Liver Disorders in Primary Care (NAFLD)

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McGill | Faculty of Medicine and Health Sciences | Continuing Professional Development

Faculty/Presenter Disclosure

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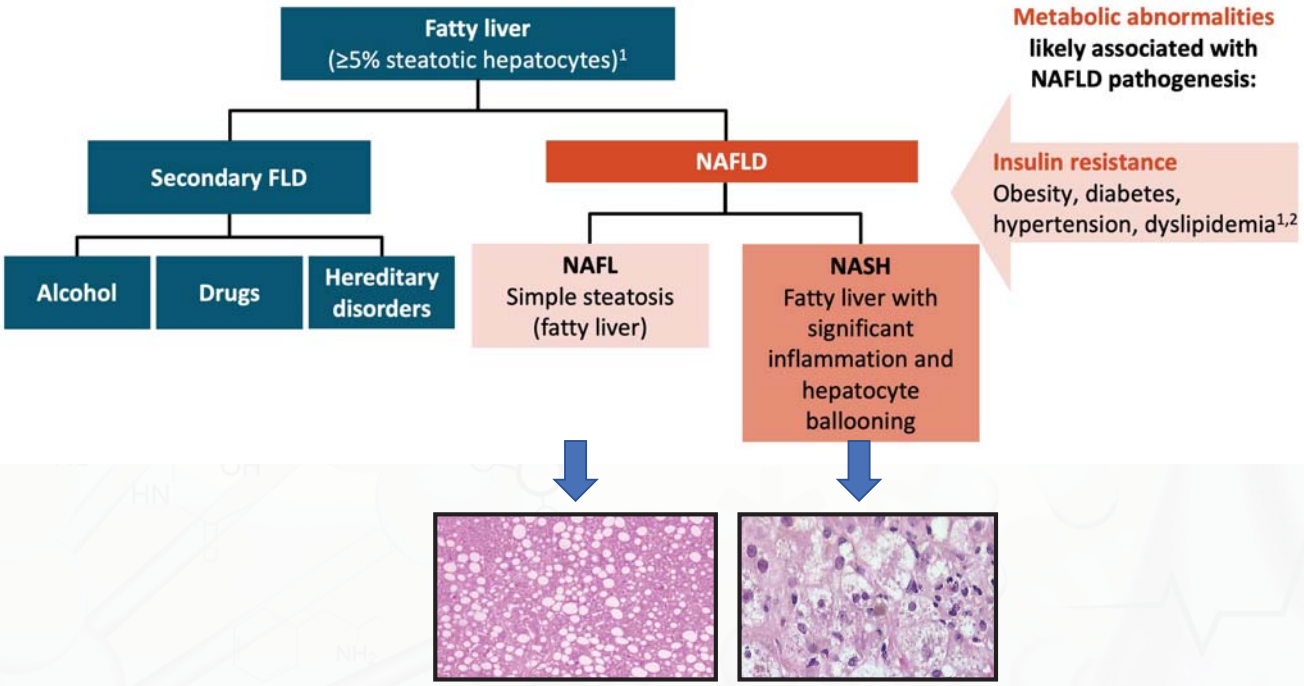
- **Part of these slides are developed by myself within Clinical Care Options** clinicaloptions.com/internalmedicine

LEARNING OBJECTIVES

At the conclusion of this presentation, participants will be able to:

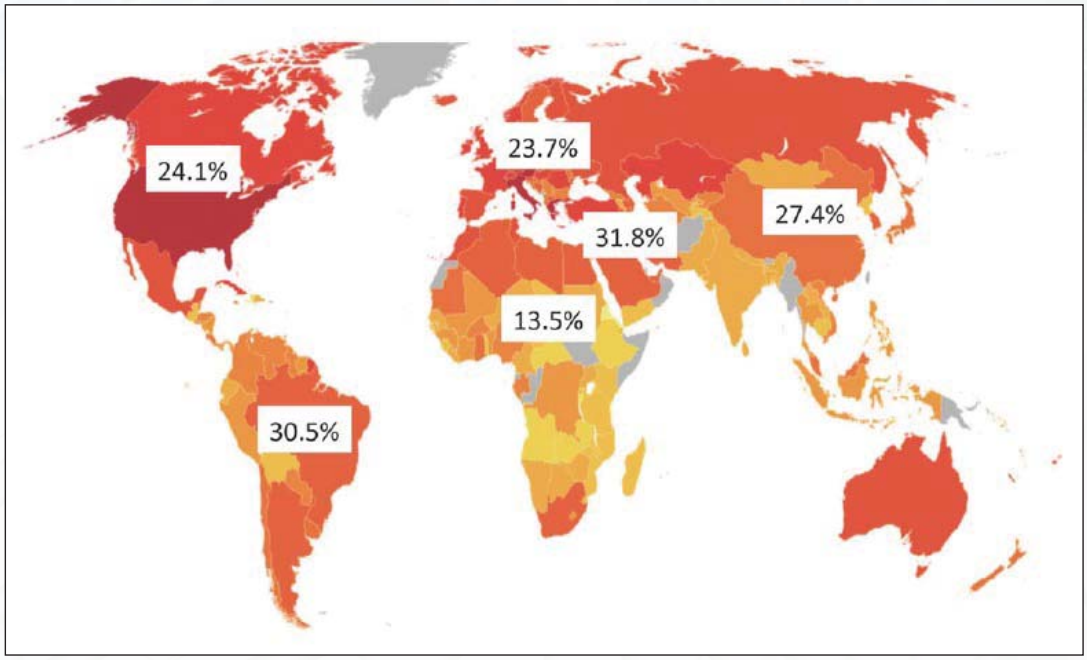
1. Understand epidemiology and pathogenesis of fatty liver
2. Be familiar with current diagnostic strategies for fatty liver
3. Integrate therapeutic principles for fatty liver into clinical practice

NAFLD Definition



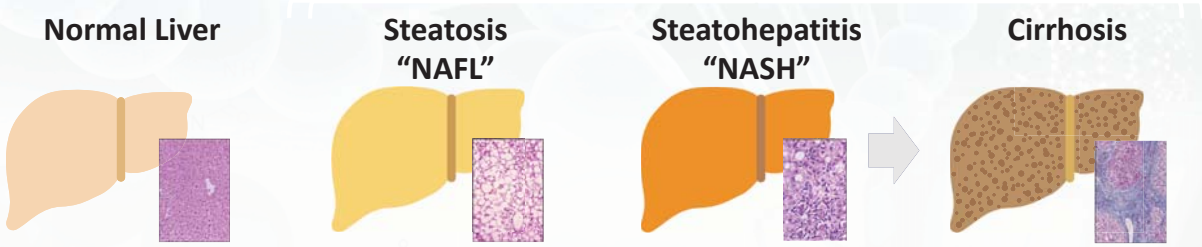
1. Chalasani. Hepatology. 2018;6:328. 2. Demir. J Dig Dis. 2015;16:541.

The global prevalence of NAFLD is at 25.24%



Rinella et al, Hepatology 2016

The NAFLD Continuum: NAFLD, NASH, Cirrhosis and burden in North America



Fatty liver with trivial or no inflammation and no hepatocyte ballooning

Fatty liver with significant inflammation and hepatocyte ballooning

Increasing fibrosis leading to cirrhosis, hepatocellular carcinoma (sometimes loss of fat)

United States prevalence:	**30%[1]**	**10-30% of NAFLD[1]**	**20-30% of NASH**
Prevalence in Canada:	**7.5 millions[2]**	**2 millions[2]**	**300,000**

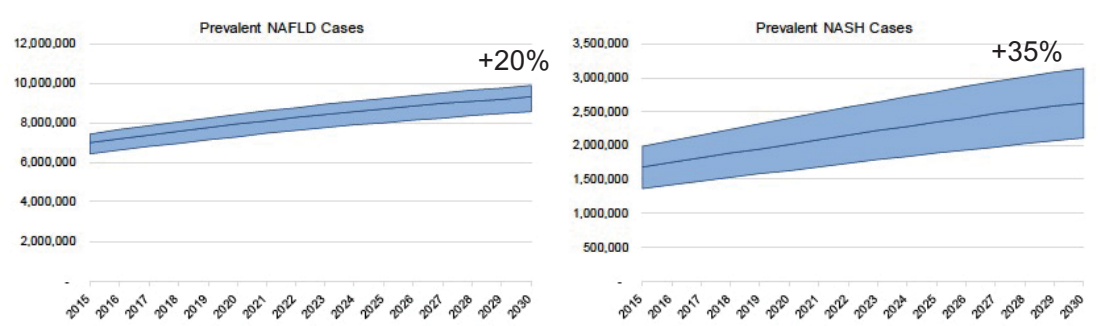
*Based on analysis of NHANES data estimating 1.74% prevalence of NASH with advanced fibrosis.[1]

1. Younossi. J Hepatol. 2019;70:531. 2. Swain et al, CMAJ Open 2020.

Slide credit: clinicaloptions.com

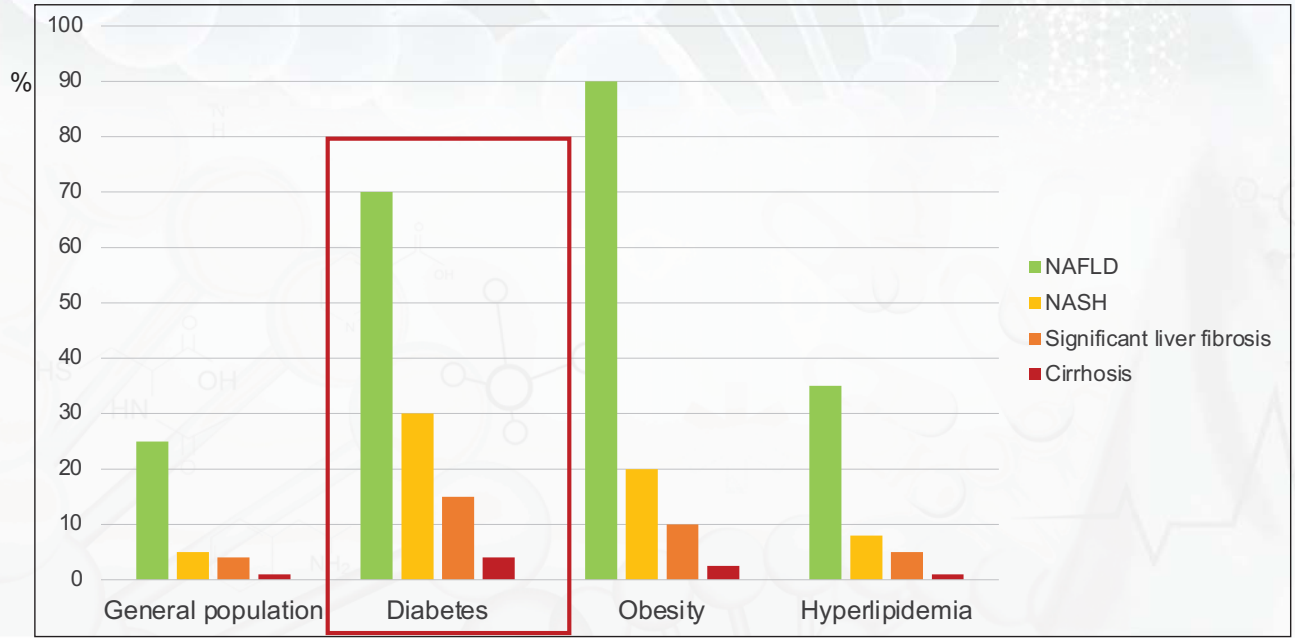
NAFLD Disease Burden – Canada, 2019-2030

Modeling the burden of NAFLD using the Markov model



Swain, Ramji, Patel, Sebastiani et al, CMAJ Open 2020

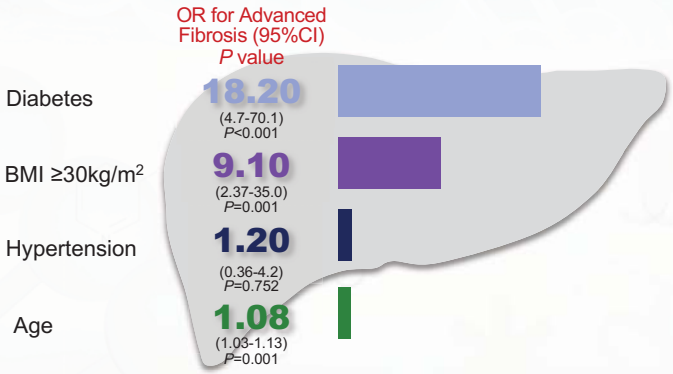
NAFLD: who is at risk ?



Ratziu et al, J Hepatol 2010

High level of suspicion for advanced liver fibrosis in Type 2 Diabetes

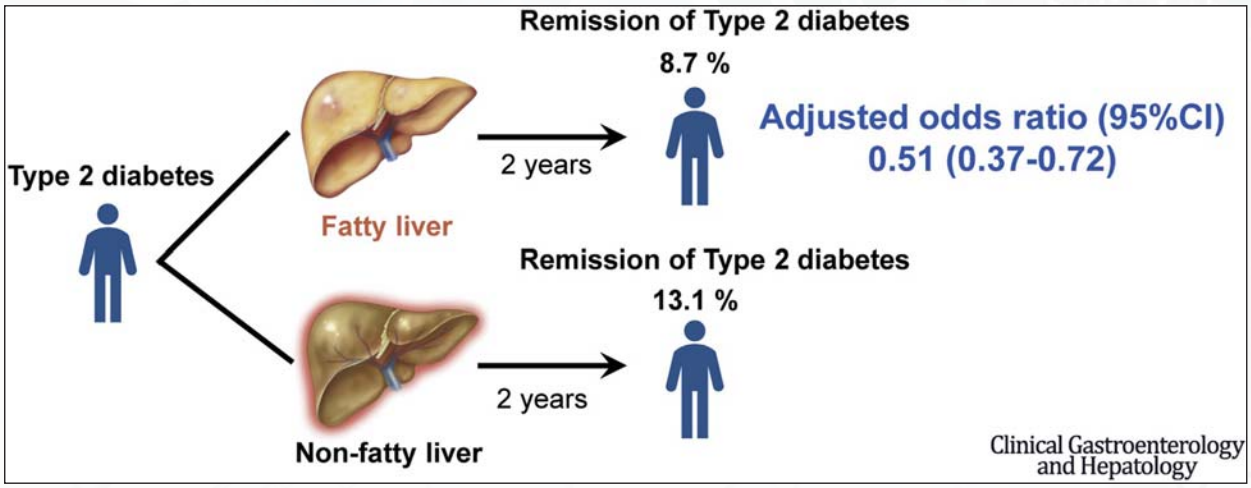
Cross-sectional study using 2011-2014 NHANES data to assess predictors of advanced fibrosis in NAFLD patients



NHANES = National Health and Nutrition Examination Survey.
Wong RJ, et al. *Aliment Pharmacol Ther.* 2017;46:974–980.

NAFLD influences clinical remission of Type 2 Diabetes

2567 patients with T2D from a single centre in Japan followed for 2 years
→Remission of T2D was less common in people with fatty liver detected by ultrasonography
→Improvement of fatty liver was independently associated with T2D remission



Yamazaki. CGH 2021;19:556-564.

Guidelines: screening for advanced liver fibrosis in patients with diabetes

AASLD[1]	EASL-EASD-EASO[2]	ADA[3]
In type 2 diabetes, suspect NAFLD and NASH and determine **patient's risk of advanced fibrosis** Increasing number of metabolic diseases = increasing risk of progressive liver disease	NAFLD **screening recommended** in persons at high CVD risk, including metabolic syndrome or type 2 diabetes	NASH and fibrosis **screening recommended** in persons with type 2 diabetes or prediabetes and elevated ALT or fatty liver

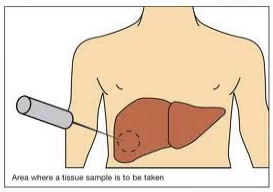
1. Chalasani. Hepatology. 2018;67:328. 2. EASL, EASD, EASO. J Hepatol. 2016;64:1388. 3. ADA. Diabetes Care. 2019;42:S34.

Slide credit: clinicaloptions.com

Diagnostic tools for NAFLD and related fibrosis

Liver biopsy

Gold standard



Invasive, costly, painful

Serum biomarkers

Simple

- Fibrosis-4
- NAFLD fibrosis score
- APRI
- BARD score
- AST/ALT Ratio

Fibroscan (elastography)

Cervo & Sebastiani, Curr Opin HIV/AIDS 2020

Noninvasive Markers: FIB-4 Effective in Ruling Out Advanced Fibrosis

FIB-4 Parameter
Age
AST
ALT
Platelet count

Patients with **advanced cirrhosis** usually have **very low platelets**

FIB-4 Score	Interpretation	NPV or PPV, %
<1.3	Rules out advanced fibrosis	95
>2.67	Rules in advanced fibrosis	75

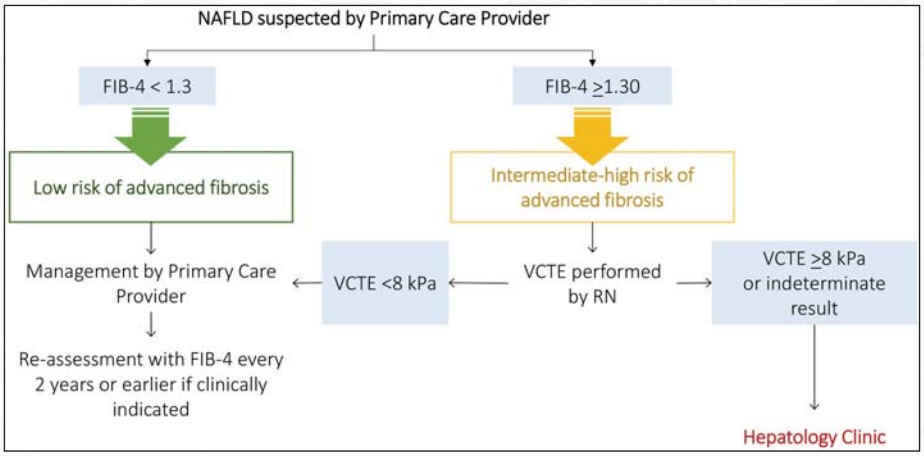
A **low** FIB-4 score indicates there is **no advanced fibrosis** and that **liver biopsy is not needed**

Shah. Clin Gastrenterol Hepatol. 2009;7:1104. McPherson. Gut. 2010;59:1265.

Slide credit: clinicaloptions.com

FIB-4 First Clinical Care Pathway

N=565 patients at risk for NAFLD identified by GPs
Up to 87% further specialistic assessment saved

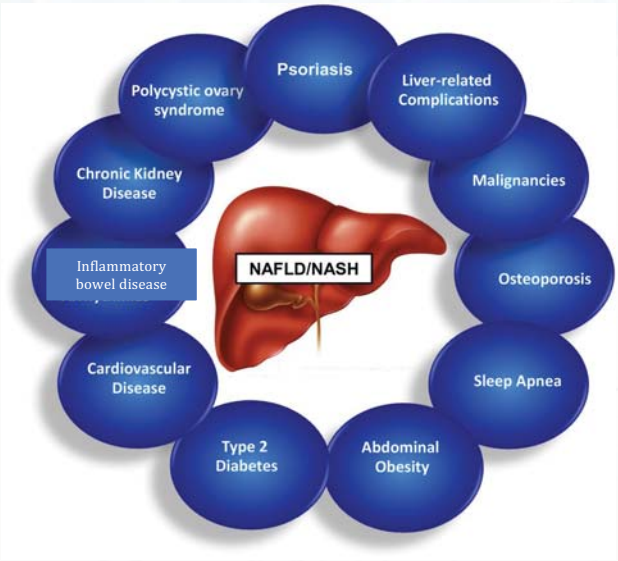


→ 4% referred using 2-Step Strategy (FIB-4 >1.3 and Fibroscan >8 kPa)

Davyduke et al HepatolComm 2019

NAFLD is not just about Liver… It is a multisystem disease

NAFLD is a multisystem disease based on a chronic inflammatory milieau



Causes of Death

1. Cardiovascular
2. Liver
3. Malignancy (hematologic, breast, colo-rectal, pancreas)

Sumida et al, J Gastroenterol 2018
Taylor et al, Gastroenterology 2020
Adams et al. Gastroenterol 2005;113-21

No need to diagnose NAFLD / fibrosis since there is no treatment…

Life-style interventions

Correction of metabolic disturbances

Pharmacotherapy

Non-pharmacological approaches

Weight loss

- 3% to 5% to improve steatosis, but 7% to 10% to improve NASH, including fibrosis;
- 500-1000 kcal energy deficit daily

Exercise

- Exercise alone can prevent/reduce steatosis, but its ability to improve other aspects of liver histology remains unknown.
- Target 150-200 min/week moderate intensity aerobic exercise

Baratric surgery

- May be considered in eligible obese persons

Best to combine hypocaloric diet (reduction by 500-1000 kcal/day) plus exercise, independent of macronutrient composition of diet

Chalasani. Hepatology. 2018;67:328.

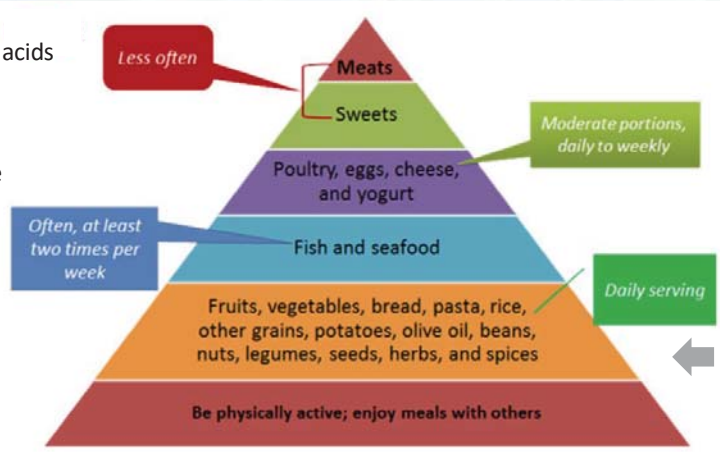
The Mediterranean Diet Pyramid

High in:

- Monounsaturated, omega-3/omega-6 fatty acids
- Polyphenols
- Dietary fiber, prebiotics
- Plant proteins
- Water as drink of choice

Low in:

- Saturated and trans fat
- Animal protein
- Simple sugars

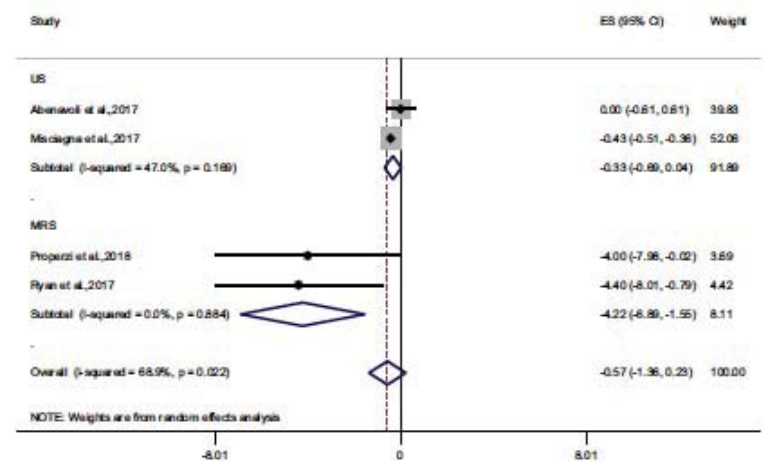


Could be adapted to different cultures but **extra virgin olive oil** is an essential component

Gray. Nutritional Recommendations for Individuals with Diabetes. 2019. endotext.org.

Mediterranean diet (MD): meta-analysis

- 7 observational studies: inverse association between MD and NAFLD
- 6 trials: effectiveness of MD was significant for steatosis
- Significant decreasing effect on BMI, triglycerides, and HOMA-IR
- No significant effect on waist circumference, cholesterol fractions, transaminases



Akhlaghi. J Diabet Met Dis. 2020;19:575-584.

Who should receive pharmacotherapy in NAFLD

YES

- NASH with significant fibrosis (≥F2)
- NASH with less severe disease but high risk of progression (diabetes, metabolic syndrome, persistently elevated ALT, high necroinflammation)

NO

- NAFLD without fibrosis
- Pt without biopsy-confirmed NASH
- Steatosis alone
  - Focus on CVD risk factor modification in primary care; no need for liver clinic

AASLD 2018, EASL 2016, APASL 2020

Pharmacotherapy in the guidelines for NAFLD

	American 2018	European 2016	Asian Pacific 2020
VITAMIN E	Recommended		No firm recommendation
PIOGLITAZONE	Recommended		
METFORMIN	Not recommended		
STATIN	- Can be used to treat dyslipidemia, not NASH - No higher risk for serious liver injury		
OMEGA-3 FATTY ACIDS	- Not recommended to treat NASH - Consider to treat hypertriglyceridemia		Not mentioned
GLP-1 AGONISTS	Further data needed		
OBETICHOLIC acid	Further data needed		

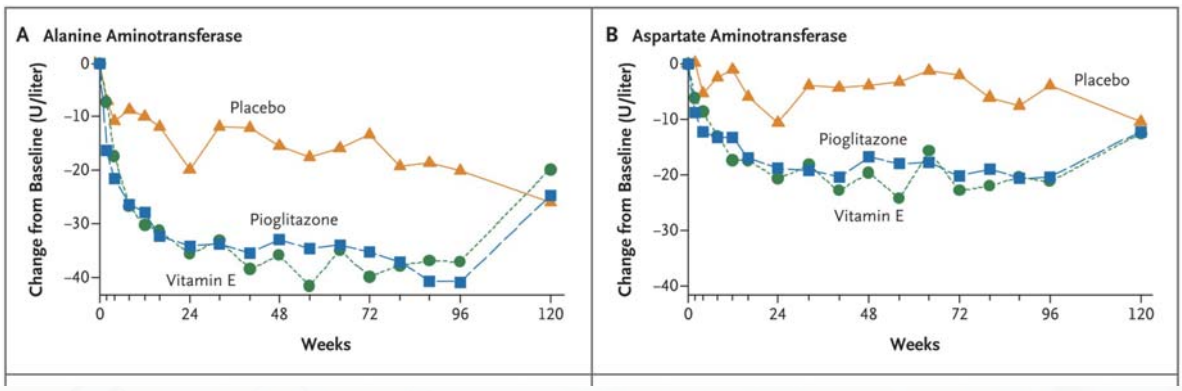
Slide credit: clinicaloptions.com

EASL The Home of Hepatology

While no firm recommendations can be made, pioglitazone (most efficacy data, but off-label outside T2DM) or vitamin E (better safety and tolerability in the short-term) or their combination could be used for NASH (**B2**)

AASLD American Association for the Study of Liver Diseases

27. Vitamin E (rrr α-tocopherol) administered at a daily dose of 800 IU/day improves liver histology in nondiabetic adults with biopsy-proven NASH and therefore may be considered for this patient population. Risks and benefits should be discussed with each patient before starting therapy.



Vitamin E 800 UI/d vs pioglitazone 30 mg/d vs placebo (no diabetes, no cirrhosis)

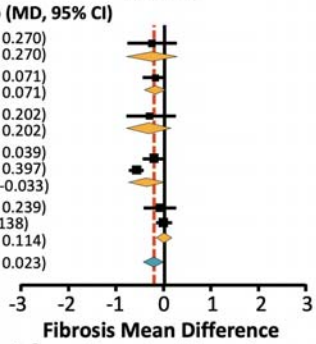
Sanyal A. New Engl J Med 2010;1675 -85

Meta-analysis:
Vitamin E Reduces NAS and Fibrosis in NAFLD

- Meta-analysis of N = 1317 patients with NAFLD in 15 RCTs
  - Study limitations: variations in definition of NAFLD; moderately small sample sizes

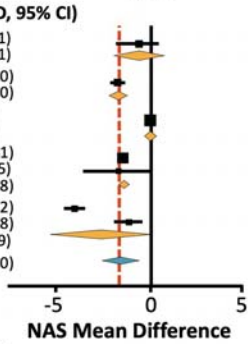
Fibrosis

Studies	Vitamin E vs Placebo (MD, 95% CI)
Harrison 2003	-0.250 (-0.770, 0.270)
--Subgroup 6 mo	-0.250 (-0.770, 0.270)
Zohrer 2017	-0.170 (-0.411, 0.071)
-Subgroup 12 mo	-0.170 (-0.411, 0.071)
Brill 2019	-0.300 (-0.802, 0.202)
--Subgroup 18 mo	-0.300 (-0.802, 0.202)
Sanyal 2010	-0.200 (-0.439, 0.039)
Dufour 2006	-0.570 (-0.743, 0.397)
--Subgroup 24 mo	-0.395 (-0.757, -0.033)
Lavine 2011	-0.100 (-0.439, 0.239)
Nobili 2008	0 (-0.138, 0.138)
--Subgroup 24 mo	-0.014 (-0.142, 0.114)
Overall (I^2 = 77.09%; P = 0)	-0.224 (-0.426, 0.023)



NAS

Studies	Vitamin E vs Placebo (MD, 95% CI)
Aller 2015	-0.600 (-1.771, 0.571)
--Subgroup first 3 mo	-0.600 (-1.771, 0.571)
Zohrer 2017	-1.700 (-2.090, -1.310)
--Subgroup 12 mo	-1.700 (-2.090, -1.310)
Brill 2019	0 (-0.190, 0.190)
--Subgroup 18 mo	0 (-0.190, 0.190)
Sanyal 2010	-1.400 (-1.639, -1.161)
Dufour 2006	-1.700 (-3.525, 0.125)
--Subgroup 24 mo	-1.405 (-1.642, -1.168)
Nobili 2008	-4.000 (-4.548, -3.452)
Lavine 2011	-1.100 (-1.872, -0.328)
--Subgroup 24 mo	-2.563 (-5.405, 0.279)
Overall (I^2 = 97.53%; P = 0)	-1.503 (-2.495, -0.510)



- Most promising patient for vitamin E treatment: an obese patient aged 15-50 yr, baseline AST >50 IU/L, daily intake of 400-800 IU vitamin E, liability to lose 5-10 kg

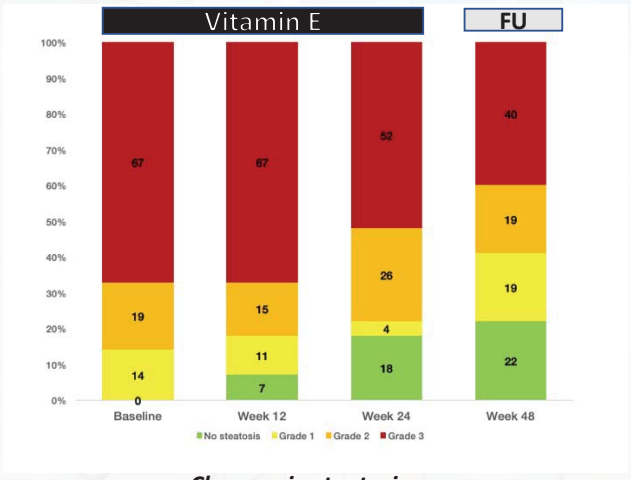
Abdel-Maboud. Therap Adv Gastroenterology. 2020;13:1756284820974917.

Slide credit: clinicaloptions.com

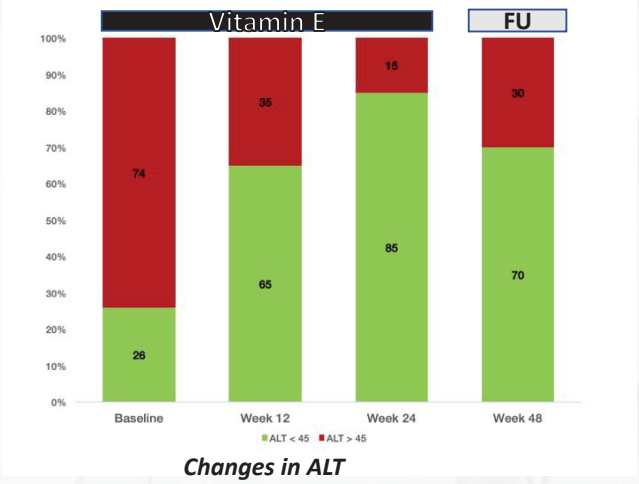
Vitamin E to treat HIV-associated NASH

LIVEHIV

Open-label, single arm trial of 800 IU/day of vitamin E for 24 wk in PWH and NASH (N = 27)



Changes in steatosis



Changes in ALT

Sebastiani et a, AIDS 2020

Vitamin E as a 'bridge' therapy for nonalcoholic steatohepatits in HIV: what is waiting on the other side of the bridge?

Giovanni Guaraldi[a,b] and Jovana Milic[a,b,c]

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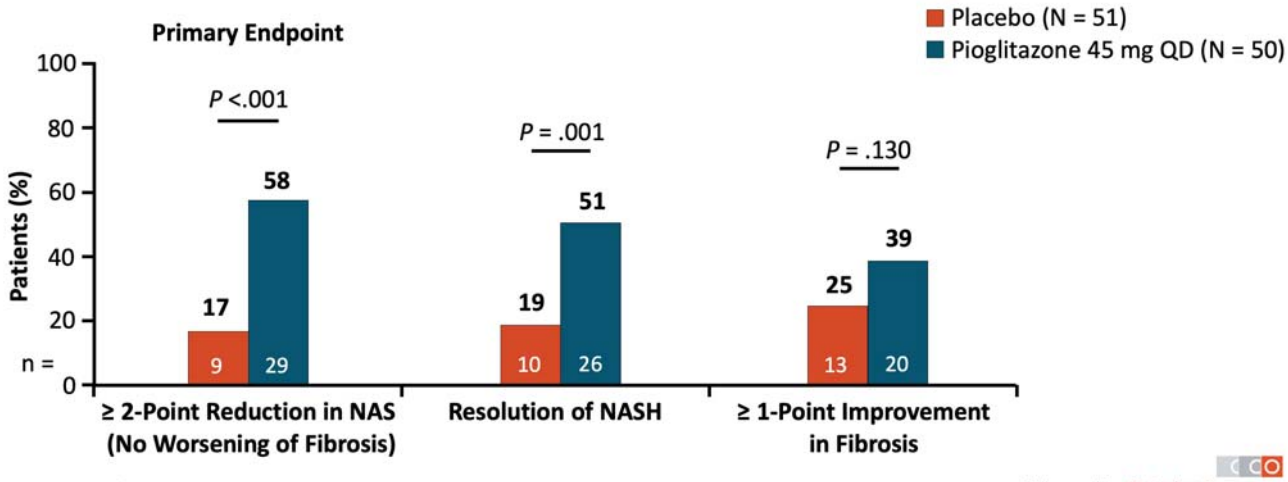
Pioglitazone in NASH With Prediabetes/T2D: 18-Mo Outcomes

- Randomized, placebo-controlled, double-blind phase IV study of patients with NASH and prediabetes or T2D (N = 101)[1]



Cusi. Ann Intern Med. 2016;165:305.

Slide credit: clinicaloptions.com

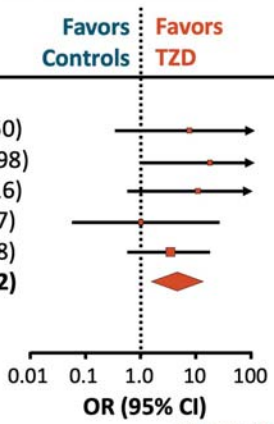
Pioglitazone in NASH Without Diabetes

- Subset of n = 8 TZD studies in systemic review and metanalysis of randomized trials examining outcomes in NAFLD/NASH (N = 516 patients)
- In biopsy-proven NASH, pioglitazone associated with **improvement in advanced fibrosis**

Source	TZD No. of Events	TZD No. of Patients	Control No. of Events	Control No. of Patients	Odds Ratio (95% CI)
Pioglitazone					
Aithal 2008	3	31	0	30	7.49 (0.37-151.50)
Belfort 2006	7	26	0	21	16.54 (0.89-308.98)
Cusi 2016	4	50	0	51	9.97 (0.52-190.16)
Sanyal 2004	1	10	1	10	1.00 (0.05-18.57)
Sanyal 2010	6	80	2	83	3.28 (0.64-16.78)
Total (95% CI)	**21**	**197**	**3**	**195**	**4.53 (1.52-13.52)**

Heterogeneity: $T^2 = 0$; $x^{2/2} = 2.39$; $P = .66$; $I^2 = 0\%$

Overall effect: $z = 2.71$; $P = .007$



Musso. JAMA Intern Med. 2017;177:633.

Slide credit: clinicaloptions.com

Safety and Tolerability of Recommended Therapies

Vitamin E (800 IU/day)

Possible all-cause mortality risk at > 800 IU/day[1], not confirmed by a subsequent meta-analysis[9]

Increased hemorrhagic stroke risk[2]

- Also shows reduced ischemic stroke risk

Increased prostate carcinoma risk (HR vs placebo: 1.17; 99% CI: 1.004-1.36; *P* = .008)[3]

Pioglitazone

Edema, weight gain (~ 2-3 kg over 2-4 yrs)[4]

Risk of osteoporosis in women[5]

Equivocal bladder cancer risk

- 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. Ann Intern Med. 2005;142:37. 2. Schurks. BMJ. 2010;341:c5702. 3. Klein. JAMA. 2011;306:1549.
4. Bril. Diabetes Care. 2017;40:419. 5. Yau. Curr Diab Rep. 2013;13:329. 6. Tuccori. BMJ. 2016;352:i1541.
7. Lewis. JAMA. 2015;314:265. 8. Davidson. Diabetes Complications. 2016;30:981; 9.Abner Curr Aging Science 2011

Statins in patients with NAFLD (AASLD guidelines)

High risk of cardiovascular morbidity and mortality

Aggressive change in CVD risk factors in all patients with NAFLD

No higher risk of serious liver damage from statins

Statins can be used to treat dyslipidemia

Statins recommended for reducing CV risk, not solving NASH

"Clinical trials of statins as a treatment for NASH are limited and have shown inconsistent results"

Chalasani. Hepatology. 2018;67:328.

Statins Lower Risk of Portal Hypertension in Cirrhosis

- Systematic review and meta-analysis of statin use in patients with cirrhosis
  - 8 studies (7 RCTs, 1 cohort study; N = 3195); pooled relative risk and 95% CI calculated by random effects model
- Relative risk for primary outcome (improvement in portal hypertension) with statins vs control: 1.91 (95% CI: 1.04-3.52; I^2 = 63%)
  - Sub-analysis showed 1 mo of statin use may be sufficient vs 3 mo

Analysis	Statin		Control		Risk Ratio (95% CI)	*P* Value
	Events*	n	Events*	n		
Overall	67	148	42	153	1.91 (1.04-3.52)	.04
1 mo statin use	35	82	17	83	2.01 (1.31-3.10)	.002
3 mo statin use	32	66	25	70	3.76 (0.36-39.77)	.27

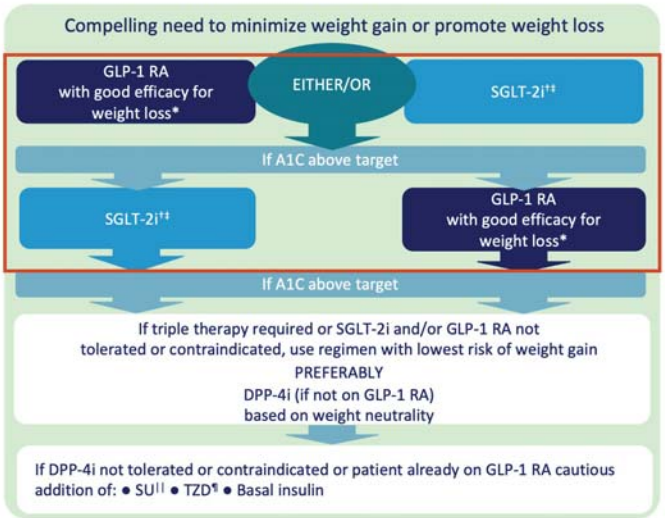
*Event: Decrease in HVPG >20% or <12 mm Hg.

Wan. BMJ Open. 2019;9:e030038.

Slide credit: clinicaloptions.com

Pharmacotherapy for T2D Patients With a Need to Address Body Weight

- In adults with need to minimize weight gain or promote weight loss, guidelines recommend[1]:
  - **GLP-1 RAs** with efficacy for weight loss
  - **SGLT2** inhibitors
- Some GLP-1 RAs and SGLT2 inhibitors may have benefits in NAFLD



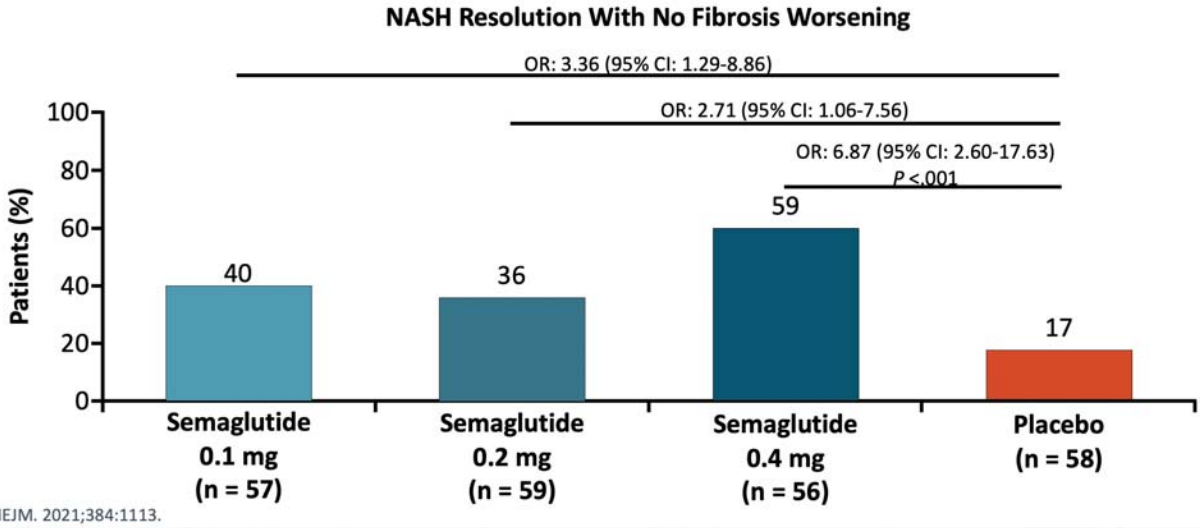
*Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide. †SGLT2i vary by region and individual agent regarding indicated level of eGFR for initiation and continued use, ‡If eGFR adequate. ¶Low dose may be better tolerated though less well studied for CVD effects. ||Choose later-generation SU with lower risk of hypoglycaemia.

American Diabetes Association. Diabetes Care 2019;42(suppl 1):S90.

Slide credit: clinicaloptions.com

Semaglutide in NASH: Primary Endpoint at 72 Wk

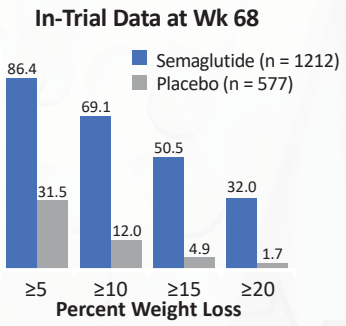
- Randomized, double-blind, multicenter phase II trial in adults with BMI >25 kg/m^2 and biopsy-proven NASH



Newsome. NEJM. 2021;384:1113.

STEP 1: Semaglutide Effect on Weight in Patients Without T2D

- Double-blind, randomized phase III trial in adults with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with comorbidities and no diabetes (N = 1961)
- All subjects also received standard lifestyle intervention (17 counseling sessions, hypocaloric diet and increased physical activity)

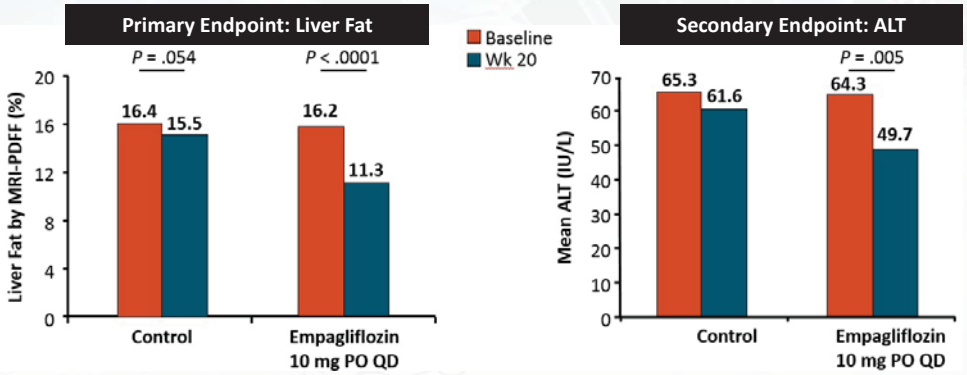


Wilding. NEJM. 2021;18:989.

Slide credit: clinicaloptions.com

Sodium-glucose cotransporters-2 (SGLT2) Inhibitors in NAFLD: Effect on Liver Fat and ALT

- E-LIFT: randomized, open-label study of **empagliflozin** vs standard diabetes treatment in 42 patients with diabetes and NAFLD[1]



- In a separate double-blind, placebo-controlled study (n = 37 patients with diabetes and NAFLD), **canagliflozin 300 mg PO QD** associated with lower hepatic triglycerides, which correlated with weight loss[2]

Slide credit: clinicaloptions.com

1. Kuchay. Diabetes Care. 2018;41:1801. 2. Cusi. Diabetes Obes Metab. 2018;1-10.

SGLT2 Inhibitors in T2D and NAFLD: Umbrella Review of Systematic Reviews

Studies

- 7 systematic reviews of SGLT2 inhibitors (including between 67 and 498 patients)
  - 4 evaluated effects on **liver enzymes**
  - 4 reported changes in **liver fat**
  - 2 reported changes in **fibrosis biomarkers**

Results

- ✗ None rated as high quality, only 1 as moderate quality
- ✓ 5 systematic reviews indicated that SGLT2 inhibitors could **decrease liver fat and liver enzymes**
- ✓ 1 small, single-arm histologic study showed **improvement in steatosis**
- ✗ No evidence of **liver fibrosis** improvement

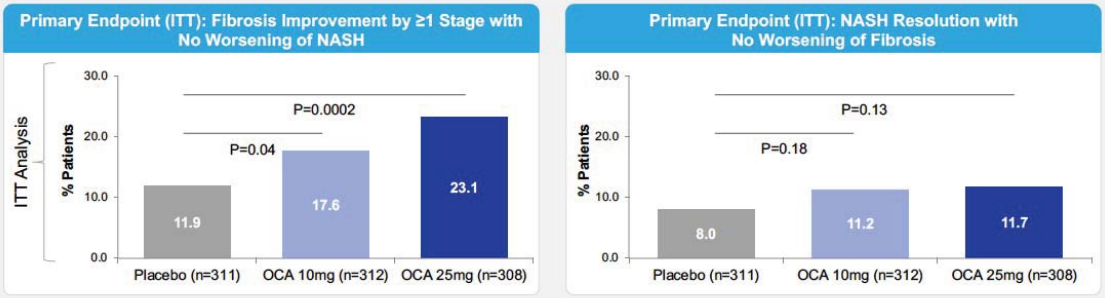
Shao. BMJ Open Diab Res Care. 2020;8:e001956.

Slide credit: clinicaloptions.com

Obeticholic acid

Bile acid, activates the farnesoid receptor X
Promotes insulin sensitivity

Phase 3 REGENERATE: Sub-set Analysis of Interim 18-month – Primary Endpoint

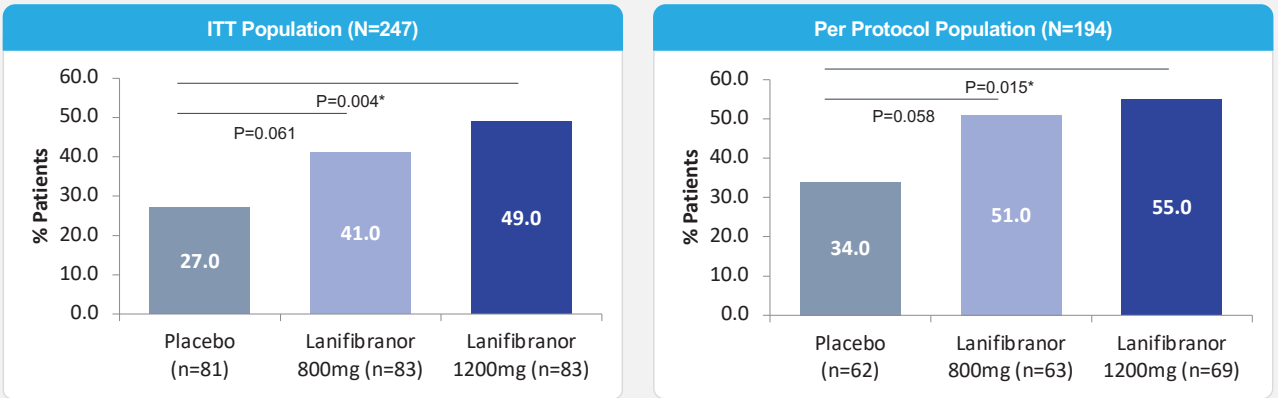


- Sub-set analysis in which patients that had completed at least 15 months of OCA Tx
- 13% of patients on the 25 mg dose demonstrated a 2-point improvement in fibrosis score (4.5% in PBO), while 38% receiving the same dose showed at least 1 stage improvement in the score (23% for PBO)
- Additional benefits were seen in ballooning, inflammation, and ALT
- Safety: AEs were mostly mild to moderate and consistent with known profile of OCA; earlier data revealed 9% of patients on the 25 mg dose discontinued therapy due to pruritis

Younossi Z et al. Positive Results from REGENERATE: A Phase 3 International, Randomized, Placebo-Controlled Study Evaluating Obeticholic Acid Treatment for NASH. EASL 2019. Oral Presentation.

Lanifibranor: PPARα/PPARδ/PPARγ agonist

Primary Efficacy Endpoint: Dose-dependent, Significant Reduction of 2 Points of Inflammation and Ballooning and No Worsening of Fibrosis



- Lanifibranor (1200mg) met the primary endpoint in both ITT and PP Populations

Primary efficacy endpoint: Response is defined as a decrease from baseline to week 24 of at least 2 points of the SAF Activity Score (SAF-A) and no worsening of the CRN Fibrosis score (CRN-F). No worsening means that the score remains stable or decreases.
Inventiva's lanifibranor meets the primary and key secondary endpoints in the Phase IIb NATIVE clinical trial in non-alcoholic steatohepatitis (NASH). June 16, 2020. Press Release

Take home messages

- NAFLD is the most frequent liver disease globally
- Type 2 diabetes (+/- obesity) is the main risk factor for NASH and fibrosis
- Guidelines recommend screening for advanced liver fibrosis in patients with type 2 diabetes, metabolic syndrome
- Multitarget therapeutic approach :

- Newer antifibrotic treatments may include GLP-1 agonists, SGLT2; pan PPAR and FXR agonists also investigated

WELCOME FROM THE HOST ORGANIZATIONS OF THE 2022 CANADIAN LIVER MEETING

We are happy to confirm that the hybrid meeting will be accredited as an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification program of The Royal College of Physicians and Surgeons of Canada and accredited by the Canadian Association for the Study of the Liver. Please sign up for our newsletter to receive the most up-to-date information on the number of study credits and updates to the scientific program.

We invite our industry partners, related associations, institutions, and other organizations to join us in Ottawa or in the comfort of your home or office to attend the 2022 Canadian Liver Meeting.

Whether we meet face-to-face or virtually, we look forward to welcoming you to another fantastic Canadian Liver Meeting.

Sincerely,

MAY 13-15, 2022

JORDAN FELD
President, CASL

NAGLAA SHOUKRY
Executive Director, CanHepC

ELIZABETH LEE
President, CAHN

GIADA SEBASTIANI
Steering Committee, CanNASH

Registration to the Canadian NASH Conference is now open!! FREE FOR TRAINEES

Register at: https://www.canadianlivermeeting.ca/registration

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