Bariatric-metabolic surgery versus lifestyle intervention plus best medical care in non-alcoholic steatohepatitis (BRAVES): a multicenter, open-label, randomized-controlled trial

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IFSO
NAPOLI
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No potential conflict of interest to report

BACKGROUND

The NEW ENGLAND JOURNAL of MEDICINE
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Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes

Philip R. Schauer, M.D., Sangeeta R. Kashyap, M.D., Kathy Wolski, M.P.H., Stacy A. Brethauer, M.D., John P. Kirwan, Ph.D., Claire E. Pothier, M.P.H., Susan Thomas, R.N., Beth Abood, R.N., Steven E. Nissen, M.D., and Deepak L. Bhatt, M.D., M.P.H.

Diabetologia (2016) 59:945–953
DOI 10.1007/s00125-016-3905-x

ARTICLE

Gastric bypass surgery vs intensive lifestyle and medical intervention for type 2 diabetes: the CROSSROADS randomised controlled trial

David E. Cummings[1] · David E. Arterburn[2] · Emily O. Westbrook[2] · Jessica N. Kuzma[3] · Skye D. Stewart[4] · Chun P. Chan[4] · Steven N. Bock[5] · Jeffrey T. Landers[6] · Mario Kratz[3] · Karen E. Foster-Schubert[3] · David R. Flum[4]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bariatric Surgery versus Conventional Medical Therapy for Type 2 Diabetes

Geltrude Mingrone, M.D., Simona Panunzi, Ph.D., Andrea De Gaetano, M.D., Ph.D., Caterina Guidone, M.D., Amerigo Iaconelli, M.D., Laura Leccesi, M.D., Giuseppe Nanni, M.D., Alfons Pomp, M.D., Marco Castagneto, M.D., Giovanni Ghirlanda, M.D., and Francesco Rubino, M.D.

Bariatric Surgery vs Lifestyle Intervention for Diabetes Treatment: 5-Year Outcomes From a Randomized Trial

Anita P. Courcoulas,[1] James W. Gallagher,[1] Rebecca H. Neiberg,[2] Emily B. Eagleton,[1] James P. DeLany,[3] Wei Lang,[4] Suriya Punchai,[1,5] William Gourash,[6] and [illegible]n M. Jakicic[7]

THE LANCET
Volume 397 · Number 10271 · Pages 253-346 · January 23-29, 2021 www.thelancet.com

"Metabolic surgery is more effective than conventional medical therapy in the long-term control of type 2 diabetes."

JAMA | Original Investigation

Lifestyle Intervention and Medical Management With vs Without Roux-en-Y Gastric Bypass and Control of Hemoglobin A_{1c}, LDL Cholesterol, and Systolic Blood Pressure at 5 Years in the Diabetes Surgery Study

Sayeed Ikramuddin, MD, MHA; Judith Korner, MD, PhD; Wei-Jei Lee, MD, PhD; Avis J. Thomas, MS; John E. Connett, PhD; John P. Bantle, MD; Daniel B. Leslie, MD; Qi Wang, MS; William B. Inabnet III, MD; Robert W. Jeffery, PhD; Keong Chong, MD; Lee-Ming Chuang, MD, PhD; Michael D. Jensen, MD; Adrian Vella, MD; Leaque Ahmed, MD; Kumar Belani, MD; Charles J. Billington, MD

The NEW ENGLAND JOURNAL of MEDICINE

THE LANCET

Bariatric–metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial

Geltrude Mingrone, Simona Panunzi, Andrea De Gaetano, Caterina Guidone, Amerigo Iaconelli, Giuseppe Nanni, Marco Castagneto, Stefan Bornstein, Francesco Rubino

THE LANCET
Diabetes & Endocrinology

Gastric bypass versus sleeve gastrectomy in patients with type 2 diabetes (Oseberg): a single-centre, triple-blind, randomised controlled trial

Dag Hofsø, PhD • Farhat Fatima, MD • Heidi Borgeraas, PhD • Prof Kåre Inge Birkeland, PhD • Hanne Løvdal Gulseth, PhD • Jens Kristoffer Hertel, PhD • et al. Show all authors

ORIGINAL ARTICLE

Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 5-Year Outcomes

Philip R. Schauer, M.D., Deepak L. Bhatt, M.D., M.P.H., John P. Kirwan, Ph.D., Kathy Wolski, M.P.H., Ali Aminian, M.D., Stacy A. Brethauer, M.D., Sankar D. Navaneethan, M.D., M.P.H., Rishi P. Singh, M.D., Claire E. Pothier, M.P.H., Steven E. Nissen, M.D., and Sangeeta R. Kashyap, M.D., for the STAMPEDE Investigators*

Metabolic surgery versus conventional medical therapy in patients with type 2 diabetes: 10-year follow-up of an open-label, single-centre, randomised controlled trial

Geltrude Mingrone, Simona Panunzi, Andrea De Gaetano, Caterina Guidone, Amerigo Iaconelli, Esmeralda Capristo, Ghassan Chamseddine, Stefan R Bornstein, Francesco Rubino

Clinical and Patient-Centered Outcomes in Obese Patients With Type 2 Diabetes 3 Years After Randomization to Roux-en-Y Gastric Bypass Surgery Versus Intensive Lifestyle Management: The SLIMM-T2D Study

BACKGROUND

- Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease globally, affecting **55%** of people with **type 2 diabetes** and **75%** of those with **obesity**.

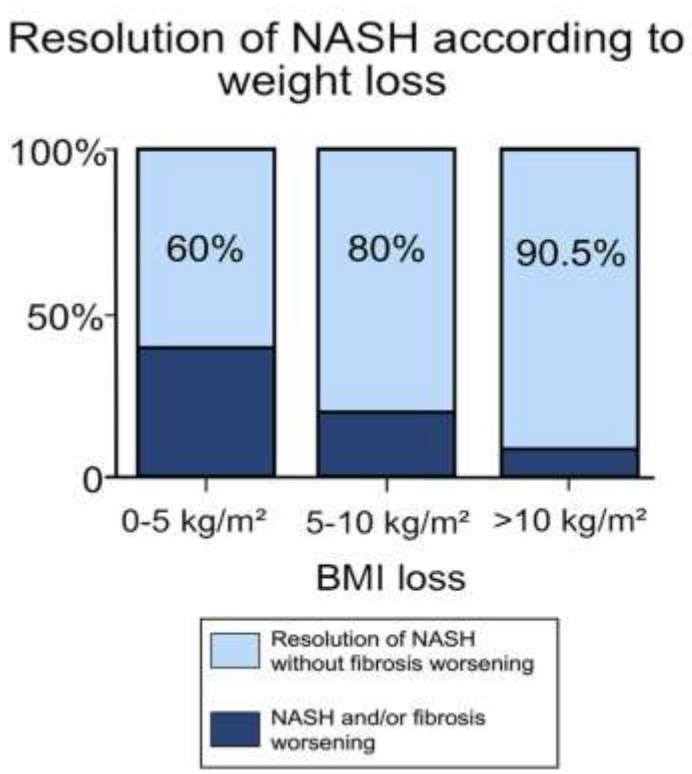
- By **2030**, NASH will affect **27 million** people in the USA alone.

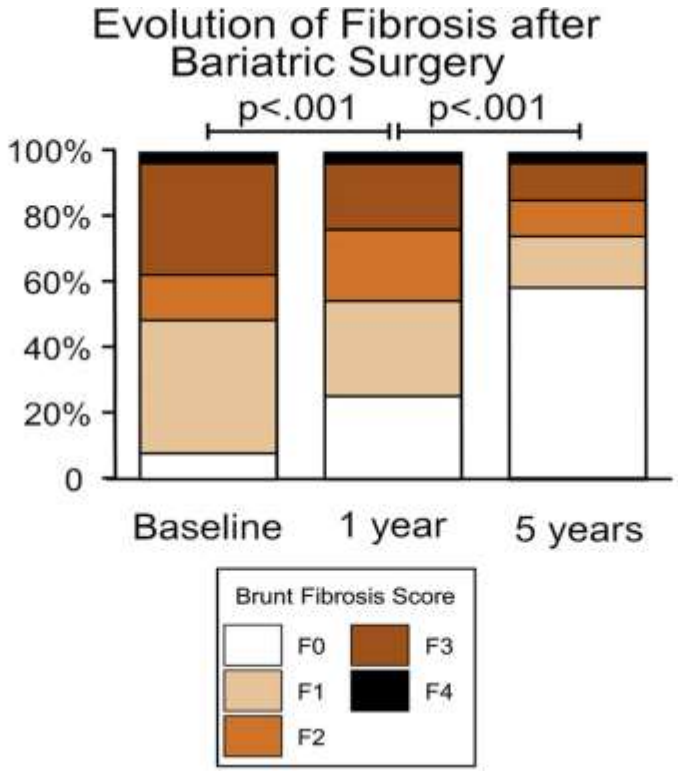
- **Weight loss** is recommended in subjects with **NAFLD/NASH**, but there are currently no specific surgical or pharmacologic interventions for these conditions.

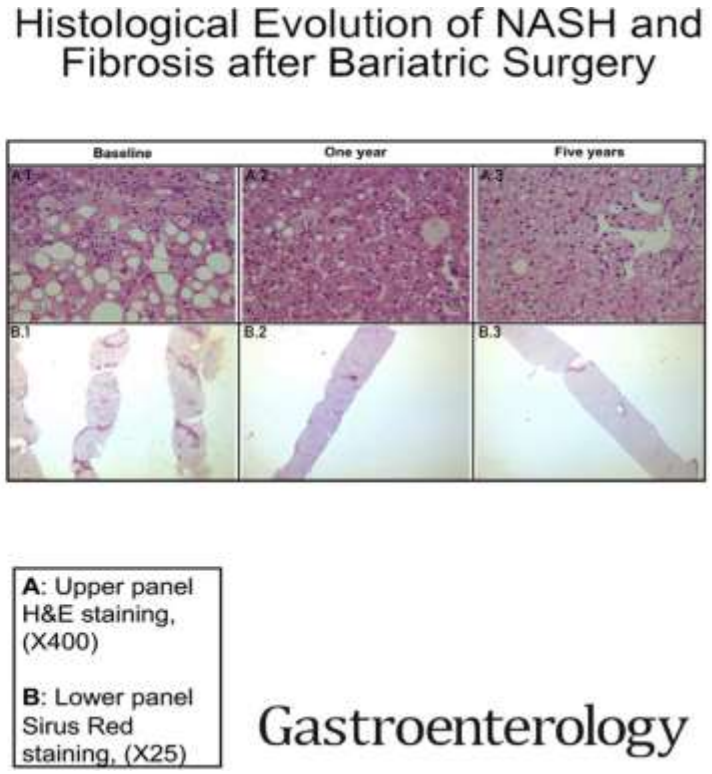
- No drugs have yet received approval by the FDA or by the EMA as a treatment for NASH.

BACKGROUND

In **observational studies**, bariatric-metabolic surgery appeared to induce dramatic **improvement of both NASH and fibrosis**. Lassailly et al.[1] reported resolution of **NASH** in **84%** of liver samples from 180 people with severe obesity at 5-year follow-up, with improved liver **fibrosis** in **70.2%** of participants[1]. Similar findings were reported also in another smaller observational study of 66 subjects[2].







1. Lassailly et al. Gastroenterology. 2020; 159:1290-1301.e5
2. Pais et al. Hepatology. 2022; 76:456-468

AIM

Open-label, multicentre, randomized trial specifically designed to investigate and compare the efficacy and safety of bariatric-metabolic surgery with lifestyle intervention plus best medical care as a treatment of histologically confirmed NASH.

OUTCOMES

Primary endpoint: **Histological resolution of NASH without worsening of fibrosis**; (the latter is defined as an increase of one stage or more on the NASH-CRN fibrosis score, at 1 year follow-up)

Secondary endpoints:

- Improvement of fibrosis of at least one stage severity without worsening of NASH,
- NAS improvement of at least 1 grade,
- Worsening of fibrosis,
- Diabetes control,
- Insulin sensitivity,
- Lipid profile,
- Safety

Post-hoc analysis

A post-hoc analysis was conducted to assess the primary endpoint as well as the main secondary endpoint of the study (improvement in liver fibrosis by ≥1 stage of the NASH-CRN fibrosis score without worsening of NASH) in participants with NAS=4 or NAS≥5 in the ITT analysis and NAS≥4 and F2-F3 in the PP analysis. Moreover, we computed the % of participants who had ≥2 point improvement in fibrosis stage in the three groups.

BRAVES trial Participating Centers:

1. Department of Medical and Surgical Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS,Università Cattolica del Sacro Cuore, Rome, Italy.
2. Department of Surgical Sciences, Sapienza University of Rome, Rome, Italy.
3. Department of Endocrine and Bariatric-metabolic surgery, San Camillo Hospital, Rome, Italy.

METHODS

Sample size calculation

The sample size calculation was based on a large sample test for proportions using the approach of a **Pairwise Comparison**. In the present study **three comparisons** were planned:

1. **RYGB vs. LM**
2. **SG vs. LM**
3. **RYGB vs. SG**

The **power** was set to **80%** and all the **tests** were **two-tailed**.
Sample size of **77 participants per group** was calculated (with the maximum sample size derived from the third comparison). **Considering an attrition rate of 20%, we enrolled 96 participants in each group for a total of 288 subjects overall**.

METHODS

Eligibility Criteria, Diagnosis of NASH and Staging of Fibrosis

- We screened subjects with obesity (age 25-70 years; BMI=30-55kg/m2), with or without T2D
- To determine the likelihood of NASH and liver fibrosis using the **NAFLD fibrosis score (NFS)**.
  - **Cut off: > −1.455** excellent negative predictive value giving high probability of fibrosis and NASH
- Ultrasound guided percutaneous liver biopsy (baseline + 1 year f-u): **NAFLD activity score (NAS)** algorithm proposed by the NASH Clinical Research Network

- **The patients enrolled in this study had at least 1 grade of hepatocyte ballooning and of inflammation and at least 1 grade of steatosis and fibrosis F1 to F3**

METHODS

Exclusion Criteria

- Coronary event or procedure (myocardial infarction, unstable angina, coronary artery bypass, surgery or coronary angioplasty) in the previous 6 months;
- Liver cirrhosis;
- End stage renal failure;
- Any other life-threatening non-cardiac disease;
- Pregnancy;
- Inability to give informed consent;
- Substantial alcohol consumption (>20g/day for women or >30g/day for men);
- Wilson's disease;
- Lipodystrophy;
- Parenteral nutrition;
- Abetalipoproteinemia;
- Interfering medications (e.g., amiodarone, methotrexate, tamoxifen, corticosteroids);
- Participation in any other concurrent therapeutic clinical trial.
- Specific exclusion criteria for subjects with T2D: HbA1c≥10.0%; recurrent major hypoglycaemia or hypoglycaemic unawareness as judged by the principal investigators (PIs).

CONSORT 2010 Flow Diagram

Assessed for eligibility (n=431)

Between April 15, 2019, and June 21, 2021, 431 subjects were screened

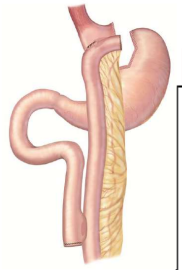
Enrollment

Excluded (n=143)
- Not meeting inclusion criteria (n=103)
- Declined to participate (n=40)

- **103 (24%)** were not eligible because of the absence of NASH
- **40 (9%)** declined to participate
- **288 (67%)** participants were deemed eligible for the study

Randomized (n=288)

Allocation



Roux en Y gastric bypass

Allocated to intervention RYGB (n=96)
- Received allocated intervention (n=89)
- Refused to receive the allocated intervention (n=7)

Sleeve gastrectomy

Allocated to intervention SG (n=96)
- Received allocated intervention (n=88)
- Refused to receive the allocated intervention (n=8)

Lifestyle int. + medical care

Allocated to intervention LM (n=96)
- Received allocated intervention (n=86)
- Refused to receive the allocated intervention (n=10)

Follow-Up

Roux en Y gastric bypass	Sleeve gastrectomy	Lifestyle int. + medical care
Lost to follow-up (geographical distance) (n=9) Discontinued intervention (IC withdrawal) (n=3)	Lost to follow-up (geographical distance) (n=7) Discontinued intervention (IC withdrawal) (n=2)	Lost to follow-up (geographical distance) (n=6) Discontinued intervention (IC withdrawal) (n=0)

Analysis

Roux en Y gastric bypass	Sleeve gastrectomy	Lifestyle int. + medical care
Analysed (n=77) Excluded from analysis (n=0)	Analysed (n=79) Excluded from analysis (n=0)	Analysed (n= 80) Excluded from analysis (n=0)

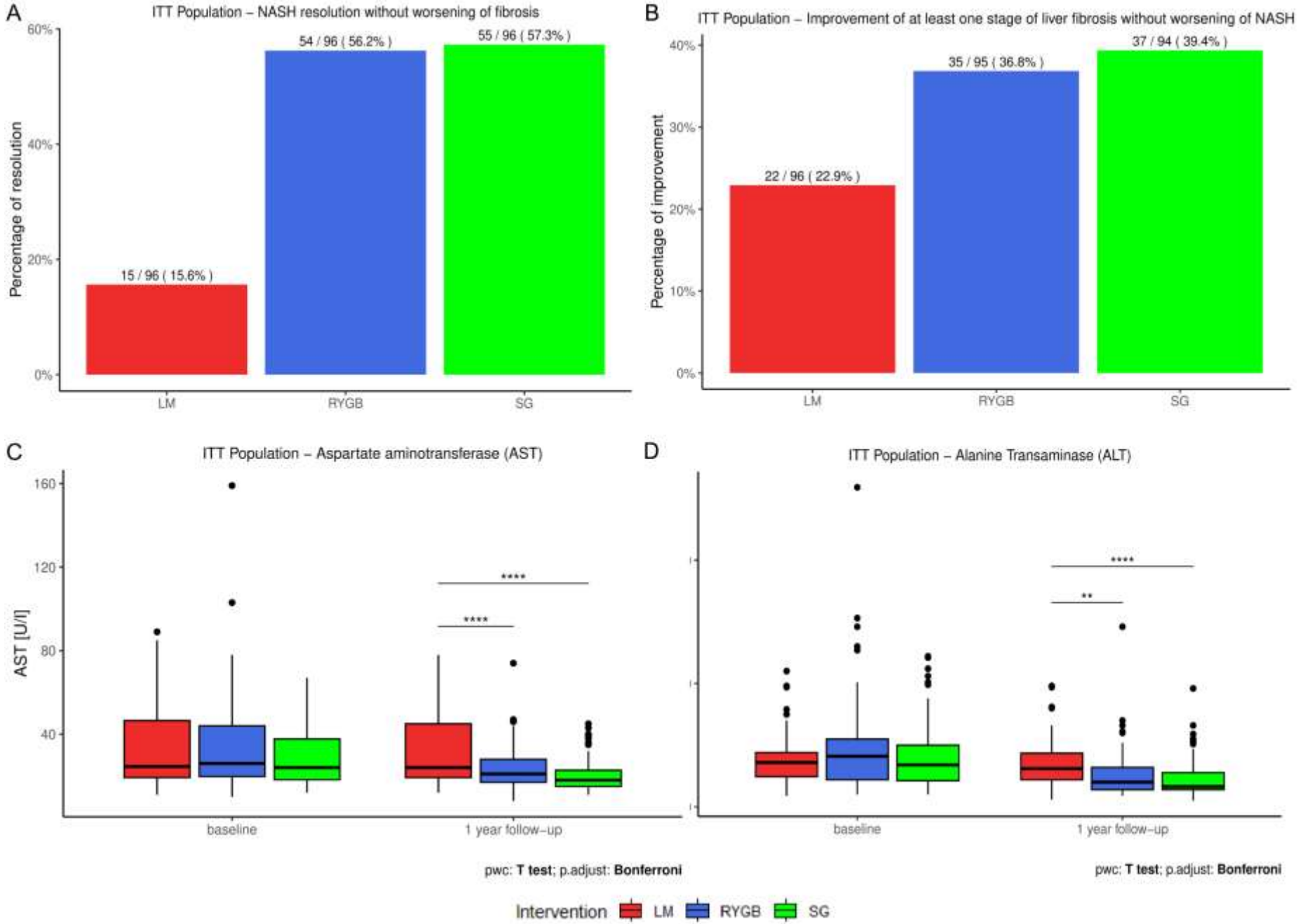
236 participants (**82%**) completed the trial

RESULTS

		LM	RYGB	SG	P Overall	P RYGB-LM	P SG-LM	P SG-RYGB
Age (years)		47.95±10.39	46.44±8.50	46.84±8.81	0.574	0.568	0.731	0.962
Weight (kg)	baseline	116.07±22.9	127.69±19.54	118.84±18.68	0.001	**0.001**	0.67	**0.02**
	1 year	109.82±24.15	87.02±15.66	89.77±16.45				
	%change	-5.48±7.57	-31.80±7.50	-23.98±11.58	<0.001	**<0.001**	**<0.001**	**<0.001**
BMI (kg/m^2)	baseline	41.16±6.4	43.39±4.14	40.76±3.74	0.002	**0.013**	0.869	**0.003**
	1 year	39.07±7.55	29.70±4.26	30.82±4.08				
	%change	-5.38±7.61	-31.50±7.92	-23.91±11.53	<0.001	**<0.001**	**<0.001**	**<0.001**
NAS score	baseline	4.21±1	4.21±1.00	4.18±1.11	0.973	1	0.975	0.982
	1 year	3.45±1.31	1.82±0.82	1.99±1.12				
	%change	-17.08±28.59	-56.20±19.57	-52.83±25.46	<0.001	**<0.001**	**<0.001**	0.674
Fibrosis number (%) F0	baseline	0 (0%)	1 (1.3%)	1 (1.3%)	0.596	0.98	0.995	1
	1 year	2 (2.5%)	7 (9.1%)	9 (11.4%)	0.090	0.152	0.058	0.834
F1	baseline	34 (42.5%)	38 (49.3%)	41 (51.9%)	0.471	0.483	0.304	0.874
	1 year	41 (51.2%)	58 (75.3%)	54 (68.3%)	0.005	**0.003**	**0.0442**	0.430
F2	baseline	31 (38.7%)	33 (42.8%)	28 (35.4%)	0.639	0.718	0.789	0.433
	1 year	26 (32.5%)	11 (14.3%)	12 (154.2%)	0.006	**0.012**	**0.018**	1
F3	baseline	15 (18.8%)	5 (6.5%)	9 (11.4%)	0.062	0.039	0.2827	0.429
	1 year	11 (13.8%)	1 (1.3%)	3 (3.8%)	0.003	**0.008**	**0.053**	0.631
AST (U/l)	baseline	35.29±21.41	36.89±24.20	29.27±14.05	0.062	0.894	0.21	0.062
	1 year	32.80±17.65	22.82±8.69	20.67±8.58				
	%change	7.75±67.83	-22.04±39.73	-23.60±21.14	<0.001	**0.001**	**<0.001**	0.976
ALT (U/l)	baseline	38.34±18.6	48.09±37.21	41.78±27.58	0.128	0.115	0.762	0.387
	1 year	33.65±16.1	22.86±11.30	22.63±16.44				
	%change	0.22±61.79	37.41±37.52	38.70±29.06	<0.001	**<0.001**	**<0.001**	0.983

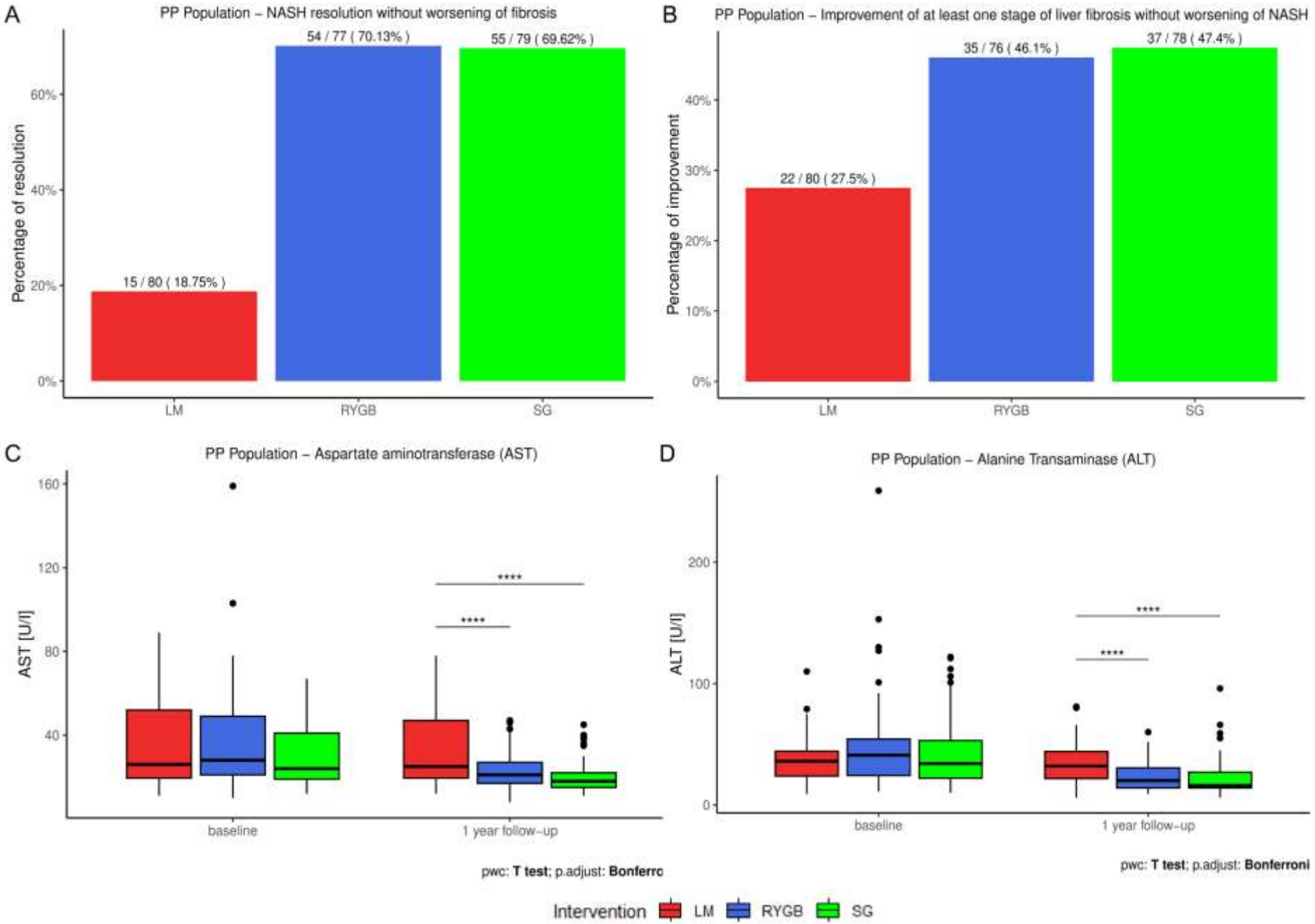
RESULTS

Intention to treat Population

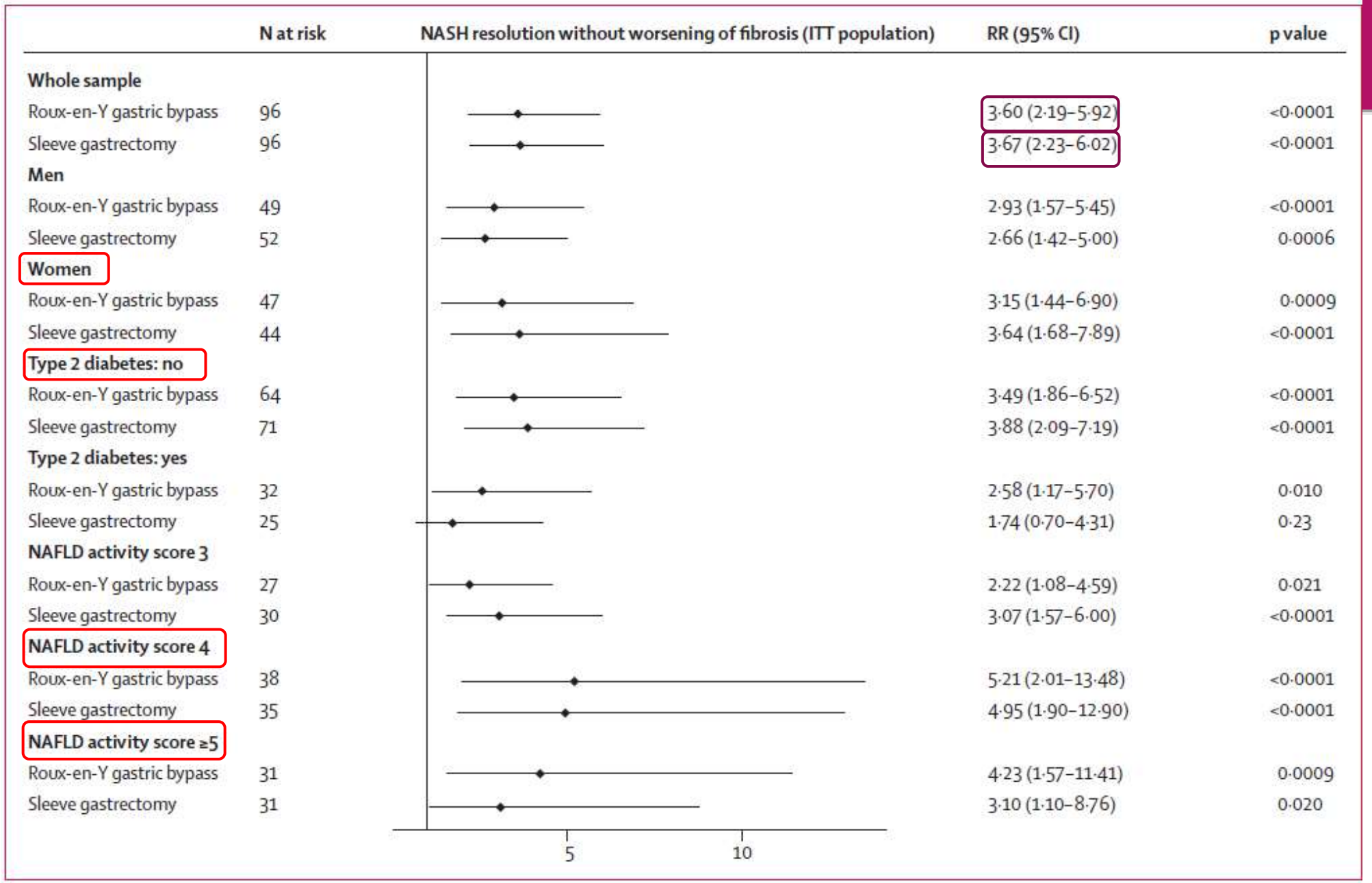


RESULTS

Per protocol Population

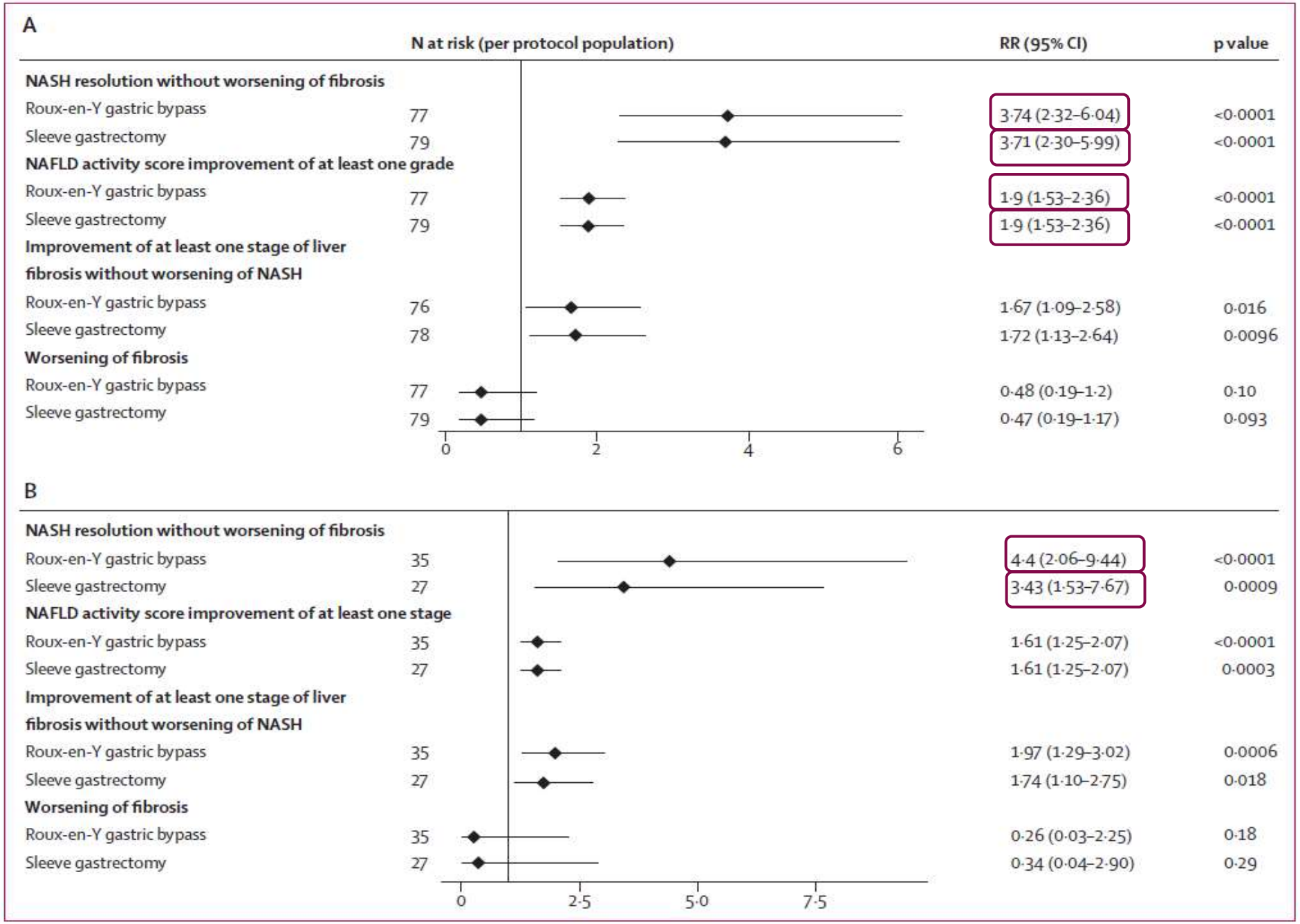


RESULTS



Response for primary histological endpoint at 1-year follow-up and subgroup analysis stratified by sex, diabetes, and NASH grade in the ITT population

RESULTS



Response for primary and secondary histological endpoints at 1-year follow-up for the per protocol population in the whole sample and in the sample with NAFLD activity score ≥4 and fibrosis stages F2 or F3 (A) Response for primary and secondary histological endpoints at 1-year follow-up in the per protocol population. (B) Response for primary and secondary histological endpoints at 1-year follow-up in the subgroup of patients with severe NASH (NAFLD activity score ≥4 and stages 2, F2, or 3, F3, fibrosis) in the per protocol population.

		LM	RYGB	SG	P RYGB-LM	P SG-LM	P SG-RYGB
HbA1C (%)	baseline	6.42±1.87	6.93±2.23	6.00±1.21	0.227	0.376	**0.006**
	1 year	5.87±1.87	5.95±1.74	5.55±0.60			
	%change	-1.49±57.16	-10.66±25.18	-3.46±28.29	0.158	0.735	0.496
Glucose (mmol/l)	baseline	6.72±2.41	6.90±3.57	5.72±1.36	0.914	**0.051**	**0.016**
	1 year	5.75±2.28	4.39±0.57	4.56±0.86			
	%change	-10.22±26.11	-27.19±20.62	-18.11±16.09	**<0.001**	0.068	**0.025**
Insulin (U/l)	baseline	21.76±7.59	28.96±11.24	31.75±19.58	**0.026**	**0.002**	0.541
	1 year	17.77±8.33	8.01±4.02	14.99±16.85			
	%change	-11.69±47.57	-52.19±131.60	-49.48±43.72	0.061	0.103	0.986
Homa-IR	baseline	6.64±3.14	9.40±6.56	8.63±7.33	0.065	0.258	0.791
	1 year	4.63±2.73	1.57±0.90	3.54±5.29			
	%change	-19.97±49.47	-62.01±119.84	-57.06±40.35	**0.032**	0.08	0.947
HDL-cholesterol	baseline	44.27±14.57	43.80±13.95	42.27±9.69	0.976	0.63	0.74
(mg/dl)	1 year	46.1±13.65	53.00±11.55	49.38±12.68			
	%change	7.25±25.55	29.92±43.55	18.53±24.10	**<0.001**	0.11	0.081
LDL-cholesterol	baseline	114.93±29.61	124.75±47.58	120.08±38.70	0.351	0.738	0.755
(mg/dl)	1 year	102.85±35.29	85.56±30.84	109.67±32.71			
	%change	-7.34±30.69	-24.60±34.75	-5.87±21.01	**0.003**	0.955	**<0.001**
Total cholesterol	baseline	190.38±37.47	199.44±46.76	193.58±43.81	0.435	0.897	0.68
(mg/dl)	1 year	174.83±41.88	158.49±34.91	182.19±37.62			
	%change	-6.58±21.68	-18.08±21.65	-4.59±13.86	**0.002**	0.811	**<0.001**
Triglycerides	baseline	152.31±83.04	160.03±69.40	156.18±72.09	0.816	0.949	0.945
(mg/dl)	1 year	131.14±73.67	98.51±43.43	115.72±53.18			
	%change	-7.26±40.04	-33.05±28.82	-18.99±45.29	**<0.001**	0.17	0.067

RESULTS

Type 2 diabetes (baseline):

- 35 (37%) people in the lifestyle modification group,
- 32 (33%) in the Roux-en-Y gastric bypass group,
- 25 (26%) in the sleeve gastrectomy

	Baseline			1-year follow-up		
	LM (n=34)	RYGB (n=25)	SG (n=17)	LM (n=32)	RYGB (n=8)	SG (n=6)
Metformin	34	25	17	32	8	6
Pioglitazone	34	0	0	32	0	0
Empagliflozin	12	15	10	12	6	4
Dapagliflozin	7	8	7	8	2	2
Liraglutide	34	0	0	32	0	0
Long-acting insulin	18	20	9	5	0	0

Diabetes remission (defined as HbA1c<6·5% without ongoing diabetes medications) occurred in:

- 2 (6%) of 34 participants in the lifestyle modification group,
- 17 (68%) of 25 in the Roux-en-Y gastric bypass group,
- 11 (65%) of 17 in the sleeve gastrectomy group (p<0·0001).

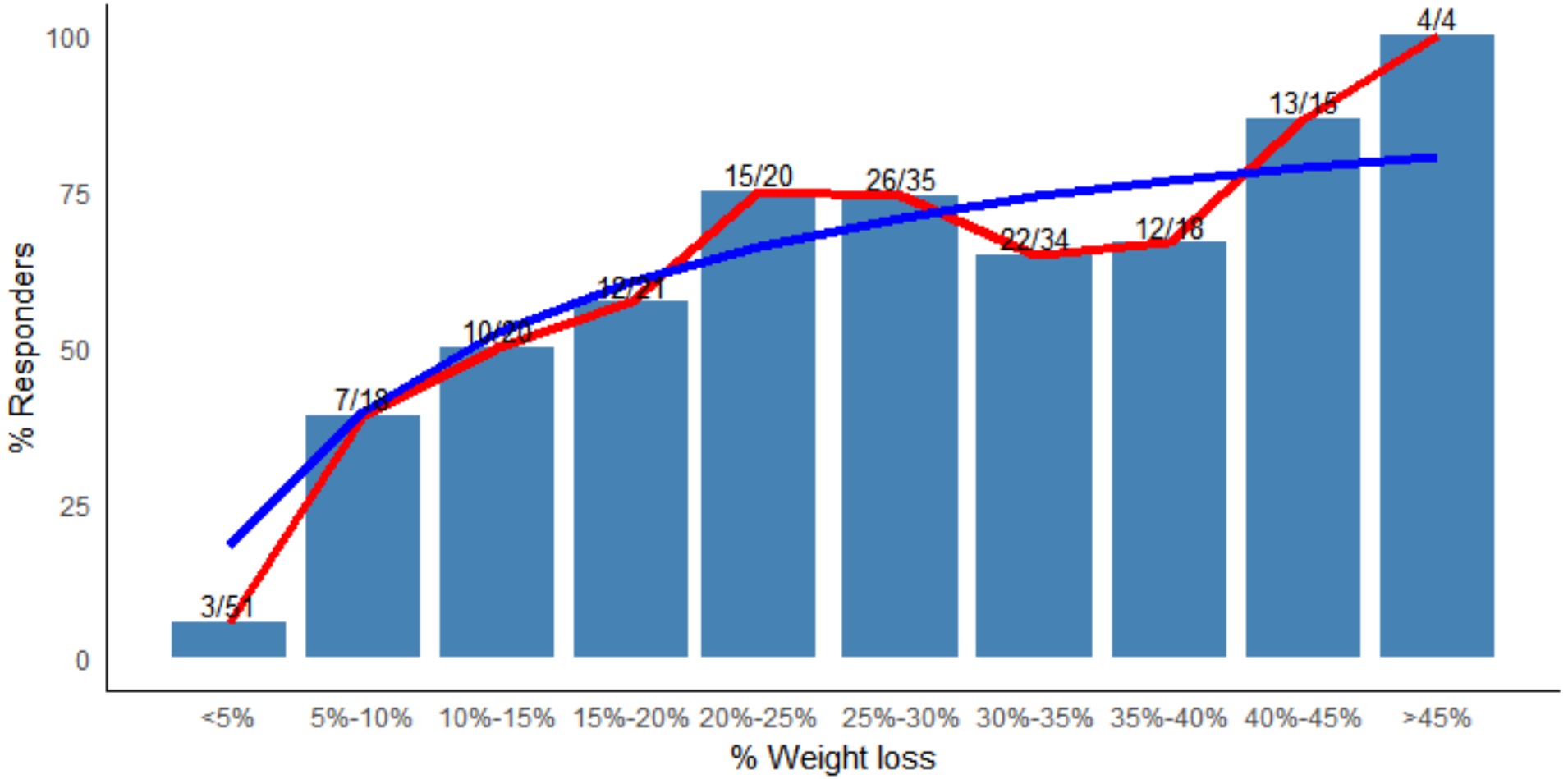
RESULTS

➢ Responders

Responders (patients who achieved the primary endpoint)

- **lost more weight,**
- **higher rates of diabetes remission (83.3% vs. 28.6%,P<0.0001),**
- **greater improvement of glycaemic control, insulin resistance and transaminase levels compared to non-responders**

RESULTS



The percentage of participants with **NASH resolution without fibrosis worsening increased almost linearly with the degree of weight loss up to <u>20% weight reduction</u>**, then the increase was non-linear indicating a relatively smaller influence of weight loss on NASH resolution rate above a 20% weight-reduction threshold.

RESULTS

SAFETY

Overview of Adverse Events That Occurred during the Treatment Period	RYGB (n= 77)	SG (n=79)	LM (n=80)
Early surgical AEs			
Intestinal Obstruction (functional stenosis of the entero-enteric anastomosis) and peritoneal abscess	1	0	0
Intussusception	2	0	0
Incisional hernia	0	1	0
Internal hernia	1	0	0
Staple line leak	0	2	0
Gastric stenosis (endoscopic balloon dilation)	0	2	0
Hemoperitoneum	0	1	0
Late medical AEs	0	0	0
Dumping syndrome	4	1	0
Constipation	4	6	3
Diarrhea	2	1	2
Gastroesophageal reflux disease	2	32	4
Kidney stones (need for nephrostomy)	1	0	1
Vomiting	2	8	3
Anaemia	2	0	0
Fatigue	2	2	3
Biliary sludge	5	4	2
Nausea	0	4	4
Epigastric pain	4	1	2
SARS Covid 19 Infection	5	3	6
Alcoholism arising 10-12 months after intervention	1	0	0
Liver biopsy related AEs	0	0	0
Pain (right side and/or shoulder)	9	10	10
Intra-parenchimal bleeding	0	1	1
Extracapsular hematoma	1	0	0
Pain associated with fever	0	0	1

CONCLUSIONS

- Bariatric-metabolic surgery is more effective than lifestyle interventions and best medical care in the treatment of NASH.

- The ability of surgery to control and even improve fibrosis associated with NASH is of particular clinical relevance given the fact that fibrosis is the main predictor of liver complications and cardiovascular mortality and morbidity in NASH.

- NASH should be considered as an important factor in decision making around prioritization of surgery in people with obesity and type-2 diabetes. Currently, there are no mechanisms for prioritization of bariatric-metabolic surgery in most healthcare systems and access to surgery is often based on a first-come-first-served basis.

12th

CONGRESS OF THE INTERNATIONAL FEDERATION
FOR THE SURGERY OF OBESITY AND METABOLIC DISORDERS
- EUROPEAN CHAPTER -

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Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Evangela Covert 301-796-4075.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2018
Clinical/Medical

2. Late Phase 2 Trials

Sponsors should consider the following during late phase 2 trials for drug development for treatment of noncirrhotic NASH with liver fibrosis.

- Once proof of pharmacological activity has been demonstrated in a NASH population of interest, the phase 2 program should explore the treatment effect on histological endpoints.
- A successful phase 2 program that supports initiation of phase 3 trials should provide the following:
  - Evidence of efficacy on a histological endpoint (i.e., reduction of inflammatory changes, improvement in fibrosis, or both).

C. Phase 3 Development Considerations

This section addresses phase 3 drug development for treatment of noncirrhotic NASH with liver fibrosis, which includes clinical trials intended to support a marketing application.

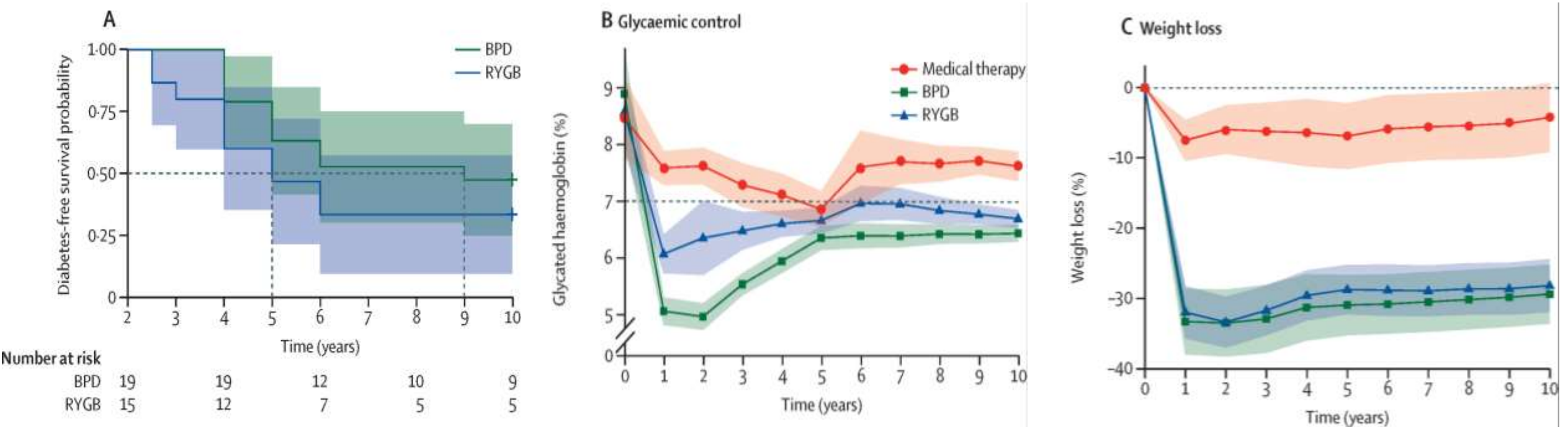
1. Patient Population/Main Enrollment Criteria

a. Patient inclusion criteria

Sponsors should consider the following patient inclusion criteria for clinical trials in drug development for treatment of noncirrhotic NASH with liver fibrosis.

- Patients should have a histological diagnosis of NASH with liver fibrosis made close to the time of trial enrollment (i.e., no more than 6 months before enrollment). Because baseline histology is critical for efficacy evaluation, liver biopsies obtained more than 6 months before enrollment may not represent an accurate status of the disease at the beginning of the trial.
- FDA has accepted as critical inclusion criteria in NASH trials a NASH activity score (NAS) greater than or equal to 4 with at least 1 point each in inflammation and ballooning *along with* a NASH Clinical Research Network (CRN) fibrosis score greater than stage 1 fibrosis but less than stage 4 fibrosis. These two criteria ensure that patients have evidence of steatohepatitis and significant liver fibrosis without cirrhosis at enrollment. Depending on the drug's mechanism of action and anticipated effect on inflammation and/or fibrosis, the sponsor can propose for discussion with the FDA alternatives to the NAS and NASH/CRN fibrosis score. The sponsor should provide adequate scientific justification for the alternatives.

BACKGROUND



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T2D was, in fact, present in 35.6% of people in LM, 33.3% in RYGB and 26.0% in SG groups (P=0.280)

A total of 139 participants (48%) had stage F1 fibrosis, 114 (40%) had stage F2, and 32 (11%) had stage F3, while 3 participants (1%) had stage F0 fibrosis; the mean NAS grade was 4.19±1.03.

METHODS

Diet

Resting calorie requirements were calculated via the Harris-Benedict equation and an activity factor, and subjects were instructed not to change their activity level other than that suggested by physicians during the study. The diet contained 1/3 kcal less than the calculated energy expenditure and 30% fat of which 10% saturated, 55% low glycaemic index carbohydrates and 15% proteins. Compliance with the diet was estimated by assessing 3-day food diaries recorded every week for the first 6 months and then every month until 1 year.

Physical Activity

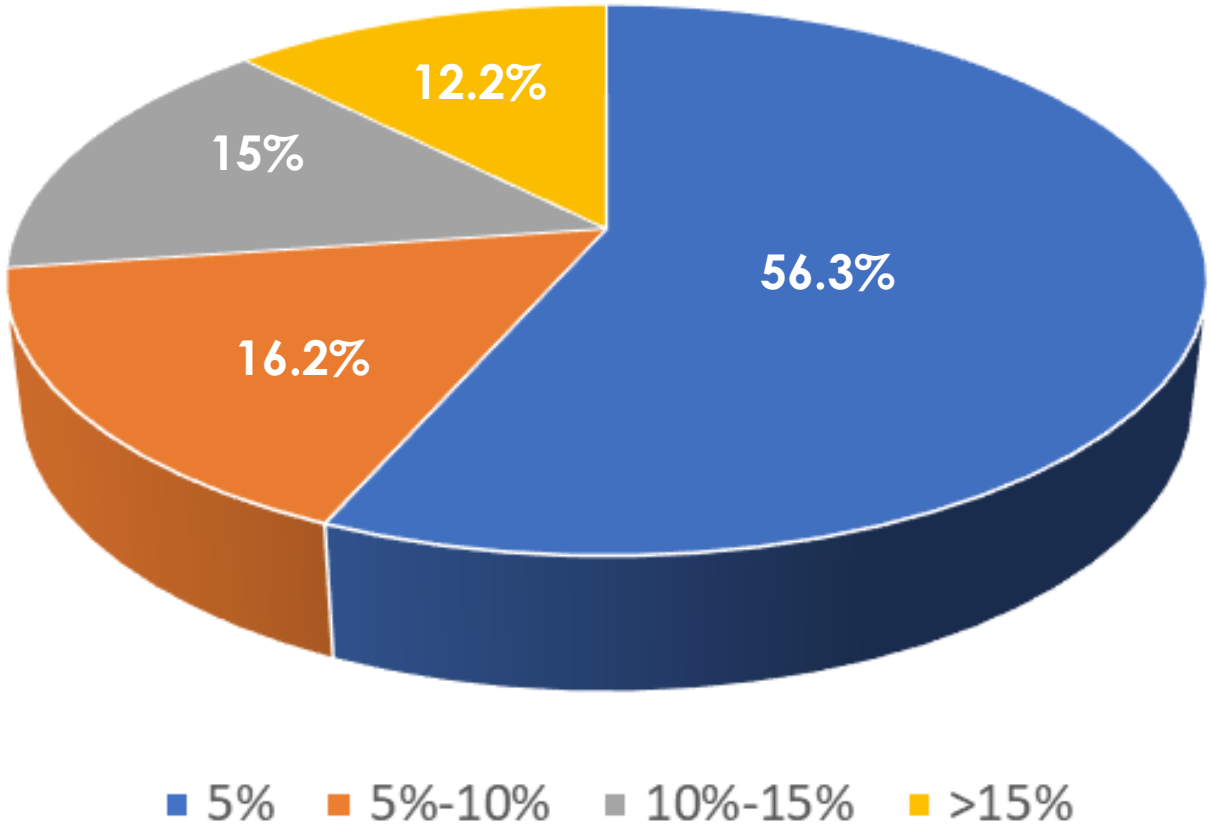
Participants were encouraged to gradually increase their walking to achieve 10,000 steps per day. A moderate intensity physical activity program of 1 hour of aerobic exercise 2-3 hours per week.

Baseline characteristics (intention-to-treat population)

	LM (n=96)	RYGB (n=96)	SG (n=96)	Surgical Interventions (n=192)
Age (years)	47.81±10.24	47.23±8.30	47.21±8.97	47.22±8.62
Weight (kg)	118.49±22.25	125.76±20.07	119.21±19.17	122.49±19.85
BMI (kg/m^2)	41.87±6.30	42.86±4.62	41.38±4.32	42.12±4.52
NAS score	4.17±0.97	4.14±0.97	4.16±1.07	4.15±1.02
HbA1C (%)	6.32±1.83	6.84±2.36	5.93±1.37	6.40±1.99
Glucose (mg/dl)	6.37±2.26	6.66±3.24	5.81±1.36	6.22±2.48
Insulin (U/l)	24.92±14.31	26.79±12.22	29.04±19.17	27.87±15.93
HOMA-IR	6.91±3.99	8.41±6.29	7.89±6.81	8.16±6.53
HDL-cholesterol(mg/dl)	43.40±13.28	45.56±16.07	44.31±15.56	44.92±15.78
LDL-cholesterol (mg/dl)	114.33±31.24	122.55±46.15	120.43±38.80	121.46±42.43
Total cholesterol (mg/dl)	189.09±37.69	199.02±43.95	196.93±44.66	197.95±44.21
Triglycerides (mg/dl)	159.99±80.52	161.11±73.28	156.72±73.61	158.89±73.28
AST (U/l)	33.48±19.93	35.04±23.03	28.52±13.32	31.84±19.12
ALT (U/l)	37.95±19.79	45.99±36.44	40.20±25.79	43.14±31.70

RESULTS

Weight loss in LM group

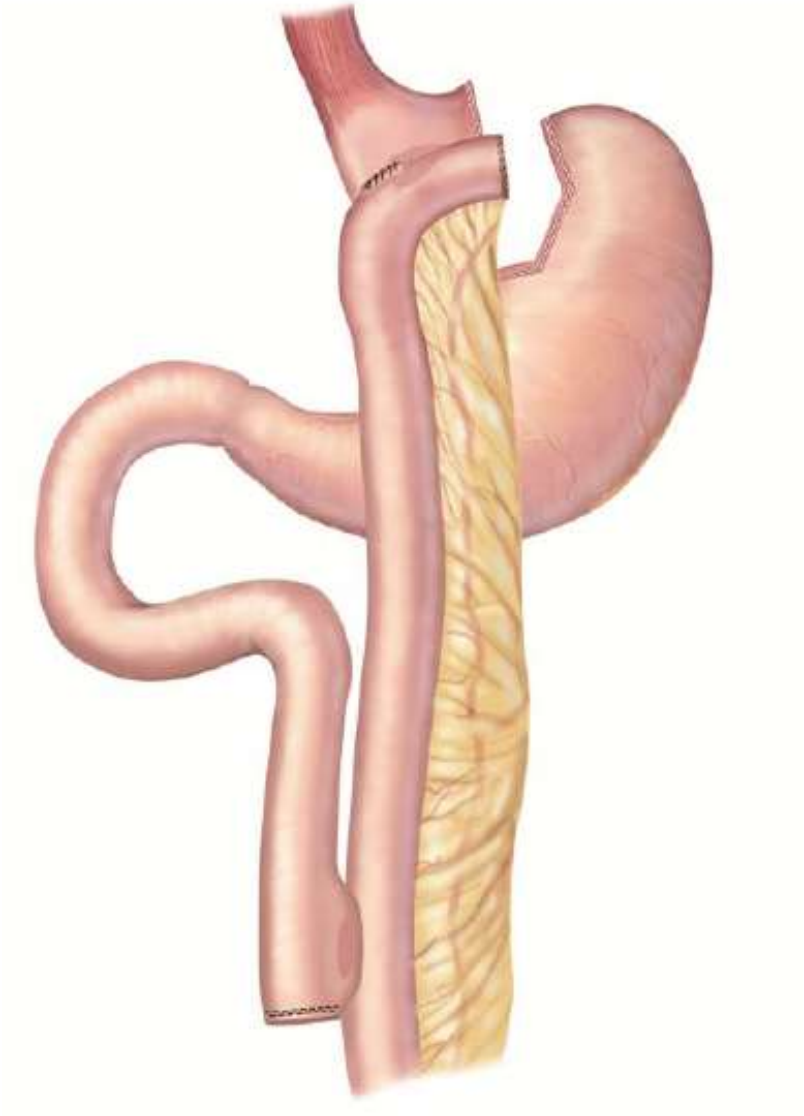


Subjects undergoing **RYGB** attained greater improvements in plasma levels of triglycerides, total-cholesterol, LDL-cholesterol and HDL-cholesterol compared to both LM and SG ($P<0.05$ for all comparisons). Similarly, people who underwent RYGB experienced greater reductions in fasting plasma glucose (from 6.9±3.57 to 4.39±0.57mmol/l; -27.19±20.62%), compared to LM (from 6.72±2.41 to 5.75±2.28 mmol/l; -10.22±26.11%,$P<0.001$) and SG (from 5.72±1.36 to 4.56±0.86 mmol/l; -18.11±16.09%,$P=0.025$). There was a greater improvement of insulin resistance among RYGB compared to the other interventions (HOMA-IR:-19.97 ±49.47%, -62.01±119.84% and -57.06±40.35% in LM, RYGB and SG, respectively, $P=0.029$).

RESULTS

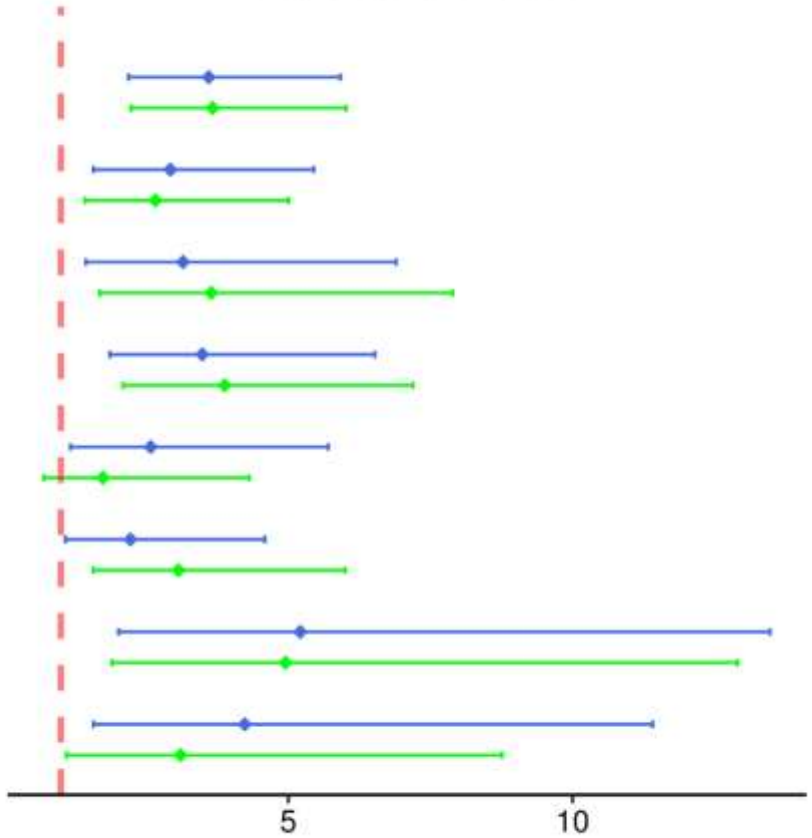
- **Stratifying by gender**, women had a higher probability to achieve the primary endpoint after bariatric-metabolic surgery as compared with men (2.93;95%CI:1.57-5.45, and 2.66; 95%CI:1.42-5.00, times higher after RYGB or SG than after LM in men and 3.15;95%CI:1.44-6.90, and 3.64;95%CI:1.68-7.89, in women, respectively).

- The probability of achieving the primary endpoint increased for individuals **without diabetes** with RRs equal to 3.49 (95%CI:1.86-6.52) and 3.88 (95%CI:2.09-7.19) for RYGB and SG, respectively.



RYGB

RESULTS



ITT Population	N at risk	RR	95% CI	P value
Whole Sample				
RYGB	96	3.6	2.19–5.92	<0.0001
SG	96	3.67	2.23–6.02	<0.0001
Men				
RYGB	49	2.93	1.57–5.45	<0.0001
SG	52	2.66	1.42–5	0.001
Women				
RYGB	47	3.15	1.44–6.9	0.001
SG	44	3.64	1.68–7.89	<0.0001
Diabetes: NO				
RYGB	64	3.49	1.86–6.52	<0.0001
SG	71	3.88	2.09–7.19	<0.0001
Diabetes: YES				
RYGB	32	2.58	1.17–5.7	0.01
SG	25	1.74	0.7–4.31	0.226
NAS=3				
RYGB	27	2.22	1.08–4.59	0.021
SG	30	3.07	1.57–6	<0.0001
NAS=4				
RYGB	38	5.21	2.01–13.48	<0.0001
SG	35	4.95	1.9–12.9	<0.0001
NAS>=5				
RYGB	31	4.23	1.57–11.41	0.001
SG	31	3.1	1.1–8.76	0.02