Brigham and Women's Hospital
Founding Member, Mass General Brigham

Diabetes Update: 2026

Marie E. McDonnell, MD

Director, Brigham and Women's Diabetes Program

Division of Endocrinology, Diabetes and Hypertension

Brigham and Women's Hospital

Associate Professor of Medicine

Harvard Medical School

CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Marie E. McDonnell, MD

Boston University School of Medicine

Medicine Residency: Columbia Presbyterian, New York

Endocrinology Fellowship: Boston Medical Center

Chief, Diabetes section, Division of Endocrinology Diabetes and Hypertension at Brigham and Women's Hospital

Associate Professor of Medicine at HMS

- *Clinical focus:* Diabetes care in complex patient populations
- *Research focus:* Health outcomes research and care model design for people with diabetes

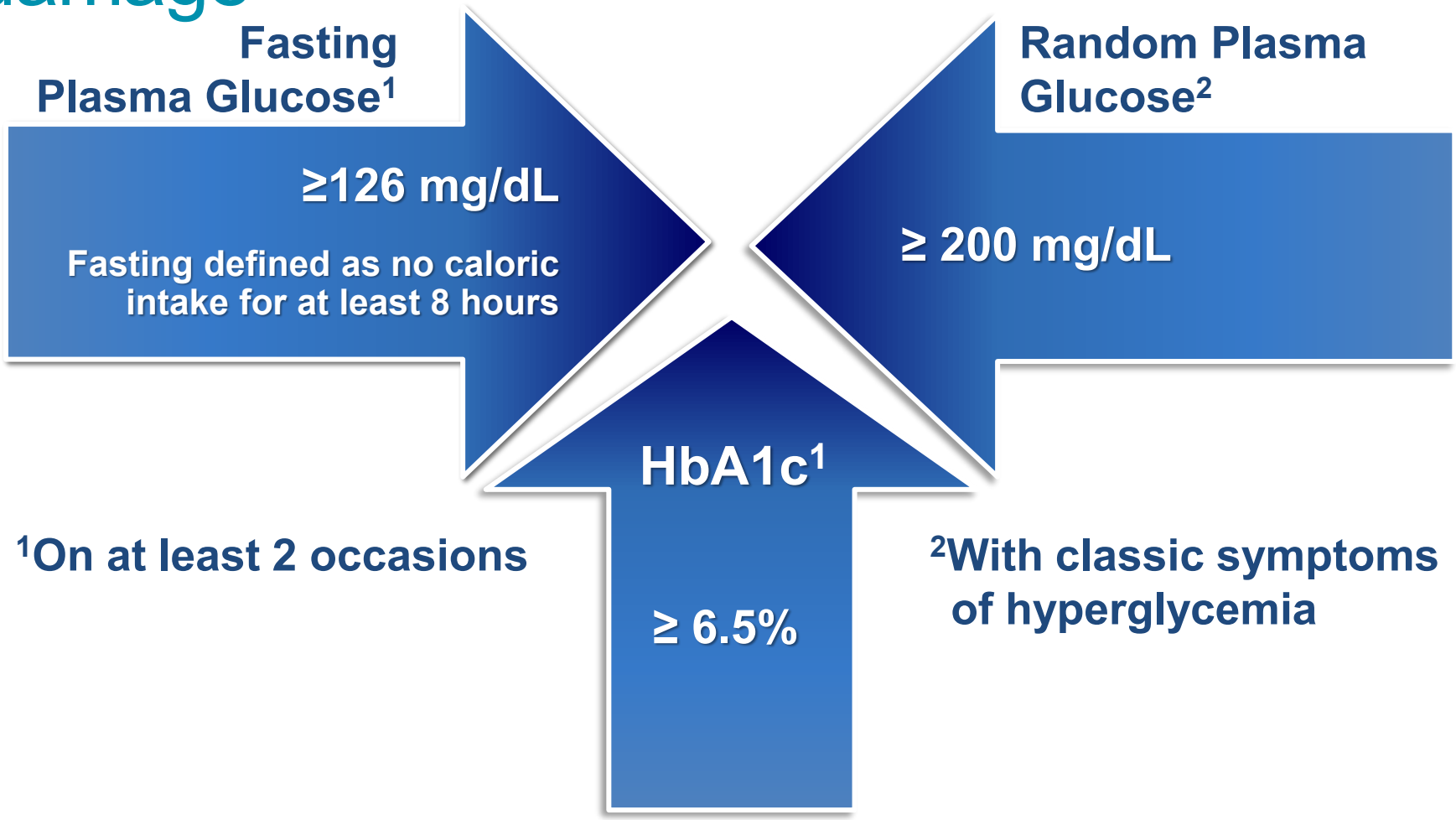
Disclosures

Research funding paid directly to institution: Abbott Industries, Inc.

Learning Objectives

- Apply modern perspectives on Diabetes diagnosis
- Understand new emphasis on “treating adiposity first” in type 2 diabetes
- Learn how to individualize therapeutic strategies for type 2 diabetes based on comorbidities, goals as well as concerns and side effects

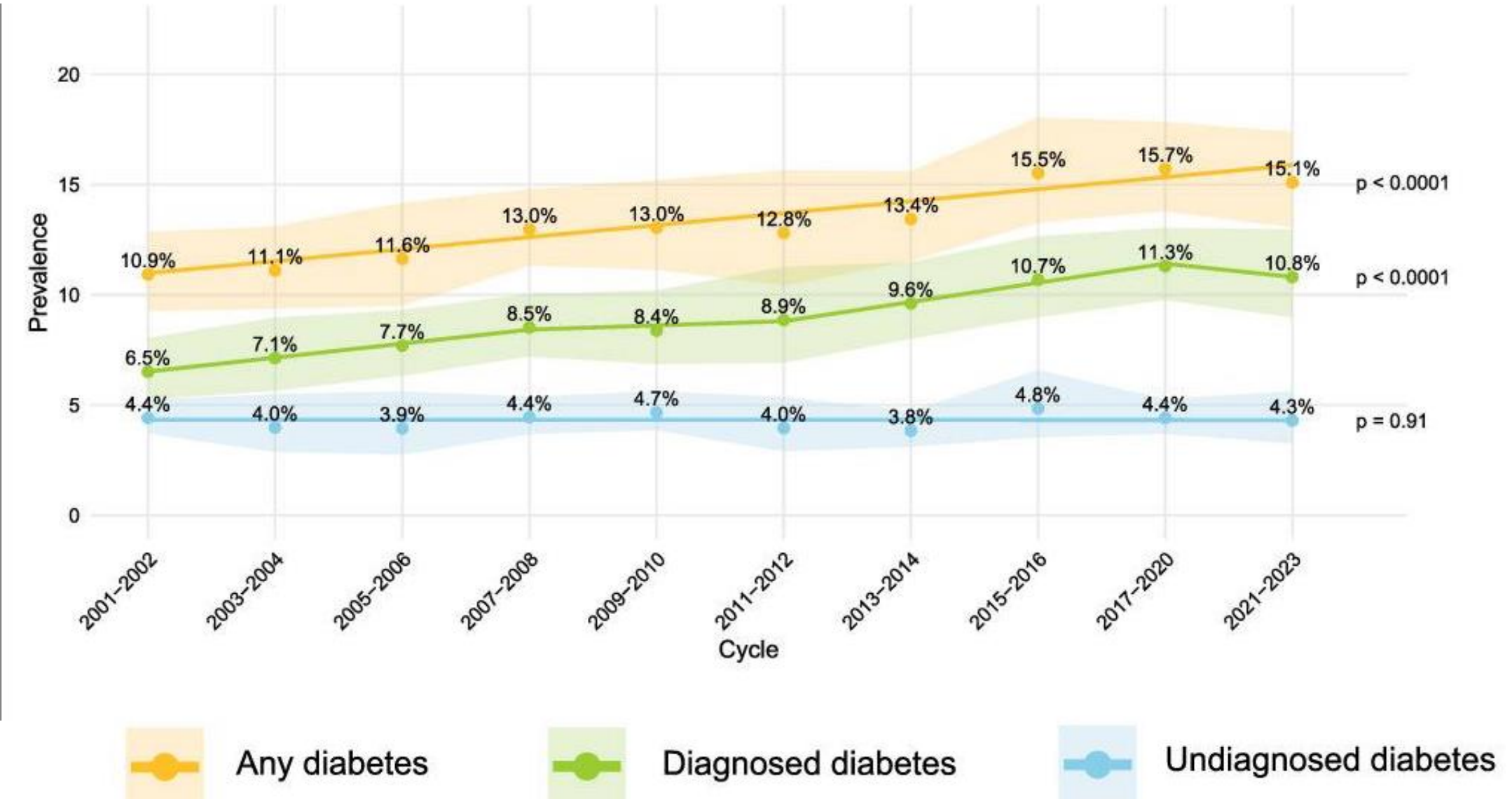
What is Diabetes?:
Persistent Hyperglycemia that over time leads to organ damage



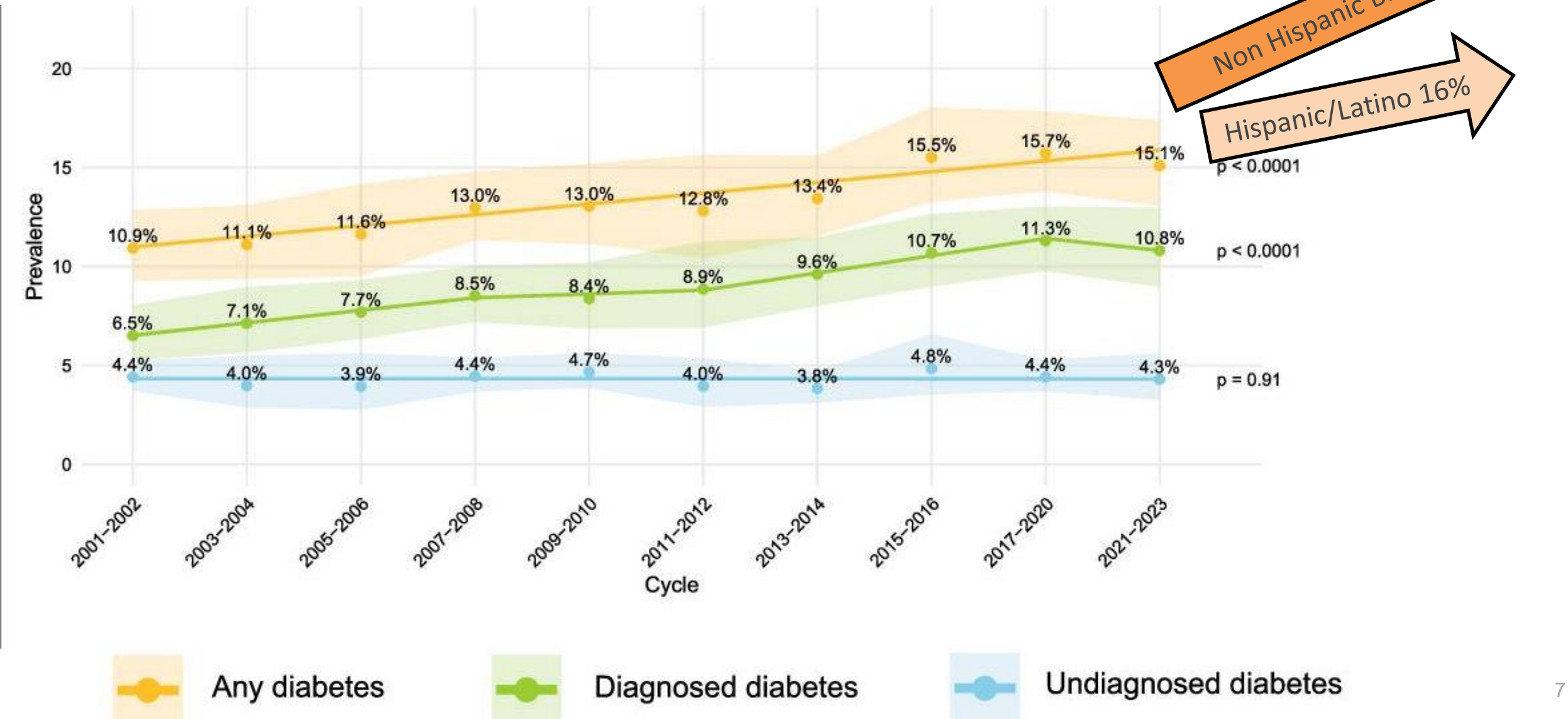
[1]On at least 2 occasions

[2]With classic symptoms of hyperglycemia

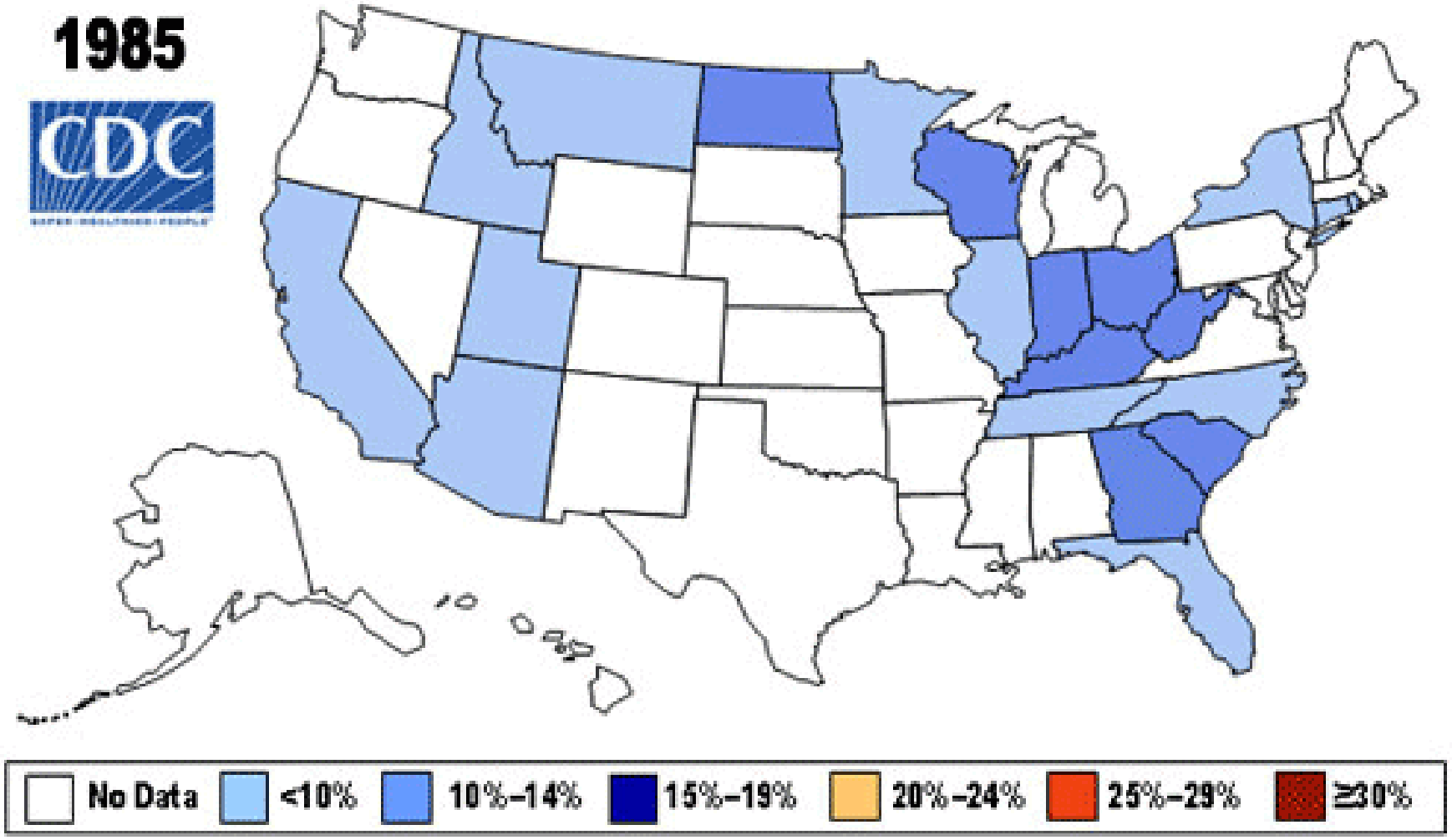
Diabetes Prevalence in US: >10% for 20 years and rising



Diabetes Prevalence in US: >10% for 20 years and rising



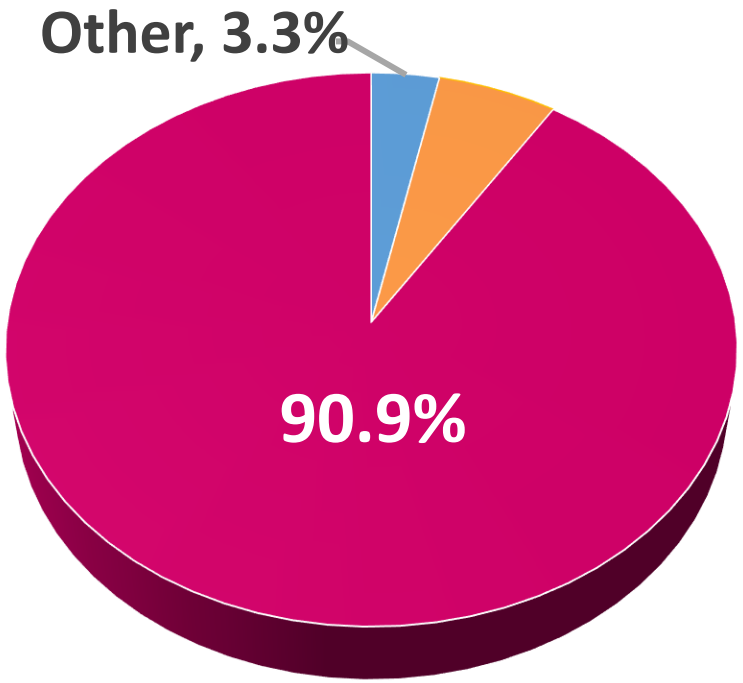
Obesity: Key Driver of the Diabetes Pandemic



Percentages of the U.S. population medically defined as obese
(BMI > 30 kg/m2, 1985-2010

https://www.theatlantic.com/health/archive/2013/04/look-how-quickly-the-us-got-fat-1985-2010-animated-map/274878/. Accessed June 7, 2024
https://archive.cdc.gov/www_cdc_gov/diabetes/library/reports/reportcard/national-state-diabetes-trends_1702491587.html. Accessed June 7, 2024

Breakdown of chronic* forms of diabetes in United States



Autoimmune diabetes 5.8%:

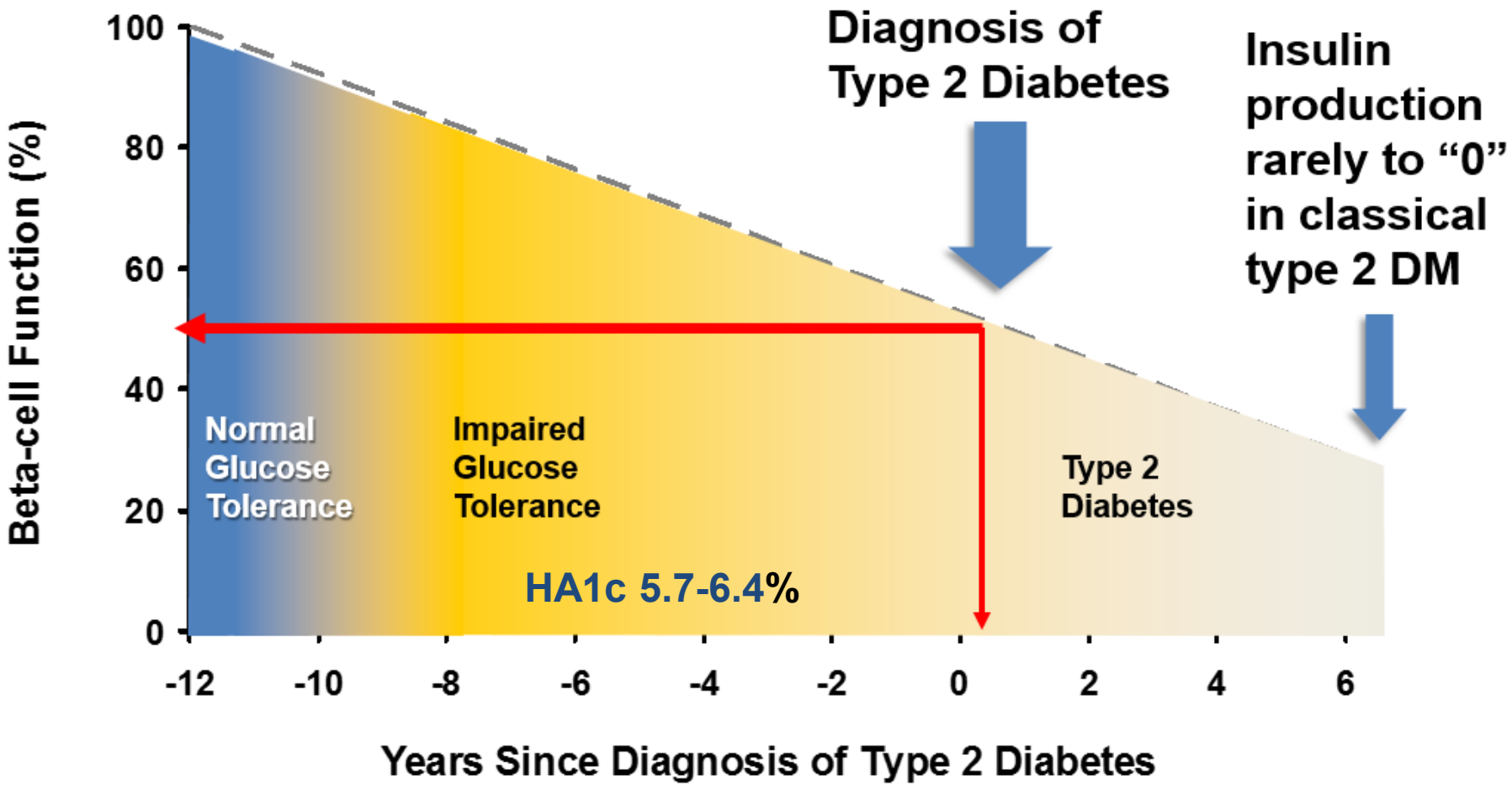
Positive GAD, IA2, insulin, or zinc ZnT8 Antibodies; Often lack features of metabolic syndrome

Type 2 diabetes: ***Older age, higher BMI, features of metabolic syndrome***

• not including Gestational Diabetes (GDM)

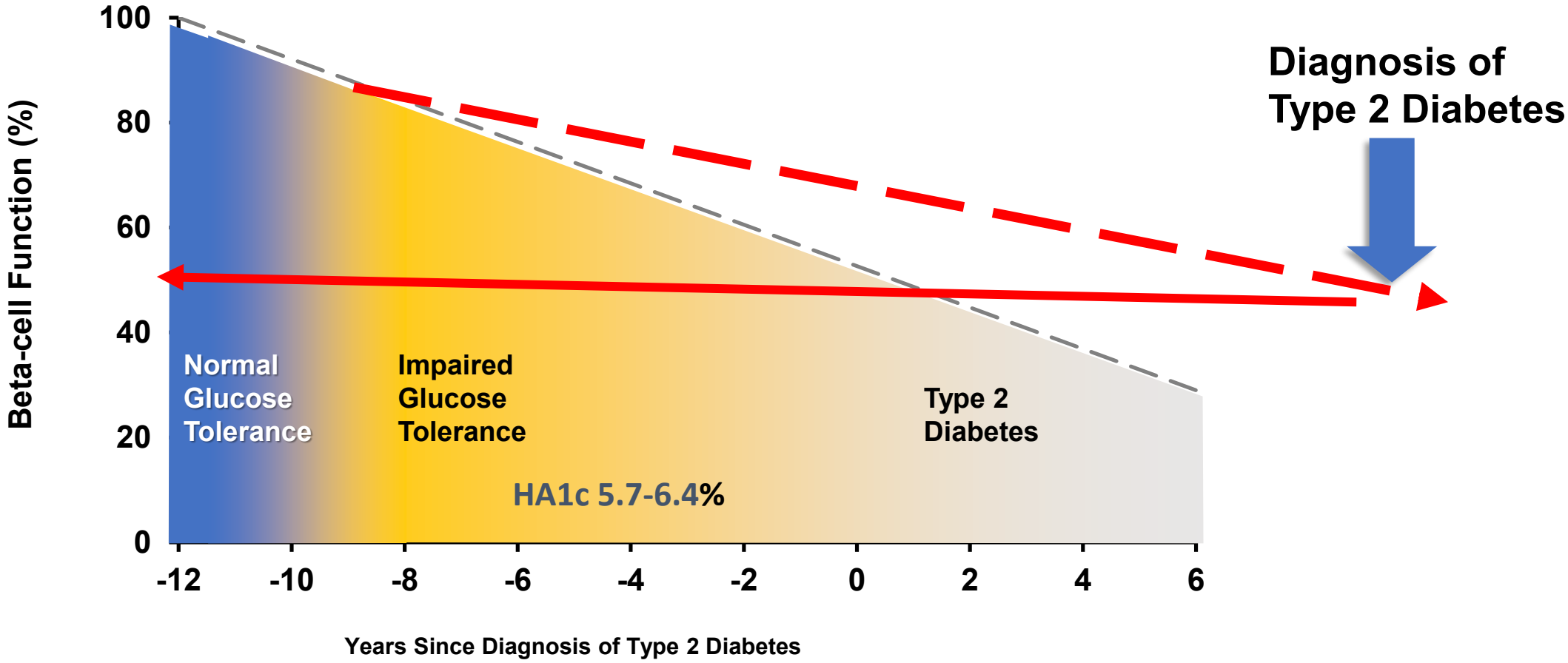
Slide :Courtesy of Miriam Udler, MD

Prediabetes precedes by several years



Adapted from UKPDS16. Diabetes. 1995:44:1249-1258.

T2D Prevention = delaying the onset so that it has less impact



Adapted from UKPDS16. Diabetes. 1995;44:1249-1258.

T2D Prevention in Pre-DM is Underutilized

Most effective in Overweight + PreDM:

- 150 minutes per week of exercise, both cardio and resistance training
- Weight loss (at least 5%, shoot for >10%)

Most effective in Obesity + PreDM:

- Behavioral lifestyle change + GLP-1 RA (best evidence for weekly tirzpetide)

When to *consider* pharmacologic therapy for prediabetes?

- **A1c >6% or history of GDM:** In the DPP study, progression was more predictable with higher baseline A1c and history of GDM
- **BMI 26-29**: limited ability to exercise, strong FH or overall cardiometabolic risk: Rx with Metformin or approved Rx for weight management
- **BMI >30**: Rx with approved Rx for weight management, ideally GLP-1 RA therapy

When to *strongly encourage* pharmacologic therapy for prediabetes?

- Woman of reproductive age: **METFORMIN is safe in pregnancy**! Can impact multiple future generations
- Age <50 and strong FH

DPP Research Group. N Engl J Med. 2002;346:393-403.
Tuomilehto J et al. N Engl J Med. 2001;344:1343-1350.
Pan XR et al. Diabetes Care. 1997;20:537-544.

Rx Vitamin D for Diabetes prevention

Recommendation 10

For adults with high-risk prediabetes, in addition to lifestyle modification, we suggest empiric vitamin D supplementation to reduce the risk of progression to diabetes. (2 | ⨁⨁⨁O

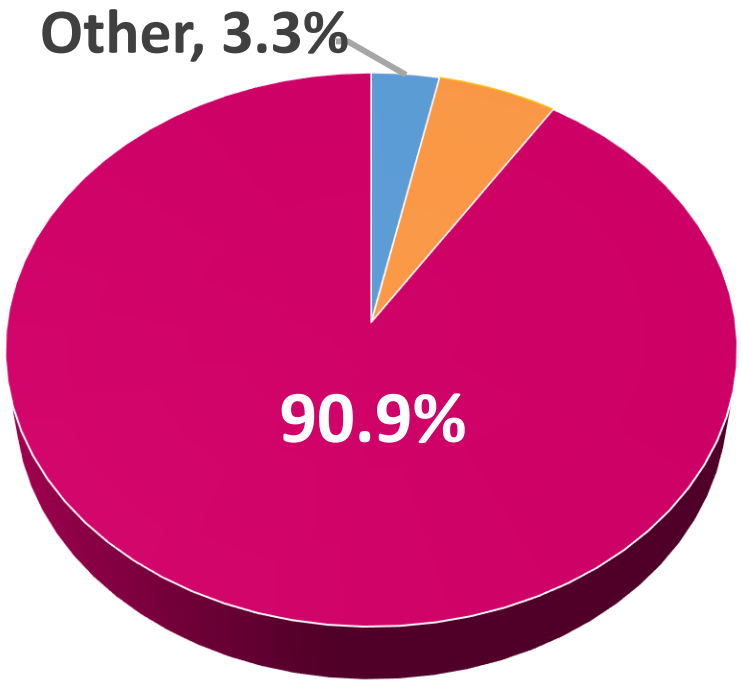
Technical remarks:

- **Lifestyle modification** must be a routine management component for adults with prediabetes.
- The clinical trials informing this recommendation primarily related to adults with **high-risk prediabetes**

- **Dose is unclear:** In the clinical trials included in the SR, the vitamin D doses ranged from 842 to 7543 IU (21 to 189 µg) daily equivalent. The estimated weighted average was approximately 3500 IU (88 µg) per day. Participants in some trials were allowed to remain on their routine supplements, including up to 1000 IU (25 µg) of vitamin D daily.
  - **My suggestion:** 2,000 IU daily for people with prediabetes

Demay MB, Pittas A, et al. Vitamin D for the Prevention of Disease: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2024

Breakdown of diabetes in United States



Autoimmune diabetes 5.8%:

Positive GAD, IA2, insulin, or zinc ZnT8 Antibodies; Often lack features of metabolic syndrome

Type 2 diabetes: ***Older age, higher BMI, features of metabolic syndrome***

When to suspect autoimmune/type 1 diabetes?

Normal or mildly overweight

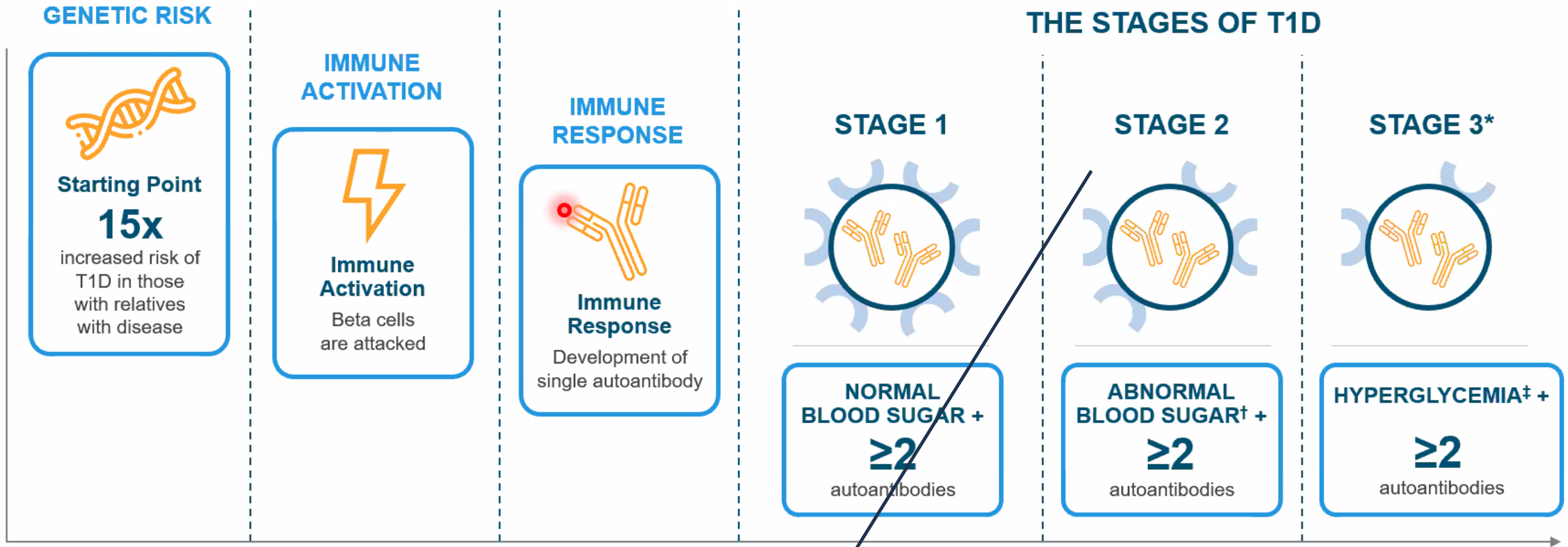
Lack of family history

Absence of other features of the metabolic syndrome (e.g. HTN, HL)

Suspect Type 1 ?

- ✓ Islet Cell Antibodies: Glutamic acid decarboxylase- 65
- ✓ Glucose and c-peptide (c-peptide *may* be lower than expected for glucose level)

New concept: Type 1 diabetes in stages



"Prediabetes" Rx available: Teplizumab

Herold KC,et cal. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. N Engl J Med. 2019 Aug 15;381(7):603-613. doi: 10.1056/NEJMoa1902226. Epub 2019 Jun 9. Erratum in: N Engl J Med. 2020 Feb 6;382(6):586.

What is monogenic diabetes?

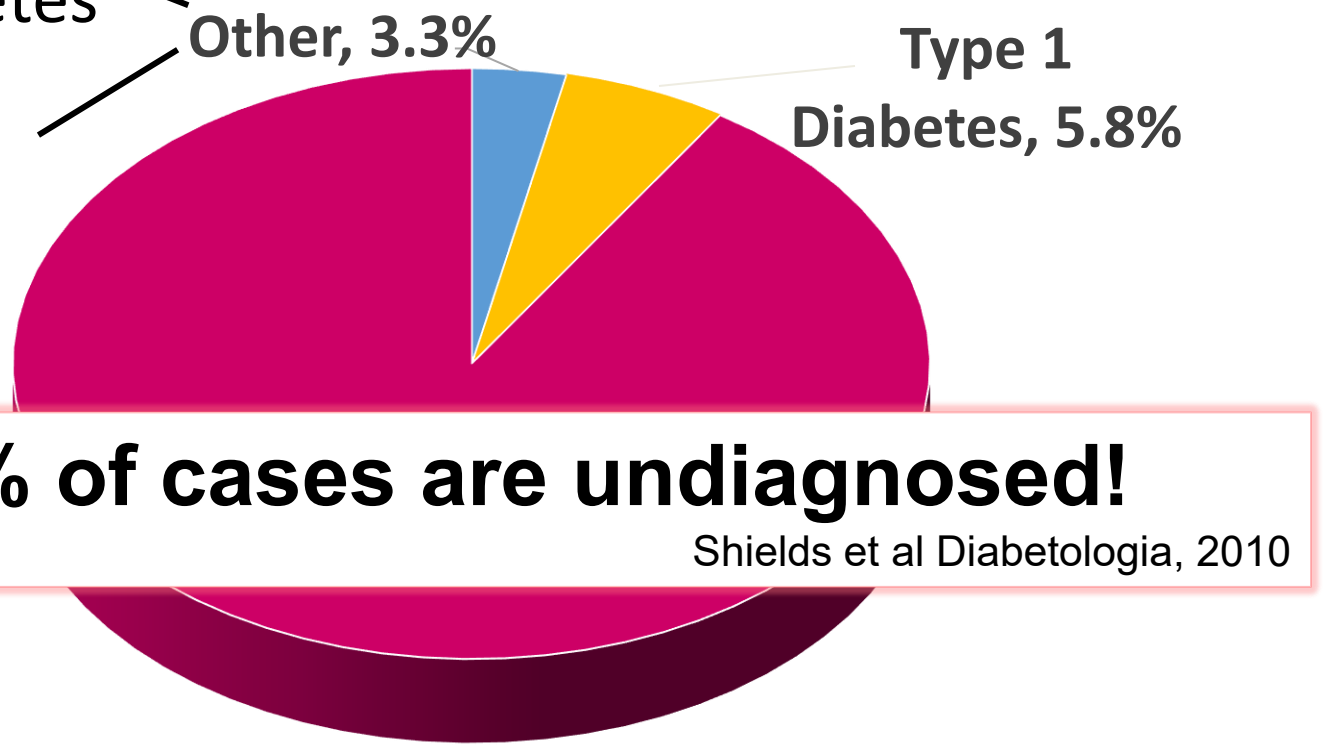
Diabetes caused by variation in <u>1 gene.</u>

Maturity Onset Diabetes of the Young (MODY) is the most common form.

~0.4% = Monogenic diabetes

- 1-3% of diabetes in young adults

~ 1/ 250 all diabetes cases



~80% of cases are undiagnosed!

Shields et al Diabetologia, 2010

Standards of Medical Care in Diabetes 2022; MMWR Morb Mortal Wkly Rep. 2018 Mar 30; 67(12): 359–361; Shields BM, et al. Diabetes Care 2017; 40: 1017-25.

When to suspect MODY?

Young Age at Onset (<35)

Parental diabetes/Runs in family

Non-obese, lack of metabolic syndrome

<u>Negative</u> Islet Cell Antibodies

Compared to Type 2

Lower BMI

Younger Age at Dx

Compared to Type 1

Older Age at Dx

Negative Antibodies

Detectable C-Peptide >3 Yrs post Dx

No history of DKA

Types of MODY and treatment implications

Most common forms of MODY:

- ~30-50% *GCK*
- ~40-60% *HNF1A* or *HNF4A*
- ~10% other genes

Patients typically **do not need diabetes medications.**

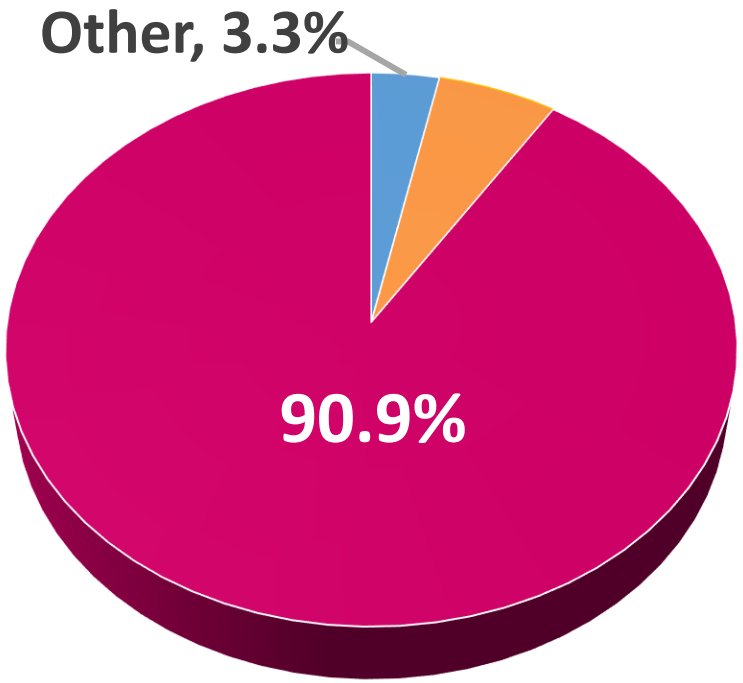
Patients can often be **transitioned from insulin injections to non-insulin agents.**

Most patients treated with insulin. **Gene can inform other related phenotypes** (e.g. *HNF1B* with renal cysts, elevated LFTs).

Slide : Miriam Udler

Pearson *et al*., Lancet 2003; Shields *et al*. Diabetologia 2010; Murphy *et a*l. Nat Clin Practice, End & Metabolism, 2008; Fajans *et al*, NEJM 2001.

Breakdown of diabetes in United States



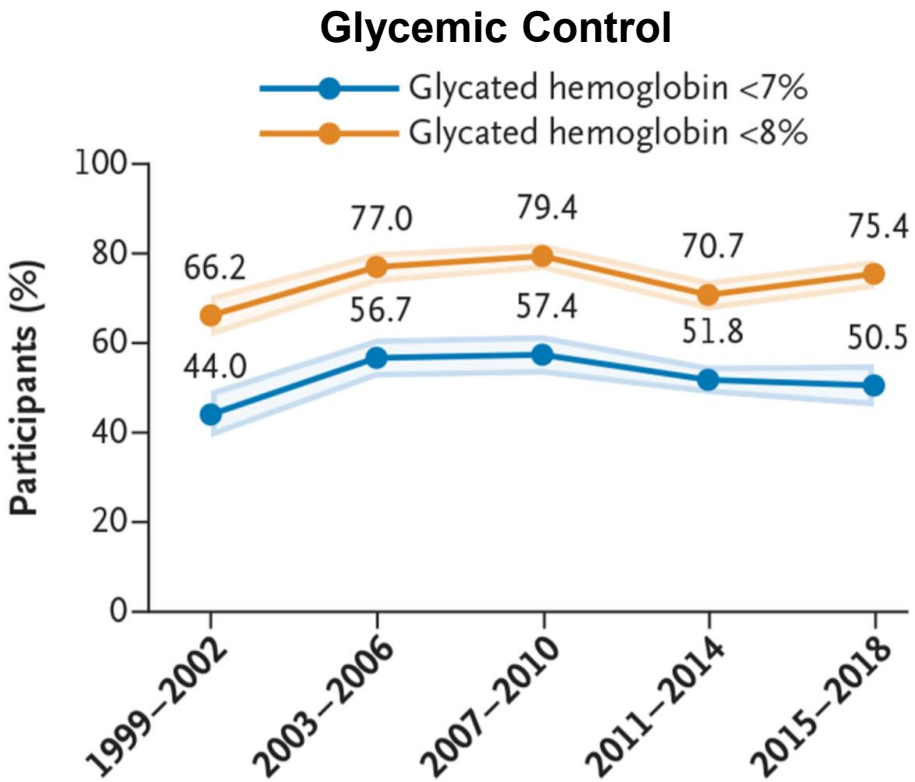
Autoimmune diabetes 5.8%:

Positive GAD, IA2, insulin, or zinc ZnT8 Antibodies; Often lack features of metabolic syndrome

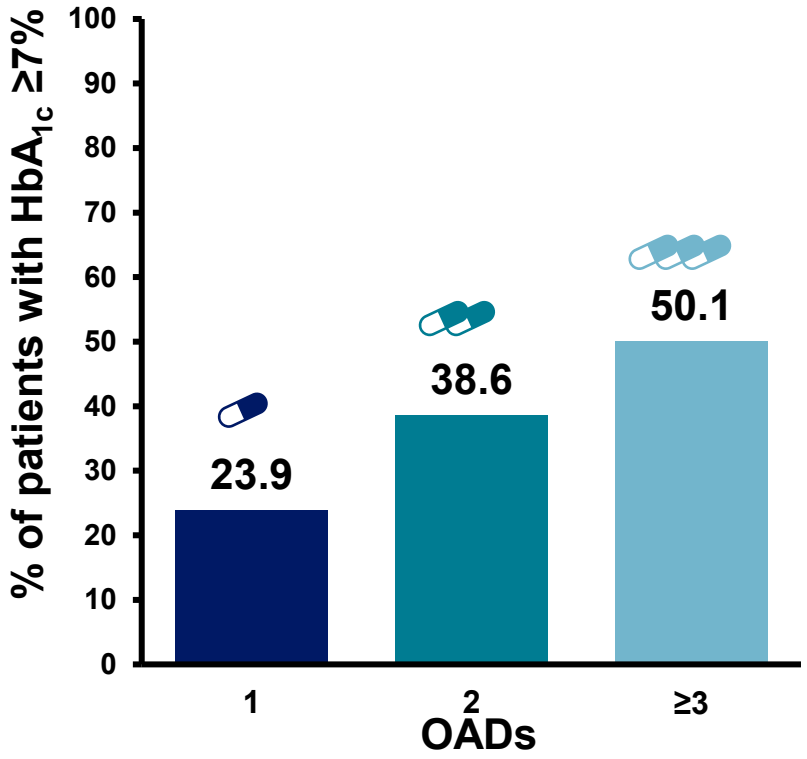
Type 2 diabetes: ***Older age, higher BMI, features of metabolic syndrome***

Glycemic control remains elusive for many with T2D despite drugs targeting multiple mechanisms

"After more than a decade of progress from 1999 to the early 2010s, glycemic and blood-pressure control declined in adult NHANES participants with diabetes."



Fang M, et al. *N Engl J Med*. 2021 Jun 10;384(23):2219-2228.



European data – PANORAMA study

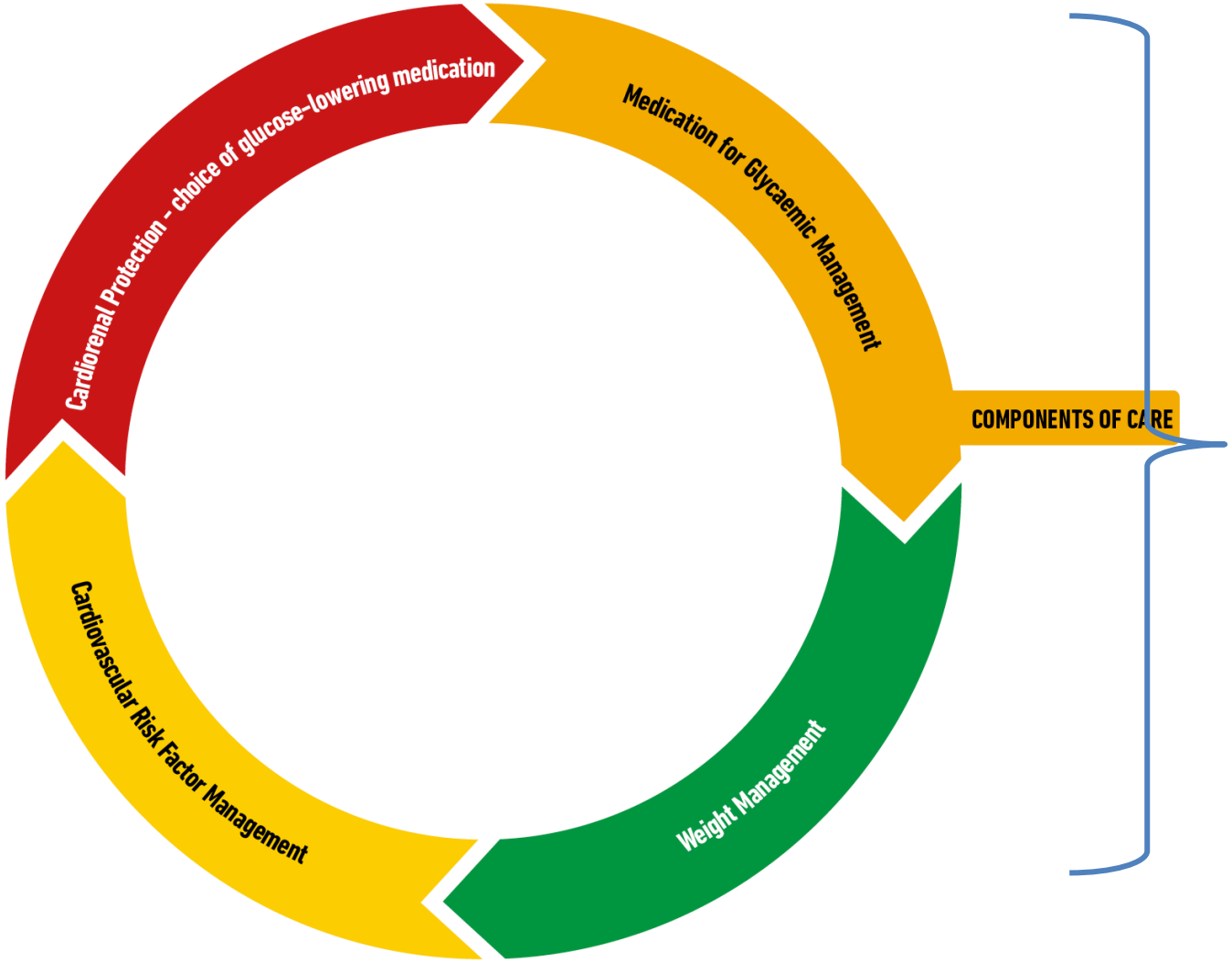
de Pablos-Velasco et al. Clin Endocrinol (Oxf). 2014 Jan;80(1):47-56.

GRADE Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study — NIDDK

70% of subjects had an A1c >7% by study end

Global Guidance: A1c reduction = Weight reduction in T2D

"I want to help to protect your organs from diabetes related problems."



"I want to help you to control your blood sugar and your weight."

1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S144–74.

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blockers; ASCVD, Atherosclerotic Cardiovascular Disease; BP, Blood Pressure; CKD, Chronic Kidney Disease; CV, Cardiovascular; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes.

Davies MJ, et al. *Diabetes Care* 2022 ; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

2025 WHO Guideline on GLP-1 RA Therapies for Treatment of Adults with **Obesity**

Recommendation 1

In adults living with obesity, GLP-1 therapies may be used as a long-term treatment for obesity. **(conditional recommendation, moderate certainty evidence)**

Recommendation 2

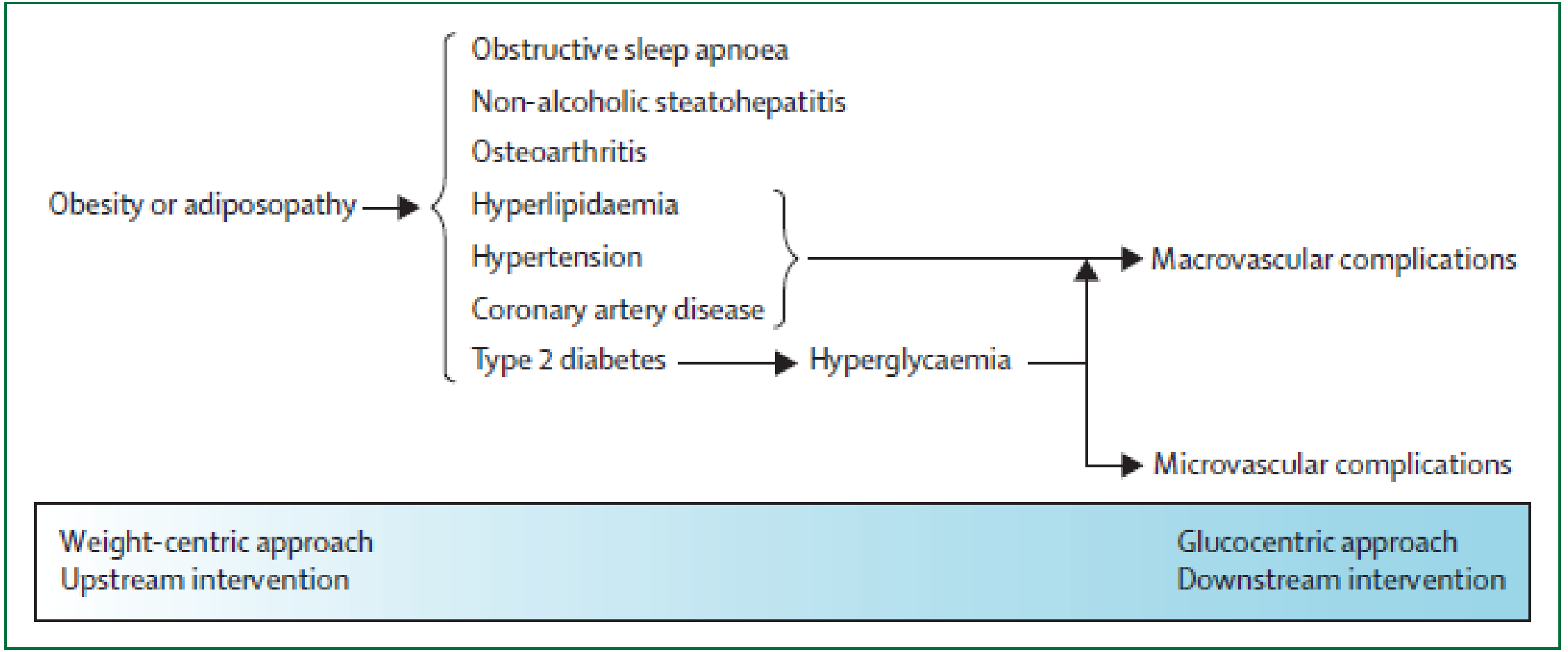
In adults living with obesity who are prescribed GLP-1 therapies, intensive behavioral therapy may be provided as part of a comprehensive multimodal clinical algorithm. **(conditional recommendation, low certainty evidence)**

Cited limitations:

- High current costs and concerns about equitable access
- Inadequate health system preparedness for delivering chronic, integrated obesity care

JAMA Published Online: December 1, 2025
2026;335;(5):434-438. doi:10.1001/jama.2025.24288

Adopting an "upstream" weight-centric approach versus a glucocentric management approach

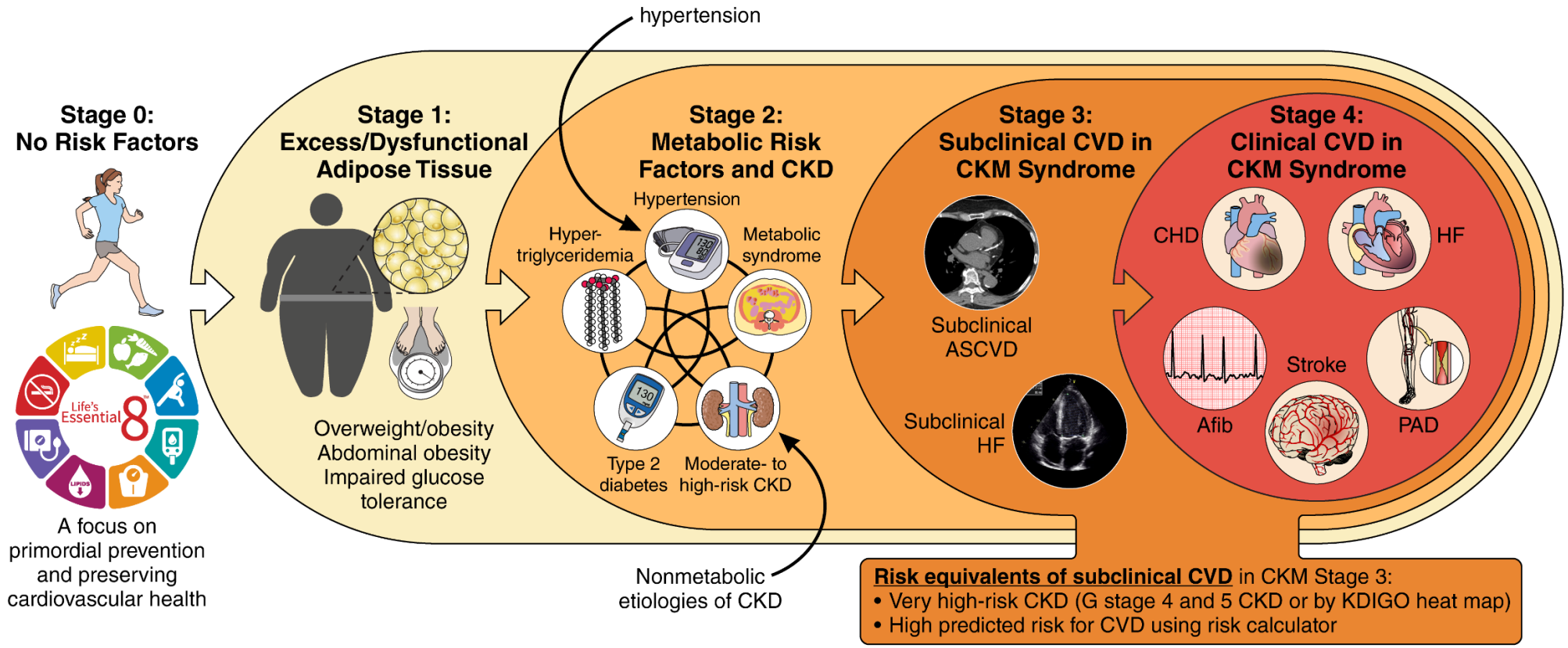


T2D, type 2 diabetes
Lingvay *et al. Lancet.* 2022;399:394–405.

2024 "CKM" concept… (should probably be CK*Liver*M)

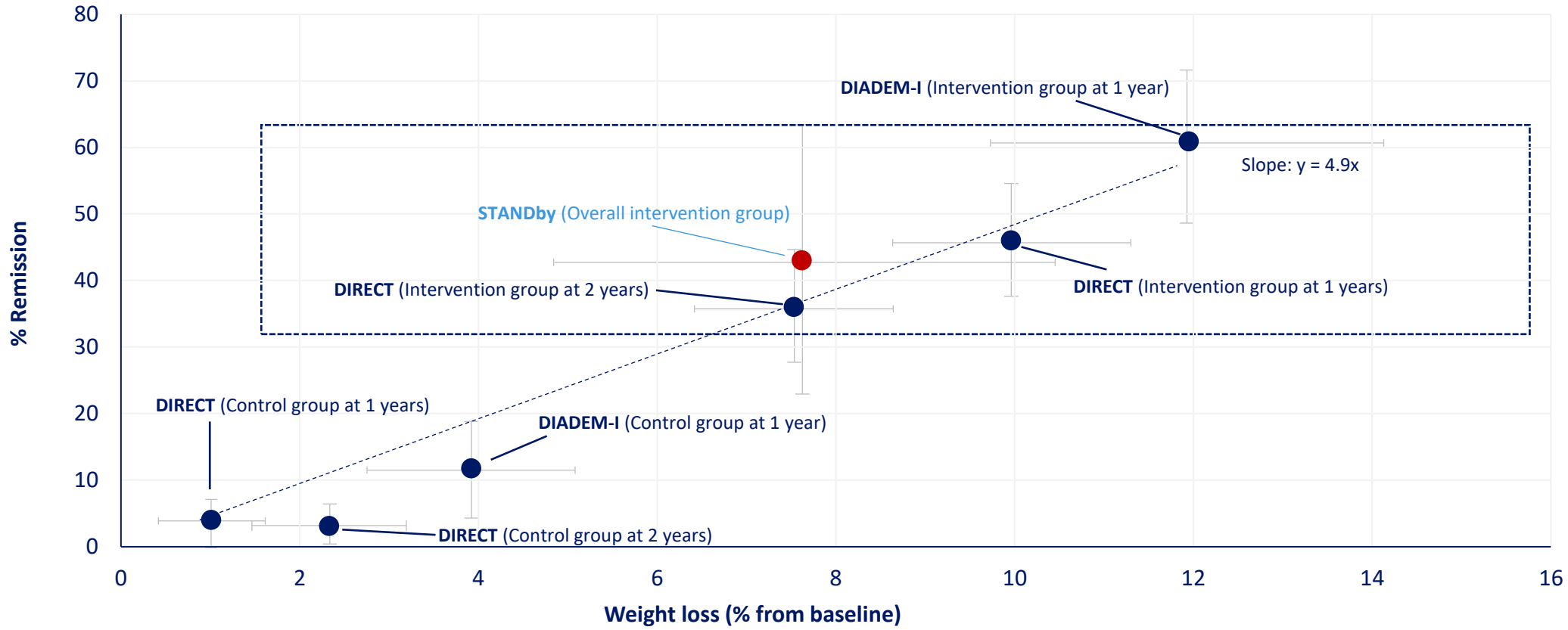
AHA PRESIDENTIAL ADVISORIES

Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association



Doc, do I need medications? Diabetes Remission in "Real World" studies

Relationship between relative weight loss and achieving remission in STANDby, DIRECT 1-and-2-year follow-up studies and DIADEM-I



CI; confidence interval; T2D, type 2 diabetes.
Sattar N et al., Lancet Reg Health Southeast Asia. 2023;9:100111.

For BMI >40 and T2D, offer Metabolic surgery EARLY

ARMMS T2D STUDY: Bariatric Surgery vs. Medical Management

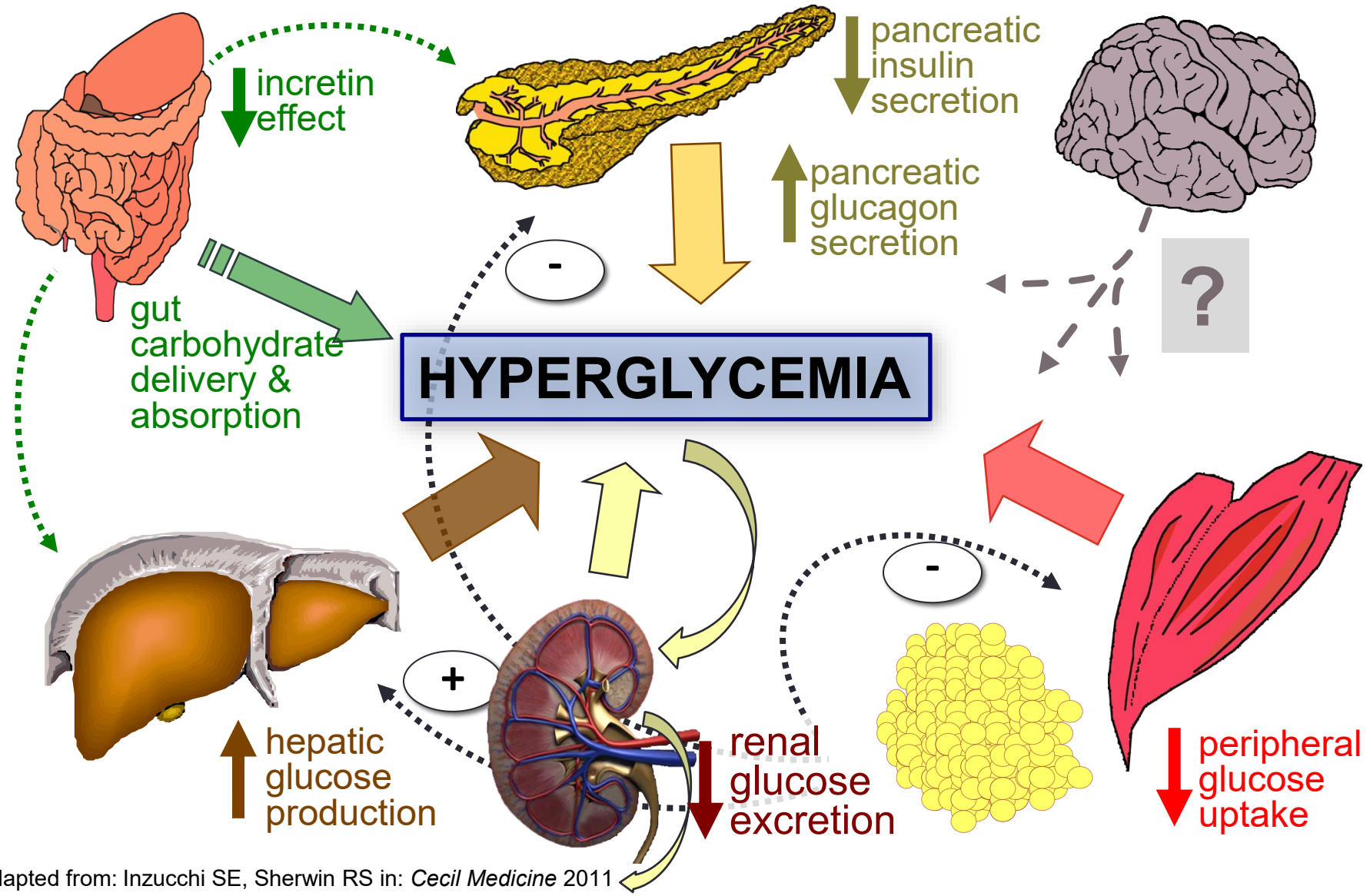
N =262 over 7-12 years

	Bariatric Surgery	Medical Management	DIRECT lifestyle study
A1c reduction	1.6%	0.2%	
Diabetes Remission (off medications)	**18.2% at 7 yrs** **12.7% at 12 yrs**	**6.2% 7 years** **0% 12 years**	12% at **2** years, not followed longer
Deaths	2	2	N/A

Courcoulas AP, Patti ME, Hu B, Arterburn DE, Simonson DC, Gourash WF, Jakicic JM, Vernon AH, Beck GJ, Schauer PR, Kashyap SR, Aminian A, Cummings DE, Kirwan JP. JAMA. 2024 Feb

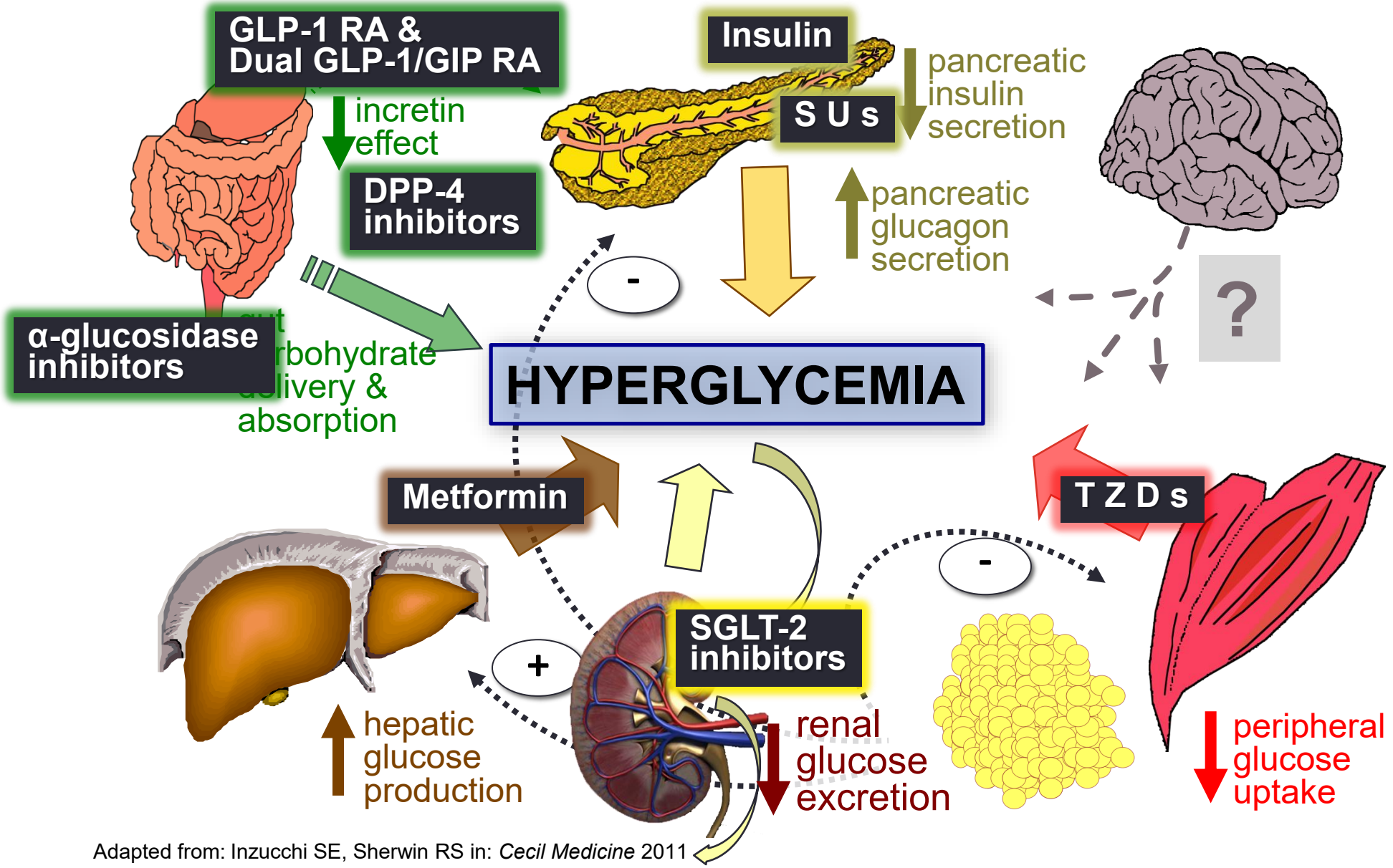
What are the available medications for the management of type 2 diabetes?

Multiple Complex Pathophysiological Abnormalities in T2DM



Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

Major Pathophysiologically-Based Therapies for T2DM



Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

GLP-1R and dual GLP1/GIP agonists

Insulin

S U s

DPP-4 inhibitors

α-glucosidase inhibitors

Metformin

T Z D s

SGLT-2 inhibitors

Commonly Rx'd Glucose Lowering Drugs Classes

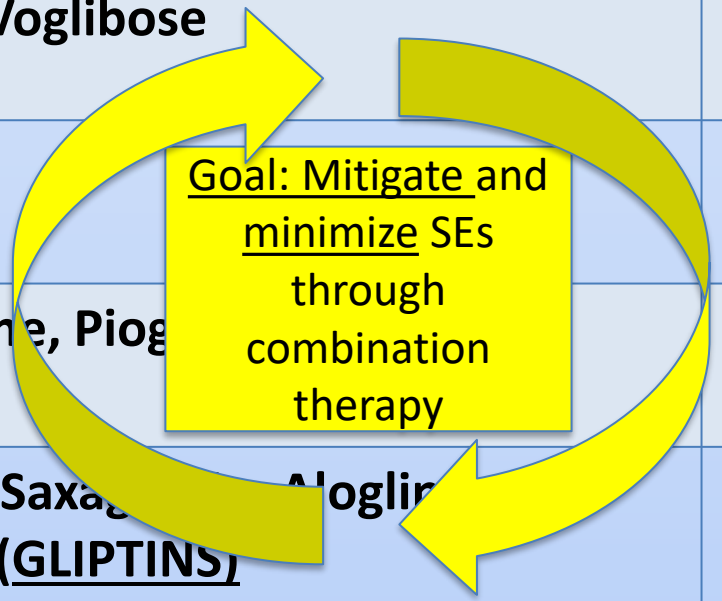
Classes	Generic Names	↓ A1c	Side effects
Insulin	Degludec, Glargine, Detemir, NPH, Regular, Lispro, Aspart, Glulisine	1+ %	Hypoglycemia, weight gain
SU	Glyburide, Glipizide, Glimeperide	1-1.5%	Hypoglycemia, weight gain
α-GLUCO-i	Acarbose, Voglibose	0.5-1%	GI, liver
Metformin	Metformin	1-1.5%	GI, B-12 deficiency, lactic acidosis (rare)
TZD	Rosiglitazone, Pioglitazone	1-1.5%	CHF, Weight gain, edema, bone fx's, ?bladder ca
DPP-4 I	Sitagliptin, Saxagliptin, Alogliptin, Linagliptin (GLIPTINS)	0.5-1%	Essentially none
Incretin RA	GLP-1: Exenatide, Lira-, Dula-,Sema- GLP-1/GIP dRA: Tirzepatide	1-1.5%	GI, gallbladder disease
SGLT2-i	Canagliflozin, Dapagliflozin, Empagliflozin, Bexaflozin (FLOZINS)	0.5-1%	GU infections, Polyuria, GU infections, DKA, falls

Commonly Rx'd Glucose Lowering Drugs Classes

Classes	Generic Names	↓ A1c	Side effects
Insulin	Degludec, Glargine, Detemir, NPH, Regular, Lispro, Aspart, Glulisine	1+ %	Hypoglycemia, weight gain
SU	Glyburide, Glipizide, Glimeperide	1-1.5%	Hypoglycemia, weight gain
α-GLUCO-i	Acarbose, Voglibose	0.5-1%	GI, liver
Metformin	Metformin	1-1.5%	GI, B-12 deficiency, lactic acidosis (rare)
TZD	Rosiglitazone, Pioglitazone	1-1.5%	CHF, Weight gain, edema, bone fx's, ?bladder ca
DPP-4 I	Sitagliptin, Saxagliptin, Alogliptin, Linagliptin (GLIPTINS)	0.5-1%	Essentially none
Incretin RA	GLP-1: Exenatide, Lira-, Dula-,Sema- GLP-1/GIP dRA: Tirzepatide	1-1.5%	GI, gallbladder disease
SGLT2-i	Canagliflozin, Dapagliflozin, Empagliflozin, Bexaflozin (FLOZINS)	0.5-1%	GU infections, Polyuria, GU infections, DKA, falls

Commonly Rx'd Glucose Lowering Drugs Classes

Classes	Generic Names	↓ A1c	Side effects
Insulin	Degludec, Glargine, Detemir, NPH, Regular, Lispro, Aspart, Glulisine	1+ %	Hypoglycemia, weight gain
SU	Glyburide, Glipizide, Glimeperide	1-1.5%	Hypoglycemia, weight gain
α-GLUCO-i	Acarbose, Voglibose	0.5-1%	GI, liver
Metformin	Metformin	1-1.5%	GI, B-12 deficiency, lactic acidosis (rare)
TZD	Rosiglitazone, Piog	1-1.5%	CHF, Weight gain, edema, bone fx's, ?bladder ca
DPP-4 I	Sitagliptin, Saxa Alogli Linagliptin (GLIPTINS)	0.5-1%	Essentially none
Incretin RA	GLP-1: Exenatide, Lira-, Dula-,Sema- GLP-1/GIP dRA: Tirzepatide	1-1.5%	GI, gallbladder disease
SGLT2-i	Canagliflozin, Dapagliflozin, Empagliflozin, Bexaflozin (FLOZINS)	0.5-1%	GU infections, Polyuria, GU infections, DKA, falls

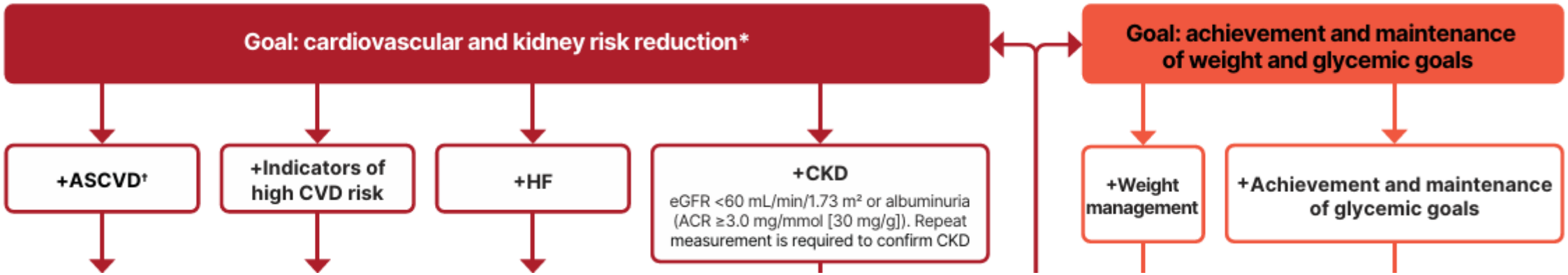


What is the recommended approach to medication selection and management in diabetes?

As a result of >10 RCTs and >50,000 patients studied… Step-wise therapy is out the window

ADA: Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. Pharmacologic approaches that provide the efficacy to achieve treatment goals should be considered, such as metformin or other agents, including combination therapy, that provide adequate efficacy to achieve and maintain treatment goals.

ADA approach: Step 1 is to decide on a priority/goal

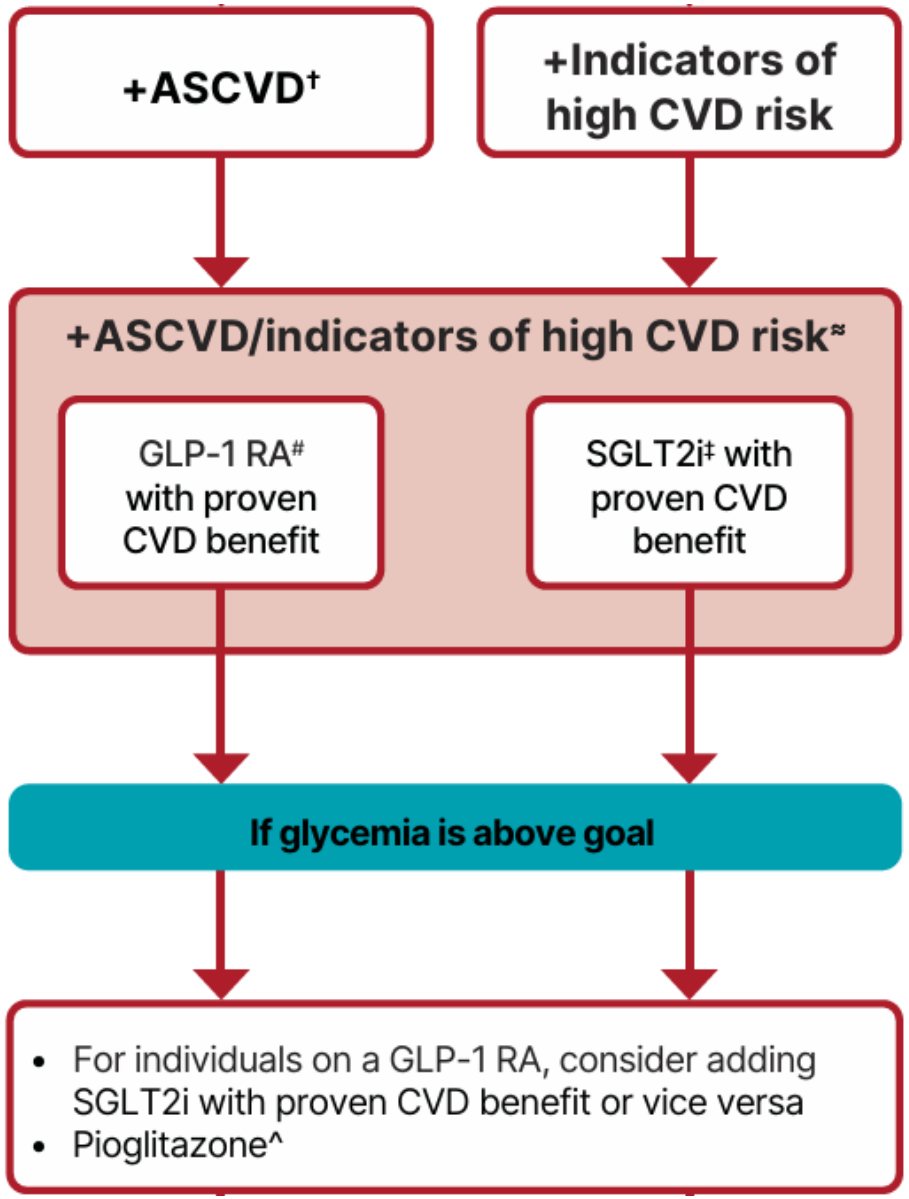


- **Ideal to choose medications that can achieve more than one of these goals; this is not always feasible**

Priority: Atherosclerotic Cardiovascular Disease (ASCVD) *

liraglutide
semaglutide (SQ) and dulaglutide

semaglutide (SQ) reduced stroke risk in subgroup analysis



Empagliflozin, canagliflozin, dapagliflozin

ASCVD or High Risk*

- ***STROKE***

**end-organ damage including retinopathy or LVH*

Or

Multiple CV risk factors (age, HTN, smoking, dyslipidemia, obesity

^Low dose, 15mg

Gen 1.5 * GLP-1 receptor-based agonists and analogs

	Initial dose	Final dose	Δ HbA1c	Δ Weight loss at max tol dose in Type 2 diabetes
Liraglutide	0.6 mg qd	1.2-1.8 mg qd	-1.5	~ 6%
Dulaglutide	0.75mg/w	4.5 mg/w	-1.5	~ 8%
Semaglutide Inj	0.25mg/w	2.0 mg/w or 2.4mg/w in weight loss packaging	-1.8	~ 10%

- *Exenatide removed as does not have proven CV or Renal benefit
- Can combine with insulin therapy (including pump therapy) and all other meds except DPP4i
- Injectable via pen (daily, BID or weekly) or oral Rybelsus (semaglutide)
- Do not cause hypoglycemia

Gen 2: GLP-1 receptor-based agonists and analogs

	Initial dose	Final dose	Δ %HbA1c	Δ Weight loss at max tol dose in Type 2 diabetes
Liraglutide	0.6 mg qd	1.2-1.8 mg qd	-1.3-1.6	~ 6%
Dulaglutide	0.75mg/w	4.5 mg/w	-1.3-1.5	~ 8%
Semaglutide Inj	0.25mg/w	2.0 mg/w or 2.4mg/w in weight loss packaging	-1.6	~ 10%
Semaglutide oral Rybelsus	3mg daily tab	14mg daily tab	-1.6	~ 5%
Tirzepetide	2.5mg/w	15mg/w	-2.1	~ 14.7%

Gen 3 *Future state* GLP-1 receptor-based agonists and analogs

	Initial dose	Final dose	Δ %HbA1c	Δ Weight loss at max tol dose in Type 2 diabetes
Orforglipron* small molecule GLP-1 RA	Daily tab	36mg	-1.8	9.6%
Semaglutide Inj	0.25mg/w	2.0 mg/w	-1.6	~ 10%
Tirzepetide	2.5mg/w	15mg/w	-2.1	14.7%
Cagrisemma (Amylin + sema-)	Weekly injection	2.4mg	-1.8	13.7%
Retatrutide (GIP/GLP-1/Glucagon)	Weekly injection	12mg	-2.2	16.9%

***Now approved*; Older agents may/will likely remain available in generic/lower cost formulations**

Tirzepatide, dual GLP-1/GIP agonist, noninferior to dulaglutide for CV safety per SURPASS- CVOT [1]

Effects on Cardiovascular Risk Factors[2]

More weight loss = more risk factor modification

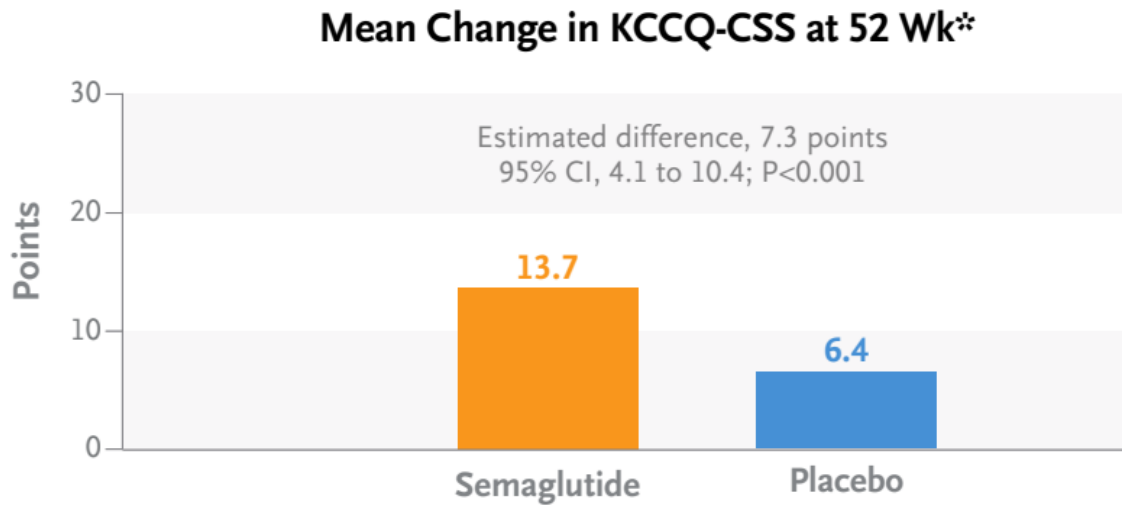
	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Semaglutide 1 mg
A1c (% change)	-2.01	-2.24	-2.3	-1.86
Weight (kg)	-7.6	-9.3	-11.2	-5.7
LDL (% change)	-7.7	-5.8	-5.2	-6.1
HDL (% change)	+6.8	+7.9	+7.1	+4.4
TG (% change)	-19.0	-24.1	-24.8	-11.5
BP (mm Hg)	-4.8/-1.9	-5.3/-2.5	-6.5/-2.9	-3.6/-1.0
Pulse (bpm)	+ 2.3	+2.2	+2.5	+2.6

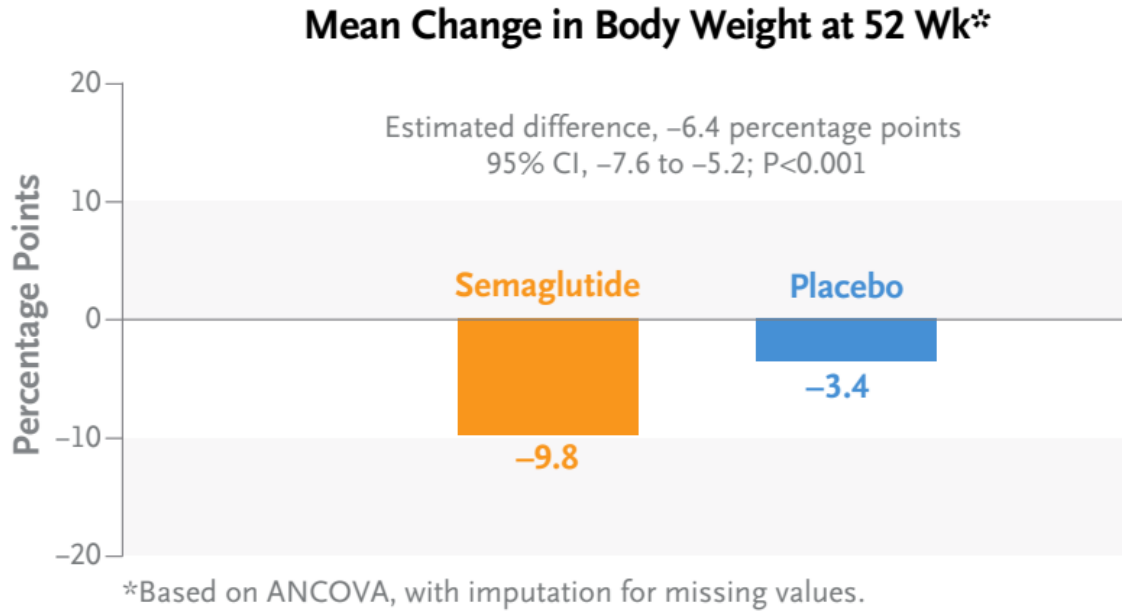
- Decrease liver fat content by MRI[3]
- Decrease albuminuria[4]
- Slower decline in eGFR over time[4]

1. Nicholls, et al. NEJM 2025 2, Frias JP, et al. *N Eng J Med*, 2021. 3. Ludvik B, et al. *Lancet*. 2021;398:583-598, 4. . Tuttle, K, presented at the 83rd Sci Sessions ADA

Results: semaglutide in adults with type 2 diabetes and heart failure

In patients with type 2 diabetes and heart failure with preserved ejection fraction, **once-weekly semaglutide led to fewer heart failure–related symptoms and physical limitations and greater weight loss than placebo at 1 year**

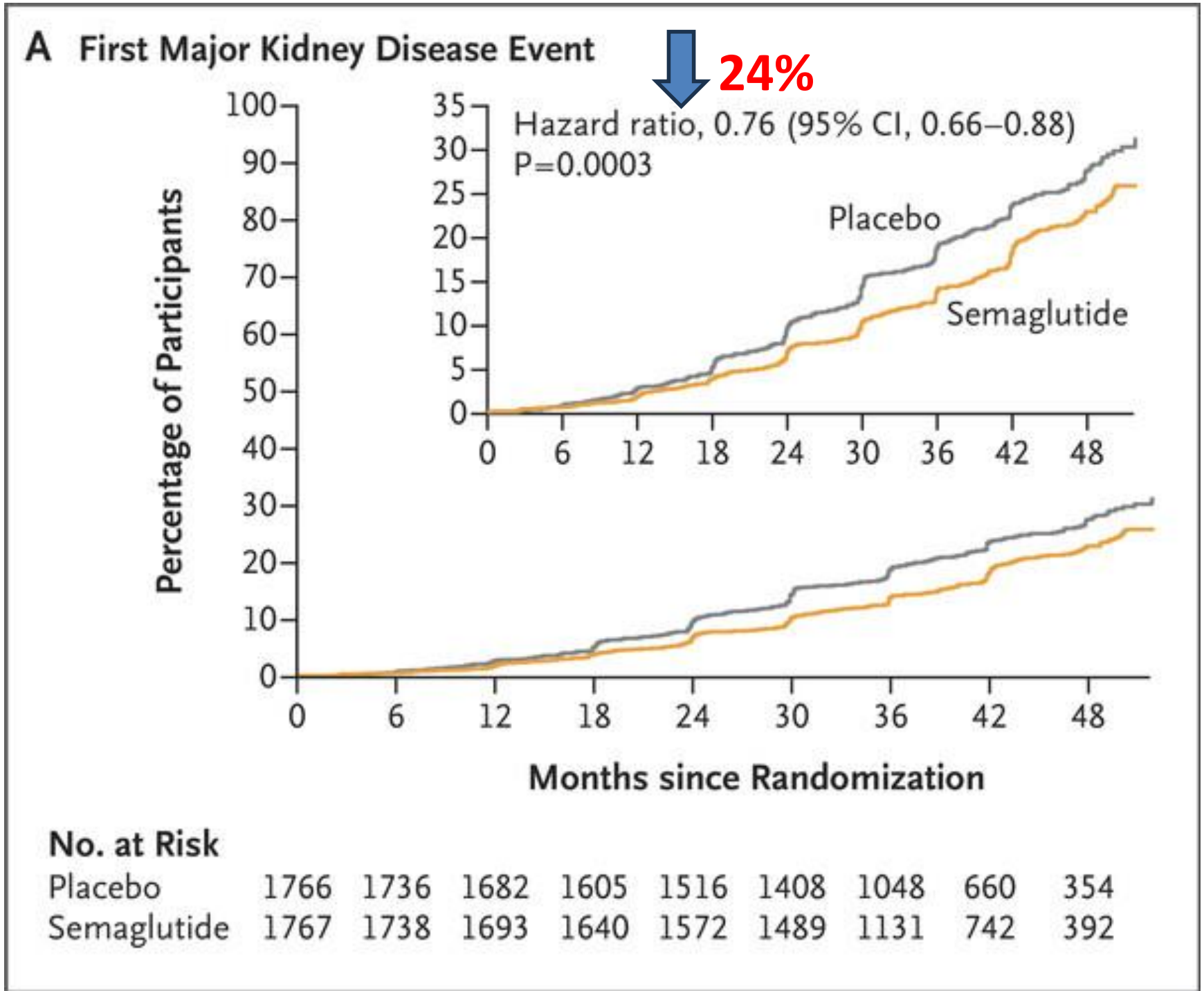




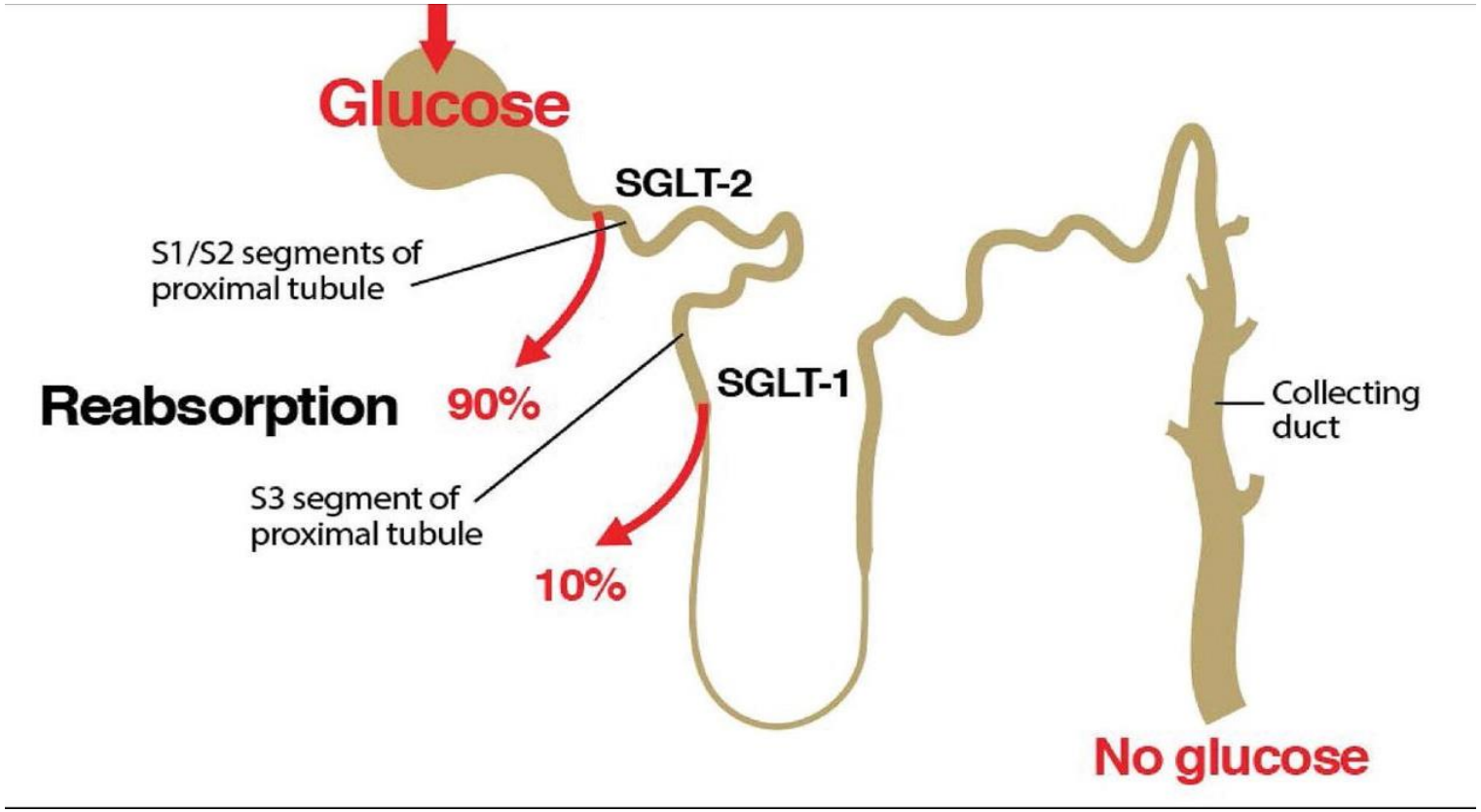
Kosiborod MN, et al. N Engl J Med. 2024 Apr 18;390(15):1394-1407.

What about GLP-1RA and the kidney?

FLOW primary outcome



The Sodium Glucose Co-Transporters



SGLT-2 inhibitors

	Initial dose	Max dose	Δ HbA1c	Δ Weight
canagliflozin	100mg qd	300mg qd	-0.5 to -1.0	-1.5-2.5kg
empagliflozin	10mg	25mg		
dapagliflozin	5mg	10mg		
ertugliflozin	5mg	15mg		
bexagliflozin**	20mg	20mg		

- **Daily tablets**
- **Complements oral and insulin therapy in T2D**
- **Does not *independently* cause hypoglycemia**
- ** **NO CVOT PLANNED and will not have CV or kidney FDA labeling.** Available for $48-60 per month using DiRx, CostPlus or Marley Drug Pharmacy

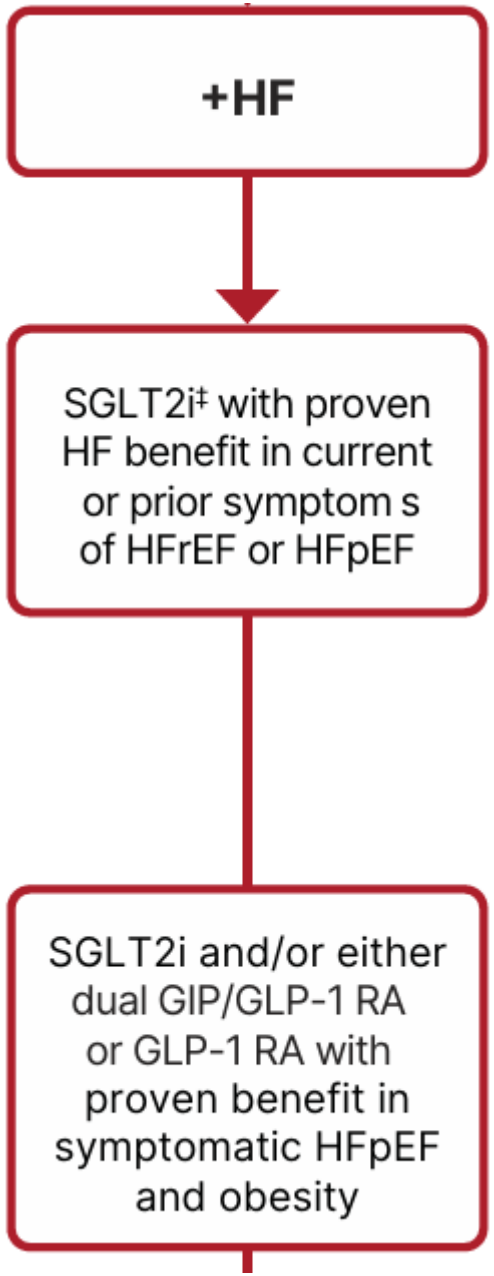
Priority: Heart Failure

- **SGLT2i now clearly indicated for <u>both</u> HFpEF and HFrEF**

Dapagliflozin and empagliflozin have **primary** <u>heart failure</u> outcome data.

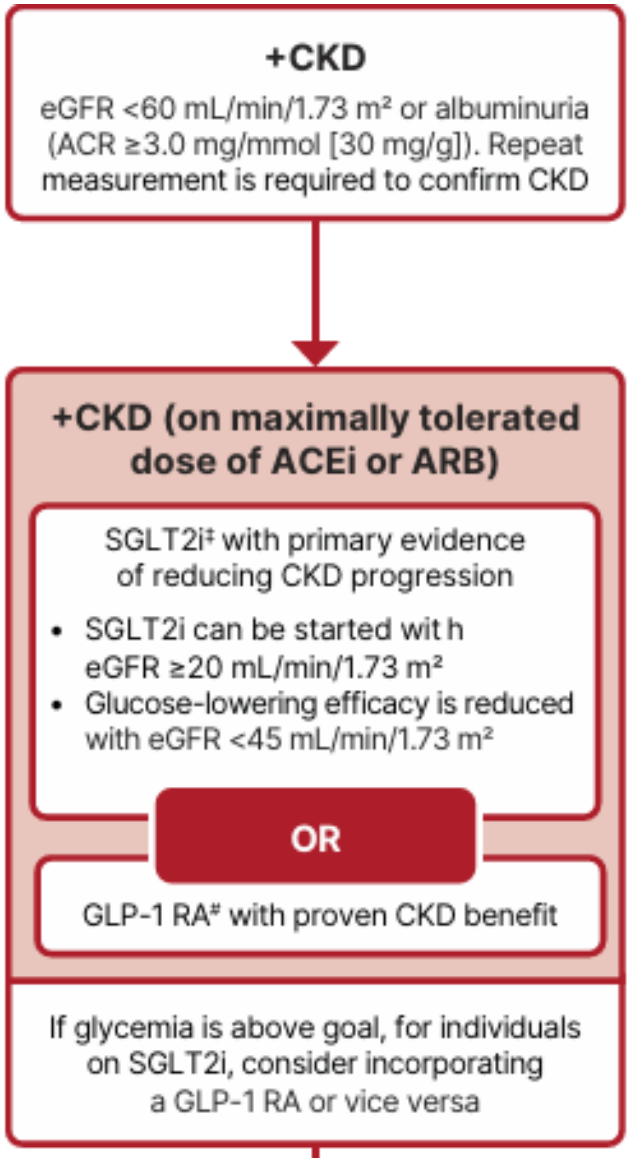
Empagliflozin, canagliflozin, and dapagliflozin and ertugliflozin have shown reduction in HF in CVOTs.

Semaglutide and tirzepetide both shown to improve outcomes in HFpEF in those with obesity.



Priority:
Kidney disease (CKD)

- **Key points:**
- **Ok to start with GFR as low as 20ml/min/1.73m²**
- **In those with UACR >/= 300 goal is to reduce UACR by 30%+**
- **Combination therapy with both SGLt2i and GLP-1 *as needed* to achieve A1c target is recommended**



canagliflozin, dapagliflozin

empagliflozin

liraglutide semaglutide (SQ) and dulaglutide

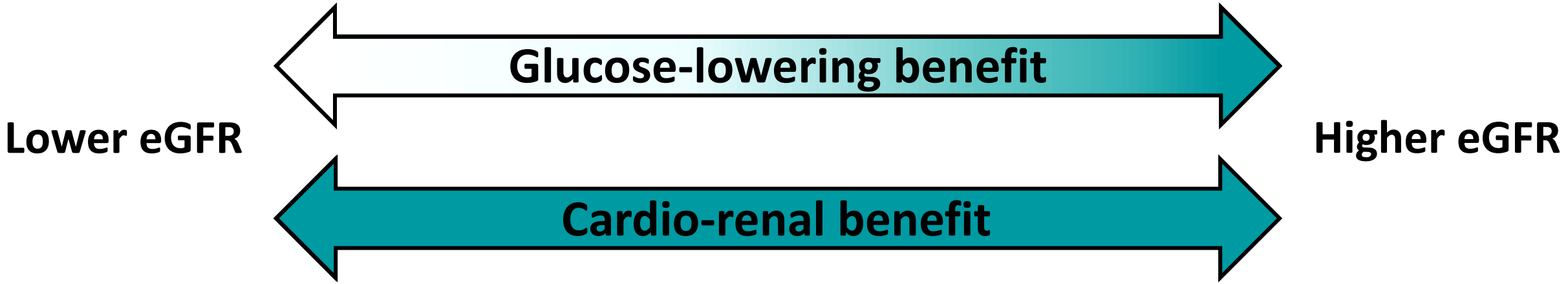
SGLT2 inhibitors: Benefits based on eGFR

eGFR <30

* **Cana + empa**: Not recommended for glycemic control

eGFR <45

* **Dapa + ertu**: Not recommended for glycemic control

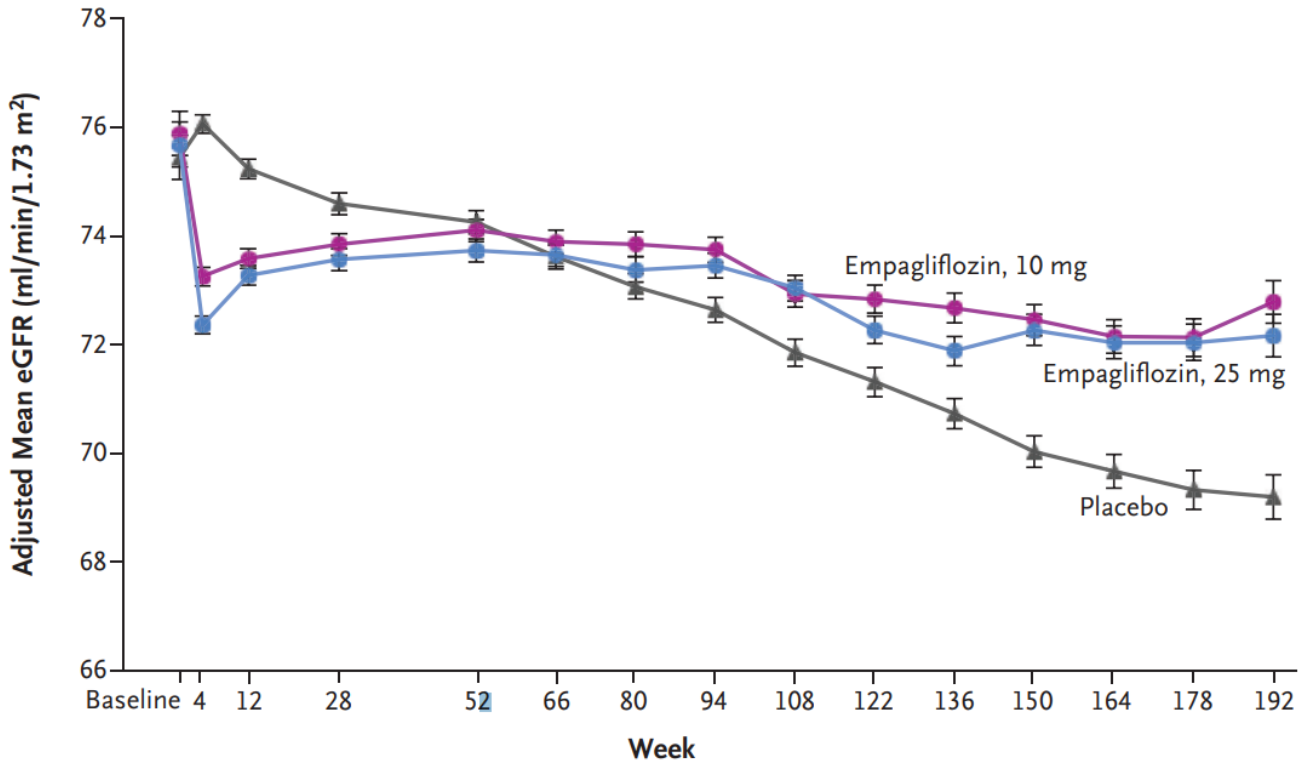


* Per prescribing information

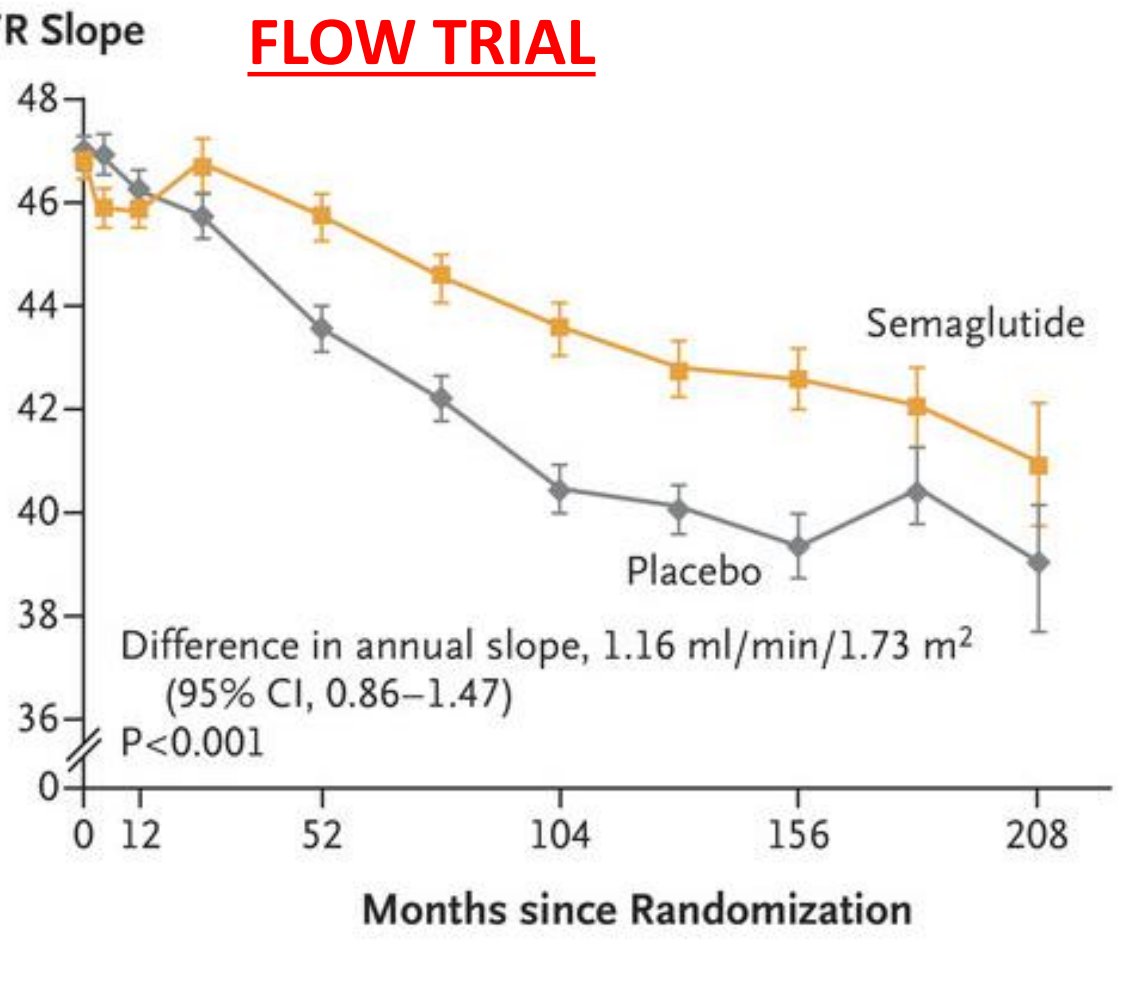
https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVOKANA-pi.pdf
https://den8dhaj6zs0e.cloudfront.net/50fd68b9-106b-4550-b5d0-12b045f8b184/0be9cb1b-3b33-41c7-bfc2-04c9f718e442/0be9cb1b-3b33-41c7-bfc2-04c9f718e442_viewable_rendition__v.pdf
https://content.boehringer-ingelheim.com/DAM/7d9c411c-ec33-4f82-886f-af1e011f35bb/jardiance-us-pi.pdf
https://www.merck.com/product/usa/pi_circulars/s/steglatro/steglatro_pi.pdf

eGFR Slope: Empagliflozin vs. Semaglutide

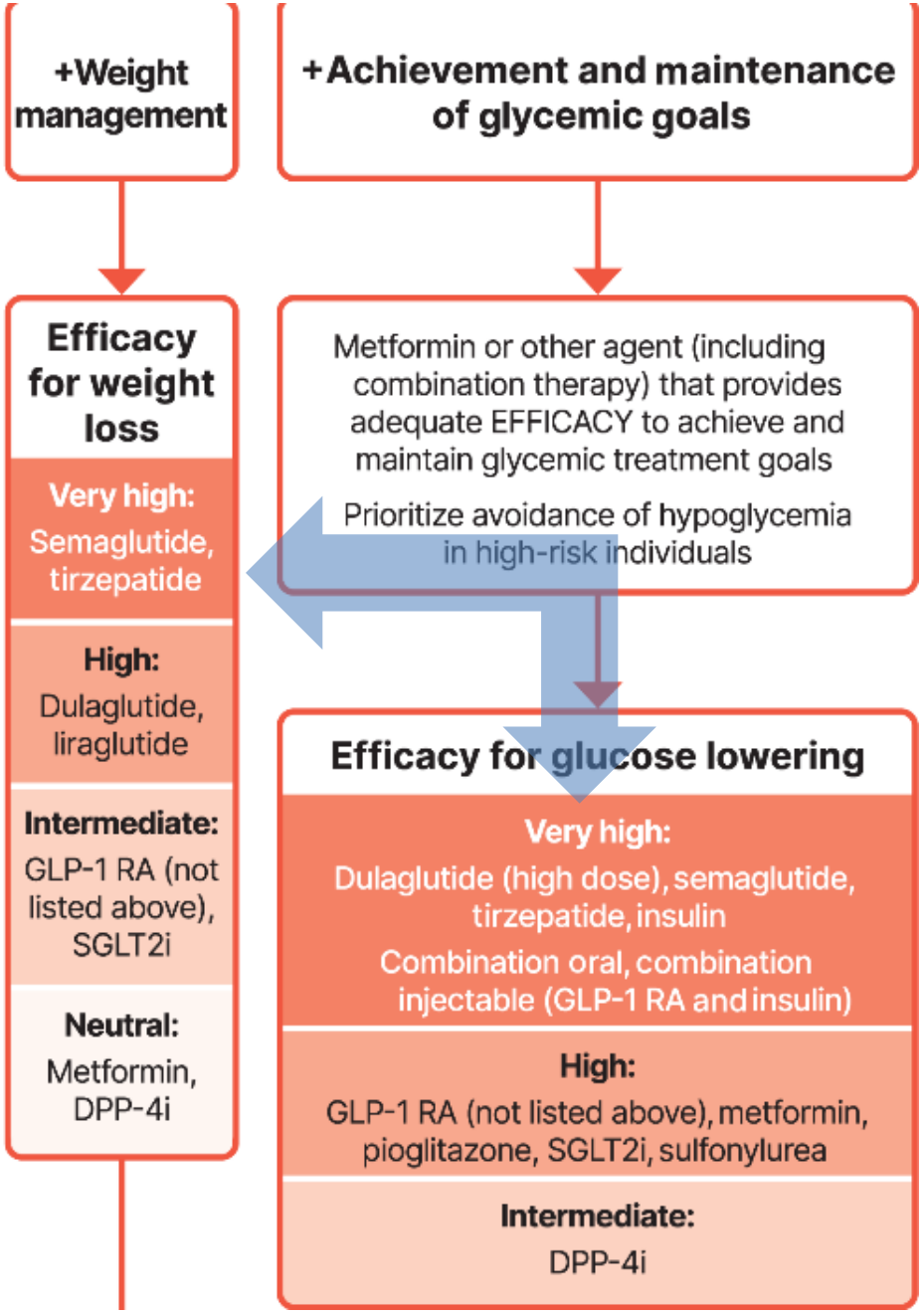
EMPA-REG OUTCOME



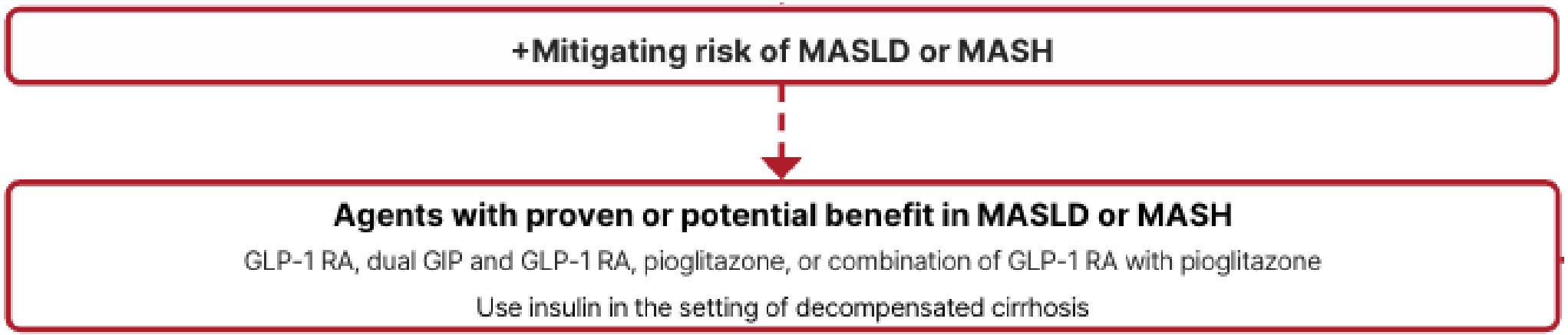
FLOW TRIAL



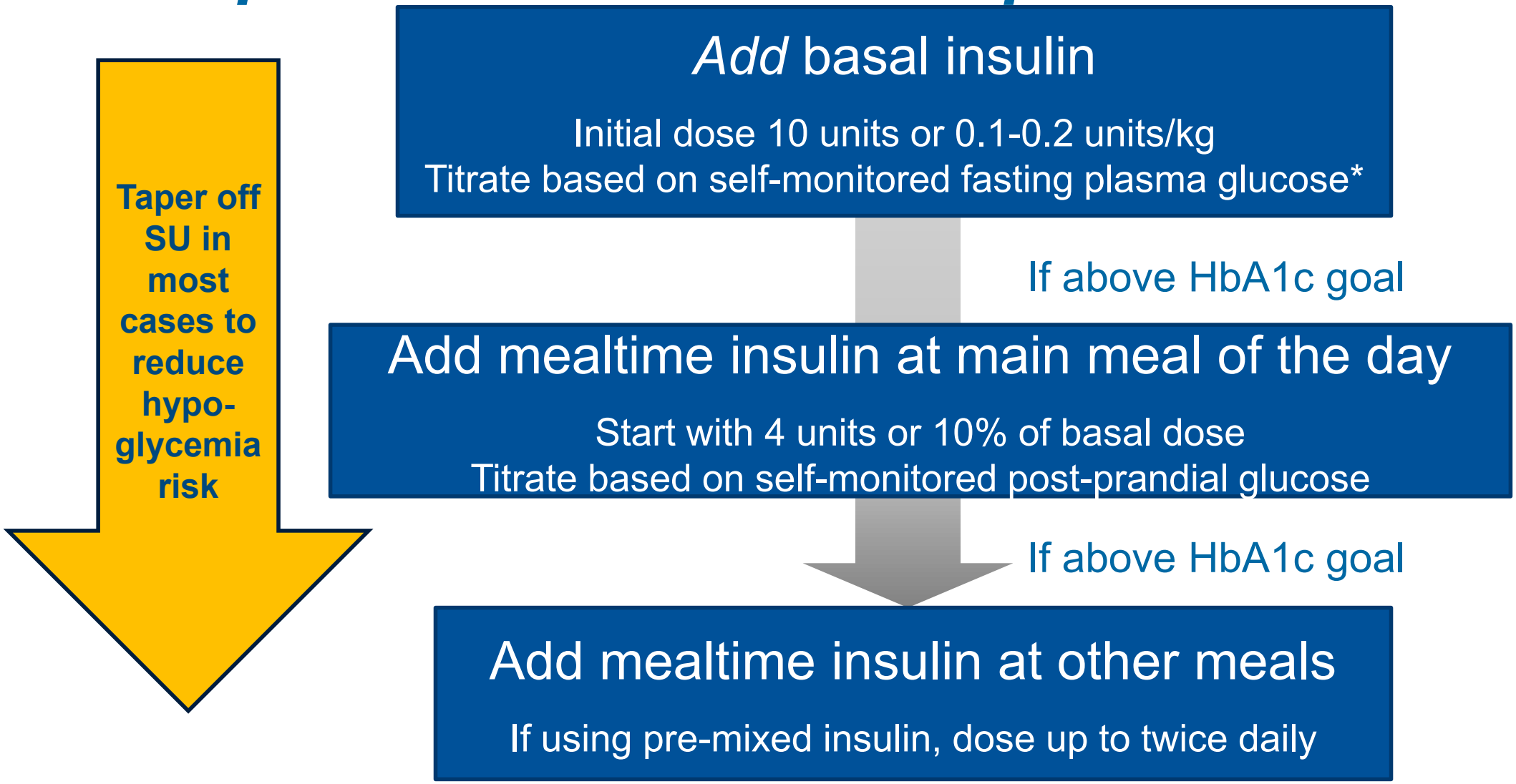
Priority: Metabolic control



Metabolic dysfunction associated liver disease



Initiating insulin: ***assuming GLP-1 RA or other noninsulin therapies considered and/or optimized***



Sulfonylureas

- **Choose glimepiride or gliclazide (outside US) as first line. Avoid glyburide**
  - Glimeperide is the only SU tested in a CVOT; compared with linagliptin no difference in CV risk and hypoglycemia risk was lower than expected
  - Gliclazide has lowest reported hypoglycemia risk
- **Remember that SUs will fail**
  - Can appear to happen suddenly
  - Typically not useful to increase beyond 10mg daily if A1c has risen >0.5%
  - Best approach is to add another agent and taper the SU off (stopping suddenly can cause hyperglycemia even when effectiveness is reduced)

Thiazolidinediones (TZD)

- **Pros:** ok in euvolemic advanced kidney disease, potent
- **Cons:** weight gain, edema/CHF, CV controversy, increased fractures in women, (urologic cancers? unclear, FDA avoid if family history)
- **Select the right *patient & dose*:**
  - Fatty liver
  - TIA, stroke history
  - MI history, normal EF, unable to take SGLT2i or GLP-1
  - **Side effects are dose-dependent – use 15mg, avoid max dose**

Nissen SE, et al. *N Engl J Med.* 2007; 356: 2457-71.
Singh S, et al. *JAMA*. 2007; 298: 1189-1195.
Lincoff AM, et al. *JAMA*. 2007; 298: 1180-1188.

Going for the Cure: Update on Cell/Organ options

- **Who to refer Pancreas transplant:**
  - Patients younger than 65, BMI <35 who have already had a kidney transplant and take insulin
  - Patients with insulin requiring diabetes, GFR below 20, BMI <35 should be evaluated for *both* kidney and pancreas transplant
  - Do NOT assume they are being referred/evaluated for pancreas transplant

- **Cadaveric Islet Cell Replacement**
  - **Lantidra is an FDA approved cadaveric islet cell therapy**
    - Operational only at sites who have offered this for >20 years (e.g. UI Chicago)
    - Only for severe recurrent hypoglycemia; requires immunosuppression and multiple treatments

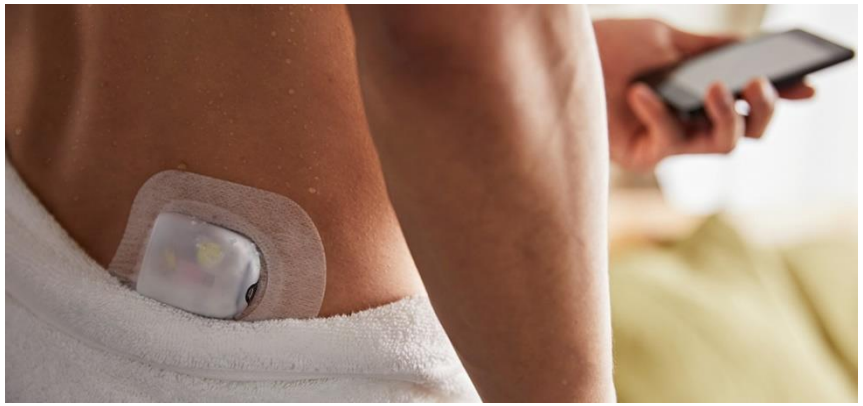
- **Stem-cell derived Islet Cell Therapy is coming**
  - One-year data very promising for cure of Type 1 Diabetes
  - Approval anticipated 2026-2027
  - Will require lifelong immunosuppression
  - Will be for a highly select group of patients in early years

More and simpler CGM-augmented insulin therapy with automatic insulin delivery, approved for T1 And T2D

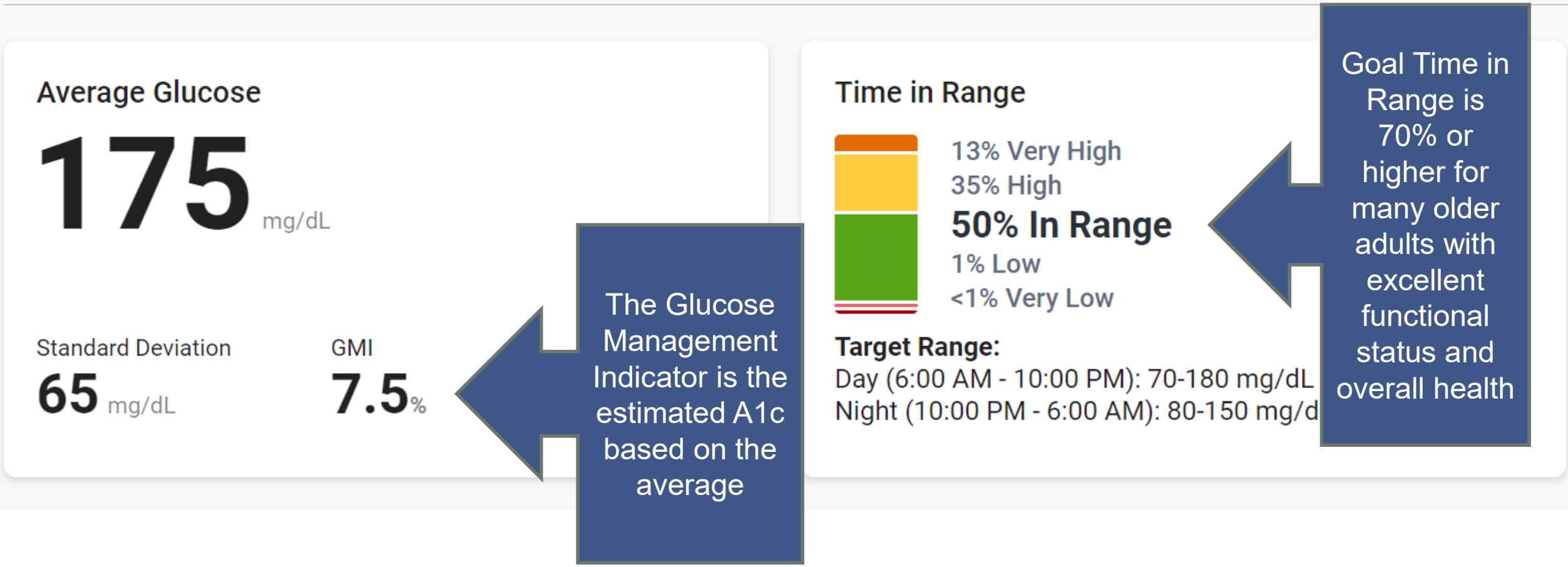
Adaptive AI and Machine learning

Some with ability to set different glucose targets

Can I do this in Primary care? Stay tuned for an Illustrative Case in the Workshop



More reliance on Continuous glucose monitoring



What *else* is on the horizon in Diabetes Care?

FDA-Approved

Icodec: The first once weekly basal insulin is approved in the US..*how will we use it?*

FlexTouch

Insulin-Naïve Patients

Starting Insulin

70 units

- Subcutaneous injection once weekly
- Titrate individually based on fasting glucose goals

Switching from Daily Insulin

Switching Regimen

Administer first dose the day AFTER last daily dose

Week 1

Loading

$$\left[1.5 \times \left[\text{Daily Dose} \times 7\right]\right] \rightarrow \left[\text{Round to nearest 10 units}\right]$$

e.g., 20 units/day → **210 units**

Week 2

$$\left[1.0 \times \left[\text{Daily Dose} \times 7\right]\right] \rightarrow \left[\text{Round to nearest 10 units}\right]$$

e.g., 20 units/day → **140 units**

Week 3+

Titrate

Adjust based on glycemic control

Missed Dose Management

Missed Dose

Within 4 days of scheduled dose
Inject as soon as possible.
Reset schedule — next dose 7 days from new injection date.

More than 4 days late

Skip missed dose. Resume on next regularly scheduled day.

Never take two doses within 3 days of each other

New drugs, some new targets

- **CagriSemma (Semaglutide + cagrilintide)**
  - **GLP-1 RA + Amylin agonist**
  - **15% weight loss in people with diabetes !**
- **Retatrutide (single peptide, 3 targets: GLP-1, GIP and Glucagon)**
  - **Will be mainly an obesity agent (may increase A1c over time)**
- **Others –**

  Myostatin inhibitors for weight loss related sarcopenia

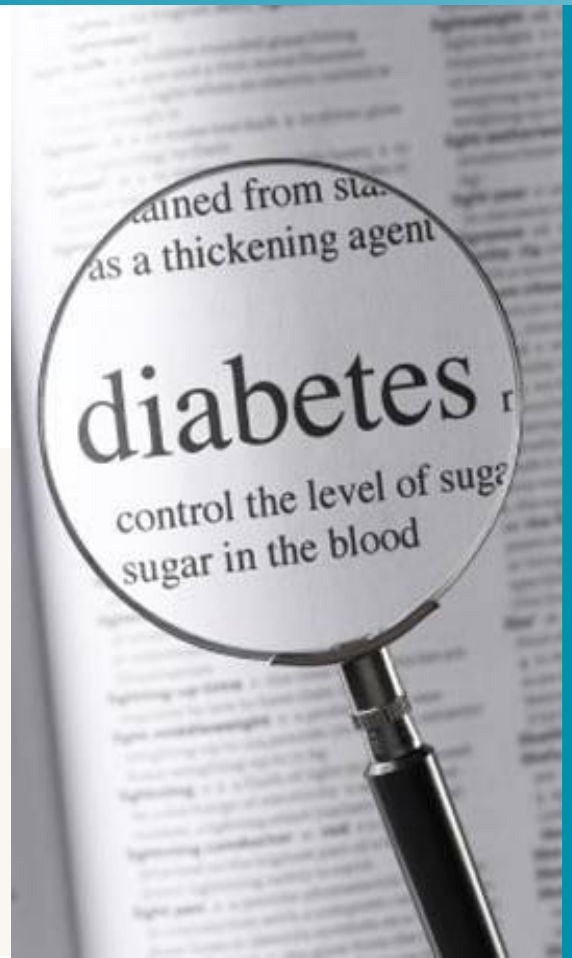
  GIP antagonists

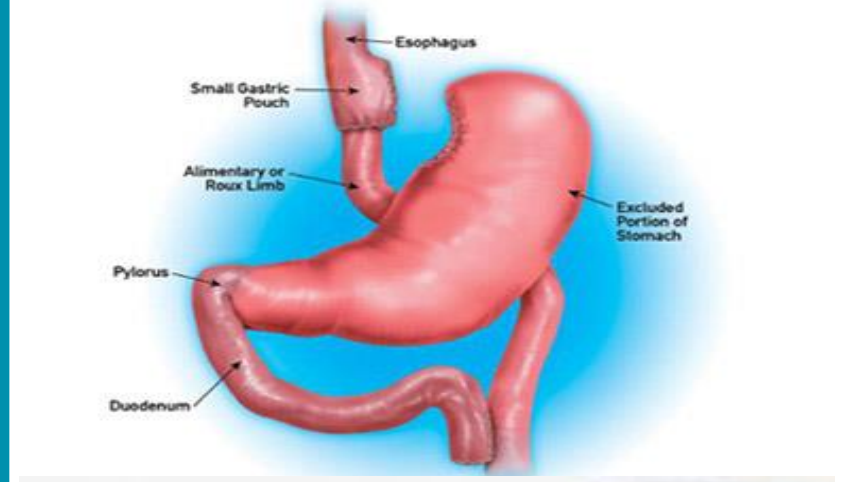
Key points for PCPs

- Type 2 diabetes management is *no longer glucocentric*
- A comorbidity-first approach *supports* durable glucose control over time
  - In other words, the right approach should achieve good glycemic control and control comorbidities


BRIGHAM AND
WOMEN'S HOSPITAL

Thank you!


as a thickening agent
diabetes
control the level of sug
sugar in the blood


Esophagus
Small Gastric Pouch
Alimentary or Roux Limb
Excluded Portion of Stomach
Pylorus
Duodenum

Selected references

- American Diabetes Association Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2026. Diabetes Care. 2026 Jan 1; 49(Supplement_1): S183-S215. doi: 10.2337/dc26-S009. PMID: 41358900

- Tsapas A, Avgerinos I, Karagiannis T, Malandris K, Manolopoulos A, Andreadis P, Liakos A, Matthews DR, Bekiari E. Comparative Effectiveness of Glucose-Lowering Drugs for Type 2 Diabetes: A Systematic Review and Network Meta-analysis. Ann Intern Med. 2020 Aug 18;173(4):278-286. PMID: 32598218.

- Wang L, Li X, Wang Z, Bancks MP, Carnethon MR, Greenland P, Feng YQ, Wang H, Zhong VW. Trends in Prevalence of Diabetes and Control of Risk Factors in Diabetes Among US Adults, 1999-2018. JAMA. 2021 Jun 25;326(8):1–13. doi: 10.1001/jama.2021.9883. Epub ahead of print. PMID: 34170288; PMCID: PMC8233946.