NASH: An Epidemic With Significant Implications for Managed Care Professionals

Wednesday, October 18, 2023

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Cindy Davidson has nothing to disclose.

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Susan Smith, MN, PhD, has ownership interest in Hepion Pharmaceuticals.

Learning Objectives

1. Summarize the morbidity and mortality associated with advanced fibrosis
2. Compare the known costs of not treating advanced fibrosis with the estimated cost of treating NASH with a new liver-directed therapy
3. Select patients who meet the likely indications for treatment of NASH with new liver-directed therapy

Epidemiology of NAFLD and NASH

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The Global Prevalence of NAFLD

Pooled Prevalence of NAFLD: 30.05% (95% confidence interval: 27.88 to 32.32%)

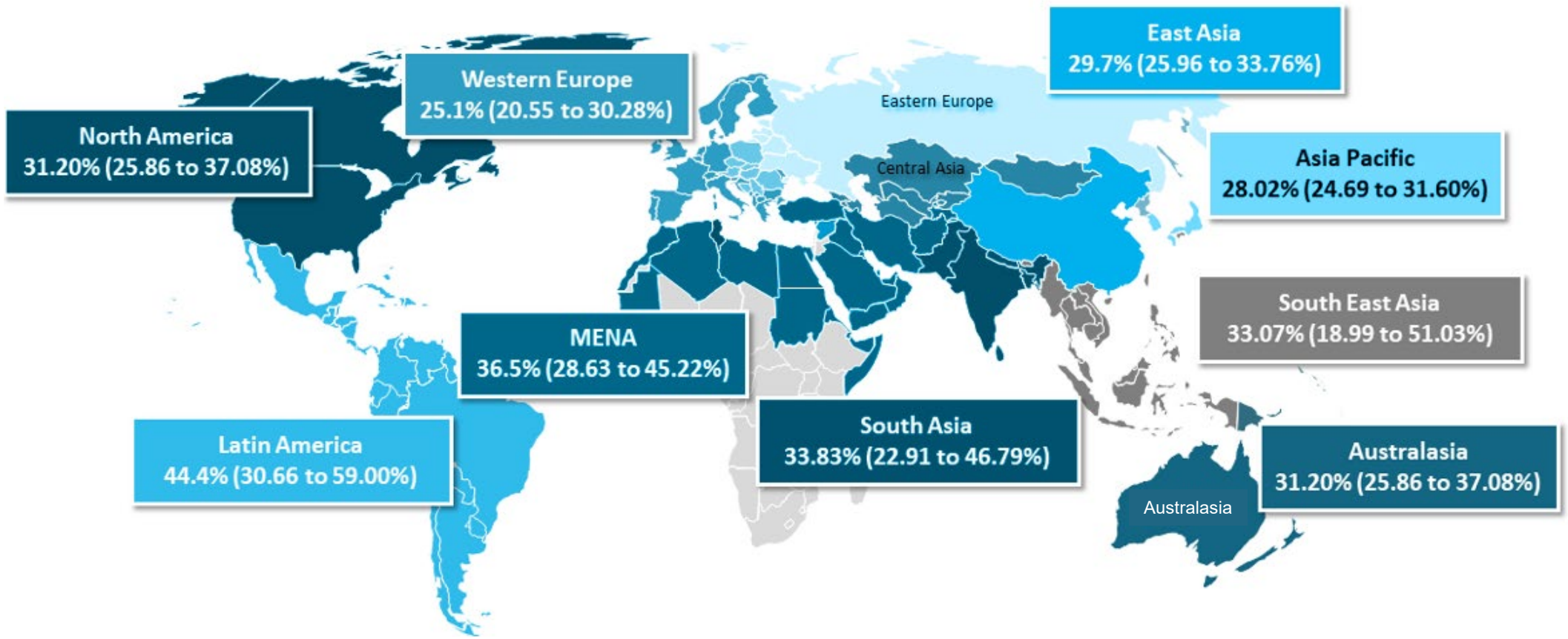


Figure adapted from Younossi ZM, et al. *Hepatology*. 2023;77(4):1335-1347.

The Global Prevalence of NASH

In 2019, the global prevalence of NASH is 5.27% (Standard Error: 2.63)

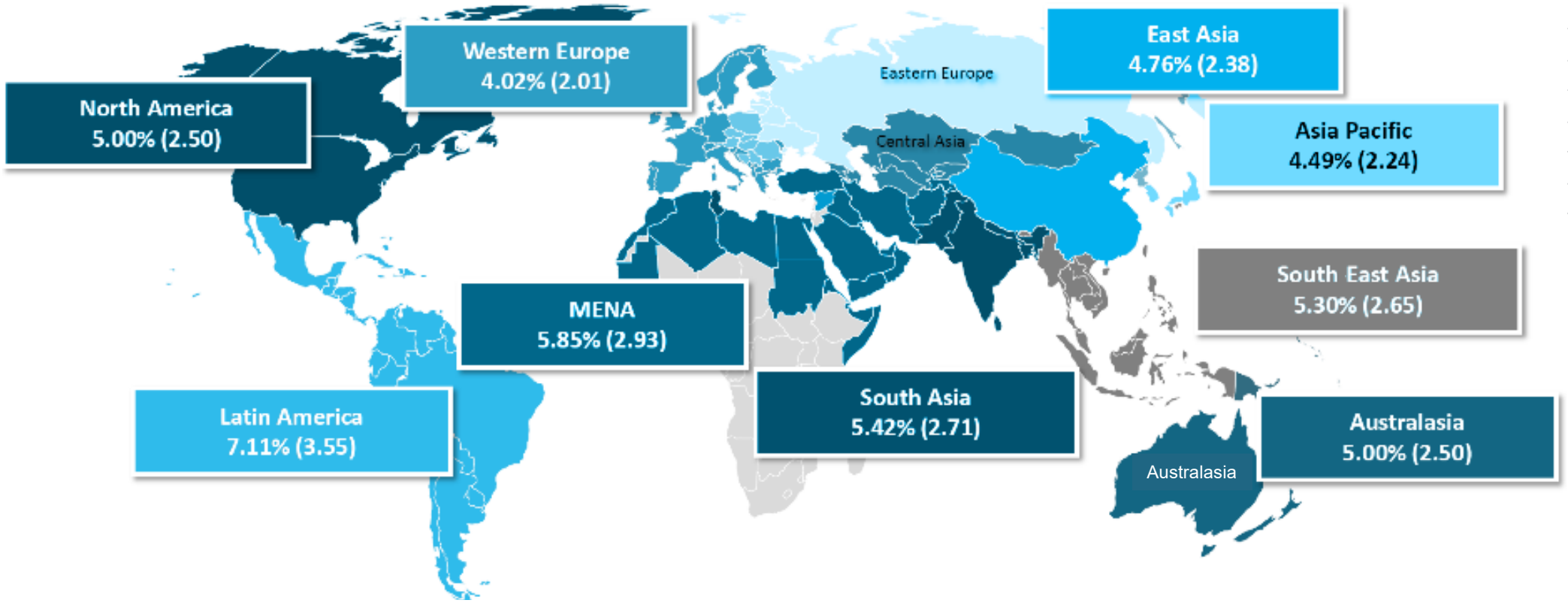
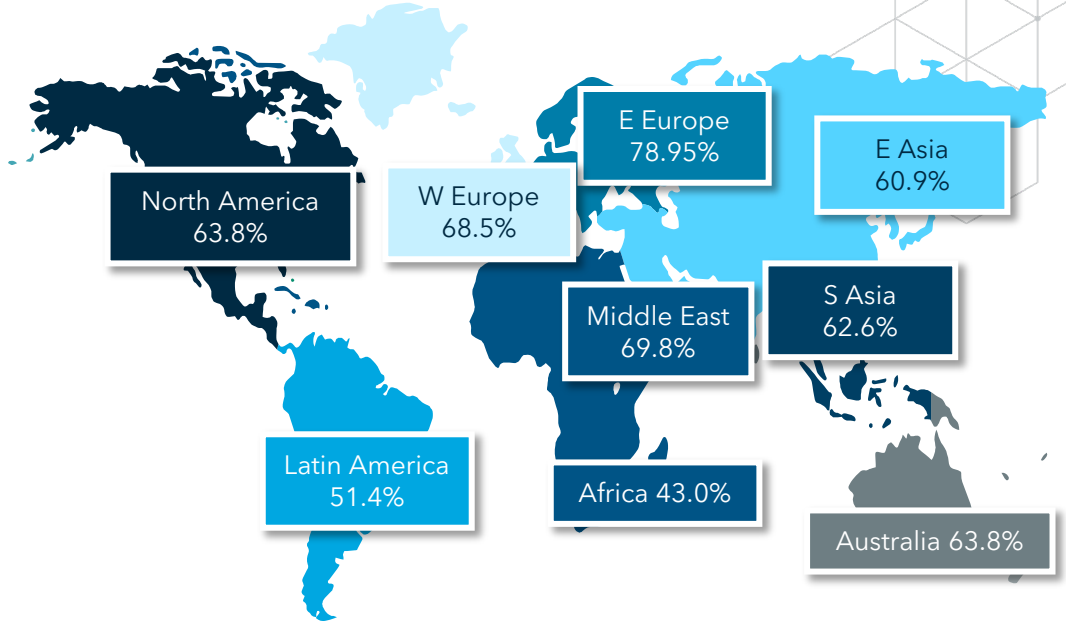


Figure adapted from Younossi ZM, et al. *Hepatology*. 2023;77(4):1335-1347.

The Global Prevalence of NAFLD and NASH Among T2D

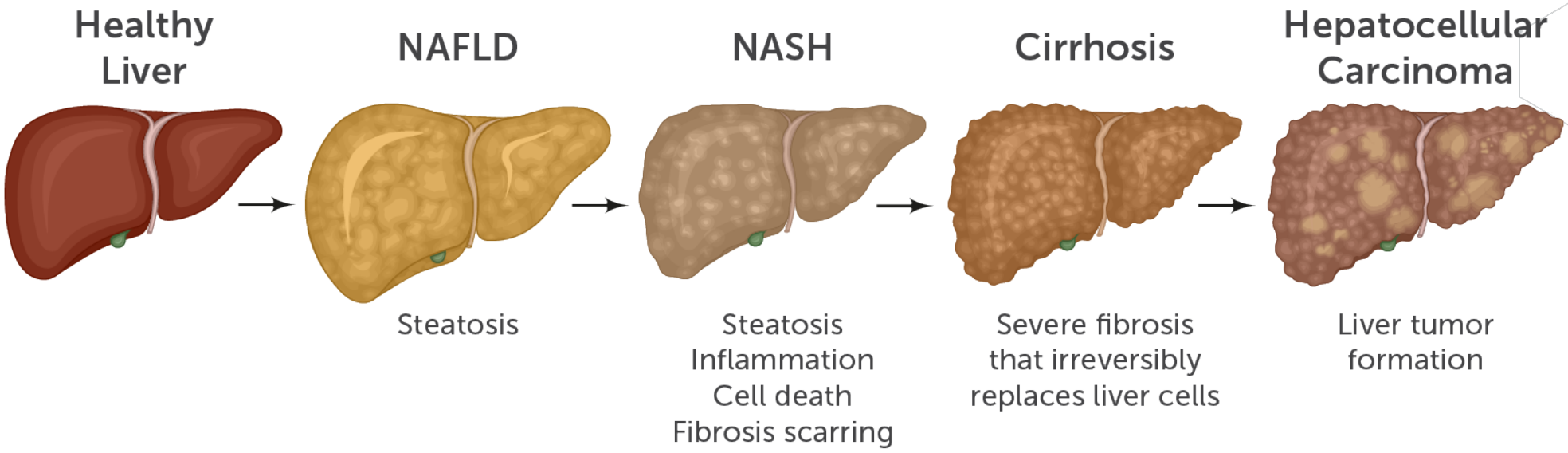
- The pooled global prevalence of NAFLD (CAP) among patients with T2D was 62.25% (1990-2021)
- In T2D, the global NAFLD prevalence has increased by +50.09% from 45.52% in 1990-2004 to 68.32% in 2016-2021 ($P = 0.008$)
- Among T2D, the global pooled prevalence of NASH, significant fibrosis (≥F2), and advanced fibrosis (≥F3) were 59.69%, 46.30%, and 25.38%, respectively

Prevalence of NAFLD in Adults With T2D



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

Nonalcoholic Fatty Liver Disease (NAFLD) Progression: About 10-15% of NASH can Progress to Cirrhosis

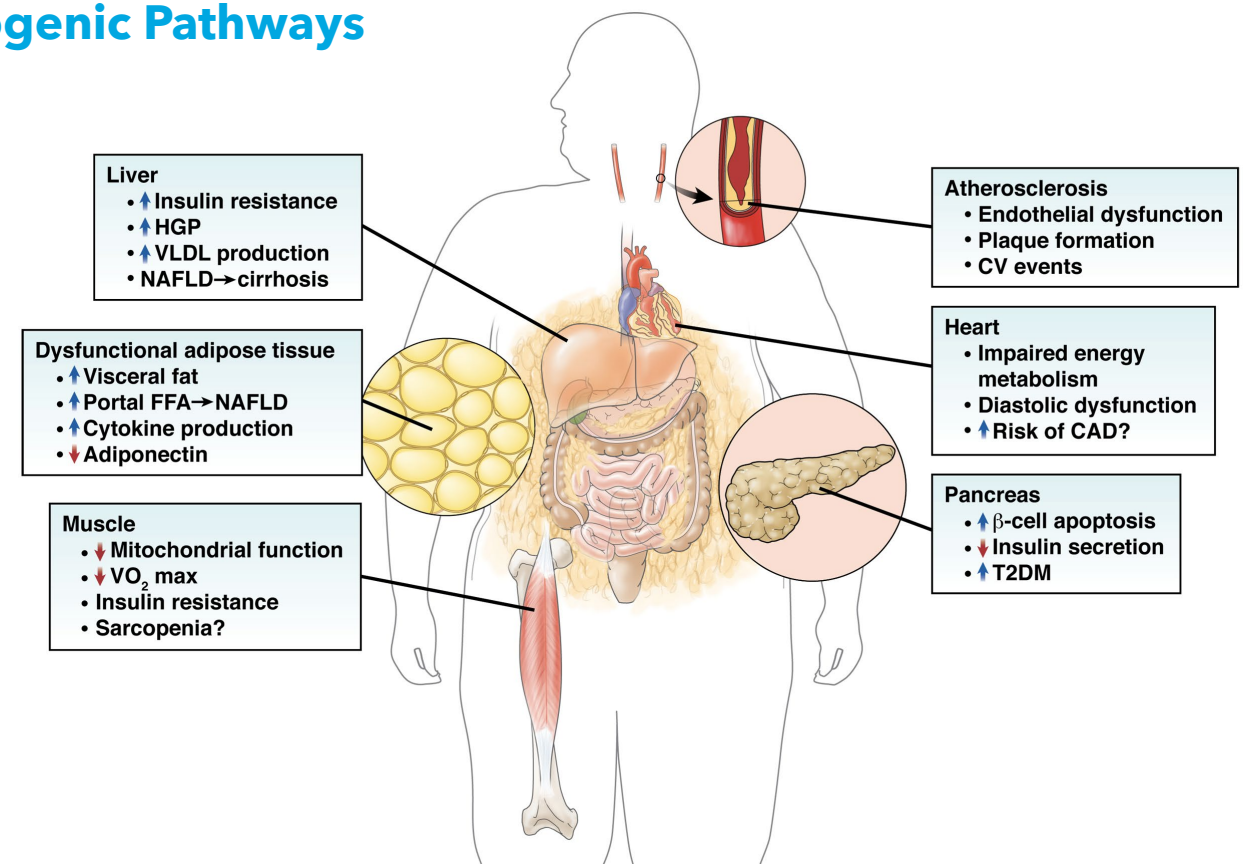


Complications of NAFLD effect the Health System

- NAFLD and NASH patients have higher rates of cardiovascular death
- Progression to cirrhosis
- Progression to liver cancer
- Greater number of liver transplantations
- Higher mortality rates overall
- Extrahepatic diseases

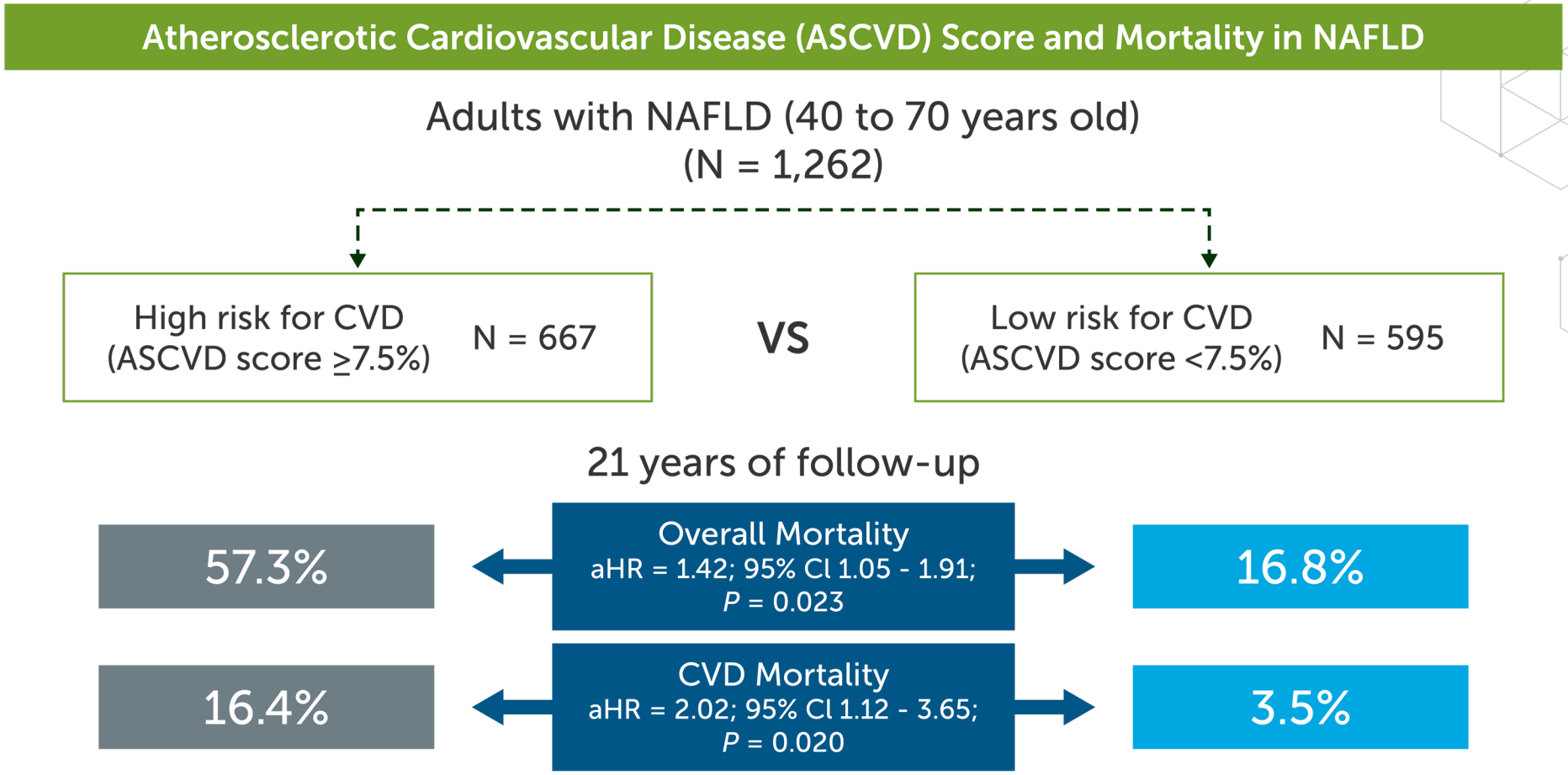
Common Extrahepatic Diseases Associated With NAFLD

Common Pathogenic Pathways



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

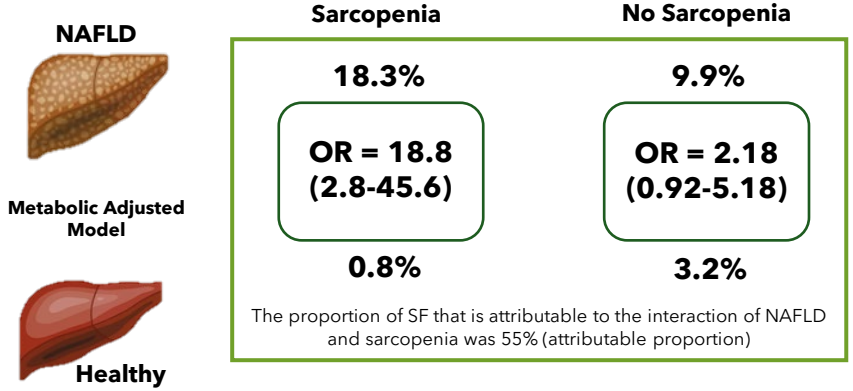
Common Extrahepatic Diseases Associated With NAFLD Cardiovascular Disease



Armandi A, Bugianesi E. *Clin Liver Dis*. 2023 (in press). Paik J, Younossi ZM. DDW; 2019. Golabi P, et al. *Hepatology Communications.* 2019;*3*(8):1050-1060. Younossi ZM, et al. *Clin Gastroenterol Hepatol*. 2020;(20)30775-8. Younossi ZM, et al. AASLD; 2021.

Common Extrahepatic Diseases Associated With NAFLD Sarcopenia

Advanced Fibrosis 12.5% adults (NHANES) with Sarcopenic NAFLD				
	Outcome : Significant Fibrosis		Outcome : Advanced Fibrosis	
	OR (95% CI)	P	OR (95% CI)	P
Healthy Liver	Reference		Reference	
Sarcopenia without NAFLD	0.23 (0.04 - 1.38)	0.1008	1.72 (0.13 - 23.53)	0.6634
Non-Sarcopenic NAFLD	**2.10 (1.00 - 4.43)**	**0.0510**	**4.43 (1.02 - 19.27)**	**0.0474**
Sarcopenic NAFLD	**3.44 (1.63 - 7.28)**	**0.0031**	**6.65 (1.19 - 37.11)**	**0.0330**

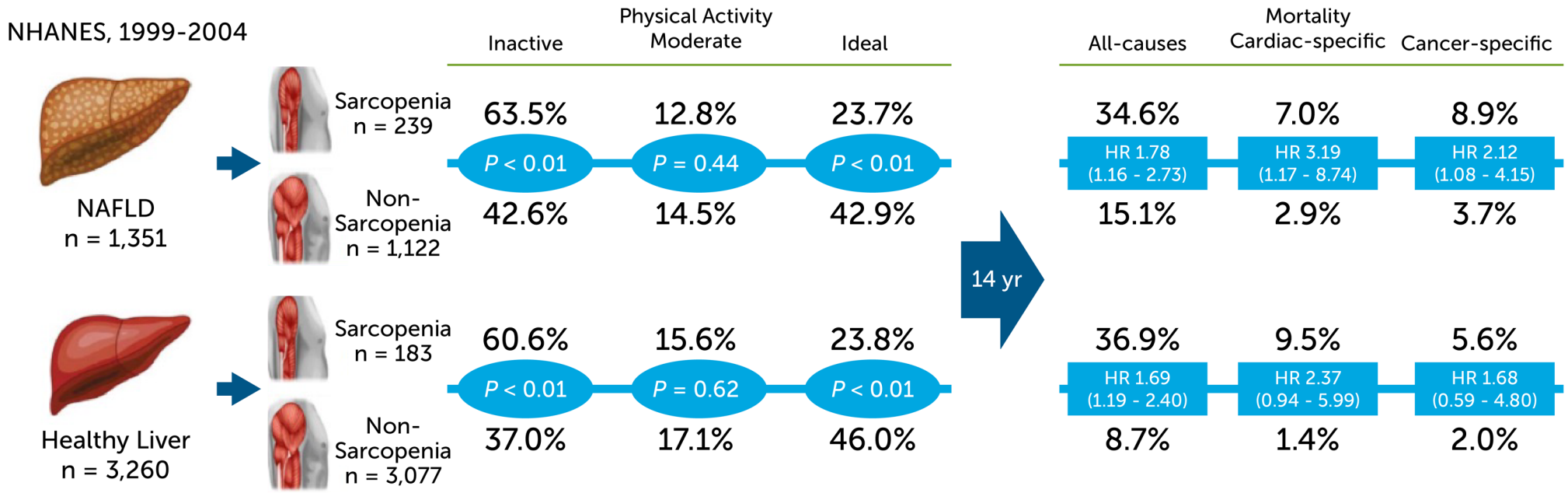


Longer physical activity and healthy diet targeted to improve sarcopenic NAFLD may reduce the risk of significant hepatic fibrosis.

Golabi P, et al. *Clin Gastroenterol Hepatol*. 2023 (in press).
Golabi P, et al. *JHEP Rep*. 2020;2(6):100171.

Common Extrahepatic Diseases Associated With NAFLD Sarcopenia

Mortality Prevalence in NAFLD vs No-NAFLD: 16.0% vs 6.4%



Physical inactivity is associated with sarcopenia and sarcopenia is associated with increased mortality among people with NAFLD

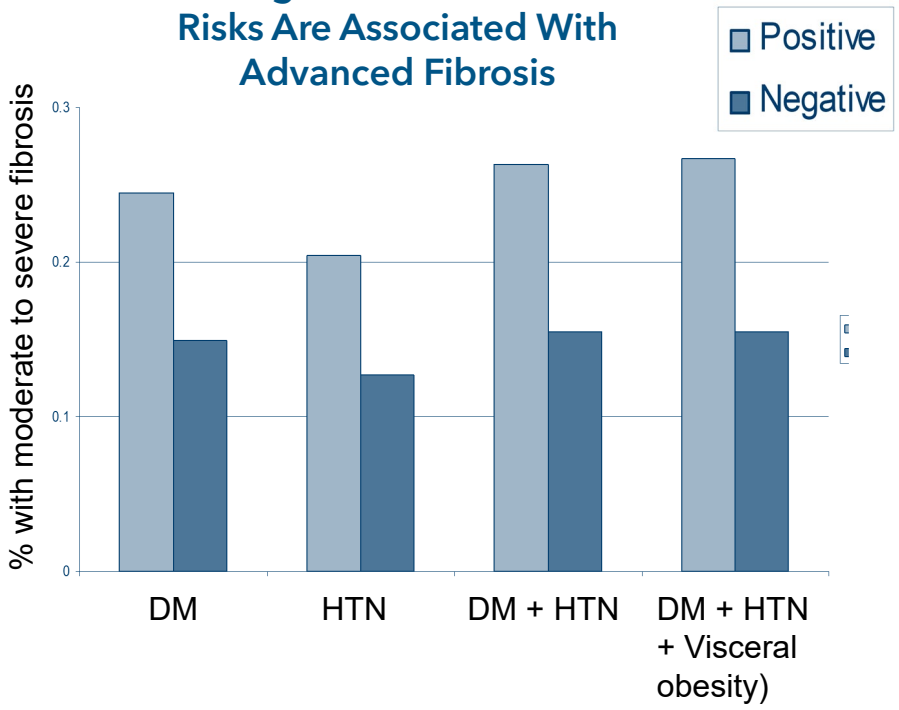
Golabi P, et al. *Clin Gastroenterol Hepatol*. 2023 (in press).
Golabi P, et al. *JHEP Rep*. 2020;2(6):100171.

High-Risk Groups With NAFLD

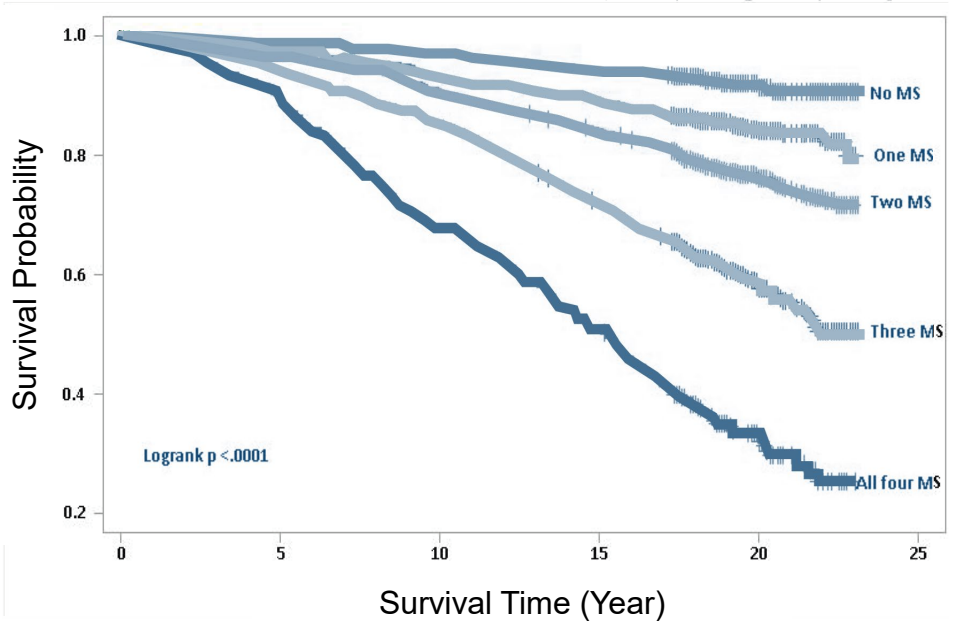
Long-Term Outcomes of Patients With Diabetes and NAFLD

- NAFLD & DM (n = 44) vs NAFLD alone (n = 88)
- Patients with NAFLD and DM have:
  - Higher rate of cirrhosis (25% vs 10.2, *P* = 0.04)
  - Higher liver-related mortality (RR = 22.83, *P* = 0.003)
  - Higher mortality (RR = 3.3, *P* = 0.002)

Increasing Number of Metabolic Risks Are Associated With Advanced Fibrosis



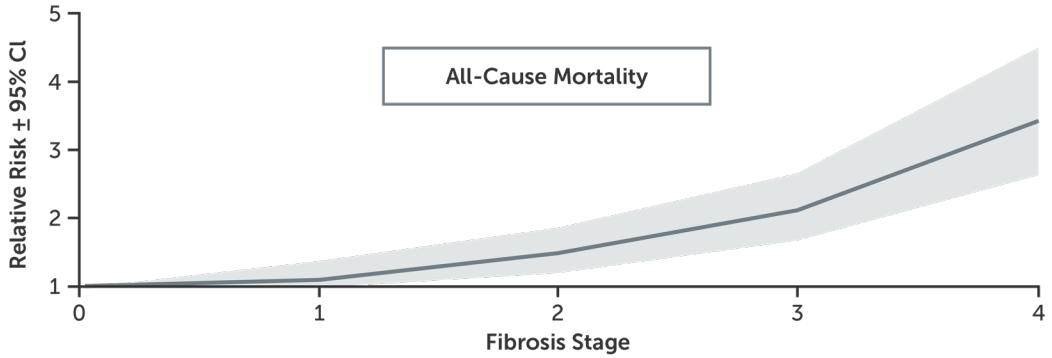
Increasing Number of Metabolic Risks Are Associated With Mortality

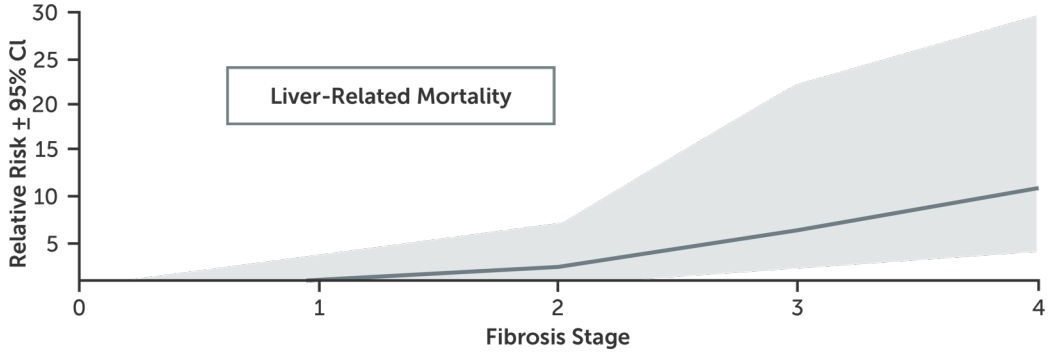


Younossi Z, et al. *Clin Gastroenterol Hepatol.* 2004;2(3):262–265.
Hossain N, et al. *Clin Gastroenterol Hepatol.* 2009;7(11):1224-1229.e1-2.
Golabi P, et al. *Medicine (Baltimore).* 2018;97(13):e0214.

Histologic Predictor of Adverse Outcomes

Systematic review and meta-analysis of 13 studies
4,428 NAFLD patients (2,875 with histological NASH)



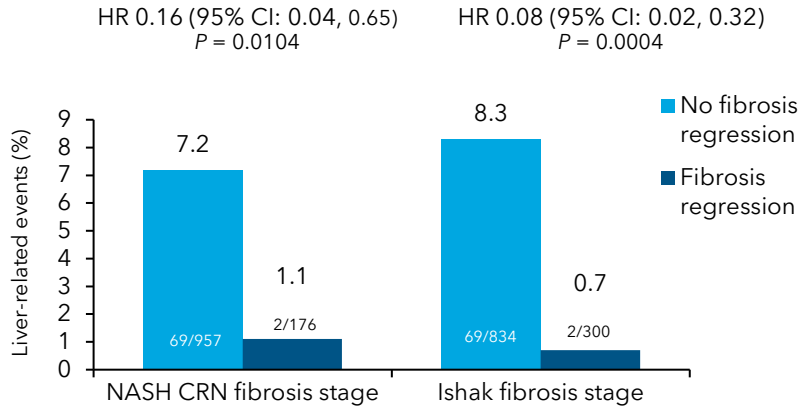


Number of studies	Stage 0 vs 1 RR (95% CI), *P* value n/N vs n/N, I^2 statistic	Stage 0 vs 2 RR (95% CI), *P* value n/N vs n/N, I^2 statistic	Stage 0 vs 3 RR (95% CI), *P* value n/N vs n/N, I^2 statistic	Stage 0 vs 4 RR (95% CI), *P* value n/N vs n/N, I^2 statistic
All-cause mortality				
8	1.12 (0.91–1.38) 135/843 vs 136/896, 0%	1.50 (1.20–1.86) 135/843 vs 103/425, 0%	2.13 (1.70–2.67) 135/843 vs 86/301, 0%	3.42 (2.63–4.46) 135/843 vs 61/169, 27%
Liver-related mortality				
7	1.05 (0.35–3.16) 3/521 vs 7/755, 0%	2.53 (0.88–7.27) 3/521 vs 10/340, 0%	6.65 (1.99–22.25) 3/521 vs 12/248, 0%	11.13 (4.15–29.84), 0% 3/521 vs 22/151

Regression of Fibrosis Leads to Improvement of Clinical Outcomes

- NASH cirrhosis (STELLAR-4 and simtuzumab clinical trials)
- Regression: Any reduction in fibrosis (NASH CRN or Ishak)
- Liver-related events: Ascites, portal hypertension hemorrhage, HE, MELD >15, LT, and death
- In NASH-cirrhosis, regression was observed in 16% over 48 weeks

Fibrosis regression and liver-related events in NASH cirrhosis



Taylor RS, et al. *Gastroenterology*. 2020;158(6):1611-1625.e12. Sanyal A, et al. AASLD TLMdX 2020. #90.

Low Awareness and Knowledge Gaps

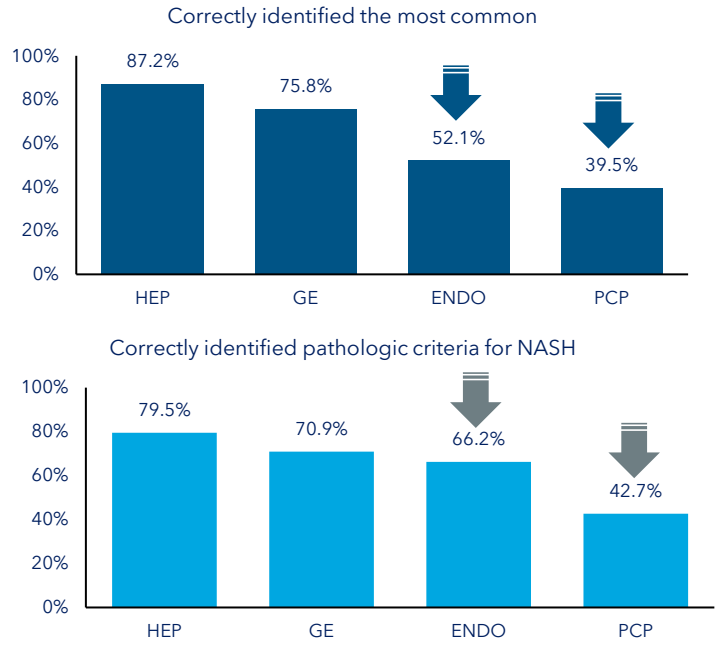
- **Patient level:** Using NHANES data, only ***4.4% NAFLD patients*** were aware of having liver disease vs 37.8% of viral hepatitis

  Alqahtani, Younossi Z. *Hepatol Commun*. 2021;5(11):1833-1847.

- **Health System level:** Using EHR of patients who were considered to have NAFLD (N = 251) from VA, only 22% had a documented diagnosis of NAFLD, 15% received lifestyle modification recommendation, and ***10% were referred to specialist (only 3% of those with possible advanced fibrosis)***

  Blais P, et al. *Am J Gastroenterol*. 2015;110(1):10-14.

- **Provider level:** Survey-Global NASH Council (54 and 59 Questions) of 2202 clinicians (HEP, GI, ENDO, and PCP) from 40 countries



Younossi Z, et al. *Clin Gastroenterol Hepatol*. 2022;20(6):e1456-e1468.

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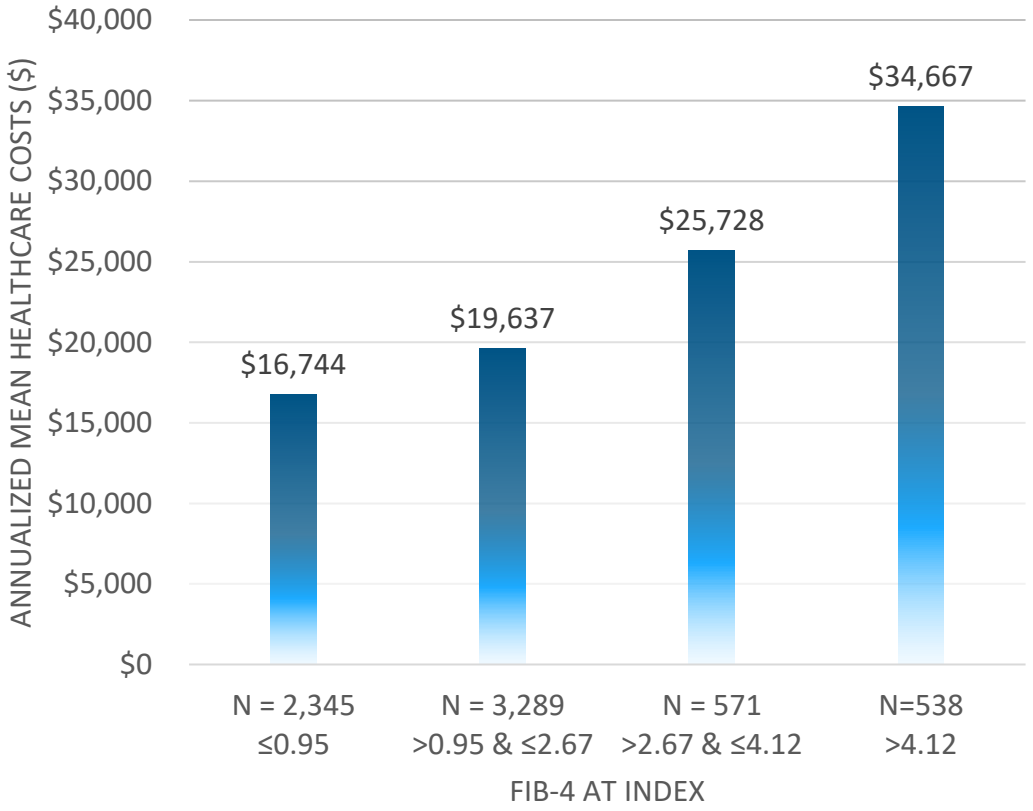
Healthcare Resource Utilization and Costs of Care in the US for Patients with NASH



- The estimated lifetime direct medical costs of US patients with NASH exceed $223 billion
- ASCVD risk could be calculated for 33.8% of patients:
  - the 10-year risk of ASCVD increased from 6.9% to 16.8%, 21.8%, and 27.2% as index FIB-4 increased from lowest to highest cohort

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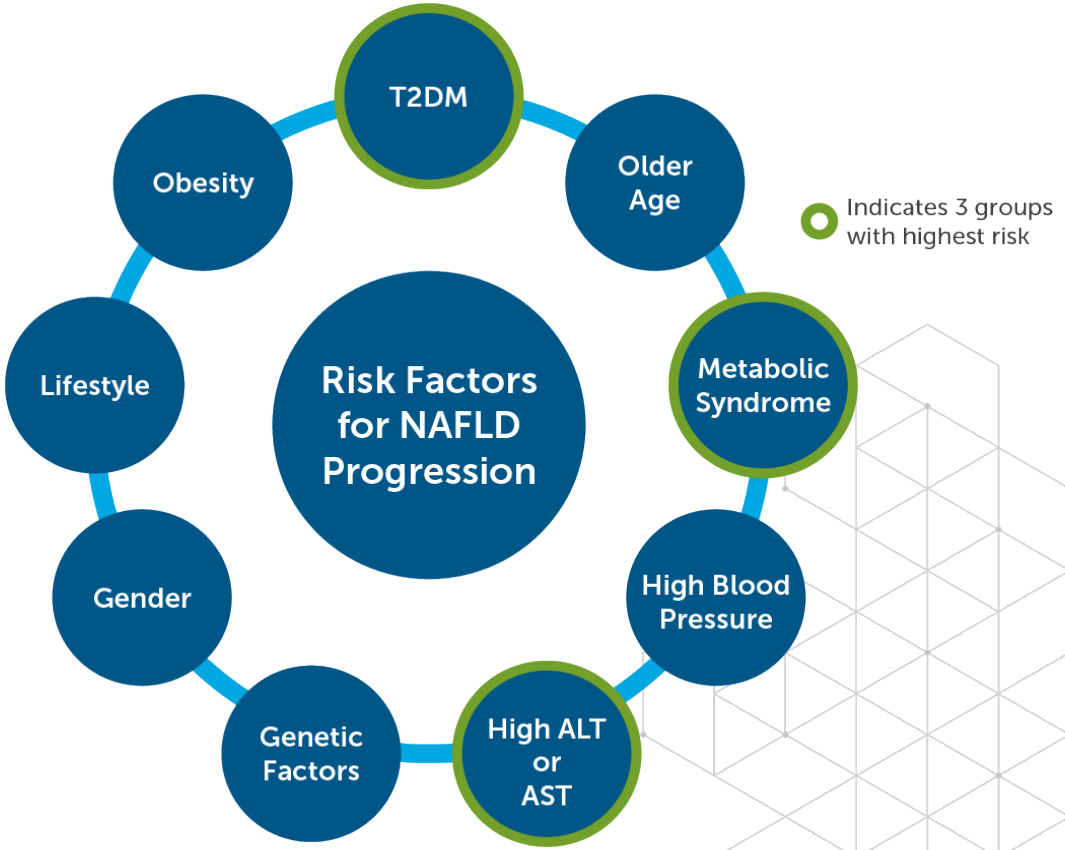
Tapper EB, Bonafede M, Fishman J, et al. *J Med Econ*. 2023;26(1):348-356.


What Do We Need to Do?

How Does One Have Initial Suspicion for NAFLD?

- Identify clinical risk factors for NAFLD
  - Obesity
  - **DM**
  - HTN
  - Dyslipidemia
  - **Metabolic syndrome**
- Patient presentation
  - Elevated liver enzymes (but often are normal)
  - Abnormal liver imaging



Who Sees Patients First With NAFLD?

- Primary care providers including APPs
- Endocrinologists
- Gastroenterologists
- Cardiologists
- Surgeons

Who Should We Be Concerned About?

- Patients with NASH
- Patients with at least S2 fibrosis
- Patients with type 2 diabetes or multiple components of metabolic syndrome
- How to identify at risk patients with NAFLD?

How to Use Non-invasive Tests to Identify High Risk Patients With Nonalcoholic Steatohepatitis ?

1. Simple Evaluation Scores

- Easily calculated using information from standard liver tests and patient data[1]
- **FIB-4,** NFS, and APRI are recognized in guidelines as clinically useful in identifying patients with a higher probability of F3/F4 fibrosis[1,2]

2. Imaging Techniques

- **Conventional ultrasound:** historically used to identify steatosis despite known limitations[1]
- **MRI/MRI-PDFF:** accurate for detecting and quantifying steatosis[1]
- **FibroScan® (VCTE):** can assess both steatosis (CAP) and fibrosis (LSM); point-of-care[1]
- **MRE:** accurate for detecting and quantifying fibrosis[1]

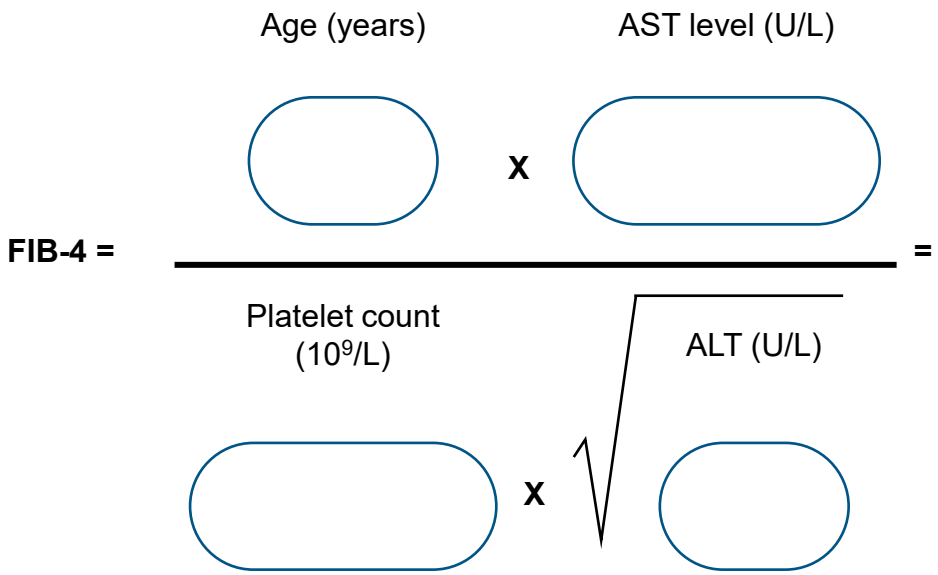
3. Proprietary Serum Tests

- Tests for biomarkers to determine the presence of advanced fibrosis (F3/F4) or active NASH[1,3]
- **ELF:** FDA recently granted marketing authorization via the De Novo review pathway, and ELF is also widely used outside the US to determine the presence of F3/F4[4]
- Other investigational serum tests include: **PRO-C3** or **NIS-4**[3,5]

1. European Association for Study of Liver. *J Hepatol*. 2021;75(3):659-89. 2. A Chalasani N, et al. *Hepatology*. 2018;67(1):328-57. 3. Loomba R, Adams LA. *Gut*. 2020;69:1343–1352. 4. https://www.siemens-healthineers.com/en-us/laboratory-diagnostics/assays-by-diseases-conditions/liver-disease/elf-test (accessed January 2022). 5. https://nis4.com/ (accessed January 2022).

FIB-4 is a strong predictive of liver-related mortality in patients with NAFLD:
Calculated from routinely captured EHR data

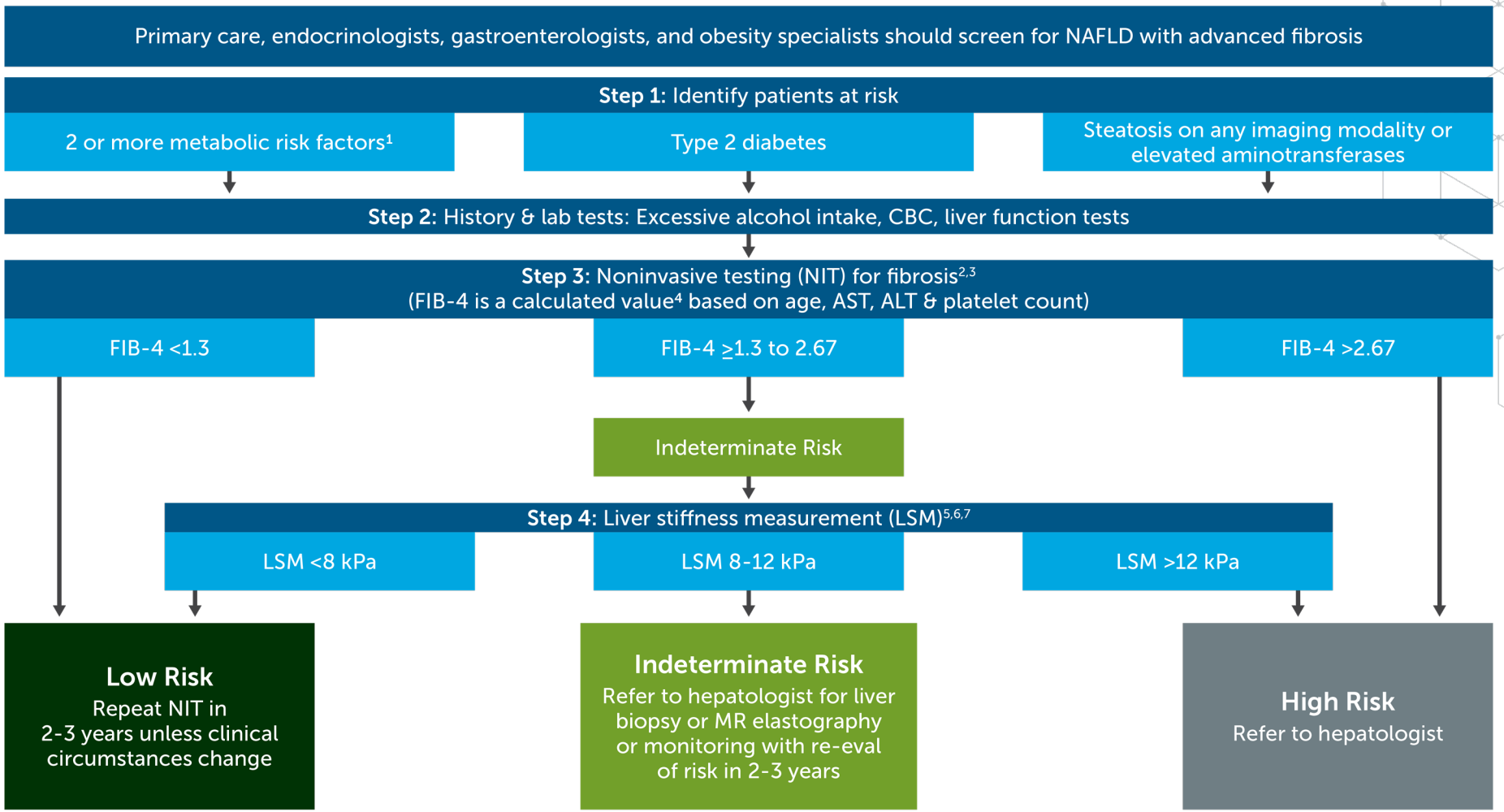
Focus on FIB-4



- 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.

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.**

Current Standard of Care

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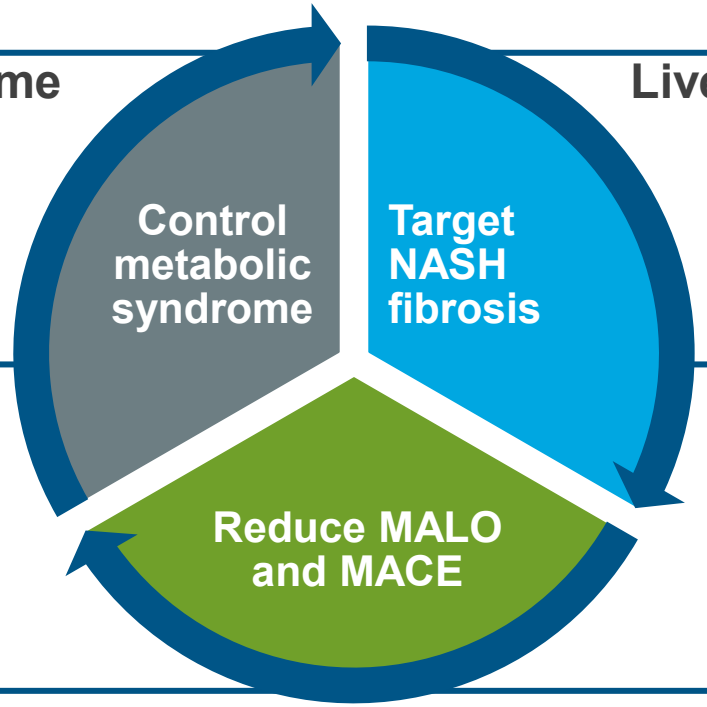
The Goals for NASH Management

Improve metabolic syndrome
- Weight loss
- T2D/hyperglycemia
- Hypertension
- Dyslipidemia



Liver-directed treatment
- NASH resolution
- Fibrosis regression
- Reduction in liver stiffness/fat
- Improvement in biomarkers

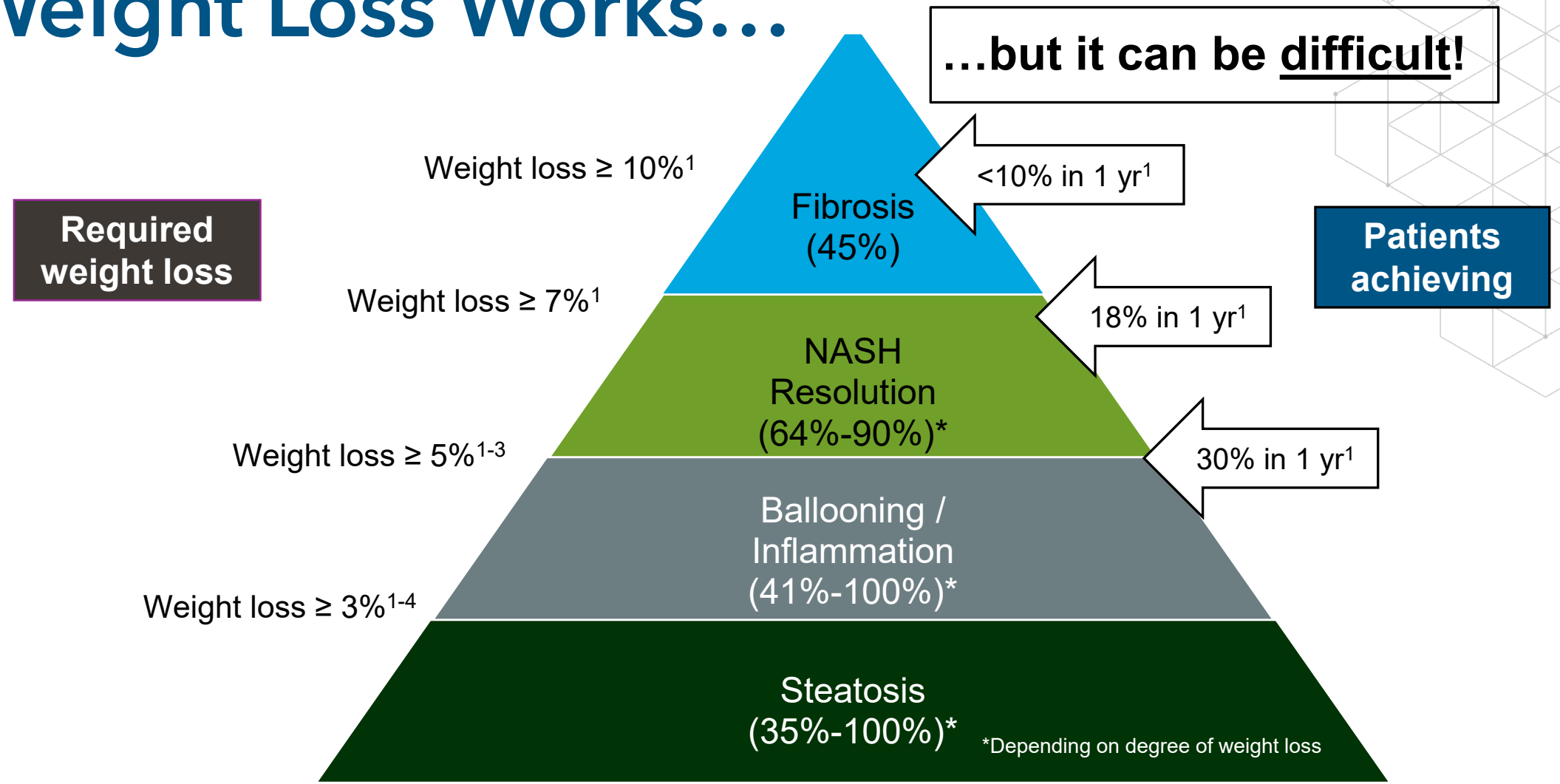
Improve outcomes
- Major adverse liver outcomes (MALO)
- Major adverse cardiac events (MACE)

→ **Cost and adverse events**

MACE, major adverse cardiac events; MALO, major adverse liver outcomes.

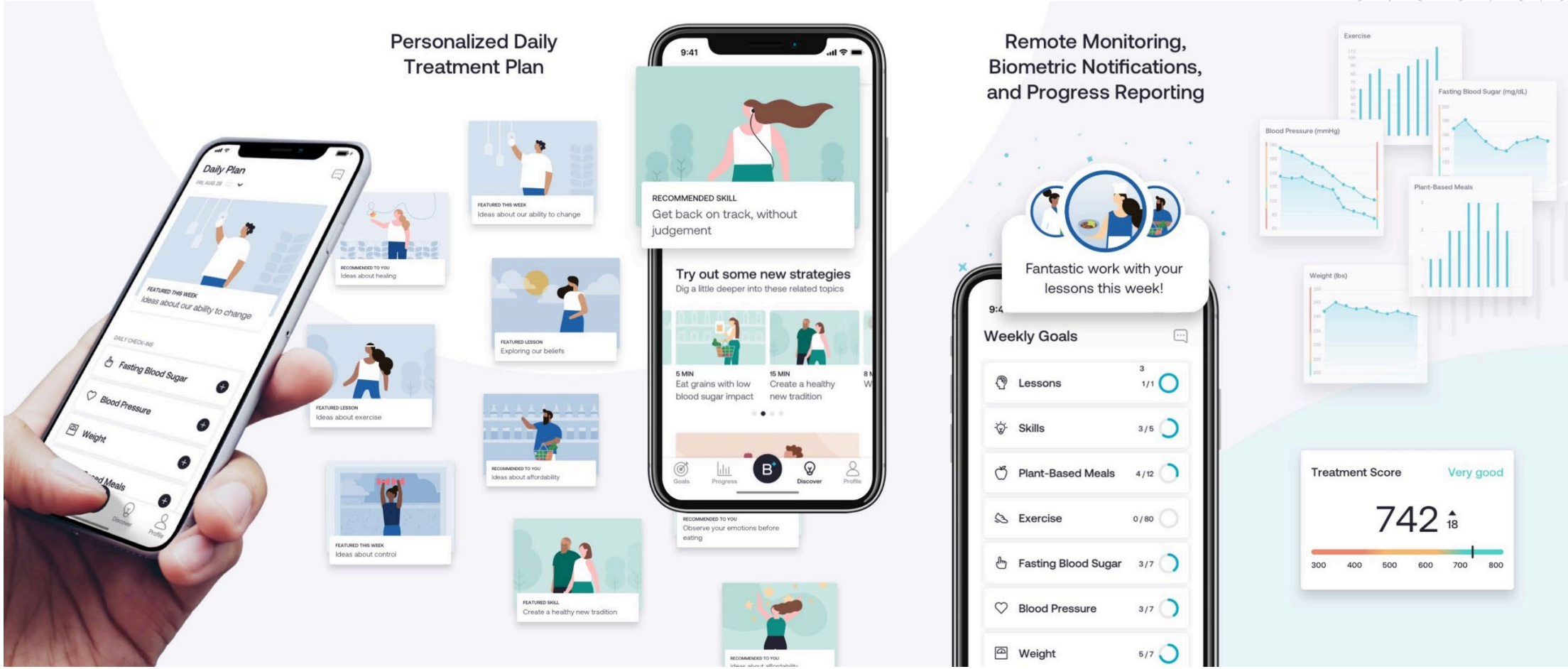
Weight Loss Works…

…but it can be 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.

Prescription Digital Therapeutics (PDT): Using Software Instead of Drugs (or in Combination With Drugs)



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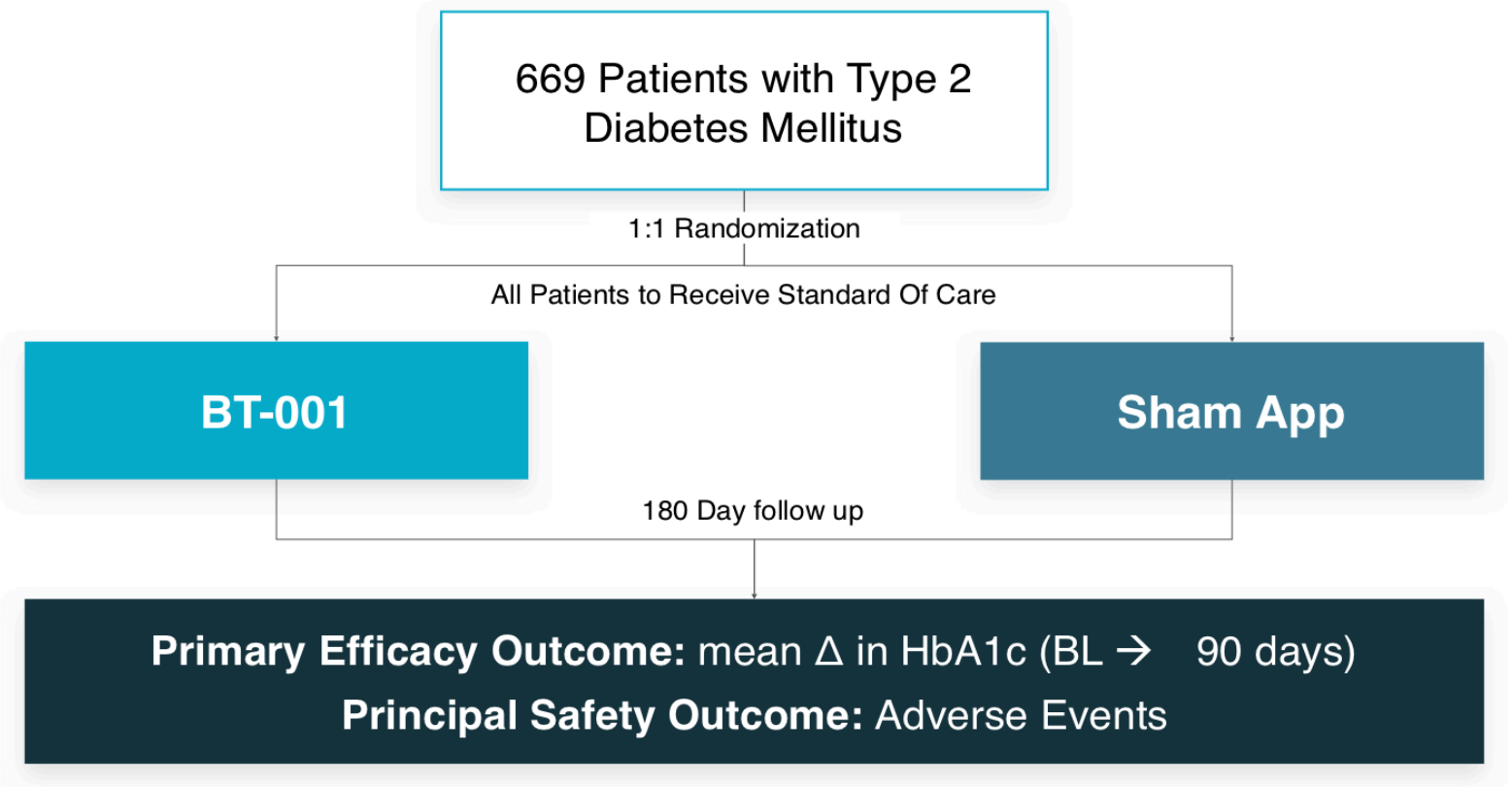
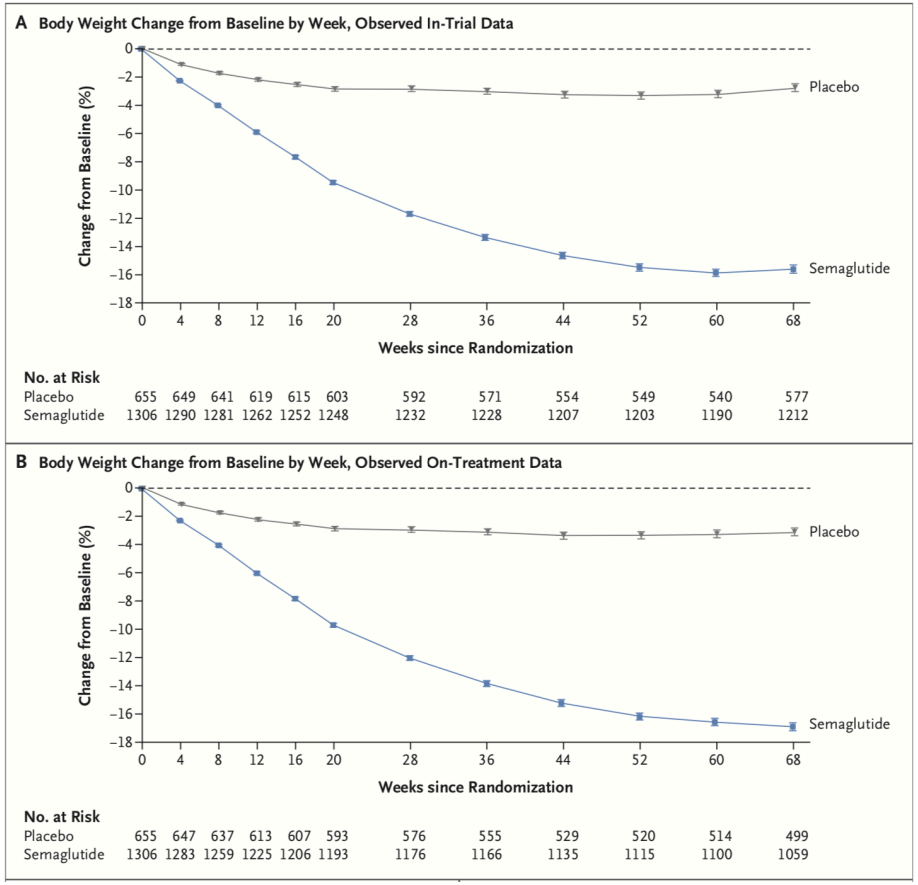
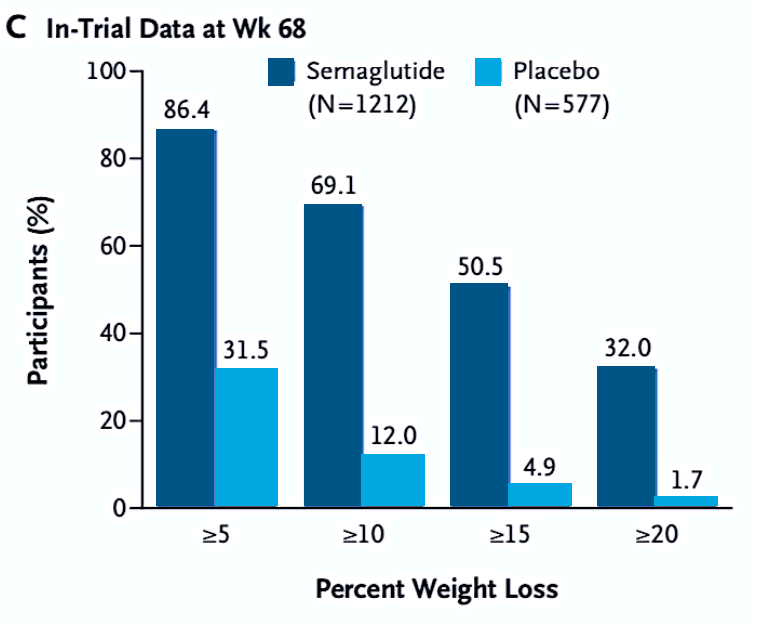
Multicenter Trial Using PDT for T2DM

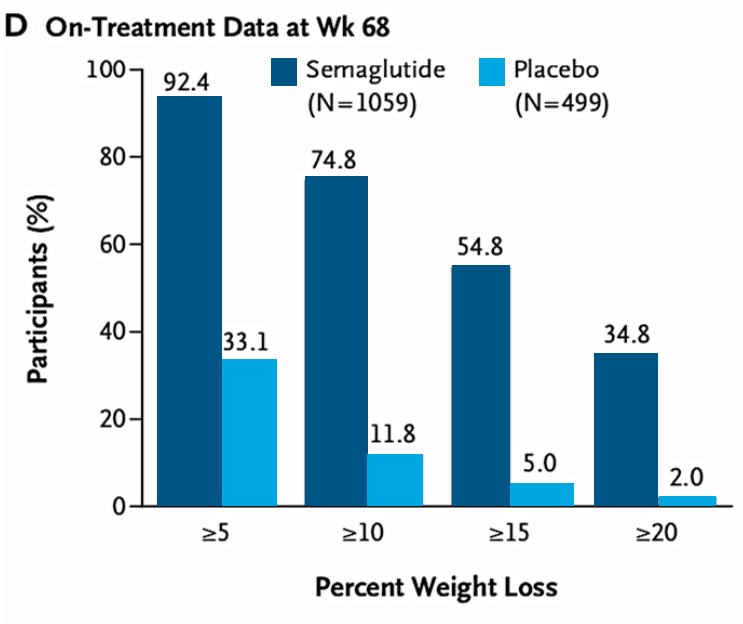


- HbA1c reductions of 0.4% or more occurred in 42.7% of the group receiving SOC + BT-001 vs 25.4% in the group receiving SOC alone (difference of 17.3%, $P < 0.001$)
- There was a clear dose response between greater engagement in nCBT and greater reductions in A1c

STEP1: Effects of Once-Weekly Semaglutide

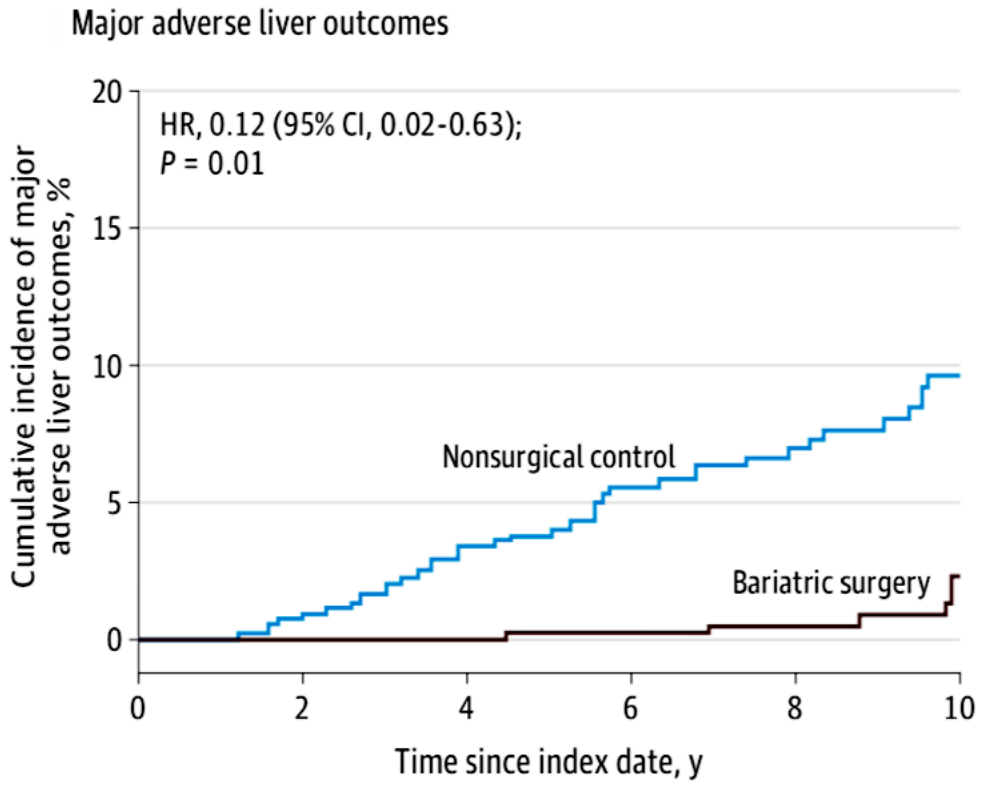


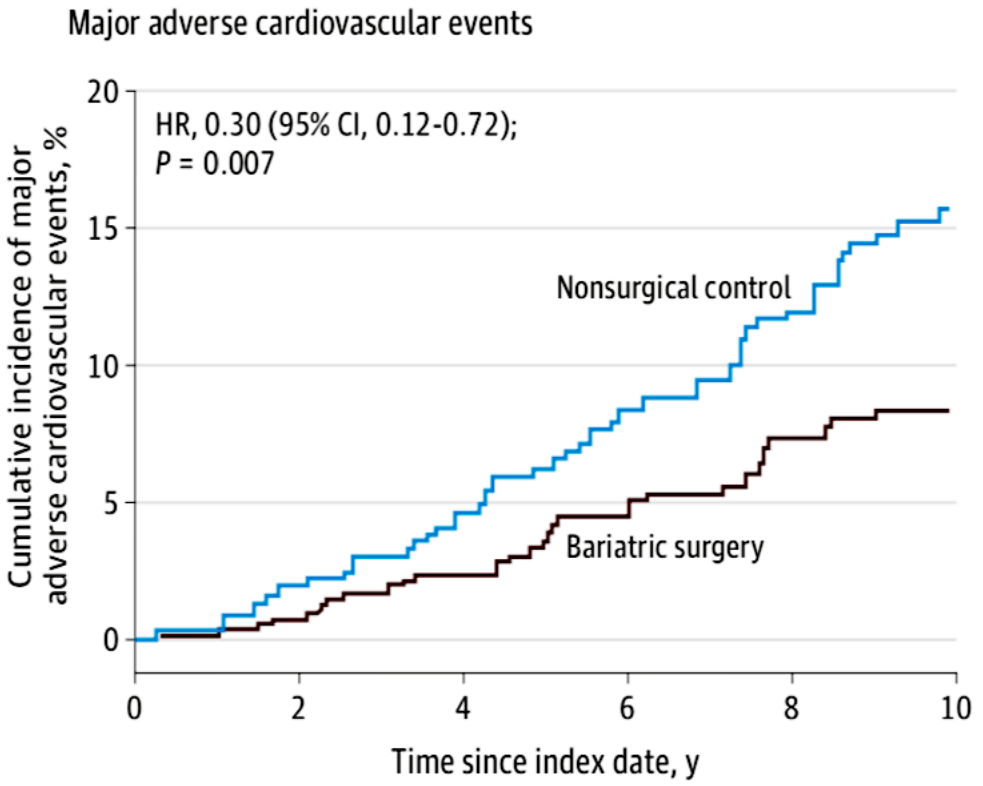




Wilding JPH, et al. *N Engl J Med.* 2021;384(11):989-1002.

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

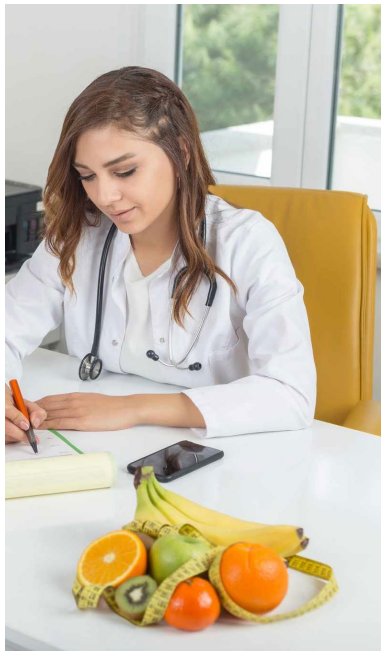
- Edema, weight gain (~ 2-3 kg over 2-4 yrs)[4]
- Risk of osteoporosis in women[5]
- Equivocal risk for bladder cancer
  - Increased in some studies[6]
  - No association in most studies[7,8]

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.

Weight Management Spectrum for NAFLD

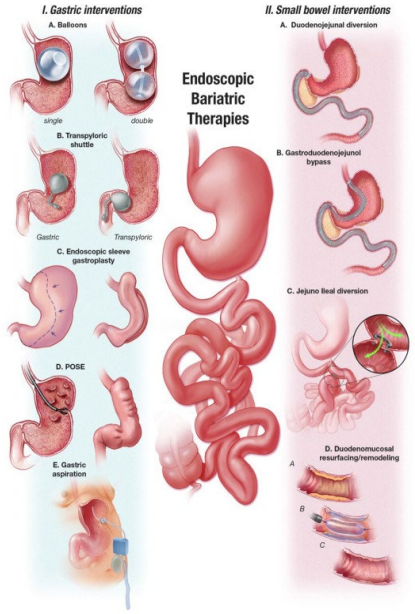
Traditional Lifestyle Intervention



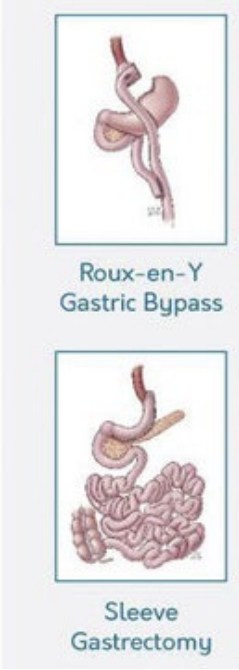
PDT for Weight Loss

AOMs - Oral - Injectable

EndoBariatric Procedures



Bariatric Surgery



What is the Role of the Managed Care Pharmacist?

Emerging Therapies for NASH Management

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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.

Biomarkers to Assess Treatment Response

Liver Fat Fraction (MRI-PDFF)

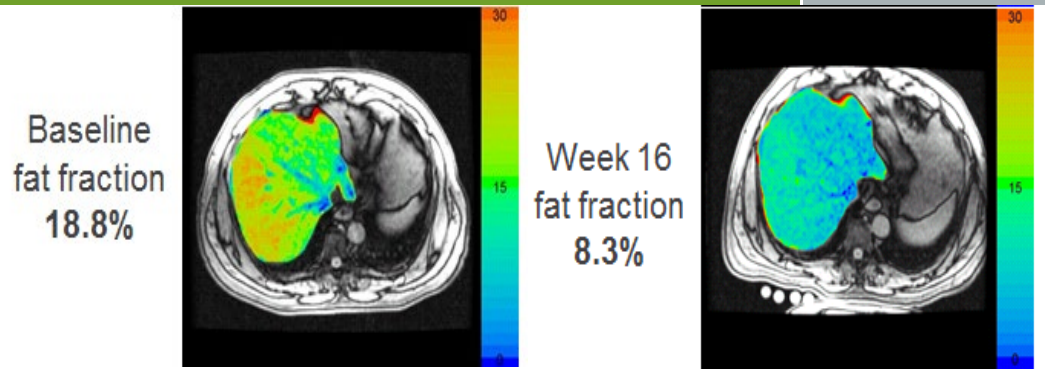
- ≥ 5% absolute/ ≥ 30% relative reduction associated with improvement in NAS

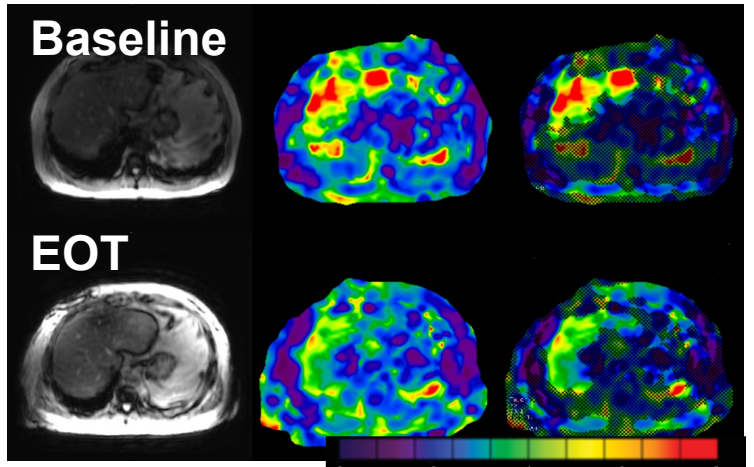
ALT/ AST

- ≥ 17 U/L reduction predicts histologic response

?MRE/ cT1/ LSM?

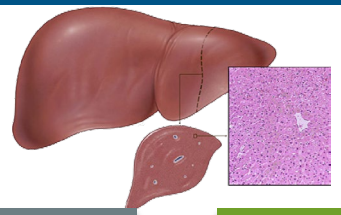
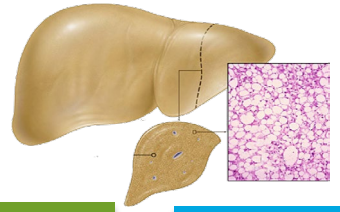
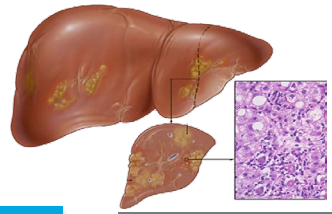
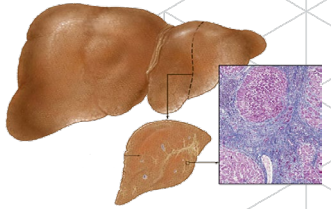
- MRE: ≥ 15% relative reduction from BL?
- cT1: > 80 ms reduction from BL (21%) or change in category?
- LSM decrease by 20%-25% from BL?





Loomba R, et al. *Gastroenterology*. 2019;156(1):88-95.e5.
Patel J, et al. *Therap Adv Gastroenterol*. 2016;9(5):692-701.

Targeting Pathophysiological Processes

NORMAL LIVER	STEATOSIS	FIBROTIC NASH	CIRRHOSIS
			

Targets related to insulin resistance and/or lipid metabolism

GLP-1:	**Semaglutide**
GLP-1/GR/GIP	MEDI0382, BI456906, Tirzepatide, Cotadutide, HM15211
SCD1:	Aramchol
SGLT1/2:	Licogliflozin
FGF21:	Efruxifermin, BIO89-100
THR-β:	**Resmetirom**, VK2809
FGFR1/KLB	BFKB8488A, MK-3655
MPC	MSDC-0602K, PXL065
Mixed ag-antag GR and antag MR	Miricorilant
Fatty acid	Icosabutate
FASN Inh	TVB-2640
GHRH analog	Tesamorelin
Berberine/UDCA	HTD1801
DGAT2 Inhib./ACCi	Ervogastat/Clesacostat
DGAT2 Inhib.	ION224
AAs	AXA1125

Targets related to lipotoxicity & oxidative stress

PPARα/∂/γ:	**Lanifibranor**
PPARα/γ:	Saroglitazar
MPC	MSDC-0602K, PXL065
FXR:	**OCA**, EYP001, TERN-101
FGF19:	Aldafermin
Testosterone prodrug	LPCN 1144

Targets related to inflammation and immune activation

Cyclo Inh	CRV431

Targets related to cell death (apoptosis and necrosis)

Cyclo Inh	CRV431

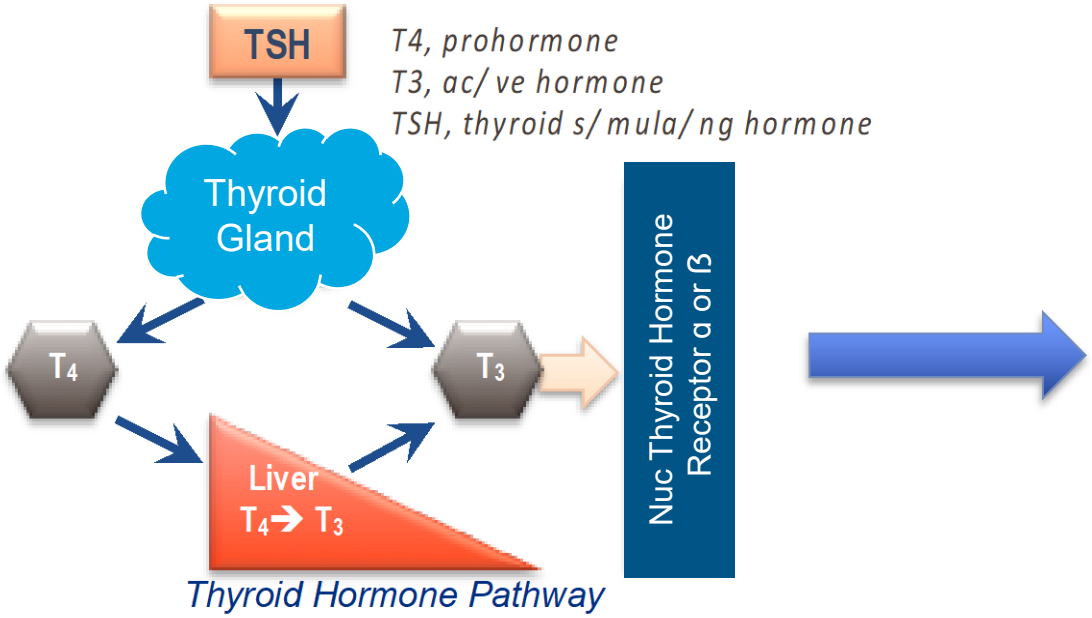
Targets related to fibrogenesis & collagen turnover

Galectin	Belapectin
Cyclo Inh	CRV431
JNK Inh.	CC-90001
GLP1 ag + ACCi + FXR	Semaglutide + Firsocostat + Cilofexor

Phase 3 drugs in red

Some drugs have pleiotropic effects

Resmetirom (MGL-3196): 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)

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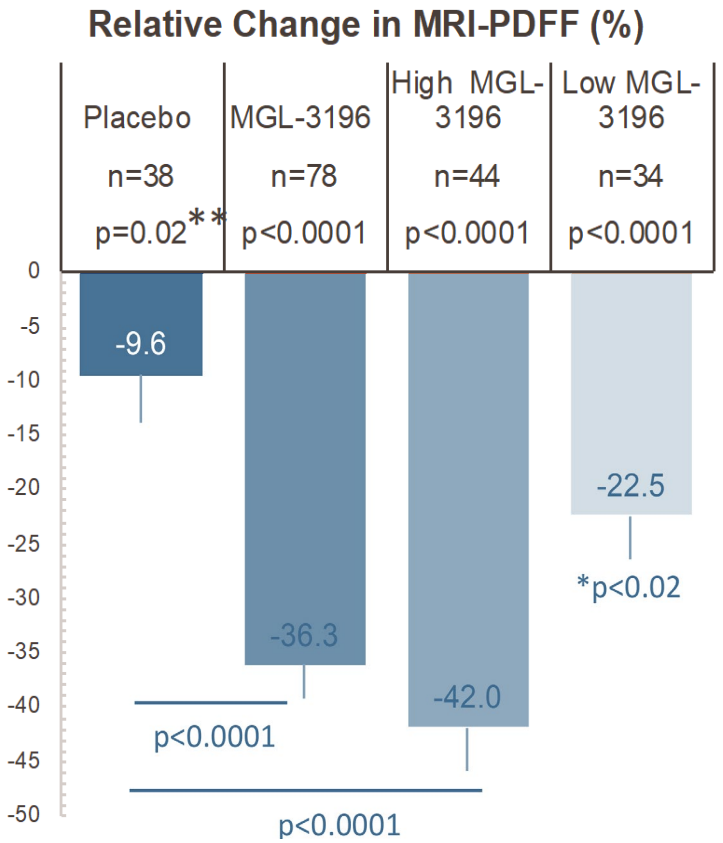
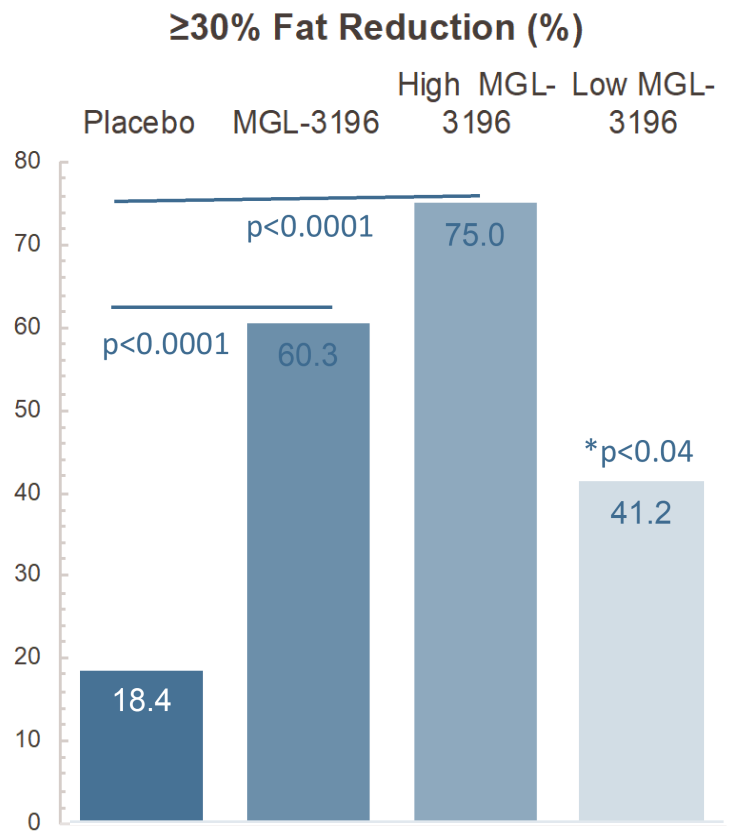
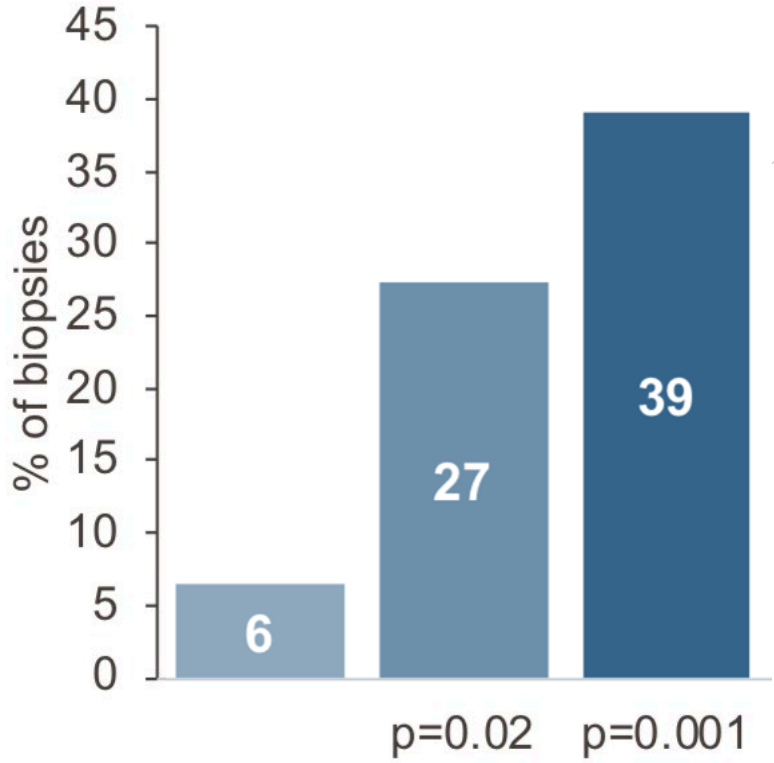
Resmetirom Significantly Decreases Hepatic Fat in Patients With NASH at Week 12 MRI-PDFF and Was Associated With NASH Resolution at Week 36 Biopsy

Fat Reduction at week 12 MRI-PDFF



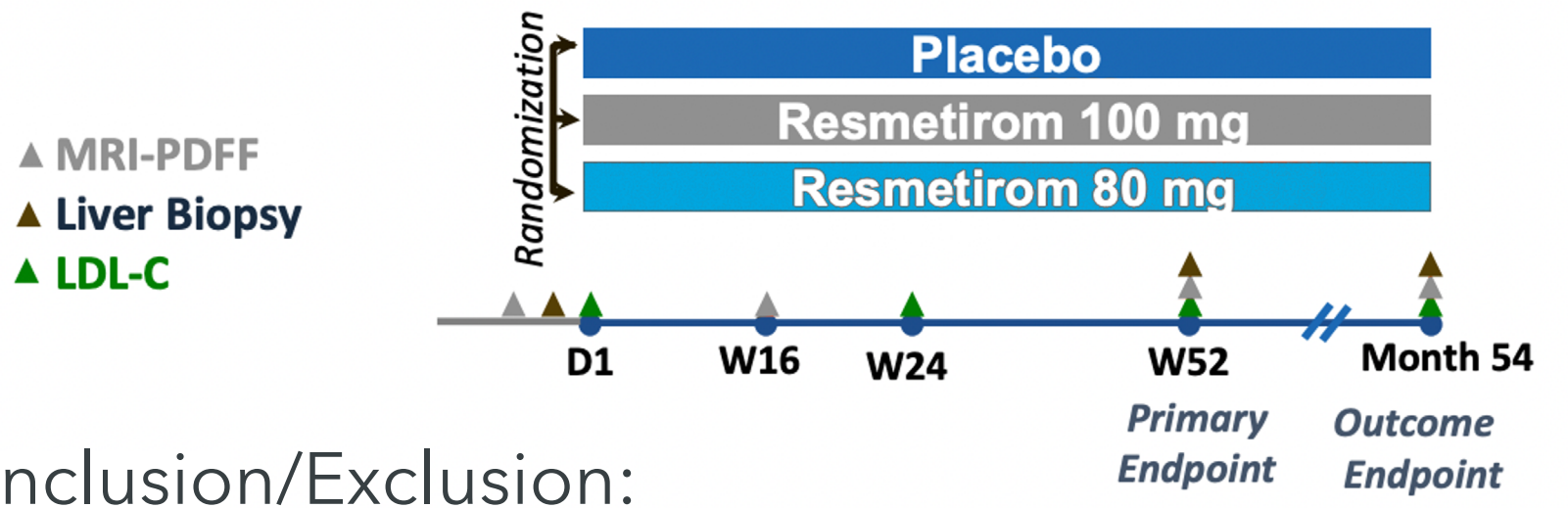


NASH Resolution at week 36 biopsy



Harrison SA, et al. *Lancet*. 2019;394(10213):2012-2024.

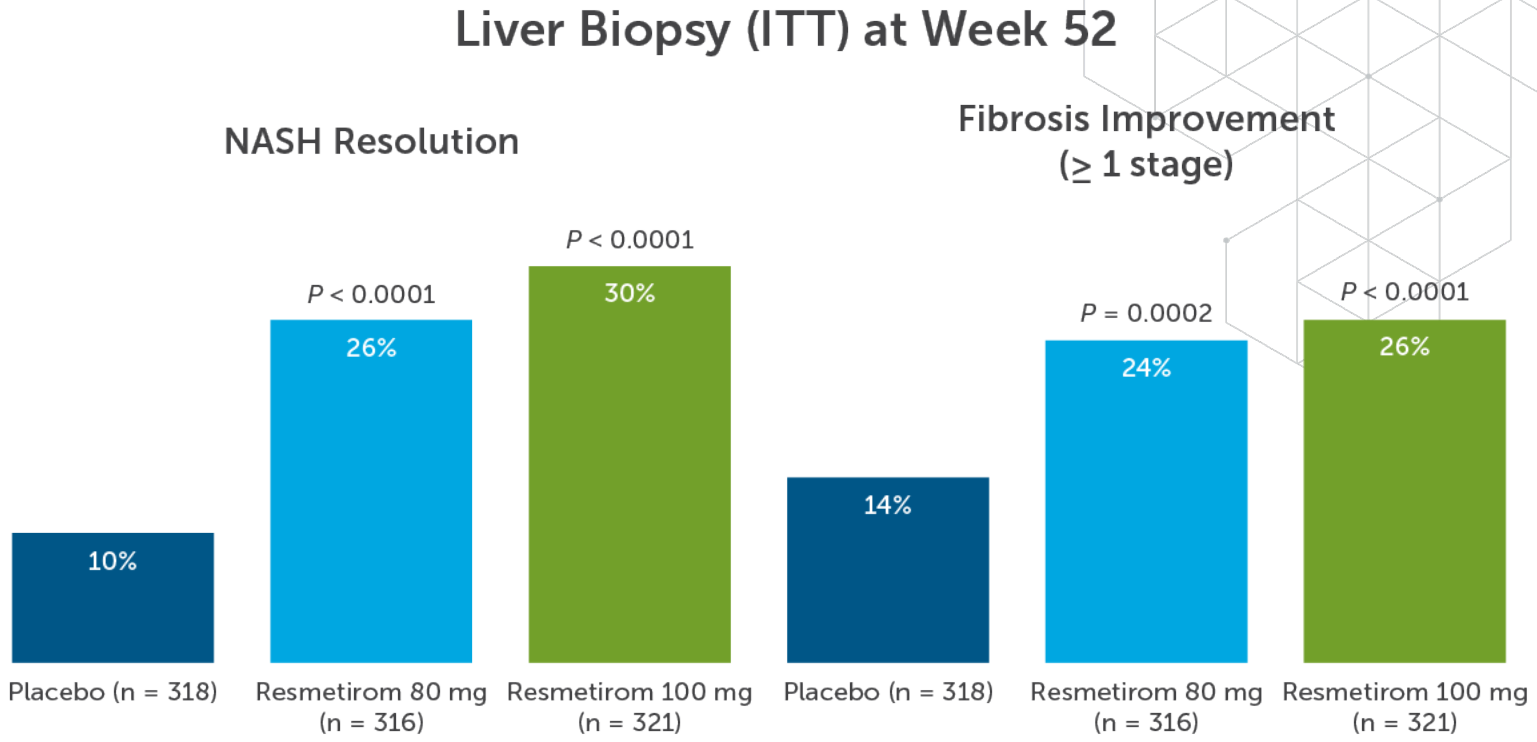
Phase 3 MAESTRO-NASH Study Design



- 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

Phase 3 MAESTRO-NASH: Resmetirom

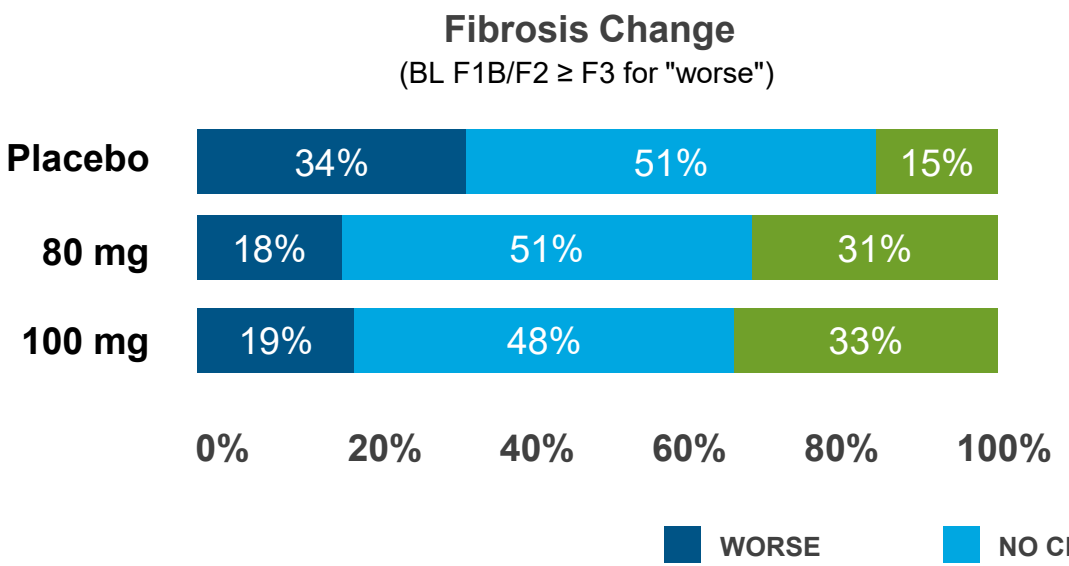
- Achieved NASH resolution
- Achieved fibrosis improvement
- Favorable effect on lipid panel

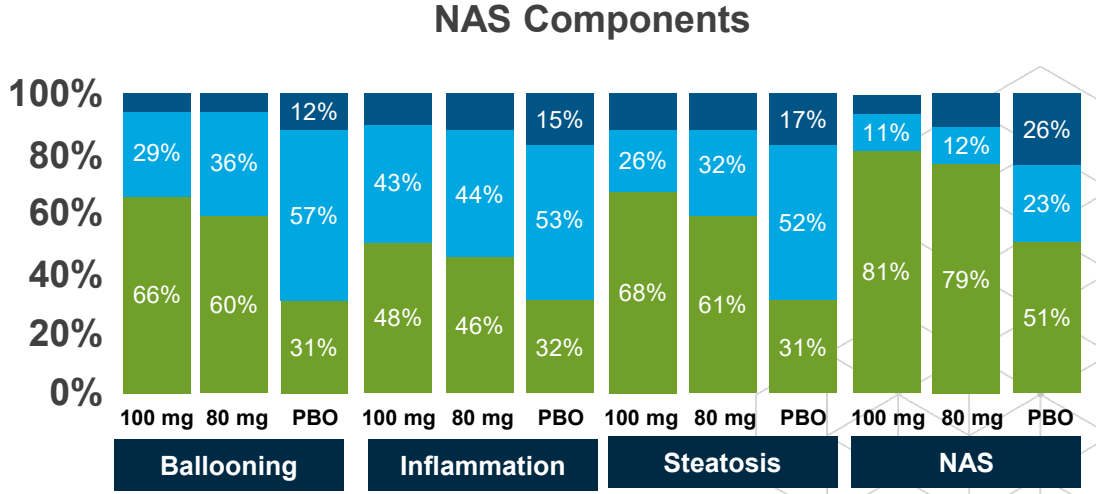


Harrison S, et al. NASH TAG 2023 Conference; Park City, UT; January 26, 2023.

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.

Resmetirom for NASH:

Summary from the Institute for Clinical and Economic Review's Midwest Comparative Effectiveness Public Advisory Council

TABLE 1 Results for the Base-Case for Resmetirom Compared With Standard Care, Health Care Sector Perspective

Treatment	Drugcosta	Totalcost	QALYs	evLYs	Incremental cost-effectiveness ratio	
					Cost per QALY gained	Cost per evLY gained
Resmetirom	$76,000	$416,000	10.66	10.74	Less costlyMore effective	Less costlyMore effective
Standard care	$0	$439,000	10.05	10.05	Comparator	Comparator

[a]*Placeholder price based on Javanbakht et al 2022.*[8]

evLY = equal value of life-year; LY = life-year; QALY = quality-adjusted life-year.

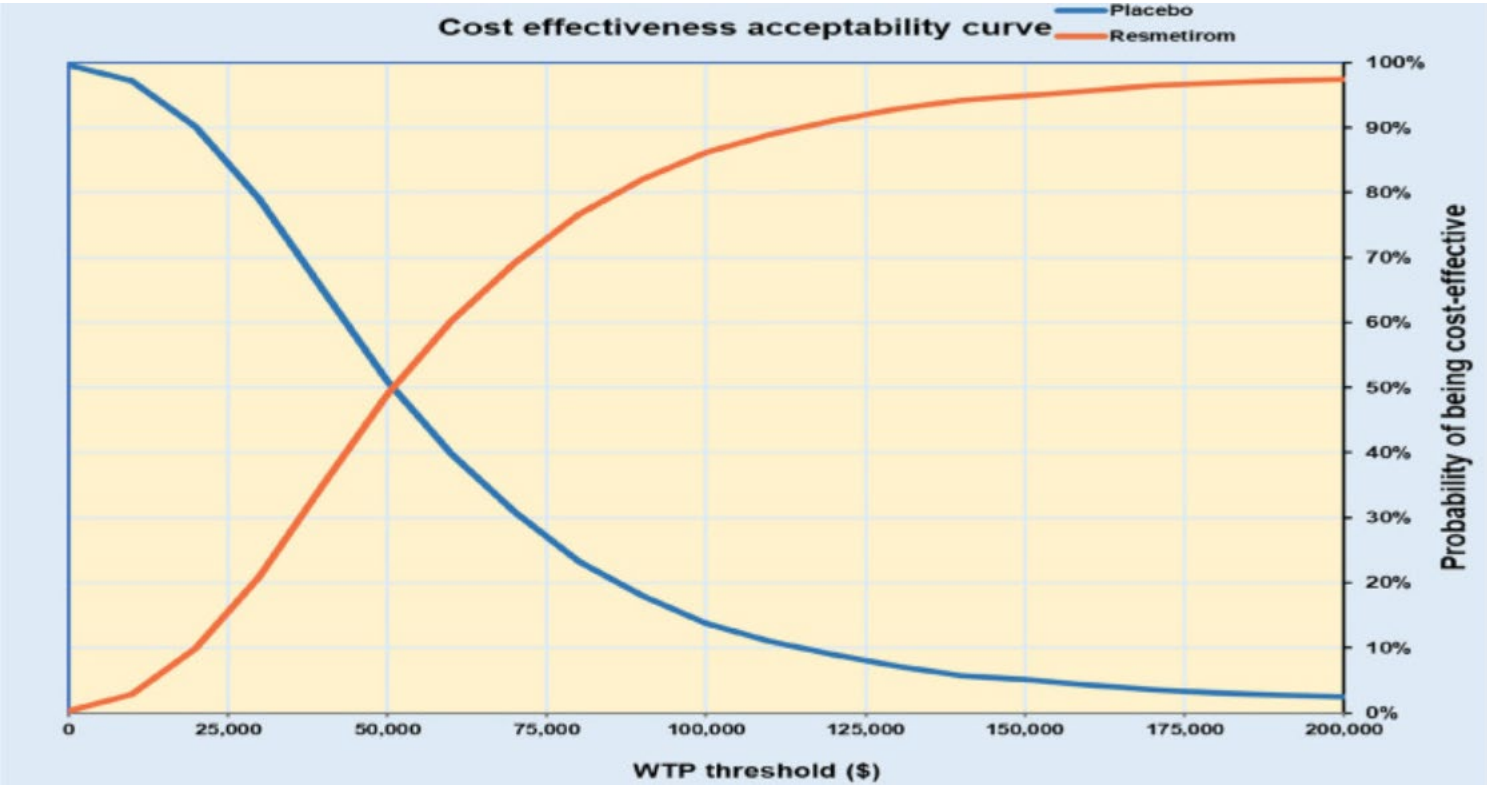
- Significant uncertainty remains regarding the magnitude of the long-term benefits of resmetirom for the treatment of NASH
- QALY gained resulted in resmetirom as the less costly, more effective treatment choices from the heath care system perspectives

Key Recommendations:

- Payers should select noninvasive diagnostic criteria that provide equitable access to early detection and treatment across communities.
- FIB-4 and noninvasive measures of liver fibrosis such as FibroScan or MRI elastography, could be combined to streamline diagnosis
- Payers should require that the prescription of initial therapy with resmetirom be done by a hepatologist.

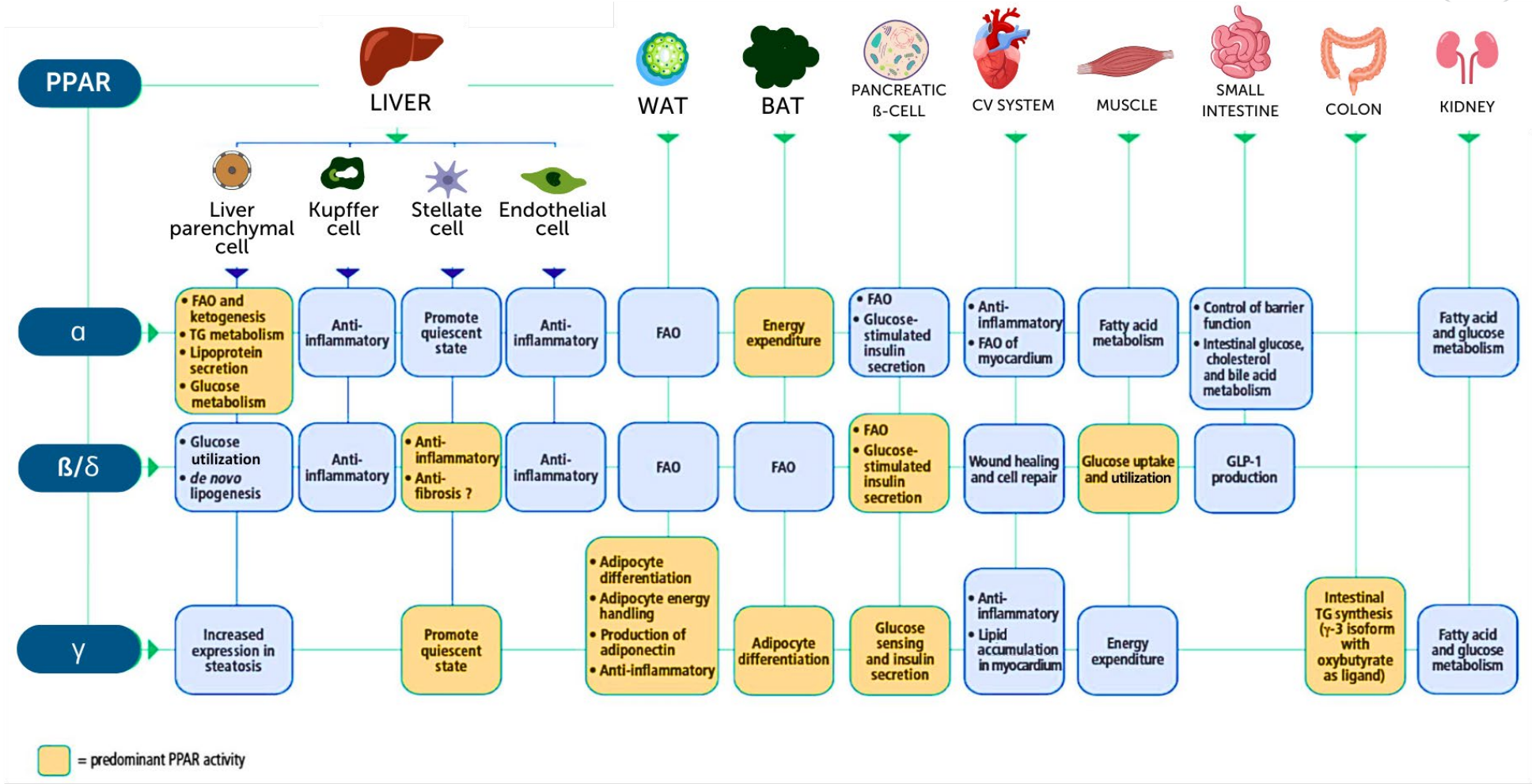
Fahim SM, et al. *J Manag Care Spec Pharm,* 2023 Oct;29(10):1169-1172.

Resmetirom has an 86.20% probability of being cost effective at a WTP threshold of US$100,000



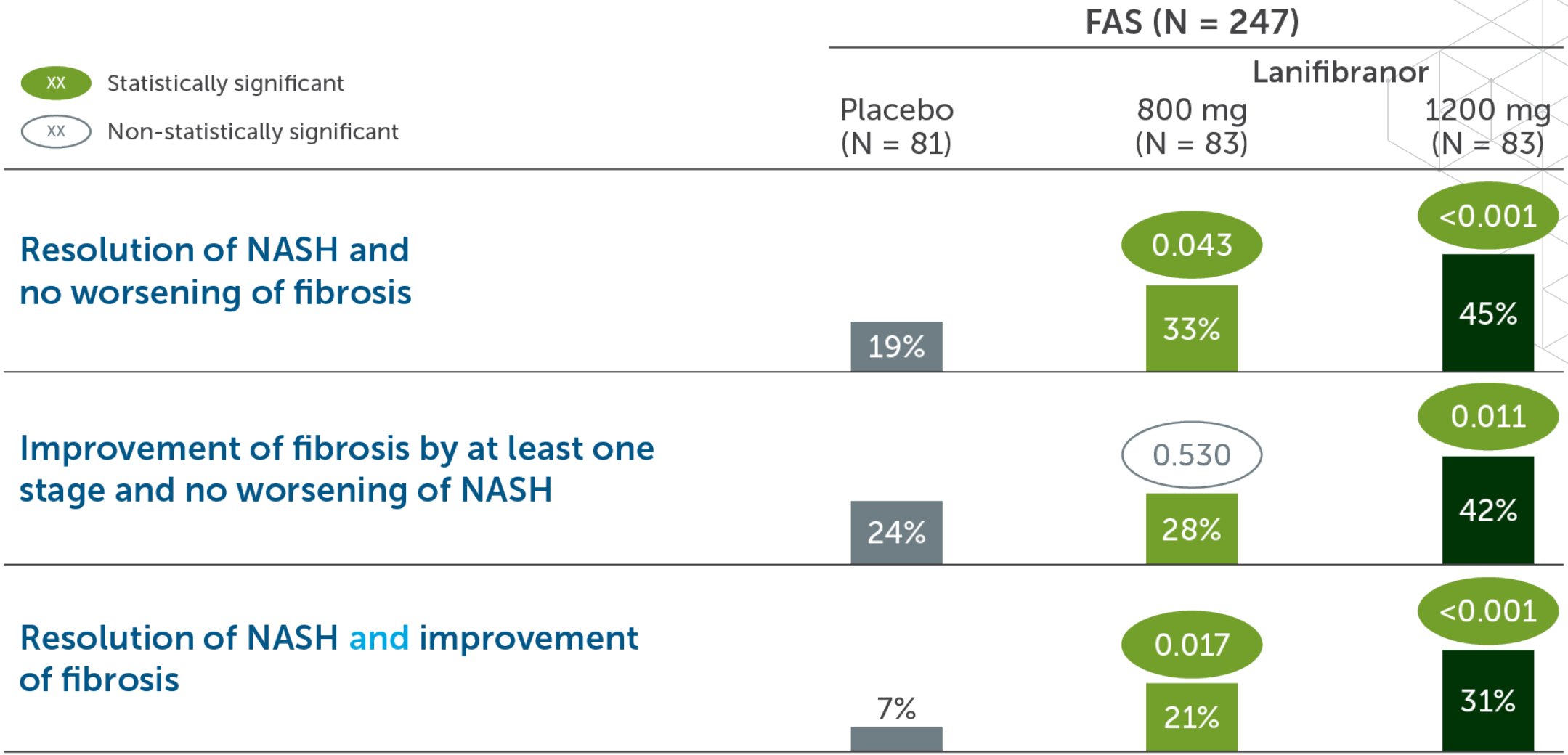
Javanbakht M, et al. *Pharmacoecon Open*. 2023;7(1):93-110.

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.

Belapectin: Galectin-3 Inhibitor

- NAVIGATE:
  - This seamless, adaptive, two-stage, Phase 2b/3, randomized, double-blind, multicenter, parallel-groups, placebo-controlled study
  - Assessing the efficacy, safety, and tolerability of belapectin compared with placebo in patients with NASH cirrhosis and clinical signs of portal hypertension but without esophageal varices at baseline.
  - The main efficacy objective:
    - primary prevention of esophageal varices
  - Interim topline data from the Phase 2b portion of NAVIGATE is expected in the fourth quarter of 2024

ClinicalTrials.gov identifier: NCT04365868

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
- F2-F3 biopsy-proven stage of liver fibrosis will likely be considered eligible for treatment with a liver-targeted therapy for NASH when available
- New drugs are in late-phase development – be prepared for major changes in how we manage NASH

Panel Discussion

- Implications of the Approval of a Liver-directed, NASH-specific therapy
- Clinical mandate (patient access)
  - Managed care mandate (coordinate distribution and movement of product)
  - Specialty drug
- Prior authorization process and reimbursement criteria: biopsy-proven fibrosis stage F2 or F3