CLINICAL CASE

2005

55 years old man

- W = 125 kg, H = 1.80m, BMI – 38.58 kg/m2
- High blood pressure (2000), controlled under triple therapy (ARB, BBL and diuretics)
- Type 2 diabetes (2002) under Metformin
- Dyslipidemia controlled under statins
- OSA – without CPAP
- Alcohol consumption – 2 glass of wine/day
- Past cigarette smoking (10 PY, stopped since 2002)

- LFT: AST = 52, ALT = 123; GGT = 121; PAL = 97; BiliT = 12 micromol/l
- Lipids: CT = 2.41 g/l; TG = 0.81; HDL = 0.84 g/l; LDL = 1.41 g/l;
- FG = 5.9 mmol/l; insulin = 11.2 ; HOMA = 2.93, HbA1c = 7.4%
- Ferritin = 525 µmol/l, transferin saturation = 35%

- **Bariatric surgery (sleeve) – LB: S3A3F2**

Q1

What benefit would you expect from bariatric surgery?

- **Weight loss of > 40% at 1 year**
- **T2DM resolution at 1 year**
- **Resolution of NASH at 1 year**
- **Resolution of NASH and fibrosis regression at 1 year**

Indications for bariatric surgery

Patients in age groups from **18 to 60** years:
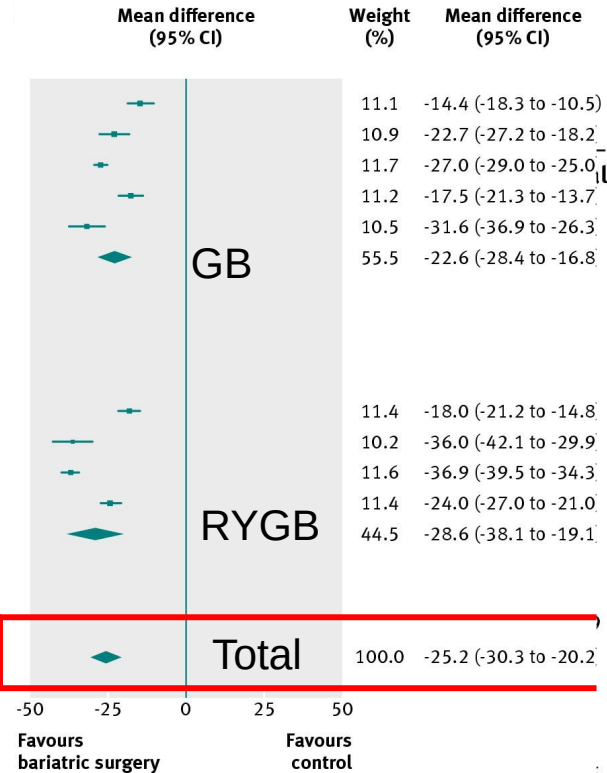
1. With **BMI ≥ 40 kg/m2**

    OR

2. With **BMI 35–40 kg/m2 with co-morbidities in which surgically induced weight loss is expected to improve the disorder** (such as metabolic disorders, cardiorespiratory disease, severe joint disease, obesity-related severe psychological problems)
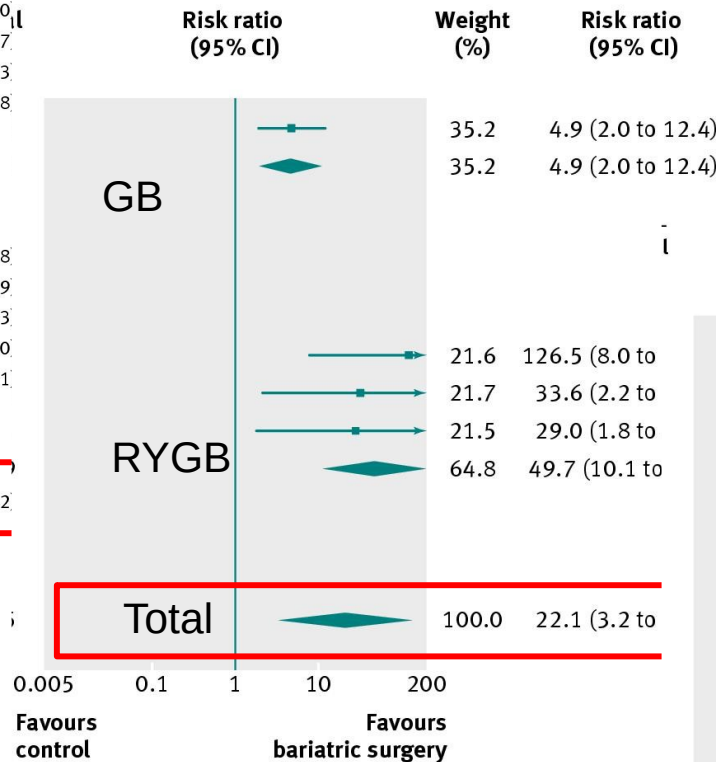
Bariatric surgery versus non-surgical treatment for obesity
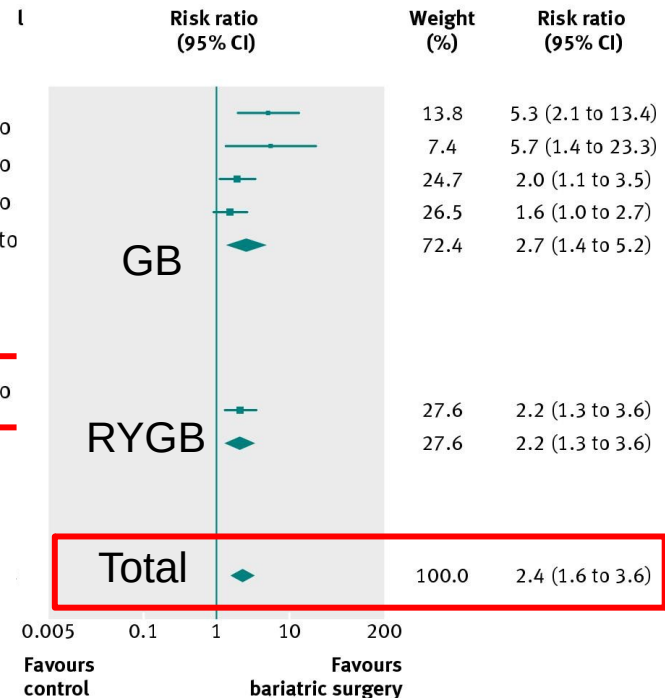
Weight loss

MA: 11 studies with 796 individuals

	Mean difference (95% CI)	Weight (%)	Mean difference (95% CI)
		11.1	-14.4 (-18.3 to -10.5)
		10.9	-22.7 (-27.2 to -18.2)
		11.7	-27.0 (-29.0 to -25.0)
		11.2	-17.5 (-21.3 to -13.7)
		10.5	-31.6 (-36.9 to -26.3)
GB		55.5	-22.6 (-28.4 to -16.8)
		11.4	-18.0 (-21.2 to -14.8)
		10.2	-36.0 (-42.1 to -29.9)
		11.6	-36.9 (-39.5 to -34.3)
		11.4	-24.0 (-27.0 to -21.0)
RYGB		44.5	-28.6 (-38.1 to -19.1)
Total		100.0	-25.2 (-30.3 to -20.2)

-50 -25 0 25 50

Favours bariatric surgery   **Favours control**

T2DM remission rate

	Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
		35.2	4.9 (2.0 to 12.4)
GB		35.2	4.9 (2.0 to 12.4)
		21.6	126.5 (8.0 to
		21.7	33.6 (2.2 to
		21.5	29.0 (1.8 to
RYGB		64.8	49.7 (10.1 to
Total		100.0	22.1 (3.2 to

0.005 0.1 1 10 200

Favours control   **Favours bariatric surgery**

Metabolic syndrome remission rate

	Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
		13.8	5.3 (2.1 to 13.4)
		7.4	5.7 (1.4 to 23.3)
		24.7	2.0 (1.1 to 3.5)
		26.5	1.6 (1.0 to 2.7)
GB		72.4	2.7 (1.4 to 5.2)
		27.6	2.2 (1.3 to 3.6)
RYGB		27.6	2.2 (1.3 to 3.6)
Total		100.0	2.4 (1.6 to 3.6)

0.005 0.1 1 10 200

Favours control   **Favours bariatric surgery**

ICAN

Prediction factor	Score
Age (years)	
[15–41]	0
[42–52]	3
[53–69]	5
HbA$_{1c}$ (%)	
[4.5–6.9]	0
[7.0–7.4]	2
[7.5–18.4]	4
Insulin	
No	0
Yes	3
Other glucose-lowering agents[a]	
No	0
Yes	1
Number of glucose-lowering agents[b]	
0	0
1	1
2	2
≥ 3	3
Diabetes duration (years)	
[0–6.9],	0
[7.0–13.9]	3
≥ 14	5
Ad-DiaRem overall score (sum of the above six components)	0–21

Ad-DiaRem Score = 9
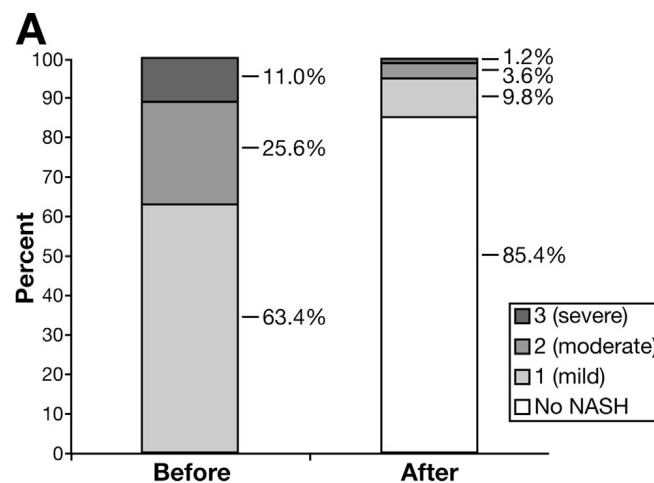
Ad-DiaRem < 10
PPV = 93%; NPV = 72%

Aron-Wisnewsky, Diabetologia 2017
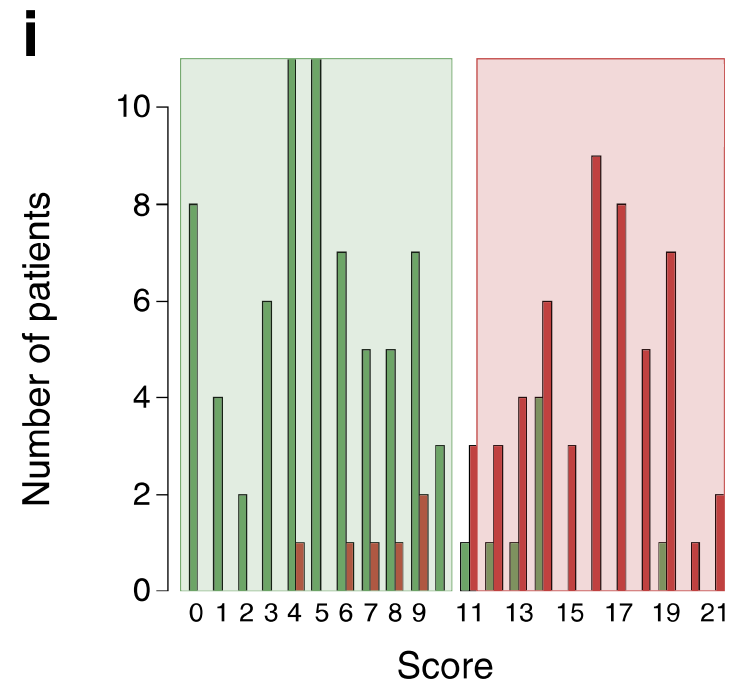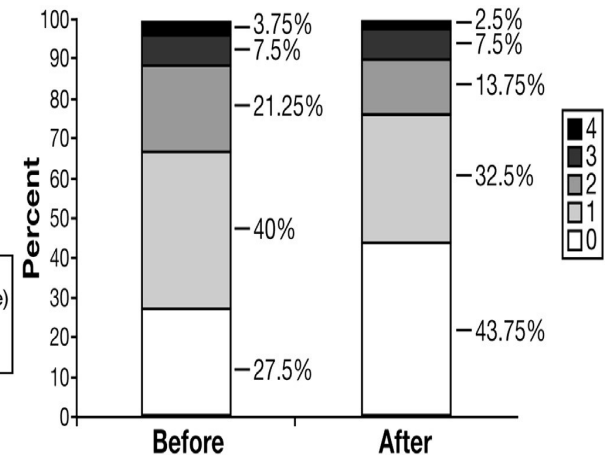
BARIATRIC SURGERY

Distribution of NAS

B

Resolution of NASH

A
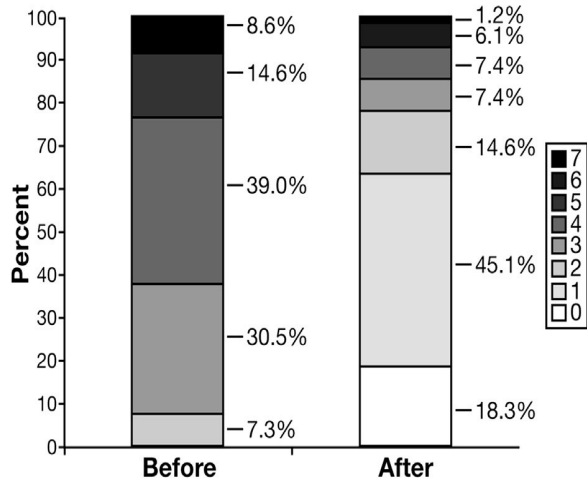
Distribution of Fibrosis

- ✓ NASH disappeared in 85.4% of cases
- ✓ Fibrosis improved in 46%.
- ✓ The rate of disappearance of NASH was higher in patients with mild NASH than in those with moderate or severe NASH
- ✓ Persistance of NASH was more frequent among GB than RYGB
- ✓ 14.6% of patients had persistent NASH 1 year after bariatric surgery. These patients had significantly lower weight loss, higher NAS and refractory IR profile

Lassailly, Gastroenterology 2015

Relationship between the evolution of T2DM after bariatric surgery and severity of liver lesions

➢ **Patients without remission of T2DM after bariatric surgery had more severe liver histology at baseline**

Courtesy of Aron J & Clement K

2010

	2005	2010
Weight (kg)	125	100
BMI (kg/m2)	38.58	**30.86**
T2DM	YES	**NO**
Dyslipidemia	YES	**NO**
High BP	YES ((ARB, BBL, Diuretics)	**YES (ARB)**
OSA	YES	**NO**

- Alcohol consumption – 2 glass of wine/day
- LFT: AST = 19, ALT = 25; GGT = 36; PAL = 97; BiliT = 9 micromol/l
- Lipids: CT = 2.05 g/l; TG = 0.81;
- FG = 5.9 mmol/l; insulin = 6.2 ; HOMA = 1.65, HbA1c = 6%
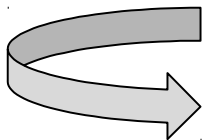
Surveillance by non invasive methods

2015

	2005	2010	2015
Weight (kg)	125	100	115
BMI (kg/m2)	38.58	**30.86**	**35.5**
T2DM	YES	**NO**	**YES**
Dyslipidemia	YES	**NO**	**YES**
High BP	YES ((ARB, BBL, Diuretics)	**YES (ARB)**	**YES (ARB)**
OSA	YES	**NO**	**NO**

- FG = 8.5 mmol/l; insulin = 12.1 ; HOMA = 4.57, HbA1c = 7.8%
- LFT: AST = 21, ALT = 30; GGT = 45; PAL = 87; BiliT = 11 micromol/l
- Lipids: CT = 2.85 g/l; TG = 1.21

Q2

Relationship between Normal ALT and liver histology?

- 29 to 33 IU/l for males,
- 19 to 25 IU/l for females

ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries,
The Am J Gastroenterol 2017

Transaminases Level and Liver Histology

	Normal ALT (N = 63)	Increased ALT (N = 395)	P
BMI	26 ± 4	27.4 ± 3.7	0.04
HOMA-IR	2.9 ± 1.4	4.6 ± 3.9	0.006
Type 2 Diabetes	11%	9%	NS
Metabolic syndrome	19%	21%	NS
NASH	**59%**	**75%**	**0.01**
> F2	**22%**	**34%**	**NS**

- **The entire spectrum of NAFLD can be seen in patients with normal ALT**

- **Normal ALT is not a valuable criterion to exclude NASH or advanced fibrosis**

Fracanzani, Hepatology 2008

2015

	2005	2010	2015
Weight (kg)	125	100	115
BMI (kg/m2)	38.58	**30.86**	**35.5**
T2DM	YES	**NO**	**YES**
Dyslipidemia	YES	**NO**	**YES**
High BP	YES ((ARB, BBL, Diuretics)	**YES (ARB)**	**YES (ARB)**
OSA	YES	**NO**	**NO**

- FG = 8.5 mmol/l; insulin = 12.1 ; HOMA = 4.57, HbA1c = 7.8%
- LFT: AST = 21, ALT = 30; GGT = 45; PAL = 87; BiliT = 11 micromol/l
- Lipids: CT = 2.85 g/l; TG = 1.21
- FT = 0.48; FS M probe= 7.8 kPa (IQR = 3.6 kPa, 27.1%, TDR = 76%); FS XL probe = 8.2 kPa; IQR = 1.2; 10%; TDR = 10%.
- **LB: S2A2F2**

Q3

Risk factors associated with diabetes recurrence?

- **Initial weight before bariatric surgery**
- **Weight changes during FU**
- **Diabetes duration and control before bariatric surgery?**
- **NAFLD?**

Bariatric Surgery and Long-term Remission of Type 2 Diabetes

Total participants			
Control	207	135	62
Surgery	303	236	115
Odds ratio	13.3	5.3	6.3
(95% CI)	(8.5-20.7)	(2.9-9.8)	(2.1-18.9)
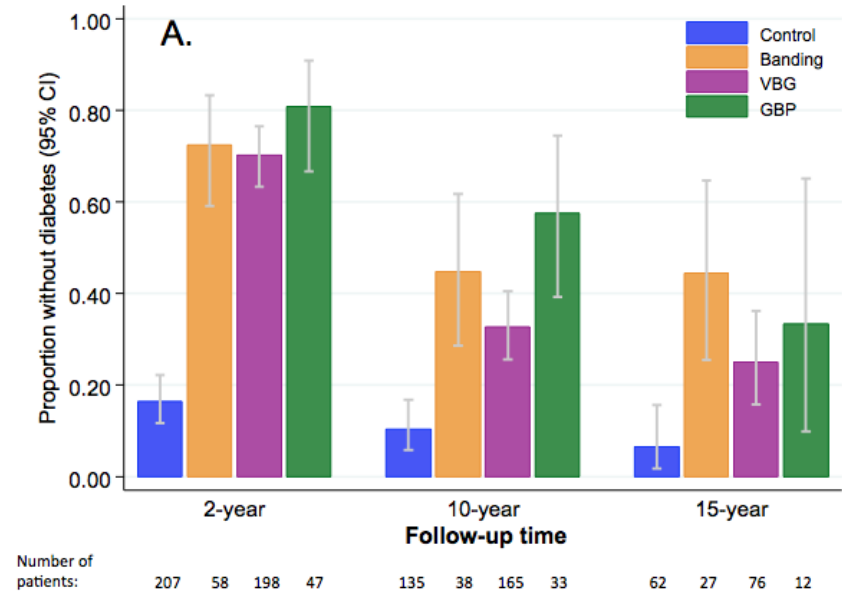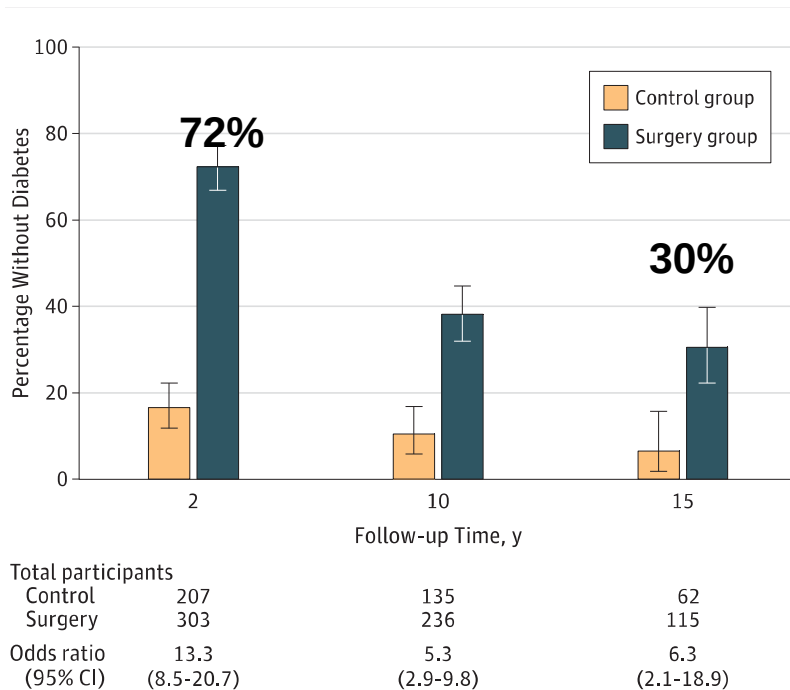
Factors associated with diabetes recurrence at 10 years

- **Initial BMI : OR = 1.37, p = 0.14**
- **Weight changes between baseline and FU: OR = 4.52, p < 0.001**
- **Diabetes duration: 3.71, p = 0.029**
- **Male sex: OR = 3.60, p = 0.001**

Sjöström, JAMA 2014

NAFLD is additive to established MRF in increasing the risk of incidentT2DM

N = 12 853 subjects from a South Korean occupational cohort

Risk factors	OR, 95% CI
IR alone	3.66 (1.89 – 7.08)
Overweight/obesity	1.29 (0.62 – 2.71)
NAFLD	2.73 (1.38 – 5.41)
IR + overweight/obesity	6.16 (3.38 – 11.22)
IR + NAFLD	6.73 (3.49 – 12.97)
Overweight/obesity + NAFLD	3.23 (1.78 – 5.89)
IR + overweight/obesity + NAFLD	**14.13 (8.99 – 22.2)**

Adjusted for age, sex, alcohol, smoking status, exercise, educational status, TG, and ALT

Sung, Diabetes Care 2012

Severity of NAFLD and incidentT2DM
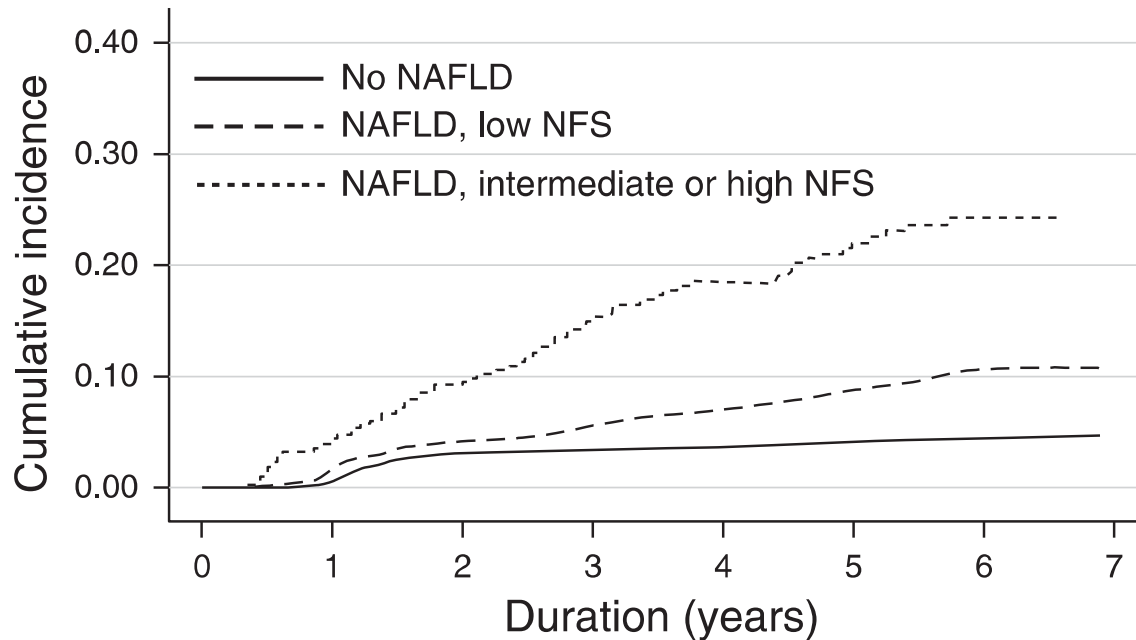
Cumulative incidence of diabetes

Chang, Am J Gastroenterol 2013

AFLD and type 2 diabetes – bidirectional relationship

Worsening of histological features and fibrosis progression

Type 2 diabetes

In patients with T2DM, the presence of NAFLD should be looked for irrespective of liver enzyme levels, since T2DM patients are at high risk of disease progression (**A2**)

In persons with NAFLD, screening for diabetes is mandatory, by fasting or random blood glucose or HbA1c (**A1**)
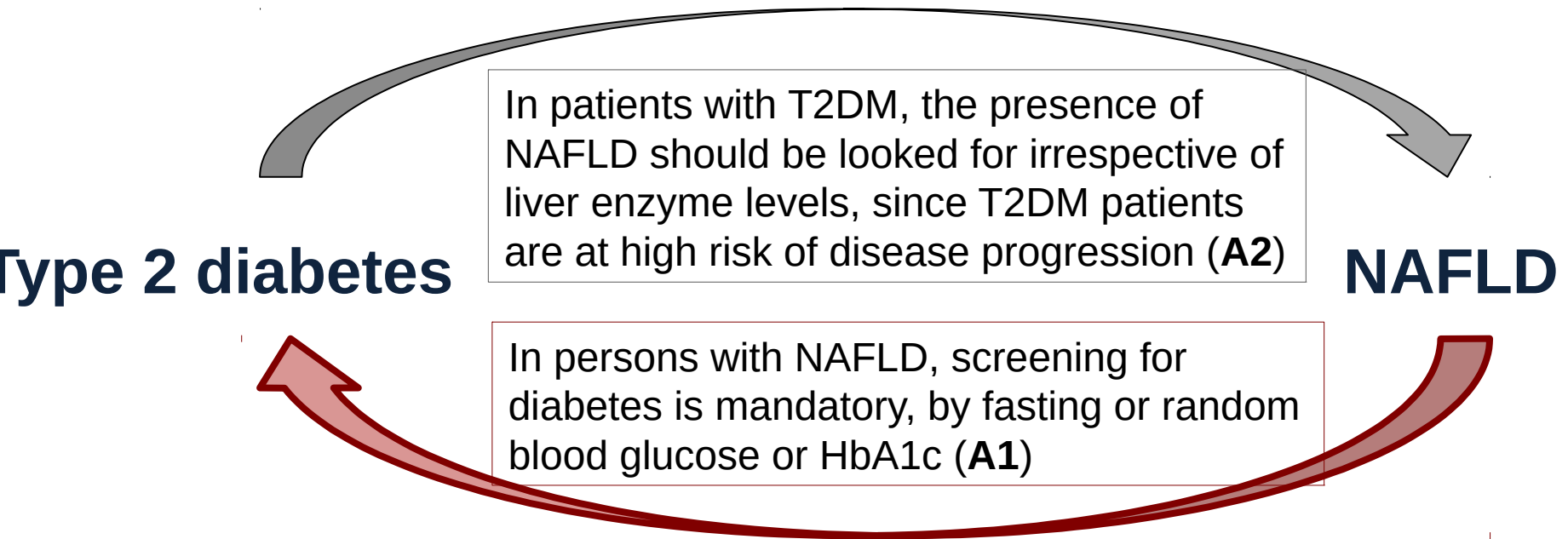
NAFLD

Increased risk of incident type 2 diabetes

CV disease is the first cause of death in non-cirrhotic patients with NAFLD

Cause of death	Cases, n N = 646	%
Psychiatric disorder (including suicide)	2	0.9
Infections	4	1.9
Kidney disease	4	1.9
External trauma	4	1.9
Gastrointestinal	5	2.4
Nervous system	6	2.8
Other	9	4.2
Endocrine (including T2DM)	11	5.1
Liver-related	17	7.9
Respiratory disease	18	8.4
Extrahepatic malignancy	55	25.7
Cardiovascular	79	36.9
Total	214	33.1

All Cause Mortality

Fibrosis Stage	0	1	2	3	4
Mortality Rate	15.2	17.1	27.9	36.0	45.8
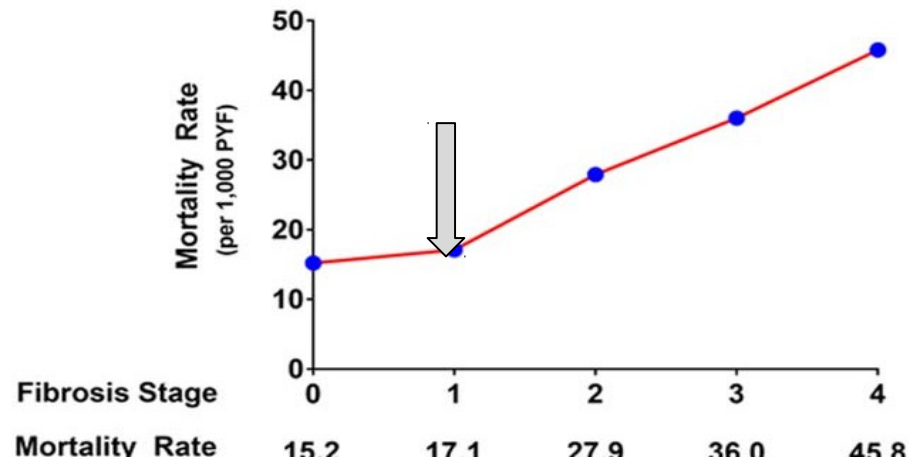
Hagstrom, J Hepatol 2017
Dulai, Hepatology 2017

Q5

How to evaluate the CV risk?

➤ **CV risk score sheets?**

➤ **Early ATS**
- **C-IMT?**
- **Coronary Ca2+ Score?**

Predictive value for future CV events?
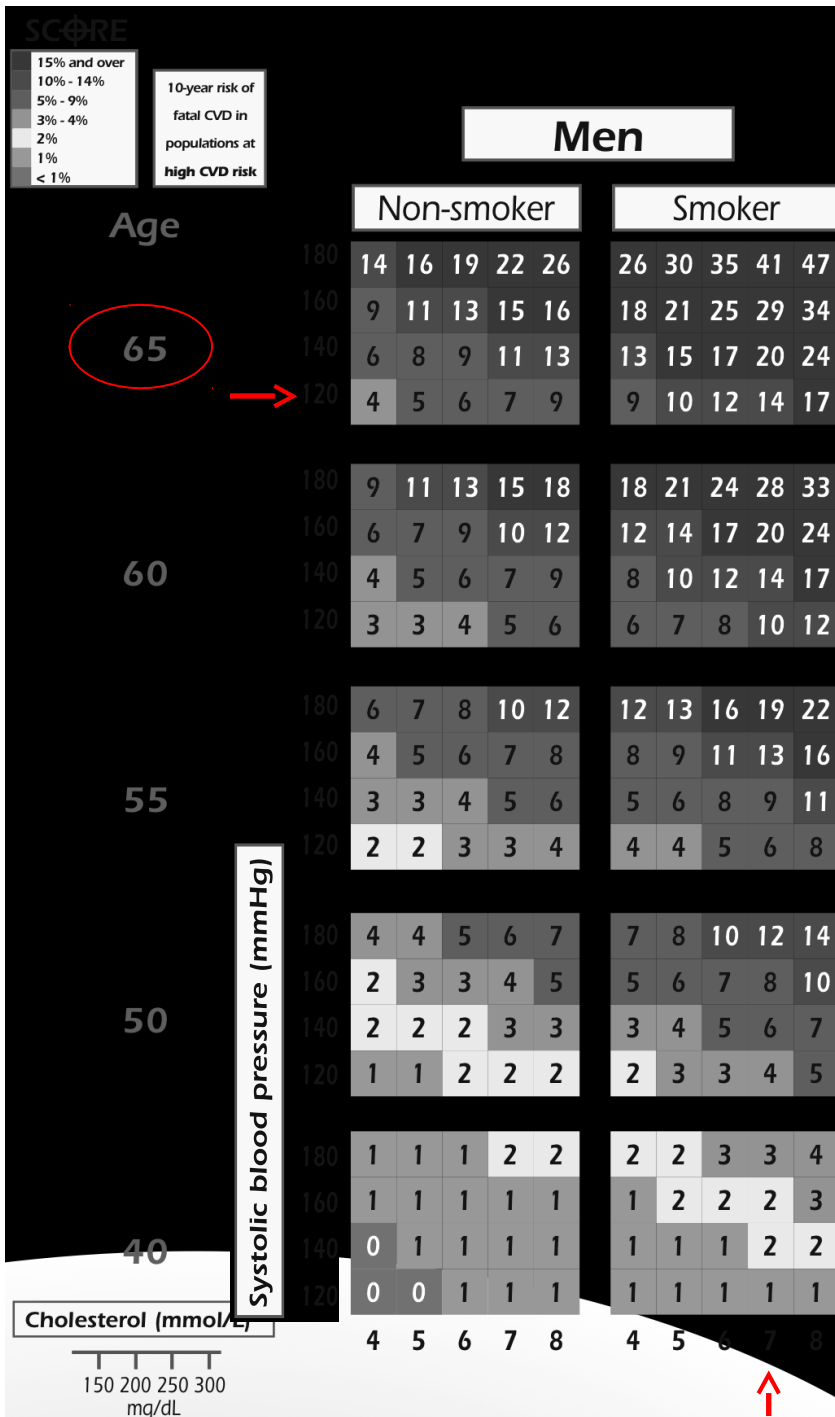
10 years risk of fatal CV disease in Europe

## 14% risk of CV events at 10 years

Traditional CHD risk prediction schemes need further improvement as the majority of the CHD events occur in the "low" and "intermediate" risk groups.

Early detection of subclinical ATS improves prediction of coronary heart disease risk

ARIC (Atherosclerosis Risk in Comunity) Study; 13145 subjects between 45 – 64 years of a

Nambi, JACC 2010
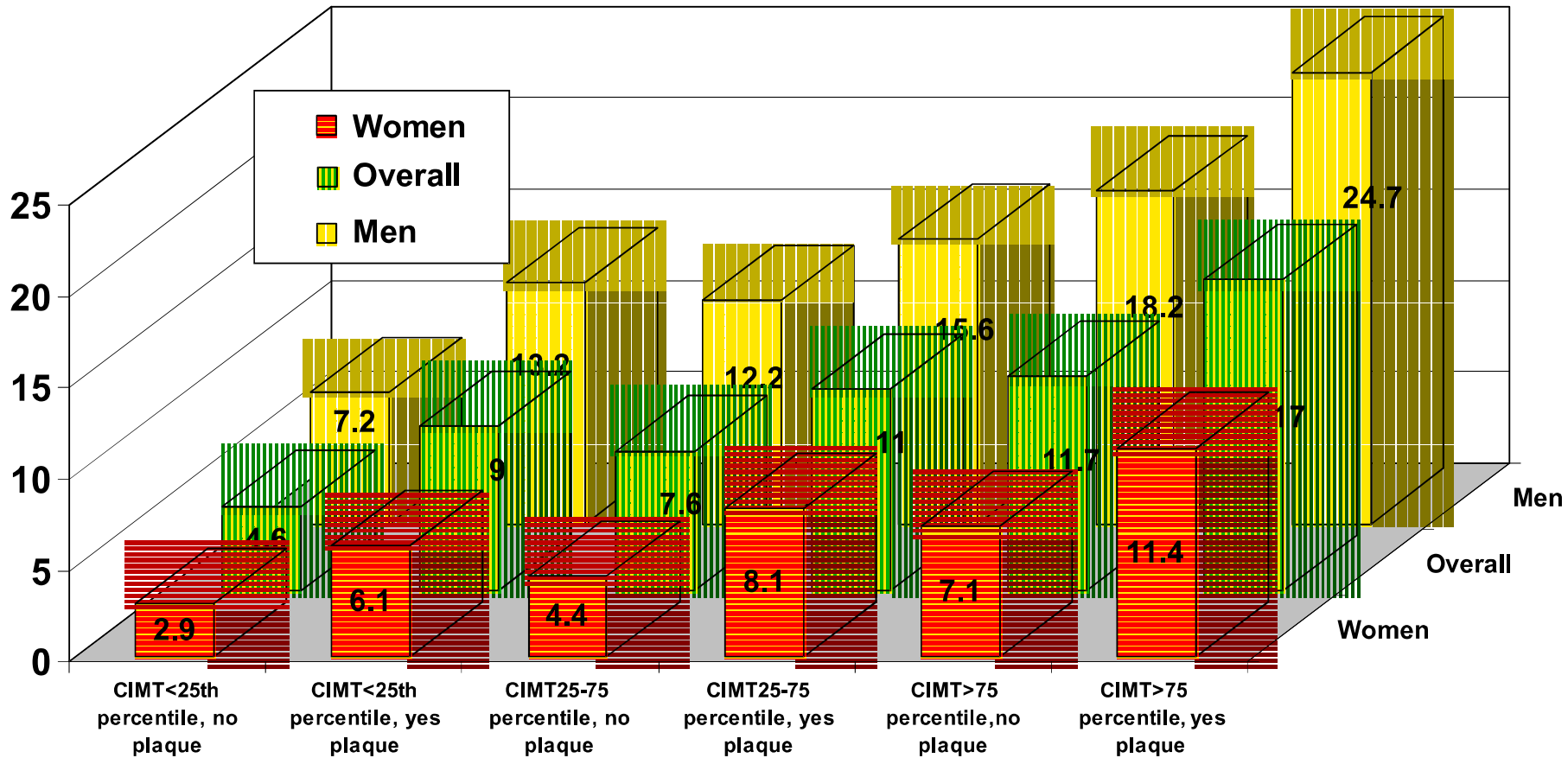
10-Year Coronary Heart Disease Risk Prediction Using Coronary Artery Calcium and Traditional Risk Factors

Risk With CAC: AUC=0.8136
Risk Without CAC: AUC=0.7600
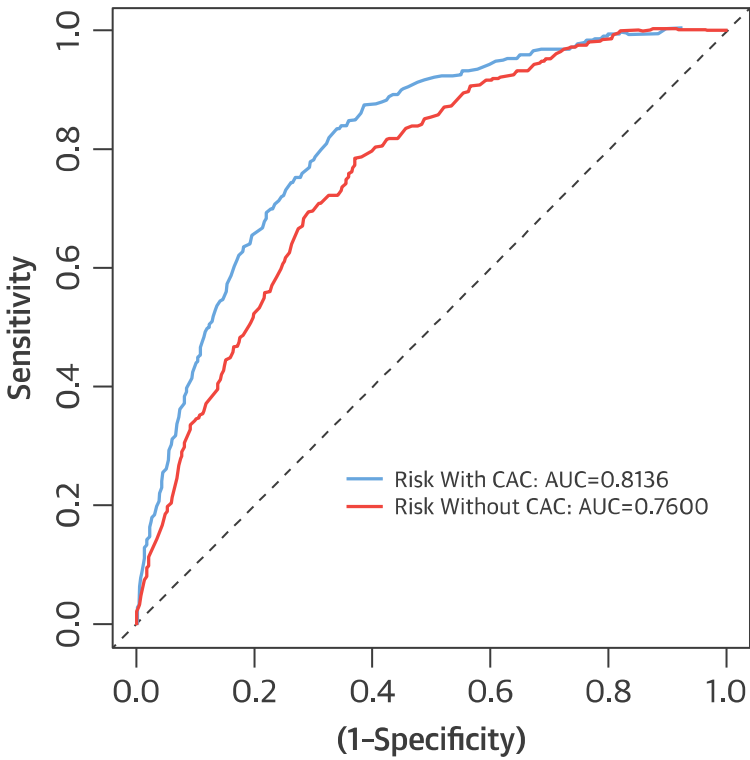
Online CV risk calculator
https://mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx

MESA 10-Year CHD Risk with Coronary Artery Calcification Back to CAC Tools

Gender	Male ● Female ○	
Age (45-85 years)	70	Years
Coronary Artery Calcification	0	Agatston

Race/Ethnicity — Choose One

Caucasian ○
Chinese ○
African American ○
Hispanic ●

25% risk for CV events

Diabetes	Yes ○	No ●
Currently Smoke	Yes ○	No ●
Family History of Heart Attack	Yes ○	No ● History in parents, siblings, or children
Total Cholesterol	190	mg/dL
HDL Cholesterol	50	mg/dL
Systolic Blood Pressure	130	mmHg
Lipid Lowering Medication	Yes ○	No ●
Hypertension Medication	Yes ●	No ○

Calculate 10-year CHD risk

(MESA)Multi-Ethnic Study of Atherosclerosis
6726 participants
10 years FU
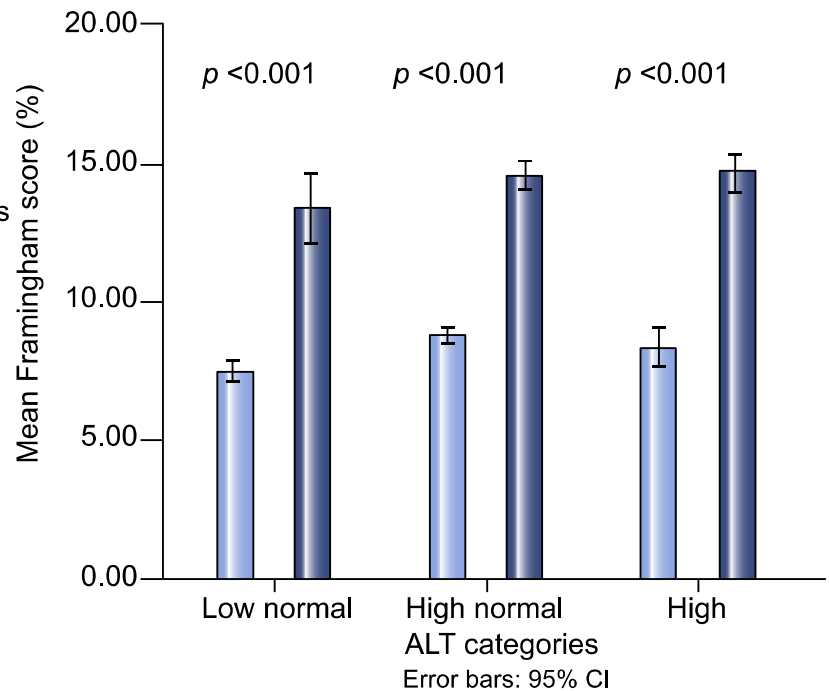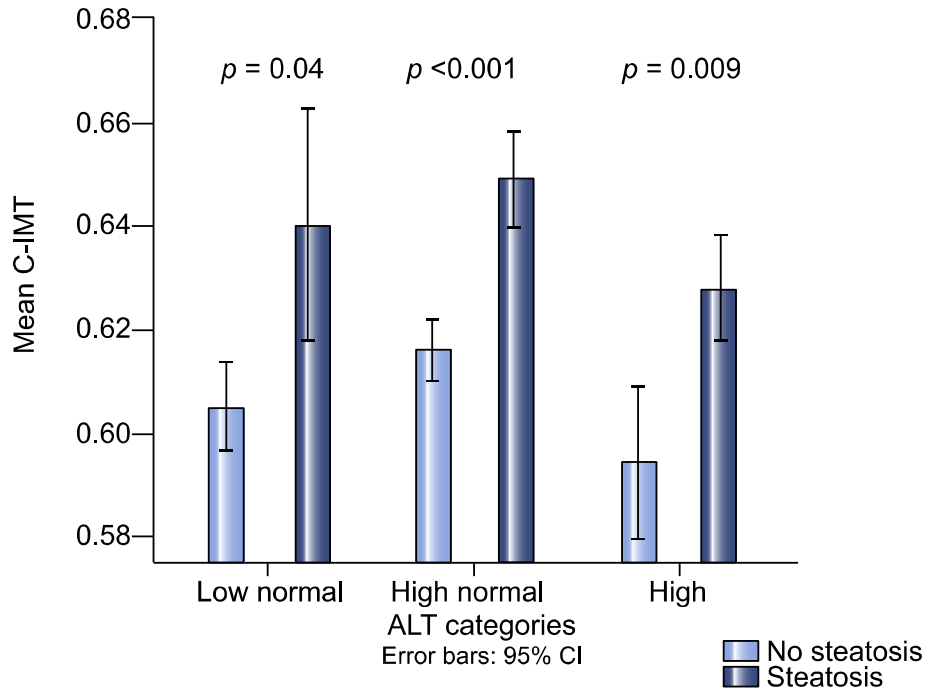Yearly evaluation for CV events

McClelland, JACC 2015

Q6

Is NAFLD an independent predictor of CV disease beyond classical CV risk factors?

Transaminases Level and risk factors for atherogenesis

Siddiqui, Gastroenterology 2013

Pais, J Hepatol 2016
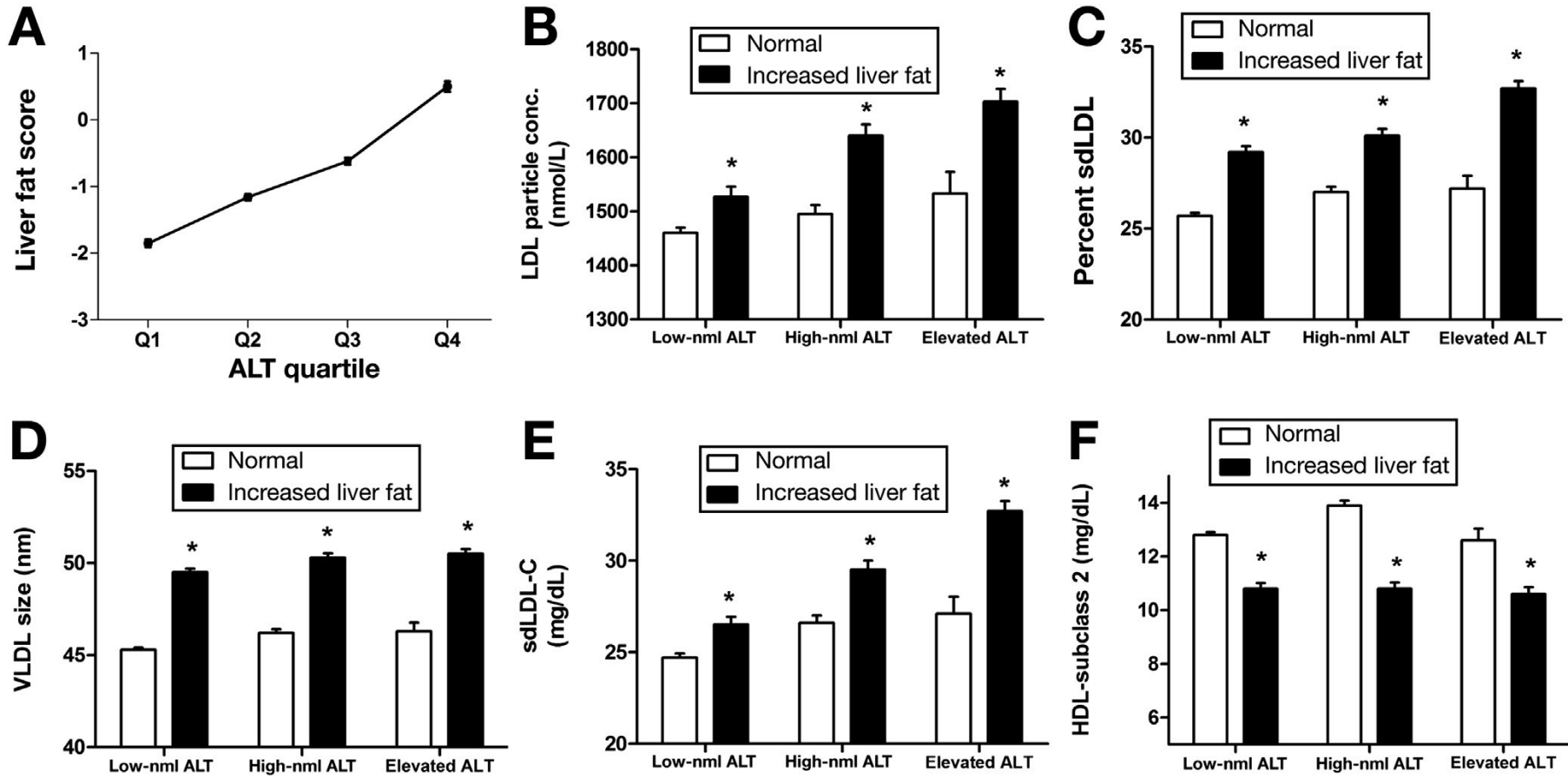
NAFLD and C-IMT

Model	Study name	Outcome	Std diff in means	Lower limit	Upper limit	p-Value	NAFLD	Controls	Total	Std diff in means and 95% CI
	Brea A et al, 2005	IMT	0.9486	0.4863	1.4108	0.000057692	40	40	80	
	Aygun C et al, 2008	IMT	1.1902	0.7147	1.6656	0.000000930	40	40	80	
	Targher G et al, 2004	IMT	1.8323	1.3251	2.3395	0.000000000	45	40	85	
	Targher G et al, 2006b	IMT	2.4083	2.0443	2.7724	0.000000000	100	100	200	
	Targher G et al, 2006	IMT	2.2421	1.9125	2.5716	0.000000000	85	160	245	
	Fracanzani et al, 2008	IMT	1.3258	1.0911	1.5605	0.000000000	125	250	375	
	Volzke H et al, 2005	IMT	0.1577	0.0767	0.2387	0.000135208	992	1440	2432	
Fixed			0.5179	0.4472	0.5885	0.000000000	1427	2070	3497	
Random			1.4391	0.6320	2.2462	0.000474500	1427	2070	3497	

Controls   NAFLD
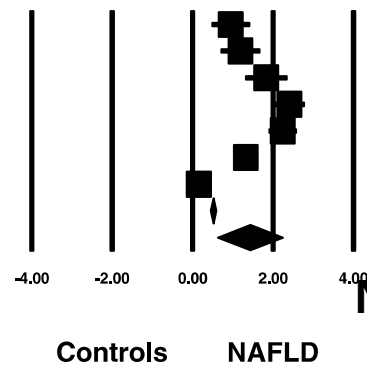
NAFLD and CAC > 100

Study name	Odds ratio	Lower limit	Upper limit	Odds ratio and 95% CI	Relative weight
Chen 2010	2.462	1.065	5.691		4.94
Chhabra 2013	2.450	1.082	5.549		5.15
Jung 2010	1.240	0.680	2.261		8.58
Kang 2014	1.617	0.908	2.880		9.11
Khashper 2013	1.170	1.046	1.308		34.54
Kim 2012	1.250	0.993	1.574		25.51
Kim 2015	0.532	0.227	1.246		4.81
Osawa 2015	0.790	0.408	1.531		7.35
	1.242	1.017	1.516		

P heterogeneity = 0.10, I2 = 42%

Favors control   Favors NAFLD

Sookoian, J Hepatol 2008
Jaruvongvanich, Dig Liv Dis, 2016

ICAN

C-IMT
1872 subjects
FU = 8 ±4 years

Coronary Calcium Score
4731 subjects
FU = 4 years

Plaque free survival

p <0.05

No steatosis at baseline
Steatosis at baseline

Years
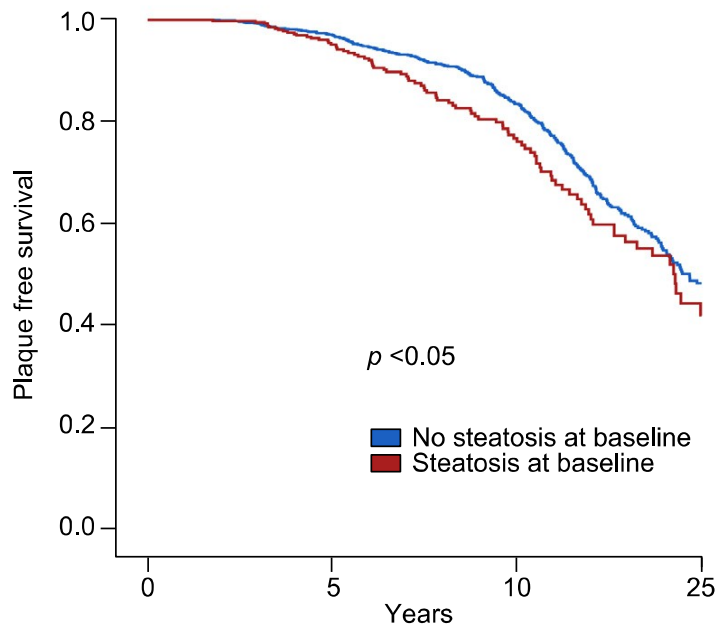
	0	5	10	25
No steatosis	1421	1103	512	100
Steatosis	451	301	115	17

CAC Score

P for difference in slopes <0.001

Time since first CAC (years)

NAFLD (-)   NAFLD (+)

Pais, J Hepatol 2016

Sinn, Gut 2016
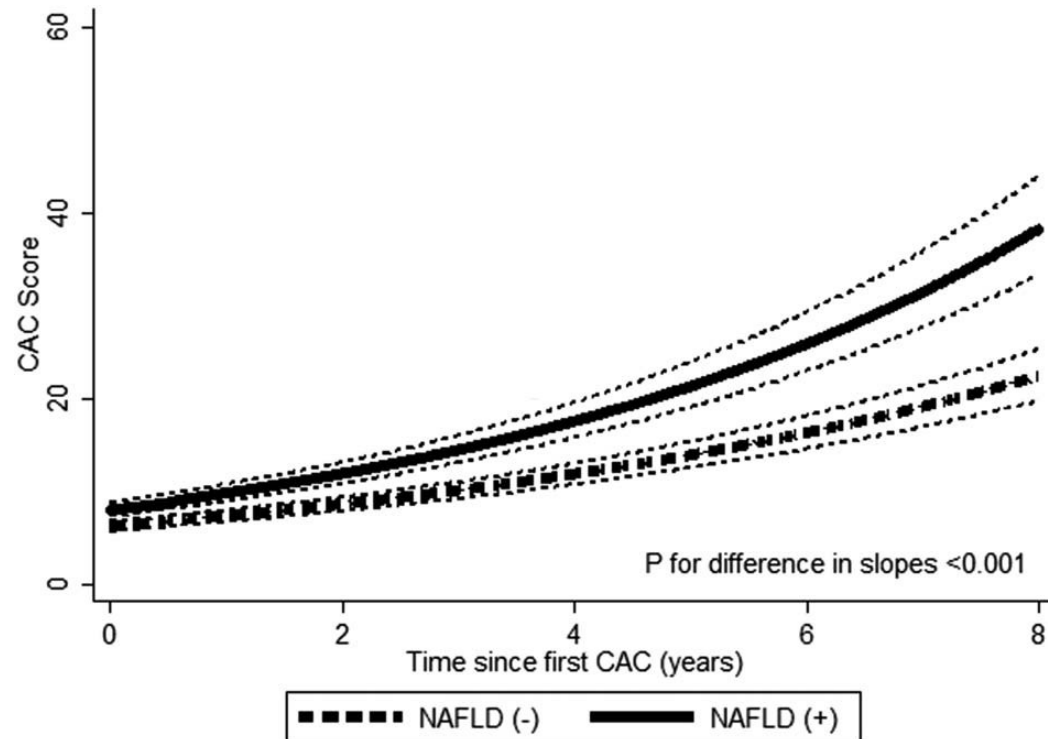
Adding NAFLD to classical CVRF or early ATS improved CV risk prediction

Intermediate/High Framingham Score

FLI: AUC = 0.761 (0.742 - 0.779)
CVRF: AUC = 0.768 (0.750 - 0.786)
FLI + CVRF: AUC = 0.848)0.833 - 0.862)
FLI + CP + FP + CAC: AUC = 0.803 (0.786 - 0.820)
CAC + FP + CP: AUC = 0.686 (0.666 - 0.707)
Reference Line

Pais et all., unpublished data
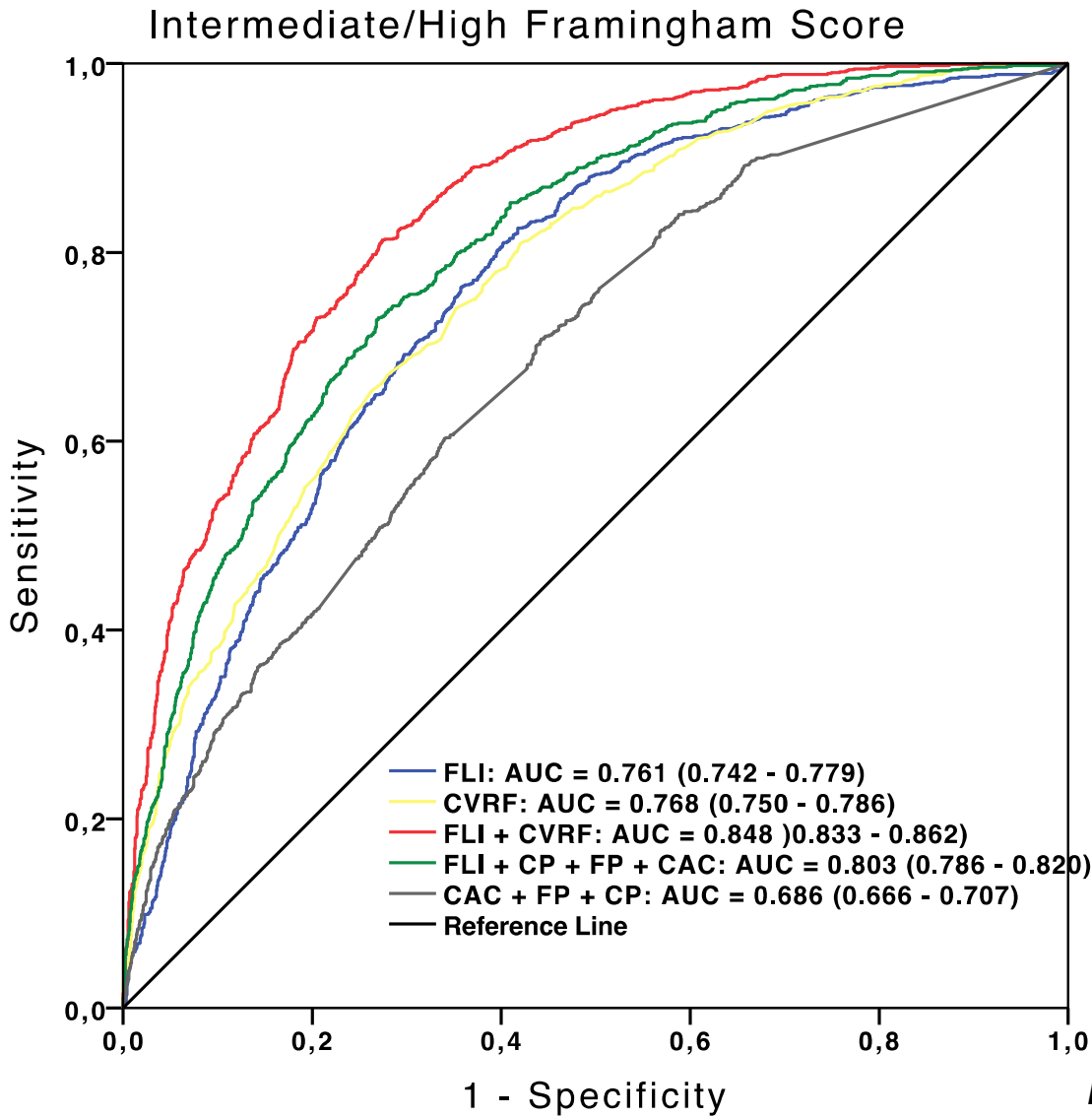
Q7

Dyslipidemia Increased CV risk

NAFLD

Is statin use recommended in this patient?

➢ No, because of safety issues
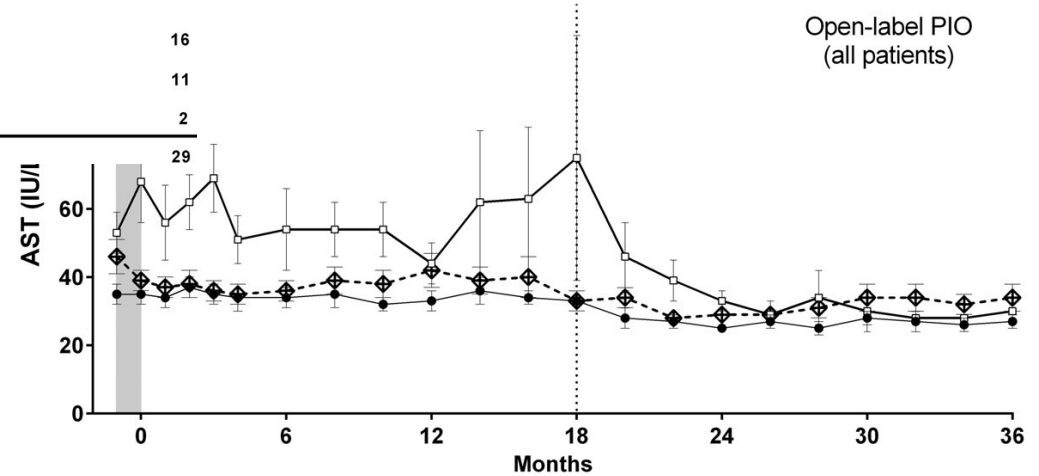➢ Yes for reducing CV risk
➢ Effect on liver histology?

Liver safety of statins in NAFLD
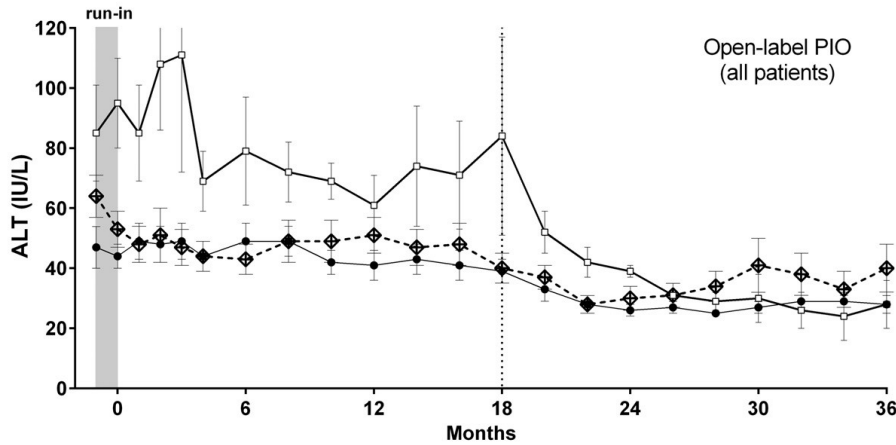
Post-hoc analyses of PIO trial

Cusi, J Clin Endocrinol Metab, 2017

Statins use – protection from severe form of NAFLD

NAFLD activity score
p = 0.006

Steatosis grade
p = 0.003

✓ Multicenter European cohort
✓ 1201 subjects
✓ 107 taking statins

Activity: ballooning + necroinflammation
p = 0.061

Fibrosis stage
p = 0.047

Dongiovani, J Hepatol 2015
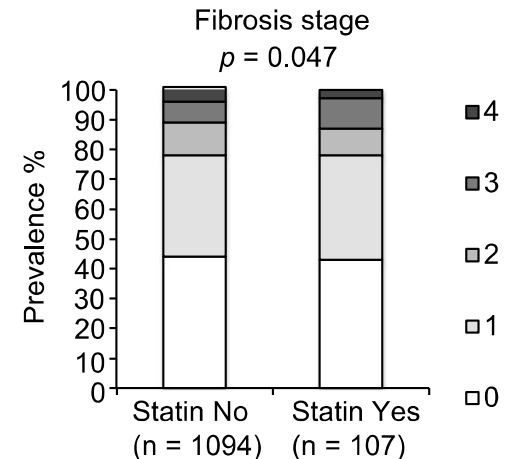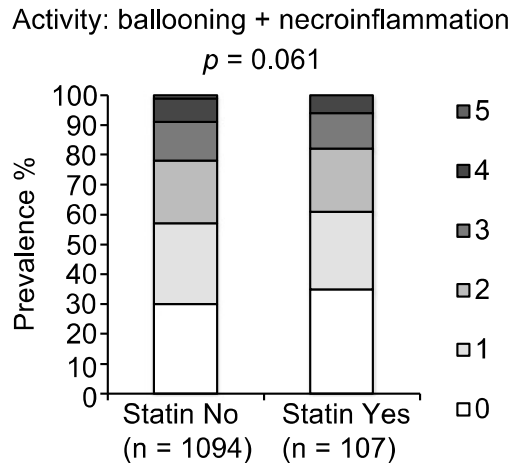
Statins use – protection from severe form of NAFLD

346 pts with T2DM and histological proven NAFLD
57% had NASH, 48% had significant fibrosis; 45% were taking statins

NASH

Significant fibrosis

Nascimbeni, BMJ Gastroenterol 2016
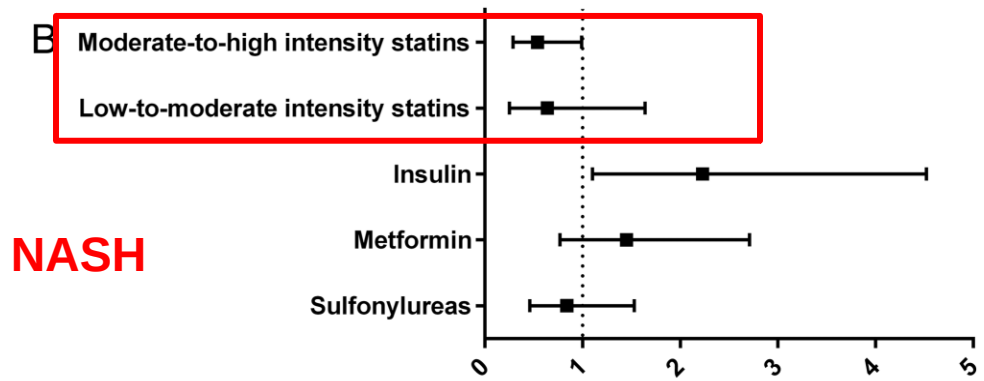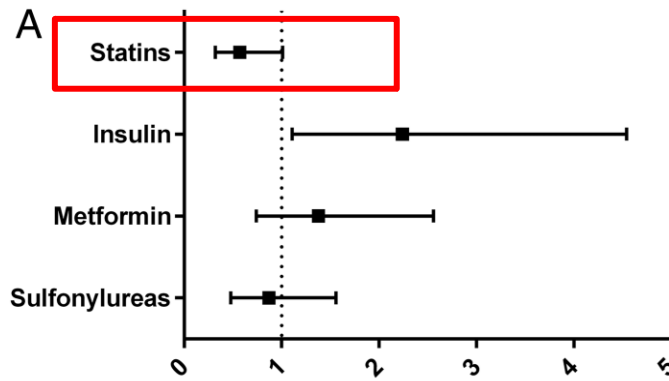
Statin Use and Risk of Cirrhosis and Related Complications in Patients With CLD

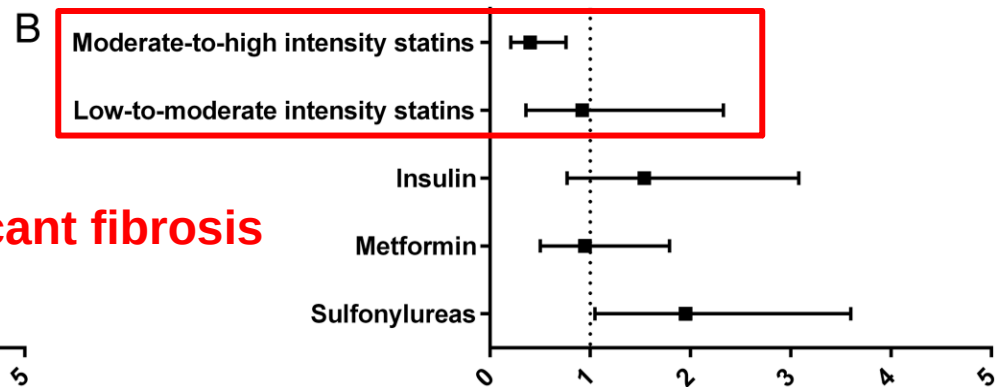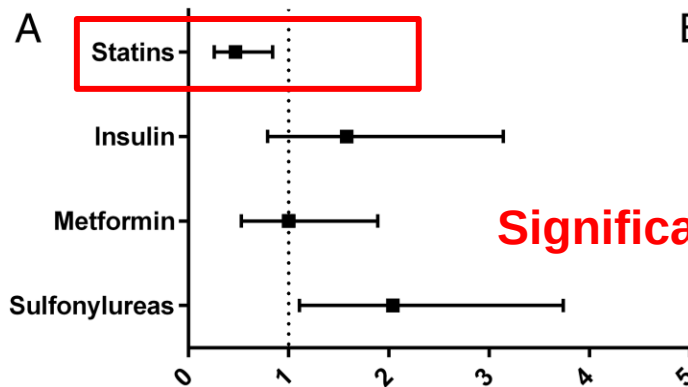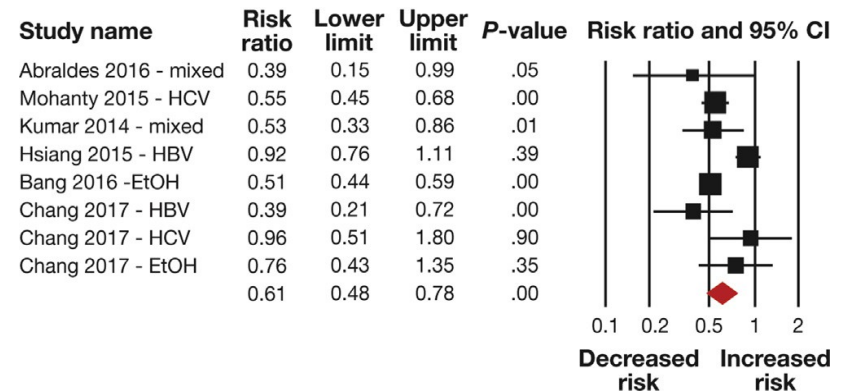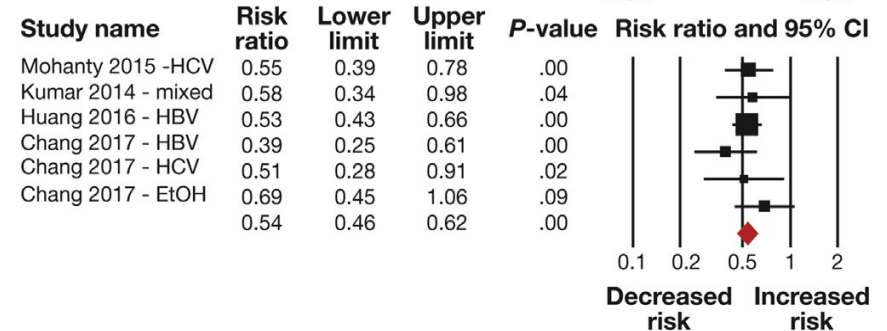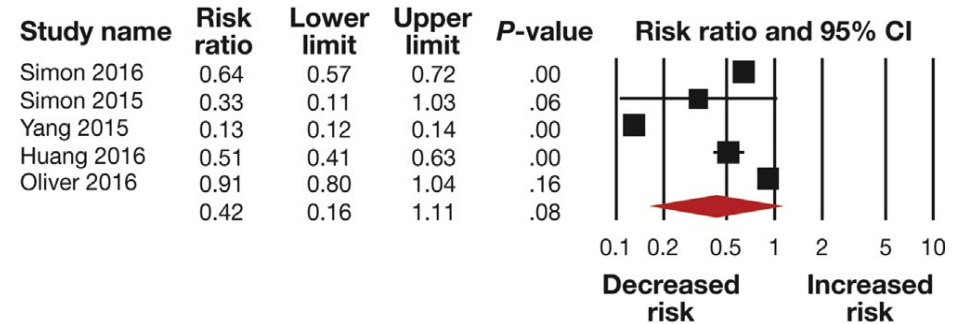- ✓ MA of patients with CLD
- ✓ 3 RCT
- ✓ 10 cohort studies
- ✓ 46% pts on statins

➤ **58% lower risk of progression of fibrosis or development of cirrhosis**

➤ **46% lower risk of progression to decompensated cirrhosis**

➤ **39% lower risk of mortality**

Kim, Clin Gastroenterol Hepatol 2017

Study name	Risk ratio	Lower limit	Upper limit	P-value
Simon 2016	0.64	0.57	0.72	.00
Simon 2015	0.33	0.11	1.03	.06
Yang 2015	0.13	0.12	0.14	.00
Huang 2016	0.51	0.41	0.63	.00
Oliver 2016	0.91	0.80	1.04	.16
	0.42	0.16	1.11	.08

Study name	Risk ratio	Lower limit	Upper limit	P-value
Mohanty 2015 -HCV	0.55	0.39	0.78	.00
Kumar 2014 - mixed	0.58	0.34	0.98	.04
Huang 2016 - HBV	0.53	0.43	0.66	.00
Chang 2017 - HBV	0.39	0.25	0.61	.00
Chang 2017 - HCV	0.51	0.28	0.91	.02
Chang 2017 - EtOH	0.69	0.45	1.06	.09
	0.54	0.46	0.62	.00

Study name	Risk ratio	Lower limit	Upper limit	P-value
Abraldes 2016 - mixed	0.39	0.15	0.99	.05
Mohanty 2015 - HCV	0.55	0.45	0.68	.00
Kumar 2014 - mixed	0.53	0.33	0.86	.01
Hsiang 2015 - HBV	0.92	0.76	1.11	.39
Bang 2016 -EtOH	0.51	0.44	0.59	.00
Chang 2017 - HBV	0.39	0.21	0.72	.00
Chang 2017 - HCV	0.96	0.51	1.80	.90
Chang 2017 - EtOH	0.76	0.43	1.35	.35
	0.61	0.48	0.78	.00

Q8

Which of the following would you consider an appropriate therapeutic option:

- ✓ Lifestyle changes
- ✓ Complete alcohol abstinence
- ✓ Switch for RYGB?
- ✓ Metformin for T2DM
- ✓ GLP1 for T2DM
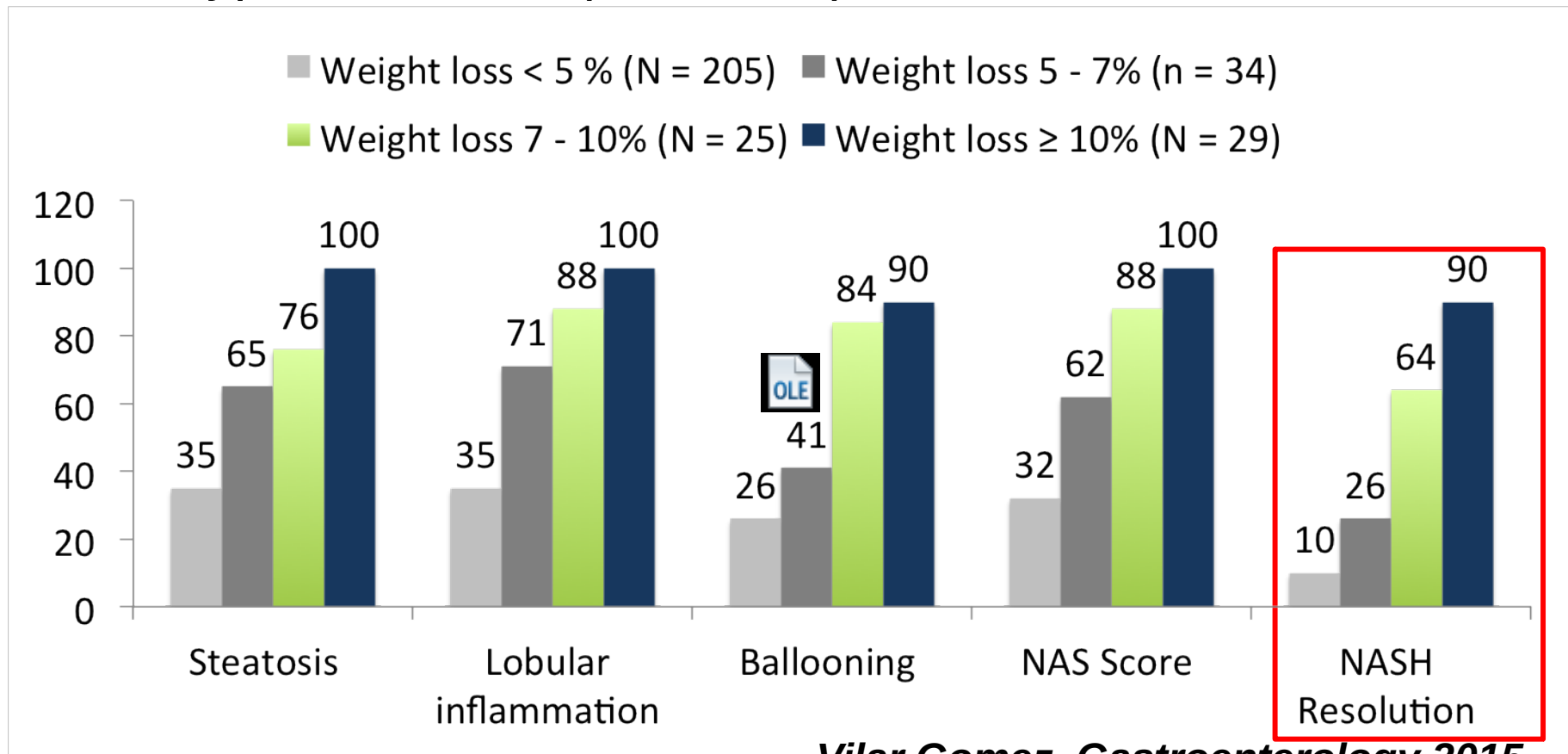- ✓ Inclusion in a clinical trial for NASH

Life style modifications – dietary interventions

1. Histological improvement
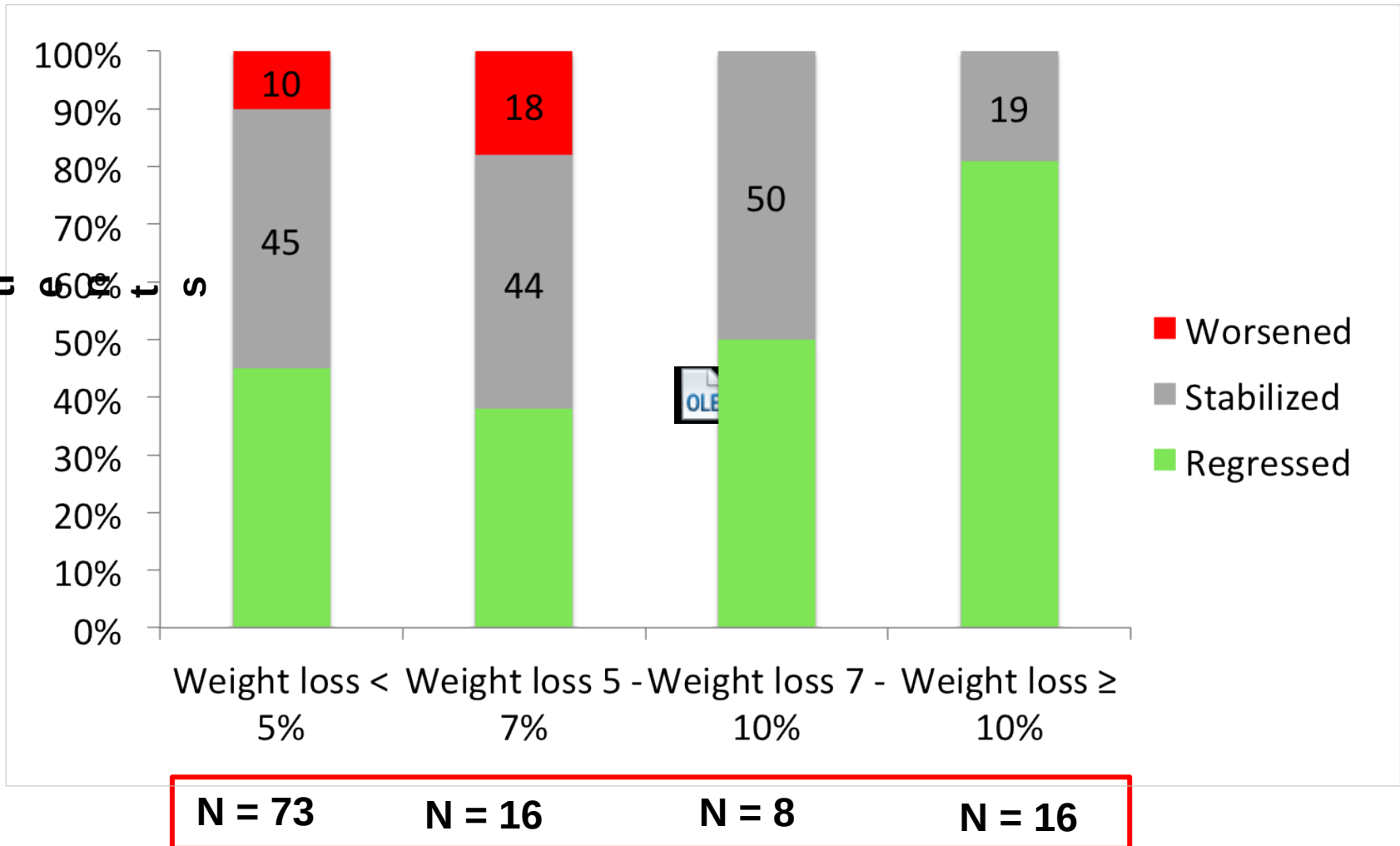
293 patients; 89% with paired liver biopsy

F/u: 52 weeks

Low-fat hypocaloric diet (- 750 kcal)

Vilar Gomez, Gastroenterology 2015

Life style modifications – dietary interventions

2. Fibrosis

Vilar Gomez, Gastroenterology 2015

- ✓ 3% - 5% weight loss to improve steatosis
- ✓ 7% - 10% for NASH resolution
- ✓ > 10% for fibrosis regression
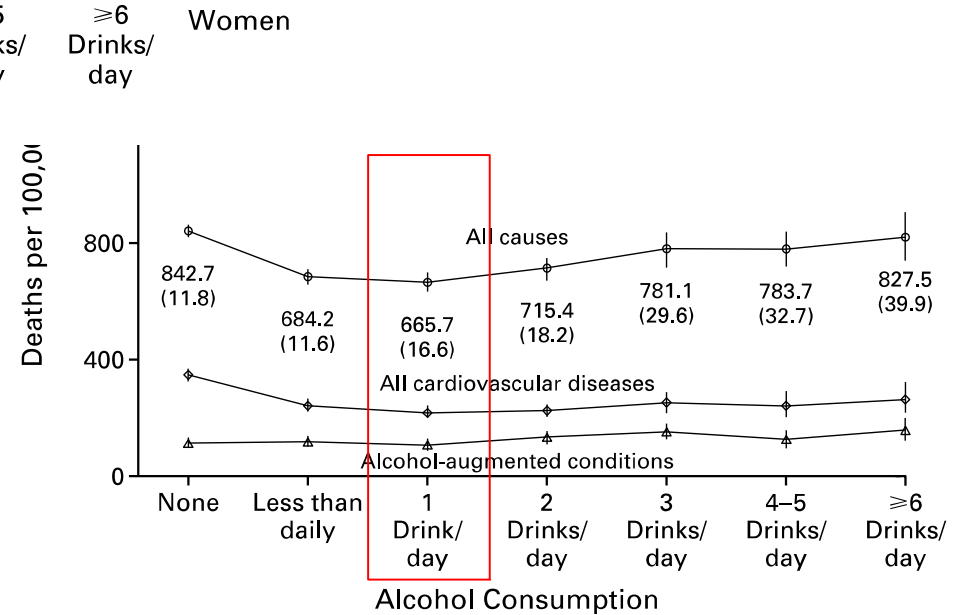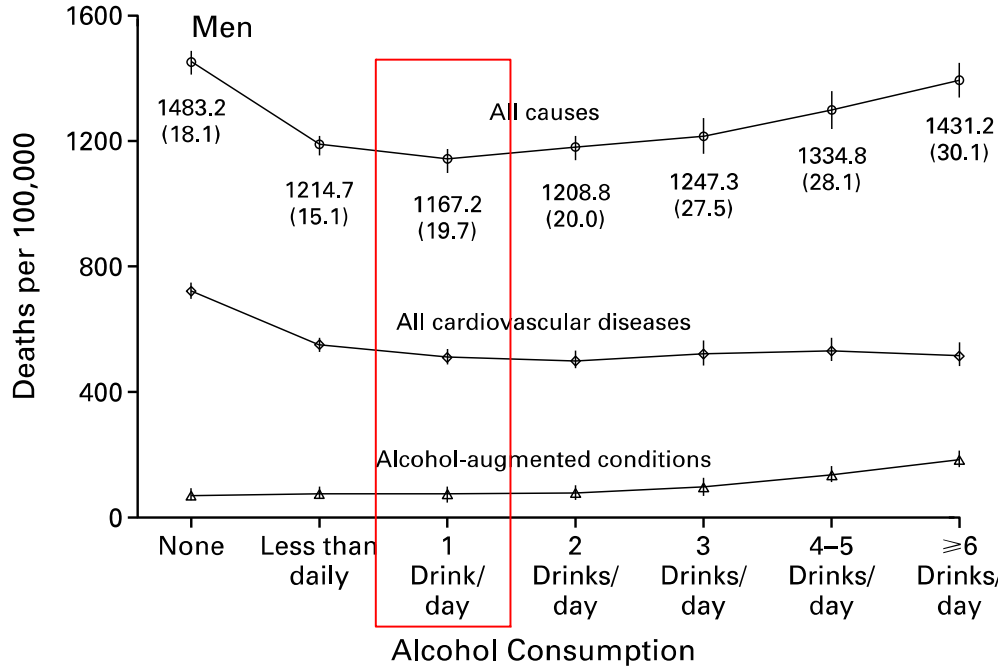
Negative predictors of response:
- Older age
- Type 2 diabetes
- More severe NASH activity

Weight loss is difficult to maintain in real-life settings :
- Maximum at 6 month
- 6% of initial body weight at 1 year
- 50% of initial weight loss is regained in 3 years

Dansinger, Ann Int Med, 2007

Is Moderate Alcohol Use in Nonalcoholic Fatty Liver Disease Good or Bad ?

Thun, NEJM, 1997

Is moderate alcohol use in NAFLD good or bad?

Sinn, 2014	Moderate alcohol use(< 20 g/day) was associated with decreased odds of carotid plaque
Dunn, 2012	The odds of NASH among moderate alcohol users was reduced compared to abstainers
Kwon 2014	The odds of severe fibrosis (F3 or F4) were significantly lower in those drinkers of ≥ 24 gram-years of alcohol vs. those drinking <24 gram-years
Cotrim, 2009	Bariatric surgery – similar risk for NASH±fibrosis in drinkers vs.non drinkers
Dixon 2011	Decreased odds of diabetes and NASH (bariatric surgery)
Ekstedt, 2009	Heavy episodic drinking, without exceeding 140 g/week, had a strong association with fibrosis progression
Asha 2010	Among patients with NASH cirrhosis followed prospectively, moderate alcohol use was associated with an increased risk of HCC

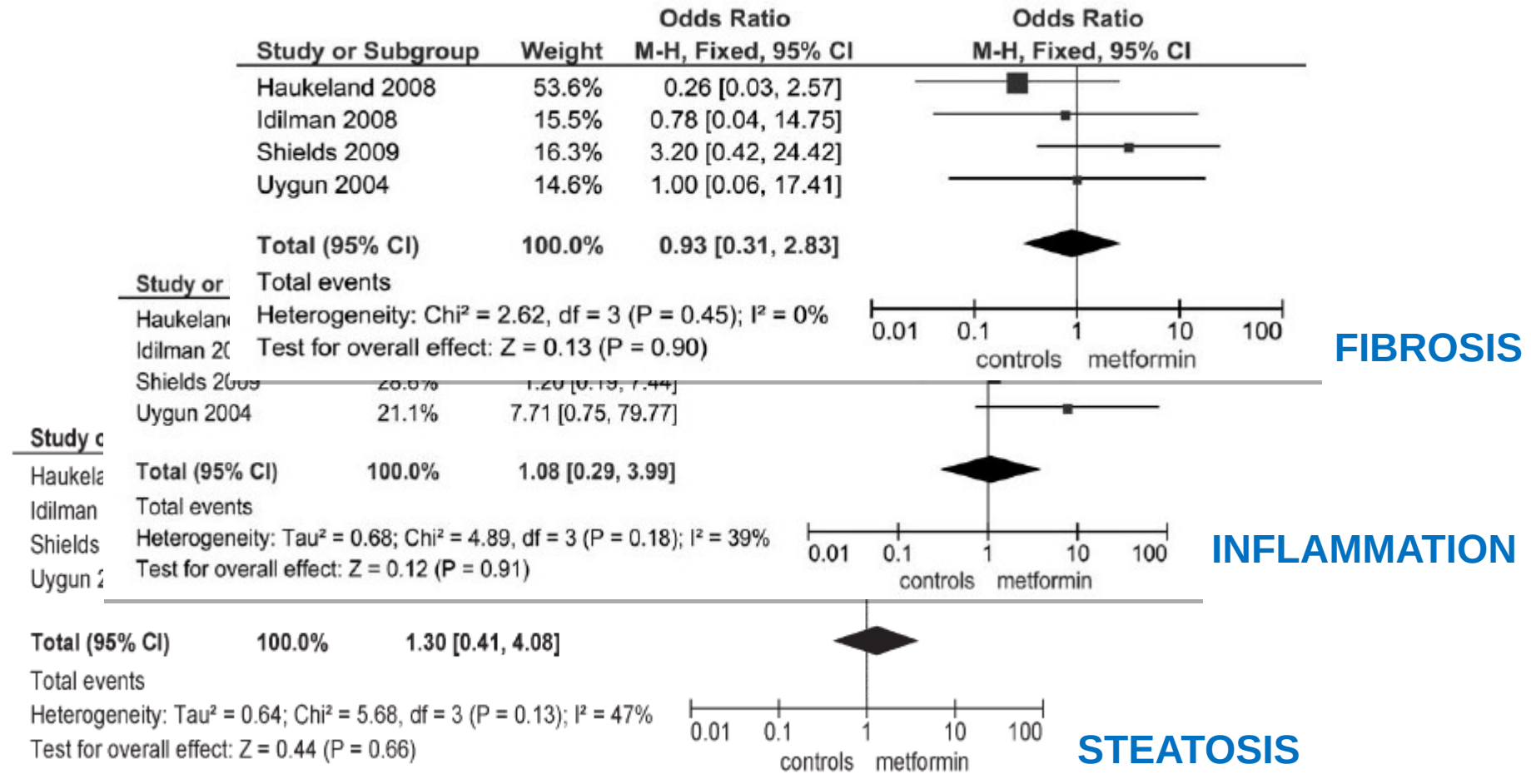*Ajmera et all., Hepatology 2017*

Is moderate alcohol use in NAFLD good or bad?.....

Limitations:

✓ Definition of moderate alcohol consumption
✓ Pattern of drinking (social drinking? Binge drinking?)
✓ Cross-sectional design (outcome and predictor measured at the same time)
✓ Causality cannot be established

A requiem for Metformin

Musso, Hepatology 2010

LEAN 'Liraglutide's Efficacy & Action in NASH'

50 patients
Randomised, Double-blinded
(stratified: site, diabetes)

Control Group

n = 25

Placebo 0.6mg OD
(Days 1-7)

Placebo 1.2mg OD
(Days 8-14)

Placebo 1.8mg OD
(Days 15-336)

Inclusion criteria:
NASH Biopsy < 6mths
Age 18-70
T2DM or non-T2DM
(HbA1c <9.0%; no insulin)

Experimental Group

n=25

Liraglutide 0.6mg OD
(Days 1 – 7)

Liraglutide 1.2mg OD
(Days 8 – 14)

Liraglutide 1.8mg OD
(Days 15 – 336)

Week 48 (visit 7)
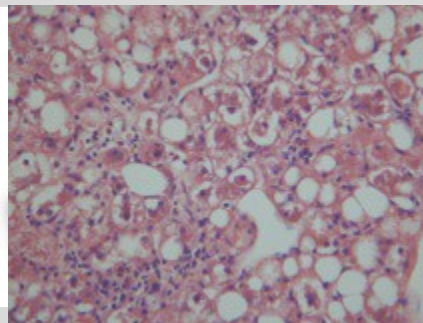
Liver Biopsy

Primary End-point:
Resolution of NASH
(disappearance of
ballooning) without
worsening of fibrosis

Secondary End-points:
Changes in NAS
Safety; liver biomarkers;
metabolic

Armstrong, The Lancet,
2015

Liraglutide : primary end-point and evolution of histological lesions

	Liraglutide (n = 23)	Placebo (n = 22)	p
Disparition de NASH et absence d'aggravation de fibrose	9 (39,1 %)	2 (9,1 %)	< 0,05
Score de fibrose Kleiner **Amélioration, n (%)** **Aggravation, n (%)**	-0,2 6 (26,1 %) 2 (8,7 %)	0,2 3 (13,6 %) 8 (36,4 %)	ns ns < 0,05
Score NAS total	-1,3	-0,8	ns
Ballonnisation **Amélioration, n (%)**	-0,5 14 (60,9 %)	-0,2 7 (31,8 %)	Ns 0.05
Stéatose **Amélioration, n (%)**	-0,7 19 (82,6 %)	-0,4 10 (45,5 %)	ns < 0,05
Inflammation lobulaire **Amélioration, n (%)**	-0,1 11 (47,8 %)	-0,2 12 (54,5 %)	ns ns

Armstrong, The Lancet,

Liraglutide :effect on metabolic parameters and LFTs

	Liraglutide (n = 26)	Placebo (n = 26)	p
Métabolique			
IMC (kg/m2)	-1,84	-0,27	0,005
Poids (kg)	-5,25	-0,58	0,003
TA systolique (mmHg)	-5,0	-3,0	ns
HbA1c (%)	-0,49	0,04	0,074
Glycémie (mmol/l)	-1,04	0,73	0,006
HDL cholestérol (mmol/l)	0,07	-0,04	0,014
Tests hépatiques			
ALAT (UI/ml)	-26,6	-10,2	ns
ASAT (UI/ml)	-15,8	-8,6	ns
GGT (UI/ml)	-33,7	-7,2	0,013
Cytokératine 18 (UI/ml)	-185	-92	0,097
ELF test	-0,25	0,09	0,052

Armstrong, The Lancet,

Liraglutide : histological benefit independent of weight loss, glycemic control or the presence of T2DM

NASH JOURNEY …

Morbid obesity
Metabolic risk factors
NASH F2

➢ Weight loss
➢ Complete/partial remission of MRF
➢ Remission of NASH/fibrosis regression

NASH

Relapse of T2DM

Weight gain

Screen for extarahepatic complications, particularly CV
Control of CVRF
Life style changes
Specific therapy/clinical trials