Evidence Synthesis Program

Endoscopic Bariatric Interventions versus Lifestyle Interventions or Surgery for Weight Loss in Patients with Obesity: A Systematic Review and Meta-analysis

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This report was prepared by the Evidence Synthesis Program Center located at the VA Greater Los Angeles Health Care System, Los Angeles, CA, directed by Isomi Miake-Lye, PhD and Paul Shekelle, MD, PhD, and funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development.

PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted health care topics of importance to clinicians, managers, and policymakers as they work to improve the health and health care of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program comprises four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, interface with stakeholders, and address urgent evidence needs. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee composed of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

The present report was developed in response to a request from the National Gastroenterology and Hepatology Program Office. The scope was further developed with input from Operational Partners (below), the ESP Coordinating Center, the review team, and the technical expert panel (TEP). The ESP consulted several technical and content experts in designing the research questions and review methodology. In seeking broad expertise and perspectives, divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Ultimately, however, research questions, design, methodologic approaches, and/or conclusions of the review may not necessarily represent the views of individual technical and content experts.

ACKNOWLEDGMENTS

The authors are grateful to Marika Booth for statistical analysis, Alireza Sedarat, MD and Erik Dutson, MD for conceptualization support, and the following individuals for their contributions to this project:

Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

Jason A. Dominitz, MD, MHS
National Program Director
National Gastroenterology and Hepatology Program Office
Veterans Health Administration

Technical Expert Panel

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

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Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence (see Appendix B for disposition of comments). Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center works to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

TABLE OF CONTENTS

FIGURES AND TABLES

ABBREVIATIONS TABLE

Abbreviation	Name
AGB	Adjustable Gastric Band
ASMBS	American Society of Metabolic and Bariatric Surgery
BMI	Body Mass Index
DM	Diabetes Mellitus
EBW	Excess Body Weight
EBWL	Excess Body Weight Loss
ESG	Endoscopic Sleeve Gastroplasty
FDA	US Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation working group
GERD	Gastroesophageal Reflux Disease
HTN	Hypertension
IGB	Intragastric Balloon
LAGB	Laparoscopic Adjustable Gastric Banding
LSG	Laparoscopic Sleeve Gastrectomy
LOS	Length of Stay
NAFLD	Nonalcoholic fatty liver disease
NH	Non-Hispanic
POSE	Primary Obesity Surgery Endolumina
RCTs	Randomized controlled trials
ROBINS-I	Cochrane Risk of Bias In Non-randomized Studies – of Interventions
RYGB	Roux-en-Y Gastric Bypass
TBWL	Total Body Weight Loss
QOL	Quality of Life

EVIDENCE REPORT

INTRODUCTION

PURPOSE

The Evidence Synthesis Program (ESP) developed the present report in response to a request from the Veterans Health Administration (VHA) National Gastroenterology and Hepatology Program Office.

BACKGROUND

The growing prevalence of obesity worldwide is notable. According to a 2016 study by the World Health Organization (WHO), over 1.9 billion adults are considered overweight and another 500 million adults are obese.[1] Obesity contributes to a range of harmful comorbidities spanning cardiovascular disease, type 2 diabetes, cancer, osteoarthritis, non-alcoholic fatty liver disease, and sleep apnea.[2,3] The economic burden on the United States healthcare system, when including direct and indirect costs, approximates $150 billion dollars per year.[4] Targeted pharmacologic, endoscopic, and surgical therapies have been developed in the effort to expand therapeutic options for treating obesity.

Bariatric surgery remains a gold-standard treatment of morbid obesity and is effective at reducing weight, along with obesity-related conditions, which translates into improved long-term survival.[5] The American Society of Metabolic and Bariatric Surgery (ASMBS) estimates that in 2019, laparoscopic sleeve gastrectomy (LSG) represented 60% of all bariatric procedures performed domestically, with Roux-en-Y gastric bypass (RYGB) encompassing 18%, and adjustable gastric band (AGB) and duodenal switch each constituting only 0.9%. The only endoscopic bariatric therapy tracked by ASMBS, intragastric balloon (IGB), comprised 1.8% of total bariatric procedures.[6] There is strong evidence from observational studies and randomized controlled trials (RCTs) that bariatric surgery is an effective intervention for substantial and durable weight loss. Long-term studies with 10-year follow-up have demonstrated mean percent excess weight loss of 60% following RYGB, 49% following AGB, and 57% following LSG in certain populations.[7] Though rare, surgery is associated with a risk of severe morbidity and mortality for an elective operation, approximately 4% and 0.1%, respectively. Additionally, most of these operations are not easily reversible.[8]

Despite the prevalence of obesity and the proven efficacy of surgery, few who qualify ultimately receive this intervention.[9] It is estimated that 256,000 bariatric surgeries were performed in 2019, which accounts for less than 1% of American patients eligible based on BMI.[6] This gap is even more pronounced in the VA population. According to the 2014 VA/Department of Defense obesity guideline summary, 78% of Veterans are overweight or obese resulting in an annual cost of $370 per patient due to medical- or non-medical-related care.[10] The VA performs approximately 500 bariatric surgeries annually across 17-21 centers. Comprehensive and interdisciplinary management thus far has focused on lifestyle modification and medications through programs like MOVE! (MOVE! Weight Management Program) or referral to bariatric surgery. However, given the large percentage of Veterans who are obese receiving care through the VA and the strong association of obesity with comorbid conditions, detailed evaluation of less-invasive therapeutic options is requested by VA stakeholders.

There remains a treatment gap for patients who experience limited weight loss with conservative therapies (*eg*, lifestyle modification, medications), and at the same time, do not qualify for or otherwise do not have access to surgery, or are reluctant because of the potential operative risks. Endoscopic bariatric therapy is a viable alternative to traditional therapies.[11] Over the past 10 years, various endoscopic modalities have been developed that focus on either primary gastric (IGB, endoscopic sleeve gastroplasty [ESG], aspiration therapy) or small bowel (luminal liners, resurfacing or shuttles) interventions. Preliminary studies have shown promising results, including mean percent total body weight loss (%TBWL) of 18-20% 1 year following ESG[1,12] and 8-12% following IGB.[13,14] Endoscopic therapies came to market quickly, as compared to their surgical counterparts, and questions remain about their efficacy and safety. Additionally, the differences in efficacy between therapies are not well described, which may lead practitioners to be uncertain about recommending them to patients who may qualify.

Systematic reviews comparing endoscopic bariatric therapies to surgical intervention, lifestyle intervention, and other endoscopic treatments have methodological variations and inconsistent reporting of obesity and metabolic syndrome-related outcomes.[14-16] This is complicated further by the wide variety of existing therapies available, as well additional novel therapies that are being considered for US Food and Drug Administration (FDA) approval in the near future. Endoscopic bariatric interventions are increasingly being utilized for a broad population of patients with morbid obesity, and it is imperative to examine how they compare to surgical and lifestyle therapies. We conducted a systematic review to help clinicians, patients, and policymakers understand these new approaches in comparison to traditional bariatric surgery. In this review, we aim to assess the impact of endoscopic bariatric therapies on weight loss, morbidity, mortality, and resolution of comorbid conditions.

METHODS

TOPIC DEVELOPMENT

This topic was developed in response to a nomination by Jason A. Dominitz, MD, MHS National Program Director, National Gastroenterology and Hepatology Program Office, Veterans Health Administration. Key questions were then developed with input from the topic nominator, the ESP Coordinating Center, the review team, and a technical expert panel (TEP).

KEY QUESTIONS

The following key questions (KQs) were the focus of this review:

KQ1: What is the comparative effectiveness of endoscopic bariatric interventions versus lifestyle interventions or bariatric surgery?

KQ2: What are the comparative harms of endoscopic bariatric interventions versus lifestyle interventions or bariatric surgery?

KQ3: Do the comparative effectiveness and/or harms vary by patient or intervention characteristics (*ie*, age, BMI, type of procedure [intragastric balloon, endoscopic gastric reduction, *etc*])?

PROTOCOL

A preregistered protocol for this review can be found on the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; registration number CRD42021270205).

DATA SOURCES AND SEARCHES

We conducted broad searches using terms relating to "gastric balloon" or "bariatric surgical procedure" or "endoscopic gastroplasty." We searched PubMed (1/1/2014-12/7/2021), Embase (1/1/2014-12/7/2021), and Cochrane (1/1/2014-12/7/2021). A search focusing on "endoscopic bariatric therapy" was conducted January 23, 2022, and utilized the same databases and search parameters as the initial search. We limited the search to 2014 onwards, as these therapies were being approved by FDA in 2015-2017. Studies published prior to 2014 would have been based on data from procedures done in 2012 or earlier, and we did not consider evidence from this period to be relevant to current practice. See Appendix A for complete search strategy.

STUDY SELECTION

Two team members working independently screened the titles of retrieved citations. For titles deemed relevant by at least 1 person, abstracts were then screened independently in duplicate by 2 team members. All disagreements were reconciled through group discussion. Full-text review was conducted in duplicate by 2 independent team members with any disagreements resolved through discussion. Studies were included at either the abstract or the full-text level if they were RCTs or observational studies comparing a bariatric endoscopic procedure to alternate bariatric therapies (pharmaceutical, endoscopic, or surgical) or lifestyle management. Studies with fewer than 10 participants were excluded during screening.

We included all RCTs regardless of outcomes studied or sample size. Observational studies were subjected to additional selection criteria. Studies with a comparative arm (regardless of sample size) were included. All cases series (*eg*, studies with no comparison treatment arm) were excluded, regardless of sample size, for analysis of the primary outcomes; however, case series with greater than 500 participants were included for complication outcomes. Additionally, observational studies from the same data source, either large databases or single institutional databases, were considered to have a large overlap if >50% of the same subjects were included in multiple publications or if there was >50% overlap in the enrollment period. In this instance, the publication with the most recent data and the most outcomes of interest was included.

We excluded studies where the bariatric procedure was used solely as a bridge to weight loss prior to bariatric surgery, as this fell outside the scope of interest of VA stakeholders. We also excluded studies where similar endoscopic mechanisms were compared to each other (*eg*, IGB vs IGB, primary obesity surgery endoluminal vs endoscopic sleeve gastroplasty, *etc*), as well as those that compared adjustments of endoscopic bariatric therapies in unapproved ways (*eg*, variable balloon inflation volume, number of intragastric balloons, *etc*) or investigational procedures (*ie*, duodenal-jejunal bypass liner, Endomina, botulinum injection, duodenal mucosal resurfacing).

DATA ABSTRACTION AND ASSESSMENT

Data extraction was completed in duplicate. All discrepancies were resolved with full group discussion. We abstracted data on study design, sample size, perioperative outcomes (weight loss, reoperations/revisions, 30-day readmissions, adverse events, effects on obesity-related comorbid conditions, mortality) and some outcomes that were procedure specific (IGB-related complications such as premature removal due to intolerance, fistula or gastric ulceration; AspireAssist-related stomal irritation, *etc*). We also abstracted data needed for the Cochrane Risk of Bias tool or Cochrane Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I). We looked for outcomes for weight loss at 6 months, 12 months, 24 months, 36 months, 48 months, and last follow-up if longer than 48 months, or the time closest to these follow-up periods.

RCTs were assessed for quality (risk of bias) with the Cochrane Risk of Bias tool. This tool requires an assessment of whether a study is at high or low (or unknown) risk of bias in 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other (see Appendix C for tool; Appendix E for table). We used ROBINS-I for observational studies. This tool requires an assessment of whether a study is at critical, serious, moderate, or low risk of bias (or no information) in 7 domains: confounding, selection bias, bias in measurement classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result (see Appendix D for tool; Appendix F for table). Since observational studies are not required to have published an a priori protocol, we operationalized the last domain (bias in selection of the reported result) as requiring that studies report the most common variables.

We used the criteria of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.[19] GRADE assesses the certainty of the evidence based on

the assessment of the following domains: risk of bias, imprecision, inconsistency, indirectness, and publication bias. This results in categories as follows:

High: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low/Insufficient: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

SYNTHESIS

Pooled Data

For comparisons with at least 3 studies of the same intervention and similar patient populations and the same outcome, we performed random-effects meta-analyses. We conducted a meta-analysis of 6-month weight loss outcomes (%TBWL and mean percent excess body weight loss [%EBWL]) for RCTs and observational studies of IGB versus lifestyle, and for observational studies of ESG versus LSG. Pooled estimates of effect are reported as mean difference (MD) with their 95% confidence intervals (CI). Random-effects meta-analyses were conducted using the Hartung-Knapp-Sidik-Jonkman method. The presence of publication bias was evaluated using Begg rank correlation[17] and Egger regression tests.[18] p-values < .05 were considered statistically significant.

Non-pooled Data

A narrative analysis was performed for the remainder of our outcomes. Continuous outcomes were analyzed using the mean or median along with a measure of dispersion (standard deviation, inter-quartile range) to calculate the difference and 95% CI between arms. For binary outcomes, the number of subjects with the outcome was collected and a risk difference was derived with its 95% CI.

We created figures for adverse events with 3 or more studies and included all in Appendix H. Graphical representations of the outcomes' risk and mean differences and 95% CI were plotted when available or estimable using counts and sample sizes. We noted where significance differed between the study-reported p-value and calculated risk or mean differences and 95% CI. For rare outcome events, risk differences were preferentially used during analysis.

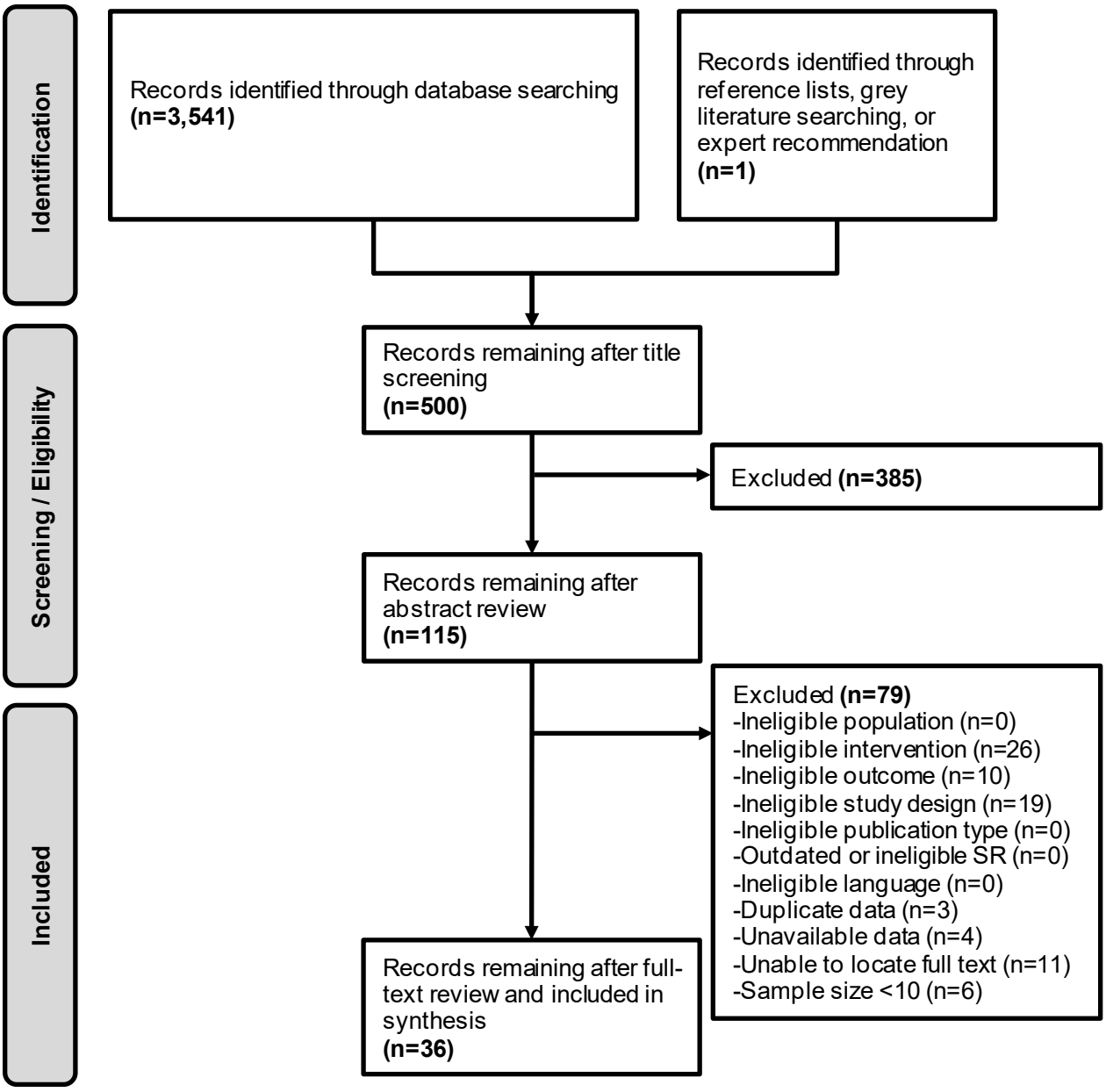
All analyses were carried out with the *metafor* package in R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

LITERATURE FLOW

The literature flow diagram (Figure 2) summarizes the results of the study selection process (full list of excluded studies available in Appendix B).

Figure 1. Literature Flowchart



LITERATURE OVERVIEW

The literature search identified 3,541 potentially relevant citations (including 1 recommended by a subject matter expert), 500 of which were included at the abstract screening level. From these, a total of 385 abstracts were excluded for the following reasons: study design (*N* = 276), no outcomes (*N* = 53), bridging therapy (*N* = 24), duplicate (*N* = 22), modified procedures (*N* = 3), adjunct therapies (*N* = 2), pediatric (*N* = 2), procedure type not included (*N* = 2), and no data available (*N* = 1). This left 115 publications for full-text review, of which 79 publications were excluded for the following reasons: study design (*N* = 19), unavailable (*N* = 11), procedure type not included (*N* = 10), adjunct therapies (*N* = 8), modified procedures (*N* = 7), non-bariatric outcomes (*N* = 6), sample size (*N* = 6), no data available (*N* = 4), short follow-up (*N* = 4), duplicate data (*N* = 3), and bridging therapy (*N* = 1). A full list of excluded studies from the full-text review is in Appendix I. A total of 36 publications were identified at full-text review as meeting initial inclusion criteria. Descriptions of included publications are available in the Evidence Table (Appendix G).

Intragastric Balloon

A total of 12 RCTs were identified, all of which compared IGB to lifestyle therapy. An additional 3 observational studies were identified comparing IGB to lifestyle therapy.

Endoscopic Sleeve Gastroplasty

One RCT was identified comparing ESG to lifestyle therapy. An additional 11 observational studies were identified, of which 5 compared ESG to lifestyle therapy, 1 compared to AGB, and 7 compared ESG to LSG (1 study compared ESG to both AGB and LSG).

Aspiration Therapy

A total of 3 RCTs were identified that compared AspireAssist to lifestyle therapy. One additional observation study compared AspireAssist to RYGB.

Risk of Bias

For the RCTs, the most common sources of bias were lack of blinding of participants and personnel, incomplete outcome data, and blinding of outcome assessment. All studies were high risk of bias in at least 1 domain. For the observational studies, the most common sources of bias were bias due to confounders, selection of participants, missing data, and measurement of outcomes. All but one observational study has unknown or high risk of bias in at least 1 domain.

KEY QUESTION 1: What is the comparative effectiveness of endoscopic bariatric interventions versus lifestyle interventions or bariatric surgery?

6 Month Total Body Weight Loss

A total of 10 studies compared %TBWL with IGB to control groups at 6 months (Figure 2).[13,20-28] All of these studies compared IGB to lifestyle; 7 were RCTs and 3 were observational studies. All of these studies but 1 found significantly greater %TBWL in patients treated with IGB. The size of weight loss benefit was mostly similar between studies, with 95% CIs for the results overlapping in 9 of the 10 studies. We pooled the 7 RCTs in a random-effects meta-analysis (Figure 3). The pooled estimate of the mean difference in %TBWL at 6 months was 6.37% (95% CI [3.94, 8.80]). There was no evidence of publication bias (Egger's test $p = 0.903$, Begg's test $p = 0.239$). For the 3 observational studies, the random effect pooled estimate of mean difference in %TBWL at 6 months was 7.37% (95% CI [6.36, 8.39]), favoring treatment with balloon. There was no evidence of publication bias (Egger's test $p = 0.595$, Begg's test $p = 1$).

A total of 9 studies compared %TBWL with ESG to control groups at 6 months (Figure 2).[29-37] One RCT and 2 observational studies[29-31] compared ESG to lifestyle, and all found significantly greater %TBWL in the patients treated with ESG. The size of the weight loss benefit was very different in the 3 studies, with the 95% CIs for the results non-overlapping. The 1 study comparing ESG to laparoscopic adjustable gastric banding (LAGB) reported no significant differences in total body weight loss at 6 months. Six observational studies compared ESG to LSG at 6 months.[32-37] These studies all reported significantly greater total body weight loss in the patients treated with LSG. We pooled these 6 observational studies in a random-effects meta-analysis (Figure 4). The pooled estimate of the mean difference in %TBWL at 6 months was 10.44% (95% CI [6.08, 14.80]), favoring treatment with LSG. There was no evidence of publication bias (Egger's test $p = 0.691$, Begg's test $p = 0.817$).

No studies compared AspireAssist %TBWL at the 6-month interval.

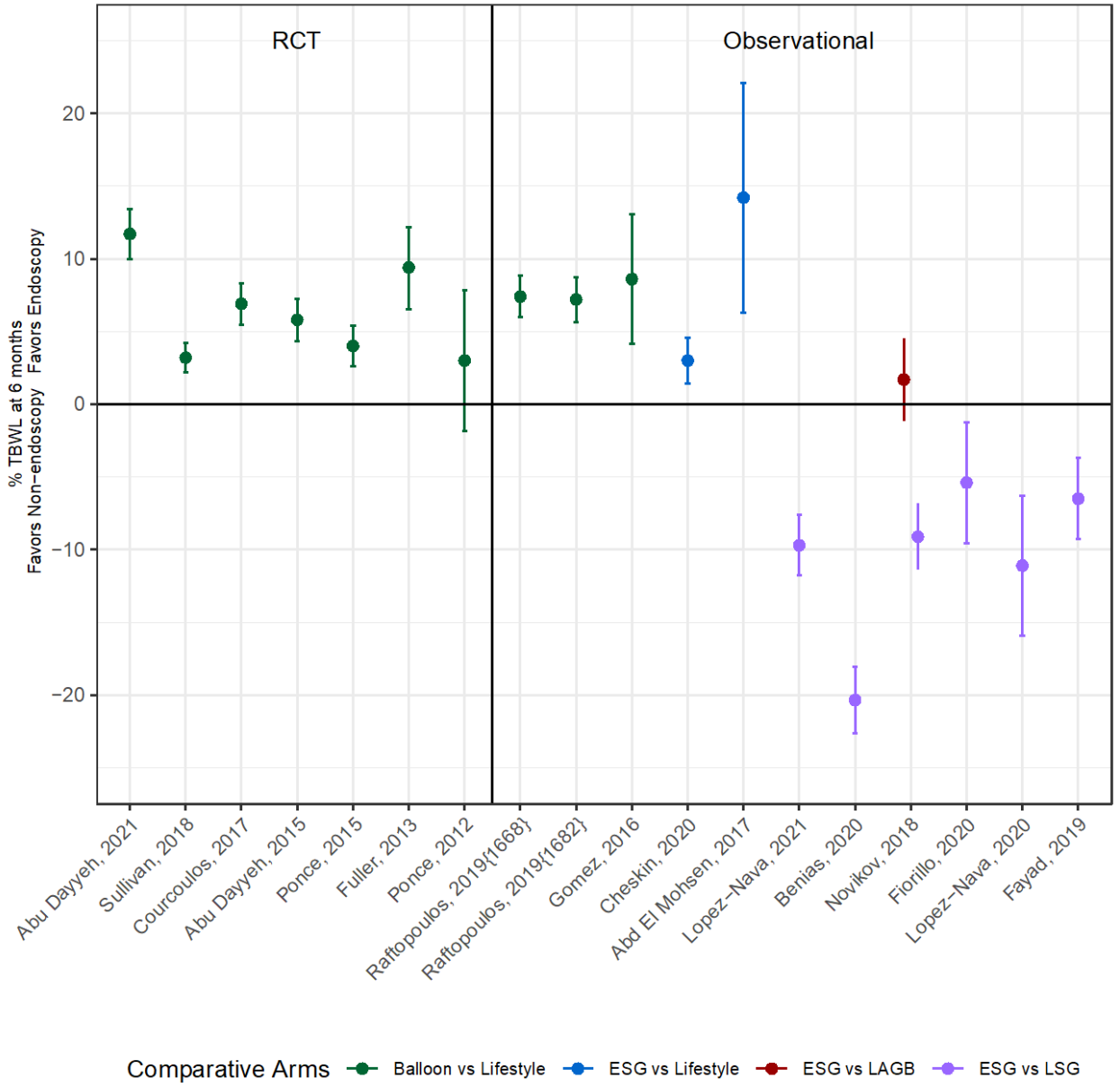
6 Month Excess Body Weight Loss

A total of 6 studies compared %EBWL with IGB to control groups at 6 months (Figure 5).[20,22,26-28,38] All of these studies compared IGB to lifestyle, and all were RCTs. All of these studies but 1 found significant %EBWL in patients treated with IGB at 6 months. The size of weight loss benefit was mostly similar between studies, with 95% CIs for the results overlapping across all studies. A random-effects meta-analysis was performed examining %EBWL after IGB versus lifestyle (Figure 6). The pooled estimate of the mean difference in %EBWL at 6 months was 17.11% (95% CI [11.65, 22.57]). There was no evidence of publication bias (Egger's test $p = 0.618$, Begg's test $p = 0.333$).

A total of 2 studies compared excess body weight loss with ESG to control groups at 6 months: 1 RCT comparing ESG to lifestyle and 1 observational study comparing ESG to LSG.[31,34] The study comparing ESG to lifestyle found significantly superior %EBWL in patients treated with ESG, whereas the observational study comparing ESG to LSG found significant %EBWL with LSG compared to ESG.

No studies compared AspireAssist %EBWL at the 6-month interval.

Figure 2. Total Body Weight Loss at 6 Months for Bariatric Endoscopic Procedures Compared to Lifestyle or Surgery



Abbreviations. %TBWL=mean percent total body weight loss; ESG=endoscopic sleeve gastroplasty; LAGB=laparoscopic adjustable gastric banding; LSG=laparoscopic sleeve gastrectomy.

Figure 3. Meta-analysis of IGB versus Lifestyle for the Outcome of Total Body Weight Loss at 6 Months

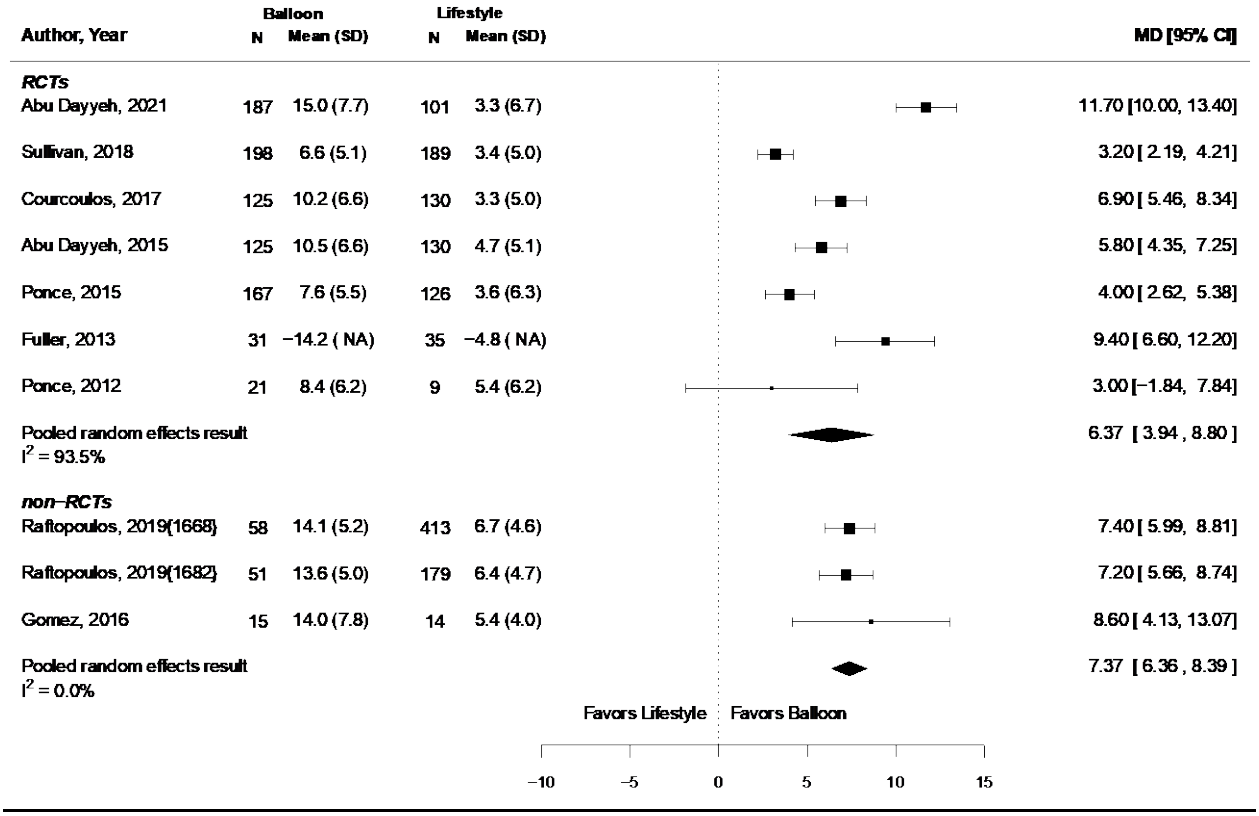
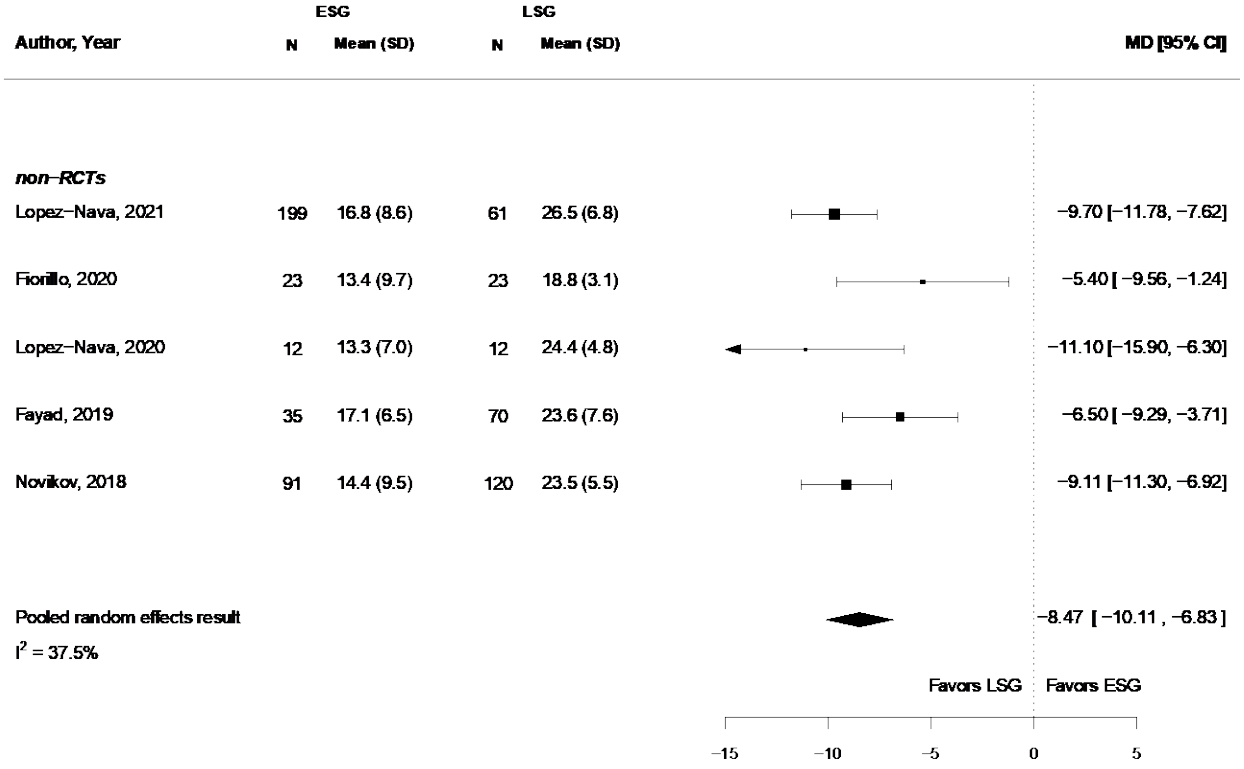
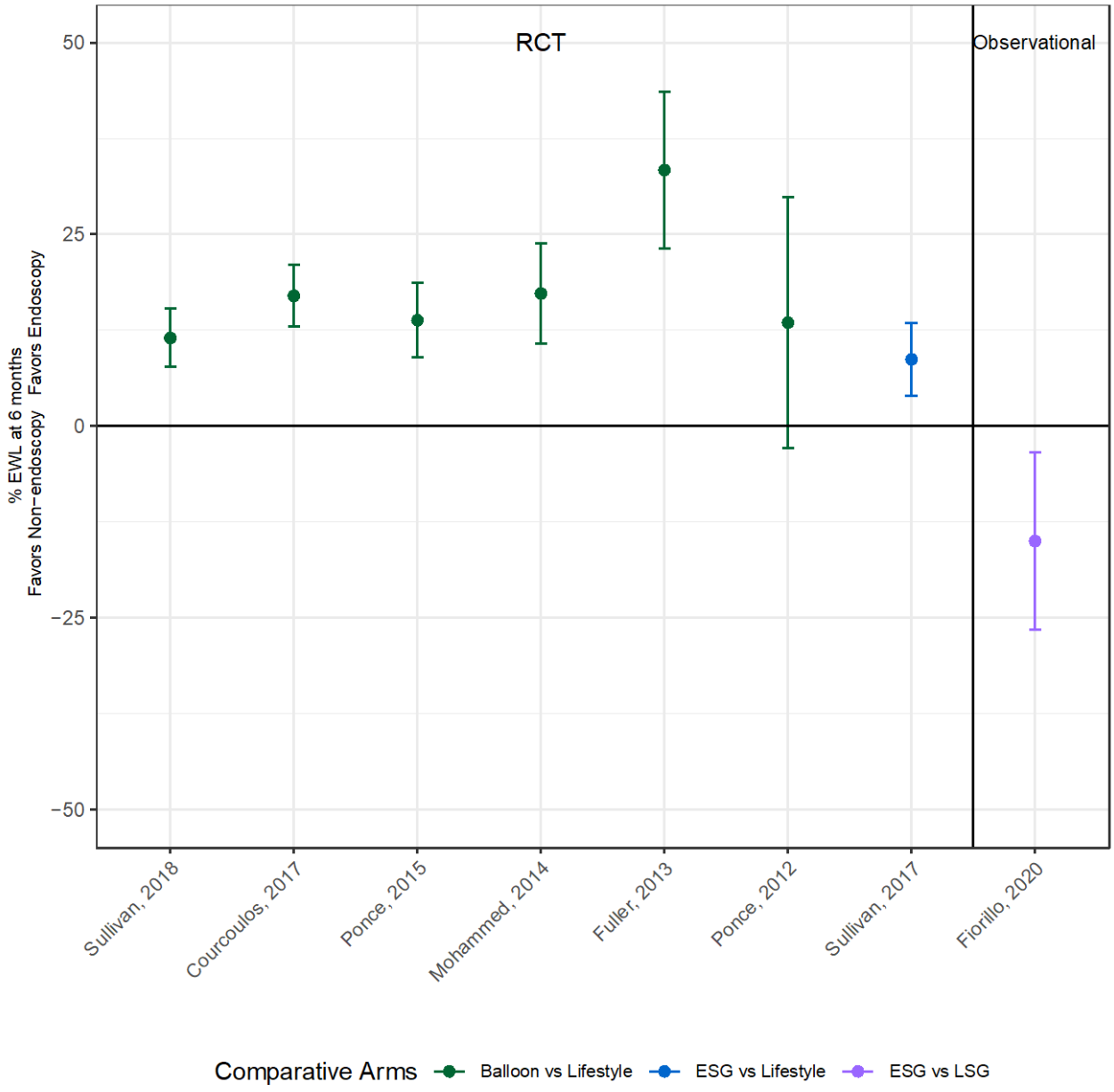


Figure 4. Meta-analysis of ESG versus LSG for the Outcome of %TBWL at 6 Months



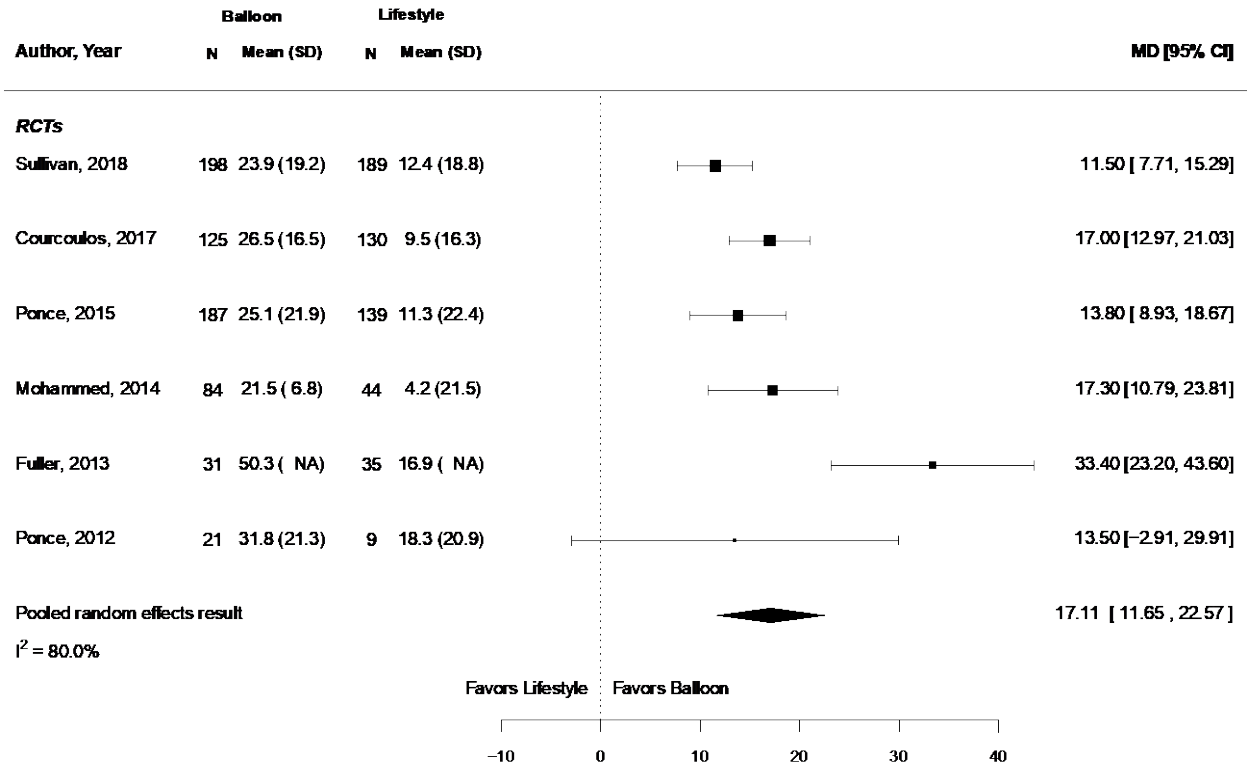
Abbreviations. ESG=endoscopic sleeve gastroplasty; LSG=laparoscopic sleeve gastrectomy.

Figure 5. Excess Body Weight Loss at 6 Months for Bariatric Endoscopy as Compared to Lifestyle or Surgery



Abbreviations. %EWL=excess weight loss; ESG=endoscopic sleeve gastroplasty; LSG= laparoscopic sleeve gastrectomy.

Figure 6. Meta-analysis of Intragastric Balloon versus Lifestyle for the Outcome of %EBWL at 6 Months



12 Month Total Body Weight Loss

A total of 5 studies compared ESG to control groups at 12 months (Figure 7).[29,31-33,37] Two studies compared ESG to lifestyle.[29,31] Both of these studies found significantly greater %TBWL in the patients treated with ESG. One study compared ESG to LAGB, reporting significant differences in weight loss at 12 months with those treated with the gastric band.[32] Three observational studies compared ESG to LSG at 12 months.[32,33,37] These studies reported significantly greater %TBWL in the patients treated with LSG.

A total of 6 studies compared IGB to lifestyle at 12 months, 4 of which were RCTs.[13,20,21,24,26,27] All studies except 1 RCT reported significant %TBWL with IGB compared to control. Of these studies, 4 used the Orbera endoscopically placed balloon, 1 reported results from the swallowable Ellipse balloon, and 1 study reported results with the Reshape dual balloon. The Reshape dual balloon result was the only trial not to be significant. We pooled these 4 RCTs in a random-effects meta-analysis (Figure 9). The pooled estimate was 4.13% (95% CI [2.99, 5.27]. There was no evidence of bias (Egger's test $p = 0.198$, Begg's test $p = 0.469$)

A total of 3 studies compared AspireAssist to control at 12 months, 1 of which was an RCT.[39-41] Two RCTs compared longitudinal outcomes from AspireAssist to lifestyle therapy at 12 months, both reporting significant %TBWL with aspiration therapy versus control.[39,41] One observational study compared AspireAssist to RYGB.[40] This study demonstrated significantly more weight loss at 12 and 24 months with RYGB compared to AspireAssist.

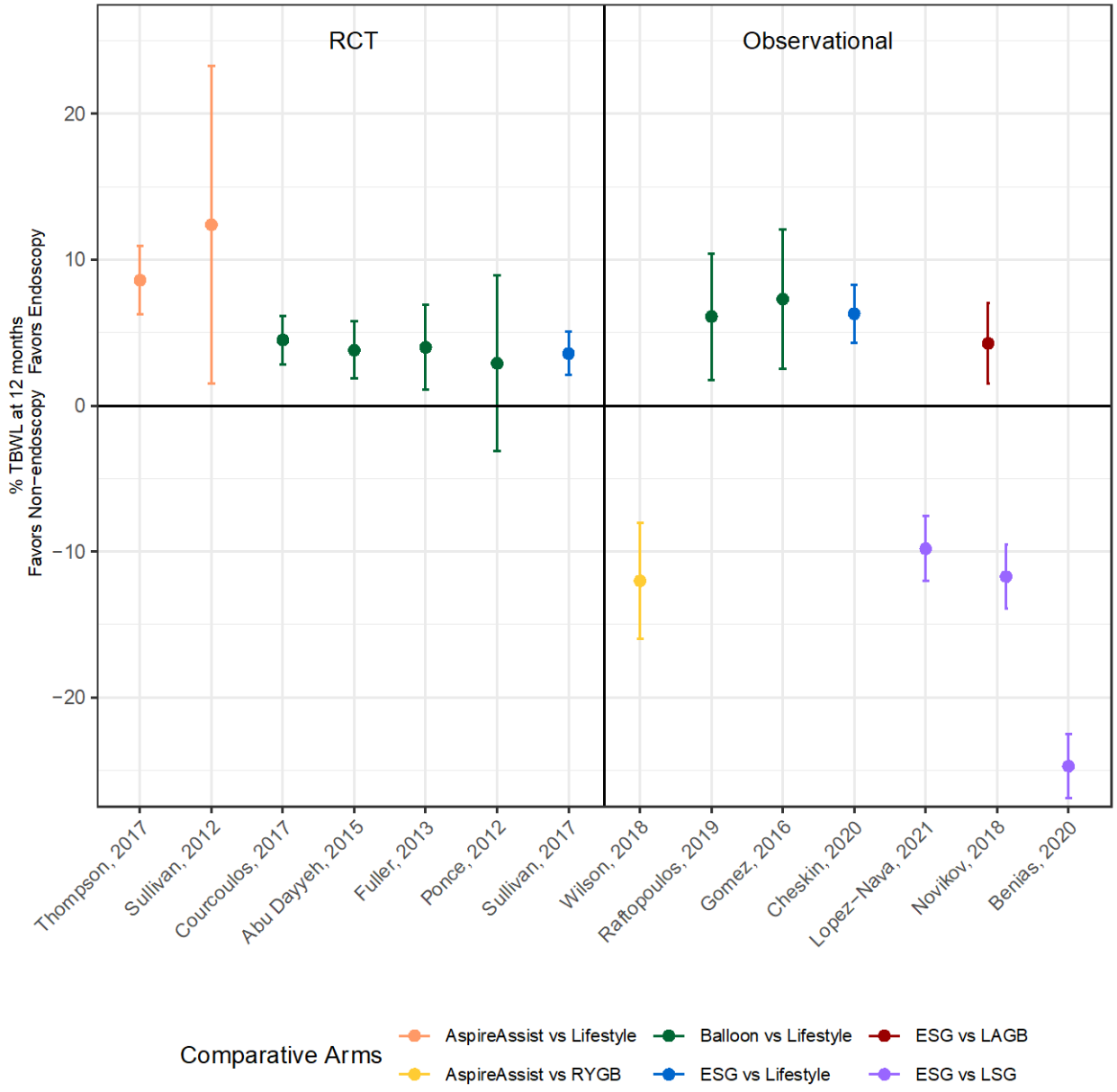
12 Month Excess Body Weight Loss

A total of 4 studies compared %EBWL with IGB versus lifestyle at 12 months, all of which were RCTs (Figure 8).[20,26,27,38] Of these studies, all but 1 demonstrated significant excess body weight loss at 12 months, and all 95% CIs overlapped.

One study reported %EBWL after ESG vs lifestyle therapy.[31] This RCT reported statistically greater excess body weight loss at 12 months with ESG compared to control.

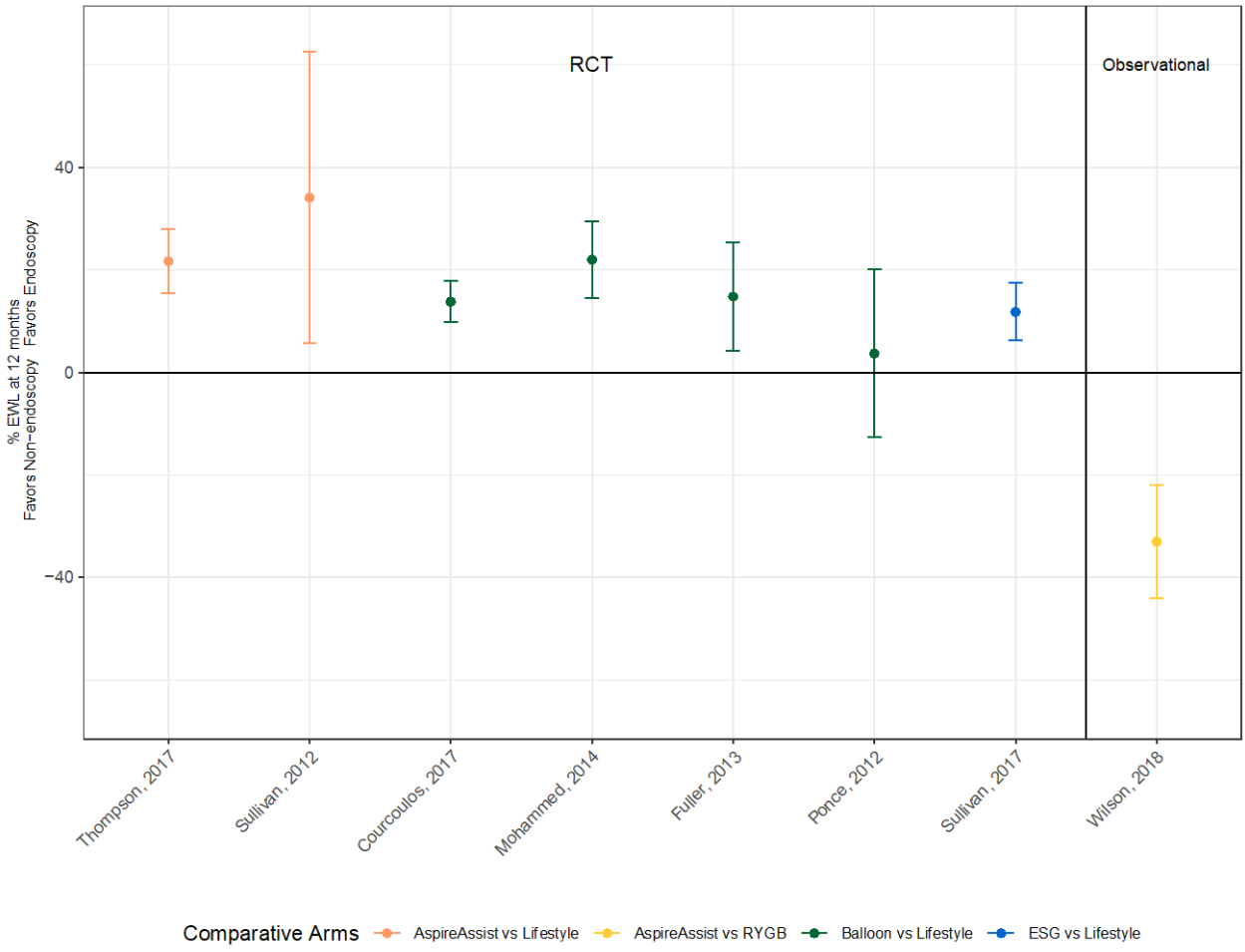
A total of 3 studies compared %EBWL with aspiration therapy to control at 12 months.[39-41] Two RCTs compared AspireAssist to lifestyle, both reporting significantly increased %EBWL with aspiration therapy at 12 months.[39,41] One observational study compared aspiration therapy to RYGB and reported significantly greater %EBWL at 12 months with RYGB compared to AspireAssist. [40]

Figure 7. Total Body Weight Loss at 12 Months for Bariatric Endoscopy as Compared to Lifestyle or Surgery



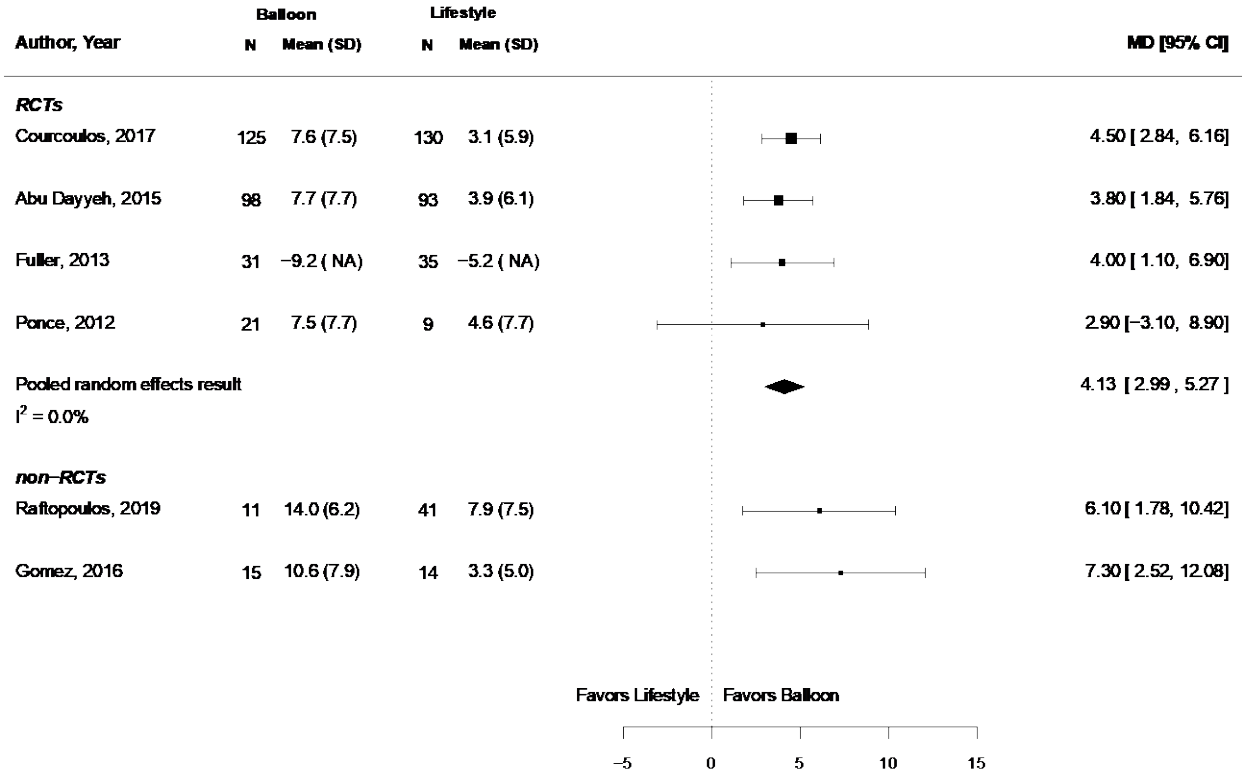
Abbreviations. %TBWL=mean percent total body weight loss; ESG=endoscopic sleeve gastroplasty; LAGB=laparoscopic adjustable gastric banding; LSG=laparoscopic sleeve gastrectomy.

Figure 8. Excess Body Weight Loss at 12 Months for Bariatric Endoscopic Procedures as Compared to Lifestyle or Surgery



Abbreviations. %EWL=excess weight loss; ESG=endoscopic sleeve gastroplasty; RYGB=Roux-en-Y gastric bypass.

Figure 9. Meta-analysis of IGB versus Lifestyle Outcome %TBWL at 12 Months



Quality of Life Outcomes (Table 1)

IGB versus Lifestyle

One study reported quality of life (QOL) outcomes at both 6 and 12 months.[20] This study found mean difference in IWQOL-Lite scores 7.5 points greater at 6 months and 6.4 points greater at 12 months after IGB compared to lifestyle treatment, but a confidence interval could not be determined (higher scores indicate better QOL).

ESG versus Lifestyle

One study reported QOL outcomes at 6 months, and 1 reported QOL outcomes at 12 months.[31,42] Courcoulos et al found mean difference in IWQOL-Lite scores 3.11 points greater after 6 months and 3.88 points greater at 12 months after ESG compared to lifestyle treatment. This study found significantly higher QOL at 12 months compared to lifestyle. Ahmed et al found significantly higher risk differences of increased QOL in the balloon group at 6 months.

ESG versus LSG

Two studies reported QOL outcomes at 6 months.[34,43] One study reported no significant difference in GIQOL scores between the 2 procedures.[34] Another study reported 7.9% less improvement in QOL after ESG compared to LSG when subjectively rated on a scale of 1-10 at 6 months.[43] This result was not statistically significant in 1 study, and in the other, no confidence interval could be determined.

Table 1. Hemoglobin A1c and Quality of Life Outcomes for Bariatric Endoscopic Procedures Compared to Lifestyle or Surgery

	HbA1c Negative is better for endoscopic treatment *MD [95% CI]*	**Quality of Life** Positive is better for endoscopic treatment *MD [95% CI]*
IGB vs Lifestyle		
Abu Dayyeh, 2021, 9 mo (RCT)	-0.73 [-1.49, 0.02][a]	
Sullivan 2018, 6 mo (RCT)	0.00 [-0.14, 0.14]	—
Courcoulos 2017, 6 mo (RCT)	—	7.5 [NR]
Courcoulos 2017, 12 mo (RCT)	—	6.40 [NR]
ESG vs Lifestyle		
Ahmed 2019, 6 mo (RCT)		0.13 [0.02, 0.231][c]
Sullivan 2017, 6 mo (RCT)	-0.03 [-0.9, 0.04]	—
Sullivan 2017, 12 mo (RCT)	-0.03 [-0.11, 0.05]	2.9 [1.6, 4.2]
AspireAssist vs Lifestyle		
Thompson 2017, 12 mo (RCT)	-0.14 [NR]	—
ESG vs LSG		
Benais 2020, 12 mo (Obs)	-7.7 [-11.0, -4.8][b]	
Fiorillo 2020, 6 mo (Obs)	—	1.00 [-8.6, 10.64]
Sadek 2017, 6 mo (Obs)	—	7.9 [NR]

Notes. [a]Only among those with type 2 diabetes and baseline HbA1c >7.5%. [b]Mean difference percent change from baseline. [c]Risk difference (different between percent reporting high QOL).
Abbreviations. ESG=endoscopic sleeve gastroplasty; IGB=intragastric balloon; LSG=laparoscopic sleeve gastrectomy.

Hemoglobin A1c (Table 1)

IGB versus Lifestyle

Two studies reported changes in HbA1c after IGB.[22,25] These studies found no significant differences in HbA1c after IGB compared to lifestyle.

ESG versus Lifestyle

One study reported changes in HbA1c after ESG compared to lifestyle.[31] At both 6 and 12 months, there was no significant improvement in HbA1c compared to lifestyle therapy.

AspireAssist versus Lifestyle

One study reported changes in HbA1c after AspireAssist compared to lifestyle.[39] This study reported a 12-month improvement in HbA1c 0.14 mg/dL greater after aspiration therapy compared to lifestyle, but statistical significance could not be calculated.

ESG versus LSG

One study reported changes in HbA1c after ESG compared to LSG.[37] This study reported significantly greater mean percent decrease in HbA1c after ESG compared to LSG.

KEY QUESTION 2: What are the comparative harms of endoscopic bariatric interventions versus lifestyle interventions or bariatric surgery?

Reporting of details of procedural adverse events was inconsistent across studies, limiting interpretation of relative harm when comparing techniques.

Total Complications

A total of 12 studies reported total complication rates, defined as any complication in any patient (Figure 10, Table 2).[20,22,25,26,28,29,31-34,36,39] One randomized trial comparing AspireAssist to lifestyle reported statistically significantly fewer complication rates with lifestyle therapy.[39] Five randomized trials looking at IGB versus lifestyle all demonstrated statistically significantly fewer complications with lifestyle therapy.[20,22,25,26,44] Two studies comparing ESG versus lifestyle found significantly fewer complication rates with lifestyle therapy.[29,31] There were 4 observational studies focusing on ESG compared to LSG.[32-34,36] Three of these studies reported no difference in complications between ESG and LSG, while 1 reported significantly higher rates of complications with ESG compared to LSG. A total of 2 case series reported total complication rates after IGB of 5.9% and 14.3%, respectively.[45,46] One study reported complication rates after IGB in terms of Clavien-Dindo classification, reporting an 89.3% rate of Grade 1 complications, 10% rate of grade 2 complications, and 0.7% rate of grade 3 complications.[47] Another case series reported major complication rates of 0.83% with IGB.[48] No large volume case series reported total complication rates after ESG or AspireAssist.

A total of 4 studies reported total complication rates at 12 months.[29,31,32,39] The 3 studies comparing intervention to lifestyle, ESG and AspireAssist, all reported significantly higher complication rates with intervention compared to lifestyle.[29,31,39] The 1 study comparing ESG to LSG noted significantly higher complication rates with LSG compared to ESG.[32]

30-day Readmissions

The 1 study comparing intervention versus lifestyle therapy that assessed readmissions between groups noted higher 30-day readmission rates with IGB placement compared to lifestyle.[22]

A total of 3 studies compared 30-day readmissions between ESG and LSG, and none found significant differences in 30-day readmissions between the groups.

30-day Reinterventions

One study reported 30-day reintervention rates comparing IGB to lifestyle, reporting no differences. However, there is low confidence in this finding given the number of patients requiring premature balloon removal noted in other studies.[40] One study of AspireAssist reported that there was 1 reintervention out of a trial of 137 patients who received AspireAssist therapy due to a skin port malfunction.[49] Two studies compared 30-day reintervention rates between ESG and LSG, 1 noting no difference between the groups and the other noting fewer 30-day

reinterventions amongst ESG compared to LSG.[32,36] One case series reported a 30-day reintervention rate of 2.4%.[50]

Abdominal Pain

Four studies compared patient-reporting of abdominal pain between IGB and lifestyle.[20,22,27,40] Three studies noted significantly higher reporting of abdominal pain among IGB patients compared to lifestyle, while the third reported no abdominal pain among its cohort. One study compared patient reporting of abdominal pain between AspireAssist and lifestyle therapy, noting a higher rate of abdominal pain among patients receiving aspiration therapy compared to lifestyle. No studies compared abdominal pain reporting after ESG to LSG. One case series reported a 5.29% incidence of abdominal pain after IGB.[46]

Gastric Ulceration

A total of 3 studies compared rates of gastric ulceration between IGB and lifestyle,[22,28,49] all reporting significantly higher rates among IGB patients compared to lifestyle. One study compared rates of gastric ulceration in ESG patients to lifestyle, also noting higher rates with intervention.[51] No studies reported rates of gastric ulceration compared to LSG or with aspiration therapy. Two case series reported rates of gastric ulceration after IGB placement as 0.82% and 0.9%, respectively.[45,46]

Bleeding

One study reported higher rates of bleeding after IGB compared to lifestyle, although not statistically significant.[22] One study reported significantly higher rates of bleeding after ESG compared to lifestyle.[31] One study reported bleeding rates after aspiration therapy, finding no significantly different rates of bleeding amongst aspiration therapy compared to lifestyle.[52] Three studies compared bleeding rates between ESG and LSG, all finding no significantly different rates of bleeding between interventions.[34-36] Two case series reported rates of bleeding after IGB placement as 0.01% and 0.6%, respectively.[45,53] One case series reported bleeding rates of ESG as 0.7%.[50]

Gastroesophageal Reflux Disease (GERD)

One study compared GERD rates between IGB and lifestyle, finding significantly higher rates of GERD after IGB.[20] One study compared GERD rates between ESG and lifestyle, finding no significant differences between interventions.[31] A total of 2 studies compared rates of GERD between ESG and LSG, 1 finding no significant difference while another found less GERD after ESG compared to LSG.[34,36] One case series reported a rate of GERD after IGB placement of 0.82%.[46]

Nausea

Four studies compared nausea rates between IGB and lifestyle, finding significantly higher rates of nausea after IGB.[20,22,25,27] One study compared nausea rates between ESG and lifestyle, finding significantly higher rates of nausea after ESG.[31] One case series reported a rate of nausea after IGB placement of 63%.[46] One additional case series reported nausea rates after ESG as 92.4%.[50]

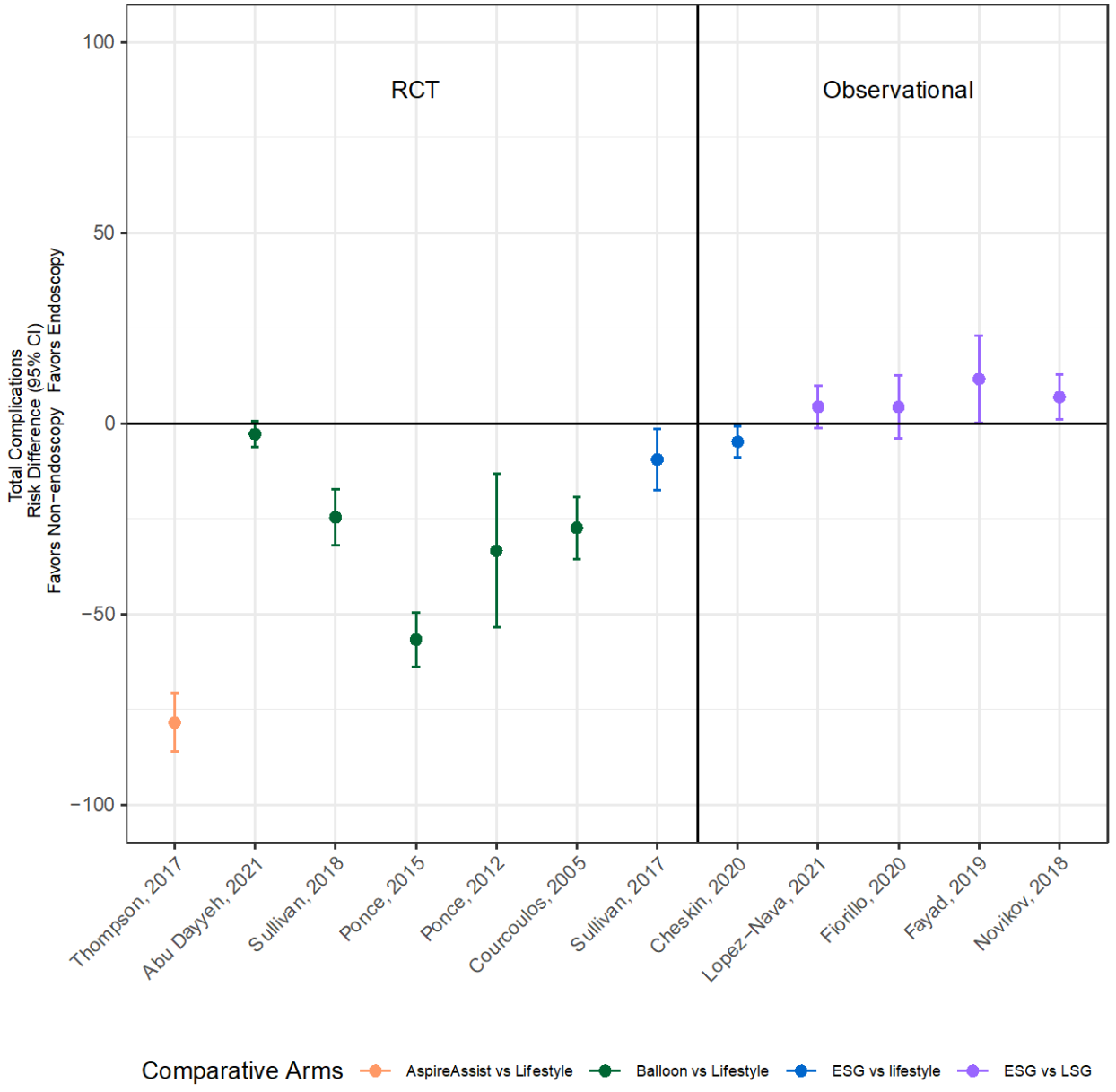
Vomiting

Four studies compared vomiting rates between IGB and lifestyle, finding significantly higher rates of vomiting after IGB.[20,22,25,27] One study compared vomiting rates between ESG and lifestyle, finding significantly higher rates of vomiting after ESG.[31] One study compared vomiting rates after AspireAssist compared to lifestyle, finding significantly higher rates after AspireAssist.[52] A total of 2 studies compared vomiting rates between ESG and LSG, one finding significantly higher rates after ESG and another finding no significant difference.[32,36] One case series reported vomiting rates after IGB placement as 31%.[46]

Dehydration

Four studies compared dehydration rates between IGB and lifestyle therapy, 2 finding significantly higher rates of dehydration after IGB while the other 2 found no significant difference.[20,22,25,27] One study compared dehydration rates after ESG versus lifestyle therapy, finding no significant difference in rates.[29] One study compared dehydration rates after ESG versus LSG, finding no significant difference.[36] Two case series reported rates of dehydration after IGB placement of 0.07% and 0.2%, respectively.[45,46]

Figure 10. Total Complications for Bariatric Endoscopic Procedures Compared to Lifestyle or LSG



Abbreviations. %TBWL=mean percent total body weight loss; ESG=endoscopic sleeve gastroplasty; LAGB=laparoscopic adjustable gastric banding; LSG=laparoscopic sleeve gastrectomy.

Table 2. Adverse Events for Bariatric Endoscopic Procedures as Compared to Lifestyle or Surgery

Study, Year *Design*	Total Complication	30-day Readmission	30-day Reintervention	Nausea	Vomiting	Dehydration	Abdominal Pain	Gastric Ulceration	Bleeding	GERD
IGB vs Lifestyle										
Moore 2019 *Case series*	14.3%			63%	31%	0.07%	5.29%	0.82%		0.82%
Sander 2017 *Case series*									0.01%	
Mathus-Vliegen 2015 *Case series*	5.9%		0.2%			0.2%		0.9%	0.6%	
Sullivan 2018 *RCT*	Risk Diff (CI) 0.25 (0.17, 0.32)			0.38 (0.29, 0.46)	0.07 (0.01, 0.14)	-0.01 (-0.02, 0.01)	0.49 (0.41, 0.58)	0.01 (0, 0.01)	0.06 (0.03, 0.09)	
Courcoulos 2017 *RCT*	0.27 (0.19, 0.35)	7.5		0.82 (0.75, 0.88)	0.70 (0.62, 0.78)	0.14 (0.09, 0.2)	0.54 (0.45, 0.62)			0.25 (0.17, 0.33)
Abu Dayyeh 2021 *RCT*	0.03 (0, 0.06)		0.00 (0, 0)	0.90 (0.86, 0.95)	0.71 (0.65, 0.78)	0.02 (0, 0.04)	0.56 (0.49, 0.63)	0.02 (0, 0.04)		
Ponce 2012 *RCT*	0.33 (0.13, 0.53)									
Pone 2015 *RCT*	0.57 (0.5, 0.64)							0.35 (0.28, 0.42)		
Fuller 2013 *RCT*				0.72 (0.55, 0.89)	0.69 (0.51, 0.86)	0.26 (0.1, 0.41)	0.56 (0.37, 0.74)			
ESG vs Lifestyle										
Alqahtani 2019 *Case series*		2.4%		92.4%					0.7%	

Sullivan 2017 *RCT*	0.09 (0.01, 0.17)			0.14 (0.07, 0.21)	0.19 (0.13, 0.24)			0.01 (0, 0.01)	0.04 (-0.02, 0.09)
Cheskin 2020 *Observ.*	0.05 (0.01, 0.09)					0.01 (-0.01, 0.03)	0.03 (0, 0.06)		
AspireAssist vs Lifestyle									
Thompson 2017 *RCT*	0.78 (0.71, 0.86)		0.01 (-0.01, 0.03)		0.17 (0.1, 0.24)		0.38 (0.29, 0.47)	0.02 (-0.01, 0.04)	
ESG vs LSG									
Fayad 2019 *Observ.*	-0.12 (-0.23, 0)	-0.06 (-0.18, 0.07)	0.00 (0, 0)		0.01 (0.01, 0.16)	-0.01 (-0.04, 0.01)		-0.03 (-0.07, 0.01)	-0.13 (-0.22, -0.03)
Fiorillo 2020 *Observ.*	-0.04 (-0.13, 0.04)	-0.04 (-0.13, 0.04)						-0.04 (-0.13, 0.04)	-0.30 (-0.49, -0.12)
Lopez-Nava 2021 *Observ.*	-0.04 (-0.1, 0.01)							-0.04 (-0.1, 0.01)	
Novikov 2018 *Observ.*	-0.07 (-0.13, -0.01)	-0.02 (-0.04, 0.01)	-0.04 (-0.09, -0.01)		-0.01 (-0.02, 0.01)				

Note. Data are presented as mean difference between comparative arms when appropriate, where positive values favor endoscopic therapy and negative values favor comparative arm. For case series, complication data are presented in percentages.
Abbreviations. ESG=endoscopic sleeve gastroplasty; IGB=intragastric balloon; LSG=laparoscopic sleeve gastrectomy.

KEY QUESTION 3: Do the comparative effectiveness and/or harms vary by patient or intervention characteristics (*ie*, age, BMI, type intragastric balloon, gastroplasty technique, *etc*)?

Study designs and procedures varied considerably, making the ability to compare effectiveness and harm of interventions based on patient characteristics or procedural technique limited. For all the studies included in this review, factors such as baseline age or BMI were not variables that were prospectively assessed or reported in terms of their association with clinical outcomes.

Intragastric Balloon

There were 7 RCTs with detailed demographic and pre-procedural data available for review. Four studies examined the Orbera intragastric balloon[13,20,38,54] and 1 the Obalon IGB[55] against lifestyle modification. Two studies investigated the Reshape dual intragastric balloon.[26,28] One study investigated the Spatz adjustable balloon.[26] There was no direct comparison between the Orbera and Obalon; therefore, conclusions about which type of IGB is more effective based on these 3 trials are limited.

We identified 1 small comparative study looking at the BioEnterics Intragastric Balloon against the Spatz Adjustable Balloon.[56] This single center experience of 20 patients showed equivocal differences in weight loss at 6 months (20kg for both) and adverse events rate. However, given the small sample size, no conclusions can be drawn. Two small observational studies assessed the effects of IGB on liver stiffness, function, and fibrosis in patients with nonalcoholic fatty liver disease (NAFLD), finding significant improvements in liver abnormalities in patients with this condition who undergo IGB placement.[57,58]

Endoscopic Sleeve Gastroplasty

There were multiple cohort studies comparing ESG to LSG.[32-34,36,37] Across all studies, the mean age was similar, ranging from 40-48 years. There were notable differences in baseline characteristics for 3 studies.[32,34,36] In the study by Novikov et al,[32] LSG patients had baseline higher BMIs (47.2 vs 38.6, respectively) and a higher percentage of patients had diabetes (20.5% vs 3.7%) compared to ESG patients. In 3 observational studies,[32,34,36] LSG patients also had significantly higher rates of hypertension. These studies demonstrate that patients with higher BMI with or without metabolic syndrome are more likely to get bariatric surgery overall, but no conclusion can be drawn regarding whether higher BMI or metabolic syndrome affects percent weight loss.

Aspiration Therapy

There are 2 RCTs evaluating AspireAssist to lifestyle with no significant baseline differences.[39,41]

High-quality randomized trials are necessary to assess these key questions in order to optimize patient selection for various bariatric therapies.

CERTAINTY OF EVIDENCE

Our assessments of the certainty of evidence, using the GRADE Framework, are presented in Table 3. In making these determinations, we factored in our assessments of risk of bias for the

studies when judging the degree of study limitations. We considered all the studies to satisfy the directness domain, as all studies measured weight loss, QOL, a metabolic outcome, or complications in standard ways. We considered the consistency and precision domains in the context of the conclusion about each outcome. As an example, for the conclusion that %TBWL is greater in patients treated with an IGB than with lifestyle therapy, we considered the results across studies as consistent and precise if they all had the same finding – that weight loss was significantly greater in patients treated with intragastric balloon therapy – even if the studies found values of %TBWL favoring balloon therapy between 4% and 12%. We did this because we judged the practice-relevant decision was "will this therapy result in greater weight loss?" and not on the precise amount of weight loss. Also, in studies where the comparison was lifestyle therapy, we drew on the large body of literature about lifestyle therapy for weight loss to conclude that complications like reintervention, bleeding, and gastric ulceration can safely be assumed to be negligible, such that the presence of any of these in the intervention groups receiving balloon therapy, gastric sleeve therapy, *etc*, can be more strongly attributed to the intervention. Likewise, the limited effectiveness of lifestyle therapies to yield sustained weight loss increases our certainty that statistically significant benefits favoring an interventional therapy are likely to be causal.

We judged 7 conclusions as being high certainty of evidence, and all were in comparisons between endoscopic interventions and lifestyle therapies: 1) IGB achieves greater %TBWL than lifestyle therapy at 6 and 12 months; 2) IGB achieves more %EBWL than lifestyle therapy at 6 months; 3) ESG achieves more %TBWL than lifestyle therapy at 6 months; and 4) AspireAssist, IGB, and ESG each have greater total complications than lifestyle therapy.

Table 3. GRADE Certainty of Evidence

Outcome	Study Limitations	Consistency	Directness	Precision	Certainty of Evidence
%TBWL					
At 6 months					
IBG > Lifestyle	RCT: No serious limitations Unmatched observational studies: Serious	Consistent	Direct	Precise	High
ESG > Lifestyle	Matched observational studies: Serious Unmatched observational studies: Serious	Consistent	Direct	Imprecise	Low
ESG < LSG	Matched observational studies: Serious Unmatched observational studies: Serious	Consistent	Direct	Precise	Low
At 12 months					
AspireAssist > Lifestyle	RCT: No serious limitations	N/A	Direct	Precise	Moderate
AspireAssist < RYGB	Unmatched observational studies: Serious limitations	N/A	Direct	Precise	Low
IGB > Lifestyle	RCT: No serious limitations	Consistent	Direct	Precise	High

Outcome	Study Limitations	Consistency	Directness	Precision	Certainty of Evidence
	Unmatched observational studies: Serious limitations				
ESG > Lifestyle	RCT: No serious limitations	Consistent	Direct	Precise	High
ESG < LSG	Unmatched observational studies: Serious limitations	Consistent	Direct	Precise	Low
%EBWL					
At 6 months					
IGB > Lifestyle	RCT: No serious limitations	Consistent	Direct	Precise	High
ESG > Lifestyle	RCT: No serious limitations	N/A	Direct	Precise	Moderate
ESG < LSG	Matched observational studies: Serious limitations	N/A	Direct	Precise	Low
At 12 months					
AspireAssist > Lifestyle	RCT: No serious limitations	N/A	Direct	Precise	Moderate
AspireAssist < RYGB	Unmatched observational studies: Serious limitations	N/A	Direct	Precise	Low
IGB > Lifestyle	RCT: No serious limitations	N/A	Direct	Precise	Moderate
ESG > Lifestyle	RCT: No serious limitations	N/A	Direct	Precise	Moderate
HbA1C					
At 6 months					
IGB = Lifestyle	RCT: No serious limitations	N/A	Direct	Precise	Moderate
ESG = Lifestyle	RCT: No serious limitations	N/A	Direct	Precise	Moderate
AspireAssist = Lifestyle	RCT: Very serious limitations	N/A	Direct	N/A	Very low
Quality of Life					
At 12 months					
ESG > Lifestyle	RCT: No serious limitations	N/A	Direct	Precise	Low
ESG = LSG	Unmatched observational studies: Serious limitations	N/A	Direct	Imprecise	Very Low
Total Complications					
At 6 months					
AspireAssist > Lifestyle	RCT: No serious limitations	N/A	Direct	Precise	High
IGB > Lifestyle	RCT: No serious limitations	Consistent	Direct	Precise	High
ESG > Lifestyle	RCT: No serious limitations	Consistent	Direct	Precise	High
ESG = LSG	Matched observational studies: Serious limitations Unmatched observational studies: Serious limitations	Consistent	Direct	Precise	Low

Abbreviations. ESG=endoscopic sleeve gastroplasty; IGB=intragastric balloon; LSG=laparoscopic sleeve gastrectomy; RYGB=Roux-en-Y gastric bypass.

DISCUSSION

SUMMARY OF EVIDENCE BY KEY QUESTION

Key Question 1

Treatment with IGBs was associated with significantly more weight loss compared to lifestyle therapy at multiple short- and intermediate-term follow-up time points (6 and 12 months). These results were consistent across RCTs and observational studies. Treatment with ESG was associated with significantly more weight loss compared to lifestyle therapy, again at 6- and 12-months follow-up. Treatment with ESG was associated with less weight loss than LSG; this conclusion is based solely on observational studies, although results are consistent. Treatment with the AspireAssist was associated with more weight loss than lifestyle therapy in 1 RCT. There was insufficient evidence on associations between treatments and QOL or HbA1C measures to reach conclusions. There are fewer studies assessing the durability of weight loss with endoscopic therapies, such as at 5 years or even 10 years following the intervention, than exist for some established bariatric surgeries (such as gastric bypass). One study by Chan et al compared IGB to sibutramine, a now discontinued weight loss medication. This RCT found no difference between IGB and sibutramine weight loss at 10 years.[59]

Key Question 2

All studies comparing endoscopic bariatric therapy to lifestyle reported more total complications and 30-day readmission or re-intervention rates in the intervention arm, which is expected given these patients underwent an invasive intervention. There were no or borderline statistically significant differences in total complications between patients treated with LSG compared to ESG, although all studies reported more complications with LSG.

Key Question 3

Regarding demographic or interventional factors that improve weight loss outcomes or increase risk for adverse events, there was insufficient evidence to answer this question. It is possible that certain patient variables may contribute to more profound weight loss post-therapy. A multicenter study asserted that younger patients may have more profound weight loss 1 year after gastric plications.[60] This study was not included in this review because the plications were performed with the RESTORe suturing system, which is no longer widely used. However, some have speculated that younger age at the time of intervention may allow for shortened recovery and quicker introduction of exercise back into the lifestyle regimen post-therapy. Higher initial BMI may be associated with more profound weight loss after intervention; however, it is unclear if this would translate to a substantial difference in %TBWL. Patients with underlying gastric motility disorders are poorer candidates for endoscopic therapy given higher complication rates of nausea, vomiting, and oral intolerance due to potentiating delayed gastric emptying with ESG or IGB therapy.[21]

LIMITATIONS

Publication Bias

In the few places where we were able to statistically test for the possibility of publication bias, no such evidence was found. It is possible, however, that the tests employed were underpowered in

the present analyses, as is commonly the case, and the large *p*-values produced by the tests are suggestive of low statistical power. Nevertheless, we feel it is unlikely that there exist high-quality randomized trials or comparative observational studies of endoscopic bariatric therapies compared to surgical or pharmacologic therapies that were not identified and similarly escaped detection by other experts in this field. On the other hand, it is likely that a large volume of case series on endoscopic bariatric therapies from individual practices and institutions exists but has not been published, especially as endoscopic bariatric therapies are often paid for out of pocket, and the available literature likely represents only a small fraction of what could have been known using case series. The decision to exclude case series was due to concerns about limited follow-up and single-institution bias present in studies of this type.

Study Quality

The RCTs were judged to have low risk of bias for outcomes such as weight loss, HbA1c, QOL, and complications. True blinding of participants is difficult with bariatric interventions, and even with a high-quality sham swallowable balloon protocol, it is likely patients were able to feel if they were given an IGB or placebo. Additionally, blinding of outcome assessment was rarely discussed, and it is unclear how weight was reported; it is also unlikely participants could remain blinded to changes in their weight. Incomplete outcome data remains a difficult challenge in bariatric studies, as was frequently seen in these RCTs with suboptimal long-term follow-up. The observational studies were judged to have moderate risk of bias due to their non-random assignment of treatments, which increases risk of procedure selection bias. Many of the observational studies did not state how patients were directed towards either endoscopic or surgical bariatric interventions, causing a risk of selection bias. However, of these studies, 4 used propensity matching to mitigate selection bias, which corresponded to a reduction in the rating of this risk from high to moderate.

Methodological Inconsistency

Included studies compared IGB to lifestyle therapy, ESG to lifestyle therapy, ESG to LSG, ESG to AGB, AspireAssist to lifestyle therapy, and AspireAssist to RYGB. Of these, only IGB versus lifestyle, ESG versus lifestyle, ESG versus LSG, and AspireAssist versus lifestyle were examined in multiple studies. Although we evaluated each comparison group separately, there were remaining inconsistencies among studies within comparison groups. For example, studies varied in choice of intragastric balloon (Obalon, Orbera, Reshape, Spatz, and Ellipse were all used); balloon placement (some balloons were endoscopically placed, whereas others were swallowable capsules); and, in the case of ESG, some procedures were traditional ESG whereas others were the Primary Obesity Surgery Endolumina (POSE) method. Additionally, lifestyle therapy represents a wide range of interventions, from providing patients with reading regarding healthy lifestyle choices, to scheduled meetings with registered dieticians, physical therapists, and psychologists.

Patient population such as age, BMI, and gender were largely similar among intervention and control groups. However, especially in endoscopic versus surgical review studies, the patient population undergoing surgery tended to have more significant metabolic comorbidities, such as higher rates of diabetes, hypertension, and super obesity, introducing heterogeneity into these comparisons in both outcomes and adverse events. This phenomenon was seen in nearly every identified endoscopic versus surgery study.

Although obesity intervention outcomes, such as weight loss and HbA1c, are largely standardized, adverse event reporting appeared more inconsistent. Multiple articles reported no adverse events among their intervention cohorts, which is possibly due to a true lack of adverse events or a study-specific definition of threshold of adverse event severity. Other studies had lower thresholds for adverse event reporting but may have had differing definitions of adverse events such as dehydration, abdominal pain, and dyspepsia.

Applicability

No studies were specific to VA populations. The applicability of these results to VA populations may depend on both the similarity of the patients studied in the trials to VA patients as well as the experience of the gastroenterologists performing endoscopic bariatric therapies in the examined studies compared to VA team experience. Additionally, management of bariatric patients requires extensive multidisciplinary care and follow-up, as often represented by the control group of lifestyle treatment. However, the benefits of endoscopic bariatric therapies may still be realized or even amplified given the population health differences among the general population in comparison to the VA, as the VA population has greater burden of comorbidities than the general population. Further studies are warranted to examine efficacy of endoscopic bariatric therapies in the VA system. Endoscopic bariatric procedures, though still representing a small fraction of all bariatric procedures performed in the US, are becoming more widely adopted and studied, which will likely translate to the VA setting.

FUTURE RESEARCH

The history of weight loss interventions is one of innovation and dissemination prior to evaluation. Vertical banded gastroplasty, prior versions of the gastric balloon, and the combination medication of fenfluramine and phentermine ("Fen-Phen") are all examples of interventions developed and widely used before sufficient studies had been done to establish their risk-benefit profile. These interventions have since been removed following research showing the benefit not to be worth the risk. It would behoove the VA to not repeat this history, and to adequately assess new interventions before they are made widely available. Several research gaps are highlighted below.

First, a majority of the endoscopic studies have follow-up timelines that terminate between the 1- to 2-year mark. There are 2 studies at present with follow up of >4 years.[52,61] Compared to the existing literature on bariatric surgeries, with some reporting follow-up data spanning past a decade, these novel endoscopic therapies lack long-term data. Studies are necessary to firmly establish the durability of weight loss following endoscopic therapy including rates of repeat or alternative endoscopic or surgical interventions due to weight recidivism.

Second, there are no high-quality RCTs comparing endoscopic bariatric procedures to surgery. We identified 3 propensity-matched trials comparing ESG to surgical procedures, mostly LSG.[29,34,36] We recognize that performing such studies has logistical limitations, but these head-to-head trials are essential. Currently, bariatric surgery is indicated per guidelines for patients with BMI >35 with at least 1 comorbid condition or BMI > 40. However, given the millions of patients who qualify under these parameters and the limited number of bariatric surgeons, endoscopic therapies could be an alternative. Trials enrolling patients with the above BMI criteria to compare effectiveness of endoscopic therapy to surgery also need to assess impact on comorbid conditions, along with long-term cost benefits. Financial impacts on closed health care

systems, such as the VA or Kaiser, offer an important opportunity for comprehensive assessments of long-term care costs related to obesity treatments.

Third, additional direct endoscopic and surgical comparisons of post-procedure complications and adverse events are also necessary to improve patient selection for certain procedures. For example, RCTs are scarce in the "super obese" population (BMI >50), who have elevated risk profiles given their baseline comorbidities and anesthesia requirements. These patients theoretically would benefit more from the aggressive mean percent weight loss provided by the surgical interventions, but greater understanding is needed of the perioperative risks and adverse events associated with surgery compared to IGB or ESG as primary therapy to better weigh risks against the extent of potential weight loss.

Additional dedicated studies are required in other subpopulations of patients:

A. *Class I Obesity*. Patients with class I obesity (BMI 30-35) are not current candidates for bariatric surgery. However, data suggest early targeted intervention prior to the development of comorbid conditions should be a goal both for morbidity prevention and decreasing health care expenditures. In these patients, comparative trials of the various endoscopic options as well as medications will be valuable.

B. *Underserved populations*. Given the financial limitations with endoscopic bariatric therapies, largely due to lack of insurance coverage, the studied patient populations for most trials are primarily privately insured and white, as seen in Appendix G. More research is needed on the effectiveness and risks of all bariatric interventions in underserved and/or underrepresented populations.

C. *Patients with obesity-related comorbid conditions such as diabetes, hypertension, non-alcoholic fatty liver disease*. Sharaiha et al demonstrated significant reduction in hypertension, lipid panel, ALT as marker for fatty liver, and HbA1c at the 12-month timepoint following ESG, with sustained results up to 5 years post-procedure.[61] Other available evidence suggests that that as little as 10% TBWL improves metabolic factors including markers for fatty liver disease.[62,63] Studies are required to distinguish which endoscopic bariatric therapies can achieve these outcomes.

D. *VA patients*. There are currently no studies evaluating endoscopic therapies in the VA population.

E. *Bridging therapy*. We did not include studies assessing the efficacy of endoscopic bariatric therapy as a bridge to definitive treatment. Studies have described using IGB as a bridge to bariatric surgery, and it remains to be determined if this use reduces cost or adverse events.

Fourth, there are limited data evaluating the effectiveness of medications on weight loss when combined with endoscopic therapy. A recently published clinical trial demonstrated optimistic results with semaglutide use in patients, with obesity resulting 15% mean TBWL.[64] There is a single study, which was excluded from our analysis due to lack of a non-endoscopic comparative arm, which demonstrated enhanced weight loss of +4% TBWL at the 4- and 7-month marks when ESG was combined with liraglutide as compared to ESG alone.[65] Prior to any invasive procedure including endoscopy, patients should be trialed on pharmacologic management if tolerated. Many patients therefore will present for endoscopic therapies while on medications

such as phentermine, orlistat, liraglutide, or semaglutide. Further studies evaluating efficacy of combination therapy are needed to assist in management of patients with obesity.

Fifth, because there are multiple bariatric endoscopy devices in development for future trials or FDA approval, standardization of primary outcomes (%TBWL, % EBWL, percentage of patients achieving >10% EBWL, percentage of patients achieving >25% EBWL, *etc*) would be beneficial to evaluate efficacy across studies. The same consideration arises when evaluating secondary outcomes associated with resolution of comorbid conditions.

CONCLUSIONS

In summary, the endoscopic therapies IGB, ESG, and AspireAssist are associated with greater short- and intermediate-term weight loss in patients with obesity compared to lifestyle management alone. However, various complications are also more likely in patients treated with endoscopic therapies than with lifestyle management. No long-term studies of weight loss have been published. The degree of weight loss with endoscopic therapies is likely less than more invasive surgical interventions, but with fewer adverse events. The field of endoscopic bariatric therapy continues to innovate and expand, with multiple devices in the pipeline for FDA approval. The MERIT trial, a multicenter randomized trial evaluating ESG vs lifestyle, reported initial 1-year follow-up data in late 2021. As the field continues to grow, future research should include more robust RCTs or well-designed prospective matched studies with adequate power and follow-up to assess long-term weight loss and the effects on obesity-related comorbid conditions.

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