Challenges and Opportunities in Drug Development for NASH with a focus on fibrosis

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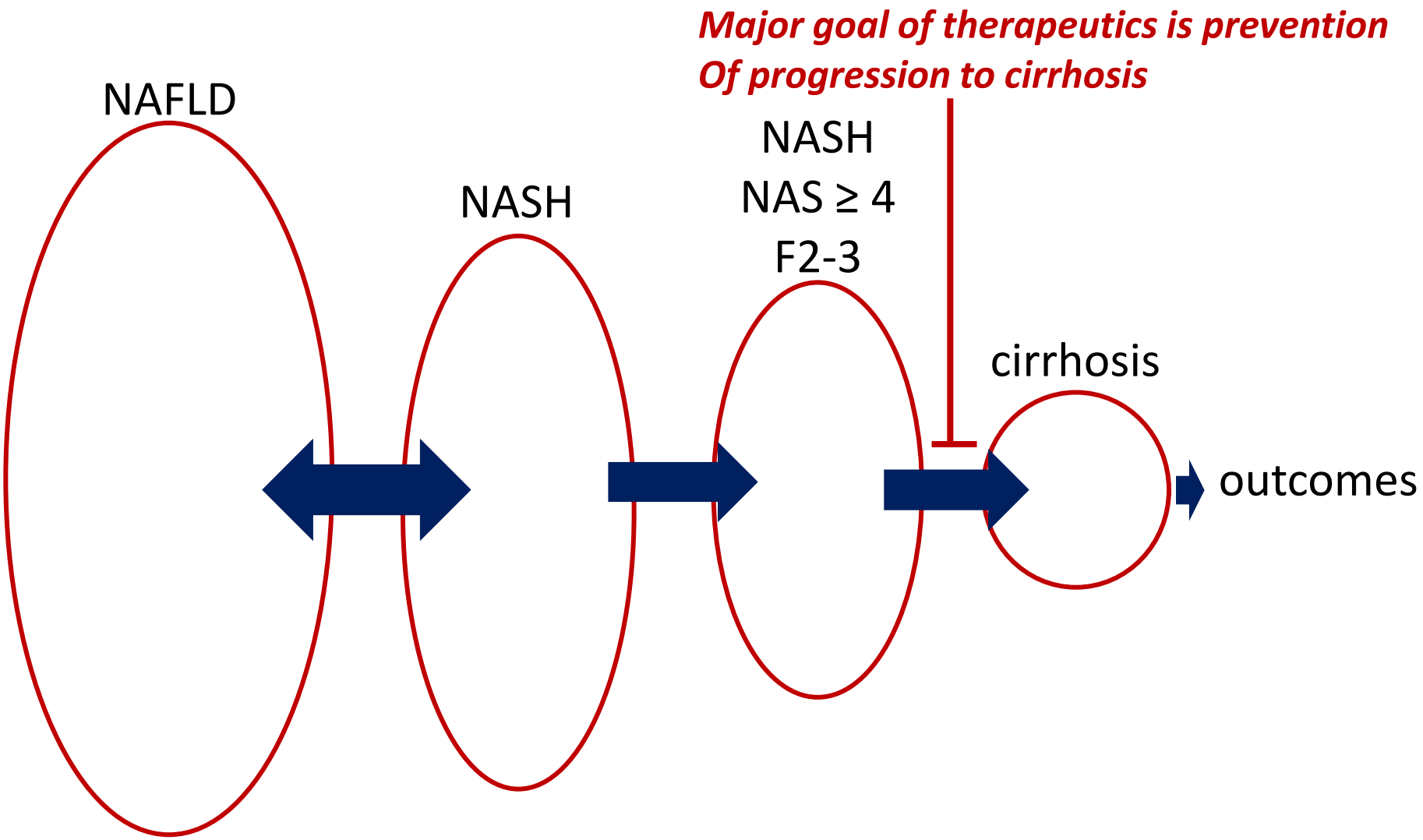
Current paradigms



Current development pathway in NASH

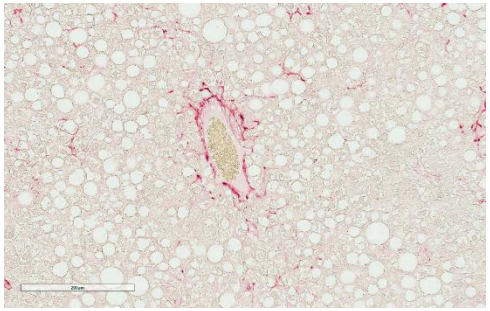
- Subpart H:
  - Resolution of steatohepatitis
  - Decrease in NAFLD activity score
  - Reduced fibrosis
- Post subpart H:
  - Reduced progression to cirrhosis

Challenging current dogma

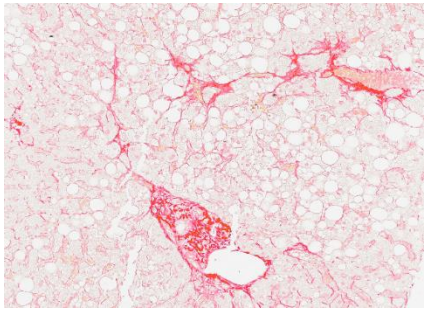
- Anchoring drug development on histology
- Activity scores versus fibrosis
- Assessment of changes in activity
- Assessment of fibrosis

Current fibrosis staging systems

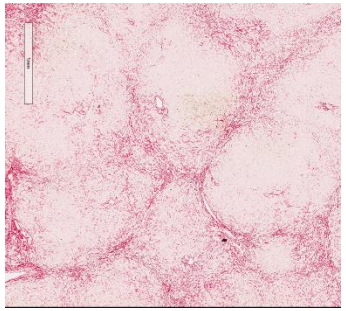
Stage 1



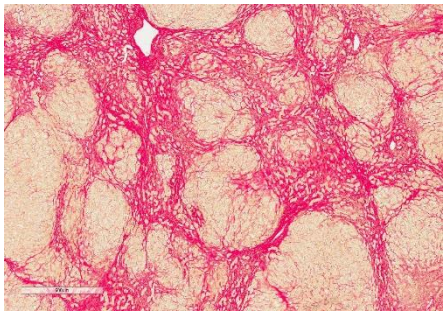
Stage 2



Stage 3



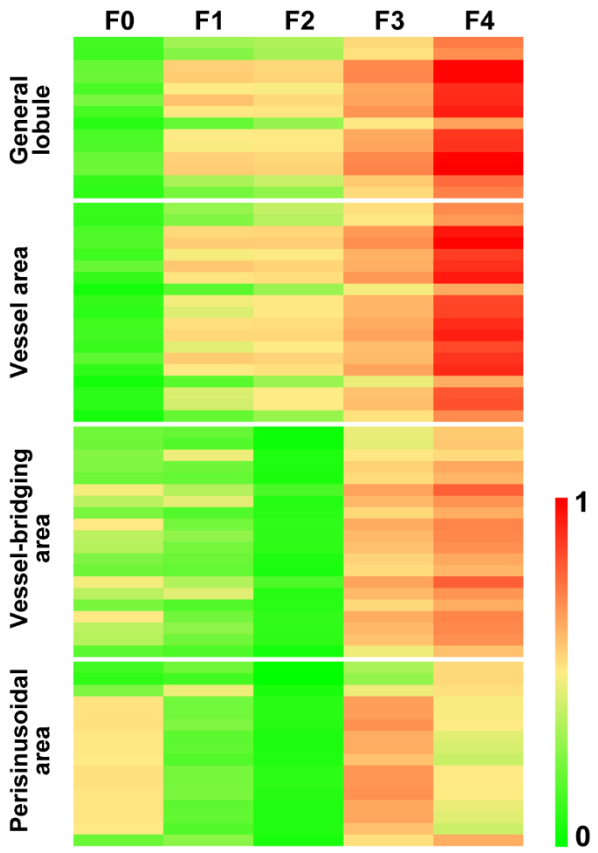
Stage 4

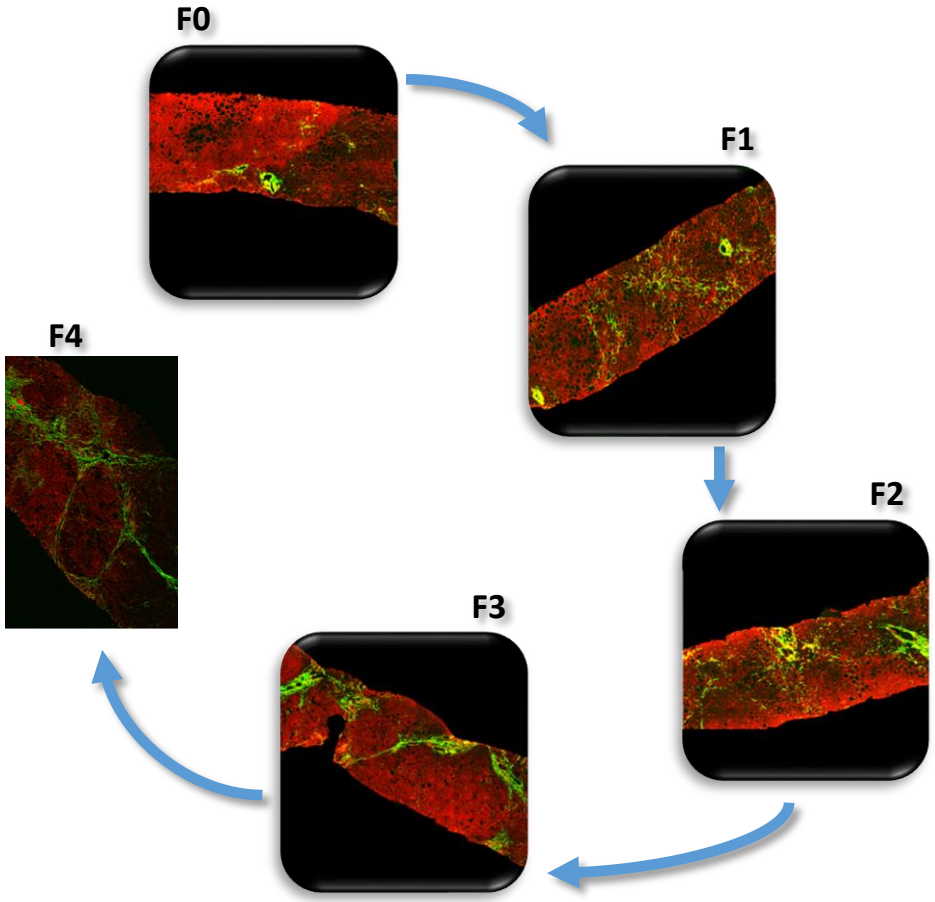


- *Stage 1 and 2 measure distribution more than amount*
- *Stage 3 and 4 measure distribution and amount*
- *How does stage 2 (sinusoidal and portal) progress to sinusoidal-sinusoidal vs sinusoidal-portal bridge?*
- *Ordinal binning of a continuous process*

Histology- courtesy Pierre Bedossa

Newer methods for quantitative assessment of fibrosis

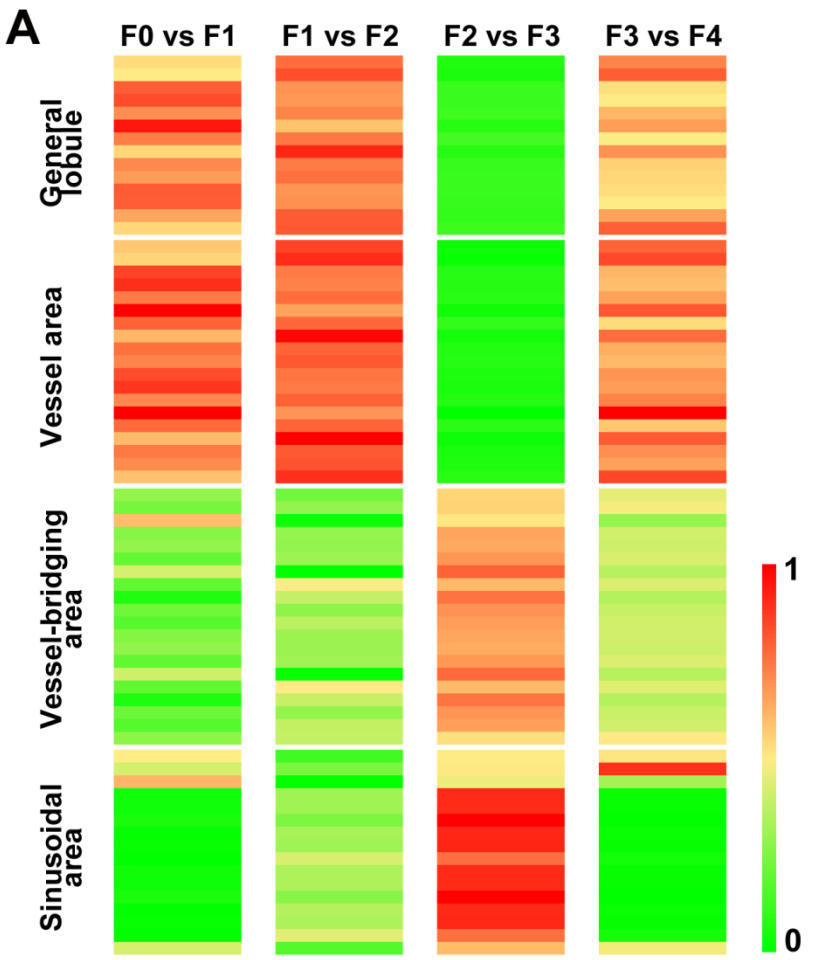


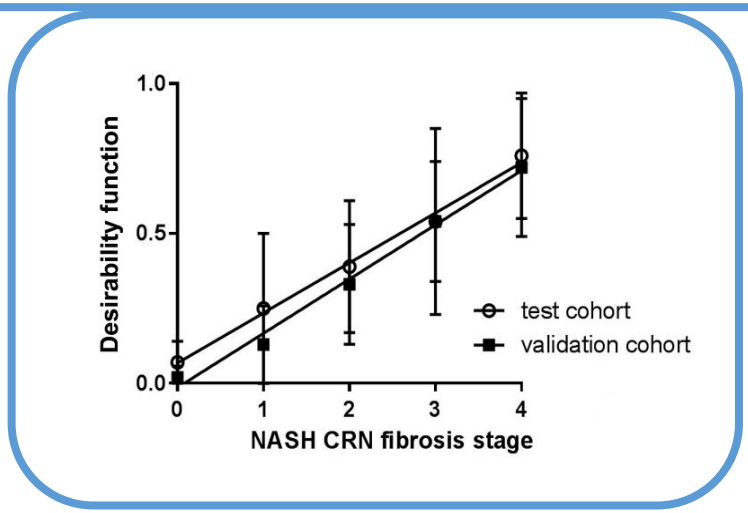


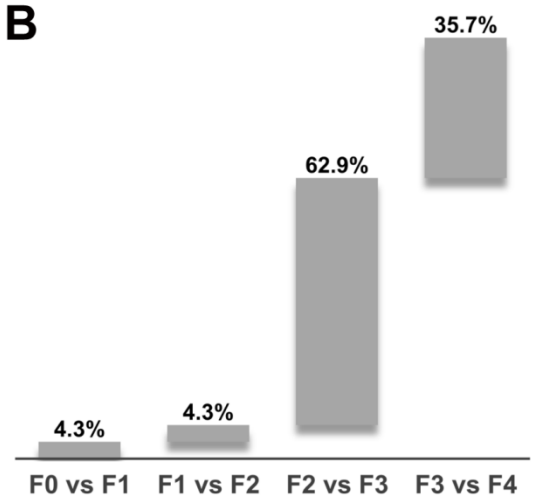
Wang et al, Hepatology 2017

Differential collagen fibrillar characteristic changes with disease progression

q-FP Desirability Index= $(d_1 \times d_2 \times \ldots \times d_4)^{1/4}$

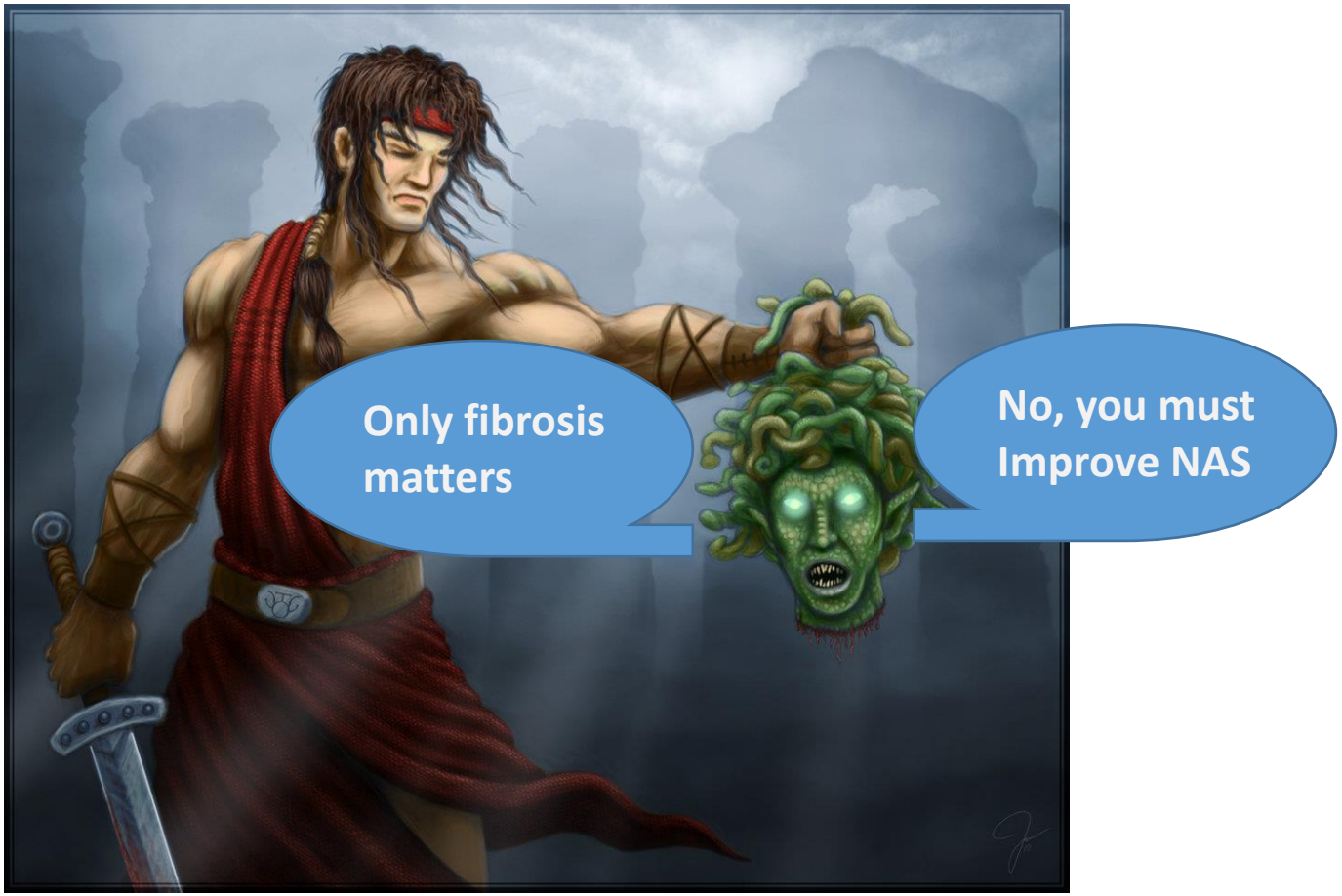






Wang et al, Hepatology 2017

The activity vs fibrosis debate



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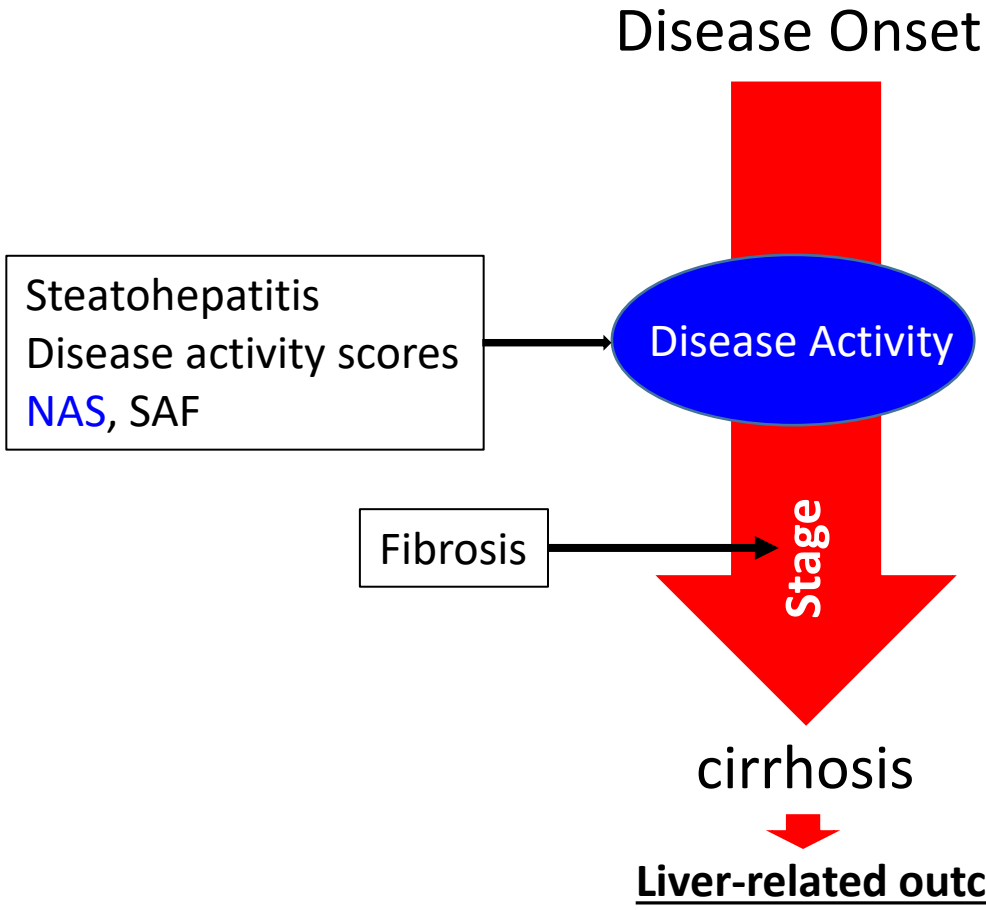
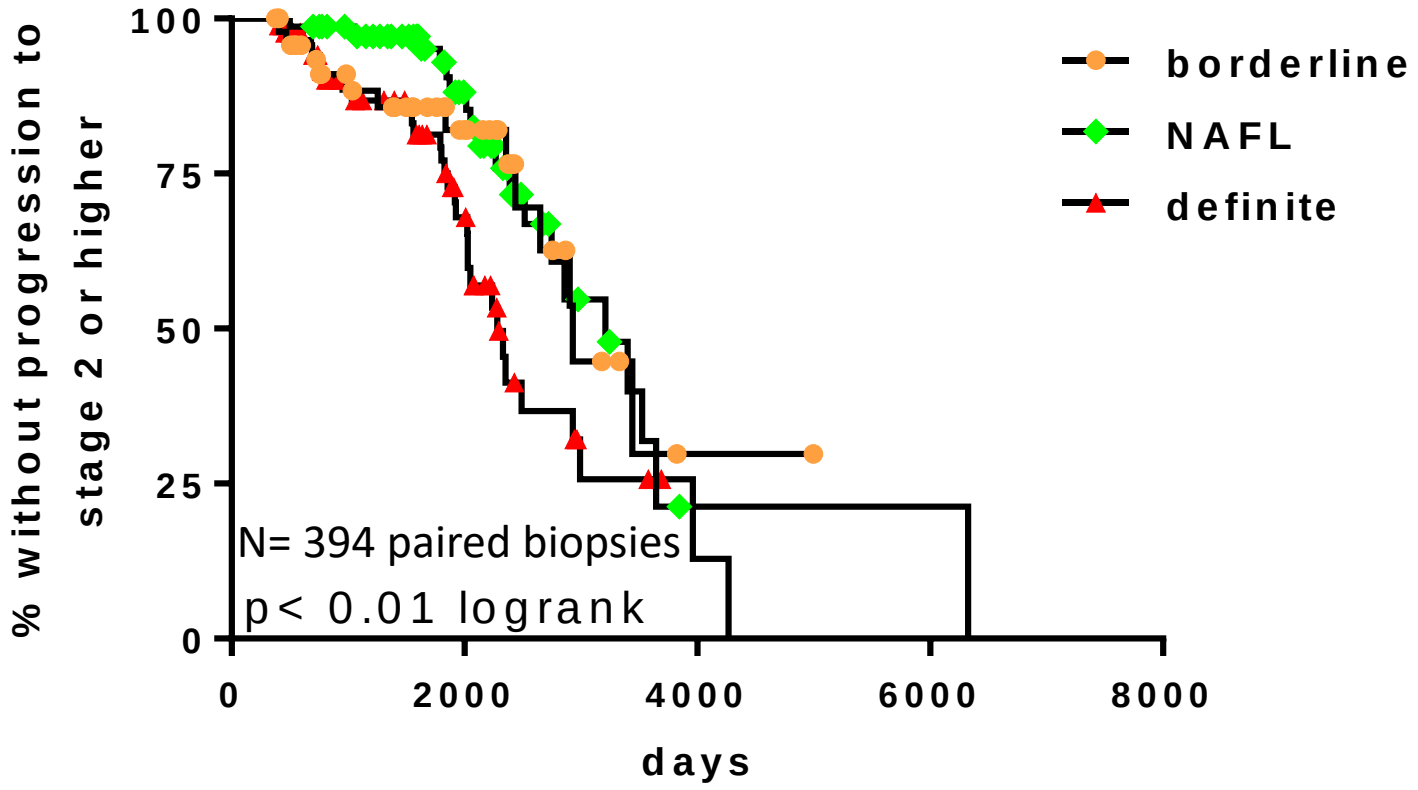
Disease activity and stage measure different things: disease stage not activity reflects proximity to cirrhosis



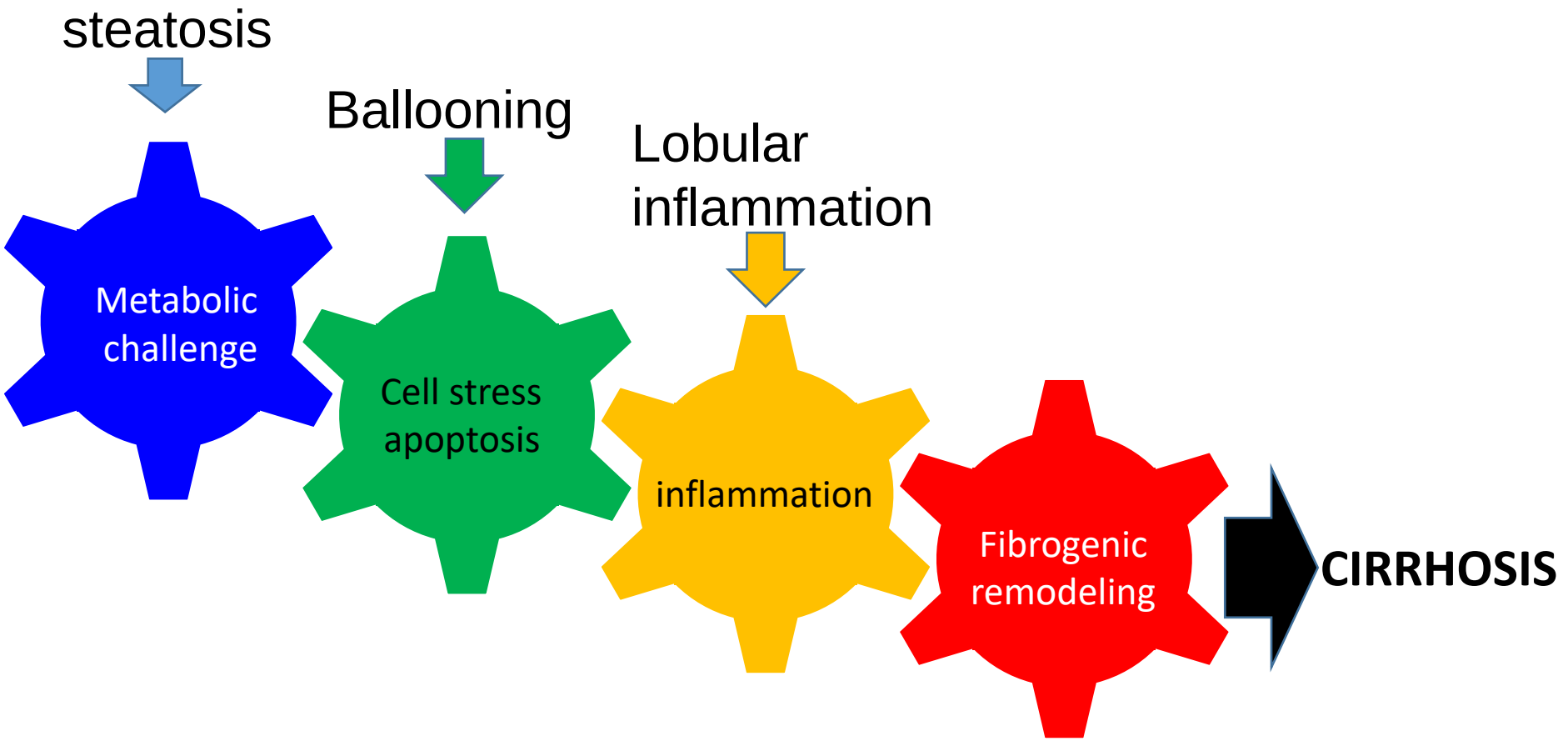
Activity is further removed from cirrhosis than stage and thus should be less likely to be related to events

Implications of steatohepatitis definition: *definition matters*



The definition used determines the amount of noise in the system and thus sample size

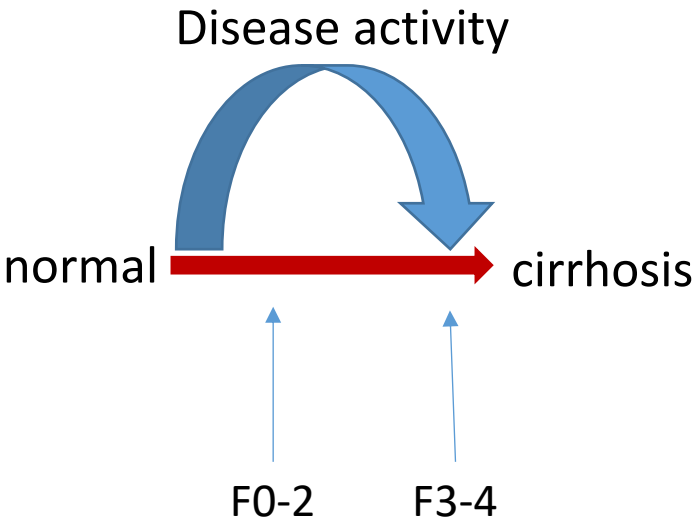
How to assess disease activity

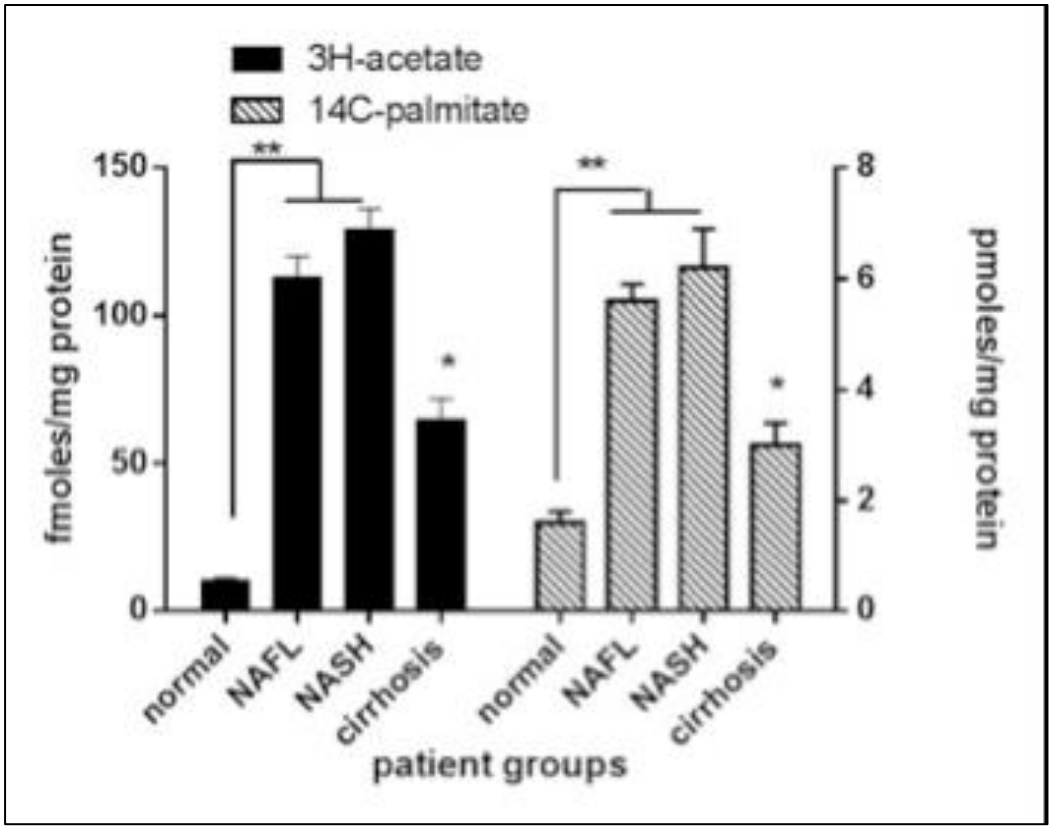


What short term changes in disease activity are relevant

	Biological plausibility	measurable	reproducible	Associated With progression	Dynamic range
Steatosis	Upstream surrogate	Yes	++	no	0-3
Lobular inflammation	Does not capture full spectrum of inflammation	Yes	+	Mixed data	0-3
Ballooning	Linked to fibrogenic signaling	Yes	+	yes	0-2
Portal inflammation	?	Yes	++	yes	0-2
Combined Activity scores	May capture interactions	Yes		?	

Disease activity burns out with progression in to cirrhosis





Siddiqui et al, Clin Gastro Hep 2015

How to assess disease activity

steatosis

Ballooning

Lobular inflammation

Metabolic challenge

Cell stress apoptosis

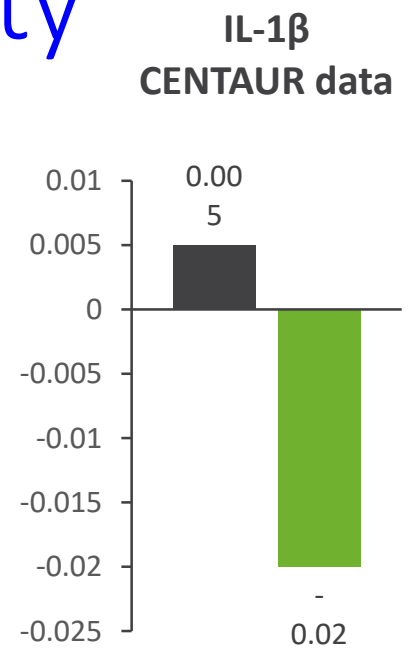
inflammation

Fibrogenic remodeling

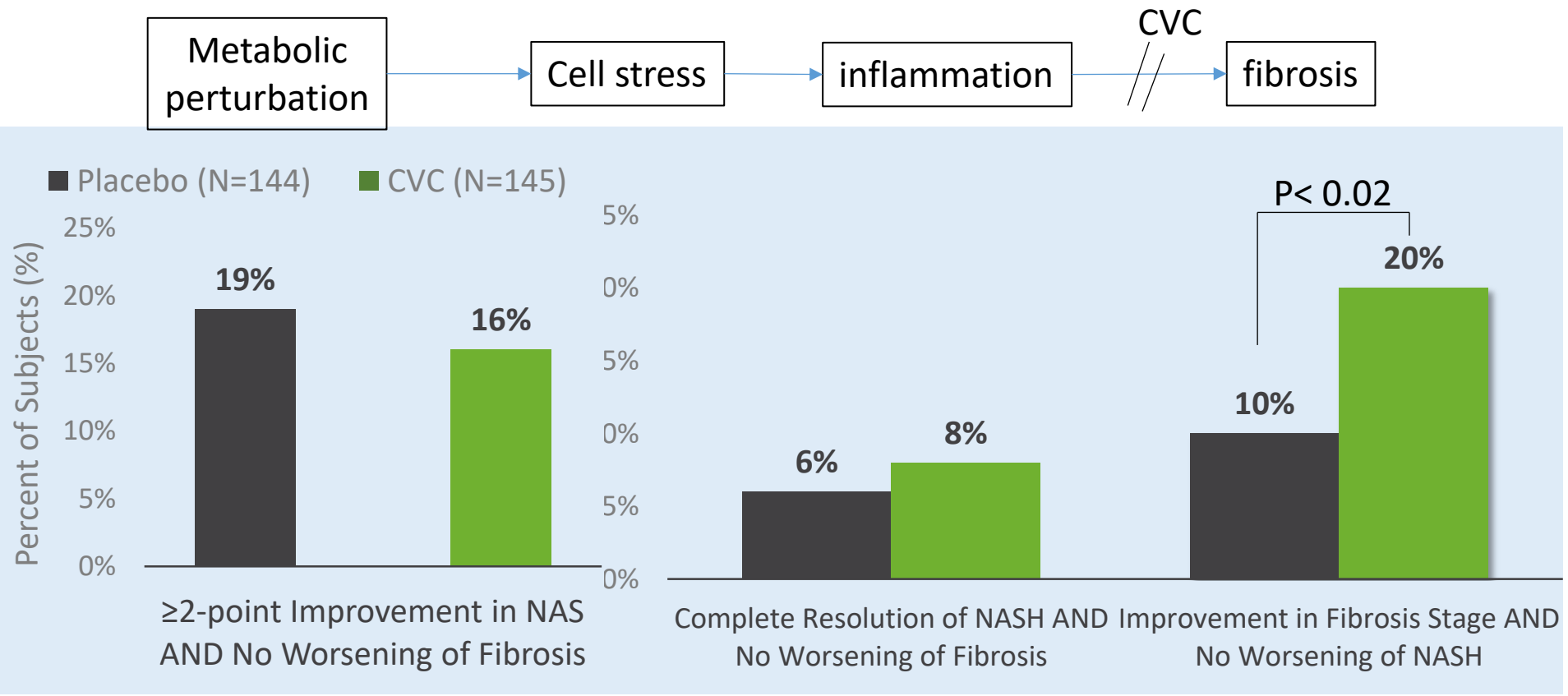
CIRRHOSIS

Free Cholesterol
Ceramides
Phospholipids
Eicosanoids

Oxidative stress-NRF
ER stress-ASK1
Mitochondrial injury
JNK-MAPK-ERK
NFkB



Even short-term endpoints must be linked to mechanism of action



PRIMARY ENDPOINT

SECONDARY ENDPOINTS

However, pure antifibrotic strategies need to consider the implications of unrestrained Upstream disease activity

Sanyal et al, AASLD 2016

Some points to consider

- Disease activity waxes and wanes even without specific intervention
- Conventional histological findings (and scores) alone do not entirely account for the risk of progression to cirrhosis.
- Changes in NAS are more important than baseline NAS
- Need to validate new histological systems (consider including portal inflammation) or models including weight change and other lab parameters.
- Even subpart H endpoints must align with mechanism of action of specific agents

Developing optimized tools to evaluate fibrosis

Criterion	Shear Wave elastography	MRE	Transient elastography
Pros	Incorporated in Standard US machines	Fixed shear wave	Single vibration stimulus
Cons	Shear wave frequency dependence on probe and depth Inter-manufacturer variance	Manual selection of ROI (3D MRE overcomes this)	Limited by severe obesity, ascites etc

2D MRE: THE PHYSICS BEHIND APPLICATION

NEED TO REMOVE

$$\rho \frac{\partial^2 \vec{u}}{\partial t^2} = (\lambda + \mu)\vec{\nabla}(\vec{\nabla}.\vec{u}) + \mu\vec{\nabla}^2\vec{u}$$

compression shear

$$\rho \frac{\partial^2 u}{\partial t^2} = \mu \Delta u = \mu \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right)$$

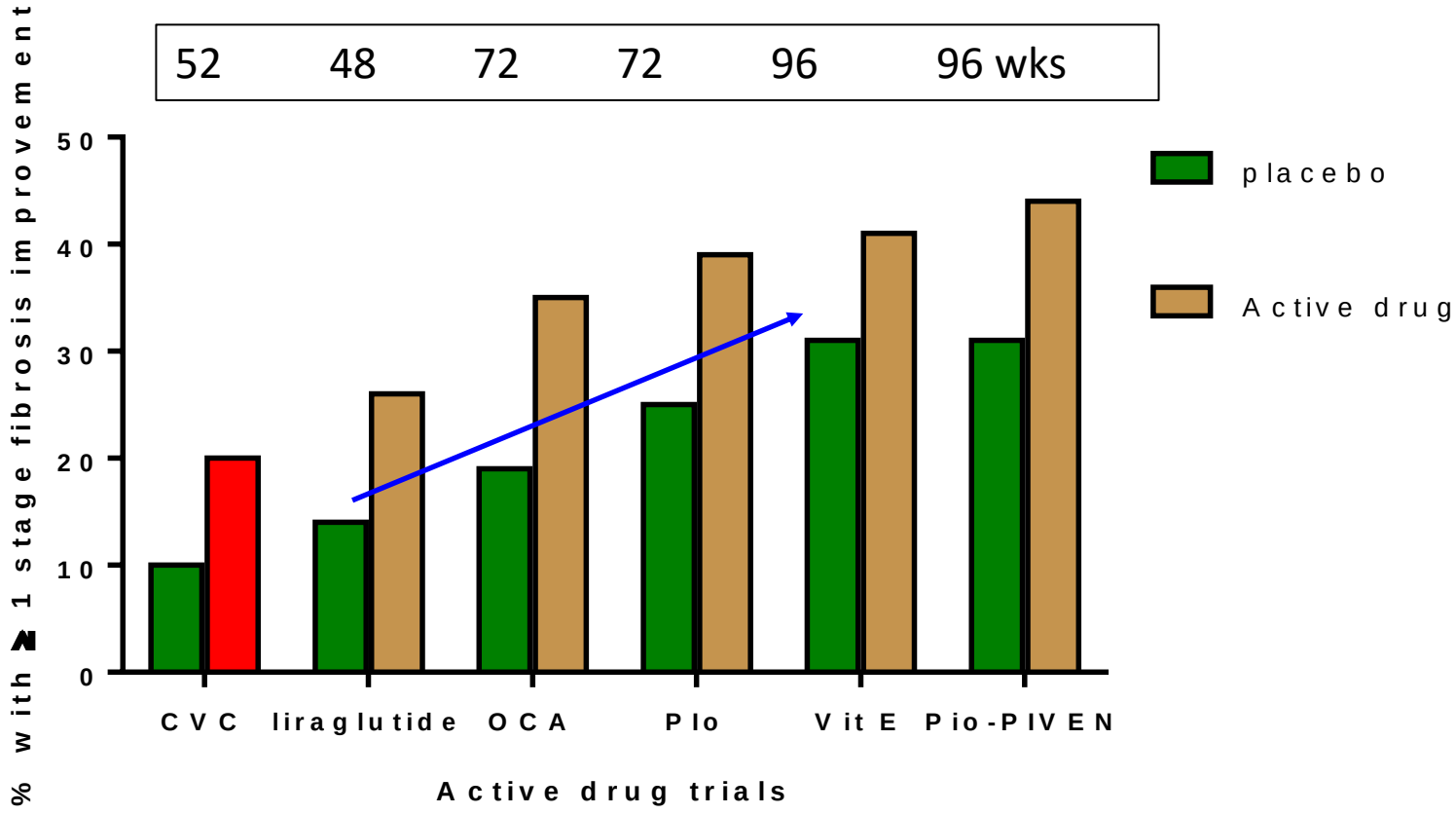
REMOVED BECAUSE UNKNOWN IN 2D

$$\rho \frac{\partial^2 u}{\partial t^2} = \mu \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} \right) \quad \text{or} \quad \frac{\partial^2 u}{\partial t^2} = V_s^2 \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} \right) \quad \text{where} \quad \mu = \rho V_s^2$$

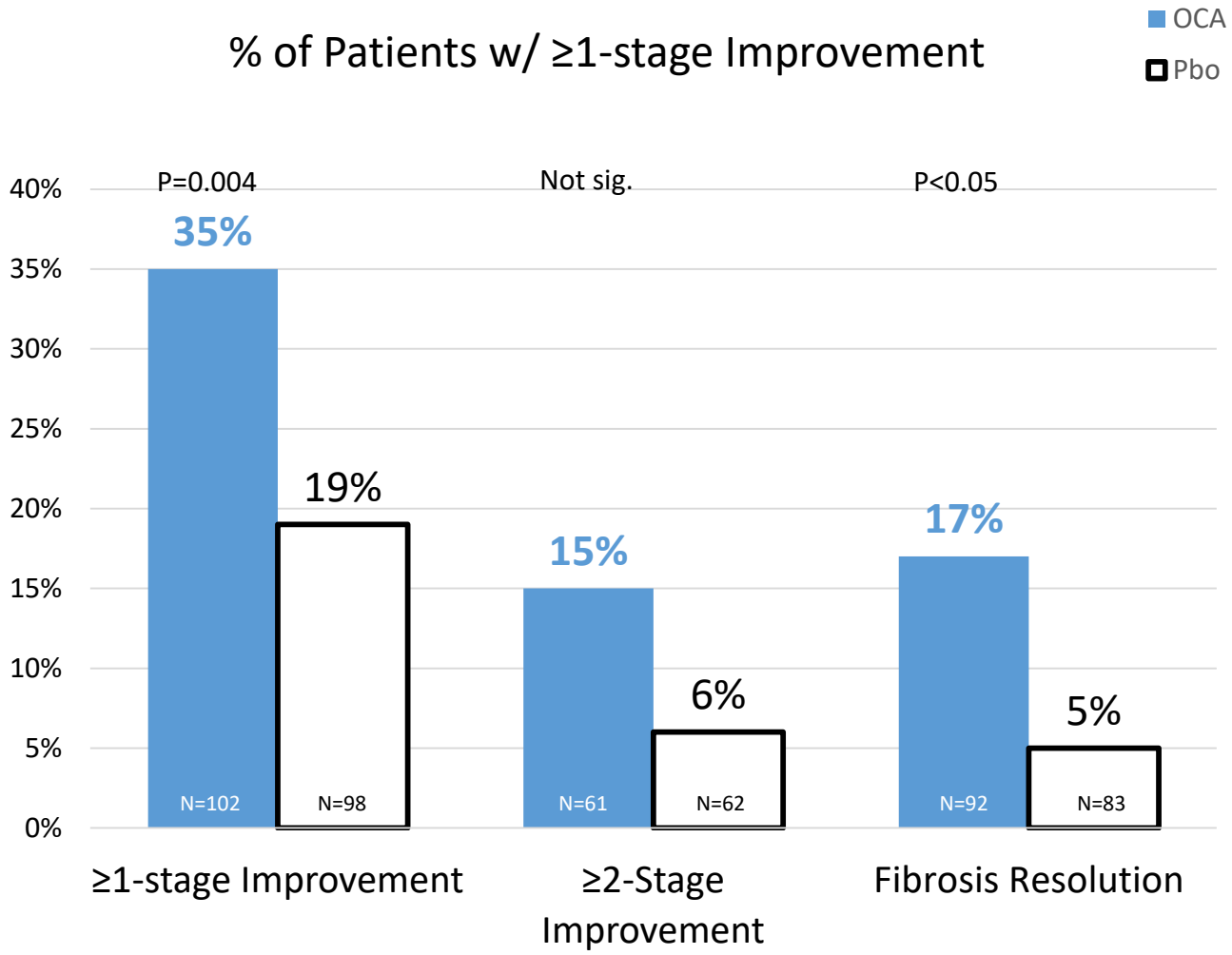
and Vs is the shear wave speed

Time dependency of fibrosis response-

proportion of placebo arm subjects with fibrosis improvement increases with time or does it?

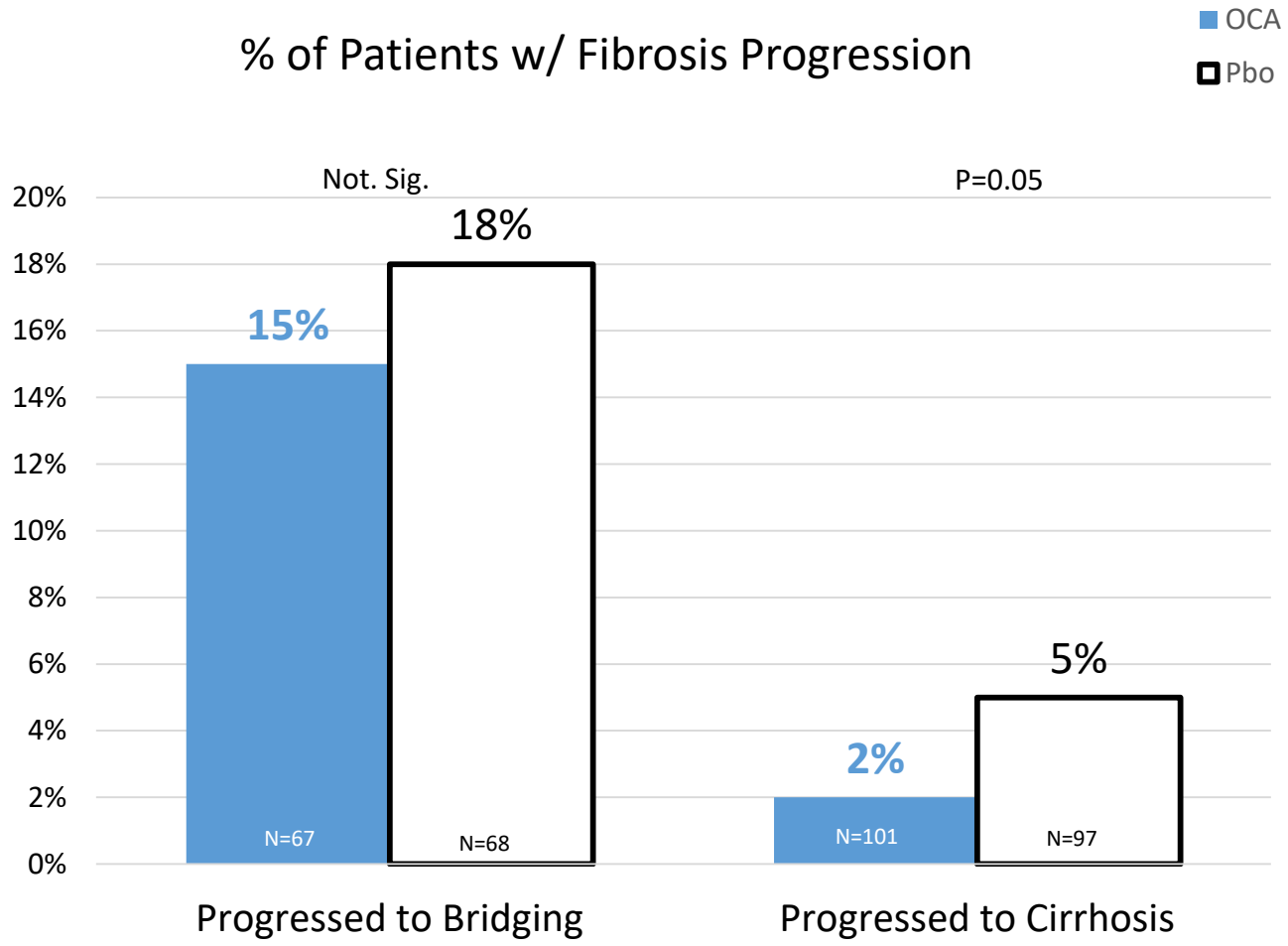


FLINT: Fibrosis Improvements of Varying Magnitude



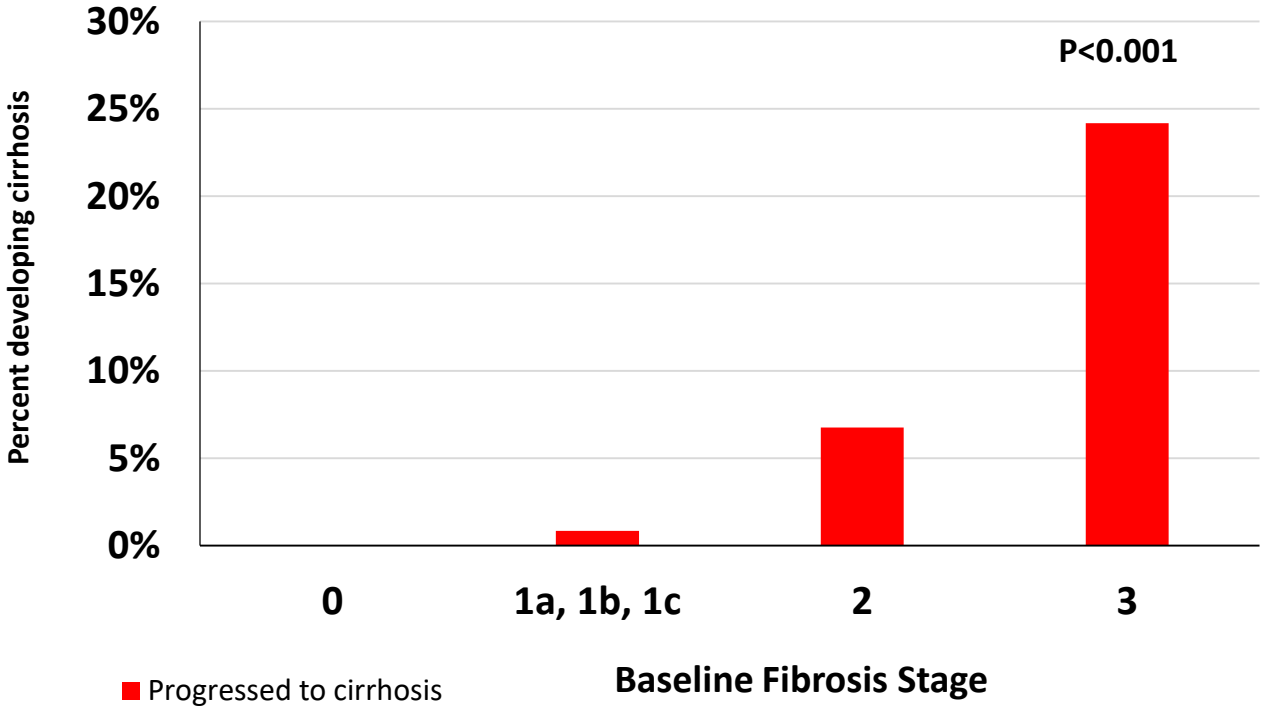
Tetri et al, Lancet Epub 2014

FLINT: Fibrosis Progression Improved



1: Data from Tetri et al. *The Lancet* and Supplementary Appendix. Published online November 7, 2014.
2: All p-values compared to placebo. P-values for Intercept analyses estimated by Intercept using Fisher's Exact test on published data in Supplementary Appendix, but not stratified.

Factors affecting disease progression to cirrhosis



Kleiner et al, AASLD 2016

Can we speed up assessment of effects of drugs on fibrosis progression

Endpoints must be:

- Clinically meaningful
- Measurable
- Reproducible
- Analyzable
- Dynamic range

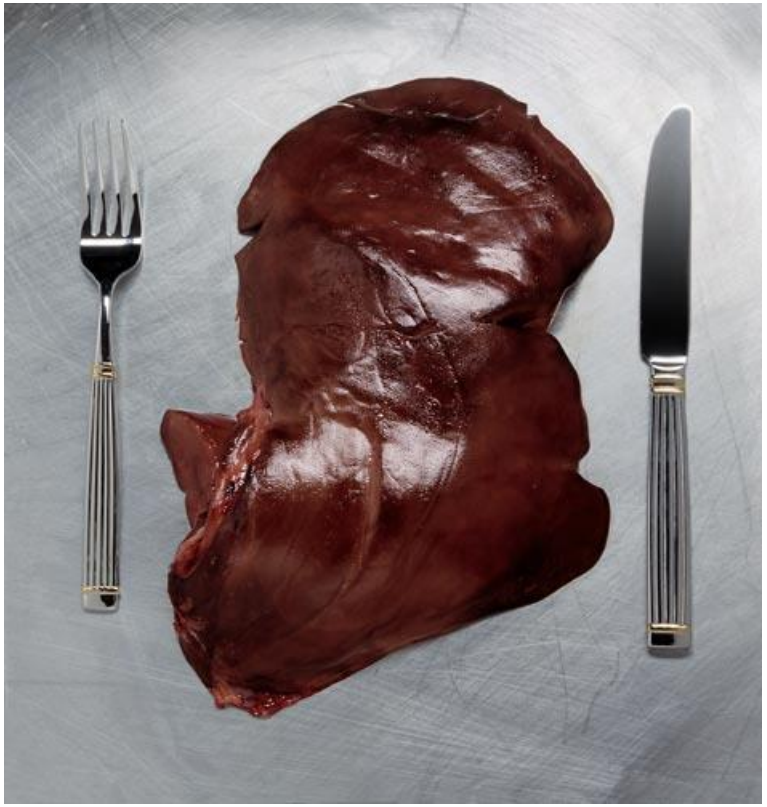
FIBROSIS BENEFIT ENDPOINT

$$\text{Benefit} = \frac{\%\ \text{fibrosis resolution (benefit)}}{\%\ \text{progression to cirrhosis (harm)}}$$

Fibrosis benefit index: $\text{benefit}^{\text{active}}\ \text{Rx}/\text{benefit}^{\text{pl}}$

Sanyal AJ, Lancet Gastro Hepatol 2017

Thank you for your attention



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