
2019
NCSCG
5TH ANNUAL
LIVER SYMPOSIUM
December 7, 2019 | San Francisco, CA

NASH: Current Treatment Options vs. Clinical Trials

7 December, 2019

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Disclosures

- None

Overview

- NAFLD Epidemiology
- Defining and identifying risk
- NASH therapies currently available
- NASH clinical trials that are ongoing
- Making the right decision

NASH: Current Treatment Options vs. Clinical Trials

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Corn, HFCS and the obesity epidemic

$2,000,000,000

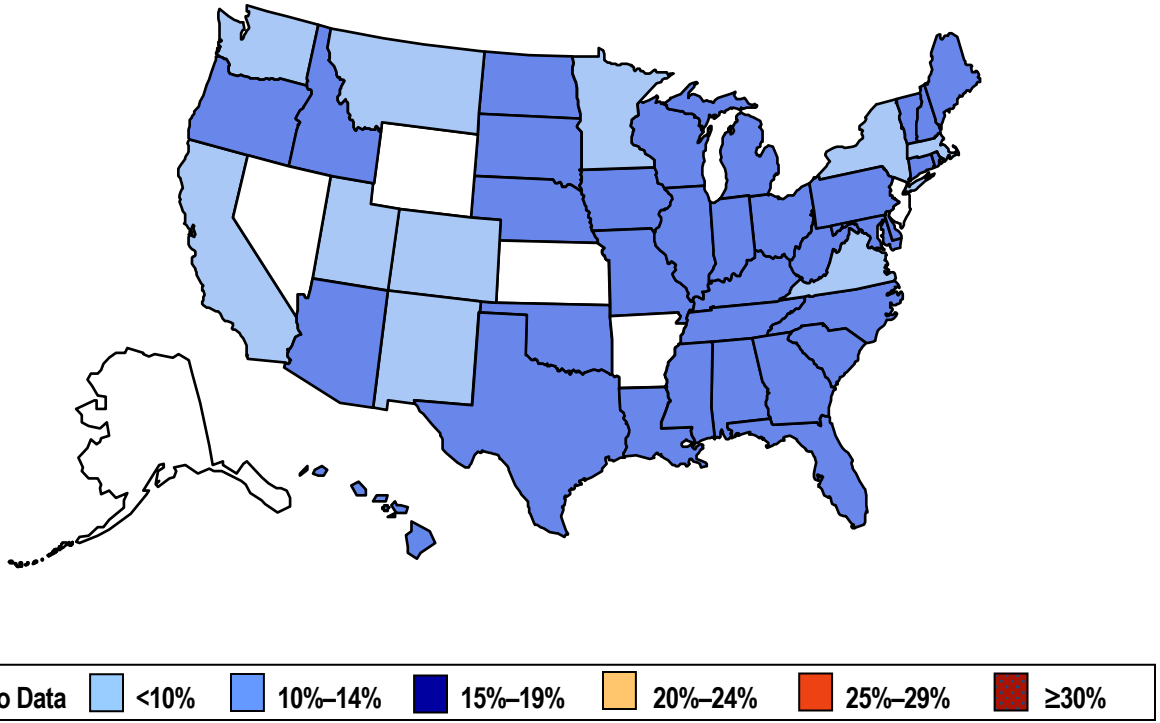
FDA

APPROVED

(“Generally Recognized As Safe” in 1976)

Obesity Trends Among U.S. Adults, 1990

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Source: Behavioral Risk Factor Surveillance System, CDC

Obesity Trends Among U.S. Adults, 2010

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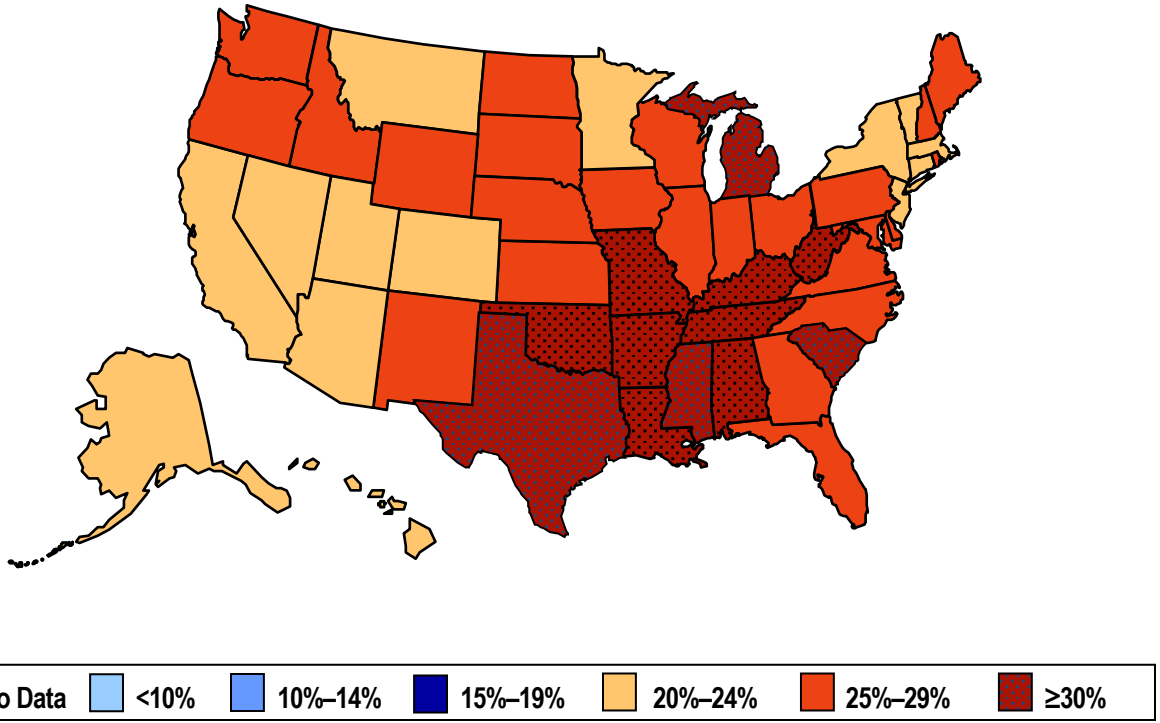
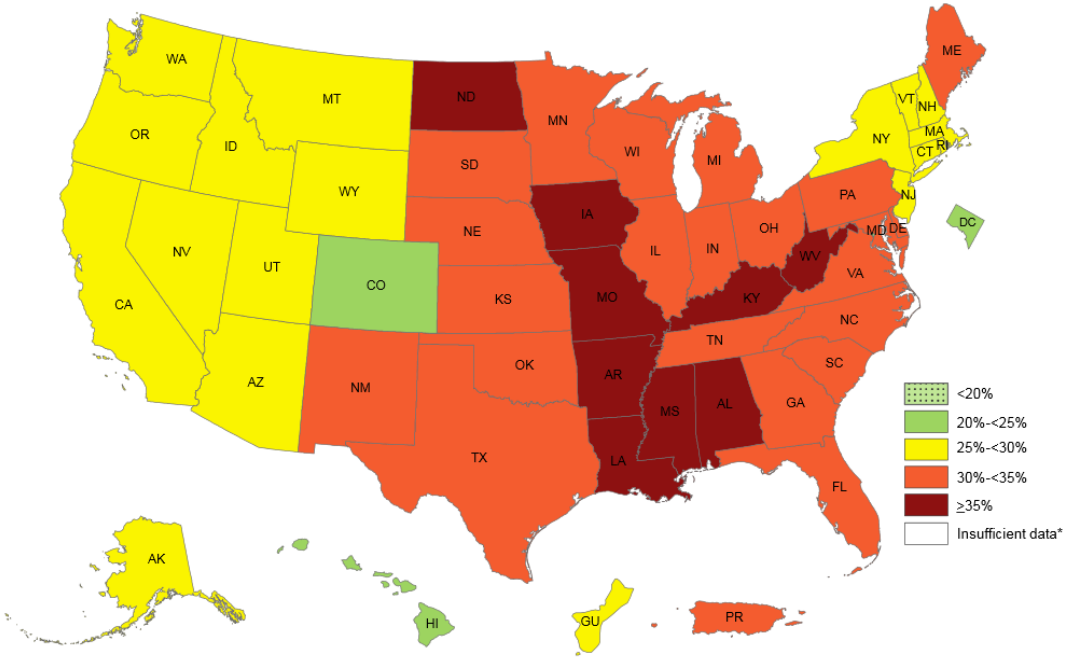


Source: Behavioral Risk Factor Surveillance System, CDC

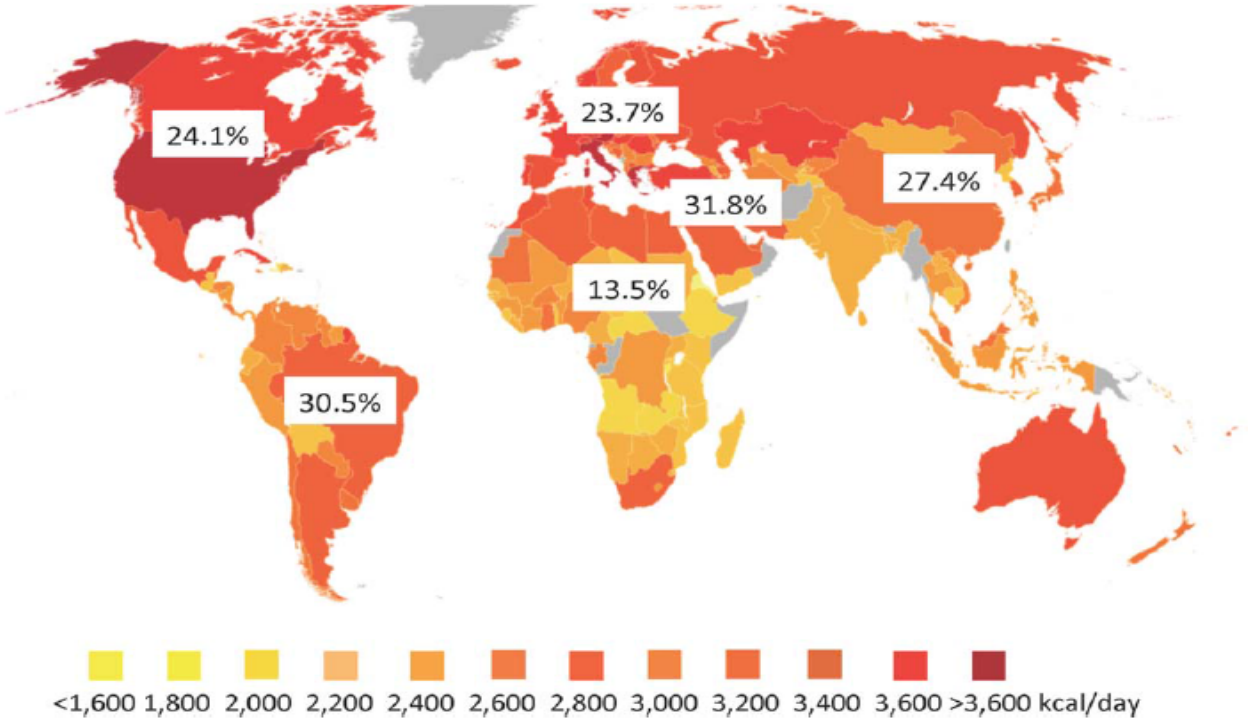
Obesity Trends Among U.S. Adults, 2018

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Source: Behavioral Risk Factor Surveillance System, CDC

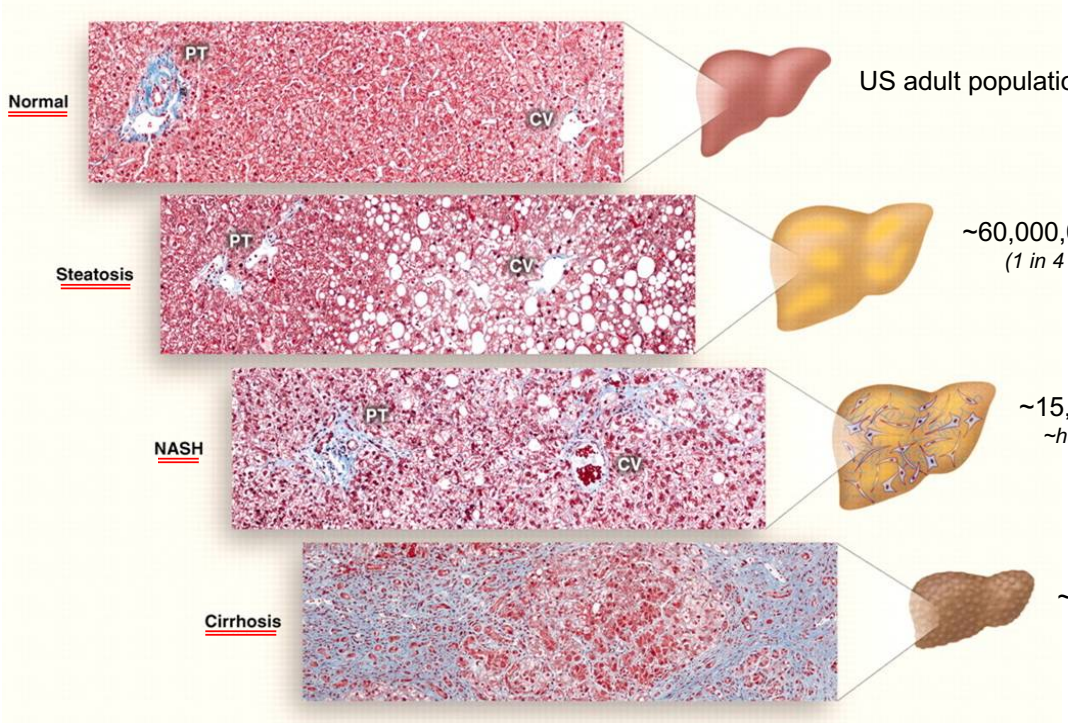
Worldwide Prevalence of NAFLD



Geographic variation in the daily energy availability per capita and in the prevalence of NAFLD

Rinella M and Charlton M, Hepatology 2016

NAFLD Epidemiology in the United States



US adult population ~250,000,000

~60,000,000 have NAFLD
(1 in 4 American adults)

~15,000,000 have NASH
~half of whom have ≥F2

~600,000 have NASH-related cirrhosis
~half are unaware of diagnosis

Cohen JC, Science 2011; Ong JP, Clin Liver Dis 2007

Prevalence of Lean NAFLD

- Fatty Liver Index and Forns Index used to identify NAFLD and advanced fibrosis among 102,344 French adults.
- 18.2% had NAFLD, including:
  - 1.9% Lean (BMI <25), 36.9% Overweight (BMI 25-30) and 61.2% Obese (BMI >30)
- Lean NAFLD subjects were more often male, had higher ALT, had more advanced fibrosis and had higher prevalence of tobacco and alcohol use

	Lean + NAFLD	Overweight + NAFLD	Obese + NAFLD	Lean No NAFLD
>10 pack years smoking	43.2%*	35.5%	30.6%	14.4%
>10g alcohol per day	38.2%*	34.5%	30.6%	22.6%

*p<0.05

Nabi O, 2019 AASLD abstract 1188

NASH: Current Treatment Options vs. Clinical Trials

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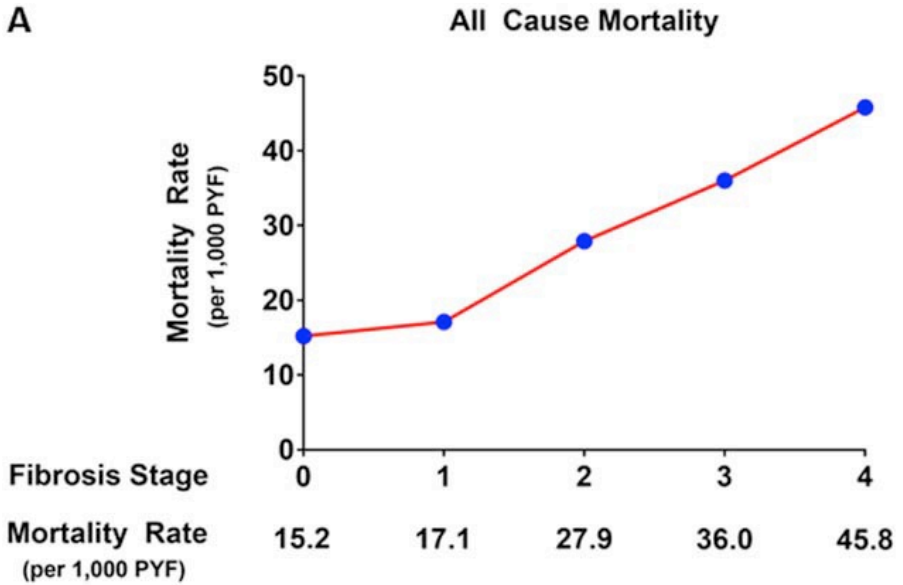
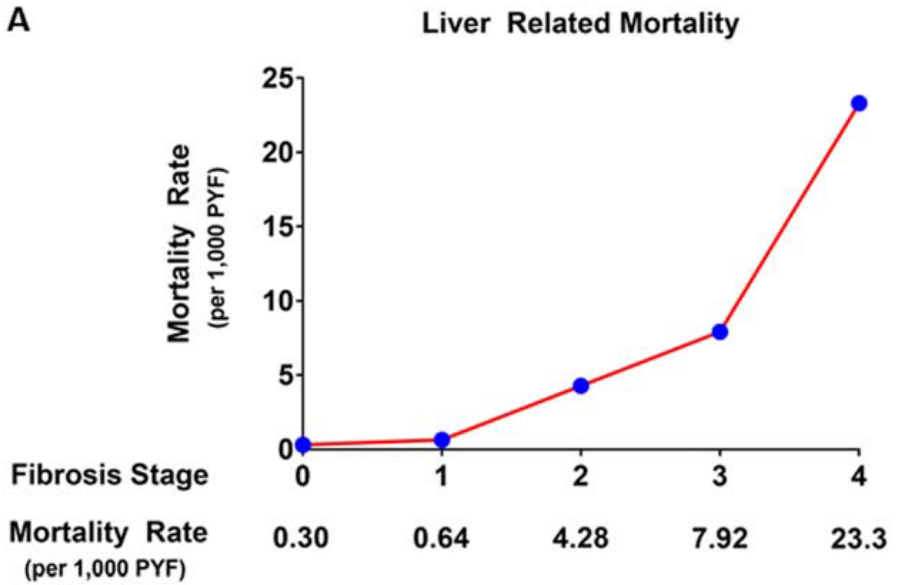
Defining and Identifying Risk

- Fatty Liver Index (FLI):
  - $(e^{0.953*\log_e(\text{triglycerides})+0.139*\text{BMI}+0.718*\log_e(\text{ggt})+0.053*\text{waist circumference}-15.745}) / (1 + e^{0.953*\log_e(\text{triglycerides})+0.139*\text{BMI}+0.718*\log_e(\text{ggt})+0.053*\text{waist circumference}-15.745}) \times 100$
- Forns Index:
  - 7.811 - 3.131 x ln [platelet count (10^9/L)] + 0.781 x ln [gamma GT(IU/L)] + 3.467 x ln [age (years)] – 0.014 x [cholesterol (mg/dL)

Fibrosis and risk of mortality in NASH





Dulai PS, Hepatology 2017

Defining and identifying the risk of fibrosis in NAFLD

FIB-4

$$\frac{\textbf{Age} \times \textbf{AST}}{\textbf{Plt} \times \sqrt{(\textbf{ALT})}}$$

<1.30, NPV = 95% for ruling out F3-4

>3.25, PPV = 75% for ruling in F3-4

NFS

-1.65 + (0.037 x **age**) + (0.094 x **BMI**) + (1.13 x **IFG/DM**, yes=1, no=) + (0.99 x **AST/ALT** ratio) – (0.013 x **platelets**) – (0.66 x **alb**)

< -1.455, NPV = 92% for ruling out F3-4

> 0.675, PPV = 79% for ruling in F3-4

ALT correlates poorly with risk of fibrosis in NAFLD

- Predictors of NAFLD with fibrosis in 306 at-risk patients
  - Using NFS to define risk of advanced fibrosis, ALT was not significantly different between those at high risk (NFS >0.675) and those at low or indeterminate risk (NFS <0.675)
  - FIB-4 outperformed NFS in a real-world cohort of 48 NAFLD patients with fibrosis stage defined by transient elastography.

	Sensitivity	Specificity	PPV	NPV
NFS	16.7	88.9	33.3	76.2
FIB-4	16.7	97.2	66.7	77.8

(low + indeterminate risk vs. high risk for both tests; fibroscan cutoff for F3 was 10 kPa)

Janizcek, 2019 NCSCG post-AASLD symposium, poster presentation

Defining and Identifying Risk of Fibrosis in NAFLD

- 108 patients at a single center had biopsy and fibroscan within 1 year; risk factors for advanced fibrosis were identified:

	F0-2	F3-4	p-value
NFS	-0.9	-0.9	0.07
FIB-4	0.5	0.8	<0.0001
APRI	1.4	2.2	<0.0001
Plt	227	180.9	0.006
Na	139.8	138.7	0.004
BUN	15.6	14.1	0.048
AST	44.5	48.7	0.08
ALT	72.6	62.2	0.59

	F0-2	F3-4	p-value
Steatosis			0.66
0	14.6%	11.1%	
1	50%	40.7%	
2	23.2%	33.3%	
3	12.2%	14.8%	
Ballooning			0.08
0	47.5%	33.3%	
1	46.3%	48.1%	
2	6.1%	18.5%	

Galoosian A, 2019 AASLD abstract 1793
(Galoosian A, 2019 NCSCG post-AASLD symposium poster presentation)

Defining and Identifying Risk of Fibrosis in NAFLD

- Patients at risk for NASH with fibrosis may be under-recognized in the primary care setting.
  - Reviewed records of 9,452 patients seen at a primary clinic over 3 years
  - Included only diabetics over the age of 50 with ALT >40
  - Excluded those with ALT >400, other causes of acute or chronic liver disease
  - Of 89 patients identified, 15 (16.7%) were at high risk for NASH with advanced fibrosis based on NFS (>0.655)
  - 1 patient at low risk (NFS <-1.455) and 1 at high risk were referred to hepatology

Tran N, 2018 NCSCG post-AASLD symposium poster presentation

NAFLD Simulator (nafldsimulator.org)

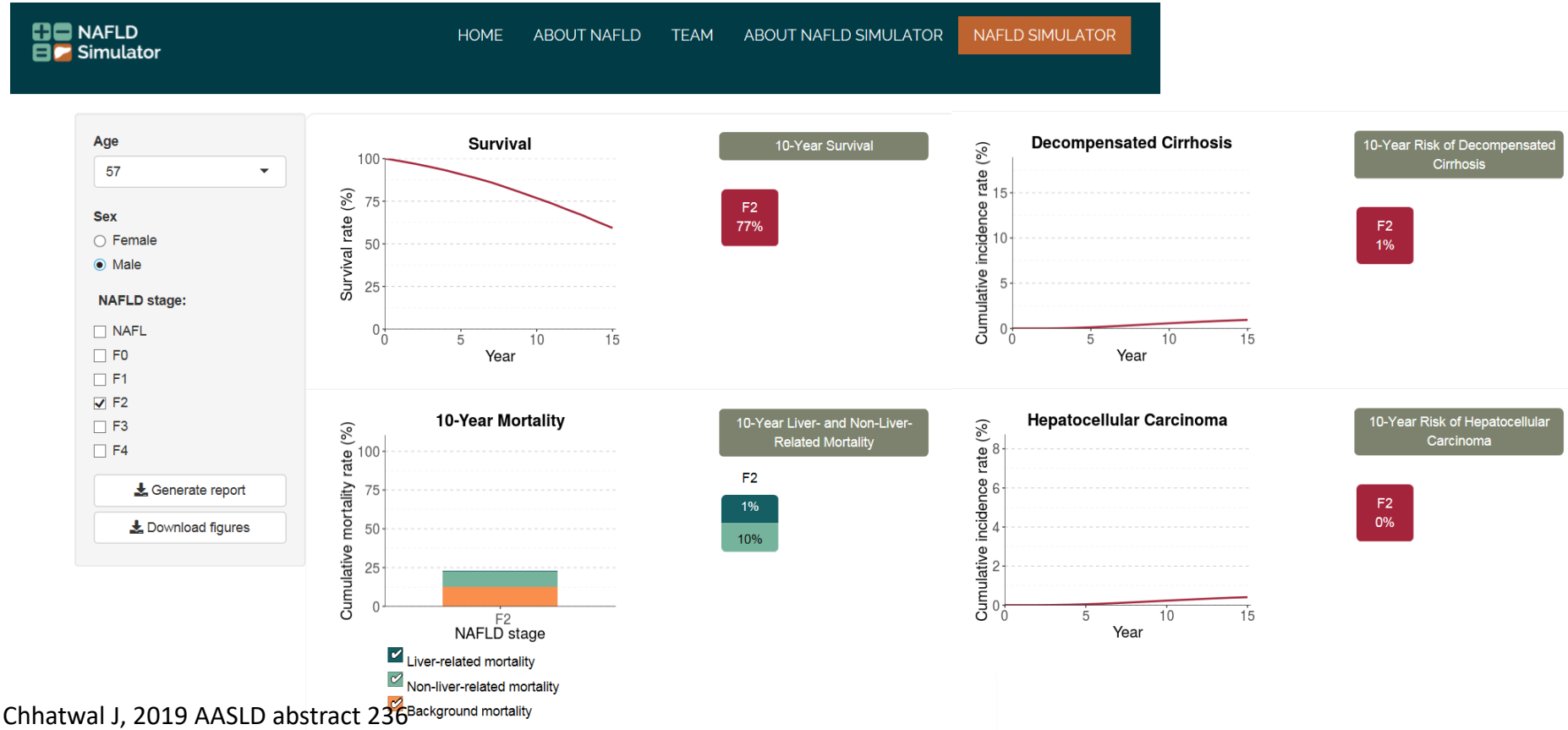
- Without any additional information, what can you tell these patients about their risk of cirrhosis, HCC and death?
  - 37F had NAFLD but no NASH or fibrosis on liver biopsy done for elevated liver enzymes.
  - 68M had NASH and bridging fibrosis on liver biopsy done after fibroscan suggested cirrhosis.

NAFLD Simulator

	10-year survival	10-year liver-related mortality	10-year all-cause mortality	10-year risk of decompensated cirrhosis	10-year risk of HCC
37F with NAFLD, no fibrosis	99%	0%	0%	0%	0%
68M with NASH, bridging fibrosis (F3)	40%	3%	42%	3%	1%

Chhatwal J, 2019 AASLD abstract 236

NAFLD Simulator



Chhatwal J, 2019 AASLD abstract 236

NASH: Current Treatment Options vs. Clinical Trials

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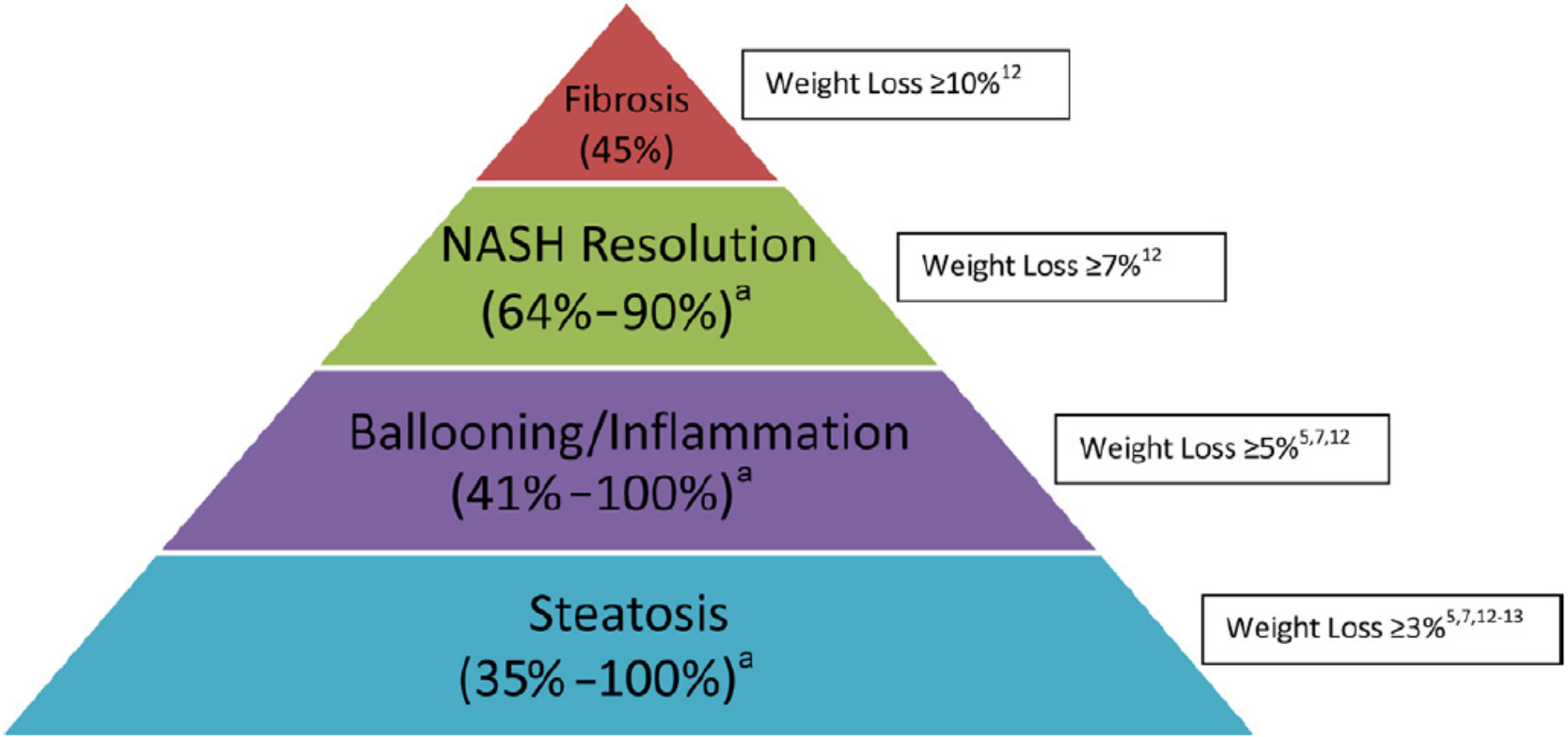
Weight loss for NAFLD



Hannah WN, Clin Liver Dis 2016

Weight loss surgery for NAFLD

- 35 of 868 French patients had peri-bariatric surgery bx 2004-2014 showing F3-4 and then follow-up liver biopsy (*fLB*) 6±3 years later.
- Only 19 patients (55%) saw resolution of F3-4

	Age	Diabetes resolution	Gastric Bypass	Time to *fLB*	Weight loss
Resolution of F3-4	49 y	50%	100%	7.5 y	23 kg
No resolution of F3-4	56 y	21%	69%	4.2 y	27 kg
(p-value for comparison)	0.031	0.09	0.014	<0.001	0.19

- Adjusting for age and sex, only type of surgery (REYGB) predicted resolution of advanced fibrosis

Pais R, 2019 AASLD abstract 62

TREATMENT OF NAFLD: BARIATRIC SURGERY

109 patients: 64.2% gastric bypass, 29.4% gastric band, 5.5% sleeve gastrectomy, 0.9% biliointestinal bypass

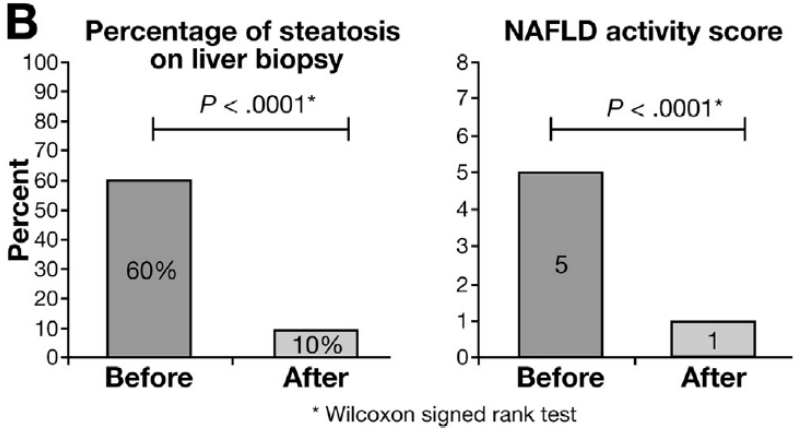


Figure 3. Change of histologic features 1 year after bariatric surgery. (*A*) Percentage of improvement in hepatocellular ballooning and in lobular inflammation 1 year after bariatric surgery. (*B*) Median of NAS and steatosis at baseline and at 1 year after surgery. *Wilcoxon signed rank test.

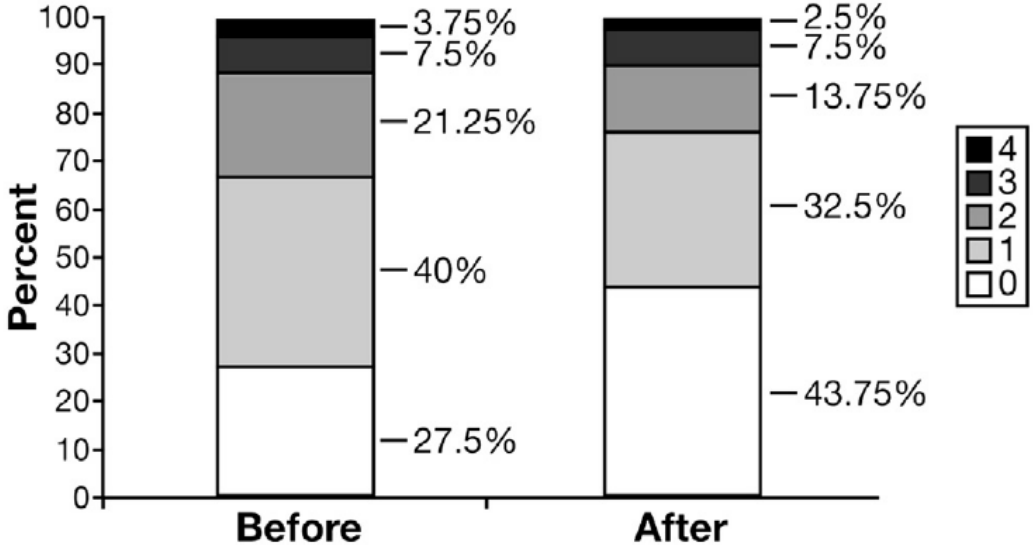


Figure 4. Distribution of fibrosis stage before and 1 year after

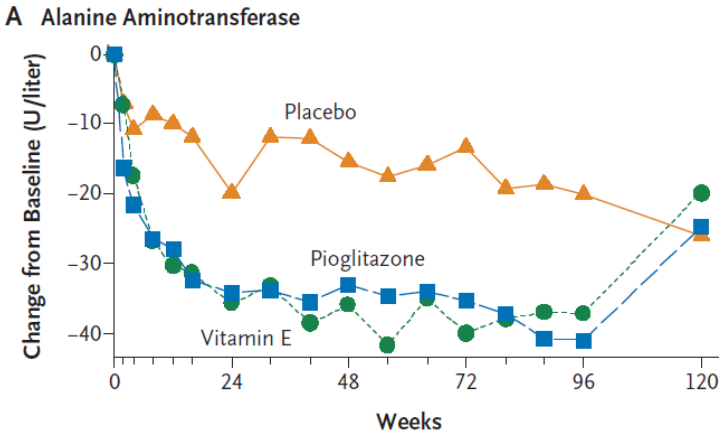
Labreuche J, Gastroenterology 2015;149:379-388.

Vitamin E for NAFLD

PIVENS

- 247 *non-diabetic* adults with NASH randomized to 96 weeks of:
  - Pioglitazone 30 mg daily (n=80) vs. Vitamin E 800 IU daily (n=84) vs. Placebo (n=83)
- Compared to placebo, both Vitamin E and pioglitazone were associated with NASH improvement (NAS)
  - ***Neither lowered fibrosis***

	placebo	Vitamin E	Pioglitazone	p (Vit E v. placebo)	p (Pioglit. v. placebo)
NAS	-0.5	-1.9	-1.9	<0.001	<0.001
Fibrosis score	-0.1	-0.3	-0.4	0.19	0.10

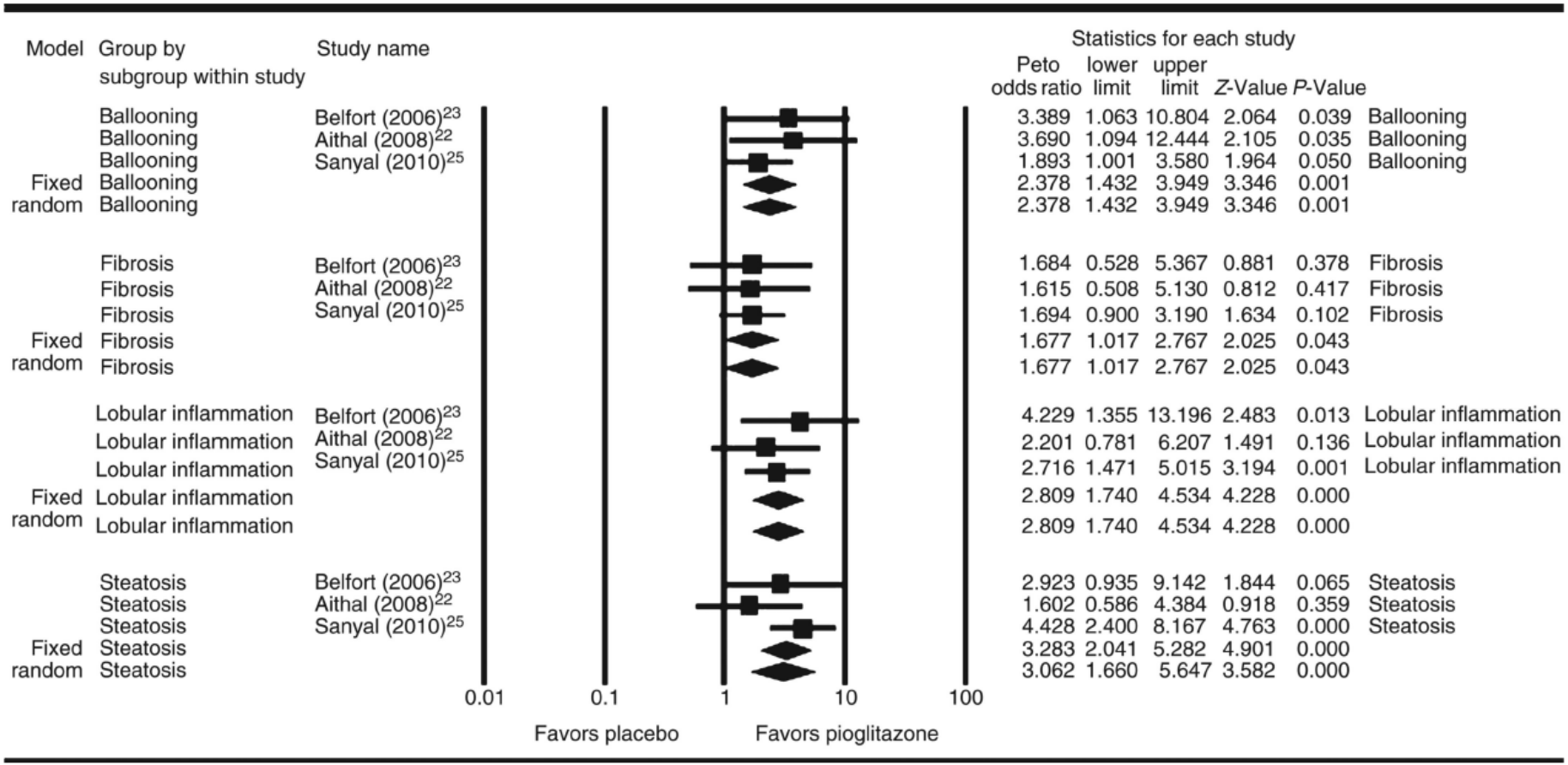


Sanyal AS, N Engl J Med 2010

Pioglitazone for NAFLD

- Meta analysis of 4 RCT's comparing TZD's to placebo for NASH
  - Compared to placebo, TZD's improved steatosis, inflammation and ballooning but not fibrosis
  - TZD's also associated with 3.99 kg weight gain and 0.73 point BMI increase
- 3 of the trials specifically compared pioglitazone to placebo for NASH
  - Compared to placebo, pioglitazone improved steatosis, inflammation, ballooning **AND fibrosis**

Boettcher E, Aliment Pharmacol Ther 2012



Boettcher E, Aliment Pharmacol Ther 2012

R-Pioglitazone for NAFLD

- Pioglitazone associated with NASH resolution in an RCT (PIVENS) and with reduction in fibrosis in a meta analysis, but is associated with weight gain
- In preclinical models, the *R*-stereoisomer of pioglitazone PXL065 exhibited NASH efficacy with little or no weight gain.
- 7 days of PXL065 at 3 doses compared to pioglitazone 45 mg daily lead to an *R*- to *S*-pio ratio 3 times higher with PXL065 and decrease in active metabolites by ~50%
- A phase 1b study is planned to explore safety, tolerability and pharmacokinetics.

Bolze S, 2019 AASLD abstract 2135

Liraglutide for NAFLD

- Liraglutide (GLP-1 RA, increases insulin, decreases glucagon, delays gastric emptying).
- LEAN: 52 adults (17 diabetic) randomized to 1.8 mg liraglutide (n=26) vs. placebo (n=26) for 48 weeks
  - Paired biopsies in 23 (liraglutide) and 22 (placebo)

Armstrong MJ, Lancet 2016

Liraglutide for NAFLD

	Liraglutide (n=23)	Placebo (n=22)	p-value	Relative Risk
NASH resolution	9 (39%)	2 (9%)	0.019	4.3 (1.0-17.7)
Ballooning Improvement	14 (61%)	7 (32%)	0.05	1.9 (1.0-3.8)
Fibrosis Worsening	2 (9%)	8 (36%)	0.04	0.2 (0.1-1.0)
Fibrosis Improvement	6 (26%)	3 (14%)	0.46	1.9 (0.5-6.7)

- NASH resolution: disappearance of ballooning with no worsening of fibrosis

Armstrong MJ, Lancet 2016

Duodenal Mucosal Resurfacing for NAFLD

- Hyperalimentation can lead to hypertrophy of the duodenal mucosa, exaggerated metabolic signaling in response to food and subsequent increases in inflammation, insulin resistance and hepatic steatosis.
- DMR uses a saline-lift & circumferential hydrothermal catheter to ablate of up to 10 cm of duodenal mucosa.
- 11 sites (9 EU, 2 Brazil) randomized 108 patients to DMR (56) or sham (52)
  - 39 DMR / 32 sham using only EU patients in mITT analysis (non-homogeneity in Brazil)
  - Outcomes assessed at 12 and 24 weeks

Bergman JJGHM, 2019 AASLD abstract LO2

Duodenal Mucosal Resurfacing for NAFLD

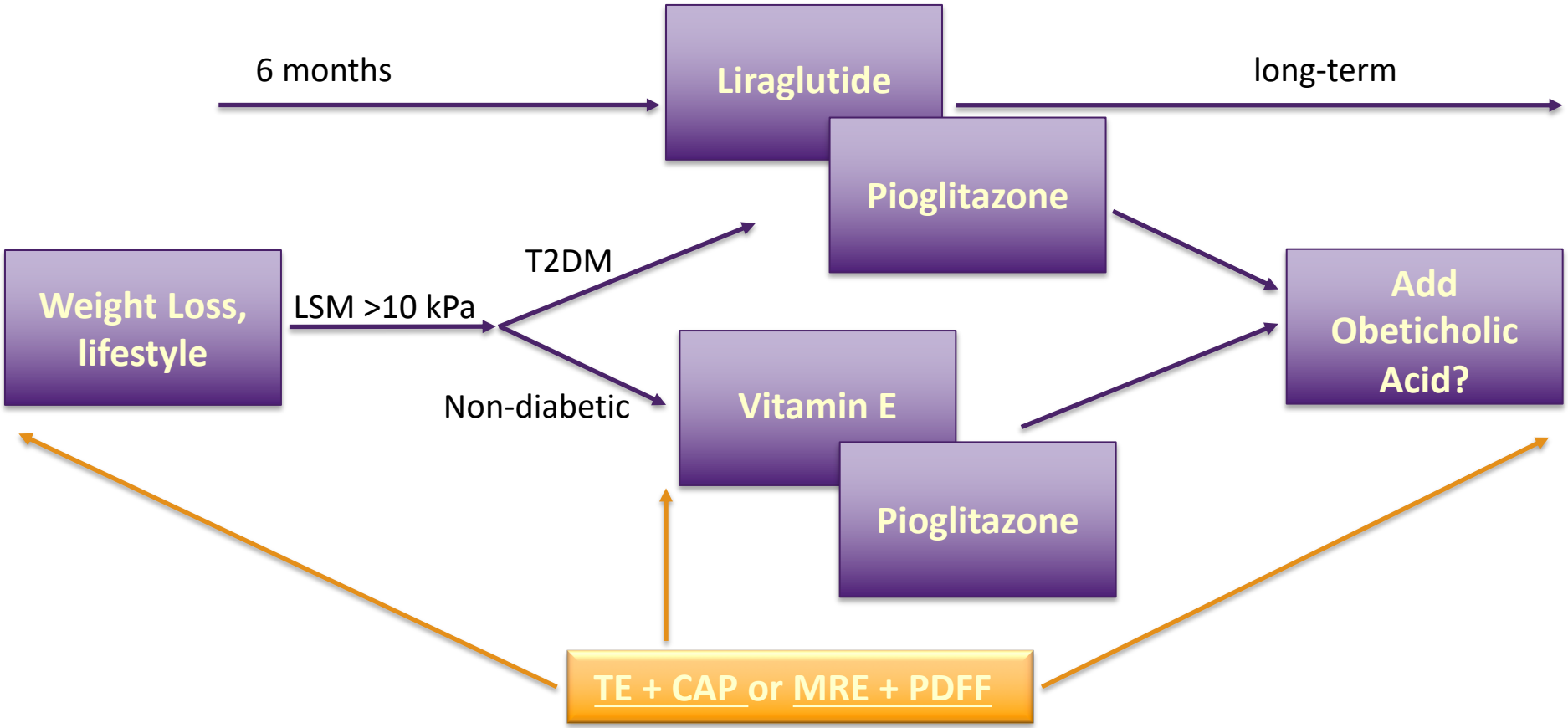
Table. Other Key Hepatic and Glycemic Study Findings

Hepatic Parameters	DMR (N = 39)	Sham (N = 36)	*P* value
Absolute change in liver MRI-PDFF from baseline at 12 weeks, %[a]	–5.4	–2.4	<0.05
Relative change in liver MRI-PDFF from baseline at 12 weeks, %[a]	n = 30 –32.1	n = 27 —18.1	<0.05
Weight change from baseline at 24 weeks, kg	n = 38 –2.4	n = 34 –1.4	<0.05
Liver MRI-PDFF at 12 weeks, n (%)[a] Reduction > 30%	16 (53)	6 (22)	<0.05
Glycemic Parameters			***P* value**
HbA1c change from baseline at 24 weeks, % (mITT)	–0.6	–0.3	<0.05
HbA1c change from baseline at 24 weeks, % (PP)	-0.8	-0.3	<0.05
Reduction in HbA1c, n (%) ≥ 0.5% at 24 weeks ≥ 0.75% at 24 weeks <7% at 24 weeks	 21 (60) 18 (51) 10 (29)	 13 (35) 10 (29) 3 (9)	 <0.05 >0.05 <0.05
FPG change from baseline at 12 weeks, mg/dL Mean	-40	-17	<0.05
Patients with baseline FPG ≥180 mg/dL HbA1c, mean % change at 12 weeks FPG, mean mg/dL change at 12 weeks	n = 19 –1.4 –75	n = 21 –0.4 –26	 <0.05 <0.05
HOMA-IR change from baseline at 24 weeks	n = 33 –1.3	n = 25 –0.4	<0.05

Median data are presented, unless otherwise noted.
[a]Data from patients with baseline liver MRI-PDFF >5%.
DMR = duodenal mucosal resurfacing; FPG = fasting plasma glucose; HbA1c = hemoglobin A1c; HOMA-IR; homeostatic model assessment of insulin resistance; mITT = modified intent to treat; MRI-PDFF = magnetic resonance imaging proton density fat fraction; PP = per-protocol.

Bergman JJGHM, 2019
AASLD abstract LO2

Treatment of NAFLD: Why wait?



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NASH phase 3 Clinical Trials

Drug	Mechanism	Actual Study Start date	Estimated Primary Completion Date	Estimated Study Completion Date	Estimated Enrollment
Obeticholic Acid	FXR agonist	September 2015	October 2022	October 2022	2,480
Elafibranor	PPAR-α/δ agonist	March 2016	December 2021		2,000
Cenicriviroc	CCR2/5 agonist	4/20/17	10/14/21	10/28/28	2,000
Resmitirom	TR-β agonist	3/28/19	6/30/21	3/31/24	2,000
Aramchol	SCD1 modulator	9/23/19	June 2022	December 2024	2,000
~~*Selonsertib*~~	~~*ASK-1 inhibitor*~~	~~*2/13/17*~~	~~*closed 6/12/19 due to lack of efficacy*~~		~~*808 (actual)*~~

Obeticholic Acid for NAFLD

10 mg vs. placebo

- Fibrosis improvement with no worsening of NASH in:
  - F2-3 (EASL 2019)
  - F1-3 (AASLD 2019)

25 mg vs. placebo

- Fibrosis improvement with no worsening of NASH in:
  - F2-3 (EASL 2019)
  - F1-3 (AASLD 2019)
- NASH resolution with no worsening of fibrosis in:
  - F1-3 (AASLD 2019)

Younossi Z, 2019 EASL abstract 6
Sanyal A, 2019 AASLD abstract 34

Obeticholic Acid for NAFLD

	Cohort	Placebo	10 mg (p-value)	25 mg (p-value)
NASH resolution	F2-3	8.0%	11.2% (0.029)	11.7% (0.1268)
	F1-3	7.9%	11.3% (0.09)	14.9 (0.001)
Ballooning Improvement	*F2-3*	23.2%	27.2% (0.2423)	35.1% (0.0011)
Fibrosis Improvement	F2-3	11.9%	17.6% (0.0446)	23.1% (0.0002)
	F1-3	10.6%	15.7 (0.0286)	21.0% (<0.0001)
Pruritis	F1-3	19%	28%	51%
SAE	F1-3	11%	11%	14%

Younossi Z, 2019 EASL abstract 6
Sanyal A, 2019 AASLD abstract 34

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Making a decision about treatment

Favors treating now

- Can’t / won’t travel
- Can’t won’t do biopsy
- Less worried about disease
- F2-3
- Starting new DM meds
- Ready for bariatric surgery
- Lost >5% body weight

Favors clinical trial

- Ready for biopsy
- Ready to travel
- Benefits from research RN
- Prior trial participation
- Cirrhotic or F1
- Already on DM treatment
- Has failed weight loss

Making a decision about treatment

Summary

- Fibrosis drives mortality in NAFLD – know the risk factors:
  - Age, diabetes, AST
- 8,000,000 Americans have NASH with F≥2 – usually unbeknownst to the patients and their doctors
- Great NASH treatment is available now:
  - Weight loss, pioglitazone, vitamin E
- Obeticholic acid could be available in 1st half of 2020

Summary

- ‘Waiting’ won’t be OK much longer – discuss with endocrinologist or refer for a trial if you suspect F ≥2
  - Is 2020 the new 2011?
  - Is NAFLD the new HCV?
  - Is OCA is the new telaprevir?
  - Is endocrinology the new front line for NASH the way primary care is the new front line for HCV?

Questions?

- Will Holt
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- 510-220-4586