

# It is time for medication: How to choose the diabetes medication in a person- centered approach

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# Disclosures:

- Speaker Bureau- Abbott, Novo Nordisk, Xeris
- Advisory Board- Corcept, Xeris

# Learning Objectives:

## Review

Review glycemic recommendations for people with diabetes

## Discuss

Discuss choosing medication for the individualized patient due to needs and comorbidities

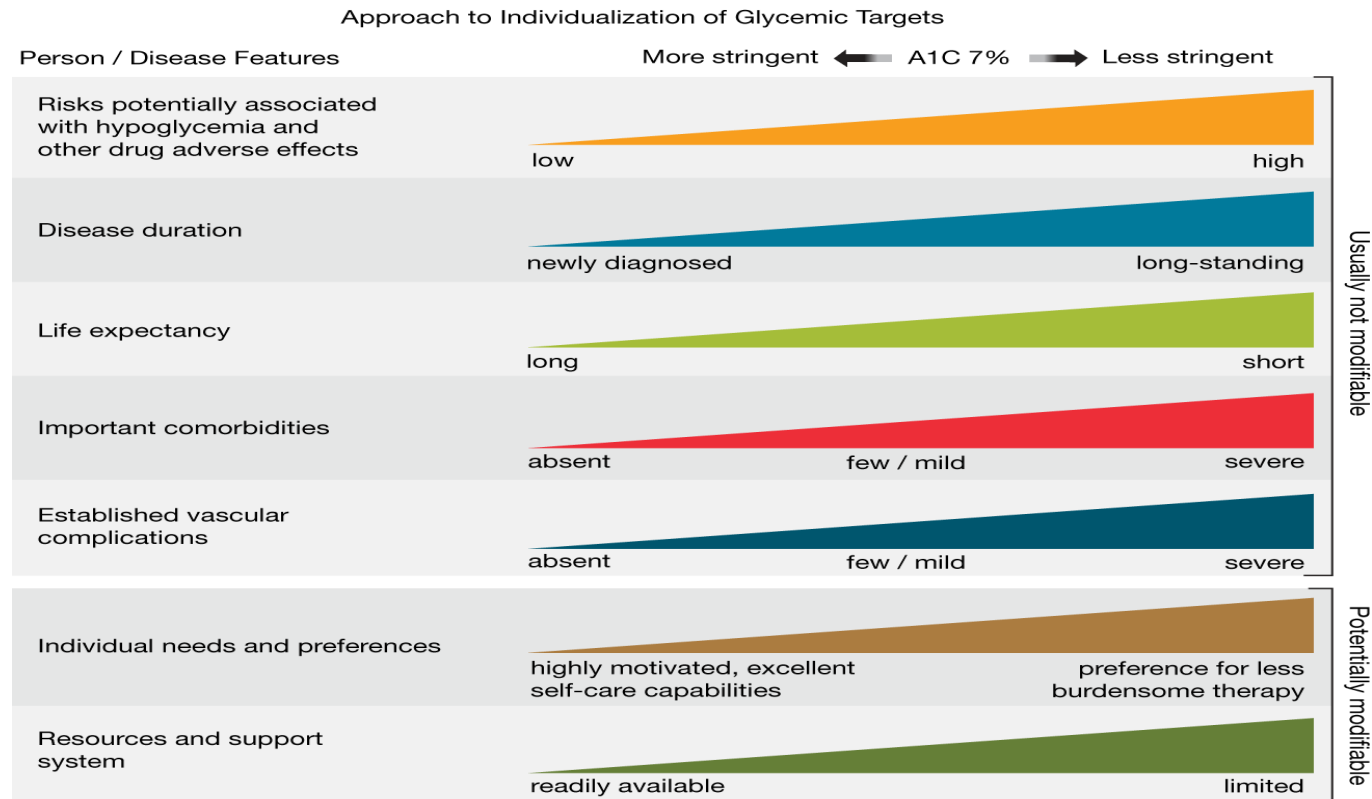
## Introduce

Introduce how to initiate and intensify insulin therapy

## Summary of glycemic recommendations for many nonpregnant adults with diabetes

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

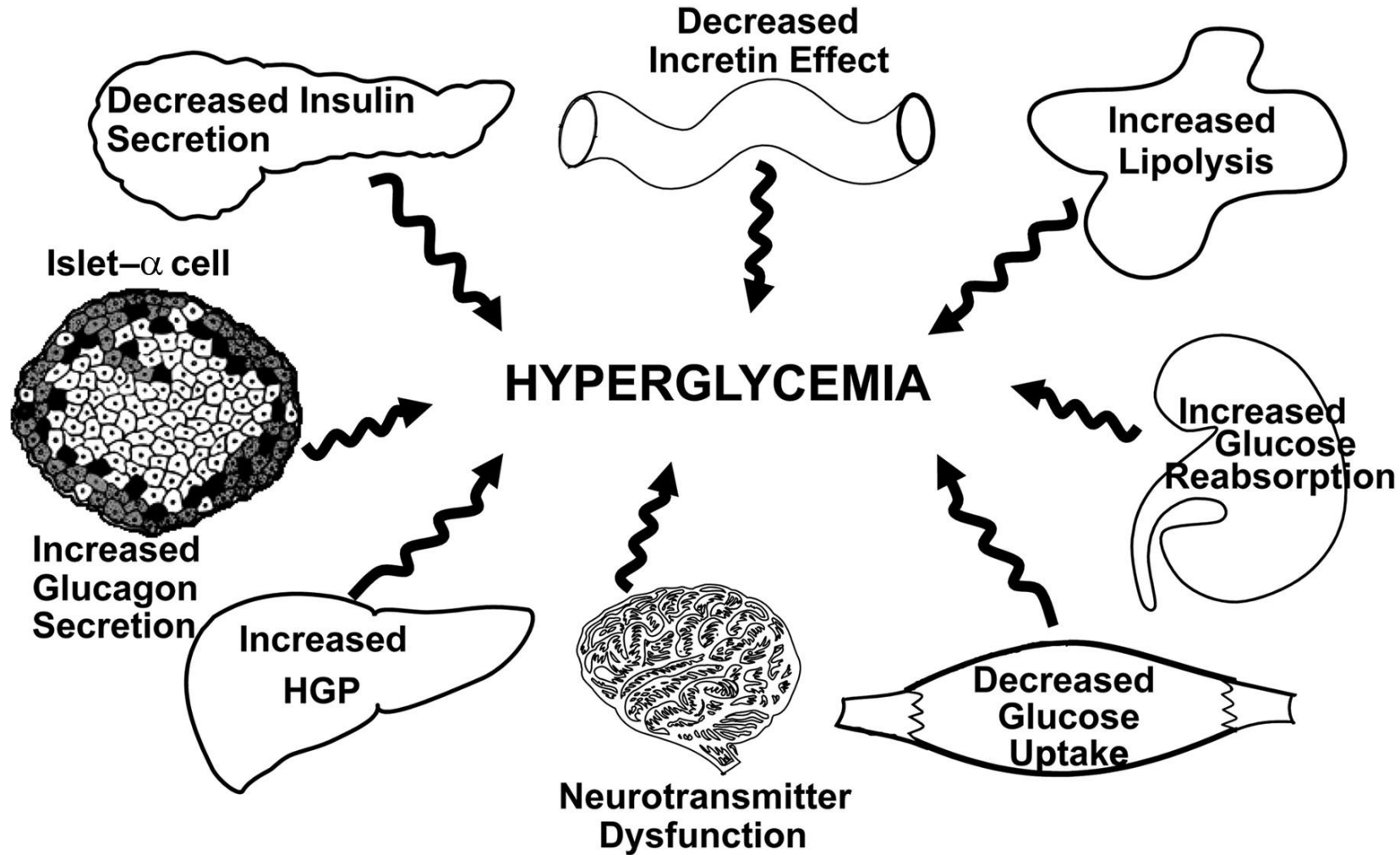
Diabetes Care. 2023;47(Supplement\_1):S111-S125. doi:10.2337/dc24-S006



**Figure Legend:**

Person and disease factors used to determine optimal glycemic targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. A1C 7% = 53 mmol/mol. Adapted with permission from Inzucchi et al. (36).

# The Ominous Octet.



Ralph A. DeFronzo Diabetes 2009;58:773-795

# Noxious Nine

Hypercortisolism may be a ninth defect in some living with diabetes that effect glycemic control

## Catalyst Trial

1 mg dexamethasone suppression test with a cut off of 1.8 ug/dl cortisol cutoff point

- 1000 T2DM people A1C= 7.5 to 11.5%
- $\geq 3$  antihyperglycemic agents
- Insulin and any other antihyperglycemic agent
- $\geq 2$  antihyperglycemic agents +  $\geq 1$  micro or macro vascular complication
- $\geq 2$  antihyperglycemic agents +  $\geq 2$  antihypertensive agents

- Dexamethasone  $> 140$
- ACTH low
- DHEA low
- Adrenal CT

# Catalyst Trial Results

24% of Catalyst participants screened had a positive dexamethasone test



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graph TD; A[24% of Catalyst participants screened had a positive dexamethasone test] --> B[253 out of 1055 participants]; B --> C[Post- DST cortisol: 3.5 ug/dl]; C --> D[Post-DST dexamethasone: 413 ng/dl];
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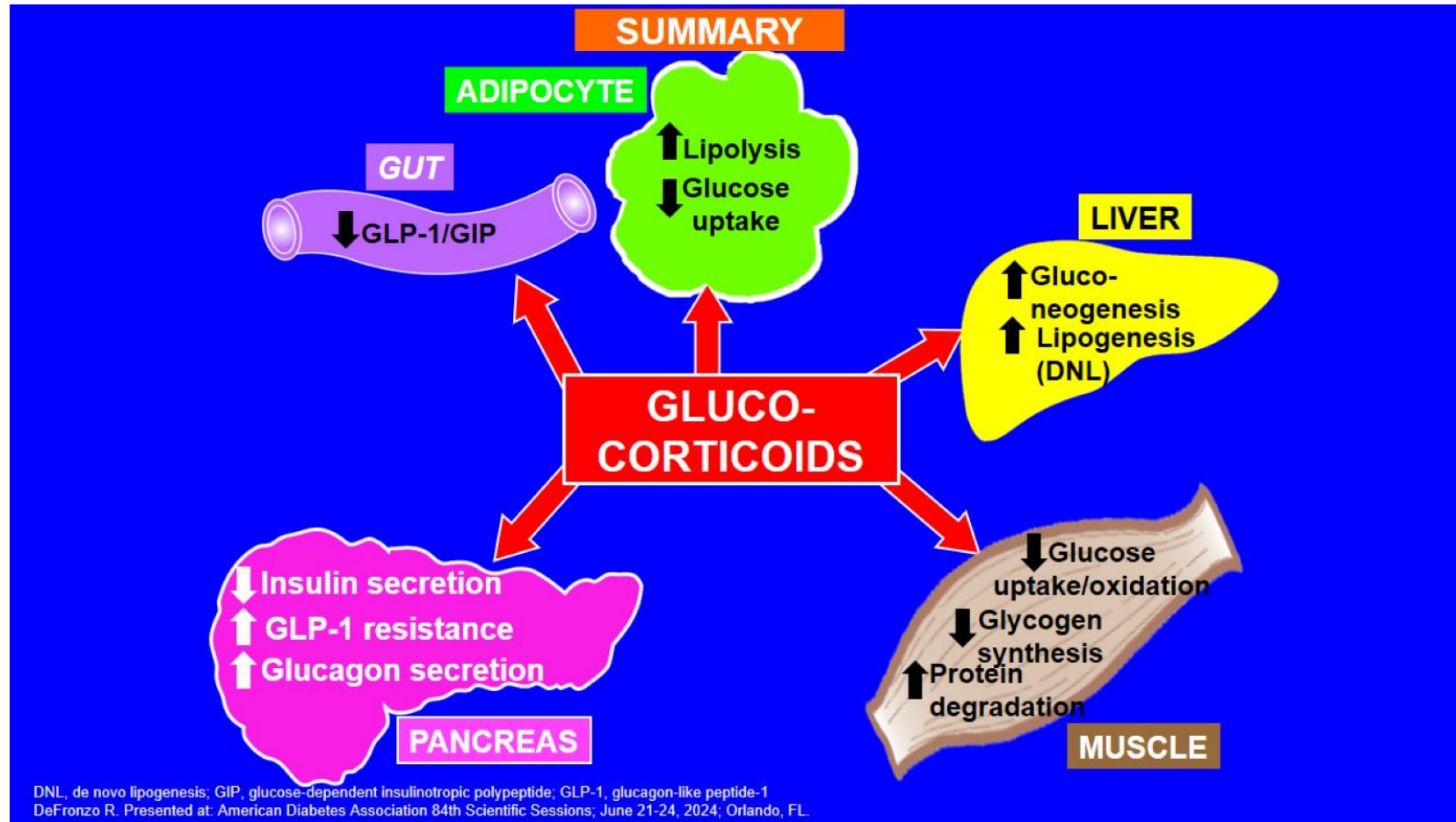
253 out of 1055 participants

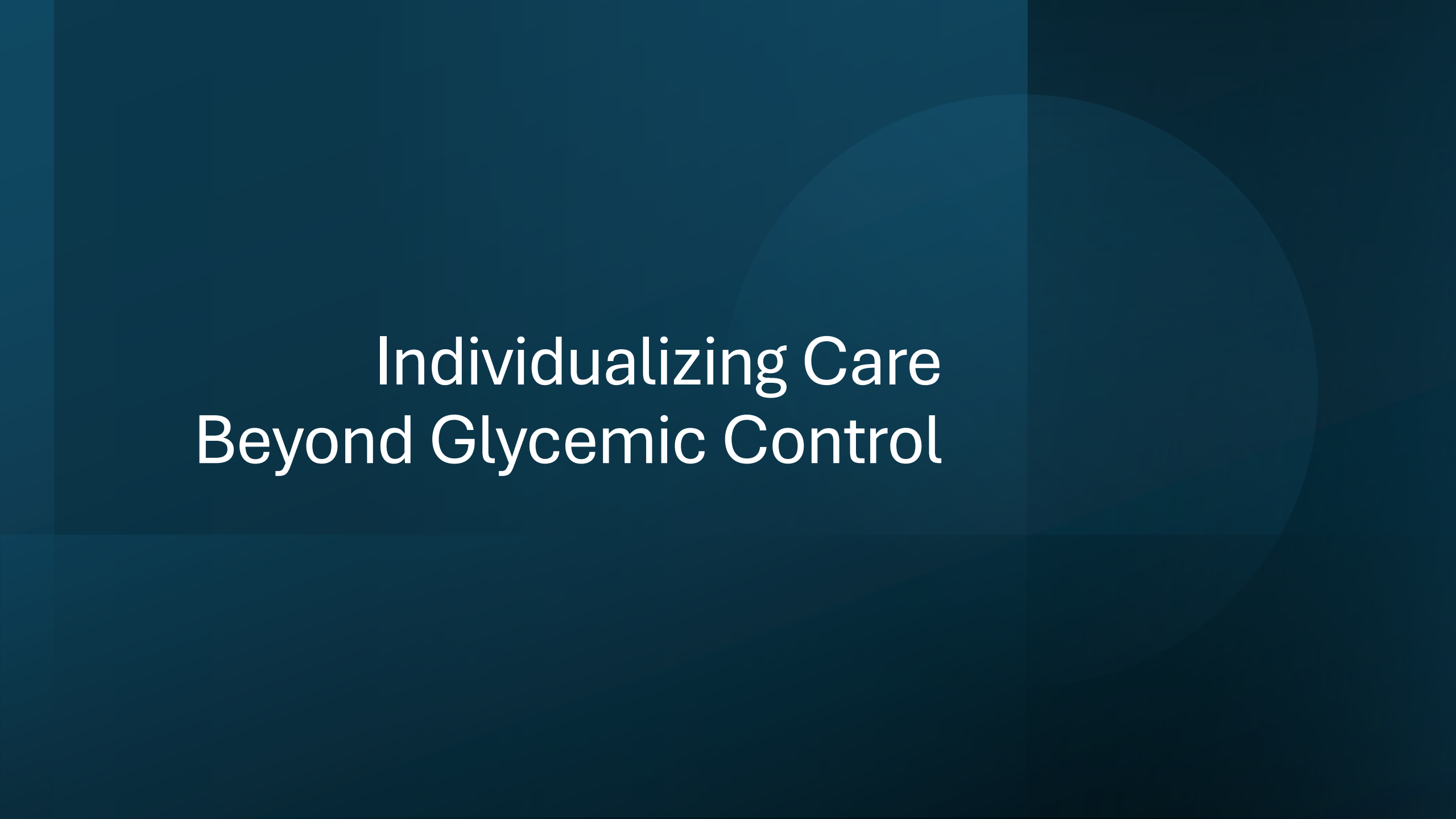
Post- DST cortisol: 3.5 ug/dl

Post-DST dexamethasone: 413 ng/dl



# Glucocorticoids Effect on Glycemic Control





# Individualizing Care Beyond Glycemic Control

# ADA Standards of Medical Care

- **9.9** A person-centered shared decision-making approach should guide the choice of pharmacologic agents for adults with type 2 diabetes. Consider the effects on cardiovascular and renal comorbidities; effectiveness; hypoglycemia risk; impact on weight, cost and access; risk for adverse reactions and tolerability; and individual preferences

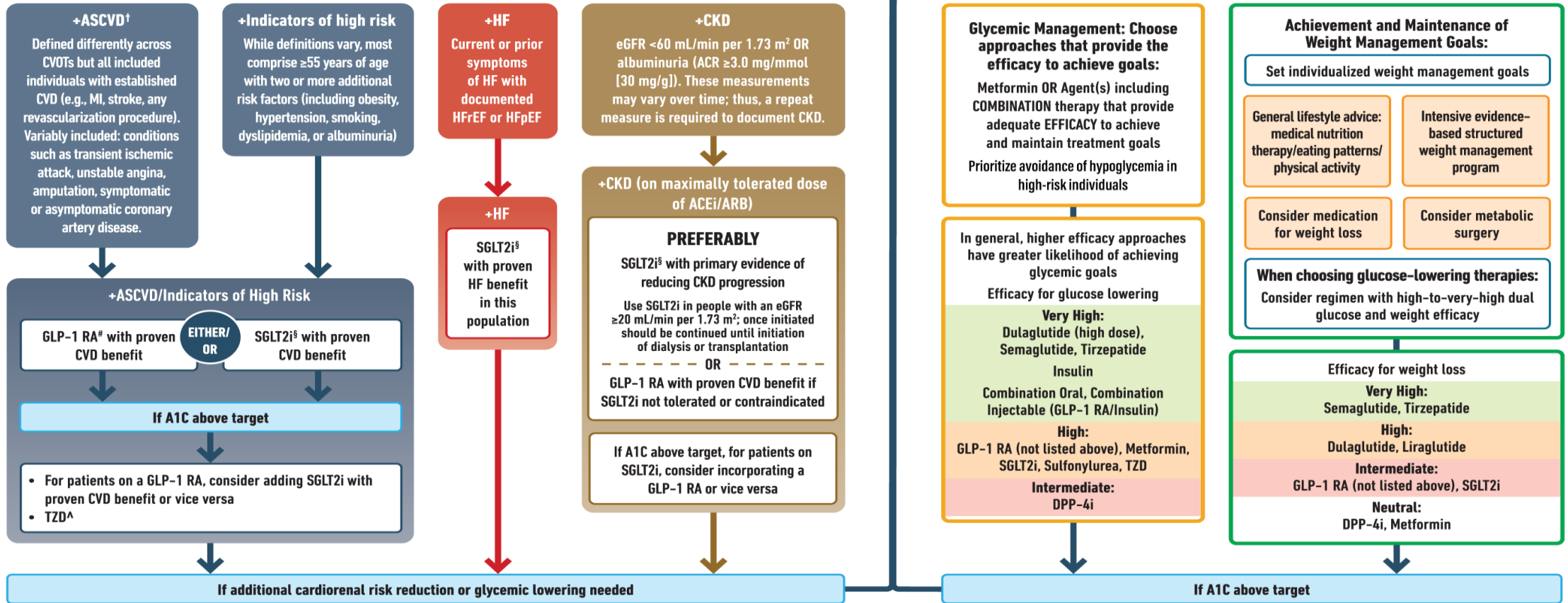
# USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)



Goal: Cardiorenal Risk Reduction in High-Risk Individuals with Type 2 Diabetes (in addition to comprehensive CV risk management)\*

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals



\* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin;† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HFrEF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

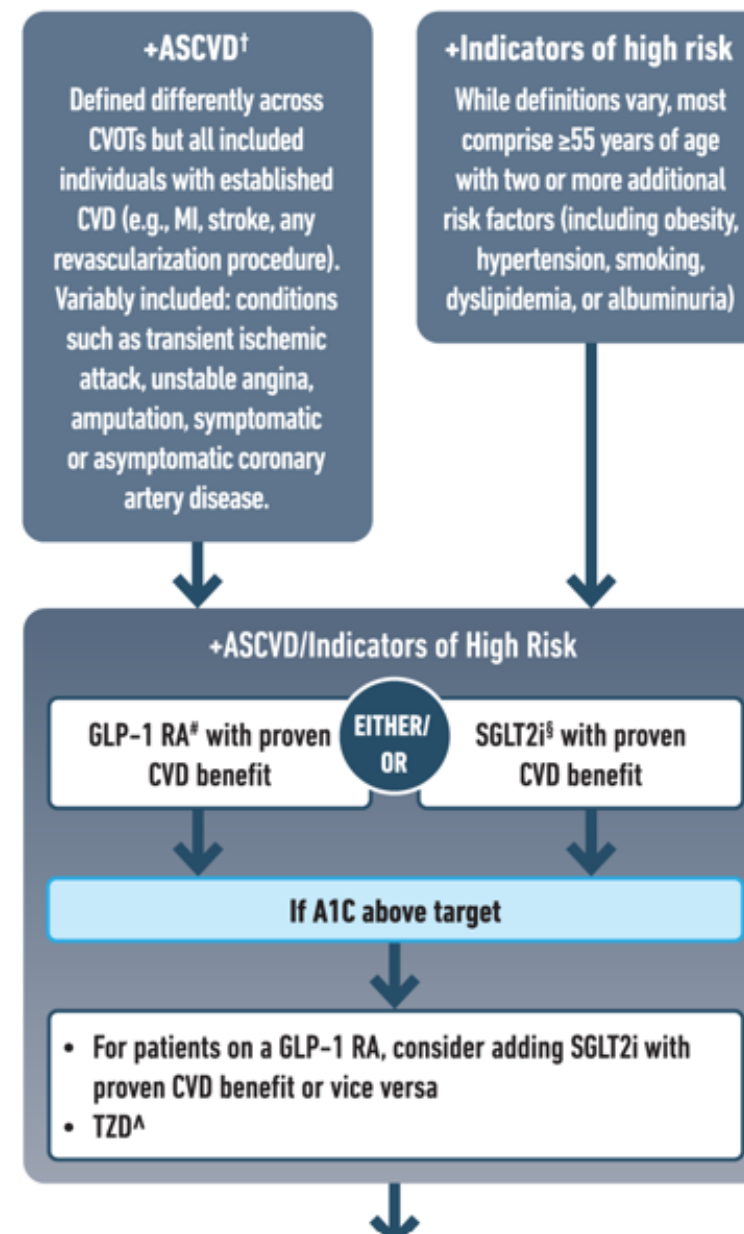
**Identify barriers to goals:**

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

# ADA Standards of Medical Care

- **9.18** In adults with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease, heart failure (HF), and/or chronic kidney disease (CKD), the treatment plan should include agent(s) that reduce cardiovascular and kidney disease risk (e.g., sodium–glucose cotransporter 2 inhibitor [SGLT2] and/or glucagon-like peptide 1 receptor agonist [GLP-1 RA]) for glycemic management and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors.

# Goal: Cardiorenal Risk Reduction in High-Risk Individuals with Type 2 Diabetes



- American Diabetes Association Professional Practice Committee; 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes—2024*. *Diabetes Care* 1 January 2024; 47 (Supplement\_1): S158–S178. <https://doi.org/10.2337/dc24-S009>



# Atherosclerotic Cardiovascular Disease (ASCVD) Benefit

## GLP1-RA

- Dulaglutide (Primary & Secondary)
- Liraglutide (Secondary)
- Semaglutide SQ (Secondary)

## SGLT 2 Inhibitor

- Canagliflozin (secondary prevention)
- Empagliflozin (secondary prevention)

# Summary of GLP-1 Receptor Agonists in T2D

	GLP-1 Receptor Agonists
Glucose-lowering efficacy	High
Hypoglycemia	No
Weight	Loss
CV indication	Benefit: liraglutide, semaglutide SC, dulaglutide
CHF	Neutral
Renal effects	Some reduction in albuminuria Dulaglutide slows deterioration of GFR
Adverse events	GI effects, potential acute pancreatitis

**GLYCEMIA**  
0.7%-2.1%  
Reduced A1C  
(percentage points)

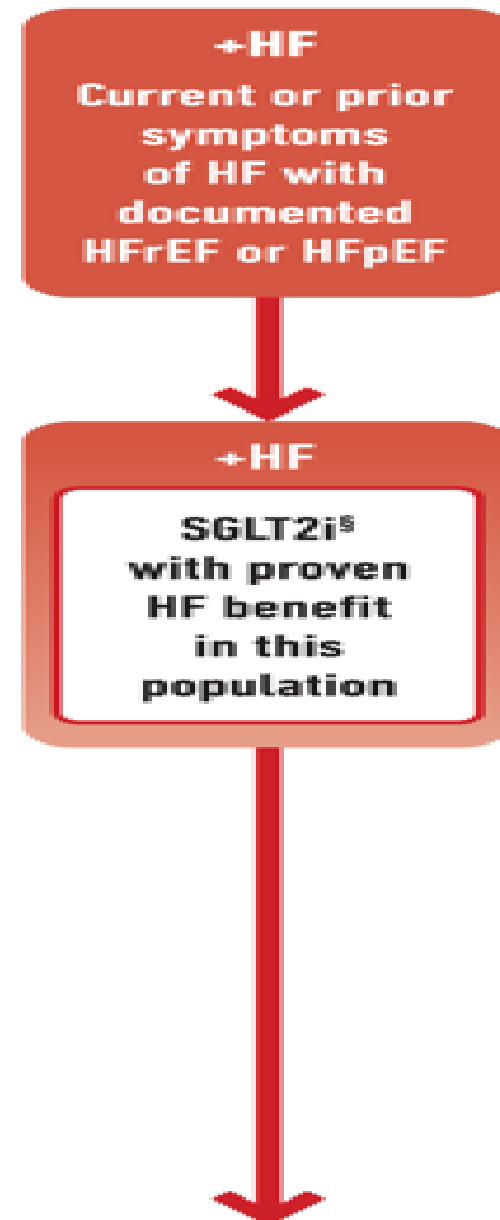
**ASCVD**  
12%-26%  
Reduced risk of major  
adverse CV events

**WEIGHT**  
8%-15%  
Reduced body weight  
from baseline

- Dulaglutide
- Liraglutide (0.6-1.8 mg)
- Semaglutide (0.5-2 mg)
- Liraglutide (3 mg)
- Semaglutide (2.4 mg)



# Goal: Cardiorenal Risk Reduction in High-Risk Individuals with Type 2 Diabetes



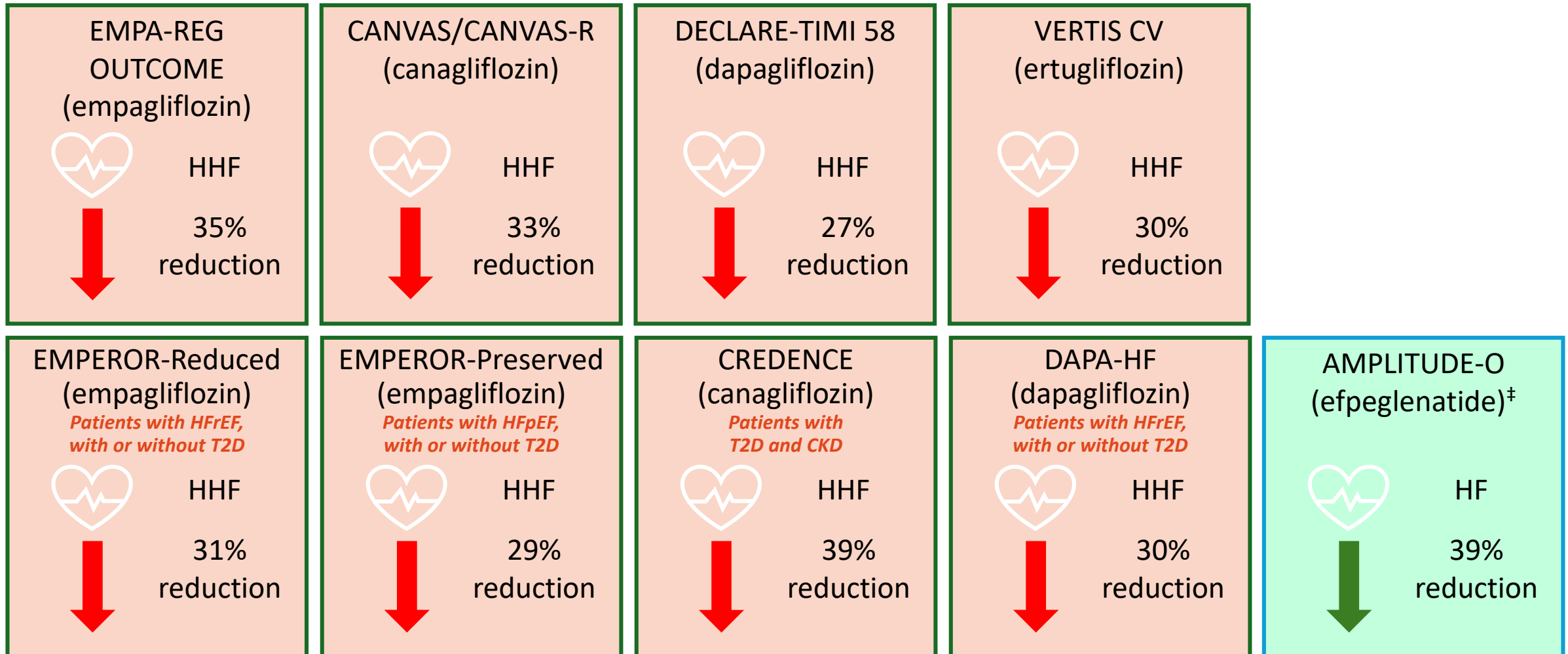
- American Diabetes Association Professional Practice Committee; 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes—2024*. *Diabetes Care* 1 January 2024; 47 (Supplement\_1): S158–S178. <https://doi.org/10.2337/dc24-S009>

# Heart Failure Benefit

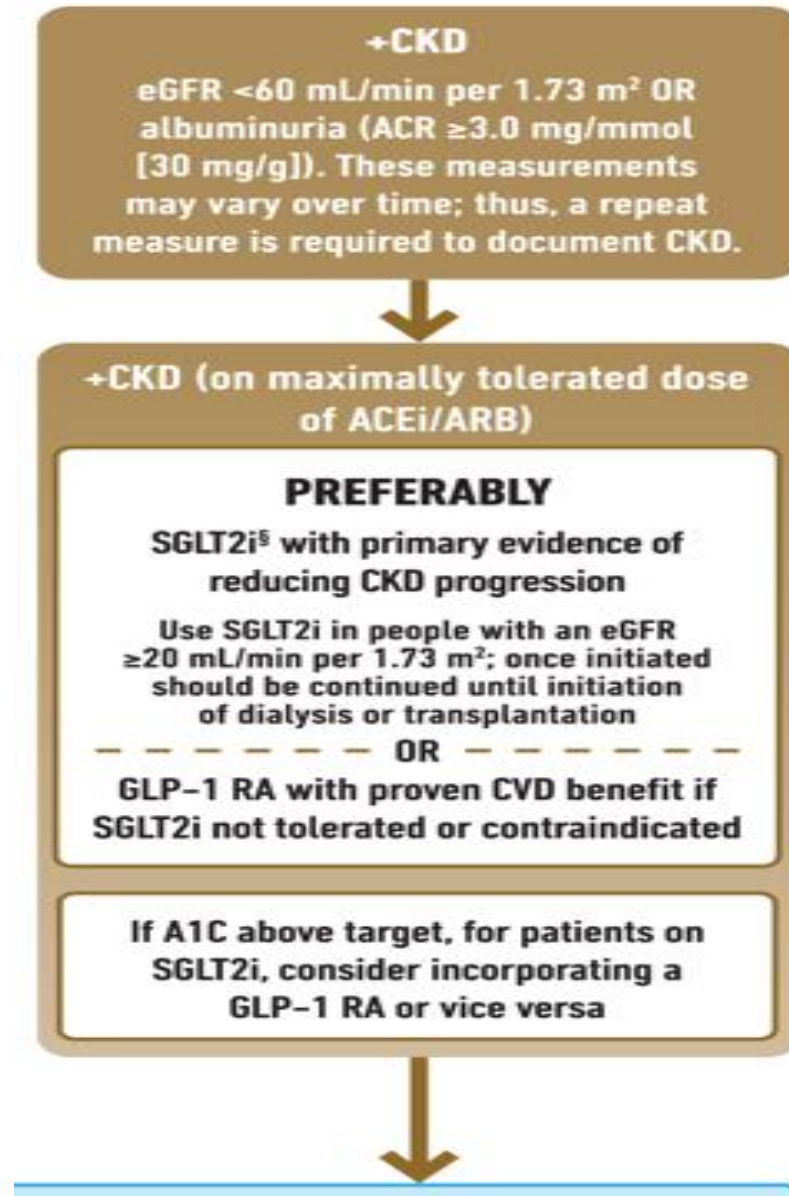
## **SGLT2 Inhibitors**

- Canagliflozin (indication)
- Dapagliflozin (indication)
- Empagliflozin (indication)
- Ertugliflozin

# Summary: SGLT2 Inhibitors and Heart Failure



# Goal: Cardiorenal Risk Reduction in High-Risk Individuals with Type 2 Diabetes



- American Diabetes Association Professional Practice Committee; 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes—2024*. *Diabetes Care* 1 January 2024; 47 (Supplement\_1): S158–S178. <https://doi.org/10.2337/dc24-S009>

# Progression of Diabetic Kidney Disease

## Benefit

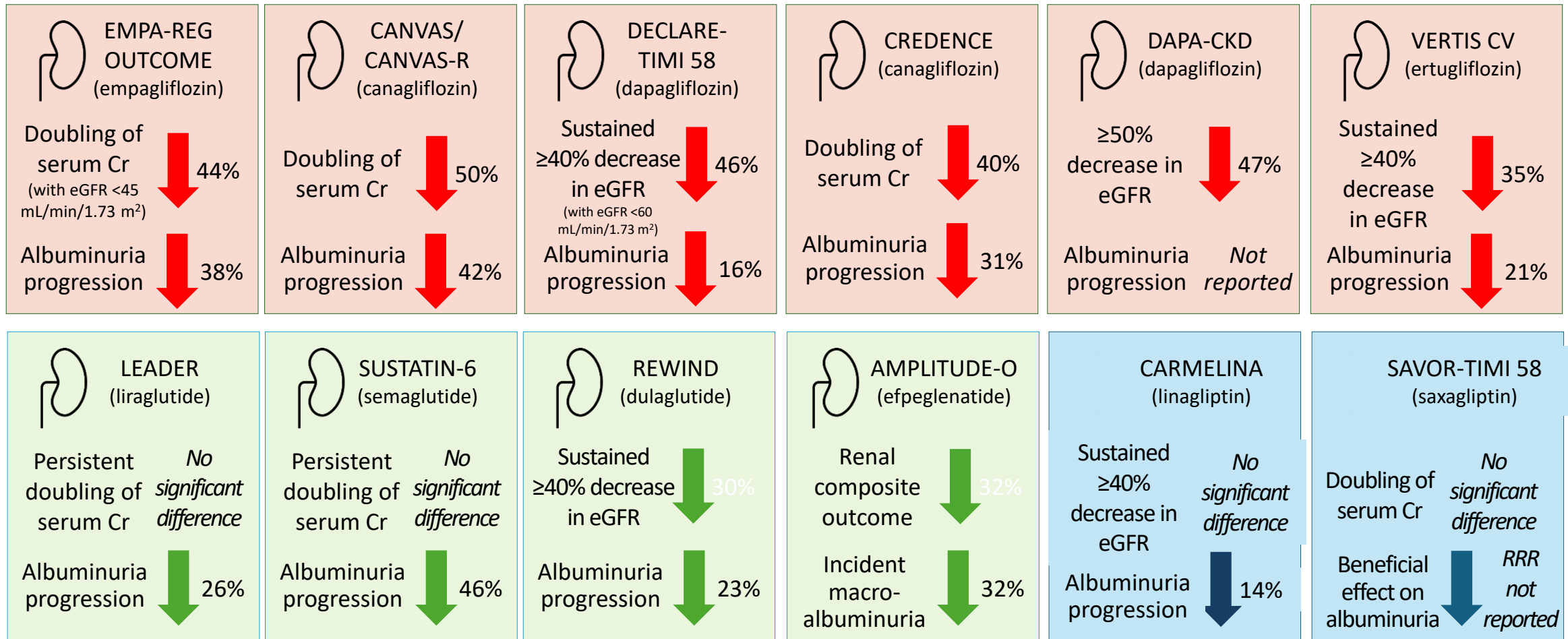
### **SGLT2 Inhibitors**

- Canagliflozin (indication)
- Dapagliflozin (indication)
- Empagliflozin (indication)

### **GLP1 RA**

- Benefit for renal endpoints in CVOTs, driven by albuminuria outcomes:
  - Dulaglutide
  - Liraglutide
  - Semaglutide (SQ)
- FLOW Trial- Dedicated Kidney Outcomes for Semaglutide (SQ)
  - 24% reduction in primary outcome

# Summary: Newer Glucose-Lowering Drugs and Renal Outcomes



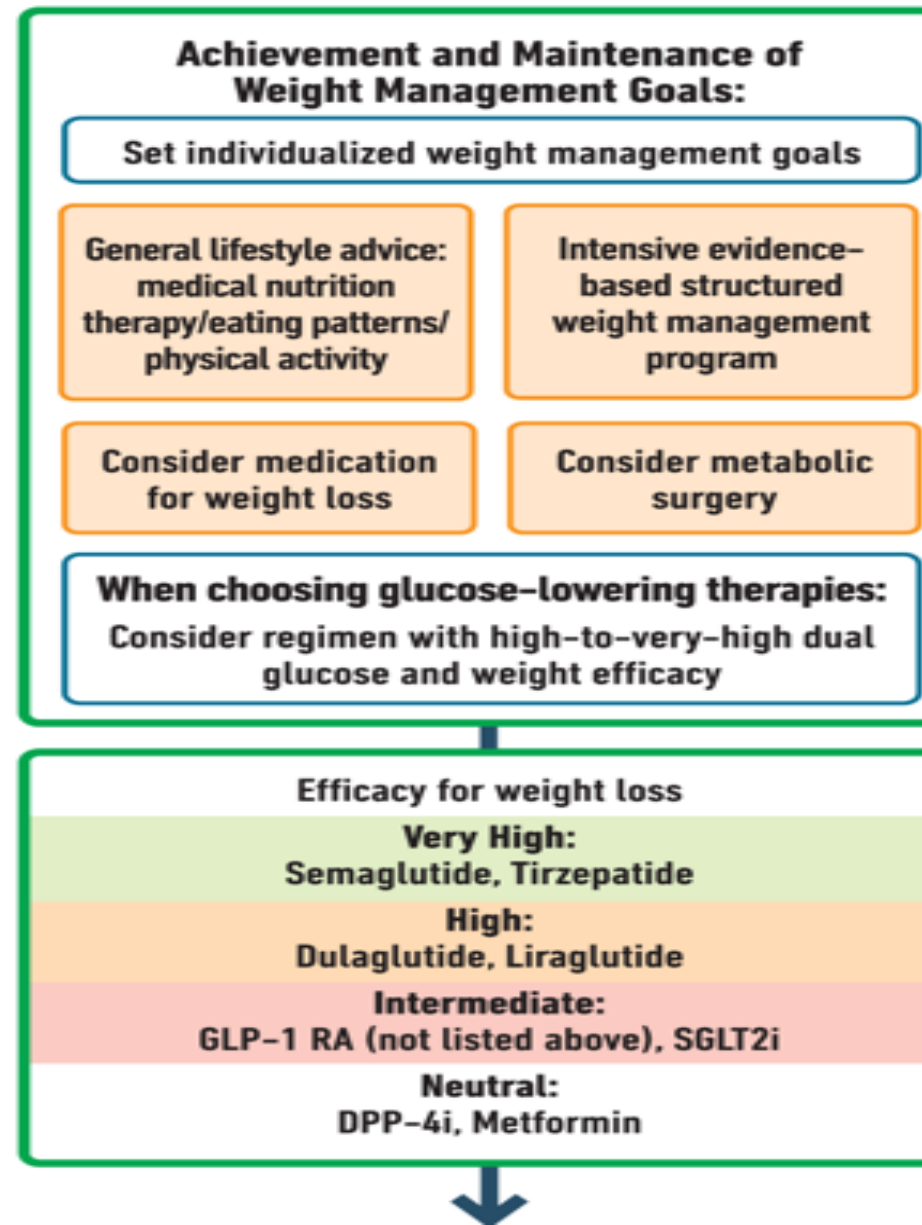
# Goal: Achievement and Maintenance of Glycemic Goals



- American Diabetes Association Professional Practice Committee; 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes—2024*. *Diabetes Care* 1 January 2024; 47 (Supplement\_1): S158–S178. <https://doi.org/10.2337/dc24-S009>



# Goal: Achievement and Maintenance of Weight Management Goals



- American Diabetes Association Professional Practice Committee; 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes—2024*. *Diabetes Care* 1 January 2024; 47 (Supplement\_1): S158–S178. <https://doi.org/10.2337/dc24-S009>





# Cost, Dosing, and Clinical Considerations

# Cost

## **Low:**

- Metformin
  - TZDs
- Sulfonylureas
- Human Insulin (SQ)

## **High:**

- SGLT-2 inhibitors
  - GLP-1 Ras
- Dual GIP & GLP-1 RA
  - DPP-4 inhibitors
  - Insulin Analogs

# Renal Dosing and Use Considerations

- **Metformin-** Contraindicated with eGFR < 30 mL/min/1.73 m<sup>2</sup>
- **SGLT-2 Inhibitors-** See labels for renal dose considerations of individual agents. Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR
- **GLP-1 RAs-** See labels for renal dose considerations of individual agents. No dose adjustment for dulaglutide, liraglutide, semaglutide. Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions
- **Dual GIP & GLP-1RA-** See label for renal considerations. No dose adjustment. Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions

# Renal Dosing and Use Considerations

- **DPP-4 inhibitors-** Renal dose adjustment required except linagliptin
- **TZDs-** No dose adjustment. Not recommended in renal impairment due to potential of fluid retention
- **Sulfonylureas-** Glyburide not recommended. Glipizide and glimepiride initiate conservatively to avoid hypoglycemia
- **Insulin-** Lower insulin doses required with decrease in eGFR; titrate per clinical response



# Clinical Considerations

# Metformin

- GI side effects common
- Consider slow dose titration, extended release formulations, and administration with food
- Potential for B12 deficiency. Monitor at regular intervals

# SGLT2 Inhibitors

- DKA risk but rare in T2DM: discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentation; discontinue before scheduled surgery (3-4 days), during critical illness, or during prolonged fasting to mitigate potential risk
- Increased risk of genital mycotic infections
- Necrotizing fasciitis of the perineum (Fournier gangrene), rare reports
- Attention to volume status, BP; adjust other volume-contracting agents as needed

# GLP-1 RAs

- Risk of thyroid C-cell tumors in rodents (liraglutide, dulaglutide, exenatide ER, semaglutide)
- Counsel on potential GI side effects and typical temporary nature; provide guidance on mitigating (reduction meal size, mindful eating practices, decrease intake of high fat and spicy food). Consider slower dose titration for patients with GI challenges
- Counsel patients about potential for ileus (semaglutide SQ)
- Pancreatitis has been reported in clinical trials. Discontinue if pancreatitis is suspected
- Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected



# Dual GIP & GLP-1 RAs

- Risk of thyroid C-cell tumors in rodents
- Counsel on potential GI side effects and typical temporary nature; provide guidance on mitigating (reduction meal size, mindful eating practices, decrease intake of high fat and spicy food). Consider slower dose titration for patients with GI challenges
- Not recommended with history of gastroparesis
- Pancreatitis has been reported in clinical trials. Discontinue if pancreatitis is suspected
- Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected

# DPP-4 inhibitors

- Pancreatitis has been reported in clinical trials. Discontinue if suspected
- Joint Pain
- Bullous Pemphigoid (postmarketing): discontinue if suspected

# Thiazolidinediones

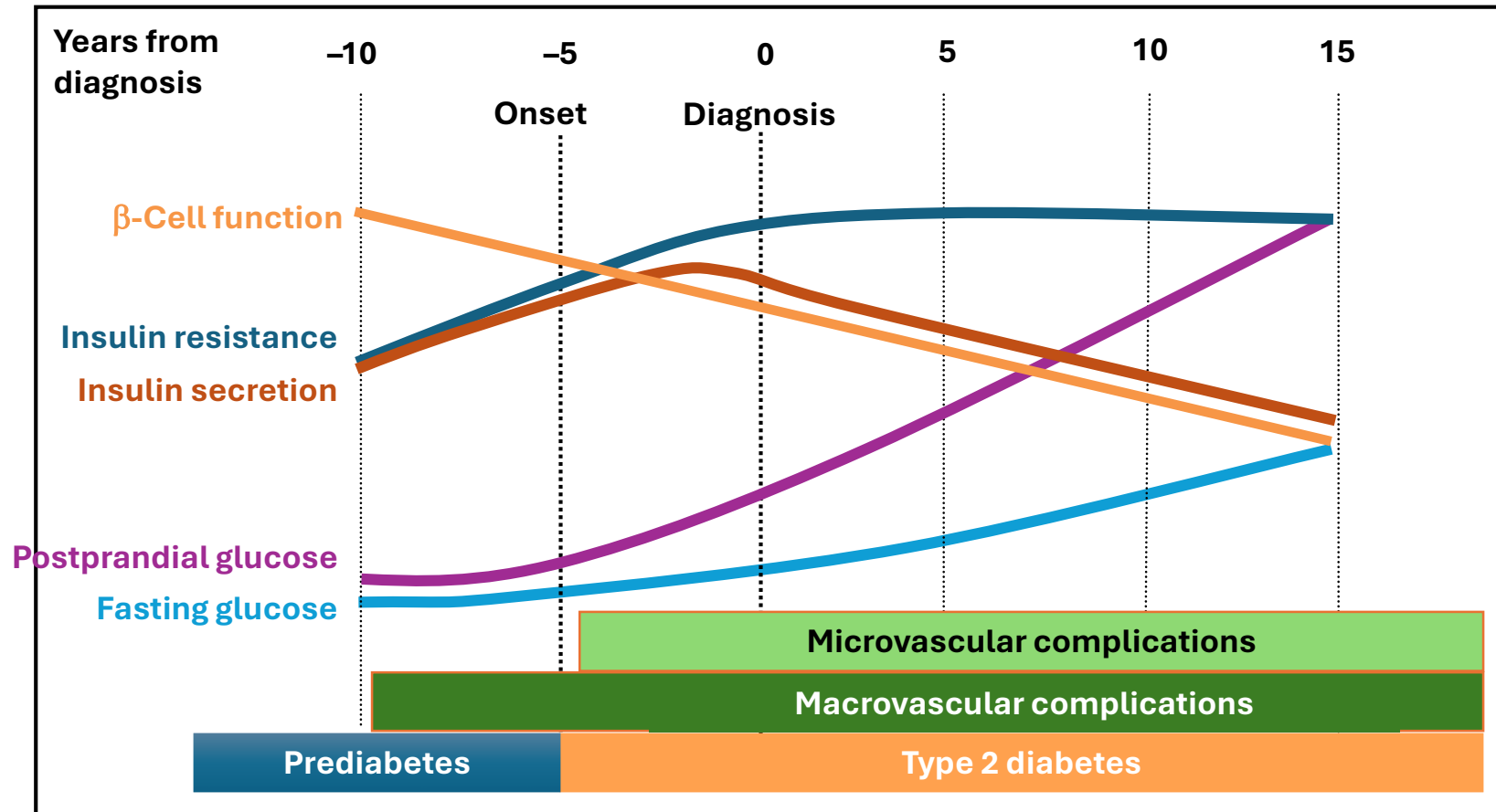
- Congestive Heart Failure
- Fluid retention (edema; heart failure)
- Benefit in NASH
- Risk of bone fractures
- Weight gain: consider lower doses to mitigate weight gain and edema

# Sulfonylureas

- FDA Special Warning: Increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be CV safe
- Use with caution in persons at risk for hypoglycemia

# Insulin Therapy Initiation and Intensification

# Natural History of Type 2 Diabetes



Beta Cell Function begins to decline 10 years prior to the diagnosis

50% Beta Cell Decline at time of diagnosis

Progressive decline 5% annually

Figure courtesy of CADRE. Accessed from [www.aace.com](http://www.aace.com), January 2019. Adapted from Holman RR. Diabetes Res Clin Pract 1998;40(Suppl.):S21–S25; Ramlo-Halsted BA, Edelman SV. Prim Care 1999;26:771 – 789; Nathan DM. N Engl J Med 2002;347:1342–1349; UK Prospective Diabetes Study Group. Diabetes 1995;44:1249–1258

# Progressive Nature of T2DM: Need for Insulin



In the UKPDS, **75%** of adults with newly diagnosed T2DM **needed insulin within 9 years**<sup>1</sup>



In the ORIGIN study, **11.4%** of adults with impaired fasting glucose, impaired glucose tolerance, or T2DM in the standard care arm **used insulin within 7 years**<sup>2</sup>

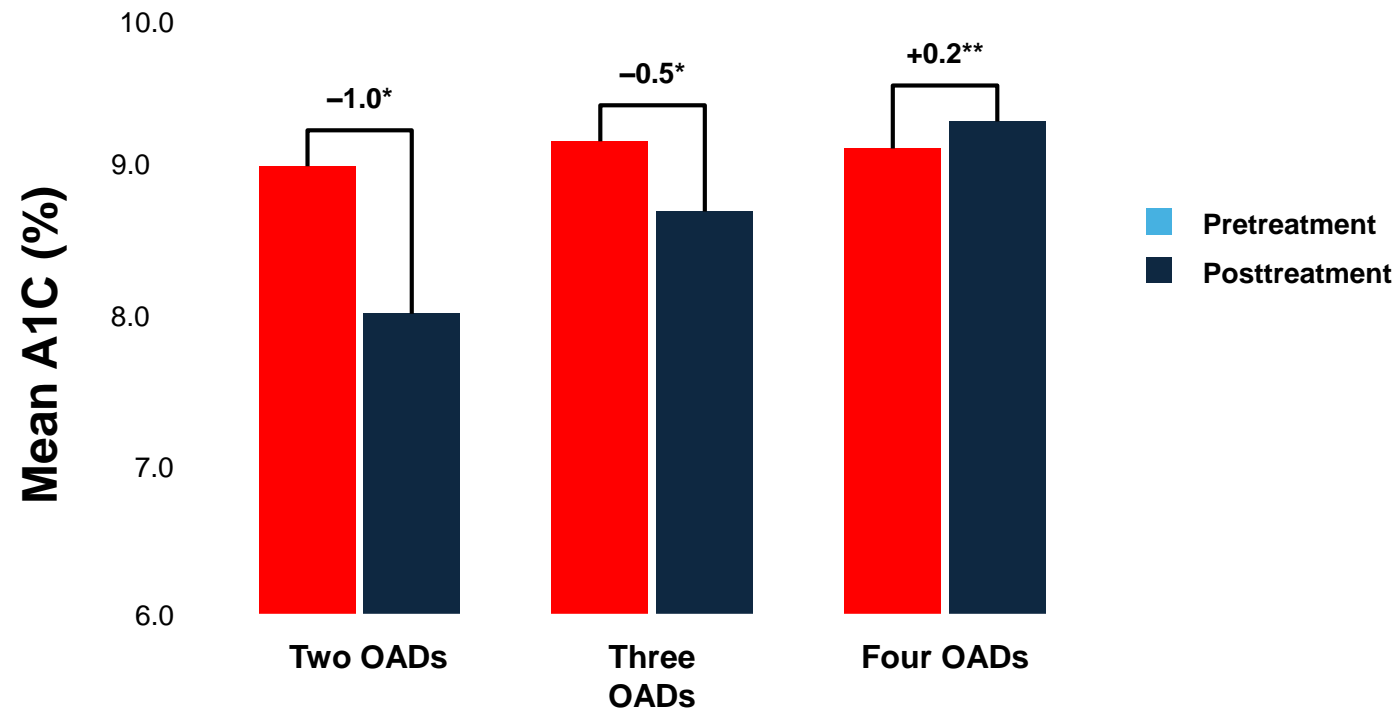


Even after **7 years with A1c >8%**, **insulin initiation is often postponed**, including patients **using 2 or 3 oral agents**<sup>4</sup>

ORIGIN = Outcome Reduction With Initial Glargine Intervention; TODAY = Treatment Options for Type 2 Diabetes in Adolescents and Youth; UKPDS = United Kingdom Prospective Diabetes Study.

1. Turner RC, et al. *JAMA*. 1999;281:2005-2012. 2. ORIGIN Trial Investigators, et al. *N Engl J Med*. 2012;367:319-328. 4. Khunti K, et al. *Diabetes Care*. 2013;36:3411-3417.

# Reduction in A1C with Multiple OADs



\* $p < 0.001$ .

\*\* $p = 0.54$

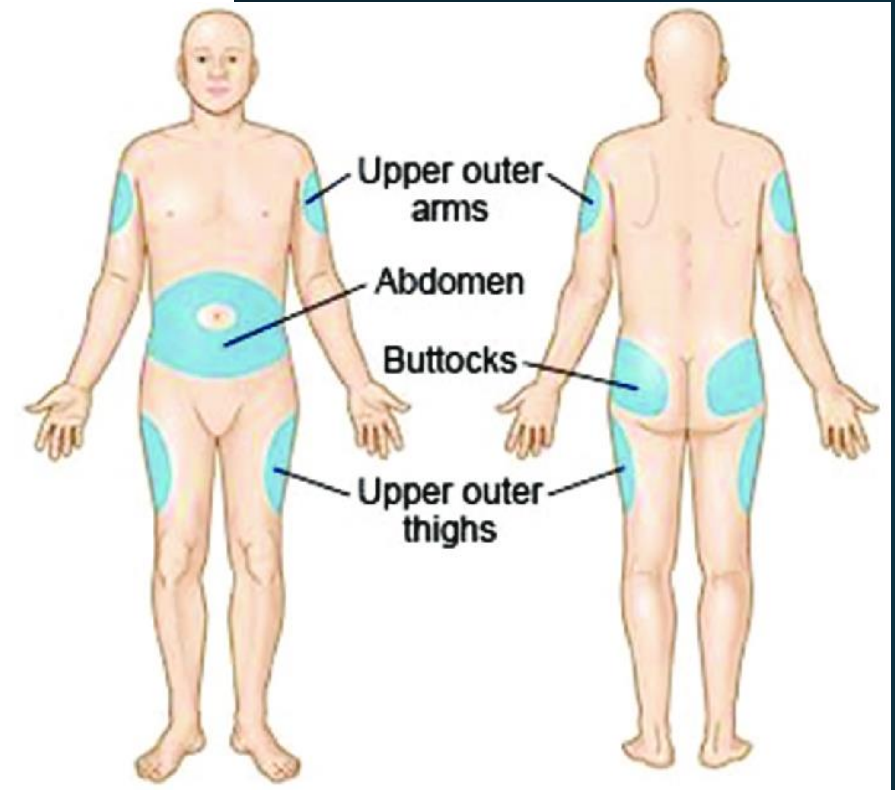
OADs = oral antidiabetic drugs.

Calvert MJ, et al. *Br J Gen Pract.* 2007;57:455-460.



# Proper Insulin Injection Technique Matters

- Subcutaneous injection
- Injection sites- abdomen, thigh, buttock, upper arm
- Short needles (4 mm needles) are effective and well tolerated in all adults with diabetes
- Injection rotation to avoid lipohypertrophy
- Education on proper insulin injection technique should occur
- Regular assessments/examination of insulin injection sites should occur

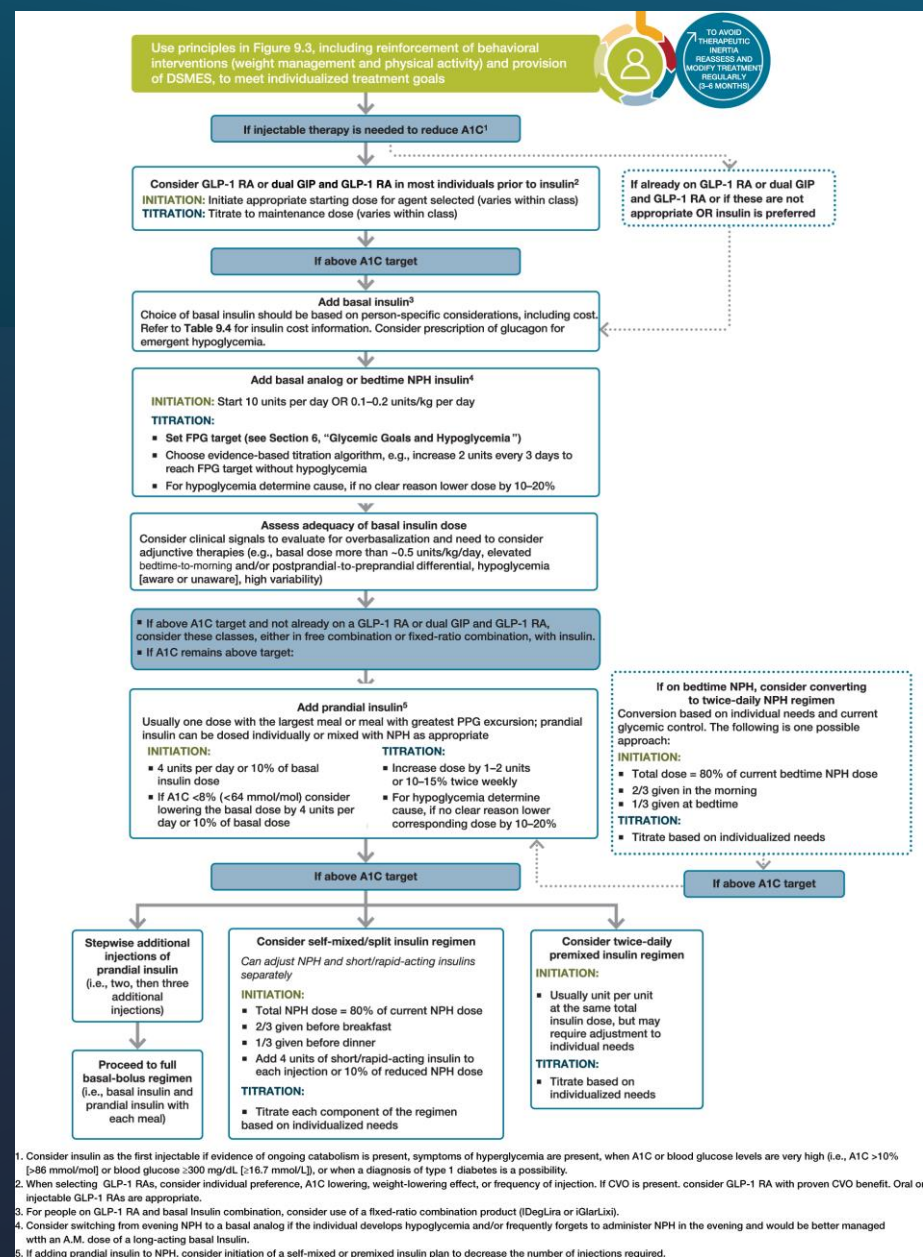


# ADA Standards of Care Recommendations

- **9.22** In adults with type 2 diabetes, initiation of insulin should be considered regardless of background glucose-lowering therapy or disease stage if there is evidence of ongoing catabolism (e.g., unexpected weight loss), if symptoms of hyperglycemia are present, or when A1C or blood glucose levels are very high (i.e., A1C >10% [ $>86$  mmol/mol] or blood glucose  $\geq 300$  mg/dL [ $\geq 16.7$  mmol/L]). **E**
- **9.23** In adults with type 2 diabetes, a GLP-1 RA, including a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA, is preferred to insulin. **A**
- **9.24** If insulin is used, combination therapy with a GLP-1 RA, including a dual GIP and GLP-1 RA, is recommended for greater glycemic effectiveness as well as beneficial effects on weight and hypoglycemia risk for adults with type 2 diabetes. Insulin dosing should be reassessed upon addition or dose escalation of a GLP-1 RA or dual GIP and GLP-1 RA. **A**

# Insulin Therapy in Adults Type 1 Diabetes

- The *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook* recommends
  - 0.5 units/kg/day as a typical starting dose for adult type 1 diabetes who are metabolically stable
  - ½ dose towards meal time insulin ½ towards basal insulin
- Lower or higher doses (0.2 to 0.6 units/kg/day) may be needed in those recently diagnosed that are in honeymoon phase or those who present in ketoacidosis



# Basal Insulin

# Basal Insulins Used in the U.S.

Name		Form	Time of Action* (h)			Comments
Generic	Brand		Onset	Peak	Duration	
Intermediate-acting ('Basal')						
NPH	Humulin Novolin Relion	Human	1-2	4-12	10-16	Increased risk of hypoglycemia when compared to analog basal insulin. Pregnancy (category B) - safe.
Long-acting ('Basal')						
Detemir U-100	Levemir (d/c)	Analog	1-2	Relatively peakless	24	
Glargine U-100	Lantus, Basaglar Semglee	Analog	1-2	Relatively peakless	24	
Glargine U-300	Toujeo	Analog	6	Relatively peakless	≥24	Expect that a higher daily dose of glargine U-300 than glargine U-100 will be needed. (Glargine - C; Degludec - C; Detemir - B)
Degludec U-100, U-200	Tresiba	Analog	1-2	Relatively peakless	≥42	
*Dose dependent (except glargine U-300, degludec)						

\*Dose dependent (except glargine U-300, degludec)

Care. 2007;30;2447-2452.

Porcellati F, et al. Diabetes Care. 2007;30:1261-1263. Hirsch IB. N Engl J Med. 2005;352(2):174-183. Meneghini L, et al. Diabetes Obes Metab. 2007;9(6):902-913. Lantus [package insert] Bridgewater, NJ: sanofi-aventis US LLC; May 2019. Basaglar [package insert]. Indianapolis, IN: Eli Lilly & Co.; January 2019. Levemir [package insert]. Plainsboro, NJ: Novo Nordisk US; January 2019. Toujeo [package insert]. Bridgewater, NJ: sanofi-aventis US LLC; March 2019. Tresiba [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; November 2018. Nasrallah S, et al. Clin Med Insights Endocrinol Diabetes. 2012;5;31-37.

# Dosing Flexibility With Basal Insulins

Insulin	Dosing Instructions
<b>NPH</b>	<ul style="list-style-type: none"><li>• Once or twice daily</li></ul>
<b>Detemir (has been discontinued)</b>	<ul style="list-style-type: none"><li>• Once or twice daily</li><li>• Once daily with dinner or at bedtime</li><li>• 12 h apart for twice daily</li></ul>
<b>Glargine and U-300 glargine</b>	<ul style="list-style-type: none"><li>• Once daily at any time, but the same time each day</li></ul>
<b>Degludec</b>	<ul style="list-style-type: none"><li>• Once daily at any time</li><li>• Missed dose when remembered, with at least 8 h between doses</li></ul>



# Hypoglycemia Risk Differs Among Basal Insulins

## DEGLADEC:

- Overall hypoglycemia ↓ **30%**<sup>2</sup>
- Nocturnal ↓ **42%**<sup>2</sup>
- Severe, in patients at high CV risk ↓ **40%**<sup>3</sup>

## U-300 GLARGINE:

- Clinically significant nocturnal ↓ **25%**<sup>4</sup>
- Risk of confirmed or severe events<sup>5</sup>
  - ↓ **15%** at night
  - ↓ **6%** during the day

Lower risk\* with  
DET *or* U-100  
GLAR vs  
NPH<sup>1</sup>

Lower risk with  
DEG *or* U-300  
GLAR vs  
U-100 GLAR<sup>1</sup>

\*Lower risk of symptomatic and nocturnal hypoglycemia.

1. American Diabetes Association. Diabetes Care. 2019;42(suppl 1):S1-S193; 2. Wysham C, et al. JAMA. 2017;318:45-56; 3. Marso SP, et al. N Engl J Med. 2017;377:723-732; 4. Diez-Fernandez A, et al. Acta Diabetol. 2019;56:355-364; 5. Ritzel R, et al. Diabetes Obes Metab. 2018;20:541-548.

# ADA's Recommendation to Initiation of Basal Insulin

Add basal analog or bedtime NPH NPH insulin

**Start 10 units a day or 0.1-0.2 units/kg a day**

Choice of basal insulin should be based on person-specific considerations, including cost. Refer to **Table 9.4** for insulin cost information. Consider a prescription of glucagon for emergent hypoglycemia

# Example of Calculating Basal Insulin

- 53 year old patient who weighs 253 lbs is ready to start basal insulin
- **10 units** initiation dose
- Or calculate weight-based dose

253 divided by 2.2= 115 kg

115 kg x 0.2 units= **23 units**

Base your starting dose on individual factors per patient

# ADA's Recommendations to Titrating Basal Insulin

## **Titrate or Adjust**

**Set Fasting Plasma Glucose Target  
(ADA recommends 80 to 130 mg/dl)**

**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%**

**Recommend to only adjust ultra long-acting insulins weekly or no more than every 3 to 4 days**

# ADA Standards of Care Recommendations

- **9.27** Monitor for signs of overbasalization during insulin therapy, such as basal dose exceeding ~0.5 units/kg/day, significant bedtime-to-morning or postprandial-to-preprandial glucose differential, occurrences of hypoglycemia (aware or unaware), and high glycemic variability. When overbasalization is suspected, a thorough reevaluation should occur promptly to further tailor therapy to the individual's needs. **E**
- **9.26** To minimize the risk of hypoglycemia and treatment burden when starting insulin therapy in adults with type 2 diabetes, reassess the need for and/or dose of glucose-lowering agents with higher hypoglycemia risk (i.e., sulfonylureas and meglitinides). **A**

American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes 2024. Diabetes Care January 2024;47(Suppl. 1):S158–S178

# Assess Adequacy of Basal Insulin Dose

- Consider clinical signals to evaluate **over basalization** and the need to consider adjunctive therapies:
  - Basal dose  $> 0.5$ units/kg/day
  - Elevated bedtime-morning and/or post-preprandial differential
  - Hypoglycemia (aware or unaware)
  - High variability

# Guidance Regarding Use of Other Glucose-Lowering Agents When Initiating Basal Insulin

## Continue

- Metformin<sup>1,2</sup>
- GLP-1 RA, DPP-4 inhibitor<sup>1,2</sup>
- SGLT2 inhibitor (to prevent diabetic ketoacidosis, do not down titrate insulin overaggressively)<sup>1,2</sup>

## Reduce dose or discontinue

- Sulfonylurea (to prevent hypoglycemia)<sup>1,2</sup>
- Thiazolidinedione (to prevent edema or heart failure)<sup>1,2</sup>

Consider discontinuation of other agents on an individual basis to avoid unnecessarily complex\* or costly regimens<sup>2</sup>

4-drug combinations.

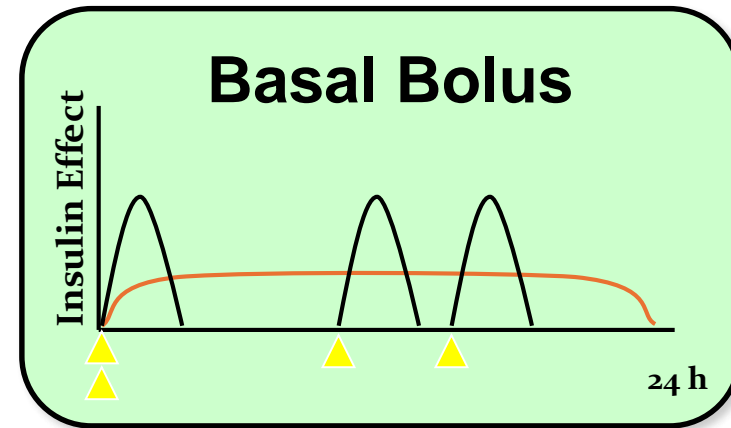
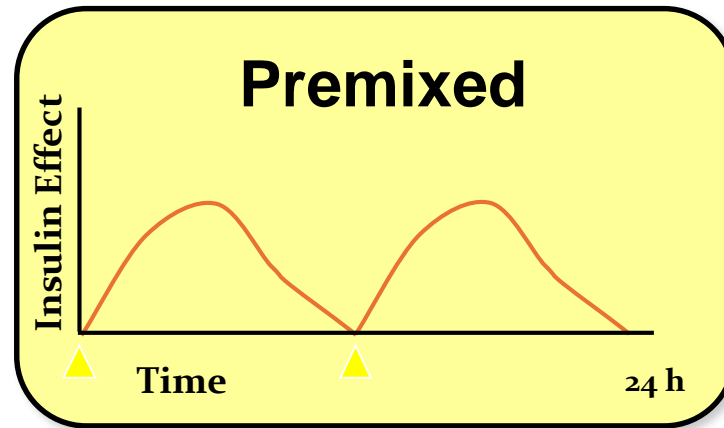
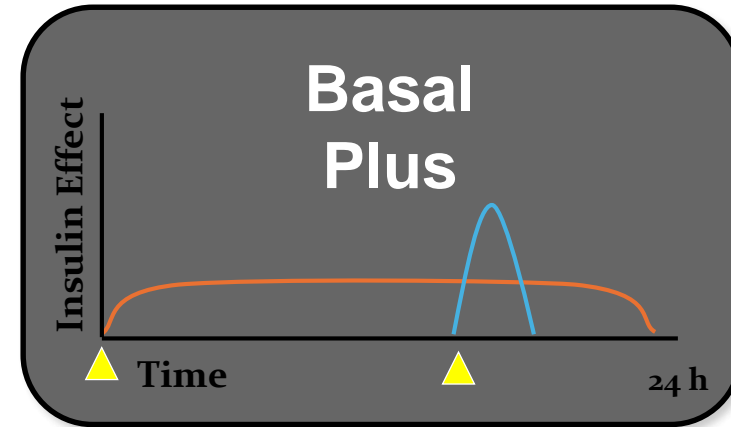
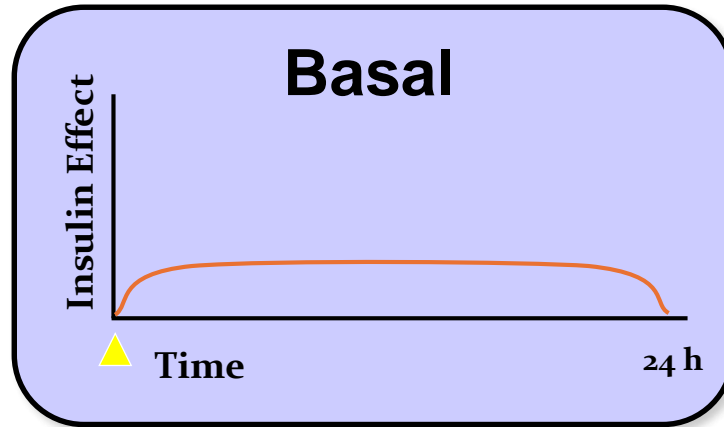
1. Davies MJ, et al. *Diabetes Care*. 2018;41:2669-2701; 2. American Diabetes Association. *Diabetes Care*. 2019;42(suppl 1):S1-S193;

3. Drugs@FDA. [www.accessdata.fda.gov/scripts/cder/daf](http://www.accessdata.fda.gov/scripts/cder/daf).

# Intensifying Insulin Therapy



# Common Insulin Regimens



▲ = insulin injection

- Del Prato S, et al. Diabetes Technol Ther. 2012;14:175-182.
- American Diabetes Association. In: Practical Insulin: A Handbook for Prescribing Providers. 3rd ed. 2011:1-68.

# The Basal/Bolus Insulin Concept



## Basal insulin:

The goal of basal insulin is to suppress hepatic glucose production and limit fasting hyperglycemia. Helps to improve both overnight and between meals control.

When using replacement therapy, **~50 percent of the total daily insulin dose is given as basal.**



## Bolus insulin (prandial/mealtime):

The goal of bolus insulin is to cover the carbohydrate in meals and to limit postprandial hyperglycemia. Ideally, blood glucose should rise only 30-60 mg/dL from pre- to post-meal.

When using replacement therapy, **~50 percent of daily needs are provided as bolus: distributed between the meals.**

# Prandial Insulins Used in the U.S.

Name		Form	Time of Action* (h)			Meal Timing (min)
Generic	Brand		Onset	Peak	Duration	
Rapid-acting ( ‘Bolus’ or ‘Prandial’ )						
Aspart	Fiasp	Analog	0.25-0.3	1.5-2	5-7	0 to +20
Lispro	Lyumjev	Analog	15-17	57min	5-7	0 to +20
Aspart	Novolog	Analog	< 0.25	1-3	3-5	-5 to -10
Glulisine	Apidra	Analog	< 0.25	0.7-3	3-5	-15 to +20
Lispro	Humalog (U-100, U-200) Admelog (U-100)	Analog	< 0.25	0.5-1.5	3-6	-15 to immediately after
Insulin Inhalation	Afrezza	Human	< 0.25	0.5-1.5	2.7	0
Short-acting ( ‘Bolus’ or ‘Prandial’ )						
Regular	Humulin R Novolin R	Human	0.25-1.25	1.5-3.5	8	-30

Fiasp [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; September 2018. Novolog [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; December 2018. Apidra [package insert]. Bridgewater, NJ: sanofi-aventis US, LLC; January 2019. Humalog [package insert]. Indianapolis, IN: Eli Lilly; March 2019. Admelog [package insert]. sanofi-aventis US, LLC; December 2018. Afrezza [package insert]. Danbury, CT: MannKind Corp.; October 2018. Humulin R [package insert]. Indianapolis, IN: Eli Lilly; November 2018. Novolin R [package insert]. Plainsboro, NJ: Novo Nordisk Inc; June 2018.

# Initiation of Prandial Insulin

- Initiation:
  - 4 units/day or 10% of basal dose
  - One dose with the largest meal or meal with the greatest PPG excursion
  - Prandial insulin can be **dosed individually** or **mixed with NPH as appropriate**
  - If A1C is <8% (64 mmol/mol), consider decreasing the basal dose by 4 units a day or 10% of basal dose

• American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes 2024. Diabetes Care January 2024;47(Suppl. 1):S158–S178

# Example of Adding Prandial

A1C is  $> 8\%$  and patient is on 36 units of basal insulin:

**36 units** basal at bedtime

**4 units** prandial with largest meal of day (most cases evening meal)

A1C is  $< 8\%$  and patient is on 36 units of basal insulin:

**32 units** of basal at bedtime

**4 units** of prandial with largest meal of day (most cases evening meal)

# Titration of Prandial Insulin

- Titration:
  - Increase dose by 1–2 units or 10–15% twice weekly
  - Test plasma glucose levels using SMBG just before and 2 hours after largest meal
- Signs or symptoms of hypoglycemia:
  - Determine and address cause
  - If no clear reason lower corresponding dose by 10–20%

• American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes 2024. Diabetes Care January 2024;47(Suppl. 1):S158–S178

# Prandial Insulin in a Stepwise Approach

Stepwise approach:

Add prandial insulin to a second meal based on post prandial readings

Individualized to the patient based on SMBG or CGM

May be breakfast or lunch

Start 4 units and titrate as previously demonstrated

May need to add to third meal after 3 months if necessary to full basal/bolus

# Traditional “Sliding Scale”

- An arbitrary insulin dosing algorithm based only on pre-meal blood glucose values; doesn't consider patients' weight, ISF, ICR, or carbs to be consumed.

Pre-Meal BG (mg/dl)	Insulin Dose (units)
Less than 151	0
151-200	2
201-250	4
251-300	6
301-350	8
351-400	10



# Problems with “Traditional Sliding Scale”

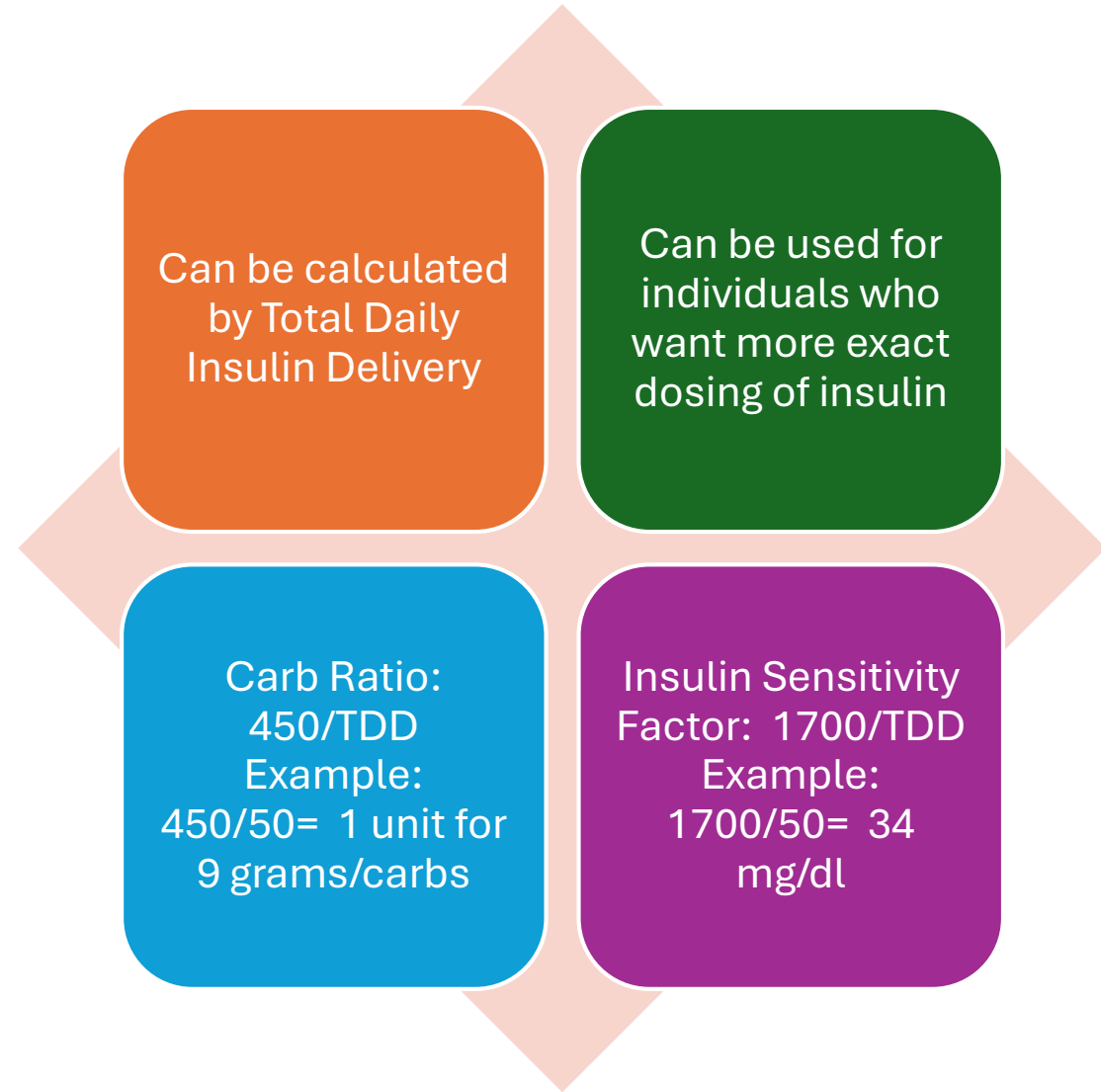
Sliding scale not specific to patient needs

- Not flexible for carbohydrate in meals
- Some meals may need more insulin
- No adjustment for portion size, lower BG, Higher BG, life in general

No meal insulin if less than 100mg/dl??

Use of correction insulin??

# Carb counting/ Insulin sensitivity factor



# Self mixed/Split insulin regimen

# Self mixed/Split insulin regimen

- Can adjust NPH insulin 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

# Pre-mixed insulin regimen

# Pre-Mixed Insulin: Rapid-Acting + Intermediate-Acting

Insulin	Onset	Peak	Duration
Lispro (Humalog) (25%), (50%) Aspart (Novolog) (30%)	~15 min	1-2 h	3-5 h
NPL, insulin lispro protamine (75%), (50%) NPA, insulin aspart protamine (70%)	2-3 h	4-10 h	10-16 h
Humalog 75/25, Humalog 50/50, Novolog 70/30			

# Twice Daily Premix Insulin Regimen

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## Initiation:

- Usually unit to unit at the same total insulin dose, but may require adjustment to individual needs

Example: 50 units of basal insulin

Change to twice daily premix to 25 units twice daily

## Titration: Titrate based on individualized needs

Fasting glucose in AM elevated

Increase evening dose 2 units every 3 days

If pre dinner glucose is elevated

Increase morning dose by 2 units every 3 days

# Hypoglycemia

	Glycemic criteria/description
Level 1	Glucose < 70 mg/dl and $\geq$ 54 mg/dl
Level 2	Glucose < 54 mg/dl
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia, irrespective of glucose level

## **Treatment:**

15 g of fast-acting carbohydrates at the hypoglycemia alert value of 70 mg/dl or less

Recheck glucose 15 min after ingesting carbohydrate and repeat if necessary

Use glucagon in people unable or unwilling to consume carbohydrates by mouth

All individuals treated with insulin or who are at high risk of hypoglycemia as discussed above should be prescribed glucagon



# Newer Glucagon Formulations



- Intra Nasal Powder Device
- >4 years old
- 3 mg dose. 2<sup>nd</sup> dose can be administered after 15 minutes

- Auto Injector prefilled pen
- >2 years old
- Age >12 years old 1 mg. Age <12 if weighs <45 KG 0.5mg, >45 KG 1.0 mg. 2<sup>nd</sup> dose can be administered after 15 minutes

- Auto Injector prefilled Pen
- >6 years old
- 0.6 mg
- 2<sup>nd</sup> dose can be administered after 15 minutes

# Summary

- Diabetes is a progressive and multifaceted disease
- Choosing medication for patients is individualized to the person living with diabetes
- Insulin initiation should be done in a stepwise approach
- It is important to supply patients with glucagon if they are utilizing insulin or any product that may increase risk of hypoglycemia