Role of vascular alterations in MASLD/MASH pathophysiology
Pre-clinical and human data on the effect of lanifibranor

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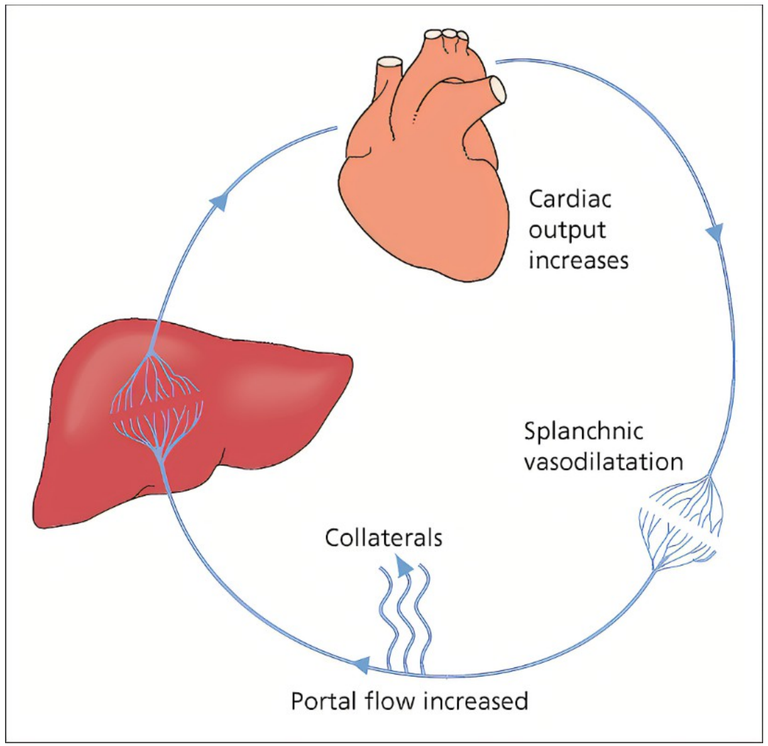
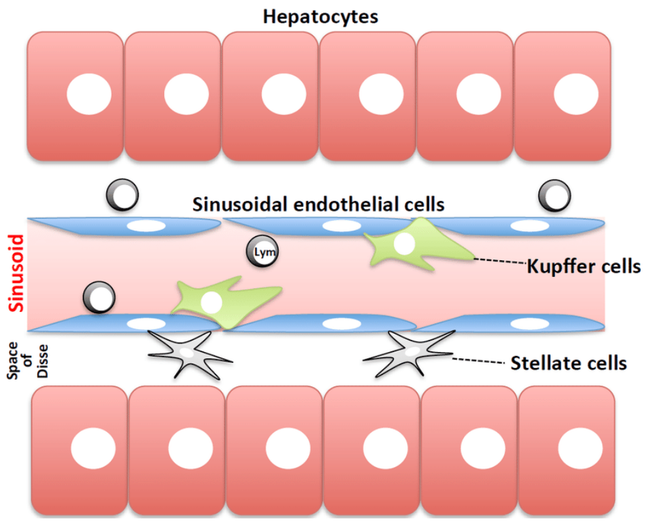
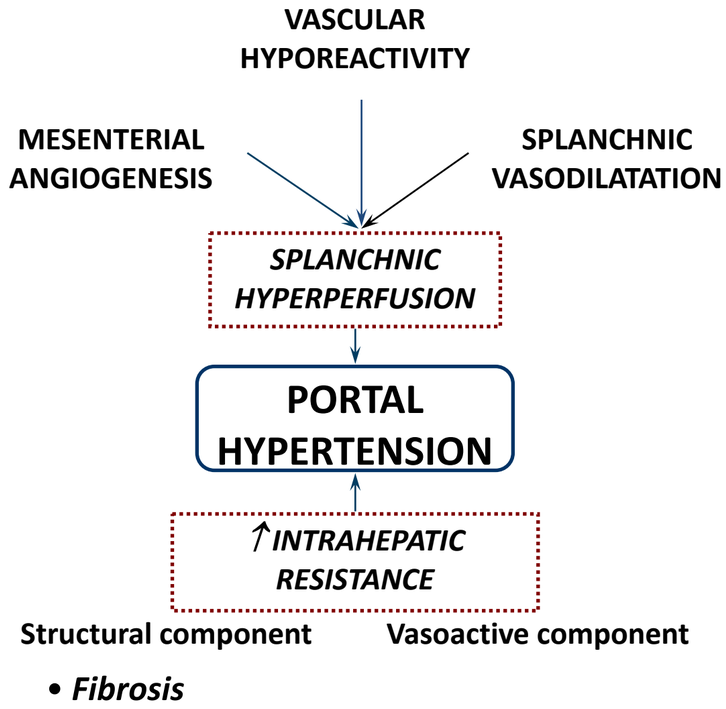
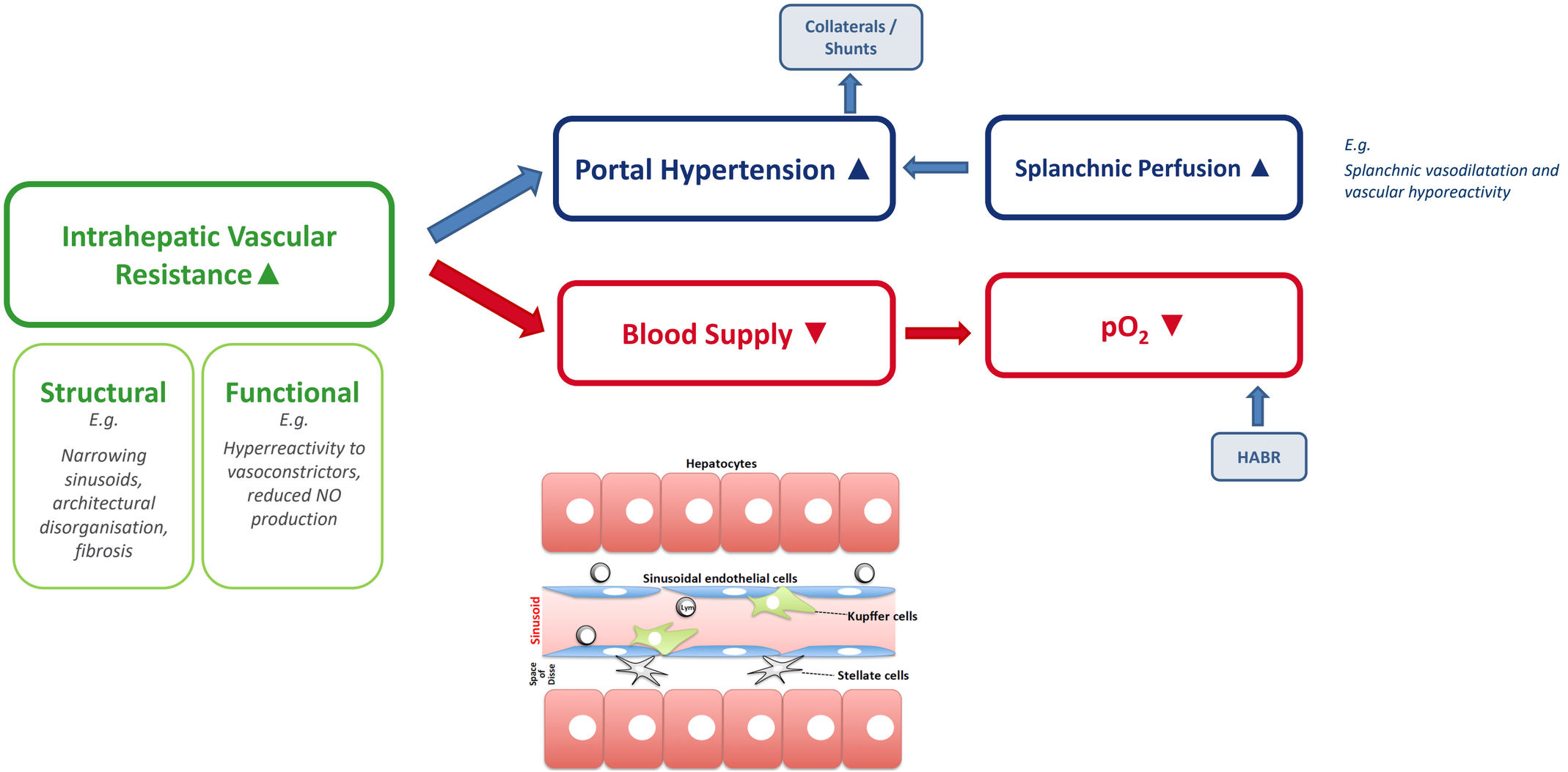
Portal Hypertension







Portal Hypertension in MASLD/MASH

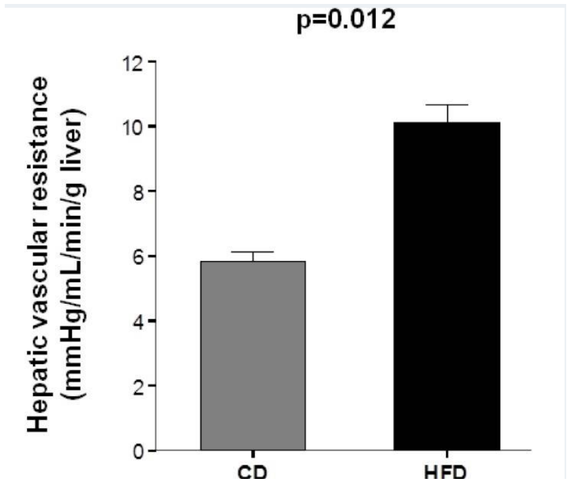


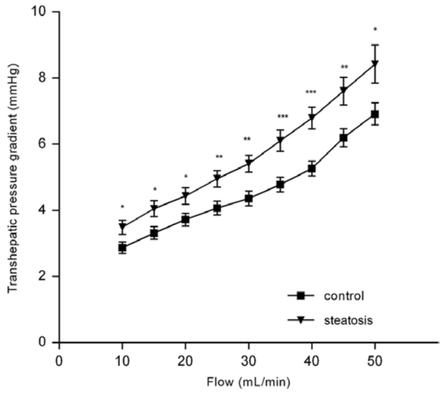
Francque et al. Lab Invest 2012

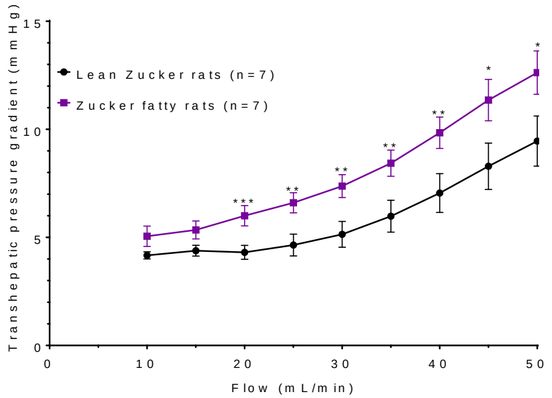
Van Der Graaff, Kwanten, Francque. Med Hypotheses 2019

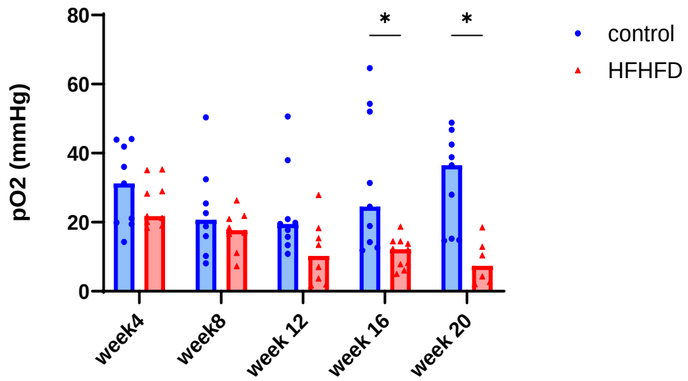
*HABR: Hepatic arterial buffer response

Portal Hypertension in MASLD/MASH







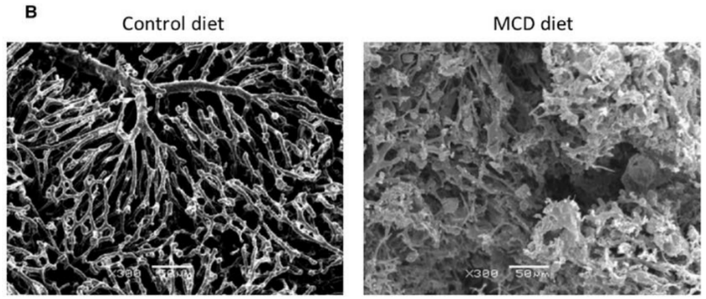


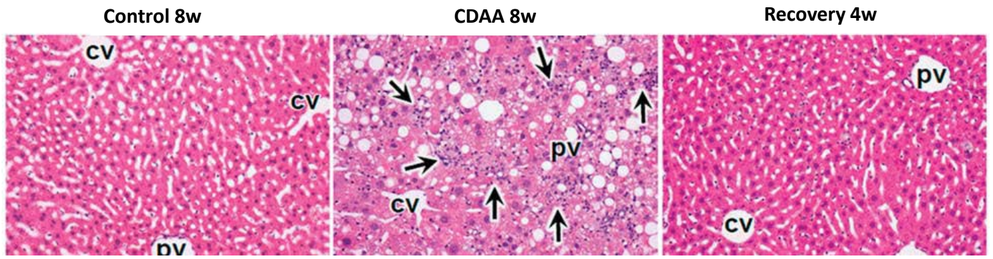
Intrahepatic Vascular Resistance ▲

Structural | **Functional**

Portal Hypertension ▲ ← **Splanchnic Perfusion ▲**

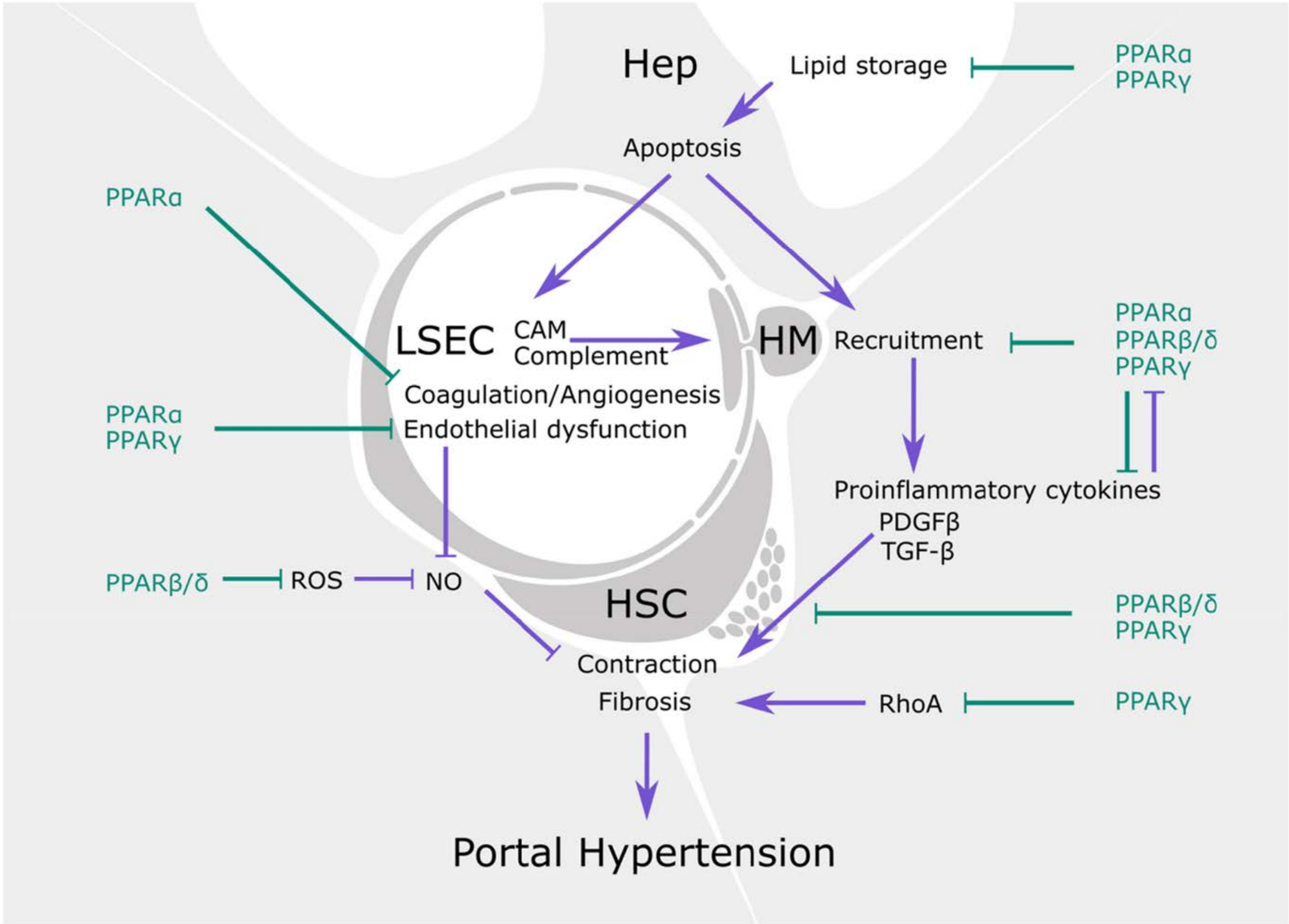
Blood Supply ▼ → **pO_2 ▼**





Gonzalez-Paredes *et al*. PLoS ONE 2016; Van Der Graaff… Francque. Lab Invest 2018; Van Der Graaff… Francque. J Hep Rep 2022; Lefere *et al*. Hepatology 2019; Miyao *et al*. Lab Invest 2015; Van Eyck…Francque… *et al*. Int J Obesity 2024; Van Der Graaff…Francque. Med Hypotheses 2019

Role of PPARs in liver vascular biology



Guixé-Muntet…Francque et al. Aliment Pharmacol Ther 2022

Pre-clinical data

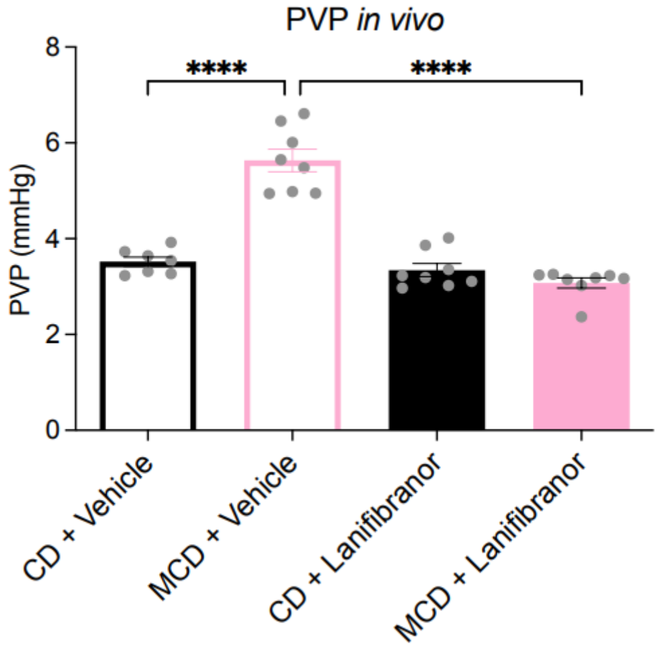
Portal hypertension in a model of MASLD

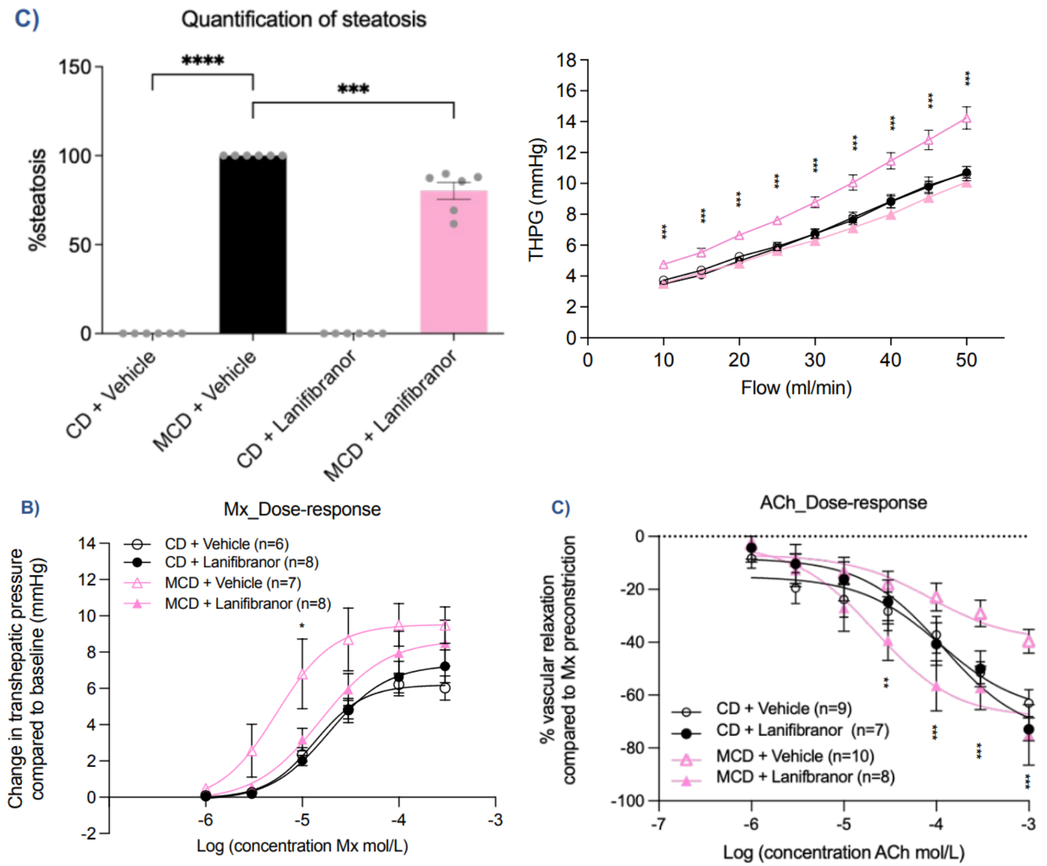
Wistar rat
250 g

Control diet (CD)
- Group 1: **Vehicle**
- Group 2: Lanifibranor (100 mg/kg)

Methionine-Choline deficient diet (MCD)
- Group 3: **Vehicle**
- Group 4: Lanifibranor (100 mg/kg)

4 weeks Diet and preventive treatment



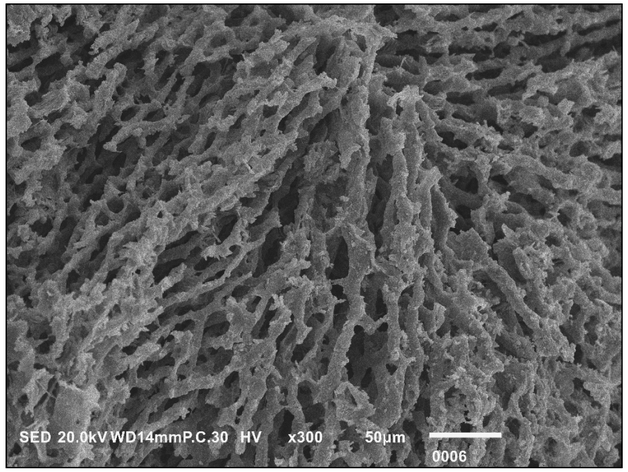


- Lanifibranor (but not single PPAR) normalises
  - portal hypertension
  - transhepatic pressure gradient
  - hyperreactivity to methoxanime
  - hyporeactivity to acethylcholine

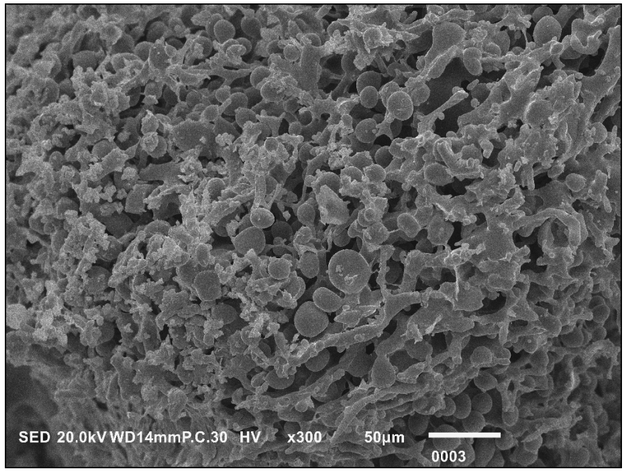
Chotkoe …Francque. EASL 2023

Portal hypertension in an early model of MASLD

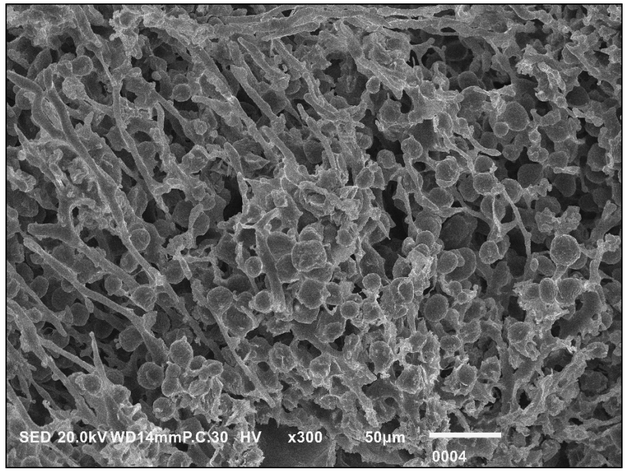
Control diet



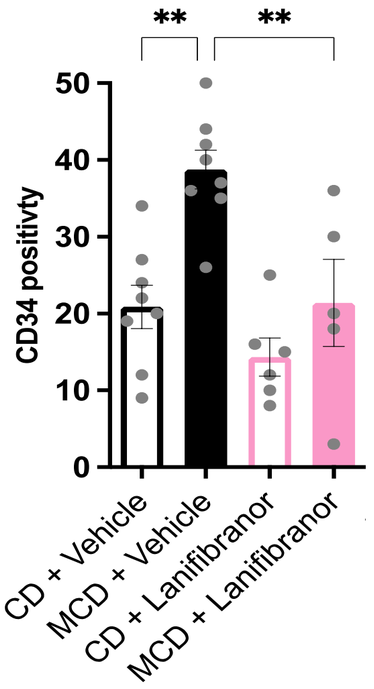
MCD diet



MCD diet + lanifibranor



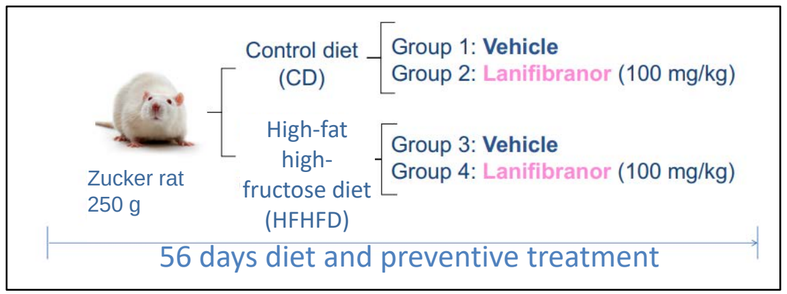
CD34 staining

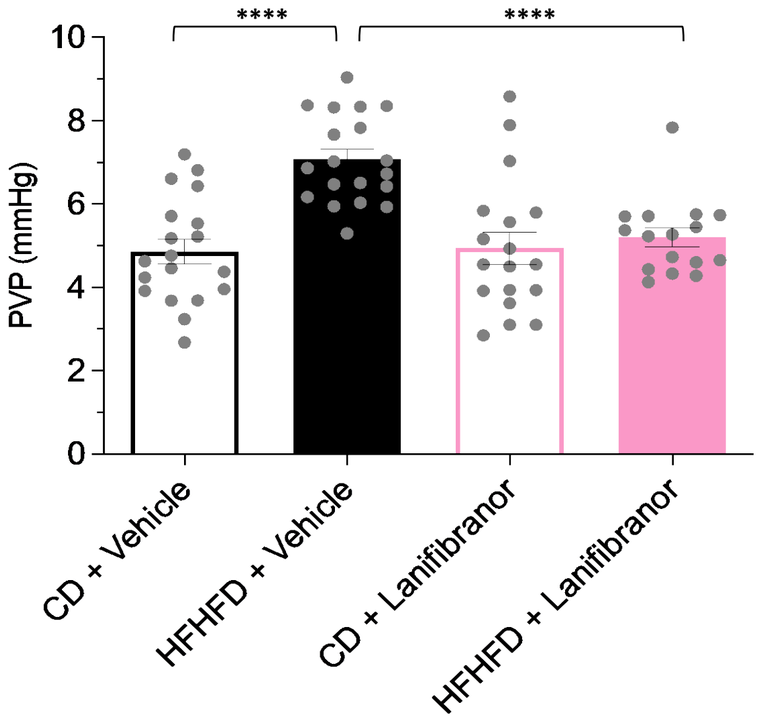


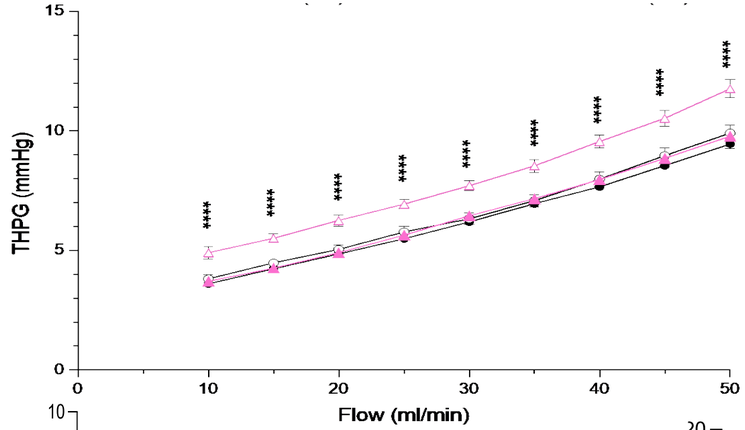
- Lanifibranor
  - improves the sinusoidal organisation
  - decreases the number of blebs
  - inhibits the capillarisation of the LSEC

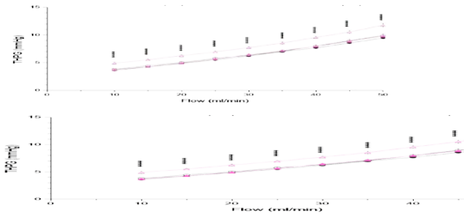
Chotkoe …Francque. EASL 2023

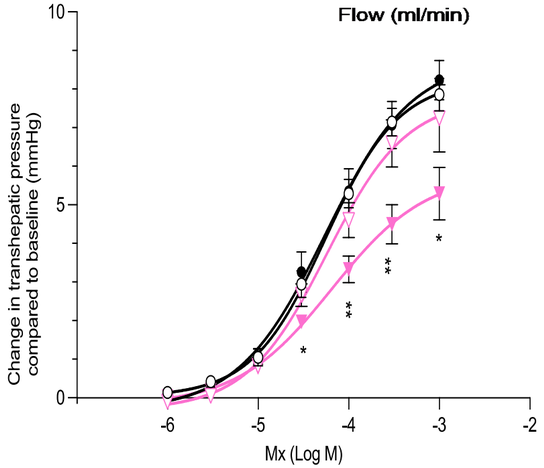
Portal hypertension in an early model of MASH

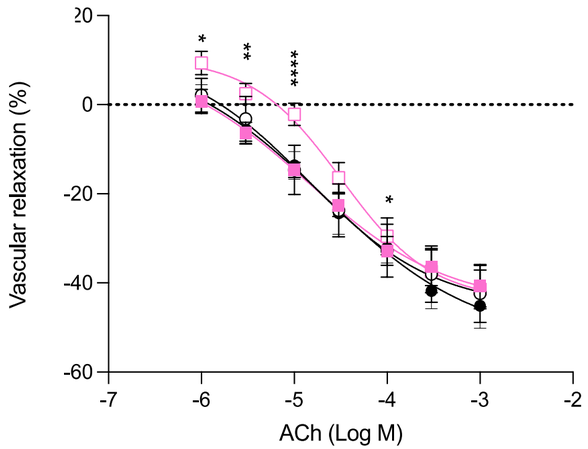












- Confirmation in a second model (being a MASH model) of
  - increase in portal pressure
  - intrahepatic vascular modifications
  - normalisation of all vascular modifications by lanifibranor

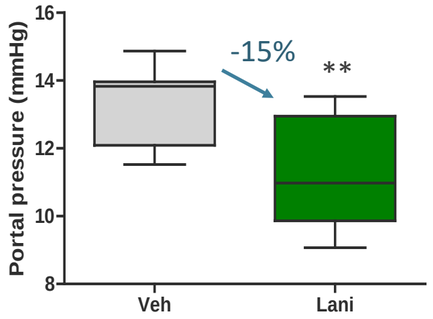
Rautou, Chotkoe …Francque. In preparation

Portal hypertension in a model of cirrhosis: effect of lanifibranor on the portal pressure

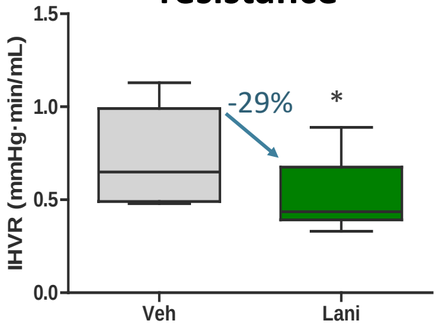
Group 1: Vehicle
Group 2: **Lanifibranor (100 mg/kg)**

12 weeks of cirrhosis induction (TAA) → 2 weeks of treatment

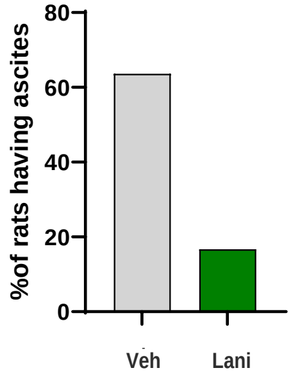
Portal pressure



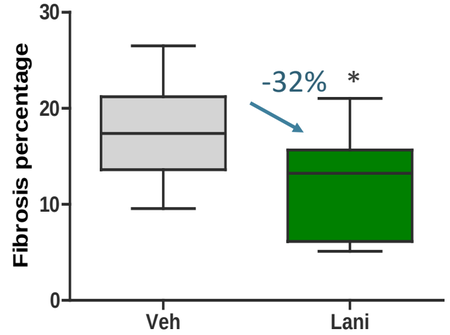
Intrahepatic vascular resistance



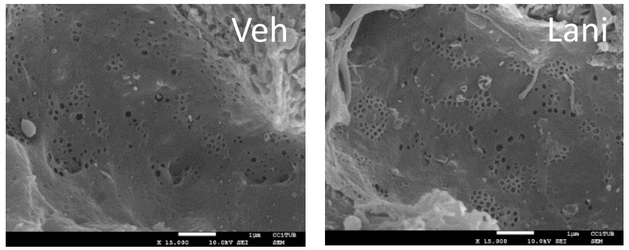
Ascites

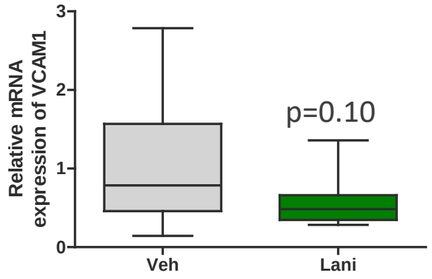


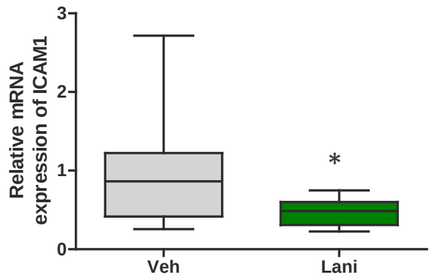
Fibrosis

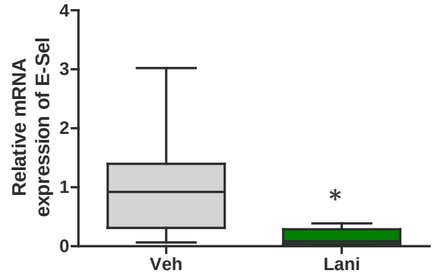


Electronic microscopy

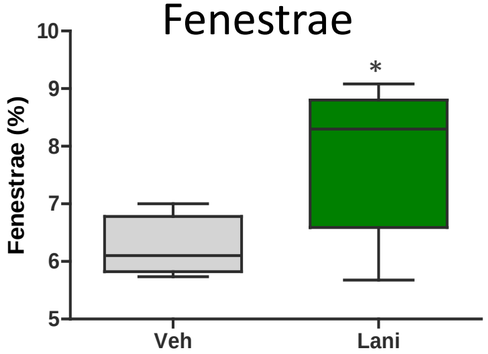








Fenestrae



- Lanifibranor
  - reduces portal pressure
  - reduces intrahepatic vascular resistance
  - reduces ascites
  - decreases fibrosis
  - effects on sinusoidal endothelial cells (LSEC)
    - restores fenestration
    - induces their decapillarisation
    - deactivation
- Data confirmed in CBDL model

Boyer-Diaz et al. 2021 J.Hep

Portal hypertension in a non-cirrhotic model: effect of lanifibranor on the portal pressure and mesenteric vasculature

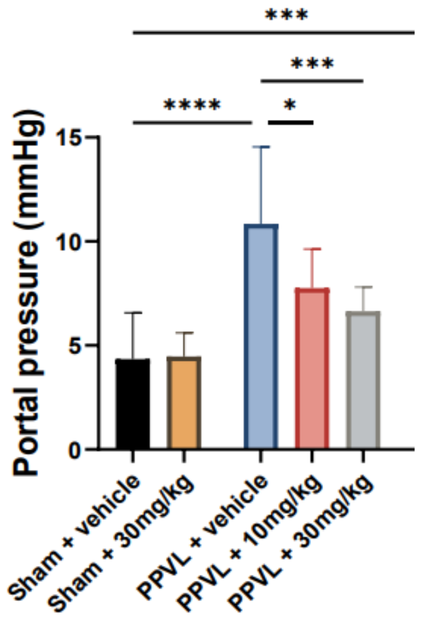
Group 1: Sham (ctrl)
Group 2: Vehicle
Group 3: Lanifibranor (10 mg/kg)
Groupe 4: Lanifibranor (30mg/kg)

1 week induction (PPVL (partial portal vein ligation)

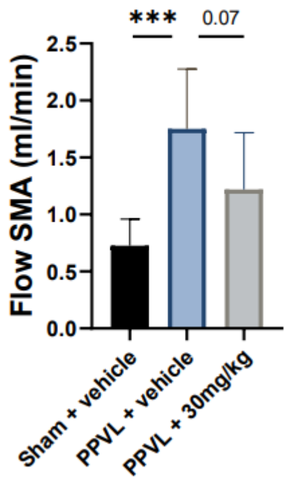
1 week of treatment

Corrosion cast of the mesentieric vasculature

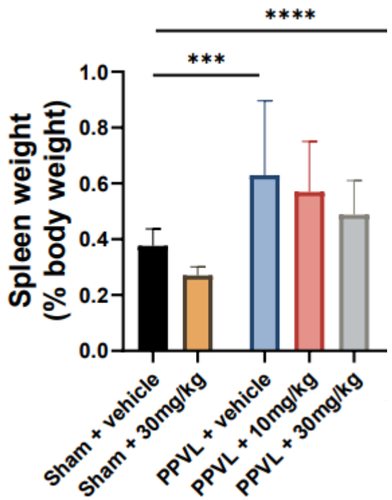
Portal pressure



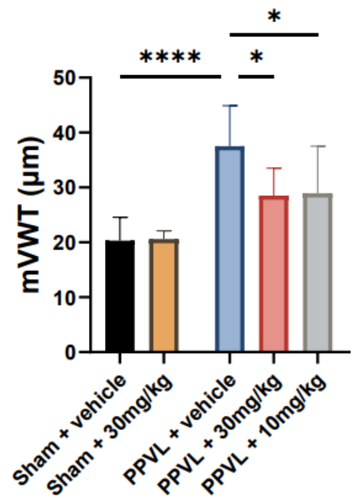
Flow superior mesenteric artery



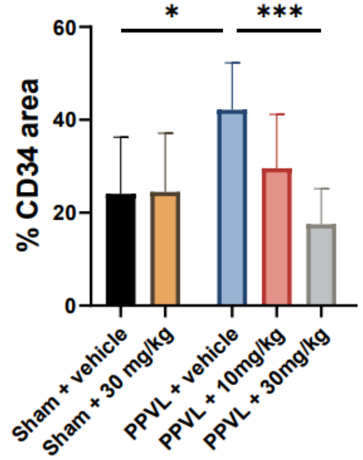
Spleen weight



Vascular wall thickness



CD34 staining

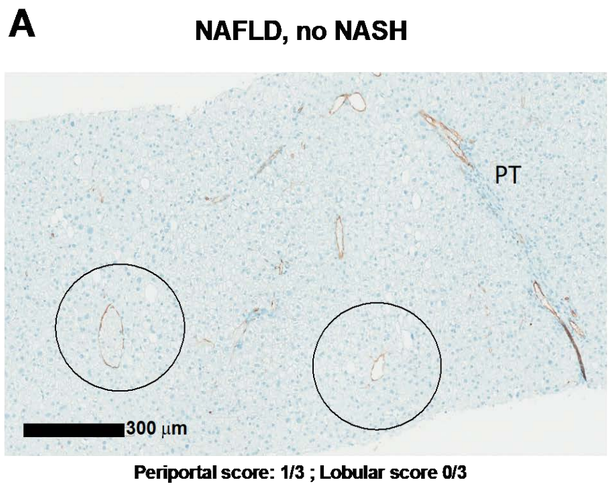


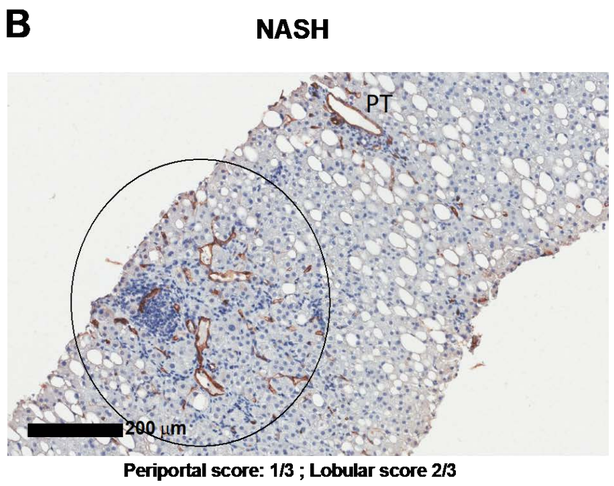
- Lanifibranor reduces portal pressure by reducing the superior mesenteric artery flow
  - Reduction of vascular wall thickness
  - Reversal of PPVL-induced vascular expansion

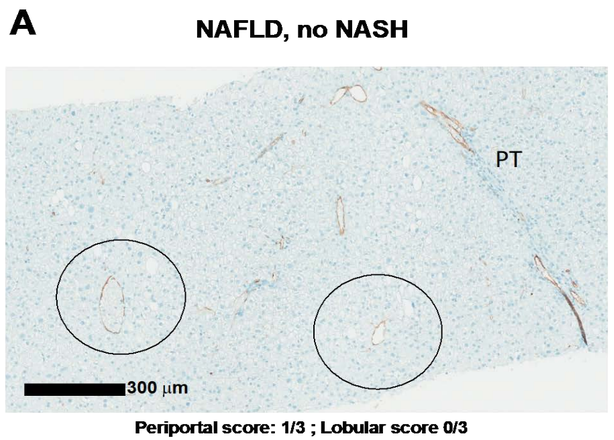
Heldens, EASL 2023

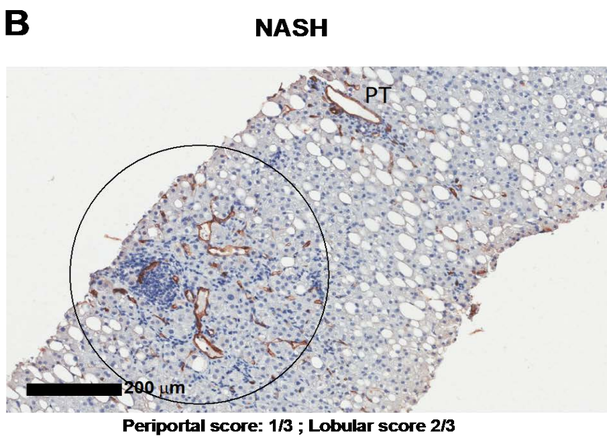
Clinical data from NATIVE demonstrating liver vasculature modification throughout MASH progression and effect of lanifibranor on the vascular architecture

Capillarisation of liver sinusoids in patients with MASH









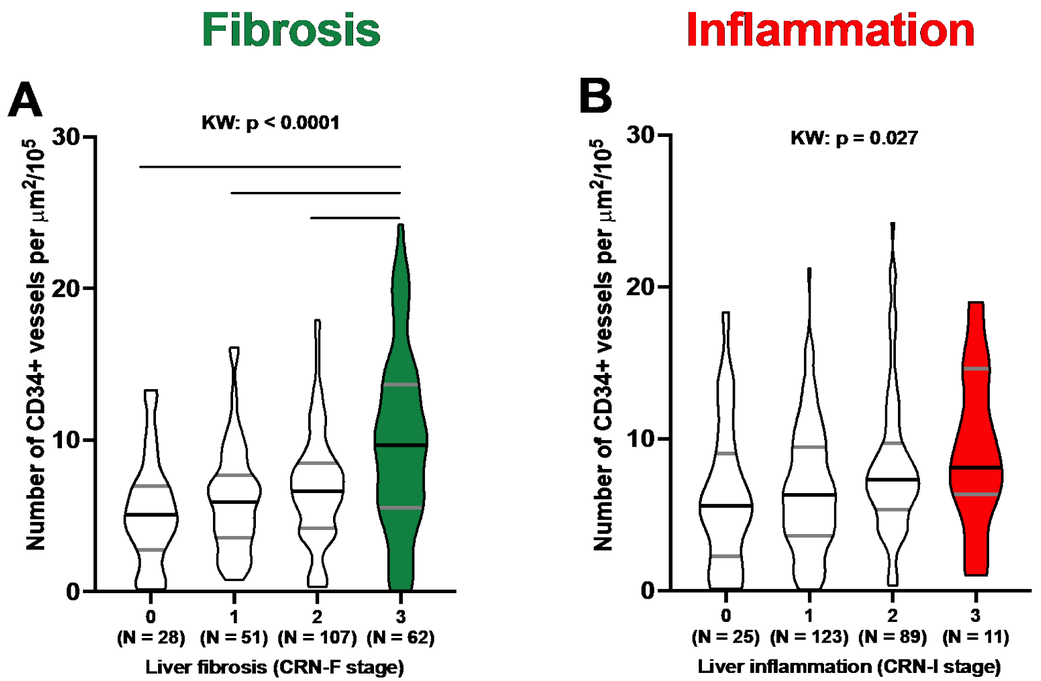
CD34 staining on slides from the NATIVE clinical trial (Phase 2b)

- CD34 positive staining is more pronounced in MASH patients than in patients without MASH
- Patients with MASH have significantly more CD34 positive staining within the lobular area
- A similar trend is observed in the periportal area

Rautou, Chotkoe …Francque. In preparation

Capillarisation of liver sinusoids in patients with MASH

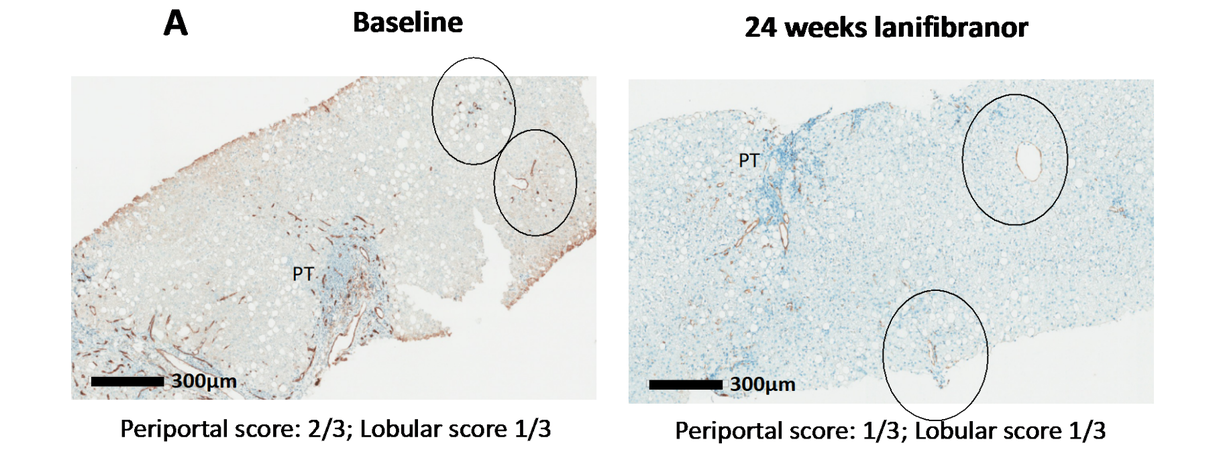
Density of CD34+ vessels

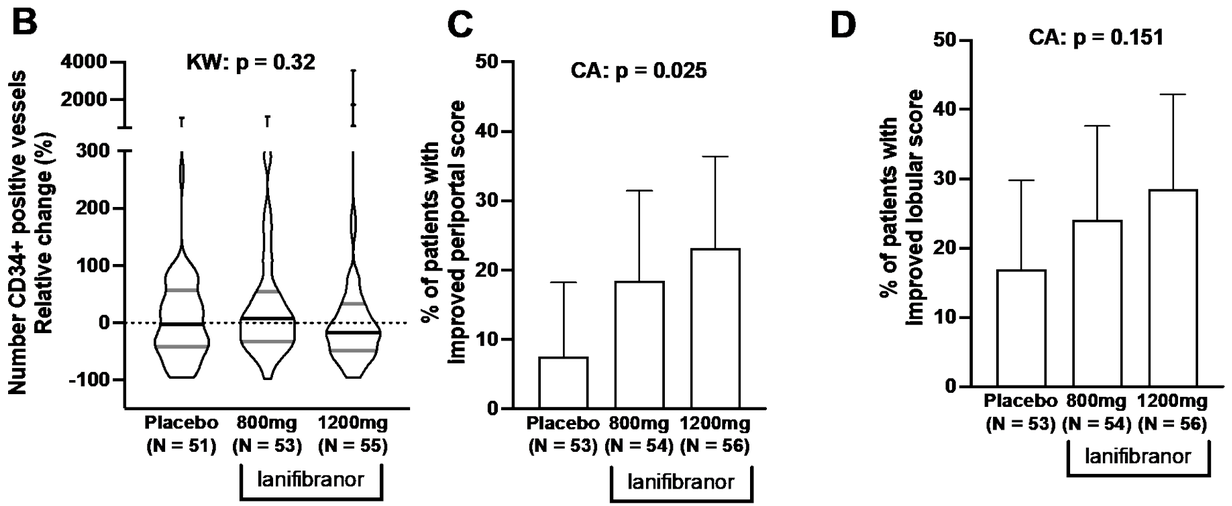


- CD34 positive staining is significantly linked to
  - the severity of liver fibrosis
  - the severity of liver inflammation

Rautou, Chotkoe …Francque. In preparation

Capillarisation of liver sinusoids in patients with MASH: effects of lanifibranor

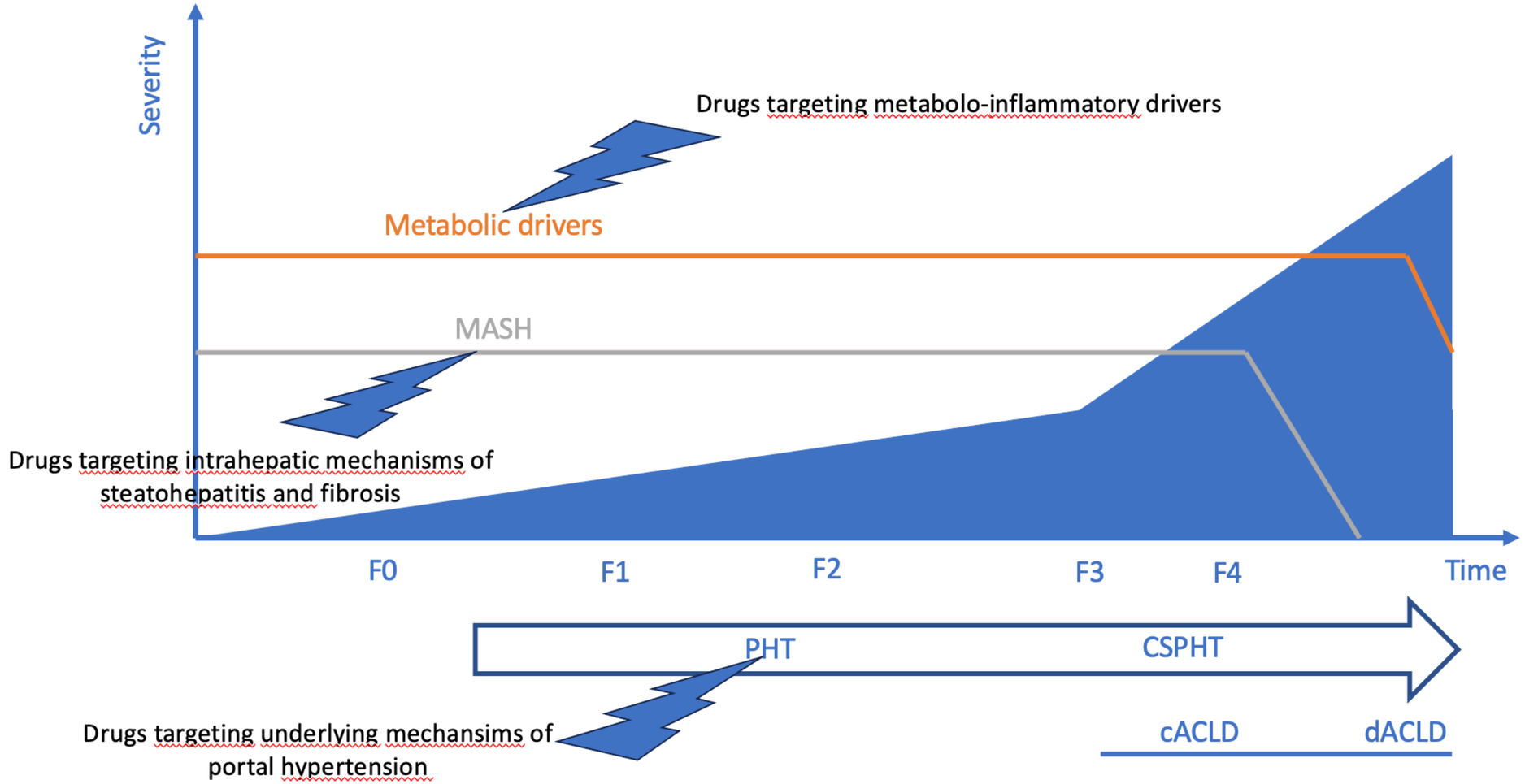




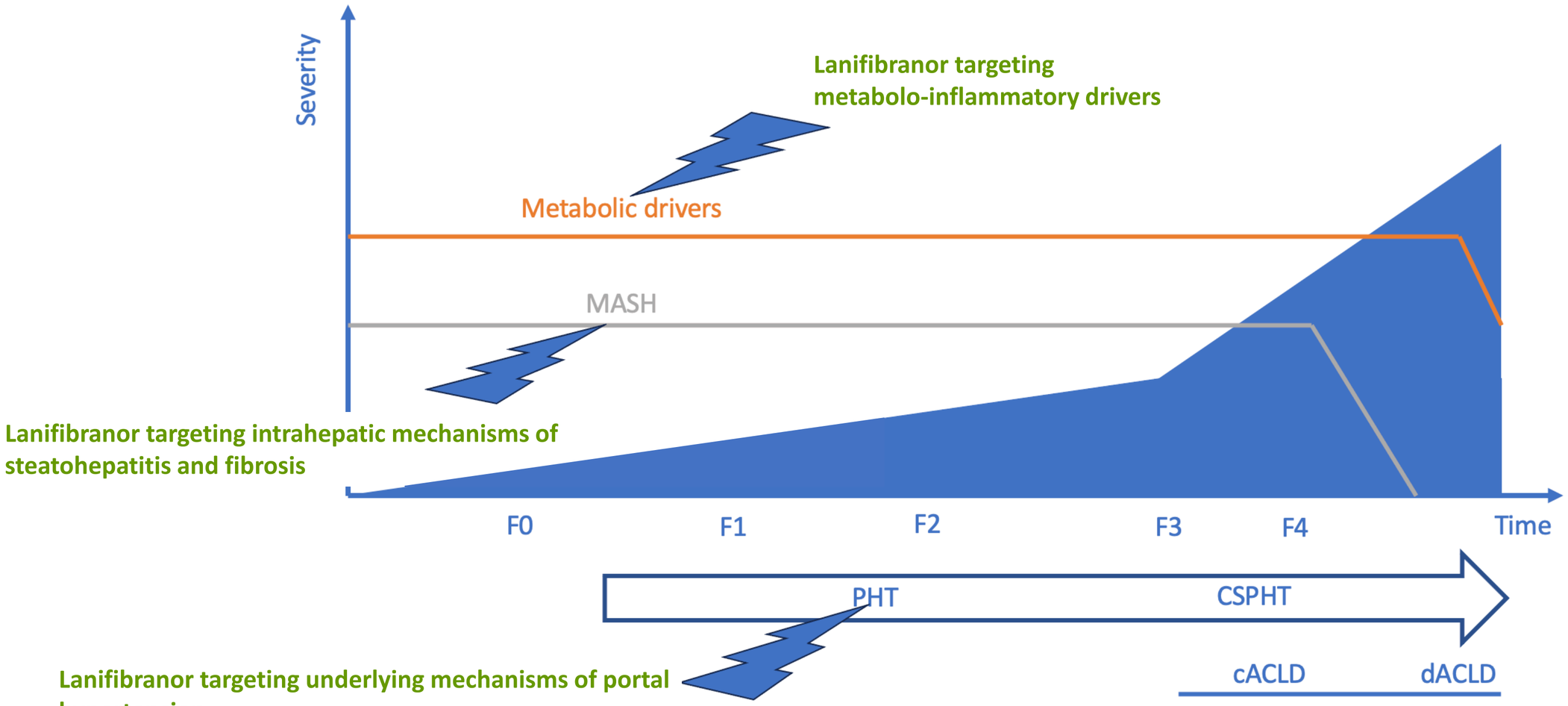
- Significant improvement in periportal CD34 score
- Trend with a dose effect in lobular CD34 score

Rautou, Chotkoe …Francque. In preparation

Mechanism to target across the disease spectrum



Mechanism to target across the disease spectrum



Conclusions

- MASLD is associated with vascular changes at all disease stages
  - Both structural and functional mechanisms
- 3 PPAR isotypes closely involved in liver vascular biology
- Lanifibranor
  - Efficacious on restoring liver vascular biology in animal models
  - Superior to mono-agonists
  - Clinical data on capillarisation suggest also clinical relevance
- Mechanisms and effect of lanifibranor are relevant along the disease spectrum
  - Pre-clinical data in cirrhosis/PHT models
  - Role of vascular mechanisms in advanced disease