بنام خداوند جان و خرد

Semaglutide in Modern Endocrinology
From Glycemic Control to Multiorgan Protection

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Introduction

- This program is specifically designed to be a reference for our colleagues to answer the needs of medical team.
- All slides are specific, and not from any company or internet source.
- I have tried to cope all aspects of semaglutice from background to recent clinical evidences.

THE GLOBAL BURDEN OF CARDIOMETABOLIC DISORDERS

A Growing Pandemic with Interconnected Impact

Cardiometabolic disorders are among the leading causes of death and disability worldwide, driven by obesity, inactivity, poor diet and aging populations.

Cardiometabolic diseases affect billions of people and pose one of the **greatest challenges** for global health in the **21st century.**

GLOBAL PREVALENCE (2024)

TYPE 2 DIABETES MELLITUS

~537 MILLION
(10.5% of adults)

Projected to reach 643 million by 2030 and 783 million by 2045

IDF Diabetes Atlas 2024

OBESITY (OVERWEIGHT & OBESITY)

~2.6 BILLION
(38% of adults)

>1 billion are living with obesity

World Obesity Atlas 2023

CARDIOVASCULAR DISEASE (CVD)

~522 MILLION
people living with CVD

CVD is the leading cause of death globally (17.9 million deaths in 2019)

WHO 2023

HYPERTENSION

~1.28 BILLION
(30% of adults)

Leading risk factor for CVD, stroke, kidney failure and dementia

WHO 2023

DYSLIPIDEMIA

~1.7 BILLION
(35% of adults)

Major contributor to atherosclerosis and cardiovascular events

IHME 2023

MASLD/MASH (FATTY LIVER DISEASE)

~1.8 BILLION
(≈25% of global population)

MASH affects ~100–150 million people and is a leading cause of chronic liver disease

Younossi ZM, Hepatology 2023

OBSTRUCTIVE SLEEP APNEA (OSA)

~1.0 BILLION
(14% of adults)

Often undiagnosed and strongly linked to CVD, HTN, DM and obesity

Lancet Respir Med 2023

CHRONIC KIDNEY DISEASE (CKD)

~850 MILLION
(≈10% of population)

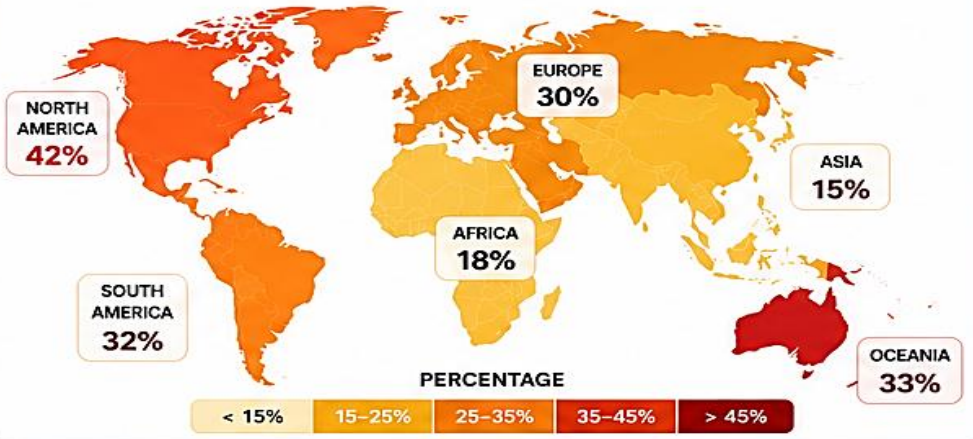
Increasing rapidly; associated with high CVD risk and mortality

KDIGO 2024

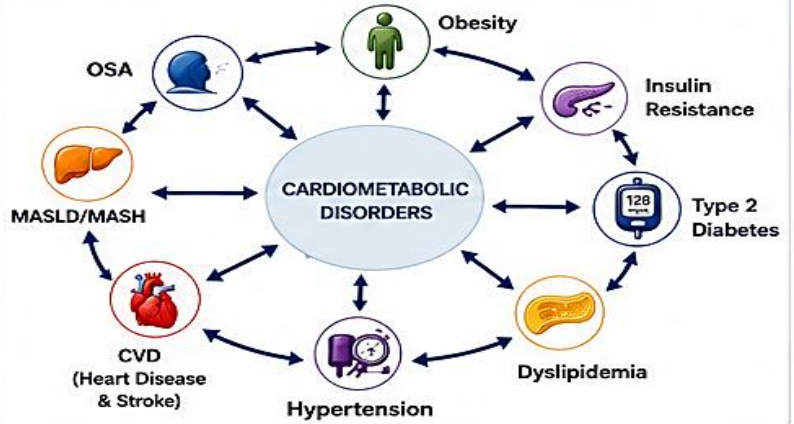
THE HUMAN AND SOCIETAL COST

- Cardiometabolic diseases are responsible for >75% of global deaths.
- They account for trillions of dollars in healthcare costs and lost productivity each year.
- Disproportionately affect low- and middle-income countries and vulnerable populations.
- Early prevention, timely treatment, and comprehensive risk reduction can prevent millions of deaths and improve quality of life.

PREVALENCE OF OBESITY (BMI ≥30 kg/m²) IN ADULTS BY REGION (2023)



A COMPLEX, INTERCONNECTED NETWORK



KEY MESSAGE

Cardiometabolic disorders are widespread, interrelated and escalating. A new era of integrated, patient-centered care is essential to change the trajectory.

THE GOAL

Better Prevention. Earlier Detection. Effective Treatment. Healthier Lives.

Abbreviations: DM = Diabetes Mellitus; CVD = Cardiovascular Disease; MASLD = Metabolic Dysfunction–Associated Steatotic Liver Disease; MASH = Obstructive Sleep Apnea; CKD = Chronic Kidney Disease; HTN = Hypertension; BMI = Body Mass Index; BMI = Body Mass Index.

Sources: IDF Diabetes Atlas 2024; World Obesity Atlas Global Health Estimates 2023; IHME Global Burden of Disease 2023; Younossi ZM, Hepatology 2023; Lancet Respir Med 2023; KDIGO 2024.

The time to act is now.
Together, we can reverse the cardiometabolic tide.

SEMAGLUTIDE: A NEXT-GENERATION GLP-1 RECEPTOR AGONIST

Designed to Mimic Physiology. Engineered for Efficacy.

One Molecule. Multiple Benefits.

Glycemic Control · Weight Loss · Cardiovascular Protection · Renal Protection · Liver Health

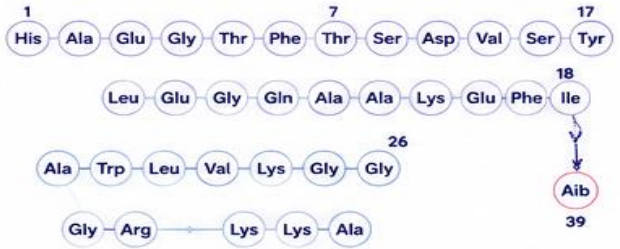
DISCOVERY & DEVELOPMENT JOURNEY

- **1986** — **GLP-1 discovered**
  Identified as an incretin hormone from intestinal L-cells.
- **2003** — **Exendin-4 discovered**
  Exendin-4 from Gila monster saliva shown to activate GLP-1 receptor.
- **2005–2007** — **GLP-1 biology established**
  Extensive research confirmed GLP-1's role in glucose regulation and appetite control.
- **2008–2012** — **Molecular engineering**
  Novo Nordisk scientists engineered semaglutide for enhanced stability and once-weekly dosing.
- **2014** — **First approval (injectable)**
  Approved in the EU for type 2 diabetes (Ozempic®).
- **2017** — **US approval for T2D**
  Ozempic® approved by FDA.
- **2021** — **Approval for chronic weight management**
  Wegovy® approved.
- **2022–2025** — **Expanding evidence & new horizons**
  Robust outcomes data across cardiovascular, renal, liver and other organ systems; oral semaglutide cardiovascular outcomes (SOUL trial) in 2025.

From discovery to global impact in less than four decades — transforming the treatment of cardiometabolic disease.

BIOCHEMISTRY: STRUCTURE OF SEMAGLUTIDE

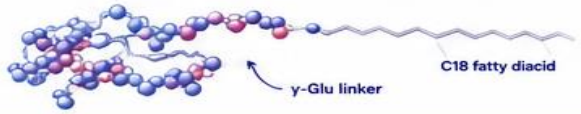
Semaglutide is a human GLP-1 analog (94% sequence homology) engineered for high potency, stability and prolonged half-life.



Aib = α-aminoisobutyric acid (confers DPP-4 resistance)

KEY STRUCTURAL MODIFICATIONS

- Ala8→Aib and Ala34→Aib — Protects from DPP-4 degradation
- Promotes reversible binding to albumin → Prolonged circulation
- Attachment of a C18 fatty diacid via a γ-Glu linker to Lys26 — Enables strong albumin binding and prolonged half-life
- Prolongs half-life (~1 week) — Allows once-weekly dosing



PHYSIOLOGY: GLP-1 PRODUCTION & SEMAGLUTIDE ACTION

Endogenous GLP-1 Physiology

1. **Nutrient ingestion** — Carbohydrates, fats and proteins enter the gut.
2. **L-cell activation** — Nutrients stimulate L-cells in the distal ileum and colon.
3. **GLP-1 secretion** — Proglucagon is cleaved by PC1/3 and PC2 enzymes to release GLP-1 (7–36 amide) into the bloodsteram.
4. **Rapid inactivation** — Native GLP-1 is degraded by DPP-4 enzyme within 1–2 minutes.

DPP-4

GLP-1 binds to GLP-1 receptor on target organs

GLP-1 Receptor

- **Pancreas** — ↑ Insulin secretion, ↓ Glucagon secretion
- **Stomach** — ↓ Gastric emptying
- **Brain (CNS)** — ↑ Satiety, ↓ Appetite
- **Liver** — ↓ Glucose production
- **Cardiovascular system** — Potential direct cardioprotective effects

Physiologic effects:
Lower glucose, reduced appetite, weight loss, cardiometabolic benefit

Semaglutide Mimics & Enhances GLP-1

- Resistant to DPP-4 degradation
- Binds reversibly to albumin → prolonged circulation (t½ ~1 week)
- Sustained activation of GLP-1 receptor
- Once-weekly dosing
- Reproduces and amplifies physiologic GLP-1 actions

Semaglutide
A long-acting GLP-1 RA that mimics natural GLP-1 and delivers durable metabolic benefits

BASIC INFORMATION

- **Generic name:** Semaglutide
- **Drug class:** GLP-1 receptor agonist
- **Molecular formula:** $C_{187}H_{291}N_{45}O_{59}$
- **Molecular weight:** ~4,113 Da
- **Route of administration:** Subcutaneous injection (Ozempic®, Wegovy®); Oral tablet (Rybelsus®)
- **Bioavailability:** SC ~89%; Oral ~0.4–1% (with absorption enhancer)
- **Half-life:** ~1 week
- **Time to steady state:** 4–5 weeks

INDICATIONS (Approved)

Injectable (SC)

- Type 2 diabetes mellitus (Ozempic®)
- Chronic weight management in adults with obesity or overweight with ≥1 weight-related comorbidity (Wegovy®)

Oral

- Type 2 diabetes mellitus (Rybelsus®)

PHARMACOKINETICS (SC)

- **Absorption:** Slow, sustained
- **Distribution:** Reversibly binds to albumin (~99%)
- **Metabolism:** Proteolytic degradation of the peptide backbone
- **Elimination:** Renal and fecal
- **Half-life:** ~7 days
- **Steady state:** 4–5 weeks

KEY CLINICAL HIGHLIGHTS

- Potent HbA1c reduction (~1.0–1.5%)
- Substantial and sustained weight loss (up to ~15–17%)
- Cardiovascular benefit: Reduced MACE in high-risk patients (SUSTAIN-6; SELECT; SOUL – oral semaglutide)
- Renal protection: Slows CKD progression (FLOW)
- Liver benefit: Improves MASH histology (ESSENCE)
- Once-weekly (SC) or once-daily (oral) convenient dosing with excellent efficacy and safety profile

KEY TAKE-HOME MESSAGE

Semaglutide is a next-generation GLP-1 receptor agonist, engineered for once-weekly (or once-daily oral) dosing, that mimics natural GLP-1 and delivers powerful and durable cardiometabolic benefits across multiple organ systems.

PROVEN BENEFITS ACROSS MULTIPLE SYSTEMS

Glycemic Control · Weight Loss · Cardiovascular Protection · Kidney Protection · Liver Health · Improved Quality of Life

ONE MOLECULE. MULTIPLE ORGANS. TRANSFORMING OUTCOMES.

Abbreviations: Aib, α-aminoisobutyric acid; CNS, central nervous system; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; RA, receptor agonist; SC, subcutaneous; t½, half-life; T2D, type 2 diabetes.

References: Nauck MA, et al. Diabetologia. 2021;64:845-867. Knudsen LB, et al. J Med Chem. 2010;53:6569-6562. Product labels: Ozempic®, Wegovy®, Rybelsus®.

SCIENTIFIC EVOLUTION OF SEMAGLUTIDE

From Incretin Discovery to a Transformative Therapy for Multiple Diseases

A Journey of Innovation, Evidence and Impact

Semaglutide has evolved from scientific discovery to a powerful, once-weekly (and oral) GLP-1 receptor agonist with proven benefits across cardiometabolic, renal, hepatic and other systems.

ONE MOLECULE. MULTIPLE BENEFITS.

Glycemic Control | Weight Loss | CV Protection | Renal Protection | Liver Health | Better Outcomes

1986 — Incretin Era Begins
GLP-1 identified as the biologically active incretin hormone derived from the proglucagon gene.

2005 — First GLP-1 RA in Clinical Use
Exenatide (from exendin-4) becomes the first GLP-1 receptor agonist approved for type 2 diabetes.

2008–2012 — Engineering Semaglutide
Molecular engineering (AA substitution and fatty-acid side chain) provides albumin binding and enables once-weekly dosing.

2016 — SUSTAIN Program (Phase 3)
SUSTAIN clinical trial program demonstrates robust and superior glycemic control and weight reduction.

2017 — FDA Approval (Ozempic®)
Ozempic® (injectable semaglutide) approved by the FDA for adults with type 2 diabetes.

2018 — EMA Approval (Ozempic®)
Ozempic® authorized by the European Medicines Agency for the treatment of type 2 diabetes.

2019 — PIONEER Program (Rybelsus®)
PIONEER trials establish oral semaglutide as the first oral GLP-1 receptor agonist for type 2 diabetes.

2021 — STEP Program & Wegovy® Approval
STEP program shows major weight loss and cardiometabolic benefits. Wegovy® approved by FDA for chronic weight management.

2022–2025 — Expanding Horizons: Multiorgan Impact
Large outcome trials demonstrate benefits across cardiovascular, renal, liver and heart failure — establishing semaglutide as a multisystem therapy.

MAJOR EVIDENCE MILESTONES

Changing the Standard of Care

SUSTAIN (2016)	PIONEER (2019)	STEP 1,2,3,4,5 (2017–2021)	SUSTAIN-6 (2016)	SELECT (2023)	FLOW (2024)	STEP-HFpEF (2023)	ESSENCE (2024)	SOUL (2025)
Glycemic control, weight loss and low hypoglycemia vs comparators.	Efficacy and safety of oral semaglutide vs placebo and active comparators.	Substantial weight loss (10–17%) and improvement in cardiometabolic risk factors.	Demonstrated CV safety and reduction in major adverse cardiovascular events (MACE).	Reduced CV events in adults with overweight/obesity and established CVD.	Slowed CKD progression and reduced kidney and CV outcomes in T2D and CKD.	Improved symptoms, exercise capacity and quality of life in HFpEF.	Improved MASH resolution and fibrosis (≥1 stage) vs placebo.	Oral semaglutide (3→7→14 mg/day) reduced major CV events in T2D.
Established high efficacy of semaglutide	First oral GLP-1 RA approved worldwide	Transformed obesity management	CV safety and risk reduction	First GLP-1 RA with proven CV event reduction in non-diabetic population	Renal protection beyond glycemic control	Benefit in heart failure with preserved EF	Breakthrough in liver disease (MASH)	CV benefit with oral semaglutide

- ✓ Millions of patients treated worldwide
- ✓ Reduced CV, renal, liver and metabolic burden
- ✓ Improved quality of life and longevity
- ✓ A new era of cardiometabolic medicine

FROM DISCOVERY TO TRANSFORMATION

Semaglutide is more than a glucose-lowering drug — it is a paradigm-shifting therapy improving healthspan and outcomes across multiple diseases.

Better Science. Better Outcomes. Better Life.

Abbreviations: GLP-1 RA = Glucagon-Like Peptide-1 Receptor Agonist; AA = Amino Acid; FDA = U.S. Food and Drug Administration; EMA = European Medicines Agency; CVD = Cardiovascular Disease; CV = Cardiovascular; CKD = Chronic Kidney Disease; HFpEF = Heart Failure with Preserved Ejection Fraction; MASH = Metabolic Dysfunction-Associated Steatohepatitis; T2D = Type 2 Diabetes.

Key References: 1. Knudsen LB, et al. *J Med Chem.* 2018;61:7377-7389. 2. Aroda VR, et al. *Lancet Diabetes Endocrinol.* 2017;5:251-260. 3. Marso SP, et al. *N Engl J Med.* 2016;375:1834-1844 (SUSTAIN-6). 4. Wilding JPH, et al. *N Engl J Med.* 2021;384:989-1002 (STEP 1). 5. Lincoff AM, et al. *N Engl J Med.* 2023;389:2221-2232 (SELECT). 6. Perkovic V, et al. *N Engl J Med.* 2024;391:109-121 (FLOW). 7. Kuchenbecker RS, et al. *N Engl J Med.* 2023;389:106-117 (STEP-HFpEF). 8. Newsome PN, et al. *N Engl J Med.* 2021;384:1113-1124 (MASH trial). 9. Husain M, et al. *N Engl J Med.* 2025 (SOUL trial).

PART I

THE EVOLUTION OF SEMAGLUTIDE

A Decade of Evidence Transforming Diabetes, Obesity and Beyond

From Glycemic Control to Multiorgan Protection

KEY PIVOTAL TRIALS THAT BUILT THE SEMAGLUTIDE EVIDENCE JOURNEY

SUSTAIN Program (2016–2019)

Established efficacy and safety in T2DM.

- Across 7 trials and >20,000 patients, semaglutide (0.5–1 mg) significantly reduced HbA1c (–1.0 to –1.8%), body weight (–2 to –6 kg). and showed a low risk of hypoglycemia.
- SUSTAIN-6 (CVOT) demonstrated 26% reduction in major adverse CV events (MACE).

PIONEER Program (2019)

Oral semaglutide enters clinical practice.

- In T2DM patients, oral semaglutide 3–14 mg significantly lowered HbA1c (–0.7 to –1.3%) and body weight (–1 to –4 kg).
- Once-daily oral formulation provides a new treatment option for patients preferring tablets.

STEP Program (2019–2024)

Semaglutide redefines obesity care.

- In adults with obesity or overweight: semaglutide 2.4 mg led to ~15% mean body weight loss at 68 weeks (STEP 1).
- Consistent and superior weight loss vs placebo across diverse populations, including those with T2DM (STEP 2) and long-term maintenance (STEP 4).

SELECT Trial (2023)

Cardiovascular protection in obesity.

- In 17,604 adults with overweight/obesity and established CVD (no diabetes), semaglutide 2.4 mg reduced MACE by 20% vs placebo.
- First GLP-1 RA to show significant CV benefit in people with obesity without diabetes.

FLOW Trial (2024)

Kidney protection proven.

- In 3,533 patients with T2DM and CKD, semaglutide 1 mg reduced risk of kidney disease progression by 24% and major CV events by 18%.
- Benefits consistent across albuminuria and eGFR subgroups.

ESSENCE Trial (2024)

Breakthrough in MASH (MASLD).

- In patients with biopsy-proven MASH, semaglutide 2.4 mg achieved NASH resolution without worsening fibrosis in 62.9% vs 34.3% with placebo.
- Significant improvement in liver stiffness and metabolic parameters.

STEP-HFpEF Trial (2023)

Improvement in heart failure with preserved EF.

- In patients with HFpEF and obesity/overweight, semaglutide 2.4 mg improved symptoms, physical limitations and exercise function vs placebo at 52 weeks.

STEP-OSA Trial (2023)

Reduction in obstructive sleep apnea severity.

- Semaglutide 2.4 mg significantly reduced apnea–hypopnea index (–20.3 events/hr) and body weight in adults with obesity and moderate-to-severe OSA.

SOUL Trial (2024)

CV event reduction with ORAL semaglutide.

- In high CV risk T2DM patients, oral semaglutide (3 → 7 → 14 mg/day) reduced MACE by 14% vs placebo.
- Confirms cardiovascular benefit across a broad spectrum of patients with T2DM.

EXPANDING EVIDENCE IMPACT

2016	2019	2021	2023	2024	2024	2023	2023	2024
	Glycemic Control	Weight Management	Cardiovascular Protection	Renal Protection	Liver Disease (MASH)	Heart Failure (HFpEF)	Sleep Apnea (OSA)	Broader CV Outcomes
	Powerful and durable HbA1c reduction	Meaningful weight loss across BMI spectrum	Benefit in T2DM and in obesity without diabetes	Slows CKD progression and reduces CV risk	Improves liver histology and metabolic health	Improves symptoms and physical function	Reduces OSA severity and daytime sleepiness	Reduces MACE in high-risk populations

KEY TAKE-HOME MESSAGE

Over the past decade, semaglutide has evolved from a powerful glucose-lowering agent to a multiorgan protective therapy, with proven benefits in weight management, cardiovascular, renal, hepatic and cardiometabolic diseases—changing the standard of care worldwide.

THE SEMAGLUTIDE JOURNEY

One molecule – multiple organs.
One goal – better health, longer life.

LOOKING AHEAD

Emerging evidence in neurology, addiction, and beyond will continue to expand the future of semaglutide.

SEMAGLUTIDE: A DECADE OF INNOVATION. A LIFETIME OF IMPACT.

Diabetes | Obesity | Heart | Kidney | Liver | Brain | Beyond

- Key Evidence: SUSTAIN Program (SUSTAIN-6, –7, –1–5, –FORTE) • PIONEER Program • STEP Program (1–5, TEENS, HFpEF, Sleep Apnea) • SELECT • FLOW • ESSENCE • SOUL (Oral Semaglutide 3–14 mg/day)

MACE: Major Adverse Cardiovascular Events | CV: Cardiovascular | T2DM: Type 2 Diabetes | CKD: Chronic Kidney Disease | MASH: Metabolic Dysfunction–Associated Steatohepatitis | MASLD: Metabolic Dysfunction–Associated Steatotic Liver Disease | OSA: Obstructive Sleep Apnea

PART 2

BEYOND GLP-1 How Semaglutide Works Across the Body

Pleiotropic Mechanisms That Drive Glycemic Control, Weight Loss and Multiorgan Protection

★ Semaglutide is a long-acting GLP-1 receptor agonist with widespread effects beyond glucose lowering.

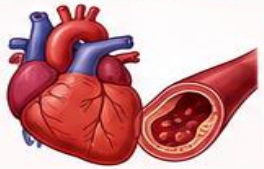
BRAIN

Acts on hypothalamus and reward centers

- Reduces appetite and calorie intake
- Increases satiety and reduces food cravings
- Modulates dopamine pathways and reward signaling
- May improve mood and cognitive function (emerging data)

Key Outcome
Reduced appetite, food intake and body weight

HEART & VASCULAR SYSTEM



Direct and indirect cardiovascular effects

- Improves endothelial function
- Reduces inflammation and oxidative stress
- Lowers blood pressure and arterial stiffness
- Improves lipid profile
- Reduces atherogenesis and plaque inflammation
- Improves cardiac function and outcomes

Key Outcome
Reduced major adverse cardiovascular events and heart failure risk

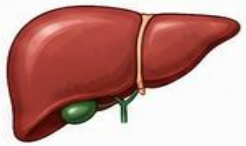
KIDNEYS

Renal protection through multiple pathways

- Reduces intraglomerular pressure and hyperfiltration
- Decreases albuminuria and proteinuria
- Slows eGFR decline
- Reduces inflammation and fibrosis
- Lowers risk of CV events in CKD

Key Outcome
Slows CKD progression and reduces kidney failure risk

LIVER



Improves liver metabolism and reduces steatosis

- Reduces liver fat accumulation
- Improves insulin sensitivity
- Decreases inflammation and hepatocellular injury
- May improve fibrosis in MASH
- Improves ALT, AST and metabolic profile

Key Outcome
Improvement in MASH and overall liver health

SKELETAL MUSCLE

Enhances muscle metabolism and function

- Improves insulin sensitivity in muscle
- Increases glucose uptake and utilization
- Promotes mitochondrial biogenesis (preclinical)
- May preserve lean mass when combined with exercise and protein

Key Outcome
Better glycemic control and muscle metabolic health

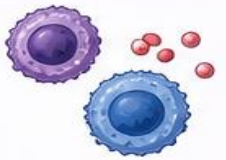
ADIPOSE TISSUE

Improves adipose tissue function and inflammation

- Reduces fat mass
- Improves adipokine profile (↑ adiponectin, ↓ leptin resistance)
- Decreases chronic low-grade inflammation
- Improves insulin sensitivity

Key Outcome
Weight loss and metabolic risk reduction

IMMUNE & INFLAMMATION



Systemic and tissue anti-inflammatory effects

- Reduces CRP and inflammatory cytokines
- Modulates innate and adaptive immune response
- Reduces macrophage activation and oxidative stress
- May stabilize atherosclerotic plaque and reduce organ inflammation

Key Outcome
Reduced inflammation and protection against chronic disease

REWARD & ADDICTION PATHWAYS

Modulates reward circuitry and addictive behaviors

- Reduces reward from palatable food
- May decrease alcohol intake and cravings
- Reduces cigarette cravings and smoking behavior (emerging data)
- Influences dopaminergic pathways in nucleus accumbens and VTA

Key Outcome
Potential benefits in addiction and compulsive behaviors

KEY TAKE-HOME MESSAGE

Semaglutide is more than a glucose-lowering medication.

It acts on multiple organs and biological systems, leading to broad metabolic benefits and protection against major chronic diseases.

- Weight Loss and Improved Metabolism
- Cardiovascular Protection
- Renal Protection
- Liver Health and MASH Improvement
- Neuroprotection and Behavioral Benefits
- Anti-inflammatory and Immune Modulation

INTEGRATED MECHANISTIC SUMMARY

GLP-1 Receptor Activation (Semaglutide) → Central & Peripheral Signaling (Nervous System) → Multiorgan Actions and Crosstalk → Improved Metabolic & Inflammatory Profile → Better Health Outcomes and Quality of Life

ONE MOLECULE. MULTIPLE TARGETS. MULTIORGAN PROTECTION. *This is the Power of Semaglutide.*

PART 3

SEMAGLUTIDE: EVIDENCE ACROSS ORGAN SYSTEMS

Robust Clinical Evidence Demonstrating Multiorgan Benefits Beyond Glycemic Control

One Molecule.
Multiple Organs. Better Outcomes.

TYPE 2 DIABETES

Glycemic Excellence and Durable Control

KEY TRIALS
- SUSTAIN 1–10
- PIONEER 1–8
- Japanese SUSTAIN
- Real-world studies

KEY FINDINGS
- → HbA1c reduction: 1.1%–1.8%
- → Significant FPG reduction
- → Low risk of hypoglycemia
- → Weight loss: 2–6 kg
- → Potential β-cell preservation
- → Durable efficacy up to 2 years

CLINICAL IMPLICATION
Powerful and durable glycemic control with weight benefit and low hypoglycemia risk across the spectrum of T2DM.

LEVEL OF EVIDENCE ★★★★★ Very High

OBESITY

Substantial Weight Loss and Maintenance

KEY TRIALS
- STEP 1
- STEP 2
- STEP 3
- STEP 4 (Maintenance)
- STEP 5
- STEP TEENS

KEY FINDINGS
- Mean weight loss up to 15.2%
- ≥20% weight loss in up to 1 in 3 participants (STEP 1)
- Superior vs placebo across all studies
- Weight maintenance with continued therapy (STEP 4)
- Improved physical function and health-related quality of life

CLINICAL IMPLICATION
Semaglutide is a highly effective obesity therapy with meaningful improvements in weight, function and quality of life.

LEVEL OF EVIDENCE ★★★★★ Very High

CARDIOVASCULAR DISEASE

Proven Reduction in Major Cardiovascular Events

KEY TRIALS
- SUSTAIN-6
- SELECT
- SOUL
- Post-hoc analyses

KEY FINDINGS
- SUSTAIN-6: MACE ↓ 26%
- SELECT: MACE ↓ 20% in overweight/obesity without DM
- SOUL: MACE ↓ 14% in T2DM with high CV risk
- Reduced nonfatal MI and nonfatal stroke
- Benefit consistent across subgroups

CLINICAL IMPLICATION
Semaglutide reduces major CV events in patients with diabetes and in overweight/obese individuals with established CV disease.

LEVEL OF EVIDENCE ★★★★★ Very High

CHRONIC KIDNEY DISEASE

Kidney Protection Proven

KEY TRIALS
- FLOW
- SUSTAIN renal analyses

KEY FINDINGS
- Composite kidney outcome ↓ 24% (sustained eGFR decline, ESKD, renal death) in FLOW
- Albuminuria reduction: ~30%
- Slower annual eGFR decline
- Benefit independent of glycemic control

CLINICAL IMPLICATION
Semaglutide slows CKD progression and reduces albuminuria across a broad range of eGFR and albuminuria levels.

LEVEL OF EVIDENCE ★★★★★ Very High

MASLD / MASH

Improvement in Liver Steatosis, Inflammation and Fibrosis

KEY TRIALS
- ESSENCE
- STEP NAFLD
- Real-world and imaging studies

KEY FINDINGS
- MASH resolution (no worsening of fibrosis): 62.9% vs 34.3% (ESSENCE)
- Liver fibrosis improvement: 37.0% vs 22.5% (ESSENCE)
- Liver fat content reduction: up to 40%
- Improvements in ALT, AST and metabolic parameters

CLINICAL IMPLICATION
Semaglutide is a leading therapy for MASH with proven resolution of steatohepatitis and fibrosis improvement.

LEVEL OF EVIDENCE ★★★★★ High

HEART FAILURE

Benefits in HFpEF and Functional Capacity

KEY TRIALS
- STEP-HFpEF
- Post-hoc CV analyses

KEY FINDINGS
- Improved KCCQ clinical summary score (+16.6 points)
- Increased 6-minute walk distance (+21.5 m)
- Reduced HF symptoms and physical limitations
- Weight-mediated and direct hemodynamic benefits

CLINICAL IMPLICATION
Semaglutide improves symptoms, functional capacity and quality of life in HFpEF.

LEVEL OF EVIDENCE ★★★★★ High

NEUROLOGY

Emerging Neuroprotection and Brain Health

KEY TRIALS / DATA
- Stroke SELECT analysis
- Alzheimer's disease (phase 2 trials)
- Parkinson's disease (early studies)
- Cognitive studies

KEY FINDINGS
- Reduced risk of ischemic stroke
- Potential slowing of cognitive decline (emerging)
- Reduced neuroinflammation and oxidative stress
- Possible dopaminergic neuron protection (preclinical/early data)

CLINICAL IMPLICATION
Semaglutide shows promise in neuroprotection and may modify risk of neurodegenerative and cerebrovascular diseases (evidence emerging).

LEVEL OF EVIDENCE ★★★☆☆ Emerging

ADDICTION & BEHAVIORAL MEDICINE

Modulation of Reward Pathways and Cravings

KEY TRIALS / DATA
- Alcohol use disorder (phase 2 trials)
- Smoking cessation (early studies)
- Food addiction and craving studies

KEY FINDINGS
- Reduced alcohol consumption and heavy drinking days
- Increased smoking cessation rates
- Reduced food cravings and reward-driven eating
- Acts on mesolimbic reward pathways

CLINICAL IMPLICATION
Semaglutide may become a novel adjunct therapy for addiction and complex behavioral disorders.

LEVEL OF EVIDENCE ★★☆☆☆ Preliminary

INTEGRATED MULTIORGAN IMPACT OF SEMAGLUTIDE

KEY TAKE-HOME MESSAGE

Semaglutide has evolved from a glucose-lowering agent into a multiorgan disease-modifying therapy, with robust evidence spanning diabetes, obesity, cardiovascular disease, chronic kidney disease, and MASH, while emerging data continue to expand its role in neurology and behavioral medicine.

LEVEL OF EVIDENCE LEGEND

★★★★★	★★★★☆	★★★☆☆	★★☆☆☆
Very High (Multiple RCTs)	High (≥1 Large RCT)	Emerging (Early RCTs)	Preliminary (Early Data)

ABBREVIATIONS

T2DM: Type 2 Diabetes Mellitus
MACE: Major Adverse Cardiovascular Events
CV: Cardiovascular HFpEF: Heart Failure with Preserved Ejection Fraction CKD: Chronic Kidney Disease MASH: Metabolic dysfunction-associated steatohepatitis

SEMAGLUTIDE IN TYPE 2 DIABETES

Evidence-Based Use Across the Entire Disease Spectrum

From Pre-Diabetes to High-Risk Complications and Injection Therapy

Semaglutide, a long-acting GLP-1 receptor agonist, improves glycemia and provides cardiovascular, renal, metabolic and weight benefits beyond ~~this~~ beyond glucose lowering.

PROVEN BENEFITS BEYOND GLYCEMIC CONTROL

- Potent A1c Reduction
- Weight Loss
- Cardiovascular Protection
- Renal Protection
- Liver Benefits
- Low Risk of Hypoglycemia

1. EARLY STAGES: PRE-DIABETES & EARLY T2DM

Pre-Diabetes

- Delays progression to type 2 diabetes
- Promotes weight loss and improves insulin sensitivity

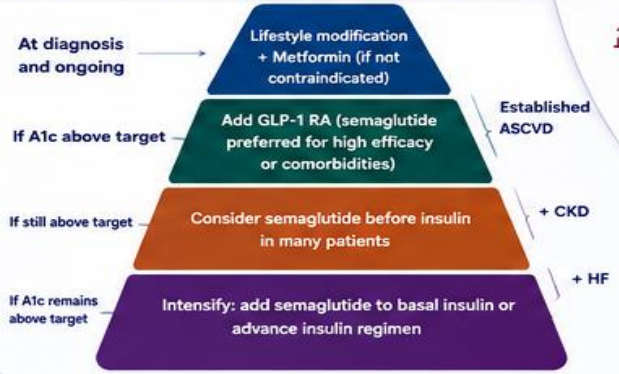
Early T2DM (Monotherapy or Initial Therapy)

Targets:

- A1c lowering (high efficacy)
- Weight reduction
- Low risk of hypoglycemia
- Preservation of β-cell function

Evidence: STEP, SUSTAIN FORTE, PIONEER
Trials show significant A1c reduction (~1.0–1.8%) and weight loss (3–6+ kg).

POSITIONING IN ADA 2024 STANDARDS OF CARE



A DISEASE-PROGRESSION–BASED APPROACH TO SEMAGLUTIDE THERAPY

SEMAGLUTIDE IN T2DM
Right Patient
Right Time
Right Benefit

2. ESTABLISHED T2DM: NEED FOR HIGH EFFICACY

When A1c is above target and high efficacy is needed, especially with:

- A1c ≥ 9%
- Marked hyperglycemia symptoms
- Need for significant weight loss
- High risk of treatment failure with other agents

3. T2DM WITH HIGH-RISK ASCVD

Semaglutide is recommended in T2DM patients with established ASCVD to reduce major adverse cardiovascular events (MACE).

Evidence: SUSTAIN-6
↓26% MACE
(CV death, nonfatal MI, or nonfatal stroke)

Benefits:

- ✓ Reduces CV death
- ✓ Reduces stroke
- ✓ Reduces nephropathy progression

4. T2DM WITH CHRONIC KIDNEY DISEASE

Recommended for patients with T2DM and CKD to slow kidney disease progression.

Evidence: FLOW Trial

- ↓24% composite of kidney failure, sustained eGFR decline ≥50%, or renal/CV death
- ↓18% CV death

5. STARTING INJECTION THERAPY

Semaglutide can be the first injectable therapy instead of insulin in many patients.

Best suited for:

- A1c above target on oral therapy
- Need for weight reduction
- Fear of injections / insulin
- To delay insulin initiation

6. INTENSIFYING INJECTION THERAPY

Add semaglutide to basal insulin (with or without oral agents) to:

- Improve glycemic control
- Promote weight loss
- Allow insulin dose reduction
- Lower hypoglycemia risk

Evidence: SUSTAIN-5
~1.4% additional A1c reduction with semaglutide + basal insulin vs placebo + basal insulin

7. ADVANCED T2DM: COMPLEX PATTERNS

Useful in complex patients with:

- Long disease duration
- Multiple comorbidities
- Polypharmacy
- Insulin resistance / obesity

Benefits:

- ✓ Glycemic control
- ✓ Weight loss
- ✓ Cardiorenal protection
- ✓ Improved quality of life

EVIDENCE ACROSS KEY OUTCOMES

OUTCOME	KEY EVIDENCE
Glycemic Control	Consistent A1c reduction ~1.0–1.8% across SUSTAIN, PIONEER and real-world studies.
Weight Loss	Average weight loss 3–7+ kg; greater with higher dose and longer duration.
Cardiovascular Protection	SUSTAIN-6: ↓26% MACE SELECT: ↓20% MACE in overweight/obese patients with CV disease (not only T2DM).
Renal Protection	FLOW: ↓24% kidney composite outcome and ↓18% CV death.
Liver Benefits	Improves steatosis, NASH resolution and fibrosis markers.
Safety	Low hypoglycemia risk; GI side effects most common; well tolerated long term.

PATIENTS WHO BENEFIT MOST

- Early T2DM or Pre-DM
- High A1c / High Efficacy Needed
- ASCVD
- CKD
- Obesity / Overweight
- Need for Injection Therapy
- Complex Patients

PRACTICAL CONSIDERATIONS

- Start low and go slow: start 0.25 mg weekly, titrate to 1 mg (or 2 mg) weekly.
- Administer once weekly, any time of day.
- Can be used with metformin, SGLT2i, DPP-4i, TZD and basal insulin.
- Monitor: A1c, weight, renal function, GI tolerance.
- Individualize treatment to patient goals and comorbidities.

KEY TAKE-HOME MESSAGE

Semaglutide is a foundational therapy across the full continuum of type 2 diabetes—from prevention and early disease to high-risk cardio-renal disease and injection therapy—offering powerful and comprehensive cardiometabolic benefits.

EARLIER USE. BETTER OUTCOMES. LONGER PROTECTION. BETTER LIFE.

Key References: 1. Davies MJ, et al. Diabetes Care. 2024;47(Suppl. 1):S1–S154. 2. Aroda VR, et al. Diabetes Care. 2024;47(10):209–238. 3. Marso SP, et al. N Engl J Med. 2016;375:1834–1844 (SUSTAIN-6). 4. Wilding JPH, et al. N Engl J Med. 2021;384:989–1002 (STEP 1). 5. Gerstein HC, et al. Lancet. 2024;403:1847–1860 (FLOW). 6. Lincoff AM, et al. N Engl J Med. 2023;389:2221–2232 (SELECT).

Abbreviations: T2DM = type 2 diabetes; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; HF = heart failure; MACE = major adverse cardiovascular events; A1c = glycated hemoglobin; GI = gastrointestinal.

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT; SOCIAL DETERMINANTS OF HEALTH

To avoid therapeutic inertia, reassess and modify treatment regularly (3–6 months)

Goal: Cardiovascular and Kidney Risk Reduction in High-Risk Individuals with Type 2 Diabetes*

+ASCVD†

+Indicators of high CVD risk

+ASCVD/indicators of high CVD risk‡

GLP-1 RA# with proven CVD benefit **OR** SGLT2i‡ with proven CVD benefit

If A1C is above goal

- For individuals on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- Pioglitazone^

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

SGLT2i‡

with proven HF benefit in this population

+CKD

eGFR <60 mL/min/1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). Repeat measurement is required to confirm CKD

+CKD (on maximally tolerated dose of ACEi or ARB)

SGLT2i‡ with primary evidence of reducing CKD progression

- SGLT2i can be started with eGFR ≥20 mL/min/1.73 m²
- Continue until initiation of dialysis or transplantation
- Glucose-lowering efficacy is reduced with eGFR <45 mL/min/1.73 m²

OR

GLP-1 RA# with proven CKD benefit

If A1C is above goal, for individuals on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiovascular and kidney risk reduction, management of other metabolic comorbidities, and/or glycemic lowering is needed

+Mitigating risk of MASLD or MASH

Agents with potential benefit in MASLD or MASH

GLP-1 RA, dual GIP and GLP-1 RA, pioglitazone, or combination of GLP-1 RA with pioglitazone

Use insulin in the setting of decompensated cirrhosis

Goal: Achievement and Maintenance of Weight and Glycemic Goals

+Weight management

Efficacy for weight loss

- **Very high:** Semaglutide, tirzepatide
- **High:** Dulaglutide, liraglutide
- **Intermediate:** GLP-1 RA (not listed above), SGLT2i
- **Neutral:** Metformin, DPP-4i

+Achievement and maintenance of glycemic goals

Metformin or other agent (including combination therapy) that provides adequate EFFICACY to achieve and maintain glycemic treatment goals

Prioritize avoidance of hypoglycemia in high-risk individuals

Efficacy for glucose lowering

- **Very high:** Dulaglutide (high dose), semaglutide, tirzepatide, insulin; Combination oral, combination injectable (GLP-1 RA and insulin)
- **High:** GLP-1 RA (not listed above), metformin, pioglitazone, SGLT2i, sulfonylurea
- **Intermediate:** DPP-4i

If A1C is above goal or significant hypoglycemia or hyperglycemia or barriers to care are identified

- Refer to DSMES to support self-efficacy in achievement of treatment goals
- Consider technology (e.g., diagnostic or personal CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of treatment goals

Use principles in Figure 9.3, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES, to meet individualized treatment goals

To avoid therapeutic inertia, reassess and modify treatment regularly (3–6 months)

If injectable therapy is needed to reduce A1C[1]

Consider GLP-1 RA or dual GIP and GLP-1 RA in most individuals prior to insulin[2]

INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Titrate to maintenance dose (varies within class)

If already on GLP-1 RA or dual GIP/GLP-1 RA, or if these are not appropriate, or if insulin is preferred

If A1C is above goal

Considerations for adding basal insulin[3]

Choice of basal insulin should be based on person-specific considerations, including cost. Refer to **Table 9.4** for insulin cost information. Consider prescription of glucagon for emergent hypoglycemia.

Initiation and titration of basal analog or bedtime NPH insulin[4]

INITIATION: Start 10 units per day OR 0.1–0.2 units/kg per day
TITRATION:

- Set FPG goal (see Section 6, "Glycemic Goals and Hypoglycemia")
- Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG goal without hypoglycemia
- For hypoglycemia: determine cause; if no clear reason, lower dose by 10–20%

Assess adequacy of insulin dose at every visit

Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., elevated bedtime-to-morning and/or postprandial-to-preprandial differential, hypoglycemia [aware or unaware], high glucose variability)

- If A1C is above goal and the individual is not already on a GLP-1 RA or dual GIP and GLP-1 RA, consider these classes in combination and with insulin (may use fixed-ratio product, if available and appropriate)
- If A1C remains above goal:

Initiation and titration of prandial insulin[5,6]

Usually one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate

INITIATION:

- 4 units per day or 10% of basal insulin dose
- If A1C <8% (<64 mmol/mol), consider lowering the basal dose by 4 units per day or 10% of basal dose

TITRATION:

- Increase dose by 1–2 units insulin dose or 10–15% twice weekly
- For hypoglycemia: determine cause; if no clear reason, lower corresponding dose by 10–20%

If on bedtime NPH, consider converting to twice-daily NPH plan

Conversion based on individual needs and current glycemic management. The following is one possible approach:

INITIATION:

- Total dose = 80% of current bedtime NPH dose
- 2/3 given in the morning
- 1/3 given at bedtime

TITRATION:

- Titrate based on individualized needs

If A1C is above goal

If A1C is above goal

Stepwise doses of prandial insulin
(i.e., two, then three additional injections)

Proceed to full basal-bolus plan
(i.e., basal insulin and prandial insulin with each meal)

Consider self-mixed/split insulin plan

Can adjust NPH and short/rapid-acting insulins separately

INITIATION:

- Total NPH dose = 80% of current NPH dose at the same total
- 2/3 given before breakfast
- 1/3 given before dinner
- Add 4 units of short/rapid-acting insulin to each injection or 10% of reduced NPH dose

TITRATION:

- Titrate each component of the plan based on individualized needs

Consider twice-daily premixed insulin plan

INITIATION:

- Usually unit per unit at the same total insulin dose, but may require adjustment to individual needs

TITRATION:

- Titrate based on individualized needs

Can patients with type 2 diabetes on complex basal–bolus (MDI) insulin regimens be safely simplified to once-weekly semaglutide plus basal insulin?

TRANSITION–T2D Trial — A Randomized, Open-Label, Controlled Trial

KEY MESSAGE

In appropriately selected patients with type 2 diabetes on complex basal–bolus (MDI) insulin regimens, switching to once-weekly semaglutide plus basal insulin maintained glycemic control, reduced total daily insulin dose and injection burden, without increasing hypoglycemia.

BACKGROUND

- Many patients with type 2 diabetes (T2D) use multiple daily injections (MDI) (basal + mealtime insulin).
- Complex regimens are associated with higher treatment burden, weight gain, and hypoglycemia risk.
- GLP-1 receptor agonists improve glycemic control and promote weight loss.
- Can MDI be safely de-intensified to once-weekly semaglutide + basal insulin?

STUDY DESIGN

SCREENING & RUN-IN
Optimize insulin doses (stable regimen)
2 to 14 weeks

RANDOMIZATION (1:1)
N = 60
2 : 1 Allocation
Open-label (40 : 20)

SEMAGLUTIDE + BASAL INSULIN
(De-intensification Arm) n = 40
- Stop all prandial (mealtime) insulin on Day 1
- Continue basal insulin (degludec)
- Start semaglutide once weekly (titrated to 1.0 mg as tolerated)

MDI (BASAL–BOLUS) INSULIN
(Control Arm) n = 20
- Continue basal–bolus insulin regimen (no change in strategy)

FOLLOW-UP 26 WEEKS
Primary endpoint: Proportion of patients with HbA1c ≤ 7.5% at 26 weeks

WHO WAS INCLUDED?

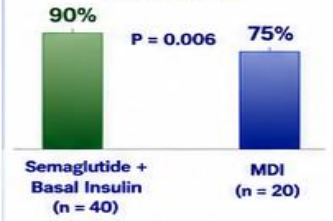
- Adults with type 2 diabetes on MDI:
  - Basal insulin + mealtime insulin
- HbA1c ≤ 7.5%
- Total daily insulin dose ≤ 120 units
- Stable insulin regimen ≥ 3 months
- BMI ≥ 25 kg/m²

KEY EXCLUSIONS

- Type 1 diabetes or LADA
- History of diabetic ketoacidosis
- Severe renal impairment (eGFR < 30)
- Very high insulin requirement (> 120 U/day)

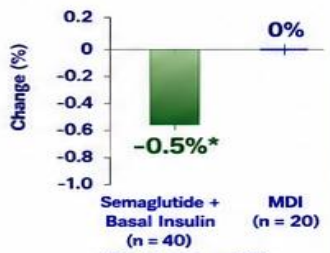
RESULTS AT 26 WEEKS

PRIMARY OUTCOME
HbA1c ≤ 7.5%
Patients achieving HbA1c ≤ 7.5%



Semaglutide was at least as effective as MDI

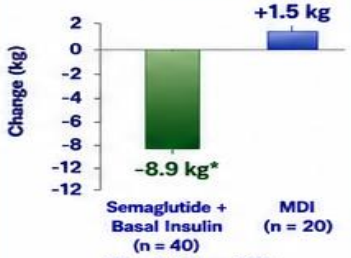
CHANGE IN HbA1c
(Mean ± SE)



*P < 0.001 vs MDI

Significant improvement in HbA1c with semaglutide

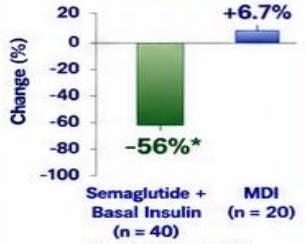
CHANGE IN BODY WEIGHT
(Mean ± SE)



*P < 0.001 vs MDI

Substantial weight loss with semaglutide

TOTAL DAILY INSULIN DOSE
(Mean ± SE)

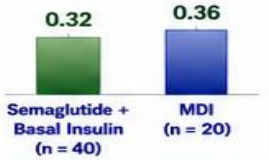


*P < 0.001 vs MDI

Marked reduction in insulin requirement

HYPOGLYCEMIA
(Events/Patient-Year)

No significant difference between groups



Similar low risk of hypoglycemia

PATIENT SATISFACTION
(Treatment Satisfaction Score)

Significantly higher with semaglutide (p < 0.001)

Improved treatment satisfaction

PATIENTS WITH ≥50% REDUCTION IN INSULIN DOSE

of patients in the semaglutide group

More than half achieved >50% reduction

CONCLUSION

In patients with type 2 diabetes on MDI who are reasonably controlled (HbA1c ≤ 7.5%) and use moderate insulin doses (≤120 units/day), immediate de-intensification of mealtime insulin and initiation of once-weekly semaglutide while continuing basal insulin:

- ✓ Maintains or improves glycemic control
- ✓ Promotes significant weight loss
- ✓ Reduces total insulin requirements substantially
- ✓ Does not increase hypoglycemia
- ✓ Improves treatment satisfaction

De-intensification to semaglutide + basal insulin is a safe, effective and patient-friendly strategy.

PRACTICAL IMPLICATION

Consider simplification to semaglutide + basal insulin in appropriate patients to reduce treatment burden, improve weight and metabolic outcomes, and enhance quality of life.

Fewer injections · Less treatment burden · Weight loss · Lower insulin dose · Better quality of life

TAKE-HOME ALGORITHM

T2D on MDI
(Basal + Mealtime Insulin)
- HbA1c ≤ 7.5%?
- Insulin ≤ 120 U/day?
- No T1D/LADA or DKA?
- Preserved renal function?
- Motivated for simplification?

→ **YES** — Candidate for De-intensification

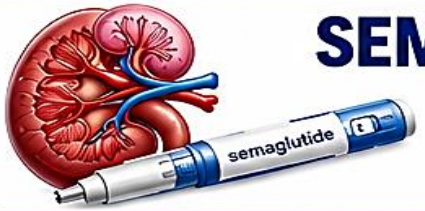
→ **Start Semaglutide** (weekly, titrate to 1.0 mg) + Continue Basal Insulin (Stop Mealtime Insulin Day 1)

→ **Monitor & Titrate Basal Insulin as needed**

Abbreviations: MDI = Multiple Daily Injections; T2D = Type 2 Diabetes; DKA = Diabetic Ketoacidosis; LADA = Latent Autoimmune Diabetes in Adults; eGFR = estimated Glomerular Filtration Rate.

Reference: Rodriguez, H., et al. TRANSITION–T2D Trial. Diabetes Obes Metab. 2025;27:760–768.

ClinicalTrials.gov Identifier: NCT05163382



SEMAGLUTIDE IN ADVANCED CKD AND DIALYSIS:

Clinical Questions, Safety, and Future Perspectives

Evidence is expanding that semaglutide can be used safely in advanced CKD, including dialysis, with meaningful cardiorenal and metabolic benefits.

PROVEN BENEFITS BEYOND GLYCEMIC CONTROL

Glycemic Control | Weight Loss | CV Protection | Renal Protection | Liver Benefits | Better Outcomes

1. CAN SEMAGLUTIDE BE USED IN ADVANCED CKD?

CKD Stage	eGFR (mL/min/1.73 m²)	Use of Semaglutide	Dose Adjustment
Stage 4	15–29	✓ Yes, can be used	No adjustment
Stage 5 (Non-dialysis)	<15	✓ Yes, can be used with caution	No adjustment
Hemodialysis (HD)	—	Limited data. PK not changed. Not removed by dialysis (>99% albumin binding).	No adjustment
Peritoneal Dialysis (PD)	—	Very limited data. Can be considered (individualized).	No adjustment

Pharmacokinetics: Semaglutide is metabolized by proteolysis and β-oxidation, not renally excreted. Not dialyzable.

2. EVIDENCE IN ADVANCED CKD & DIALYSIS

Clinical Trial Data

FLOW Trial (2024) T2DM with CKD (eGFR ≥25)
- ✓ Kidney failure by 24%
- ✓ Sustained ≥50% eGFR decline by 22%
- ✓ CV death by 20%
- ✓ Albuminuria by 30%

SUSTAIN-6 Included patients with eGFR as low as 15
- ✓ Major CV events by 26%
- ✓ Trend toward lower renal outcomes

Observational Data in Dialysis Patients
- ✓ Glycemic improvement
- ✓ Weight reduction
- ✓ No unexpected safety signals (ongoing real-world studies)

KEY TAKEAWAY

Evidence supports efficacy and safety in advanced CKD. FLOW establishes semaglutide as a kidney-protective therapy in T2DM with CKD down to eGFR 25.

3. SAFETY CONSIDERATIONS IN ADVANCED CKD & DIALYSIS

Common Adverse Effects
- Nausea
- Vomiting
- Diarrhea
- Constipation
- Decreased appetite

Usually mild to moderate and dose-dependent.

Risk of AKI

No direct nephrotoxicity.

AKI usually occurs due to:
- Dehydration from GI adverse effects
- Reduced oral intake
- Concomitant diuretics
- Acute illness

Prevent dehydration and monitor closely.

Patients at Higher Risk
- Elderly and frail
- eGFR <30
- On diuretics
- Low BP
- Poor oral intake

Start low, go slow, and monitor closely.

Monitoring Recommendations

Renal function (eGFR, Cr) | Hydration status & volume | Weight & BP | Electrolytes (as indicated) | GI tolerance & nutrition

Baseline, after dose escalation (if needed), and periodically (every 3–6 months) or as clinically indicated.

4. COMBINATION & CONCOMITANT THERAPIES

Therapy	Can be Combined with Semaglutide?	Clinical Notes
ACEi / ARB	✓ Yes	Foundation therapy for CKD. Continue unless contraindicated.
SGLT2 inhibitor	✓ Yes	Complementary benefits on kidney, heart and metabolism.
Finerenone	✓ Yes	Useful in albuminuric diabetic CKD (with eGFR ≥25). Monitor K⁺.
Insulin	✓ Yes	May require dose reduction. Monitor for hypoglycemia.
Other glucose-lowering medications	⚠ Use with caution	Adjust doses based on eGFR (hypoglycemia risk).

5. PRACTICAL PRESCRIBING IN ADVANCED CKD & DIALYSIS

Starting dose	0.25 mg once weekly (SC)
Titration	Increase every 4 weeks as tolerated (0.5 mg → 1 mg → 2 mg)
Titration speed	Consider slower titration in frail, elderly, or advanced CKD (to improve GI tolerability).
Missed dose	Follow standard guidance: If ≤5 days late, give when remembered; if >5 days, skip and resume at next scheduled dose.
When to hold	• Severe GI symptoms or dehydration • Acute illness or hospitalization • Before major surgery (individualized)

6. SPECIAL POPULATIONS

Dialysis Patients	PK not affected by HD; not removed by dialysis. Limited outcomes data. Use individualized with close monitoring.
Peritoneal Dialysis	Very limited data. Can be considered in experienced centers.
Kidney Transplant Recipients	Limited case series. Monitor for GI tolerance and potential interaction with immunosuppressants (theoretical).
Non-Diabetic CKD	Emerging evidence of kidney benefit, but routine use solely for CKD not yet established.

7. FUTURE PERSPECTIVES

- More data in dialysis populations and very advanced CKD (eGFR <15).
- Long-term outcome studies in non-diabetic CKD.
- Exploring benefits on inflammation, fibrosis, and kidney structure.
- Combination strategies for cardio–kidney–metabolic protection.
- Real-world evidence and registries will define optimal use.

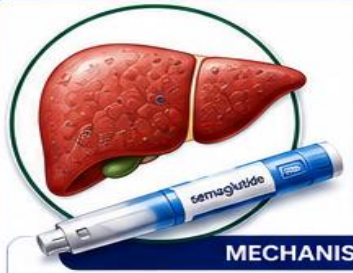
KEY TAKE-HOME MESSAGES

- Semaglutide can be used safely in advanced CKD, including dialysis, without dose adjustment.
- FLOW trial confirms significant kidney and cardiovascular benefits in T2DM with CKD down to eGFR 25.
- Prevent dehydration. Monitor kidney function and GI tolerance carefully.
- Combine with SGLT2i, ACEi/ARB, and other appropriate therapies for maximal benefit.

Better Kidney Health. Better Heart Health. Better Life.

Abbreviations: CKD = Chronic Kidney Disease; eGFR = estimated Glomerular Filtration Rate; HD = Hemodialysis; PD = Peritoneal Dialysis; PK = Pharmacokinetics; GI = Gastrointestinal; ACEi = Angiotensin-Converting Enzyme inhibitor; ARB = Angiotensin II Receptor Blocker; SGLT2i = Sodium–Glucose Cotransporter 2 inhibitor; CV = Cardiovascular; T2DM = Type 2 Diabetes Mellitus; BP = Blood Pressure.

References:
1. ADA Standards of Care in Diabetes—2026. Diabetes Care. 2026.
2. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.
3. Perkovic V, et al. Semaglutide and Kidney Outcomes in Type 2 Diabetes. N Engl J Med. 2024;391:109–121 (FLOW Trial).
4. Marso SP, et al. N Engl J Med. 2016;375:1834–1844 (SUSTAIN-6).
5. Jorsal A, et al. Diabetes Obes Metab. 2021;23:2450–2460.



SEMAGLUTIDE IN MASLD/MASH

Targeting the Root Causes. Improving Liver Health. Changing Outcomes.

Semaglutide, a long-acting GLP-1 receptor agonist, improves steatosis, inflammation and fibrosis in MASLD/MASH primarily through weight reduction, improved insulin sensitivity and direct metabolic and anti-inflammatory effects.

ONE MOLECULE. MULTIPLE BENEFITS.

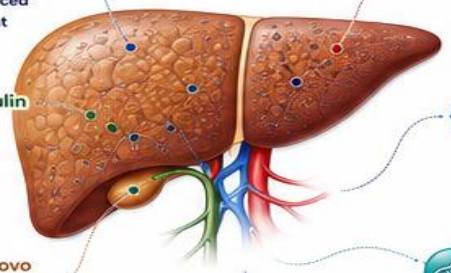
- Weight Loss
- Metabolic Improvement
- Liver Protection
- Anti-Inflammatory
- Better Outcomes

MECHANISMS OF ACTION IN MASLD/MASH

Weight reduction
Caloric restriction, reduced adiposity and visceral fat

Improved insulin sensitivity
Lower insulin resistance reduces hepatic fat accumulation

Reduced de novo lipogenesis
↓ SREBP-1c activity and hepatic fat synthesis



Anti-inflammatory effects
↓ Pro-inflammatory cytokines (TNF-α, IL-6, CRP)
↑ Adiponectin

Antifibrotic effects
↓ Hepatic stellate cell activation
↓ Collagen deposition
Potential fibrosis regression

Improved mitochondrial function & oxidative stress
Enhances mitochondrial biogenesis and reduces lipotoxicity

↓
GLP-1 RECEPTOR ACTIVATION
(Liver, Kupffer cells, Stellate cells, Endothelium)
↓

↓ Hepatic fat ↓ Inflammation ↓ Fibrosis
Improved liver function & clinical outcomes

EVIDENCE FROM CLINICAL TRIALS

Phase 2 Trial (Newsome et al., NEJM 2021)
Patients with NASH and fibrosis (F1–F3)
Semaglutide 0.1–0.4 mg once daily for 72 weeks

NASH Resolution (no worsening of fibrosis)	Fibrosis Improvement (≥1 stage, no worsening of NASH)
59%	**43%**
vs 17% with placebo (p<0.001)	vs 33% with placebo (NS)

ESSENCE Trial (Lancet Gastro Hep 2024)
Patients with biopsy-proven MASH and fibrosis (F2–F3)
Semaglutide 2.4 mg once weekly for 240 weeks

MASH Resolution (no worsening of fibrosis)	Fibrosis Improvement (≥1 stage, no worsening of MASH)
63%	**37%**
vs 34% with placebo (p<0.0001)	vs 22% with placebo (p=0.0008)

Real-World & Observational Data
- ✓ Consistent improvement in ALT, AST, GGT and liver stiffness
- ✓ Greater reduction in liver fat content on MRI-PDFF
- ✓ Benefits amplified with ≥10% weight loss
- ✓ Well tolerated with favorable safety profile

KEY BENEFITS IN MASLD/MASH

- **Reduces hepatic steatosis**
  Significant decrease in liver fat content (MRI-PDFF, CAP)
- **Promotes MASH resolution**
  High rates of NASH/MASH resolution without fibrosis worsening
- **Improves hepatic fibrosis**
  Significant improvement in fibrosis stage
- **Improves liver biochemistry & stiffness**
  ↓ ALT, AST, GGT and liver stiffness (elastography)
- **Cardiometabolic benefits**
  Weight loss, improved glycemic control, lipid profile and BP
- **Reduces progression to cirrhosis and liver-related events**
  Potential to modify long-term clinical outcomes

EFFECTS BEYOND THE LIVER

- Cardiovascular Risk Reduction
- Renal Protection
- β-cell Function Improvement
- Visceral Fat Reduction
- Systemic Anti-inflammatory

WHO MAY BENEFIT MOST?

- Obesity with MASLD/MASH
- Type 2 Diabetes with MASLD/MASH
- Biopsy-proven MASH (F1–F3)
- Metabolic Syndrome
- High Cardiovascular Risk

Guidelines (AASLD 2023): GLP-1 RAs are not yet approved for MASH, but can be considered for patients with NASH/MASH and comorbid obesity or T2D for their proven metabolic and hepatic benefits.

PRACTICAL CONSIDERATIONS

- Start low, go slow: 0.25 mg weekly → titrate to 2.4 mg weekly (as tolerated).
- Combine with lifestyle intervention: diet, exercise, weight loss (≥7–10% for maximum liver benefit).
- Monitor: weight, glycemia, liver enzymes, and non-invasive fibrosis tests (e.g., FibroScan®, FIB-4).
- Long-term therapy likely needed to sustain benefits.
- Well tolerated; GI side effects are most common and usually transient.

SAFETY CONSIDERATIONS

- GI adverse effects (nausea, vomiting, diarrhea) are dose-dependent.
- Risk of gallbladder disease—monitor in predisposed patients.
- Pancreatitis is rare; counsel patients about symptoms.
- No known direct hepatotoxicity.
- Contraindicated in personal/family history of medullary thyroid carcinoma or MEN 2.
- Use caution in severe gastroparesis.

KEY TAKE-HOME MESSAGE

Semaglutide is a powerful disease-modifying therapy in MASLD/MASH, delivering significant improvements in steatosis, inflammation and fibrosis while providing comprehensive cardiometabolic benefits.

BETTER LIVER HEALTH.
BETTER METABOLIC CONTROL.
BETTER FUTURE.

References: 1. Newsome PN, et al. NEJM. 2021;384:1113-1124. 2. Armstrong MJ, et al. Lancet Gastroenterol Hepatol. 2024;9:213-226 (ESSENCE Trial). 3. AASLD Practice Guidance on the Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease. Hepatology. 2023.
4. Cusi K, et al. Diabetes Care. 2022;45:2272-2287. 5. Mann JFE, et al. AGA Clinical Practice Update on Pharmacological Interventions for MASH. Gastroenterology. 2024.

Abbreviations: MASLD = Metabolic dysfunction-associated steatotic liver disease; MASH = Metabolic dysfunction-associated steatohepatitis; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CRP = C-reactive protein; BP = Blood pressure; GLP-1 RA = GLP-1 receptor agonist.

SEMAGLUTIDE IN HEART FAILURE

Beyond Weight Loss: Improving Symptoms, Functional Capacity and Quality of Life in HFpEF

Targeting obesity, inflammation and cardiorenal dysfunction to improve HFpEF outcomes

ONE MOLECULE MULTIPLE BENEFITS

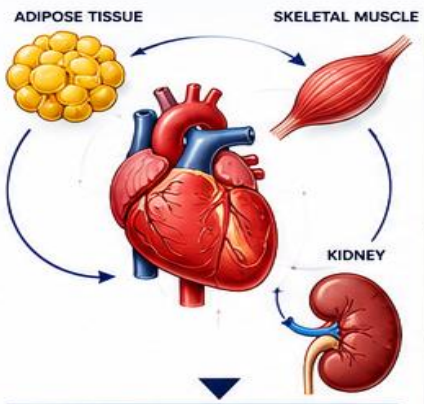
Heart | Weight | Kidney | Exercise | Quality of Life

Semaglutide improves heart failure outcomes primarily through **weight reduction**, **decreased systemic inflammation**, improved **endothelial function**, lower **cardiac workload**, enhanced **exercise capacity** and better **cardiorenal health**.

MECHANISMS OF ACTION IN HEART FAILURE

GLP-1 RECEPTOR ACTIVATION

- Improved vascular function
- Reduced oxidative stress
- Reduced myocardial energy demand
- Improved metabolic efficiency



- Obesity ↓
- Inflammation ↓
- Epicardial fat ↓
- Blood pressure ↓
- Insulin resistance ↓
- Diastolic dysfunction ↓
- Pulmonary congestion ↓
- Exercise tolerance ↑
- Quality of life ↑

MAJOR CLINICAL BENEFITS

- Significant weight reduction
- Better NYHA functional class
- Improved KCCQ score (Kansas City Cardiomyopathy Questionnarie)
- Increased 6-minute walk distance
- Improved exercise tolerance and physical function
- Lower systemic inflammation (CRP)
- Reduced congestion and hospitalization risk
- Better quality of life and daily functioning

LANDMARK TRIALS & EVIDENCE

STEP-HFpEF (2023)

Patients with obesity and HFpEF (without diabetes)
- Significant improvement in KCCQ-CSS (primary endpoint)
- Greater weight loss vs placebo (~13% vs ~2%)
- Improved 6-minute walk distance
- Reduced inflammatory markers (e.g., CRP, NT-proBNP)

STEP-HFpEF DM (2024)

HFpEF with obesity and type 2 diabetes
- Similar improvement in KCCQ-CSS
- Better physical limitation and symptoms
- Improved quality of life and exercise capacity

SELECT (2023)

Cardiovascular outcomes in patients with overweight/obesity and established CVD
- Reduced major adverse CV events by 20%
- Reduced heart failure–related outcomes (exploratory analyses)

FLOW (2024)

Chronic kidney disease with type 2 diabetes
- Slows kidney disease progression and reduces CV death, supporting HF management in CKD patients

OVERALL EVIDENCE LEVEL

HFpEF symptoms & quality of life	★★★★★	Functional capacity	★★★★☆
Weight loss	★★★★½	Cardiorenal protection	★★★★☆

PATIENTS WHO MAY BENEFIT

HFpEF (preserved EF) | Obesity-related heart failure | Type 2 diabetes with HF | CKD with HF | Metabolic syndrome | OSA-associated heart failure

Greatest evidence in HFpEF, but benefits extend across a broad range of cardiometabolic phenotypes.

CLINICAL PEARLS

1. Evidence for HFpEF is strongest; benefits are clinically meaningful.
2. Use as add-on to guideline-directed medical therapy for HF.
3. Monitor volume status; adjust diuretics if needed.
4. Continue SGLT2 inhibitor when indicated—complementary benefits.
5. Weight loss contributes substantially to benefit, but semaglutide improves cardiac structure, function and inflammation beyond weight reduction.

SAFETY & TOLERABILITY

- Generally well tolerated.
- Gastrointestinal adverse effects are most common; use slow dose escalation.
- Maintain hydration and monitor volume status.
- Monitor renal function, especially in advanced CKD.
- No signal for worsening heart failure in clinical trials.

! Use with caution in patients with a history of medullary thyroid carcinoma or MEN 2 and during pregnancy.

KEY TAKE-HOME MESSAGE

Semaglutide has become the first GLP-1 receptor agonist with robust evidence for improving symptoms, functional status and quality of life in patients with obesity-related HFpEF, representing a major advance in cardiometabolic medicine.

References: 1. Kosiborod M, et al. Semaglutide in Patients with Obesity-Related HFpEF. N Engl J Med. 2023;389:1069-1080. (STEP-HFpEF) | 2. Kosiborod M, et al. Semaglutide in HFpEF with Obesity and Type 2 Diabetes. Lancet. 2024;403:1637-1650. (STEP-HFpEF DM) | 3. Lincoff AM, et al. Semaglutide and Cardiovascular Outcomes in Patients with Overweight or Obesity. N Engl J Med. 2023;389:2221-2232. (SELECT) | 4. Gerstein HC, et al. Semaglutide and Kidney Outcomes in T2D and CKD. N Engl J Med. 2024;390:1236-1248. (FLOW)

Abbreviations: HFpEF = Heart Failure with Preserved Ejection Fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; CRP = C-Reactive Protein; OSA = Obstructive Sleep Apnea; CKD = Chronic Kidney Disease; CVD = Cardiovascular Disease.

SEMAGLUTIDE IN NEUROLOGY

Beyond Glycemia and Weight: Neuroprotection, Neuroinflammation Reduction and Functional Recovery

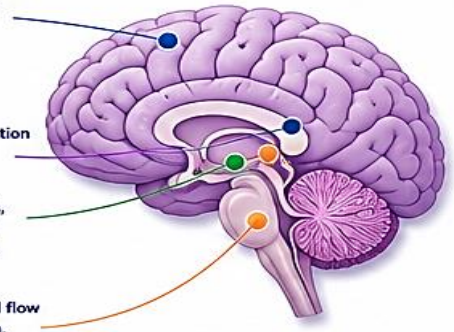
ONE MOLECULE. MULTIPLE BENEFITS.

- Neuroprotection
- Anti-Inflammatory
- Synaptic Support
- Metabolic Support
- Better Function & Quality of Life

Semaglutide, a long-acting GLP-1 receptor agonist, crosses the blood–brain barrier and acts on central and peripheral GLP-1 receptors to improve neuronal survival, reduce neuroinflammation and oxidative stress, and enhance functional outcomes in many neurologic disorders.

MECHANISMS OF ACTION IN THE NERVOUS SYSTEM

- GLP-1 receptors are widely expressed in the brain: cortex, hippocampus, substantia nigra, hypothalamus and brainstem.
- Reduces neuroinflammation and oxidative stress.
- Enhances neurogenesis, synaptic plasticity and mitochondrial function.
- Improves cerebral blood flow and endothelial function.



Cortex · Hippocampus · Substantia Nigra · Hypothalamus · Brainstem

KEY NEUROLOGIC BENEFITS

Neuroprotection
Reduces neuronal apoptosis and protects against excitotoxicity.

Anti-inflammatory Effects
Decreases microglial activation and pro-inflammatory cytokines (e.g., IL-1β, TNF-α).

Cognitive Benefits
Improves learning, memory and executive function through hippocampal effects.

Metabolic Support
Enhances neuronal energy metabolism and reduces mitochondrial dysfunction.

Improved Cerebral Perfusion
Improves endothelial function and cerebral blood flow regulation.

Functional Outcomes
Improves disability, daily functioning and quality of life.

EVIDENCE FROM CLINICAL TRIALS & STUDIES

Stroke (SELECT Trial)
Reduced risk of stroke by 28% in people with overweight/obesity and established CVD without diabetes.

Alzheimer's Disease (Phase 2 Trial)
Semaglutide slowed cognitive decline and reduced brain atrophy in early Alzheimer's disease.

Parkinson's Disease (Preclinical & Early Clinical Data)
Improved motor function and dopaminergic neuron survival in models; early human studies show potential symptomatic benefit.

Multiple Sclerosis (Preclinical Data)
Reduced neuroinflammation and demyelination; improved axonal integrity.

Migraine & Headache Disorders (Emerging Evidence)
May reduce attack frequency and severity via central anti-inflammatory and metabolic effects.

Idiopathic Intracranial Hypertension (IIH)
Promotes weight loss and may reduce intracranial pressure and symptoms.

POTENTIAL APPLICATIONS IN NEUROLOGY

- Stroke Prevention & Recovery
- Alzheimer's Disease
- Parkinson's Disease
- Multiple Sclerosis
- Migraine & Chronic Headache
- Depression (Adjunct)
- Epilepsy (Adjunct)
- Neuropathic Pain (Adjunct)

METABOLIC–NEUROLOGIC CONNECTION

- Obesity / Overweight →
- Insulin Resistance →
- Chronic Inflammation →
- Endothelial Dysfunction →
- Oxidative Stress →

Neuronal Injury & Dysfunction

- Cognitive Decline
- Motor Dysfunction
- Neurodegeneration

SEMAGLUTIDE

- Improves Metabolism
- Reduces Inflammation
- Enhances Perfusion
- Protects Neurons
- Improves Outcomes

SAFETY & TOLERABILITY IN NEUROLOGIC POPULATIONS

- Generally well tolerated.
- No signal for increased neuropsychiatric adverse events in major trials.
- Monitor in patients with history of depression or eating disorders.
- Use as part of a comprehensive, multidisciplinary approach.

COMMONLY REPORTED (GI)

- Nausea
- Vomiting
- Diarrhea / Constipation
- Decreased appetite
- Abdominal discomfort

Start low, go slow and individualize therapy.
Focus on long-term neurologic and metabolic benefits.

KEY TAKE-HOME MESSAGE

Semaglutide offers a unique opportunity in neurology by targeting the interface of metabolism, inflammation and neurodegeneration—leading to better brain health and improved quality of life.

A MULTIDISCIPLINARY APPROACH

- Neurology
- Endocrinology
- Psychiatry
- Rehabilitation
- Nutrition

**Better Brain Health.
Better Function.
Better Life.**

Abbreviations: GLP-1 = Glucagon-Like Peptide-1; CVD = Cardiovascular Disease; IL = Interleukin; TNF-α = Tumor Necrosis Factor-alpha; IIH = Idiopathic Intracranial Hypertension; GI = Gastrointestinal.

References: 1. Marso SP, et al. N Engl J Med. 2016;375:1834-1844 (SELECT Trial). 2. Athauda D, et al. Lancet Neurol. 2017;16:177-186. 3. McClean PL, et al. Nat Rev Neurol. 2021;17:207-223. 4. Wang F, et al. Front Neurosci. 2022;16:800688. 5. Mehta A, et al. Neurology. 2021;96:e2945-e2957.

Semaglutide is not approved for the treatment of neurologic disorders. Use should be individualized and based on current evidence and guidelines.

EVIDENCE FROM CLINICAL TRIALS & STUDIES

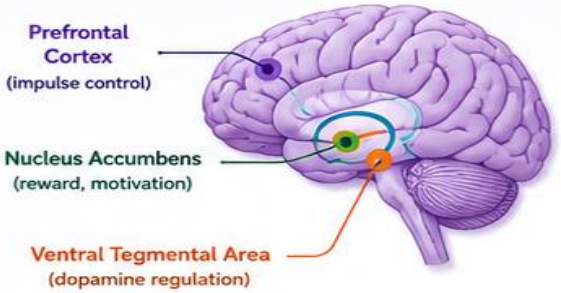
- **Stroke (SELECT Trial)**
  Reduced risk of stroke by 28% in people with overweight/obesity and established CVD without diabetes.
- **Alzheimer's Disease (Phase 2 Trial)**
  Semaglutide slowed cognitive decline and reduced brain atrophy in early Alzheimer's disease.
- **Parkinson's Disease (Preclinical & Early Clinical Data)**
  Improved motor function and dopaminergic neuron survival in models; early human studies show potential symptomatic benefit.
- **Multiple Sclerosis (Preclinical Data)**
  Reduced neuroinflammation and demyelination; improved axonal integrity.
- **Migraine & Headache Disorders (Emerging Evidence)**
  May reduce attack frequency and severity via central anti-inflammatory and metabolic effects.
- **Idiopathic Intracranial Hypertension (IIH)**
  Promotes weight loss and may reduce intracranial pressure and symptoms.

SEMAGLUTIDE
IN ADDICTION & BEHAVIORAL MEDICINE
Modulating Reward Pathways and Cravings

★ ONE MOLECULE.
MULTIPLE ORGANS.
BETTER OUTCOMES.

Semaglutide, a long-acting GLP-1 receptor agonist, acts on **brain reward circuits** to reduce cravings, addictive behaviors and substance use—supporting recovery and improving behavioral health outcomes.

MECHANISMS OF ACTION IN THE BRAIN



- GLP-1 receptors are expressed in key reward regions.
- Reduces dopaminergic overactivity in mesolimbic pathways.
- Enhances prefrontal cortex function and impulse control.
- Decreases reward salience and cue-induced craving.
- Promotes satiety, stress resilience and mood stability.

EVIDENCE ACROSS ADDICTIONS

SUBSTANCE / BEHAVIOR	EVIDENCE SUMMARY	KEY FINDINGS
Alcohol Use Disorder	Multiple RCTs & observational studies	Reduced alcohol consumption, heavy drinking days and craving
Smoking Cessation	RCTs (semaglutide + behavioral support)	Higher abstinence rates and lower craving intensity
Food Addiction & Binge Eating	RCTs in binge eating disorder and food addiction	Reduced cravings, binge episodes and emotional eating
Other Substance Use (eg, opioids, stimulants)	Preclinical and emerging clinical studies	Lower cue reactivity and drug-seeking behavior (promising early data)

CLINICAL BENEFITS

- Reduces cravings and reward-driven behavior
- Supports abstinence and relapse prevention
- Improves impulse control and decision-making
- Improves weight, metabolic health and inflammatory profile
- Enhances mood, quality of life and treatment adherence
- Complements psychotherapy and behavioral interventions

KEY CLINICAL TRIALS & STUDIES

- **STEP-AD:** Semaglutide reduced alcohol intake and craving in people with overweight/obesity and alcohol use disorder.
- **Randomized trials in smokers:** Higher quit rates and reduced cravings with semaglutide vs placebo.
- **Binge Eating Disorder trials:** Significant reduction in weekly binge episodes and food cravings.
- **Preclinical models:** Semaglutide reduces drug-seeking behavior and reinstatement across substances.

PATIENTS WHO MAY BENEFIT

- Alcohol Use Disorder
- Nicotine Dependence
- Binge Eating Disorder
- Other Substance Use Disorders
- Obesity with Addictive Behaviors

SAFETY CONSIDERATIONS

- Generally well tolerated; GI side effects most common.
- No known abuse potential.
- Monitor for mood changes and suicidal ideation (rare).
- Use as part of a comprehensive, multidisciplinary approach.

KEY TAKE-HOME MESSAGE

Semaglutide goes beyond metabolic control—
it targets the brain's **reward system** to reduce cravings and support recovery from addiction.

INTEGRATED CARE APPROACH

Semaglutide + Psychotherapy + Lifestyle Interventions + Support Systems

**Better Control.
Fewer Cravings.
Stronger Recovery.
Better Lives.**

Semaglutide is not approved specifically for addiction treatment. Use should be individualized and combined with standard therapies.

References: STEP-AD Trial (2023); Addolorato G, et al. Gut. 2022;71:239–250; Marrone G, et al. J Clin Endocrinol Metab. 2022;107:e2340–e2350; Davies MJ, et al. Diabetes Care. 2021;44:2656–2667; Weinstein A, et al. JAMA Psychiatry. 2023;80:1095–1105.

PART 4

SEMAGLUTIDE vs TIRZEPATIDE

10 Key Clinical Questions for Evidence-Based Choice

Two Powerful Incretin Therapies.
One Goal — Better Health for Each Patient.

CLINICAL QUESTION	SEMAGLUTIDE (GLP-1 RA)	TIRZEPATIDE (Dual GIP/GLP-1 RA)	WINNER / KEY POINT
1 Which lowers HbA1c more?	1.5–1.8% (STEP / SUSTAIN)	2.0–2.4% (SURPASS)	Tirzepatide — Greater glycemic efficacy
2 Which produces greater weight loss?	~15% (STEP 1, 68 weeks)	~20–22.5% (SURMOUNT-1)	Tirzepatide — Greater weight loss
3 Which has stronger cardiovascular evidence?	SELECT: MACE ↓ 20% SUSTAIN-6: MACE ↓ 26% SOUL: MACE ↓ 14% (T2DM)	SURPASS-CVOT: Non-inferior to insulin (superior trend)	Semaglutide — More robust CV outcome data
4 Which has better CKD evidence?	FLOW: Kidney outcome ↓ 24% Albuminuria ↓ 30%	Renal benefit signals (secondary analyses)	Semaglutide — Dedicated renal outcome trial
5 Which is better in MASH / MASLD?	ESSENCE: MASH resolution 62.9% STEP NAFLD: liver fat ↓ up to 40%	SURMOUNT-MASH: MASH resolution 62.4%, fibrosis improvement 51%	= Very close — Both show marked benefit
6 Which is better tolerated?	GI AEs: usually mild–moderate, tend to plateau	Slightly higher rate of GI AEs, but manageable with slow titration	Semaglutide — Slightly better tolerability
7 Which preserves lean mass better?	Less lean mass loss vs placebo with exercise & adequate protein	Similar or slightly more lean mass preservation (early analyses)	= Similar — Preserve muscle with protein + exercise
8 Which has better long-term maintenance evidence?	STEP 4: weight regain when stopped; continued therapy maintains loss	SURMOUNT-MAINTAIN: Continue MTD: −15.5% vs Stop: −0.8% at 52 weeks	Tirzepatide — Newer, strong maintenance data
9 Which is more evidence-based today?	Longest real-world and RCT experience across multiple organ systems	Rapid and impressive evidence but shorter track record	Semaglutide — More extensive evidence base
10 Which drug would I choose?	Best for patients with CVD, CKD, MASH, HFpEF, or if moderate weight loss with proven outcome data is a priority	Best for patients needing maximal weight loss and glycemic control, or after inadequate response to GLP-1 RA	= No overall winner — Choose the right drug for the right patient

KEY TAKE-HOME MESSAGES

- Both semaglutide and tirzepatide are highly effective, safe, and transformative therapies for T2DM and obesity.
- Tirzepatide lowers HbA1c and body weight more than semaglutide.
- Semaglutide has more mature evidence for cardiovascular, renal, hepatic and broader organ protection.
- Both improve cardiometabolic risk, quality of life, and long-term health outcomes.
- Treatment choice should be individualized based on patient characteristics, comorbidities, goals, and values—not a "one-drug-fits-all" approach.

CLINICAL CONSIDERATIONS

- Use slow titration to improve tolerability.
- Ensure adequate protein intake and exercise to preserve muscle mass.
- Continue long-term therapy whenever possible—obesity is a chronic, relapsing disease.
- Monitor and manage gastrointestinal side effects, hydration, and nutritional status.

PRACTICAL PATIENT-SELECTION GUIDE

Choose SEMAGLUTIDE when...

- Established ASCVD or high CV risk
- Chronic kidney disease
- MASH / MASLD
- Heart failure with preserved EF
- Need for proven long-term outcome data
- If prior GLP-1 experience preferred

Choose TIRZEPATIDE when...

- Greater weight loss is the primary goal
- Higher baseline HbA1c or inadequate response to GLP-1 RA
- Severe obesity (BMI ≥35 kg/m²)
- Need for maximal cardiometabolic improvement
- Patient willing to accept slightly more GI AEs

Either drug is appropriate when...

- Obesity without major comorbidities
- Early intervention for cardiometabolic risk
- Patient preference or formulary decision
- Both expected to deliver substantial health benefits

APPROVED DOSES

Semaglutide
- T2DM: up to 1 mg weekly
- Obesity: 2.4 mg weekly

Tirzepatide
- T2DM: up to 15 mg weekly
- Obesity: up to 15 mg weekly

THE BOTTOM LINE

The optimal incretin therapy is not the drug with the largest average weight loss—it is the drug whose evidence and clinical profile best match the individual patient.

Right Patient ✓ Right Drug ✓ Better Outcomes

Precision Incretin Therapy | Individualized Choice | Longer, Healthier Lives

Different Strengths. Shared Success.

PART 5

SEMAGLUTIDE: EMERGING INDICATIONS AND THE FUTURE

From One Molecule to Multiorgan, Lifespan Impact

Semaglutide is poised to transform the future of medicine across multiple disease domains and patient populations.

EMERGING INDICATIONS: EXPANDING THE HORIZON

Neurology – Alzheimer's Disease

Key Evidence
- Reduced amyloid burden in early studies
- Slower cognitive decline signals (phase 2 trials)

Potential Benefits
Neuroprotection, reduced neuroinflammation, cognitive preservation

Status: Phase 2 / 3

Neurology – Parkinson's Disease

Key Evidence
- Improved motor function in early studies
- May reduce neuro-inflammation

Potential Benefits
Slowing disease progression, improved motor outcomes, quality of life

Status: Early Phase 2

Addiction Medicine

Key Evidence
- Reduced alcohol consumption (phase 2 trials)
- Decreased cravings for alcohol and food
- Reduced smoking in preclinical and early trials

Potential Benefits
Support for alcohol use disorder, smoking cessation, food addiction

Status: Phase 2

PCOS (Polycystic Ovary Syndrome)

Key Evidence
- Improved weight and insulin resistance
- Improved menstrual regularity
- Reduced androgen levels (preliminary data)

Potential Benefits
Metabolic improvement, fertility potential, symptom relief

Status: Early Phase 2 / 3

MASLD / MASH

Key Evidence
- ESSENCE: MASH resolution 62.9% vs 34.3% (placebo)
- STEP NAFLD: liver fat ↓ up to 40%
- Fibrosis improvement signals

Potential Benefits
Resolution of steatohepatitis, fibrosis regression, reduced liver-related events

Status: Phase 3

CKD in Non-Diabetic Populations

Key Evidence
- Albuminuria reduction in preclinical & early studies
- eGFR preservation signals
- Anti-inflammatory and hemodynamic effects

Potential Benefits
Kidney protection beyond glycemic effects

Status: Early Phase 2 / 3

Heart Failure with Preserved EF (HFpEF)

Key Evidence
- STEP-HFpEF: improved KCCQ score (+16.6)
- Increased 6-minute walk distance (+21.5 m)
- Reduced symptoms and physical limitations

Potential Benefits
Improved symptoms, exercise capacity and quality of life

Status: Phase 3

Prevention of Type 2 Diabetes

Key Evidence
- PIONEER & STEP data show delay in diabetes progression
- Improved insulin sensitivity and weight reduction

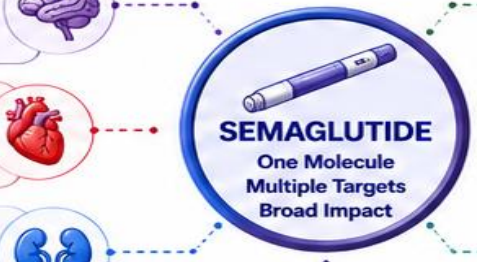
Potential Benefits
Delay or prevention of T2DM in high-risk individuals

Status: Supported by Strong Data

THE FUTURE OF SEMAGLUTIDE: A MULTIORGAN ROADMAP

STRENGTH OF EVIDENCE

- **Approved Indications**
  T2DM, Obesity, CVD Risk Reduction (SELECT)
- **Strong Phase 3 Evidence**
  CKD (FLOW), MASH (ESSENCE), HFpEF (STEP-HFpEF), OSA (STEP-OSA)
- **Phase 2 Evidence**
  Alzheimer's, Parkinson's, Addiction, PCOS, Non-diabetic CKD
- **Early / Exploratory**
  Cancer, Longevity, Sarcopenia, Pain Modulation



BRAIN
Neuroprotection, reduced neuroinflammation, slow potential in Alzheimer's, Parkinson's, stroke recovery, and addiction.

HEART & VASCULATURE
Reduces Major Adverse CV Events (SELECT), improves HFpEF symptoms, lowers blood pressure and inflammation.

KIDNEYS
Slows CKD progression, reduces albuminuria, preserves eGFR—benefits extend beyond glycemic control.

LIVER
Resolves MASH, reduces liver fat, improves liver inflammation and fibrosis.

ADIPOSE TISSUE
Reduces fat mass, improves adipokine profile, reduces inflammation, improves metabolic health.

MUSCLE
Improves insulin sensitivity, mitochondrial function and physical performance.

IMMUNE & INFLAMMATION
Lowers systemic inflammation, reduces CRP, improves immune function and endothelial health.

LOOKING AHEAD

- **Disease Modification**
  Moving from risk reduction to disease modification.
- **Personalized Medicine**
  Biomarker-guided therapy and patient-specific benefits.
- **Combination Strategies**
  Synergy with other agents for additive or complementary benefits.
- **Longer, Healthier Lifespan**
  Potential to improve quality of life and healthy aging.

KEY TAKE-HOME MESSAGE

Semaglutide is evolving from a metabolic therapy to a multiorgan disease-modifying agent. Its future lies in expanding beyond current indications to transform outcomes in neurology, behavioral health, liver, kidney, heart failure, and healthy aging.

ULTIMATE VISION

From managing disease to preserving function and extending healthspan across the lifespan.

ONE MOLECULE. INFINITE POSSIBILITIES.

Cardiometabolic Protection · Organ Protection · Neuroprotection · Inflammation Control · Better Health, Longer Life

10 GOLDEN RULES FOR SAFE & EFFECTIVE SEMAGLUTIDE PRESCRIBING

Evidence-Based Principles for Long-Term Success

UPDATED WITH LATEST EVIDENCE
Including SELECT, FLOW, ESSENCE & STEP 4/5

1 CONFIRM APPROPRIATE INDICATION & GOALS

- Use for T2D, obesity, CVD risk reduction, or other approved indications.
- Define individualized goals: HbA1c, weight, CV/renal benefit, NAFLD/MASH, or HFpEF.
- Set realistic, shared goals (5–15% weight loss, organ protection, quality of life).

2 SCREEN & THINK SAFETY BEFORE YOU START

- Rule out personal/family history of MTC or MEN2.
- Assess pancreatitis risk, gallbladder disease, severe GI disease.
- Review all medications and comorbidities (renal, hepatic, GI).
- Baseline: weight, vitals, renal & liver function, HbA1c.

3 START LOW & TITRATE SLOWLY

- Start at 0.25 mg weekly.
- Increase every ≥4 weeks as tolerated.
- Go slower if GI side effects occur.
- Titrate to the maximum tolerated dose (2.4 mg) for greatest benefit.
- No additional benefit above 2.4 mg.

4 MANAGE SIDE EFFECTS PROACTIVELY

- Anticipate GI effects (nausea, vomiting, diarrhea, constipation).
- Use dietary adjustments: smaller meals, low-fat, avoid large portions.
- Ensure hydration and adequate fiber intake.
- Consider temporary dose hold or slower titration if needed.
- Most side effects are mild, transient, and dose-related.

5 OPTIMIZE NUTRITION & PHYSICAL ACTIVITY

- Protein intake 1.0–1.2 g/kg/day.
- Engage in resistance exercise 2–3 times/week.
- Calorie deficit if weight loss desired.
- Ensure adequate micronutrients (Vit D, B12, iron, calcium, etc.).
- Prevent and monitor malnutrition and sarcopenia—especially in older adults.

6 TAILOR DOSE TO PATIENT & INDICATION

- T2D glycemic control: 0.5–1.0 mg (1.0 mg if more needed).
- Weight management: target 2.4 mg.
- Elderly or frail: titrate more slowly.
- Consider renal/hepatic function.
- Use lowest effective dose that achieves goals.

7 MONITOR & ADJUST REGULARLY

- Every 4–12 weeks assess:
  - ✓ Weight, BMI, waist
  - ✓ HbA1c, fasting glucose
  - ✓ BP, lipids
  - ✓ Renal function (eGFR, UACR)
  - ✓ Liver enzymes (if indicated)
- Adjust dose or add therapies based on response and tolerability.

8 PLAN FOR LONG-TERM THERAPY

- Obesity and T2D are chronic—long-term therapy is usually needed.
- Stopping leads to weight regain and loss of glycemic benefit.
- Reassess goals, benefits, and risks periodically.
- Use evidence (STEP 4/5) to support long-term continuation.

9 LEVERAGE EVIDENCE ACROSS ORGAN SYSTEMS

Use semaglutide for its proven multi-organ benefits:

- ✓ Cardiovascular (SELECT, SUSTAIN-6)
- ✓ Kidney (FLOW)
- ✓ Liver (ESSENCE, STEP NAFLD)
- ✓ HFpEF (STEP-HFpEF)
- ✓ Sleep apnea, osteoarthritis & more

10 SHARED DECISION-MAKING & PATIENT ENGAGEMENT

- Discuss benefits, risks, expectations, alternatives, and cost.
- Respect preferences and cultural values.
- Empower patients—education, support, and follow-up drive adherence and success.
- Partner in care for the best long-term outcomes.

KEY BENEFITS

- Substantial and sustained weight reduction
- Powerful glycemic control
- Cardiovascular risk reduction (SELECT, SUSTAIN-6)
- Kidney protection (FLOW)
- Improvement in MASH (ESSENCE)
- Better quality of life
- Multi-organ protection & potential longevity benefit

POTENTIAL RISKS

- Gastrointestinal side effects
- Gallbladder & biliary disease
- Pancreatitis (rare)
- Hypoglycemia (with insulin/SU)
- Dehydration & AKI (rare)
- Nutritional deficiencies
- Contraindications: MTC, MEN2

SAFETY FIRST

- No thyroid C-cell tumors observed in humans; risk limited to MTC/MEN2.
- Monitor for severe or persistent GI symptoms.
- Ensure hydration: hold during severe illness or dehydration.
- Educate patients: when to seek care and report symptoms.

THE FOUNDATION OF SUCCESS

Right Patient | Right Drug (Semaglutide) | Right Dose (0.25→2.4 mg) | Right Time | Right Monitorihp | Right Partnership

WHEN TO SEEK EXPERT HELP

- Severe or persistent GI symptoms
- History of pancreatitis or gallbladder disease
- Complex comorbidities or polypharmacy
- Rapid deterioration or uncertain diagnosis
- Failure to achieve expected response

COLLABORATE. MONITOR. SUPPORT.

A multidisciplinary, patient-centered approach ensures safety, maximizes benefit, and sustains success.

THE GOLDEN BOTTOM LINE: Use semaglutide thoughtfully, monitor diligently, and stay the course.
The right patient — the right dose — for the right duration = lasting health benefits.

Assess → Personalize → Support → Sustain → Thrive

Key Evidence: SUSTAIN Program — SELECT — FLOW — ESSENCE — STEP 1–5 — STEP-HFpEF — STEP-Sleep Apnea

10 GOLDEN RULES FOR CLINICAL USE OF GLP-1 RECEPTOR AGONISTS & DUAL GIP/GLP-1 RECEPTOR AGONISTS

Evidence-Based. Patient-Centered. Outcome-Driven.

THE GOLDEN PRINCIPLES
Right Patient ✓ Right Drug ✓ Right Dose
Right Time ✓ Right Support ✓ Right Outcomes

1 SELECT THE RIGHT PATIENT FOR THE RIGHT REASON

- Use for approved indications: T2DM, obesity/overweight, and cardiometabolic risk reduction (as per FDA/EMA labels).
- Prioritize patients with high unmet needs: poor glycemic control, obesity, ASCVD, CKD, HFpEF, MASH.
- Consider patient goals, preferences, comorbidities, and individualized targets.

Individualize. Do not generalize.

2 SCREEN CAREFULLY & KNOW CONTRAINDICATIONS

- Check personal/family history of MTC or MEN2 (contraindicated).
- History of pancreatitis: use with caution.
- Assess renal, hepatic function and concomitant medications.
- Evaluate gallbladder disease risk.

Safety first. When in doubt, evaluate.

3 START LOW & TITRATE SLOWLY

GLP-1 RAs (e.g., Semaglutide SC)

0.25 mg	0.5 mg	1.0 mg	1.7 mg*	2.4 mg*
Week 1–4	Week 5–8	Week 9–12	Week 13–16	Week 17+

*For obesity (Wegovy®)

Dual GIP/GLP-1 RA (e.g., Tirzepatide)

2.5 mg	5 mg	7.5 mg	10 mg	12.5–15 mg*
Week 1–4	Week 5–8	Week 9–12	Week 13–16	Week 17+

*As tolerated for additional benefit

- Titrate based on tolerability and clinical response.
- Go slower if GI side effects occur.
- Do not exceed the maximum recommended dose.

Slow and steady wins the race.

4 ANTICIPATE & MANAGE SIDE EFFECTS PROACTIVELY

- GI effects (nausea, vomiting, diarrhea, constipation) are most common.
- Educate patients—most are mild to moderate and transient.
- Strategies: smaller meals, low-fat diet, adequate hydration, avoid large portions.
- Consider temporary dose hold or slower titration if needed.

Prepare, educate, support.

5 PRESERVE MUSCLE & OPTIMIZE NUTRITION

- Ensure adequate protein intake (1.0–1.2 g/kg/day).
- Encourage resistance exercise 2–3 times/week.
- Ensure adequate micronutrients (Vit D, B12, iron, calcium, etc.).
- Prevent and monitor malnutrition and sarcopenia—especially in older adults.

Weight loss should be fat loss, not muscle loss.

6 CHOOSE THE RIGHT AGENT & DOSE FOR EACH PATIENT

GLP-1 RAs
(e.g., Semaglutide, Liraglutide, Dulaglutide, Exenatide)

Dual GIP/GLP-1 RAs
(e.g., Tirzepatide)

- Consider efficacy, safety, dosing frequency, route (SC vs oral for semaglutide), patient preference, comorbidities, access and cost.
- Use lowest effective dose that achieves goals.
- Reassess regularly and adjust as needed.

Personalize the molecule, route and dose.

7 MONITOR & ADJUST REGULARLY

- Assess every 4–12 weeks:
  - ✓ HbA1c, fasting glucose
  - ✓ Weight, BMI, waist circumference
  - ✓ BP, lipids
  - ✓ Renal function (eGFR, UACR)
  - ✓ Liver enzymes (if indicated)
- Assess adherence, tolerability, side effects and patient satisfaction.

What gets monitored gets improved.

8 COMMIT TO LONG-TERM THERAPY FOR SUSTAINED BENEFIT

- Obesity and T2DM are chronic diseases—continuation is usually required.
- Stopping leads to weight regain and loss of glycemic benefit.
- Reassess goals, benefits and risks periodically.
- Use evidence (e.g., STEP 4/5, SURMOUNT-MAINTAIN) to support long-term continuation.

Discontinuation = relapse.

9 USE WHERE OUTCOME EVIDENCE EXISTS

CV	Kidney	Liver	Heart	Lungs
ASCVD (SUSTAIN-6, SOUL‡)	CKD (FLOW)	MASH (ESSENCE, SYNERGY-NASH‡)	HFpEF (STEP-HFpEF)	OSA (STEP OSA)

- Apply agents with proven benefit for patients with these conditions.
- Think beyond glucose—protect organs and improve outcomes.

Use the right tool for the right organ.

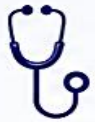
10 ENGAGE IN SHARED DECISION-MAKING & PROVIDE ONGOING SUPPORT

- Discuss benefits, risks, expectations, alternatives and cost.
- Align treatment with patient values and lifestyle.
- Empower patients—education, digital tools, follow-up and support improve adherence.
- Partner in care for the best long-term health outcomes.

Patients are partners, not passive recipients.

THE FOUNDATION OF SUCCESS

WHEN TO SEEK EXPERT HELP



- ✓ Severe or persistent GI symptoms
- ✓ History of pancreatitis or gallbladder disease
- ✓ Complex comorbidities or polypharmacy
- ✓ Rapid deterioration or uncertain diagnosis
- ✓ Failure to achieve expected response or adherence issues

SAFETY REMINDERS

- No evidence of increased MTC risk in humans; however, contraindicated in patients with personal/family history of MTC or MEN2.
- Monitor for severe or persistent GI symptoms and pancreatitis.
- Ensure hydration: hold during severe illness or dehydration.
- Educate patients: when to seek care and report symptoms.

COLLABORATE. MONITOR. SUPPORT.

A mutidisciplinary, patient-centered approach ensures safety, maximizes benefit, and sustains success.

THE GOLDEN BOTTOM LINE: Use GLP-1 RAs and Dual GIP/GLP-1 RAs thoughtfully, monitor diligently, and stay the course—at the right dose for the right duration.

Assess → Personalize → Support → Sustain → Thrive

Key Evidence: SUSTAIN Program (SUSTAIN-6, -7, -1–5, -FORTE) • PIONEER Program • STEP Program (1–5, TEENS, HFpEF, Sleep Apnea) • SELECT • FLOW • ESSENCE • SOUL Trial (Oral Semaglutide 3→7→14 mg/day) • SURPASS Program • SURMOUNT Program

‡ SOUL (2025): Oral semaglutide (3→7→14 mg/day) reduced major adverse cardiovascular events (MACE) in T2DM with established ASCVD and/or CKD.
‡ SYNERGY-NASH (Tirzepatide): Improved MASH and fibrosis in adults with biopsy-proven MASH.

MASH: Metabolic Dysfunction-Associated Steatohepatitis ASCVD: Atherosclerotic Cardiovascular Disease CKD: Chronic Kidney Disease HFpEF: Heart Failure with Preserved Ejection Fraction
OSA: Obstructive Sleep Apnea OSA: Obstructive Sleep Apnea MTC: Medullary Thyroid Carcinoma MEN2: Multiple Endocrine Neoplasia Type 2 GI: Gastrointestinal

Thank you for your attention