



Sun H. Kim MD MS
April 9, 2026

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Objective

- 1. Explain the pathophysiology of excess adiposity, cardiometabolic dysfunction, and cardiovascular risk in patients with and without diabetes
- 2. Explore current and future trends in cardiometabolic pharmacologic management
- 3. Review pharmacologic mechanism of action of guideline-directed therapies including GLP-1 receptor agonists, SGLT2 inhibitors
- 4. Discuss care models that bridge cardiology, endocrinology, nutrition, and behavioral health to address obesity as a chronic disease

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Comprehensive
Care

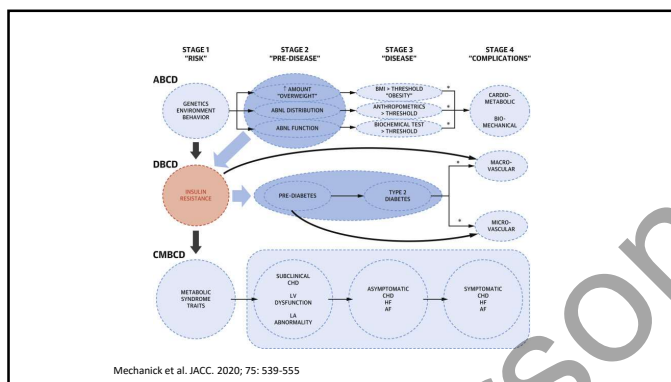
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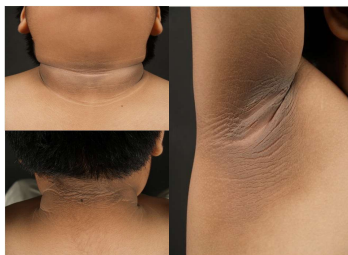
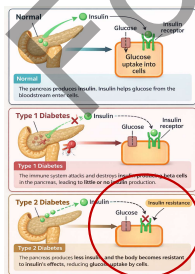
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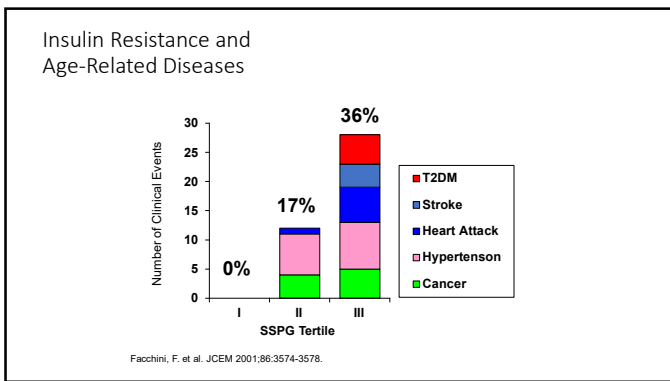


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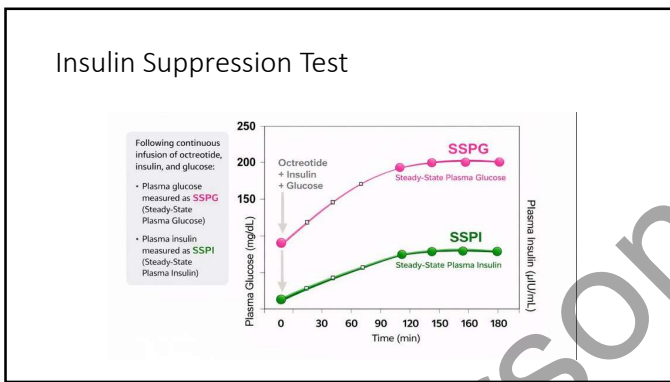
Insulin Resistance



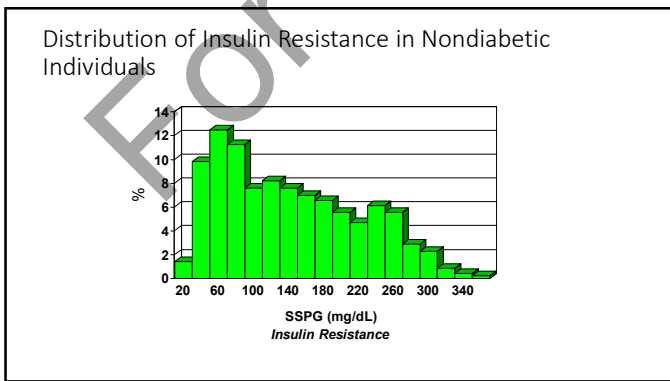
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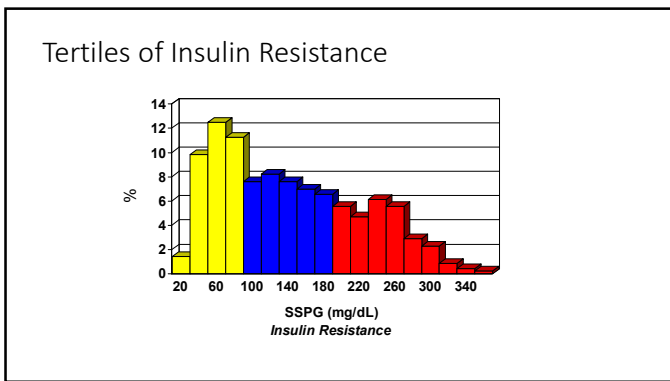
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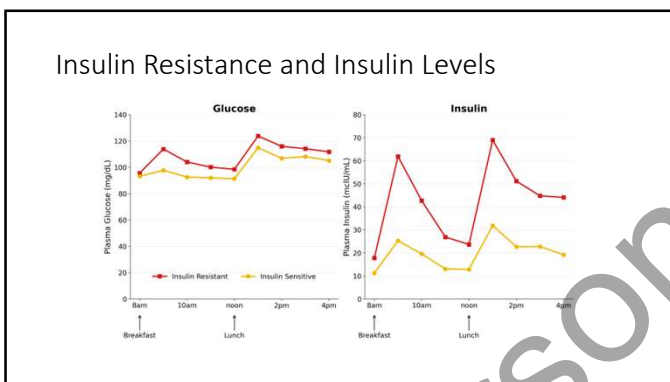
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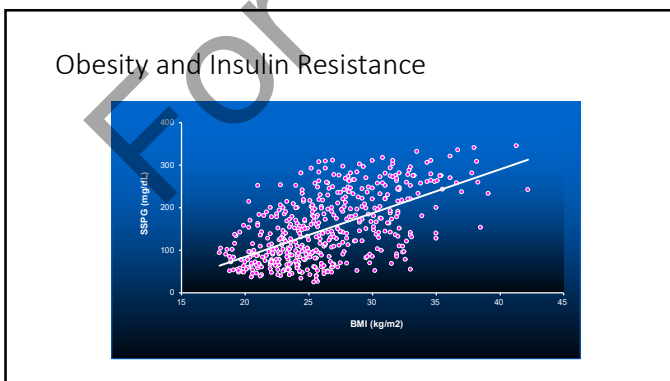
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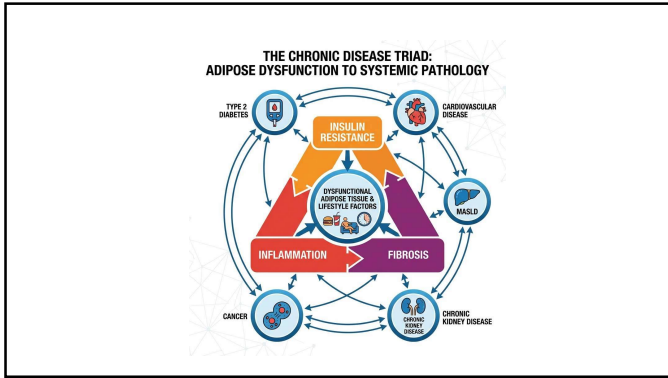
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Obesity

Definition:
condition characterized by the **excessive** accumulation and storage of **fat** in the body

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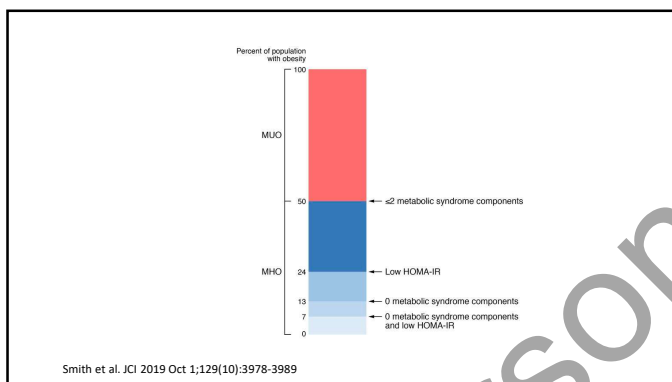
How should obesity be measured?

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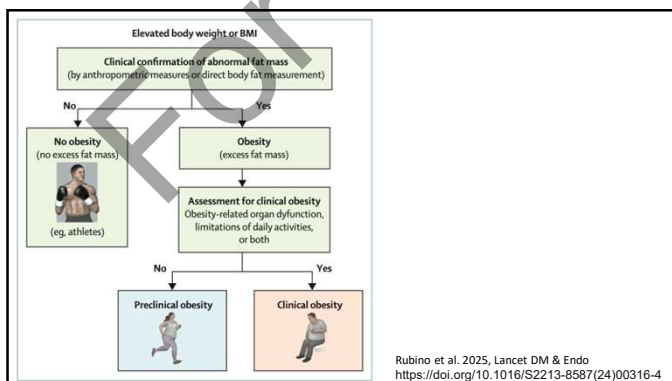
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Is obesity sufficient?

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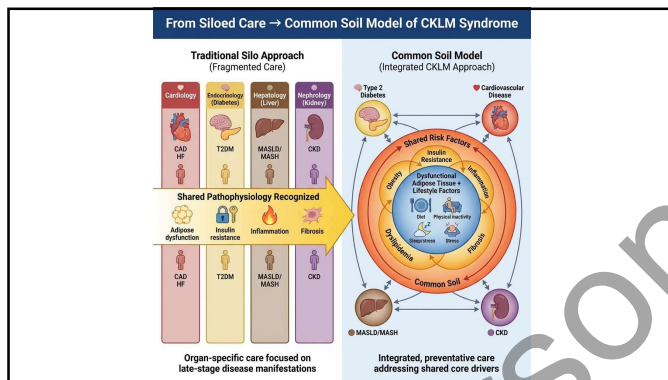


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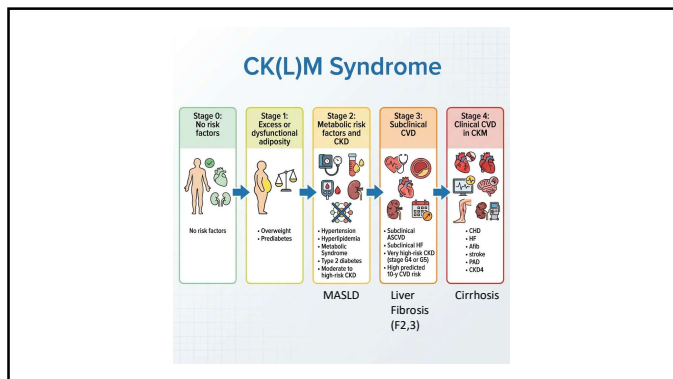


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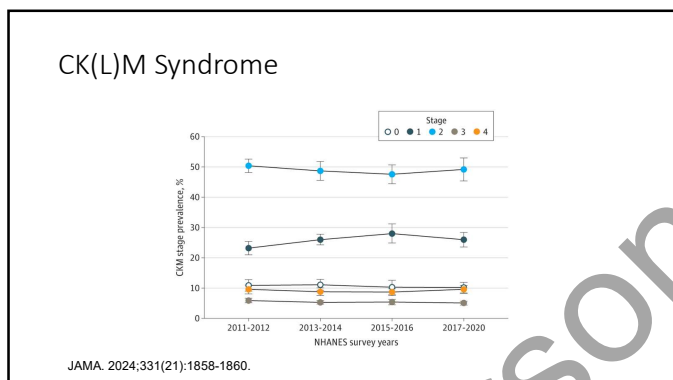
CKM Syndrome



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- ### PRINCIPLES OF THE AACE ALGORITHM FOR MANAGEMENT OF ADULTS WITH TYPE 2 DIABETES
1. Lifestyle modification is the foundation for all therapy.
 2. Use a comprehensive approach for weight loss to achieve clinical goals.
 3. Choice of pharmacologic therapy is guided by glycemic targets and comorbidities (overweight/obesity, ASCVD, CHF, CKD, MASLD, OSA).
 4. Choice of therapy considers ease of use and access.
 5. Individualize glycemic targets (A1C, GMI, TIR, FBG, PPG).
 6. Optimal A1C (or GMI) is $\leq 6.5\%$ (48 mmol/mol) or as close to normal as is safe and achievable.
 7. Avoid therapeutic inertia and get to goal as soon as possible (adjust ≤ 3 months).
 8. Avoid hypoglycemia.
 9. CGM is highly recommended to reach glycemic goals in adults with diabetes.
 10. Comorbidities and complications must be managed for comprehensive care.

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PROFILES OF PHARMACOTHERAPY FOR TYPE 2 DIABETES										
	METFORMIN	GLP-1RA	DPP-4I	SGLT2I	TZD	INS	INS	INS	INS	INS
INDICATION FOR GLUCOSE LOWERING*	++	+++	+++	+++	++	++	++	++	++	++
MACE		Benefit ¹	Benefit ²	Benefit ³	Benefit ⁴					
ASCVD		Benefit ⁵	Benefit ⁶	Benefit ⁷	Benefit ⁸					
STROKE		Benefit ⁹	Benefit ¹⁰	Benefit ¹¹	Benefit ¹²					
CHF*		Potential Benefit ¹³	Potential Benefit ¹⁴	Benefit ¹⁵	Benefit ¹⁶	Contraindicated ¹⁷	Contraindicated ¹⁸	Contraindicated ¹⁹	Contraindicated ²⁰	Contraindicated ²¹
CKD		Benefit ²²	Benefit ²³	Benefit ²⁴	Benefit ²⁵					
RENAL IMPAIRMENT	Caution (avoid in eGFR 30 to 45) ²⁶	Caution (avoid in eGFR 30 to 45) ²⁷	Caution (avoid in eGFR 30 to 45) ²⁸	Caution (avoid in eGFR 30 to 45) ²⁹	Caution (avoid in eGFR 30 to 45) ³⁰	Caution (avoid in eGFR 30 to 45) ³¹	Caution (avoid in eGFR 30 to 45) ³²	Caution (avoid in eGFR 30 to 45) ³³	Caution (avoid in eGFR 30 to 45) ³⁴	Caution (avoid in eGFR 30 to 45) ³⁵
HYPOGLYCEMIA RISK										
WEIGHT	High/Low	Low	Low	Mild/Low	High					
HEPATIC STATUS										
MASH		Potential Benefit ³⁶	Potential Benefit ³⁷	Potential Benefit ³⁸	Potential Benefit ³⁹					
FIBROSIS PROGRESSION		Potential Benefit ⁴⁰	Potential Benefit ⁴¹	Potential Benefit ⁴²	Potential Benefit ⁴³					
FIBROSIS REGRESSION		Potential Benefit ⁴⁴	Potential Benefit ⁴⁵	Potential Benefit ⁴⁶	Potential Benefit ⁴⁷					
GI ADVERSE SYMPTOMS	Mild to Moderate ⁴⁸	Moderate ⁴⁹	Moderate ⁵⁰	Moderate ⁵¹	Moderate ⁵²					
OTHER CONSIDERATIONS										
ADVERSE/COYT	1	2	3	4	5	6	7	8	9	10

■ Benefit¹⁻¹⁵
 ■ Use with caution¹⁶⁻²¹
 ■ Contraindicated²²⁻³⁵
 ■ Neutral, not studied, or insufficient evidence³⁶⁻⁵²

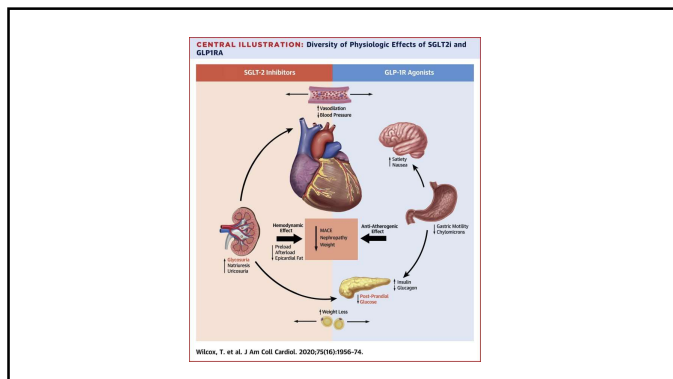
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Current Indications		
	GLP-1	SGLT2i
Type 2 diabetes	Indicated	Indicated
Obesity (BMI ≥ 30kg/m ² or 27 kg/m ² with co-morbidities)	Indicated	
ASCVD	Indicated	Indicated
Stroke	✓	
PAD	✓	
Heart Failure ^{reduced}		Indicated
Heart Failure ^{preserved}	✓	Indicated
CKD	Indicated in DM2	Indicated
MASH	Indicated	
Atrial Fibrillation	✓	✓
Sleep Apnea	Indicated	
Gout, Kidney stones		✓
SIADH		✓

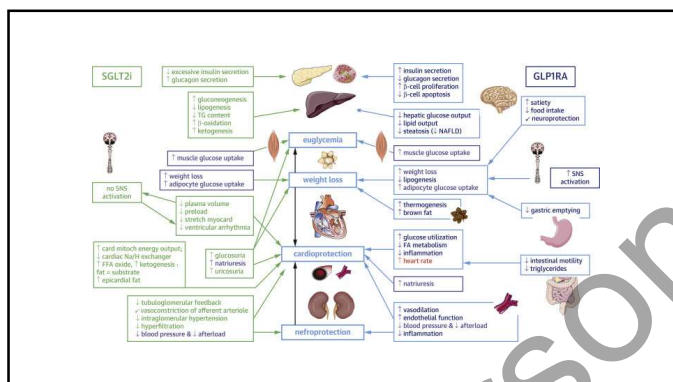
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Weight Loss

<5-10%

- Qsymia (phentermine/topiramate)
- Contrave (bupropione/naltrexone)
- Orlistat
- Phentermine

~15%

~20%

>20%

Retatrutide

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Weight Loss

<p>Semaglutide ~15%</p> <ul style="list-style-type: none"> DM2: <10% Men 12% vs 18% women (STEP1) 15% do not lose ≥ 5% <p>STEP 1. NEJM. 2021;384:989-1002</p>	<p>Tirzepatide ~20%</p> <ul style="list-style-type: none"> DM2: <15% Men 18% vs 25% women (SURMOUNT-1) 10% do not lose ≥ 5% <p>SURMOUNT 1. NEJM. 2022;387:205-216 SURMOUNT 5. NEJM. 2025;393:26-36 SURPASS 2. NEJM. 2021;385:503-515</p>
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Weight Loss Impact

The diagram illustrates the health benefits of weight loss in four stages: 5%, 10%, 15%, and ≥20%. Each stage is represented by a colored arrow pointing right, with corresponding icons and lists of health impacts.

- 5%:** Improved: insulin resistance, glycemia, blood pressure. (Icon: blood glucose meter)
- 10%:** Further improvement and remission of: type 2 diabetes, hypertension, MASLD/MASH, sleep apnea. (Icon: liver)
- 15%:** (Icon: heart)
- ≥20%:** Potential prevention of: malignancy, cardiovascular disease. (Icon: cancer cell)

Muhundan et al. Advances in Therapy. 2026;43:1082-1097

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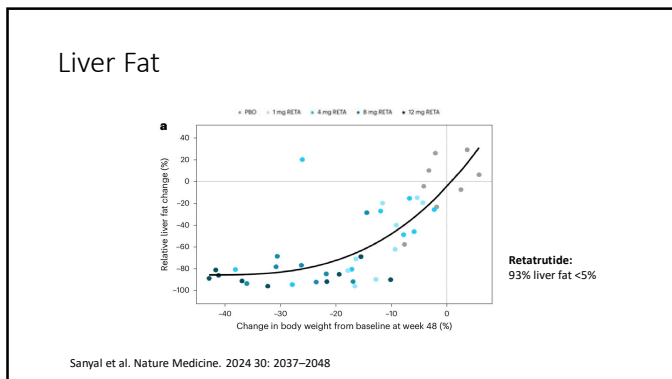
Weight-Dependent Benefit

The graph shows a positive correlation between weight gain and the incidence rate of T2DM. The x-axis represents the change in weight from baseline in kilograms (kg), ranging from -15 to 5. The y-axis represents the incidence rate per 100 person-years, ranging from 0 to 20. A curve starts at approximately (-15, 1) and rises to approximately (5, 16). A specific point is marked at (-5, 5) with the label 'Prediabetes in DPP'.

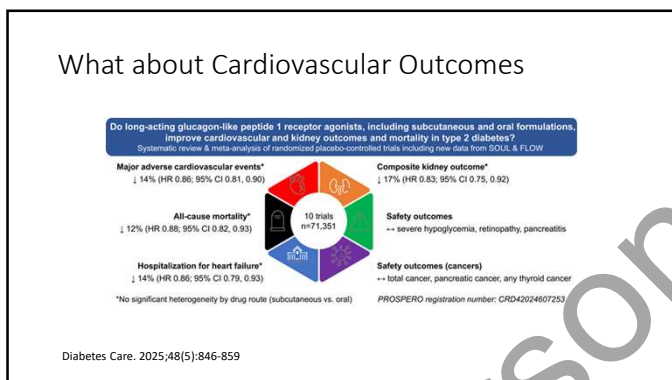
For every kilogram of weight loss, there was a 16% reduction in risk of T2DM, adjusted for changes in diet and activity.

Hamman et al. Diabetes Care. 2006;29(9):2102-2107

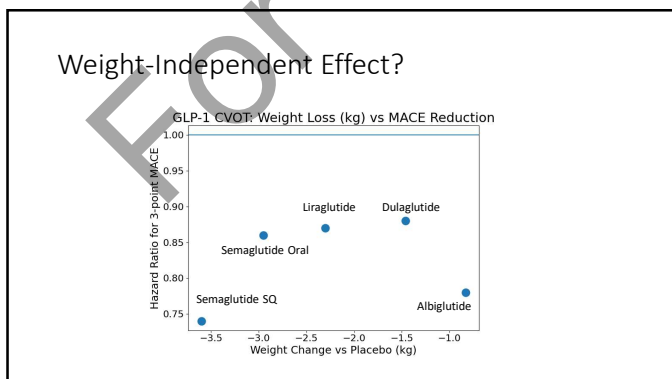
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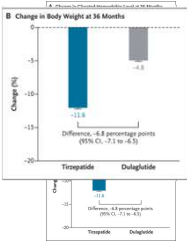


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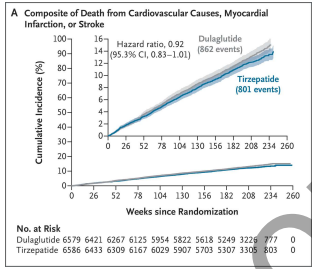
CVOT:
Tirzepatide
(15mg) vs
Dulaglutide
(1.5mg)



SURPASS-CVOT. NEJM. 2025;393:2409-2420

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CVOT:
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(15mg) vs
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SURPASS-CVOT. NEJM. 2025;393:2409-2420

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Formulations: Oral semaglutide

SNAC, sodium N-[8-[2-hydroxybenzoyl]amino] caprylate

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Oral Semaglutide

Bioavailability is
0.8%

Overgaard et al. Clinical Pharmacokinetics. 2021 60:1335-1348

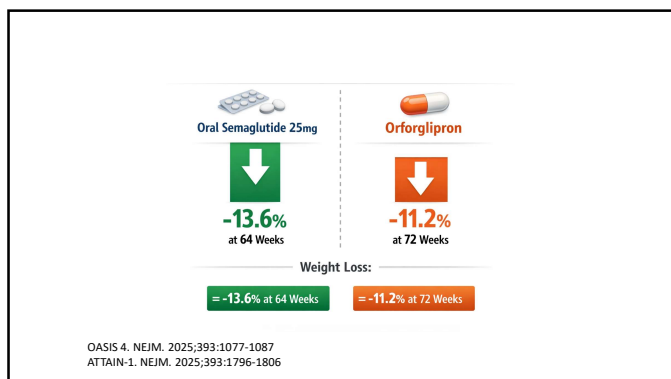
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Another oral coming...

- Orforglipron, a **non-peptide**, small-molecule, oral GLP-1RA

Semaglutide

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To watch

- Approved:
 - Finerenone
 - Resmetirom
- Coming:
 - Retatrutide
 - Baxdrostat

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Adverse Events

Common Side Effects of GLP-1 Medications

Nausea 33% - 44%	Diarrhea 23% - 31%
Vomiting 11% - 25%	Constipation 17% - 23%
Dyspepsia 9% - 10%	

GLP-1 Side Effect Management

Start With Behavior → Small meals • Eat slowly • Low-fat foods • Avoid carbonation & alcohol	If Nausea → PRN Ondansetron → Add H2 blocker / PPI for dyspepsia
Prevent Constipation (Start Early) → Fiber + hydration	Persistent Constipation / Delayed Gastric Emptying → Psyllium → Docusate → PEG → Stimulant laxative (stepwise)

Mehrtash et al. JAMA Internal Med. 2025 Sep 1;185(9):1151-1152

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Dysesthesia

GLP-1 Receptor Agonists → Dysesthesia (Central Nervous System Response)

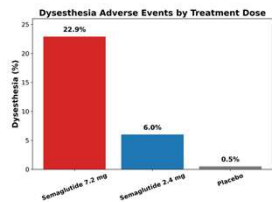
Abnormal Unpleasant Sensations
• Dysesthesia
• Paraesthesia

Pain from Non-Painful Stimuli
• Allodynia

Burning/Packal Quality
• Burning Sensation
• Pains of Site
• Skin Itch/Pruritus

Sensory Amplification
• Hyperaesthesia
• Hyperpathia
• Sensation Skin

STEP UP. Lancet. 2025;13(11) 949-963



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JAMA Ophthalmology | Brief Report

New-Onset Nonarteritic Anterior Ischemic Optic Neuropathy and Initiators of Semaglutide in US Veterans With Type 2 Diabetes

Kent Heberer, PhD, Adam P. Bress, PharmD, MS, Steven Cogill, PhD, Ana I. Maldonado, PhD, Sun H. Kim, MD, MS, Shiram Nallamshetty, MD, Ying Q. Chen, PhD, Mei-Chung Shih, PhD, Julie A. Lynch, PhD, Jennifer S. Lee, MD, PhD

IMPORTANCE Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are considered safe, effective medications for type 2 diabetes (T2D) and weight loss, used by millions worldwide. While their cardiometabolic benefits are well established, emerging observations suggest a potential association between GLP-1RA use and new-onset nonarteritic anterior ischemic optic neuropathy (NAION).

Supplemental content

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Risk of NAION in US Veterans: Semaglutide vs. SGLT2i Inhibitors

11,478 Semaglutide Initiators | 90,883 SGLT2i Initiators

Average Age: 60.1 years | BMI: 37.8 | Hemoglobin A1c: 7.0% | 85.5% Male | 14.5% Female
20.7% Black | 8.1% Hispanic | 61.9% White | 61.9% White

NAION Incidence Rates

Semaglutide: 123 per 100,000 person-years
SGLT2i: 67 per 100,000 person-years

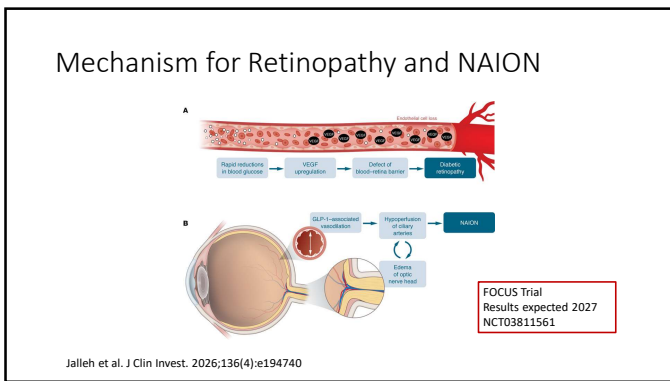
2.33x Higher Risk with Semaglutide
Hazard Ratio: 2.33 (95% CI: 1.54 - 3.54) P < 0.001

Absolute Risk (Overlap Weighted)

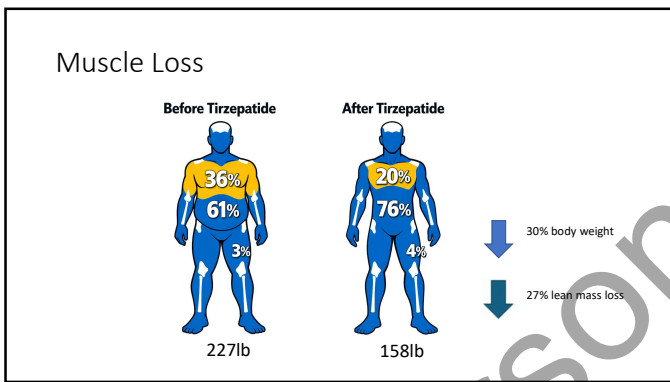
0.29% Semaglutide initiators | 0.13% SGLT2i initiators
Absolute Risk Difference: Only +0.16%

Absolute risk remains low in both groups.

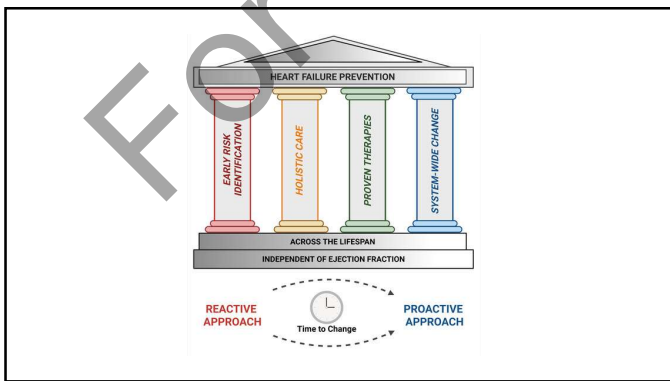
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