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

Diabetes Update 2025: New guidelines, approaches and drugs

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

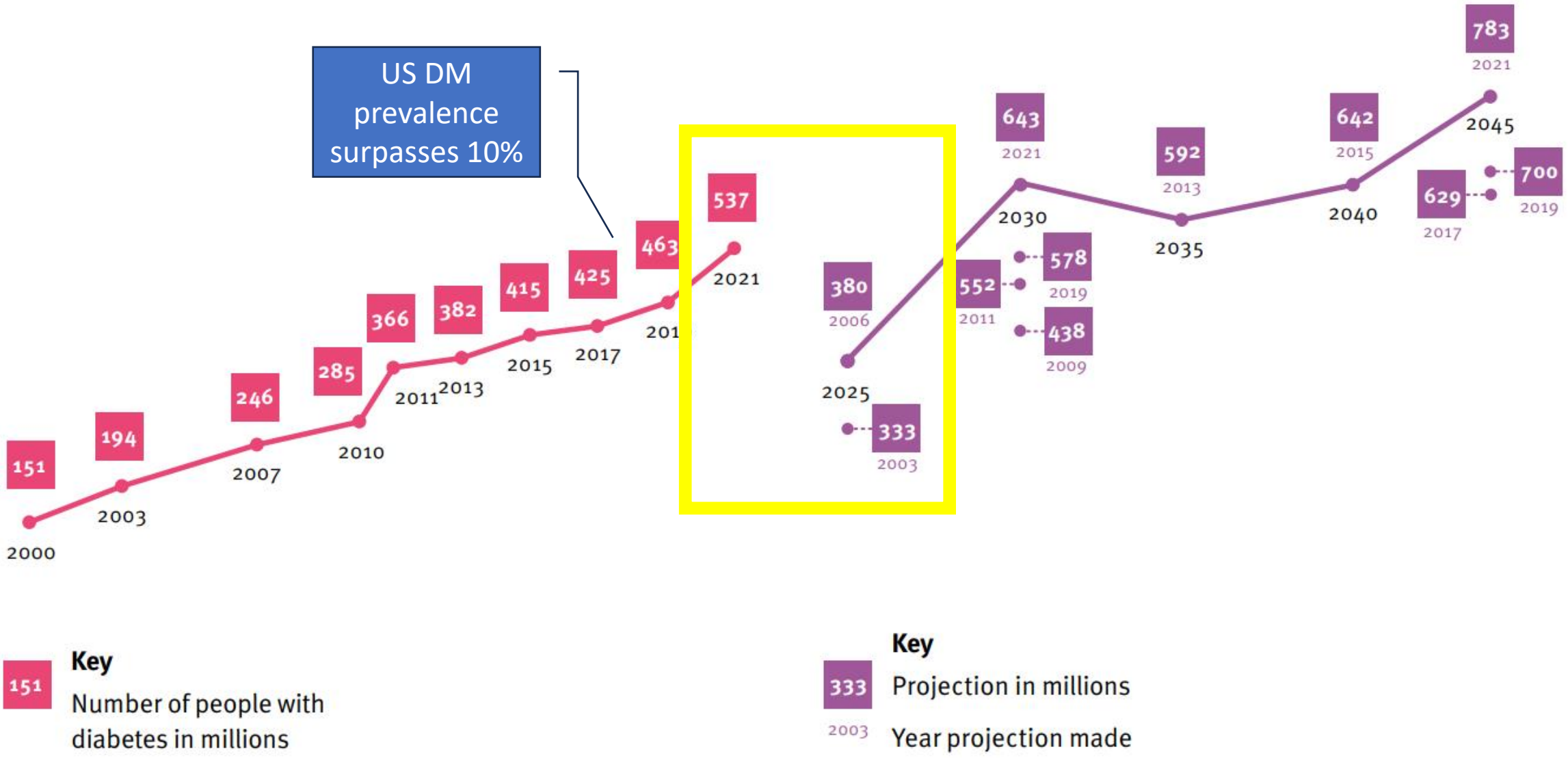
Disclosures

Research funding paid directly to institution: Dexcom, Inc

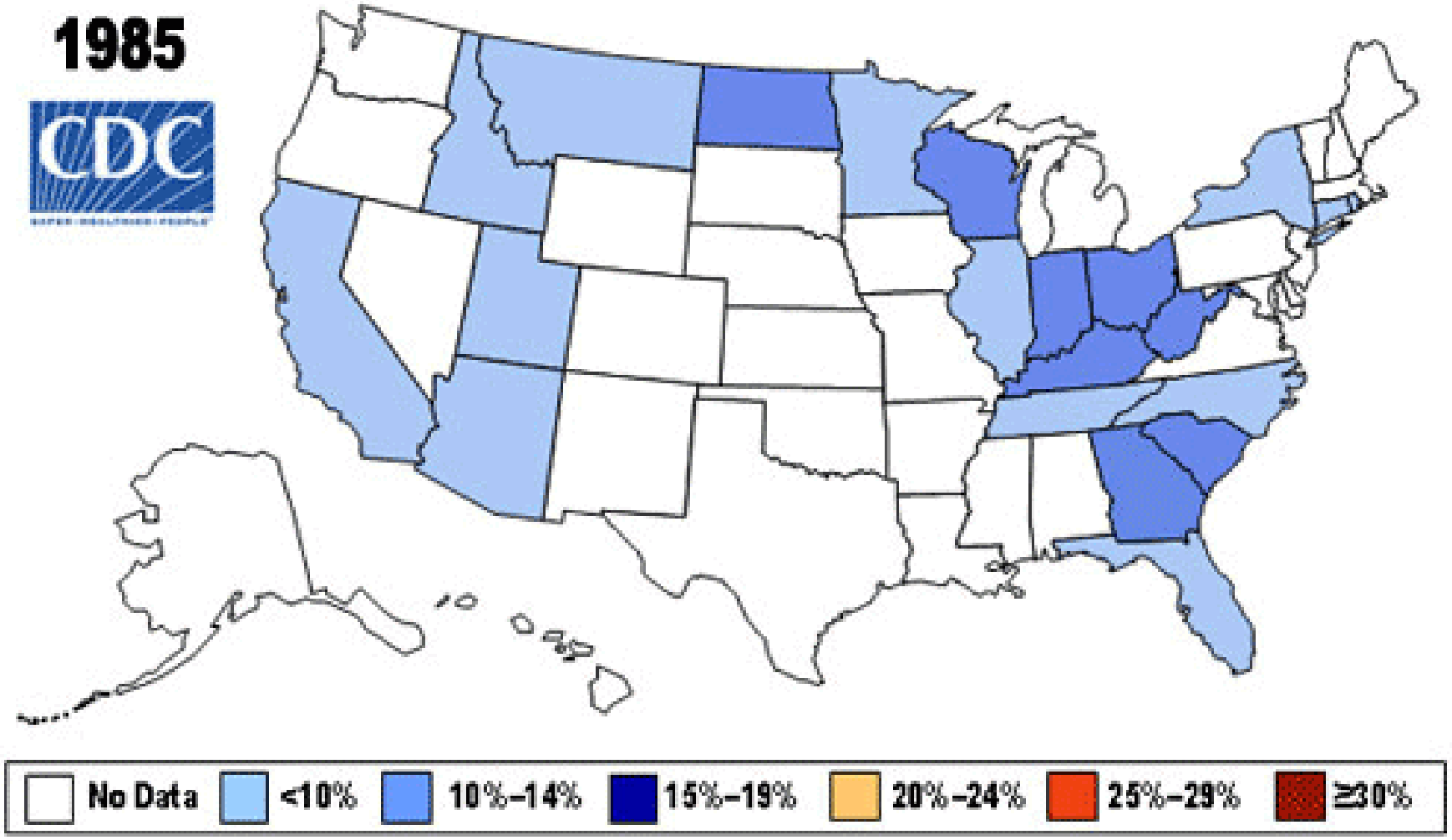
Learning Objectives

- Review basics of diagnosis and when to think beyond type 2
- Understand how to prescribe the available noninsulin pharmacologic therapies for type 2 diabetes
- Learn how to individualize therapeutic strategies for type 2 diabetes based on comorbidities, goals as well as concerns and side effects

Diabetes Is Globally OUTPACING Projections



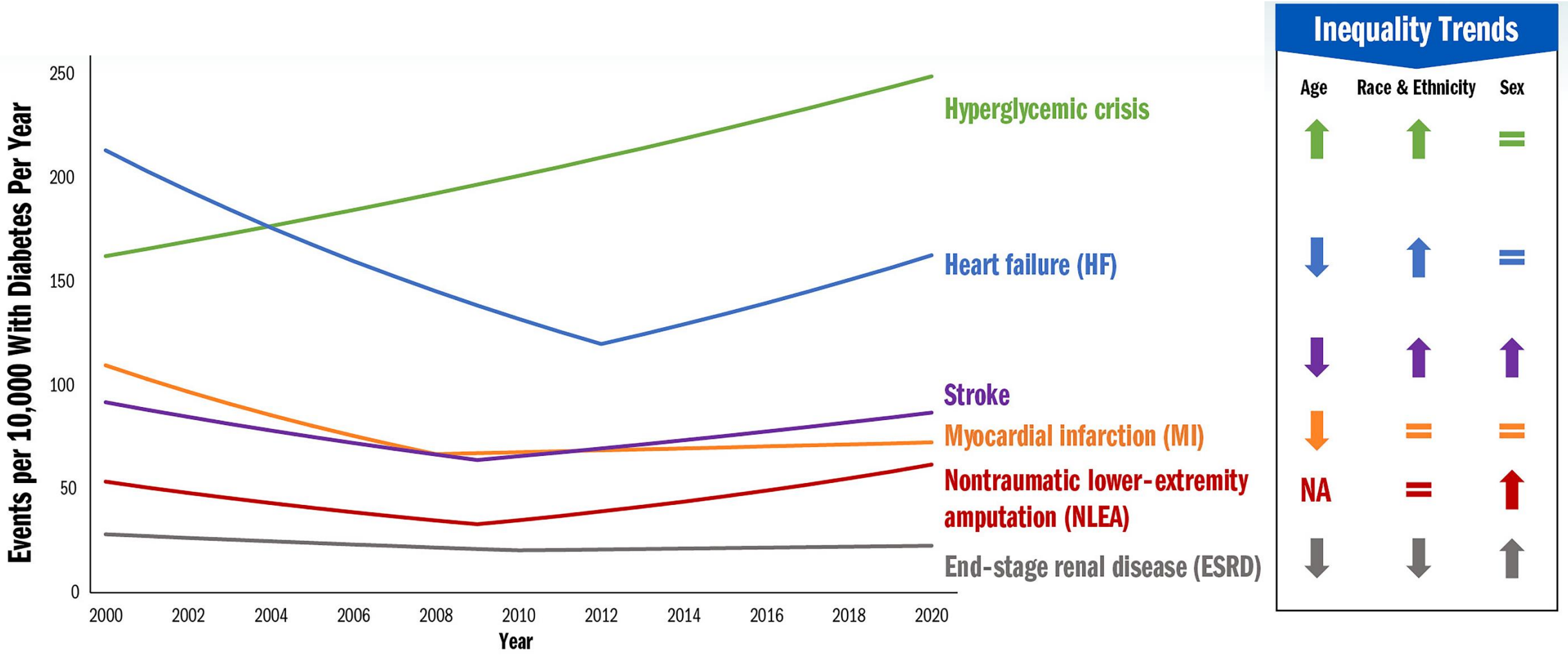
Obesity: Key Driver of the Diabetes Pandemic



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

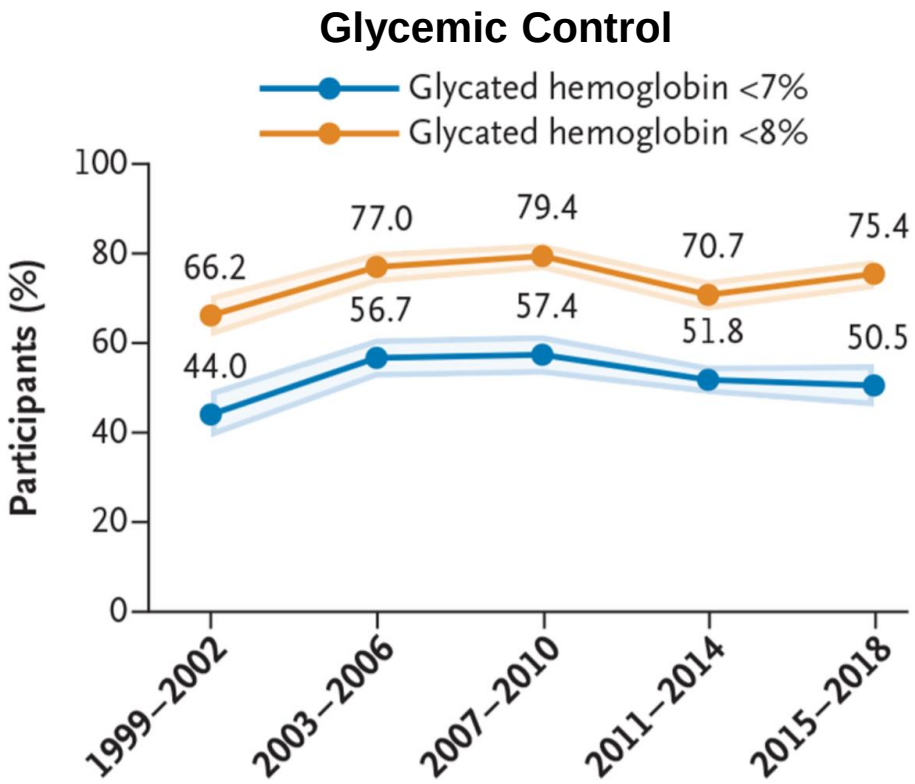
Trends and Inequalities in Diabetes-Related Complications Among U.S. Adults, 2000–2020



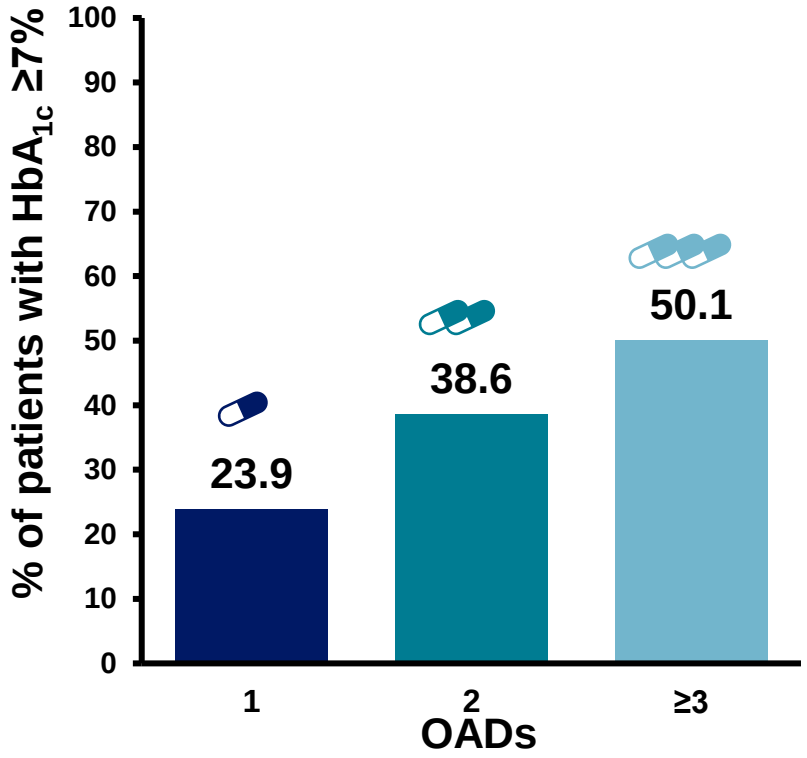
Diabetes Care. 2024;48(1):18-28. doi:10.2337/dci24-0022

Sole Focus on Glycemic Control Has Been Ineffective

"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

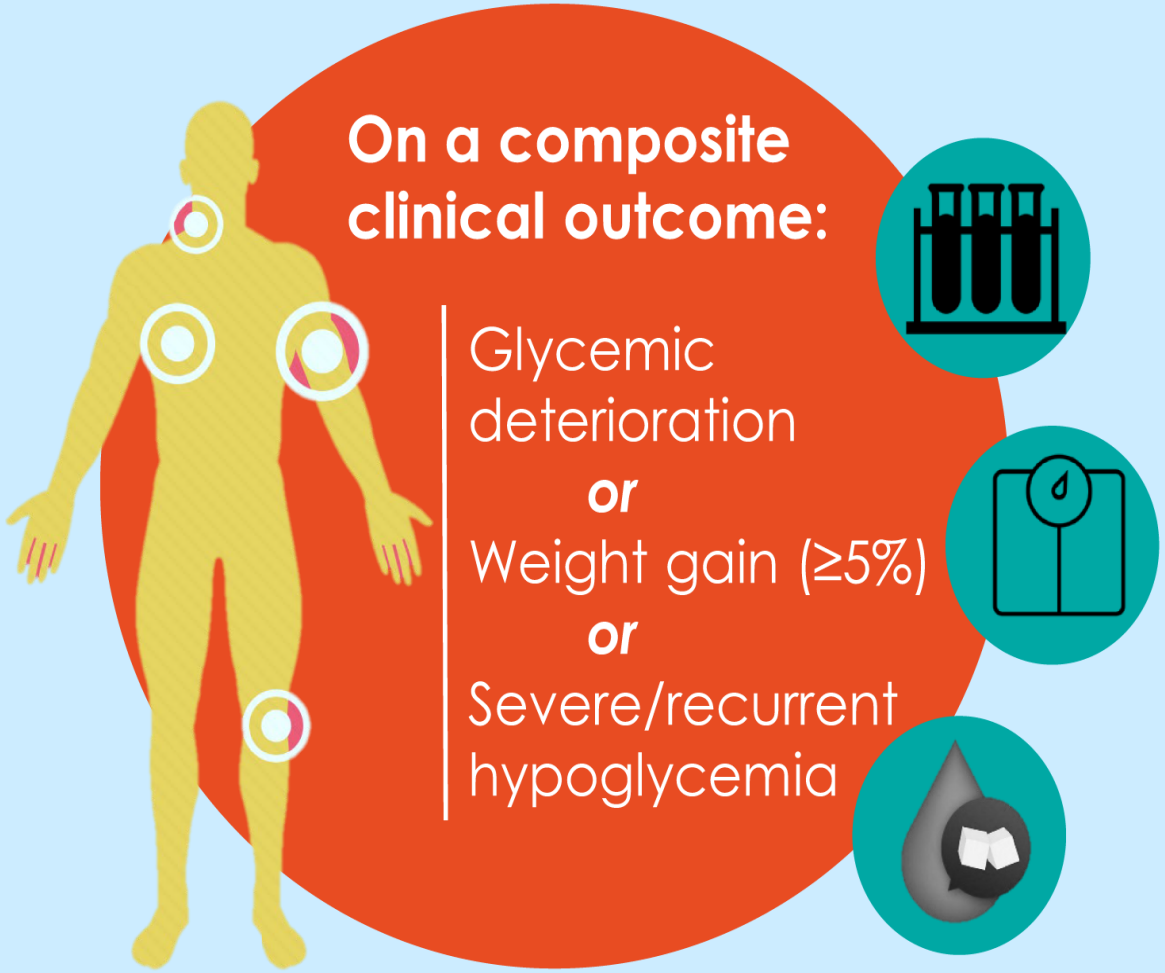
de Pablos-Velasco et al. Clin Endocrinol (Oxf). 2014 Jan;80(1):47-56.

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

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

To compare effects of 1 of 4 randomized study drugs added to metformin monotherapy:

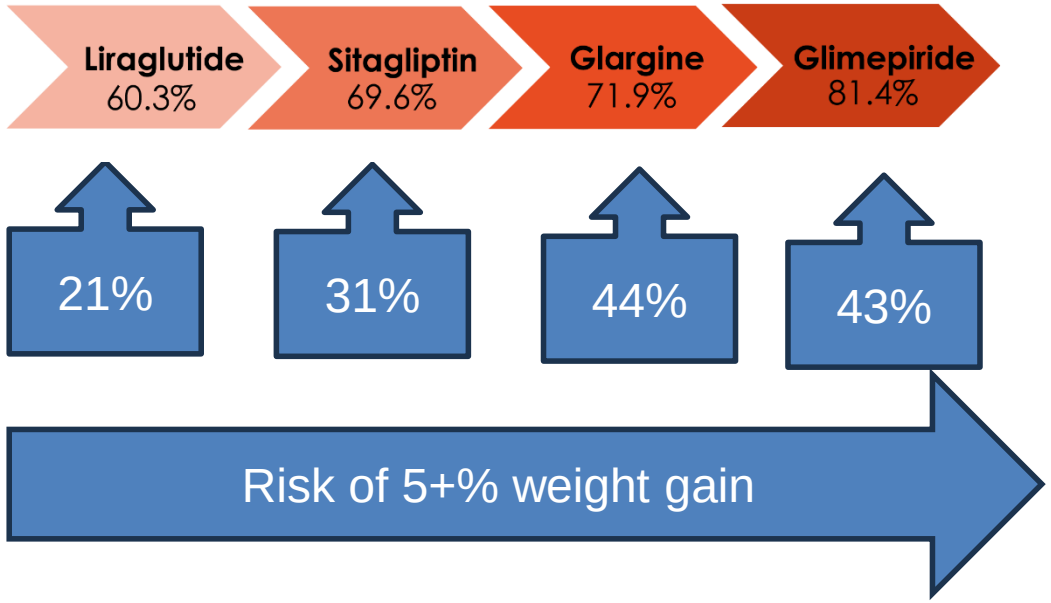
Glargine | Glimepiride | Liraglutide | Sitagliptin



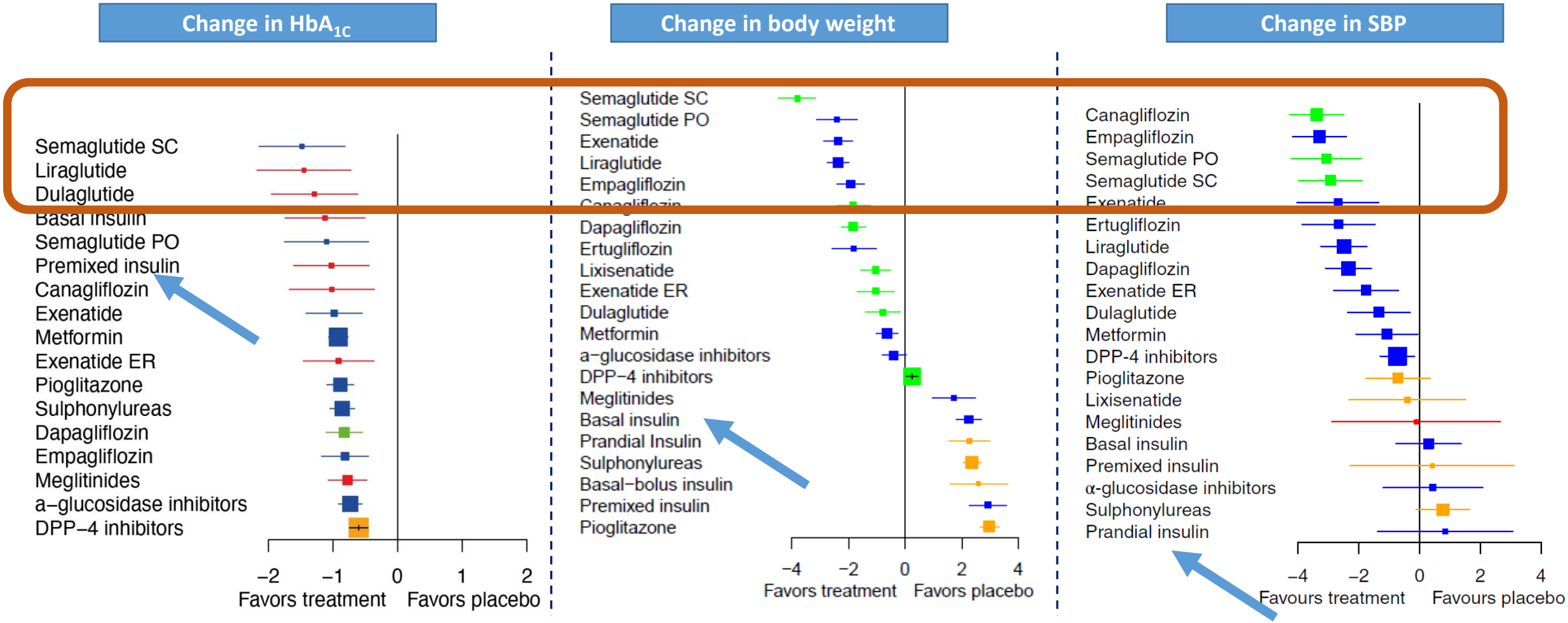
GRADE Study

N= 5,047 with T2D ≤ 10y Followed for 7 Years

- **The risk of reaching the composite outcome was,** from lowest to highest:



Increased Metabolic Effectiveness of Diabetes Meds

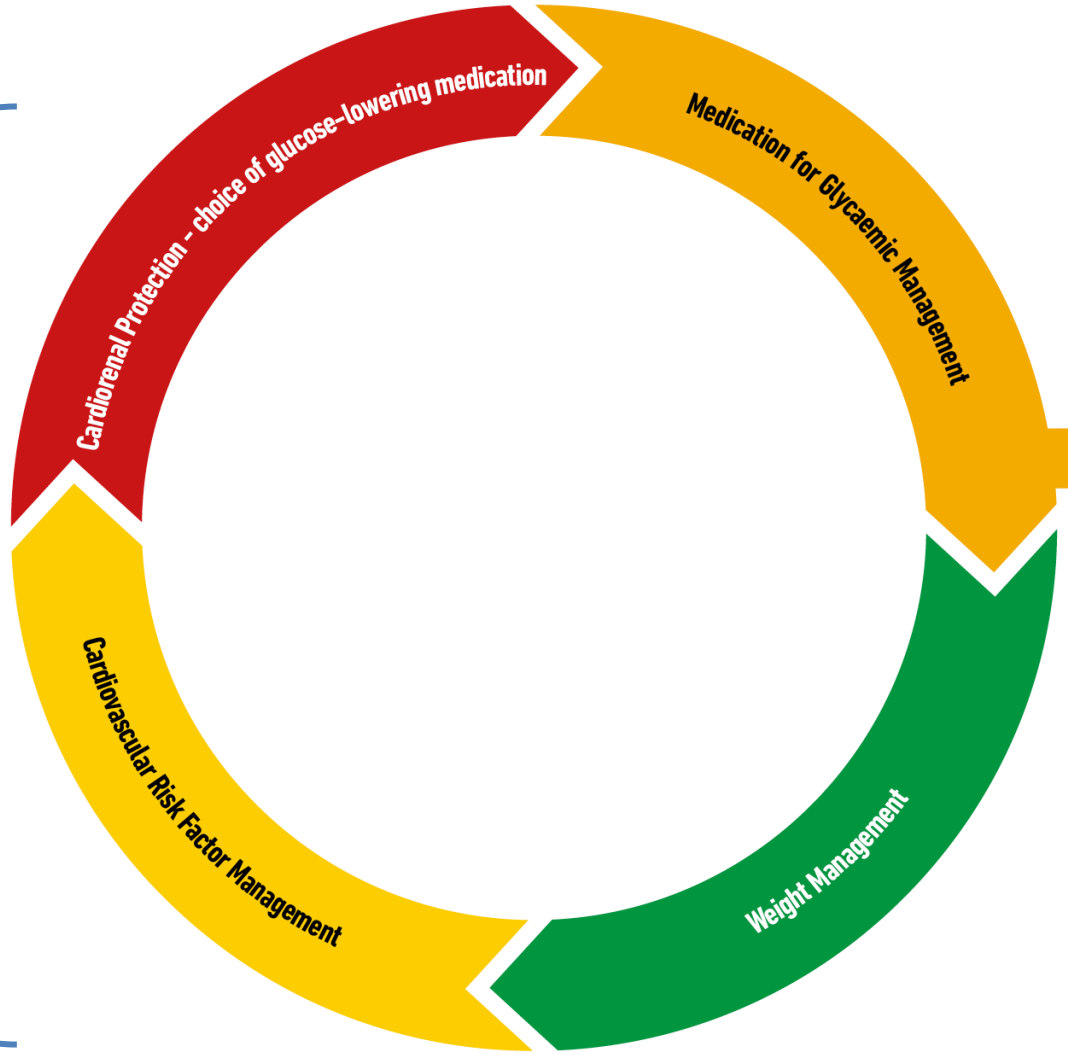


HbA_{1c}, glycated hemoglobin; SBP, systolic blood pressure

Tsapas A et al. Ann Intern Med 2020; 173: 278-286; Tsapas A et al. Diabetes Obes Metab 2021; 1-9.

2025 Guidance: *Giving Equal Weight*

"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.

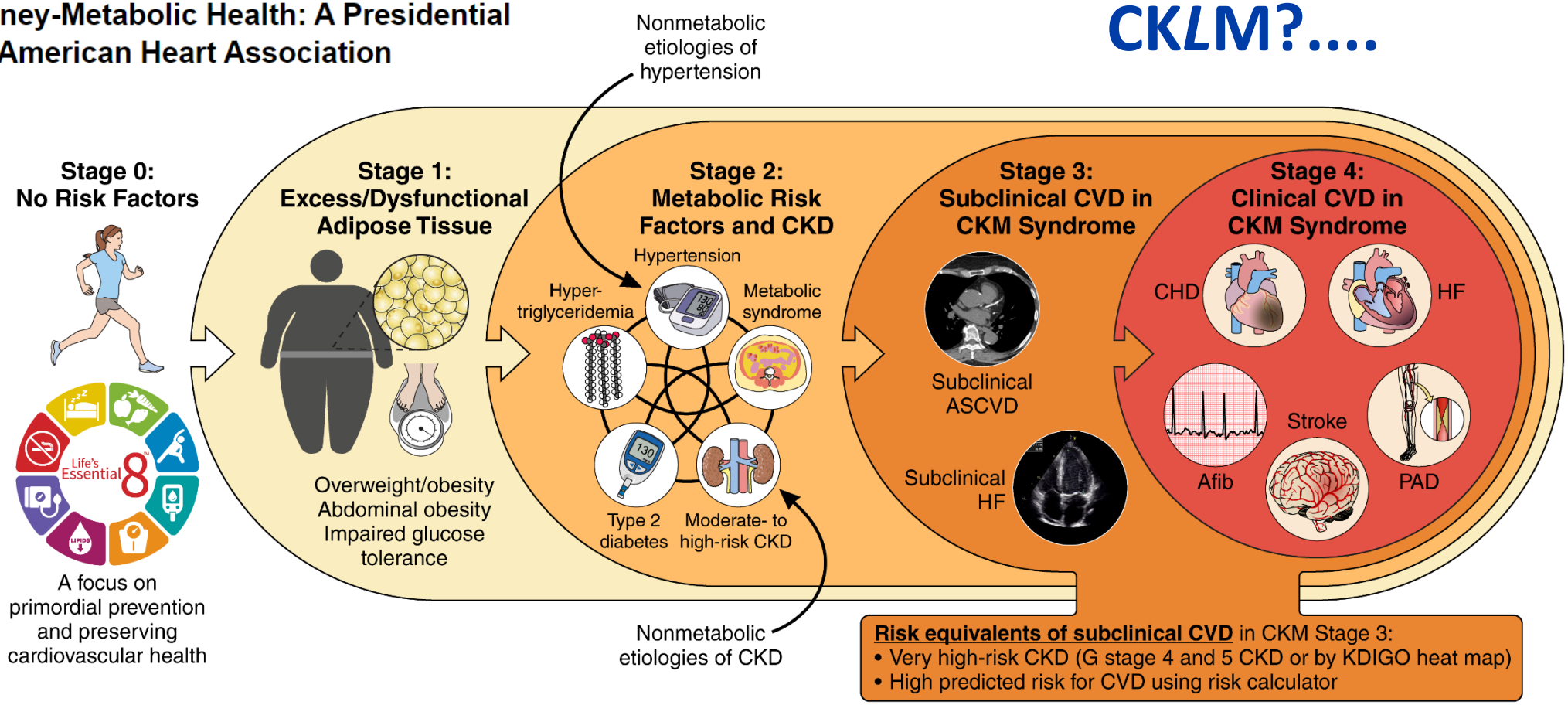
Davies MJ, et al. *Diabetes Care* 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

CKM disease in stages…Stage 1 = Too much/abnormal adipose

Should be CK*L*M?....

AHA PRESIDENTIAL ADVISORIES

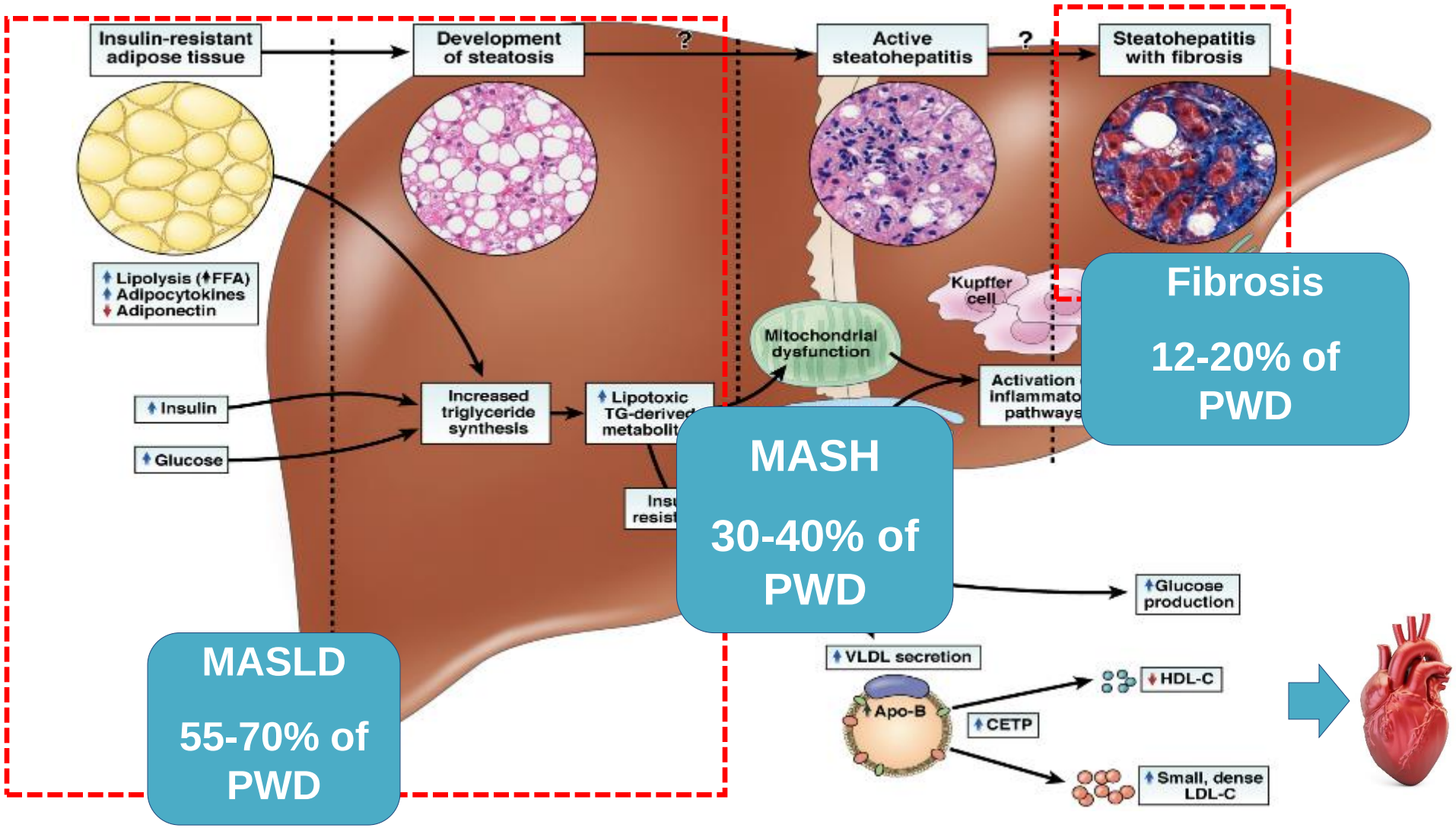
Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association



May, 2024

The Natural History of MASLD:

Rx: prevent/treat steatosis to prevent cirrhosis



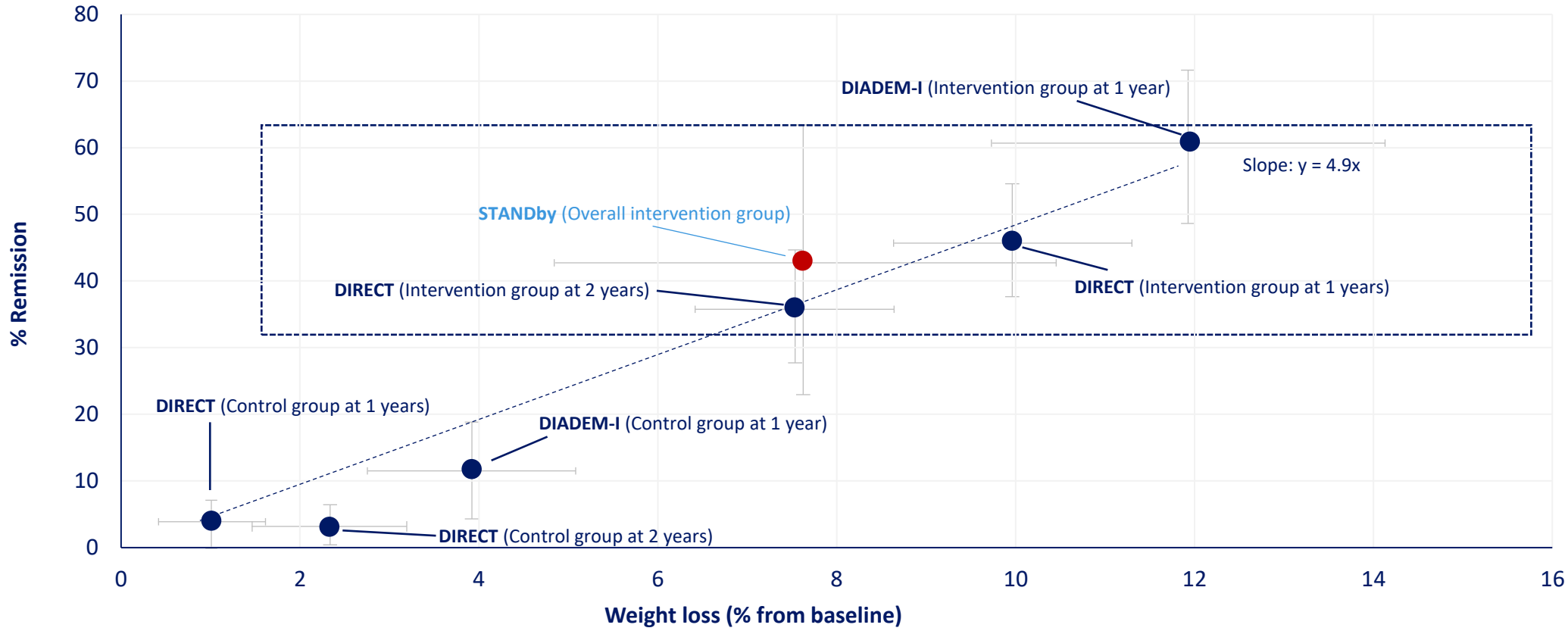
Adapted from **both** Cusi K, Gastroenterology, April 2012, 142:711-725

And Stefan N, Cusi K. Lancet Diabetes Endocrinol. Feb 17,2022

“Do I need to take medications? …
Tell me how much weight I need to lose and I’ll do it!”

Diabetes Remission in "Real World" Studies is Driven by >10% weight loss within one year

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.

Slide: courtesy Dr. Vanita Aroda

ReTUNE study: Is weight loss also effective in normal to overweight BMI? Do we have a "personal fat threshold?"

Weight loss in adults with T2DM with non-obese BMI induced T2D remission: "Aetiology of Type 2 diabetes does not depend on BMI."

Intervention: 1–3 cycles of 2–4 weeks at 800 kcal/day to reach HbA_{1c} <6.5%

Baseline

N=20 (T2DM, BMI < 27 kg/m^2)

59.3 ± 7.1 years

BMI 24.8 ± 1.7 kg/m^2

Key results

70% (14/20) achieved sustained remission at 12 months, defined as HbA_{1c} <6.5%, off all hypoglycemic medications

Reduction in intrahepatic and intrapancreatic fat percentage, fasting plasma insulin level

Conclusion

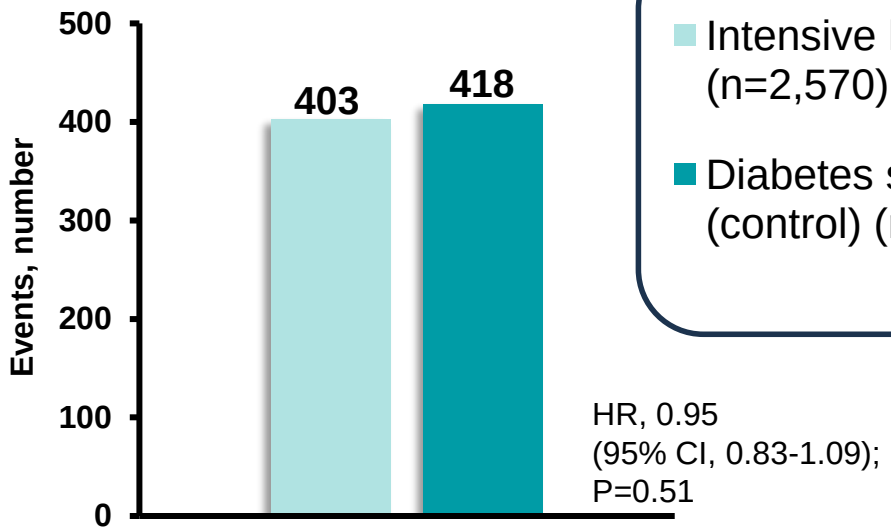
- **Weight loss can bring about T2D remission in people with a 'normal' BMI**
- **Threshold of remission achieved with median weight loss of 6.5% (range 5.5–10.2)%**
- **Mechanistic changes behind remission are similar in obese and non-obese individuals**

- BMI, body mass index; HbA_{1c}, glycated haemoglobin; T2D, type 2 diabetes.

Taylor R et al. Clin Sci (Lond). 2023;137(16):1333 -1346.

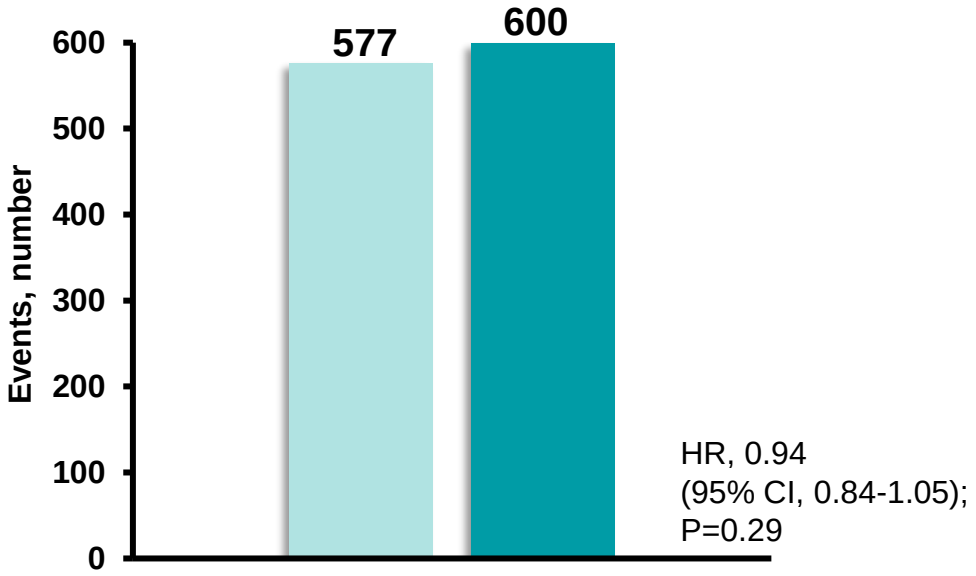
But does weight loss help the heart? taking a second look at Look AHEAD:

Primary outcome: composite of first occurrence of death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for angina



- Intensive lifestyle intervention (n=2,570)
- Diabetes support & education (control) (n=2,575)

Secondary outcome: death from any cause, nonfatal I, nonfatal stroke, hosp for angina, CABG, PCI, hosp fpr heart failure, carotid endarterectomy, or PVD



Look AHEAD=Action for Health in Diabetes
CI=confidence interval; CV=cardiovascular; HR=hazard ratio; MI=myocardial infarction; CABG= coronary artery bypass grafting; PCI=percutaneous coronary intervention; PVD=peripheral vascular disease

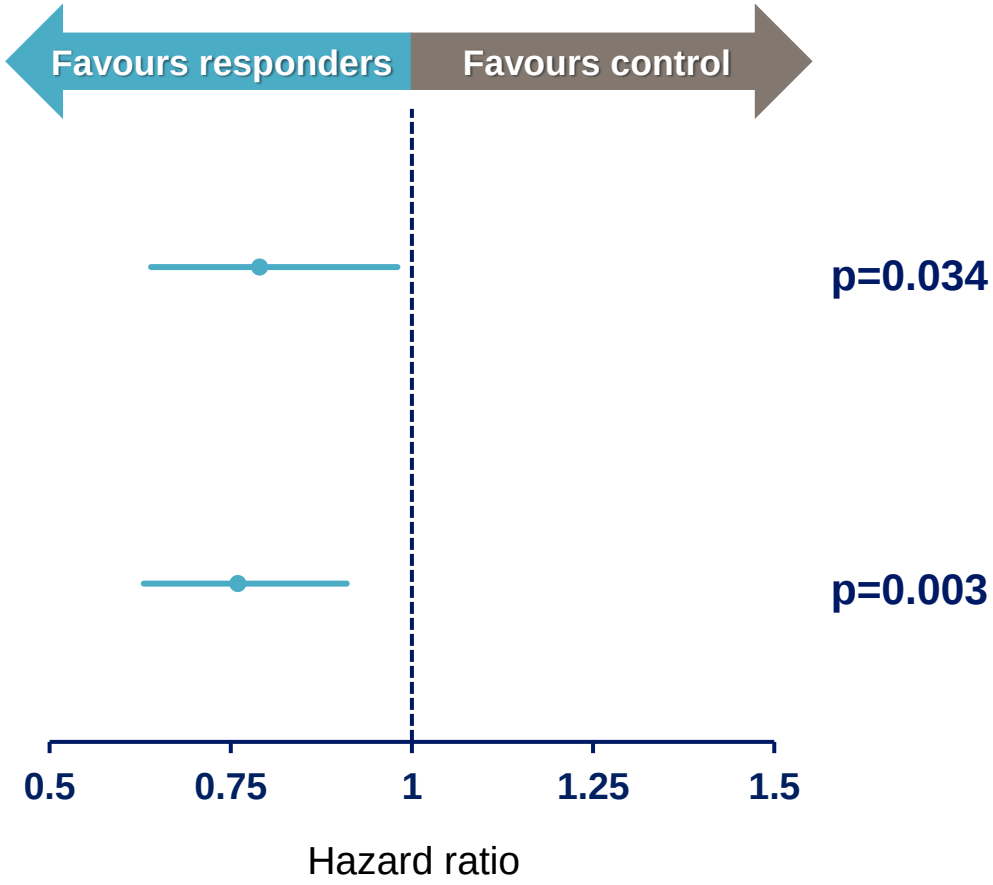
The Look AHEAD Research Group. *N Engl J Med* 2013;369;145.

Weight-loss responders DO have improved CV outcomes

A *post hoc* analysis of the Look AHEAD randomised clinical trial

Responders: lost **at least 10%** of their body weight in the 1st year of the study

- **Primary outcome – 21% lower**
  - CV death, non-fatal acute MI, non-fatal stroke, or admission to hospital for angina
- **Secondary outcome – 24% lower**
  - As above plus CABG, carotid endarterectomy, PCI, hospitalisation for CHF, peripheral vascular disease, or total mortality



N=4406 participants with T2D to an intensive lifestyle intervention or diabetes support and education.
AHEAD, The Action for Health Diabetes; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CV, cardiovascular; MI, myocardial infarction; PCI, percutaneous coronary intervention; T2D, type 2 diabetes.
Look AHEAD Research Group. *Lancet Diabetes Endocrinol* 2016;4:913–21.a

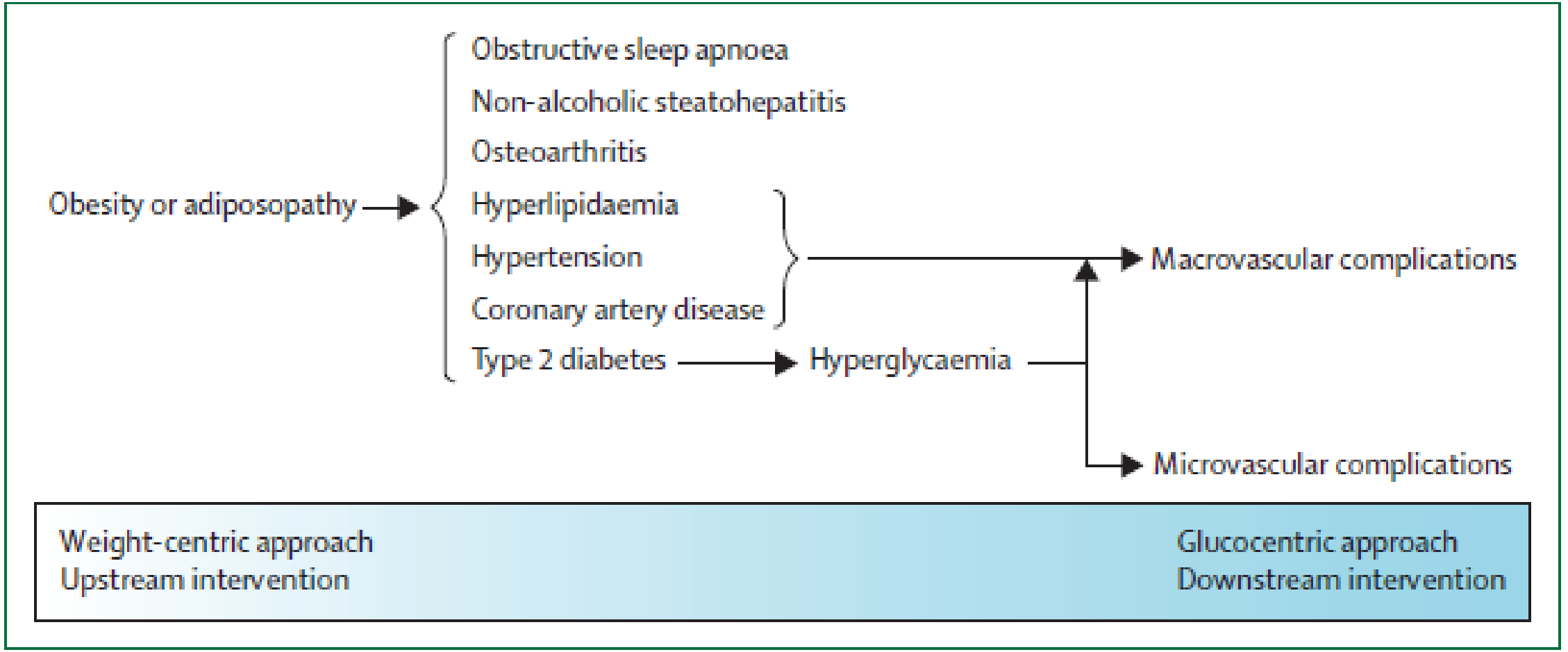
ARMMS T2D STUDY: Bariatric Surgery vs. Medical Management

	Bariatric Surgery *ARMMS T2D STUDY	Medical/lifestyle Management ARMMS T2D STUDY
A1c reduction	1.6%	0.2%
Diabetes Remission (off medications)	**38% at 3 years** 13% at 12 yrs	**3% at 3 years** 0% 12 years
% Weight loss	**23% at 3 yrs**	**5% at 3 yrs**
Deaths	**2**	**2**

*N =262 over 7-12 years

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; Sattar N et al., Lancet Reg Health Southeast Asia. 2023;9:100111.

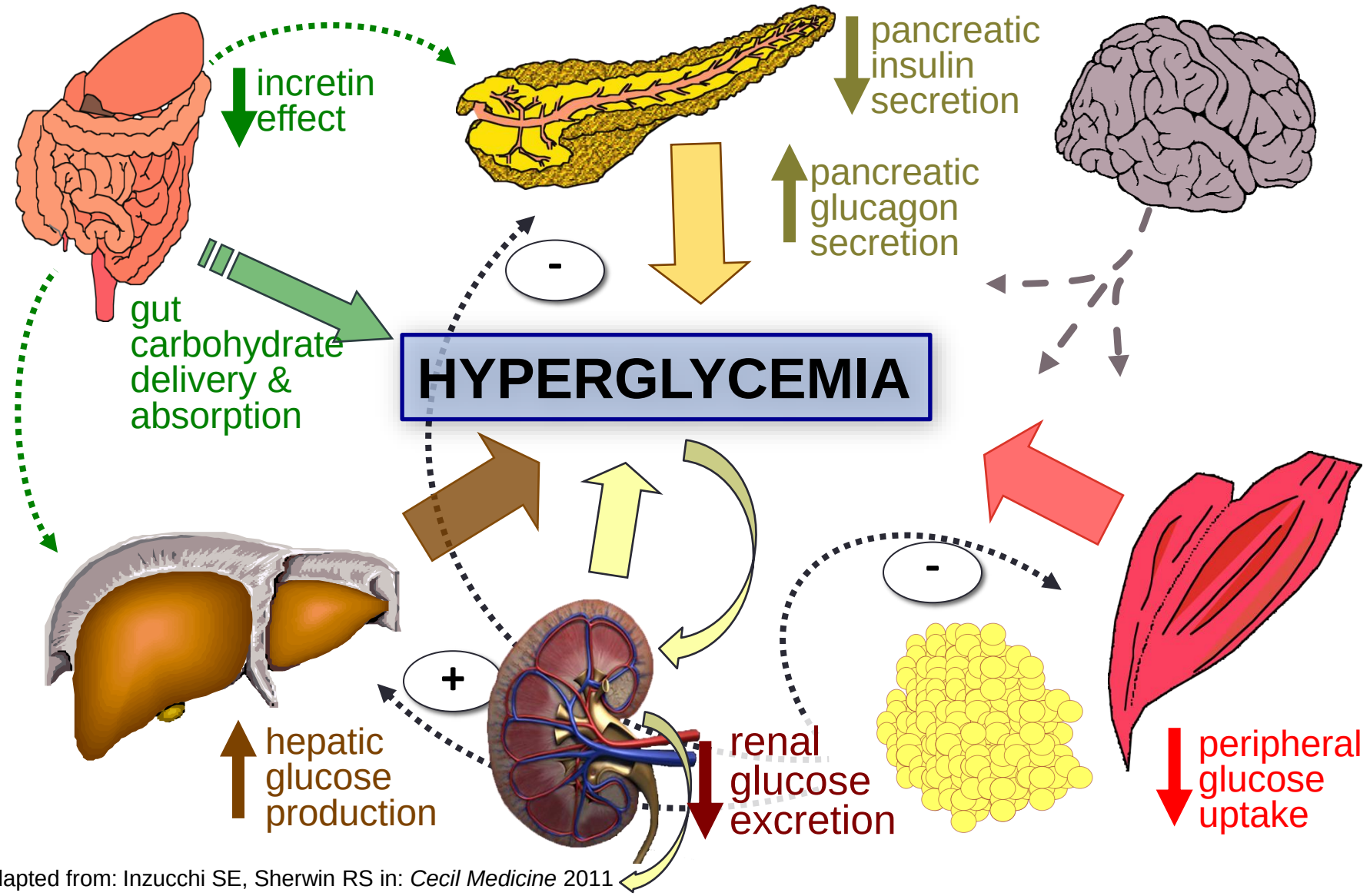
New Concept in a Nutshell: Adopting an "Upstream" Weight-centric Approach *instead of* a Glucocentric Management Approach



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

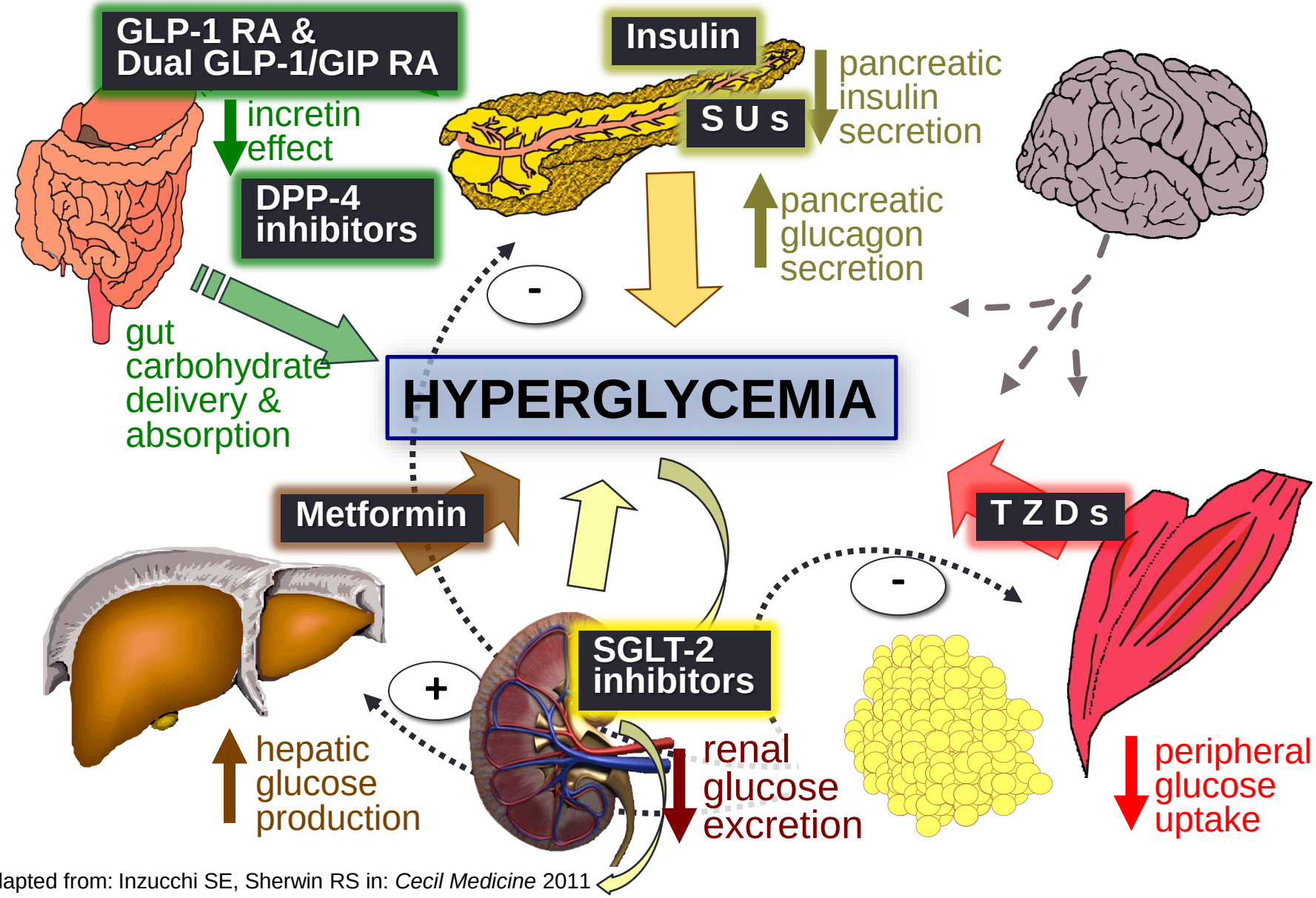
What are the options for medication management in Type 2 Diabetes: *An Overview*

Multiple Complex Pathophysiological Abnormalities in T2DM

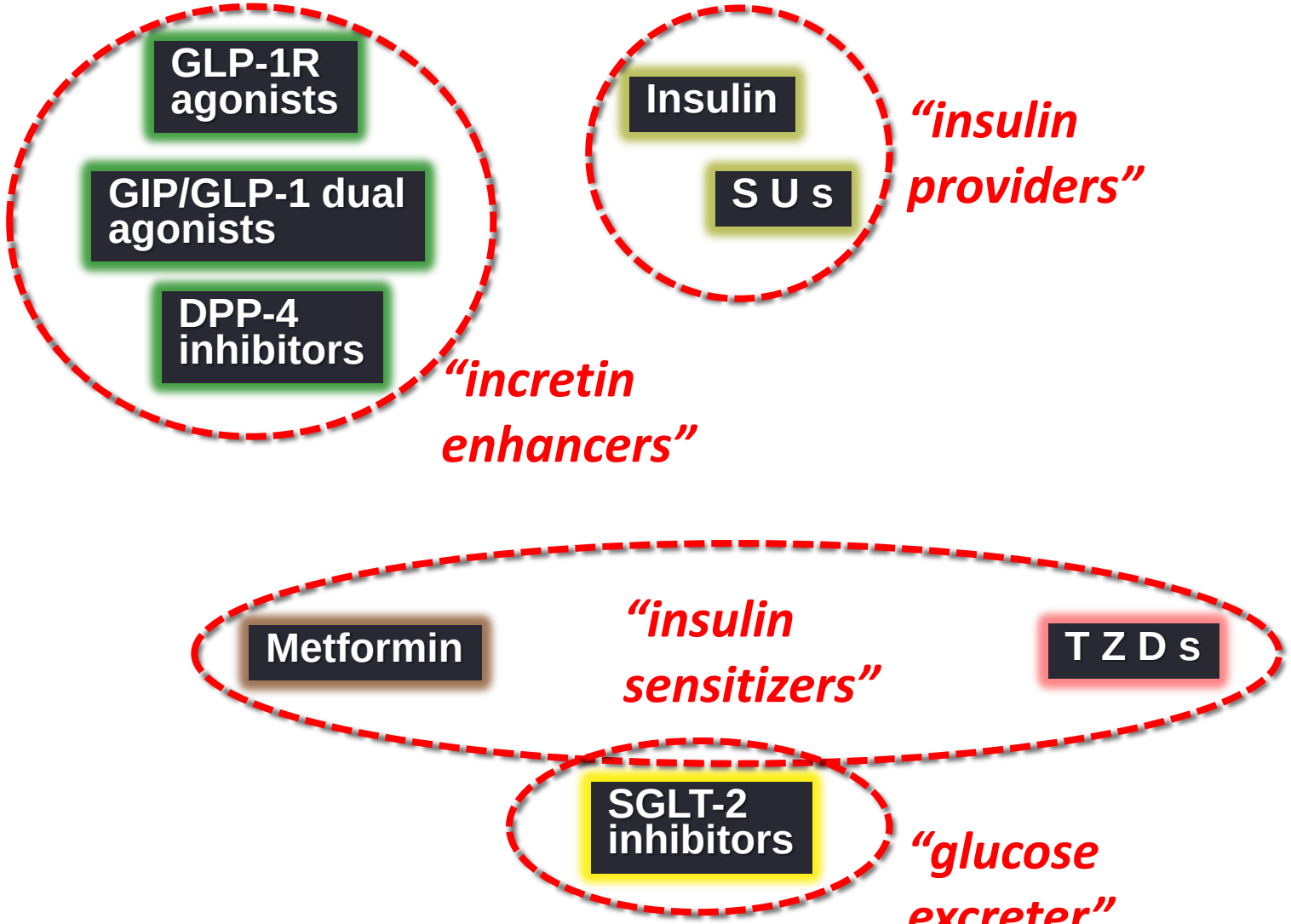


Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

Major Pathophysiologically-Based Therapies for T2DM



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


GLP-1R agonists
GIP/GLP-1 dual agonists
DPP-4 inhibitors
"incretin enhancers"
Insulin
S U s
"insulin providers"
Metformin
"insulin sensitizers"
T Z D s
SGLT-2 inhibitors
"glucose excreter"

GLP-1R and dual GLP1/GIP agonists

Insulin

S U s

DPP-4 inhibitors

Metformin

T Z D s

SGLT-2 inhibitors

Glucose Lowering Drugs Classes

Classes	Generic Names	↓ A1c	Side effects
Insulin	Degludec, Glargine, Detemir, NPH, Regular, Lispro, Aspart, Glulisine	1+ %	Hypoglycemia, weight gain, Injections
SU's	Glyburide, Glipizide, Glimepiride	1-1.5%	Hypoglycemia, weight gain
Metformin	Metformin	1-1.5%	GI, B-12 deficiency, lactic acidosis,
TZD's	Rosiglitazone, Pioglitazone	1-1.5%	CHF, Weight gain, edema, bone fx's, ?bladder ca
DPP-4 i's	Sitagliptin, Saxagliptin, Alogliptin, Linagliptin (GLIPTINS)	**0.5-1%**	Urticaria, arthralgias (rare) pancreatitis
Incretin RAs	GLP-1: Exenatide, Lira-, Dula-,Sema- GLP-1/GIP dRA: Tirzepatide	1-1.5%	GI, gallbladder, ?pancreatitis, injections
SGLT2-i's	Canagliflozin, Dapagliflozin, Empagliflozin, Bexaflozin (FLOZINS)	**0.5-1%**	GU infections, Polyuria, GU infections, DKA, ?fractures

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, Injections
SU	Glyburide, Glipizide, Glimepiride	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, Saxag ogli Linagliptin (GLIPTINS)	0.5-1%	Urticaria, arthralgias (rare) pancreatitis
Incretin RA	GLP-1: Exenatide, Lira-, Dula-,Sema- GLP-1/GIP dRA: Tirzepatide	1-1.5%	GI, gallbladder, ?pancreatitis
SGLT2-i	Canagliflozin, Dapagliflozin, Empagliflozin, Bexaflozin (FLOZINS)	0.5-1%	GU infections, Polyuria, GU infections, DKA, ?fractures

Goal: Mitigate and minimize SEs through combination therapy

Cardioprotective Drug Classes are Born!*

GLP-1 RA:

Major Adverse Cardiovascular Events:

HR 0.86

14% REDUCTION

CV Death:

HR 0.87

13% REDUCTION

Fatal or Non-fatal Myocardial Infarction:

HR 0.90

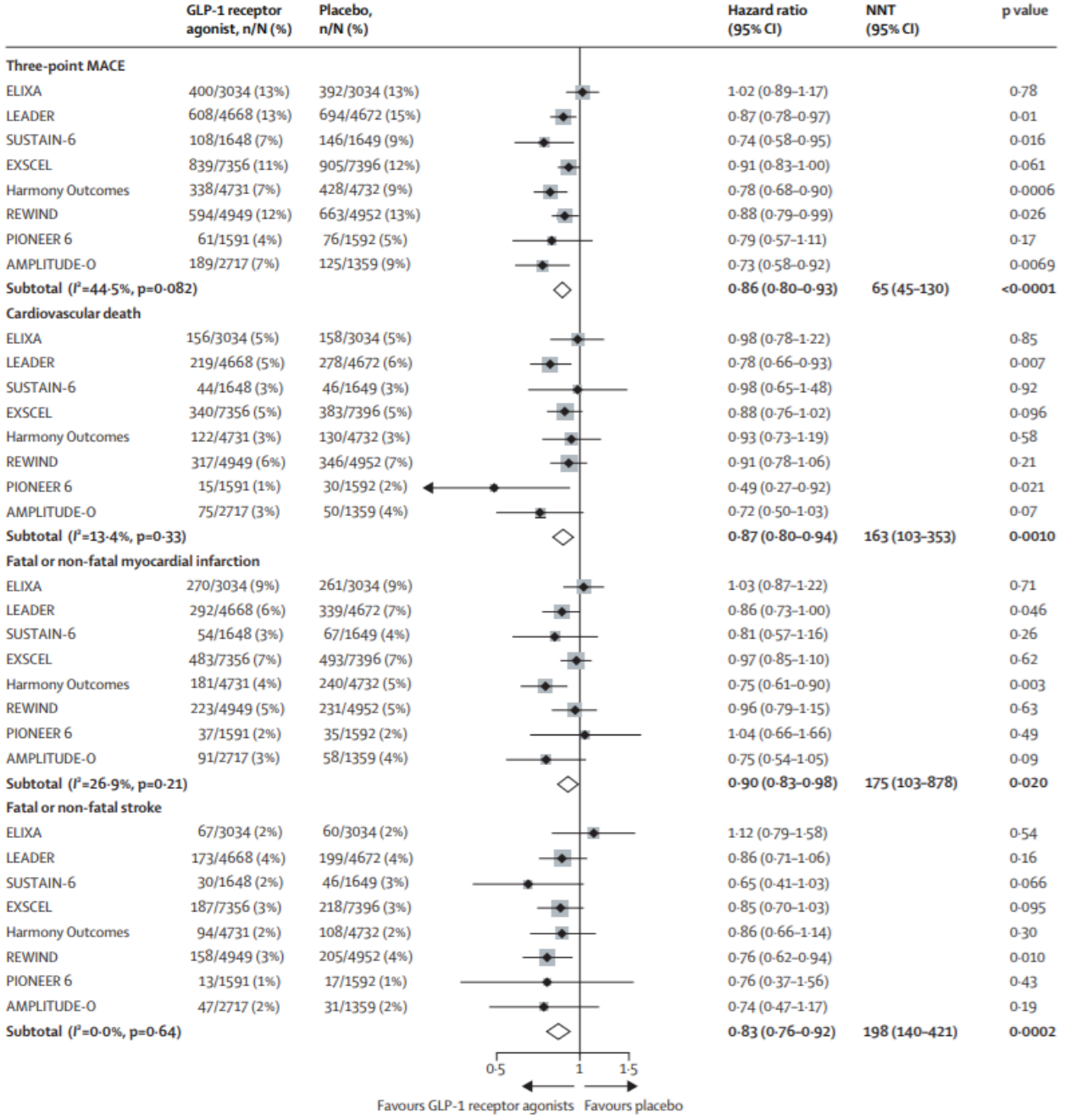
10% REDUCTION

Fatal or Non-fatal Stroke:

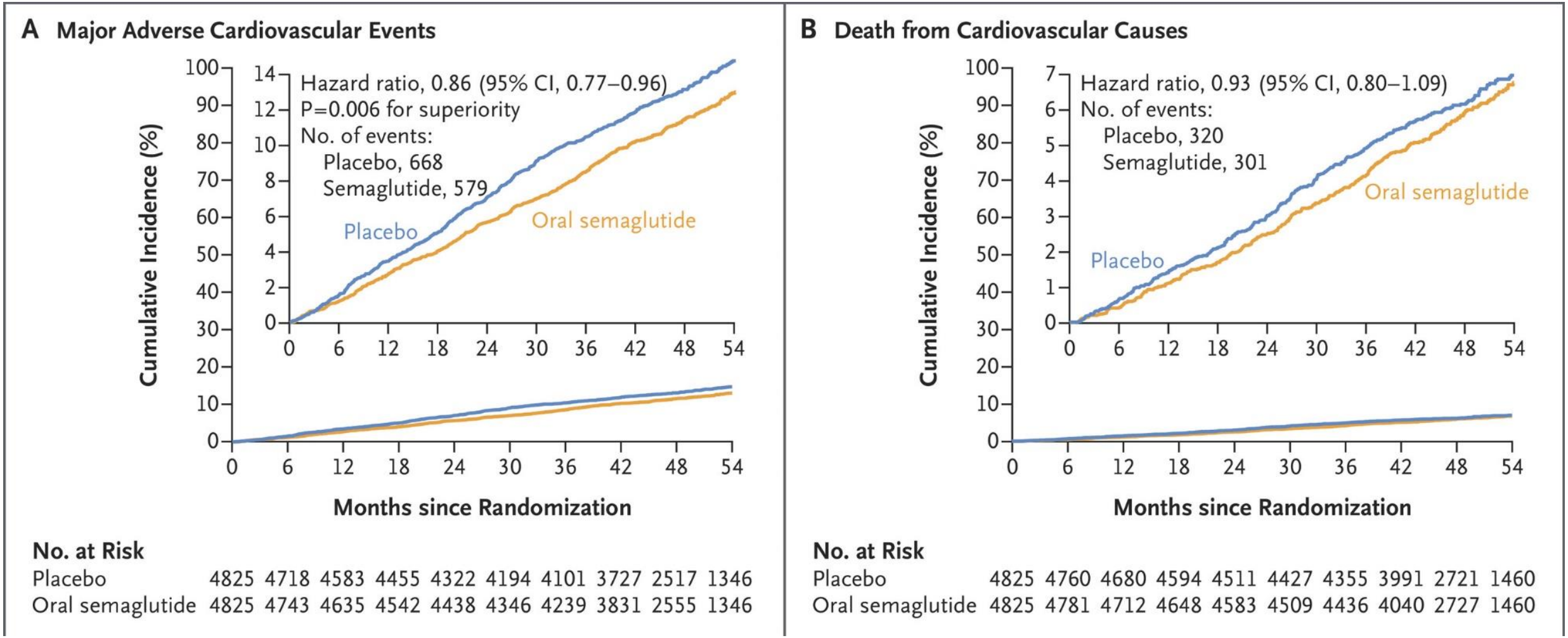
HF 0.83

17% REDUCTION

*exenatide, and lixisenatide were not shown to reduce MACE. Oral semaglutide did not show benefit in the first CVOT PIONEER

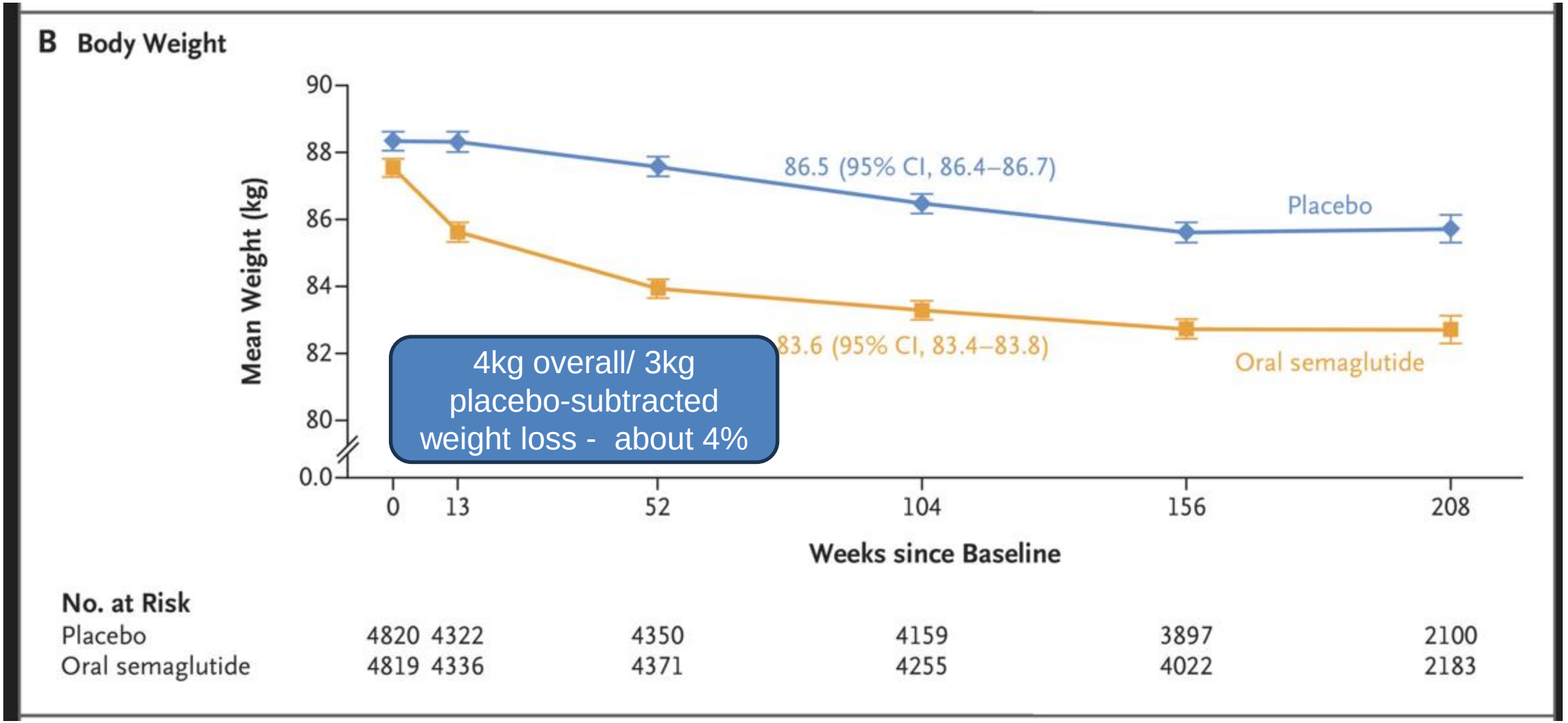


Oral Semaglutide in **T2D + CVD or CKD**: the SOUL trial



McGuire DK, et al N Engl J Med. 2025 Mar 29.

Oral semaglutide and weight loss in SOUL trial



Tirzepatide, Dual GLP-1/GIP Agonist

Effects on Cardiovascular Risk Factors[1]

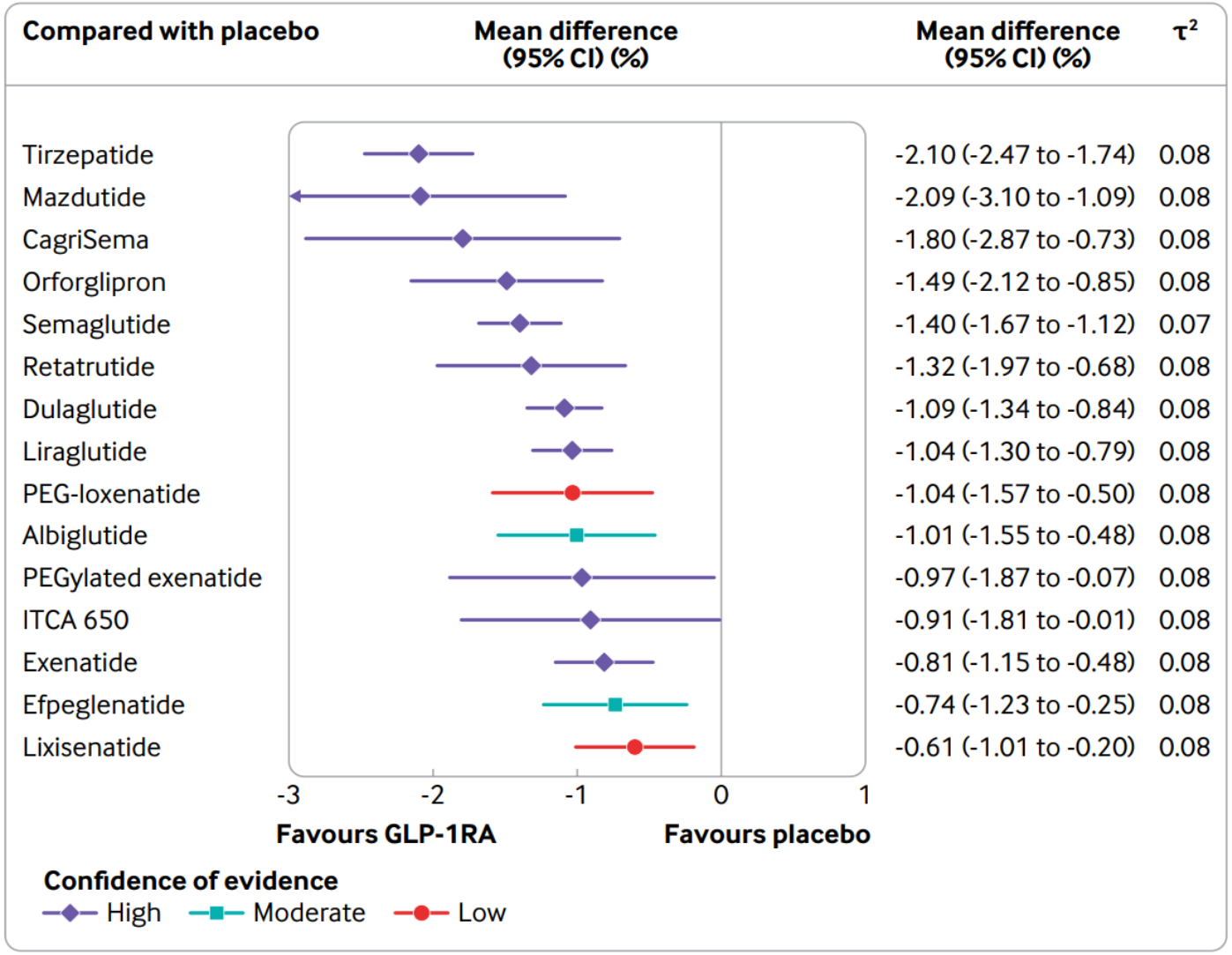
More weight loss = more risk factor modification

	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[2]
- Decrease albuminuria[3]
- Slower decline in eGFR over time[3]

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

Incretin agents vs. Placebo for HbA1c Reduction



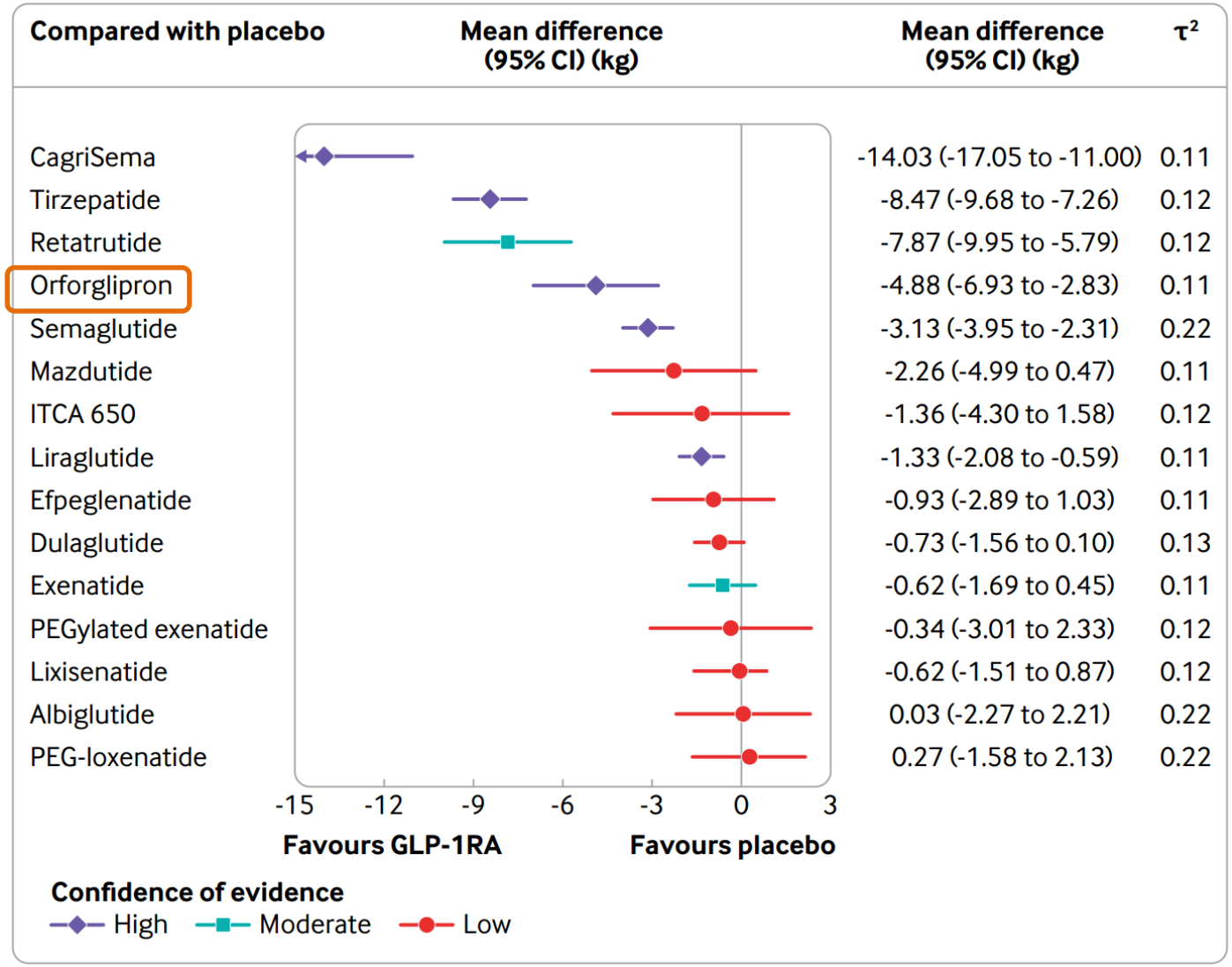
- **56 trials**
- **n=26,343 Adults with Type 2 Diabetes**
- **All 15 GLP-1RA drugs showed significant efficacy in reducing HbA1c levels compared with placebo in adults with type 2 diabetes**

- **Mean difference vs placebo:**

Tirzepatide −2.10% (95% CI)
Induced most significant HbA1c reduction

Yao H, et al. BMJ. 2024 Jan 29;384:e076410.

Incretin agents vs. Placebo for Body Weight Reduction in Diabetes



- **53 trials**
- **n = 21,349 Adults with Type 2 Diabetes**
- **Mean difference vs placebo:**

CagriSema:

Combination semaglutide + amylin analog

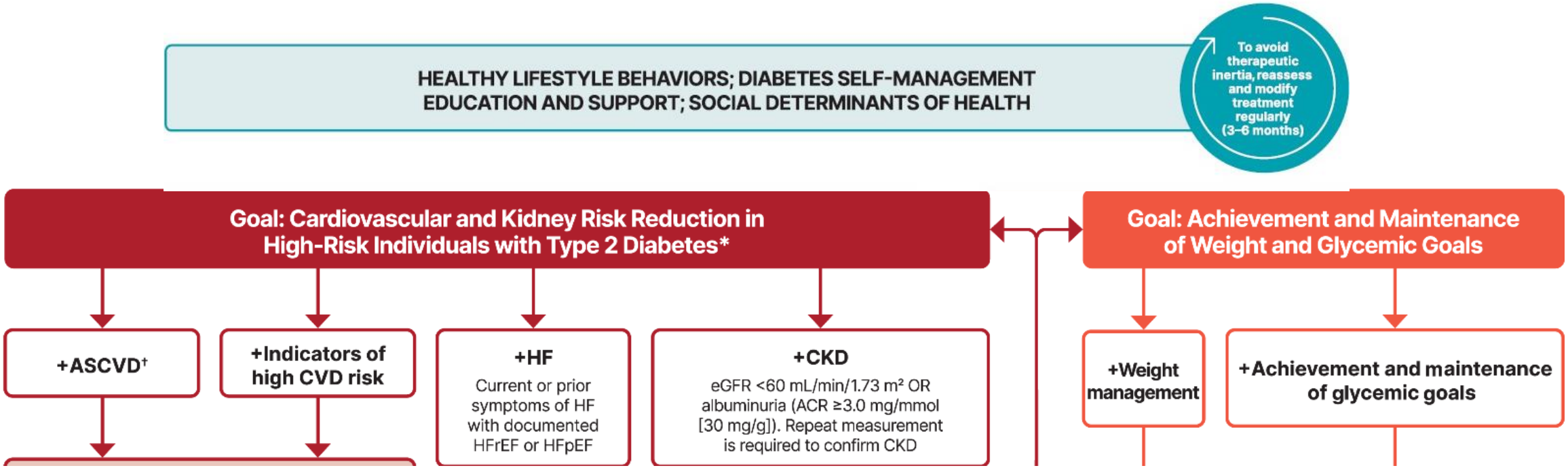
−14.03 kg (>10%) : Most effective in lowering body weight in people with diabetes; NOT superior to tirzepetide in non-diabetes obesity

Yao H, et al. BMJ. 2024 Jan 29;384:e076410.; Apovian CA, McDonnell ME, Lancet, 2023

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

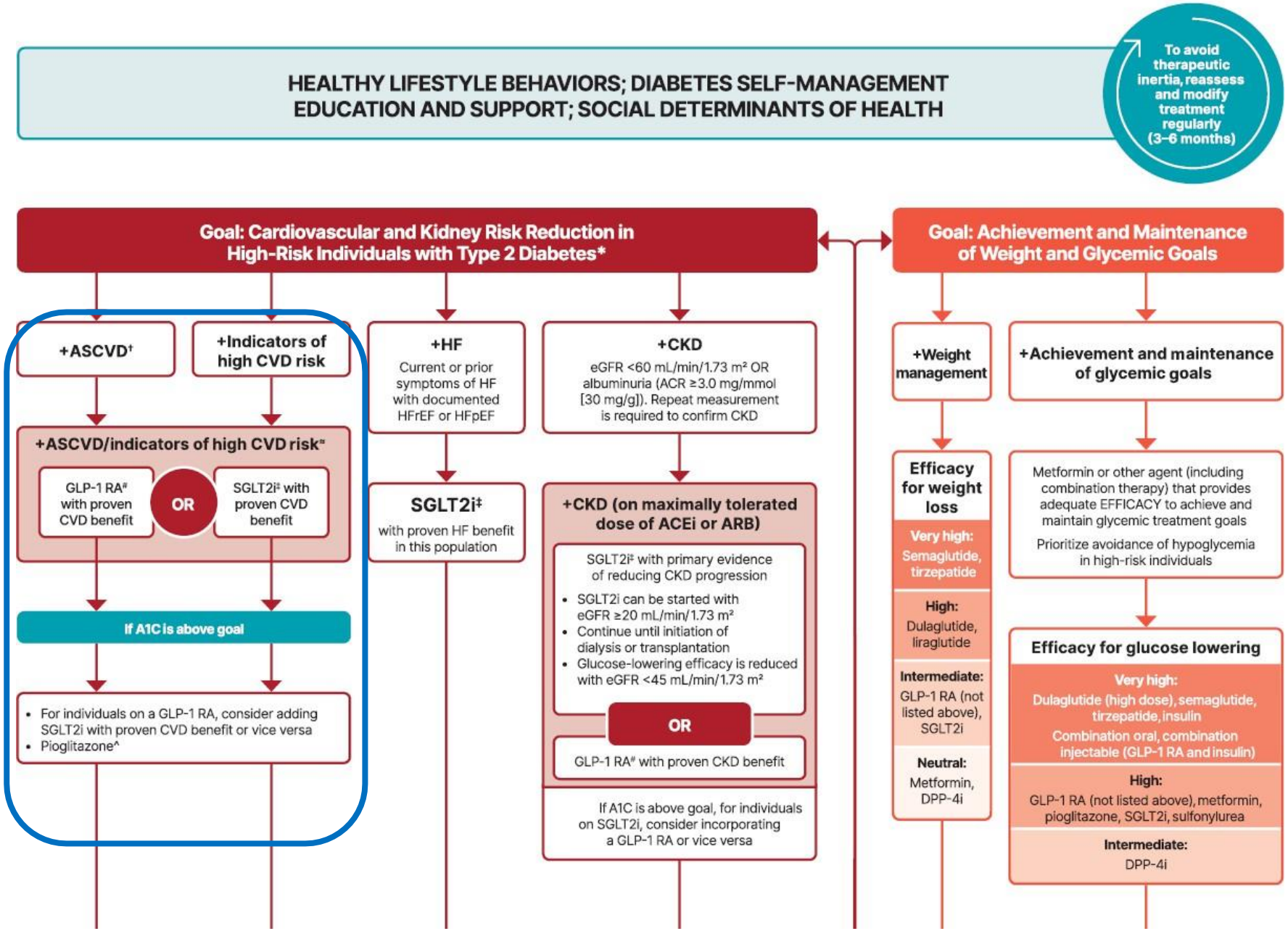
ADA: Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. Pharmacologic approaches that provide the efficacy to achieve treatment goals should be considered, such as metformin or other agents, including combination therapy, that provide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

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



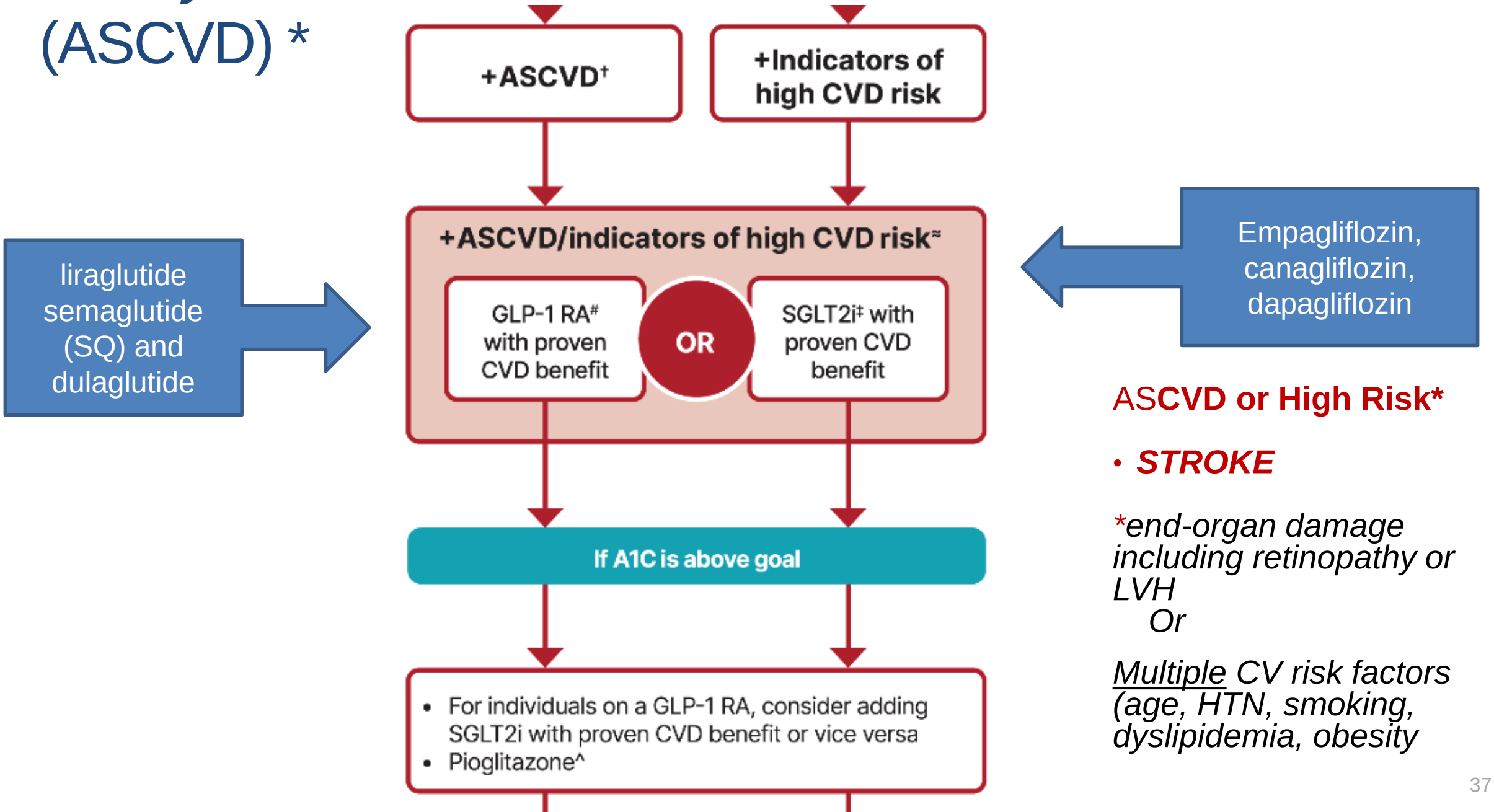
<u>Implied point throughout the guidance</u>: It is ideal to choose medications that can achieve more than one of these goals simultaneously; this is not always feasible

Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes



Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes - 2025 Diabetes Care* 2025;48(Suppl. 1):S181-S206

Priority: Atherosclerotic Cardiovascular Disease (ASCVD) *



ASCVD or High Risk*

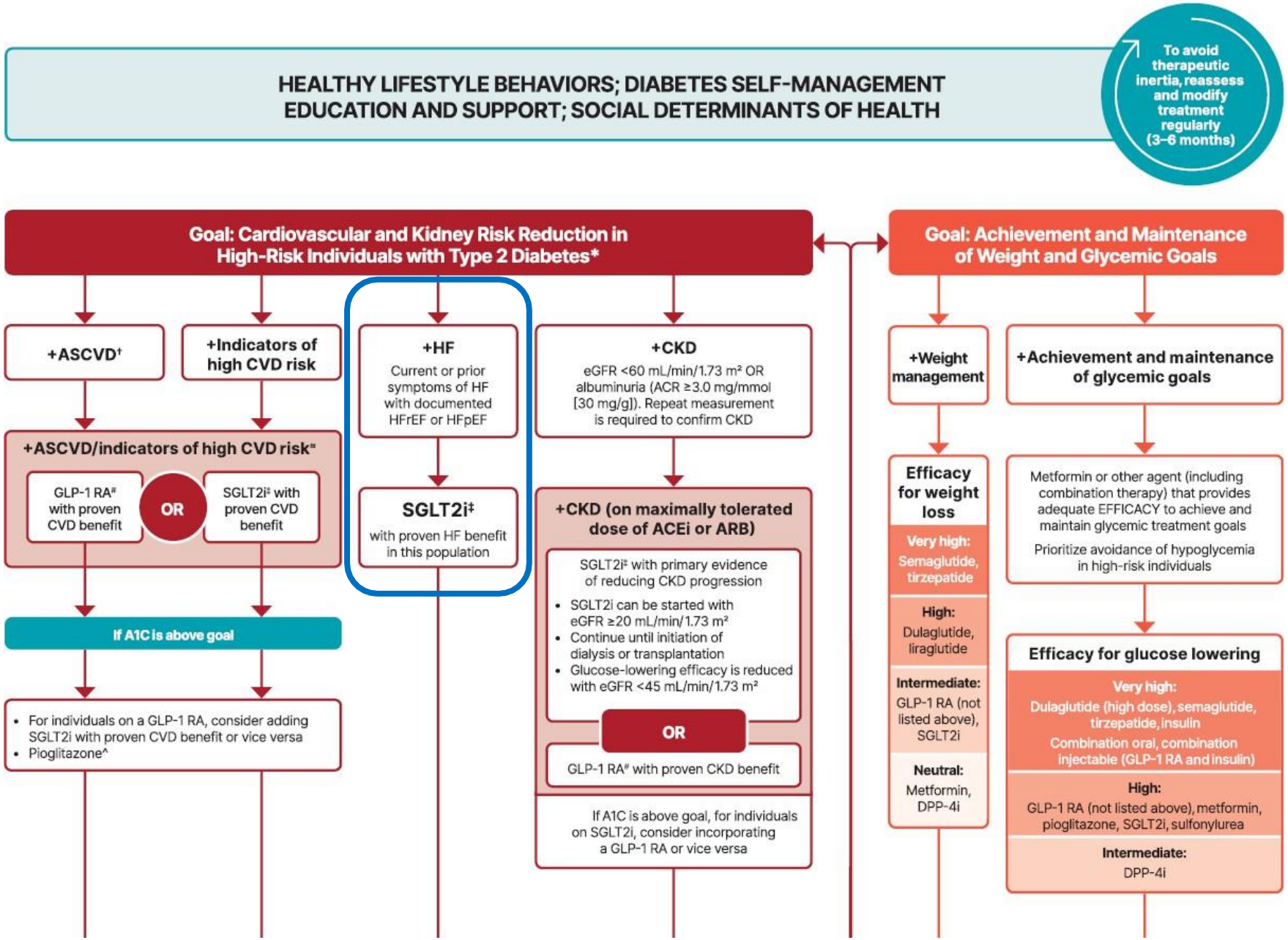
- ***STROKE***

**end-organ damage* *including retinopathy or LVH*

Or

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

Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes



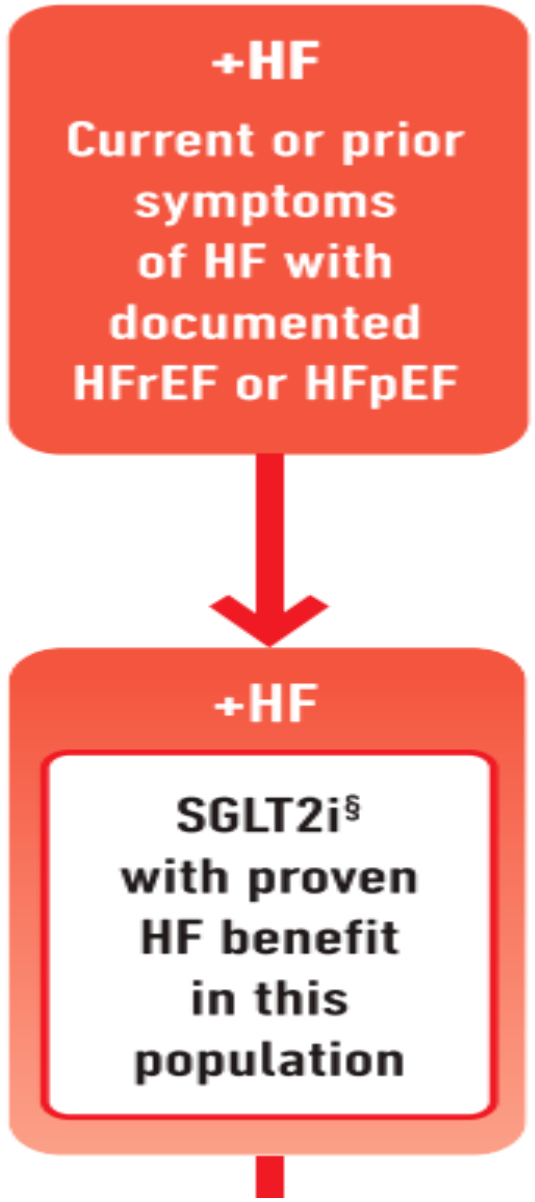
Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes - 2025 Diabetes Care* 2025;48(Suppl. 1):S181-S206

Priority: Heart Failure

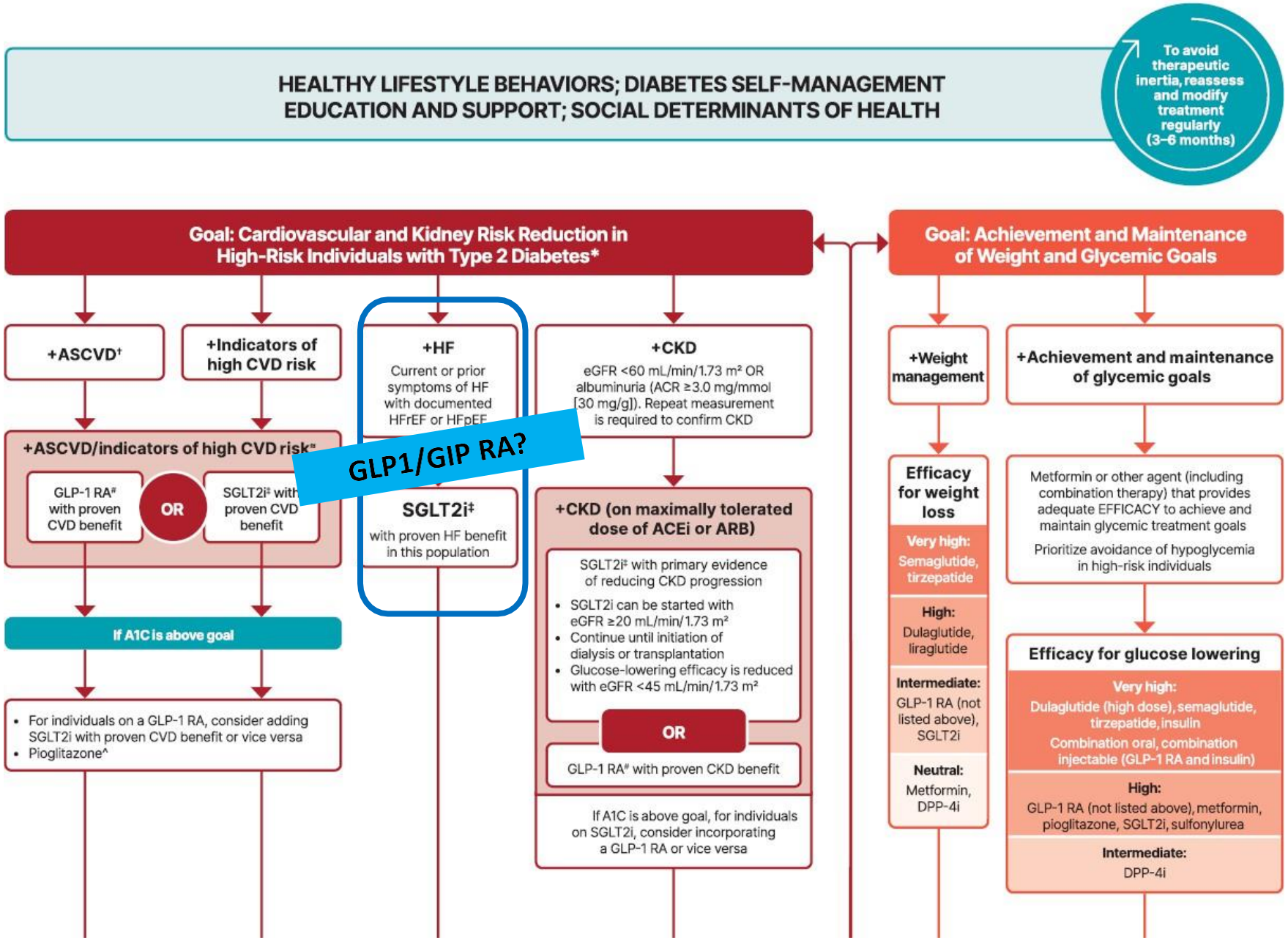
- **SGLT2i now clearly indicated for <u>both</u> HFpEF and HFrEF**

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

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



Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes

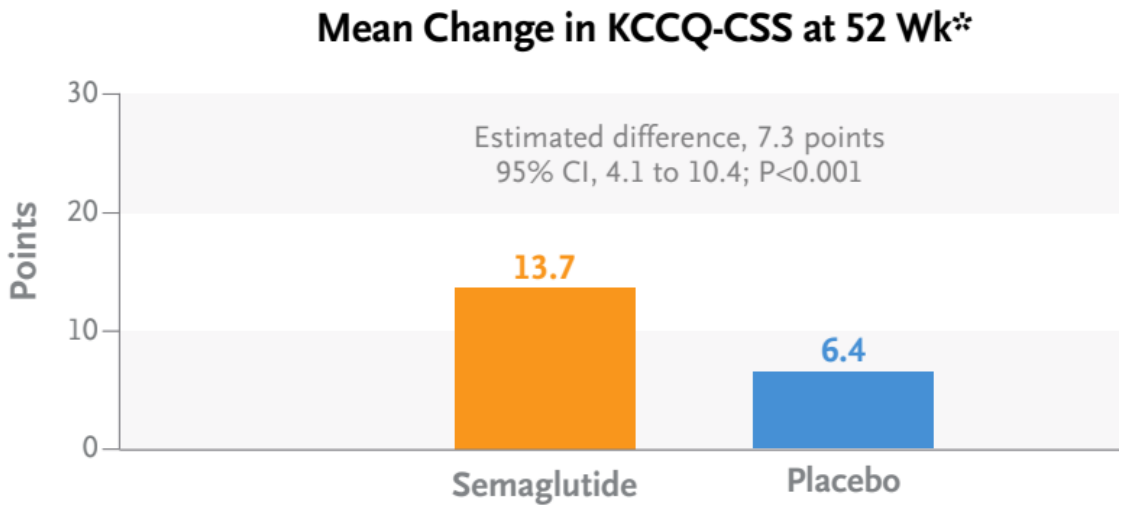


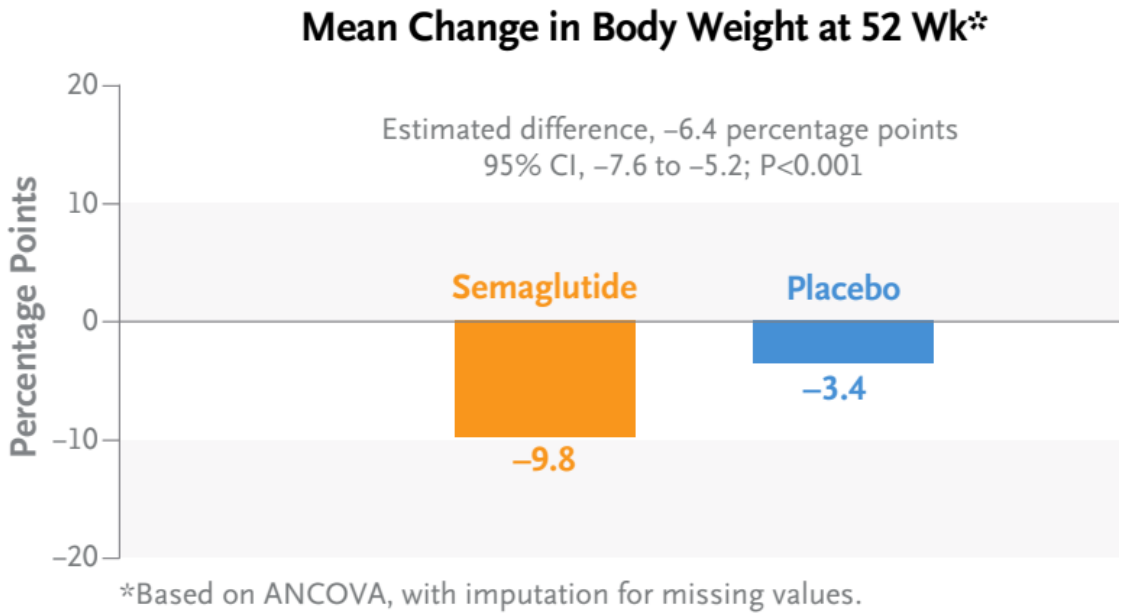
Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes - 2025 Diabetes Care* 2025;48(Suppl. 1):S181-S206

GLP-1 benefit found in HF*p*EF …*HFrEF benefit is unclear*

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**

Some concerns remain re: initiating GLP-1 RA in HFrEF due to equivocal study results with liraglutide (LIVE and FIGHT trials)

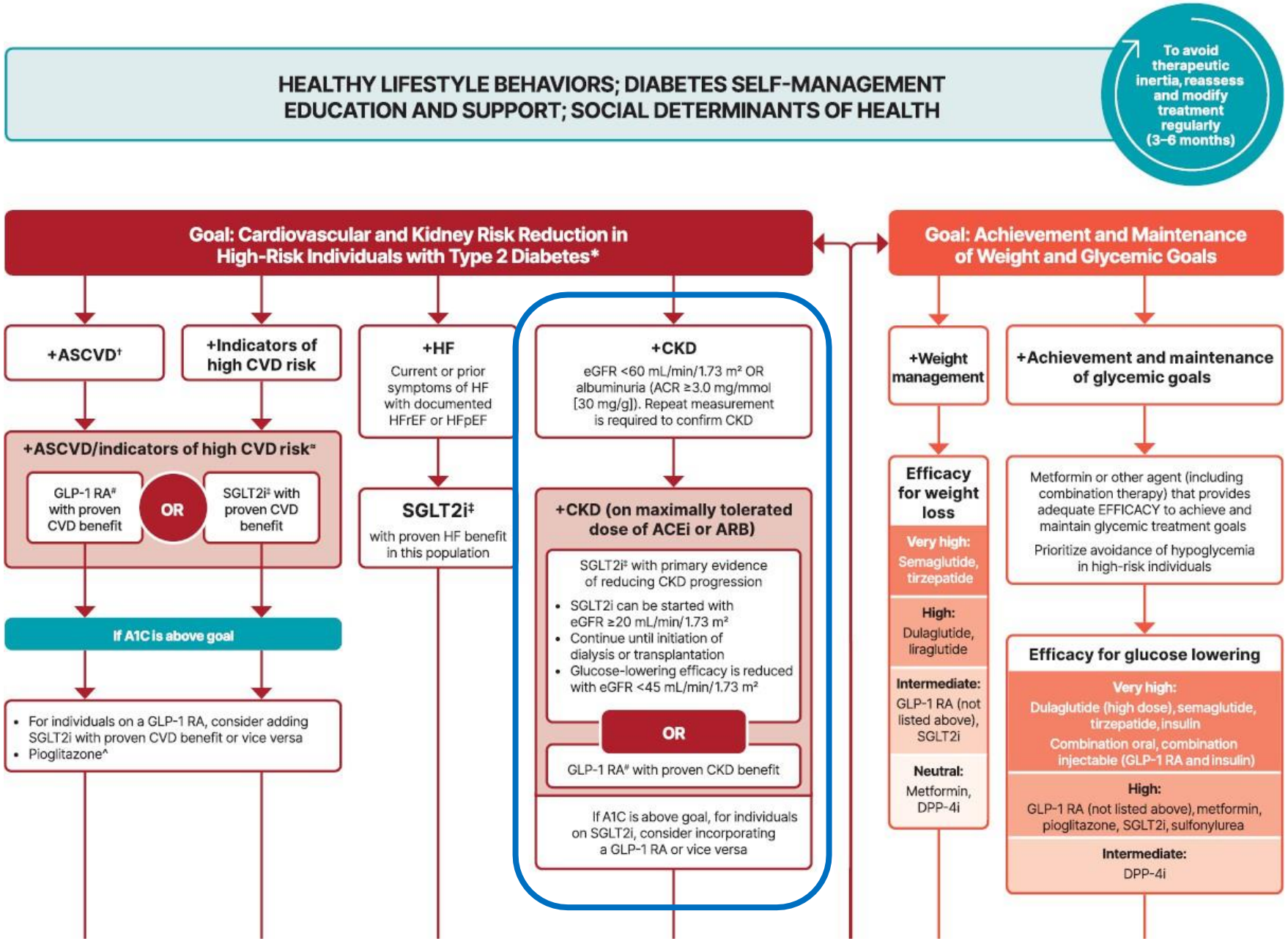




Kansas City Cardiomyopathy Questionnaire

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

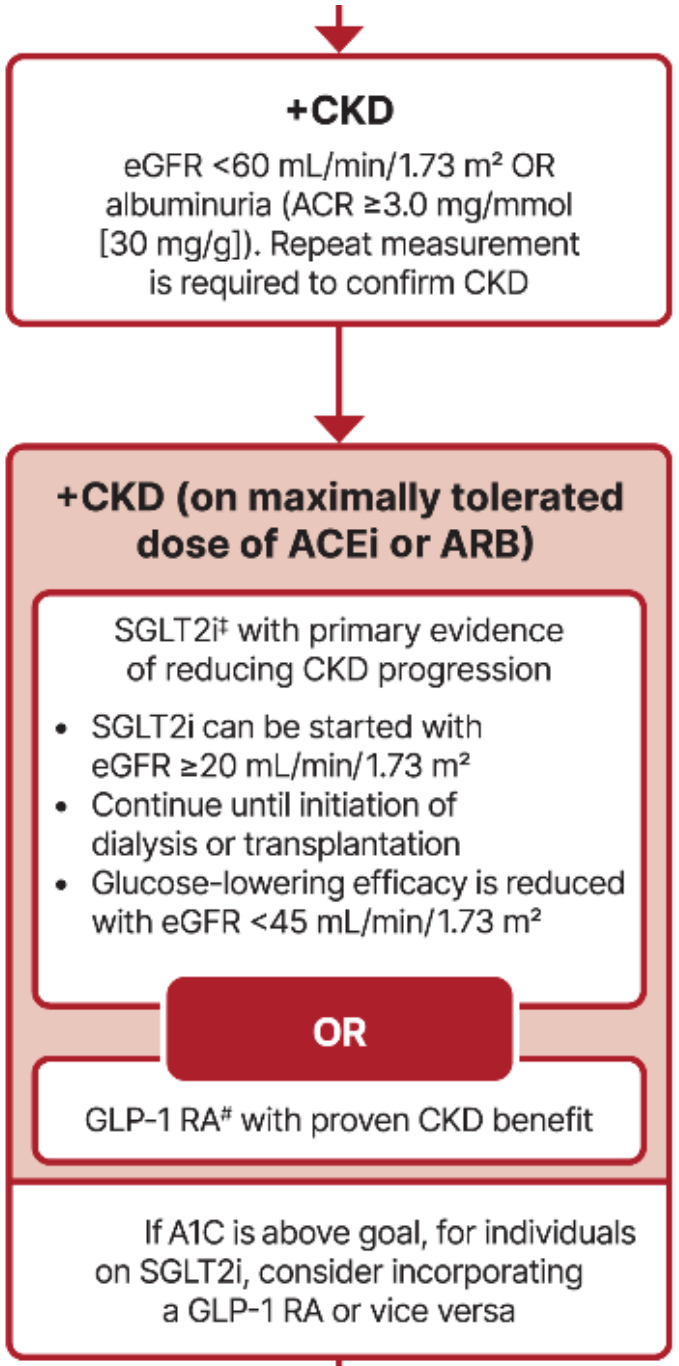
Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes



Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes - 2025 Diabetes Care* 2025;48(Suppl. 1):S181-S206

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**



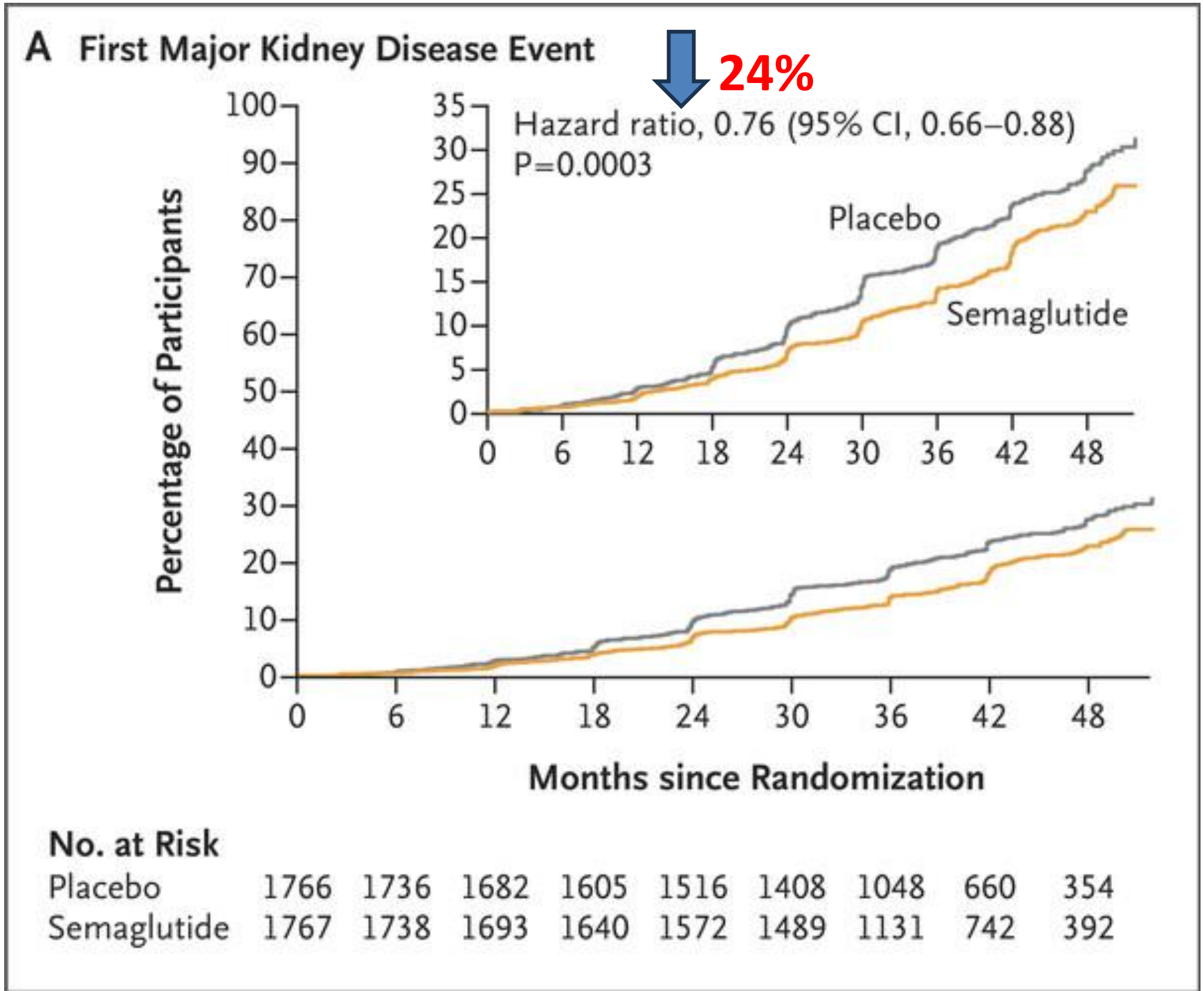
canagliflozin, dapagliflozin

empagliflozin

liraglutide semaglutide (SQ) and dulaglutide

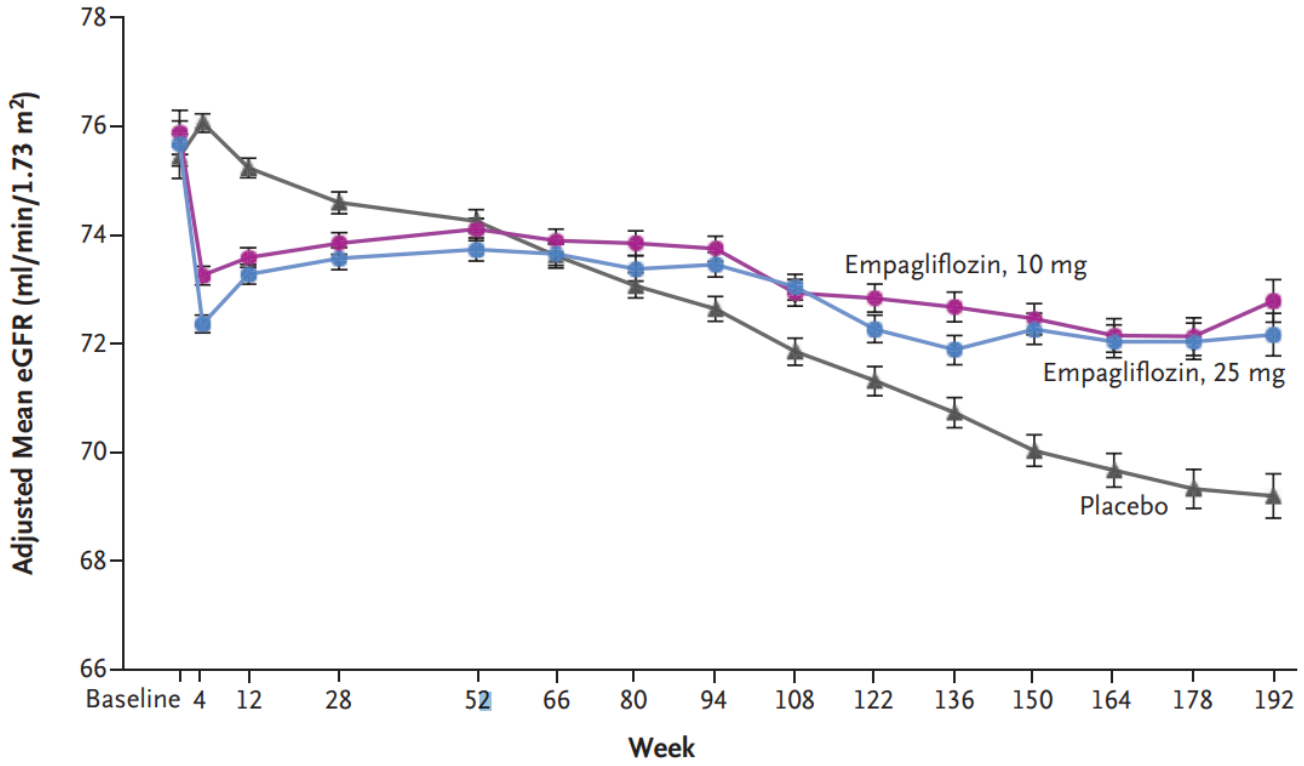
GLP-1 RA kidney benefit is probably real

FLOW primary outcome

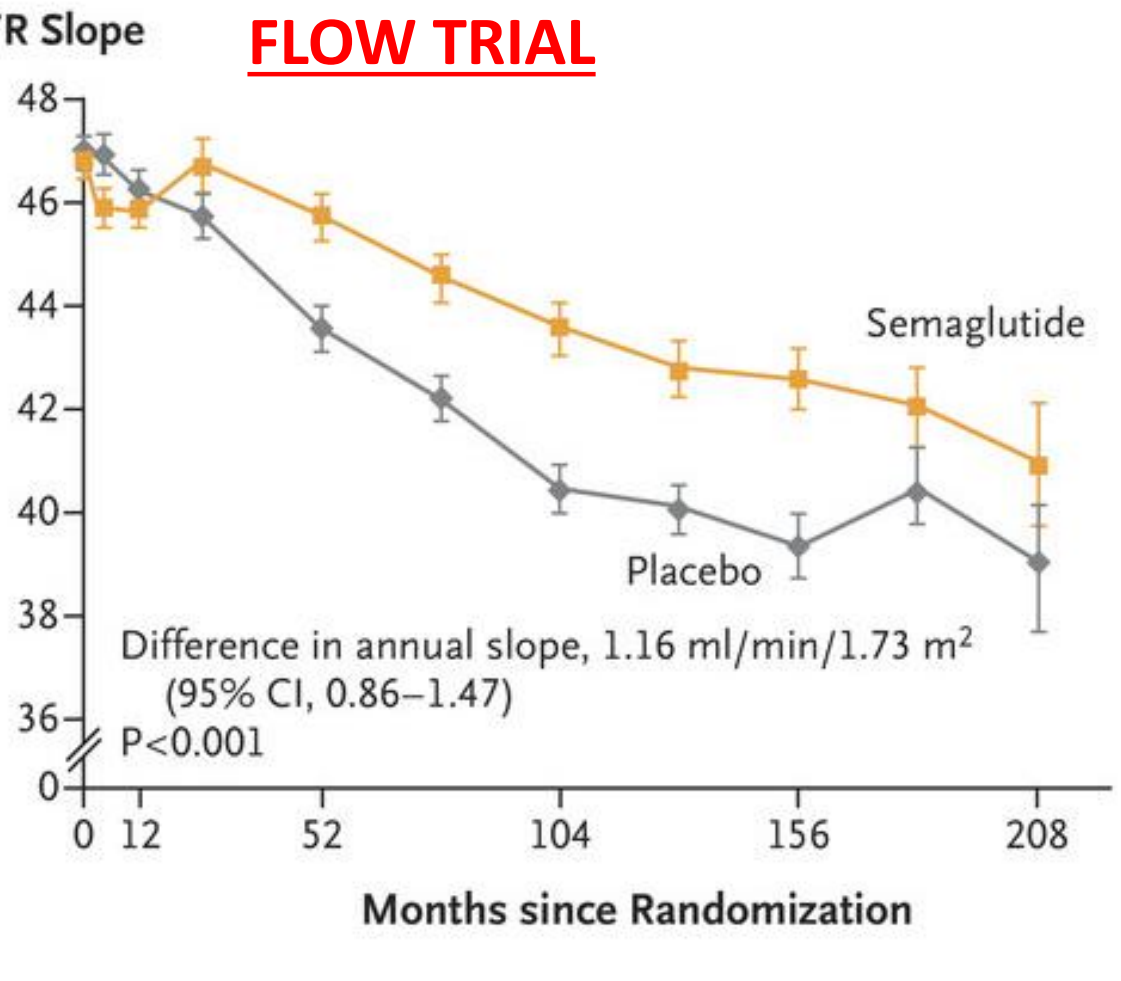


eGFR Slope: Empagliflozin vs. Semaglutide

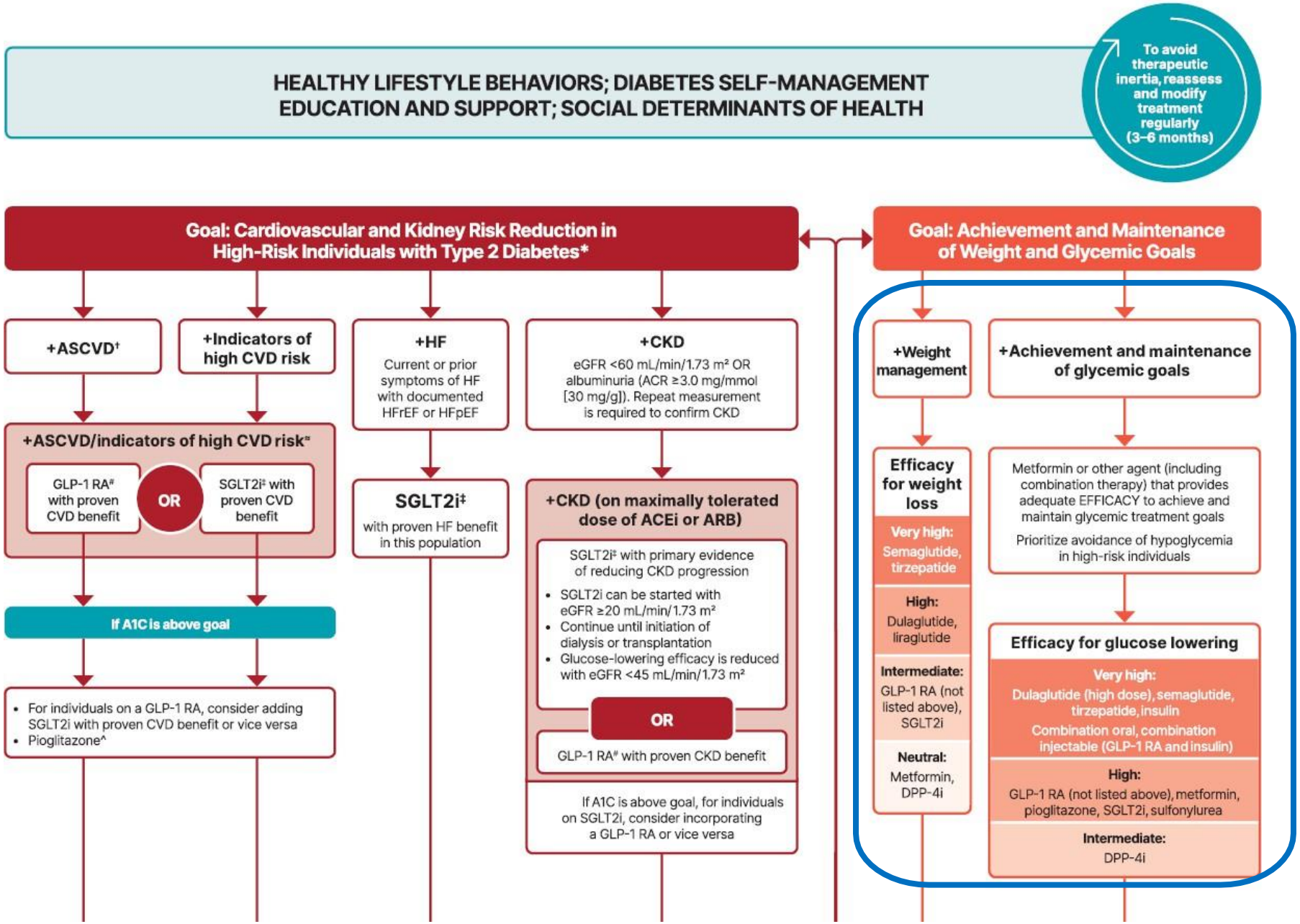
EMPA-REG OUTCOME



FLOW TRIAL

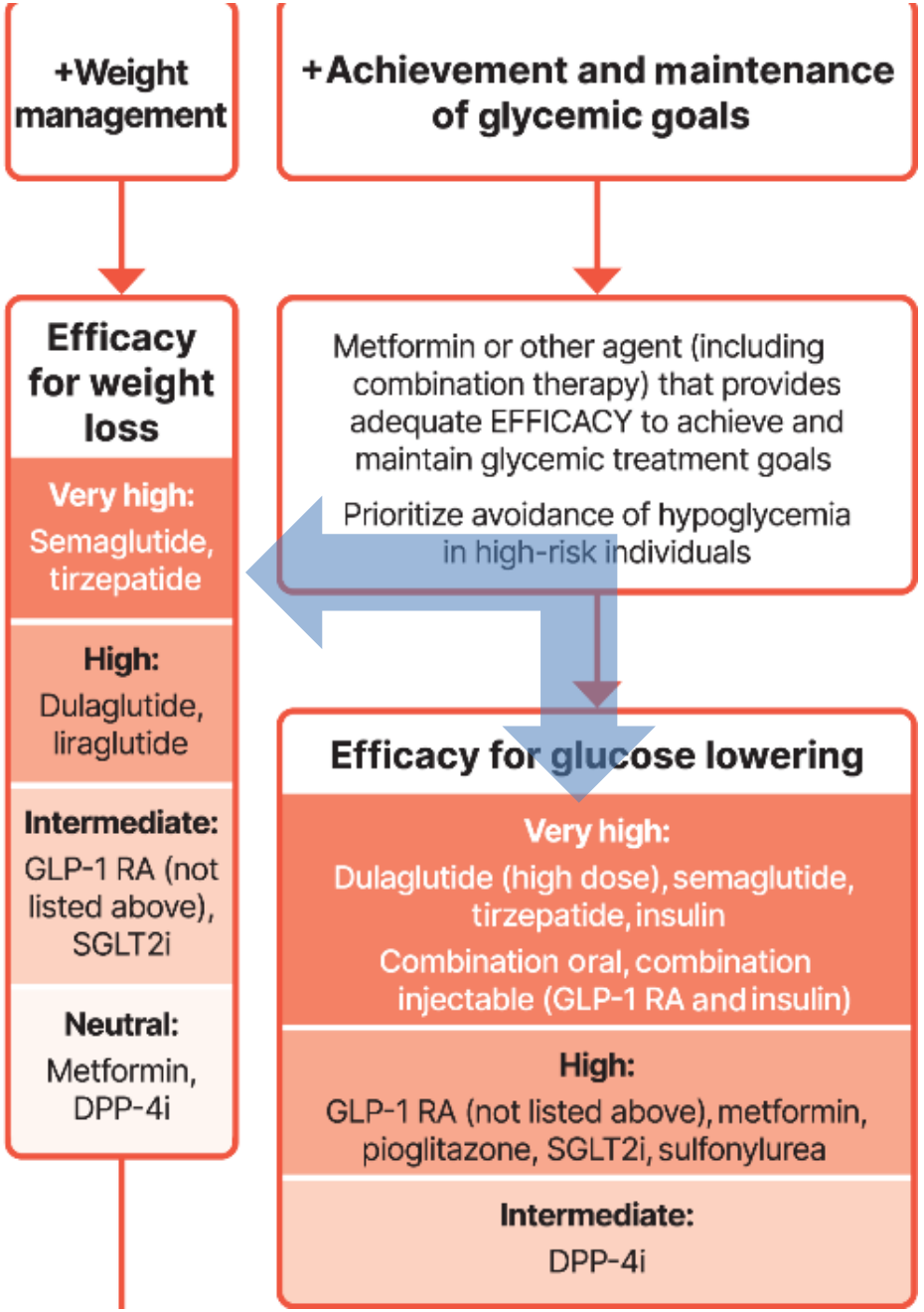


Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes



Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes - 2025 Diabetes Care* 2025;48(Suppl. 1):S181-S206

Priority: Metabolic control



Sulfonylureas

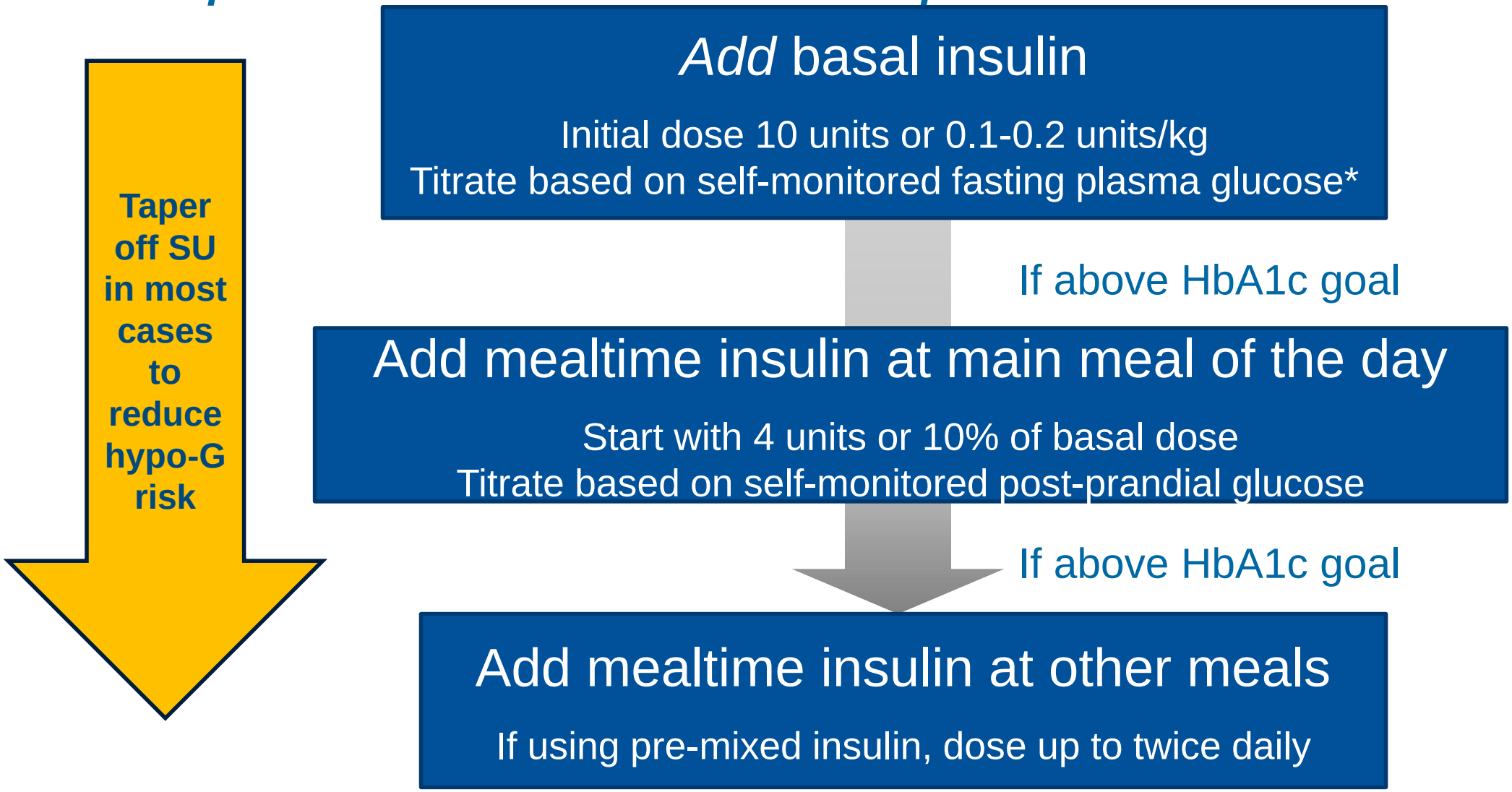
- **Choose glimepiride or gliclazide (outside US) as first line. Avoid glyburide**
  - Glimeperide is the only SU tested in a CVOT; compared with linagliptin no difference in CV risk and hypoglycemia risk was lower than expected
  - Gliclazide has lowest reported hypoglycemia risk
- **Remember that SUs 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.

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



Beta cell replacement therapy for insulin deficient diabetes: *Overview*

Whole organ pancreas transplant

- Most commonly available to those with advanced kidney disease in the form of Simultaneous Pancreas and Kidney (SPK) transplant or Pancreas after Kidney (PAK) due to increased overall benefit relative to risk
- Some centers in the US and Europe offer Pancreas alone for patients who demonstrate serious morbidity related to hyperglycemia/hypoglycemia

Cell therapy

- Cadaveric islets infused into portal vein is offered at select sites in the US; requires multiple infusions; FDA approved for those with recurrent, severe hypoglycemia
- Stem cell-derived islet cell therapies look promising but still in safety trials

Summary

- ***Priority*-focused approach to diabetes management is superior to a "glucocentric" approach**
- **Treating obesity *effectively* (10-15% loss/10-20kg)** by any means yields optimal outcomes for both prevention and disease control in type 2 diabetes
- **Long-term maintenance of lost weight/reduced** adiposity for metabolic control is best achieved with metabolic surgery, but the Rx landscape continues to expand
- **Improved access to effective therapies** for obesity-focused, holistic care of people with type 2 diabetes should be a global priority along with prevention

Selected references

- American Diabetes Association Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2025. Diabetes Care. Vol.48, S181-S206, December 2024

- 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.

- Franz, M, Evert A. The American Diabetes Association Guide to Nutrition Therapy for Diabetes,3rd ed. Arlington, VA: American Diabetes Association; 2017:17-44. (update in 2025)