Sun H. Kim MD MS
April 9, 2026

1

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

2

Comprehensive Care

3

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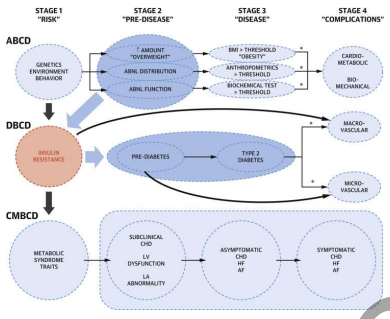
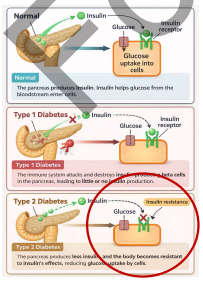
4

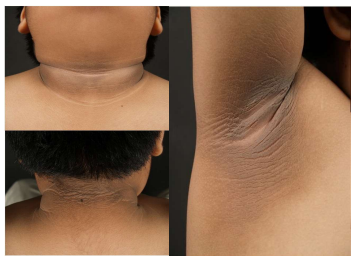


Mechanick et al. JACC. 2020; 75: 539-555

5

Insulin Resistance





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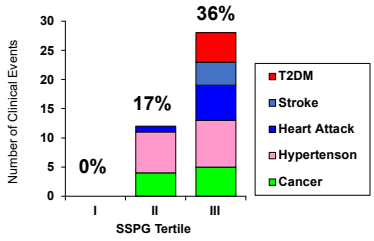
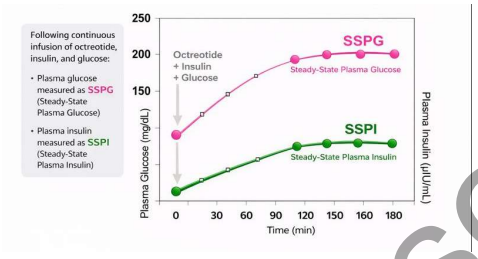
Insulin Resistance and Age-Related Diseases



Facchini, F. et al. JCEM 2001;86:3574-3578.

7

Insulin Suppression Test



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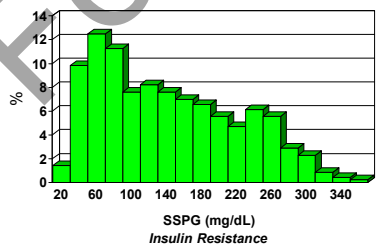
Distribution of Insulin Resistance in Nondiabetic Individuals



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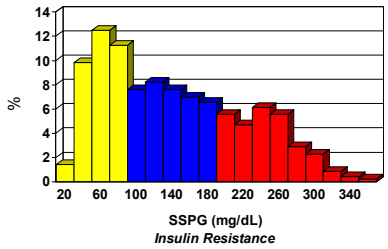
Tertiles of Insulin Resistance



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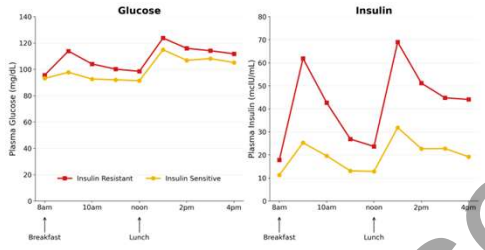
Insulin Resistance and Insulin Levels



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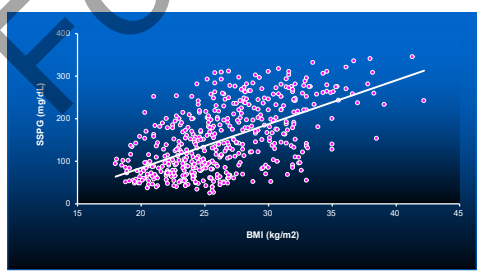
Obesity and Insulin Resistance



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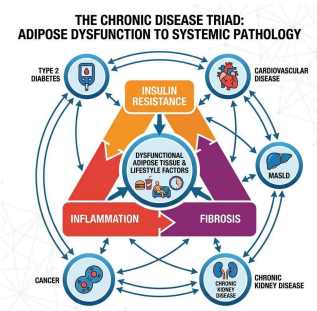

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Obesity

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

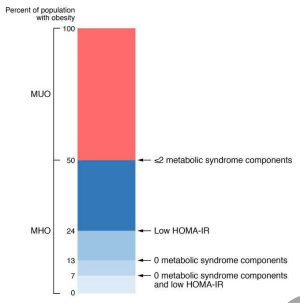
14

How should obesity be measured?

15

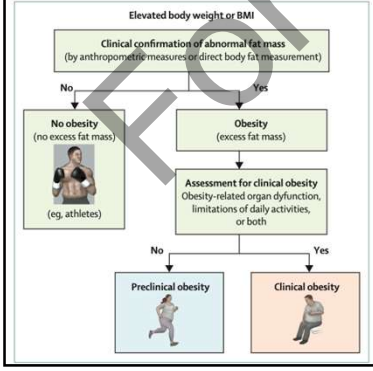
Is obesity sufficient?

16



Smith et al. JCI 2019 Oct 1;129(10):3978-3989

17



Rubino et al. 2025, Lancet DM & Endo
https://doi.org/10.1016/S2213-8587(24)00316-4

18

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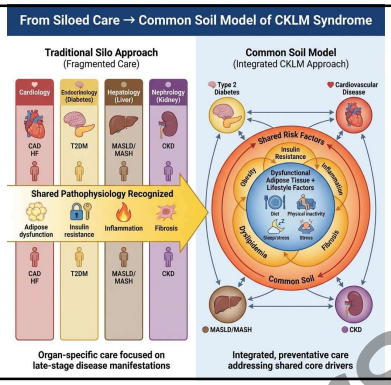

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CKM Syndrome

CKLM SYNDROME

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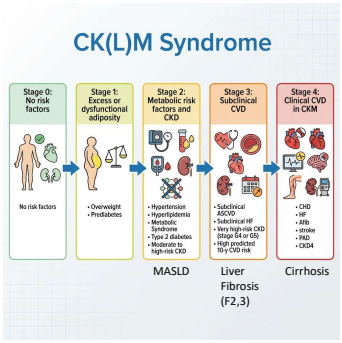

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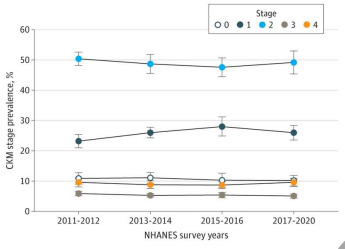
CK(L)M Syndrome



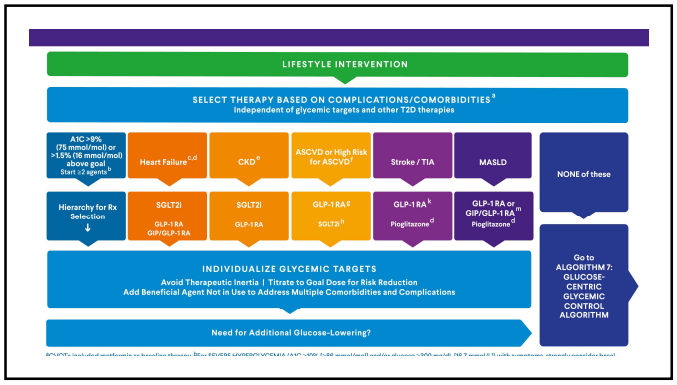
JAMA. 2024;331(21):1858-1860.

23

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 ≤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.

24



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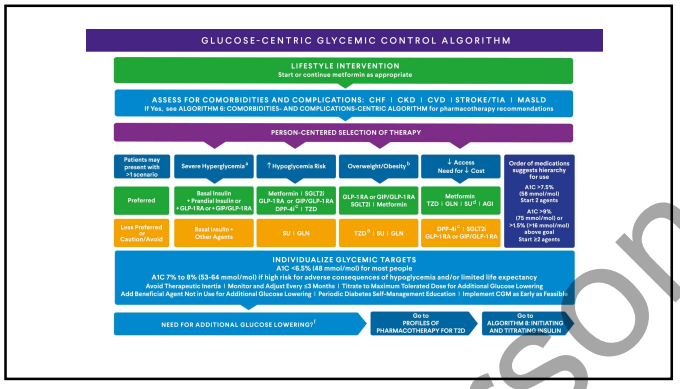

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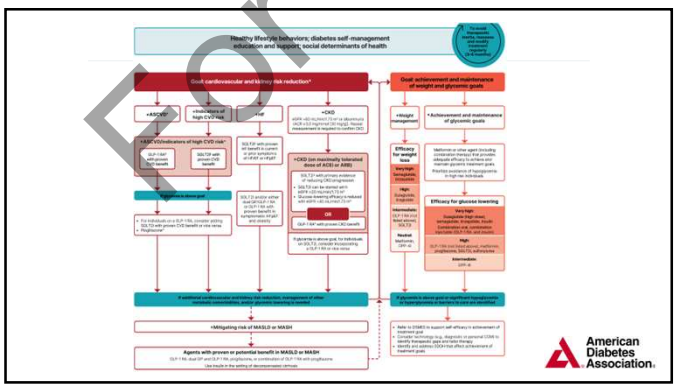

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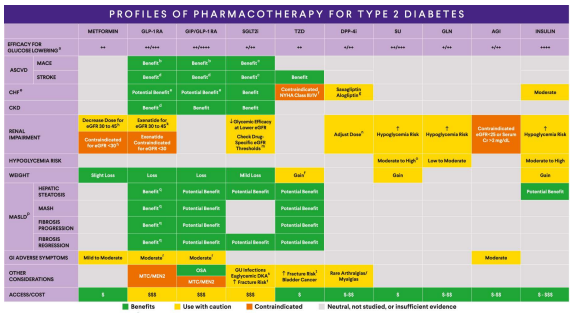

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Current Indications

	GLP-1	SGLT2i
Type 2 diabetes	Indicated	Indicated
Obesity (BMI ≥ 30kg/m² or 27 kg/m² 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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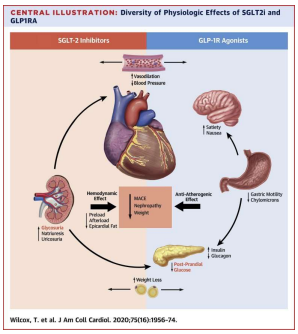

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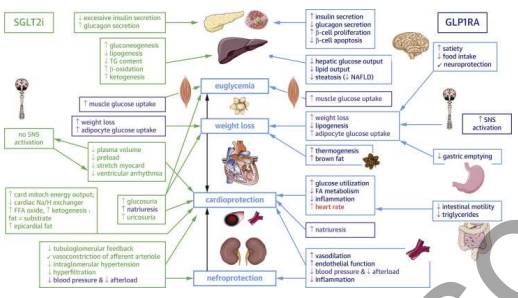

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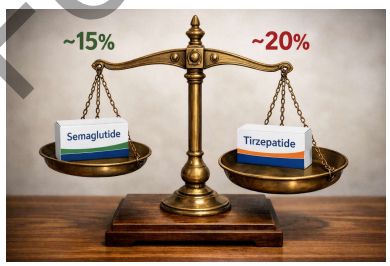
Weight Loss

<5-10%

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



>20%

Retatrutide

33

Weight Loss

Semaglutide ~15%
- DM2: <10%
- Men 12% vs 18% women (STEP1)
- 15% do not lose ≥ 5%

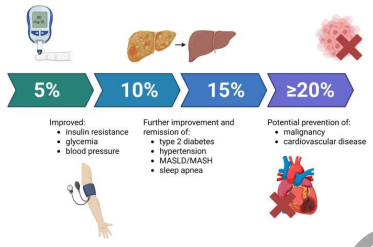
STEP 1. NEJM. 2021;384:989-1002

Tirzepatide ~20%
- DM2: <15%
- Men 18% vs 25% women (SURMOUNT-1)
- 10% do not lose ≥ 5%

SURMOUNT 1. NEJM. 2022;387:205-216
SURMOUNT 5. NEJM. 2025;393:26-36
SURPASS 2. NEJM. 2021;385:503-515

34

Weight Loss Impact



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

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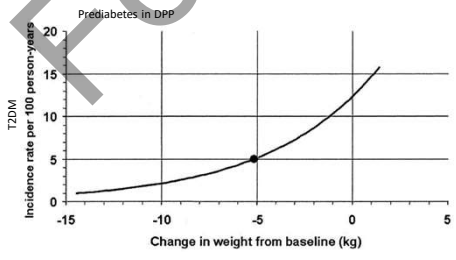
Weight-Dependent Benefit

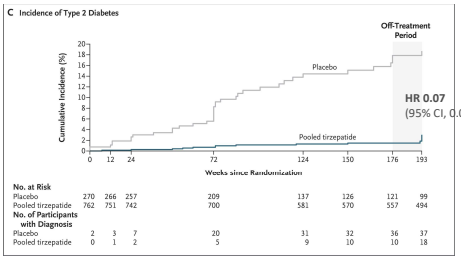


For every kilogram of weight loss, there was a 16% reduction in risk of T2DM, adjusted for changes in diet and activity.

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

36

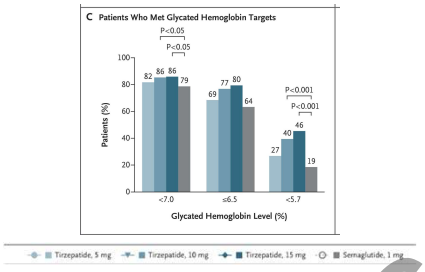
Prediabetes



SURMOUNT-1. NEJM. 2022;392:958-971

37

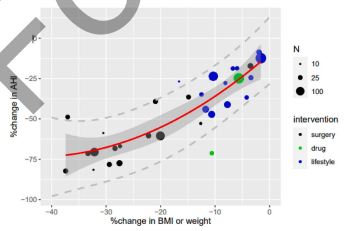
T2DM



SURPASS-2. NEJM. 2021; 385:503-515

38

Sleep Apnea



Tirzepatide:
Weight loss 20%
57% decrease in AHI

Malhotra et al. Sleep Medicine. 2024; Volume 121, Pages 26-31
Surmount OSA. NEJM. 2024;391:1193-205

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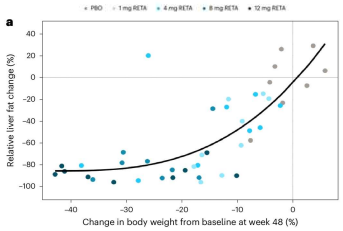
Liver Fat

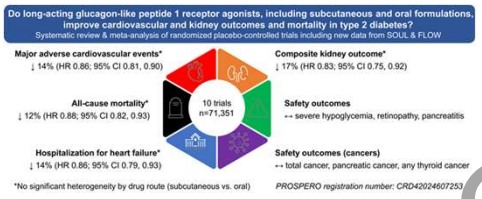


Retatrutide:
93% liver fat <5%

Sanyal et al. Nature Medicine. 2024 30: 2037–2048

40

What about Cardiovascular Outcomes



Diabetes Care. 2025;48(5):846-859

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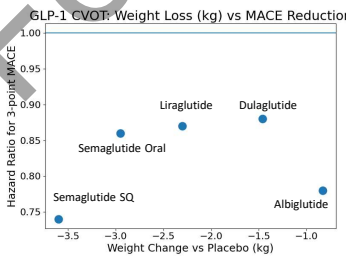
Weight-Independent Effect?



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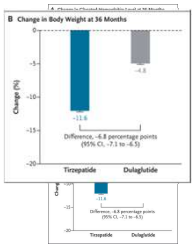
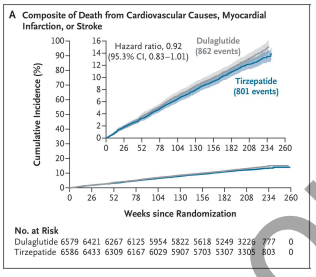
CVOT: Tirzepatide (15mg) vs Dulaglutide (1.5mg)



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

43

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



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

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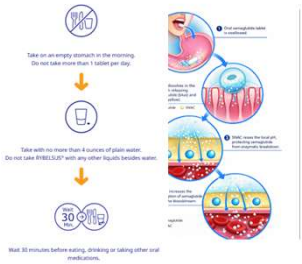
Formulations: Oral semaglutide



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

46

Oral Semaglutide

Bioavailability is 0.8%

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

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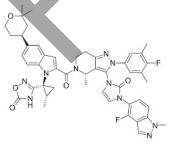
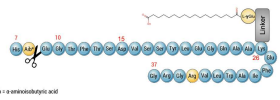
Another oral coming…

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





Semaglutide

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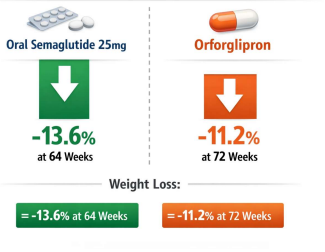

OASIS 4. NEJM. 2025;393:1077-1087
ATTAIN-1. NEJM. 2025;393:1796-1806

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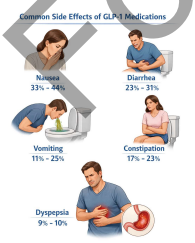
To watch

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

50

Adverse Events



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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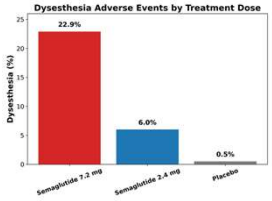
Dysesthesia



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; Shriram Nallamshetty, MD; Ying Q. Chen, PhD; Mei-Chiung Shih, PhD; Julie A. Lynch, PhD; Jennifer S. Lee, MD, PhD

Supplemental content

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).

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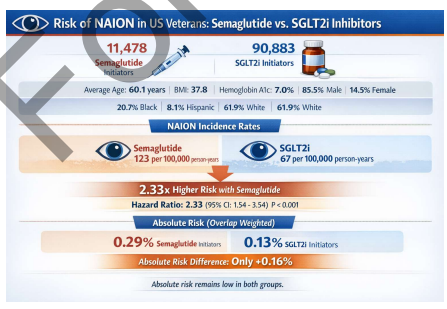

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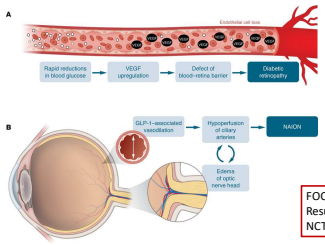
Mechanism for Retinopathy and NAION



FOCUS Trial
Results expected 2027
NCT03811561

Jalleh et al. J Clin Invest. 2026;136(4):e194740

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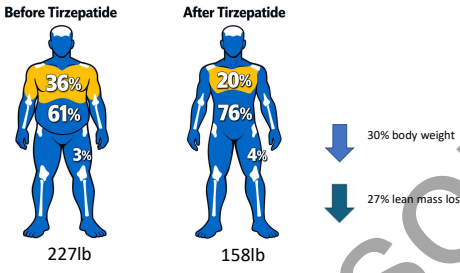
Muscle Loss



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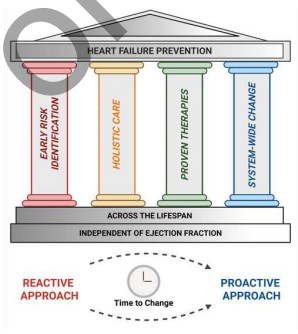

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