

Approach to Glycemic Management of Type 2 Diabetes

Margo Hudson, MD

Assistant Professor of Medicine

Harvard Medical School

None of the individuals in a position to influence the content for this educational activity have a relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

MAVEN Project is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

MAVEN Project designates this live activity for a maximum of 1 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Objectives

- To understand the relationship of glucose and outcomes in diabetes
- To understand the different medications used to control glucose
- To understand the new priorities for choosing and combining medications

JANUARY 2026

Diabetes Care

JANUARY 2026 | VOLUME 49 | SUPPLEMENT 1
DIABETESJOURNALS.ORG/CARE

Diabetes Care®



Standards of Care in Diabetes—2026

VOLUME 49 | SUPPLEMENT 1 | PAGES S1-S371

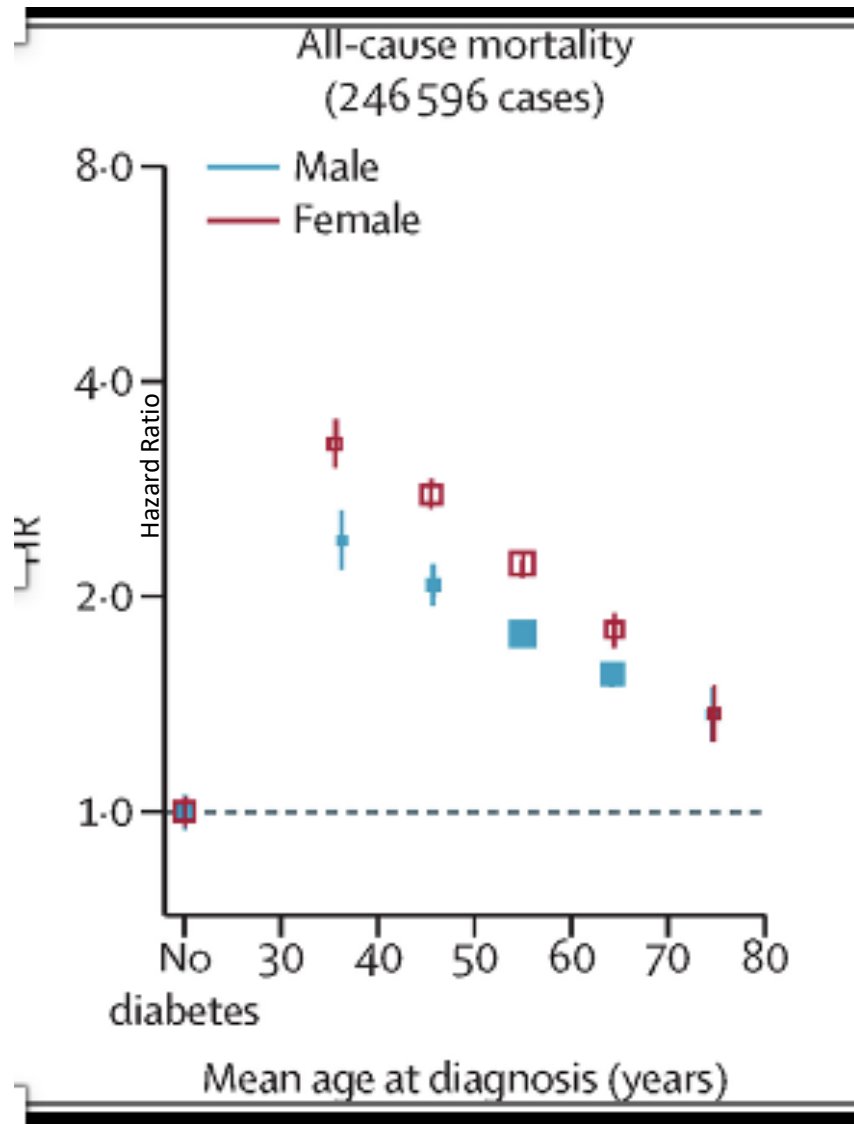


ISSN 0149-5992

Outline

- Goals of therapy
- What are the priorities?
- Mechanisms of action of different classes
- Specifics of the different classes
- Tips on combination therapy
- (BTW this talk doesn't discuss insulin in any detail)

Imperative to Treat: Adverse Outcomes in T2DM

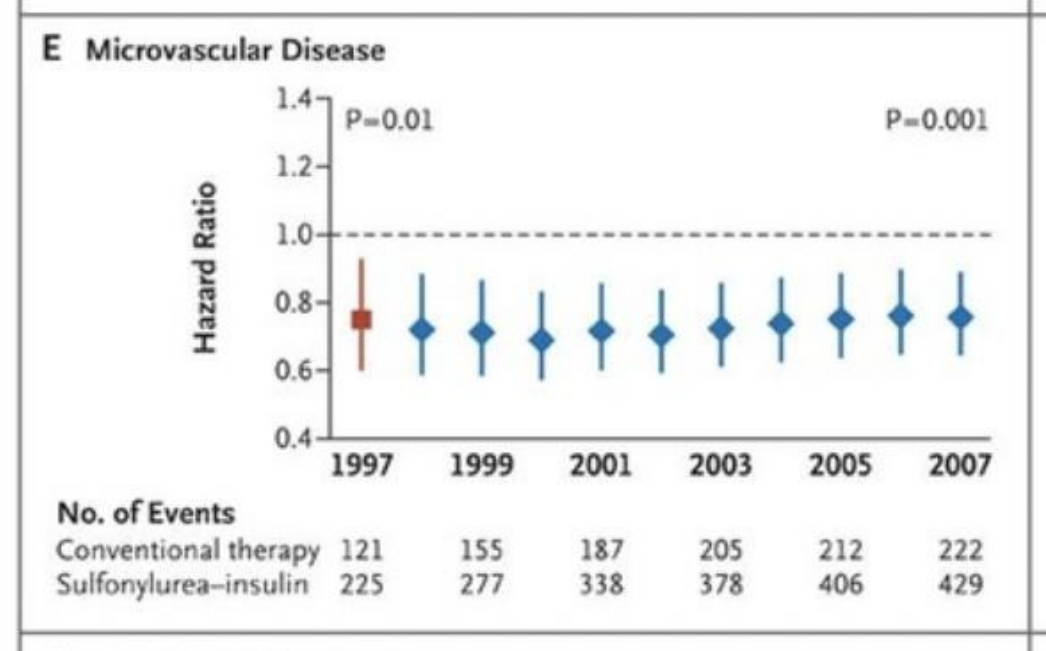
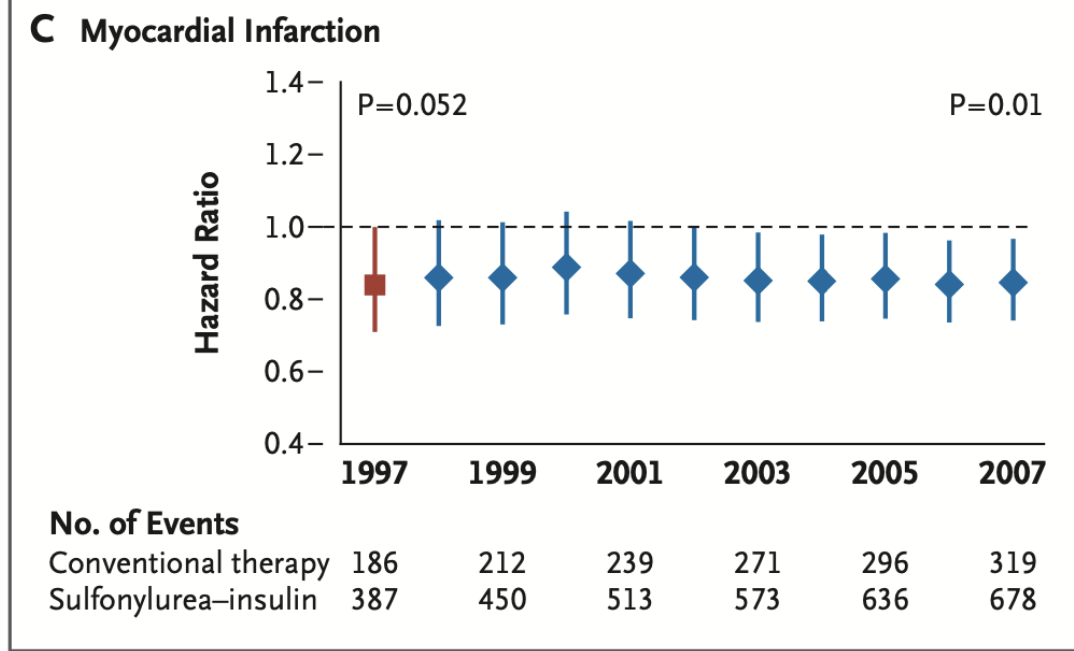


A woman diagnosed with T2DM in her 40's has **3 times** the mortality of age matched women without diabetes
A man has about **twice** the risk as men without diabetes

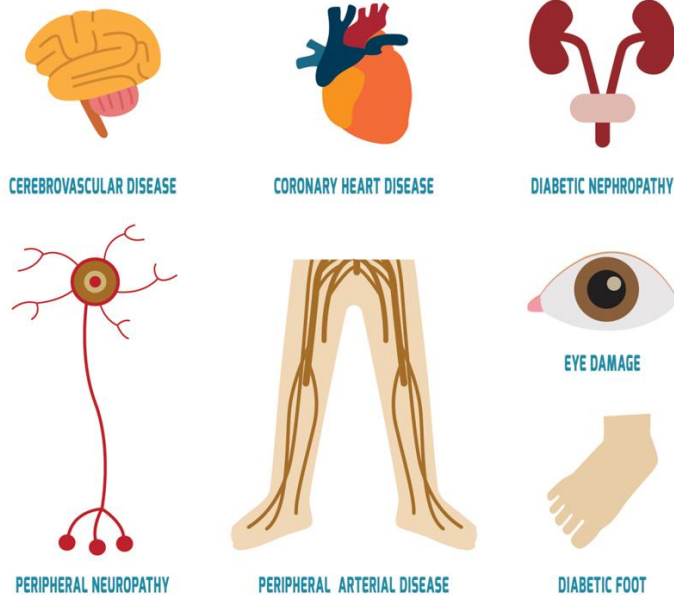
Long-term benefit for glycemic control in T2DM: Metabolic Memory

Persistent CVD benefit after UKPDS

Persistent microvascular benefit in UKPDS



What can be achieved with glucose control?



1% lower A1c translates to a risk reduction of:

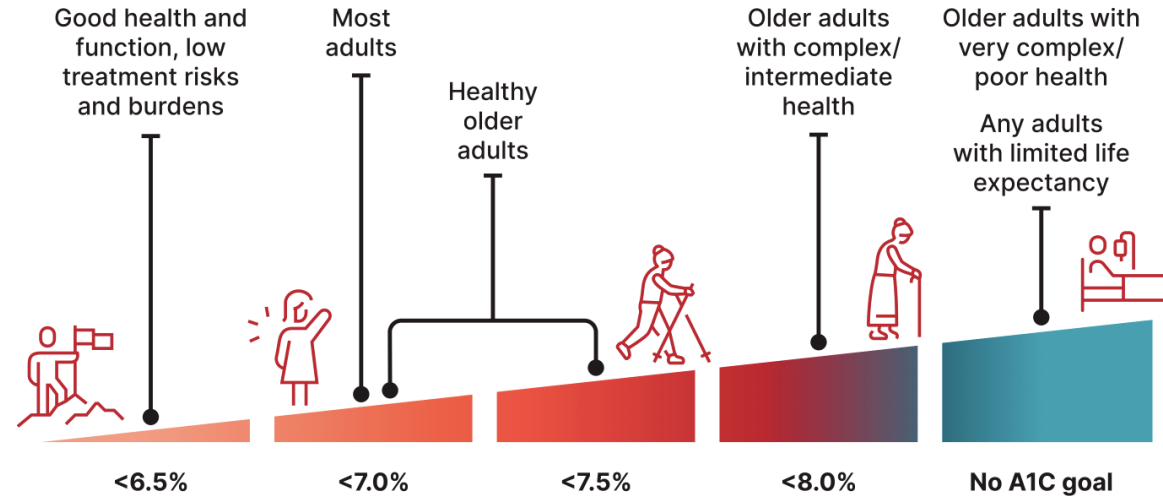
- 43% PVD
- 37% for microvascular complications
- 21% DM-related death
- 14% all-cause mortality
- 14% MI
- 11% CVA

UKPDS Stratton IM et al. *BMJ*. 2000;321:405-412

UKPDS 75. *Diabetologia* 49:1761-9, 2006

Turner R *Annals of Internal Medicine* 124: 136-145, 1996

Treating Diabetes: Set a glycemic target



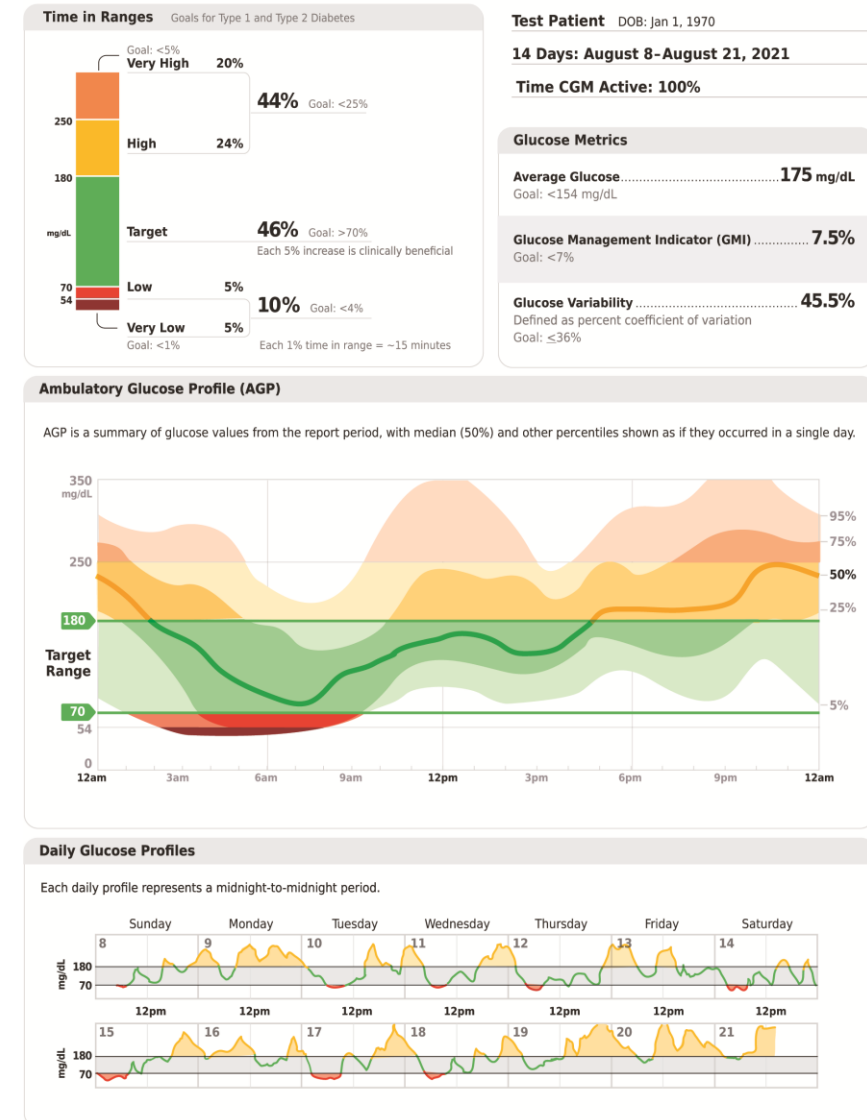
Modifying Factors

Favor more stringent goal	Favor less stringent goal
Short diabetes duration	Long diabetes duration
Low hypoglycemia risk	High hypoglycemia risk
Low treatment risks and burdens	High treatment risks and burdens
Pharmacotherapy with cardiovascular, kidney, weight, or other benefits	Pharmacotherapy without nonglycemic benefits
No cardiovascular complications	Established cardiovascular complications
Few or minor comorbidities	Severe, life-limiting comorbidities

Continuous Glucose Monitoring: Time in Range

- If using continuous glucose monitoring the targets are:
 - "In Range" target 70-180 mg/dl
 - >70% time in range
 - <4% time below range
 - <1% time below 54 mg/dl

AGP Report: Continuous Glucose Monitoring



Knowledge Question 1

- Which of the following is true (select all that apply):
 - A. Glucose control lowers risk of complications in Type 2 DM
 - B. Diabetes has a greater impact on mortality in men than women
 - C. “Metabolic memory” is the long-term benefit on complication rate from obtaining good glucose control early after onset of diabetes
 - D. A1C goal should be <7% for patients with T2DM

Knowledge Question 1

- Which of the following is true (select all that apply):
 - A. Glucose control lowers risk of complications in Type 2DM**
 - B. Diabetes has a greater impact on mortality in men than women
 - C. “Metabolic memory” is the long term benefit on complication rate from obtaining good glucose control early after onset of diabetes**
 - D. A1C goal should be <7% for patients with T2DM

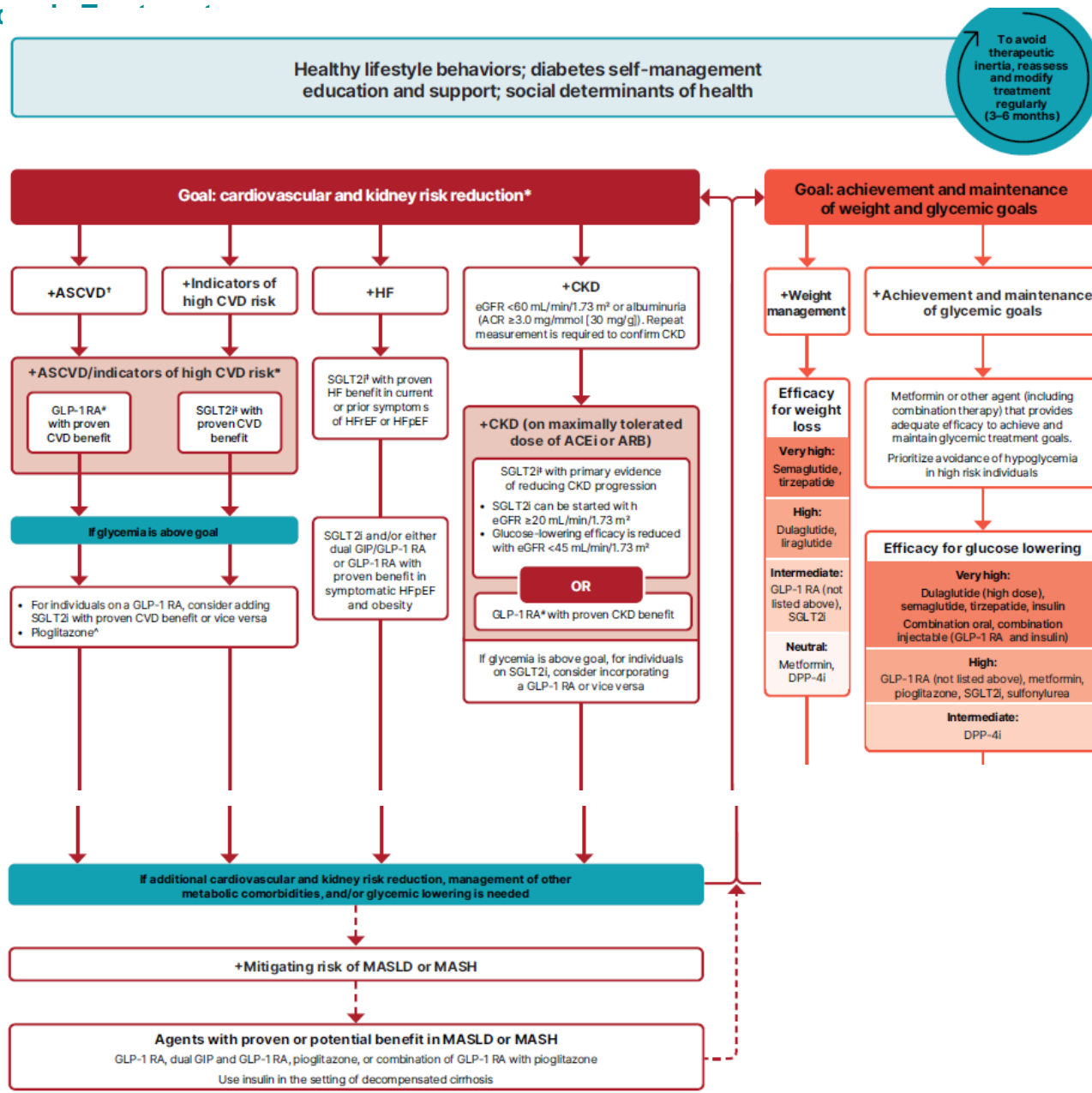
Lifestyle Management is the Foundation for Glycemic Control

- Diet
 - For overweight and obese patients aim for 3%-7% weight loss
 - Individualize meal plans
 - Emphasize minimally processed foods
 - No specific macronutrient mix is “right” for everyone
- Physical behaviors
 - Limit sitting
 - 5-6 minute brisk walk per day can add years to life expectancy
 - Aim for over 150 minutes of moderate intensity exercise a week
 - Resistance exercise and balance training can reduce frailty and falls

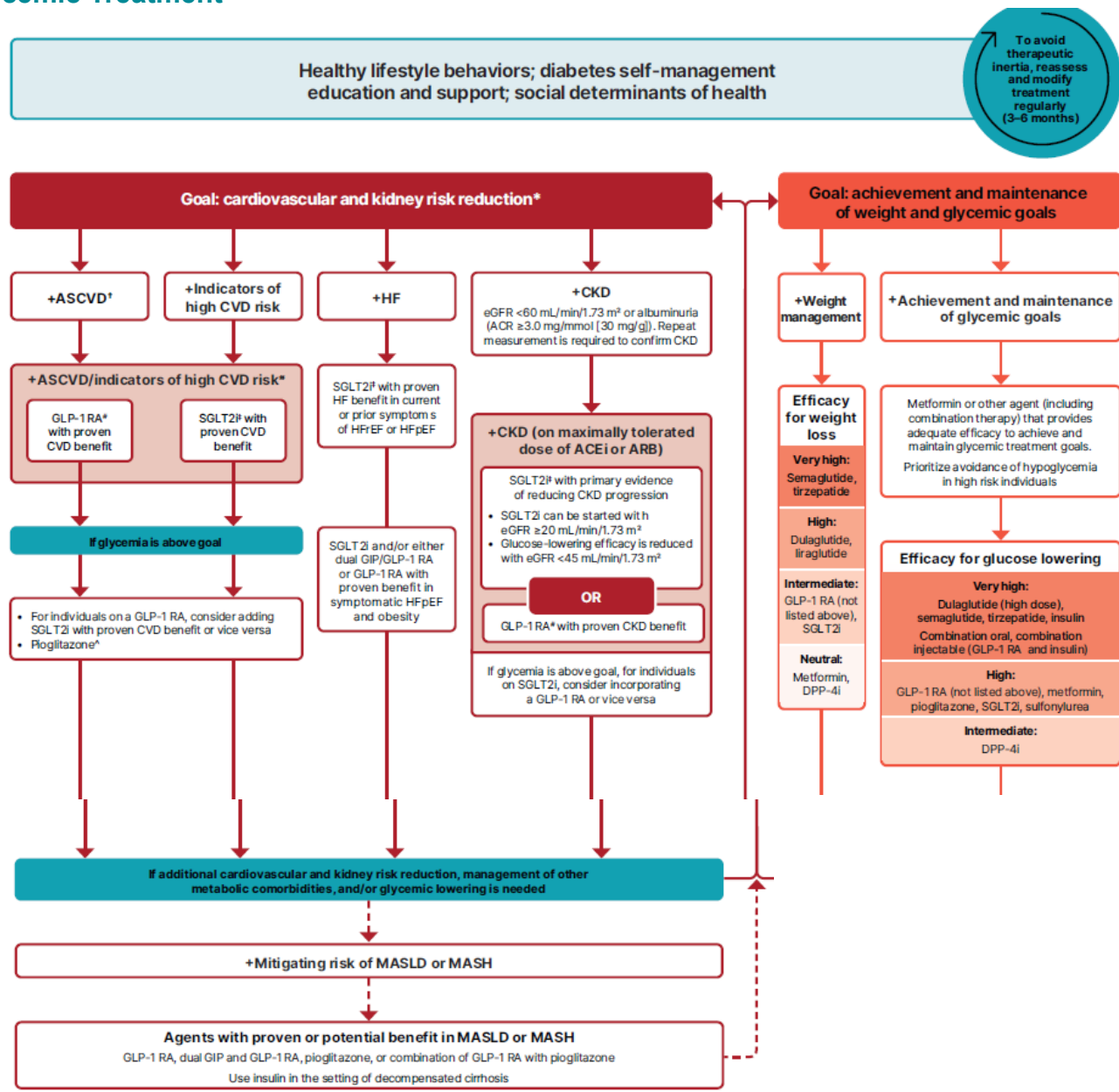
Paradigm for medications has changed

- “Old” Paradigm
 - Glucose lowering efficacy
 - Side effects
 - Cost
- New Paradigm
 - Non-glucose targets
 - Cardiovascular benefit
 - Renal benefit
 - Weight Reduction
 - Liver benefits
 - Glucose lowering efficacy
 - Side effects
 - Cost

9. Pharmacologic Approaches to Glycemic Treatment



9. Pharmacologic Approaches to Glycemic Treatment



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be made irrespective of attainment of glycemic goal.

[†] ASCVD: Defined differently across CVDs but all included individuals with established CVD (e.g., MI, stroke, and arterial revascularization procedure) and variably included conditions such as transient ischemic attack, unstable angina, amputation, and symptomatic or asymptomatic coronary artery disease. Indicators of high risk: While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria).

[‡] A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high risk CVD. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details.

[§] For GLP-1 RAs, CVDs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and kidney endpoints in individuals with T2D with established or high risk of CVD. One kidney outcome trial demonstrated benefit in reducing persistent eGFR reduction and CV death for a GLP-1 RA in individuals with CKD and T2D.

[¶] For SGLT2i, CV and kidney outcomes trials demonstrate their efficacy in reducing the risks of composite MACE, CV death, all-cause mortality, MI, HF, and kidney outcomes in individuals with T2D and established or high risk of CVD.

* Low-dose pioglitazone may be better tolerated and similarly effective as higher doses.

Figure 9.4 Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes - 2026*. *Diabetes Care* 2026;49(Suppl. 1):S183-215

9. Pharmacologic Approaches to Glycemic Treatment

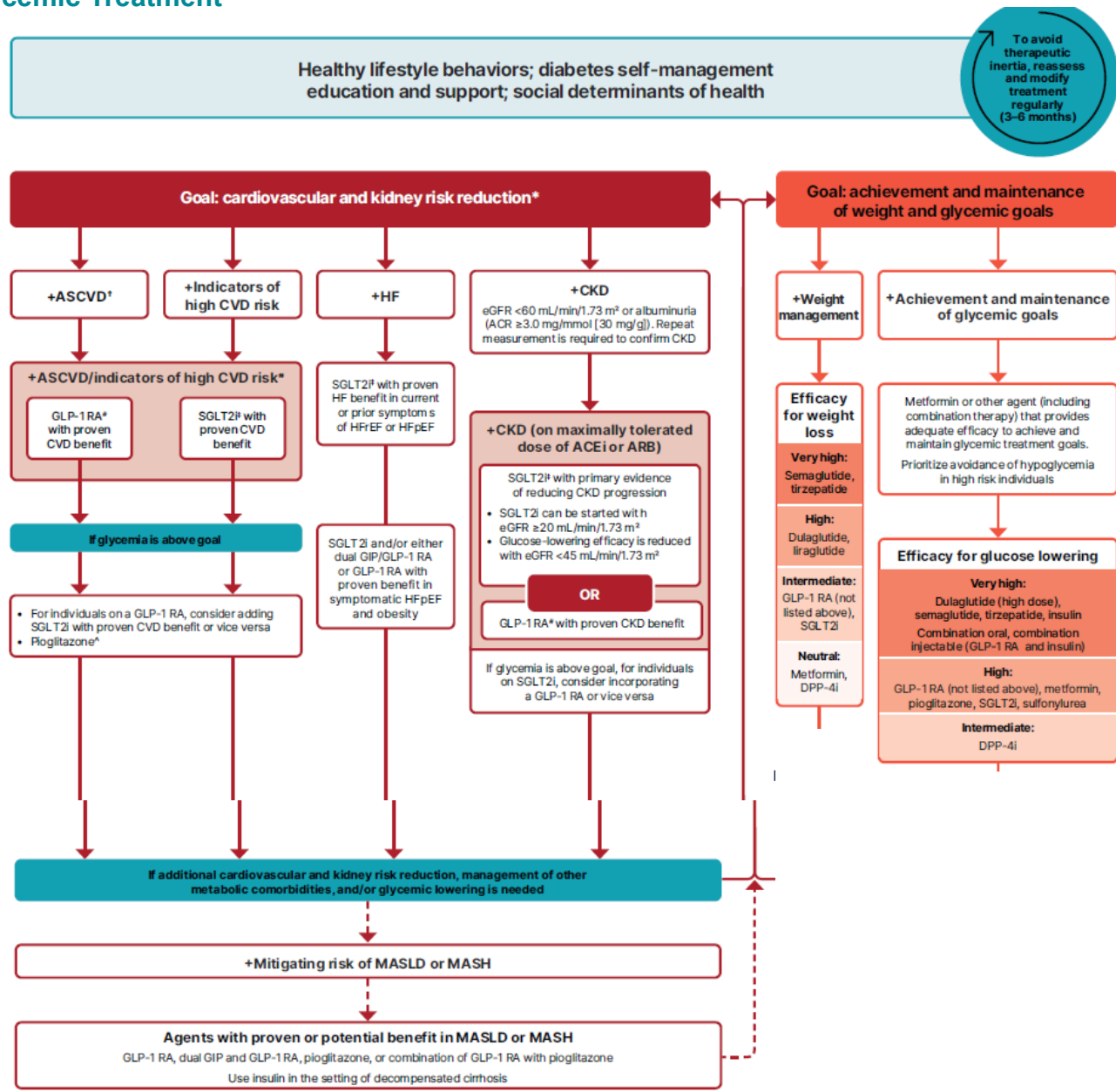


Figure 9.4 Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes - 2026. Diabetes Care 2026;49(Suppl. 1):S183-215*

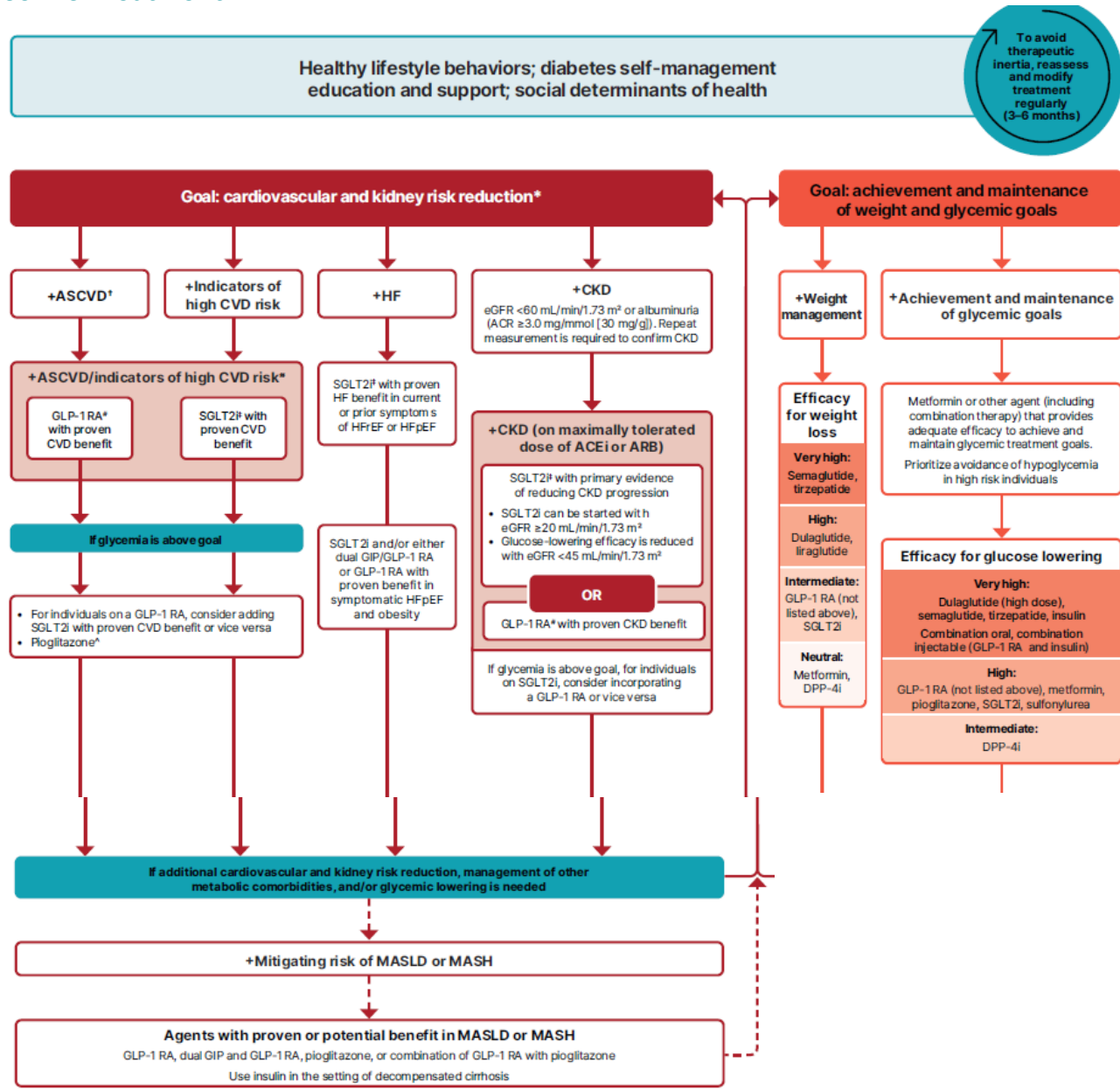
Metformin

- Has been the foundation of T2DM pharmacotherapy.
- ADA 2022: “First-line therapy depends on comorbidities, patient-centered treatment factors, and management needs and generally includes metformin and comprehensive lifestyle modification.”
- ADA 2024 : No longer given primacy as “first-line” but “may reduce CVD and death”
- Metformin use can be associated with vitamin B12 malabsorption so periodically check B12 level

eGFR	Initiation	Continuation
>45	OK to initiate	Max dose 2550 mg total daily
30-45	Not recommended	- FDA: If already on metformin and eGFR falls to between 30-45, assess risks/benefits of continuing - In practice: Consider lowering the dose to maximum of 1000 mg total daily
<30	Contraindicated	Discontinue



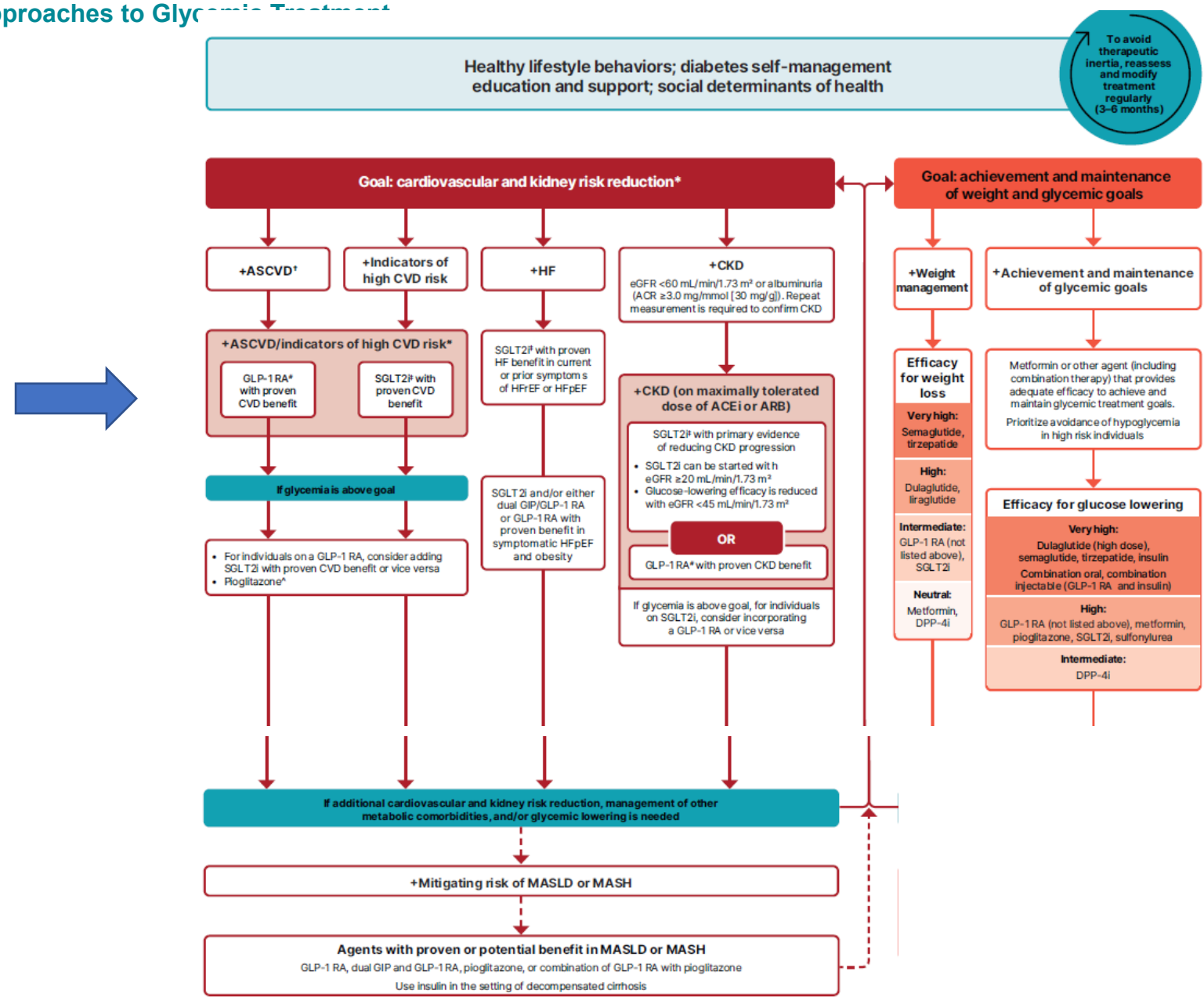
9. Pharmacologic Approaches to Glycemic Treatment



What is meant by Atherosclerotic Cardiovascular Disease?

- Established CVD
 - MI
 - CVA
 - Peripheral vascular disease
 - History of revascularization procedure
 - Angina
 - TIA
- “High risk for ASCVD”
 - Diabetes and age over 55 with 2 or more risk factors
 - Obesity
 - HTN
 - Smoking
 - Hyperlipidemia
 - Albuminuria

9. Pharmacologic Approaches to Glycemic Treatment



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be made irrespective of attainment of glycemic goal.

[†] ASCVD: Defined differently across CVDs but all included individuals with established CVD (e.g., MI, stroke, and arterial revascularization procedure) and variably included conditions such as transient ischemic attack, unstable angina, amputation, and symptomatic or asymptomatic coronary artery disease. Indicators of high risk: While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria).

[‡] A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high risk CVD. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details.

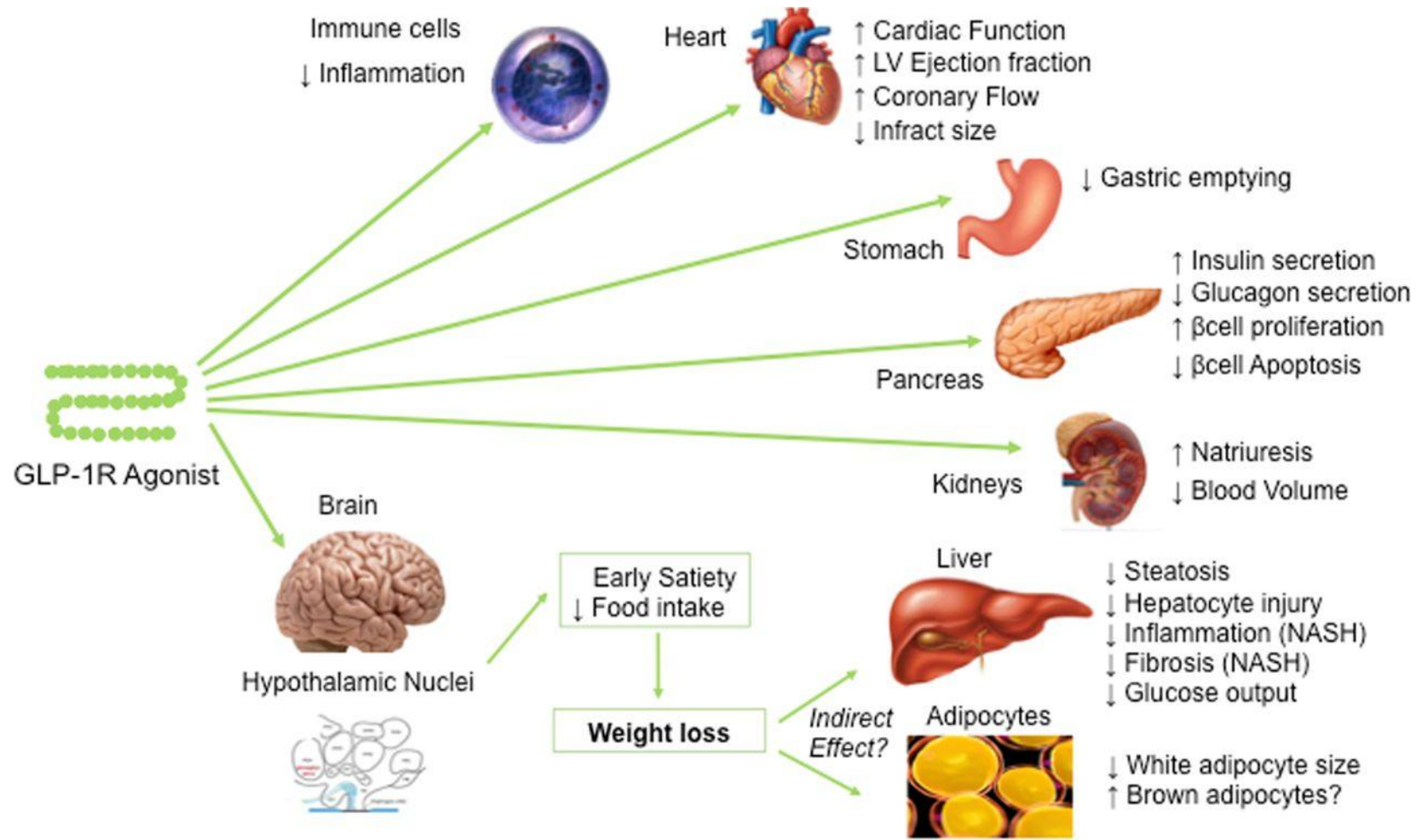
[§] For GLP-1 RA_s, CVDs demonstrate their efficacy in reducing composite MAACE, CV death, all-cause mortality, MI, stroke, and kidney and points in individuals with T2D with established or high risk of CVD. One kidney outcome trial demonstrated benefit in reducing persistent eGFR reduction and CV death for a GLP-1 RA in individuals with CKD and T2D.

[¶] For SGLT2i, CV and kidney outcomes trials demonstrate their efficacy in reducing the risks of composite MAACE, CV death, all-cause mortality, MI, HF, and kidney outcomes in individuals with T2D and established or high risk of CVD.

^{||} Low-dose pioglitazone may be better tolerated and similarly effective as higher doses.

Figure 9.4 Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes - 2026. Diabetes Care 2026;49(Suppl. 1):S183-215*

Glucagon-like peptide-1 receptor agonists (GLP-1RAs)



First line therapy for T2DM with ASCVD or High risk: GLP 1 RA or SGLT-2 inhibition

- Let's look at GLP 1 RA therapy first
 - Liraglutide
 - Daily injection
 - Dosing .6 mg/d -3 mg/d(diabetes dosing up to 1.8 mg/day)
 - Improves CV outcomes 13%
 - Dulaglutide
 - Weekly injection
 - Dosing .75 mg/week up to 4.5 mg/week
 - Improves CV outcomes 12%
 - Semaglutide
 - Weekly injection or daily oral tablet
 - Dosing .5mg/week-2.4 mg/week sc or 3mg-14 mg/day po(starting dose .25 mg/week and max dose for diabetes 2.0 mg/week)
 - Improves CV outcomes up to 25%
 - Tirzepatide (GLP 1 RA plus GIP receptor agonist)
 - Weekly injection
 - Dosing 2.5 mg/week-15 mg/week
 - Improves composite HF and CV 40%(**N Engl J Med 2025;392:427-437**)

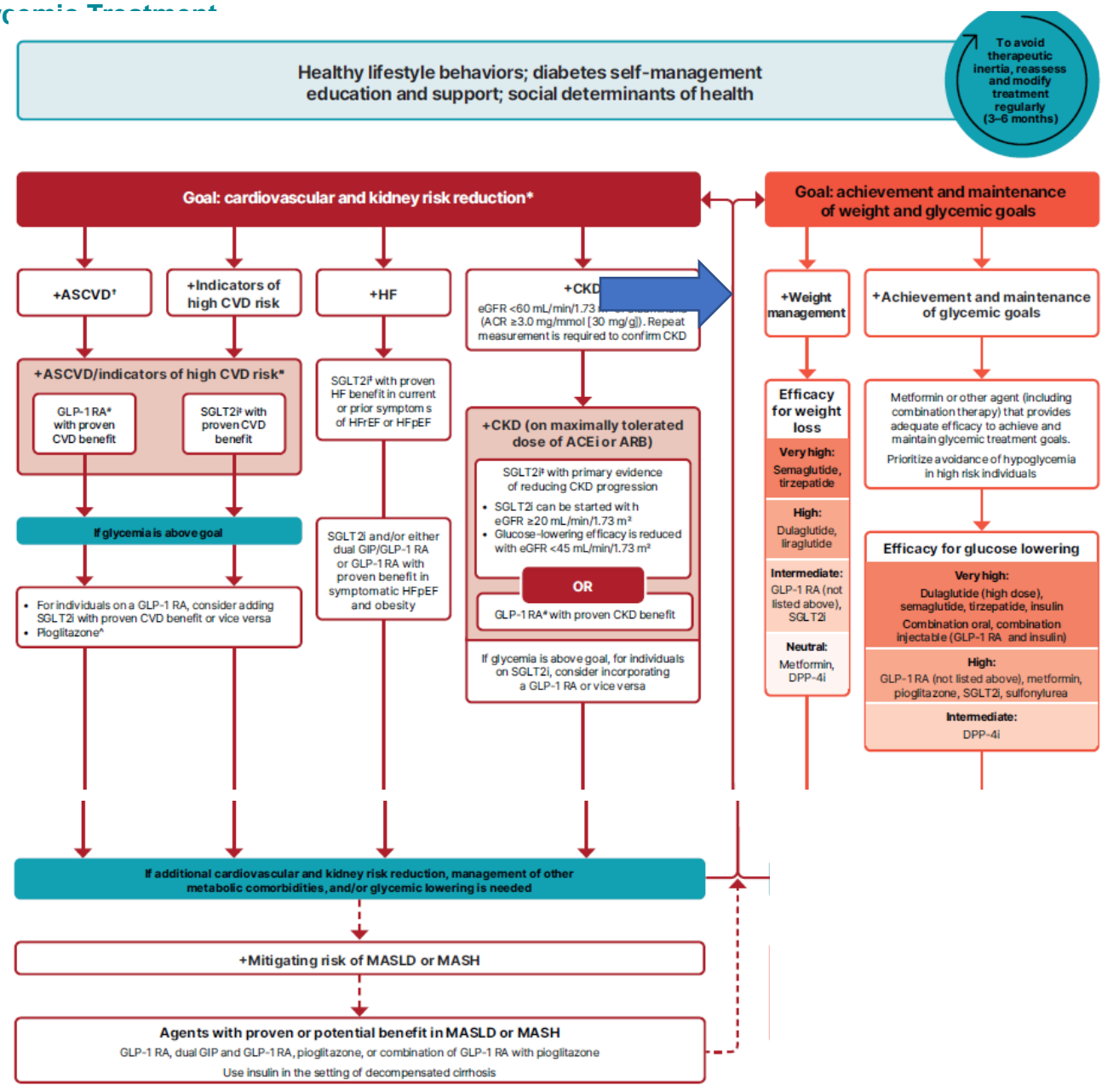
Caveats on prescribing GLP-1 RA therapy

- Side effects are mainly gastro-intestinal such as nausea, diarrhea and abdominal discomfort and gall-stones
- Black box warning for **medullary** cancer of the thyroid
- Most large studies do not see increased risk of pancreatitis, but warning remains on label

Meta-analysis of recent GLP 1 RA trials

- Major cardiovascular outcomes(MACE): reduced 14%
- Each component of MACE: reduced 14%
- Hospitalization for heart failure: reduced 14%
- Composite kidney outcomes: reduced 17%
- All cause mortality: reduced 12%
- No increased risk of retinopathy or pancreatic events

9. Pharmacologic Approaches to Glycemic Treatment



To avoid therapeutic inertia, reassess and modify treatment regularly (3-6 months)

* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be made irrespective of attainment of glycemic goal.

[†] ASCVD: Defined differently across CVDs but all included individuals with established CVD (e.g., MI, stroke, and arterial revascularization procedure) and variably included conditions such as transient ischemic attack, unstable angina, amputation, and symptomatic or asymptomatic coronary artery disease. Indicators of high risk: While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria).

[‡] A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high risk CVD. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details.

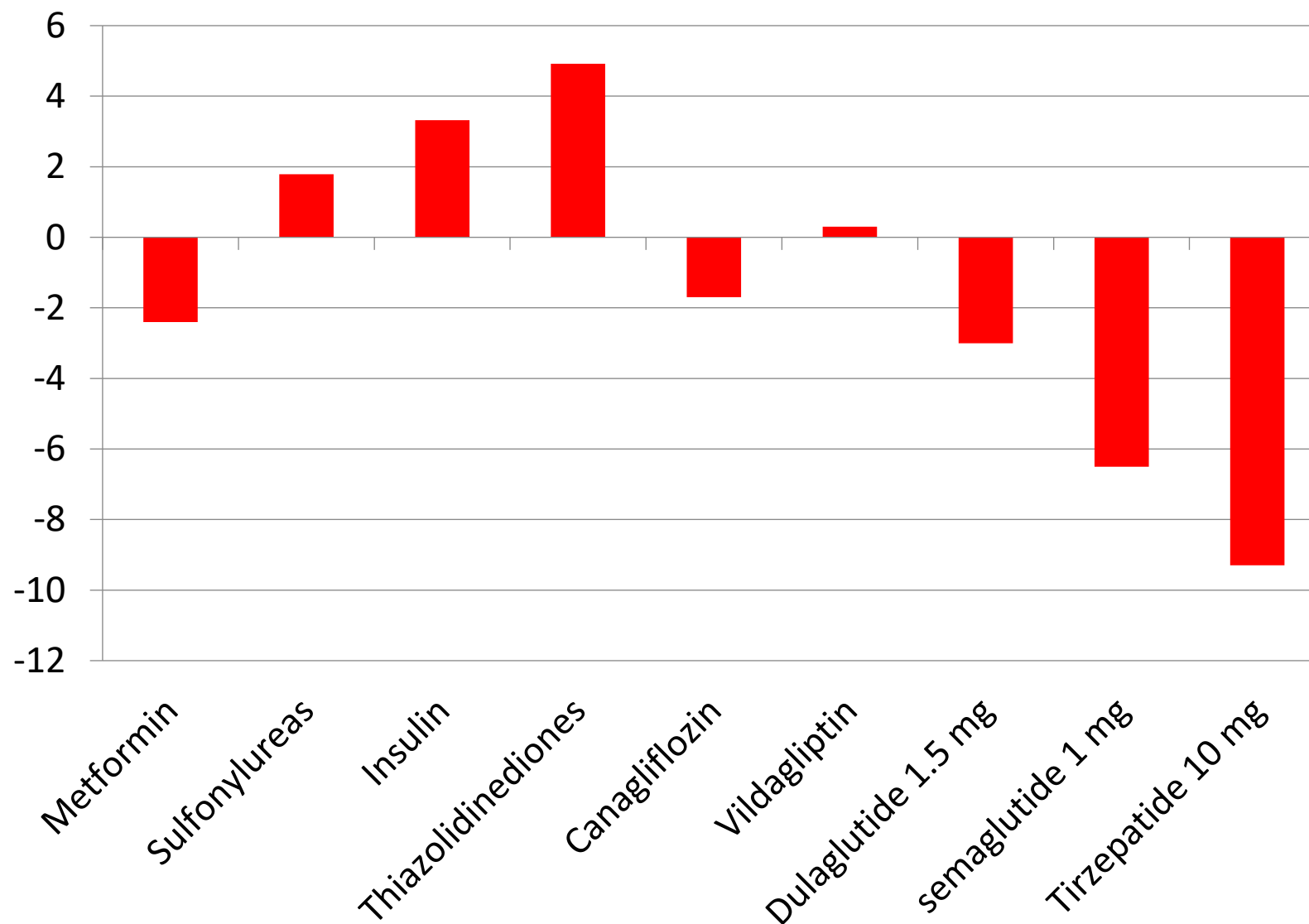
[§] For GLP-1 RAs, CVDs demonstrate their efficacy in reducing composite MAACE, CV death, all-cause mortality, MI, stroke, and kidney and points in individuals with T2D with established or high risk of CVD. One kidney outcome trial demonstrated benefit in reducing persistent eGFR reduction and CV death for a GLP-1 RA in individuals with CKD and T2D.

[¶] For SGLT2i, CV and kidney outcomes trials demonstrate their efficacy in reducing the risks of composite MAACE, CV death, all-cause mortality, MI, HF, and kidney outcomes in individuals with T2D and established or high risk of CVD.

^{||} Low-dose pioglitazone may be better tolerated and similarly effective as higher doses.

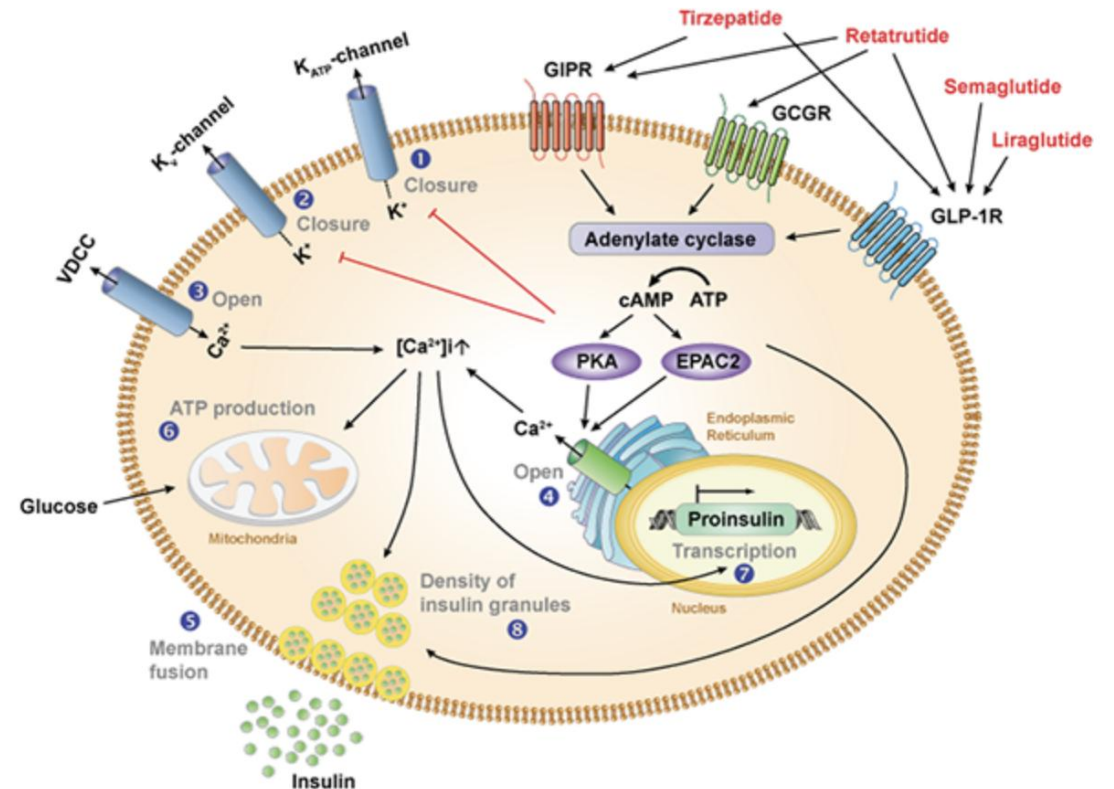
Figure 9.4 Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes - 2026. Diabetes Care 2026;49(Suppl. 1):S183-215*

Weight Effect (kg)

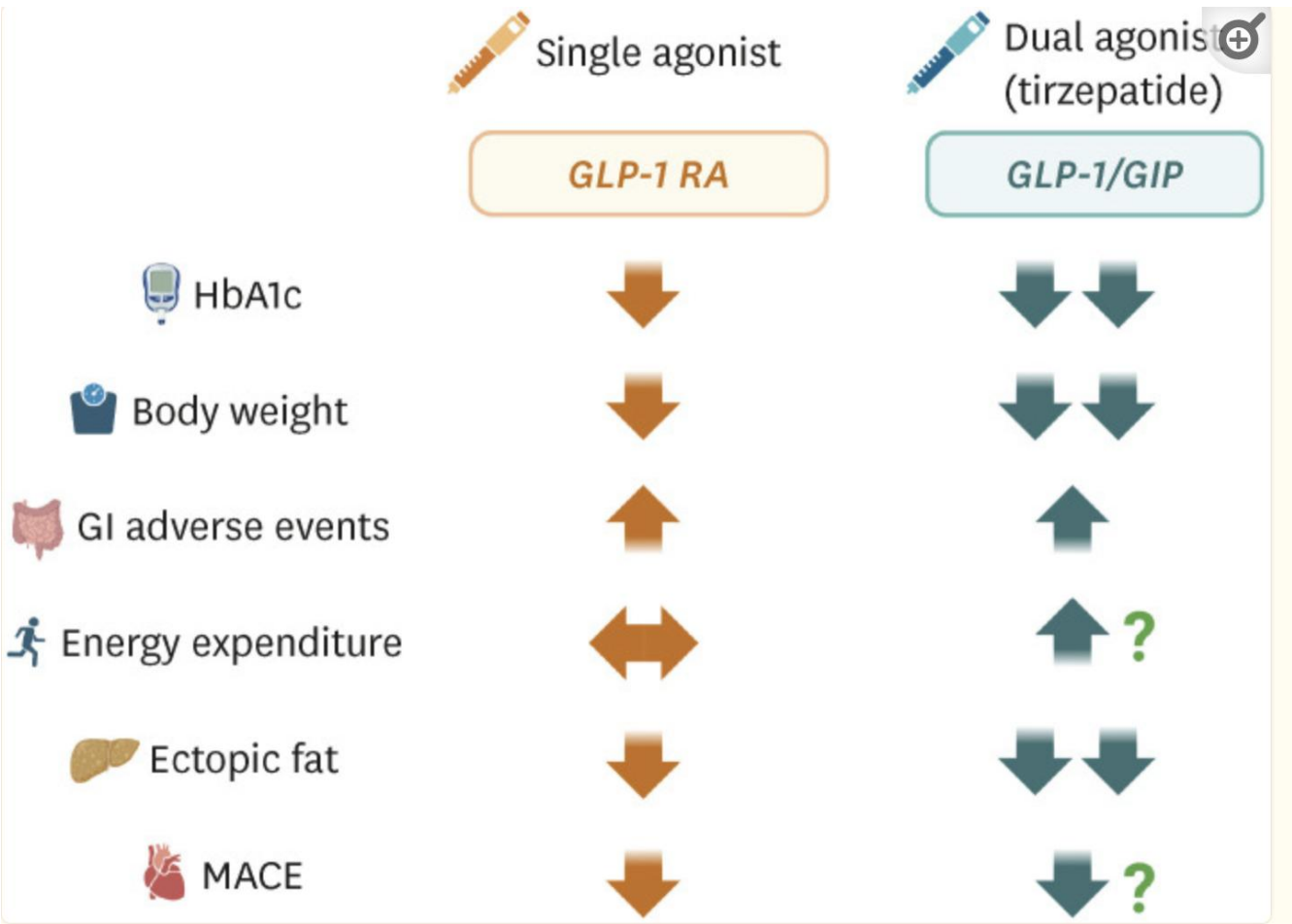


Tirzepatide: Miracle Drug?

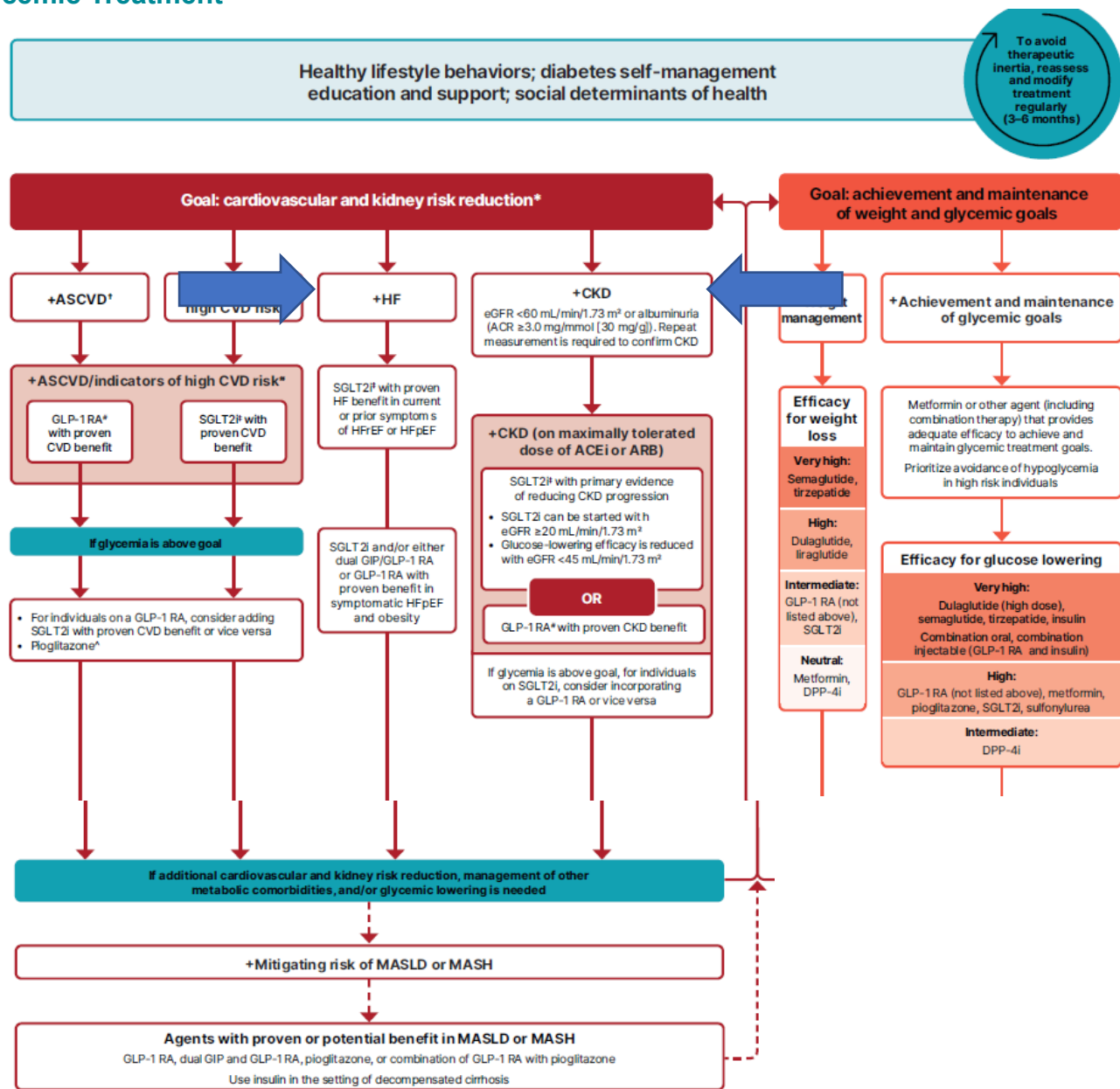
- Tirzepatide is a “dual receptor” agonist for GLP-1 and GIP receptors
- Glucose-dependent Insulinotropic Polypeptide agonist
- Glucagon Receptor agonists in the “works”



Dual vs Single Agonist

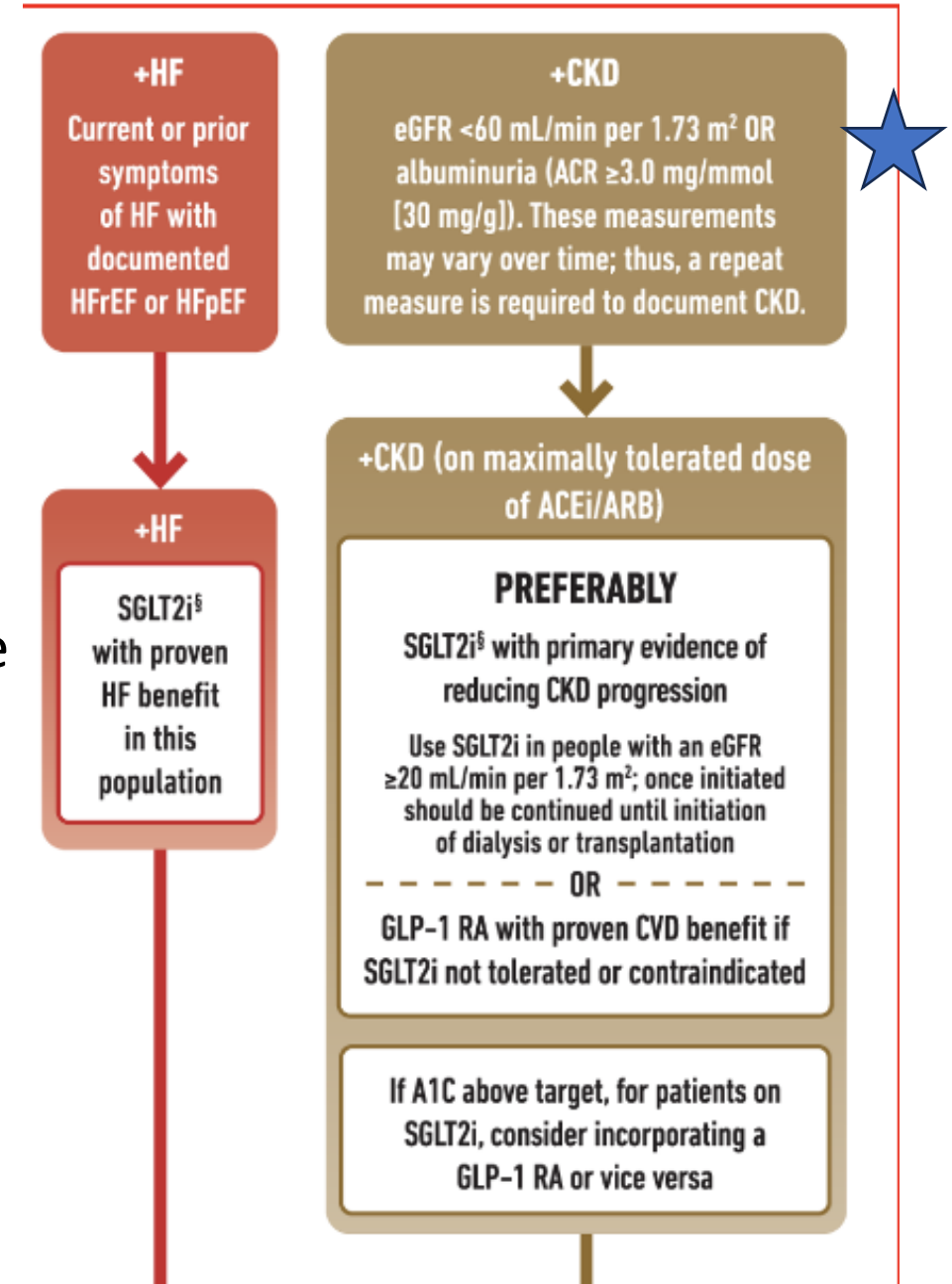


9. Pharmacologic Approaches to Glycemic Treatment

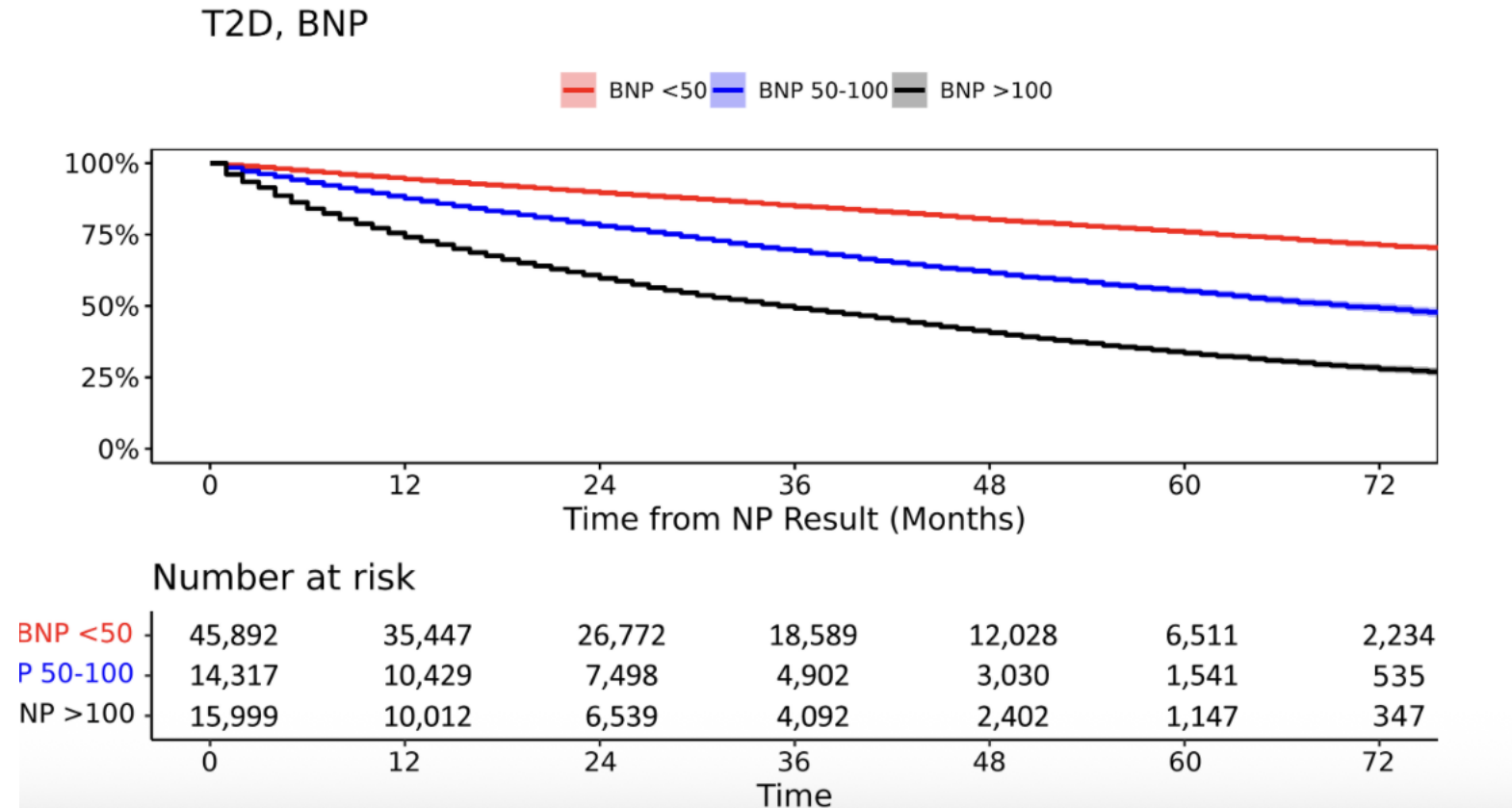


What is HF or CKD?

1. ADA SOC 2026 suggests screening patients with BNP(>50pg/ml) or NT-proBNP(>125pg/ml).
2. If elevated, check cardiac echo
3. Stage B heart failure(asymptomatic) should receive SGLT-2i
4. SGLT-2 inhibitors improve risk for both HF and CKD by 40%

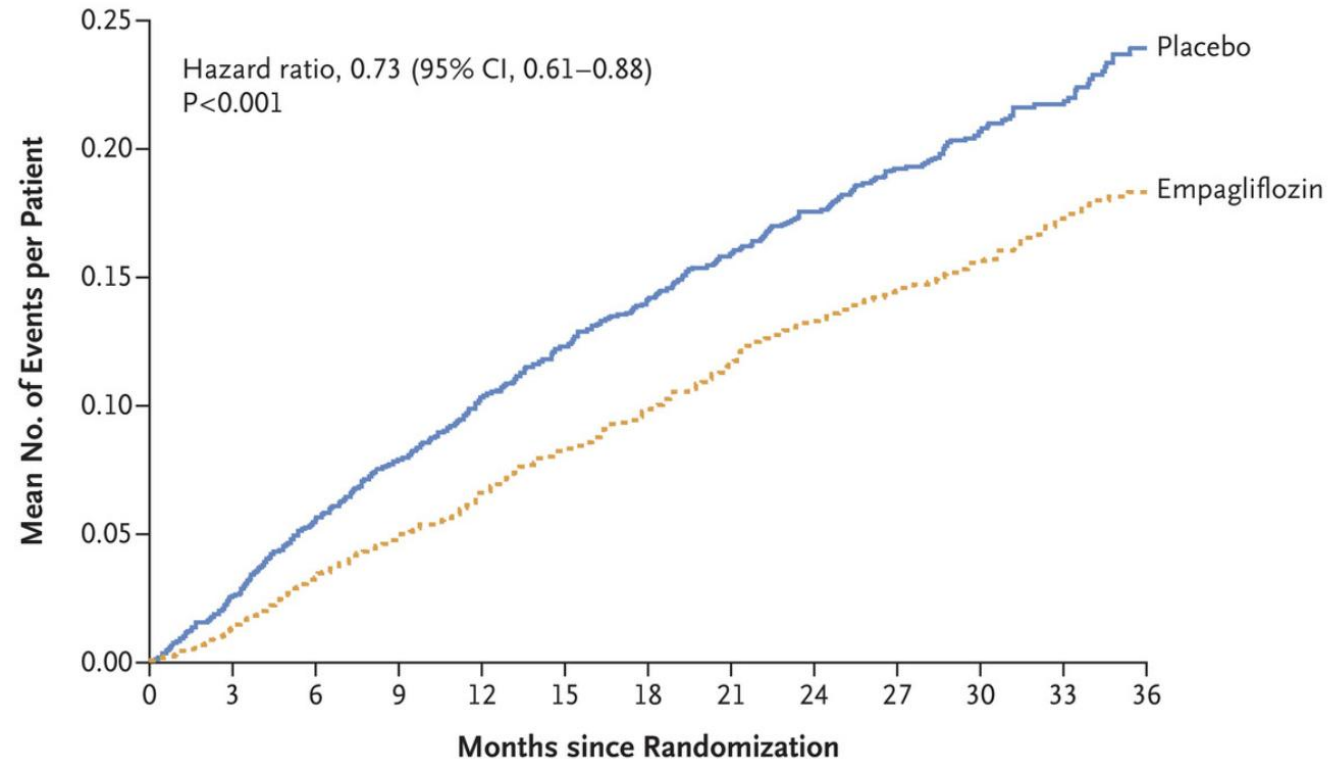


Heart failure onset stratified by BNP in asymptomatic T2DM



Diabetes Care 2025;48(12):2145–2153

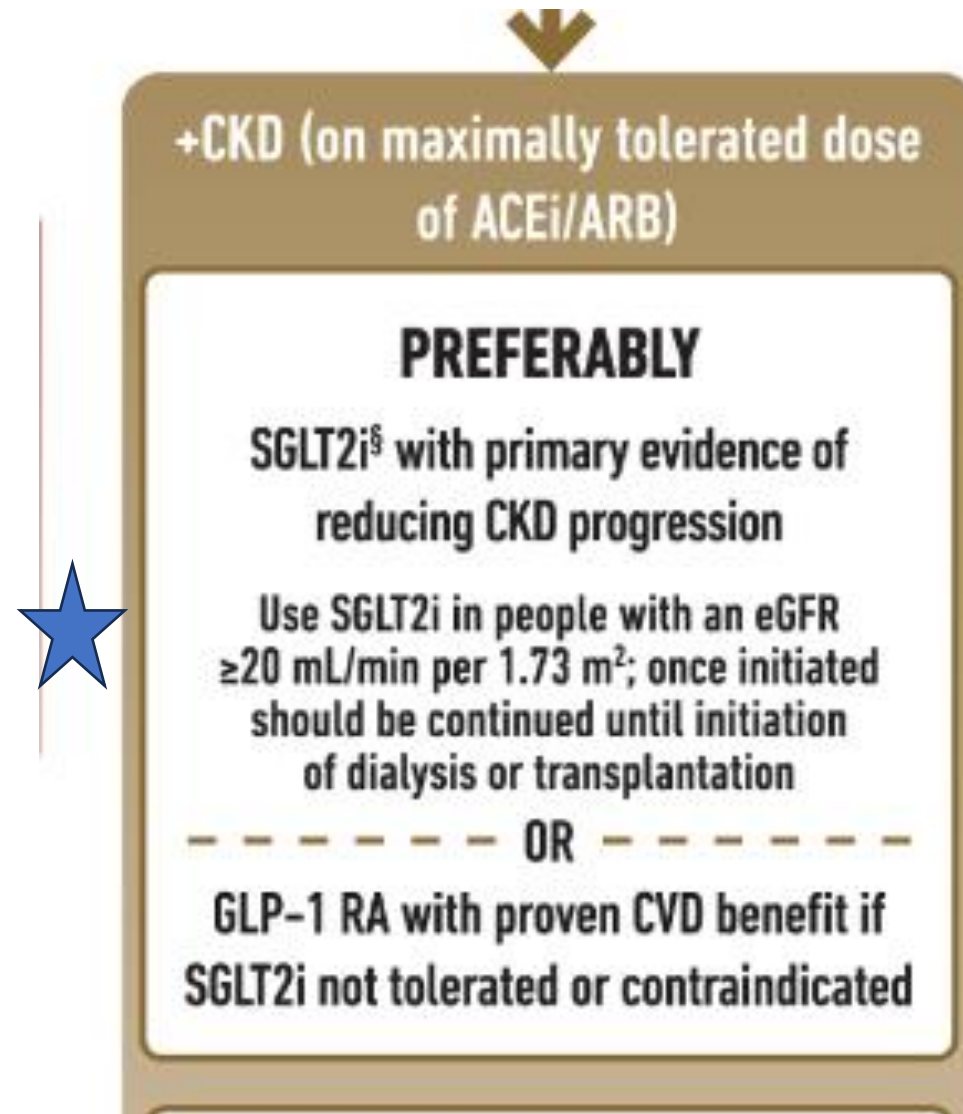
Use of Empagliflozin in HF with Preserved EF



No. at Risk

Placebo	2991	2945	2901	2855	2816	2618	2258	1998	1695	1414	1061	747	448
Empagliflozin	2997	2962	2913	2869	2817	2604	2247	1977	1684	1429	1081	765	446

Use in Renal Insufficiency: Update!



+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

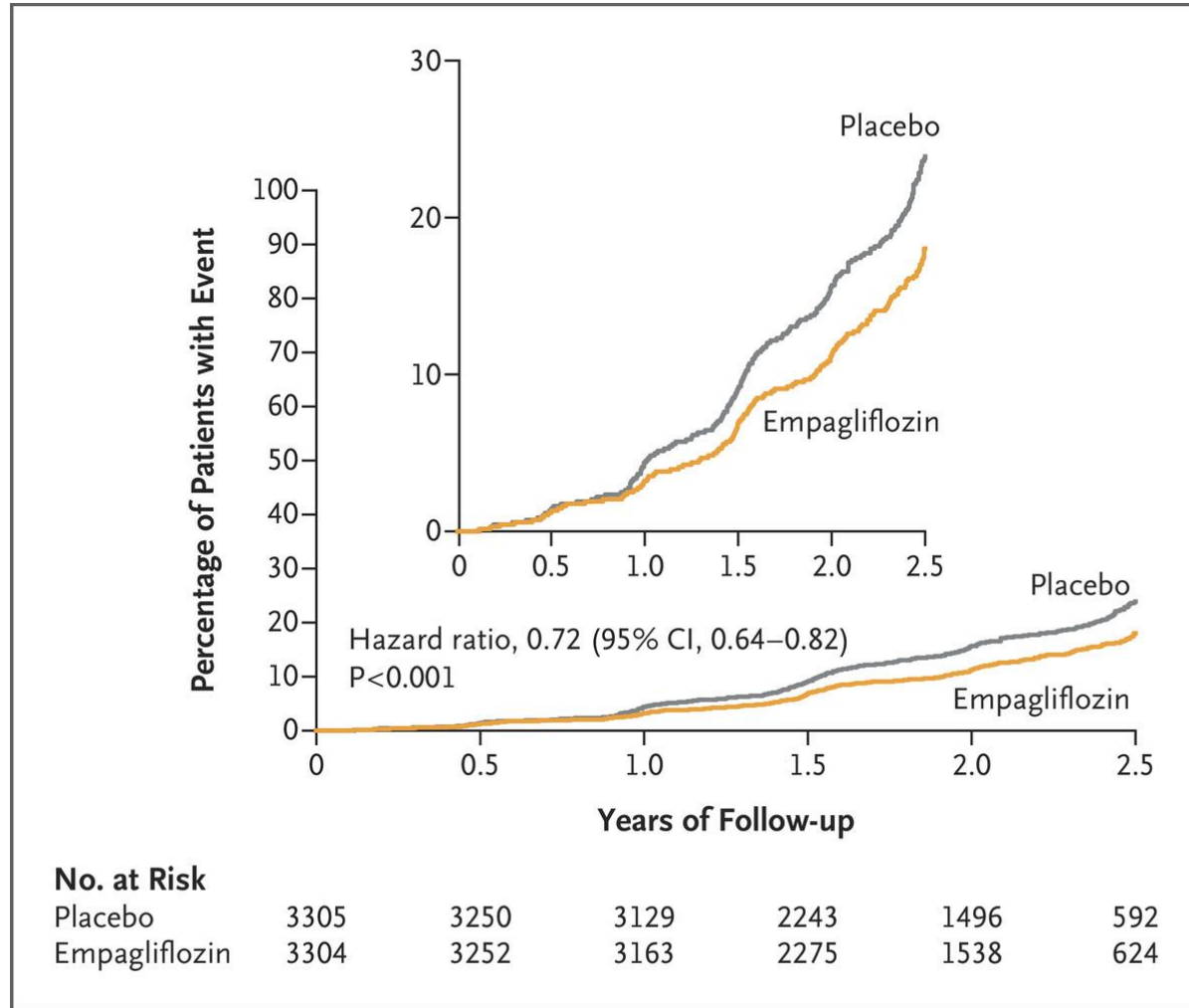
SGLT2i[§] with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥ 20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

----- OR -----

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

Progression of Kidney Disease or Death from Cardiovascular Causes with Empagliflozin in patients with egfr 20-45



Caveats on prescribing SGLT 2 inhibitors

- Most commonly prescribed SGLT 2 Inhibitors
 - Empagliflozin 10 mg or 25 mg tablet daily
 - Canagliflozin 100 mg or 300 mg tablet daily
 - Dapagliflozin 5 mg or 10 mg tablet daily
- Dosing comment
 - There is no greater efficacy on any measure for the higher doses!
 - For cost savings, consider cutting higher dose in half
- Side effects
 - Increase in urination
 - Candida infections
 - Dehydration, esp. in older patients
 - “Euglycemic” DKA(DKA with glucose values below 250 mg/dl)
 - Patients should avoid “keto” diets if on SGLT-2 I to avoid DKA

Knowledge Question 2

Which medication might be the best one to start in a patient with new onset type 2 diabetes with A1C of 7.2% and longstanding heart failure?

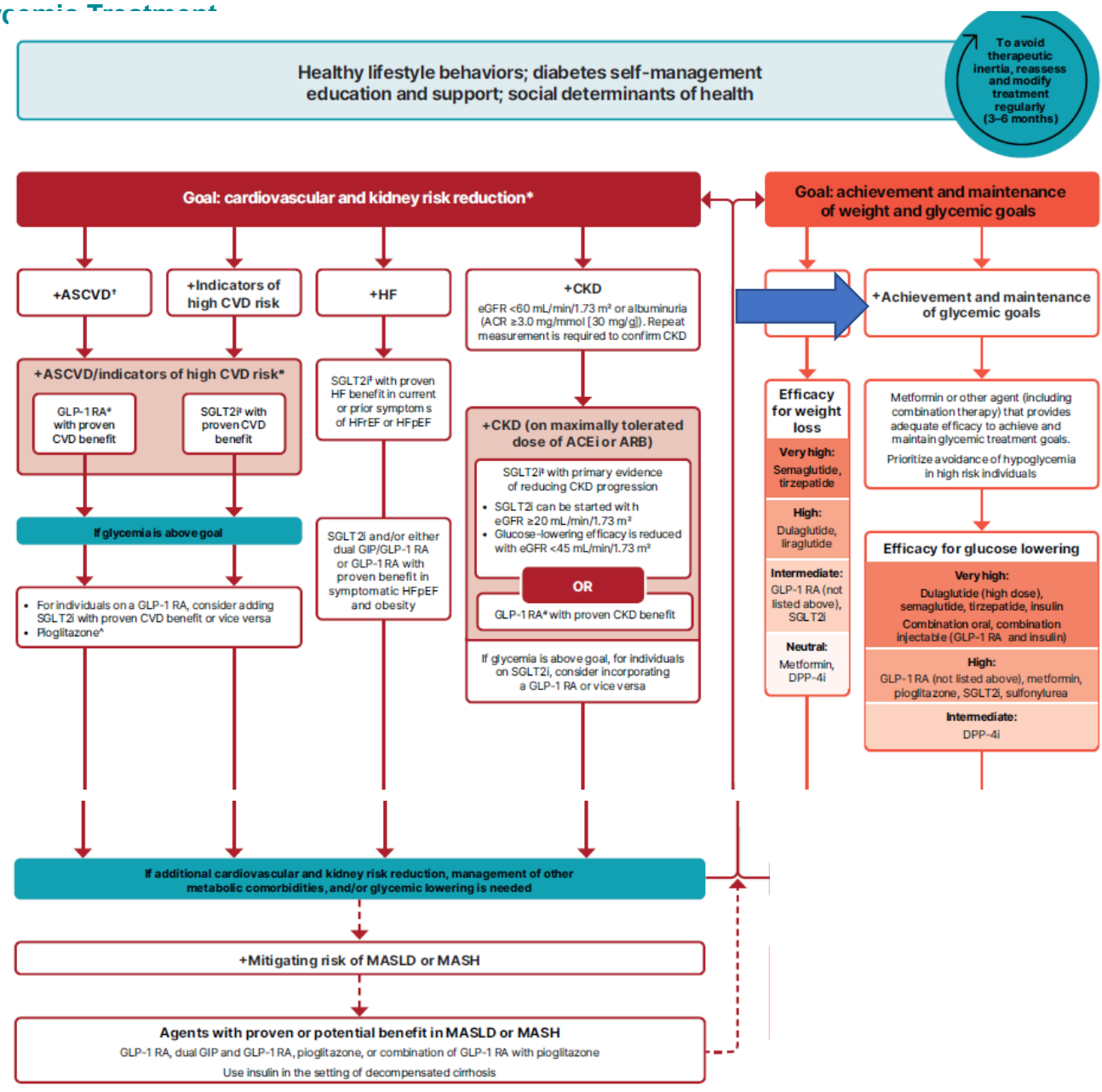
- A. Glipizide
- B. Pioglitazone
- C. Sitagliptin
- D. Canagliflozin
- E. Metformin

Knowledge Question 2

Which medication might be the best one to start in a patient with new onset type 2 diabetes with A1C of 7.2% and longstanding heart failure?

- A. Glipizide
- B. Pioglitazone
- C. Sitagliptin
- D. Canagliflozin**
- E. Metformin

9. Pharmacologic Approaches to Glycemic Treatment



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be made irrespective of attainment of glycemic goal.

[†] ASCVD: Defined differently across CVDs but all included individuals with established CVD (e.g., MI, stroke, and arterial revascularization procedure) and variably included conditions such as transient ischemic attack, unstable angina, amputation, and symptomatic or asymptomatic coronary artery disease. Indicators of high risk: While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria).

[‡] A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high risk CVD. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details.

[§] For GLP-1 RAs, CVDs demonstrate their efficacy in reducing composite MAACE, CV death, all-cause mortality, MI, stroke, and kidney and points in individuals with T2D with established or high risk of CVD. One kidney outcome trial demonstrated benefit in reducing persistent eGFR reduction and CV death for a GLP-1 RA in individuals with CKD and T2D.

[¶] For SGLT2i, CV and kidney outcomes trials demonstrate their efficacy in reducing the risks of composite MAACE, CV death, all-cause mortality, MI, HF, and kidney outcomes in individuals with T2D and established or high risk of CVD.

^{||} Low-dose pioglitazone may be better tolerated and similarly effective as higher doses.

Figure 9.4 Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes - 2026. Diabetes Care 2026;49(Suppl. 1):S183-215*

Balance A1C vs Hypoglycemia:

Risk for
hypoglycemia:
Insulin
Sulfonyurea

In general, higher efficacy approaches
have greater likelihood of achieving
glycemic goals

Efficacy for glucose lowering

Very High:

Dulaglutide (high dose),
Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination
Injectable (GLP-1 RA/Insulin)

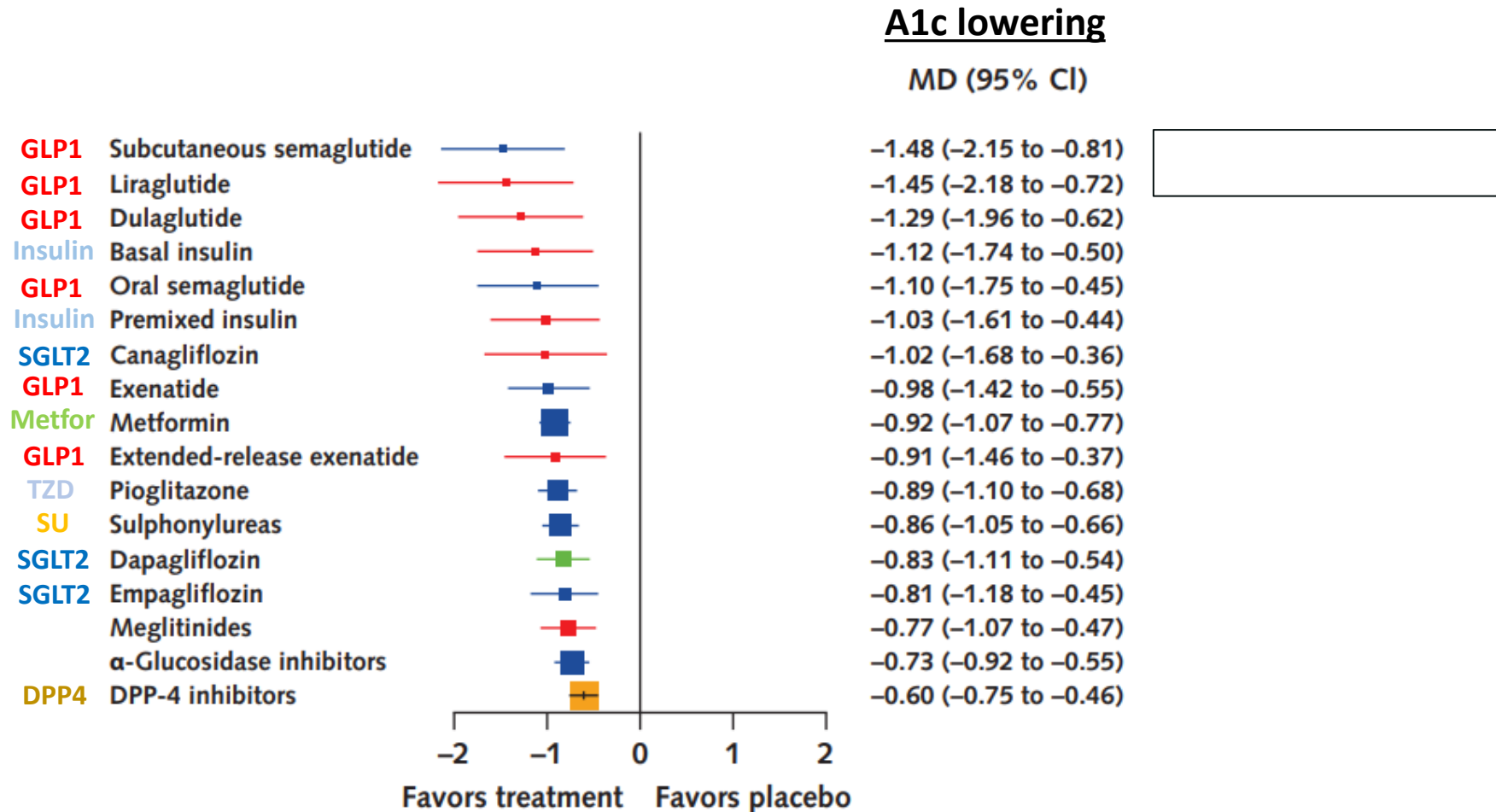
High:

GLP-1 RA (not listed above), Metformin,
SGLT2i, Sulfonylurea, TZD

Intermediate:

DPP-4i

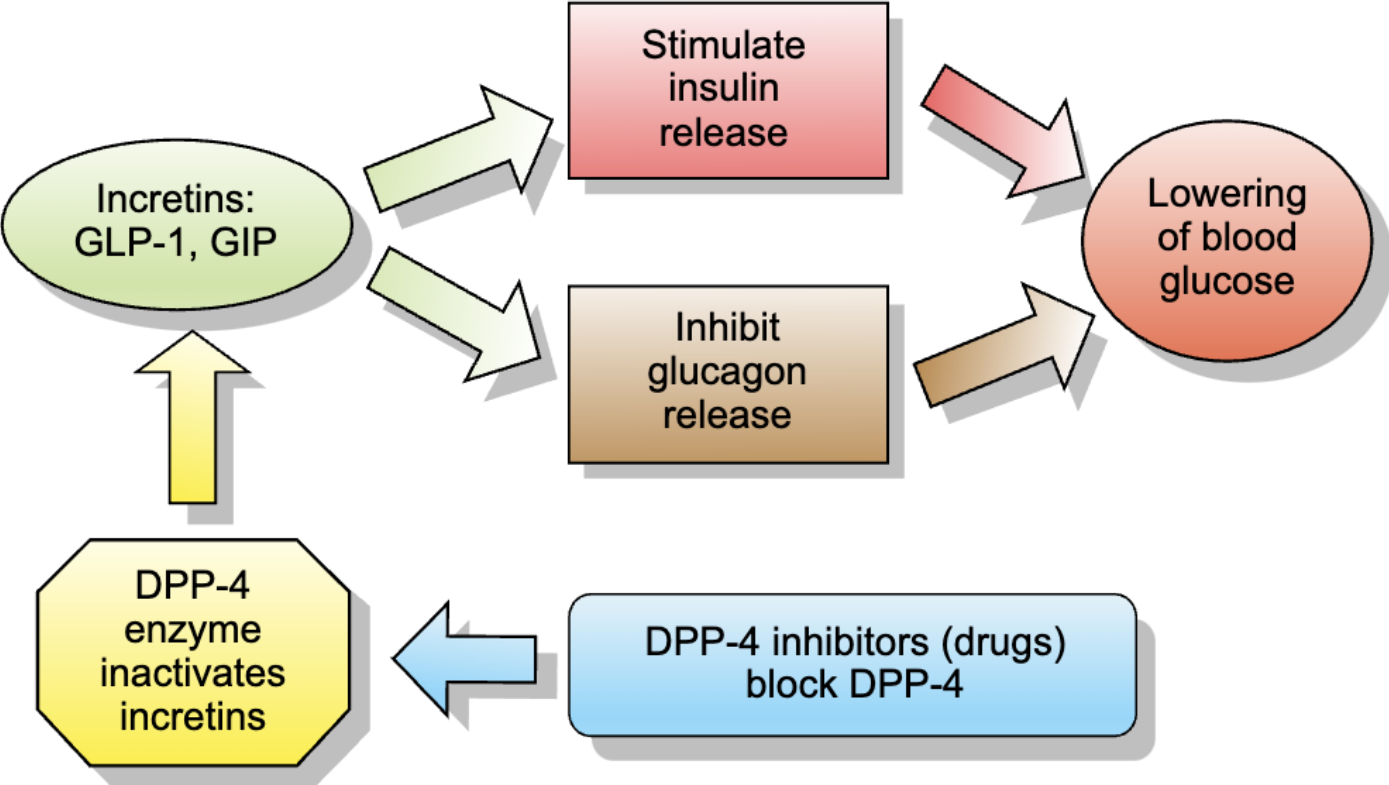
Comparative effectiveness of T2D meds in lowering HbA1c



Risk of serious hypoglycemia in older patients

- Serious hypoglycemia defined as ER visit or hospitalization(US Medicare Database)
- Insulin: 25/1000 patient years
- Metformin: 1.5/1000 patient years
- Sulfonylurea users: 11.2/1000 patient years

DPP-4 Inhibitors



DPP4 inhibitors

	Pros	Cons
Efficacy		Intermediate
Risk of hypoglycemia	Minimal	
Effect on weight	Neutral	
CV effects	Neutral (except saxagliptin contraindicated in HF)	
Cost		High
Route of administration	Oral	
Other side effects		Arthralgias ?Pancreatitis
Use in renal insufficiency	Yes: No dose adjustment for linagliptin	

DPP4 inhibitors - use

- Good medication to consider in patients who are at risk of hypoglycemia, have CKD, and/or decline injectables (if they can afford it)
- For example, an ideal patient to consider a DPP4 inhibitor is an older patient with T2DM (at risk of hypoglycemia) with CKD
- Most commonly used
 - Sitagliptin dose: 25 mg/day(CKD) to 100 mg/day(normal eGFR)
 - Linagliptin 5 mg: no dose adjustment in CKD



Sulfonylureas:

Glyburide: 5-10 mg/day
Glipizide: 5-10 mg/day
Glimepiride_1-4 mg/day

	Pros	Cons
Efficacy	High	
Risk of hypoglycemia		Yes
Effect on weight		Weight gain
CV effects	Neutral	
Cost	Low	
Route of administration	Oral	

Thiazolidinediones

- Available since 1997
- Pioglitazone (preferred) and rosiglitazone (not recommended)
- Mechanism: PPAR- γ activation, increased peripheral glucose uptake, decrease lipolysis.
- Dosing: daily, takes weeks-months for full effect, max effective dose = max dose.
- A1c lowering: 1-2%
- Pros: efficacy, metabolic effects, daily dosing, no hypoglycemia, ?preservation of beta-cell function, MASH
- Cons: weight gain, edema/CHF, CV controversy, fractures, urologic cancers?

Is pioglitazone the new thalidomide(re-purposed life)?

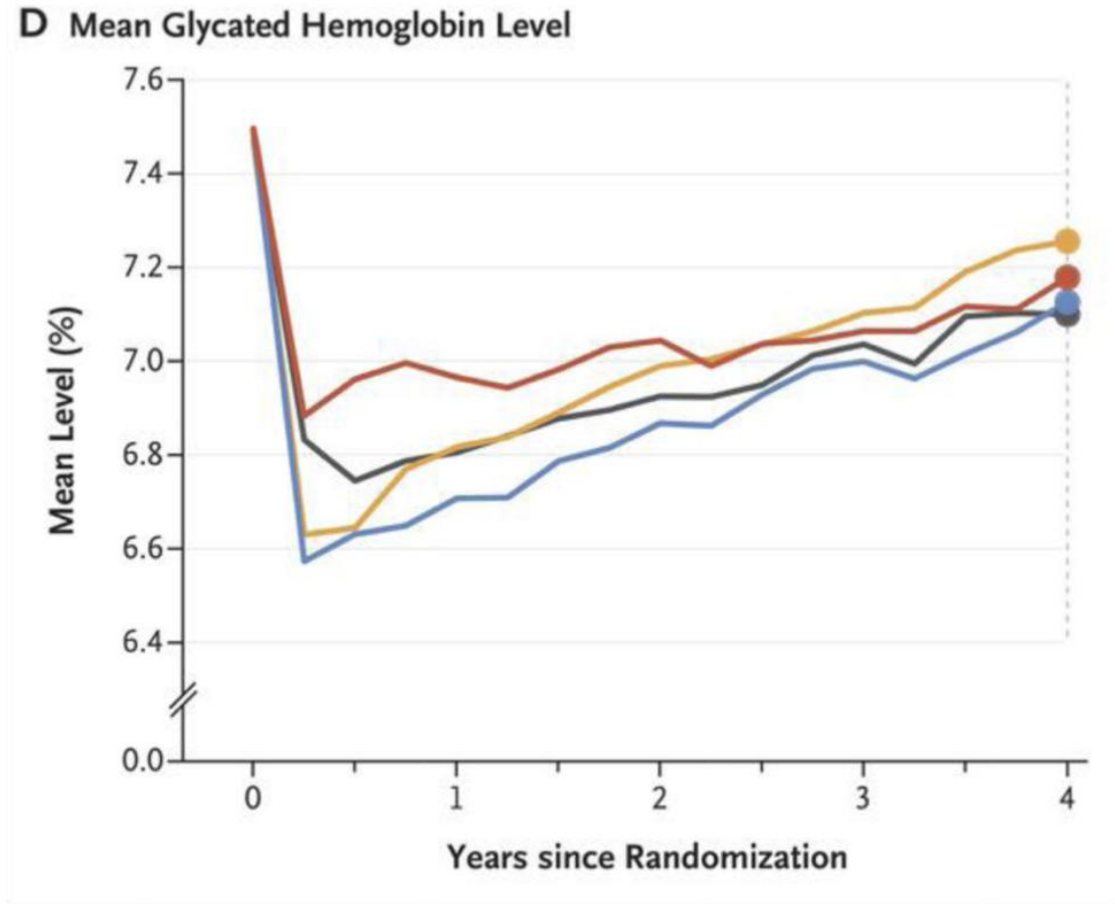
- Pioglitazone has been found to be successful for MAFLD and MASH
 - 15% of T2DM patients already have MASH and hepatic fibrosis
 - Pioglitazone can reverse steatohepatitis and slow fibrosis progression
- Pioglitazone can decrease cardiovascular disease risk
- Pioglitazone can be considered in patients with high FIB-4 scores

Combination therapy

- Appropriate combinations help achieve A1C goals while potentially adding other benefits
- Considerations in thinking of combination therapy
 - Side effects
 - Risk for hypoglycemia
 - Cost
- Some combinations are problematic and some are complimentary

GRADE: Add On to Metformin

— Sitagliptin — Glimepiride — Liraglutide — Glargine



Problematic combinations

- Short-acting and long-acting sulfonylurea agents: more hypoglycemia and no improvement in glucose control
- Insulin and sulfonylurea agents: more weight gain and more hypoglycemia
- Insulin and thiazolidinediones: more weight gain, more edema
- GLP-1 RA and DPP4-I: no added benefit of DPP4-I so it should be stopped

Combinations that make sense

- Metformin and anything else
- SGLT-2 I and anything else
- GLP 1RA and basal insulin
- SGLT2-I and DPP-4 I in renal insufficiency

Case 1: M.H.

M.H. is a 66 y/o man with an 8-year history of T2D. He is currently taking metformin 1000 mg PO BID and reports excellent compliance with this.

Scenario	1
BMI (kg/m ²)	41
A1C	8.1%
ASCVD	None
HF	None
Kidney	eGFR 82 UACR <30

Of the following medications, which single medication would you recommend that he start, after discussing with him and assuming no contraindications?

- A) Sulfonylurea
- B) SGLT2i
- C) GLP1 RA
- D) DPP4i
- E) Basal insulin
- F) None

Case 1: M.H.

M.H. is a 66 y/o man with an 8-year history of T2D. He is currently taking metformin 1000 mg PO BID and reports excellent compliance with this.

Scenario	1	2
BMI (kg/m ²)	41	33
A1C	8.1%	8.1%
ASCVD	None	MI at 61 y/o
HF	None	None
Kidney	eGFR 82 UACR <30	eGFR 82 UACR <30

Of the following medications, which single medication would you recommend that he start, after discussing with him and assuming no contraindications?

- A) Sulfonylurea
- B) SGLT2i
- C) GLP1 RA
- D) DPP4i
- E) Basal insulin
- F) None

Case 1: M.H.

M.H. is a 66 y/o man with an 8-year history of T2D. He is currently taking metformin 1000 mg PO BID and reports excellent compliance with this.

Scenario	1	2	3
BMI (kg/m ²)	41	33	33
A1C	8.1%	8.1%	8.1%
ASCVD	None	MI at 61 y/o	None
HF	None	None	HFrEF (EF 37%)
Kidney	eGFR 82 UACR <30	eGFR 82 UACR <30	eGFR 82 UACR <30

Of the following medications, which single medication would you recommend that he start, after discussing with him and assuming no contraindications?

- A) Sulfonylurea
- B) SGLT2i
- C) GLP1 RA
- D) DPP4i
- E) Basal insulin
- F) None

Case 1: M.H.

M.H. is a 66 y/o man with an 8-year history of T2D. He is currently taking metformin 1000 mg PO BID and reports excellent compliance with this.

Scenario	1	2	3	4
BMI (kg/m ²)	41	33	33	33
A1C	8.1%	8.1%	8.1%	8.1%
ASCVD	None	MI at 61 y/o	None	None
HF	None	None	HFrEF (EF 37%)	None
Kidney	eGFR 82 UACR <30	eGFR 82 UACR <30	eGFR 82 UACR <30	eGFR 54 UACR 384

Of the following medications, which single medication would you recommend that he start, after discussing with him and assuming no contraindications?

- A) Sulfonylurea
- B) SGLT2i
- C) GLP1 RA
- D) DPP4i
- E) Basal insulin
- F) None

Case 1: M.H.

M.H. is a 66 y/o man with an 8-year history of T2D. He is currently taking metformin 1000 mg PO BID and reports excellent compliance with this.

Scenario	1	2	3	4	5
BMI (kg/m ²)	41	33	33	33	24
A1C	8.1%	8.1%	8.1%	8.1%	6.6%
ASCVD	None	MI at 61 y/o	None	None	None
HF	None	None	HFrEF (EF 37%)	None	None
Kidney	eGFR 82 UACR <30	eGFR 82 UACR <30	eGFR 82 UACR <30	eGFR 54 UACR 384	eGFR 54 UACR 384

Of the following medications, which single medication would you recommend that he start, after discussing with him and assuming no contraindications?

- A) Sulfonylurea
- B) SGLT2i
- C) GLP1 RA
- D) DPP4i
- E) Basal insulin
- F) None

Parting points

- When adding a drug, don't forget to:
 - Continue to emphasize diet and exercise (can be just as effective or even more effective than meds!)
 - Time follow-up (typically at least 3 months is needed to see full effect, but 1 year is too long)
 - Know the maximal effective dose
 - Target complementary mechanisms
 - Monitor for side effects and reinforce patient education
 - Don't underestimate the importance of weight gain, hypoglycemia, and patient education
 - Non-adherence is a common cause of treatment failure

JANUARY 2026

Diabetes Care

JANUARY 2026 | VOLUME 49 | SUPPLEMENT 1
DIABETESJOURNALS.ORG/CARE

Diabetes Care®



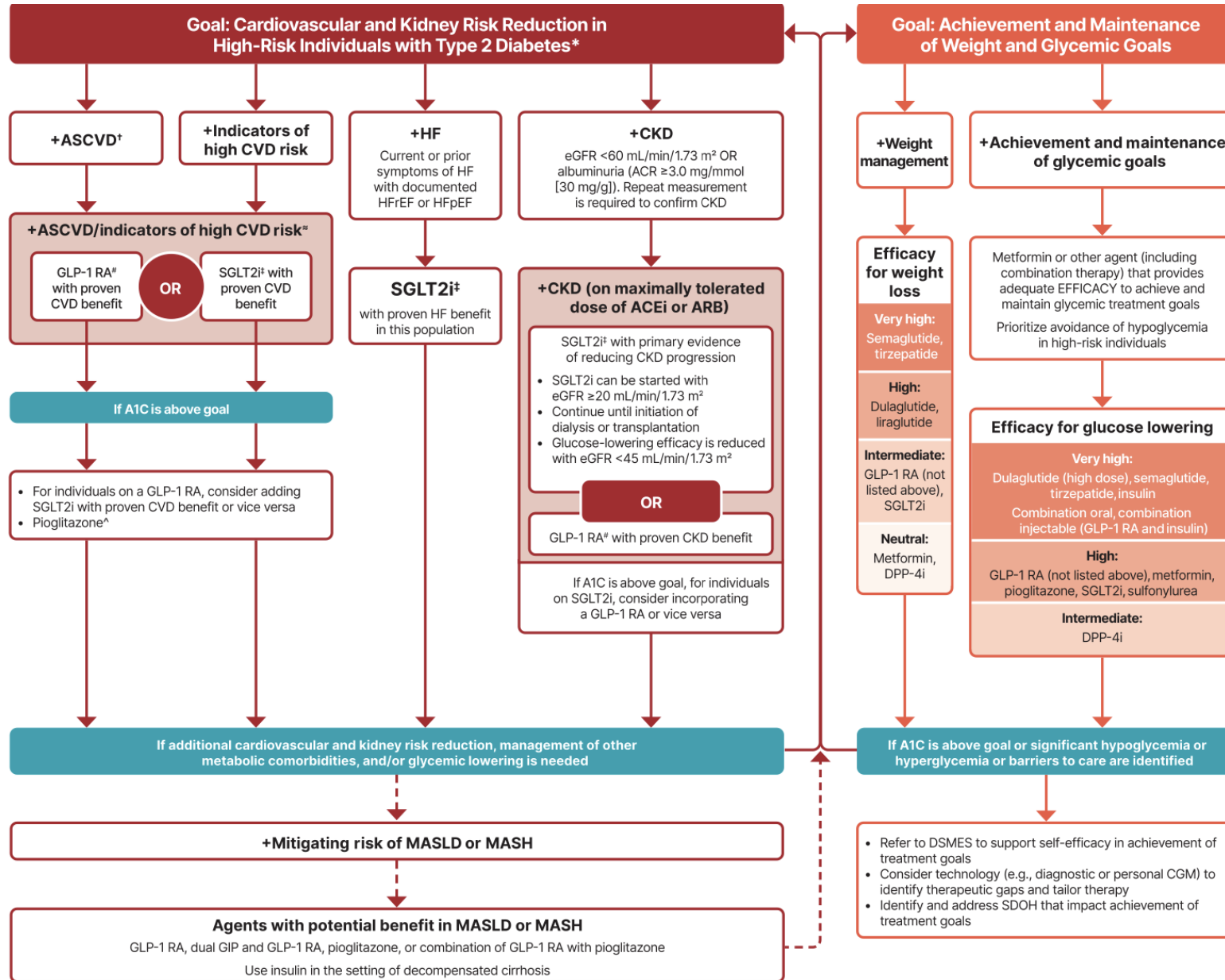
Standards of Care in Diabetes—2026

VOLUME 49 | SUPPLEMENT 1 | PAGES S1–S371



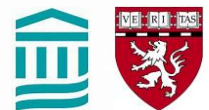
ISSN 0149-5992

Questions?



GLP1 RA – dosing and prescribing

GLP1 RA	Doses	How supplied	Pen needles	Instructions
Liraglutide (Victoza) Once daily	Once daily SQ 0.6 mg 1.2 mg 1.8 mg	Victoza: Each 3 mL pen contains 18 mg (1 pen = 30-day supply at 0.6 mg dose 15-day supply at 1.2 mg dose 10-day supply at 1.8 mg dose)	Prescriber needs to prescribe pen needles separately.	Start 0.6 mg daily x1 week. Initial dose is intended to reduce GI symptoms; does not provide effective glycemic control. Then increase to 1.2 mg once daily. May increase further to 1.8 mg once daily if further glycemic control is needed.
Semaglutide (Ozempic, Rybelsus, Wegovy)	Once weekly SQ 0.25 mg 0.5 mg 1 mg 1.7mg 2mg 2.4mg	For 0.25 mg or 0.5 mg doses: Dispense quantity: 1 pen per box = 2 mg = 1.5 mL For 1 mg dose: Dispense quantity: 1 pen has 4 mg = 3 mL	No need to prescribe pen needles. Pen needles are included in each box (6 pen needles per box for 0.25 or 0.5 mg doses; 4 pen needles per box for 1 mg dose).	Start 0.25 mg once weekly x4 weeks. Initial dose is intended to reduce GI symptoms; does not provide effective glycemic control. Then increase to 0.5 mg once weekly for at least 4 weeks. May increase thereafter to a maximum of 1 mg once weekly if further glycemic control is needed.
	Daily oral 3 mg 7 mg 14 mg	Tablets (3, 7, and 14 mg per tablet)	N/A	Administer ≥30 minutes before the first food, beverage, or other medications of the day. Take with exactly 4 oz of water. Initial: 3 mg once daily for 30 days, then increase to 7 mg once daily; May increase to 14 mg once daily after 30 days on the 7 mg dose if needed.
Dulaglutide (Trulicity) Once weekly	Once weekly SQ 0.75 mg 1.5 mg 3.0 mg 4.5 mg	1 dose per pen (disposable, single use pens): 0.75 mg /0.5 mL pen 1.5 mg / 0.5 mL pen 3.0 mg / 0.5 mL pen 4.5 mg / 0.5 mL pen	No need to prescribe pen needles. Each pen contains its own internal pen needle in the injector device.	Start 0.75 mg once weekly. After 30 days, may increase to 1.5 mg once weekly if further glycemic control is needed. After at least 30 days on this dose, can increase to 3.0 mg and ultimately 4.5 mg once weekly, if needed.

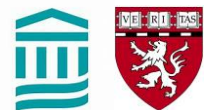


Tirzepatide dosing

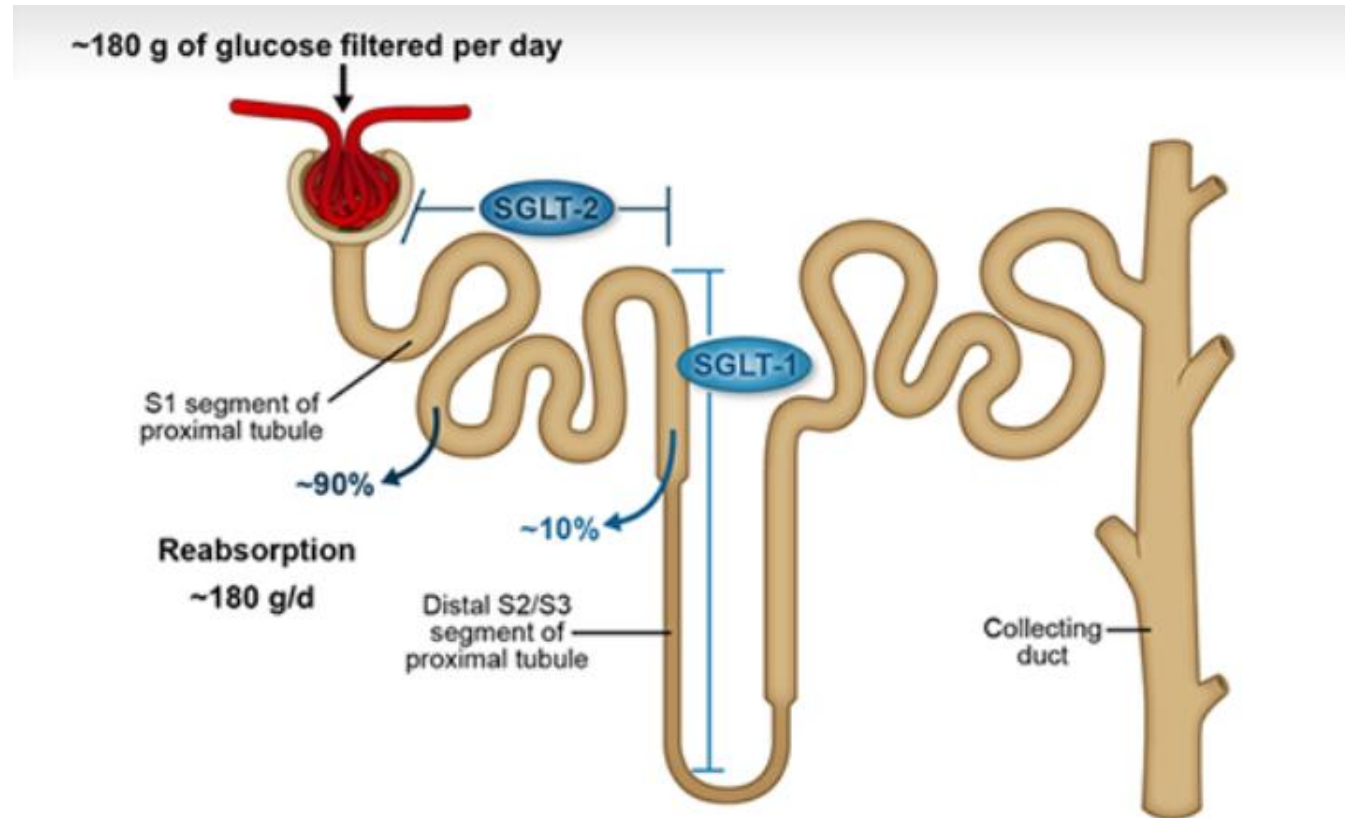
- Injectable given weekly
- Starting dose 2.5 mg/week
- Available doses
 - 5mg
 - 7.5 mg
 - 10 mg
 - 12.5 mg
 - 15 mg
- Supplies very tight
- If switching from another GLP 1 RA, start with one less of equivalent dose

DPP4 inhibitors - dosing

	Max dose	eGFR 45-60	eGFR 30-45	eGFR 15-30	eGFR <15	CV effects?
Sitagliptin	100 mg once daily	No dose adjustment	50 mg once daily	25 mg once daily	25 mg once daily	n/a
Linagliptin	5 mg once daily	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment	n/a
Saxagliptin	5 mg once daily	No dose adjustment	2.5 mg once daily	2.5 mg once daily	2.5 mg once daily	Increased risk of HF hospitalization
Alogliptin	25 mg once daily	12.5 mg once daily	12.5 mg once daily	6.25 mg once daily	6.25 mg once daily	n/a



HF or CKD predominates: SGLT2 inhibitors



Chao EC, Henry RR. *Nat Rev Drug Discov.* 2010;9:551-559.^[2]

Virtually no glucose excreted in the urine



A word about glyburide

- aka glibenclamide
- Added to the American Geriatric Society Beers list of unsafe medications in the elderly
- Still prescribed because low cost, on the market and widely known

Table 2. (Contd.)

Organ System or Therapeutic Category or Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Insulin, sliding scale	Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting	Avoid	Moderate	Strong
Megestrol	Minimal effect on weight; increases risk of thrombotic events and possibly death in older adults	Avoid	Moderate	Strong
Sulfonylureas, long duration Chlorpropamide Glyburide	Chlorpropamide: prolonged half-life in older adults; can cause prolonged hypoglycemia; causes syndrome of inappropriate antidiuretic hormone secretion. Glyburide: greater risk of severe prolonged hypoglycemia in older adults	Avoid	High	Strong



GLP-1RA and CVOT

Trial	Agent	Primary outcome	Individual components of MACE			Secondary outcomes of interest		
		Primary outcome (3-point MACE)	Death from CV causes	Nonfatal MI	Nonfatal stroke	Hosp. for HF	All-cause mortality	Worsening nephropathy
ELIXA (n=6,068)	Lixisenatide	1.02 (0.89-1.17)*	0.98 (0.78-1.22)	1.03 (0.87-1.22)	1.12 (0.79-1.58)	0.96 (0.75-1.23)	0.94 (0.78-1.13)	n/a
LEADER (n=9,340)	Liraglutide *	0.87 (0.78-0.97)	0.78 (0.66-0.93)	0.86 (0.73-1.00)	0.86 (0.71-1.06)	0.87 (0.73-1.05)	0.85 (0.74-0.97)	0.78 (0.67-0.92)
SUSTAIN-6 (n=3,297)	Semaglutide (injectable) *	0.74 (0.58-0.95)	0.98 (0.65-1.48)	0.74 (0.51-1.08)	0.61 (0.38-0.99)	1.11 (0.77-1.61)	1.05 (0.74-1.50)	0.64 (0.46-0.88)
EXSCEL (n=14,752)	Exenatide weekly	0.91 (0.83-1.00)	0.88 (0.76-1.02)	0.97 (0.85-1.10)	0.85 (0.70-1.03)	0.94 (0.78-1.13)	0.86 (0.77-0.97)	n/a
Harmony Outcomes (n=9,463)	Albiglutide	0.78 (0.68-0.90)	0.93 (0.73-1.19)	0.75 (0.61-0.90)	0.86 (0.66-1.14)	n/a	0.95 (0.79-1.16)	n/a
REWIND (n=9,901)	Dulaglutide *	0.88 (0.79-0.99)	0.91 (0.78-1.06)	0.96 (0.79-1.15)	0.76 (0.62-0.94)	0.93 (0.77-1.12)	0.90 (0.80-1.01)	0.85 (0.77-0.93)
PIONEER 6 (n=3,183)	Semaglutide (oral)	0.79 (0.57-1.11)	0.49 (0.27-0.92)	1.18 (0.73-1.90)	0.74 (0.35-1.57)	n/a	0.51 (0.31-0.84)	n/a
AMPLITUDE-O (n=4,076)	Efpeglenatide	0.73 (0.58-0.92)	0.72 (0.50-1.03)	0.78 (0.55-1.10)	0.80 (0.48-1.31)	n/a	0.78 (0.58-1.06)	0.68 (0.57-0.79)

Green boxes indicate significant outcomes.

† DECLARE-TIMI 58 had co-primary outcomes: 1) 3-point MACE: HR 0.93 (0.84-1.03) and 2) combined CV death or hosp. for HF: 0.83 (0.73-0.95)

* In ELIXA, the primary outcome was 4-point MACE (3-point MACE + hospitalization for unstable angina)

* FDA approval for CV risk reduction

CVOT and SGLT2-I: Benefit for renal and HF outcomes

SGLT2i

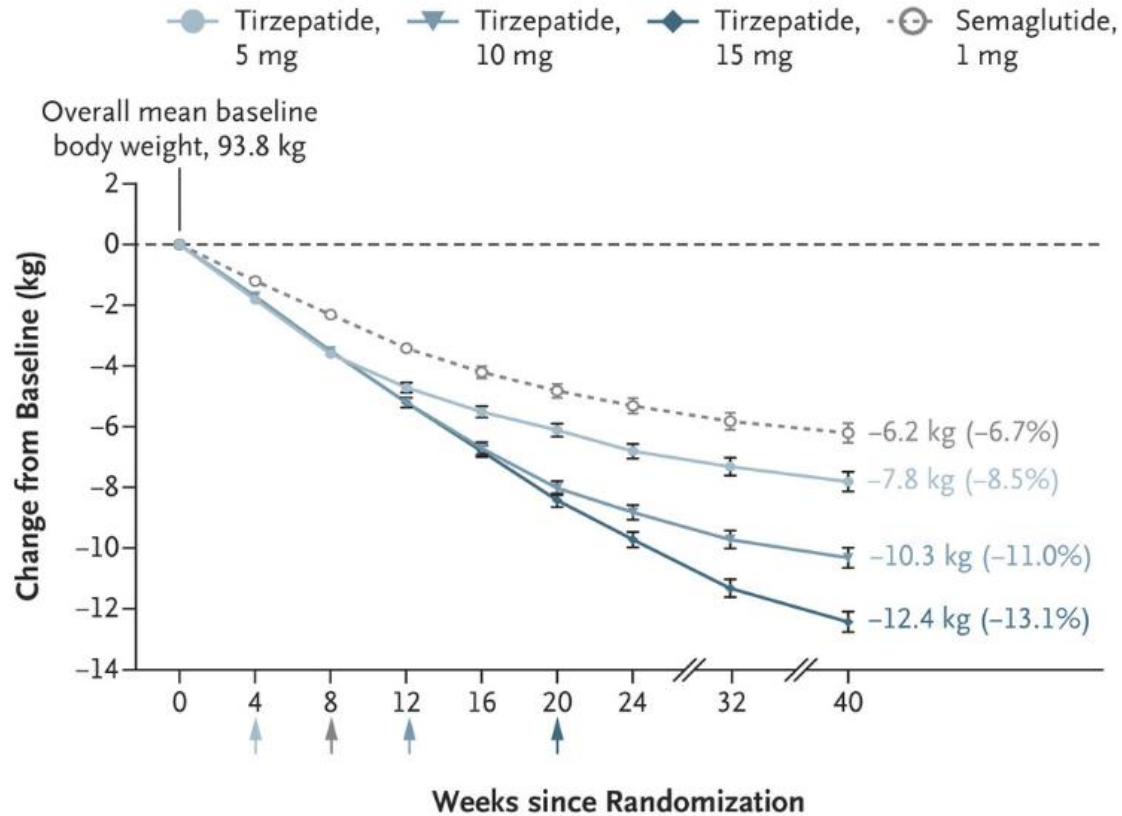
Trial	Agent	Primary outcome	Individual components of MACE			Secondary outcomes of interest		
		Primary outcome (3-point MACE)	Death from CV causes	Nonfatal MI	Nonfatal stroke	Hosp. for HF	All-cause mortality	Worsening nephropathy
EMPA-REG OUTCOME [n=7,020]	Empagliflozin	0.86 (0.74-0.99)	0.77 (0.69-0.77)	0.87 (0.70-1.09)	1.18 (0.89-1.56)	0.65 (0.50-0.85)	0.68 (0.57-0.82)	0.61 (0.53-0.70)
CANVAS program [n=10,142]	Canagliflozin	0.86 (0.75-0.97)	0.87 (0.77-1.18)	0.89 (0.73-1.09)	0.87 (0.69-1.09)	0.67 (0.52-0.87)	0.87 (0.74-1.01)	0.60 (0.47-0.77)
DECLARE-TIMI 58 [n=17,160]	Dapagliflozin	0.93 (0.84-1.03)	0.89 (0.82-1.17)	0.89 (0.77-1.01)	1.01 (0.84-1.21)	0.73 (0.61-0.88)	0.93 (0.82-1.04)	0.76 (0.67-0.87)
VERTIS [n=8,246]	Ertugliflozin	0.97 (0.85-1.11)	0.97 (0.77-1.11)	1.04 (0.86-1.27)	1.00 (0.76-1.32)	0.70 (0.54-0.90)	0.93 (0.80-1.08)	0.81 (0.63-1.04)

CVOT and SGLT2-I: Benefit for renal and HF outcomes

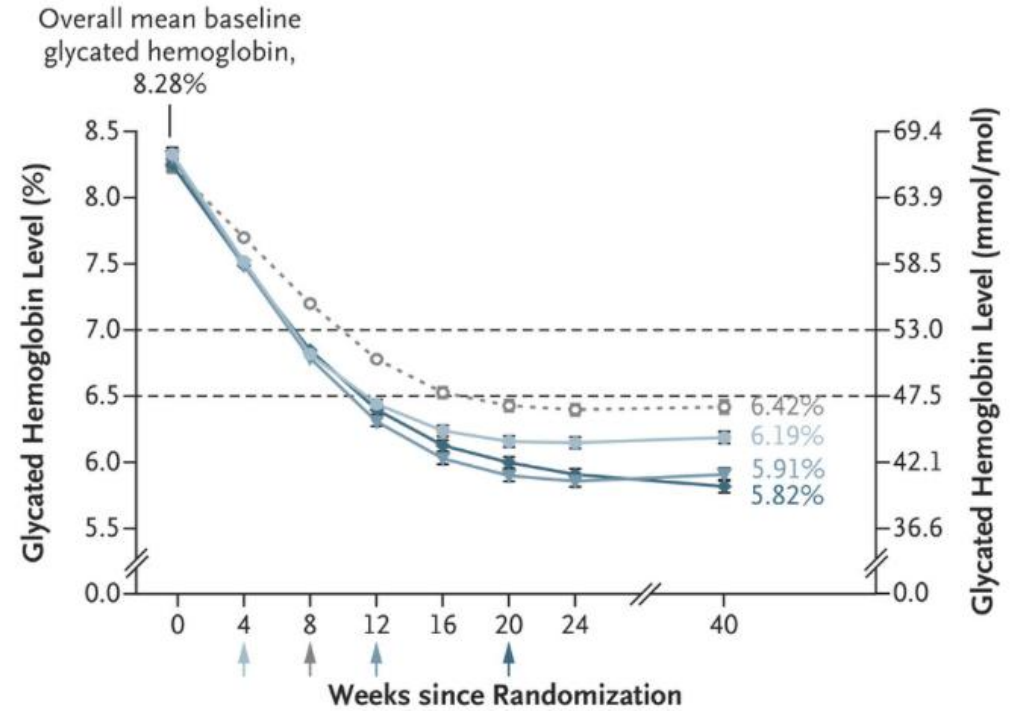
SGLT2i	Trial	Agent	Primary outcome	Individual components of MACE			Secondary outcomes of Interest		
			Primary outcome (3-point MACE)	Death from CV causes	Nonfatal MI	Nonfatal stroke	Hosp. for HF	All-cause mortality	Worsening nephropathy
	EMPA-REG OUTCOME [n=7,020]	Empagliflozin	0.86 (0.74-0.99)	0.62 (0.49-0.77)	0.87 (0.70-1.09)	1.18 (0.89-1.56)	0.65 (0.50-0.85)	0.68 (0.57-0.82)	0.61 (0.53-0.70)
	CANVAS program [n=10,142]	Canagliflozin	0.86 (0.75-0.97)	0.96 (0.77-1.18)	0.89 (0.73-1.09)	0.87 (0.69-1.09)	0.67 (0.52-0.87)	0.67 (0.54-1.01)	0.60 (0.47-0.77)
	DECLARE-TIMI 58 [n=17,160]	Dapagliflozin	0.93 (0.84-1.03)	0.98 (0.82-1.17)	0.89 (0.77-1.01)	1.01 (0.84-1.21)	0.73 (0.61-0.88)	0.73 (0.62-1.04)	0.76 (0.67-0.87)
	VERTIS [n=8,246]	Ertugliflozin	0.97 (0.85-1.11)	0.92 (0.77-1.11)	1.04 (0.86-1.27)	1.00 (0.76-1.32)	0.70 (0.54-0.90)	0.73 (0.60-1.08)	0.81 (0.63-1.04)

Tirzepatide vs Semaglutide

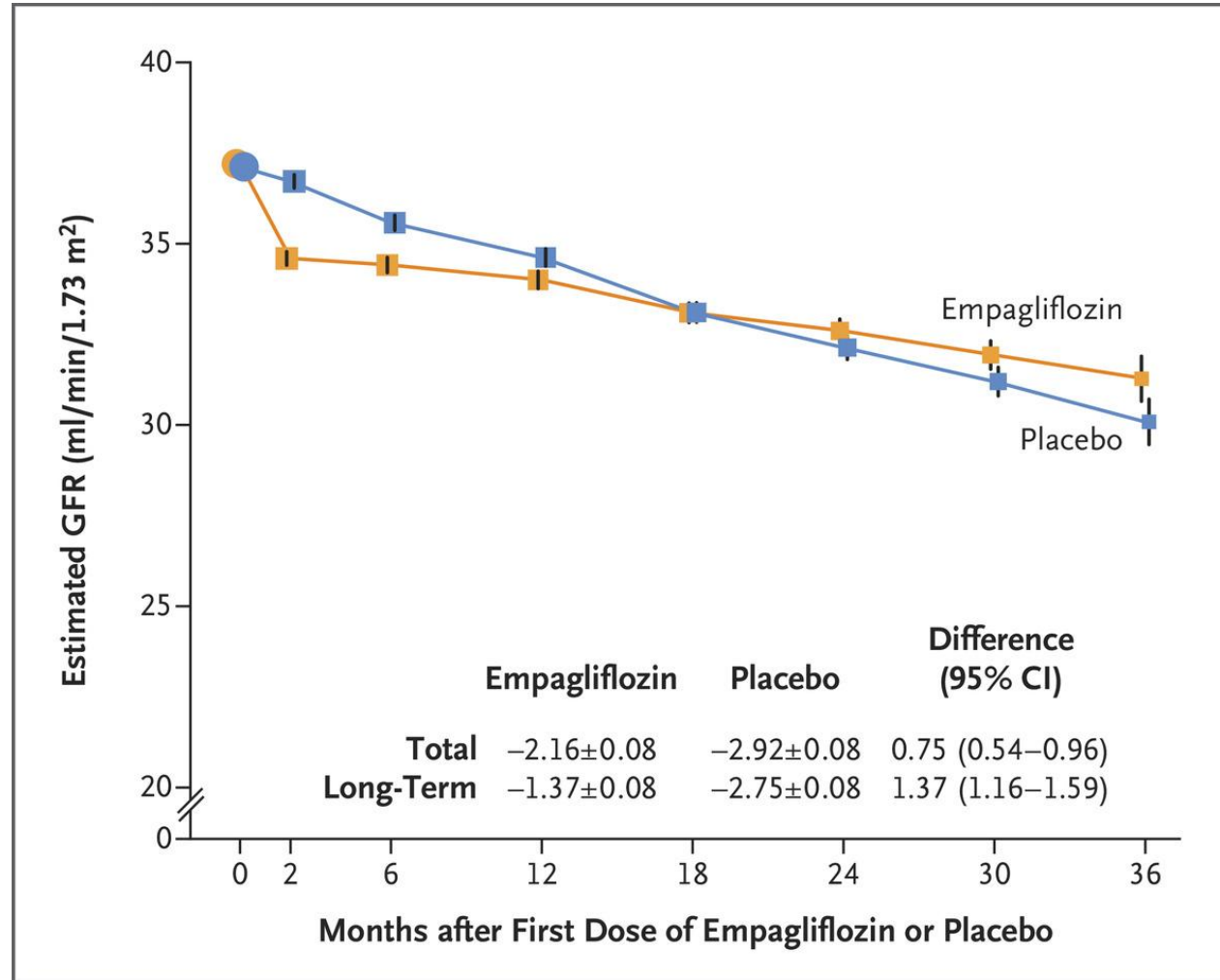
B Change in Body Weight from Wk 0 to Wk 40



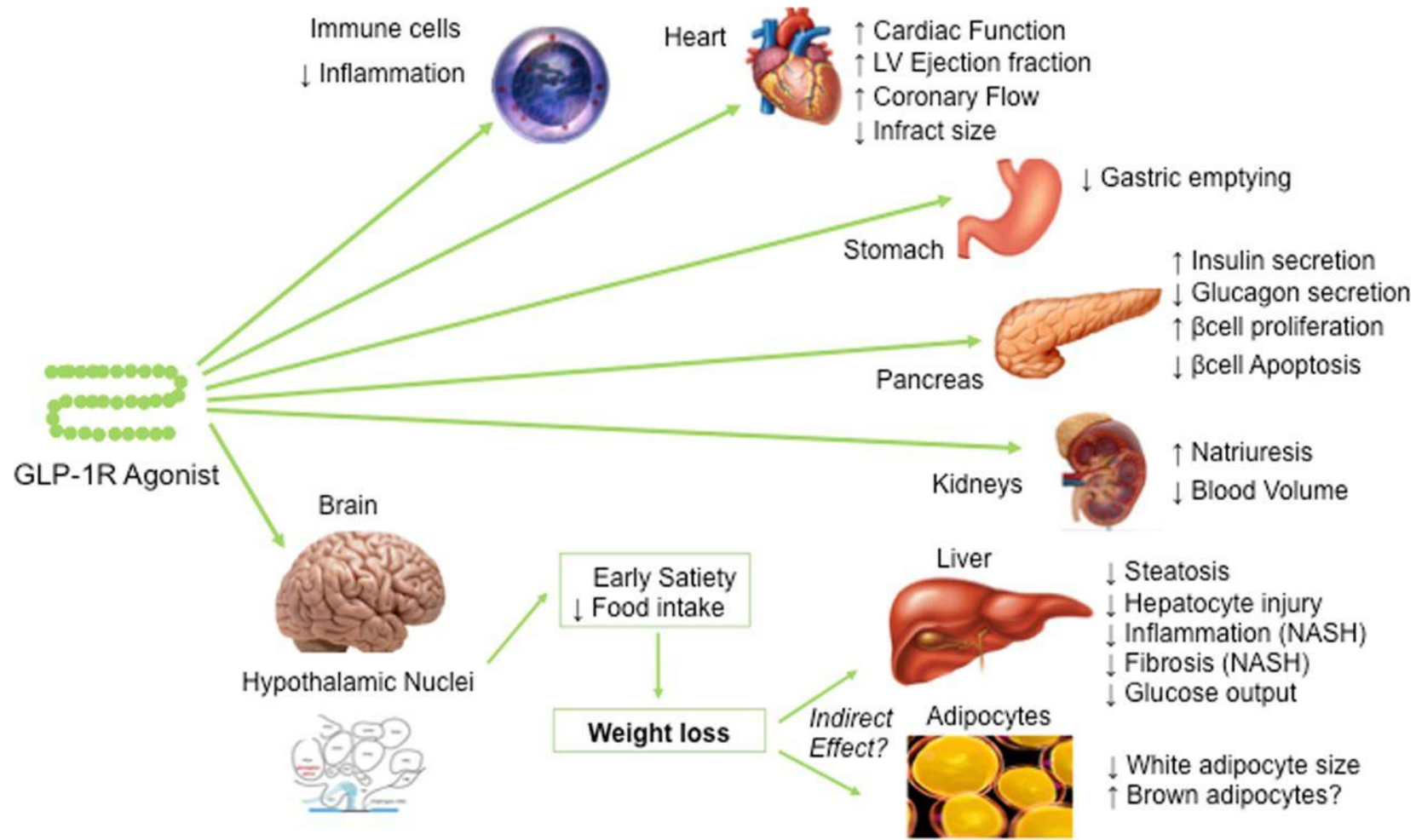
B Glycated Hemoglobin Level



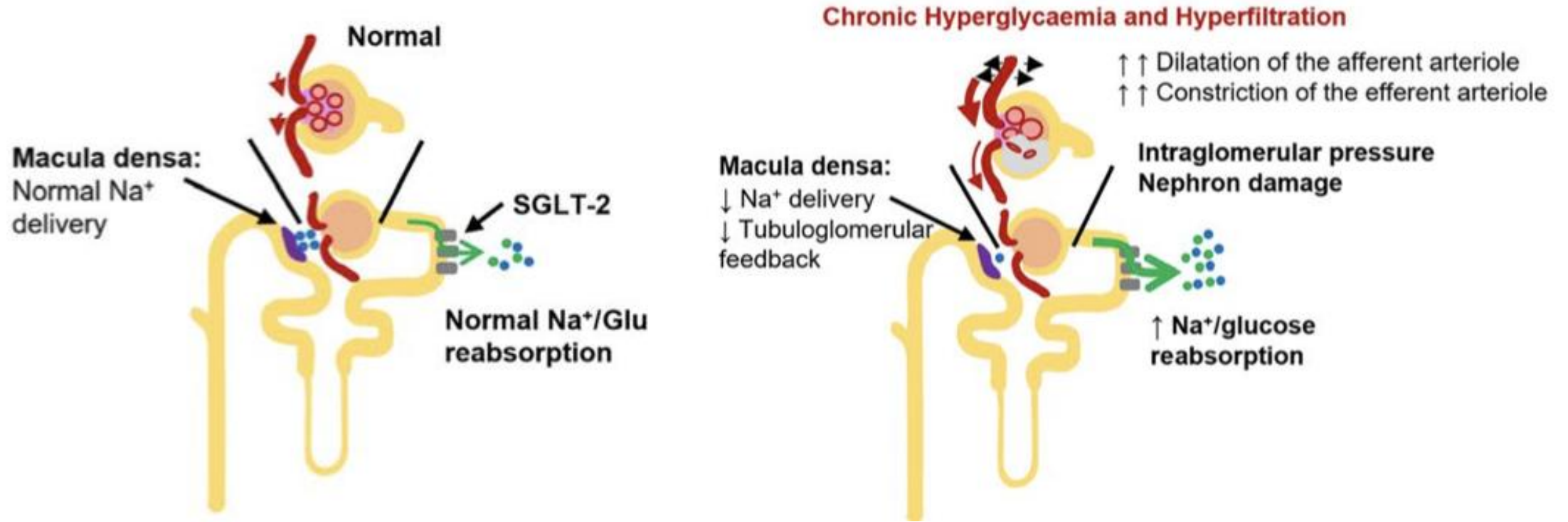
Change from Baseline in Estimated GFR Don't Worry, Be Happy



Glucagon-like peptide-1 receptor agonists (GLP-1RAs)



Tubular Hypothesis of DKD



[Nature Reviews Nephrology](#) volume 14, pages 361–377 (2018)

[Nature Reviews Nephrology](#) volume 16, pages 317–336 (2020)

FDA indications beyond glycemic control

<u>Empagliflozin</u>	<p>T2D: Risk reduction of CV death in adult patients with T2D and established CVD and hospitalization for HF in adults with HFrEF.</p> <p>CHF: Risk reduction of CV death and HF hospitalization in adults regardless of LVEF.</p>
<u>Canagliflozin</u>	<p>T2D: Risk reduction of MACE in adults with T2D and established CVD</p> <p>T2D and DKD: Risk reduction of ESKD, doubling of serum Cr, CV death, and hospitalization for HF in adults with T2D and diabetic nephropathy with albuminuria.</p>
<u>Dapagliflozin</u>	<p>T2D: Risk reduction of hospitalization for HF in adults with T2D and established CVD or multiple CV risk factors.</p> <p>HF: Risk reduction of CV death and hospitalization for HF in adults with HFrEF (NYHA class II-IV).</p> <p>CKD: with UMA 200-5000 mg/g who are receiving other first-line therapies.</p>

SGLT-2 I and CVOT Meta-analysis of MACE

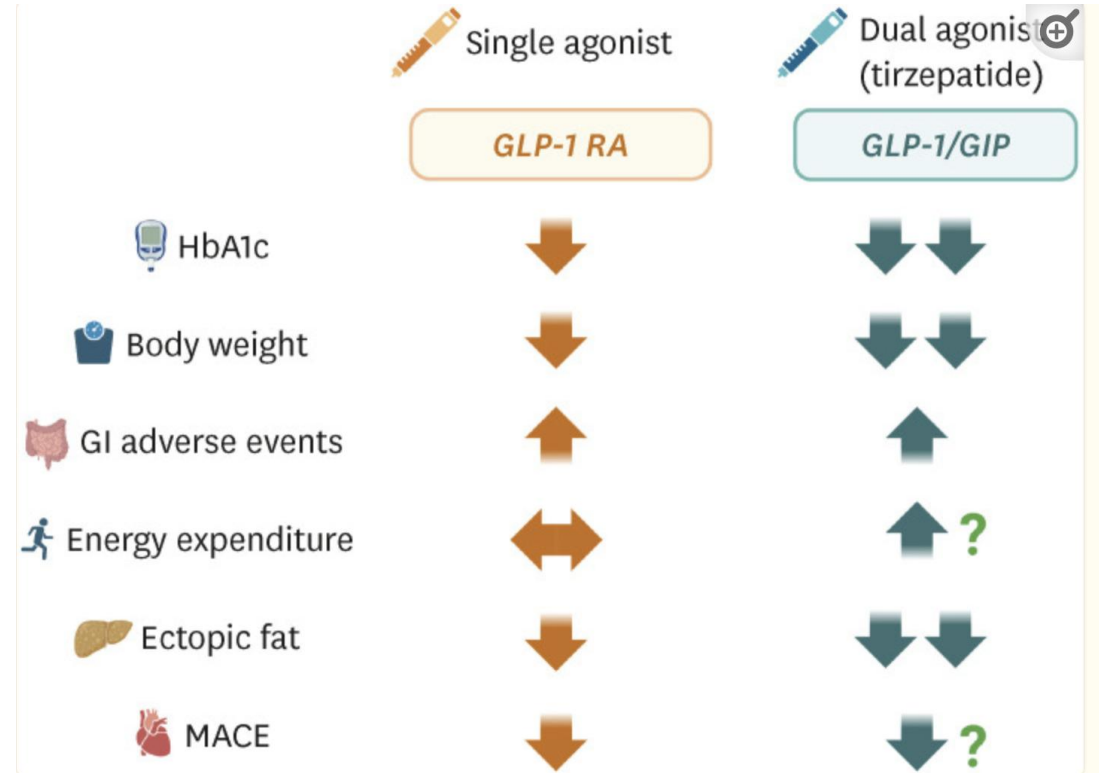
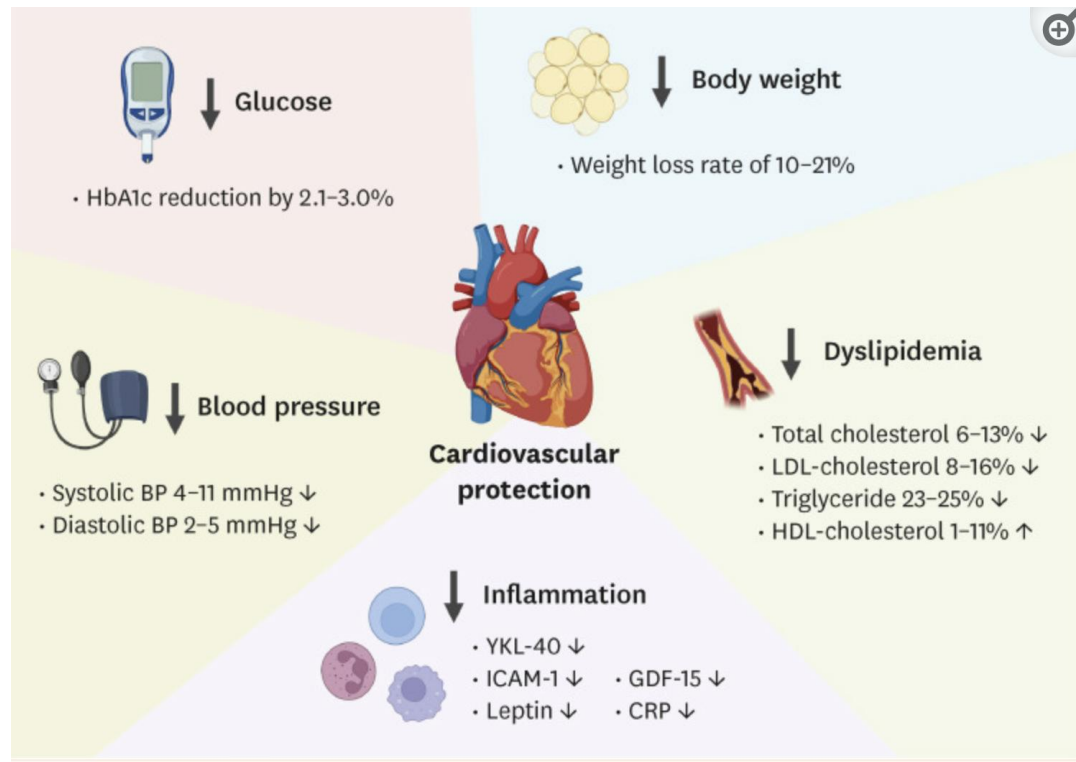
- Meta-analysis of MACE with SGLT-2 I vs placebo
- For patient with known CVD
 - Per 1000 patients SGLT2-I treatment resulted in 18 fewer events over 5 years than those on placebo
 - NNT to prevent one episode: 56
- For patient without known CVD
 - Per 1000 patients SGLT-2 I treatment resulted in 8 fewer events over 5 years than those on placebo
 - NNT to prevent one episode: 125

Glucose Targets To Achieve A1C Goals

- Usual glucose goals
 - Fasting 80 -130 mg/dl
 - Post meal glucose < 180 mg/dl
- Elderly or complicated medical problems
 - Fasting 100-180 mg/dl
 - Bedtime 110-200 mg/dl
- No hypoglycemia



Dual vs Single Agonist



GLP 1RA therapy and CVOT: Meta-analysis

- Meta-analysis of the recent CVOT for GLP1-RA shown in understandable terms
 - For patient with known CVD
 - Per 1000 patients GLP 1RA treatment resulted in 30 fewer events over 5 years than those on placebo
 - Number needed to treat to prevent an episode is 33
 - For patient without known CVD
 - Per 1000 patients GLP 1RA resulted in 14 fewer events over 5 years
 - NNT was 71
- Statins as a comparison
 - NNT for secondary prevention is around 30

Metformin - considerations

- **Contraindications** (mainly due to increased risk of lactic acidosis):
 - Cirrhosis(extent not specified)
 - Unstable or acute heart failure at risk of hypoperfusion/hypoxia
 - Active alcohol abuse (such as binge drinking)
- **Symptoms of lactic acidosis:** fatigue, weight loss, nausea, abdominal pain, dyspnea, and arrhythmia
- **Remember:** Metformin use can be associated with vitamin B12 malabsorption and worsening of symptoms of neuropathy so periodically check B12 level

