ORAL THERAPY FOR TYPE 2 DM

Treatment Options FOR TYPE 2 DM

Prof. Lobna farag Eltoony

Endocrinology & Diabetes Unit
Internal medicine department
Assuit University

Agenda

Pathophysioogy of diabetes
Old antidiabetics
New antidiabetics
ADA 2020 guidelines
Insulin therapy

Treatment of Type 2 diabetes

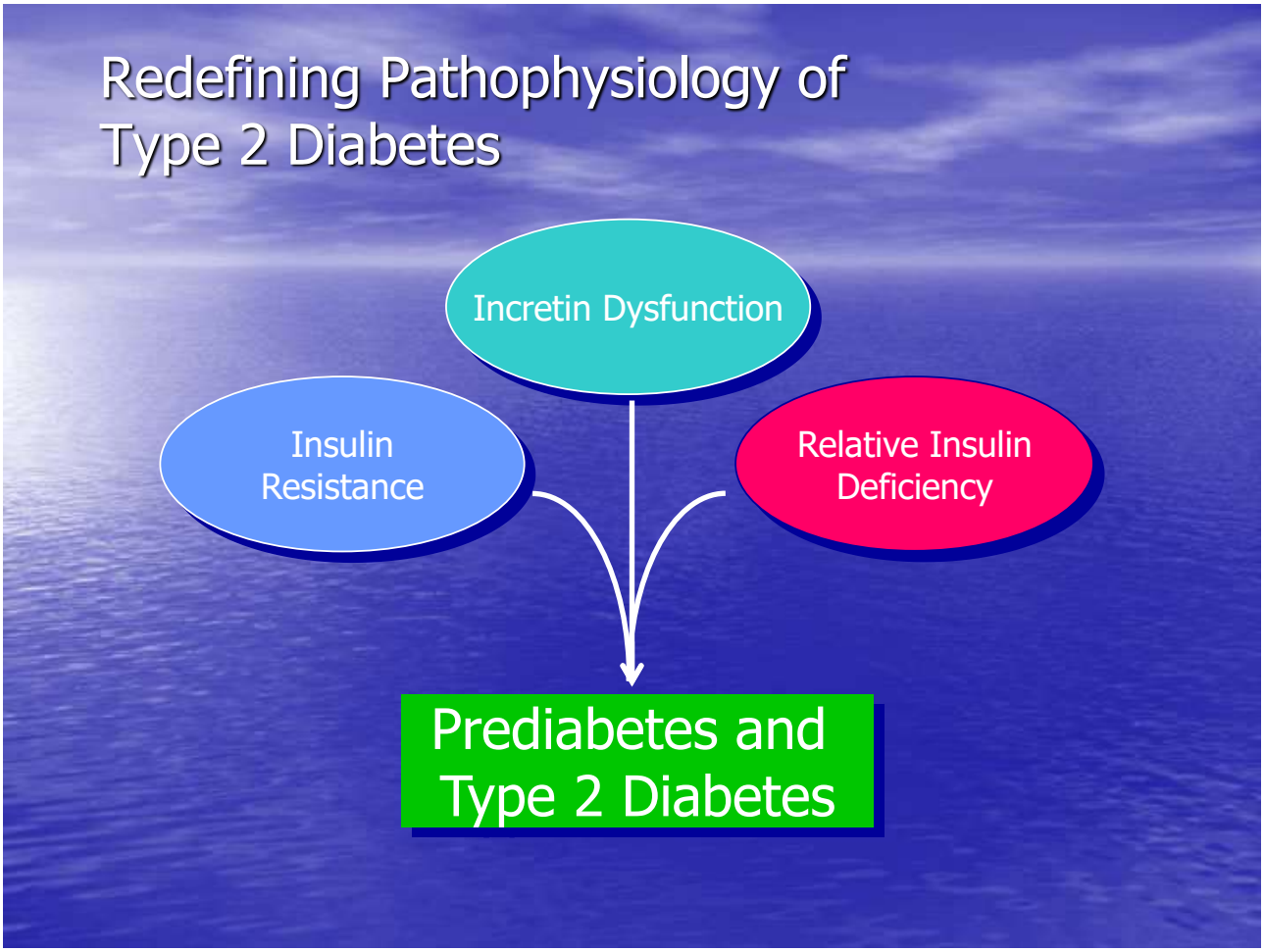
- **Treatment process:**

Diet and exercise

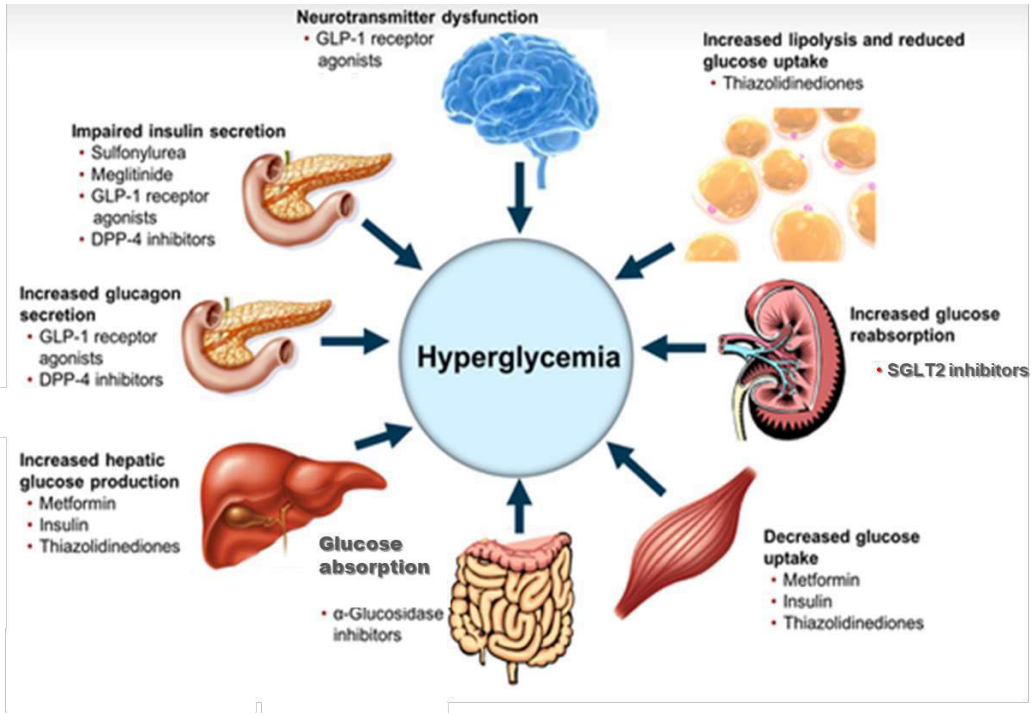
Oral tablet(s) mono/combo

Insulin

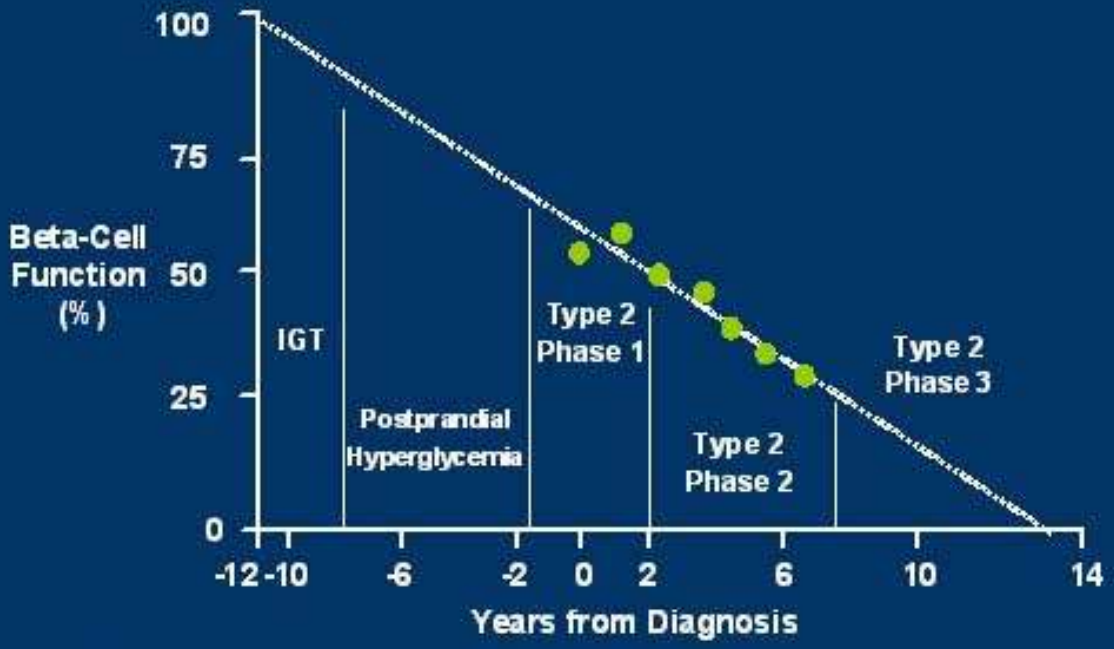
With OHA's or alone



Medications - Mechanism of action (The ominous octet)

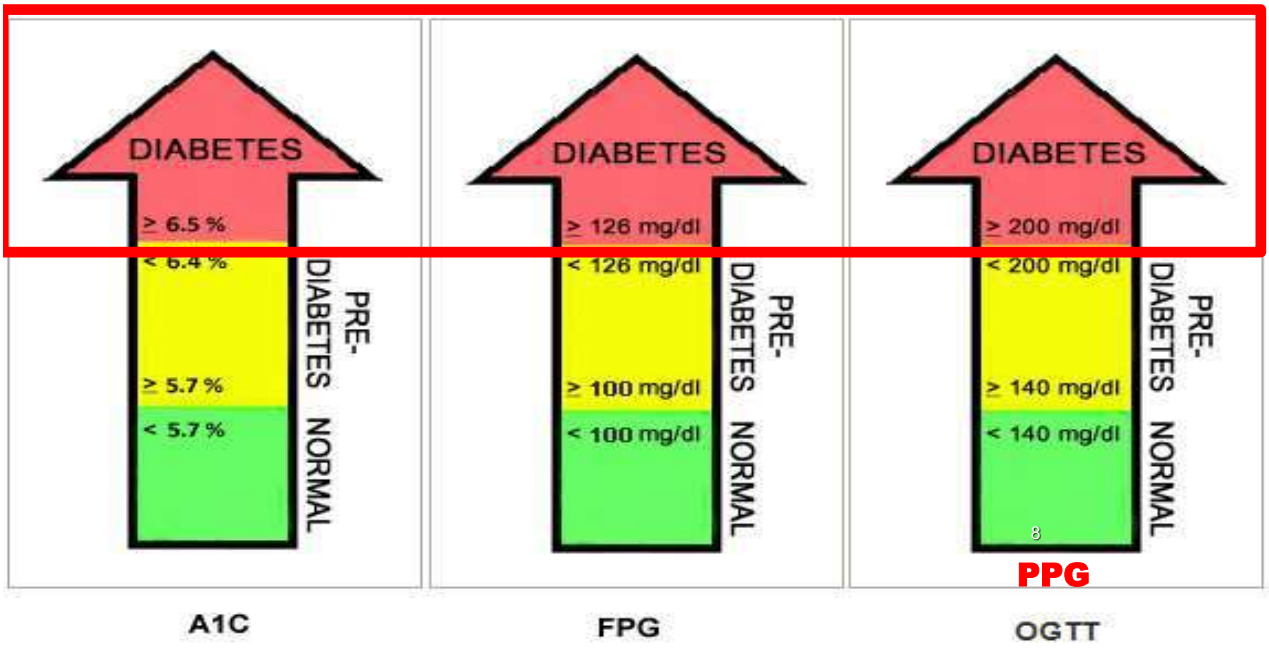


Stages of Type 2 Diabetes Related to Beta-Cell Function



Adapted from Lebovitz HE. *Diabetes Reviews*. 1999;7(3).

Diagnosis of diabetes



Glycemic Recommendations: Individualized Treatment

A1C
- <7.0%*

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)

* More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations.

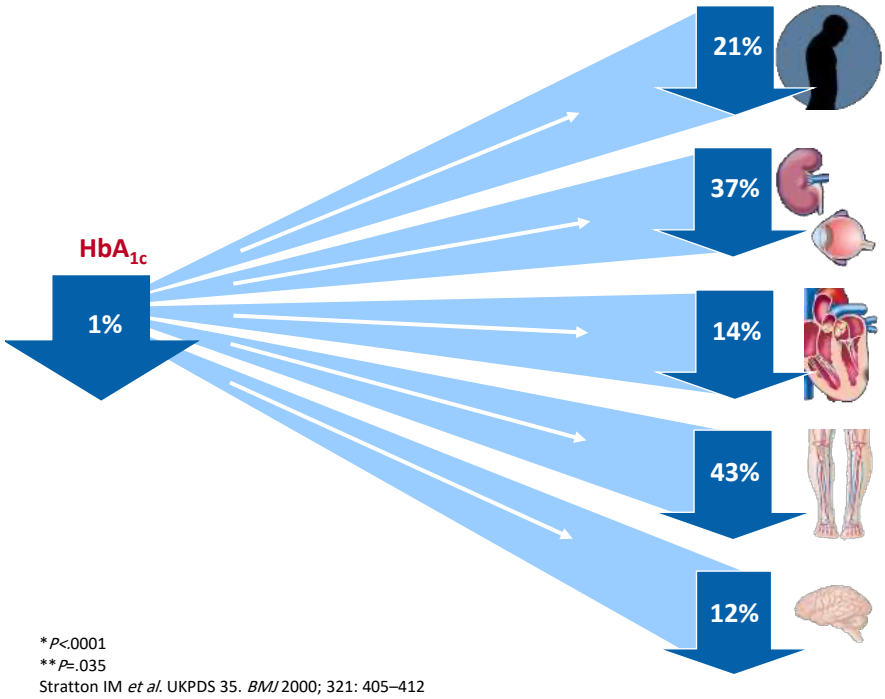
† Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes

American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes. *Diabetes Care* 2018; 41 (Suppl. 1): S73-S85

American Diabetes Association.

UKPDS : Glycemic Control Reduces Complications

Epidemiological extrapolation showing benefit of a 1% reduction in mean HbA_{1c}



* *P*<.0001
** *P*=.035
Stratton IM *et al.* UKPDS 35. *BMJ* 2000; 321: 405–412

Pharmacotherapy Options

Traditional Commonly Used	Traditional Not Commonly Used	Newer Commonly Used	Newer Not Commonly Used
Biguanides	AGIs	DPP-4 inhibitors	Dopamine agonists
Sulfonylureas	Glinides	GLP-1 agonists	Amylinomimetic
Thiazolidinediones		SGLT-2 inhibitors	Bile acid sequestrant
Insulin			

Insulin Sensitizers

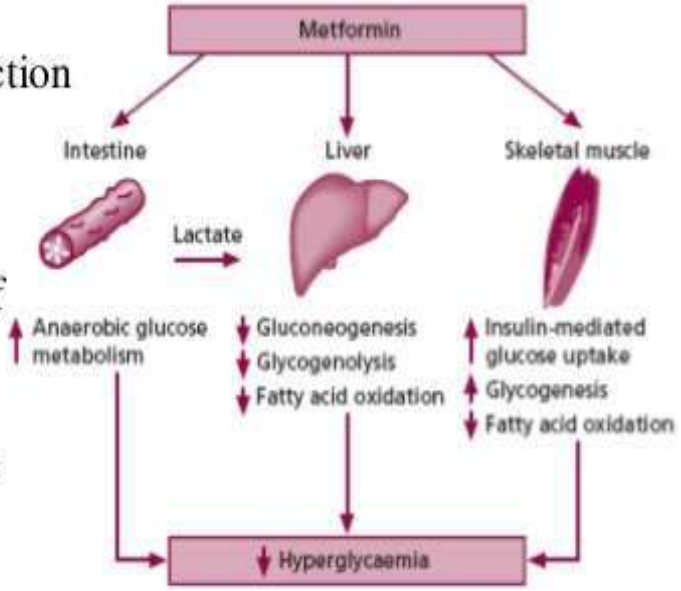
- **Metformin (Biguanides)**
- **Thiazolidinediones (TZD)**

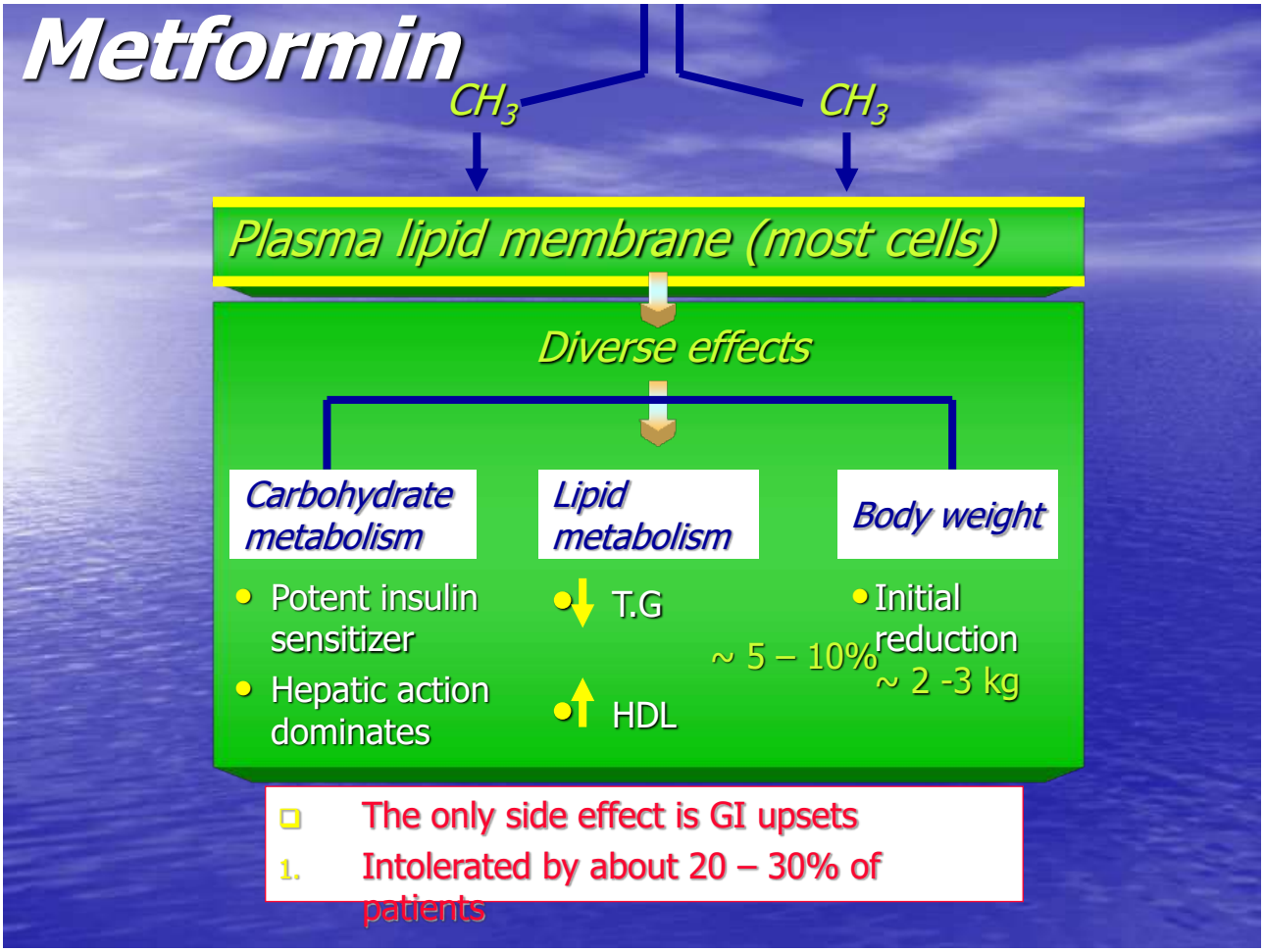
Biguanides: Metformin

Sites of Action of Metformin

MECHANISM OF ACTION

- Decrease hepatic glucose production through a mild inhibition of the mitochondrial respiratory-chain complex 1.[2]
- Decrease intestinal absorption of glucose
- anti-oxidative properties of metformin on endothelial cells[2]





Metformin

- Weight neutral
- Low cost
- GI side effects common (~30%/5%)
  - Slow titration and administration with meals
  - Consider extended release
- Vitamin B12 malabsorption
- Cardioprotective?

UKPDS (34). *Lancet*. 1998;352:854-65.
Johnson JA. *Diabetes Care. 2002*;25:2244-2248.
Tomkin GH. *Br Med J* 1973;3:673-675.
Bell DS. *South Med J*. 2010;103(3):265-267.
Dujic T. *Diabetes Care* Nov 2016,39 (11) 1896-1901.

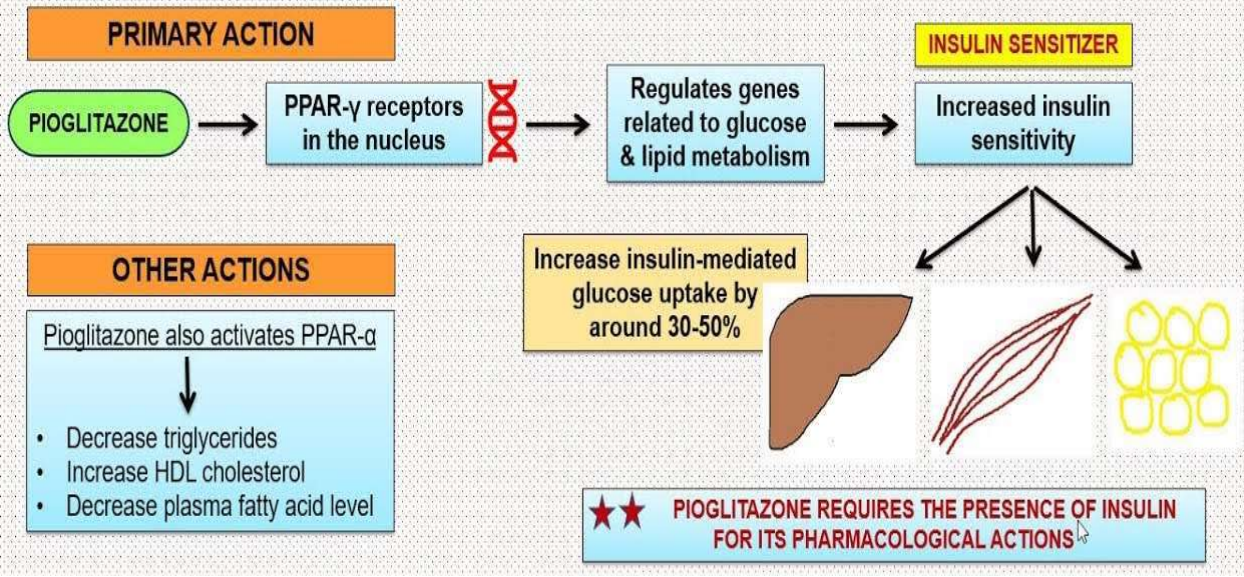
Updated Guidelines For Use in CKD Patients

- Contraindicated eGFR < 30
- Starting with eGFR 30-45 is not recommended
- Obtain eGFR at least annually
  - More often if at risk to develop of renal impairment
- If eGFR later falls below 45 assess risks vs benefits
- Discontinue if eGFR later falls below 30
- The National Kidney Foundation recommends using the CKD-EPI Creatinine Equation to estimate GFR

eGFR=estimated glomerular filtration rate (units=mL/minute/1.73 m^2).
http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm.
https://www.kidney.org/professionals/KDOQI/gfr_calculator.

WHAT IS PIOGLITAZONE?

- Oral antidiabetic drug
- Belongs to the Thiazolidinedione class
- 2 members currently available – Pioglitazone & Rosiglitazone
- Ligand of the nuclear receptor - peroxisome proliferator activator receptor-γ (PPAR-γ) in liver, muscle and adipose tissue



Thiazolidinediones

- Directly reduce insulin resistance
  - Targets fasting and postprandial hyperglycemia
- No hypoglycemia
- No renal metabolism
- Indirect markers of CVD
- β-cell preservation

DeFronzo RA. *Ann Intern Med.* 1999 Aug 17;131(4):281-303.

Thiazolidinediones

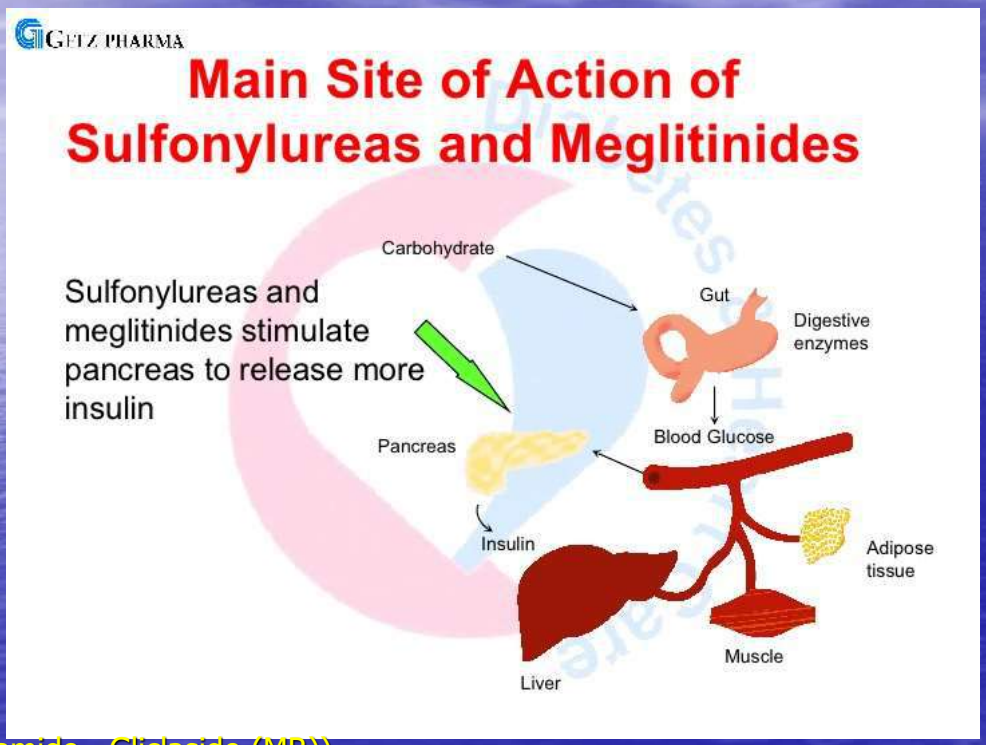
- Weight gain
- Edema
- Anemia
- Bone fractures
- Bladder cancer
- Cardiovascular affects
- Max dose with strong inhibitors of CYP2C8 (gemfibrozil) pioglitazone 15 mg

DeFronzo RA. *Ann Intern Med*. 1999 Aug 17;131(4):281-303.
Lancet. 2009, Volume 373, Issue 9681, 2125-2135.
Lewis JD et al. *Diabetes Care*. April 2011 vol. 34 no. 4 916-922.
Lewis JD et al. JAMA. 2015 Jul;314(3):265-77.
Kaul S et al. Circulation. 2010;121(16):1868.
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

SECRETAGOUGES

- Sulphonylureas
- GLINIDES

Sites of Action of Sulphonlyureas



Glibenclamide , Gliclaside (MR))
Glimiperide

Sulphonylureas: Mode of action

- **Bind to beta cell in pancreas**
  - stimulate endogenous insulin secretion
- **Some also increase insulin action at cells i.e. address the problem of insulin resistance**

Sulfonylureas

- 1st Generation
  - Chlorpropamide, tolazamide, acetohexamide or tolbutamide
- 2nd Generation
  - Glyburide, glipizide or glimepiride
- Can target fasting hyperglycemia/postprandial
  - Enhance insulin secretion

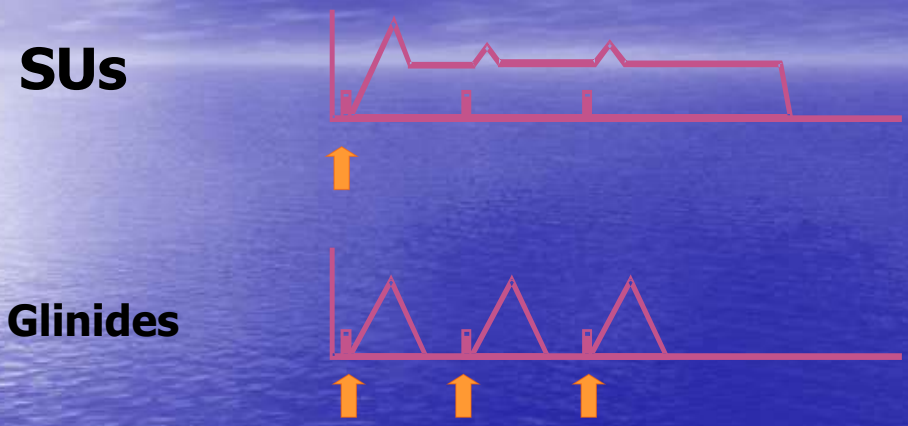
DeFronzo RA. *Ann Intern Med*. 1999 Aug 17;131(4):281-303.

Sulfonylureas

- Secondary failure rate
- Hypoglycemia
  - Elderly
  - Impaired renal function
  - Irregular meal schedule
- Weight gain
- Low cost
- Increase cardiovascular events?

DeFronzo RA. *Ann Intern Med*. 1999 Aug 17;131(4):281-303.
Monami M. *Diabetes Obes Metab*. 2013; Oct;15(10):938-53.

Glinides Vs SUs



- Short Acting, meal related, no meal no tablet
- Better control of prandial glucose but less effective on fasting
- More flexibility fitting free life style

Repaglinide and Nateglinide

- Targets postprandial hyperglycemia
  - Stimulates insulin secretion
  - Rapid onset; short acting
- No dose adjustment in renal insufficiency
- Less hypoglycemia than sulfonylureas
- No sulfa moiety

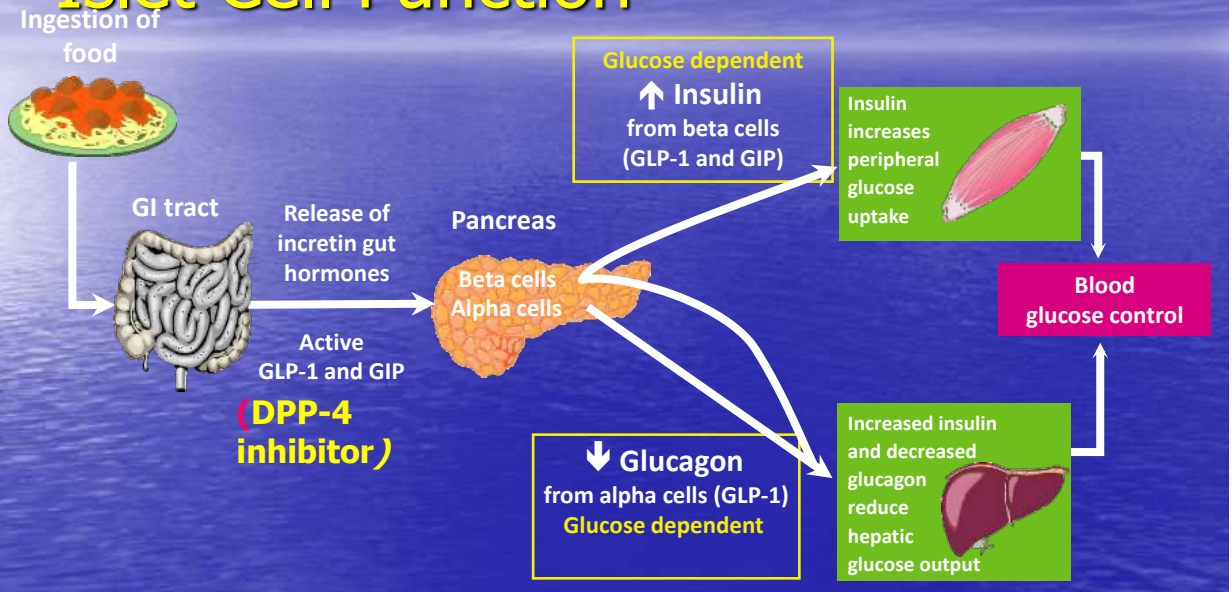
DeFronzo RA. *Ann Intern Med.* 1999 Aug 17;131(4):281-303.

Gut Hormones

Incretin

DPP-4 inhibitors (oral)
GLP -1 RA (injectable)

Incretins Regulate Glucose Homeostasis Through Effects on Islet Cell Function



Adapted from Brubaker PL, Drucker DJ *Endocrinology* 2004;145:2653–2659; Zander M et al *Lancet* 2002;359:824–830; Ahrén B *Curr Diab Rep* 2003;3:365–372; Buse JB et al. In *Williams Textbook of Endocrinology*. 10th ed. Philadelphia, Saunders, 2003:1427–1483.

DPP4 Inhibitors

- No significant hypoglycemia or weight gain
- Most common ADRs: URI, nasopharyngitis, headache
- No head-to-head trials
- Neutral CV outcomes/CHF
- Can be used in CKD/ESRDwith dose adjusted

Premier Health
Premier HealthNet

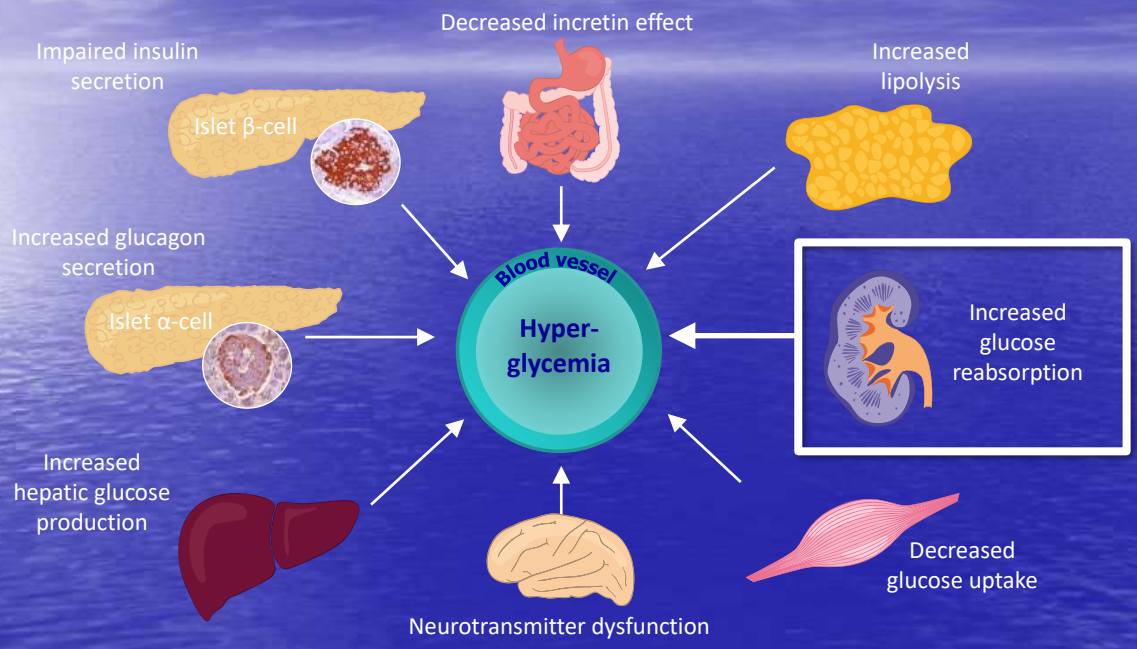
Drucker DJ. *Lancet*. 2006 Nov 11;368(9548):1696-705.
N Engl J Med 2013;369:1327-35.
N Engl J Med 2013;369:1317-26.
N Engl J Med 2015;373: 232-42.

premierhealthnet.com

" SGLT-2 Inhibitors:
New Treatment Options in Individualized T2D Management "

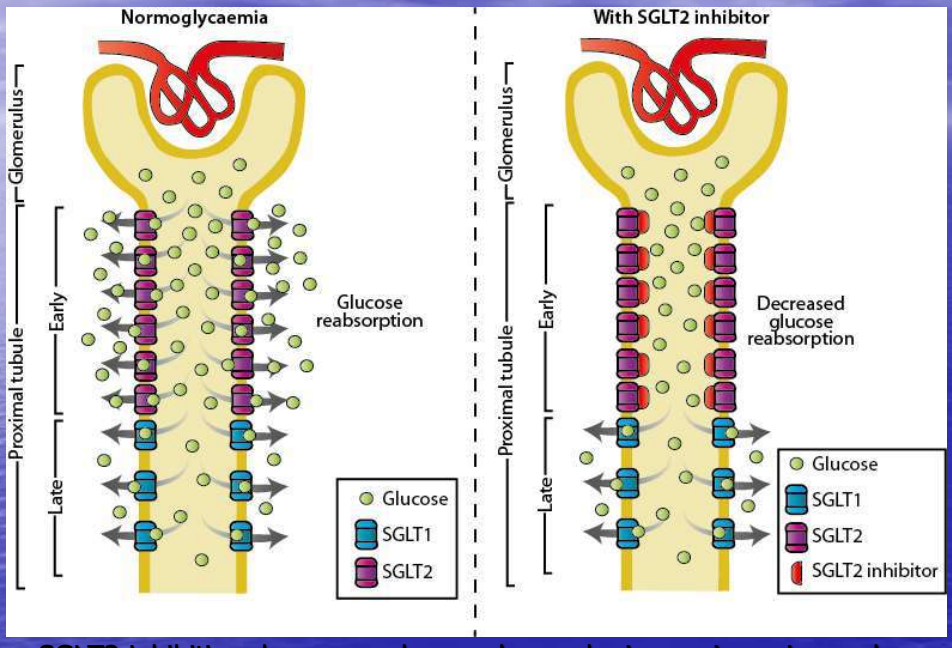
Sodium glucose transporter 2 inhibitors

Multiple Pathophysiological Failures Contribute to Hyperglycaemia: The 'Ominous Octet'



Adapted from DeFronzo RA. *Diabetes* 2009;58:773–795. ©Wolters Kluwer Health

SGLT2 Inhibition: A Novel Approach to Reduce Hyperglycaemia



- SGLT2 inhibition decreases plasma glucose by increasing urinary glucose excretion
- Canagliflozin is a potent inhibitor of SGLT2

Rothenberg P et al. Poster presented at EASD 2010; Stockholm, Sweden

SGLT-2 Inhibitors

- Mechanism is not insulin-dependent
- Reduction of weight and BP
- Increased genital mycotic infections
- Cannot be used with reduced eGFR
- Hyperkalemia, renal insufficiency, hypotension and LDL elevation

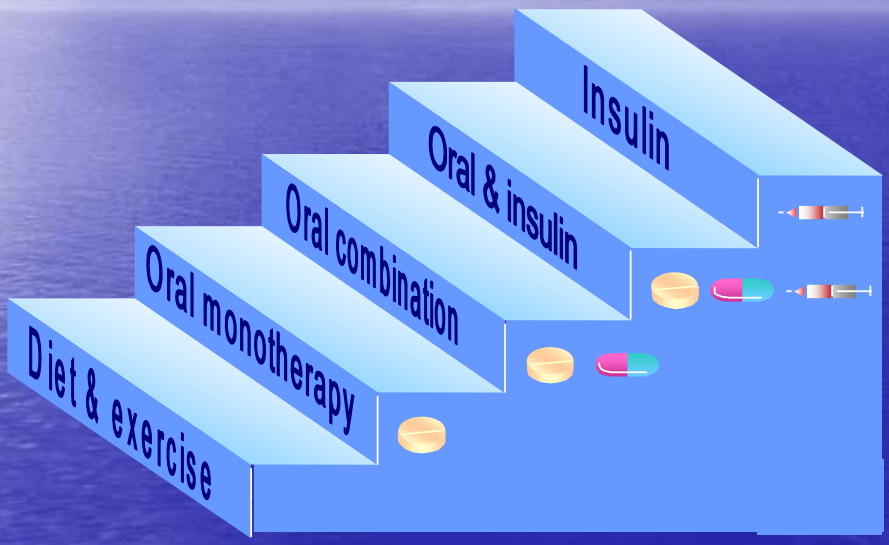
Clar C et al. BMJ Open. 2012;2(5).

SGLT-2 Inhibitors

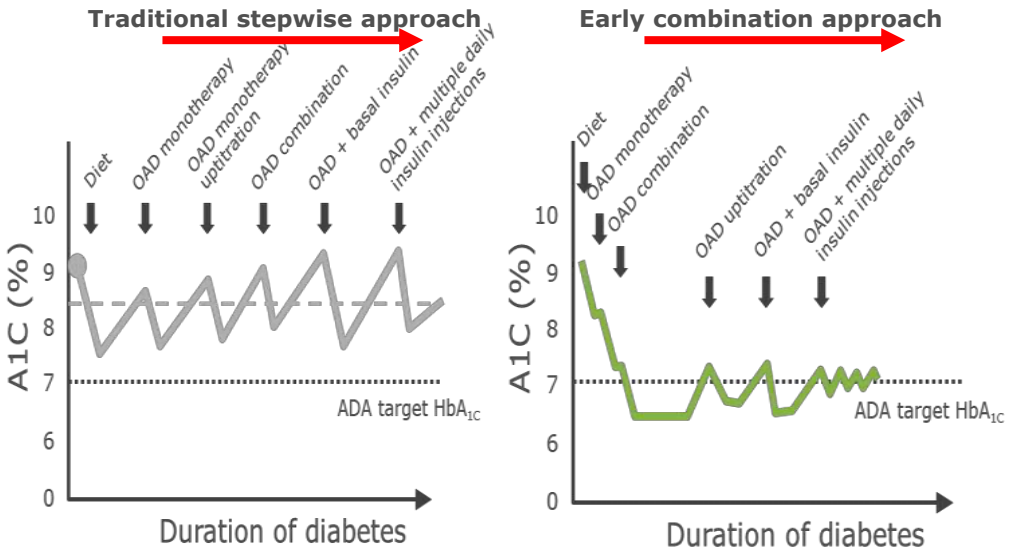
- Euglycemic diabetic ketoacidosis
- Bladder cancer incidence higher with dapagliflozin
- Amputations higher with canagliflozin
- Non significant incidence of bone fx
- CV benefits with empagliflozin in patients with established cv disease

Peters AL et al. Diabetes Care. 2015;38(9):1687.
Watts NB et al. J Clin Endocrinol Metab. 2016 Jan;101(1):157-66.
Zinman B et al. Engl J Med. 2015;373(22):2117.

Stepped management of type 2 diabetes

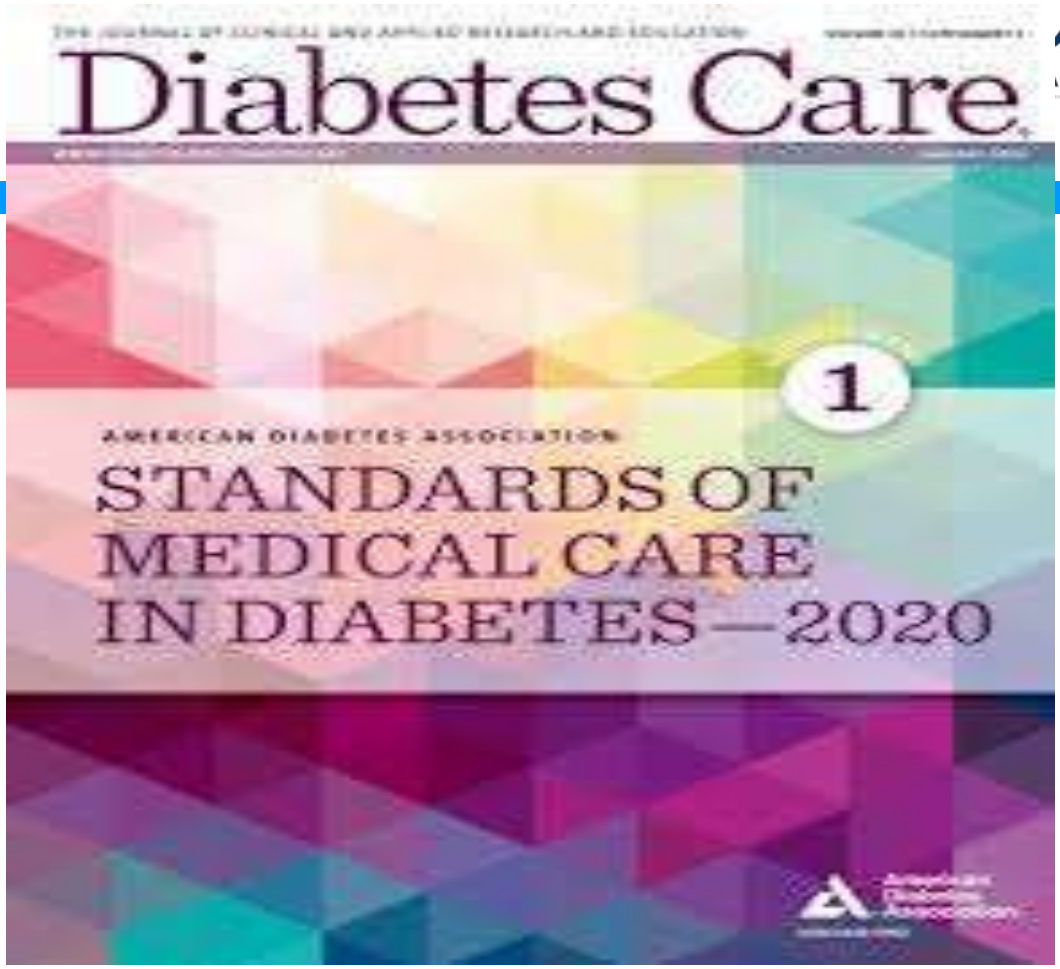


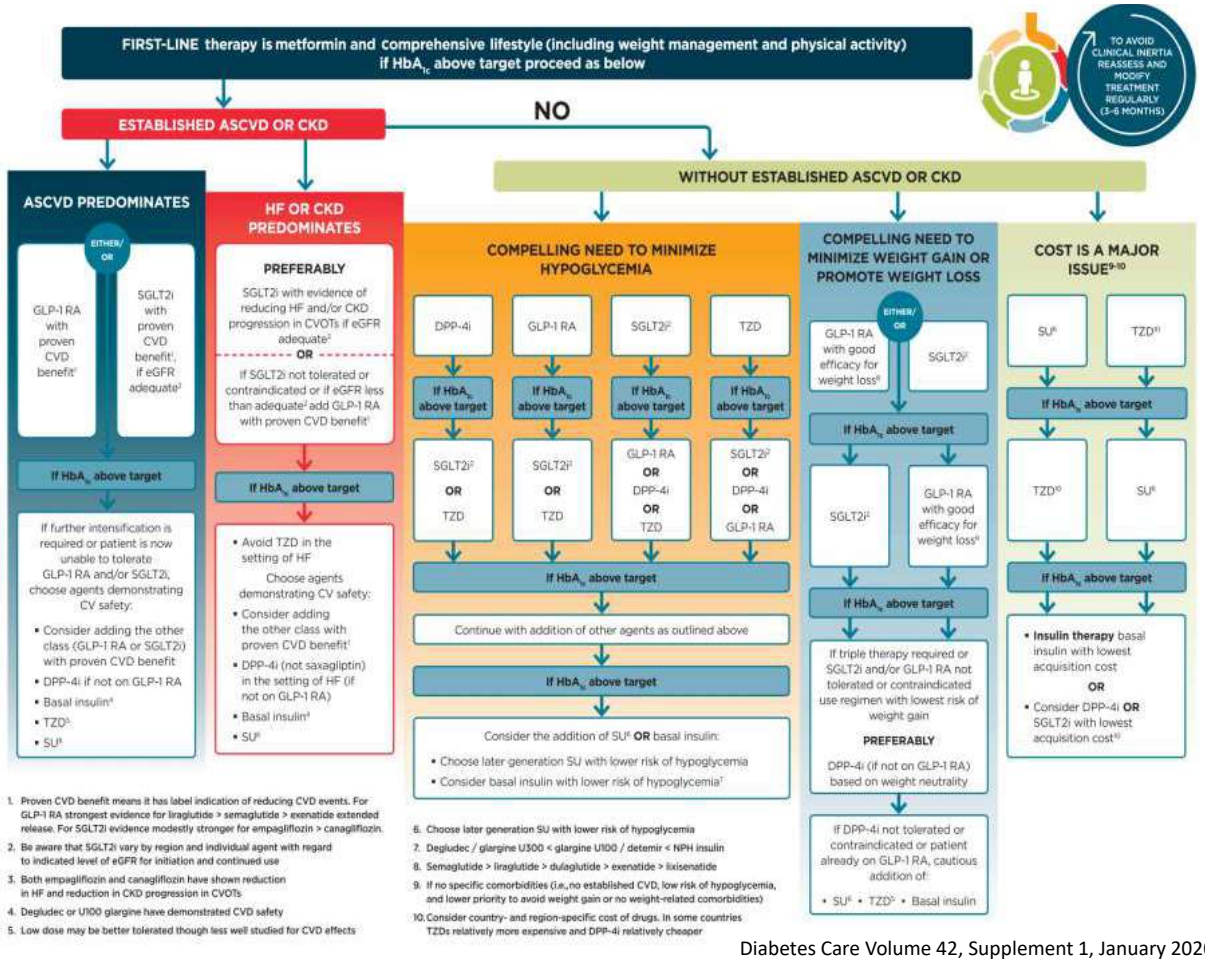
Early Intensive Treatment is Important in Management of Glycemia in T2DM



Early intensive treatment can minimize the hyperglycemia that underlies complications of T2DM

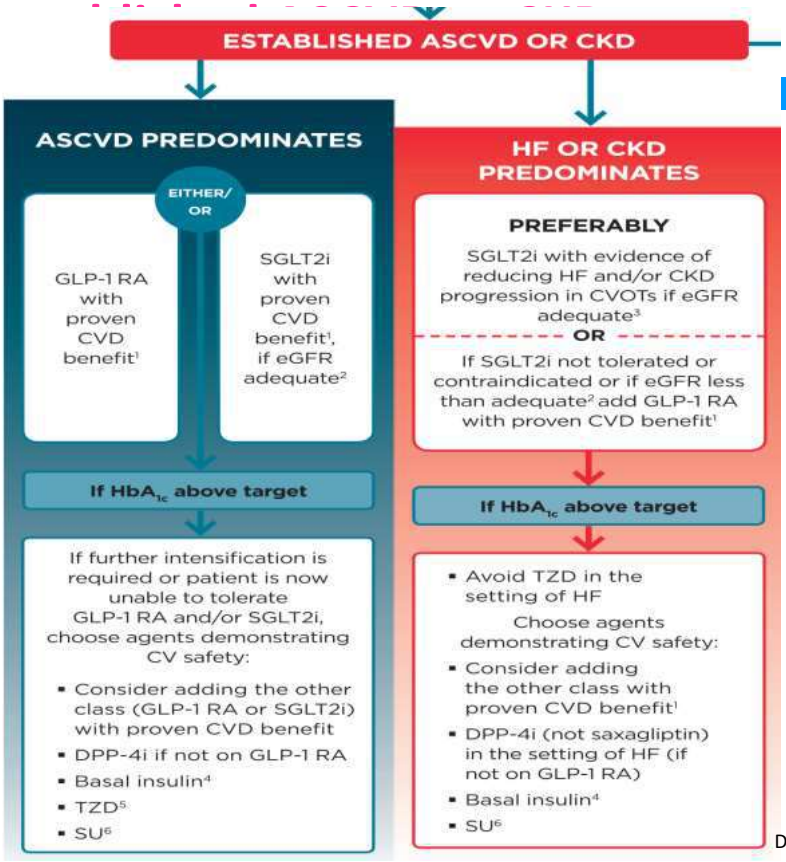
HbA1c, glycosylated hemoglobin; OAD, oral antidiabetic drug
Adapted from Campbell. Br J Cardiol 2000;7:625–31; Del Prato et al. Int J Clin





Diabetes Care Volume 42, Supplement 1, January 2020

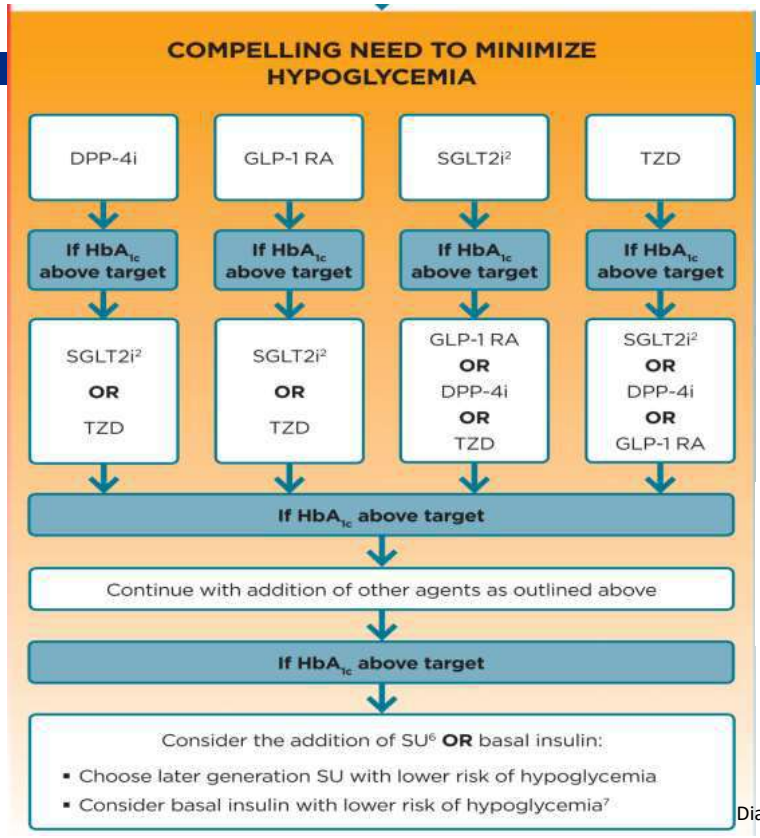
Epatients with Estabished ASCVD OR CKD



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects

Diabetes Care Volume 42, Supplement 1, January 2019

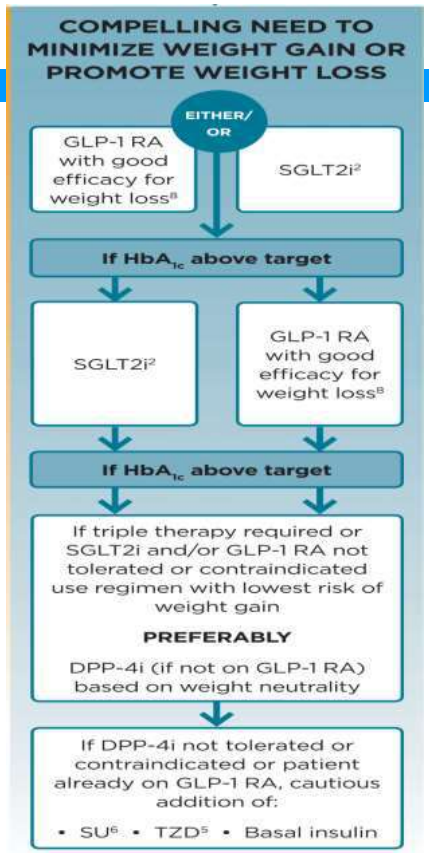
Compelling need to minimize hypoglycemia



6. Choose later generation SU with lower risk of hypoglycemia
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

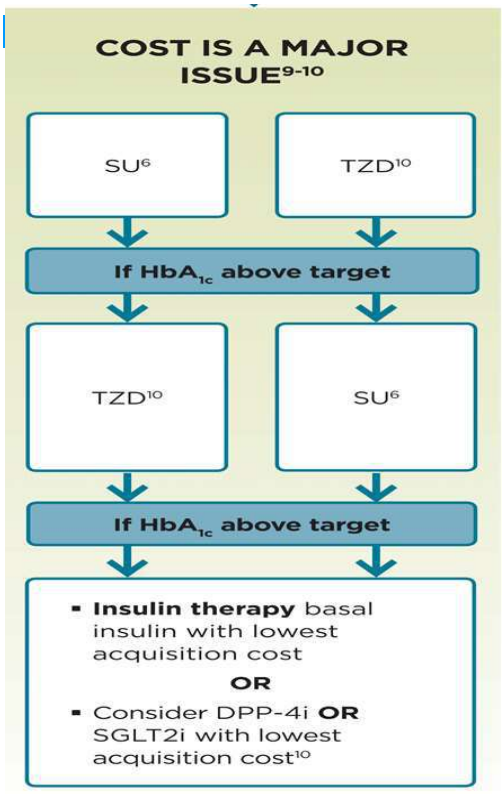
Diabetes Care Volume 42, Supplement 1, January 2019

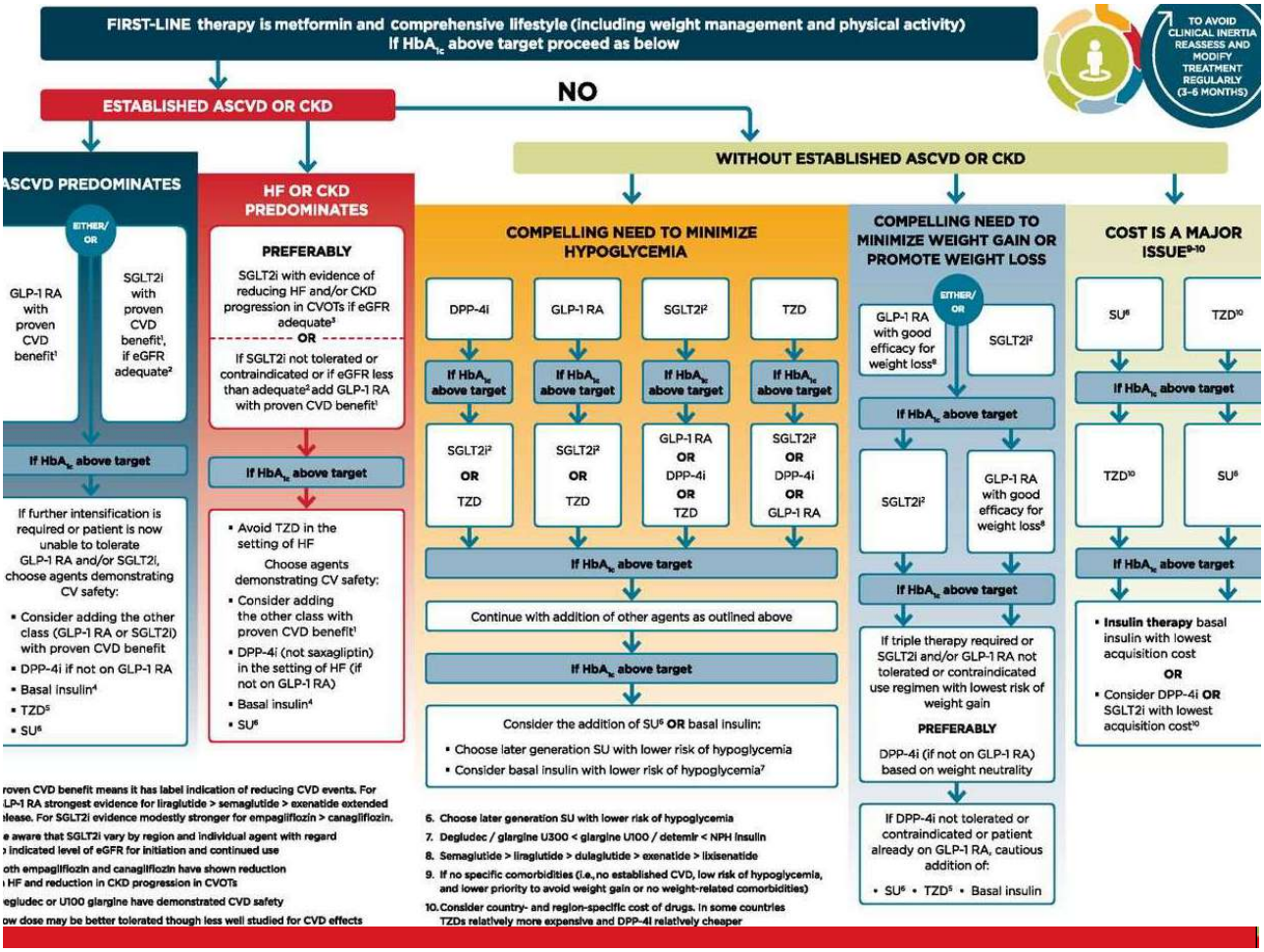
Compelling need to minimize weight gain



Diabetes Care Volume 42, Supplement 1, January 2019

When the cost is a major issue





PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	DPP-4i	GLP-1 RA	TZD	AGI	COLSVL	BCR-QR	SU / GLN	INSULIN	SGLT-2	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/ Severe / Mild	Moderate to Severe	Neutral	Neutral
WEIGHT	Slight Loss	Neutral	Loss	Gain	Neutral	Neutral	Neutral	Gain	Gain	Loss	Loss
RENAL/ GU	Contra-indicated Stage 3B,4,5	Dose Adjustment May be Necessary (Except Linagliptin)	Exenatide Contra-indicated CrCl < 30	May Worsen Fluid Retention	Neutral	Neutral	Neutral	More Hypo Risk	More Hypo Risk & Fluid Retention	Infections	Neutral
GI Sx	Moderate	Neutral	Moderate	Neutral	Moderate	Mild	Moderate	Neutral	Neutral	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
CVD	Benefit			Neutral			Safe	?			
BONE	Neutral	Neutral	Neutral	Moderate Bone Loss	Neutral	Neutral	Neutral	Neutral	Neutral	? Bone Loss	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects

Insulin Therapy in DM2: Indications

- Significant hyperglycemia at presentation
- Hyperglycemia on effective doses of oral agents
- Intolerance of orals
- Need more flexibility
- Renal or hepatic disease
- Surgery
- Pregnancy
- Unable to afford orals
- Decompensation
  - Acute injury, stress, infection, myocardial ischemia, stroke
  - Hyperglycemia with ketones, weight loss
  - Use of diabetogenic medications

Hirsch IB. *N Engl J Med* 2005; 352:174-183.

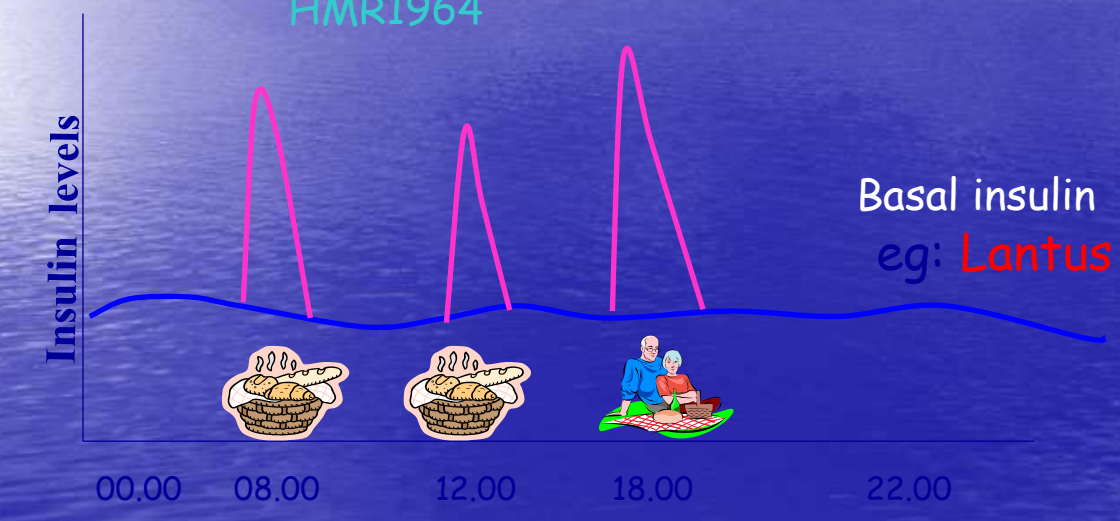
Adding Insulin

- **HOW?**
  - **Simple initiation: single injection (NPH or glargine), single AM blood glucose measurement.**

Insulin Therapy in Type 2 Diabetes

- Basal Insulin Therapy.(
- Bedtime intermediate insulin (NPH or lente).
- Long-acting insulin (ultralente or insulin glargine).
- Insulin pump (CSII) basal delivery.

Basal Bolus Therapy



The future: can type 2 diabetes be prevented and treated? Diabetes remission

MCQ

A-Oral antidiabetic use in obese patients :
1- Sulfonylurea
2- Insulin
3- TZD
4- SGTI2
B- Oral antidiabetic suitable in patient with renal impairment (eGFR<30:
1-Metformin
2--DPP4I
3- SGLT2I
4-Insulin

C-Target of management of diabetes :

- 1-Fasting BG >170 mg/dl
- 2- HbAiC >9%
- 3-PP BG 150-180 mg/dl
- 4- HbAiC <6%

D-Indication of insulin therapy in type 2 diabetes

- Obese patient
- Hypertensive patient
- Pregnant diabetic woman
- Patients with thyrotoxicosis