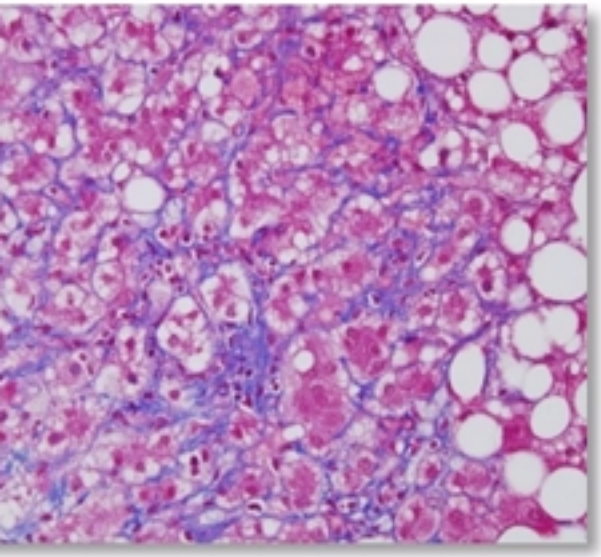
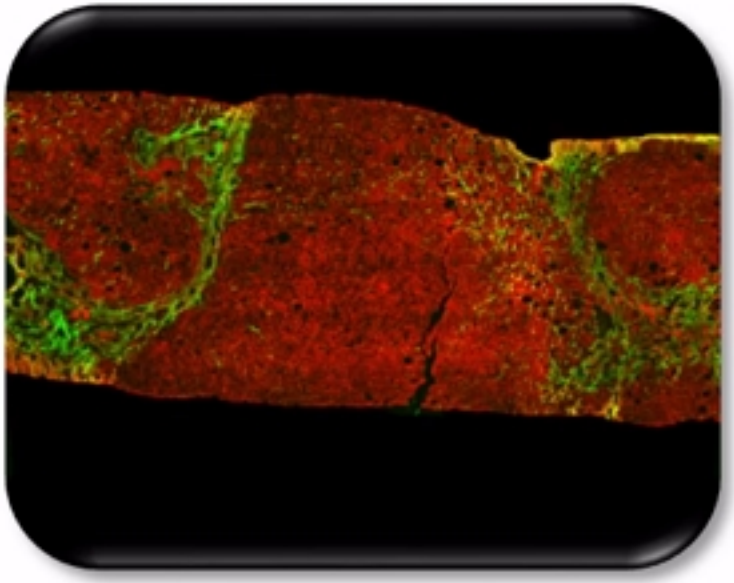
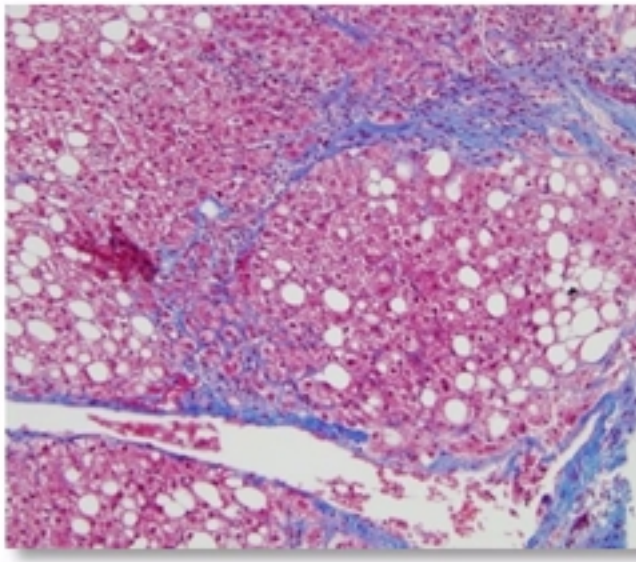




Fibrosis-What Will Be Needed For Approva

Arun J. Sanyal MBBS, MD

Professor of Medicine, Physiology and Molecular Pathology

Virginia Commonwealth University School of Medicine

ts of Interest

nt, Sanyal Biotechnologies

ptions: Genfit, Akarna, Tiziana, Indalo, Durect, Exhale
near

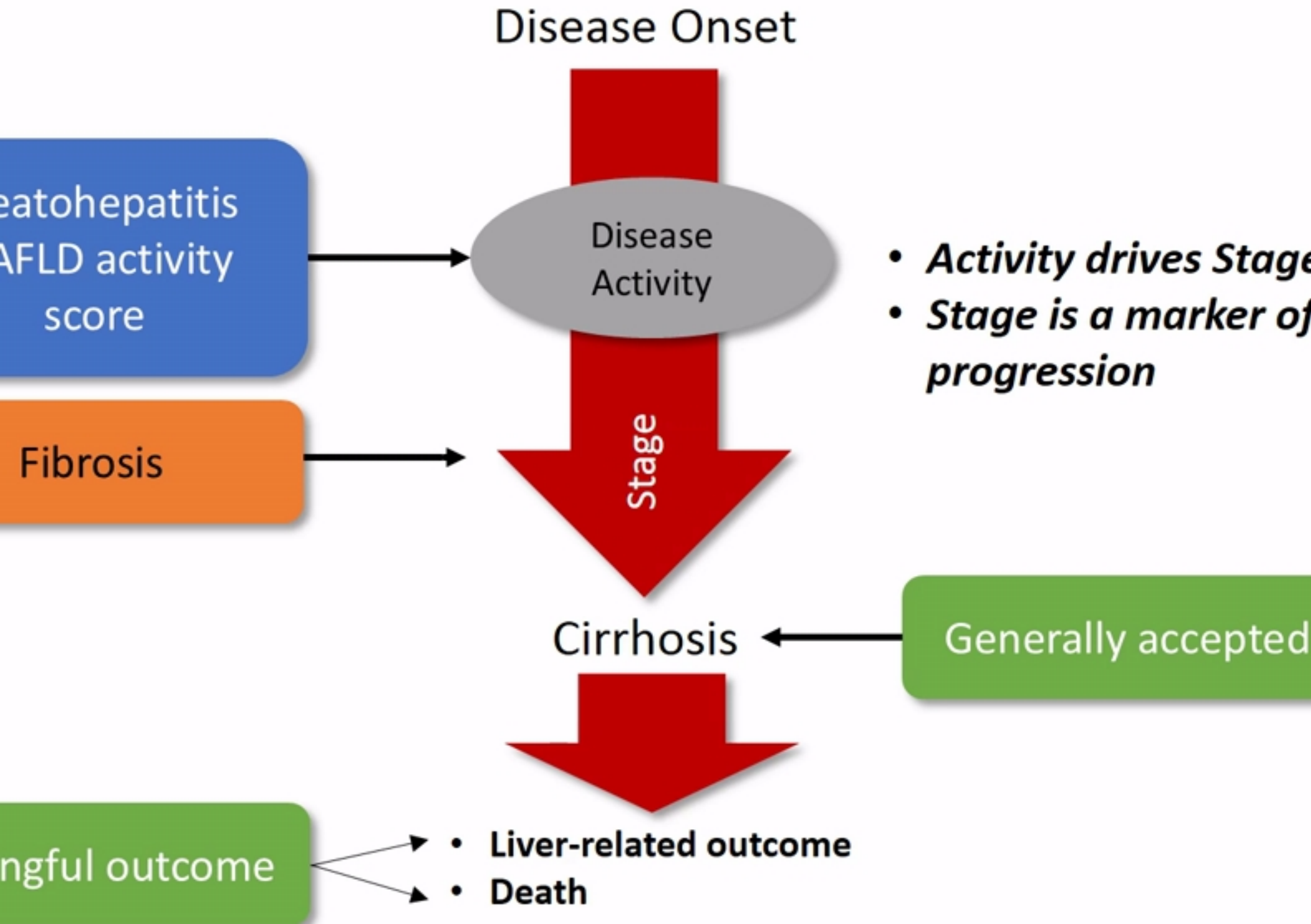
with compensation: Lilly, Pfizer, Novartis, Ardelyx, Sa
near

without compensation: Galectin, Intercept, Merck, B
mmuron, Gilead, Chemomab, Affimmune, Protalix, N
Novo Nordisk, Cirius, Boehringer Ingelhiem

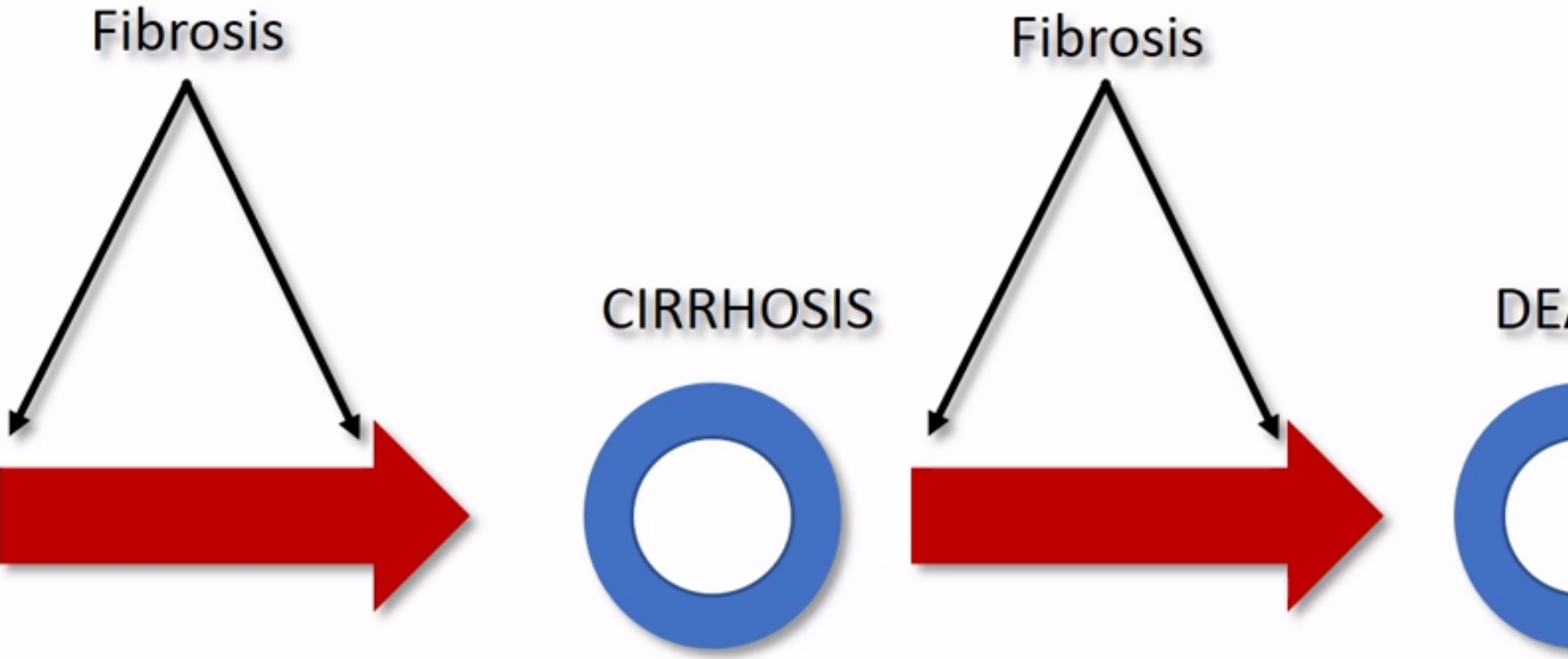
o institution: Gilead, Tobira, Allergan, Merck, Bristol
neca, Immuron, Intercept, Novo Nordisk, Shire, Boeh
m, Cirius

here is an unmet need to improv
inical outcomes, quality of life a
ultimately premature mortality

e activity versus disease stage

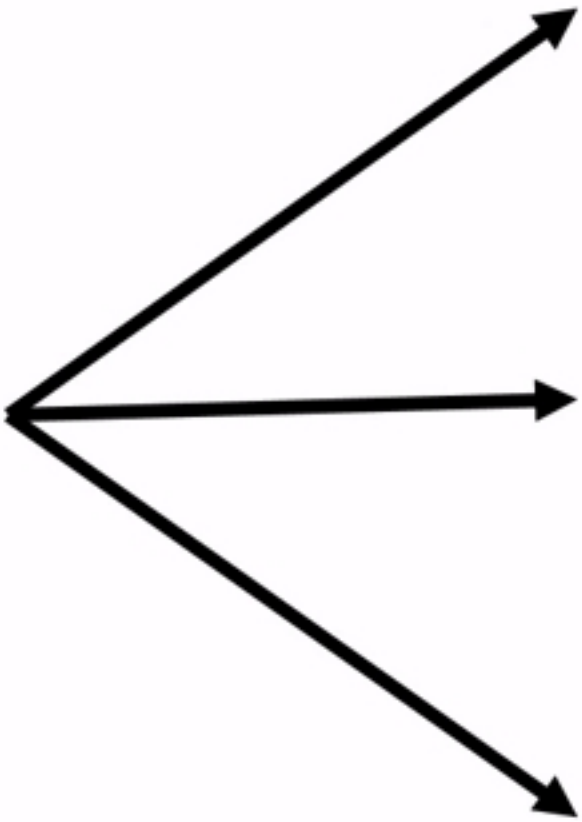


levant is fibrosis?



ngful outcomes?

NING FIBROSIS
STAGE 0-1 TO 3



HOW A PATIENT FEELS

- *Need more data (? NASH-CH*

HOW A PATIENT FUNCTIONS

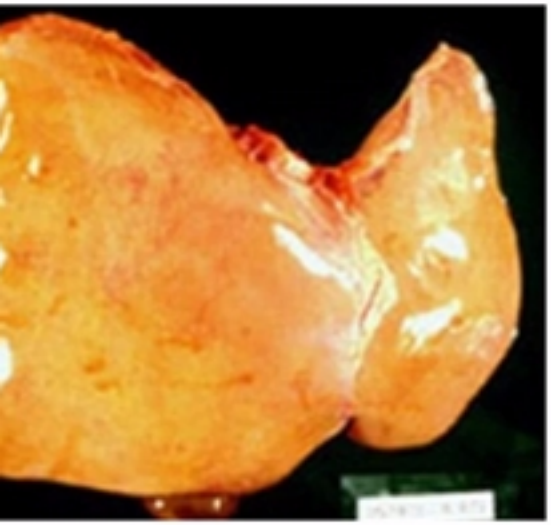
- *No evidence of a relationship*

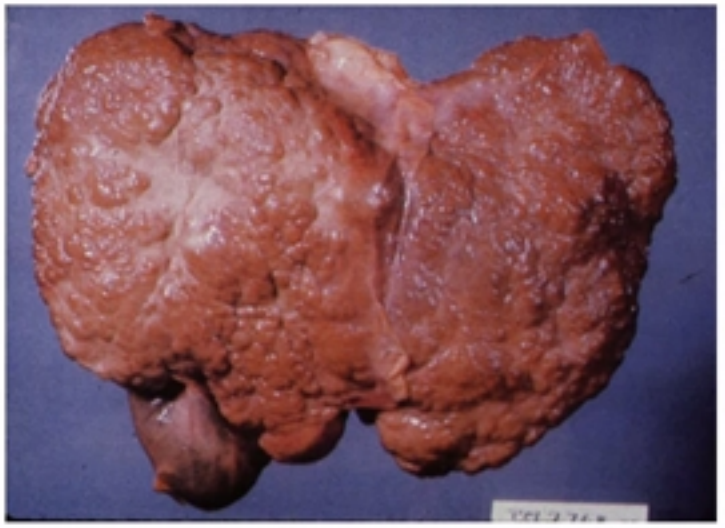
HOW A PATIENT SURVIVES

- *Main outcome is cardiovascu*

of *disease progression* towards cirrhosis

ssion to cirrhosis is a generally accepted surrogate endpoint for appro

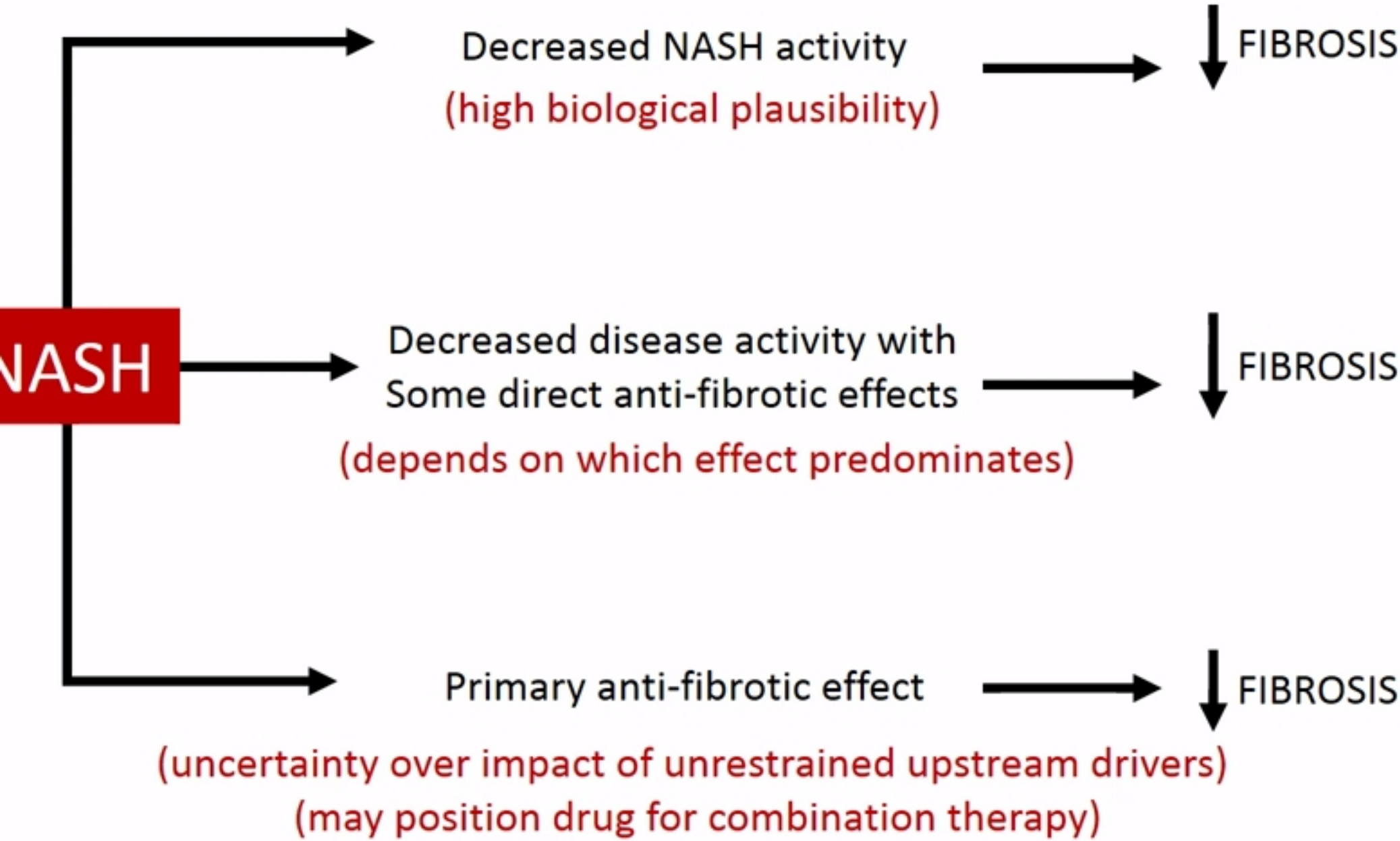




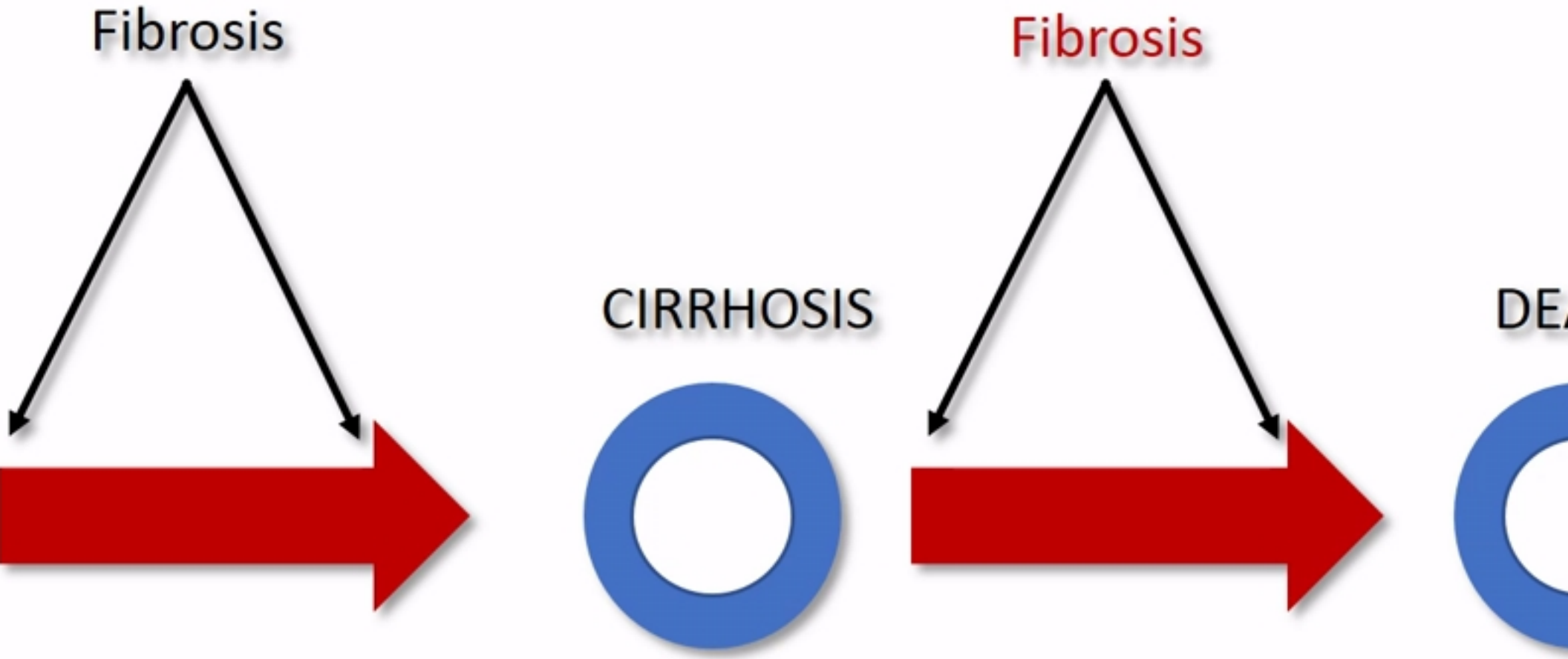
PRE
WORS
OU

ression includes metabolic reprogramming, cell death, stem cell recru
e activity, cell differentiation, changes in microcirculation, matrix, bile
rosis is an easily visible and quantifiable surrogate for this process.

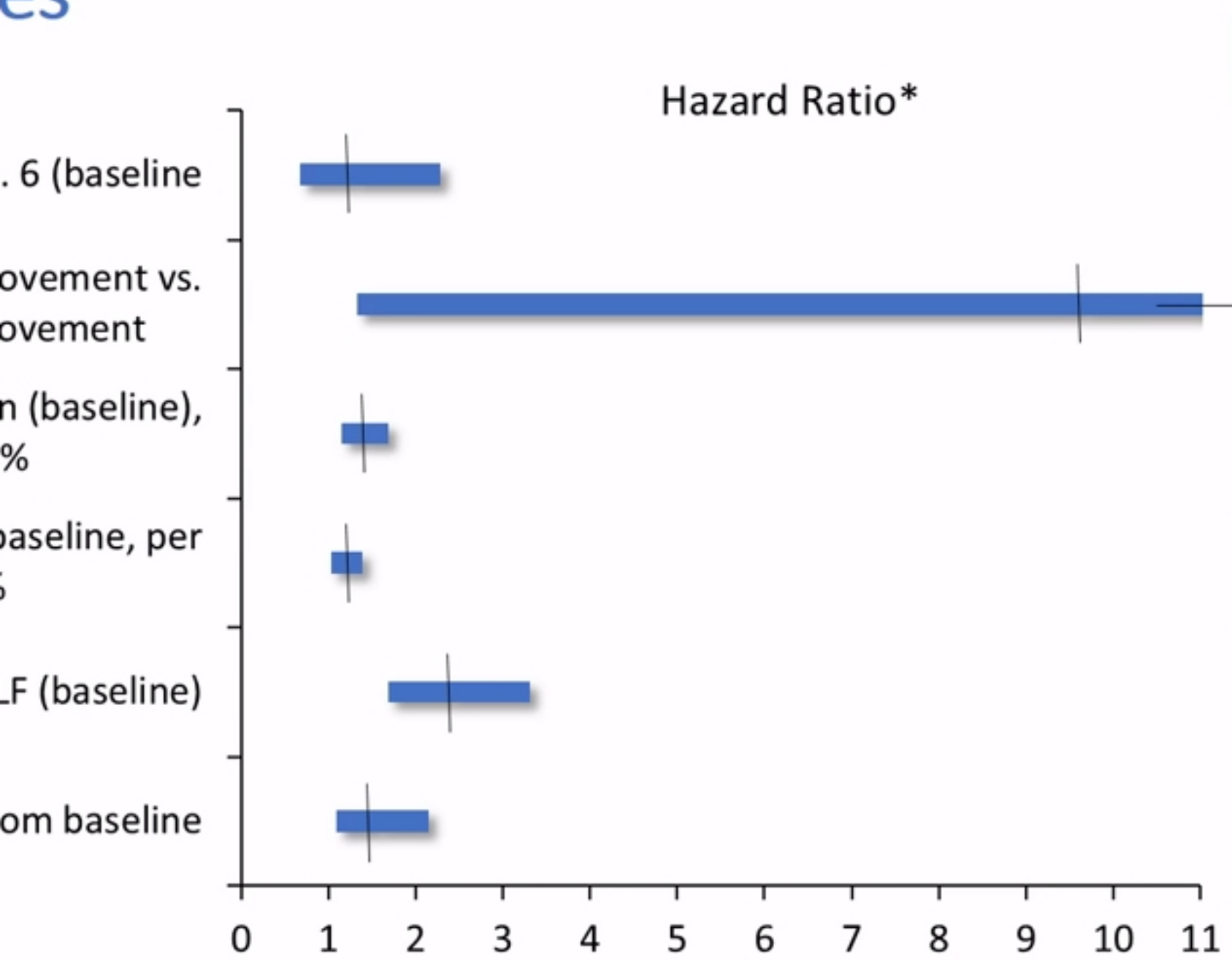
# of NASH is linked to drug mechanism of a



levant is fibrosis?



es



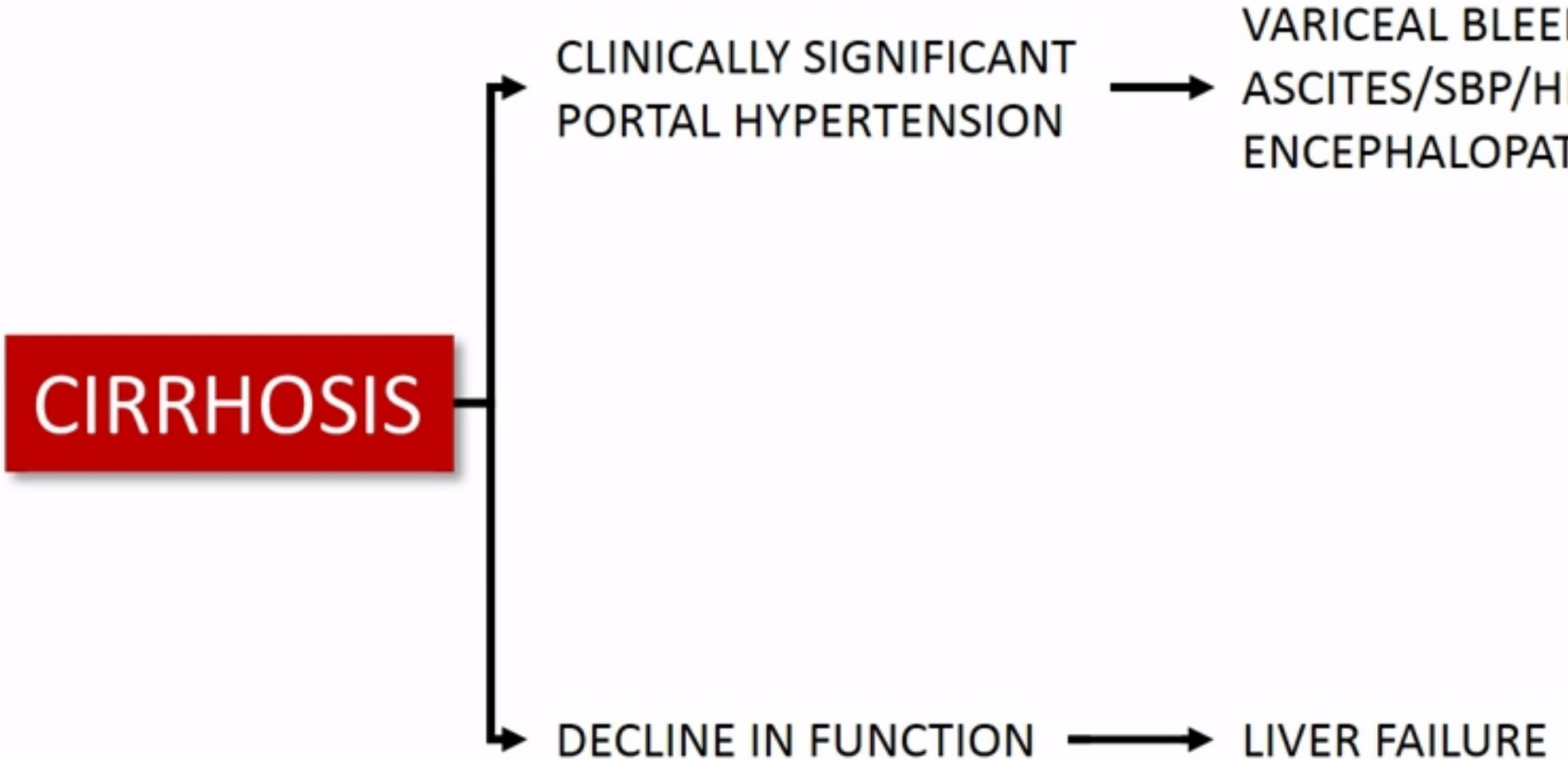
1.25	0.
9.63	1.
1.39	1.
1.2	1.
2.37	1.
1.54	1.

nical events with:

line hepatic collagen content and ELF

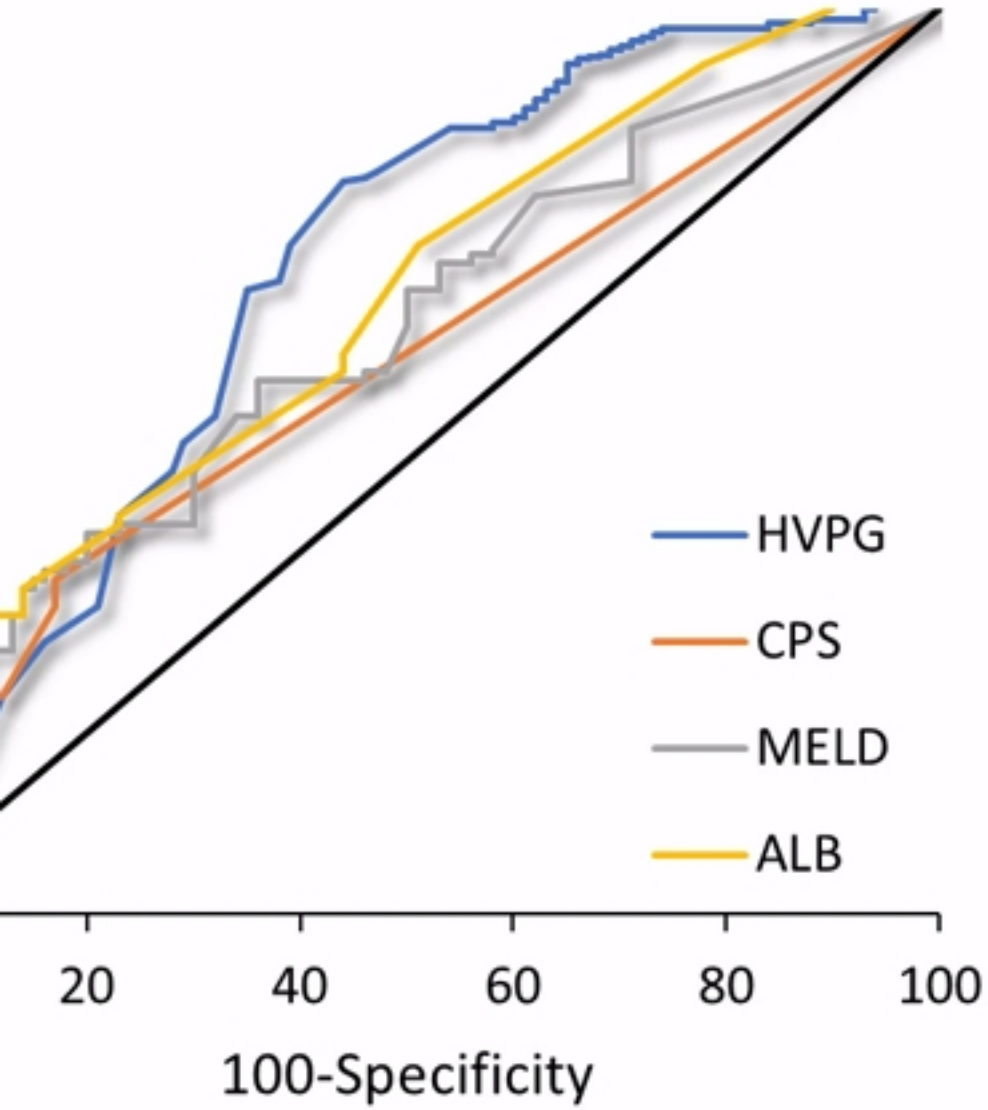
of fibrosis (by Ishak stage, collagen content, ELF)

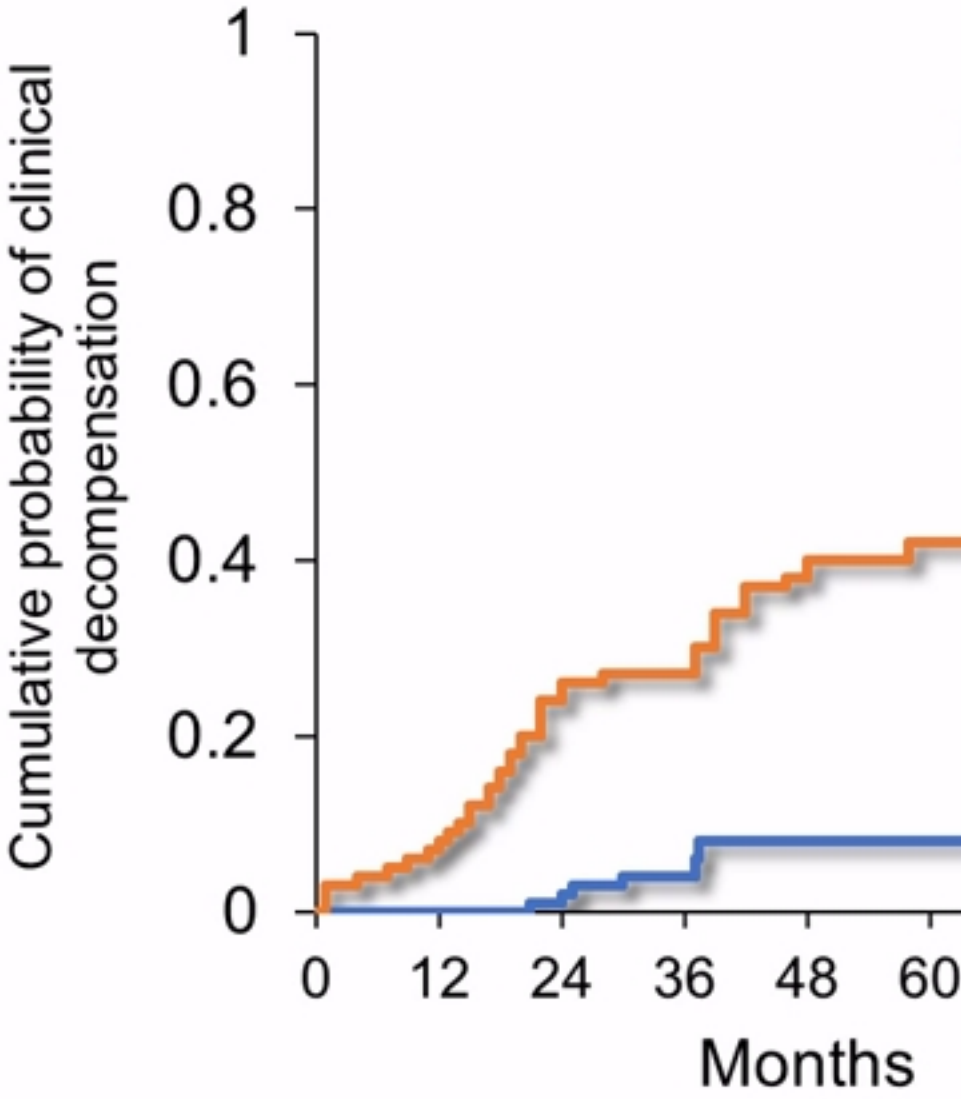
rrhosis leads to clinically meaningful outc



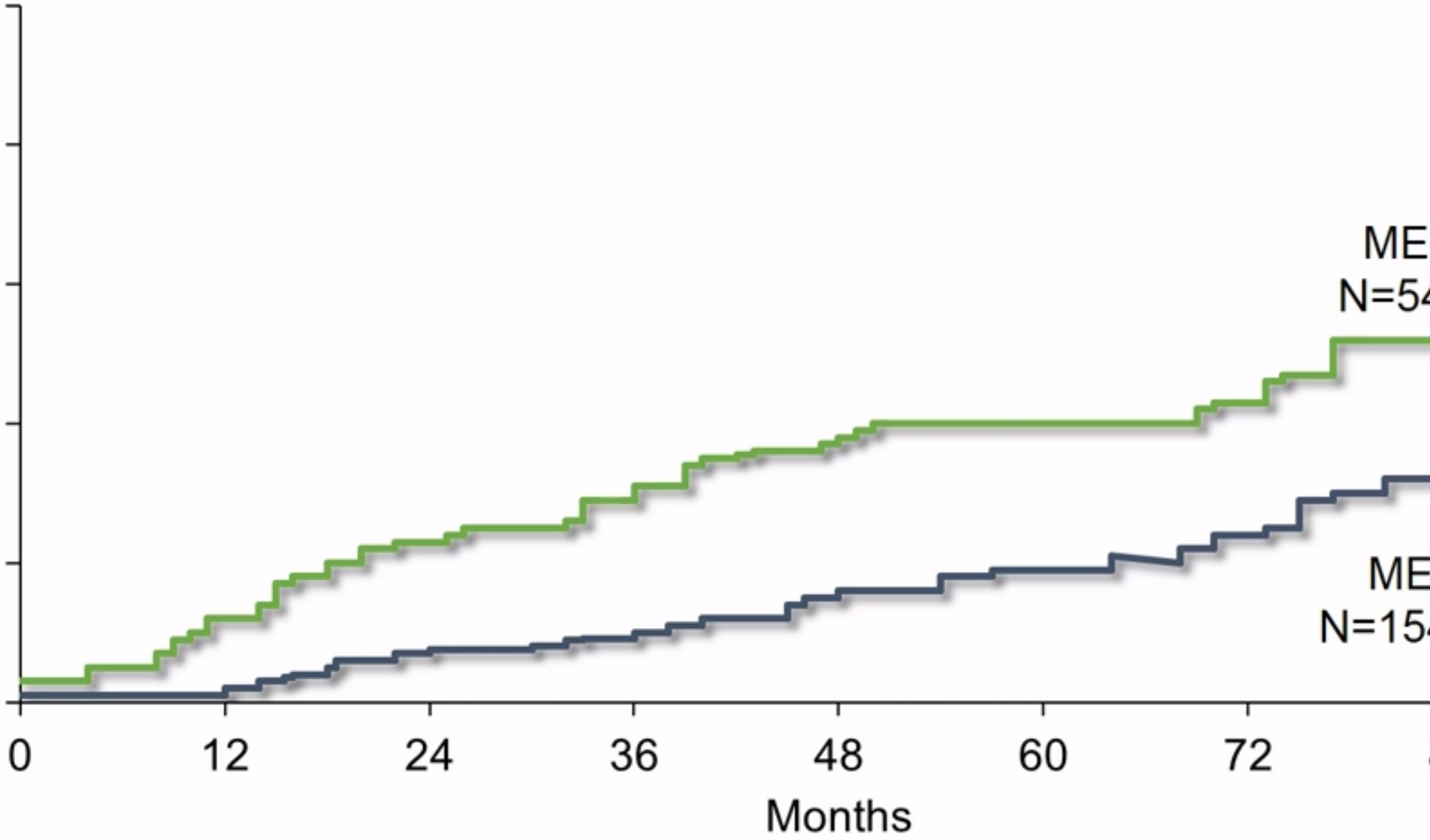
≥ 10 mmHg Predicts Clinical Stability

of HVPG increase are clear; implications of a decrease are Context- a





y



s an endpoint

	Cons
to mortality own to clinicians available measure ld value of 10 or 14 identifies tant stage in clinical course	• Inter-lab variability • Related to 3 month mortal • Rate of progression of MEL not linear • Most patients with compe cirrhosis have a MELD < 10

se in MELD to ≥ 15 represents a point in course of diseas

Transplant should be considered

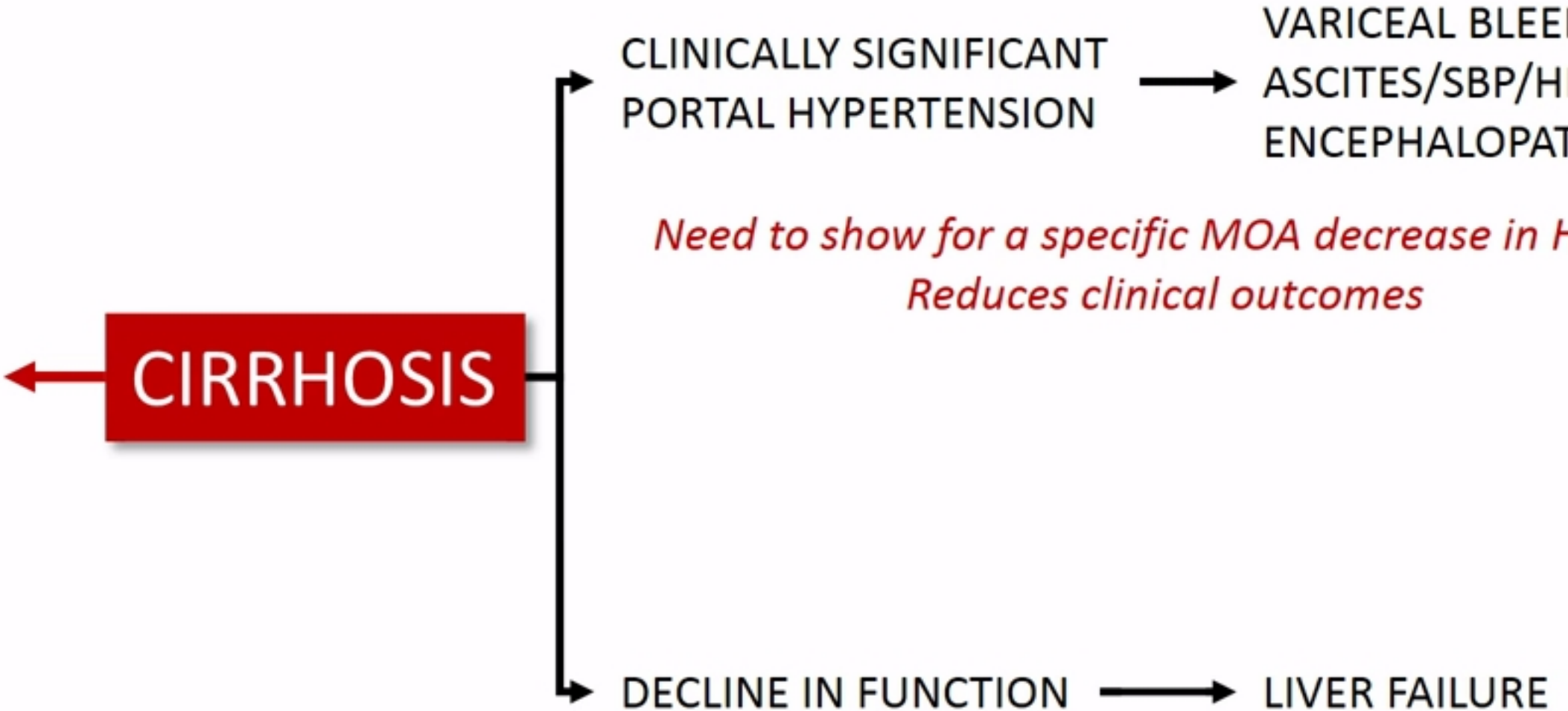
on

en morphometry and other quantitative measu
n

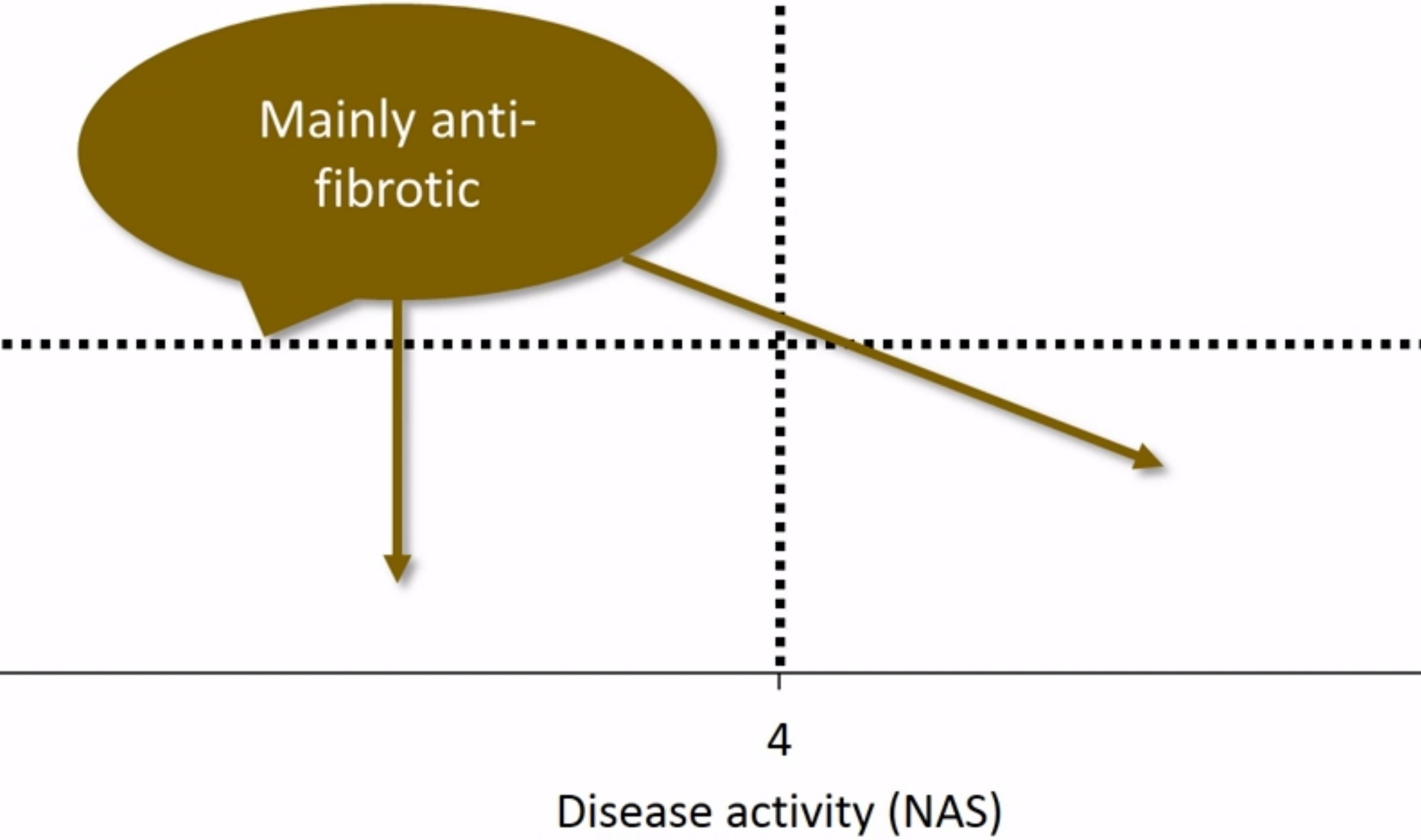
rs of collagen synthesis or turnover

tative liver function tests

rrhosis leads to clinically meaningful outc



gical endpoints: one size does not fit all



ıry

progression is reflected in increased fibrosis; in pre-cirrhotic st
er se does not lead to clinically meaningful outcomes and cha
tage is a surrogate for disease progression

rhotic stages, the implications of decreased fibrosis are mech
lated and will need to be validated to translate in to decrease

of uncertainty is if fibrosis alone if decreased without altered i
c substrate in to the liver, what the long-term outcomes will b

e with cirrhosis, multiple paths to approval exist:

al of fibrosis to pre-cirrhotic stages followed by demonstration of decreas

ased progression to MELD ≥ 15 and then outcomes

needs substantial additional validation as an endpoint before it can be use
of collagen quantitative scores.