3rd Paris NASH Symposium

French-US Meetings

July 6 & 7, 2017

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3rd Paris NASH Symposium

July 6 & 7 2017 • Institut Pasteur, Paris

The place of bariatric surgery in NASH: can we extend the indications? - No

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How to extend the indications?

- Extending traditional indications for bariatric surgery
  - NASH in patients with BMI > 40 kg/m^2
  - NASH as a comorbidity in patients with BMI > 35 kg/m^2
- Bariatric surgery for patients with a BMI < 35 kg/m^2
- Bariatric surgery in patients with cirrhosis

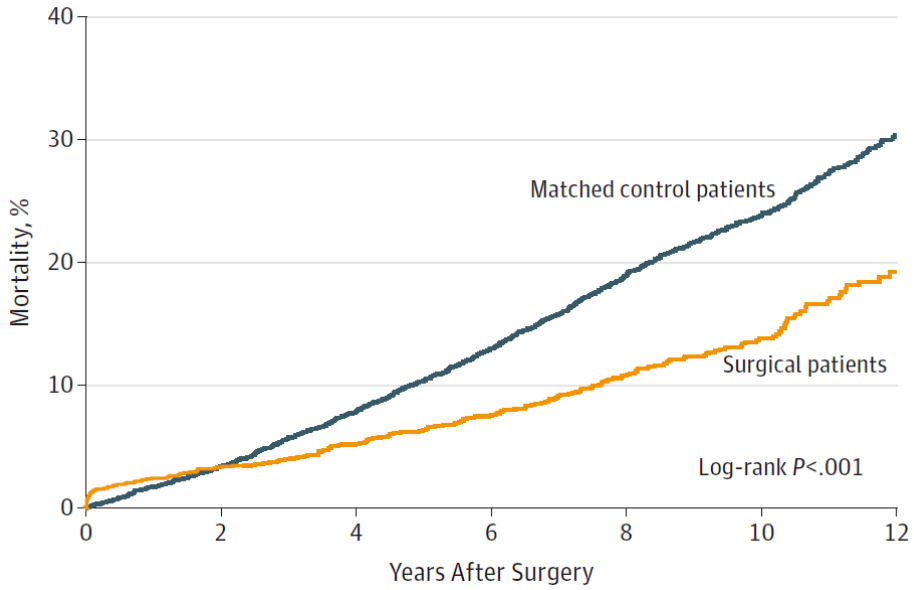
What are the indications for Bariatric Surgery?

Table 2 National guidance for bariatric surgery

Country	BMI level, kg/m^2		Comorbidities	Requirements for conservative treatment prior to bariatric surgery
	Without comorbidities	With comorbidities		
Belgium	40	35	T2DM, hypertension, OSA	Not available
Denmark	40	35	T2DM, hypertension, OSA, PCOS, knee osteoarthritis	Sustainable weight loss not achieved by conventional treatment
	50	35		
England	40	35	T2DM, hypertension, OSA, knee osteoarthritis	Failure of non-surgical methods for at least 6 months
	50			Bariatric surgery is recommended as a first-line treatment option
	40			Weight loss programme for 12–24 months
	50			Weight loss programme for 6 months minimum
France	40	35	T2DM, hypertension, OSA, knee osteoarthritis, **NASH**	Failure of nutritional, dietary and medical treatment; psychotherapy conducted for 6–12 months; absence of sufficient weight loss or lack of maintenance of weight loss
Germany	40	35	T2DM, hypertension	Failure of conservative management
Italy	40	35	T2DM, hypertension, knee osteoarthritis, severe psychological problems	Failure of proper medical treatment including inadequate weight loss or poor maintenance of weight loss
Sweden	40	35	T2DM, OSA, pregnancy issues, knee osteoarthritis	Failure of weight loss using non-surgical methods
USA	40	35	T2DM, HT, OSA, **NAFLD**, osteoarthritis, dylipidemia, GI disorders, or heart disease.	Inability to achieve a healthy weight loss sustained for a period of time with prior weight loss efforts.
Switzerland	35 (since 2011)	(30)	Comorbidities such as T2DM	Failure of weight loss despite 2 years of non-operative therapy

Borisenko et al, Obes Surg 2015; US: Mechanik et al, Obesity 2013; France: Haute Autorité de la Santé 2009; Switzerland: LAMAL

What are the results of bariatric surgery?

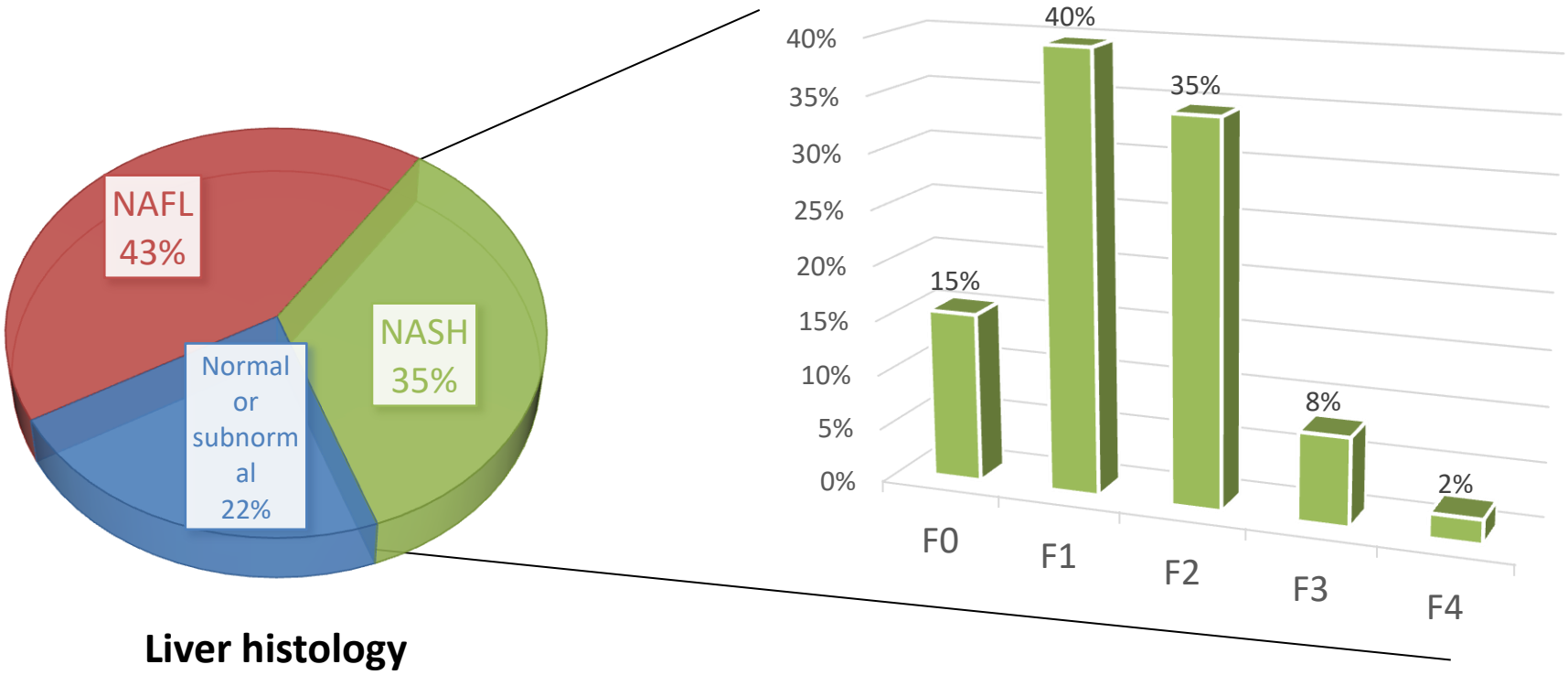


Systematic review of 164 studies including 161 756 patients:

- 30-day **mortality** 0.08% (RCT) to 0.2% (obs)
- Complication rate 17%, reoperation rate 7%
- 5y BMI loss: 12-17kg/m^2
- Remission of T2DM 92%, remission of HT 75%

Arterburn et al, *JAMA*, 2015; Chang et al JAMA Surg 2014

Prevalence of NAFLD / fibrosis in bariatric surgery



Liver histology

798 subjects undergoing bariatric surgery in a French center
Baseline: Age 42.7y, Female 78%, HT 48%, T2DM 39%, BMI 47.5kg/m^2

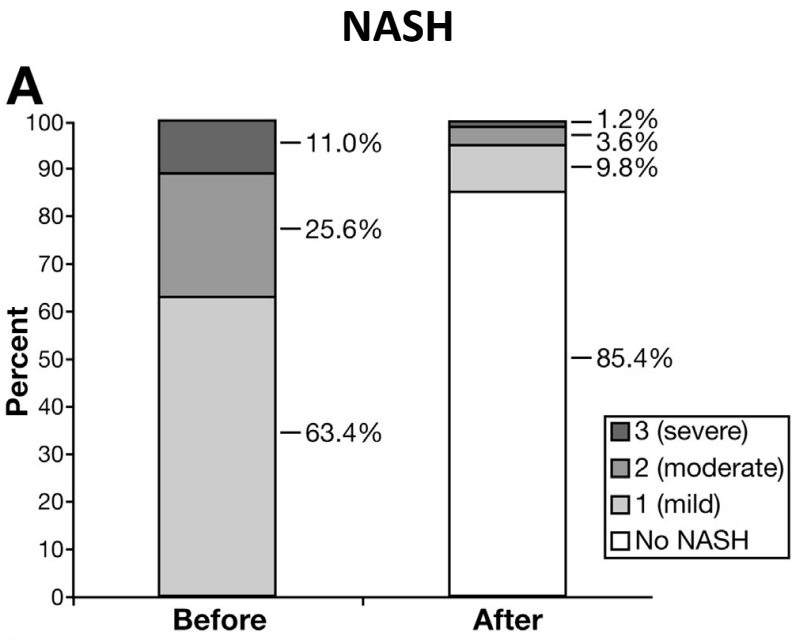
Bedossa et al, Gut 2016

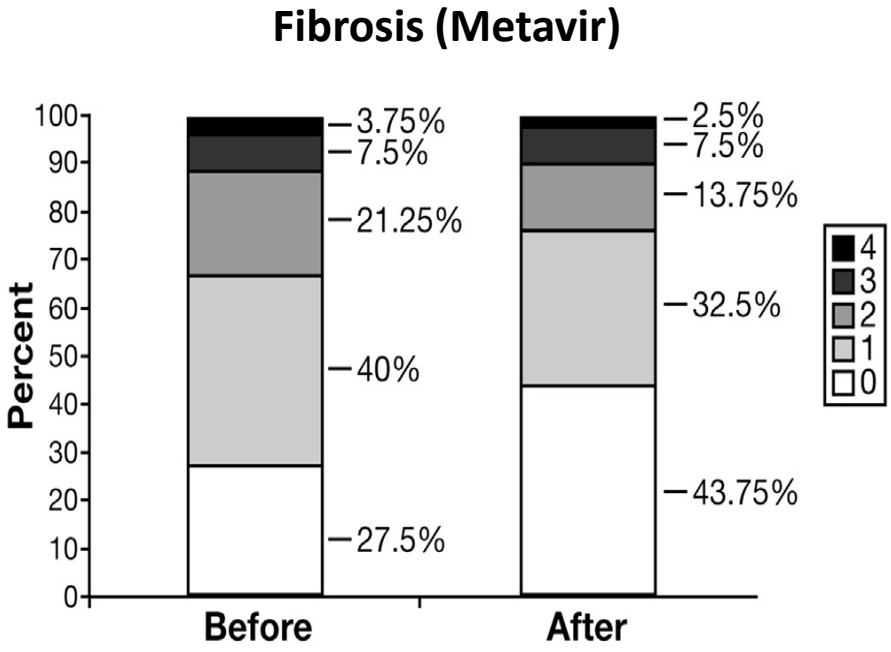
Clinical case

- 46 y obese woman, requesting bariatric surgery
- Failure of 12 months weight loss program
- BMI 37 kg/m^2
- No arterial hypertension, OSA, diabetes
- Liver work-up due to elevated LFTs and slightly decreased platelets
  - Fibroscan 8.9kPa
  - Liver biopsy: NASH, fibrosis stage 2

- Would you consider this patient for bariatric surgery?

Effect of bariatric surgery in NASH (n=109)





All subjects BMI > 40 or BMI > 35 with comorbidity
Multiple surgical procedures
Baseline: 46.2y, 48.9kg/m^2, female 63%, T2DM 63%, HT 66%

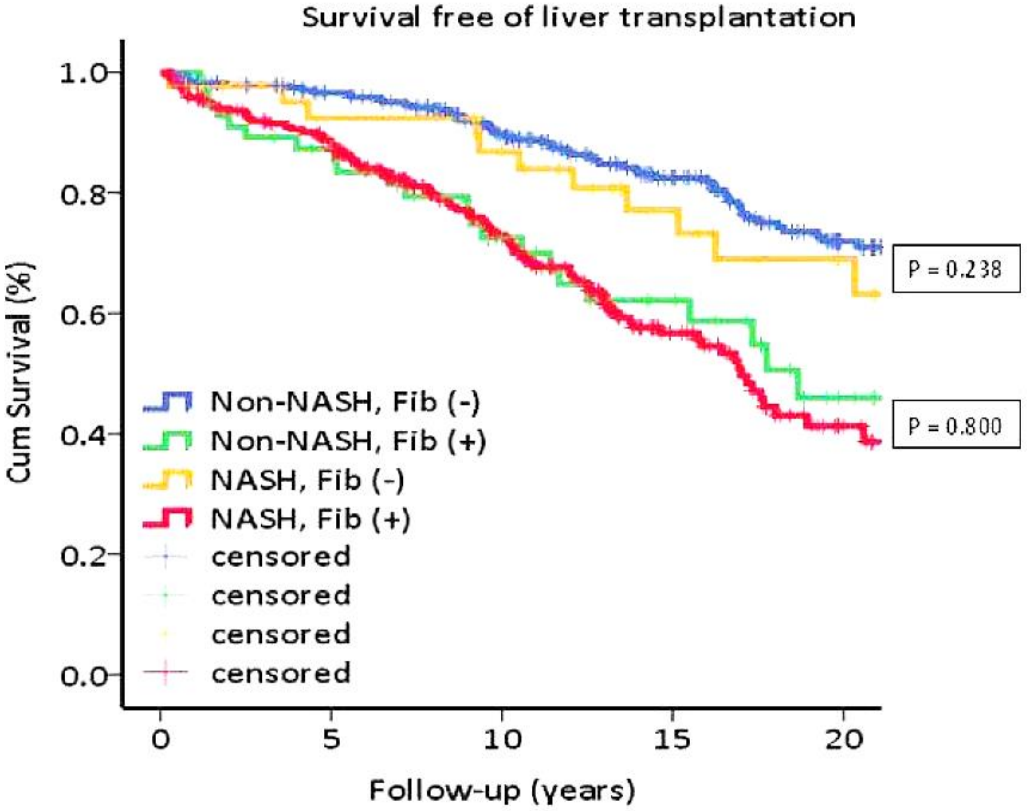
Lassailly et al, Gastro 2015

Effect of bariatric surgery on NAFLD-related fibrosis

Surgery	Author	Year	Design	N	Follow-up (months)	Basal BMI (g/m^2)	Final BMI (kg/m^2)	Baseline Kleiner or MFS ≥2 n (%)	Final Kleiner or MFS ≥2 n (%)	Complete fibrosis resolution n (%)
Roux-en-Y gastric bypass	Caiazzo [55]	2014	Cohort	6	60	46.8 ± 6.5	37.5 ± 7.5	6 (100)	3 (50)	1 (17)
	Tai [84]	2012	Not specified	21	12	43.8 ± 7.5	28.3 ± 4.6	6 (28.6)	0 (0)	9 (42.9)
	Moretto [99]	2012	Retrospective	78	12	45.4 ± 8.1	29.3 ± 5.8	35 (44.9)	24 (30.8)	15 (48.4)
	Liu [85]	2007	Retrospective	39	18	47.7 ± 6.2	29.5 ± 5.6	35 (89.7)	29 (74)	–
	Furuya [86]	2007	Cohort	18	24	51.7 ± 7.0	32.43 ± 6.0	3 (17)	1 (6)	6 (33)
	de Almeida [87]	2006	Cohort	16	24	53.4 ± 8.8	31.1 ± 4.7	4 (25)	2 (12.5)	1 (6.25)
	Barker [89]	2006	Retrospective	19	21.4	47 ± 4.4	29 ± 5.2	3 (15.8)	1 (5.3)	9 (56.2)
	Clark [57]	2005	Cohort	16	10.2	51.1 ± 6.1	32.9 ± 5.1	3 (18.8)	2 (12.5)	5 (31.3)
Gastric banding	Moschen [65]	2009	Cohort	18	12	42.6 ± 0.7	33.8 ± 0.9	5 (28)	5 (28)	2 (11)
	Caiazzo [55]	2014	Cohort	7	60	46.8 ± 6.5	37.5 ± 7.5	6 (100)	3 (43)	1 (14)
	Dixon [92]	2006	Retrospective	60	29.5	45.9 ± 7.4	34.0 ± 5.5	25 (41.6)	5 (8.3)	24 (40)

Aguilar-Olivos et al, Metabolism 2016

Fibrosis is associated with long-term mortality



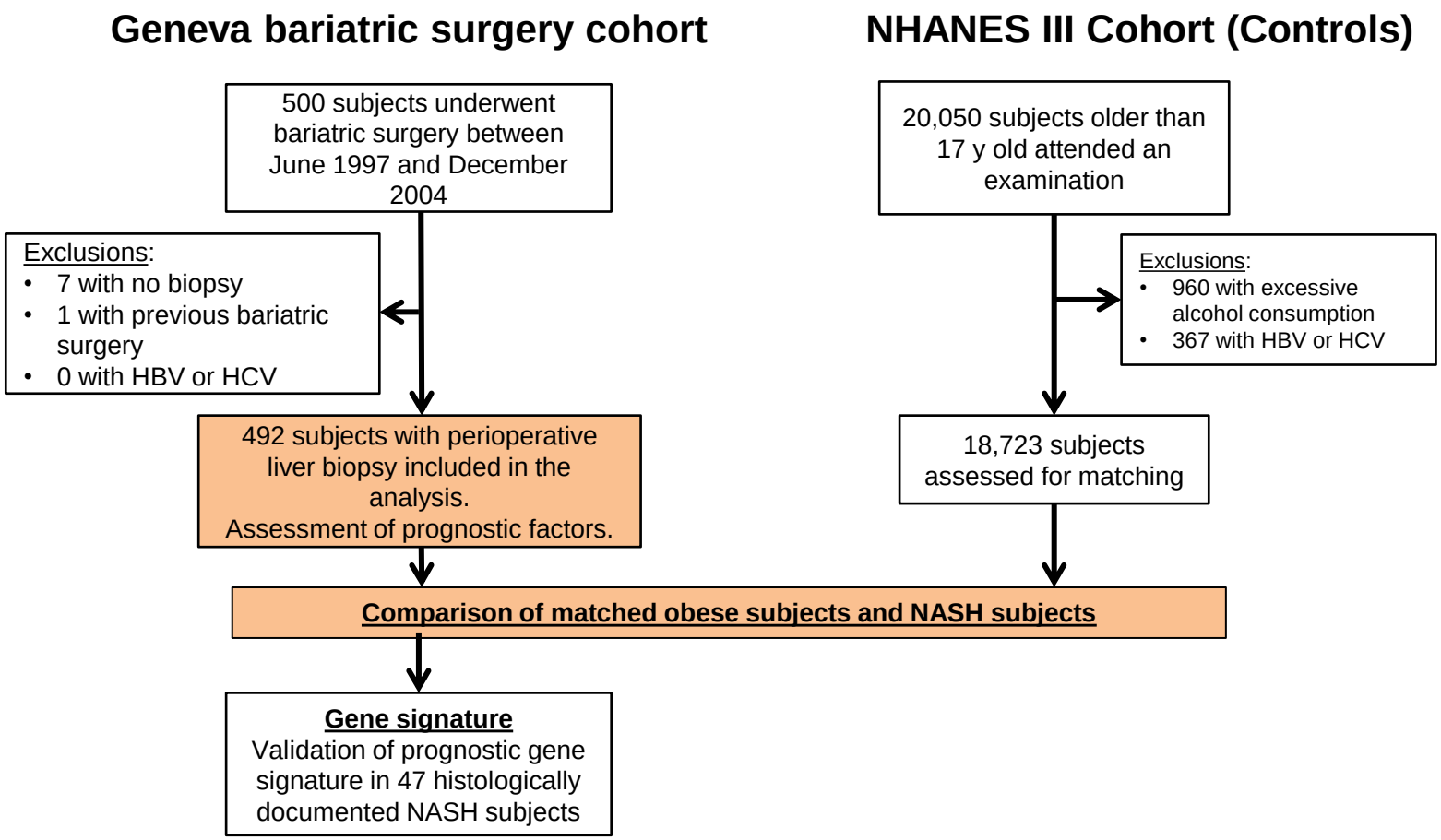
N=619 biopsy-proven NAFLD, FU 12.6 yrs

Causes of death: cardiovascular 38%, cancer 19%, cirrhosis 8%, HCC 1%

Independent predictors : fibrosis, diabetes, smoking, no statins

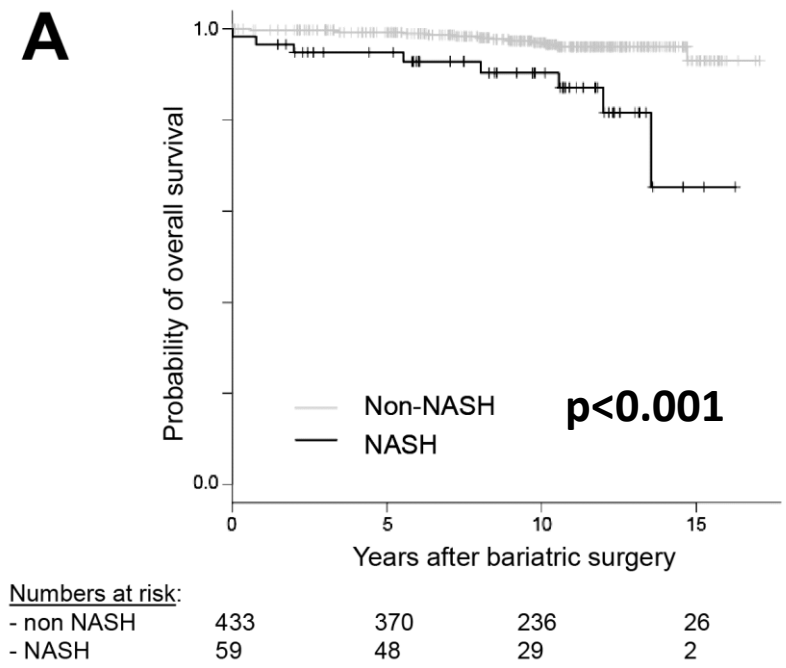
Angulo et al, *Gastro*, 2015

Long-term survival in NASH patients undergoing bariatric surgery



Goossens et al, CGH 2016

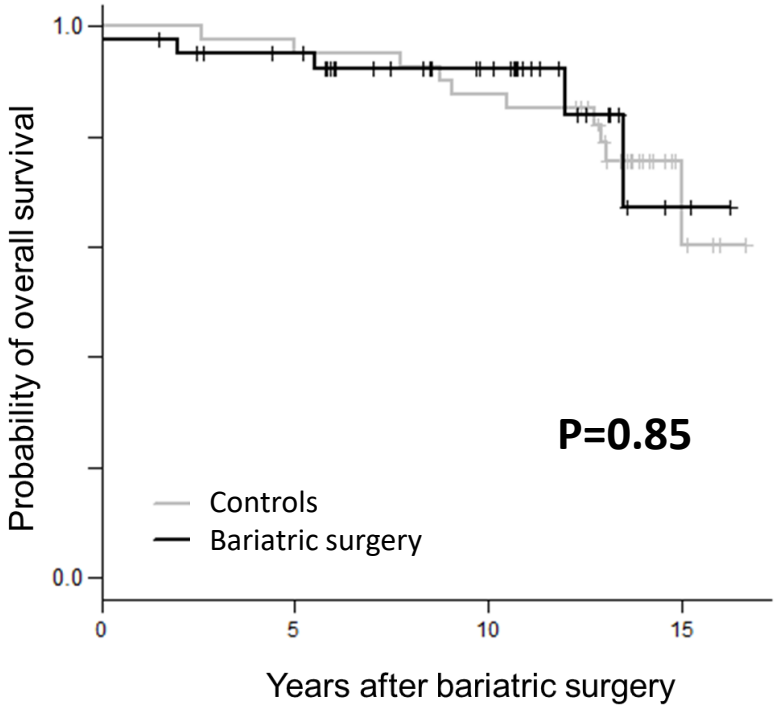
NASH is an independent predictor of long-term mortality after bariatric surgery



- 492 subjects undergoing RYGB in Geneva
- Baseline: 41y, female 82%, BMI 43.6 kg/m^2, HT 32%, T2DM 17%, NAFLD 89%, NASH 12%
- NASH associated with long-term mortality (HR 3.4, p<0.01) in multivariate model selected by AIC (including HT, sex, age, BMI, T2DM, fibrosis)

Goossens et al, CGH 2016

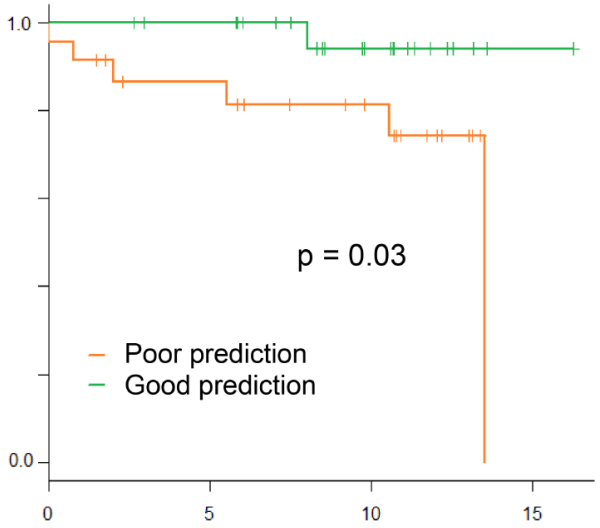
No significant improval of survival in NASH subjects compared to matched non-surgical obese controls

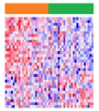


- Comparison of bariatric surgery subjects with NASH to control non-surgical obese subjects (NHANES 3)
- Propensity-score matching
- Unlike the general population, NASH subjects did not have improved survival after surgery
- Limitations: different populations, limited numbers

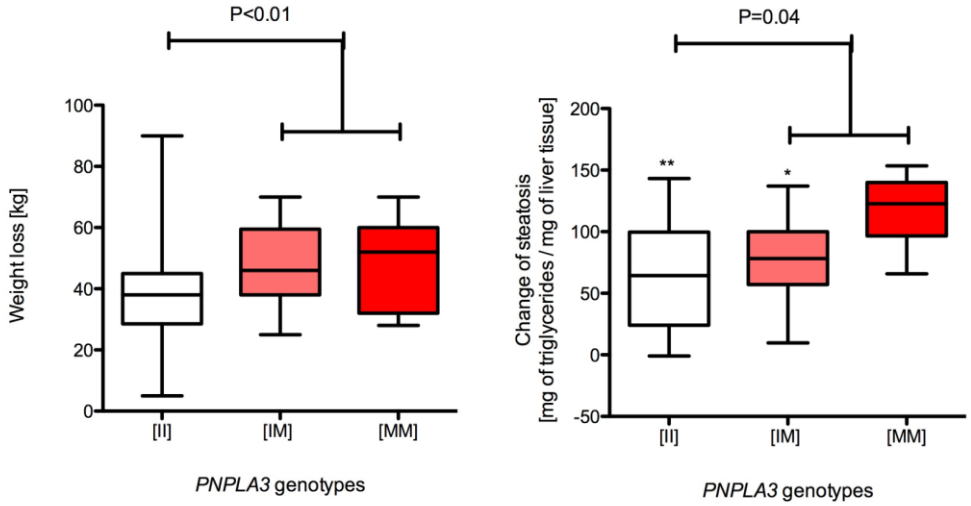
Goossens et al, CGH 2016

Improved identification of high-risk patient subgroups: molecular biomarkers?





Gene Expression liver-based signature



PNPLA3 I148M SNP genotype

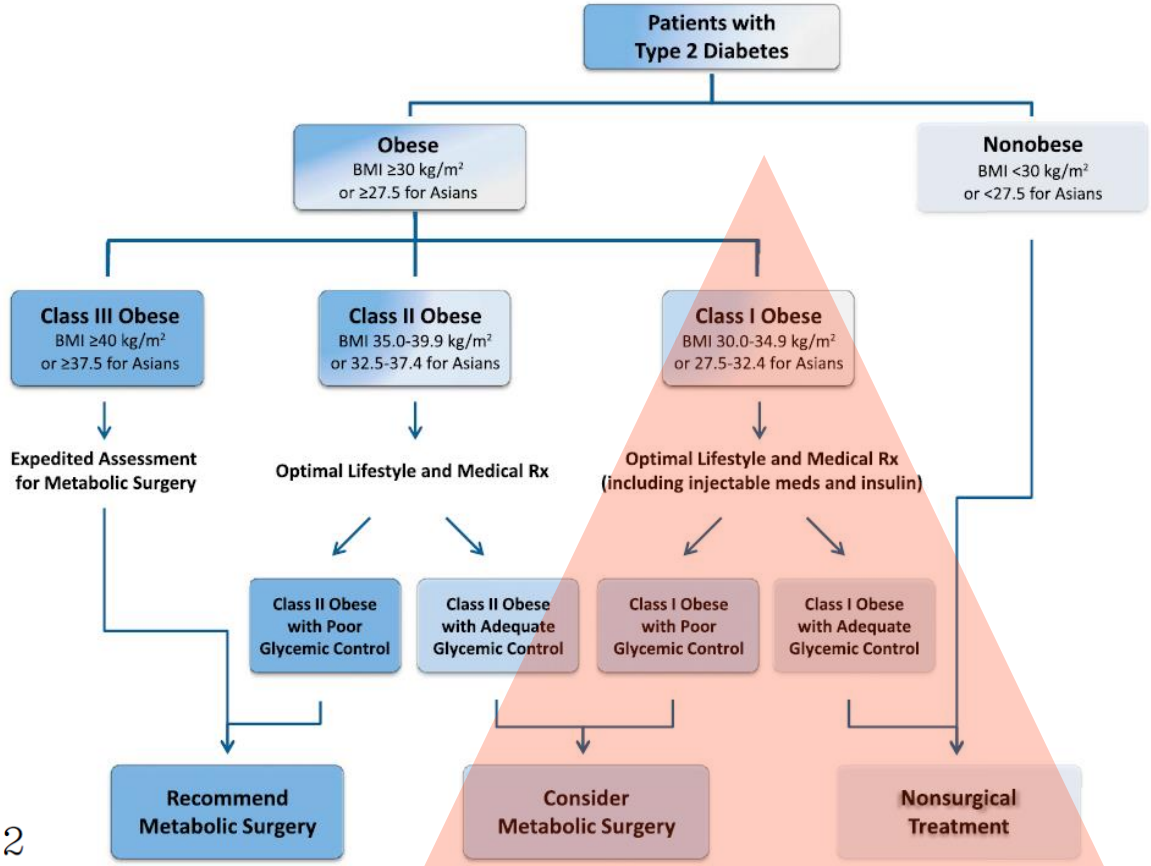
Krawczyk et al, Surg Obes Rel Dis 2017; Hoshida et al, NEJM 2008; Goossens et al, CGH 2016

Clinical case

- 38 y obese man, liver clinic
- NASH at liver biopsy, fibrosis stage F3
- BMI 33 kg/m^2, raised HOMA score but no diabetes, arterial hypertension, OSA
- Failure to lose weight.
- Does not want to participate in drug clinical trials

- Would you consider this patient for bariatric surgery?

Metabolic surgery in patients with BMI < 35kg/m^2



Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: A Joint Statement by International Diabetes Organizations

Diabetes Care 2016;39:861–877 | DOI: 10.2337/dc16-0236

Metabolic surgery: pushing the boundaries

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

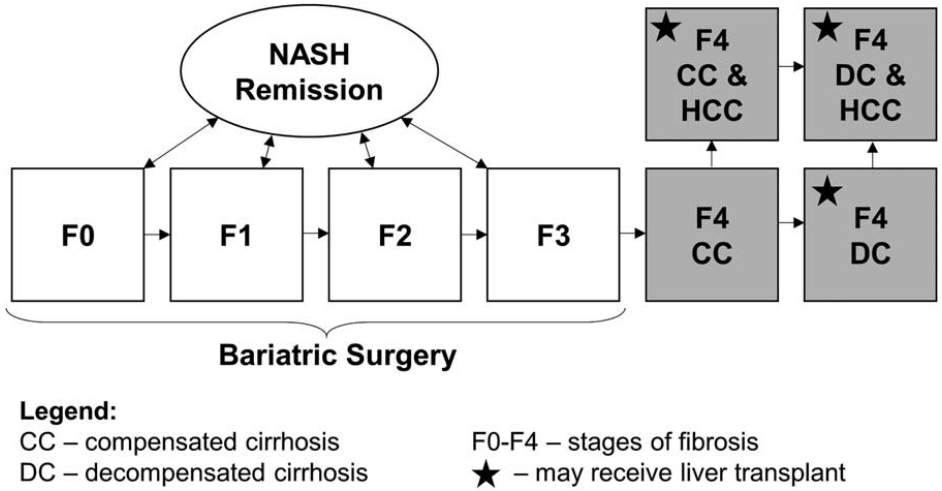
Philip R. Schauer, M.D., Deepak L. Bhatt, M.D., M.P.H., John P. Kirwan, Ph.D., Kathy Wolski, M.P.H., Ali Aminian, M.D., Stacy A. Brethauer, M.D., Sankar D. Navaneethan, M.D., M.P.H., Rishi P. Singh, M.D., Claire E. Pothier, M.P.H., Steven E. Nissen, M.D., and Sangeeta R. Kashyap, M.D., for the STAMPEDE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

CONCLUSIONS

Five-year outcome data showed that, among patients with type 2 diabetes and a BMI of 27 to 43, bariatric surgery plus intensive medical therapy was more effective than intensive medical therapy alone in decreasing, or in some cases resolving, hyperglycemia. (Funded by Ethicon Endo-Surgery and others; STAMPEDE ClinicalTrials.gov number, NCT00432809.)

Schauer et al, NEJM 2017

Metabolic surgery and NASH / NAFLD



- Markov model for assessing cost-effectiveness
- Compared to lifestyle interventions, bariatric surgery was cost-effective in stage 1 obesity ($48,836/QALY) and stage 2/3 obesity (< $25,000/QALY). Not cost-effective in overweight subjects
- **Limitations**: Lack of robust key transitional probabilities. Some probabilities based on diabetes results

Klebanoff et al, Hepatology 2017

Clinical case

- Hepatology referral:
- 45y old man
- BMI 43kg/m^2 arterial hypertension, T2DM
- Liver biopsy: Steatosis, cirrhosis
- Grade 1 (small) esophageal varices at endoscopy
- Bilirubin N, creatinine 86umol/L, albumin 37g/L, platelets 120 x10^9/L, no ascites, no encephalopathy

- Would you consider this patient for bariatric surgery?

Bariatric surgery and cirrhosis with portal HT

- Numerous case series…

- N=14 Child A cirrhosis
- Mayo Clinic
- 11/14 NASH cirrhosis
- 1/11 had EV, 4/11 had PHG
- 0 complications, 0 mortality (1 episode of HE 2y after unrelated)

TABLE 2. Metabolic Outcomes[a,b]

Variable	Presurgery (n=14)	Postsurgery 6 mo (n=12)	Postsurgery 1 y (n=12)	Postsurgery 2 y (n=6)
Weight (kg)	125±18	102±16	94±17	93±17
P value vs presurgery		<.001	<.001	<.001
% total body weight change		18.4	24.8	25.6
Diabetes	10 (71.4)	6 (50.0)	4 (33.3)	1 (16.7)
P value vs presurgery		.09	.01	.02
Insulin use	9 (90.0)	3 (50.0)	1 (25.0)	1 (100)
P value vs presurgery		.07	.03	.14
Dyslipidemia	5 (35.7)	5 (41.7)	3/11[c] (27.3)	0
P value vs presurgery		1.0	.65	.32
Hypertension	9 (64.3)	8 (66.7)	6 (50.0)	2 (33.3)
P value vs presurgery		.90	.15	.08
Hypertension medication				
0 drugs (no HTN)	5 (35.7)	4 (33.3)	6 (50.0)	4 (66.7)
1 drug	2 (14.3)	4 (33.3)	3 (25.0)	2 (33.3)
≥2 drugs	7 (50.0)	4 (33.3)	3 (25.0)	0
P value vs presurgery		.39	.11	.39

[a]HTN = hypertension.
[b]Values are presented as mean ± SD or as No. (percentage).
[c]Only 11 of 12 patients had lipid studies available.

Petana et al, Mayo Clin Proc 2015

Bariatric surgery and cirrhosis

- US Nationwide Inpatient Sample data from 1998-2007
- ICD-9-CM procedural codes
- 3888 bariatric procedures in compensated cirrhosis (mortality 0.9%)
- 62 procedures in decompensated cirrhosis (mortality 16%)

Table 2. Multivariate Analysis of Predictors of In-Hospital Mortality

	Adjusted odds ratio (95% confidence interval)	*P* value
Liver disease status		
No cirrhosis	Ref	
Compensated cirrhosis	2.2 (1.0–4.6)	.041
Decompensated cirrhosis	21.1 (5.4–82.3)	<.0001

Table 3. Multivariate Analysis of Predictors of In-Hospital Length of Stay

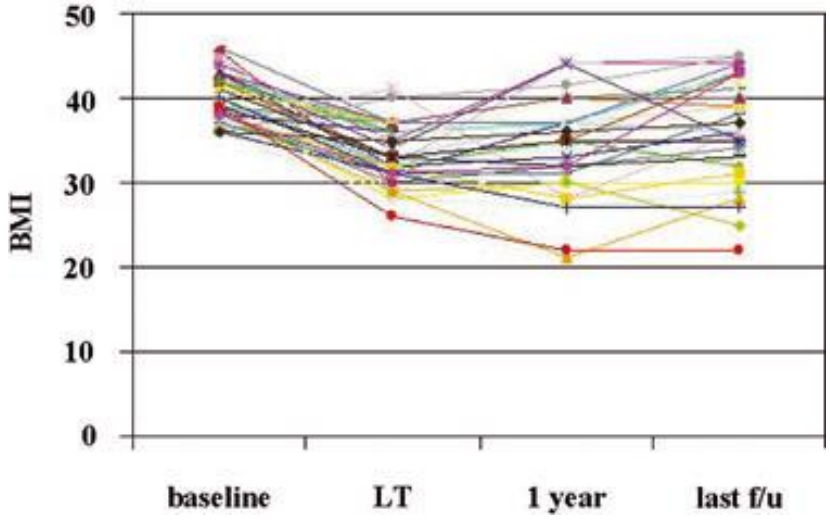
	Relative change, % (95% confidence interval)	*P* value
Liver disease status		
No cirrhosis	Ref	
Compensated cirrhosis	16 (9%–23%)	<.0001
Decompensated cirrhosis	37 (–26% to 156%)	.311

Adjusted for age, Charlson index, sex, race/ethnicity, insurance status, hospital status, hospital surgical volume

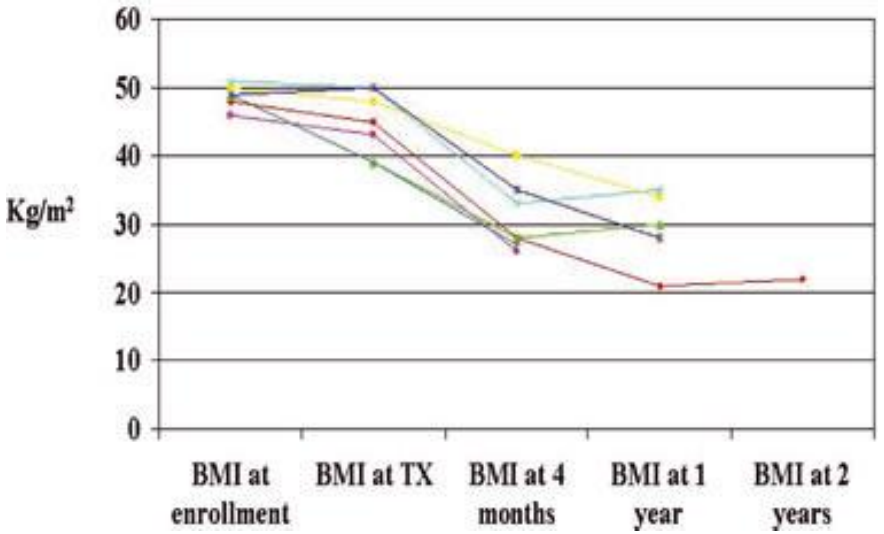
Mosko et al, CGH 2011

Place of bariatric surgery in the context of LT?

LT alone, n=37



LT + sleeve gastrectomy, n=7



- Program of LT + sleeve gastrectomy in LT candidates who fail to lose weight before LT
- 6/37 death or graft loss in LT arm vs 0/7 in LT+SG arm
- 12/34 vs 0/7 post-LT diabetes

Heimbach et al, Am J Transplant 2013

EASL and AASLD recommendations

- By improving obesity and diabetes, bariatric (metabolic) surgery reduces liver fat and is likely to reduce NASH progression; prospective data have shown an improvement in all histological lesions of NASH, including fibrosis (**B1**)

Recommendations

25. Foregut bariatric surgery is not contraindicated in otherwise eligible obese individuals with NAFLD or NASH (but without established cirrhosis). (Strength – 1, Quality – A)

26. The type, safety and efficacy of foregut bariatric surgery in otherwise eligible obese individuals with established cirrhosis due to NAFLD are not established. (Strength – 1, Quality – B)

27. It is premature to consider foregut bariatric surgery as an established option to specifically treat NASH (1B)

EASL, J Hep 2016; Chalasani et al, Hepatology 2012

Unanswered questions

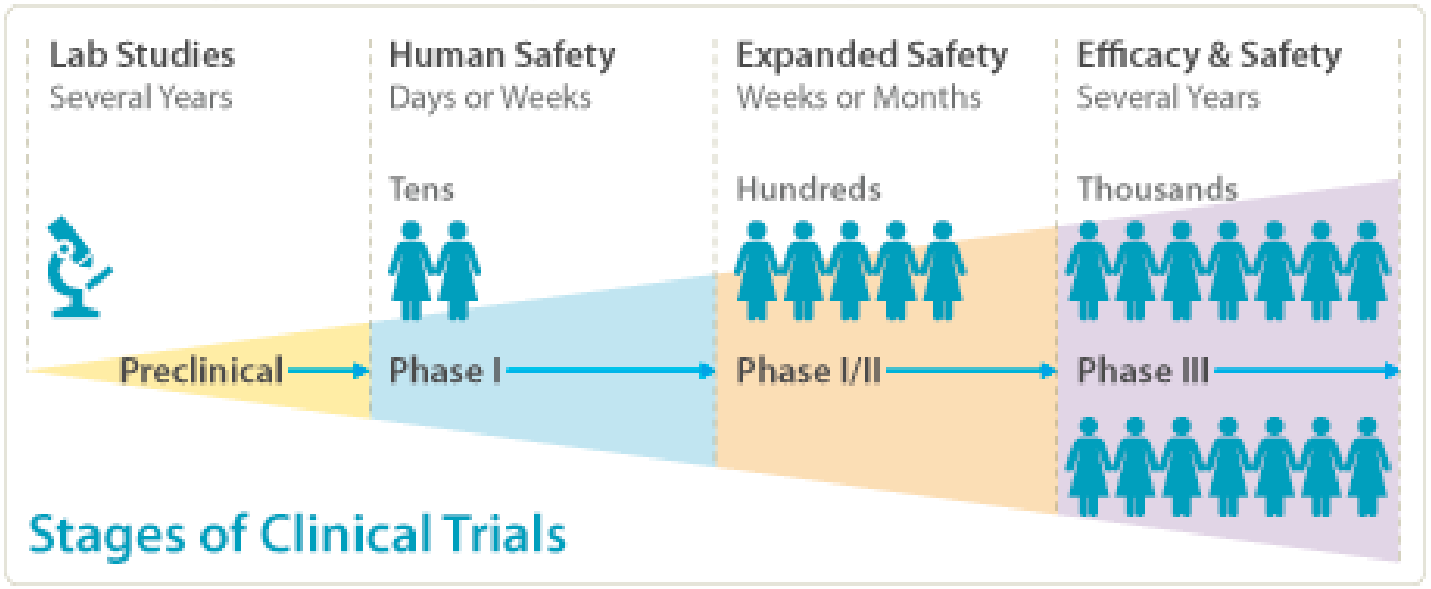
- The long-term survival benefit of bariatric surgery in NASH
- The role of different bariatric surgeries in NASH
- The role and benefit of bariatric surgery in NASH-cirrhosis
- The role of metabolic surgery in NASH
- Can we translate our knowledge of NASH natural history / therapy to a bariatric surgery context

If bariatric surgery were a drug…

Metabolic surgery in NASH with BMI<35

Bariatric surgery in cirrhosis

Bariatric surgery for stage II obesity and NASH



Conclusion

- Bariatric surgery is associated with histological improvement in NAFLD/NASH
- However, data showing improvement in long-term survival in NASH patients is lacking
- Bariatric surgery is associated with rare but existing mortality/morbidity
- Further prospective studies with hard clinical outcomes are needed before indications for bariatric surgery can be extended for NASH patients
- Need for additional tools to identify subgroups of NAFLD subjects at high risk of surgery or at high risk of progression without surgery.

How to extend the indications?

- NASH in patient with BMI 37 kg/m^2 with no other obesity-related comorbidities **– weigh risk/benefit**
- NASH in patient with BMI 33 kg/m^2 **– no evidence**
- Well compensated NASH-cirrhosis **– weigh risk/benefit**