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Efficacy of anti-obesity medication (AOM) and endoscopic gastric remodeling (EGR): Analysis of combination therapy with optimal timing and agents

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ABSTRACT

Background and study aims Endoscopic gastric remodeling (EGR) and anti-obesity medications (AOMs) are effective weight loss therapies. While the efficacy of EGR and AOMs has been established, the effect of combination therapy and its optimal approach remain unknown.

Patients and methods This was a single-center retrospective review of prospectively collected data from patients who underwent EGR. Patients were categorized as: 1) monotherapy – EGR alone; 2) combination therapy – an AOM prescribed within 6 months of EGR; and 3) sequential therapy – an AOM prescribed greater than 6 months of EGR. Outcomes included percent total weight loss (%TWL) at 12 months, response rate (≥ 10%TWL at 12 months), and serious adverse event rate.

Results A total of 208 patients were included. Of them, 65 (34%), 61 (31%), and 82 (35%) underwent monotherapy, combination therapy, and sequential therapy, respectively. At 12 months, patients who received EGR + GLP-1RA combination therapy achieved the greatest weight loss (23.7 ±4.6% TWL), while those who began with AOM followed by EGR more than 6 months later had the lowest weight loss (12.0±7.7%TWL) compared with monotherapy (17.3 ±10.0% TWL) (P = 0.04 and 0.03, respectively). The response rate was 100% for EGR + GLP-1RA combination therapy and 56% for AOM followed by EGR sequential therapy (P = 0.02).

Conclusions Combining AOM with EGR appears to result in greater weight loss compared with other strategies, with GLP-1RA as the preferred agent and optimal initiation of both therapies occurring within 6 months of each other. Prolonged medication use prior to EGR appears to be associated with suboptimal weight loss, suggesting the importance of early referral for adjunctive therapy.

Introduction

Obesity is a pandemic that affects over 650 million adults worldwide [1]. In the United States, it is predicted that by 2030, over 50% of the adult population will be affected by obesity [2]. Traditionally, obesity is treated with lifestyle modification via diet and exercise. However, fewer than 10% of patients undergoing lifestyle modification achieve sustained clinically significant weight loss [3]. On the other end of the spectrum, bariatric surgery is effective in inducing weight loss and im-

proving obesity-related comorbidities. Nevertheless, fewer than 2% of eligible patients undergo bariatric surgery, likely due to its perceived invasiveness [4].

Two recent alternative approaches to obesity treatment include endoscopic bariatric and metabolic therapy (EBMT) and anti-obesity medication (AOM). Specifically, for EBMT, one of the procedures that has been increasingly performed is endoscopic gastric remodeling (EGR). The procedure involves using an endoscopic suturing or plication device to reduce gastric volume along the greater curvature by approximately 70% [5]. Studies have demonstrated its efficacy to be approximately 17.3% total weight loss (TWL) at 1 year with the majority of patients maintaining their lost weight for at least 5 to 10 years [6, 7, 8].

For AOM, there are currently seven medications approved and available in the United States for treatment of obesity. These include orlistat, phentermine, phentermine/topiramate, bupropion/naltrexone, liraglutide, and the more recent semaglutide and tirzepatide. The amount of weight loss ranged from 6.1% to 8% TWL for most oral AOMs [9] and up to 14.9% to 20.9% TWL for the more recent injectable AOMs [10, 11]. In contrast to EGR, which is a one-time procedure, long-term administration of these AOMs is necessary to maintain weight loss and prevent recurrent weight gain upon discontinuation [12, 13]. Nevertheless, similar to EGR, AOMs offer higher efficacy than lifestyle modification alone, coupled with a less invasive safety profile than bariatric surgery. These factors likely contribute to the increasing popularity of both among providers and patients suffering from obesity.

While EGR and AOMs are effective in treating obesity, the impact of combining both treatments remains unknown. This study aimed to assess the efficacy and safety of combination therapy utilizing EGR and AOM. In addition, the effects of combining various AOMs with EGR and timing of administration in relation to the procedure were evaluated to determine the optimal regimen.

Patients and methods

Study design and patient selection

This study was a retrospective review of prospectively collected data from patients who underwent EGR for treatment of obesity. It was conducted at a single tertiary referral center with the bariatric center of excellence from September 2017 to July 2022. All patients with obesity, defined as having a body mass index (BMI) of at least 30 kg/m^2, or those who were overweight, defined as having a BMI of at least 27 kg/m^2, with at least one obesity-related comorbidity, including hypertension, hyperlipidemia, diabetes/prediabetes and metabolic dysfunction-associated liver disease, who underwent EGR via a suturing or plication technique were included. Patients with prior bariatric surgery, active alcohol use disorder, or a recent smoking history were excluded. Patients in other EBMT or EGR trials were excluded. In addition, patients who discontinued the prescribed AOM within 3 months were excluded. EGR procedures and AOMs, as well as possible benefits and adverse events (AEs), were discussed in detail with the patients prior to obtaining written informed consent as per the standard protocol. All patients underwent concomitant moderate lifestyle modification after the procedure with routine follow-ups with bariatric dietitians, bariatric endoscopists and/or obesity medicine physicians. The study was approved by hospital Institutional Review Board (IRB number 2022P001757).

Interventions

Endoscopic gastric remodeling

All patients underwent EGR via a suturing or plication technique. The procedures were performed by two bariatric endoscopists (CT from September 2017 to July 2022 or PJ from October 2019 to July 2022) with the assistance of bariatric endoscopy fellows. Details of the procedures have been reported in previous studies [14, 15, 16].

The EGR procedure was performed using the Overstitch endoscopic suturing device (Boston Scientific, Marlborough, Massachusetts, United States) or the Incisionless Operating Platform (USGI Medical, San Clemente, California, United States). During the procedure, sutures or plications were placed along the greater curvature of the gastric body to reduce its width and length using a standard pattern (▶ **Fig. 1**). The procedure was performed on an outpatient basis. All patients were prescribed a 900 to 1200 kcal liquid diet, proton pump inhibitor, and carafate for 6 weeks per institutional protocol.

Anti-obesity medications

For some patients, an AOM was prescribed prior to or after EGR by medical providers in the bariatric endoscopy or medical weight loss clinics, both of which were part of a bariatric center of excellence. The AOMs included were orlistat, phentermine, topiramate, phentermine/topiramate, bupropion, naltrexone, bupropion/naltrexone, dulaglutide, liraglutide, and semaglutide. Both generic and brand-name versions were included. Potential benefits and AEs of each AOM were discussed with the patients prior to initiation and at all follow-up visits. AOM selection was dependent on patient comorbidities and insurance coverage. If a patient did not achieve 5% TWL at 3 months following AOM initiation, the medication was discontinued.

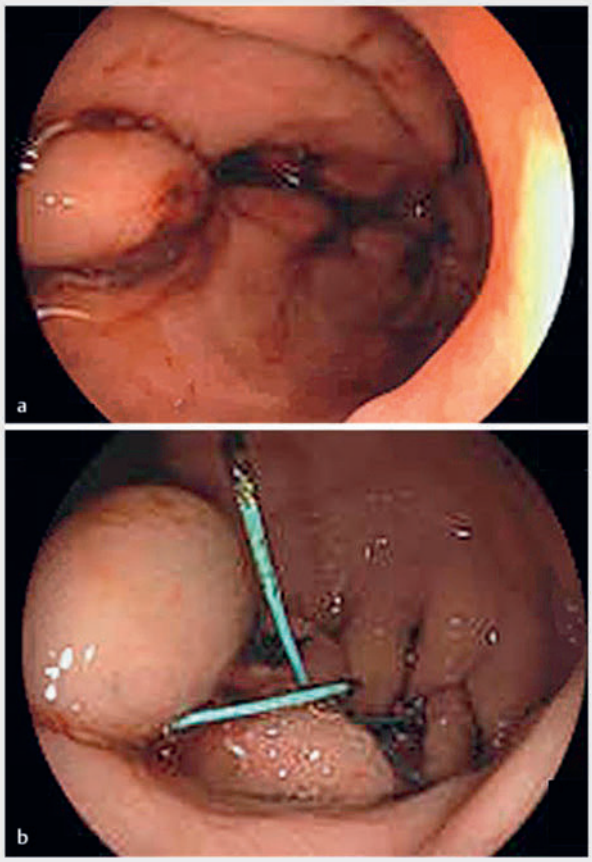
Study cohorts

Monotherapy

The monotherapy group referred to patients who underwent EGR without any AOMs added.

Combination therapy

The combination therapy group referred to patients who were started on an AOM within 6 months prior to or after EGR. This group was divided into two subgroups: 1) EGR + glucagon-like peptide-1 receptor agonist (GLP-1RA), which included dulaglutide, liraglutide or semaglutide, and 2) EGR + other AOM.



▶ **Fig. 1** Endoscopic gastric remodeling via **a** suturing and **b** plication techniques.

Sequential therapy

The sequential therapy group referred to patients who were started on an AOM outside of the 6-month window before or after EGR. This group was divided into two subgroups: 1) AOM then EGR and 2) EGR then AOM.

Outcomes

The primary outcome was percent total weight loss (%TWL) at 12 months following EGR (for the monotherapy group) or % TWL 12 months after initiation of initial therapy (EGR or AOM for the combination and sequential therapy groups). A subgroup analysis was performed to compare %TWL among five subgroups: 1) monotherapy; 2) EGR + GLP-1RA combination therapy; 3) EGR + other AOM combination therapy; 4) AOM then EGR sequential therapy; and 5) EGR then AOM sequential therapy. Secondary outcomes were response and serious adverse event (SAE) rates for each cohort and subgroup, as well as predictors of %TWL at 12 months. Response rate was defined as the proportion of patients achieving at least 10% TWL at 12 months. SAEs were defined as events classified as grade III-IV according to the Clavien-Dindo classification for patients who underwent EGR [17] or events meeting the Food and Drug Administration (FDA) criteria, including life-threatening incidents, hospitalization, disability or permanent changes for those who received an AOM [18].

Statistical analysis

Data were presented as mean ± standard deviation (SD) for continuous variables or proportion (%) for categorical variables. Means were compared using a student's *t*-test. Proportions were compared using a Chi-squared test. Predictors of weight loss were evaluated using multivariable regression analysis. $P < 0.05$ was deemed statistically significant. Statistics were performed using SAS OnDemand for Academics (Cary, North Carolina, United States).

Results

A total of 208 consecutive patients who underwent EGR were included in the study. Of these, 65 (34%), 61 (31%), and 82 (35%) were in the monotherapy, combination therapy and sequential therapy groups, respectively. Baseline characteristics are shown in ▶ **Table 1**. Specifically, baseline age and BMI were similar among the three groups. However, the proportion of female patients was higher in the AOM then EGR sequential therapy group compared with the monotherapy group (93% versus 73%, respectively, $P = 0.04$). In addition, the proportion of pa-

▶ **Table 1** Baseline characteristics.

	EGR Monotherapy (n = 65)	Combination therapy (n = 61)		Sequential therapy (n = 82)	
		EGR + GLP-1RA (n = 19)	EGR + other AOM (n = 42)	EGR then AOM (n = 21)	AOM then EGR (n = 61)
Age (years)	46 ± 14	45 ± 13	43 ± 13	46 ± 13	43 ± 10
Female sex (n (%))	53 (73)	18 (95)	37 (88)	17 (81)	57 (93)
Baseline BMI (kg/m^2)	38.4 ± 5.5	39.0 ± 9.8	39.1 ± 7.3	36.7 ± 4.1	39.1 ± 7.3
History of DM/pre-DM (n (%))	32 (49)	12 (63)	10 (24)	13 (62)	27 (44)

AOM, anti-obesity medication; BMI, body mass index; DM, diabetes mellitus; EGR, endoscopic gastric remodeling.

▶ **Table 2** Procedure and anti-obesity medication details.

	EGR monotherapy (n = 65)	Combination therapy (n = 61)		Sequential therapy (n = 82)	
		EGR + GLP-1RA (n = 19)	EGR + other AOM (n = 42)	EGR then AOM (n = 21)	AOM then EGR (n = 61)
Procedure details					
Baseline gastric length (cm)	25 ± 6	25 ± 5	24 ± 5	25 ± 6	26 ± 5
Gastric length reduction (%)	73 ± 15	74 ± 12	74 ± 11	78 ± 10	75 ± 12
Anti-obesity medication details					
GLP-1RA (n (%))	–	21 (100)	0 (0)	6 (40)	39 (62)
Phentermine/topiramate (n (%))	–	4 (19)	24 (50)	6 (40)	27 (43)
Topiramate (n (%))	–	1 (5)	17 (35)	3 (20)	16 (25)
Phentermine (n (%))	–	1 (5)	7 (15)	–	5 (8)
Bupropion/naltrexone (n (%))	–	1 (5)	0 (0)	2 (13)	4 (6)
Bupropion (n (%))	–	1 (5)	1 (2)	–	5 (8)

AOM, anti-obesity medication; EGR, endoscopic gastric remodeling.

tients with baseline diabetes or prediabetes was higher in the EGR + GLP-1RA combination therapy group compared with the EGR + other AOM combination therapy group (63% versus 24%, respectively, $P = 0.003$). Three patients were in the overweight category prior to therapy, with obesity-related comorbidity indications including hypertension (n = 1), hypertension and hyperlipidemia (n = 1), and type 2 diabetes (n = 1).

Baseline gastric length prior to EGR, measured from the gastroesophageal junction to the incisura, was 25 ± 6 cm. Following the procedure, gastric length measured 6 ± 3 cm, representing a 74% ± 13% reduction from the baseline length.

Details of AOMs prescribed in the combination therapy and sequential therapy groups are shown in ▶ **Table 2**. Specifically, for the EGR + GLP-1RA combination therapy group, all patients received at least one GLP-1RA agent. For the EGR + other AOM combination therapy group, the most commonly prescribed medications were phentermine/topiramate (50%), followed by topiramate alone (35%) and phentermine alone (15%). For the sequential therapy group, the most commonly prescribed medications were GLP-1RA, followed by phentermine/topiramate and topiramate alone.

Primary outcomes

At 1 year, the EGR + GLP-1RA combination therapy group experienced the greatest weight loss. Specifically, the EGR + GLP-1RA combination therapy group experienced 23.7% ± 4.6% TWL, which was significantly higher than that for the EGR monotherapy group, who experienced 17.3% ± 10.0% TWL ($P = 0.04$). The group that achieved the least weight loss was those who were on an AOM for longer than 6 months prior to undergoing EGR. This group experienced 12.0% ± 7.7% TWL, which was significantly lower than that for the EGR monotherapy group, who experienced 17.3% ± 10.0% TWL ($P = 0.03$) (▶ **Fig. 2a**).

Secondary outcomes

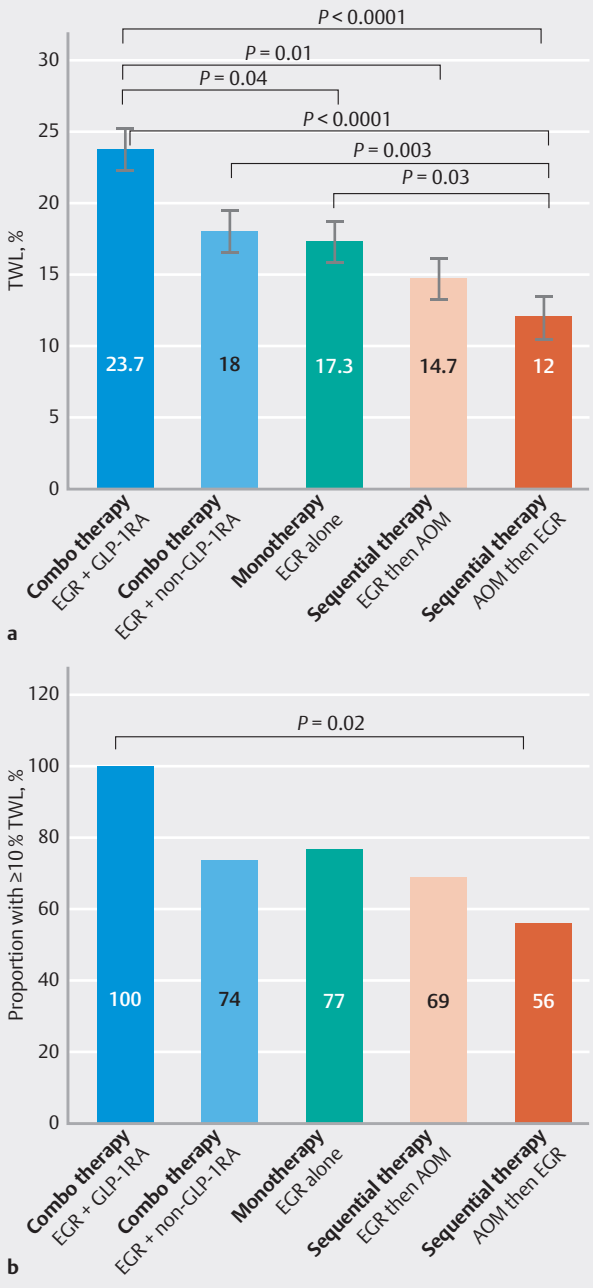
At 1 year, the response rate was the highest in the EGR + GLP-1RA combination therapy group. Specifically, all patients (100%) in the EGR + GLP-1RA combination group achieved at least 10% TWL. Response rates in the EGR monotherapy group and the AOM then EGR sequential therapy group were 77% and 56%, respectively (▶ **Fig. 2b**).

The SAE rate for EGR was 1.9% (4/208). Two patients were diagnosed with a perforation the day of the procedure and were treated with laparoscopic repair, one patient with advanced hepatic fibrosis had a pulmonary embolism treated with anticoagulation and ultimately died, and one patient had upper gastrointestinal bleeding in the setting of heparin for a metallic heart valve, which was treated conservatively. The medication-related SAE rate was 1.4% (2/143). One patient developed aphasia on topiramate and one patient developed depression and paresthesia on topiramate.

In a multivariable regression analysis, adding GLP-1RA to EGR within 6 months of the procedure remained a significant predictor of greater weight loss at 1 year after controlling for age, sex, and prediabetes/diabetes status (β-coefficient = 6.0, $P = 0.036$ compared with the EGR monotherapy group) (▶ **Table 3**).

Discussion

This study demonstrated that combining AOM with EGR resulted in greater weight loss compared with sequential therapy or monotherapy, with the optimal timing for adding an AOM being within 6 months of EGR. In addition, GLP-1 RAs yielded higher weight loss outcomes compared with other AOMs when combined with EGR. Furthermore, prolonged medication use prior to EGR was associated with poor weight loss outcomes, suggesting that combination therapy is preferable, or if sequential



▶ **Fig. 2** **a** Percent total weight loss (%TWL) and **b** proportion of patients who experienced at least 10% TWL at 12 months following endoscopic gastric remodeling (EGR) monotherapy, EGR + anti-obesity medication (AOM) combination therapy and EGR + AOM sequential therapy.

▶ **Table 3** Multivariable regression analysis of predictors for percent total weight loss at 12 months, with EGR monotherapy as the reference group.

Predictors	B-coefficient	Standard error	*P* value
Age	0.02	0.08	0.80
Sex	2.36	2.54	0.36
Diabetes or prediabetes	1.01	2.12	0.63
EGR + GLP-1RA combination therapy	5.98	2.80	0.04
Sequential therapy	0.65	2.14	0.76

EGR, endoscopic gastric remodeling.

therapy is utilized, EGR should be performed prior to initiation of AOM.

This study was among the first to report the experience of combining two different modalities for treatment of obesity. Although combination therapy is commonly employed in clinical practice for patients with obesity and type 2 diabetes, it typically involves combining medications that are from different mechanistic classes. Specifically, for AOMs, if patients achieve at least 5% TWL at 3 months, that specific medication may be continued. However, once patients plateau, the recommendation is to consider adding a second AOM from a different mechanistic class [19]. Similarly, for patients with type 2 diabetes, metformin is typically the first-line agent. If glycemic control remains suboptimal, the recommendation is to add a second agent [20]. In this study, rather than incorporating various medications, we combined two obesity treatment modalities—one medical and the other endoscopic. In 2021, Badurdeen et al. reported on the Brazilian experience of combining EGR with liraglutide, one of the older GLP-1RA agents. In that study, 26 patients underwent EGR, followed by the addition of liraglutide 5 months later. At 1 year, patients in the combination therapy group experienced 24.7% TWL compared with 20.5% TWL in the EGR-alone group ($P < 0.001$) [21]. This study was unique compared with Badurdeen et al., because it reported the first experience from a large US patient cohort who underwent combination therapy with EGR with all available AOMs, including the new weekly injectable GLP-RAs. In addition, because this study reflected real-world experience, it enabled us to analyze the effects of adding different AOMs and timing of their addition to better understand the optimal approach.

In this study, the group that achieved the highest weight loss was the EGR plus GLP-1RA combination group. Specifically, this cohort experienced a 23.7% TWL at 12 months, a result similar to that for individuals undergoing sleeve gastrectomy, who typically achieve about 23% TWL at the same time point [22, 23]. Superiority of the EGR plus GLP-1RA combination over other AOM regimens likely stems from enhancement of similar mechanisms between the two modalities. Specifically, a few small studies have demonstrated that EGR delays gastric emptying, enhances satiety hormones including GLP-1 and peptide YY (PYY), and improves insulin sensitivity [24, 25, 26] — mechanisms similar to those for GLP-1RAs [27].

As usage of GLP-1RAs continues to gain popularity, the combination therapy of EGR plus GLP-1RA is likely to be increasingly employed, making the timing of adding the second modality crucial. In this study, adding a GLP-1RA within 6 months prior to or after EGR appeared to result in greater weight loss compared with adding the medication outside the 6-month win-

dow, even after controlling for patient demographics and diabetes/prediabetes status. In clinical practice, weight loss following EGR is fastest during the first 3 months and appears to plateau after 6 months following the procedure. Similarly, a few mechanistic studies demonstrated that peak changes in gut hormones or gastric emptying appeared to occur between 3 to 6 months after the procedure [26]. Therefore, adding an AOM at the time when the weight loss from EGR starts to slow down but has not yet plateaued likely leads to the most effective augmentation of the weight loss effects of both treatment modalities.

This study had a few limitations. First, it was a single-center, retrospective review of prospectively collected data, which may limit generalizability and introduce bias. The exact timing of the initiation and discontinuation of an AOM may be challenging to determine because patients might have started or stopped the medication before or after the clinic appointments. For example, there might be a discrepancy between the prescription date and actual starting date of a medication due to the necessary prior authorization process for most GLP-1RAs. Nevertheless, thorough documentation was encouraged during clinic visits, and a comprehensive chart review was conducted to minimize the aforementioned bias. Furthermore, given the retrospective nature of the study, some patients were on multiple AOMs, reflecting real-world experience. Therefore, the effect of individual AOMs on weight loss should be interpreted with caution, because other factors, such as patient engagement and frequency of clinic visits, may also have influenced the outcomes. Second, at the beginning of the study, combination therapy was primarily employed as a rescue therapy. In other words, if patients did not achieve optimal weight loss, i. e. at least 10% TWL within 6 months following EGR, they were offered an AOM. Therefore, the reported efficacy of combination therapy in this study could potentially appear lower than it would if all patients were offered an AOM within 6 months following EGR, irrespective of their weight loss status at that time. Furthermore, the group that had been on an AOM for at least 6 months prior to undergoing EGR may represent patients who were more resistant to obesity treatment, because they likely did not achieve adequate weight loss on AOMs. Further studies are warranted to assess whether this group was also more likely to be poor responders to EGR or if the timing of adding the second modality influenced outcomes. Furthermore, there could be selection bias wherein patients with baseline diabetes or prediabetes were more likely to be prescribed a GLP-1RA as opposed to other AOMs. Nevertheless, this reflected real-world experience. In addition, compared with patients without comorbidity, individuals with diabetes or prediabetes usually experience less weight loss following any intervention, which suggests that reported efficacy of the EGR + GLP-1RA group in this study is likely underestimated. Future prospective studies are encouraged to assess the impact of combination therapy across different patient populations and its effects on other outcomes, such as comorbidities, quality of life, and durability [28].

Conclusions

In conclusion, this study shows that combining AOM with EGR appears to result in greater weight loss than other strategies. Optimal timing for adding an AOM is likely within 6 months of EGR, with the preferred agents being GLP-1 RAs. Prolonged medication use prior to EGR appears to be associated with suboptimal weight loss, suggesting the importance of early referral for adjunctive therapy.

Conflict of Interest

P.J. has received research support from Apollo Endosurgery, Boston Scientific, Fractyl, GI Dynamics and USGI Medical, has served as a consultant to Apollo Endosurgery, Boston Scientific, Cook Medical, ERBE, Fractyl, GI Dynamics, Madrigal and Spatz Medical, has served as a co-founder for Bariendo, and has received royalty from Endosim. A.J has no conflict of interest. C.T. has served as a consultant for Apollo Endosurgery, Boston Scientific, Endoquest Robotics, Enterasense, EnVision Endoscopy, Fractyl, USGI Medical, Medtronic/Covidien, Olympus/Spiration, GI Dynamics, and Xenter, has served as an advisory boards member for USGI Medical and Fractyl, has received research grant and support from USGI Medical, Apollo Endosurgery, Boston Scientific, Endoquest Robotics, ERBE, FujiFilm, Lumendi Olympus/Spiration, Aspire Bariatrics and GI Dynamics, has served as a general partners for Blueframe Healthcare, has served as a founder for Enterasense, EnVision Endoscopy and GI Windows, and holds stock and royalties for GI Windows.

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