Building Bridges, Closing Gaps in NASH Care: The Pivotal Role of Gastroenterologists

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Learning Objectives

1. Determine the next step for a patient being evaluated for NAFLD based on their FIB-4 score
2. Determine if a patient with a given transient elastography score is at risk for clinically significant fibrosis
3. Interpret data from phase 3 clinical trials of novel therapies being investigated for the treatment of NASH
4. Have increased confidence in assisting primary care providers in linking patients with clinically significant fibrosis to care

Characterizing the Epidemic

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The Global Prevalence of NAFLD

Pooled Prevalence of NAFLD: 30.05% (95% CI: 27.88–32.32%)

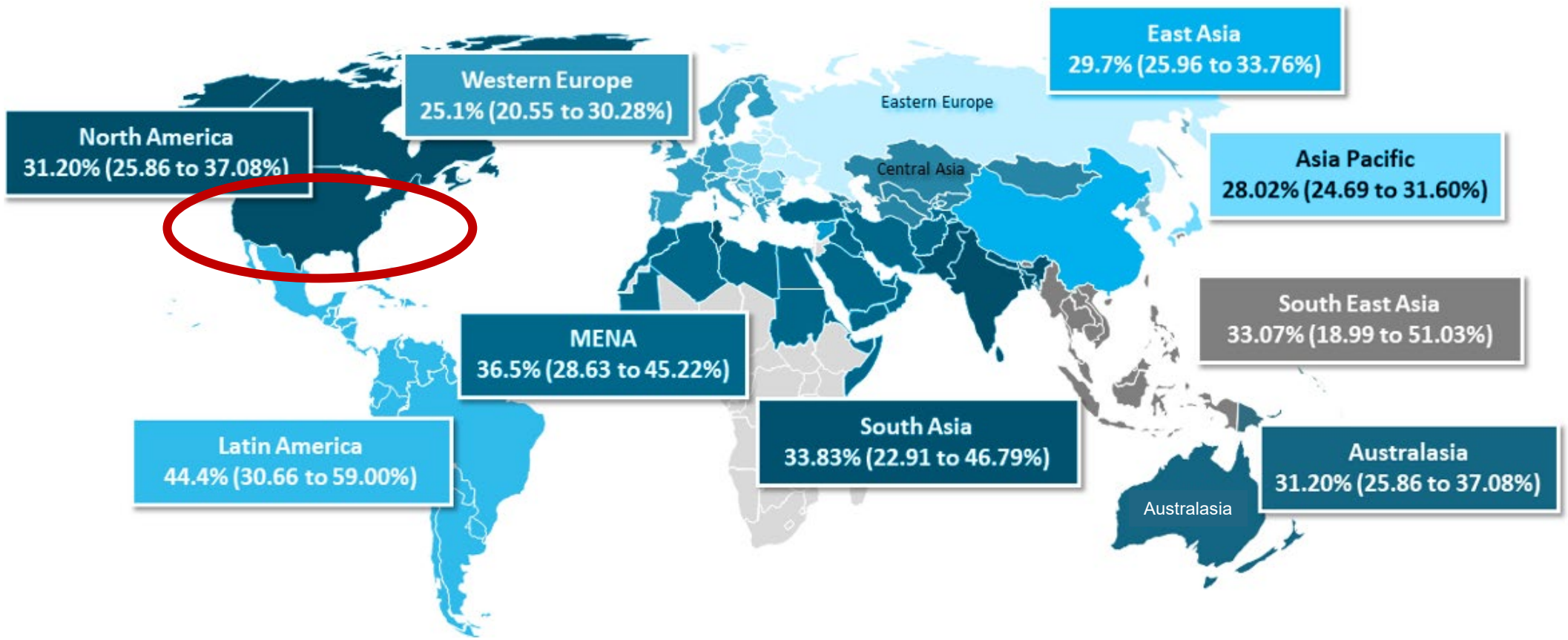


Figure adapted from Younossi ZM, et al. *Hepatology*. 2023;77(4):1335-1347.

The Global Prevalence of NASH

In 2019, the global prevalence of NASH: 5.27% (SE: 2.63)

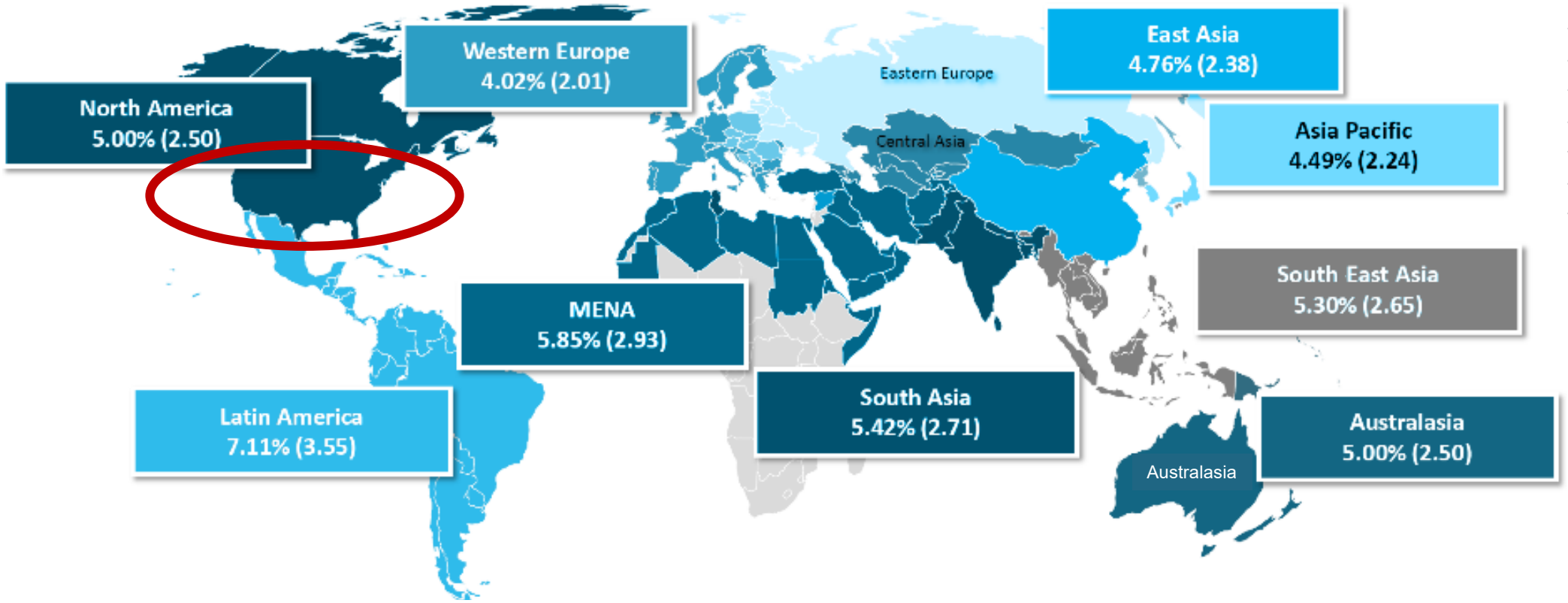
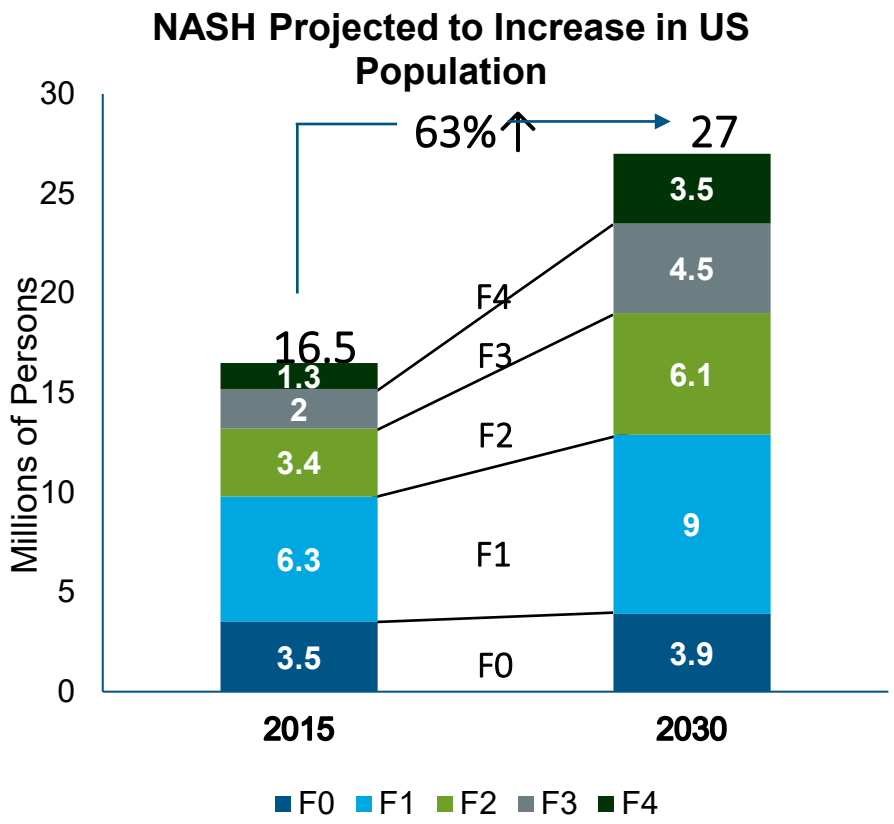


Figure adapted from Younossi ZM, et al. *Hepatology*. 2023;77(4):1335-1347.

And It's Going to Get Worse



- NAFLD in US projected to increase 21% from 2015 to 2030
- NASH in US projected to increase 63% from 2015 to 2030

NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.
Adapted from Estes C, et al. *Hepatology.* 2018;67:123-133.


What Do We Need to Do?

Start Thinking NAFLD When …

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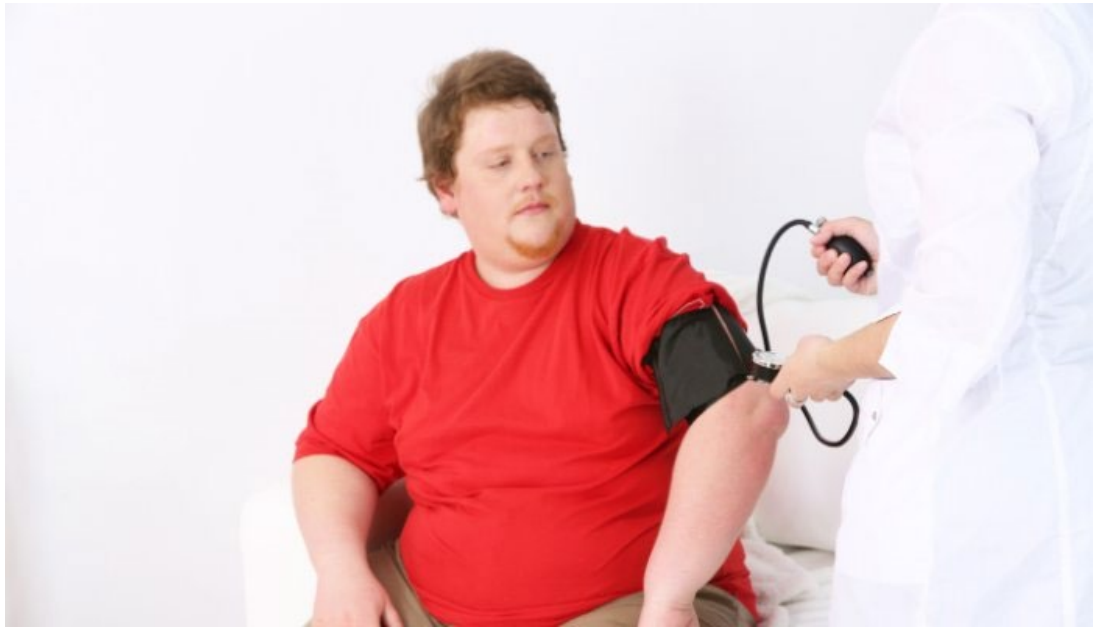
Patients With NAFLD Are Hiding in Plain Sight



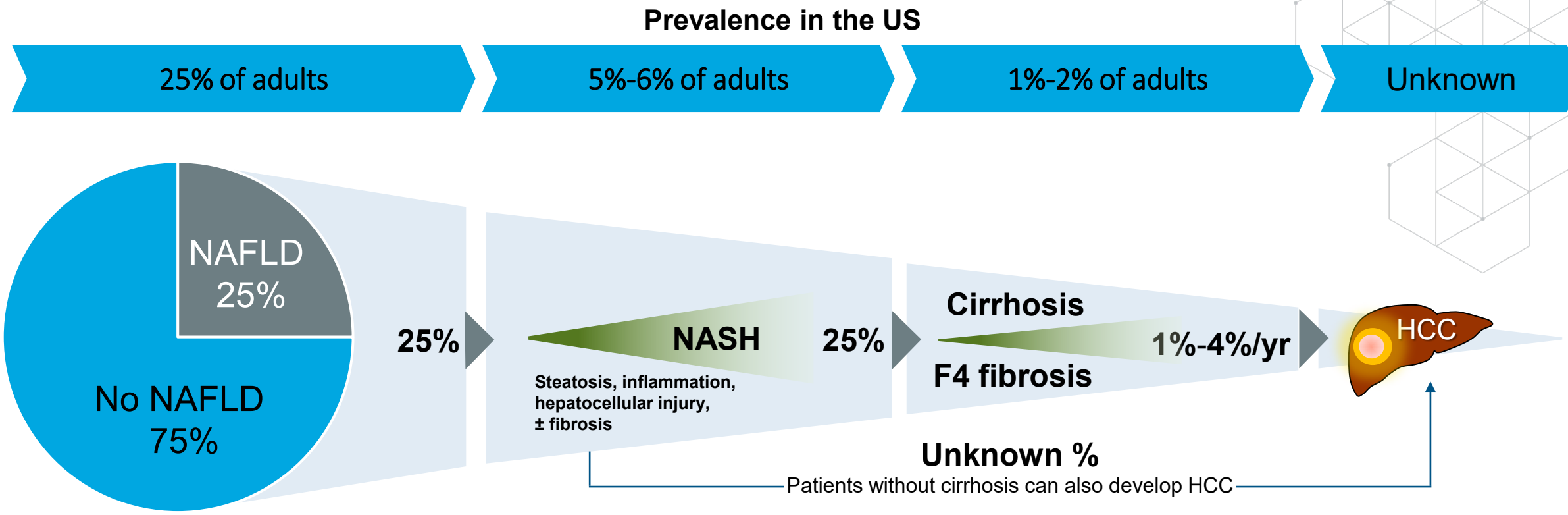
Who are they?

- Obesity
- Diabetes
- Metabolic syndrome

Where are they?

- Primary care clinics
- Endocrinology clinics
- Gastroenterology clinics

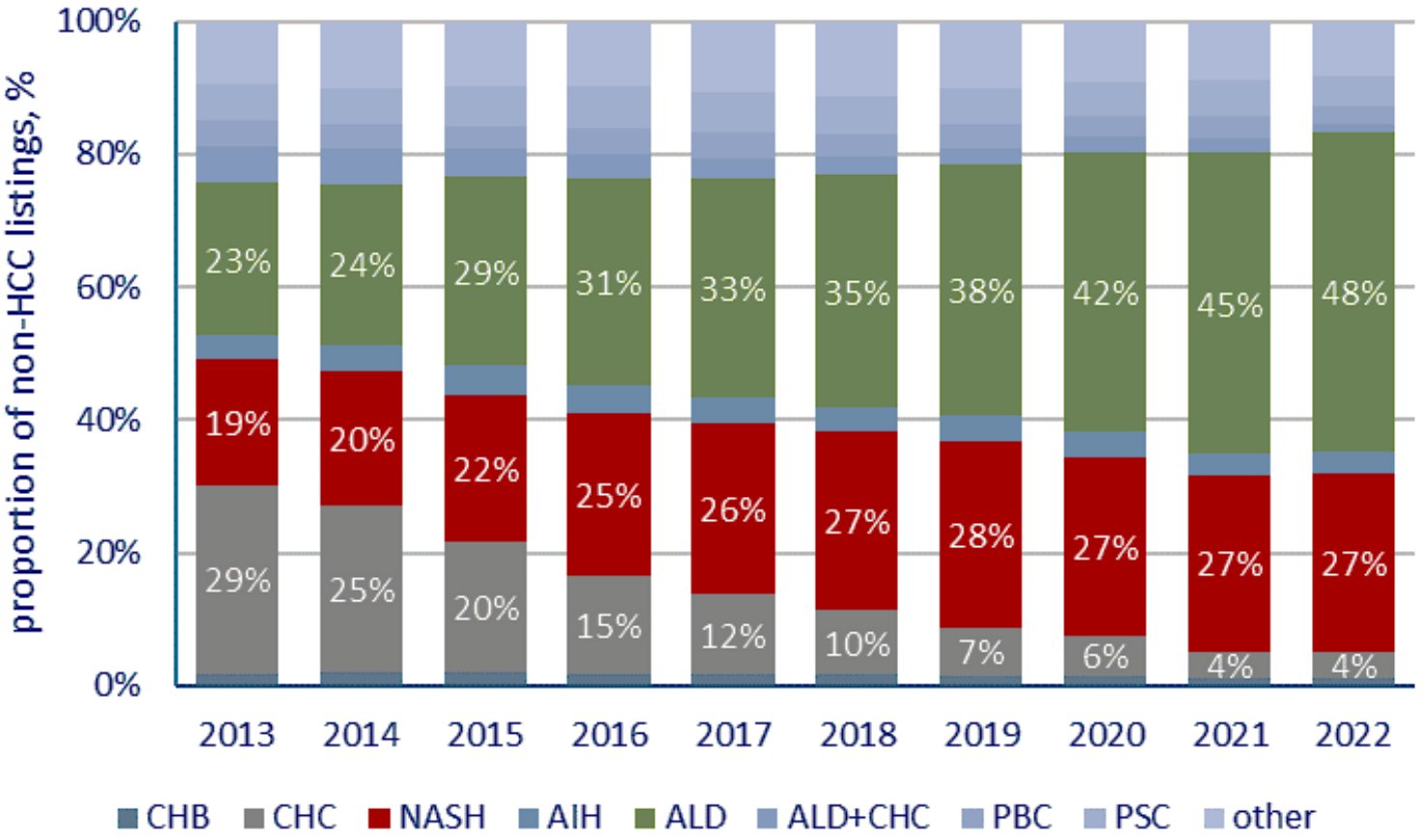
Why Is It Important to Take Action? NASH Is A Progressive Disease



F, fibrosis stage; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

1. Diehl AM, Day C. *N Engl J Med*. 2017;377:3063-3072. 2. Fan JG, et al. *J Hepatol*. 2017;67(4):862-873.

Why is It Important to Take Action? NASH Is Emerging As the Most Common Cause of Need for Liver Transplantation



Younossi ZM, et al. *Hepatology*. 2023;77(4):1335-1347.

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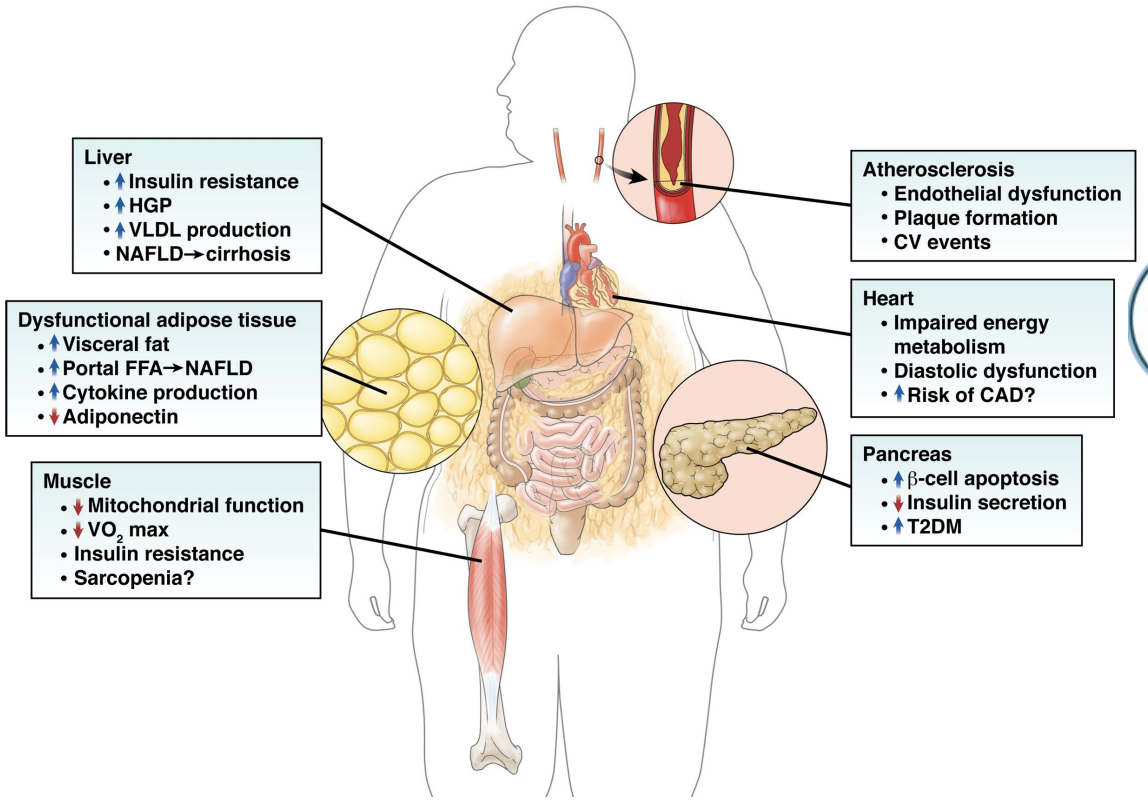
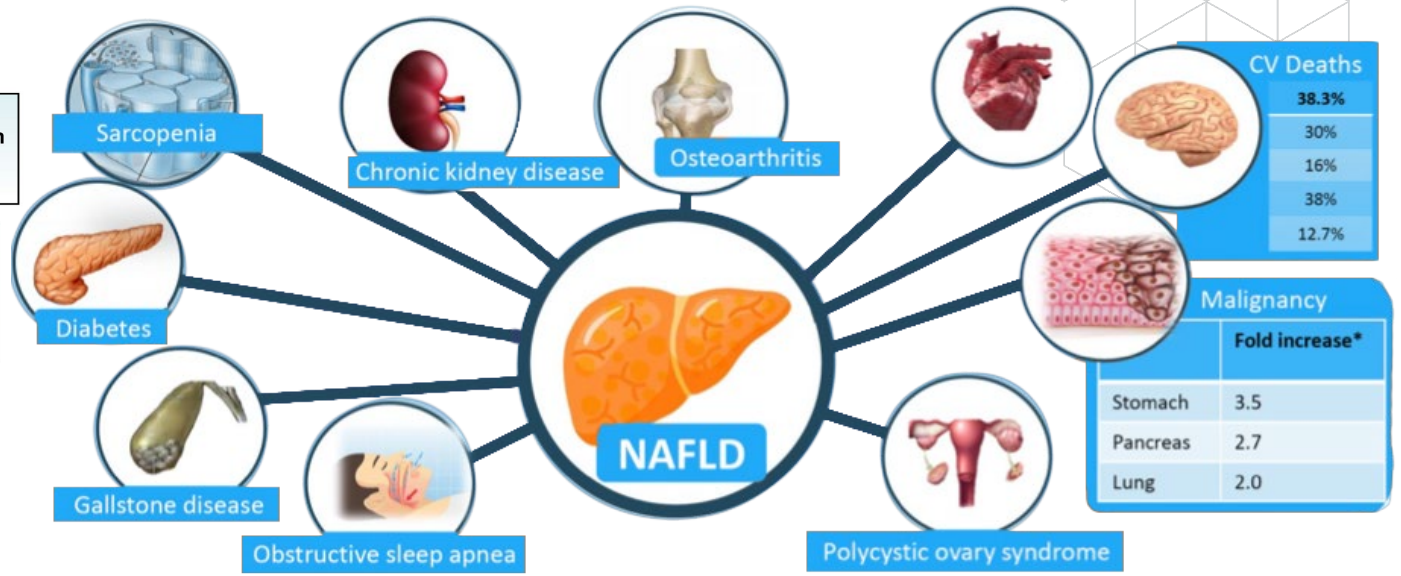
Why is It Important to Take Action? Extrahepatic Morbidity and Mortality Associated With NAFLD

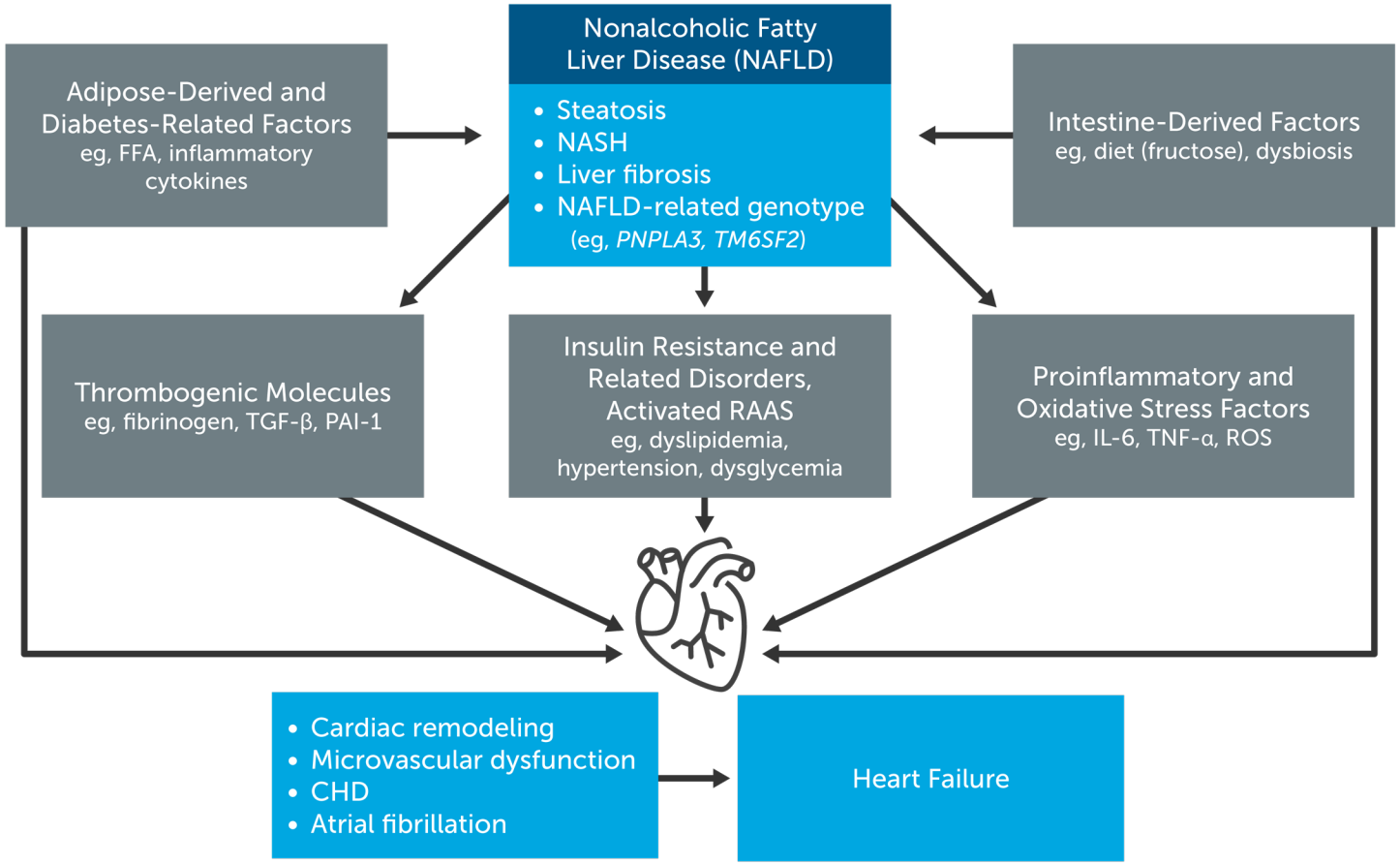
Common Pathogenic Pathways





Younossi Z, et al. *Hepatology*. 2018;69(6):2672-2682.
Cusi K. *Gastroenterology*. 2012;142(4):711-725.e6.

Hepatic and Extrahepatic Factors Affecting Risk of Heart Failure in NAFLD



Mantovani A, et al. *J Am Coll Cardiol.* 2022;79(2):180-191.

Identifying and Engaging Patients in NAFLD/NASH-Directed Care

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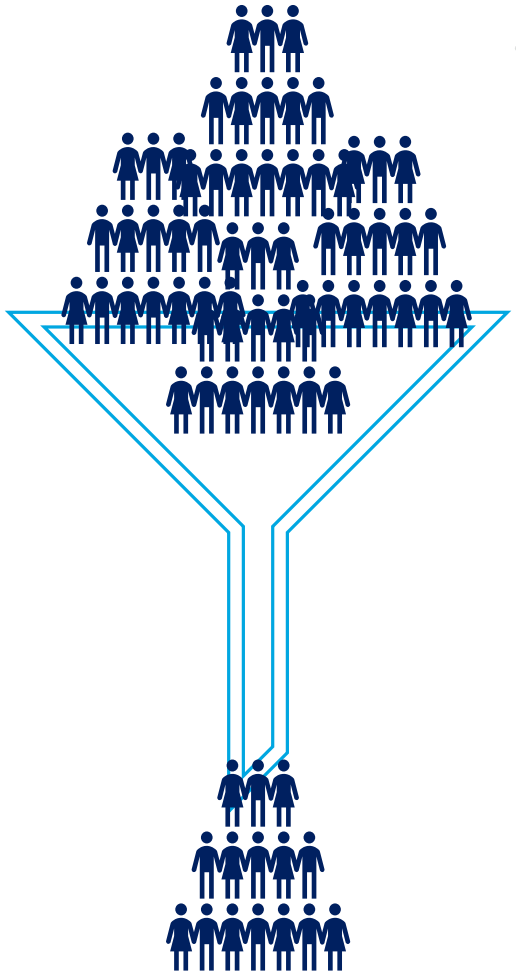
Why? The NASH Tsunami in the US



Linking Patients With Clinically Significant Fibrosis To Care: Role of Gastroenterologists in Bridging the Gaps

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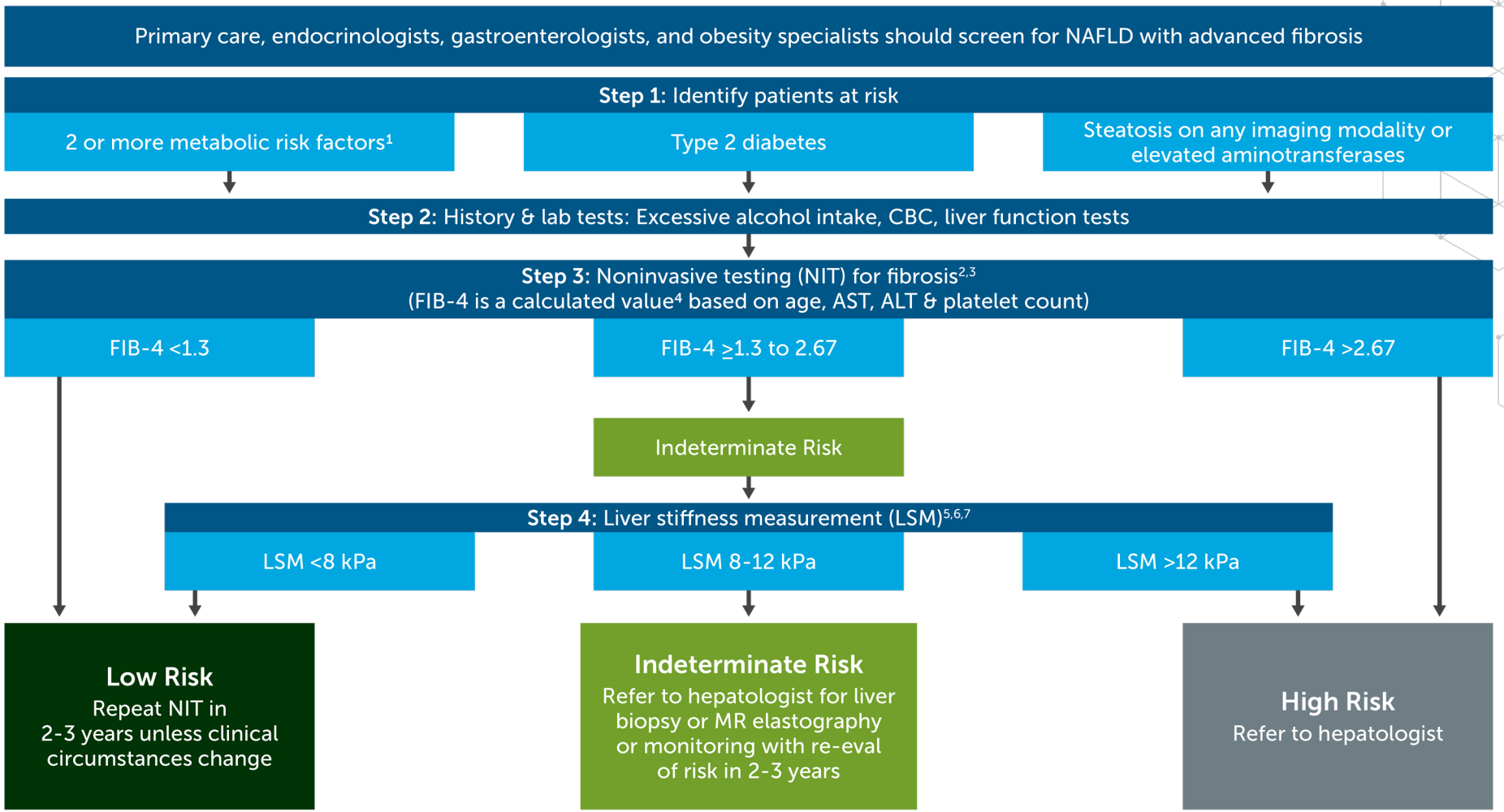
How? NAFLD Clinical Care Pathway



1. Metabolic risk factors: central obesity, high triglycerides, low HDL cholesterol, hypertension, prediabetes, or insulin resistance. 2. For patients age >65, use FIB-4 <2.0 as the lower cutoff. Higher cutoff does not change. 3. Other NITs derived from routine laboratories can be used instead of FIB-4. 4. Many online FIB-4 calculators are available such as https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis. 5. Ultrasound acceptable if vibration-controlled transient elastography (VCTE, FibroScan®) is unavailable. Consider referral to hepatologist for patients with hepatic steatosis on ultrasound who are indeterminate or high risk based on FIB-4. 6. LSM values are for VCTE (FibroScan®). Other techniques such as bidimensional shear wave elastography or point shear wave elastography can also be use used to measure LSM. Proprietary commercially available blood NITs may be considered for patients considered indeterminate or high risk based on FIB-4 or APRI, or where LSM unavailable. 7. Eddowes et al. uses 8.2 and 12.1 kPa as cutoffs for LSM using VCTE. Validation of simple (rounded) cutoffs reported by Papatheodoridi et al. **Adapted from: Kanwal F, et al. *Gastroenterology*. 2021;161(5):1657-1669.**

Step 1: Identify Patients At Risk for Clinically Significant Fibrosis

- T2D
- ≥2 metabolic risk factors
- Incidental finding of hepatic steatosis or elevated serum aminotransferases

Kanwal F, et al. *Gastroenterology*. 2021;161(5):1657-1669.

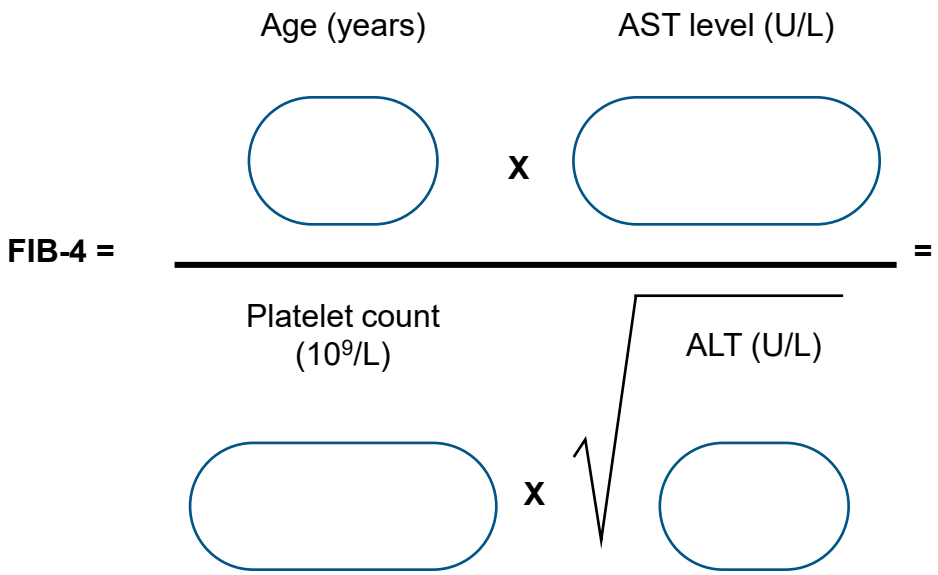
Step 2: Conduct Standard History and Blood Tests to Obtain Key Measures

- Screen adults ≥18 years for amount of alcohol use
  - Alcohol intake history: ≥14 drinks/wk for women or ≥21 drinks/wk for men
- Assess aminotransferases, CBC
- Evaluate for presence of other chronic liver and biliary diseases
- Evaluate for liver mass lesions

Kanwal F, et al. *Gastroenterology*. 2021;161(5):1657-1669.

Step 3: Conduct Noninvasive Testing for Liver Fibrosis Using Simple Scores

Focus on FIB-4



- Risk stratification for clinically significant fibrosis
  - **<1.3:** excludes advanced fibrosis
  - **≥1.3 – 2.67:** indeterminate
  - **>2.67:** high risk for advanced fibrosis

Kanwal F, et al. *Gastroenterology*. 2021;161(5):1657-1669.

You Know the FIB-4 Score: What Next?

- **<1.3:** low risk, excludes advanced fibrosis
  - No further evaluation needed
  - Repeat FIB-4 in 2-3 years
- **≥1.3 – 2.67:** indeterminate risk
  - Obtain a liver stiffness measurement
  - Refer to hepatologist for liver biopsy, MR elastography or monitoring and re-evaluation in 2-3 years
- **>2.67:** high risk for advanced fibrosis
  - Refer to hepatologist

Step 4: Obtain a Liver Stiffness Measurement

- **LSM <8 kPa:** low risk
- **LSM 8-12 kPa:** intermediate risk
- **LSM ≥12 kPa:** high risk

Kanwal F, et al. *Gastroenterology*. 2021;161(5):1657-1669.

Current Standard of Care

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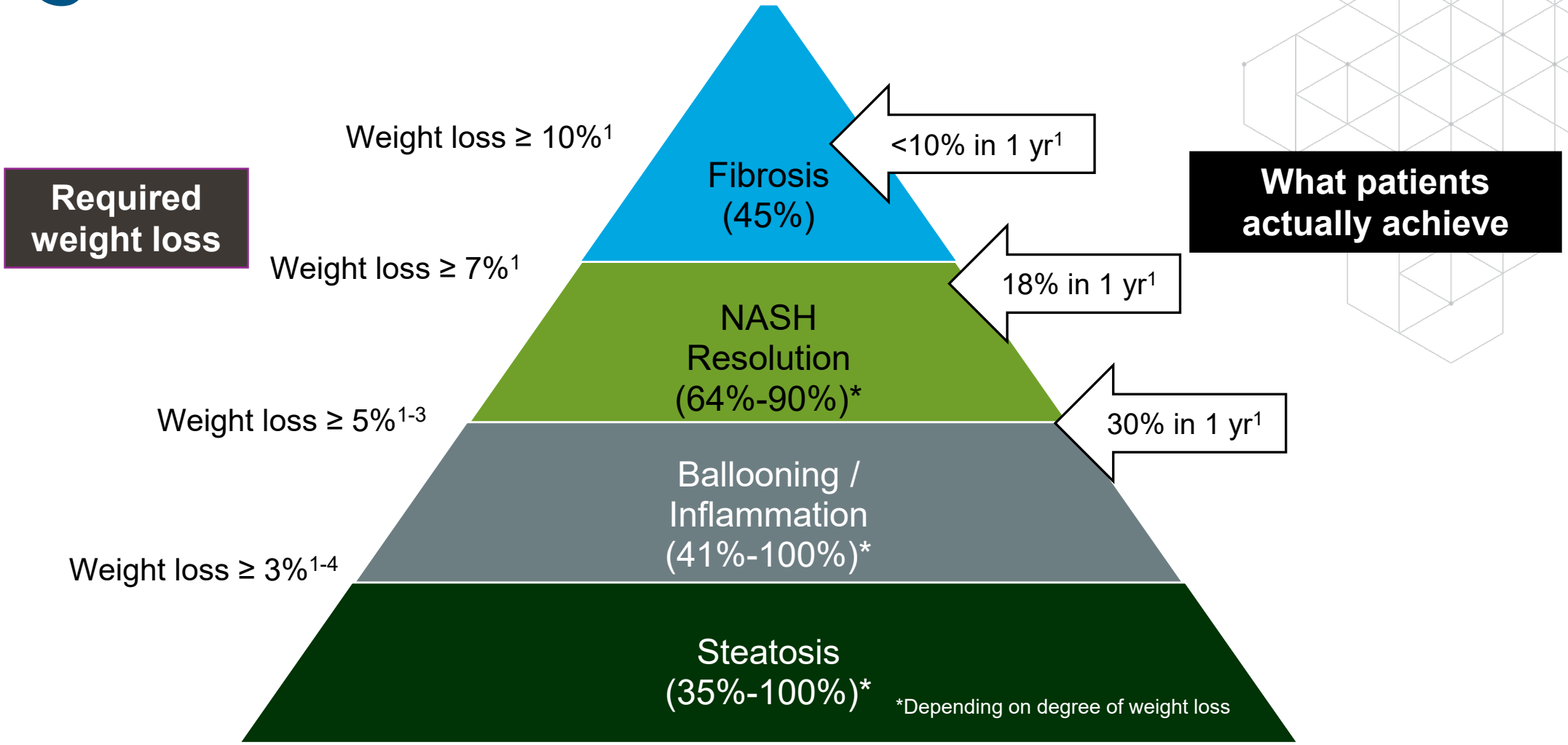
Managing the Low-Risk Patient: FIB-4 <1.3

- No further evaluation needed
- Repeat FIB-4 in 2-3 years

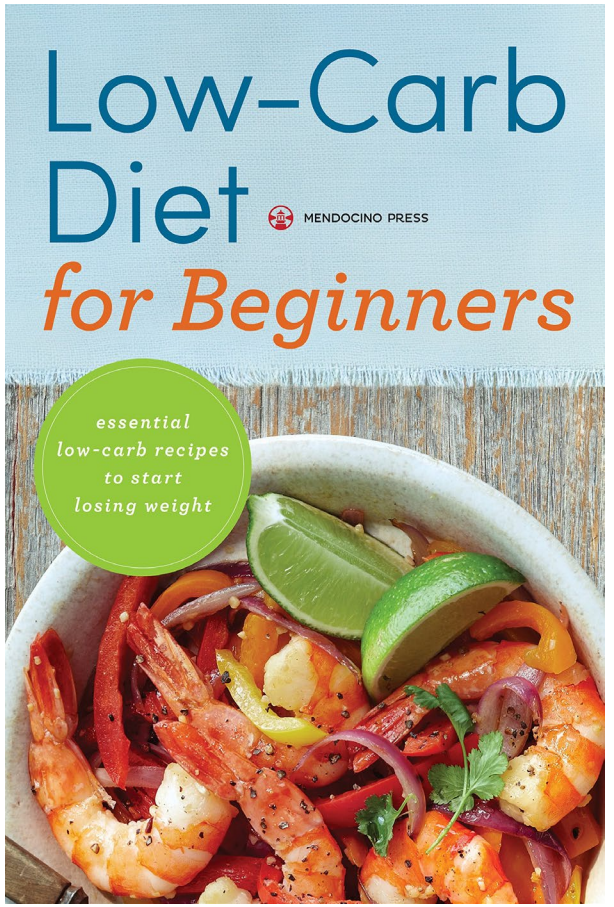
	LOW RISK FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1	INDETERMINATE RISK FIB-4 1.3 - 2.67 and/or LSM 8 - 12 kPa and liver biopsy not available	HIGH RISK[1] FIB-4 > 2.67 or LSM > 12 kPa or liver biopsy F2-F4
	Management by PCP, dietician, endocrinologist, cardiologist, others	Management by hepatologist with multidisciplinary team (PCP, dietician, endocrinologist, cardiologist, others)	
Lifestyle intervention[2]	Yes	Yes	Yes
Weight loss recommended if overweight or obese[3]	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes[4, 5, 6]	Yes[4, 5, 6, 7]
CVD risk reduction[8]	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)

Weight Loss Can Work … But Is Difficult!



[1]Vilar-Gomez E, et al. *Gastroenterology.* 2015;149(2):367-78.e5. [2]Promrat K, et al. *Hepatology.* 2010;51(1):121-129. [3]Harrison SA, et al. *Hepatology.* 2009;49(1):80-86.
[4]Wong VWS, et al. *J Hepatol.* 2013;59(3):536-542. Musso G, et al. *Diabetologia.* 2012;55(4):885-904.

Diet Can Work But Is Difficult!



Diet Associations With NAFLD in an Ethnically Diverse Population: The Multiethnic Cohort

- Nested case-control
- 2,974 NAFLD cases
  - 518 with cirrhosis
  - 2,456 without cirrhosis
- 29,474 matched controls
- Cases identified using Medicare claims ICD9/10
- Controls individually matched to cases on birth year, sex, ethnicity
- FFQ

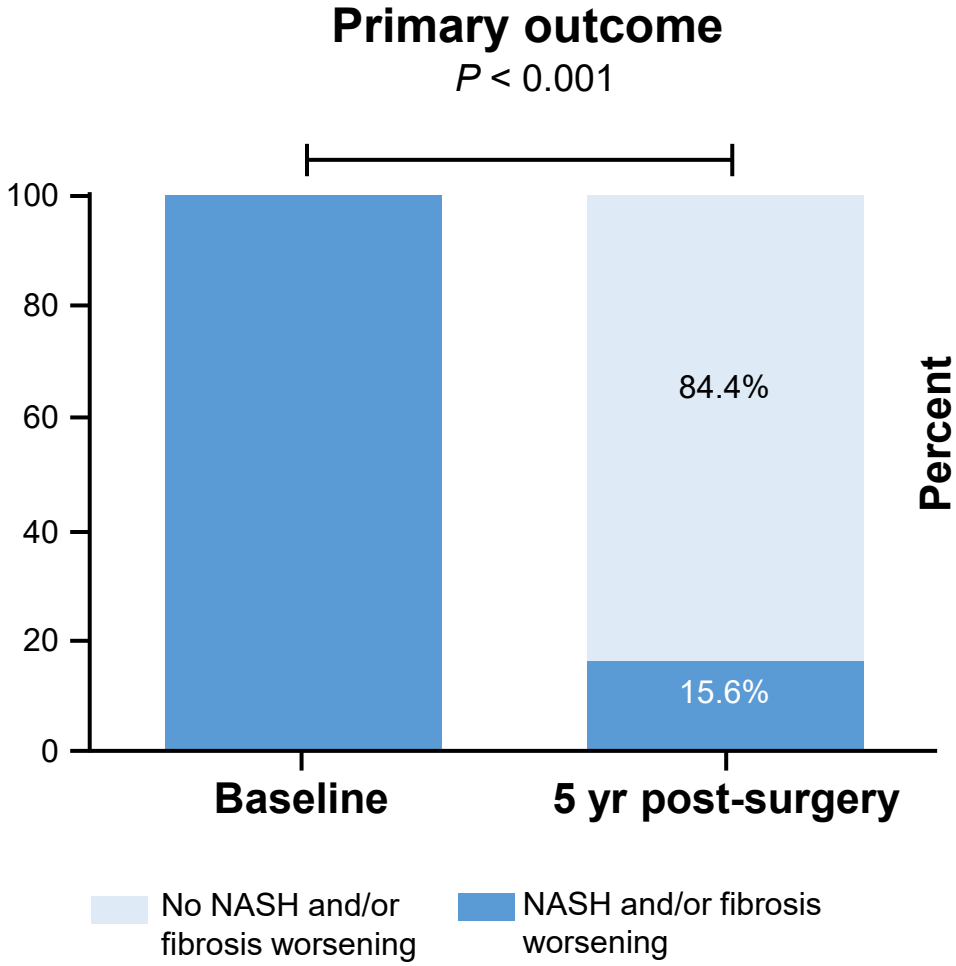
(g/1,000 kcal/day)	NAFLD No Cirrhosis	NAFLD With Cirrhosis
Q 1st vs. 4th	OR (95% CI)	OR (95% CI)
Cholesterol		
≤ 75.4	1.00 (ref.)	1.00 (ref.)
> 121.4	1.09 (0.96-1.23)	1.52 (1.15-2.01)
P-value for trend	0.0889	0.0018
Fiber		
≤ 8.5	1.00 (ref.)	1.00 (ref.)
> 14.0	0.86 (0.75-0.98)	0.75 (0.55-1.02)
P-value for trend	0.0123	0.1018

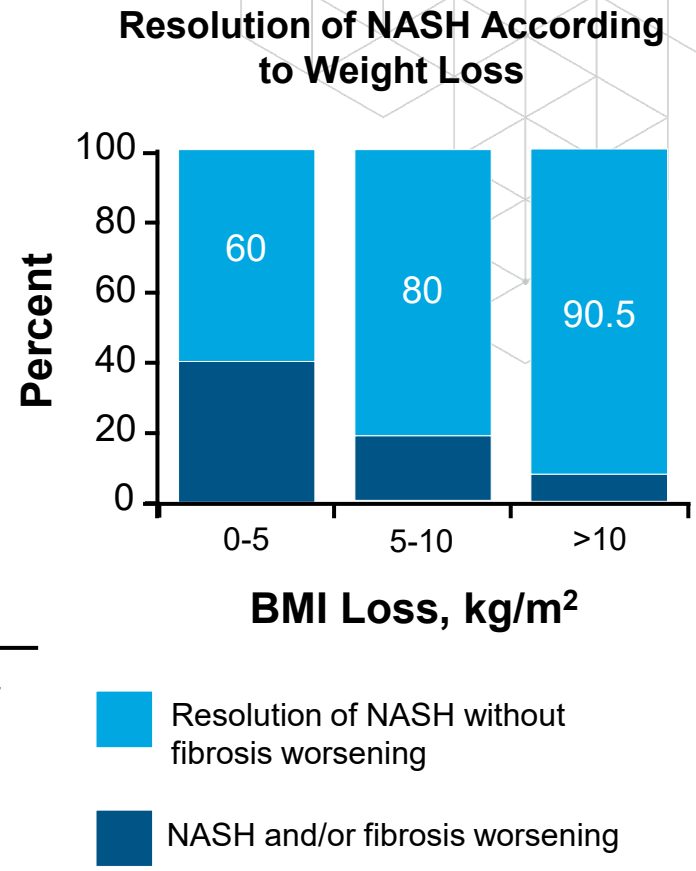
(g/1,000 kcal/day)	NAFLD No Cirrhosis	NAFLD With Cirrhosis
Q 1ST vs. 4th	OR (95% CI)	OR (95% CI)
Total red meat		
≤ 13.7	1.00 (ref.)	1.00 (ref.)
> 34.0	1.10 (0.97-1.25)	1.43 (1.08-1.90)
P-value for trend	0.1190	0.0121
Red unprocessed meat		
≤ 9.3	1.00 (ref.)	1.00 (ref.)
> 24.1	1.10 (0.97-1.25)	1.52 (1.15-2.01)
P-value for trend	0.1223	0.0033
Processed red meat		
≤ 3.0	1.00 (ref.)	1.00 (ref.)
> 10.0	1.17 (1.03-1.32)	1.31 (0.99-1.71)
P-value for trend	0.0097	0.1123
Total poultry		
≤ 11.4	1.00 (ref.)	1.00 (ref.)
> 27.6	1.19 (1.05-1.35)	1.03 (0.79-1.35)
P-value for trend	0.0028	0.7717

Noureddin M, et al. *Hepatology*. 2020;71(6):1940-1952.

Bariatric Surgery Can Work

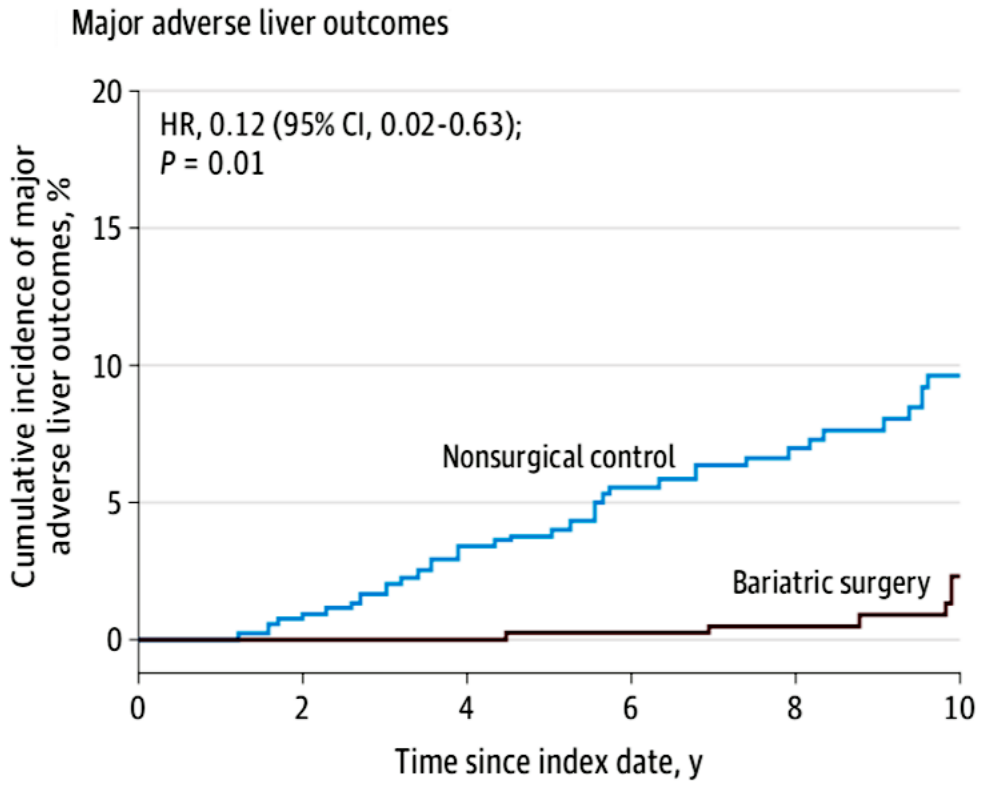
- French single-center study of bariatric surgery in severely obese patients with biopsy-confirmed NASH (N = 180)
- At 5 yr post-surgery, 84% had NASH resolution with no worsening of fibrosis
  - NASH improvement correlated with weight loss

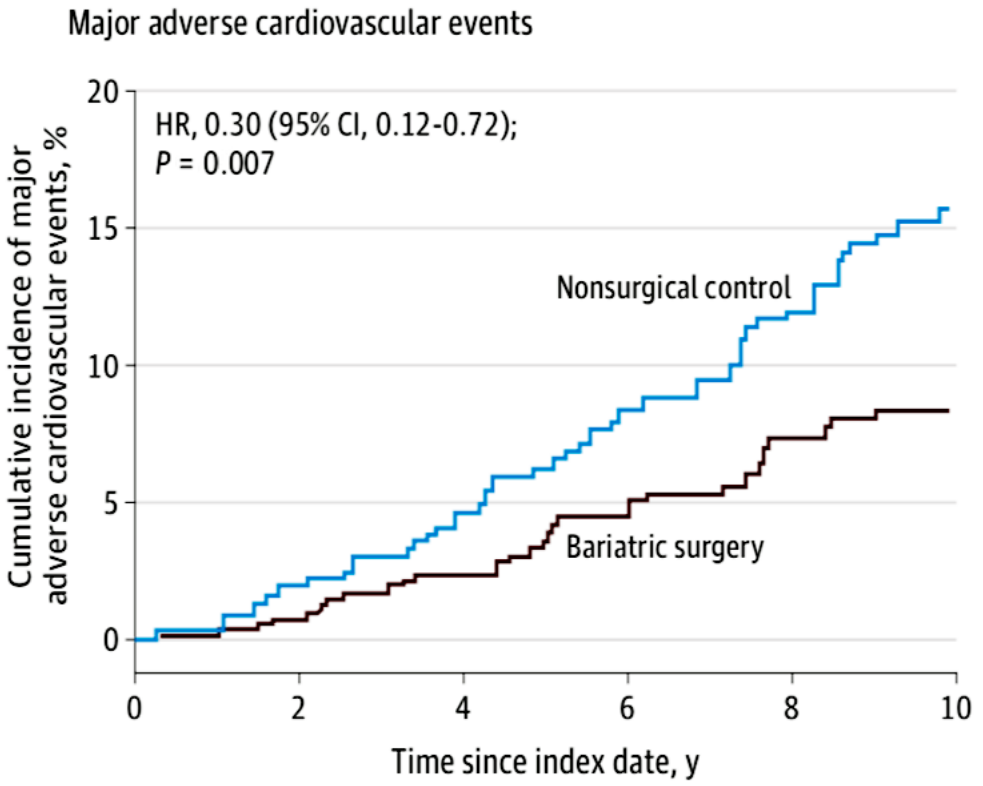




Lassailly G, et al. *Gastroenterology*. 2020;159(4):1290-1301.e5.

Cumulative Incidence Estimates for MALO and MACE





No. at risk						
Nonsurgical control	508	422	376	283	211	146
Bariatric surgery	650	525	463	381	252	153

508	417	370	270	202	136
650	523	455	365	234	141

Aminian A, et al. *JAMA*. 2021;326(20):2031-2042.

There Are No FDA-Approved Drugs for NASH: Use of Off-Label Therapies

Vitamin E (800 IU/day)

- Possible all-cause mortality risk at dose > 800 IU/day[1]
- Increased risk for hemorrhagic stroke[2]
  - Also shows reduced ischemic stroke risk
- Increased risk for prostate cancer (HR vs placebo: 1.17; 99% CI: 1.004-1.36; *P* = 0.008)[3]

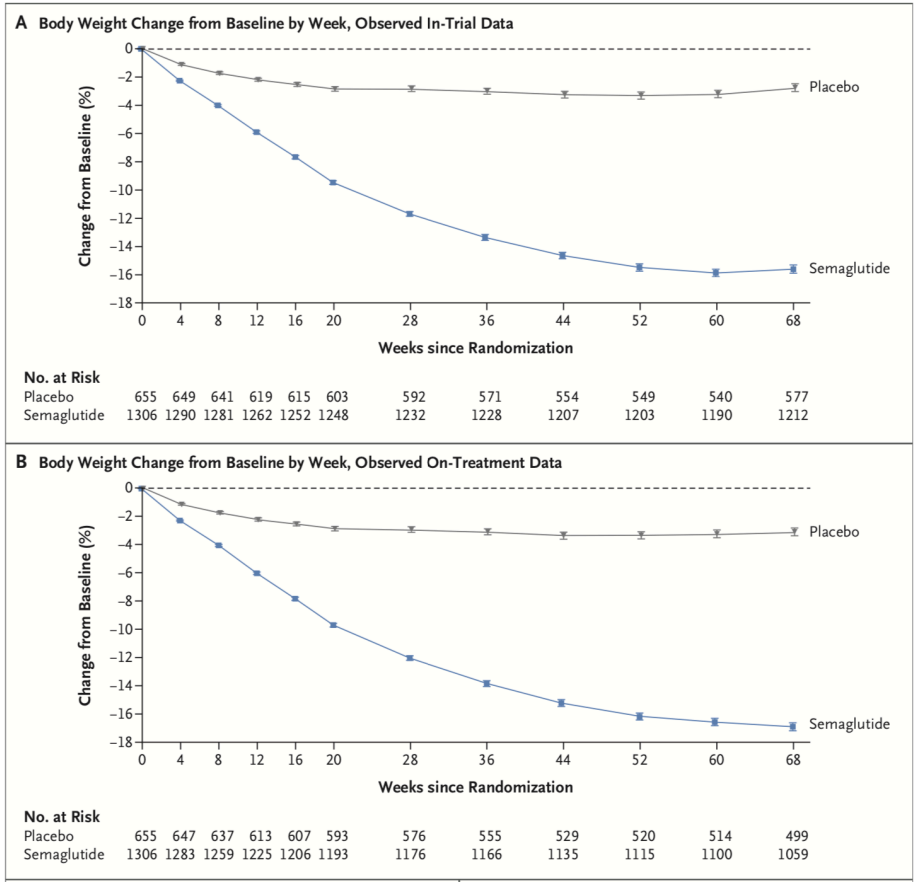
Pioglitazone

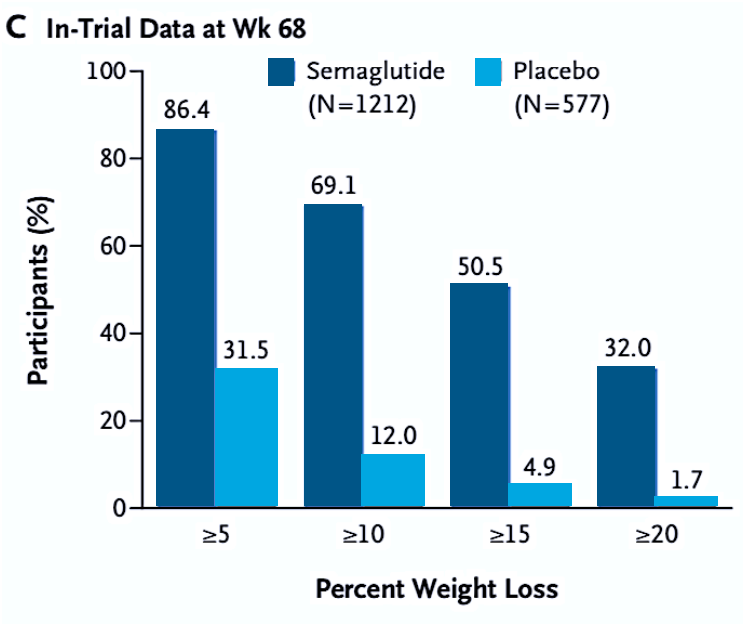
- Edema, weight gain (~ 2-3 kg over 2-4 yrs)[4]
- Risk of osteoporosis in women[5]
- Equivocal risk for bladder cancer
  - Increased in some studies[6]
  - No association in most studies[7,8]

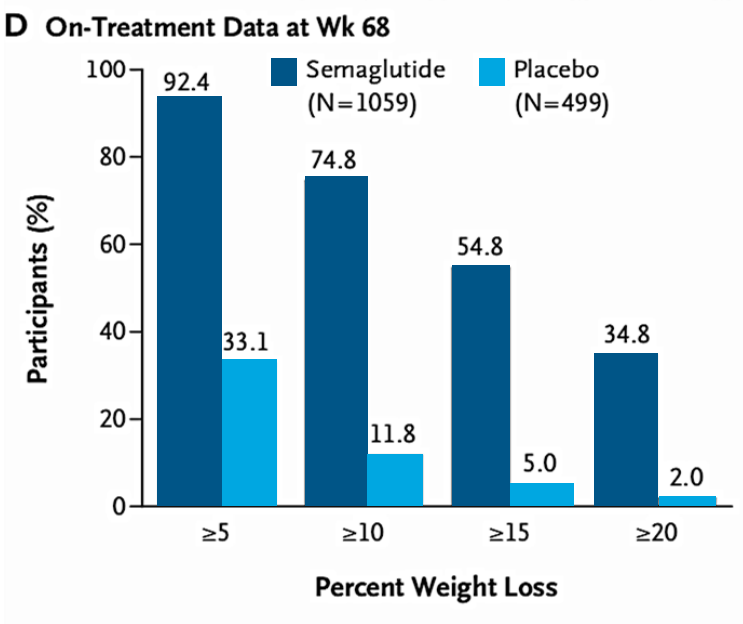
Use of these agents should be personalized for selected patients with histologically confirmed NASH after careful consideration of risk/benefit ratio

1. Miller ER 3rd, et al. *Ann Intern Med.* 2005;142(1):37-46. 2. Schürks M, et al. *BMJ.* 2010;341:c5702. 3. Klein EA, et al. *JAMA.* 2011;306(14):1549-1556.
4. Bril F, et al. *Diabetes Care.* 2017;40(3):419-430. 5. Yau H, et al. *Curr Diab Rep.* 2013;13(3):329-341. 6. Tuccori M, et al. *BMJ*. 2016;352:i1541.
7. Lewis JD, et al. *JAMA.* 2015;314(3):265-277. 8. Davidson MB. *J Diabetes Complications*. 2016;30(6):981-985.

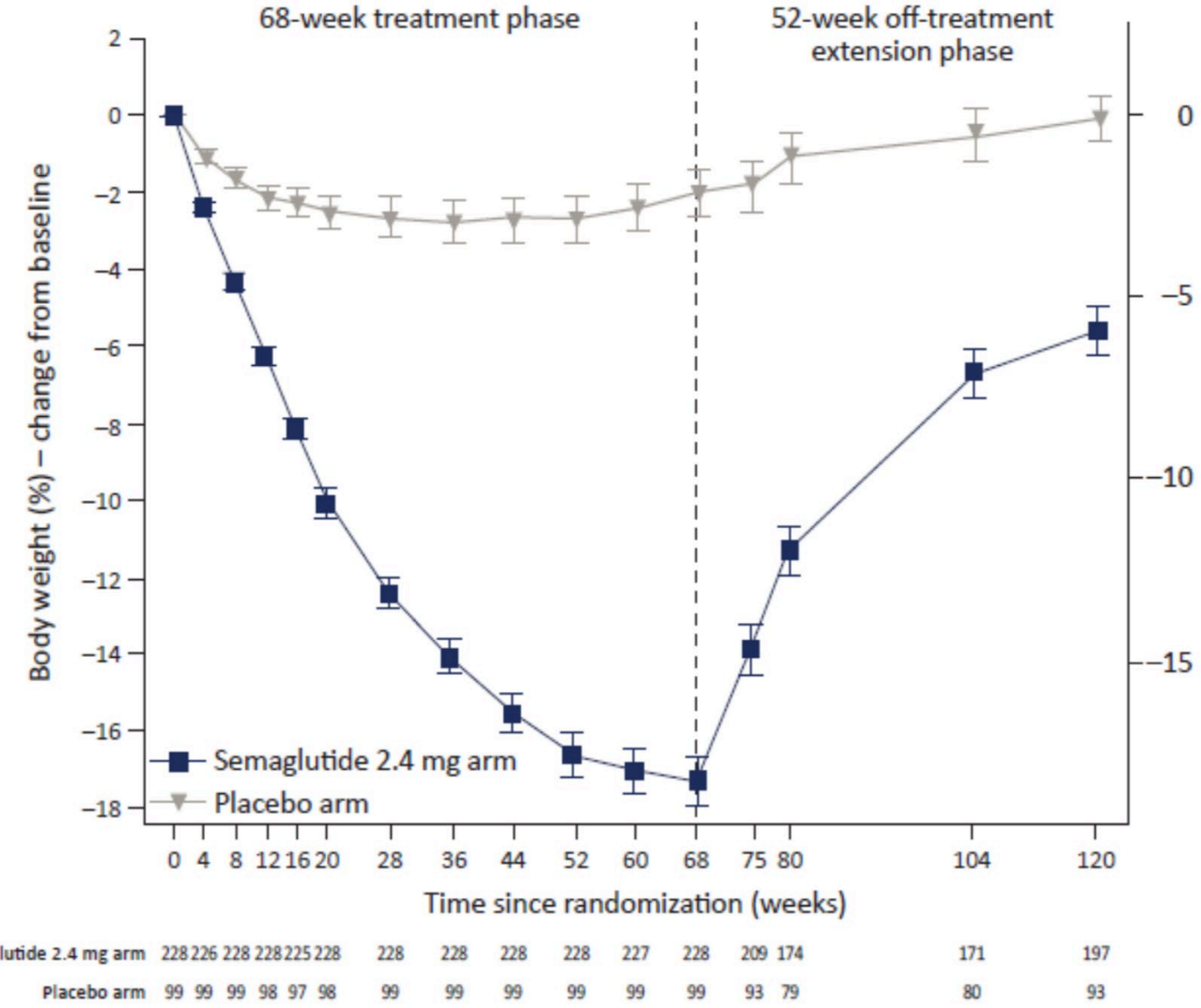
Once-Weekly Semaglutide for Weight Loss



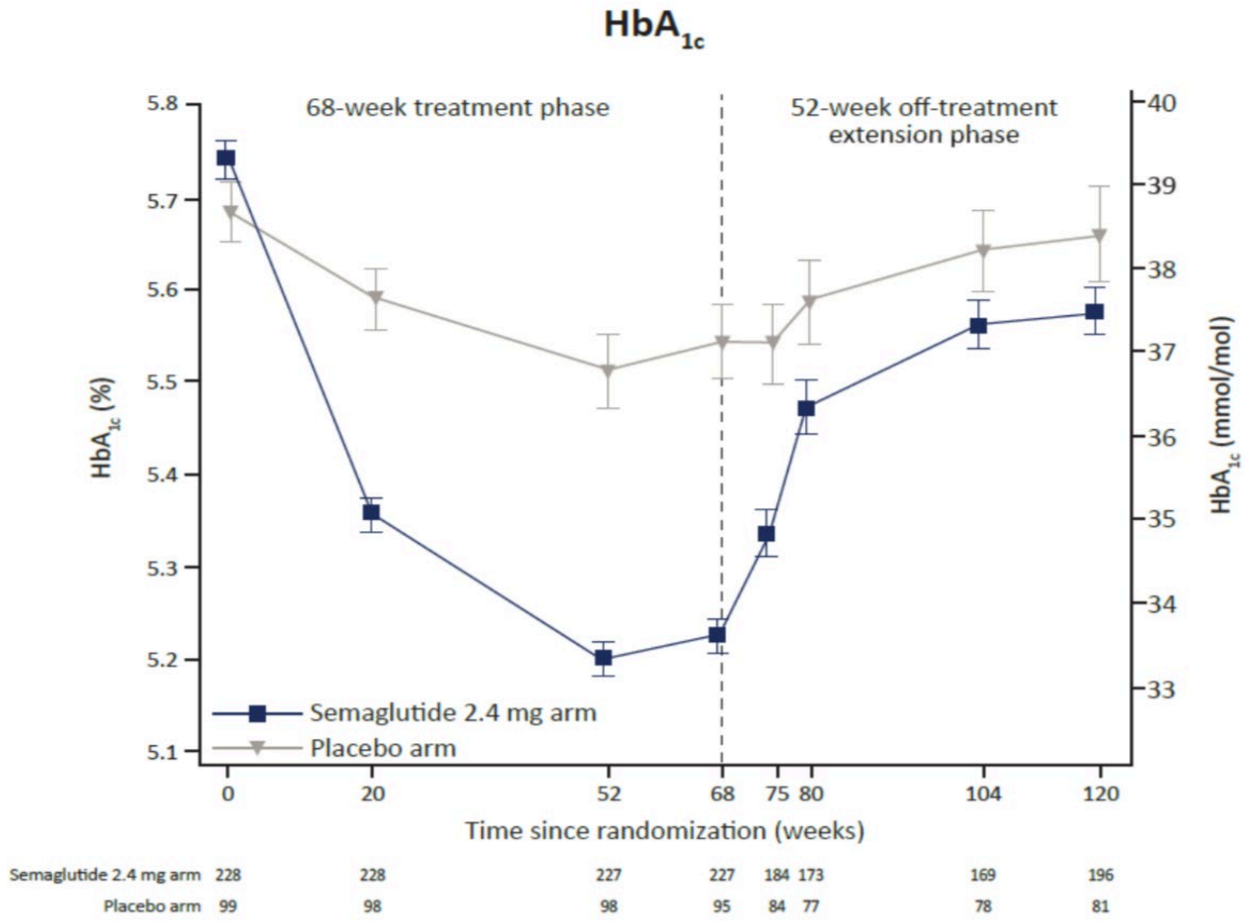


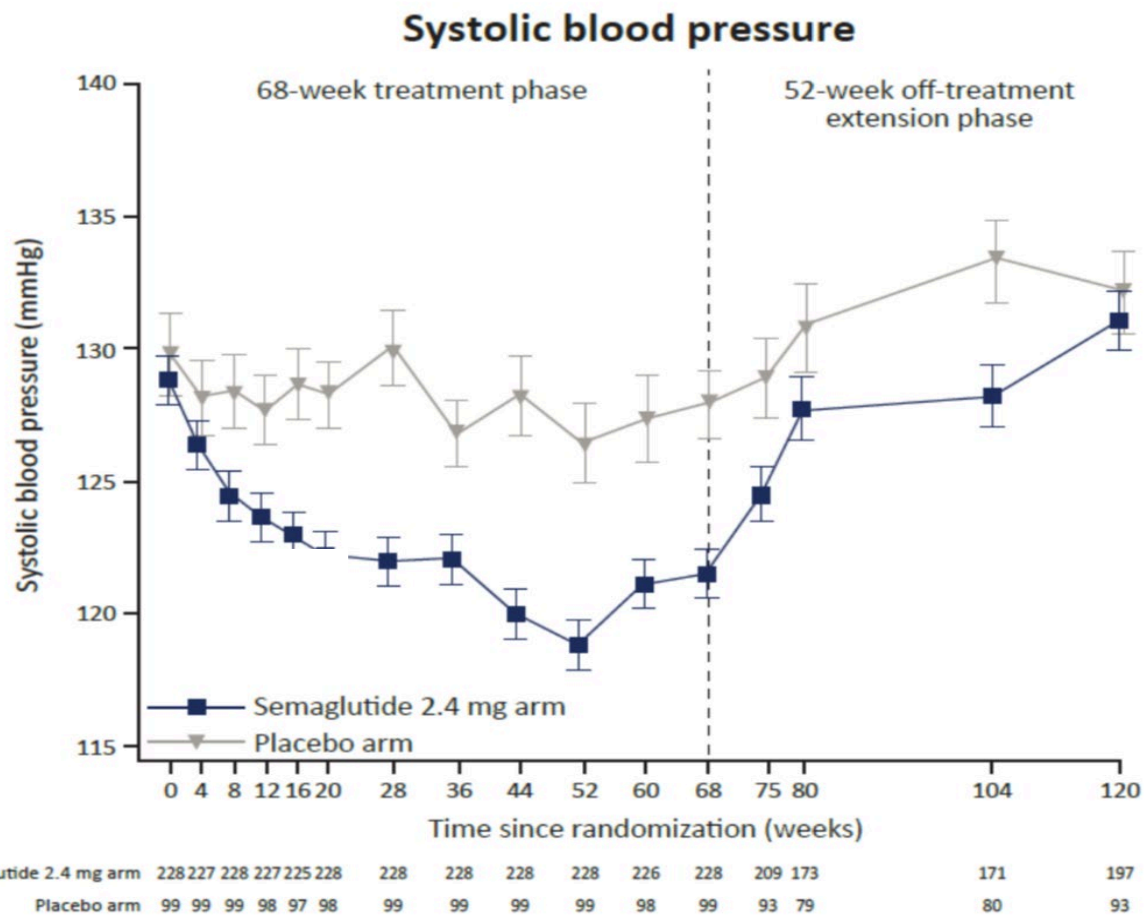


Wilding JPH, et al. *N Engl J Med.* 2021;384(11):989-1002.



Wilding JPH, et al. *Diabetes Obes Metab.* 2022;24(8):1553-1564.





Wilding JPH, et al. *Diabetes Obes Metab.* 2022;24(8):1553-1564.

Managing the Indeterminate and High-Risk Patient: FIB-4 ≥1.3 – 2.67 or >2.67

- Refer to hepatologist

	LOW RISK FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1	INDETERMINATE RISK FIB-4 1.3 - 2.67 and/or LSM 8 - 12 kPa and liver biopsy not available	HIGH RISK[1] FIB-4 > 2.67 or LSM > 12 kPa or liver biopsy F2-F4
	Management by PCP, dietician, endocrinologist, cardiologist, others	Management by hepatologist with multidisciplinary team (PCP, dietician, endocrinologist, cardiologist, others)	
Lifestyle intervention[2]	Yes	Yes	Yes
Weight loss recommended if overweight or obese[3]	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes[4, 5, 6]	Yes[4, 5, 6, 7]
CVD risk reduction[8]	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)

Update on the NASH Treatment Pipeline

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FDA Efficacy Endpoints for Phase 2b or Phase 3 Trials: Liver Histologic Improvement

NASH Resolution

- Resolution of steatohepatitis on overall histopathologic reading

AND

- No worsening of liver fibrosis

Fibrosis Improvement

- Improvement ≥1 fibrosis stage

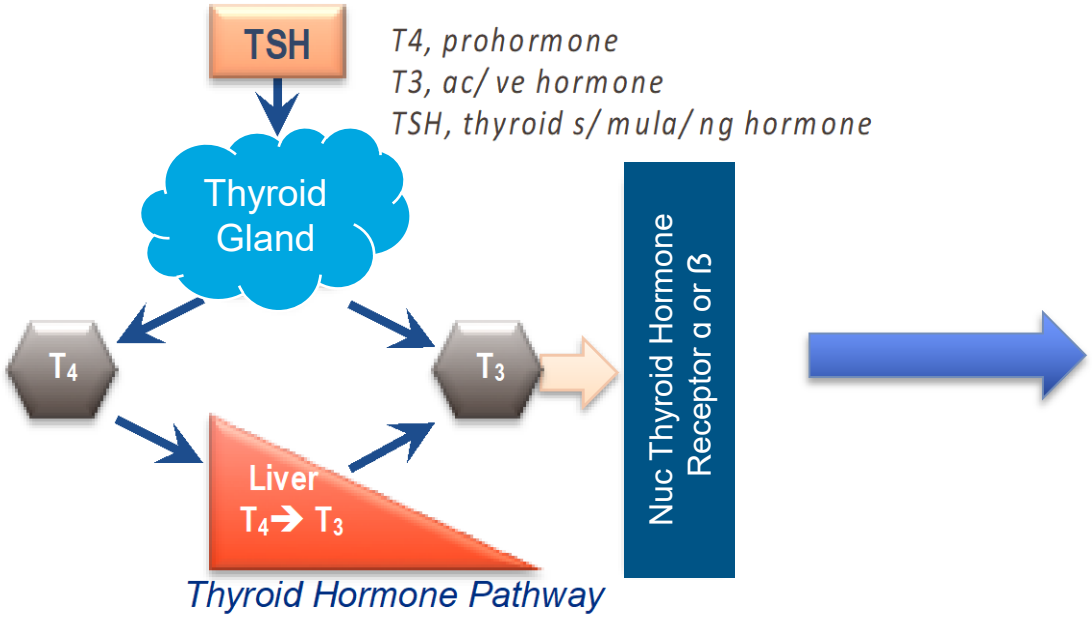
AND

- No worsening of steatohepatitis

Or Both

US FDA. Draft guidance. Noncirrhotic NASH with liver fibrosis. December 2018.

Resmetirom: Selective Thyroid Hormone Receptor-Beta Agonist

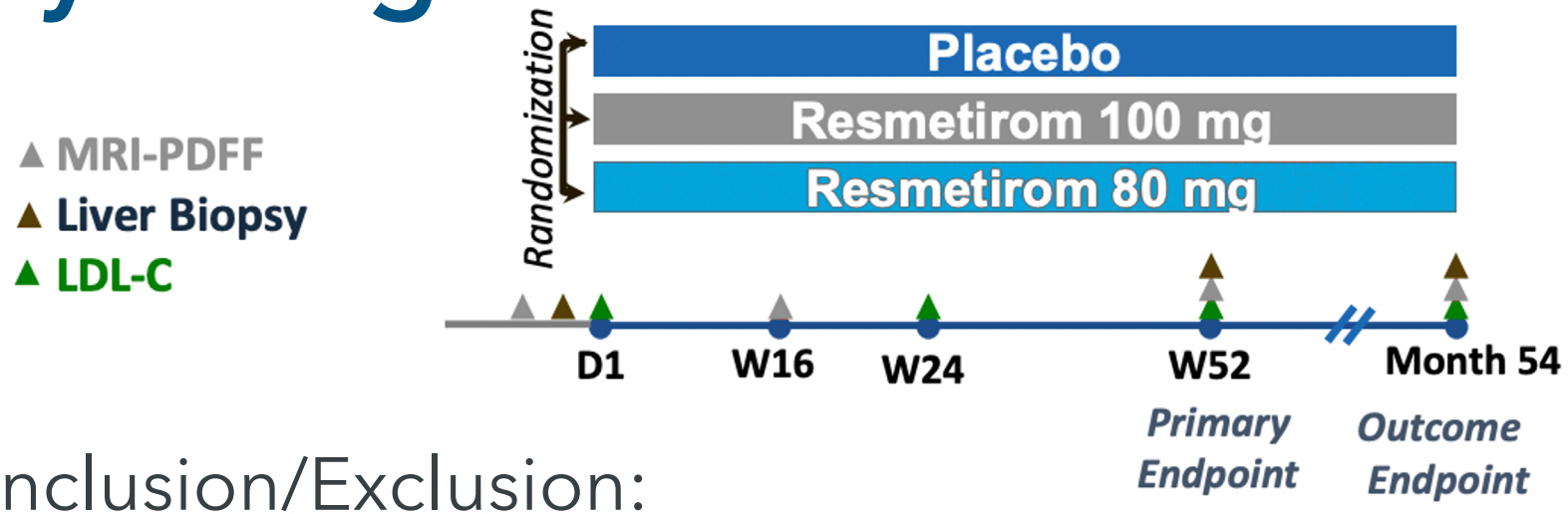


In humans THR-β agonism:

- Lowers LDL-cholesterol
- Lowers triglycerides
- Lowers liver fat, potentially reducing lipotoxicity, NASH

No thyrotoxicosis (THR-α effect)

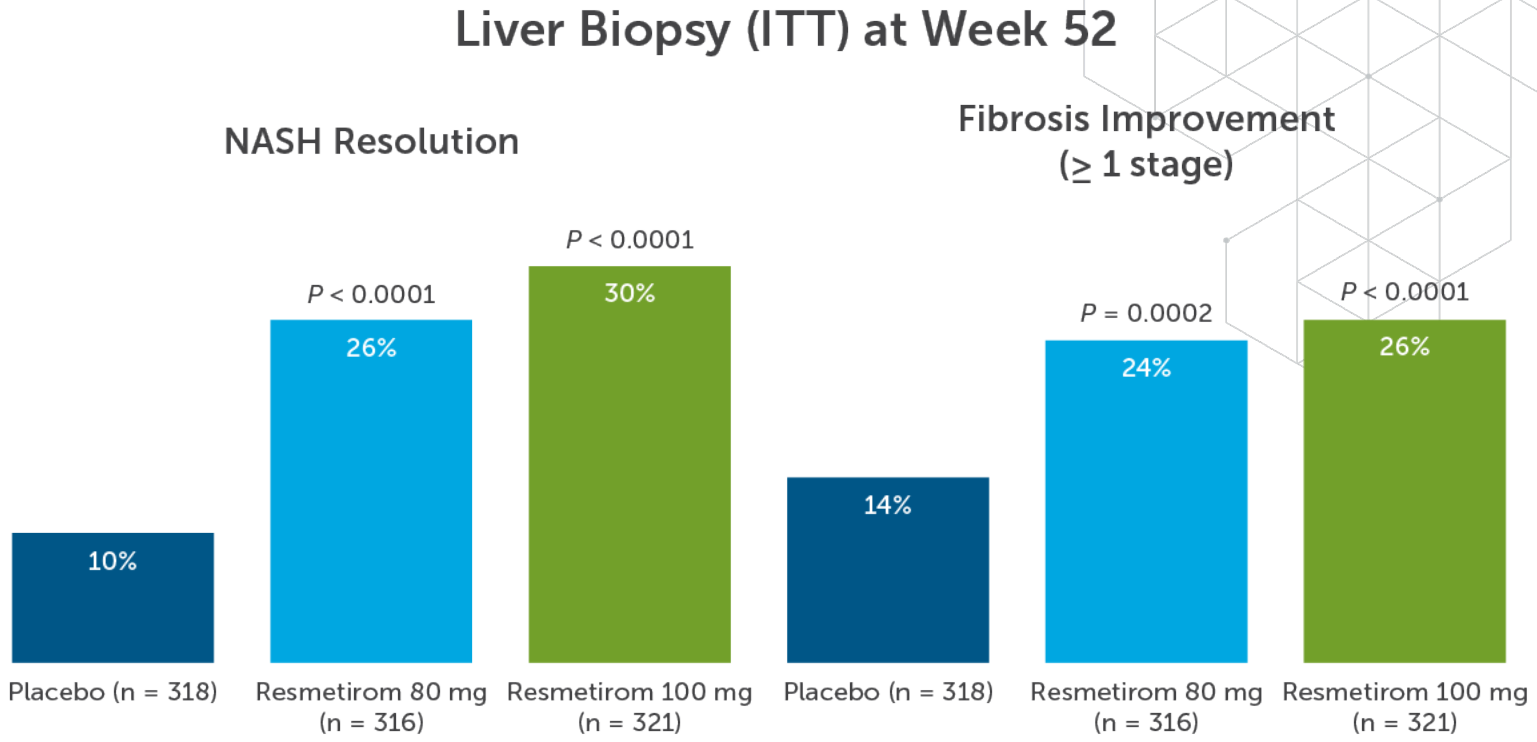
Resmetirom: Phase 3 MAESTRO-NASH Study Design



- Key Inclusion/Exclusion:
  - Requires 3 metabolic risk factors (metabolic syndrome)
  - FibroScan kPa consistent with F2-F3, CAP≥280
  - NASH on liver biopsy: NAS≥4 with fibrosis stage 1-3
  - ≥8% liver fat on MRI-PDFF

Resmetirom: Phase 3 MAESTRO-NASH

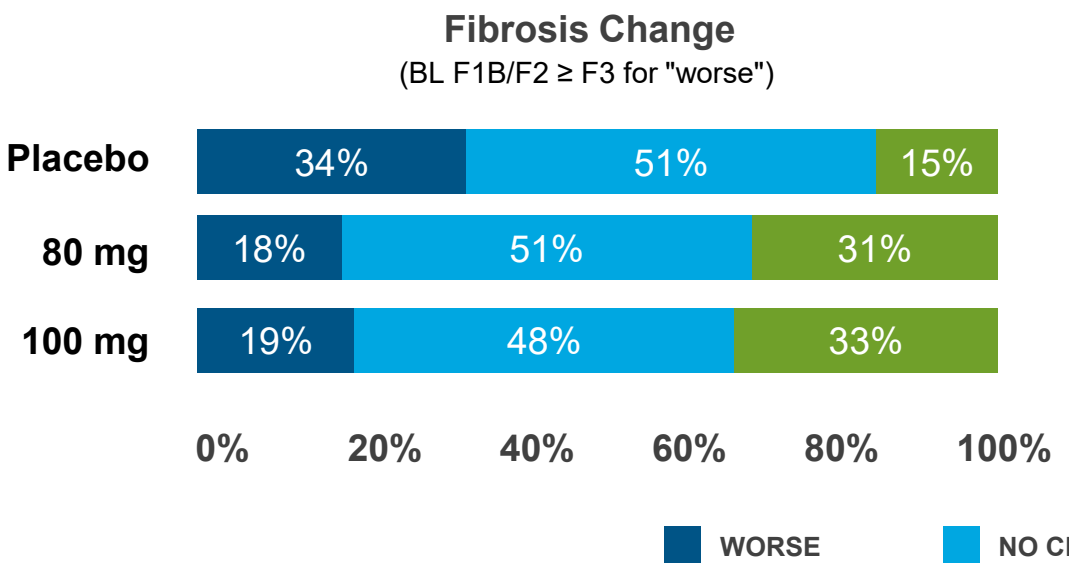
- Achieved NASH resolution
- Achieved fibrosis improvement
- Favorable effect on lipid panel

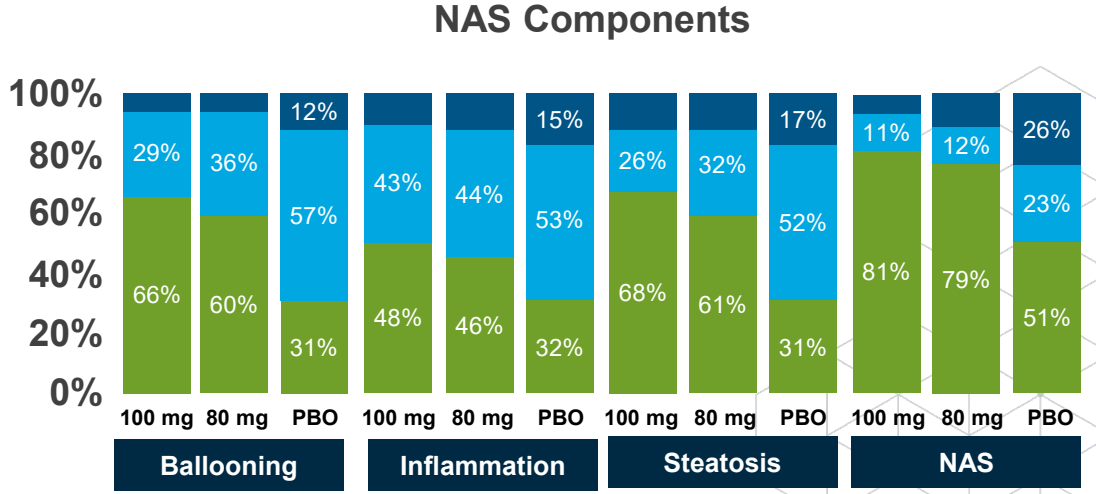


Harrison S, et al. NASH TAG 2023 Conference; Park City, UT; January 26, 2023.

NASH Biopsy Component Responses

- For public data release, FDA restricted data on worsening of fibrosis to baseline F1B and F2 biopsies because conversion of F3 to F4 is an outcome in the blinded ongoing 54-month primary endpoint of MAESTRO-NASH
- Resmetirom-treated showed improvement in NAS components and fibrosis and less worsening compared with placebo





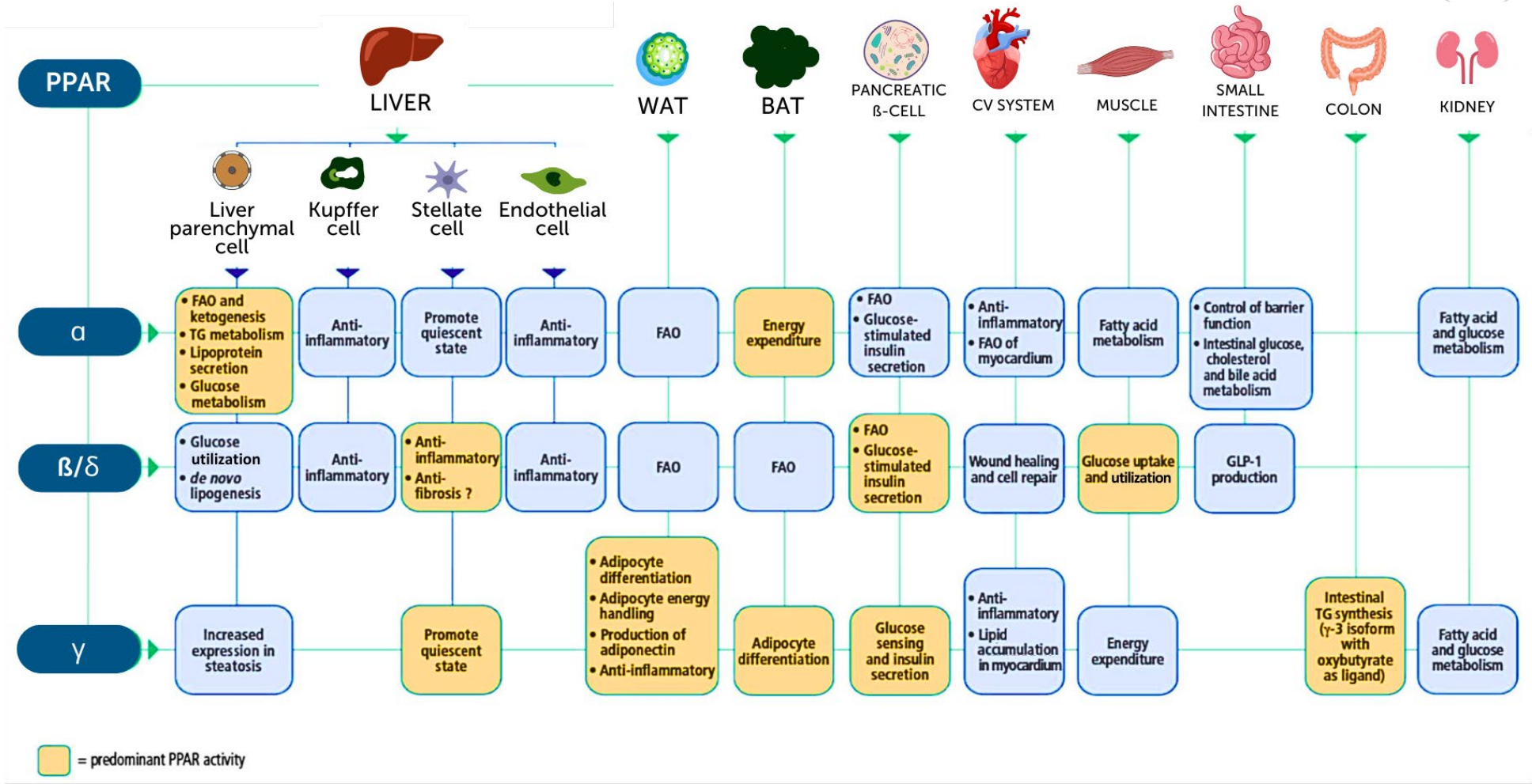
Harrison S, et al. EASL 2023; Vienna, Austria.

Resmetirom for NAFLD: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial

- MAESTRO-NAFLD-1 was a 52-week randomized phase 3 trial
  - Primary end point: incidence of treatment-emergent adverse events (TEAEs)
    - No specific serious TEAEs were numerically increased in the resmetirom arms compared to placebo
    - Diarrhea/nausea occurred more frequently compared to placebo in the first 12 weeks but did not increase after 12 weeks
  - Secondary end points at 80mg, 100mg resmetirom:
    - LDL-C: -11.1%, -12.6%
    - ApoB: -15.6%, -18.0%
    - Triglycerides (over 24 weeks): -15.4%, -20.4%
    - Hepatic fat (over 16 weeks): -34.9%, -38.6%
    - Hepatic fat (over 52 weeks): -28.8, 33.9
    - liver stiffness (over 52 weeks): -1.02, 1.70

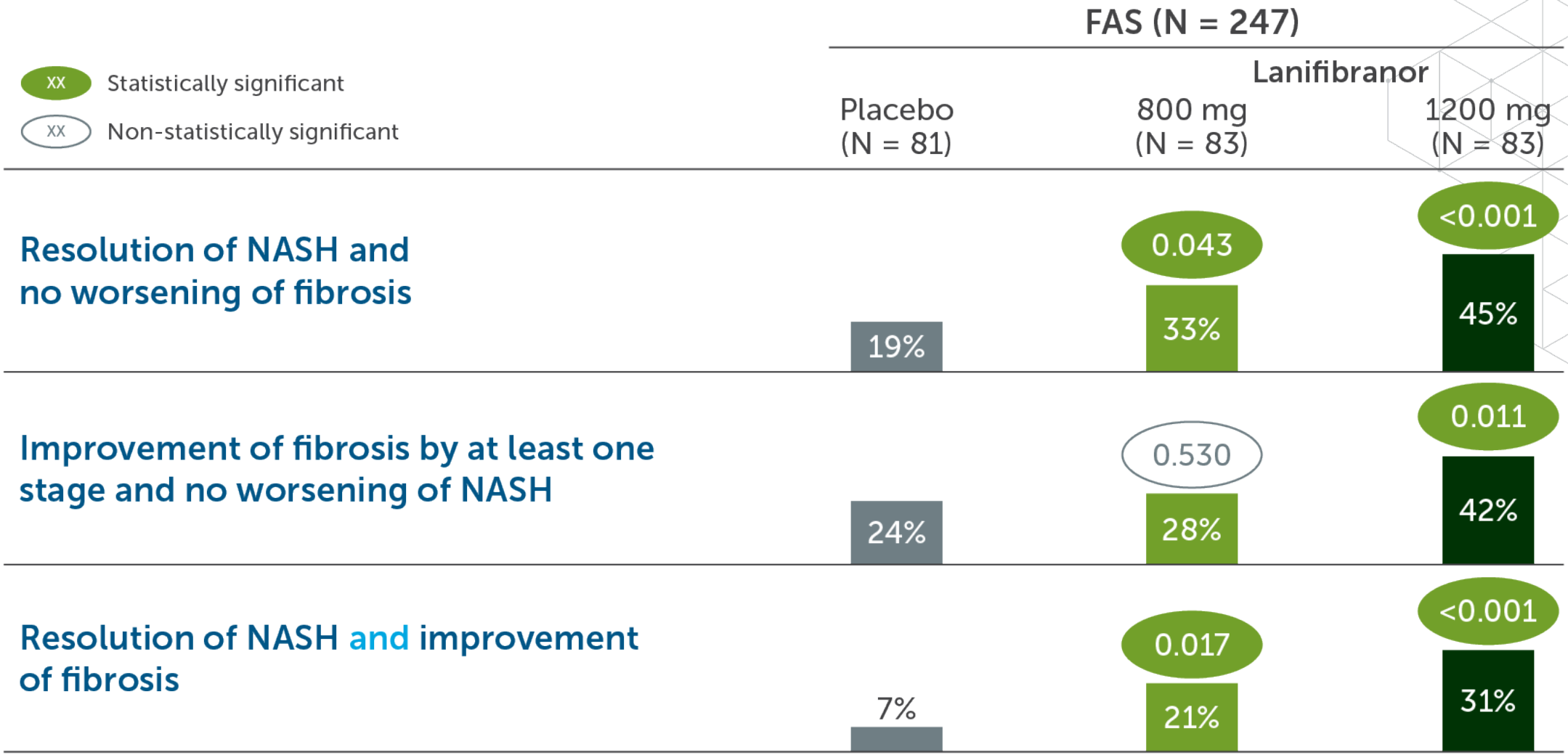
Harrison S, et al. *Nat Med.* 2023;10.1038/s41591-023-02603-1.

Lanifibranor: Pan-PPAR Agonist



Francque S, et al. Nat Rev Gastroenterol Hepatol. 2021;18(1):24-39.

Lanafibranor: Phase 2b NATiV-3 Study



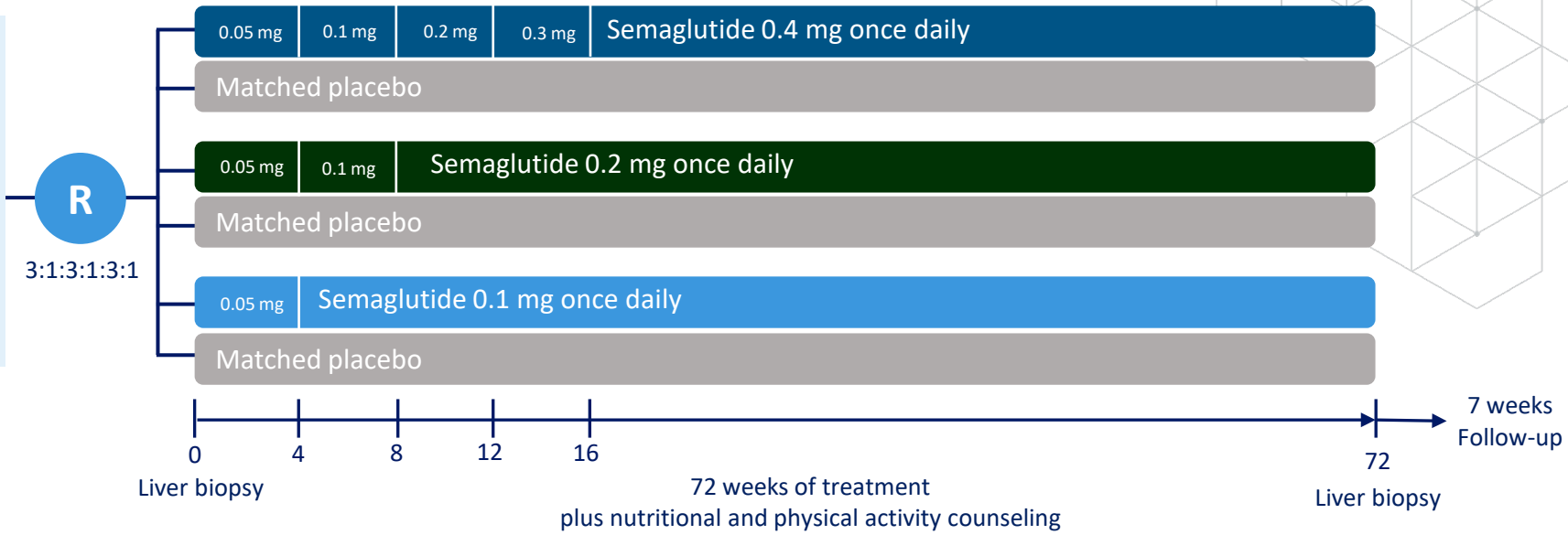
Francque SM, et al. *N Engl J Med*. 2021;385(17):1547-1558.

Semaglutide (GLP1 Agonist): Efficacy and Safety of Once-Daily SQ

Trial objective: To compare the effect of 3 different doses of semaglutide subcutaneous (s.c.) once daily versus placebo on histological resolution of NASH

Eligible patients

Biopsy confirmed NASH
NAS ≥ 4
Fibrosis stage 1, 2 or 3
BMI > 25 kg/m^2
HbA_{1c} ≤ 10%



Primary endpoint:

Resolution of steatohepatitis and no worsening in liver fibrosis in patients with baseline fibrosis stage 2 or 3

Confirmatory secondary endpoint:

Improvement in liver fibrosis and no worsening in steatohepatitis with baseline fibrosis stage 2 or 3

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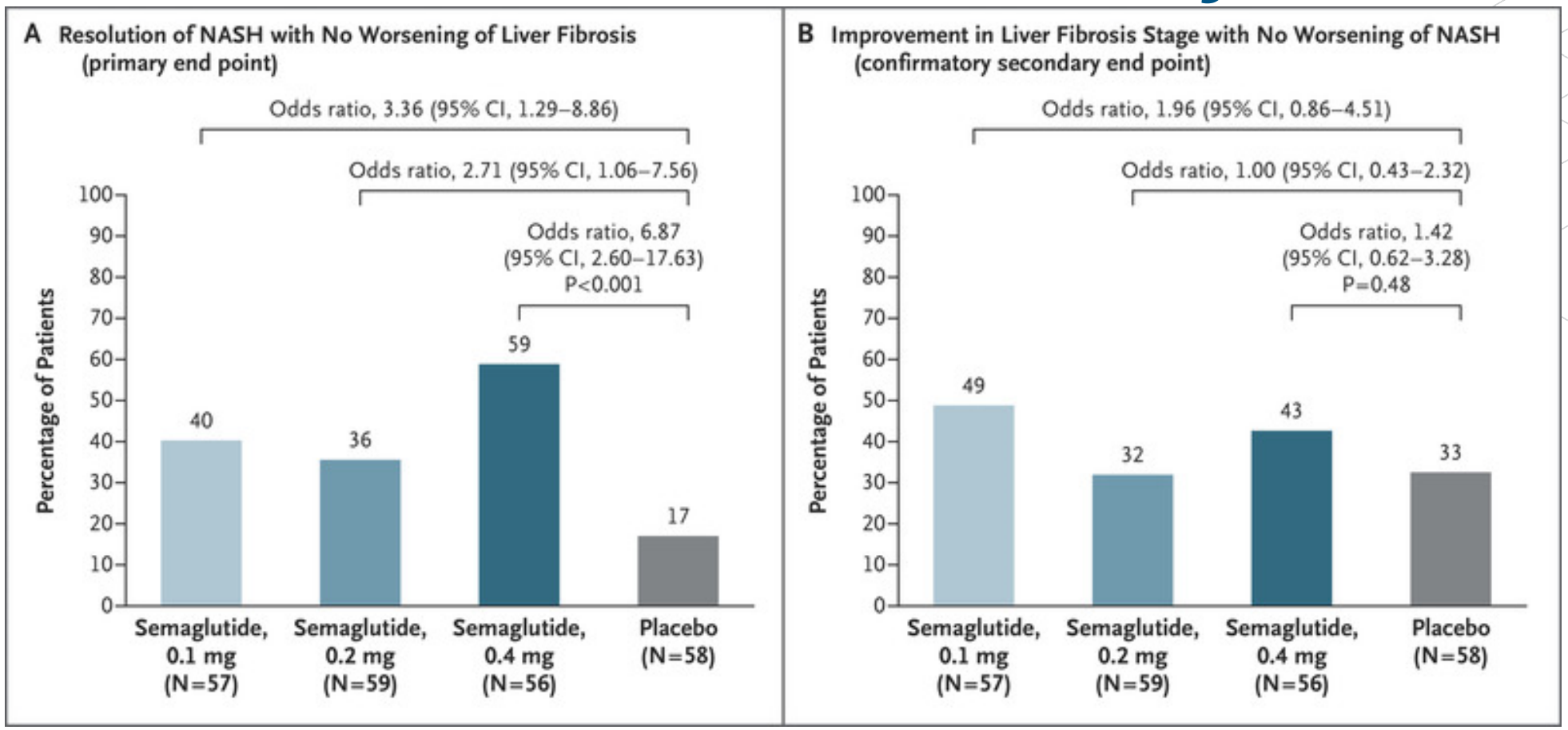
BMI, body mass index; HbA1c, glycated hemoglobin; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis.
Newsome PN, et al. *N Engl J Med*. 2021;384(12):1113-1124.

NASH 72-Week Phase 2 Study



BMI, body mass index; HbA1c, glycated hemoglobin; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis.

Newsome PN, et al. *N Engl J Med*. 2021;384(12):1113-1124.

Take-Home Message

- NITs are available to risk stratify patients with NAFLD and identify advanced fibrosis and fibrotic NASH
- Several options are available today to manage patients with NAFLD through weight loss
- New drugs are in late-phase development – be prepared for major changes in how we manage NASH

Q&A

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