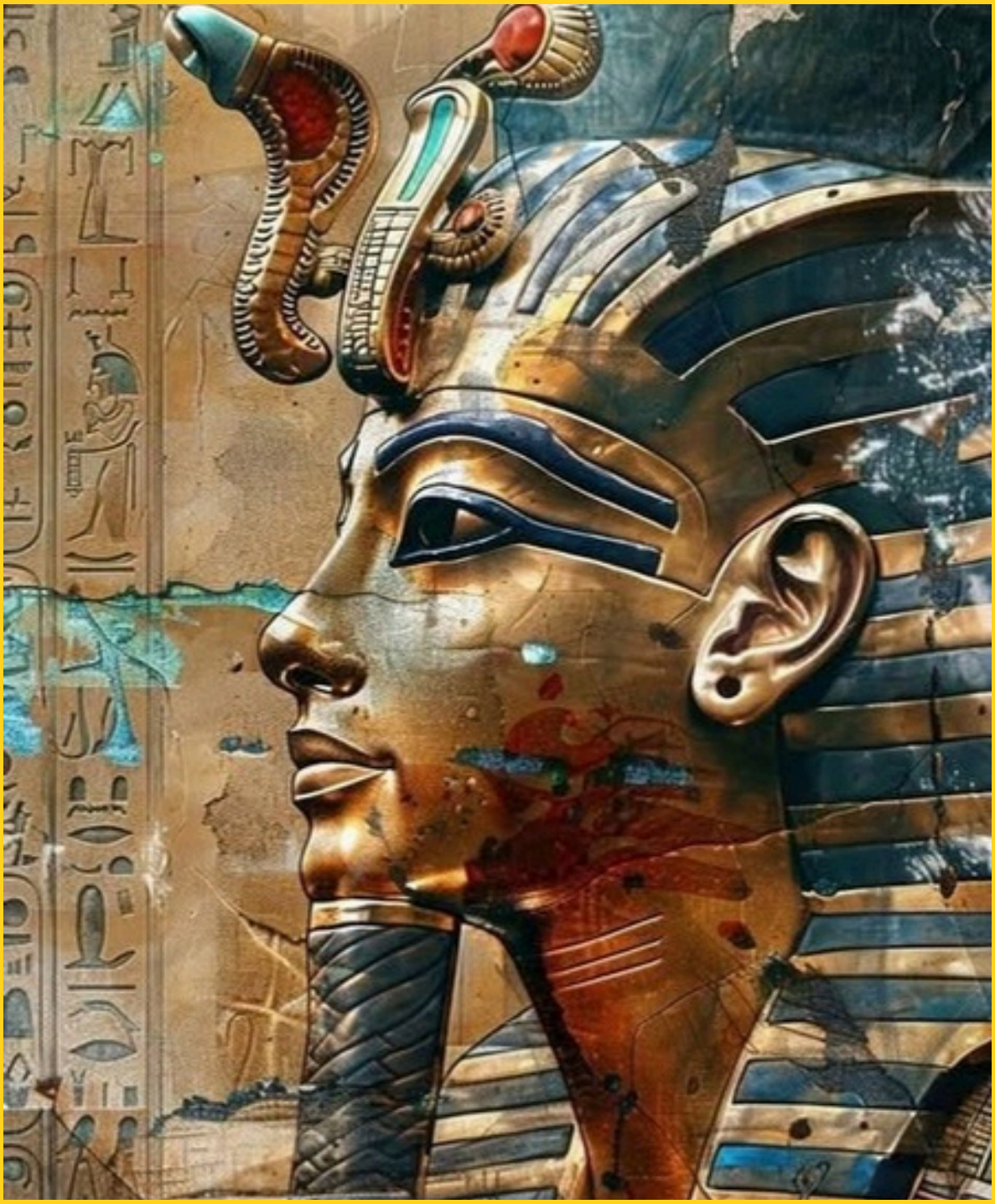


GLP-1 and the Heart

deep studies and more

Uncovering the Latest papers

ESMA

CARDIOMETABOLIC ISSEU EVERY SATURDAY

GLP 1 Agonist exploring new horizons

Egyptian Society of Metabolic Syndrome
ESMA
الجمعية المصرية لمتلازمة الأيض
IDF Member

Facts about GLP1

ESMA CARDIOMETABOLIC

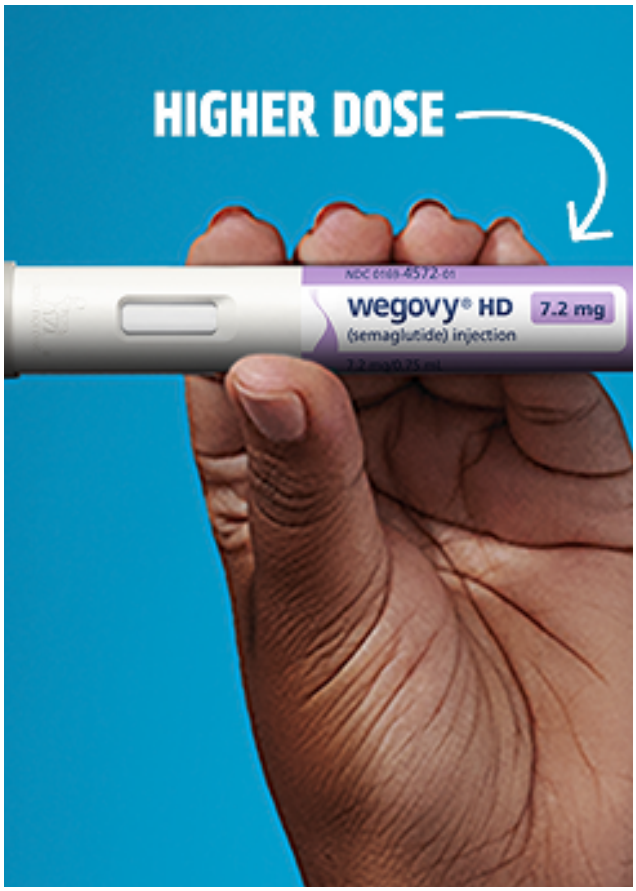
- HbA1C reduction with sulfonylurea 1-2%,
- GLP-1 receptor agonist 0.5-1.1%,
- SGLT-2 inhibitors 0.8-0.9%
- GLP-1 receptor agonists reduce major adverse cardiovascular events in people with type 2 diabetes, with meta-analytic and CVOT evidence showing lower MACE, stroke, cardiovascular death, and possibly myocardial infarction
- Benefits appear to come from multiple mechanisms beyond glycemia, including weight loss, lower blood pressure, improved lipids, anti-inflammatory effects, better endothelial function, and plaque stabilization or reduced atherosclerosis
- Heart failure effects are mixed: some studies report symptom, remodeling, biomarker, or exercise-capacity improvements, especially in HFpEF or obesity-related HF, but pooled trial data and reviews do not show a clear class-wide improvement in HF outcomes or cardiac function

- **In broad diabetes/obesity trial populations, GLP-1 receptor agonists modestly lower HF hospitalization risk, including a 21% reduction in incident HF hospitalization in one 2025 meta-analysis, but dedicated HF meta-analyses often show little or no benefit once patients already have established HFdd a heading**
- **For atrial fibrillation, randomized evidence mostly shows no excess risk and possibly a modest reduction, but estimates vary by population and agent; observational studies more often suggest benefit than trials designed for other endpoints.**

OMARHHASSOUNA

DONT GET CONFUSED

- **Semaglutide** mimics one gut hormone (GLP-1), whereas **tirzepatide** is a dual agonist that mimics two gut hormones (GLP-1 and GIP).
- Brand Names: Semaglutide is sold as **Ozempic** (diabetes) and **Wegovy** (weight loss).
- **Tirzepatide** is sold as **Mounjaro** (diabetes) and **Zepbound** (weight loss)



Tirzepatide results in greater average weight loss.

At maximum doses, tirzepatide patients typically lose about 20% of their body weight compared to 15-16% with semaglutide

compare!

	Tirzepatide	Semaglutide
Manufacturer	Eli Lilly and Company	Novo Nordisk
Drug class	GLP-1/GIP receptor agonist	GLP-1 receptor agonist
Brand name	Mounjaro/Zepbound	Ozempic/Wegovy/Rybelsus
Indications (US)	**Mounjaro**: Diabetes, **Zepbound**: Weight loss, obesity related obstructive sleep apnea	**Ozempic**: Type 2 diabetes, Reduce cardiovascular risk, Reduce eGFR decline in T2DM with chronic kidney disease, **Wegovy**: Weight loss, Reduce cardiovascular risk, Treatment of nonalcoholic steatohepatitis
Age	Zepbound : Adults Mounjaro: 10yo and above	Wegovy- 12yo and above Ozempic: adults
FDA approval	Mounjaro: May 2022 Zepbound: November 2023	Ozempic: December 2017 Rybelsus: September 2019 Wegovy: June 2021
Dosage form	Once weekly injection	Once weekly injection, Once daily tablet

What is Foundayo?

- Foundayo (orforglipron) is an FDA-approved oral GLP-1 weight loss pill
- taken once daily for chronic weight management in adults with obesity, or in some adults who are overweight and have weight-related medical problems. It is used together with a reduced-calorie diet and increased physical activity to help reduce excess body weight and maintain weight loss long term.
- Foundayo contains orforglipron, a small-molecule, non-peptide GLP-1 receptor agonist. Unlike some other oral GLP-1 medicines, Foundayo can be taken at any time of day, with or without food, and without water restrictions, which may make it a more convenient option for some patients.
- The FDA approved Foundayo for weight management on April 1, 2026, by Eli Lilly.

Foundayo pill

- *Weight loss increased as the Foundayo dose increased.*
- *Foundayo 17.2 mg produced the greatest average weight loss: 11.1%, or about 25.2 pounds.*
- *Across the doses studied, average weight loss with Foundayo ranged from 16.8 to 25.2 pounds.*

- *In Lilly's Phase 3 ATTAIN-1 trial, adults with obesity who received the highest dose of orforglipron (36mg) for 72 weeks lost an average of 27.3 pounds (12.4%), compared with 2.2 pounds (0.9%) with the placebo. The 36 mg orforglipron capsules used in investigational trials are equivalent in dose to the FDA-approved Foundayo 17.2 mg tablets*
- *The study also found improvements in several cardiometabolic risk markers, including waist circumference, non-HDL cholesterol, triglycerides, and systolic blood pressure.*

- In September 2025, clinical research was published on weight loss for two **oral incretin** therapies: an oral version of semaglutide and Orforglipron, also a GLP-1 receptor agonist.
- **The former showed a mean weight loss of 13.6%, while the latter showed a mean weight loss of 11.2%.**
- **Both showed gastrointestinal adverse events consistent with GLP-1 receptor agonists.**
- Novo Nordisk received approval for Wegovy tablets in December 2025.

Wegovy titration

OZEMPIC titration

0.25 mg

once-weekly for first 4 weeks

0.5 mg

once-weekly for at least 4 weeks

Use the pen that delivers 0.25 mg or 0.5 mg only

1 mg

once-weekly for at least 4 weeks if additional blood sugar control is needed

Use the pen that delivers 1 mg only

2 mg

once-weekly if additional blood sugar control is needed

Use the pen that delivers 2 mg only

⊖zempic nevers

(Never to Use)

- **Thyroid Cancer Risks: You must not use Ozempic if patient or anyone in his family has ever had Medullary Thyroid Carcinoma (MTC), or Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).**
- **Ozempic carries an official FDA Boxed Warning because it increased the risk of thyroid C-cell tumors in animal studies.**

(Relative Contraindications)

- ***Pancreatitis: Ozempic can cause acute inflammation of the pancreas (pancreatitis).***
- **Severe Stomach/Bowel Issues: Because Ozempic slows digestion, it is not recommended for individuals with severe gastroparesis (stomach paralysis). The FDA also warns of risks regarding ileus (intestinal obstruction) and severe constipation.**
- ***Kidney Disease: The medication can cause acute kidney injury or worsen chronic renal failure, typically triggered by dehydration from severe nausea and vomiting.***
- **Diabetic Retinopathy: Rapid improvements in blood sugar can temporarily worsen diabetic eye disease and vision changes.**
- ***Pregnancy and Breastfeeding: Ozempic is not recommended during pregnancy or breastfeeding. The manufacturer advises stopping the medication at least 2 months before trying to conceive to ensure it is completely out of your system.***

FUTURE DRUGS

🟢 **Recently Launched (2026)**

- The primary milestone of this year has been the shift to oral weight-loss pills that remove the need for weekly injections.
- Foundayo (orforglipron)
  - Status: Approved and Available
  - Details: Eli Lilly's once-daily pill received historically fast FDA approval on April 1, 2026. It is highly notable as the first non-peptide oral option, meaning it can be taken at any time of day with no food or water restrictions.

🟡 **Expected Next Wave (Late 2026 – 2027)**

These therapies have completed or are finalizing late-stage clinical trials and are heading into the regulatory approval pipeline.

- CagriSema (Injectable Combination)
  - Expected Approval: Late 2026
  - Details: Novo Nordisk officially submitted its New Drug Application (NDA) to the FDA. Despite some mixed trial results in head-to-head comparisons against Eli Lilly's Zepbound, its dual-action (amylin + GLP-1) pathway remains on track for regulatory review by the end of the year.

- Oral Amycretin (Pill Formulation)
  - Expected Approval: 2027
  - Details: Novo Nordisk's highly anticipated once-daily oral tablet is currently navigating its Phase 3 trials, aiming to compete directly with Foundayo.

🟠 **Advanced Powerhouse Therapies (2027 – 2028)**

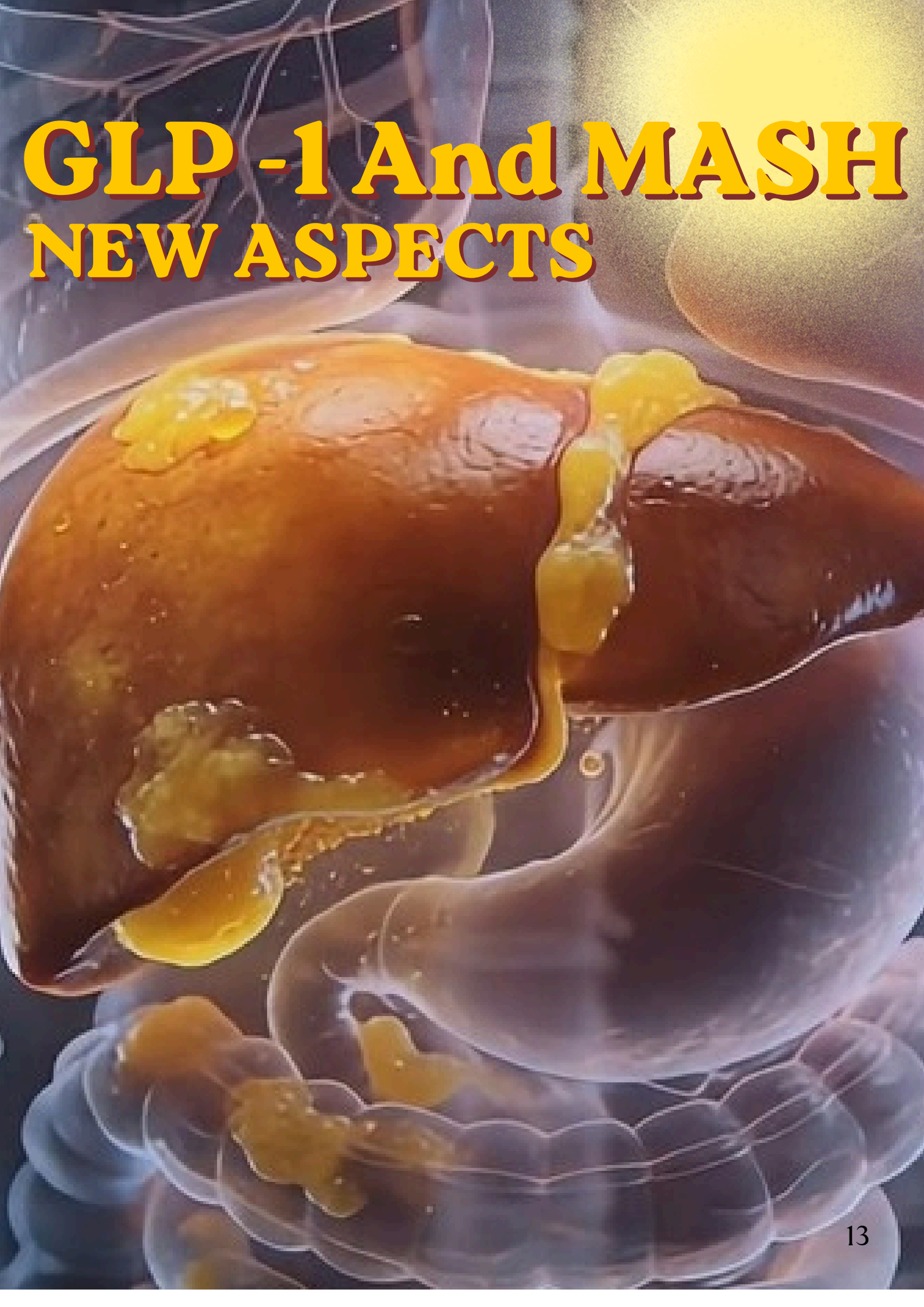
These represent the most potent medications in clinical development, introducing "triple-agonist" mechanics.

- **Retatrutide ("Triple G" Injectable)**
  - Expected Approval: Late 2027 / Early 2028
  - Details: Developed by Eli Lilly, the drug recently generated immense buzz after multiple Phase 3 trials (the TRIUMPH programs) confirmed unprecedented weight loss averages of over 28%. Lilly is expected to file its official regulatory application with the FDA in late 2026, leading to a standard 10-month review timeline.
- **Survodutide (Dual Glucagon/GLP-1 Injectable)**
  - Expected Approval: 2027–2028
  - Details: Progressing through Phase 3 global trials with a specific focus on treating both chronic obesity and MASH (fatty liver disease).

🔴 **Long-Term Pipeline (2028 and Beyond)**

These focus on optimizing how patients maintain their weight long-term, reducing injection frequencies, or protecting overall physical health.

- **MariTide (Monthly/Quarterly Injection)**
  - Expected Approval: 2028+
  - Details: Amgen's antibody-peptide conjugate is currently progressing through its extensive global Phase 3 MARITIME trials. Because it targets a prolonged maintenance schedule, trials will run longer to prove safety and durability after treatment stops.
- **Bimagrumab (Muscle Preservation Therapy)**
  - Expected Approval: 2029+
  - Details: Currently being tested in mid-to-late-stage trials in combination with existing GLP-1s to see if it successfully stops muscle loss during rapid weight reduction.


GLP -1 And MASH
NEW ASPECTS

GLP-1 receptor agonists benefit MASH (NASH):

1. Reducing Hepatic Fat (Steatosis)
   - Suppresses De Novo Lipogenesis: Turns off genes in the liver responsible for creating new fat cells.
   - Enhances Fatty Acid Oxidation: Accelerates the liver's ability to burn off existing fat stores.
   - Lowers Influx of Free Fatty Acids: Reduces the amount of circulating fats entering the liver from adipose tissue.
   - Drastically Lowers Liver Fat Fraction: Consistently reduces hepatic fat content by significant percentages on MRI-PDFF scans.

2. Calming Liver Inflammation & Cell Injury
   - **Resolves Steatohepatitis: Successfully clears active liver inflammation and ballooning hepatocyte injury.**
   - **Reduces Liver Enzymes: Lowers elevated blood markers of liver damage, specifically ALT and AST.**
   - **Mitigates Endoplasmic Reticulum (ER) Stress: Protects liver cells from cellular stress that leads to cell death.**
   - **Blocks Pro-inflammatory Cytokines: Decreases systemic inflammatory markers like TNF-alpha and IL-6.**

3. Reversing and Halting Fibrosis (Scarring)
   - **Halts Fibrosis Progression: Prevents early-stage liver scarring from advancing into severe bridging fibrosis.**
   - **Deactivates Hepatic Stellate Cells: Quiets the specific liver cells responsible for laying down scar tissue.**
   - **Promotes Long-Term Tissue Remodeling: Allows the liver to gradually heal and break down old collagen over multi-year therapy.**
   - **Prevents Progression to Cirrhosis: Significantly lowers the long-term risk of transitioning into end-stage liver failure (Stage F4).**

4. Improving Systemic Metabolic Health
   - **Reverses Insulin Resistance: Enhances insulin sensitivity in both the liver and peripheral muscle tissues.**
   - **Achieves High-Dose Weight Loss: Drives a 10% to 15% reduction in total body weight, which directly correlates with MASH clearing.**
   - **Optimizes Lipid Profiles: Lowers harmful circulating VLDL cholesterol and blood triglyceride levels.**
   - **Enhances Glycemic Control: Stabilizes blood sugar levels, removing a major metabolic driver of liver disease.**

5. Strengthening the Gut-Liver Axis
   - **Improves Gut Barrier Function: Restores the structural integrity of the intestinal lining.**
   - **Reduces Endotoxemia: Blocks toxic bacterial components from leaking out of the gut and into the portal vein.**
   - **Decreases Portal Inflammation: Lessens the inflammatory burden traveling directly from the digestive tract to the liver.**
   - **Works Synergistically in Combination Therapies: Amplifies all the above benefits when paired with GIP or Glucagon receptors (such as in Tirzepatide or Retatrutide).**

David Perlmutter, MD
@DavidPerlmutter

GLP-1 drugs are changing your brain.

"Neuroprotection and Cognitive Health:

- *Reduces Neuroinflammation: Inhibits microglial activation in the brain, lowering the production of harmful, inflammatory cytokines.*
- *Prevents Amyloid-Beta Accumulation: Helps block the buildup of toxic plaques associated with Alzheimer's disease progression.*
- *Decreases Tau Hyperphosphorylation: Reduces the formation of neurofibrillary tangles, protecting the structural integrity of brain cells.*
- *Boosts Synaptic Plasticity: Enhances long-term potentiation, improving communication between neurons and supporting better memory formation.*

"Vascular and Cellular Defense

- *Protects the Blood-Brain Barrier: Minimizes endothelial damage, keeping the brain's protective barrier tight against circulating toxins.*
- *Stimulates Neurogenesis: Promotes the birth and maturation of new neural stem cells in the hippocampus.*
- *Suppresses Oxidative Stress: Enhances mitochondrial efficiency inside neurons, preventing cell death caused by harmful free radicals.*
- *Lowers Ischemic Stroke Damage: Minimizes the volume of brain tissue lost or damaged during an acute stroke event by preserving cell viability.*

"Mood and Behavioral Modulation

- *Regulates Stress Responses: Interacts directly with the amygdala to modulate emotional processing and stress-induced eating.*
- *Improves Energy Homeostasis: Optimizes how the brain senses and utilizes systemic glucose, preventing sudden energy crashes.*
- *Stabilizes Sleep-Wake Cues: Indirectly aids sleep architecture by stabilizing nighttime blood sugar and eliminating heavy, late-night digestion.*
- *Mitigates Metabolic Depression: Alleviates the specific type of low mood and fatigue that stems directly from chronic systemic insulin resistance.*

Retatrutide (Triple Agonist): Data presented at the American Diabetes Association (ADA) sessions showed that this triple-acting needle-free peptide (targeting GLP-1, GIP, and Glucagon) exceeds 30% total weight loss in long-term extension trials.

CagriSema: This highly anticipated drug combines semaglutide with cagrilintide (an amylin analogue). A final FDA approval decision is expected by December, with clinical trials boasting an impressive 22.7% weight loss

Survodutide:
A dual GLP-1/Glucagon agonist designed to rapidly melt liver fat. It has advanced into late-stage trials specifically to treat MASH/NASH and liver scarring

Wegovy HD (7.2 mg): Approved by the FDA in March under an expedited national priority voucher program. Clinical trials show that this ultra-high-dose injection increases average weight loss to 20.7%

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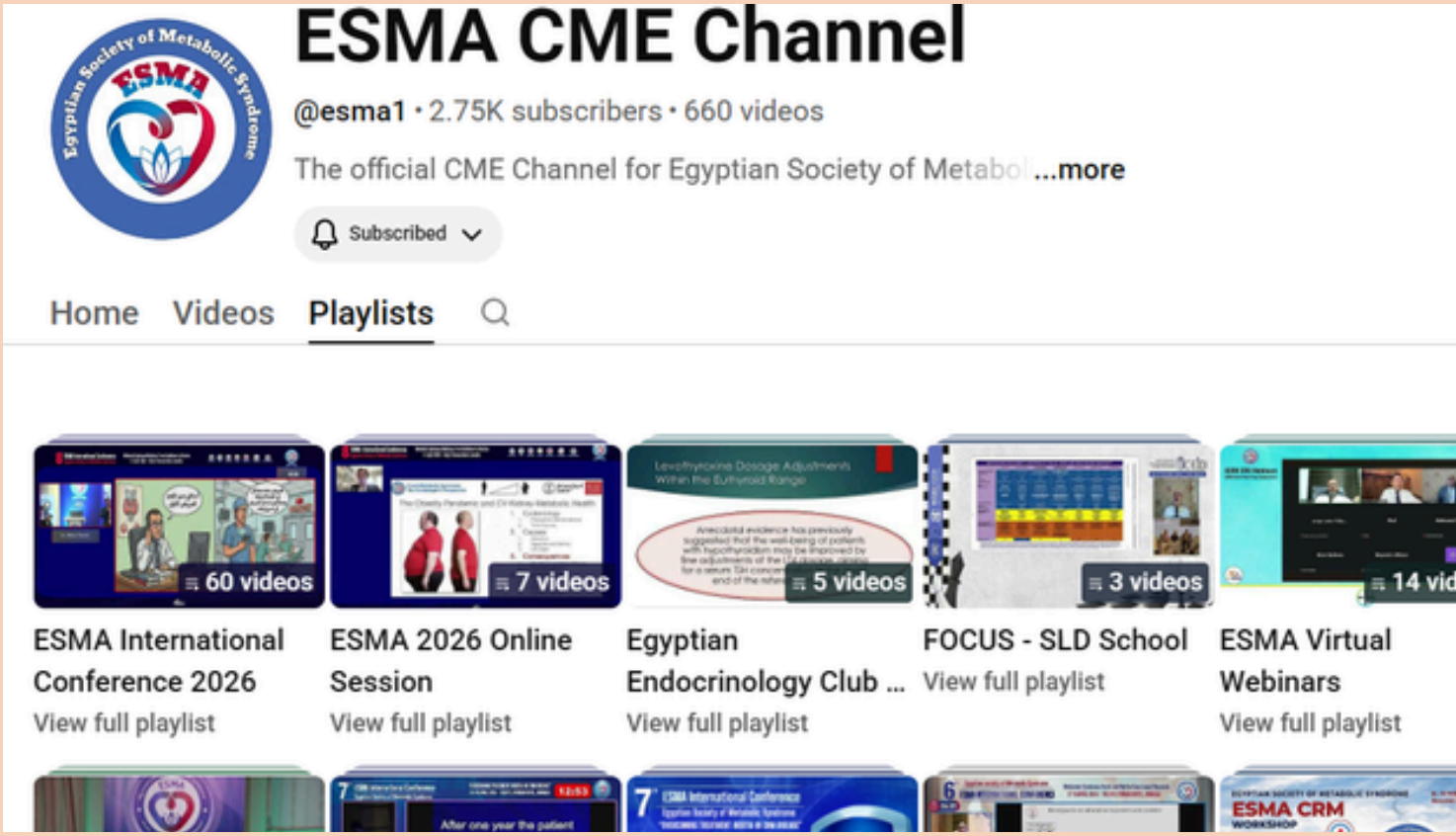

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