Approach to Glycemic Management of Type 2 Diabetes

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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

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

Diabetes Care

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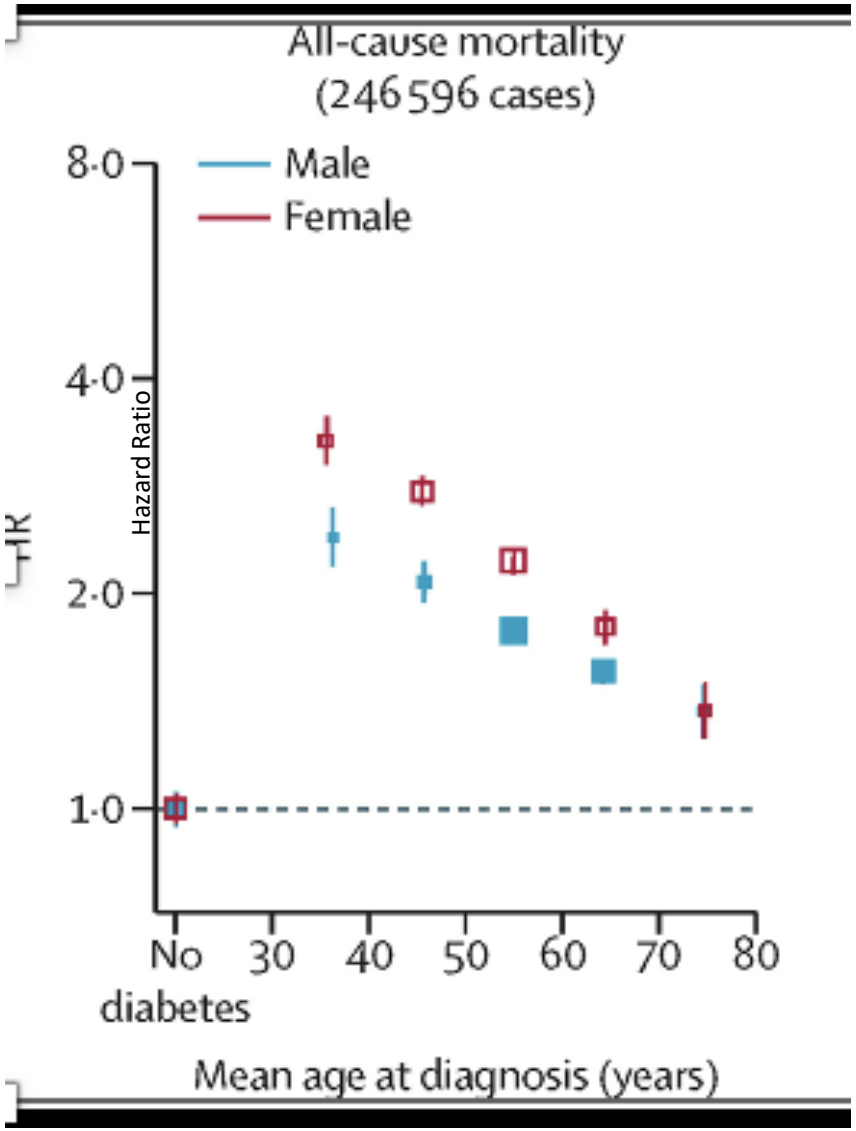
Standards of Care in Diabetes 2025

American Diabetes Association.
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

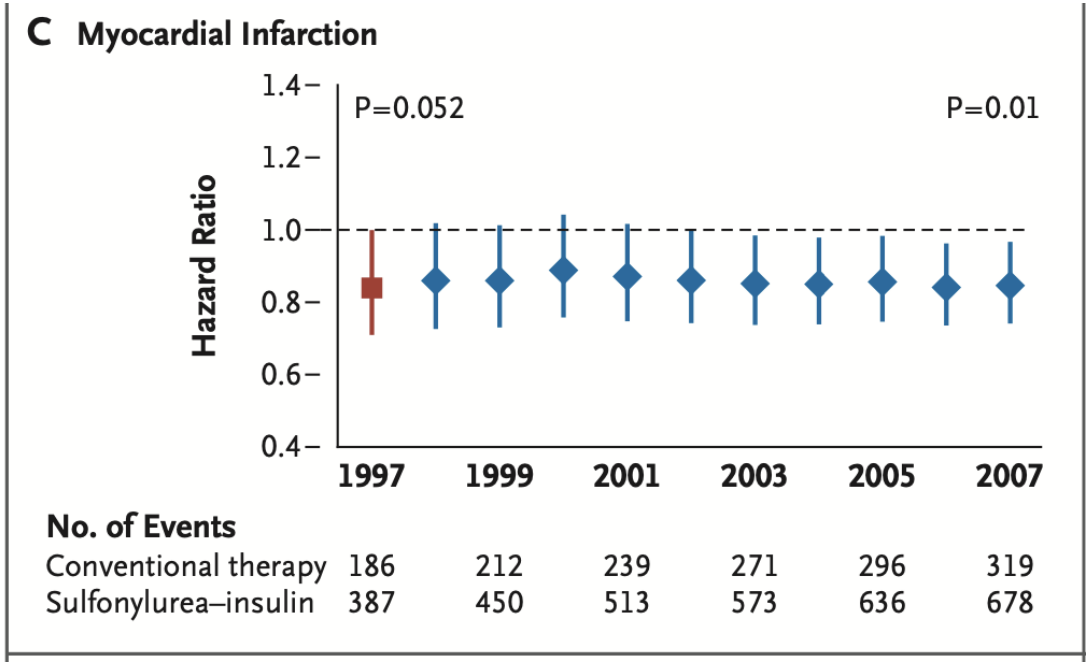


A woman diagnosed with T2DM in her 40's has **3 times** the mortality of age matched women without diabetes
A man has about **twice** the risk as men without diabetes

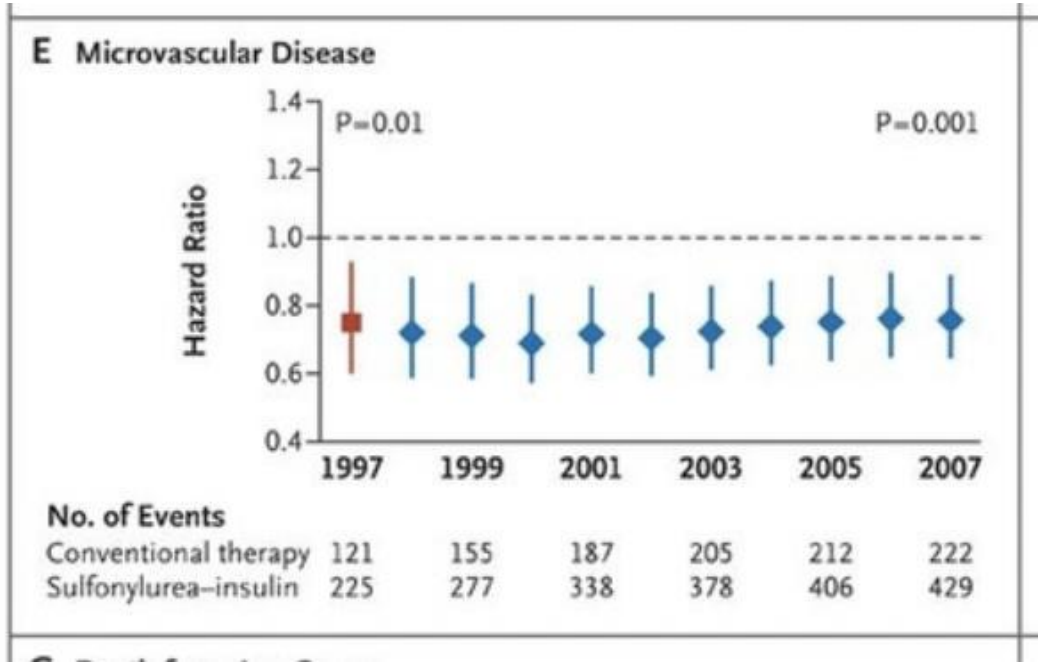
Lancet Diabetes Endoc 11:731-742, 2023

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

Persistent CVD benefit after UKPDS

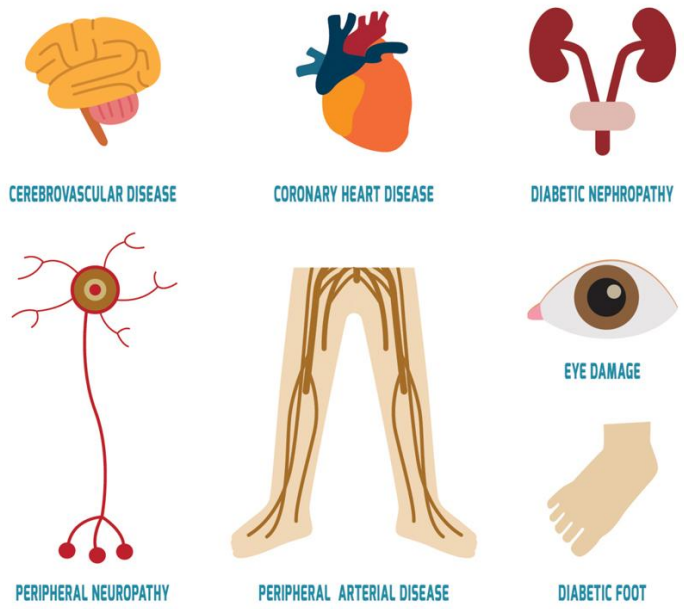


Persistent microvascular benefit in UKPDS



N Engl J Med 2008; 359:1577-1589

What can be achieved with glucose control?

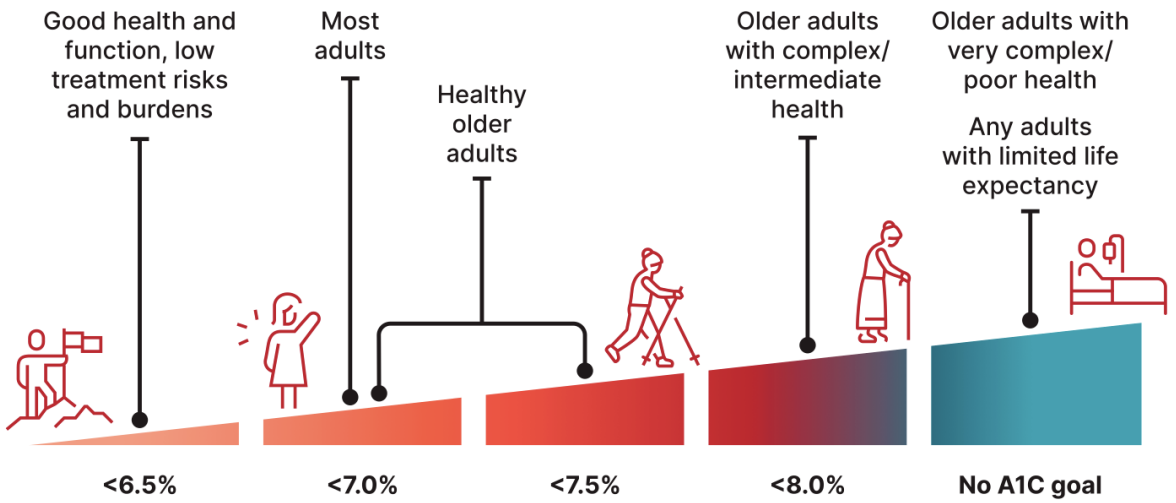


1% lower A1c translates to a risk reduction of:

- 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



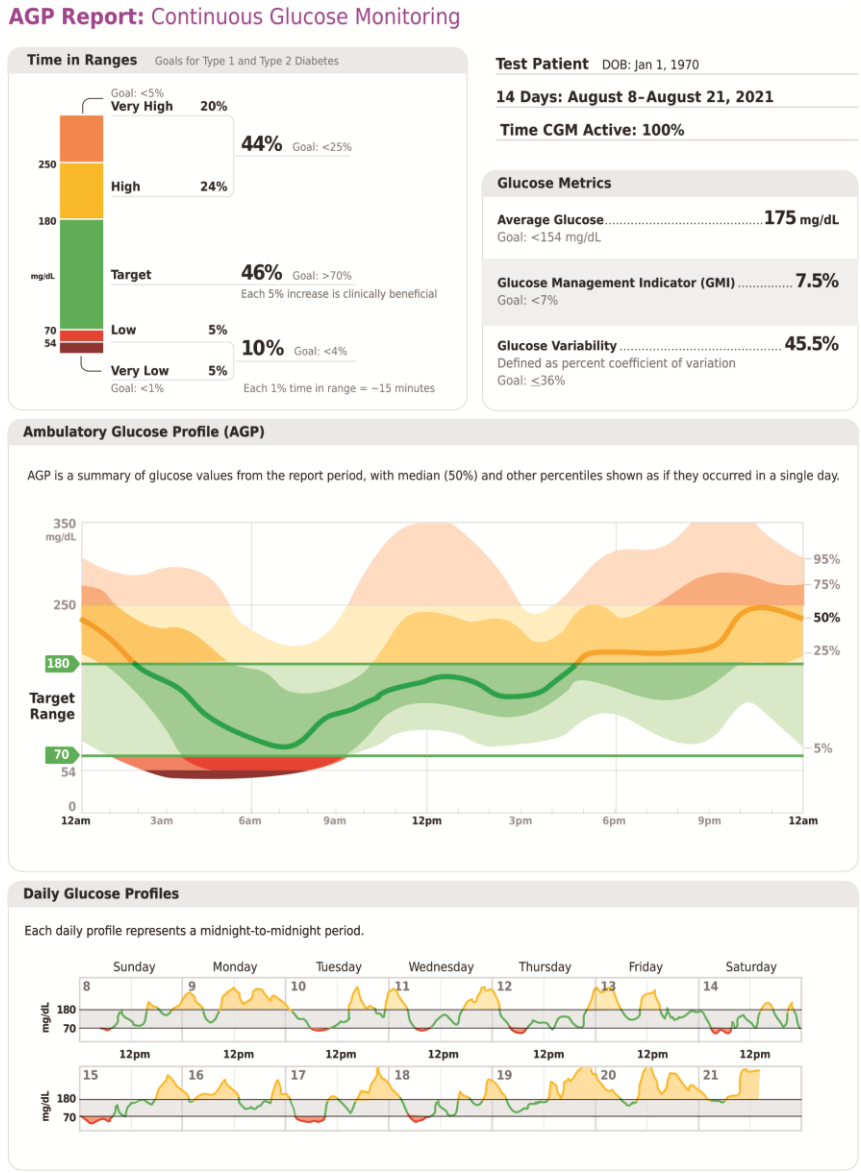
Modifying Factors

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

Diabetes Care 2025; 45 (Suppl. 1): S128–S147

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



Diabetes Care 2022; 45 (Suppl. 1): S83–S96

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

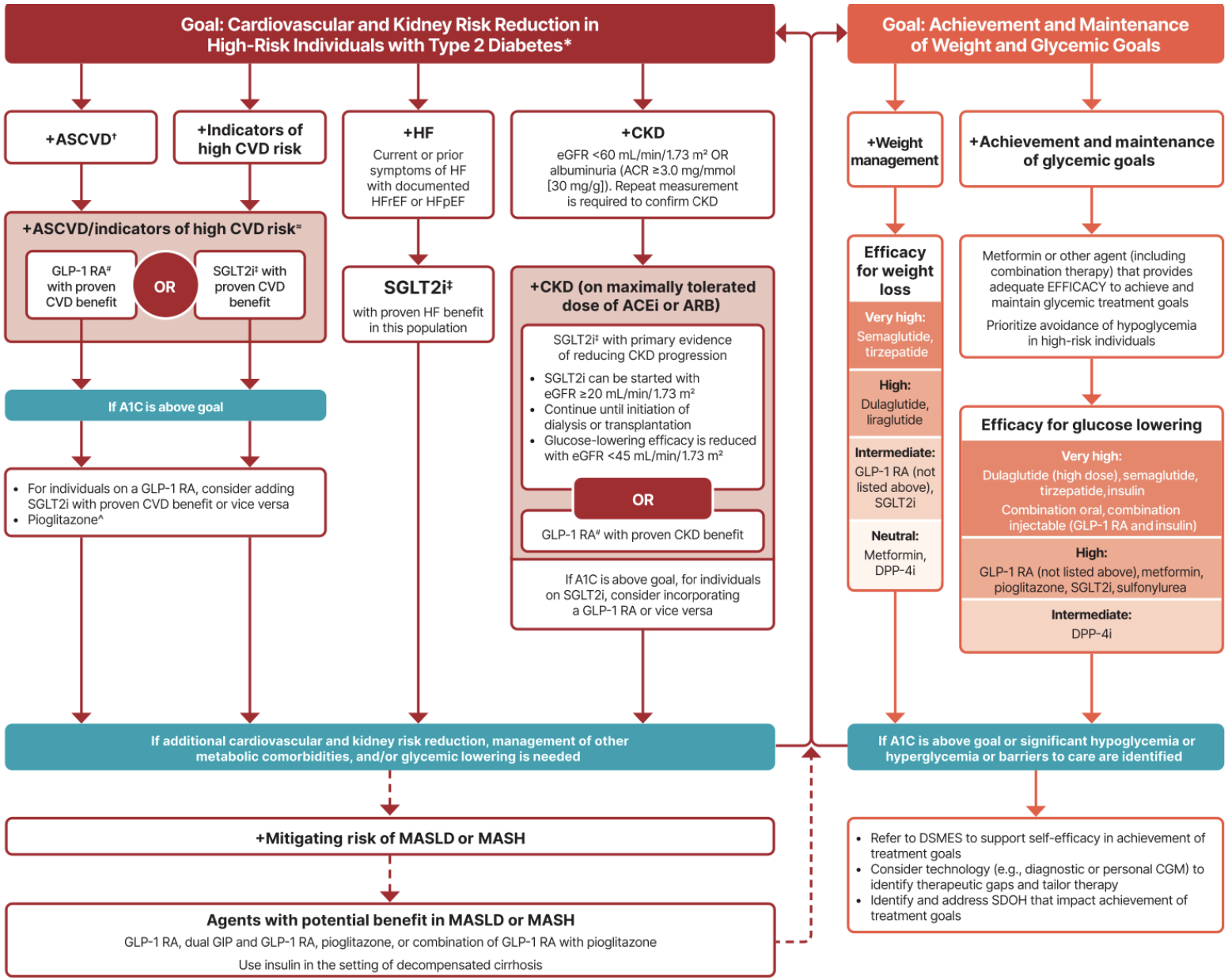
D.A1C goal should be <7% for patients with T2DM

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
  - Glucose lowering efficacy
  - Side effects
  - Cost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OR
SGLT2i‡ with proven CVD benefit
If A1C is above goal
For individuals on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
Pioglitazone^
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eGFR <60 mL/min/1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). Repeat measurement is required to confirm CKD
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SGLT2i‡ with primary evidence of reducing CKD progression
SGLT2i can be started with eGFR ≥20 mL/min/1.73 m²
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Agents with potential benefit in MASLD or MASH
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Use insulin in the setting of decompensated cirrhosis
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Very high:
Semaglutide, tirzepatide
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ADA SOC 2025

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”

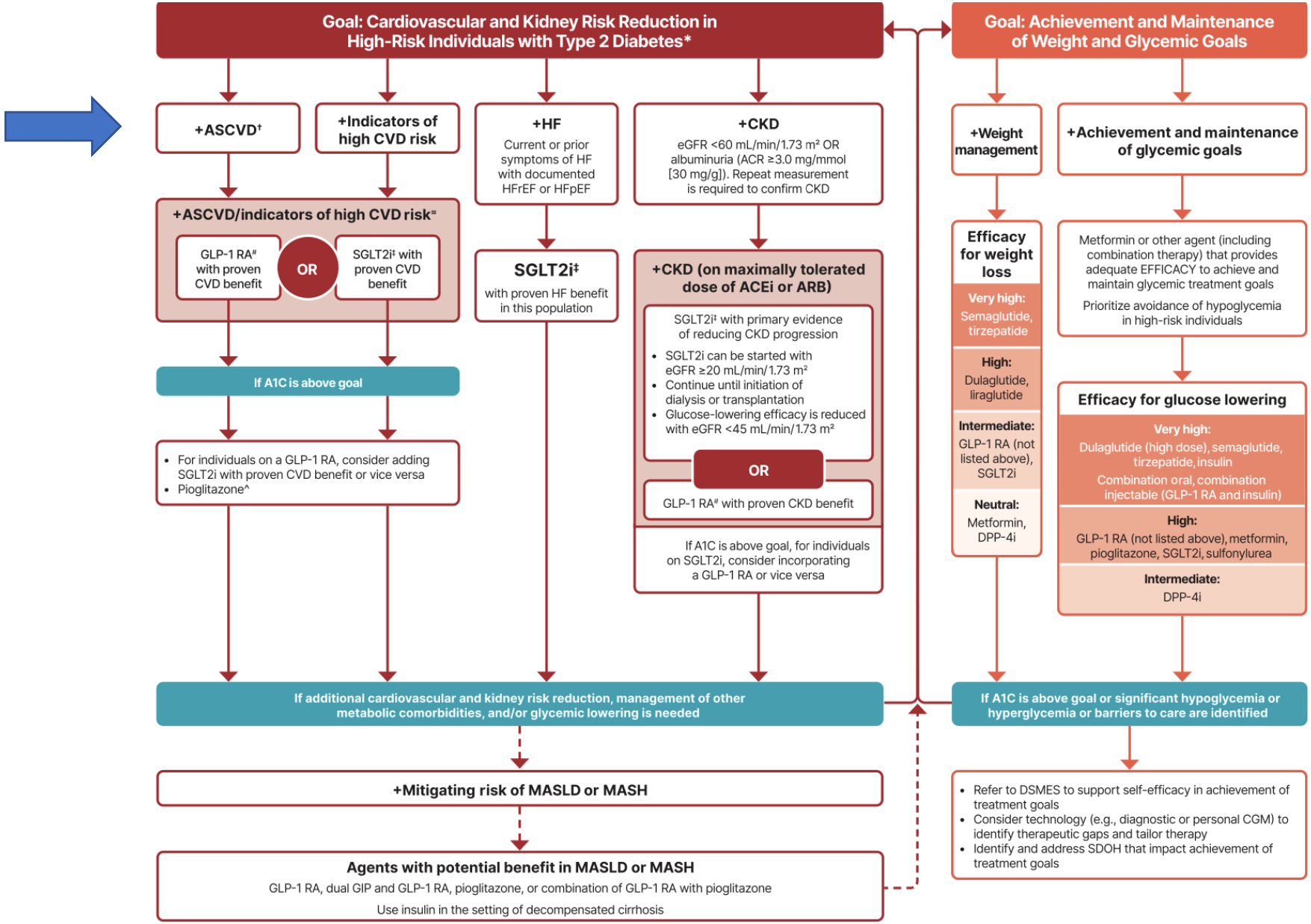
eGFR	Initiation	Continuation
>45	OK to initiate	Max dose 2550 mg total daily
30-45	Not recommended	- FDA: If already on metformin and eGFR falls to between 30-45, assess risks/benefits of continuing - In practice: Consider lowering the dose to maximum of 1000 mg total daily
<30	Contraindicated	Discontinue

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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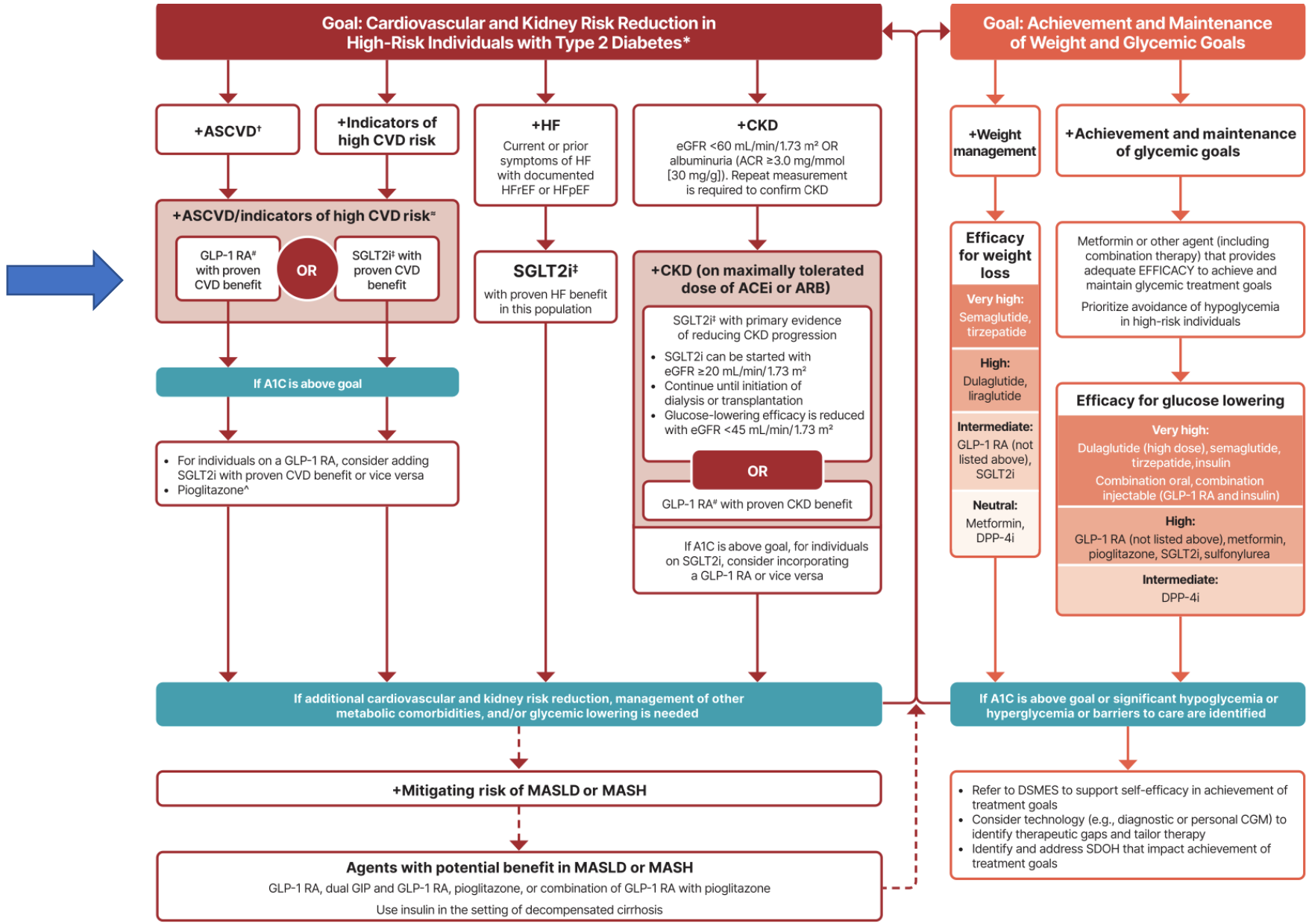
ADA SOC 2025

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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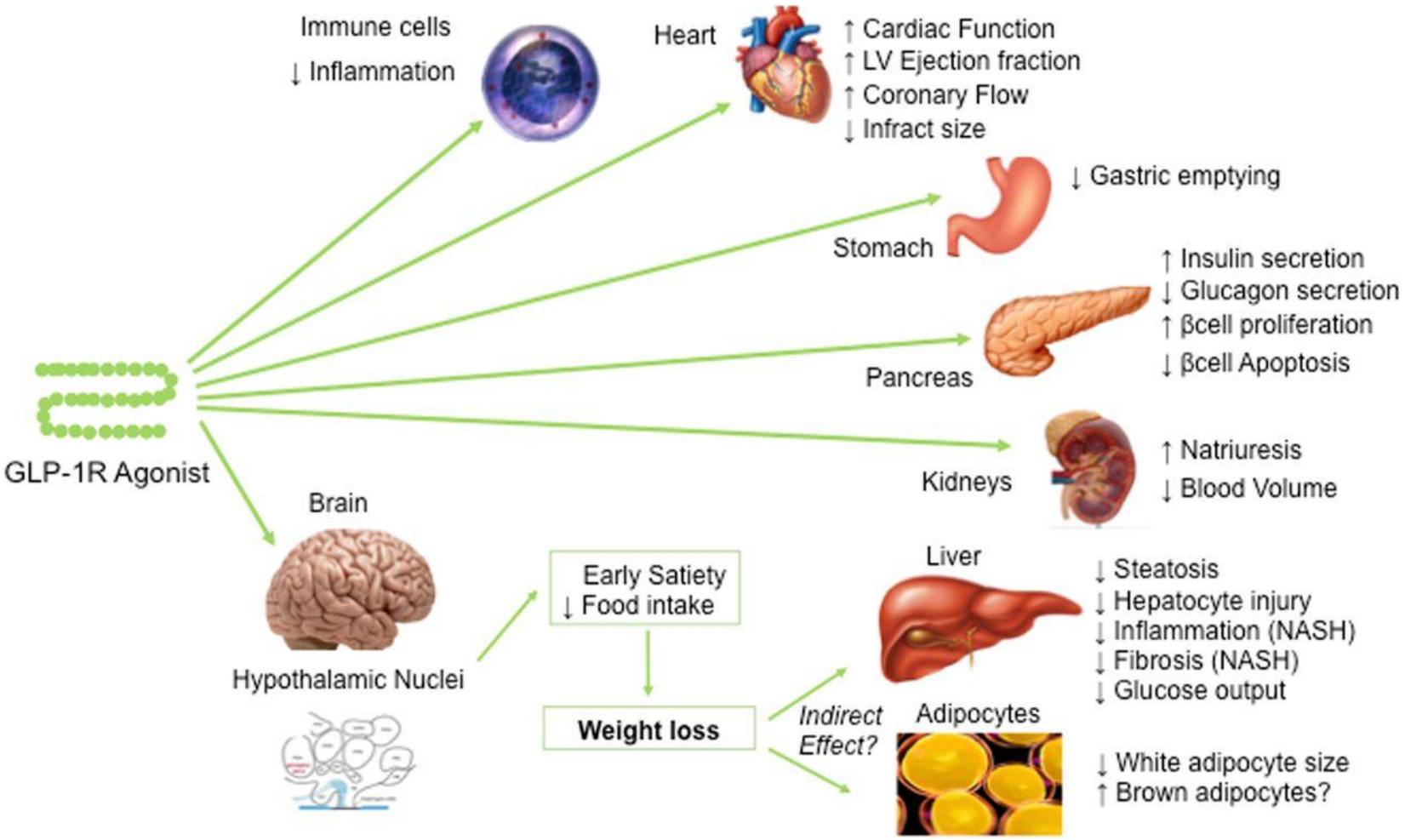
ADA SOC 2025

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



Gauri Dhir, and Kenneth Cusi J Investig Med 2018;66:7-10

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)**

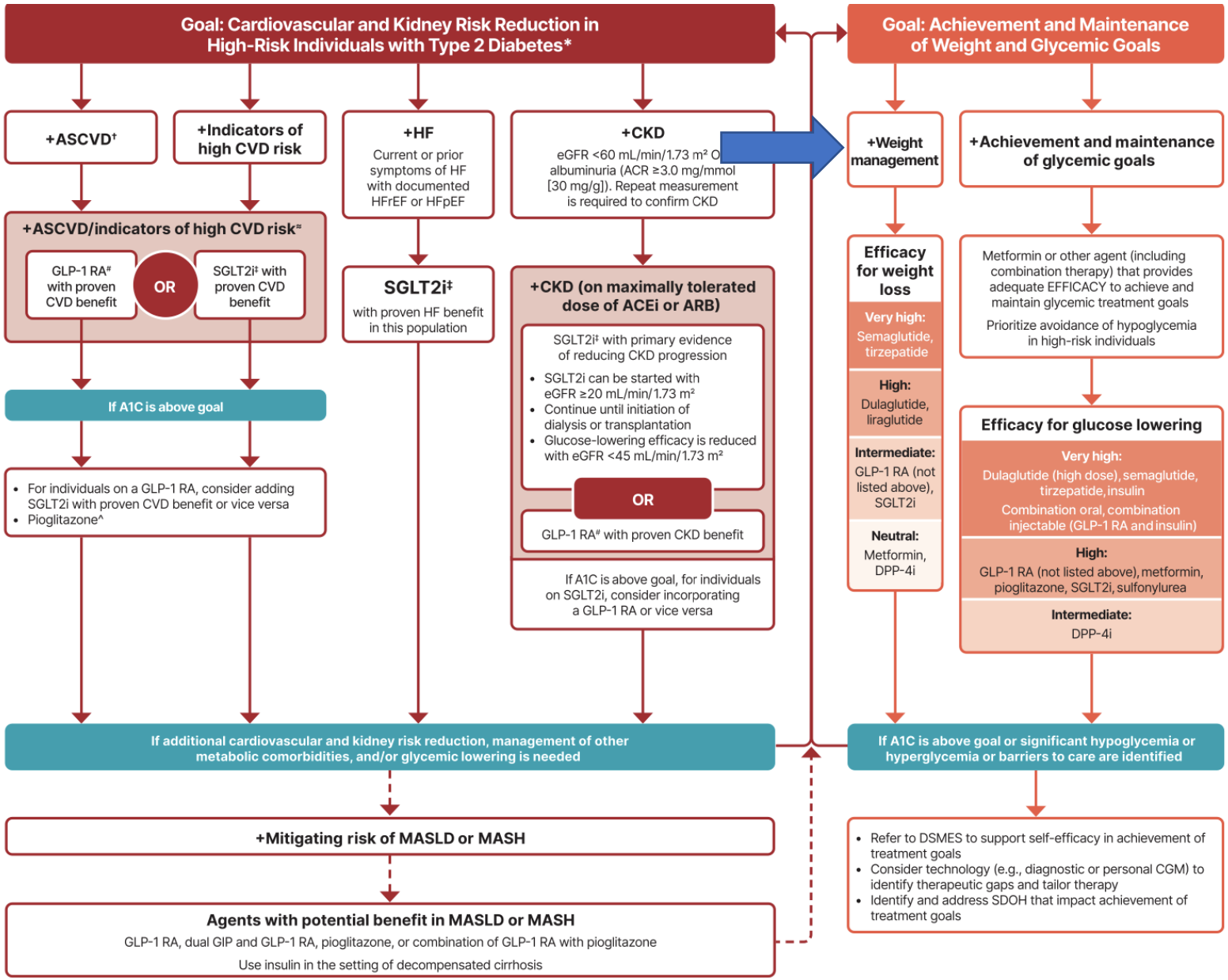
Caveats on prescribing GLP-1 RA therapy

- 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

DC 48:846-859. 2025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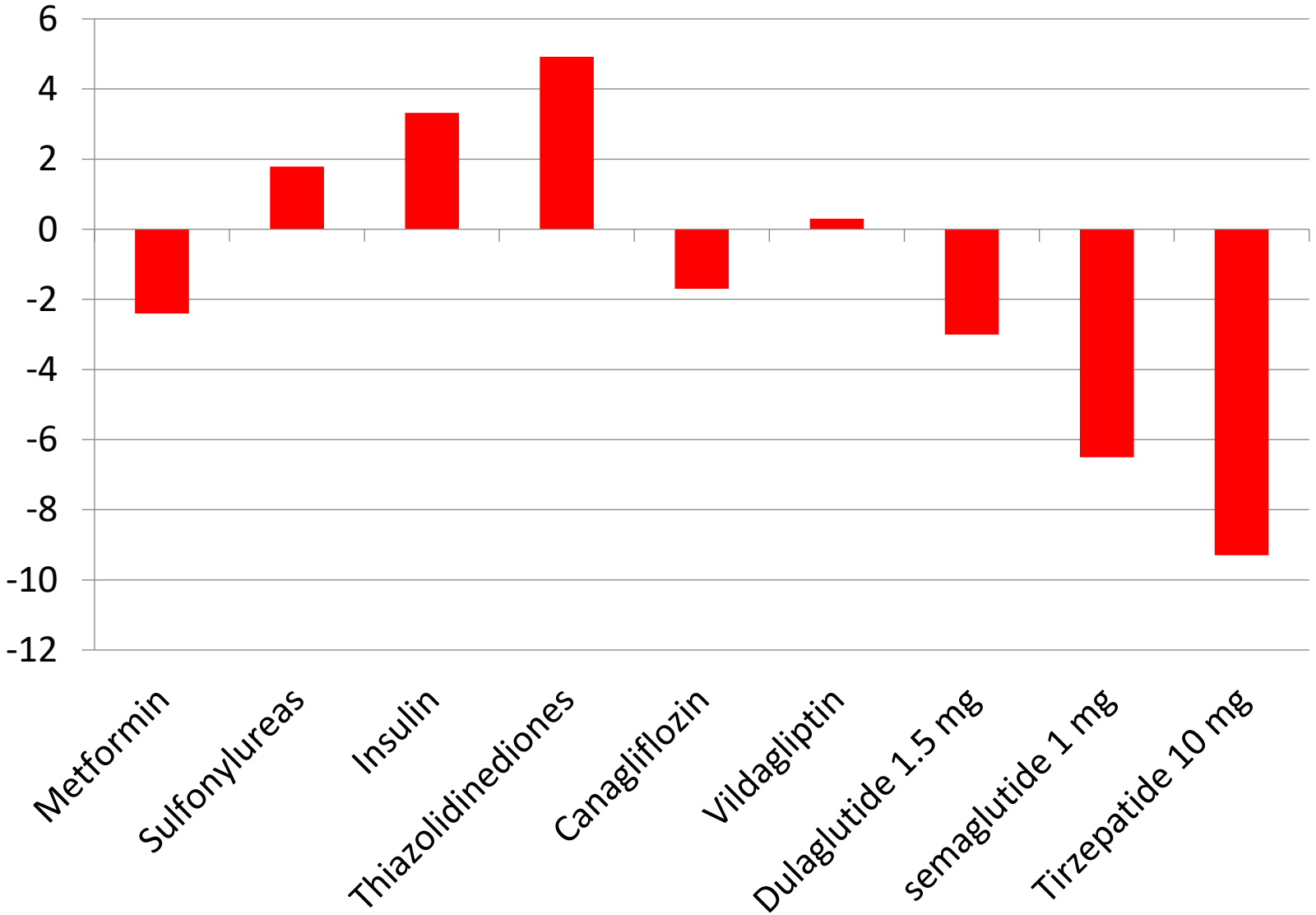
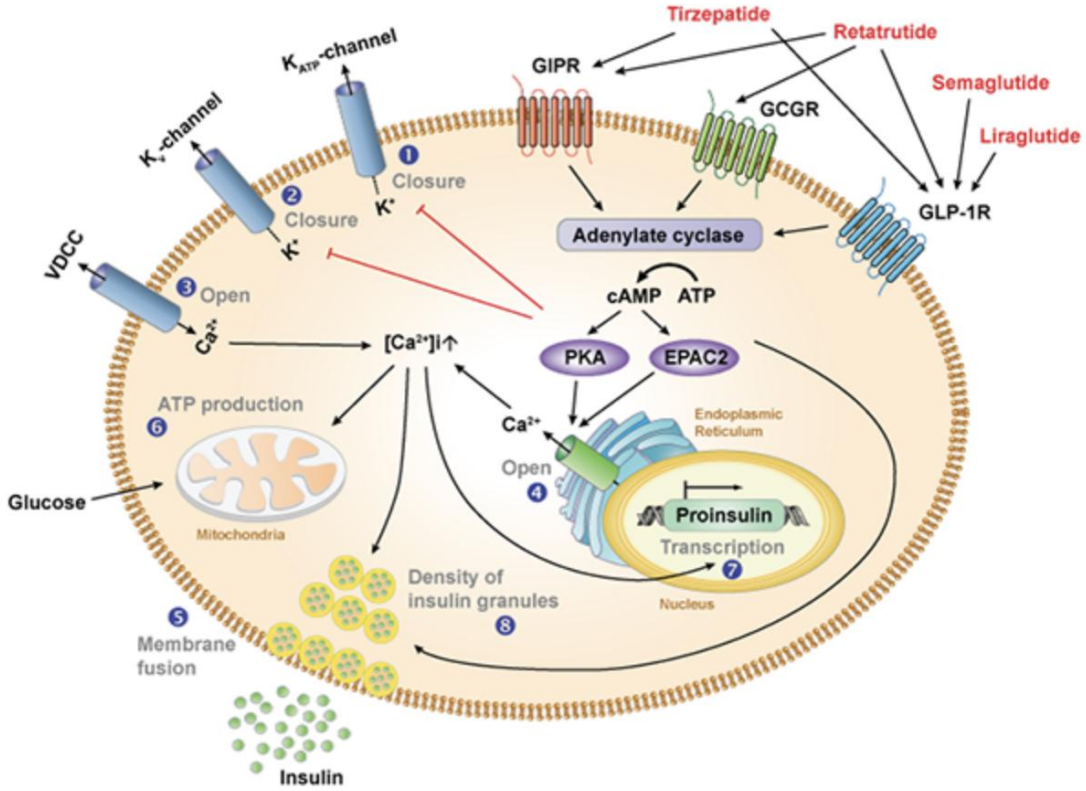
Weight Effect (kg)



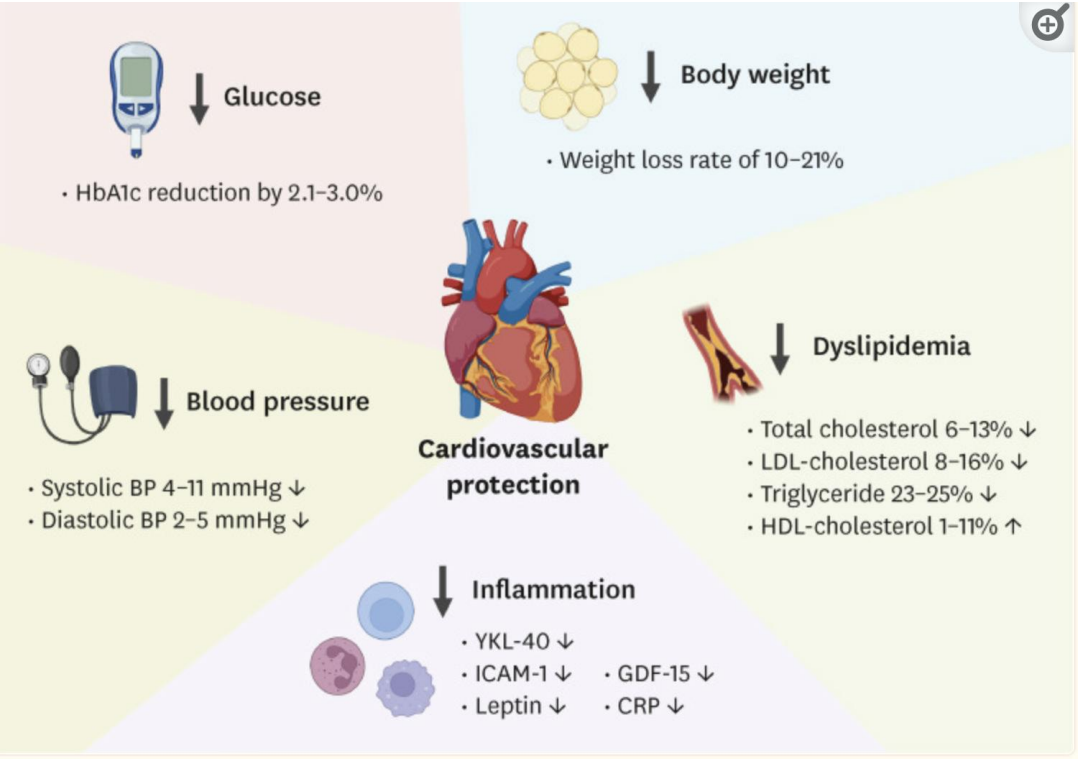
Tirzepatide: Miracle Drug?

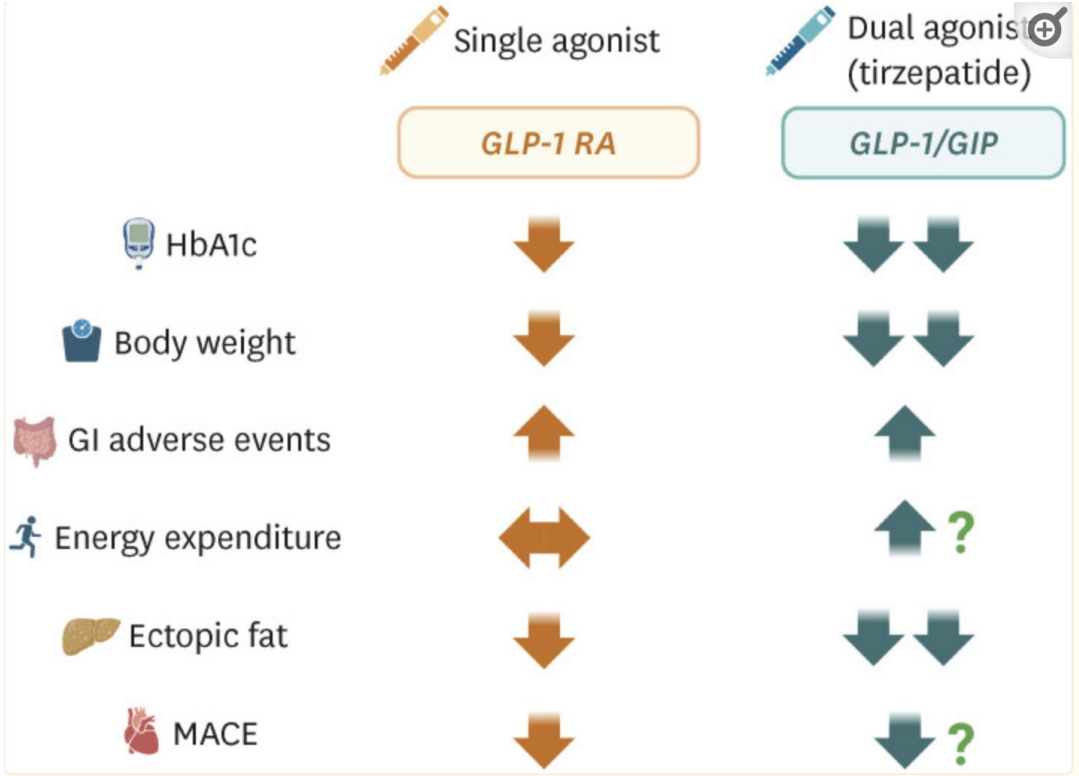
- Tirzepatide is a “dual receptor” agonist for GLP-1 and GIP receptors
- Glucose-dependent Insulinotropic Polypeptide agonist
- Glucagon Receptor agonists in the “works”



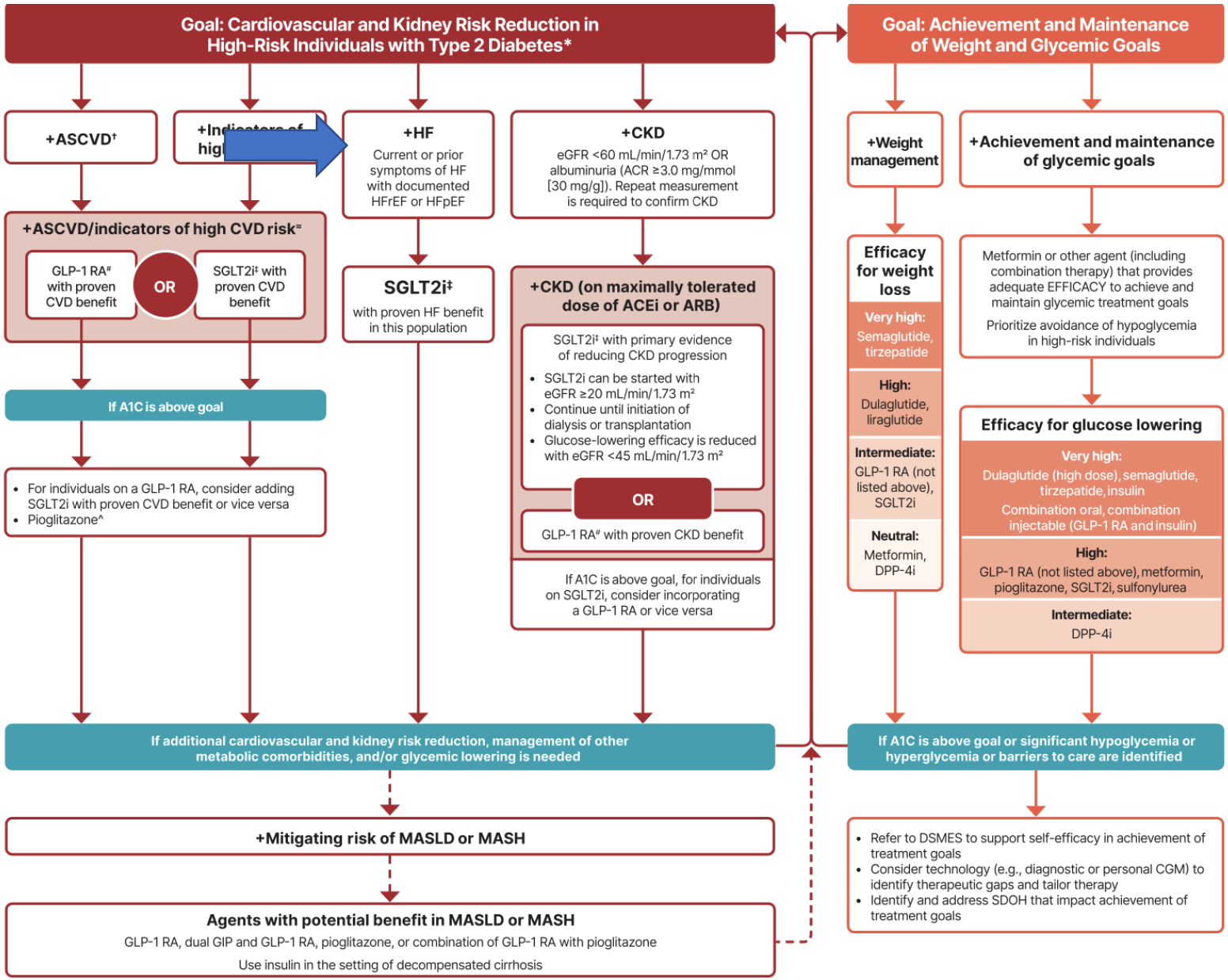
AdipoGen Website

Dual vs Single Agonist





J Lipid Atheroscler. 2023 Sep; 12(3): 213–222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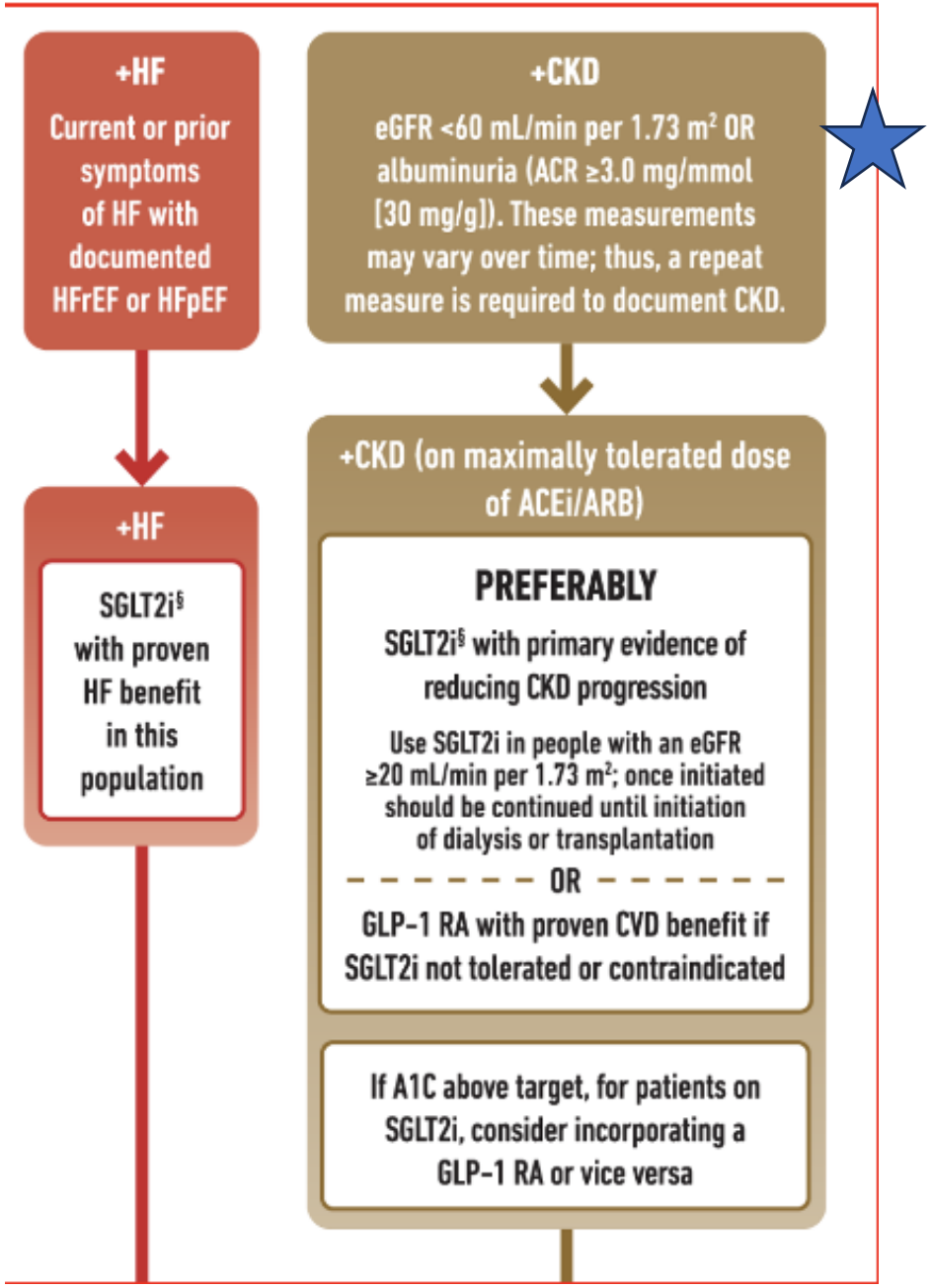
Consider technology (e.g., diagnostic or personal CGM) to identify therapeutic gaps and tailor therapy
Identify and address SDOH that impact achievement of treatment goals

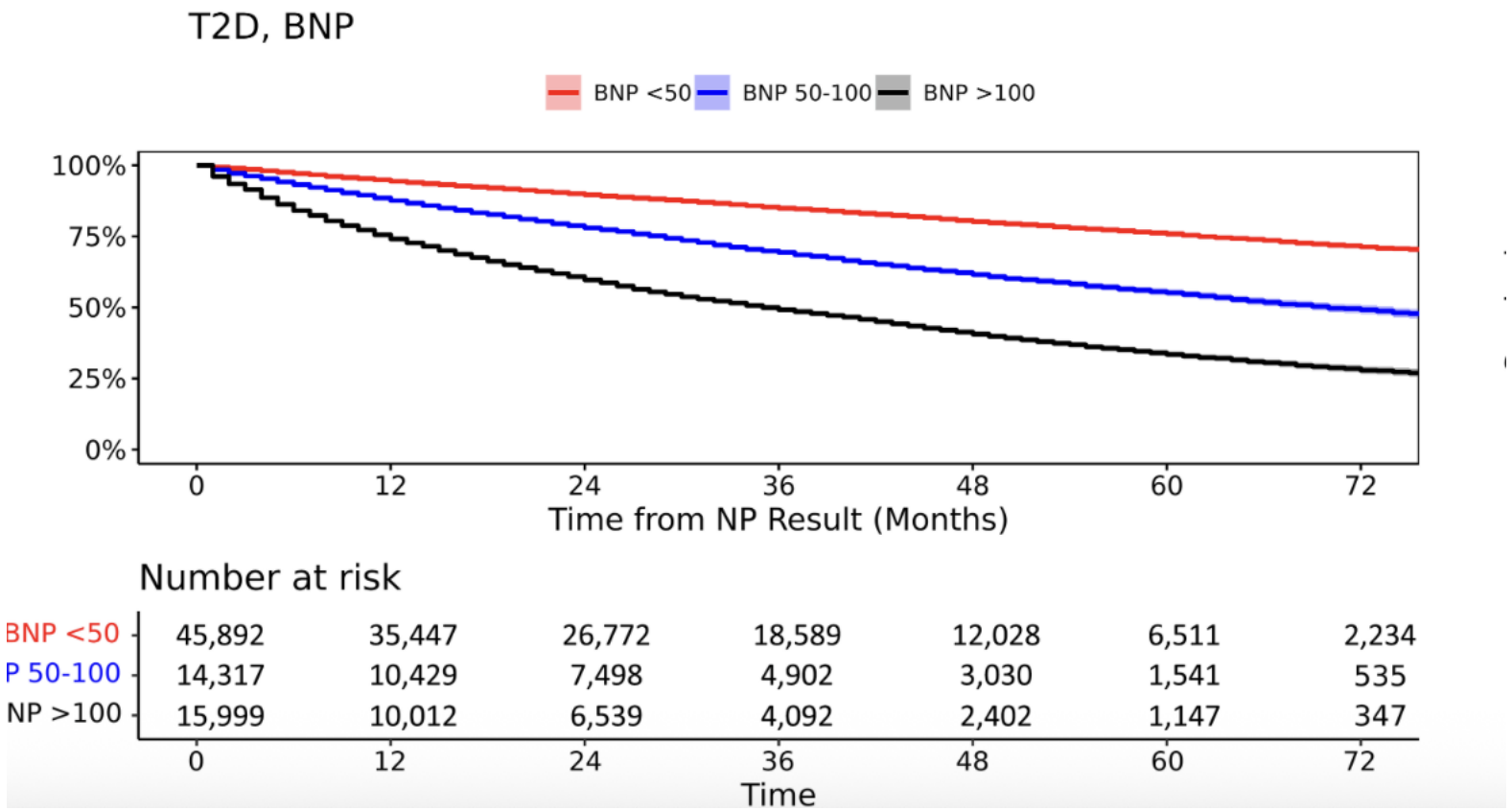
ADA SOC 2025

What is HF or CKD?

1. ADA SOC 2024 suggests screening all 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%

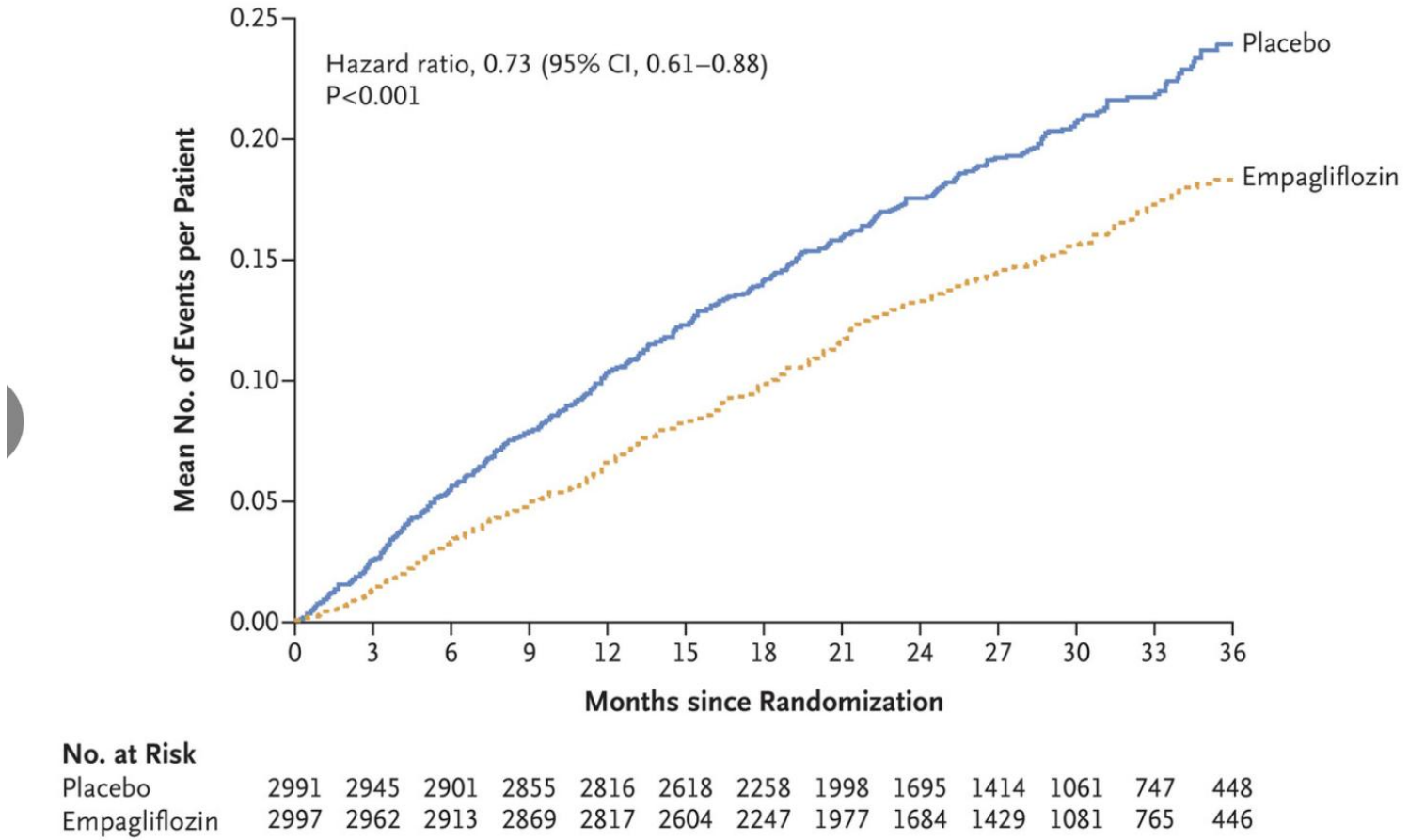


Heart failure onset stratified by BNP in asymptomatic T2DM



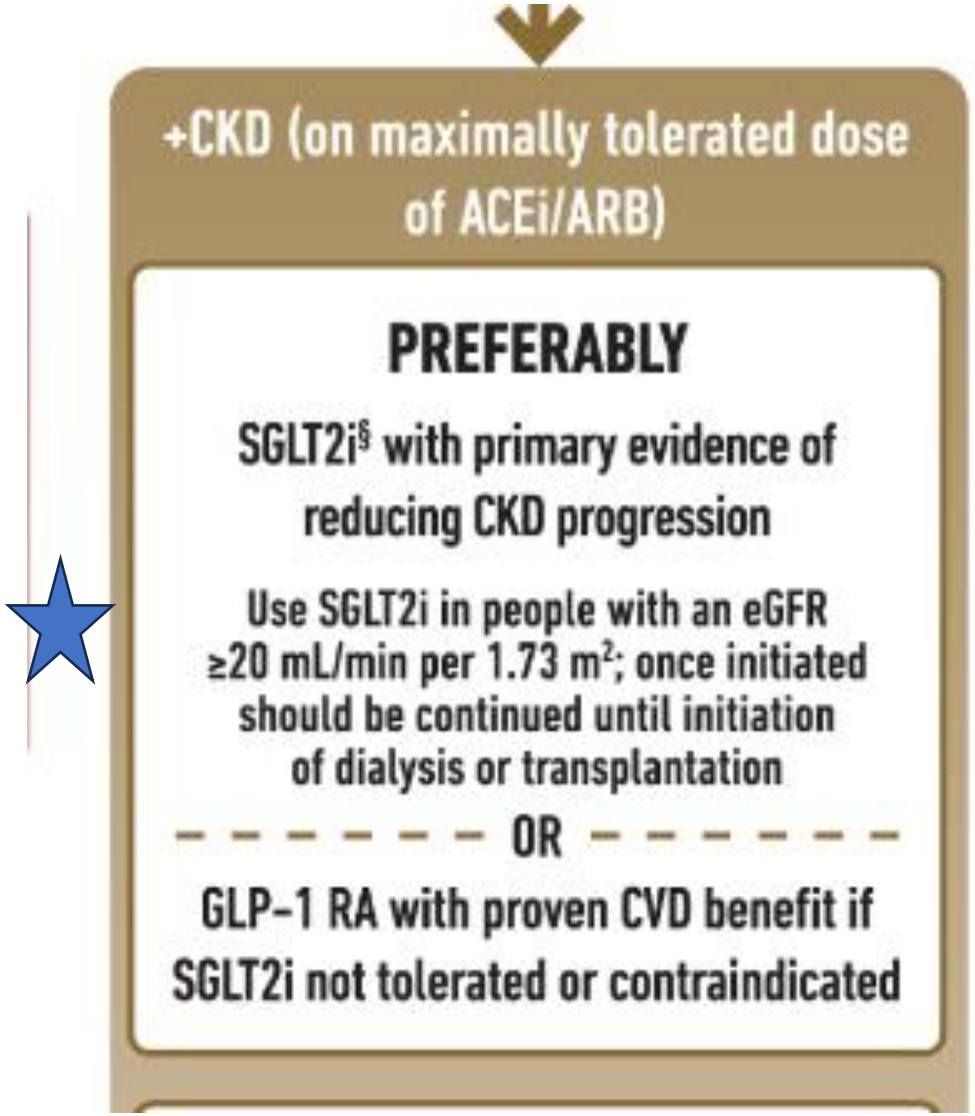
Diabetes Care 2025;48(12):2145–2153

Use of Empagliflozin in HF with Preserved EF



N Engl J Med 2021;385:1451-1461

Use in Renal Insufficiency: Update!



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?

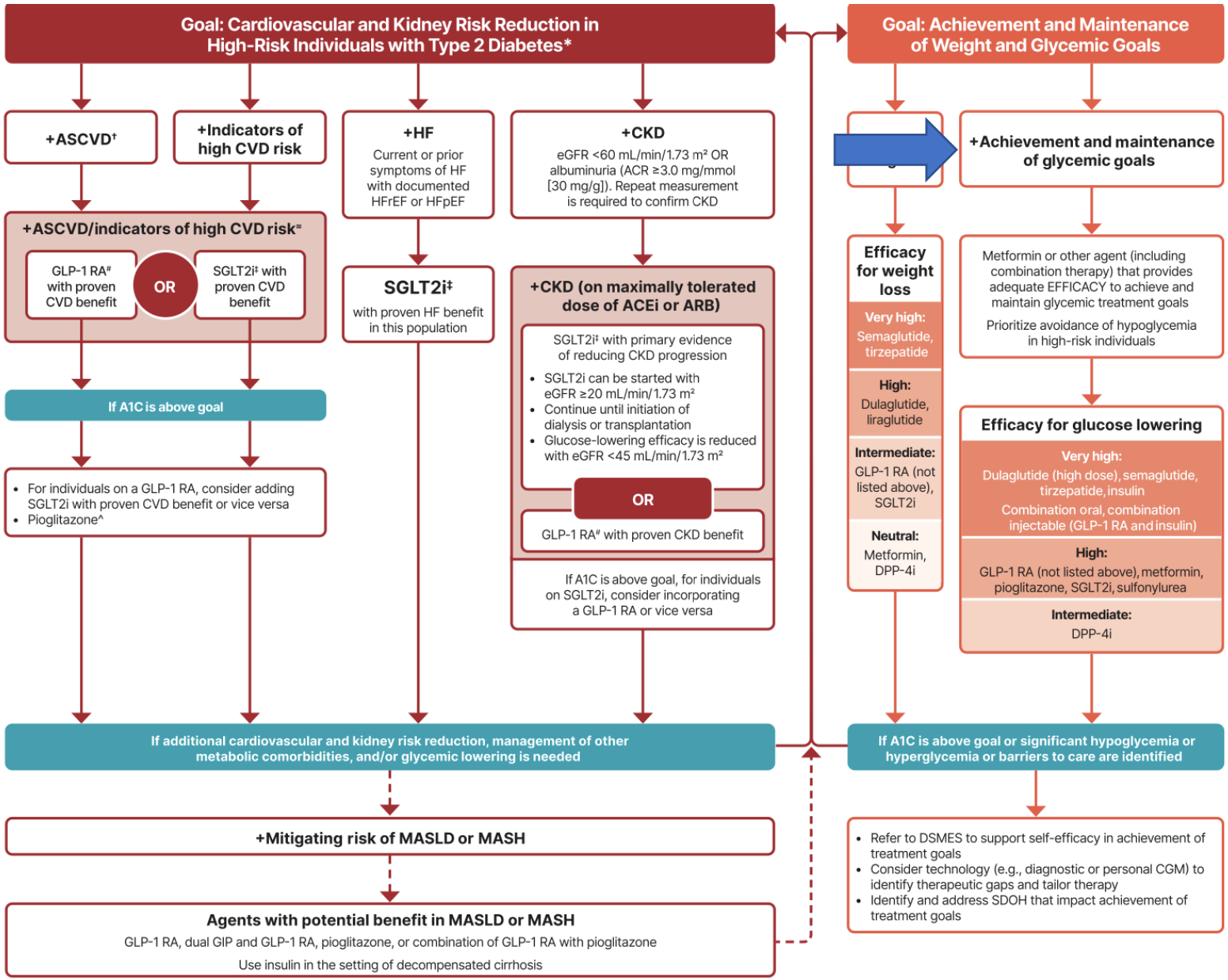
A.Glipizide

B.Pioglitazone

C.Sitagliptin

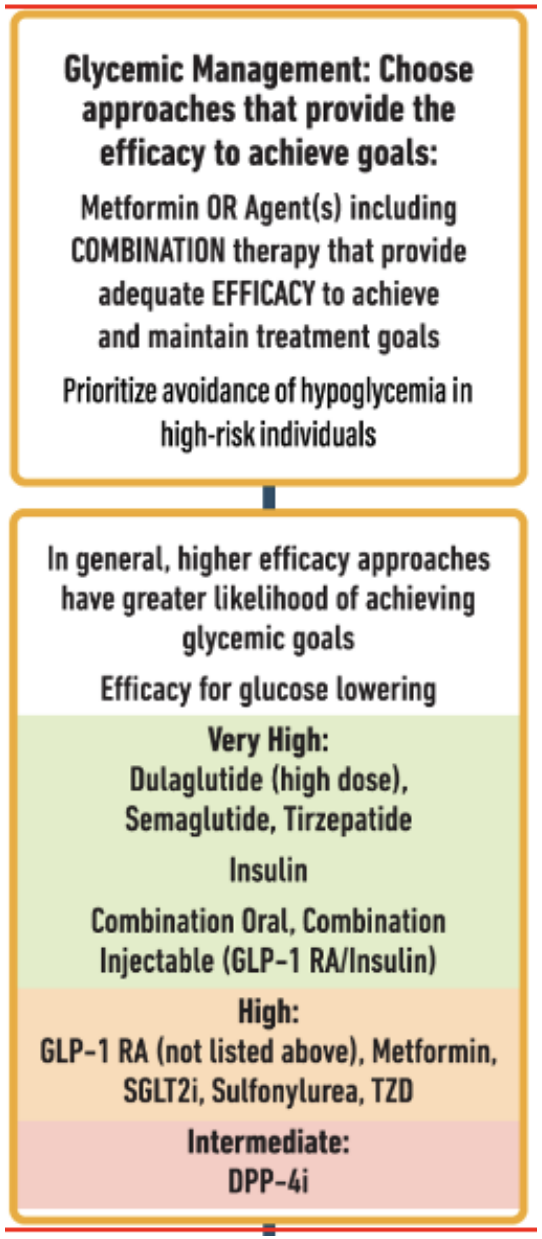
D.Canagliflozin

E.Metformin

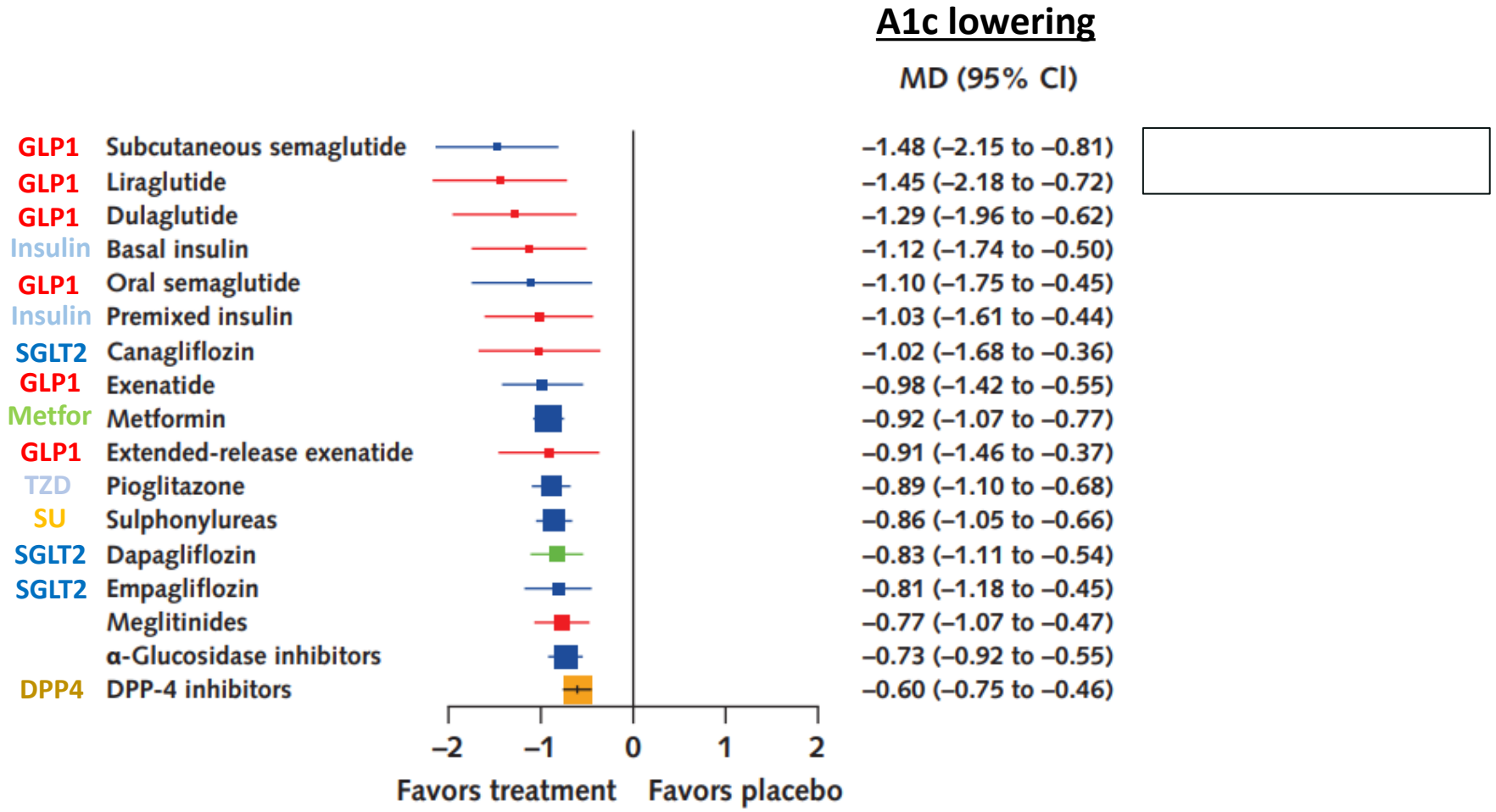

Goal: Cardiovascular and Kidney Risk Reduction in High-Risk Individuals with Type 2 Diabetes*
+ASCVD†
+Indicators of high CVD risk
+ASCVD/indicators of high CVD risk≈
GLP-1 RA# with proven CVD benefit
OR
SGLT2i‡ with proven CVD benefit
If A1C is above goal
For individuals on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
Pioglitazone^
+HF
Current or prior symptoms of HF with documented HFrEF or HFpEF
SGLT2i‡
with proven HF benefit in this population
+CKD
eGFR <60 mL/min/1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). Repeat measurement is required to confirm CKD
+CKD (on maximally tolerated dose of ACEi or ARB)
SGLT2i‡ with primary evidence of reducing CKD progression
SGLT2i can be started with eGFR ≥20 mL/min/1.73 m²
Continue until initiation of dialysis or transplantation
Glucose-lowering efficacy is reduced with eGFR <45 mL/min/1.73 m²
OR
GLP-1 RA# with proven CKD benefit
If A1C is above goal, for individuals on SGLT2i, consider incorporating a GLP-1 RA or vice versa
If additional cardiovascular and kidney risk reduction, management of other metabolic comorbidities, and/or glycemic lowering is needed
+Mitigating risk of MASLD or MASH
Agents with potential benefit in MASLD or MASH
GLP-1 RA, dual GIP and GLP-1 RA, pioglitazone, or combination of GLP-1 RA with pioglitazone
Use insulin in the setting of decompensated cirrhosis
Goal: Achievement and Maintenance of Weight and Glycemic Goals
+Achievement and maintenance of glycemic goals
Efficacy for weight loss
Very high:
Semaglutide, tirzepatide
High:
Dulaglutide, liraglutide
Intermediate:
GLP-1 RA (not listed above), SGLT2i
Neutral:
Metformin, DPP-4i
Metformin or other agent (including combination therapy) that provides adequate EFFICACY to achieve and maintain glycemic treatment goals
Prioritize avoidance of hypoglycemia in high-risk individuals
Efficacy for glucose lowering
Very high:
Dulaglutide (high dose), semaglutide, tirzepatide, insulin
Combination oral, combination injectable (GLP-1 RA and insulin)
High:
GLP-1 RA (not listed above), metformin, pioglitazone, SGLT2i, sulfonylurea
Intermediate:
DPP-4i
If A1C is above goal or significant hypoglycemia or hyperglycemia or barriers to care are identified
Refer to DSMES to support self-efficacy in achievement of treatment goals
Consider technology (e.g., diagnostic or personal CGM) to identify therapeutic gaps and tailor therapy
Identify and address SDOH that impact achievement of treatment goals

ADA SOC 2025

Balance A1C vs Hypoglycemia



Comparative effectiveness of T2D meds in lowering HbA1c



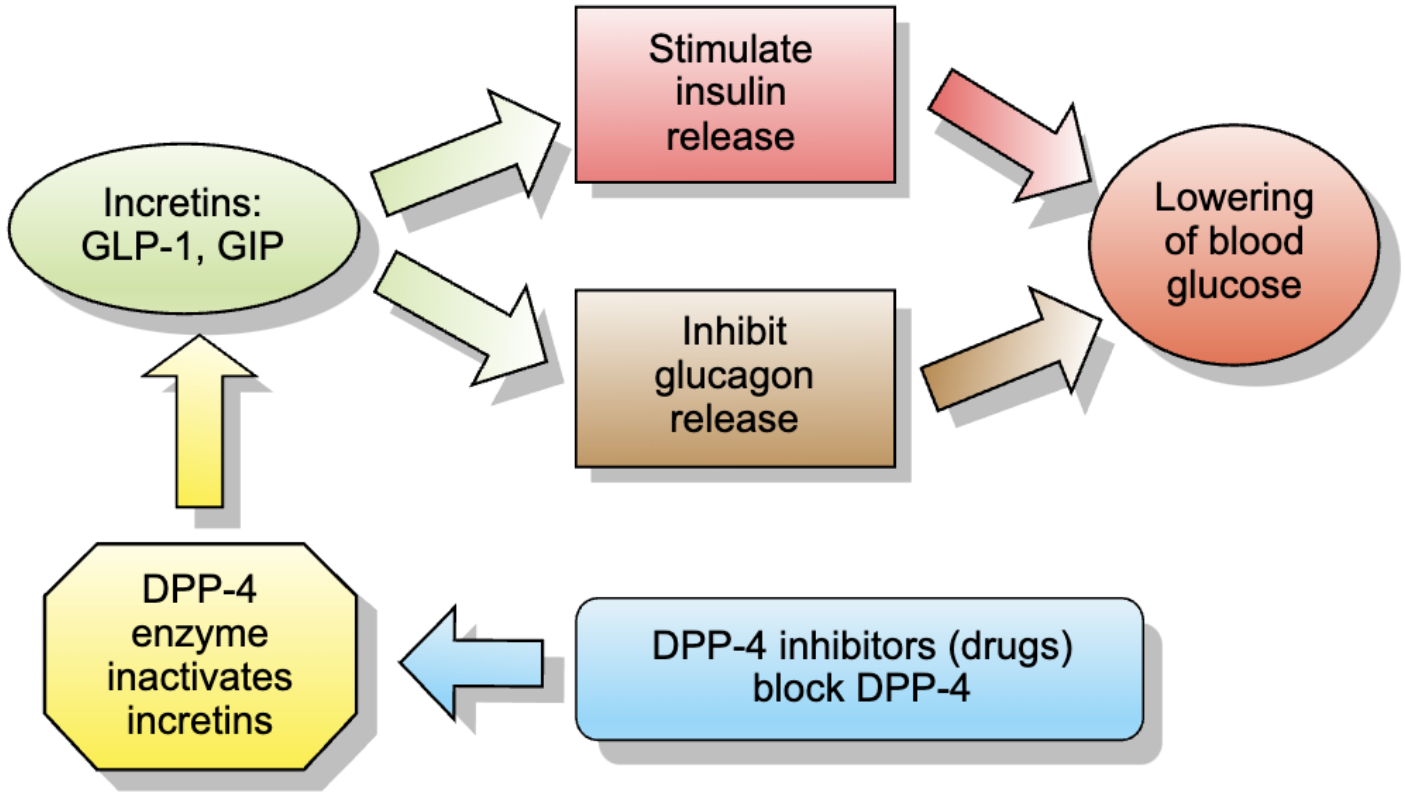
Tsapas et al. *Ann Int Med*. 2020; 18;173(4):278-286.

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

DC 47:233,2024

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?

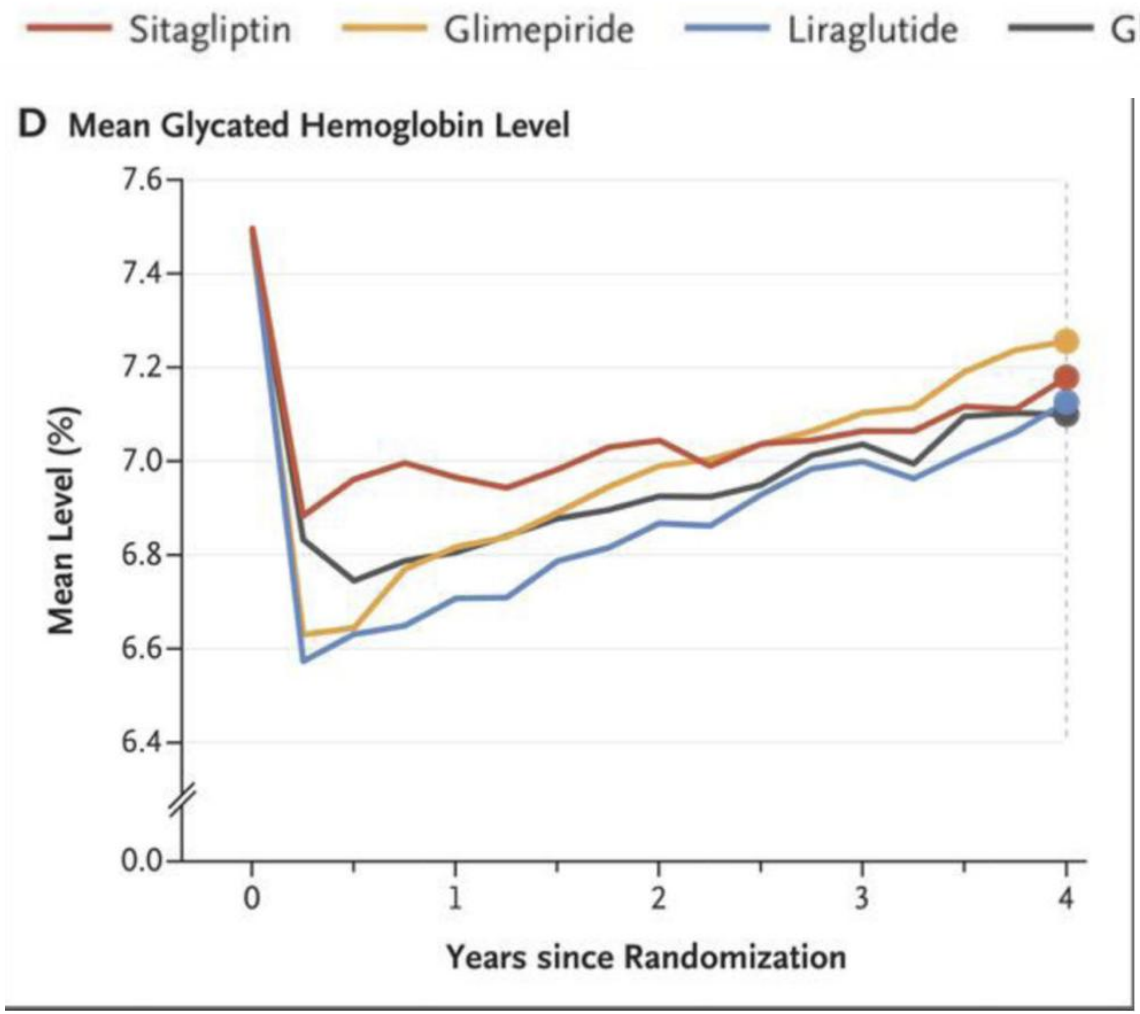
Is pioglitazone the new thalidomide(re-purposed life)?

- 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



N Engl J Med 2022;387:1063-1074

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 thiazolidiendiones: 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
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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
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F) None

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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

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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

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.

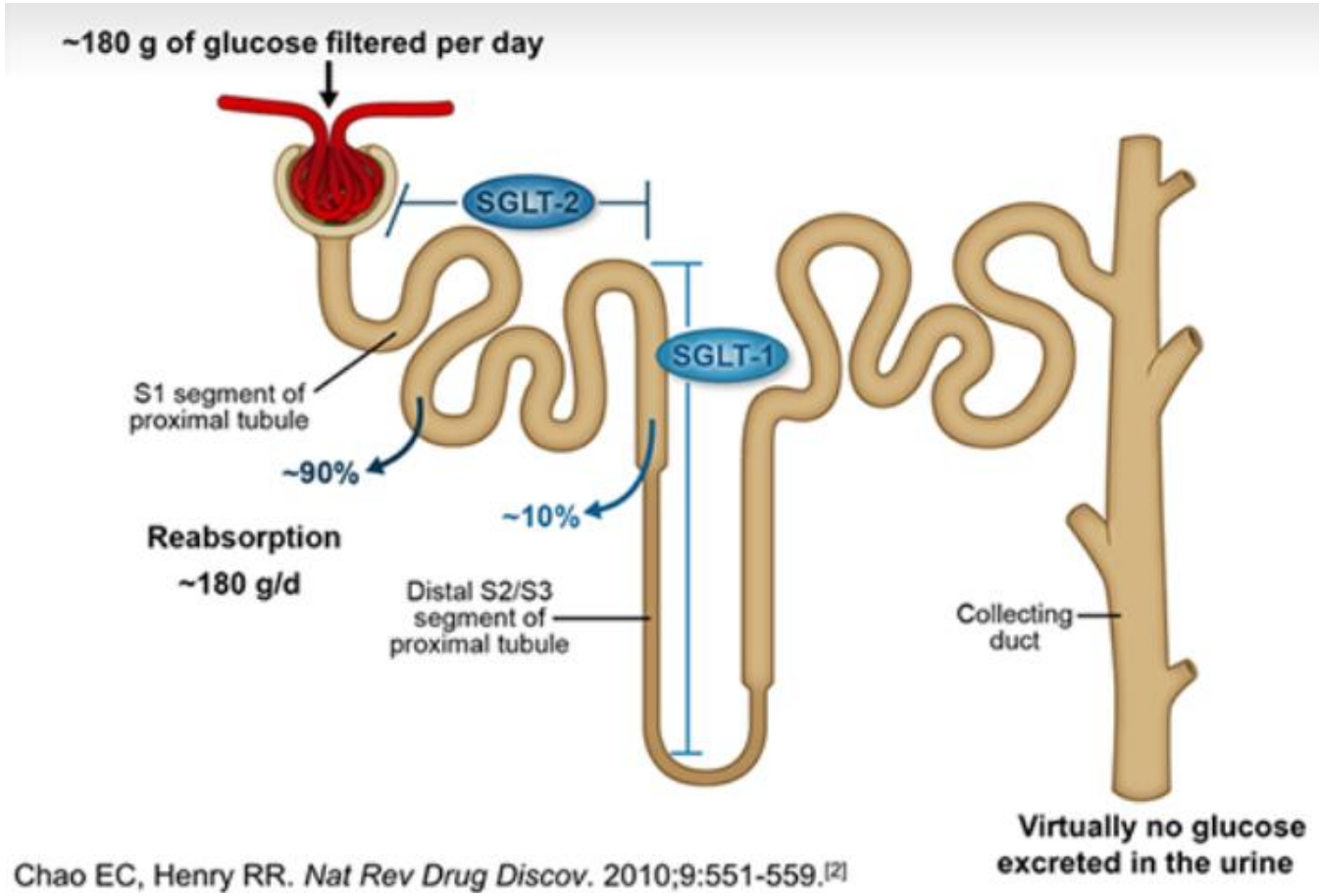
Tirzepatide dosing

- 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]

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

BEERs List Pocket Card: www.americangeriatrics.org/files/documents/beers/PrintableBeersPocketCard.pdf

GLP-1RA and CVOT

			Primary outcome	Individual components of MACE			Secondary outcomes of interest		
	Trial	Agent	Primary outcome (3-point MACE)	Death from CV causes	Nonfatal MI	Nonfatal stroke	Hosp. for HF	All-cause mortality	Worsening nephropathy
GLP1 RA	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

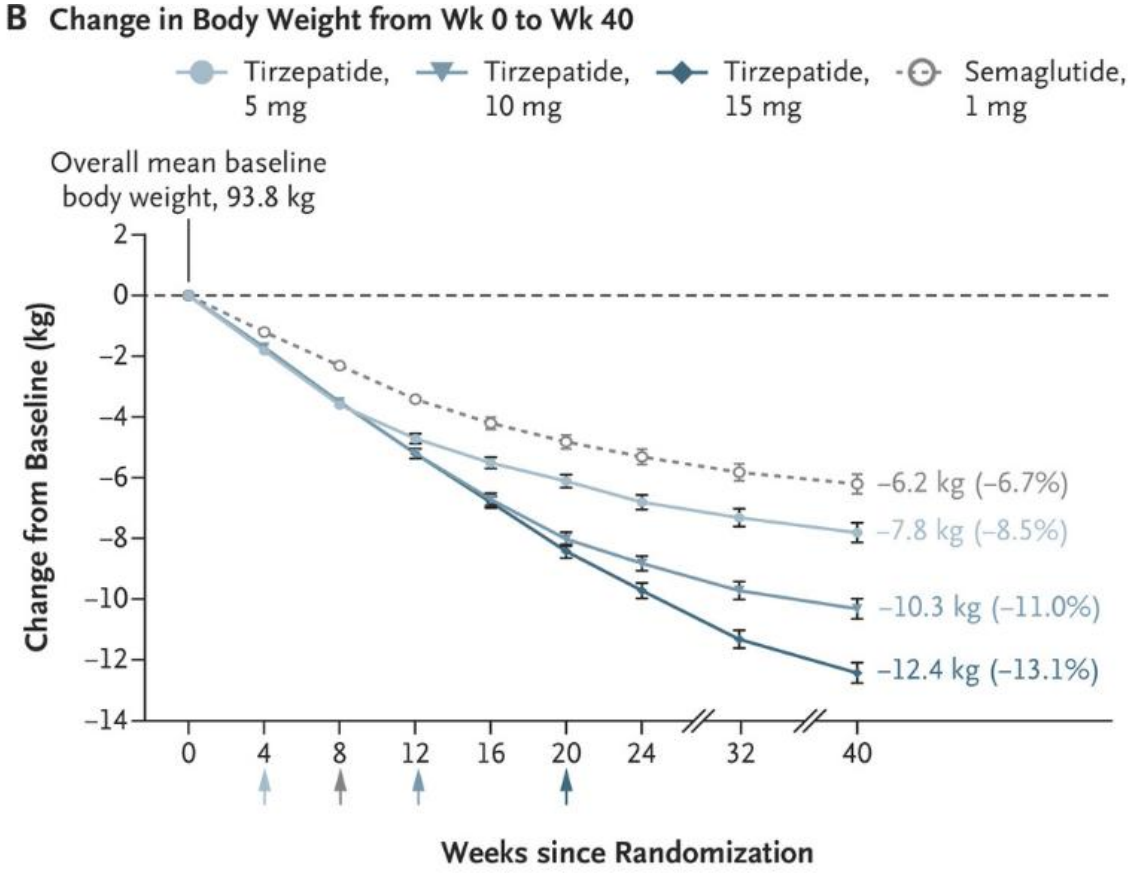
CVOT and SGLT2-I: Benefit for renal and HF outcomes

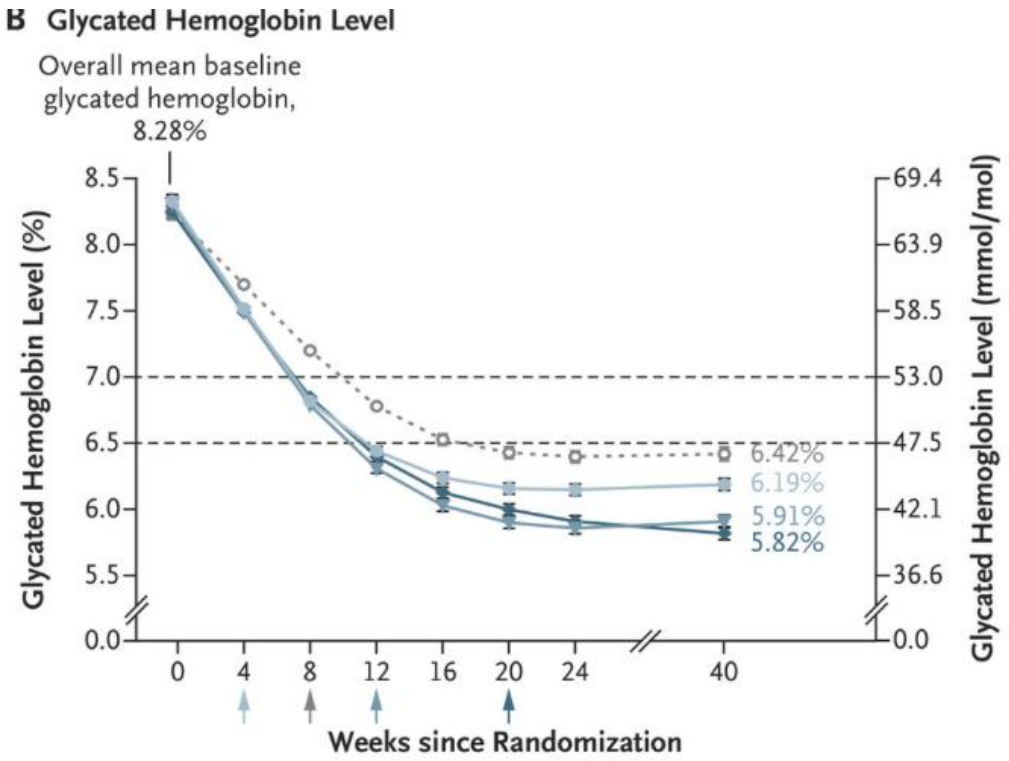
			Primary outcome	Individual components of MACE			Secondary outcomes of Interest		
	Trial	Agent	Primary outcome (3-point MACE)	Death from CV causes	Nonfatal MI	Nonfatal stroke	Hosp. for HF	All-cause mortality	Worsening nephropathy
SGLT2i	EMPA-REG OUTCOME (n=7,020)	Empagliflozin	0.86 (0.74-0.99)	0.62 (0.49-0.77)	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)	0.87 (0.72-1.18)	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 (0.84-1.02)	0.98 (0.82-1.17)	0.89 (0.77-1.01)	1.01 (0.84-1.21)	0.73 (0.61-0.88)	0.93 (0.82-1.04)	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)	0.93 (0.80-1.08)	0.81 (0.63-1.04)

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

			Primary outcome	Individual components of MACE			Secondary outcomes of Interest		
	Trial	Agent	Primary outcome (3-point MACE)	Death from CV causes	Nonfatal MI	Nonfatal stroke	Hosp. for HF	-cause ortality	Worsening nephropathy
SGLT2i	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)	8 57-0.82)	0.61 (0.53-0.70)
	CANVAS program (n=10,142)	Canagliflozin	0.86 (0.75-0.97)	0.86 (0.77-1.18)	0.89 (0.73-1.09)	0.87 (0.69-1.09)	0.67 (0.52-0.87)	7 74-1.01)	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)	3 82-1.04)	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)	3 80-1.08)	0.81 (0.63-1.04)

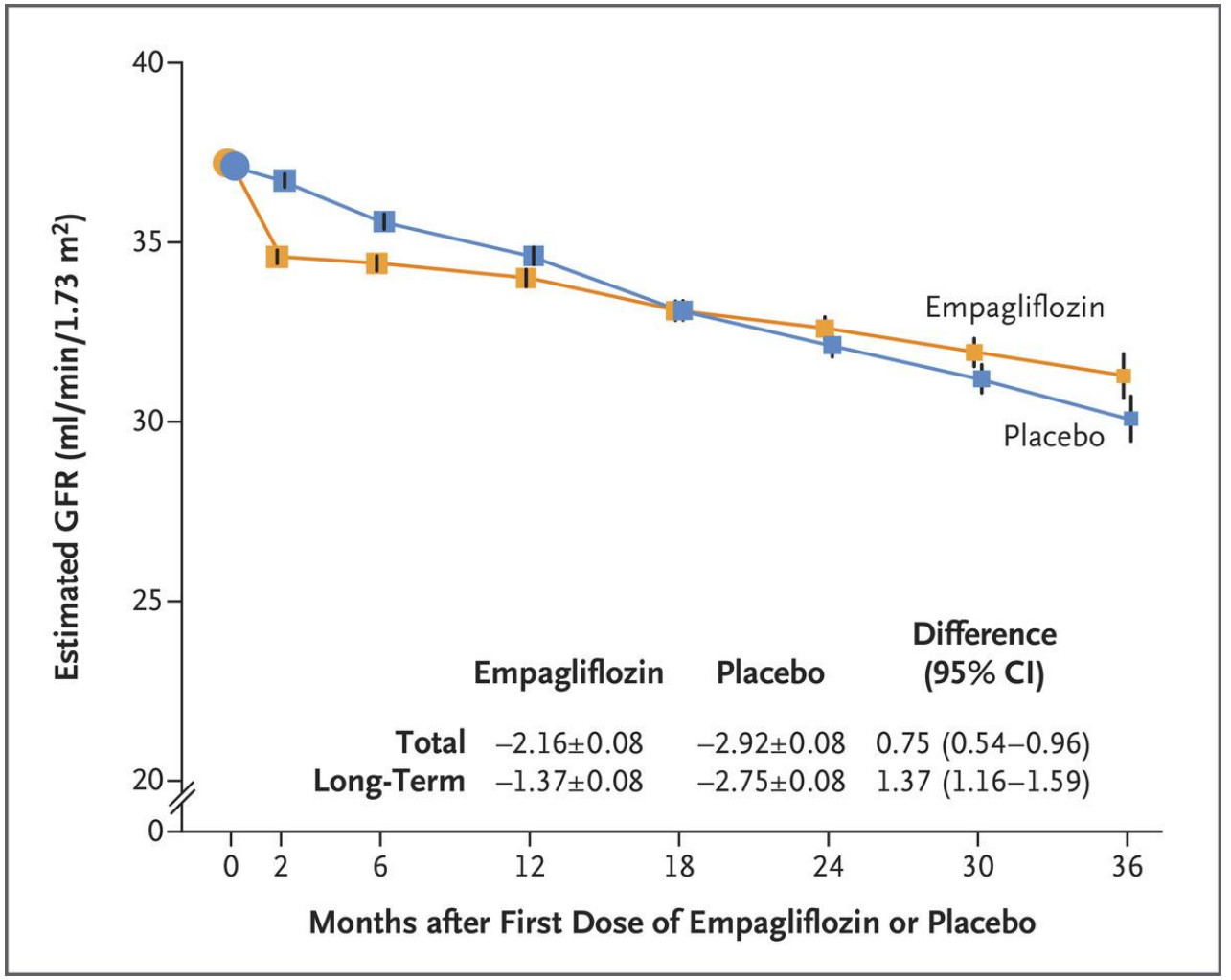
Tirzepatide vs Semaglutide





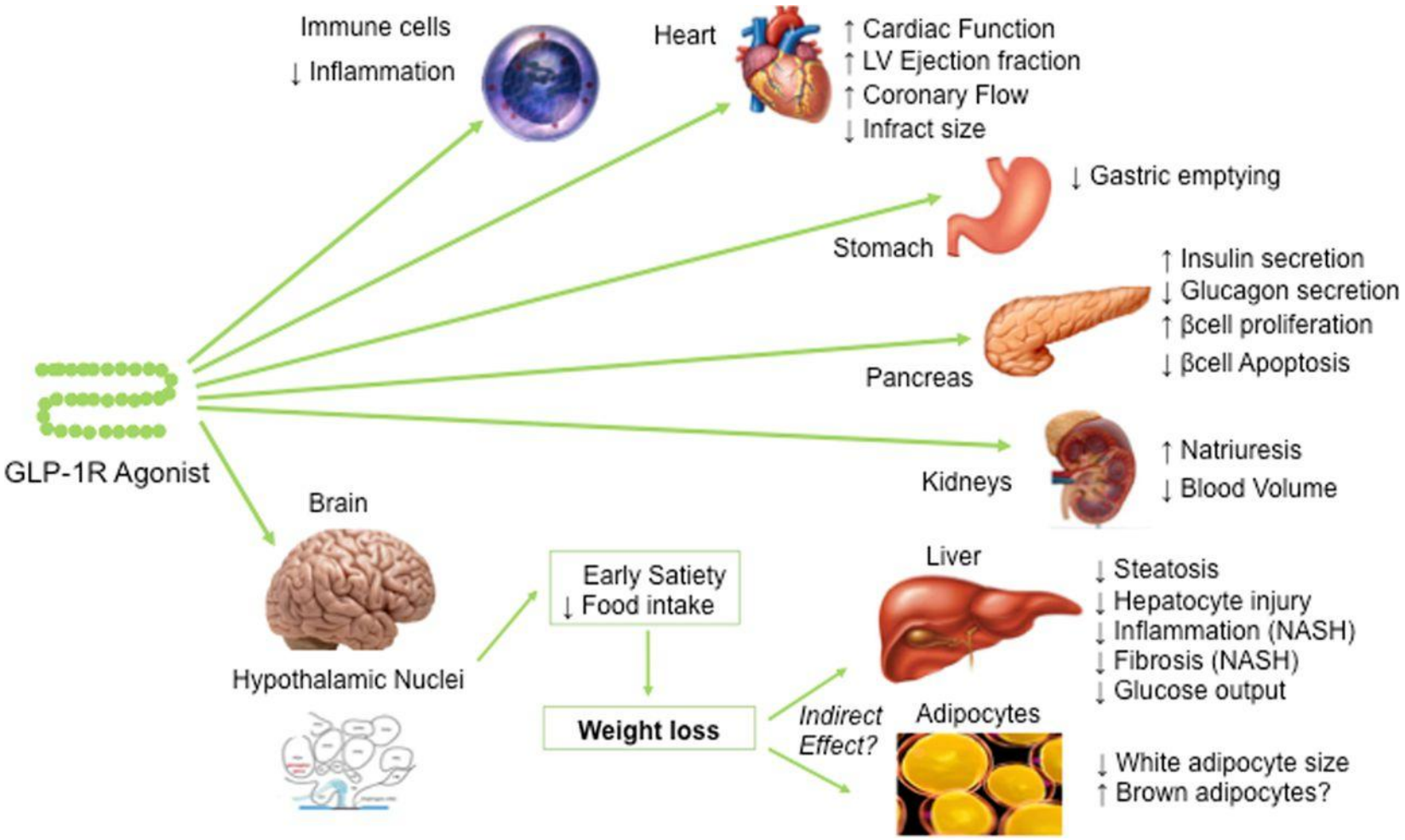
N Engl J Med 2021; 385:503-515

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



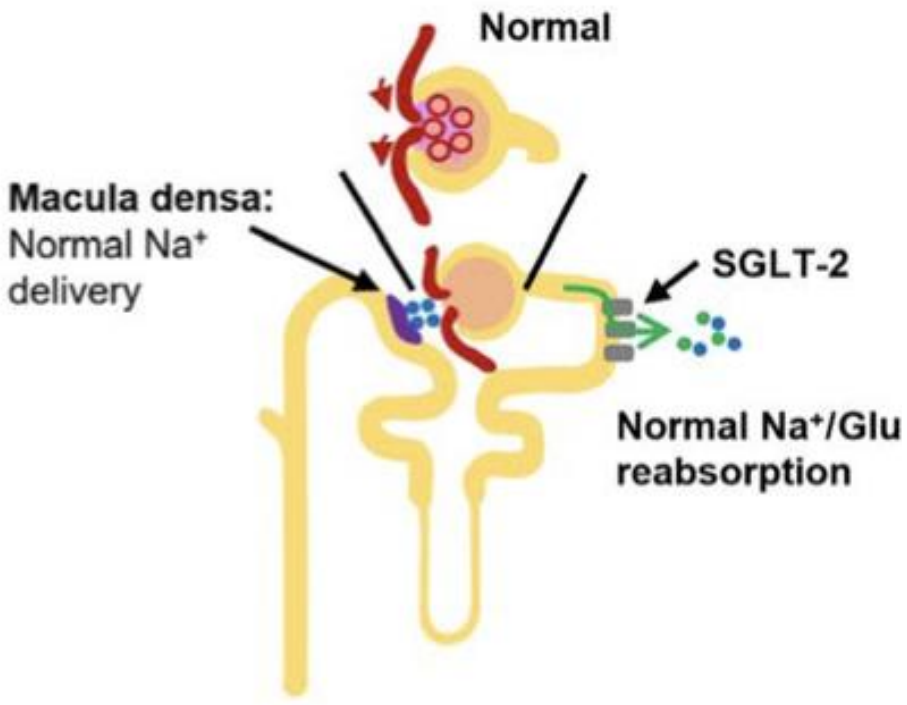
EMPA-KIDNEY Collaborative Group. N Engl J Med 2023;388:117-127.

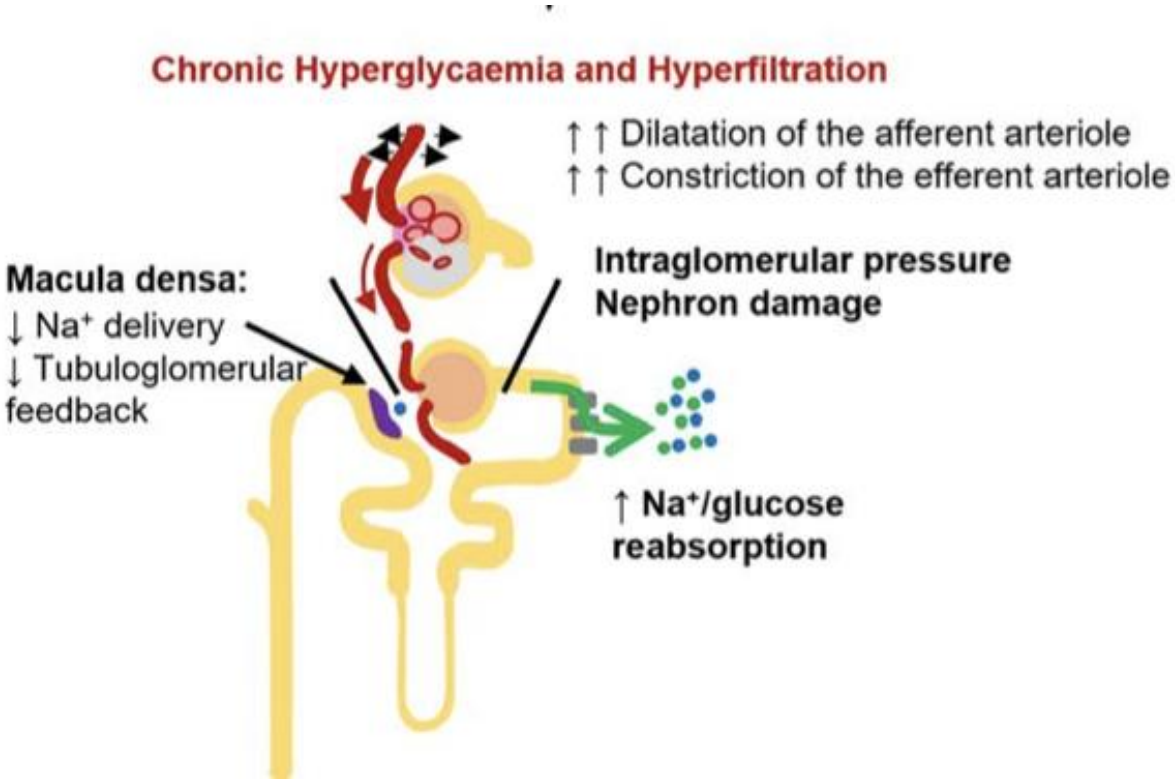
Glucagon-like peptide-1 receptor agonists (GLP-1RAs)



Gauri Dhir, and Kenneth Cusi J Investig Med 2018;66:7-10

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

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

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

DC 47: 184, 2024

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

Diabetes Care 2022; 45 (Suppl. 1): S83–S96

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

DC 47: 184, 2024