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

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

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45

46 **Summary**

47 **Background**

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

51 **Method**

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

55 **Findings**

56 From May 2014 to March 2016, 253 patients were randomly assigned to OAGB (n=129) or RYGB (n=124).
57 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)
58 confirming non-inferiority (mean difference -3.3% [-9.1;2.6], non-inferiority limit 7%). Mean decrease in
59 HbA1c was significantly higher in the OAGB arm (-1.2% +/- 1.4 vs -0.6% +/- 0.8, p=0.0037). Incidence of
60 diarrhea was significantly higher in the OAGB arm (19.7%, 14/71) vs. RYGB (7%, 5/71, p=0.04; OR= 3.07,
61 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
62 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
63 OAGB arm vs. 6.3% (n=4/63) and 3.1% (n=2/63) for RYGB. Sixty-six Serious Adverse Events (SAE) related to
64 surgery were reported (RYGB:24 vs OAGB:42, p=0.042), of which 21.4% (n=9/42) were nutritional
65 complications in the OAGB arm versus none in the RYGB arm (p=0.0034).

66 **Interpretation**

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

70 ClinicalTrials.gov Identifier: NCT02139813
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81 **Introduction**

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

90 With more than 40 years of practice, the Roux-en-Y Gastric Bypass (RYGB) remains one of the gold standard
91 procedure for patients with morbid obesity and metabolic disorders in most of the reference centers.¹⁰ More
92 recently, a modified gastric bypass that consists of a single gastro-jejunal anastomosis between a long gastric
93 pouch and a jejunal omega loop has been described.¹¹ This new procedure, initially called “mini-gastric bypass”
94 or “One Anastomosis Gastric Bypass” (OAGB), seemed to have the advantage of being less technically
95 demanding and potentially less morbid. Weight loss and metabolic outcomes initially published were as good as
96 those reported for the RYGB or even better.¹²⁻¹⁵ Nevertheless, OAGB, which is derived from the loop gastric
97 bypass initially described by Mason and Ito is considered by many surgeons at risk of biliary reflux and
98 anastomotic ulcers.¹⁶⁻¹⁹ Many surgeons who do not perform the procedure also fear the risk of gastric and
99 esophageal cancer.²⁰⁻²² Published data essentially come from retrospective studies and one recent metaanalysis,²³
100 although two randomised trials comparing OAGB to RYGB have been reported.^{12,15} The first was published in
101 2005 and included 80 patients.¹² The authors concluded that OAGB is a simpler and safer procedure at 2 years
102 follow-up. However, the statistical power of this study and, in particular the methodology used to calculate the
103 sample size, is open to criticism. The second randomised trial was recently published,¹⁵ and compared 200
104 OAGB to 200 RYGB and 200 Sleeve Gastrectomies (SG). The authors concluded that OAGB achieved better
105 weight loss and remission of comorbidities compared to the two other procedures. Nevertheless, the
106 methodology of this trial is also questionable with an obvious lack of data regarding selection of patients and
107 biological outcomes, but also missing data were not reported. Therefore, despite strong initial enthusiasm that
108 spread rapidly around the world, the value of this procedure remains debated. In the absence of high-level
109 evidence regarding the efficacy and safety of OAGB, we conducted a randomised controlled trial that compared
110 it to the validated RYGB.

111

112 **Research in context**

113 **Evidence before this study**

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

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

128 **Added value of this study**

129 This multicenter randomised trial has been designed to answer controversial issues regarding weight loss,
130 metabolic outcomes, and most of the safety questions regarding gastrointestinal and nutritional consequences.
131 The findings indicate that OAGB is not inferior to RYGB in terms of weight loss and metabolic improvement at
132 2 years. However, the higher incidence of diarrhea, steatorrhea, and nutritional adverse events observed with
133 OAGB indicate that there is a nutritional risk associated with this procedure when the biliopancreatic limb is 200
134 cm long. Endoscopic findings at 2 years of follow-up reporting a 15.5% rate of bile exposure in the stomach in
135 the OAGB arm advocate for other studies with endoscopic controls over the long term.

136 **Implications of all the available evidence**

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

145

146 **Methods**

147 *Study design and inclusion criteria*

148 YOMEGA trial is a prospective multicenter, open-label, non-inferiority randomised controlled trial, with two
149 arms comparing OAGB to RYGB in terms of weight loss (primary endpoint). Efficacy in terms of metabolic
150 parameters and safety were secondary endpoints (Figure 1). Nine high-volume bariatric institutions (over 150
151 procedures a year) with a large experience in gastric bypass were involved in the study. Patients were included if
152 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
153 Diabetes mellitus – T2D, high blood pressure, obstructive sleep apnea, dyslipidemia, or arthritis), aged between
154 18 and 65 years, after multidisciplinary evaluation and written informed consent. They benefited from a
155 preoperative upper gastrointestinal (GI) endoscopy with biopsies. History of esophagitis, severe Gastro-
156 Esophageal Reflux Disease (GERD) resistant to Proton Pump Inhibitors (PPI), Barrett's esophagus, and history
157 of previous bariatric surgery were exclusion criteria. Recruitment was from May 2014 to March 2016, and the
158 last visit of the last patient included occurred in March 2018, after a 2-year follow-up. Patients were considered
159 as lost to follow-up if no information was obtained before database lock.

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

162

163 ***Primary and secondary endpoints***

164 The primary endpoint was Excess BMI Loss percentage (EBL%) at 2 years after randomisation defined as (BMI
165 at 2 years - initial BMI) / (initial BMI - 25). The secondary endpoints were assessed at 1, 3, 6, 18, and 24 months
166 of follow-up; these included weight and BMI, as well as the early and late complications and their severity at 2
167 years. We also assessed the incidence of GERD and diarrhea (Gastro Intestinal Quality of Life Index – GIQLI –
168 self-administered questionnaire), steatorrhea at 6 months (g of lipids / 100g of stools on the 24h stools), dumping
169 syndrome (Sigstad score > 7). Metabolic profile was evaluated by measuring Fasting Glycemia (FG), HbA1c,
170 Triglycerides (TG), High Density Lipoprotein cholesterol (HDL-c), Low Density Lipoprotein cholesterol (LDL-
171 c), and total cholesterol; antidiabetic, antihypertensive and lipid-lowering medications were also recorded.
172 Diabetes remission status at 2 years was defined as complete remission if HbA1c < 6% and fasting glycemia <
173 5.6 mmol/l without active pharmacological therapy or ongoing procedures, and partial remission if HbA1c <
174 6.5% and fasting glycemia between 5.6 and 6.9 mmol/l without active pharmacological therapy or ongoing
175 procedures. Nutritional status was assessed via serum albumin, prealbumin, hemoglobin, ferritin, transferrin
176 saturation coefficient, Parathyroid Hormone (PTH), calcemia, and vitamins B1, B9, B12, D. Malnutrition was
177 defined as albumin < 30 g/l and/or prealbumin < 0.20 g/l. A patient was considered as having vitamin deficiency
178 if s/he had at least one of the following: vitamin B1 < 66 nmol/l, vitamin B9 < 6 ng/ml, vitamin B12 < 145
179 pmol/l, vitamin D < 50 nmol/l, or PTH > 50 pg/ml. Hemoglobin < 12 g/dl was considered as anemia, and iron
180 deficiency was defined as ferritin < 15 µg/l and/or transferrin saturation coefficient < 20%. An upper GI
181 endoscopy was performed at 2 years of follow-up with systematic biopsies to evaluate the histological
182 modifications of the gastric and esophageal mucosa. We also recorded the overall number and type of Serious
183 Adverse Events (SAE) and those related to surgery as well as early (within 30 days) and late (over 30 days)
184 surgical complications. Quality of life was assessed with self-administered questionnaires: the Bariatric Analysis
185 and Reporting Outcome System (BAROS) that has five levels (failure, fair, good, very good, excellent) and the
186 Impact of Weight on Quality Of Life (IWQOL) assessment tool. The IWQOL questionnaire consists of 31 items
187 exploring five dimensions: mobility, self-esteem, social life, working conditions and sexual life, the most
188 pejorative score being 155 whereas the best score is 31.

189

190 ***Randomisation and sample size***

191 Randomisation was performed at a 1:1 ratio stratified by center with blocks of variable size. Considering a mean
192 EBL% of 60% in the RYGBP group at 2 years,^{9,10} the hypothesis was that OAGB would not be inferior to
193 RYGB if the difference in EBL was less than seven percentage points (≤ 5 kg). Assuming a standard deviation of
194 21% in both groups with a 10 % lost to follow-up, 128 patients per group (256 subjects in total) were needed to
195 conclude to the non-inferiority of OAGB with a statistical power of 80% and an α risk of 5 %.

196

197 ***Surgical techniques (Figure 2)***

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

200 OAGB consisted of a long gastric tube beginning at the landmark of the incisura angularis and calibrated with a
201 37 French bougie. A single gastrojejunal anastomosis was performed using a linear stapler with a biliopancreatic
202 limb of 200 cm (Figure 2b). A systematic supplementation of multivitamins, iron, calcium, vitamin B12 and D
203 was prescribed associated with 40 mg of PPI and 500 mg of ursodeoxycholic acid during 6 months to prevent
204 marginal ulcer and gallstones.

205

206 *Statistics*

207 Primary and secondary efficacy outcome analyses were performed in the per protocol population; this included
208 all randomised patients who contributed data excluding patients with major deviation to the protocol (pregnancy,
209 death, withdrawal of consent, switch of surgical procedure). A 90% confidence interval (CI) of the difference for
210 the primary endpoint was determined (one sided 5% alpha level) so that non-inferiority was concluded if the
211 upper bound of this interval was inferior to the non-inferiority limit (seven percentage points). Analyses of
212 secondary outcomes were not corrected for multiple comparisons, so the results cannot be used for hypothesis
213 testing or inference. Comparisons were performed using the Student t-test or the non-parametric Wilcoxon test
214 for quantitative endpoints, and the Chi² test or the Fisher exact test for categorical endpoints. For quantitative
215 normal endpoints, the 95% bilateral confidence intervals were given for the mean difference (two sided 5% alpha
216 level). The incidence of Serious adverse events per patient in both groups was compared using the likelihood test
217 from Poisson regression.

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

225 Analyses were performed using SAS[®] Software version 9.4 (SAS Institute, Cary, NC, US).

226

227 *Role of the funding source*

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

233

234 **Results**

235 From May 2014 to March 2016, 253 patients were randomly assigned to OAGB (n=129) or RYGB (n=124),
236 safety population. There were 234 patients who contributed data to the study, per protocol population (n=117 in
237 each arm); 22.5% of patients were lost to follow-up for the primary end-point: an hypothetical weight was
238 therefore imputed to them so as to contribute to the analysed sample (Figure 3).” In the per protocol population,
239 mean age was 43.5 years (SD 10.8), mean BMI was 43.8 kg/m² (SD 5.6). There were 75.2% of female

240 (176/234) and 27.5% of Type 2 Diabetic patients (58/211). Characteristics of the study population are presented
241 in Table 1.

242

243 ***Surgical outcomes***

244 The mean operative time was significantly shorter in the OAGB arm (85 min, SD 35) than RYGB (111 min, SD
245 42; $p < 10^{-4}$). The median length of stay was 5 days for both groups (OAGB: IQR 4-5, RYGB: IQR 4-6).
246 Intraoperative complications occurred in 4 cases in the RYGB group (hemorrhage $n=3$, bowel injury $n=1$) vs. 8
247 cases in the OAGB (hemorrhage $n=4$, bowel injury $n=2$, stapling of the nasogastric tube $n=2$). In the RYGB arm
248 two patients had a switch of technique: one had a sleeve due to severe bowel adhesions and the other one had
249 OAGB due to the thickness of the mesenteric fat and intraoperative difficulties. In the per protocol population,
250 the rates of early and late surgical complications in the RYGB arm were 6.8% (8/117) and 12.8% (15/117)
251 versus in the OAGB arm 3.4% (4/117, $p=0.24$) and 16.2% (19/117, $p=0.45$) respectively. Among early surgical
252 complications, we observed in the RYGB arm ($n=8$) 1 bowel obstruction, 2 wall abscesses, 1 wall hematoma, 1
253 haemoperitoneum, 2 trocar hemorrhages and 1 severe constipation; only 2 of them were complications over
254 Grade 3 of Dindo-Clavien score and required surgical management. In the OAGB arm, among early surgical
255 complications ($n=4$) we reported 1 peritonitis, 1 stenosis of the gastro-jejunal anastomosis, 1 wall hematoma, 1
256 hematoma of the gastro-jejunal anastomosis; only one of them was over Grade 3 of Dindo-Clavien score and
257 required a surgical management.

258

259 ***Weight loss outcomes***

260 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;
261 Figure 4). The mean difference of EBL% was -3.3 percentage point [-9.1;2.6] in favor of OAGB and the upper
262 bound of confidence interval was 2.6 percentage point (p for non-inferiority=0.0024). This was lower than the
263 non-inferiority limit of seven percentage point, confirming that OAGB is not inferior to RYGB in terms of
264 EBL%. This result was confirmed by the sensitivity analyses (maximal upper bound was 3.9 in the first scenario,
265 $p=0.007$; 2.2 in the second scenario, $p=0.002$; 5.9 in the third scenario, $p=0.024$). Mean % total body weight
266 loss was -35.4% (SD8.1) in the RYGB arm versus -37.1% (SD10.3) in the OAGB arm, confirming non-
267 inferiority (mean difference -1.4% [-3.7;0.99], p for non-inferiority $<10^{-4}$).

268

269 ***Metabolic outcomes***

270 In the per protocol population, mean HbA1c at 2 years was not statistically different in the OAGB arm (5.2%,
271 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
272 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
273 was also significant in the sub-group of patients with T2D; the mean decrease in HbA1c was -2.3% (SD 1.6) in
274 the OAGB group vs. -1.3% (SD 1.02) in the RYGB group ($p=0.025$; Table 2). There was a 60.0% ($n=12/20$)
275 complete T2D remission rate, and a 10.0% ($n=6/60$) partial T2D remission rate in the OAGB group vs. 37.5%
276 ($n=6/16$) and 6.3% (1/16), respectively, in the RYGB group; the proportions of T2D remission were not
277 significantly different ($p=0.28$; Figure 5). There was no significant difference at 2 years between arms in the
278 values and decrease of FG, TG, LDL-C, HDL-C, and total cholesterol (Table 2).

279

280 ***Nutritional status***

281 In the per protocol population, mean serum albumin and prealbumin values were not significantly different
282 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
283 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
284 different (OAGB: 10.8%, $n=7/65$ vs. RYGB: 16.7%, $n=10/60$; $p=0.34$). There was a significant difference in the
285 mean decrease of hemoglobin in the OAGB arm (-10.3 g/l, SD 20.57) compared to the RYGB arm (-3 g/l, SD
286 10.07; $p=0.036$, Table 3); there was no significant difference regarding the incidence of anemia or iron
287 deficiency (OAGB: 28.3%, $n=17/60$ vs. RYGB: 36.2%, $n=21/58$; $p=0.36$). We did not find any significant
288 difference neither in the levels of vitamins nor in the frequency of vitamin deficiencies (OAGB: 84.5%, $n=$
289 49/58 vs. RYGB: 83.3%, $n=40/48$, $p=0.87$) at 2 years of follow-up.

290

291 ***Side effects and endoscopic data***

292 There was a significantly higher incidence of diarrhea in the OAGB arm compared to the RYGB arm at 3
293 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%
294 $n=14/71$ vs. 7% $n=5/71$, $p=0.04$, OR= 3.07; 95%CI [1.04; 9.08]). There was also a significantly higher mean
295 steatorrhea in the OAGB arm at 6 months (11 g of lipids/ 100g stools) than in the RYGB arm (7 g of lipids/ 100g
296 stools, $p<10^{-3}$). There was a significantly lower frequency of dumping syndrome in the OAGB arm at 3 months
297 (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
298 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;
299 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
300 ($p=0.5$; OR=0.15, 95%CI [0.19; 1.3]). Fifty-two percent of the patients ($n=121/234$) had an upper GI endoscopy
301 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
302 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 ($n=9/58$)
303 had bile in the gastric pouch vs. none in the RYGB arm, and one case in the same patient of intestinal metaplasia
304 and dysplasia on the gastric and esophageal biopsies was also found (Table 4).

305

306 ***Serious Adverse Events***

307 At 2 years of follow-up, there were nearly twice as many overall SAE and SAE related to surgery in the OAGB
308 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).
309 Among the SAE related to surgery, 21.4% ($n=9$) were nutritional complications in the OAGB arm vs. none in
310 the RYGB arm, $p=0.0034$ (Table 5). Among these 9 patients with nutritional complications, all had at least one
311 vitamin deficiency and/or malnutrition and/or anemia or iron deficiency (Table 6); the mean absolute weight loss
312 in this subgroup was -58.4 kg (SD -28.8). Most of the SAE in the RYGB arm were hospitalization due to
313 abdominal pain 20.8% ($n=5$), which was not reported in the OAGB arm. There was no significant difference in
314 the proportion of patients with at least one SAE between arms (OAGB: 28/129 (21.7%) vs RYGB: 19/124
315 (15.3%), $p=0.19$). There was a significantly higher number of SAE related to surgery per patient in the OAGB
316 arm ($p=0.042$). Four patients with OAGB required conversion to RYGB: one for anastomotic leak, one for
317 Wernicke encephalopathy and 2 because of severe biliary reflux reluctant to medical therapy.

318

319

320 ***Evolution of quality of life***

321 At 2 years of follow-up, the improvement of quality of life was not significantly different in both arms with
322 good, very good and excellent BAROS scores for 54/63 (85.9%) patients in the RYGB arm vs. 63/67 (94%)
323 patients in the OAGB arm ($p=0.15$). Regarding IWQOL scores, all dimensions explored improved significantly
324 with both techniques during the 2-year follow-up ($p<10^{-4}$), except for sexual life which was not assessed due to
325 missing data for this item. There was no significant difference between both arms regarding the scores of the 4
326 dimensions studied: mean physical function improved by 20.4 points for OAGB (SD 11.9) vs. 21.5 points for
327 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
328 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
329 RYGB (SD 3.8, $p=0.52$) and mean working conditions improved by 4 points for OAGB (SD 3.2) vs. 4.7 points
330 for RYGB (SD 3.3, $p=0.26$).

331

332 **Discussion**

333 This multicenter randomised trial found that OAGB is not inferior to RYGB in terms of EBL% at 2 years, using
334 a 200 cm biliopancreatic limb in the OAGB arm and a 150 cm alimentary limb and 50 cm biliopancreatic limb in
335 the RYGB arm. This finding is in accordance with the first randomised trial published by Lee et al. in 2005,¹²
336 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
337 trial, the length of the afferent limb of the OAGB was also 200 cm, which is the standard and initially described
338 in the first report of the technique.¹¹ In the second randomised trial, which was reported by Ruiz-Tovar et al,¹⁵
339 the authors found a significantly higher EBL% in the OAGB group compared to the RYGB group at 2 years of
340 follow-up (103.4% vs. 87.2%, $p<0.001$), which was also found at 5 years. In this study, the length of the
341 biliopancreatic limb was longer; it varied from 200 cm to 350 cm depending on the length of the total bowel
342 following the ratio Biliopancreatic limb 60%/Common limb 40%. The longer afferent limb could explain the
343 greater weight loss observed in this study compared to herein. However, the validity of this result may be
344 questioned; although the authors reported a very low rate of loss to follow-up (9% at 5 years) which has never
345 been reached before in bariatric studies, they do not provide any information regarding missing data for the
346 EBL% which was the primary endpoint.

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

353 The good weight loss and metabolic outcomes of OAGB could be explained by the malabsorptive effect of the
354 procedure. This hypothesis seems to be supported by the significant increase rate of diarrhea in the OAGB arm at
355 2 years, as well as the higher mean steatorrhea. Another strong argument in favor of this malabsorptive effect is
356 the high frequency of nutritional complications among the SAEs related to surgery; all those concerned had at
357 least vitamin deficiency and/or malnutrition and/or anemia or iron deficiency. Despite systematic use of
358 multivitamin supplementation and close follow-up, there was a case of Wernicke encephalopathy in the OAGB
359 arm that required conversion to RYGB. However, it is of note that recent publications have also reported severe

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

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

384 The length of the biliopancreatic limb has been considered as a strong factor implicated in malnutrition. Since
385 2017, KK Mahawar and others have published several articles regarding the nutritional risk of a too long
386 biliopancreatic limb when performing OAGB, suggesting not to exceed 150 cm.²⁸⁻³⁰ In the randomised trial
387 reported by Ruiz-Tovar et al.¹⁵ the length of the biliopancreatic limb was between 200 cm and 350 cm.
388 Surprisingly, the authors did not report a high rate of malnutrition: among the 200 OAGB only 3 subjects
389 presented hypoproteinemia, coinciding with period of illness, and which were satisfactorily managed with a
390 course of hyperproteinated supplements. We are again struck here by the very low rate of complications in each
391 group (4 internal hernia and 3 anastomotic ulcers among 200 RYGB, and 2 uncontrolled biliary reflux, 2
392 anastomotic ulcers and 3 hypoproteinemia among 200 OAGB).

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

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

417

418 **Contributors**

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

426

427 **Declaration of interest**

428 All contributors report grants from French ministry of Health (Direction Générale de l'Offre de Soins, study
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437 Baptiste Cazauran.

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440

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509

Figure 1: Study design

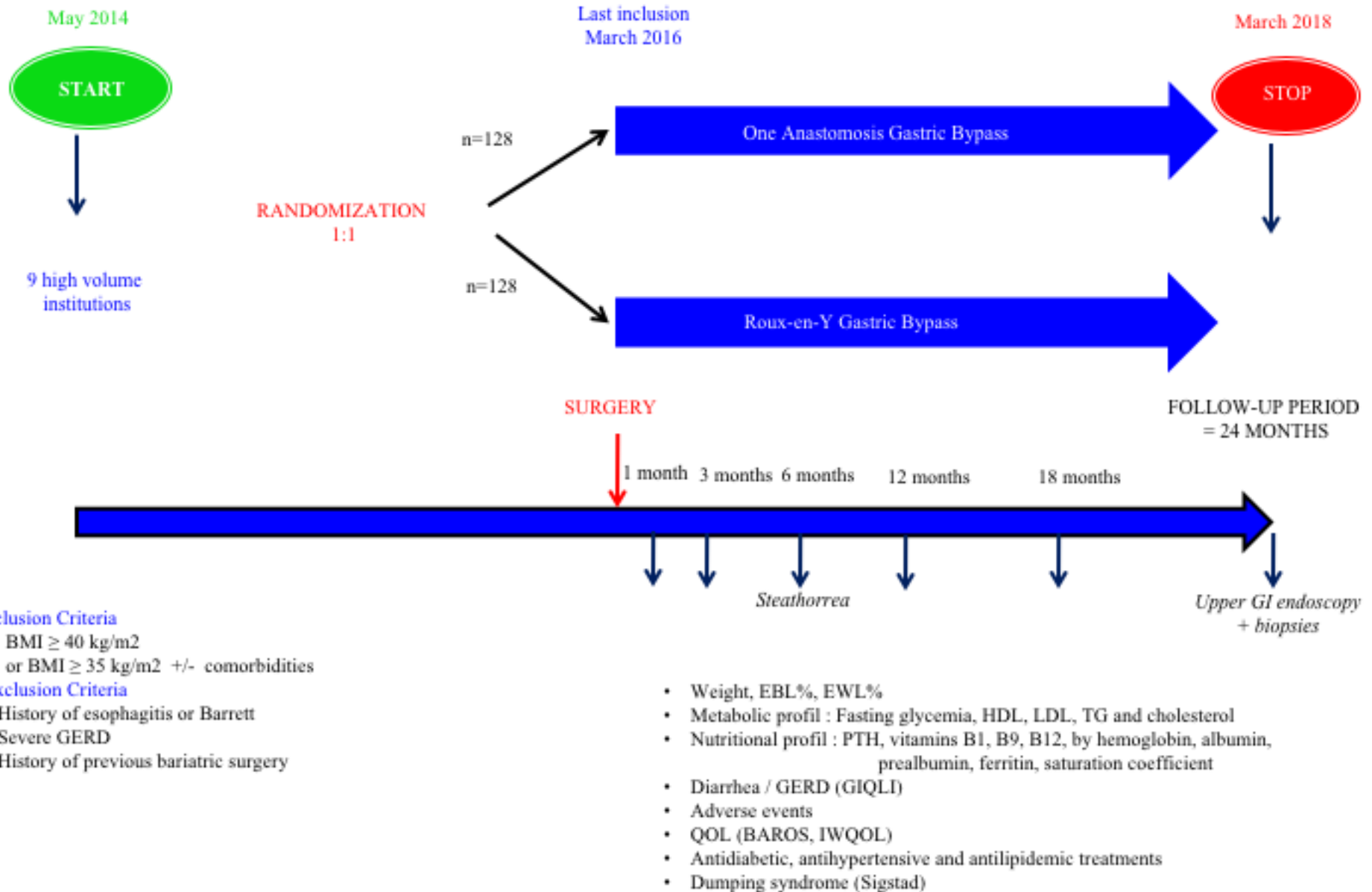


Figure 2
Surgical procedures

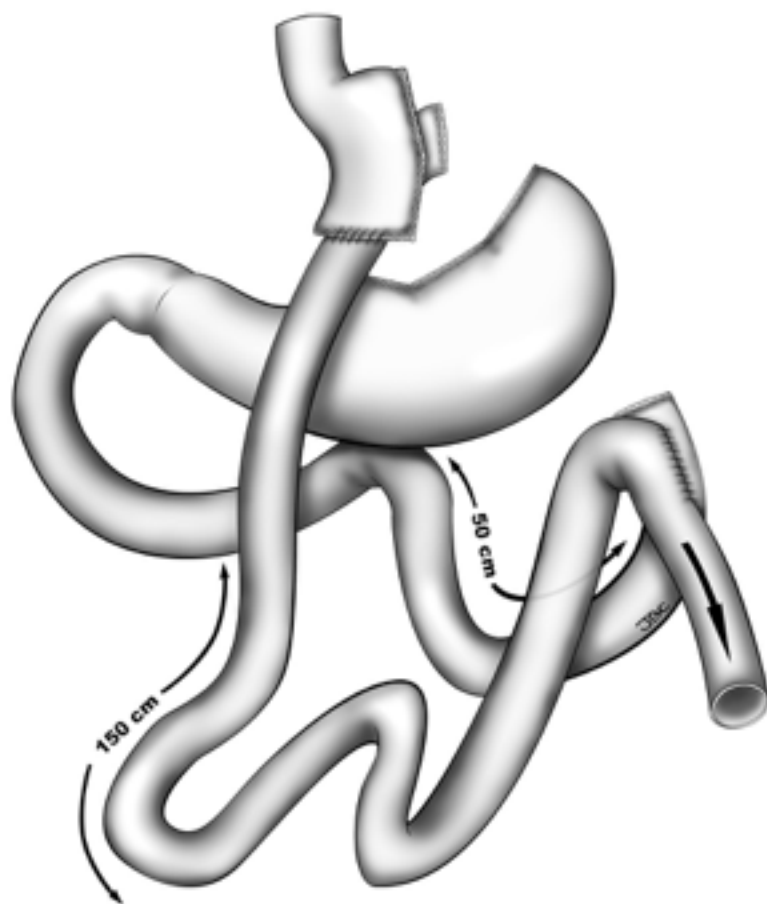


Figure 2a: Roux-en-Y Gastric Bypass

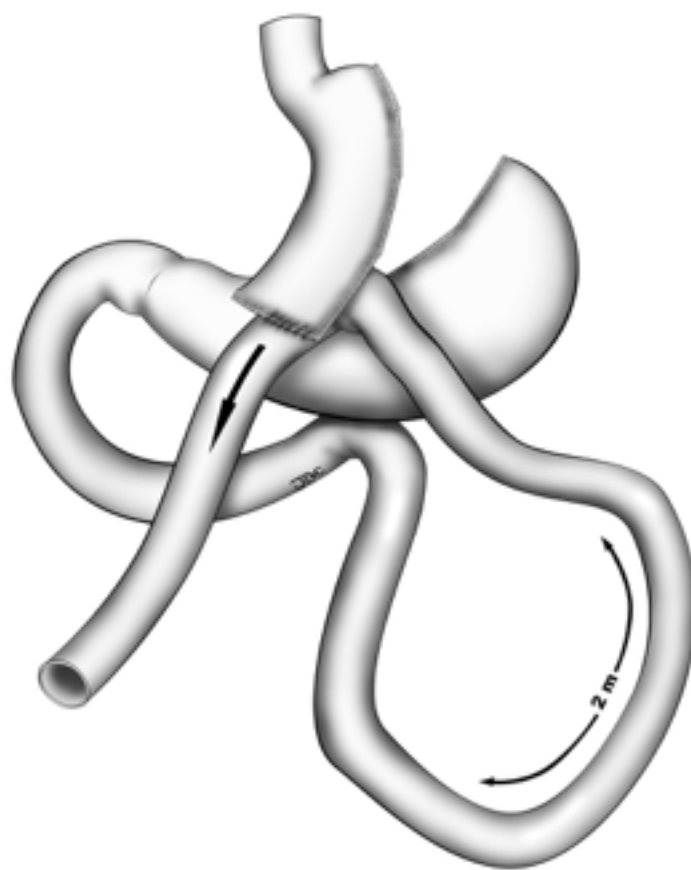


Figure 2b: One Anastomosis Gastric Bypass

Figure 3: flow-chart

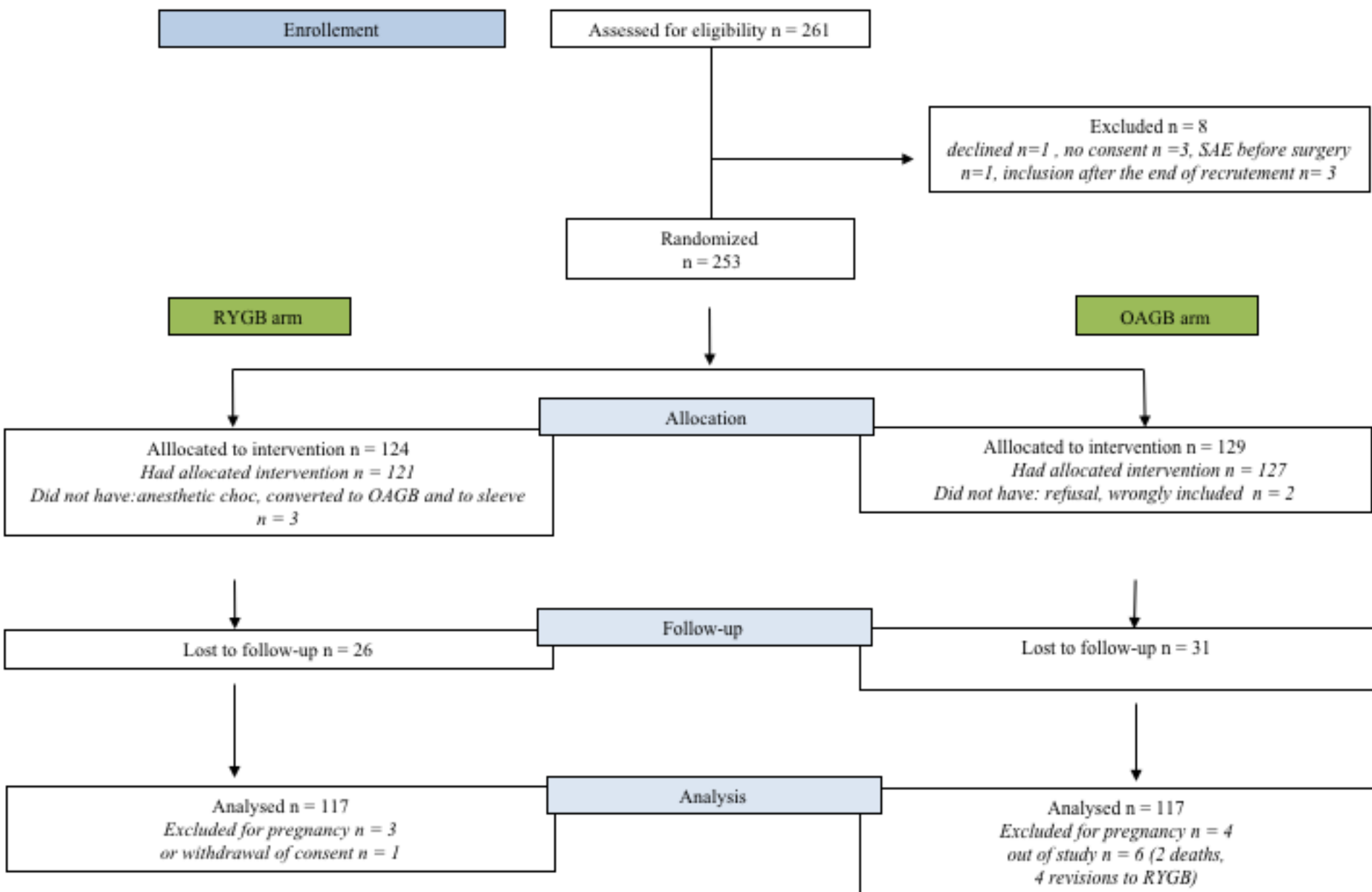
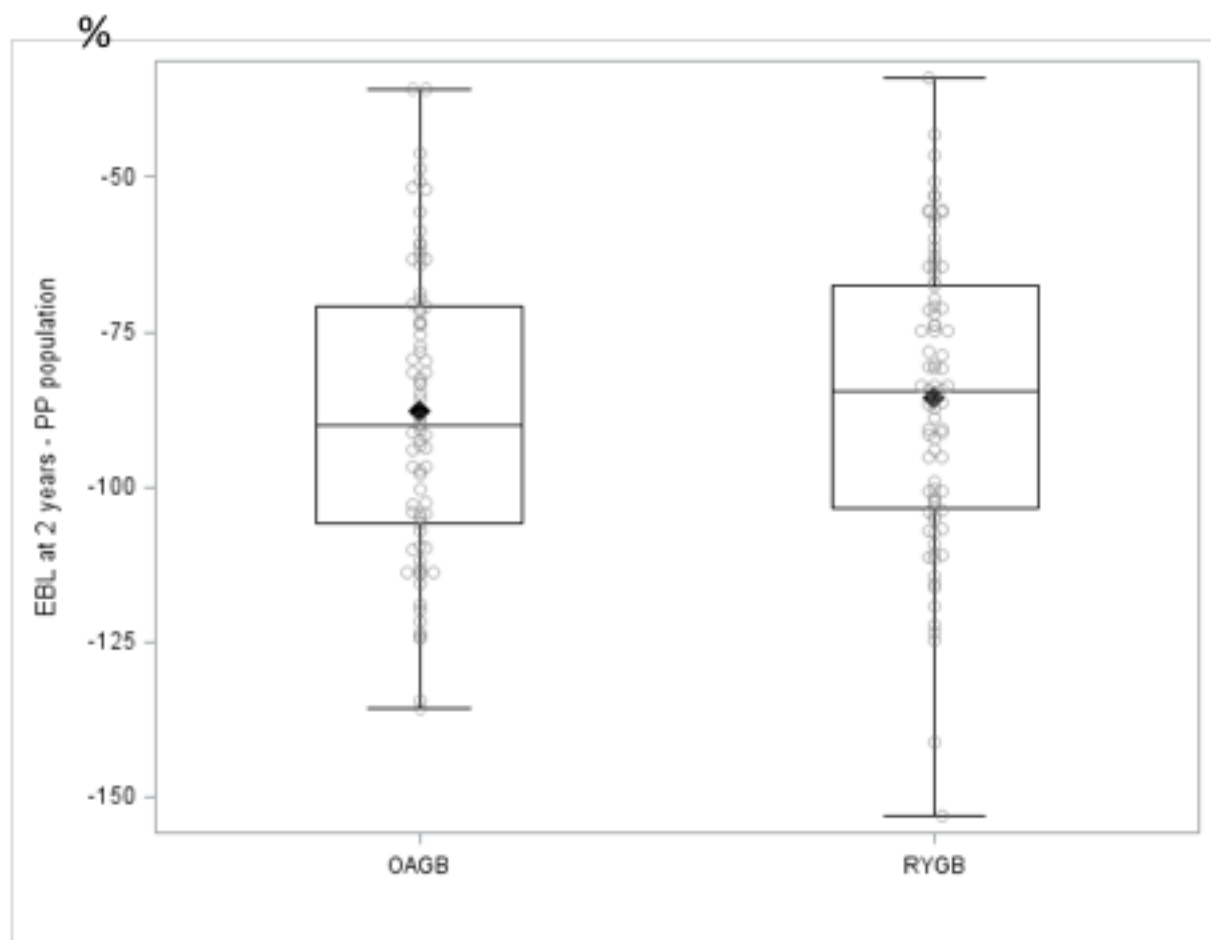


Figure 4: Weight Loss outcomes at 2 years



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

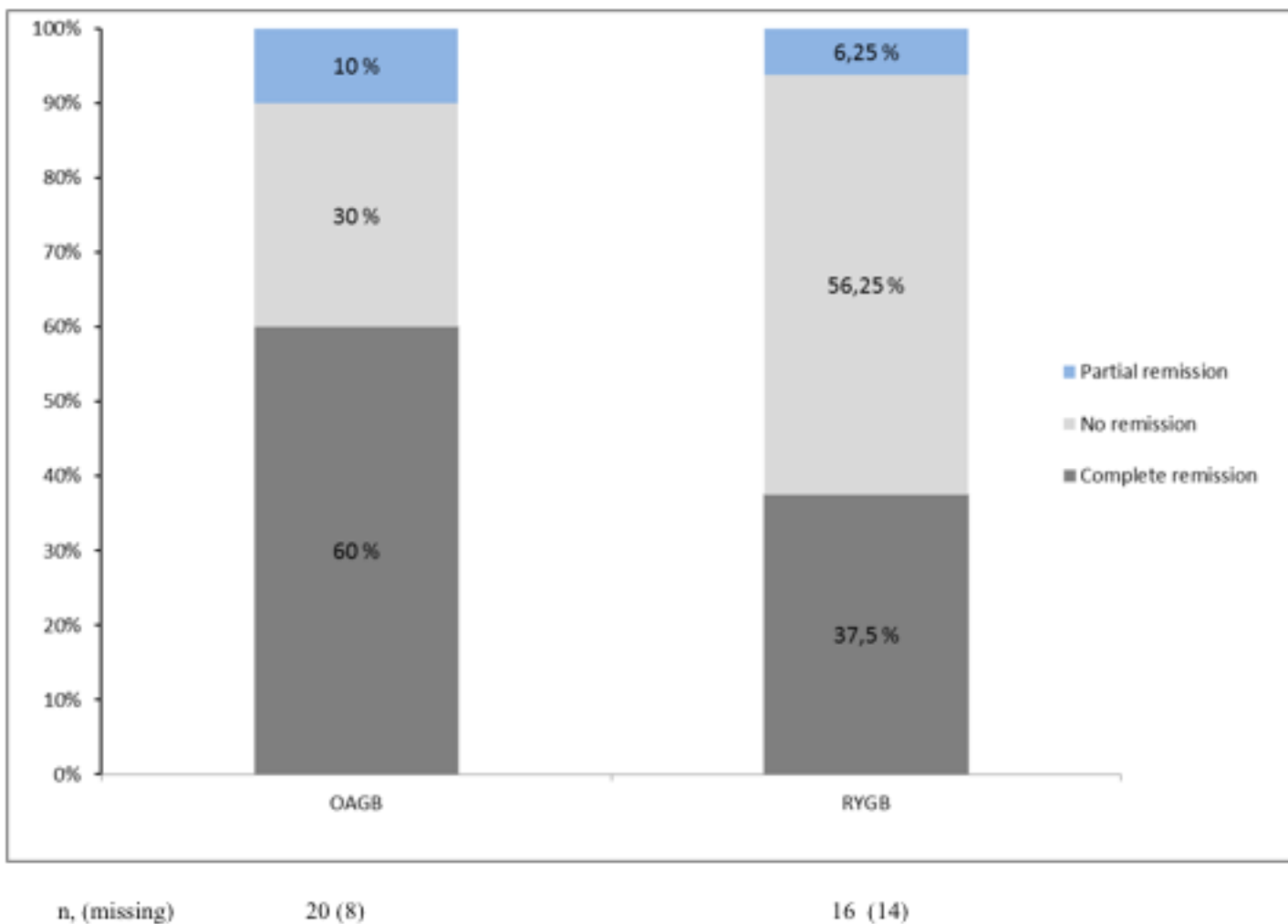


Table 1: Baseline characteristics of the population

Characteristics at baseline	Per protocol population	RYGBP	OAGB
Mean age, years (SD)	43.5 (10.8)	42.6 (10.2)	44.4 (11.4)
n (missing data)	234 (0)	117 (0)	117 (0)
Female gender, n (%)	176 (75.2%)	91 (77.8%)	85 (72.7%)
n (missing data)	234 (0)	117 (0)	117 (0)
Mean weight, kg (SD)	120.5 (21.7)	119.91 (18.7)	121.2 (24.4)
n (missing data)	234 (0)	117 (0)	117 (0)
Mean BMI, kg/m² (SD)	43.9 (5.6)	43.9 (5.1)	43.8 (6.1)
n (missing data)	234 (0)	117 (0)	117 (0)
BMI ≥ 50 kg/m², n (%)	29 (12.4%)	14 (11.9%)	15 (12.58%)
n (missing data)	234 (1)	117 (0)	117 (0)
Type 2 Diabetes, n (%)	58 (27.5%)	30 (28.6%)	28 (26.4%)
n (missing data)	211 (23)	105 (12)	106 (11)
Mean HbA1c, % (SD)	7.6 (1.8)	7.5 (1.7)	7.8 (1.8)
n (missing data)	57 (1)	30 (0)	27 (1)
Mean Duration of diabetes, years (SD)	7.8 (7.2)	7.8 (8.4)	7.8 (6.1)
n (missing data)	48 (10)	23 (7)	25 (3)
On oral anti-diabetic agents, n (%)	43 (89.6%)	22 (91.7%)	21 (87.5%)
n (missing data)	48 (10)	24 (0)	24 (0)
On GLP-1 agonist, n (%)	13 (27.1%)	6 (25.0%)	7 (29.2%)
n (missing data)	48 (0)	24 (0)	24 (0)
On Insulin, n (%)	18 (37.5%)	8 (33.3%)	10 (41.7%)
n (missing data)	48 (0)	24 (0)	24 (0)
Mean Duration of insulin therapy, years (SD)	8.3 (8.5)	11.5 (10.4)	5.5 (5.5)
n (missing data)	17 (1)	8 (0)	9 (1)
Arterial hypertension, n (%)	71 (30.7%)	33 (28.5%)	38 (33.0%)
n (missing data)	231 (3)	116 (1)	115 (2)
Dyslipidemia, n (%)	42 (18.2%)	20 (17.2%)	22 (19.1%)
n (missing data)	231 (3)	116 (1)	115 (2)
Sleep apnea, n (%)	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
Mean HbA1c, % (SD)	5.8 (0.9)	6.1 (0.9)	5.6 (0.8)	0.055
n (missing data)	39 (19)	17 (13)	22 (6)	
Mean Decrease in HbA1c from baseline, % (SD)	-1.9 (1.5)	-1.3 (1.0)	-2.3 (1.6)	0.025
n (missing data)	38 (20)	17 (13)	21 (7)	
Mean fasting glycemia, mmol/l (SD)	5.8 (2.2)	6.1 (2.9)	5.6 (1.5)	0.801
n (missing data)	42 (16)	20 (10)	22 (6)	
Mean decrease in FG from baseline, mmol/l (SD)	-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
Decrease in LDL-C from baseline, mmol/l (SD)	-0.4 (1.0)	-0.4 (1.0)	-0.4 (1.1)	0.97
n (missing data)	102 (132)	49 (68)	53 (64)	
Increase in HDL-C from baseline, mmol/l (SD)	+0.3 (0.3)	+0.3 (0.3)	+0.3 (0.3)	1
n (missing data)	105 (129)	50 (67)	55 (62)	
Decrease in Total cholesterol from baseline, mmol/l (SD)	-0.3 (1.0)	-0.3 (1.0)	-0.4 (1.1)	0.82
n (missing data)	105 (129)	49 (68)	56 (61)	
Decrease in Triglycerides from baseline, mmol/l (SD)	-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 (SD) 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
Type of SAE:	66	24	42	
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%)	1	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