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**Efficacy and safety of one anastomosis gastric bypass versus Roux-en-Y gastric bypass for obesity: a randomised, open-label, multicenter trial of non-inferiority (YOMEGA trial).**

Prof Maud Robert MD, Department of Digestive and Bariatric Surgery, Hospices Civils de Lyon, Hôpital Edouard Herriot, 5 Place d'Arsonval, 69437 Lyon, France

Dr Philippe Espalieu MD, Hôpital Privé de la Loire, 39 Bd de la Palle, 42100 Saint-Etienne - France

Dr Elise Pelascini MD, Department of Digestive and Bariatric Surgery, Hospices Civils de Lyon, Hôpital Edouard Herriot, 5 Place d'Arsonval, 69437 Lyon, France

Prof Robert Caiazzo MD, General and Endocrine Surgery Department, Huriez Hospital, 2 Av. Oscar Lambret, 59037 Lille, France

Dr Adrien Sterkers MD, Department of Digestive, Hepatobiliary Surgery, Centre Hospitalier Privé Saint Grégoire, 6 Bd de la Boutière, 35760 Saint Grégoire, France

Dr Lita Khamphommala MD, Department of Digestive, Hepatobiliary Surgery, Centre Hospitalier Privé Saint Grégoire, 6 Bd de la Boutière, 35760 Saint Grégoire, France

Dr Tigran Poghosyan MD, Digestive Surgery Department, Hôpital Européen Georges Pompidou, 20 Rue Leblanc, 75908 Paris, France

Prof Jean-Marc Chevallier MD, Digestive Surgery Department, Hôpital Européen Georges Pompidou, 20 Rue Leblanc, 75908 Paris, France

Dr Vincent Malherbe MD, General and Endocrine Surgery Department, Hôpital Privé Drôme et Ardèche, 180 Rue Pierre Curie, 07500 Guilhaing-Granges, France

Dr Elie Chouillard MD, Department of General and Digestive Surgery, Centre Hospitalier Intercommunal Poissy – Saint-Germain-en-Laye, 20 Rue Armagis, 78100 Saint-Germain-en-Laye, France

Prof Fabian Reche MD, Digestive Surgery Department, CHU Grenoble, BP 217, 38043 Grenoble, France

Dr Adriana Torcivia MD, Department of Digestive, Hepatobiliary Surgery, Hôpital Pitié Salpêtrière, 47 Bd de l'Hôpital, 75013 Paris, France

Prof Delphine Maucort-Boulch MD, Biostatistics Department, Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, 165, Chemin du Grand Revoyet, 69495 Pierre Benite, France

Dr Sylvie Bin-Dorel MD, Clinical Research Unit, Hospices Civils de Lyon, 162 Av. Lacassagne, 69424 Lyon, France

Carole Langlois-Jacqueq MSc, Biostatistics Department, Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, 165, Chemin du Grand Revoyet, 69495 Pierre Benite, France

Dr Dominique Delaunay PhD, Department of Digestive and Bariatric Surgery, Hospices Civils de Lyon, Hôpital Edouard Herriot, 5 Place d'Arsonval, 69437 Lyon, France

Prof François Pattou MD, General and Endocrine Surgery Department, Huriez Hospital, 2 Av. Oscar Lambret, 59037 Lille, France

Prof Emmanuel Disse MD, Department of Endocrinology, Diabetology and Nutrition, Specialized Center for Obesity Management, Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, 165, Chemin du Grand Revoyet, 69495 Pierre Bénite, France

Correspondence to:

Prof Maud Robert MD, Department of Digestive and Bariatric Surgery, Hospices Civils de Lyon, Hôpital  
Edouard Herriot, 5 Place d'Arsonval, 69437 Lyon, France, e-mail: [maud.robert@chu-lyon.fr](mailto:maud.robert@chu-lyon.fr), Phone: +33 4 72  
11 62 63

## Summary

### Background

One Anastomosis Gastric Bypass (OAGB) is increasingly used in the treatment of morbid obesity. The efficacy and safety outcomes of this procedure remain however debated. We report the results of YOMEGA, a randomised trial comparing the outcomes of OAGB vs standard Roux-en-Y gastric bypass (RYGB).

### Method

This prospective, multicenter, randomised trial of non-inferiority was conducted in nine French obesity centers. The primary endpoint was excess body mass index loss (EBL) % at 2 years. Metabolic efficacy and safety were secondary endpoints. A per protocol analysis was performed.

### Findings

From May 2014 to March 2016, 253 patients were randomly assigned to OAGB (n=129) or RYGB (n=124). After 2 years, mean EBL% was -87.9% in the OAGB arm (SD 23.6) and -85.8% in the RYGB arm (SD 23.1) confirming non-inferiority (mean difference -3.3% [-9.1;2.6], non-inferiority limit 7%). Mean decrease in HbA1c was significantly higher in the OAGB arm (-1.2% +/- 1.4 vs -0.6% +/- 0.8, p=0.0037). Incidence of diarrhea was significantly higher in the OAGB arm (19.7%, 14/71) vs. RYGB (7%, 5/71, p=0.04; OR= 3.07, IC[1.04;9.08]) with a higher median steatorrhea (OAGB: 11 g of lipids/ 100g stools, IQR 7.9-12.8 vs. RYGB: 7 g, IQR 5.5-10, p=0.0002). We observed 18.9% (n= 11/58) of gastritis and 10.3% (n=6/58) of esophagitis in the OAGB arm vs. 6.3% (n=4/63) and 3.1% (n=2/63) for RYGB. Sixty-six Serious Adverse Events (SAE) related to surgery were reported (RYGB:24 vs OAGB:42, p=0.042), of which 21.4% (n=9/42) were nutritional complications in the OAGB arm versus none in the RYGB arm (p=0.0034).

### Interpretation

OAGB is not inferior to RYGB regarding weight loss and metabolic improvement at 2 years. Higher rates of diarrhea, steatorrhea and nutritional adverse events were observed with a 200cm biliopancreatic limb OAGB, suggesting a malabsorptive effect.

ClinicalTrials.gov Identifier: NCT02139813

## Introduction

Obesity and its comorbidities remain a priority public health issue for most countries worldwide.<sup>1</sup> Bariatric surgery has now demonstrated through several prospective trials and meta-analysis its efficacy, not only in terms of weight loss, but also glycemic control and reduction in cardiovascular risk.<sup>2-5</sup> Since the early 2000s, the number of bariatric procedures has increased exponentially.<sup>6</sup> In parallel, the surgical techniques have evolved with the objective to find the best procedure in terms of weight loss and metabolic control that is associated with the fewest number of side effects and complications, and decreased invasiveness.<sup>7</sup> Most learned societies have published guidelines regarding validated bariatric procedures,<sup>8,9</sup> but the many emergent techniques are not all well evaluated in terms of outcomes and safety.

With more than 40 years of practice, the Roux-en-Y Gastric Bypass (RYGB) remains one of the gold standard procedure for patients with morbid obesity and metabolic disorders in most of the reference centers.<sup>10</sup> More recently, a modified gastric bypass that consists of a single gastro-jejunal anastomosis between a long gastric pouch and a jejunal omega loop has been described.<sup>11</sup> This new procedure, initially called “mini-gastric bypass” or “One Anastomosis Gastric Bypass” (OAGB), seemed to have the advantage of being less technically demanding and potentially less morbid. Weight loss and metabolic outcomes initially published were as good as those reported for the RYGB or even better.<sup>12-15</sup> Nevertheless, OAGB, which is derived from the loop gastric bypass initially described by Mason and Ito is considered by many surgeons at risk of biliary reflux and anastomotic ulcers.<sup>16-19</sup> Many surgeons who do not perform the procedure also fear the risk of gastric and esophageal cancer.<sup>20-22</sup> Published data essentially come from retrospective studies and one recent metaanalysis,<sup>23</sup> although two randomised trials comparing OAGB to RYGB have been reported.<sup>12,15</sup> The first was published in 2005 and included 80 patients.<sup>12</sup> The authors concluded that OAGB is a simpler and safer procedure at 2 years follow-up. However, the statistical power of this study and, in particular the methodology used to calculate the sample size, is open to criticism. The second randomised trial was recently published,<sup>15</sup> and compared 200 OAGB to 200 RYGB and 200 Sleeve Gastrectomies (SG). The authors concluded that OAGB achieved better weight loss and remission of comorbidities compared to the two other procedures. Nevertheless, the methodology of this trial is also questionable with an obvious lack of data regarding selection of patients and biological outcomes, but also missing data were not reported. Therefore, despite strong initial enthusiasm that spread rapidly around the world, the value of this procedure remains debated. In the absence of high-level evidence regarding the efficacy and safety of OAGB, we conducted a randomised controlled trial that compared it to the validated RYGB.

## Research in context

### Evidence before this study

We searched PubMed from January 1, 2000 and November 1, 2018 for randomised controlled trials comparing OAGB to RYGB. We also used the following search terms: “One anastomosis gastric bypass”, “minigastric bypass”, “omega loop gastric bypass”, “Roux-en-Y gastric bypass”, “bariatric surgery”, “biliary reflux”, “malnutrition”. Published data essentially come from retrospective studies including one recent meta-analysis, suggesting similar weight loss and metabolic outcomes with both procedures, or even better outcomes with OAGB. To the best of our knowledge, two randomised trials comparing OAGB to RYGB have been published but none had previously published protocols on official sites and they do not meet high quality criteria. The first

of these published randomised trials had a small sample size that was calculated on the basis of a difference in operative time although they concluded on the efficacy and safety; both procedures achieved similar weight loss and metabolic outcomes at 2 years, OAGB appearing as a simpler and safer procedure. The methodology of the second randomised trial comparing OAGB to RYGB and SG is also criticable, with an obvious lack of data regarding selection of patients, biological outcomes, but also missing data that were not reported. Nevertheless, there is still a controversy regarding the risk of dysplastic modifications of esophageal and gastric mucosa due to biliary exposure after OAGB, as well as a potential higher nutritional risk.

#### **Added value of this study**

This multicenter randomised trial has been designed to answer controversial issues regarding weight loss, metabolic outcomes, and most of the safety questions regarding gastrointestinal and nutritional consequences. The findings indicate that OAGB is not inferior to RYGB in terms of weight loss and metabolic improvement at 2 years. However, the higher incidence of diarrhea, steatorrhea, and nutritional adverse events observed with OAGB indicate that there is a nutritional risk associated with this procedure when the biliopancreatic limb is 200 cm long. Endoscopic findings at 2 years of follow-up reporting a 15.5% rate of bile exposure in the stomach in the OAGB arm advocate for other studies with endoscopic controls over the long term.

#### **Implications of all the available evidence**

The results of the present study support the efficacy of OAGB in terms of weight loss and metabolic improvement as compared to the validated RYGB, and is in favor of a stronger malabsorptive effect. The greater nutritional risk observed with a 200 cm biliopancreatic limb requires close follow-up by physicians with specific bariatric training. Endoscopic findings confirm bile exposure of esophageal and gastric mucosa after OAGB. Other studies with long-term follow-up are necessary to determine the consequences of biliary exposure in order to dispel ambiguity and avoid any controversy. The present trial also promotes further discussion on potential modifications of the technical aspects of OAGB, such as the biliary limb length, with a view to limit postoperative side effects.

## **Methods**

### ***Study design and inclusion criteria***

YOMEGA trial is a prospective multicenter, open-label, non-inferiority randomised controlled trial, with two arms comparing OAGB to RYGB in terms of weight loss (primary endpoint). Efficacy in terms of metabolic parameters and safety were secondary endpoints (Figure 1). Nine high-volume bariatric institutions (over 150 procedures a year) with a large experience in gastric bypass were involved in the study. Patients were included if their Body Mass Index (BMI)  $\geq 40 \text{ kg/m}^2$  or  $\geq 35 \text{ kg/m}^2$  with the presence of at least one comorbidity (Type 2 Diabetes mellitus – T2D, high blood pressure, obstructive sleep apnea, dyslipidemia, or arthritis), aged between 18 and 65 years, after multidisciplinary evaluation and written informed consent. They benefited from a preoperative upper gastrointestinal (GI) endoscopy with biopsies. History of esophagitis, severe Gastro-Esophageal Reflux Disease (GERD) resistant to Proton Pump Inhibitors (PPI), Barrett's esophagus, and history of previous bariatric surgery were exclusion criteria. Recruitment was from May 2014 to March 2016, and the last visit of the last patient included occurred in March 2018, after a 2-year follow-up. Patients were considered as lost to follow-up if no information was obtained before database lock.

The study was approved by the national ethics committee (CPP Sud-Est IV 14/027) and by the competent authority (Agence Française de Sécurité du Médicament, ANSM 140244B-21).

### ***Primary and secondary endpoints***

The primary endpoint was Excess BMI Loss percentage (EBL%) at 2 years after randomisation defined as (BMI at 2 years - initial BMI) / (initial BMI - 25). The secondary endpoints were assessed at 1, 3, 6, 18, and 24 months of follow-up; these included weight and BMI, as well as the early and late complications and their severity at 2 years. We also assessed the incidence of GERD and diarrhea (Gastro Intestinal Quality of Life Index – GIQLI – self-administered questionnaire), steatorrhea at 6 months (g of lipids / 100g of stools on the 24h stools), dumping syndrome (Sigstad score > 7). Metabolic profile was evaluated by measuring Fasting Glycemia (FG), HbA1c, Triglycerides (TG), High Density Lipoprotein cholesterol (HDL-c), Low Density Lipoprotein cholesterol (LDL-c), and total cholesterol; antidiabetic, antihypertensive and lipid-lowering medications were also recorded. Diabetes remission status at 2 years was defined as complete remission if HbA1c < 6% and fasting glycemia < 5.6 mmol/l without active pharmacological therapy or ongoing procedures, and partial remission if HbA1c < 6.5% and fasting glycemia between 5.6 and 6.9 mmol/l without active pharmacological therapy or ongoing procedures. Nutritional status was assessed via serum albumin, prealbumin, hemoglobin, ferritin, transferrin saturation coefficient, Parathyroid Hormone (PTH), calcemia, and vitamins B1, B9, B12, D. Malnutrition was defined as albumin < 30 g/l and/or prealbumin < 0.20 g/l. A patient was considered as having vitamin deficiency if s/he had at least one of the following: vitamin B1 < 66 nmol/l, vitamin B9 < 6 ng/ml, vitamin B12 < 145 pmol/l, vitamin D < 50 nmol/l, or PTH > 50 pg/ml. Hemoglobin < 12 g/dl was considered as anemia, and iron deficiency was defined as ferritin < 15 µg/l and/or transferrin saturation coefficient < 20%. An upper GI endoscopy was performed at 2 years of follow-up with systematic biopsies to evaluate the histological modifications of the gastric and esophageal mucosa. We also recorded the overall number and type of Serious Adverse Events (SAE) and those related to surgery as well as early (within 30 days) and late (over 30 days) surgical complications. Quality of life was assessed with self-administered questionnaires: the Bariatric Analysis and Reporting Outcome System (BAROS) that has five levels (failure, fair, good, very good, excellent) and the Impact of Weight on Quality Of Life (IWQOL) assessment tool. The IWQOL questionnaire consists of 31 items exploring five dimensions: mobility, self-esteem, social life, working conditions and sexual life, the most pejorative score being 155 whereas the best score is 31.

### ***Randomisation and sample size***

Randomisation was performed at a 1:1 ratio stratified by center with blocks of variable size. Considering a mean EBL% of 60% in the RYGBP group at 2 years,<sup>9,10</sup> the hypothesis was that OAGB would not be inferior to RYGB if the difference in EBL was less than seven percentage points ( $\leq 5$  kg). Assuming a standard deviation of 21% in both groups with a 10 % lost to follow-up, 128 patients per group (256 subjects in total) were needed to conclude to the non-inferiority of OAGB with a statistical power of 80% and an  $\alpha$  risk of 5 %.

### ***Surgical techniques (Figure 2)***

Bariatric procedures were performed laparoscopically and were standardized. RYGB consisted of a small gastric pouch (30 cc), a 150 cm alimentary limb and a 50 cm biliary limb (Figure 2a). Mesenteric defects were closed.

OAGB consisted of a long gastric tube beginning at the landmark of the incisura angularis and calibrated with a 37 French bougie. A single gastrojejunal anastomosis was performed using a linear stapler with a biliopancreatic limb of 200 cm (Figure 2b). A systematic supplementation of multivitamins, iron, calcium, vitamin B12 and D was prescribed associated with 40 mg of PPI and 500 mg of ursodeoxycholic acid during 6 months to prevent marginal ulcer and gallstones.

### **Statistics**

Primary and secondary efficacy outcome analyses were performed in the per protocol population; this included all randomised patients who contributed data excluding patients with major deviation to the protocol (pregnancy, death, withdrawal of consent, switch of surgical procedure). A 90% confidence interval (CI) of the difference for the primary endpoint was determined (one sided 5% alpha level) so that non-inferiority was concluded if the upper bound of this interval was inferior to the non-inferiority limit (seven percentage points). Analyses of secondary outcomes were not corrected for multiple comparisons, so the results cannot be used for hypothesis testing or inference. Comparisons were performed using the Student t-test or the non-parametric Wilcoxon test for quantitative endpoints, and the Chi<sup>2</sup> test or the Fisher exact test for categorical endpoints. For quantitative normal endpoints, the 95% bilateral confidence intervals were given for the mean difference (two sided 5% alpha level). The incidence of Serious adverse events per patient in both groups was compared using the likelihood test from Poisson regression.

Missing data in the primary outcome analysis were imputed with the use of multiple imputation techniques (five imputed data sets)<sup>24</sup> with prediction based on surgical group, gender, age, and weight at baseline. Sensitivity analyses were performed for the primary outcome based on i) the full per protocol population dataset, ii) all the included patients according to their arm randomly allocated, irrespective of actual arm, with multiple imputation, iii) the per protocol population with multiple imputation and addition of seven percentage points to the imputed values in the OAGB arm. Safety end points were assessed in the safety population (all patients included and randomised) in which patients were assigned to the group to which they were randomised.

Analyses were performed using SAS<sup>®</sup> Software version 9.4 (SAS Institute, Cary, NC, US).

### **Role of the funding source**

The clinical research department of the Hospices Civils de Lyon received financial support from the French ministry of Health (Direction Générale de l'Offre de Soins, study number 2013-037) to perform this randomised trial. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. MR, ED, SBD, and DMB had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## **Results**

From May 2014 to March 2016, 253 patients were randomly assigned to OAGB (n=129) or RYGB (n=124), safety population. There were 234 patients who contributed data to the study, per protocol population (n=117 in each arm); 22.5% of patients were lost to follow-up for the primary end-point: an hypothetical weight was therefore imputed to them so as to contribute to the analysed sample (Figure 3). In the per protocol population, mean age was 43.5 years (SD 10.8), mean BMI was 33.8 kg/m<sup>2</sup> (SD 5.6). There were 75.2% of female

(176/234) and 27.5% of Type 2 Diabetic patients (58/211). Characteristics of the study population are presented in Table 1.

### ***Surgical outcomes***

The mean operative time was significantly shorter in the OAGB arm (85 min, SD 35) than RYGB (111 min, SD 42;  $p < 10^{-4}$ ). The median length of stay was 5 days for both groups (OAGB: IQR 4-5, RYGB: IQR 4-6). Intraoperative complications occurred in 4 cases in the RYGB group (hemorrhage  $n=3$ , bowel injury  $n=1$ ) vs. 8 cases in the OAGB (hemorrhage  $n=4$ , bowel injury  $n=2$ , stapling of the nasogastric tube  $n=2$ ). In the RYGB arm two patients had a switch of technique: one had a sleeve due to severe bowel adhesions and the other one had OAGB due to the thickness of the mesenteric fat and intraoperative difficulties. In the per protocol population, the rates of early and late surgical complications in the RYGB arm were 6.8% (8/117) and 12.8% (15/117) versus in the OAGB arm 3.4% (4/117,  $p=0.24$ ) and 16.2% (19/117,  $p=0.45$ ) respectively. Among early surgical complications, we observed in the RYGB arm ( $n=8$ ) 1 bowel obstruction, 2 wall abscesses, 1 wall hematoma, 1 haemoperitoneum, 2 trocar hemorrhages and 1 severe constipation; only 2 of them were complications over Grade 3 of Dindo-Clavien score and required surgical management. In the OAGB arm, among early surgical complications ( $n=4$ ) we reported 1 peritonitis, 1 stenosis of the gastro-jejunal anastomosis, 1 wall hematoma, 1 hematoma of the gastro-jejunal anastomosis; only one of them was over Grade 3 of Dindo-Clavien score and required a surgical management.

### ***Weight loss outcomes***

Mean EBL% at 2 years was -85.8% in the RYGB arm (SD 23.1) and -87.9% in the OAGB arm (SD 23.6; Figure 4). The mean difference of EBL% was -3.3 percentage point [-9.1;2.6] in favor of OAGB and the upper bound of confidence interval was 2.6 percentage point ( $p$  for non-inferiority=0.0024). This was lower than the non-inferiority limit of seven percentage point, confirming that OAGB is not inferior to RYGB in terms of EBL%. This result was confirmed by the sensitivity analyses (maximal upper bound was 3.9 in the first scenario,  $p=0.007$ ; 2.2 in the second scenario,  $p=0.002$ ; 5.9 in the third scenario,  $p=0.024$ ). Mean % total body weight loss was -35.4% (SD8.1) in the RYGB arm versus -37.1% (SD10.3) in the OAGB arm, confirming non-inferiority (mean difference -1.4% [-3.7;0.99],  $p$  for non-inferiority  $<10^{-4}$ ).

### ***Metabolic outcomes***

In the per protocol population, mean HbA1c at 2 years was not statistically different in the OAGB arm (5.2%, SD 0.6) than in the RYGB arm (5.5%, SD 0.7;  $p=0.066$ ). The mean decrease in HbA1c at 2 years was significantly greater in the OAGB arm (-1.2%, SD 1.4) than in the RYGB arm (-0.6%, SD 0.8;  $p=0.0037$ ). This was also significant in the sub-group of patients with T2D; the mean decrease in HbA1c was -2.3% (SD 1.6) in the OAGB group vs. -1.3% (SD 1.02) in the RYGB group ( $p=0.025$ ; Table 2). There was a 60.0% ( $n=12/20$ ) complete T2D remission rate, and a 10.0% ( $n=6/60$ ) partial T2D remission rate in the OAGB group vs. 37.5% ( $n=6/16$ ) and 6.3% (1/16), respectively, in the RYGB group; the proportions of T2D remission were not significantly different ( $p=0.28$ ; Figure 5). There was no significant difference at 2 years between arms in the values and decrease of FG, TG, LDL-C, HDL-C, and total cholesterol (Table 2).



## ***Nutritional status***

In the per protocol population, mean serum albumin and prealbumin values were not significantly different between arms at 2 years: respectively, OAGB: 42.1 g/l SD 3.03 and 0.25 g/l SD 0.05 vs. RYGB: 42.2 g/l SD 3.08 and 0.24 g/l SD 0.04;  $p=0.51$  and  $0.78$ . The incidence of malnutrition at 2 years was also not significantly different (OAGB: 10.8%,  $n=7/65$  vs. RYGB: 16.7%,  $n=10/60$ ;  $p=0.34$ ). There was a significant difference in the mean decrease of hemoglobin in the OAGB arm (-10.3 g/l, SD 20.57) compared to the RYGB arm (-3 g/l, SD 10.07;  $p=0.036$ , Table 3); there was no significant difference regarding the incidence of anemia or iron deficiency (OAGB: 28.3%,  $n=17/60$  vs. RYGB: 36.2%,  $n=21/58$ ;  $p=0.36$ ). We did not find any significant difference neither in the levels of vitamins nor in the frequency of vitamin deficiencies (OAGB: 84.5%,  $n=49/58$  vs. RYGB: 83.3%,  $n=40/48$ ,  $p=0.87$ ) at 2 years of follow-up.

## ***Side effects and endoscopic data***

There was a significantly higher incidence of diarrhea in the OAGB arm compared to the RYGB arm at 3 months (26%  $n=25/96$  vs. 3.2%  $n=3/94$ ,  $p=0.0003$ , OR=11.53; 95%CI [3.03; 43.86]) and at 2 years (19.7%  $n=14/71$  vs. 7%  $n=5/71$ ,  $p=0.04$ , OR= 3.07; 95%CI [1.04; 9.08]). There was also a significantly higher mean steatorrhea in the OAGB arm at 6 months (11 g of lipids/ 100g stools) than in the RYGB arm (7 g of lipids/ 100g stools,  $p<10^{-3}$ ). There was a significantly lower frequency of dumping syndrome in the OAGB arm at 3 months (8.4%  $n=8/95$ ) vs. RYGB (23.9%  $n=22/92$ ,  $p=0.004$ , OR=0.29; 95%CI [0.12; 0.68]), and no significant difference at 2 years (OAGB: 14%  $n=10/71$  vs. RYGB: 15.4%  $n=11/71$ ,  $p=0.82$ , OR= 0.91; 95%CI [0.39; 2.14]). The frequency of GERD was 5.6%,  $n=4/71$  in the OAGB arm vs. 1.4%,  $n=1/71$  in the RYGB arm ( $p=0.5$ ; OR=0.15, 95%CI [0.19; 1.3]). Fifty-two percent of the patients ( $n=121/234$ ) had an upper GI endoscopy at 2 years of follow-up. We observed 18.9% ( $n=11/58$ ) of gastritis and 10.3% ( $n=6/58$ ) of esophagitis in the OAGB arm vs. 6.3% ( $n=4/63$ ) and 3.1% ( $n=2/63$ ) for RYGB. In the OAGB arm, 15.5% of the patients ( $n=9/58$ ) had bile in the gastric pouch vs. none in the RYGB arm, and one case in the same patient of intestinal metaplasia and dysplasia on the gastric and esophageal biopsies was also found (Table 4).

## ***Serious Adverse Events***

At 2 years of follow-up, there were nearly twice as many overall SAE and SAE related to surgery in the OAGB arm ( $n=67$  and  $n=42$ , respectively) as in the RYGB arm ( $n=38$  and  $n=24$ ,  $p=0.009$  and  $p=0.042$  respectively). Among the SAE related to surgery, 21.4% ( $n=9$ ) were nutritional complications in the OAGB arm vs. none in the RYGB arm,  $p=0.0034$  (Table 5). Among these 9 patients with nutritional complications, all had at least one vitamin deficiency and/or malnutrition and/or anemia or iron deficiency (Table 6); the mean absolute weight loss in this subgroup was -58.4 kg (SD -28.8). Most of the SAE in the RYGB arm were hospitalization due to abdominal pain 20.8% ( $n=5$ ), which was not reported in the OAGB arm. There was no significant difference in the proportion of patients with at least one SAE between arms (OAGB: 28/129 (21.7%) vs RYGB: 19/124 (15.3%),  $p=0.19$ ). There was a significantly higher number of SAE related to surgery per patient in the OAGB arm ( $p=0.042$ ). Four patients with OAGB required conversion to RYGB: one for anastomotic leak, one for Wernicke encephalopathy and 2 because of severe biliary reflux reluctant to medical therapy.

### *Evolution of quality of life*

At 2 years of follow-up, the improvement of quality of life was not significantly different in both arms with good, very good and excellent BAROS scores for 54/63 (85.9%) patients in the RYGB arm vs. 63/67 (94%) patients in the OAGB arm ( $p=0.15$ ). Regarding IWQOL scores, all dimensions explored improved significantly with both techniques during the 2-year follow-up ( $p<10^{-4}$ ), except for sexual life which was not assessed due to missing data for this item. There was no significant difference between both arms regarding the scores of the 4 dimensions studied: mean physical function improved by 20.4 points for OAGB (SD 11.9) vs. 21.5 points for RYGB (SD 8.4,  $p=0.57$ ), mean self-esteem improved by 11.2 points for OAGB (SD 9.3) vs. 12.1 points for RYGB (SD 6.8,  $p=0.52$ ), mean public distress improved by 5.5 points for OAGB (SD 6.2) vs. 6.1 points for RYGB (SD 3.8,  $p=0.52$ ) and mean working conditions improved by 4 points for OAGB (SD 3.2) vs. 4.7 points for RYGB (SD 3.3,  $p=0.26$ ).

### **Discussion**

This multicenter randomised trial found that OAGB is not inferior to RYGB in terms of EBL% at 2 years, using a 200 cm biliopancreatic limb in the OAGB arm and a 150 cm alimentary limb and 50 cm biliopancreatic limb in the RYGB arm. This finding is in accordance with the first randomised trial published by Lee et al. in 2005,<sup>12</sup> who reported 64.4 EWL% in the OAGB at 2 years of follow-up vs. 60% in the RYGB arm ( $p=0.154$ ). In this trial, the length of the afferent limb of the OAGB was also 200 cm, which is the standard and initially described in the first report of the technique.<sup>11</sup> In the second randomised trial, which was reported by Ruiz-Tovar et al.,<sup>15</sup> the authors found a significantly higher EBL% in the OAGB group compared to the RYGB group at 2 years of follow-up (103.4% vs. 87.2%,  $p<0.001$ ), which was also found at 5 years. In this study, the length of the biliopancreatic limb was longer; it varied from 200 cm to 350 cm depending on the length of the total bowel following the ratio Biliopancreatic limb 60%/Common limb 40%. The longer afferent limb could explain the greater weight loss observed in this study compared to herein. However, the validity of this result may be questioned; although the authors reported a very low rate of loss to follow-up (9% at 5 years) which has never been reached before in bariatric studies, they do not provide any information regarding missing data for the EBL% which was the primary endpoint.

Regarding glucose homeostasis, in the present study a significantly higher decrease in HbA1c% at 2 years was found in the OAGB arm. Among patients with T2D, a better improvement in HbA1c% in the OAGB group was observed, but despite a trend towards more frequent remission of T2D in this group, the difference was not statistically significant. This may be related to the number of subjects with T2D included as in the meta-analysis reported by Magouliotis et al.<sup>23</sup> T2D remission rate was greater with OAGB. Regarding the lipid profile, no significant difference between arms was found, which is in accordance with the previous meta-analysis.<sup>23</sup>

The good weight loss and metabolic outcomes of OAGB could be explained by the malabsorptive effect of the procedure. This hypothesis seems to be supported by the significant increase rate of diarrhea in the OAGB arm at 2 years, as well as the higher mean steatorrhea. Another strong argument in favor of this malabsorptive effect is the high frequency of nutritional complications among the SAEs related to surgery; all those concerned had at least vitamin deficiency and/or malnutrition and/or anemia or iron deficiency. Despite systematic use of multivitamin supplementation and close follow-up, there was a case of Wernicke encephalopathy in the OAGB arm that required conversion to RYGB. However, it is of note that recent publications have also reported severe

nutritional complications after OAGB. For instance, Genser et al.<sup>25</sup> published 26 cases of severe and refractory malnutrition after OAGB leading to reversal to normal anatomy; the mean delay of reversal surgery was 20.9 months (SD 13.4). Intraoperative measurement of biliopancreatic limb length was assessed in 12 patients: 66.5% of them had a biliopancreatic limb longer than 200 cm – the mean length was 320 cm (SD 63.9) and 87.5% had chronic diarrhea. The mean length of the efferent loop was assessed in 9 patients and was greater than 400 cm meters, suggesting that the length of the biliopancreatic limb is the one that is determinant for nutritional status. Betry et al. also reported 12 cases of severe malnutrition after bariatric surgery and 58.3% of them had a OAGB.<sup>26</sup> The authors found low rates of liposoluble vitamins especially vitamins A and E, 2 cases of Wernicke encephalopathy in the OAGB group, and concluded that OAGB could be a more malabsorptive procedure, tending to demonstrate that it is not a “mini” procedure. In addition, a recent study reported 17 cases of conversion from OAGB to RYGB for severe complications.<sup>27</sup> Among them, 58.8% received preoperative nutritional support for undernutrition. The authors concluded that conversion from OAGB to RYGB allows for weight correction in patients with undernutrition, reduces disabling digestive disorders, and improves the nutritional status of patients. A greater incidence of malnutrition after OAGB compared to RYGB was also reported in the metaanalysis of Magouliotis et al.<sup>23</sup>

In the YOMEGA trial, we did not observe any biological difference between the arms regarding mean serum albumin, prealbumin and vitamin deficiencies. We found a significant decrease in hemoglobin in the OAGB arm compared to the RYGB arm, but the rates of anemia or iron deficiency were not significantly different. One limitation of the study could be that we did not assess specifically levels of vitamins A, E, and K which could be more impacted by fat malabsorption. Regarding the level of vitamin D, another fat-soluble vitamin, there was no significant difference between arms at 2 years, but this vitamin was systematically supplemented after both procedures; furthermore, the number of missing data could have impacted the power of this analysis. Another limitation is that although all patients were supplemented with iron, calcium, and multivitamins, we did not record adherence.

The length of the biliopancreatic limb has been considered as a strong factor implicated in malnutrition. Since 2017, KK Mahawar and others have published several articles regarding the nutritional risk of a too long biliopancreatic limb when performing OAGB, suggesting not to exceed 150 cm.<sup>28-30</sup> In the randomised trial reported by Ruiz-Tovar et al.<sup>15</sup> the length of the biliopancreatic limb was between 200 cm and 350 cm. Surprisingly, the authors did not report a high rate of malnutrition: among the 200 OAGB only 3 subjects presented hypoproteinemia, coinciding with period of illness, and which were satisfactorily managed with a course of hyperproteinated supplements. We are again struck here by the very low rate of complications in each group (4 internal hernia and 3 anastomotic ulcers among 200 RYGB, and 2 uncontrolled biliary reflux, 2 anastomotic ulcers and 3 hypoproteinemia among 200 OAGB).

Another point to consider is the impact of a short biliopancreatic limb on the rate of biliary reflux as the greater the afferent limb is short the more the bile should be concentrated. The risk of biliary reflux exposure is a matter of concern for most digestive surgeons as reported recently from a survey of 417 surgeons not performing OAGB that aimed to understand their objections: 51% feared gastric cancer and 45% feared of esophageal cancer.<sup>22</sup> In an experimental study assessing biliary reflux after OAGB in rats, Bruzzi et al. reported an increased bile acid concentrations in the esogastric segment of OAGB rats compared to sham:<sup>20</sup> the authors found a mean bile acid concentration 2.8 times higher in the OAGB group at 7 weeks, that increased to 4.2 times higher at 16

weeks follow-up. On gastric cardia biopsies, they reported a significant increase of eosinophilic polynuclear cell infiltration into the chorion of OAGB rats, but no intestinal metaplasia. The authors concluded that the 4-month evaluation in rats represents an equivalent exposure to biliary reflux of 12 to 16 years of human life, and this may be insufficient when analyzing esogastric carcinogenesis risk. Herein, upper GI endoscopies performed at 2 years found that 15.5% of patients in the OAGB arm had bile in their stomach, which was not found in any of the RYGB patients. Furthermore, in the OAGB arm 10.3% of patients had esophagitis and there was one case of dysplasia on gastric and esophageal biopsies whereas 3.2% of patients in the RYGB arm had esophagitis and there was no case of dysplasia. Although we are not able to conclude yet on a potential carcinogenic risk of OAGB related to biliary reflux in humans because of the lack of long-term data, we should keep in mind that duodeno-esophageal reflux has been shown to promote esophageal carcinogenesis in experimental models.<sup>21</sup> The limited number of patients included in this trial, the relatively short follow-up and the low follow-up rate are limitations of this study. Other complications such as those related to malabsorption, that can take years to develop, were not possible to assess with our trial. In conclusion, OAGB is not inferior to RYGB in terms of weight loss and metabolic improvement at 2 years. Higher rates of diarrhea, steatorrhea, and nutritional adverse events were observed in the OAGB arm, suggesting a malabsorptive effect of this bariatric procedure. Prospective studies with long-term follow-up are needed, especially to assess the risk of biliary reflux in the long term and the impact of modifying the length of the biliopancreatic limb on the outcomes.

#### **Contributors**

MR and ED drafted the Article. MR, SBD, DMB, and DD conceived the study and designed the study. MR, PE, EP, RC, AS, LK, TP, JMC, VM, EC, FR, AT, and FP performed the surgical procedures. DD and SBD were responsible for data acquisition. DMB and CLJ were responsible for analysis. MR, ED, SBD, DD, CLJ and DMB have access to the data. MR, ED, and DMB interpreted the data. DMB and FP critically reviewed the manuscript for important intellectual content. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the Article are appropriately investigated and resolved.

#### **Declaration of interest**

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Figure 1: Study design

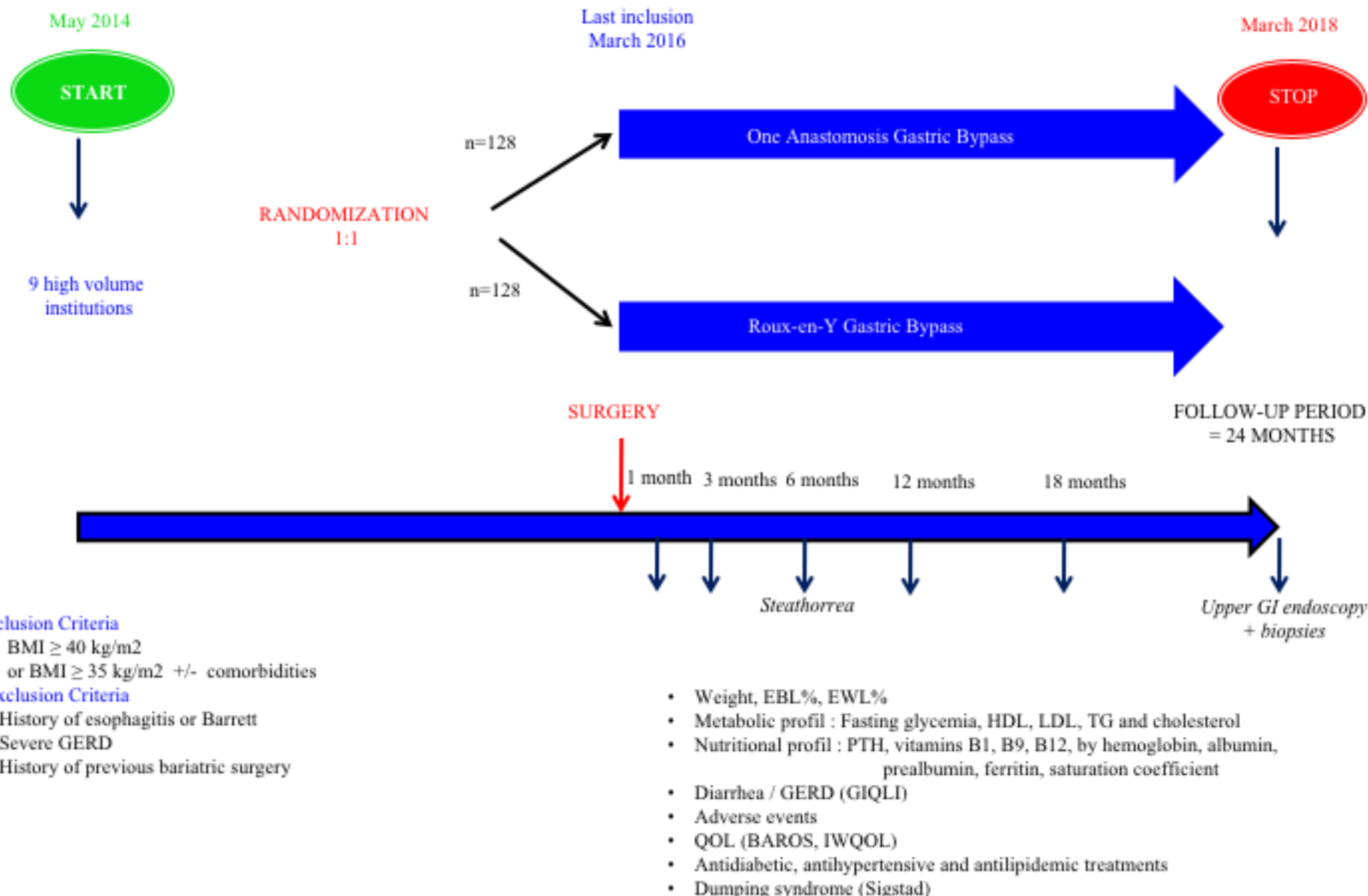


Figure 2  
Surgical procedures

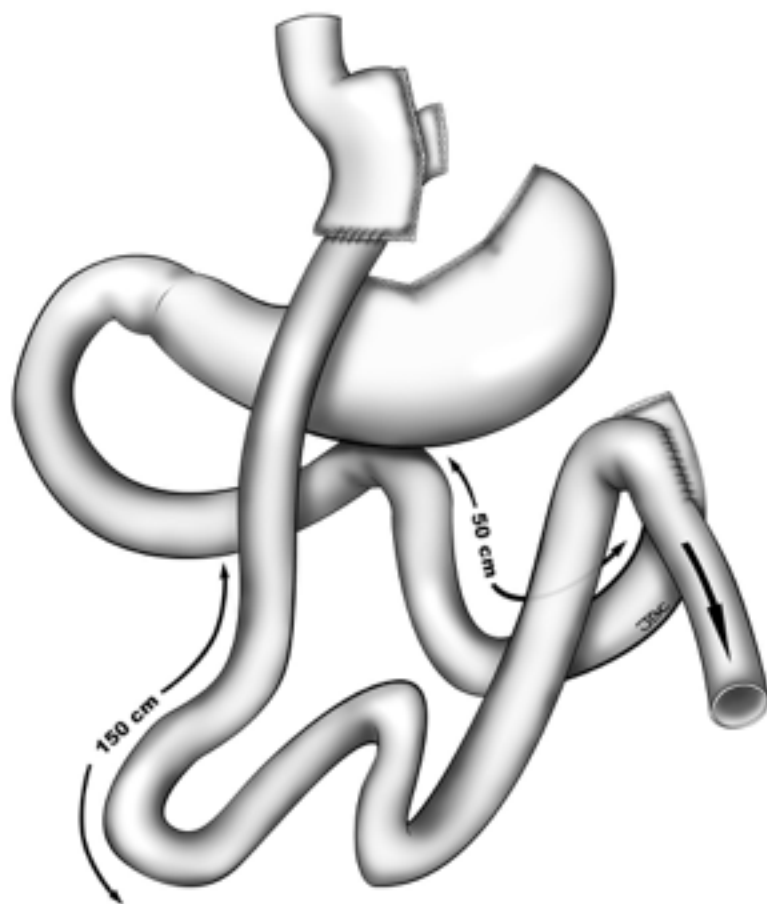


Figure 2a: Roux-en-Y Gastric Bypass

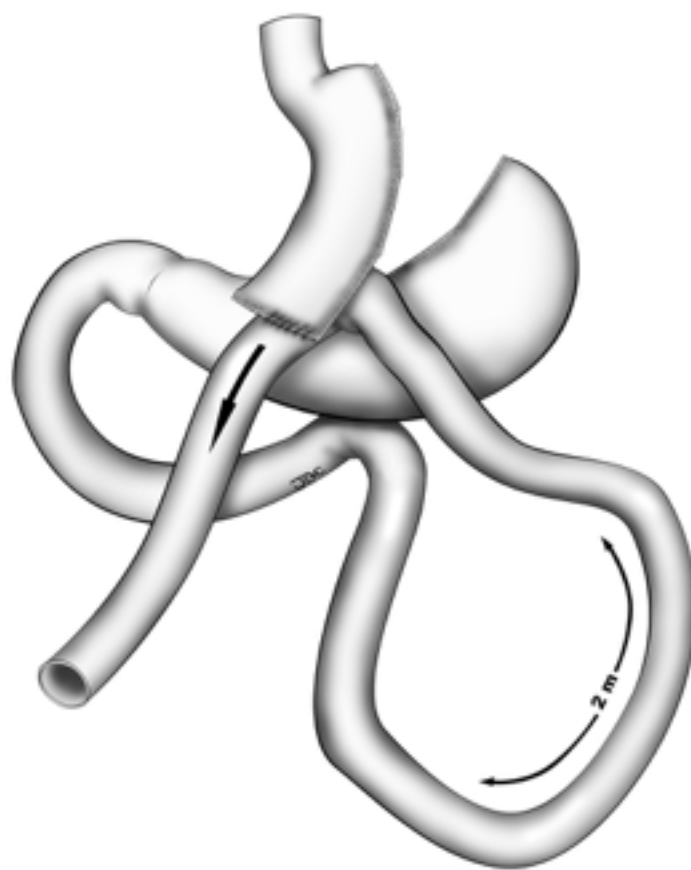


Figure 2b: One Anastomosis Gastric Bypass



Figure 3: flow-chart

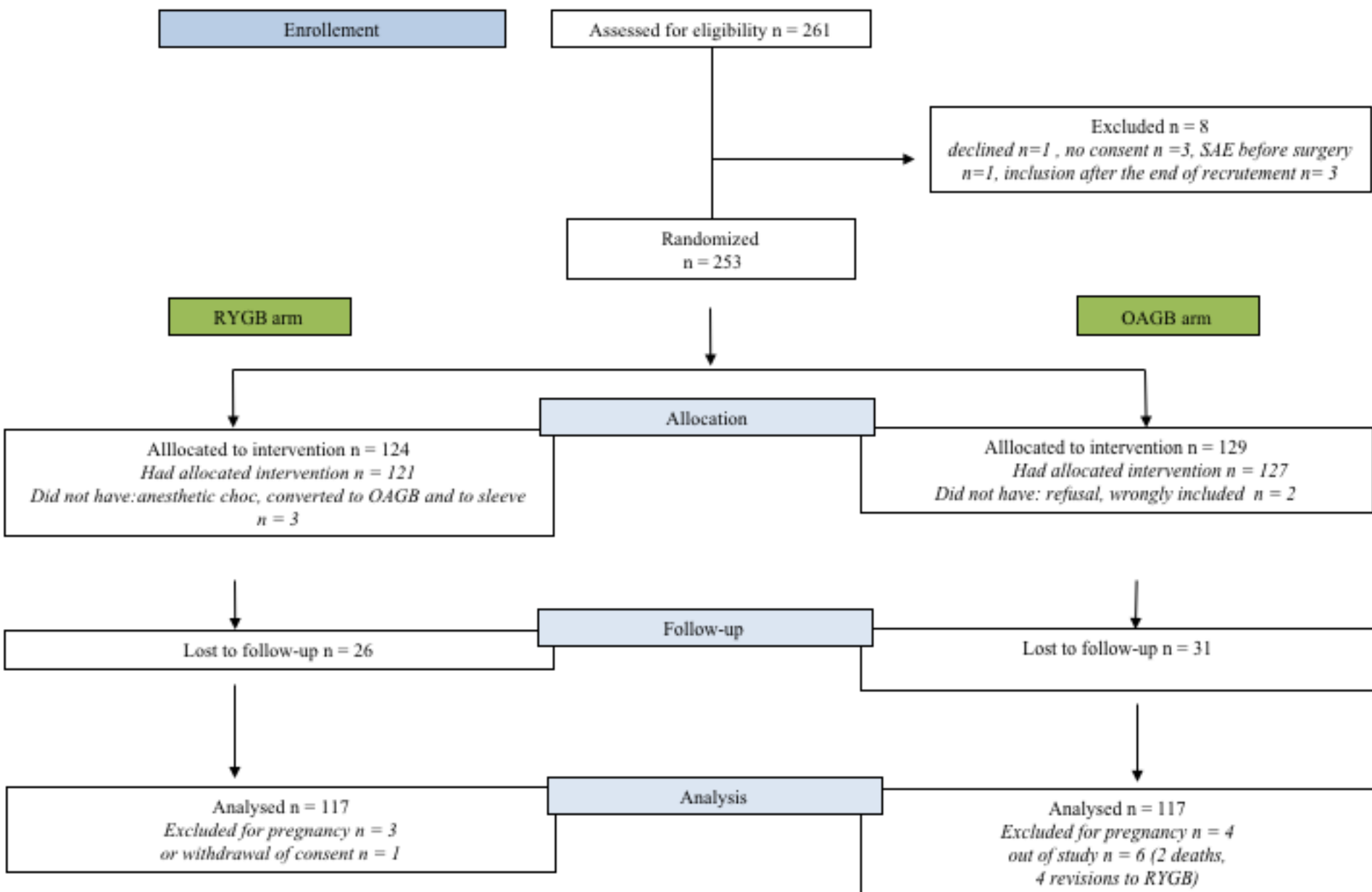
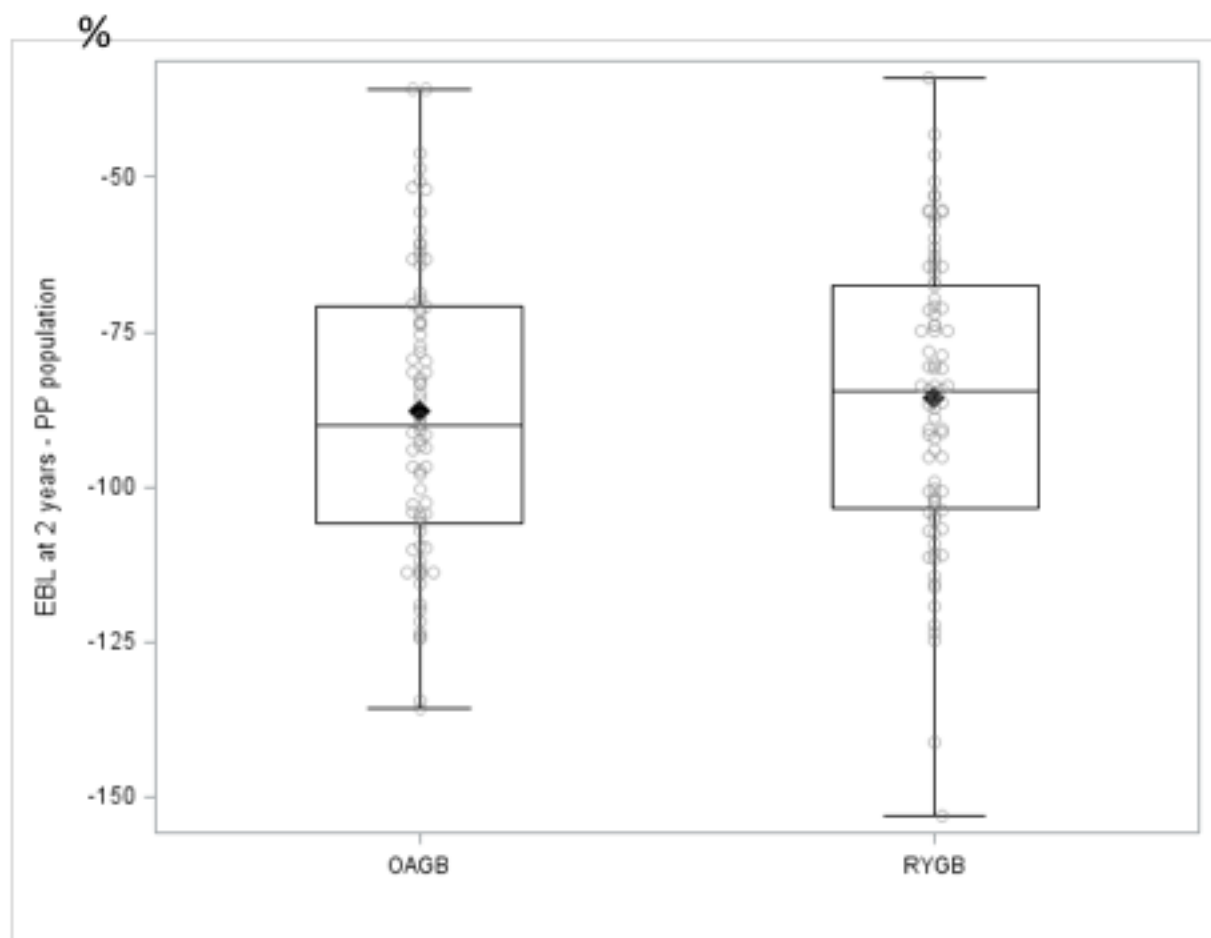


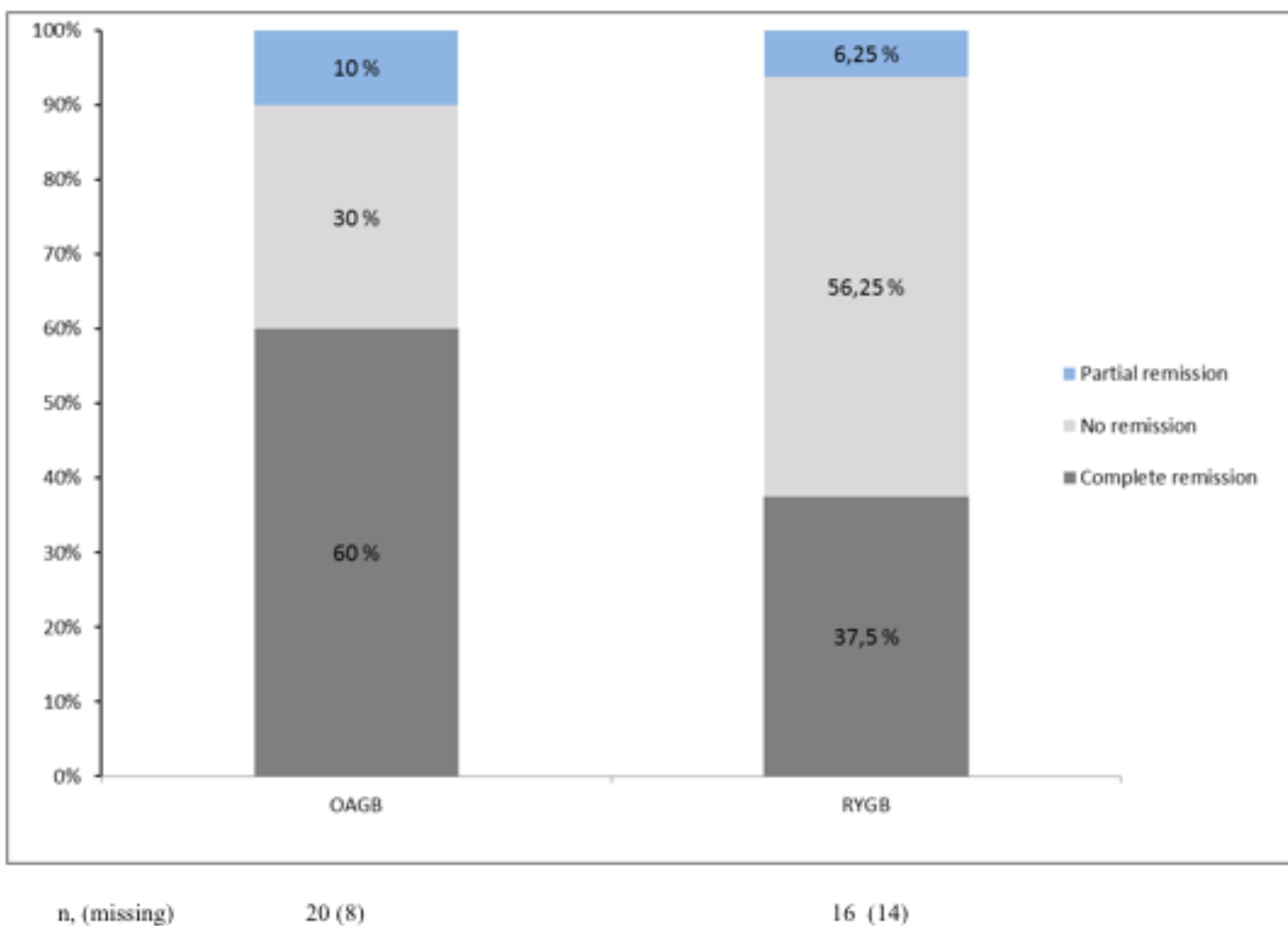
Figure 4: Weight Loss outcomes at 2 years



OAGB : One Anastomosis Gastric Bypass  
RYGB: Roux en Y Gastric Bypass  
EBL: Excess Body Mass Index Loss  
PP population: per protocole population

— Median  
◆ Mean

Figure 5 : Type 2 Diabetes remission rates in both arms



**Table 1: Baseline characteristics of the population**

Characteristics at baseline	Per protocol population	RYGBP	OAGB
<b>Mean age, years (SD)</b>	43.5 (10.8)	42.6 (10.2)	44.4 (11.4)
n (missing data)	234 (0)	117 (0)	117 (0)
<b>Female gender, n (%)</b>	176 (75.2%)	91 (77.8%)	85 (72.7%)
n (missing data)	234 (0)	117 (0)	117 (0)
<b>Mean weight, kg (SD)</b>	120.5 (21.7)	119.91 (18.7)	121.2 (24.4)
n (missing data)	234 (0)	117 (0)	117 (0)
<b>Mean BMI, kg/m<sup>2</sup> (SD)</b>	43.9 (5.6)	43.9 (5.1)	43.8 (6.1)
n (missing data)	234 (0)	117 (0)	117 (0)
<b>BMI ≥ 50 kg/m<sup>2</sup>, n (%)</b>	29 (12.4%)	14 (11.9%)	15 (12.58%)
n (missing data)	234 (1)	117 (0)	117 (0)
<b>Type 2 Diabetes, n (%)</b>	58 (27.5%)	30 (28.6%)	28 (26.4%)
n (missing data)	211 (23)	105 (12)	106 (11)
<b>Mean HbA1c, % (SD)</b>	7.6 (1.8)	7.5 (1.7)	7.8 (1.8)
n (missing data)	57 (1)	30 (0)	27 (1)
<b>Mean Duration of diabetes, years (SD)</b>	7.8 (7.2)	7.8 (8.4)	7.8 (6.1)
n (missing data)	48 (10)	23 (7)	25 (3)
<b>On oral anti-diabetic agents, n (%)</b>	43 (89.6%)	22 (91.7%)	21 (87.5%)
n (missing data)	48 (10)	24 (0)	24 (0)
<b>On GLP-1 agonist, n (%)</b>	13 (27.1%)	6 (25.0%)	7 (29.2%)
n (missing data)	48 (0)	24 (0)	24 (0)
<b>On Insulin, n (%)</b>	18 (37.5%)	8 (33.3%)	10 (41.7%)
n (missing data)	48 (0)	24 (0)	24 (0)
<b>Mean Duration of insulin therapy, years (SD)</b>	8.3 (8.5)	11.5 (10.4)	5.5 (5.5)
n (missing data)	17 (1)	8 (0)	9 (1)
<b>Arterial hypertension, n (%)</b>	71 (30.7%)	33 (28.5%)	38 (33.0%)
n (missing data)	231 (3)	116 (1)	115 (2)
<b>Dyslipidemia, n (%)</b>	42 (18.2%)	20 (17.2%)	22 (19.1%)
n (missing data)	231 (3)	116 (1)	115 (2)
<b>Sleep apnea, n (%)</b>	128 (56.1%)	68 (58.6%)	60 (53.6%)
n (missing data)	228 (6)	116 (1)	112 (5)

BMI = Body Mass Index

RYGBP = Roux-en-Y Gastric Bypass

OAGB = One Anastomosis Gastric Bypass

**Table 2: Metabolic outcomes at 2 years of follow-up**

Type 2 Diabetes population	Per protocol population	RYGB	OAGB	p value
<b>Mean HbA1c, % (SD)</b>	5.8 (0.9)	6.1 (0.9)	5.6 (0.8)	0.055
n (missing data)	39 (19)	17 (13)	22 (6)	
<b>Mean Decrease in HbA1c from baseline, % (SD)</b>	-1.9 (1.5)	-1.3 (1.0)	-2.3 (1.6)	0.025
n (missing data)	38 (20)	17 (13)	21 (7)	
<b>Mean fasting glycemia, mmol/l (SD)</b>	5.8 (2.2)	6.1 (2.9)	5.6 (1.5)	0.801
n (missing data)	42 (16)	20 (10)	22 (6)	
<b>Mean decrease in FG from baseline, mmol/l (SD)</b>	-3.6 (4.3)	-2.6 (4.8)	-3.8 (3.8)	0.505
n (missing data)	42 (16)	20 (10)	22 (6)	
Whole Population	Per protocol population	RYGB	OAGB	p value
<b>Decrease in LDL-C from baseline, mmol/l (SD)</b>	-0.4 (1.0)	-0.4 (1.0)	-0.4 (1.1)	0.97
n (missing data)	102 (132)	49 (68)	53 (64)	
<b>Increase in HDL-C from baseline, mmol/l (SD)</b>	+0.3 (0.3)	+0.3 (0.3)	+0.3 (0.3)	1
n (missing data)	105 (129)	50 (67)	55 (62)	
<b>Decrease in Total cholesterol from baseline, mmol/l (SD)</b>	-0.3 (1.0)	-0.3 (1.0)	-0.4 (1.1)	0.82
n (missing data)	105 (129)	49 (68)	56 (61)	
<b>Decrease in Triglycerides from baseline, mmol/l (SD)</b>	-0.6 (1.2)	-0.6 (0.62)	-0.7 (1.5)	0.31
n (missing data)	107 (127)	49 (68)	58 (59)	

FG= fasting glycemia

RYGBP = Roux-en-Y Gastric Bypass

OAGB = One Anastomosis Gastric Bypass

**Table3: Nutritional status at 2 years of follow-up (results of blood test samples)**

Difference between Inclusion and 2 year visit	Per protocol population	RYGB	OAGB	P value
Mean Hemoglobin, g/l (SD) n (missing data)	-6.6 (16.5) 129 (105)	-3.0 (10.0) 65 (52)	-10.3 (20.6) 64 (53)	0.036
Mean Albumin, g/l (SD) n (missing data)	0.3 (3.7) 124 (110)	0.1 (3.5) 61 (56)	0.5 (3.9) 63 (54)	0.51
Mean Prealbumin, g/l (SD) n (missing data)	-0.0 (0.1) 113 (121)	-0.0 (0.1) 54 (63)	-0.0 (0.1) 59 (58)	0.78
Mean Ferritin, in µg/l (SD) n (missing data)	-27.9 (174.3) 119 (115)	-31.3 (136.6) 57 (60)	-24.7 (204.1) 62 (55)	0.85
Mean Transferrin saturation coefficient, % (SD) n (missing data)	6.0 (14.00) 99 (135)	5.8 (10.3) 49 (68)	6.2 (16.9) 50 (67)	0.94
Mean Vitamin B1, nmol/l (SD) n (missing data)	-2.0 (28.4) 73 (161)	-0.6 (25.5) 35 (82)	-3.2 (31.1) 38 (79)	0.57
Mean Vitamin B9, ng/l (SD) n (missing data)	12.9 (20.6) 91 (143)	15.5 (21.8) 47 (70)	10.0 (19.2) 44 (73)	0.12
Mean Vitamin B12, pmol/l (SD) n (missing data)	10.9 (174.6) 119 (115)	-6.4(136.6) 60 (57)	28.5 (206.0) 59 (58)	0.94
Mean Vitamin D, nmol/l n (missing data)	21.3 (32.1) 114 (120)	25.2 (34.5) 56 (61)	17.4 (29.5) 58 (59)	0.51
Mean PTH, pg/ml (SD) n (missing data)	-0.7 (32.2) 89 (145)	-8.2 (27.7) 39 (78)	5.2 (34.5) 50 (67)	0.1

PTH: Parathyroid Hormon

RYGBP = Roux-en-Y Gastric ByPass

OAGB = One Anastomosis Gastric Bypass

**Table 4: Endoscopic findings at 2 years of follow-up**

	RYGB	OAGB
Endoscopy, n (missing data)	63 (54)	58 (59)
Gastritis, n (%)	4 (6.3%)	11 (18.9%)
Presence of bile in the stomach, n (%)	0	9 (15.5%)
Esophagitis, n (%)	2 (3.1%)	6 (10.3%)
Grade A, n	1	4
Grade B, n	1	1
Grade C, n	0	1
Gastric biopsies, n	63	57
Normal mucosa, n (%)	51 (80.9%)	44 (77.2%)
Gastritis, n	11	12
Dysplasia, n	0	1
Esophageal biopsies, n	59	56
Normal mucosa, n (%)	51 (86.4%)	43 (76.7%)
Esophagitis, n	8	12
Dysplasia, n	0	1

RYGBP = Roux-en-Y Gastric Bypass

OAGB = One Anastomosis Gastric Bypass

**Table 5: Type of Serious Adverse Events related to surgery at 2 years of follow-up**

Serious Adverse Events	Total, n (%)	RYGB	OAGB	p value
<b>Type of SAE:</b>	<b>66</b>	<b>24</b>	<b>42</b>	
Nutritional complications,	9 (13.64%)	-	9 (21.43%)	0.0034
Anastomotic ulcer	5 (7.57%)	3 (12.5%)	2 (4.76%)	
Reflux	3 (4.54%)	-	3 (7.14%)	
Bowel obstruction	4 (6.06%)	3 (12.5%)	1 (2.38%)	
Abdominal pain	5 (7.58%)	5 (20.83%)	-	
Diarrhea/Anal fissures	6 (9.09%)	-	6 (14.29%)	
Vesicular lithiasis	13 (19.70%)	5 (20.83%)	8 (19.05%)	
Urinary lithiasis	3 (4.5%)	-	3 (7.14%)	
Early peritonitis	4 (6.06%)	1 (4.17%)	3 (7.14%)	
Abdominal wall hematoma / abscess	3 (4.5%)	3 (12.5%)	-	
Vomiting	2 (3%)	2 (8.3%)	-	
Incisional hernia	1 (1.5%)	-	1 (2.38%)	
Haemoperitoneum	1 (1.5%)	1 (4.17%)	-	
Kidney failure by dehydration	1 (1.5%)	-	1 (2.38%)	
Gastro-gastric fistula	1 (1.5%)	1 (4.17%)	-	
Anticoagulant overdose	1 (1.5%)	-	1 (2.38%)	
Revision from OAGB to RYGB	4 (6.06%)	-	4 (9.52%)	

SAE: Serious Adverse Events

RYGBP = Roux-en-Y Gastric ByPass

OAGB = One Anastomosis Gastric Bypass

**Table 6: Type of nutritional complications in the One Anastomosis Gastric Bypass arm**

Patient	Type of nutritional complication	Mean weight loss (kg)	Vitamin deficiency	Malnutrition	Anemia or iron deficiency	Steatorrhea > 7g/24h
1	Wernicke encephalopathy	- 64 Converted to RYGB	yes	yes	no	25
2	Malnutrition	-52	yes	no	no	9.74
3	Malnutrition	Converted to RYGB	yes	no	no	MD
4	Severe diarrhea / malnutrition	-39	yes	yes	no	MD
5	Malnutrition / anorexia	-40	yes	yes	yes	14
6	Feeding difficulties	-53	yes	yes	yes	MD
7	Anorexia	-126	yes	yes	yes	MD
8	Food intolerance	-38	yes	yes	yes	10
9	Anemia	-55	yes	yes	yes	MD

MD : missing data

RYGBP = Roux-en-Y Gastric ByPass