

Original article

The REDUCE pivotal trial: a prospective, randomized controlled pivotal trial of a dual intragastric balloon for the treatment of obesity

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Abstract

Background: Saline-filled intragastric balloon devices are reversible endoscopic devices designed to occupy stomach volume and reduce food intake. Objective: To evaluate the safety and effectiveness of a dual balloon system plus diet and exercise in the treatment of obesity compared to diet and exercise alone. Setting: Academic and community practice, United States.

Methods: Participants (n = 326) with body mass index (BMI) 30–40 kg/m² were randomized to endoscopic DBS treatment plus diet and exercise (DUO, n = 187) or sham endoscopy plus diet and exercise alone (DIET, n = 139). Co-primary endpoints were a between-group comparison of percent excess weight loss (%EWL) and DUO subject responder rate, both at 24 weeks. Thereafter DUO patients had the DBS retrieved followed by 24 additional weeks of counseling; DIET patients were offered DBS treatment.

Results: Mean BMI was 35.4. Both primary endpoints were met. DUO weight loss was over twice that of DIET. DUO patients had significantly greater %EWL at 24 weeks (25.1% intent-to-treat (ITT), 27.9% completed cases (CC, n = 167) compared with DIET patients (11.3% ITT, P = .004, 12.3% CC, n = 126). DUO patients significantly exceeded a 35% response rate (49.1% ITT, P < .001, 54.5% CC) for weight loss dichotomized at 25%EWL. Accommodative symptoms abated rapidly with support and medication. Balloon deflation occurred in 6% without migrations. Early retrieval for nonulcer intolerance occurred in 9%. Gastric ulcers were observed; a minor device change led to significantly reduced ulcer size and frequency (10%).

Conclusion: The DBS was significantly more effective than diet and exercise in causing weight loss with a low adverse event profile. (Surg Obes Relat Dis 2015;11:874–881.) © 2015 American Society for Metabolic and Bariatric Surgery. All rights reserved.

Keywords: Obesity; Nonsurgical weight loss; Intragastric balloon; Randomized controlled trial; Weight loss therapy; Endoscopic bariatric therapy

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Modern saline-filled intragastric balloons are designed to cause weight loss by occupying space in the stomach, inducing satiety and reduced food intake. Such devices have been used outside the United States since 1997, and result in 25–40 percent excess weight loss (%EWL) in most clinical series [1,2]. The literature contains several randomized studies of saline-filled intragastric balloons against diet and exercise controls [3–7], but all were smaller than 50 patients and showed mixed results. Large recent clinical series show weight loss exceeding 40%EWL [8–10], as well as multiyear follow-up showing maintenance of weight loss [11]. Intragastric balloons have been used sequentially resulting in augmented weight loss [7,9,12–14], as well as with weight loss drugs for greater loss or improved post-implant weight loss maintenance [15–16]. Modern balloons have an acceptable safety profile but can be associated with initial accommodative symptoms, reflux and gastric ulcers; serious complications are rare and include periprocedural gastrointestinal tract perforation, and intestinal obstruction arising from balloon deflation and migration out of the stomach [1–2,11,17–22].

The ReShape Duo® Integrated Dual Balloon System (ReShape Medical, Inc, San Clemente, CA) is a dual-balloon implant that is endoscopically placed and retrieved following 6 months of treatment. The dual balloon design provides enhanced gastric space filling while potentially reducing the risk of intestinal migration (Fig. 1) [3]. The REDUCE Pivotal Trial was a prospective randomized trial designed to evaluate the safety and effectiveness of 6 months of treatment with the

ReShape dual balloon plus a supervised diet and exercise regimen, compared with diet and exercise alone.

Methods

The REDUCE Pivotal Trial was a prospective, sham-controlled, double-blinded, randomized multicenter clinical study that enrolled patients between August 13, 2012 and February 18, 2013. Participants were between the ages of 21 and 60 years of age with a baseline body mass index (BMI) of ≥ 30 kg/m² and ≤ 40 kg/m² with one or more obesity-related co-morbid conditions who provided written informed consent, were not at risk of pregnancy, and had failed to lose weight within the prior 36 months with a medically supervised weight loss program. Exclusions included a history or ongoing clinically significant conditions of the gastrointestinal tract or medical conditions which prevented use of the dual balloon or confounded the assessment of study outcomes.

An enrollment of up to 330 patients at up to 15 clinical sites in United States was planned; informed consent for each subject and Investigational Review Board approval was required. Patients, who received all care without cost, were randomized to receive either endoscopic dual balloon insertion plus diet and exercise (DUO) or a sham endoscopy followed by diet and exercise alone (DIET). All patients underwent monthly diet and exercise counseling and assessment consistent with the National Heart, Lung, and Blood Institute Practical Guide [23] during the primary evaluation period (weeks 0–24). Nonsteroidal anti-inflammatory agents were forbidden, and therapeutic proton pump inhibition was mandatory. At Week 24, DUO patients had the dual balloon retrieved and received continued counseling through Week 48. DIET patients were offered optional dual balloon treatment at Week 24; accepting patients continued through dual balloon retrieval at Week 48 plus a safety follow-up at Week 52. The trial was registered with www.clinicaltrials.gov on August 15, 2012 (NCT 01673698). Initially all patients received a total dual balloon fill volume of 900 cc; this was reduced on November 26, 2012 for short stature patients (<64.5 inches) to 750 cc for reasons of comfort and tolerability.

The primary study objective was to demonstrate that treatment with the ReShape nonsurgical weight loss procedure resulted in greater weight loss than diet and exercise alone after 24 weeks. The primary outcome measure for this trial was %EWL calculated using BMI = 25 as ideal weight, which was assessed in 2 co-primary endpoints. The first endpoint was a comparison of the mean %EWL between DUO and DIET patients at 24 weeks with a minimum superiority margin of 7.5%. The second endpoint was a comparison of the proportion of DUO patients achieving at least a 25% EWL to a prespecified proportion of 35%. Other prespecified outcome measures included weight loss characterizations, assessment of weight loss maintenance, changes in measures of co-morbid conditions, and quality of life instruments, including the Impact of Weight on Quality of

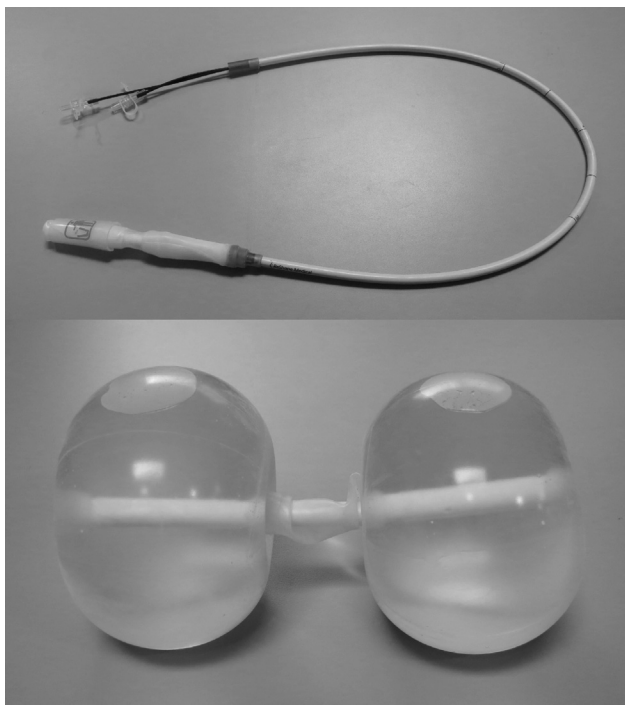


Fig. 1. The ReShape Duo® Integrated Dual Balloon System. Note: Device on delivery catheter (top) and inflated with saline (bottom).

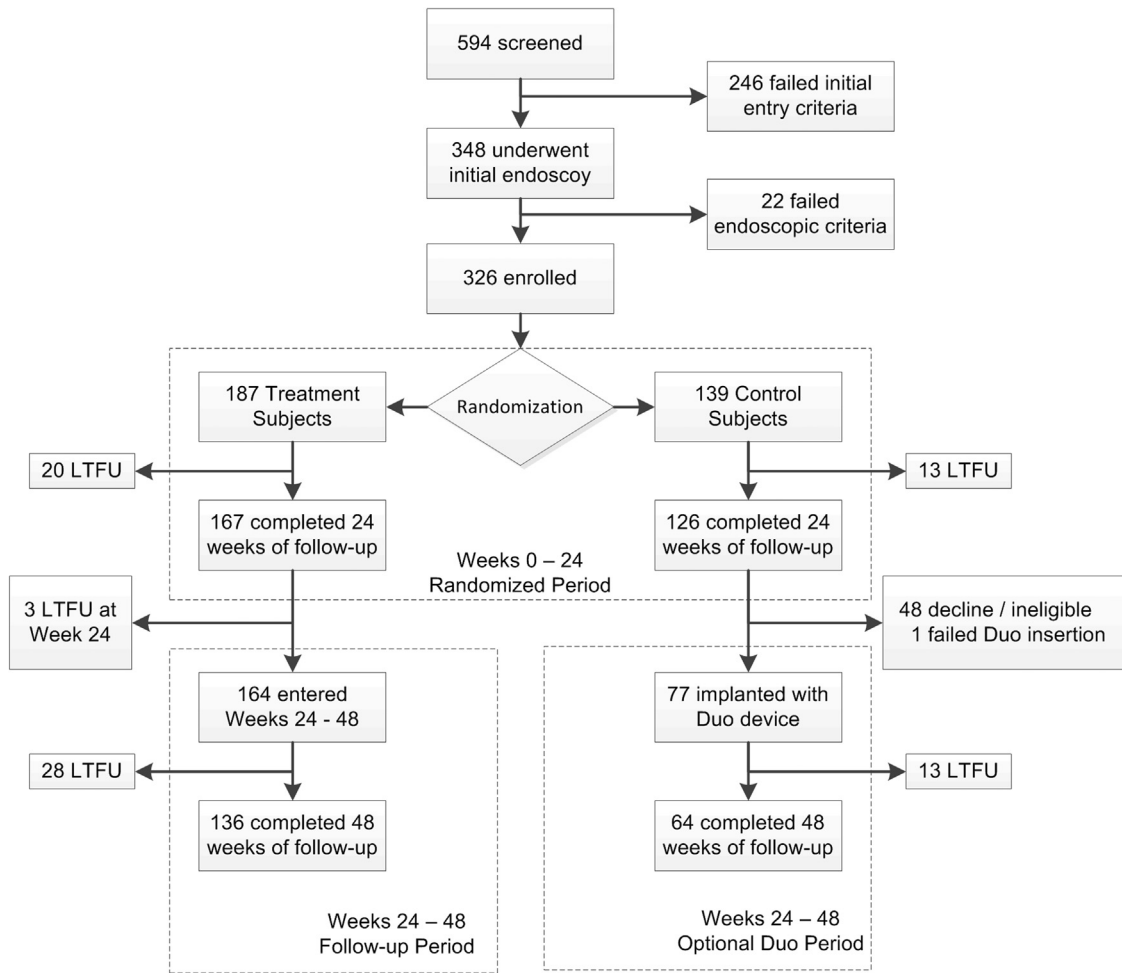


Fig. 2. Excess weight loss differences between DUO and DIET groups. Note: %EWL = percent excess weight loss (BMI 25 method). DUO = diet and exercise; DIET = sham endoscopy plus diet and exercise alone.

Life-Lite (IWQOL-Lite), the Short Form Health Survey (SF-36) and a subject satisfaction survey. All adverse events and safety related outcomes in the study were documented, monitored and categorized using standard, prespecified, FDA-approved definitions, and were reviewed and adjudicated by an independent Clinical Events and Data Monitoring Committee. Accommodative symptoms were assessed using an abdominal pain visual analogue score (VAS) and the Rhodes Index of Nausea, Vomiting, and Retching.

The sample size for the study was determined by the evaluations of the first of the 2 coprimary effectiveness endpoints, using a one-sided alpha level of .025, a power of 80% and a superiority margin of 7.5%EWL, resulting in an estimated size of 150 evaluable patients per group, leading to a total enrollment of 330 patients to allow for potential losses. A prespecified interim analysis by an independent, unblinded statistician was planned when 12 week follow-up data for 50% of patients, allowing early trial termination for futility or an adaptive increase of as much as 50% of the original study size, with an alpha spending adjustment using a Lan-DeMets spending function with O’Brien-Fleming boundaries.

Patients were randomized after the diagnostic portion of the endoscopy procedure by site personnel using a centralized computer-generated, site-specific randomization assignment stratified by center, height and BMI category (30–34.9 and

Table 1
Baseline subject characteristics

Physical parameter	DUO (N = 187) Mean ± SD	DIET (N = 139) Mean ± SD
Age (years)	43.8 ± 9.5	44.0 ± 10.2
Weight (lb)	209.2 ± 25.8	213.2 ± 25.5
BMI (kg/m ²)	35.3 ± 2.8	35.4 ± 2.6
Waist circumference (in)	43.4 ± 4.4	43.2 ± 4.4
Hip circumference (in)	47.1 ± 3.5	47.7 ± 2.9
Systolic BP (mm/Hg)	130.4 ± 13.9	133.2 ± 14.0
Diastolic BP (mm/Hg)	81.8 ± 10.1	82.8 ± 10.2
Heart rate (beats/min)	78 ± 11.2	79 ± 12.7
Hemoglobin A1c (%)	5.7 ± .7	5.7 ± .88
Cholesterol	200 ± 38	196 ± 40
Triglycerides (mg / dL)	141 ± 87	137 ± 88

BMI = Body mass index; BP = Blood pressure; DIET = Sham endoscopy plus diet and exercise alone; DUO = Diet and exercise.

Table 2
Gender, ethnicity and baseline co-morbidities

Parameter	DUO (N = 187) %	DIET (N = 139) %
Sex (female)	95.2%	95.0%
Ethnicity (Hispanic/Latino)	8.0%	5.8%
White	81.8%	85.6%
Black/African American	13.4%	11.5%
Other/Refused	4.2%	3.6%
Co-morbidity		
Joint disease	38.5%	33.8%
Back pain	29.9%	30.2%
Dyslipidemia	29.4%	28.1%
Hypertension	28.9%	35.3%
GERD	27.8%	24.5%
Depression	23.0%	20.1%
Stress urinary incontinence	19.8%	23.7%
Lower extremity edema	15.0%	12.2%
Sleep apnea syndrome	8.6%	6.5%
Diabetes	7.0%	7.2%
Psychosocial impairment	7.0%	9.4%
Polycystic ovarian syndrome	3.2%	3.6%

DIET = Sham endoscopy plus diet and exercise alone; DUO = Diet and exercise; GERD = Gastroesophageal reflux disease.

35–40) using a permuted block design. The original 1:1 allocation between study groups was adjusted during the study to achieve a target 1:1 allocation between groups meeting the modified balloon fill volume guidelines. Study procedures were followed to maintain double blinding, including sham endoscopy by separate operators, avoidance of between-subject contact during the study, the use of blinded evaluators, and control of medical records that might reveal assignment.

The primary analyses were performed on the intent-to-treat (ITT) population, which included all randomized patients, as well as a predefined completed cases (CC) population. Co-primary endpoint 1 was analyzed using analysis of covariance adjusted for baseline BMI strata (30–34.9, 35–40), gender, and a minimum superiority margin of 7.5%, using the F-test statistic for treatment group assignment. Coprimary endpoint 2 was analyzed using an exact binomial test, comparing the DUO 25% EWL responder rate to a performance goal of 35%. Missing data were addressed by prespecified imputation rules, assigning no treatment effect for withdrawals due to study treatment or procedure (e.g., lack of benefit or adverse events) and multiply imputed values for withdrawals unrelated to study effects (e.g., emergent medical condition, relocation). Other outcomes were summarized using standard descriptive statistical measures. Subgroup analyses were performed for gender and pooling of sites; as were exploratory multivariable analyses to identify contributions of baseline predictive factors for weight loss and adverse events.

Results

A total of 326 consented patients (187 DUO, 139 DIET) were randomized between August 13, 2012 and February 18, 2013 at 8 U.S. academic and community practice sites.

Ninety percent (167 DUO patients and 126 DIET) of patients completed the 24 week randomized assessment period and all were assessed for primary endpoints as randomized. One-hundred-thirty-six (136) DUO patients went on to complete Weeks 24–48 of posttreatment follow-up for assessment of weight loss maintenance, and 77 DIET patients were eligible for and opted to receive dual balloon treatment during Weeks 24–48. A total of 264 patients (187 DUO and 77 DIET) underwent dual balloon treatment by the end of trial and constitute the safety population (Fig. 2).

Baseline demographic and clinical characteristics for each group were comparable (Tables 1 and 2). Most patients were female (95%) with a mean age of 44 years, mean weight 211 pounds, mean BMI 35.3, and mean waist and hip circumference of 43 and 47 inches, respectively. The racial composition of the trial approximated that of the United States, and patients had multiple obesity co-morbidities.

There were a total of 531 study-related endoscopic procedures: 265 dual balloon insertion procedures (with one failure), 264 retrieval procedures, and 2 replacement procedures. Insertion procedures averaged 8 minutes in duration and were successful in 99.4% of attempts. Retrieval procedures averaged 14 minutes in duration and were 100% successful in achieving endoscopic retrieval. Operators consistently rated device insertion, balloon inflation, and disengagement of the dual balloon from the insertion catheter as easy.

The REDUCE Pivotal Trial met both primary effectiveness endpoints. DUO patients had a 25.1 ± 1.6 (standard error, SE) %EWL and DIET patients 11.3 ± 1.9 (SE) %EWL (intent-to-treat basis, *P* value .0041 accounting for 7.5% superiority margin). For completed cases, DUO patients lost 27.9 ± 21.3 (standard deviation, SD) %EWL, 2.7 ± 1.9 BMI units, $7.6\% \pm 5.5\%$ of total weight, and 15.9 ± 11.9 pounds; DIET patients lost 12.3 ± 22.1 (SD) %EWL, 1.3 ± 2.3 BMI units, $3.6\% \pm 6.3\%$ of total weight,

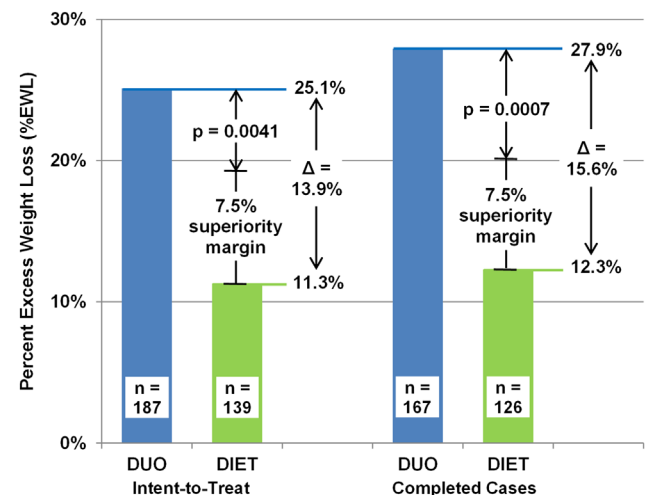


Fig. 3. Patient Flow Chart. Note: LTFU = lost to follow-up. DUO = diet and exercise.

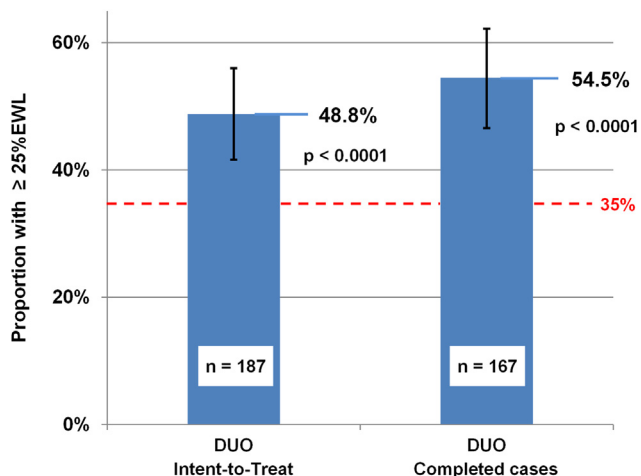


Fig. 4. Change in quality of life. Note: IWQoL-Lite = Impact of Obesity on Quality of Life – Lite Instrument.

and 7.8 ± 14.1 pounds (Fig. 3). The intent-to-treat proportion of DUO patients who achieved a 25 %EWL or greater weight loss at 24 weeks was 48.8%, with a lower confidence bound of 41.6%, which was significantly greater than the required responder rate of 35% (P < .0001); this proportion was 54.5% for completed DUO patients (Fig. 4). Multi-variate analysis showed that older age, greater fill volume and nonwhite race were associated with greater weight loss. Mean %EWL in DUO patients completing 48 weeks of follow-up was 18.8 %EWL, 66% of the weight lost at the completion of dual balloon implantation.

Co-morbid conditions improved substantially and often significantly, and these beneficial changes persisted through 48 weeks of follow-up, including significant changes in hemoglobin A1 c, high and low density lipoproteins, systolic and diastolic blood pressures, and waist and hip circumference (Table 3).

Table 3
Change in Co-morbidity Laboratory Tests

DUO Patients Laboratory Values	Value at Baseline	Change from Baseline at:			
		Week 12	Week 24	Week 36	Week 48
		During DBS Treatment		After DBS Treatment	
Glucose	93.2	-1.0	0.3	-1.5	0.9
Insulin	17.8	-4.8	-3.8	-0.7	-1.0
HbA1 c	5.7	-0.1	-0.2	-0.3	-0.2
TG	140.9	-17.9	-15.7	-6.7	-9.0
HDL	52.0	-0.9	1.0	1.6	1.9
LDL	121.0	-3.0	-4.1	-6.8	-4.6
Systolic BP	130.4	-8.2	-8.3	-9.3	-6.6
Diastolic BP	81.8	-2.7	-4.3	-4.3	-4.4
Waist (inches)	42.3		-2.9		-2.2
Hip (inches)	47.1		-2.2		-1.5

BP = Blood pressure; DBS = dual balloon system; DIET = Sham endoscopy plus diet and exercise alone; DUO = Diet and exercise; HbA1 c = hemoglobin A1 c; HDL = high density lipoproteins; LDL = low density lipoproteins; TG = Triglycerides.

Figures in bold P < .05. Number of patients varied slightly among tests: baseline, 184–187; Week 12, 168–173; Week 24, 166–169; Week 36, 115–123; and Week 48, 131–136.

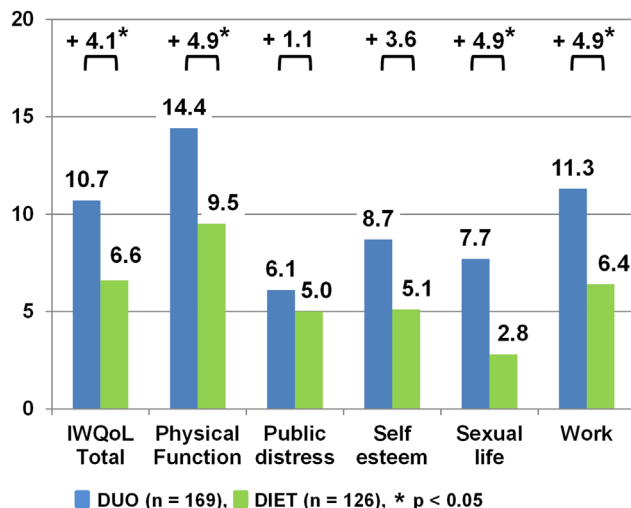


Fig. 5. Proportion of DUO patients achieving at least a 25% EWL. Note: % EWL = percent excess weight loss (BMI 25 method). DUO = diet and exercise.

Improvements were noted in measures of quality of life including SF-36 and the obesity-specific IWQoL. The IWQoL scale showed greater improvement in DUO patients compared with DIET patients overall and in all subscales at Week 24, and DUO subject changes persisted through 48 weeks with the total IWQoL score increasing from 76.5 to 78.7 (Fig. 5). Two-thirds of patients would have dual balloon treatment again, and 77% said they would recommend treatment to a friend.

Treatment with the dual balloon had a good safety profile. Accommodative symptoms were expected and observed following implantation, including nausea, vomiting and/or abdominal pain or discomfort (Figs. 6 and 7). These symptoms generally resolved in 3–7 days, were only infrequently severe (1–2%), and could be treated success-

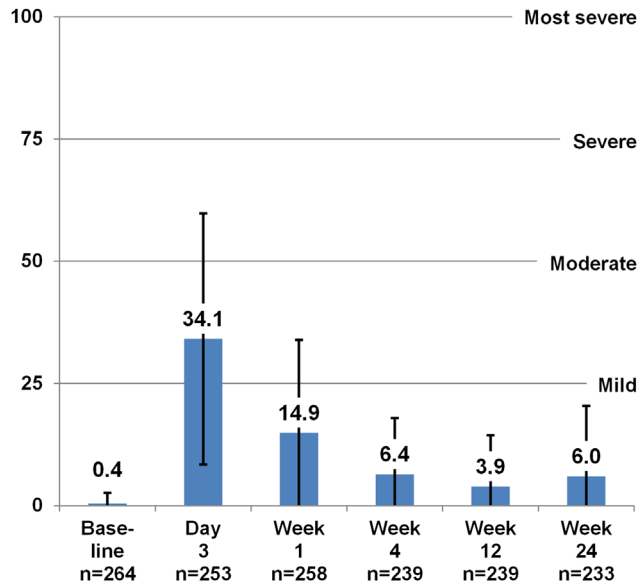


Fig. 6. Rhodes index of nausea and vomiting for DBS-Treated Patients.

fully with reassurance, medication, fluids and as needed with early retrieval. Nonulcer-related early retrievals for intolerance occurred in 9.1% (24) of all treated patients almost all within the first 2 months, the reduction of fill volumes for short stature patients reduced this rate to 7.7%.

There were no deaths, no intestinal obstructions, no gastric perforations and no device migrations during the REDUCE Pivotal Trial. Most device-related serious adverse events (75%, 21/28) were visits to the emergency room for medical management of accommodative symptoms. Other adverse events of note included esophageal mucosal tear during retrieval requiring placement of hemostatic clips (1), gastroesophageal junction ulcer-associated GI hemorrhage requiring transfusion (1), contained cervical esophageal perforation during retrieval requiring IV antibiotic treatment (1) and postretrieval pneumonitis requiring antibiotic treatment (1). The proportion of dual balloon-attempted patients with one or more nonaccommodative device- or procedure-related serious adverse events was low (3.0%).

Gastric ulceration, located in almost all cases at or near to the gastric incisura, was observed in 35% of dual balloon-treated patients, and in all but one case was inconsequential and discovered on routine retrieval. Ulcers were attributed to pressure from the distal device tip, which underwent a minor modification to be softer, smaller and smoother during the trial, resulting in a 74% reduction in ulcer frequency (original tip design 39%, modified tip design 10%, $P < .0001$) and a 49% reduction in mean ulcer size (from 1.6 cm to .8 cm, $P = .0002$). Device deflations occurred in 6% of dual balloon-treated patients usually late in the treatment phase when most weight loss had occurred.

There was no inadvertent unblinding by investigators or staff, but surveys revealed that patients guessed their treatment status correctly significantly more often than by chance

at 4 and 24 weeks by both the James [24] and Bang [25] indices of blinding, primarily related to different perceptions of satiety or self-assessment of the presence or absence of the dual balloon based on abdominal sensation.

Discussion

Novel treatments are needed to fill the treatment gap in obesity interventions [26]. Conventional therapies with diet and exercise have modest treatment effects and low compliance. Pharmacotherapy may be somewhat more effective, but to date has been hampered by cost, compliance failures, and concerns regarding adverse effects and the potential for congenital defects; the latter is a major concern given the preponderance of women of childbearing age in the target population. Bariatric surgery has proven efficacy, but only a small proportion of eligible patients elect this option due to perceived perioperative and long term risks. Intra-gastric balloons do not compete with bariatric surgery, but as shown in this study offer effective, reversible treatments for patients with lower body mass index who have failed diet and exercise. Other potential uses include the treatment of high-risk super-obese patients (BMI > 60), obese adolescents, and obese patients requiring weight loss before other procedures.

The ReShape dual balloon demonstrated more than twice the weight loss after 24 weeks than a medically supervised diet and exercise program, and two thirds of this loss was maintained on average through an additional 24 weeks of posttreatment follow-up. Quality of life and co-morbidity measures improved significantly through the completion of 48 weeks of follow-up. Insertion and retrieval procedures were short, easy and associated with minimal complications. Accommodative symptoms could generally be managed by medication and counseling; however, 9% of

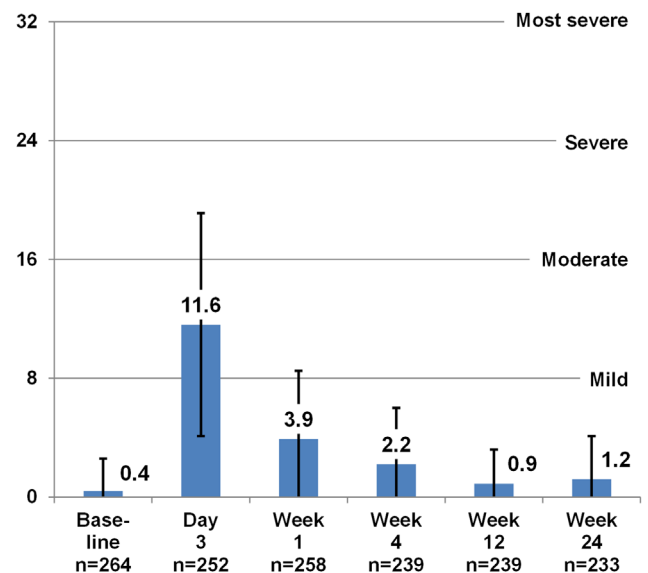


Fig. 7. Abdominal pain scores for DBS-Treated Patients.

patients in this study had the device removed for accommodative symptoms before completing 24 weeks of therapy. The early retrieval rate was substantially reduced by a reduction in fill volumes for short stature patients. Ulcers were found in over one third of patients treated with the initial design of the dual balloon; after a minor modification to the device's distal tip, this rate fell to a 10% occurrence of small, clinically inconsequential ulcers all of which were treated successfully with device retrieval and proton pump inhibitor treatment. This rate is consistent with that occurring in patients taking regular nonsteroidal anti-inflammatory drug therapy [27–29].

The REDUCE Pivotal Trial was a large, sham-blinded randomized controlled trial of an intragastric balloon compared with a medically supervised diet and exercise regimen, and is generalizable to the American population of BMI 30–40 patients. Subject loss through 24 weeks was relatively low, and treatment effects were assessed on a strict intent-to-treat basis. Subject self-unblinding did occur to some degree in both groups due to device-related symptoms. While this was unavoidable, it may have impacted subject willingness to remain in the study. The standardized nature of the diet and exercise program and the relative lack of subject commitment compared with self-pay patients may have diminished the reported effectiveness as European clinical experience with the ReShape dual balloon at specialized centers results in substantially higher weight loss and posttreatment maintenance [30]. Minor modification of the distal tip of the device occurred midtrial, but this had no effect on effectiveness or safety measures other than substantially reducing the incidence of gastric ulceration.

Conclusion

The REDUCE Pivotal Trial of the ReShape Duo® Integrated Dual Balloon System in the treatment of patients with obesity demonstrated that the dual balloon is significantly more effective than diet and exercise alone in causing weight loss with a low adverse event profile. Treatment with the dual balloon supports diet compliance through 24 weeks, potentially allowing patients to relearn eating and exercise habits while undergoing an effective, low risk, reversible treatment with demonstrated benefits through one year of follow-up. Comprehensive weight loss programs in combination with temporary devices such as the ReShape dual balloon are emerging therapies that will be important in the management of the obesity pandemic.

Disclosures

J. Ponce: ReShape Medical: consulting fees, funding for clinical research

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R. Holcomb: ReShape Medical: consulting fees

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Other information

The REDUCE Pivotal Trial was registered with www.clinicaltrials.gov on August 15, 2012. Funding and dual balloon devices were provided by ReShape Medical, Inc.

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Statistical expertise: R. Holcomb

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Final approval of the article: J. Ponce

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