Bariatric surgery : What can we learn from responders and non responders ?

Guillaume Lassailly

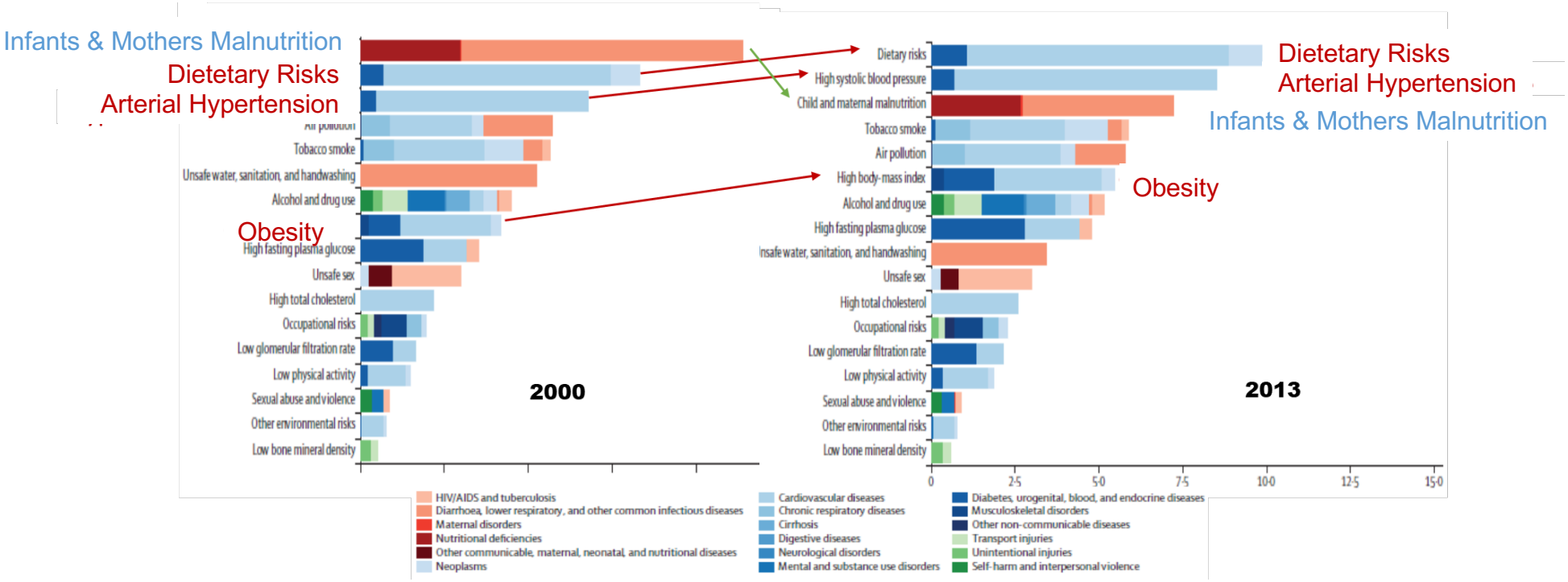
CHU de Lille, France

Conflict of interest

No conflict of interest

Introduction: A world threatened by the obesity pandemic.

A paradigme shift during the past two decades: from malnutrition to obesity

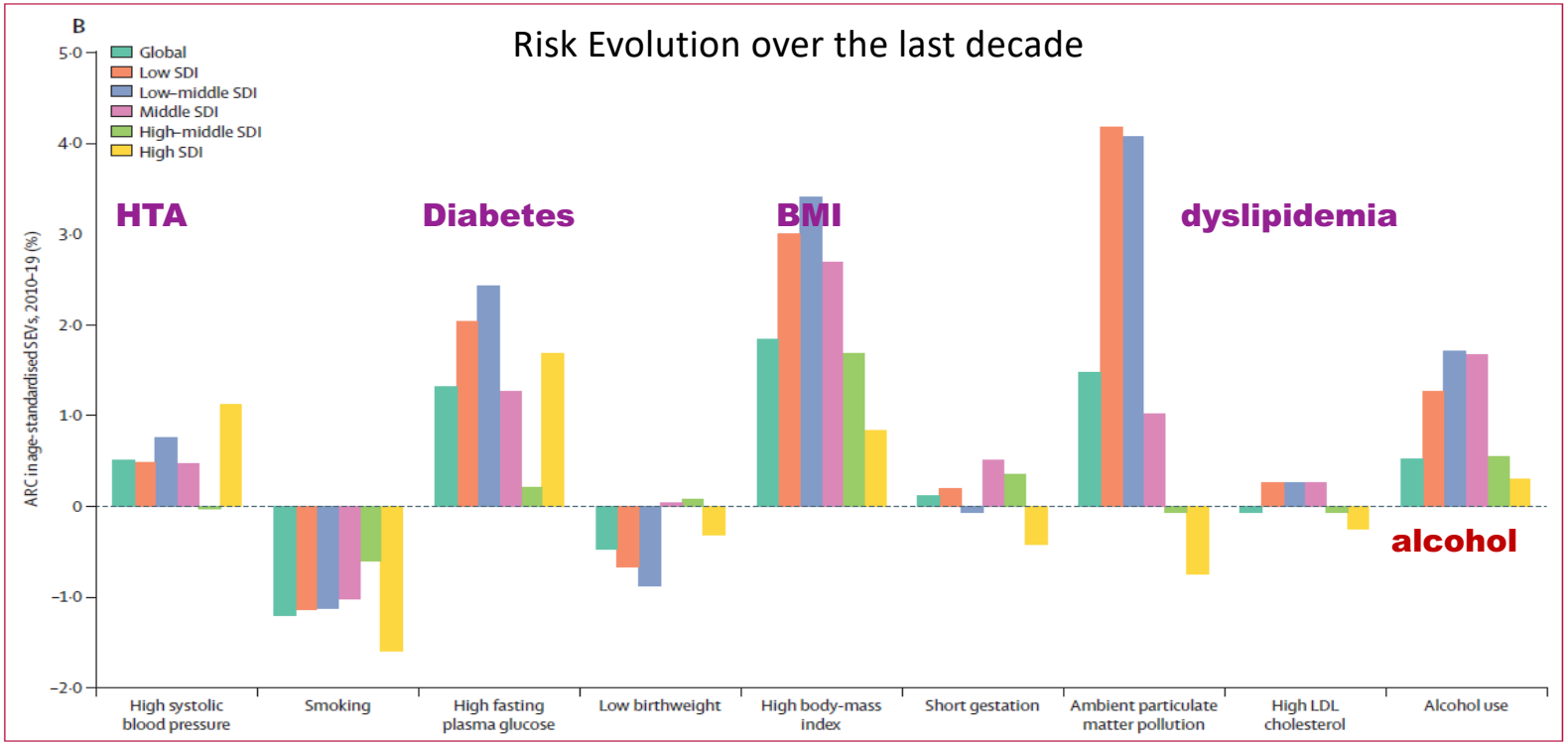


Gobal Burden Disease, Lancet 2015

Paradigm shift over twenty years

Overweight and Obesity are now responsible of more death than malnutrition.

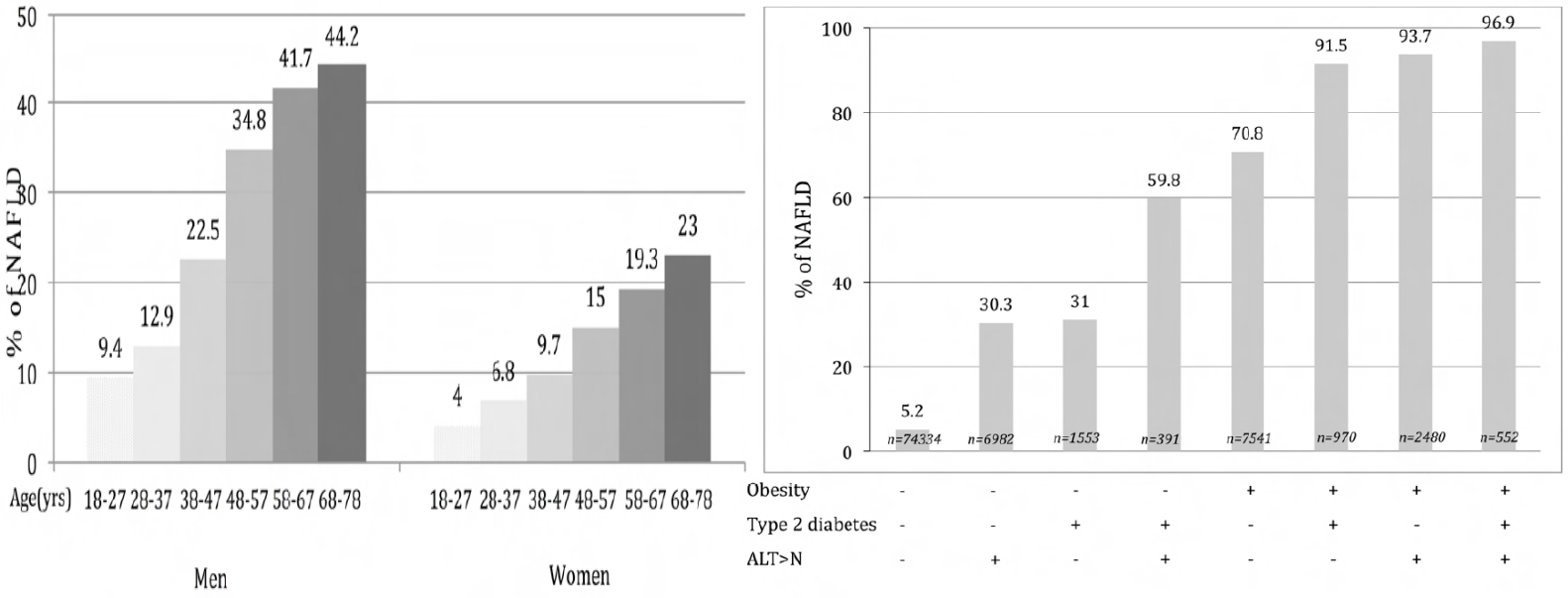
Worldwide progression of all metabolic risks … as well as alcohol



Gobal Burden Disease, Lancet 2020

Impact on the prevalence of NAFLD (France)

Prevalence of NAFLD increases with diabetes and obesity

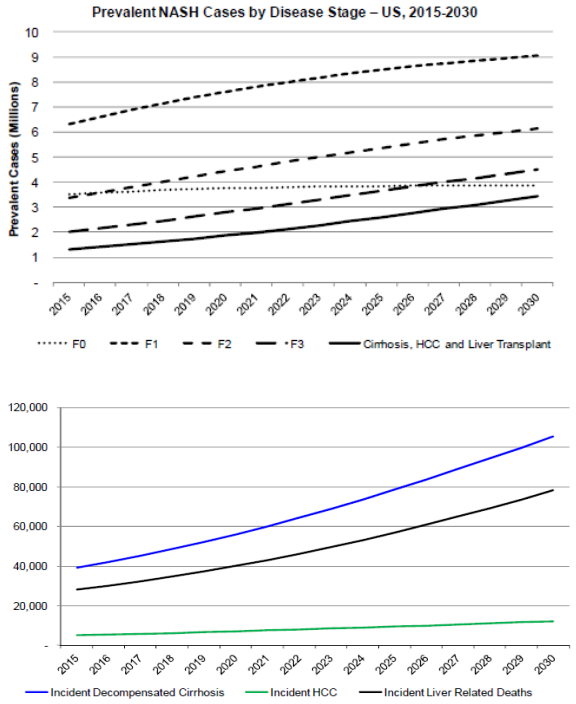


Nabi O et al, Gastroenterology 2020

Prevalence of NAFLD in France : 18% (Fatty Liver Index)
First cause of liver disease worldwide (Younossi et al, CGH 2011).
First cause of cirrhosis in the USA (Setiawan et al, Hepatology 2017)

Epidemiological projections & modelisation

Prediction of NASH progression between 2015-2030 in the USA



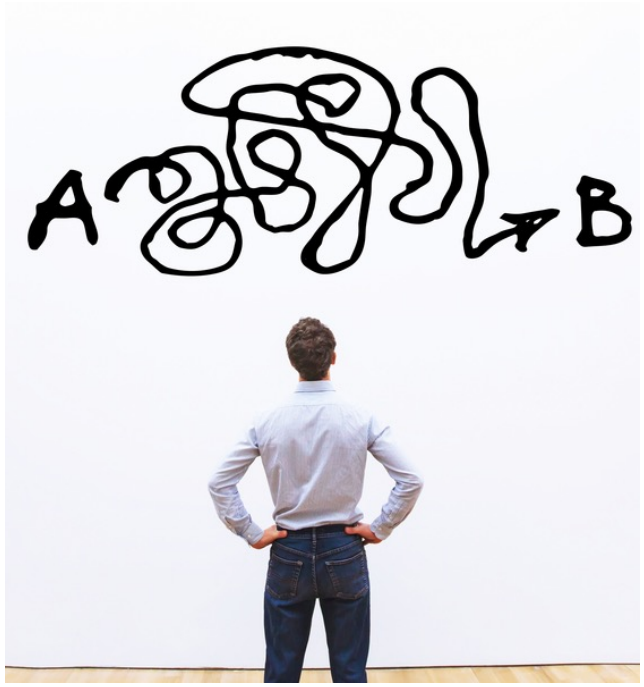
Increase in NASH prevalence
↑ 63%, (+ 16.5 millions - 27 millions patients).

Consequences: rase of morbidity and mortality

- **Decompensated Cirrhosis : + 168%**
- **HCC : + 137%**
- **Liver-related death : + 178%**

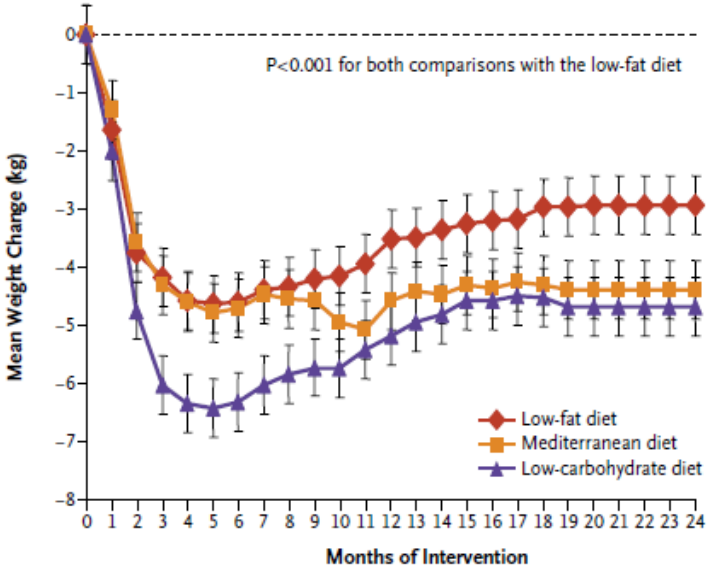
Estes C et al, Hepatology 2018

Is Bariatric surgery an answer to obesity and NAFLD ?



Therapeutic Strategies for obesity
Medical approach: Diet & lifestyle

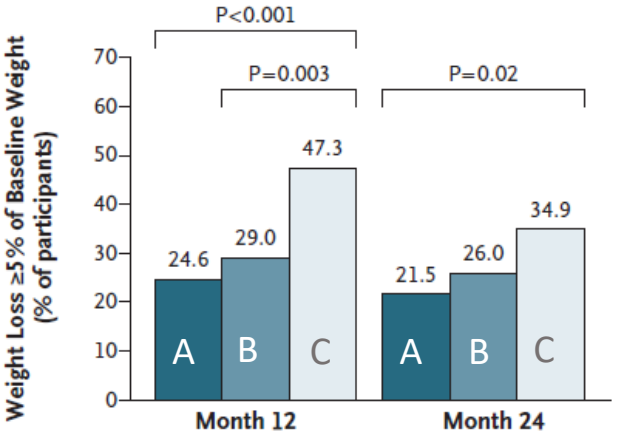
In each group:
Weight 90 kg.
BMI 30 kg/m²



Between – 3 to – 5 kg after 2 year of diet and follow up

Shai I et al nejm 2008

Groups: A: Usual Care
B: Brief counseling
C: Enhanced brief counseling



6 to 17 % of patients with 10% weight loss at 2 years

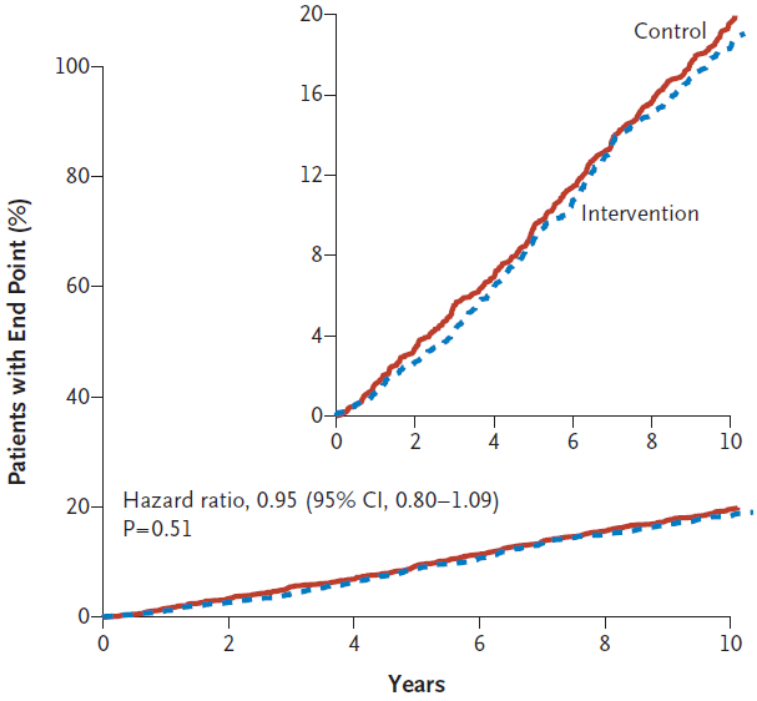
Wadden et al nejm 2011

Benefit on cardiovascular risk ?

Medical benefit of medical strategies is debated among high risk patients

Endpoint : mortality & cardiovascular morbidity

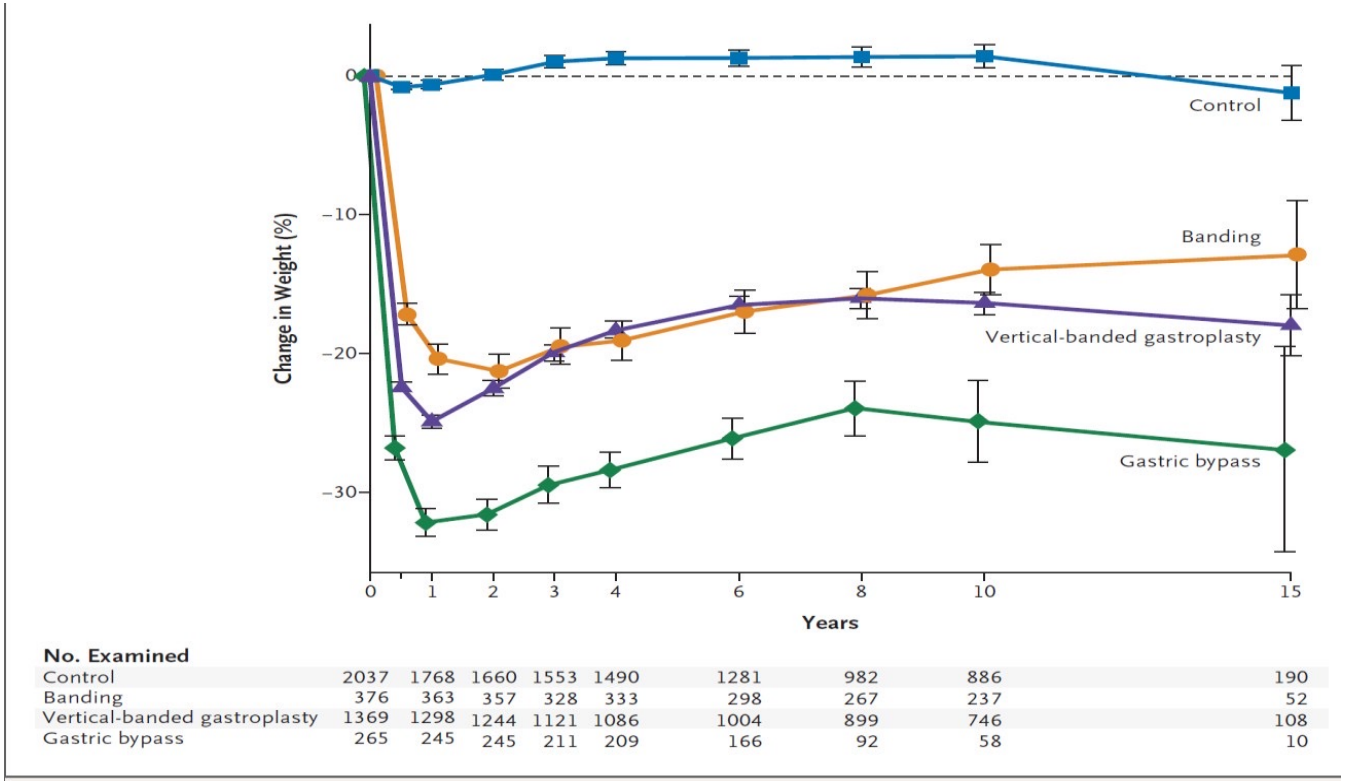
Randomised study with
Type 2 diabetes patients



AHEAD Research group nejm 2014

Efficacy of Bariatric surgery for weight loss

Banding: 10-20% WL
Sleeve : 15-20% WL
Bypass: 20-35 WL

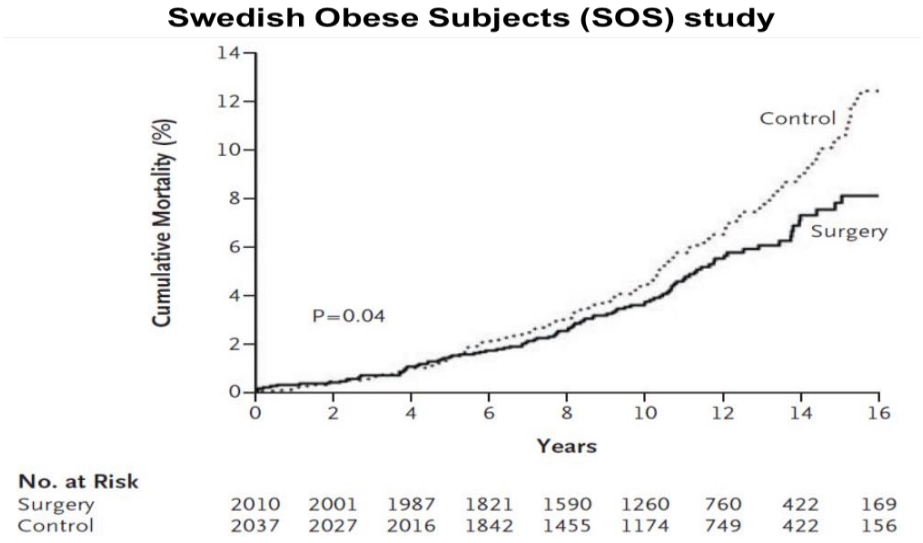


No. Examined									
Control	2037	1768	1660	1553	1490	1281	982	886	190
Banding	376	363	357	328	333	298	267	237	52
Vertical-banded gastroplasty	1369	1298	1244	1121	1086	1004	899	746	108
Gastric bypass	265	245	245	211	209	166	92	58	10

Sjöström L et al, nejm 2007

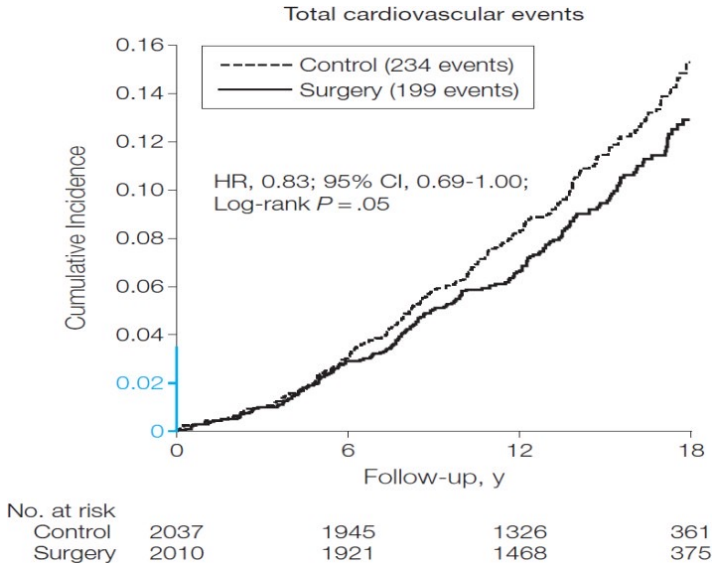
Results of bariatric surgery

Reduces overall mortality



Sjöström L et al nejm 2007

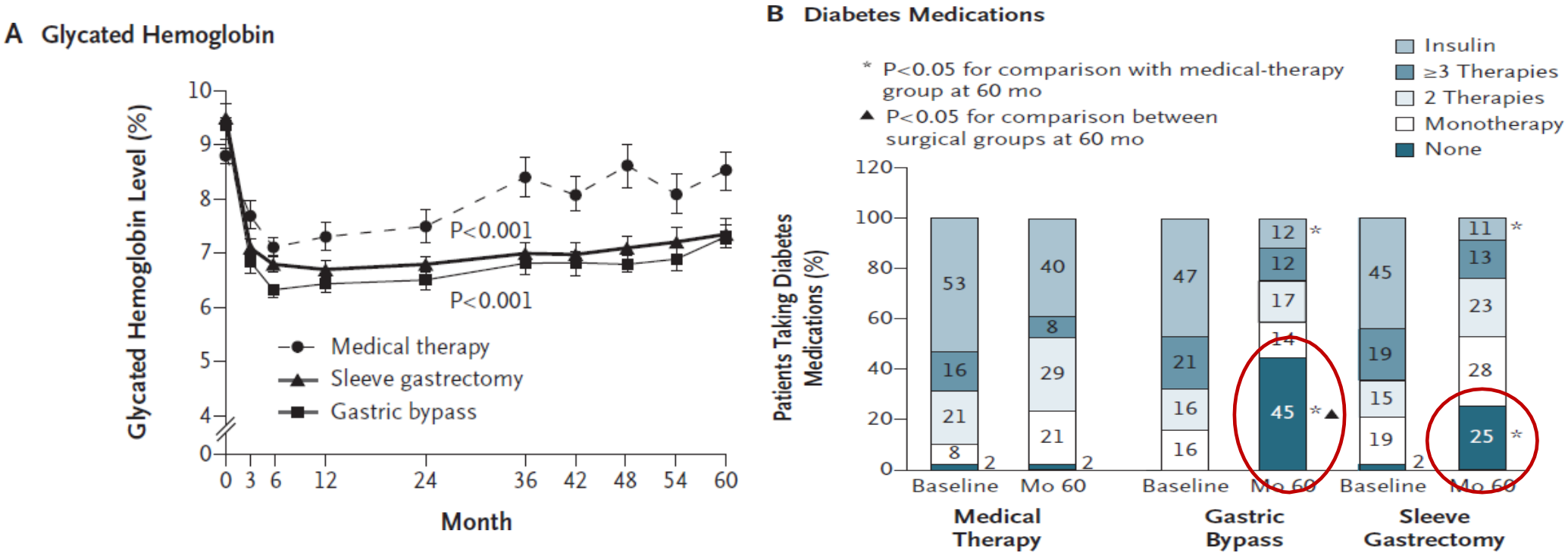
Reduces CV events



Sjostrom L et al, JAMA 2012

Bariatric surgery & diabetes

Bariatric surgery improves and can « cure » (diabetes remission) in 25-45% 5 years after surgery

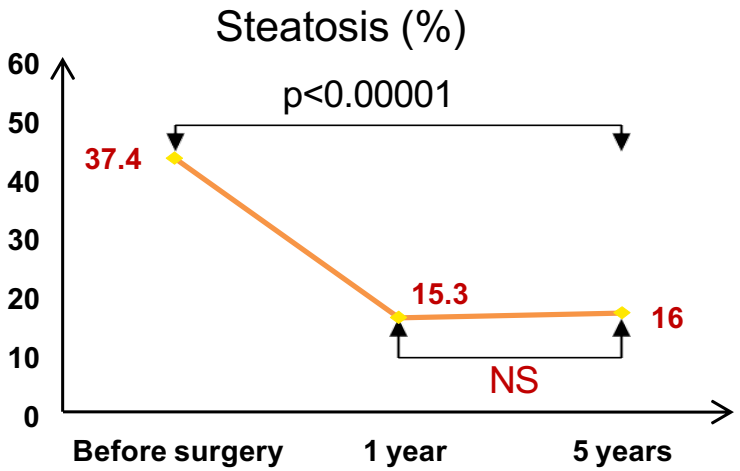


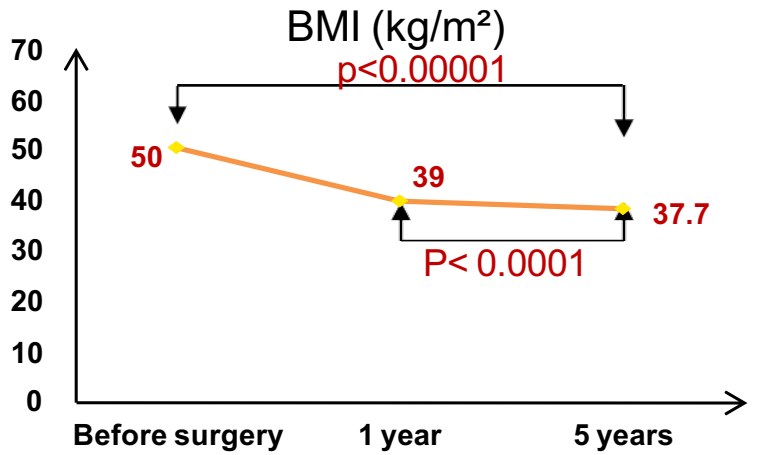
Schauer PR et al nejm 2012
Schauer PR et al nejm 2017

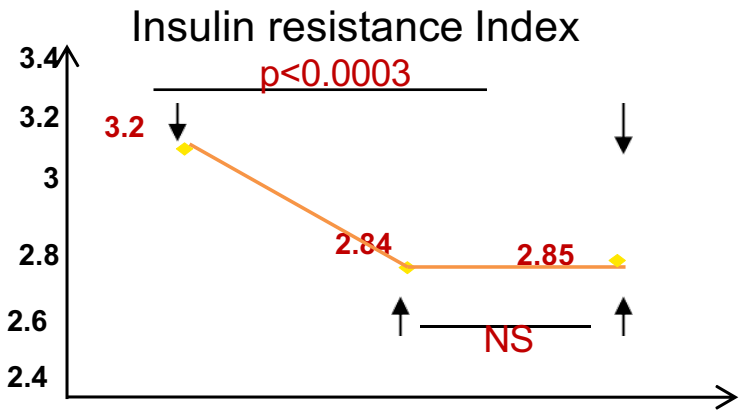
What is the impact of bariatric surgery on NASH ?

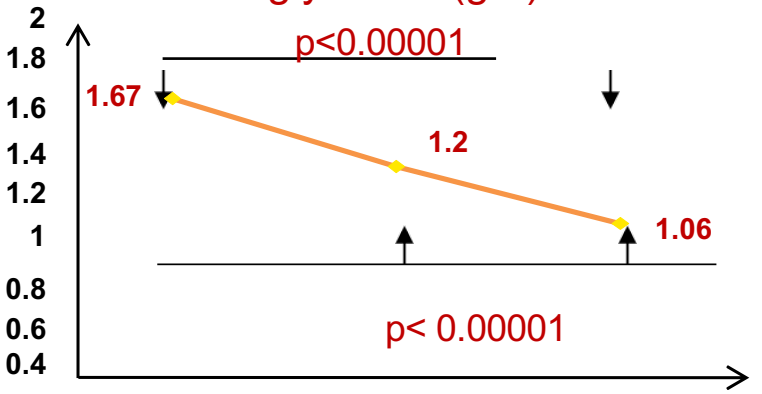
We may have to adjust the gastric band a little

Effect of surgery in NAFLD patients.







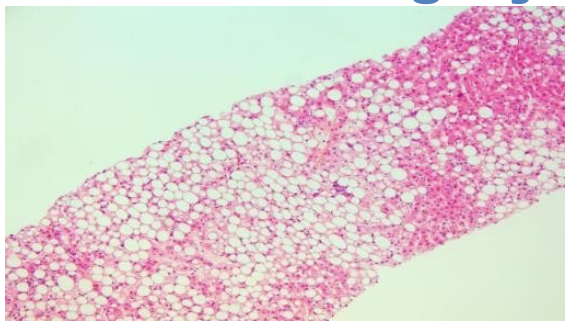


Mathurin P et al, Gastroenterology 2009

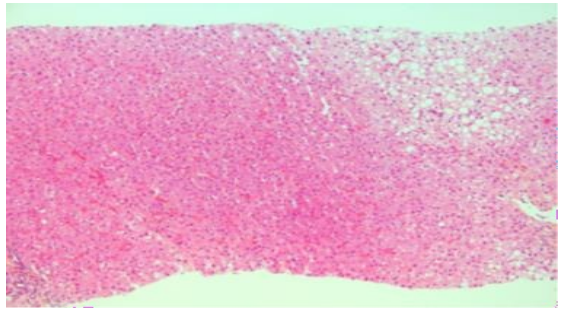
Histological progression after surgery, in NASH

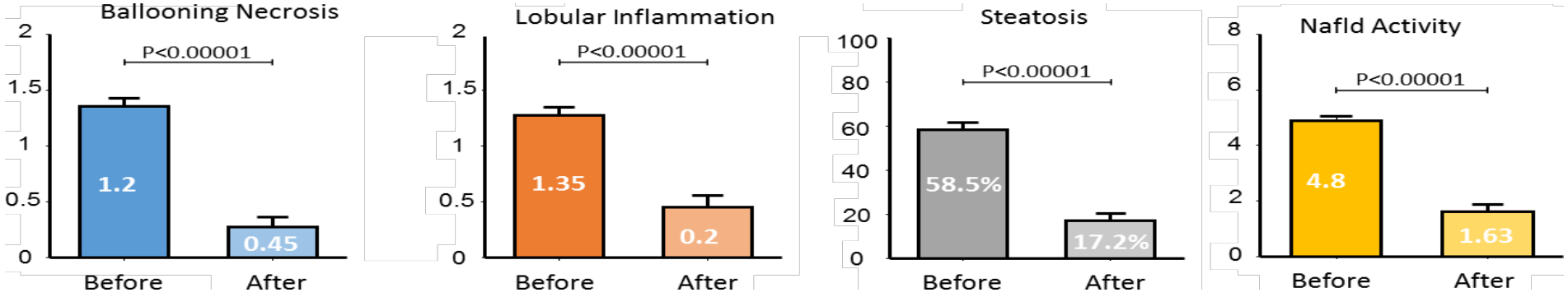
Progression after 1 year

Before surgery



After surgery

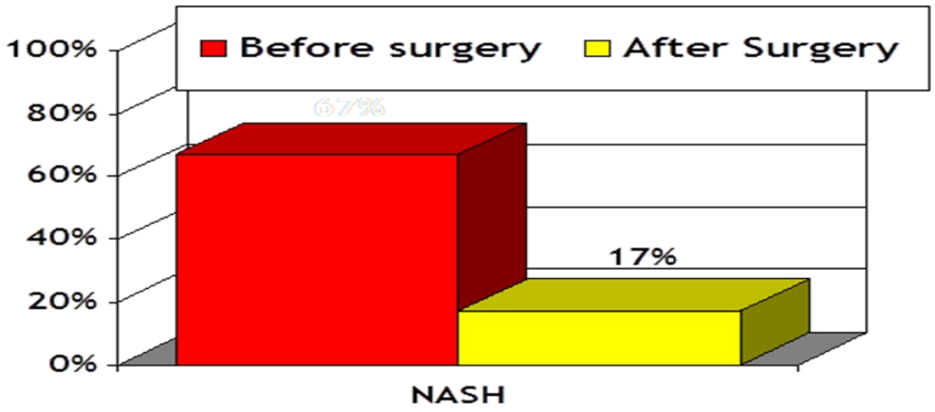




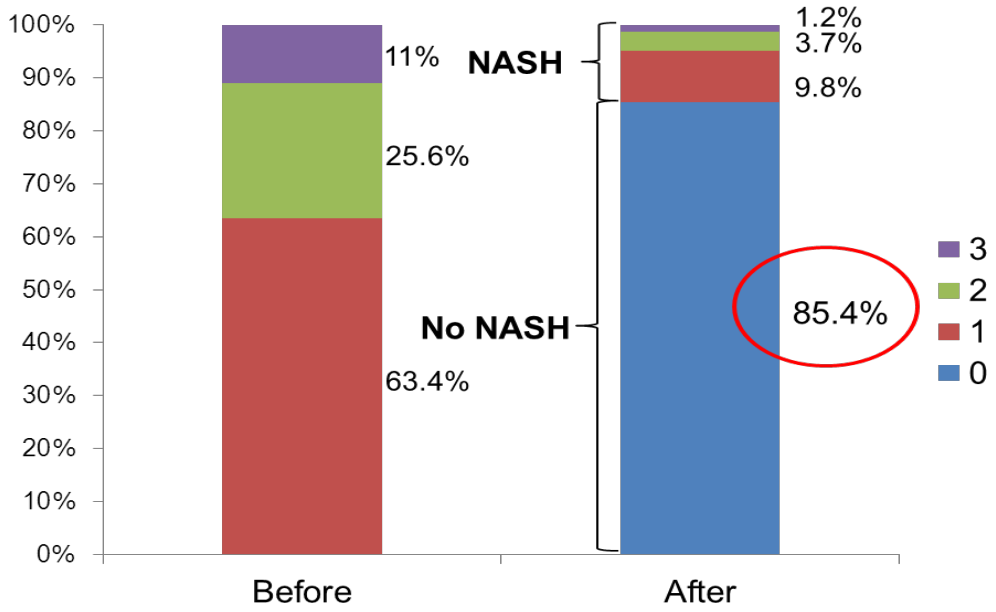
Lassailly et al . Gastroenterology 2015

NASH resolution: Effect of Bariatric surgery

Cohorts results 80-85 % of NASH disappearance



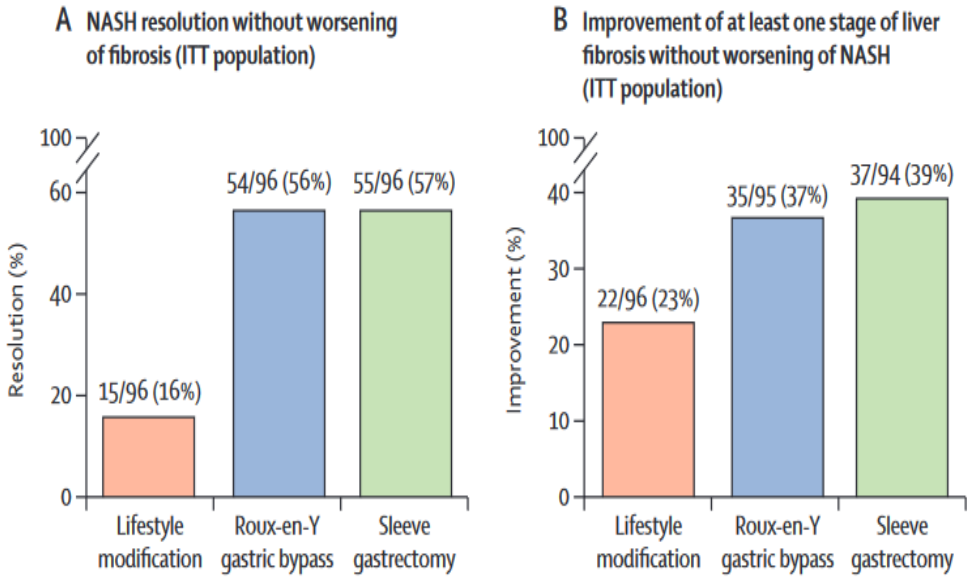
Dixon et al, Hepatology 2004



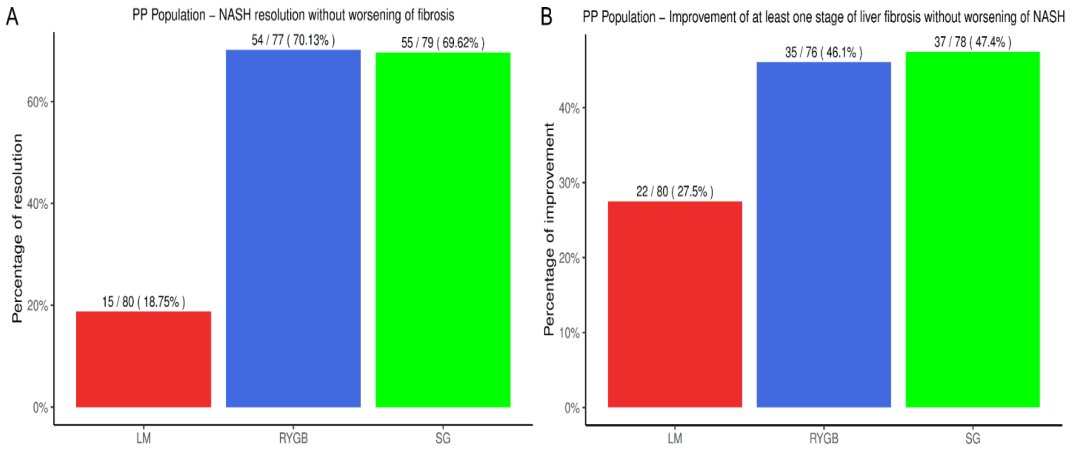
Lassailly et al , Gastroenterology 2015

NASH resolution after Bariatric surgery

ITT population analysis

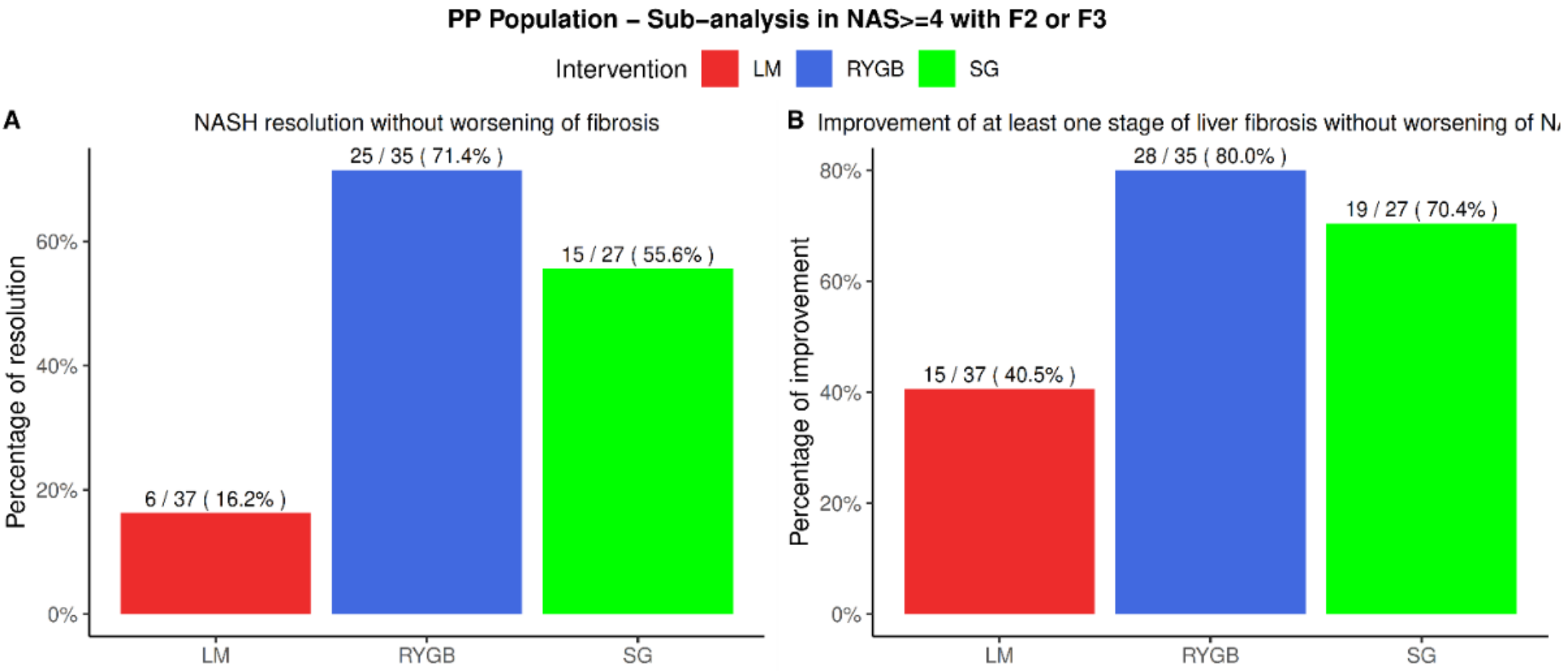


Per Protocol population analysis



Verrastro O et al, Lancet 2023

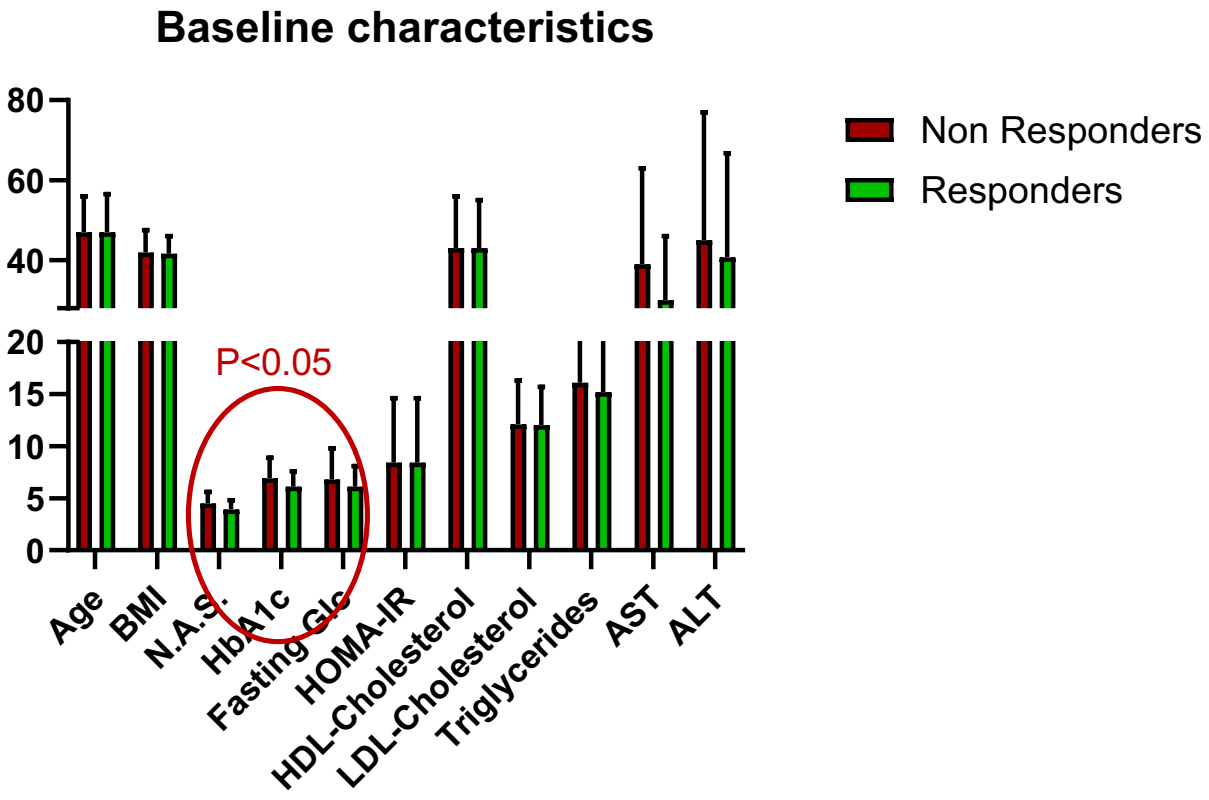
NASH resolution in High Risk Patients



Verrastro O et al, Lancet 2023

Responders vs Non-Responders

Responders are less severe than non-responders

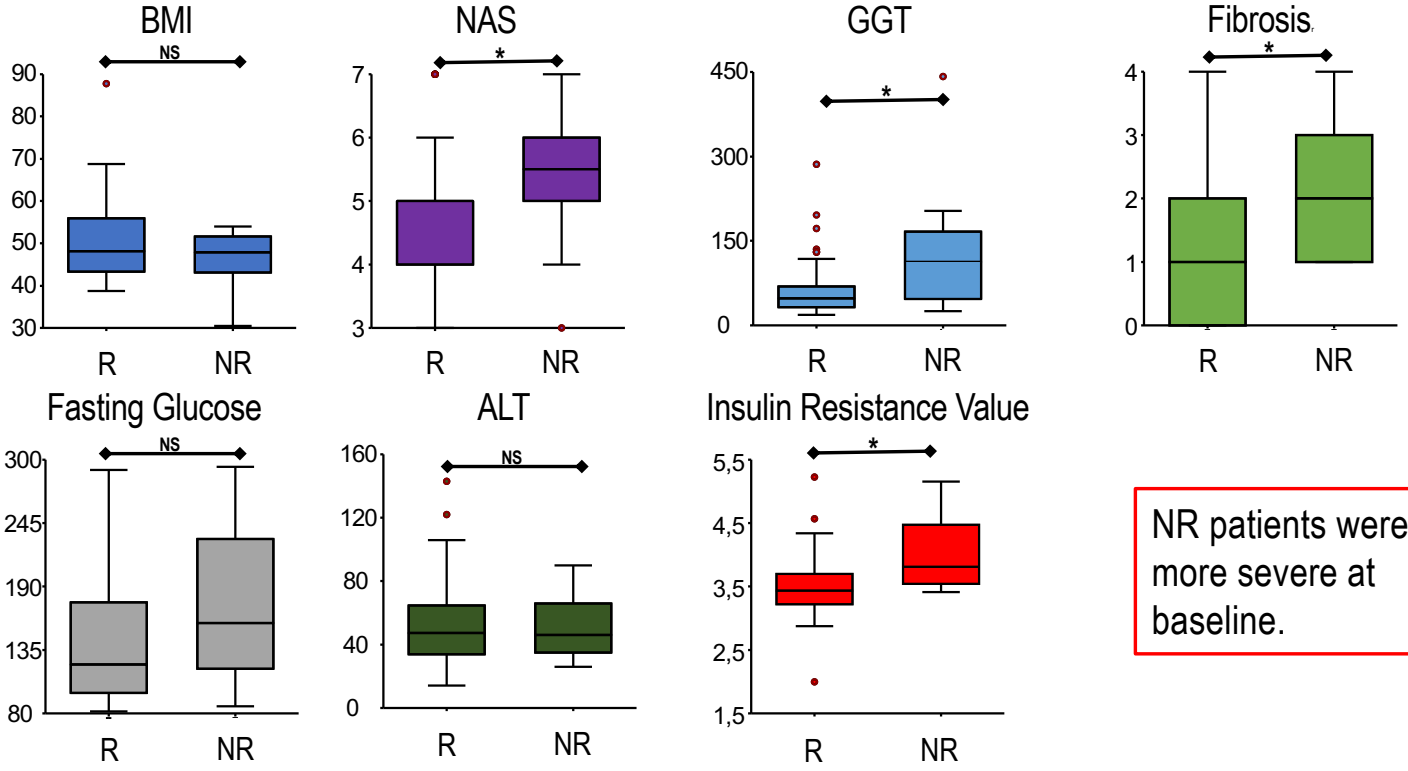


		Non-responders N=112	Responders N=124	
		%	%	P value
gender	Males	64 (57)	68 (55)	0.822
	Females	48 (43)	56 (45)	
Diabetes	no	65 (58)	93 (75)	0.009
baseline	yes	47 (42)	31 (25)	
1 year	no	73 (65)	119 (96)	<0.0001
	yes	39 (35)	5 (4)	
NAS score	3	23 (20.5)	45 (36.3)	0.003
baseline	4	35 (31.2)	49 3(9.5)	
	5	36 (32.1)	24 (19.3)	
	6	13 (11.6)	5 (4.0)	
	7	4 (3.6)	1 (0.8)	
	8	1 (0.9)	0 (0)	
Fibrosis	0	2 (1.8)	0 (0)	0.012
baseline	1	50 (44.6)	63 (50.8)	
	2	39 (34.8)	53 (42.7)	
	3	21 (18.8)	8 (6.5)	

Verrastro O et al, Lancet 2023

Responders vs Non Responders

Baseline characteristics comparison of patients with NASH persistante at 1 year (**non responders: NR**) vs patients with NASH disappearence (**Responders: N**):

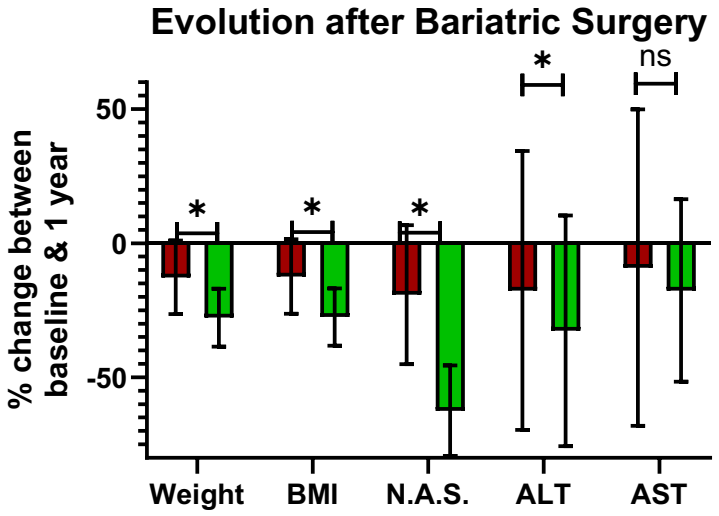


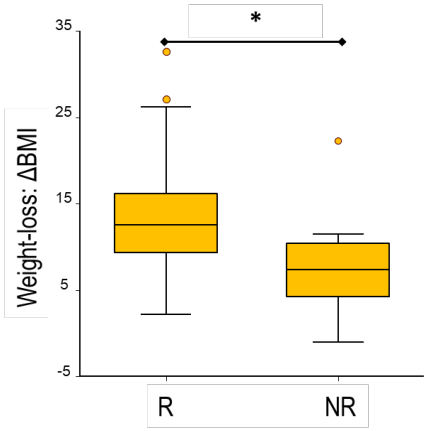
NR patients were more severe at baseline.

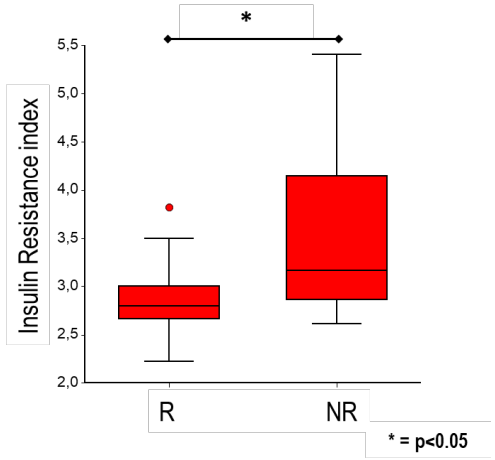
*** = p<0.05**

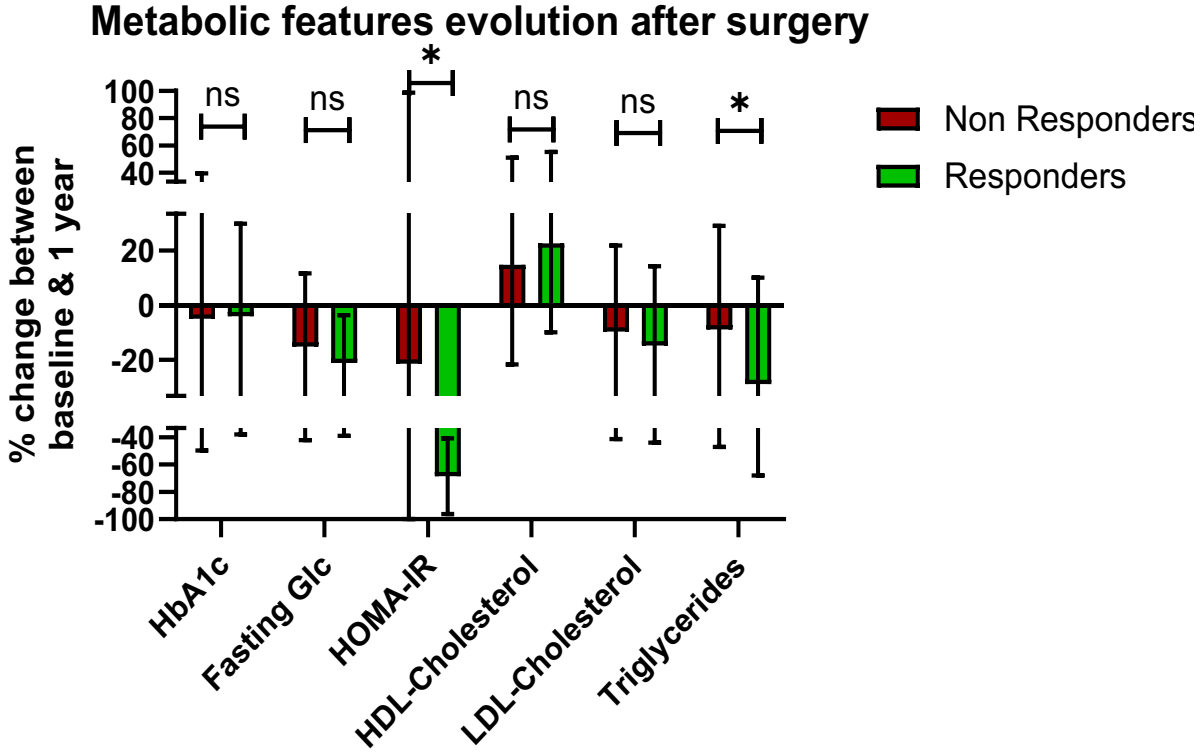
Lassailly et al, AASLD 2014

Responders vs Non-Responders







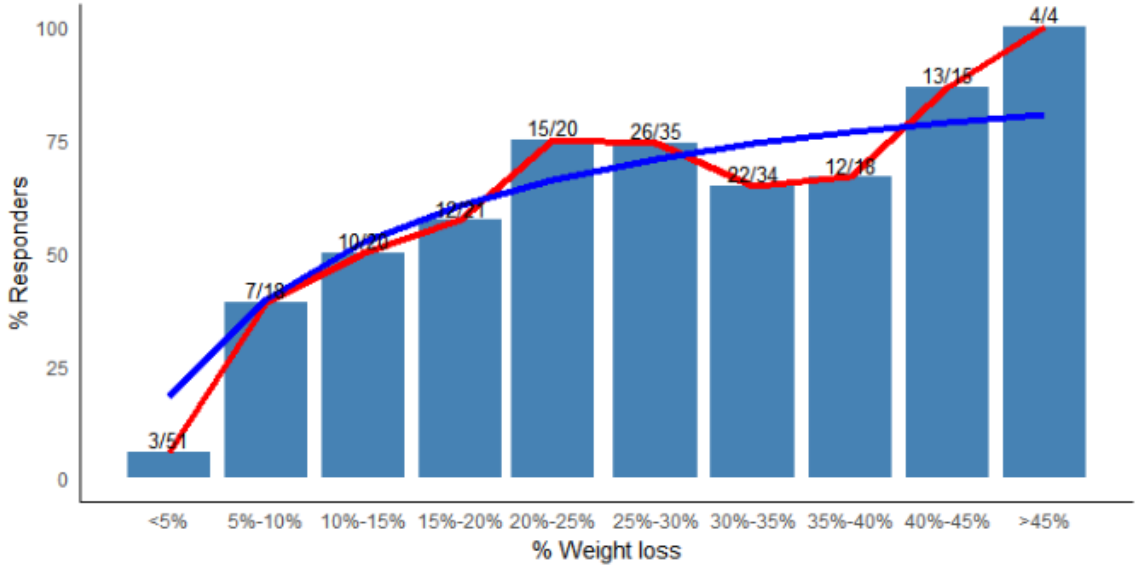


Non-Responders: Less weight-loss and less reduction in insulin resistance

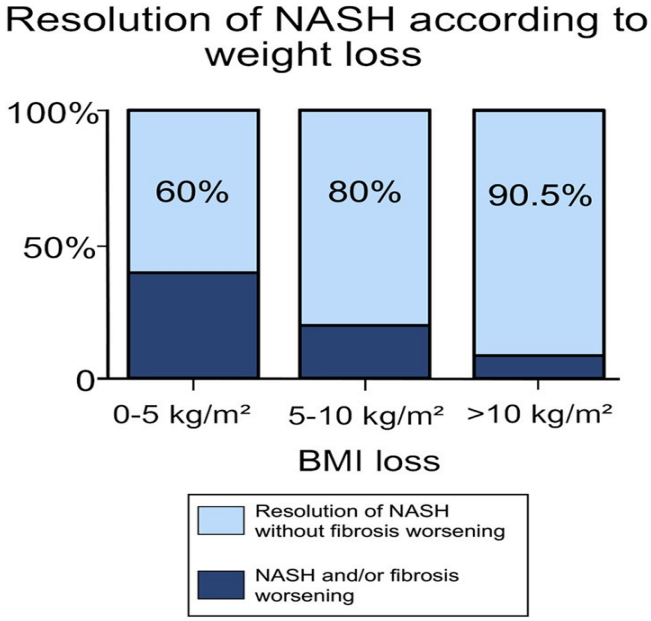
Verrastro O et al, Lancet 2023
Lassailly G et al, Gastroenterology 2015

NASH Resolution according to weight-loss

The histological response depends on weight-loss magnitude



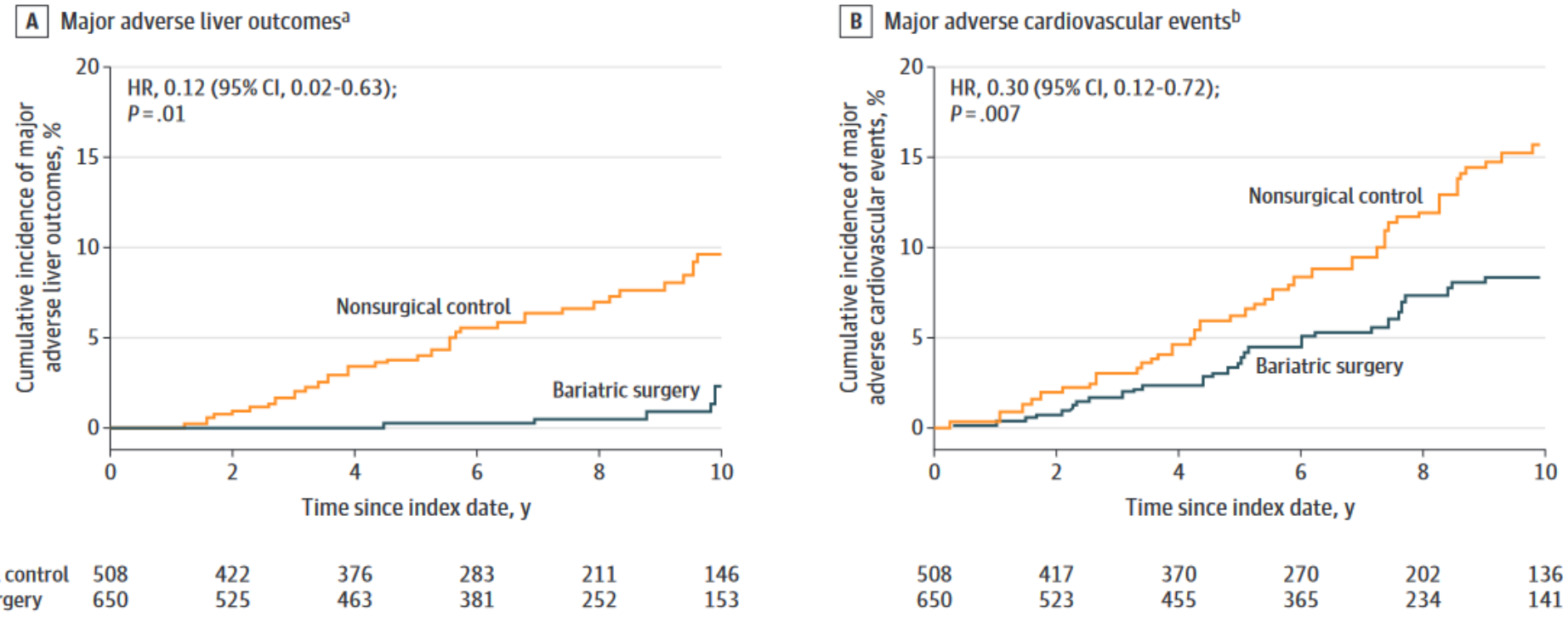
Verrastro O et al, Lancet 2023



Lassailly et al, Gastroenterology 2020

Long term effect of Bariatric surgery

Figure 2. Cumulative Incidence Estimates (Kaplan-Meier) for 2 Composite End Points in the Overlap-Weighted Analysis

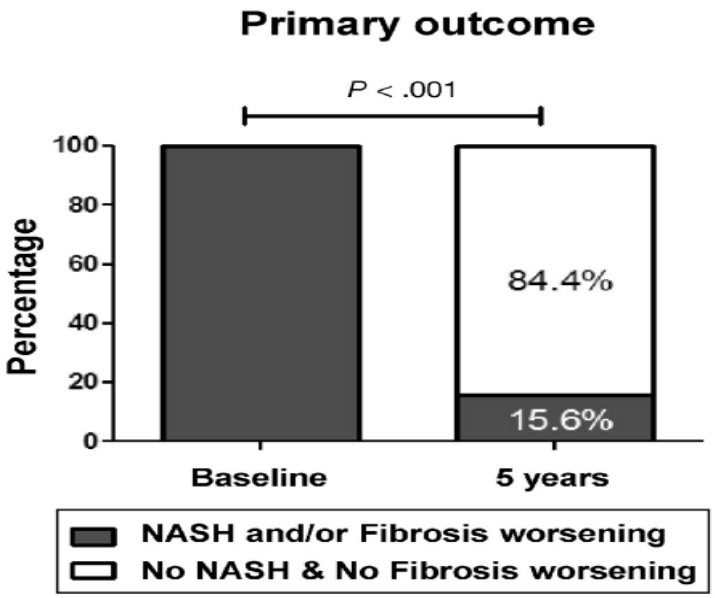


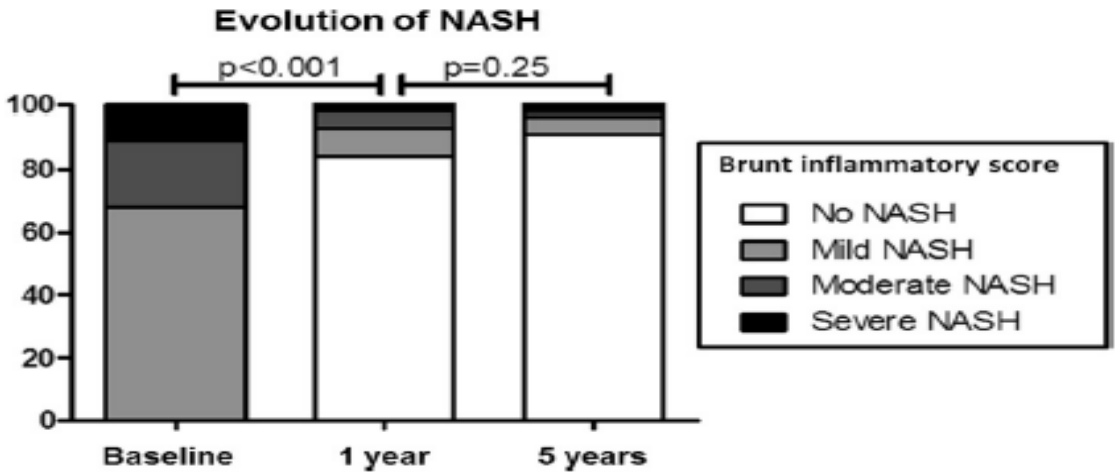
No. at risk						
Nonsurgical control	508	422	376	283	211	146
Bariatric surgery	650	525	463	381	252	153

508	417	370	270	202	136
650	523	455	365	234	141

Aminian A et al, JAMA 2021

Long term effect of Bariatric surgery

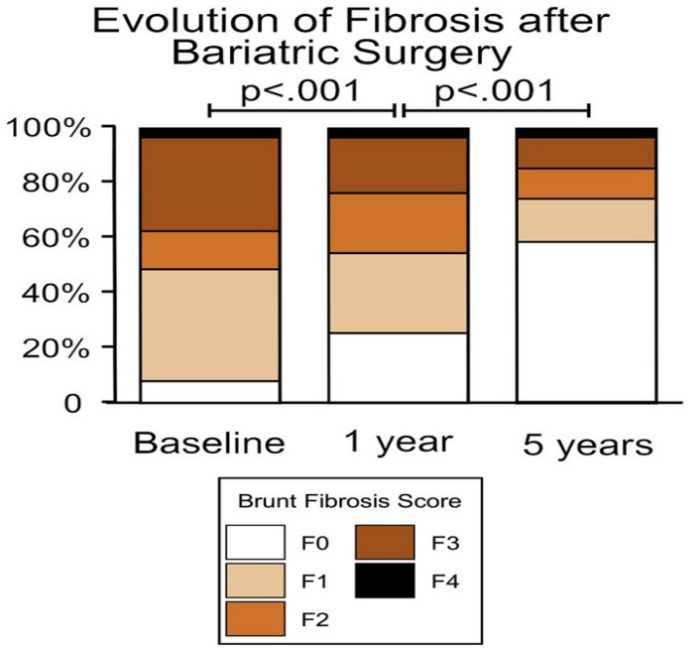


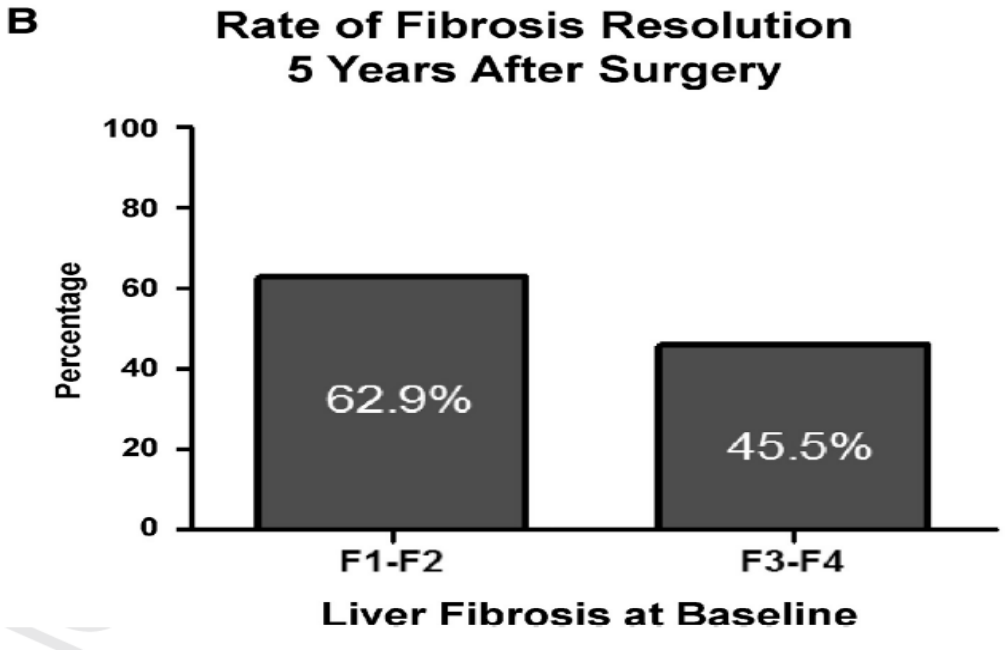


Lassailly G et al Gastroenterology 2020

Long term effect on fibrosis

Unlike NASH, fibrosis regression continues beyond the first year.





Lassailly G et al Gastroenterology 2020

Non responders vs Responders: Long term impact

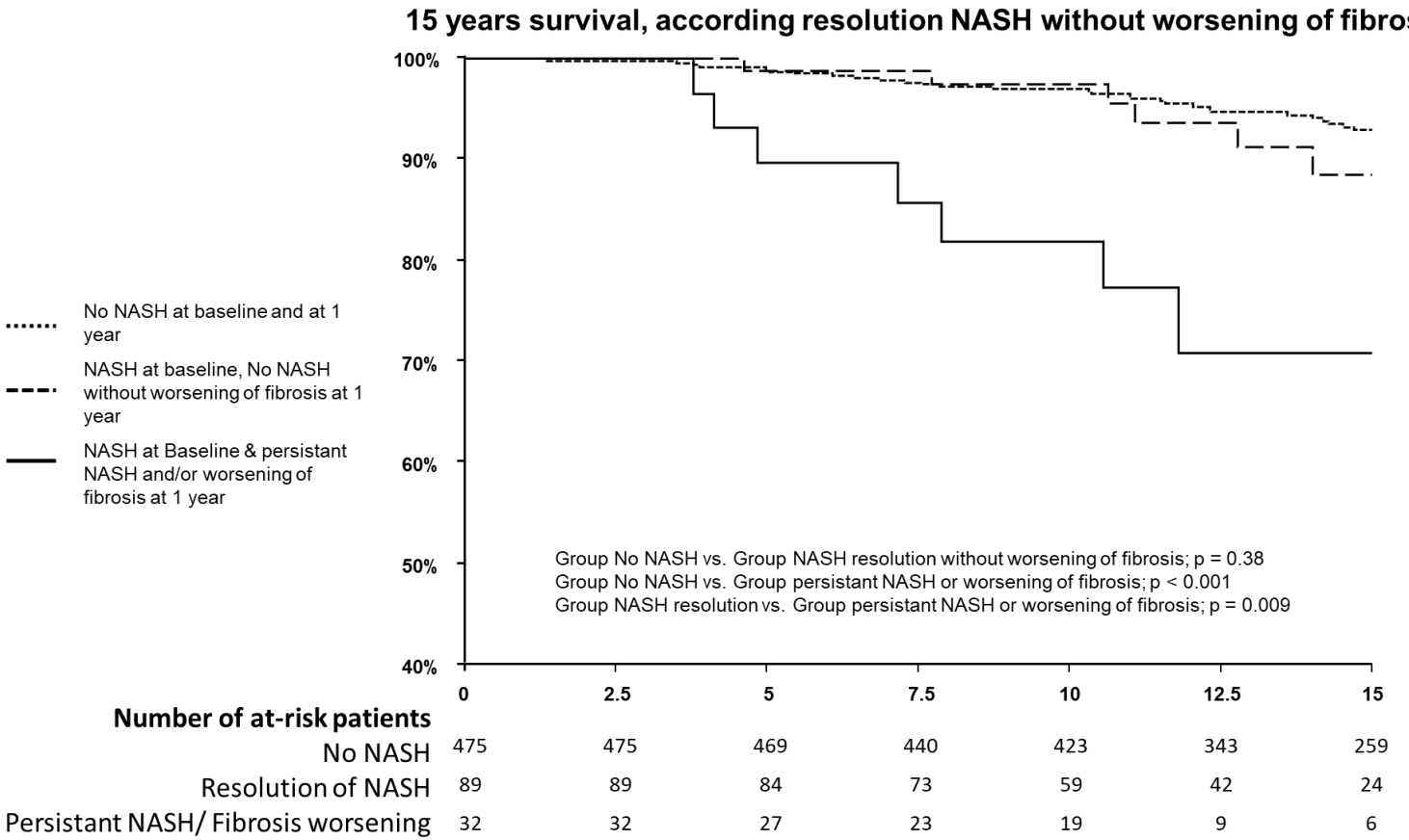
Non-Response (NASH persistence) is associated with fibrosis progression

Table 4. Patients With Resolution of NASH Without Worsening of Fibrosis (Meeting Primary Outcome) Compared With Those With Persistent NASH or Worsening of Fibrosis at 5 Years, or Both

Characteristics of patients at 5 years	Resolution of NASH without worsening of fibrosis	Persistence of NASH and/or worsening of fibrosis	*P* value
Baseline BMI, kg/m^2	49.3 ± 7.0	47.7± 7.9	.86
BMI at 5 years, kg/m^2	35.3 ± 7.1	40.9 ± 10.7	.028[a]
Evolution of BMI	−13.4 ± 7.4	− 6.3 ± 4.1	.017[a]
Histological characteristics			
Brunt's fibrosis score	0 (0–1)	2 (2–3)	<.001[b]
Brunt's fibrosis evolution	−1 (0 to −2)	1 (0–1.3)	.003[b]
NAS	1 (0–2)	4 (3.5–5.5)	<.001[b]
NAS evolution	−4 (−5 to −2)	0 (−2 to 0)	.005[b]
Steatosis, %	5 (1–10)	60 (30–75)	<.001[b]
Biological characteristics			
Fasting glucose, *mg/dL*	104 (89–117)	128 (85–165)	.17[b]
HbA_{1c}, %	5.8 (5.5–6.4)	6.8 (5.5–7.5)	.21[b]
Insulin resistance index[c]	2.9 (2.7–3.1)	3.5 (3.1–4.1)	.001[b]
AST, *IU/L*	20 (17–24)	43 (33–63)	<.001[b]
ALT, *IU/L*	18 (17–25)	46 (33–52)	.010[b]
GGT, *IU/L*	18 (12–28)	72 (25–146)	<.001[b]
Total bilirubin, *mg/dL*	0.5 (0.4–0.5)	0.7 (0.4–1)	.10[b]
LDL cholesterol, *mmol/L*	2.7 (2.4–3.2)	3.3 (2.2–5.0)	.46[b]
HDL cholesterol, *mmol/L*	1.4 (1.2–1.5)	1.3 (1.0–1.6)	.58[b]
Triglycerides, *mmol/L*	1 (0.7–1.6)	1.6 (1.3–2.2)	.037[b]
Albumin, g/L	42 ± 3	44 ± 4	.51[a]
Platelets, *G/L*	248 ± 51	233 ± 76	.48[a]
Prothrombin time, %	96 ± 7	90 ± 12	.12[a]

Lassailly et al, Gastroenterology 2020

Responders vs. Non Responders: Long term survival after bariatric surgery



Lassailly G. et al, Accepted for AASLD presentation 2023

Which procedure should be proposed for the best weight loss ?

We may have to adjust the gastric band a little

Gastric Banding vs Bypass

Figure 4. Multivariable Adjusted and Inverse Intensity-Weighted Change in BMI After Bariatric Surgery by Procedure Type

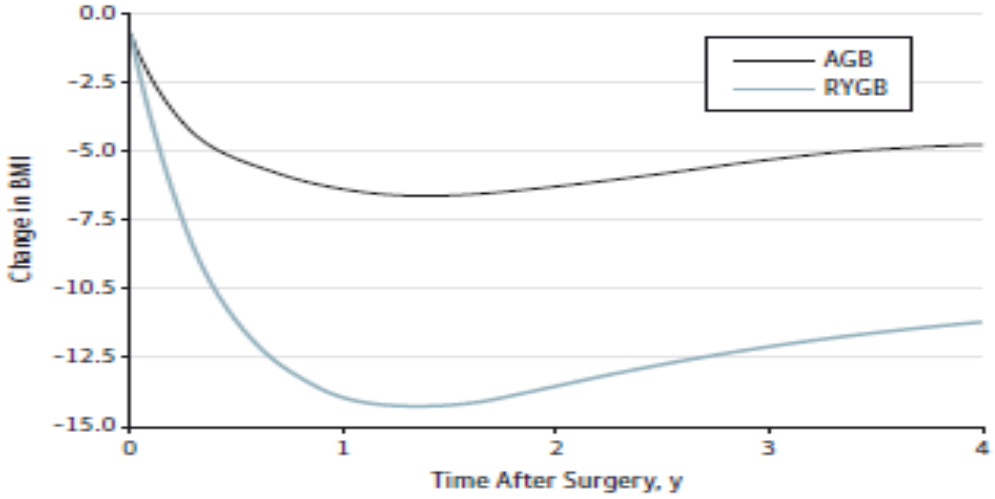
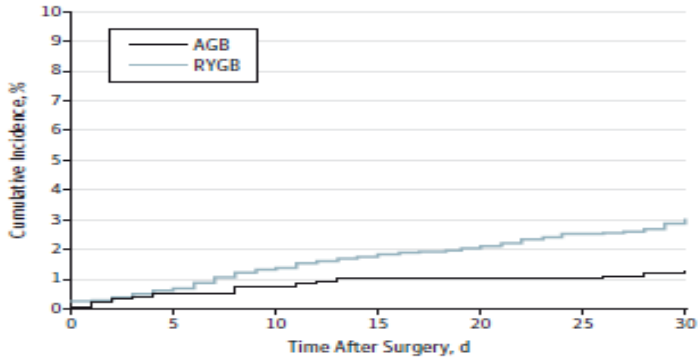


Figure 1. Cumulative Incidence of Major Adverse Events at 30 Days After Bariatric Surgery by Procedure Type



Major adverse events include death, failure to discharge from hospital, deep vein thrombosis, pulmonary embolism, or subsequent procedural intervention. AGB indicates adjustable gastric band; RYGB, Roux-en-Y gastric bypass. Propensity score–adjusted between-procedure comparison $P < .05$.

Patients present more complications after bypass than gastric banding.
But efficacy is higher

Aterburn D et al, JAMA surg 2014

Bypass or gastric band ?

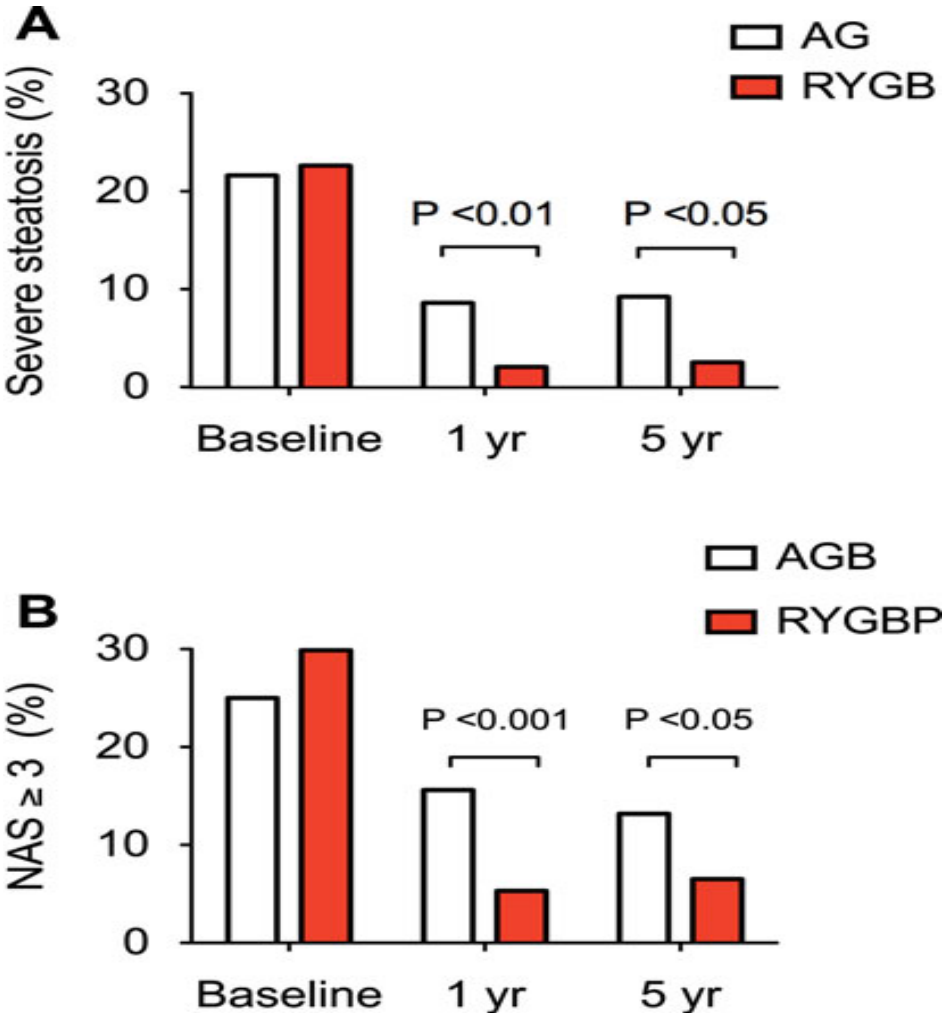


TABLE 2. Multivariate Analysis of Predictive Factors of Steatosis and NAS 5 Years After AGB and RYGB (Step-by-Step Linear Regression Model)

	Steatosis, %		NAS	
	P	Relative Contribution, %	*P*	Relative Contribution, %
Baseline value	**<0.001**	32.9	**<0.001**	32.6
Weight loss	**<0.001**	60.1	**<0.001**	57.2
RYGB	**0.007**	4.6	**0.044**	2.6
T2DM	0.054	2.4	**0.001**	7.5

Caiazzo R et al, Annals of Surgery 2014

Conclusions

1. Bariatric surgery induces a sustained weigh-loss and a significant improvement of IR, which is responsible of 70% of NASH resolution without worsening of fibrosis

2. Non Response (Persistence of NASH) is associated with increased 15 years mortality.

3. Non response is associated with less weight-loss and less effect on IR

4. Performing a new liver biopsy after bariatric surgery should be proposed.

Merci pour votre attention