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th PARIS HEPATOLOGY

How to manage patients with NASH?

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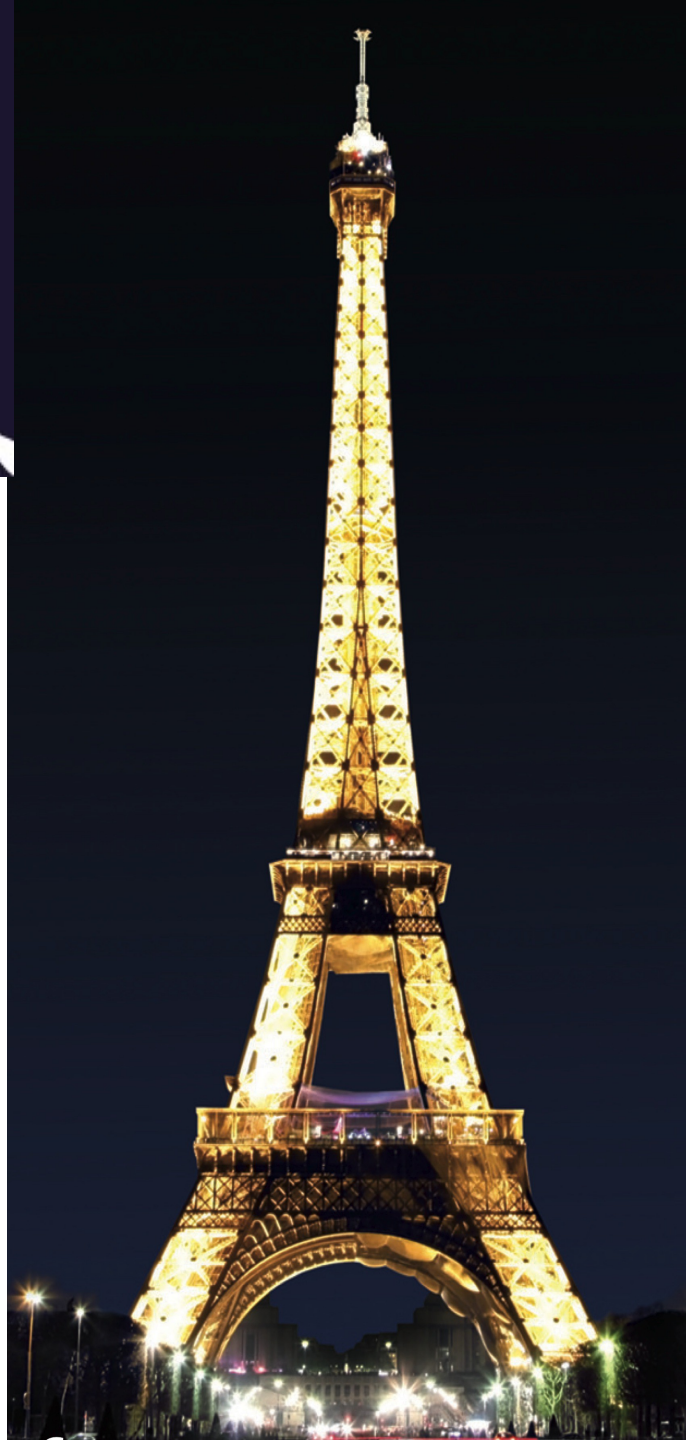
ICAN



CLINICAL CASE

1996.

54 years old female
Department of Primary CV Prevention

- ATCD of autoimmune thyroiditis since 1972, Levothyrox 50 µg. No diabetes or HBP.
- W = 83 kg, H = 1.68 m, BMI = 29.4 kg/m2; WC = 94 cm (1978 – weight = 78kg)
- DXA – fat mass = 41.6 kg (50% of body weight)
- No alcohol consumption
- Never smoked
- Dietary: 2000 cal/day; CH = 18.7%; Lipids = 40.7%

CLINICAL CASE

- LFT: AST = 31, **ALT = 42; GGT = 121**; PAL = 97; BiliT = 12 micromol/l
- Serologiy B, C, HIV, neg.
- AutoATc neg ; cuivre ceruloplasmine negatif ; fer – nle.
- **Echo – steatosis**

LB: 40% macrovesicular steatosis; no ballooning, lobular inflammation or iron load. No perisinusoidal or portal fibrosis.

SAF = S2A0F0

Simple fatty liver

- Hb, WBC, Plt = nle
- Lipids: CT = 2.41 g/l; TG = 0.81; **HDL = 0.84 g/l;** LDL = 1.41 g/l; Apo B = 1.14 g/l; ApoA= 2.46; **Lp(A-I) = 0.74g/l. (VN = 0.5 – 0.7); Lp (A-I/A-II) = 1.72 (VN = 0.8 – 1.1 g/l)**. Apo A – I = 2.46 (VN = 1.3 – 1.6). ApoAII = 0.56 (VN = 0.4 – 0.55 g/l).
- Gly = 5.9 mmol/l; insuline = 11.2 ; HOMA = 2.93

Carotid plaque of 10% L and R

CLINICAL CASE

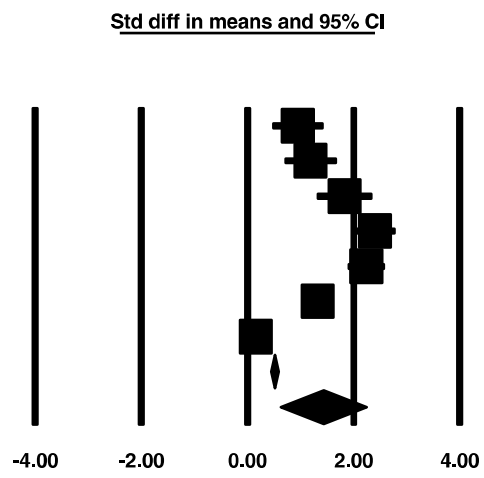
Q1

Is fatty liver a risk factor or just a marker of early carotid ATS?

CLINICAL CASE

Systematic review – 7 studies

Model	Study name	Outcome	Statistics for each study				Sample size		
			Std diff in means	Lower limit	Upper limit	p-Value	NAFLD	Controls	Total
	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



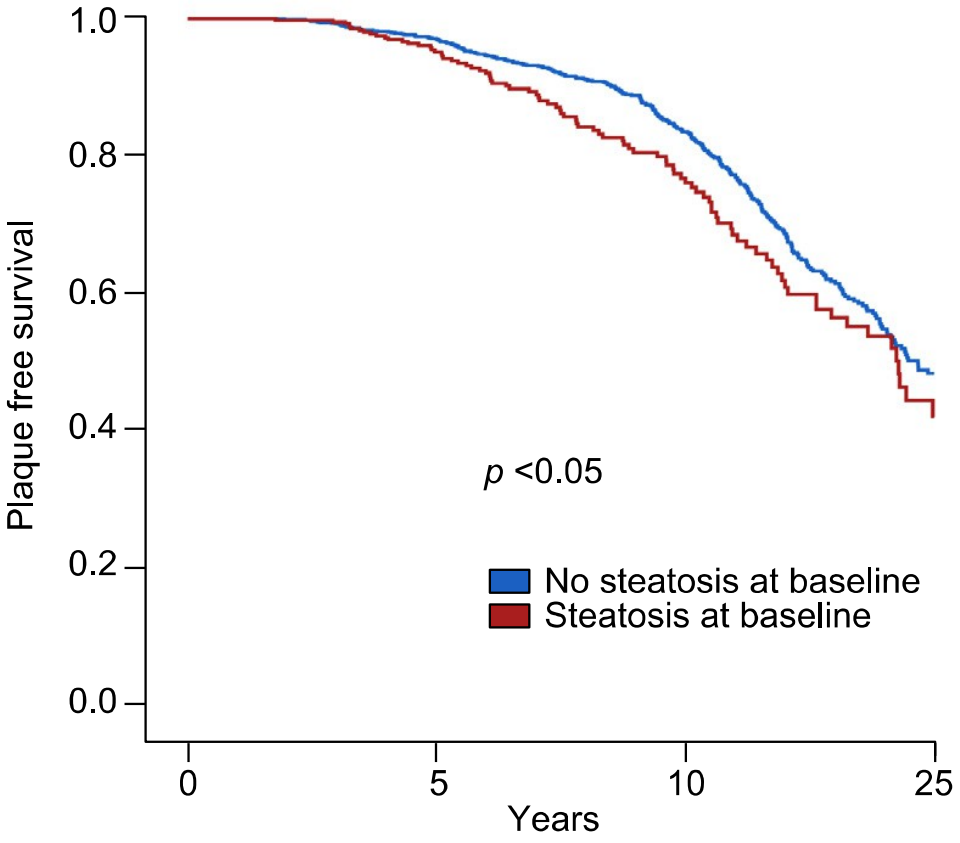
OR: 3.13, 95% CI: 1.75–5.58, P < 0.002 (random model)

13% increase in IMT in patients with steatosis
Carotid plaques occurred at younger age

Sookoian, J Hepatol 2008

CLINICAL CASE

Occurrence of CP during follow-up



No steatosis	1421	1103	512	100
Steatosis	451	301	115	17

N = 1872 pts
F/U = 8 ± 4 years
32% baseline steatosis (FLI)

OR = 1.63 (1.10-2.41) 0.014

Pais, J Hepatol 2016

CLINICAL CASE

Q2

Management:

- ✓ **Lifestyle changes**
- ✓ **Pharmacologic therapy**

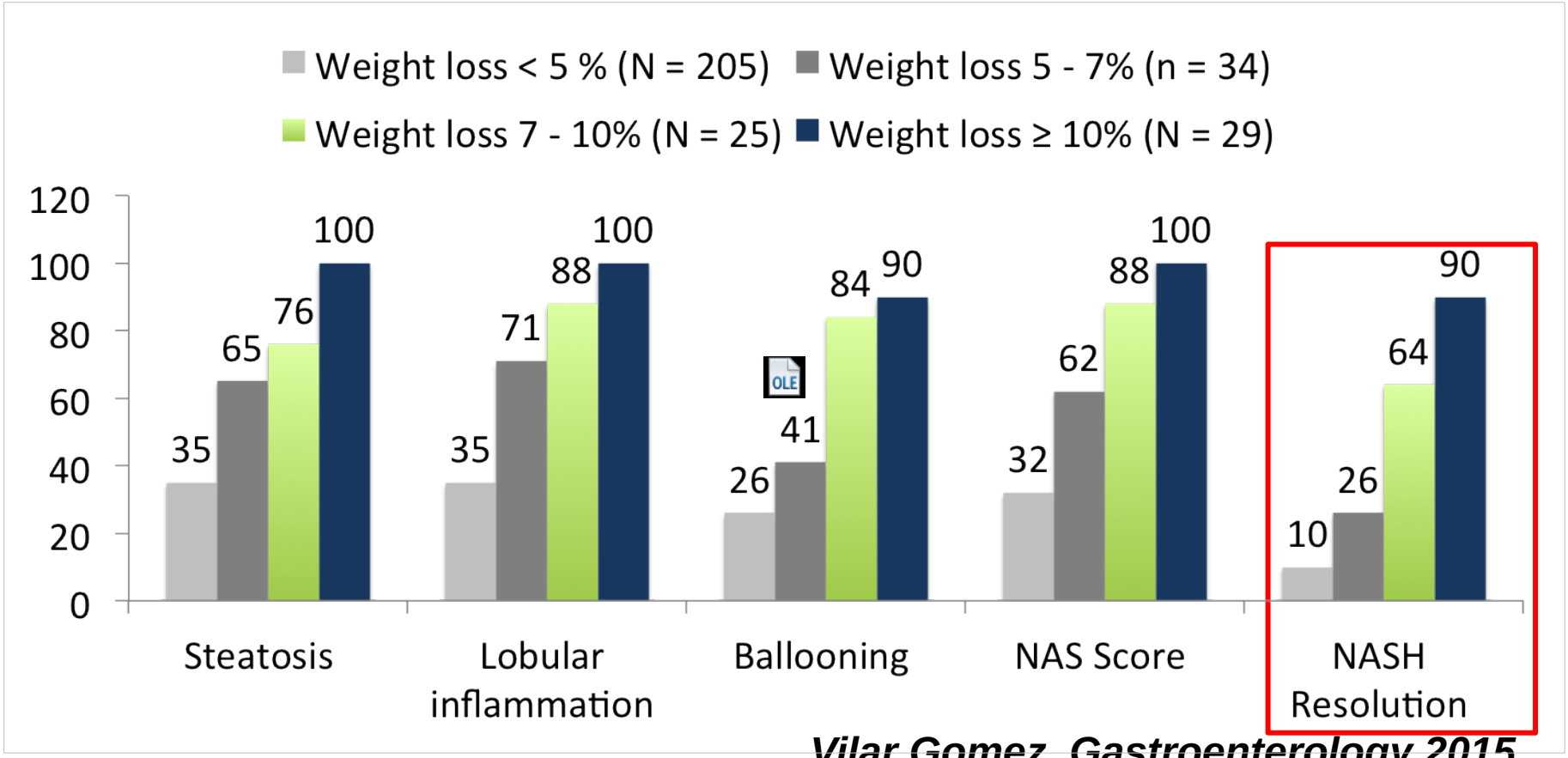
Life style modifications – dietary interventions

1. Histological improvement

293 patients; 89% with paired liver biopsy

F/u: 52 weeks

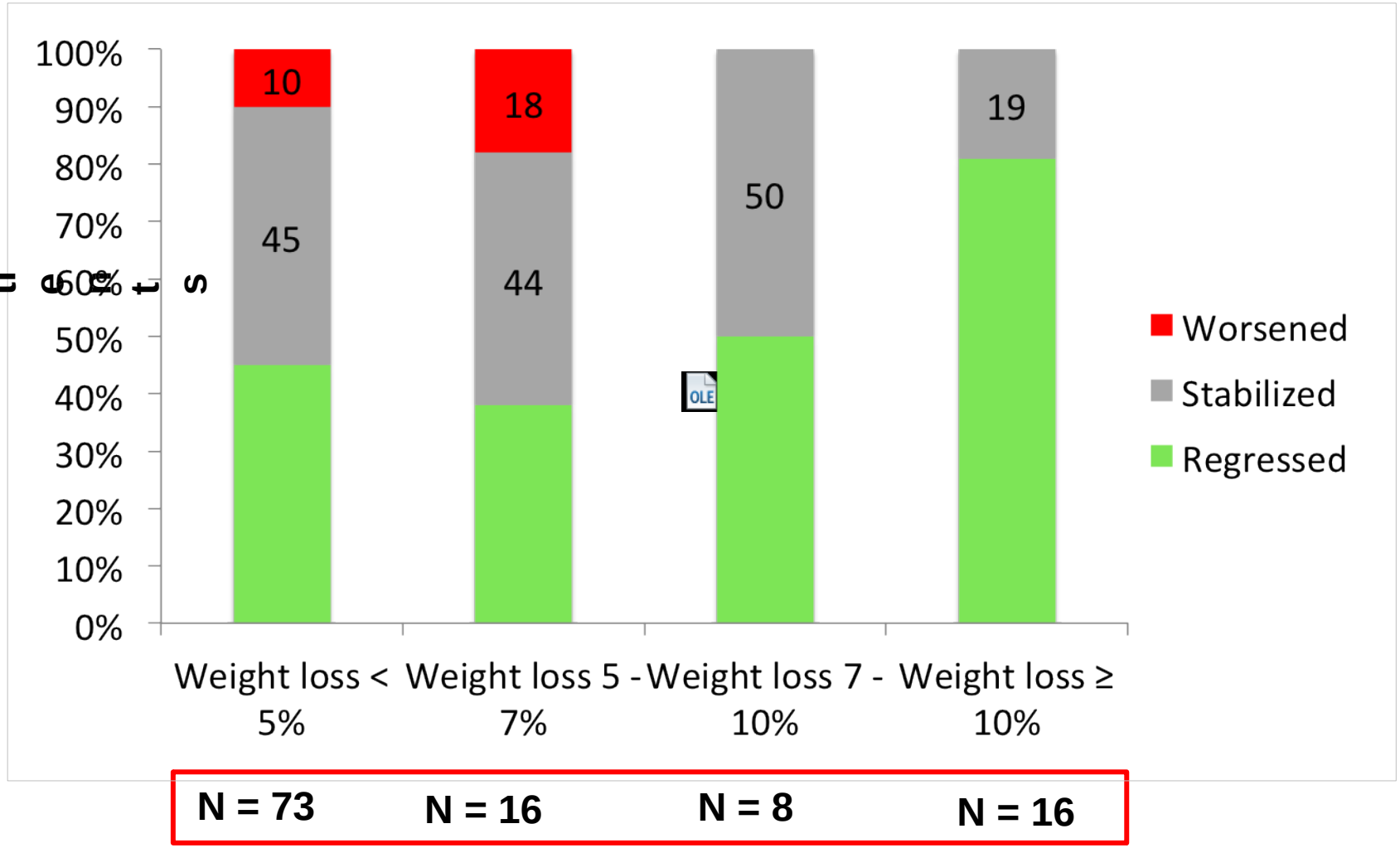
Low-fat hypocaloric diet (- 750 kcal)



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

<u>Negative predictors of response:</u>

- Older age
- Type 2 diabetes
- More severe NASH activity

<u>Weight loss is difficult to maintain in real-life settings :</u>

- 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

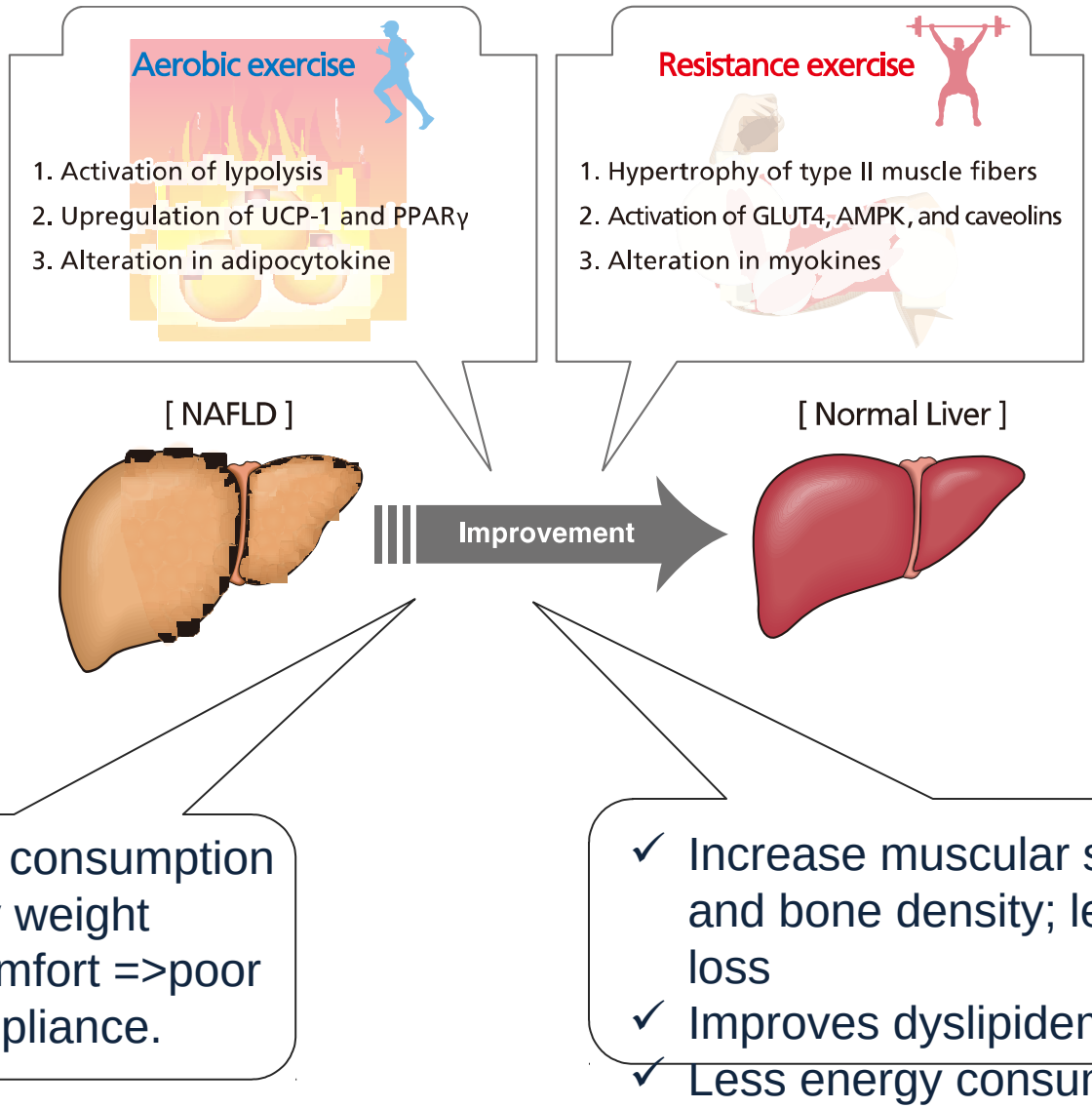
CLINICAL CASE

Q3

Older age
Comorbidities:
ATS and CV disease , T2DM , OSA , Arthrosis

- ✓ Aerobic or resistance exercise ?
- ✓ Improvement without weight loss

Life style modifications – physical activity



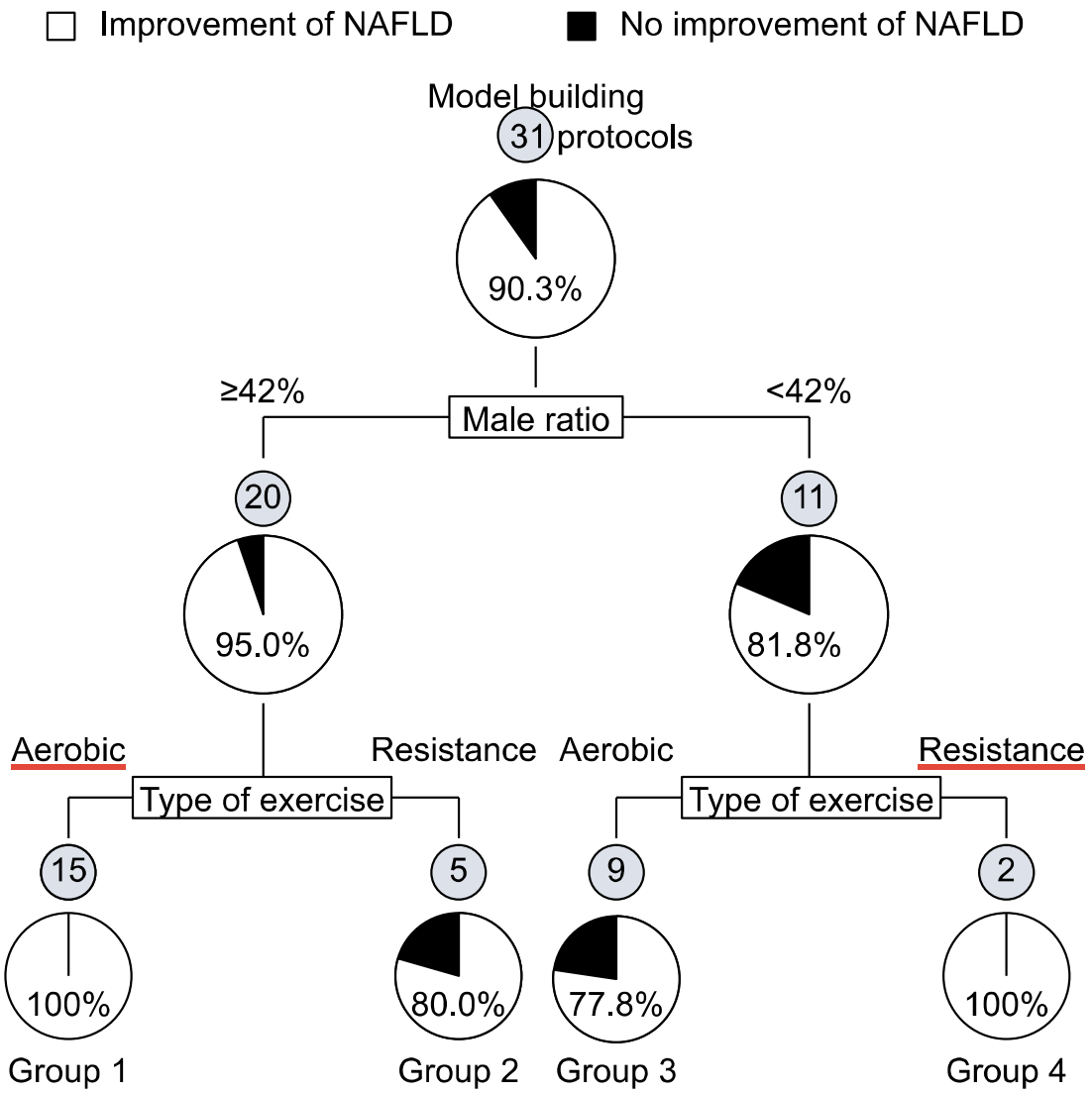
- ✓ Higher energy consumption
- ✓ Reduces body weight
- ✓ Fatigue, discomfort =>poor long-term compliance.

- ✓ Increase muscular strength, mass and bone density; less weight loss
- ✓ Improves dyslipidemia, HBP, IR
- ✓ Less energy consumption

Improvement in 50% of cases without weight loss

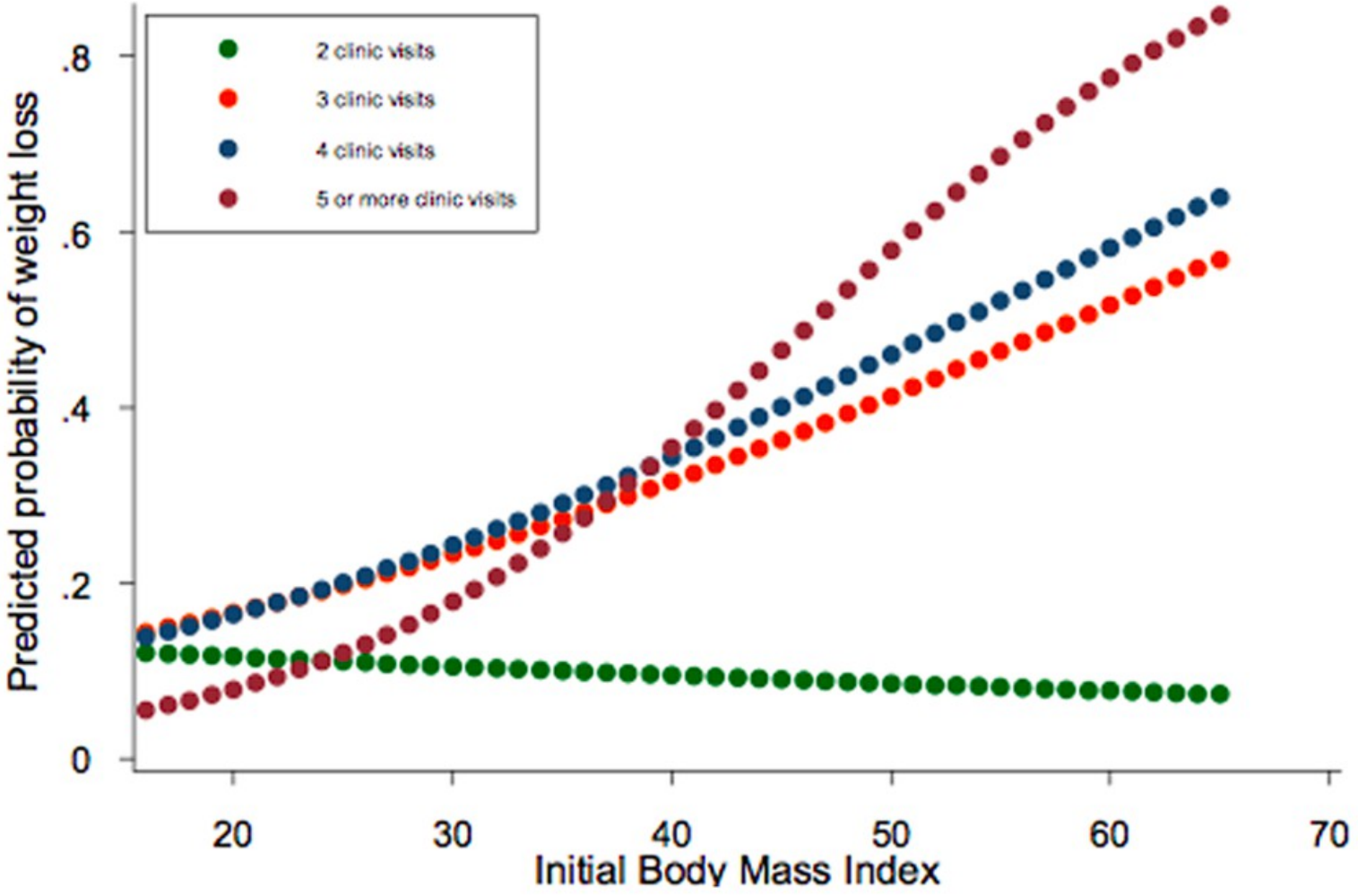
Hashida, J Hepatol 2017

Algorithm decision tree in prescribing physical activity in NAFLD



Hashida, J Hepatol 2017

Weight loss correlates with the frequency of medical visits



Dudekula, PlosOne 2014 9(11)

CLINICAL CASE

2008

Weight: 90 kg ; BMI = 31.8 kg/m2, WC = 116 cm
Occurrence of HBP (Moduretic)
Fasting glucose = 6 mmol/l; fasting insuline = 12 µmol/l ; HOMA = 3.2
Lipids: CT = 5.13 mmol/l; TG = 1.21 mmol/l; HDL = 1.55 mmol/l; LDL = 3.04 mmol/l.
LFT: AST = 42 IU/l; ALT = 45 IU/l; GGT = 156 IU/l
FT = 0.43

LB: 30 mm; 19 portal spaces; 60% steatosis;
NAS = 2 steatosis + 1 lobular inflammation + 2 ballooning = 5; No portal or perisinusoidal fibrosis

SAF = S2A3F0 (NASH)

CLINICAL CASE

Q 4

Weight gain
Occurrence of HBP
Progression to NASH without fibrosis

Management:

- ✓ **Lifestyle changes**
- ✓ **Pharmacologic therapy**

CLINICAL CASE

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)

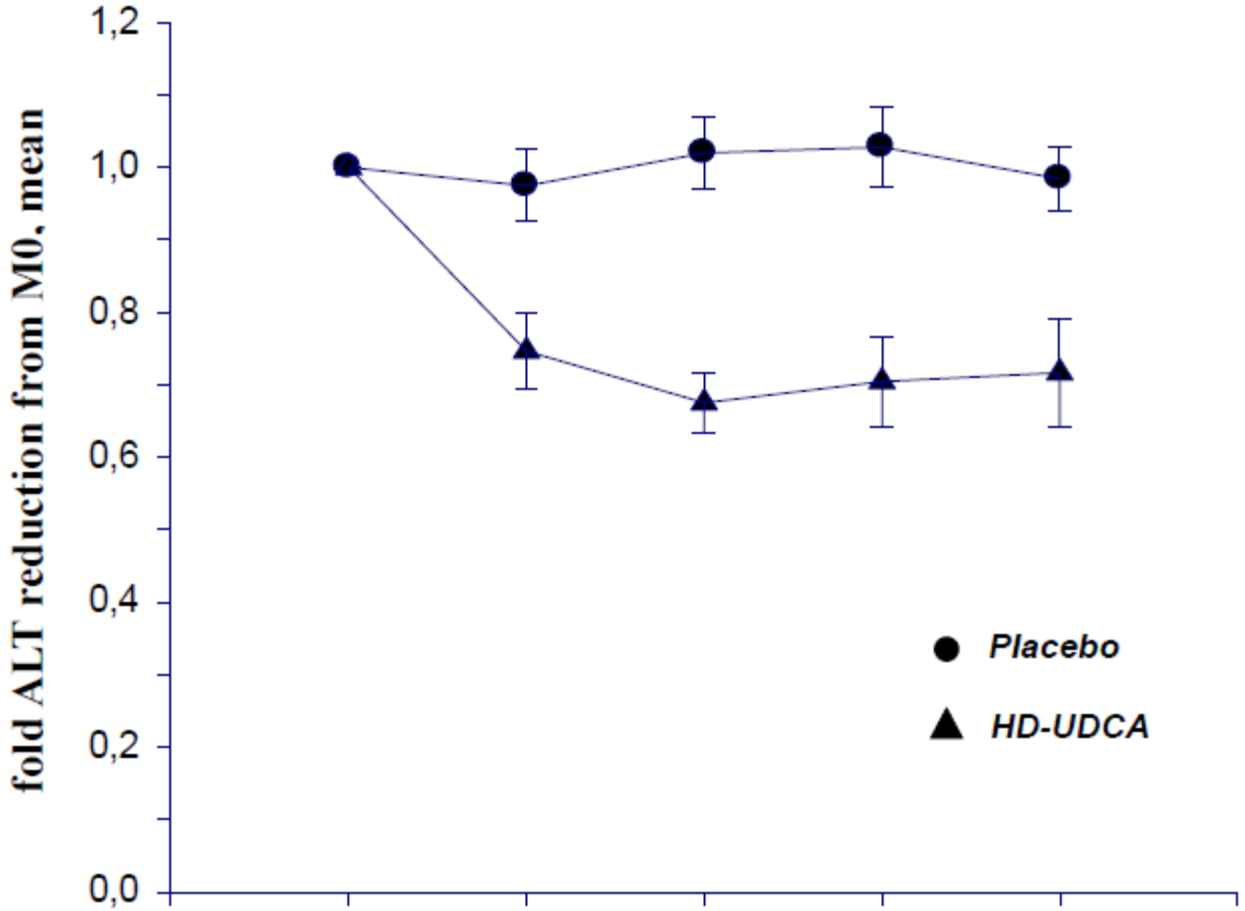
Drug therapy should be indicated for progressive NASH (bridging fibrosis and cirrhosis) but also for early-stage NASH with increased risk of fibrosis progression (age >50 years; diabetes, MetS, increased ALT) or active NASH with high necroinflammatory activity

Results of large UDCA RCTs

Study	*Duration*	*Dose*	*↓ALT vs PLB*	*Histological improvement*
Lindor	*2 yrs*	**Low** **13 – 15 mg/kg/d**	**No**	**No**
Leuschner	*2 yrs*	**Medium** **23 – 28 mg/kg/d**	**No**	**No***
URSONASH	*1 yr*	**High** **28 – 35 mg/kg/d**	**Yes**	

Lindor, Hepatology 2004; Leuschner, Hepatology 2010; Ratziu, J Hepatol 201

Reduction in ALT levels



	M0	M3	M6	M9	M12
Placebo	81	79	83	88	78
HD-UDCA	85	62	59	58	55

Ratziu, J Hepatol 2011

Histological improvement in Vit E RCTs

	Steatosis	Inflammation	Ballooning	NASH resolution	Fibrosis
Harrison/1yr	-	-	-	-	-
PIVENS/2yrs	+	+	+	+	-
Nobili/2yrs	-	-	-	-	-
TONIC/2yrs	-	-	+	+	-

+ denotes improvement;
vs. placebo

CLINICAL CASE

2011

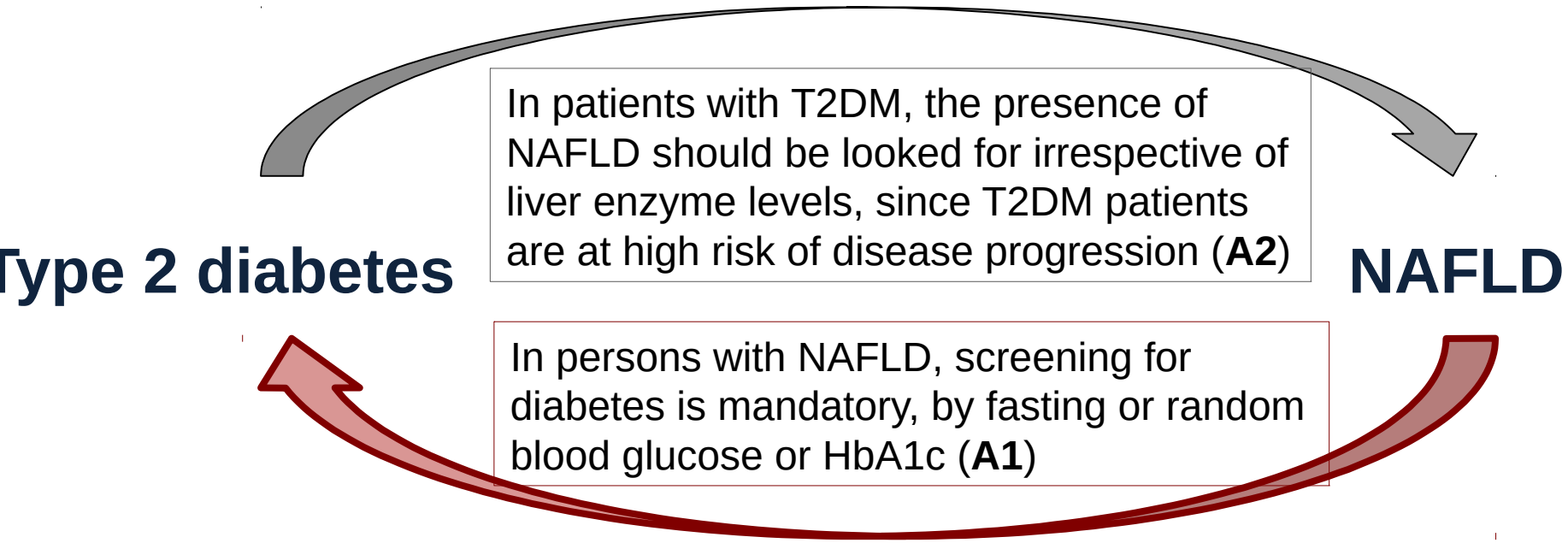
W = 100 kg; BMI = 35.43 kg/m2 (+ 10 kg)
AST = 33 IU/l, ALT = 32 IU/l, GGT = 103 IU/l, PAL = 93 IU/l
HDL = 1.55 mmol/l, LDL = 3.04 mmol/l, TG = 1.21 mmol/l; CT = 5.13 mmol/l.
Gly = 7.1 mmol/l ; insuline = 22.9 mUI/l; HOMA IR = 7.2; HbA1C = 6.6%.
FT = 0.58; FS = 11.6 kPa, TDR = 100%, IQR = 2.9 kPa (25%)

New onset type 2 diabetes

Screen for extra-hepatic complications!

➢ Type 2 diabetes

Worsening of histological features and fibrosis progression



NAFLD is an independent predictor for incident T2DM

Balkau, BMC Gastroenterology 2010 DESIR Study

NAFLD is associated with a 2-5 fold risk of developing T2DM

Ekstedt, Hepatology 2006
Adams, AJG 2009

CLINICAL CASE

2011

W = 100 kg; BMI = 35.43 kg/m2 (+ 10 kg); WC = 120 cm
AST = 33 IU/l, ALT = 32 IU/l, GGT = 103 IU/l, PAL = 93 IU/l
HDL = 1.55 mmol/l, LDL = 3.04 mmol/l, TG = 1.21 mmol/l; CT = 5.13 mmol/l.
Gly = 7.1 mmol/l ; insuline = 22.9 mUI/l; HOMA IR = 7.2; HbA1C = 6.6%.
FT = 0.58; FS = 11.6 kPa, TDR = 100%, IQR = 2.9 kPa (25%)

New onset type 2 diabetes

LB: length = 35 mm, 18 PS, 70% macrovesiculqr steatosis; moderate lobular inflammation; severe ballooning. Portal fibrosis with rare septa, perisinusoidal fibrosis. NAS = 7.

SAF = S3A4F3

CLINICAL CASE

Q 5

Management:

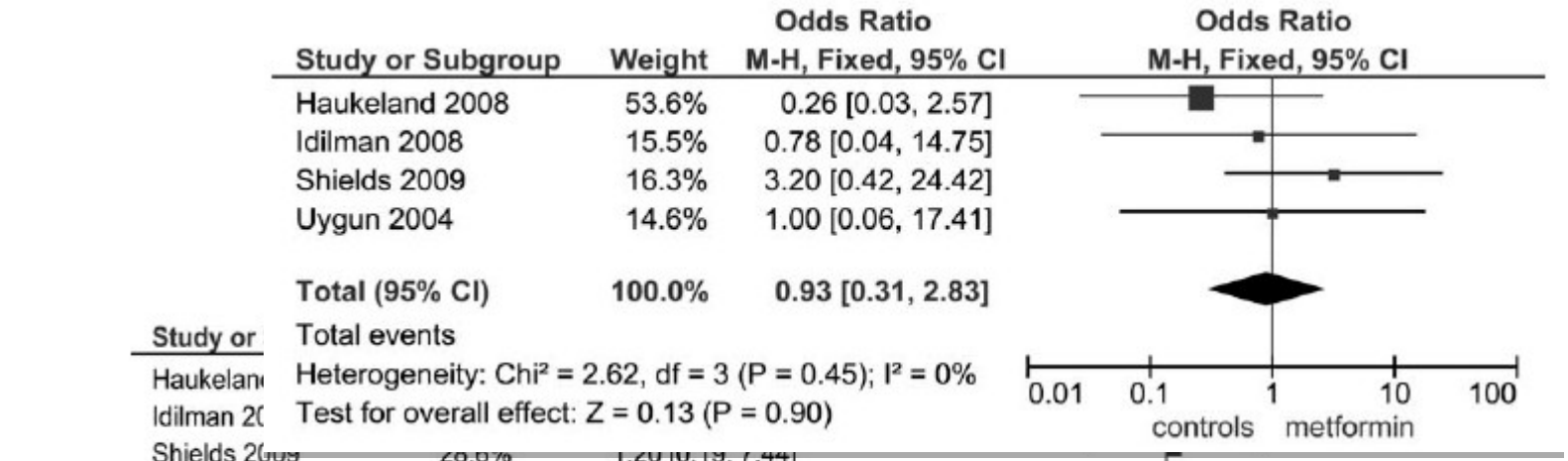
More weight gain
Incident T2DM
Progression to NASH with advanced fibrosis

- ✓ Continue UDCA + Life style changes
- ✓ Metformine + Life style changes
- ✓ UDCA + Metformine + Life style changes

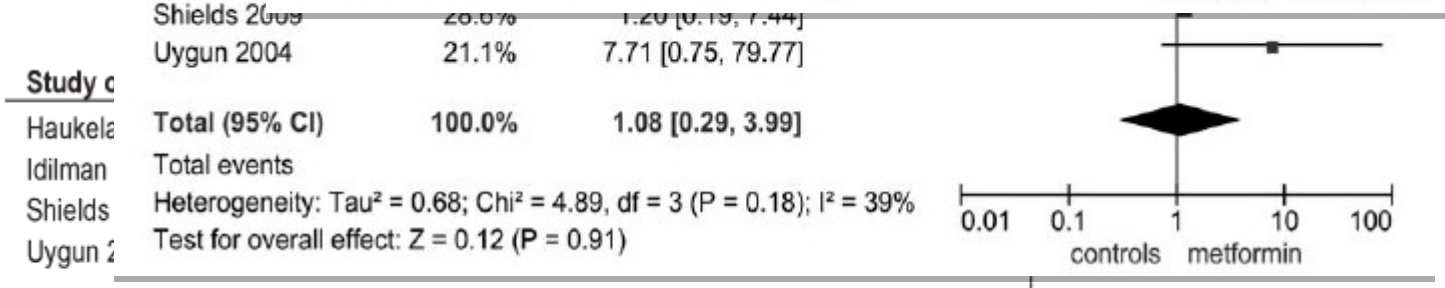
Metformine for:

- ✓ Type 2 diabetes
- ✓ NASH

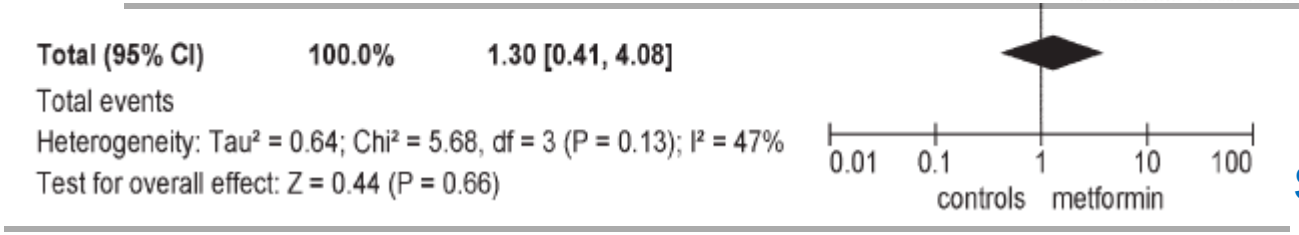
A requiem for Metformin



FIBROSIS



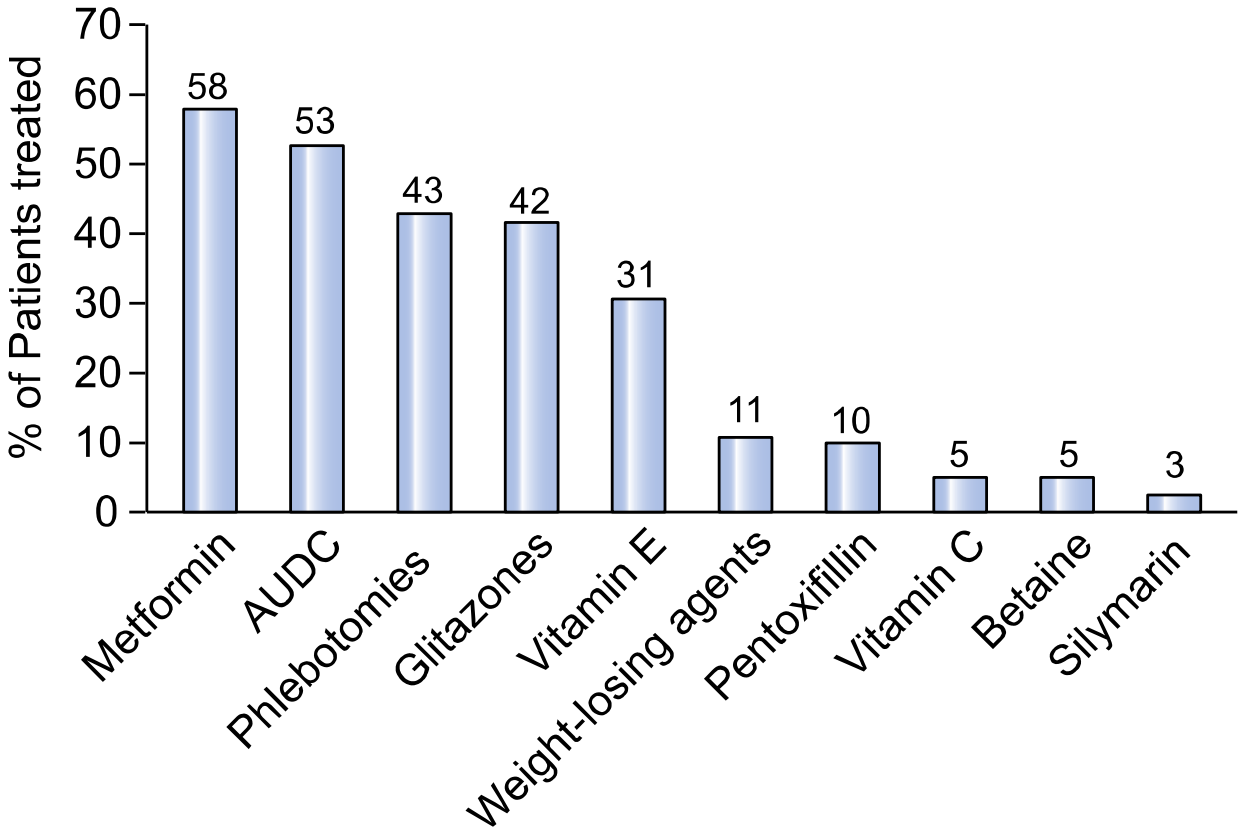
INFLAMMATION



STEATOSIS

Musso, Hepatology 2010

Daily practice: % of patients treated with pharmacological agents.



Ratziu, J Hepatology 2012

CLINICAL CASE

2012

W = 86 kg (- 14 kg)
LFT: ALT = 44 IU/l; AST = 43 IU/l; GGT = 36 IU/l.
Gly = 6.9 mmol/l; insuline – 16 mU/l; HOMA = 4.90; HbA1c = 6.3%
Lipids: CT = 5.1 mmol/l; TG = 1.02 mmol/l
FT = 0.52; FS M probe= 13.3 kPa (IQR = 3.6 kPa, 27.1%, TDR = 76%); FS XL probe = 11.8 kPa; IQR = 1.2; 10%; TDR = 10%.

LB: length: 18 mm; 21 PS; 30-40% macrovesicular steatosis; moderate lobular inflammation; mild ballooning; portal fibrosis without septa; perisinusoidal fibrosis; NAS = 7

SAF: S2A3F2

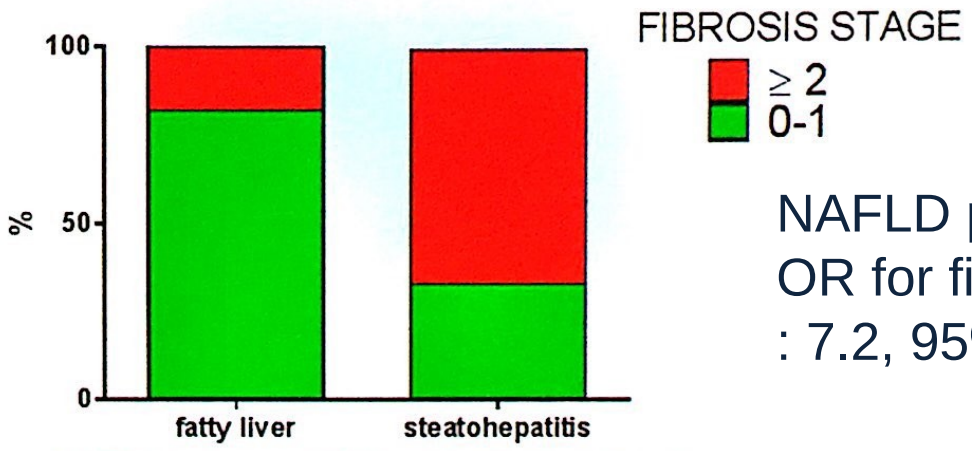
METAANALYSIS

- ✓ 411 pts with biopsy proven NAFLD
- ✓ Fibrosis progression rate: 1 stage/14 years in NAFL, 1 stage/7 years in NASH
- ✓ Rapid progressors: progression form stage 0 to stage 3-4 over 6 years fu

Singh, CGH 2015

Fibrosis progression in those with NAFL was linked to evolution to NASH

NASH CRN
N = 396 pts



NAFLD progression:
OR for fibrosis progression
: 7.2, 95% CI 2.4 – 21.5

Sanyal, AASLD 2016

CLINICAL CASE

2013

P = 78 kg; WC = 92 cm; BMI = 27.63 kg/m2
LFT: ALT = 17 IU/l; AST = 25 IU/l; GGT = 56 IU/l
Lipids: CT = 6.1 mmol/l, TG = 0.88 mmol/l
Gly = 9.5 mmol/l ; Insuline = 13.5 mUi/l; HOMA = 5.7; HbA1c = 7.2%
FT = 0.68;

CLINICAL CASE

Q 6

Weight loss
Normalized transaminases
BUT
Diabetes control
NASH with advanced fibrosis

Management:

- ✓ Continue Metformin + UDCA
- ✓ Liraglutide (Victoza) (GLP1 – analogue)
- ✓ Sitaglipin (DPP – 4 inhibitor)
- ✓ Inclusion in a clinical protocol for NASH

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)

Experimental Group

n=25

Liraglutide 0.6mg OD

(Days 1 – 7)

Liraglutide 1.2mg OD

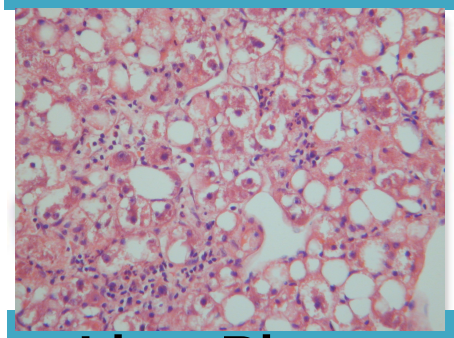
(Days 8 – 14)

Liraglutide 1.8mg OD

(Days 15 – 336)

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

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,

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

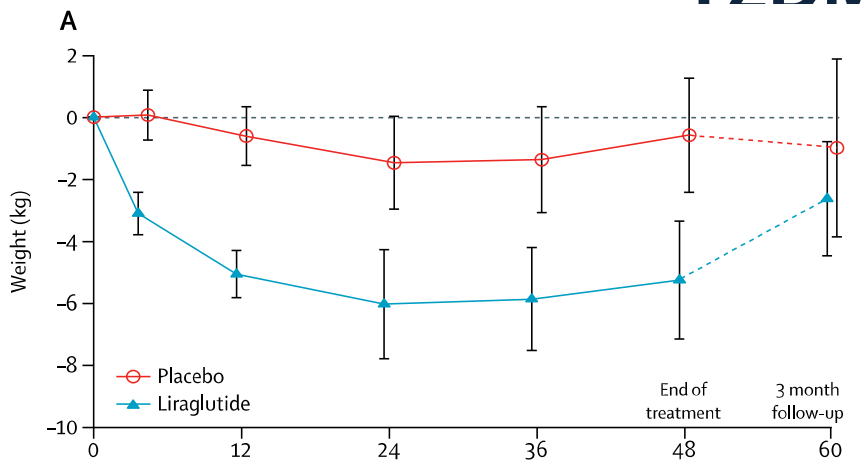
Armstrong, The Lancet,

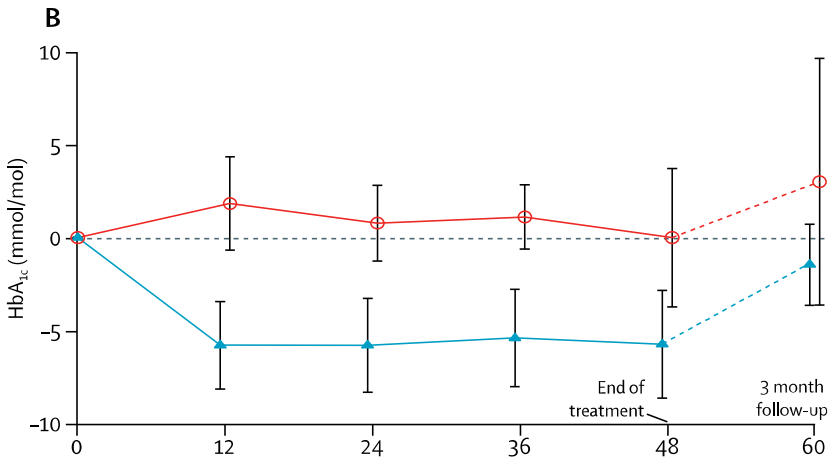
Liraglutide :effect on metabolic parameters and LFTs

	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,

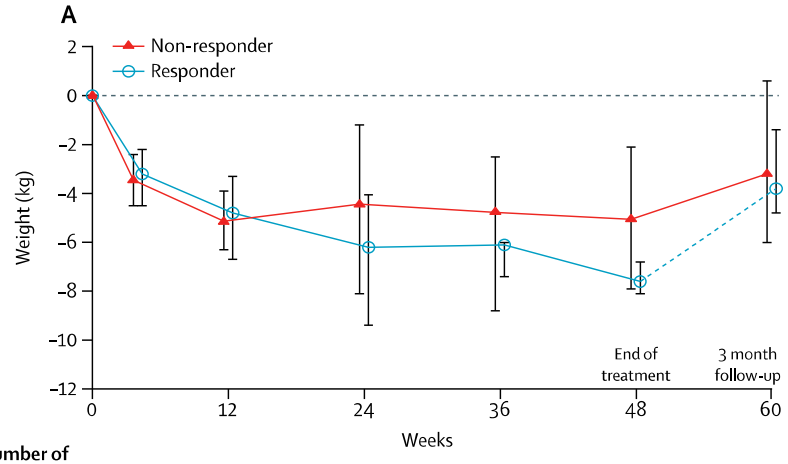
Liraglutide : histological benefit independent of weight loss, glycemic control or the presence of T2DM

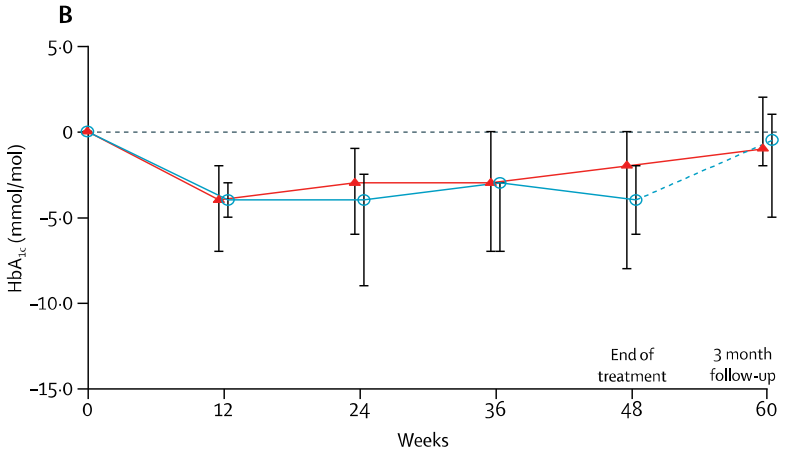




Number of evaluable patients						
Liraglutide	26	25	23	24	23	23
Placebo	25	24	23	22	22	20

22	23	23	22	22
23	23	19	21	16





Number of evaluable patients						
Non-responder	14	14	14	14	14	14
Responder	9	9	8	9	9	9

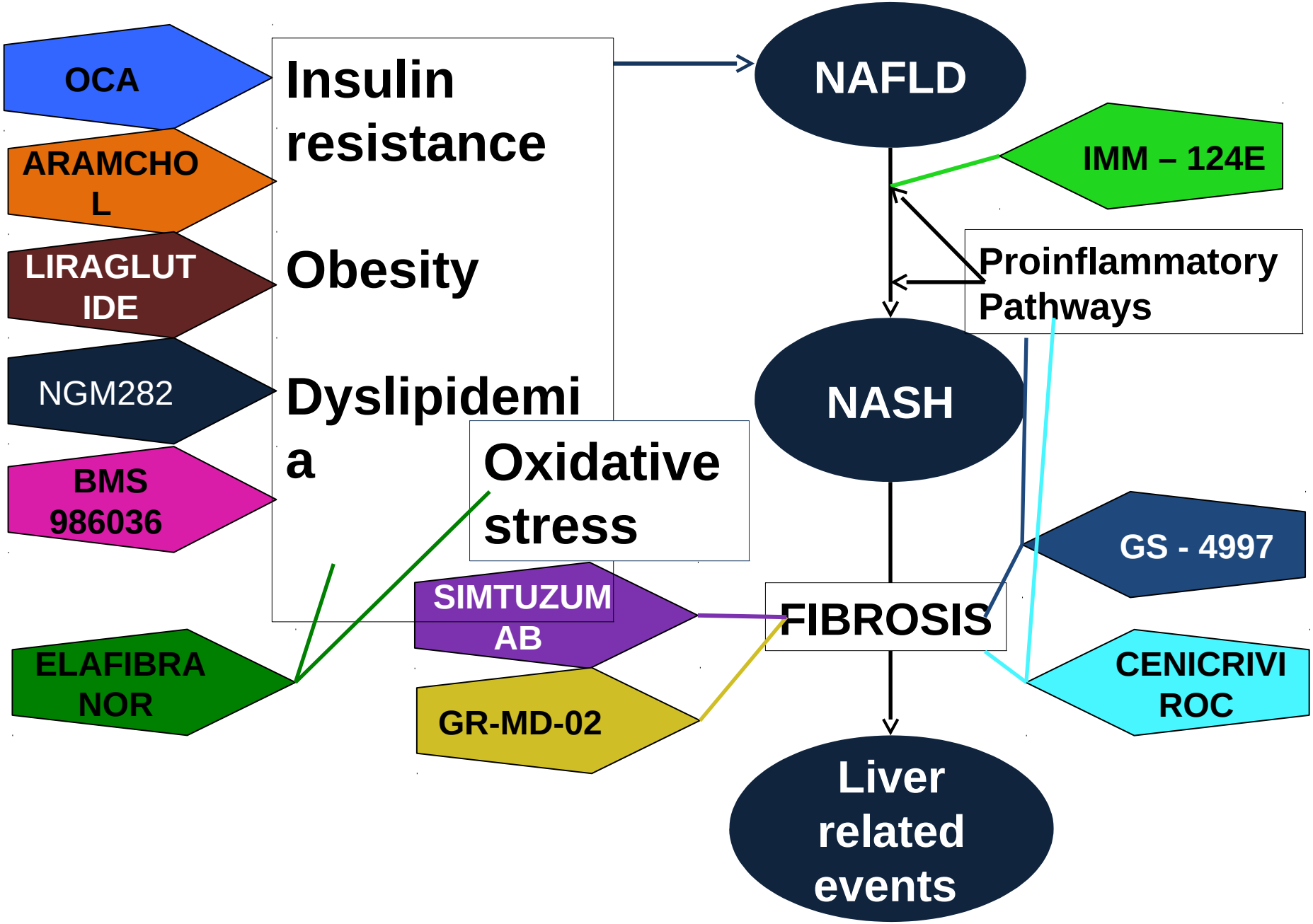
12	14	13	13	14
9	8	9	9	8

CLINICAL CASE

2013

LB: 13 mm length; 12 PS; 40% macrovesicular steatosis; moderate lobular inflammation, mild ballooning. Portal fibrosis with septa, perisinusoidal fibrosis.
NAS = 5

SAF = S2A3F3


OCA
ARAMCHOL
LIRAGLUTIDE
NGM282
BMS 986036
Insulin resistance
Obesity
Dyslipidemia
Oxidative stress
NAFLD
IMM – 124E
Proinflammatory Pathways
NASH
GS - 4997
SIMTUZUMAB
FIBROSIS
ELAFIBRANOR
GR-MD-02
CENICRIVIROC
Liver related events

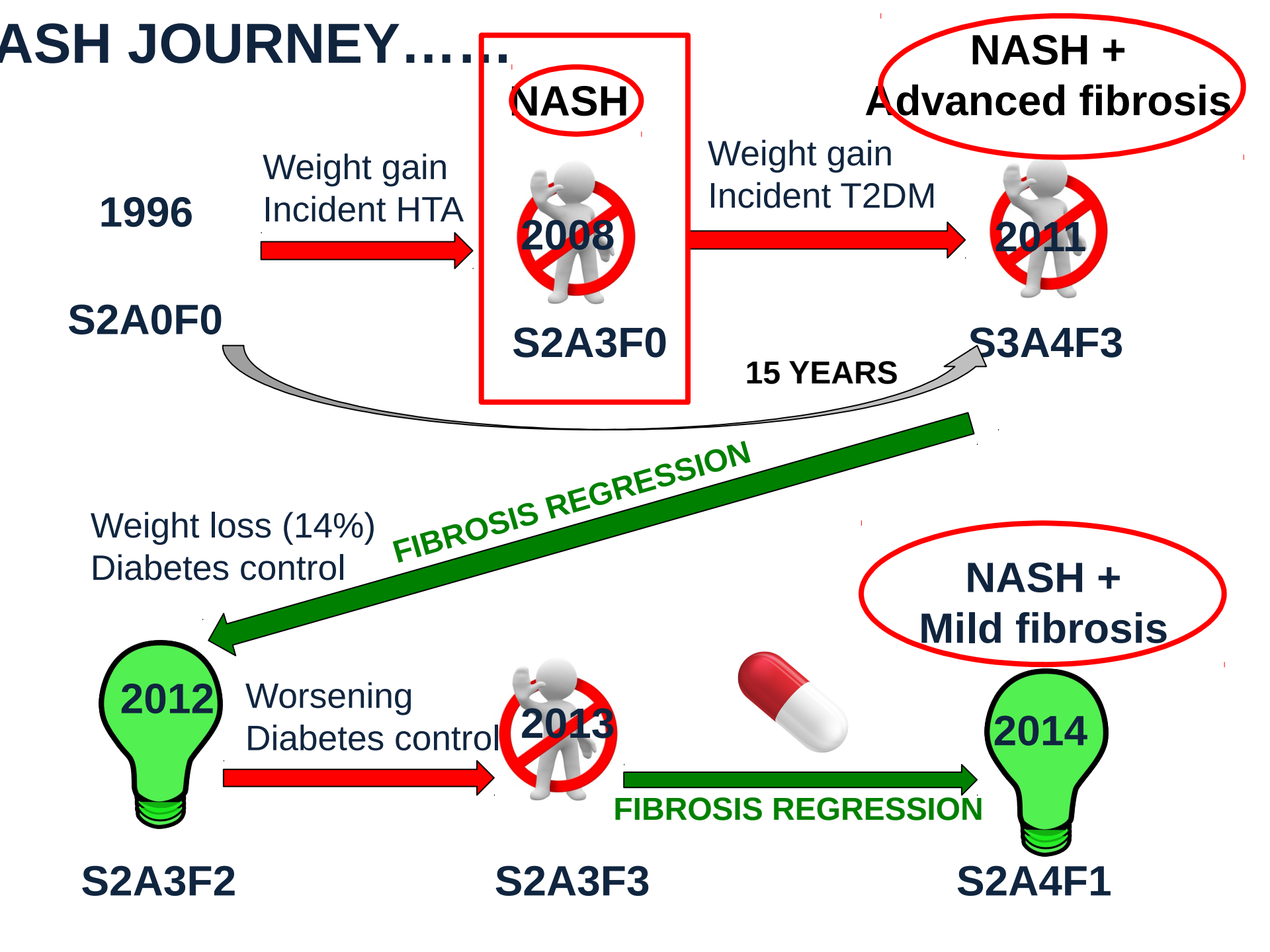
CLINICAL CASE

2014

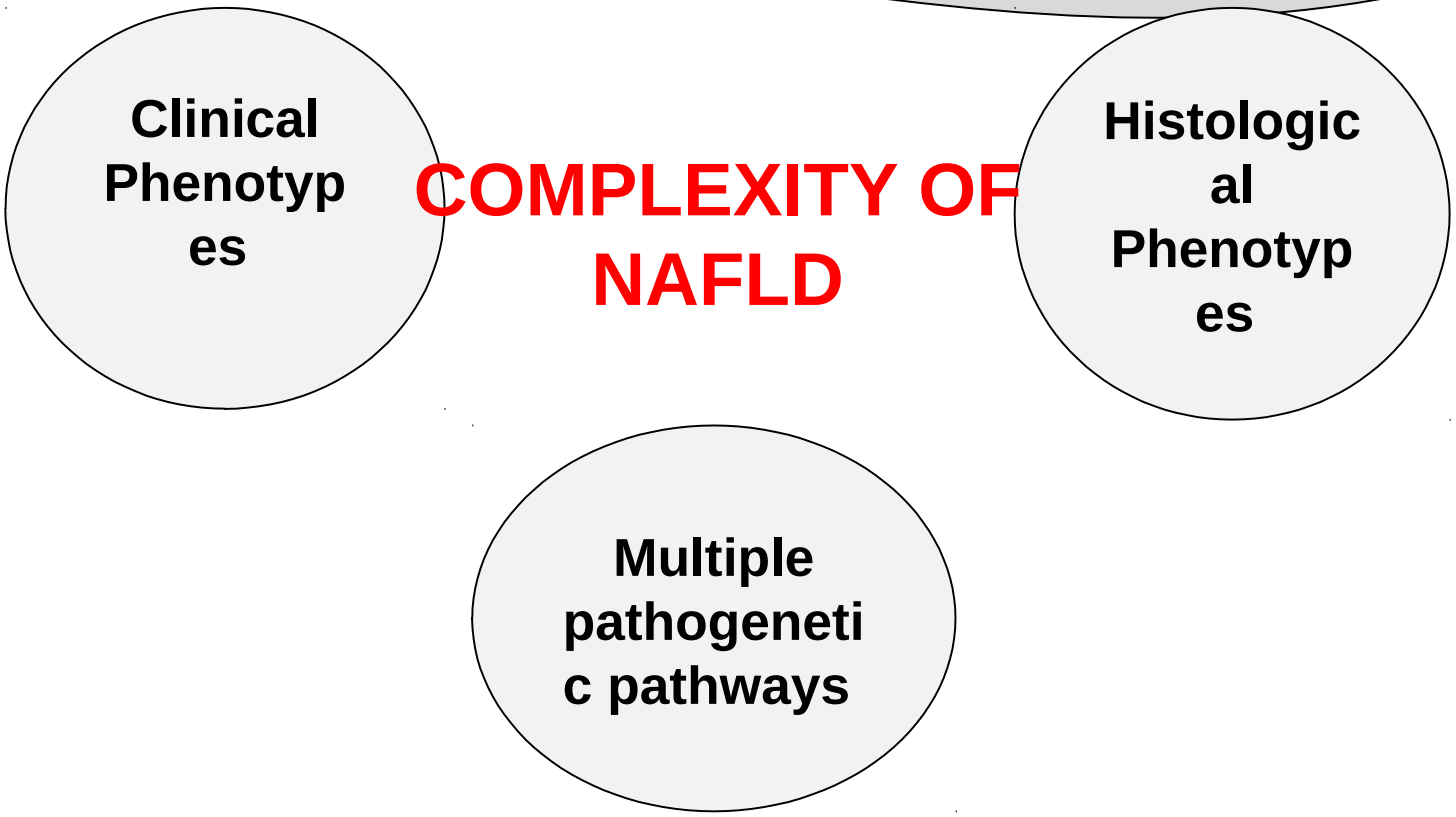
- ✓ End of treatment (elafibranor) 80 mg
- ✓ LB: 15 mm length; 8 PS; macrovesicular steatosis 50%, moderate lobular inflammation, severe ballooning. Mild perisinusoidal fibrosis, no portal fibrosis. NAS = 6;
- ✓ **SAF: S2A4F1**

LFT: AST = 20 UI/l, ALT = 16 UI/l, GGT = 121 UI/l
Lipids: TC = 6 mmol/l, TG = 1.32 mmol/l
Fasting glucose = 5.73 mmol/l, Fasting insuline = 12.5 mUI/l, HOMA = 3.18, HbA1c = 6.1%
Stable weight (79 kg)

CONCLUSIONS


ASH JOURNEY……
NASH
NASH +
Advanced fibrosis
1996
Weight gain
Incident HTA
2008
Weight gain
Incident T2DM
2011
S2A0F0
S2A3F0
S3A4F3
15 YEARS
FIBROSIS REGRESSION
Weight loss (14%)
Diabetes control
NASH +
Mild fibrosis
2012
Worsening
Diabetes control
2013
2014
FIBROSIS REGRESSION
S2A3F2
S2A3F3
S2A4F1

Therapeutic response rate in NAFLD stuck between 40 – 50%



- ✓ Multiple pathways are being targeted
- ✓ It is doubtful that a single pathway will work for every patients

Potential approach to solve the problem

Therapeutic choice

- Nodal target of strategic importance
- Combination therapy
- Individual approaches to Individual patient