



Endothelium as a driver of cirrhosis progression and target for therapy

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Disclosures

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He has acted as consultant for Abbvie, Actelion, Aelin Therapeutics, AgomAb, Aligos Therapeutics, Allergan, Alnylam, Astellas, Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol-Meyers Squibb, CSL Behring, Coherus, Echosens, Eisai, Enyo, Galapagos, Galmed, Genetech, Genfit, Gilead Sciences, Intercept, Inventiva, Janssens Pharmaceutica, Julius Clinical, Madrigal, Medimmune, Merck Sharp & Dome, NGM Bio, Novartis, Novo Nordisk, Promethera, Roche.

SF has been lecturer for Abbvie, Allergan, Bayer, Eisai, Genfit, Gilead Sciences, Janssens Cilag, Intercept, Inventiva, Merck Sharp & Dome, Novo Nordisk, Promethera, Siemens.

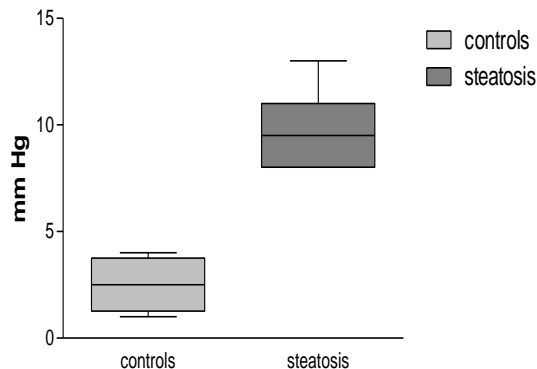
Hypothesis

based on observation of flow changes in steatosis

MASLD induces increase
intrahepatic vascular resistance
(leading to portal hypertension)
without significant fibrosis or
cirrhosis.

Francque *et al*, Liv Int 2010

Van der Graaff, Kwanten, Francque. Med Hypotheses 2017

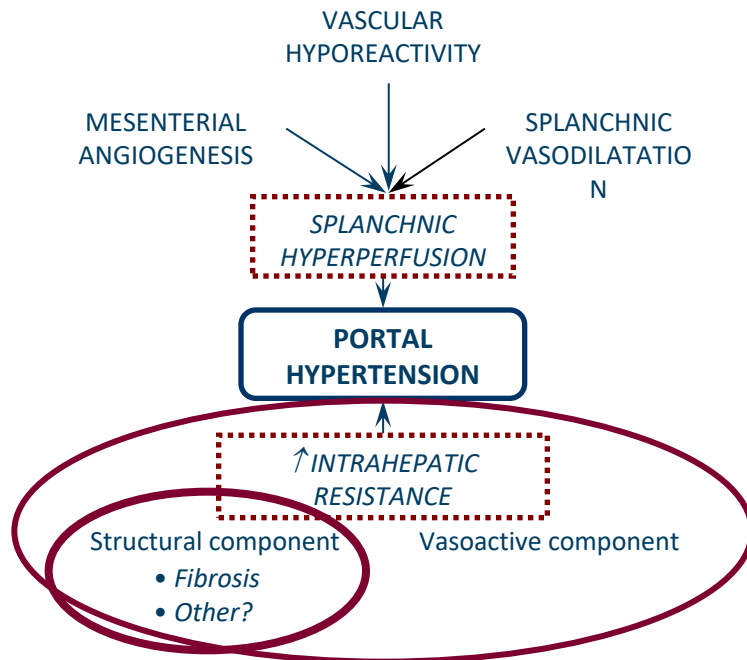


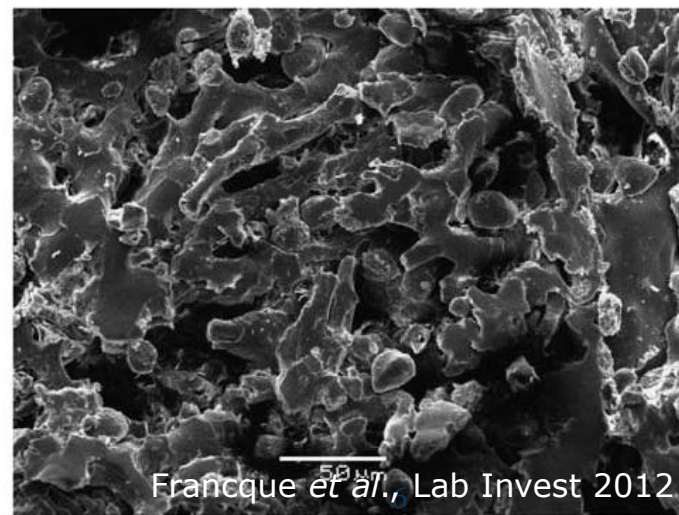
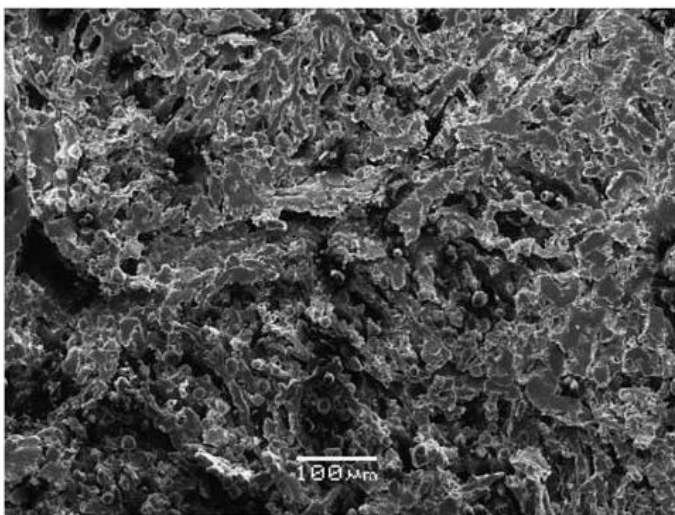
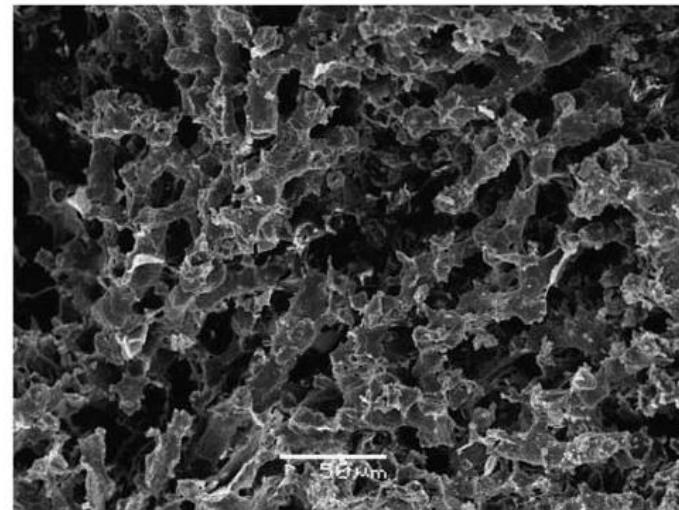
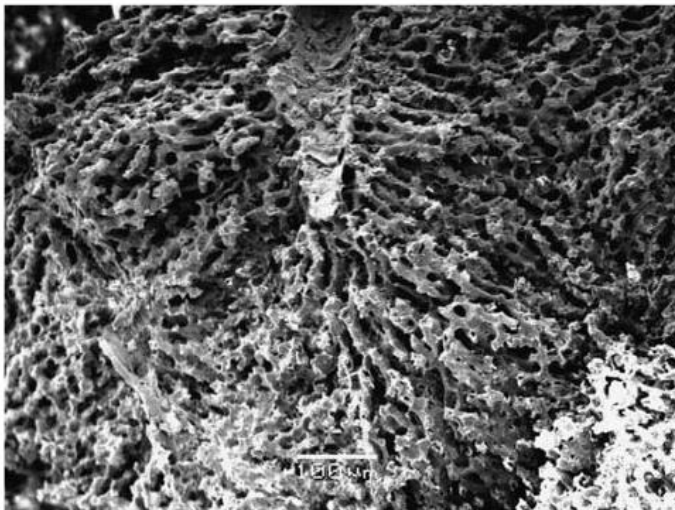
Conclusions data in MCD model

- Severe non-fibrotic MASLD is accompanied by a significant rise in portal pressure.
- The PHT develops with severe steatosis and precedes inflammatory changes.

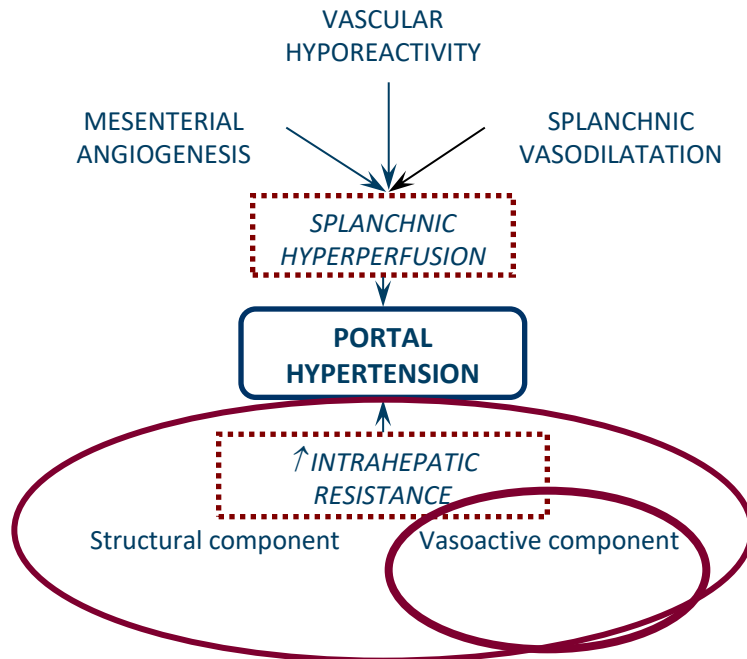
Francque *et al*, Liv Int 2010
Francque *et al*., Lab Invest 2012

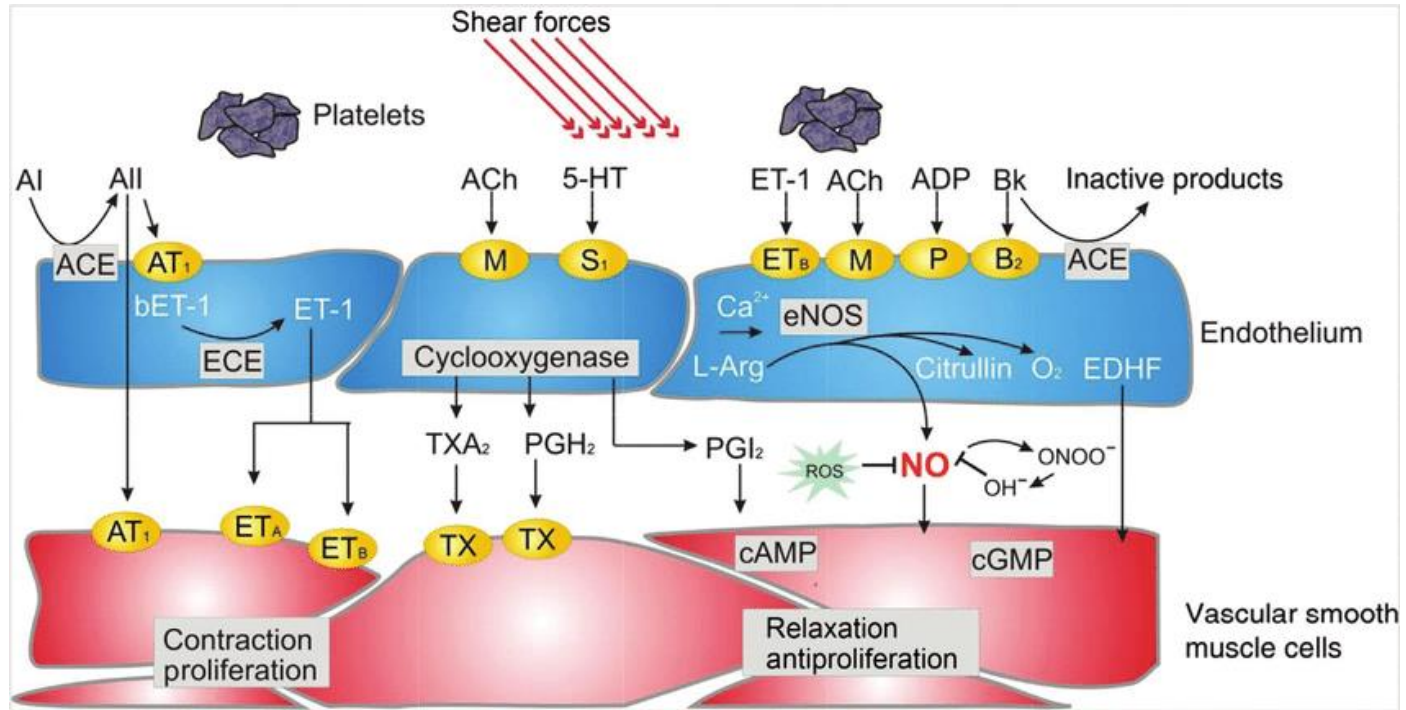
Portal Hypertension



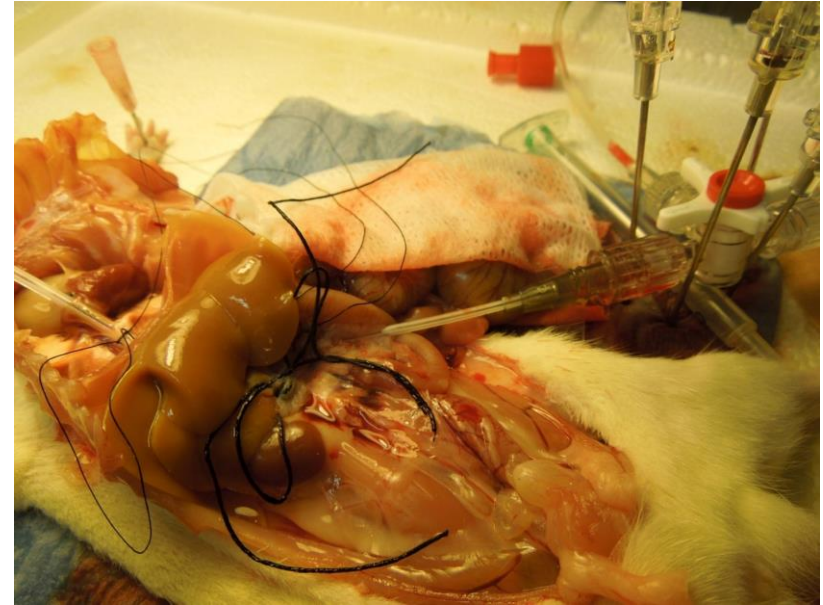
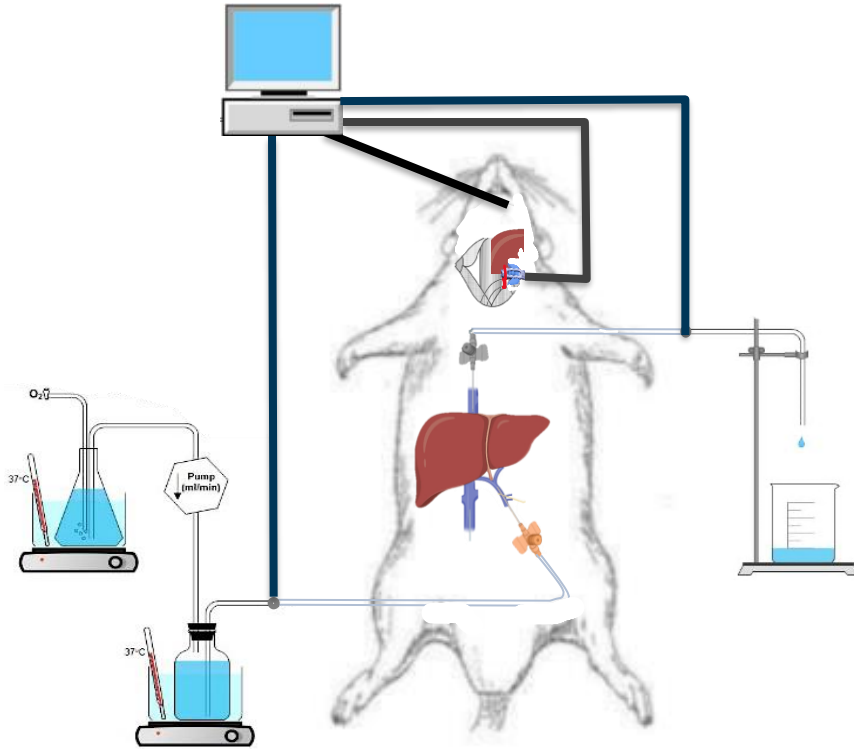


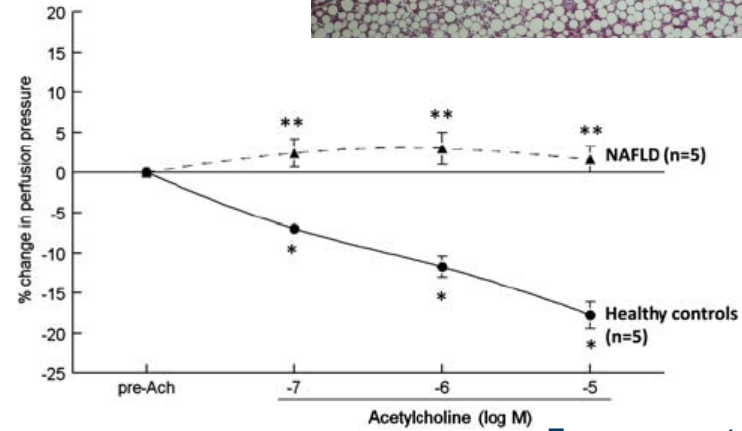
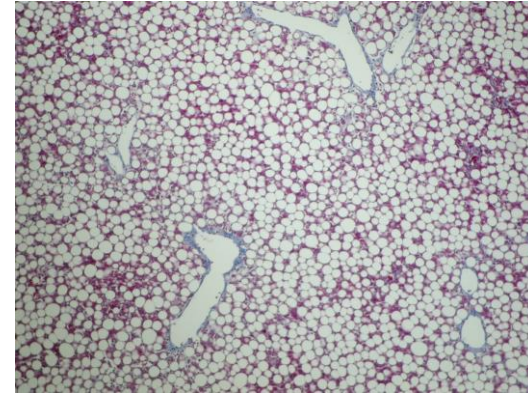
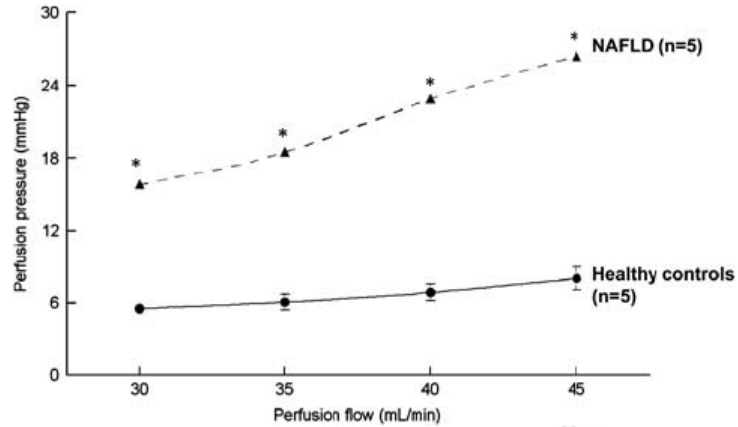
Portal Hypertension



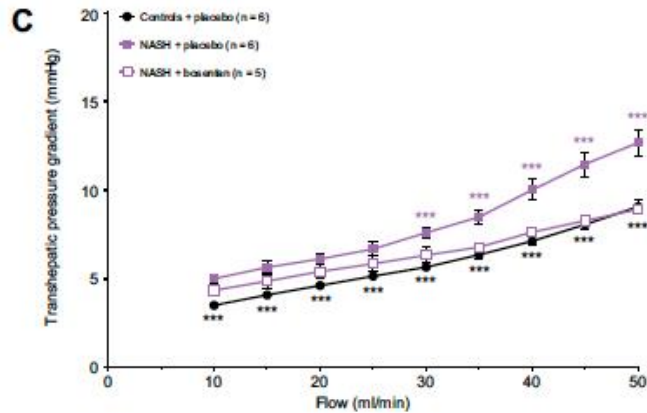
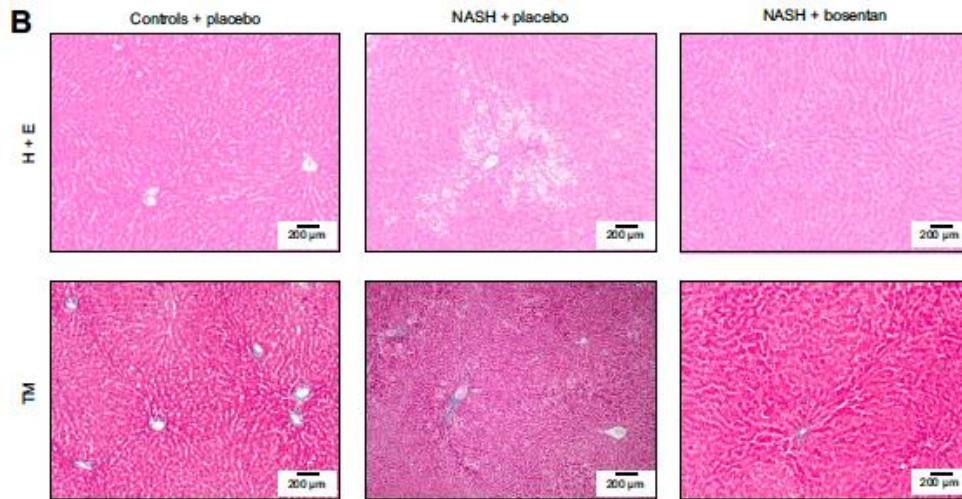


Goodwill, Tune. Comprehensive Physiology 2017

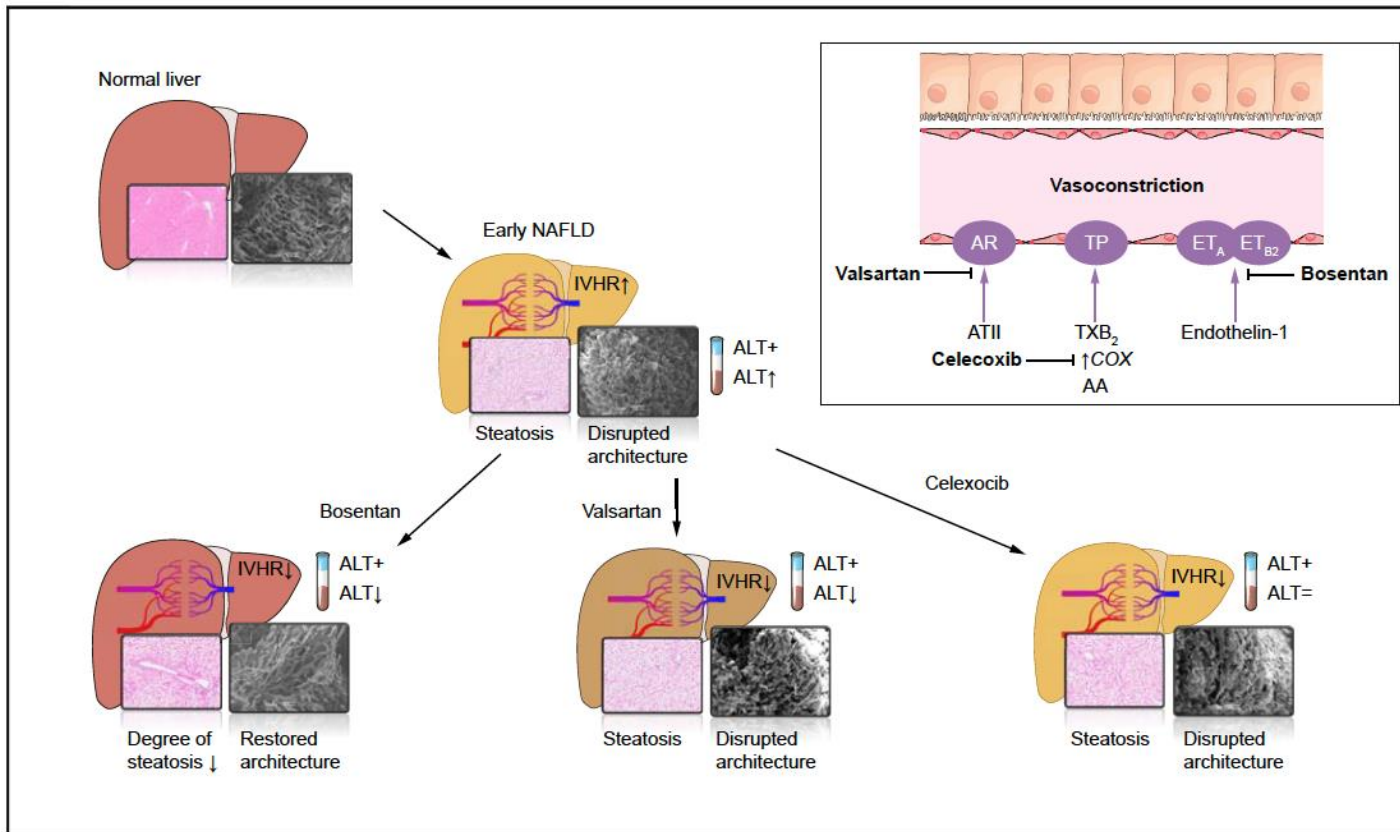




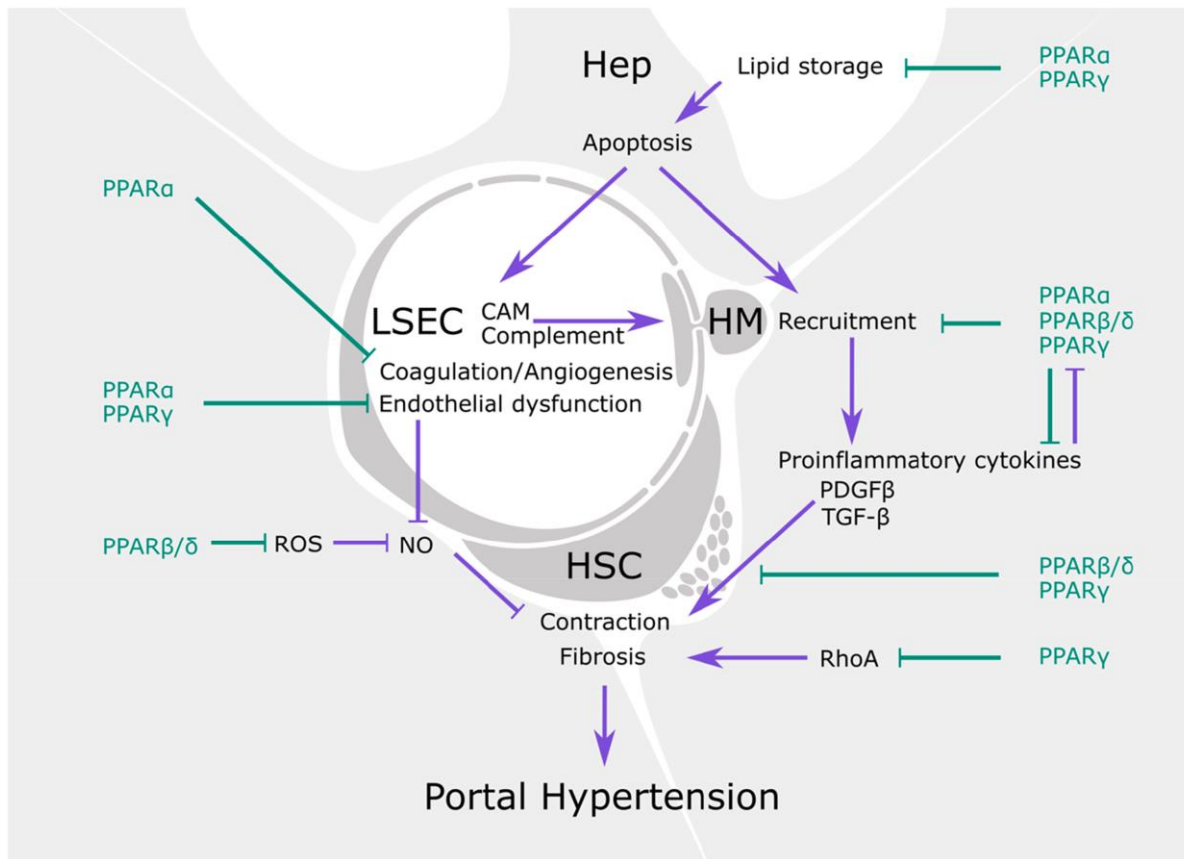
Francque *et al.*, Lab Invest 2012



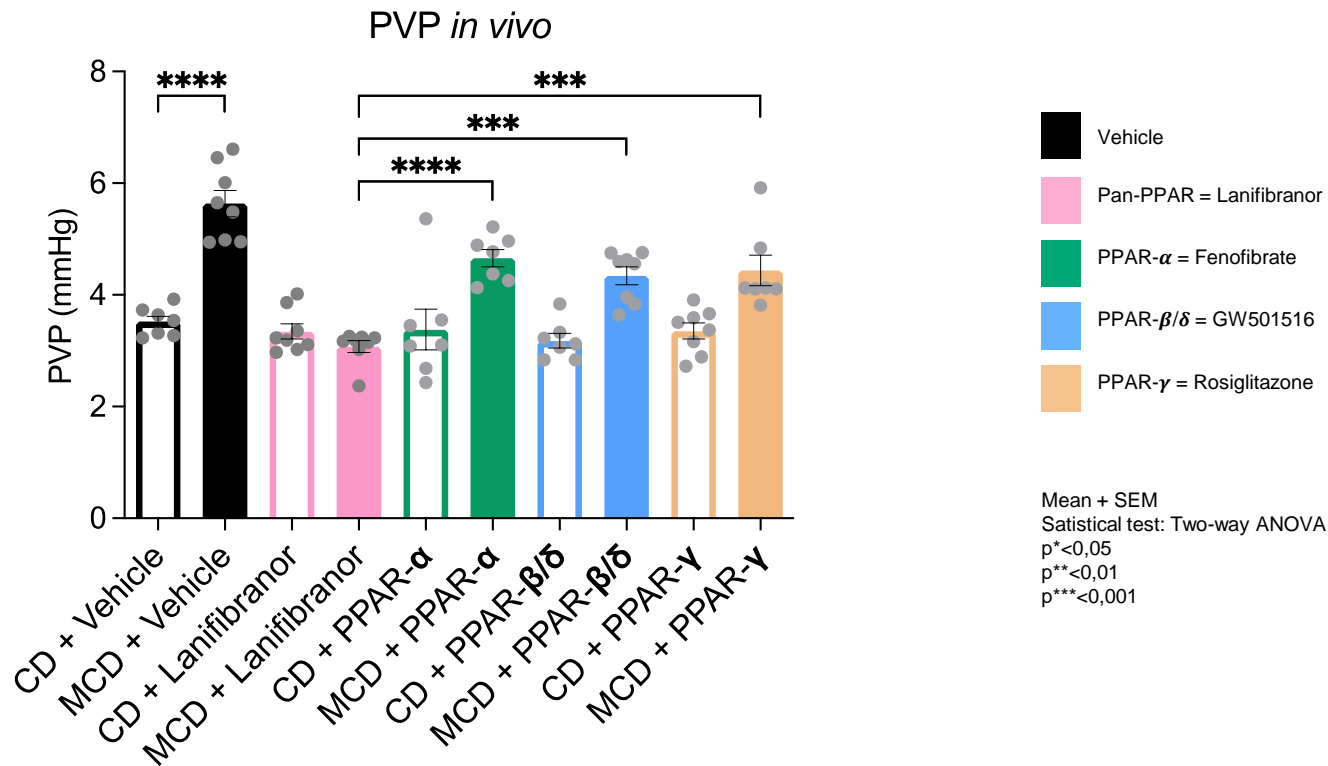
Van der Graaff, Francque *et al.* J Hep Rep 2022



Van der Graaff, Francque *et al.* J Hep Rep 2022

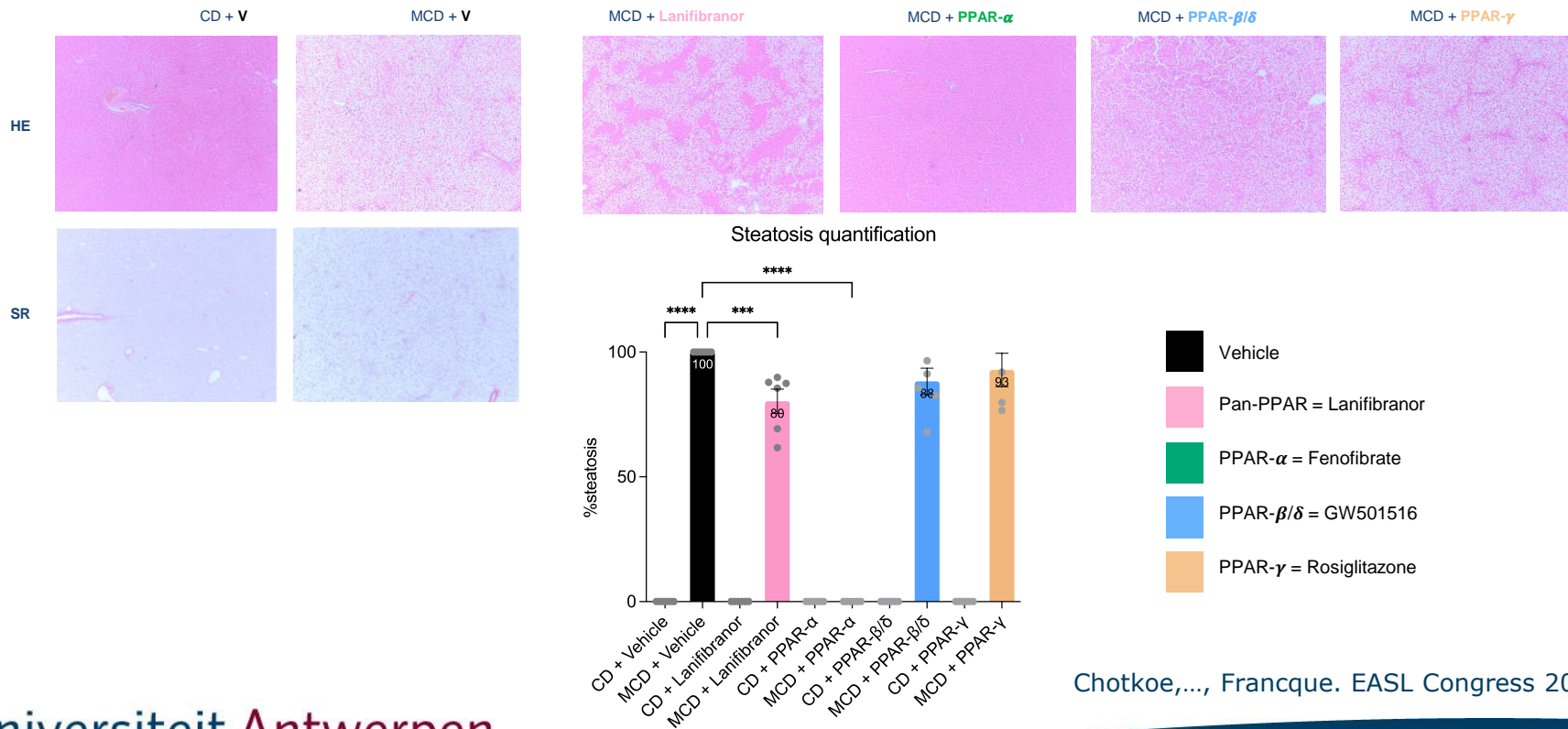


Guixé-Muntet... Francque...Gracia-Sancho. AP&T 2022



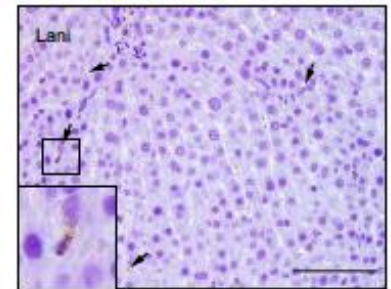
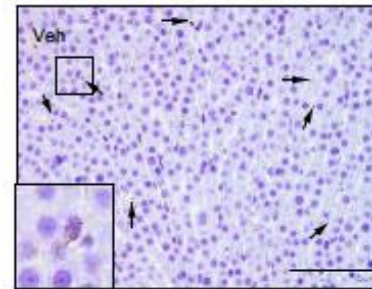
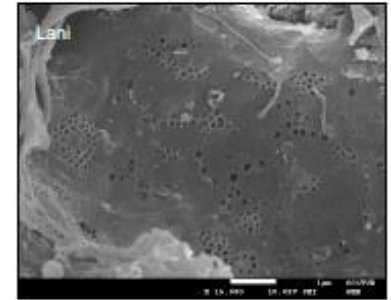
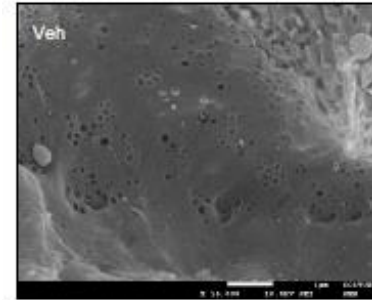
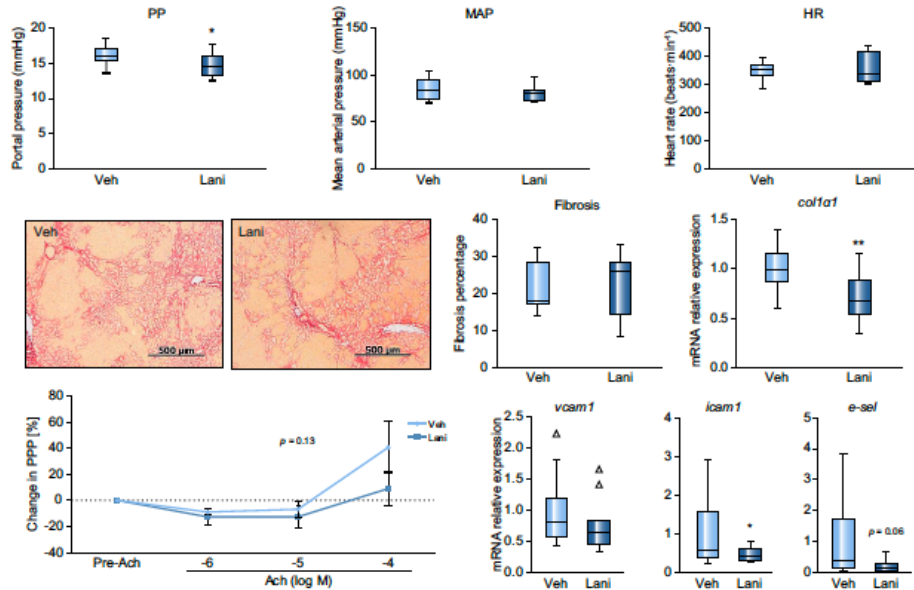
Chotkoe,..., Francque. EASL Congress 2024

Effect of PPAR agonists in MASLD; Liver histology H&E, and Sirius red staining



Chotkoe,..., Francque. EASL Congress 2024

Lanifibranor and PHT in cirrhosis

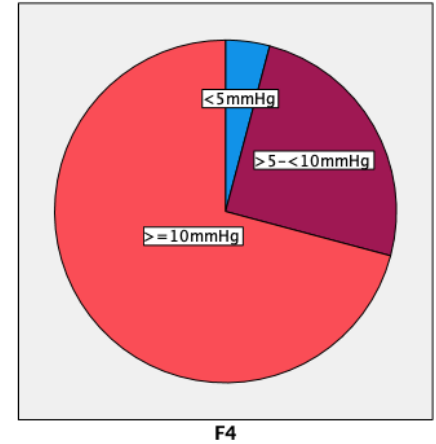
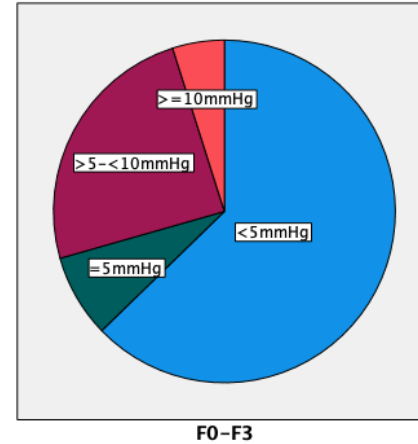
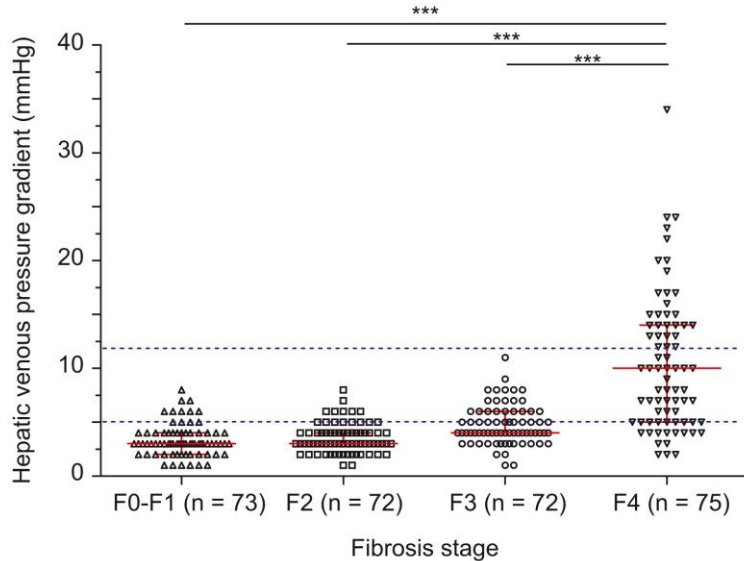


Boyer-Diaz *et al*, J Hep 2021

Clinically relevant?

Portal Hypertension in non-cirrhotic MASLD

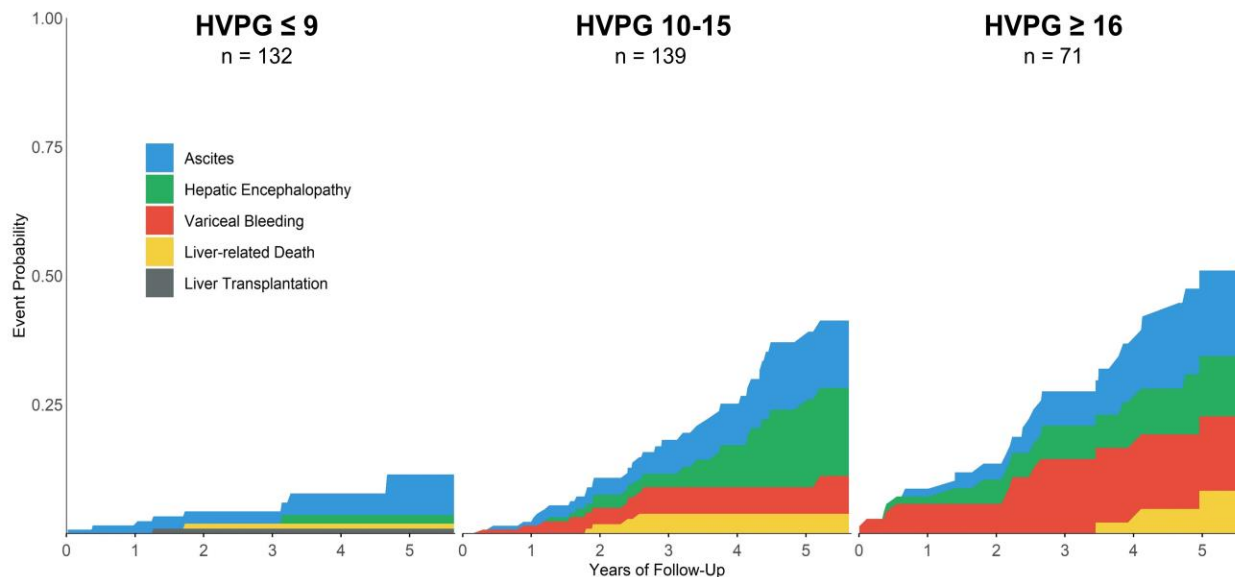
Early MASLD, without cirrhosis, can already lead to portal hypertension



Moga *et al.* J Hep 2021

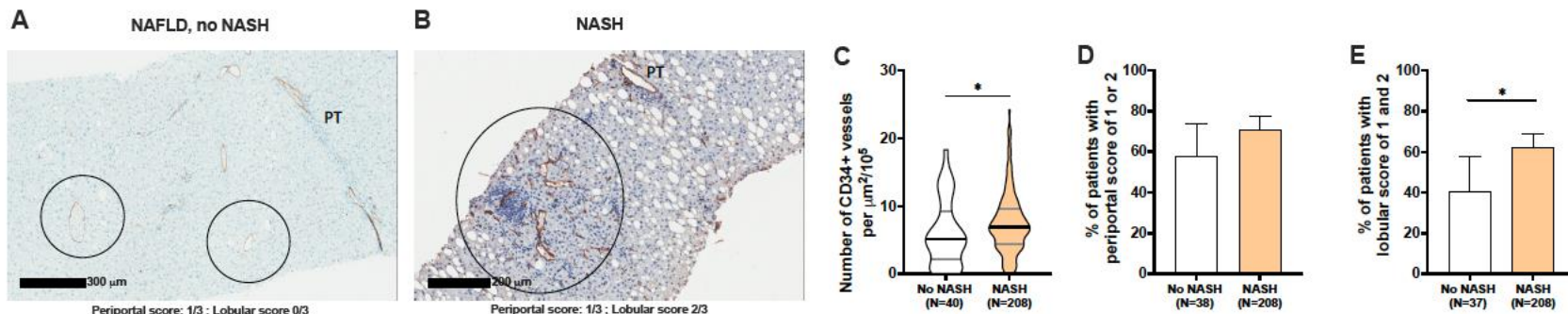
Geens, Gestels, ... Francque. SLD SUMMIT 2023

Clinical data in follow-up



Paternostro R, Francque S *et al.* J Hep 2024

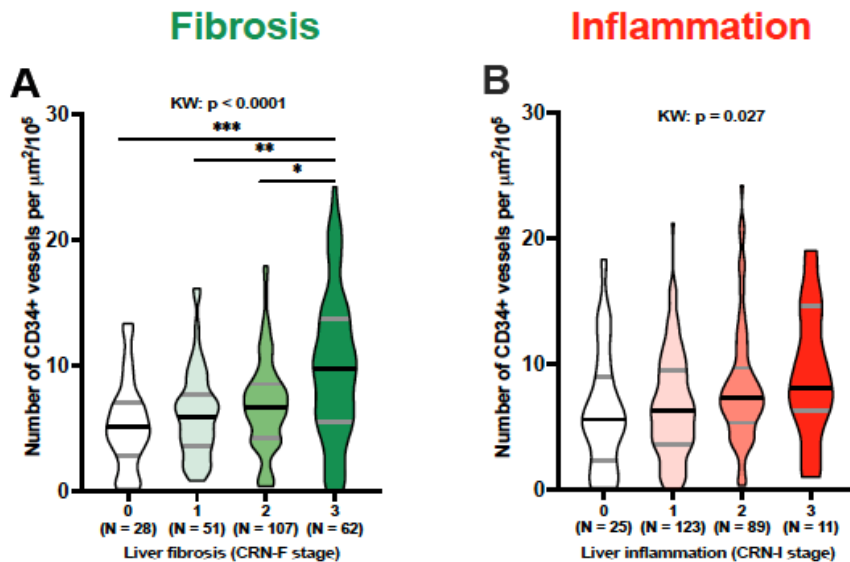
LSEC capillarisation



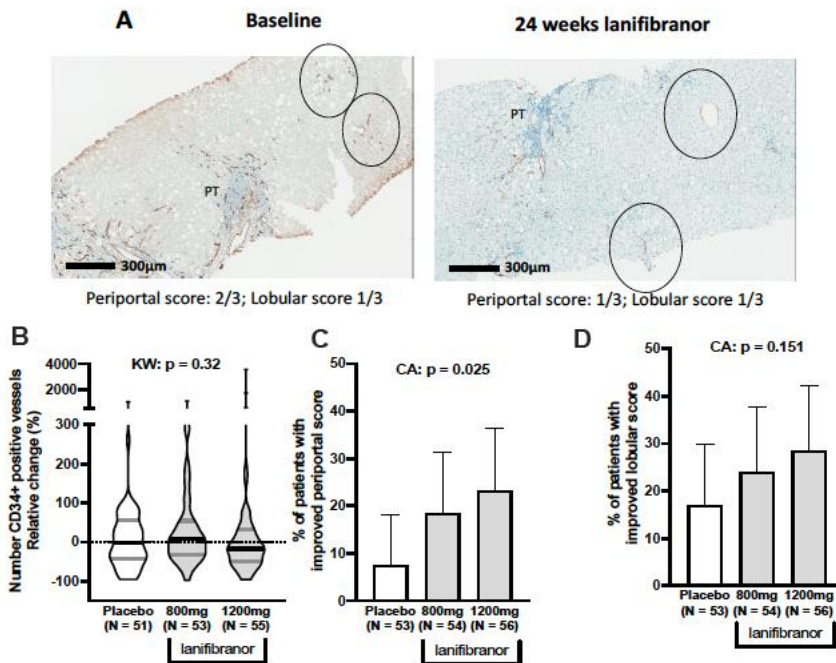
CD34 staining on slides from the NATIVE clinical trial (Phase 2b)

- 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, Francque *et al.* AASLD 2021

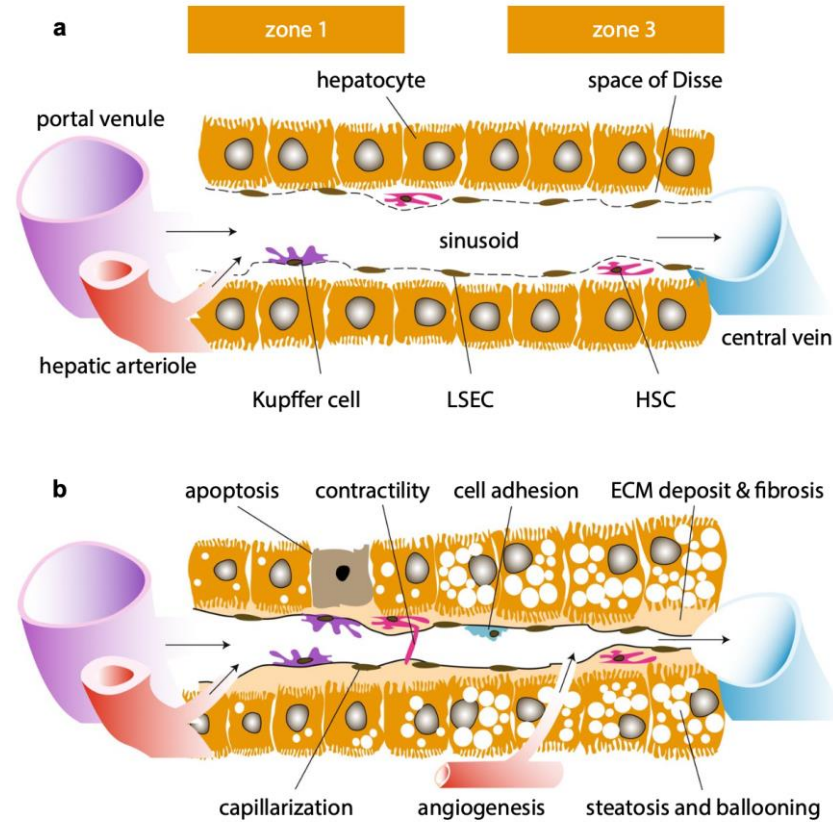


- CD34 positive staining is significantly linked to
 - the severity of liver fibrosis
 - the severity of liver inflammation



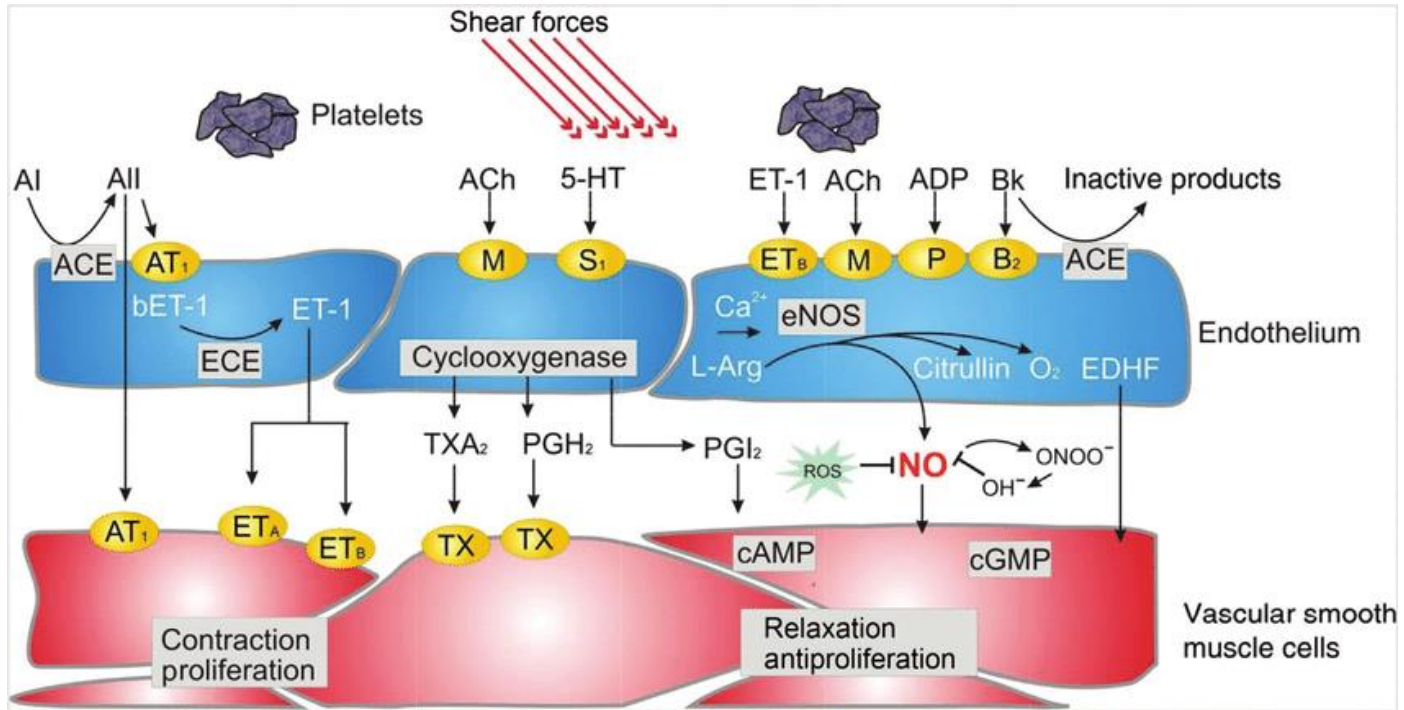
- Significant improvement in periportal CD34 score
- Trend with a dose effect in lobular CD34 score

Rautou, Francque *et al.* AASLD 2021



Baffy G. Dig Dis Sci 2018

What about platelets?

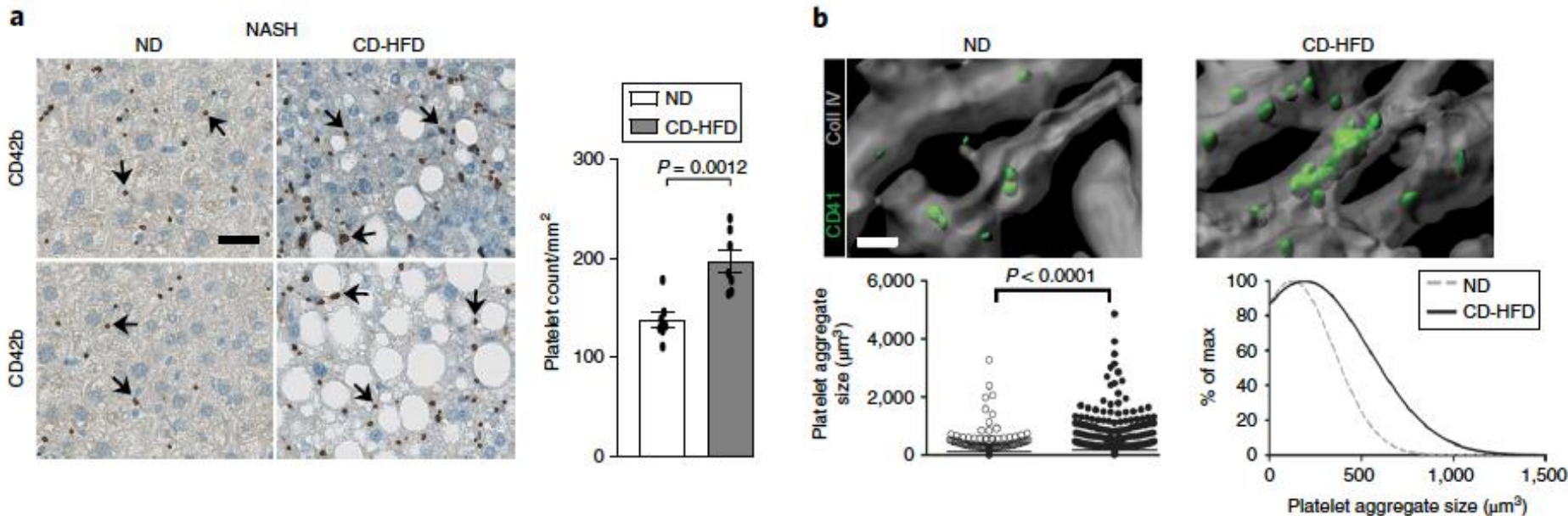


Goodwill, Tune. Comprehensive Physiology 2017

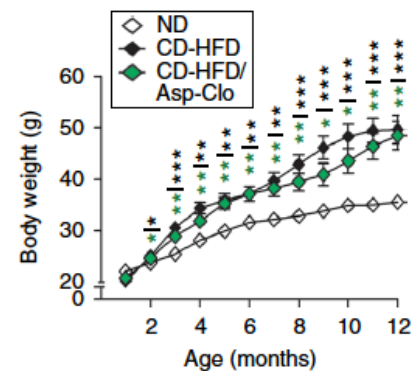
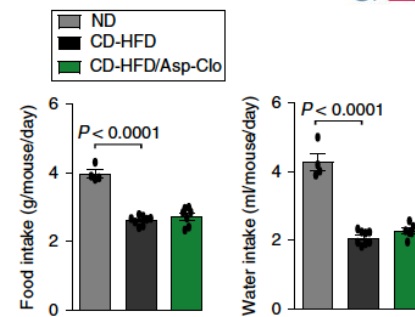
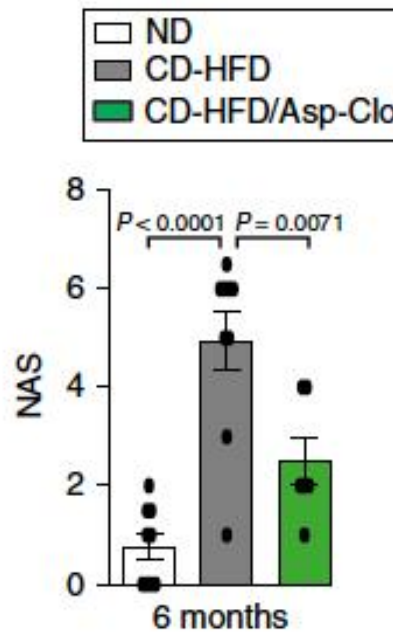
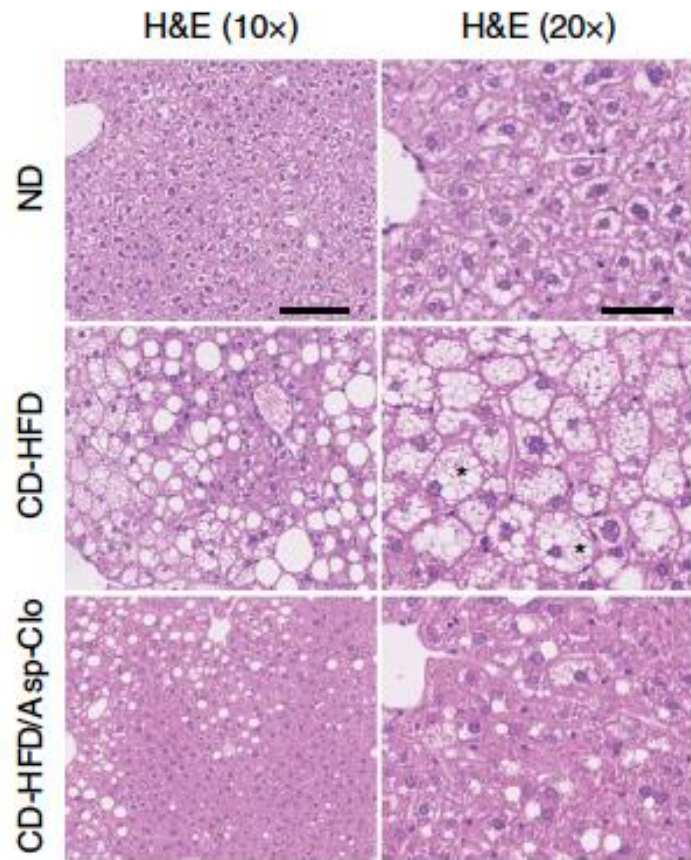


Preclinical data

In several models of MASH but not in isolated steatosis



Malehmir *et al.* Nature Med 2019

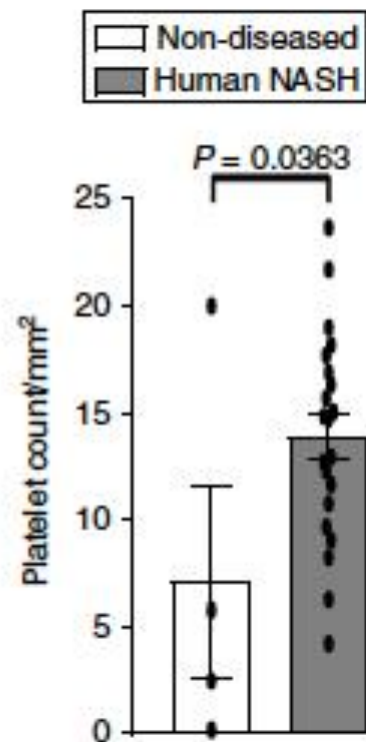
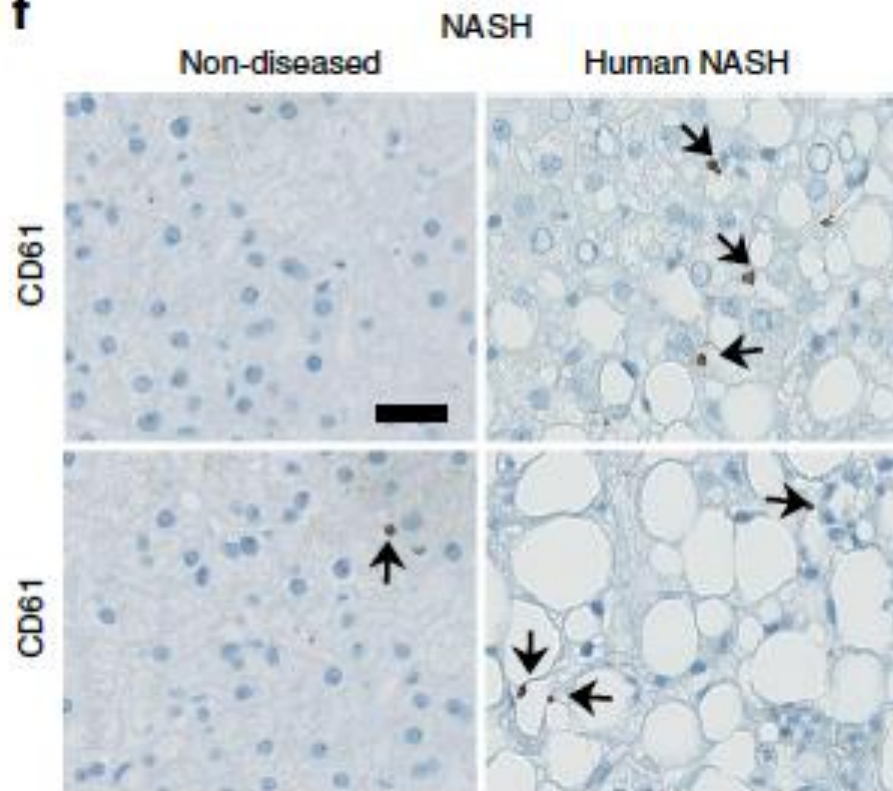


Malehmir et al. Nature Med 2019



Clinical data

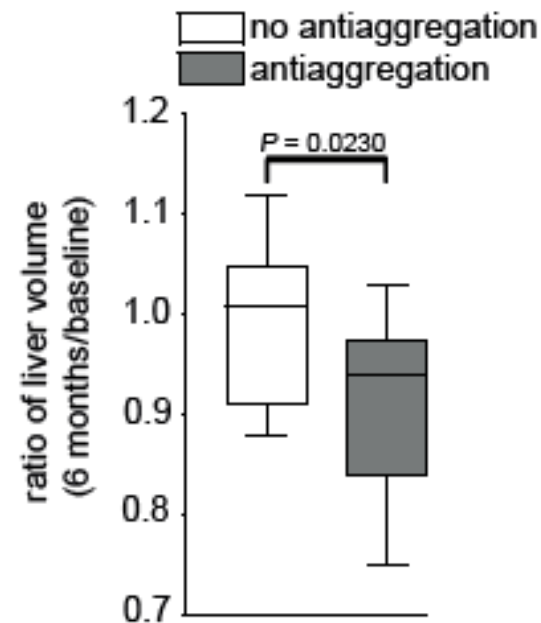
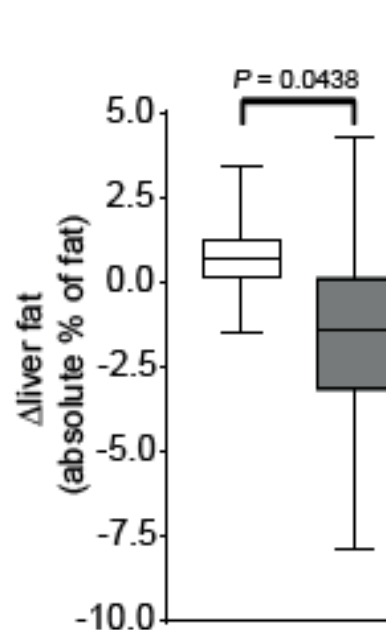
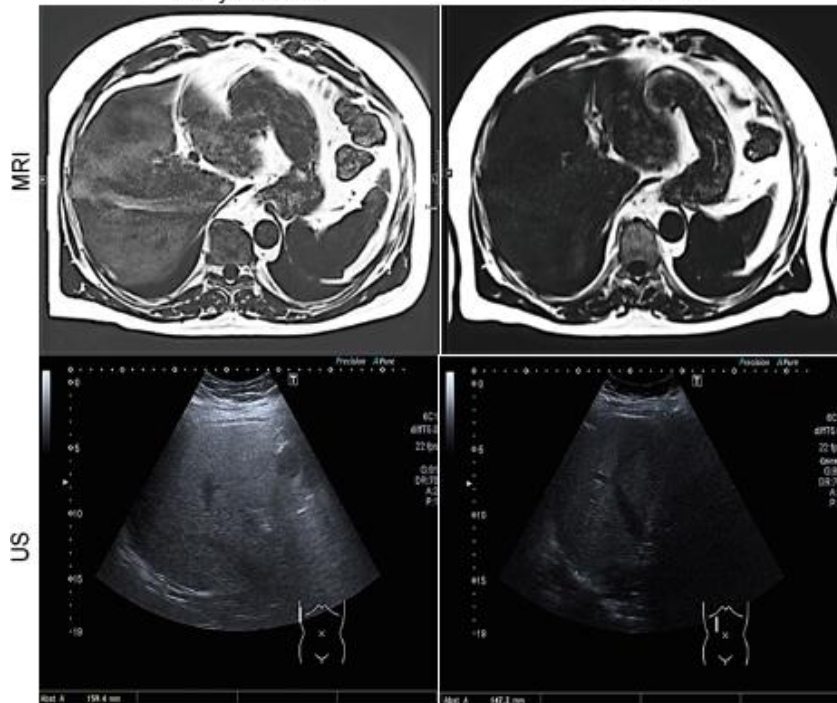
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Malehmir et al. Nature Med 2019

Study inclusion

After 6M of APT



Malehmir et al. Nature Med 2019

Phase 2 RCT

- 40/40 aspirin 80 mg vs. PBO for 6 m
- Primary endpoint
 - liver fat content absolute change by MRS

Simon *et al.* JAMA 2024

PRIMARY END POINT

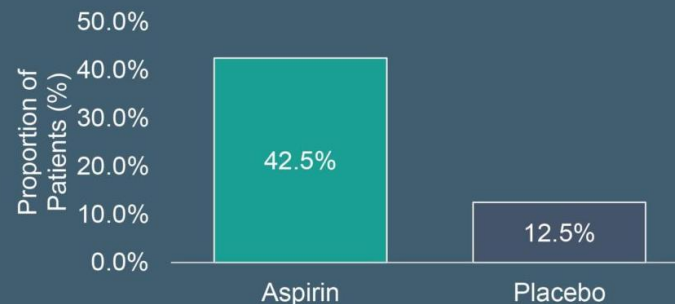
Mean absolute change in hepatic fat content at 6 months, measured by proton magnetic resonance spectroscopy (MRS)



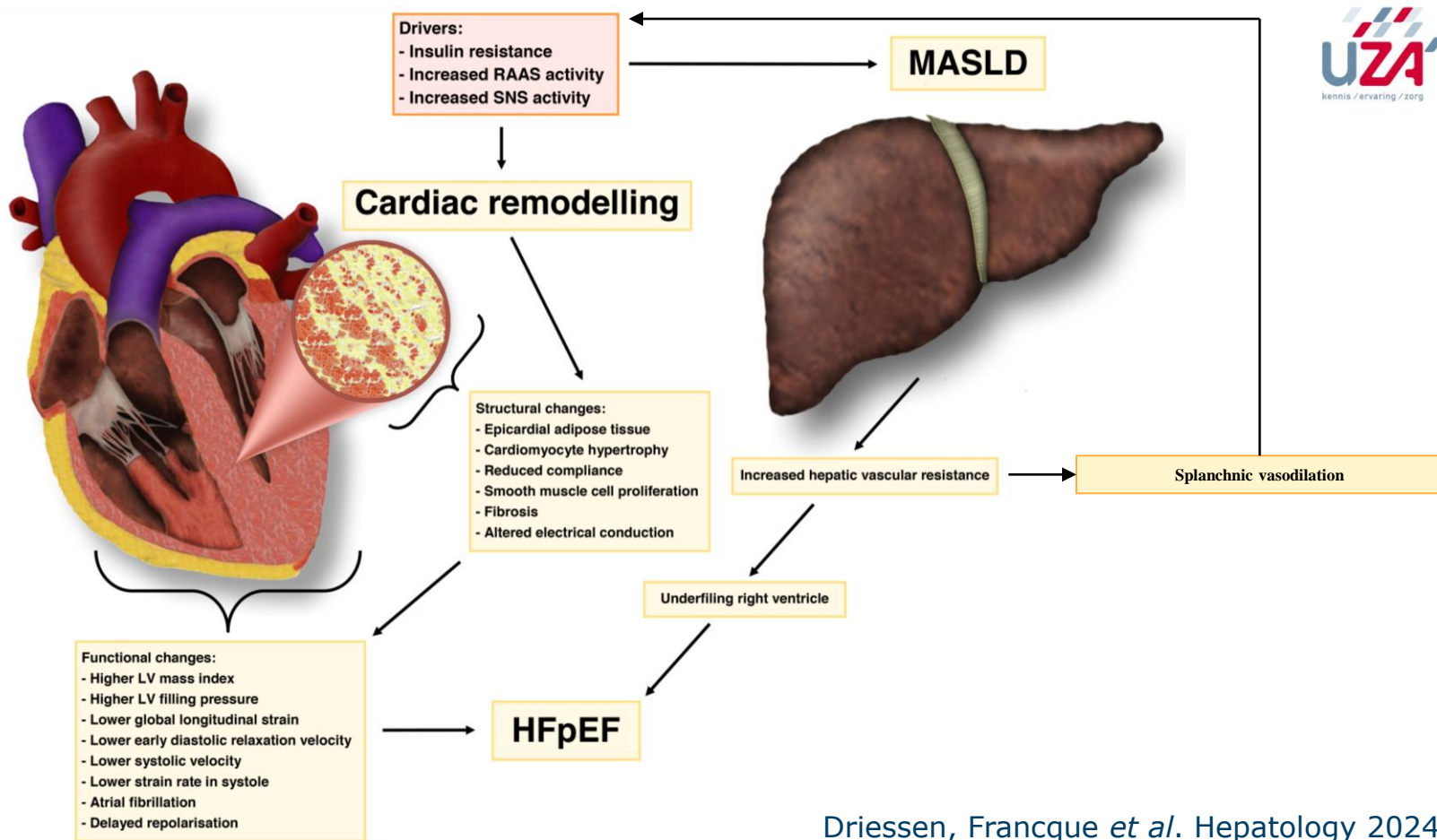
Difference -10.2% 95% CI, -27.7% to -2.6%
P = 0.009

SECONDARY END POINTS

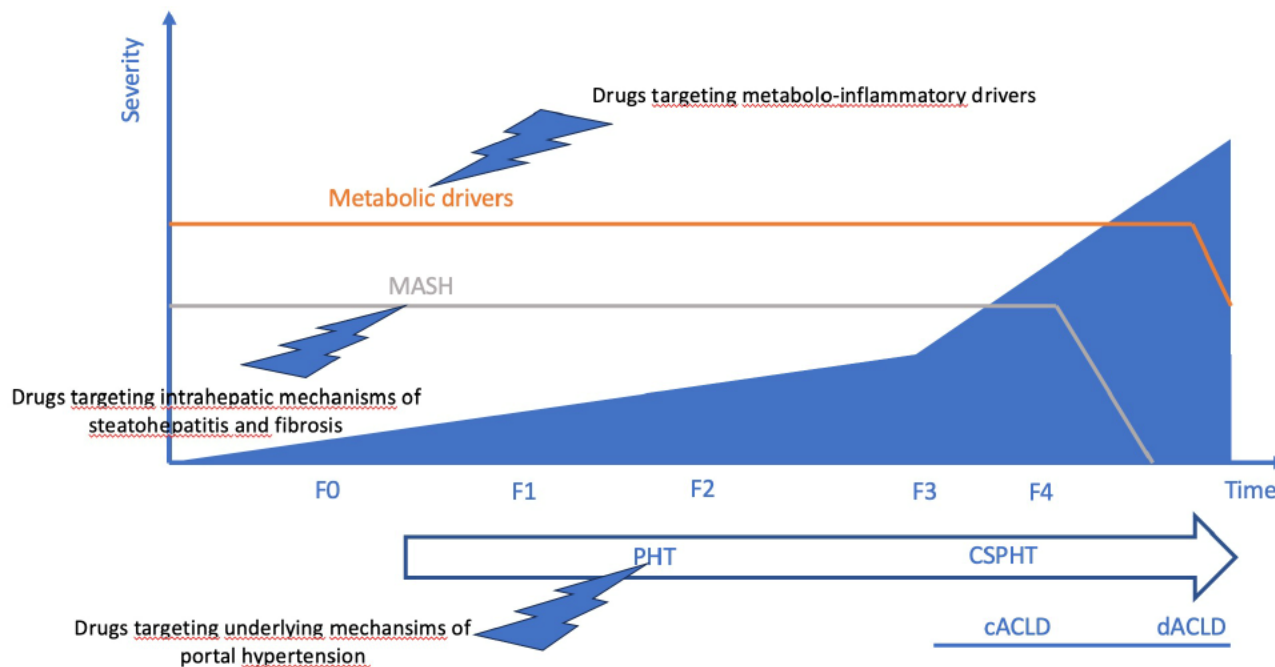
Proportion of patients with 30% or greater relative reduction in hepatic fat content



Mean Difference -30.0% 95% CI, 11.6% to 48.4%
P = 0.006



Driessen, Francque et al. Hepatology 2024



Pericas J... Francque S et al. Nat Rev Gastro Hep 2024

Conclusions

- Intrahepatic vascular resistance increased in MASLD
 - Structural and functional mechanism (endothelin, PPAR)
 - Potentially leading to hypoxia triggering disease progression
- Clinically relevant in patients with MASH
 - Some degree of PHT by HVPG in early MASLD
 - PHT in MASH cirrhosis
 - Different from viral hepatitis and ALD?
 - HVPG tends to underestimate real portovenous pressure gradient
- Potential role of drugs
 - targeting vasoactive mechanisms
 - platelets and antiaggregant therapy
- Role in HFpEF?



EASL

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23-25 January

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easl.eu/sld2025