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Semaglutide after metabolic and bariatric surgery: advancing treatment for suboptimal weight loss and weight regain

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INTRODUCTION

Approximately 10%-30% of persons undergoing metabolic and bariatric surgery (MBS) will exhibit suboptimal clinical response, defined as < 20% total body weight loss[1]. Suboptimal weight loss after MBS portends worse metabolic health, recurrence of obesity-related comorbidities, and poor quality of life outcomes[2]. The mechanisms underlying this variable response remain unclear, but are most likely related to biologic, physiologic, and behavioral factors beyond operative factors alone. Until recently, treatment options were limited to revision surgery, with evidence suggesting only modest incremental effects on body weight and metabolic outcomes[3]. Expansion of effective weight management strategies for persons with severe obesity and insufficient weight loss or weight recurrence after surgery is critical to reduce morbidity and mitigate metabolic cardiovascular disease risk.

In *Nature Medicine*, Stanley *et al.* report results from a randomized, double-blind, placebo-controlled trial of injectable semaglutide 2.4 mg weekly among 63 adults with suboptimal clinical response at least 1 year after gastric bypass or sleeve gastrectomy (BARI-STEP trial)[4]. Participants had a mean body mass index (BMI) of 41.5 kg/m^2, 7 (10%) had type 2 diabetes mellitus, 55 (79%) underwent sleeve gastrectomy and 15 (21%) gastric bypass, and mean weight loss after surgery prior to enrollment was 7.5%. The primary outcome was percentage weight loss at 68 weeks of treatment using intention-to-treat analyses (63 included participants). Participants randomized to the semaglutide arm had a mean weight loss of 18.0%, with a standard deviation (SD) of 9.2%, compared with 0.4% (SD = 7.0%) weight gain in the placebo arm [mean adjusted between-group difference -19.1%, 95% confidence interval (CI): -23.4% to -14.8%] along with favorable changes in glycated hemoglobin (HbA1c), cholesterol, body composition, and self-reported quality of life. Weight loss efficacy did not differ between men and women or for those with or without diabetes.

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WEIGHT LOSS

BARI-STEP was a randomized trial designed to evaluate the potential benefit of treatment with the glucagon-like peptide-1 receptor agonist (GLP-1 RA), semaglutide, as an adjunctive therapy to treat individuals with inadequate weight loss after MBS. The mean incremental weight loss observed in BARI-STEP with semaglutide of 18.0% is numerically greater than the average 14.9% weight loss reported from the STEP-1 trial, which randomized persons with severe obesity (mean BMI 37.9 kg/m^2) without diabetes to semaglutide 2.4 mg weekly *vs*. placebo over 68 weeks[5]. Although one cannot conclude greater treatment efficacy in surgically treated *vs*. medically treated persons from between-trial comparisons, nonetheless, the results from the BARI-STEP trial confirm the expected complementary treatment effect of adjunctive use of GLP-1 RAs. For context, a meta-analysis of 8 retrospective studies reported -11.0% weight loss with semaglutide and -13.6% weight loss with tirzepatide among 964 patients with recurrent weight gain after MBS[6]. Although retrospective in nature, these data support further investigation of newer combination weight loss therapies, such as dual glucose-dependent insulinotropic polypeptide and GLP-1 RA, for patients with suboptimal clinical response after MBS.

An additional noteworthy finding from the BARI-STEP trial results is the cumulative reduction in weight over time, which had not yet plateaued at 68 weeks, implying the possibility of an even greater weight loss if semaglutide treatment extended beyond 68 weeks. Future studies should incorporate longer treatment duration to determine maximal therapeutic effect.

METABOLIC OUTCOMES

Many persons pursue MBS to mitigate metabolic-associated cardiovascular disease risk, in addition to losing weight. Unfortunately, after MBS, those who experience limited weight loss also have less favorable effects on cardiometabolic risk factors, attenuating the impact on cardiovascular disease risk[6].

Weight regain > 20% of maximal weight lost after MBS is associated with a higher risk of poorer control for diabetes/hyperglycemia, hypercholesterolemia, and hypertension[6,7]. Importantly, the results from the BARI-STEP trial address the potential role of semaglutide adjunctive therapy after MBS to incrementally mitigate cardiometabolic risk factors. Longer follow-up is needed to examine the duration of these benefits and potential risk reduction of adverse cardiovascular disease outcomes.

Of particular relevance to persons undergoing MBS is to what extent GLP-1 RA therapy may contribute to surgery-induced loss of lean mass. Although absolute lean mass decreased by approximately 5.5 kg in the semaglutide group, the proportion of lean mass relative to total body weight improved in the semaglutide arm (+5.5%) compared with placebo (-0.8%). These findings imply that the weight loss is predominantly fat mass, resulting in a metabolically favorable change in body composition.

SAFETY OUTCOMES

Side effects of GLP-1 RAs are important to consider for persons post-MBS, who are prone to gastrointestinal intolerance and are at risk for nutritional deficiencies, bowel obstruction, and pancreatitis. Reassuringly, in the BARI-STEP trial, only the frequency of nausea (69% *vs*. 23%) and decreased appetite (43% *vs*. 11%) differed between intervention and placebo arms, with no adverse clinical outcome consequences observed otherwise.

QUALITY OF LIFE OUTCOMES

Another key finding of the BARI-STEP trial is the improvement in self-reported quality of life, measured by the Impact of Weight on Quality of Life-Lite score. Participants experienced benefits of semaglutide particularly in the domains of physical function, work, and self-esteem. The consideration of

patient-centered quality of life effects is valuable for promoting adherence, renewing confidence to achieve weight loss goals, and encouraging weight self-management.

INTEGRATING SURGICAL AND PHARMACOLOGIC TREATMENT INTO SHARED DECISION-MAKING PATHWAYS FOR THE MANAGEMENT OF OBESITY

Personal preference, access to therapy, and response to interventions vary widely among individuals living with obesity. Current guidelines emphasize shared decision-making to individualize treatment goals and therapy. GLP-1 RA therapy can be integrated with surgical treatment for obesity through one of three approaches: (1) "neoadjuvant" to planned surgery; (2) "adjuvant" with simultaneous surgery; and (3) complementary adjunctive long-term therapy. The 2026 American Heart Association/American College of Cardiology Cardio-Kidney Metabolic Disease Guideline highlights the promising role of GLP-1 therapy to mitigate weight regain after metabolic surgery based on observational data[8-10]. From the results of the BARI-STEP trial, we now have randomized trial evidence to support the incremental efficacy of GLP-1 RA adjunctive therapy following MBS, as well as a template for timing, duration, and expected treatment effects. Clinicians should provide anticipatory guidance regarding the long-term duration of therapy, the importance of monitoring nutritional status, and the potential for weight regain with discontinuation. Future trials should implement longer follow-up to clarify the optimal duration of treatment and to assess the potential impact on major adverse cardiovascular outcomes.

The chronic, relapsing-remitting nature of obesity calls for a longitudinal and multidisciplinary model of care. Although not specifically addressed by this trial, the findings suggest that GLP-1 RA therapy may provide additional benefits for persons who have an initially favorable response to MBS, but in whom the treatment effects attenuate over years. With demonstrated efficacy for improving weight and metabolic outcomes, GLP-1 RA therapy may be useful prior to revision surgery as an alternative or complementary therapy.

The results from the BARI-STEP trial signify a stride forward in the treatment of severe obesity with insufficient weight loss or weight recurrence after surgery. The next step will be comparative trials of the most contemporary treatments within the evolving landscape of nutrient-stimulated hormonal modulating therapies for the management of overweight and obesity.

DECLARATIONS

Authors' contributions

Conceptualization, literature search, writing, and original draft preparation: White A
Conceptualization, supervision, interpretation of data, review and editing, and critical revision: McGuire DK

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Both authors declared that there are no conflicts of interest.

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Not applicable.

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