JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 76, NO. 20, 2020

PUBLISHED BY ELSEVIER

Transcatheter Bariatric Embolotherapy for Weight Reduction in Obesity

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ABSTRACT

BACKGROUND Obesity is well-appreciated to result in poor cardiovascular and metabolic outcomes. Dietary and medical weight loss strategies are frequently unsuccessful and unsustainable. Bariatric surgery is quite effective, but is reserved for the most obese patients because of the associated intraoperative/post-operative risks. In preclinical and early clinical case series, a novel therapy, transcatheter bariatric embolotherapy (TBE) of the left gastric artery, has been reported to promote weight loss by reducing ghrelin, an appetite-stimulating hormone secreted from the gastric fundus.

OBJECTIVES The purpose of this study was to examine TBE in a single-blind, sham procedure randomized trial.

METHODS Obese subjects (body mass index 35 to 55 kg/m^2) were randomized 1:1 to either sham or TBE targeting the left gastric artery using an occlusion balloon microcatheter to administer 300- to 500-μm embolic beads. All patients entered a lifestyle counseling program. Patients and physicians performing follow-up were blind to the allocated therapy. Endoscopy was performed at baseline and 1-week post-procedure. The primary endpoint was 6-month total body weight loss (TBWL).

RESULTS Eligible subjects (n = 44; age 45.5 ± 9.4 years; 8 men/36 women; body mass index 39.6 ± 3.8 kg/m^2) were randomized to undergo the sham or TBE procedure with no device-related complications and 1 vascular complication. Patients reported mild nausea and vomiting, and endoscopy revealed only minor self-limiting ulcers in 5 patients. At 6 months, in both the intention-to-treat and per-protocol populations, the TBWL was greater with TBE (7.4 kg/6.4% and 9.4 kg/8.3% loss, respectively) than sham (3.0 kg/2.8% and 1.9 kg/1.8%, respectively; p = 0.034/0.052 and p = 0.0002/0.0011, respectively). The TBWL was maintained with TBE at 12 months (intention-to-treat 7.8 kg/6.5% loss, per-protocol 9.3 kg/9.3% loss; p = 0.0011/0.0008, p = 0.0005/0.0005, respectively).

CONCLUSIONS In this randomized pilot trial, we have established the proof-of-principle that transcatheter bariatric embolotherapy of the left gastric artery is well-tolerated and promotes clinically significant weight loss over a sham procedure.(The Lowering Weight in Severe Obesity by Embolization of the Gastric Artery Trial [LOSEIT]; NCT03185949) (J Am Coll Cardiol 2020;76:2305–17) © 2020 by the American College of Cardiology Foundation.

Since 1980, the prevalence of obesity has doubled in more than 70 countries across the world (1). Approved treatments for weight loss are limited and vary depending on the patient's body mass index (BMI) and comorbidities. Bariatric surgery is the most effective treatment for patients with a BMI ≥40 kg/m^2 (or ≥35 kg/m^2 plus diabetes), but its invasiveness can result in intraprocedural and post-operative complications (1). In overweight individuals (25 to 29.9 kg/m^2), the most common therapy is a combination of diet and lifestyle modification. However, this first-line therapy has limited efficacy: few can maintain even a 1% to 2% total body weight loss (TBWL) at 2 to 3 years (2,3).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

Manuscript received June 23, 2020; revised manuscript received August 28, 2020, accepted September 12, 2020.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2020.09.550

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

ITT = intention-to-treat

LGA = left gastric artery

OBC = occlusion balloon microcatheter

PP = per protocol

TBE = transcatheter bariatric embolotherapy

TBWL = total body weight loss

Pharmacological therapies with varying mechanisms of action are available. However, their efficacy is at best, modest, and some patients have contraindications (e.g., history of heart disease) that limit their utilization (4). Intragastric balloons are a recent advancement, but have demonstrated serious side effects and unproven long-term efficacy (5).

Transcatheter bariatric embolotherapy (TBE) is a promising, nonsurgical treatment modality for weight loss that might address the treatment gap of BMI ranging between 30 and 40 kg/m^2. This percutaneous procedure involves catheter-directed embolization of the left gastric artery (LGA). The LGA provides blood supply to the gastric fundus, which contains the majority of cells that produce ghrelin, the only known orexigenic (appetite stimulating) hormone secreted from the gastrointestinal tract (6). Several feasibility studies have demonstrated promising effects of LGA embolization targeted specifically for weight loss using commercially available equipment (7–10). Herein, we conducted a sham-control randomized clinical trial to assess the safety and efficacy of TBE in obese individuals using an occlusive balloon microcatheter and infusion system designed for this application (11).

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METHODS

TRIAL DESIGN. This study was a first-in-human, single-center, sham-controlled, randomized clinical trial conducted at O.B. Klinka, Prague, a European Center for Excellence for the Multidisciplinary Treatment of Obesity. This center conducted all aspects of the trial (including patient enrollment, weight management counseling, follow-up testing) *except* randomization and the TBE procedures, which were performed at Homolka Hospital, Prague.

Consenting patients underwent baseline testing, including a baseline endoscopy, and within 14 days, underwent randomization in a 1:1 fashion using a web-based system, and subsequently the procedure—either TBE or sham. Patients randomized to sham were unblinded at 6 months and permitted to crossover to TBE. Only the initial treatment group was then followed to 12 months for long-term efficacy.

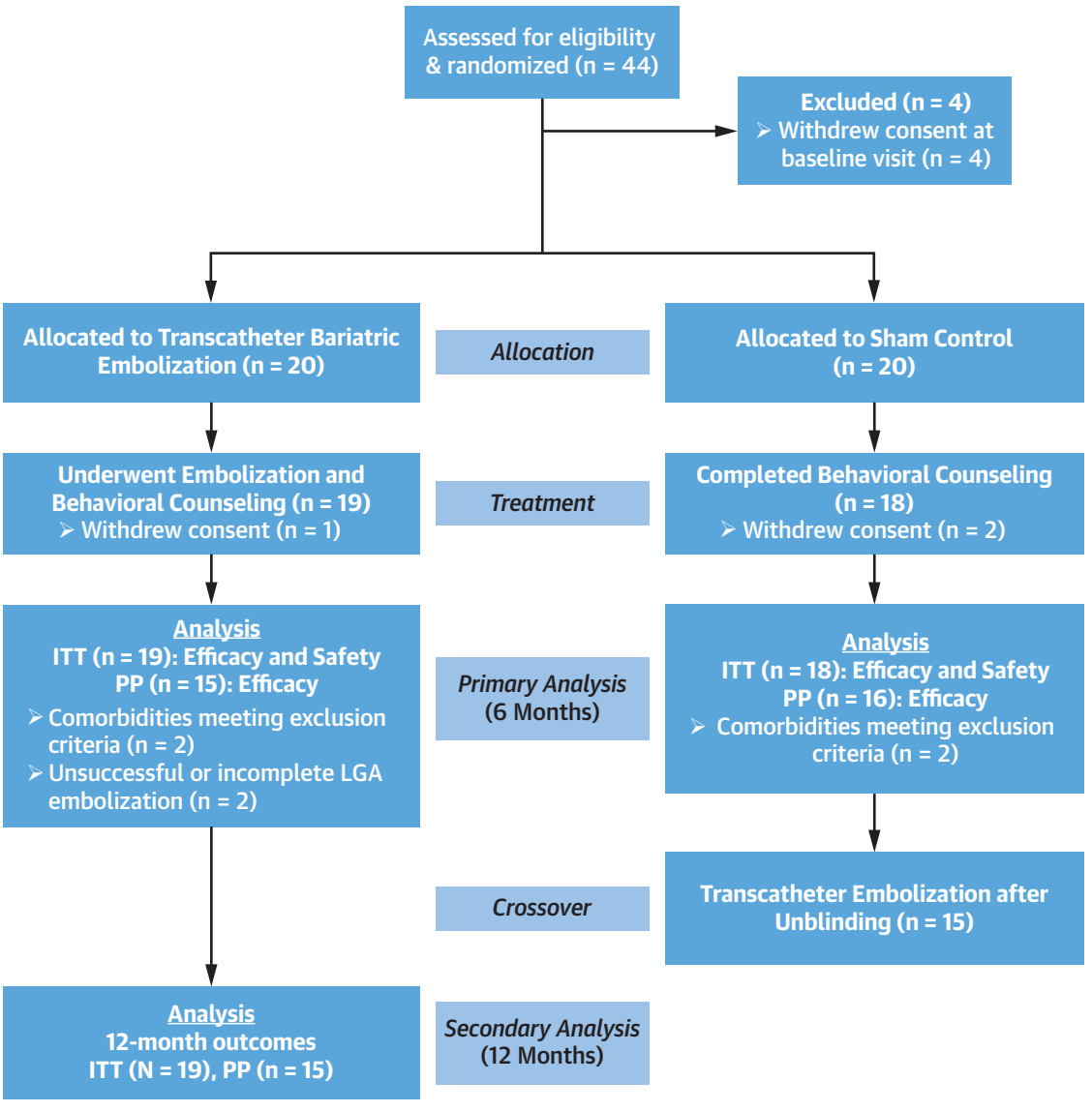
Key inclusion criteria included a BMI of 35.0 to 55.0 kg/m^2 and age 21 to 60 years. Key exclusion criteria included previous bariatric, gastric, or intra-abdominal surgery, which could compromise gastric blood supply; type 2 diabetes mellitus; a history of duodenal or gastric ulcers; regular use of medications that could cause ulcers (e.g., aspirin, nonsteroidal anti-inflammatory drugs); or active *Helicobacter pylori* infection. The Supplemental Appendix contains a full list of inclusion/exclusion criteria. The study (NCT03185949) was approved by the Czech National Competent Authority, SÚKL, and the local ethics committees. Informed consent was obtained from all subjects.

INTERVENTIONS. Transcatheter bariatric embolotherapy. Following intravenous propofol sedation, femoral arterial access was obtained, and intravenous unfractionated heparin administered for a goal ACT >250 s. Using standard 6-F guiding catheters, celiac artery angiography was performed to delineate the celiac trunk and its branches: LGA, hepatic artery, splenic artery, gastroduodenal artery, and gastroepiploic artery. The target vessel(s) was chosen after initial celiac angiography based on the identified supply of the gastric fundus. An occlusion balloon microcatheter (OBC) (Supplemental Figure 1) (Endobar Solutions LLC, Orangeburg, New York) was advanced into the target artery over a standard guidewire. Injections of nitroglycerin (200 μg) or verapamil (2.5 mg) were administered through the microcatheter to minimize arterial spasm. A balloon at the OBC tip was inflated to prevent retrograde reflux, with tip pressure/resistance monitored to prevent overembolization and antegrade reflux (11).

A robotic manifold (Supplemental Figure 1) (Endobar Solutions LLC) was used to deliver 300- to 500-μm microspheres (BeadBlock, Biocompatibles Ltd., Farnham, United Kingdom) into the LGA in low velocity injection mode. The microspheres, packaged in a wet solution involving 2 ml of beads plus 4 ml of saline (~6 ml total volume), were diluted 1:1 with contrast (Optiray 300 [Libel-Flarsheim Company LLC, Raleigh, North Carolina]). Then, the balloon was deflated and selective angiography was performed to verify adequate embolization. Embolization was repeated until adequate angiographic stasis was achieved with the balloon deflated over 5 cardiac cycles. A final angiogram was performed ~5 min post-TBE via the guiding catheter and/or microcatheter placed in the celiac trunk. The OBC and guidewire were removed, and a vascular closure device (Angioseal, Terumo Interventional Systems, Somerset, New Jersey) was typically employed for hemostasis.

Patients were monitored overnight. An oral proton pump inhibitor (e.g., omeprazole 40 mg orally daily) was administered 4 days before and for 6 weeks after

FIGURE 1 Consort Diagram



This figure shows the participant flowchart through enrollment, allocation, follow-up, and analysis. ITT = intention-to-treat; LGA = left gastric artery; PP = per protocol.

the procedure, and Sucralfate (1 g orally twice daily) was given for 6 weeks post-procedure.

Sham control. Patients randomized to sham also received propofol sedation. Lidocaine was infiltrated subcutaneously, but arterial access was not obtained. Patients remained sedated for 1 h, and were monitored for 24 h post-procedure.

FOLLOW-UP AND BLINDING. Both treatment groups returned every week for the first month, every 2 weeks to month 4, and monthly thereafter until week 52 (Supplemental Table 1). Both groups underwent a 19-session lifestyle therapy program targeted at diet and behavioral education for weight loss, including an individualized and structured low-caloric diet eating plan. All follow-up visits included an assessment of weight, BMI, vitals, and hunger score. Patients were also assessed for gastrointestinal hormones, lipids, glucose, weight-related quality of life (Impact of Weight on Quality of Life-Life Scale), hunger score, office blood pressure, and depression (Beck's depression score II) (12). Repeat endoscopies

TABLE 1 Baseline Characteristics

	Treatment* (n = 22)	Control* (n = 22)
Sex		
Female	21	15
Male	1	7
Age, yrs	44.7 ± 9.4	46.4 ± 10.3
Weight, kg	109.9 ± 15.2	119.0 ± 16.8
Height, cm	167.9 ± 8.4	171.9 ± 11.6
BMI	38.9 ± 3.8	40.2 ± 3.7
Previous weight loss attempts		
Diet alone	16 (72.7)	15 (68.2)
Diet and exercise	1 (4.6)	1 (4.6)
Diet and medication	4 (18.2)	5 (22.7)
Diet, exercise, and medication	1 (4.6)	0 (0)
Blood pressure, categorized		
Normal	2 (9.1)	1 (4.6)
Elevated	1 (4.6)	1 (4.6)
HTN stage 1	10 (45.5)	8 (36.4)
HTN stage 2	9 (40.9)	12 (54.6)

Values are n, mean ± SD, or n (%). *There were no statistically significant differences between groups.

BMI = body mass index; HTN = hypertension.

were performed at 1-week post-procedure and were repeated, if ulcers were observed, until resolution. Satiety was tested by consuming a nutritional shake until reaching a sensation of fullness followed by symptom assessment after 30 min (13). See the Supplemental Appendix for details on ghrelin collection and satiety testing.

Subjects were blinded to their treatment assignment. Since the primary procedure (TBE or sham) was performed in a separate hospital from the site of follow-up, the physicians and support staff at the follow-up clinic were also blinded to the treatment assignment. At 6 months post-sham, subjects were unblinded and permitted crossover to TBE.

STUDY OUTCOMES. The primary efficacy endpoints of the study were the differences in TBWL between groups at 6 and 12 months post-embolization. Success was defined as ≥5% TBWL in the TBE group with statistical superiority to the sham group at 6 months, and ≥5% TBWL in the treatment group at 12 months (details in the Supplemental Appendix). Adverse events were categorized according to the Society of Interventional Radiology Classification (14).

STATISTICAL METHODS. This study was powered to detect an absolute difference of 5% TBWL between groups at 85% power and 5% alpha. It was estimated that 10% of patients would be lost to follow-up, therefore requiring a total of 20 patients per treatment group. Analyses were performed on both the intent-to-treat (ITT) and per protocol (PP) populations. See the Supplemental Appendix for details on statistical methodology.

RESULTS

PARTICIPANT FLOW. As shown in the CONSORT diagram (Figure 1), from 44 total enrolled subjects, 4 withdrew consent prior to any treatment, 2 from each group. A total of 3 additional subjects withdrew after enrollment, 1 of whom had undergone TBE. Accordingly, a total of 37 subjects ultimately completed follow-up in the ITT population. Due to additional protocol violations (n = 4) and failed procedures (n = 2), 31 subjects comprised the PP population. Supplemental Tables 2 and 3 provide detailed explanations for censoring.

BASELINE DATA. There were no statistically significant differences in baseline characteristics between groups (Table 1). The average age of enrolled subjects was 45.5 ± 9.4 years, with a majority being women (n = 36; 81.8%). Their mean weight was 114.5 ± 16.5 kg, with a BMI of 39.6 ± 3.8 kg/m^2. Prior to enrollment, most subjects reported dieting alone (70.5%), with diet plus medications (20.5%) being the second most frequent attempted method for weight loss. Hypertension was stage 1 or 2 in 40.9% and 47.7%, respectively.

PROCEDURAL PERFORMANCE. The procedure was performed in 20 subjects using 4.2 ± 1.6 ml (1.4 ± 0.5 ml dry volume) of microspheres, 127.0 ± 59.5 ml of contrast, and taking 82.3 ± 28.2 min (Table 2). Most subjects received injection into a single vessel (n = 16; examples in Figure 2, Supplemental Figure 2, and Videos 1 and 2). The estimated KAP was 163 ± 124 Gy/cm^2. A retrospective review of the angiographic data revealed 2 failed procedures: 1 inadvertent embolization of the left hepatic artery, and another with incomplete LGA stasis (Supplemental Figures 3 and 4).

SAFETY. In the TBE group, the most common side effects were nausea (n = 7) and vomiting (n = 7), all minor severity, as well as epigastric pain (n = 4) treated with paracetamol; there was no hematemesis. For comparison, nausea (n = 4) and epigastric pain (n = 3) were each reported in the sham control group. All side effects were reported within the first 2 weeks following therapy, without delayed presentation of side effects.

Endoscopy performed 1 week after embolization demonstrated a total of 5 cases of asymptomatic ulceration in the treatment group: 4 small superficial ulcers in the subcardiac region of the stomach, and 1 superficial ulcer in the greater curvature

(Supplemental Figure 5). All occurred upon single-vessel embolization of the LGA. The ulcerations were reported within the first 4 weeks post-intervention, and most resolved upon repeat endoscopy 1 week later (1 resolved at 2 weeks) (Supplemental Figure 6). Three subjects received temporary increases in the protocol-required, oral proton pump inhibitors.

There were no instances of pancreatitis, and only 1 serious adverse event in this study, which was unrelated to the embolization procedure or device (14). Briefly, a patient with previously unrecognized chronic high-grade atherosclerotic stenosis of the external iliac artery underwent surgical correction. A full list of adverse events is listed in Supplemental Tables 4 and 5.

WEIGHT LOSS OUTCOMES. At 6 months post-randomization, there were differences between groups in both the absolute TBWL and %TBWL for the ITT population (**Table 3**). The mean absolute and percentage weight loss with TBE (7.4 kg, 6.4%) was greater than observed with sham (3.0 kg, 2.8%; $p = 0.034$, $p = 0.052$, respectively), representing an additional 3.6% absolute TBWL. Of note, the %TBWL at 6 months of both groups were non-normally distributed. Accordingly, a Mann-Whitney *U* test was performed to compare *median* weight changes between groups; this confirmed a significant difference ($p = 0.035$).

A PP analysis was also conducted to better isolate and define the effect of TBE (**Table 3**). Again, the 6-month mean absolute TBWL and %TBWL were greater with TBE (9.4 kg, 8.3%) than sham (1.9 kg, 1.8%; $p = 0.0002$, $p = 0.0011$, respectively). **Figure 3** illustrates the %TBWL of both groups from weeks 2 to 26 post-intervention, displayed for both the ITT and PP populations (individual patient data in Supplemental Figure 7). Consistent with these differences between groups, the absolute change in the BMI at 6 months in the ITT population was also greater with TBE (-2.6 kg/m^2) than sham (-1.1 kg/m^2; $p = 0.042$) (**Table 3**).

Patients randomized to TBE continued follow-up to the 12-month time point. Compared with baseline weight, the ITT analysis revealed that the absolute TBWL (7.8 kg) and %TBWL (6.5%) were maintained at 12 months ($p = 0.0011$ and $p = 0.0008$, respectively) (**Table 3**). The outcome of the PP analysis at 12 months was again significant, and somewhat more favorable, for both the absolute TBWL (9.3 kg; $p = 0.0005$) and the %TBWL (9.3%; $p = 0.0005$). Not surprisingly, the absolute change in the BMI was also maintained to 12 months in the ITT population (-2.6 kg/m^2; $p = 0.001$) (**Table 3**).

TABLE 2 Transcatheter Bariatric Embolotherapy Procedural Data (N = 20)

Contrast used, ml	127.0 ± 59.5
Procedure time, min	82.3 ± 28.2
Total volume of microspheres injected (dry volume ml)	1.4 ± 0.5
Radiation dose, Gy/cm^2	163 ± 124
Size of microspheres used, μm	300-500
Vessels embolized, n	
Left gastric artery	18
Gastroduodenal artery → left gastric artery	1
Left hepatic artery	1

Values are mean ± SD or n.

At 6 months post-intervention, 60% of TBE subjects achieved a ≥5% TBWL, compared with only 12.5% of sham control subjects achieving this magnitude of TBWL ($p = 0.009$). At 12 months post-intervention, 33% of TBE subjects achieved ≥10% TBWL, 27% achieved between 10% and 5% TBWL, and 40% of treated subjects achieved <5% TBWL. Only 1 TBE patient gained weight back at 12 months.

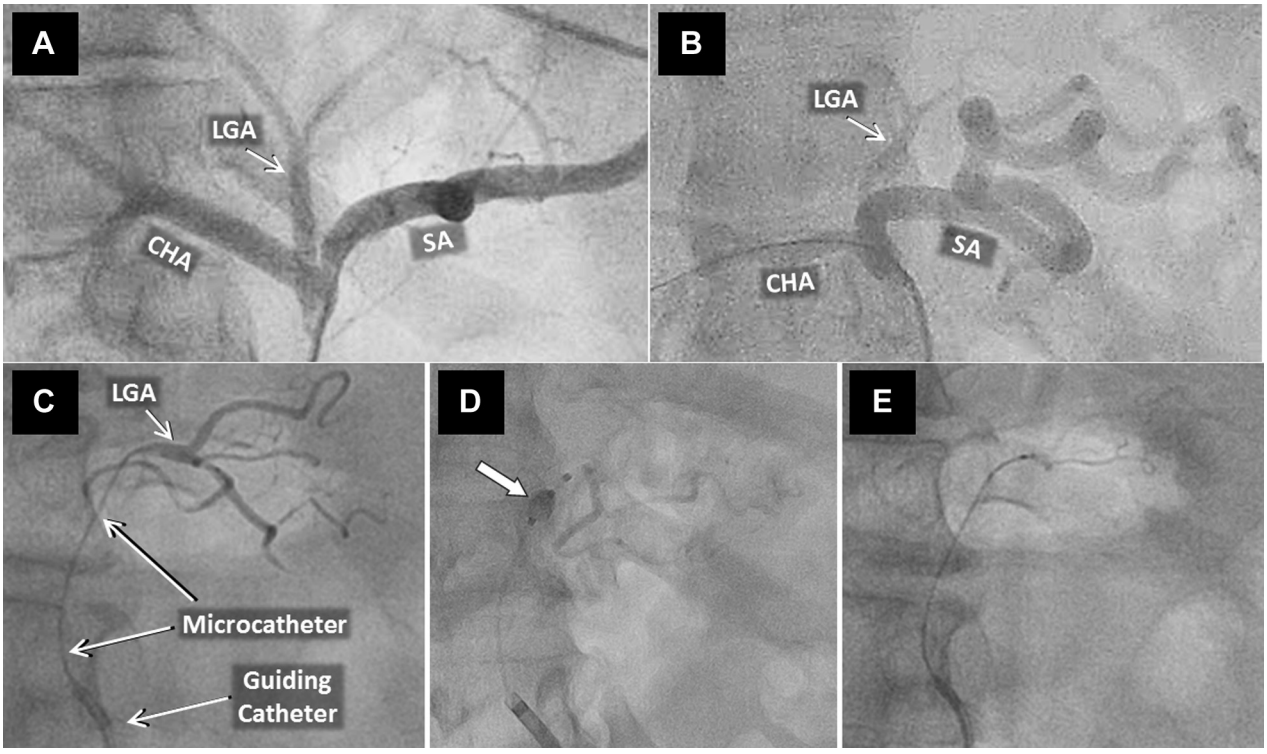
When the 6-month %TBWL was stratified by the presence or absence of ulcerations post-procedure, there was no significant difference between groups: the ulceration ($n = 4$) and nonulceration ($n = 15$) groups achieved 5.7 ± 1.8% and 6.6 ± 7.5% TBWL, respectively ($p = 0.70$).

POST-TBE BARIATRIC SURGERY. Two subjects treated with TBE subsequently underwent bariatric surgery ~1.5 years later: one a sleeve gastrectomy (**Figure 4**), and the other gastric plication. Gross intraoperative examination demonstrated healthy, well-healed tissue; post-operative courses were uneventful.

HYPERTENSION. There were no significant differences in either the systolic or diastolic blood pressures by the 6-month time point. At 12 months post-procedure, there was a statistically significant mean decrease of 9.71 ± 15.6 mm Hg in diastolic blood pressure in the TBE group ($p = 0.02$) and a nonsignificant decrease in systolic blood pressure of 1.83 ± 13.1 mm Hg ($p = 0.58$) (**Table 4**). Compared with baseline, fewer TBE subjects presented with stage 2 hypertension at 12 months post-procedure (25% vs. 62.5%; $p = 0.173$), so most TBE subjects (56.3%) were in stage 1 hypertension at 12 months.

QUALITY-OF-LIFE AND HUNGER SCORE. The Impact of Weight on Quality of Life-Life Scale survey was employed to assess for any changes in quality of life between baseline and the 6-month time point. As

FIGURE 2 Angiography of the Celiac Trifurcation and the Embolotherapy Procedure



Angiography from 2 patients **(A and B)** depicts the trifurcation of the celiac artery into the left gastric artery (LGA), common hepatic artery (CHA), and splenic artery (SA). Also shown from another patient is selective angiography of the left gastric artery **(C)**, balloon inflation **(arrows)** followed by delivery of a mixture of embolic beads with contrast **(D)**, and a post-embolization control angiogram and cessation of blood flow to fundus **(E)**.

shown in **Figure 5A** (and Supplemental Figure 8A), compared with baseline, there were statistically significant improvements in the TBE group in 2 of 5 domains, physical function and self-esteem, as well as the overall quality of life; however, none of the changes in the sham group were significant. These quality-of-life improvements with TBE were sustained at 12 months: in physical function (13.1 points; 95% confidence interval [CI]: 4.0 to 22.2 points; $p = 0.007$), self-esteem (16.2 points; 95% CI: 5.3 to 27.1 points; $p = 0.006$), and overall quality of life (12.9 points; 95% CI: 4.2 to 21.5; $p = 0.007$). However, there were no statistically significant differences between groups in any of the domains, perhaps because of insufficient sample size.

Compared with baseline, there were improvements in the self-perceived hunger score in both groups: the sham and TBE groups demonstrated mean decreases of 1.1 points (95% CI: 0.3 to 1.9; $p = 0.01$) and 2.9 points (95% CI: 0.9 to 5.1; $p = 0.009$), respectively (**Figure 5B,** Supplemental Figure 8B). However, the between-group differences in improvement did not reach statistical significance ($p = 0.09$)—again possibly because of insufficient sample size. On the other hand, compared with baseline, the improvement in the TBE group hunger score was maintained at 12 months post-procedure (decrease of 2.4 points; $p = 0.02$).

GHRELIN HORMONE. The levels of ghrelin were 482 ± 304 pg/ml and 466 ± 246 pg/ml pre-procedure in both groups. These levels increased in both groups at the 2-week time point. Then, these trends diverged: the TBE and sham groups demonstrated median decreases in ghrelin levels of 12.2% and 3.4% at 6 months ($p = 0.45$). At 12-month follow up, the TBE group demonstrated a significant median decrease of 15.5% (difference from baseline: $p = 0.035$).

SATIETY TESTING. As shown in **Table 5**, at 6 months, the time to achieve satiety in the TBE group decreased by a median of 5 min, whereas in the sham group, the time decreased by only a median of 2.5 min. Similarly, at 6 months, the TBE group required less volume

TABLE 3 Primary and Secondary Weight Loss Endpoints

	Treatment, Mean (95% CI)	Patients	Control, Mean (95% CI)	Patients	Difference Between Groups, Mean (95% CI)	p Value*
TBWL (absolute loss in kg vs. baseline)						
At 6 months post-procedure						
ITT	7.4 (3.8 to 11.0)	19	3.0 (0.9 to 5.0)	18	4.4 (2.1 to 6.7)	0.0336
PP	9.4 (5.6 to 13.2)	15	1.9 (0.5 to 3.3)	16	7.5 (5.6 to 9.4)	0.0002
At 12 months post-procedure						
ITT	7.8 (3.6 to 12.0)	19				0.0011†
PP	9.3 (4.9 to 13.8)	15				0.0005†
TBWL (% loss vs. baseline)						
At 6 months post-procedure						
ITT		19		18		
Mean (95% CI)	6.4 (3.2 to 9.6)		2.8 (0.9 to 4.7)		3.6 (0.05 to 7.3)	0.0521
Median	4.3		1.4		2.9	0.0350‡
PP		15		16		
Mean (95% CI)	8.3 (4.9 to 11.6)		1.8 (0.5 to 3.0)		6.5 (3.2 to 9.8)	0.0011
Median	6.9		1.1		5.8	<0.0001‡
At 12 months post-procedure						
ITT	6.5 (3.0 to 10.0)	19				0.0008†
PP	9.3 (5.3 to 13.3)	15				0.0005†
EBWL (% loss vs. baseline)						
At 6 months post-procedure						
ITT	17.1 (8.5 to 25.7)	19	8.6 (2.5 to 14.7)	18	8.5 (1.8 to 18.7)	0.1035
PP	22.3 (13.4 to 31.1)	15	5.4 (1.7 to 9.1)	16	16.9 (8.0 to 25.8)	0.0013
At 12 months post-procedure						
ITT	17.3 (7.9 to 26.8)	19				
PP	21.8 (11.1 to 32.4)	15				
Change in BMI at 6 months (ITT)	−2.6 (−1.3 to 3.9)	19	−1.1 (−0.4 to −1.8)	18	−1.5 (−0.5 to −2.5)	0.0422
Change in BMI at 12 months (ITT)	−2.6 (−1.2 to −4.1)	19				0.0010†

*p Values of 2-sample Student's *t*-test, unless otherwise specified. †Paired sample Student's *t*-test. ‡Wilcoxon 2-sample Student's *t*-test
CI = confidence interval; EBWL = excess body weight loss; ITT = intention-to-treat; PP = per protocol; TBWL = total body weight loss.

(mean 5.4% less) to achieve satiety in comparison to the sham group (mean 5.0% less). The TBE subjects reported a 2.5-point decrease in feeling bloated versus a 0.8-point decrease with sham. Compared with baseline, the 12-month change in time to achieve fullness was, on average, 1.7 min less for the TBE group. Similarly, it took approximately 9% less volume (ml) to achieve satiety at 12 months.

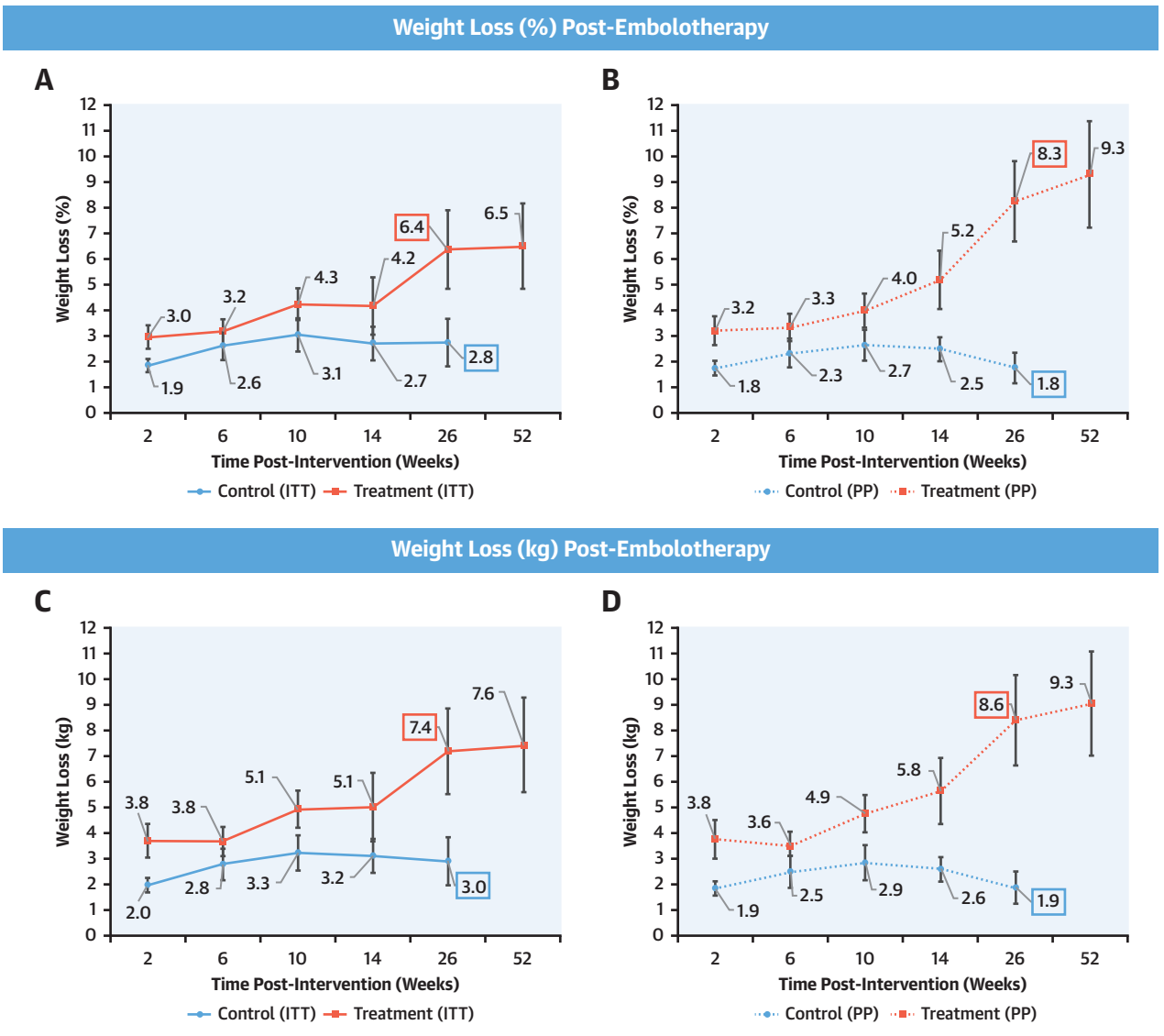
DISCUSSION

This randomized-controlled clinical trial studied the effect of TBE on facilitating weight reduction. TBE-treated subjects demonstrated superior weight loss compared with the sham-control group at 6 months post-procedure, by both ITT and PP analyses (**Central Illustration**). Furthermore, TBE-treated subjects maintained the weight loss at 12 months post-embolization. TBE was also shown to be a safe procedure with minimal complications. Ulcerations were all reported within 1 week of the procedure, were of minimal severity, and were easily treated.

TBE AND WEIGHT LOSS. Bariatric surgery is highly effective for weight reduction, with losses up to 19% and 36% TBWL by gastric banding or Roux-en-Y gastric bypass, respectively (14). Initially, it was believed that the mechanism of weight loss was from a combination of the physical reduction of the stomach and impaired absorption of macronutrients. However, it is now appreciated that other factors may play a more significant role than mechanical restriction; indeed, surgery is associated with significant metabolic alterations, including profound changes to hormonal profiles that appear to contribute substantially to the observed weight reduction (15). To this point, TBE is a nonsurgical catheter procedure that, in preclinical animal and early clinical studies, appears to influence appetite-mediating hormones in a less invasive manner than surgery.

Although the overall sample was not particularly large, our study was nonetheless able to establish that this novel therapeutic modality can successfully promote weight reduction. The study design had several favorable aspects: 1) the sham control minimized placebo effects; 2) blinding was facilitated by

FIGURE 3 Weight Loss Post-Embolotherapy

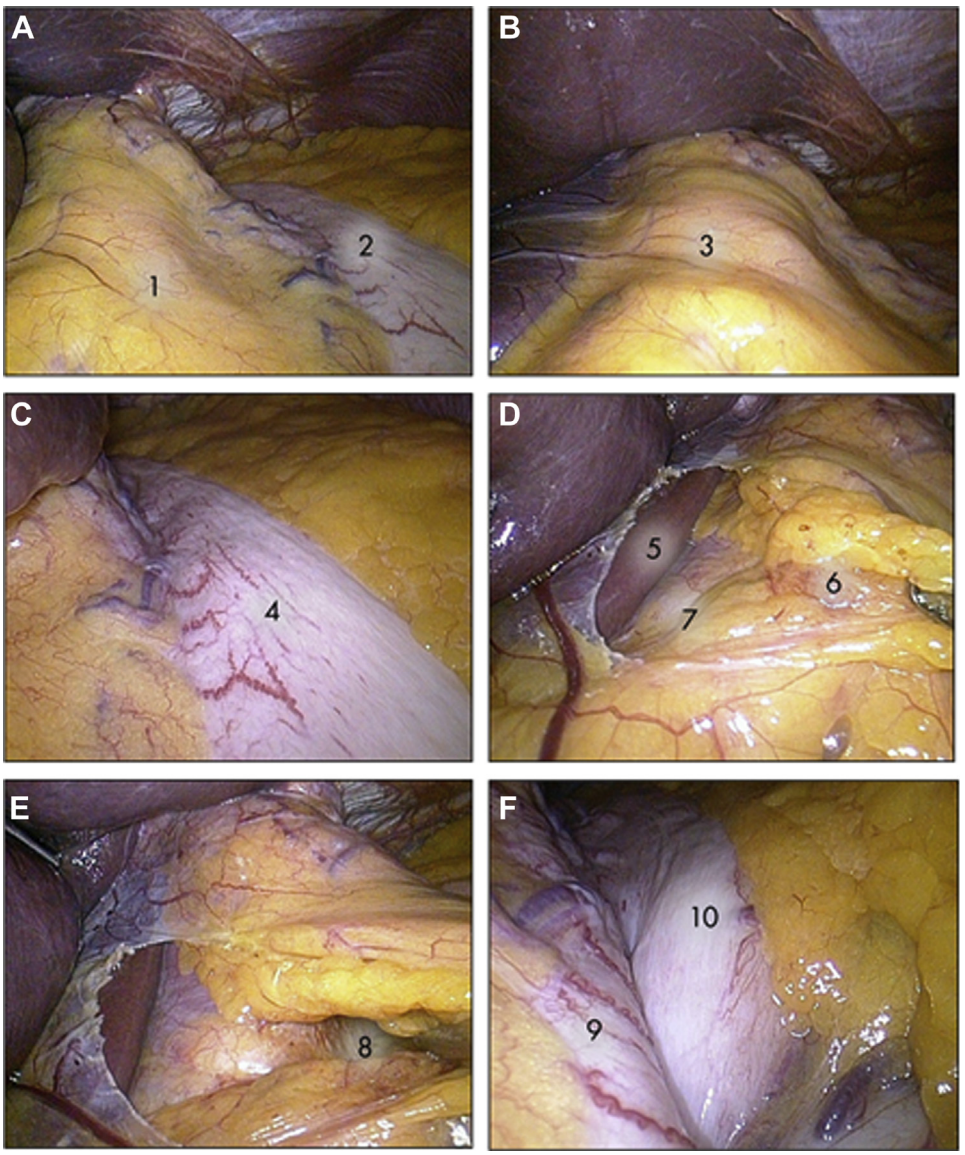


The total body weight loss are shown both as a percent decline from baseline **(A and B)** and on an absolute level of change in kg from baseline **(C and D)**, for both the transcatheter bariatric embolotherapy (TBE) treatment **(red)** and sham control **(blue)** groups analyzed for both the ITT **(A and C)** and PP **(B and D)** populations at 2, 6, 10, 14, 26, and 52 weeks post-intervention—the last time point includes only the TBE group. Note that upward trends indicate weight loss, whereas downward trends indicate weight gain. **Error bars** indicate standard error of the mean. Abbreviations as in Figure 1.

the fact that the site performing the procedures was different than the site that recruited/consented the patients, provided weight reduction counseling, and conducted the follow-up assessments (including primary endpoint adjudication); 3) a potential mechanistic link between TBE-related weight loss and decreases in ghrelin levels was observed (the TBE group demonstrated a statistically significant decrease by 12 months, although between-groups did not reach statistical significance because of insufficient sample size); and 4) a single site with the same procedural team performed all procedures. Although the latter prevents any conclusions regarding generalization of the technique, the concentration of experience engendered a relatively uniform application of the procedure to the patient cohort.

The largest previous experience was the BEAT-Obesity (Bariatric Embolization of Arteries for the Treatment of Obesity) trial—a nonrandomized study in

FIGURE 4 **Bariatric Surgery in a Patient Who Had Previously Underwent Embolotherapy**



Shown are internal anatomy images from a patient who elected to undergo gastric bypass surgery ~1.5 years after initial transcatheter bariatric embolotherapy. **(A)** Left gastric artery region **(1)** and embolized arteries **(2)**. **(B)** No adhesions or irritation to the surrounding structures and tissue and left gastric artery after embolotherapy **(3)**. **(C)** Embolized arteries (spiral-shaped, thicker vasculature) entering the stomach wall **(4)**. **(D)** The right crus **(5)** and cardia region **(6)** are shown with no evidence of adhesions or irritation to surrounding structures **(7)**. **(E)** The retro-esophageal area **(8)**. **(F)** Embolized **(9)** and nonembolized arteries **(10)** are shown, with the former appearing thick/fuzzy, and the latter appearing thin/straight.

which 20 subjects underwent TBE using commercially available equipment (9). The 6-month excess body weight loss, defined as the percentage of weight loss beyond ideal body weight (Supplemental Table 5), was 12.8%. In comparison, our study demonstrated 17% and 22% excess body weight loss in the ITT and PP populations, respectively (**Table 3**).

A recent meta-analysis of 47 subjects from 6 nonrandomized trials including BEAT-Obesity demonstrated an average weight loss of 8.1% at 12 months—which is concordant with our findings (16). Adverse events were rare; there was only 1 major adverse event involving nontarget embolization resulting in pancreatitis, splenic infarction, and late gastric

TABLE 4 Blood Pressure Changes in the ITT Population

Endpoint	Treatment*	p Value	Control*	p Value
6-month blood pressure				
Systolic blood pressure				
Mean value, mm Hg	134.2		133.8	
Mean change (95% CI)	−3.7 (−13.6 to 6.2)	0.44	2.3 (−5.0 to 9.7)	0.51
Diastolic blood pressure				
Mean value, mm Hg	88.6		86.7	
Mean change (95% CI)	−0.6 (−6.6 to 5.5)	0.85	2.8 (−0.3 to 5.9)	0.07
12-month blood pressure				
Systolic blood pressure				
Mean value, mm Hg	127.2			
Mean change (95% CI)	−1.8 (−8.6 to 4.9)	0.58		
Diastolic blood pressure				
Mean value, mm Hg	85.2			
Mean change (95% CI)	−9.7 (−17.7 to −1.7)	0.02		

The p values represent paired sample Student's *t*-test versus baseline. *At the 6-month time point, 19 and 18 patients each were included in the treatment and control groups, respectively; at the 12-month time point, 19 patients were included in the treatment group.

CI = confidence interval; ITT = intention-to-treat.

perforation. There was no correlation between weight loss and ghrelin reduction; however, only 25 patients were included in the ghrelin analysis, and the observed wide variation in ghrelin levels would limit the power to detect such a correlation.

There has been speculation that the weight loss achieved through bariatric embolization is only temporary, without long-term maintenance. However, subjects in our study maintained weight loss out to 12 months, with 84% losing weight at 12 months. The TBE responder rate in this study was as high as what has been reported in studies assessing responder rates in bariatric surgery (17). Only 1 patient from the ITT group of our study who had lost weight at 6 months had gained weight (greater than baseline) at 12 months post-procedure. Similarly, the BEAT-Obesity trial also demonstrated a long-term maintenance of the weight loss initially achieved at 6 months (9). Furthermore, ghrelin levels, which are believed to translate to hunger levels, are shown to decrease even further at the 12-month time point, suggesting the potential for ongoing weight loss.

Another emerging minimally invasive therapy is endoscopic placement of an intragastric balloon to provide a space-occupying effect for a period of 6 months, after which the balloon is removed by a second procedure. TBWL with this technique reaches 13.2% at 6 months with certain technologies; however, adverse effects including pain and nausea are frequent, occasionally requiring premature balloon removal (18). Furthermore, weight gain can relapse with undemonstrated long-term success, leaving a need for additional minimally invasive options. In some individuals, weight loss beyond the scope achieved by TBE may be desired (19). In our study, 2 subjects treated with TBE subsequently underwent successful bariatric surgery (20). The bariatric surgeon who performed the procedures (M.F.) is highly experienced and was confident that this would provide no additional risk to patients. This is based on his observation that during various gastric surgeries, including bariatric procedures, occlusion of 1 or even 2 major arteries supplying the stomach does not affect its vitality, allowing one to perform bariatric surgery without compromising the stomach.

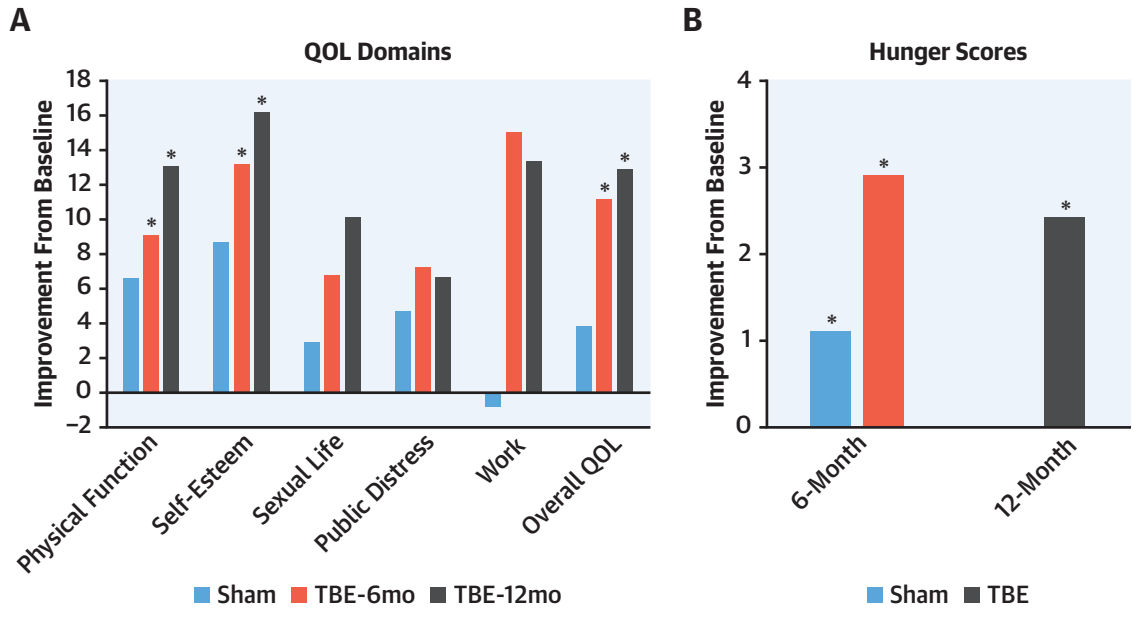
SAFETY OF TBE. Beyond self-limited nausea/vomiting, the procedures were very well tolerated. Although other gastric embolization studies (8,10,21) have reported moderate ulceration rates, routine post-procedure endoscopy in our study demonstrated only minor superficial ulcerations not exceeding 2 cm in diameter. In a few cases of ulcerations in our study, retrospective analysis of the pre-operative endoscopy revealed that subjects had pre-existing gastritis, erosion of the stomach body by prior pharmacotherapy, or a hiatal hernia. For example, the patient with a reported superficial ulcer in the greater curvature had, upon baseline endoscopy, gastritis and erosion of the stomach body. Similarly, one of the subjects reporting a small, superficial ulcer demonstrated gastritis with inflammation of the antrum and atypical whitish coating during the baseline endoscopy. It is possible that ulceration rates may be further reduced by delaying TBE in patients with any endoscopic evidence of irritation, inflammation, or gastritis until treated.

Also of interest, Alonso (22) postulated that the weight loss demonstrated by gastric embolization was not a result of metabolic changes, but rather from post-operative ulcerations. However, in our study, when TBWL was stratified by the presence or absence of post-operative ulcerations, there was no difference between groups. Indeed, the nonulceration group had a numerically greater amount of weight loss.

QUALITY OF LIFE. Significant improvements in quality of life have been demonstrated with a variety of bariatric surgeries including Roux-en-Y gastric bypass, sleeve gastrectomy, and adjustable gastric banding. Subjects treated with TBE saw significant improvements in physical function, self-esteem, and overall quality of life at both 6 and 12 months.

CARDIOVASCULAR OUTCOMES. If TBE's efficacy and safety are confirmed in large multicenter trials, it might be employed not only in the general population with obesity, but also in patients with cardiovascular or metabolic comorbidities who seldom visit

FIGURE 5 Changes in Quality-of-Life and Hunger Scores



(A) Changes in quality-of-life (QOL) scores in various Impact of Weight on Quality of Life-Life Scale domains: 6-month sham (n = 18; **blue**), 6-month transcatheter bariatric embolotherapy (TBE) (n = 19; **red**), and 12-month TBE (n = 19; **gray**). **Asterisks** indicate statistically significant ($p < 0.05$) changes from baseline. **(B)** Compared with baseline, hunger scores are shown for the 6-week sham (n = 18; **blue**) and the 6-month (n = 16; **red**) and 12-month (n = 17; **gray**) TBE groups.

specialized weight loss clinics. A 5% to 10% weight loss, an effect achievable with TBE, has been associated with clinically meaningful reductions in hemoglobin A1c, triglycerides, low-density lipoprotein cholesterol, and systolic blood pressure. Although our study was not powered to directly assess changes in these outcomes, there was evidence for an almost 10-mm Hg decrease in mean diastolic blood pressure in the treatment group.

Intentional weight loss has also been demonstrated to be beneficial in the treatment of established cardiovascular disease, such as atrial fibrillation, heart failure, or coronary artery disease. Catheter ablation studies demonstrated an association between arrhythmia-free survival with increased weight loss (22). Obesity has also been linked to the development of and worsening of heart failure, with recent research showing a correlation between increases in visceral fat and its influence on epicardial fat depots (23). Although there is still debate regarding the obesity paradox in patients experiencing coronary artery disease, a recent meta-analysis by Wang et al. (24) revealed a linear relationship between BMI and repeat revascularization rates post-PCI.

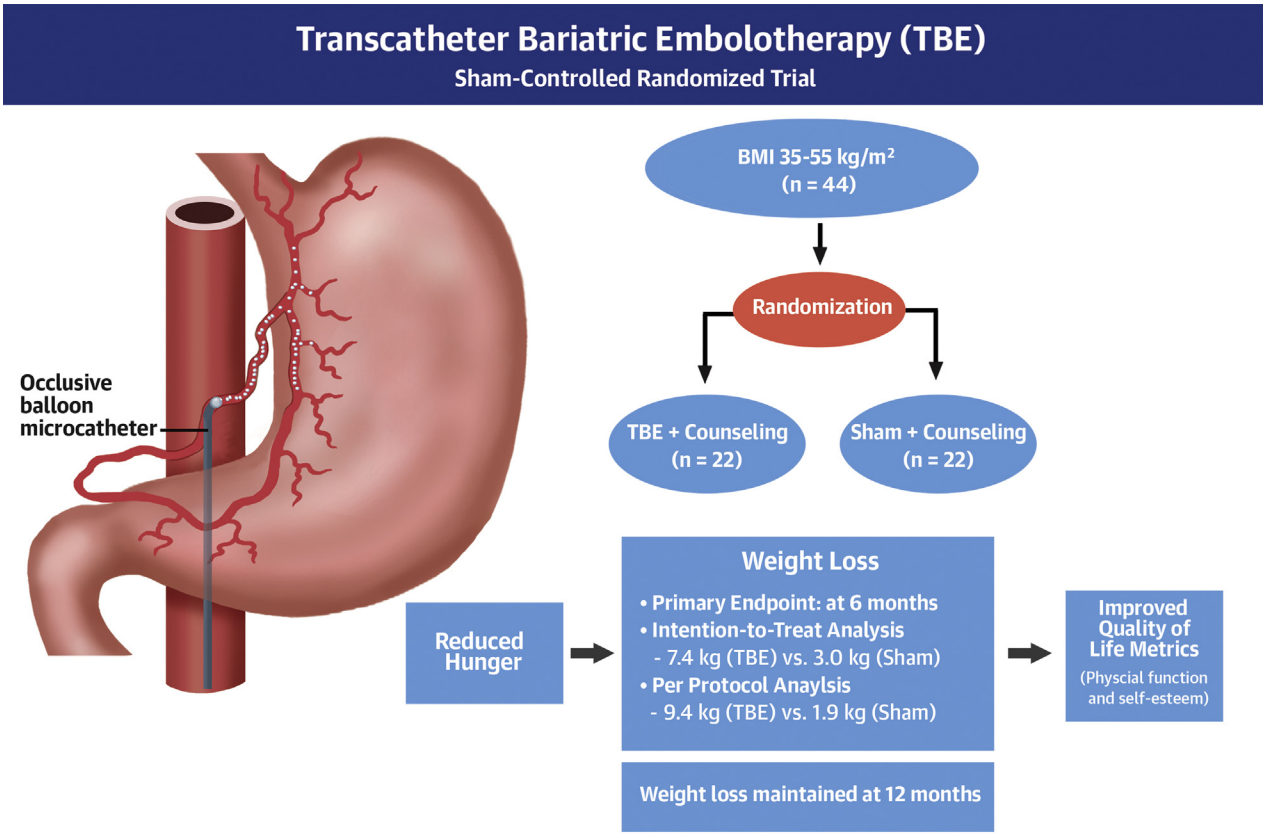
STUDY LIMITATIONS. Our study was performed at only a single pair of centers in Europe. Larger multicenter studies are required to assess the generalizability of this treatment. There was no control group after 6 months, so changes between 6 to 12 months may have been influenced by unblinding. Furthermore, little has been reported on the effect of TBE beyond 12 months. We are currently extending the

TABLE 5 Satiety Test Outcomes

Endpoint	Treatment*	Control*	p Value
6 months post-intervention			
Change in time to achieve fullness (min), median	−5.00	−2.50	0.87
Change in volume to achieve fullness (%), mean	−5.36	−4.96	0.097
Point change in feeling of			
Fullness	−0.56	0.33	0.042
Nausea	−0.44	−0.94	0.057
Bloated	−2.50	−0.78	0.15
Pain	0.06	−0.39	0.42
12 months post-intervention			
Change in time to achieve fullness (min), median	−1.67		0.047
Change in volume to achieve fullness (%), mean	−9.03		0.46

*At the 6-month time point, 19 and 18 patients each were included in the treatment and control groups, respectively; at the 12-month time point, 19 patients were included in the treatment group.

CENTRAL ILLUSTRATION **The Impact of Transcatheter Bariatric Embolotherapy**



Reddy, V.Y. et al. J Am Coll Cardiol. 2020;76(20):2305–17.

Shown are the effects of transcatheter bariatric embolotherapy on hunger, weight loss, and quality of life. BMI = body mass index.

follow-up of the TBE cohort in this study to 3 years to assess the durability of weight loss, and incidence of potentially late adverse events.

The impact of weight loss achieved with TBE on relevant cardiovascular outcomes, such as hypertension, diabetes, atrial fibrillation, and heart failure, remains to be determined. Larger, properly powered studies need to be conducted to directly examine these cardiovascular outcomes.

Finally, as with structural heart interventions, TBE should be utilized not in isolation, but in the context of a weight loss team that includes interventional specialists, a nutritionist, a bariatric surgeon, and a weight loss specialist. Indeed, an essential component of the efficacy of TBE was likely subject participation in the weight management counseling program. Just as with bariatric surgery, TBE's efficacy is predicated on the willing, active participation of a motivated patient. It is unknown if TBE alone would have *any* impact on obesity without lifestyle counseling.

CONCLUSIONS

In this prospective, randomized, sham-controlled clinical trial of transcatheter bariatric embolotherapy, obese subjects experienced well-tolerated and effective weight loss at 6-month follow-up compared with the sham control, and this weight loss was sustained at 12 months. Although a panacea for obesity is unlikely, these data indicate that, if confirmed to be safe and effective in larger future trials,

embolotherapy might play an important role in mitigating this global health epidemic.

AUTHOR RELATIONSHIP WITH INDUSTRY

This study was funded by Endobar Solutions LLC. Dr. Reddy has served as a consultant for Abbott, Abiomed, Ablacon, Actus Medical, Affera, Apama Medical, Aquaheart, Autonomix, Axon, Backbeat, BioSig, Biosense-Webster, Biotronik, Boston Scientific, Cardiofocus, Cardionomic, CardioNXT/AFTx, Circa Scientific, Corvia Medical, East End Medical, EBR, EPD, Epix Therapeutics, EpiEP, Eximo, Farapulse, Firel, Impulse Dynamics, Javelin, LuxMed, Medlumics, Medtronic, Nuvera, Philips, Pulse Biosciences, and Valcare; and has equity in Ablacon, Acutus Medical, Affera, Apama Medical, Aquaheart, Atacor, Autonomix, Backbeat, BioSig, Circa Scientific, Corvia Medical, Dinova, East End Medical, EPD, Epix Therapeutics, EpiEP, Eximo, Farapulse, Firel, Intershunt, Javelin, LuxMed, Manual Surgical Sciences, Medlumics, Newpace, Nuvera, Sirona, Surecor, Valcare, and Vizaramed. Drs. Neužil and Fried have received research grants from Endobar Solutions LLC. Dr. Nicholas Kipshidze is a founder of and Chief Medical Officer of, and holds stock in Endobar Solutions LLC. Dr. Nodar Kipshidze is a consultant to Endobar Solutions LLC. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

Used in concert with lifestyle counseling, TBE is technically feasible, safe, and effective in achieving weight loss in obese individuals, and is associated with improvements in quality of life.

TRANSLATIONAL OUTLOOK:

Larger, multicenter trials are needed to compare the clinical outcomes and safety of this technique with conventional weight loss measures.

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KEY WORDS bariatric embolization, embolotherapy, ghrelin, left gastric artery, obesity, weight loss

APPENDIX For an expanded Methods section as well as supplemental videos, tables, and figures, please see the online version of this paper.