

# **Type 2 Diabetes Mellitus**

**New Medications to Treat**

**Co-Morbidities**

**2024**

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# Disclosure

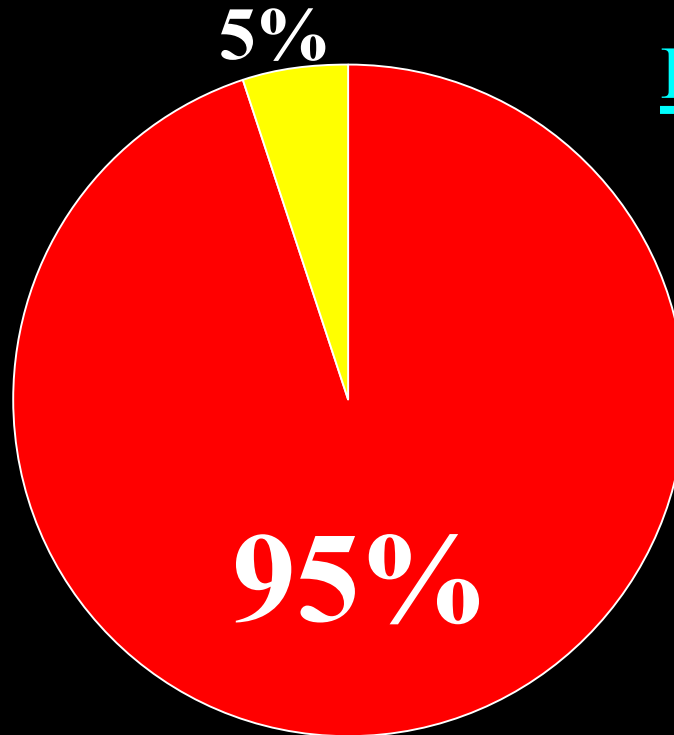
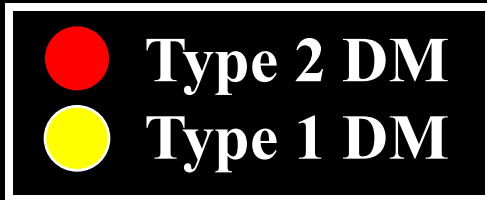
**Michael McDermott** has no conflict of interest or relationships to disclose in relation to this educational activity.

# Learning Objectives

- **Review mechanism of action of Glucagon-like Peptide Receptor Agonists (GLP-1 RA) and Sodium Glucose Transporter Inhibitors (SGLT2-I).**
- **Discuss effects of GLP-1 RA and SGLT2-I on Co-morbidities associated with Type 2 Diabetes Mellitus.**
- **Develop strategies for optimal use of GLP-1 RA and SGLT2-I in people with Type 2 Diabetes Mellitus.**

# Diabetes Mellitus

**36 Million Americans in 2023**



Leading US Cause

Kidney Failure  
Amputations  
Blindness

Major CV  
Risk Factor

**5,000** New Cases Every Day  
**2,000,000** New Cases Every Year

# Excess Caloric Intake



# Reduced Exercise



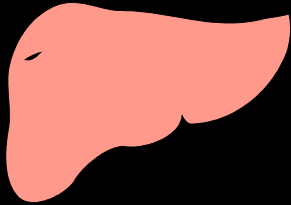
# No Exercise



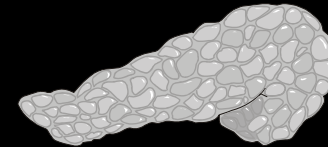
# Type 2 Diabetes Mellitus

## Pathophysiology

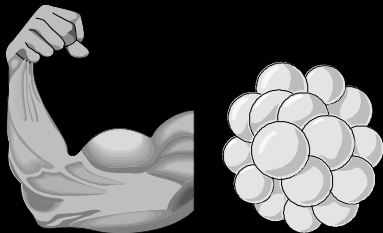
↑ Glucose  
Production



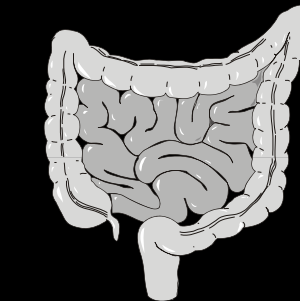
↓ Insulin  
Secretion



**Hyperglycemia**



↑ Insulin  
Resistance



↓ Incretin  
Effect



# Type 2 Diabetes Mellitus

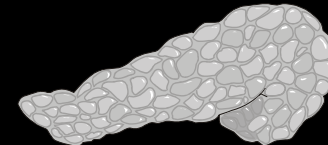
## Pathophysiology Based Therapy

↓ Glucose  
Production



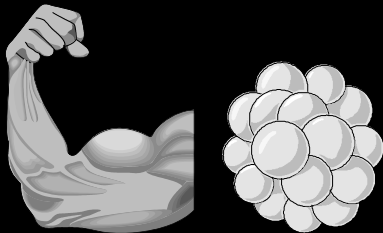
**Metformin**

↑ Insulin  
Secretion



**Sulfonylurea  
Meglitinide**

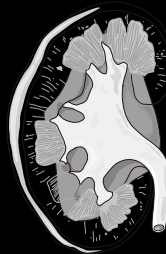
**Euglycemia**



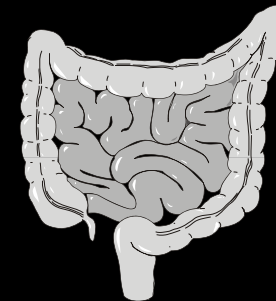
↓ Insulin  
Resistance

**Thiazolidinedione**

**SGLT-2  
Inhibitor**



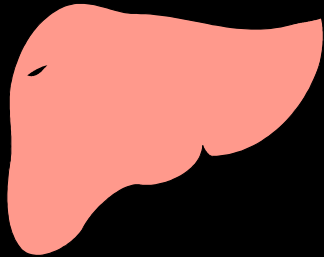
↑ Glycosuria



↑ Incretin Effect  
**GLP-1 RA  
GLP-1/GIP RA  
DPP4 Inhibitor**

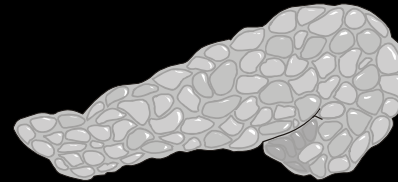
# Incretin Physiology

↓ Glucose  
Production



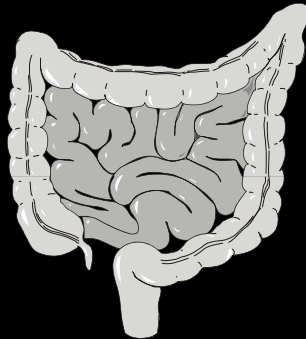
↑ Insulin  
↓ Glucagon

↓ Appetite  
↑ Satiety



Glucose  
Dependent

↓ Gastric  
Emptying



**GLP-1/GIP**

$T_{1/2} = 2 \text{ min}$  (Due to DPP4)



**GLP-1** = Glucagon Like Peptide-1

**DPP4** = Dipeptidyl Peptidase 4

**GIP** = Glucose Dependent Insulinotropic Peptide

# Incretin Based Therapy



## GLP-1/GIP Receptor Agonists

- Resistant to DPP4
- Prolonged duration of action

**GLP-1** = Glucagon Like Peptide-1

**DPP4** = Dipeptidyl Peptidase 4

**GIP** = Glucose Dependent Insulinotropic Peptide

# Incretin Based Therapy

## **GLP-1 Receptor Agonists**

**Exenatide (Byetta) SQ BID**

**Liraglutide (Victoza) SQ Daily**

**Lixisenatide (Adlyxin) SQ Daily**

**Exenatide QW (Bydureon) SQ Weekly**

**Dulaglutide (Trulicity) SQ Weekly**

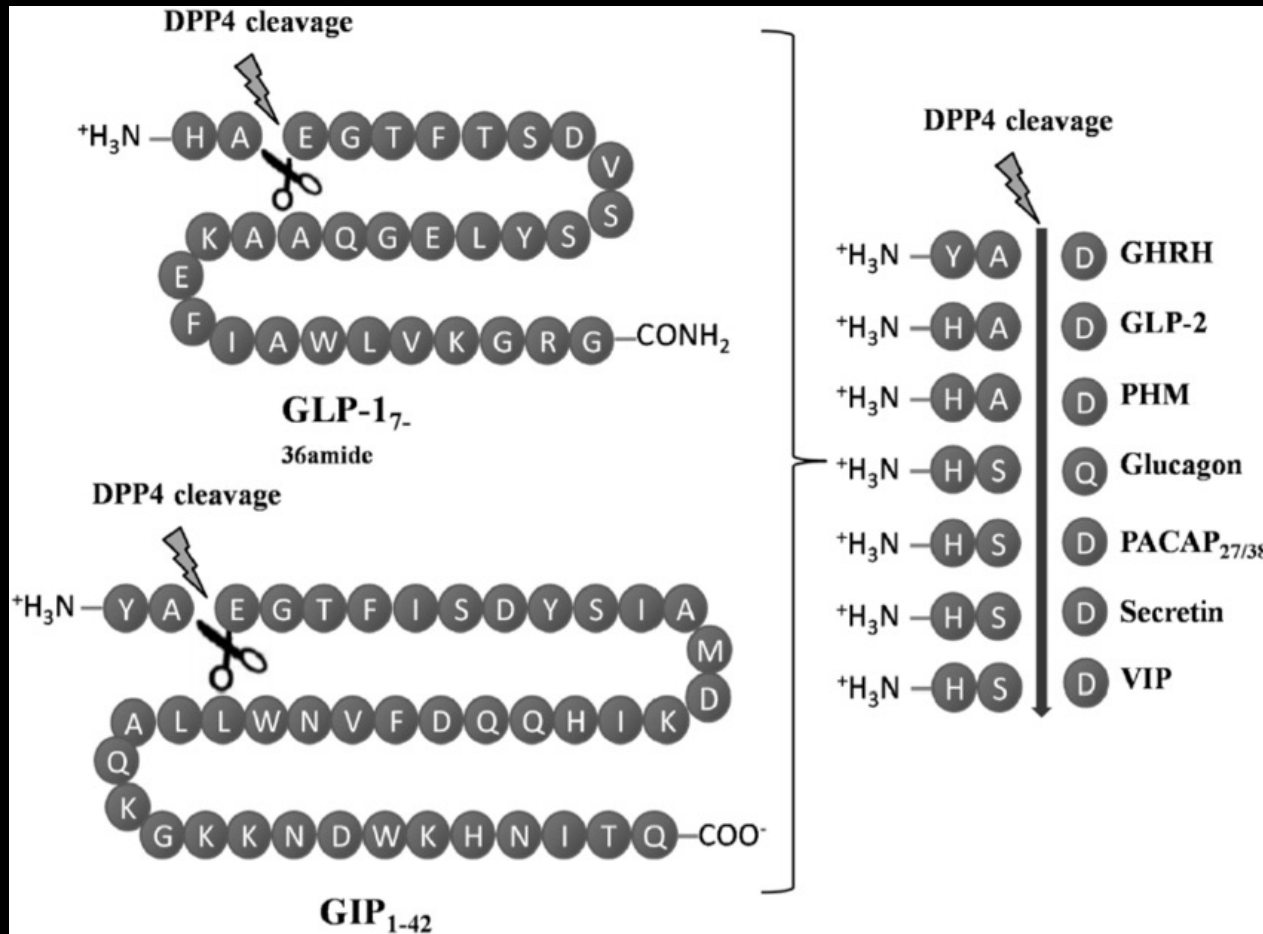
**Semaglutide (Ozempic) SQ Weekly**

**Semaglutide (Rybelsus) PO Daily**

## **GLP-1 / GIP Receptor Agonist**

**Tirzepatide (Mounjaro) SQ Weekly**

# GLP-1 and GIP



**GLP-1: Glucagon Like Peptide 1**

**GIP: Glucose Dependent Insulinotropic Peptide**

# GLP-1 and GIP Receptors

**GLP-1**



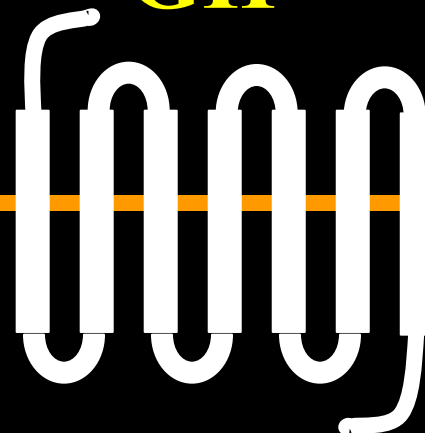
**↑ Insulin**

**↓ Glucagon**

**↓ Appetite**

**↓ Gastric Emptying**

**GIP**



**↑ Insulin**

**↓ Glucagon**

**↓ Appetite**

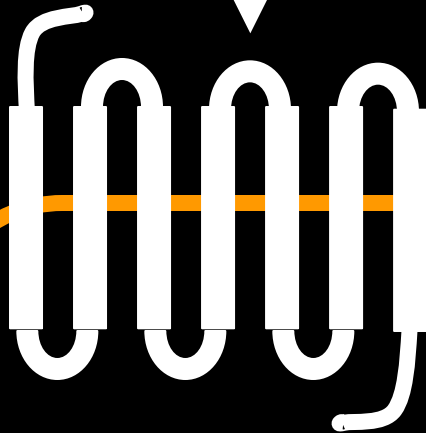
**↓ Gastric Emptying**

# GLP-1 Receptor Agonist

**GLP-1 RA**



**GLP-1  
Receptor**



**↑ Insulin**

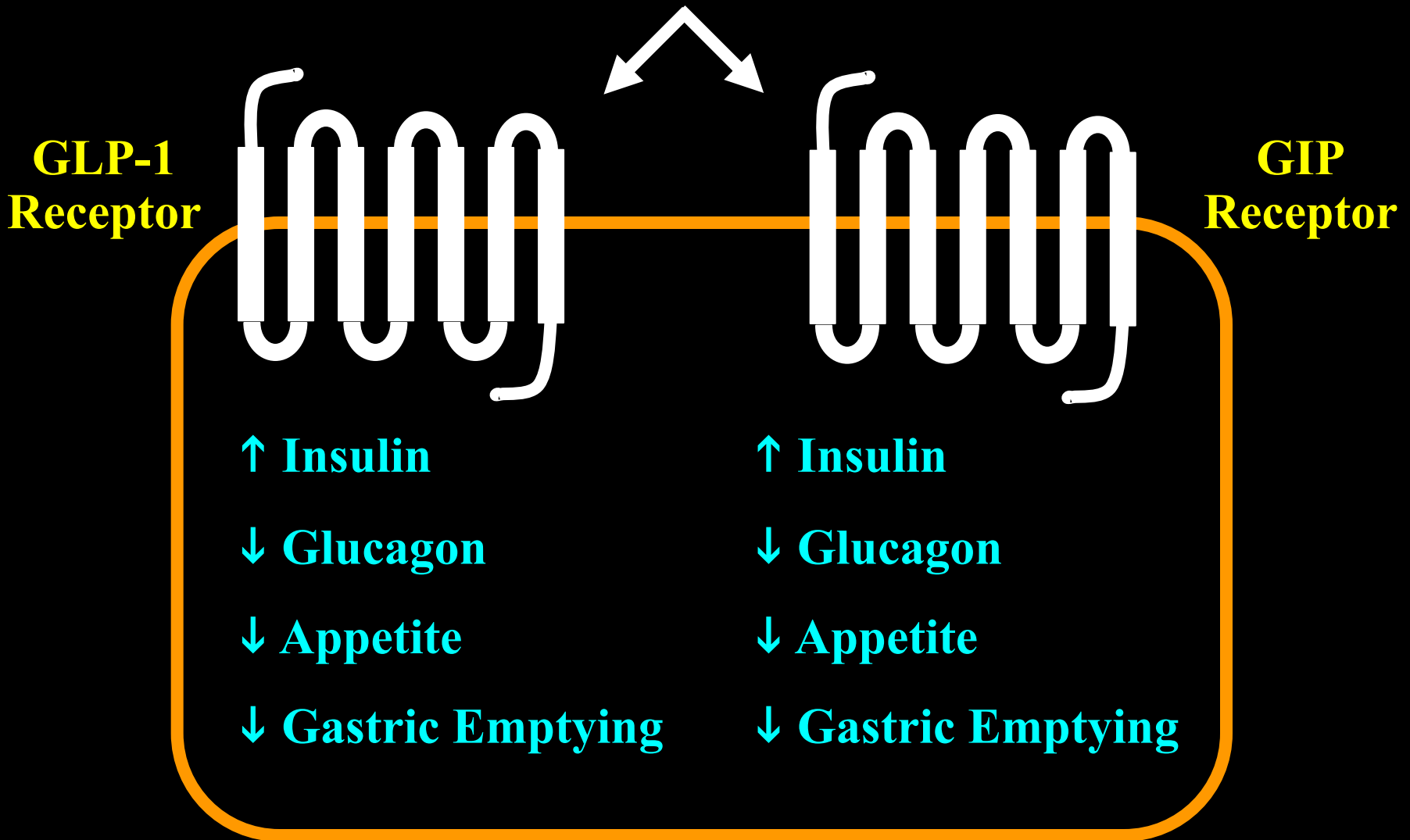
**↓ Glucagon**

**↓ Appetite**

**↓ Gastric Emptying**

# GLP-1 and GIP Receptor Agonist

## Tirzepatide





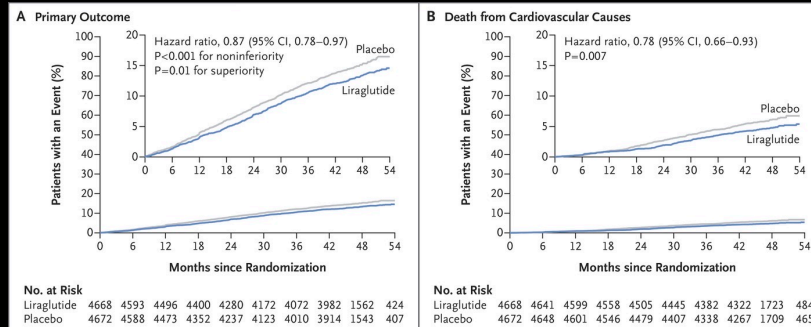
# Liraglutide: LEADER

## Cardiovascular Death, Nonfatal MI, Nonfatal Stroke

### RCT (9340 DM2 Patients): Liraglutide or Placebo x 4.5 years

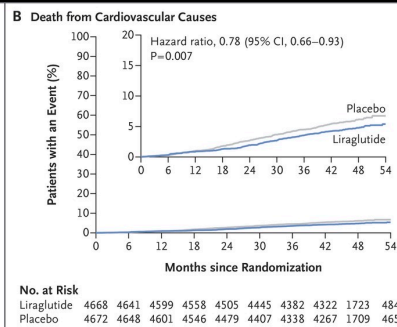
#### Primary Outcome

**HR: 0.87**  
**CI: 0.78-0.97**  
**P = 0.01**



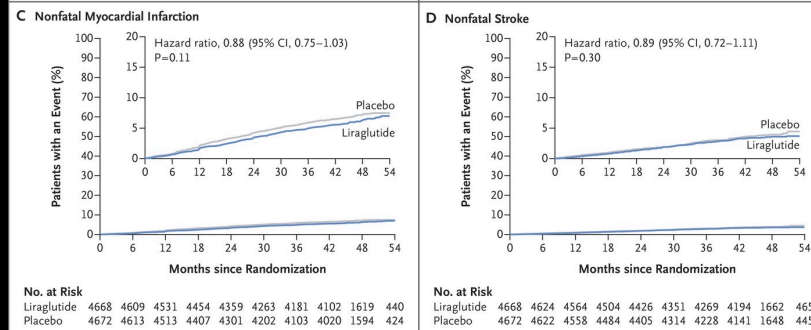
#### CV Mortality

**HR: 0.78**  
**CI: 0.66-0.93**  
**P = 0.007**



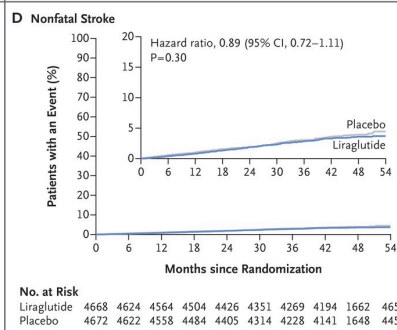
#### Nonfatal MI

**HR: 0.88**  
**CI: 0.75-1.03**  
**P = 0.11**



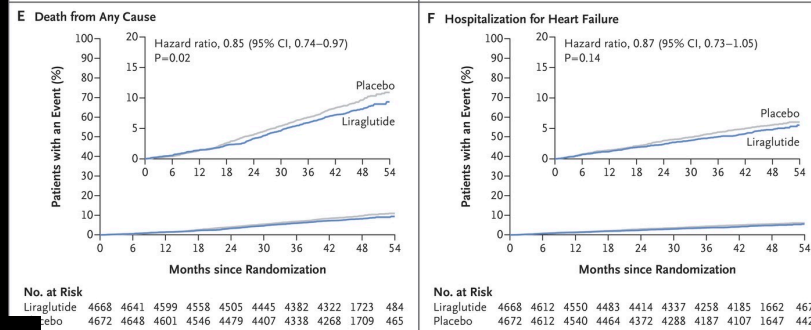
#### Nonfatal Stroke

**HR: 0.89**  
**CI: 0.72-1.11**  
**P = 0.30**



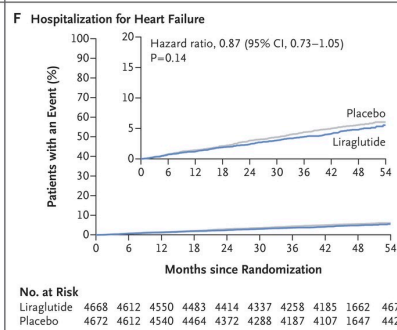
#### All Cause Mortality

**HR: 0.85**  
**CI: 0.74-0.97**  
**P = 0.02**



#### Heart Failure Hospitalization

**HR: 0.87**  
**CI: 0.73-1.05**  
**P = 0.14**

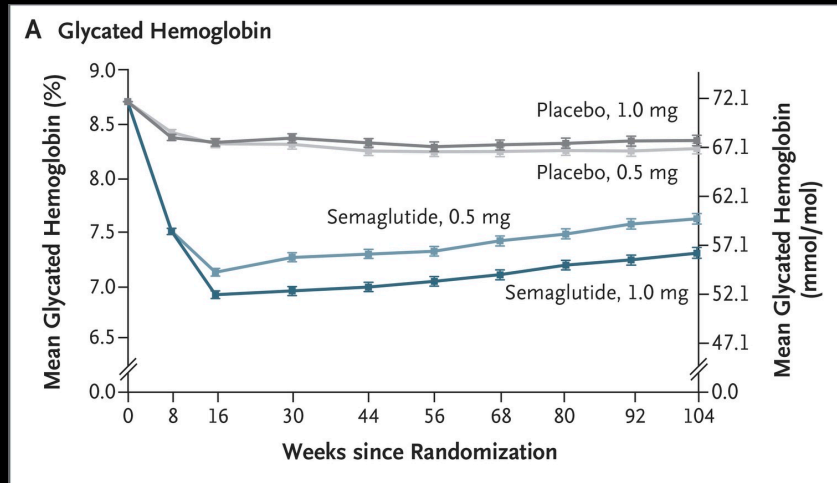


# Semaglutide: Sustain-6

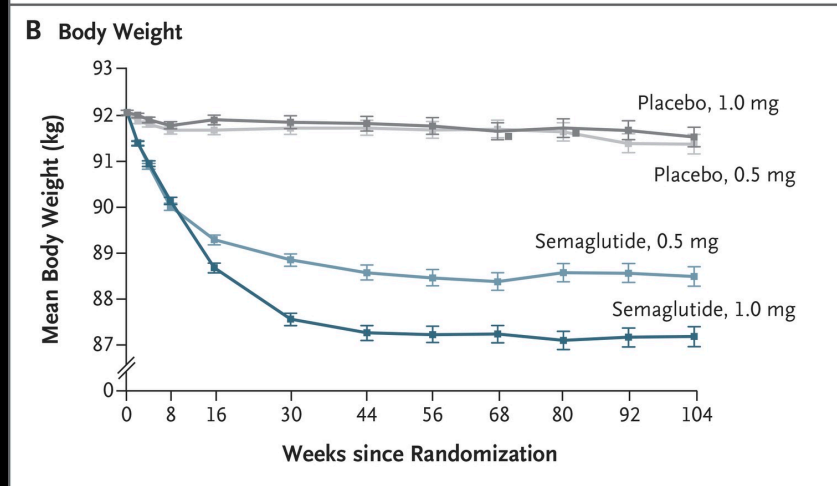
## Cardiovascular Death, Nonfatal MI, Nonfatal Stroke

RCT (3297 DM2 Patients – High CV Risk): Semaglutide or Placebo x 2.1 years

**A1C**



**Body Weight**





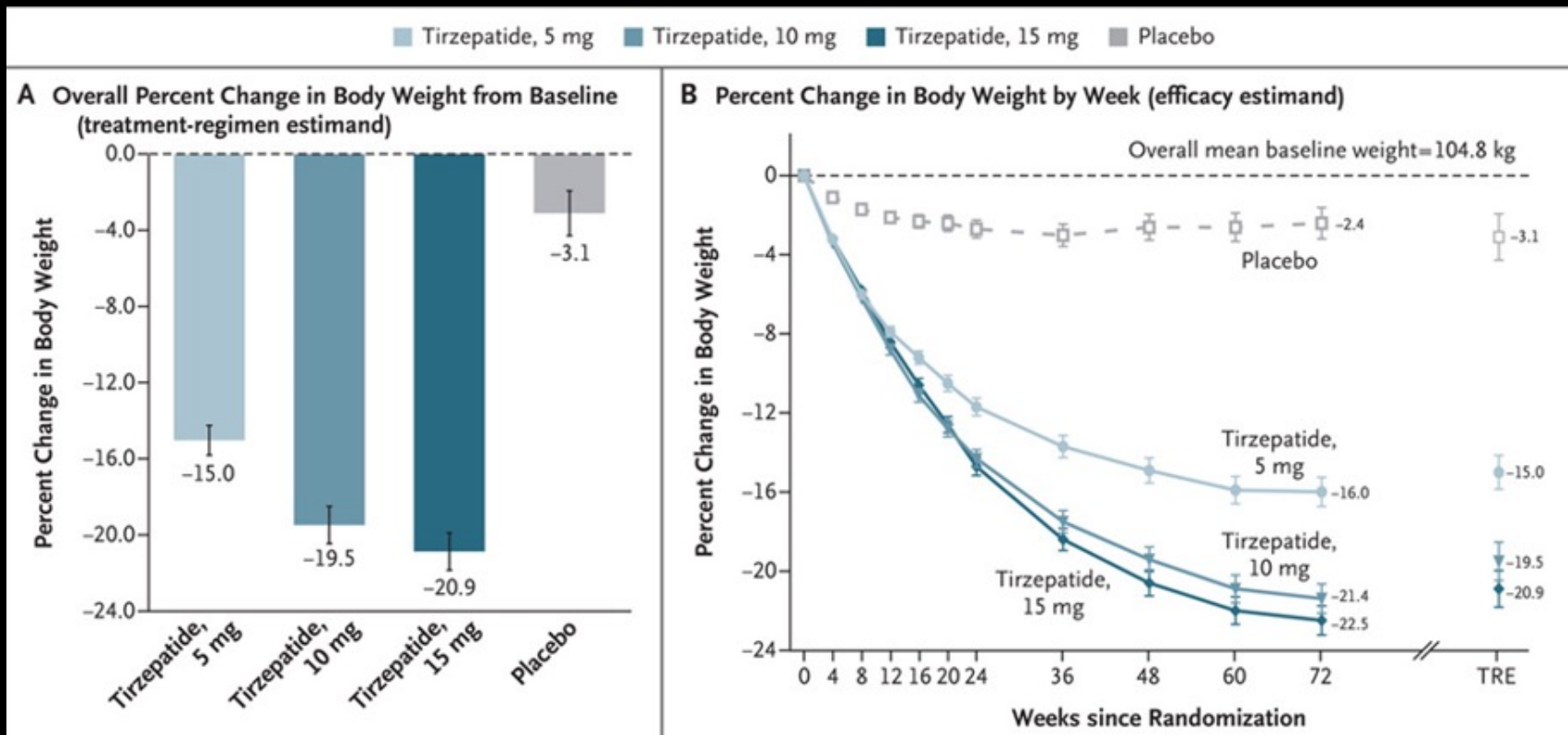
# GLP-1/GIP Receptor Agonist

**2539 Obese Adults (BMI > 30 or > 27 + Co-morbidity)**

**Tirzepatide vs Placebo x 72 weeks**

**Body Weight  
% ↓ c/w Baseline**

**Body Weight  
% ↓ by Week**

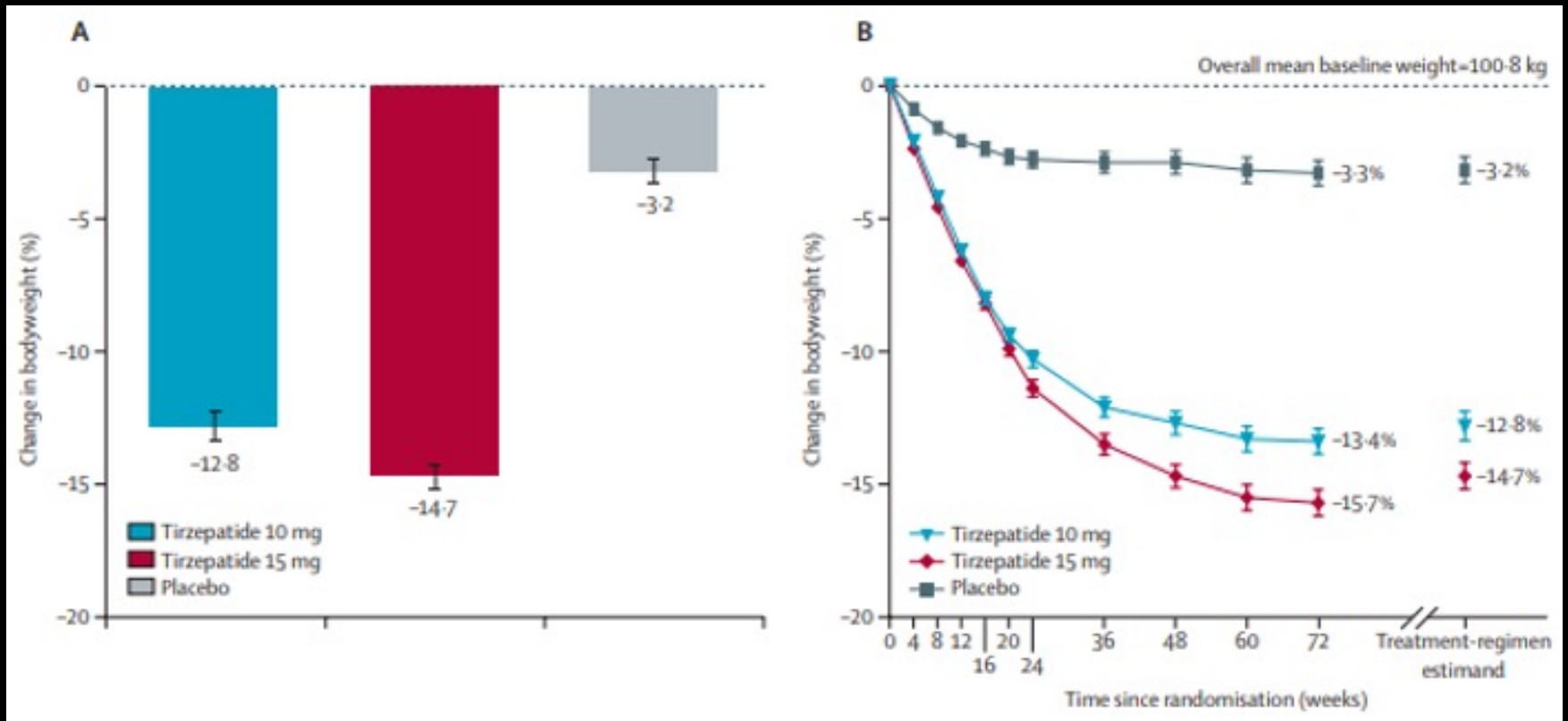


# GLP-1/GIP Receptor Agonist

**938 DM2 Adults (BMI > 27): Tirzepatide vs Placebo x 72 weeks**

**Body Weight  
% ↓ c/w Baseline**

**Body Weight  
% ↓ by Week**

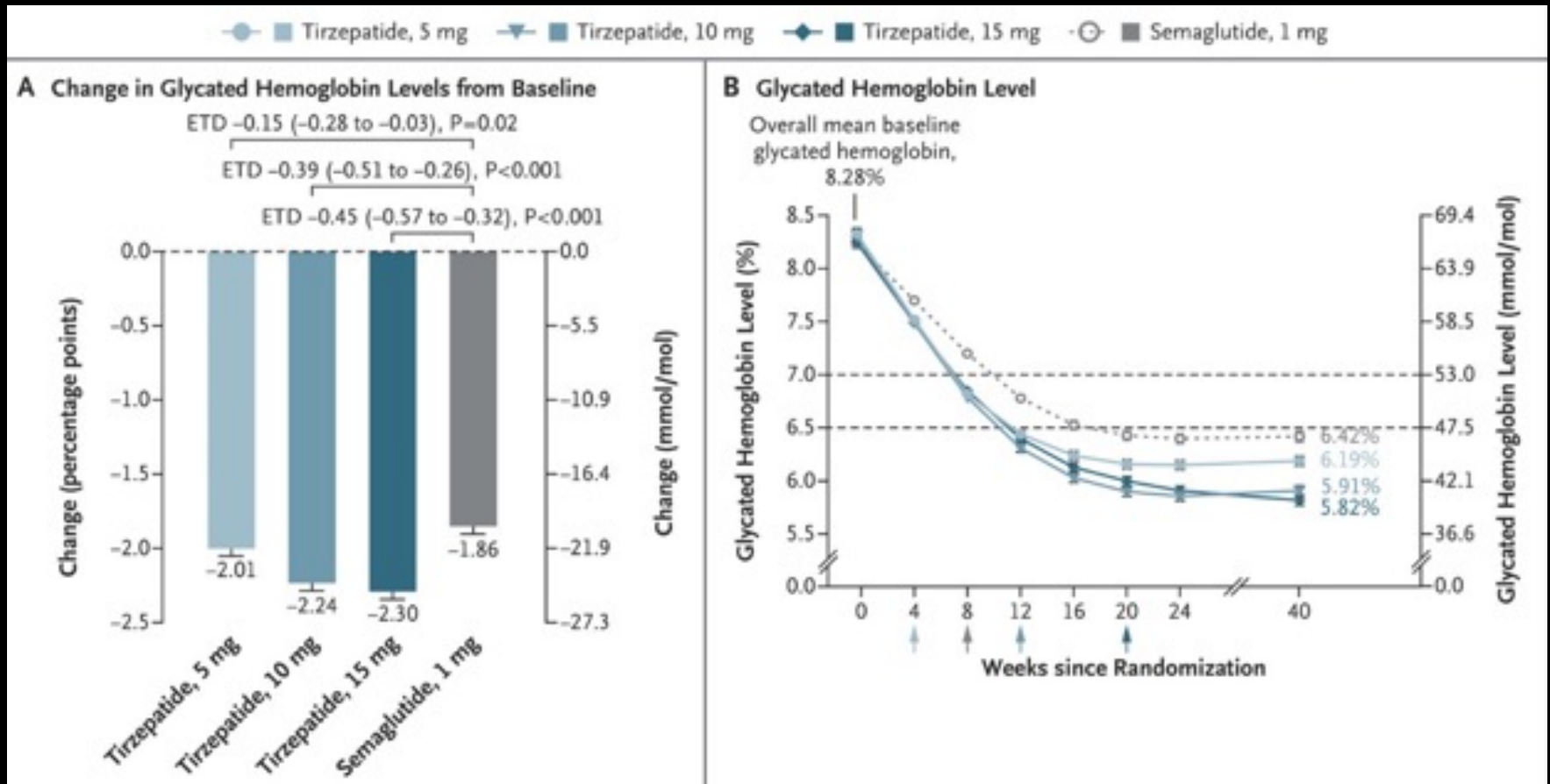


# GLP-1/GIP Receptor Agonist

**1879 DM2 Adults: Tirzepatide vs Semaglutide x 40 weeks**

**A1C % ↓ c/w Baseline**

**A1C % ↓ by Week**

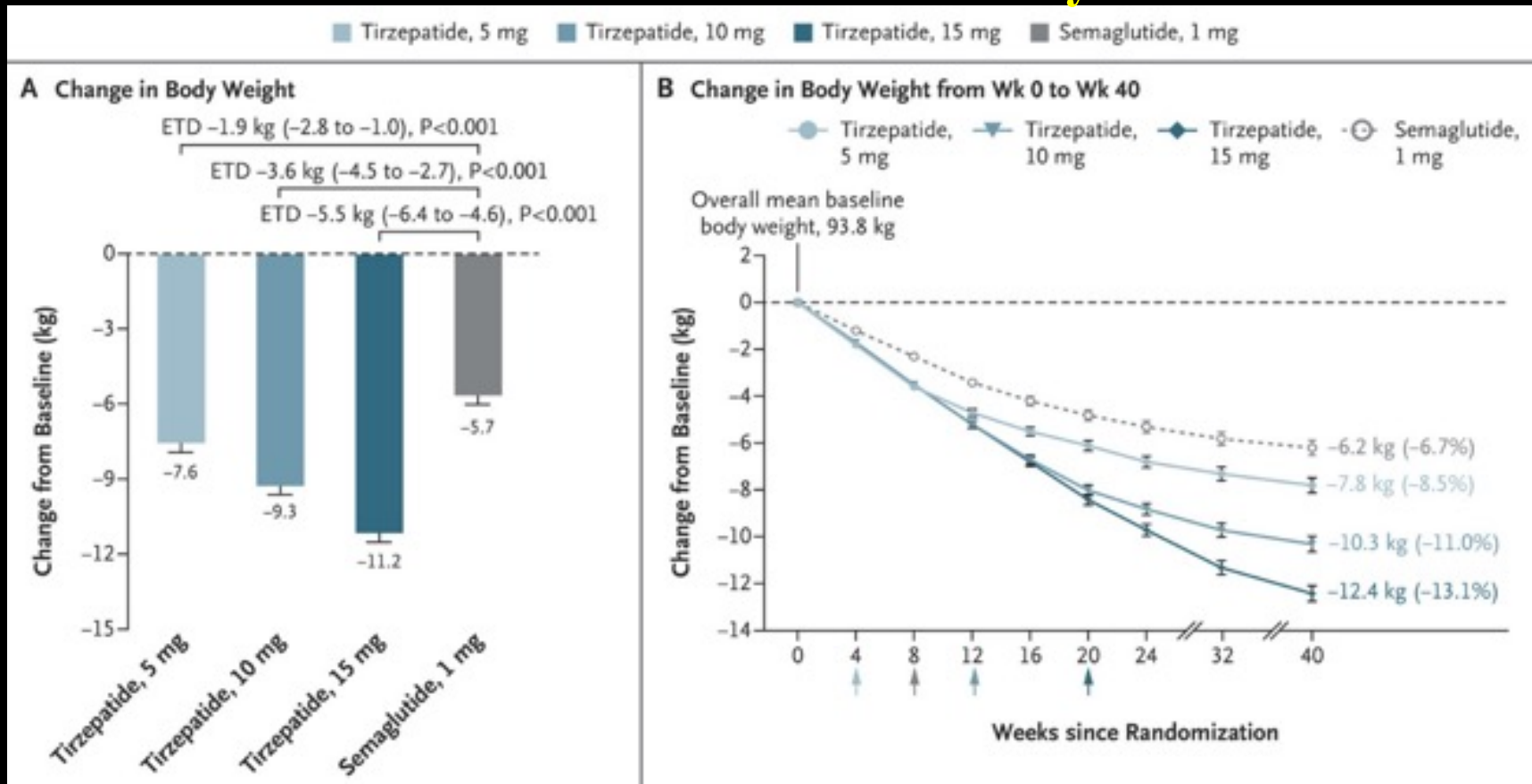


# GLP-1/GIP Receptor Agonist

1879 DM2 Adults: Tirzepatide vs Semaglutide x 40 weeks

Body Weight  
% ↓ c/w Baseline

Body Weight  
% ↓ by Week



# GLP-1 Receptor Agonist **Benefits**

- **Glucose Lowering (1.0-1.5% ↓ A1C)**
- **Cardiovascular Benefit**
- **Stroke Benefit**
- **Renal Benefit**
- **NAFL Benefit**
- **Weight Loss (10-15 lb)**



# GLP-1/GIP Receptor Agonist **Benefits**

- **Glucose Lowering (2.0-2.8% ↓ A1C)**
- **Weight Loss (20-50 lb)**
- **Under Investigation**
  - **Cardiovascular Benefit**
  - **Stroke Benefit**
  - **Renal Benefit**
  - **NAFL Benefit**

# GLP-1/GIP Receptor Agonist **Risks**

- **Medullary Thyroid Cancer**
- **Retinopathy Worsening**
- **Acute Pancreatitis**
- **Gall Bladder / Biliary Disease**
- **Gastroparesis**

# GLP-1/GIP Receptor Agonist Medullary Thyroid Cancer

- **Medullary Thyroid Cancer Risk (Black Box\*)**
- **Differentiated Thyroid Cancer - Uncertain**

\* Contraindicated in people with personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)

# GLP-1/GIP Receptor Agonist **Acute Pancreatitis**

- **Post-marketing case reports: potential link**
- **Retrospective and observational studies: inconsistent**
- **Systematic reviews and meta-analyses: no association**
- **FDA: causal relationship could not be established**
- **Use with caution in people with prior history of pancreatitis, particularly when cause is unknown or persists**

Egan AG. New Engl J Med 2014;370:794-797

Monami M. Diabetes Obes Metab 2017;19:1233-1241

Storgaard H. Diabetes Obes Metab 2017;19:906-908

# GLP-1/GIP Receptor Agonist Retinopathy Worsening

## Meta-Analyses

- **Bethel: GLP-1 RA use not associated with worsening retinopathy (OR 1.10; 95% CI 0.93-1.30)**
  - **Positive association with magnitude of A1C reduction**
- **Yoshida: GLP-1 RA use associated with worsening retinopathy (OR 1.23; 95% CI 1.05-1.44)**

Bethel MA. Diabetes Care 2021; 44:290-96.

Yoshida Y. J Diab Complications 2022; 36(8):108255

# GLP-1/GIP Receptor Agonist Anesthesia

## Prior to Procedure:

**Daily GLP-1 RA:** consider holding GLP-1 RA the day of the procedure.

**Weekly GLP-1 RA:** consider holding GLP-1 RA a week prior to procedure.

If GLP-1 RA are held for longer than the dosing schedule, consider consulting an endocrinologist for bridging the antidiabetic therapy to avoid hyperglycemia.

## Day of Procedure:

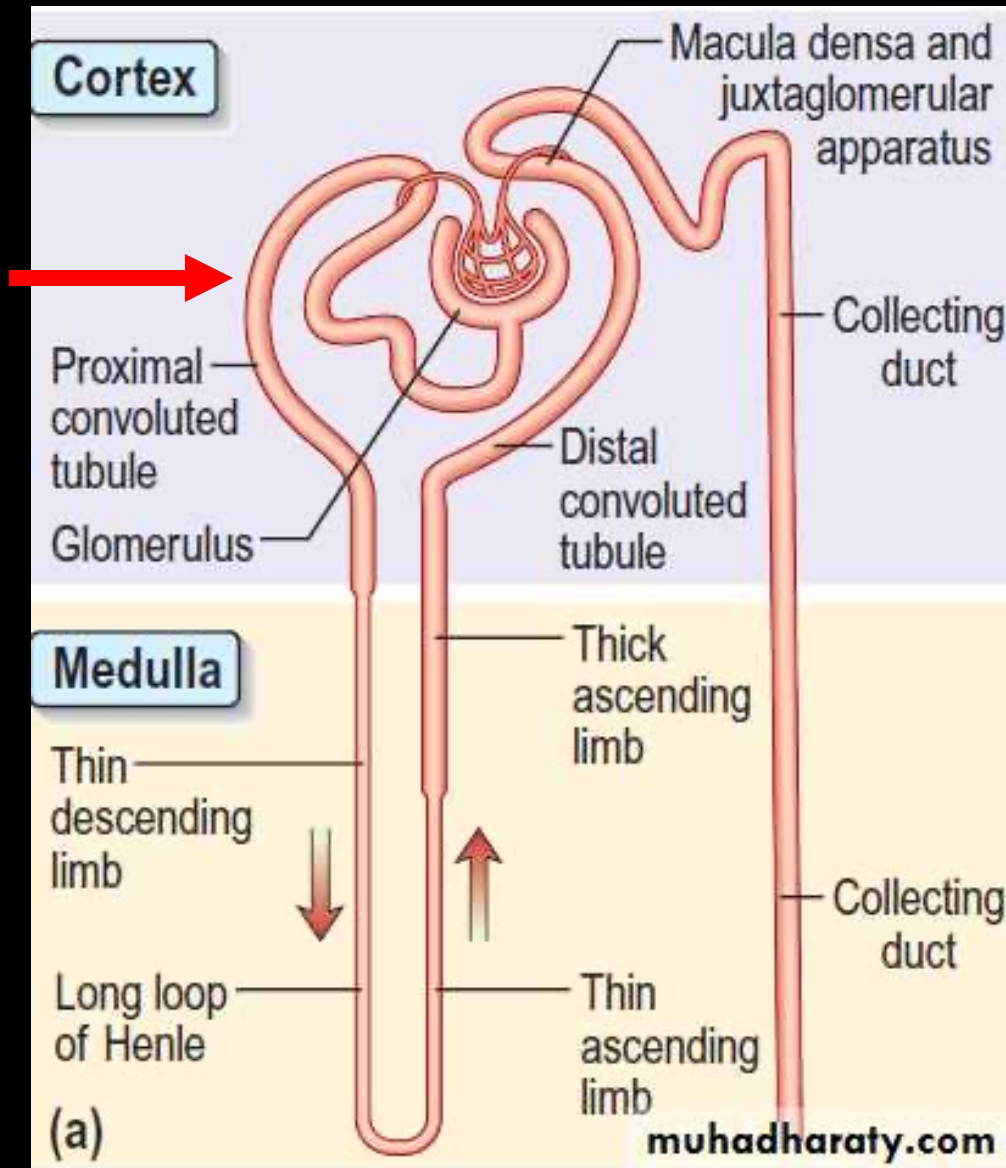
**GI symptoms present (severe nausea/vomiting/retching/bloating/pain):** consider delaying elective procedure and discuss concerns of potential risk of regurgitation and pulmonary aspiration of gastric contents with the proceduralist and patient.

**GI symptoms absent, but GLP-1 RA was not held as advised:** proceed with 'full stomach' precautions or consider evaluating gastric volume by ultrasound. If the stomach is empty, proceed. If the stomach is full or if gastric US inconclusive, consider delaying the procedure or treat the patient as 'full stomach'.

Joshi GP. American Society of Anesthesiologists Consensus Based Guidance on Preoperative Management of Patients on Glucagon-Like Peptide-1 Receptor Agonists

# Sodium Glucose Transporter 2 Inhibitors

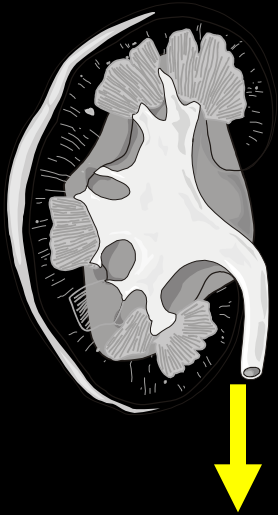
**SGLT2**



# Sodium Glucose Transporter 2 Inhibitors

**Kidneys Filter + Reabsorb Glucose: 180 g/day**  
**SGLT2 (proximal tubules): 90%**

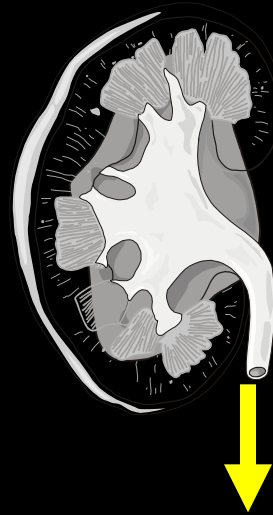
**Normal**



**Glycosuria**

**BG > 180 mg/dl**

**SGLT2 Inhibitor**



**Glycosuria**

**BG > 80 mg/dl**

**Glucose Loss**

**80-100 g/day**

**320-400 kcal/day**

**Blood Glucose ↓**

**Weight Loss**

**No Renal Damage**

**GU Infections / UTI**



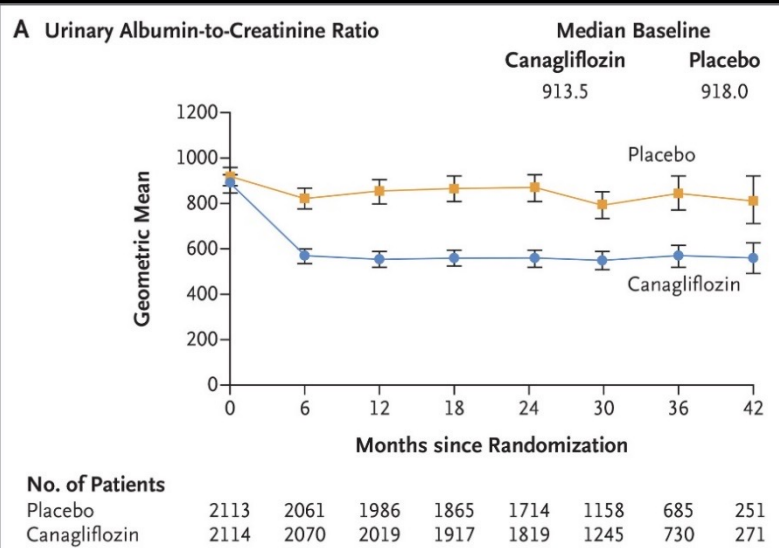
# Sodium Glucose Transporter 2 Inhibitors

<u>Generic</u>	<u>Trade Name</u>	<u>Doses</u>
Canagliflozin	Invokana	100, 300 mg
Dapagliflozin	Farxiga	5, 10 mg
Empagliflozin	Jardiance	10, 25 mg
Ertugliflozin	Steglatro	5, 15 mg
Bexagliflozin	Brenzavvy	20 mg

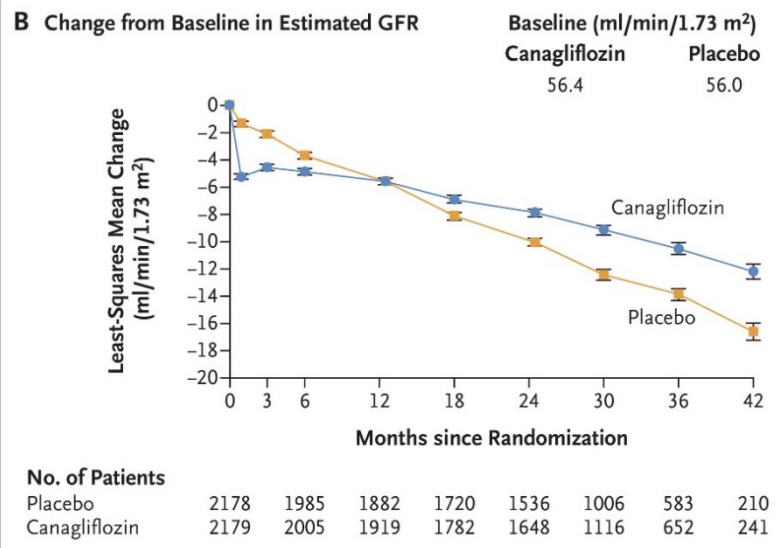
# Canagliflozin - Credence Trial

## Renal Outcomes

**Albumin/Creatinine Ratio**

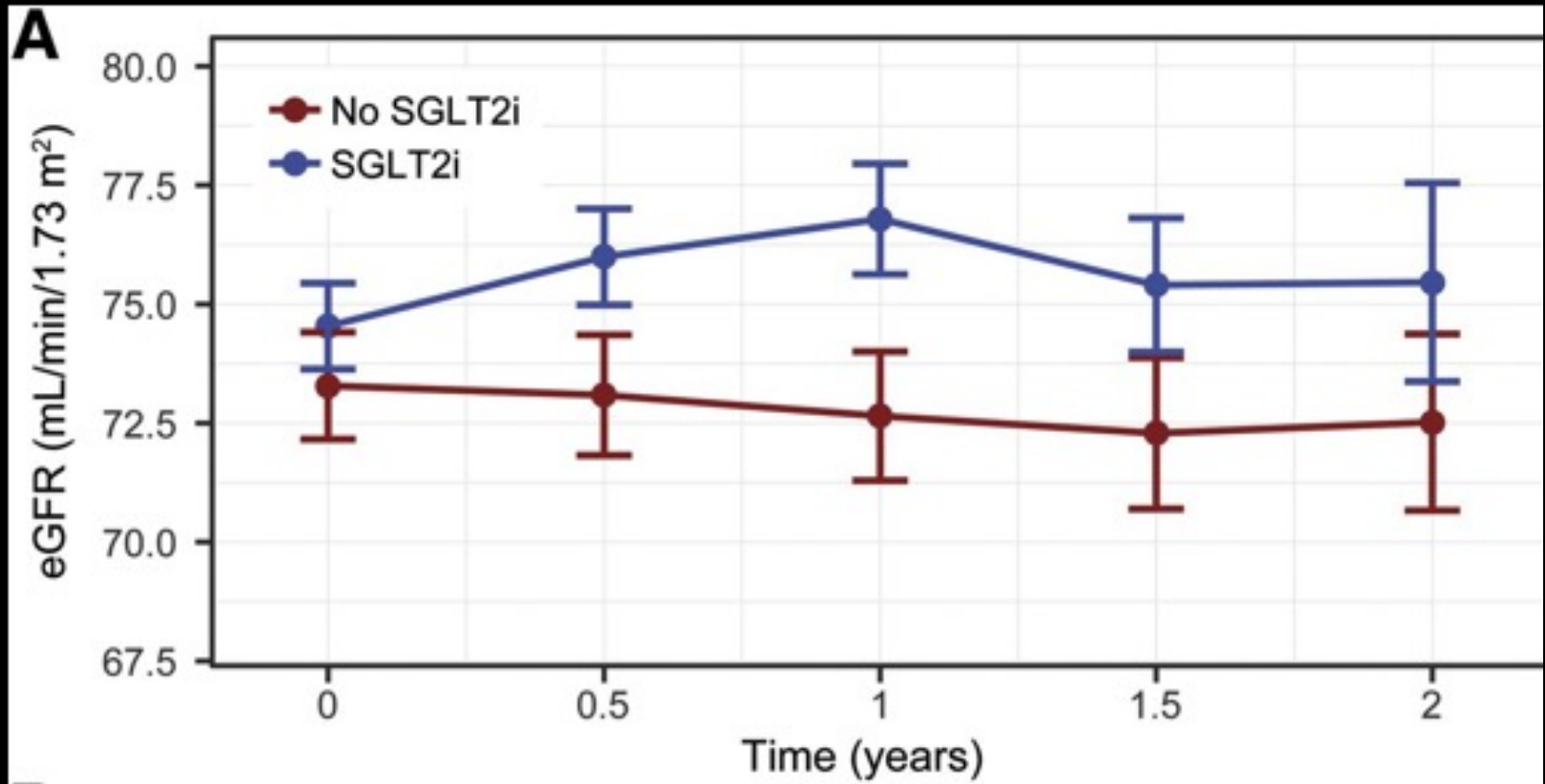


**GFR: Change From Baseline**



# SGLT2 Inhibitors

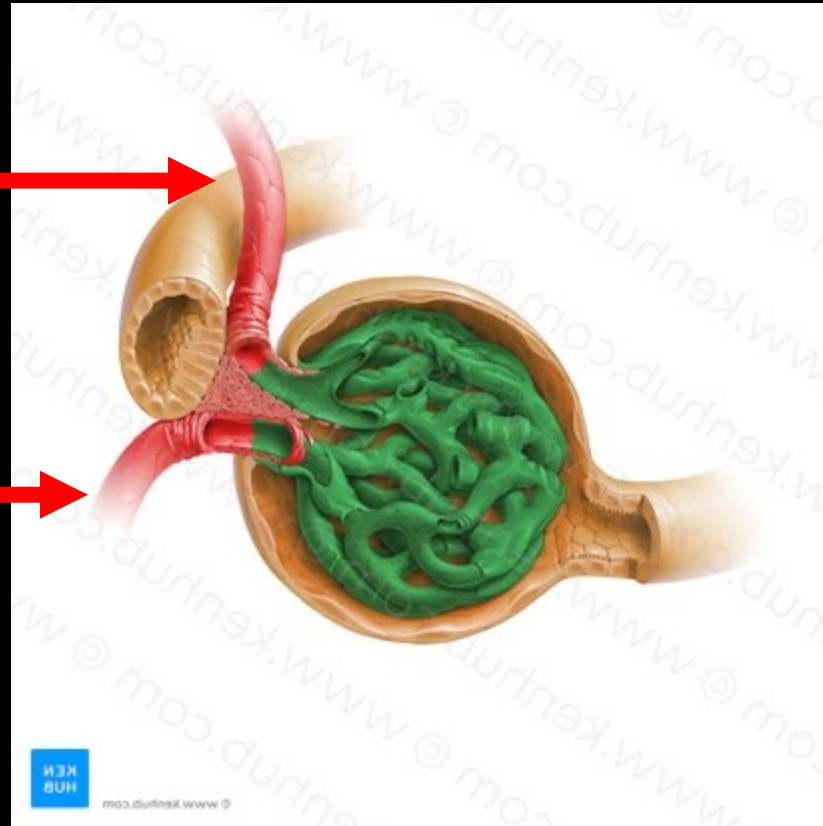
## Renal



# Intraglomerular Pressure Effects of SGLT2-I and ACE/ARB

**Afferent  
Arteriole**

**Efferent  
Arteriole**



**SGLT2-I  
Constrict AA**

**ACE/ARB  
Dilate EA**

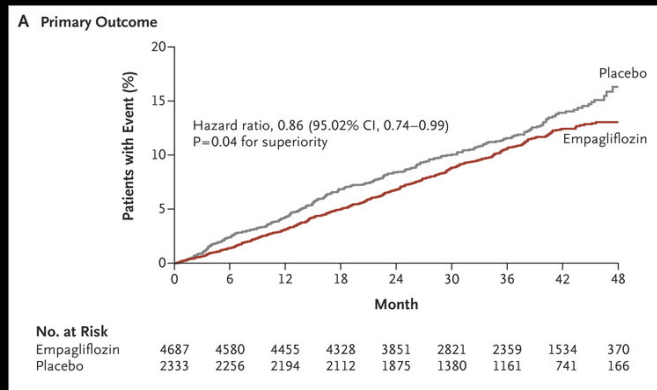
**SGLT2-I and ACE/ARB Reduce Hyperfiltration Synergistically**

# Empagliflozin: EMPA-REG

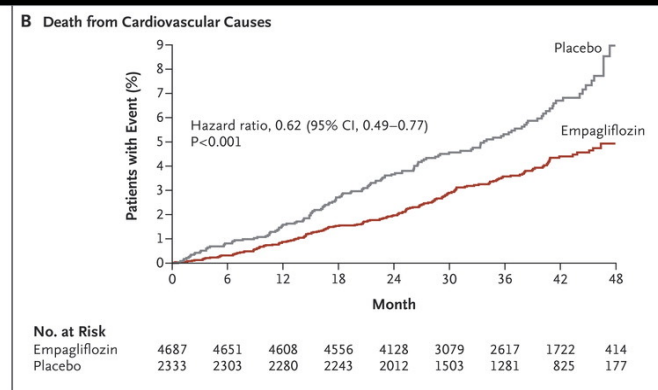
## Cardiovascular Death, Nonfatal MI, Nonfatal Stroke

RCT (7020 DM2 Pts): Empagliflozin 10 mg, 25 mg or Placebo x 3.1 yr

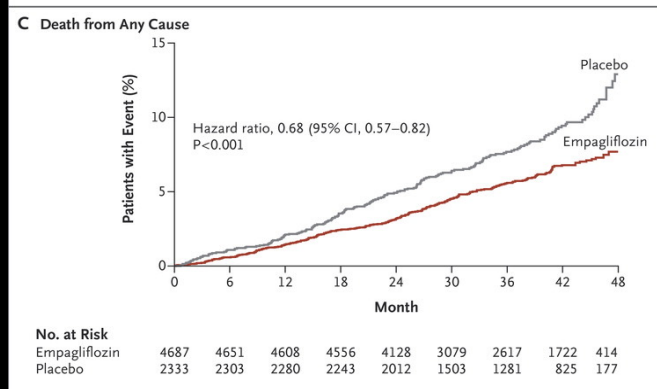
**Primary Outcome**  
**HR 0.86**  
**P = 0.04**



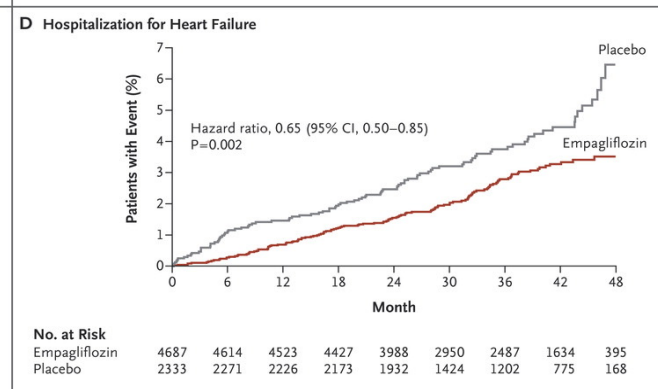
**CV Death**  
**HR 0.62**  
**P < 0.001**



**All Cause Death**  
**HR 0.68**  
**P < 0.001**



**HF Hospitaliz**  
**HR 0.65**  
**P = 0.002**

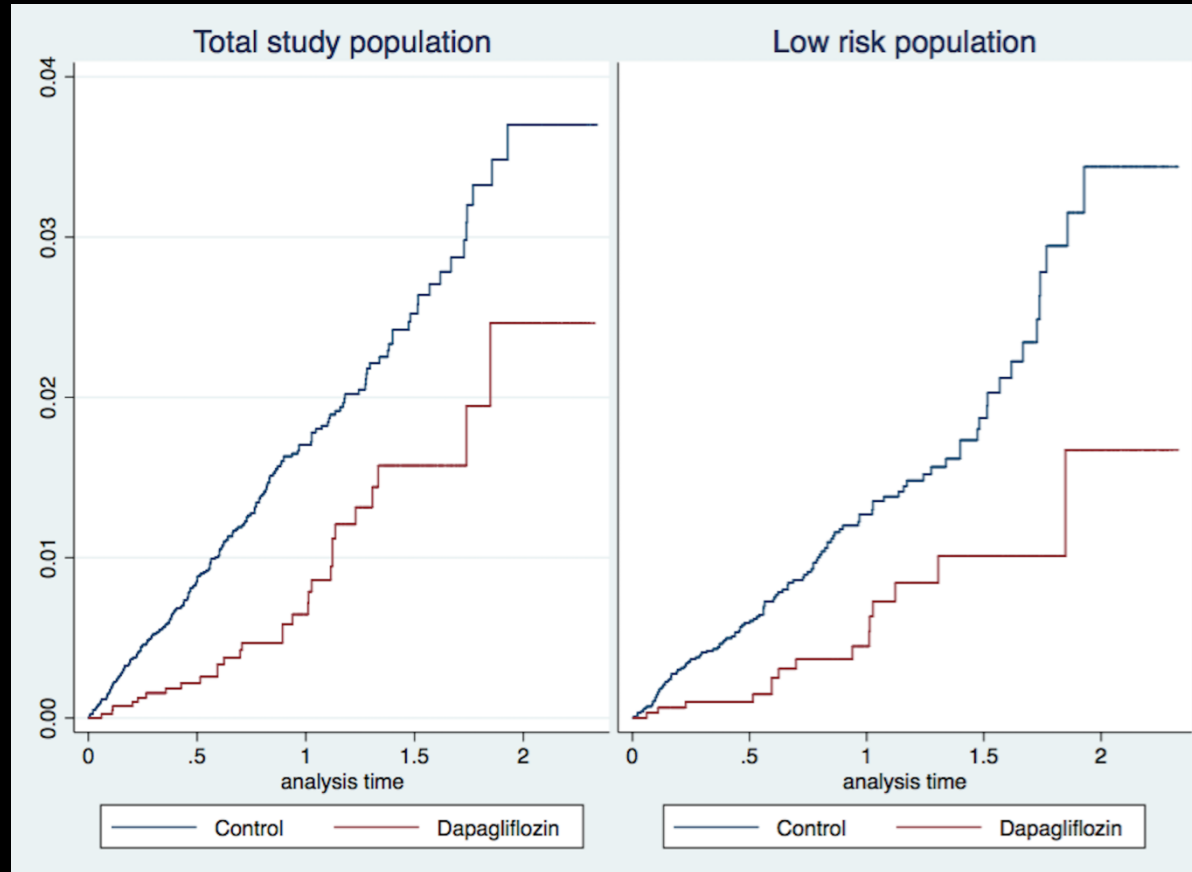


# Dapagliflozin

## All Cause Mortality

Retrospective Cohort (22,124 DM2 Patients): Dapagliflozin in 4,444 Patients

**P = .0001**



**P = .002**

**aIRR: 0.50, CI: 0.33-0.75    aIRR: 0.44, CI: 0.25-0.78**

aIRR=adjusted incidence rate ratio

# Sodium Glucose Transporter 2 Inhibitors

## Benefits

- **Glucose Lowering (0.5-1.0% ↓ A1C)**
- **Cardiovascular Benefit**
- **Heart Failure Benefit**
- **Renal Benefit**
- **NAFL Benefit**
- **Weight Loss (5-10 lb)**

# Sodium Glucose Transporter 2 Inhibitors

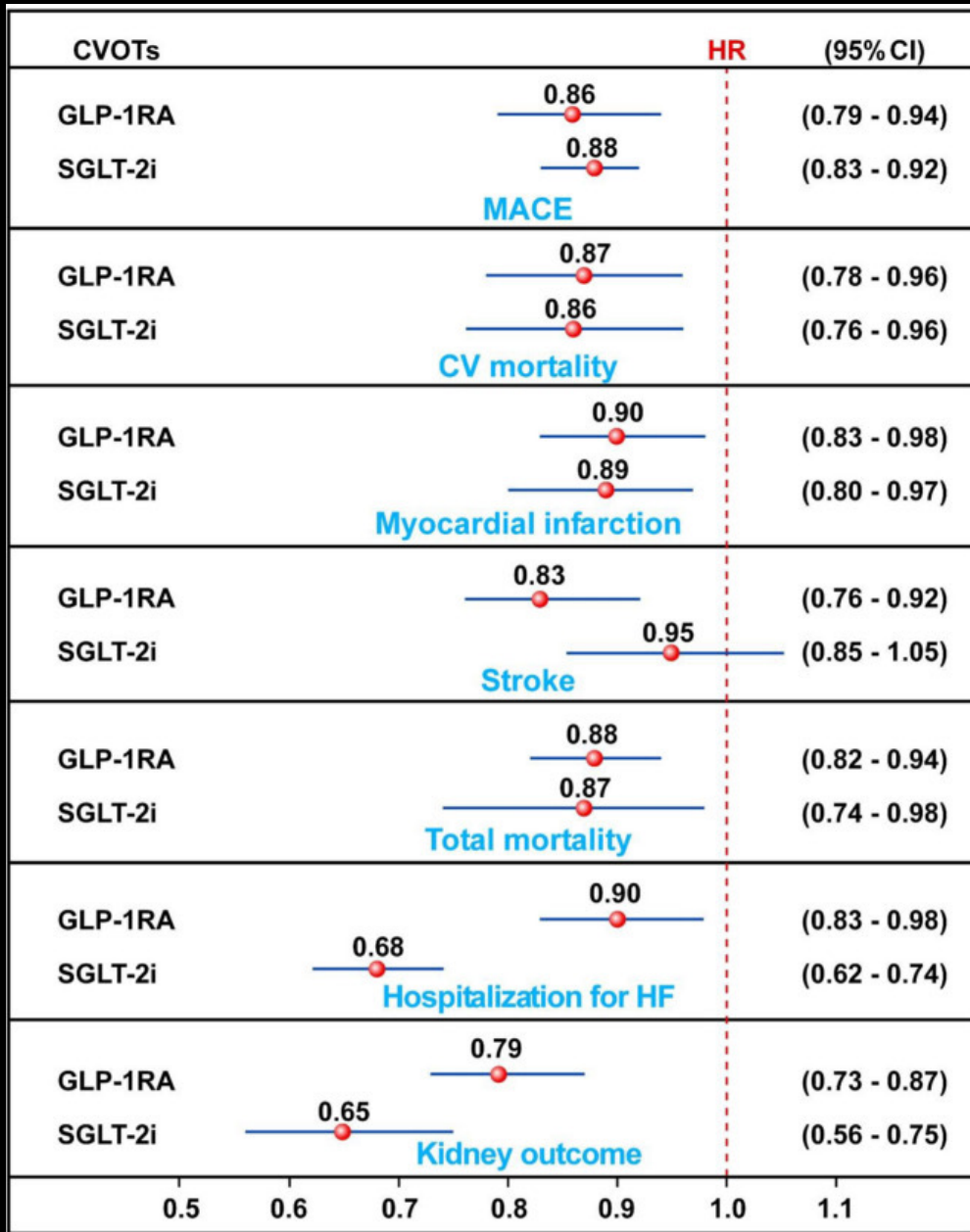
## Risks

- Genitourinary Mycotic Infections
- Urinary Tract Infections
- Euglycemic DKA\*
- Dehydration
- Fournier's Gangrene – Perineum
- Lower Limb Amputations (Canagliflozin)

\* Euglycemic DKA (BG < 200): Occasionally Develops  
**Common Precipitants:** Fasting, NPO, Low Carb Diets



# GLP-1 RA vs SGLT2 Inhibitors



# GLP-1 RA vs SGLT2 Inhibitors

	<b>SGLT2-I</b>	<b>GLP-1 RA</b>	<b>GLP-1/GIP RA</b>
<b>A1C Reduction</b>	<b>0.5-1.0%</b>	<b>1.0-1.5%</b>	<b>2.5-2.8%</b>
<b>Weight Loss</b>	<b>5-10 lb</b>	<b>10-15 lb</b>	<b>20-50 lb</b>
<b>Hypoglycemia</b>	<b>Low Risk</b>	<b>Low Risk</b>	<b>Low Risk</b>
<b>CKD Protection</b>	<b>Benefit</b>	<b>Benefit</b>	<b>Probable</b>
<b>CVD Protection</b>	<b>Benefit</b>	<b>Benefit</b>	<b>Probable</b>
<b>HF Protection</b>	<b>Benefit</b>	<b>Benefit</b>	
<b>Stroke Protection</b>		<b>Benefit</b>	
<b>NAFL/NASH</b>	<b>Benefit</b>	<b>Benefit</b>	

# Personalized Diabetes Care

**Choose Agent with Adequate Potency to Achieve Goal**

**↓ A1C > 2%**

**Insulins  
GLP-1 RA  
GLP-1/GIP RA**

**Usually With  
Metformin**

**↓ A1C > 1-2%**

**Metformin  
Pioglitazone  
Sulfonylureas  
GLP-1 RA  
GLP-1/GIP RA  
Insulins**

**↓ A1C > 0.5-1%**

**SGLT-2 Inhibitors  
DPP4 Inhibitors**

# Personalized Diabetes Care

**Choose Agent with Proven Benefits for Co-Morbidities**

**CKD**

**GLP-1 RA  
SGLT-2 Inhibitors**

**CVD**

**GLP-1 RA  
SGLT-2 Inhibitors**

**HF**

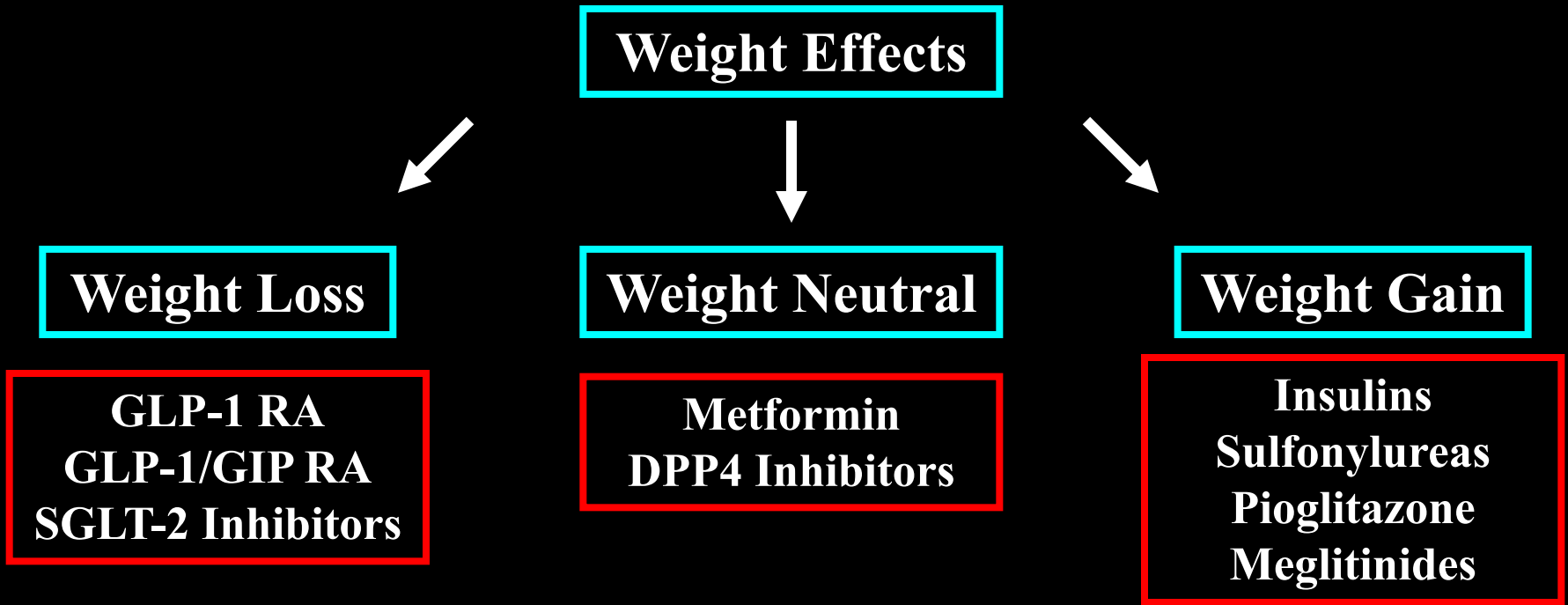
**SGLT-2 Inhibitors  
GLP-1 RA?**

**NAFL/NASH**

**Pioglitazone  
GLP-1 RA**

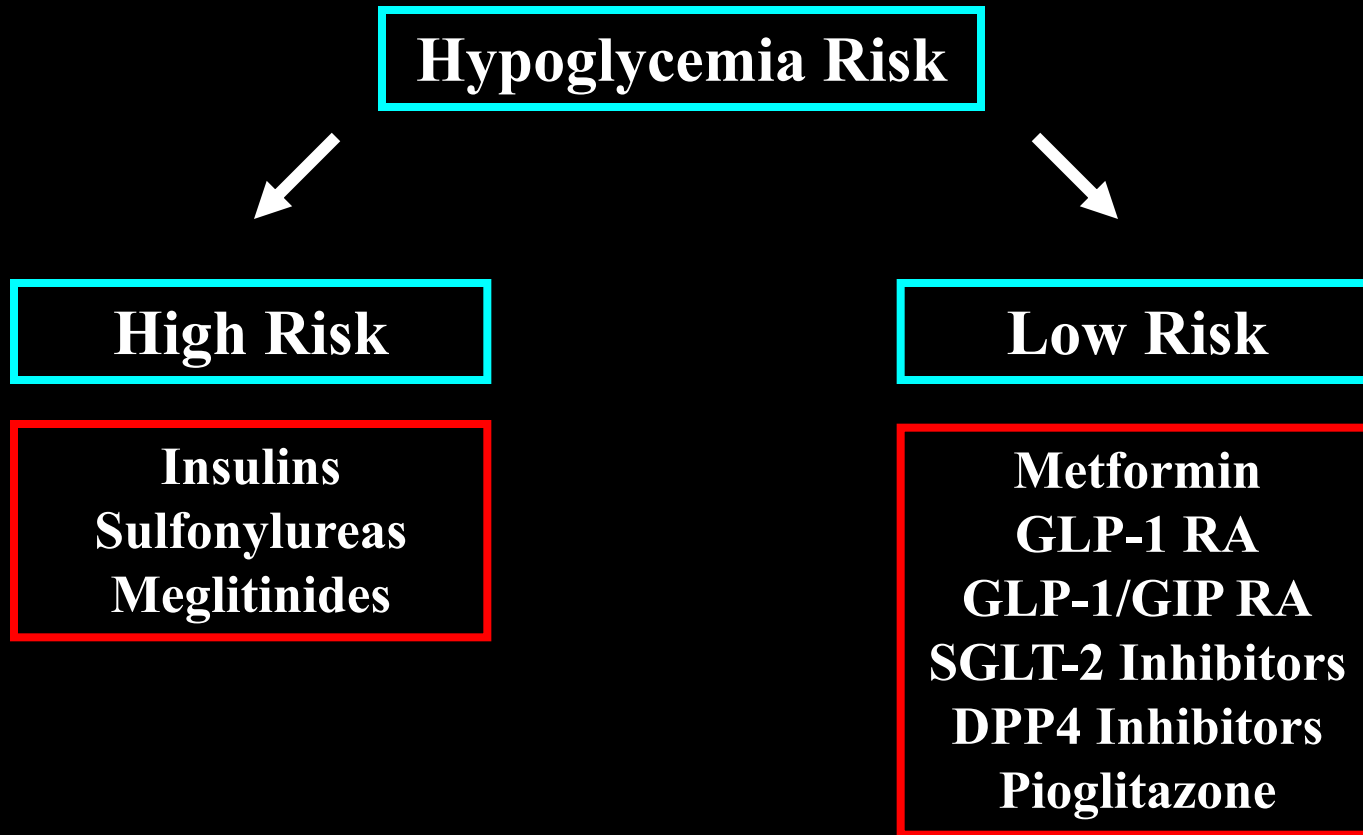
# Personalized Diabetes Care

Promote Weight Loss or Minimize Weight Gain



# Personalized Diabetes Care

## Minimize Hypoglycemia



# Personalized Diabetes Care

## Minimize Cost

**High Cost**

**GLP-1 RA  
GLP-1/GIP RA  
SGLT-2 Inhibitors  
DPP4 Inhibitors  
Insulin Analogs**

**Low Cost**

**Metformin  
Sulfonylureas  
Pioglitazone  
Human Insulins  
(NPH, Regular)**

# Thank You

