AASLD November 13-16, 2020
The Liver Meeting®
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THE BEST OF THE LIVER MEETING® 2020

NAFLD and NASH

AASLD
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About the program:

Best of The Liver Meeting 2020 was created by the Scientific Program Committee for the benefit of AASLD members, attendees of the annual conference, and other clinicians involved in the treatment of liver diseases. The program is intended to highlight some of the key oral and poster presentations from the meeting and to provide insights from the authors themselves regarding implications for patient care and ongoing research.

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Use of these slides:

BALANCED phase 2a study: efruxifermin (EFX) substantially improved liver fat, ALT, lipids, and histology

Objective

Evaluate the safety and efficacy of EFX in patients with NASH (F1-F3), including measures of hepatic fat (MRI-PDFF), ALT, lipoproteins, glycemic control, and liver histology

Methods

16-week randomized, double-blind, placebo-controlled trial, including responder-based analysis of liver histology

Main Findings

- 50% 2-stage improvement among patients with F2-3 fibrosis
- Generally well tolerated with mild/moderate GI events

Conclusions

EFX led to robust and clinically meaningful improvements in all core aspects of NASH pathology.

Measure	Treatment Arm			
Dose	pbo	28 QW	50 QW	70 QW
≥1 Stage Fibrosis Improvement and No Worsening of NASH, % of Subjects	0	46	62	36
NASH Resolution and No Worsening of Fibrosis, % of Subjects	50	46	54	43
MRI-PDFF, % relative reduction	0	-63	-71	-72
ALT, absolute change	-5.9	-24	-30	-32
Triglycerides, % change	+6	-39	-48	-46
HDL-C, % change	+4	+34	+39	+41
LDL-C, % change	0	-16	-2	-6
% HbA1c, absolute change	+0.1	-0.1	-0.4	-0.5
Adiponectin, % change	-8	+65	+80	+122

Harrison S, et al., Abstract 8

Subcutaneous semaglutide once-daily versus placebo in patients with non-alcoholic steatohepatitis

Objective

To compare the effect of three different doses of subcutaneous semaglutide (0.1, 0.2, or 0.4 mg) once daily versus placebo on histological resolution of NASH

Methods

A 72-week, double-blind phase 2 trial in which patients with biopsy-confirmed NASH and liver fibrosis stage F1-F3 were randomized to semaglutide or placebo

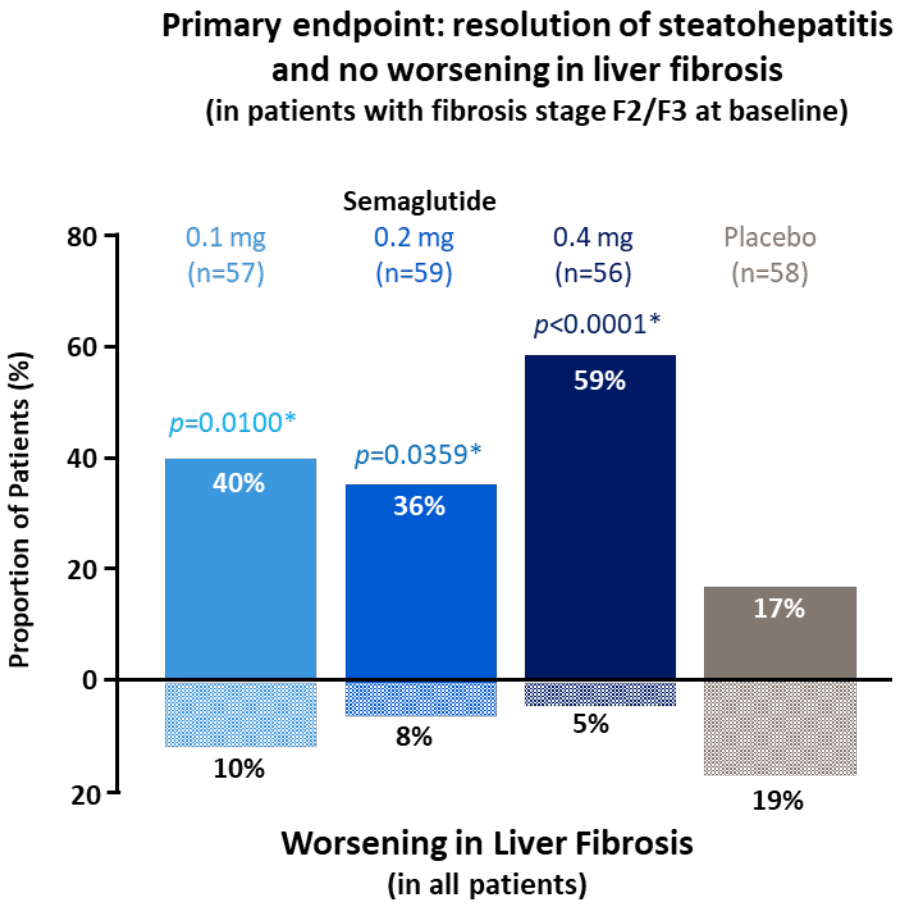
Main Findings

Compared with placebo, semaglutide resulted in:

- A significantly higher percentage of patients (F2-F3 only) achieving NASH resolution with no worsening of fibrosis (primary endpoint)
- No significant difference in percent of patients with improvement in fibrosis (secondary endpoint), but fewer had fibrosis progression and biomarkers of fibrosis improved
- Improvements in multiple metabolic characteristics, including body weight (0.4 mg: 13% vs 1%) and HbA_{1c} (patients with T2D, 0.4 mg: −1.15 vs −0.01%-points)

Conclusions

Semaglutide resulted in more patients achieving NASH resolution than placebo.



Newsome PN, et al., Abstract 10; *N Engl J Med*. 2020 Nov 13. doi: 10.1056/NEJMoa2028395

Lanifibranor demonstrated statistically significant positive effects on key histological NASH endpoints

Objective

To assess safety and efficacy of a 24-week treatment of two doses of the panPPAR agonist lanifibranor (800, 1200 mg/24h) in patients with NASH

Methods

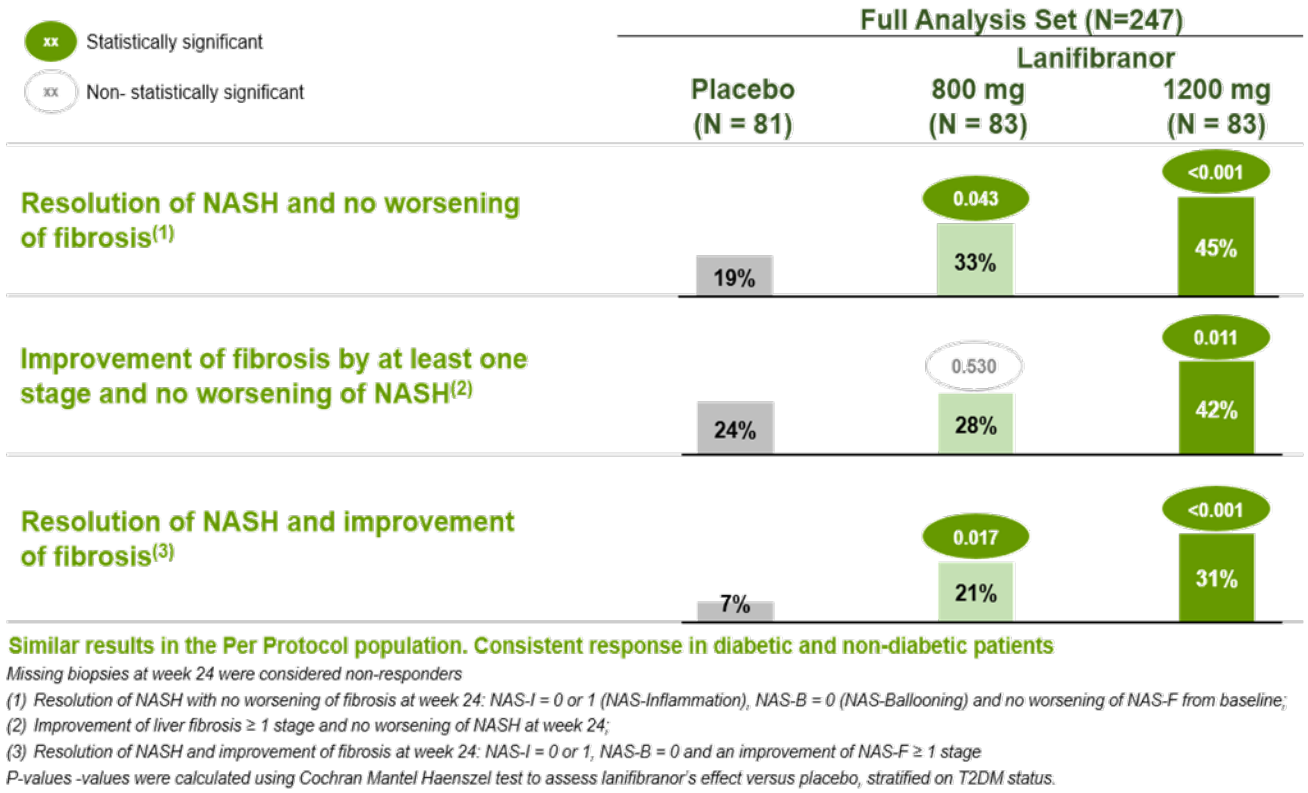
Randomised, double-blind, placebo-controlled trial in patients with biopsy-proven non-cirrhotic NASH with high activity (SAF activity score of 3 or 4 [inflammation + ballooning])

Main Findings

NATIVE phase 2b trial (see Figure)

Conclusions

- Lanifibranor results in highly significant improvement in both resolution of NASH and regression of fibrosis after a 24-week treatment in non-cirrhotic NASH.
- Lanifibranor will be evaluated in a pivotal phase 3 study.



Similar results in the Per Protocol population. Consistent response in diabetic and non-diabetic patients

Missing biopsies at week 24 were considered non-responders

(1) Resolution of NASH with no worsening of fibrosis at week 24: NAS-I = 0 or 1 (NAS-Inflammation), NAS-B = 0 (NAS-Ballooning) and no worsening of NAS-F from baseline;

(2) Improvement of liver fibrosis ≥ 1 stage and no worsening of NASH at week 24;

(3) Resolution of NASH and improvement of fibrosis at week 24: NAS-I = 0 or 1, NAS-B = 0 and an improvement of NAS-F ≥ 1 stage

P-values -values were calculated using Cochran Mantel Haenszel test to assess lanifibranor's effect versus placebo, stratified on T2DM status.

Francque S, et al., Abstract 12

Novel, first-in-class, FASNi, TVB-2640 demonstrates significant reduction in liver fat by MRI-PDFF in NASH

Hypothesis

TVB-2640 would be better than placebo in reducing liver fat by MRI-PDFF and in modulating biomarkers in patients with NASH.

Methods

Phase 2a, multicenter, randomized, placebo-controlled trial

- N=99: ≥8% liver fat and MRE ≥2.5 kPa, 25 mg: 50 mg: placebo (1:1:1)
- Oral, once-daily for 12 weeks

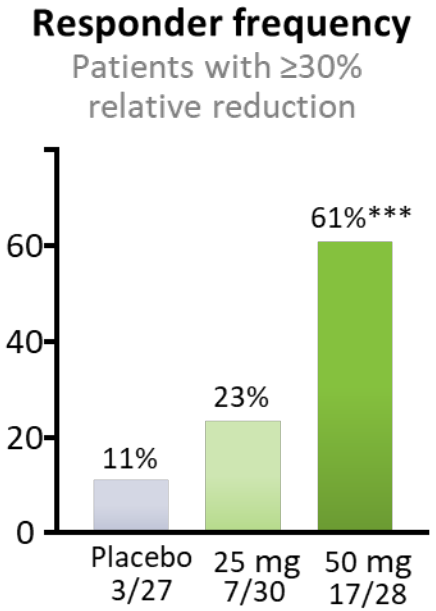
Main Findings

- Benign safety profile (mainly Gr. 1 AEs/no SAEs)
- Potent, dose-dependent reduction of liver fat, with high responder rate
- Improvement of multiple biomarkers including CK-18, ProC3, PIIINP, and ceramides

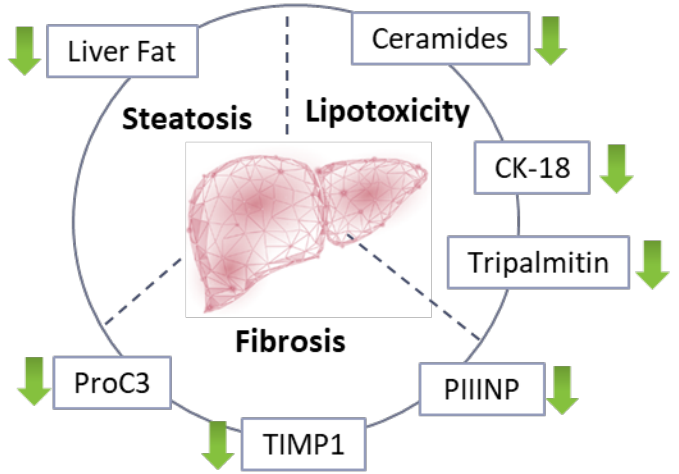
Conclusion

TVB-2640 therapy improves steatosis, inflammation, fibrosis, and metabolism. Biomarker changes indicate improvement in several key nodes of NASH pathology.

Loomba R, et al., Abstract 67



***p<0.001.
LSM difference versus placebo. mean/SEM.



Cardiovascular benefits

LDL

Liver disease improvement

ALT

Increased insulin sensitivity

FGF21

Adiponectin

Final analysis of a 24-week, randomized, double-blind, placebo-controlled, multicenter study of aldafermin (NGM282) in patients with NASH

Objective

To evaluate the effect of aldafermin, an engineered FGF19 analog, in a 24-week study with paired liver biopsy

Methods

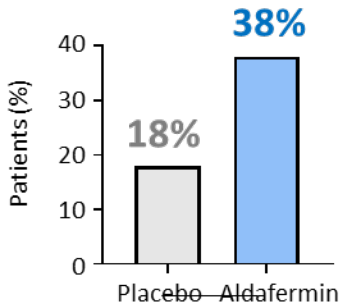
- 78 patients were randomized 1:2 to receive placebo (n=25) or aldafermin 1 mg (n=53).
- Inclusion criteria included biopsy-proven NASH with NAS ≥4, stage 2-3 fibrosis and absolute liver fat content (LFC) ≥8%.
- Patients underwent MRI-PDFF and liver biopsies at baseline (BL) and week 24 (W24).

Conclusions

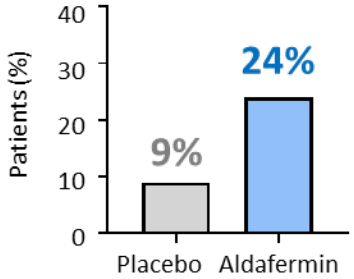
- Among patients with NASH, aldafermin treatment resulted in liver fat reduction, fibrosis improvement, and NASH resolution.
- Aldafermin maintained a favorable tolerability and safety profile.

Harrison SA, et al., Abstract 72

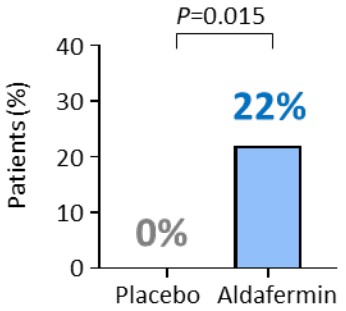
Fibrosis improvement with no worsening of NASH



NASH resolution with no worsening of fibrosis



Fibrosis improvement AND NASH resolution



Change from BL to W24	Placebo (n=25)	Aldafermin (n=52)	*P* value
Δ Absolute LFC, %	−2.7 (1.3)	−7.7 (0.8)	0.002
Δ Relative LFC, %	−13.1	−38.8	0.008
Δ ALT, %	−6.1	−49.1	<0.001
Δ AST, %	1.1	−33.0	0.004
Δ Pro-C3, %	−4.4	−27.6	0.001
Δ C4, %	0.9	−65.1	<0.001
Δ Total Bile Acids, %	35.3	−54.6	<0.001

Combinations of SEMA with CILO and/or FIR are well tolerated and offer potential for greater efficacy

Hypothesis/Aim/Objective

Evaluate the safety and efficacy of semaglutide (SEMA), a GLP-1 RA, alone and in combination with the FXR agonist cilofexor (CILO) and/or the ACC inhibitor firsocostat (FIR) in patients with NASH

Methods

Patients with F2-F3 fibrosis due to NASH (n=108) randomized equally to SEMA, SEMA+FIR 20 mg, SEMA+CILO 30 mg, SEMA+CILO 100 mg, or SEMA+CILO 30 mg+FIR 20 mg for 24 weeks (SEMA target dose 2.4 mg weekly for all groups, dose escalated over 16 weeks)

Main Findings

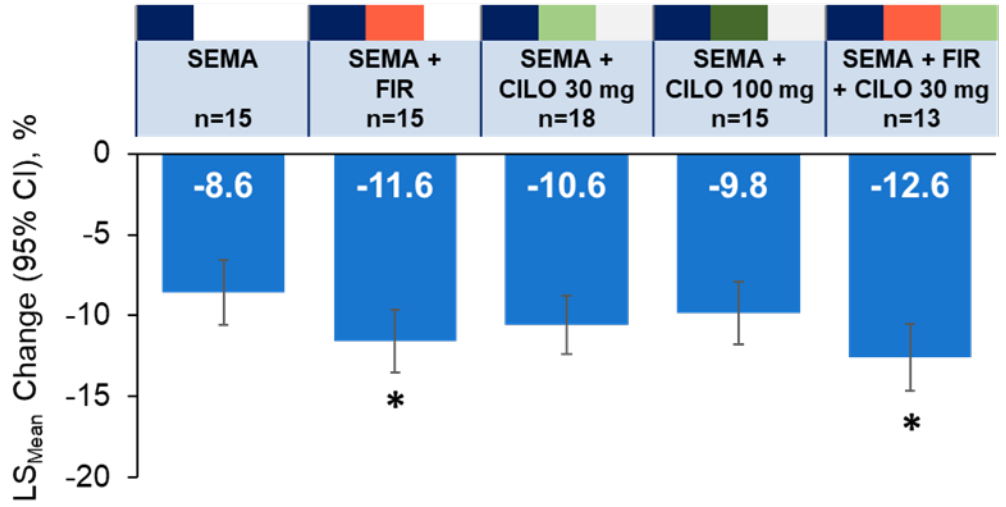
- Similar rates of AEs across groups, primarily GI, no increased rate of discontinuation in combination groups
- Greater improvements in serum ALT and AST, and liver steatosis with combinations. All groups with improvement in body weight, glycemic parameters, ELF score, and liver stiffness by transient elastography

Conclusions

Combinations of SEMA with CILO and/or FIR are well tolerated and offer potential for improved efficacy versus SEMA monotherapy.

Alkhouri N, et al., Abstract LO2

MRI-PDFF Absolute Change at Week 24



PDFF Responder Rates at Week 24, n (%)

≥30% ↓	12 (80)	14 (93)	17 (94)	13 (87)	12 (92)
≥50% ↓	6 (40)	10 (67)	14 (78)	8 (53)	11 (85)
≥70% ↓	1 (7)	4 (27)	6 (33)	5 (33)	4 (31)

*p<0.05 vs SEMA alone. LSmean, least squares mean

Aldafermin (NGM282) produces greater anti-fibrotic response in patients with non-alcoholic steatohepatitis and advanced fibrosis

Objective

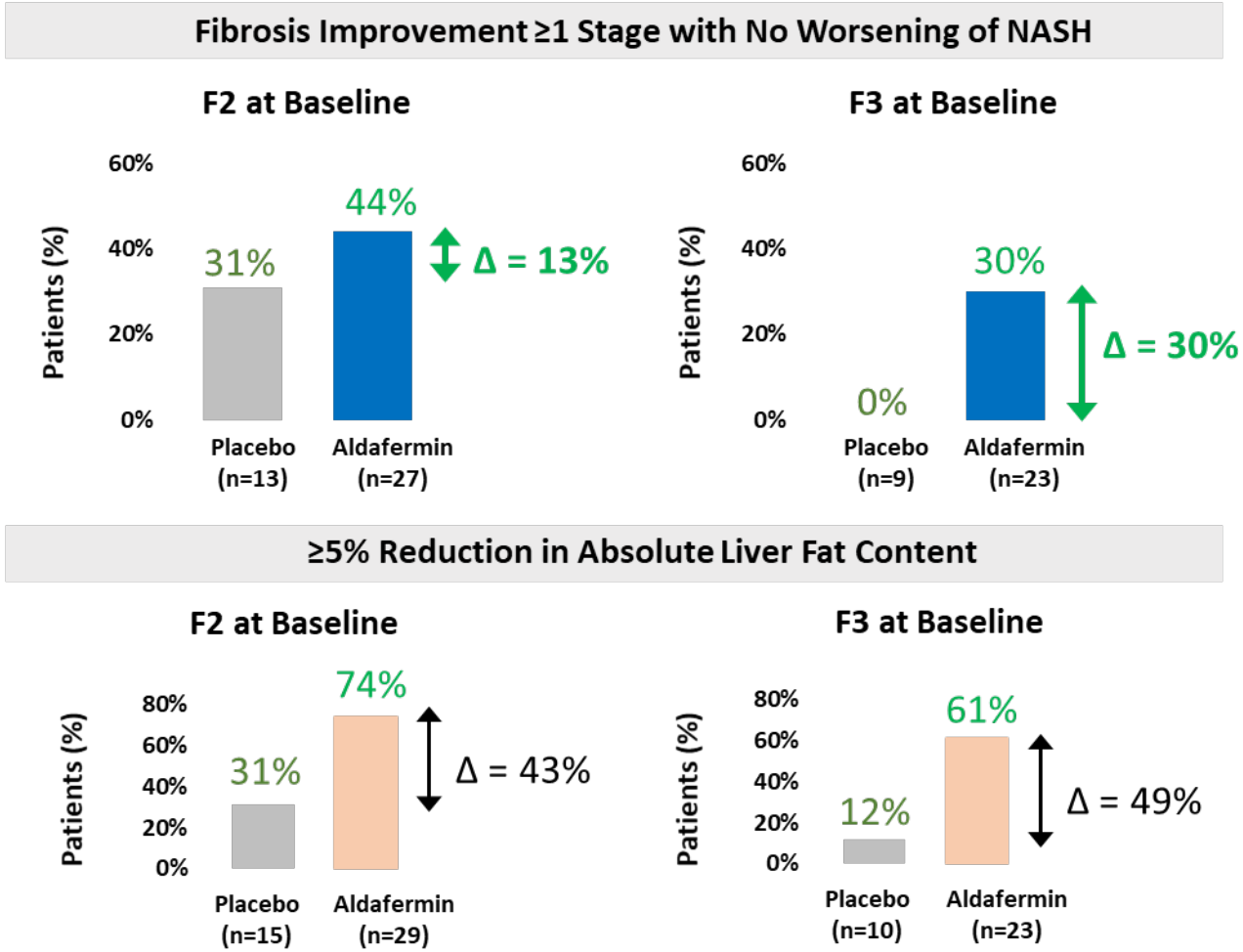
To evaluate the effect of aldafermin, an engineered FGF19 analog, in pre-specified subgroups of NASH patients with stage 2 (F2) or stage 3 (F3) fibrosis

Methods

- 78 patients were randomized 1:2 to receive placebo (n=25) or aldafermin 1 mg (n=53) for 24 weeks.
- Inclusion criteria included biopsy-proven NASH with NAS ≥4, F2-3 fibrosis (NASH CRN criteria) and absolute liver fat content (LFC) ≥8%.
- Patients underwent MRI-PDFF and liver biopsies at baseline (BL) and week 24 (W24).

Conclusions

- Placebo response rates in LFC reduction and fibrosis improvement were lower in F3 than in F2 patients.
- Aldafermin produced greater placebo-subtracted anti-fibrotic response in F3 patients than in F2 patients.



Neff G, et al., Abstract LO3

A phase 2 study of the efficacy and safety of namodenoson in treating NAFLD/NASH

Objective

Look at the safety and efficacy of namodenoson in NAFLD/NASH patients

Methods

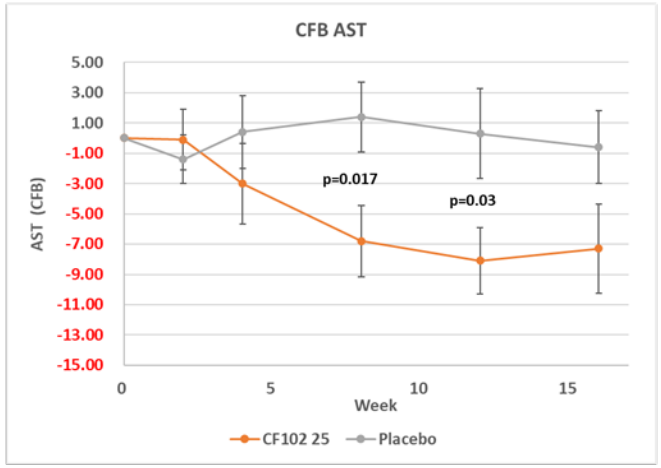
- Randomized, double-blind, placebo-controlled, dose finding comparing the efficacy of namodenoson in patients with NAFLD/NASH
- Patient population: diagnosis of NAFLD/NASH defined as hepatic steatosis ≥10% (by MRI-PDFF) and serum ALT ≥60 IU/L

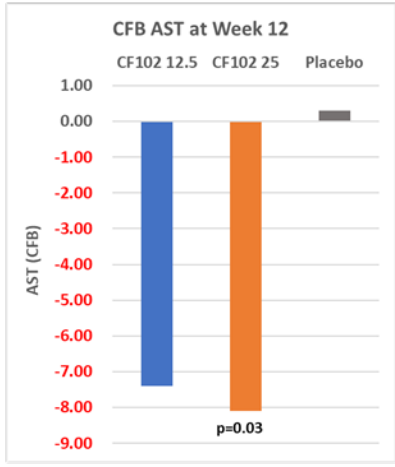
Main Findings

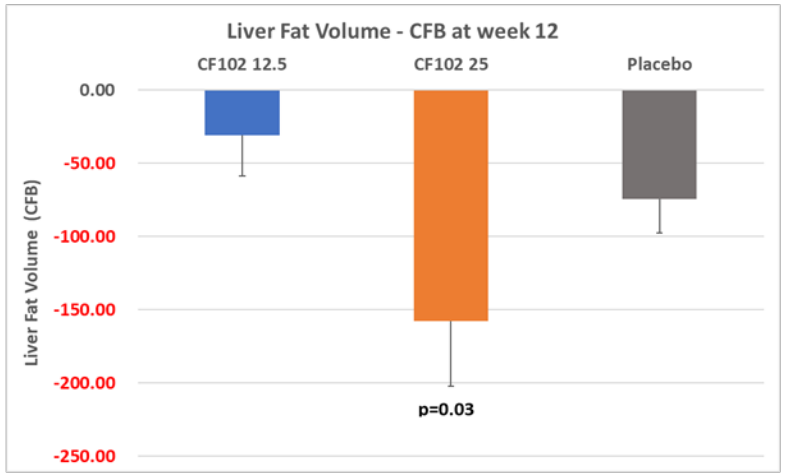
A significant decrease in ALT, AST, % of liver fat volume, FIB-4, and FAST with an increase in adiponectin was recorded.

Conclusions

Namodenoson was safe and inhibiting hepatic inflammation, fibrosis, and fat content.







Safadi R, et al., Abstract LO1

Clinical characteristics used for machine learning identification of fast progressors in NASH patients

Aim

To compare characteristics of NASH fast (≤3 years) and standard (>6 years) progressors to cirrhosis/HCC used for a machine learning (ML) model to predict risk of fast progression

Methods

- The study cohort is patients with NASH and cirrhosis after excluding all other liver diseases. Progression time was identified by time from earliest evidence of disease to cirrhosis.
- Features around the index date were used to develop a ML model to predict risk of fast progression. The 44 model features were compared between fast and standard progressors.

Conclusions

Machine learning may help identify patients at risk of fast progression and complement clinical assessment from a large number of features with complex interactions.

Reinhart B, et al., Abstract 60

Predictive Importance	Model Feature, Mean (SD)	Fast Progressors (n = 951)	Standard Progressors (n = 992)
1	*Albumin (g/dL)	3.9 (0.5)	4.1 (0.4)
2	BMI	34.6 (7.3)	35.0 (7.3)
3	*Platelets (x10^3/µL)	198.5 (78.3)	222.2 (68)
8	*No. of Anxiety diag.	0.8 (3.3)	0.2 (0.8)
10	*Age	59.5 (13.6)	57.2 (11.6)
11	*Triglycerides (mg/dL)	161.4 (91)	179.1 (91.5)
15	*AST (U/L)	46.5 (29.8)	39.9 (23.5)
16	*AST/ALT	1.1 (0.4)	1 (0.4)
20	HbA1C (%)	7.0 (1.5)	7.0 (1.3)
23	*ALP (U/L)	100.4 (45.8)	87.6 (36.7)
24	*LDL (mg/dL)	96.3 (33.8)	102.1 (33.8)

*Significant difference between groups, *p*-value <0.05

A retrospective observational cohort study to assess the prevalence & survival of patients with NASH in Ontario, Canada

Objective

To describe the prevalence of NASH for each fiscal year between 2008 -2017 stratified by age group in Ontario

Methods

Case identification by ICD-10-CA diagnostic and procedure codes, organized by increasing NASH severity [NC-NASH (non-cirrhotic), CC (compensated cirrhosis), DCC (decompensated cirrhosis)] using a diagnostic algorithm with clinical identifiers

Main Findings

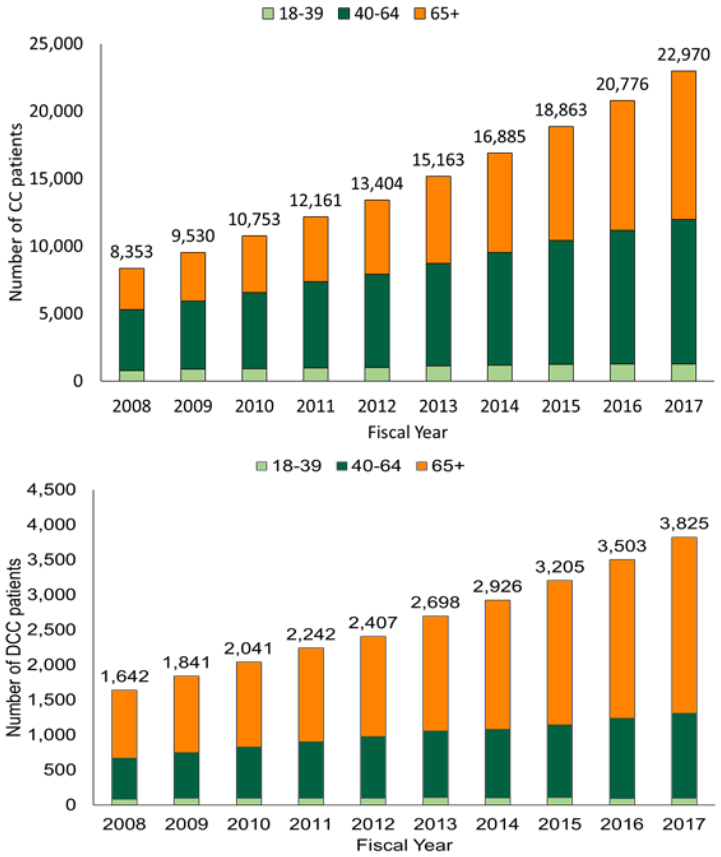
CC and DCC increased at 12% and 9.4% per year, with higher observed rates in age ≥65 years; CC and DCC were associated with reduced 10-year probability of survival relative to NC.

Conclusions

Rapid rate of increase in NASH-CC and DCC prevalence in Ontario over the past decade, especially in older patients

Patel K, et al., Abstract 85

Prevalence of Compensated and Decompensated Cirrhosis by Age



The natural history of lean NAFLD: a longitudinal US population study

Aim

To compare the natural history of lean, overweight, and obese NAFLD in a US population with 20-years follow-up

Methods

- Retrospective study of NAFLD adults grouped by BMI into lean, overweight, obese
- Outcomes ascertained by detailed medical record review

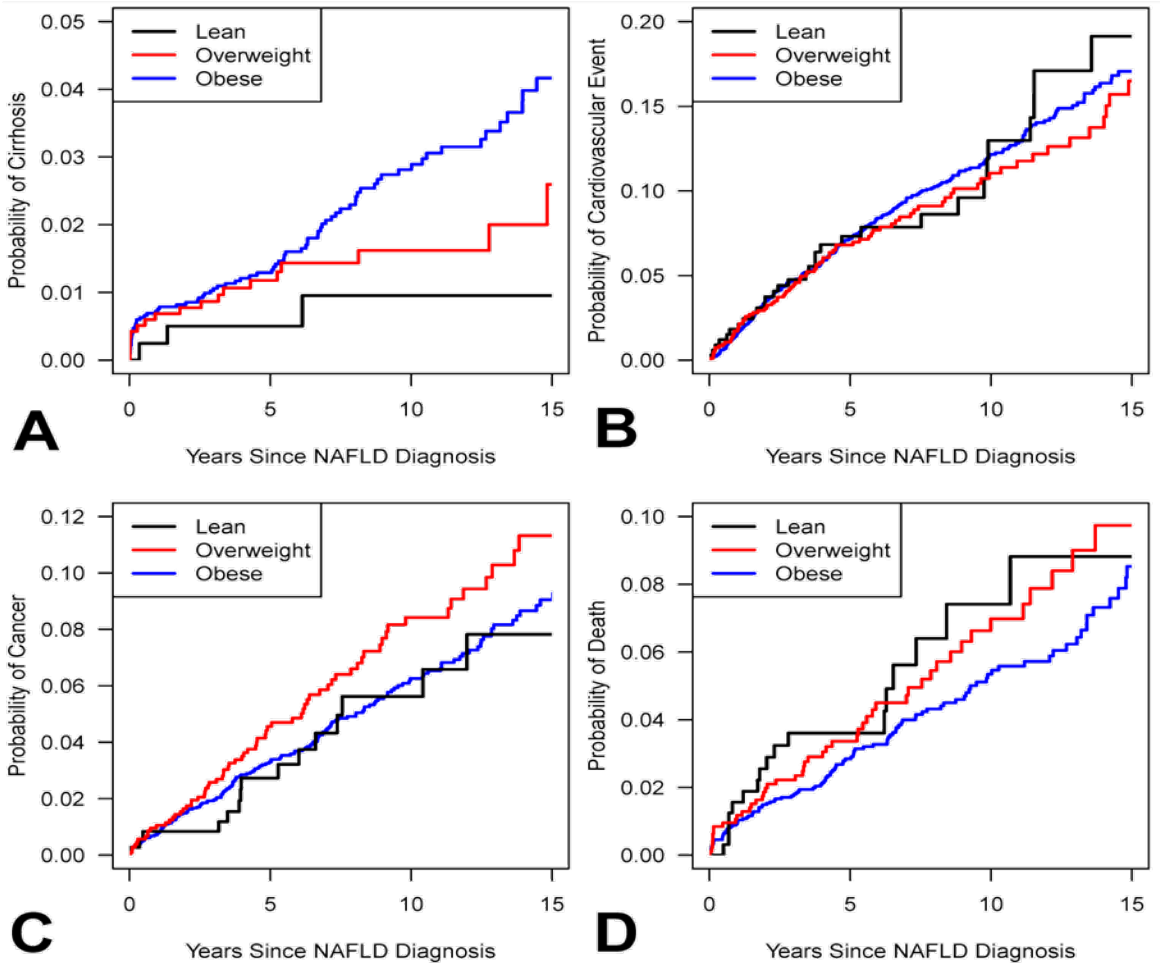
Main Findings

Compared to obese, lean NAFLD had:

- A trend towards lower risk of cirrhosis (HR 0.33, *P*=0.06) (see Figure A)
- Similar risk of cardiovascular events (see Figure B) and cancer (see Figure C)
- Higher risk of death (HR 1.63, *p*=<0.001) (see Figure D)

Conclusions

Lean NAFLD had lower risk of liver disease progression but higher mortality.



Ahmed OT, et al., Abstract 86

Breastfeeding is associated with a decreased risk of hepatic fibrosis among young women with NAFLD

Hypothesis

Women who breastfed are protected from developing more severe form of NAFLD while the benefit may diminish after age 50 years, a proxy of menopause.

Methods

A cross-sectional, hypothesis-refining analysis on 429 women (age 51 ± 11 years) using data from the Duke NAFLD Clinical Database to evaluate if history of live birth and cumulative breastfeeding duration are associated with clinical and histologic features of NAFLD among women, considering potential effect modification by age 50 years

Conclusions

Women with NAFLD who breastfed more than 3 months in their lifetime were associated with less severe fibrosis, while the benefit appears to diminish after the age of 50 years.

Breastfeeding history was associated with less portal inflammation and less severe fibrosis among women with age ≤50

Adj. OR with 95% CI	Fibrosis Total	Fibrosis Age ≤50	Fibrosis Age >50
Breastfeeding >3M, yes vs. no	0.65 [0.43, 0.99], p=0.043	0.41[0.21, 0.80], p<0.009	0.83 [0.48, 1.4], p=0.50
Breastfeeding >6M, yes vs. no	0.71 [0.46, 1.10], p=0.13	0.53[0.27, 1.0], p=0.059	0.86 [0.48, 1.5], p=0.62

Adj. OR with 95% CI	Portal inflammation Total	Portal inflammation Age ≤50	Portal inflammation Age >50
Breastfeeding >3M, yes vs. no	0.70 [0.44, 1.12], p=0.13	0.36 [0.17, 0.77], p=0.008	1.0 [0. 6, 1.9], p=0.91
Breastfeeding >6M, yes vs. no	0.58 [0.35, 0.95], p=0.03	0.31 [0.14, 0.69], p=0.004	0.9 [0.5, 1.7], p=0.67

Covariates: age at liver biopsy, age category (age ≤ or >50 years), race, and enrollment sites (ie, liver clinic, bariatric clinic)

No associations with steatosis, lobular inflammation, hepatocyte ballooning

Suzuki A, et al., Abstract 87

Change in lipid markers throughout early adulthood is associated with prevalent MAFLD in mid-life: CARDIA

Aim

- Identify groups of individuals by slope of change in triglycerides (TG), HDL-C, non-HDL-C, LDL-C, and total cholesterol (TC) from young adulthood to mid-life
- Examine the association between rate of lipid change and prevalent CT-assessed MAFLD in mid-life

Methods

Use of data from the CARDIA study to categorize participants based on quartiles of change for each lipid marker and then evaluate the association of each group and MAFLD

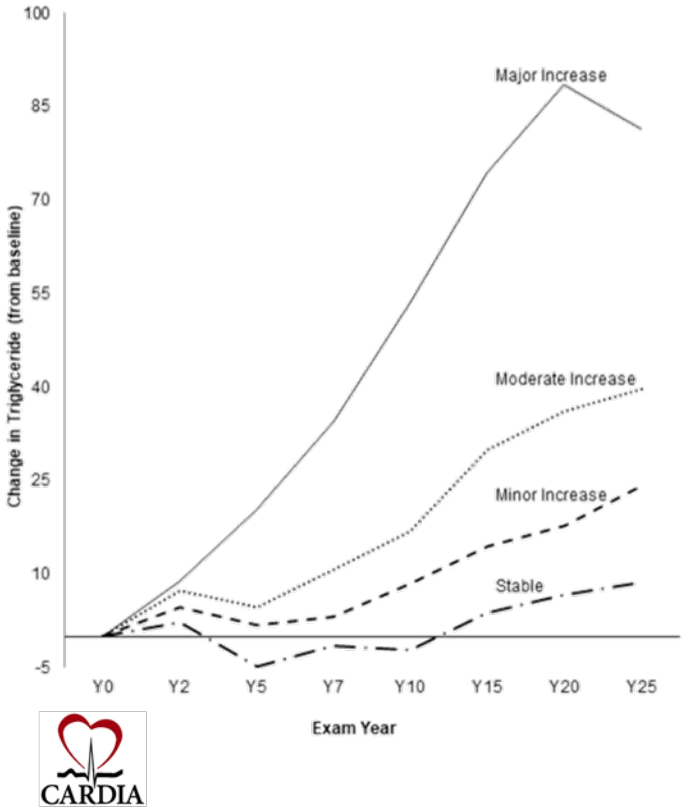
Conclusions

Increased triglycerides throughout early adulthood is associated with the greatest odds of MAFLD in mid-life.

Khanna S, et al., Abstract 88

(A) Example of change in triglycerides from 1985-1986 (Y0) to 2010-2011 (Y25) and
(B) Adjusted odds ratio for association between lipid markers and prevalent MAFLD

PANEL A



PANEL B

	Model 1	Model 2
Triglyceride (Panel A)		
Stable (n=676)	Reference	Reference
Minor Increase (n=668)	1.74 (1.20, 2.53)	1.78 (1.22, 2.60)
Moderate Increase (n=662)	2.72 (1.90, 3.88)	2.84 (1.96, 4.12)
Major Increase (n=638)	5.88 (4.11, 8.42)	6.41 (4.28, 9.62)
HDL-C		
Stable (n=660)	Reference	Reference
Minor Increase (n=677)	0.58 (0.45, 0.75)	0.56 (0.42, 0.74)
Moderate Increase (n=662)	0.51 (0.38, 0.68)	0.44 (0.31, 0.61)
Major Increase (n=645)	0.31 (0.21, 0.44)	0.22 (0.14, 0.34)
Non-HDL-C		
Stable (n=638)	Reference	Reference
Minor Increase (n=663)	1.02 (0.74, 1.41)	1.12 (0.80, 1.57)
Moderate Increase (n=676)	1.38 (1.01, 1.88)	1.63 (1.15, 2.30)
Major Increase (n=667)	2.08 (1.54, 2.81)	2.55 (1.74, 3.73)
LDL-C		
Stable (n=632)	Reference	Reference
Minor Increase (n=668)	1.04 (0.77, 1.40)	1.12 (0.81, 1.53)
Moderate Increase (n=670)	1.16 (0.86, 1.56)	1.36 (0.98, 1.89)
Major Increase (n=674)	1.36 (1.02, 1.82)	1.77 (1.23, 2.55)
Total Cholesterol		
Stable (n=664)	Reference	Reference
Minor Increase (n=6661)	1.01 (0.75, 1.35)	1.03 (0.76, 1.41)
Moderate Increase (n=666)	1.21 (0.91, 1.62)	1.28 (0.93, 1.75)
Major Increase (n=663)	1.36 (1.02, 1.81)	1.41 (0.98, 2.01)

Abbreviations: HDL-C, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; MAFLD, metabolic associated liver disease

Model 1: Adjusted for age, sex, race, field center, highest educational attainment, pack-years of smoking exposure, cumulative alcohol use (drinks/year), cumulative physical activity, cumulative BMI, cumulative years with diabetes, cumulative systolic blood pressure (mmHg-years), and number of years with blood pressure or lipid-lowering medications

Model 2: Adjusted for Model 1 + baseline (Y0) total cholesterol or LDL-C or HDL-C or triglycerides or non-HDL-C + level of other lipids per year

Can low liver fat be bad for your heart?

The high visceral fat low liver fat phenotype – a risk factor for coronary heart disease

Aim

To validate the association between the high visceral fat low liver fat phenotype with coronary heart disease (CHD) using imaging biomarkers and health outcome data in UK Biobank

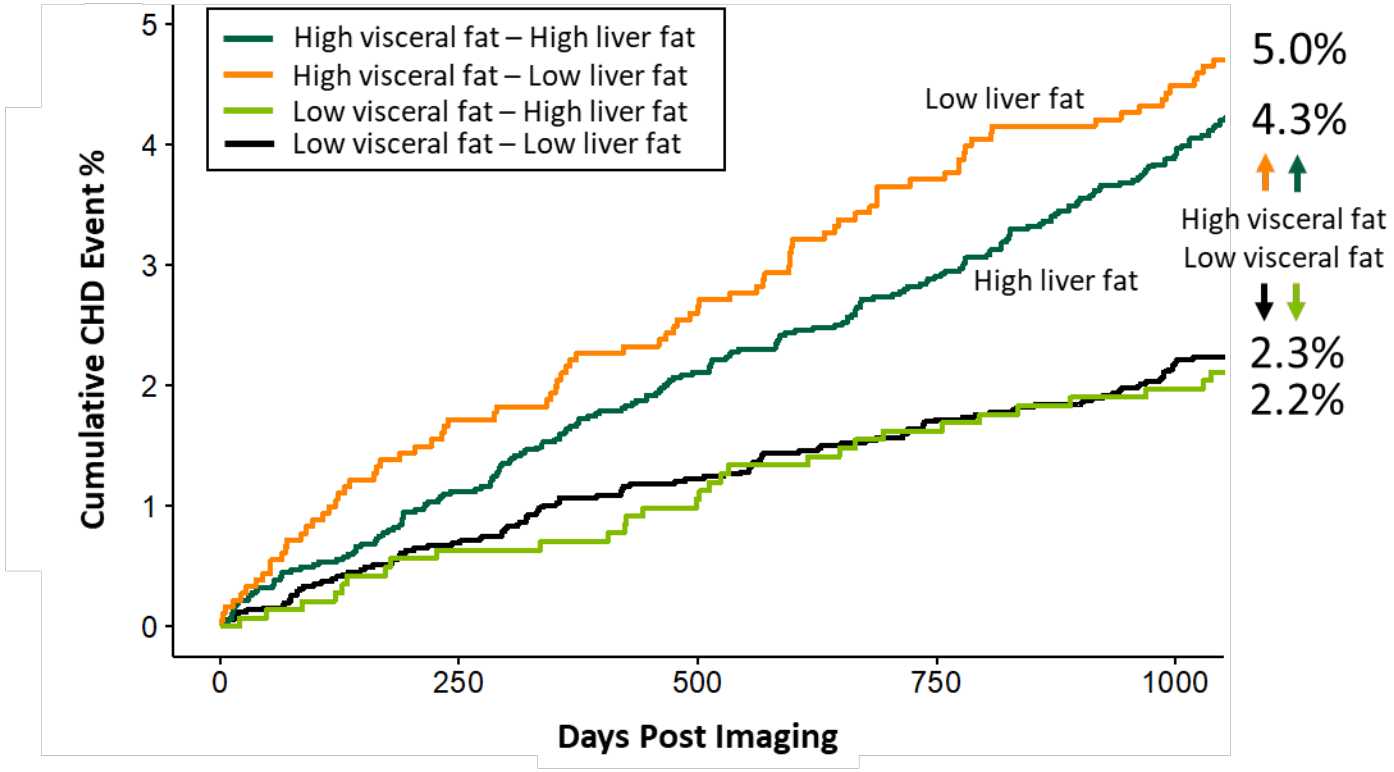
Methods

In 12,276 participants, incident CHD was compared between four phenotype groups created by applying the sex-specific median of visceral fat (VF) and liver fat (LF) as cut-offs: low VF-low LF, low VF-high LF, high VF-low LF, high VF-high LF.

Conclusions

Visceral fat most effectively identified individuals at high risk for CHD and in the presence of high visceral fat, a low liver fat was strongly associated with higher CHD risk.

3-Year Risk of Coronary Heart Disease (CHD)



Linge J, et al., Abstract 89

People with HIV with hepatic steatosis have a unique plasma lipidome

Objective

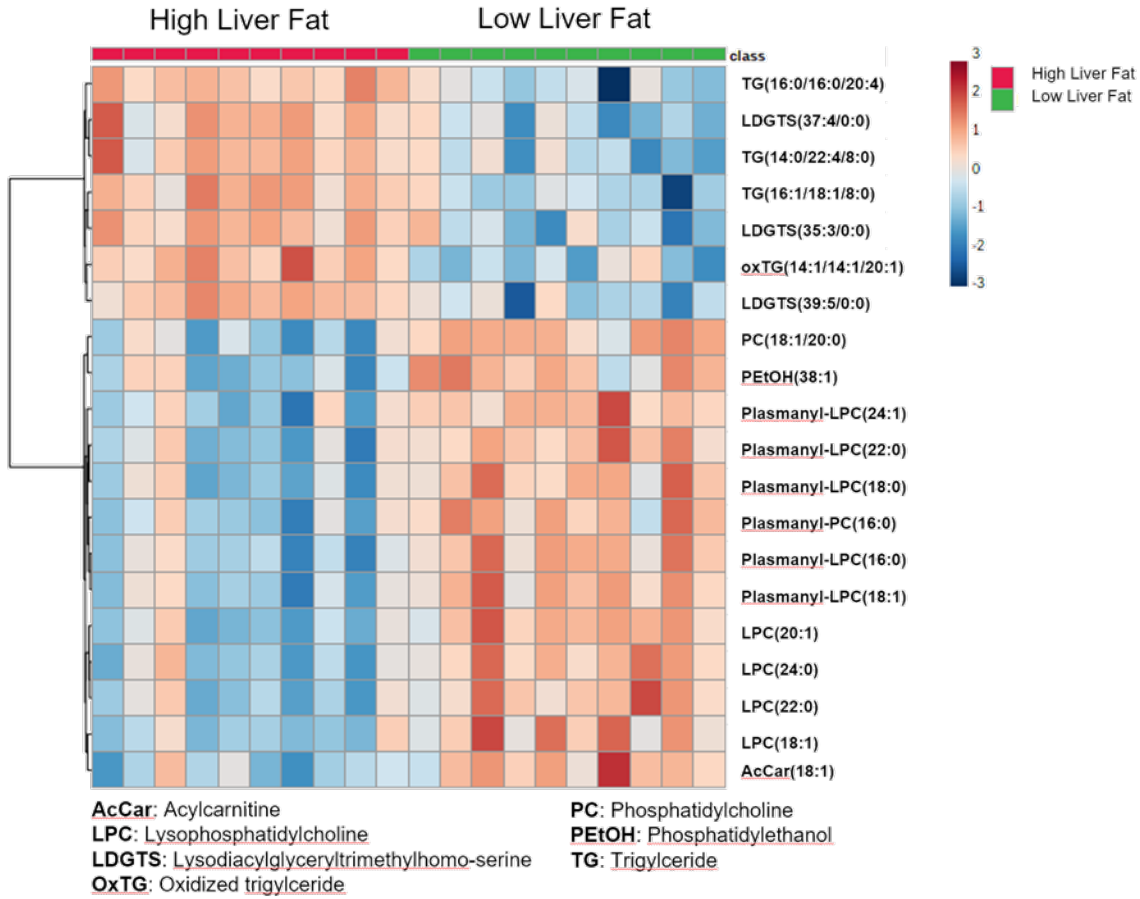
To characterize the plasma lipidome in people with HIV with hepatic steatosis

Methods

We used untargeted liquid chromatography-mass spectrometry and computed tomography liver imaging to identify relationships between hepatic steatosis and plasma lipid species in a cohort of 20 people with well-controlled HIV.

Conclusions

People with HIV with high levels of liver fat had a lower abundance of plasma phosphocholine species and a higher abundance of plasma triglycerides relative to participants with low levels of liver fat. These differences in the plasma lipidome were also observed in people with HIV with greater visceral fat volume and pericardial fat volume.



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