درمانهای تزریقی در دیابت

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Objectives

- ADA 2024 guideline in treatment of diabetes:
- GLP1 agonists
- Dual agonist (GIP+GLP1)
- Insulin Treatment

Glucagon-like peptide-1 (GLP-1)

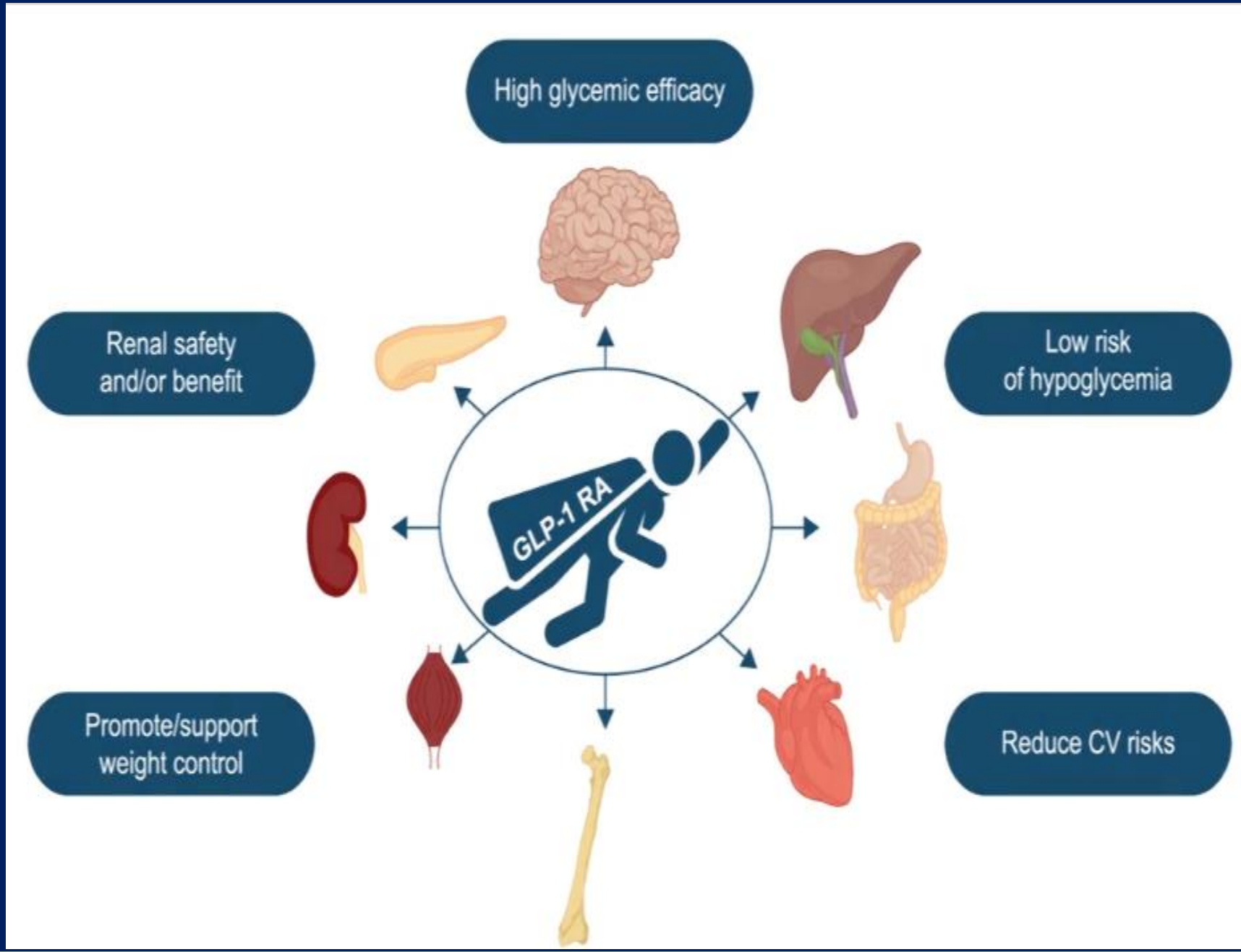
A 30-amino acid peptide secreted in response to the oral ingestion of nutrients by L cells, primarily in the ileum and colon.

There are GLP-1 receptors in islet cells and in the central nervous system, among other places.

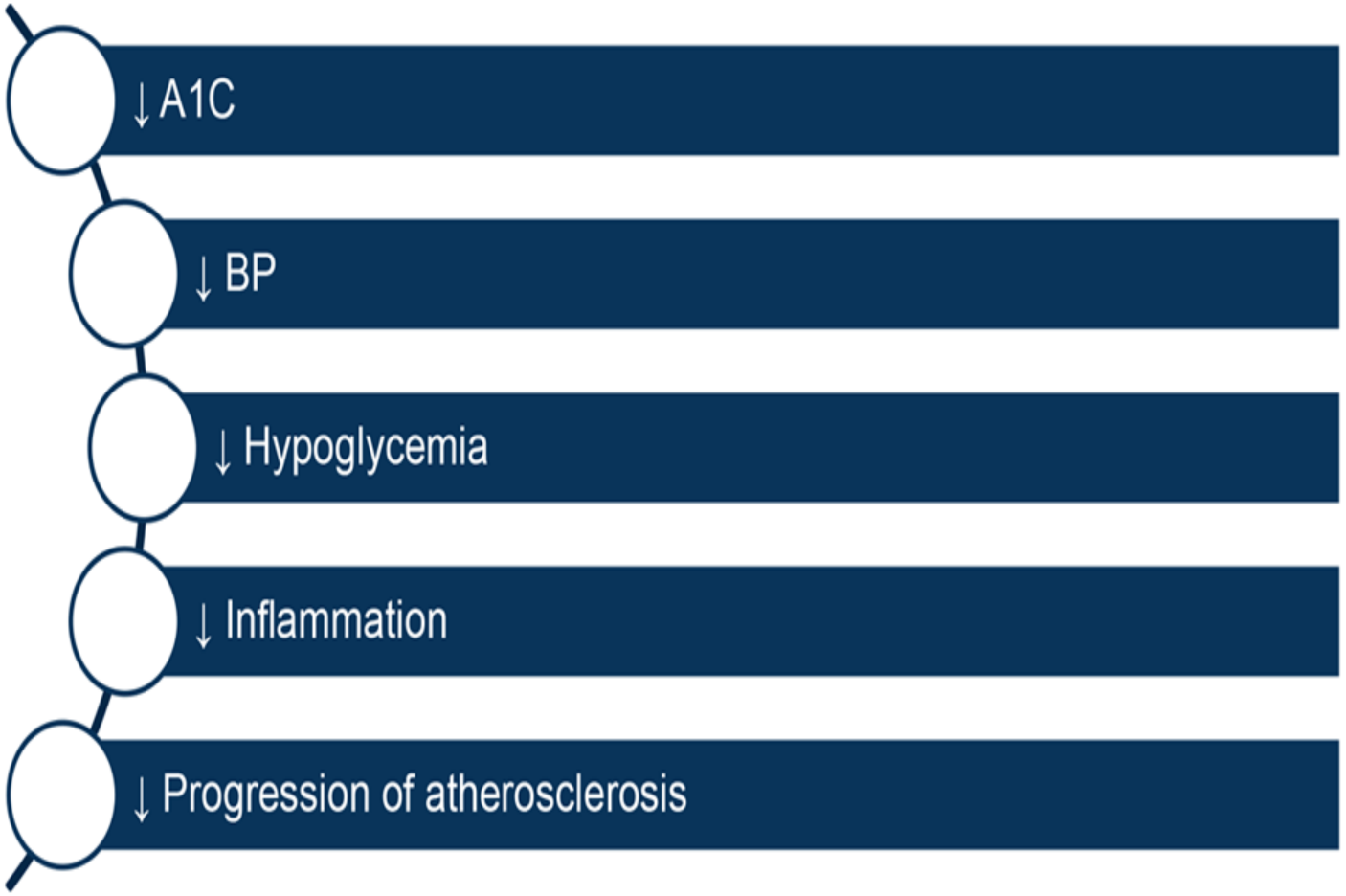
GLP-1 is metabolized by the enzyme dipeptidyl peptidase-IV (DPP-IV) .

Actions of GLP-1

- It enhances glucose-dependent insulin secretion.
- Inhibits glucagon secretion and therefore hepatic glucose production.
- Slows gastric emptying.
- Increases satiety resulting in less food intake.
- Appears to stimulate insulin gene transcription and insulin synthesis.

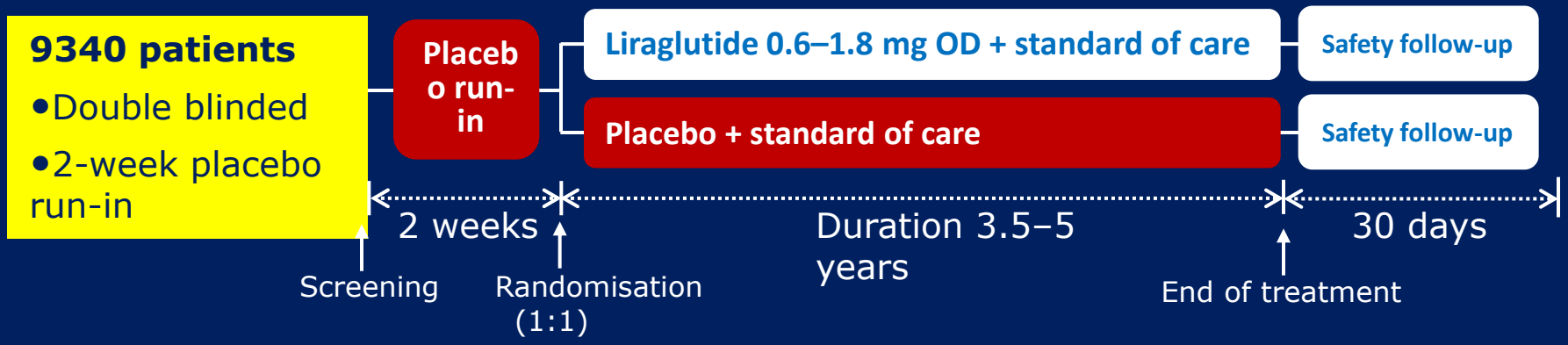

High glycemic efficacy
Low risk of hypoglycemia
Reduce CV risks
Promote/support weight control
Renal safety and/or benefit
GLP-1 RA

Factors That May Contribute to the Beneficial Effects of GLP-1 RAs on CV Outcomes[1-3]



1. Müller TD et al. *Mol Metab*. 2019;30:72-130. 2. Nauck M et al. *Circulation*. 2017;136:849-870. 3. Baggio LL, Drucker DJ. *Mol Metab*. 2021;46:101090.

LEADER: Study design



Key inclusion criteria

- T2DM, HbA_{1c} ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/premix insulin
- Age ≥50 years and established CV disease or chronic renal failure

  or
- Age ≥60 years and risk factors for CV disease

Key exclusion criteria

- T1DM
- Use of GLP-1RAs, DPP-4i, pramlintide, or rapid-acting insulin
- Familial or personal history of MEN-2 or MTC

CV, cardiovascular; HbA_{1c}, glycosylated haemoglobin; OAD, oral antidiabetic drug; OD, once daily; T2DM, type 2 diabetes mellitus.

Marso SP et al. *N Engl J Med* 2016; 375:311-322.

Primary and key secondary outcomes

Primary outcome

Time to first MACE composed of

- CV death
- Non-fatal MI
- Non-fatal stroke

Key secondary outcomes

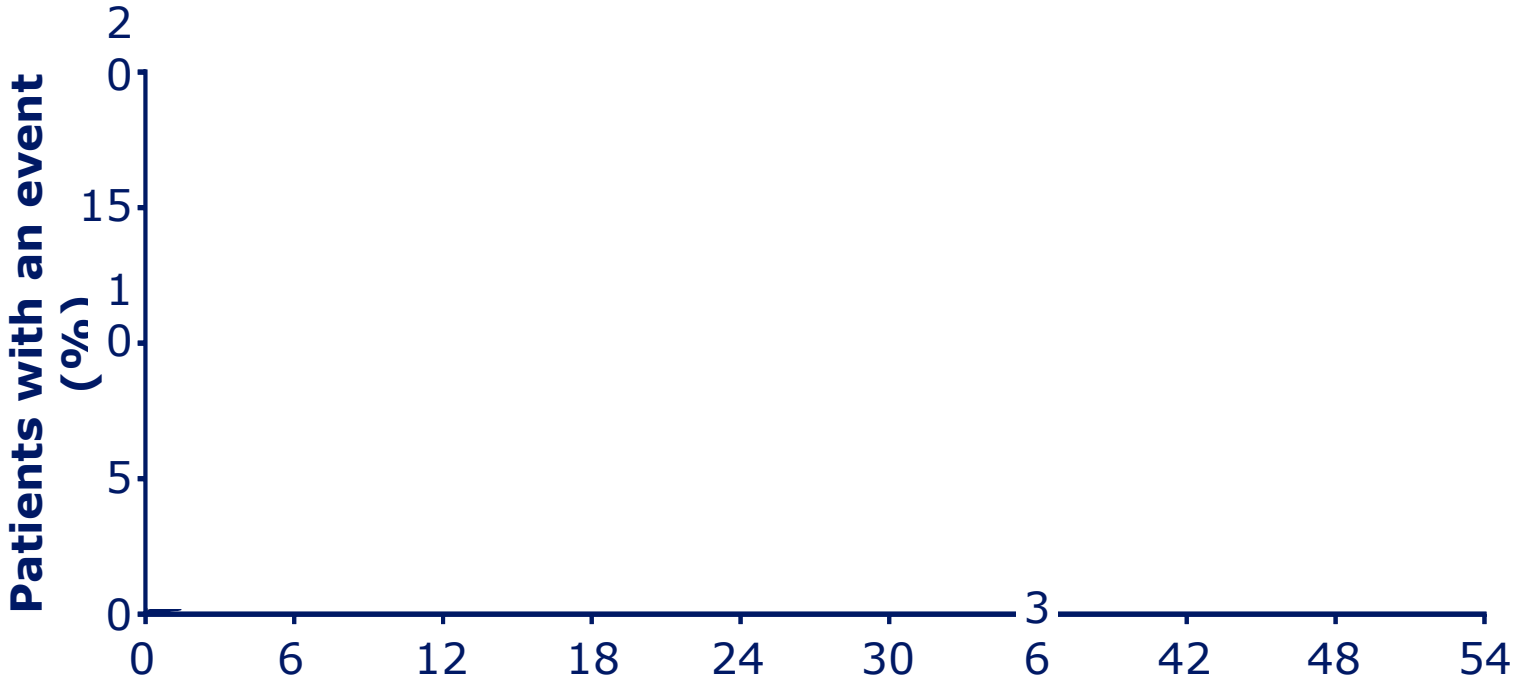
Time to first occurrence of

- Expanded composite CV outcome (CV death, non-fatal MI, non-fatal stroke, coronary revascularisation, unstable angina pectoris requiring hospitalisation, or hospitalisation for heart failure)
- All-cause death
- Each individual component of expanded composite CV outcome

CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction.
Marso SP et al. *N Engl J Med* 2016; 375:311-322.

Primary outcome

CV death, non-fatal myocardial infarction, or non-fatal stroke

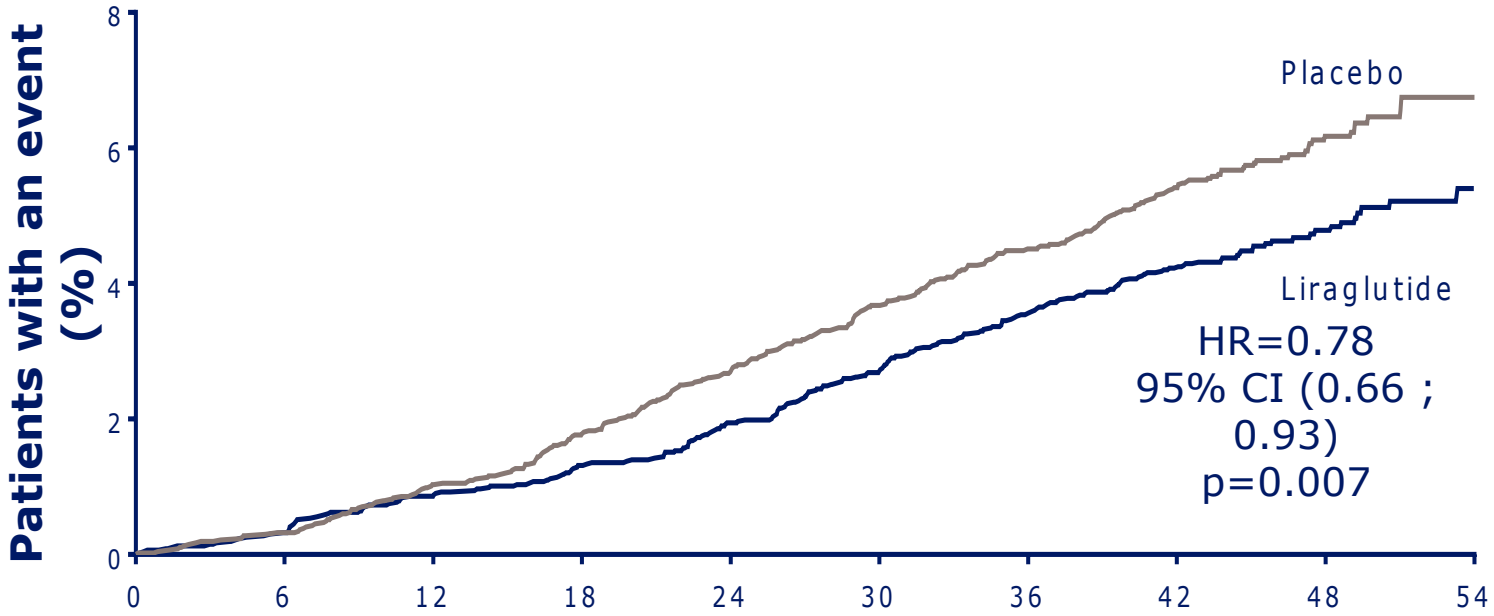


Patients at risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox-proportional hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.
CI, confidence interval; CV, cardiovascular; HR, hazard ratio.
Marso SP et al. *N Engl J Med* 2016; 375:311-322.

CV death



Patients at risk

Liraglutide	4668	4641	4599	4558	[illegible]	[illegible]	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox-proportional hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.
CI, confidence interval; CV, cardiovascular; HR, hazard ratio.
Marso SP et al. *N Engl J Med* 2016; 375:311-322.

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Original Article

Cardiol Res. 2023;14(4):250-260

The Impact of Glucagon-Like Peptide-1 Receptor Agonist on the Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus: A Meta-Analysis and Systematic Review

Ali Rahman[a, e], Sura Alqaisi[a], Sunil E. Saith[b], Rana Alzakhari[c], Ralph Levy[d]

Methods: Systematically, the databases were searched for observational studies reporting compound CV events and deaths in type 2 diabetics without having the risk of cardiovascular diseases (CVDs) compared to other glucose-lowering agents. A meta-analysis was car-

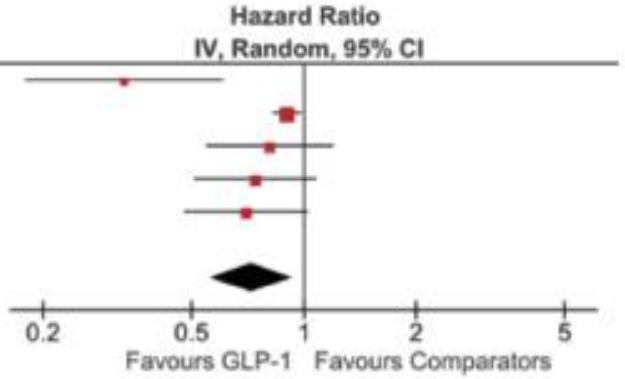
A total of 504,029 enrolled participants (patients: 64,452 vs. comparators: 439,577)

MACE

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Paul, S,K. et al. 2015 [30]	-1.1087	0.3093	11.5%	0.33 [0.18, 0.61]	2015
Svanström, H., et al. 2019 [20]	-0.1054	0.0413	31.6%	0.90 [0.83, 0.98]	2019
Nathan LIR vs GLIM [21]	-0.2107	0.1975	18.6%	0.81 [0.55, 1.19]	2022
Nathan LIR vs GLA [21]	-0.3011	0.1899	19.3%	0.74 [0.51, 1.07]	2022
Nathan LIR vs SIT [21]	-0.3567	0.1925	19.0%	0.70 [0.48, 1.02]	2022
Total (95% CI)			**100.0%**	**0.72 [0.56, 0.93]**	

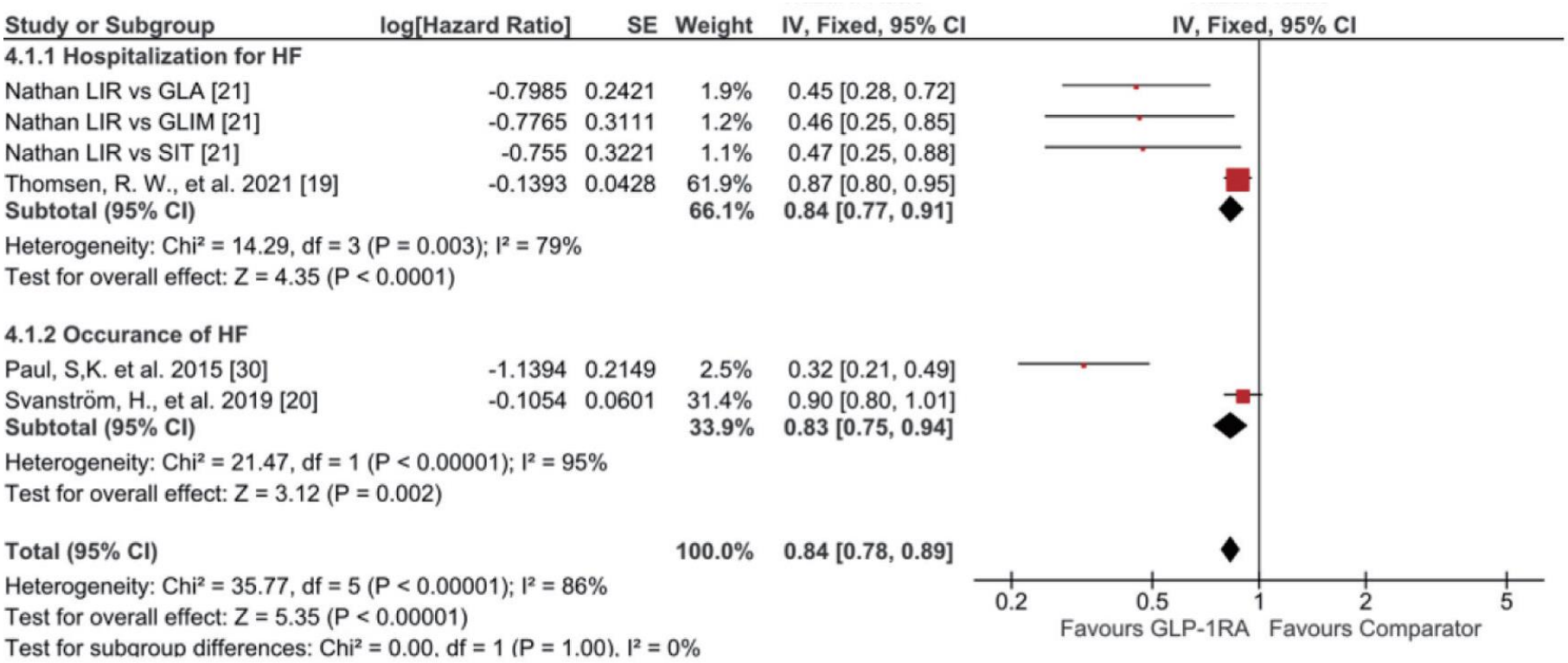
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 12.62$, df = 4 (P = 0.01); $I^2 = 68\%$

Test for overall effect: Z = 2.50 (P = 0.01)



Ali Rahmana, et al.Cardiol Res. 2023;

Heart failure



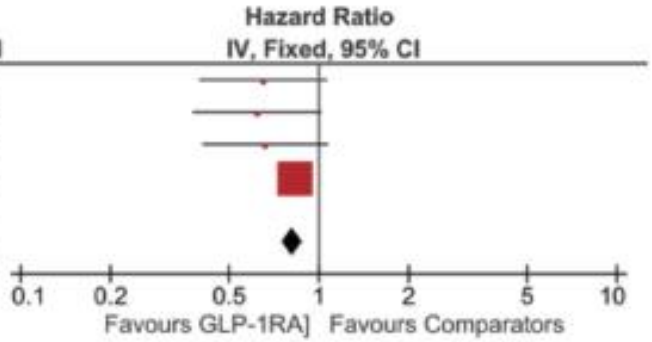
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% CI
4.1.1 Hospitalization for HF				
Nathan LIR vs GLA [21]	-0.7985	0.2421	1.9%	0.45 [0.28, 0.72]
Nathan LIR vs GLIM [21]	-0.7765	0.3111	1.2%	0.46 [0.25, 0.85]
Nathan LIR vs SIT [21]	-0.755	0.3221	1.1%	0.47 [0.25, 0.88]
Thomsen, R. W., et al. 2021 [19]	-0.1393	0.0428	61.9%	0.87 [0.80, 0.95]
Subtotal (95% CI)			**66.1%**	**0.84 [0.77, 0.91]**
Heterogeneity: Chi² = 14.29, df = 3 (P = 0.003); I² = 79%				
Test for overall effect: Z = 4.35 (P < 0.0001)				
4.1.2 Occurance of HF				
Paul, S,K. et al. 2015 [30]	-1.1394	0.2149	2.5%	0.32 [0.21, 0.49]
Svanström, H., et al. 2019 [20]	-0.1054	0.0601	31.4%	0.90 [0.80, 1.01]
Subtotal (95% CI)			**33.9%**	**0.83 [0.75, 0.94]**
Heterogeneity: Chi² = 21.47, df = 1 (P < 0.00001); I² = 95%				
Test for overall effect: Z = 3.12 (P = 0.002)				
Total (95% CI)			**100.0%**	**0.84 [0.78, 0.89]**
Heterogeneity: Chi² = 35.77, df = 5 (P < 0.00001); I² = 86%				
Test for overall effect: Z = 5.35 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%				

Ali Rahmana, et al.Cardiol Res. 2023;

all cause mortality

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Nathan LIR vs GLA [21]	-0.4308	0.2477	2.2%	0.65 [0.40, 1.06]
Nathan LIR vs GLIM [21]	-0.478	0.2498	2.2%	0.62 [0.38, 1.01]
Nathan LIR vs SIT [21]	-0.4155	0.2429	2.3%	0.66 [0.41, 1.06]
Svanström, H., et al. 2019 [20]	-0.1863	0.0383	93.3%	0.83 [0.77, 0.89]
Total (95% CI)			**100.0%**	**0.82 [0.76, 0.88]**

Heterogeneity: Chi² = 3.01, df = 3 (P = 0.39); I² = 0%
Test for overall effect: Z = 5.50 (P < 0.00001)



Ali Rahmana, et al.Cardiol Res. 2023;

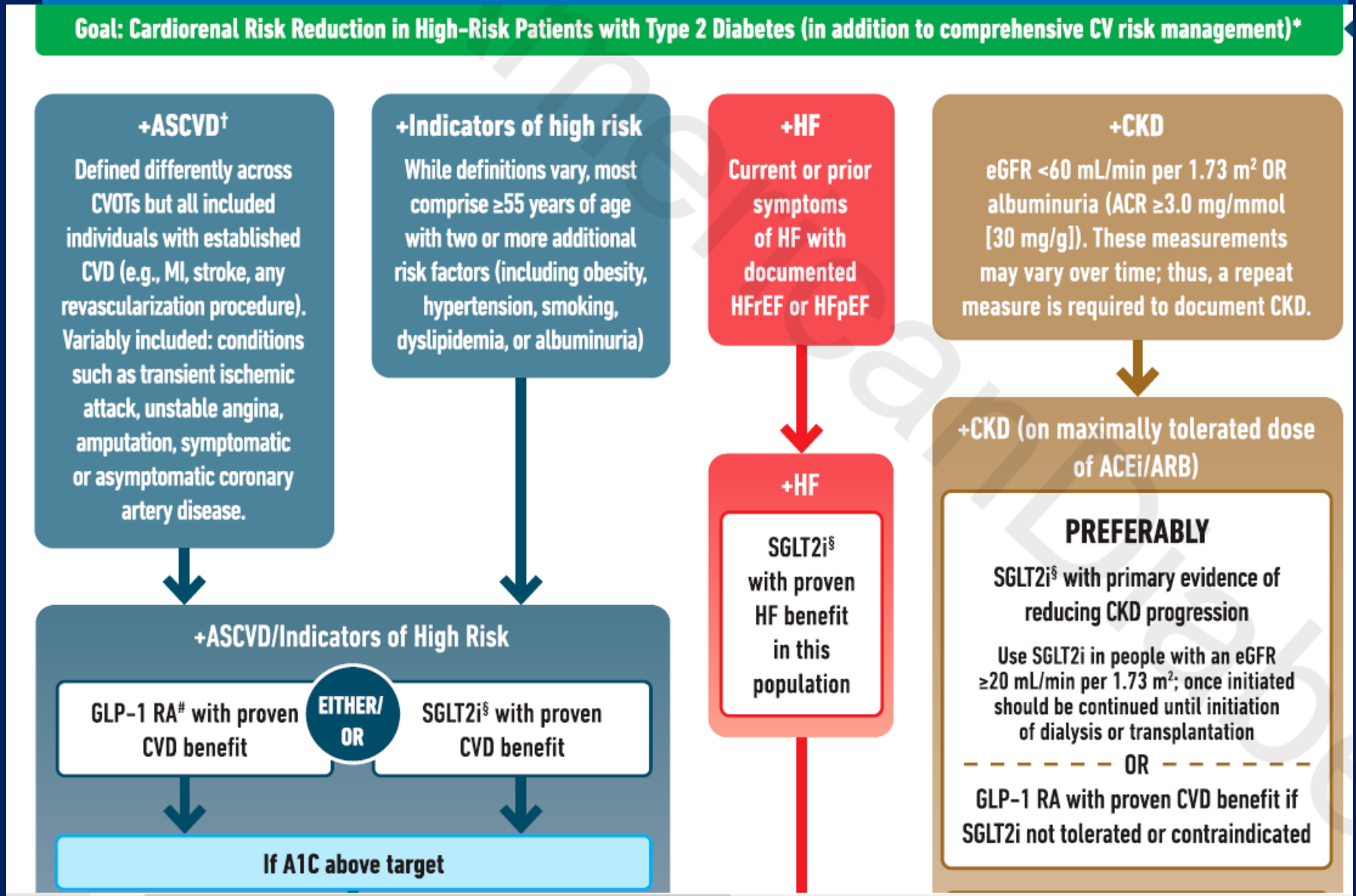
Composite Kidney Outcomes Including Macroalbuminuria: Results From CVOTs

ELIXA[1]	EXSCEL[2]	LEADER[3]	REWIND[4]	SUSTAIN-6[5]
Lixisenatide	Exenatide ER	Liraglutide	Dulaglutide	Semaglutide injection
HR = 0.84 (95% CI, 0.68-1.02); *P* = .083	HR = 0.88 (95% CI, 0.76-1.01); *P* = .065	HR = 0.78 (95% CI, 0.67-0.92); *P* = .003	HR = 0.85 (95% CI, 0.77-0.93); *P* = .0004	HR = 0.64 (95% CI, 0.46-0.88); *P* = .006

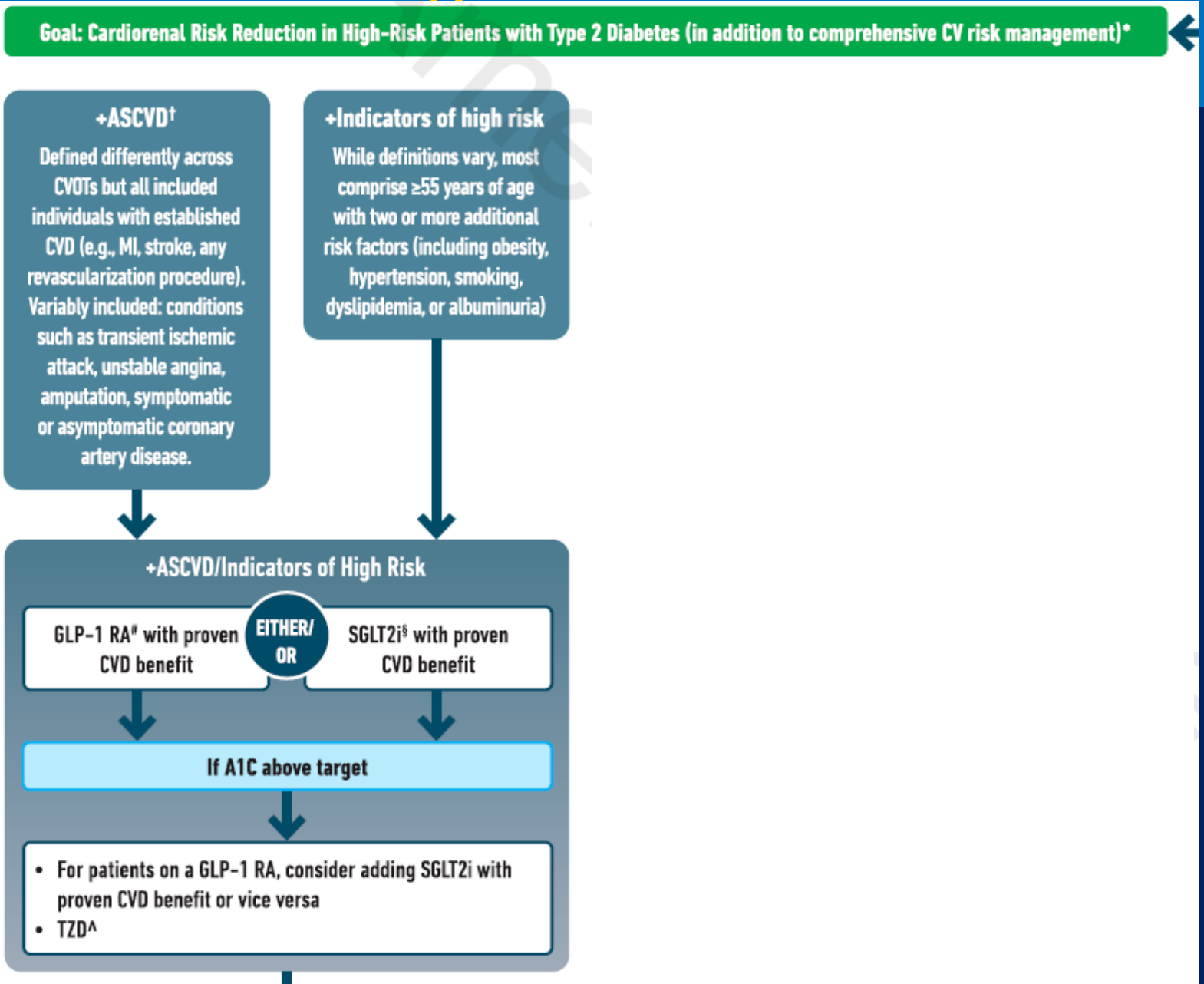
- Overall, GLP-1 RAs reduce composite kidney outcomes including macroalbuminuria[6]
- Individually, most of these reductions were statistically significant[3-5]
- ELIXA and EXSCEL demonstrated neutrality[1,2]

1. Pfeffer MA et al. *N Engl J Med*. 2015;373:2247-2257. 2. Holman RR et al. *N Engl J Med*. 2017;377:1228-1239.
3. Marso SP et al. *N Engl J Med*. 2016;375:311-322. 4. Gerstein HC et al. *Lancet*. 2019;394:121-130.
5. Marso SP et al. *N Engl J Med*. 2016;375:1834-1844. 6. Kristensen SL et al. *Lancet Diabetes Endocrinol*. 2019;7:776-785.

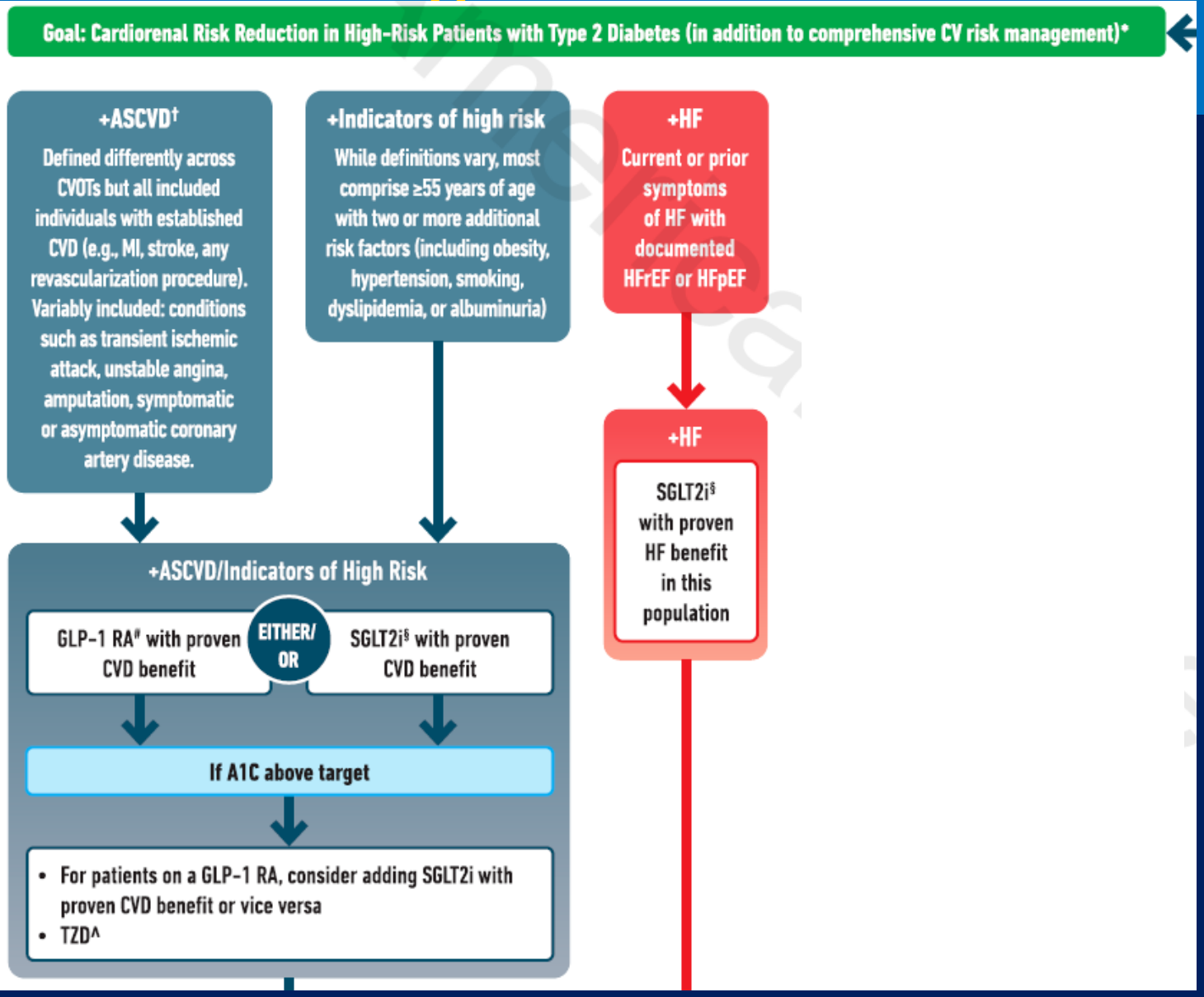
ADA guideline 2024

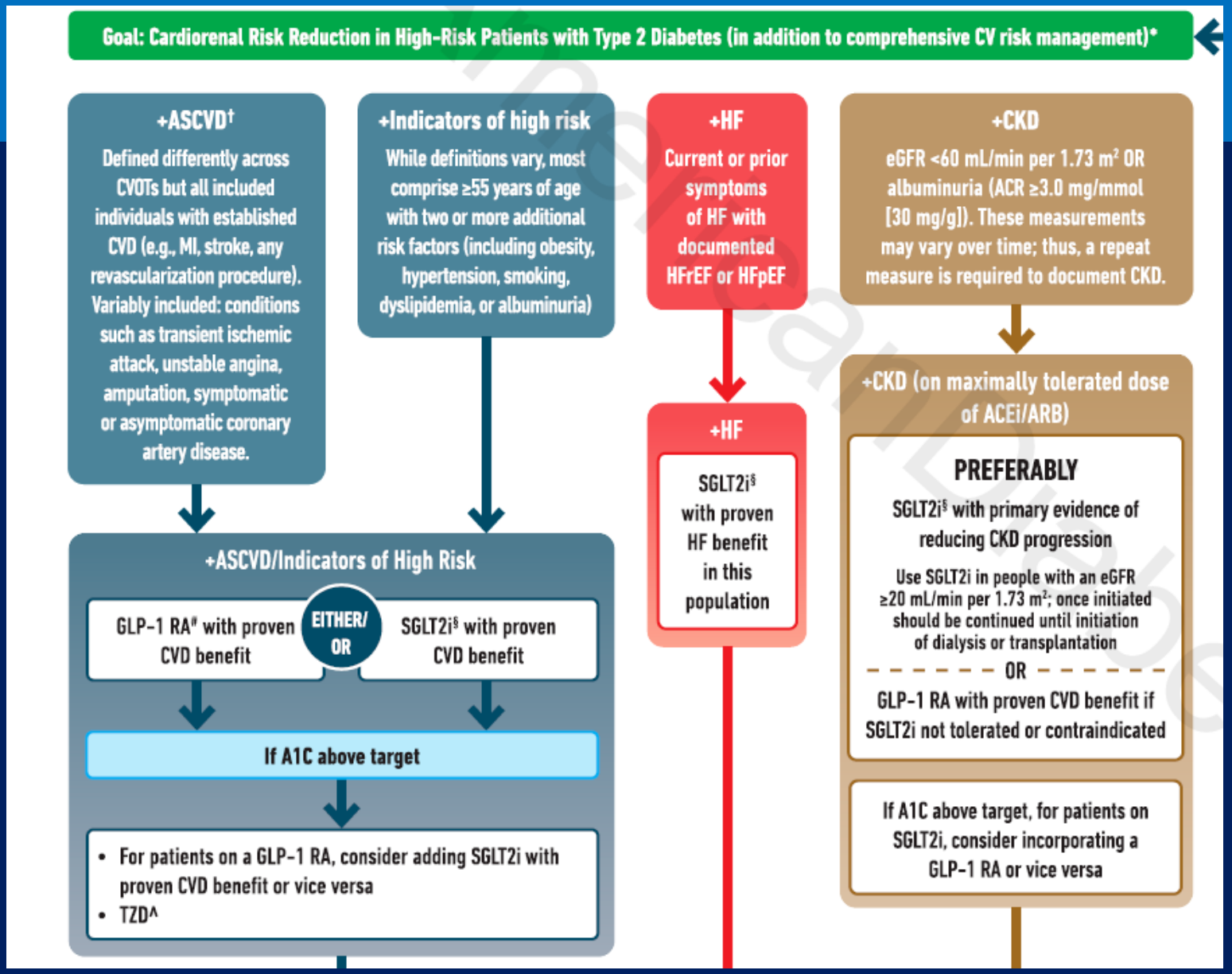


ADA guideline 2024

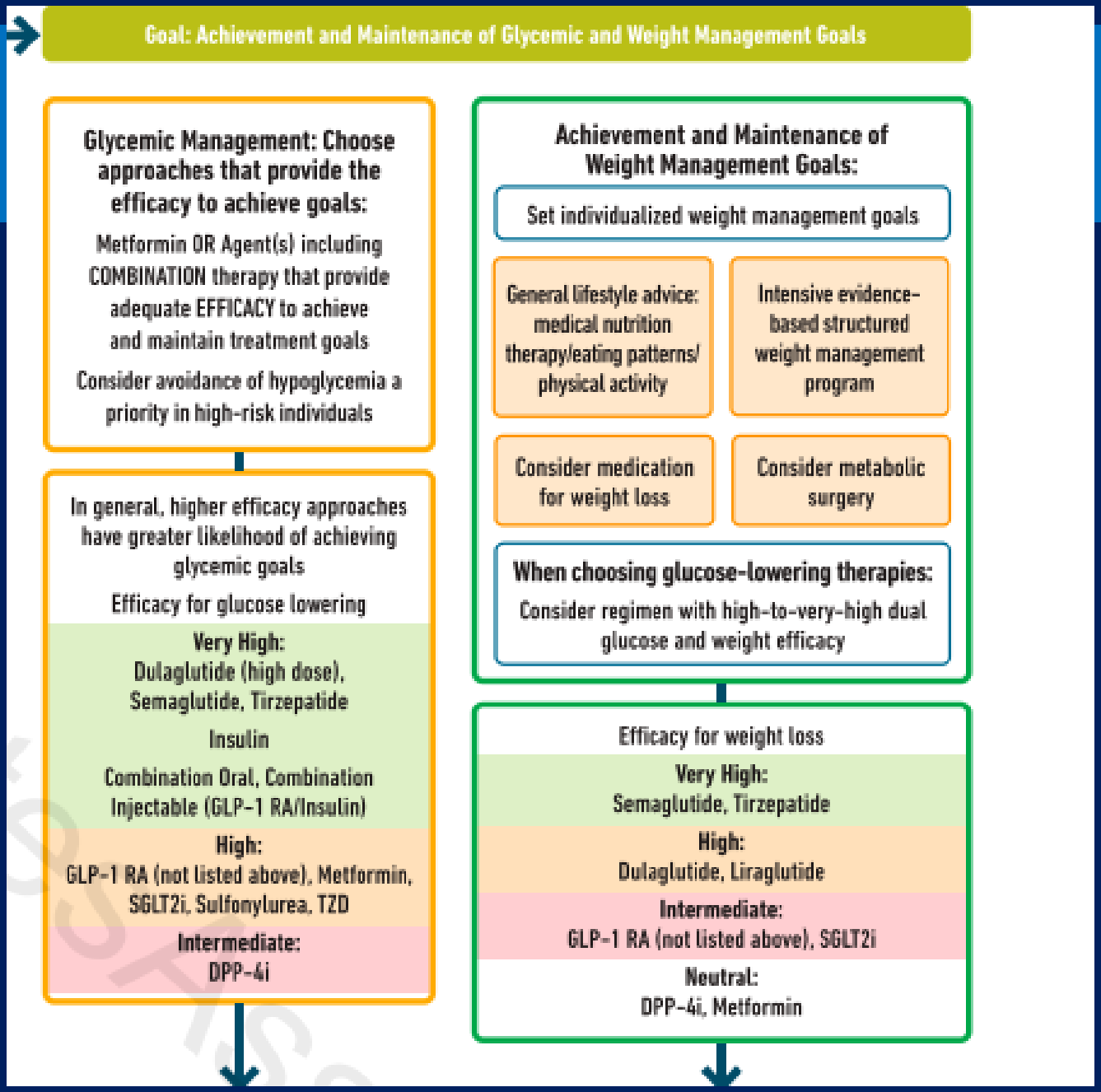


ADA guideline 2024





ADA guideline 2023

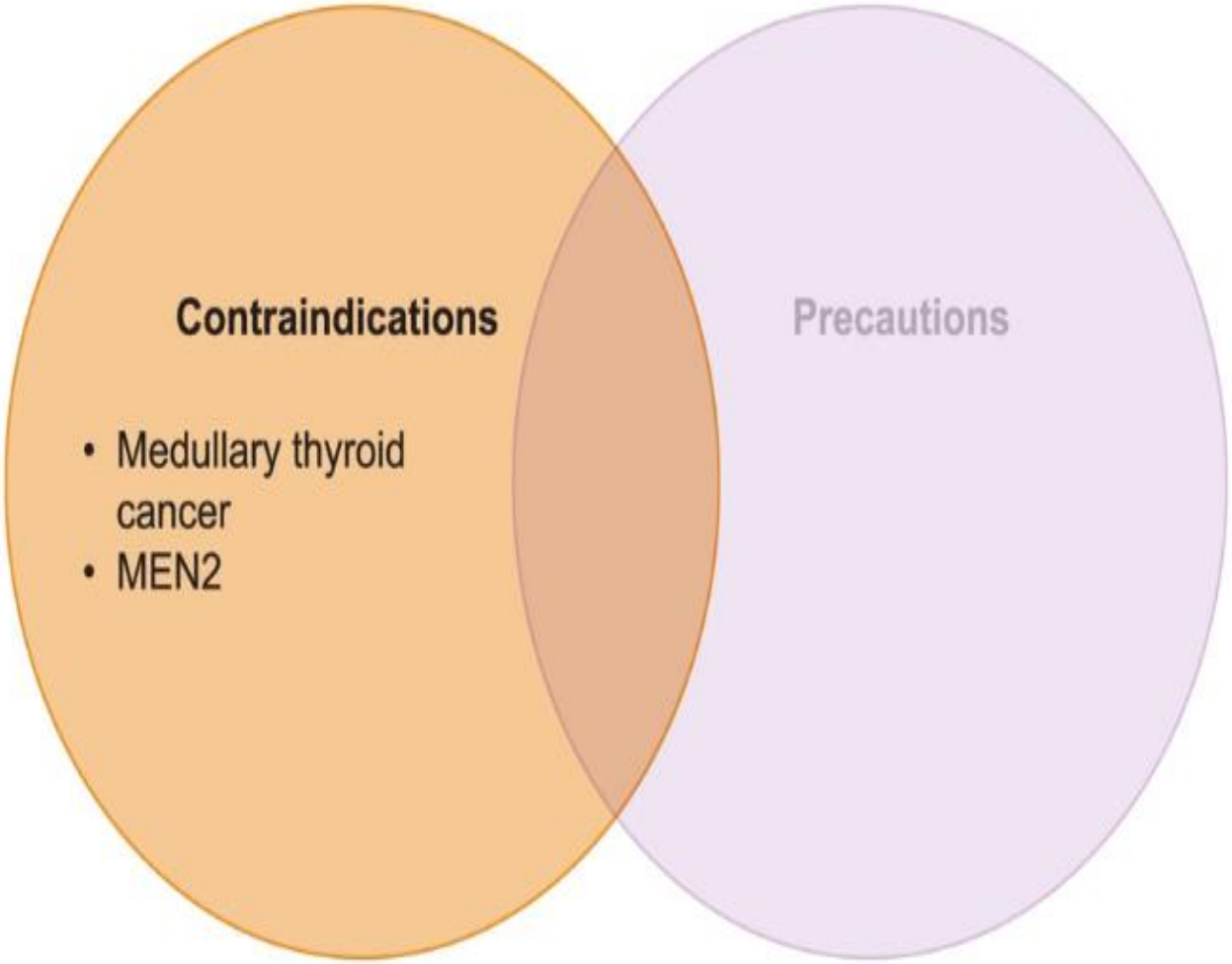


ADA guideline 2023

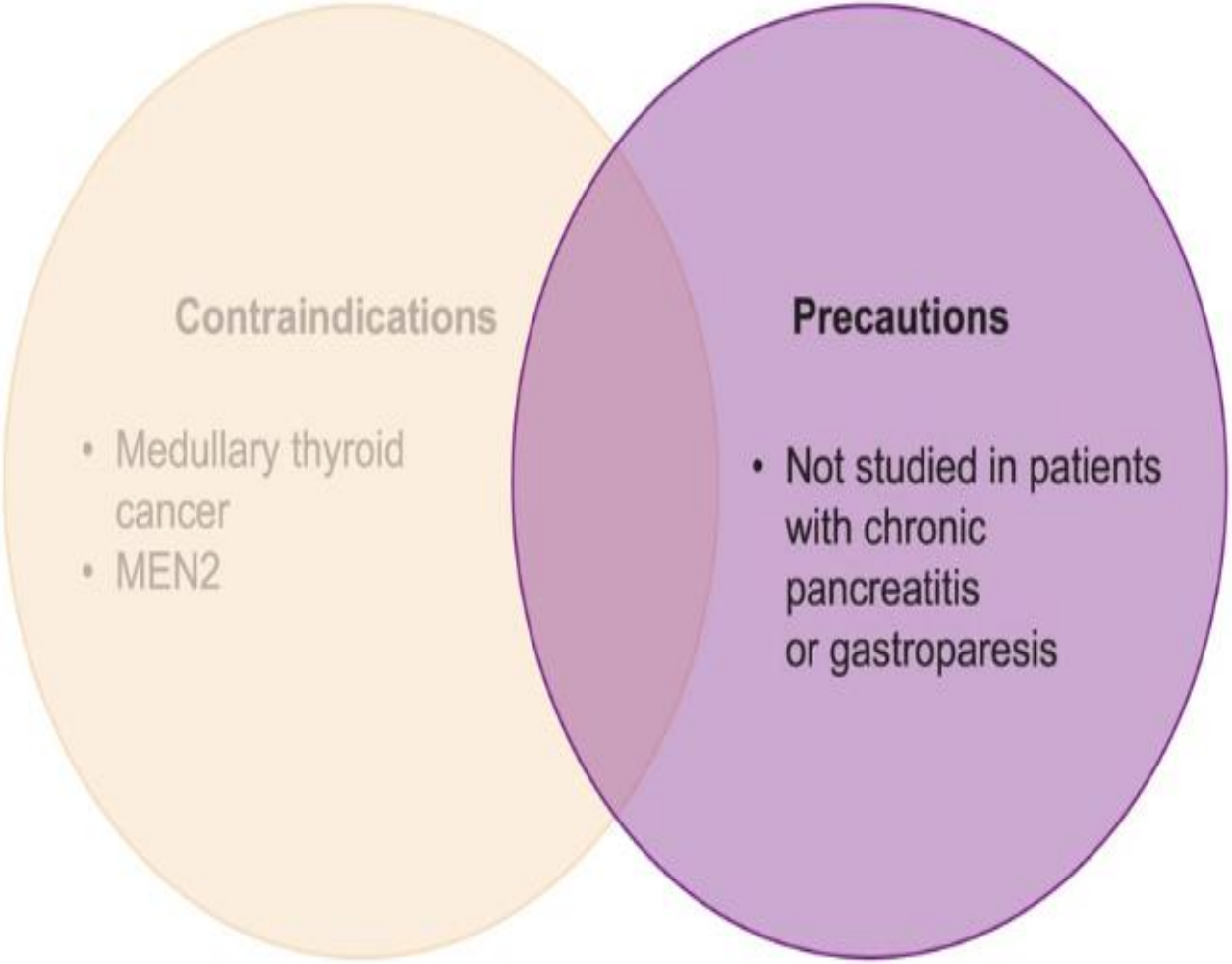
GLP-1 RAs	• Exenatide (extended release)	2 mg powder for suspension or pen
	• Exenatide	10 μg pen
	• Dulaglutide	4.5 mg mL pen
	• Semaglutide	1 mg pen 14 mg (tablet)
	• Liraglutide	1.8 mg pen
	• Lixisenatide	20 μg pen
GLP-1/GIP dual agonist	• Tirzepatide	15 mg pen

ADA guideline 2023

Factors That May Affect Treatment Selection[11-21]



Factors That May Affect Treatment Selection[11-21]



Education of the patient is key

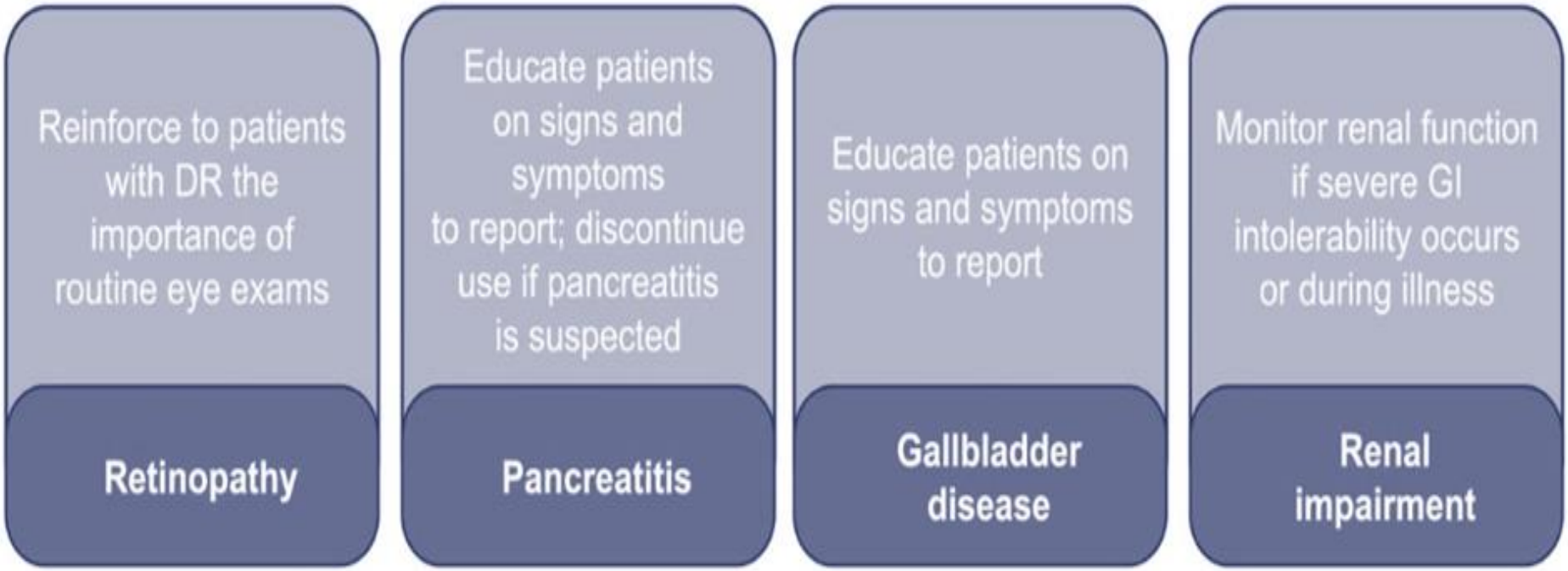
Eat smaller meals and less high-fat food

Stop eating as soon as you feel full

Be mindful of your own eating patterns and responses

Nausea

- Typically transient during initiation and dose escalation
- Dosing flexibility, such as slower titration, may help
- Eating beyond satiety can cause nausea


Reinforce to patients with DR the importance of routine eye exams
Retinopathy
Educate patients on signs and symptoms to report; discontinue use if pancreatitis is suspected
Pancreatitis
Educate patients on signs and symptoms to report
Gallbladder disease
Monitor renal function if severe GI intolerability occurs or during illness
Renal impairment

Gastric Inhibitory Peptide

- glucose-dependent insulinotropic polypeptide
- higher insulin secretion in response to oral glucose
- GIP is considered the most potent incretin hormone, and along with glucagon-like peptide-1 (GLP-1), it contributes to 25 to 70% of the postprandial insulin response

Dual GIP/GLP-1 receptor agonists: New advances for treating type-2 diabetes

- Exert complementary actions
- Dual GIP/GLP-1 receptor agonists (RAs) are more potent than pure GLP-1 Ras
- Reduction in HbA1c and body weight

André J. Scheen, Annales d'Endocrinologie (2023)

Case1

- A 57-year-old man with T2DM, peripheral vascular disease , coronary artery disease, chronic kidney disease, obesity, hyperlipidemia, and hypertension presents for evaluation.
- Medications: sitagliptin; insulin glargine 10 units once daily; aspirin; losartan;furosemide; rosuvastatin.
- BMI 38 kg/m2, and BP: 144/86 mm Hg.
- A1c :8.4% (68 mmol/mol), and GFR: 18 mL/min per 1.73 m2. He has had no problems with hypoglycemia on his current regimen

Case 1

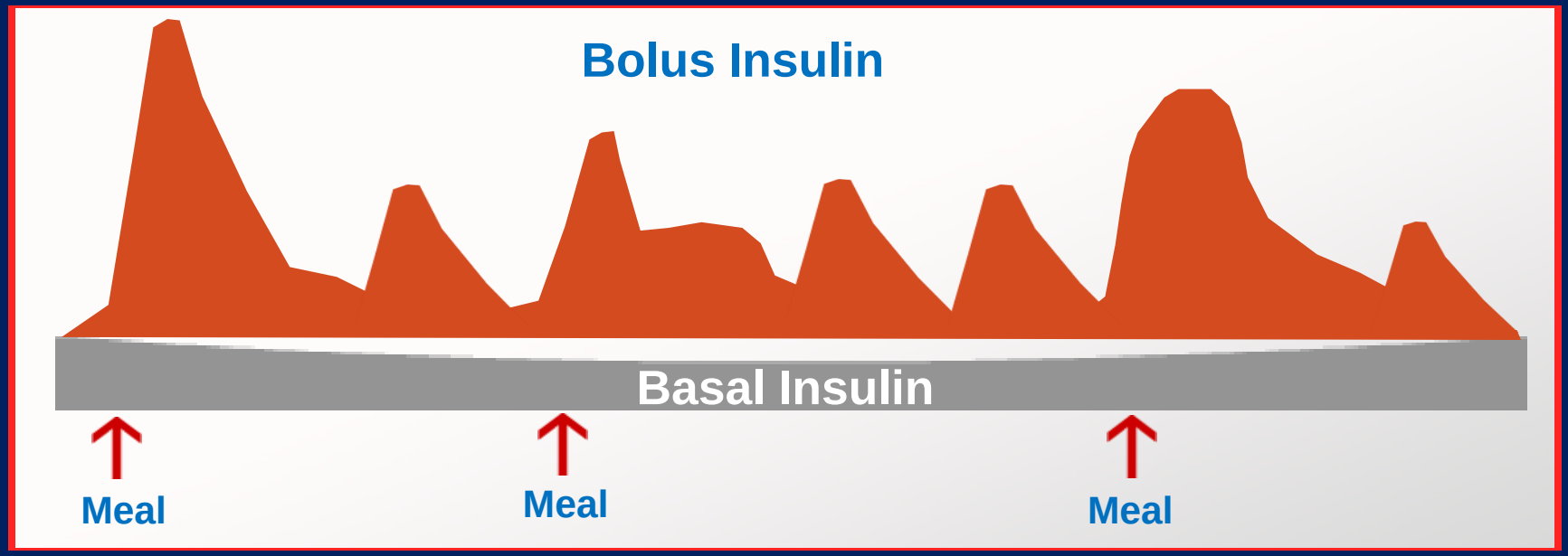
- **Which of the following change(s) to his medication regimen would be recommended at this time?**
- A. No change
- B. Add empagliflozin
- C. Add liraglutide
- D. Substitute liraglutide for sitagliptin

Insulin treatment

Case

- A 57 year old woman with 20 year history of diabetes and CKD on insulin detemir 40 unit BD
- Nocturnal hypoglycemia and A1C :8.5
- Often forgot the evening dose
- What is the best approach?

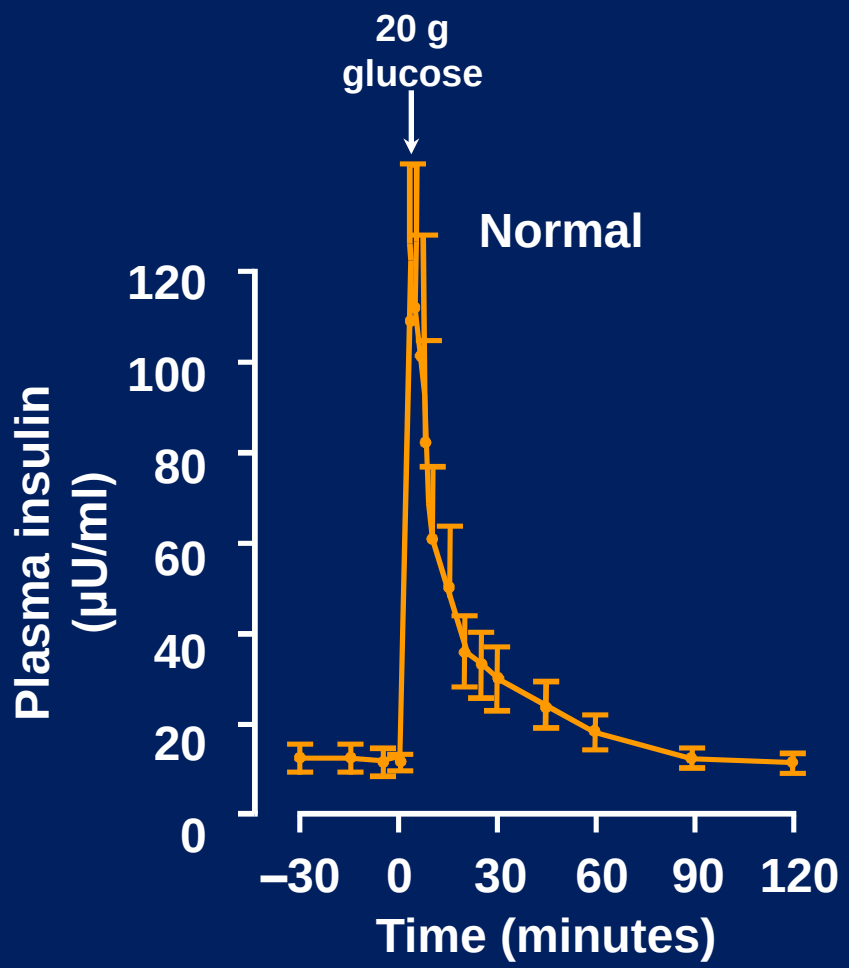
Normal Pancreatic Function

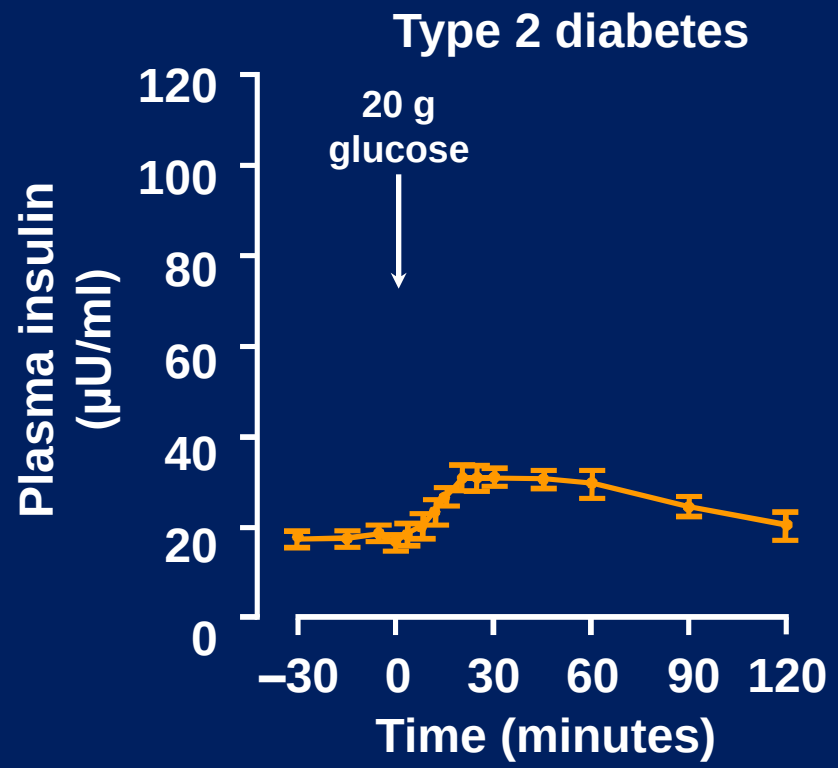


Expected insulin changes during the day for individuals with a healthy pancreas.

*

Loss of first-phase insulin response





Pfeifer MA et al. Am J Med 1981;70:579–88

Metabolic Abnormalities

Chronic hyperglycemia paradoxically impairs islet function ("glucose toxicity") and leads to a worsening of hyperglycemia.

Improvement in glycemic control is often associated with improved islet function.

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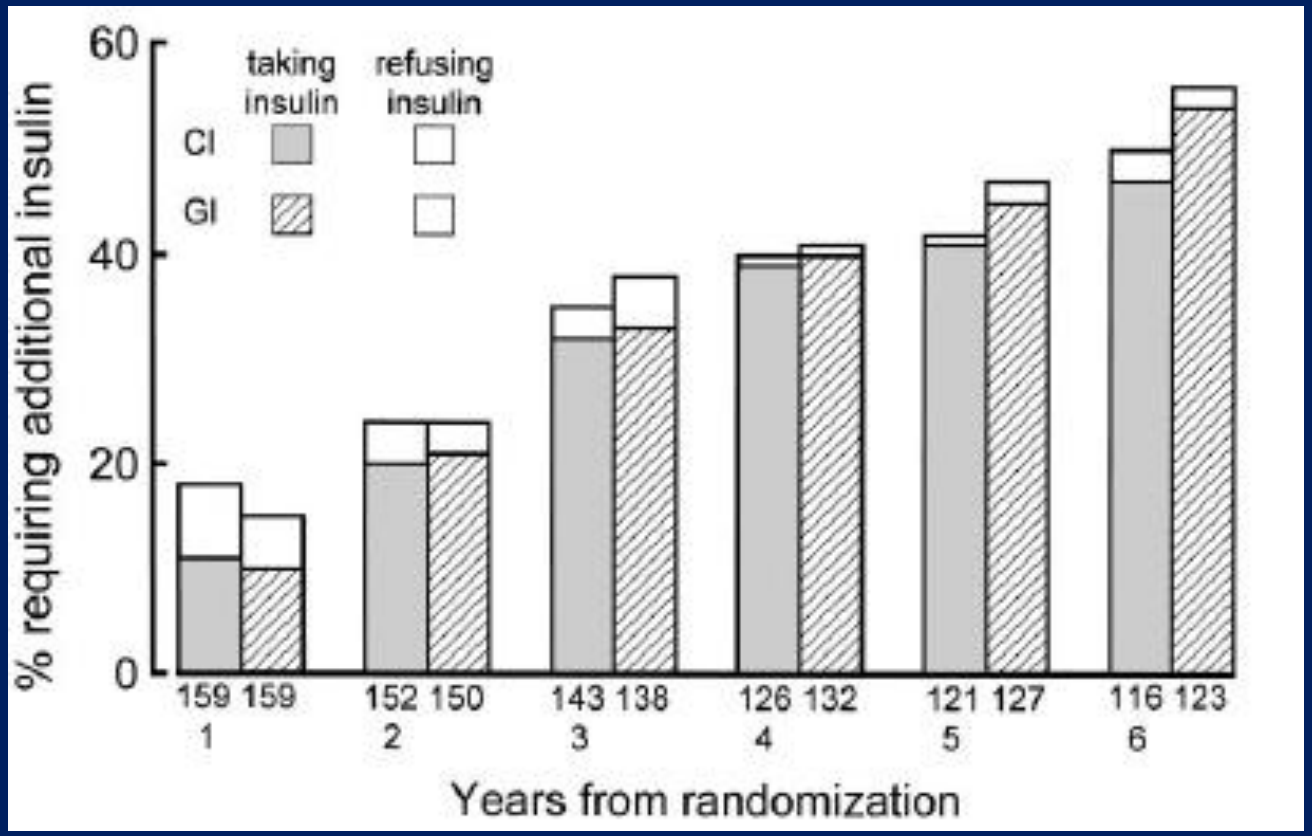
Need for insulin increase overtime



Wright A,et al. Diabetes care.2002

Insulin therapy

- Used to treat all patients with Type I diabetes
- 1/3 of patients with Type 2 diabetes
- Women with GDM
- DKA , NKHC
- Acute stress

Basal insulin in type2 DM

- Basal insulin may be second agent after metformin
- When combination of oral agents become inadequate
- High FBS
- Side effect of other agents
- Patients with advanced hepatic or renal disease

Benefit of early insulin use

- Most effective in reducing blood glucose
- Effective targeting fasting glucose
- Potential for preservation of beta cell function
- Good safety record other than hypoglycemia

(no evidence of cancer or heart disease in Origin trial)

Weng J,et al. Lancet. 2008, Pennartz c et al. Diabetes care 2011, ORIGIN trial investigators,N Engl J Med 2012

Challenges with use of basal insulin

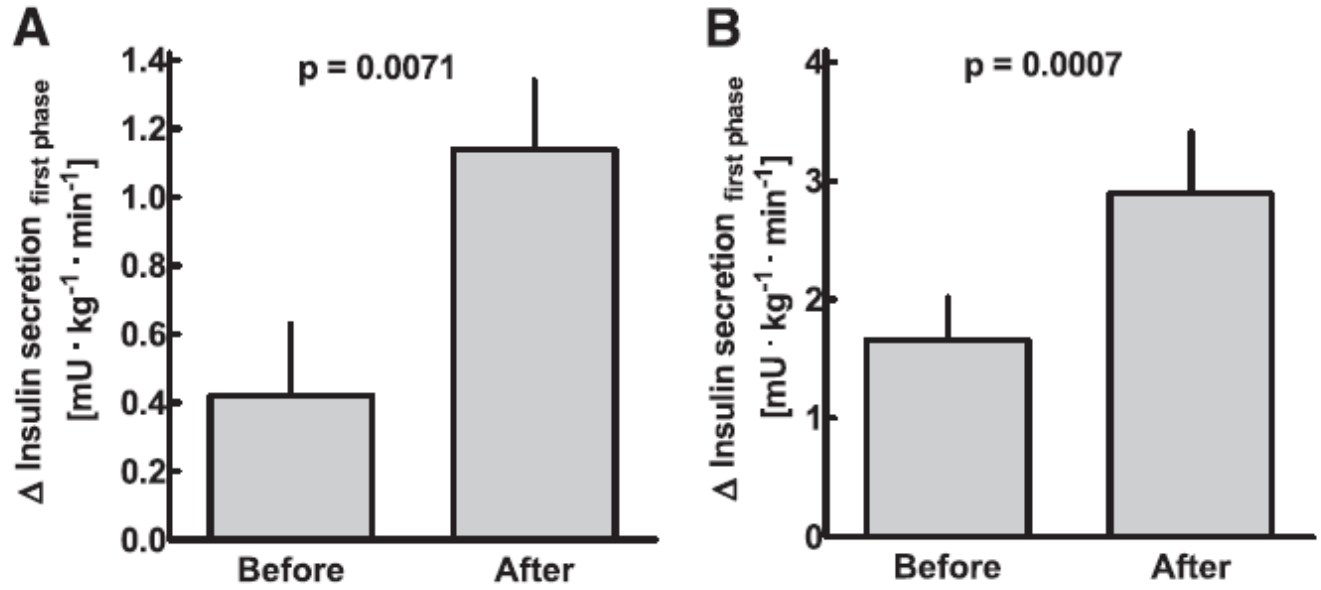
Provider

- Knowledge of new basal insulins
- Selection of appropriate basal insulin
- Balancing control and hypoglycemia
- Appropriate titration

Patients

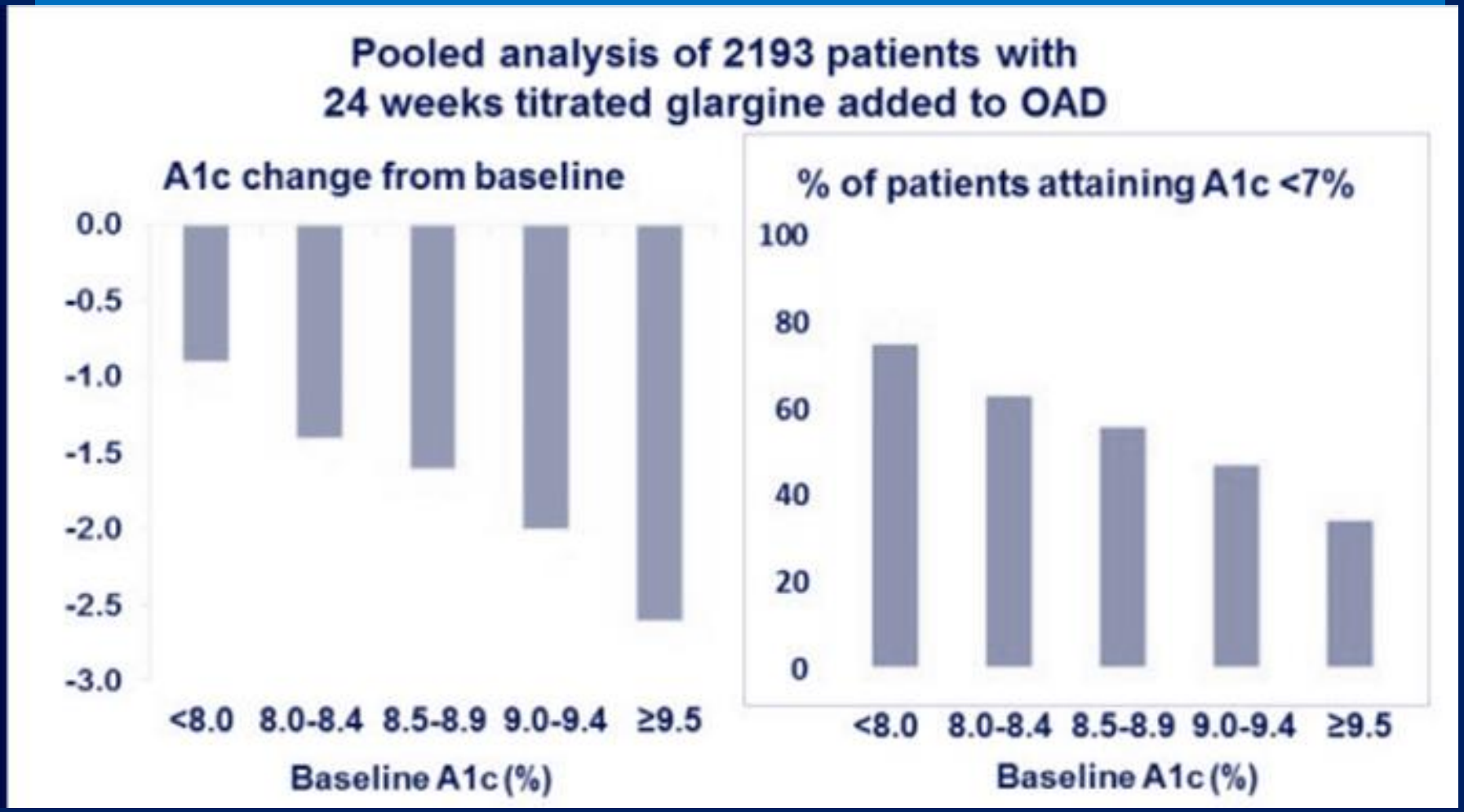
- Fears of injection
- Fears of insulin and hypoglycemia
- Obtaining education
- Administration techniques
- Cost

Improvement of Insulin secretion after adding basal insulin to oral agents



Pennartz c et,al. Diabetes care. 2011

A1c Reduction with basal insulin



Riddle MC, et al. Diabetes. 2009

Insulin options in type2 DM

- **Basal only** added to oral agents
- **Basal plus**: adding one rapid acting analogs starting with largest meal
- **Basal bolus**: rapid acting analogs before each meals
- **Premix** insulin

Overcoming the barrier of hypoglycemia

- Less hypoglycemia with basal insulin only
- Less hypoglycemia with analog insulins
- Proper patient education
- Appropriate dosing
- Individualized targeting

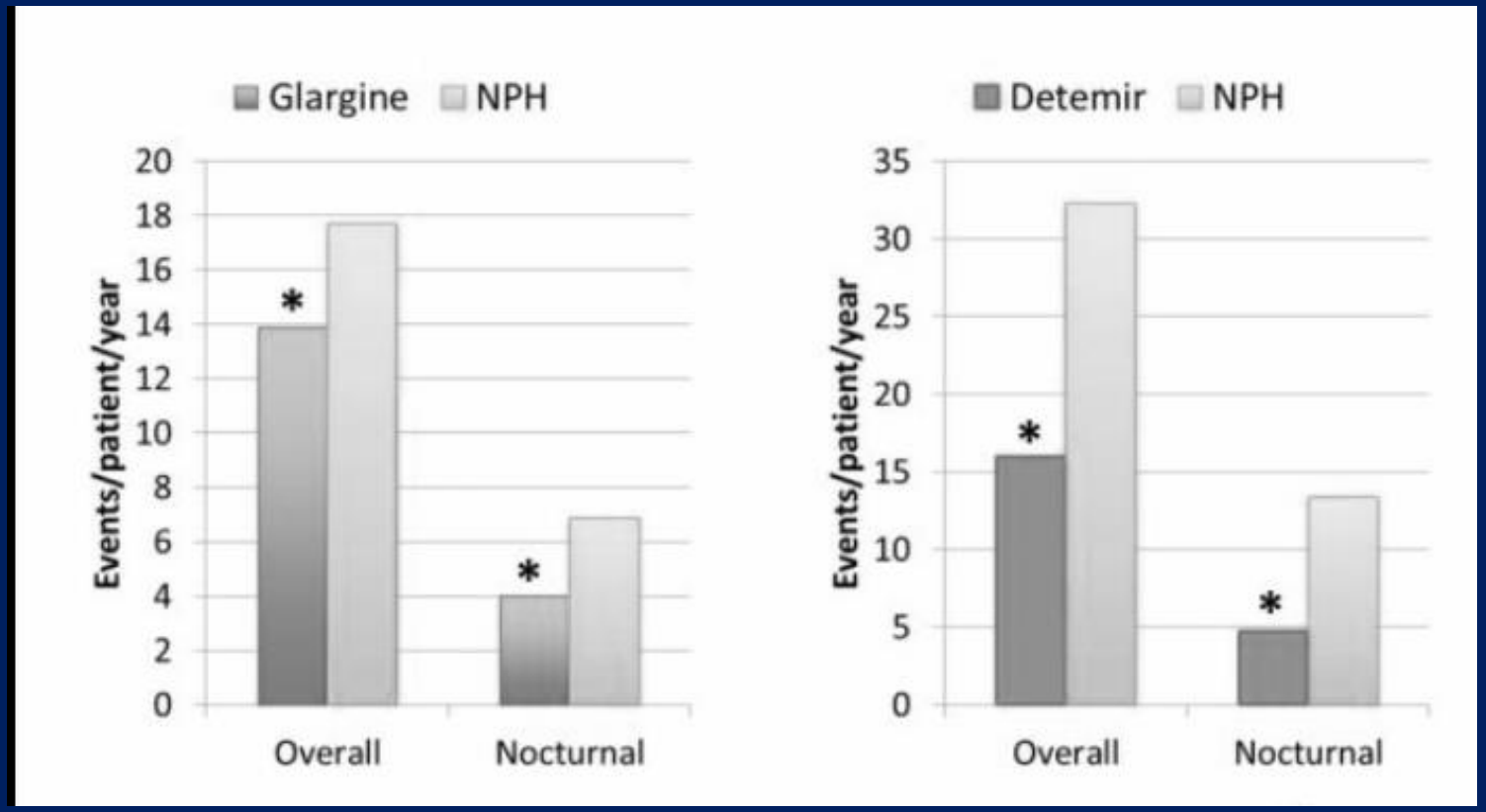
Characteristics of Available Basal Insulin Analogs

Benefits over NPH

- Longer duration of action
- Less variability
- Less weight gain
- Less hypoglycemia

Simon ACR,Diabetes Technol Ther . 2011

Less hypoglycemic event with basal analogs compared to NPH



Riddle et al. Diabetes care. 2003
Philis Tsimikas et al. Clin Ther 2006

The Basal/Bolus Insulin Concept

- Basal Insulin
  - Suppresses glucose production between meals and overnight
  - Nearly constant levels
  - 50% of daily needs

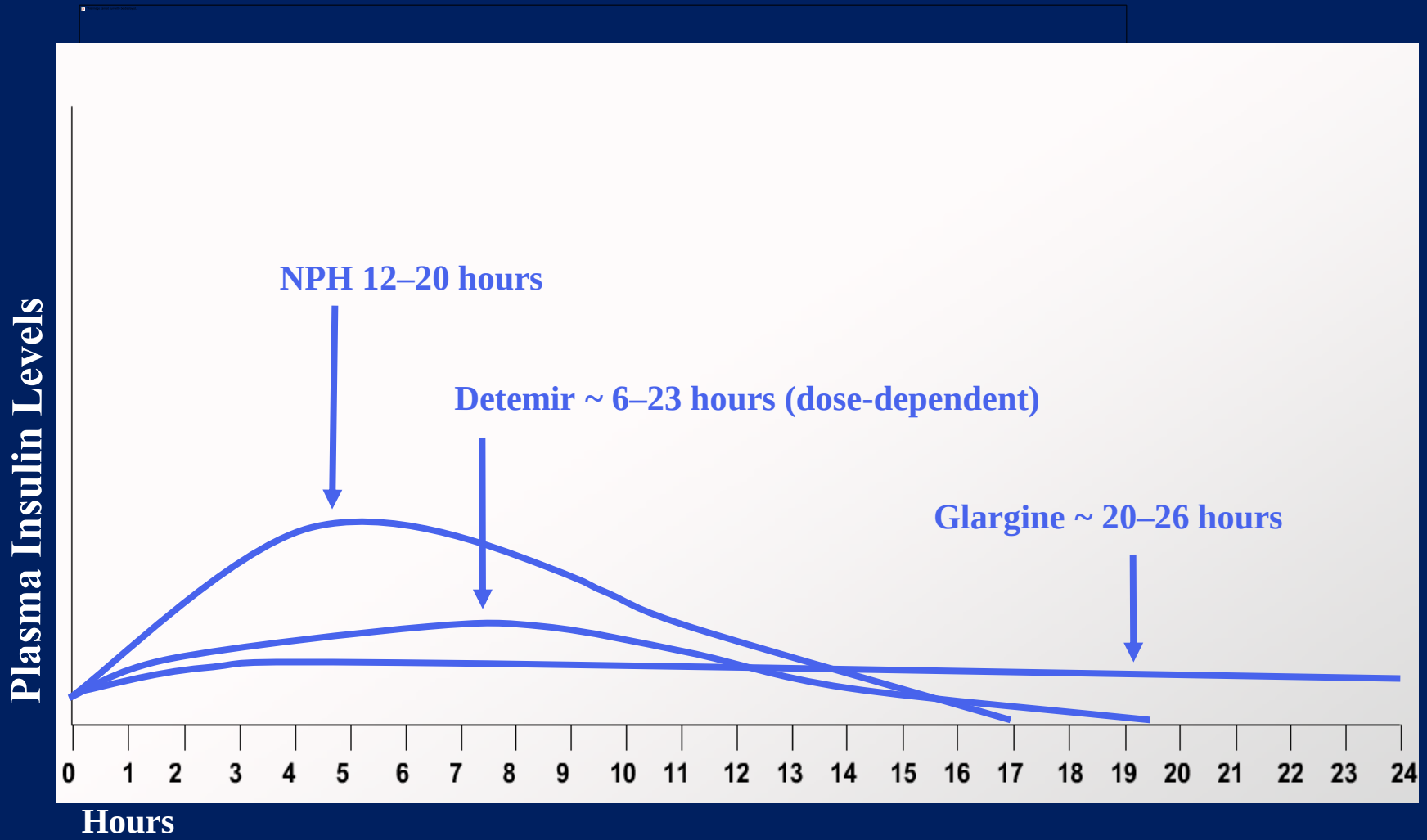
- Bolus Insulin (mealtime or prandial)
  - Limits hyperglycemia after meals
  - Immediate rise and sharp peak at 1 hour
  - 10% to 20% of daily requirement at each meal

Owens DR, et al. *Lancet.* 2001;358:739-746.

Comparison of Available Insulins

Type	Onset	Peak	Duration
Short-acting			
Regular insulin (R)	30–60 min	2–5 hrs	5–8 hrs
Rapid-acting			
Insulin lispro	15–30 min	30–90 min	3–5 hrs
Insulin aspart	10–20 min	40–50 min	3–5 hrs
Insulin glulisine	20–30 min	30–90 min	1–2.5 hrs
Intermediate-acting			
NPH	1–2 hrs	4–12 hrs	18–24 hrs
Long-acting			
Insulin glargine	1–1.5 hrs	No pronounced peak	20–24 hrs
Insulin detemir	1–2 hrs	Relatively flat	up to 24 hrs
Premixed Insulins			
Regular/NPH insulin 70/30	30 min	2–12 hrs	14–24 hrs
Lispro protamine 75/25, 50/50	15 min	0.5–2.5 hrs	16–20 hrs
Biphasic insulin aspart 70/30	10–20 min	1–4 hrs	up to 24 hrs
Degludec + aspart	10-20 min		up to 42 hrs

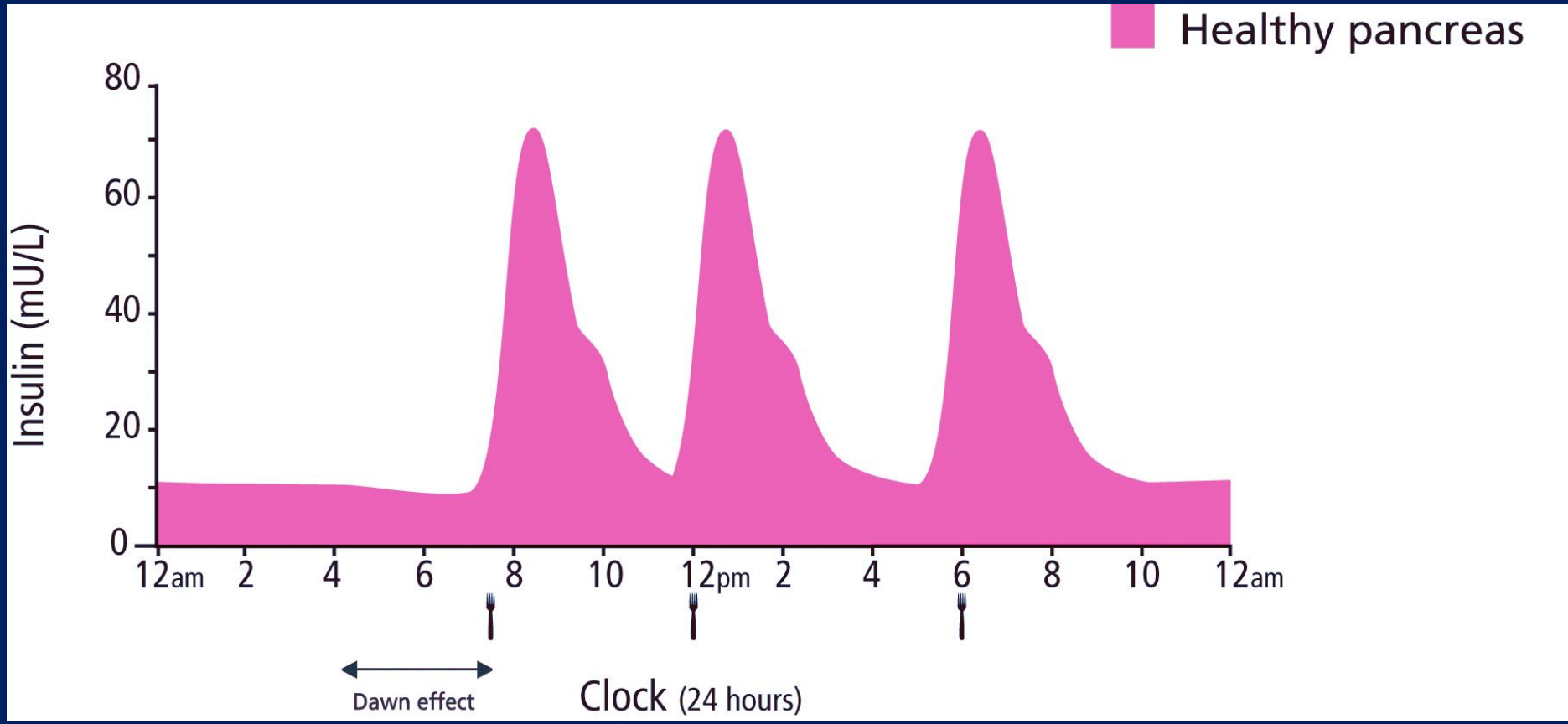
Action Profiles of Basal Insulins



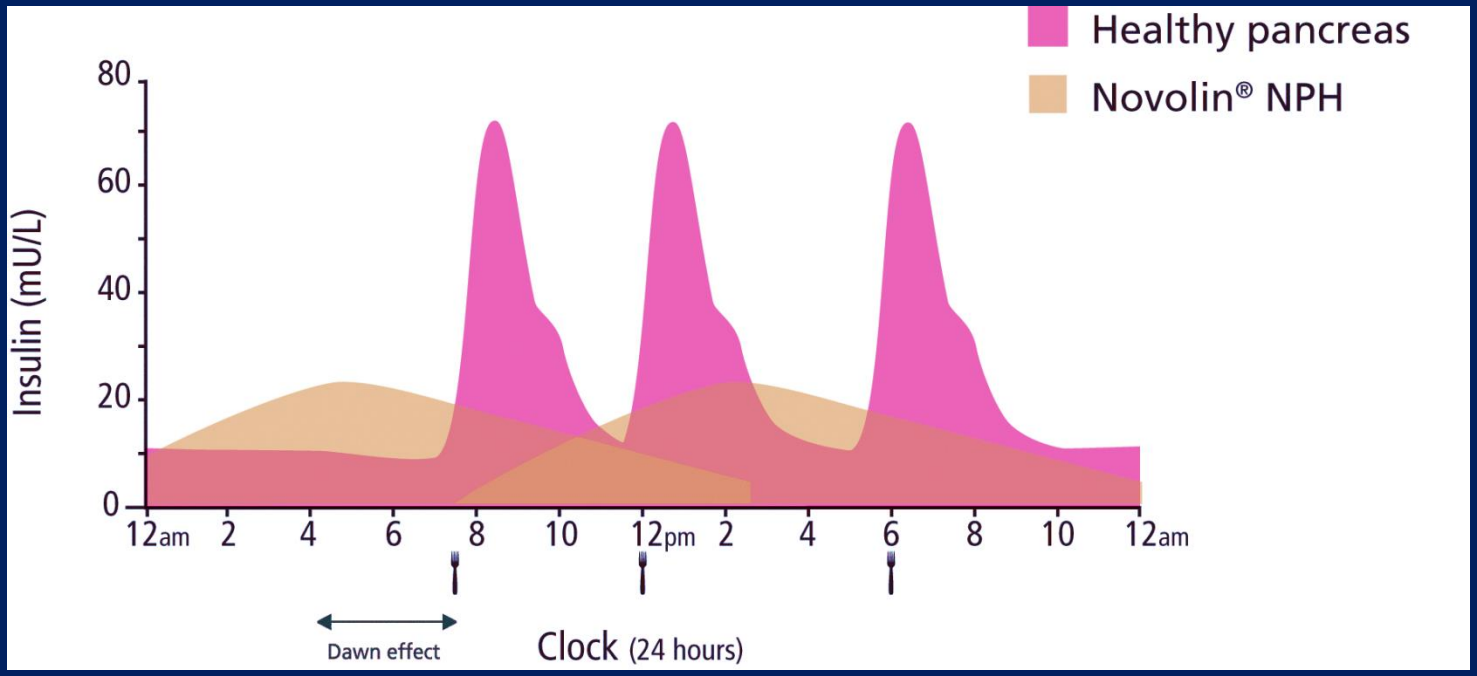
Note: Action curves are approximations for illustrative purposes. Actual patient response will vary.

Adapted from *Insulin Therapy for the 21st Century.* American Diabetes Association; information from insulin glargine, insulin detemir, and NPH product monographs

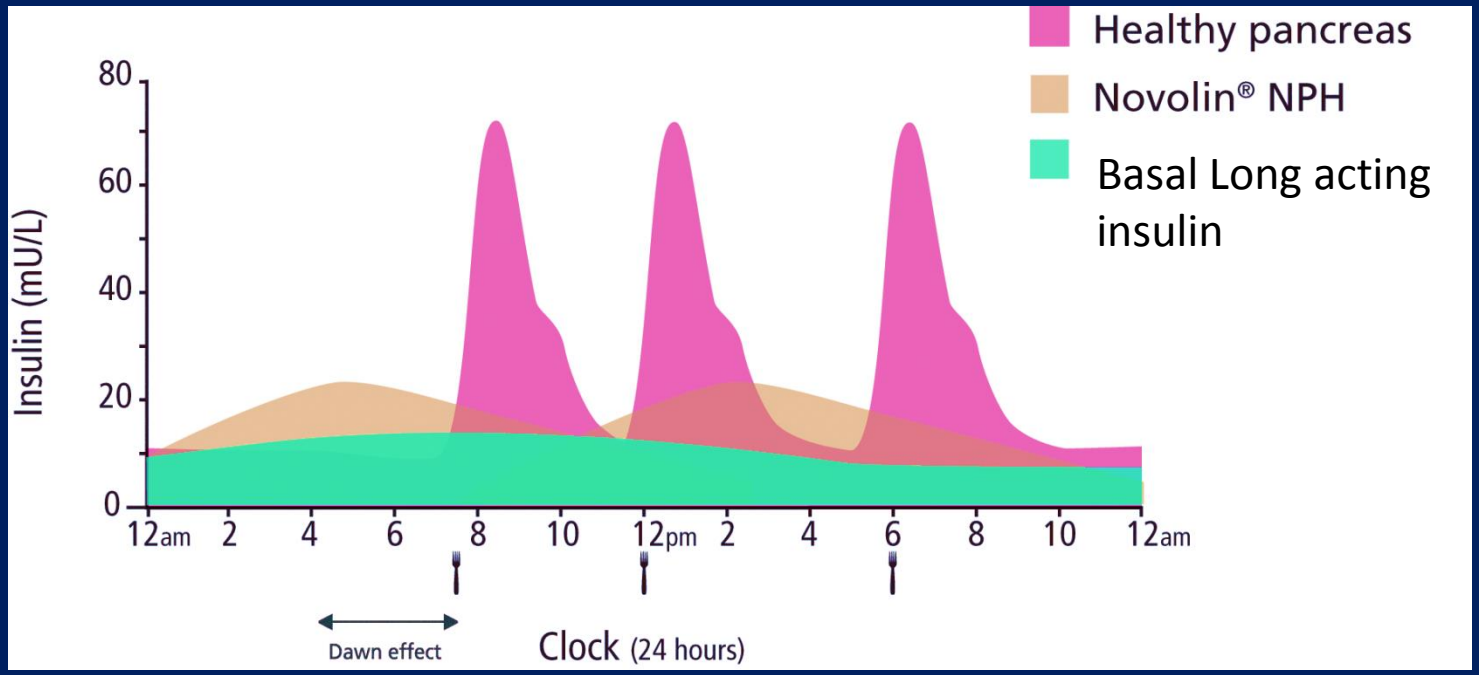
The healthy pancreas



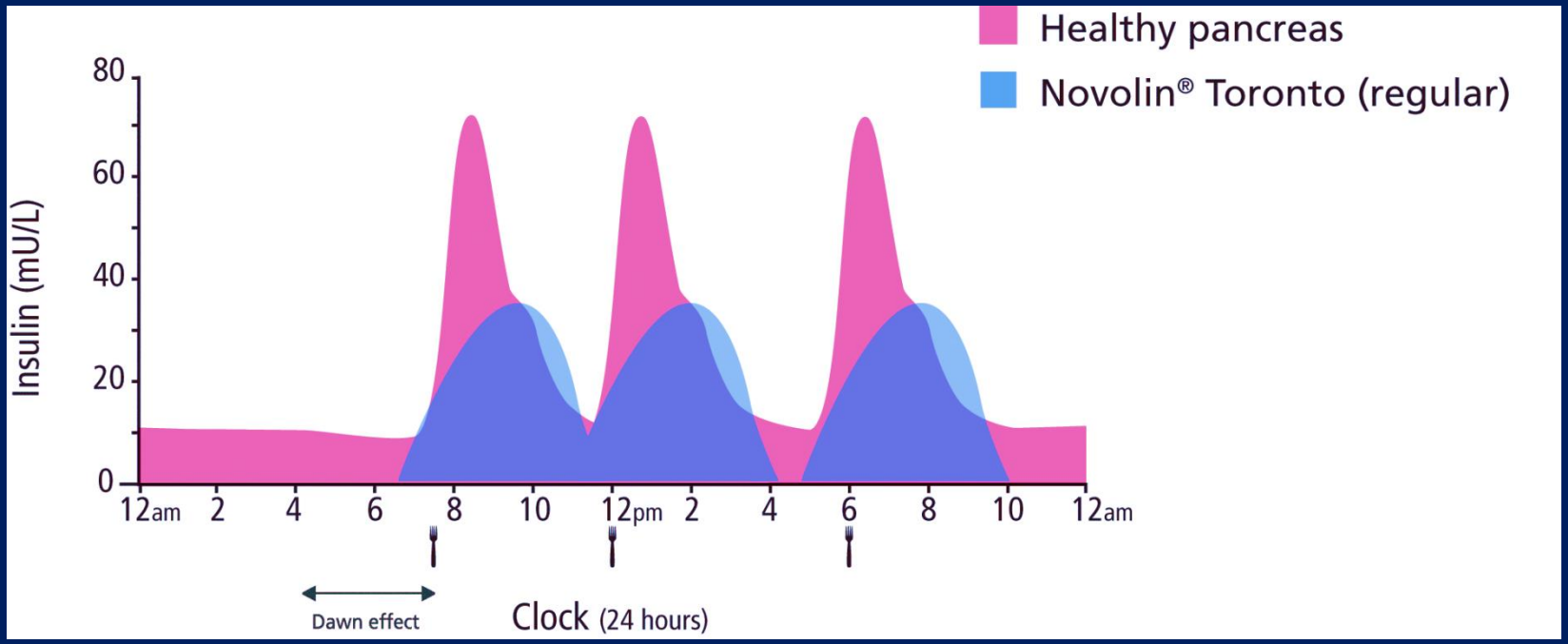
The healthy pancreas / Time-action profile of NPH



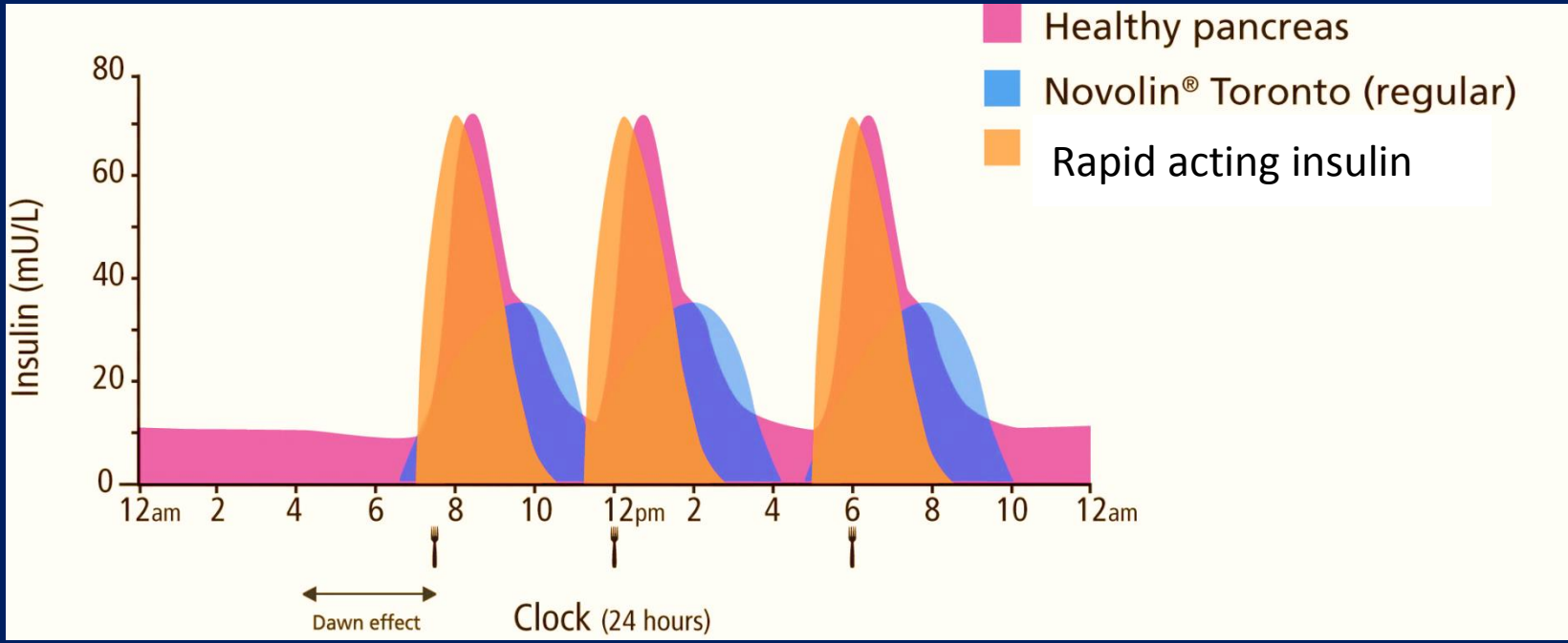
The healthy pancreas / Time-action profile of NPHand basal long acting detemir



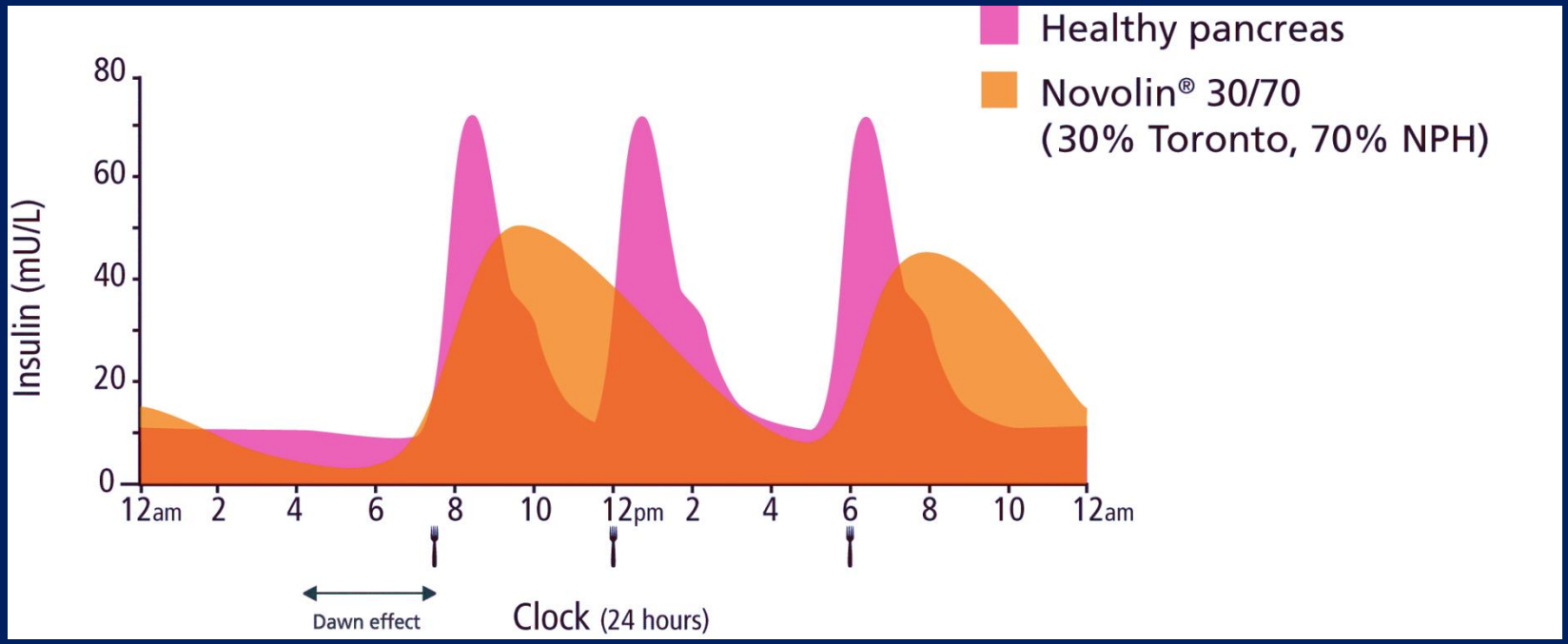
The healthy pancreas / Time-action profile of regular insulin



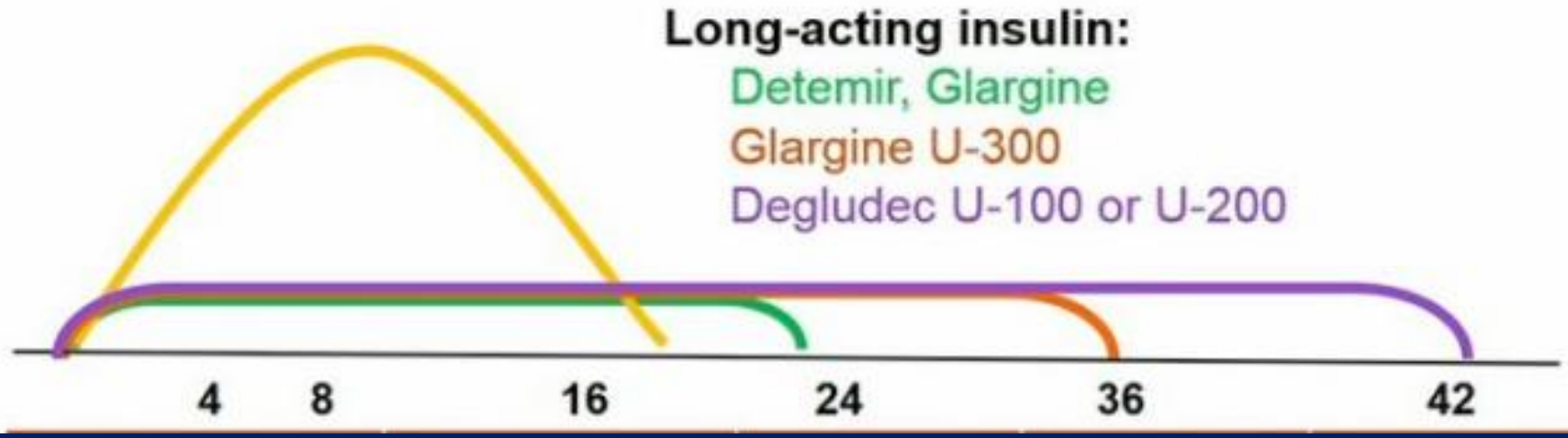
The healthy pancreas / Time-action profile of regular insulin and Rapid acting insulin



The healthy pancreas / Time-action profile of Novolin® ge 30/70



Basal Insulins



Pharmacokinetic profiles

- Basal insulin pharmacokinetic profiles are mostly flat

There is still some peak at :

7 to 14 hours for insulin detemir

4 to 12 hours for Lantus

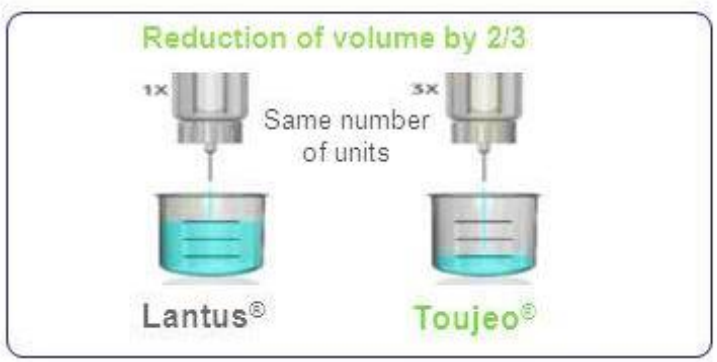
Glargine U300 versus U100

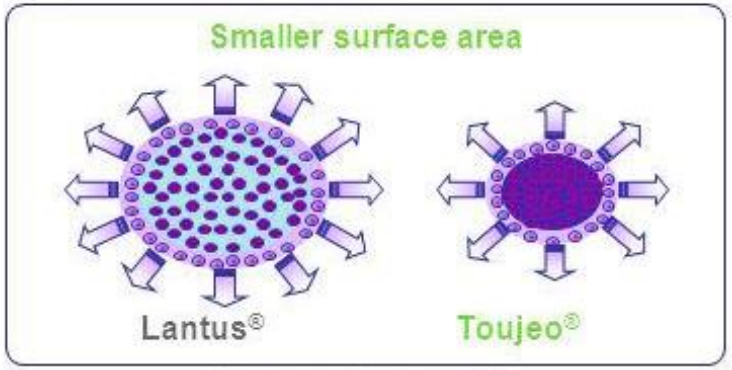
Smaller volume of injection for Toujeo® vs Lantus®

Smaller subcutaneous depot for Toujeo® vs Lantus®

Different absorption kinetics "More gradual release"

Distinct Toujeo® PK/PD profile compared to Lantus®



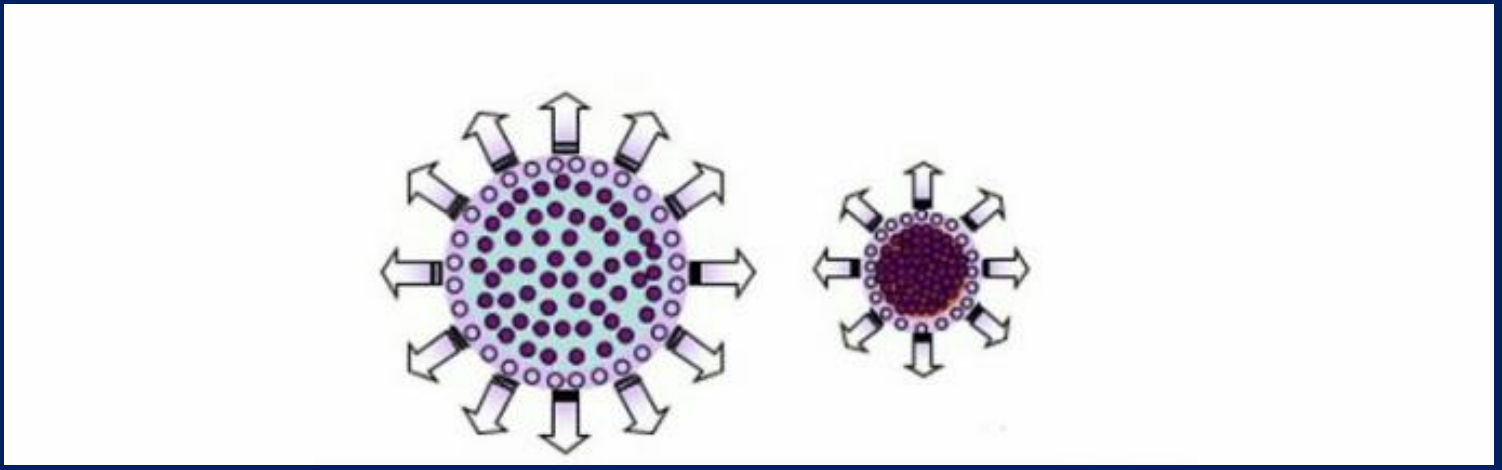


For illustrative purposes only

PD, pharmacodynamics; PK, pharmacokinetic

Dallsy G, Lavemis F. Diabetes Obes Metab. 2015 Jul 3. doi: 10.1111/dom. 12501. [Epub ahead of print]; Steinstraesser A et al. Diabetes Obes Metab. 2014; 16:873-6; Becker RH et al. Diabetes Care. 2015; 38:637-43

Dallsy G lavemis , Diabetes obesity and Metabolism.2015



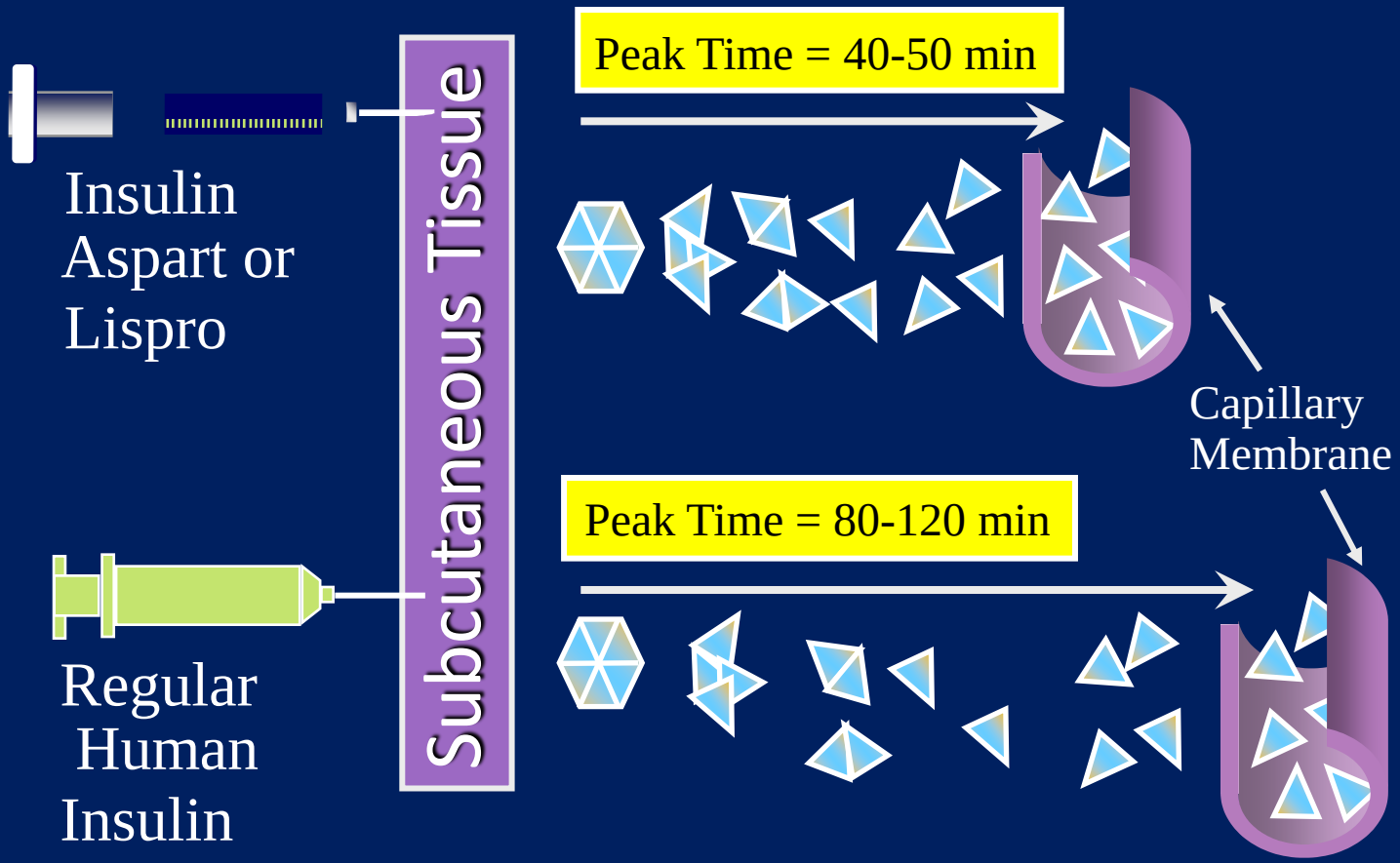
- 3 fold more concentrated formulation of glargine
- Reduced volume (1/3)
- Reduced surface area (1/2)
- Slower rate of absorbtion

Longer acting concentrated basal insulin U300

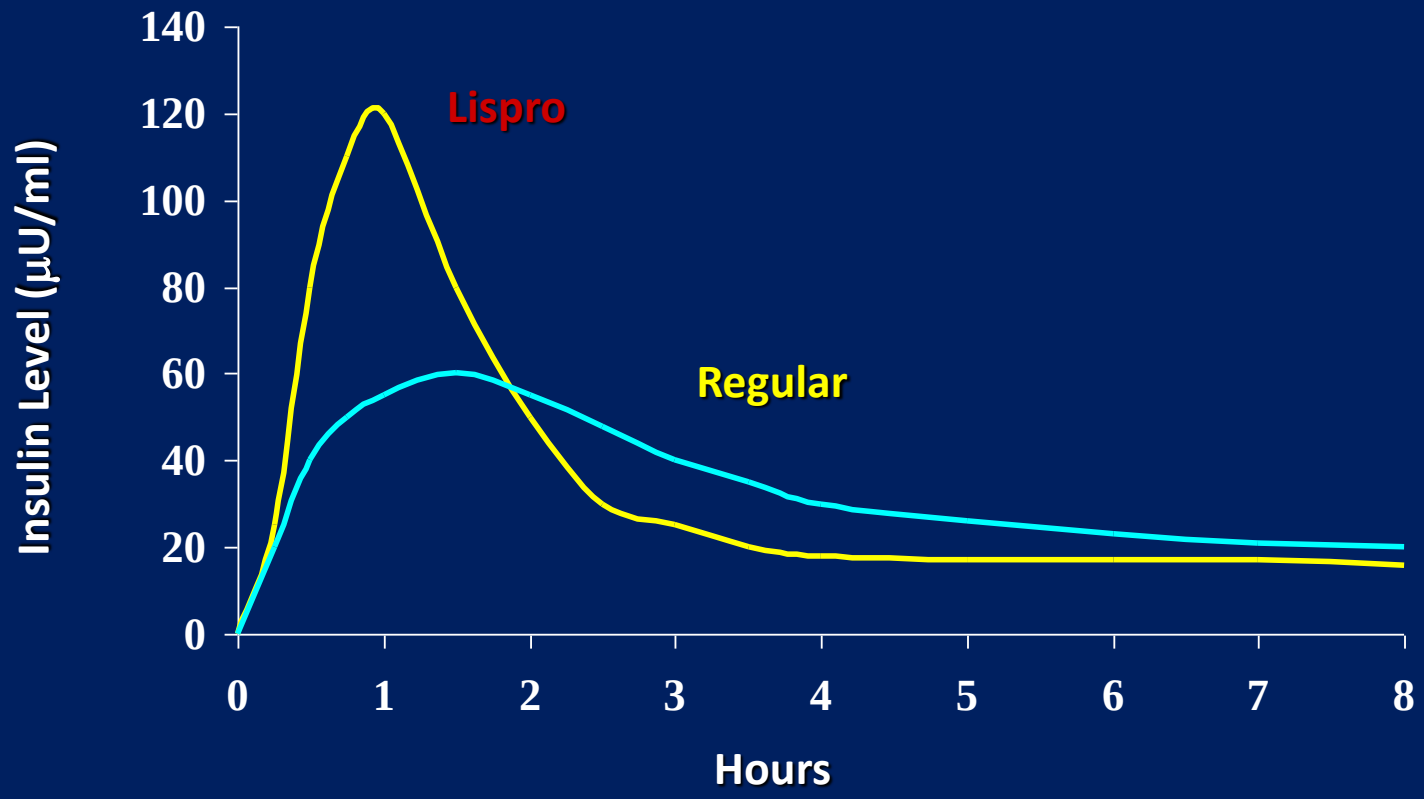
- Reduction of overall and nocturnal and severe hypoglycemia
- Reduction of variability of glucose
- Improve adherence

Rapid/short acting insulins

Dissociation & Absorption of Aspart / Lispro



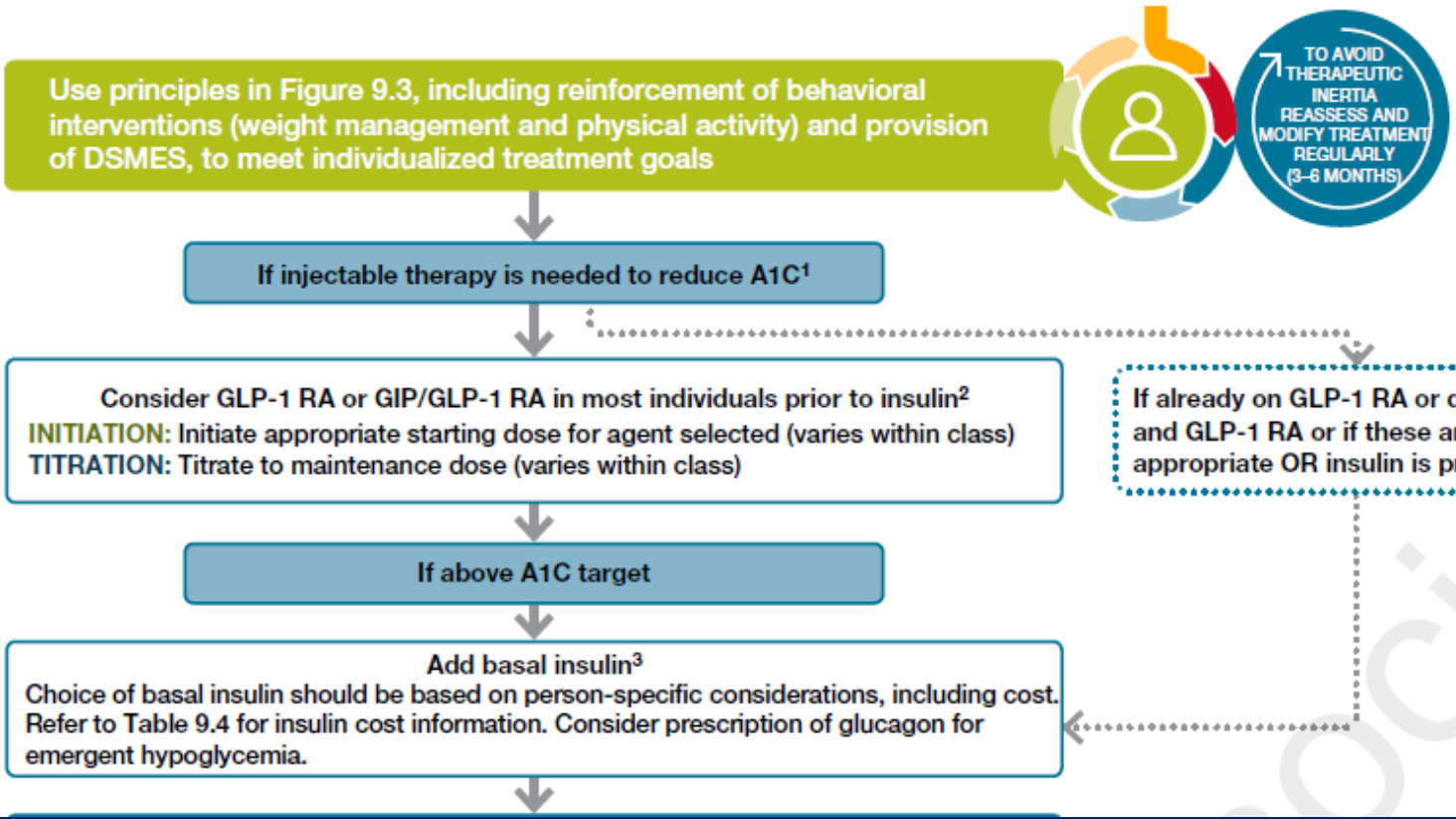
Insulin Action:
Lispro and Regular Insulin



Howey DC. *Diabetes* 1994;43:396-402.

If patients fails to respond to OAD

ADA 2024


Use principles in Figure 9.3, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES, to meet individualized treatment goals
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
If injectable therapy is needed to reduce A1C[1]
Consider GLP-1 RA or GIP/GLP-1 RA in most individuals prior to insulin[2]
INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Titrate to maintenance dose (varies within class)
If already on GLP-1 RA or dual GIP and GLP-1 RA or if these are not appropriate OR insulin is preferred
If above A1C target
Add basal insulin[3]
Choice of basal insulin should be based on person-specific considerations, including cost. Refer to Table 9.4 for insulin cost information. Consider prescription of glucagon for emergent hypoglycemia.

ADA 2024

Add basal analog or bedtime NPH insulin*

INITIATION: Start 10 units per day OR 0.1–0.2 units/kg per day

TITRATION:

- Set FPG target (see Section 6, "Glycemic Targets")
- Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
- For hypoglycemia determine cause, if no clear reason lower dose by 10–20%

Assess adequacy of basal insulin dose

Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., basal dose more than ~0.5 units/kg/day, elevated bedtime–morning and/or post–preprandial differential, hypoglycemia [aware or unaware], high variability)

ADA 2024

- If above A1C target and not already on a GLP-1 RA or dual GIP and GLP-1 RA, consider these classes, either in free combination or fixed-ratio combination, with insulin.
- If A1C remains above target:

Add prandial insulin[5]

Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate

INITIATION:

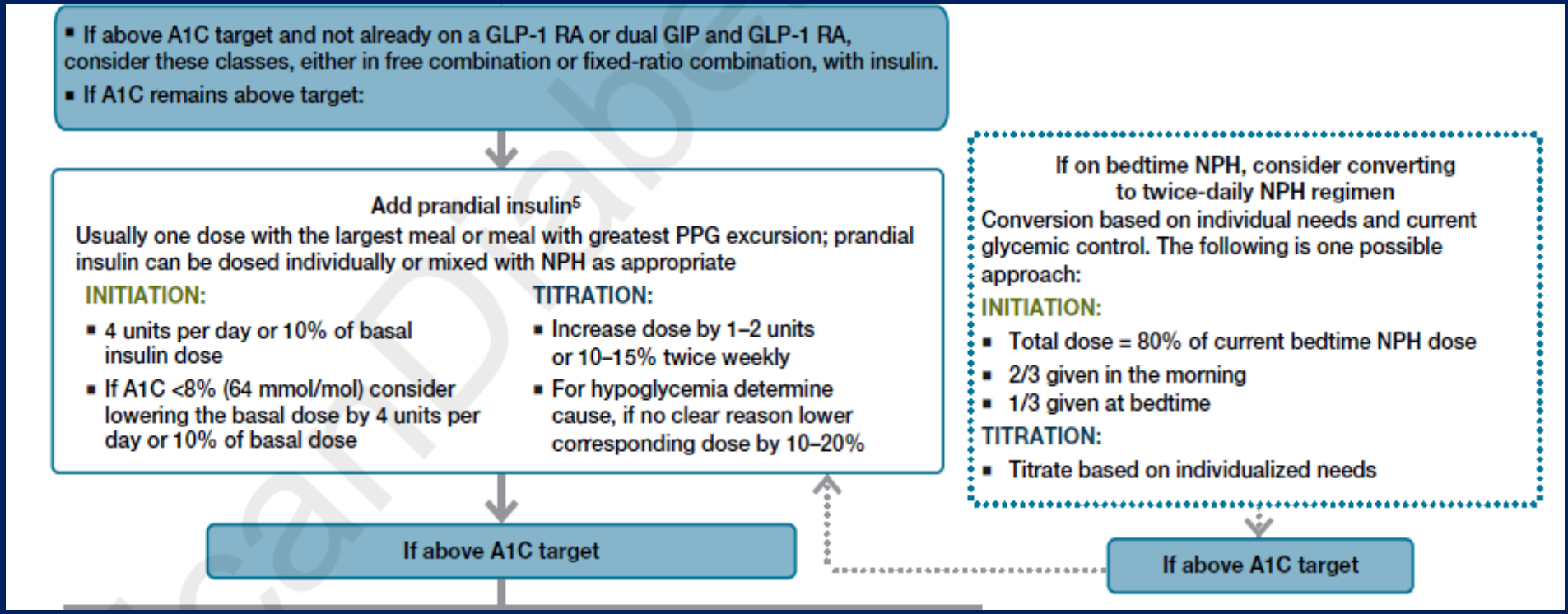
- 4 units per day or 10% of basal insulin dose
- If A1C <8% (64 mmol/mol) consider lowering the basal dose by 4 units per day or 10% of basal dose

TITRATION:

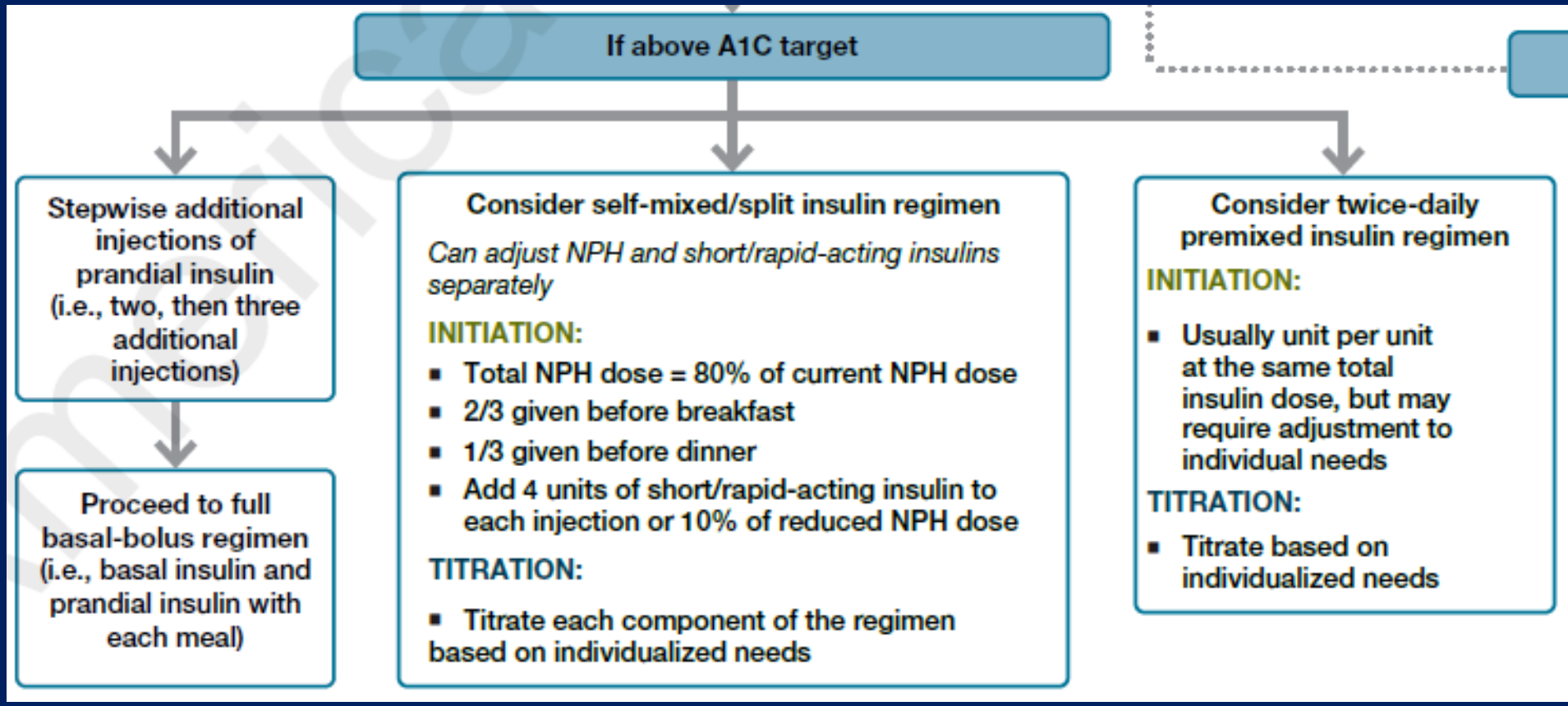
- Increase dose by 1–2 units or 10–15% twice weekly
- For hypoglycemia determine cause, if no clear reason lower corresponding dose by 10–20%

If above A1C target

ADA 2024


▪ If above A1C target and not already on a GLP-1 RA or dual GIP and GLP-1 RA, consider these classes, either in free combination or fixed-ratio combination, with insulin.
▪ If A1C remains above target:
Add prandial insulin[5]
Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate
INITIATION:
▪ 4 units per day or 10% of basal insulin dose
▪ If A1C <8% (64 mmol/mol) consider lowering the basal dose by 4 units per day or 10% of basal dose
TITRATION:
▪ Increase dose by 1–2 units or 10–15% twice weekly
▪ For hypoglycemia determine cause, if no clear reason lower corresponding dose by 10–20%
If above A1C target
If on bedtime NPH, consider converting to twice-daily NPH regimen
Conversion based on individual needs and current glycemic control. The following is one possible approach:
INITIATION:
▪ Total dose = 80% of current bedtime NPH dose
▪ 2/3 given in the morning
▪ 1/3 given at bedtime
TITRATION:
▪ Titrate based on individualized needs
If above A1C target

ADA 2024


If above A1C target
Stepwise additional injections of prandial insulin (i.e., two, then three additional injections)
Proceed to full basal-bolus regimen (i.e., basal insulin and prandial insulin with each meal)
Consider self-mixed/split insulin regimen
Can adjust NPH and short/rapid-acting insulins separately
INITIATION:
Total NPH dose = 80% of current NPH dose
2/3 given before breakfast
1/3 given before dinner
Add 4 units of short/rapid-acting insulin to each injection or 10% of reduced NPH dose
TITRATION:
Titrate each component of the regimen based on individualized needs
Consider twice-daily premixed insulin regimen
INITIATION:
Usually unit per unit at the same total insulin dose, but may require adjustment to individual needs
TITRATION:
Titrate based on individualized needs

- The progressive nature of T2DM should be regularly and objectively explained to patients

- clinicians should avoid using insulin as a threat or describing it as a sign of :

1. personal failure
2. punishment

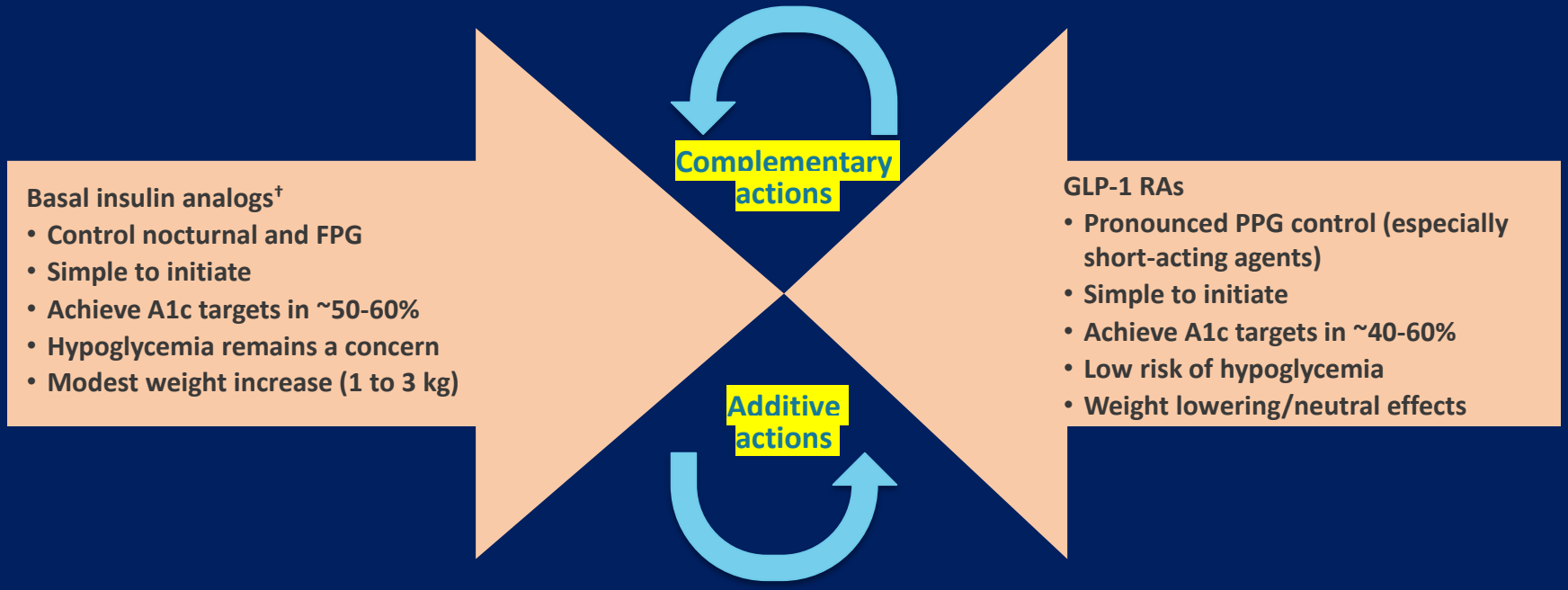
Transition between insulins

From	To	Dose change
Glargine U100	Glargine U300	10-15% ↑
Glargine U300	Glargine U100	10-15% ↓
BD NPH, Detemir	Any	20% ↓
Glargine U100	Degludec	10-15% ↓
Glargine U300	Degludec	20-35% ↓
Degludec	Glargine U100	10% ↑

If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for:

1. Greater efficacy
2. Durability of treatment effect

Combination of Basal Insulin with a GLP-1 RA Has a Scientific Basis



Little S, et al. *Diabetes Technol Ther.* 2011:13(suppl 1):S53-S64.
Cohen ND, et al. *Med J Aust.* 2013;199(4):246-249.
Carris NW, et al. *Drugs.* 2014;74(18):2141-2152.

Thank you