results in insulin release.


Sulfonylurea
ATP-Sensitive
Potassium Channel
K_{ATP}
GLUT2
Glucose
Glucokinase
P Glucose-6-Phosphate
Krebs
Cycle
ADP
ATP
ATP / ADP
ratio
Mitochondria
ATP
K^+
[K^+]
DEPOLARIZATION
Ca^{2+}
Voltage Sens
Calcium Chan
Pancreas β (Beta) Cell
Insulin
Vesicles
Insulin

- In general, sulfonylureas increase insulin acutely and thus should be taken shortly before a meal.

- Most sulfonylureas are metabolized in the liver to compounds (some of which are active) that are cleared by the kidney. Thus, their use in individuals with significant hepatic or renal dysfunction is not advisable.
- Weight gain, a common side effect of sulfonylurea therapy, results from the increased insulin levels and improvement in glycemic control

- **Glibenclamide** (glyburide) is metabolized in the liver and excreted by the kidneys equally and intestine.
- Hypoglycemia may be serious and lasting more than 24 h in CKD.
- The drug is contraindicated in eGFR < 60 mL/min.

- Gliclazide causes less hypoglycemia than other sulfonylureas.
- In eGFR > 30 mL/min gliclazide can be used.

- 1 tablet of **Gliclazide MR 30 mg** is comparable to 1 tablet of **Gliclazide 80 mg** Tablets.
- The recommended **starting dose** is 30 mg daily; taken orally in a single intake at breakfast time.
- The **maximum** recommended daily dose is 120 mg.

Non sulfonylurea secretagogues

Non sulfonylurea secretagogues

- Meglitinides (Repaglinide , Nateglinide) help the pancreas produce .
- They act on the same potassium channels as sulfonylureas, but at a different binding site. By closing the potassium channels of the pancreatic beta cells, they open the calcium channels, thereby enhancing insulin secretion.

- They are taken with or shortly before meals to boost the insulin response to each meal.
- Typical reductions in glycated hemoglobin (A1C) values are 0.5–1.0%. Adverse reactions include weight gain and hypoglycemia.

- **Repaglinide** is exclusively metabolized in the liver to inactive metabolites and secreted in the bile.
- Repaglinide can be used even in CKD stages 4 and 5 **without dose reduction**.
- In patients with a GFR ≤30 ml/min/1.73 m2 **starting** with a 0.5 mg does before each meal and gradually increasing the dose.

Thiazolidinedione

- Thiazolidinediones reduce insulin resistance by binding to the PPAR-y (peroxisome proliferatoractivated receptor y) nuclear receptor (which forms a heterodimer with the retinoid X receptor).
- The PPAR-y receptor is found at highest levels in adipocltes but is expressed at lower levels in many other tissues. Agonists of this receptor regulate a large number of genes, promote adipocyte differentiation, reduce hepatic fat accumulation.

- Troglitazone was the first of these to be approved for the treatment of Type 2 diabetic, but was withdrawn after a number of deaths due to hepatotoxicity were reported.
- Presently, two members of this class are available, pioglitazone and rosiglitazone.

Adverse Effects:

- Thiazolidinediones are associated with weight gain (2-3 kg
- Peripheral edema and CHF are more common in individuals treated with these agents. These agents are contraindicated in patients with liver disease or CHF (class III or IV).

- It does not cause hypoglycemia and it can be given theoretically without dose adjustment at all stages of CKD.

α-Glucosidase Inhibitors

- a-Glucosidaseinhibitors (acarbose and miglitol) reduce post prandial hyperglycemia by delaying glucose absorption; they do not affect glucose utilization or insulin secretion .
- These drugs, reduce glucose absorption by inhibiting the enzyme that cleaves oligosaccharides into simple sugars in the intestinal lumen.

- Therapy should be initiated at a low dose (25 mg of acarbose or miglitol) with meal and may be increased to a maximal dose over weeks to months (50-100 mg for acarbose or 50 mg for miglitol with each meal).
- The major side effects (diarrhea, flatulence, abdominal distention) are related to increased delivery of oligo saccharides to the large bowel and can be reduced somewhat by gradual upward dose titration.

- The National Kidney Foundation (NKF) advise avoiding acarbose if the GFR <30 ml/min/1.73 m2.

Dipeptidyl peptidase IV [DPP-IV] inhibitors

- DPP-4 inhibitors or gliptins, are a class of oral hypoglycemics that block DPP-4.
- The first agent of the class - sitagliptin - was approved by the FDA in 2006.

Mechanism of action:

- Sitagliptin inhibits the enzyme DPP-IV, which is responsible for the inactivation of incretin hormones, such as glucagon-like peptide-1 (GLP-1). Prolonging the activity of incretin hormones results in increased insulin release in response to meals and a reduction in inappropriate secretion of glucagon.

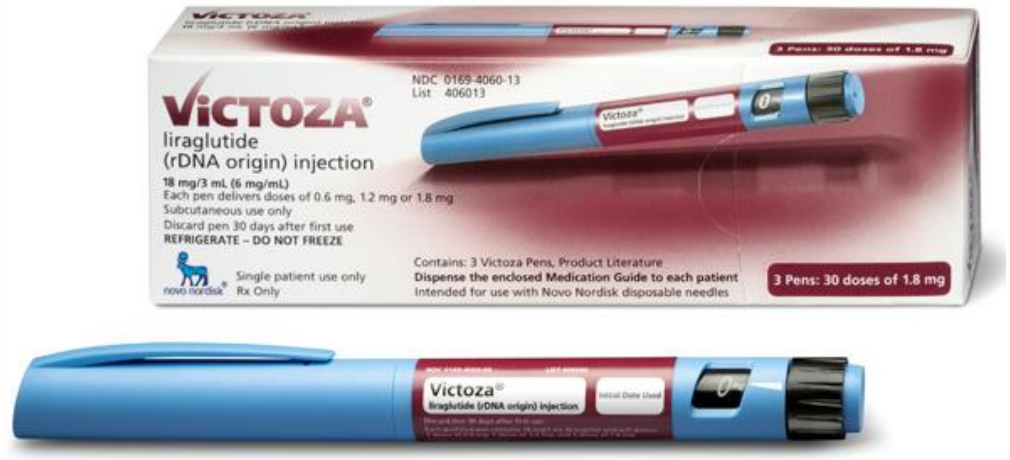
- These agents have subsequent HbA1c reductions of approximately 0.7%.
- They are remarkably well tolerated ,there is no weight loss with DPP4 inhibitors; they tend to be weight neutral .

- **Sitagliptin:**
- 100 mg daily, regardless of food.
- Dose to be reduced to

  50 mg/d if GFR 30-50 or

  25 mg/d if GFR <30.

Linagiptin it can be given theoretically without dose adjustment at all stages of CKD.



- Injectable Glucagon-like peptide analogs and agonists

- GLP-1 stimulates insulin secretion in a glucose-dependent fashion, inhibits inappropriate hyper glucagonemia, slows gastric emptying, reduces appetite and improves satiety.
- GLP-1 has a very short half-life in plasma (1 to 2 minutes) due to amino terminal degradation by the enzyme dipeptidyl peptidase 4 (DPP4).

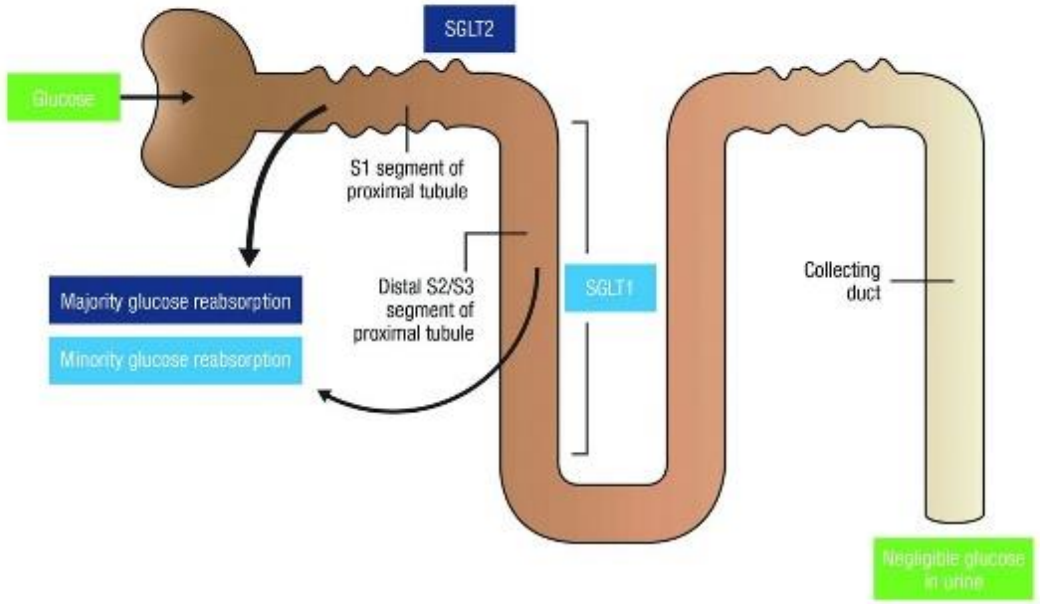
- Agents in this class do not cause hypoglycemia because of the glucose-dependent nature of incretin-stimulated insulin secretion (unless there is concomitant use of an agent that can lead to hypoglycemia sulfonylureas, etc.).

- These agents do not promote weight gain; in fact, most patients experience modest weight loss and appetite suppression. Treatment with these agents should start at a low dose to minimize initial side eflects (nausea being the limiting one).

- The major side effects are nausea, vomiting, and diarrhea; pancreatitis .
- Liraglutide is contraindicated in individuals with medullary carcinoma of the thyroid and multiple endocrine neoplasia.

Sodium–Glucose Cotransporter 2 Inhibitors

SGLT-2 Inhibitors



Valentine V. *Clin Diabetes* 2015;33:5-13.

- SGLT2 are the newest class of anti hyperglycemic medications, first marketed in 2013 for the treatment of T2DM.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors provide insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2.

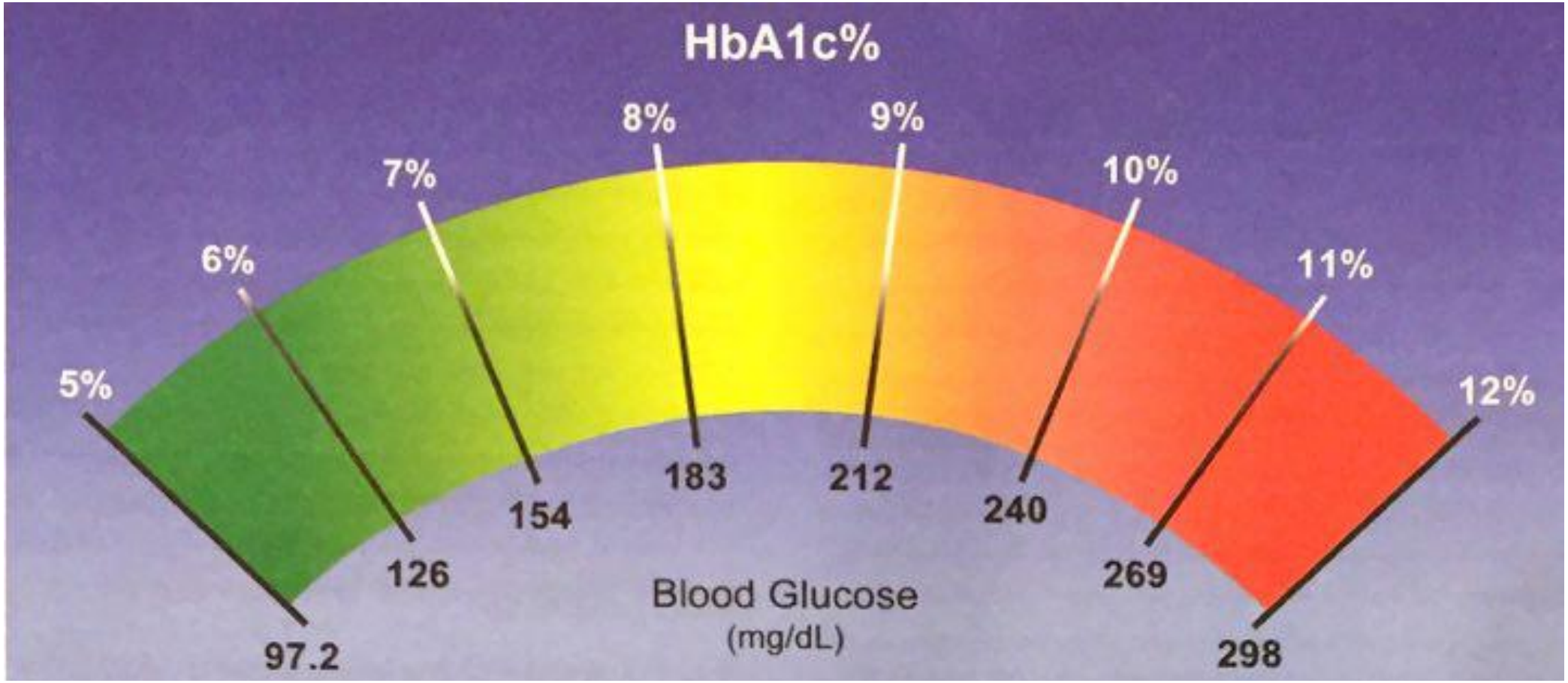
- Furthermore, they are associated with moderate weight loss—2 to 3 kg over placebo in 26-week studies—as well as blood pressure reduction.
- The most common side effects are related to glycosuria and include urinary frequency, genital infections, and relatively rare episodes of lower urinary tract infections as well as dehydration and its consequences.

- The National Kidney Foundation (NKF) advise avoiding SGLT2I if the GFR <25 ml/min/1.73 m2.

Treatment goals

A1C	<7.0% (53 mmol/mol)*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

HbA1C


HbA1c%
5%
6%
7%
8%
9%
10%
11%
12%
97.2
126
154
183
212
240
269
298
Blood Glucose
(mg/dL)

Initial Therapy

Metformin monotherapy should be started at diagnosis of type 2 diabetes unless there are contraindications.

Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death

Combination Therapy

If the A1C target is not achieved after approximately 3 months, consider a combination of metformin and one of the six available treatment options:

- sulfonylurea
- thiazolidinedione
- DPP-4 inhibitor
- SGLT2 inhibitor
- GLP-1 receptor agonist

or basal insulin

- If A1C target is still not achieved after ;3 months of dual therapy, proceed to three-drug combination .
- Again, if A1C target is not achieved after ;3 months of triple therapy, proceed to combination injectable therapy

- The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10%)or blood glucose levels (≥300 mg/dL) are very high.

- A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include effect on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences.

- Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor or glucagon- like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen independent of A1C and in consideration of patient-specific factors .

Case:

- بیمارخانم 44 ساله تحت درمان با متفورمین 1000 میلی گرم در روز و% HbA1C=8 و BMI=33.
- بیمارخانم 65ساله تحت درمان با متفورمین 1000 میلی گرم در روز و% HbA1C=7.1 بستری در بخش قلب به علت ادم پولمونری
- بیماراقای74 ساله تحت درمان با گلی کلازید 80 میلی گرم در روز و7.5% HbA1C=وضعف وبی حالی مکرر وعدم کمپلیانس مناسب دارویی
- بیماراقای 60 ساله تحت درمان با متفورمین 1500 میلی گرم در روز و% HbA1C=8 وسابقه انفارکتوس قلبی
- بیمارخانم 53 ساله تحت درمان با متفورمین 1000 میلی گرم و گلی کلازید 160 میلی گرم در روز و% HbA1C=9.5 وکاهش وزن

سپاسگزارم از توجه شما