Practical Guidance in Pharmacotherapy for DM 2



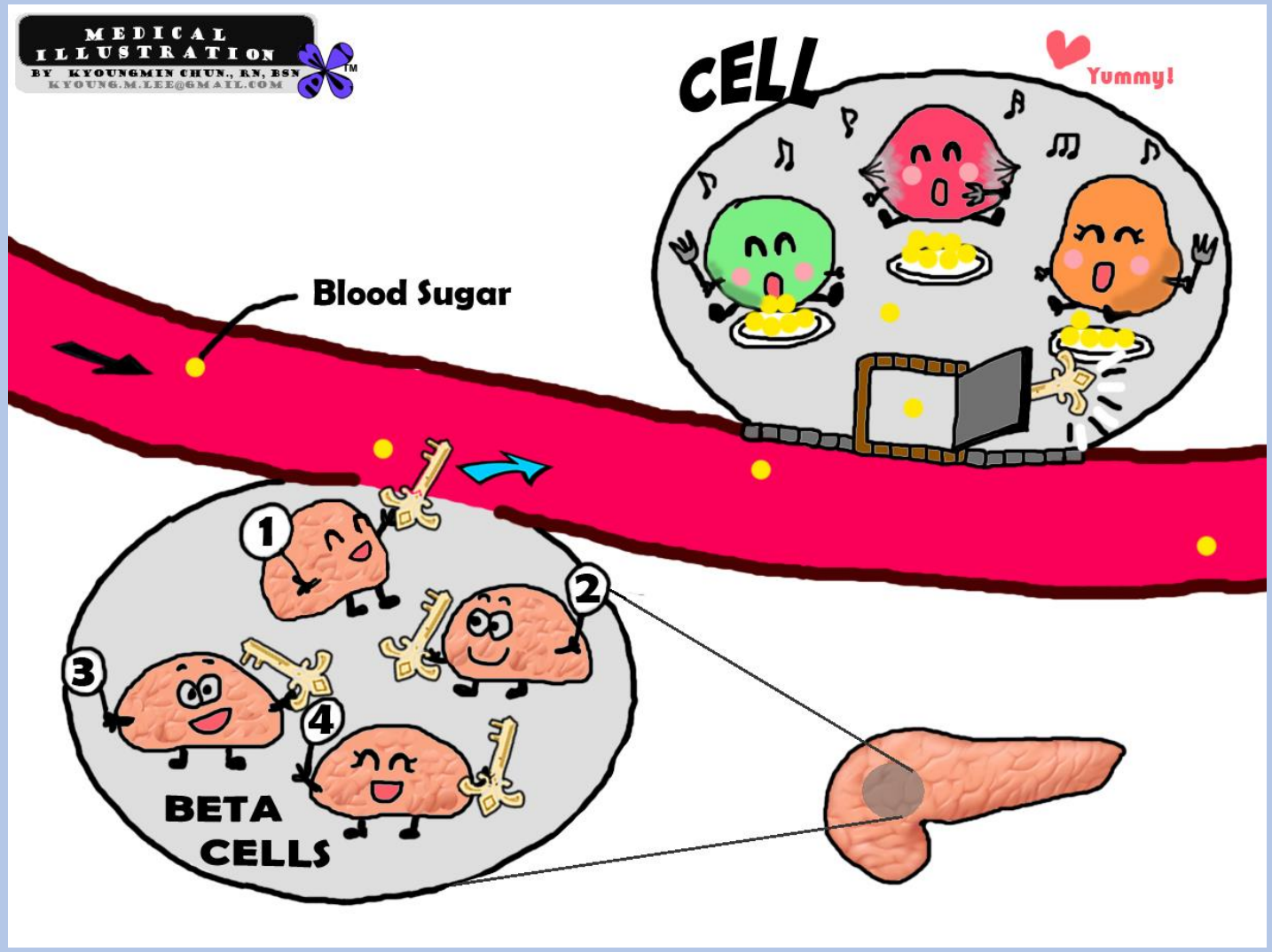
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Disclosure

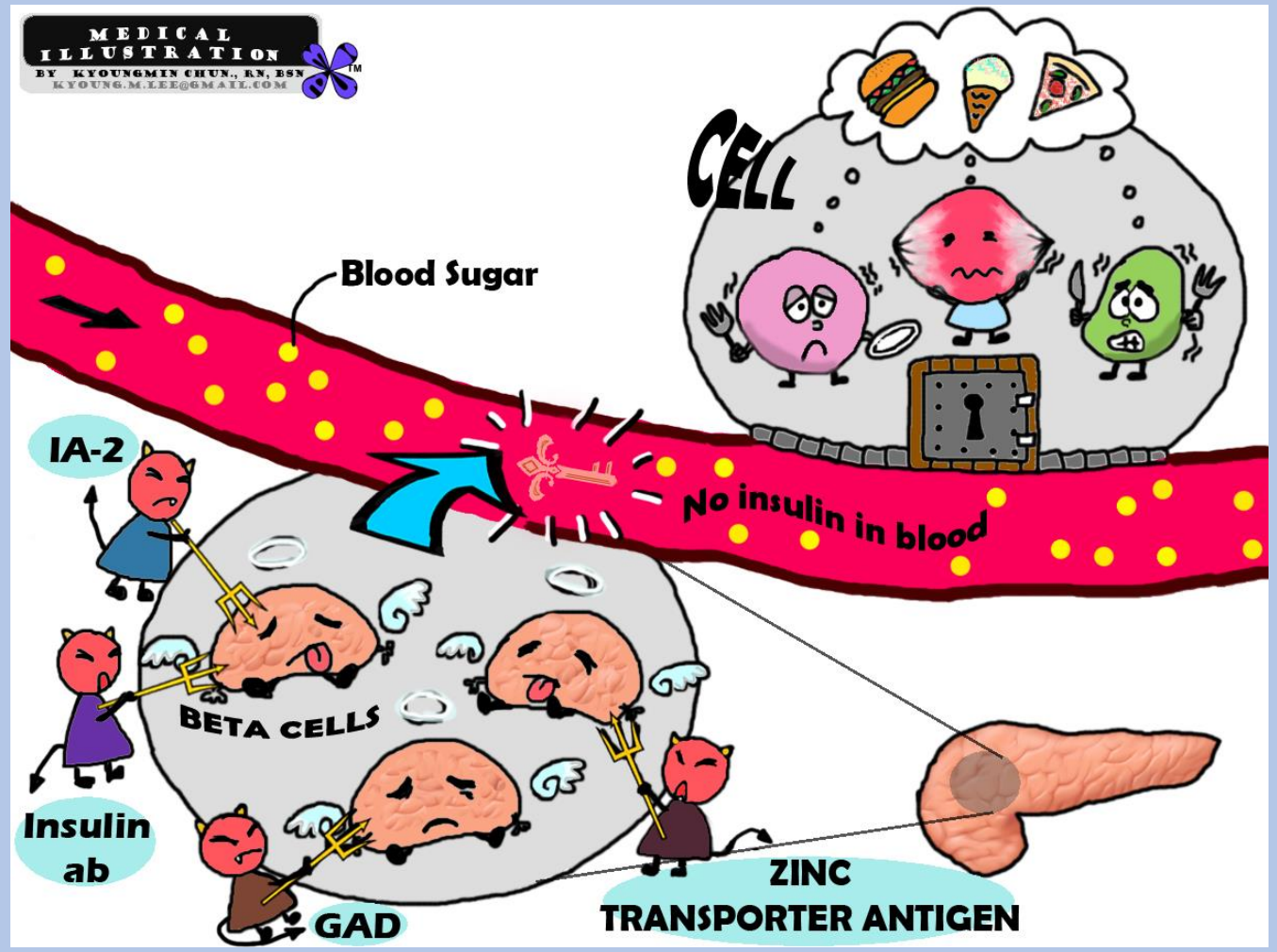
- None

*Employee of Corcept therapeutics. No conflict of interest in disease state and therapeutic interest.

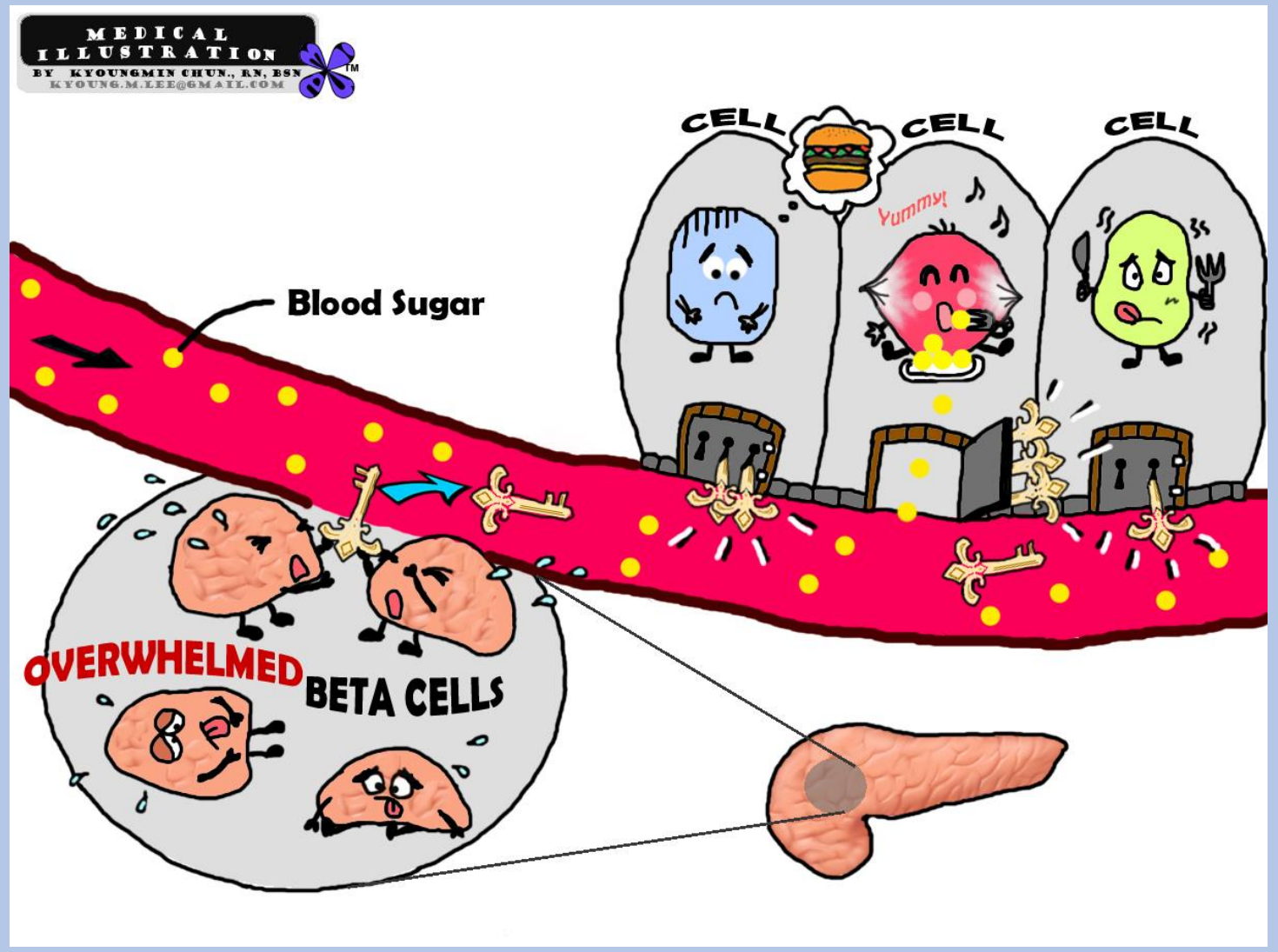
Normal insulin-glucose action



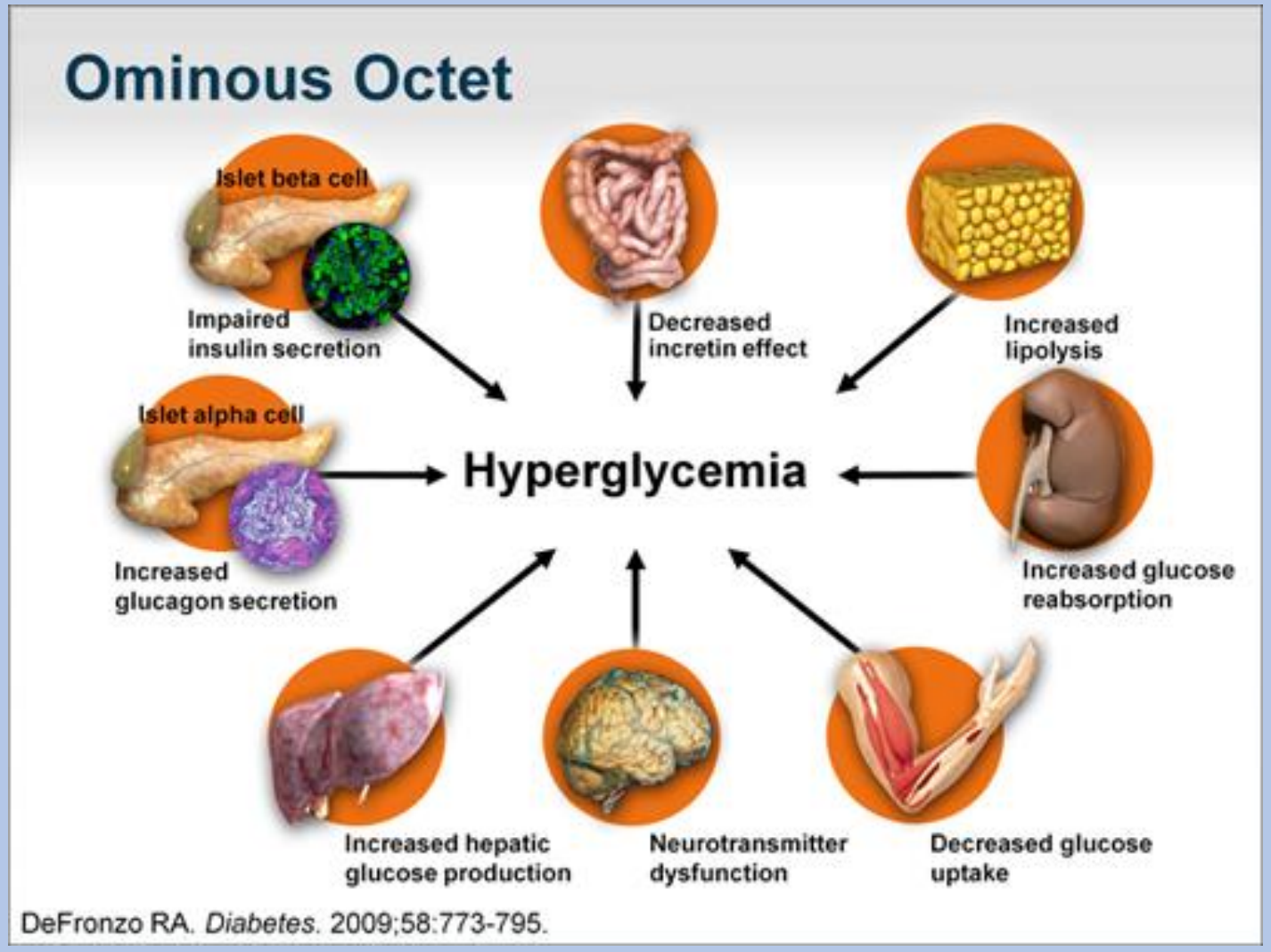
Type 1: immune destruction of b-cells



Type 2: insulin resistance



Ominous Octet



Patho/physiology of Diabetes

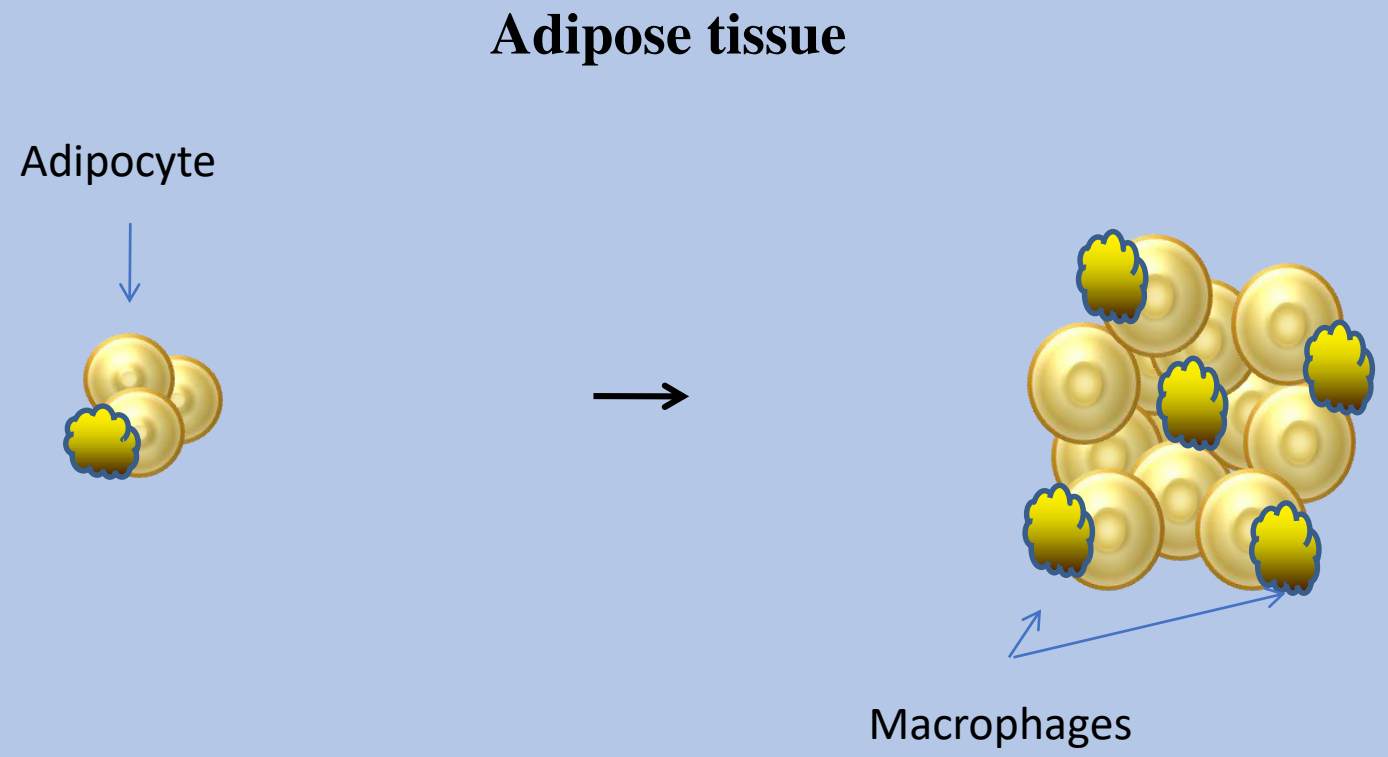
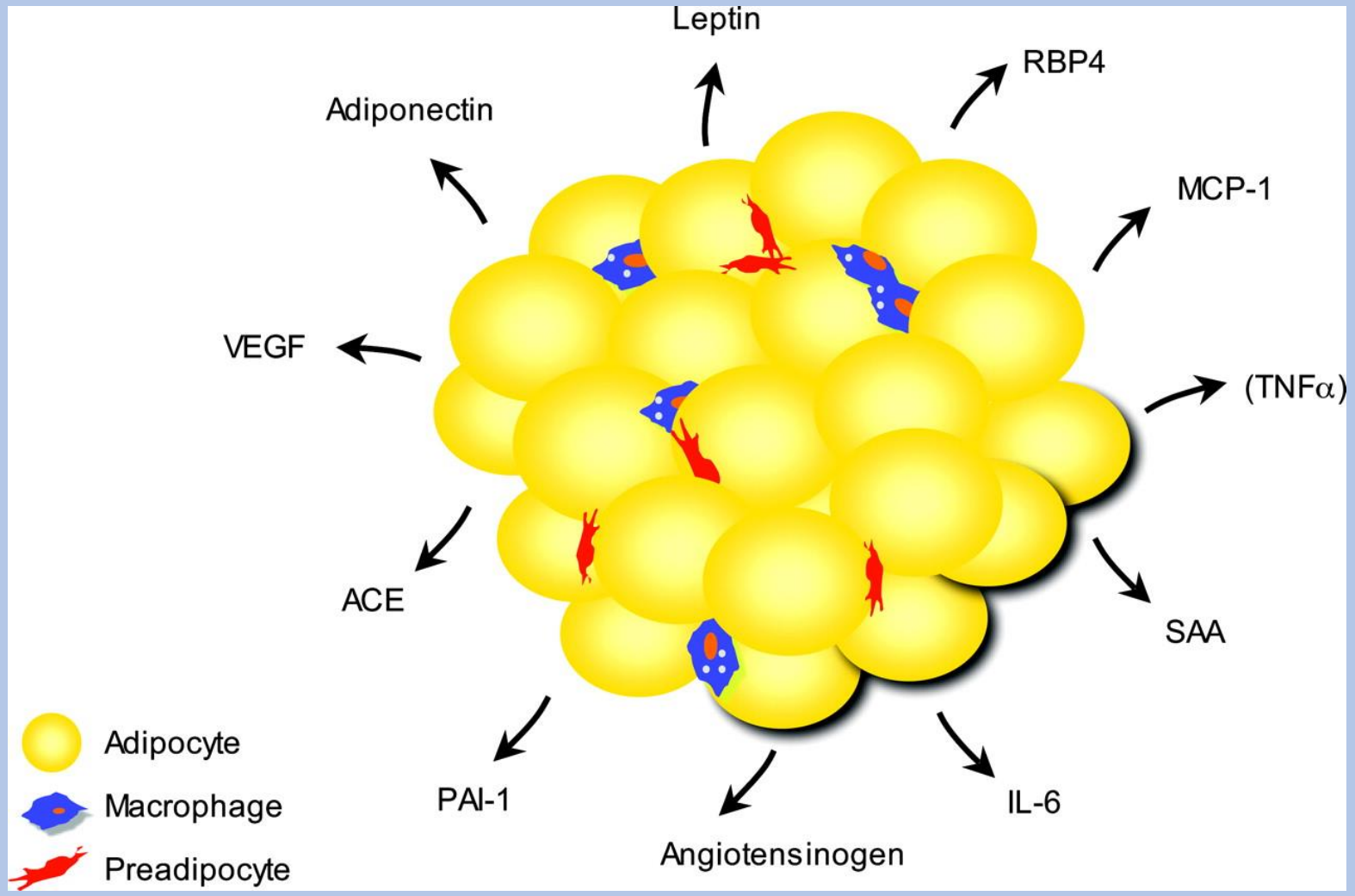


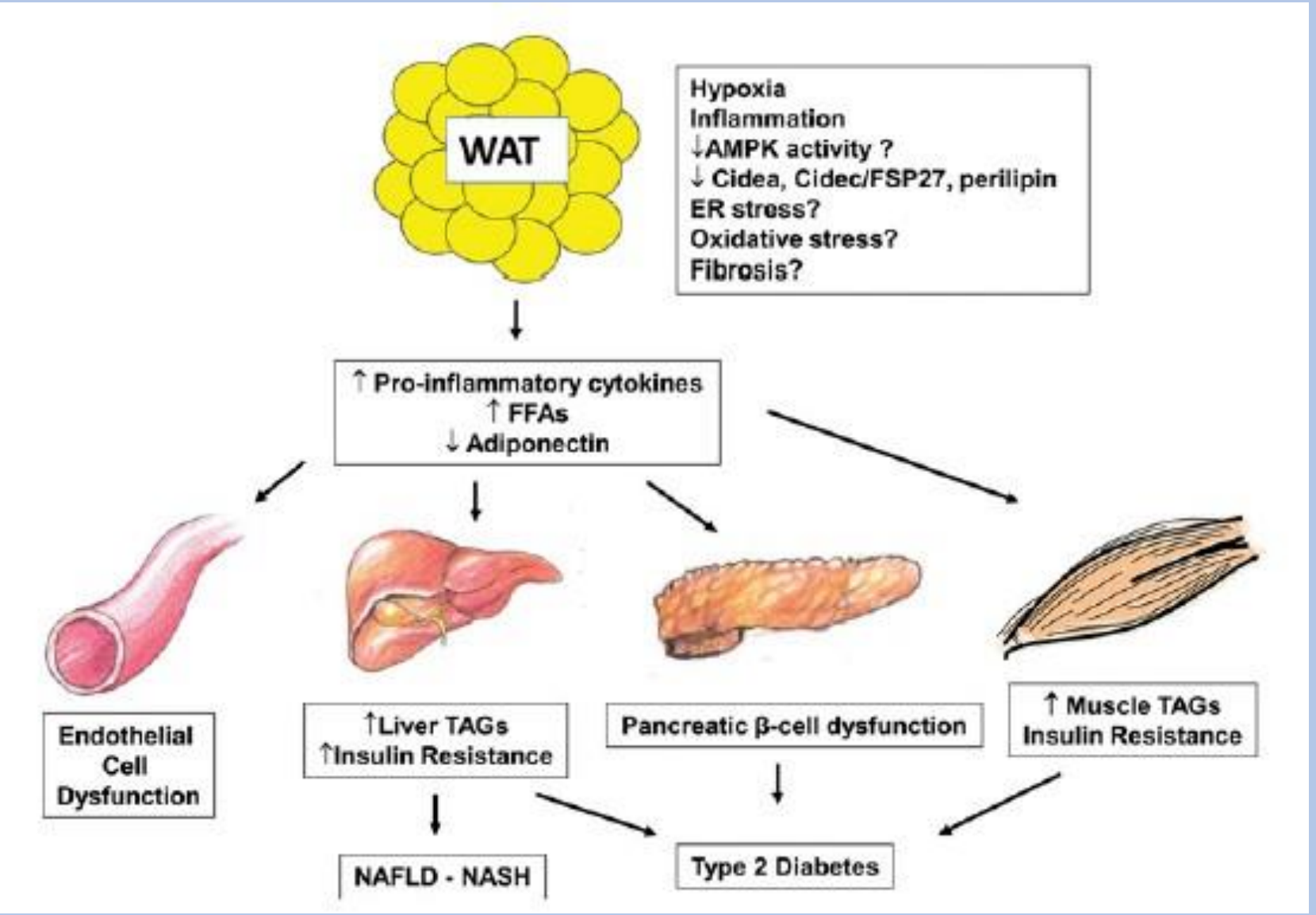
Figure 2. The figure shows different adipokines released by the adipose tissue.



Birgit Gustafson et al. Arterioscler Thromb Vasc Biol. 2007;27:2276-2283

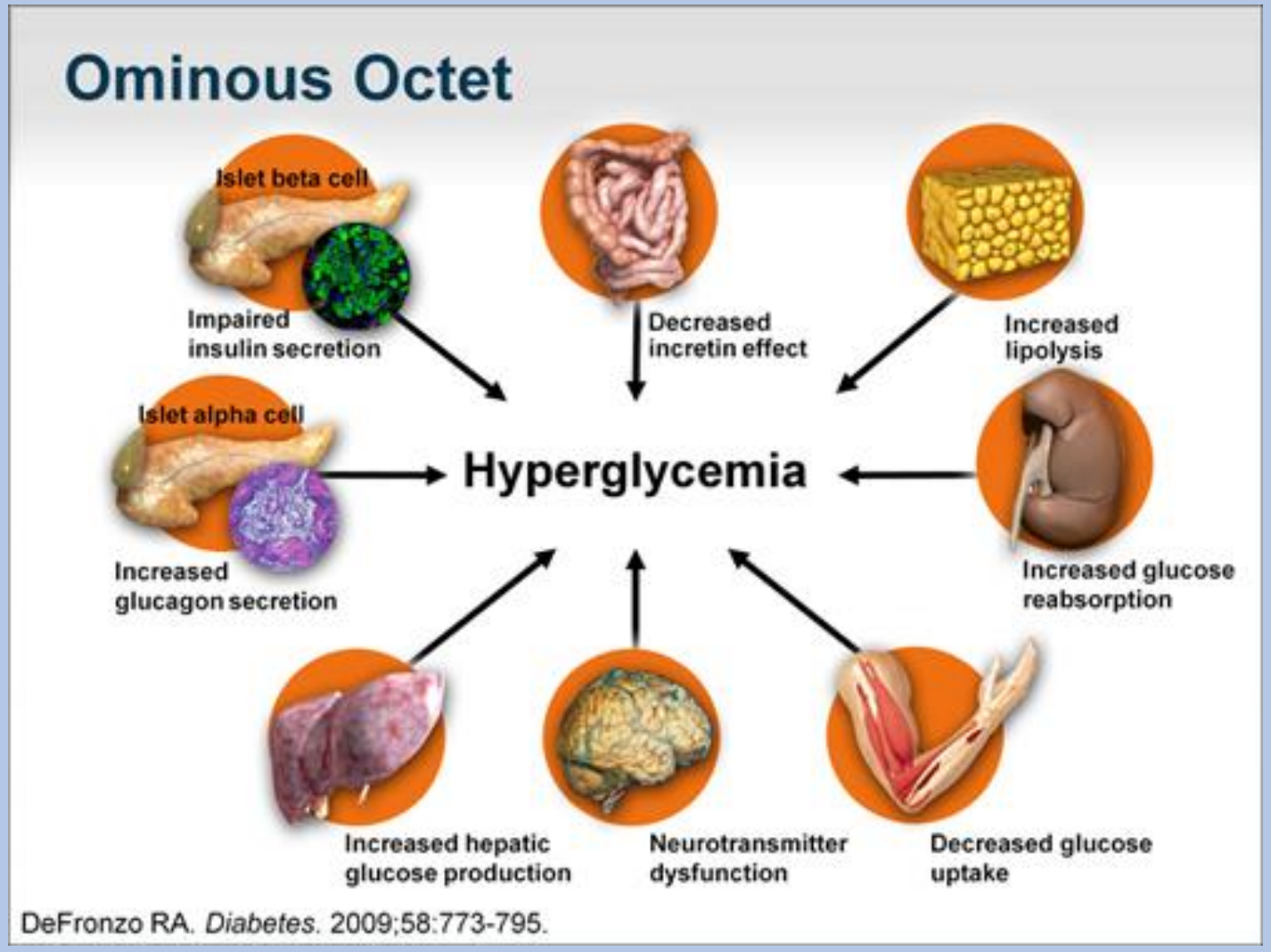
American Heart Association.

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Gautier, MS and Ruderman, NB. Biochem. J. (2010) 430, e1-e4

Ominous Octet



Maria

- 51yo female
- HPI: here for annual physical, feeling well overall
- PE: BP 128/71, BMI 32
- Med list: lisinopril 10mg/d, atorvastatin 20mg/d
- PMHx: prediabetes/HTN/dyslipidemia
- FHx: (+)DM2, ASCVD

Maria

Lab from last year

- A1c 5.8% (<5.7)
- FBG 108 (<100)
- Dyslipidemia with LDL 81
- eGFR 81 (>60)
- UMA/creatinine 3 (<30)
- CBC, TSH, UA wnl

Recent lab

- A1c 7.2% (<5.7%)
- FBG 152 (<100)
- Dyslipidemia with LDL 93
- eGFR 75 (>60)
- UMA/creatinine 11 (<30)
- CBC, TSH, UA wnl

Q

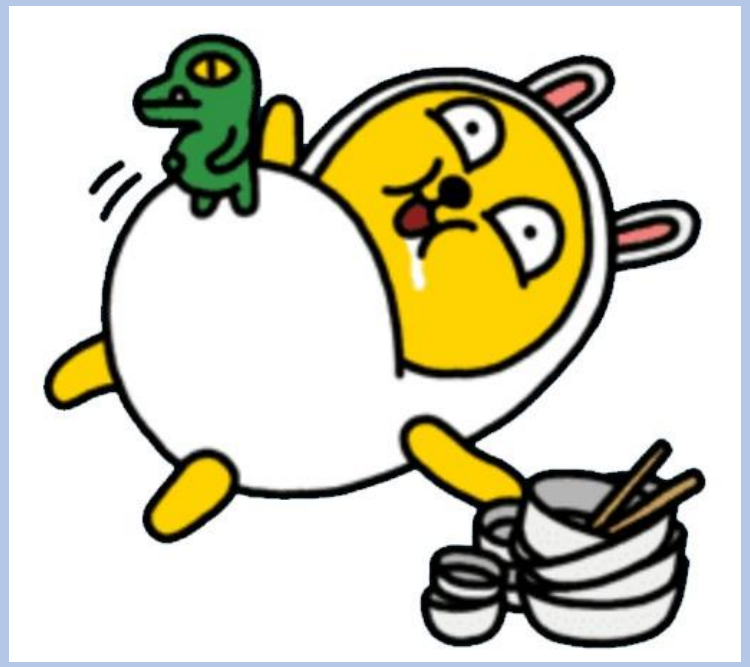
- Which of the following is the cornerstone of DM 2 management?

A. Lifestyle intervention
B. Metformin
C. Bariatric surgery
D. Islet cell transplant

Treatment options

- Always lifestyle intervention first, last, and anytime in-between

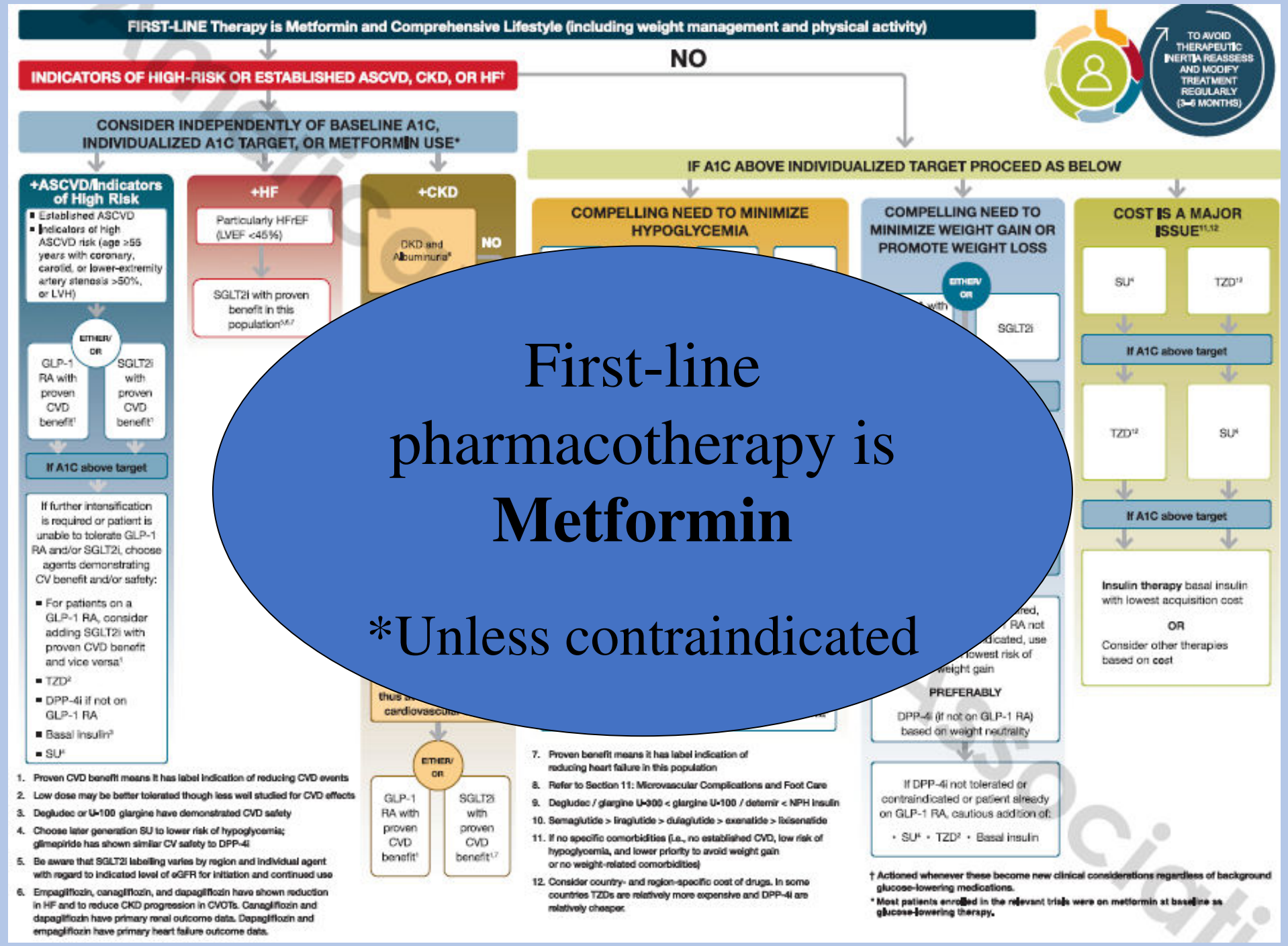




Q

- Which of the following is recommended for initial pharmacotherapy for DM 2?

A. Metformin
B. Sulfonylurea
C. Thiazolidinedione (TZD)
D. GLP 1 receptor agonist
E. SGLT-2 inhibitor



First-line pharmacotherapy is **Metformin**

*Unless contraindicated

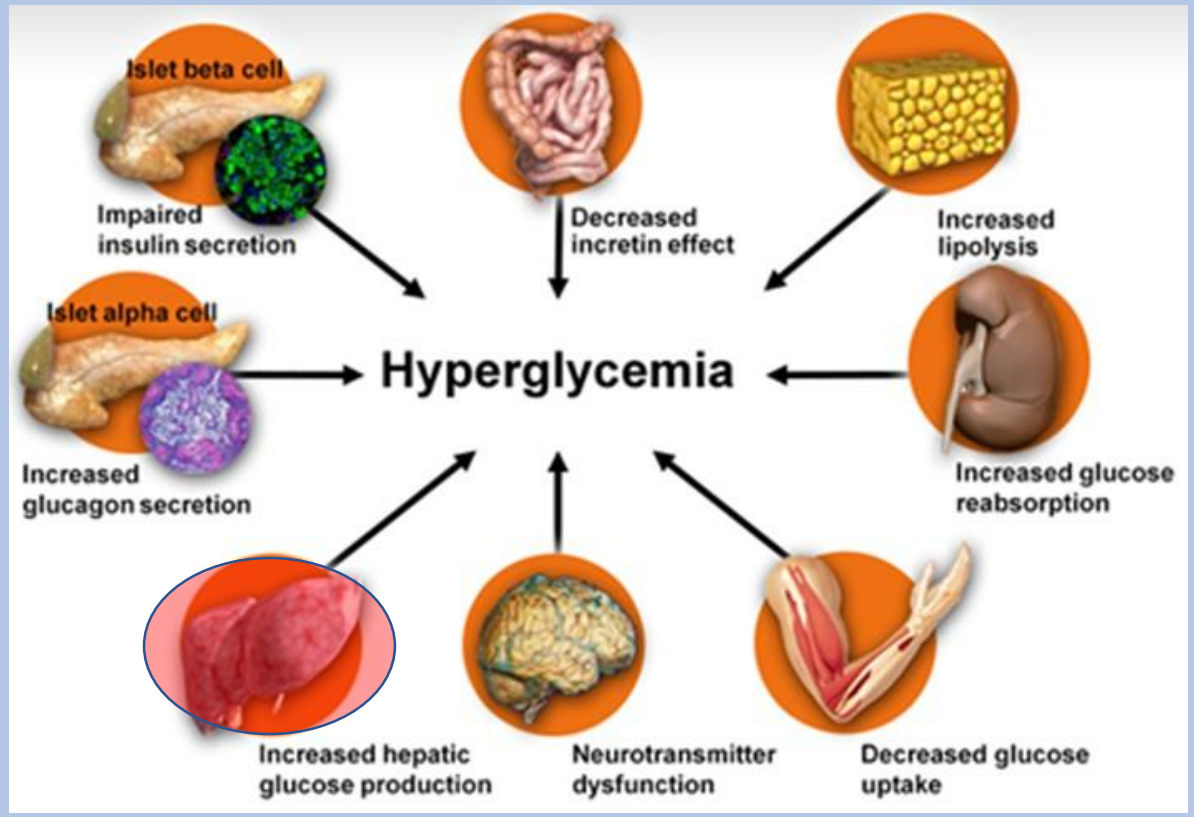
Pharmacologic Approaches to Glycemic Treatment. Diabetes Care. Vol 44, Suppl 1, Jan 2021

HYPO	Neutral
WEIGHT	Slight Loss

FPG	Mod
PPG	Mild

Metformin

CV effects		
ASCVD	HF	CKD
Potential benefit	neutral	



Handelsman Y et al. Endocr Pract. 2015;21(suppl 2):14 / DeFronzo RA. Diabetes. 2009;58:773-795

Metformin

- 1st line pharmacotherapy (unless contraindicated)
- $
- Lower A1c by about 1-1.5%
- Side effect: GI upset
- Tips: use XR/ER form in 500/750mg form. Take it with food or after food (no empty stomach). Titrate the dose up and use max **tolerated** dose.
- Potential for vitamin B12 deficiency

D'Allesio DA and Hirsch IB. Glycemic Management of Type 2 DM. Translational Endocrinology & Metabolism. 2011; 2(1):75.

Q

- Metformin is contraindicated in patients with renal status of

A. Creatinine >1.4
B. GFR <30
C. GFR <45
D. GFR <60

Metformin

- Metformin is nephrotoxic??

Metformin

Renal dosing

- Old:
  - CI if creatinine >1.5mg/dL for men and >1.4mg/dL for women or abnormal creatinine clearance
- New:
  - Measure renal function by eGFR (mL/min per 1.73m^2)
  - 30 - 45: do not initiate. Max dose 1000mg/day. Reconsider the benefit/risk of continuing therapy.
  - < 30: Stop

US Food and Drug Administration. FDA Drug Safety Communication: April 8, 2016. Accessed August 2, 2016

Maria

- Patient referred to DM educator, met with nutritionist and also joined gym.
- Started with metformin ER 500mg 1tab/d and slowly titrated up to 2000mg/d.
- Lost 10lbs.
- A1c at 3months: 6.2%

Maria

- Did well with A1c <6.5% for 3yrs on lifestyle intervention and metformin therapy.
- Returns after long hiatus after suffering an MI (s/p 2 stents). A1c in hospital was 8.5%
- Admits that she returned to her old habit and gained 15lbs back.
- Has been only 30-50% adherent with her meds

Q

- When adding second agent after metformin, what should be first assessed?

A. Cost of medication
B. Risk of hypoglycemia
C. Patient weight status
D. History of ASCVD/HF/CKD

Till 2017

Dual Therapy — **Metformin +** — **Lifestyle Management**

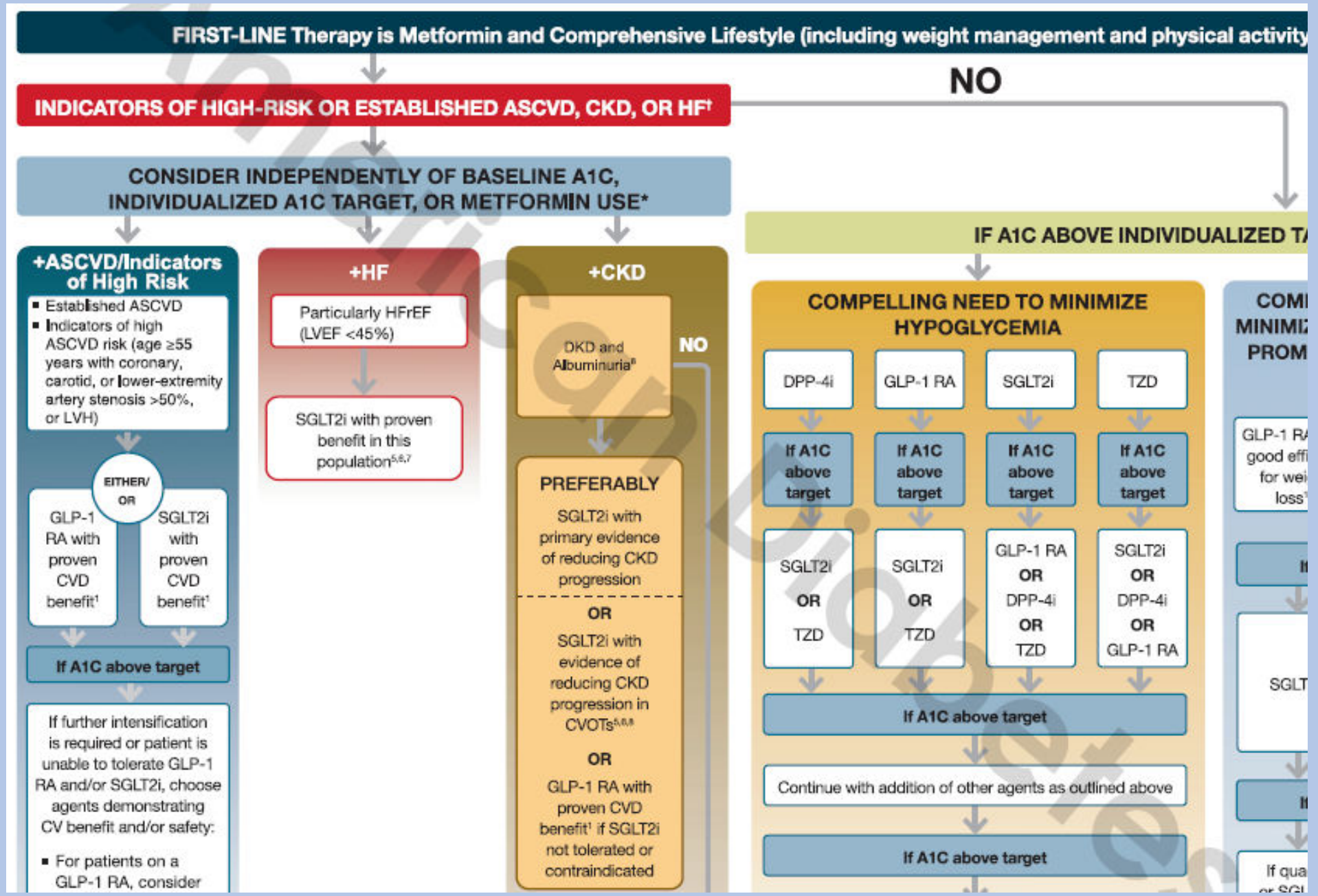
	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

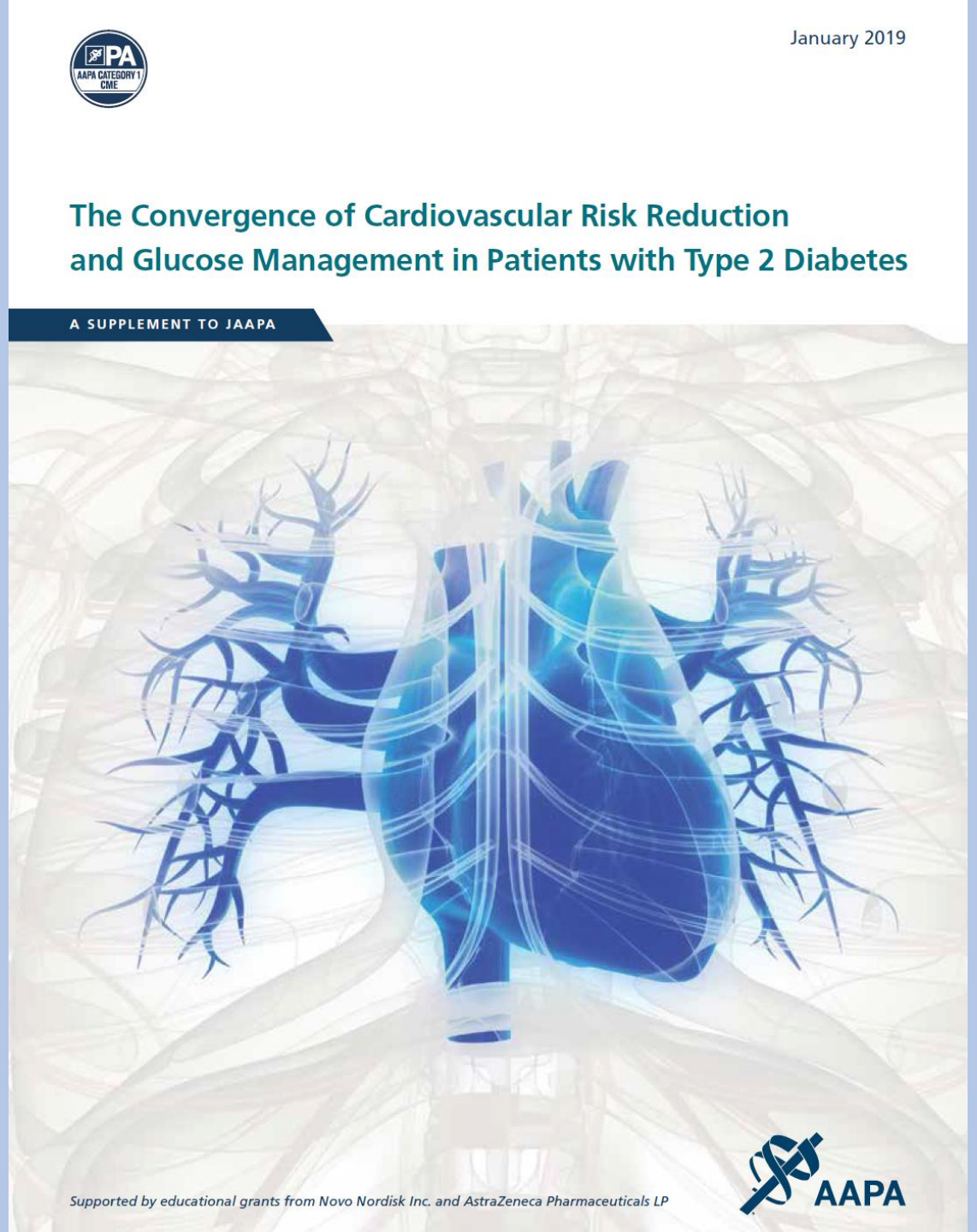
Triple Therapy — **Metformin +** — **Lifestyle Management**

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin§	or GLP-1-RA	or Insulin§	or GLP-1-RA
or Insulin§	or Insulin§		or Insulin§		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).



Presence of
- ASCVD
- CKD
- HF



- Print available in JAAPA

- Online module available on AAPA Learning Central

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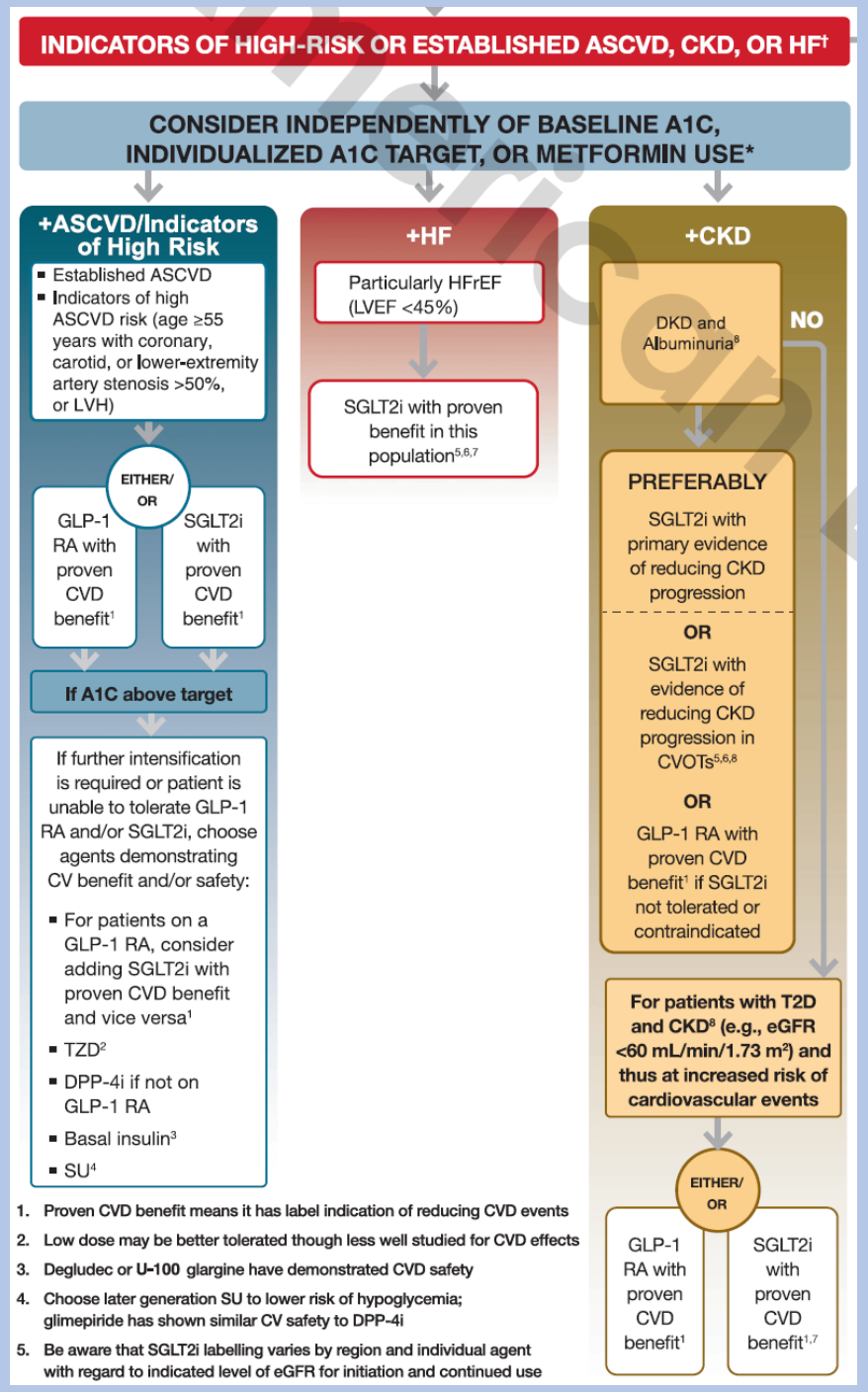
- Which of the following is most appropriate second agent after metformin, who has established ASCVD, CHF or CKD?

A. Sulfonylurea (SU) or Thiazolidinedione (TZD)

B. SGLT-2 inhibitor or GLP-1 Receptor agonist

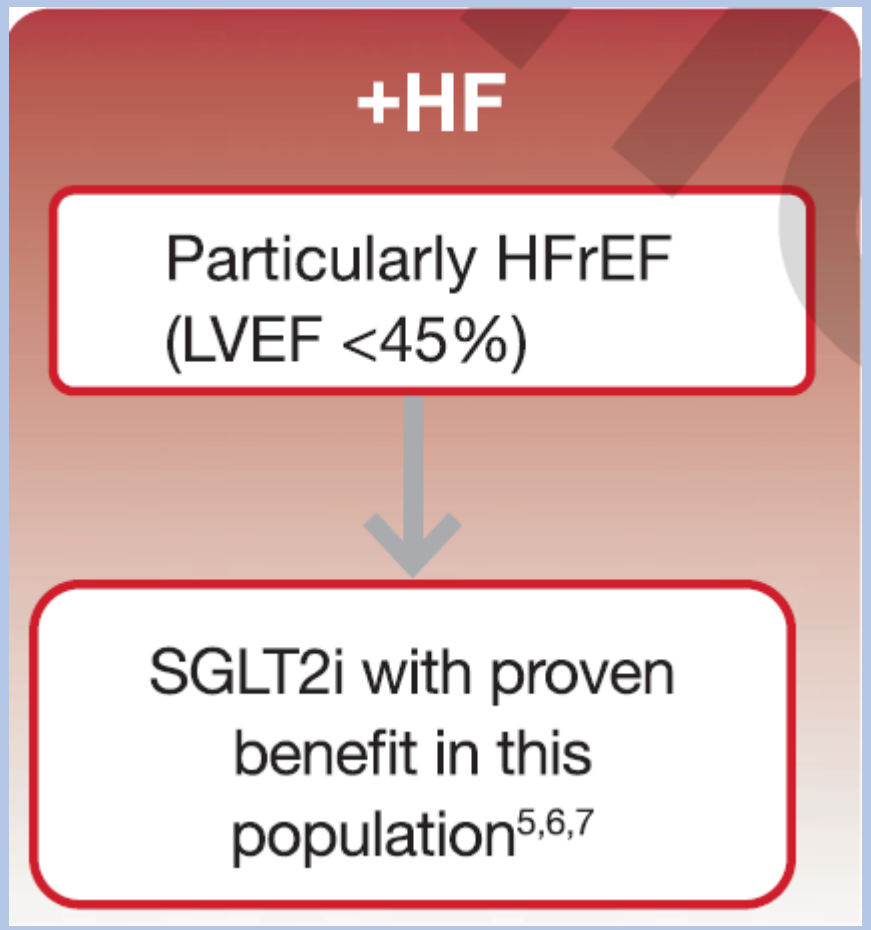
C. DPP4 inhibitor

D. Insulin



- SGLT2i:
empagliflozin
canagliflozin
dapagliflozin
ertugliflozin

- GLP-1RA:
dulaglutide
liraglutide
semaglutide
exenatide ER



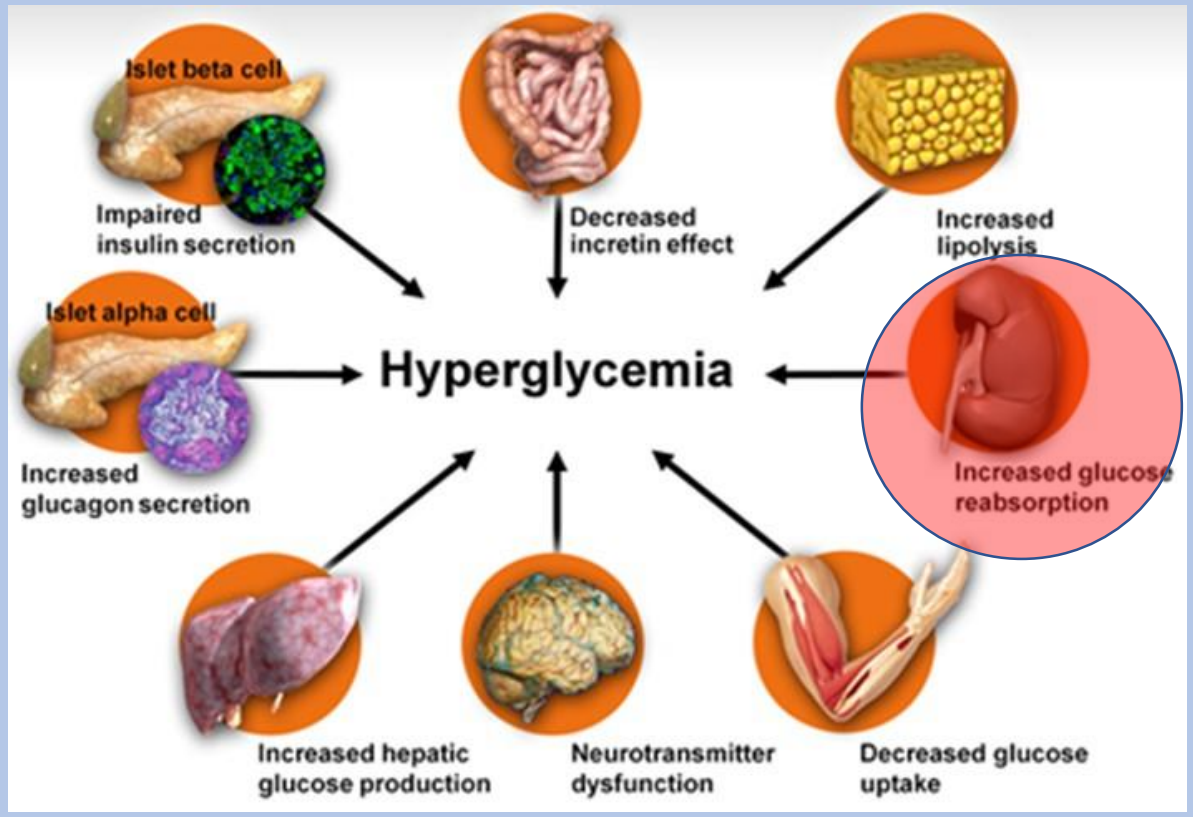
SGLT-2 inhibitors with proven HF benefit

- canagliflozin
- dapagliflozin
- empagliflozin

HYPO	Neutral	FPG	Mod
WEIGHT	Loss	PPG	Mild

SGLT-2 inhibitors

CV effects		
ASCVD	HF	CKD
Benefit: Empagliflozin Canagliflozin	Benefit: Empagliflozin Canagliflozin Dapagliflozin	



Handelsman Y et al. Endocr Pract. 2015;21(suppl 2):14 / DeFronzo RA. Diabetes. 2009;58:773-795

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
- Ertugliflozin (Steglatro)

Q

- Which of the following is the most common adverse event of SGLT-2 inhibitors?

A. Hypotension
B. Acute kidney injury
C. Genital mycotic infection
D. Lower extremity amputation
E. Diabetes ketoacidosis

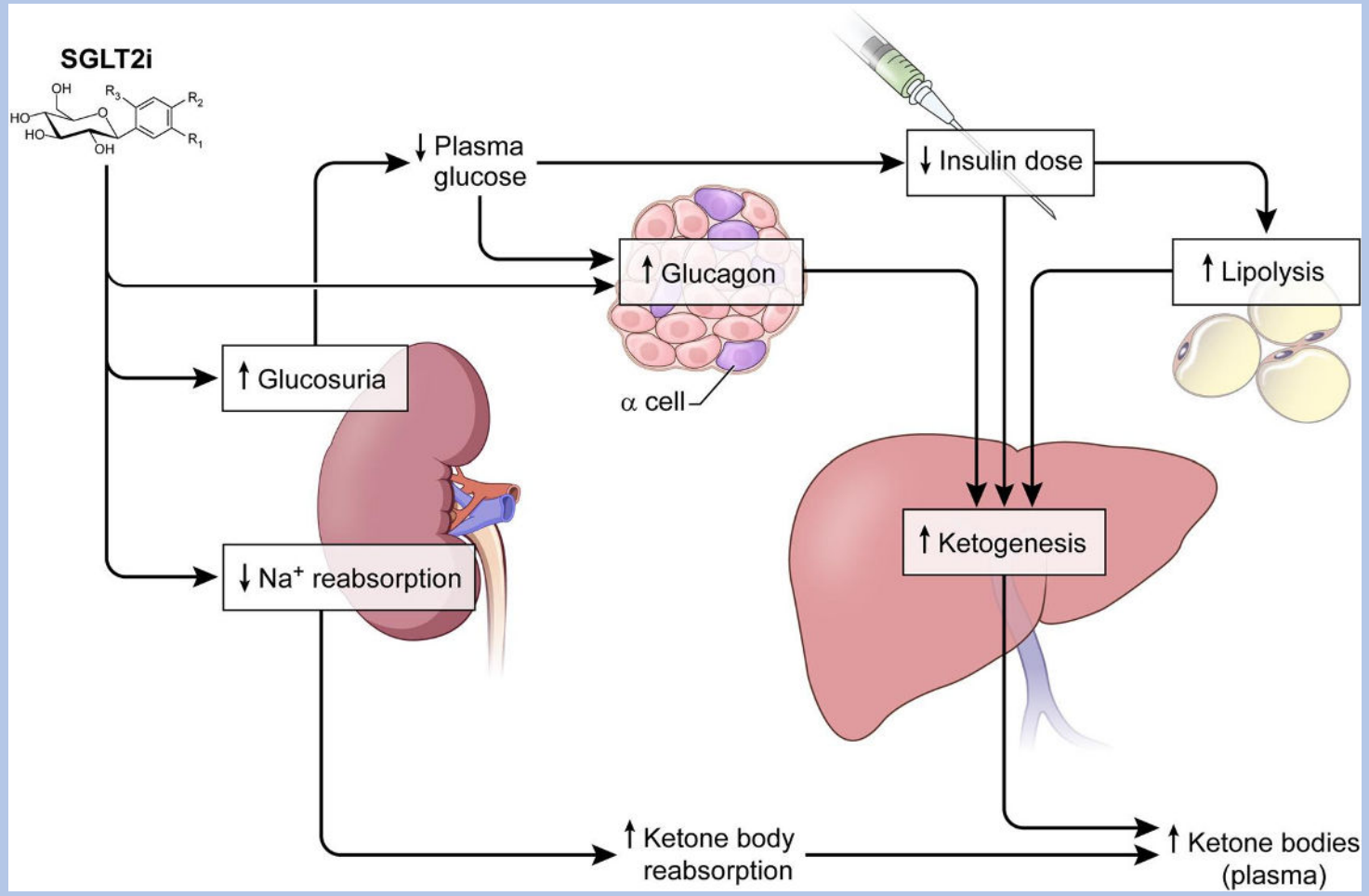
SGLT-2 inhibitors

- Lowers A1c by 0.9%
- $$$
- Lowers BP (diuretic effect)
- SEs:
  - genital mycotic infection (most common)
  - Acute kidney injury (volume related)
    - Tips: well hydration, good hygiene
- Warning: DKA

- GFR cut-off:
  - Canagliflozin: ≥ 30 (do not start if <30, but may continue if on tx and albuminuria >300mg/d for CV/renal protection)
  - Dapagliflozin: ≥ 25 (do not start if <25, but may continue if on tx for HF/renal protection)
  - Empagliflozin: ≥ 45 for DM/CV
  - Ertugliflozin: ≥ 60 for DM (no other indication)

D'Allesio DA and Hirsch IB. Glycemic Management of Type 2 DM. Translational Endocrinology & Metabolism. 2011; 2(1):75.

SGLT2i and DKA



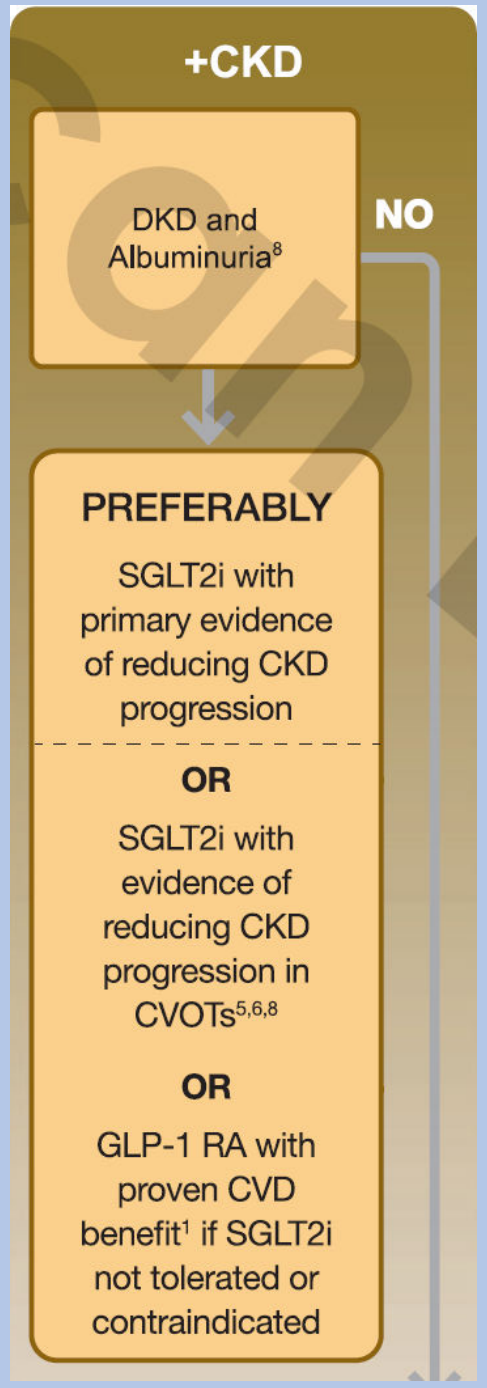
Taylor SI, Blau, JE, and Rother KI. SGLT2 Inhibitors May Predispose to Ketoacidosis. J Clin Endocrinol Metab 100: 2849-2853. 2015

SGLT2i and DKA

DM 2	Empagliflozin (N= 10,078)	Comparator (N= 5,599)
Any DKA	7 (<0.1%)	5 (0.1%)
Serious	6 (<0.1%)	4 (0.1%)
DM 1	**Canagliflozin (N= 234)**	**Placebo (N= 117)**
Any DKA	18 (7.7%)	0
Serious	12 (5.1%)	0

Modified from Inzucchi SE, Diabetes 2016 from 52nd EASD. Volume 34(1) / Henry RR, Diabetes Care 2015.

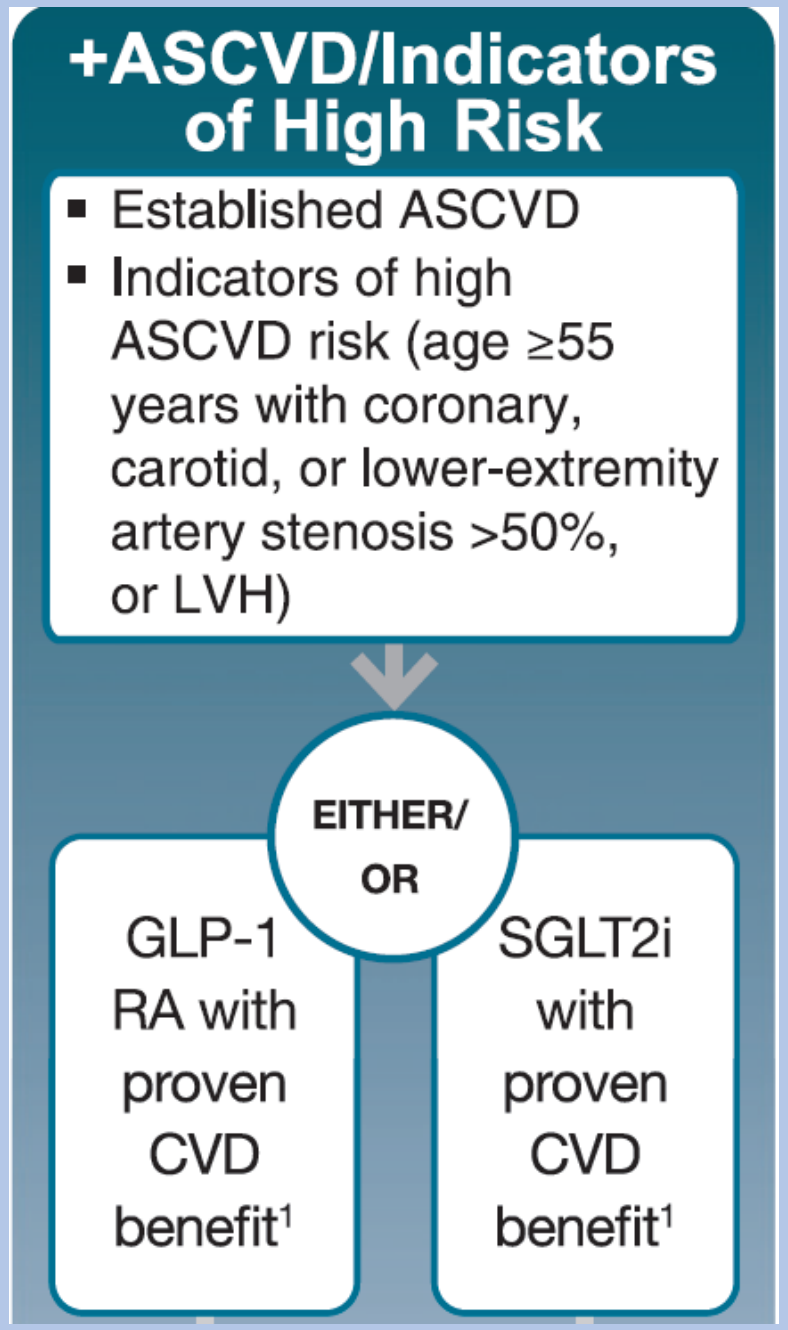
- Tips:
  - Well hydration
  - d/c during high stress (i.e., surgery)
  - Avoid insulinopenia
  - Suspect LADA / DM 1.5
  - Avoid / extra caution in DM 1



Agents with proven CKD benefit

- (preferred) **SGLT-2 inhibitor**:
canagliflozin
dapagliflozin
empagliflozin

- GLP-1RA:
dulaglutide
liraglutide
semaglutide



Agents with proven ASCVD benefit

- GLP-1RA:
dulaglutide
liraglutide
semaglutide

- SGLT2i:
empagliflozin
canagliflozin

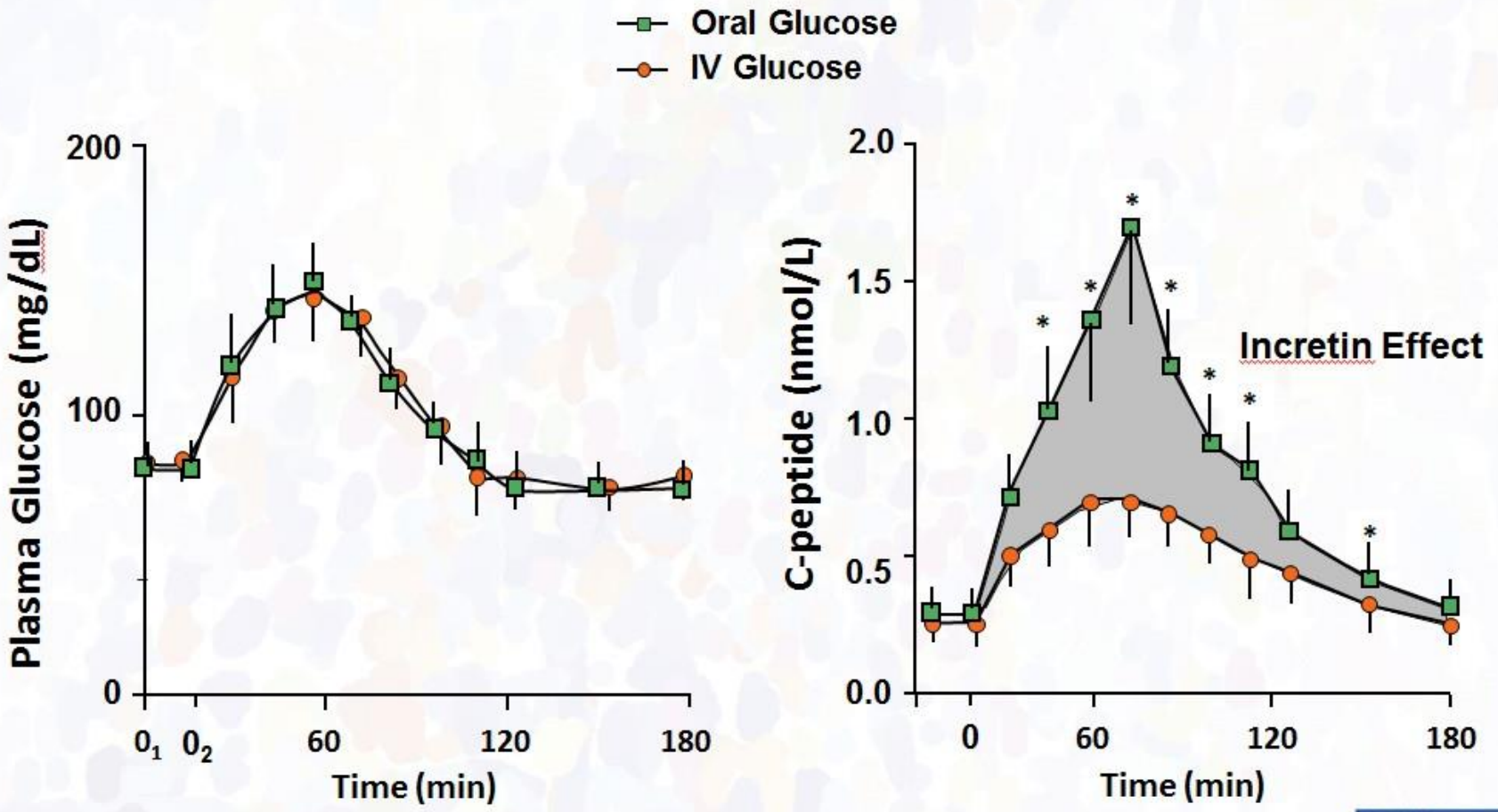
Incretin based therapy

- **GLP-1 agonist *(injectable)***
  - Dulaglutide (Trulicity)
  - Exenatide ER (Bydureon)
  - Liraglutide (Victoza)
  - Semaglutide (Ozempic)
- **GLP-1 agonist *(oral)***
  - Semaglutide (Rybelsus)

- **DPP4 inhibitor (oral)**
  - Alogliptin (Nesina)
  - Linagliptin (Tradjenta)
  - Saxagliptin (Onglyza)
  - Sitagliptin (Januvia)

Use one or the other class. Not both

The Incretin Effect in Healthy Subjects



Mean ± SE; N = 6; *$P \leq .05$; 0_1-0_2 = glucose infusion time.

Nauck MA, et al. *J Clin Endocrinol Metab.* 1986;63:492-498.

Role of Incretins in Glucose Homeostasis





↑ satiety
↓ appetite

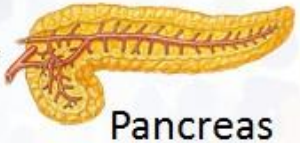


↑ glucose uptake by muscles



Release
⇄
↓ gut motility

Active GLP-1 and GIP



Pancreas

Decreased blood glucose

- ↑ glucose-dependent insulin release, ↑ β-cell regeneration? (GLP-1 & GIP)
- ↓ glucose-dependent glucagon release from α-cells (GLP-1)

DPP-4

Inactive



↓ glucose production

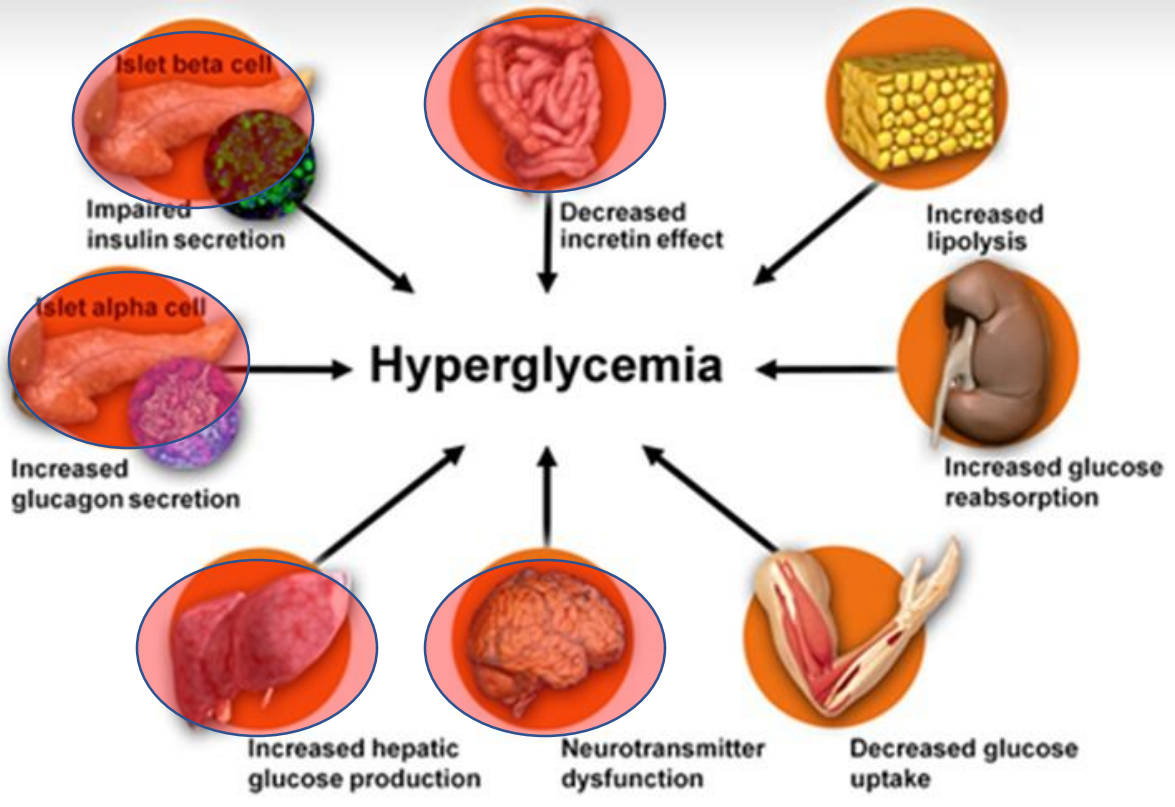


Adapted from Drucker DJ. *Cell Metab*. 2006;3(3):153-165.
Nauck MA. *Am J Med*. 2011;124(1 Suppl):S3-18.

HYPO	Neutral	FPG	Mild to Mod
WEIGHT	Loss	PPG	Mod to Marked

GLP-1 agonists

CV effects		
ASCVD	HF	CKD
Benefit: liraglutide, semaglutide, dulaglutide	neutral	Benefit: liraglutide



Handelsman Y et al. Endocr Pract. 2015;21(suppl 2):14 / DeFronzo RA. Diabetes. 2009;58:773-795

Twice daily

- Exenatide (Byetta)

Once daily

- Liraglutide (Victoza)
- **Oral** semaglutide (Rybelsus)

Once weekly

- Exenatide ER (Bydureon)
- Dulaglutide (Trulicity)
- Semaglutide (Ozempic)

GLP-1 agonist

- Lowers A1c by 1-2%
- $$$
- Side effect: GI upset
- Tips: pre-warn patients regarding gastric slowing and to eat slower and smaller portion (“wanted” side effect). Consider “unmasking gastroparesis.” Use ER/XR form of metformin.

D’Allesio DA and Hirsch IB. Glycemic Management of Type 2 DM. Translational Endocrinology & Metabolism. 2011; 2(1):75.

GLP-1 agonist

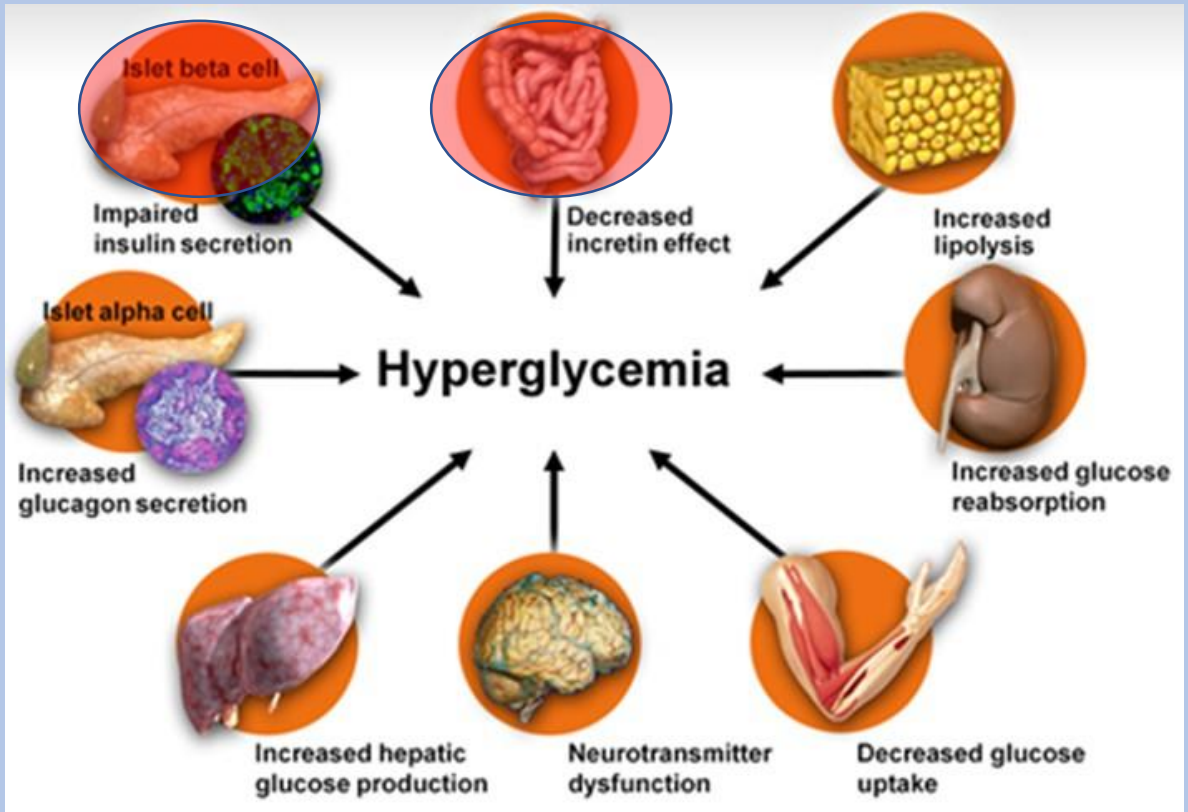
- Warning: ?Pancreatitis, ?Pancreatic cancer
- Boxed warning
  - Thyroid C-cell Tumor risk

  *Multiple Endocrine Neoplasia 2
    - Medullary Thyroid Carcinoma
    - Pheochromocytoma
    - Hyperparathyroidism

HYPO	Neutral	FPG	Mild
WEIGHT	Neutral	PPG	Mod

DPP4 inhibitors

CV effects		
ASCVD	HF	CKD
neutral	Potential risk: saxagliptin	neutral



Handelsman Y et al. Endocr Pract. 2015;21(suppl 2):14 / DeFronzo RA. Diabetes. 2009;58:773-795

- Sitagliptin (Januvia)
- Saxagliptin (Onglyza)
- Linagliptin (Tradjenta)
- Alogliptin (Nesina)

DPP4 inhibitors

- Lowers A1c by 0.5-0.8%
- $$$ (generic alogliptin(Nesina)?)
- Well tolerated
- Heart failure risk? (saxagliptin, alogliptin)
- Pancreatitis, pancreatic cancer?
- Severe joint pain?

D'Allesio DA and Hirsch IB. Glycemic Management of Type 2 DM. Translational Endocrinology & Metabolism. 2011; 2(1):75.

Maria

- Added empagliflozin (Jardiance) 10mg/d.
- Advised to be consistent with metformin.
- Referred back to nutritionist but deferred. Will work on her own and will resume exercise as well.
- Increased atorvastatin to 40mg.

- Over the years, her DM progressed and added Liraglutide.
- She turned 65 and went on medicare. Her cost of antiDM meds got too expensive and asks for cheaper medications

Q

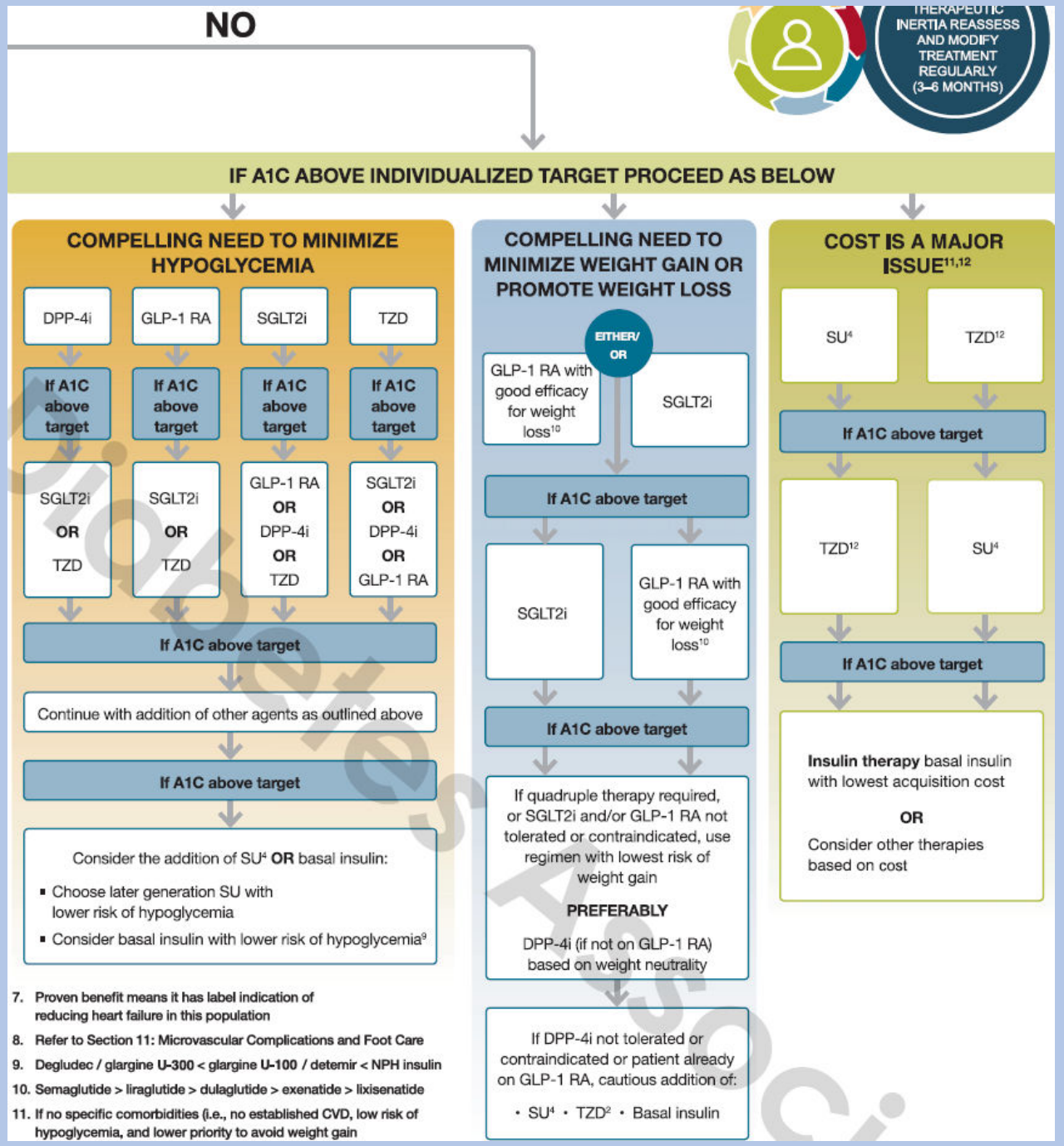
- Which of the following has the highest risk for hypoglycemia?

A. Metformin
B. Sulfonylurea
C. Thiazolidinedione
D. GLP-1 RA
E. SGLT-2 inhibitors

Q

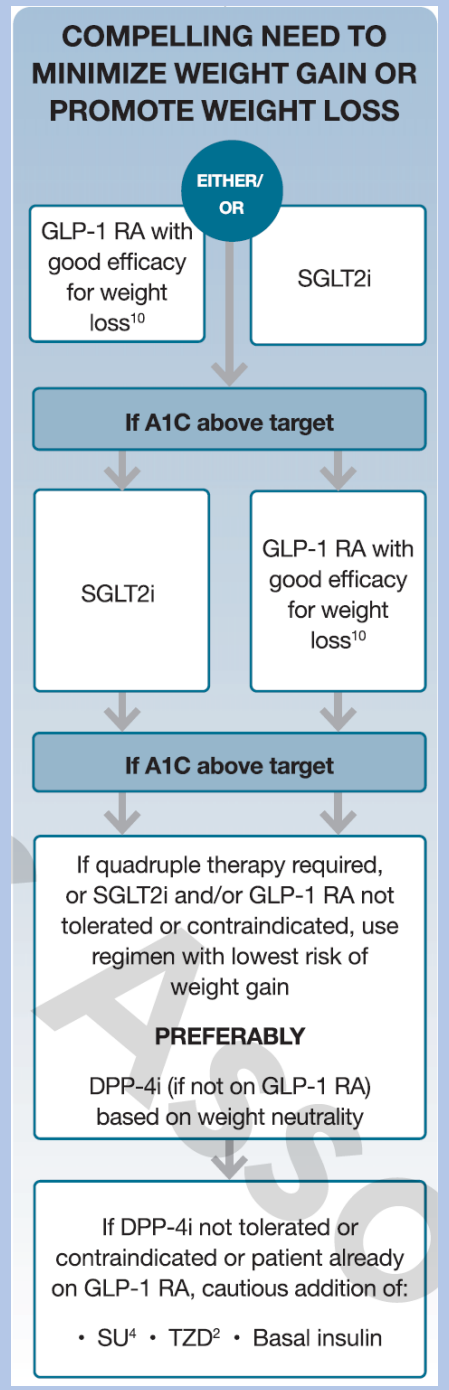
- When obesity is a major concern, which agent should be avoided?

A. Metformin
B. SU
C. TZD
D. GLP-1 RA
E. SGLT-2 inhibitors



Without apparent risk of ASCVD/HF/CKD

- Risk of hypoglycemia
- Weight
- Cost



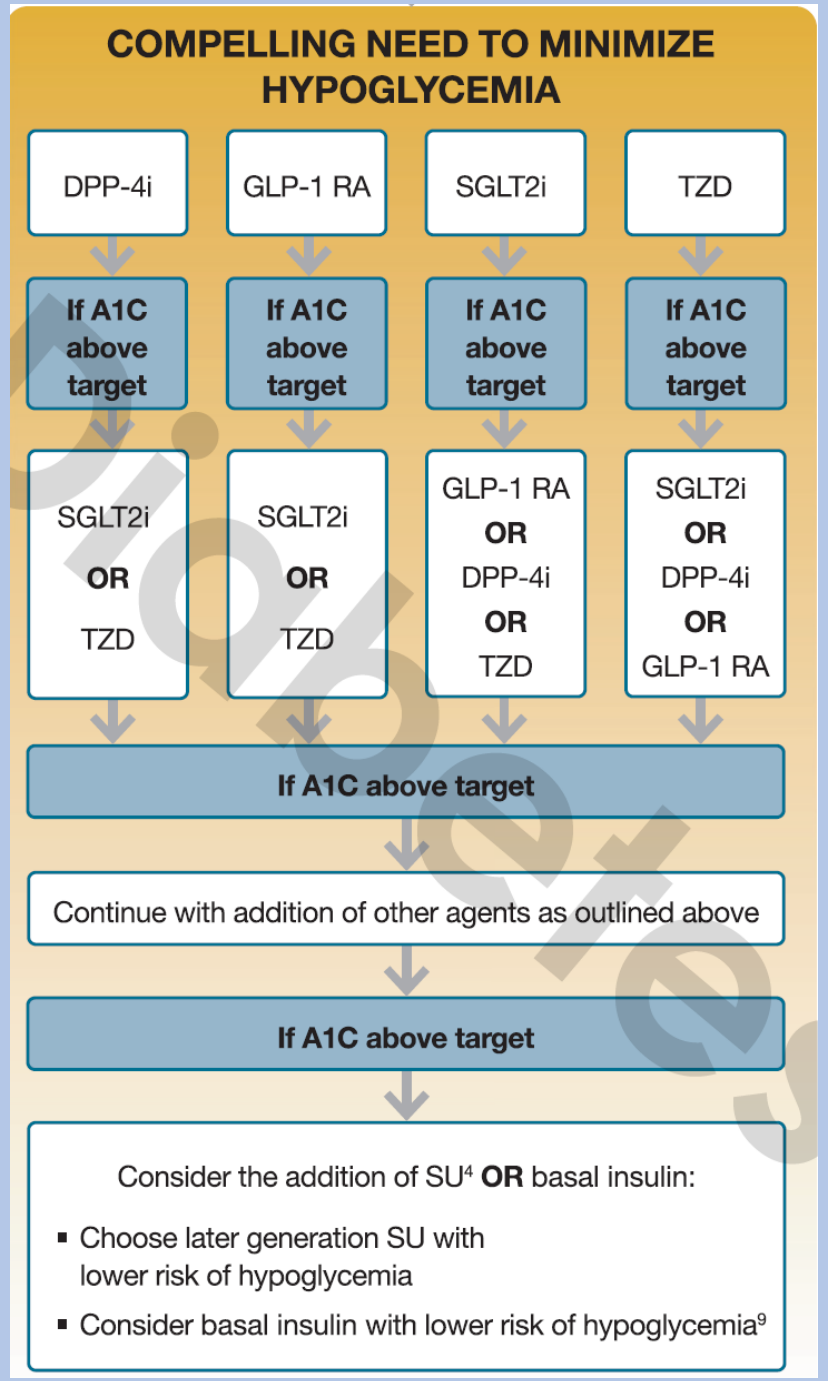
Weight Loss Desired

- GLP1 RAs:

  Semaglutide > Liraglutide > Dulaglutide > exenatide ER

- SGLT-2 inhibitors

  (no superiority among class)



Minimize hypoglycemia

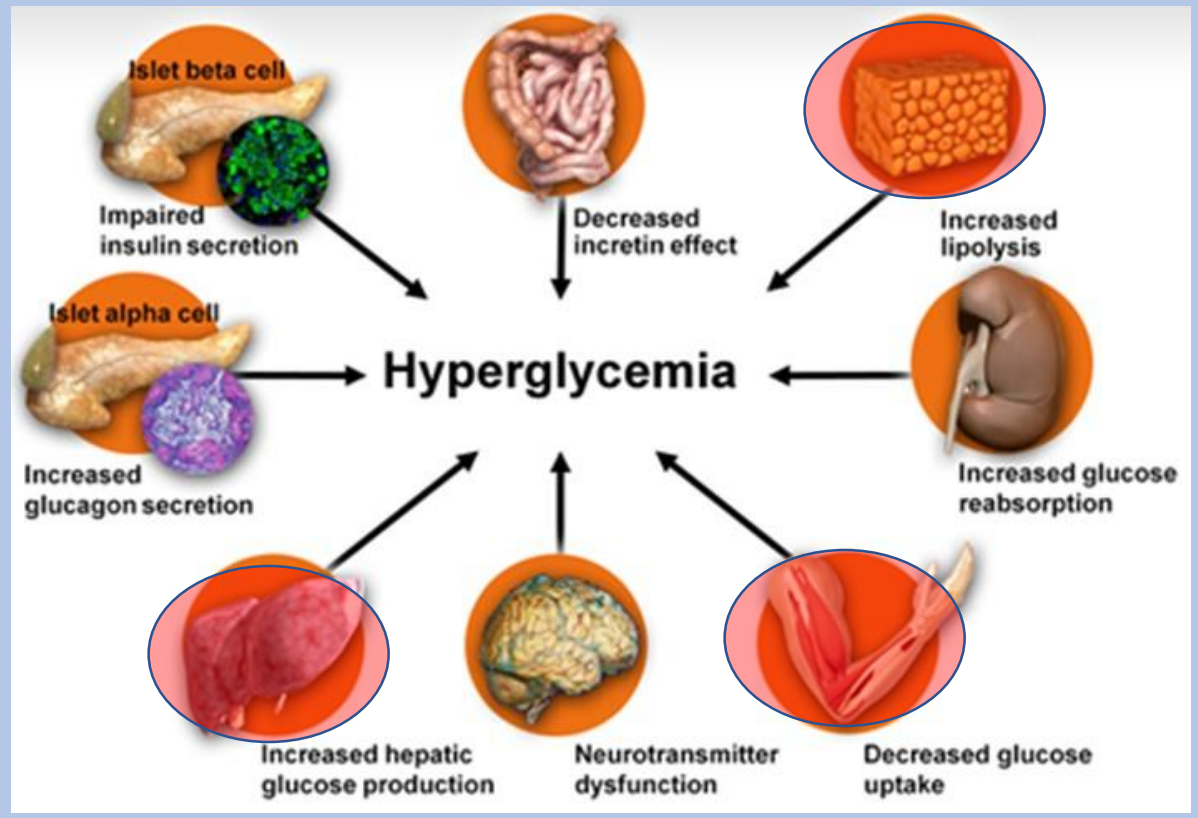
- DPP4 inhibitors
- GLP1 RAs
- SGLT-2 inhibitors
- Thiazolidinediones

*avoid sulfonylurea, insulin

HYPO	Neutral	FPG	Mod
WEIGHT	Gain	PPG	Mild

Thiazolidinediones (TZD)

CV effects		
ASCVD	HF	CKD
Potential benefit	risk	neutral



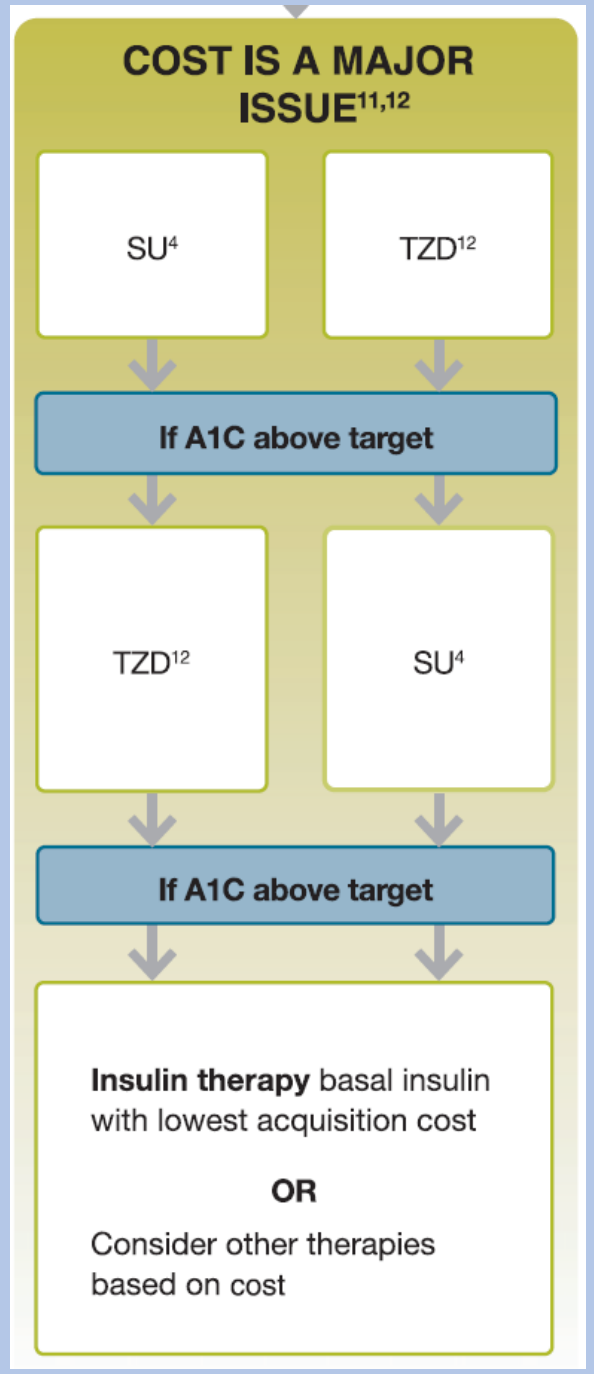
Handelsman Y et al. Endocr Pract. 2015;21(suppl 2):14 / DeFronzo RA. Diabetes. 2009;58:773-795

- Pioglitazone (Actos)

Thiazolidinediones (TZD)

- Lowers A1c by 1-1.5%
- $$ (generic pioglitazone)
- SEs: weight gain, fluid retention / CHF
  - Use low dose

  Fracture: caution in post menopausal women

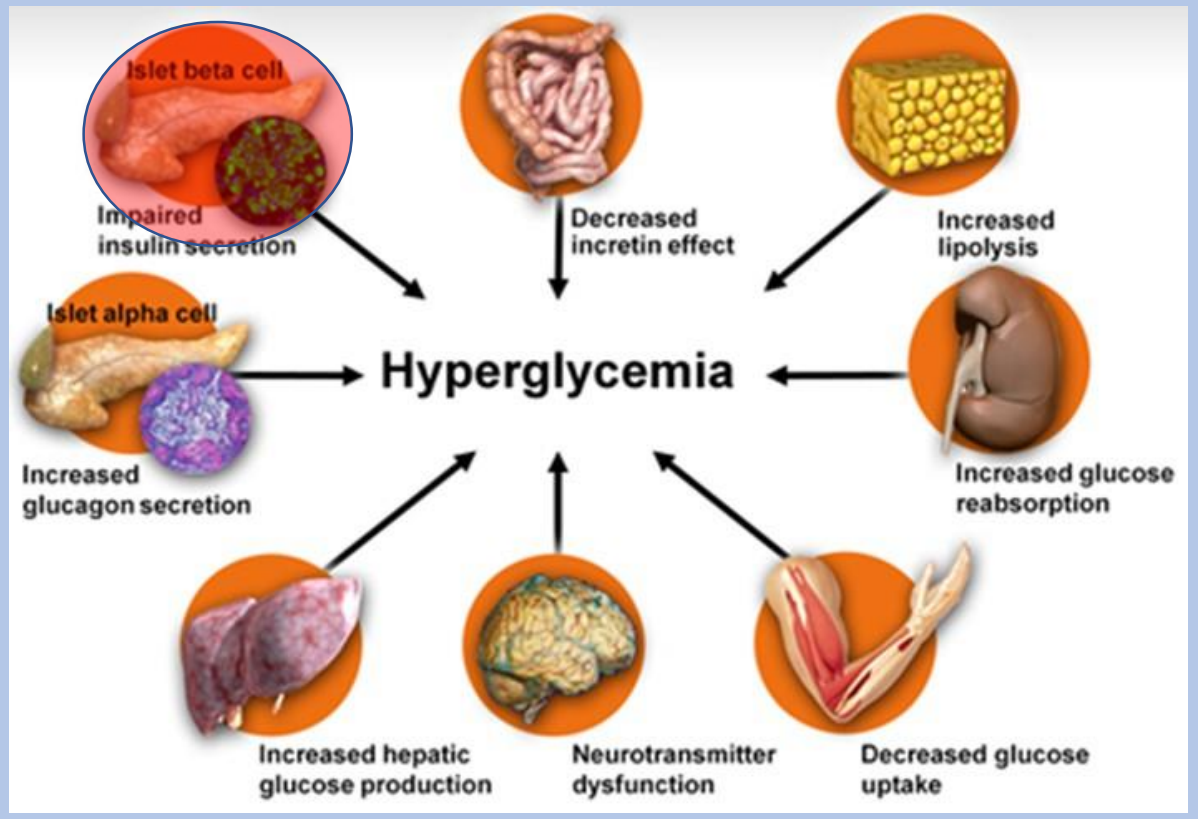


Acquisition Cost

- Sulfonylurea
- Thiazolidinedione
- Low cost Insulin
  - Relion from Walmart
    Novolin N, R, 70/30mix
  ~$25 per vial (1,000 units)
  Can be purchased without Rx

	SU / GLN	FPG	SU: Mod Glinide: Mild
HYPO	Moderate/ Severe / Mild		
WEIGHT	Gain	PPG	Mod

CV effects		
ASCVD	HF	CKD
neutral		



Handelsman Y et al. Endocr Pract. 2015;21(suppl 2):14
/ DeFronzo RA. Diabetes. 2009;58:773-795

Sulfonylureas

- Glyburide
- Glipizide
- Glimepiride

Meglitinides

- Nateglinide (Starlix)
- Rapeglinide (Prandin)

Sulfonylureas/Meglitinides

- Lowers A1c by ~1.5%
- $
- Insulin secretogauge
- SEs: weight gain. Hypoglycemia
  - Use with caution. Know the mechanism, length of action. Avoid using glyburide

D'Allesio DA and Hirsch IB. Glycemic Management of Type 2 DM. Translational Endocrinology & Metabolism. 2011; 2(1):75.

Maria

- After dual/triple/quadruple therapy, Maria diabetes progresses.
- Due to low back pain and knee pain (OA), exercise is limited. She eats out of boredom

Insulin Initiation and Titration in Patients With Type 2 Diabetes

Ji Chun,[1] Jodi Strong,[2] and Scott Urquhart[3]

■ ABSTRACT

Insulin initiation and titration can be challenging for many primary care providers who are involved in the treatment of patients with type 2 diabetes. Despite the introduction of advanced insulin analogs and improvements in insulin delivery devices, many patients with type 2 diabetes continue to experience suboptimal glycemic control. With an increasing number of treatment options available, type 2 diabetes management is moving away from a "one-size-fits-all" approach and toward individualized treatment regimens based on particular patient needs. Given this, nurse practitioners, physician assistants, pharmacists, and certified diabetes educators are becoming increasingly valuable resources in busy primary care practices.

Insulin initiation and titration is a challenge for many primary care providers (PCPs) involved in the treatment of patients with type 2 diabetes (1). Clinical inertia, the failure to initiate or intensify insulin therapy when indicated, is a multifactorial problem resulting from barriers to insulin initiation and intensification, including treatment regimen inconvenience, needle phobia, and fear of hypoglycemia (2–5) and has important consequences for patients, significantly increasing the risk of microvascular complications such as retinopathy, nephropathy, and neuropathy (6).

A desirable basal insulin therapy regimen includes an insulin analog possessing a pharmacokinetic profile that mimics the naturally occurring basal endogenous insulin secretion profile, which can provide adequate and reproducible glucose control. Basal insulin analogs from recombinant DNA technology represent a significant advancement from human NPH insulin, an intermediate-acting insulin that, despite the need for twice-daily dosing and a relatively high incidence of hypoglycemia, remains in use today (7). The first-generation basal insulin analogs, insulin glargine 100 units/mL (Gla-100) and insulin detemir 100 units/mL provided a near–24-hour glucose-lowering effect with low variability in insulin action and a lower incidence of hypoglycemia than NPH insulin (8). The more recently approved second-generation basal insulin analogs, insulin glargine 300 units/mL (Gla-300) and insulin degludec 100 units/mL (IDeg U100) or 200 units/mL (IDeg U200), with their prolonged duration of action and more evenly distributed activity profiles, are associated with reduced incidences of hypoglycemia and similar A1C control compared to earlier basal analogs (9,10). They also provide the advantage of once-daily dosing with reduced intra-individual variability (11).

Despite the introduction of insulin analogs, refinement of insulin regimens, and improvements in injection devices such as pens with fine-gauge needles, advocacy for early

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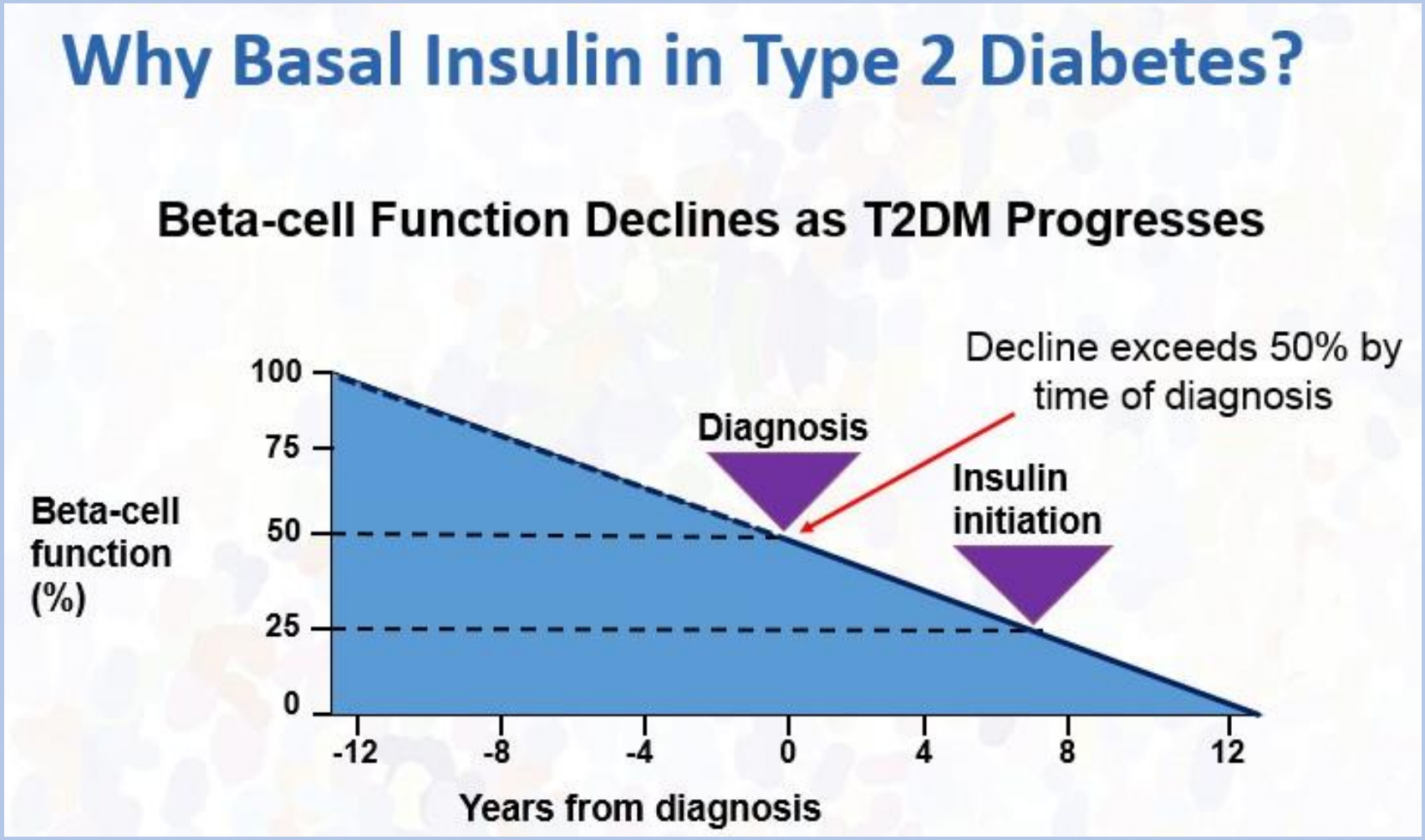
When to start insulin?

How to start?

How to titrate?

When to stop pushing basal and add prandial control?

Why Basal Insulin in Type 2 Diabetes?



Lebovitz H. Diabetes Rev. 1999;7:139-153

Consider Insulin

- Not reaching goal with multiple noninsulin options
- Very high A1c (>11%)
- Symptoms/evidence of catabolism (weight loss, polyuric/polydipsic)
- DM 1 is a possibility

*Basal insulin as first insulin choice

Comparison of Basal Insulins

Basal Insulin	Starting dose	Onset of Action*	Peak	Duration of action*	Rate of severe hypoglycemia†
NPH	0.2 U/kg/d	1-3 h	4-12 h	12-16 h	2.6%
Detemir (Levemir)	10 U qd in the evening	1-3 h	6-8 h	12-24 h	0.4 – 1%
Glargine (Lantus, Basaglar)	0.2 U/kg or up to 10 U qd	1-3 h	No pronounced peak	Up to 24 h	1.4%
Glargine U-300 (Toujeo)	0.2 U/kg or up to 10 U qd	6 h	No pronounced peak	>30 h	0.9 – 1%
Degludec U100 or U200 (Tresiba)	10 U qd	0.5-1.5 h	No pronounced peak	42 h or more	0.3 – 0.9%

*The time course of action of insulins may vary between individuals and within the same individual.

†Rates of severe hypoglycemia depend on the definition used, insulin dose, intensity of glucose control, background therapies, and other intrinsic and extrinsic patient factors.

DailyMed. https://dailymed.nlm.nih.gov/dailymed/index.cfm.; DiabetesNet. http://www.diabetesnet.com/about-diabetes/insulin/insulin-action-time. Lamos EM, et al. *Ther Clin Risk Manag*. 2016;12: 389-400 .Rosenstock J, et al. *Diabetes Care* 2005;28:950-955; Shubrook JH. *J Fam Prac.* 2014;63:76-81.



Initiation and titration

ADA[1]	AACE[2]	CDA[3]
• Start at 10 U/d • Increase 2-4 U 1-2 times/wk until FPG target is reached*	• A1C <8.0: Start at 0.1- 0.2 U/kg • A1C >8.0: Start at 0.2-0.3 U/kg • Increase by 2 U/d every 2-3 d until FPG target is reached*	• Start at 10 U/d at bedtime • Increase 1 U/d until FPG target is reached

Fasting target: < 120 or less
(adjust depending on patient age/risk/comorbidities)

1. American Diabetes Association. *Diabetes Care.* 2017;40(Suppl. 1):S48–S56.
2. American Association of Clinical Endocrinologists. 2017 aace.com/publications/algorithm.
3. Diabetes Canada. *Can J Diabetes* .2013; 37:S197–S212 guidelines.diabetes.ca/browse/appendices/appendix3

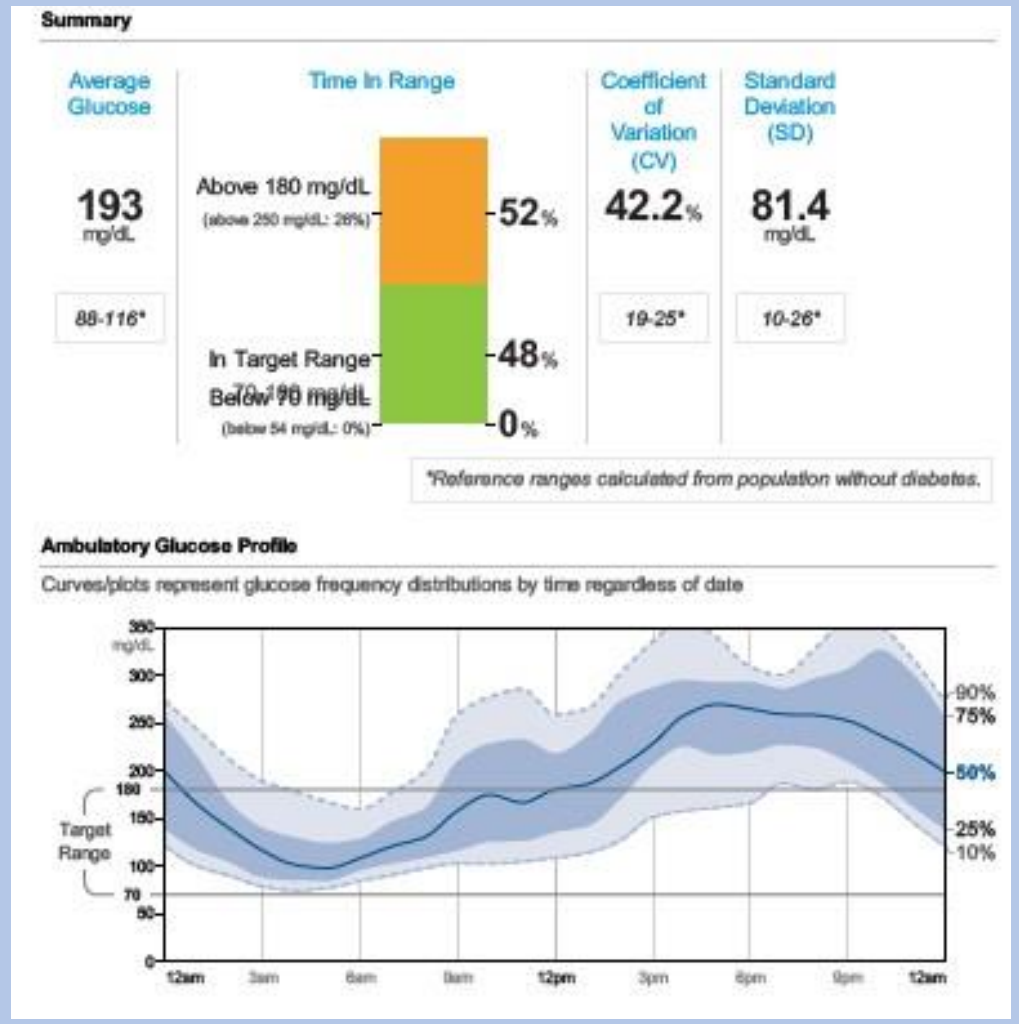
Q

- Which of the following is sign of overbasalization?
  - A. High FPG and high A1c
  - B. > 50-pt drop in glucose overnight
  - C. Daytime hypoglycemia
  - D. > 2.0 U/kg/d on basal insulin

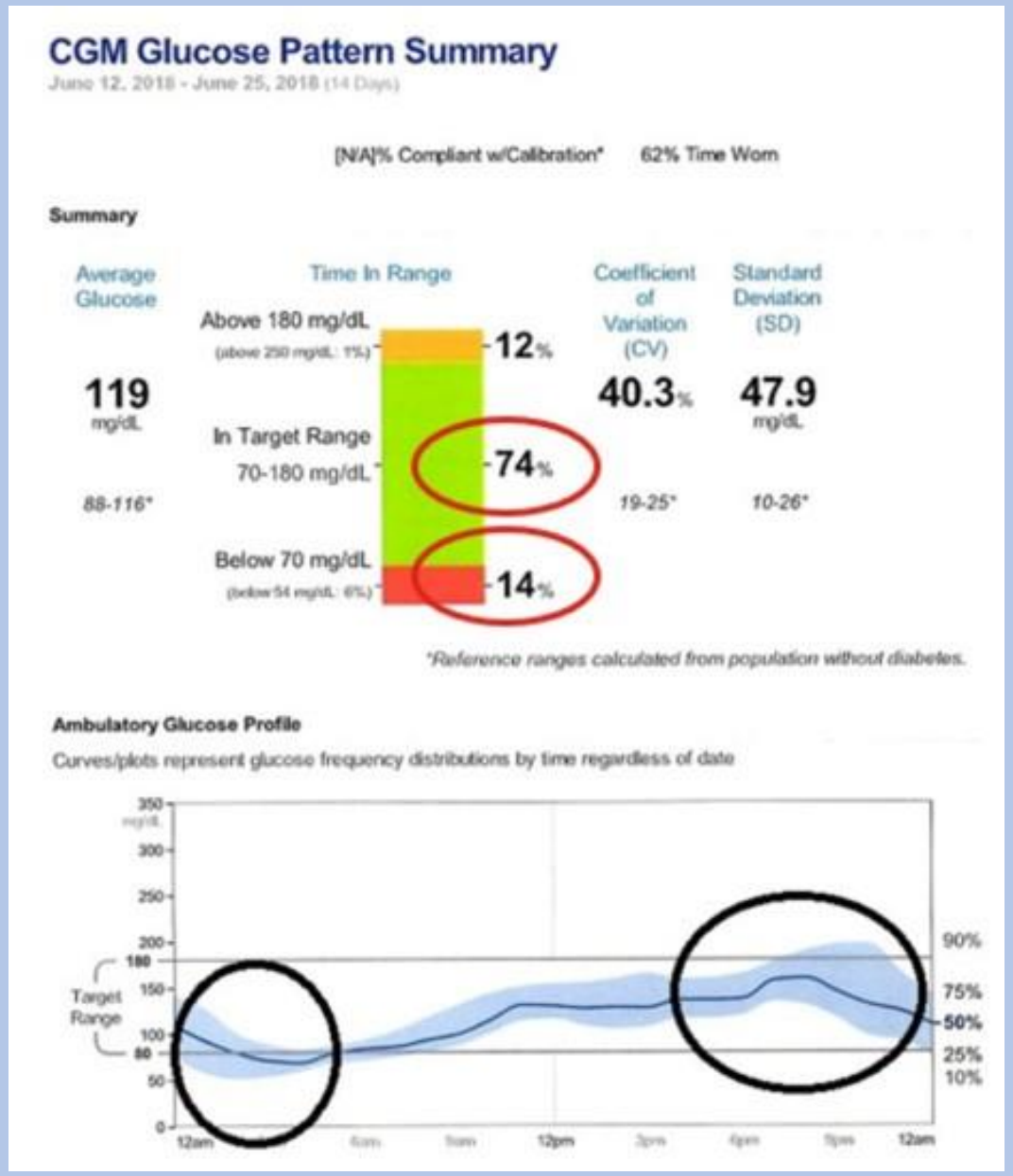
When to add prandial control?

- “Overbasalization”
  - FPG at or below target but high A1c
  - >50-pt drop in glucose overnight
  - Nocturnal hypoglycemia
  - >0.5 U/kg/d on basal insulin

Overbasalization



- FPG at or below target but high A1c
- **>50-pt drop in glucose overnight**
- **Nocturnal hypoglycemia**
- >0.5 U/kg/d on basal insulin



- FPG at or below target but high A1c
- **>50-pt drop in glucose overnight**
- **Nocturnal hypoglycemia**
- >0.5 U/kg/d on basal insulin

Adding prandial control

- GLP (if not already on). Available as fixed dose combination w/ basal
  - Glargine/lixesenatide, degludec/liraglutide
- Bolus insulin
  - Human (Novolin R, Humulin R),
    Analog (lispro/aspart/glulisine), ultra-rapid, inhaled
- Premixed insulin
  - 70/30 mix, 75/25 mix, 50/50 mix
- Concentrated insulin (for severe insulin resistance)
  - Humulin U500

Adding prandial control

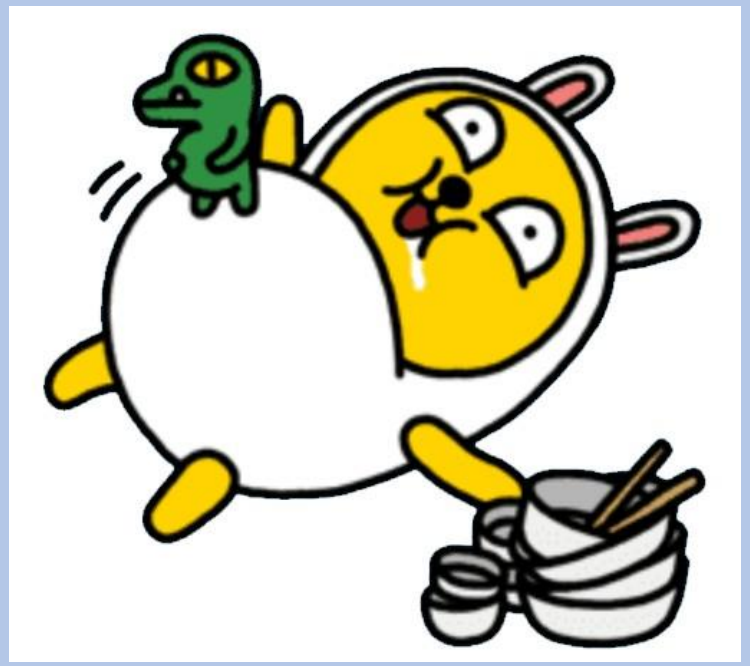
- Prandial insulin
  - Start with biggest meal of the day and escalate
  - Start with 4units or 10% of basal dose at each meal
  - Consider reducing basal
- Premixed insulin
  - 70/30 and 75/25: give 2/3 with breakfast, 1/3 with dinner
  - 50/50: 1/3 with each meal

***when adding prandial insulin, consider stopping SU, DPP4i**

Don’t Forget!!

- Always lifestyle intervention first, last, and anytime in-between





Questions

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