Latest Updates in GLP-1 Agonists

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Disclosures

In accordance with ACCME guidelines, I disclose that **I have no relevant financial relationships with any ineligible companies** whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

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Objectives

At the conclusion of this presentation, participants will be able to:

Describe the current understanding of the pathophysiology of GLP-1 receptor agonists (RA)

Identify FDA approved indications for use of GLP-1 RA

Discuss recent and ongoing research findings exploring use of GLP-1 RA in neurological disease.

Evaluate available therapeutic options using current guidelines and recent clinical trial data.

Apply emerging evidence and best practices to optimize patient management and multidisciplinary care.

Recognize gaps in knowledge and **integrate** strategies for ongoing research, quality improvement, or future investigation.

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Overview

- Introduction to incretins, GLP-1 and GIP
- FDA-approved indications for GLP-1 RA
- Current evidence for GLP-1 RA in neurological disease

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GLP-1 and GIP (Incretins)

- Gut-derived hormones released after eating
- Account for majority of postprandial insulin secretion
- Act on pancreas, brain, GI tract, adipose tissue
- Two major incretins: GLP-1 and GIP

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GLP-1

- GLP-1: Glucagon-like peptide-1
- Released after eating (esp. carbohydrates and fats)
- Coordinated metabolic and CNS effects
- ↑ Insulin (glucose-dependent)
- ↓ Glucagon
- Slows gastric emptying
- Strong appetite suppression

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GLP-1 Cardiovascular and Renal effects

- Lowers blood pressure
- Improves endothelial function
- Reduces inflammation, oxidative stress
- Provides renal protection in diabetic kidney disease

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GIP

- GIP = Glucose-Dependent Insulinotropic Polypeptide
- Stimulates insulin secretion and suppresses glucagon
- **Modulates fat metabolism in adipose tissue**
- Acts in the brain to regulate appetite and reward pathways
- Has complementary effects to GLP-1

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GLP-1 RA

Generic Name	Brand Name(s)	FDA-Approved Indications
Exenatide	Byetta (BID), Bydureon BCise (weekly)	• Type 2 diabetes mellitus (T2DM) — glycemic control
Liraglutide	Victoza	• T2DM • Reduce risk of MACE in adults with T2DM + ASCVD
	Saxenda	• Chronic weight management (obesity/overweight + risk factors)
Dulaglutide	Trulicity	• T2DM • Reduce risk of MACE in adults with T2DM + ASCVD
Semaglutide (injectable)	Ozempic	• T2DM • Reduce risk of MACE in T2DM + ASCVD • Reduce kidney disease progression in T2DM-associated CKD (2025 approval)
	Wegovy	• Chronic weight management • Reduce risk of major adverse cardiovascular events (MACE) in adults with obesity/overweight + CVD • Treatment of noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH), formerly known as nonalcoholic steatohepatitis (NASH), with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis) in adults
Semaglutide (oral)	Rybelsus	• T2DM
Lixisenatide	Adlyxin	• T2DM

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Dual GLP1 + GIP RA

Generic Name	Brand Name(s)	FDA-Approved Indications
Tirzepatide	Mounjaro	• T2DM
	Zepbound	• Chronic weight management (obesity/overweight + risk factors) • Treatment of moderate–severe OSA in adults with obesity

Structurally, tirzepatide is:

- A GIP-dominant dual incretin peptide
- Stabilized against enzymatic breakdown
- Lipidated for prolonged circulation
- Optimized for synergistic metabolic and CNS effects

That combination explains why tirzepatide produces greater weight loss and glycemic control than GLP-1–only agents.

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Type 2 Diabetes Mellitus (T2DM)

Primary, original indication for the class

FDA-approved GLP-1 receptor agonists for glycemic control in adults with T2DM:
Exenatide
Liraglutide
Dulaglutide
Semaglutide (injectable and oral)
Lixisenatide
Tirzepatide (dual GIP/GLP-1)

Clinical basis:
Robust A1c reduction (≈1–2.4%)
Glucose-dependent insulin secretion
Low hypoglycemia risk (unless combined with insulin/sulfonylureas)

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Chronic Weight Management (Obesity)

Adults with:
BMI ≥30 kg/m² **or**
BMI ≥27 kg/m² with ≥1 weight-related comorbidity

- **FDA-approved agents:**
  - Liraglutide 3.0 mg (Saxenda)
  - Semaglutide 2.4 mg (Wegovy)
  - Tirzepatide (Zepbound)

- **Clinical basis:**
  - Mean weight loss:
  - Liraglutide: ~8%
  - Semaglutide: ~15%
  - Tirzepatide: ~20–25%

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Cardiovascular Risk Reduction (MACE)

Reduction in major adverse cardiovascular events (CV death, nonfatal MI, nonfatal stroke)

FDA-approved GLP-1 agonists with CV indications:

Liraglutide (Victoza) - T2DM + established ASCVD
Dulaglutide (Trulicity) - T2DM + CV risk
Semaglutide (Ozempic, Wegovy) -
T2DM + ASCVD
Obesity/overweight + established CVD (Wegovy)

- **Clinical basis:**
  Large cardiovascular outcome trials (LEADER, REWIND, SUSTAIN-6, SELECT)

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Chronic Kidney Disease (CKD) in T2DM

FDA-approved:

Semaglutide (Ozempic) -

T2DM + ASCVD

Obesity/overweight + established CVD (Wegovy)

- **Clinical basis:**

Reduce risk of:

Sustained eGFR decline

End-stage kidney disease

CV death in adults with T2DM and CKD

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Obstructive Sleep Apnea (OSA)

SURMOUNT-OSA trials demonstrated substantial reductions in AHI and sleep apnea severity with tirzepatide (>50%) compared with placebo (~3%).

FDA-approved:

Tirzepatide (Zepbound)

Indication

Treatment of **moderate–to–severe OSA** in adults with obesity

Mechanism

Weight-loss mediated improvement in apnea–hypopnea index (AHI)

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Summary of FDA-approved uses of GLP-1 RA

Indication	FDA-Approved GLP-1 agonists
Type 2 diabetes	Exenatide, liraglutide, dulaglutide, semaglutide, lixisenatide, tirzepatide
Chronic weight management	Liraglutide (Saxenda), semaglutide (Wegovy), tirzepatide (Zepbound)
MACE reduction	Liraglutide, dulaglutide, semaglutide
CKD progression (T2DM)	Semaglutide
Obstructive sleep apnea	Tirzepatide

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Despite strong interest and ongoing trials, **GLP-1 agonists are NOT FDA-approved for any neurological disease**

Any neurologic benefit remains **secondary, indirect, or investigational**.

We will review existing efforts to ascertain benefit in neurological disease

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Idiopathic Intracranial Hypertension (IIH) (NOT FDA-Approved)

- Why GLP-1 Signaling Is of Interest in IIH

  - IIH is strongly linked to obesity and metabolic dysregulation; sustained weight loss can induce remission
  - GLP-1 pathway drugs produce large, durable weight loss (obesity indication) → plausible IIH benefit
  - Preclinical work suggests GLP-1R agonism may reduce CSF secretion at the choroid plexus
  - Key clinical question: is there benefit beyond weight loss (direct ICP lowering)?

Background: Mitchell et al. Brain 2023; Sinclair et al. IIH-Advance trial materials.

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Idiopathic Intracranial Hypertension (IIH) (NOT FDA-Approved)

- Best RCT Evidence: Exenatide (IIH:Pressure) — Rapid ICP Lowering
  - Randomized, placebo-controlled, double-blind phase 2 trial in active IIH (telemetric ICP monitoring)
  - Primary endpoints: ICP at 2.5 hours, 24 hours, and 12 weeks
  - Exenatide lowered ICP at 2.5h (~−5.7 cmCSF) and 24h (~−6.4 cmCSF) vs placebo; signal persisted at 12 weeks
  - Safety: no major safety signals in this small trial; GI effects expected
  - Key takeaway: proof-of-mechanism for GLP-1RA lowering ICP; clinical outcome confirmation needs larger trials

Mitchell JL, et al. Brain. 2023;146(5):1821–1833. PMID:36907221.

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Idiopathic Intracranial Hypertension (IIH) (NOT FDA-Approved)

- Real-world / Observational Evidence (Hypothesis-Generating)
    - EHR cohort studies suggest GLP-1RA use in IIH may be associated with improved clinical outcomes
    - Reported signals include reduced symptoms and reduced medication/surgery utilization
    - Limitations: confounding (weight loss, indication bias), variable ascertainment of papilledema/visual outcomes

Sioutas GS, et al. JAMA Neurol. 2025 (cohort study of GLP-1 RAs in IIH).

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Idiopathic Intracranial Hypertension (IIH) (NOT FDA-Approved)

- Adjunct Therapy Reports (Semaglutide, Tirzepatide)
  - Retrospective/adjunct series report improvement in IIH-related outcomes (papilledema, headache, visual symptoms) with semaglutide or tirzepatide
  - Evidence level: low (non-randomized); useful for hypothesis generation and trial justification

Azzam AY, et al. 2024 (tirzepatide, PubMed 39677436); Azzam AY, et al. 2024 (semaglutide, PubMed 39677446).

Idiopathic Intracranial Hypertension (IIH) (NOT FDA-Approved)

- Ongoing / Registered Trials (Examples)
  - Exenatide sustained-release (Presendin) in IIH (IIH EVOLVE): NCT05347147 (ICP-focused, ~240 planned)
  - IIH-Advance: tirzepatide-based weight loss/maintenance strategy in IIH (UK study)
  - Tirzepatide in IIH Trial: NCT07191873 (randomized, placebo-controlled)
  - New-onset IIH + semaglutide weight intervention trial: NCT06027567 (diet + GLP-1RA)
  - Exploratory semaglutide in IIH: NCT06361823 (listed in registries)

Azzam AY, et al. 2024 (tirzepatidClinicalTrials.gov: NCT05347147; NCT07191873; NCT06027567; NCT06361823. IIH-Advance: University of Birmingham, site, PubMed 39677436); Azzam AY, et al. 2024 (semaglutide, PubMed 39677446).

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Idiopathic Intracranial Hypertension (IIH) (NOT FDA-Approved)

- Clinical Interpretation (2026)
  - No GLP-1RA is FDA-approved for IIH
  - Exenatide RCT provides proof-of-concept for direct ICP lowering
  - Weight loss remains the most established modifiable driver of IIH remission
  - Best current approach: consider GLP-1/GIP agents within obesity/T2D indications; IIH-specific use remains investigational

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Peripheral Neuropathy (NOT FDA-Approved)

- Why GLP-1 Signaling Is of Interest in Peripheral Neuropathy
  - Peripheral neuropathy (especially diabetic) linked to metabolic dysfunction, inflammation, and microvascular injury
  - GLP-1 receptors expressed in peripheral nerves and dorsal root ganglia (preclinical data)
  - GLP-1 signaling improves glucose control, weight, lipids, and endothelial function
  - Hypothesis: indirect metabolic and direct neurotrophic effects could slow or improve neuropathy

Reviews: Jolivalt et al. Diabetologia 2018; Kalousová et al. Int J Mol Sci 2023

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Peripheral Neuropathy (NOT FDA-Approved)

- Preclinical Evidence
  - Rodent diabetic neuropathy models: GLP-1RAs improve nerve conduction velocity
  - Reduced oxidative stress and inflammatory signaling in peripheral nerves
  - Improved small-fiber density and reduced axonal degeneration in some models
  - Suggests potential neurotrophic and neuroprotective effects

Jolivalt CG, et al. Diabetologia. 2018;61:1881–1894.

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Peripheral Neuropathy (NOT FDA-Approved)

- Human Evidence: What We Know
  - No FDA-approved indication for peripheral neuropathy
  - No large randomized trials designed with neuropathy as a primary endpoint
  - Most human data are indirect, exploratory, or secondary analyses
  - Primary benefits likely mediated via improved metabolic control rather than direct nerve regeneration

Jolivalt CG, et al. Diabetologia. 2018;61:1881–1894.

Stroke (NOT FDA-Approved)

- Why GLP-1 Signaling Is of Interest in Stroke
  - Vascular biology: improved endothelial function; reduced inflammation/atherosclerosis
  - Risk-factor modification: weight loss, BP and lipids → lower long-term stroke risk
  - Preclinical neuroprotection: reduced excitotoxicity and inflammation; mitochondrial support; smaller infarcts in models
  - Two clinical questions: (1) stroke prevention? (2) acute neuroprotection after stroke?

Reviews: Maskery et al. 2020 (scoping review); Bellastella et al. Stroke 2020

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Stroke (NOT FDA-Approved)

- Stroke Prevention: What CVOTs and Meta-analyses Show
  - Across GLP-1RA cardiovascular outcome trials, nonfatal stroke is reduced as part of 3-point MACE
  - Pooled analyses suggest ~10–20% relative reduction in nonfatal/ischemic stroke in high-risk T2D populations
  - REWIND exploratory analysis: dulaglutide may reduce clinically relevant ischemic stroke
  - Semaglutide pooled analyses suggest benefit across stroke subtypes

Bellastella et al. Stroke 2020; Gerstein et al. Lancet 2019; Gerstein et al. Lancet Diabetes Endocrinol 2020; Strain et al. Stroke 2022.

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Stroke (NOT FDA-Approved)

- Acute Ischemic Stroke Trial: Exenatide (TEXAIS)
  - Randomized trial of exenatide in acute ischemic stroke
  - Primary: neurological impairment at day 7 (NIHSS)
  - Result: no reduction in NIHSS at day 7 vs control/placebo
  - Safety: fewer hyperglycemic events; no excess hypoglycemia; generally safe

Bladin CF, et al. Stroke. 2023; doi:10.1161/STROKEAHA.123.044568. Trial: NCT03287076.

Stroke (NOT FDA-Approved)

- Acute/Peri-reperfusion Signal: Semaglutide in Large Vessel Occlusion (Phase 2)
  - Phase 2 RCT in acute LVO stroke evaluated semaglutide safety and exploratory neurological outcomes
  - Reported: acceptable safety; exploratory outcome signal in subgroup not receiving IV thrombolysis
  - Interpretation: hypothesis-generating; requires confirmatory phase 3

Wang H, et al. Nat Commun. 2025; s41467-025-66167-z. Trial referenced: NCT05920889

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Stroke (NOT FDA-Approved)

- Acute Minor Stroke / High-risk TIA + T2D: Liraglutide (2025)
  - Randomized clinical trial in T2D patients with minor acute ischemic stroke or high-risk TIA

    Primary outcome: recurrent stroke (ischemic or hemorrhagic)
    13.8% control (44/319) vs **7.9%** liraglutide (25/317)
    HR 0.56 (95% CI, 0.34–0.91), P=0.02
  - Provides dedicated acute-stroke RCT evidence beyond prevention CVOTs
  - **Interpretation:** liraglutide *might* reduce 90-day recurrence and improve outcomes, but the trial is **underpowered**, so results should be interpreted cautiously.

Zhu H, et al. JAMA Intern Med. 2025 (online ahead).

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Parkinsons Disease (NOT FDA-Approved)

- GLP-1R activation may support dopaminergic neuron survival (mitochondrial, trophic, anti-oxidant effects)
- Modulates neuroinflammation (microglia/astrocytes) and reduces pro-inflammatory signaling in models
- Improves systemic and brain metabolic signaling (insulin resistance ↔ neurodegeneration hypothesis)
- Strong preclinical signals → repurposing trials of diabetes/obesity drugs in PD

Selected reviews: Hung et al. Neurotherapeutics 2020; Kalinderi et al. Int J Mol Sci 2024.

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Parkinsons Disease (NOT FDA-Approved)

- Lixisenatide (LIXIPARK) — Phase 2 Signal in Early PD
  - Randomized, double-blind, placebo-controlled; early PD; 12 months
  - Primary: MDS-UPDRS Part III (ON medication)
  - Change at 12 months: −0.04 (lixisenatide) vs +3.04 (placebo) → difference 3.08 points (P=0.007)
  - Caveat: higher GI adverse effects; longer/larger trials needed

Meissner WG, et al. N Engl J Med. 2024; DOI:10.1056/NEJMoa2312323

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Parkinsons Disease (NOT FDA-Approved)

- Exenatide — Early Signal, Then Phase 3 Negative
  - 2017 RCT (single-center): improved OFF-med motor scores; durability beyond exposure raised DMT interest
  - Exenatide-PD3 (multicenter, longer): no evidence of disease-modifying benefit vs placebo
  - Interpretation: target engagement/heterogeneity and trial design may matter; current evidence does not support DMT

Athauda D, et al. Lancet. 2017;390:1664–1675. Vijiaratnam N, et al. Lancet. 2025; (Exenatide-PD3).

Parkinsons Disease (NOT FDA-Approved)

- NLY01 (pegylated exenatide analogue) — Negative Phase 2
    - Randomized, double-blind, placebo-controlled; early untreated PD; 36 weeks
    - No improvement in motor or non-motor outcomes vs placebo
    - Exploratory subgroup: possible signal in younger participants (hypothesis-generating only)

McGarry A, et al. Lancet Neurol. 2024; PIIS1474-4422(23)00378-2.

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Parkinsons Disease (NOT FDA-Approved)

- So… Is GLP-1 a Disease-Modifying Strategy in PD?
    - Evidence is mixed: phase 2 signals (lixisenatide; early exenatide) but larger/other trials negative (exenatide-PD3; NLY01)
    - No GLP-1RA is FDA-approved for Parkinson's disease
    - If benefit exists, it may require: earlier intervention, different molecules, biomarkers for responders, or combination approaches

Standaert DG. N Engl J Med. 2024 (editorial on LIXIPARK). Parkinson's UK summary of Exenatide-PD3 (Feb 2025).

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Parkinsons Disease (NOT FDA-Approved)

- Ongoing / Registered GLP-1–Pathway Trials in PD (Examples)
    - Semaglutide in idiopathic PD: NCT03659682 (registered; status listed as unknown/not-yet-recruiting in recent updates)
    - Exenatide with imaging biomarker focus: NCT04305002 (FDG-PET pattern/outcomes)
    - Sustained-release exenatide (PT320): NCT04269642 (phase 2a)
    - Exenatide in atypical parkinsonism (MSA): NCT04431713 (MSA proof-of-concept)

ClinicalTrials.gov: NCT03659682; NCT04305002; NCT04269642; NCT04431713

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Alzheimers Disease (NOT FDA-Approved)

- Alzheimer’s disease associated with brain insulin resistance
- GLP-1 receptors expressed in hippocampus and cortex
- Improves neuronal insulin signaling and glucose metabolism
- Anti-inflammatory and synaptic protective effects in animal models
  - Reduces microglial activation and oxidative stress
  - Improves synaptic plasticity and neuronal survival
  - Reduces amyloid and tau pathology in animal models
  - Improves learning and memory behaviors in rodents

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Early Human Data

- Small liraglutide studies showed effects on brain metabolism or atrophy
- Observational data suggest reduced dementia incidence in diabetics on GLP-1s
- No conclusive clinical disease-modifying signal

Alzheimers Disease (NOT FDA-Approved)

EVOKE / EVOKE+ Phase 3 Trials (Semaglutide)

- Large randomized trials of oral semaglutide
- Population: MCI or mild Alzheimer's dementia
- Primary endpoints: cognitive and functional decline

RESULTS:

- Did not meet primary clinical endpoints
- No significant slowing of cognitive decline vs placebo
- Some biomarker and imaging effects observed
- Extension programs discontinued

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Alzheimers Disease (NOT FDA-Approved)

Interpretation:

- Biologic plausibility did not translate to clinical efficacy
- Unlikely effective as monotherapy in symptomatic AD
- Metabolic benefits may be preventive rather than therapeutic

Future Directions:

- Prevention trials in high-risk metabolic populations
- Combination therapy approaches
- Earlier intervention windows
- Focus on vascular and metabolic dementia risk

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Summary of GLP-1 RA in Neurological disease (NOT FDA-Approved)

Condition	Biologic Rationale	Best Human Evidence	Current Verdict
Alzheimer's disease	Insulin resistance, inflammation, synaptic effects	Phase 3 EVOKE/EVOKE+ negative	No clinical benefit; not approved
Parkinson's disease	Neurotrophic & anti-inflammatory signaling	Phase 2 signals; phase 3 negative	Investigational only
Stroke	Vascular risk reduction; experimental neuroprotection	CVOTs show ↓ stroke risk; acute trials mixed	Prevention benefit only
Peripheral neuropathy	Metabolic & microvascular protection	Preclinical/observational data only	No proven treatment role
Idiopathic intracranial hypertension	Weight loss + direct CSF/ICP effects	RCT shows direct ICP lowering	Strongest neurologic signal; trials ongoing

Bottom line: Outside IIH (ICP lowering) and stroke prevention via cardiometabolic effects, neurologic indications remain investigational.

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Summary of GLP-1 RA in Neurological disease (NOT FDA-Approved)

Condition	Brief Rationale / Evidence Signal
Migraine / chronic headache	Small clinical studies suggest reduced headache frequency in obesity; possible ICP-related mechanism (hypothesis-generating).
Multiple sclerosis	Preclinical anti-inflammatory effects; human data limited to safety/weight loss and observational cohorts; no proven disease modification.
Aneurysmal subarachnoid hemorrhage	Observational registry data suggest improved outcomes; no prospective interventional trials yet.
Hemorrhagic stroke	Registry/retrospective analyses suggest possible outcome benefit; causality unproven.
Traumatic brain injury	Preclinical models show reduced secondary injury; human interventional data lacking.
Cognitive impairment (non-AD)	Metabolic–vascular risk reduction; cognition-focused trials ongoing in diabetes/obesity populations.

Evidence level ranges from preclinical to observational; none of these indications are FDA-approved.

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Obesity:
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Questions