WELCOME TO
AK LIVER DISEASE ECHO

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

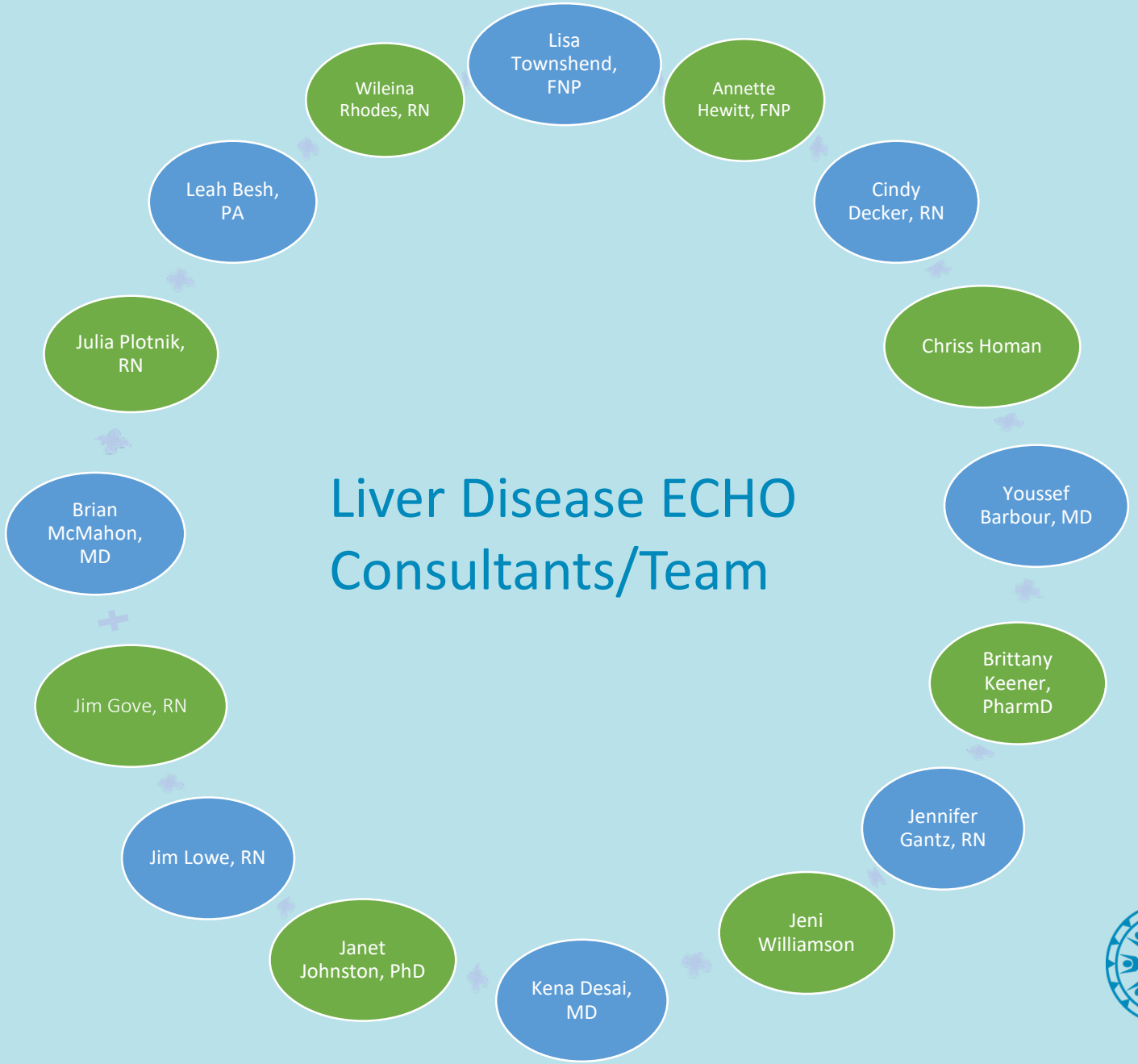
NPAIHB
Indian Leadership for Indian Health

This project is supported by a grant from the Northwest Portland Area Indian Health Board and funding is provided from the HHS Secretary's Minority HIV/AIDS Fund.

What we do

- Provide education related to liver disease management
  - Didactic presentations
  - Patient case presentations and questions
  - Expert panelist case review
- 2023 Theme: How You Can Help Reduce Liver Disease Mortality and Morbidity
  - addressing challenges to HCV screening and linkage to care
  - screening for metabolic associated fatty liver disease
  - managing cirrhosis
  - safe medication prescribing, and
  - nutrition for liver health

Liver Disease ECHO Consultants/Team



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Welcome to AK Liver Disease ECHO

Approved Provider Statements:

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, Alaska Native Medical Center (ANMC) is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Contact Hours:

ANMC designates this activity for a maximum of 12 contact hours, including 3 total pharmacotherapeutics contact hours, commensurate with participation.

Financial Disclosures:

Youssef Barbour, MD & Lisa Townshend-Bulson, APRN / faculty for this educational event, are primary investigators in an ANTHC sponsored hepatitis C study funded in part by Gilead Sciences. All of the relevant financial relationships listed have been mitigated.

Requirements for Successful Completion:

To receive CE credit please make sure you have actively engaged in the entire activity, your attendance is recorded by the facilitator, and complete the course evaluation form found here: https://forms.gle/R8vibUZgMbRcoScw9.

For more information contact
jlfielder@anthc.org or (907) 729-1387

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Treatment of Insulin Resistance in MAFLD/ NASH

Kena K. Desai MD

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Objectives

- Simplify the understanding of metabolic homeostasis in the pancreas and liver.
- Discuss interventions that decrease insulin resistance and improve MAFLD/NASH.
- Review the risks of these interventions.

Question 1

Mr. J is on Semaglutide 2 mg SubQ weekly for Type 2 Diabetes and weight management. He presents to the local emergency with RUQ abdominal pain and new transaminitis and elevation in total bilirubin.

What diagnosis should I consider first?

- A. Covid-19 infection
- B. Viral gastroenteritis
- C. Alcohol induced hepatitis
- D. Gallbladder disease
- E. Pancreatitis

Question 2

PARR agonists (peroxisome proliferator-activated receptor) are showing great potential in the treatment of MAFLD/ NASH by decreasing insulin resistance. Do we have a PARR agonist on our formulary?

A. No

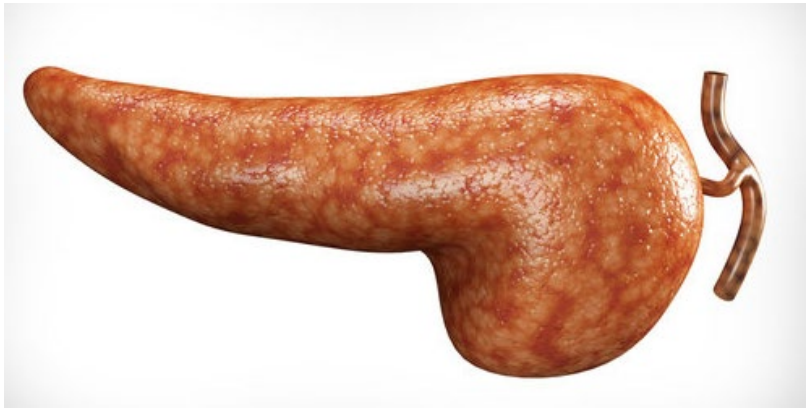
B. Yes -> Acarbose

C. Yes -> Glimepiride

D. Yes -> Pioglitazone

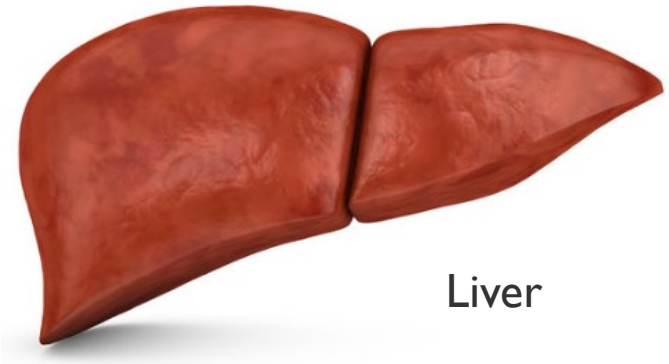
Signal: Hormones

Insulin/ glucagon

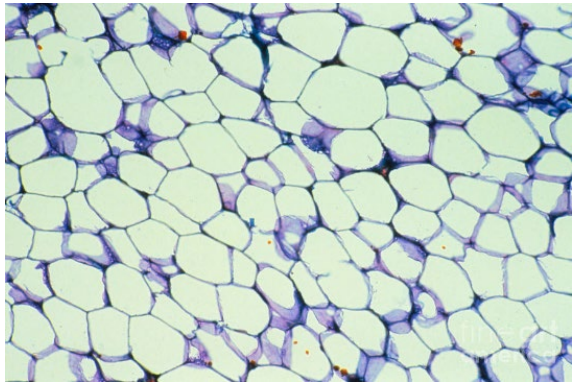


pancreas

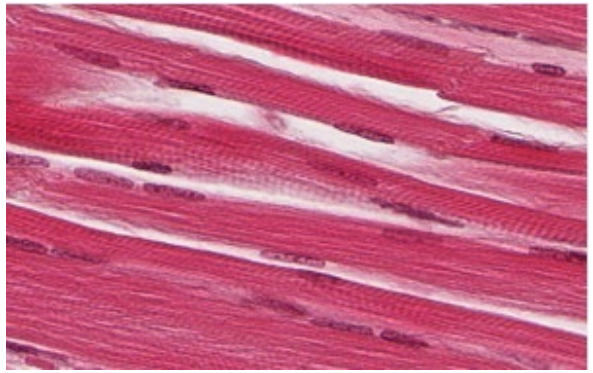
Receivers: Tissue



Liver



Adipose tissue



Skeletal muscle

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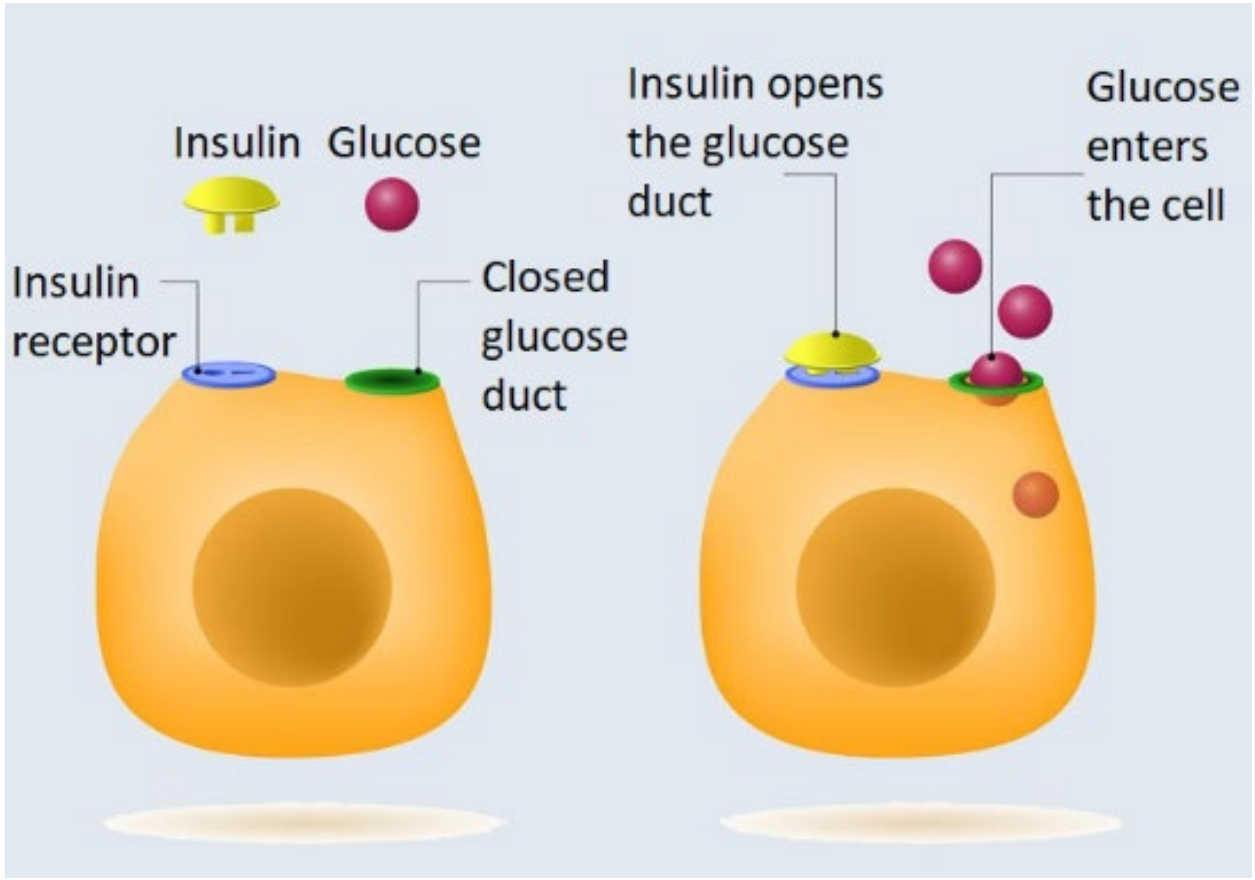
Insulin resistance:



Homeostasis: Balance in the insulin/glucagon ratio

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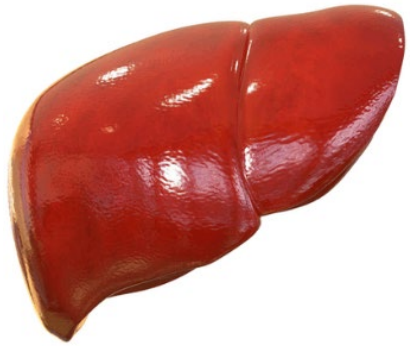
Fed state:

INSULIN / glucagon

Increase glycogen synthesis and decrease gluconeogenesis

Inhibition of lipolysis



Healthy Liver

Fasting state:

Insulin/ **GLUCAGON**

Increase gluconeogenesis and glycolysis

Stimulation of lipolysis

Insulin Resistance: loss of balance

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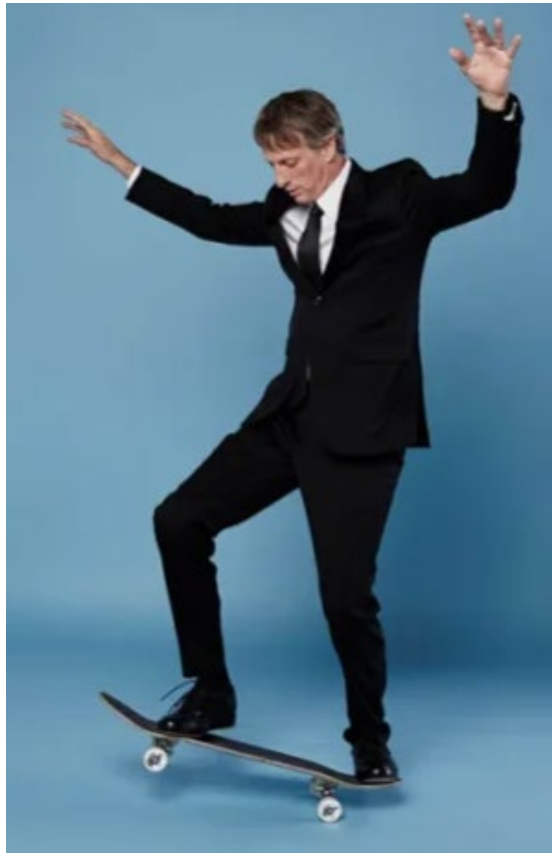
Fed state:

Insulin

glucagon



Fasting state:

Insulin

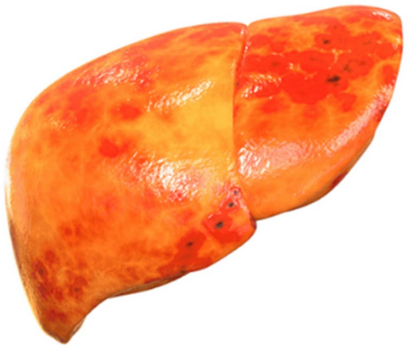
Glucagon

Increased metabolic load

Hepatic Lipid Accumulation

→ Lipotoxicity
Inflammation
Cell injury

→ Fibrosis



Disease Liver

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

Philip N. Newsome, M.B., Ch.B., Ph.D., Kristine Buchholtz, M.D., Ph.D., Kenneth Cusi, M.D., Martin Linder, M.Sc., Takeshi Okanoue, M.D., Ph.D., Vlad Ratziu, M.D., Ph.D., Arun J. Sanyal, M.D., Anne-Sophie Sejling, M.D., Ph.D., and Stephen A. Harrison, M.D. for the NN9931-4296 Investigators*

NEJM, volume 384, number 12, March 2021

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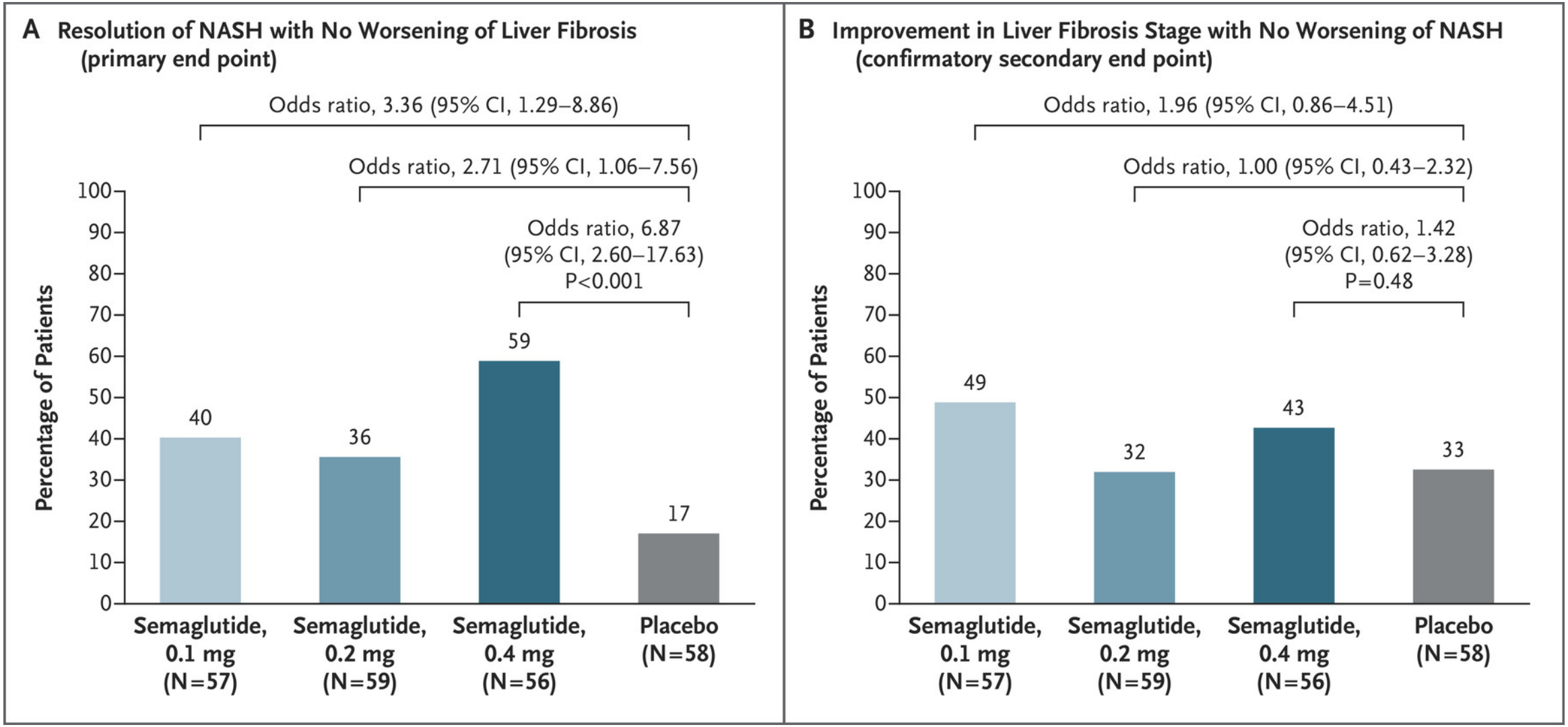
- Double-blind phase 2 trial, 72 weeks
- 320 patients with biopsy-confirmed NASH and liver fibrosis of stage F1, F2 or F3
- Randomly assigned to receive semaglutide at doses 0.1, 0.2 and 0.4 mg daily or corresponding placebo dose.

- Primary end point

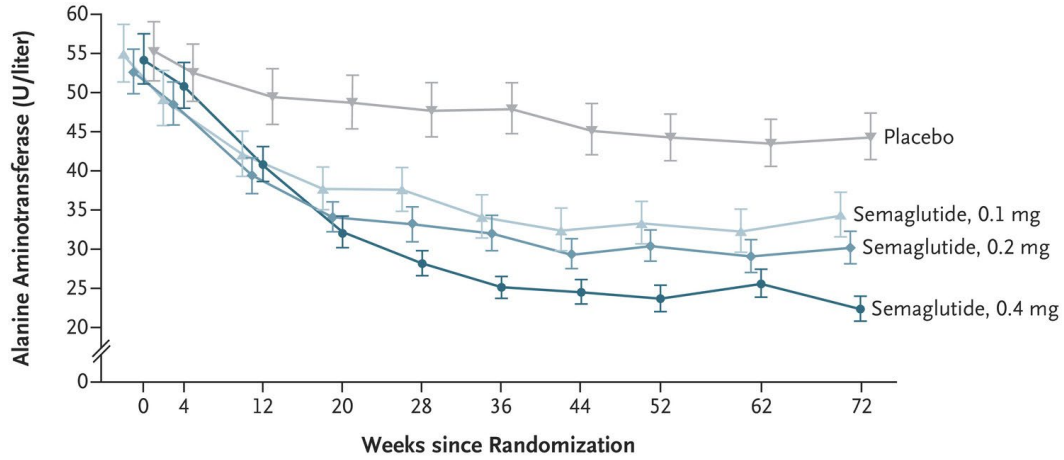
- Resolution of NASH with no worsening of fibrosis

- Secondary end point

- Improvement in at least 1 fibrosis stage with no worsening of NASH

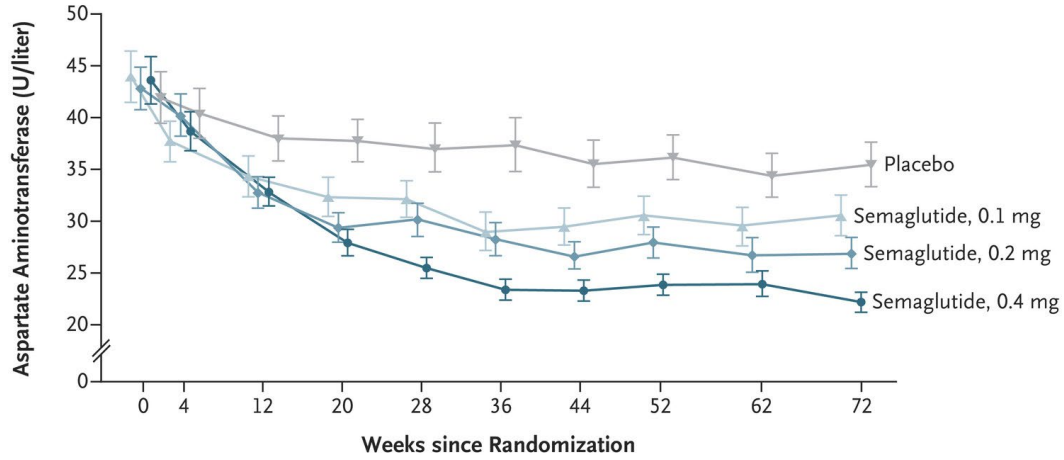

A Resolution of NASH with No Worsening of Liver Fibrosis (primary end point)
Odds ratio, 3.36 (95% CI, 1.29–8.86)
Odds ratio, 2.71 (95% CI, 1.06–7.56)
Odds ratio, 6.87 (95% CI, 2.60–17.63) P<0.001
Percentage of Patients
100
90
80
70
60
50
40
30
20
10
0
40
36
59
17
Semaglutide, 0.1 mg (N=57)
Semaglutide, 0.2 mg (N=59)
Semaglutide, 0.4 mg (N=56)
Placebo (N=58)
B Improvement in Liver Fibrosis Stage with No Worsening of NASH (confirmatory secondary end point)
Odds ratio, 1.96 (95% CI, 0.86–4.51)
Odds ratio, 1.00 (95% CI, 0.43–2.32)
Odds ratio, 1.42 (95% CI, 0.62–3.28) P=0.48
Percentage of Patients
100
90
80
70
60
50
40
30
20
10
0
49
32
43
33
Semaglutide, 0.1 mg (N=57)
Semaglutide, 0.2 mg (N=59)
Semaglutide, 0.4 mg (N=56)
Placebo (N=58)

A Alanine Aminotransferase



No. of Patients										
Placebo	80	80	79	79	77	78	76	75	76	75
Semaglutide, 0.1 mg	80	80	77	76	76	75	75	77	76	76
Semaglutide, 0.2 mg	78	76	76	72	71	70	71	70	70	71
Semaglutide, 0.4 mg	82	80	80	77	75	76	76	76	76	77

B Aspartate Aminotransferase



No. of Patients										
Placebo	80	80	79	79	78	78	76	74	75	74
Semaglutide, 0.1 mg	80	79	77	75	76	75	75	77	76	74
Semaglutide, 0.2 mg	78	76	76	72	71	70	72	70	70	69
Semaglutide, 0.4 mg	82	81	79	76	75	77	76	76	76	77

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Table 2. Changes between Baseline and Week 72 in Selected Supportive Secondary End Points.*

End Point	Semaglutide 0.1-mg Group (N=80)	Semaglutide 0.2-mg Group (N=78)	Semaglutide 0.4-mg Group (N=82)	Placebo Group (N=80)
Ratio of value at wk 72 to value at baseline				
Alanine aminotransferase	0.63	0.58	0.42	0.81
Aspartate aminotransferase	0.70	0.65	0.52	0.84
Caspase-cleaved cytokeratin-18 fragment M30†	0.55	0.50	0.47	0.78
Caspase-cleaved cytokeratin-18 fragment M65†	0.53	0.52	0.42	0.71
Total cholesterol	0.97	1.00	0.93	0.94
Triglycerides	0.88	0.90	0.73	0.97
Liver stiffness, as assessed by FibroScan‡	0.76	0.71	0.72	1.02
Change from baseline to wk 72				
Enhanced liver fibrosis test score	–0.34	–0.39	–0.56	0.01
Body weight — %	–4.84	–8.91	–12.51	–0.61
Glycated hemoglobin level among patients with type 2 diabetes — percentage points§	–0.63	–1.07	–1.15	–0.01

* Data are from all the patients during the in-trial observation period (from randomization until the last study-related procedure). A lower ratio of the value at week 72 to the value at baseline indicates a larger reduction.
† Higher levels of cytokeratin-18 fragments are a biomarker of hepatocyte apoptosis.
‡ This assessment was performed only at sites at which FibroScan equipment was available. Changes in liver steatosis were assessed in 161 patients, and changes in liver stiffness were assessed in 212 patients.
§ These values were based on the number of patients with type 2 diabetes in each group (49, 51, 49, and 50 patients in the 0.1-mg, 0.2-mg, 0.4-mg, and placebo groups, respectively).

Table 3. Selected Adverse Events.*

Event	Semaglutide 0.1-mg Group (N=80)	Semaglutide 0.2-mg Group (N=78)	Semaglutide 0.4-mg Group (N=81)	Placebo Group (N=80)
	number of patients (percent)			
Nausea	24 (30)	29 (37)	34 (42)	9 (11)
Constipation	13 (16)	17 (22)	18 (22)	10 (12)
Decreased appetite	16 (20)	18 (23)	18 (22)	4 (5)
Diarrhea	23 (29)	22 (28)	16 (20)	11 (14)
Vomiting	14 (18)	17 (22)	12 (15)	2 (2)
Back pain	7 (9)	5 (6)	10 (12)	7 (9)
Headache	7 (9)	10 (13)	10 (12)	8 (10)
Nasopharyngitis	11 (14)	15 (19)	10 (12)	12 (15)
Arthralgia	0	4 (5)	9 (11)	7 (9)
Fatigue	7 (9)	8 (10)	7 (9)	7 (9)
Abdominal pain	9 (11)	8 (10)	6 (7)	3 (4)
Abdominal distension	1 (1)	8 (10)	4 (5)	4 (5)
Dyspepsia	4 (5)	9 (12)	4 (5)	5 (6)
Adverse events that resulted in premature discontinuation of treatment				
All adverse events	3 (4)	10 (13)	4 (5)	4 (5)
Gastrointestinal disorders	1 (1)	6 (8)	2 (2)	0
Serious adverse events				
Any serious adverse event	12 (15)	15 (19)	12 (15)	8 (10)
Gastrointestinal disorders	2 (2)	2 (3)	4 (5)	0

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JAMA | Original Investigation

Association of Bariatric Surgery With Major Adverse Liver and Cardiovascular Outcomes in Patients With Biopsy-Proven Nonalcoholic Steatohepatitis

Ali Aminian, MD; Abbas Al-Kurd, MD; Rickesha Wilson, MD; James Bena, MS; Hana Fayazzadeh, MD; Tavankit Singh, MD; Vance L. Albaugh, MD, PhD; Faiz U. Shariff, MD; Noe A. Rodriguez, MD; Jian Jin, MS; Stacy A. Brethauer, MD, MBA; Srinivasan Dasarathy, MD; Naim Alkhouri, MD; Philip R. Schauer, MD; Arthur J. McCullough, MD; Steven E. Nissen, MD

JAMA, Volume 326: 20, Nov 2021

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- Retrospective cohort study
- 1158 adult patients with obesity (median BMI – 44.1) and histologically confirmed diagnosis of NASH and liver fibrosis
- 650 patients underwent bariatric surgery and 508 patients were in the nonsurgical control group
- Median follow-up 7 years (IQR, 4-10 years)

- Primary end point:
- Major adverse liver outcomes
  - progression to clinical or histological cirrhosis, development of hepatocellular carcinoma, liver transplantation, or liver related mortality
- Major adverse cardiovascular events (MACE)
  - a composite of coronary artery events, cerebrovascular events, heart failure or cardiovascular death

Figure 3. Trend Curves of Mean Change in Body Weight and Hemoglobin A_{1c} Level Over 10 Years of Follow-up in the Overlap-Weighted Analysis

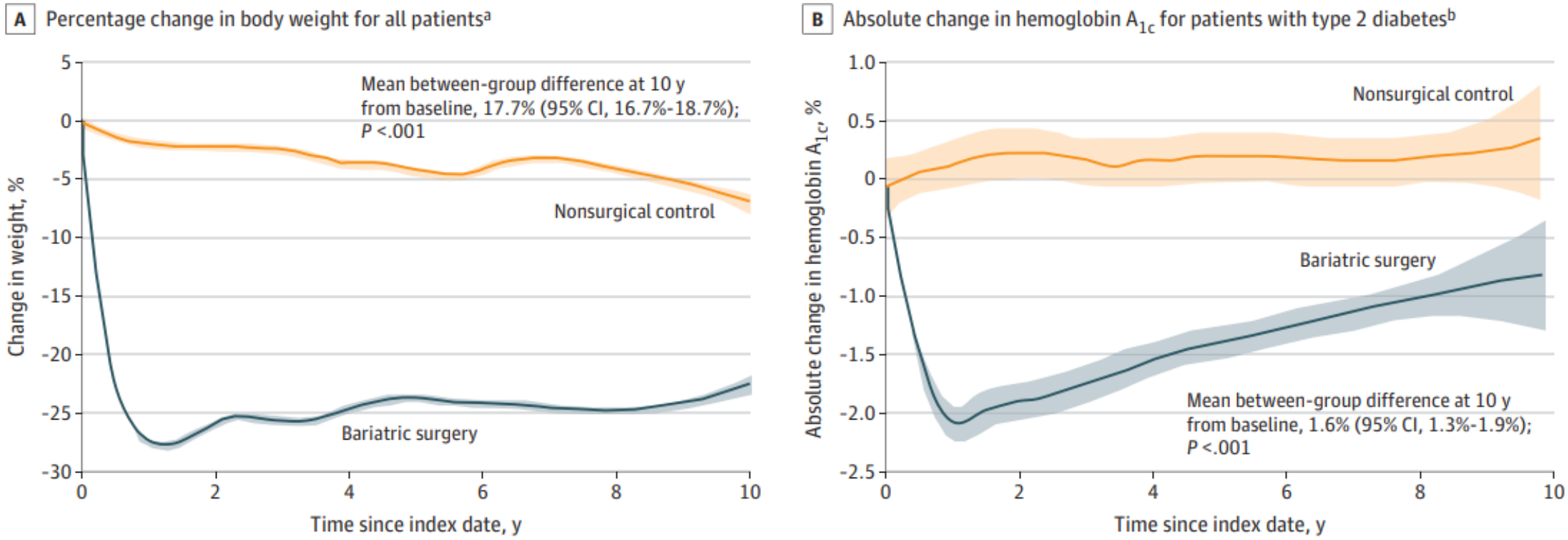

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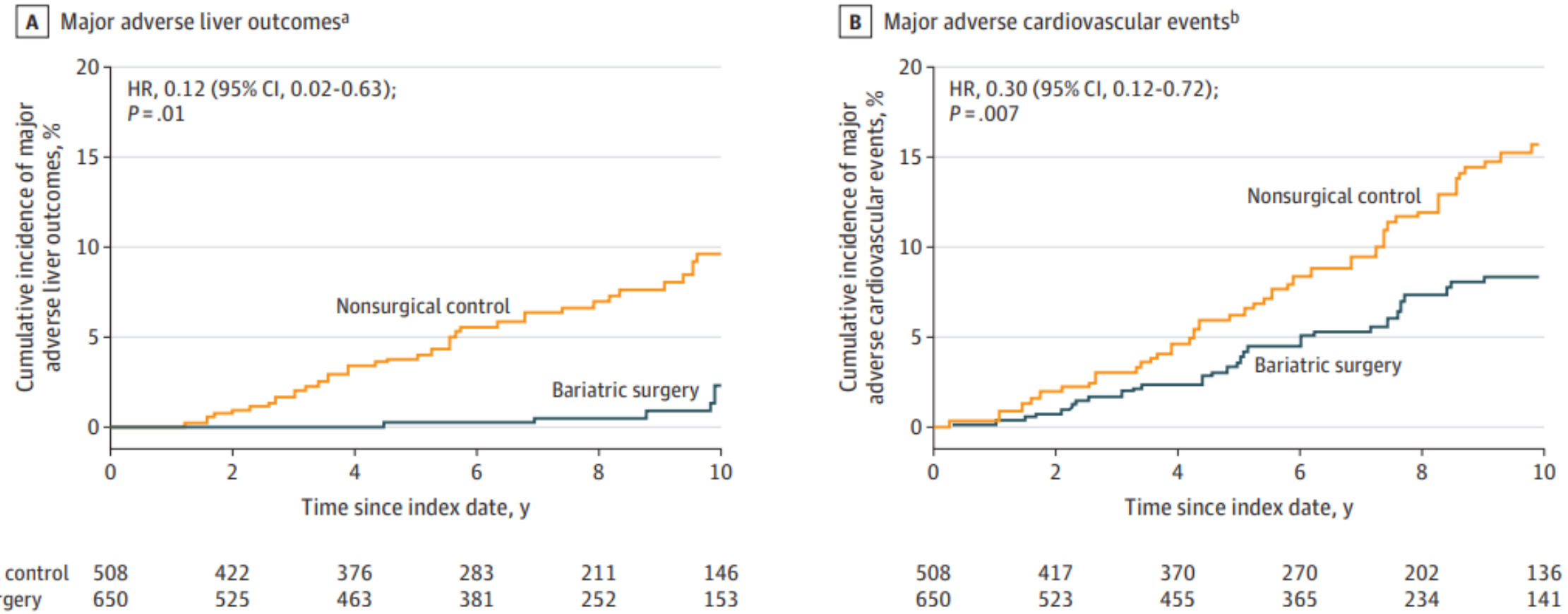
Figure 2. Cumulative Incidence Estimates (Kaplan-Meier) for 2 Composite End Points in the Overlap-Weighted Analysis



No. at risk

Nonsurgical control	508	422	376	283	211	146
Bariatric surgery	650	525	463	381	252	153

Nonsurgical control	508	417	370	270	202	136
Bariatric surgery	650	523	455	365	234	141

Bariatric surgery group = 5 patients (2.3%)
Nonsurgical control group = 40 patients (9.6%)

Bariatric surgery group = 39 patients (8.5%)
Nonsurgical control group = 60 patients (15.7%)

A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH

S.M. Francque, P. Bedossa, V. Ratziu, Q.M. Anstee, E. Bugianesi, A.J. Sanyal, R. Loomba, S.A. Harrison, R. Balabanska, L. Mateva, N. Lanthier, N. Alkhouri, C. Moreno, J.M. Schattenberg, D. Stefanova-Petrova, L. Vonghia, R. Rouzier, M. Guillaume, A. Hodge, M. Romero-Gómez, P. Huot-Marchand, M. Baudin, M.-P. Richard, J.-L. Abitbol, P. Broqua, J.-L. Junien, and M.F. Abdelmalek, for the NATIVE Study Group*

NEJM, volume 385: 17, 10/2021

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- Lanifibranor – pan-PARR agonist (peroxisome proliferator-activated receptor)
  - Reduces insulin resistance in adipose tissue, muscle and liver

- Phase 2b, double-blind, randomized, placebo-controlled trial
- Patients – highly active NASH, patients with cirrhosis were excluded

- Primary end point (powered)
  - Decrease of at least 2 points on SAF-A score (range 0-4)
  - Without worsening of fibrosis

- Secondary end points
  - Resolution of NASH
  - Regression of Fibrosis

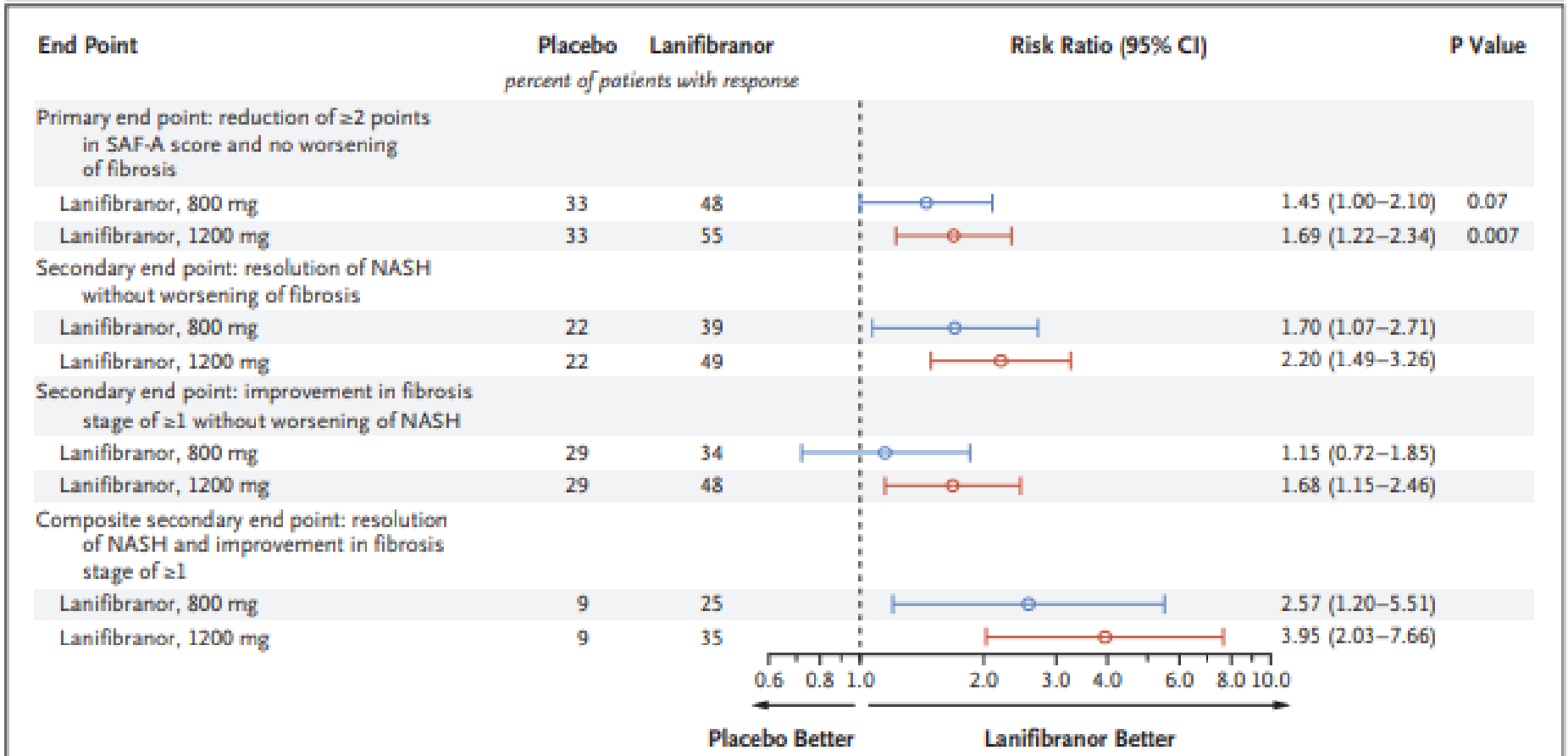

Figure 1. Response for Primary and Secondary Histologic End Points at Week 24.

Analyses were performed with multiple imputation of missing data. Risk ratios, 95% confidence intervals, and P values were calculated with the Cochran–Mantel–Haenszel test stratified according to diabetic status at baseline. In the analysis of the primary end point, an ascending Hochberg procedure was used to adjust for multiplicity testing (each dose of lanifibranor was compared with placebo). Missing data for the 34 patients in the full analysis population (11 in the 800-mg lanifibranor group, 9 in the 1200-mg lanifibranor group, and 14 in the placebo group had missing biopsy samples at week 24) were handled with multiple imputation (details are provided in the Supplementary Appendix). The Steatosis, Activity, Fibrosis–Activity (SAF-A) score represents the activity part of the SAF scoring system that incorporates the scores for hepatocellular ballooning and lobular inflammation; SAF-A scores range from 0 to 4, with higher scores indicating more-severe disease activity. NASH denotes nonalcoholic steatohepatitis.

Main points:

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- Obese Adults in the USA: 42% in 2022
- Children and Adolescents in the USA: 20% in 2022

- The best way to treat disease is to prevent it from occurring.

- The interventions for decreasing obesity and insulin resistance are good, however, they carry their own set of disadvantages and risks.

- Much more cost-effective and good for our lives would be changing the way we live day-to-day. (this will never be studied because there is no financial incentive to investigate this).

Question 1

- Mr. J is on Semaglutide 2 mg SubQ weekly for Type 2 Diabetes and weight management. He presents to the local emergency with RUQ abdominal pain and new transaminitis and elevation in total bilirubin.

  What diagnosis should I consider first?

A. Covid-19 infection

B. Viral gastroenteritis

C. Alcohol induced hepatitis

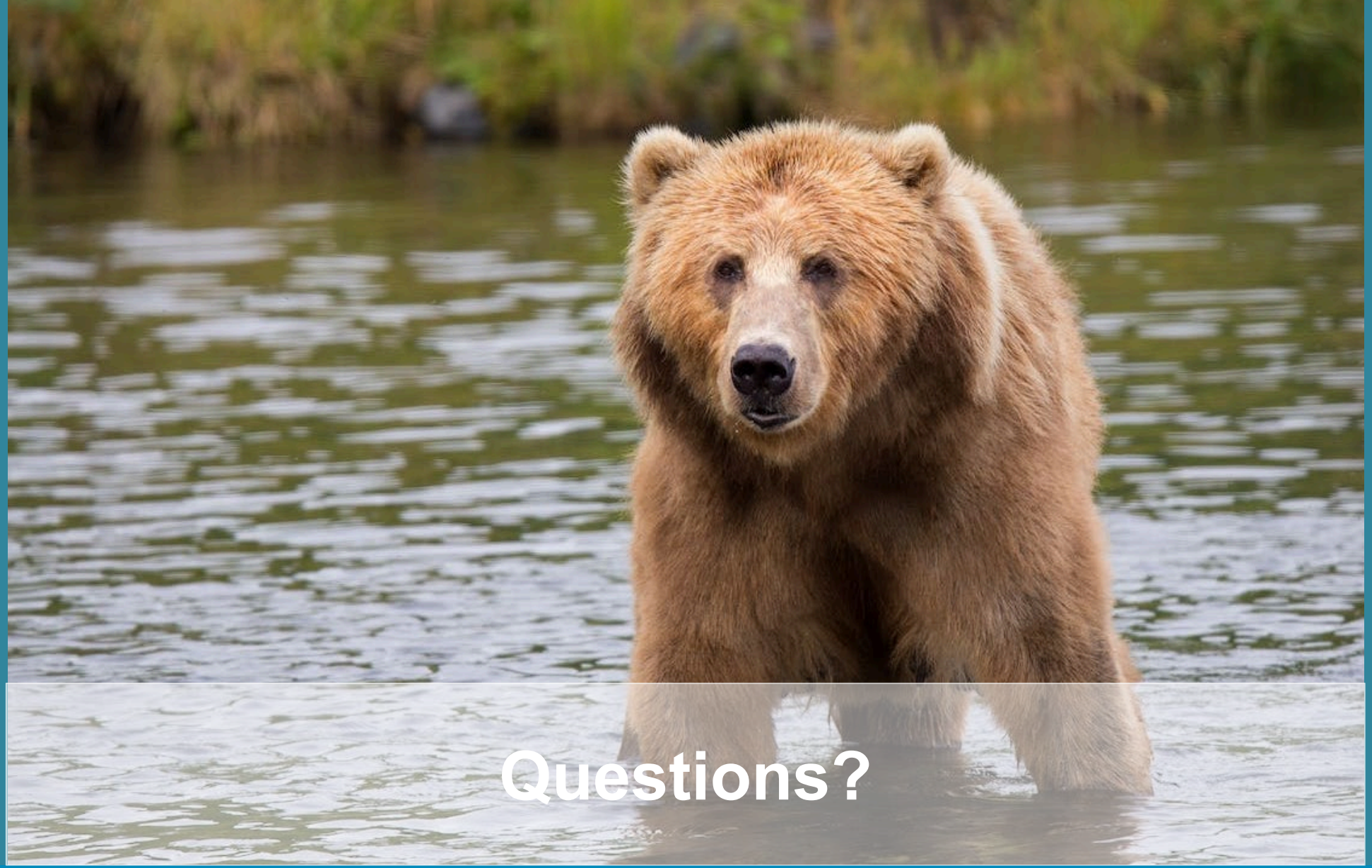
D. Gallbladder disease

E. Pancreatitis

Question 2

PARR agonists (peroxisome proliferator-activated receptor) are showing great potential in the treatment of MAFLD/ NASH by decreasing insulin resistance. Do we have a PARR agonist on our formulary?

A. No
B. Yes -> Acarbose
C. Yes -> Glimepiride
D. Yes -> Pioglitazone



Questions?

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Case Presentation

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AK Liver Disease ECHO

- Third Thursday of every month from noon-1:00PM AKST
- 1CE/CME offered per session
- www.anthc.org/AK-LD-ECHO
- 2023 Theme: Ways You Can Reduce Morbidity and Mortality From Liver Disease
  - September 21: Recognizing Common Autoimmune Liver Disease Seen in Alaska Native and American Indian Peoples
  - October 19: Stressing Importance of Exercise as NAFLD Treatment Now that it is Getting Dark and Cold

Additional learning opportunities

- AK ID ECHO: HCV, HIV, PrEP, STIs
  - Second Tuesday of every month from noon-1:00PM AKST
    - 1CE/CME offered per session
  - anthc.org/ak-id-echo
- LiverConnect Webinar Program
  - Second Tuesday of every month 8:00-9:00AM AKST
    - Full hour didactic topics on Liver Disease and related topics 1CE/CME offered
  - anthc.org/what-we-do/clinical-and-research-services/hep/liverconnect

AK Liver Disease ECHO – Team Contacts

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Northwest Portland Area Indian Health Board

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