Diabetes Treatment: Beyond Metformin

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Disclosure Statement

- Financial Disclosure: Azra Khan has no financial conflicts of interest to disclose.

- Government Disclosure: Azra Khan is a government employee. All authored materials are the personal statements of Azra Khan and are not intended to constitute an endorsement by the US Army or any other federal government entity.

Objectives

- PreDm and T2DM prevalence
- Review pathophysiology of T2DM (‘ominous octet’)
- Review traditional agents for the treatment of T2DM
- Describe the kidney’s response to hyperglycemia and role of SGLT2i therapy
- Explain the incretin effect and glucose depended insulin release from GLP1 therapy
- Review newer concentrated basal insulins

PREDIABETES

COULD IT BE YOU?

96 Million

96 million American adults—**more than 1 in 3**—have prediabetes

More than 8 in 10
adults with prediabetes **don't know they have it**

BLOOD SUGAR

With prediabetes, your **blood sugar levels are higher than normal**, but not high enough yet to be diagnosed as type 2 diabetes

PREDIABETES RISKS

Prediabetes increases your risk of:

TYPE 2 DIABETES HEALTH RISKS

If you ignore prediabetes, your risk for type 2 diabetes goes up — **type 2 diabetes increases your risk for serious health complications:**

DIABETES IN THE U.S

A SNAPSHOT

DIABETES

37 Million

37 million people **have diabetes** — That's about **1 in every 10** people — **1 in 5** people **don't know they have it**

PREDIABETES

96 Million

96 million American adults—**more than 1 in 3**—have prediabetes

More than 8 in 10
adults with prediabetes **don't know they have it**

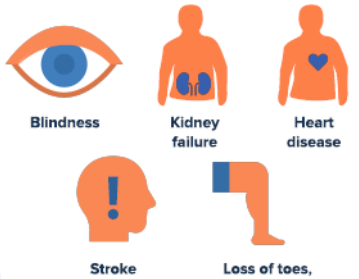
COST

$327 Billion
Total medical costs & lost work & wages for people with diagnosed diabetes

Medical costs for people with diabetes are **more than twice as high** as for people without diabetes

RISKS

People who have diabetes are at **higher risk of serious health complications:**



Are you at risk for
type 2 diabetes?

WRITE YOUR SCORE IN THE BOX.

1. **How old are you?** .....
   Less than 40 years (0 points)
   40–49 years (1 point)
   50–59 years (2 points)
   60 years or older (3 points)

2. **Are you a man or a woman?** .....
   Man (1 point) Woman (0 points)

3. **If you are a woman, have you ever been diagnosed with gestational diabetes?** .....
   Yes (1 point) No (0 points)

4. **Do you have a mother, father, sister or brother with diabetes?** .....
   Yes (1 point) No (0 points)

5. **Have you ever been diagnosed with high blood pressure?** .....
   Yes (1 point) No (0 points)

6. **Are you physically active?** .....
   Yes (0 points) No (1 point)

7. **What is your weight category?** .....
   See chart at right.

Height	Weight (lbs.)		
4′ 10″	119–142	143–190	191+
4′ 11″	124–147	148–197	198+
5′ 0″	128–152	153–203	204+
5′ 1″	132–157	158–210	211+
5′ 2″	136–163	164–217	218+
5′ 3″	141–168	169–224	225+
5′ 4″	145–173	174–231	232+
5′ 5″	150–179	180–239	240+
5′ 6″	155–185	186–246	247+
5′ 7″	159–190	191–254	255+
5′ 8″	164–196	197–261	262+
5′ 9″	169–202	203–269	270+
5′ 10″	174–208	209–277	278+
5′ 11″	179–214	215–285	286+
6′ 0″	184–220	221–293	294+
6′ 1″	189–226	227–301	302+
6′ 2″	194–232	233–310	311+
6′ 3″	200–239	240–318	319+
6′ 4″	205–245	246–327	328+
	1 point	2 points	3 points
If you weigh less than the amount in the left column: 0 points			

Adapted from Bang et al., Ann Intern Med 151:775–783, 2009.
Original algorithm was validated without gestational diabetes as part of the model.

If you scored 5 or higher:

ADD UP YOUR SCORE.

You are at increased risk for having type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes, a condition in which blood glucose levels are higher than normal but not yet high enough to be diagnosed as diabetes. Talk to your doctor to see if additional testing is needed.

Type 2 diabetes is more common in African Americans, Hispanics/Latinos, Native Americans, Asian Americans, and Native Hawaiians and Pacific Islanders.

Higher body weight increases diabetes risk for everyone. Asian Americans are at increased diabetes risk at lower body weight than the rest of the general public (about 15 pounds lower).

The good news is you can manage your risk for type 2 diabetes. Small steps make a big difference in helping you live a longer, healthier life.

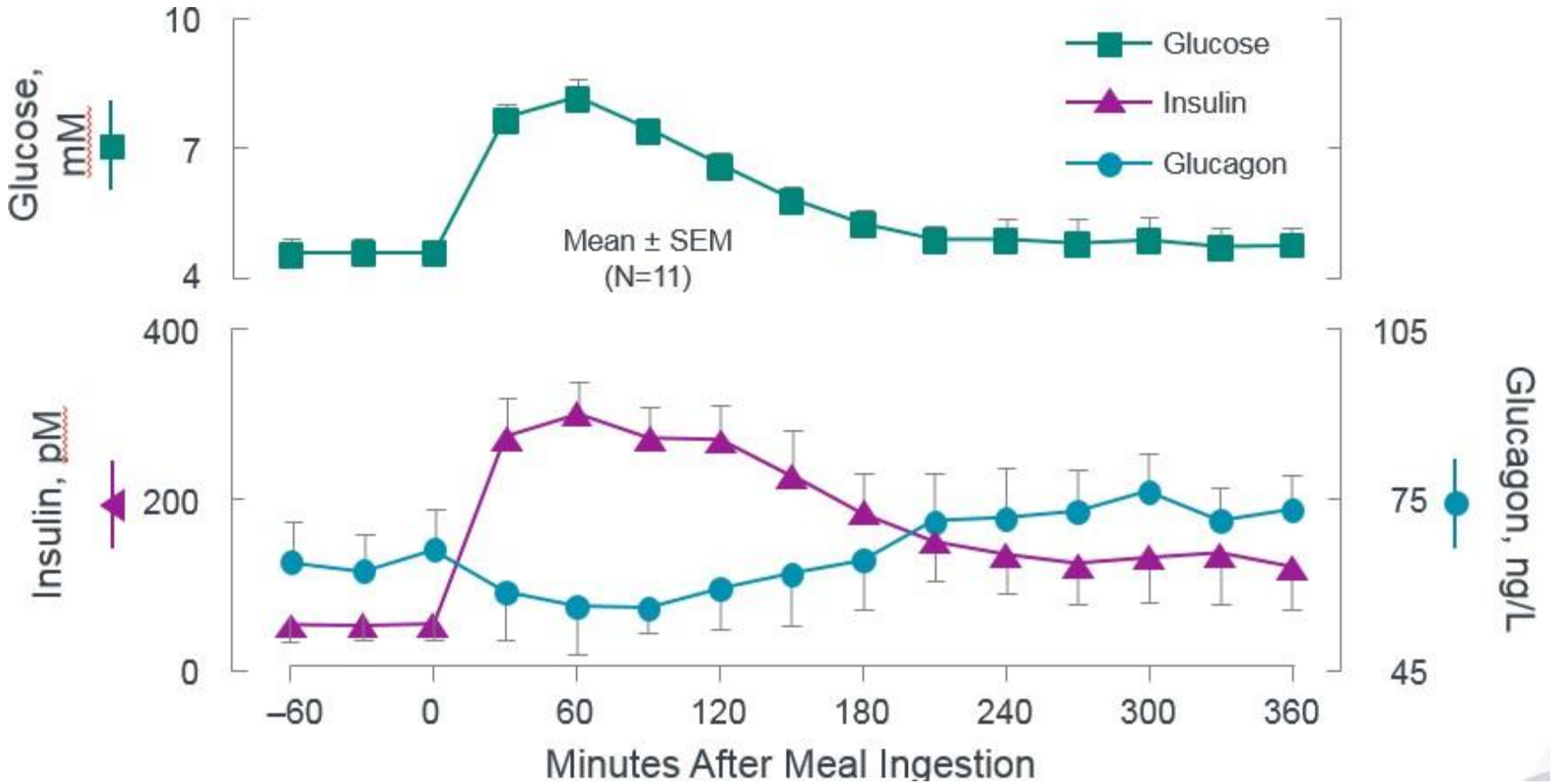
For more information, visit us at **diabetes.org/alertday** or call **1-800-DIABETES (800-342-2383).**

See your Primary Care Team for more information on your risk for type 2 diabetes.

American Diabetes Association.

Normal Glucose Physiology

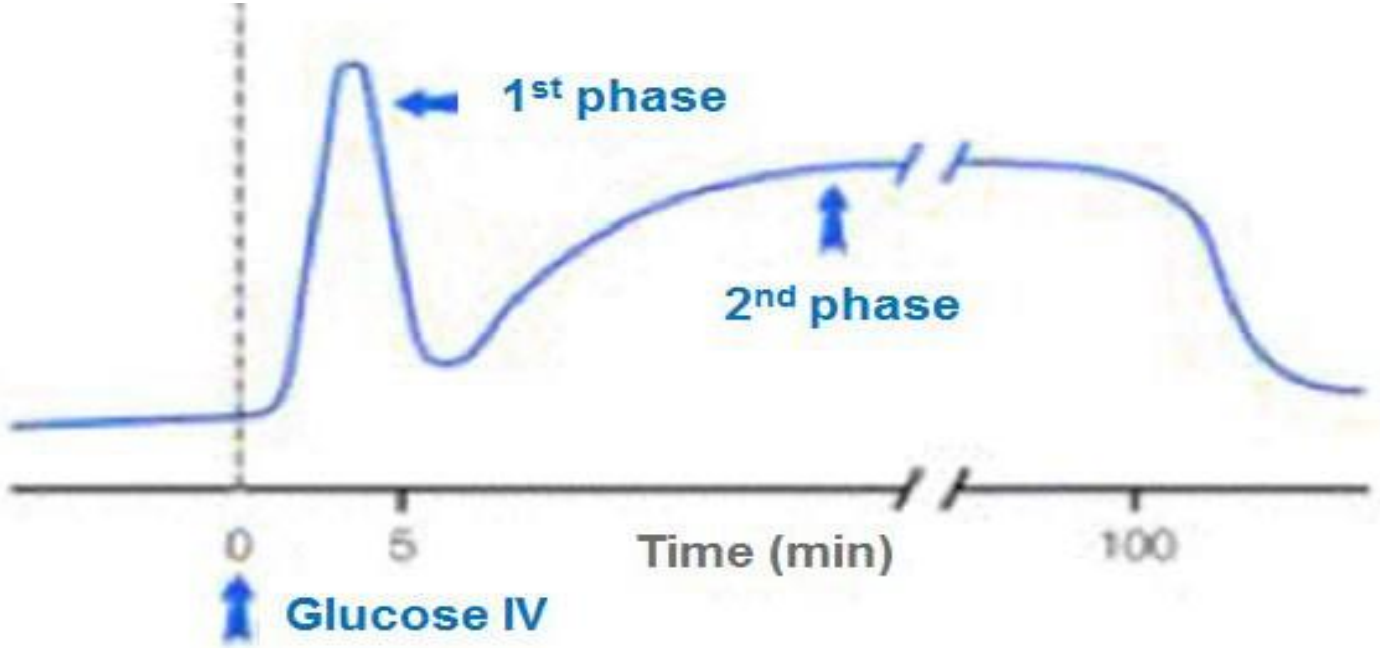
Insulin and Glucagon Meal Response: Normal



Woerle HJ et al. Am J Physiol Endocrinol Metab 2003;284

Normal Insulin Secretion

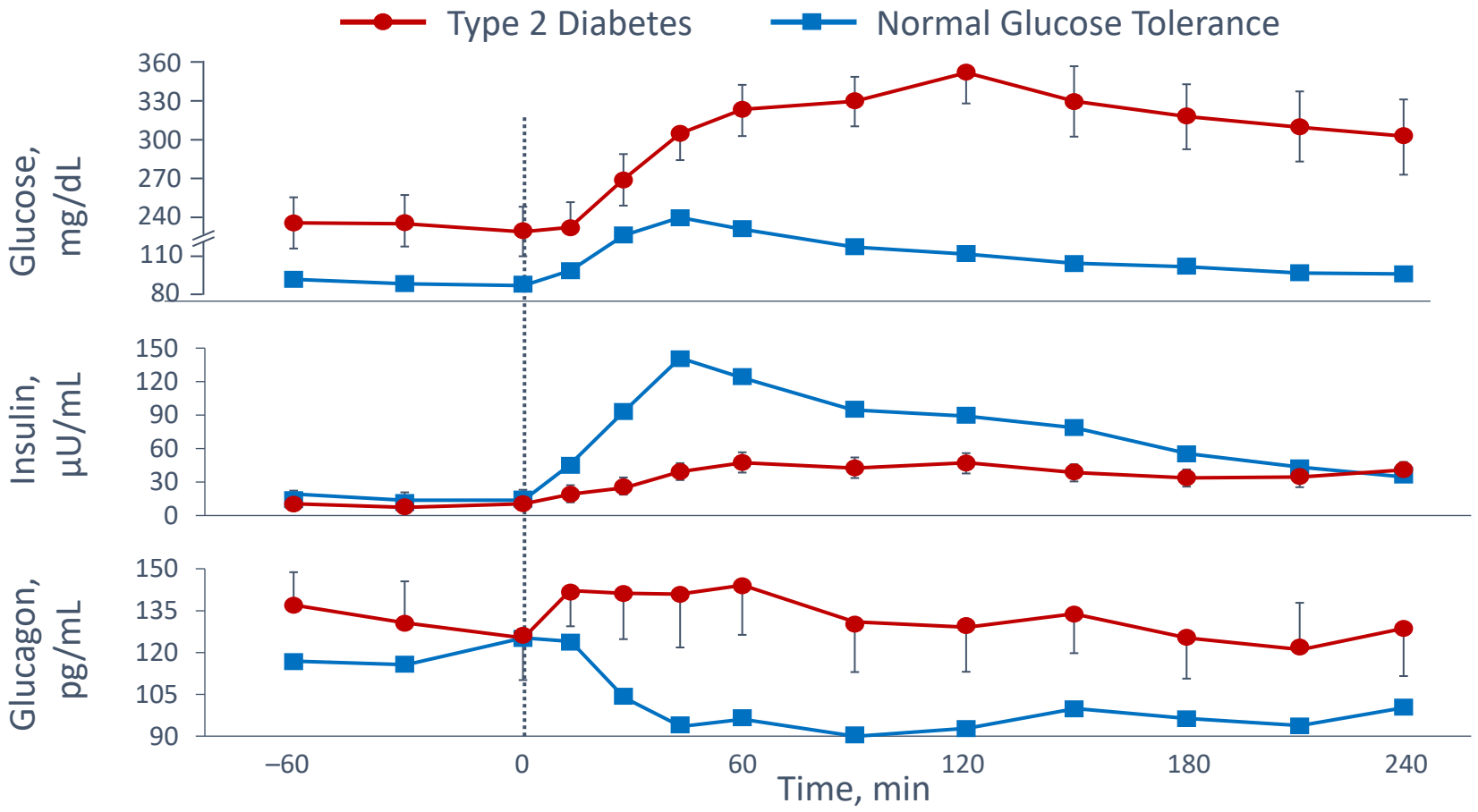
- 1st Phase
  - Readily releasable insulin within beta cells
  - Lost in DM2
- 2nd Phase
  - Sustained insulin release related to level of hyperglycemia



Physiologic Defects in TDM2

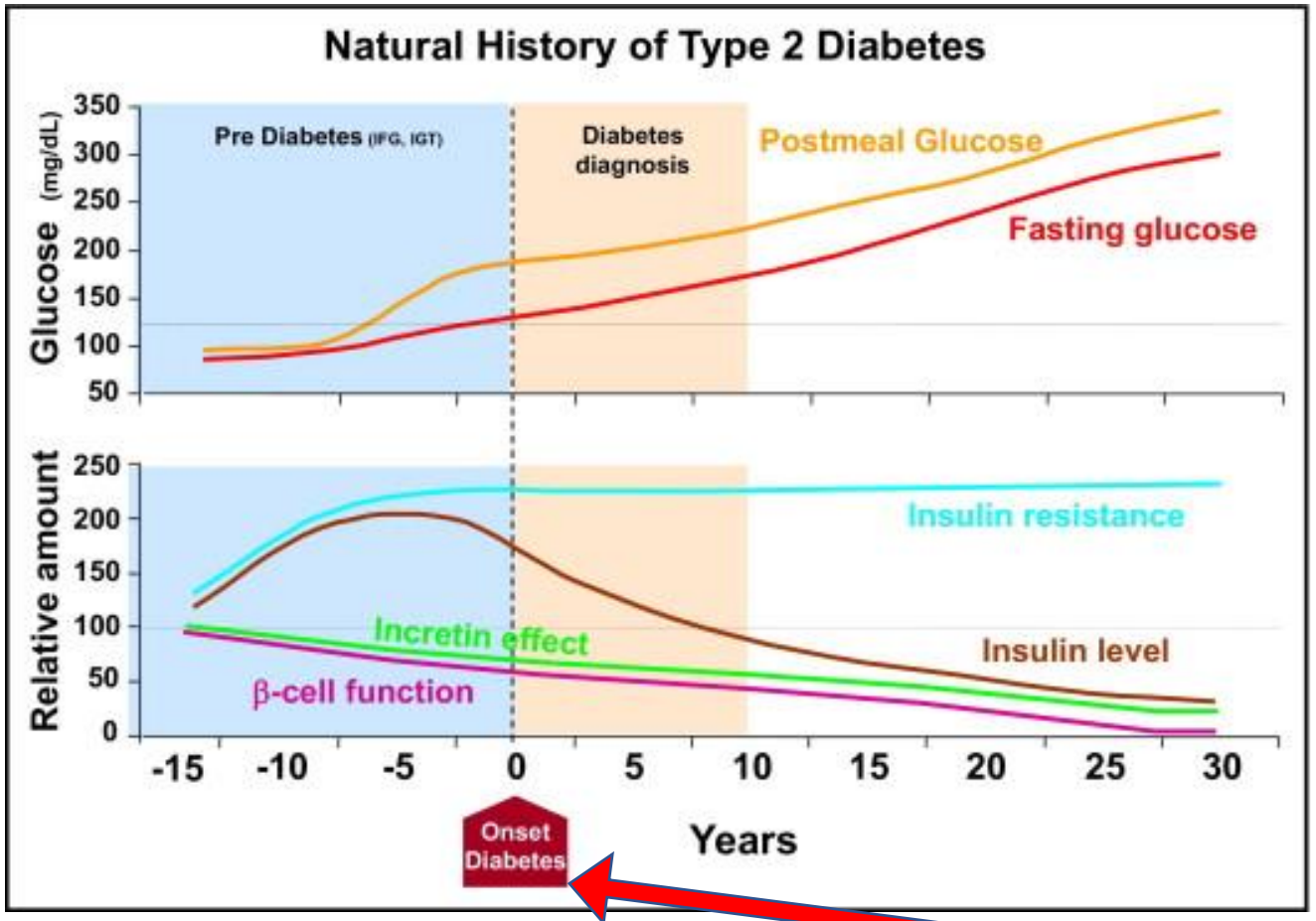
Insulin and Glucagon Meal Response: Abnormal

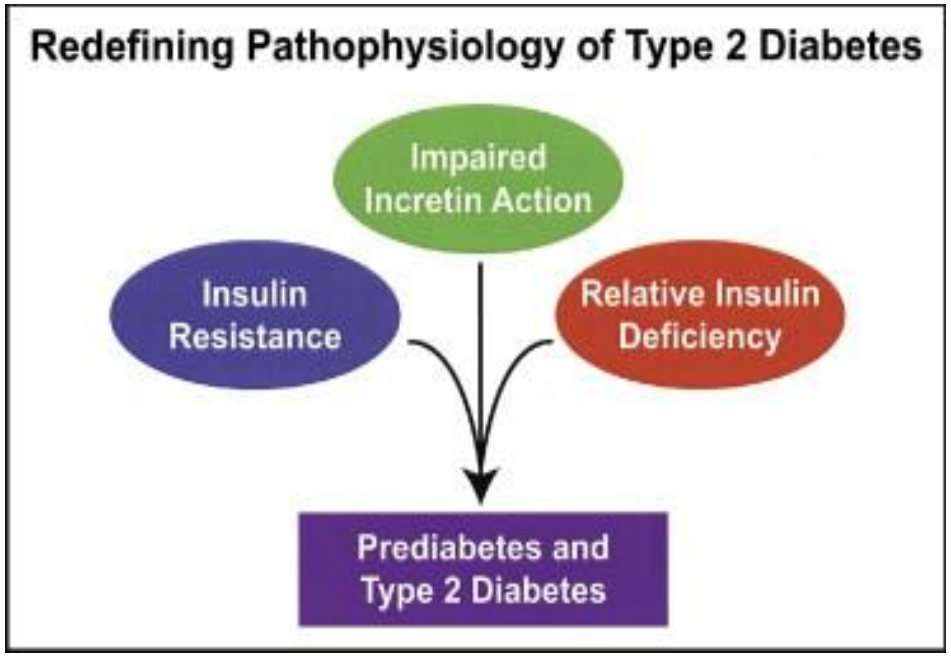
Following a carbohydrate meal: low insulin levels, and glucagon levels were not suppressed in patients with T2DM (n=12) compared to healthy subjects (n=14)



Müller WA et al. *N Engl J Med.* 1970;283:109–115.

Natural History of DM2





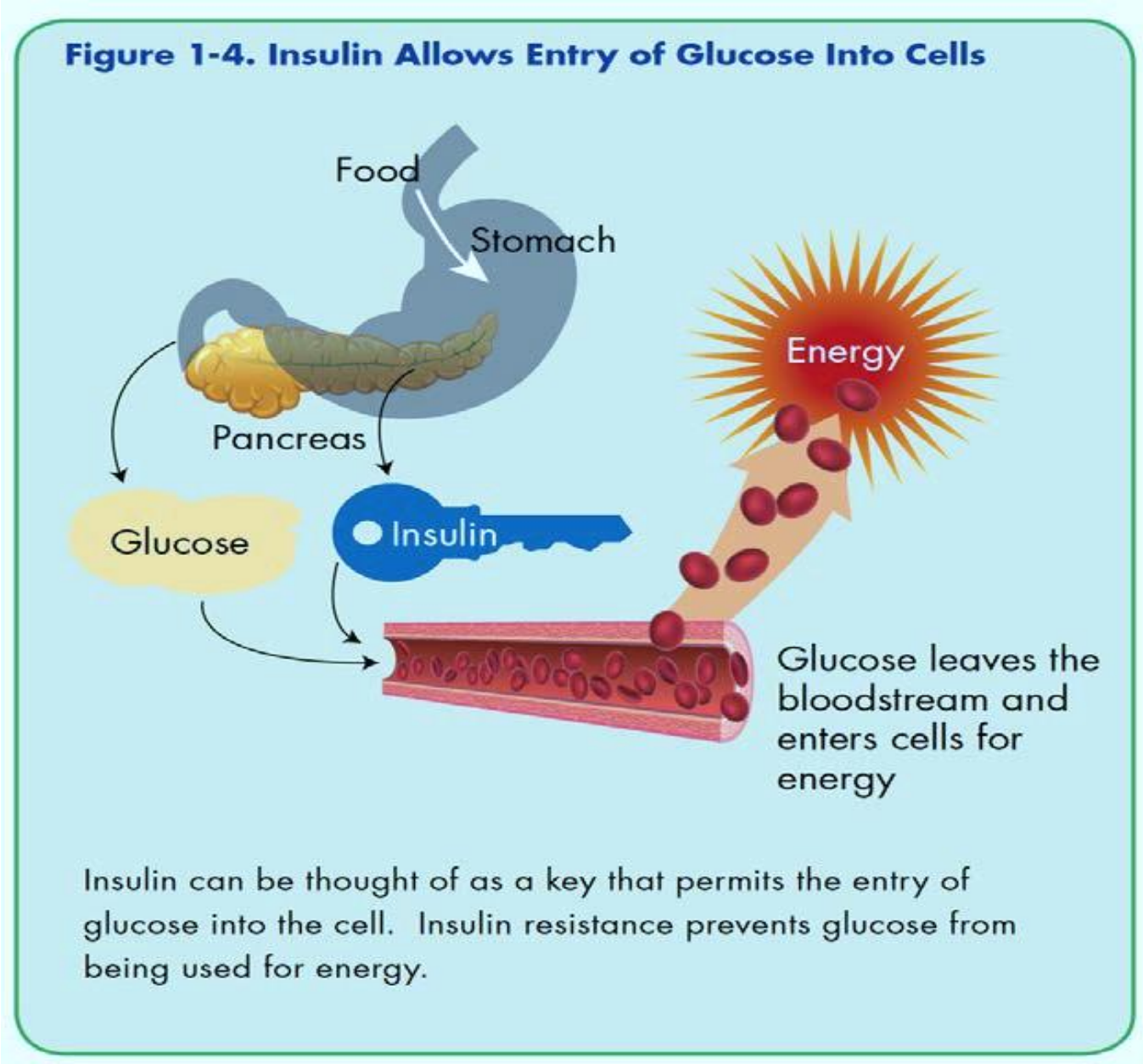
>50% loss of Beta-cell function at diagnosis

Insulin Resistance

Type II Diabetes

- Initially produce insulin
- Tissues do not response to it (resistance)
- This results in greater glucose production and hyperglycemia without satisfying the energy needs of the cells:

  Cells are STARVING!



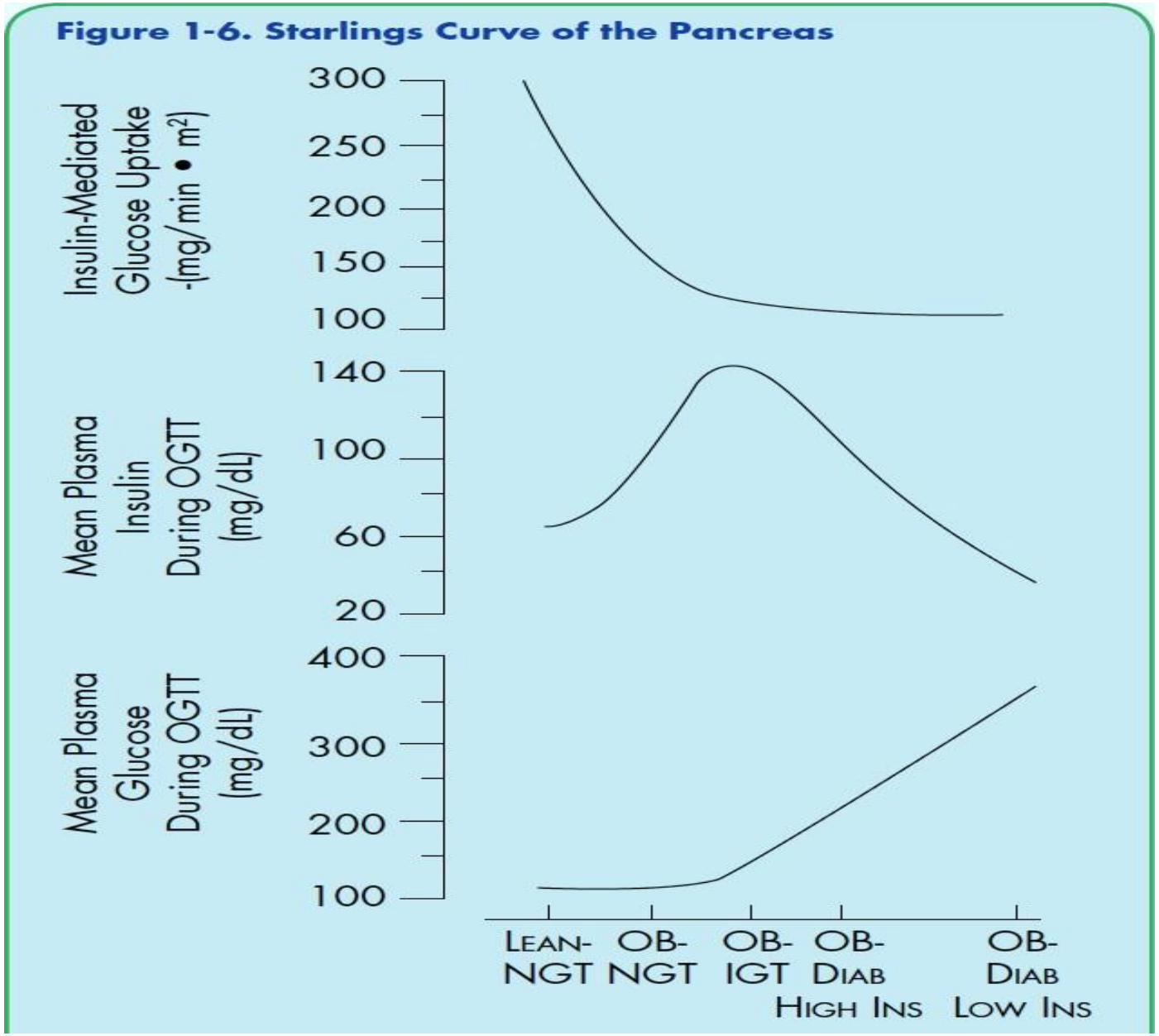
B-Cell failure

Risk Factors

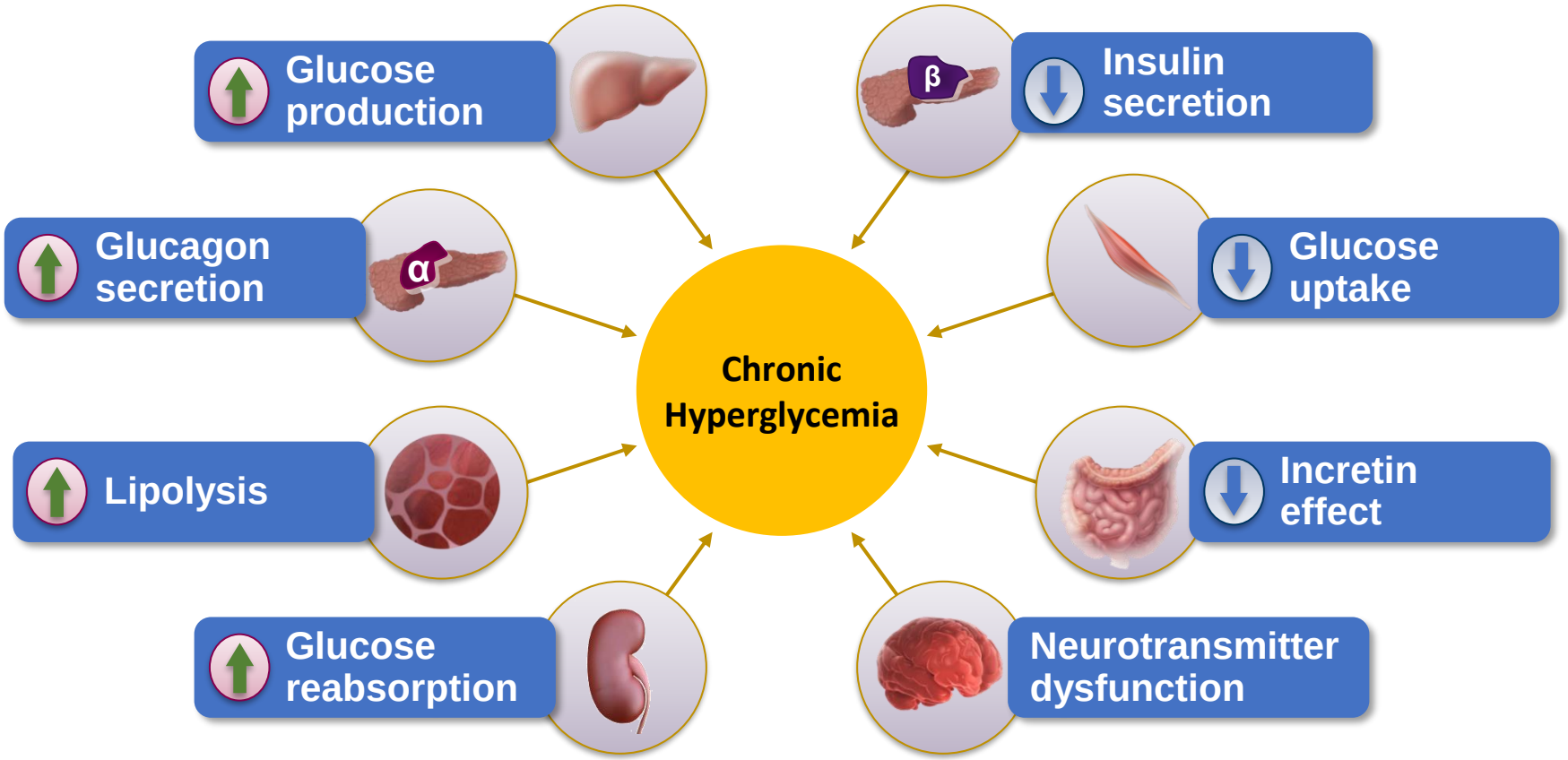
- Hyperglycemia
- Excess free fatty acids
- Age
- Genetics
- Insulin resistance

B-cell failure will determine the rate of diabetes progression

Starlings curve shows us the relationship between glycemia, insulin secretion and the diabetic state



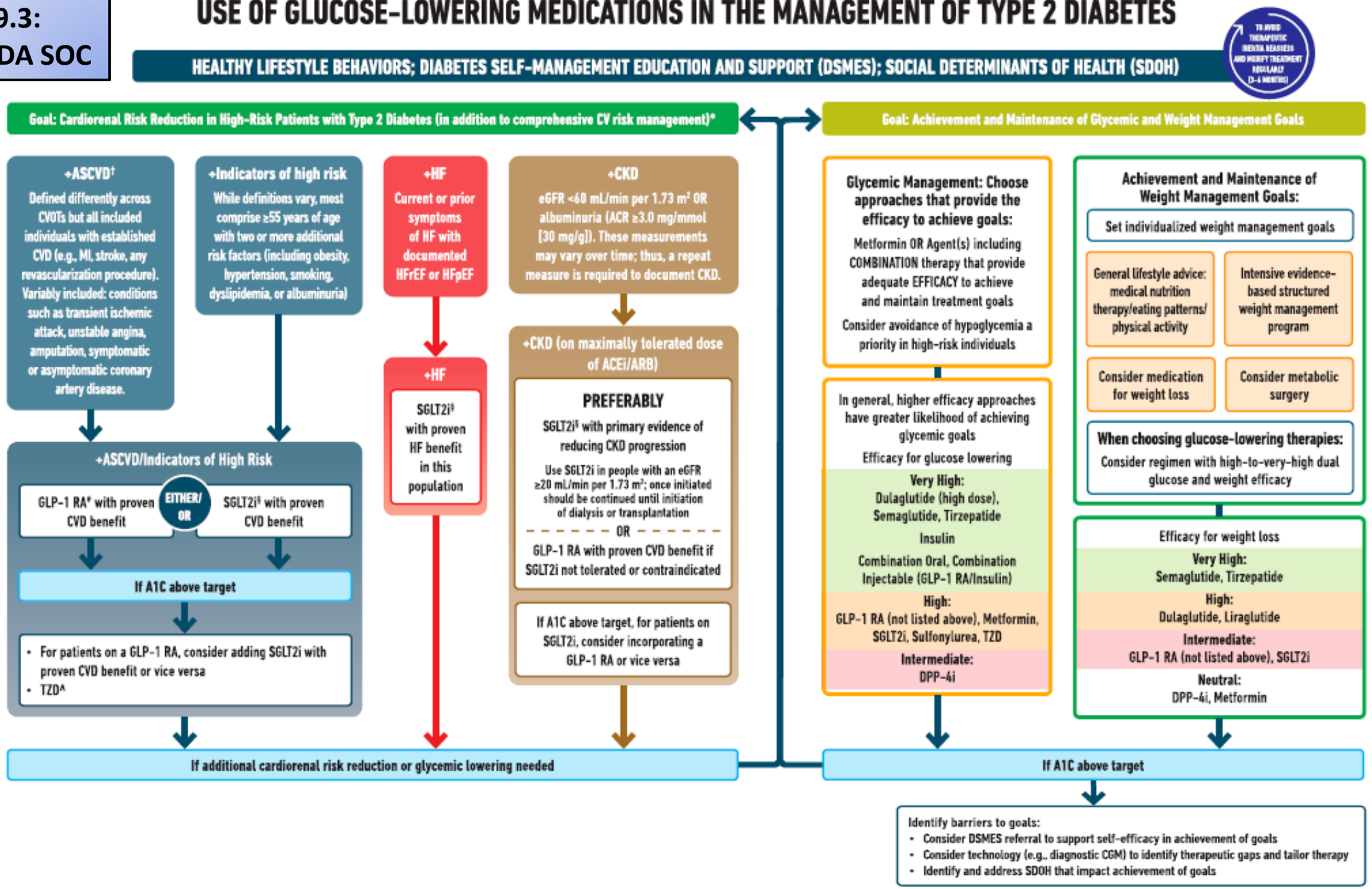
Ominous Octet



DeFronzo RA. *Diabetes*. 2009;58(4):773-795.

Medications for T2DM

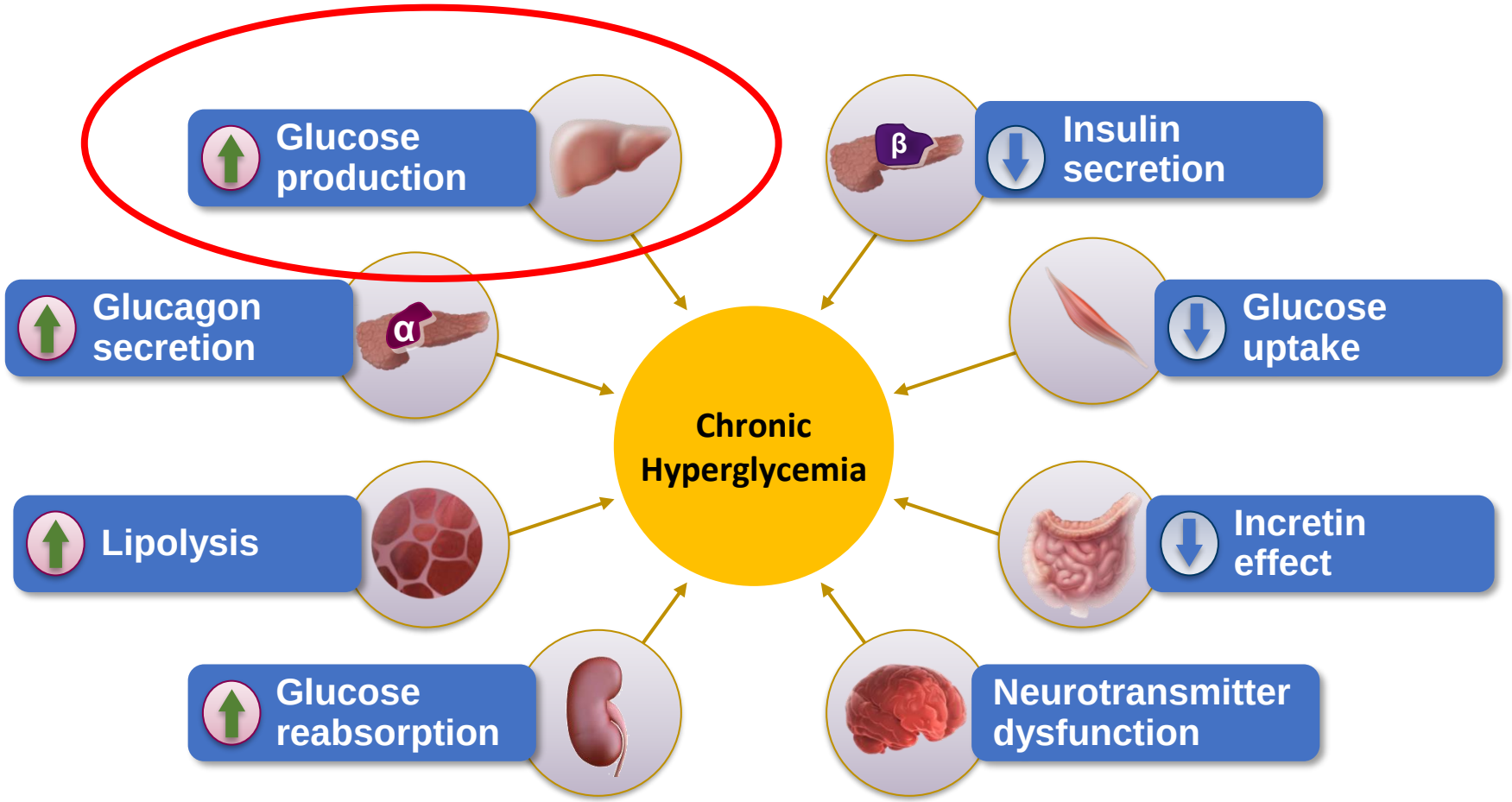
Figure 9.3: 2023 ADA SOC



Lowering Blood Glucose

- Remember, ONLY insulin directly lowers blood glucose
- Stimulate release of patient's insulin (make more insulin)
  - Sulfonylurea, DPP4i, GLP1 agonist
- Reduce insulin resistance (makes insulin more effective)
  - Metformin (liver), TZD (muscle/fat)
  - But still need insulin to lower glucose (endogenous/exogenous)
- Decrease glucose entering body (need less insulin)
  - SGLT2i, alpha glucosidase inhibitors
  - But still need insulin to lower glucose (endogenous/exogenous)

Ominous Octet: Metformin therapy



DeFronzo RA. *Diabetes*. 2009;58(4):773-795.

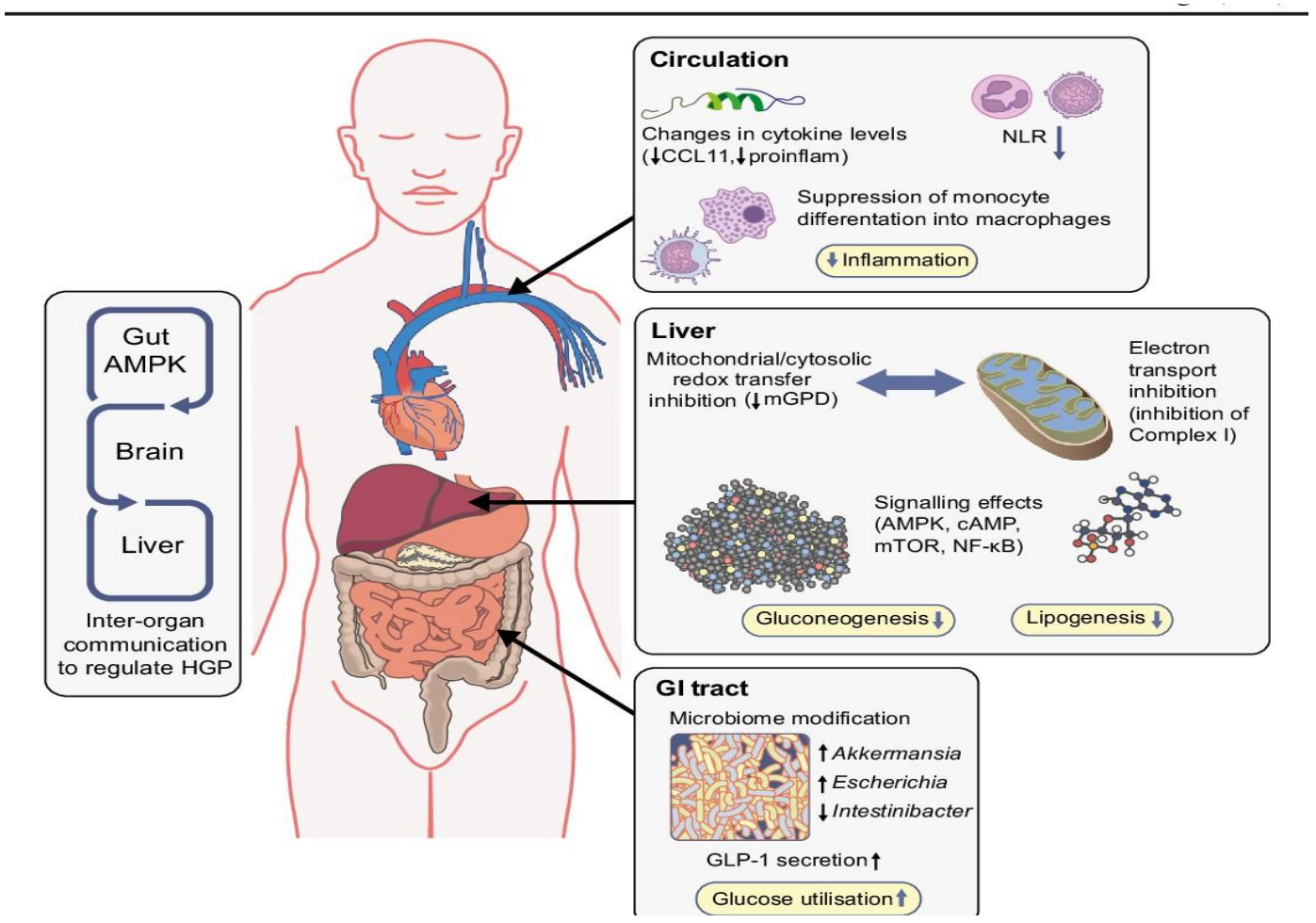
Metformin MOA

Mechanism of Action (MOA):

- MOA is not completely understood

Effects:

- Suppress elevated hepatic glucose production in the fasting state by decreasing gluconeogenesis
- Improves the ability of insulin to suppress hepatic glucose production in the postprandial state and improves insulin sensitivity in muscle and liver tissues.



Metformin

Onset of action: within days; max effects up to 2 weeks

Metabolism: Not metabolized by the liver

Excretion: Urine (90% as unchanged drug)

Major side effects:

- GI: diarrhea (IR:53%, ER: 10%), nauseas/vomiting (IR: 26%, ER: 7%),
- Lactic acidosis: avoid in patients with severe kidney disease or advance HF
- Vitamin B12 deficiency (long term use)

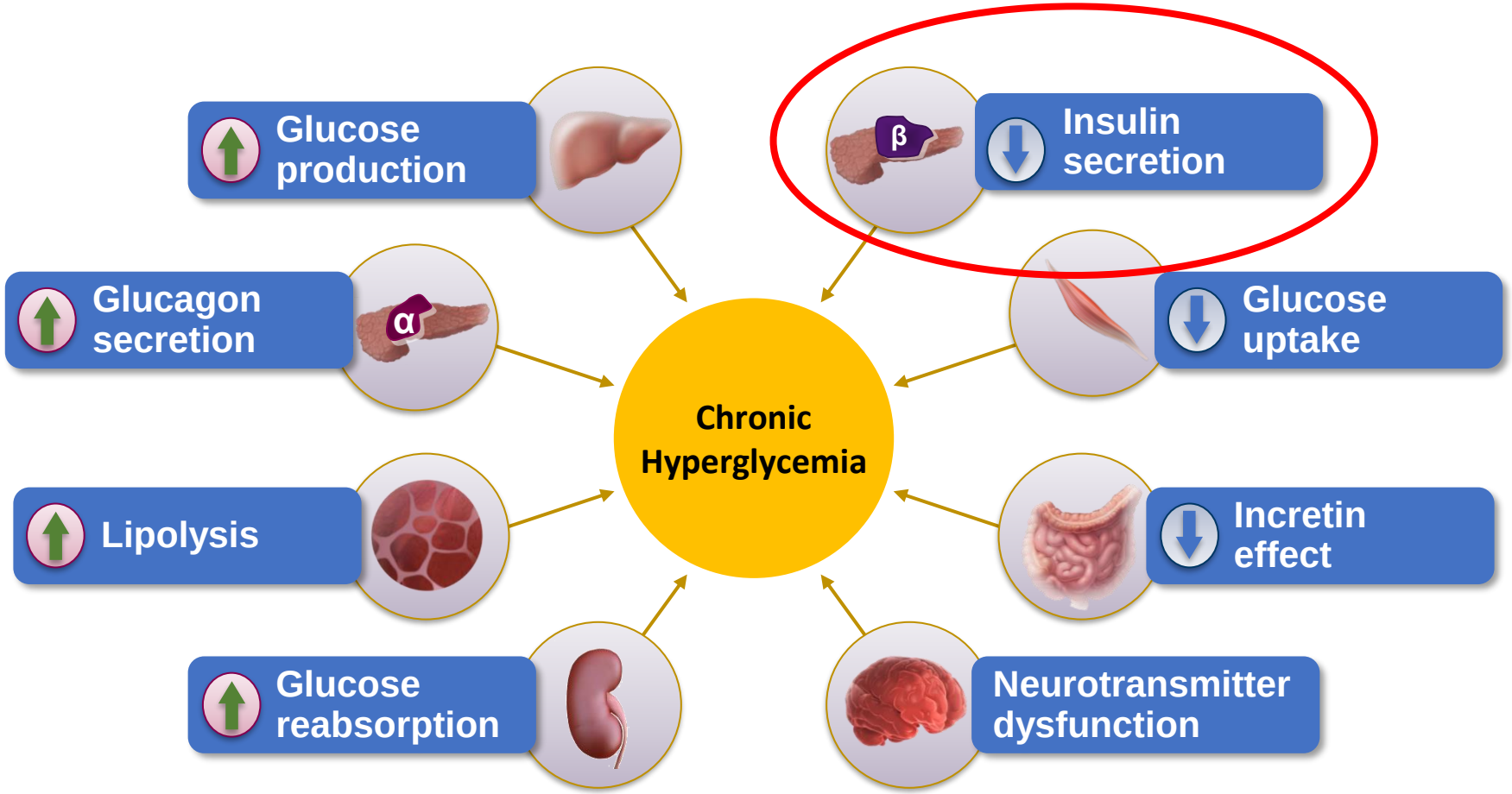
Dose:

- Prediabetes: 850mg BID
- Diabetes: 2000 to 2550mg/day in divided doses for IR; divided or once a day for ER

Key takeaways:

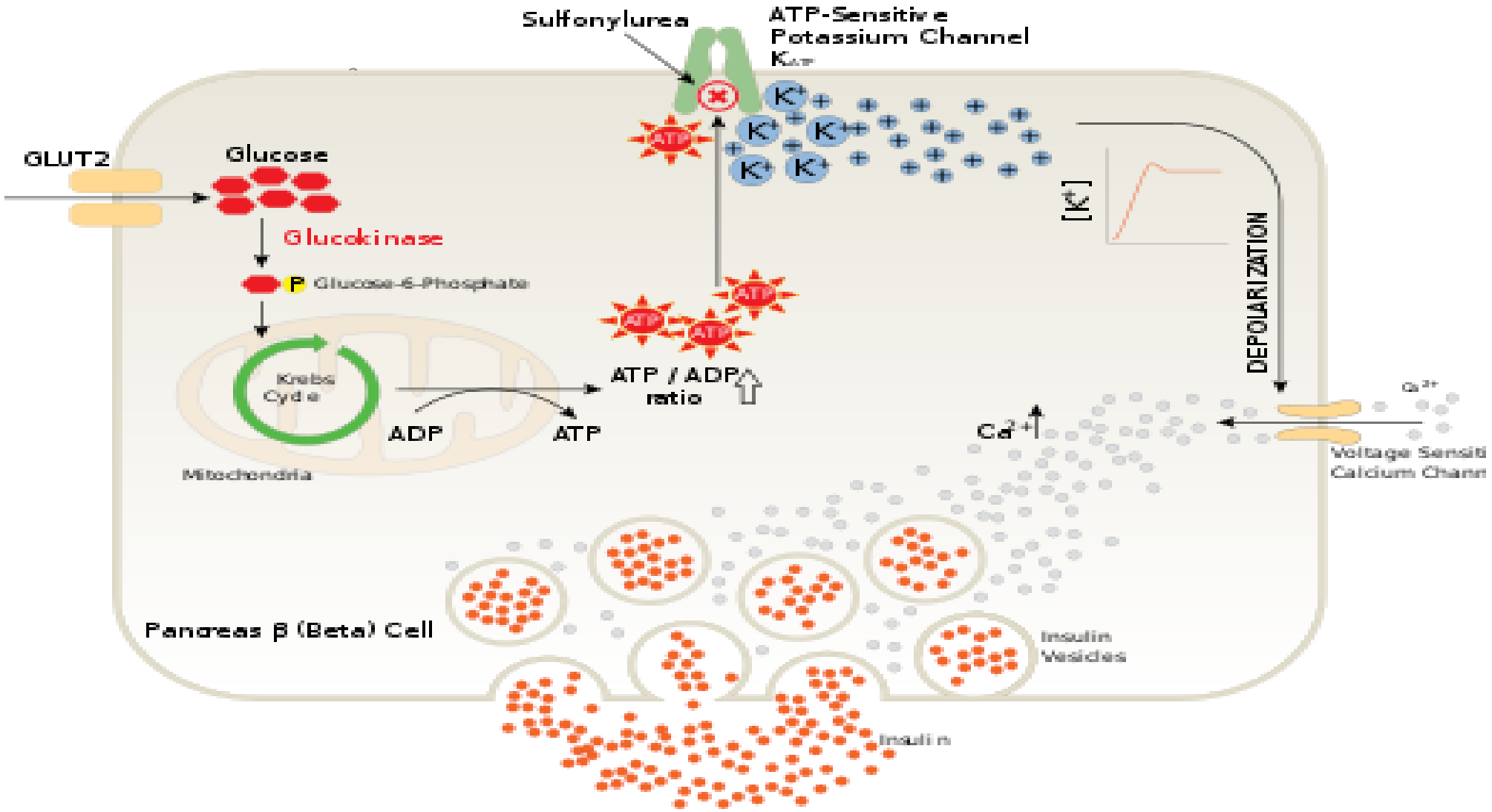
- Highly effective for glucose control
- Neutral for weight management
- Reduces risk of vascular complications with long term use
- Use ok with reduced GFR as low as 30ml/min

Ominous Octet: Sulfonylurea Therapy



DeFronzo RA. *Diabetes*. 2009;58(4):773-795.

Sulfonylureas MOA



SUR1, SUR2A or SUR2B receptor subunits

Limited effectiveness of sulfonylureas

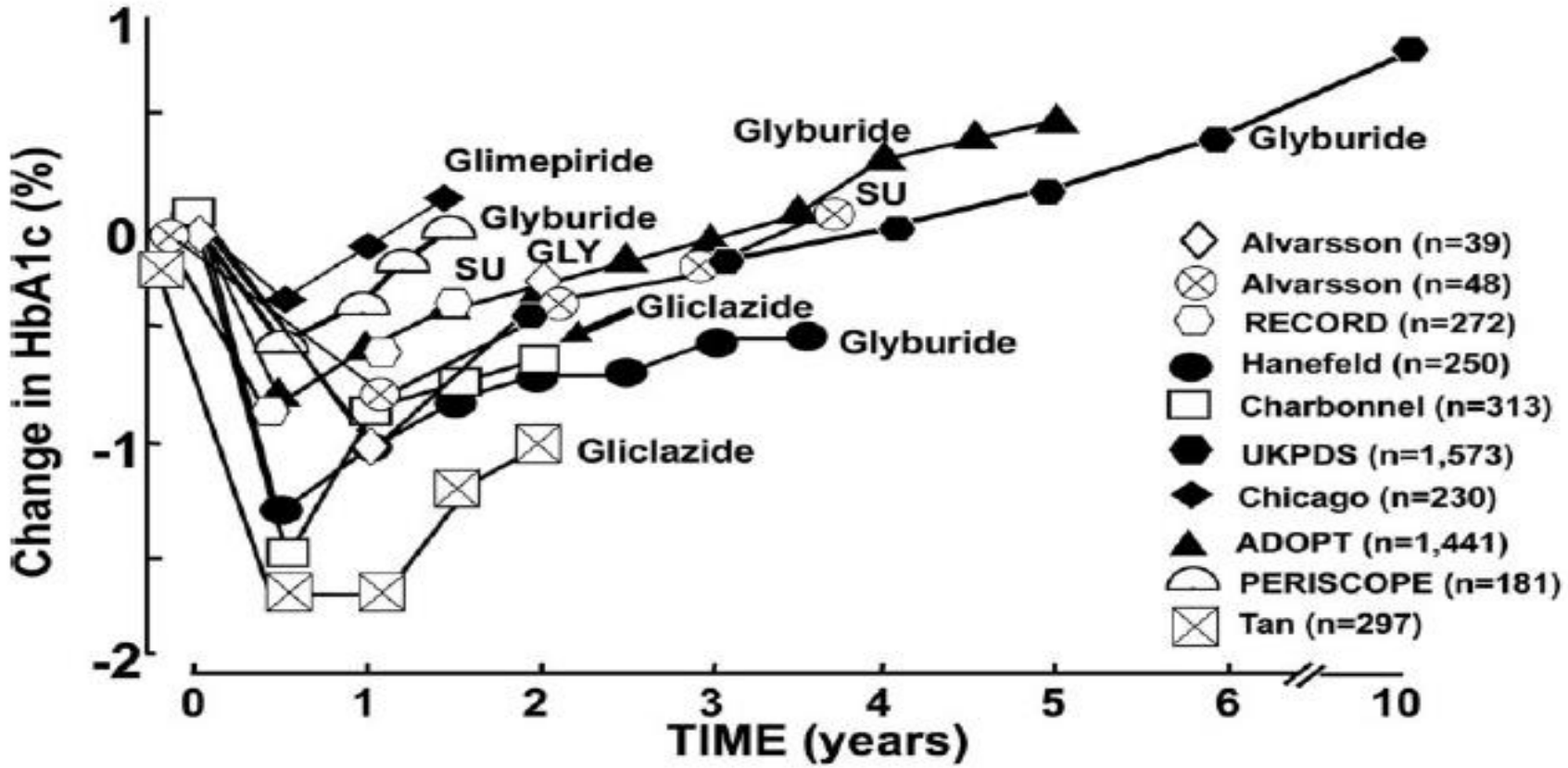


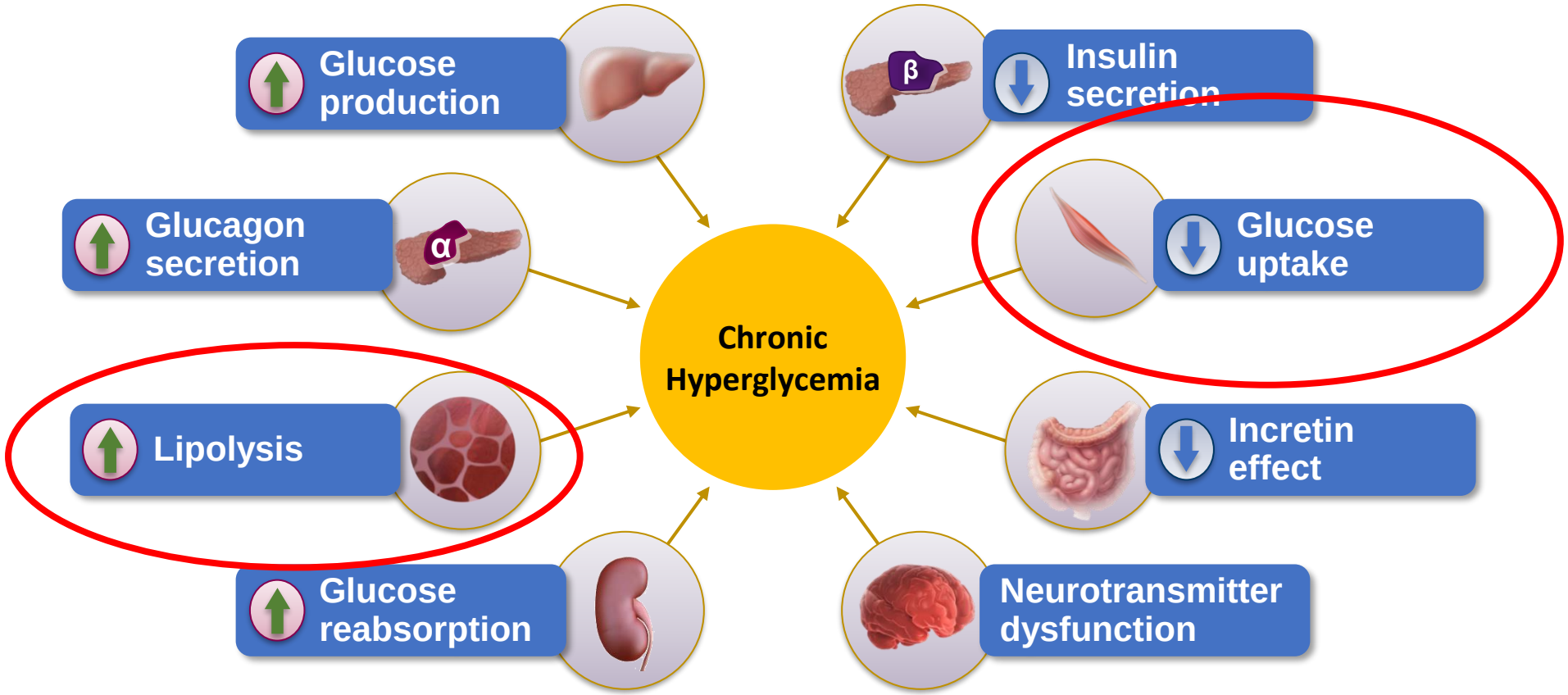
FIG. 16. Summary of studies examining the effect of sulfonylurea (SU) treatment versus placebo or versus active-comparator on A1C in type 2 diabetic subjects (36,166,167,260,269–273,279–285). See text for a more detailed discussion. GLY, glyburide.

Defronzo, R. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. Diabetes. 58: 773-796. April 2009.

Sulfonylurea Class Takeaways

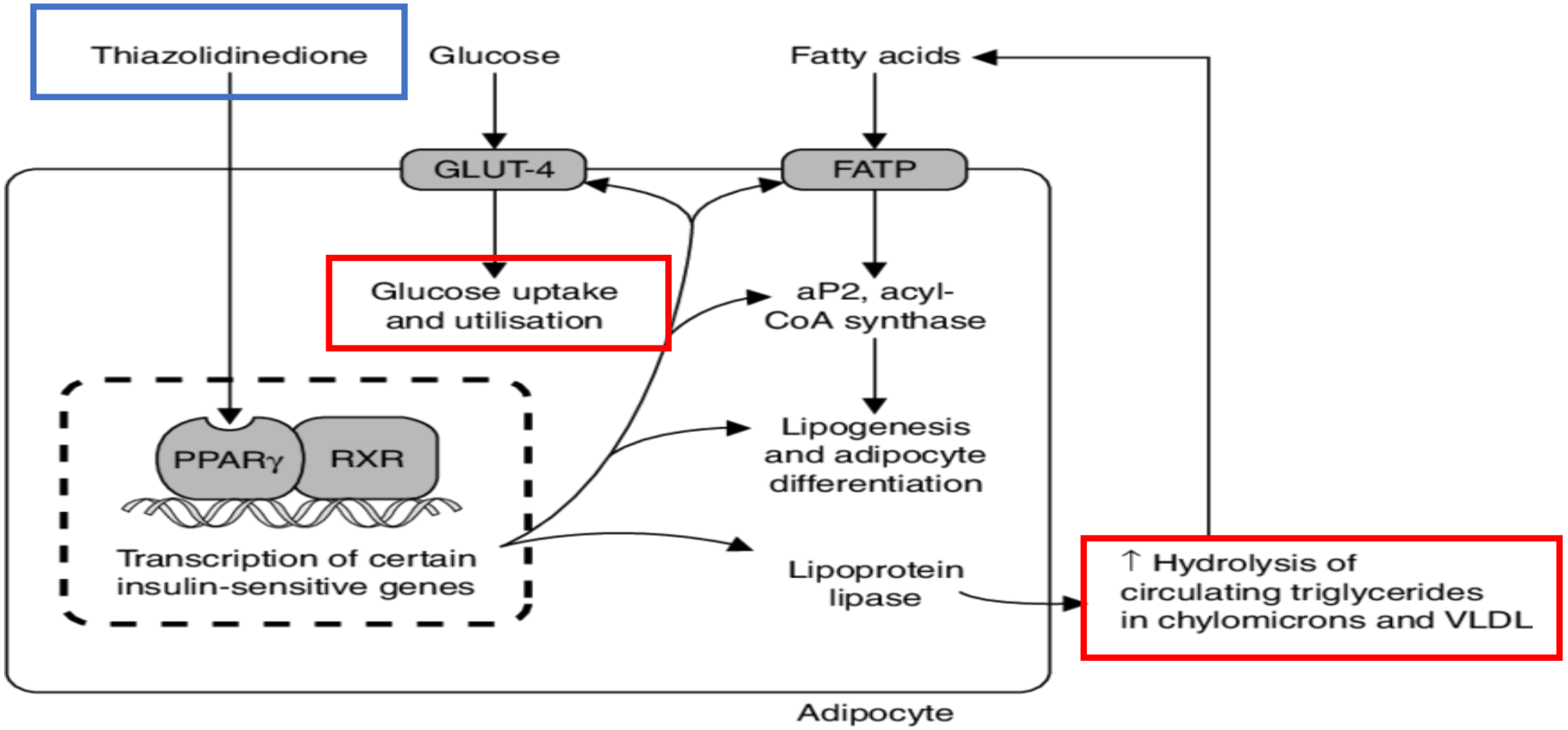
- Take dose 30 minutes prior to meal
- Extended-release formulations should be swallowed whole. Breaking the tablet will release too much medication at once
- Do not skip meals while taking this medication---risk of hypoglycemia!
- Causes weight gain and hypoglycemia
- No cardiorenal benefit
- Lose effectiveness after 3-5yrs of use

Ominous Octet: TZD therapy



DeFronzo RA. *Diabetes*. 2009;58(4):773-795.

TZDs Mechanism of Action



TZDs reverse lipotoxicity

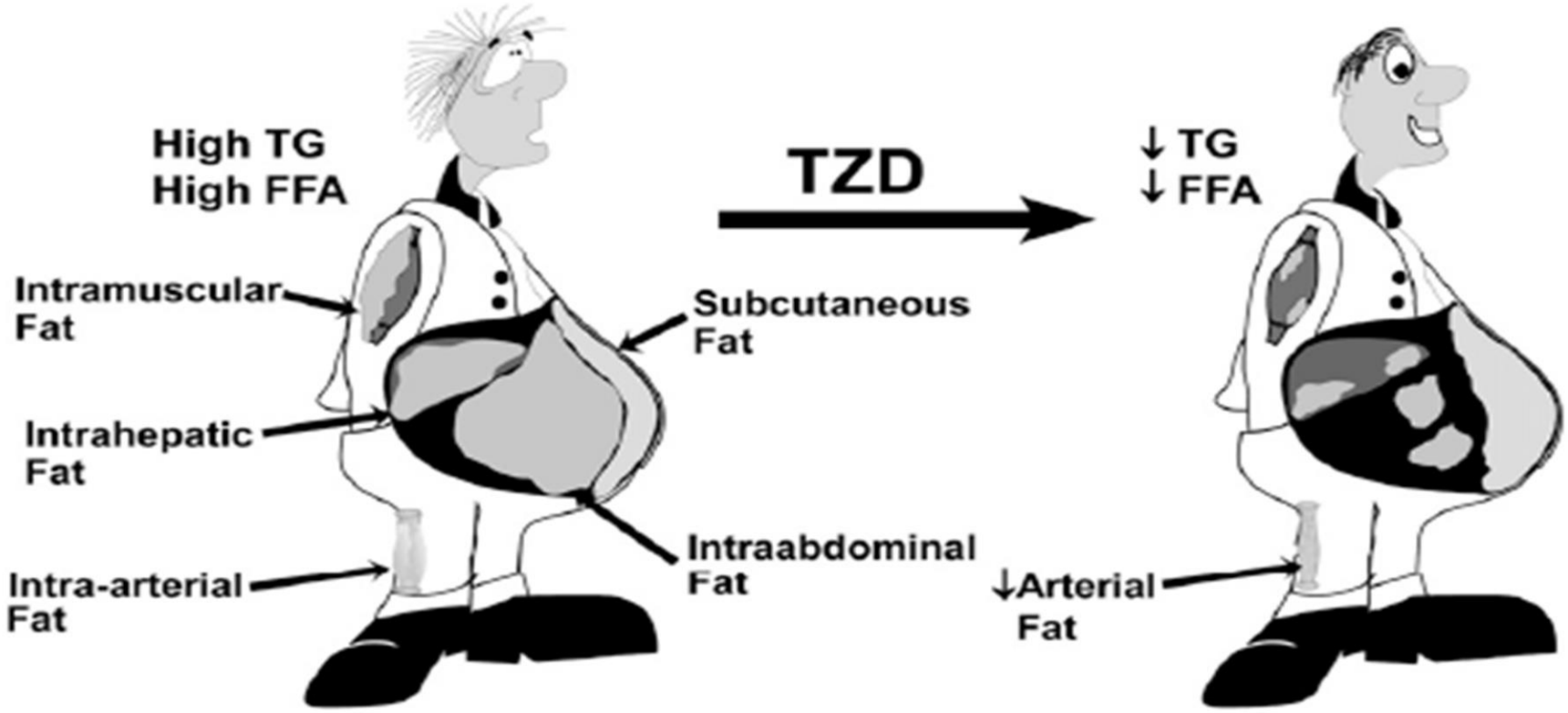
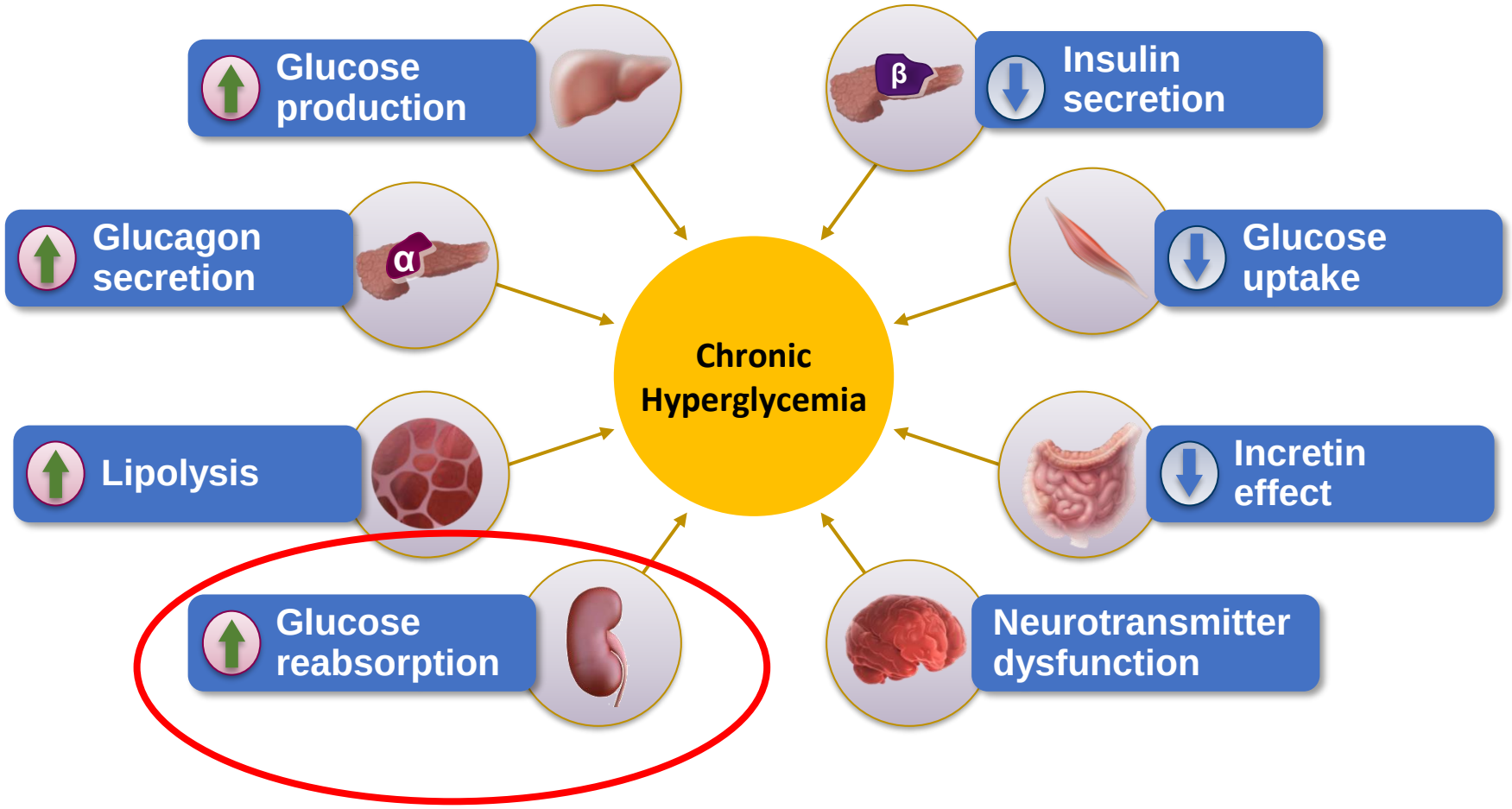


Figure 3—*Body fat distribution in T2DM patients and its redistribution with thiazolidinediones (TZD). (See text for a detailed discussion.) TG, triglyceride. Reprinted with permission from DeFronzo and colleagues (79).*

TZD Class Takeaways

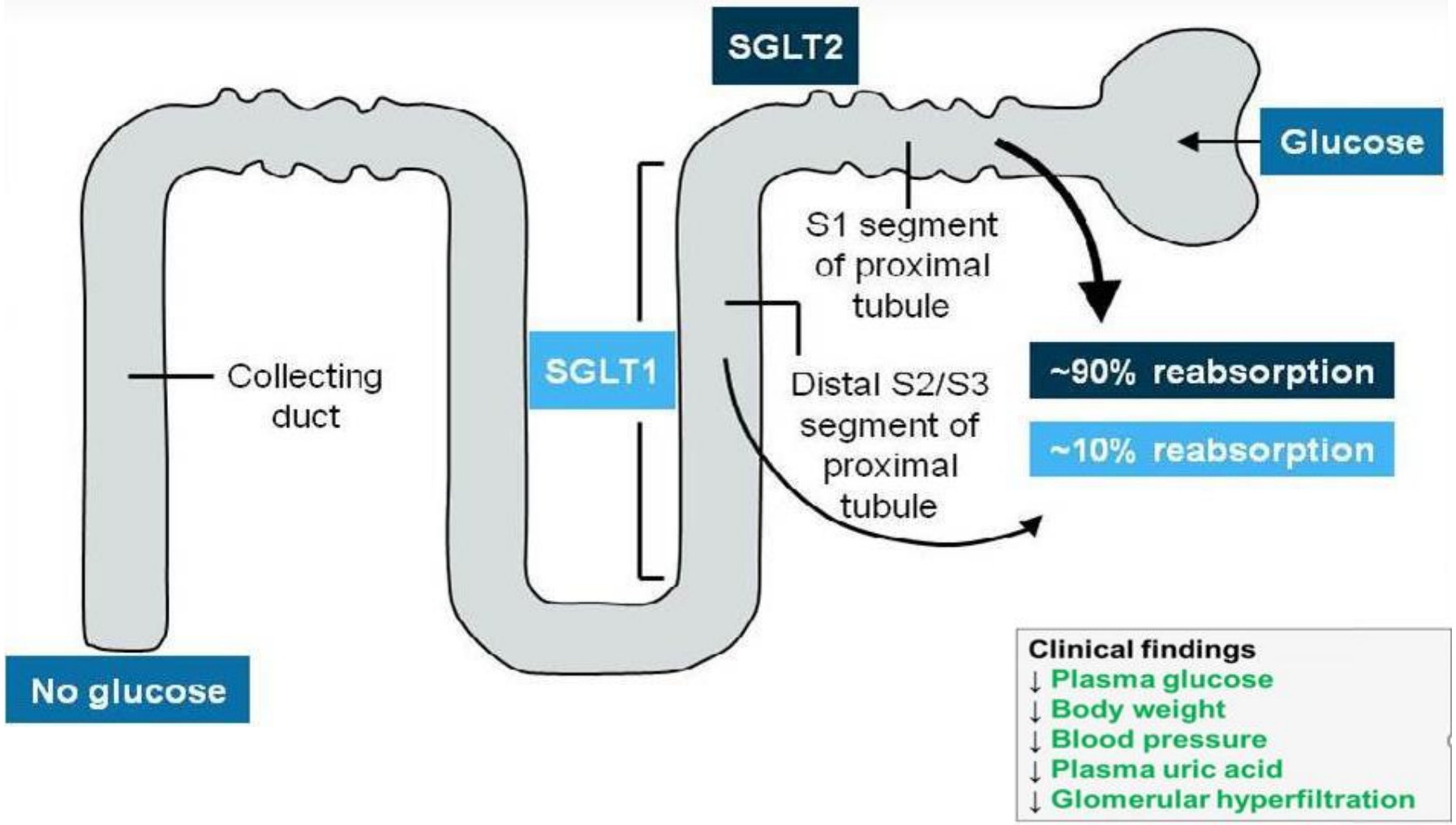
- Slows progressive deterioration of beta cell function in T2DM
- Beneficial in PreDM
- May take several weeks to take effect
- May cause edema which can worsen congestive heart failure
- Increased risk of fracture
- 2023 guidelines:
  - recommend for stroke + PreDM for secondary prevention
  - Add on to GLP1 or SGLT2i for additional CV benefit

Ominous Octet: SGLT2i therapy



DeFronzo RA. *Diabetes*. 2009;58(4):773-795.

SGLT2 Inhibitor MOA



Chao EC, et al. Natural Review Drug Discovery. 2010;9:551-559.

SGLT2i

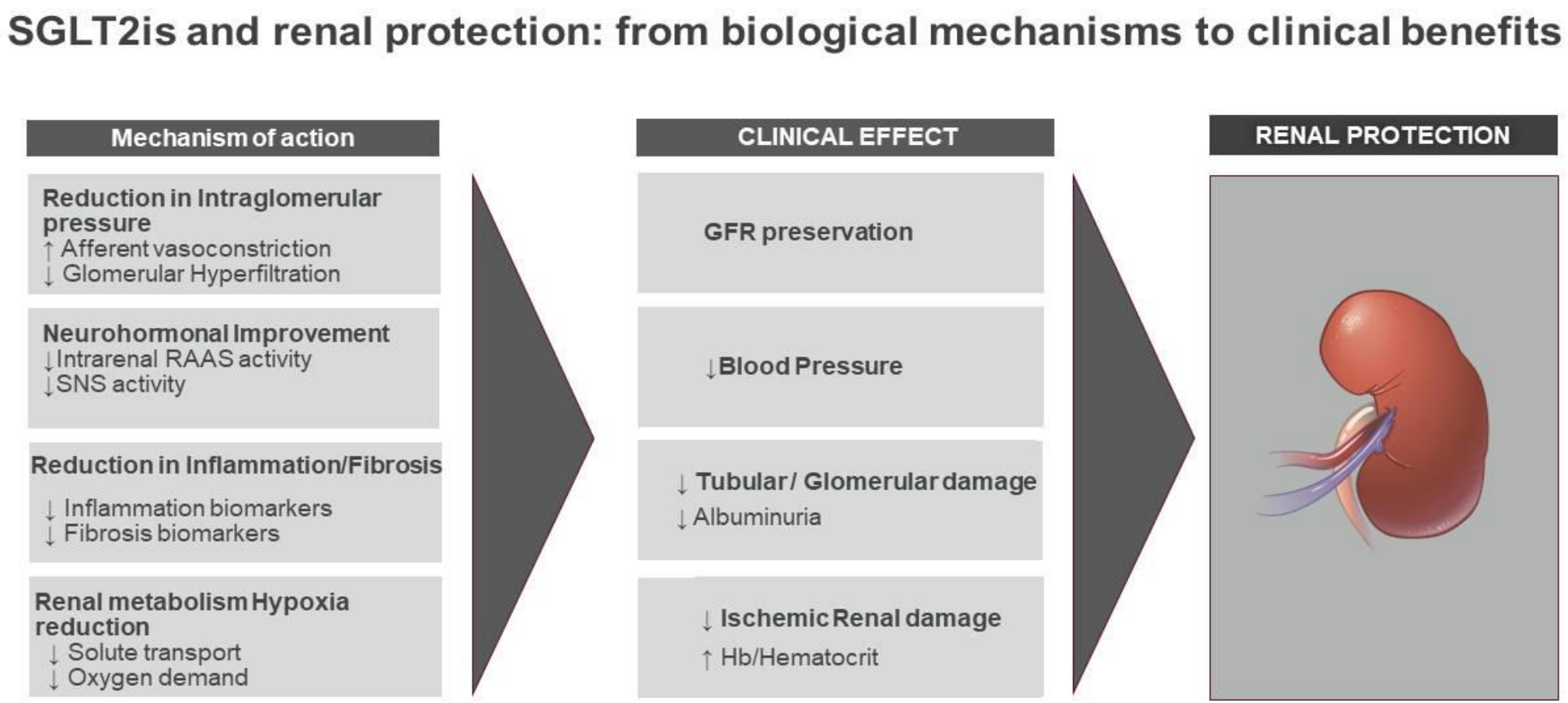
Generic	Brand	FDA Approval	Dose	Side Effects	Renal Dosing
Canagliflozin	Invokana™	29 Mar 2013	100, 300mg	• UTI (6-12%) • Increased urination (5-10%) • Genital fungal infections (<10% *mainly canagliflozin*) • Volume depletion (<10%) • Ketoacidosis (euglycemic) • Electrolyte disturbances • Necrotizing fasciitis of perineum, rare but significant (Fournier gangrene) • Limb amputations risk (*canagliflozin*)	GFR<30: use caution; do not initiate; continue if already taking
Dapagliflozin	Farxiga™*	8 Jan 2014	5, 10 mg		GFR<25: do not initiate; continue if already taking
Empagliflozin	Jardiance™*	1 Aug 2014	10, 25 mg		GFR<20: Do not initiate; continue if already taking
Ertugliflozin	Steglatro™	22 Dec 2017	5, 15 mg		GFR<45: do not use

*HF indication

SGLT2i HF Clinical Trial Summary

SGLT2i	Trial	Patients (Number)	Duration of the Study (in Years)	Diabetes	HFrEF *	% Reduction of Primary Outcome	Adverse Effects	% Reduction in Hospitalization
Empagliflozin	EMPEROR-reduced	3730	1.4	With/without	Yes	21%	Uncompleted genital tract infection in patients treated with empagliflozin was reported more frequently compared to the placebo group. However, hypoglycemia, lower limb amputation, and bone fracture were not observed to be significantly different between the two groups.	15.4%
	EMPA-REG	7020	3.1	Yes	N/A	14%		35%
	Emperor-presrved	5988	2.4	With/without	No (LVEF >40%)	N/A		N/A
Dapagliflozin	Declare-TIMI	17,160	4.2	Yes	N/A	N/A	volume depletion, renal dysfunction, and hypoglycemia, were not reported significantly different from the placebo group	17%
	DAPA-HF	4744	1.7	With/without	Yes	21.1%		30%
Canagliflozin	CANVAS	10,142	3.6	Yes	N/A	N/A	with a higher risk of amputation primarily at the level of toe or metatarsal	14.4%
	CREDENCE	4401	2.6	Yes	N/A	N/A		37.5%
Ertugliflozin	VERTIS CV	8246	3.5	Yes	N/A	N/A	urinary infections, observed with ertugliflozin were similar to the known risks of the medicines in the SGLT2 inhibitor class.	N/A

The ‘other’ effects of SGLT2i

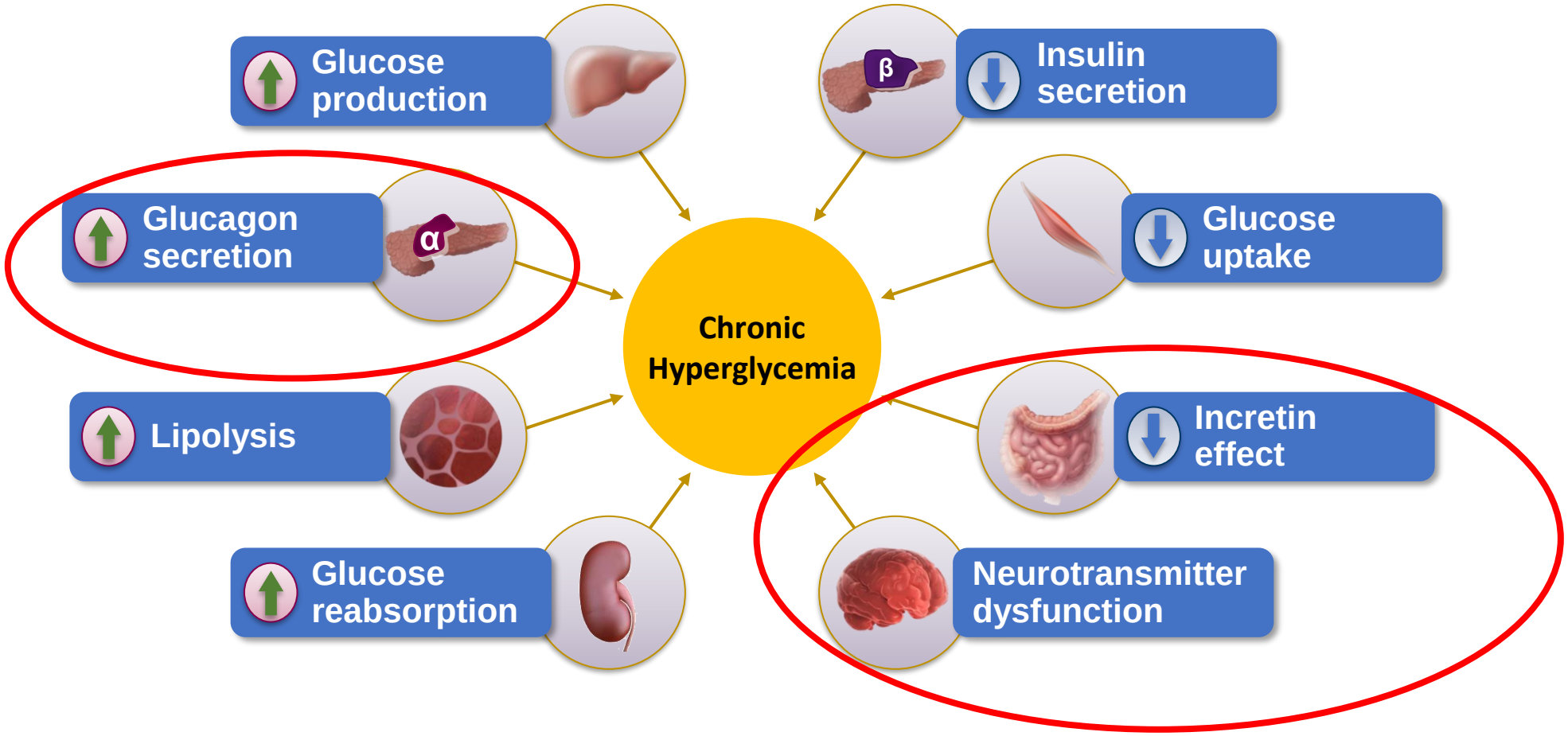


SGLT2 Inhibitors Class Takeaways

- Because of glucosuria, there is an increased risk of urinary tract infections, dehydration and hypotension
- Glucosuria may result in loss of 300calories/day→ weight loss!
- Patients will test positive for urine in glucose while using
- Should be discontinued before any scheduled surgery to avoid increased risk of DKA
- Euglycemic DKA risk—rare but significant
- Contraindicated in T1DM or others at risk of DKA
- Can use with <u>any</u> other medication class in DM2 pts
- Adjust diuretic dose -- dehydration/hypotension
- Monitor renal function after starting therapy (2-4 wks)
- Efficacy strongly depends on renal function and filtered glucose load
- May require decrease in insulin or sulfonylurea dose

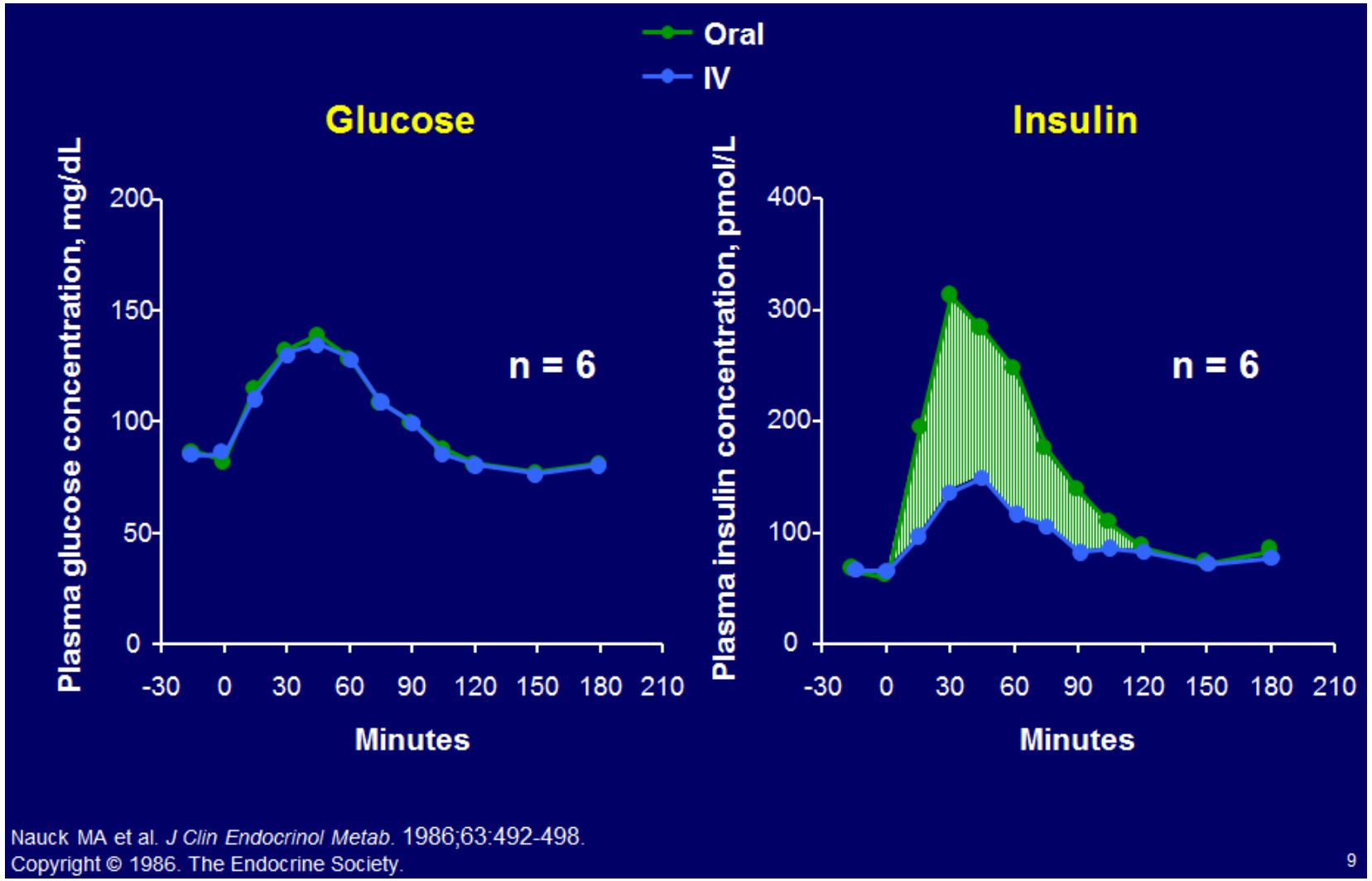
Incretin Based Therapy

Ominous Octet: incretin therapy

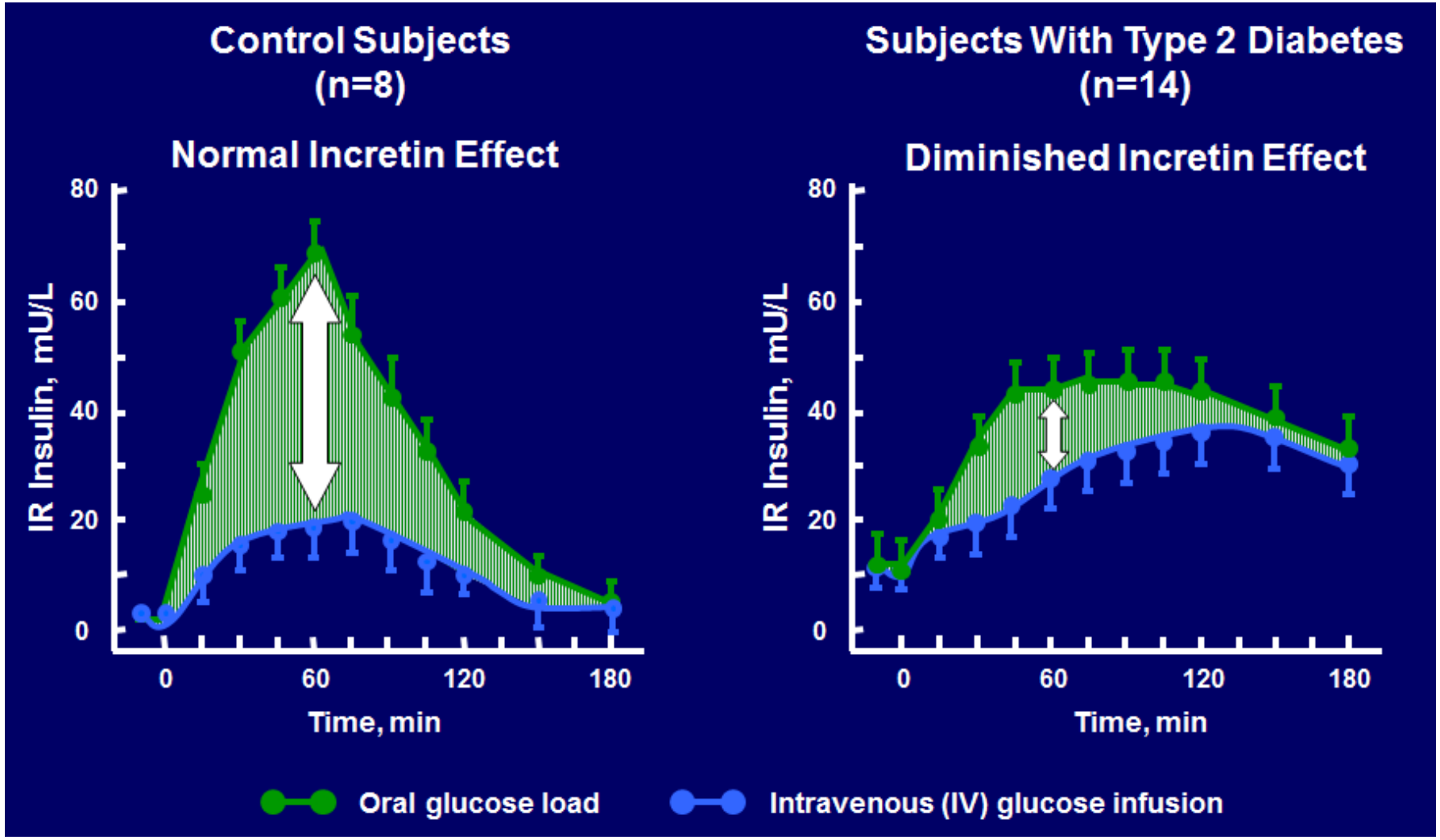


DeFronzo RA. *Diabetes*. 2009;58(4):773-795.

The Incretin Effect



Incretin Effect Diminished

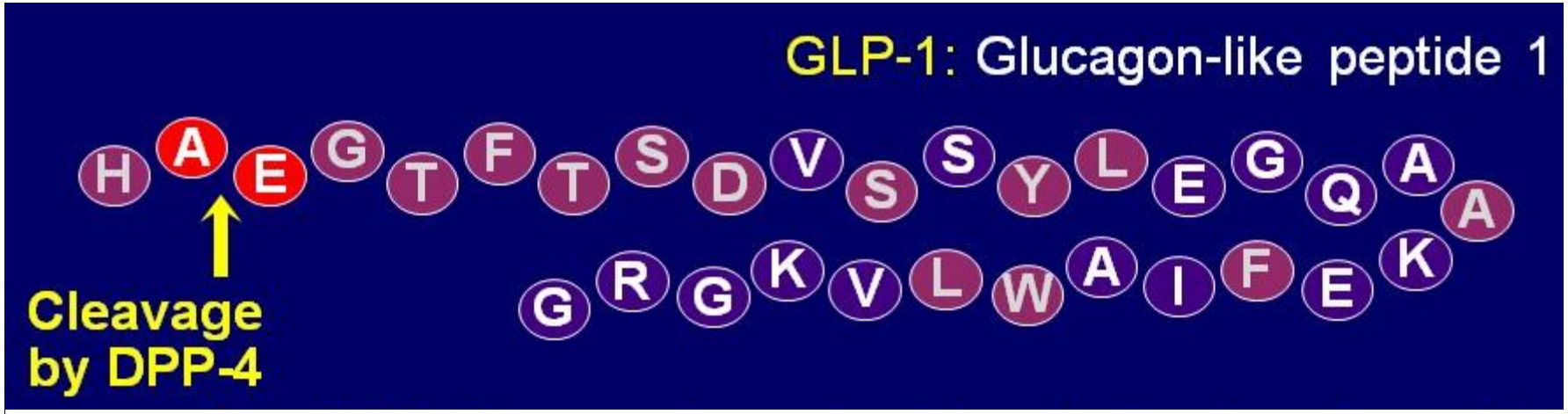


Endogenous GLP1 Production / Effect

GLP1 (Glucagon Like Peptide 1) and GIP [glucose dependent insulinotropic peptide]

- Considered incretin hormones because they:
    1. Released from the GI tract in response to ingestion of food, particularly glucose
    2. The circulating concentration of the hormone must be sufficiently high to stimulate the release of insulin.
    3. The release of insulin in response to GLP1 occurs only when glucose levels are elevated – glucose-dependent insulin release (as opposed to sulfonlyureas that increase release of insulin regardless of glucose levels)
- Effect: Approximately 70% increase in C- peptide and insulin production in response to oral carbohydrate load
- Stimulates insulin response from beta cells in a glucose-dependent manner
- Inhibits gastric emptying
- Reduces food intake -→ reduce body weight
- Inhibits glucagon secretion from alpha cells in a glucose-dependent manner

Inactivation of GLP-1



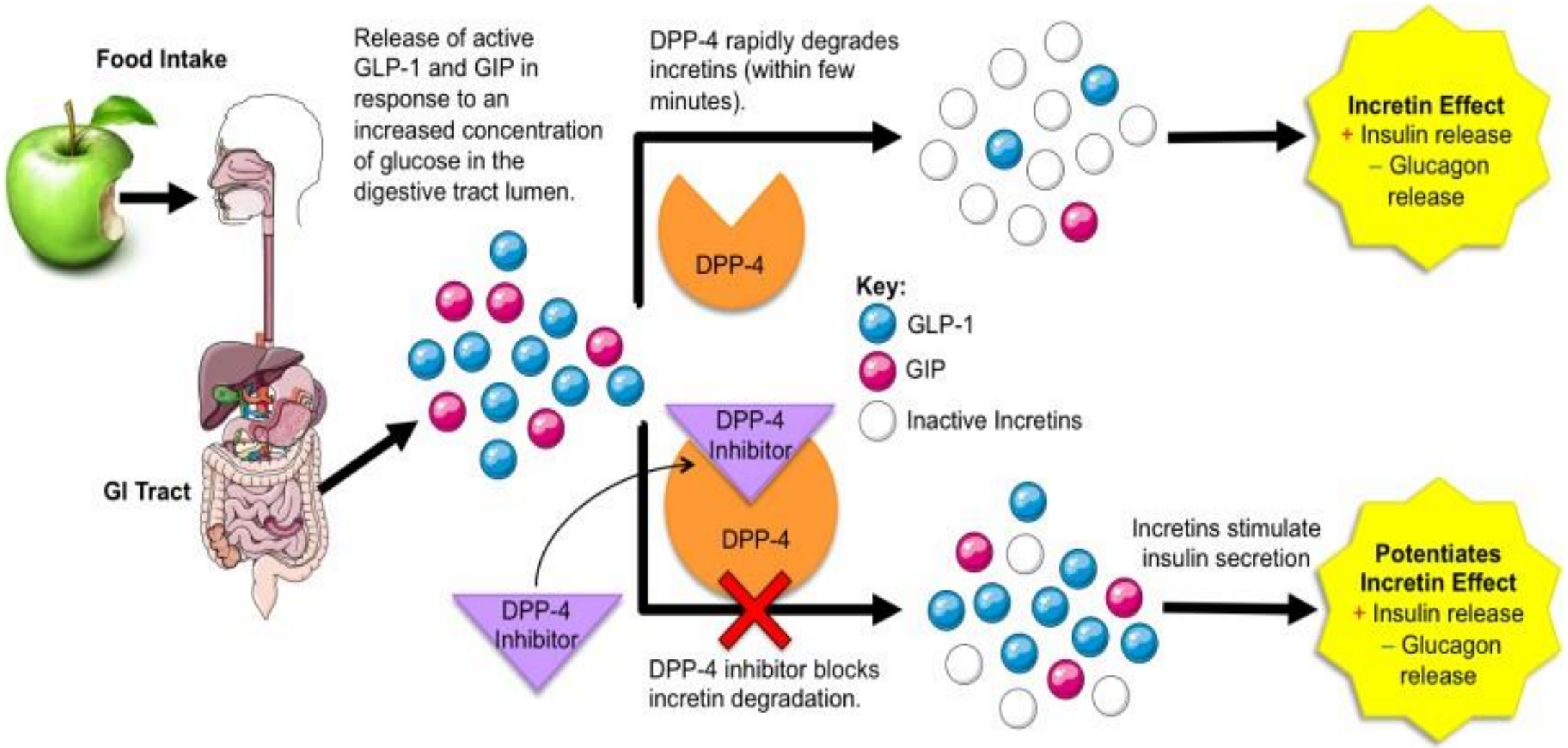
DPP4

GLP-1 → Inactive

t ½ life is <2 min

Drucker DJ. *Diabetes Care.* 2003;26:2929–2940.

DPP4 Inhibitor MOA



Dipeptidyl Peptidase-4 Enzyme Inhibitors (DPP4i)

MOA:

- Prevents breakdown of GLP-1, a compound that lowers blood glucose
- GLP-1 receptors are activated causing the sensitizing beta cells and reducing the threshold for insulin release

Effects:

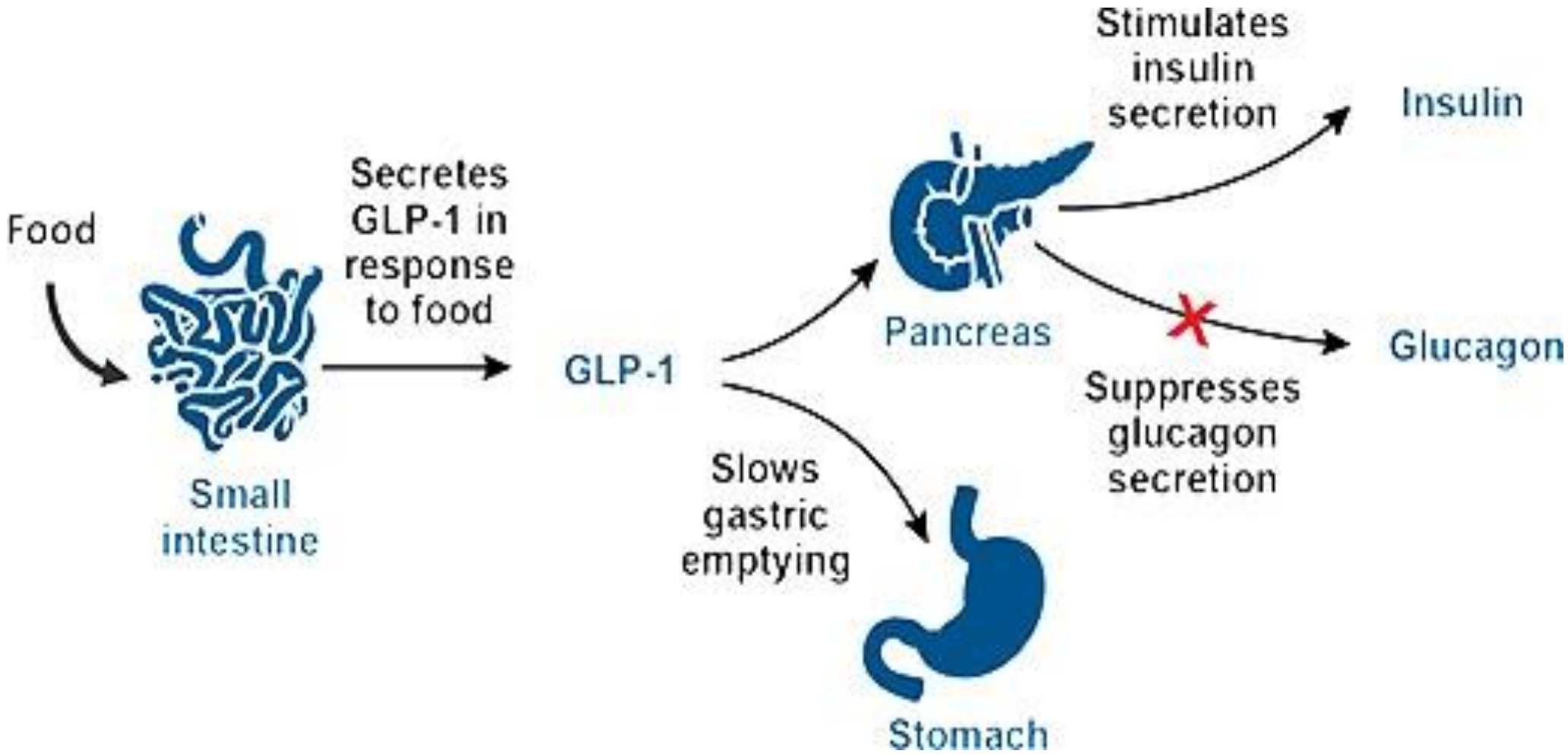
- Glucose dependent insulin secretion by increasing endogenous GLP1 levels
- 2-4x native GLP-1 concentration with DPP-4 inhibitor
- Suppression of postprandial glucagon secretion, potential delayed gastric emptying and reduced appetite and food intake

But do DPP4i work if there is no endogenous GLP1?

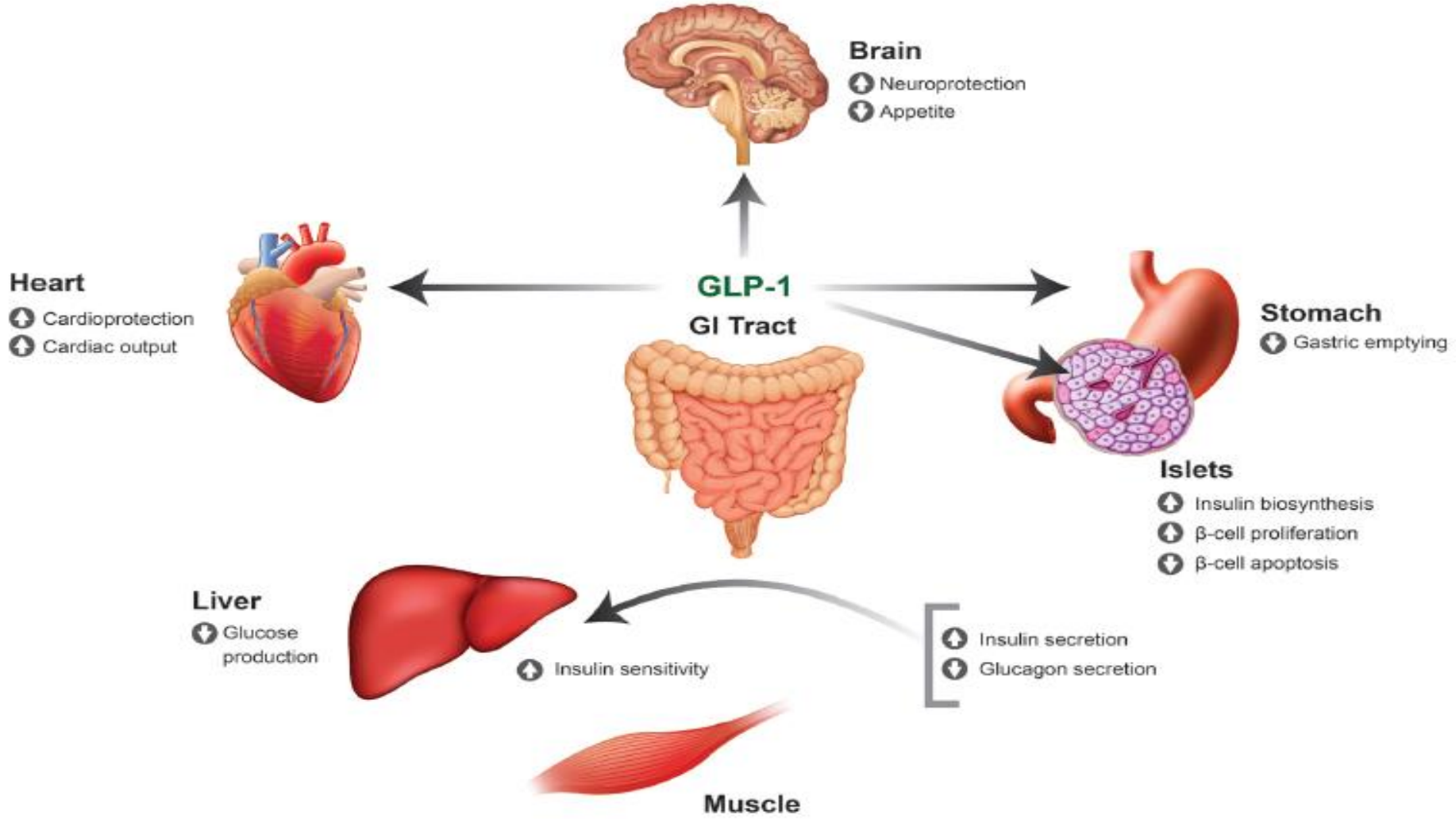
DPP4 Inhibitors

Generic	Brand	Doses	Renal Dosing	Notes
sitagliptin	Januvia™	25, 50, 100mg	• >50 CrCl (100 mg) • 30-50 CrCl (50 mg) • <30 CrCl (25 mg)	• Once a day dosing, no dose titration • Generally mild side effect profile: Headaches, Nasopharyngitis; Caution with someone who has a history of pancreatitis • Do not take with GLP1 agonist; no added benefit • No need for dose titration
saxagliptin	Onglyza™	2.5, 5mg	• >50 CrCl (5 mg) • <50 CrCl (2.5 mg)	
linagliptin	Trajenta™	5mg	No renal adjustment	
alogliptin	Nesina™	6.25, 12.5, 25mg	• >50 CrCl (25 mg) • 30-50 CrCl (12.5mg) • <30 CrCl (6.25 mg)	

GLP1 Receptor Agonist MOA



GLP1 Glucose/non glucose actions



Deborah Hinnen Diabetes Spectr 2017;30:202-210

Generic	Brand	Dose		Route	Renal dosing
GLP1 agonist					
Exenatide	Bydureon ER™	2mg	Once a week	SQ injection	GFR < 30: do not use
	Byetta™	5-10mcg	Twice a day with a meal		
Liraglutide	Victoza™	0.6mg 1.2mg 1.8mg	Every morning	SQ injection	Mild to severe renal impairment: use caution
Dulaglutide	Trulicity™	0.75mg 1.5mg 3mg 4.5mg	Once a week	SQ injection	Mild to severe renal impairment: use caution
Semaglutide	Ozempic™	0.25mg 0.5mg 1mg 2mg	Once a week	SQ injection	Mild to severe renal impairment: use caution
	Rybelsus™	3mg 7mg, 14mg	Every morning before meal	Oral	
GLP1 and GIP agonist					
Tirzepatide	Mounjaro™	2.5mg 5mg 7.5mg 10mg 12.5mg 15mg	Once a week	SQ injection	No dose adjustment needed

When not to use GLP1s

- Contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2)—rare endocrine conditions

- Use caution in patients with history of pancreatitis

- Do not use with DPP4i

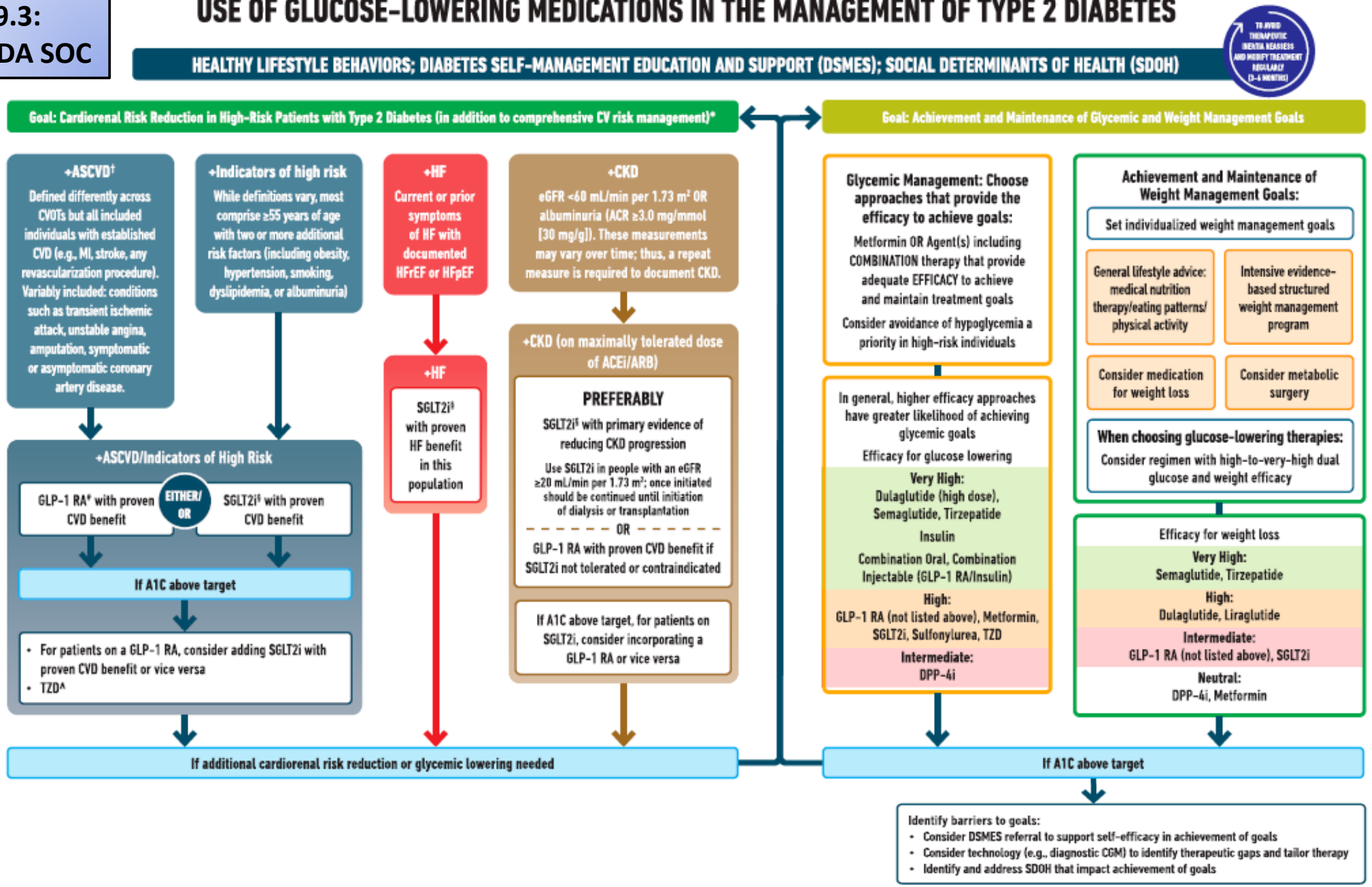
GLP1 therapy Takeaways

- Lower initial doses are to reduce likelihood of GI side effects --these doses do not provide effective glycemic control
- Needle gauge:
    - Bydureon ER—23G
    - Trulicity– 29G
    - Victoza, Byetta, Mounjaro, Ozempic—32G
- Counsel patients: May need to reduce portions to avoid GI side effects because this will cause you to feel fuller faster
- Once a week formulations will take 3 - 4 weeks for full effect, increase dose every 4 week
- Can use in renal impairment (except exenatide)—monitor regularly
- Rarely causes hypoglycemia
- Possible reduction in fatty liver

Incretin therapy Takeaways

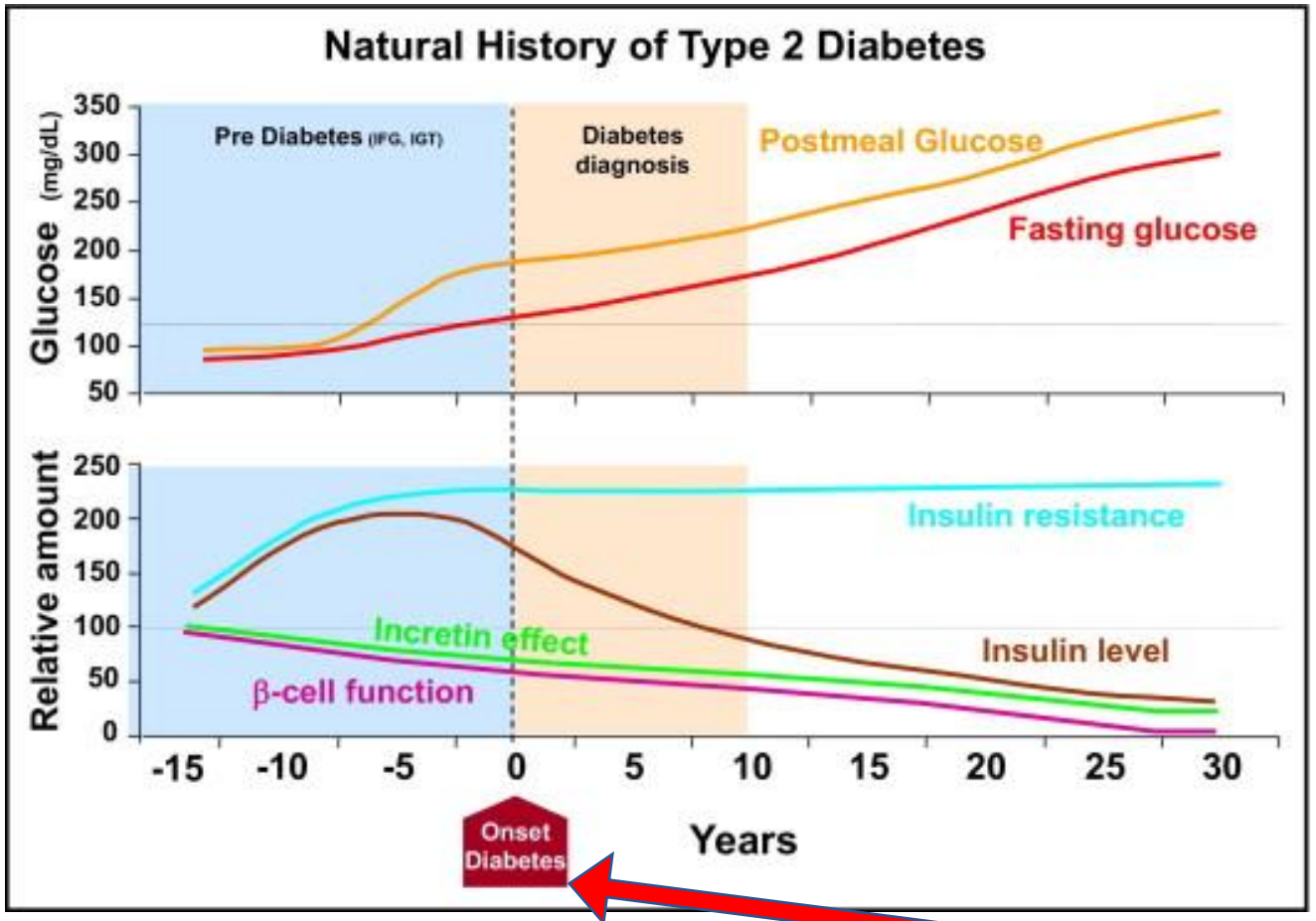
- Incretin effect accounts to 70% post-prandial insulin release
- GLP1 is the predominate incretin hormone
- GLP1 $t_{1/2}$ is 1-2 min – rapidly degraded by DPP-4
- DPP4 inhibitors are well tolerated with moderate glucose effect and are weight neutral
- GLP1 agonist have more side effects, but are more potent with advantage of weight reduction
- Incretin therapy has very low hypoglycemia rate
- Higher risk when used with sulfonylurea

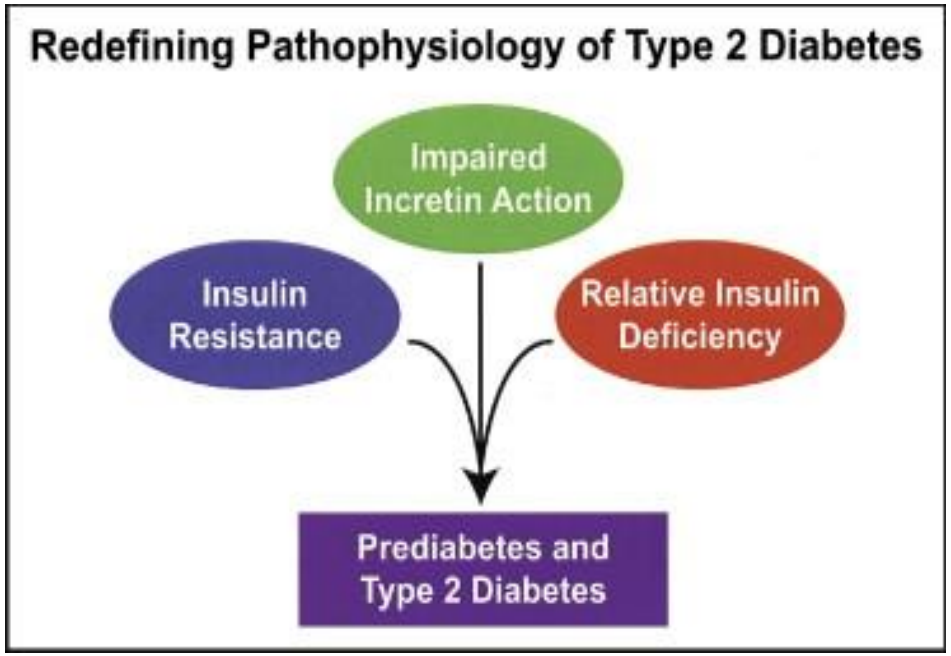
Figure 9.3: 2023 ADA SOC



Concentrated Basal Insulins

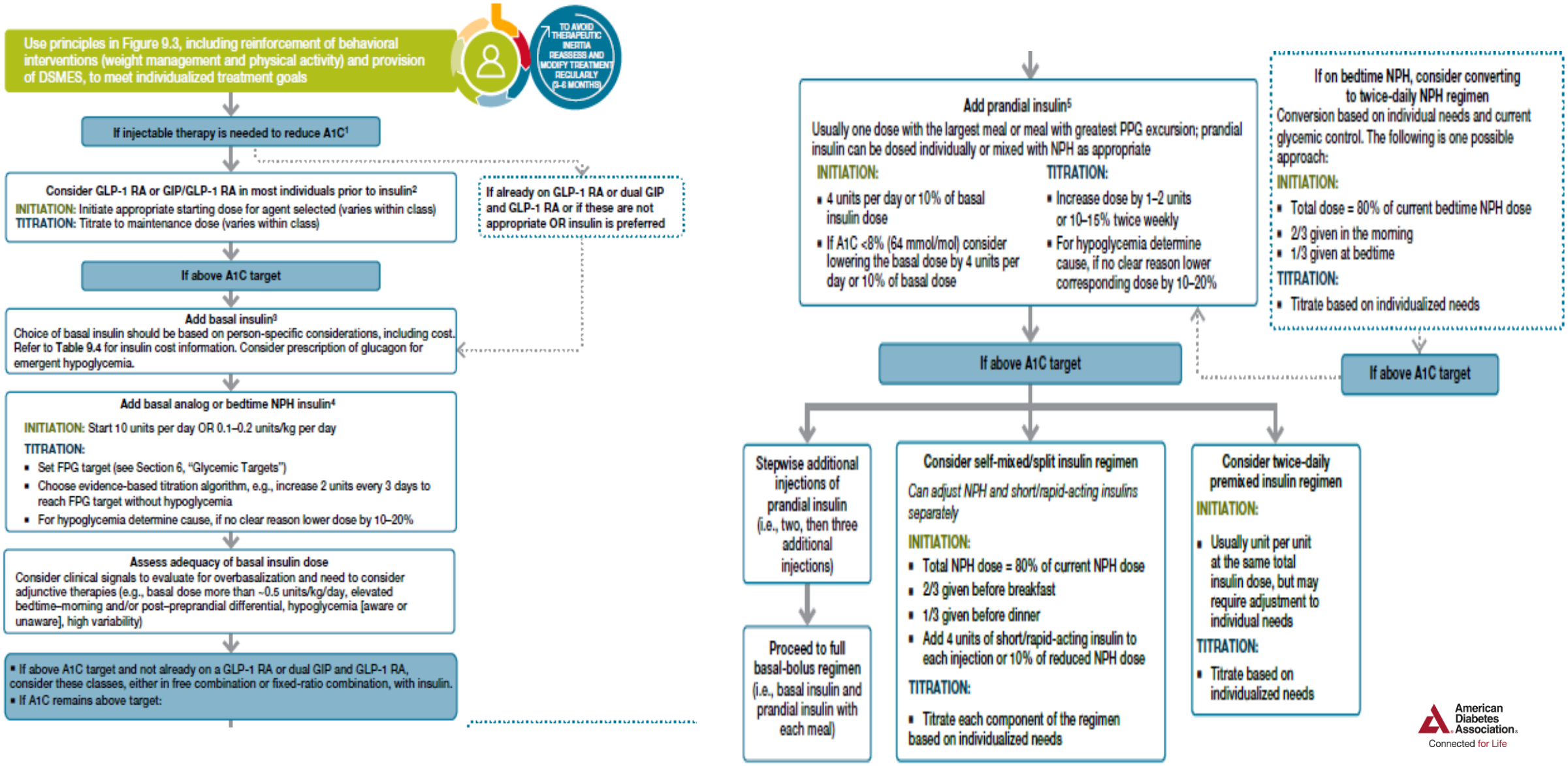
Natural History of DM2





>50% loss of Beta-cell function at diagnosis

Intensifying to injectable therapies: 2023 ADA



American Diabetes Association.
Connected for Life

Intensifying to injectable therapies

If HgA1c is >10% OR glucose is >300mg/dl:

- *Consider GLP1 prior to insulin if possible
- If the patient is already on a GLP1 or the A1c is still not at goal → then add basal insulin
- Basal insulin starting dose: 10units OR 0.1-0.2u/kg/day

If the A1c still not at goal after adding on GLP1 and/or basal insulin:

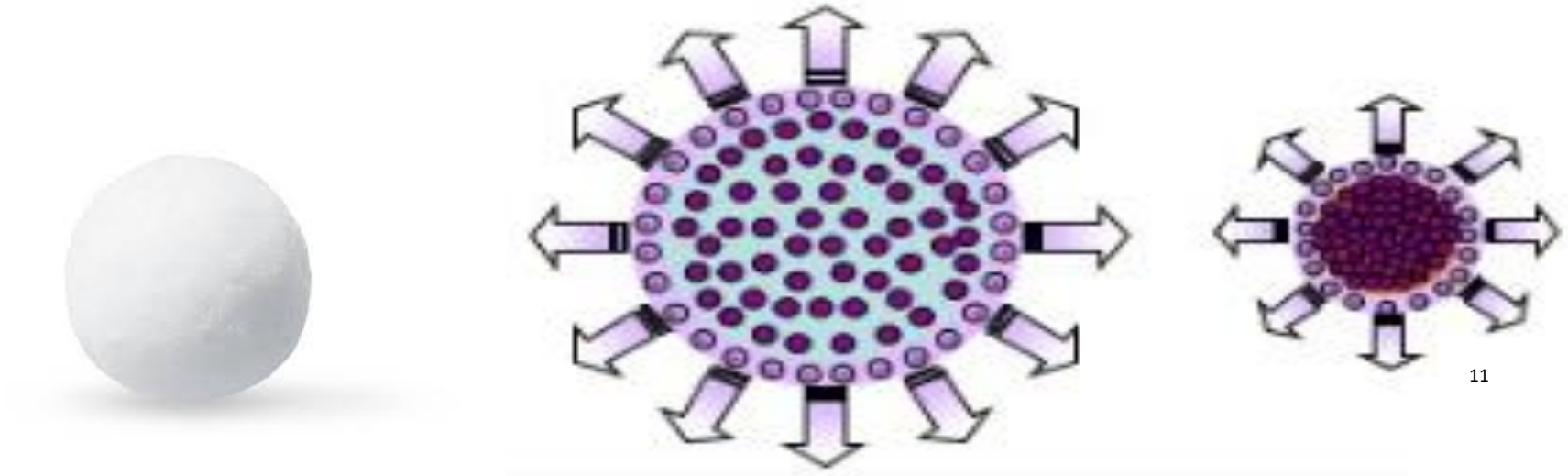
- Add on prandial insulin
- can start with largest meal of the day and titrate as needed
- Prandial insulin starting dose: 4units before largest meal of the day
- Reevaluate every 3 to 4 days and increase by 1-2units of 10-15%

Volume and Absorption, Basal Insulin Conc.

- Inverse relationship between concentration and rate of absorption

Concentration ↑ ↓ **Slower absorption**

- Large volume (larger surface area)→ increase variability of absorption→ reduce therapeutic effectiveness



U100
- **100units/mL**

U200
- **200units/mL**

U300
- **300units/mL**

U500
- **500units/mL**

Action Profiles of Basal Insulin

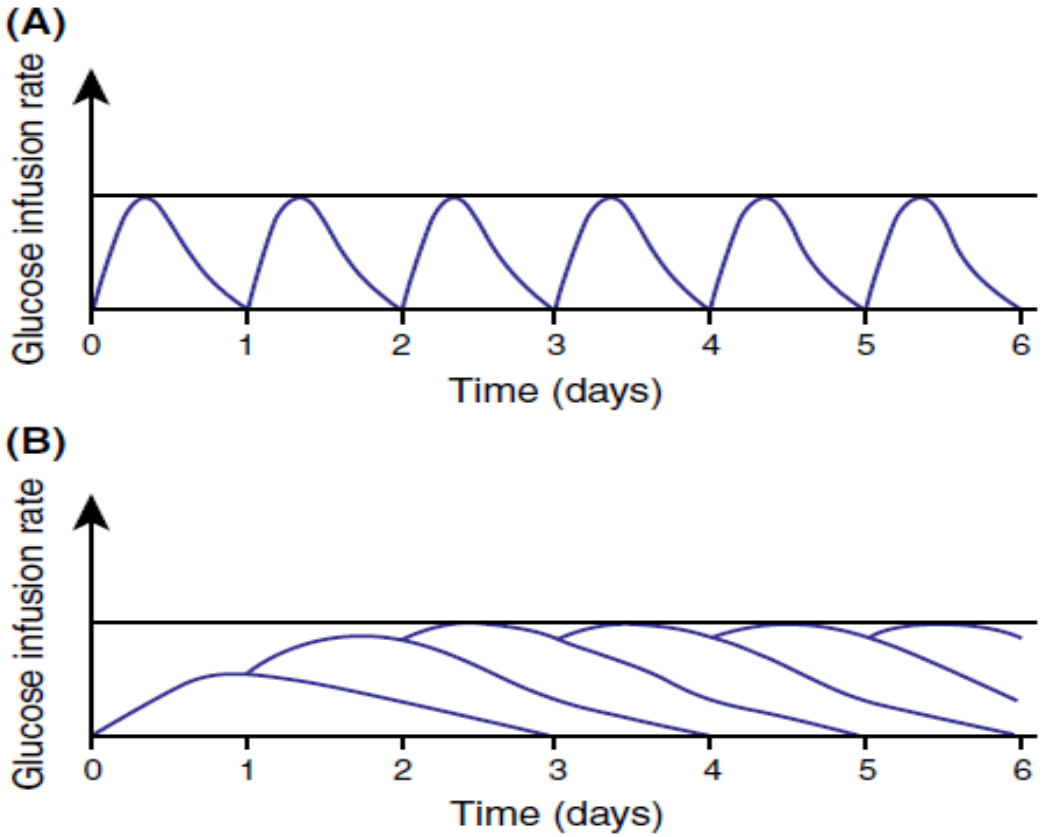


Fig. 1 Conceptual model demonstrating action profiles with once-daily dosing of a basal insulin with duration of action **a** ≤24 h and **b** substantially longer than 24 h [14]

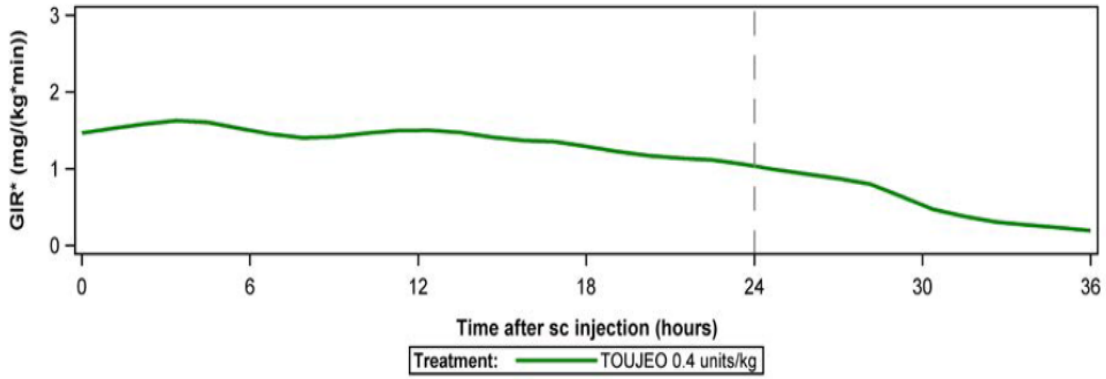
Haahr H, Heise T. A review of the pharmacological properties of insulin degludec and their clinical relevance. *Clinical Pharm*. 2014;53(9):787-800

Basal insulins

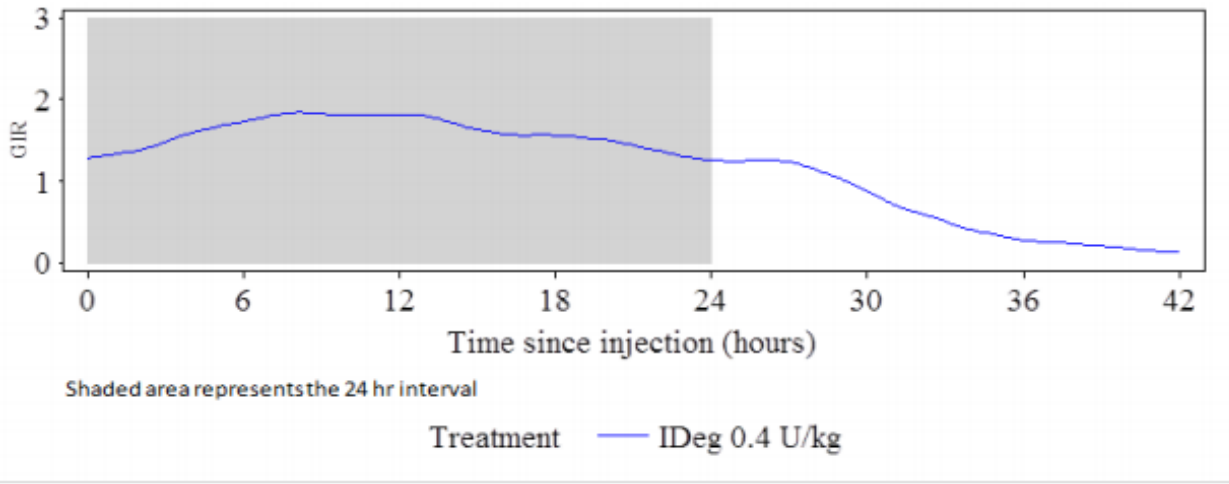
Generic	Brand/Concentration	Onset	Peak activity	$t_{1/2}$ life	Duration of action
NPH insulin		2-4 h	6-10 h	6-8h	12-18 h
Detemir	Levemir™ 100u/ml	2-4 h	6-8 h	5-7	20-24 h
Glargine	Lantus™ 100u/ml	3-4 h	10 -12 h (None)	12 h	10-24 h
Glargine	Toujeo™ 300u/ml	3-6 h	12-16 h	---	24h +
Degludec	Tresiba™ 100, 200u/ml	3-6 h	9 h (None)	25 h	36-42 h
Insulin with Basal/bolus action					
U500 Regular insulin	Humulin R U-500™ 500u/ml	<15min	0.5 – 8 h	4.5h	13 -24 h

Concentrated insulin duration of action

Toujeo (glargine 300u/ml)

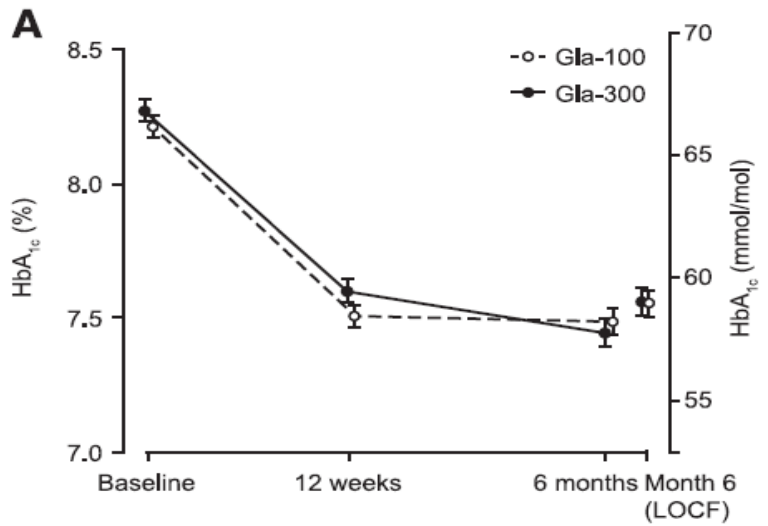


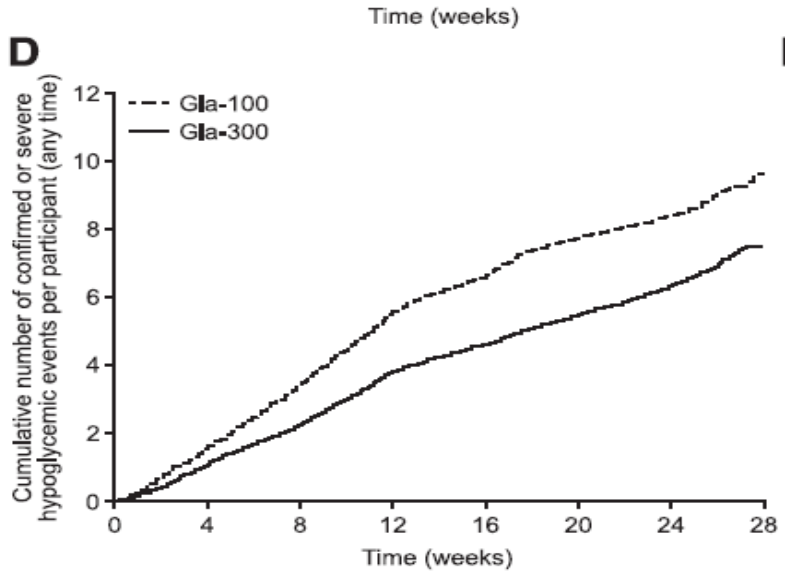
Tresiba (degludec) 100, 200u/ml



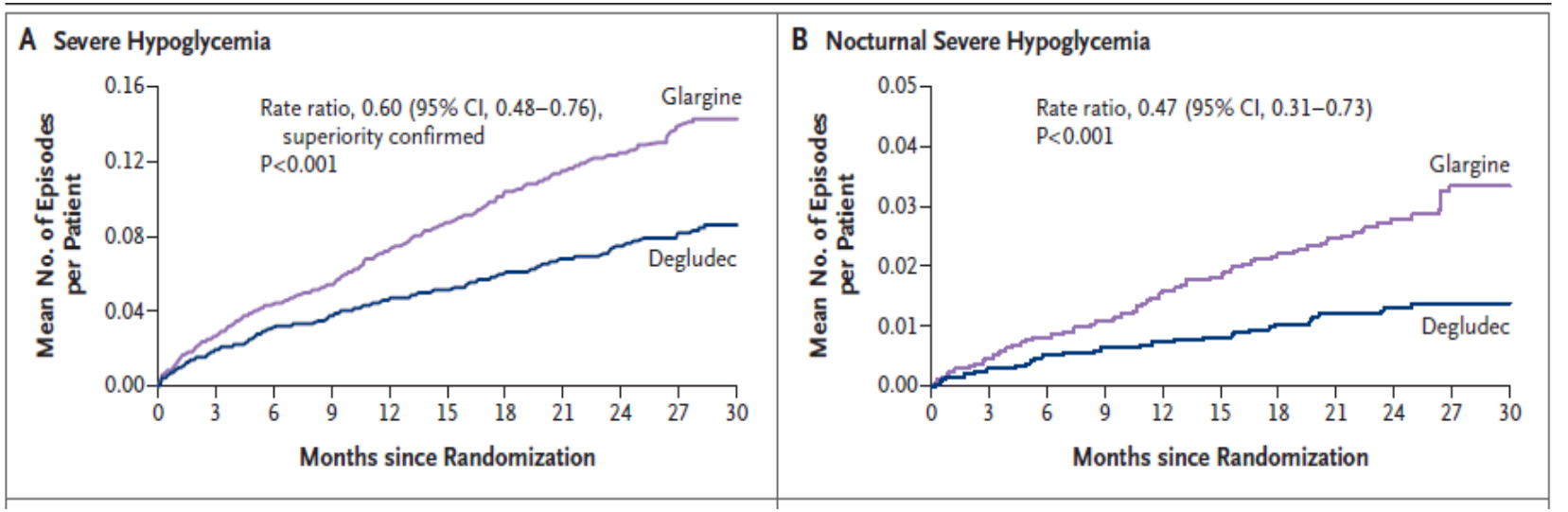
Glargine U300 vs Glargine U100

- U300 compared to U100 (EDITION 2)
  - Lower risk of hypoglycemia (~10%)
  - Non-inferior (<0.4% difference in A1c)
  - Less weight gain (negligible)
  - 10% higher dose required of U300





DEVOTE: degludec vs glargine



- Reduced hypoglycemia (compared to glargine)
  - ➢9% Overall reduction
  - ➢17% Lower nocturnal hypoglycemia (0000-0559)
- DEVOTE – looked at CV benefits of Degludec v. Glargine
  - ➢NO CV benefit (but less hypoglycemia)

Benefits of Concentrated Insulin

- Decreased volume
- Decreased number of injections
- Decreased pain
- Less frequent pen changes
- Greater ease in delivering larger doses
- Insulin pump enhancements
- Altered PK/PD profiles
- Improved adherence

Summary

- T2DM is a disorder of energy metabolism involving several organs, including adipose tissue, muscle tissues, the liver, pancreas, gastrointestinal tract, nervous system, and kidneys. It's the combination of these multiple defects that contributes to the pathogenesis of T2DM
- Guidelines recommend to identify cardiorenal risk factors to guide medication choices
- Guidelines recommend to address glucose control along with weight management for the treatment of T2DM
- Newer concentrated insulins are available and may provide longer duration of action for basal insulin, and less hypoglycemia

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Questions