NON-ALCOHOLIC FATTY LIVER
FOR PRIMARY CARE PHYSICIANS

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Disclosure

- Nothing to disclose

Outline

- Background
- How to stratify risk
  - Which patient need to be referred to the Hepatology Clinic
- Management
  - Life-Style Intervention
  - Current Therapies
  - Phase III Trials

Background

- NAFLD is the most common cause of chronic liver disease and elevated liver enzymes.
- >80 million individuals affected in US and increasing annually
- NAFLD is one of the leading causes of cirrhosis.
- NASH is the 2nd leading cause of Liver transplant
- Most rapidly increasing indication for Liver transplant

Chalasani N HEPATOLOGY, VOL. 67, NO. 1, 2018
Younossi Z et al Clin Gastroenterol Hepatol, 2020.

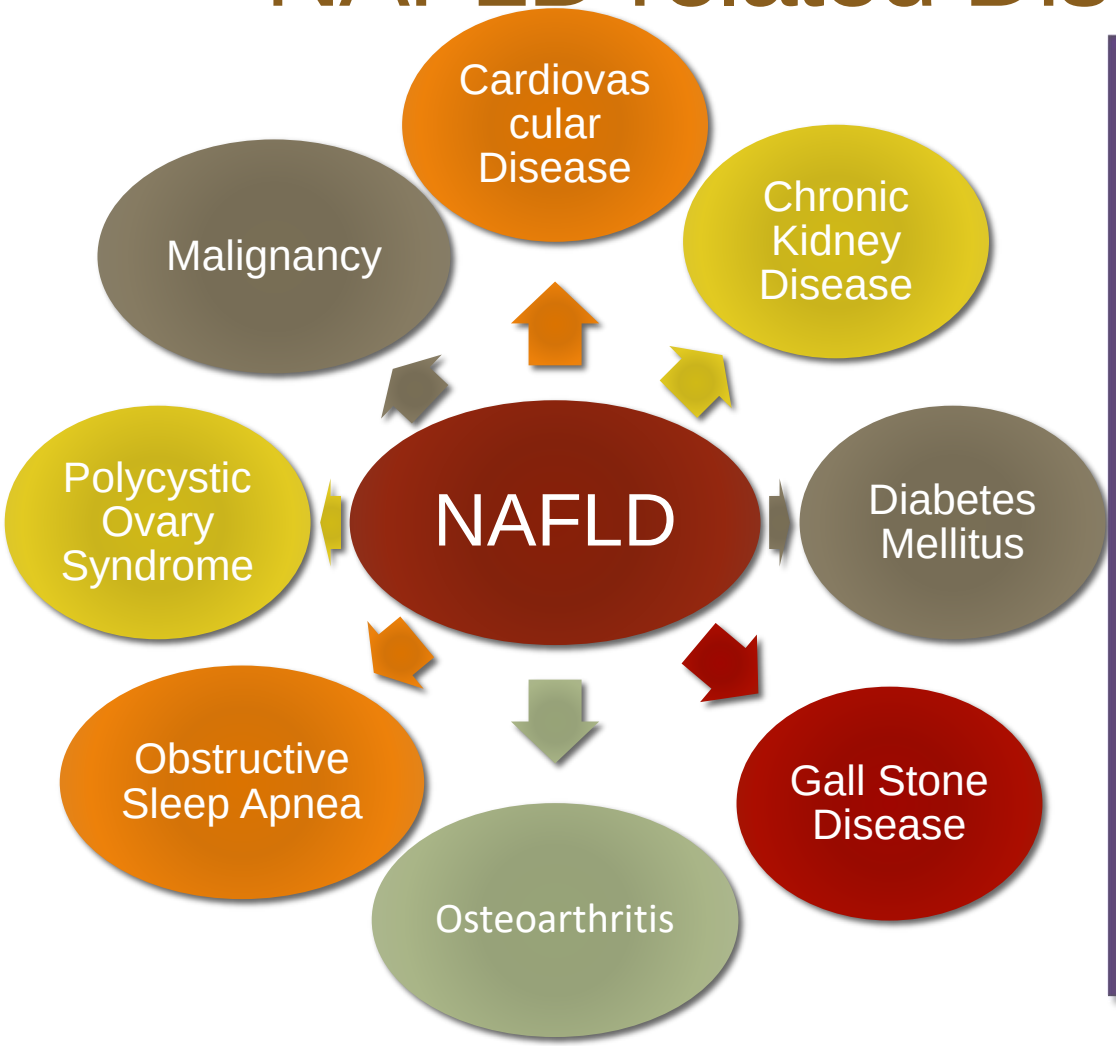
Adam et al JAMA. 2020;323(12):1175-1183.

Rick Factors (High Risk) NAFLD

Morbid Obesity (BMI≥35)	80-90% in bariatric surgery patients
Obesity	70%
T2DM	70%
Metabolic syndrome	Central obese, Hyperglycemia, HTN, Dyslipidemia: 53%
Dyslipidemia	High TG, low HDL: 50%
Race	Hispanic, SE Asia >Caucasian>>African American: 45-50%
PCOS	15-55%

Chalasani N HEPATOLOGY, VOL. 67, NO. 1, 2018

NAFLD related Disease

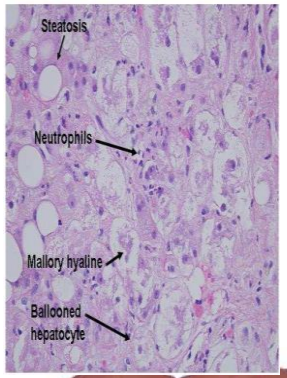


The incidence rate of cancers in NAFLD individuals and the referent cohort.

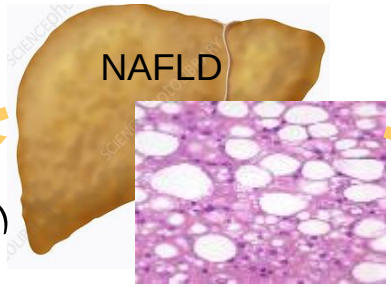
Type of cancer	Incidence* per 100,000-person years	
	NAFLD	Referent cohort
Gastrointestinal/Liver cancers		
Liver	56.0(29.3, 82.7)	18.1 (14.7, 21.8)
Colon	297.6 (245.1, 350.1)	141.6 (130.7, 152.3)
Pancreas	81.4 (36.9, 125.9)	37.7 (28.7, 46.5)
Stomach/cardia	41.8 (20.0, 64.0)	15.3 (12.4, 18.2)
Esophagus	36.1 (27.2, 44.9)	20.7 (18.2, 23.2)
Hormone-sensitive cancers		
Breast	923.9 (789.5, 1057.5)	692.0 (630.7, 753.3)
Prostate	1355.9 (1115.7, 1596.1)	1243.6 (1127.0, 1360.2)
Uterus/endometrium	439.8 (344.5, 555.1)	217.3 (178.9, 255.7)
Ovary	89.8 (48.4, 131.2)	70.3 (50.0, 90.7)
Lung/bronchus	261.1 (184.2, 331.2)	161.9 (142.7, 181.0)

*Incidence shown at age 65.

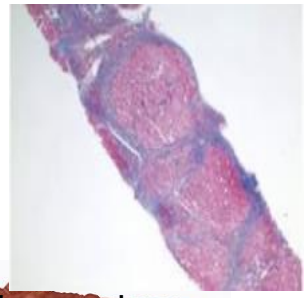
Natural History & Disease Spectrum of NAFLD



~10-45%
(over 3-4 years)
~7%
(over 3-7 years)



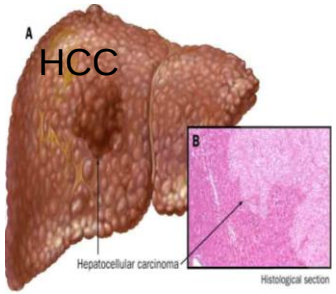
22-24%
~14 yrs to progress 1 fibrosis stage



NAFLD Activity Score (NAS)	
Steatosis (0-3)	
5-33%	1
34-65%	2
≥66%	3
Inflammation (0-3)	
<2 under 20x	1
2-4 under 20x	2
>4 under 20x	3
Ballooning (0-2)	
Few	1
Many	2

10-25%
(over 8-14 years)

0.16%
ver 6 years)



2-13%
(over 3-7 y

No fibrosis	**Stage 0**
Portal fibrosis	**Stage I**
Peri-portal fibrosis	**Stage II**
Bridging fibrosis	**Stage III**
Cirrhosis	**Stage IV**

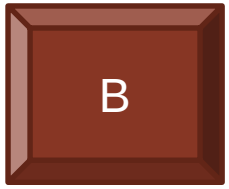
Younossi ZM et. al. Cl -94
Goh GB Dig Dis Sci 2
Mc Pherson S J Hepatol 2015:62.1148-1155
Pais R. J Hepatol 2013:59. 550-556
Wang VW. Gut 2010:59.969-974
Argo CK J Hepatol 2009-51:371-369
Singh S. CGH 2015;13-643-654

Case 1- Question 1

A 60 YOF with diabetes mellitus, hypertension who comes to primary care office for regular medical check up. On examination, her BMI 33 kg/m2, the rest of the examination are negative. Her medications include Glyburide and lisinopril. Lab include AST 90 IU/L, ALT 110 IU/L, Alkaline phosphatase 210 IU/L, bilirubin 0.5, platelet 150K. Ultrasound showed bright liver. SMA 1:20, IgG 1010, AMA negative. Hepatitis A, B and C serologies were negative.

What is the next investigation ?

A. Check Fibrosure
B. Calculate FIB 4 score
C. CT scan abdomen
D. MRI abdomen

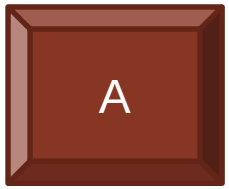


Case 1 – Question 2

A 60 YOF with diabetes mellitus, hypertension who comes to primary care office for regular medical check up. On examination, her BMI 33 kg/m2, the rest of the examination are negative. Her medications include Glyburide and lisinopril. Lab include AST 90 IU/L, ALT 110 IU/L, Alkaline phosphatase 210 IU/L, platelet 150K. Ultrasound showed bright liver. SMA 1:20, IgG 1010, AMA negative. Hepatitis A, B and C serologies were negative. FIB4 score 3.43.

What is the next step ?

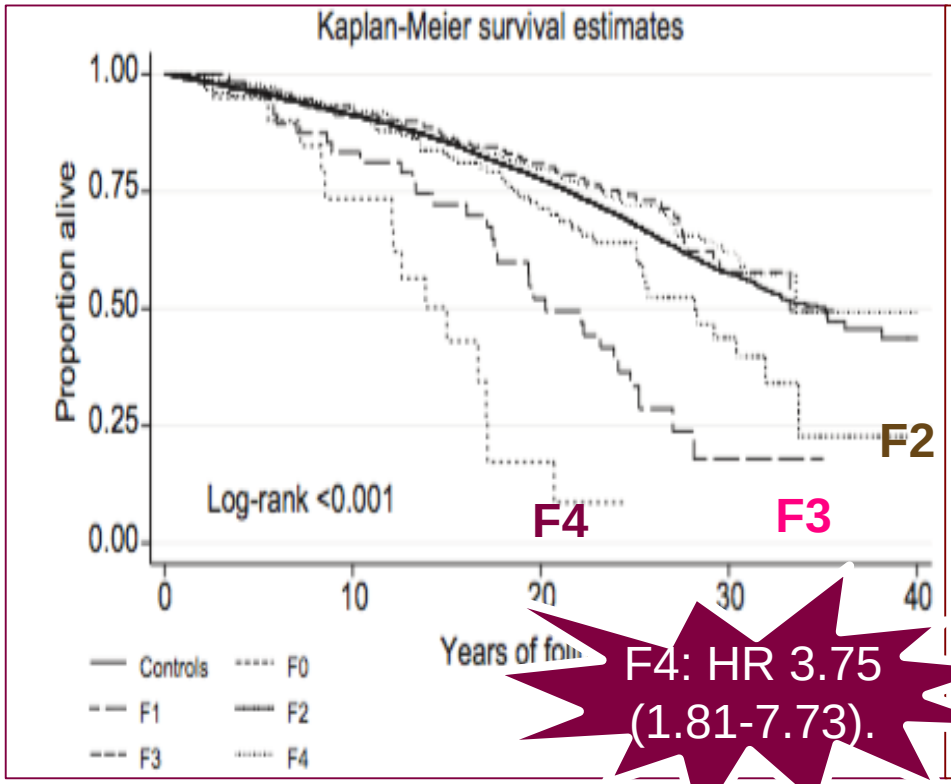
A. Refer to hepatology clinic
B. CT scan abdomen
C. MRI abdomen
D. Liver biopsy



WHO IS THE HIGH-RISK PATIENT?

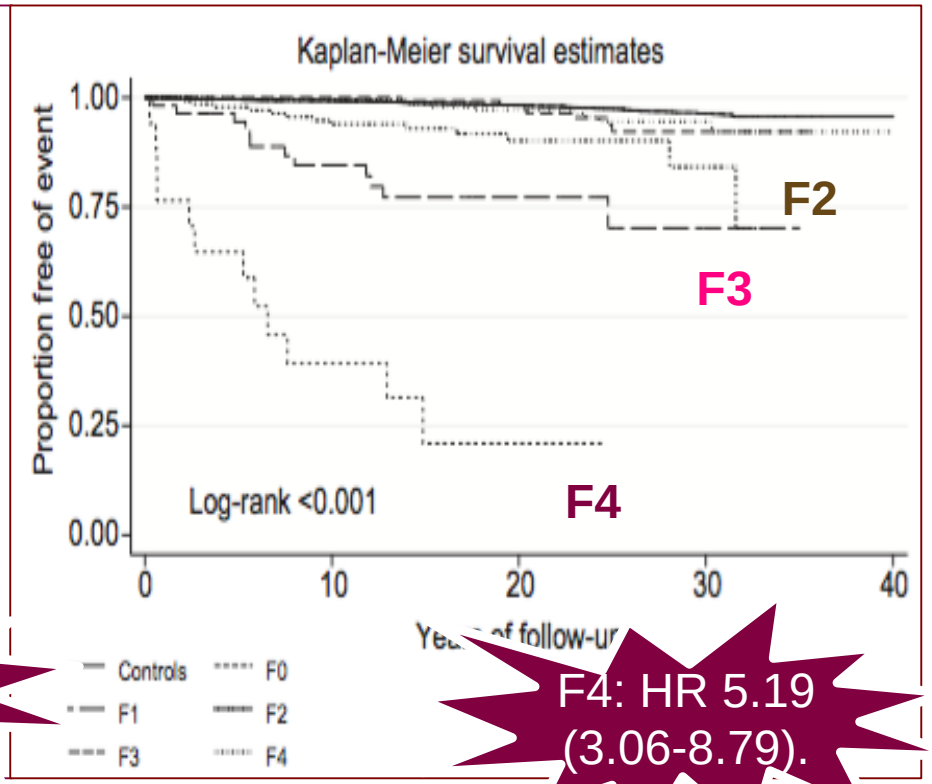
Baseline fibrosis stage, not NASH predicts mortality and time to development of severe liver disease

Overall Mortality



F4: HR 3.75 (1.81-7.73).

Severe Liver Disease



F4: HR 5.19 (3.06-8.79).

There was no significant difference in the number of severe liver disease cases in patients without and with NASH (9.8% vs. 12.8%, p=0.29)

Severe Liver disease- Liver failure (ICD), cirrhosis, HCC or Decompensation

Hagstrom H J Hepatol 2017;67:1265-1273

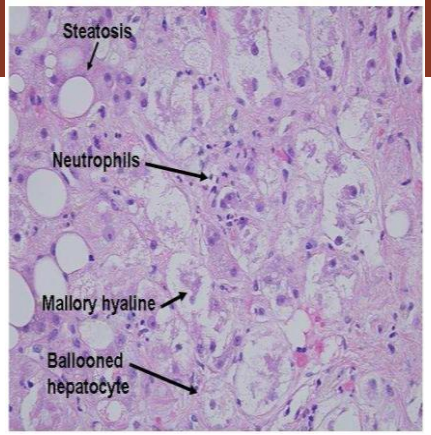
HOW TO STRATIFY RISK

Which patient need to be referred to Hepatology Clinic?

STAGING OF NAFLD - FIBROSIS

- Invasive staging (Gold Standard)
- Non Invasive Tests (NIT) staging

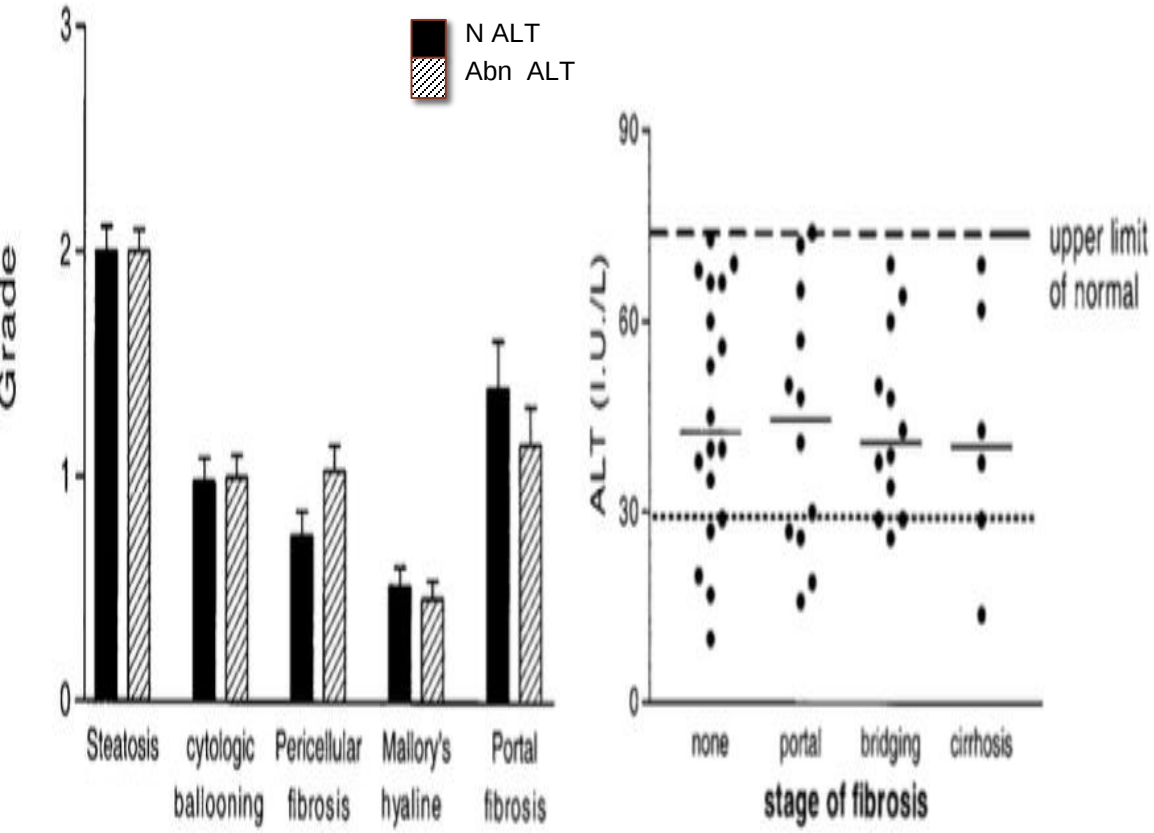
Invasive: Liver biopsy



- Gold standard –
  - Clinical – staging, differentiate/detect concomitant disease
  - End points of phase 3 clinical trials
- Limitations –
  - Invasive
  - Small risk of complications
  - Risk of sampling error or variability
  - Low acceptance by patients
  - Inconvenience for monitoring of disease status
  - Cost

Bedossa P Hepatology 2003;38:1449-57.
Siddiqui MS Hepatology 2018;67:2001-2012.

Challenges in Liver enzymes

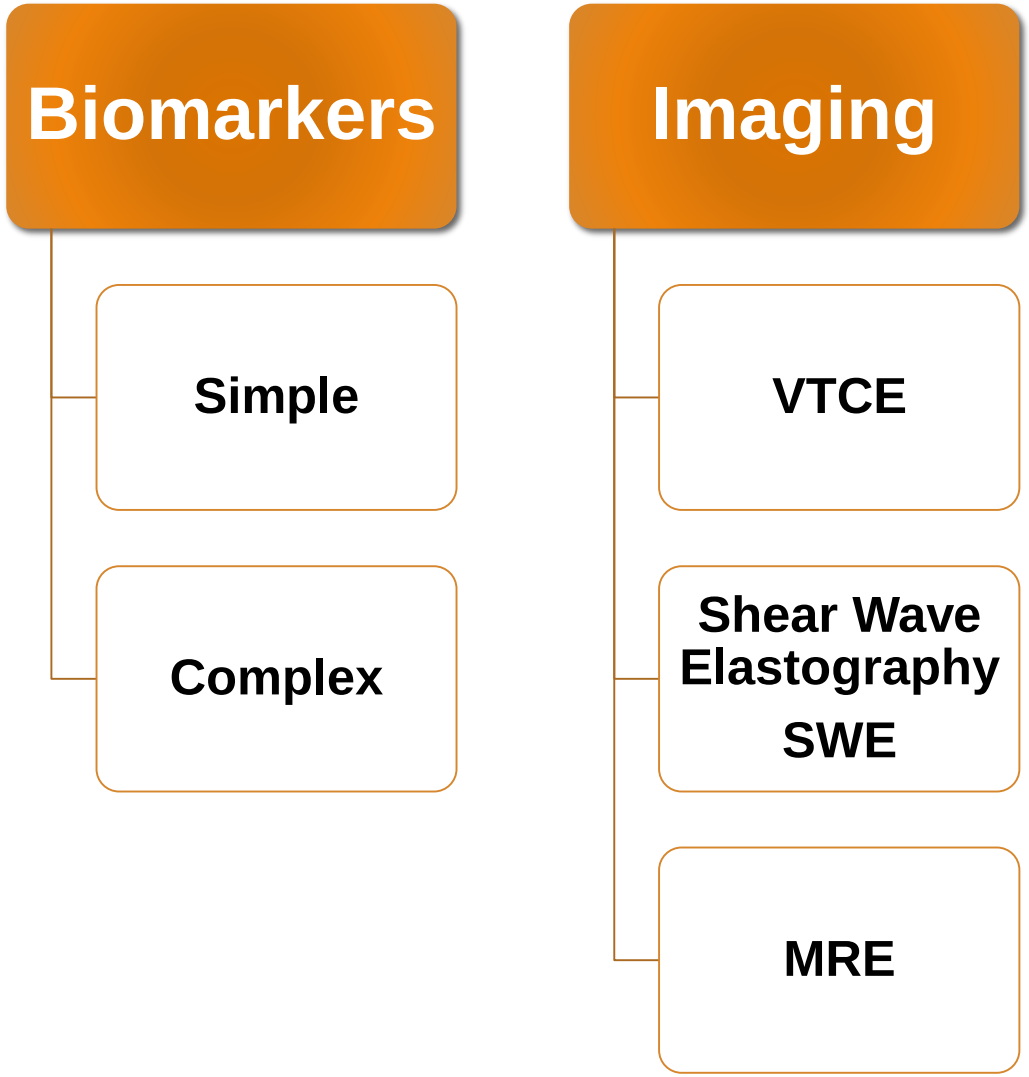


- ALT can be normal in >50% of NASH
- ALT can be elevated in >50% of NAFLD without NASH

- Normal ALT does not preclude NASH/progressive disease
- Elevated ALT cannot predict NASH or fibrosis

Mofrad P. Hepatology 2003 Jun:37(6):1286-92
Browning. Hepatology. 2004;40:1387
Dyson. Frontline Gastroenterol.2014;5:211

Non invasive Tests (NIT) for staging



Simple NIT biomarkers

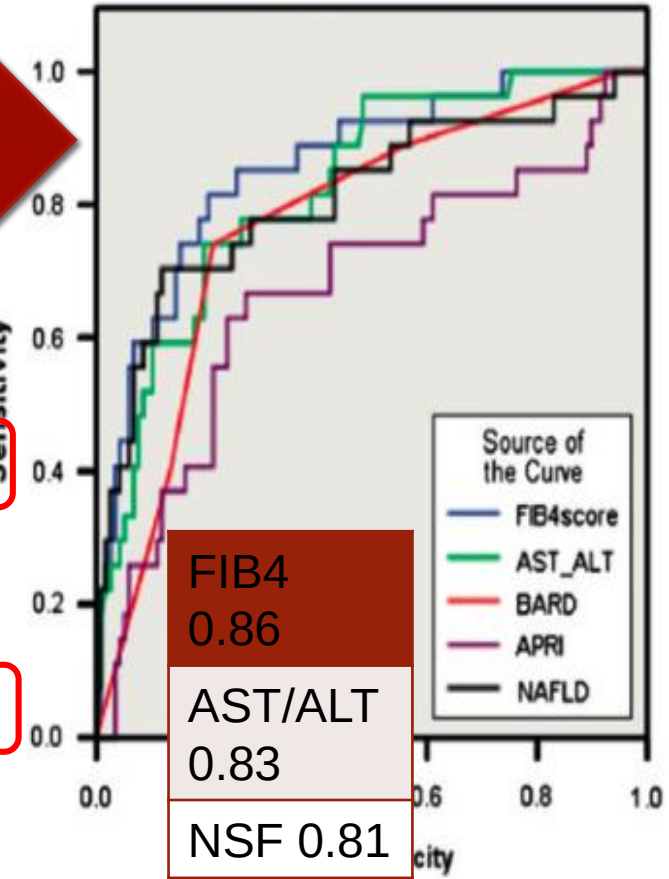
Score	Formula
FIB4	Age x AST (IU/l)/platelet count (x10^9/litre)x $\sqrt{}$ALT (IU/l).
NFS (NAFLD fibrosis score)	1.675+0.0373age (years)+0.0943BMI (kg/m2)+1.133impaired fasting glycaemia or diabetes (yes1⁄41, no1⁄40)+0.993AST/ALT ratio 0.0133platelet (31x9/litre) 0.663albumin (g/dl)

Accuracy of simple NIT biomarkers (no/Mild vs advanced fibrosis)

No/Mild Fibrosis F0-2 → **Indeterminate ?** → **Advanced Fibrosis F3-4**

TESTS	CUT-OFF
FIB4	<1.3
AST/ALT	<0.8
NSF	<-1.455

TESTS	CUT-OFF
FIB4	>2.67
AST/ALT	>1
NSF	>0.676



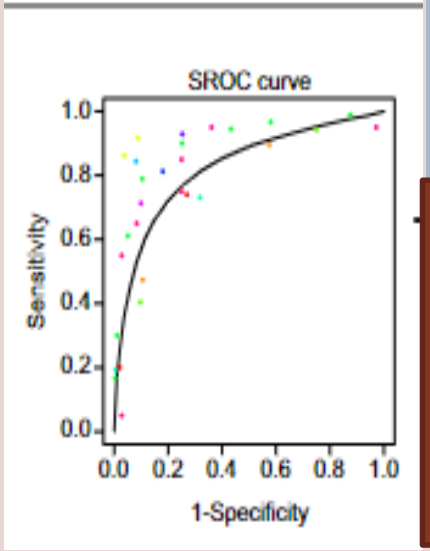
FIB4 0.86
AST/ALT 0.83
NSF 0.81
BARD 0.77

Indeterminate stage?

McPherson S Gut. 2010 Sep;59(9):1265-9

Shah. Clin Gastroenterol Hepatol. 2009;7:1104

COMPLEX TESTS

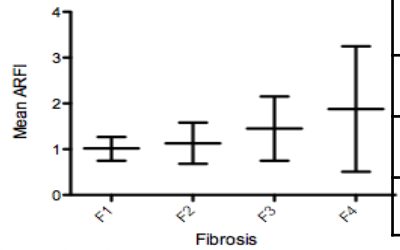
Test		Data
ELF (Enhanced Liver Fibrosis panel) To assess ≥F3	DS= -7.412+(ln(HA)*0.681)+(ln(P3NP)*0.775)+ (ln(TIMP1)*0.494) HA=Hyaluronic acid P3NP=Pro-collagen 3 TIMP1=Tissue Inhibitor of matrix metalloproteinase 1	 11 studies were included in the meta-analysis of advanced fibrosis AUC: 0.83 (0.71, 0.90) Sensitivity: 0.73 (0.60, 0.83) Specificity: 0.80 (0.68, 0.88) • Sensitivity of >0.90 for excluding fibrosis at threshold of 7.7 • Specificity of 0.90 for advanced and significant fibrosis ,thresholds of 10.18 (sensitivity: 0.57) and 9.86 (sensitivity: 0.55)
Pro-C3 based predictive fibrosis score To assess ≥F3	**ABC3D** = **A**ge>50, **B**MI>30, **C**=Platelet **c**ount <200, **3**= Pro-C**3**>15.5 ng/ml, **D**iabetes= present (each score 1, DM score 2= max 6) **FIBC3 =** : -5.939 + (0.053*Age) + (0.076*BMI) + (1.614*T2DM) – (0.009*platelets) + (0.071*PRO-C3)	 + Age BMI T2DM **ABC3D** (Age >50 = 1, BMI >30 = 1, Platelet count <200, Pro-C3 >15.5 = 1, T2DM = 2 Score >3 **FIBC3** FIBC3 score >-0.4

	FIBC3	FIB4	ABC3D
AUROC	0.83	0.76	0.81
Sensitivity	75.00	21.00	66.00
Specificity	75.00	94.00	75.00

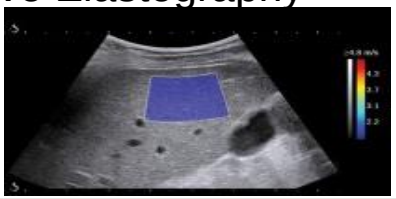
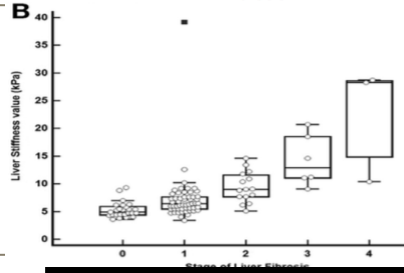
Vali et al. J.Hepatol. 2020, 73, 252–262 Boyle J Hep Reports. 2019 Jul 4;1(3):188-198
Daniels SJ. Hepatology. 2019 Mar;69(3):1075-1086

IMAGING

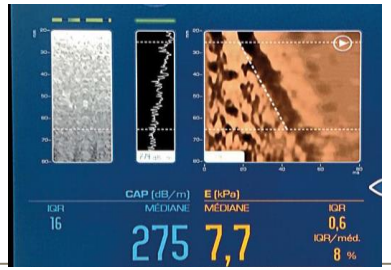
Liver Stiffness Measurement

Technique		Data
Acoustic Radiation Force Impulse (ARFI) 	• High intensity acoustic beam to tissue • Monitor tissue displacement response	

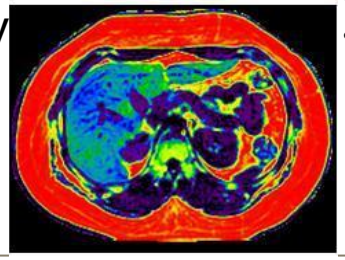
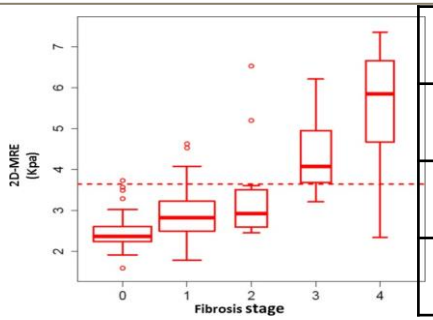
Fibrosis	m/s	AUROC
≥F2	1.32	0.77
≥F3	1.53	0.84
F4	2.04	0.84

Shear Wave Elastography (SWE) 	• Shear waves generated from acoustic pulse at 5 different tissue depth levels	

Fibrosis	kPa	AUROC
≥F1	6.3	0.82
≥F2	7.6	0.87
≥F3	9	0.95

Tranisent Elastography (TE)  	• Shear waves propagates through liver parenchyma • Limit: obese, ascites, inflammation, congestion, post prandial

Fibrosis Stage	Youden's Threshold (kPa)	AUROC
F0-F1 vs > F2	8.2	0.77
F0-F2 vs F3	9.7	0.71
F0-F3 vs F4	13.6	0.89

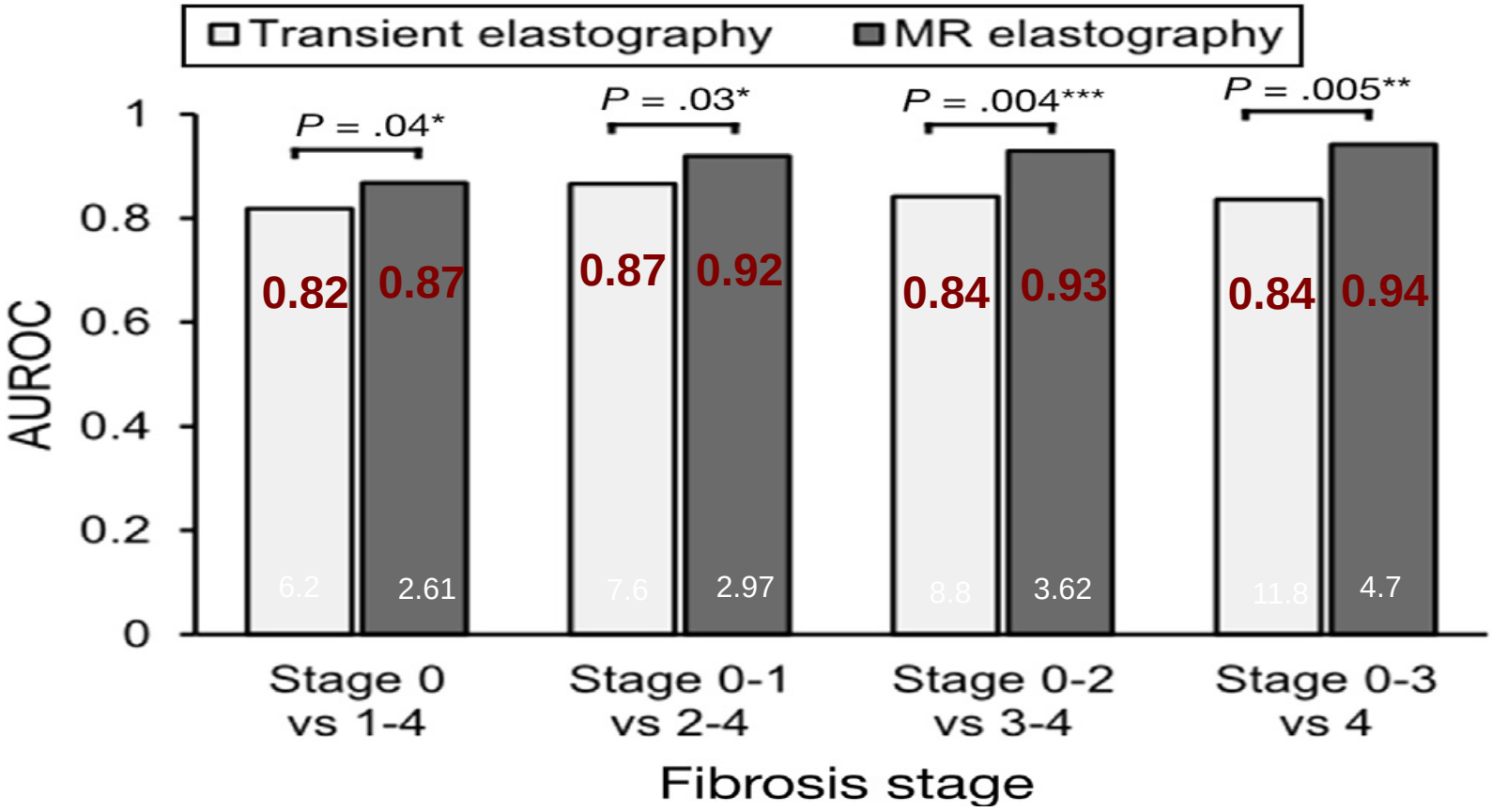
Magnetic Resonance Elastography (MRE) 	• Most accurate NIT • Costly • No point of care access	

Fibrosis	kPa	AUROC
≥F1	3.02	0.838
≥F2	3.58	0.856
≥F3	3.64	0.924

Cassinotto C et al.Hepatology: 2016 Jun;63(6):1817-27, Lee H et al. Clin Gastroenterol Hepatol 2020 May 22;S1542-3565(20)30693-5
Eddowes PJ Gastroenterology. 2019 May;156(6):1717-1730 Loomba.el.al Hepatology, 2014:60-1920

ACCURACY OF MRE AND TE

POOLED ANALYSIS: 2005-2017- 3 studies with NAFLD with TE, MRE and biopsy



Hsu C.et al. Clin Gastroenterol Hepatol. 2019 Mar;17(4):630-637.e8

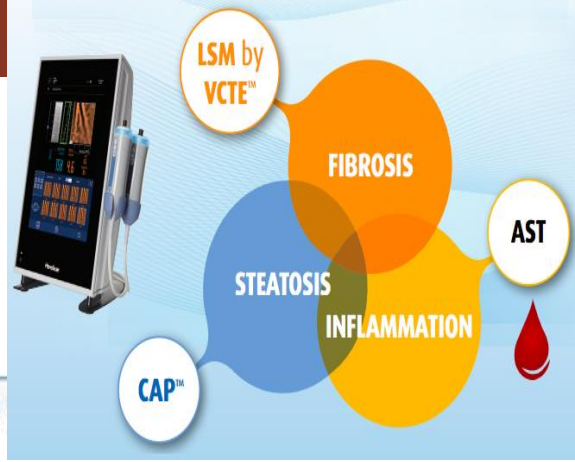
Discordance in Fibrosis Stage in Obese patients MRE vs TE

Discordance rate	Training Cohort (n=199)	Validation Cohort (n=75)
TE vs Biopsy	51.9%	58.8%
MRE vs Biopsy	21%	14.7%

- Discordance worsen with increased BMI
- Significantly higher for BMI >35 kg/m^2

Caussy C. Clin Gastroenterol Hepatol. 2018 Dec;16(12):1974-1982.e7

FAST (Fibroscan-AST)



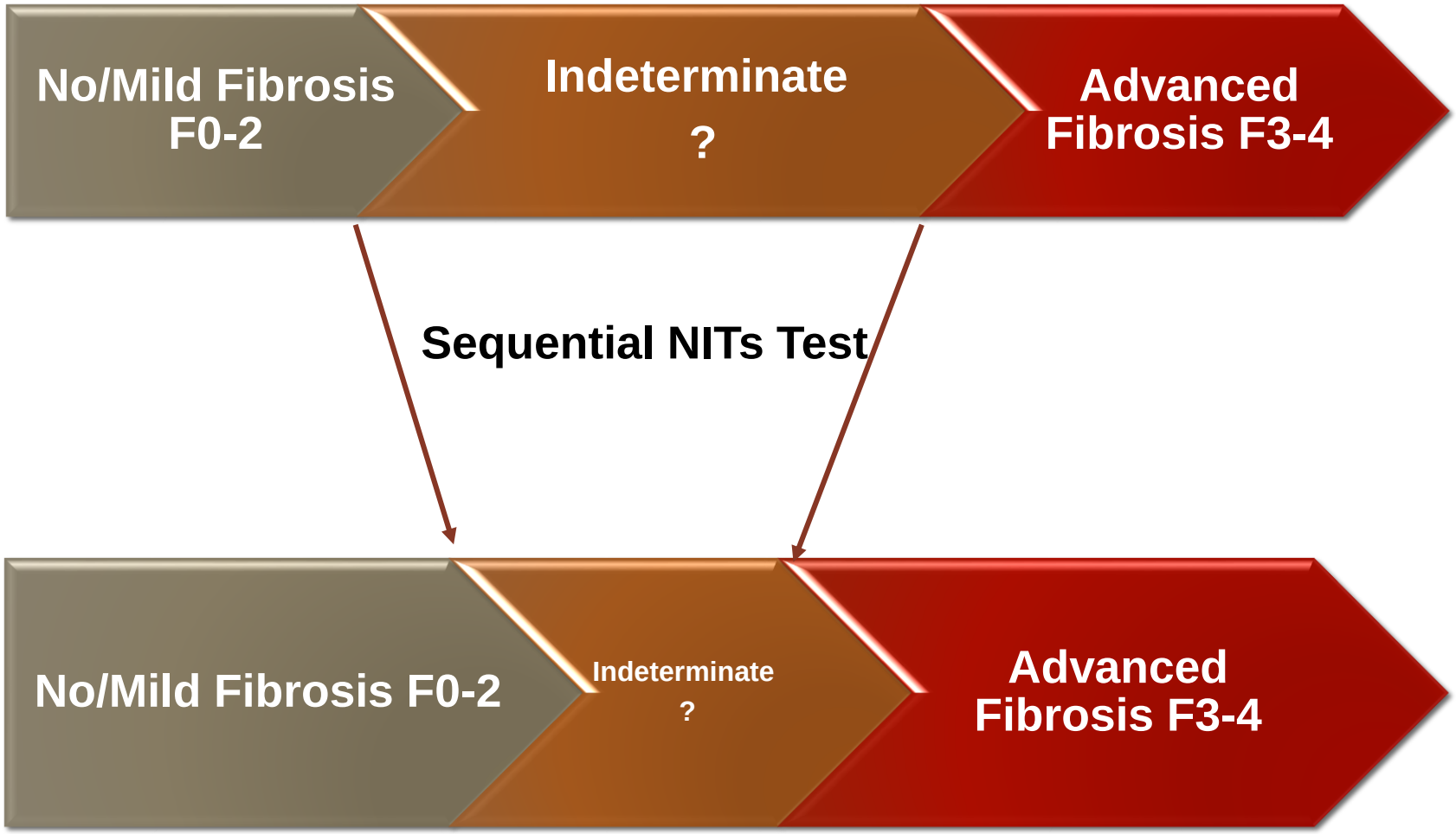
Main outcome=NASH+NAS ≥4+F≥2

$$FAST = \frac{e^{-1.65+1.07 \times \ln(LSM) + 2.66^{*}10^{-8} \times CAP^{3} - 63.3 \times AST^{-1}}}{1 + e^{-1.65+1.07 \times \ln(LSM) + 2.66^{*}10^{-8} \times CAP^{3} - 63.3 \times AST^{-1}}}$$

	AUROC (95% CI)	n	Prevalence of NASH + NAS ≥ 4 + F ≥ 2	Rule-out zone (FAST ≤0·35)			Grey zone (FAST 0·35–0·67), n (%)	Rule-in zone (FAST ≥0·67)			
				n (%)	Sensitivity	Specificity	NPV		n (%)	Sensitivity	Specificity	PPV
Derivation cohort	0·80 (0·76–0·85)	350	174 (50%)	113 (32%)	0·90 (157/174)	0·53 (93/176)	0·85 (93/110)	136 (39%)	101 (29%)	0·90 (159/176)	0·48 (84/174)	0·83 (84/101)
French bariatric surgery cohort	0·95 (0·91–0·99)	110	16 (15%)	69 (63%)	1·00 (16/16)	0·73 (69/94)	1·00 (69/69)	22 (20%)	19 (17%)	0·93 (87/94)	0·75 (12/16)	0·63 (12/19)
USA screening cohort	0·86 (0·80–0·93)	242	28 (12%)	194 (80%)	0·64 (18/28)	0·86 (183/214)	0·95 (183/193)	39 (16%)	9 (4%)	0·99 (212/214)	0·25 (7/28)	0·78 (7/9)
China Hong-Kong NAFLD cohort	0·85 (0·76–0·93)	83	36 (43%)	28 (34%)	0·94 (34/36)	0·55 (26/47)	0·93 (26/28)	29 (35%)	26 (31%)	0·89 (42/47)	0·58 (21/36)	0·81 (21/26)
China Wenzhou NAFLD cohort	0·84 (0·73–0·95)	104	9 (9%)	55 (53%)	0·89 (8/9)	0·56 (53/95)	0·98 (58/67)	37 (36%)	12 (11%)	0·92 (87/95)	0·44 (4/9)	0·33 (4/12)
French NAFLD cohort	0·80 (0·73–0·86)	182	78 (43%)	67 (37%)	0·88 (69/78)	0·56 (58/104)	0·87 (58/67)	69 (38%)	46 (24%)	0·89 (93/104)	0·45 (35/78)	0·76 (35/46)
Malaysian NAFLD cohort	0·85 (0·78–0·91)	176	36 (20%)	78 (44%)	0·94 (34/36)	0·54 (75/140)	0·97 (75/77)	59 (34%)	39 (22%)	0·87 (122/140)	0·58 (21/36)	0·54 (21/39)
Turkish NAFLD cohort	0·74 (0·65–0·82)	129	74 (57%)	26 (20%)	0·91 (67/74)	0·35 (19/55)	0·73 (19/26)	57 (44%)	46 (36%)	0·82 (45/55)	0·49 (36/74)	0·78 (36/46)
Pooled external patients cohort	0·85 (0·83–0·87)	1026	277 (27%)	517 (51%)	0·89 (246/277)	0·64 (483/749)	0·94 (483/514)	312 (30%)	197 (19%)	0·92 (688/749)	0·49 (136/277)	0·69 (136/197)

Newsome et.atl Lancet Gastroenterol Hepatol. 2020 Feb 3
Epub ahead of print

Narrow Indeterminate Zone



Sequential NITs to Reduce Indeterminate Zone

- Single tests

(either NFS, FIB4,ELF, VTE)

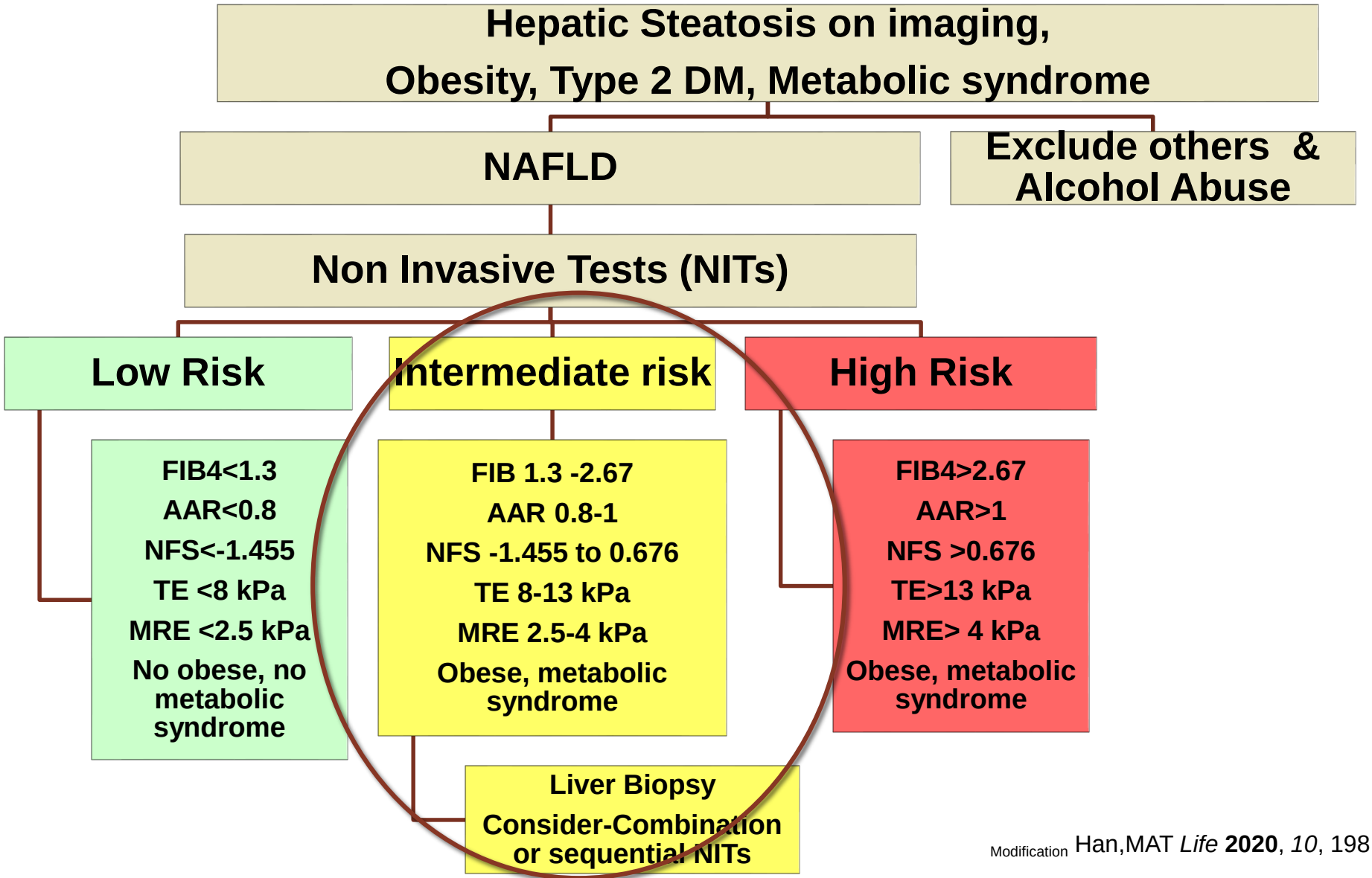
- Up to 50% indeterminate

TABLE 6. Performance of Sequential Algorithms Using Two NITs to Discriminate Advanced Fibrosis (F3-F4 vs. F0-F2)

Variable	FIB-4 (1.3, 2.67)→ ELF (9.8, 11.3) (n = 3,180)	FIB-4 (1.3, 2.67)→ LS by VCTE (9.9, 11.4) (n = 3,141)
Prevalence of F3-F4	71%	71%
Sensitivity*	69 (67, 71)	77 (75, 78)
Specificity*	92 (90, 94)	89 (87, 91)
PPV*	96 (94, 97)	95 (93, 96)
NPV*	55 (53, 58)	60 (58, 63)
Indeterminate*	24 (23, 26)	20 (18, 21)
Misclassified*	24 (23, 26)	20 (18, 21)

Anstee.et. al. Hepatology. 2019;70:1521.

Algorithm For Hepatic Fibrosis Risk Stratification



Modification Han,MAT *Life* **2020**, *10*, 198

Guideline for Primary Care & Diabetology

1. AST/ALT elevation (1.5 x ULN x ≥ 6 months)
2. History of fatty liver (US, CT, MRI or Liver biopsy)
3. T2DM with 1 additional component of metabolic syndrome
4. Non-diabetes with 3 components of metabolic syndrome

- For those with elevated AST/ALT x 6 months- other cause of liver disease should be excluded
- For those without previous imaging, US should be performed

FIB-4 <1.3

- Follow up by PCP
- Management of CV risks through life style modification & appropriate treatment

FIB-4 ≥1.3

- Further assessment
  - TE
  - Complex Serum biomarkers (? ELF when available)
- Management of CV risks through life style modification & appropriate treatment

Younossi Z et al *Aliment Pharmacol Ther*. 2020;52(3):513-526.

Case 1- Answer 1

A 60 YOF with diabetes mellitus, hypertension who comes to primary care office for regular medical check up. On examination, her BMI 33 kg/m2, the rest of the examination are negative. Her medications include Glyburide and lisinopril. Lab include AST 90 IU/L, ALT 110 IU/L, Alkaline phosphatase 210 IU/L, bilirubin 0.5, platelet 150K. Ultrasound showed bright liver. SMA 1:20, IgG 1010, AMA negative. Hepatitis A, B and C serologies were negative.

What is the next investigation ?

A. Check Fibrosure
B. Calculate FIB 4 score
C. CT scan abdomen
D. MRI abdomen

- Risk stratification is important
- FIB4 3.43 which is >1.3

B

Case 1 – Answer 2

A 60 YOF with diabetes mellitus, hypertension who comes to primary care office for regular medical check up. On examination, her BMI 33 kg/m2, the rest of the examination are negative. Her medications include Glyburide and lisinopril. Lab include AST 90 IU/L, ALT 110 IU/L, Alkaline phosphatase 210 IU/L, platelet 150K. Ultrasound showed bright liver. SMA 1:20, IgG 1010, AMA negative. Hepatitis A, B and C serologies were negative.

What is the next step ?

A. Refer to hepatology clinic
B. CT scan abdomen
C. MRI abdomen
D. Liver biopsy

FIB4 3.43 which is >1.3 → refer to Hepatology clinic

A

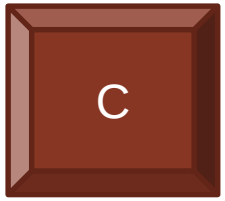
MANAGEMENT

Case 3 - Question

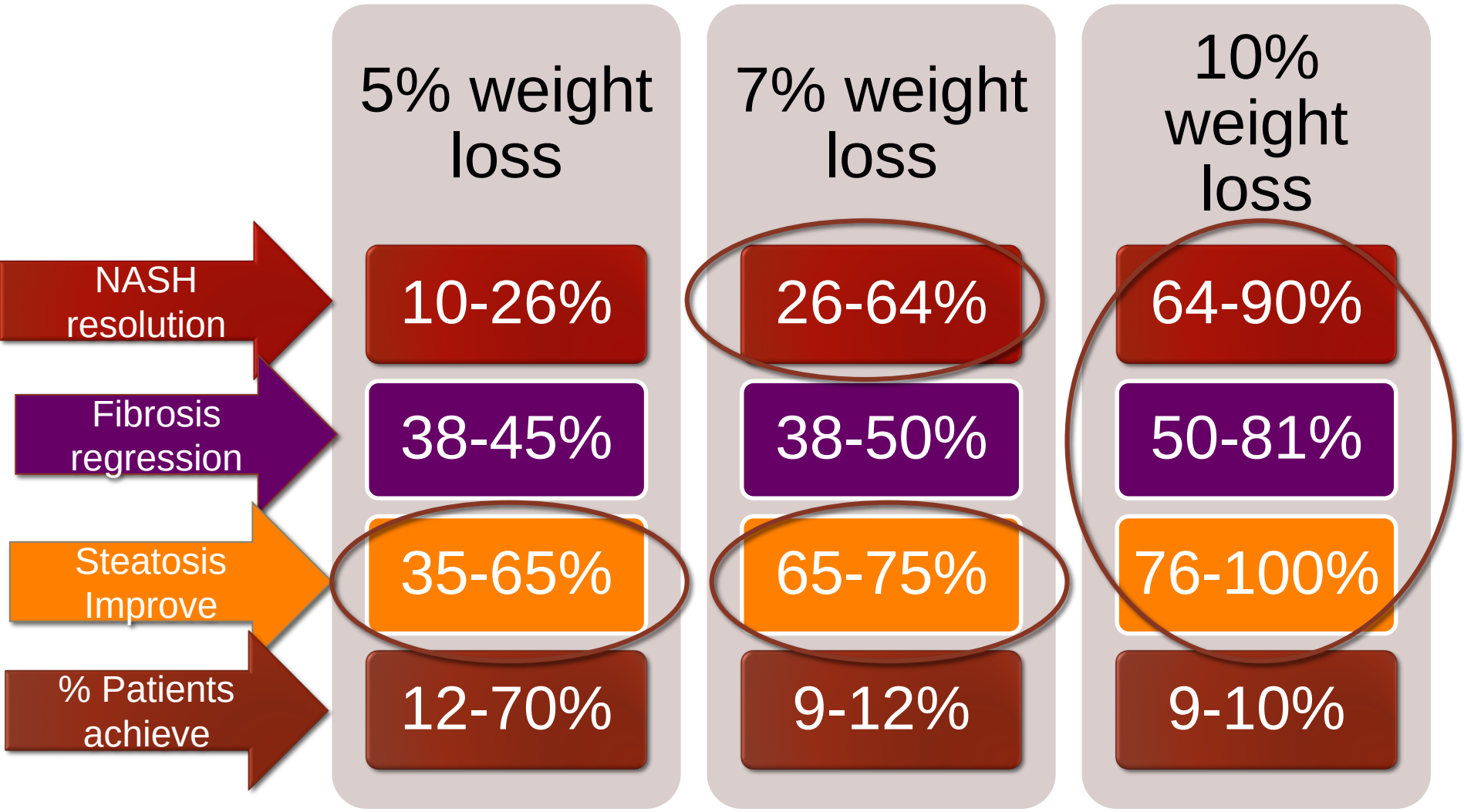
A 60 YOF with diabetes mellitus, hypertension who comes to primary care office for regular medical check up. She denied drinking alcohol. On examination, her BMI 31 kg/m2, the rest of the examination are negative. Lab include AST 90 IU/L, ALT 110 IU/L, Alkaline phosphatase 210 IU/L, platelet 150K. Ultrasound showed bright liver. SMA 1:20, IgG 1010, AMA negative. Ferritin 600, % saturation iron 25%, Hepatitis A, B and C serologies were negative.

What is the most beneficial therapy ?

A. Phlebotomy
B. Weight loss
C. Pioglitazone
D. Prednisone

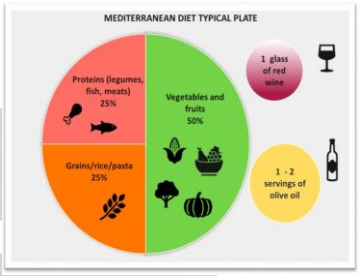


Life-style Intervention



Romero-Gómez M, et al. J Hepatol. 2017Oct;67(4):829-846
Vilar-Gomez E et al. Gastroenterology.2015 Aug;149(2):367-78.35

Dietary Changes

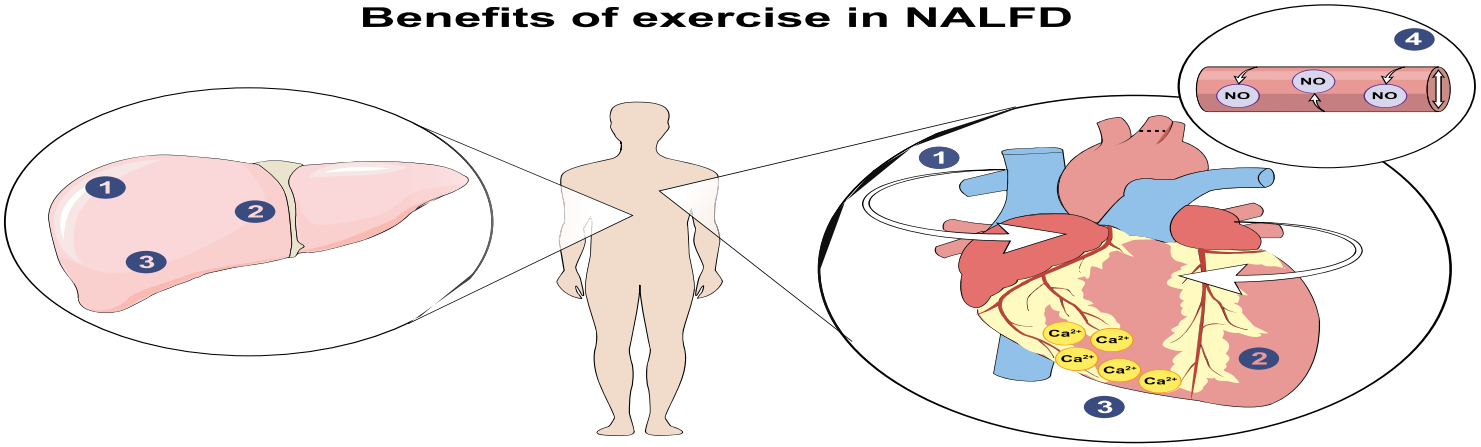


Daily Calories	• 1200-1600 calories
Lipids	• 20-30% of daily calories • Rich in MUFA and PUFA
Proteins	• 1.5 g/kg/day • Rich in plant-based protein
Carbohydrates	• <45-65% of daily calories with decreased simple sugar

Low CHO diet	Mediterranean diet	Coffee (caffeinated, filtered)	Alcohol consumption
• Improves liver fat metabolism	• Improves steatosis, IR, even without weight loss • Reduce CV events, metabolic syndrome	• ≥3 cups/day- decrease mortality • Reduce fibrosis	• Reduce or abstinence • Limit ≤2 drinks/d for female, ≤3 drinks/d for male • Limit 20g/d for female, 30 g/d for male

Vlad Ratziu 1, et al. Transplantation. 2019 Jan;103(1):28-38. Romero-Gómez M, et al. J Hepatol. 2017Oct;67(4):829-846.Torres M et al. Nutrients. 2019 Dec; 11(12): 2971.

Exercise



Ex alone without diet	Intensity	Wt changes	NAFLD/Markers
Pugh et al, n = 21 (2014) vs diet	30 min 3 x/wk		↓ LF
Kawaguchi et al, n = 28 (201			↓ LF, ALT, IL-6
Ex without diet vs no inter			
Shojaee-Moradie et al, n = 1			LF ↔
Levinger et al, n = 25 (2009)			ALT ↔
Sullivan et al, n = 18 (2012)			↓ LF 10%
Johnson et al, n = 19 (2009)			↓ LF 21%, ALT
Thompson et al, n = 41 (200		↓ 2.5%	↓ ALT, IL-6
Hallsworth et al, n = 21 (2011)		↔	↓ LF 13%

- Physical activity ≥150 min/wk-asso: w decrease AST/ALT
- ≥5 times/wk-asso: w long term NAFLD prevention & improvement

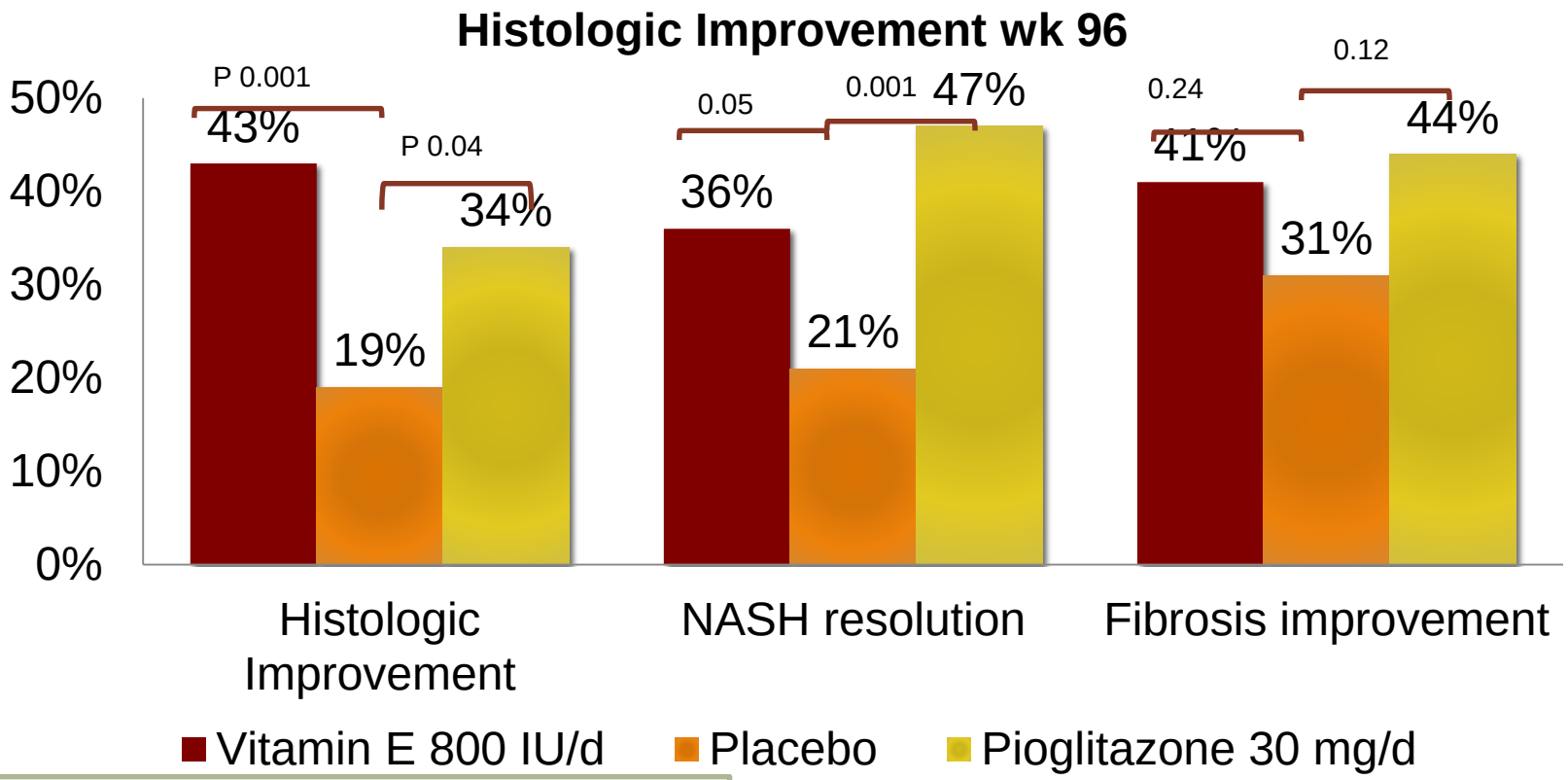
Romero-Gómez M, et al. J Hepatol. 2017Oct;67(4):829-846
Vilar-Gomez E et al. Gastroenterology.2015 Aug;149(2):367-78.35

THERAPIES FOR NAFLD/NASH

Medical and Surgical/Endoscopic Therapies

PIVENS Study

- RCT phase 3 trial -247 biopsy proven NASH without DM or cirrhosis



Vitamin E>400 IU/d
-increase risk of prostate cancer (HR 1.17)

Wt gain 4.7kg
Risk of osteoporosis
? Risk bladder cancer

Sanyal et al. N Engl J Med 2010;362:1675-85
Ann Intern Med. 2005;142(1):37-46
Klein, et al, JAMA 2011

AASLD Guideline

Pioglitazone

- with and without T2DM with biopsy-proven NASH

Vitamin E

- Non DM adults with biopsy-proven NASH
- Not in DM, non biopsy, NASH cirrhosis or cryptogenic cirrhosis
  - May be considered to treat biopsy proven NASH in diabetic patients
  - Need more data on safety & long term mortality

AASLD guideline 2018 CHALASANI ET AL. HEPATOLOGY, Vol. 67, No. 1, 2018

Weight Loss Therapies

Pharmacotherapy

- GLP-1 RA (Liraglutide)
- Others- orlistat, Phentermine, Natrexone/Bupropion

Mean 8-13% total body wt loss

Endoscopic Bariatric

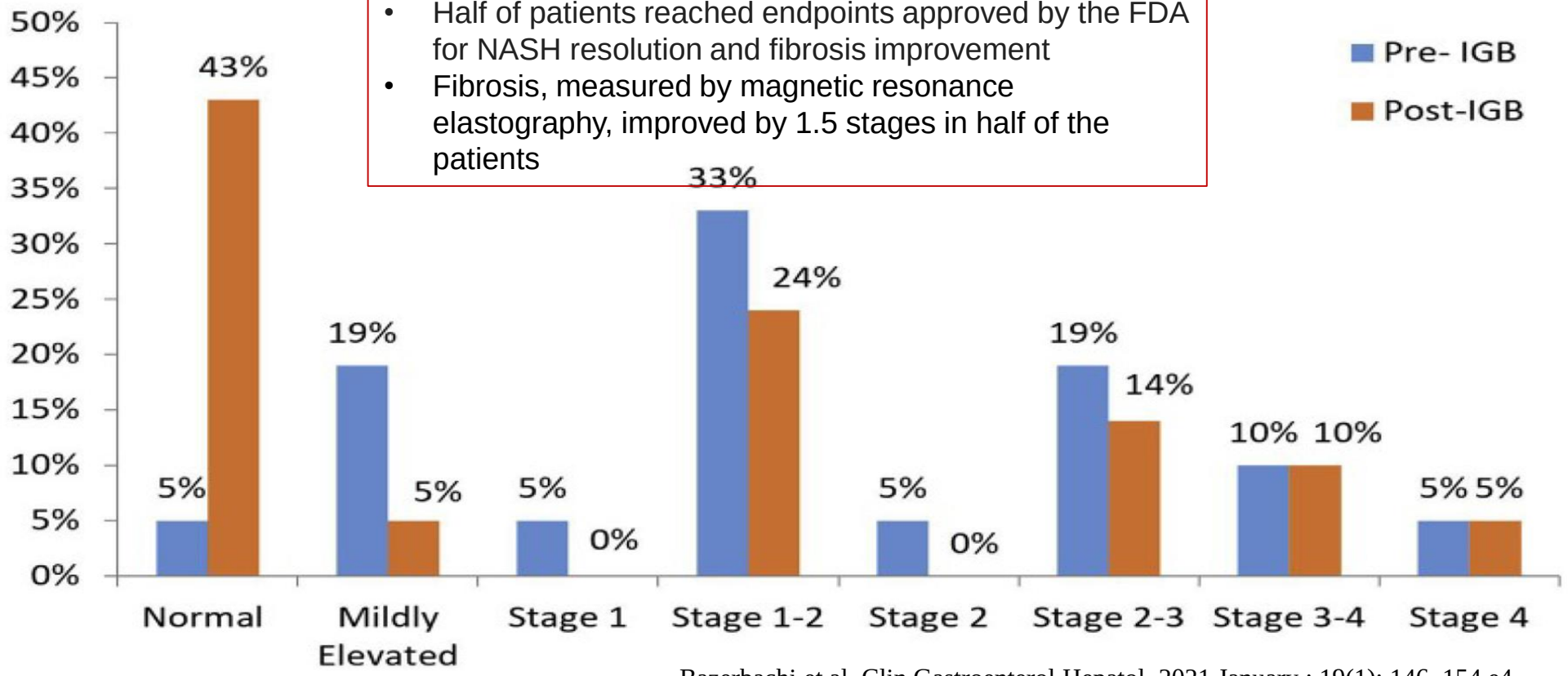
- Gastric Balloon
- Sleeve Gastroplasty
- DMR (duodenal mucosal resurfacing)
- Gastric emptying
- Duodenal-jejunal bypass sleeves

Bariatric Surgery

- Rou-en-Y Gastric by-pass
- Sleeve Gastroplasty

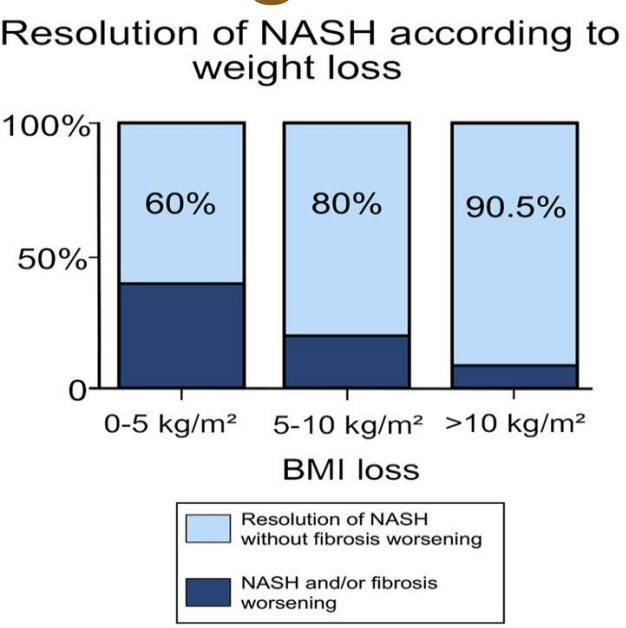
Intragastric Gastric Balloon Placement induces Significant Metabolic & Histologic Improvement in patients with NASH

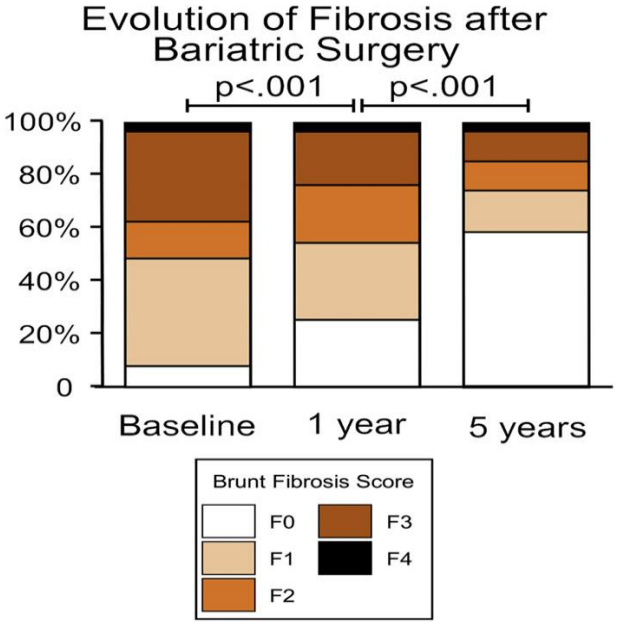
- Half of patients reached endpoints approved by the FDA for NASH resolution and fibrosis improvement
- Fibrosis, measured by magnetic resonance elastography, improved by 1.5 stages in half of the patients

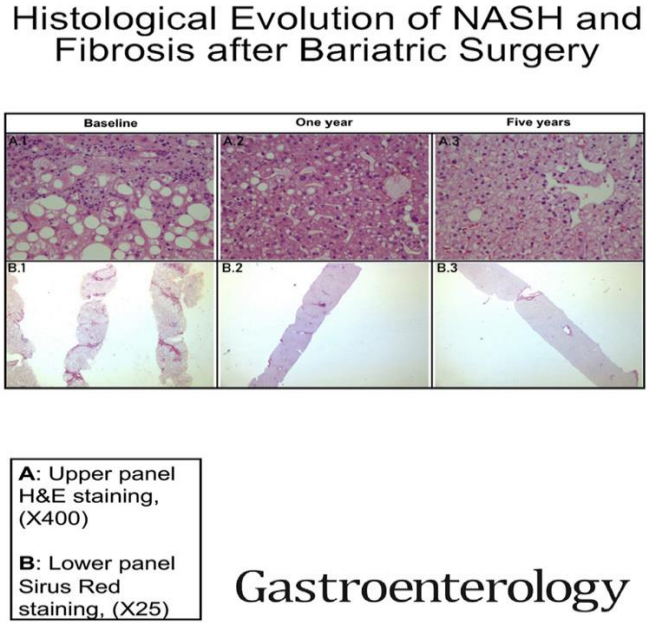


Bazerbachi et.al. Clin Gastroenterol Hepatol. 2021 January ; 19(1): 146–154.e4.

Bariatric Surgery Provides Long-Term Resolution of NASH and Regression of Fibrosis







NASH was resolved, without worsening fibrosis, in samples from 84% of patients (n = 64; 95% confidence interval,73.1%-92.2%)

main surgical procedure was gastric bypass (66.1%)

In a subgroup analysis comparing gastric banding to gastric bypass, gastric bypass was significantly more effective in achieving the primary endpoint p=.03.

Lassailly et al. Gastroenterology Volume 159, Issue 4, October 2020, Pages 1290-1301.e5.

Bariatric Surgery Reduces Cancer Risk in Adults with NAFLD & Severe Obesity

- Retrospective cohort study of 18 - 64 years old newly diagnosed NAFLD patients with severe obesity between 2007 and 2017
- Total of 98,090 patients were included → 33,435 (34.1%) received bariatric surgery

Table 3. Hazard Ratios of Obesity-Related Cancer in Patients With Versus Without Bariatric Surgery,[a] Adults With Nonalcoholic Fatty Liver Disease and Severe Obesity, 2008–2017 (N = 98,090)

Type of obesity-related cancer	Events, No.	HR (95% CI)	
		Unadjusted	Adjusted[b]
Any obesity-related cancer	911	0.62 (0.54–0.72)	0.65 (0.56–0.75)
Colon cancer	116	0.64 (0.41–0.96)	0.66 (0.42–1.00)
Rectal cancer	15	0.41 (0.09–1.31)	0.44 (0.10–1.37)
Postmenopausal breast cancer	131	0.75 (0.51–1.08)	1.08 (0.74–1.54)
Hepatocellular carcinoma	49	0.32 (0.15–0.65)	0.48 (0.24–0.89)
Kidney cancer	120	0.81 (0.54–1.18)	0.90 (0.60–1.32)
Esophageal cancer	16	0.31 (0.07–1.01)	0.33 (0.06–1.18)
Cancer of the gastric cardia	8	0.30 (0.02–1.70)	0.46 (0.03–2.44)
Gallbladder cancer	4	1.04 (0.11–9.33)	0.99 (0.05–12.58)
Pancreatic cancer	44	0.35 (0.15–0.73)	0.46 (0.21–0.93)
Ovarian cancer	74	0.70 (0.42–1.14)	0.70 (0.41–1.15)
Endometrial cancer	135	0.45 (0.30–0.66)	0.49 (0.31–0.73)
Thyroid cancer	143	0.69 (0.47–0.98)	0.61 (0.41–0.89)
Multiple myeloma	50	0.40 (0.19–0.77)	0.33 (0.14–0.69)
Meningioma	6	0.66 (0.09–3.45)	0.52 (0.05–2.90)

[a] Bariatric surgery status included as a time-dependent covariate.
[b] Using IPTW adjusted for age, health insurance type, region of residence, year of NAFLD diagnosis, sex, smoking, asthma, obstructive sleep apnea, obesity hypoventilation syndrome, osteoarthritis, diabetes, hypertension, cardiovascular disease, dyslipidemia, chronic kidney disease, congestive heart failure, peripheral vascular disease, and cerebrovascular disease.

Bariatric surgery significantly decreases the risk of any cancer and obesity-related cancer in individuals who copresent with severe obesity and NAFLD, especially those with NAFLD-cirrhosis.

Variable	Participants, No.	cancer		Obesity-related cancer[b]		
		Events, No.	HR (95% CI)		Events, No.	HR (95% CI)	
			Unadjusted	Adjusted[c]		Unadjusted	Adjusted[c]
Cirrhosis[d,e]							
No	95,235	2695	0.77 (0.71–0.84)	0.83 (0.76–0.90)	859	0.64 (0.55–0.74)	0.67 (0.57–0.78)
Yes	2855	128	0.50 (0.33–0.73)	0.52 (0.34–0.77)	52	0.39 (0.19–0.71)	0.32 (0.15–0.64)

Rustgi V et.al. Gastroenterology 2021;161:171–184

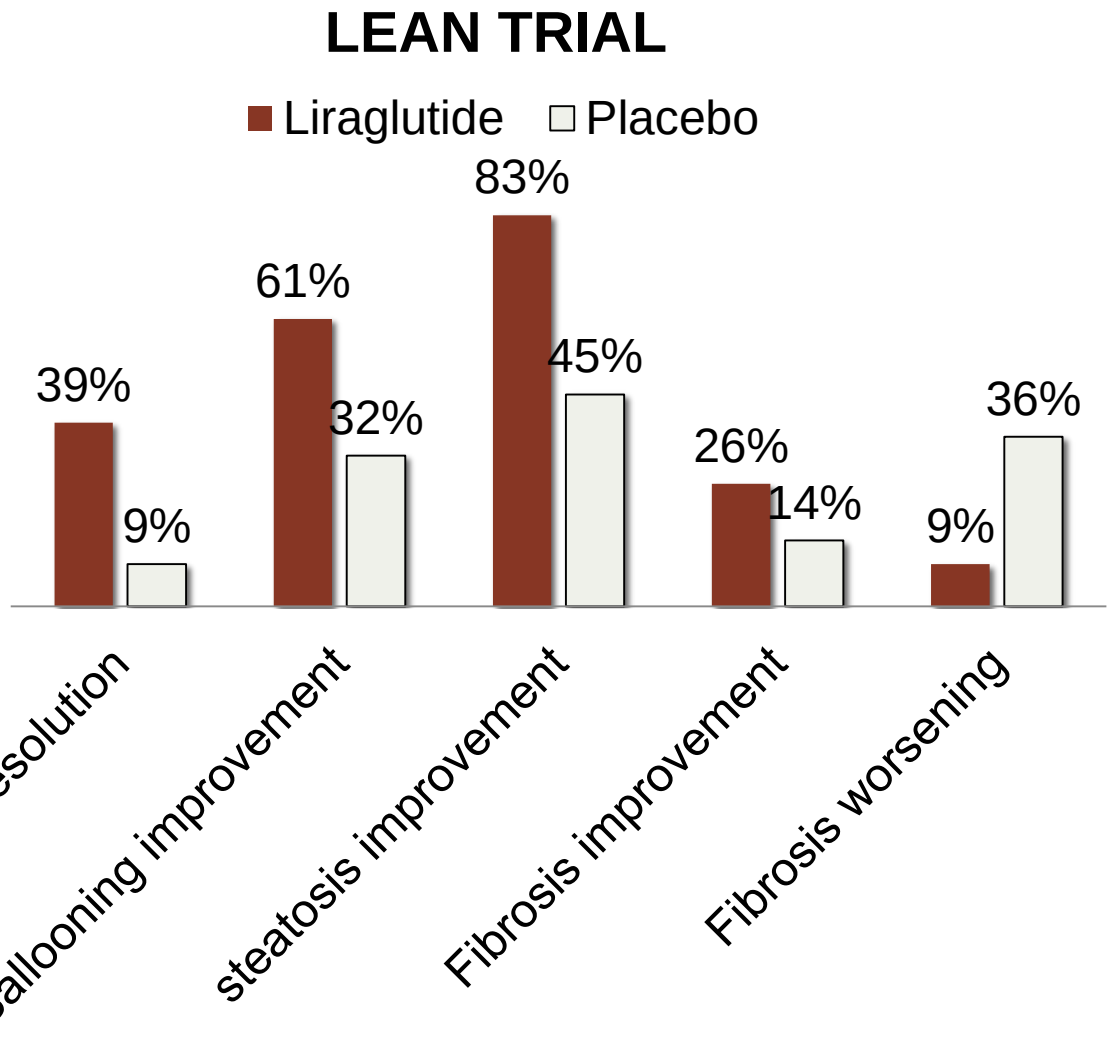
PATIENTS WITH T2DM

- GLP-1 agonist –proven CV benefit
- SGLT 2 inhibitor – proven HF and CKD benefit

American Diabetes Association. Diabetes Care 2019;42(suppl 1):S90

Glucagon-Like Peptide-1 (GLP-1) Agonists (Liraglutide)

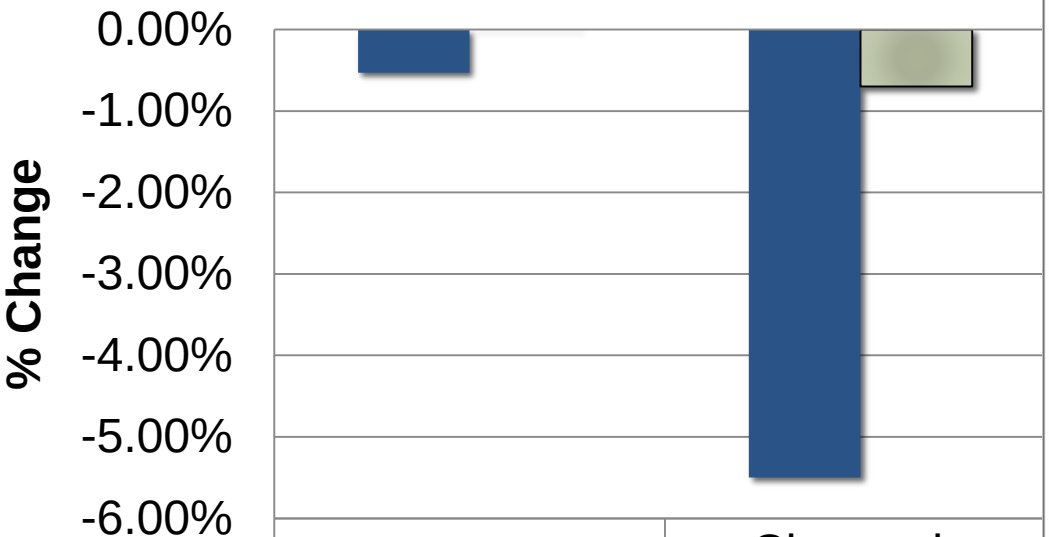
- Phase 2: LEAN Trial: RCT 52 pts (Histo proven NASH) – 1.8 mg/d Liraglutide SC or Placebo for 48 weeks.
- Primary Endpoint: resolution of NASH with no worsening of fibrosis at the end of the study
- 39% vs 9% relative risk 4.3 [95% CI 1,0–17,7]; *P* .019



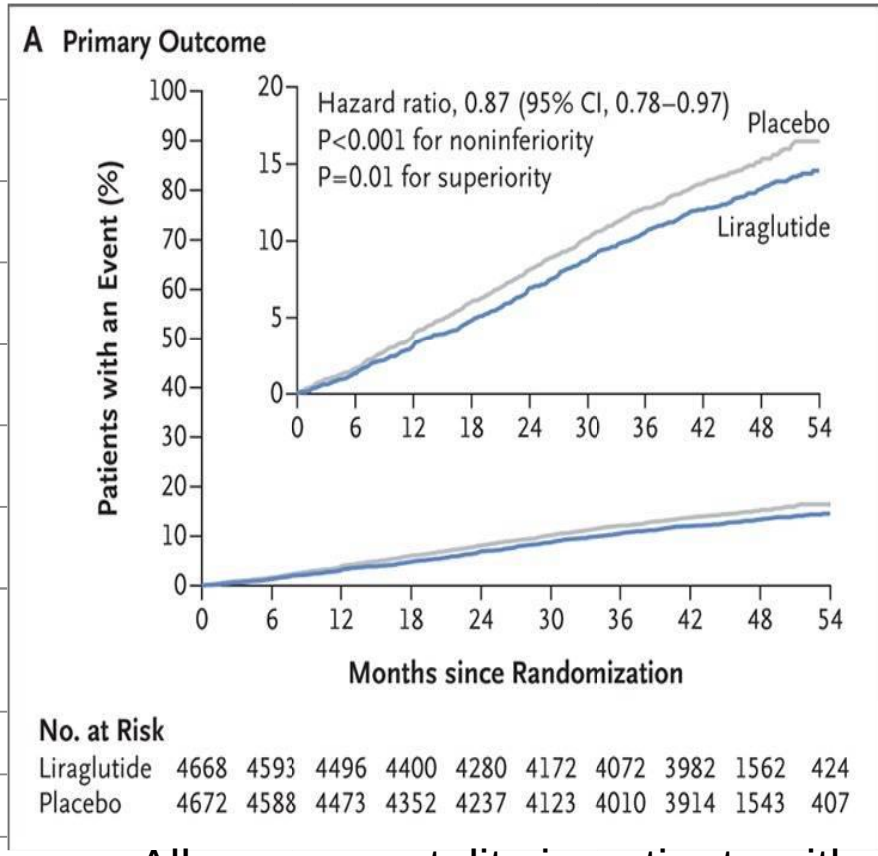
Armstrong MJ et al. Lancet 2016;387(10019):679–90.

Glucagon-Like Peptide-1 (GLP-1) Agonists (Liraglutide)

LEAN Trial



	HbA1C (%)	Change in weight (%)
Lraglutide	-0.53%	-5.5%
Placebo	0.00%	-0.7%

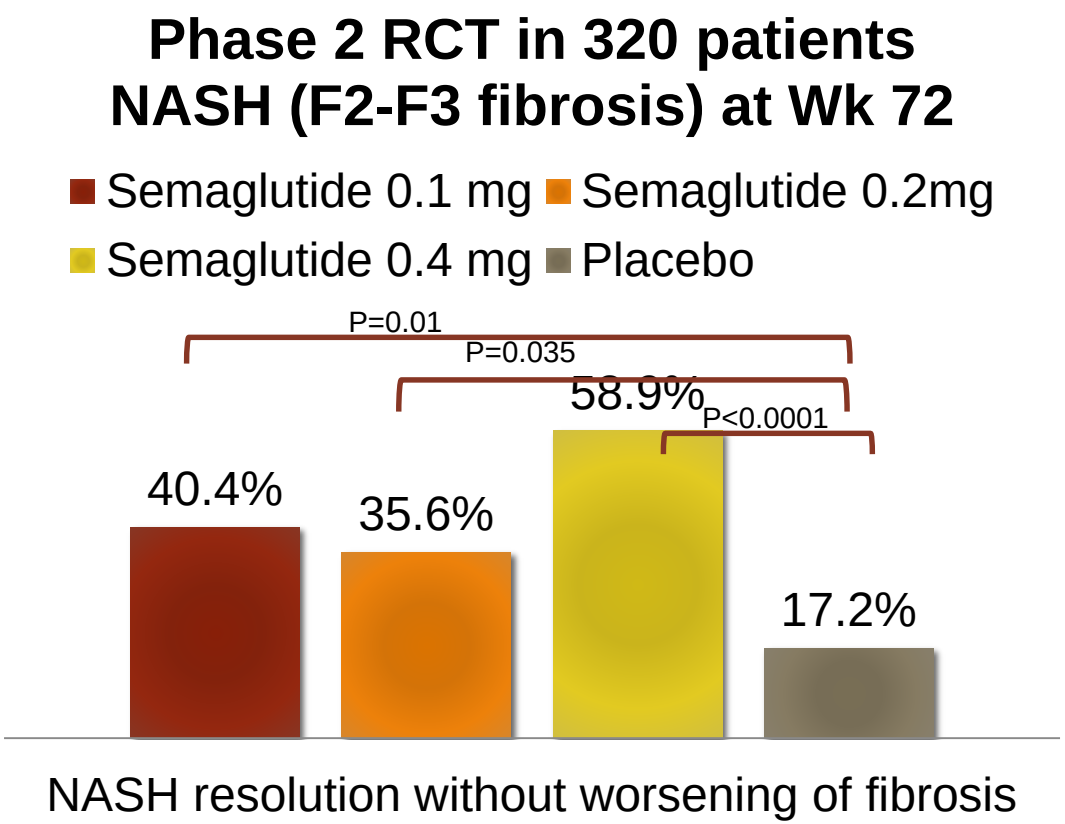


All cause mortality in patients with Type 2 DM

Armstrong MJ et al. Lancet 2016;387(10019):679–90.

Marso et al, N Engl J Med. 2016 Jul 28;375(4):311-22

Semaglutide (GLP1 Agonist)



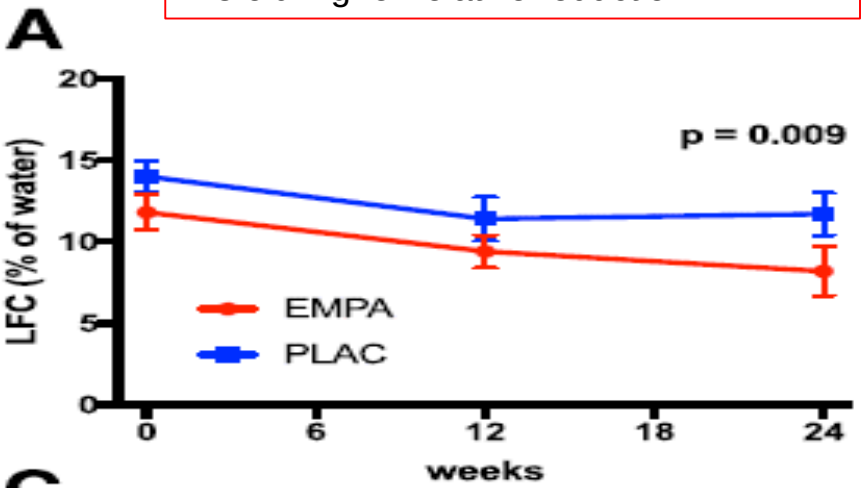
- Less fibrosis progression
- Dose dependent improved in AST, ALT,GGT
- Weight loss up to 12.5% vs 0.6% placebo
- Reduced HbA1C

Newsome P et al. N Engl J Med. 2021 Mar 25;384(12):1113-1124

Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitor-Empagliflozin in NAFLD with type 2 DM

Patients with T2D (n=84) (HbA_{1c} 6.6±0.5% [49610 mmol/mol], known disease duration 39 ± 27 months) were randomly assigned to 24 weeks of treatment with 25 mg PO daily EMPA or placebo

2.3fold higher relative reduction in EMPA



LFC (liver fat content)- measured by volume-selective proton MRS (1H-MRS)
N = 42 EMPA vs N= 42 Placebo

At 24 weeks, a placebo-corrected absolute (21.8% [23.4, 20.2]; P 5 0.02) and relative decrease in LFC (222%; P 5 0.009) was observed

Kahl et al. Diabetes Care 2020;43:298–305

Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitor-Empagliflozin in NAFD without type 2 DM

Double-blind, placebo-controlled clinical trial, participants with NAFLD were randomized to empagliflozin (10 mg/day) (n = 43) or placebo (n = 47) for 24 weeks
Hepatic steatosis and fibrosis were assessed using transient elastography to measure the controlled attenuation parameter (CAP) and liver stiffness measurement (LSM).
primary outcome →the change in CAP score at 24 weeks

	Empagliflozin ($n^{\S}$)			Placebo ($n^{\S}$)			P value^{+}
	Enrollment	EOT	P value	Enrollment	EOT	P value	
CAP score	306.5 (24.0)	277.7 (31.9)	0.001	304.6 (27.2)	281.2 (34.7)	0.001	0.396
S1 > 302 dB/m (%)	41.9	16.3	0.010	29.8	23.4	0.001	0.035
S2 > 331 dB/m (%)	0	0		2.1	0		
S3 > 337 dB/m (%)	11.6	0		12.8	4.3		
S ≥ S1	53.5	16.3		44.7	27.7		
LSM, kPa	6.03 (1.40)	5.33 (1.08)	0.001	5.56 (1.05)	5.35 (0.96)	0.139	0.039

- Moderate intensity physical activity

3–6 times the metabolic equivalent task (METs) for at least 45 min without interruption x > 3times/week

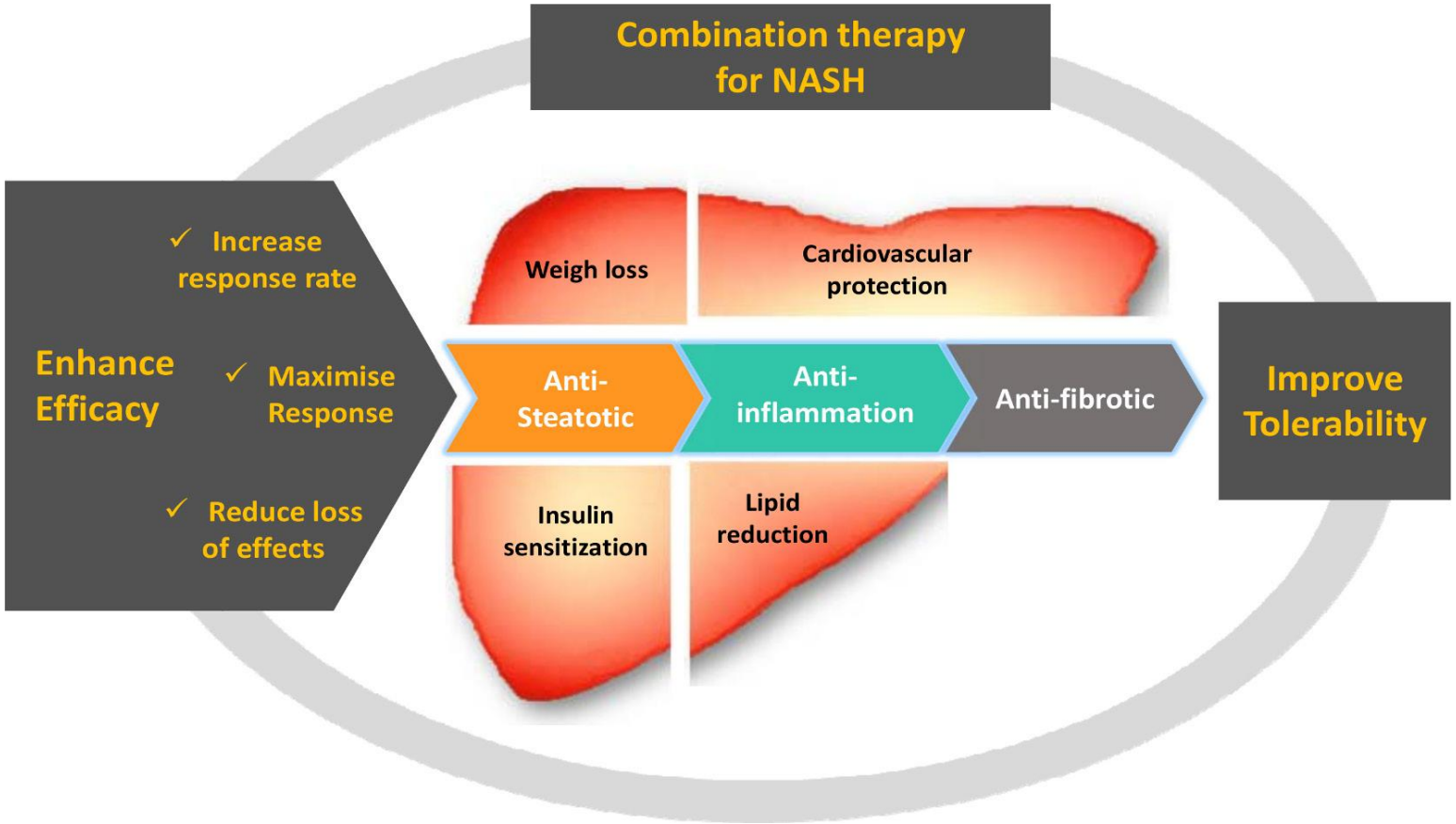
- Standard dietary advice as well

Taheri H et al. Adv Ther (2020) 37:4697–4708

PHASE III CLINICAL TRIALS

- Obeticholic acid – FXR agonist
- Lanifibranor – PPAR agonists
- Resmetirom – THR-beta Agonists
- Aramchol –a partial inhibitor of hepatic stearoyl-CoA desaturase (SCD1)/SCD-1 Modulator
- Semaglutide – GLP=1 (injectable)

Combination Therapy for NASH- Rationale, Opportunities and Challenges



Dufour J-F, et al. Gut 2020;0:1–8. doi:10.1136 gutjnl-2019-319104

Case 3 - Answer

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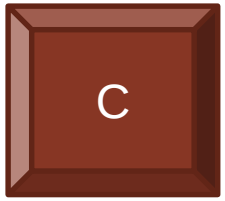
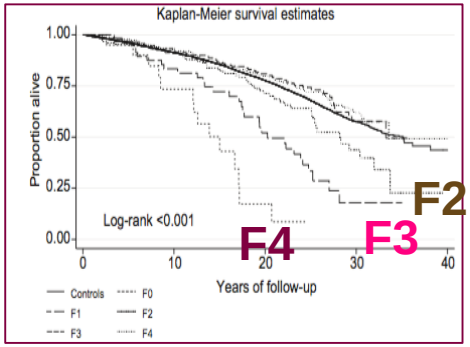
What is the most beneficial therapy ?

A. Phlebotomy
B. Pioglitazone
C. Weight loss
D. Prednisone



Take Home Message



Fatty Liver

- Obese
- DM
- metabolic
- PCOS

Stage (Bx, NITs)

- DM- GLP-1, SGLT2
- Weight loss Tx

(Drug, endoscope/bariatric)

Biopsy

FIB4>2.67
NFS>0.676

ELF
Pro C

VTCE>13
MRE>4

Therapies

Combined

Resolution of NASH	Improvement of Fibrosis ≥1
1. Resmetirom 2. Lanifibranor 3. Semiglutide 4. Amarchol	1. Obeticholic acid 2. Lanifibranor 3. Semiglutide

Thank you!