

# Diabetes: A Cardiovascular-Renal Update

Robert S. Busch, MD, FACE



# Presentation Outline



Review current guideline medication treatment recommendations for patients with diabetes

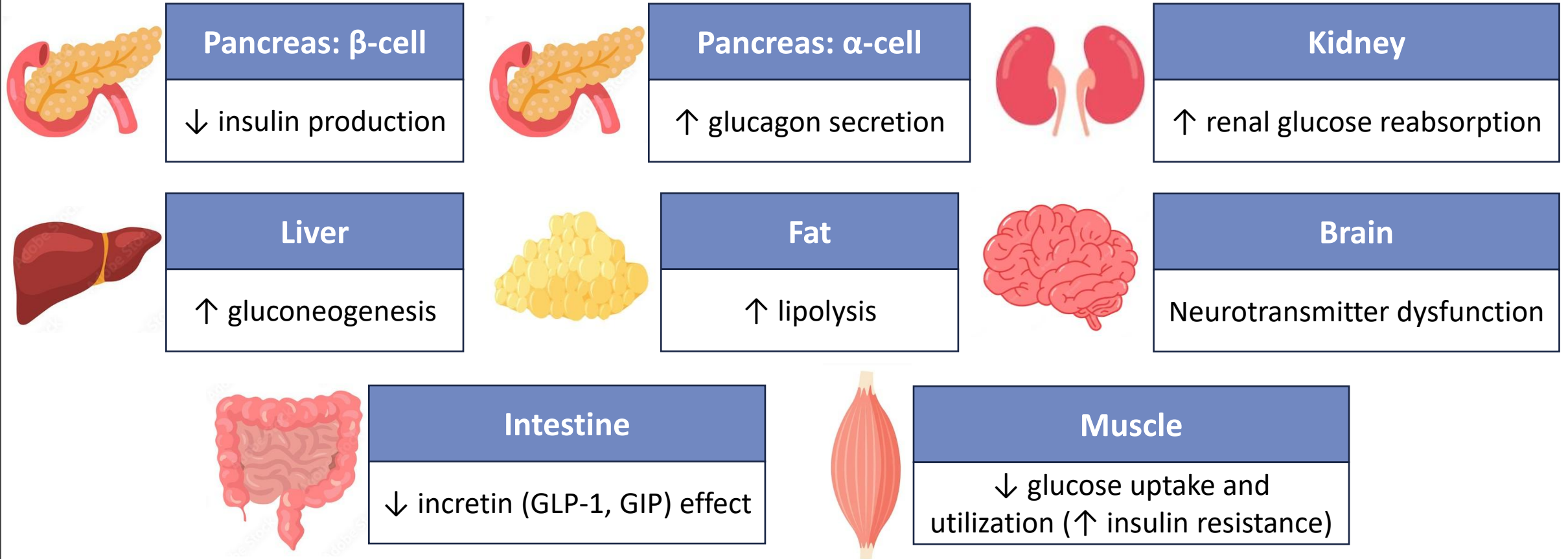


Discuss the role of GLP-1 RA and SGLT2i therapy regarding glycemic control, weight loss, ASCVD risk reduction, renal protection, and heart failure management in T2D patients

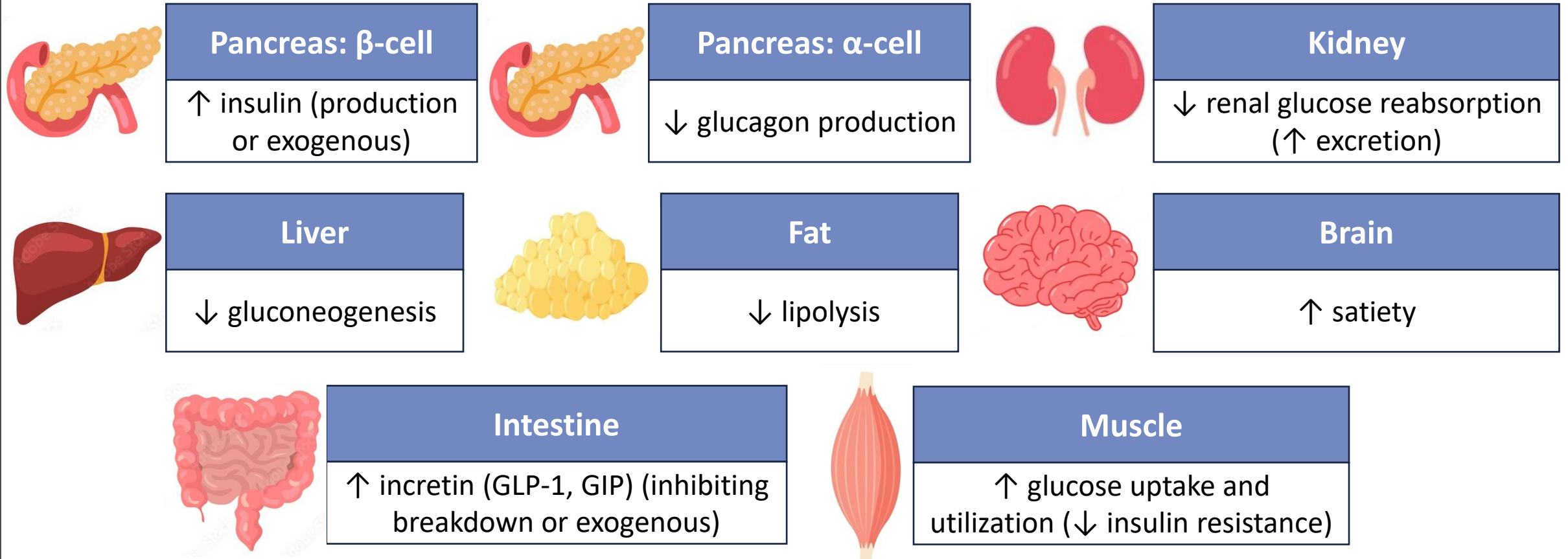


Evaluate special circumstance considerations for diabetes therapy

# Type 2 Diabetes Pathophysiology



# Type 2 Diabetes Therapeutic Targets



# The **ABC's** of Diabetes

- **A**1C (and consider **A**SA)
  - < 7.0% ADA (< 6.5% AACE)
- **B**lood Pressure
  - < 130/80 mmHg
- **C**holesterol
  - LDL-C < 70 mg/dL (< 55 mg/dL for those with established ASCVD)
    - Statin therapy (moderate to high intensity doses)
  - HDL-C > 40 mg/dL (> 50 mg/dL in women)
  - TG's < 150 mg/dL (the addition of icosapent ethyl can be considered)
- **S**moking Cessation

# Diabetes Treatment Options

## Oral

- Alpha-glucosidase inhibitors
- Biguanide
- Bile acid sequestrant/resin binder
- Dopamine Agonist
- DPP-4i
- GLP-1RA
- Meglitinide\*
- SGLT2i
- Sulfonylurea\*
- TZDs

## Injectable

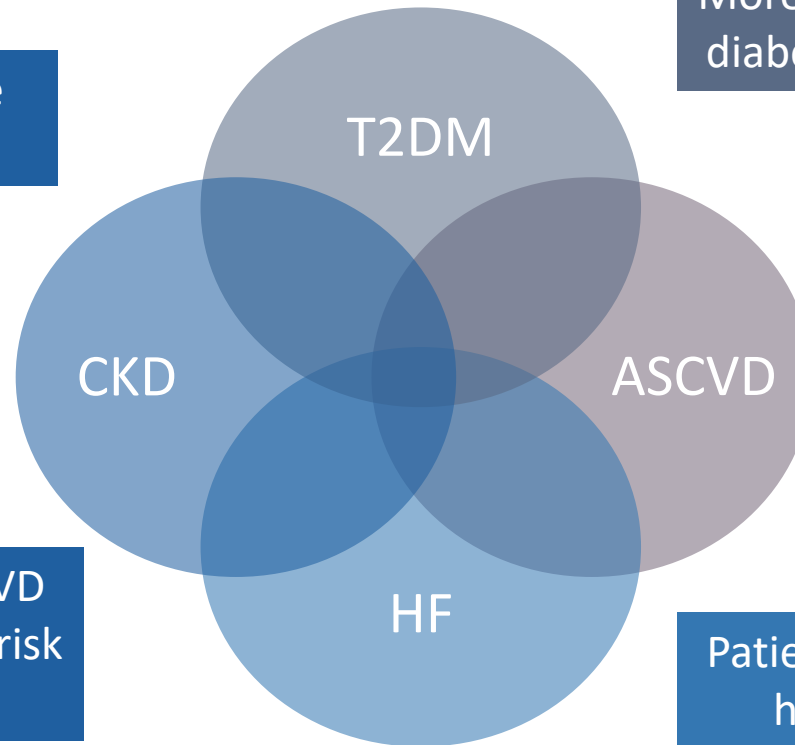
- Amylin analogue
- Dual GLP-1/GIP RA
- GLP-1RA
- Insulin\*

\*Hypoglycemia associated with use

# Diabetes and Cardio-Renal Risk

Diabetes and CVD are the main causes of CKD

More than 37 million Americans have diabetes – 95% of whom have T2DM

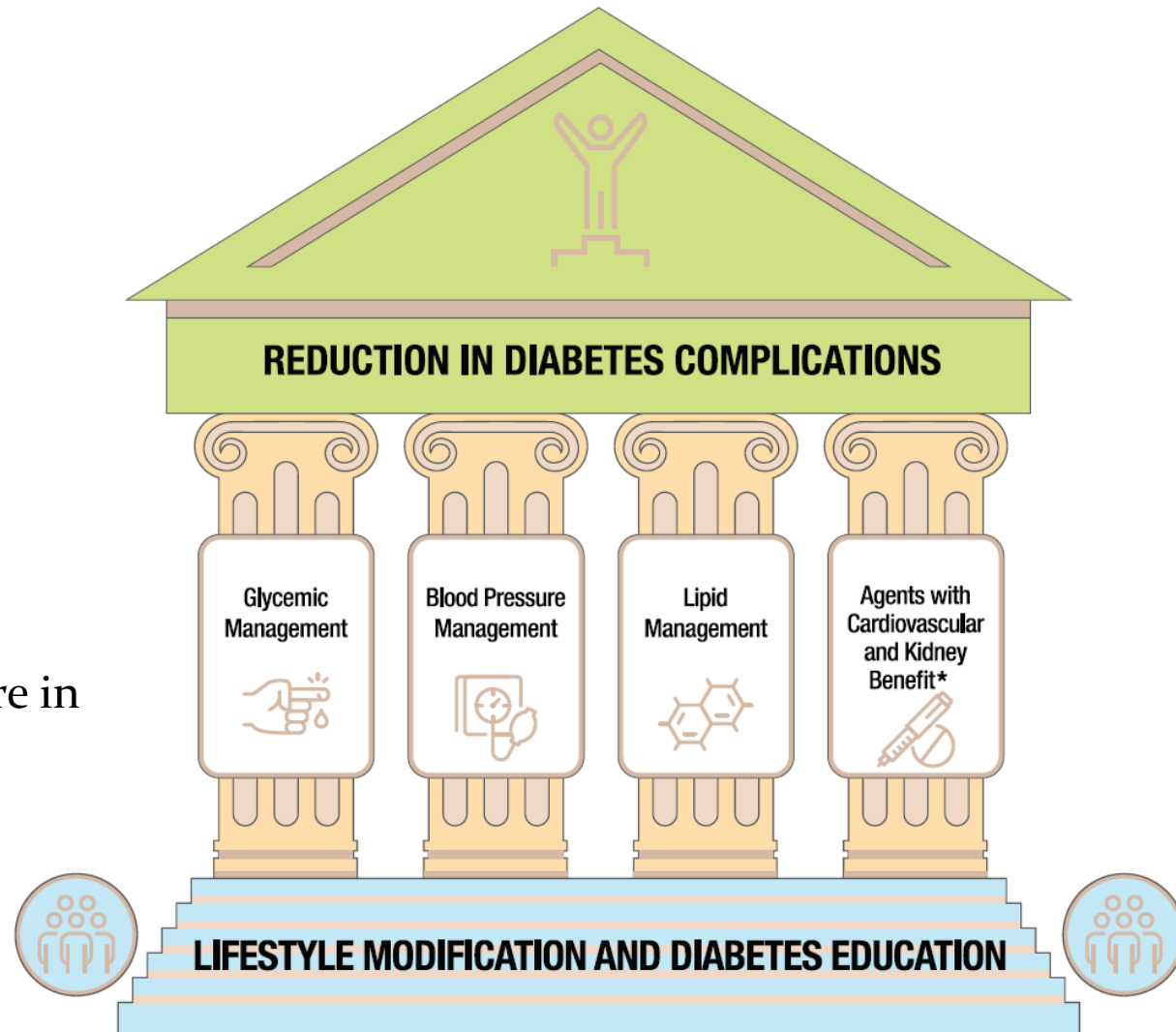


Adults with T2DM are twice as likely to have heart disease, a stroke, or heart failure

The presence of diabetes and CVD in adults with CKD increases the risk of morbidity and mortality

Patients with diabetes and heart failure have a 50% 5-year mortality rate

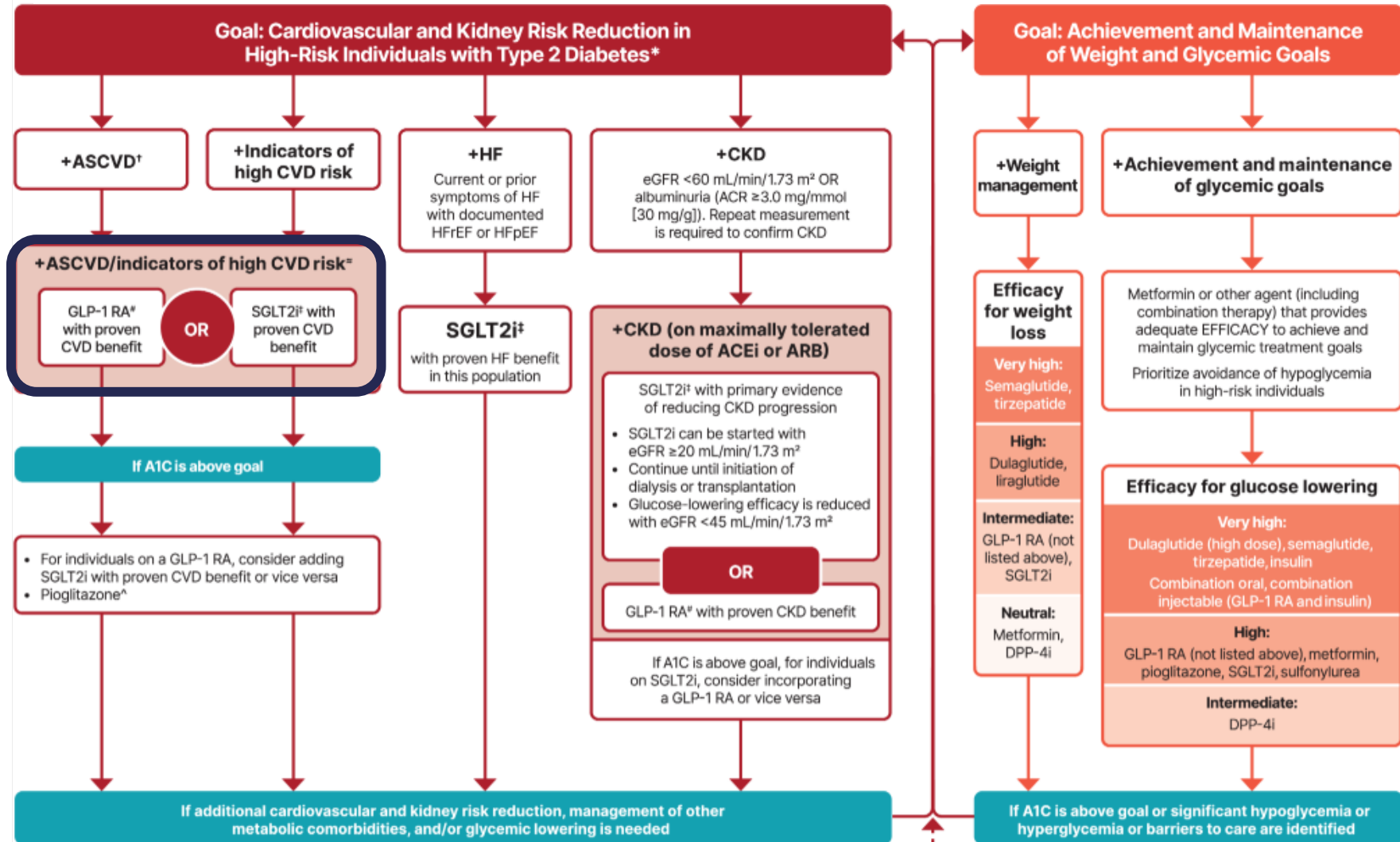
# Multifactorial approach to reduction in risk of diabetes complications



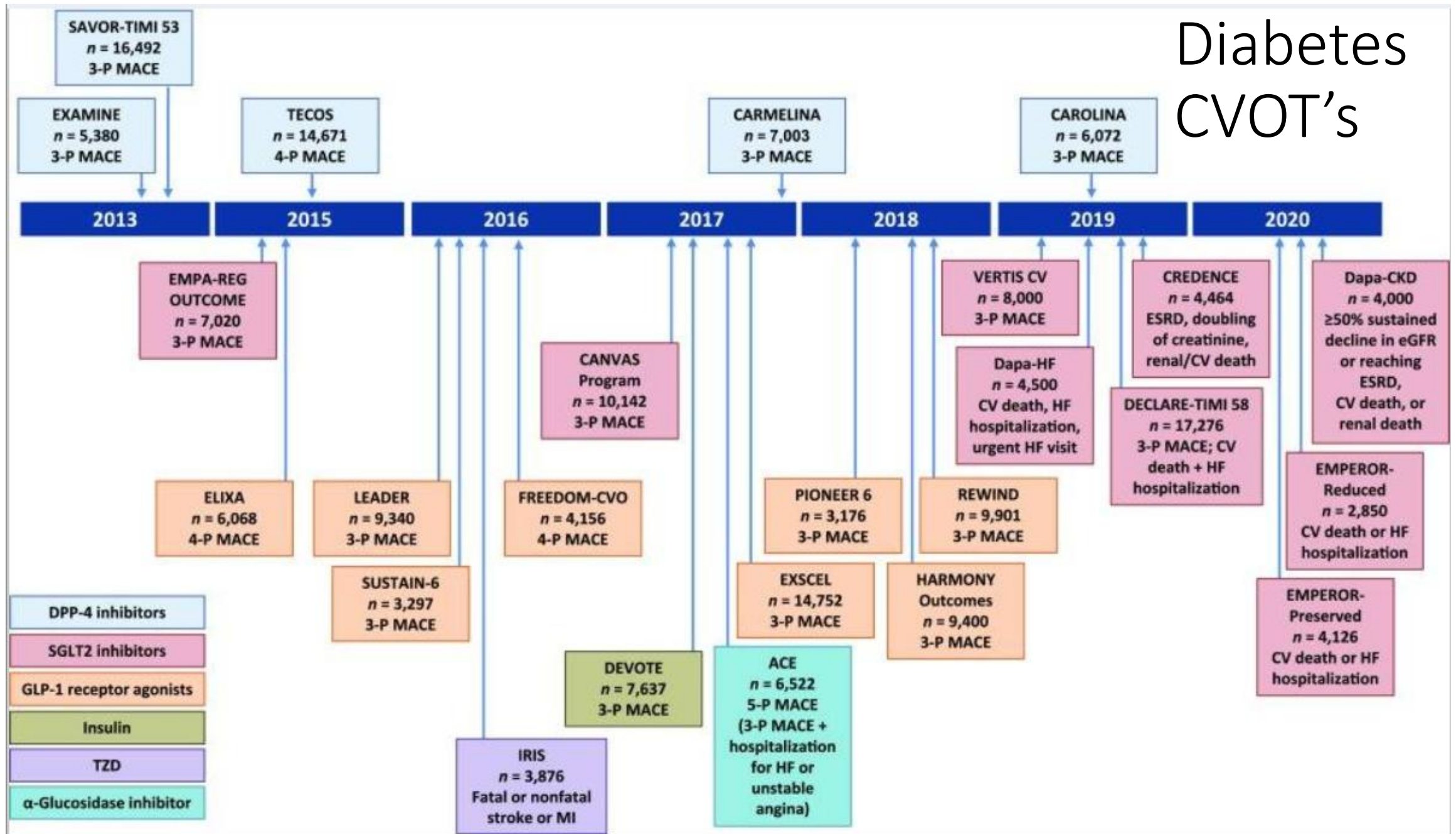
ADA. Standards of Medical Care in Diabetes – 2022. Diabetes Care 2022;45(Suppl. 1):S144–S174.

# 2025 ADA Glycemic Management

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT; SOCIAL DETERMINANTS OF HEALTH



# Diabetes CVOT's



ORIGINAL ARTICLE

# Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

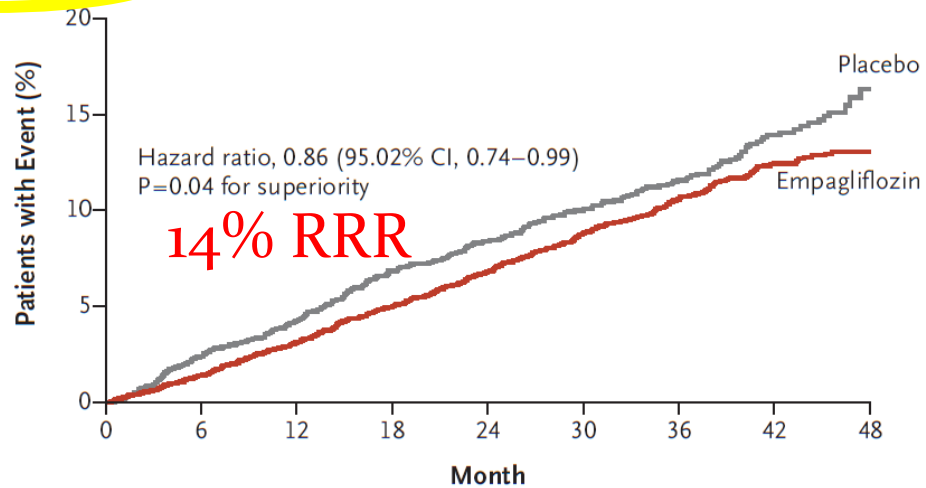
Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D.,  
David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D.,  
Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H.,  
Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D.,  
and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

7,020 people with T2DM, 100% with established CVD

Empa 10 or 25 mg vs placebo (all +SOC); Median observation time of 3.1 years

Primary Endpoint: Composite of CV death, non-fatal MI and non-fatal stroke (3-pt MACE)

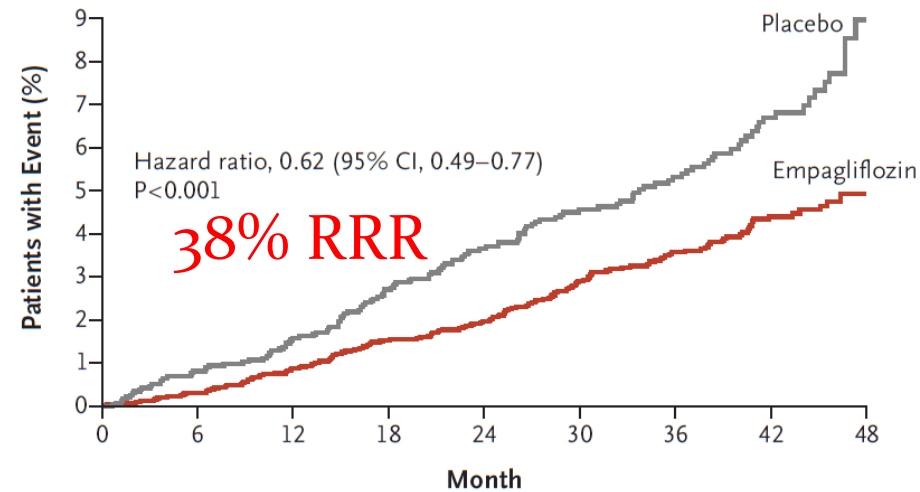
**A Primary Outcome**



**No. at Risk**

Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

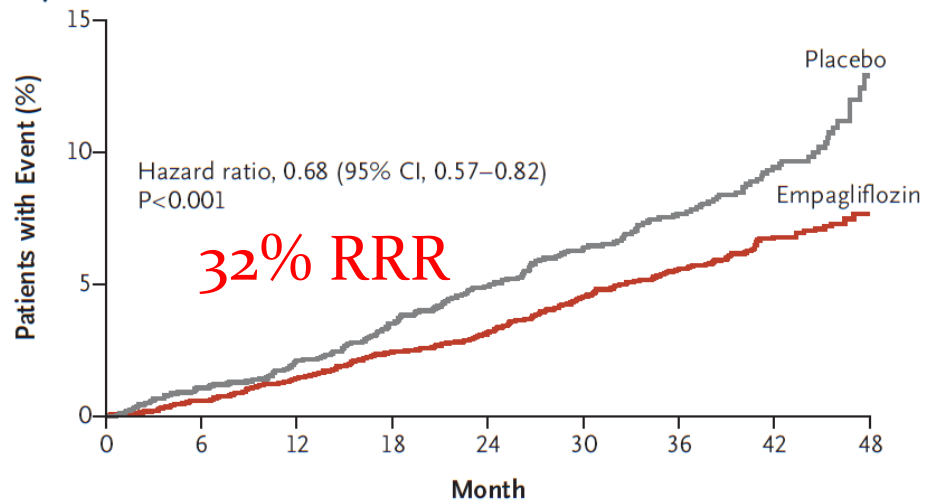
**B Death from Cardiovascular Causes**



**No. at Risk**

Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

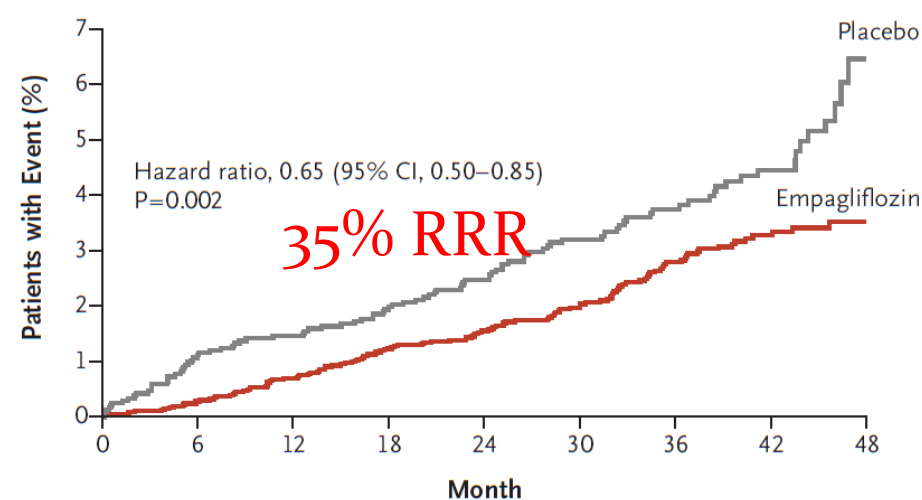
**C Death from Any Cause**



**No. at Risk**

Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

**D Hospitalization for Heart Failure**



**No. at Risk**

Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Sept 16, 2016.

## Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators\*

3,297 patients with T2DM at high risk of MACE (83% with CVD and/or CKD)

Semaglutide 0.5 or 1 mg; Median 2.1 yrs f/u

Primary Endpoint: 3-point MACE

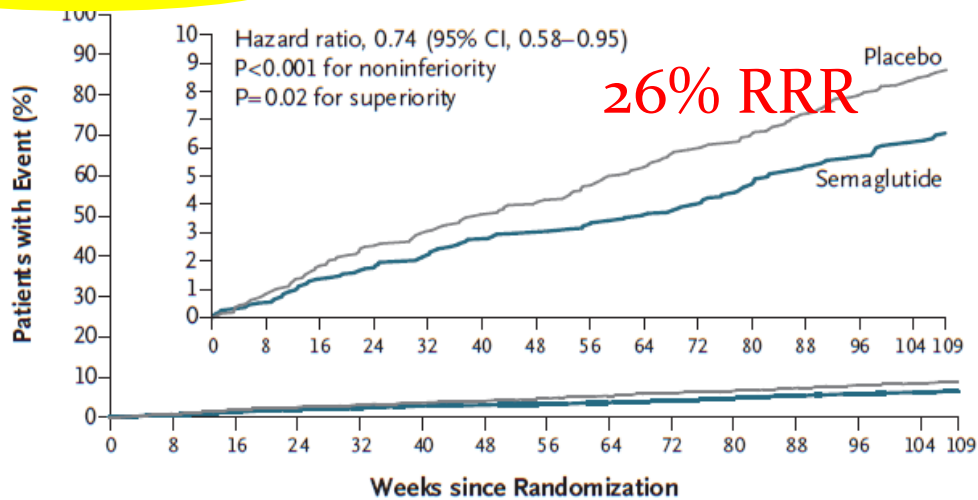
**BACKGROUND**  
Regulatory guidance specifies the need to establish cardiovascular safety of new diabetes therapies in patients with type 2 diabetes in order to rule out excess cardiovascular risk. The cardiovascular effects of semaglutide, a glucagon-like peptide 1 analogue with an extended half-life of approximately 1 week, in type 2 diabetes are unknown.

### **METHODS**

We randomly assigned 3297 patients with type 2 diabetes who were on a standard-care regimen to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks. The primary composite outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. We hypothesized that semaglutide would be noninferior to placebo for the primary outcome. The noninferiority margin was 1.8 for the upper boundary of the 95% confidence interval of the hazard ratio.

From the Research Medical Center, Kansas City, MO (S.P.M.); School of Medicine, Swansea University, Swansea, United Kingdom (S.C.B.); Department of Medicine and Aging Science and Center of Excellence on Aging and Translational Medicine, G. d'Annunzio University, Chieti-Pescara, Italy (A.C.); CPclin Research Center/Hospital Israelita Albert Einstein, São Paulo (F.G.E.); Hospital Universitario Quirón Salud Madrid, Facultad de Ciencias de la Salud, Universidad Europea de Madrid, Madrid (E.J.); Li Ka Shing Knowledge Institute and Keenan Research Centre for Biomedical Science, St. Michael's Hospital, University of Toronto, Toronto (L.A.L.), and the University of Manitoba, Winnipeg (V.W.) —

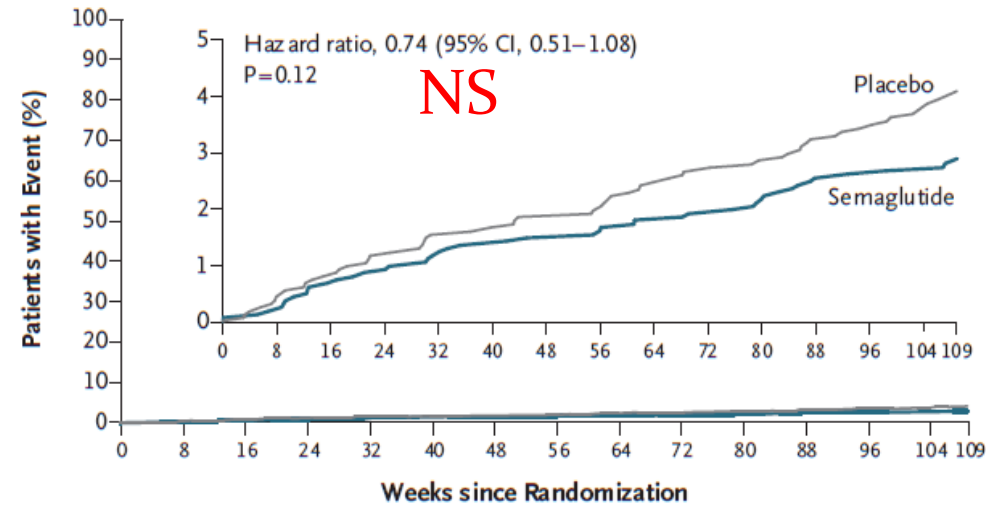
**A Primary Outcome**



**No. at Risk**

Placebo	1649	1616	1586	1567	1534	1508	1479
Semaglutide	1648	1619	1601	1584	1568	1543	1524

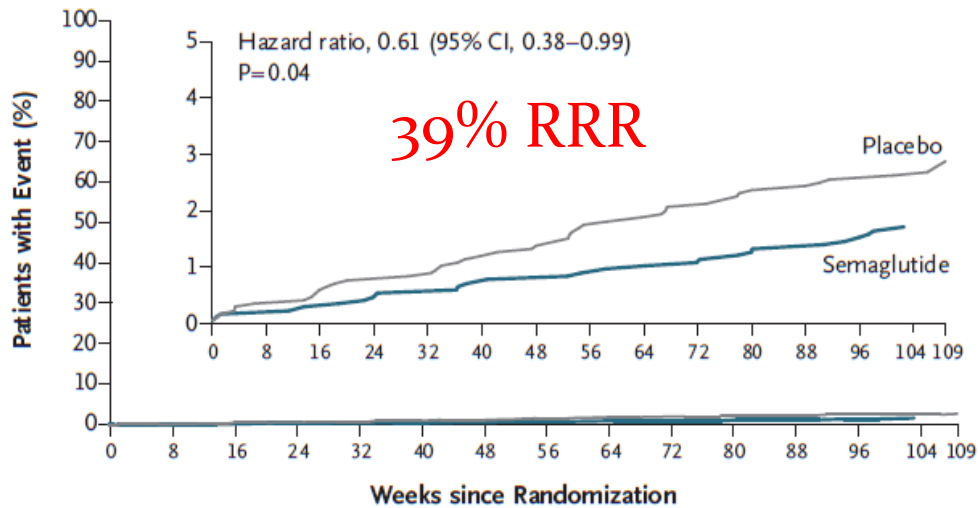
**B Nonfatal Myocardial Infarction**



**No. at Risk**

Placebo	1649	1624	1598	1587	1562	1542	1516
Semaglutide	1648	1623	1609	1595	1582	1560	1543

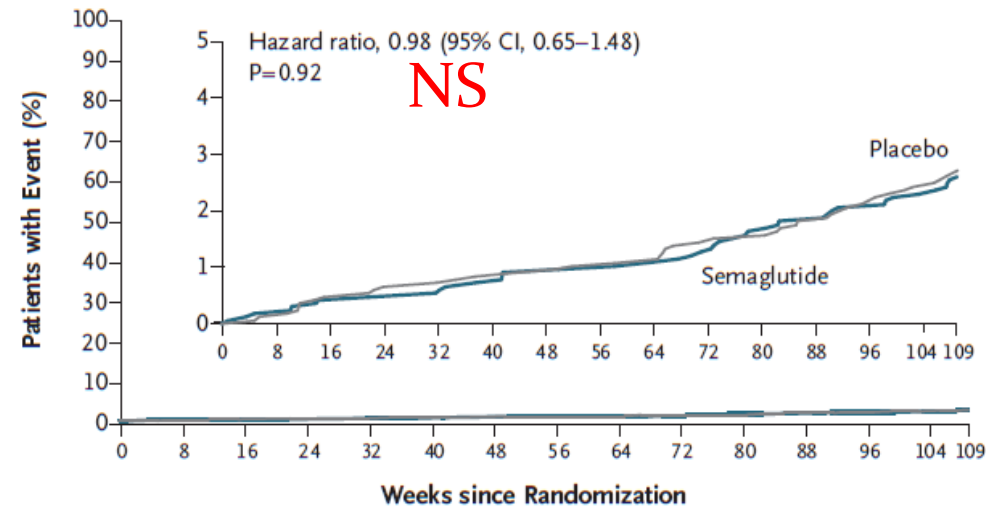
**C Nonfatal Stroke**



**No. at Risk**

Placebo	1649	1629	1611	1597	1571	1548	1528
Semaglutide	1648	1630	1619	1606	1593	1572	1558

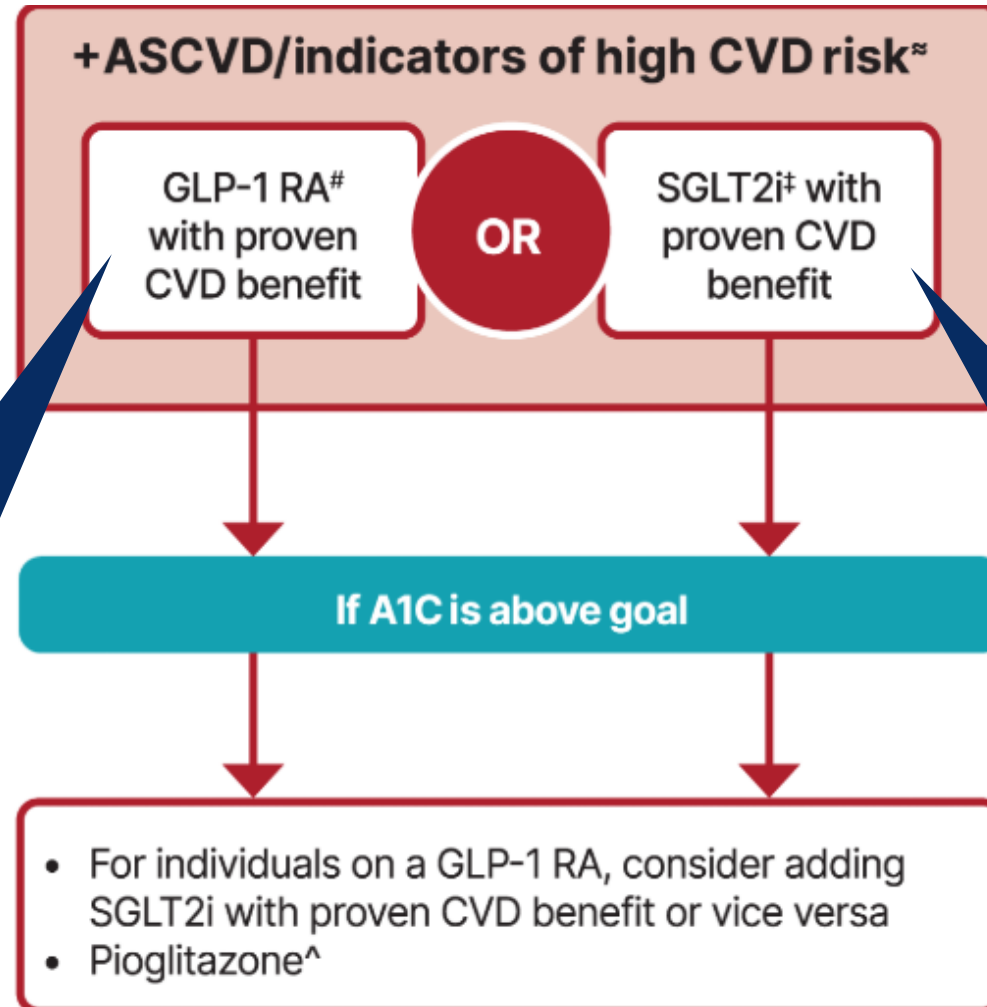
**D Death from Cardiovascular Causes**



**No. at Risk**

Placebo	1649	1637	1623	1617	1600	1584	1566
Semaglutide	1648	1634	1627	1617	1607	1589	1579

# ASCVD or Indicators of High CV Risk



GLP-1 RA with the strongest evidence:

- liraglutide
  - LEADER (13% ↓ in MACE)
- dulaglutide
  - REWIND (12% ↓ in MACE)
- semaglutide
  - SUSTAIN 6 (26% ↓ in MACE)

SGLT2i with the strongest evidence:

- empagliflozin
  - EMPA-REG (14% ↓ in MACE)
- canagliflozin
  - CANVAS (14% ↓ in MACE)
  - CREDENCE (20% ↓ in MACE)



## **Lilly's Mounjaro (tirzepatide), a GIP/GLP-1 dual agonist, demonstrated cardiovascular protection in landmark head-to-head trial, reinforcing its benefit in patients with type 2 diabetes and heart disease**

July 31, 2025

*Mounjaro met the primary objective of non-inferiority vs. Trulicity with an 8% lower rate of MACE-3 events, while delivering greater reductions in A1C and weight*

*In the trial, Mounjaro was associated with a 16% lower rate of all-cause death compared to Trulicity, suggesting more comprehensive health benefits*

*Results from the largest and longest Mounjaro trial to date reaffirm its established safety and tolerability profile*

INDIANAPOLIS, July 31, 2025 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced topline results from SURPASS-CVOT, a first-of-its-kind head-to-head Phase 3 cardiovascular outcomes trial comparing two incretin therapies in adults with type 2 diabetes and established atherosclerotic cardiovascular disease. Mounjaro (tirzepatide), a GIP/GLP-1 dual receptor agonist, was compared to Trulicity (dulaglutide), a GLP-1 receptor agonist that showed a definitive cardiovascular benefit in the REWIND study. In SURPASS-CVOT, Mounjaro achieved the primary objective by demonstrating a non-inferior rate of major adverse cardiovascular events (MACE-3), including cardiovascular death, heart attack or stroke vs. Trulicity. In addition, while not controlled for multiplicity-adjusted type-1 error, Mounjaro showed improvements on key measures of A1C, weight, renal function and all-cause mortality. The trial, which enrolled more than 13,000 participants across 30 countries and lasted more than four and a half years, is the largest and longest study of tirzepatide to date.

# Table I. SURPASS-CVOT eligibility criteria

## Key inclusion criteria

---

Men or women  $\geq 40$  Y old with type 2 diabetes (HbA1c  $\geq 7\%$  and  $\leq 10.5\%$ ) and BMI  $\geq 25\text{kg/m}^2$

Established atherosclerotic cardiovascular disease, including  $\geq 1$  of the following

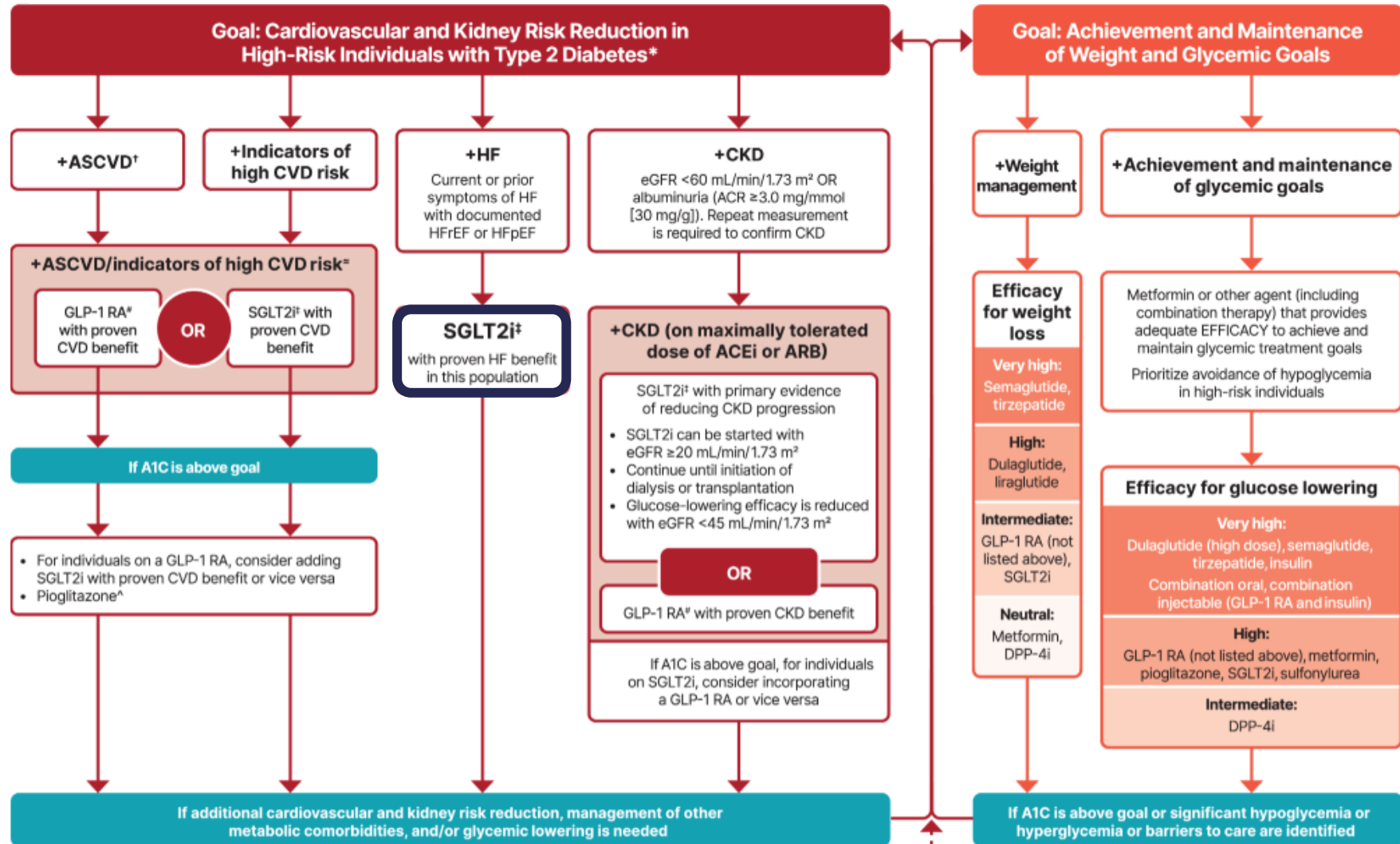
1. Coronary artery disease with any of the following:
  - a. Documented history of myocardial infarction
  - b.  $\geq 50\%$  stenosis in  $\geq 1$  major coronary arteries determined by invasive angiography
  - c.  $\geq 50\%$  stenosis in 2 or more major coronary arteries, determined by computed tomography coronary angiography
  - d. History of surgical or percutaneous coronary revascularization procedure
2. Cerebrovascular disease (any of the following):
  - a. Documented history of ischemic stroke
  - b. Carotid arterial disease with  $\geq 50\%$  stenosis, documented by carotid ultrasound, MRI, or angiography
  - c. History of carotid stenting or surgical revascularization
3. Peripheral arterial disease with either of the following:
  - a. Intermittent claudication and ankle-brachial index  $< 0.9$
  - b. Prior nontraumatic amputation or peripheral vascular procedure (eg, stenting or surgical revascularization), due to peripheral arterial ischemia

**Primary and Select Secondary Endpoints:**

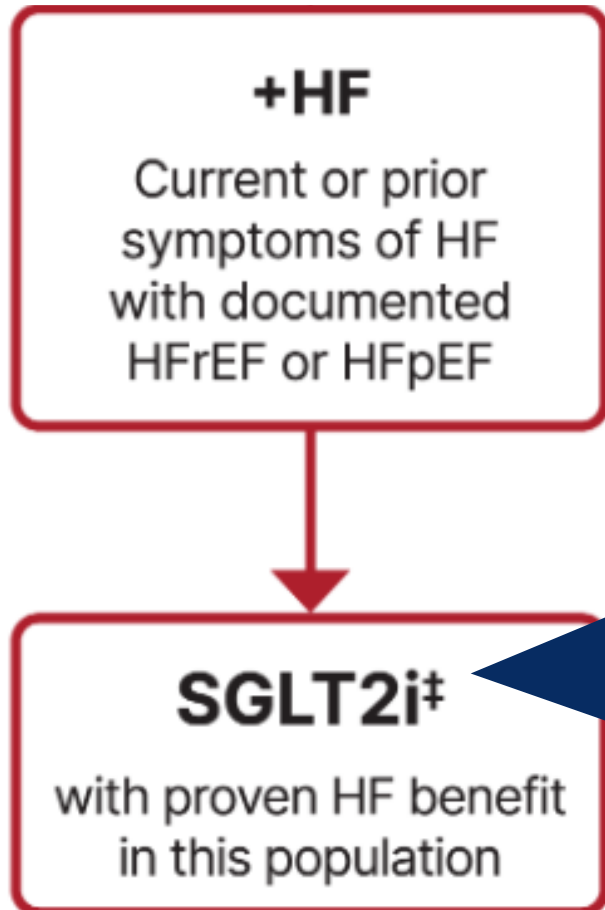
	<b>Mounjaro (tirzepatide)</b>	<b>Trulicity (dulaglutide)</b>
<b>Primary Endpoint</b>		
Time-to-first occurrence of MACE-3 <sup>i</sup>	Hazard ratio = 0.92 95.3% <sup>ii</sup> CI: 0.83 to 1.01 <sup>iii</sup> p = 0.086	
<b>Secondary Endpoints</b>		
Time to all-cause death <sup>i</sup>	Hazard ratio = 0.84 95.0% CI: 0.75 to 0.94 p = 0.002 <sup>iv</sup>	
Change in eGFR in chronic kidney disease population from mean baseline of 53.4 mL/min/1.73 m <sup>2</sup> at 36 months <sup>v</sup>	-4.97 mL/min/1.73 m <sup>2</sup>	-8.51 mL/min/1.73 m <sup>2</sup>
	Estimated treatment difference: 3.54 mL/min/1.73 m <sup>2</sup> (95.0% CI: 2.57 to 4.50) p < 0.001 <sup>iv</sup>	
A1C reduction from mean baseline of 8.39% at 36 months <sup>v,vi</sup>	1.73 %	0.90 %
	Estimated treatment difference: -0.83% (95.0% CI: -0.88 to -0.78) p < 0.001 <sup>iv</sup>	
Change from mean baseline of 92.6 kg (204.15 lbs) in body weight at 36 months <sup>v,vi</sup>	-12.06% (-11.43 kg / -25.20 lbs)	-4.95% (-4.65 kg / -10.25 lbs)
	Estimated treatment difference: -7.1% (95.0% CI: -7.4 to -6.8) p < 0.001 <sup>iv</sup>	

# 2025 ADA Glycemic Management

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT; SOCIAL DETERMINANTS OF HEALTH



# Heart Failure



## empagliflozin

- EMPA-REG (35% ↓ in HHF)
- EMPEROR-REDUCED (31% ↓ in HHF)
- EMPEROR-PRESERVED (29% ↓ in HHF)

## canagliflozin

- CANVAS (33% ↓ in HHF)
- CREDENCE (39% ↓ in HHF)

## dapagliflozin

- DECLARE-TIMI (27% ↓ in HHF)
- DAPA-HF (30% ↓ in HHF)
- DELIVER (23% ↓ in HHF)

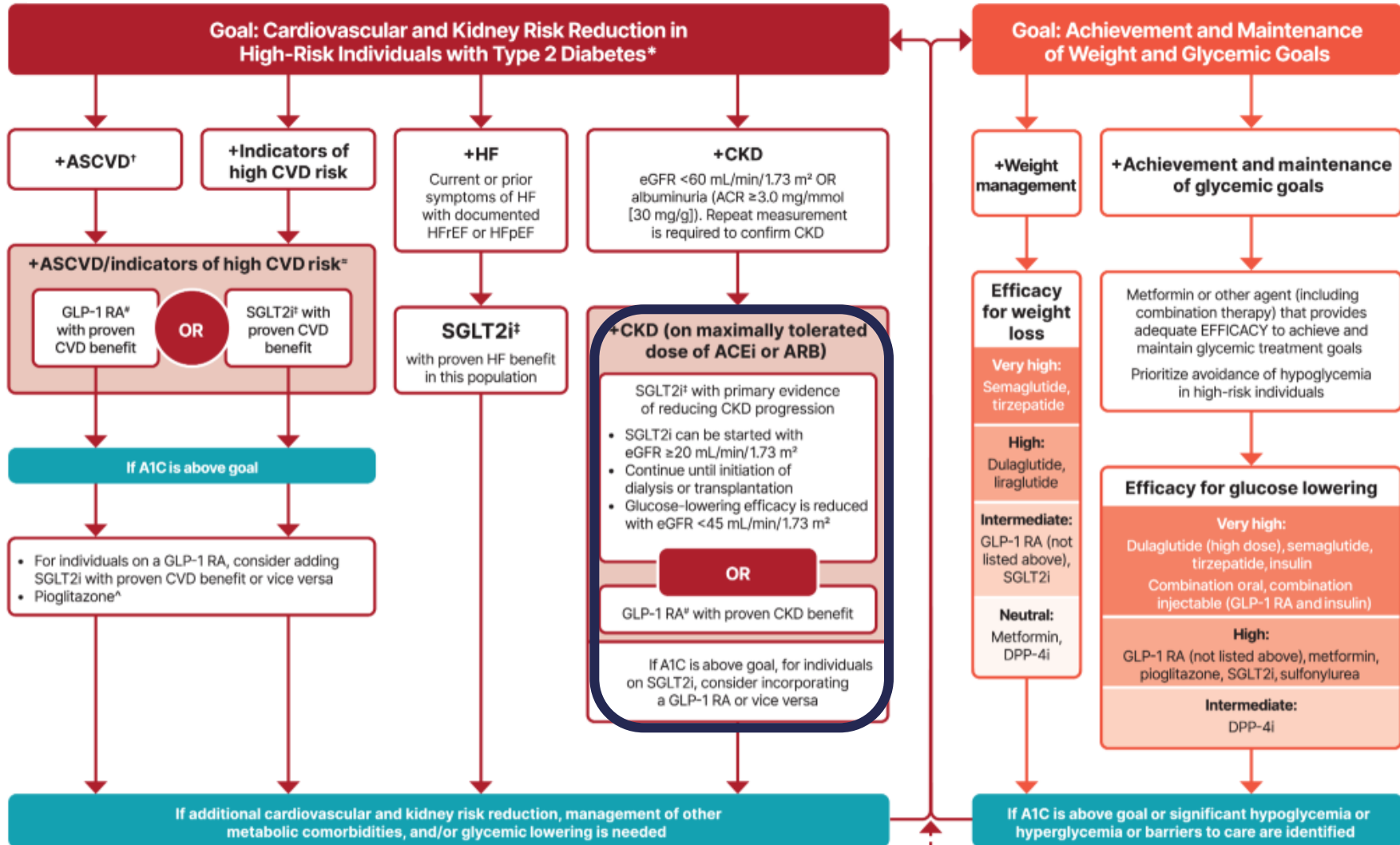
## ertugliflozin

- VERTIS-CV (30% ↓ in HHF)

Consider adding a GLP-1 RA if symptomatic HFpEF and obesity

# 2025 ADA Glycemic Management

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT; SOCIAL DETERMINANTS OF HEALTH



# Chronic Kidney Disease

## +CKD (on maximally tolerated dose of ACEi or ARB)

SGLT2i<sup>†</sup> with primary evidence of reducing CKD progression

- SGLT2i can be started with eGFR  $\geq 20$  mL/min/1.73 m<sup>2</sup>
- Continue until initiation of dialysis or transplantation
- Glucose-lowering efficacy is reduced with eGFR  $< 45$  mL/min/1.73 m<sup>2</sup>

OR

GLP-1 RA<sup>#</sup> with proven CKD benefit

If A1C is above goal, for individuals on SGLT2i, consider incorporating a GLP-1 RA or vice versa

semaglutide

- FLOW (24% ↓ in composite progression of CKD)

empagliflozin

- EMPA-KIDNEY (28% ↓ in composite progression of CKD)

canagliflozin

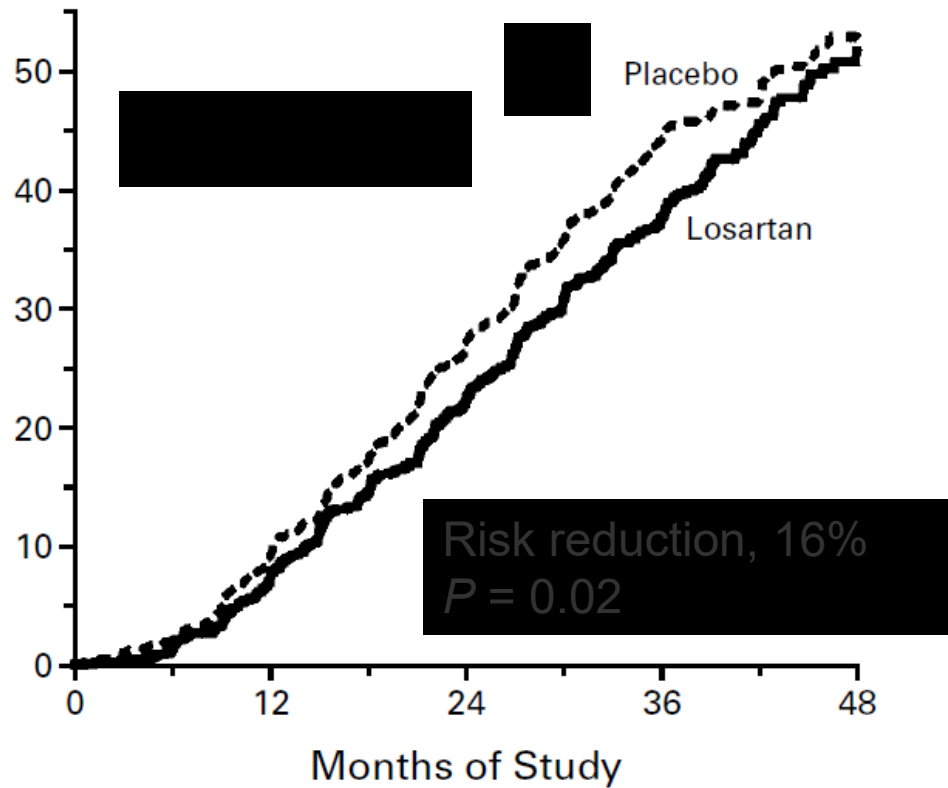
- CREDENCE (30% ↓ in composite progression of CKD)

dapagliflozin

- DAPA-CKD (39% ↓ in composite progression of CKD)

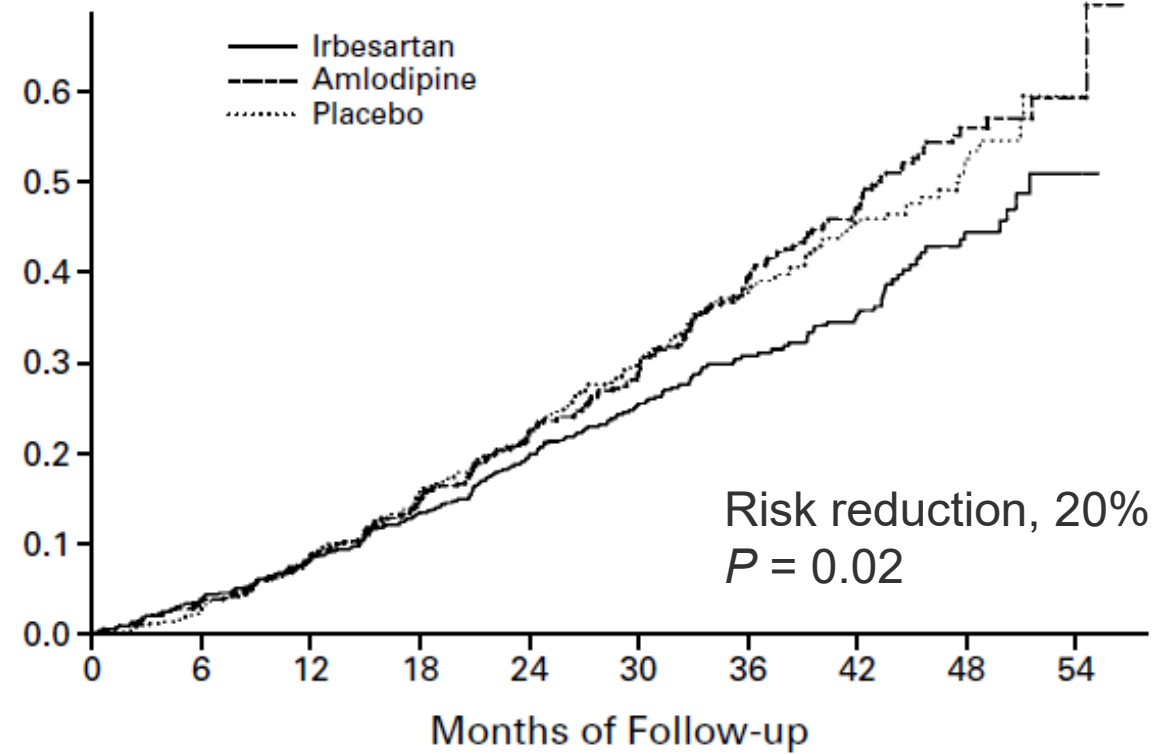
# Proven Renoprotection in T2DM: RENAAL & IDNT

Doubling of serum creatinine, ESKD, or death  
**RENAAL**



Brenner et al. *N Engl J Med.* 2001; 345:861-869.

**IDNT**



Lewis et al. *N Eng J Med.* 2001; 345:851-860.

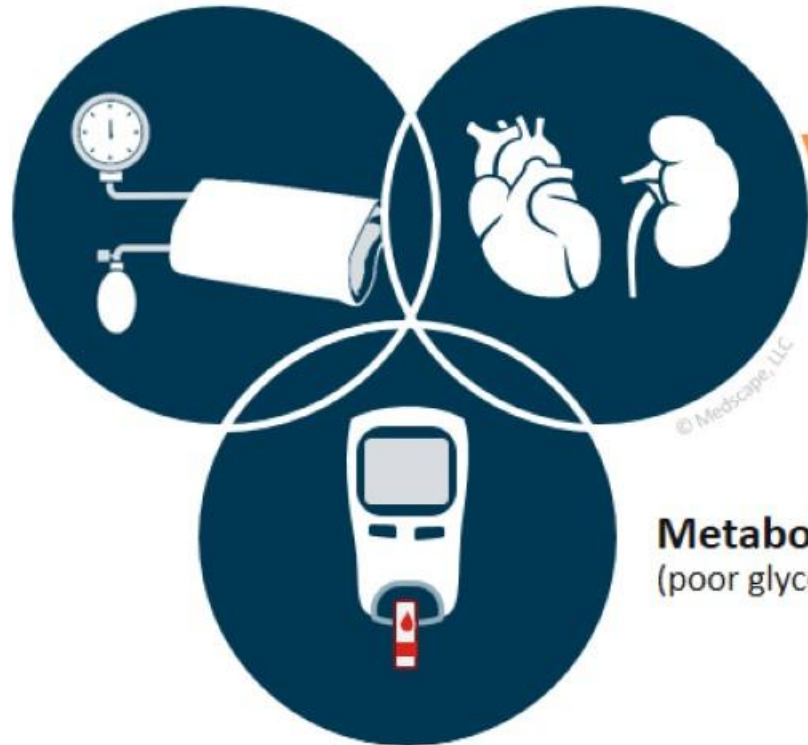
# Unmet Need

## Addressing the 3 Drivers of CKD Progression in T2D

### 3 Drivers of CKD Progression in T2D

#### Hemodynamic

(elevated blood pressure and/or intraglomerular pressure)



Inflammation  
and fibrosis

Not specifically  
targeted by existing  
treatments<sup>[a,d]</sup>

#### Metabolic

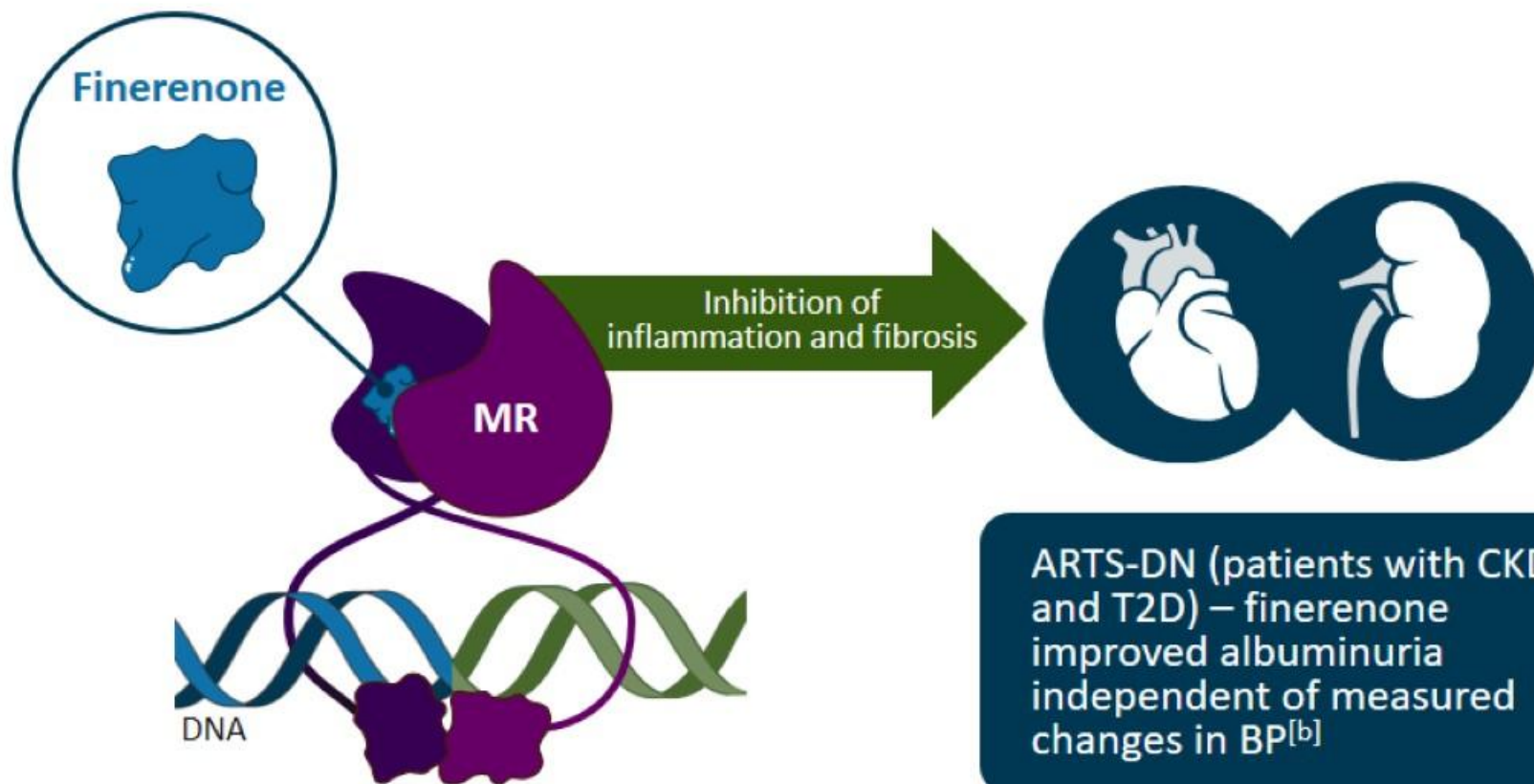
(poor glycemic control)

\*Composite of doubling of serum creatinine, ESKD, or death.

a. Alicic RZ, et al. *Clin J Am Soc Nephrol*. 2017;12:2032-2045; b. Mora-Fernández C, et al. *J Physiol*. 2014;18:3997-4012; c. Bauersachs J, et al. *Hypertension*. 2015;65:257-263; d. Alicic RZ, et al. *Adv Chronic Kidney Dis*. 2018;25:181-191.

# The Rationale for a Mineralocorticoid Receptor Antagonist to Treat CKD in T2D

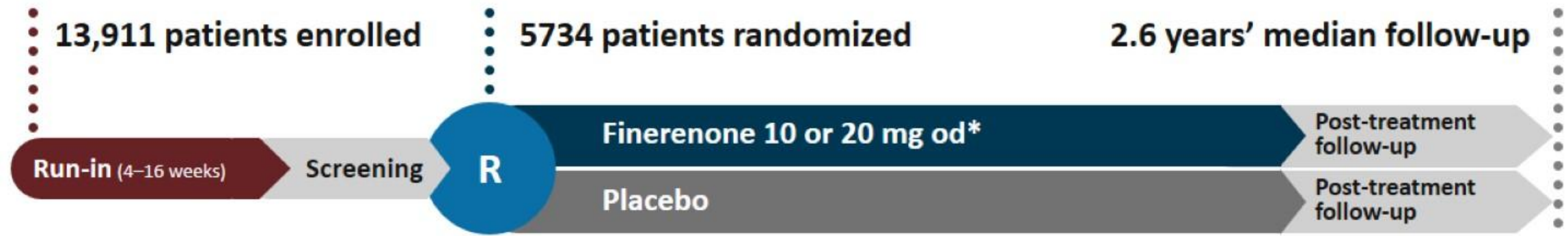
Finerenone is a novel, selective, non-steroidal MRA that inhibits inflammation and fibrosis and protects against progressive kidney and CV dysfunction in preclinical models<sup>[a]</sup>



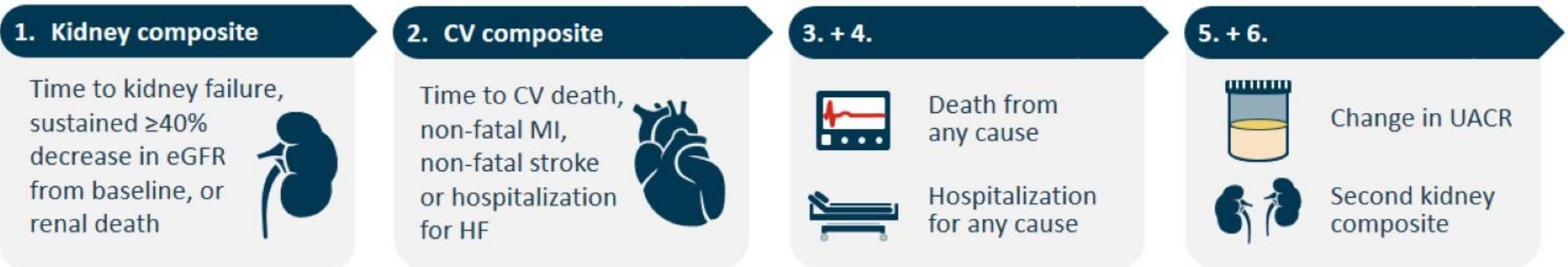
ARTS-DN (patients with CKD and T2D) – finerenone improved albuminuria independent of measured changes in BP<sup>[b]</sup>

Hypothesis: MR antagonism with finerenone slows CKD progression and reduces CV morbidity and mortality in patients with advanced CKD and T2D<sup>[c]</sup>

# FIDELIO-DKD Study Design



## Hierarchical endpoints



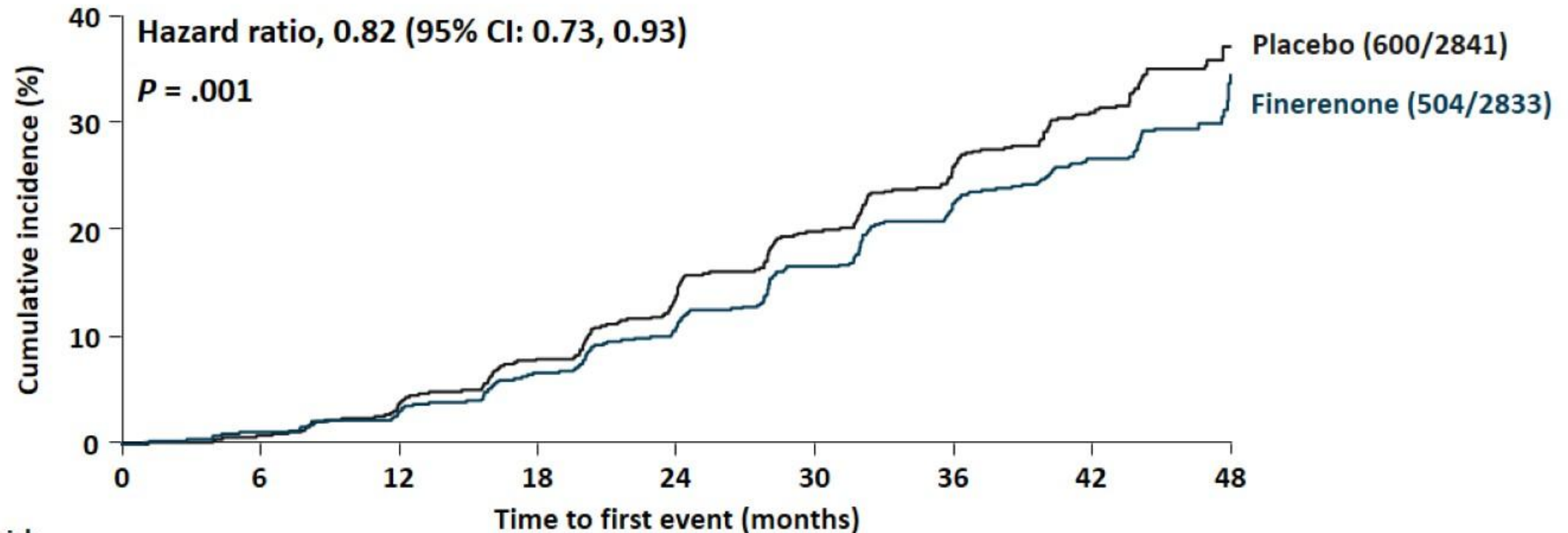
© Medscape, LLC

\*10 mg if screening eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>; 20 mg if  $\geq 60$  mL/min/1.73 m<sup>2</sup>; uptitration encouraged from month 1 if serum potassium  $\leq 4.8$  mEq/L and eGFR stable.

Bakris GL, et al. *N Eng J Med.* 2020. [Epub ahead of print]; Bakris GL, et al. *Am J Nephrol.* 2019;50:333-344.

# FIDELIO-DKD (Finerenone) Primary Endpoint

Kidney failure\*, sustained  $\geq 40\%$  decrease in eGFR from baseline, or renal death

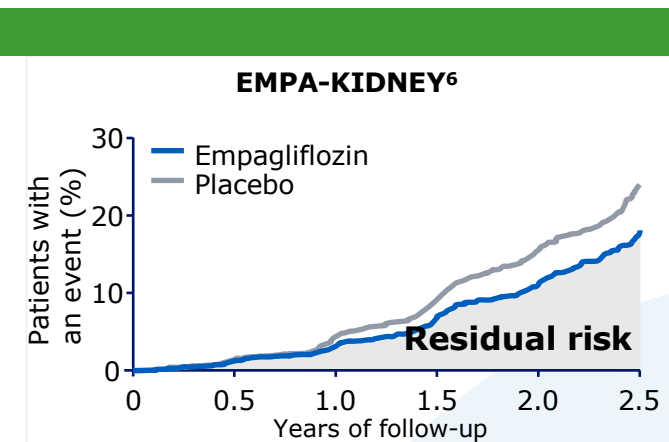
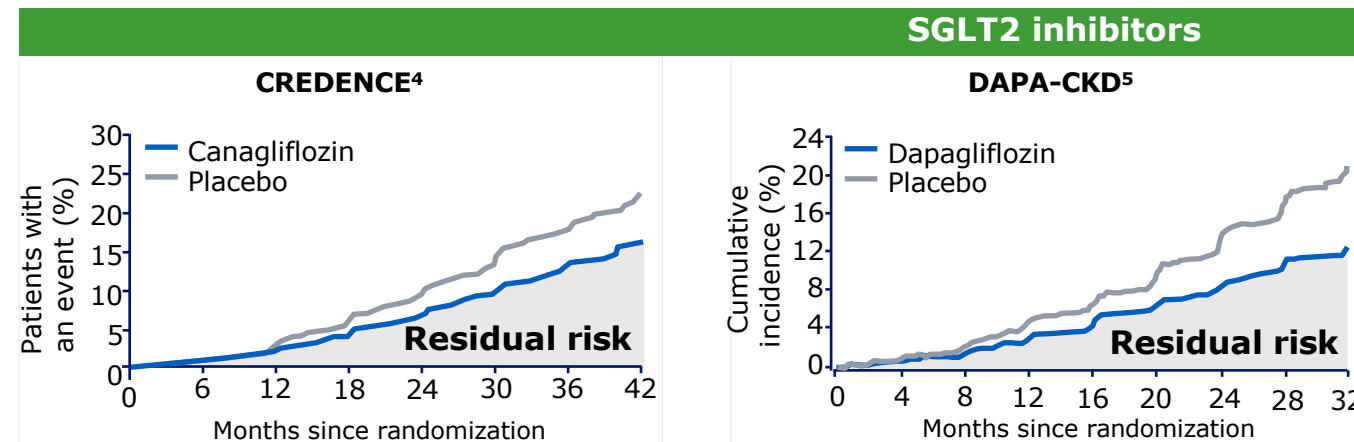
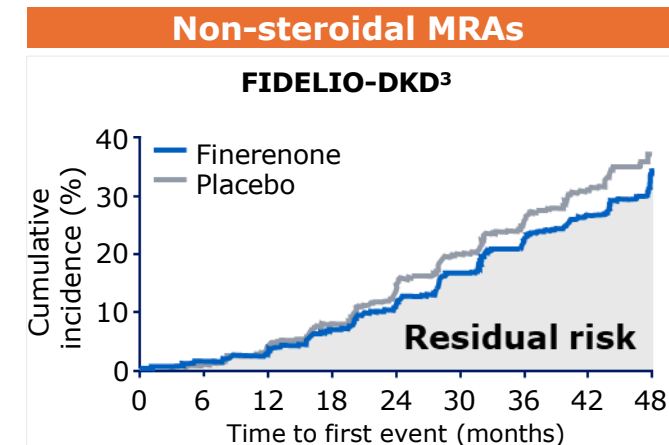
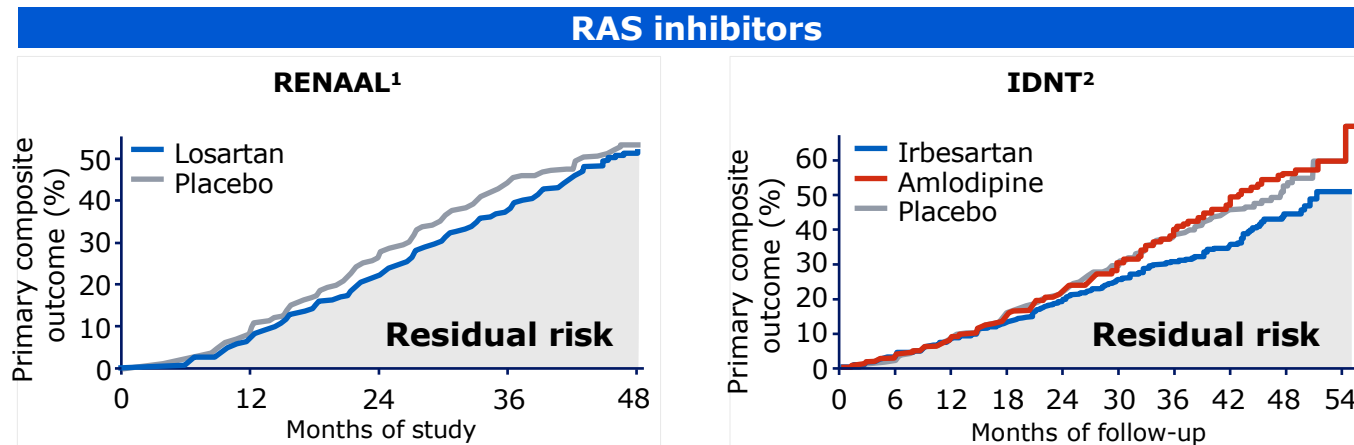


No. at risk

Finerenone	2833	2607	1808	787	83
Placebo	2841	2586	1758	792	82

\*End-stage kidney disease or an eGFR  $< 15$  mL/min/1.73 m<sup>2</sup>.  
Bakris GL, et al. *N Eng J Med*. 2020. [Epub ahead of print]

# Residual risk despite available treatment options



MRA, mineralocorticoid receptor antagonist; RAS, renin-angiotensin-aldosterone system; SGLT2, sodium-glucose cotransporter-2.  
 1. Brenner BM et al. *N Engl J Med* 2001;345:861-869; 2. Lewis EJ et al. *N Engl J Med* 2001;345:851-860; 3. Bakris GL et al. *N Engl J Med* 2020;383:2219-2229;  
 4. Perkovic V et al. *N Engl J Med* 2019;380:2295-2306; 5. Heerspink HJL et al. *N Engl J Med* 2020;383:1436-1446; 6. The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2023;388:117-127.

# CONFIDENCE - Methods

- Inclusion criteria: **CKD** (eGFR 30 to 90 mL/min/1.73 m<sup>2</sup>; UACR ≥100 to <5000 mg/g) and **T2D**
- Already receiving renin–angiotensin system inhibitor therapy
- 1:1:1 randomization: Finerenone (10-20 mg) + Empagliflozin(10mg); Finerenone + Placebo; Empagliflozin + Placebo
- Primary endpoint: relative change in UACR from baseline at Day 180

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## Finerenone with Empagliflozin in Chronic Kidney Disease and Type 2 Diabetes

Rajiv Agarwal, M.D.,<sup>1,2</sup> Jennifer B. Green, M.D.,<sup>3</sup> Hiddo J.L. Heerspink, Ph.D.,<sup>4</sup> Johannes F.E. Mann, M.D.,<sup>5,6</sup>  
Janet B. McGill, M.D.,<sup>7</sup> Amy K. Mottl, M.D.,<sup>8</sup> Julio Rosenstock, M.D.,<sup>9</sup> Peter Rossing, M.D.,<sup>10,11</sup>  
Muthiah Vaduganathan, M.D., M.P.H.,<sup>12</sup> Meike Brinker, M.D.,<sup>13</sup> Robert Edfors, M.D., Ph.D.,<sup>14</sup> Na Li, M.D., Ph.D.,<sup>15</sup>  
Markus F. Scheerer, Ph.D.,<sup>16</sup> Charlie Scott, M.Sc.,<sup>17</sup> and Masaomi Nangaku, M.D., Ph.D.,<sup>18</sup> for the CONFIDENCE Investigators\*

### ABSTRACT

#### BACKGROUND

Limited evidence exists to support the simultaneous initiation of sodium–glucose cotransporter-2 inhibitors and finerenone, a nonsteroidal mineralocorticoid receptor antagonist, in persons with chronic kidney disease and type 2 diabetes.

#### METHODS

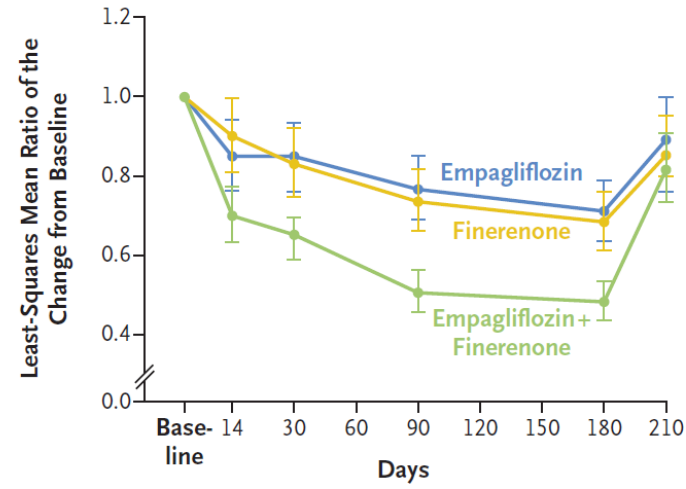
We randomly assigned participants with chronic kidney disease (estimated glomerular

Author affiliations are listed at the end of the article. Dr. Agarwal can be contacted at [ragarwal@iu.edu](mailto:ragarwal@iu.edu) or at Richard L. Roudebush VA Medical Center, 1481 W. 10th St., 111N, Indianapolis, IN 46202.

\*The investigators in the CONFIDENCE

# Results - Efficacy

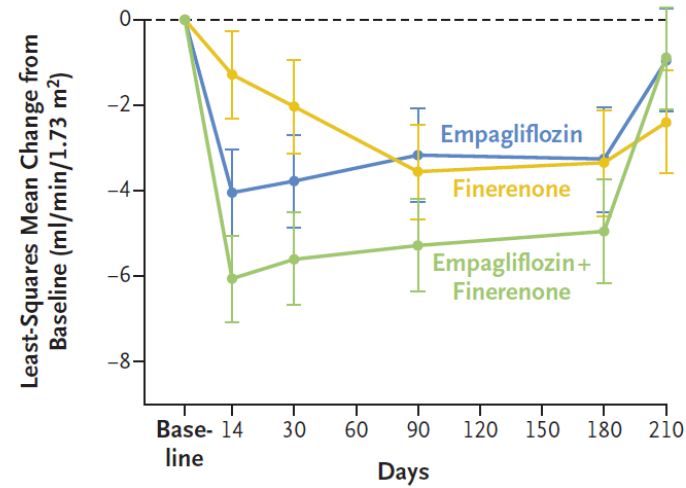
**A** Change in Urinary Albumin-to-Creatinine Ratio



**No. of Patients**

Finerenone	258	247	248	237	236	227
Empagliflozin	261	254	252	246	238	232
Empagliflozin+ finerenone	265	248	253	248	240	238

**C** Change in eGFR

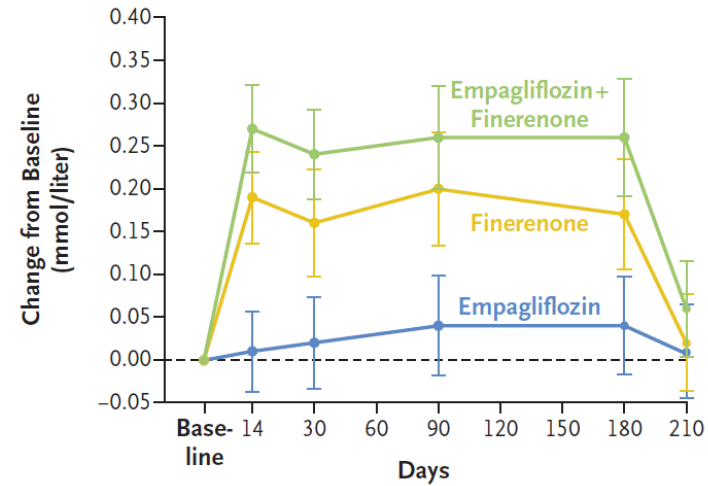


**No. of Patients**

Finerenone	262	250	251	243	239	234
Empagliflozin	265	258	255	249	242	243
Empagliflozin+ finerenone	269	253	261	254	243	253

# Results - Safety

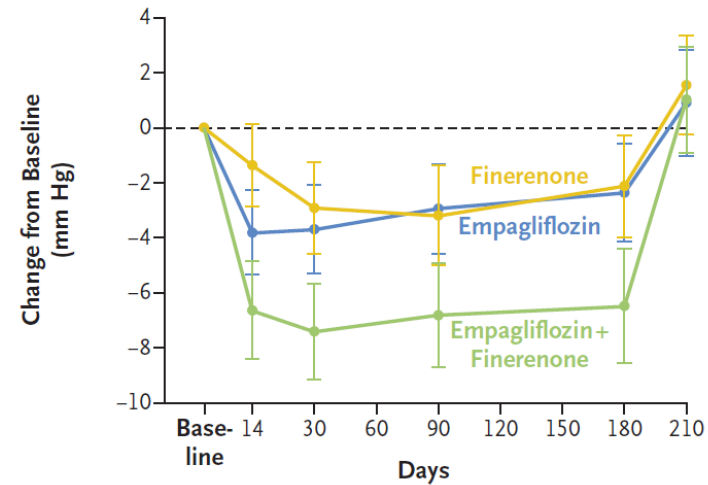
**B Change in Serum Potassium Level**



**No. of Patients**

Finerenone	264	250	252	242	240	235
Empagliflozin	266	260	254	250	244	245
Empagliflozin+ finerenone	267	253	261	254	244	253

**D Change in Systolic Blood Pressure**



**No. of Patients**

Finerenone	264	257	256	248	244	243
Empagliflozin	266	261	259	253	247	248
Empagliflozin+ finerenone	268	255	262	256	247	253

# Study conclusion

- Among persons with both chronic kidney disease and type 2 diabetes, initial therapy with finerenone plus empagliflozin led to a greater reduction in the urinary albumin-to-creatinine ratio than either treatment alone.

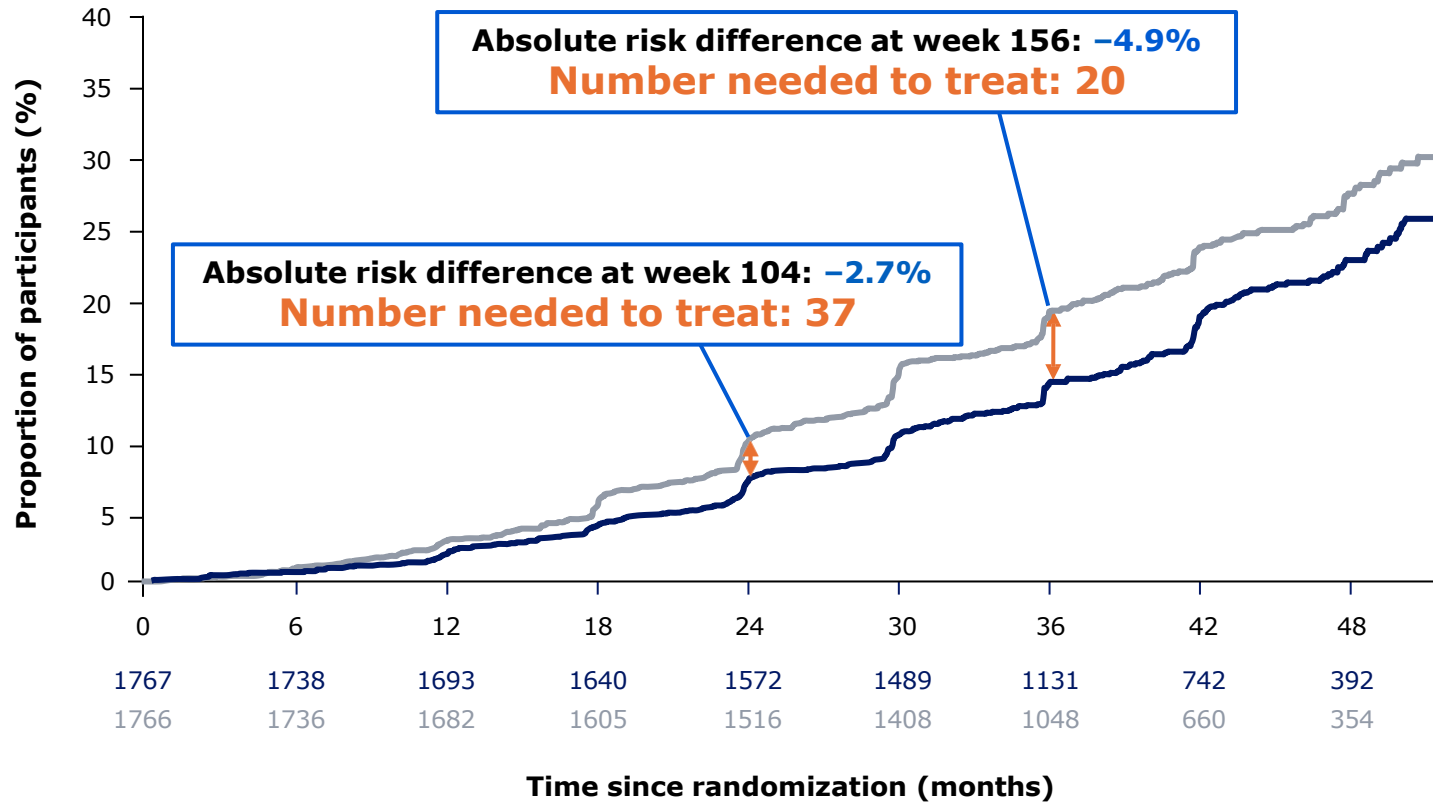
# FLOW

semaglutide | kidney  
outcomes trial

The First Dedicated Kidney Outcome Trial with  
a GLP-1 Receptor Agonist—Once-Weekly  
Semaglutide and the FLOW Trial Results

# Composite kidney outcome

## Primary outcome



**Placebo 23.2%**  
(410/1766)

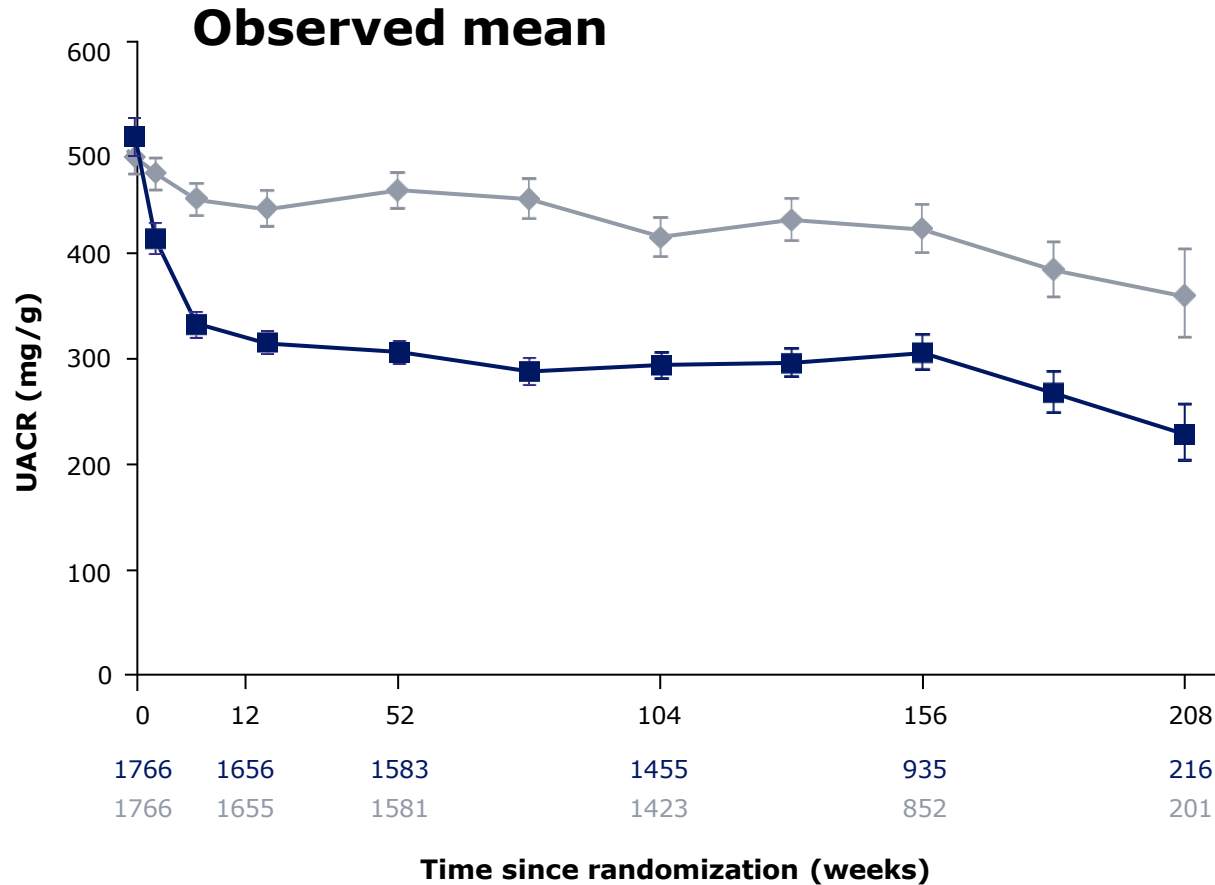
**Semaglutide 18.7%**  
(331/1767)

**HR 0.76** (95% CI 0.66, 0.88)  
**p=0.0003**

Full analysis set. Data from the in-trial period. Numbers shown in the lower panels represent the number of participants at risk. Event rates: 5.8 and 7.5 per 100 patient-years of follow-up for participants receiving semaglutide and placebo, respectively. CI, confidence interval; HR, hazard ratio. Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

Superiority if two-sided  
p value <0.0322

# Change in UACR



**Ratio to baseline at week 104:**

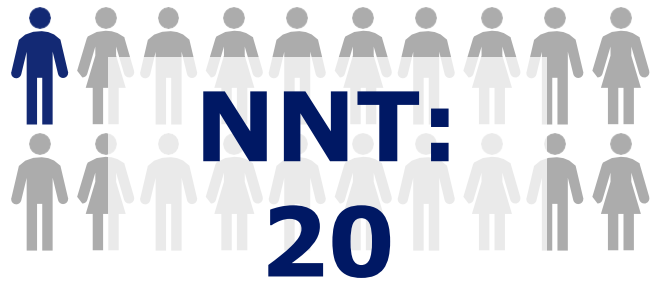
**Placebo 0.88**

**Semaglutide 0.60**

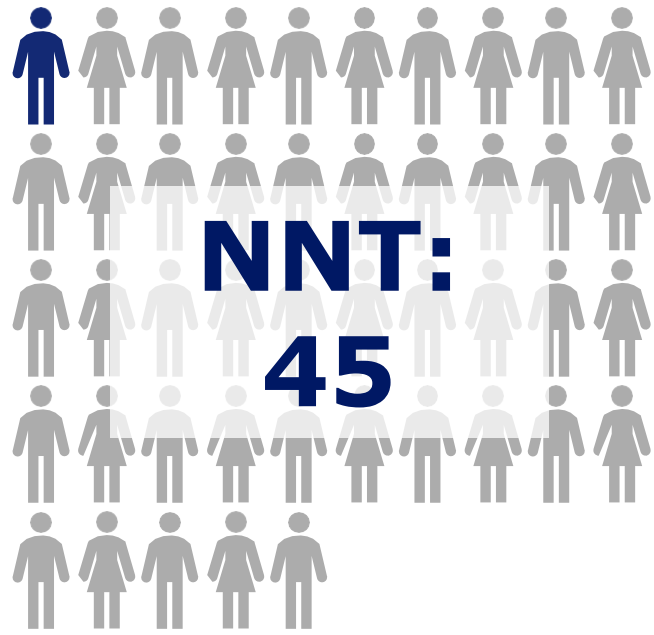
**Estimated treatment ratio  
0.68 (95% CI 0.62, 0.75)**

# Benefits of semaglutide over 3 years

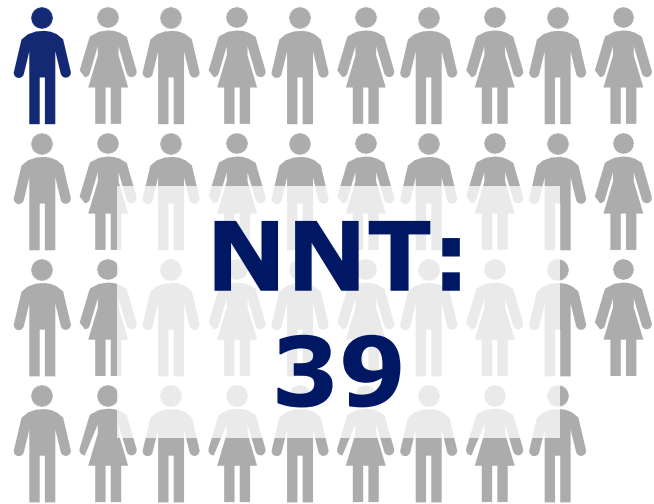
To prevent one primary outcome:<sup>†</sup>



To prevent one MACE:<sup>‡</sup>



To prevent one death due to any cause:



<sup>†</sup>Onset of persistent  $\geq 50\%$  reduction in eGFR compared with baseline, onset of persistent eGFR  $< 15$  mL/min/1.73 m<sup>2</sup>, initiation of chronic kidney replacement therapy dialysis, or kidney transplantation, kidney death, or CV death; <sup>‡</sup>Non-fatal MI, non-fatal stroke, or CV death. CV death includes undetermined cause of death. CV, cardiovascular; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular event; MI, myocardial infarction; NNT, number needed to treat. Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

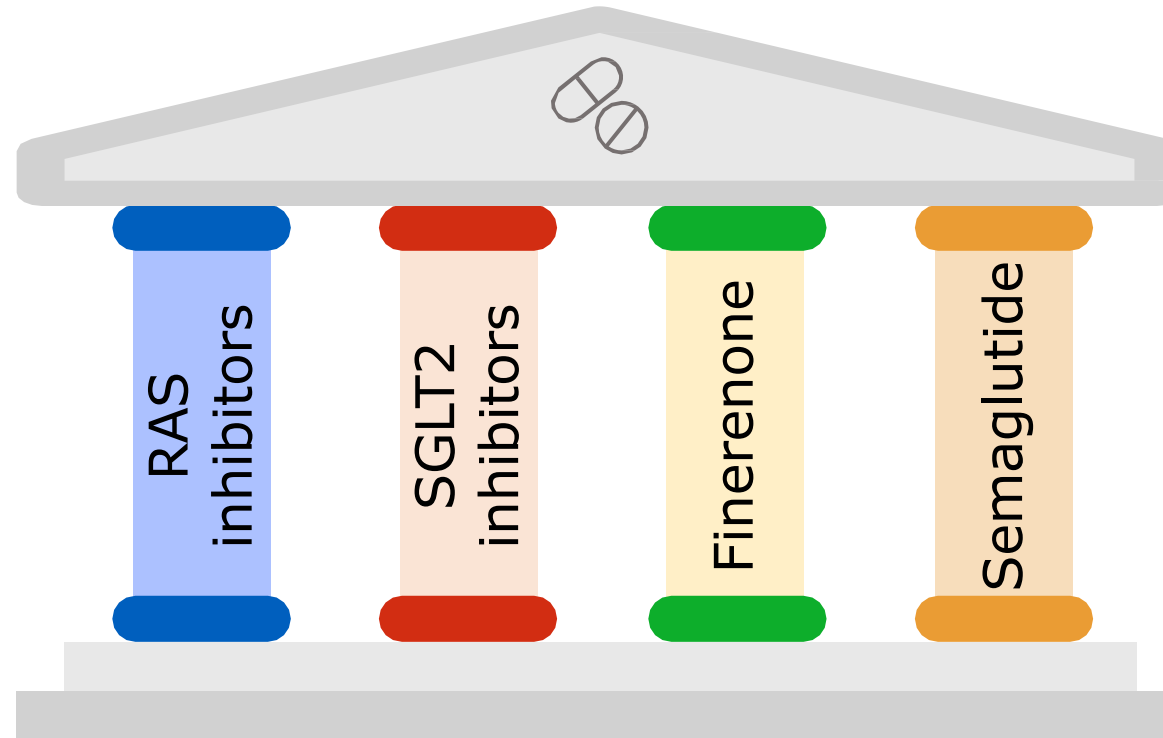
# A pillared approach is recommended to treat CKD and diabetes

## RAS inhibitors

- Decrease efferent arteriole tone
- Decrease hyperfiltration
- Decrease endothelial dysfunction
- Decrease cardiac remodeling

## SGLT2 inhibitors

- Increase afferent arteriole tone
- Improve tubuloglomerular feedback
- Decrease hyperfiltration
- Decrease proteinuria
- Decrease oxidative stress
- Increase anti-inflammatory and anti-fibrotic effects



## Finerenone

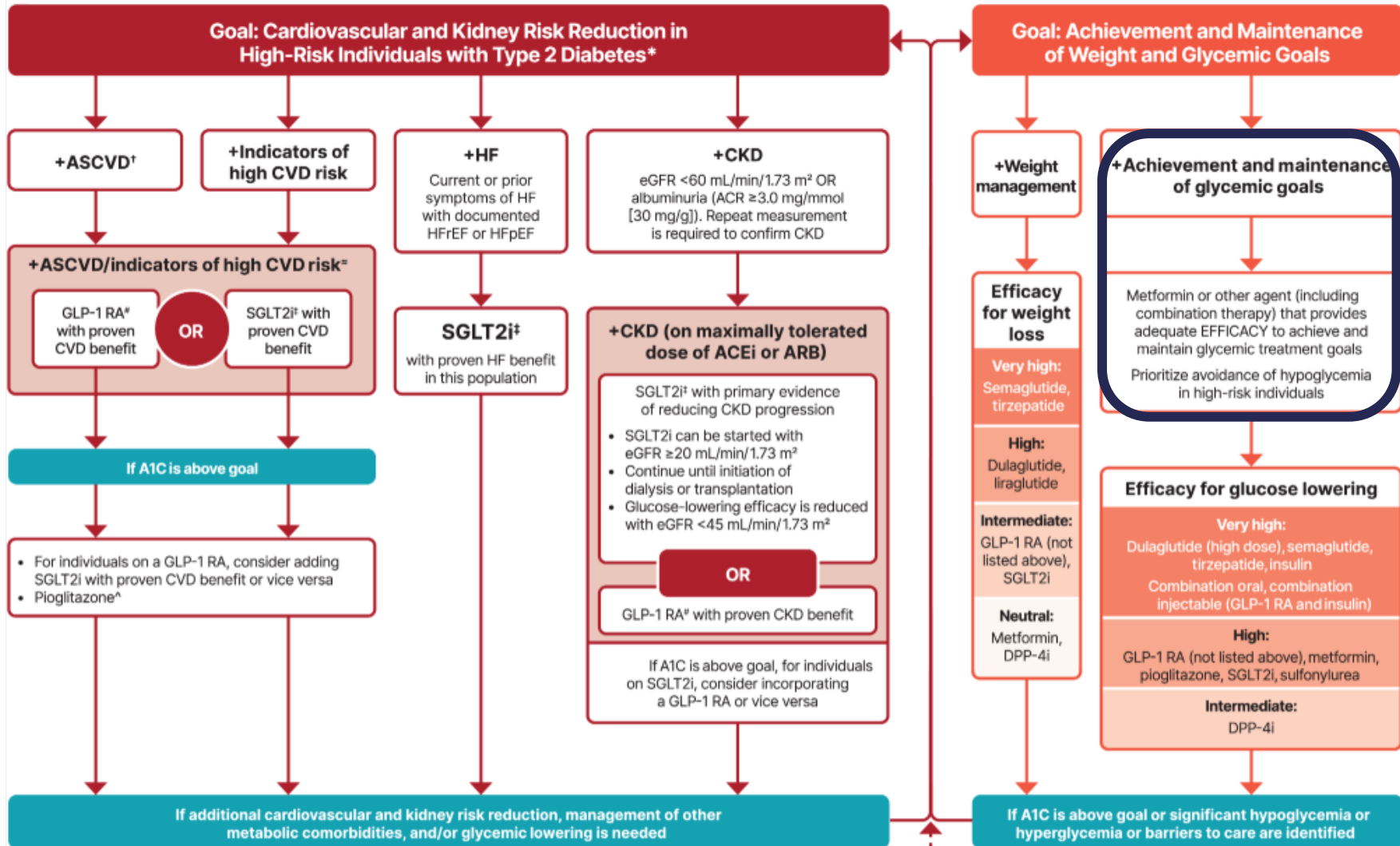
- Decreases inflammation
- Decreases fibrosis
- Decreases endothelial dysfunction
- Decreases tissue remodeling
- Decreases proteinuria

## Semaglutide

- Decrease weight
- Decrease dyslipidemia
- Decrease oxidative stress
- Decrease endothelial dysfunction

# 2025 ADA Glycemic Management

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT; SOCIAL DETERMINANTS OF HEALTH





# Glycemic Management

## **Efficacy for glucose lowering**

### **Very high:**

Dulaglutide (high dose), semaglutide, tirzepatide, insulin

Combination oral, combination injectable (GLP-1 RA and insulin)

### **High:**

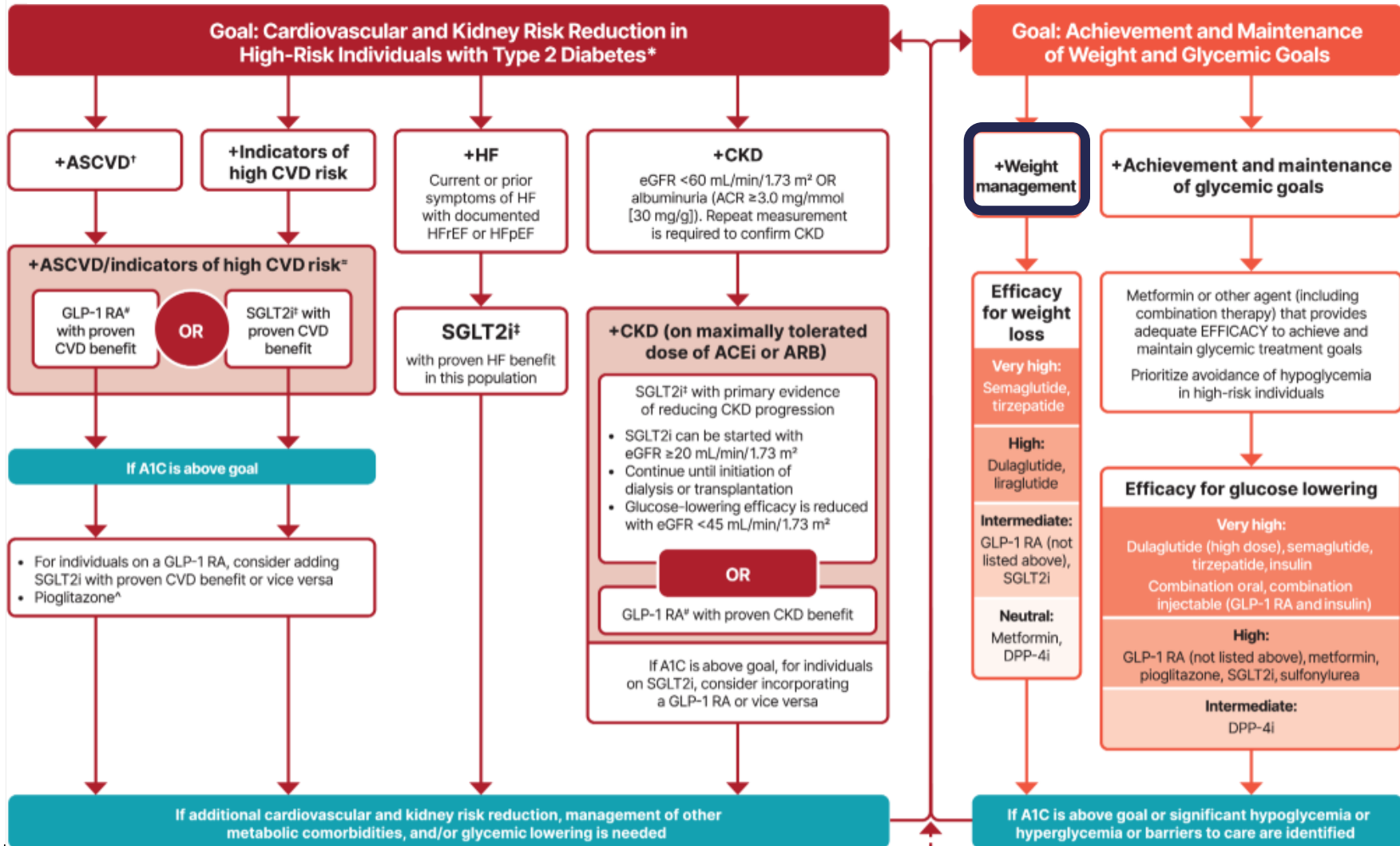
GLP-1 RA (not listed above), metformin, pioglitazone, SGLT2i, sulfonylurea

### **Intermediate:**

DPP-4i

# 2025 ADA Glycemic Management

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT; SOCIAL DETERMINANTS OF HEALTH



# MASLD/MASH Pathophysiology

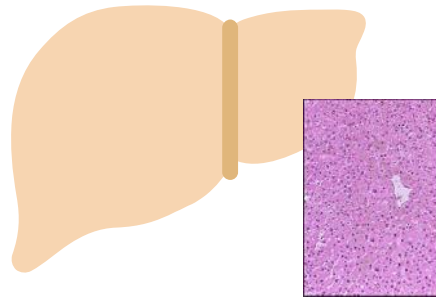


powered by CEA

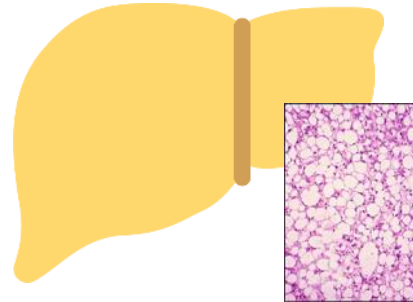
# Prevalence of MASLD and MASH

## MASLD

### Normal Liver

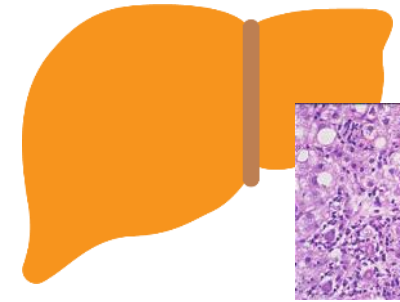


### Steatosis "MASLD"



Fatty liver with trivial or no inflammation and no hepatocyte ballooning

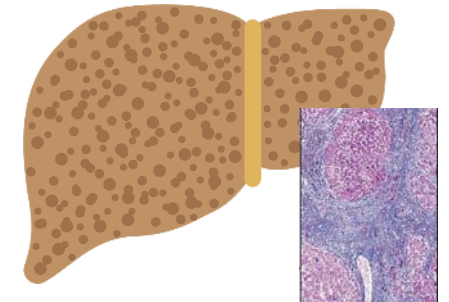
### Steatohepatitis "MASH"



Fatty liver with significant inflammation and hepatocyte ballooning



### Cirrhosis



Increasing fibrosis leading to cirrhosis, hepatocellular carcinoma

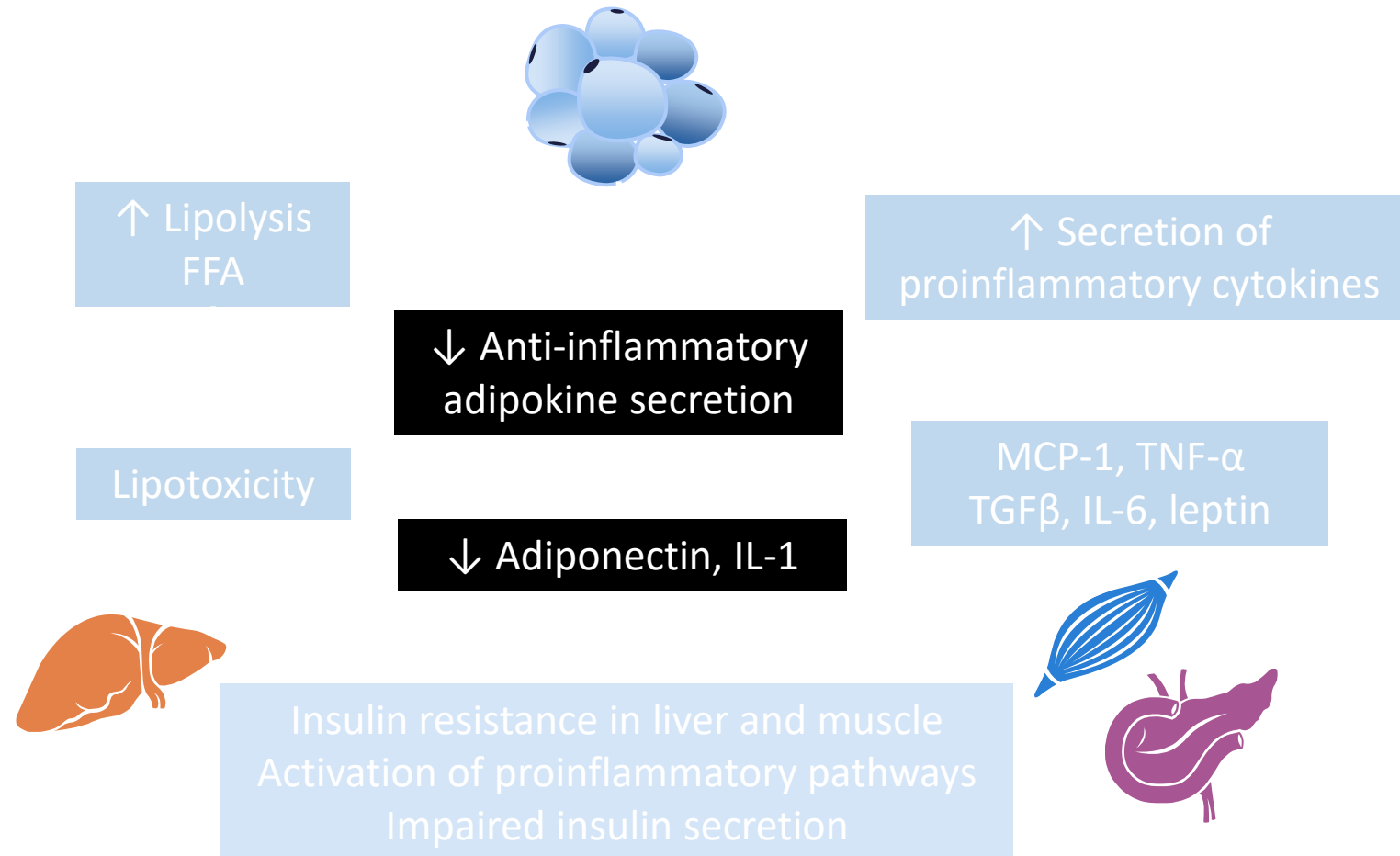
Worldwide prevalence:

25%<sup>1</sup>

3%-5%<sup>1</sup>

1%-2% at risk\*

# The Pathogenic Relationship Between Diabetes and MASH



# Screening for MASLD/MASH

Primary care, endocrinologists, gastroenterologists, and obesity specialists should screen for MASLD with advanced fibrosis

## Step 1: Identify patients at risk

≥2 metabolic risk factors	Type 2 diabetes	Steatosis on any imaging modality or elevated aminotransferases
---------------------------	-----------------	---

## Step 2: History and laboratory tests: Excessive alcohol intake, CBC, liver function tests

## Step 3: Noninvasive testing for fibrosis (FIB-4 is a calculated value based on age, AST, ALT, and platelet count)

FIB-4 <1.3	FIB-4 1.3 to 2.67	FIB-4 >2.67
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INDETERMINATE RISK

## Step 4: Liver stiffness measurement

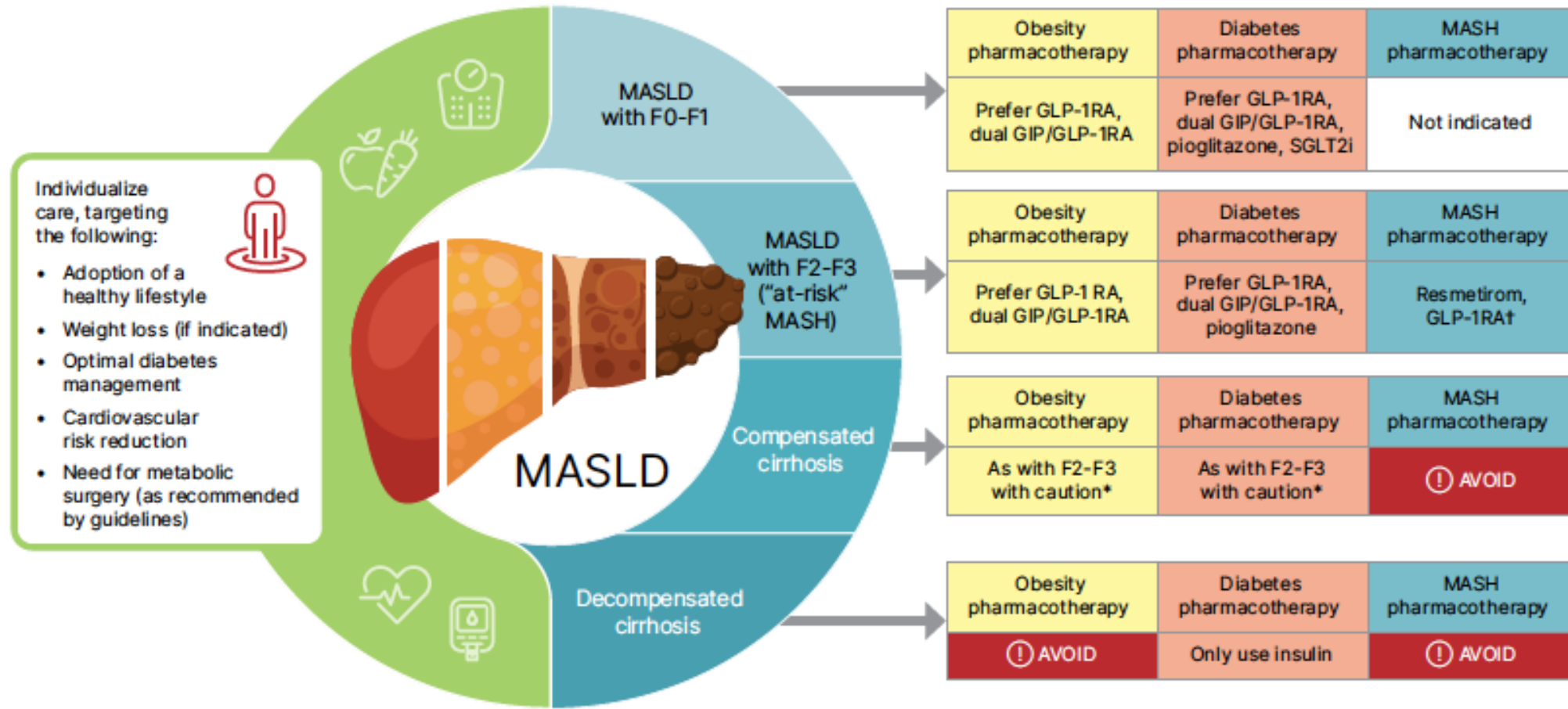
LSM <8 kPa	LSM 8-12 kPa	LSM >12 kPa
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**LOW RISK**  
Repeat NIT in 2-3 yr unless clinical circumstances change

**INDETERMINATE RISK**  
Refer to hepatologist for liver biopsy or MR elastography or monitoring with re-eval of risk in 2-3 yr

**HIGH RISK**  
Refer to hepatologist

# ADA 2025 MASLD Treatment Algorithm for Individuals With Prediabetes or Diabetes



# Metabolic Dysfunction-Associated Steatohepatitis

**+Mitigating risk of MASLD or MASH**

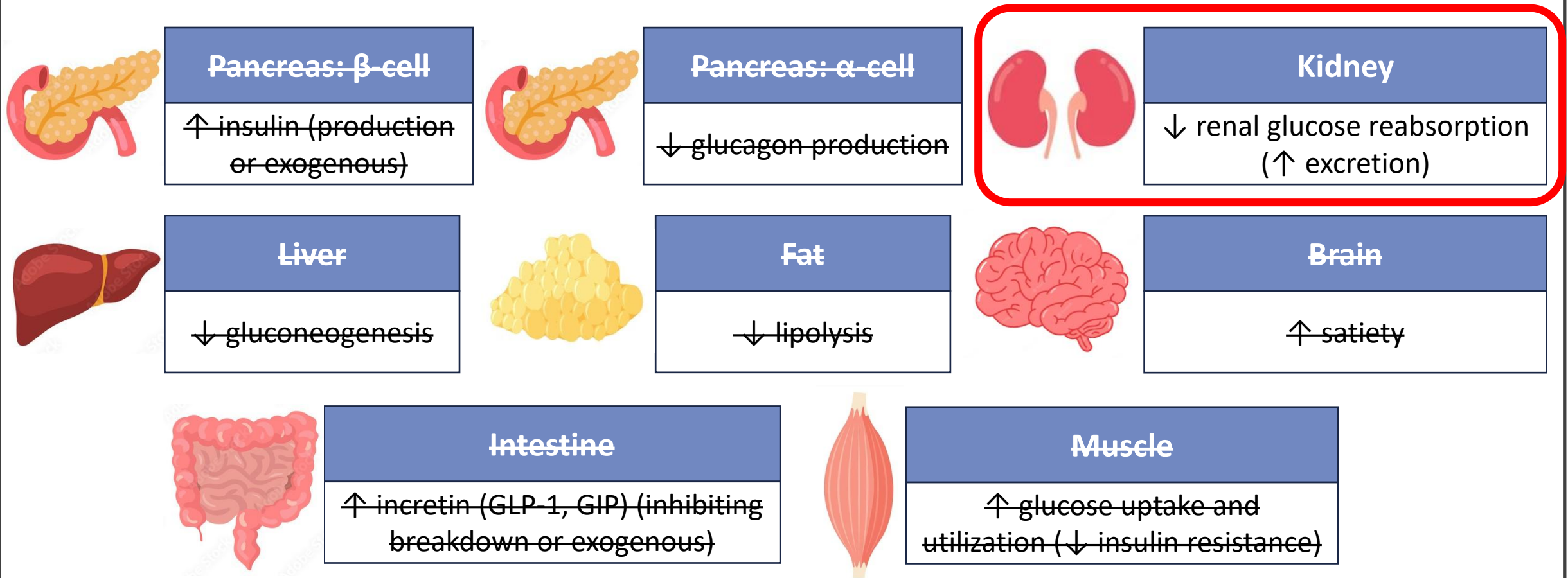


**Agents with potential benefit in MASLD or MASH**

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

# Sodium glucose co-transporter 2 inhibitors (SGLT2i) empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, bexagliflozin



# SGLT2 Inhibitors

	empagliflozin	dapagliflozin	canagliflozin	ertugliflozin	bexagliflozin
Doses available	10 mg, 25 mg	5 mg, 10 mg	100 mg, 300 mg	5 mg, 15 mg	20 mg
Max dose	25 mg once daily	10 mg once daily	300 mg once daily	15 mg once daily	20 mg once daily
Renal dosing	Not recommended for GFR <30 for DM*	Initiation not recommended for GFR <25  Can continue 10mg dose without adjustment*	GFR 30-60: adjust dose to 100mg daily  GFR <30: Initiation not recommended*	Not recommended for GFR <45	Not recommended for GFR <30
ASCVD	<b>Yes</b> (EMPA-REG)	No (DECLARE-TIMI)	<b>Yes</b> (CANVAS + CREDENCE)	No (VERTIS CV)	No
Heart Failure	<b>Yes</b> (EMPEROR PRESERVED + REDUCED)	<b>Yes</b> (DAPA-HF + DELIVER)	<b>Yes in T2DM</b> (CANVAS + CREDENCE)	<b>Yes in T2DM</b> (VERTIS CV)	No
CKD	<b>Yes</b> (EMPA-KIDNEY)	<b>Yes</b> (DAPA-CKD)	<b>Yes in T2DM</b> (CREDENCE)	No (VERTIS CV)	No

\*Renal dosing is for initiation, can be continued

# SGLT-2 Inhibitors

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## Advantages

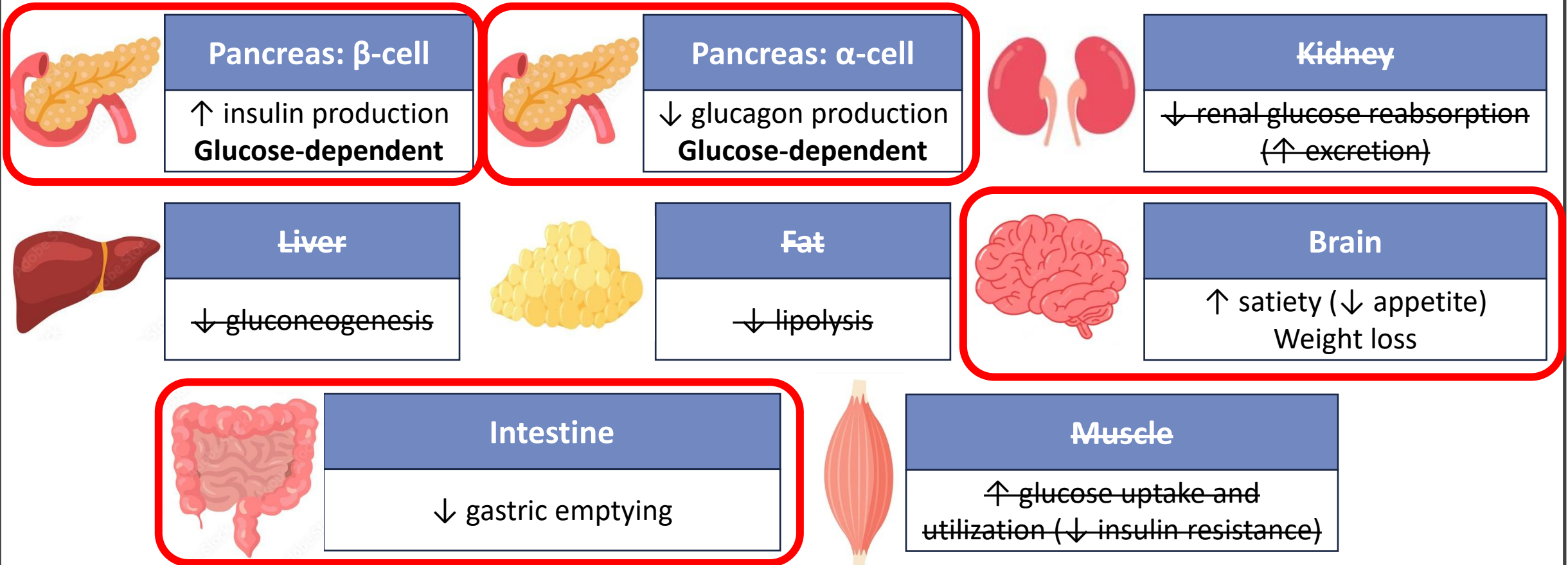
- A1c ↓0.7–1.1%
- **ASCVD risk reduction (Em, C)**
- **Decrease in HF hospitalizations (Em, D, C, Er)**
- **Renal protection (Em, D, C)**
- Weight loss (2-4 kg)
- BP reduction (5-6/1-2 mmHg)
- No hypoglycemia as monotherapy
- Uric acid reduction

## Disadvantages

- Genital mycotic infections
- Volume depletion/Hypotension
- Acute Kidney Injury
- Euglycemic ketoacidosis
- Bone loss/fractures (C)
- Cost

# Incretin Mimetics (GLP-1 RA's)

exenatide, liraglutide, dulaglutide, lixisenatide, semaglutide



# GLP-1 RA's

	exenatide	liraglutide	exenatide ER	semaglutide	dulaglutide
Doses available	5 mcg, 10 mcg	0.6 mg, 1.2 mg, 1.8 mg	2 mg	0.25 mg, 0.5 mg, 1 mg, 2 mg	0.75 mg, 1.5 mg, 3 mg, 4.5 mg
Max dose	10 mcg	1.8 mg	2 mg	2 mg	4.5 mg
Frequency	Twice Daily	Daily		Weekly	
Renal dose	CrCl <30: not recommended	None	eGFR <45: not recommended	None	None
Autoinjector?	No	No	Yes	No	Yes
MACE benefits	No	Yes (LEADER)	No	Yes (SUSTAIN-6)	Yes (REWIND)
CI in MTC or MEN2	No	Yes	Yes	Yes	Yes

# Oral semaglutide

- 3, 7 and 14 mg daily doses; increases after 30 days at lower doses
- Take at least 30 minutes before the first food, beverage or other oral medication of the day, with no more than 4 ounces of plain water.
- Slows digestion, potential impact on other medications absorption including oral contraception
- PIONEER-6 CVOT 3-point MACE HR 0.79 (0.57-1.11)
  - CV death HR 0.49 (0.27-0.92)

# GLP-1 RA's

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## Advantages

- A1c ↓0.8–2.1%
- **CV benefit** (L,D,S)
- **Renal benefit** (L,D,S)
- No hypoglycemia as monotherapy
- Weight loss
- Convenient dosing
- B-cell sparing effect?

## Disadvantages

- Gastrointestinal adverse effects
- Pancreatitis risk
- Caution for use with gastroparesis
- Most require an injection
- Aspiration risk with surgery
- Impact on oral contraception
- Cost

# Bottom Line ...

- T2DM is associated with multiple complications.
- SGLT2i's decrease CV events, hospitalizations for heart failure and are renal protective.
- GLP-1 RA's decrease CV events and are renal protective.
- Consider these therapies for appropriate patients, including CKD and HF patients, with or without diabetes.

## Glucagon-like Peptide-1 Receptor Agonism

## Glucose-dependent Insulinotropic Polypeptide Receptor Agonism

### Central Nervous System

- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

### Pancreas

- ↑ Insulin
- ↓ Glucagon

### Stomach

- ↓ Gastric Emptying

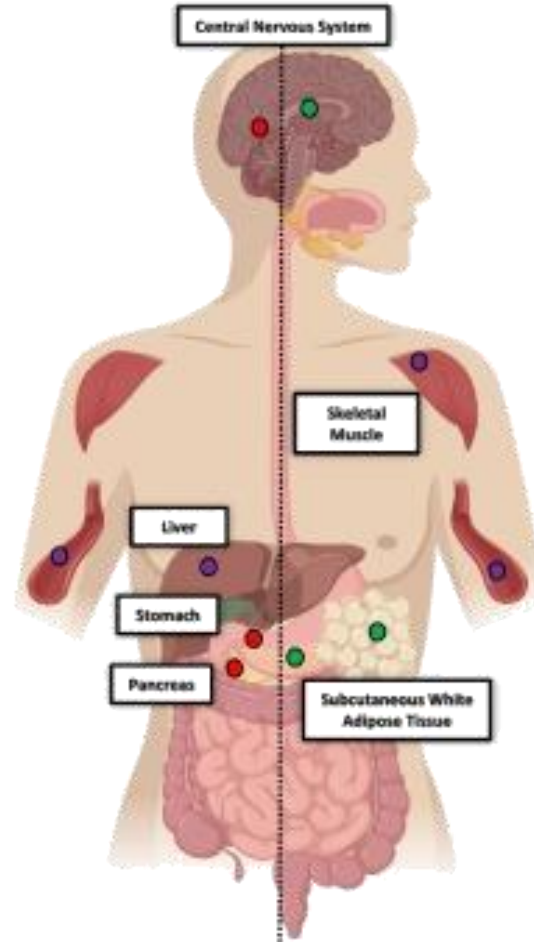
### Systemic

- ↓ Hyperglycemia

### Liver

- ↑ Insulin Sensitivity
- ↓ Hepatic Glucose Production
- ↓ Ectopic Lipid Accumulation

- Glucose-dependent Insulinotropic Polypeptide Receptor Agonism
- Glucagon-like Peptide 1 Receptor Agonism
- Indirect Action



### Central Nervous System

- ↓ Food Intake
- ↓ Nausea
- ↓ Body Weight

### Pancreas

- ↑ Insulin
- ↑ Glucagon

### Subcutaneous White Adipose Tissue

- ↑ Insulin Sensitivity
- ↑ Lipid Buffering Capacity
- ↑ Blood Flow
- ↑ Storage Capacity
- ↓ Proinflammatory Immune Cell Infiltration

### Systemic

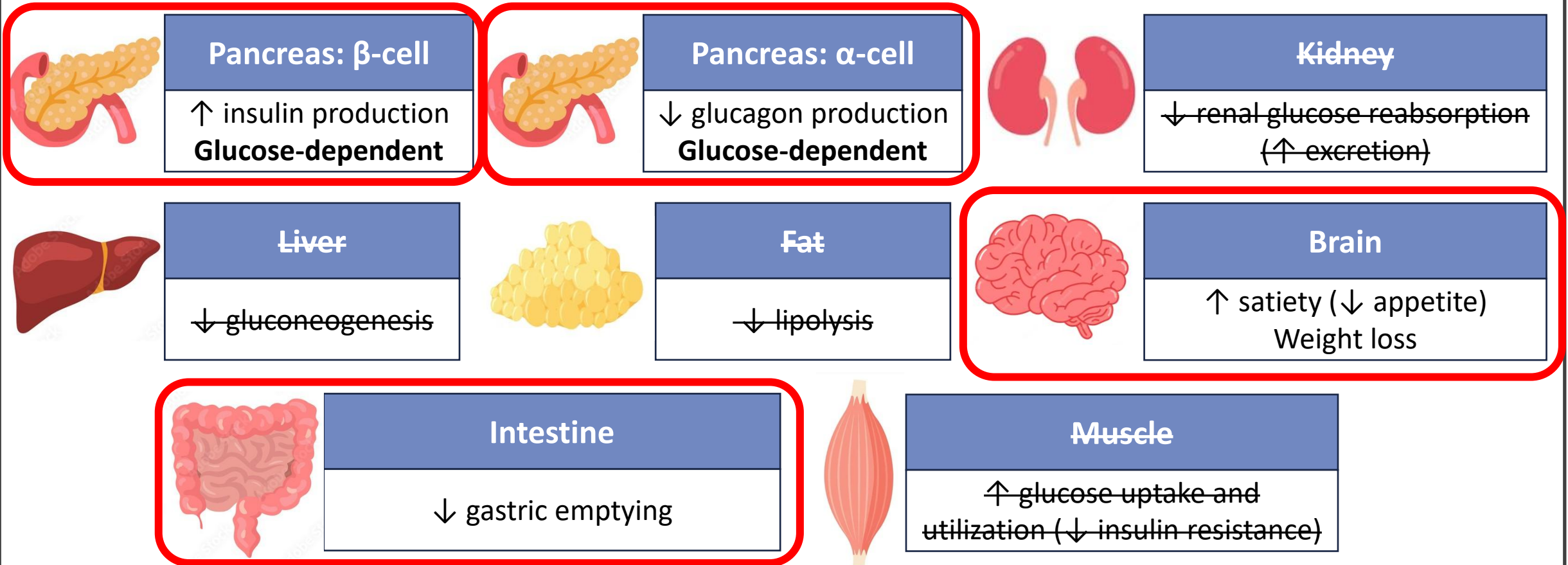
- ↓ Hyperglycemia
- ↓ Dietary Triglyceride

### Skeletal Muscle

- ↑ Insulin Sensitivity
- ↑ Metabolic Flexibility
- ↓ Ectopic Lipid Accumulation

# Dual Incretin Mimetics (GLP-1/GIP RA)

## tirzepatide



# Dual GLP-1/GIP RA's

Drug	Average $\Delta$ HbA1C (%) from Baseline	Confidence Interval	Difference in Average $\Delta$ HbA1C (%) Relative to Semaglutide 1 mg	P-Value
Tirzepatide 5 mg	-2.01%	(-0.28 to -0.03)	-0.15%	0.02
Tirzepatide 10 mg	-2.25%	(-0.51 to -0.26)	-0.39%	P < 0.001
Tirzepatide 15 mg	-2.30%	(-0.57 to -0.32)	-0.45%	P < 0.001
Semaglutide 1 mg	-1.86%		0 %	-

Drug	Average $\Delta$ in Body Weight (kg)	P-Value
Tirzepatide 5 mg	-7.6	P < 0.001
Tirzepatide 10 mg	-9.3	P < 0.001
Tirzepatide 15 mg	-11.2	P < 0.001
Semaglutide 1 mg	-5.7	-

# Dual GLP-1/GIP RA's

---

## Advantages

- Superior efficacy
- A1c ↓2–2.3%
- Post-hoc decreased albuminuria and total eGFR decline
- No hypoglycemia as monotherapy
- Significant weight loss
- Convenient dosing

## Disadvantages

- Gastrointestinal adverse effects
- Pancreatitis risk
- Caution for use with gastroparesis
- Injectable agent
- Aspiration risk with surgery
- Impact on oral contraception
- Cost

Trial	GLP-1 RA Studied	Population	Baseline Risk	Primary Outcome	Key Findings
SURMOUNT-OSA	Tirzepatide	Moderate-to-severe OSA and obesity (n=469)	49.9% unable or unwilling for CPAP; 50.1% on CPAP	Change in AHI	<p>↓ <b>20 events per hour</b> (P &lt; 0.001) for trial 1;</p> <p>↓ <b>23.8 events per hour</b> for trial 2 (P &lt; 0.001); significant reductions in patient reported outcome measurements</p>

Tirzepatide gained approval for moderate to severe OSA in people with obesity in January 2025

# Incretin Agonist Summary: Indications

Drug	Glucose Lowering	Cardiovascular Effects		Kidney Effects	Liver Disease
		MACE Effect To reduce the risk of death in T2D and established CV	HF	Slow progression of DKD	MASH
Semaglutide (injectable)	✓	✓	⌚	✓	✓
Liraglutide	✓	✓			
Tirzepatide*	✓	⌚	⌚	⌚	⌚
Exenatide	✓				
Dulaglutide	✓	✓			
Semaglutide (oral)	✓	✓			

# Initial Patient Case

RP is a 54-year-old male with newly diagnosed T2DM presenting for initial management.

- Past Medical History: HTN, MI in 2019, hyperlipidemia, obesity
- Current Medications: rosuvastatin 20mg daily, aspirin 81mg daily, losartan 100mg daily, amlodipine 5mg daily
- Labs: A1C 7.42%, Al/Cr 15 mg/g, eGFR 98, LDL 50 mg/dL
- Vitals: BP 128/74 mmHg, BMI 31.2

In addition to lifestyle changes, what would be an appropriate initial regimen?

- a) DPP-4i
- b) SGLT2i
- c) GLP-1 RA
- d) Metformin

# Initial Patient Case

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In addition to lifestyle changes, what would be an appropriate initial regimen?

- a) DPP-4i
- b) SGLT2i (with ASCVD benefit)
- c) GLP-1 RA (with ASCVD benefit)
- d) Metformin

# Initial Patient Case

SL is a 62-year-old women diagnosed one year ago with T2DM. She is very concerned about taking medication that may cause hypoglycemia or weight gain.

- Past medical history: T2DM, HTN, CKD stage 3a, hyperlipidemia
- Medications: metformin 1000mg twice daily, aspirin 81mg daily, atorvastatin 40mg daily, lisinopril 10mg daily
- Labs: A1C 7.6%, Al/Cr 320 mg/g, eGFR 56
- Vitals: 122/74 mmHg, BMI 24

What approach would you take to this patient's follow up management?

- a) Pioglitazone
- b) Ertugliflozin
- c) Semaglutide
- d) Glipizide

# Initial Patient Case

SL is a 62-year-old women diagnosed one year ago with T2DM. She is very concerned about taking medication that may cause hypoglycemia or weight gain.

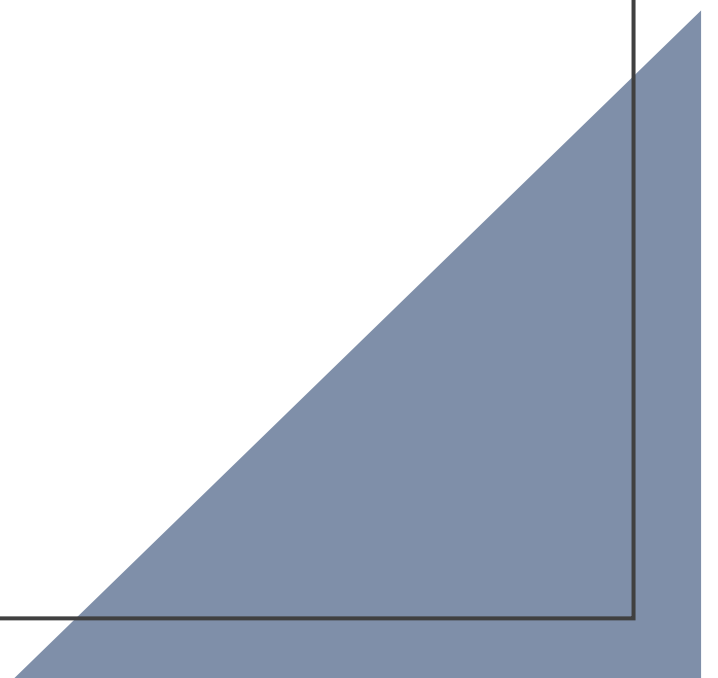
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# 2025 Approach to the Pharmacotherapy of Diabetes

- Emphasis on Cardio-Renal protection
- No longer glucose (A1C) centric
- Individualization of therapy
- Hypoglycemia avoidance
- Weight stable or weight loss
- Use of SGLT-2 inhibitors and GLP-1 receptor agonists early



# The dynamic duo: GLP-1 Receptor Agonists and SGLT2 Inhibitors

Robert S. Busch, MD, FACE

Albany Medical center Division of community  
Endocrinology

Director of research





**Questions??**

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