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

Diabetes Overview 2025

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

NIH

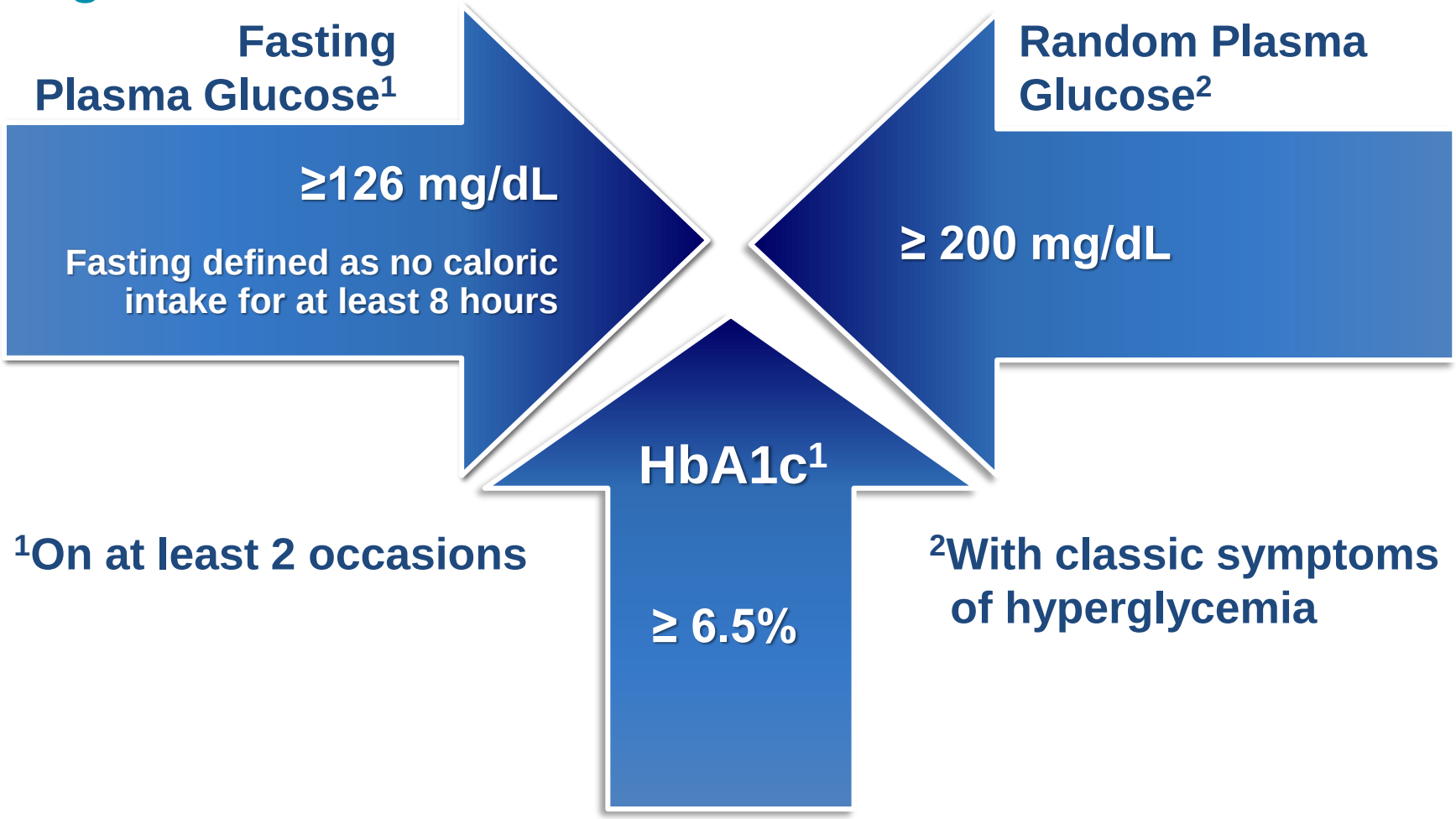
Patient-Centered Outcomes Research Institute

Learning Objectives

- Review epidemiology, when (and why) to think beyond type 2 and updates around patient assessment
- Understand the current noninsulin pharmacologic therapies for type 2 diabetes from key perspectives: potency for glucose and weight control and combination therapy
- Guidelines update: Learn how to individualize therapeutic strategies for type 2 diabetes based on comorbidities, goals as well as concerns and side effects

Diabetes definition has not changed in 30 years

Diabetes is Persistent Hyperglycemia that over time leads to organ damage



[1]On at least 2 occasions

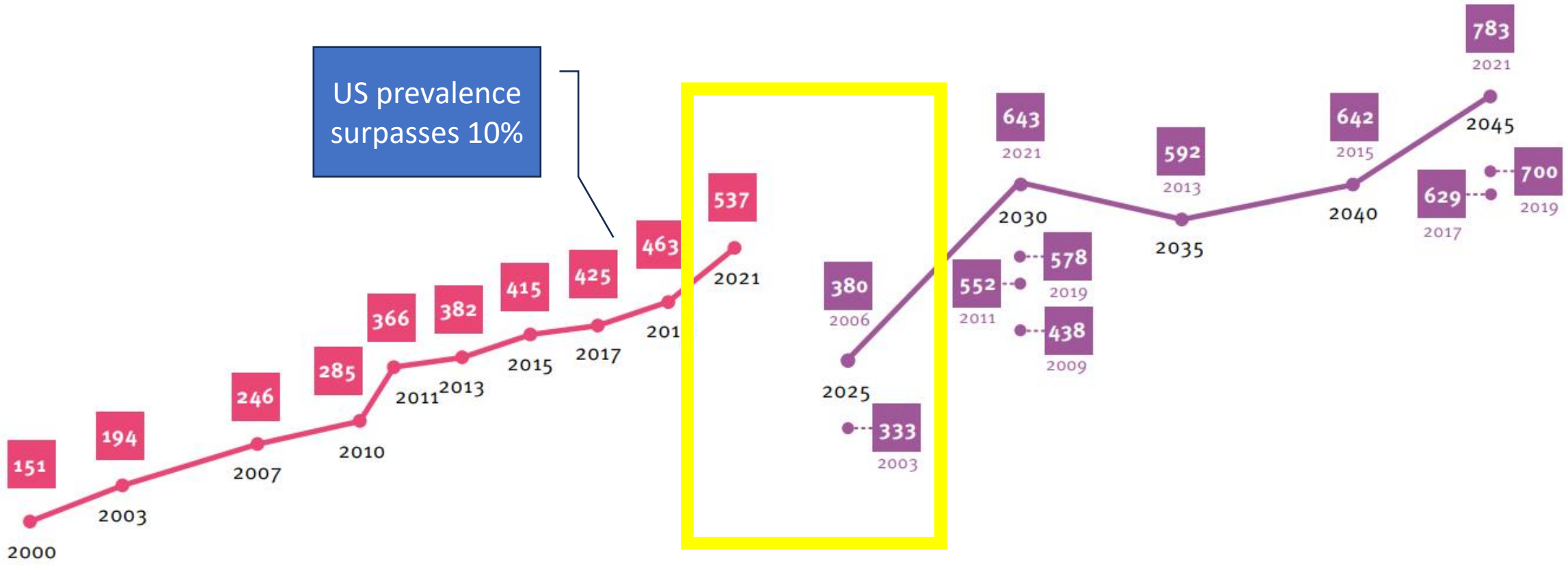
[2]With classic symptoms of hyperglycemia

What is Glycemic Control? A Case of *Target* vs. *Achieved*

Organization	HbA1c goal
American Association of Clinical Endocrinologists (AACE) – American College of Endocrinology (ACE)	**≤6.5%**
American Diabetes Association (ADA) – European Association for the Study of Diabetes (EASD) ADA Standards of Care	**≤7% - emphasis on *target A1c***
American College of Physicians (ACP) -- endorsed by American Academy of Family Physicians (AAFP)*	**7-8% - emphasis on *achieved A1c***
American Geriatric Society (AGS)*	**7.5-8%**

* Both statements have caveats allowing for more aggressive HbA1c goals based on patient preference and overall health.

GLOBALLY: OUTPACING PROJECTIONS



Key

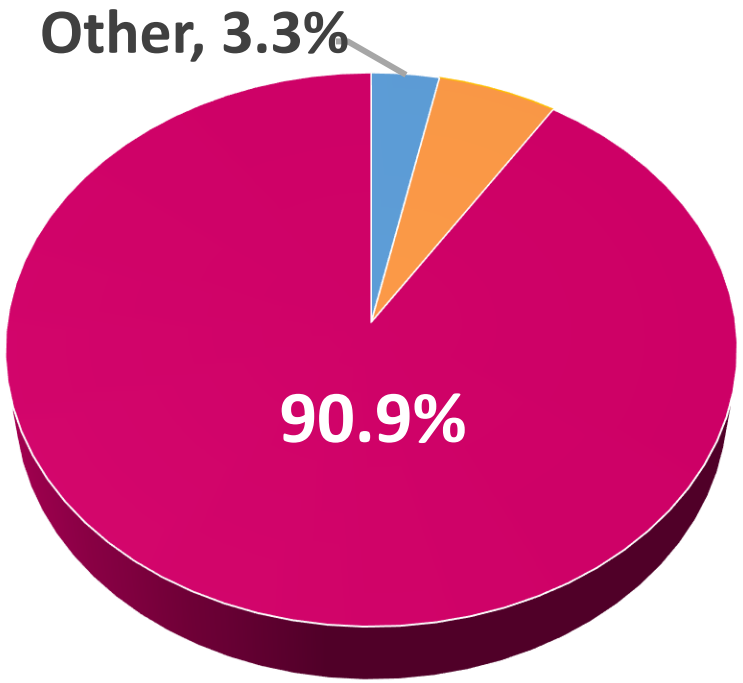
151 Number of people with diabetes in millions

Key

333 Projection in millions

2003 Year projection made

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***

Slide :Courtesy of Miriam Udler, MD

Case 1: Jerome

38 year old previously healthy man is seeing you 1 week after presenting to the ED with severe fatigue, frequent urination and presyncope at a football game. In the ED he had the following lab results:

- Glucose 320mg/dl
- Bicarbonate 19 with anion gap of 15
- 2+ ketones urine

He was treated with IV fluids, 8 units of regular insulin and was discharged home on metformin

One year ago he had an HA1c test performed due to complaints about poor concentration and fatigue. It was 5.9%

Case 1: Jerome

There is no prior family history of diabetes
His medications include a multivitamin daily
His BMI is 25 and he has recently lost 8lbs. BP is 126/68 with HR 98. He appears overall fatigued.
His blood glucose is 225mg/dl and he has not yet eaten breakfast

Which test is the most useful to guide next steps in therapy?

A. HDL
B. LDL
C. Glutamic acid decarboxylase antibody
D. C-peptide

Case 1: Jerome

There is no prior family history of diabetes
His medications include a multivitamin daily
His BMI is 25 and he has recently lost 8lbs. BP is 126/68 with HR 98. He appears overall fatigued.
His blood glucose is 225mg/dl and he has not yet eaten breakfast

Which test is the most useful to guide next steps in therapy?

A. HDL
B. LDL
C. Glutamic acid decarboxylase antibody
D. C-peptide

When to suspect autoimmune/type 1 diabetes?

Normal or mildly overweight

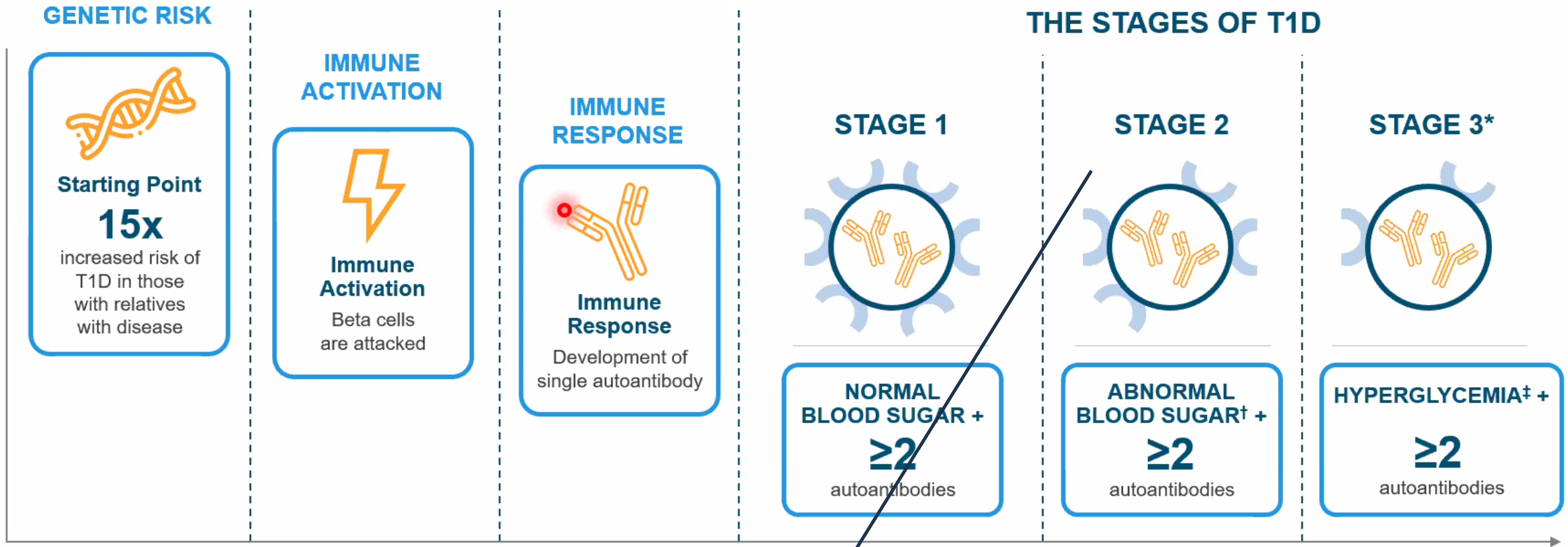
Lack of family history

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?

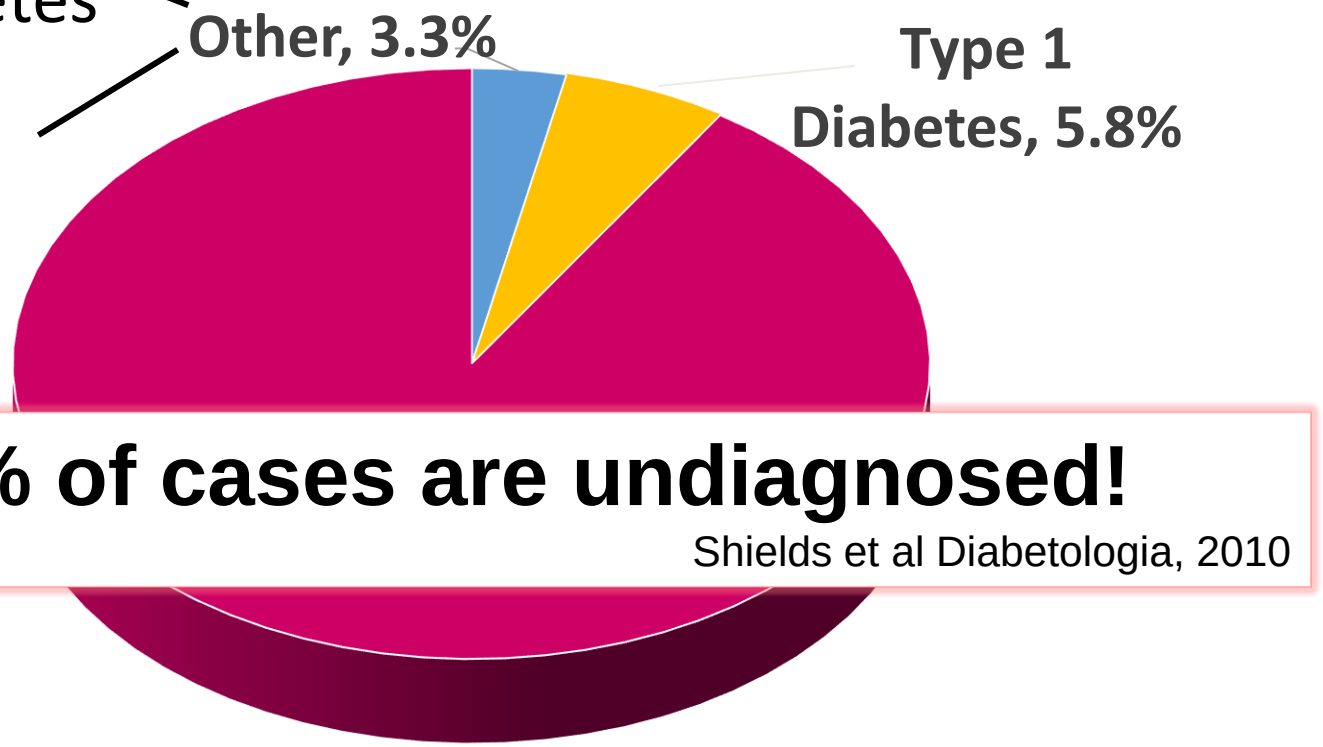
Diabetes caused by variation in <u>1 gene.</u>

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

Is it really important to diagnose?

Most patients do respond to usual T2d therapy

However many are mis-treated with insulin therapy and can come off with a sulfonylurea

Compared to Type 2

Lower BMI

Younger Age at Dx

Compared to Type 1

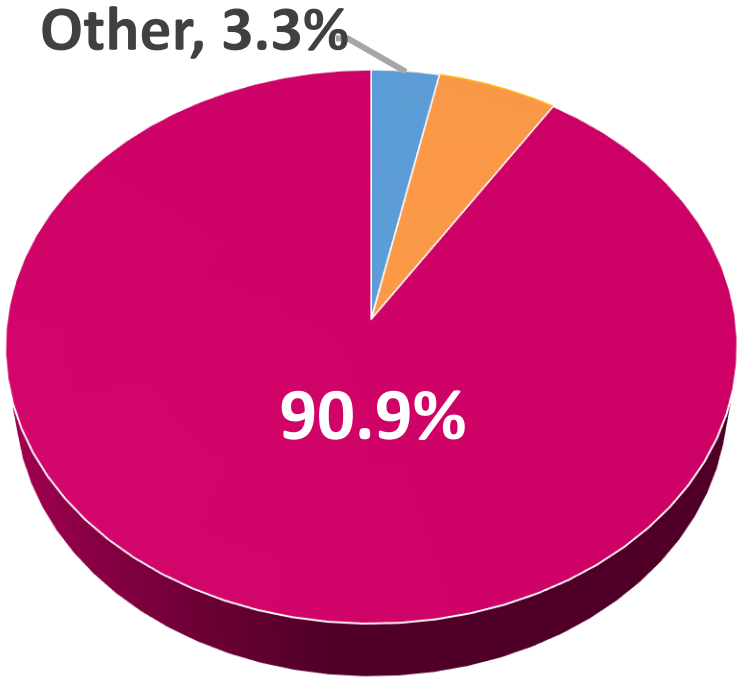
Older Age at Dx

Negative Antibodies

Detectable C-Peptide >3 Yrs post Dx

No history of DKA

Breakdown of diabetes in United States

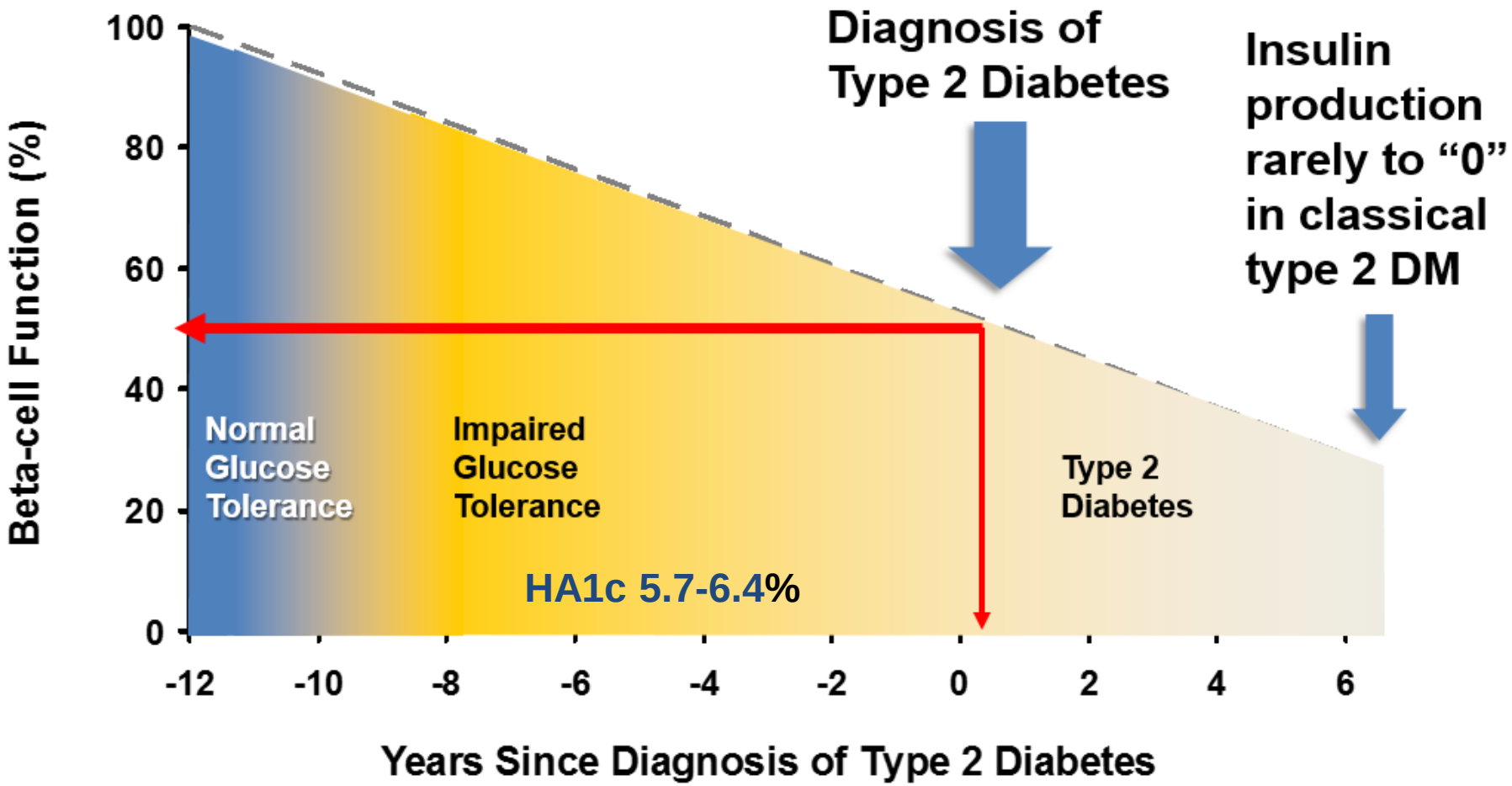


Autoimmune diabetes 5.8%:

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

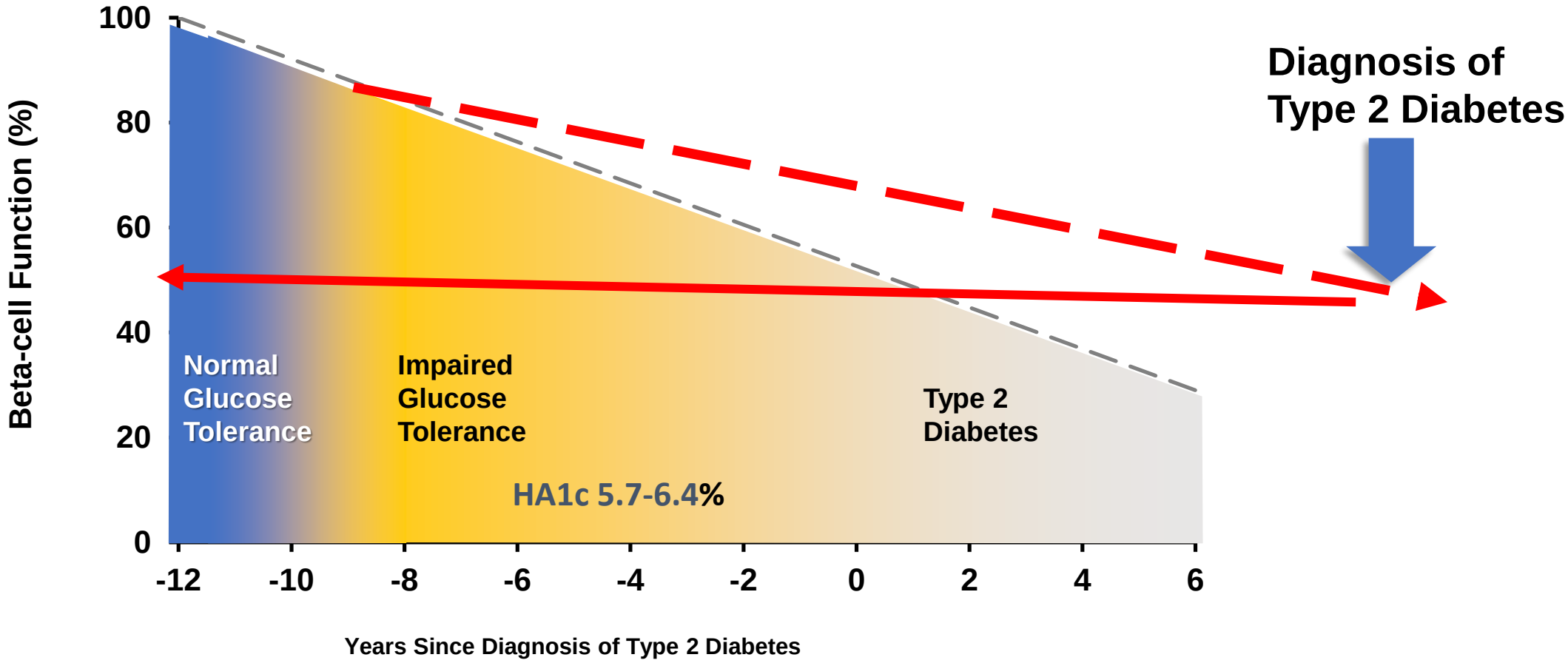
Type 2 diabetes: ***Older age, higher BMI, features of metabolic syndrome***

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 or GLP-1 RA/GIP dual agonist

When to *consider* pharmacologic therapy for prediabetes?

- A1c >6%: In the DPP progression was more predictable with higher baseline A1c; other data in predicting GDM as well
- 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

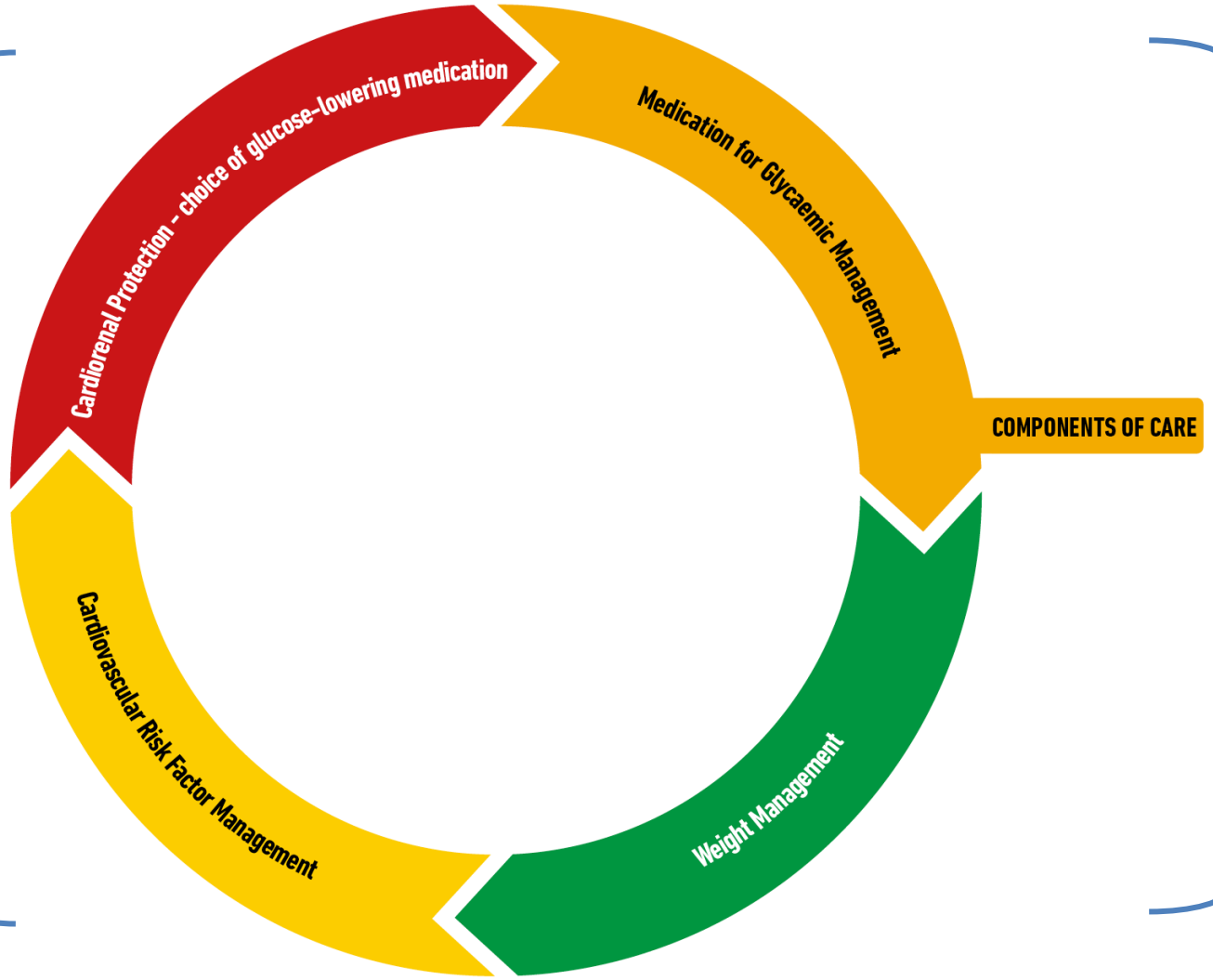
When to *strongly encourage* pharmacologic therapy for prediabetes?

- Woman of reproductive age: METFORMIN – 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.

Current Guidance: for Most T2D Weight reduction = A1c reduction

"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.

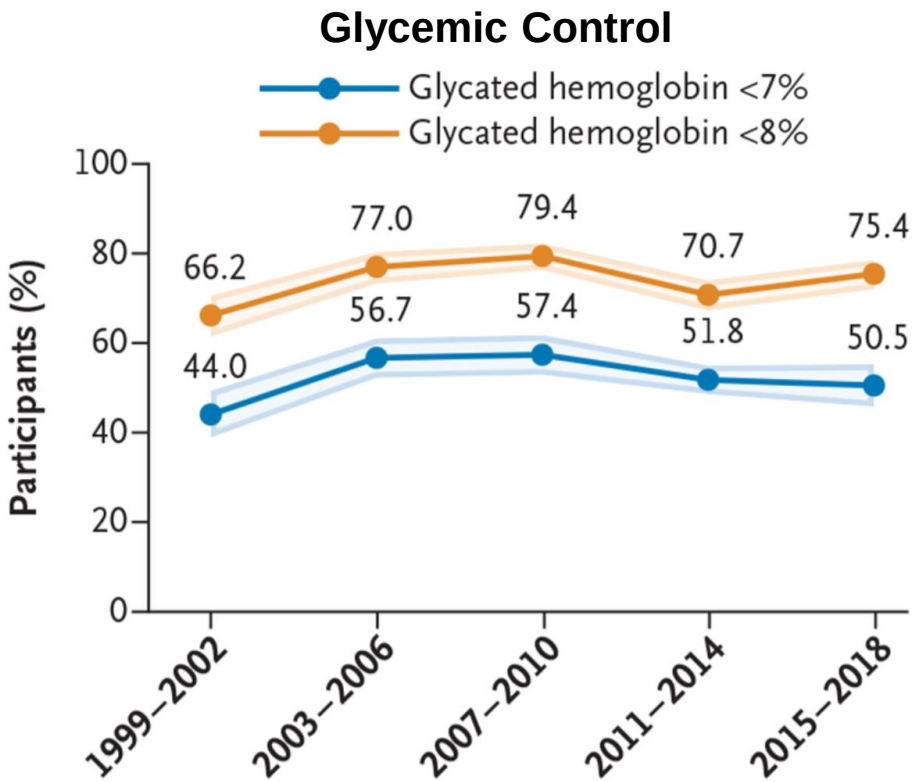
Newer guidance for Diabetes care in recent years

- **Select GLP-1 RA before insulin for type 2 diabetes with high A1c unless insulin deficiency is present**
- **Screen all type 2 DM pts for MASLD with the Fib 4 test**
- **Screen high risk patients for heart failure with the N-terminal Pro B-type Natriuretic Peptide (NT-proBNP) Test**
- **Consider measuring LP(a) to identify subsets of patient at risk of accelerated CAD**

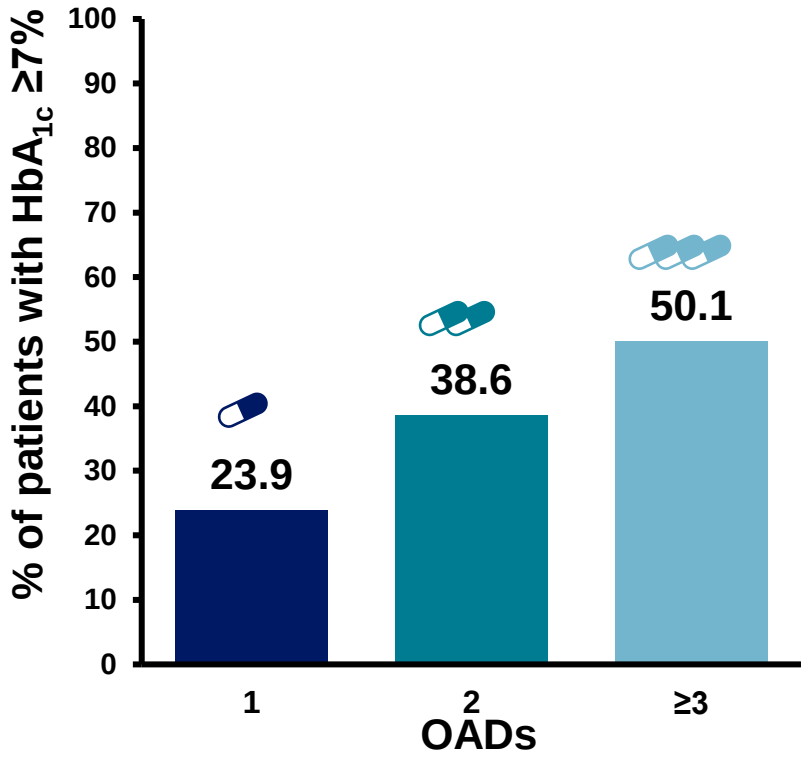
What Factors Finally Drove This Guideline Evolution?

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
NIDDK
Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study

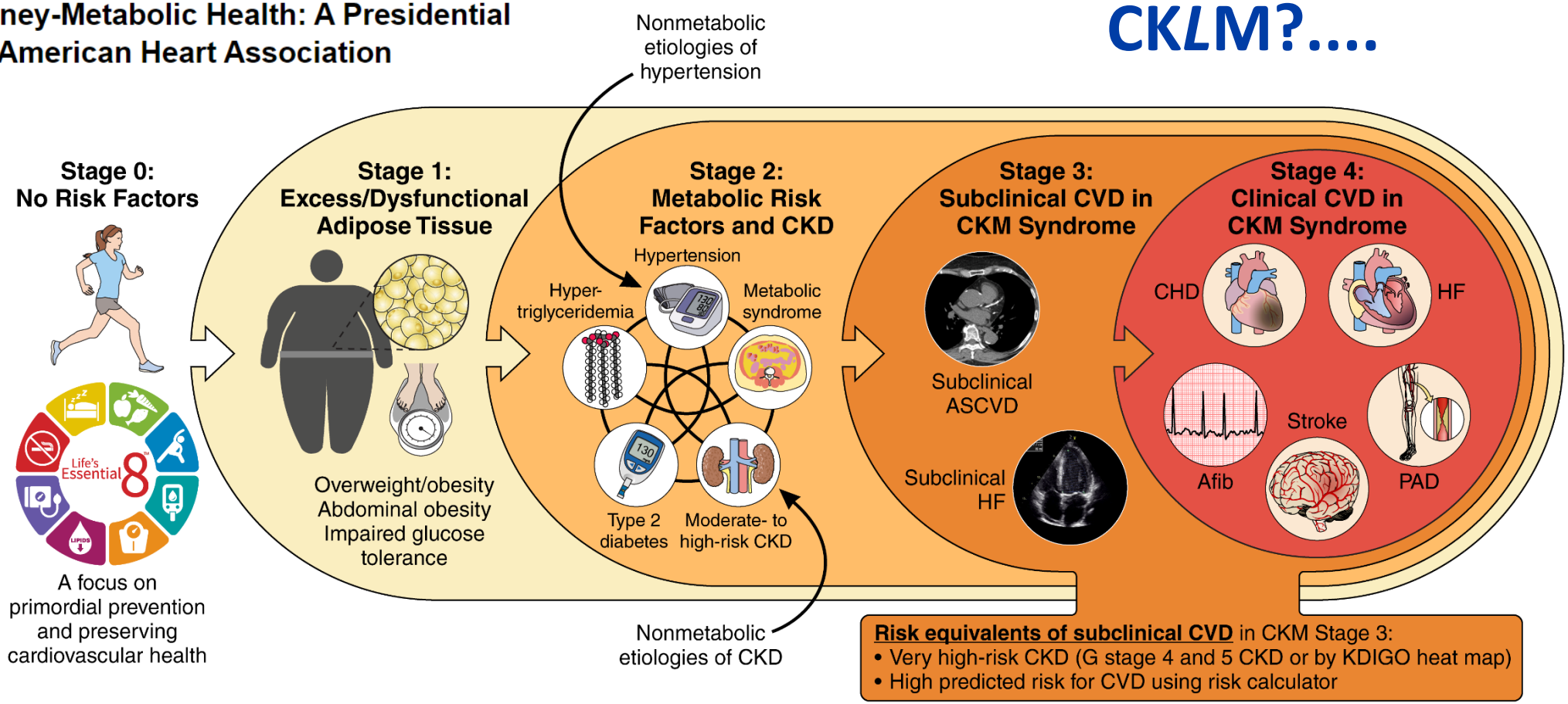
70% of subjects had an A1c >7% by study end

Cardiovascular –Kidney-Metabolic Health …Excess adipose is the problem

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

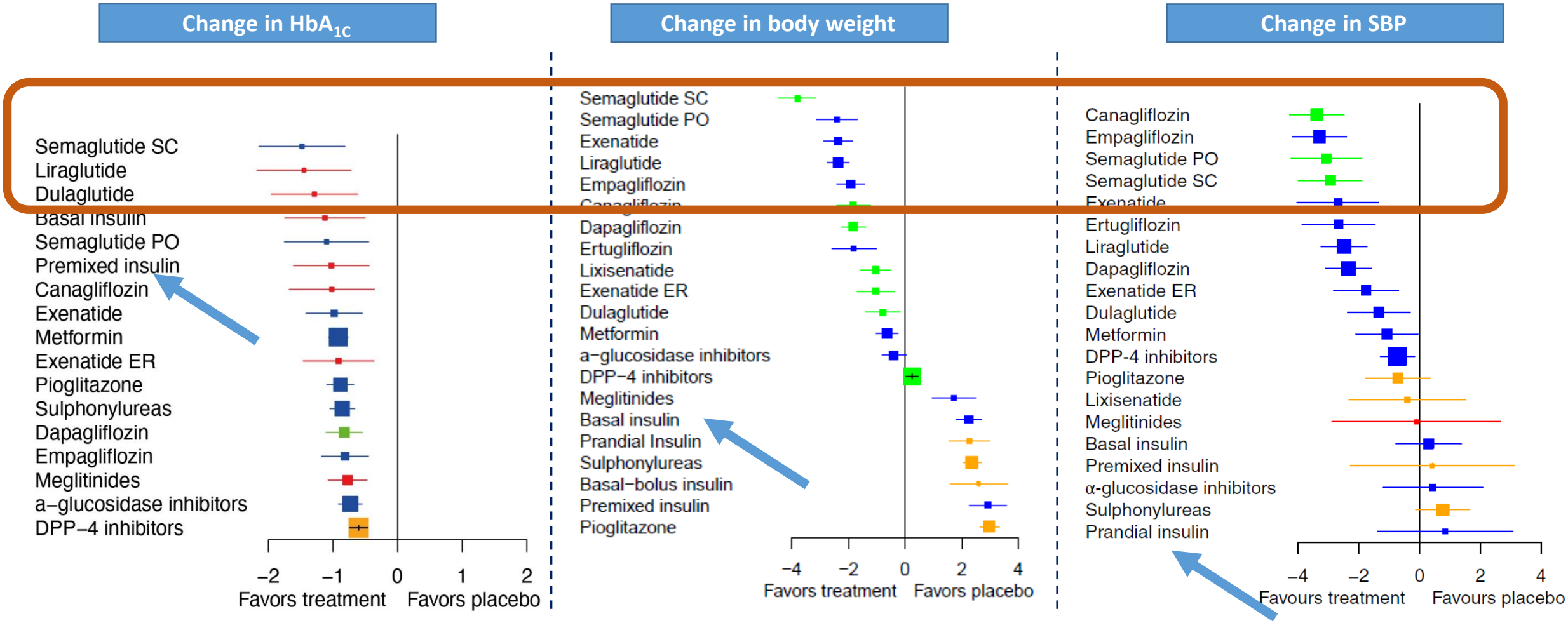
AHA PRESIDENTIAL ADVISORIES

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



May, 2024

Increased Metabolic Effectiveness of Diabetes Meds that reduce adipose mass - *GLP-1 rec'd before insulin*



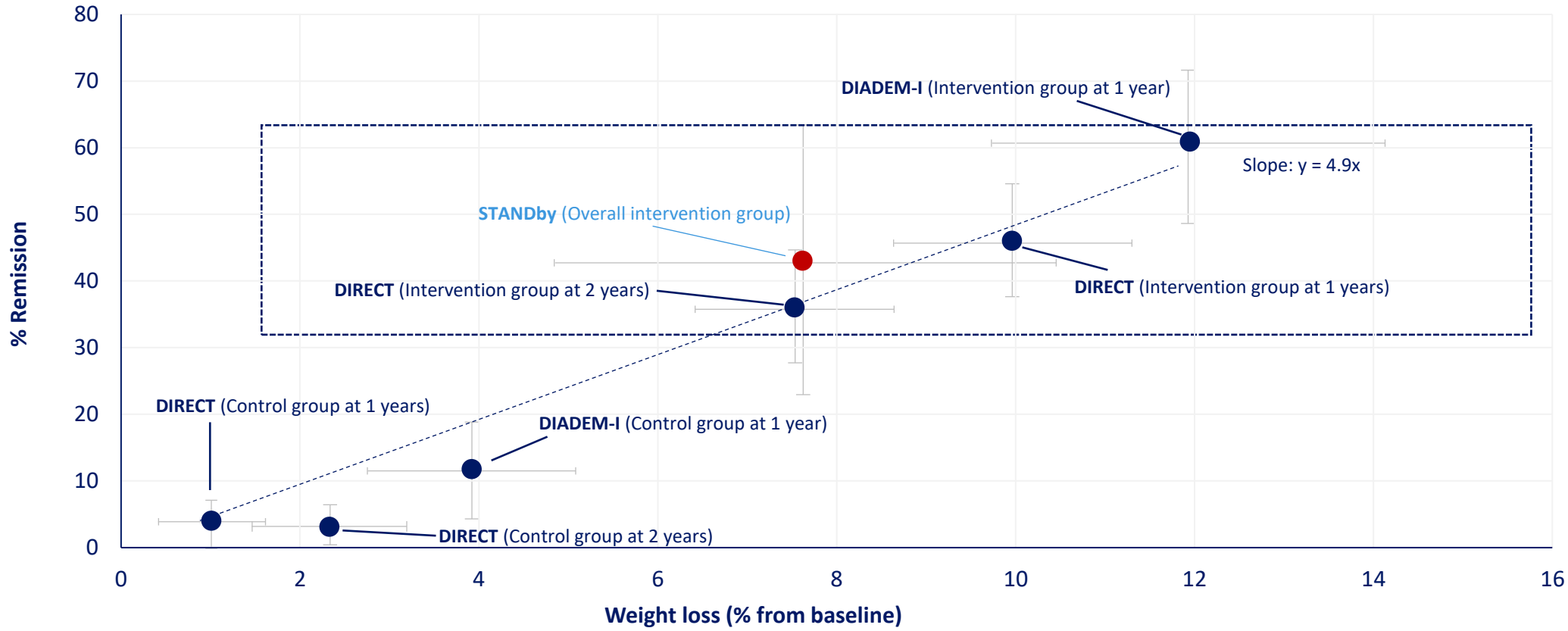
HbA_{1c}, glycated hemoglobin; SBP, systolic blood pressure

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

Are medications always necessary to treat type 2 diabetes?

Diabetes Remission in "Real World" Studies Is Driven by >10% Weight Loss in Year 1

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

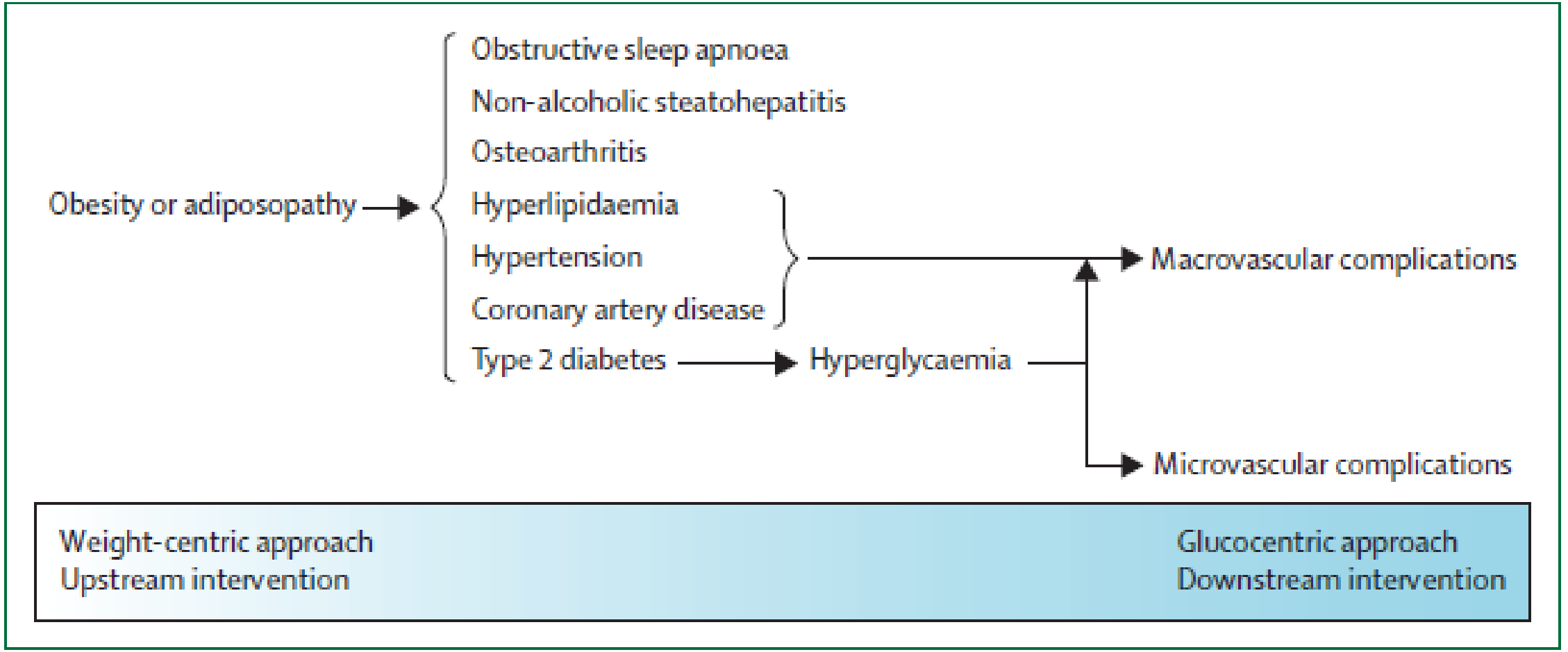
Conclusion

- **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.

Adopting an "Upstream" Weight-centric Approach versus a Glucocentric Management Approach



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

ARMMS T2D STUDY:
Bariatric Surgery vs. Medical Management

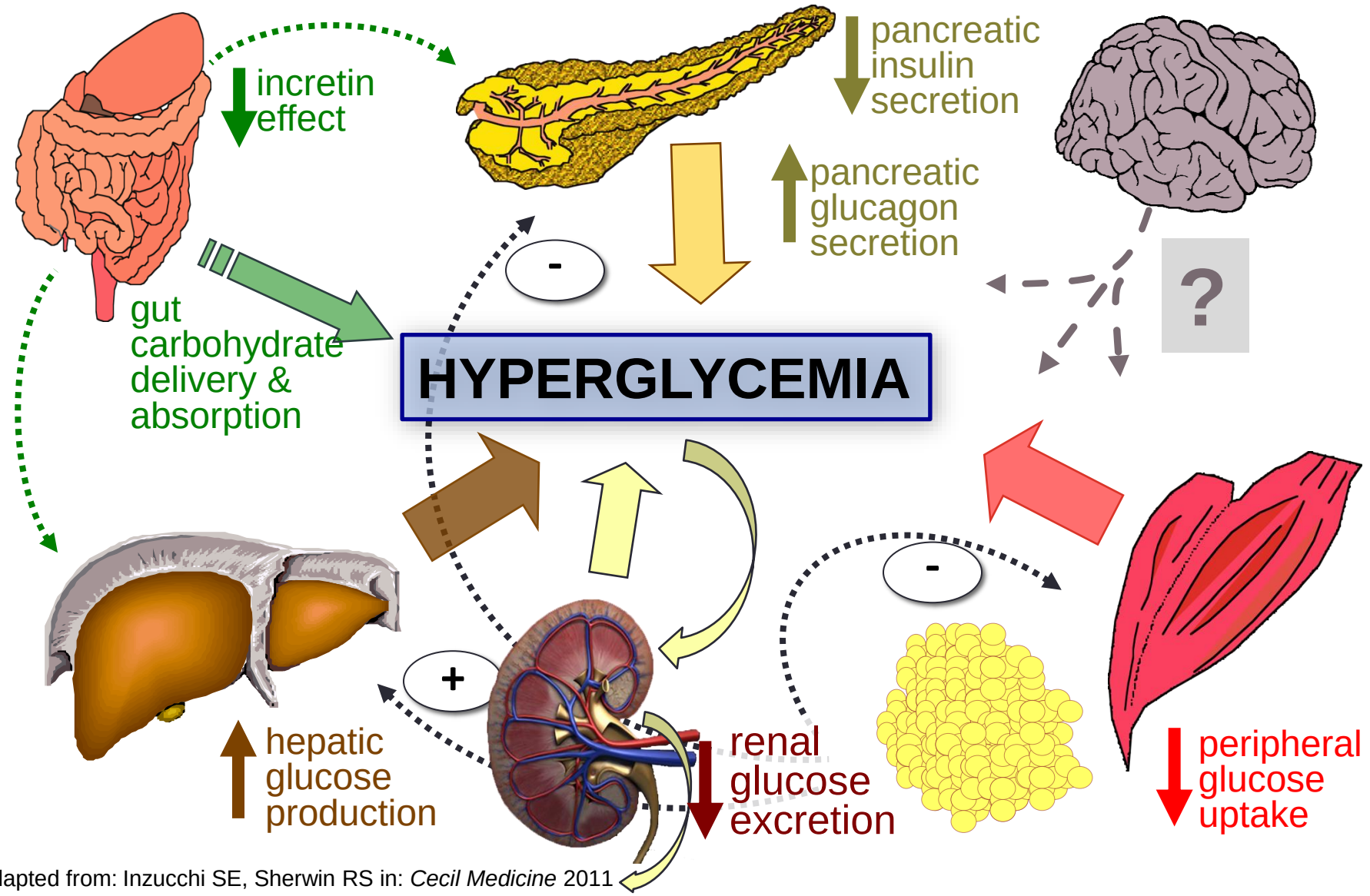
	Bariatric Surgery *ARMMS T2D STUDY	Medical/lifestyle Management ARMMS T2D STUDY
A1c reduction	1.6%	0.2%
Diabetes Remission (off medications)	**38% at 3 years** 13% at 12 yrs	**3% at 3 years** 0% 12 years
% Weight loss	**23% at 3 yrs**	**5% at 3 yrs**
Deaths	**2**	**2**

*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.

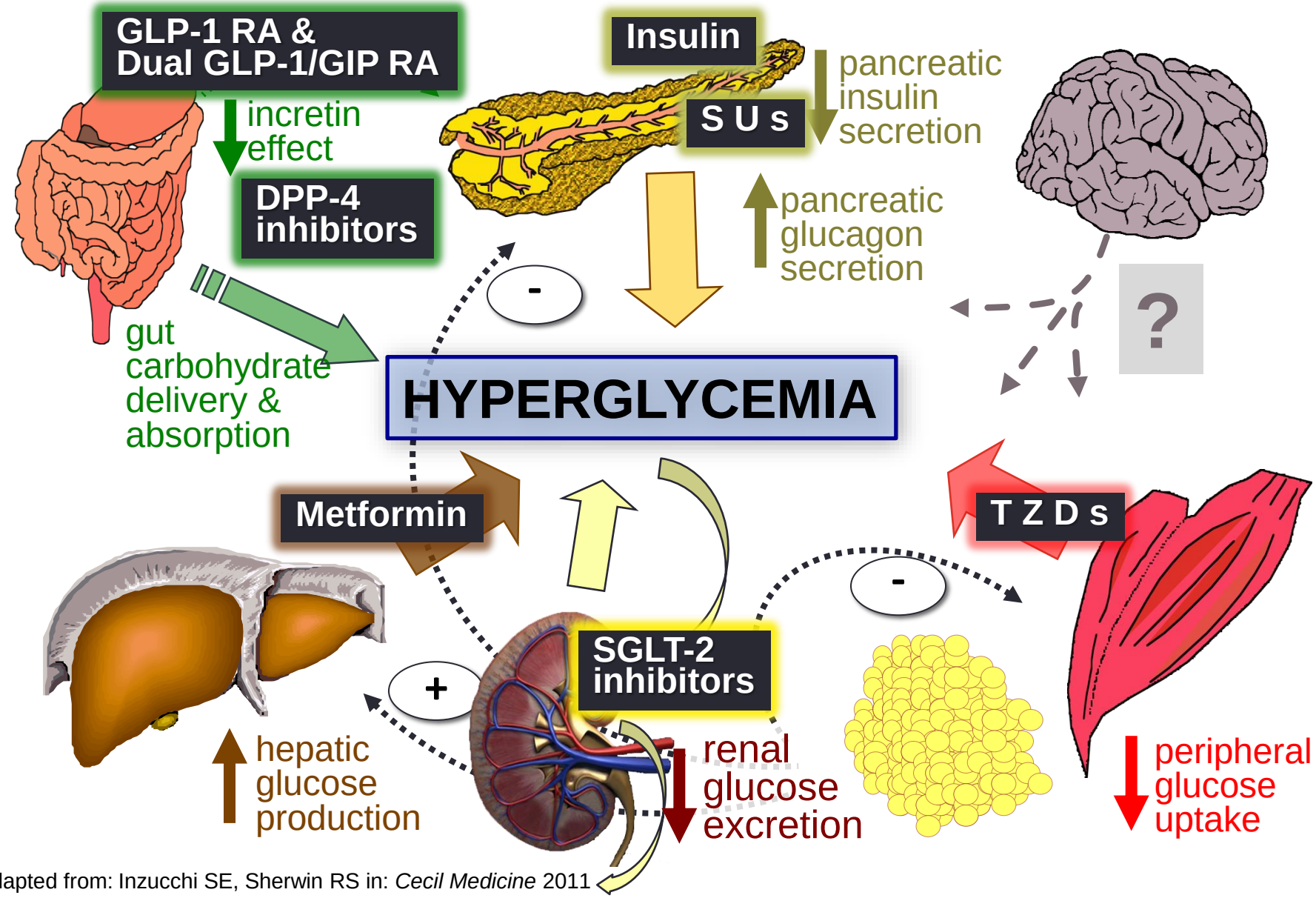
What Are the Options for Medication Management in Type 2 Diabetes: *An Overview*

Multiple Complex Pathophysiological Abnormalities in T2DM

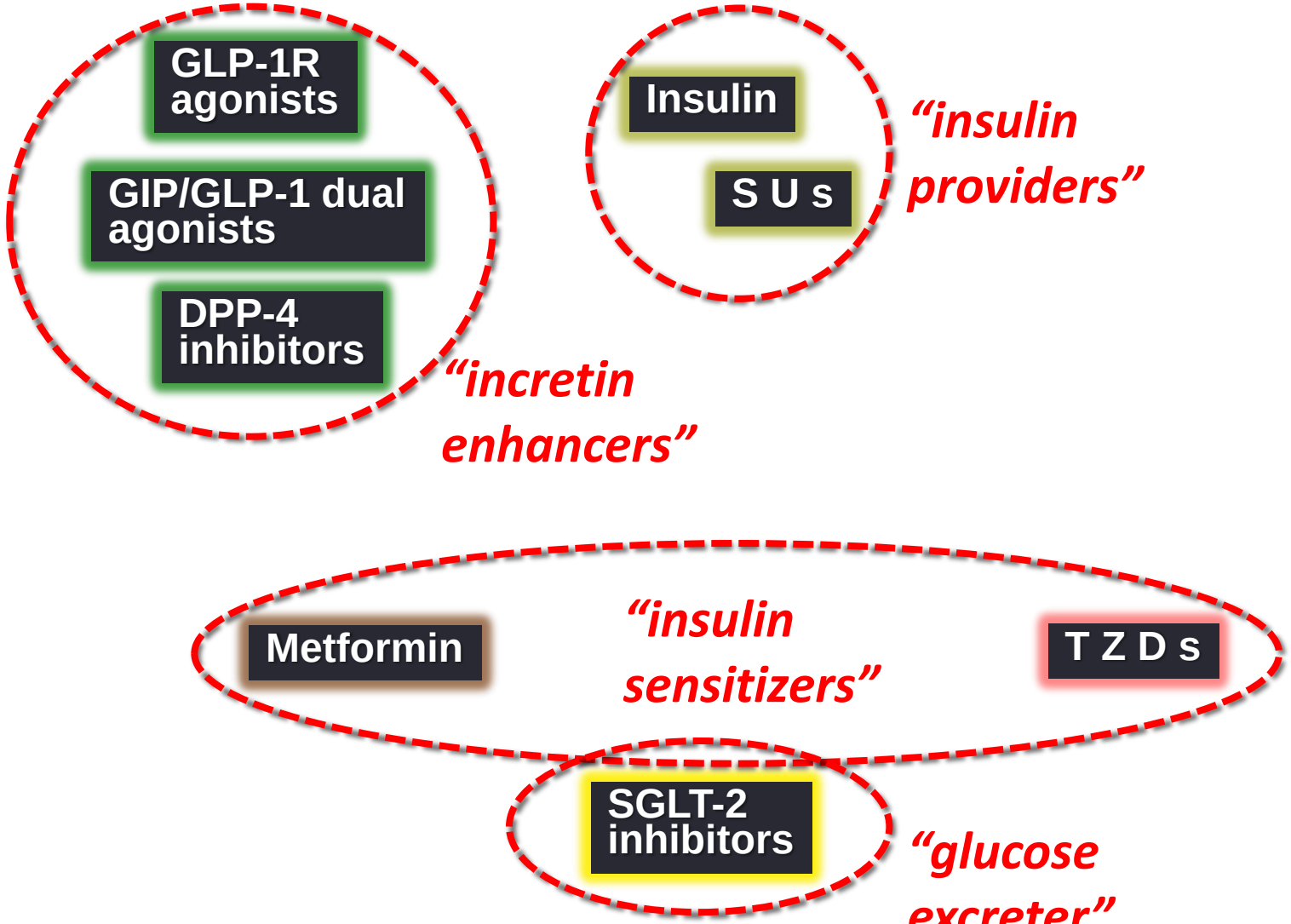


Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

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

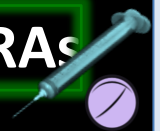
DPP-4 inhibitors

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

2016 and beyond…Cardioprotective Drug Classes are Born!*

*exenatide, and lixisenatide were not shown to reduce MACE.

Oral semaglutide did not show benefit in the first CVOT PIONEER

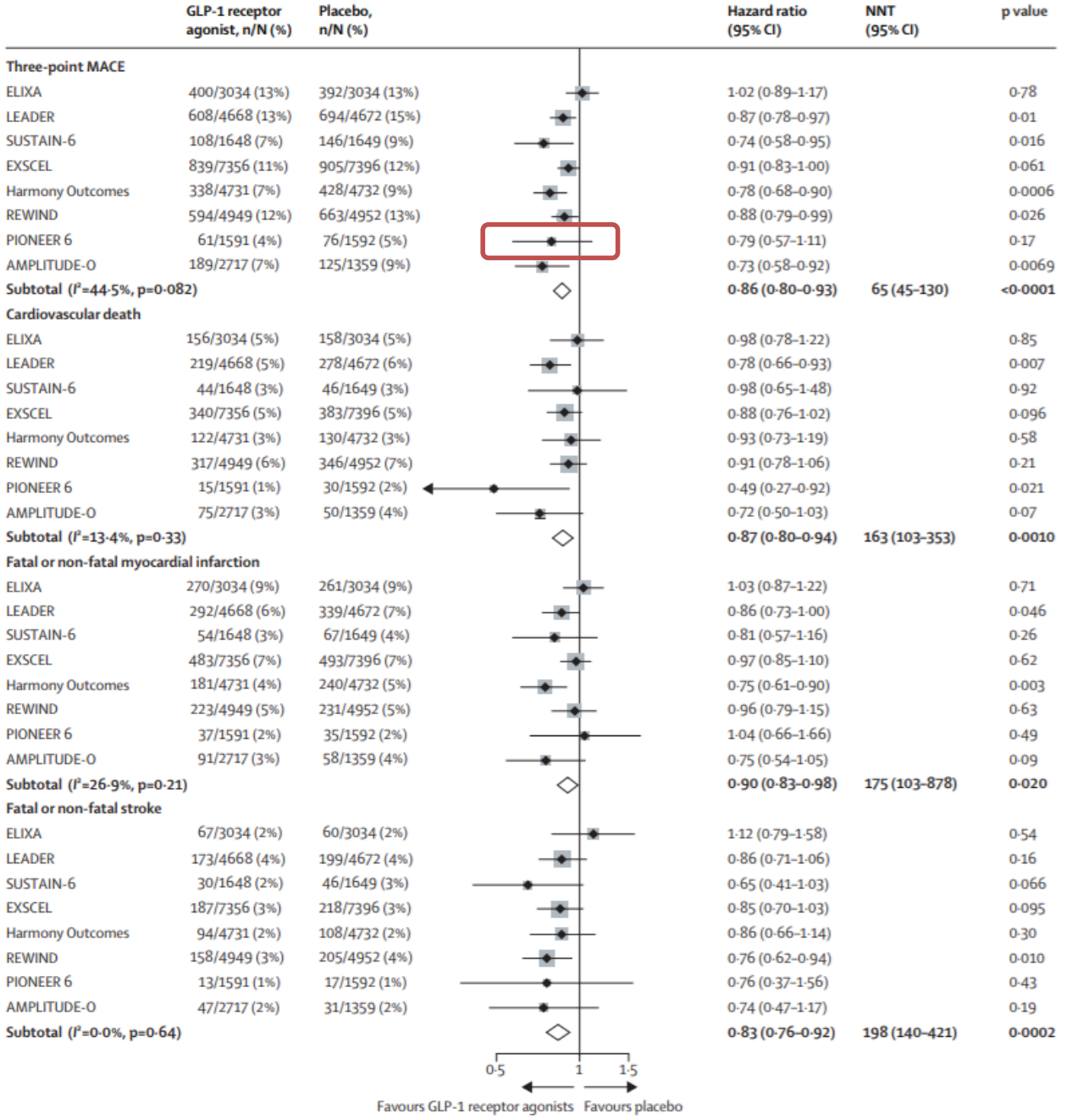
GLP-1 RA:

Major Adverse Cardiovascular Events:
HR 0.86
14% REDUCTION

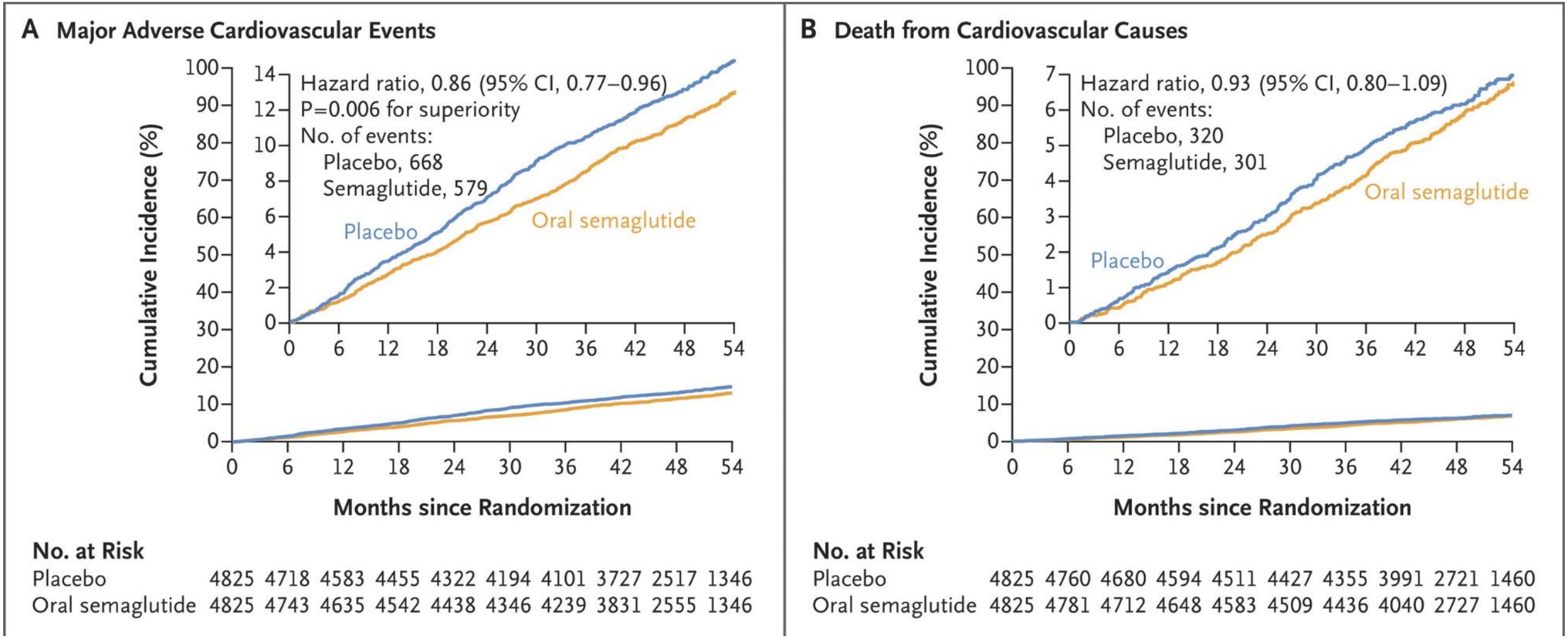
CV Death:
HR 0.87
13% REDUCTION

Fatal or Non-fatal Myocardial Infarction:
HR 0.90
10% REDUCTION

Fatal or Non-fatal Stroke:
HF 0.83
17% REDUCTION

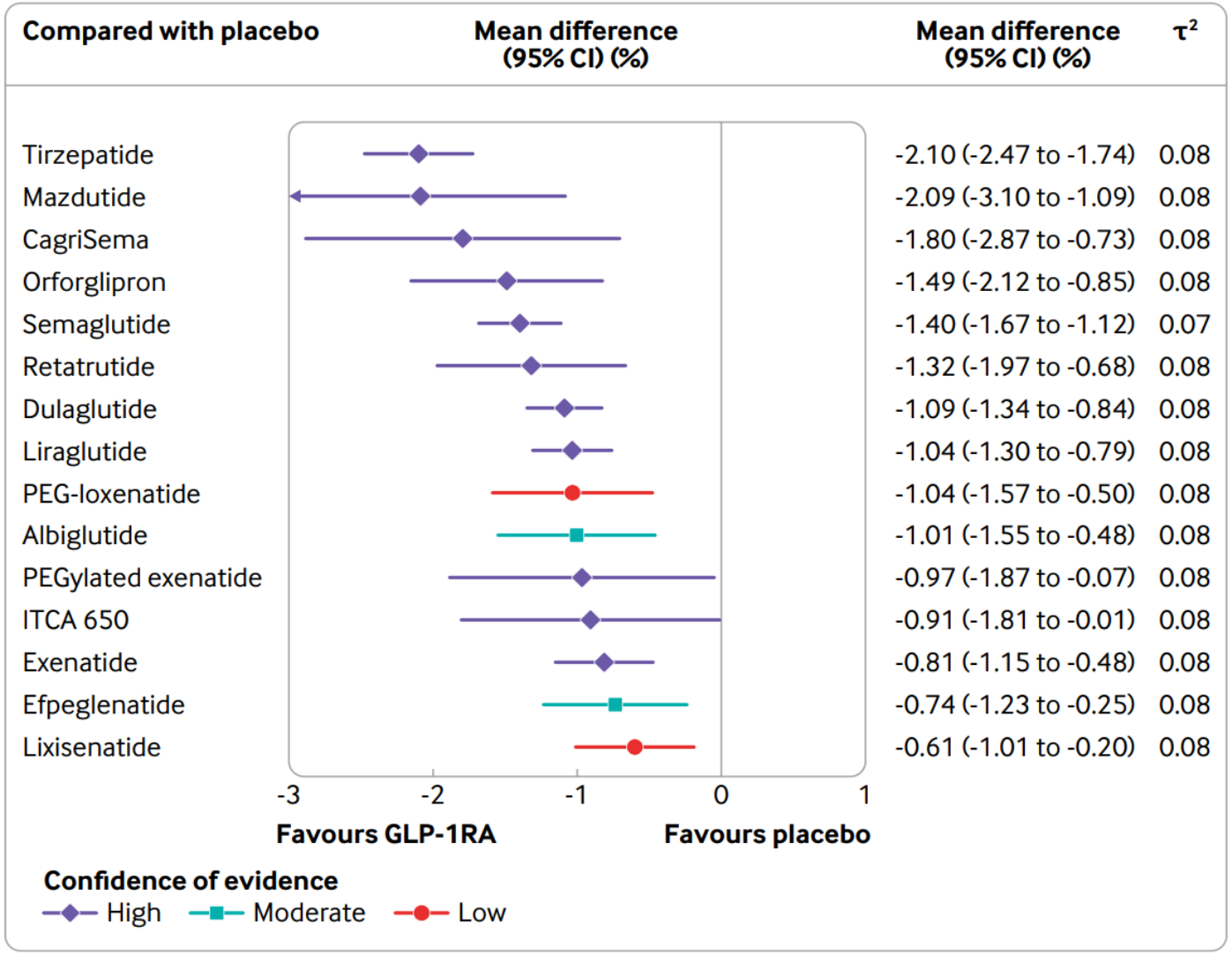


Oral Semaglutide in **T2D + CVD or CKD**: the SOUL trial



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

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:**

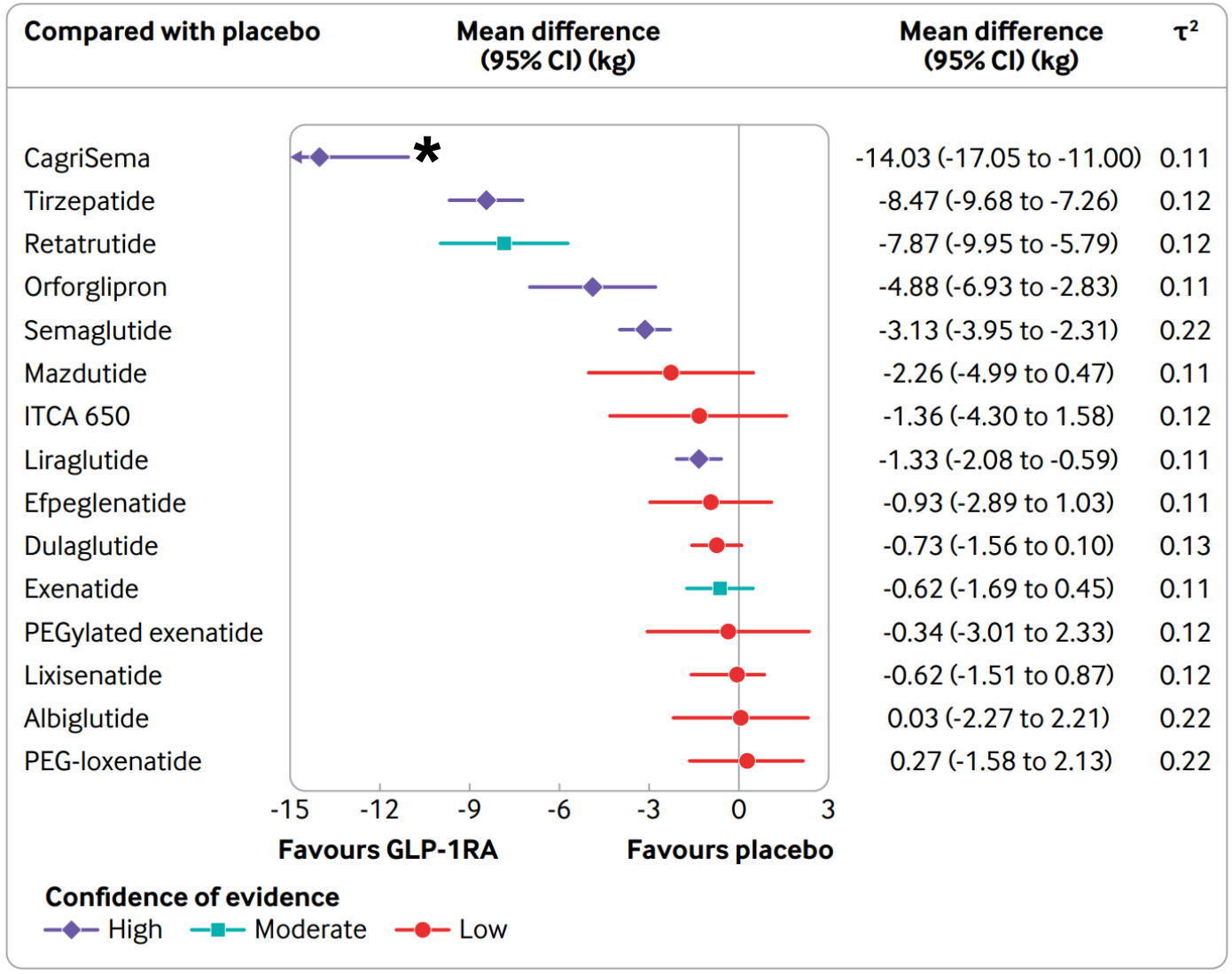
  Tirzepatide −2.10% (95% CI)

  Induced most significant HbA1c reduction
- **SUCRA 94.2%, high confidence of evidence**

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

The Weight Loss Wars

Incretin Agents vs. Placebo for Body Weight Reduction



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

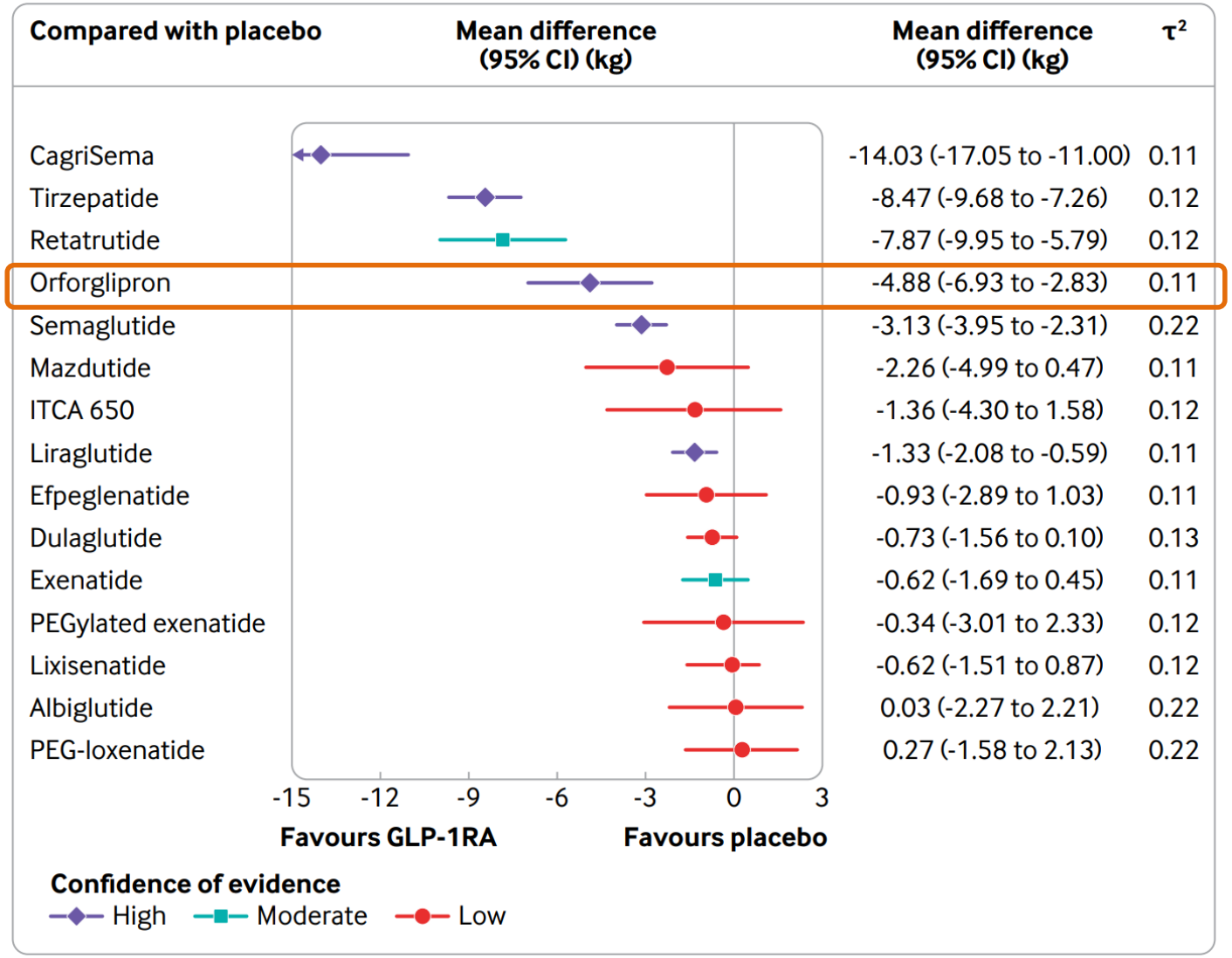
* **Which is *really* better for weight loss in type 2 diabetes?**

Yao H, et al. BMJ. 2024 Jan 29;384:e076410.; Apovian CA, McDonnell ME, Lancet, 2023 Frias JP. Lancet. 2023 Aug 26;402(10403):720-730

Caution when reading the "Headlines":
>10% weight reduction is a major game changer in T2D

TRIAL	DRUG/ DESIGN	BASELINE BMI	BASELINE A1C	% ON INSULIN	% WEIGHT LOSS AT HIGHEST DOSE	PLACEBO SUBTRACTED	NO OF WEEKS
SURPASS-1	TIRZEPETIDE VS. PLACEBO	31.9	7.9	EXCLUDED	-11%	-10.2%	40
SURMOUNT -2	TIRZEPETIDE VS. PLACEBO	36	8.02%	EXCLUDED	-14.7%	-11.6%	72
REDEFINE-2	CAGRISEMMA VS. PLACEBO	36.1	8.0%	EXCLUDED	-13.7%	-10.4	68

Incretin Agents vs. Placebo for Body Weight Reduction



- **New small peptide GLP-1 RA (not a "biologic")**
- **Opportunity for widespread access**
- **The metformin of the future?**

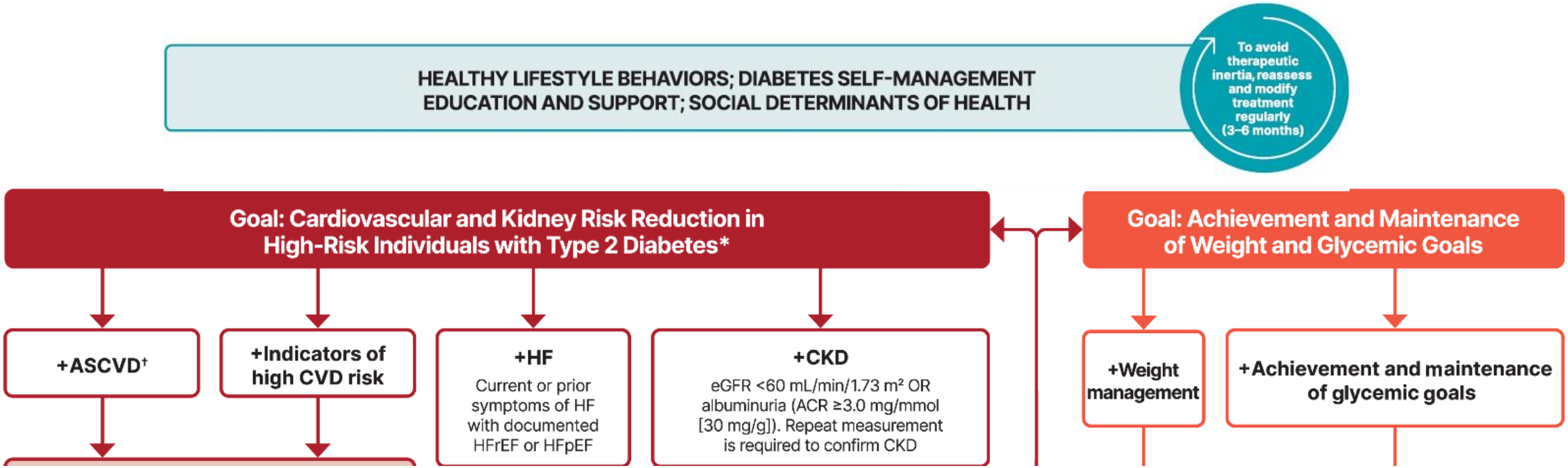
Yao H, et al. BMJ. 2024 Jan 29;384:e076410.; Apovian CA, McDonnell ME, Lancet, 2023 Frias JP. Lancet. 2023 Aug 26;402(10403):720-730

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

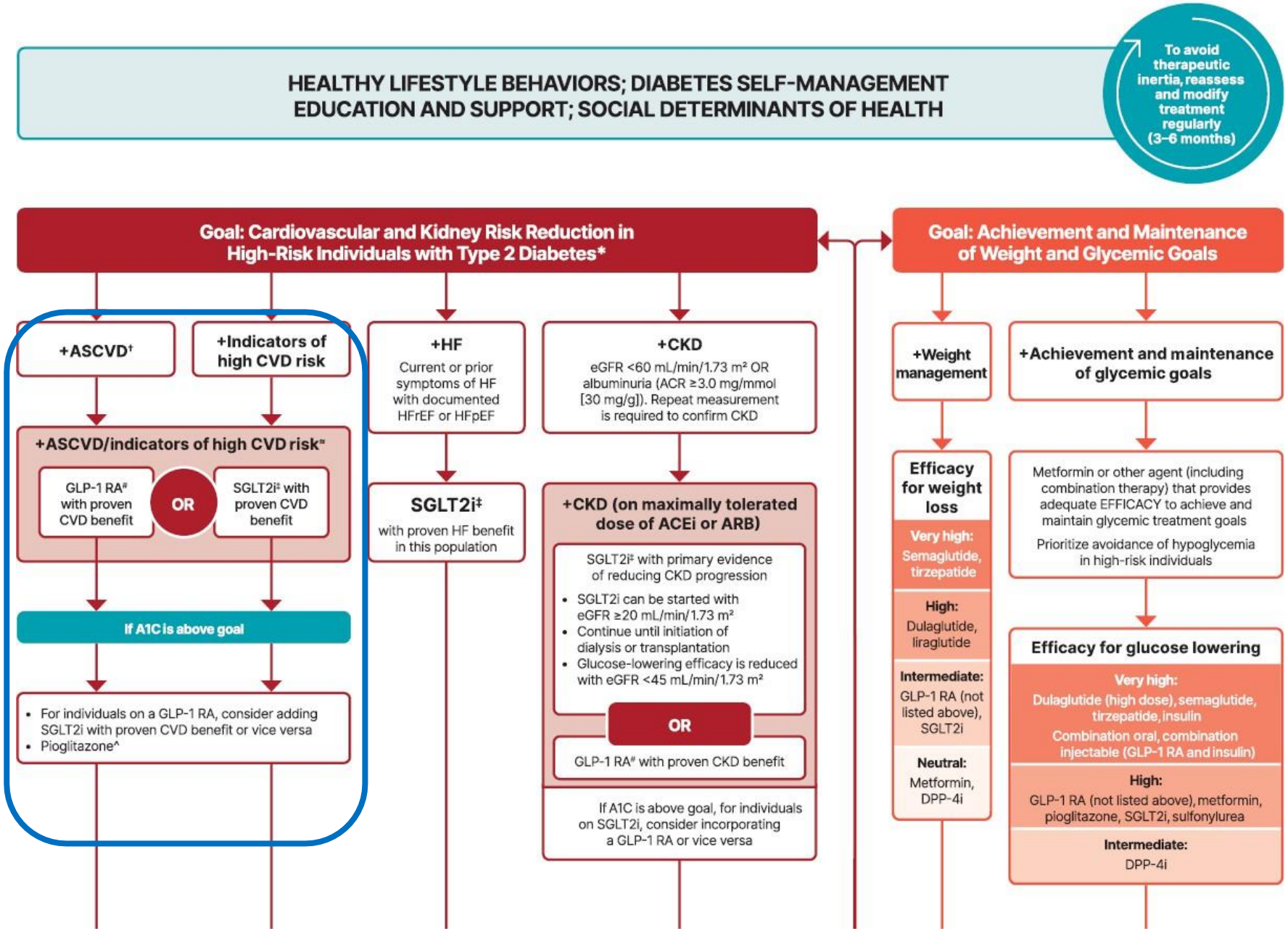
ADA: Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. Pharmacologic approaches that provide the efficacy to achieve treatment goals should be considered, such as metformin or other agents, including combination therapy, that provide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

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



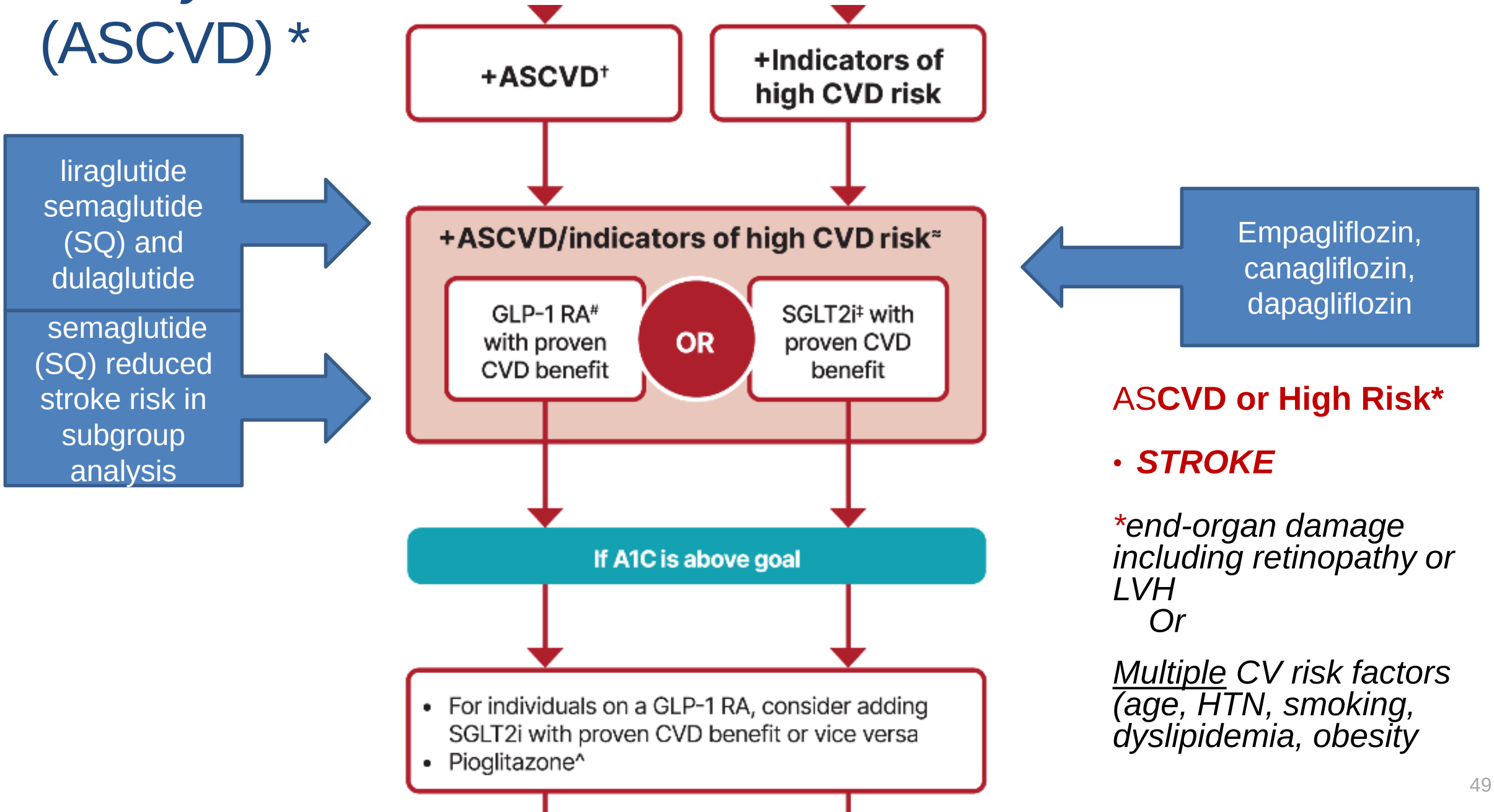
<u>Implied point throughout the guidance</u>: It is ideal to choose medications that can achieve more than one of these goals simultaneously; this is not always feasible

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*

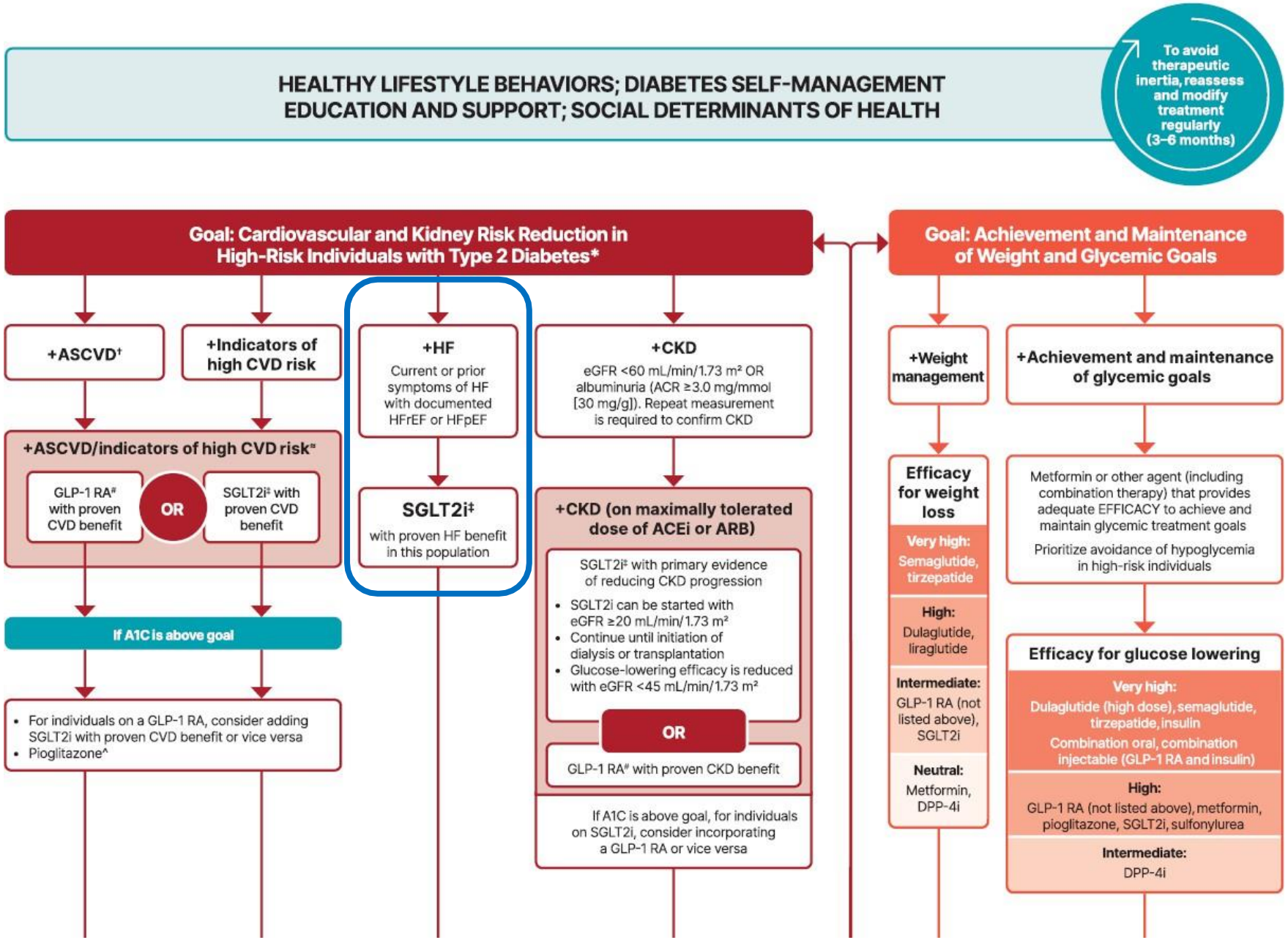
- ***STROKE***

**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



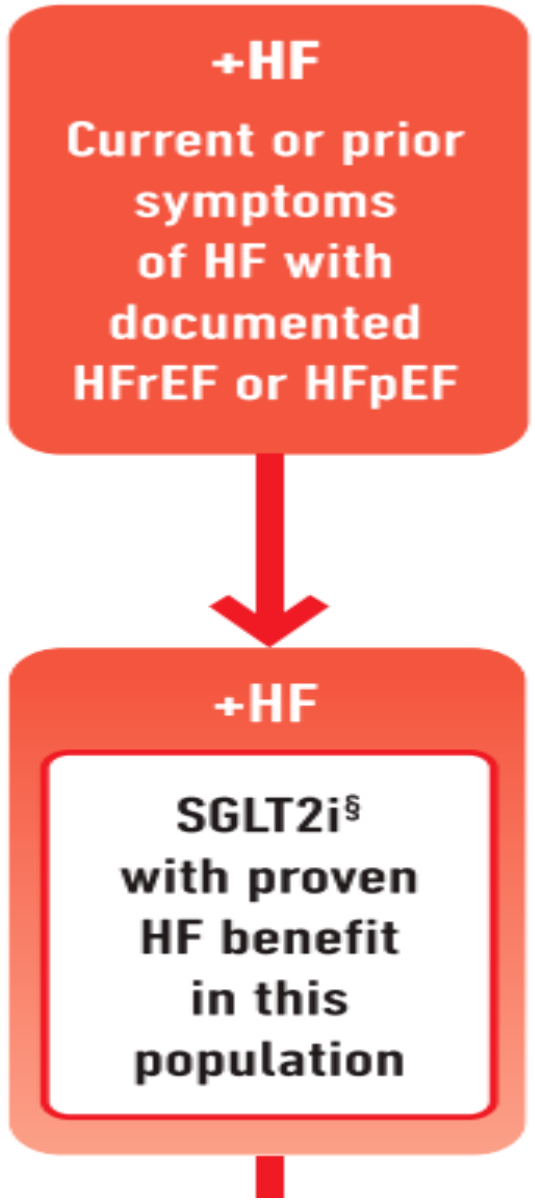
Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes - 2025 Diabetes Care* 2025;48(Suppl. 1):S181-S206

Priority: Heart Failure

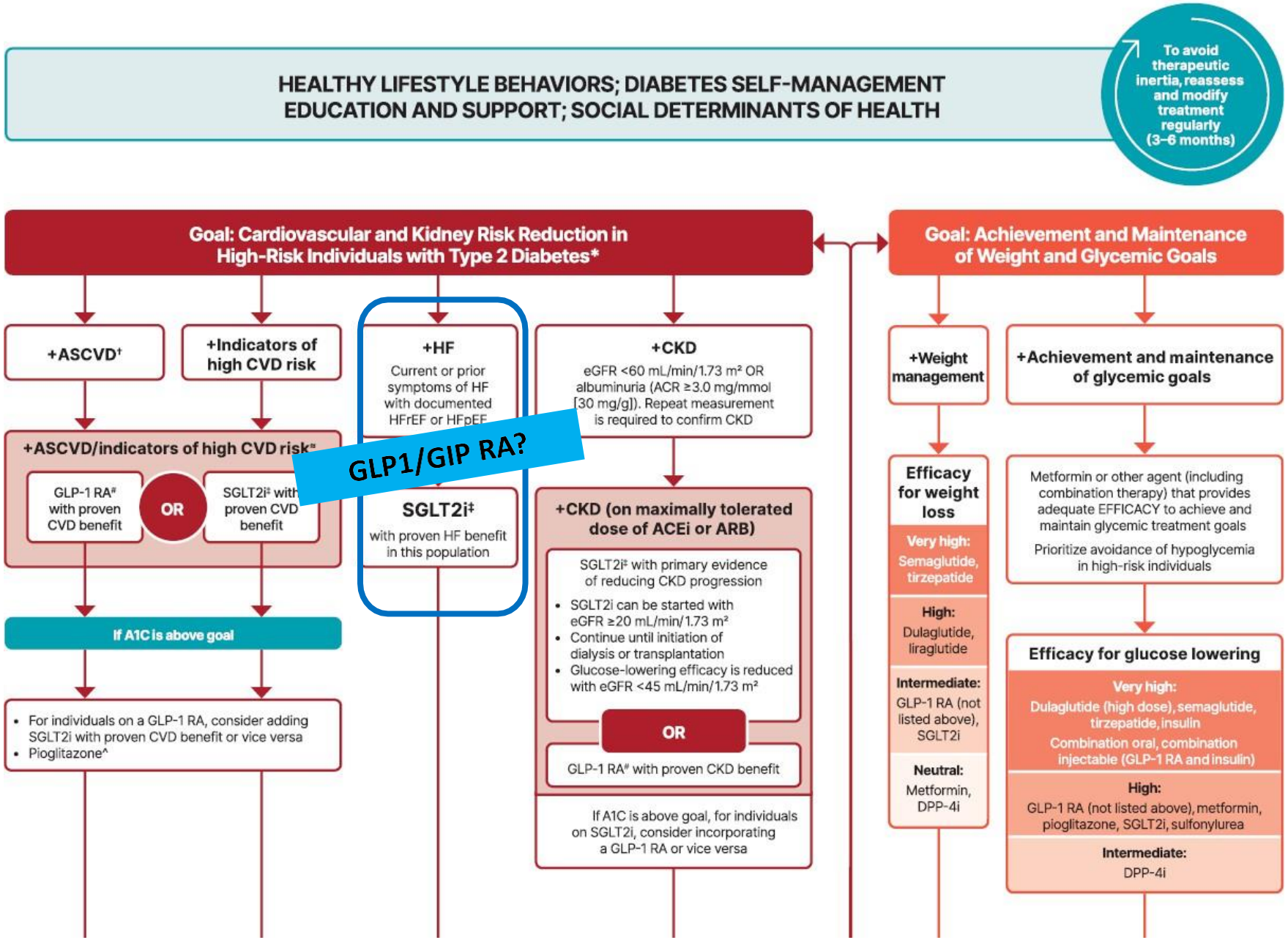
- **SGLT2i now clearly indicated for <u>both</u> HFpEF and HFrEF**

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

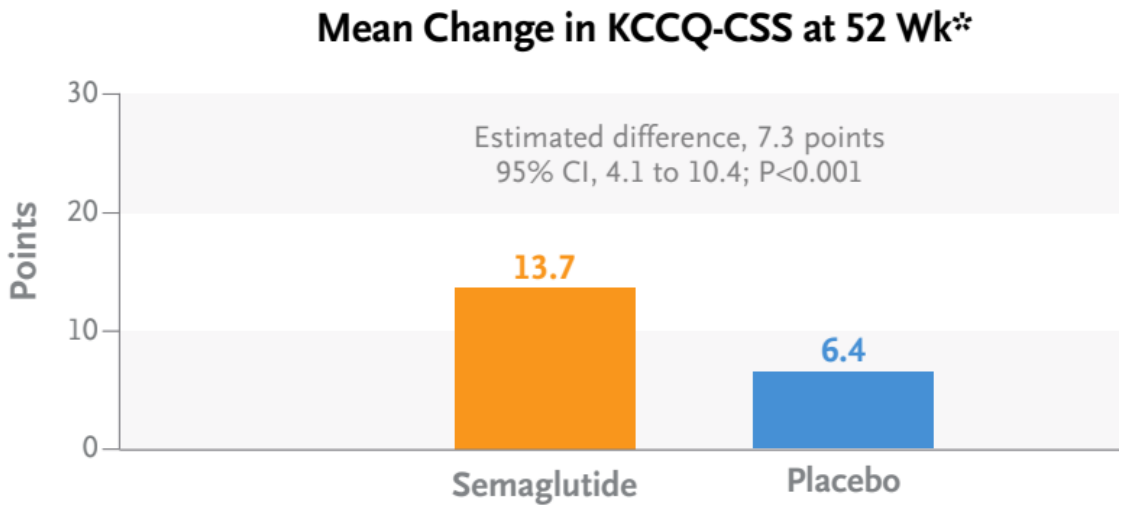


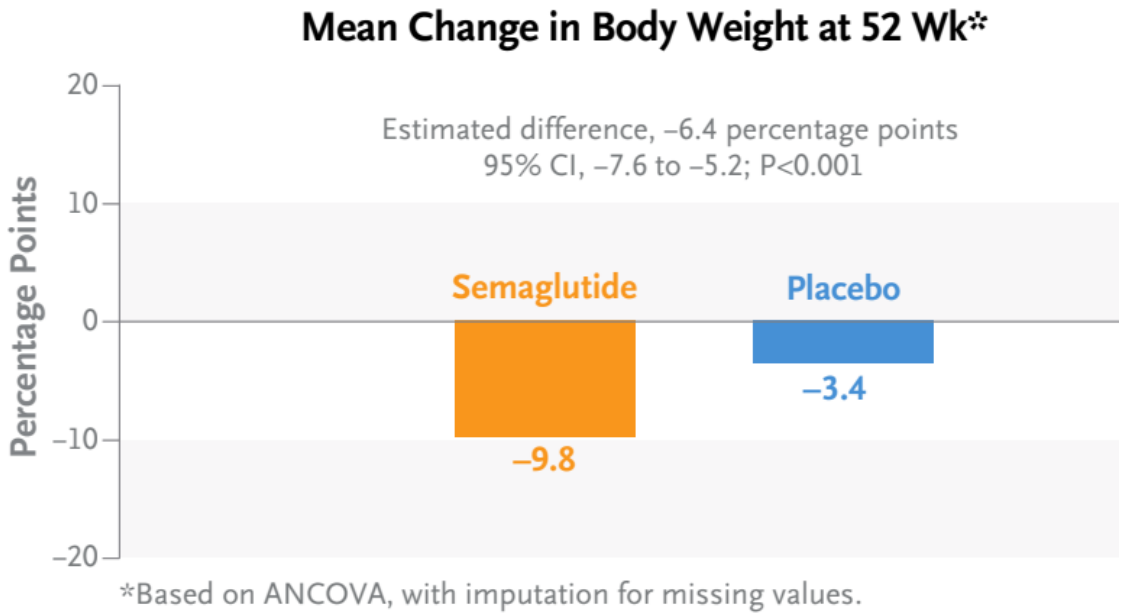
Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes - 2025 Diabetes Care* 2025;48(Suppl. 1):S181-S206

Results: semaglutide in adults with type 2 diabetes and HF*p*EF

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)

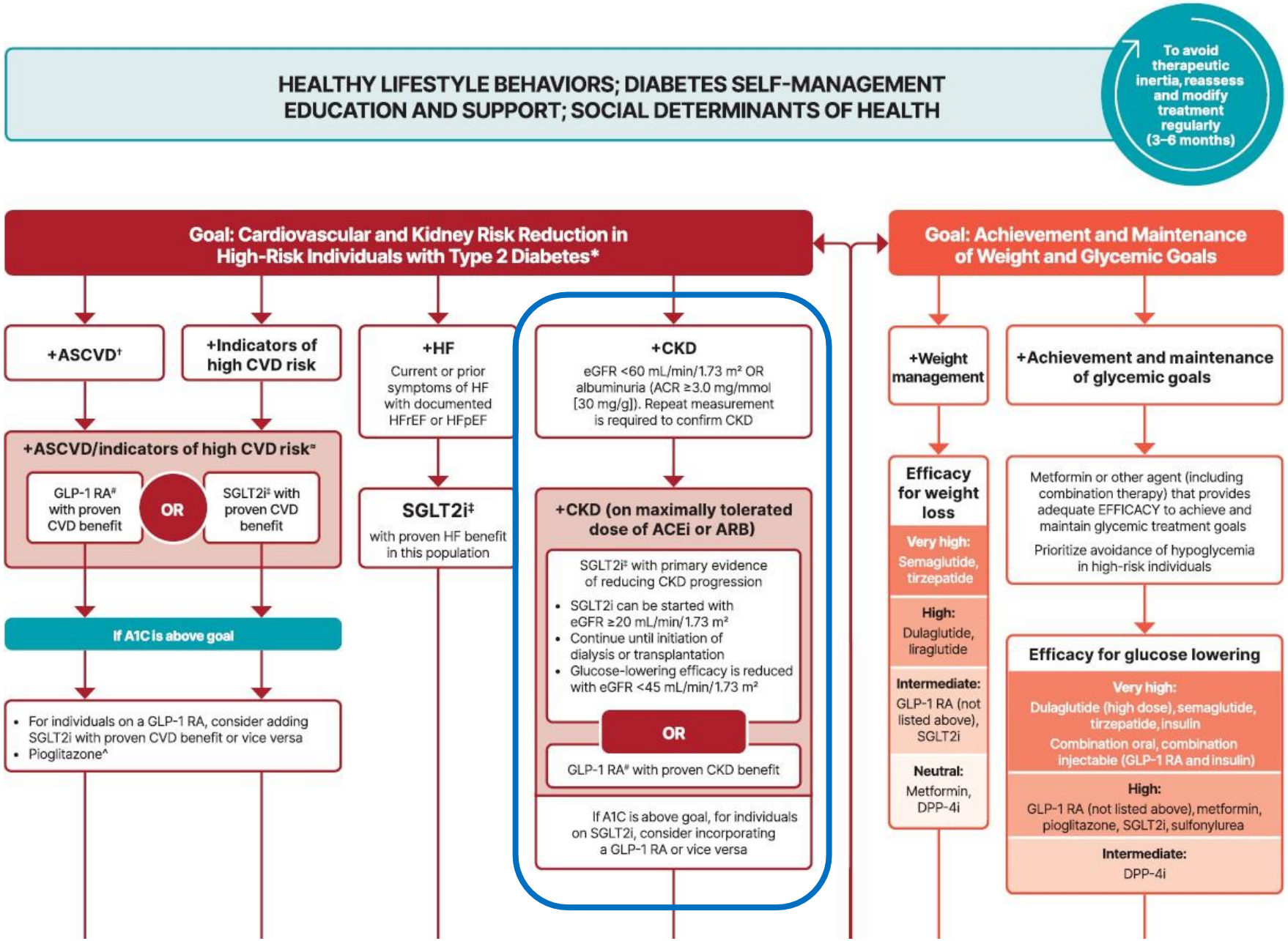




Kosiborod MN, et al. N Engl J Med. 2024 Apr 18;390(15):1394-1407.

Kansas City Cardiomyopathy Questionnaire

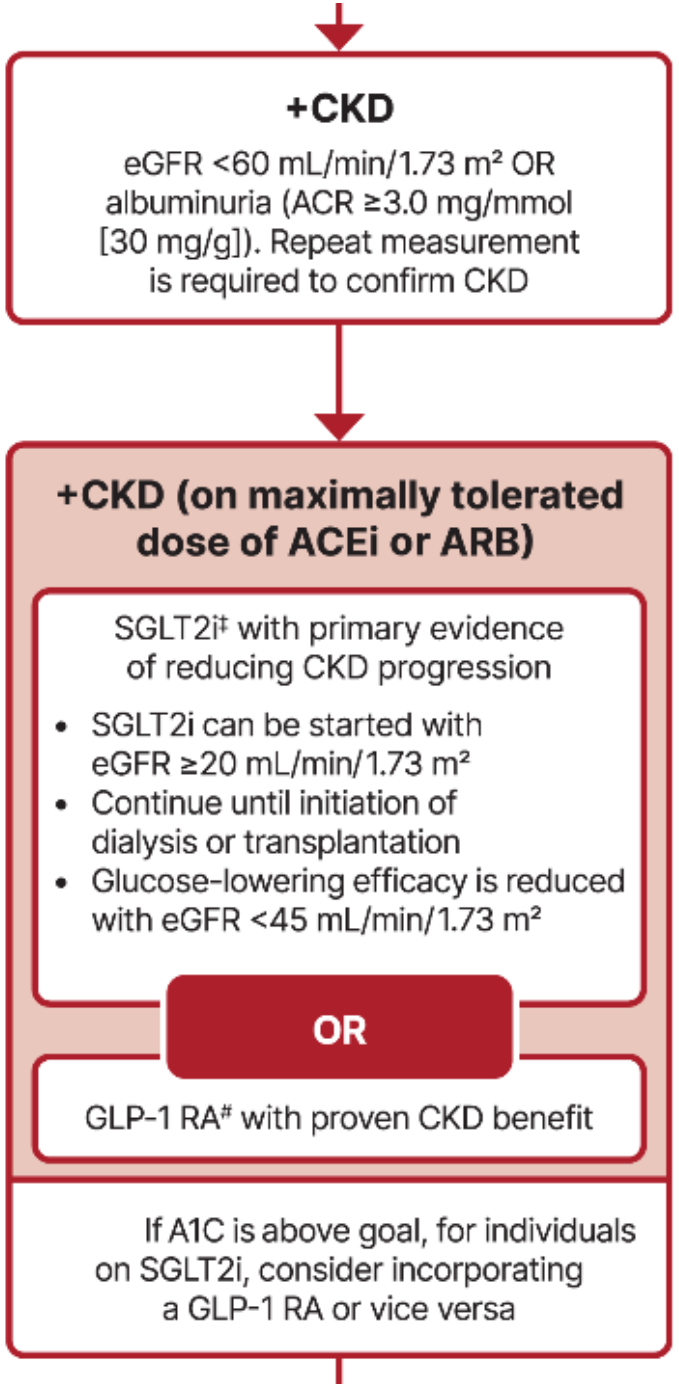
Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes



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**



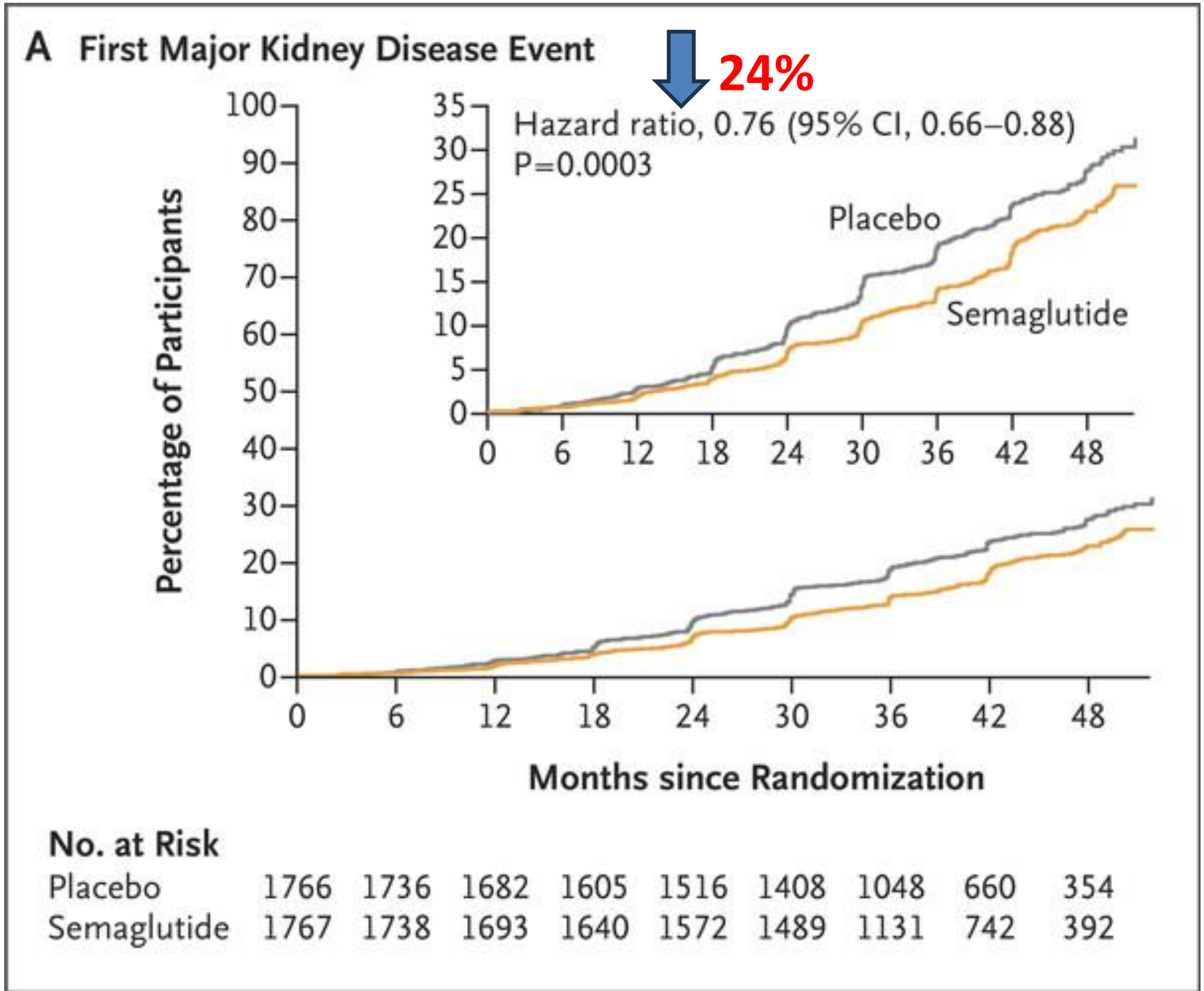
canagliflozin, dapagliflozin

empagliflozin

liraglutide semaglutide (SQ) and dulaglutide

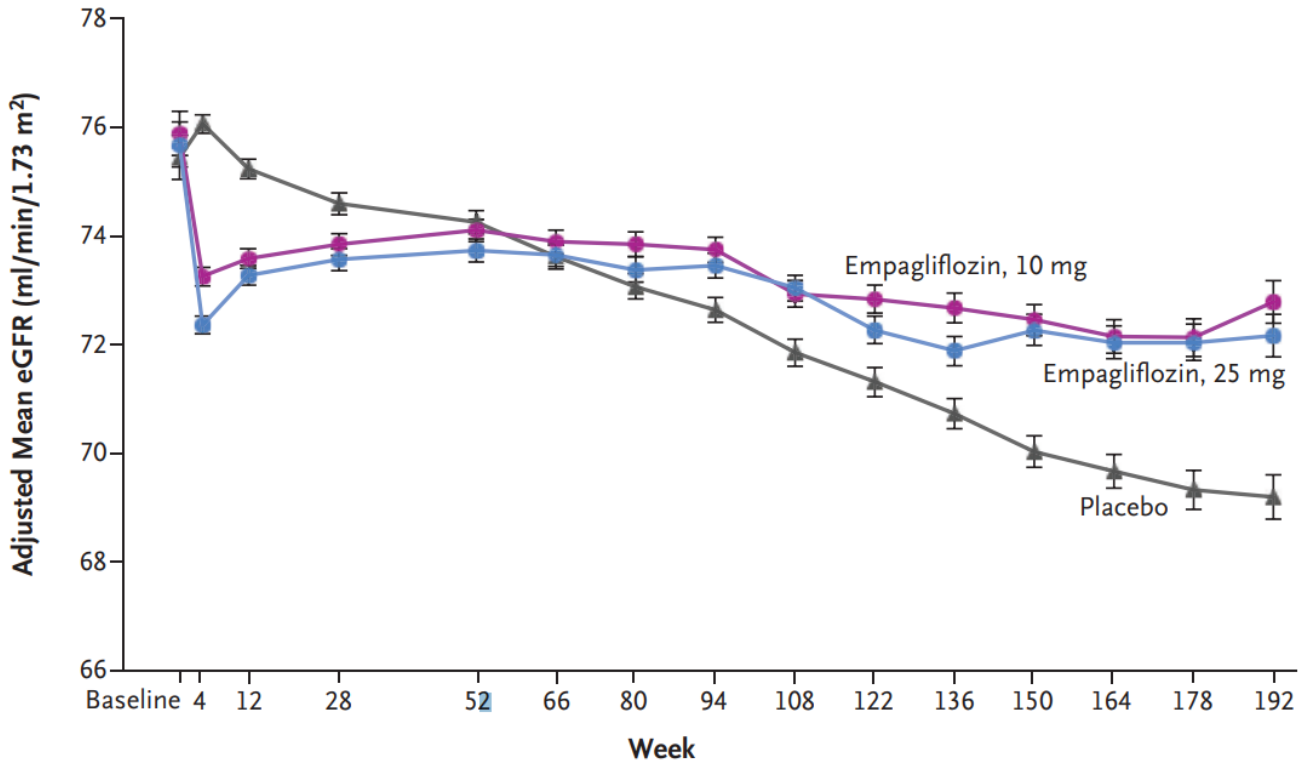
GLP-1 RA kidney benefit is probably real

FLOW primary outcome

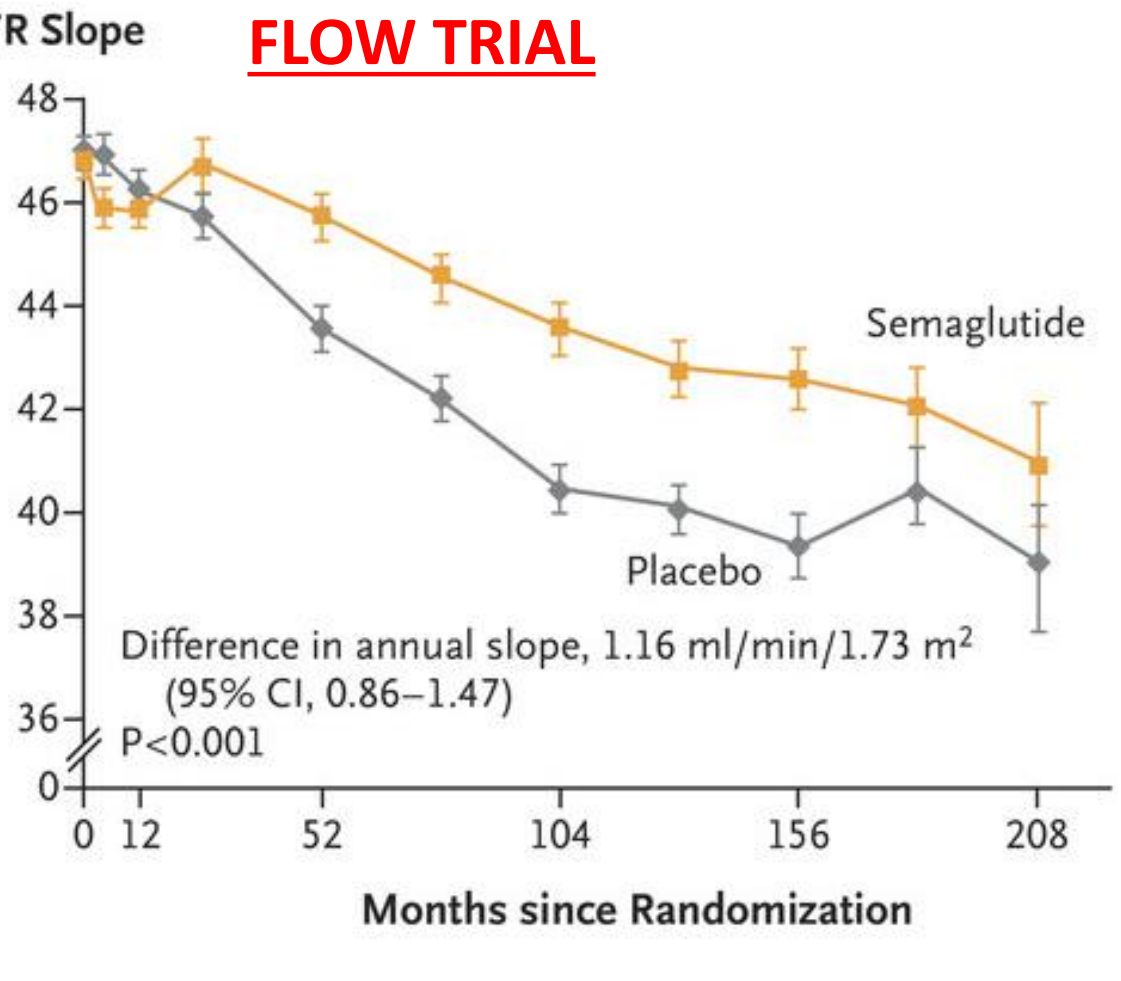


eGFR Slope: Empagliflozin vs. Semaglutide

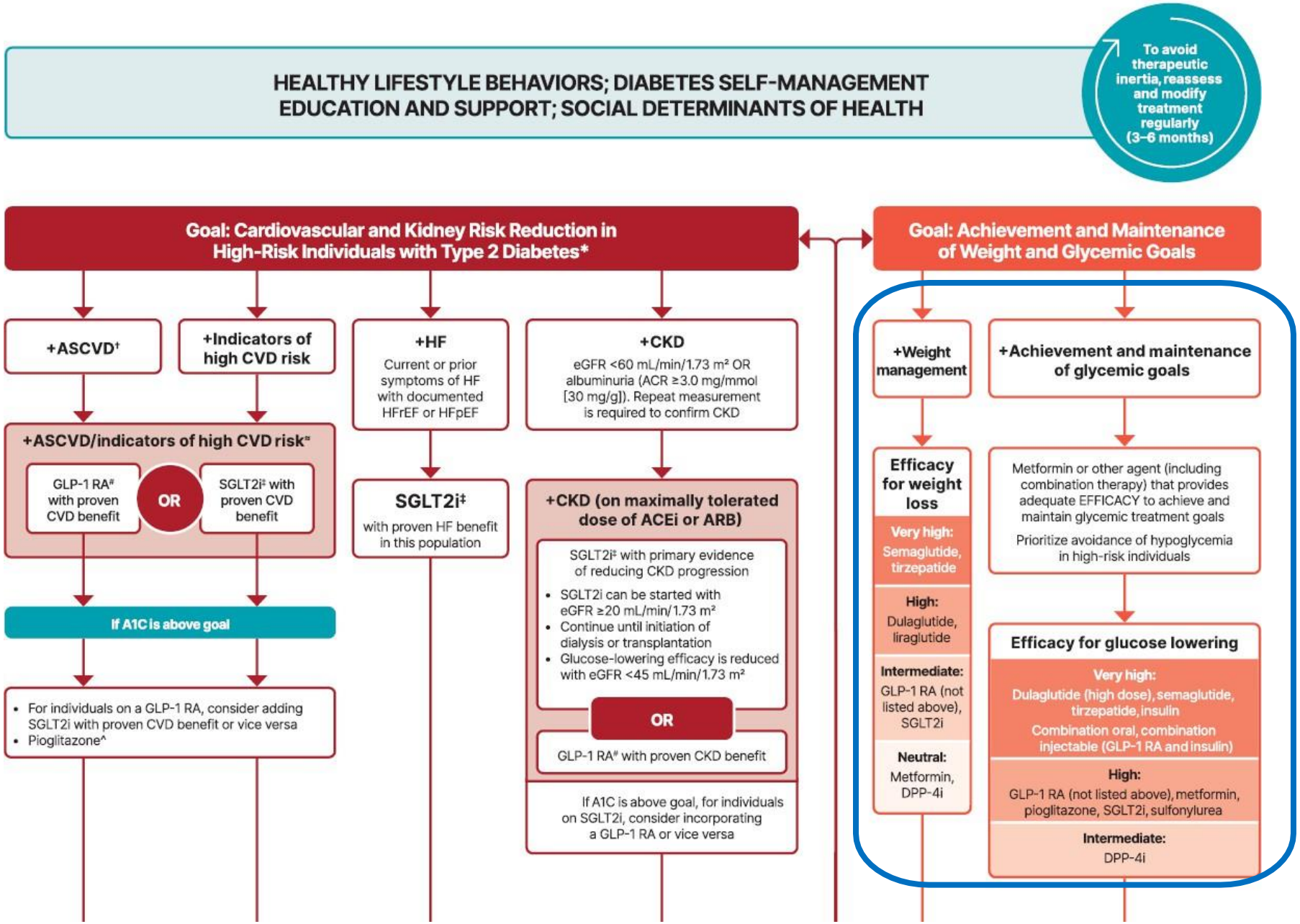
EMPA-REG OUTCOME



FLOW TRIAL

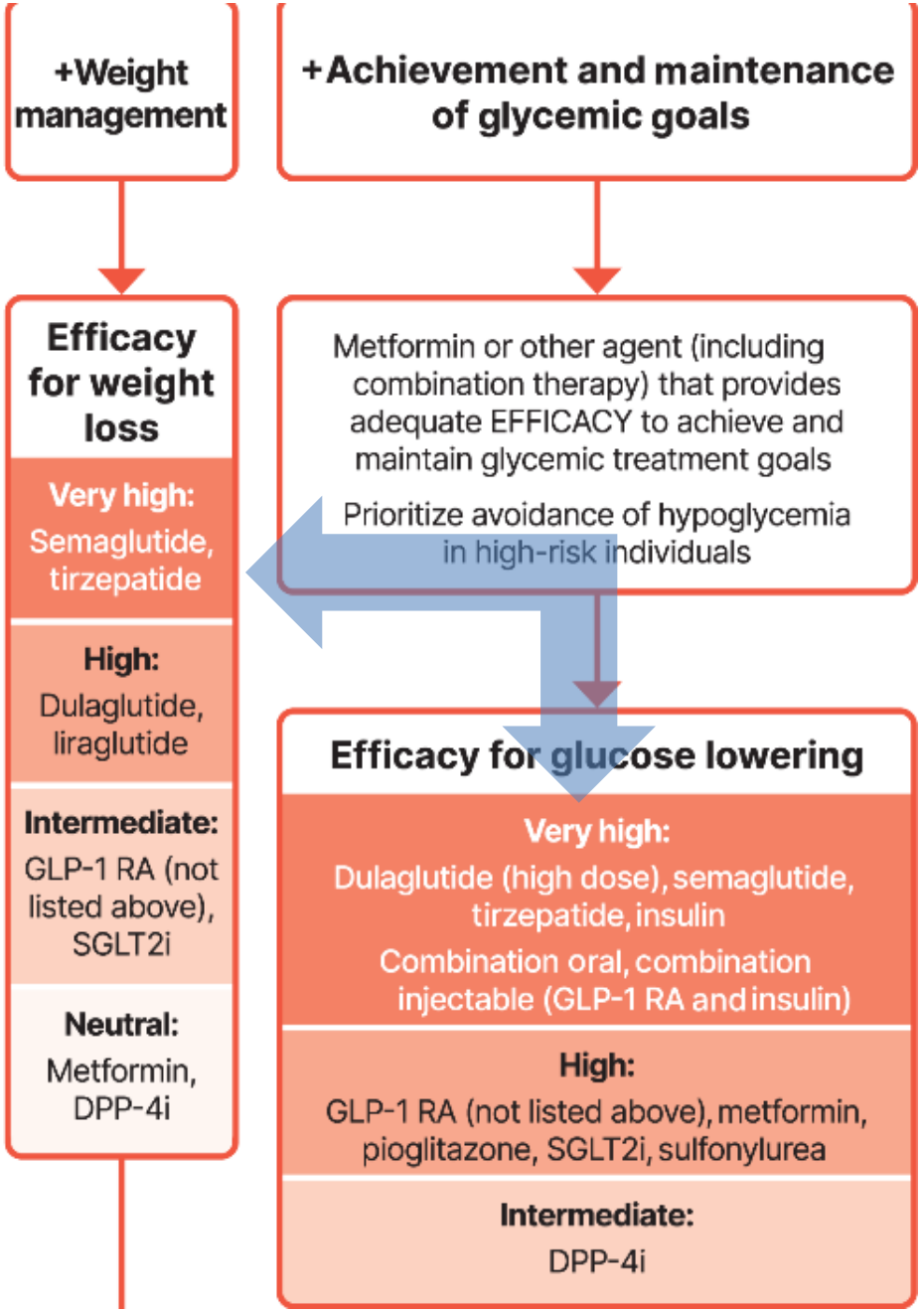


Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes



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

Priority: Metabolic control



Sulfonylureas

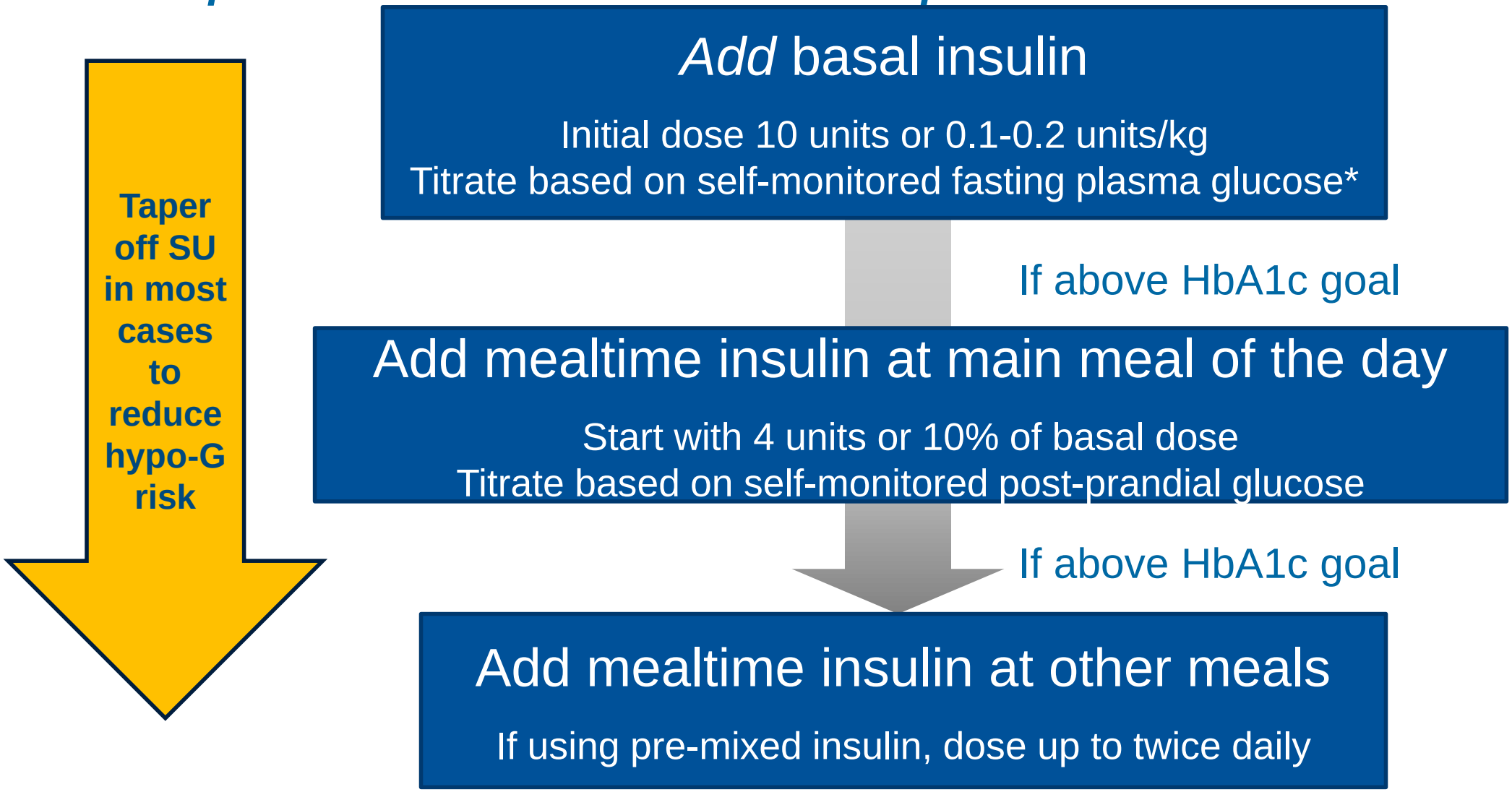
- **Choose glimepiride or gliclazide (outside US) as first line. Avoid glyburide**
  - Glimeperide is the only SU tested in a CVOT; compared with linagliptin no difference in CV risk and hypoglycemia risk was lower than expected
  - Gliclazide has lowest reported hypoglycemia risk
- **Remember that SUs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

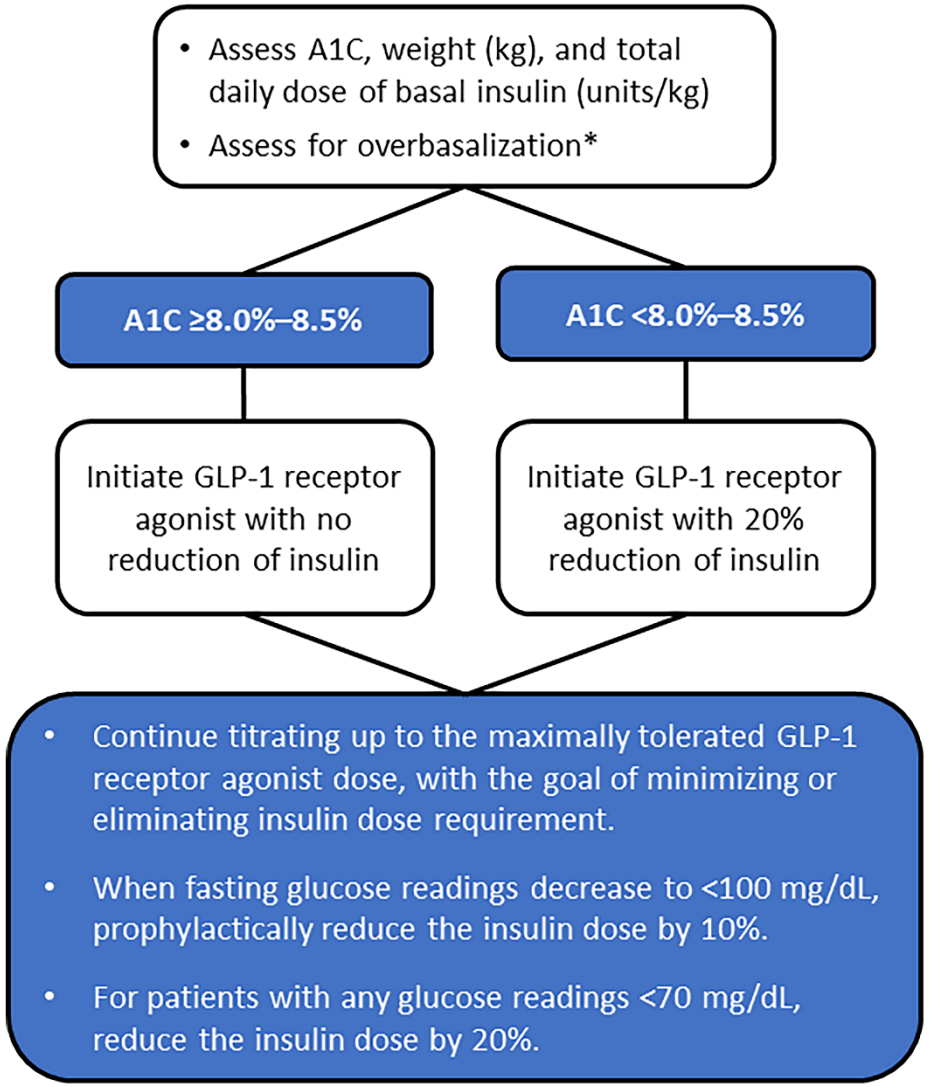
- **Pros:** ok in euvolemic advanced kidney disease, potent
- **Cons:** weight gain, edema/CHF, CV controversy, increased fractures in women, (urologic cancers? unclear, FDA avoid if family history)
- **Select the right *patient & dose*:**
  - Fatty liver
  - TIA, stroke history
  - MI history, normal 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*



Best Practices for Adding GLP-1 to Insulin



Consider placing a CGM to assess short term improvements in glucose control and to anticipate & prevent hypoglycemia

Initiation GLP-1 RA at the lowest dose and in most cases, titrate slowly. There is no downside to slow titration, only upside!

Reduce sulfonylurea dose and try to taper off (not always easy – suggest not stopping abruptly)

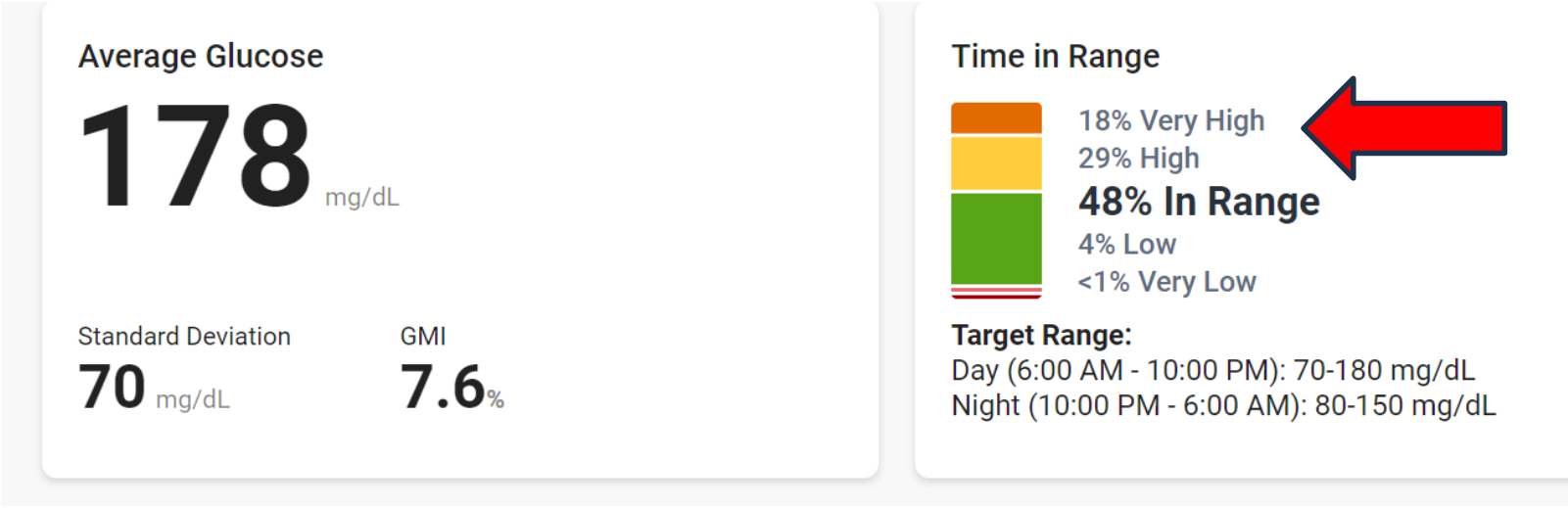
Clin Diabetes. 2023;42(2):341-350. doi:10.2337/cd23-0047

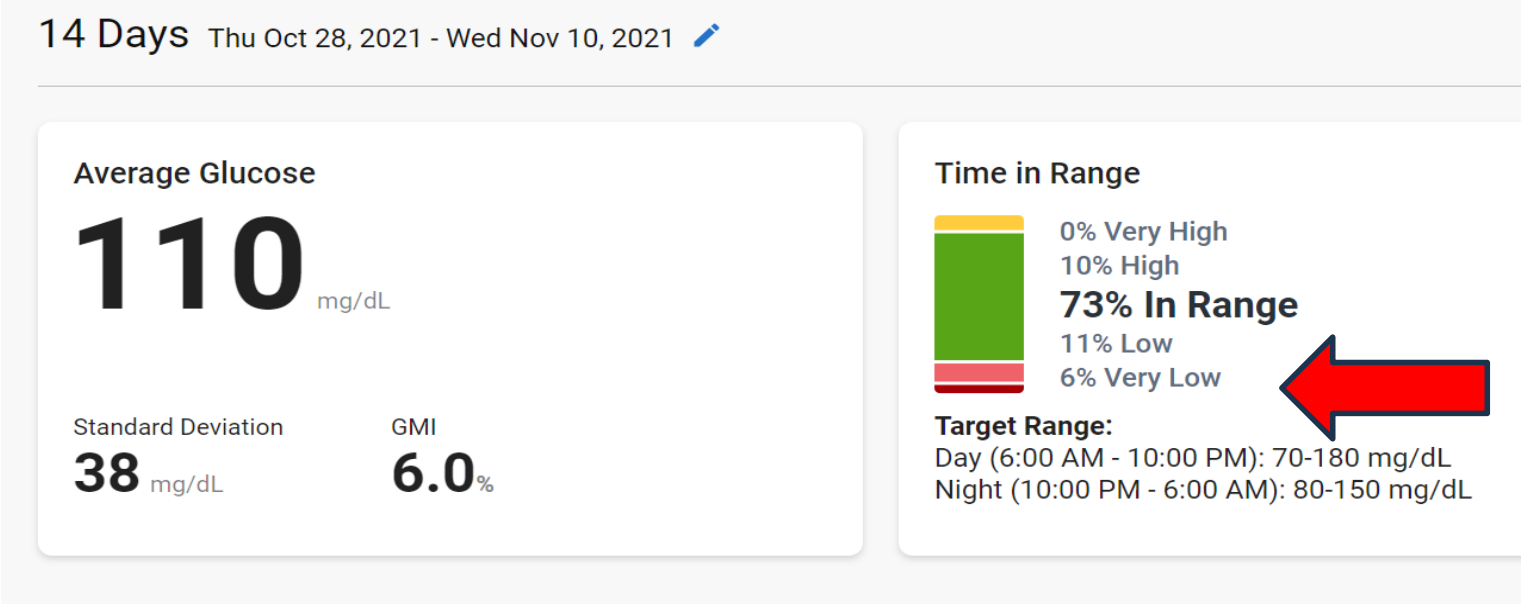
Newer concepts

Time in Range" or TIR on CGM is a new target

International Consensus in TIR: Goal is >70% of time spent in 70-180mg/dl

TIR was validated as an outcome measures for clinical trials.

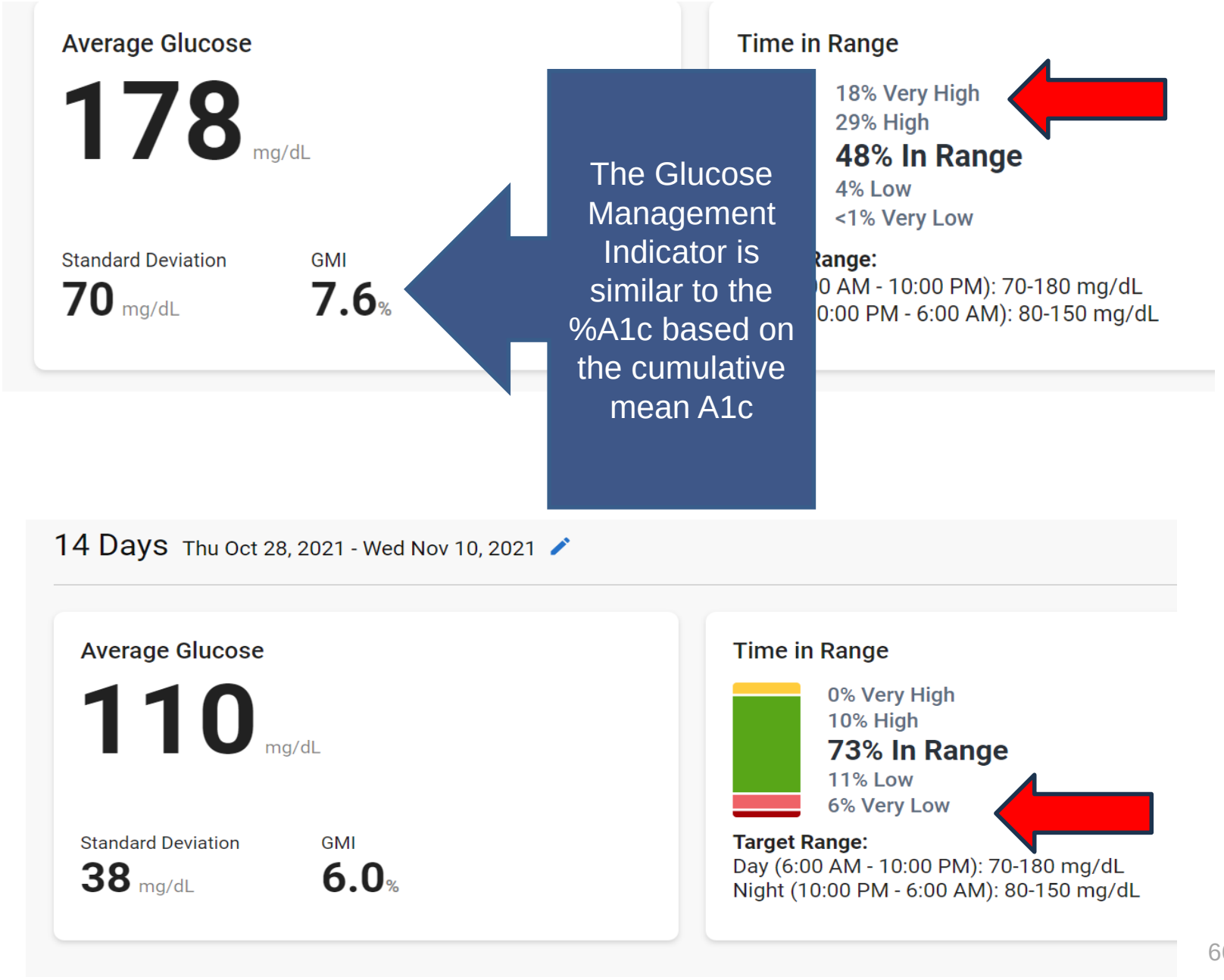




Time in Range" or TIR on CGM is a new target

International Consensus in TIR: Goal is >70% of time spent in 70-180mg/dl

TIR was validated as an outcome measures for clinical trials.



Oldies but goodies: *special considerations*

Sulfonylureas

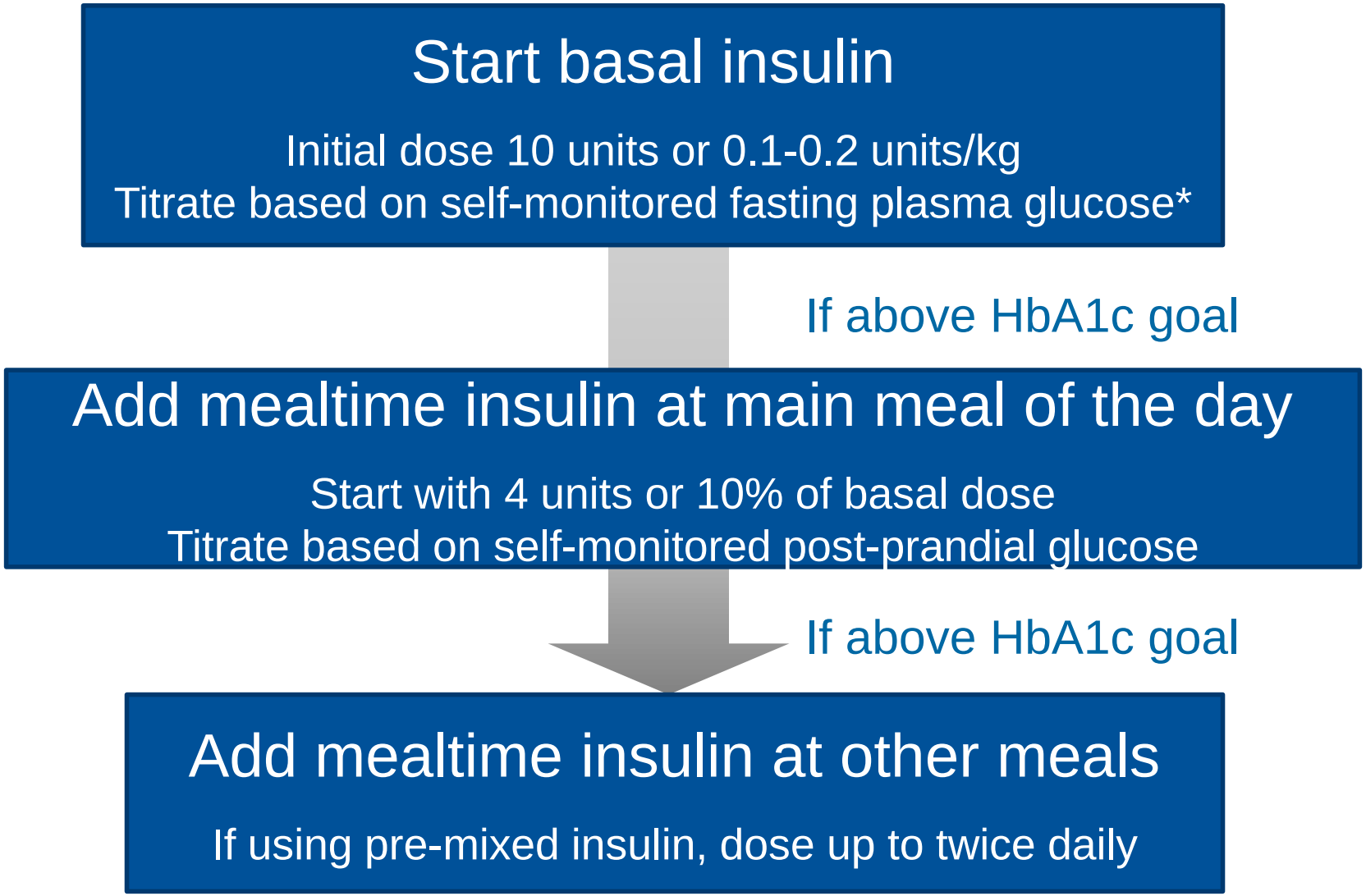
- **Choose glimepiride as first line**
  - Only SU tested in a CVOT
  - Was compared with linagliptin
  - No difference in CV risk and hypoglycemia risk was lower than expected
- **Remember that SUs will fail**
  - Can appear to happen suddenly
  - Typically not useful to increase beyond 10mg daily if 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: *nothing new*



Based on ADA Standards of Care. 2023.

What is on the horizon in Diabetes Care?

Once weekly basal insulin

- ***Icodec (Novonordisk)***

November 26, 2020
N Engl J Med 2020; 383:2107-2116
DOI: 10.1056/NEJMoa2022474
Chinese Translation 中文翻译

  FDA rejected last week

  Approved T1 and T2D: Europe, Canada, Australia, Japan, Switzerland

  Type 2 diabetes: Compared with Glargine, no difference in efficacy, modest increase in hypoglycemia risk

  Type 1 diabetes: The ONWARDS phase 3 studies of icodec vs. glargine show similar results (higher rates of hypoglycemia than degludec in type 1 diabetes)

  Takes 3-4 weekly injections to achieve steady state

  Will require a dosing ramp-up

- ***efsitora alfa (Eli Lilly): Phase 3 studies nearing completion,*** *QWINT-2 and QWINT-4*

More and simpler CGM-augmented insulin therapy with automatic insulin delivery

The ILET: "Bionic pancreas"

Will sense start of meals and deliver boluses automatically or with simple indication from wearer

Great for first time pumpers who have not already formed "pump habits"

Patients only enter their weight to start

OMNIPOD 5 integration with Dexcom
Requires usual detailed pump programming

In automated mode after 2 days of regular use insulin delivery depends on learned algorithm

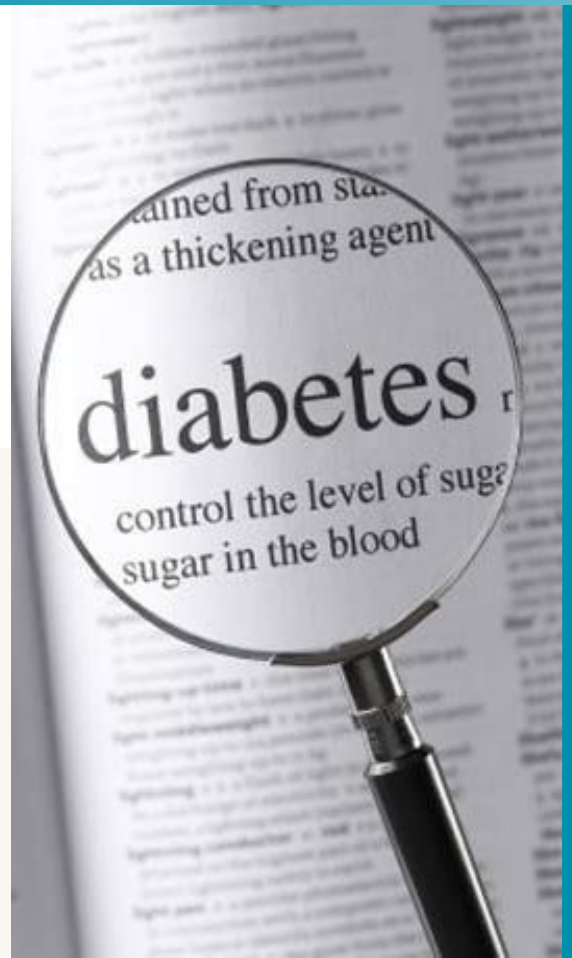
Can choose from 5 glucose targets (110-150) with flexible programming over 24 hour period

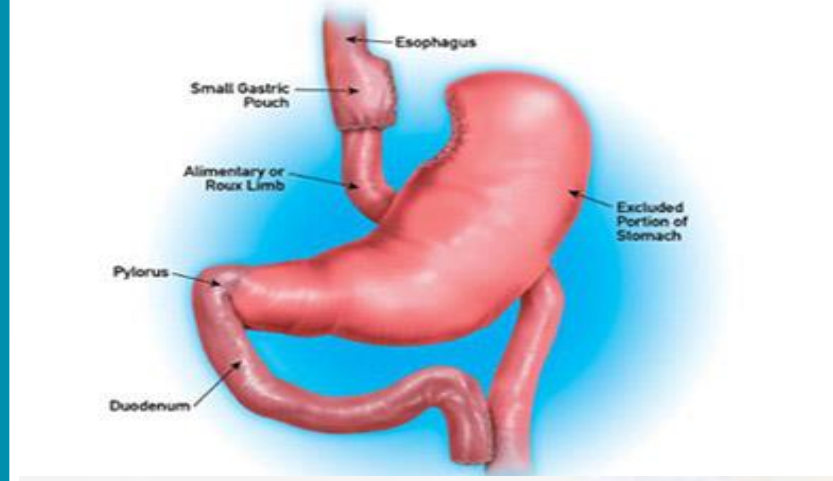
MOC Reflective Statement

- Remember that not all Diabetes is Type 2
- 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 comorbities
- *Preventing and treating obesity* as the underlying disease in most prediabetes and type 2 diabetes (along with other key features of the obesity syndrome) is a priority for overall health and survival of the individual


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-2025. Diabetes Care. 2025 Jan 1;48(1 Suppl 1):S181-S206. doi: 10.2337/dc25-S009. PMID: 39651989; PMCID: PMC11635045.

- 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.