

Optimizing Management in BMI ≥ 35 with Metabolic Syndrome: Why Escalate to GLP-1RA Before Bariatric Surgery?

Dr. Mohsin Aslam MD, FACP, FICP

Consultant Physician

Asian Institute of Gastroenterology, Hyderabad

The risk with BMI>35

- Patient with BMI ≥ 35 and metabolic syndrome represents a **high and imminent cardiometabolic risk** profile.
- Lifestyle modification (LSM) is essential but **rarely sufficient** to deliver durable ≥ 10 – 15% weight loss in this risk tier.
- GLP-1 receptor agonists (GLP-1RA) and dual GIP/GLP-1 agonists have emerged as **guideline-endorsed pharmacologic anchors** for obesity with cardiometabolic disease.
- Bariatric surgery remains a powerful option but is **invasive, irreversible and resource-intensive**, and not the mandated first step in most guidelines

Clinical Burden: BMI ≥ 35 + Metabolic Syndrome

- BMI ≥ 35 + Metabolic syndrome confers a **1.5–2-fold increase in cardiovascular events and mortality** compared with individuals without the syndrome.
- In such patients, even modest weight loss (5–10%) improves risk factors, but **$\geq 15\%$ weight loss** can drive partial disease remission.
- Early, aggressive, multi-modal intervention is therefore **risk-modifying, not cosmetic**.

Management of Obesity

	BMI 25-26.9 kg/m ²	BMI 27-29.9 kg/m ²	BMI 30-34.9 kg/m ²	BMI 35-39.9 kg/m ²	BMI ≥40 kg/m ²
 Lifestyle modification ^{1,2}	+	+	+	+	+
 Pharmacotherapy ^{1,2}	-	With adiposity-related complications	+	+	+
 Surgery ^{1,2}	-	-	With adiposity-related complications, when optimal medical and lifestyle management has been insufficient	With adiposity-related complications	+
	All individuals, regardless of body size or composition, benefit from a healthy, well-balanced eating pattern and regular physical activity				

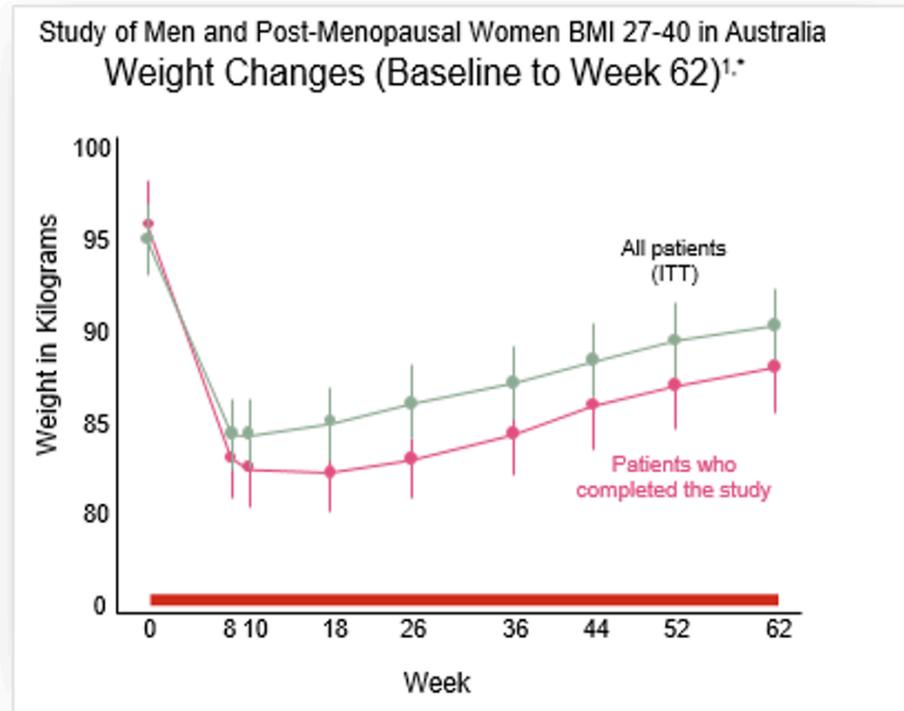
BMI = Body Mass Index.

1. Wharton S, et al CMAJ 2020; 192 (31) E875-E891. 2. Garvey WT, et al. Endocrine Practice. 2016;22(7):842-884.

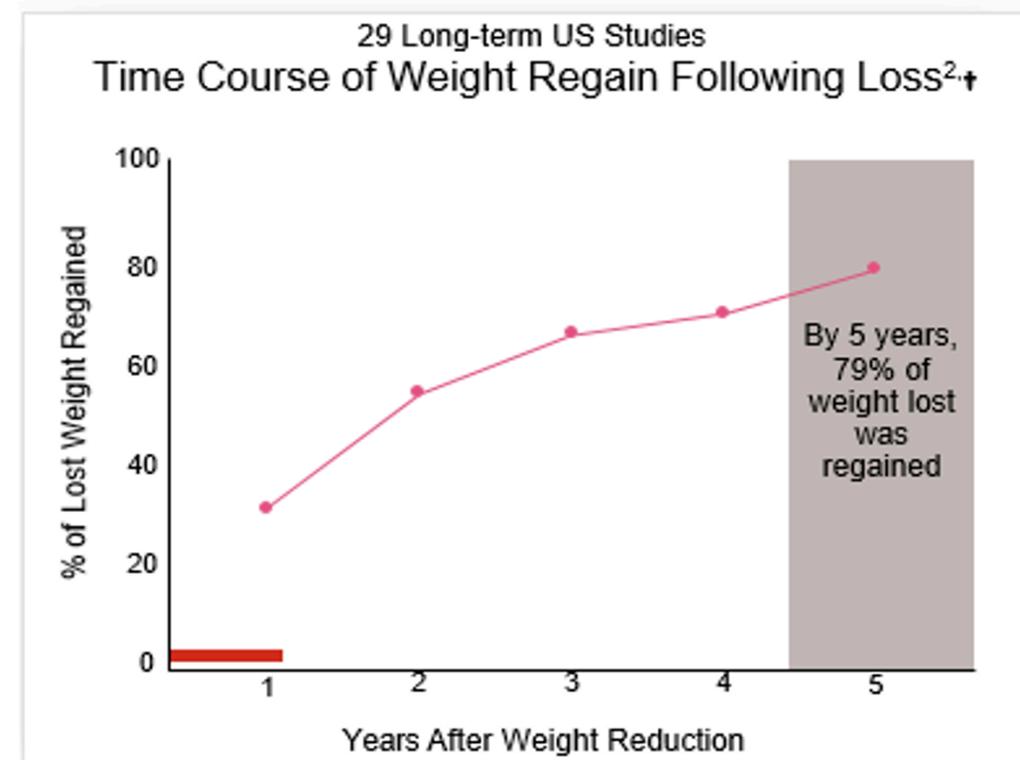
Guideline Sequencing: LSM → Pharmacotherapy → Surgery

- ADA and AACE algorithms recommend **behavioral therapy + anti-obesity medications** for BMI ≥ 30 or ≥ 27 with comorbidities before considering surgery.
- GLP-1RA (and dual GIP/GLP-1 agonists) are **preferred pharmacologic options** in patients with T2DM and/or ASCVD due to weight and CV benefits.
- 2022 ASMBS/IFSO guidelines recommend MBS for **BMI ≥ 35 kg/m² regardless of comorbidities**, but do not position surgery as obligatory first escalation.
- This creates a **structured treatment ladder**: maximize GLP-1RA-based pharmacotherapy first, reserve surgery for non-responders or specific indications.

Following Weight Reduction, Most is Regained Over Time^{1,2}



Sumithran et. al. showed that during the follow-up period from the end of the weight loss program at week 10 to week 62, participants regained approximately **5.5 ± 1.0 kg on average** ($P < 0.001$).



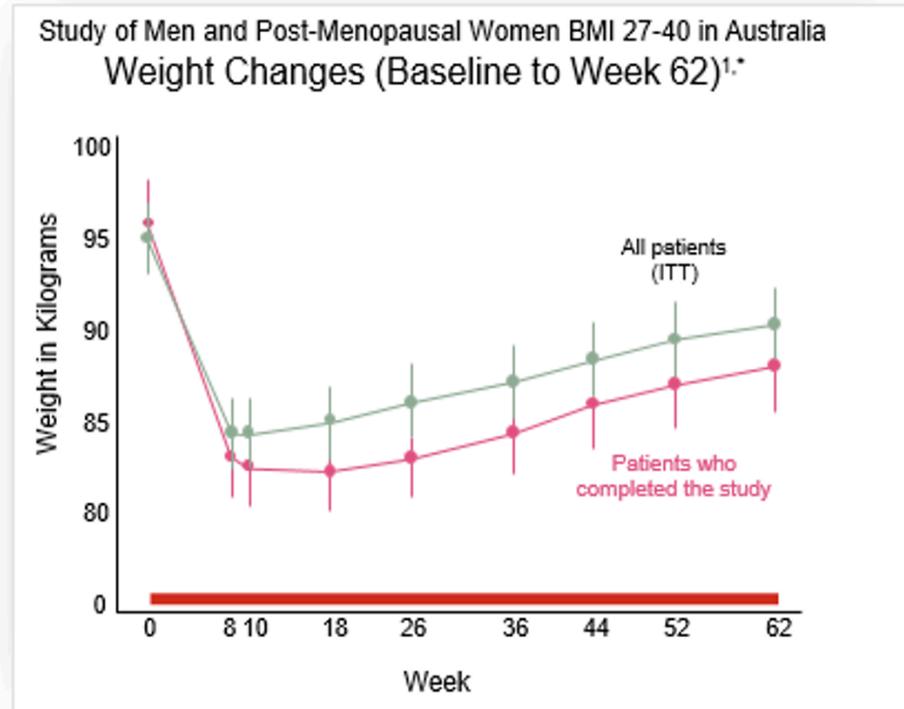
Anderson et. al. study showed that percentage weight-loss maintenance and reduced weight at 5 y were significantly lower than the values at 3 y. 79% of weight lost was regained by the end of 5 years.

The assertion that lifestyle modifications, including dietary changes, alone are **insufficient for maintaining weight loss** can be supported by scientific evidence

References:

1. Sumithran P, et al. N Engl J Med. 2011;365(17):1597-1604.
2. Anderson JW, et al. Am J Clin Nutr. 2001;74(5):579-584.

Following Weight Reduction, Most is Regained Over Time^{1,2}



Sumithran et. al. showed that during the follow-up period from the end of the weight loss program at week 10 to week 62, participants regained approximately 5.5 ± 1.0 kg on average ($P < 0.001$).

Following weight loss;

Hormonal Changes Persist for 12 Months

- **Promote Weight Regain:** Leptin ↓, Ghrelin ↑, PYY ↓, Amylin ↓, CCK ↓
- **Reduce Appetite:** Pancreatic Polypeptide ↑

Why?

- The body produces more hunger-promoting hormones (ghrelin)
- It reduces satiety hormones (leptin, PYY, amylin, CCK)
- These changes drive hunger and weight regain

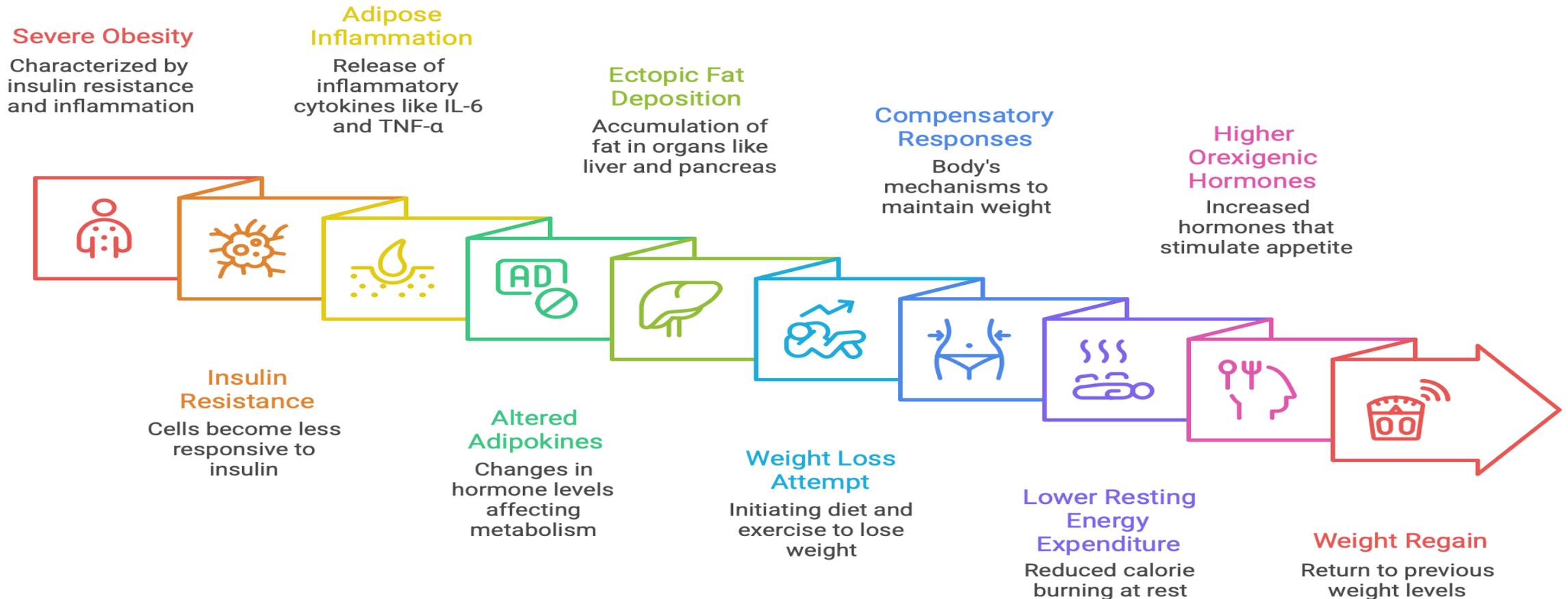
The assertion that lifestyle modifications, including dietary changes, alone are **insufficient for maintaining weight loss** can be supported by scientific evidence

References:

1. Sumithran P, et al. N Engl J Med. 2011;365(17):1597-1604.
2. Anderson JW, et al. Am J Clin Nutr. 2001;74(5):579-584.

Pathophysiology: Why Simple Diet/Exercise Often Fails

Pathophysiology of Obesity and Weight Loss Challenges



Evidence on Lifestyle Intervention Alone

- Meta-analyses of long-term lifestyle programs show that **>50% of lost weight is regained within ~2 years**, and ~80% by 5 years.
- Only ~20% of overweight/obese individuals maintain $\geq 10\%$ weight loss long term with lifestyle alone.
- While LSM improves glycemia and BP, the **magnitude and durability** of change are insufficient for high-risk BMI ≥ 35 + metabolic syndrome.
- Hence, current guidelines place **structured pharmacotherapy as the next escalation step** rather than jumping directly to surgery.

GLP-1RA Mechanism: Central and Peripheral Actions

- GLP-1R activation **enhances glucose-dependent insulin secretion and suppresses glucagon**, improving glycemic control with low hypoglycemia risk.
- It slows **gastric emptying**, blunts post-prandial glucose excursions and contributes to early satiety.
- In the CNS (hypothalamus, brainstem), GLP-1RA modulate **appetite and reward pathways**, reducing energy intake.
- Peripheral anti-inflammatory and endothelial effects support **blood pressure and vascular benefits** beyond glycemia.

Dual GIP/GLP-1 Agonism with Tirzepatide

- Tirzepatide is a **dual agonist** at the GIP and GLP-1 receptors, designed to exploit complementary incretin pathways.
- GIPR activation may **augment insulin secretion and adipocyte lipid handling** (LPL activity, reduced ApoC3), enhancing insulin sensitivity.
- Combined GIP/GLP-1 agonism delivers **greater weight loss and glycemic improvement** than GLP-1RA alone in multiple phase 3 trials.
- These mechanistic features translate into **superior reductions in body weight, TG and non-HDL cholesterol** versus comparators.

GLP-1RA and Systemic Inflammation/ Endothelial Function

- GLP-1RA have been shown to **reduce hs-CRP and other inflammatory markers**, reflecting improved adipose and vascular inflammation.
- They improve measures of **endothelial function**, likely via decreased oxidative stress and better NO bioavailability.
- These pleiotropic effects complement weight loss and glycemic control, contributing to **observed CV risk reduction** in outcome trials.

Why Mechanism Matters Clinically

- Unlike purely restrictive interventions, GLP-1RA address **neurohormonal drivers of overeating**, supporting sustained behavioural change.
- They improve **multi-organ metabolic dysfunction** (pancreas, liver, vasculature) in parallel, not just body weight.
- This mechanistic breadth explains **consistent effects on HbA1c, BP, lipids and liver fat** across trials.

Semaglutide 2.4 mg: STEP 1 Weight-Loss Data

- STEP 1 randomized adults with obesity/overweight without diabetes to semaglutide 2.4 mg weekly + LSM vs placebo + LSM for 68 weeks.
- Mean **percentage weight loss was –14.9% with semaglutide vs –2.4% with placebo**, yielding a ~12.4-percentage-point treatment difference.
- This degree of weight loss approximates early post-MBS outcomes in many series, but with a **non-surgical, reversible intervention**.

Tirzepatide: SURMOUNT-1 Weight-Loss Data

- Mean weight reductions were **-15.0%**, **-19.5%** and **-20.9%** for 5, 10 and 15 mg respectively vs \sim -3% with placebo.
- Up to **50–57% of patients achieved \geq 20% weight loss**, approaching typical bariatric weight-loss ranges.
- Long-term follow-up suggests **limited weight regain in most patients** when therapy is continued.

Glycemic and Insulin-Sensitivity Benefits

- In obesity with or without diabetes, semaglutide and tirzepatide produce **HbA1c reductions of ~1.5–2.4 percentage points**, depending on baseline status.
- Both agents reduce **fasting glucose and HOMA-IR**, indicating improved insulin sensitivity.
- Reduced need for additional antihyperglycemics and insulin supports **treatment simplification** in metabolic syndrome.

Cardiovascular Outcomes: SELECT and GLP-1RA CVOTs

- SELECT enrolled >17,000 adults with BMI ≥ 27 and established CVD but no diabetes, randomized to semaglutide 2.4 mg vs placebo.
- Semaglutide reduced the risk of **MACE (CV death, MI, stroke) by ~20%** vs placebo over a median follow-up of ~3.5 years.
- Importantly, this level of randomized CV outcome data is **not available for bariatric surgery** in a comparable design.

Semaglutide 2.4 mg reduced MACE soon after randomisation

A secondary analysis of SELECT

Red lines show upper and lower CIs and the blue line shows HR for each day, estimated using a Cox proportional hazards model with treatment group as a fixed factor. The dashed blue line shows the HR for the full trial. Data are from the in-trial period for the full analysis set. Estimated HRs and 95% CIs are shown from week 0 to week 208 post-randomisation. A two-sided significance level of 5% was used. No adjustments for multiplicity were performed. First sustained statistically significant effect defined as the time-point at which the upper limit of the 95% CI is below 1 and subsequently remains below 1.
CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events.
Lincoff AM, et al. N Engl J Med 2023;389:2221–2232.

Semaglutide 2.4 mg reduced MACE soon after randomisation

A secondary analysis of SELECT

1

Day 20: First statistically significant MACE reduction with semaglutide 2.4 mg vs placebo

2

Day 86: First sustained statistically significant difference in MACE reduction with semaglutide 2.4 mg

3

This early MACE reduction preceded meaningful weight loss, suggesting an effect of semaglutide 2.4 mg beyond weight loss

Blood Pressure Effects of GLP-1RA

- Meta-analyses in overweight/obese populations report **systolic BP reductions of ~3–5 mmHg and modest diastolic reductions** with GLP-1RA.
- These BP changes, though numerically modest, translate into **meaningful CV risk reduction** at population level.

Lipid Profile: Semaglutide and Tirzepatide

- Semaglutide therapy improves **LDL-C, non-HDL-C and TG**, with evidence for favorable remodeling of atherogenic lipoprotein subfractions.
- Tirzepatide produces **dose-dependent reductions in total cholesterol, LDL-C and TG and increases HDL-C**, across 5–15 mg doses.
- These shifts contribute to overall **atherosclerotic risk reduction**, especially in metabolic syndrome with baseline dyslipidemia.

Liver Outcomes: NAFLD/MASLD and MASH

- Semaglutide improves **NAFLD activity score, liver fat and liver stiffness** in non-diabetic and diabetic populations with fatty liver disease.
- Tirzepatide has shown **marked reductions in liver fat and improvement in NASH/MASH histology** in recent phase 3 data.
- Given the strong link between MASLD and cardiometabolic disease, these effects are highly relevant in a BMI ≥ 35 metabolic syndrome patient.

Safety and Tolerability of GLP-1RA

- Most frequent adverse events are **GI symptoms (nausea, vomiting, diarrhea, constipation)**, typically dose-dependent and manageable with titration.
- Discontinuation rates due to AEs are modest and usually lower than the **absolute surgical complication rate** of MBS.
- Rare risks (e.g., gallbladder disease, pancreatitis signals) are **monitored in routine practice**, but overall benefit–risk remains strongly favorable in high-risk obesity.

GLP-1RA as “Metabolic Bridge” Before Surgery

- Optimizing weight, glycemia, BP and liver fat with GLP-1RA **reduces peri-operative risk** if MBS is pursued later.
- Emerging multi-society guidance suggests **most patients can continue GLP-1RA around elective surgery** with individualized planning.
- Using GLP-1RA first allows selection of **responders who may avert or defer surgery**, reserving MBS for non-responders or anatomical indications (e.g., severe reflux, large hiatal hernia).

GLP-1RA vs Immediate Surgery: Value Comparison

- **Weight loss:** GLP-1RA (15–22%) vs MBS (25–35%) – gap has narrowed substantially with semaglutide and tirzepatide.
- **CV outcomes:** robust RCT evidence for MACE reduction with semaglutide; surgery lacks an equivalent large-scale randomized CVOT.
- **Metabolic markers (BP, lipids, liver fat):** consistently improved with GLP-1RA; surgery also improves but with added surgical and nutritional risk.
- **Reversibility and scalability:** GLP-1RA is titratable and reversible; surgery is permanent and capacity constrained.

Strategic Positioning: Why Not “Surgery First”?

- In a BMI ≥ 35 metabolic syndrome patient, the priority is **rapid but safe cardiometabolic optimization**.
- Immediate MBS commits the patient to **permanent anatomical alteration** without testing the response to potent modern pharmacotherapy.
- GLP-1RA allows **reversible, titratable and individualized therapy**, preserving MBS as a future option if needed.
- This aligns with a **stepwise, risk-stratified, guideline-consistent** approach rather than a one-shot irreversible intervention.

Conclusion: Why Choose GLP-1RA First in This Case

- For a male with BMI ≥ 35 and metabolic syndrome, **LSM + GLP-1RA/dual agonist** offers:
 - ≥ 15 – 20% weight loss,
 - substantial HbA1c, BP, lipid and liver fat improvements,
 - proven CV event reduction.
- GLP-1RA provides a **non-surgical, reversible, guideline-aligned escalation** that can stabilize or reverse cardiometabolic risk.
- Bariatric surgery remains a **high-impact but invasive option**, best reserved for non-responders or those with specific anatomical/clinical indications.

Strategic Message For The Tribate

“In a high-risk BMI ≥ 35 metabolic-syndrome patient, GLP-1RA is the most rational first advanced step—optimizing risk, preserving options, and aligning with contemporary evidence and guidelines.”

THANK YOU

Indications for Bariatric/Metabolic Surgery

- **2022 ASMBS/IFSO:**
 - MBS is recommended for **BMI ≥ 35 kg/m²**, and
 - can be considered from BMI ≥ 30 with inadequately controlled metabolic disease.
- Common procedures:
 - Roux-en-Y gastric bypass (RYGB),
 - sleeve gastrectomy (SG),
 - biliopancreatic diversion with duodenal switch (BPD-DS).
- These surgeries can produce **25–35% total body weight loss at 1–2 years**, with substantial improvement in glycemia and BP.
- However, they require **specialized centers, multidisciplinary teams, and lifelong follow-up**, which limits scalability.

Surgical Risks and Irreversibility

- MBS entails early peri-operative risks: bleeding, anastomotic leak, VTE, infections and anesthesia-related complications.
- Long-term complications include **dumping syndrome, internal hernias, hypoglycemia**, and procedure-specific risks (e.g., strictures).
- All major procedures lead to clinically relevant **micronutrient deficiencies** (vitamin D, B12, iron, vitamin A, calcium) requiring lifelong supplementation.
- Most importantly, surgery is **anatomically irreversible**; reversal or revisional surgery carries additional risk.

Real-World Outcomes: Weight Regain After Surgery

- Long-term data show **substantial weight regain** after RYGB and gastric banding, with attenuation of comorbidity benefits in some patients.
- Revisional bariatric procedures are increasingly performed due to **inadequate initial weight loss or recurrence of obesity**, with added nutritional challenges.
- Thus, while MBS remains highly efficacious, it is **not uniformly curative** and still demands intensive long-term management.

Patient-Level Barriers to Immediate Surgery

- Many patients are **unwilling or unprepared** for an invasive, irreversible procedure at first consult.
- Psychological readiness, family support, work leave, and financial capacity often **delay or preclude surgery** in real life.
- In countries with constrained surgical capacity, **waiting times** can be long, during which cardiometabolic risk remains unaddressed.
- Pharmacologic optimization with GLP-1RA provides a **timely and scalable intervention** while decisions on surgery are matured.