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BEST: Bypass equipoise sleeve trial; rationale and design of a randomized, registry-based, multicenter trial comparing Roux-en-Y gastric bypass with sleeve gastrectomy☆

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ABSTRACT

Background: Laparoscopic gastric bypass (LGBP) is a well-documented surgical intervention for severe obesity. Recently, laparoscopic sleeve gastrectomy (LSG) has gained increased popularity. Short-term follow-up in limited-sized randomized trials comparing LGBP and LSG show no major differences in weight-loss, adverse events, or effect on comorbidities; however, there is a lack of sufficiently powered, pragmatic, randomized controlled trials comparing the mid- and long-term results of the two methods.

Method: BEST is a randomized, registry-based, multicenter trial comparing LGBP and LSG. The trial has two primary outcomes; rates of substantial complications (SC) and total body weight loss. We hypothesize that patients treated with LSG will experience 35% fewer substantial complications during the 5-year follow-up compared to patients treated with LGBP, and that the efficacy of LSG will remain within a non-inferiority margin of 5% in terms of weight loss. Our sample size calculation, using data from the Scandinavian Obesity Surgery Registry (SOReg), shows a power of 80% for SC and > 95% for weight loss at $p < .025$ with a total of 2100 included patients.

The design of the trial will also enable comparisons within several relevant patient subgroups.

Conclusions: As a large-sized, pragmatic, randomized trial, BEST will provide robust data comparing LGBP with LSG by generating long-term results on weight loss and SC's, as well as secondary outcomes and comparisons within patient subgroups. The use of a well-established registry for registration of all data facilitates a large multicenter trial, and combines the strengths of registry studies with those of a randomized trial.

Clinical Trials registry: NCT 02767505.

1. Introduction

Laparoscopic gastric bypass (LGBP) has long been the standard surgical intervention for severe obesity in Sweden [1]. The long-term effects of LGBP are well documented, with an overall decrease in mortality and morbidity [2,3]. There are well-known adverse events; i.e., internal herniation, even when the mesenteric defects are closed [4]. Additionally, a small number of patients develop long-term severe complications after LGBP such as chronic abdominal pain and post-prandial hypoglycemia.

Laparoscopic sleeve gastrectomy (LSG) has, during the past decade, been introduced as an alternative surgical technique and is increasingly

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used both internationally and in Scandinavia. The long-term effects of LSG are largely unknown, although available data suggest a slightly lower complication rate and somewhat lower efficacy in terms of weight loss [5]. There are also reports suggesting that LSG may be associated with worsening or de novo development of gastroesophageal reflux disease (GERD) [6], and even Barrett's esophagus, possibly constituting an increased risk of esophageal adenocarcinoma in the long term.

However, data from limited-sized randomized clinical trials (RCTs) report no major differences between LSG and LGBP in terms of weight loss, adverse events, or resolution of comorbidities at short- and intermediate-term follow up [7,8].

The objective of BEST is to evaluate the safety and effectiveness of LSG compared to LGBP in obese patients eligible for both types of surgery. The trial has two primary objectives, evaluating superiority and non-inferiority, respectively. The trial hypothesis for superiority is that patients treated with LSG will experience fewer severe adverse events (SC's) during the 5-year follow-up. For non-inferiority, the trial hypothesis is that the efficacy of LSG, regarding differences in weight loss when compared to LGBP, is within a margin of 5% after 5 years.

Secondary objectives of the trial include rates of inpatient hospital stay, outpatient care, medications, alcohol abuse, fractures, bone quality, diabetes, cancer, mortality, patients' quality of life and health economic outcomes.

Predefined subgroup analyses will be performed by sex, age, diabetes state, and body mass index (BMI).

2. Methods

2.1. Trial design

BEST is a randomized, Scandinavian, multicenter trial comparing the outcomes of two bariatric surgery techniques; LGBP and LSG. The trial design is a parallel group study with a 1:1 allocation.

Currently, 17 bariatric surgery clinics in Sweden and three in Norway are participating in the study, and additional centers are under recruitment. In total, the trial will include 2100 obese patients approved for bariatric surgery.

The follow-up time for the primary objectives is 5 years.

2.2. Trial setting

To be eligible, participating centers must perform a minimum of 100 bariatric procedures annually and report to the national register in Sweden/Norway for bariatric surgery (Scandinavian Obesity Surgery Register, SOReg) [9]. In order to be certified as a participating center in the study, at least 20 procedures of each technique should have been performed. Also, a video recording illustrating the techniques should have been approved by the Clinical Trial Steering Committee (CTSC). Almost all surgical procedures and subsequent medical care is publicly funded, with the majority being run by regional councils, although some are run by private organizations. The centers include both university hospitals and tertiary referral centers in larger cities as well as hospitals in smaller communities.

2.3. Eligibility criteria

The following eligibility criteria will be applied:
Inclusion criteria

- Aged > 18 years at inclusion
- BMI 35–50 kg/m^2 prior to pre-operative weight reduction.
- Able to understand the trial information and to make an informed decision regarding participation.

Exclusion criteria

- Not suitable for either surgical procedure according to the surgeon's assessment or local clinical guidelines.
- Uncontrolled substance abuse.
- Uncontrolled psychiatric disease.
- Previous bariatric surgery or major upper abdominal surgery assumed to complicate surgery.
- Moderate-to-severe GERD (defined as not symptom-free on PPI, esophagitis LA grade A or higher at a dose equivalent to 20 mg omeprazole/day, and/or regurgitation), hiatal hernia of > 4 cm axial length, or Barrett's esophagus.
- Other concomitant surgical procedures are scheduled; e.g., cholecystectomy.
- Inflammatory bowel disease.

There is a strong recommendation, though it is not mandatory, to perform a preoperative gastroscopy, especially to provide relevant information with respect to GERD.

2.4. Recruitment strategy

If a patient's referral makes it likely that he/she is eligible for participation in BEST, he/she will receive written information about the trial by mail. There are local variations, including medical bariatric units, but typically the patient will first attend a group lecture with general information regarding the different types of bariatric surgery and expected outcomes and risks. At this meeting, the patient will also receive information about BEST. At their eventual appointment with a surgeon, further information and an opportunity to ask questions will be given. If the patient is eligible and willing, he/she will sign the informed consent form and be included.

There is no economic incentive to participate in BEST for either the participants or surgeons/centers. Funding received will be used exclusively to facilitate and optimize data collection and analysis.

For recruitment of patients, there has been no press release or advertising to the general public, but there is a trial web site (www.beststudien.se) where those included as well as potential participants can receive detailed information.

2.5. Assignment of interventions/randomization

The randomization sequence is generated using Stata® version 12.1, with a fixed block size of 10. Patients will be randomized at the ratio of 1:1, and stratified according to the participating clinics. The randomization is centrally distributed via a computerized system within SOReg.

2.6. Blinding

The surgeon performing the operation will be aware of the group allocation a maximum of one day before surgery. For safety reasons, patients will not be blinded to the surgical method used. Typically, they will be informed about their allocation immediately after surgery. However, upon request, they can be informed a maximum of one day before surgery.

2.7. Interventions/surgical technique and considerations

The LGBP will be performed with an antecolic-antegastric Roux-limb according to the Lönroth technique (Fig. 1) [10,11]. The gastric pouch is created using 3–4, 45 mm linear staples, giving a pouch volume of approximately 20–30 ml. Both the gastro-jejunostomy and the jejunojejunostomy (JJ) are created with a combination of linear stapling and hand-sewn closure of the remaining opening. The JJ is created by double or single stapling, which might be ante- or retrograde as documented. The Roux-limb is typically 120 cm (100–150 cm), and the biliopancreatic limb is 50–75 cm. Mesenteric defects are closed and either hand sewn with non-resorbable sutures or closed with clips.

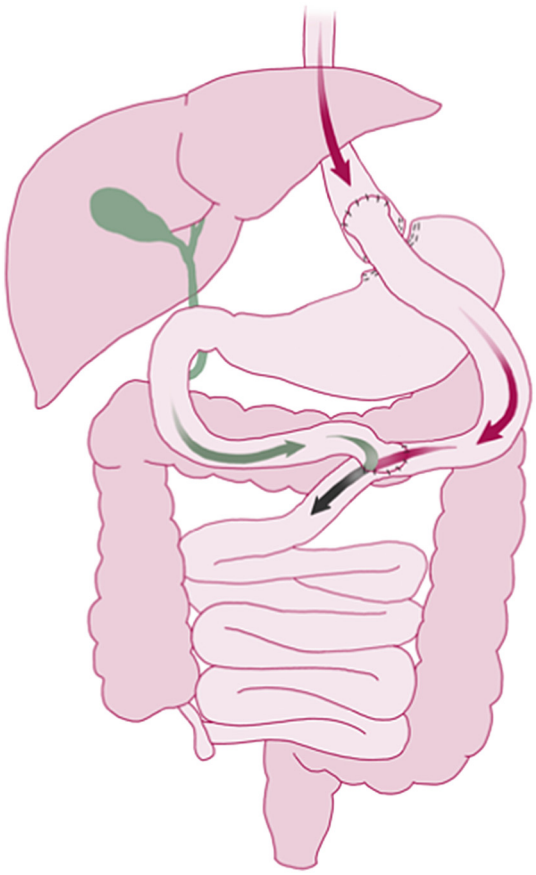

Fig. 1. Laparoscopic Roux-en-Y Gastric Bypass, (Lönroth technique)

Particular care will be taken to avoid kinking of the JJ when closing the mesenteric defect at the JJ.

The LSG is constructed by resection along the lesser curve of the stomach over a 35-36Ch bougie (Fig. 2) [12]. The type of staples used are at the discretion of the surgeon, but must be documented. The resection of the stomach starts 4–6 cm from the pylorus and ends approximately 1 cm from the angle of His, with special care taken not to create a stricture at the angulus of the stomach. Over-sewing of the staple line or buttressing are optional, but the technique used must be documented.

If a hiatal hernia is observed, this should be documented. Hernias with an axial length of 2–4 cm should be taken down, and it is recommended that the hiatal opening is narrowed with a cruroplasty in order to reduce the risk of herniation. If the hernia has an axial length exceeding 4 cm, the patient is excluded from the trial and the surgeon proceeds in the way deemed appropriate.

If complicating circumstances appear during surgery prohibiting or complicating performance of the allocated technique, the patient may be excluded from the trial. The operation will then progress at the surgeons' discretion. Complicating findings may include but are not limited to severe adhesions or anatomical aberrations.

All participants will receive antibiotic prophylaxis and thrombosis prophylaxis according to local guidelines. All participants will be treated with proton pump inhibitors for one month postoperatively (20 mg of omeprazole or pantoprazole once daily). Any further such treatment will be decided based on clinical symptoms or findings.

Postoperative supplementation with vitamins and minerals will be prescribed at a minimum in accordance with the Nordic recommendations [13]: iron 60 mg daily; vitamin B12, 1 mg daily; calcium/vitamin D, 500 mg/800 IE daily; and a multivitamin containing a minimum of 1.4 mg thiamin, 400 μg folate, and 9 mg zinc taken twice daily.

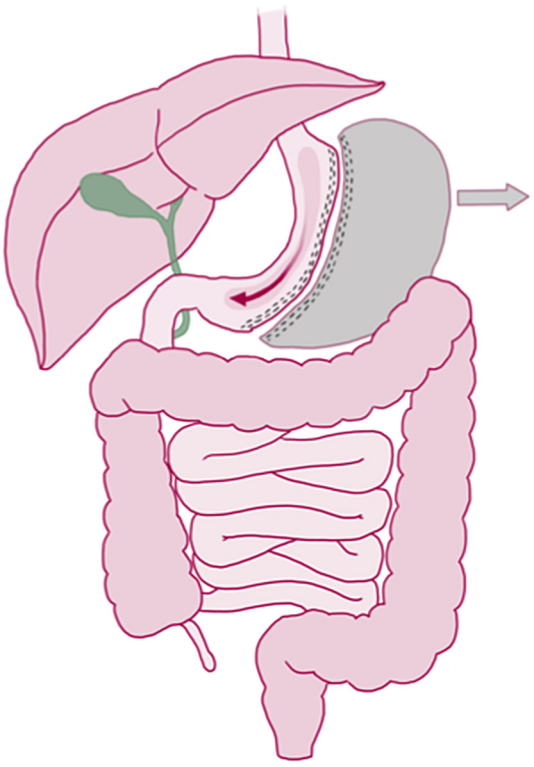

Fig. 2. Laparoscopic Sleeve Gastrectomy

2.8. Data management

Baseline data regarding demographics and health parameters will be collected by the participating centers using standardized questionnaires and measurements. The registration of the collected data is facilitated by the central computerized system of the Scandinavian Obesity Surgery Registry (SOReg), which also constitutes the case report form (CRF) for BEST. SOReg contains data from all operating centers for bariatric surgery in Sweden since 2013 and from all but two centers in Norway since 2017. The Swedish audits show an accuracy of data of > 98% [9].

Post-surgical clinical health examinations of participants will be conducted 6 weeks and 1, 2, and 5 years postoperatively. Key parameters include weight, blood analyses, and completed quality of life questionnaires (RAND-36, OP (Obesity Problem scale) and EQ-5D-5 L) as well as any complications that arise and the presence of comorbidities. These trial time points are the standard SOReg time-points, which simplify the documentation of data and should minimize drop-outs. It also enables comparisons between randomized and non-randomized patients in the registry.

Several other Swedish and Norwegian national health registries will be used to facilitate the follow-up of patients with SC's. In general, these registries have almost 100% coverage since individuals can be monitored using the unique personal identification number assigned to every person residing in Sweden and Norway.

For collection of data on primary and secondary outcomes, the following registries will be used: Scandinavian Obesity Surgery Registry; Patient Registry; Prescribed Drug Registry; Critical Care Registry, registries of the Social Insurance Agency; National Diabetes Registry; and Cancer Registry.

The trial's primary objectives will be evaluated after 5 years of follow-up. Data from SOReg will be complemented and cross-checked against the national registries, enabling identification of significant

Table 1
Substantial complications that may have a significant and/or longstanding effect on patients' health and/or everyday life.

Substantial complication	Explanation
Death	Death associated with bariatric surgery
Intervention under general anesthesia	Clavien-Dindo 3b or higher [14] for complications associated with the bariatric intervention (excluding gallstone interventions, preexisting hernia at bariatric surgery, and plastic surgery for removal of excess skin). A sub analysis of negative diagnostic laparoscopies is planned
Admission to intensive care unit (ICU)	Admission to ICU due to complications from the obesity surgery
Revision surgery	Change of surgical method; reversal or significant change to the original method. Revision surgery will be done according to clinical practice. The indication for revision surgery (e.g. unsatisfactory weight loss or gastro-esophageal reflux [GERD]) should be documented
In-hospital care	Due to complications related to the surgery (excluding observation without diagnosis for < 24 h)
Frequent and severe food-related problems	Affecting everyday living for at least 3 months (such as hypoglycemia, pain, vomiting, nausea) in accordance with the "BEST/SOReg template" available on the website
Severe postprandial hypoglycemia	Hypoglycemic episodes associated with loss of consciousness/seizures or requiring drug treatment
Severe GERD	GERD symptoms that cannot be controlled with medication (e.g., heartburn, volume reflux). Barrett's esophagus (with endoscopy performed within 2 years before surgery showing absence of Barrett)
Serious nutritional problems	Need for enteral (using a feeding tube to the gastrointestinal tract) or total/supplemental parenteral nutrition
Chronic abdominal pain	Pain (> 6 months) requiring regular (> 1 time/week) medication with opioids (ATC code N02A, including tramadol and codeine) and/or abdominal pain significantly affecting daily life (prohibiting normal work, leisure activities, etc.)
Substantial micronutrient deficiencies	Clinically relevant, symptomatic, vitamin and/or mineral deficiencies. (Mandatory laboratory analyses include: B-Hb, B-HbA1c, S-cobalamine, S-folate, S-ferritin, S-CRP, fP-glucose, Lipids, Creatinine and S-25-OH-vitamin D)
Severe anemia	Hemoglobin < 100 g/l in women and < 110 g/l in men
Other substantial complication	Not pre-defined but, after assessment by a reference group, deemed to be a substantial complication related to the surgery

adverse events in patients that declined their follow-up.

Extended follow-ups of the patients beyond the 5-year trial period are planned in order to evaluate the long-term health effects of the two methods.

2.9. Trial outcomes

2.9.1. Primary outcomes

1. For evaluation of superiority, SC's will be identified from the national registries during 5 years of follow-up. The superiority margin for LSG in comparison to LGBP is set to a reduction in adverse events of 35%. SC's (Table 1) were chosen due to having a significant and/or longstanding effect on patients' health and/or everyday life.
2. For evaluation of non-inferiority, the total percentage of weight loss over 5 years in patients operated on with LSG as compared to LGBP will be evaluated with regards to the non-inferiority margin of 5%.

2.9.2. Secondary outcomes

The trial's secondary outcomes include arterial and venous cardiovascular events, hypertension, dyslipidemia, diabetes improvement and/or remission, quality of life, psychiatric morbidity, and alcohol consumption. In the longer time-frame, the incidence of malignancies, fractures, and GERD as well as overall mortality and cause of death will be evaluated. We will also analyze nutritional status regarding vitamins and minerals. Secondary outcomes also include health care effectiveness and cost-effectiveness analyses. The primary and secondary outcomes in the two groups will also be compared within relevant subgroups.

3. Statistical methods

3.1. Sample size and power

The sample size calculation is based on evaluation of the primary objectives. Based on retrospective analyses of data from SOReg, it is assumed that 13% of patients who undergo LGBP will have SC's (as defined in the trial outcomes) over 5 years. It is further assumed that this risk is 35% lower in patients in the SG group. Based on these assumptions, it is estimated that a total of 2100 patients (1050 in each group) will be required to detect this difference with 80% power at a two-sided 2.5% significance level using Cox proportional hazards regression model.

The initial power calculation of SC's estimated a 5% incidence for LGBP. However, new SOReg data demonstrated a SC frequency of around 13% over 5 years, which prompted a recalculation and reduction in the number of study participants needed.

The sample size of 2100 patients will also give $> 95\%$ power to evaluate non-inferiority defined as 5%-unit differences in % total weight loss over 5 years between the two groups, assuming 15% standard deviation in weight loss over the follow-up with a two-sided 2.5% significance level.

3.2. Principles of analysis

The primary conclusions from this study will be based on analyses conducted under the principle of intention-to-treat. Thus, all randomized patients, with the exception of those who withdraw their consent, will be included in the analyses. Patients who are randomized but withdraw their consent will be censored at the date of withdrawal.

For primary outcomes, a two-sided 2.5% significance level will be used to define statistically significant differences. The corresponding confidence intervals to be reported will be 97.5%. The use of a 2.5% significance level is due to having two primary endpoints.

There will not be any interim analyses on primary outcomes. A Data and Safety Monitoring Committee (DSMC) is responsible for monitoring adverse events and complications during the trial follow-up, as described below.

3.3. Statistical analyses

Summary tables (descriptive statistics and frequency tables) will be provided for all baseline, outcome, and safety variables as appropriate. Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation, median, range, and interquartile ranges). Frequency counts and percentage of subjects within each category will be provided for categorical data. The primary conclusions will be based on a model, which includes study center as a covariate together with indicator for treatment. Exploratory analyses will be conducted using sex, age, body mass index, smoking, and diabetes at baseline as covariates.

Incidence of SC's will be analyzed with time-to-event models. Time from primary surgery to first SC will be recorded. Kaplan-Meier estimates of the cumulative incidence of adverse events will be calculated

for both treatment groups. Treatment effect will be calculated as a hazard ratio, together with corresponding confidence intervals and the *p*-value for the test of equal hazard ratio, from the Cox proportional hazard regression model. The proportionality assumption of the Cox models will be evaluated graphically using "log-log" plots.

For non-inferiority, the difference in weight loss between treatment groups and its confidence interval will be calculated and evaluated against the non-inferiority margin of 5%. The weight loss difference at the 5-year follow-up will be estimated with a multilevel, mixed-effect, regression model utilizing body-weight measurements at all available time points. This model takes into account the repeated measurements nested within patients over time. All randomized patients will be included in this analysis, independent of the availability of body weight data during the previous follow-up.

For secondary outcomes, the incidence of comorbidities during the follow-up will be evaluated with time-to-event models. Continuous variables mixed-effect regression models will be used to evaluate differences between the treatment groups.

A priori defined subgroup analyses will be conducted by sex, age, diabetes, and baseline BMI for all outcomes. Age will be categorized in three groups (18–29, 30–45, and $>$ 45 years), and BMI in two groups ($<$ 42 and $\geq$ 42 kg/m^2).

3.4. Trial follow-up and missing data

In the evaluation of the incidence of SC's, we expect close to 100% retention rate because data will be collected through the national register linkage. Patients who withdraw consent will be censored right after their withdrawal in time-to-event models. Patients who emigrate from Sweden or Norway, or die before the end of the 5-year follow-up will be censored at the date of emigration or death, respectively. All other patients not experiencing SC's during the study follow-up will be censored at the date of their individual 5-year follow-up. The primary conclusions of the study will be based on intention-to-treat analyses of data on all randomized patients who did not withdraw their consent.

For evaluation of non-inferiority, a sensitivity analysis will be conducted using both multiple imputation of missing body weight data and last-observation carried forward imputation. These results will be reported together with the primary analysis.

3.5. Milestones

Participant recruitment is planned to be completed by the end of 2019. The five-year follow-up for all participants should therefore be completed in 2024. Analyses and the results on primary outcomes will be reported during 2025.

3.6. Monitoring

The trial has an independent DSMC, with 3 members.

The DSMC will review data for the primary endpoints and safety at 30 days and after 1, 2, 3, and 4 years of follow-up. These data will be presented to the DSMC by the trial monitor and independent statisticians. Any additional information of interest will be provided by the principal investigator. Presentations will be blinded so that treatment groups cannot be identified. The DSMC will inform and advise the Clinical Trial Study Committee (CTSC) regarding any concerns about surgical performance or outcomes in either group.

3.7. Auditing

The surgical technique was audited by the BEST CTSC by reviewing videos of both surgical techniques (LGBP and LSG) used at each participating center. The videos were available to members of the CTSC, but one member of the committee was primarily designated to review them.

Data audit will occur both through the standardized audit procedure of the SOReg and by designated BEST regional coordinators. The SOReg audit includes visits by representatives from the registry at participating centers biannually, with control of data on randomly selected patients. Also, control of participant data with outlying datasets, as well as cross-checking of certain data with national registries, will be performed. The regional coordinators regularly visit all centers in their designated area for coordination and auditing. The regional audit is focused on minimizing missing data as well as ensuring the accuracy of registered data.

3.8. Ethics

BEST will be conducted in accordance with the ethical standards of the Helsinki declaration, and was approved by the Regional Ethical Review Board at the University of Gothenburg on June 25, 2015 (#0.478–15). Amendments needed for significant changes to the original plan have been approved before implementation.

Potential participants are informed as outlined above. If they consent to participate, they sign an informed consent form, but are free at any time to withdraw their consent without explanation. Because only patients that fulfill the criteria for bariatric surgery are asked to participate and there is no economic gain, there are no underlying incentives to participate that may skew the results.

All data will be analyzed and presented on a group level so that no individual patient can be identified.

3.9. Dissemination

The results and analyses of BEST are planned for publication in peer-reviewed scientific journals. Among the planned publications are the following: perioperative results (30-day mortality and morbidity), 2-year results (weight and adverse events), and 5-year results (weight and adverse events; cost-effectiveness). Subgroup analyses, etc., are expected to generate data for further publications as well as the 10-, 15-, 20-, and 30-year results.

3.10. Trial status

Enrollment started in the fall of 2015 at five centers. Additional centers have been recruited and, to date, there are 18 participating centers in Sweden and three in Norway. Recruitment of additional centers is ongoing. The first patient underwent surgery on Oct 6, 2015. As of Dec 19th, 2018, 916 randomized patients had undergone surgery.

The protocol has been registered in the Clinical Trials database: NCT 02767505.

4. Discussion

Due to well documented effects on weight and comorbidities, the number of bariatric surgical procedures has increased during the past decades. In 2016, there were almost 700,000 bariatric procedures performed world-wide [15]. In Scandinavia, LGBP has long been considered the gold standard technique, with well-documented effects such as marked and sustained weight-loss, and positive effects on obesity-related comorbidities including remission of diabetes. Moreover, short- and long-term complications are well described. Over the past years, there has been an increase in the number of LSG performed in Scandinavia as well as in the rest of the world. LSG was initially used as a first stage procedure in biliopancreatic diversion with duodenal switch in patients with super-obesity [16,17]. However, after demonstrating unexpectedly good results in terms of weight-loss in most patients, the procedure has been increasingly used as a stand-alone procedure. Potential advantages of LSG compared to LGBP include technical simplicity, shorter operating time, and a lower risk of adverse events such as internal herniation, chronic abdominal pain, and reactive hypoglycemia. Currently the LSG constitutes approximately 50% of all bariatric procedures performed worldwide [18].

Most comparisons between LSG and LGBP, including case series and small- to medium-sized RCT's, report similar results regarding important outcomes such as weight reduction and resolution of comorbidities [1,7,8,19,20]. However, level 1 evidence for the superiority of either LSG or LGBP is still lacking for weight-loss, SC's, and effects on comorbidities, particularly during long-term follow-up. The lack of reported differences between outcomes may be explained by either a true similarity, or that studies have been underpowered to detect differences that do in fact exist.

With the increasing volume of surgeries and experience, the incidence of short- and long-term SC's after bariatric surgery is low. In order to identify any differences between groups, large sized studies are needed. In the BEST study, we will use a national registry with almost 100% coverage to conduct a multicenter RCT. Based on retrospective analysis of register data on SC's, our power calculation indicates that inclusion of 2100 patients is needed in order to address the two primary hypotheses raised. This number is by far larger than earlier RCT's comparing LGBP with LSG, even if data are pooled, and will therefore enable us to better address the hypotheses raised.

The large number of included patients will also enable comparisons between the techniques within subgroups of participants. Although we may lack power for definitive conclusions, we expect to be able to compare outcomes at various BMI and age levels, in different sexes, and in patients with or without diabetes. Assuming a prevalence of 15% of patients with diabetes [21], we expect about 300 diabetic patients to be randomized and, depending on the effect-size, we should be able to compare diabetes remission and improvement in HbA1c between the groups.

BEST is a register-based RCT, which provides several advantages. First, data on all patients undergoing bariatric surgery during the inclusion period in Sweden and Norway will be captured in the registry, regardless of whether or not they are included in the trial. We will therefore have the possibility of comparing included versus non-included patients during the same time period. Moreover, use of the registry as the CRF simplifies and secures the collection and storage of data. Finally, there is an established routine for audit in place, which should maintain a high level of accuracy of the data.

Another advantage is the possibility to cross-match the BEST/SOReg registry data to other national health care registries, which is enabled by the use of personal identification numbers given to all individuals in Sweden and Norway. For example, this means that we can cross-match data from the National Diabetes Registry and the Prescribed Drug Registry with BEST data, and thereby receive information on whether patients receive any pharmacological treatment for diabetes and their HbA1c levels, even if they decline to attend their follow-up visits after bariatric surgery.

BEST is a pragmatic study, meaning that the results should be representative of “real life experience”. The BEST-protocol requires a high, but realistic surgical standard. Although every procedure may not be perfectly performed in all patients at all centers, the multicenter design provides the strength of generalizability, representing current bariatric surgical practice in Scandinavia.

One challenge is that many patients have a preconceived opinion regarding the preferred procedure, making inclusion difficult. To mitigate this, we aim to provide information about BEST at the earliest possible stage, and consistently communicate equipoise between LSG and LGBP by all team members, as well as in information given at the trial web site.

Long-term follow-up after bariatric surgery is challenging. Therefore, the CTSC is working together with the SOReg to strengthen structures for long-term follow-up in all regions, which will be an ongoing endeavor as the trial progresses.

An additional limitation of this trial refers to assessment of any development of GERD. At the drafting of BEST, the awareness of the potential seriousness of this problem was not as widespread as it is today, and it was therefore deemed neither necessary nor feasible for all participants to undergo a preoperative gastroscopy. During the progression of the trial there has been a strengthening of the recommendations for preop gastroscopy and subsequently an increasing number of participants undergo gastroscopy. We expect that by this change, BEST will provide data on a large number of patients undergoing upper endoscopy before surgery. We are also assessing the use of PPI before and after surgery. While this might be considered a blunt measure of GERD, we consider this information relevant in order to avoid underestimation of the prevalence of GERD.

Inclusion in BEST is limited to BMI 35–50 kg/m^2 which may be perceived as a limitation for generalization. However, this BMI range cover the majority (87%) of the bariatric surgery patients in Scandinavia. Since BMI > 50 can be considered an independent risk factor for adverse events, we believe that this limitation will help clarify the comparison between LGBP and SG rather than confound it.

We firmly believe that this large, randomized, pragmatic, multicenter trial is the appropriate design for obtaining valid data that will guide future recommendations of LSG or LGBP. In BEST, we combine the scientific strength of the randomized trial with the pragmatic, real-life design of a registry study. BEST also has the potential to provide information on patient outcomes in relevant subgroups and thereby further increase the knowledge gained from the study.

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Declaration of Competing Interest

AT is recipient of lecture honoraria from Ethicon Endo-Surgery and Fresenius Kabi and member of Advisory board for Ethicon Endo-Surgery and NovoNordisk. TO has received lecture honoraria (to institution) from Johnson & Johnson, NovoNordisk, Mölnlycke and Merck, and member of Advisory Board for Johnson & Johnson and NovoNordisk. JO is a member of the Advisory Board for Johnson & Johnson and Vifor Pharma.

The remaining authors declare that there are no conflicts of interest.

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