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Excellence is just the beginning.

Rush University Medical Center

Pharmacological Advances in the Treatment of MASLD

5th Annual
CURRENT PERSPECTIVES IN HEPATOLOGY

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Disclosures

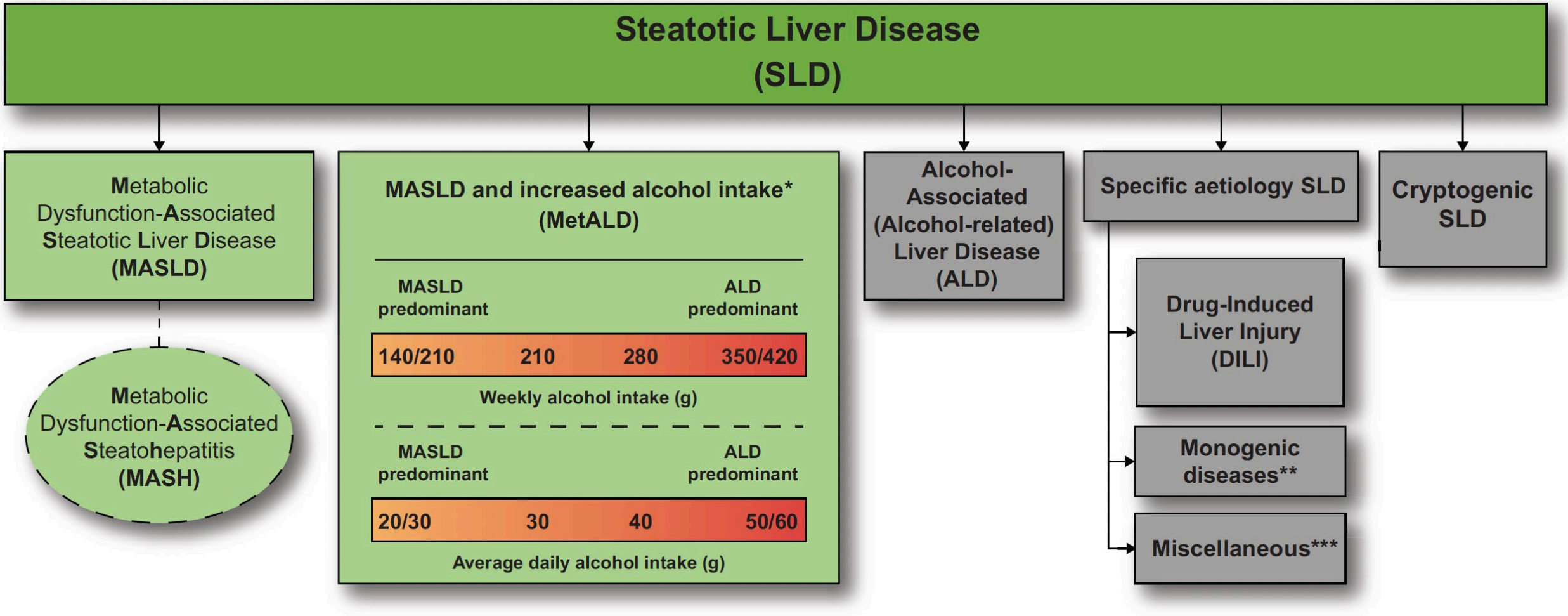
- Consultation: AbbVie, Gilead, Arbutus, Intercept, Salix, VIR
- Research Support: AbbVie, Gilead, Salix

DISCLAIMER:
I know the terminology has changed to MASLD/MASH, however if the publication occurred prior to this I am leaving the original terminology

New Terminology

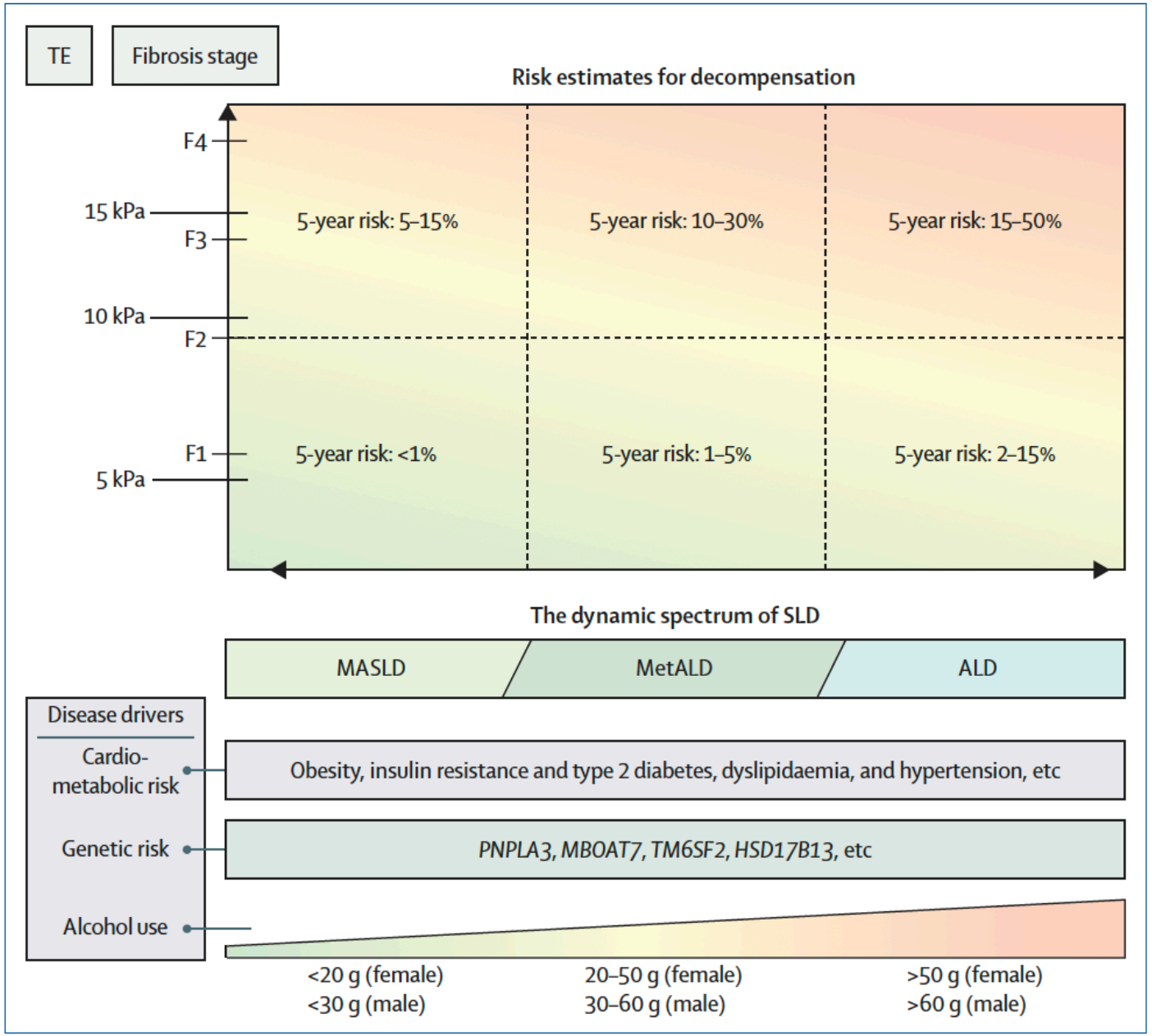
Definition

- Affirmative set of diagnostic criteria for MASLD
- Near universal agreement to err on side of being inclusive
- Simple, readily available and easily measurable parameters
- The diagnostic criteria were also selected to align with cardiometabolic risk factors already well established and validated in other metabolic health disorders



*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease, human immunodeficiency virus (HIV)

Dynamic spectrum of MASLD-MetALD-ALD



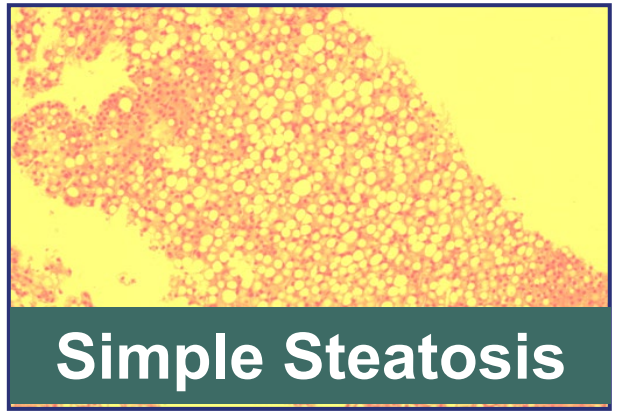
Alcohol use interacts with cardiometabolic risk factors and impacts risk of decompensation

Israelsen et al. MetALD: new opportunities to understand the role of alcohol in steatotic liver disease. Lancet GI Hep 2023

Context

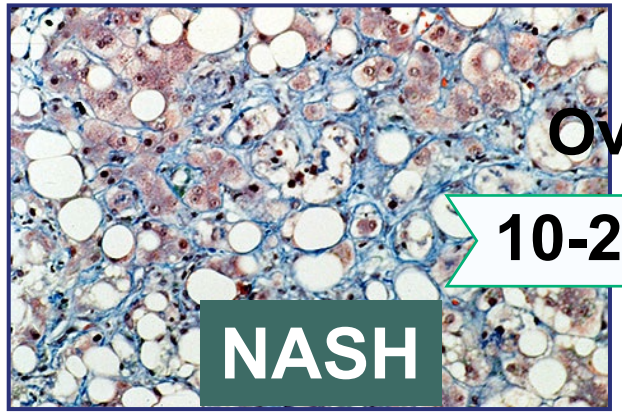
Natural History of NAFL and NASH

80%



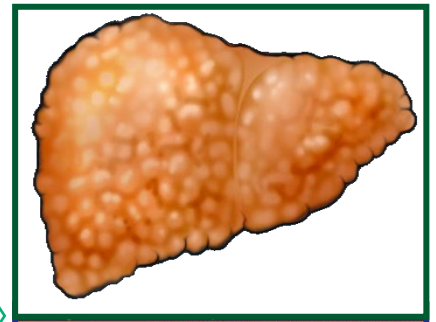
- Slowly progressive
  - NAFL: 1 fibrosis stage q14 yrs
  - NASH q7 yrs
  - Doubled by HTN
- Rapid ~20% of cases
- Progression is not linear

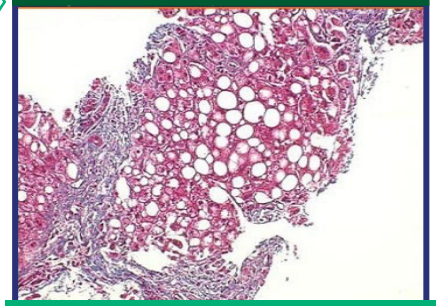
10-20%



Overall

10-20%



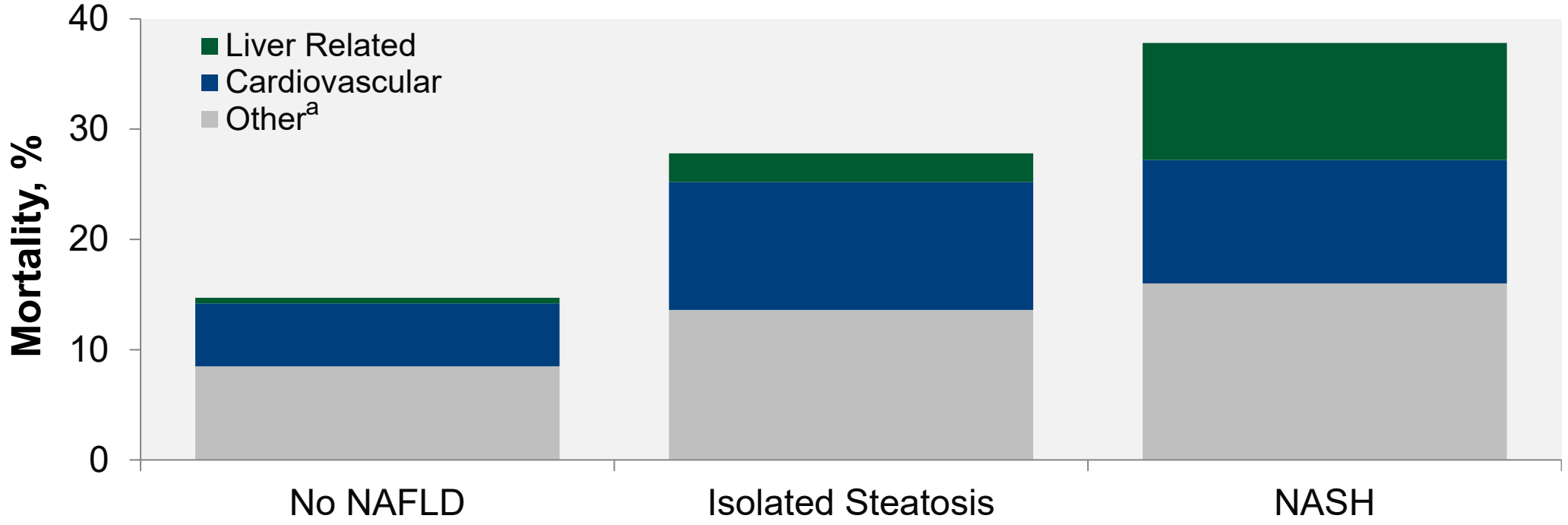


Cirrhosis

Younossi ZM, et al. *Medicine*. 2012
Chalasani N, et al. *Hepatology*. 2018;67:328–357; .

Mortality Is Higher in Those With NASH Compared to Those With Isolated Steatosis

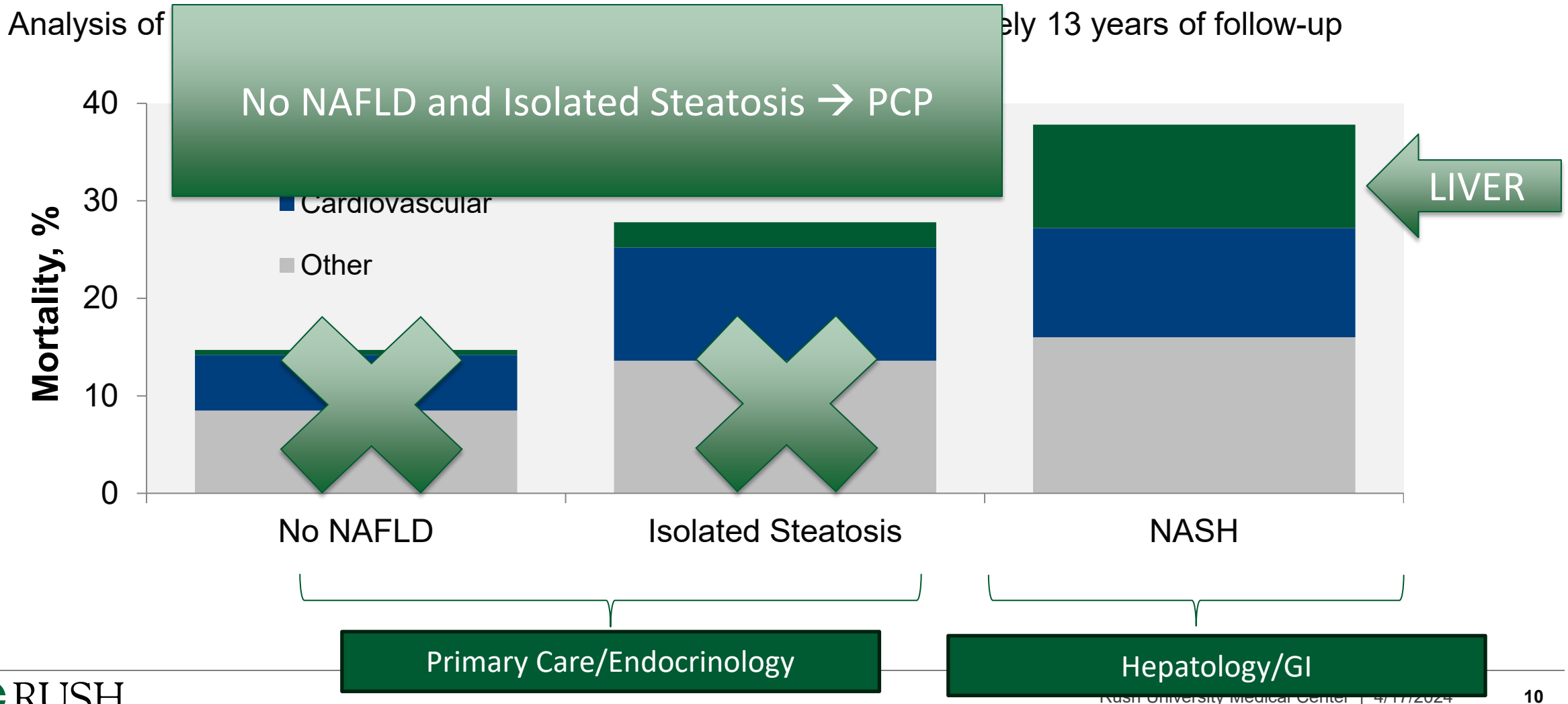
Analysis of all-cause mortality in six separate studies with approximately 13 years of follow-up



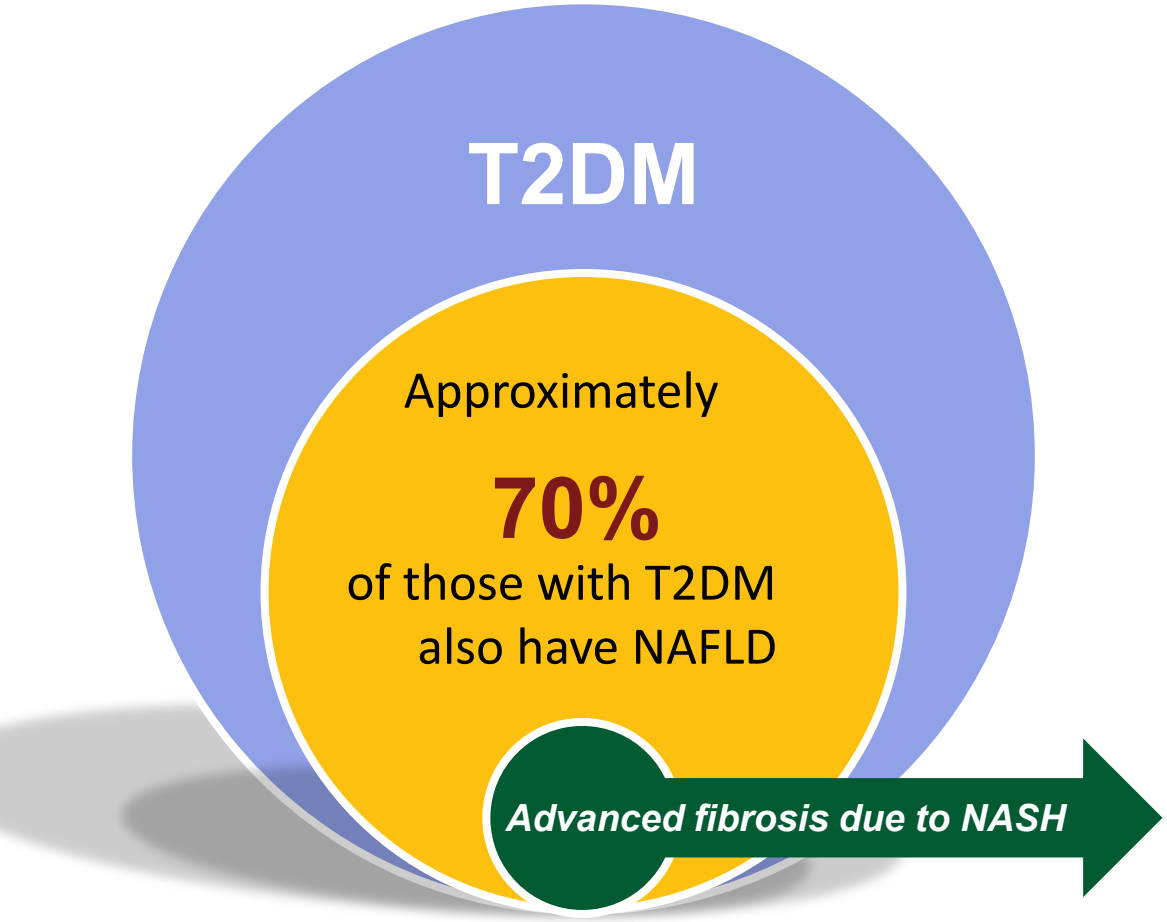
[a]Other causes of death include extrahepatic malignancy, diabetes-related complications, renal disease, neurological disease, respiratory disease, infections, and accidents.

Bril F and Cusi K. *Endocrinol Metab Clin North Am*. 2016;45:765–781.

Mortality Is Higher in Those With MASH Compared to Those With Isolated Steatosis



Approximately 7% to 13% of Those With T2DM Have Advanced Fibrosis Due to NASH



”Hold on to”
MASLD + MetS

Four studies in 2,720 T2DM patients evaluated for NAFLD and advanced fibrosis due to NASH

7% to 13%
of patients with T2DM may have
advanced fibrosis due to NASH

1. Arab JP, et al. *Ann Hepatol*. 2016;15:721–728; 2. Doycheva I, et al. *Aliment Pharmacol Ther*. 2016;43:83–95; 3. Kwok R, et al. *Gut*. 2015;65:1359–1368; 4. Lai LL, et al. *J Gastroenterol Hepatol*. 2018. [Epub ahead of print].

Analysis of a Simulation Model to Estimate Long-term Outcomes in Patients with Nonalcoholic Fatty Liver Disease

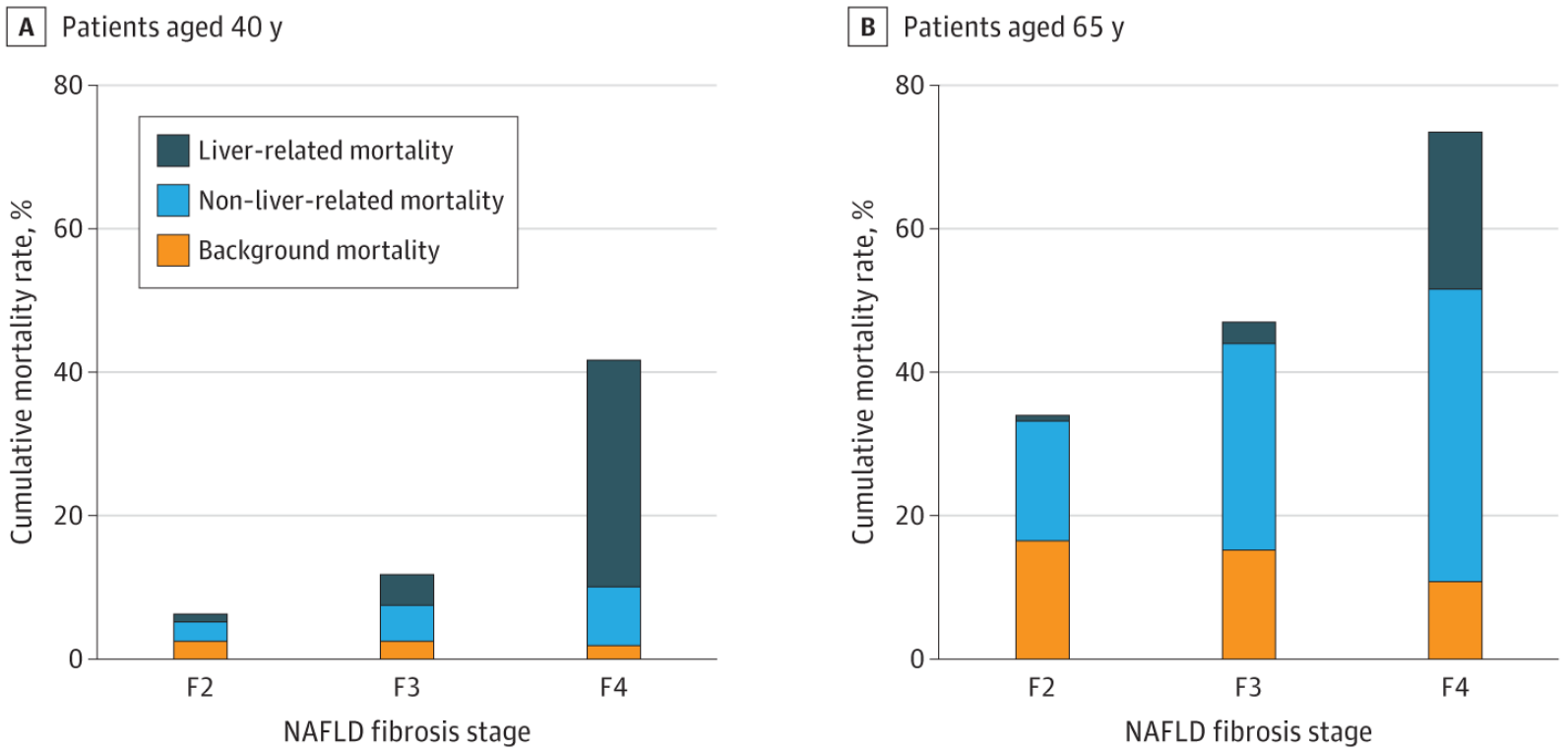
JAMA Netw Open. 2022;5(9):e2230426. doi:10.1001/jamanetworkopen.2022.30426

JAMA Network™

"Hold on to" the Young

Patients aged 65 years, estimated 10-year non–liver-related mortality was higher than liver-related **mortality in all fibrosis stages**
F2: 16.7% vs 0.8%
F3: 28.8% vs 3.0%
F4: 40.8% vs 21.9%

Patients aged 40 years, non–liver-related mortality was higher than liver-related mortality in stage F2 (2.7% vs 1.1%) or F3 (5.0% vs 4.3%); **But reversed in stage F4 (8.2% vs 31.6%)**

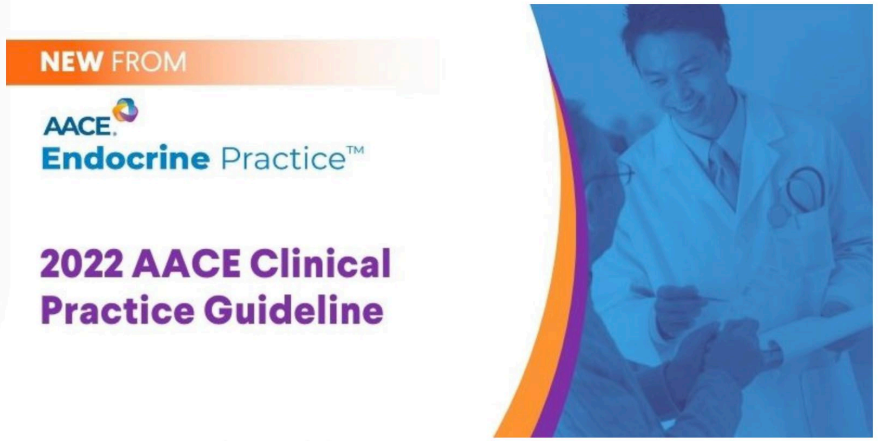


Competing Liver-Related and Non–liver-related Mortality in Patients Aged 40 Years or 65 Years With Nonalcoholic Fatty Liver Disease (NAFLD) by Fibrosis Stage

Tools to help you

AACE Disease State Resources Education and Events Publications Careers About

American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings



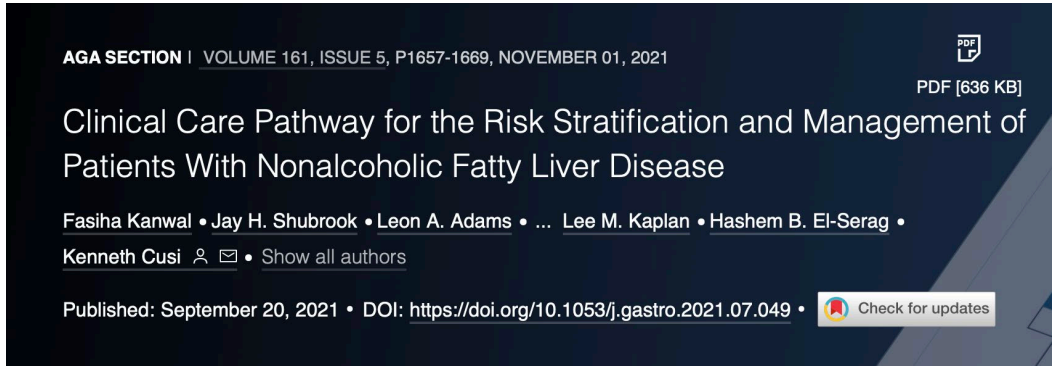
Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD)

Received: 18 January 2023 | Accepted: 18 January 2023
DOI: 10.1097/HEP.0000000000000323

PRACTICE GUIDANCE

AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease

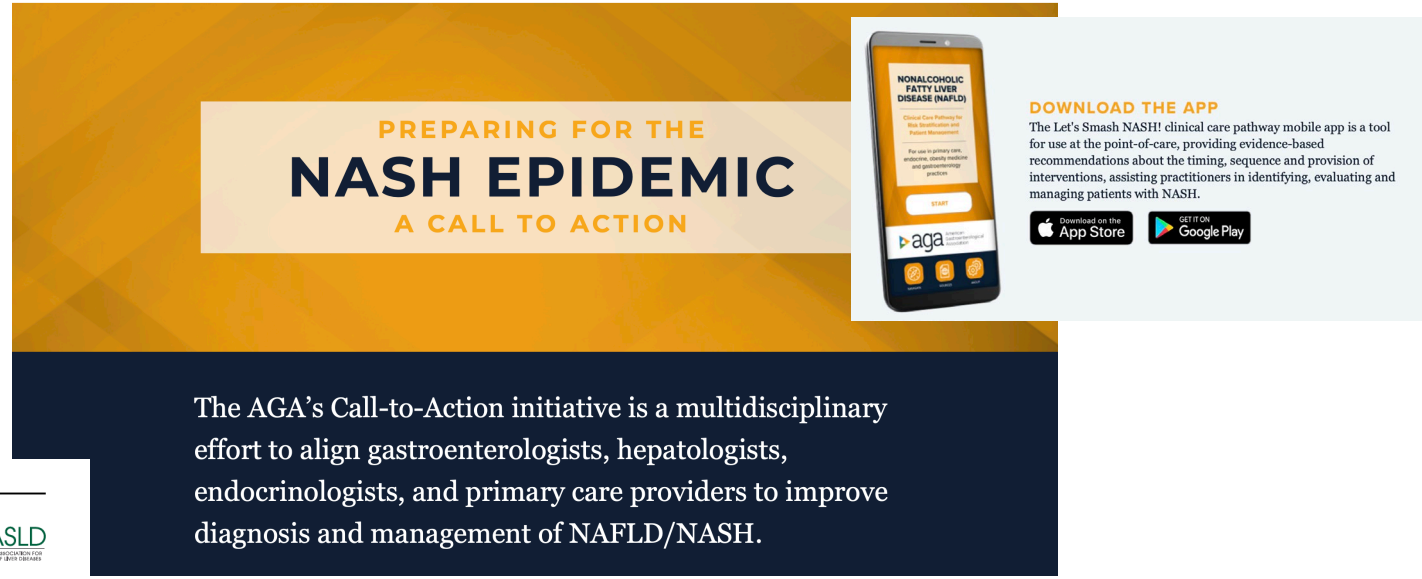
Mary E. Rinella[1] | Brent A. Neuschwander-Tetri[2] | Mohammad Shadab Siddiqui[3] | Manal F. Abdelmalek[4] | Stephen Caldwell[5] | Diana Barb[6] | David E. Kleiner[7] | Rohit Loomba[8]



https://www.gastrojournal.org/article/S0016-5085(21)03384-9/fulltext

aga American Gastroenterological Association

CONFERENCE | FACULTY | ABOUT | RESOURCES



https://nash.gastro.org

Screen AND Stage

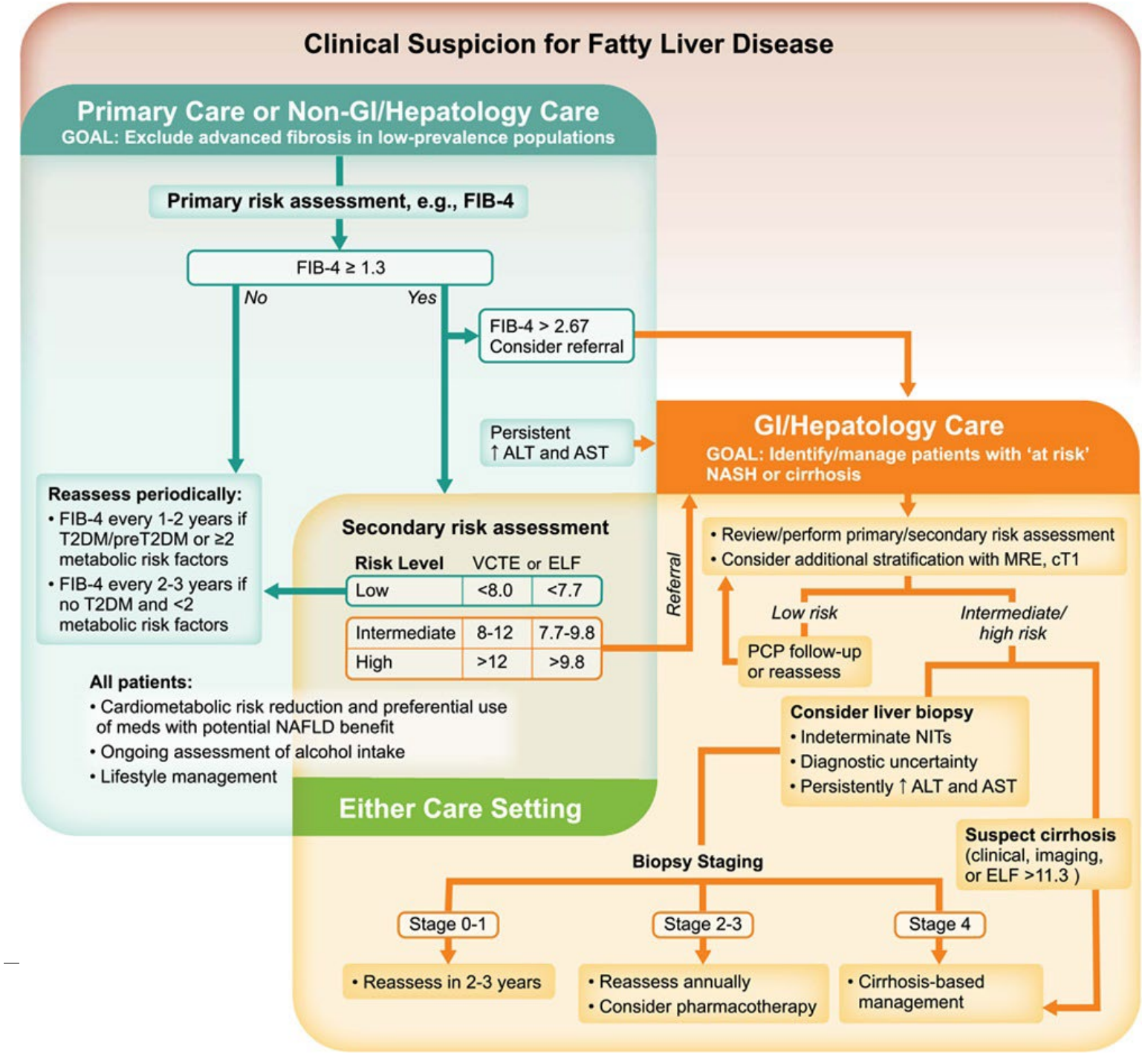
<u>If you return patients to primary care that are not currently at risk for liver related disease</u>

- Offer clear plan on follow with links to guidelines and FIB4 calculator and ELF CPT code
- Radiology offers both LSM and MRE
- Place recall reminder to get staging in chart

- Schedule follow-up at 5 year interval in those <65 years old

This could change w/ drug development

13. Patients with NASH cirrhosis are at the highest risk for liver-related outcomes and require routine surveillance for HCC, esophageal varices, and monitoring for decompensation.



16. First-degree relatives of patients with NASH cirrhosis should be counseled regarding their increased individual risk and offered screening for advanced hepatic fibrosis.

Prevalence of advanced fibrosis in background MASLD population (0.9-2%) [20-23]

Screening recommended	Prevalence of advanced fibrosis
Type 2 diabetes mellitus (T2DM)	6-19% [1-8]
Medically complicated obesity	4-33% [9-17]
MASLD in context of moderate alcohol use	17% [18]
First degree relative of a patient with cirrhosis due to NAFLD	18% [19]

Rinella et al. Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2022 (accepted)

Treat Co-Morbid Conditions like a Hepatologist (would want you to) Off Label Therapy

Weight Management in NAFLD

Fibrosis Risk Stratification

	 **Low Risk** FIB-4: <1.3 LSM <8 kPa ELF <7.7	 **Indeterminate Risk** FIB-4: 1.3 - 2.67 LSM 8 - 12 kPa ELF 7.7 - 9.8	 **High Risk** FIB-4: >2.67 LSM >12 kPa ELF >9.8
General lifestyle changes	Decrease sedentary time and increase daily movement. Stress reduction through exercise and other methods.		
Dietary recommendations	Creating an energy deficit is the priority with reduction of saturated fat, starch, & added sugars. Persons with cirrhosis need an individualized nutritional assessment and treatment plan.		
Exercise	To improve cardiometabolic health, support weight loss and mitigate sarcopenia. Aerobic exercise for 30-60 min (3-5 days/week) + resistance training 20-30 min (2-3 times/week).		
Alcohol intake	Minimize	Minimize	Avoid if F3 or cirrhosis (F4)[1]
Weight loss goal to treat NAFLD (if overweight or obesity)[2]	Greater weight loss associated with greater liver and cardiometabolic benefit.		
Weight loss tools	Behavioral modification counseling. In person or remote programs.	Greater intensity of weight loss to reverse steatohepatitis and fibrosis.	Specialized obesity management, with a structured program, anti-obesity medications, bariatric surgery.
Medical therapy to treat obesity	Phentermine, phentermine/topiramate ER, naltrexone/bupropion, orlistat, liragluitde 3 mg/d, semaglutide 2.4 mg/wk	GLP-1 RA preferred for NASH.[3,4]	GLP-1 RA preferred for NASH.[3,4]
Bariatric surgery	Consider to treat obesity and comorbidities.	Strong consideration to treat steatohepatitis and fibrosis.	Stronger consideration to treat steatohepatitis and fibrosis. Avoid in decompensated cirrhosis.

GLP1

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Endocrine Practice 2022 28528-562DOI: (10.1016/j.eprac.2022.03.010)

Diabetes Management in NAFLD

AACE

PPAR/GLP1

Fibrosis Risk Stratification

	 Low Risk FIB-4: <1.3 LSM <8 kPa ELF <7.7	 Indeterminate Risk FIB-4: 1.3 - 2.67 LSM 8 - 12 kPa ELF 7.7 - 9.8	 High Risk[1] FIB-4: >2.67 LSM >12 kPa ELF >9.8
General goal	Optimize glycemic control using preferred agents that reverse steatohepatitis, whenever possible. Prefer GLP-1 RA and SGLT2i in CVD. Prefer SGLT2i in CKD and HF.		
Dietary recommendations	Glycemic load reduction via emphasis on whole food carbohydrates (vegetables, legumes, fruit) versus sugar/processed carbohydrates.		
Individualize A1c target	≤6.5% for persons without concurrent serious illness and at low hypoglycemic risk (>6.5% otherwise).		In advanced cirrhosis[1], caution with risk of hypoglycemia and avoid oral agents[2]
Preferred diabetes pharmacotherapy	Consider agents that reduce liver fat (pioglitazone, GLP-1 RA, SGLT2i).	Strongly consider agents with efficacy in NASH: Pioglitazone and/or GLP-1 RA[3]. No evidence that SGLT2i improve steatohepatitis.	Strongly consider agents with efficacy in NASH: Pioglitazone and/or GLP-1 RA[3]. No efficacy data in cirrhosis.
Metformin, sulfonylurea, DPP-4i, acarbose and insulin	May continue but limited benefit on liver histology in NAFLD.	May continue but limited benefit on liver histology in NAFLD.	May continue (F2-F3) but avoid oral agents if advanced cirrhosis present. Cannot avoid insulin in patients with advanced liver cirrhosis – often only option

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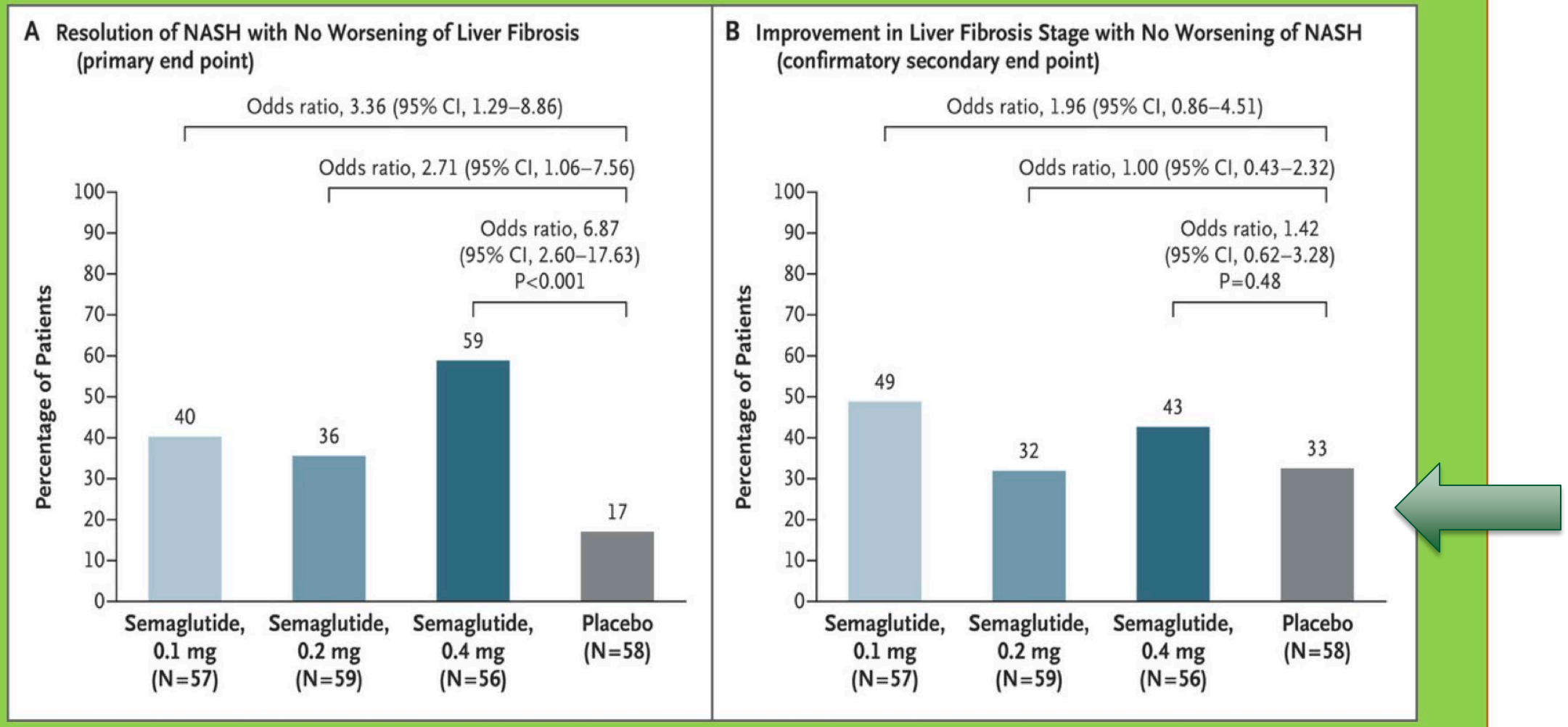
Endocrine Practice 2022 28528-562DOI: (10.1016/j.eprac.2022.03.010)

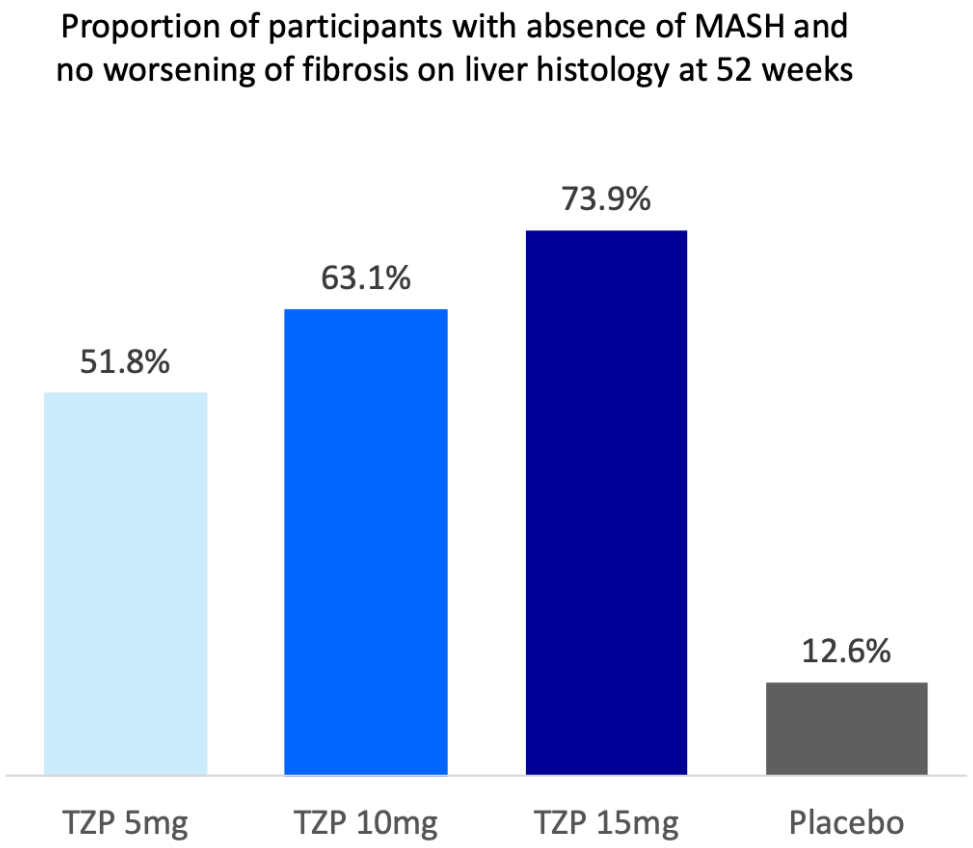
Semaglutide in NASH: Primary and Secondary Endpoints



Mean weight loss was 13% in 0.4 mg group vs. 1% in placebo

PN Newsome et al. N Engl J Med 2020

Tirzepatide SYNERGY-NASH Phase 2 Study



- Phase 2 study in adults with biopsy-proven MASH with stage 2 or 3 fibrosis
- All doses met primary endpoint of absence of MASH with no worsening of liver histology
- Secondary endpoint of decrease in fibrosis by at least one stage with no worsening of MASH on liver histology was clinically meaningful across doses
- Adverse events were consistent with other tirzepatide studies in people living with obesity or type 2 diabetes

TZP = tirzepatide; MASH = metabolic dysfunction-associated steatohepatitis

https://trials.lilly.com/en-US/trial/226499

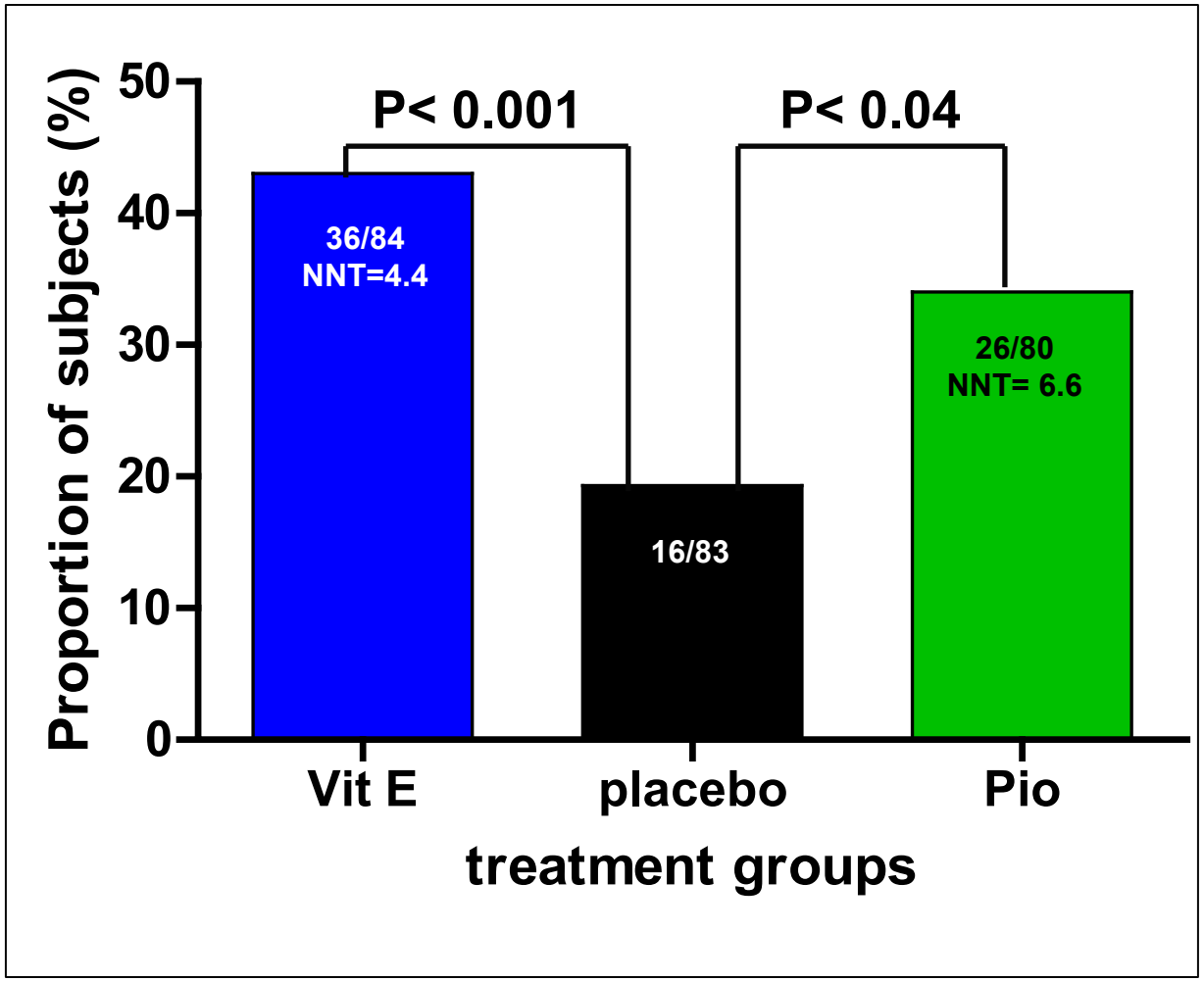
PIVENS: Vitamin E not Pioglitazone met primary endpoint

- **Improved histology**
  - **> 1 drop in ballooning**
  - **No increase in fibrosis**

  AND
- **Reduction in NAS ≤ 3 or**
- **NAS decrease of ≥ 2**

- **Both resolved NASH**
- **Neither impacted Fibrosis**

Pioglitazone improves insulin sensitivity @ PPAR gamma ½ and lipid metabolism through PPAR alpha



Sanyal et al., *NEJM* 2010

RESEARCH SUMMARY

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

Francque SM et al. DOI: 10.1056/NEJMoa2036205

PPAR Agonist

Metabolism
PPARα,δ,γ
- Insulin sensitivity
- HDLc
- TG

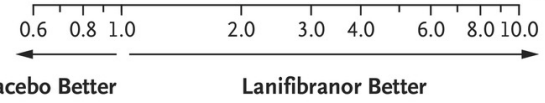
Steatosis
PPARγ
- FA uptake
- FA catabolism
- Lipogenesis

Inflammation and Ballooning
PPARα,δ,γ
- NFkB-dependent gene activation
- Inflammasome
- Ballooning

Fibrosis
PPARγ,δ
- Stellate cell proliferation and activation
- Collagen and fibronectin production

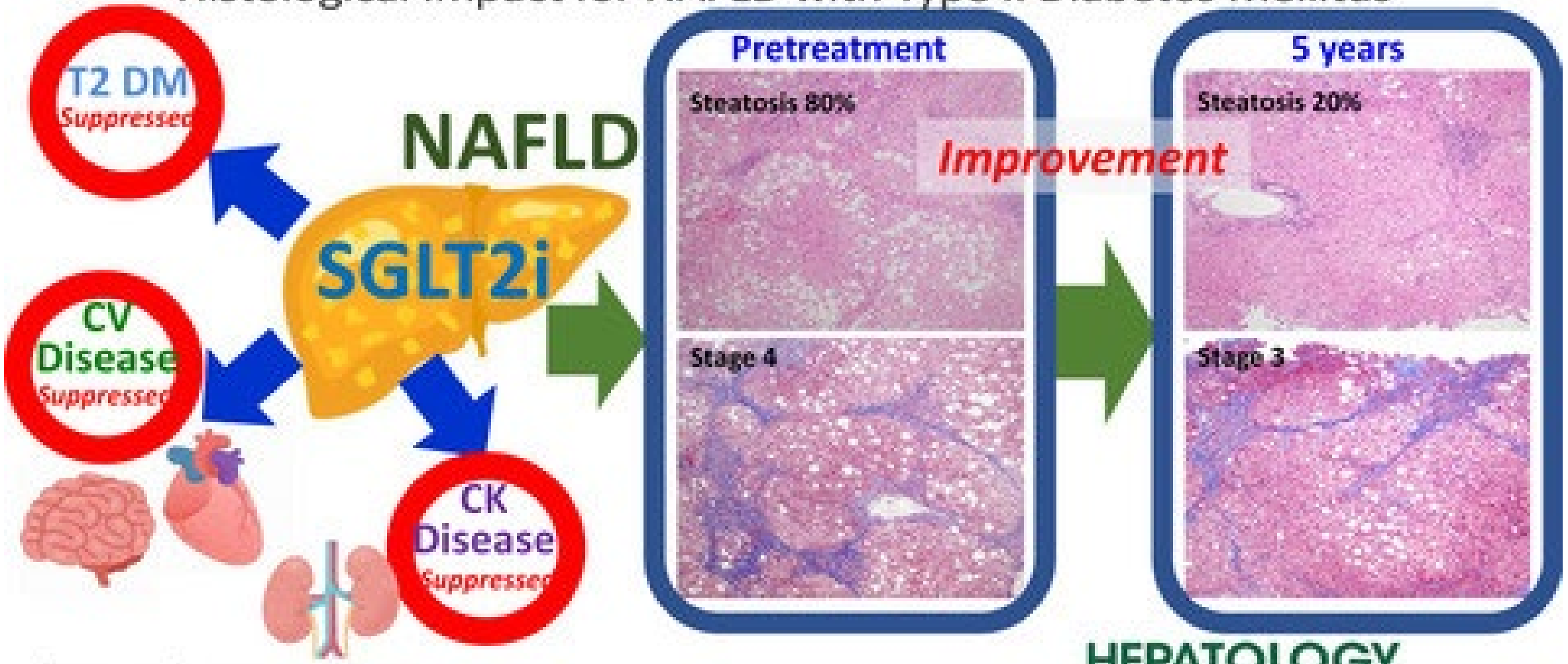
Vascular
PPARα,γ
- Portal pressure
- LSEC capillarization
- Intrahepatic vascular resistance

End Point	Placebo	Lanifibranor	Risk Ratio (95% CI)	P Value
	percent of patients with response			
Primary end point: reduction of ≥2 points in SAF-A score and no worsening of fibrosis				
Lanifibranor, 800 mg	33	48	1.45 (1.00–2.10)	0.07
Lanifibranor, 1200 mg	33	55	1.69 (1.22–2.34)	0.007
Secondary end point: resolution of NASH without worsening of fibrosis				
Lanifibranor, 800 mg	22	39	1.70 (1.07–2.71)	
Lanifibranor, 1200 mg	22	49	2.20 (1.49–3.26)	
Secondary end point: improvement in fibrosis stage of ≥1 without worsening of NASH				
Lanifibranor, 800 mg	29	34	1.15 (0.72–1.85)	
Lanifibranor, 1200 mg	29	48	1.68 (1.15–2.46)	
Composite secondary end point: resolution of NASH and improvement in fibrosis stage of ≥1				
Lanifibranor, 800 mg	9	25	2.57 (1.20–5.51)	
Lanifibranor, 1200 mg	9	35	3.95 (2.03–7.66)	



October 21, 2021 N Engl J Med 2021; 385:1547-1558 DOI: 10.1056/NEJMoa2036205

5-year Follow-Up Study with SGLT2 Inhibitor Indicated the Favorable Histological Impact for NAFLD with Type II Diabetes Mellitus

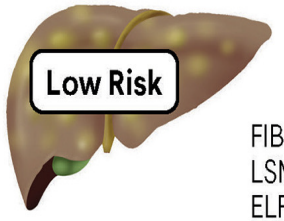
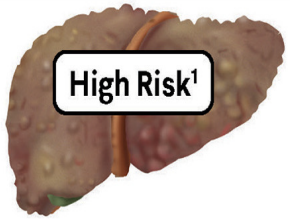


Akuta, et al. *Hepatol Commun*, 2022.

HEPATOLOGY COMMUNICATIONS

Hypertension Management in NAFLD

AACE

	Fibrosis Risk Stratification		
	 **Low Risk** FIB-4: <1.3 LSM <8 kPa ELF <7.7	 **Indeterminate Risk** FIB-4: 1.3 - 2.67 LSM 8 - 12 kPa ELF 7.7 - 9.8	 **High Risk[1]** FIB-4: >2.67 LSM >12 kPa ELF >9.8
General goal	Optimize BP control and improve cardiovascular health using preferred agents, whenever possible. Assess every 3 months and intensify therapy until goal achieved.		
Goal (individualize) [2,3,4]	Systolic < 130 mm Hg / Diastolic < 80 mm Hg	Systolic < 130 mm Hg / Diastolic < 80 mm Hg	Systolic < 130 mm Hg / Diastolic < 80 mm Hg; individualize if decompensated cirrhosis
Dietary recommendations	In addition to general dietary recommendations, reduce sodium & increase high potassium foods (e.g., DASH diet).		
Pharmacotherapy for hypertension[5]	First-line therapy: ACEIs and ARBs.	First-line therapy: ACEIs and ARBs.	Same but avoid ACEI or ARB if decompensated cirrhosis.
Intensification of therapy	Second agent: CCB, BB[6] or thiazide diuretic (as additional agents as needed).		Same but individualize if decompensated cirrhosis. Use diuretics with caution (risk of excessive diuresis).
Additional options	Additional BP medication choices: alpha blockers, central agents, vasodilators, aldosterone antagonist.		Same but individualize if decompensated cirrhosis.

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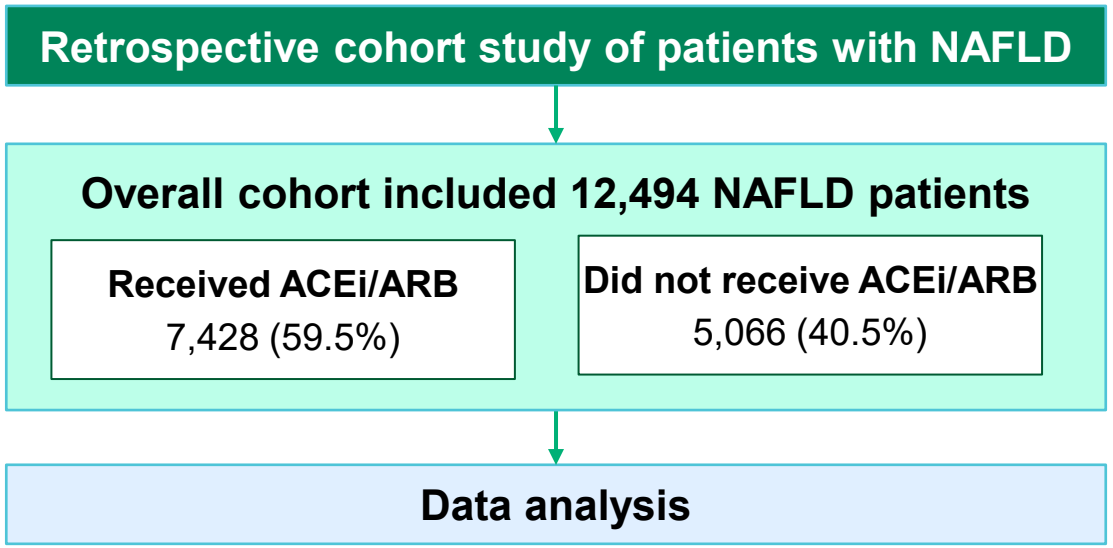
ACEi and ARBs associated with lower risk of HCC and cirrhotic complications in patients with NAFLD

BACKGROUND

- ACEi and ARBs inhibit hepatic stellate cells and liver fibrosis in animal studies

METHODS



RESULTS

	Weighted SHR (95% CI)	p-value
Liver-related events	0.44 (0.33–0.59)	<0.001
HCC	0.46 (0.30–0.72)	<0.001
Cirrhotic complications	0.42 (0.29–0.61)	<0.001

CONCLUSION

- ACEi/ARB treatment was associated with a lower risk of liver-related events, HCC, and cirrhotic complications in patients with NAFLD

Zhang X, et al. ILC 2021; OS-931

Atherogenic Dyslipidemia Management in NAFLD

Lipid risk levels are similar in the presence of NAFLD or NASH

General goal	Early intensive management of dyslipidemia needed to reduce cardiovascular risk. Intensify therapy until lipid goal is reached.		
Dietary recommendations	Increase fiber intake (>25 g/d), prioritize vegetables, fruits whole grains, nuts, reduce saturated fat & added sugars (e.g., Mediterranean diet).		
Lipid risk levels	**High CV Risk[1]** ≥2 risk factors and 10-year risk 10-20% Diabetes or CKD ≥3 with no other risk factors	**Very high CV Risk[1]** Established CVD or 10-year risk >20% Diabetes with >1 risk factor, CKD ≥3, HeFH	**Extreme CV Risk[1]** Progressive CVD CVD + diabetes or CKD ≥3 or HeFH FHx premature CVD (<55 yrs male <65 yrs female)
LDL-C goal (mg/dL)	<100	<70	<55
Non-HDL-C goal (mg/dL)	<130	<100	<80
Triglycerides goal (mg/dL)	<150	<150	<150
Apo B goal (mg/dL)	<90	<80	<70
First line pharmacotherapy: Statins	Use a moderate-to-high intensity statin[2], unless contraindicated. Statins are safe in NAFLD or NASH but do not use in decompensated cirrhosis (Child C).		
Intensify statin therapy	Use higher dose or higher potency statin.		
If LDL-C not at goal (or statin intolerant)[4]: add 2nd agent, then add 3rd agent	Ezetemibe, PCSK9 inhibitor, bempedoic acid, colesevelam, inclisiran.		
If triglycerides > 500 mg/dL	Fibrates, Rx grade omega 3 FA, icosapent ethyl (if diabetes, optimize glycemic control and consider pioglitazone).[5]		
If TG 135-499 mg/dL on max statin dose	Emphasize diet (as above).	Add icosapent ethyl.[6]	Add icosapent ethyl.[6]

Adapted from Handelsman Y, et al. Endocr Pract. 2020;26:1196-1224.

Abbreviations: CKD = Chronic kidney disease, CVD = cardiovascular disease, FA = Fatty acids, HeFH = Heterozygous familial hypercholesterolemia, HTN = Hypertension, Rx = Prescription

1. Major risk factors: age >40, DM, HTN, FHx of early CVD, low HDL C, elevated LDL, Smoking, CKD 3,4
2. High intensity statin therapy: rosuvastatin 20, 40 mg/d, atorvastatin 40, 80 mg/d.
3. Other lipid modifying agents should be used in combination with maximally tolerated statins if goals not reached: ezetimibe, PCSK9 inhibitor, bempedoic acid, colesevelam, or inclisiran.
4. Assess adequacy and tolerance of therapy with focused laboratory evaluations and patient follow up.
5. Niacin may lower triglycerides but does not reduce CVD and worsens insulin resistance. It may promote hyperglycemia in a population at high-risk of diabetes.
6. Icosapent ethyl 4g/d is recommended as an adjunct to maximally tolerated statin therapy to reduce risk of cardiovascular disease in high-risk persons.

Algorithm Figure 3

Treat MASLD in those at risk for progression

- **LIFESTYLE MODIFICATIONS FOR ALL**
- Referral to preventative health or behavioral therapy
- Therapy in those at highest risk for progression (F2/F3)
- Bariatrics/Endo-bariatrics
- Consider clinical trials

Lifestyle modifications

Energy restriction

- Calorie restriction (500–1,000/day)
- 7–10% weight loss target
- Long-term maintenance approach

Coffee consumption

- No liver-related limitations

Macronutrient composition

- Low-to-moderate fat
- Moderate-to-high carbohydrate
- Low-carbohydrate ketogenic diets or high protein

Comprehensive lifestyle approach

Weight loss works!
Don't forget Bariatrics

Fructose intake

- Avoid fructose-containing food and drink

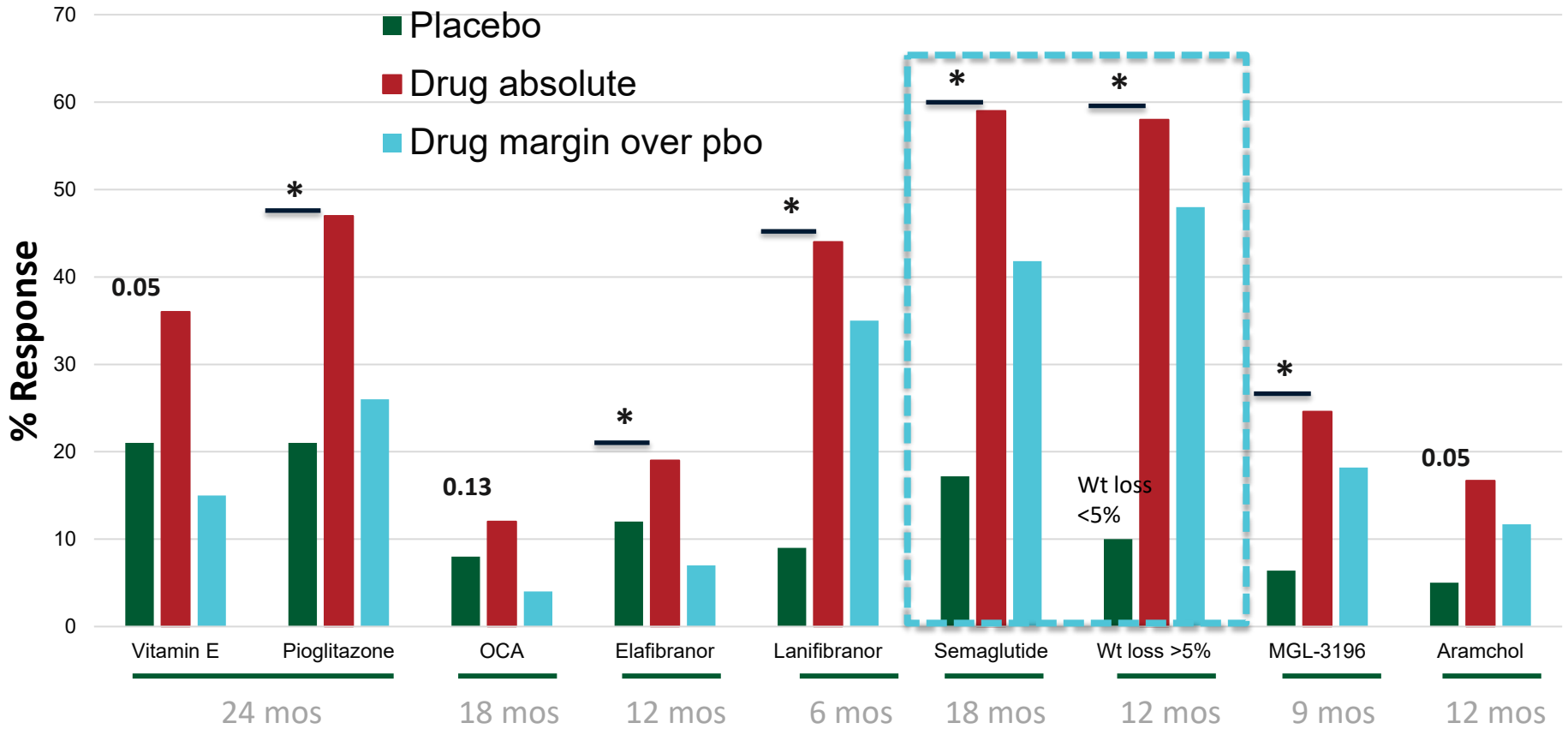
Daily alcohol intake

- Strictly below 30 g men and 20 g women

Physical activity

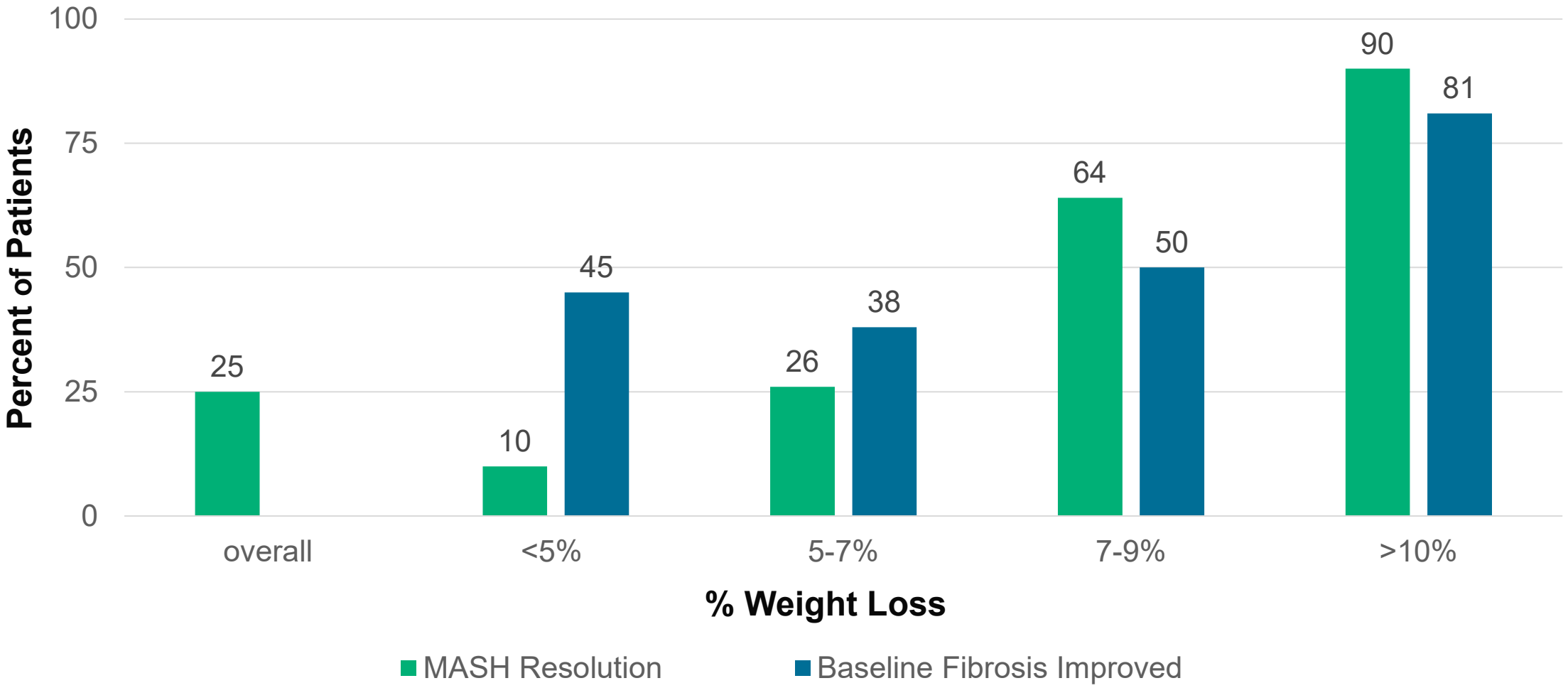
- 150–200 min/week moderate intensity in 3–5 sessions
- Resistance training to promote musculoskeletal fitness and improve metabolic factors

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402



NASH Resolution

Weight Loss Reverses Fibrosis



(Vilar-Gomez et al., 2015)

1| INDICATIONS AND USAGE

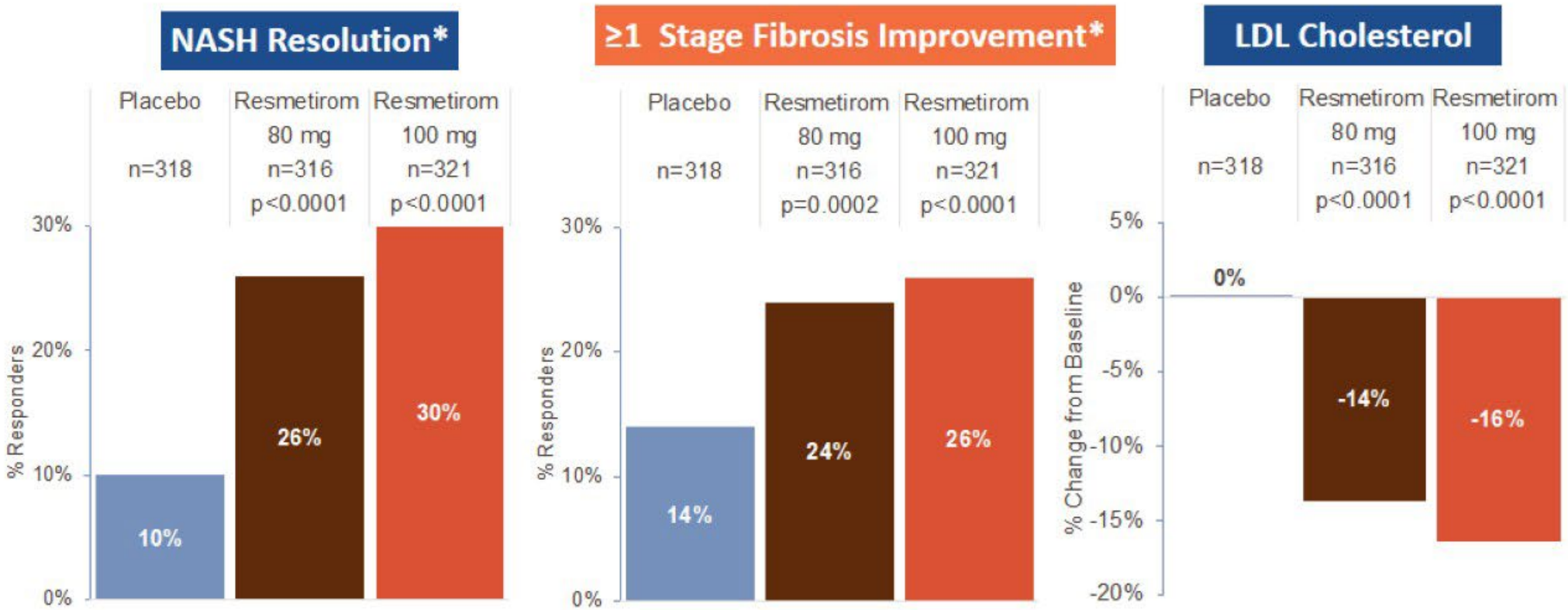
BACK

- REZDIFFRA is indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis).
- This indication is approved under accelerated approval based on improvement of NASH and fibrosis *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Limitations of use:

- Avoid use of REZDIFFRA in patients with decompensated cirrhosis *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

Dual Primary Endpoints (Week 52): Primary Analysis



Both primary liver biopsy endpoints and the key secondary endpoint of LDL cholesterol lowering were met

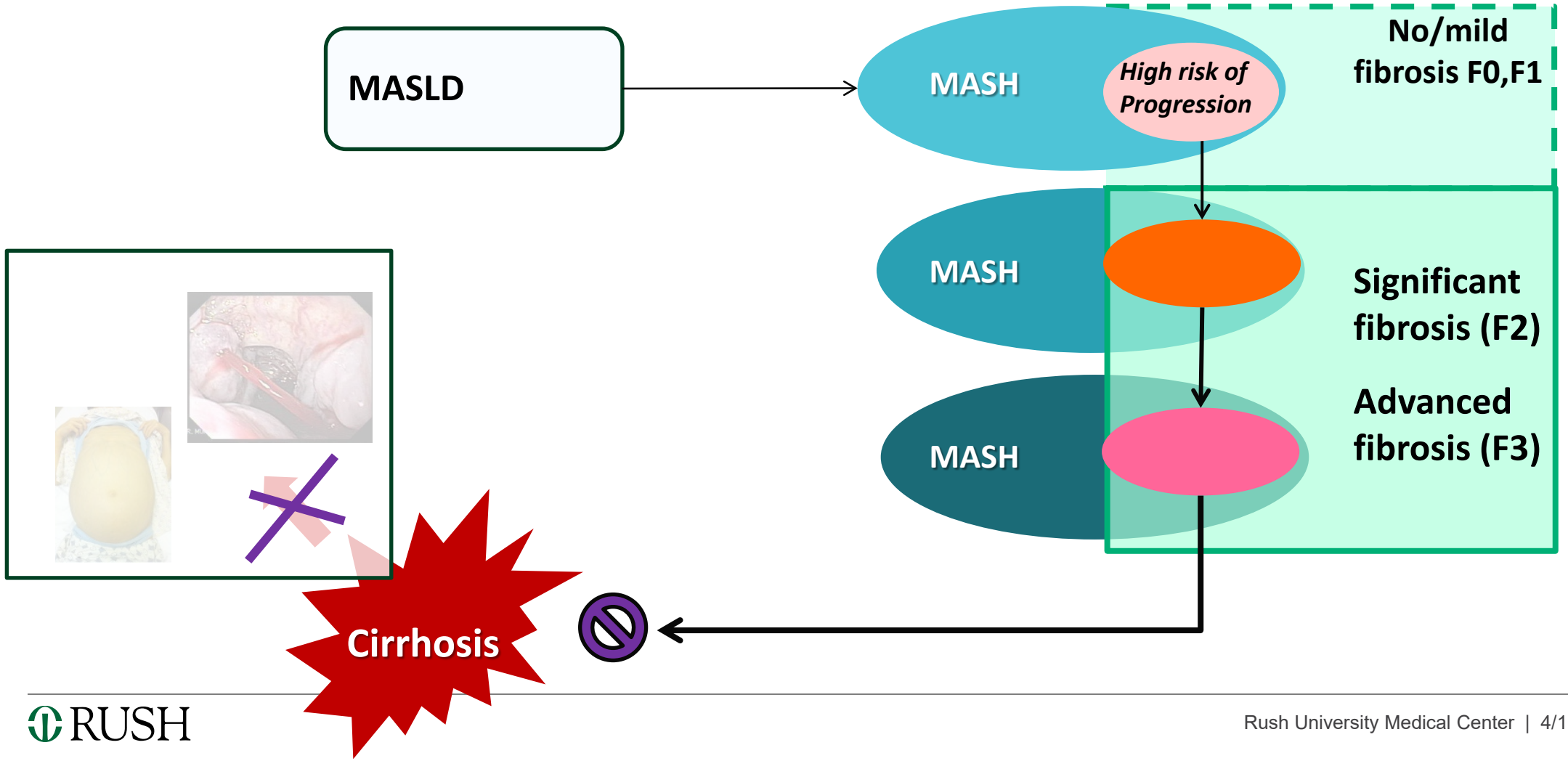
*NASH Resolution with no worsening of fibrosis; ≥1 Stage Fibrosis Improvement with no worsening of NAS

NASH, nonalcoholic steatohepatitis.

Madrigal

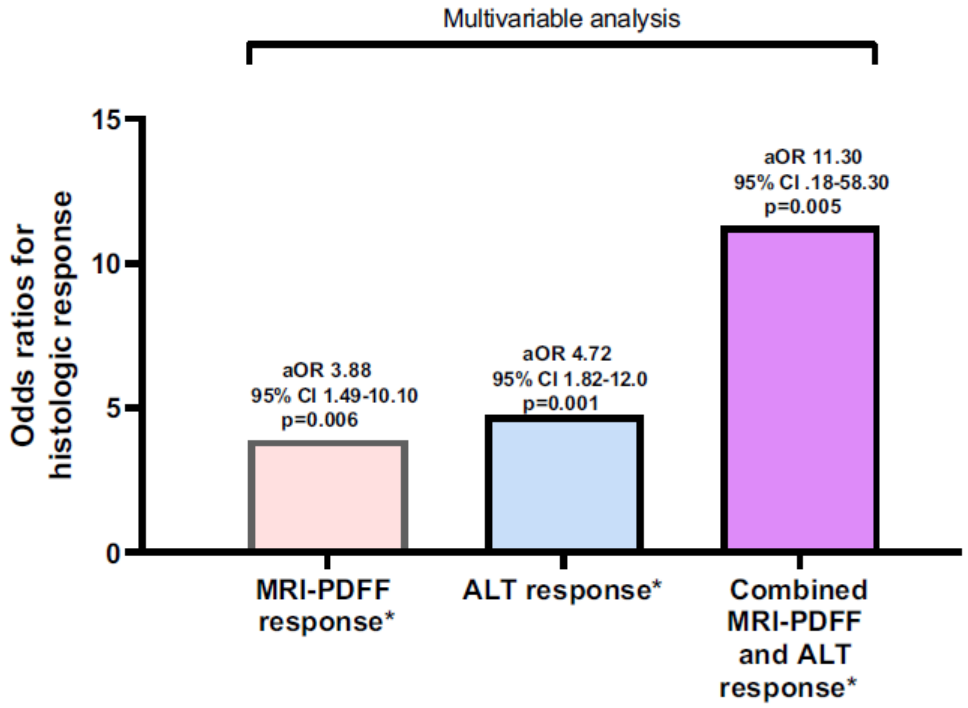
Harrison, NEJM 2024

Current view of candidates for pharmacotherapy: non-cirrhotic MASH

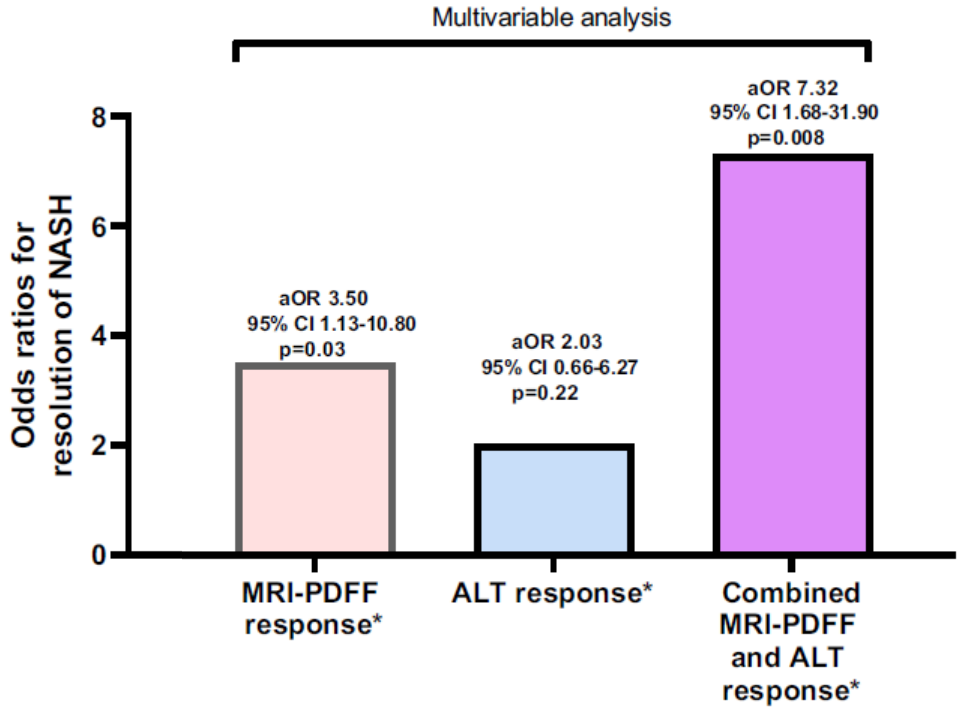


Liver fat content (>30% relative decrease) and a ≥17 IU/L ALT reduction predict histological improvement

NAS ≥2 pt reduction

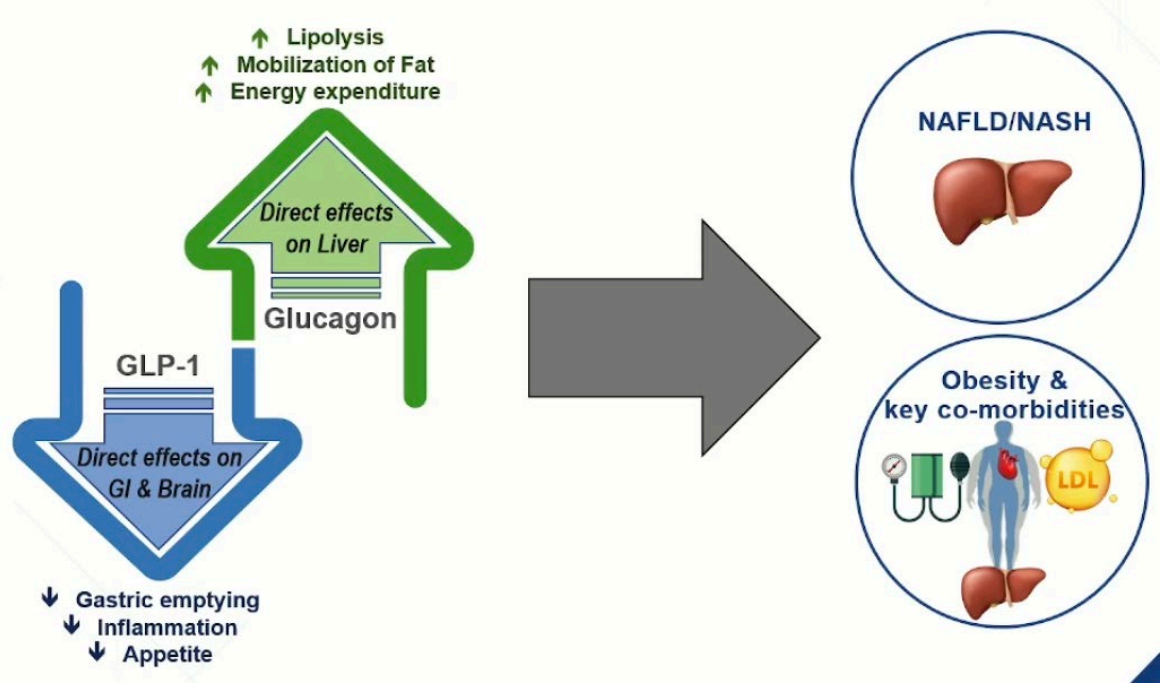


NASH resolution



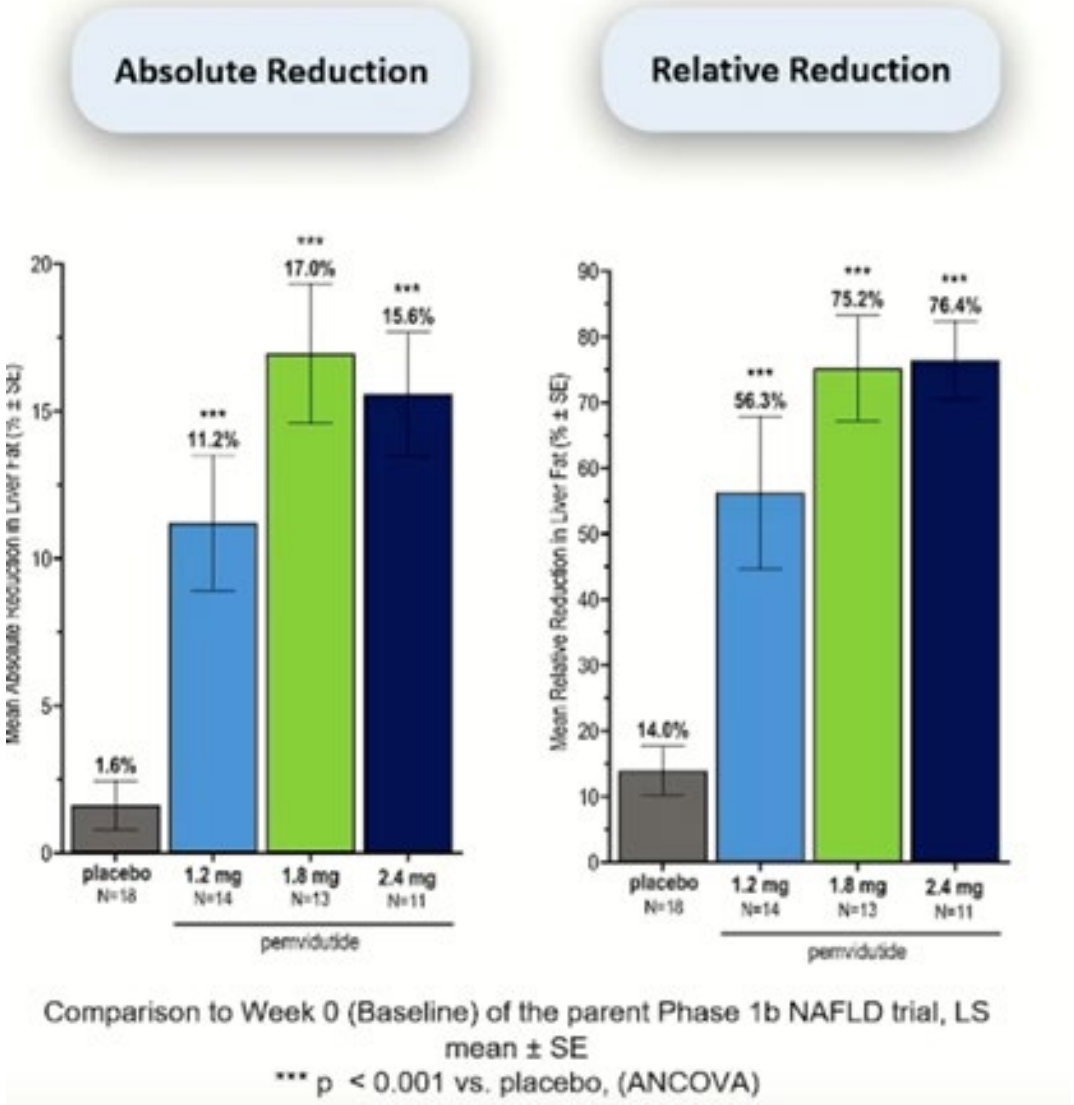
Huang, Clin Gastro Hepatol 2023

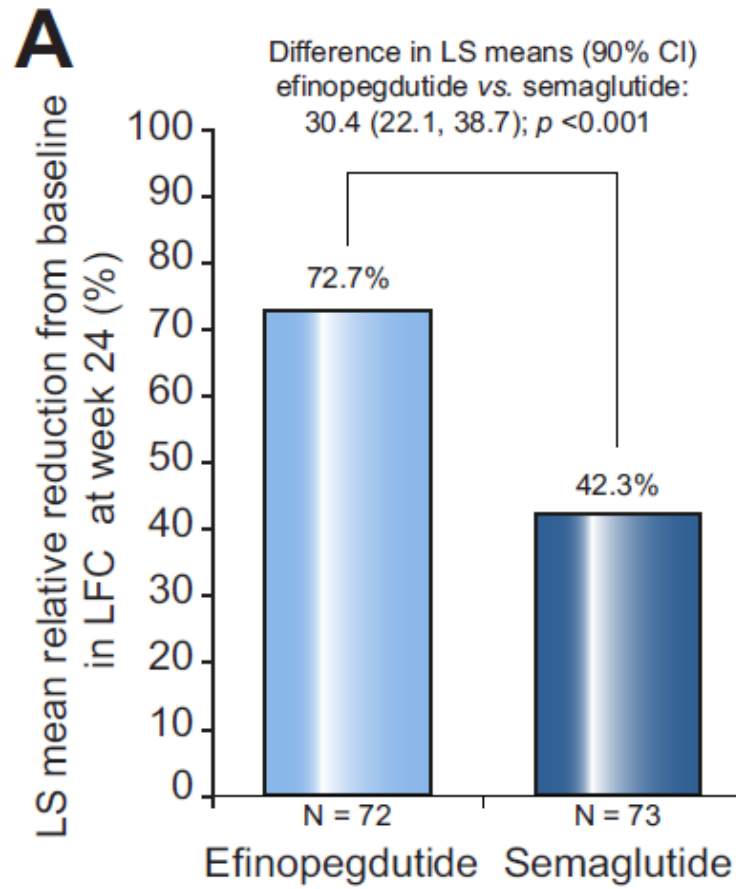
GLP1 dual and triple agonism



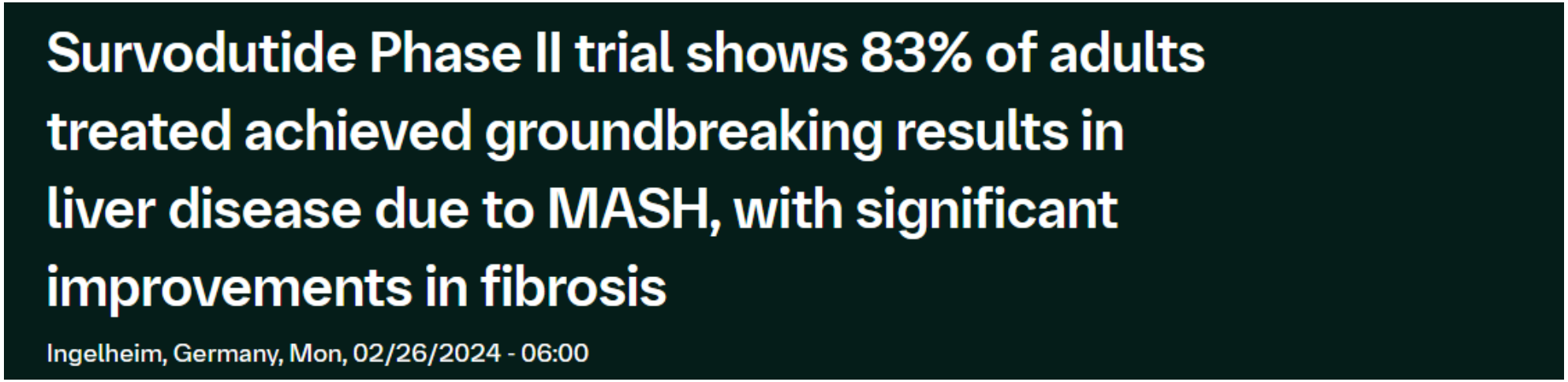
Active name	brand name	GLP 1 agonist	GIP	Glucagon
Semaglutide	Ozempic, Wegovy and Rybelsus	✓		
Tirzepatide	Mounjaro	✓	✓	
Retatrutide	Phase III	✓	✓	✓
Survodutide	Phase III	✓		✓

Liver fat reduction at week 24 GLP1-Glucogon R co-agonist





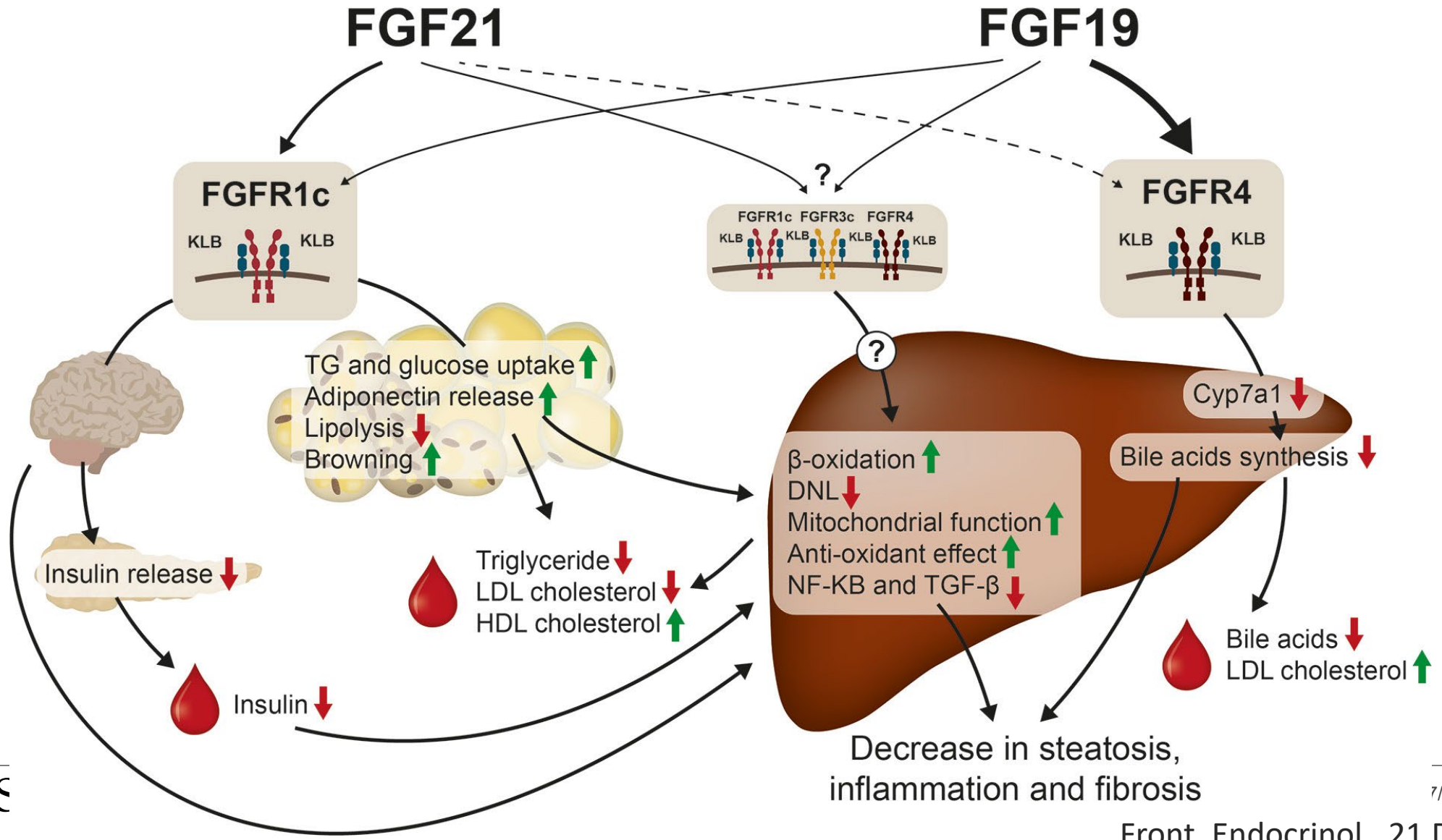
Romero-Gomez, J Hepatol 2023



- 83.0% of adults treated with survodutide achieved a statistically significant improvement of metabolic dysfunction-associated steatohepatitis (MASH) versus placebo (18.2%)
- Primary endpoint biopsy-proven improvement in MASH after 48 weeks, without worsening of fibrosis
- Survodutide also met all secondary endpoints, including a statistically significant improvement in liver fibrosis

https://www.boehringer-ingelheim.com/human-health/metabolic-diseases/survodutide-top-line-results-mash-fibrosis-0#:~:text=Boehringer%20Ingelheim%20today%20announced%20that,%25)%2C%20p%3C0.0001%5D.

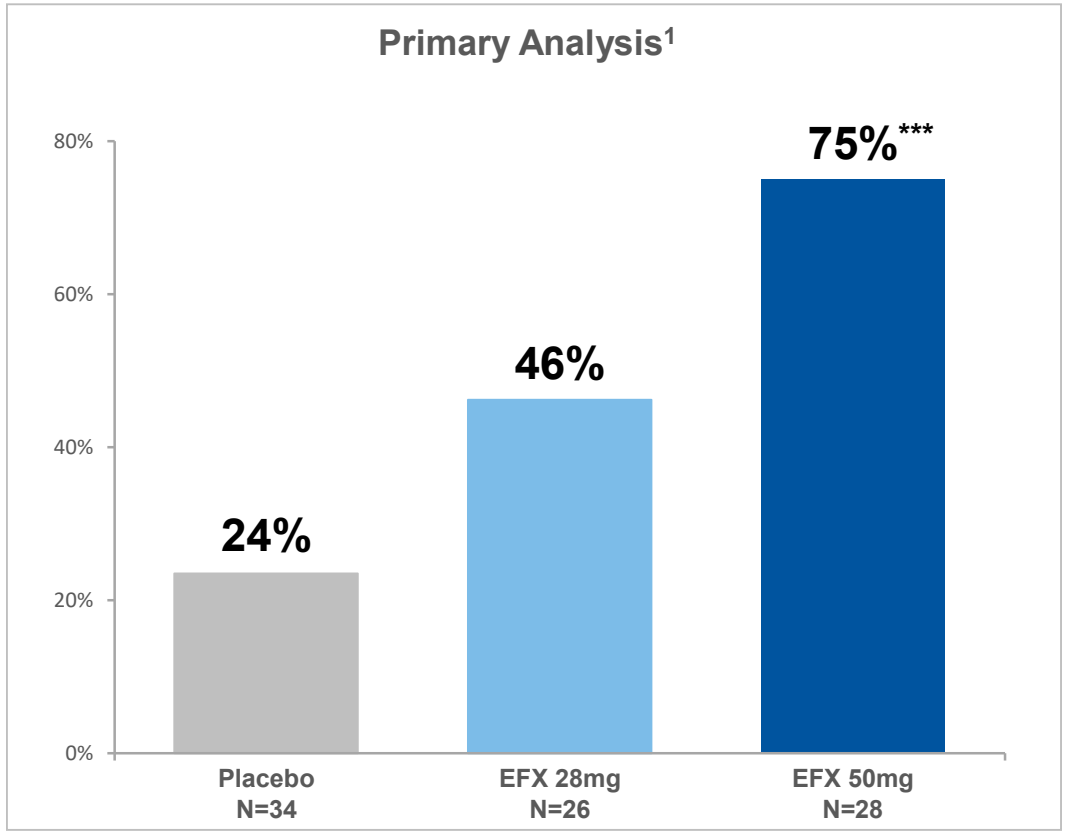
Metabolic Regulators: FGF21 and FGF19



Front. Endocrinol., 21 December 2020

Histological improvement in efruxifermin Phase 2b HARMONY study (F2-F3 NASH)

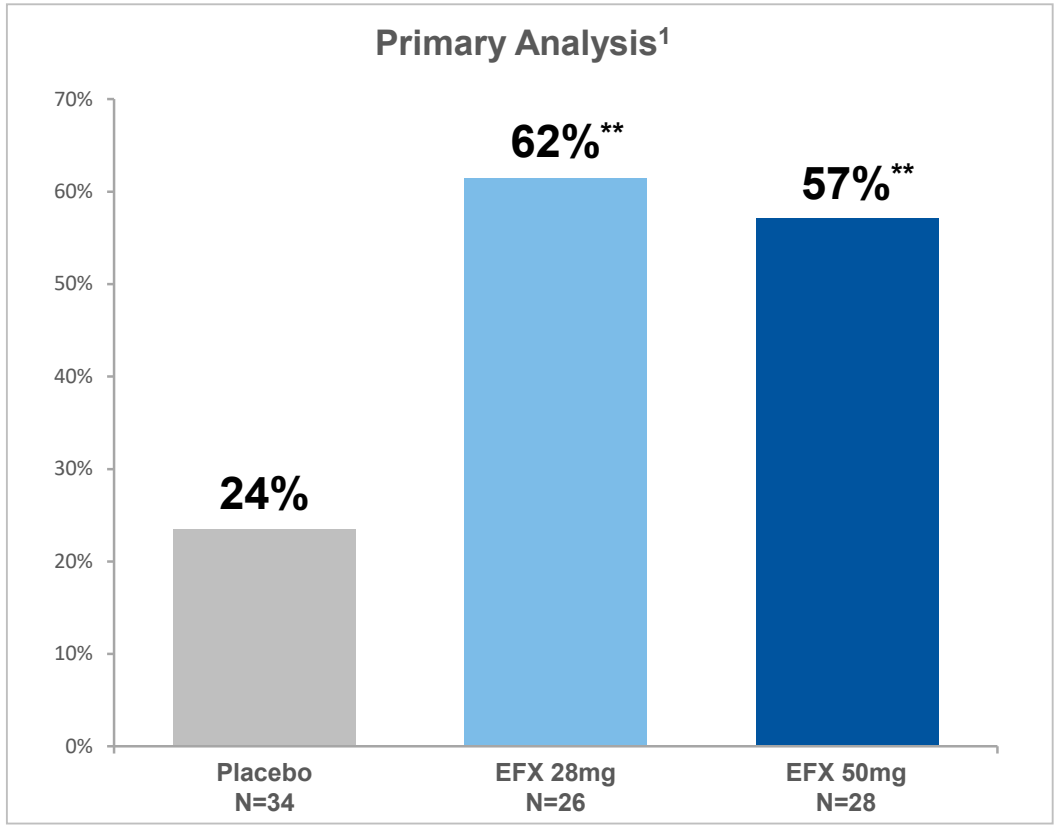
Fibrosis Improvement ≥1 Stage & No Worsening of MASH at Week 96



[1] All subjects with baseline and Week 96 biopsies

*** p<0.001, versus placebo (Cochran-Mantel-Haenszel Test [CMH])

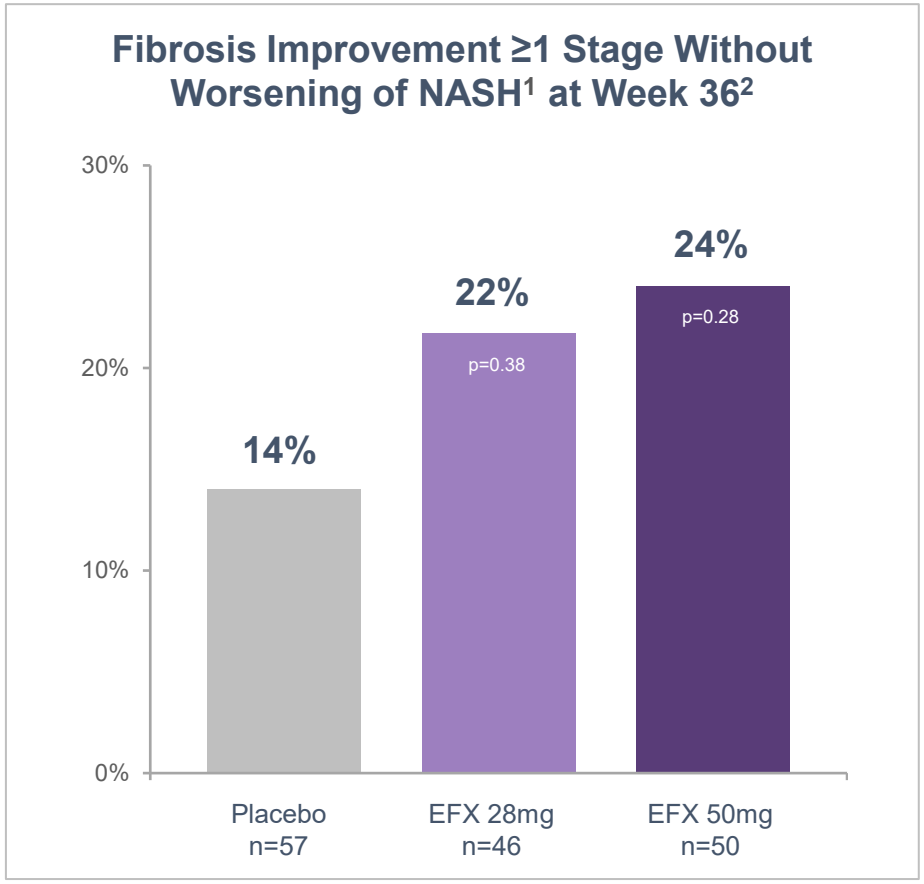
MASH Resolution & No Worsening of Fibrosis at Week 96

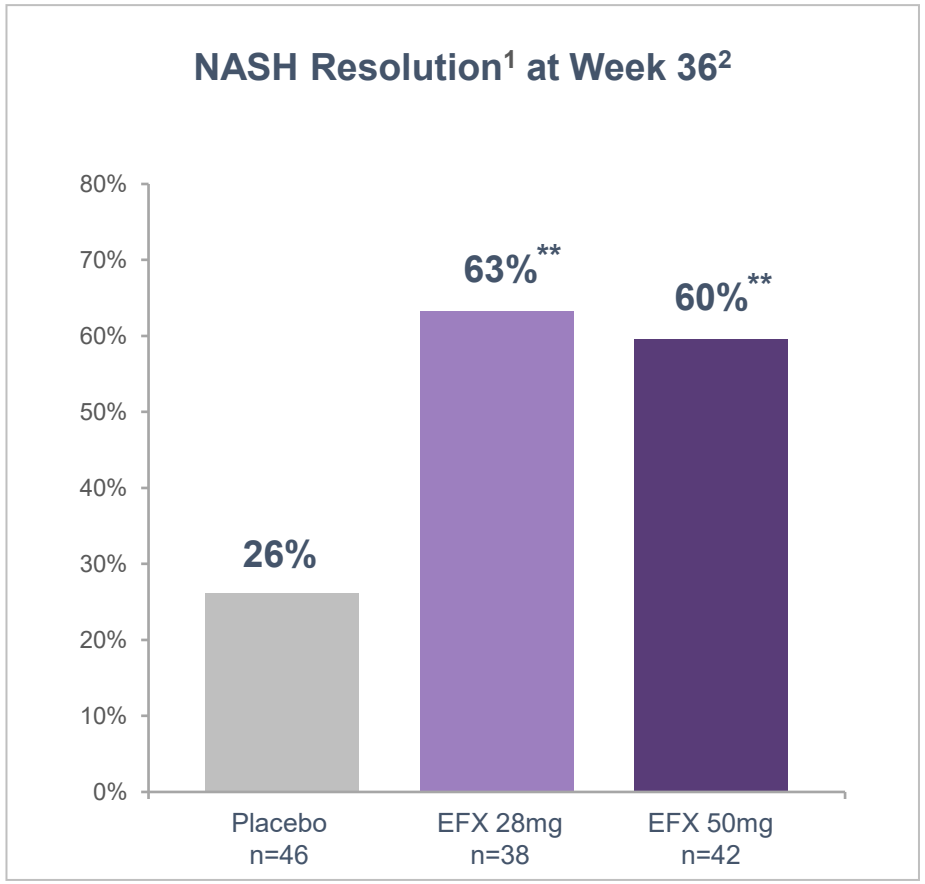


[1] All subjects with baseline and Week 96 biopsies

** p<0.01, versus placebo (CMH test)

Improvements in Fibrosis and Steatohepatitis





** p<0.01, versus placebo (Cochran–Mantel–Haenszel test [CMH])

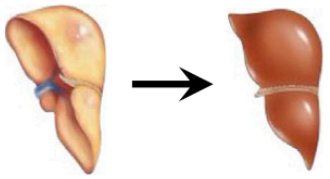
Source Data: Liver Biopsy Analysis Set; Topline preliminary data

Safety and Efficacy of Efruxifermin in Combination With a GLP-1 Receptor Agonist in Patients With NASH/MASH and Type 2 Diabetes

Administration of once-weekly efruxifermin, for 12 weeks, to patients with type 2 diabetes and MASH with fibrosis (F1–F3) receiving a stable GLP1-RA:

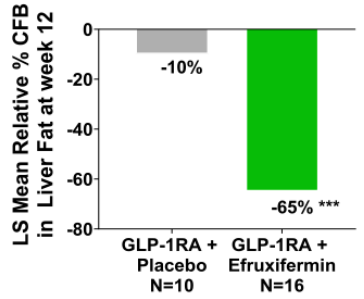
50 mg efruxifermin (n=21)

vs placebo (n=10)

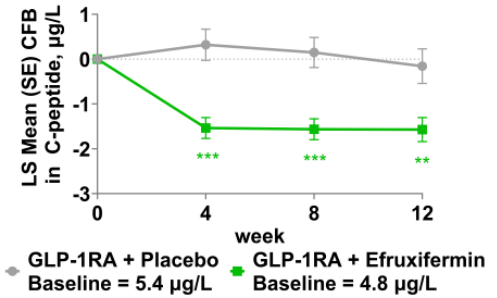


Improved liver and metabolic health:

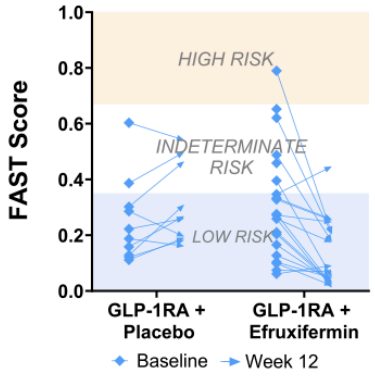
Decreased liver fat



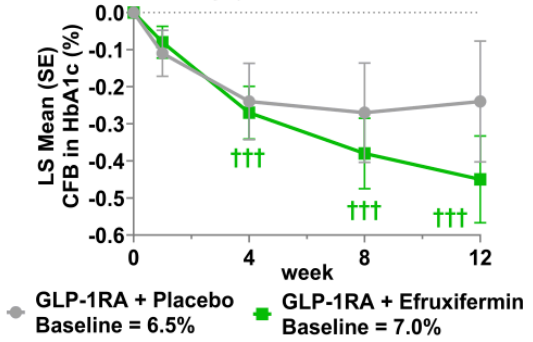
Improved insulin sensitivity



Reduced risk of MASH progression

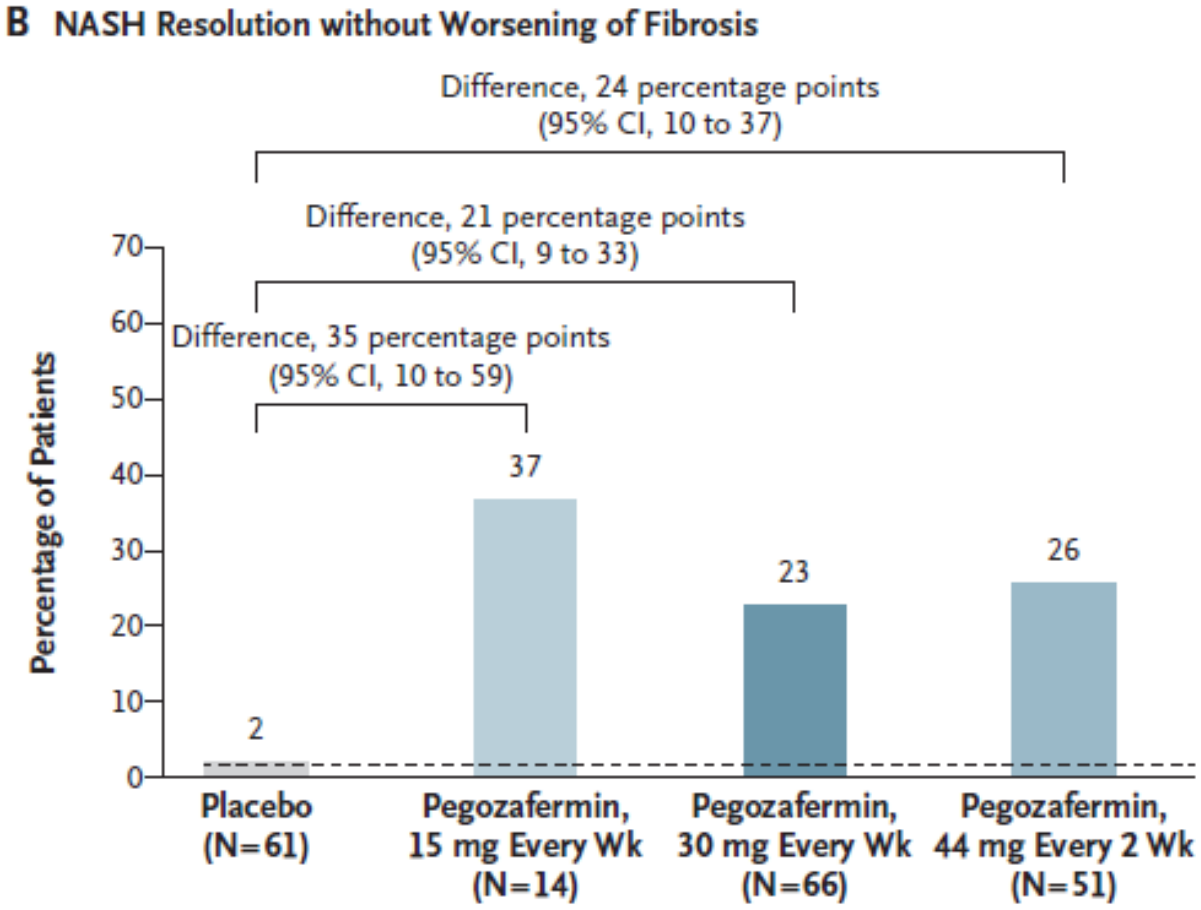


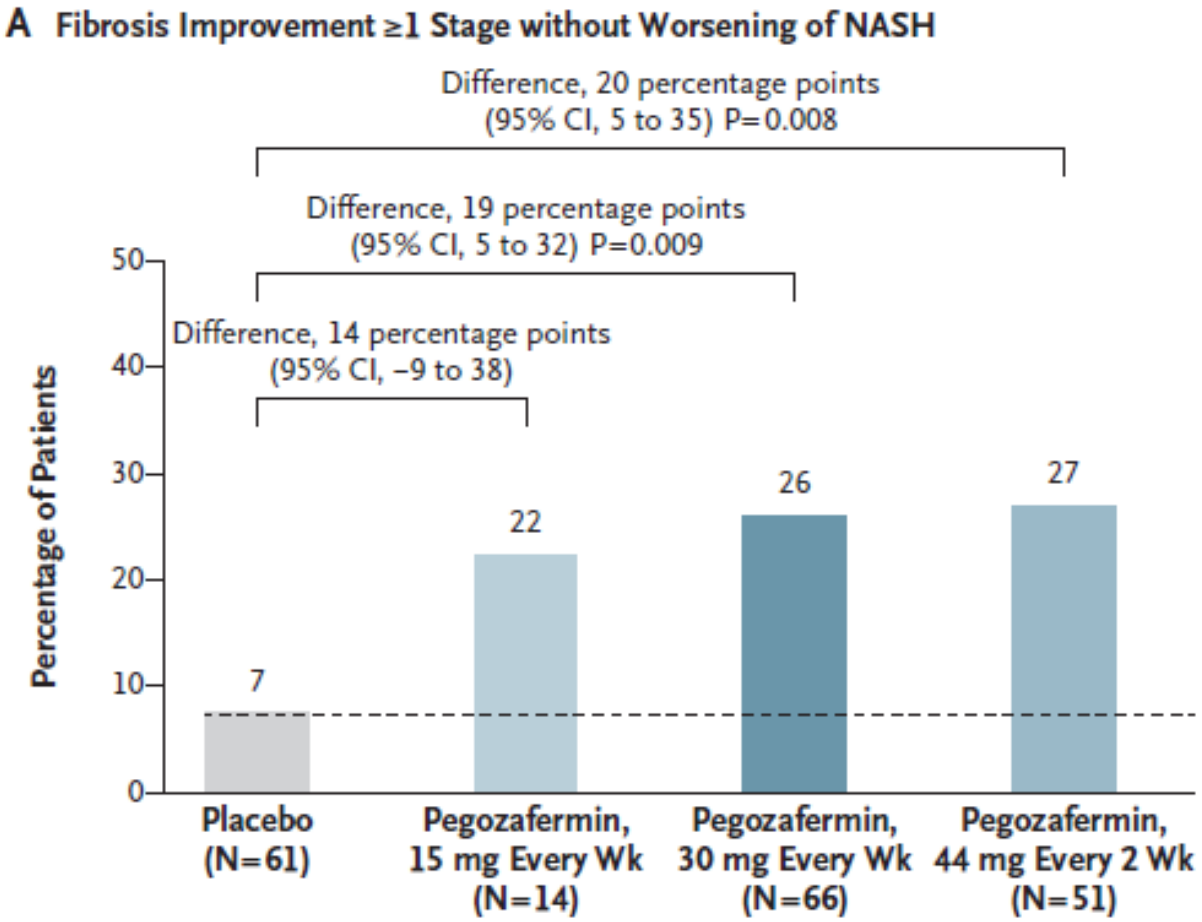
Improved glycemic control



Clinical Gastroenterology and Hepatology

FGF21 Analogue Pegozafermin in NASH





Loomba et al N Engl J Med 2023;389:998-1008

Agents in phase 3 trials for NASH –efficacy data available

	Hepatic effects	Metabolic effects	Weight loss
~~*Obeticholic acid*~~	Yes	No	No
Resmetirom- Approved	Yes	Yes (lipids)	No
Lanifibranor	Yes	Yes (glycemia, lipids)	No
GLP1, GLP/GIP	?	Yes	+ (major)
GLP/Glucagon	Yes	Yes	+ (moderate)
FGF21	Yes	Yes	No

Conclusions:

- MASLD is present in more than 30% of Americans
  - Concentrate the effort in those with risk for liver disease
- Fibrosis is associated with liver related morbidity and mortality
  - **We have our first agent for F2/F3!!!**
- Lifestyle intervention is the cornerstone of therapy
- Treat co-morbid conditions in a liver friendly way
  - **Treat Obesity**
- Follow your patient (on or off therapy!)
- Drug pipeline is rich…

Thank you.

RUSH
Rush University Medical Center

Excellence is just the beginning.