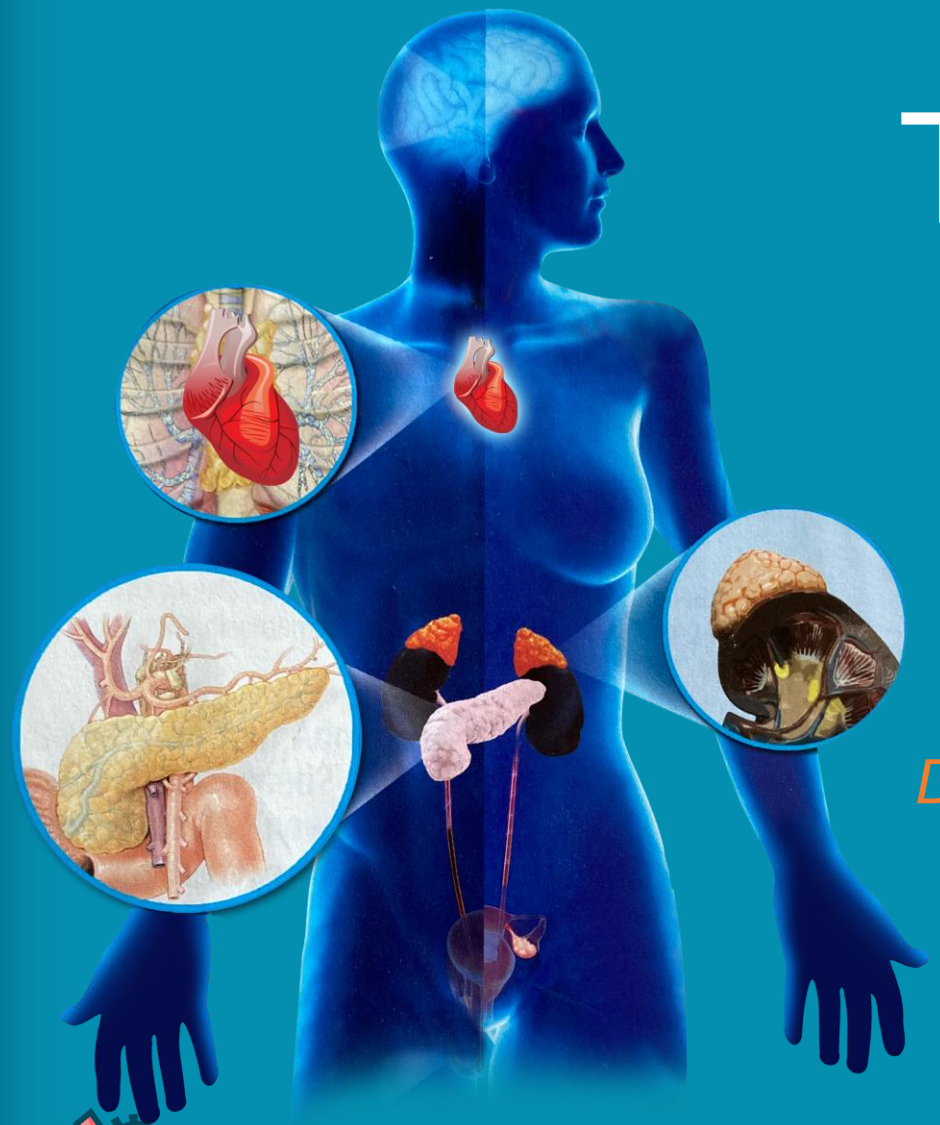


T2DM & CVD

Elkin A. Nunez MD

Director of Endocrinology, Diabetes & Metabolism

Atlantic Health System

Section Chair of Endocrinology

Morristown Medical Center

Cors at the Shore 2023

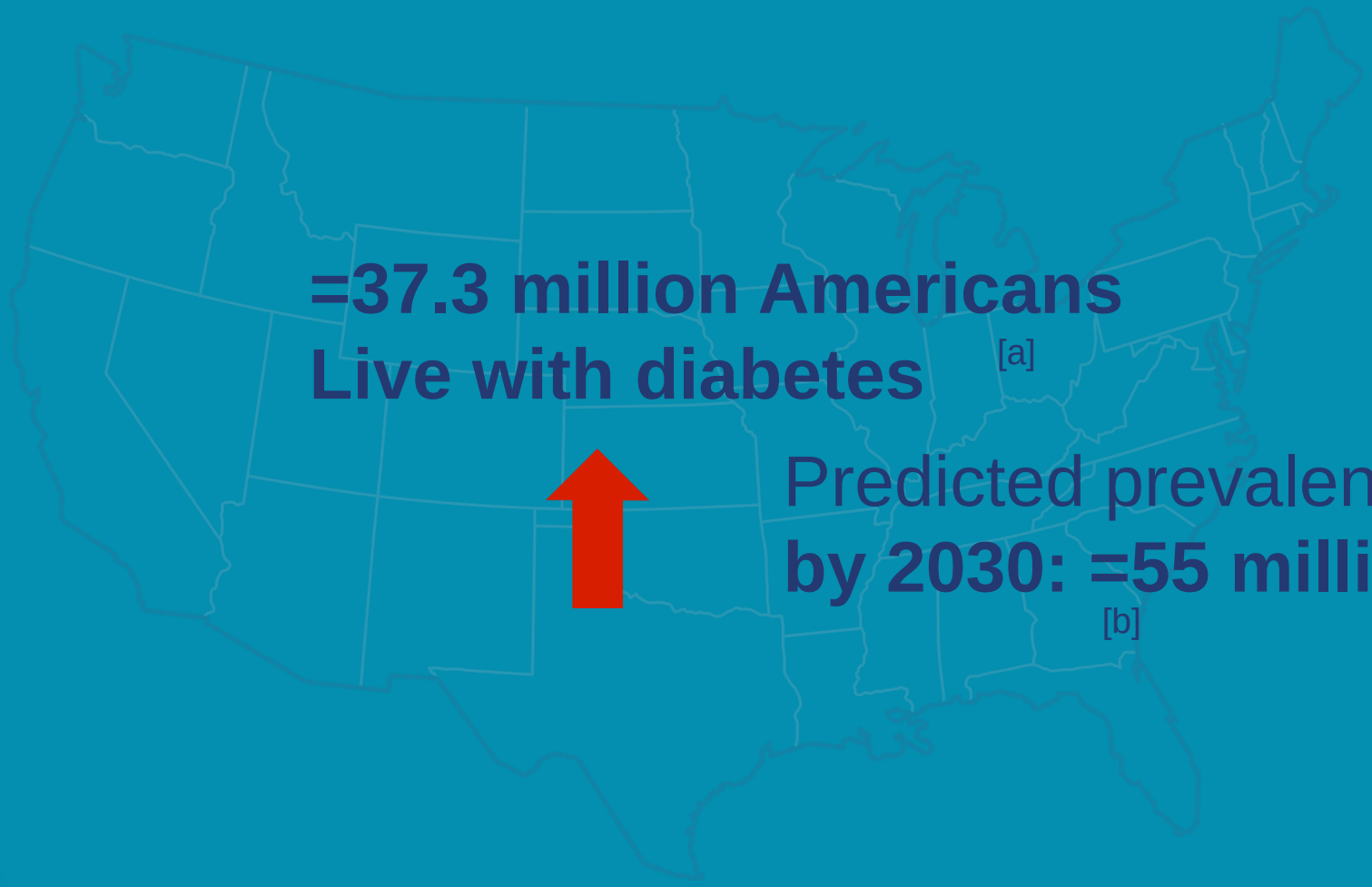
The Prevalence of T2DM is Rapidly Increasing

=37.3 million Americans
Live with diabetes [a]

Cors at the Shore 2023

a. Centers for Disease Control and Prevention. July 18, 2017. Accessed November 10, 2021. https://www.cdc.gov/media/releases/2017/p0718-diabetes-report.html; b. Rowley WR, et al. Popul Health Manag. 2017;20:6-12.

The Prevalence of T2D Is Rapidly Increasing



=37.3 million Americans
Live with diabetes [a]

Predicted prevalence
by 2030: =55 million [b]

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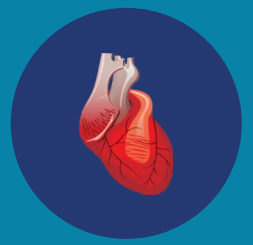
a. Centers for Disease Control and Prevention. July 18, 2017. Accessed November 10, 2021. https://www.cdc.gov/media/releases/2017/p0718-diabetes-report.html; b. Rowley WR, et al. Popul Health Manag. 2017;20:6-12.

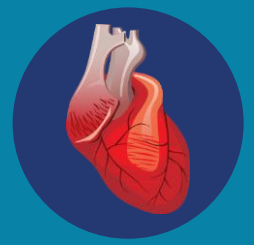
The Link Between T2D and CV Disease

CVD is the Leading Cause of Death in Adults With T2D



2-4 x rate of CVD[a]

Risk of stroke (RR 1.8-6.0)[a]



2 x rate Of HF[a]

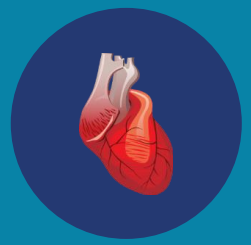
50% greater rate Of CV death[b]

Cors at the Shore 2023

*For adults ≥ 50 years old.
CVD, cardiovascular disease; HF, heart failure.

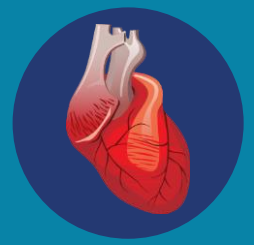
a. Go AS et al. Circulation. 2014;129:e28-e292. b. Franco OH et al. Arch Intern Med. 2007;167:1145-1151.

CVD is the Leading Cause of Death in Adults With T2D



2-4 x rate of CVD [a]

Risk of stroke (RR 1.8-6.0) [a]

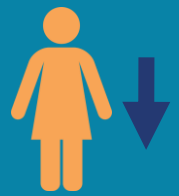


2 x rate Of HF [a]

50% greater rate Of CV death [b]

Reduction in life expectancy associated with diabetes* [b]

7.5 years



8.2 years

2023 Cors at the Shore

*For adults ≥ 50 years old.
CVD, cardiovascular disease; HF, heart failure.

a. Go AS et al. Circulation. 2014;129:e28-e292. b. Franco OH et al. Arch Intern Med. 2007;167:1145-1151.

REPORTCARD

Among US adults aged 18 years or older with diagnosed diabetes, crude estimates for 2015–2018

- 89.8% were overweight or had obesity, defined as a body mass index (BMI) of 25 kg/m^2 or higher
- 49.4% had an A1C value of 7.0% or higher
- 69.0% had a systolic blood pressure of 140 mmHg or higher or diastolic blood pressure of 90 mmHg or higher or were on prescription medication for their high blood pressure
- 44.3% had a non-HDL level of 130 mg/dL or higher

Cors at the Shore 2023

Centers for Disease Control and Prevention. National Diabetes Statistics Report website. https://www.cdc.gov/diabetes/data/statistics-report/index.html. Accessed 04/25/2023

So, what is the good news doc?

From: **Standards of Medical Care in Diabetes—2018 Abridged for Primary Care Providers**

Clin Diabetes. 2018;36(1):14-37. doi:10.2337/cd17-0119

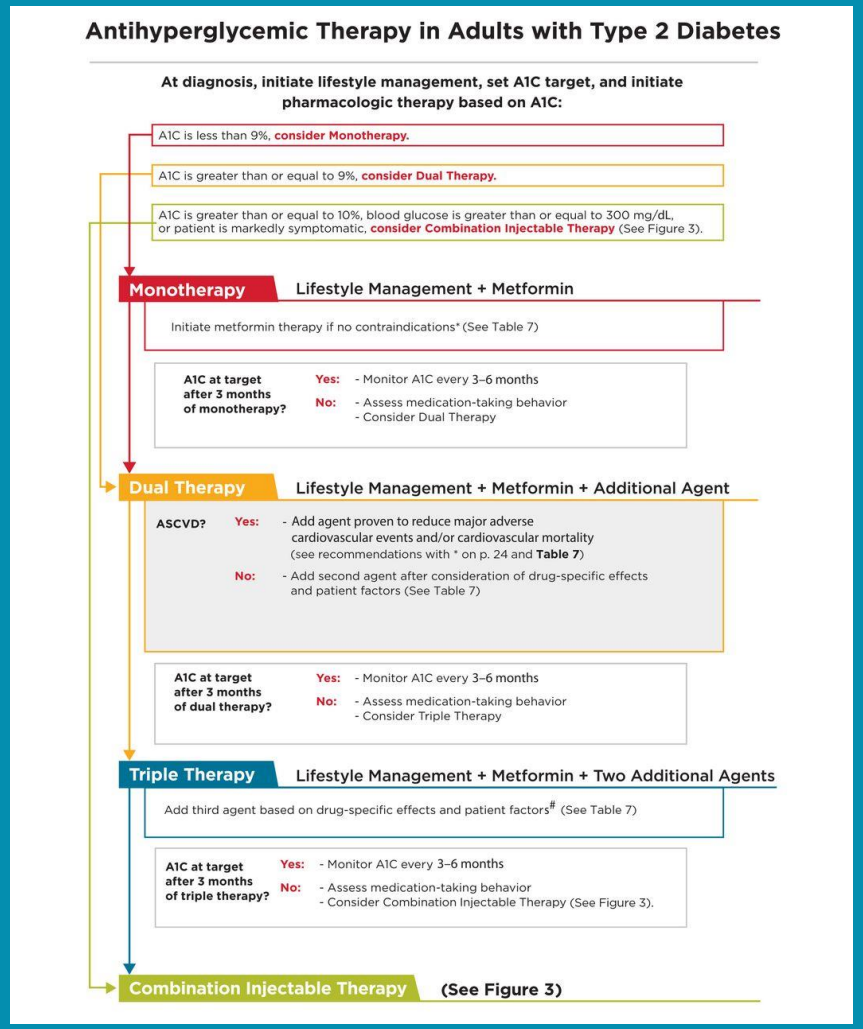


Figure Legend:

Antihyperglycemic therapy in type 2 diabetes: general recommendations. *If patient does not tolerate or has contraindications to metformin, consider agents from another class in Table 7. #GLP-1 receptor agonists and DPP-4 inhibitors should not be prescribed in combination. If a patient with ASCVD is not yet on an agent with evidence of cardiovascular risk reduction, consider adding.

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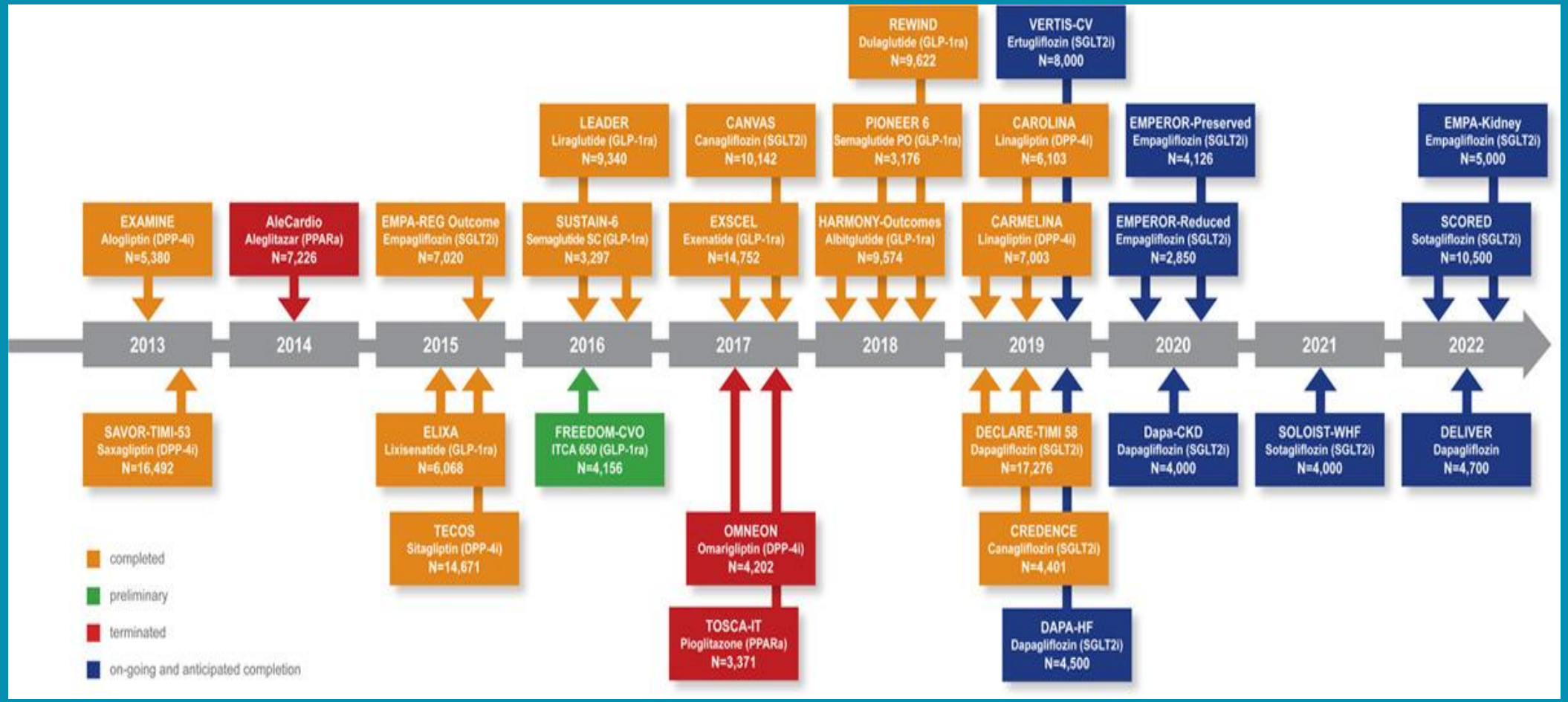
2023 Cors at the Shore

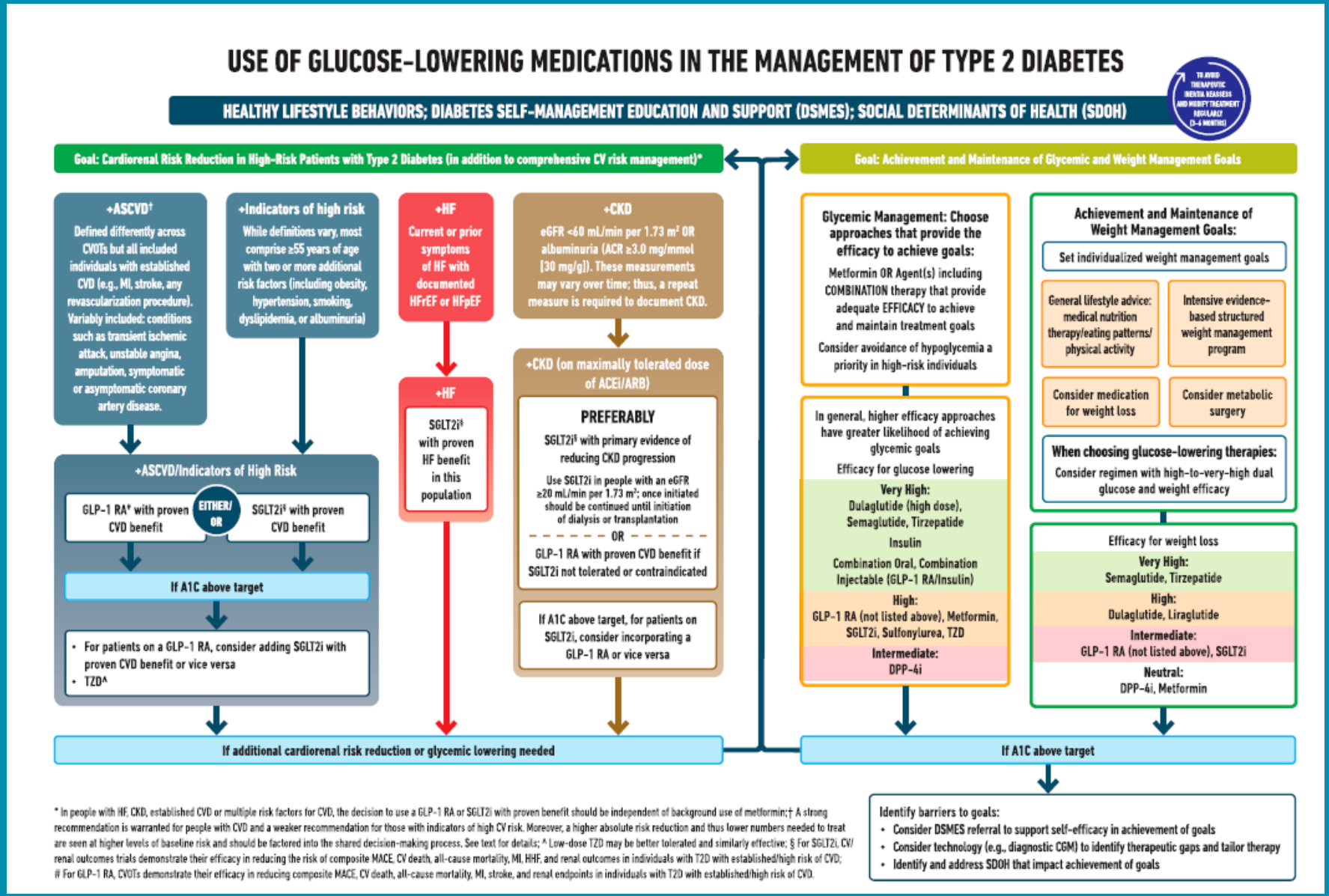
CV & Renal Outcomes Trials in T2DM



Cors at the Shore 2023

Abhinav Sharma. Circulation. Impact of Regulatory Guidance on Evaluating Cardiovascular Risk of New Glucose-Lowering Therapies to Treat Type 2 Diabetes Mellitus, Volume: 141, Issue: 10, Pages: 843-862, DOI: (10.1161/CIRCULATIONAHA.119.041022)

© 2020 American Heart Association, Inc.

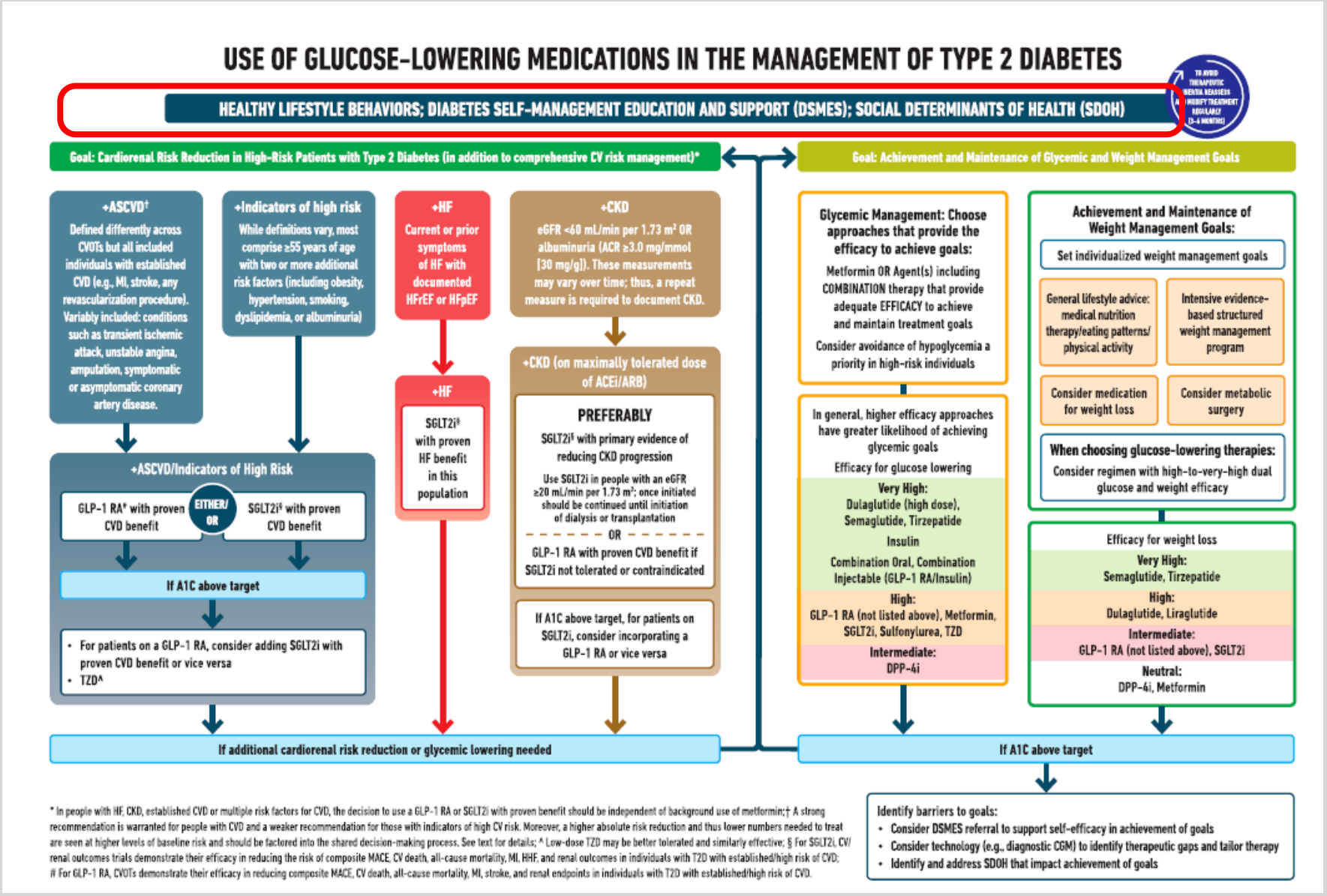


Cors at the Shore 2023

Pharmacologic Approaches to Glycemic Management:
Standards of Care in Diabetes - 2023. *Diabetes Care* 2023;46(Suppl. 1):S140-S157

American Diabetes Association

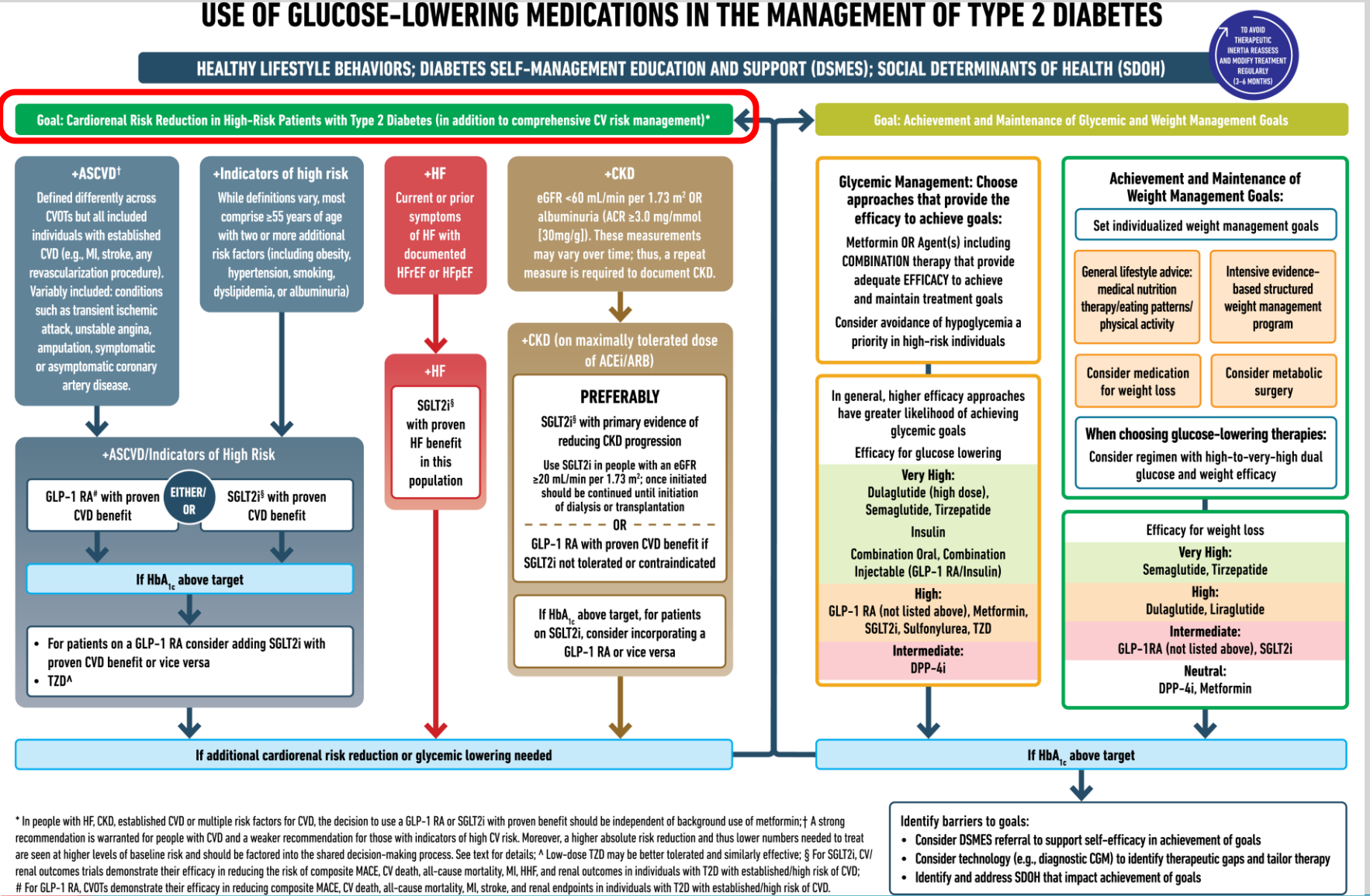
Standards of Medical Care in Diabetes (2023)



First-line: Metformin + Lifestyle Changes

American Diabetes Association

Standards of Medical Care in Diabetes (2022)



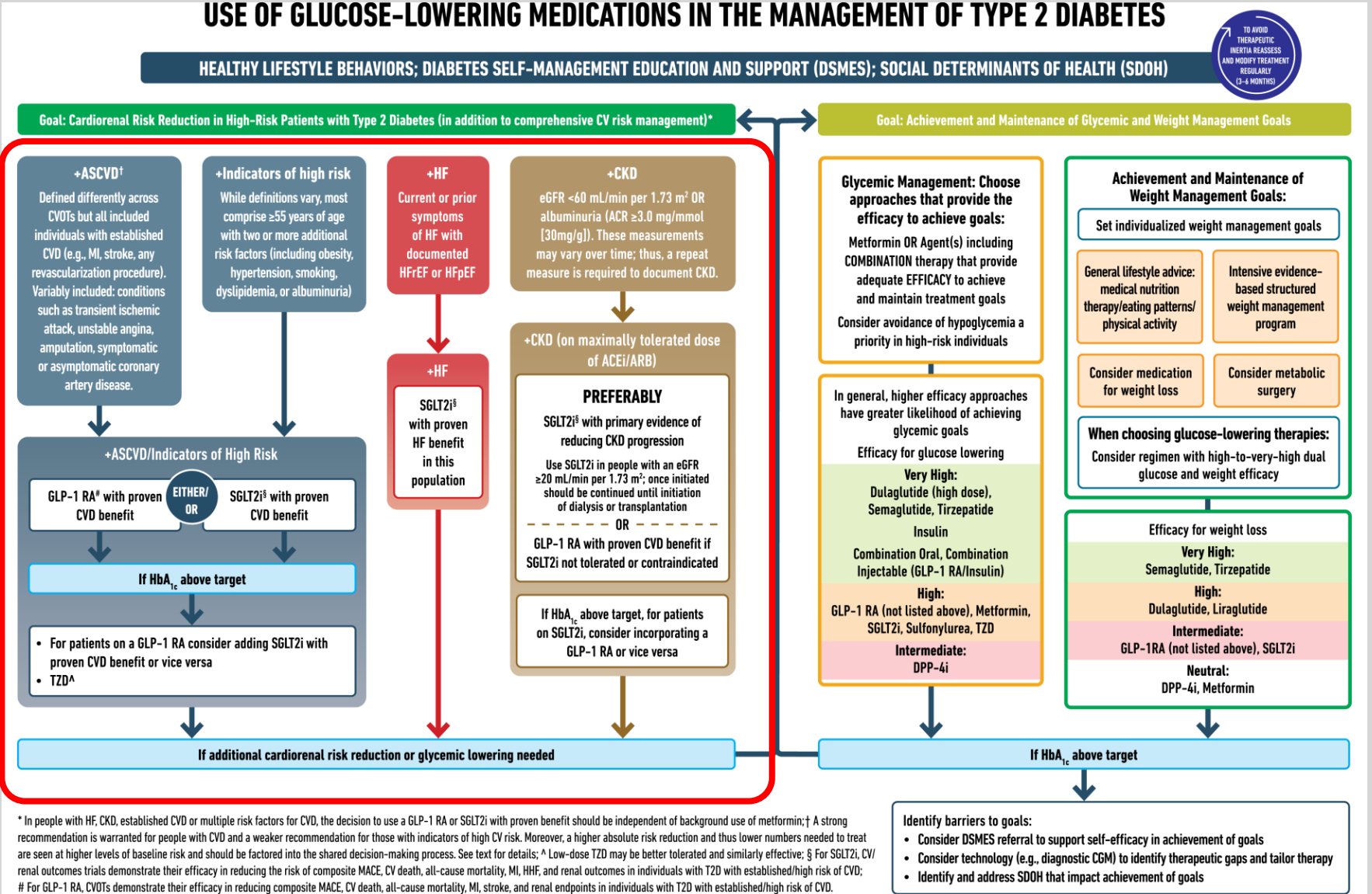
First-line: DSME +/- Metformin

↓

ASCVD, High risk, CKD, or HF?

American Diabetes Association

Standards of Medical Care in Diabetes (2022)



First-line: DSME +/- Metformin

↓

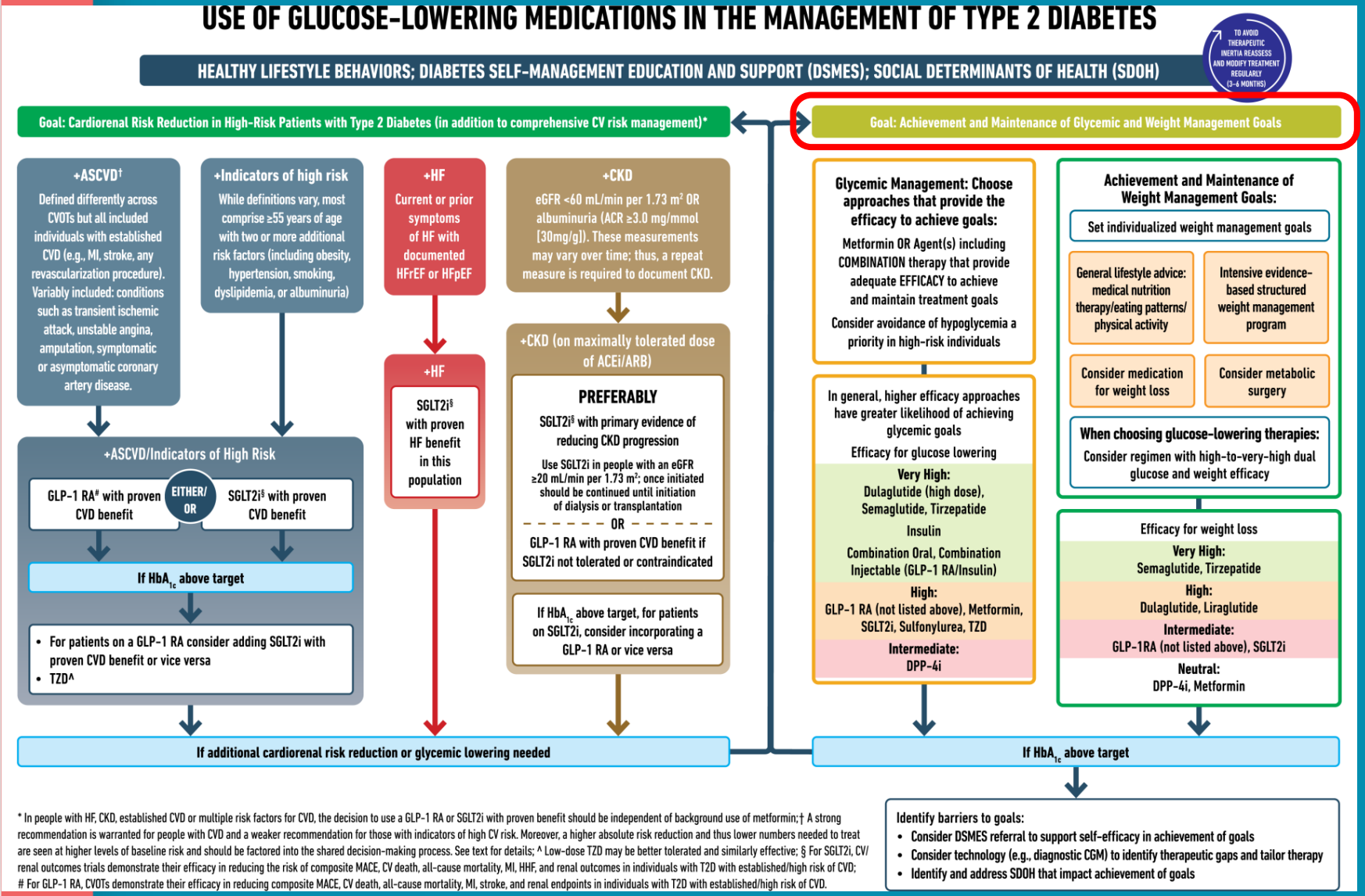
ASCVD, High Risk, CKD, or HF?

↓ **Yes**

GLP-1 RA or SGLT2i

American Diabetes Association

Standards of Medical Care in Diabetes (2023)



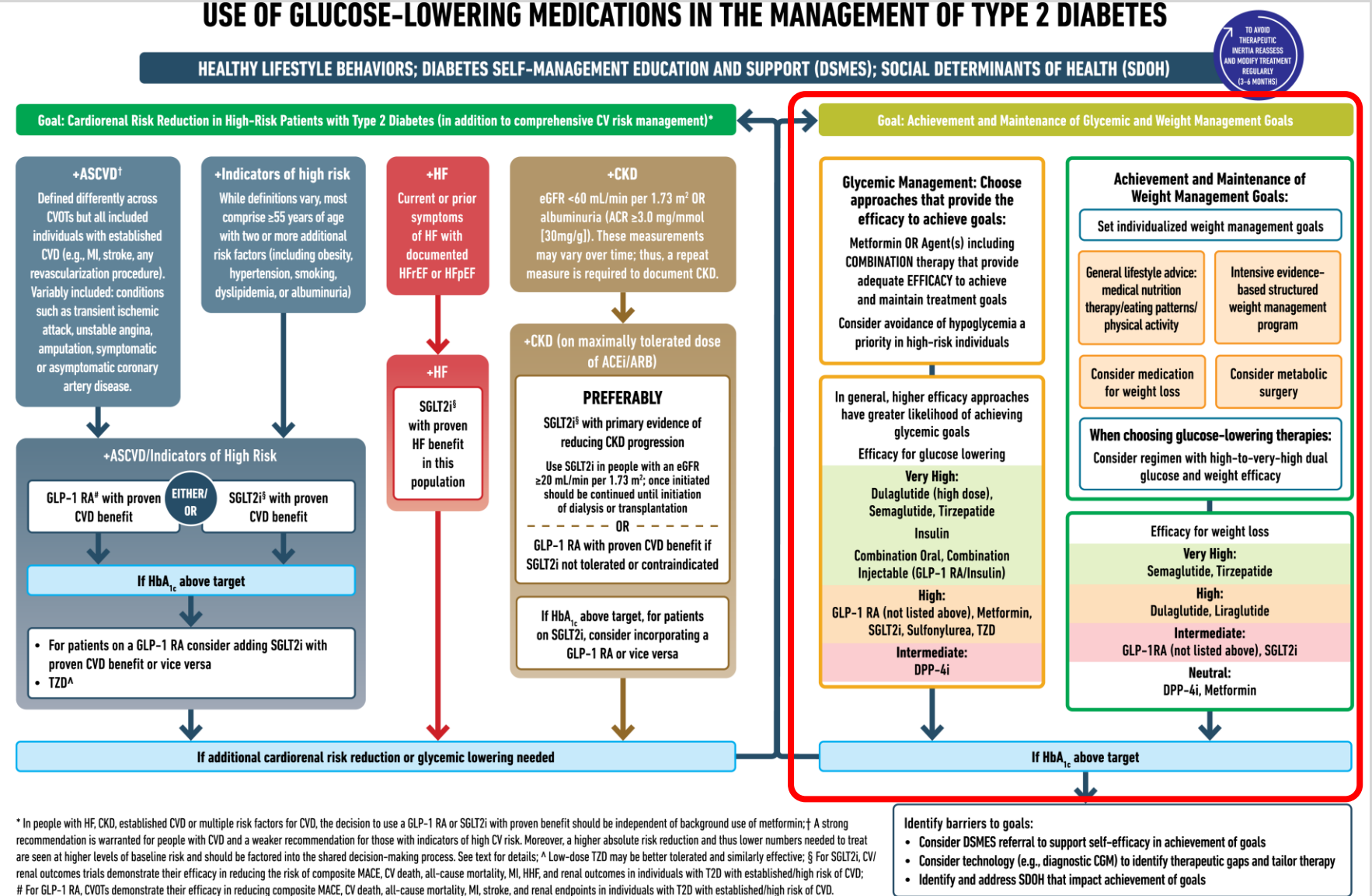
First-line:DSME +/- Metformin

ASCVD, High Risk, CKD, or HF?

No

American Diabetes Association

Standards of Medical Care in Diabetes (2023)



First-line:DSME +/- Metformin

↓

ASCVD, High Risk, CKD, or HF?

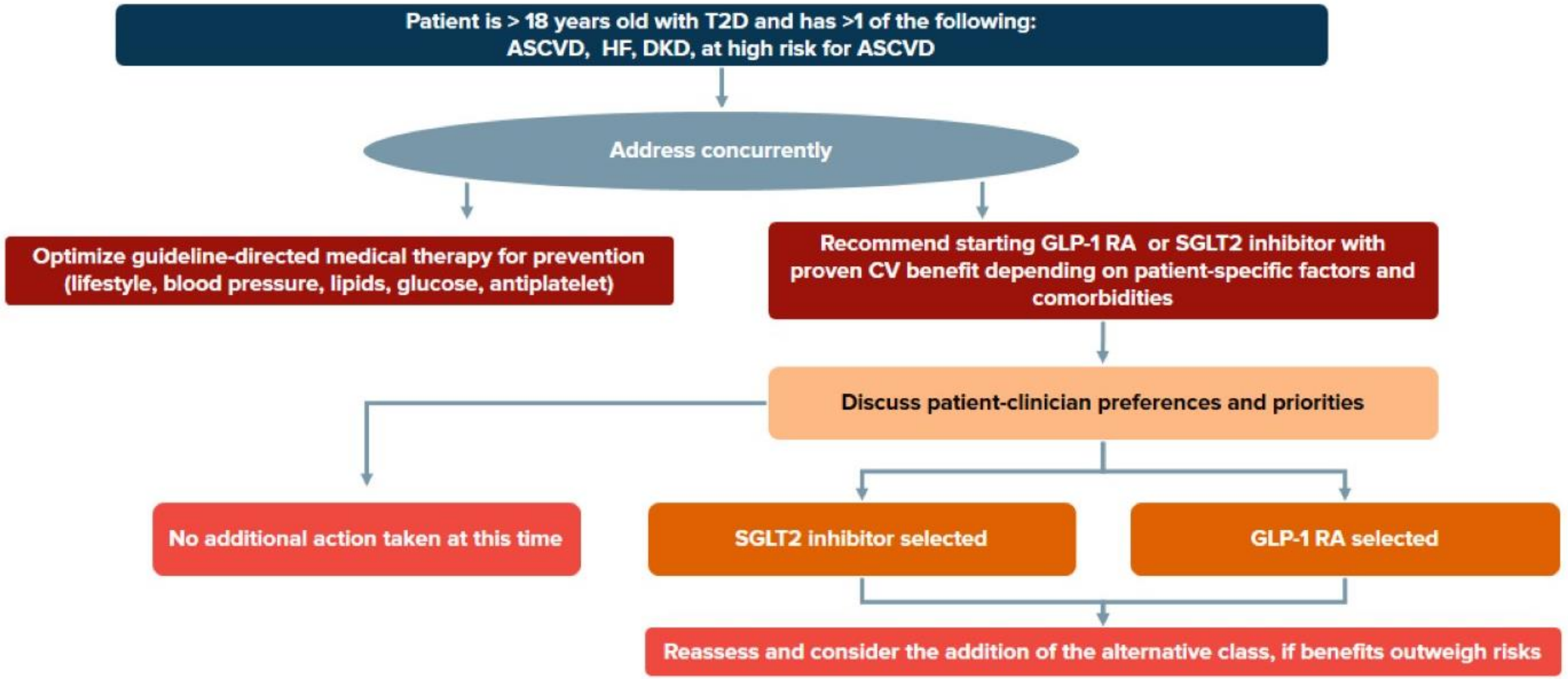
↓

Treatment decisions should Account for hyperglycemia, Weight, and cost

American College of Cardiology

2020 Expert Consensus Decision Pathway

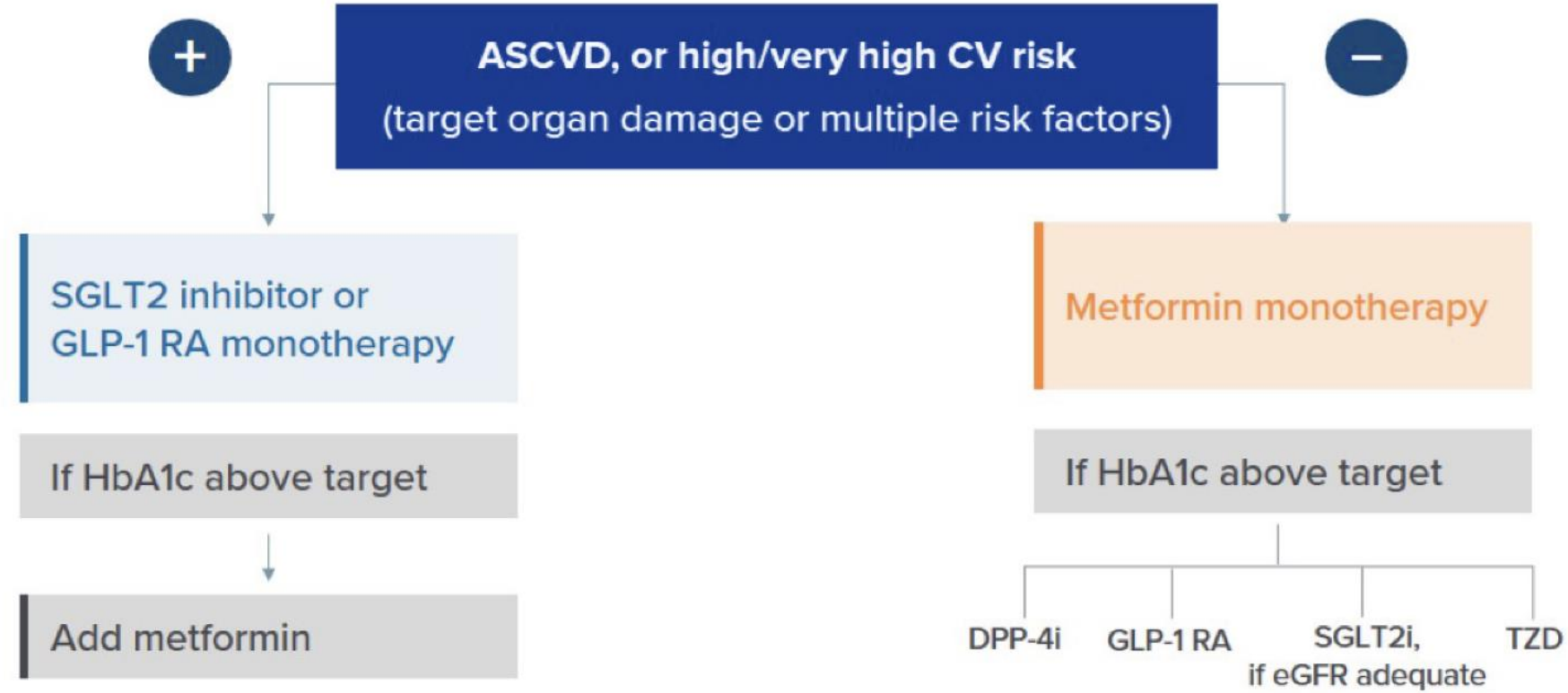
CV Risk Reduction in Patients With T2D



DKD, diabetic kidney disease; ECDP, expert consensus decision pathway.

Das SR, et al. J Am Coll Cardiol. 2020;76:1117-1145.

Treatment algorithm for drug-naive patients with T2D and ASCVD or high/very high CV risk



EASD, European Association for the Study of Diabetes; ESC, European Society of Cardiology.

Cosentino F, et al. Eur Heart J. 2020;41:255-323.

Case Study

Age: 62 years
T2D: 8 years
HbA1c: 8.6%

Medications	Metformin, 1000 mg twice daily Glyburide, 10 mg twice daily
Blood Pressure	128/76 mmHg
BMI	35 kg/m^2
(Cr) eGFR	(1.3) 65 mL/min/1.73 m^2
UACR	28 mg/g

6 weeks post STEMI

- Discharged on Glargine 20 u Hs
- Increase in hypoglycemic episodes (PM and overnight)
- Maybe TIA 2 years ago
- LVEF: 45%
- LDL-C: 110 mg/dl
- Normal physical exam
- ASA 81 mg, Ramipril 10 mg, Pravastatin 40 mg daily, Ticagrelor 30 mg BID, Metoprolol SR 25 mg daily

Cors at the Shore 2023

Question

Taking into consideration the patient's full clinical picture, would you recommend any of the following changes to reduce the patient's cardiovascular risk?

1. Increase the basal insulin
2. Remain on current treatment regimen
3. Add a GLP1-RA
4. Add an SGLT2 inhibitor
5. Switch to high-intensity statin therapy

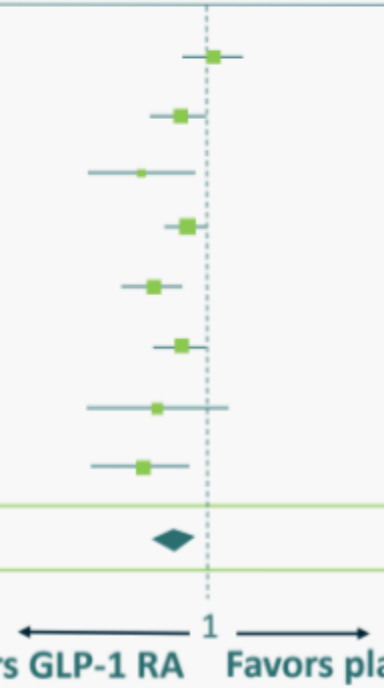
2023 Cors at the Shore

2021 Meta-Analysis of GLP-1 RAs

MACE Outcomes

8 Trials Included, Total of ~60,000 Patients

	GLP-1 RA, %	Placebo, %	MACE HR [95% CI]	*P* value
ELIXA	13	13	1.02 [0.89, 1.17]	.78
LEADER	13	15	0.87 [0.78, 0.97]	.01
SUSTAIN-6	7	9	0.74 [0.58, 0.95]	.016
EXSCEL	11	12	0.91 [0.83, 1.00]	.061
Harmony Outcomes	7	9	0.78 [0.68, 0.90]	.0006
REWIND	12	13	0.88 [0.79, 0.99]	.026
PIONEER 6	4	5	0.79 [0.57, 1.11]	.17
AMPLITUDE-O	7	9	0.73 [0.58, 0.92]	.0069
Subtotal			**0.86 [0.80, 0.93]**	**.0001**



NNT (95% CI) = 65 (45-130)

NNT, number needed to treat

Sattar et al. *Lancet Diabetes Endocrinol.* 2021;9(10):653-662.

Cors at the Shore 2023

2021 Meta-Analysis of GLP-1 RAs
Composite Kidney Outcome (inc. ↓ Albuminuria)

8 Trials Included, Total of ~60,000 Patients

	GLP-1 RA, %	Placebo, %	Composite kidney outcome*, HR [95% CI]	*P* value
LEADER	6	7	0.78 [0.67, 0.92]	.003
SUSTAIN-6	4	6	0.64 [0.46, 0.88]	.005
EXSCEL	6	7	0.88 [0.76, 1.01]	.065
REWIND	17	20	0.85 [0.77, 0.93]	.0004
AMPLITUDE-O	13	18	0.68 [0.57, 0.79]	<.0001
Subtotal (I^2 = 57.4%, *P*=.052)			**0.78 [0.71, 0.87]**	**<.0001**

NNT (95% CI) = 43 (33-74)

NNT, number needed to treat

*Composite kidney outcome: development of macroalbuminuria, doubling of serum creatinine or ≥40% decline in eGFR, kidney replacement therapy, or death due to kidney disease

Sattar et al. *Lancet Diabetes Endocrinol*. 2021;9(10):653-662.

Cors at the Shore 2023

Case Study

Age: 52 years
T2D: 5 years
HbA1c: 8.3%

Medications	Metformin, 1000 mg twice daily Amaryl 2 mg daily, Lisinopril 20 mg daily, Atorvastatin 20 mg daily
Blood Pressure	132/78 mmHg
BMI	36 kg/m^2
eGFR	91 mL/min/1.73 m^2
UACR	26 mg/g

Routine follow-up visit:

- Admits to eating large portions at each meal and exercises 30 minutes 2-3 times a week
- FHx of DM and Obesity
- Lipids are at target
- Glucose control 170-250 mg/dl
- Normal physical exam
- The weight is the patient's primary concern today

Cors at the Shore 2023

Case Study

Age: 52 years
T2D: 5 years
HbA1c: 8.3%

Medications	Metformin, 1000 mg twice daily Amaryl 2 mg daily, Lisinopril 20 mg daily, Atorvastatin 20 mg daily
Blood Pressure	132/78 mmHg
BMI	36 kg/m^2
eGFR	91 mL/min/1.73 m^2
UACR	26 mg/g

What would you recommend for this patient?

A. Continue treatment and increase exercise to 150 min/week

B. Stop the Amaryl and add a DDP IV inh

C. Start SGLT2 inh

D. Start GLP1 RA

E. Start GIP/GLP1 RA

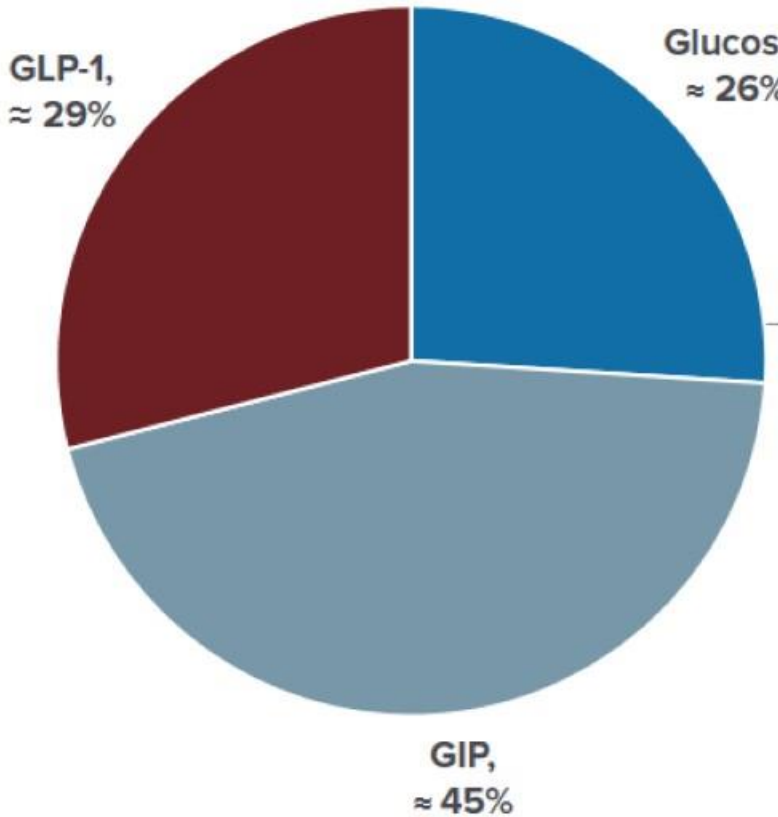
Cors at the Shore 2023

Introduction

GLP-1 Receptor Agonist Class	▪ First agent approved by US FDA in 2005[a] ▪ Since then, 7 agents approved
Proven Glycemic Efficacy	▪ GLP-1 RAs are most efficacious at lowering HbA1c[b] ▪ Low risk of hypoglycemia when used as monotherapy[a,b]
Unmet Needs	▪ People on GLP-1 RAs still fail to achieve glycemic control[b] ▪ PPG control continues to be a challenge[c]

a. Hinnen D, et al. Diabetes Spectr. 2017;30:202-210; b. Nauck MA, et al. Mol Metab. 2021;46:101102; c. van Dijk JW, et al. Diabetes Res Clin Pract. 2011;93:31-37.

Exploring New Treatment Strategies for T2D



- GLP-1 is one of many incretin hormones
- GIP plays a significant role in postprandial glucose control
- Can we harness GIP's effects?

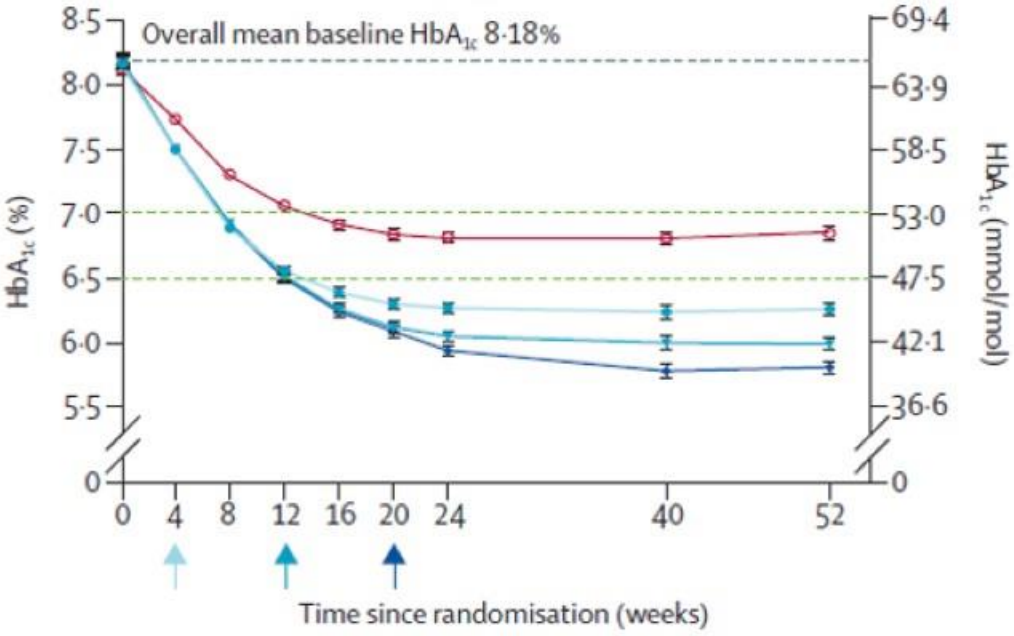
GIP, glucose-dependent insulinotropic polypeptide; T2D, type 2 diabetes.

Holst JJ, et al. Endocrinology. 2021;162:bqab065.

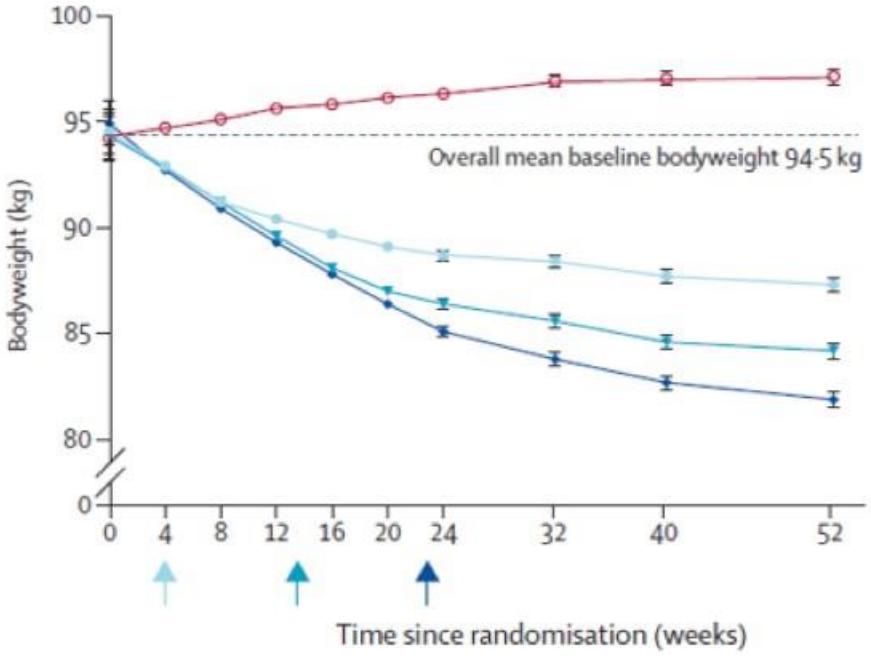
SURPASS-3 (Once-Weekly Tirzepatide vs Once-Daily Degludec)

Tirzepatide 5 mg | Tirzepatide 10 mg | Tirzepatide 15 mg | Insulin degludec

HbA1c Over Time and Change From Baseline at Week 52



Body Weight Over Time From Baseline at Week 52

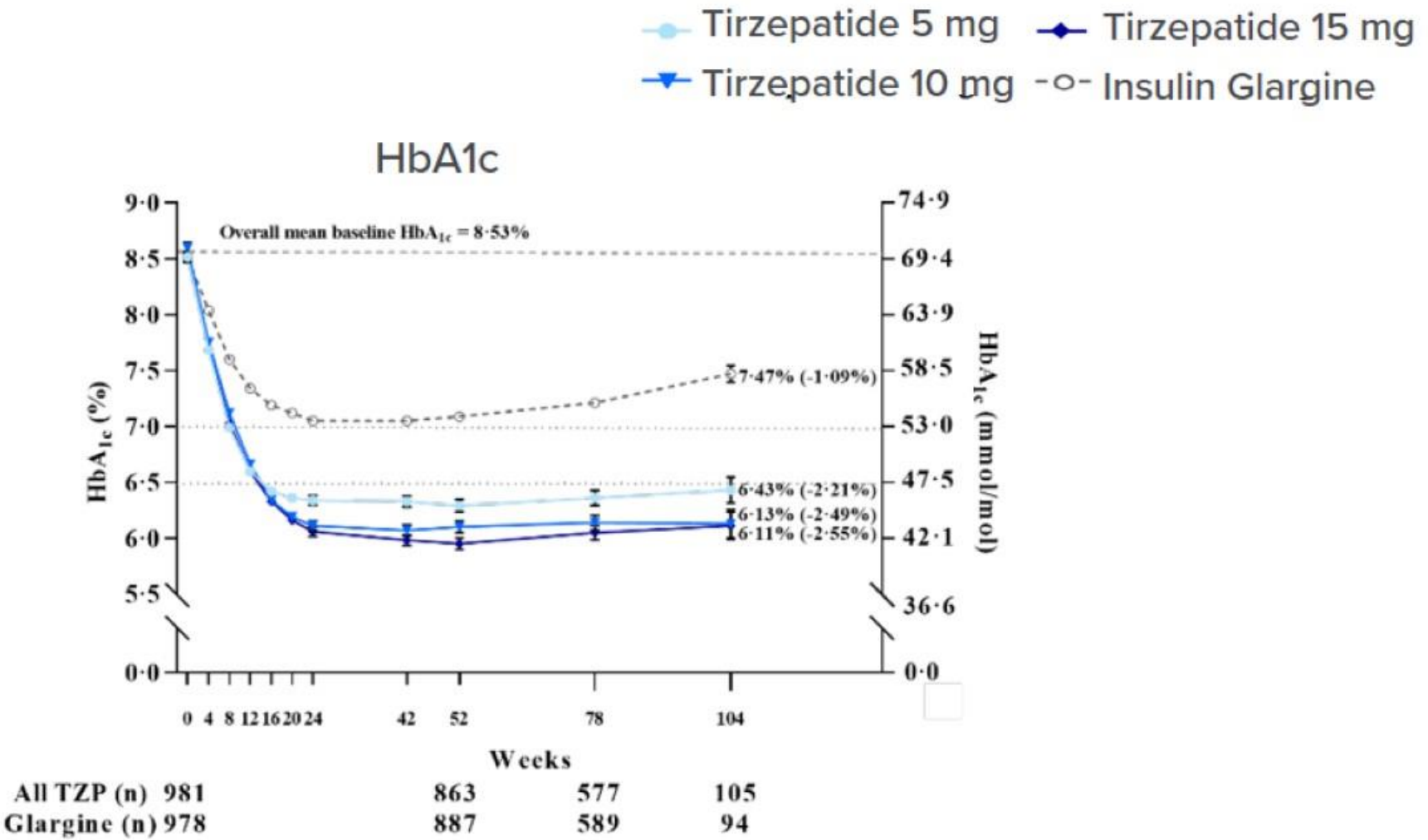


Study Limitations

- Open-label design
- Self-report of GI adverse events
- Exclusion of patients with asymptomatic gastroparesis
- Low proportion of Black and African American participants

Ludvik B, et al. Lancet. 2021;398:583-598.

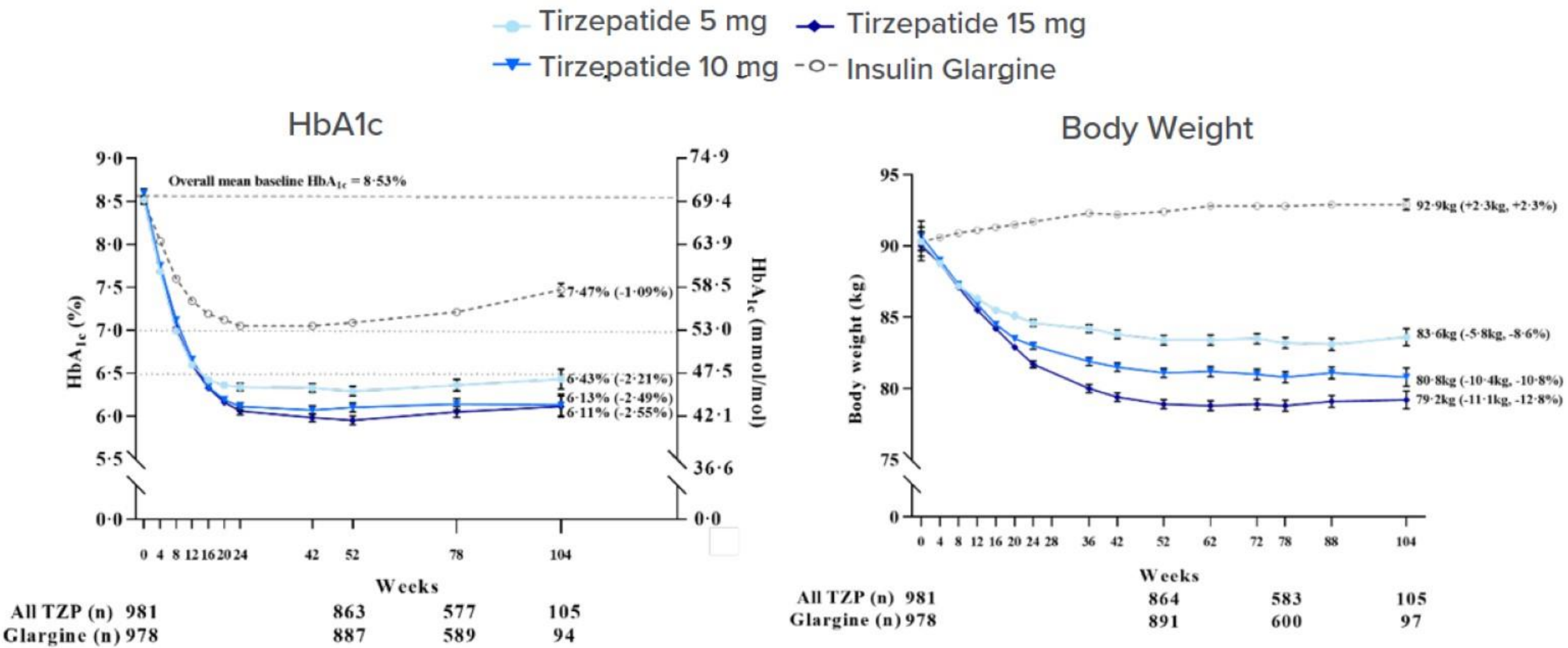
SURPASS-4
HbA1c and Body Weight Change Over Time



mITT population (efficacy analysis set). Data are LSM (SE) over time, MMRM analysis up to 104 weeks. Arrows indicate time of primary endpoint. Dashed lines show baseline values and dotted lines show target values.

Del Prato S, et al. Lancet. 2021;398:1811-1824.

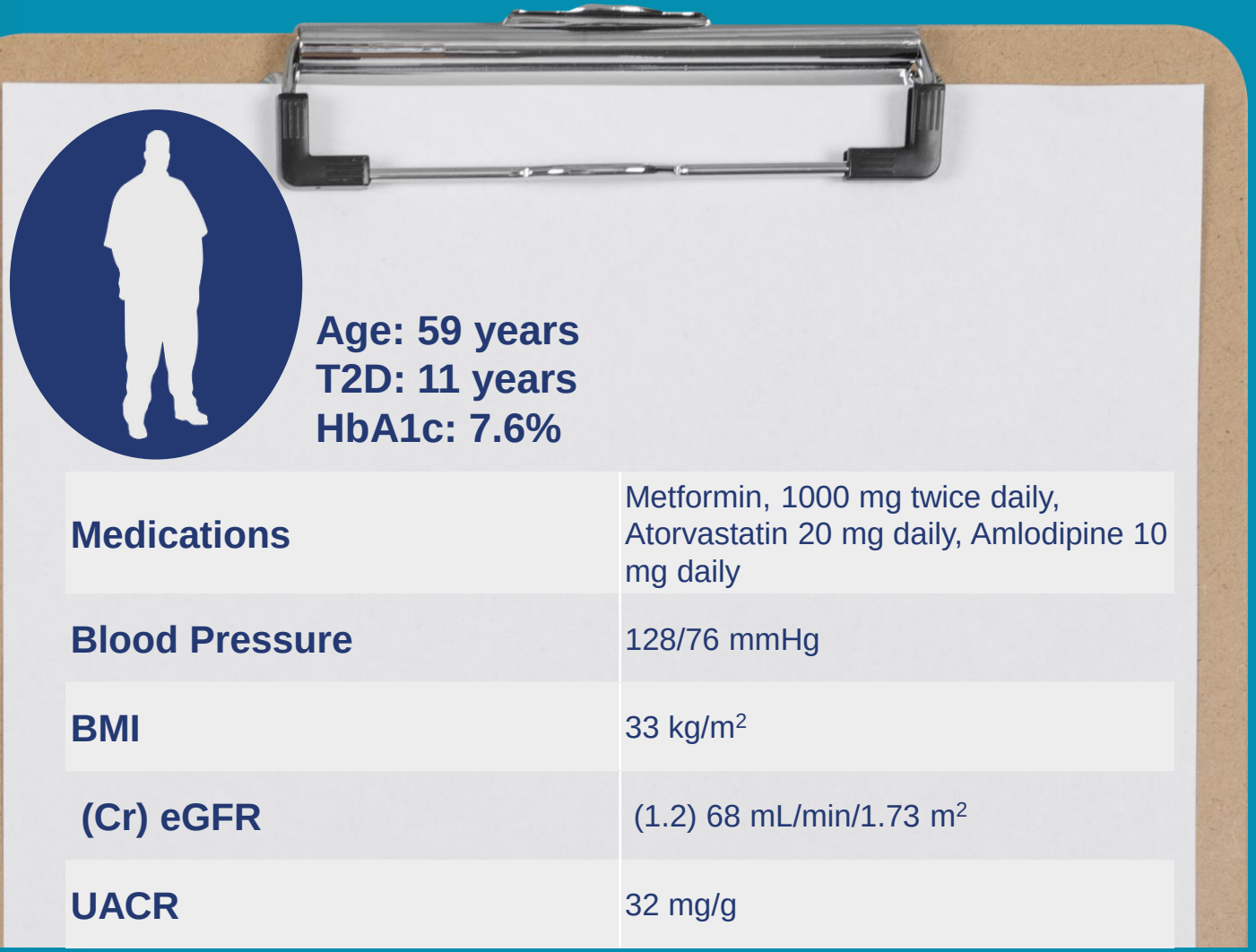
SURPASS-4
HbA1c and Body Weight Change Over Time



mITT population (efficacy analysis set). Data are LSM (SE) over time, MMRM analysis up to 104 weeks. Arrows indicate time of primary endpoint. Dashed lines show baseline values and dotted lines show target values.

Del Prato S, et al. Lancet. 2021;398:1811-1824.

Case Study



Age: 59 years
T2D: 11 years
HbA1c: 7.6%

Medications	Metformin, 1000 mg twice daily, Atorvastatin 20 mg daily, Amlodipine 10 mg daily
Blood Pressure	128/76 mmHg
BMI	33 kg/m^2
(Cr) eGFR	(1.2) 68 mL/min/1.73 m^2
UACR	32 mg/g

Presented to the hospital ER with chest pressure waxing and waning for 2h.

+ diaphoresis, nausea and SOB

- HTN & Obesity
- Smoked 1PPD x 30 yrs
- He underwent cath-> stent to 90% stenosis in LAD; Also had 40%LCx and 30% RCA stenoses
- LVEF: 35-40%
- LDL-C: 110 mg/dl
- Normal physical exam today
- D/C on ASA, Ramipril 10 mg, Rosuvastatin 40 mg daily, Ticagrelor, Metoprolol SR 50 mg daily, Amlodipine 100 mg

Cors at the Shore 2023

What do you want to do next?

- Leave him alone
- Add DDP-4 inhibitor
- Add Basal insulin
- Add Pioglitazone
- Add SGLT-2 inhibitor

Cors at the Shore 2023

Reduction in Mortality, Hospitalization, and Urgent Visits With SGLT2i

- A meta-analysis of >20,000 patients from 15 RCTs noted a:[1]
  - 31% reduction in hospitalization for heart failure
  - 61% reduction in urgent visits for heart failure
  - 14% reduction in all-cause mortality
  - 14% reduction in cardiovascular mortality

Trial Name	SGLT2i
CANVAS	Canagliflozin
CREDENCE	Canagliflozin
DAPA-HF[2]	Dapagliflozin
DECLARE-TIMI	Dapagliflozin
EMPA-REG OUTCOME	Empagliflozin
EMPEROR-REDUCED[3]	Empagliflozin
SOLOIST-WHF[4]	Sotagliflozin
VERTIS-CV	Ertugliflozin

Considerations for Selecting GLP-1 RAs vs SGL T2 inhibitors

GLP-1 RA[a-d]

- ASCVD predominates
- Prevention of MACE is critical
- eGFR < 30 mL/min/1.73 m^2
- Greater HbA1c reduction needed
- Weight loss is a priority
- Individual patient traits and preferences

SGLT2 Inhibitor[a-c]

- HF or CKD predominates
- Gallbladder disease or history of pancreatitis
- Family or personal history of medullary thyroid cancer or MEN2
- Individual patient traits and preferences

GLP-1 RAs and SGLT2 inhibitors can be used in combination in many patients[a]

MACE, major adverse cardiovascular events; MEN2, multiple endocrine neoplasia 2.

a. Buse JB et al. Diabetes Care. 2020;43:487-493. b. American Diabetes Association. Diabetes Care. 2019;42(suppl 1):s1-s193. c. US Food and Drug Administration. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed November 2, 2021. d. Thong KY et al. Prim Care Diabetes. 2018;12:45-50.

CARDIOVASCULAR DISEASE AND RISK MANAGEMENT

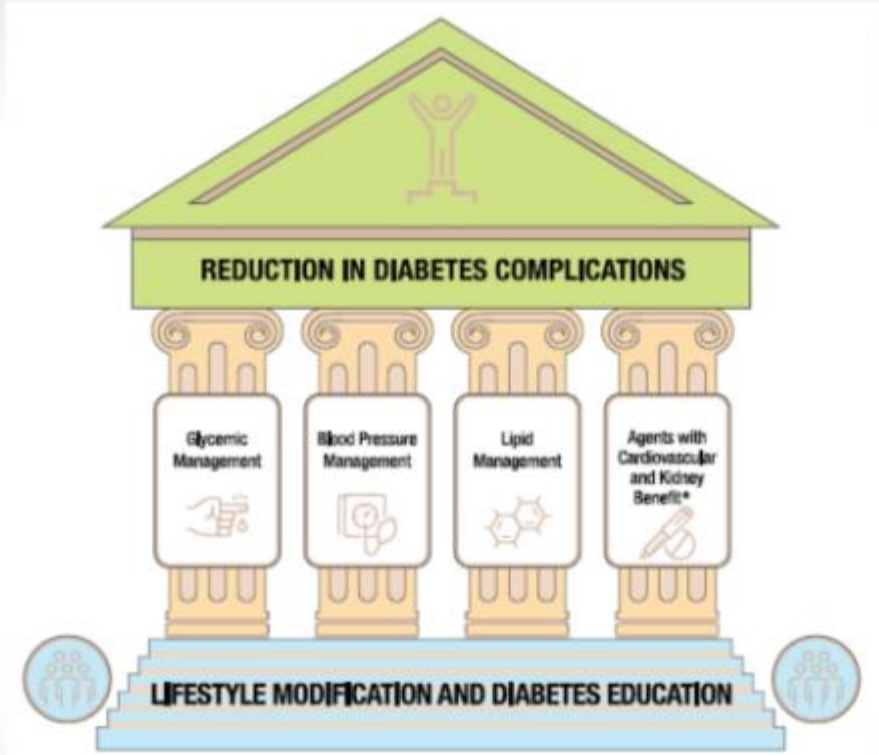


Figure 10.1—Multifactorial approach to reduction in risk of diabetes complications. *Risk reduction interventions to be applied as individually appropriate.

Cardiovascular Disease and Risk Management:
Standards of Medical Care in Diabetes – 2023 Diabetes Care 2023;46(Suppl. 1):S140–S157

American Diabetes Association.
Connected for Life

Cors at the Shore 2023

Take home message

We need to shift from just thinking about the glucose and ask why not a GLP 1RA or SGLT 2 inh and assess CV risk (e.g. for ASCVD, ASCVD risk, CKD and/or HF)

Multidisciplinary Care for Effective T2D Management

Cors at the Shore 2023