UPDATE EPATOLOGIA

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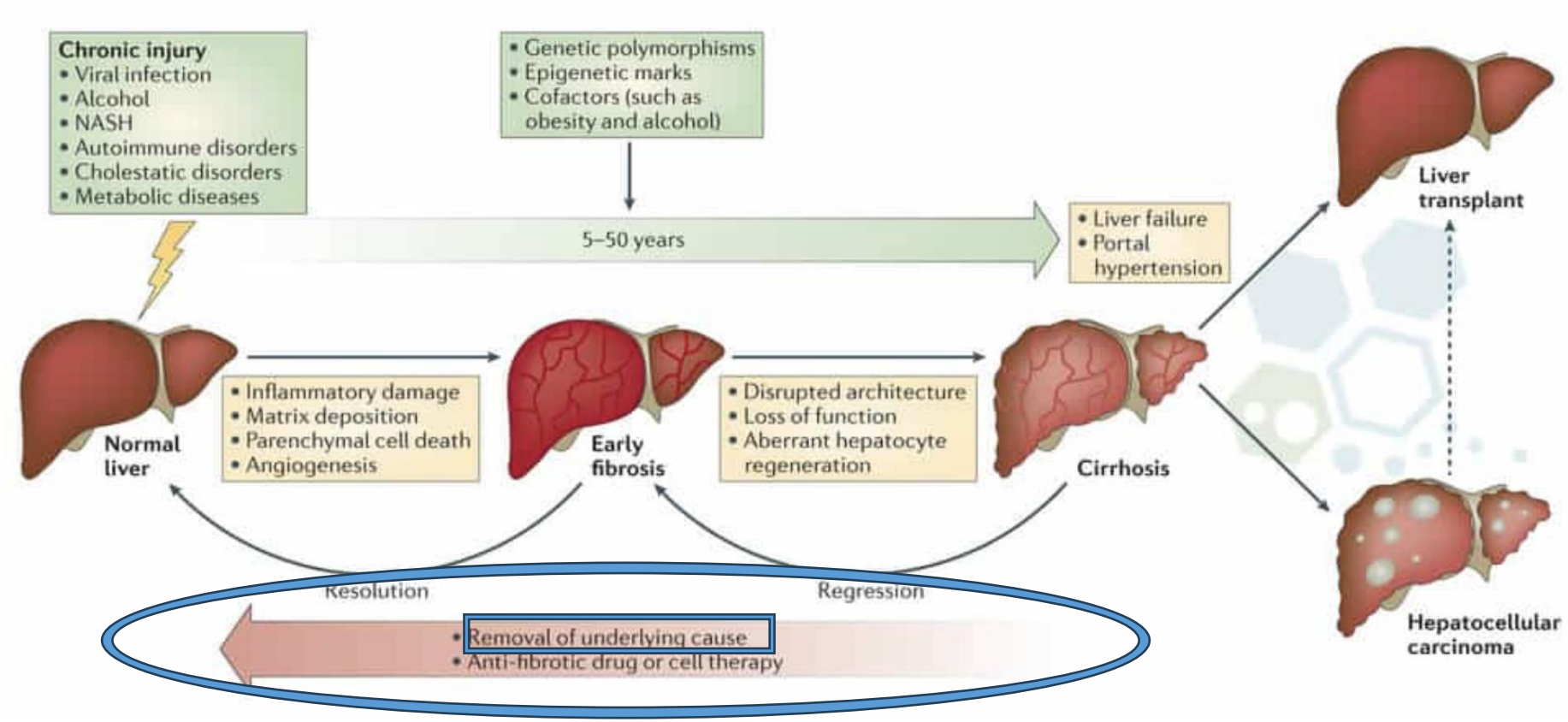
1. Diagnosi non invasiva di
   compensated Advanced Chronic Liver Disease

2. MASLD:
nuova nomenclatura, screening nello studio medico, nuovi farmaci

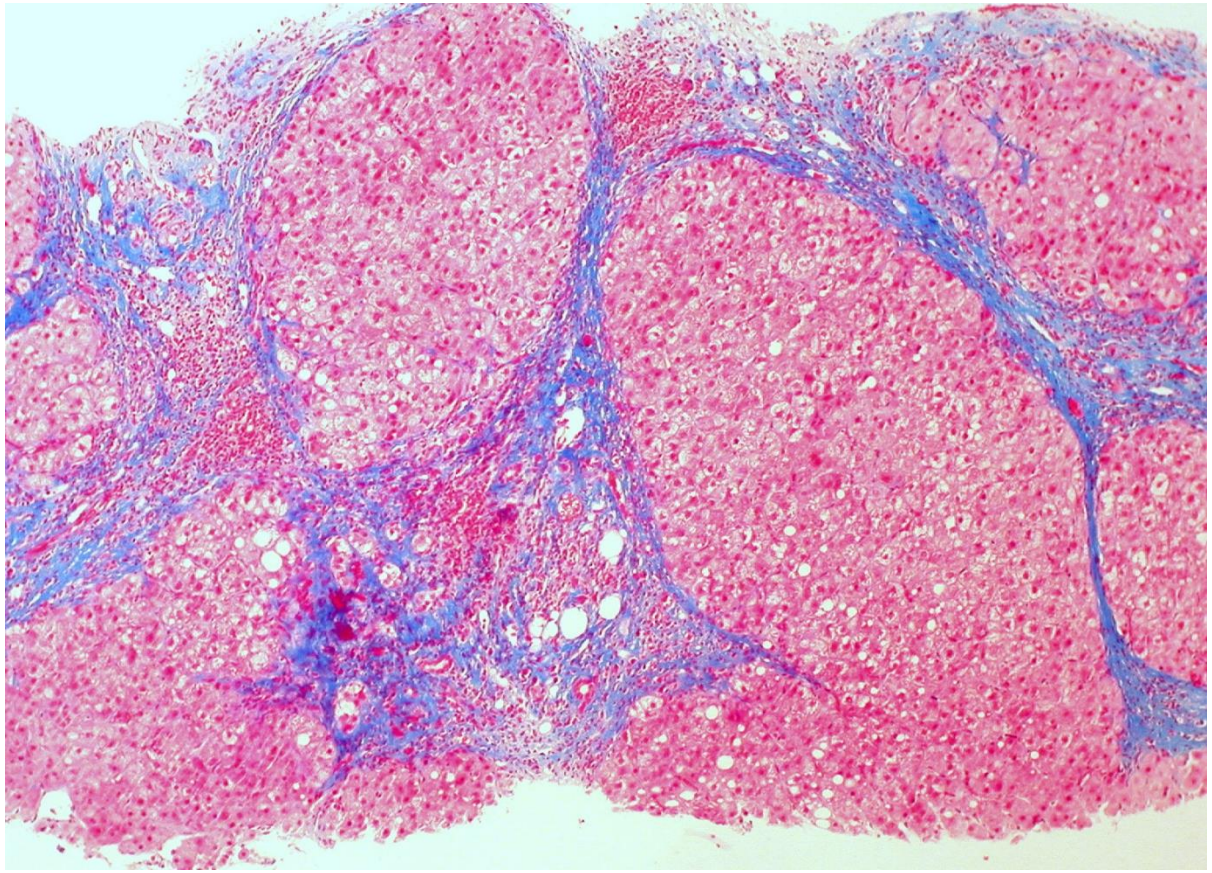
3. Epatite delta:
   nuova terapia

Qualsiasi insulto al fegato porta nel tempo alla cirrosi e all'HCC



Fibrosi correla con complicanze epatiche e mortalità

Diagnosi di cirrosi nello studio medico



Cirrosi: diagnosi

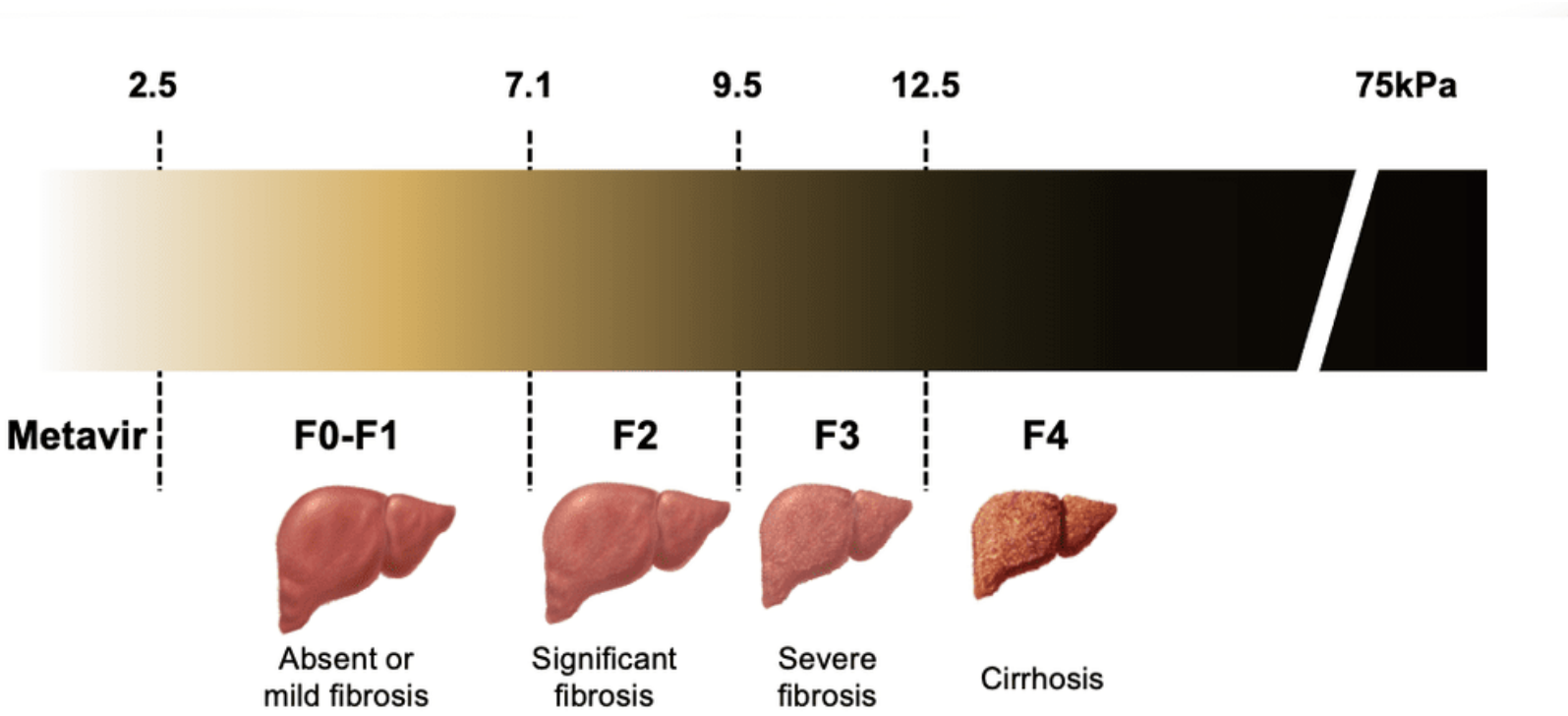
- Radiologia: cirrosi senza ipertensione portale non è diagnosticabile con esami radiologici
- Segni suggestivi di cirrosi: fegato rimpicciolito, splenomegalia
- Segni certi di ipertensione portale: presenza di collaterali venosi (varici periesofagee, ricanalizzazione vena ombelicale, shunts splenorenali)

compensated Advanced Chronic Liver Disease - cACLD

Castera, Gastroenterol 2005
Tapper, NEJM 2017

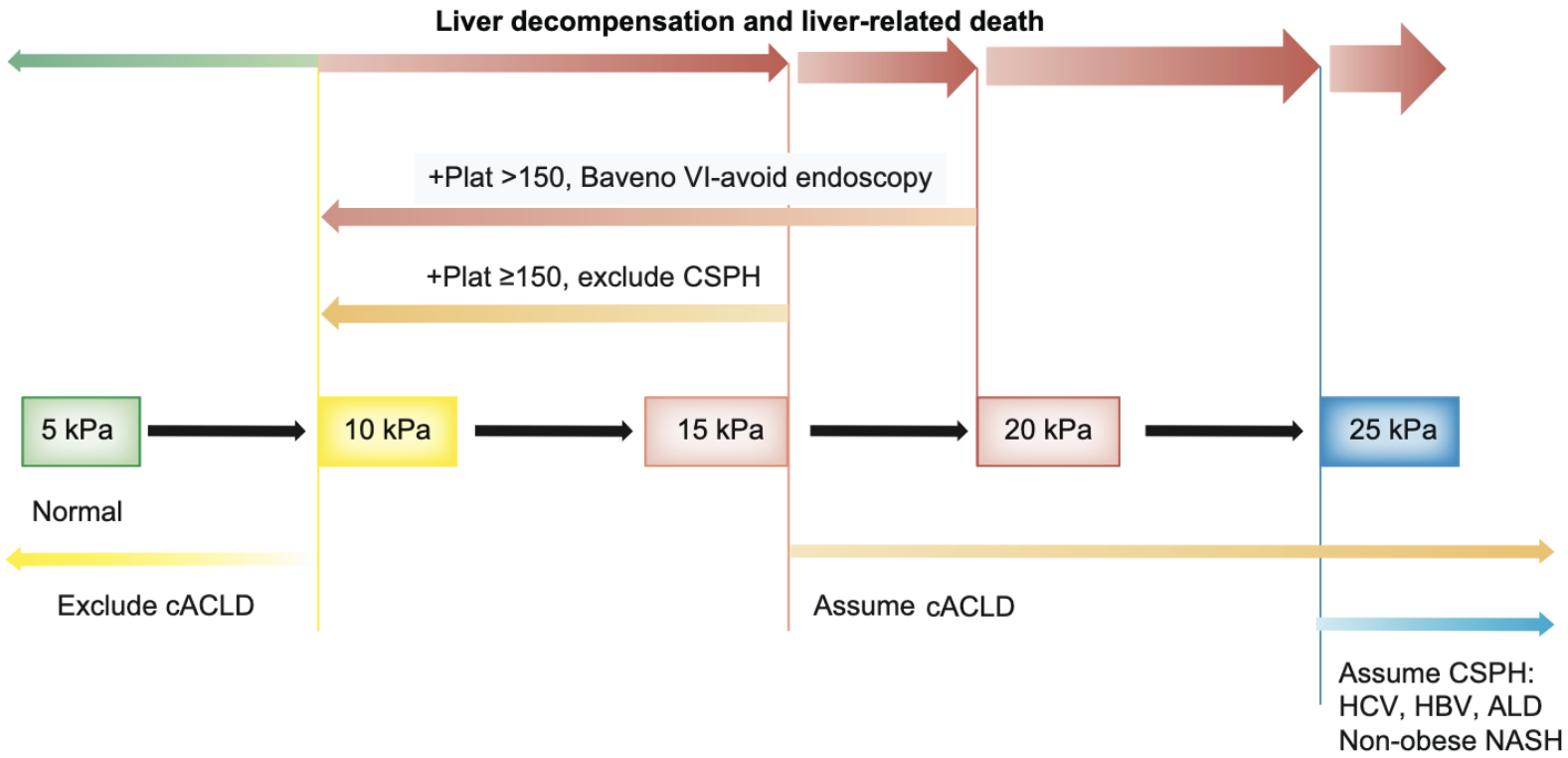
Cirrosi: diagnosi

Cirrosi: diagnosi



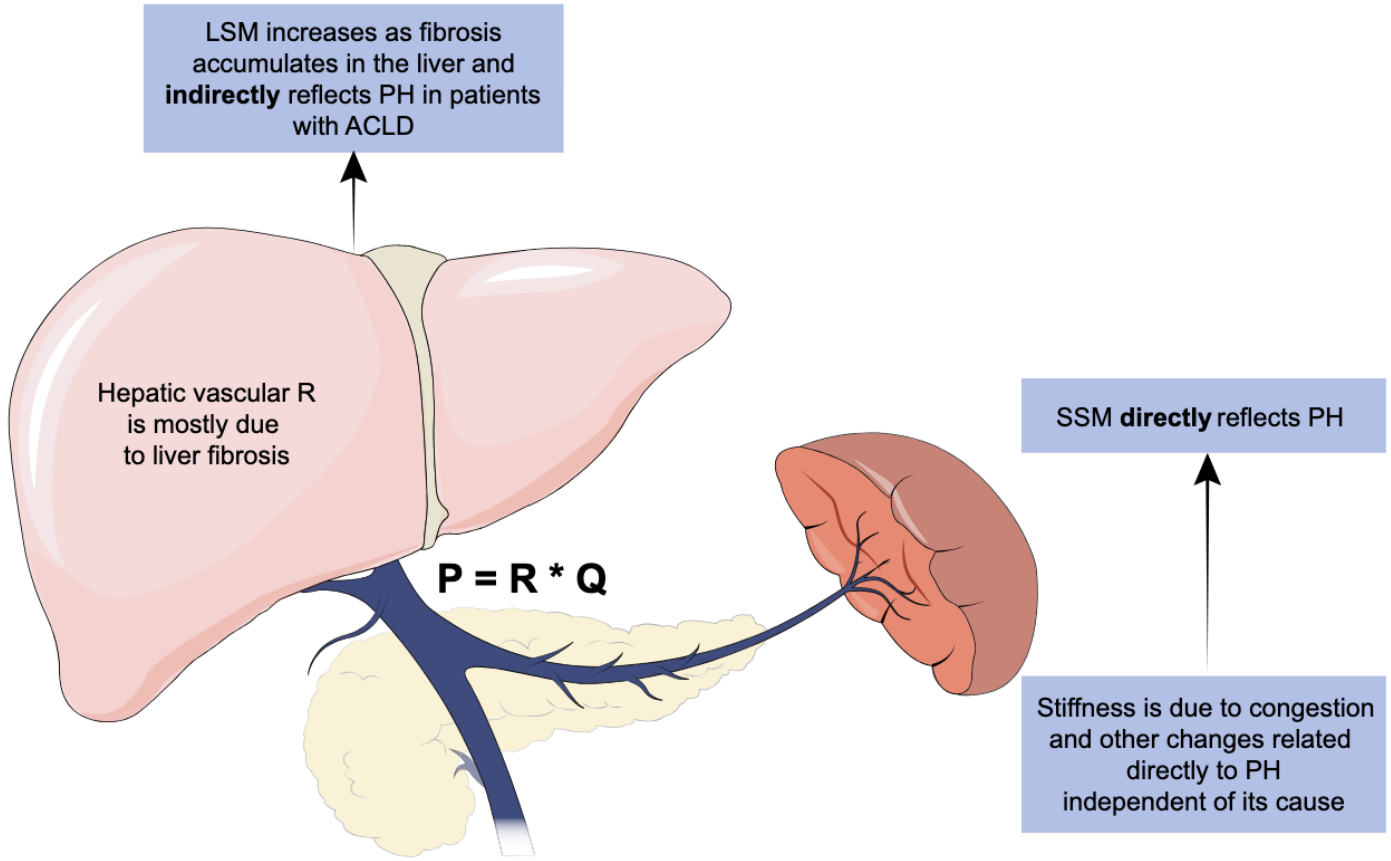
Castera, Gastroenterol 2005
Tapper, NEJM 2017

Cirrosi: diagnosi e prognosi



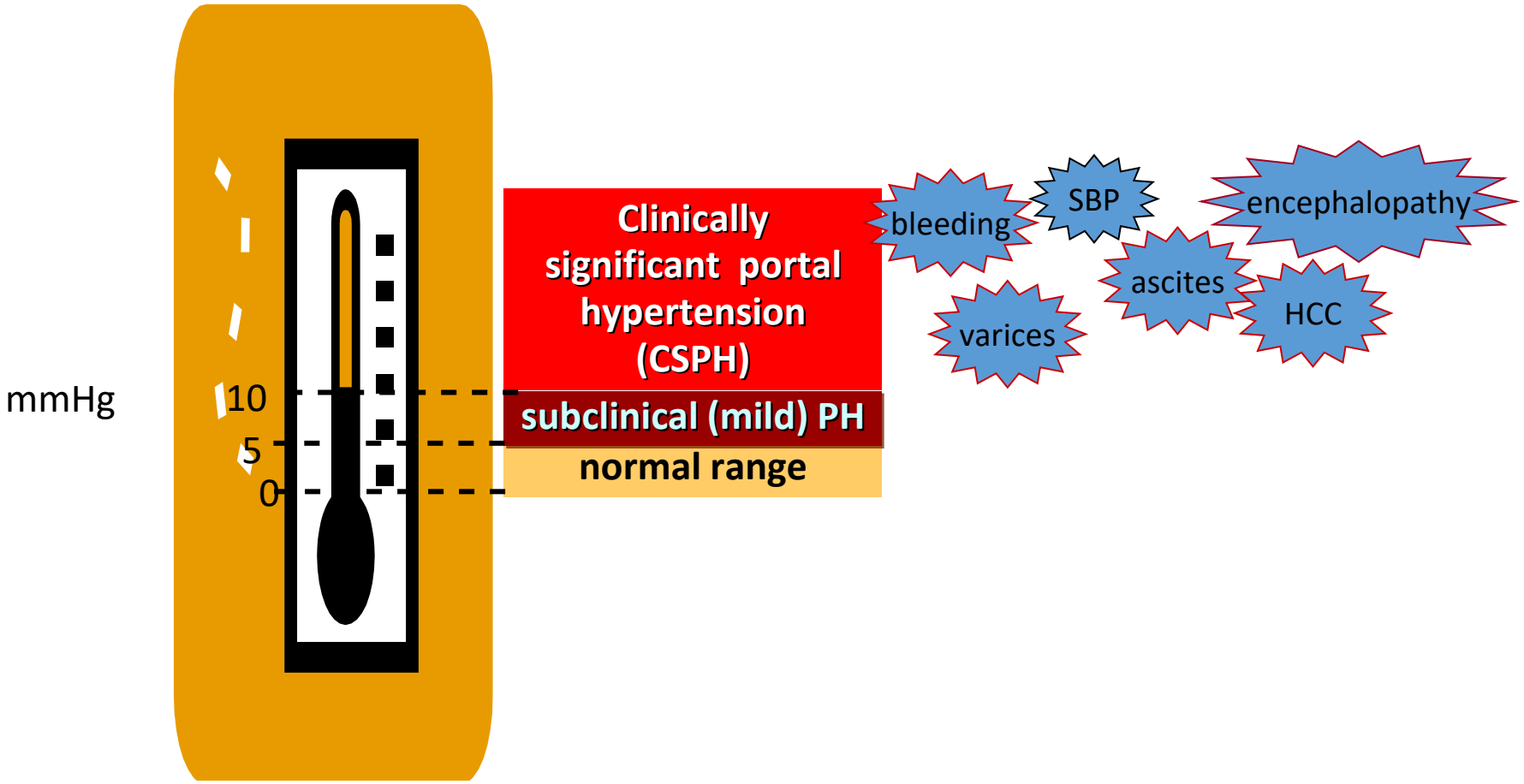
De Franchis, JHEP 2022

Ipertensione portale: patofisiologia



Berzigotti, JHEP 2017

Ipertensione portale: patofisiologia



Courtesy of J. Bosch

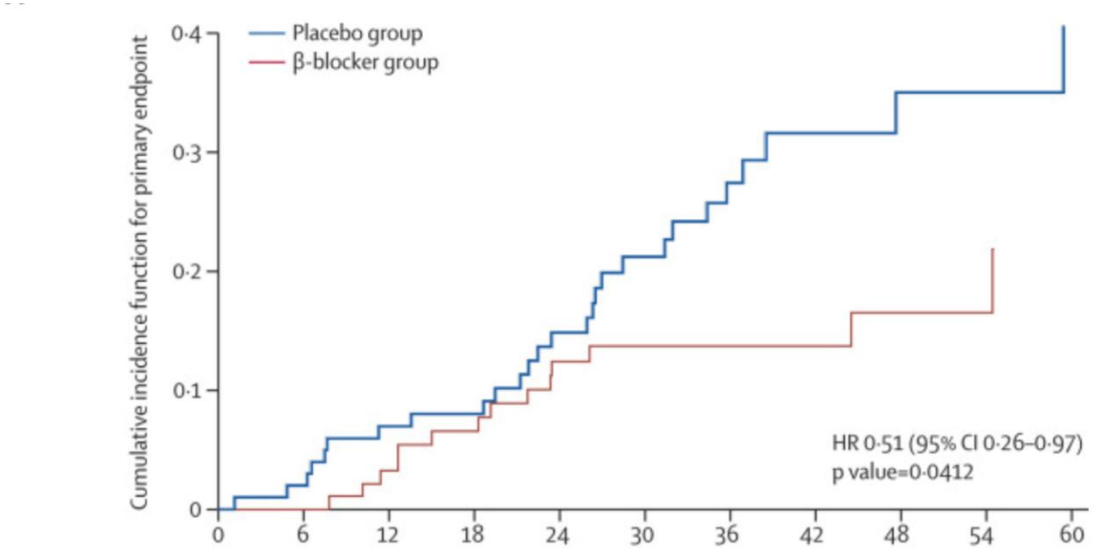
Ipertensione portale: classificazione

Classification	Level	Examples
Prehepatic	Portal vein and branches	Portal vein thrombosis
Intrahepatic	Presinusoidal (portal triads)	Schistosomiasis, primary biliary cholangitis, sarcoidosis, portosinusoidal vascular disorder
	Sinusoidal	Cirrhosis (all causes), alcohol-associated hepatitis
	Postsinusoidal (central veins)	Sinusodial obstruction syndrome
Posthepatic	Hepatic veins, inferior vena cava	Budd-Chiari syndrome, congestive hepatopathy (multiple causes including but not limited to pulmonary hypertension, heart failure, constrictive pericarditis)

Ipertensione portale è reversibile!

Kaplan, Hepatol 2023

Terapia: beta bloccanti non cardio-selettivi



Patients at risk											
β blockers	100	96	87	80	69	60	48	31	20	15	7
Placebo	101	99	94	86	72	59	42	26	19	13	6
Primary outcome (deaths)											
β blockers		1 (1)	3 (1)	4 (2)	5 (2)	1 (1)	0	0	1 (1)	0	1
Placebo		2 (2)	5 (1)	1	6 (2)	5 (1)	4 (3)	2 (1)	1 (1)	0	1
Censoring events											
β blockers		3	6	3	6	8	12	17	10	5	7
Placebo		0	0	7	8	8	13	14	6	6	6

Villanueva et al, Lancet 2019

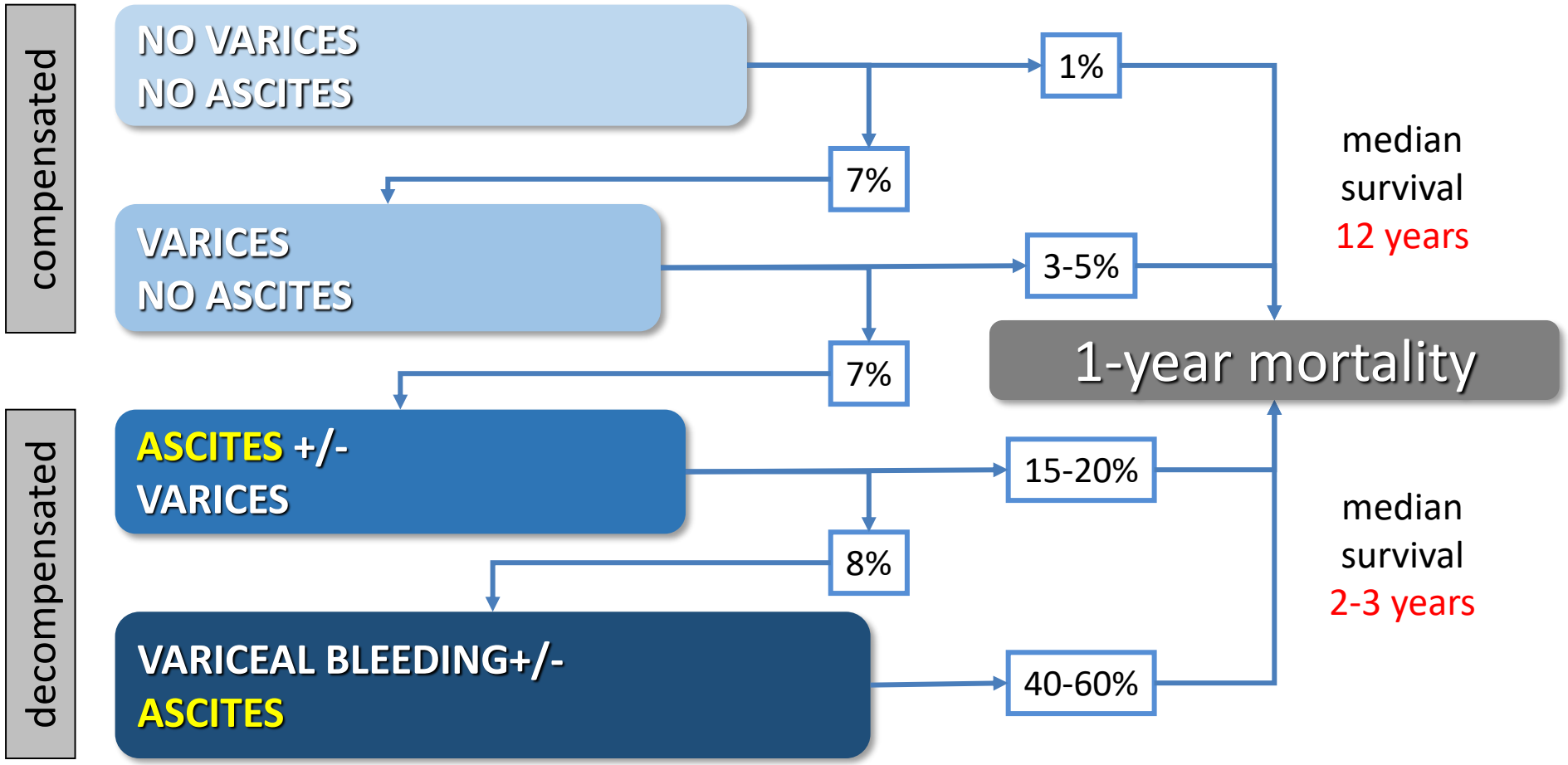
Terapia: beta bloccanti non cardio-selettivi

TABLE 3 Nonselective beta-blockers used in portal hypertension

Therapy	Mechanism of action	Starting dose	Titration	Maximal dose	Goal	Common adverse effects	Maintenance
Propranolol	Decreased cardiac output; caused by decreased heart rate and contractility from beta-1 adrenergic blockade, plus	20–40 mg twice daily	Increase the dose every 2–3 d until treatment goal	Without ascites: 320 mg/day; with ascites: 160 mg/day	HR of 55–60 bpm if tolerated; SBP should be maintained ≥90 mm Hg	Fatigue, bradycardia, dyspnea, orthostasis, hypotension, constipation	Indefinitely or until TIPS or liver transplant. No indication for routine upper endoscopy
Nadolol	Splanchnic arterial vasoconstriction; caused by beta-2 blockade leading to unopposed alfa-adrenergic vasoconstriction	20–40 mg at bedtime		Without ascites: 160 mg/day; with ascites: 80 mg/day			
Carvedilol	Above plus decreased intrahepatic vascular resistance; caused by anti-alpha-adrenergic activity	6.25 mg once daily	Increase to 6.25 mg twice daily after 3 d	12.5 mg/day (higher doses could be considered for nonhepatic indications)	No HR goal; SBP should be maintained ≥90 mm Hg		

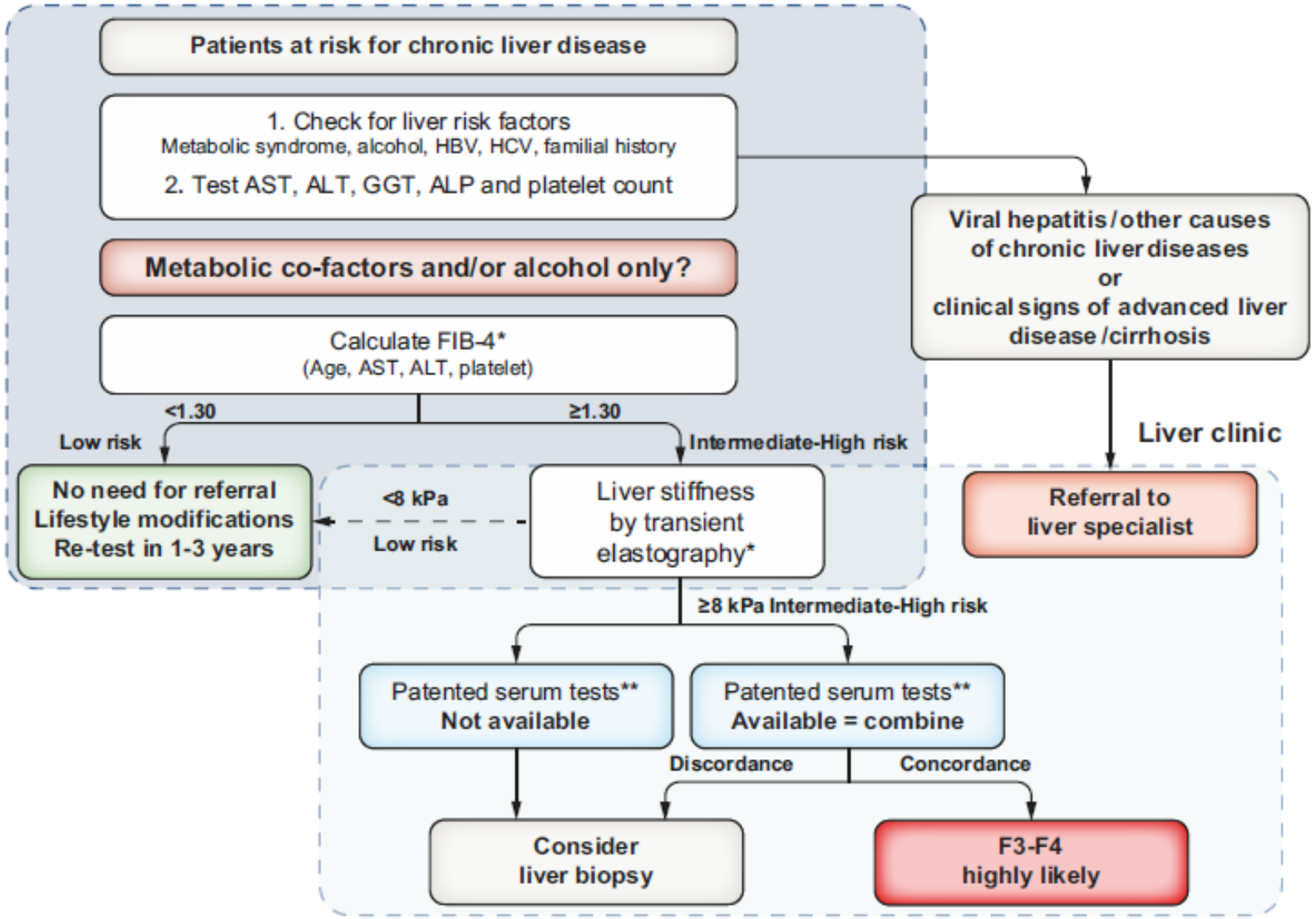
Abbreviations: SBP, spontaneous bacterial peritonitis; HR, heart rate.

Prognostic impact of decompensation



El Serag, Am J Gastro, 2000. D'Amico, Gastroenterology, 2001. Stokkeland, Hepatology, 2006

Proposed use of NITs in primary care/diabetology clinic



EASL CPG: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2021;73(3):659–689.

Fibrosis-4 (FIB-4) Index for Liver Fibrosis

Noninvasive estimate of liver scarring in HCV and HBV patients, to assess need for biopsy.

When to Use | Pearls/Pitfalls | Why Use

Age Use with caution in patients <35 or >65 years old, as the score has been shown to be less reliable in these patients		years
AST Aspartate aminotransferase	Norm: 15 - 41	U/L
ALT Alanine aminotransferase	Norm: 1 - 35	U/L
Platelet count	Norm: 150 - 350	× 10^3/µL

Sterling et al, Hepatol 2006

NAFLD (Non-Alcoholic Fatty Liver Disease) Fibrosis Score

Estimates amount of scarring in the liver based on several laboratory tests.

INSTRUCTIONS

The accuracy of results can be impacted by extremely elevated BMI. If your patient is morbidly obese, consider using a fibrosis score that does not incorporate BMI, such as FIB4.

When to Use | Pearls/Pitfalls | Why Use

Age		years
BMI	Norm: 20 - 25	kg/m²
Impaired fasting glucose/diabetes	No 0 / Yes +1	
AST	Norm: 15 - 41	U/L
ALT	Norm: 1 - 35	U/L
Platelet count	Norm: 150 - 350	× 10³/µL
Albumin	Norm: 3.5 - 5.5	g/dL

Angulo et al, Heptol 2007

Gender
Age
Glucose
Cholesterol
AST
ALT
GGT
Platelets

Serra-Burriel et al, Lancet 2023

LiverPRO

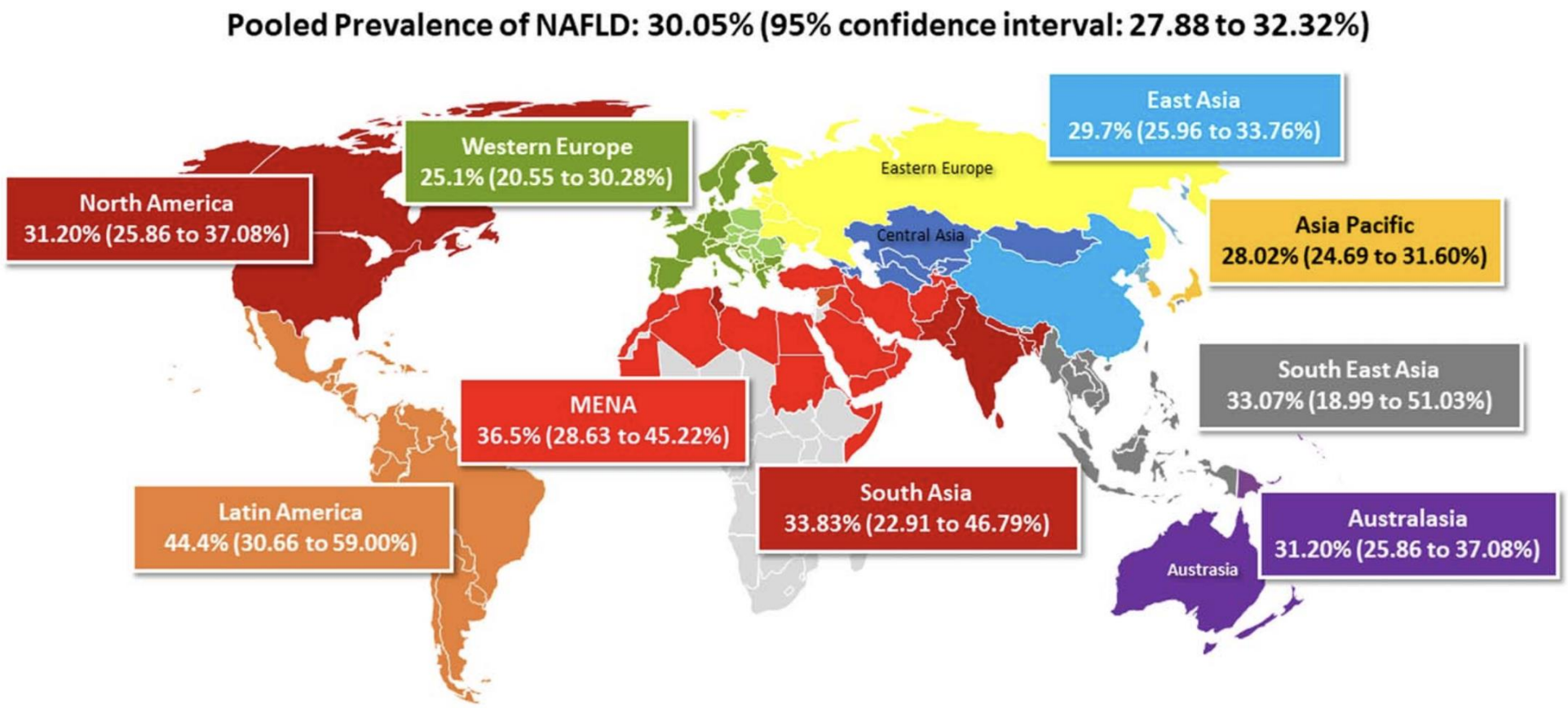
Age
AST
gGT
ALP
Cholesterol
Sodium
INR
Bilirubin
Albumin
Platelets

Development, validation, and prognostic evaluation of LiverPRO for the prediction of significant liver fibrosis in primary care: a prospective cohort study

The promise of automated liver disease risk stratification in primary care

Lindvig et al, ***Lancet Gastroenterol Hepatol 2025***
Aberg & Männistö, Lancet Gastroenterol Hepatol 2025

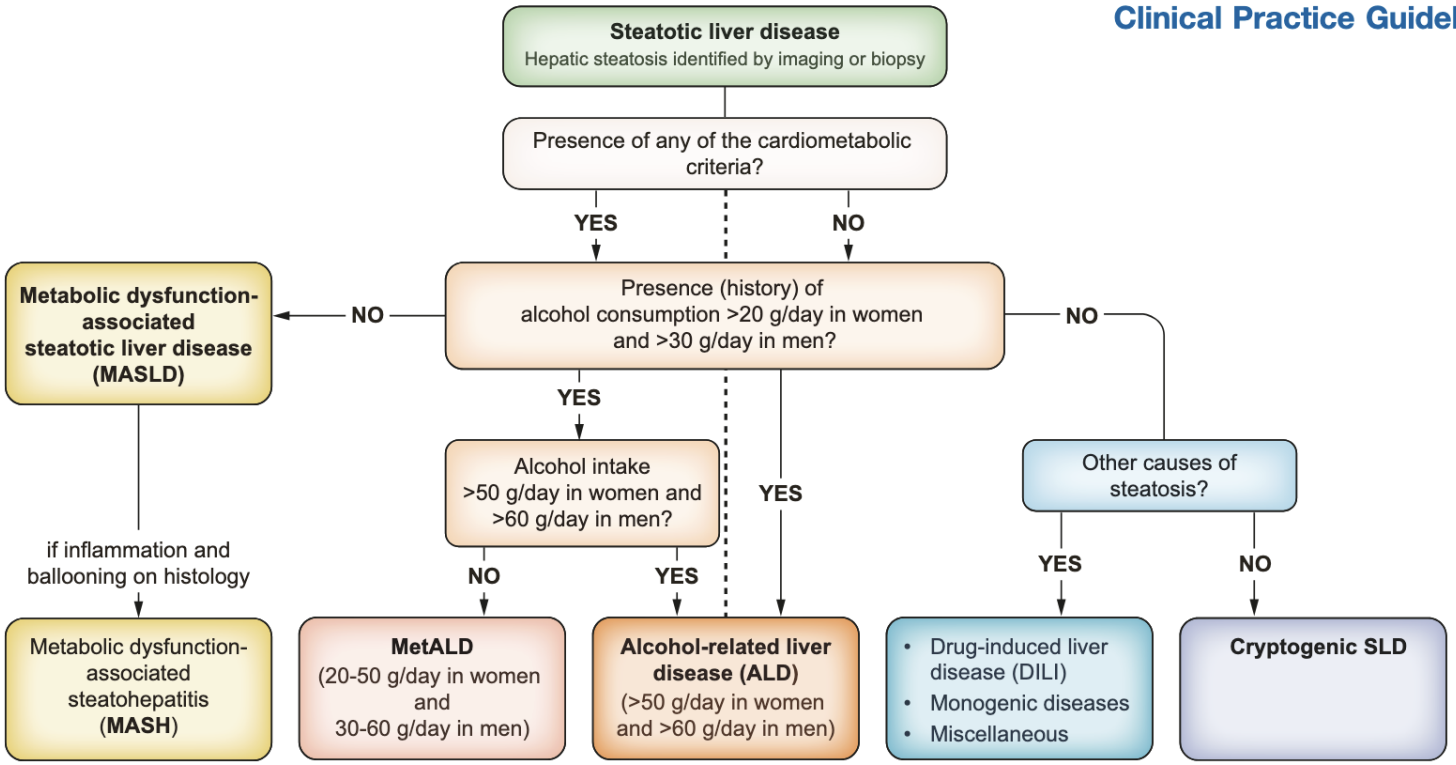
Metabolic Dysfunction Associated Liver Disease



MASH global prevalence 4-6%

Younossi et al, Hepatol 2023
Harrison et al, NEJM 2024

Metabolic Dysfunction Associated Liver Disease (MASLD)



EASL CPG 2024

MASLD definition criteria

Strongest risk factors for aggressive course:

- Obesity
- Tyoe 2 diabetes

Adult Criteria

At least 1 out of 5:

- ☐ BMI ≥ 25 kg/m² [23 Asia] **OR** WC > 94 cm (M) 80 cm (F) **OR** ethnicity adjusted equivalent
- ☐ Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** type 2 diabetes **OR** treatment for type 2 diabetes
- ☐ Blood pressure ≥ 130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] **OR** lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) **OR** lipid lowering treatment

AASLD CPG 2023
EASL CPG 2024

Lifestyles

Weight loss

Sport

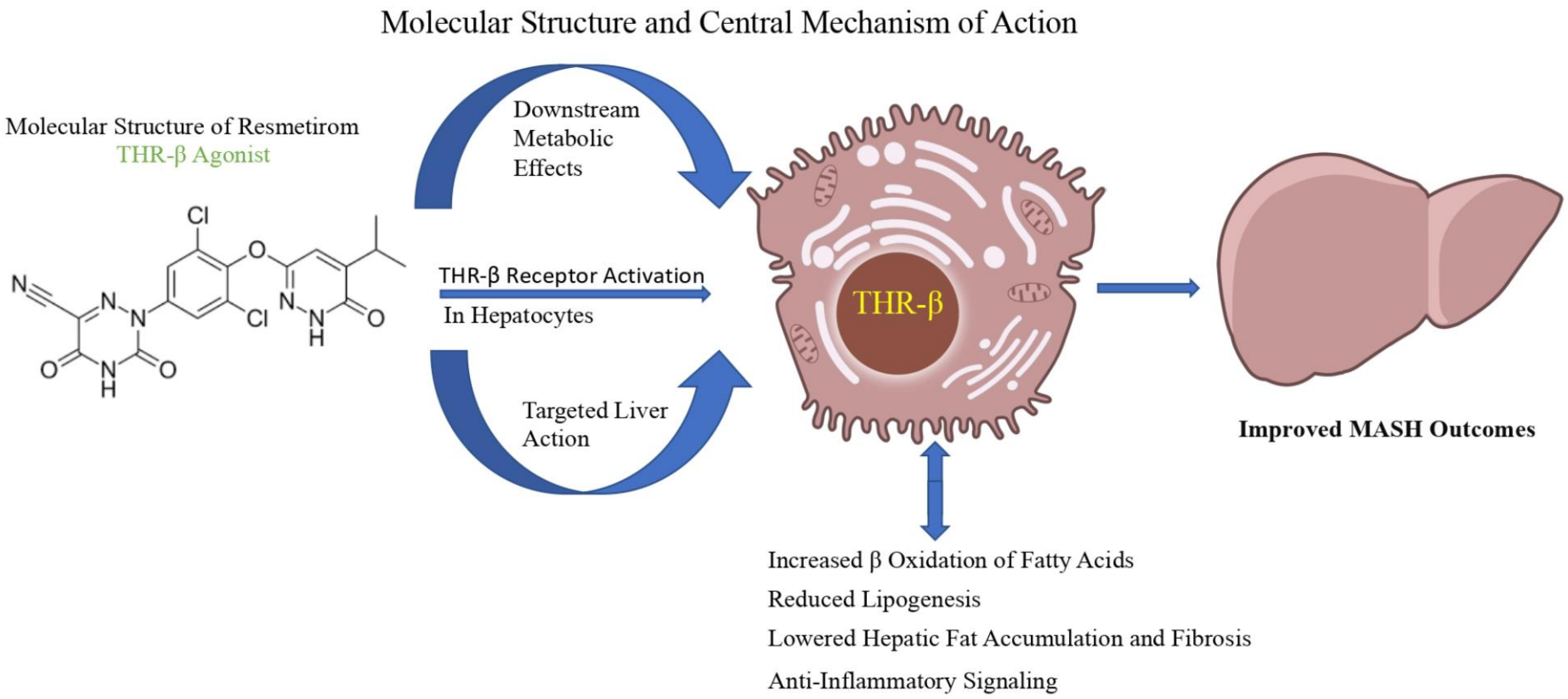
Diet

Drinks

Smoking

Sleep

Resmetiron, Thyroid Hormon Receptor-β agonist



Tiwari et al, Biomedicines 2025
Harrison, NEJM 2024

Resmetiron

Key inclusion criteria:
- ≥ 3 metabolic risk factors
- CAP > 280 dB/m, FS > 8.5 kPa
- Histological evidence of MASH
- 50% of study population ≥ F3

Key exclusion criteria:
- F4
- Excessive alcohol consumption

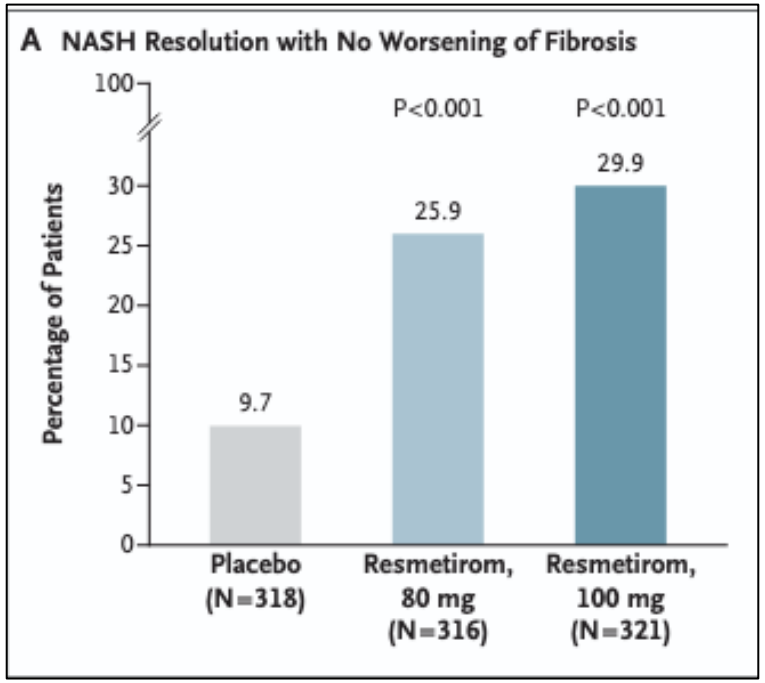
Characteristic	Resmetirom, 80 mg (N=322)	Resmetirom, 100 mg (N=323)	Placebo (N=321)
Age — yr	55.9±11.5	57.0±10.8	57.1±10.5
Male sex — no. (%)†	140 (43.5)	141 (43.7)	143 (44.5)
Race or ethnic group — no. (%)†			
White	291 (90.4)	291 (90.1)	281 (87.5)
Black	5 (1.6)	5 (1.5)	9 (2.8)
Asian	10 (3.1)	9 (2.8)	9 (2.8)
Other‡	12 (3.7)	11 (3.4)	18 (5.6)
Missing data	4 (1.2)	7 (2.2)	4 (1.2)
Hispanic or Latino ethnic group — no. (%)†	71 (22.0)	81 (25.1)	52 (16.2)
Body weight — kg	100.1±22.3	101.9±22.9	100.2±23.1
Body-mass index	35.5±6.4	36.2±7.4	35.3±6.5
Type 2 diabetes — no. (%)	224 (69.6)	213 (65.9)	210 (65.4)
Hypertension — no. (%)	243 (75.5)	254 (78.6)	257 (80.1)
Dyslipidemia — no. (%)	229 (71.1)	236 (73.1)	224 (69.8)
Hypothyroidism — no. (%)§	39 (12.1)	46 (14.2)	45 (14.0)

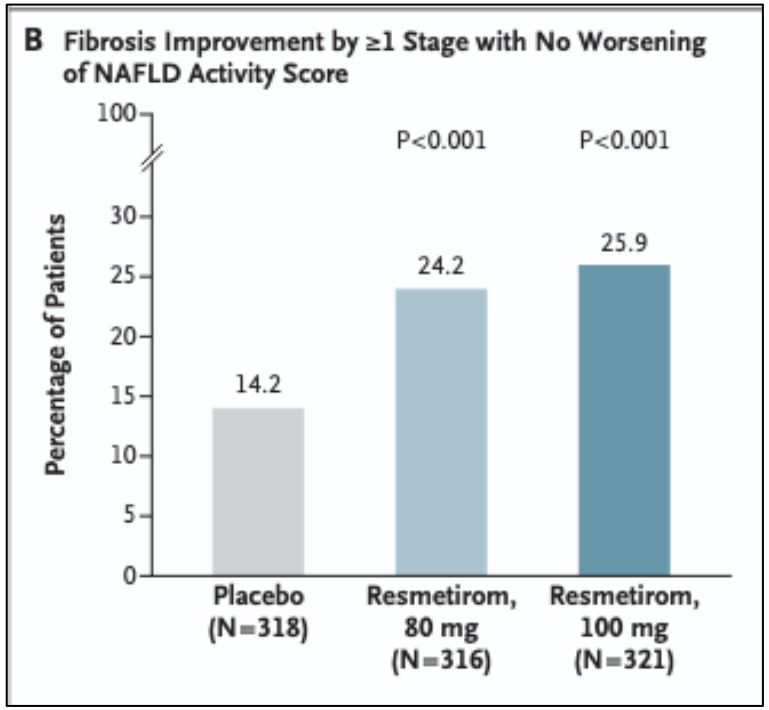
Harrison, NEJM 2024

Resmetiron

Primary endopoints at 52 weeks:

1. MASH resolution with no worsening of fibrosis
2. Fibrosis improvement with no worsening of MASH





Harrison, NEJM 2024

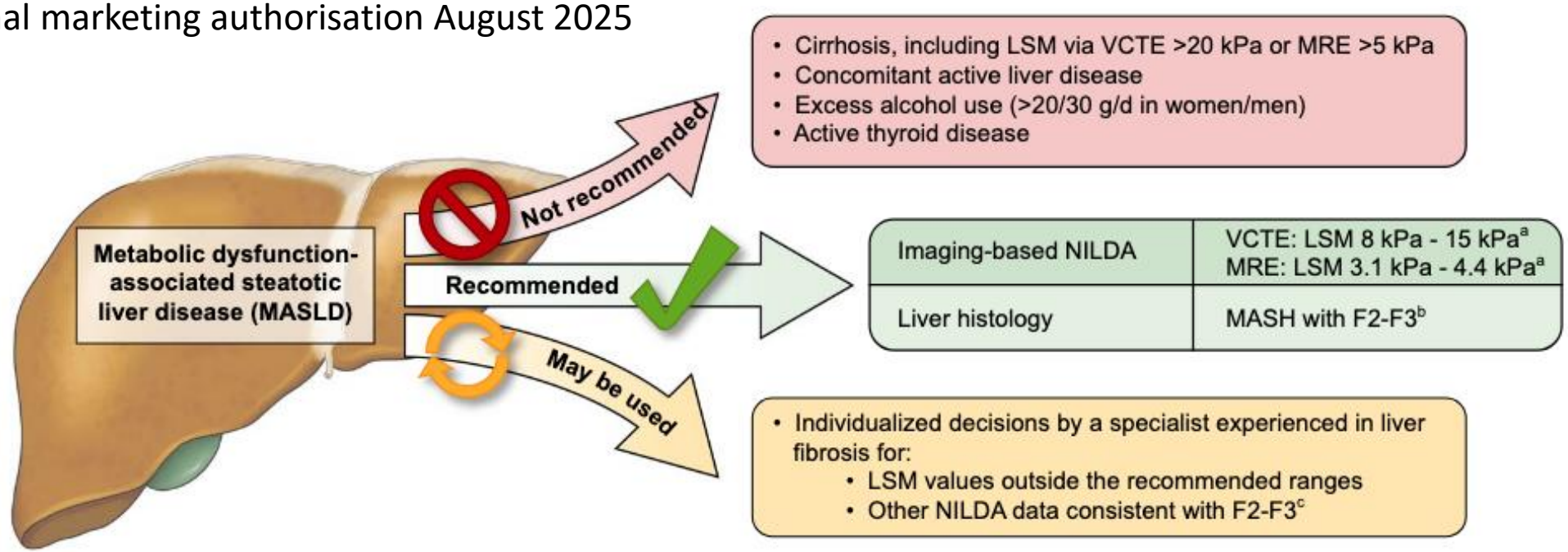
Resmetiron

Event	Resmetirom, 80 mg (N=322)	Resmetirom, 100 mg (N=323)	Placebo (N=321)
	number of patients (percent)		
≥1 Adverse event	296 (91.9)	296 (91.6)	298 (92.8)
Grade 1: mild	73 (22.7)	66 (20.4)	77 (24.0)
Grade 2: moderate	180 (55.9)	183 (56.7)	169 (52.6)
Grade 3 or higher: severe	43 (13.4)	47 (14.6)	52 (16.2)
≥1 Adverse event attributed to resmetirom or placebo*	124 (38.5)	134 (41.5)	88 (27.4)
≥1 Serious adverse event	35 (10.9)	41 (12.7)	37 (11.5)
≥1 Serious adverse event attributed to resmetirom or placebo*	2 (0.6)	0	1 (0.3)
Adverse event leading to trial discontinuation before wk 52†	6 (1.9)	22 (6.8)	7 (2.2)
Adverse event leading to trial discontinuation during entire treatment period†	9 (2.8)	25 (7.7)	11 (3.4)
Fatal adverse event	1 (0.3)	2 (0.6)	1 (0.3)
Major adverse cardiovascular event‡	1 (0.3)	1 (0.3)	1 (0.3)
Other cardiovascular event‡	0	1 (0.3)	3 (0.9)
Adverse events affecting >10% of patients in any group			
Diarrhea	87 (27.0)	108 (33.4)	50 (15.6)
Covid-19	69 (21.4)	54 (16.7)	66 (20.6)
Nausea	71 (22.0)	61 (18.9)	40 (12.5)
Arthralgia	48 (14.9)	35 (10.8)	40 (12.5)
Back pain	35 (10.9)	27 (8.4)	38 (11.8)
Urinary tract infection	33 (10.2)	27 (8.4)	27 (8.4)
Fatigue	33 (10.2)	26 (8.0)	28 (8.7)
Pruritus	26 (8.1)	37 (11.5)	22 (6.9)
Vomiting	28 (8.7)	35 (10.8)	17 (5.3)

Harrison, NEJM 2024

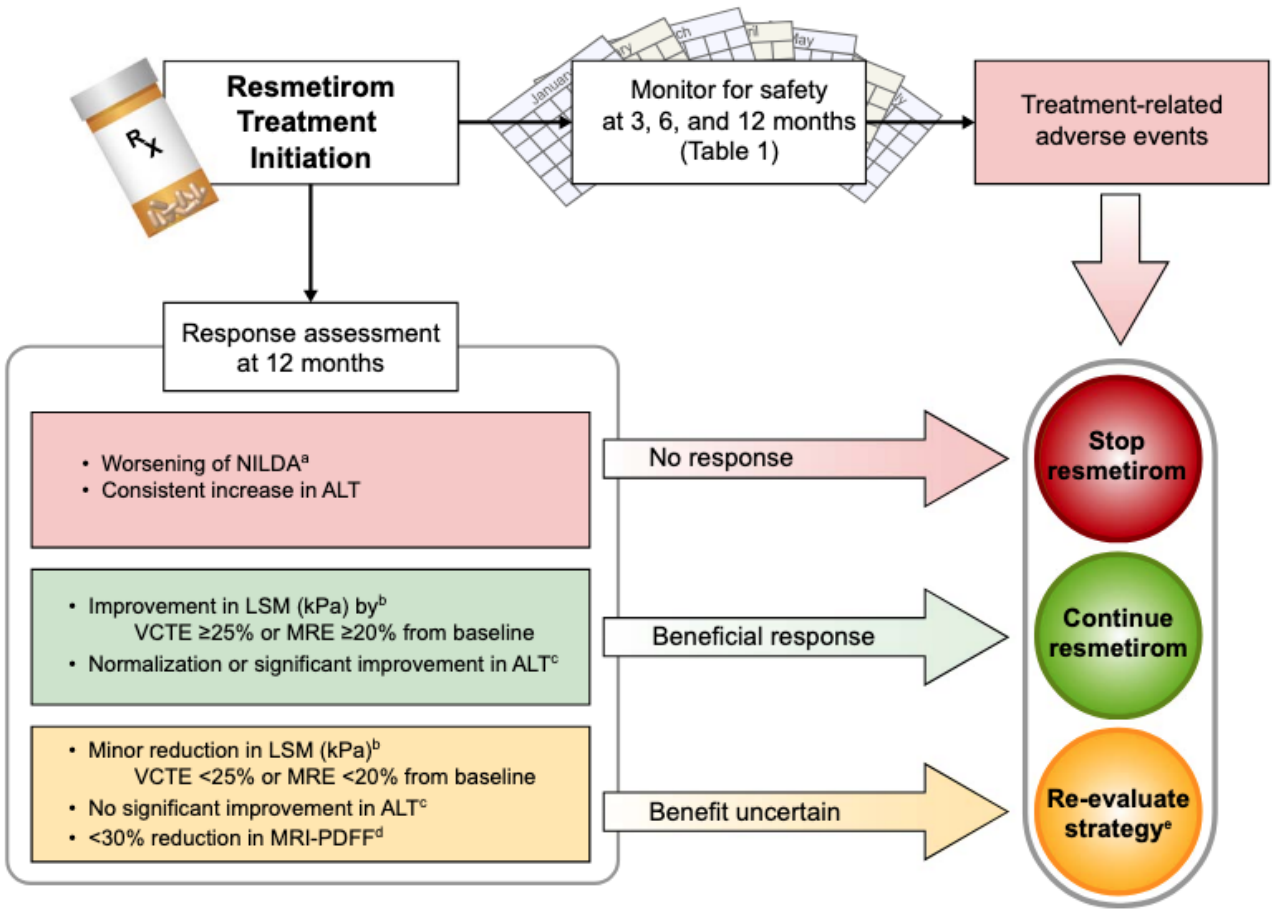
Resmetiron

FDA approval March 2024
EU conditional marketing authorisation August 2025



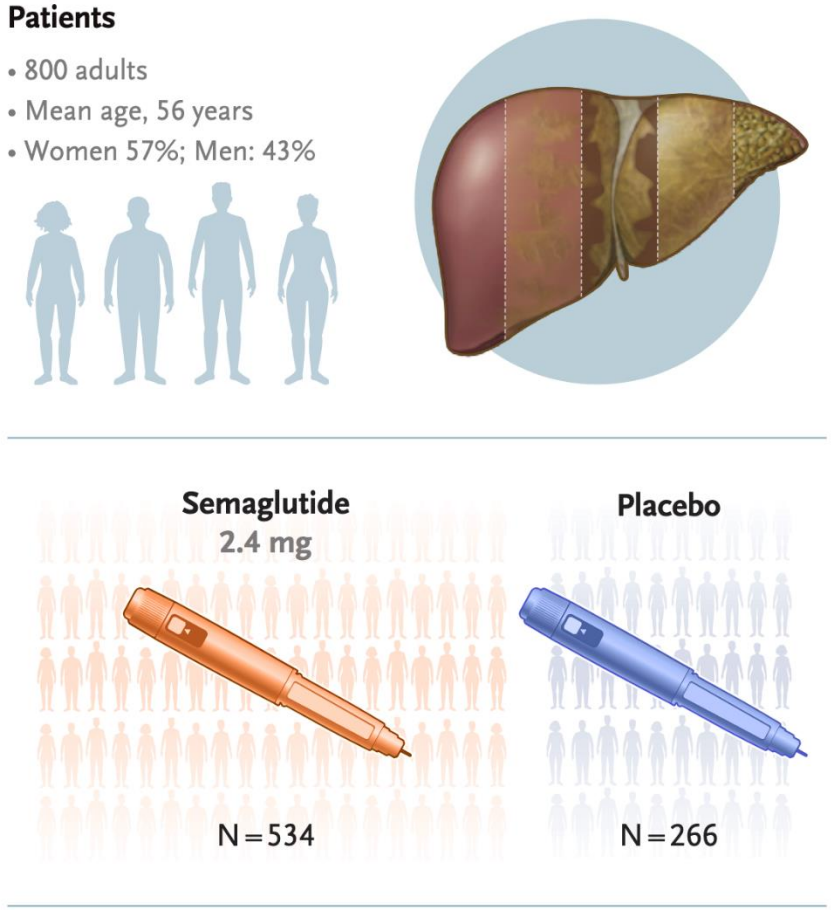
Chen et al, Hepatol 2025

Resmetiron



Chen et al, Hepatol 2025

Semaglutide



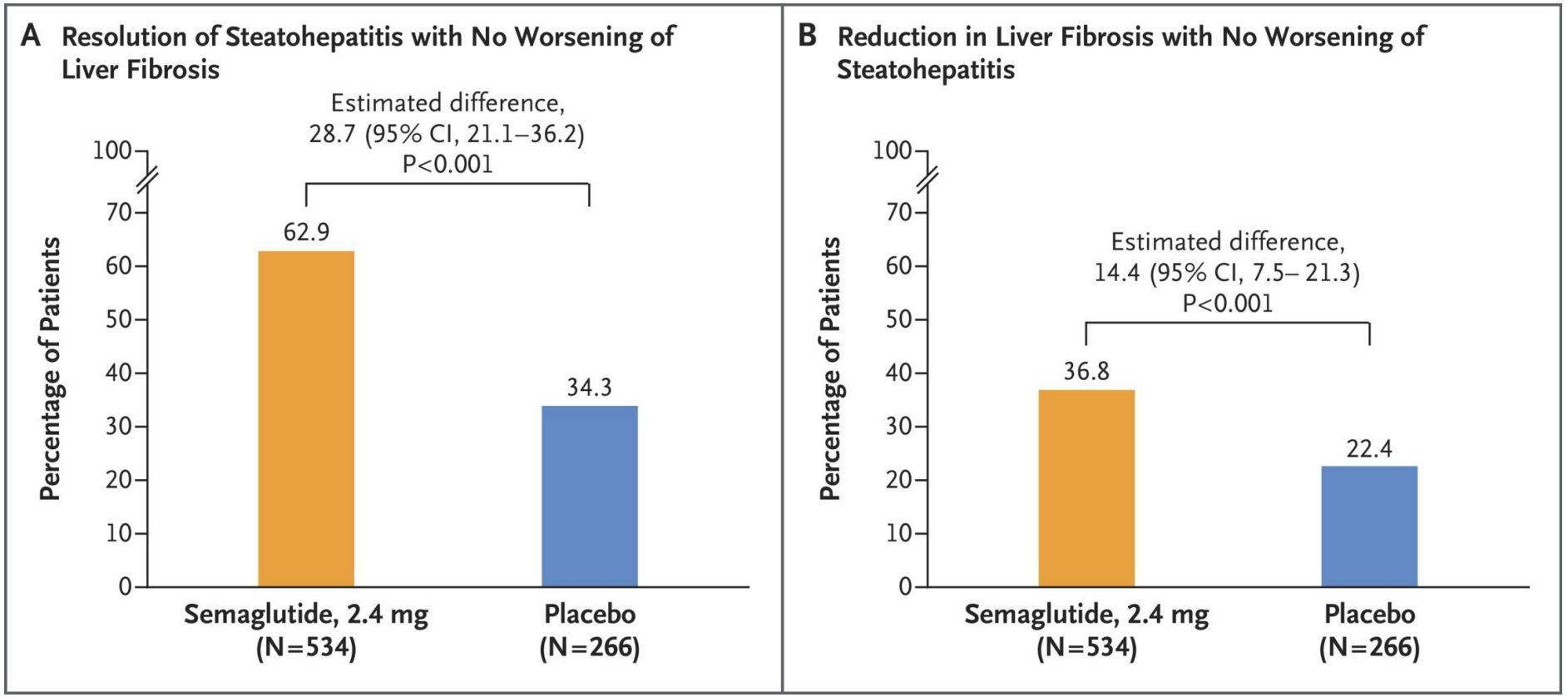
Accelerated approval by FDA 15.8.2025

Fibrosis stage 2 or 3 at liver biopsy with MASH

Interim analysis week 72

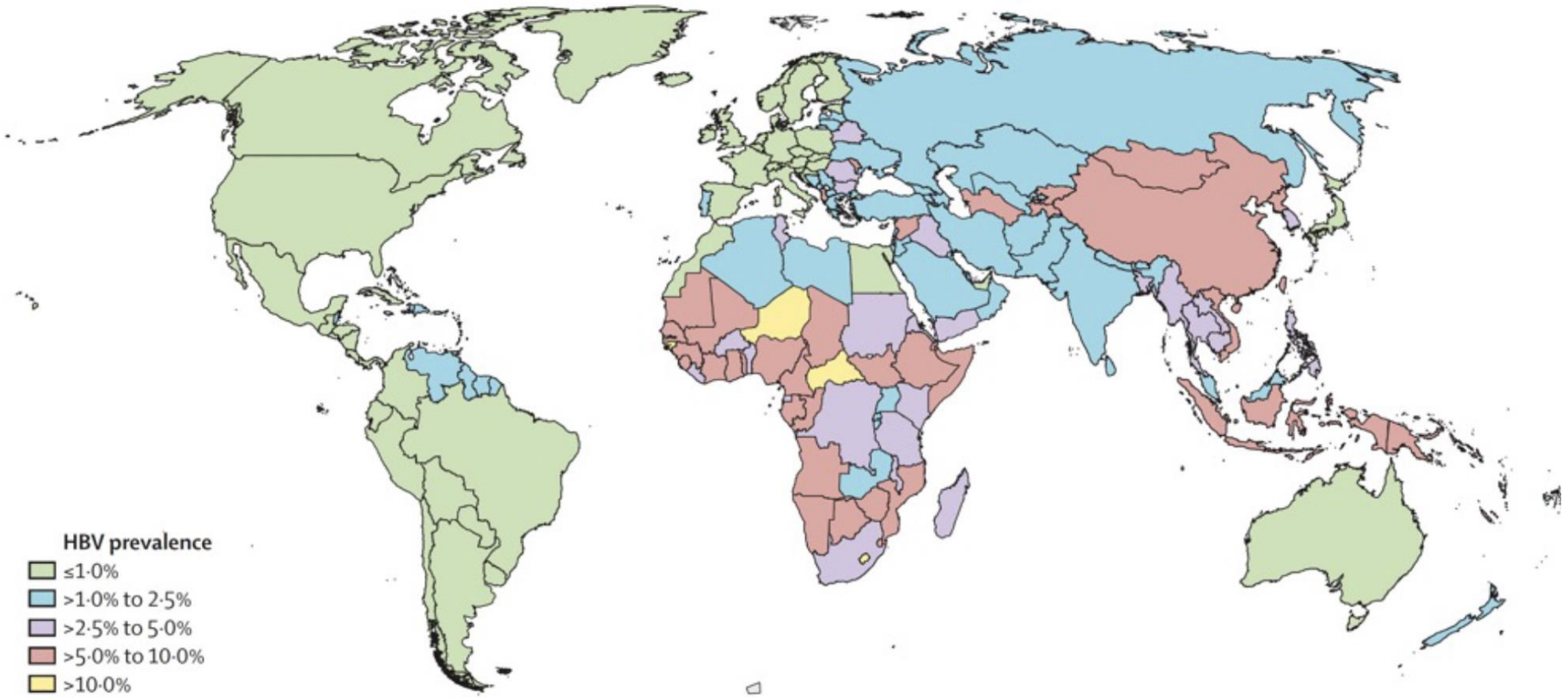
Sanyal et al, NEJM 2025

Semaglutide



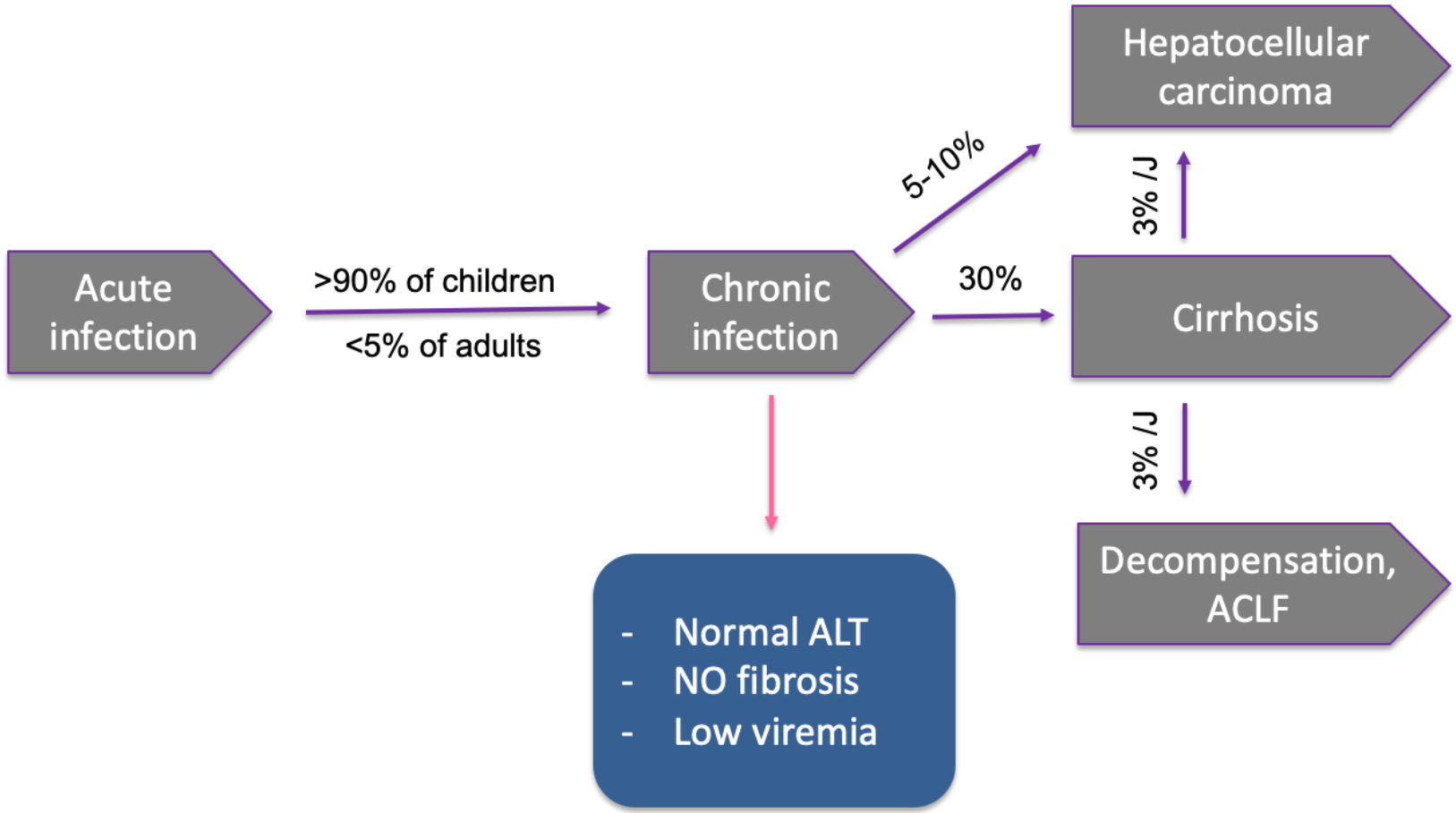
Sanyal et al, NEJM 2025

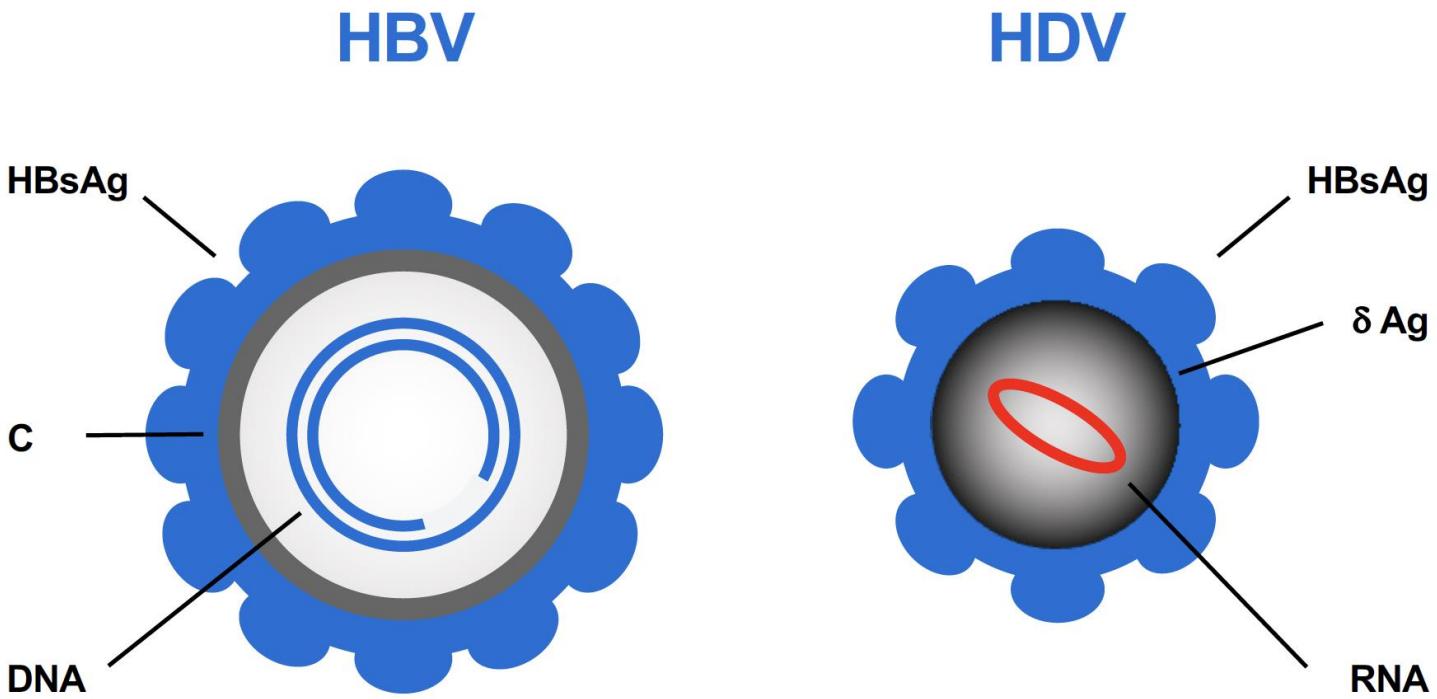
Current Epidemiology of Hepatitis B



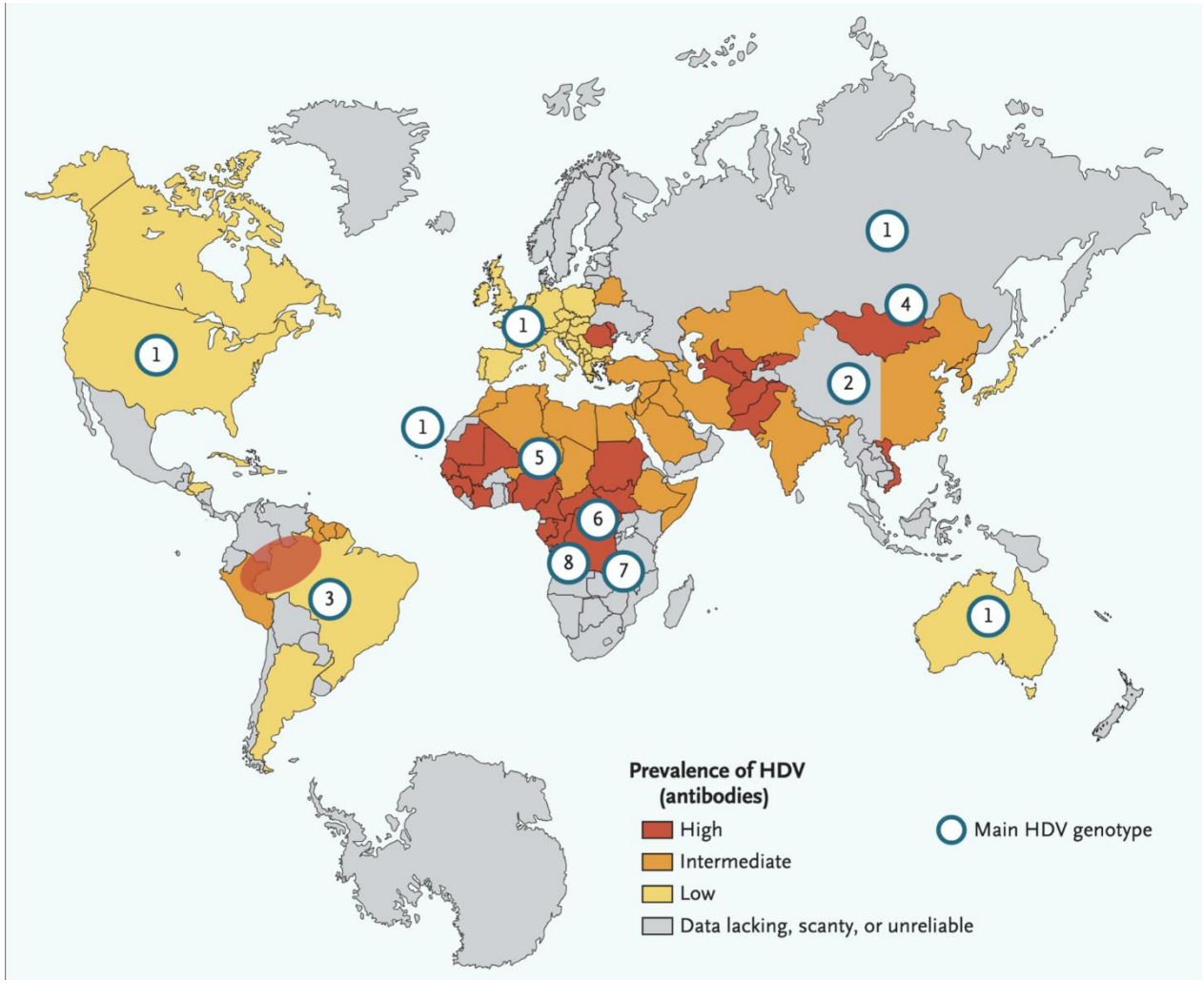
The Polaris Observatory Collaborators, Lancet Gastroenerol Hepatol 2023

HBV natural history




HBV
HBsAg
C
DNA
HDV
HBsAg
δ Ag
RNA

HDV Epidemiology



Rizzetto & Asselah, NEJM 2024

HDV Epidemiology in Switzerland

Anti-HDV+/HBsAg+	Setting	Author
5/61 (**8.2%**)	Pregnant women	Bart PA, *et al.* Liver 1996;16:110-6
101/169 (**5.9%**)	Outpatients	Genné D, Rossi I. Swiss Med Wkly 2011;141:w13176
15/338 (**4.4%**)	University Hospital, Berne	Hirzel C, *et al.* BMC Infect Dis 2015;15:483
119/771 (**15.4%**)	HIV-coinfected	Béguelin C, *et al.* J Hepatol 2017;66:297-303
46/672 (**7.1%**)	University Hospital, Lausanne	Vieira Barbosa, *et al.* PLoS One 2021;16:e0250347
41/529 (**7.8%**)	University Hospital, Geneva	Author's own data

Estimated HBV pool (44,100[1] – 62,700[2]) → **Estimated anti-HDV+ among HBsAg+ 6%** → **Estimated HDV RNA+ among anti-HDV+ 60%** → **Total HDV RNA+ 1,600 – 2,250**

Negro et al, Swiss Medical Weekly 2023

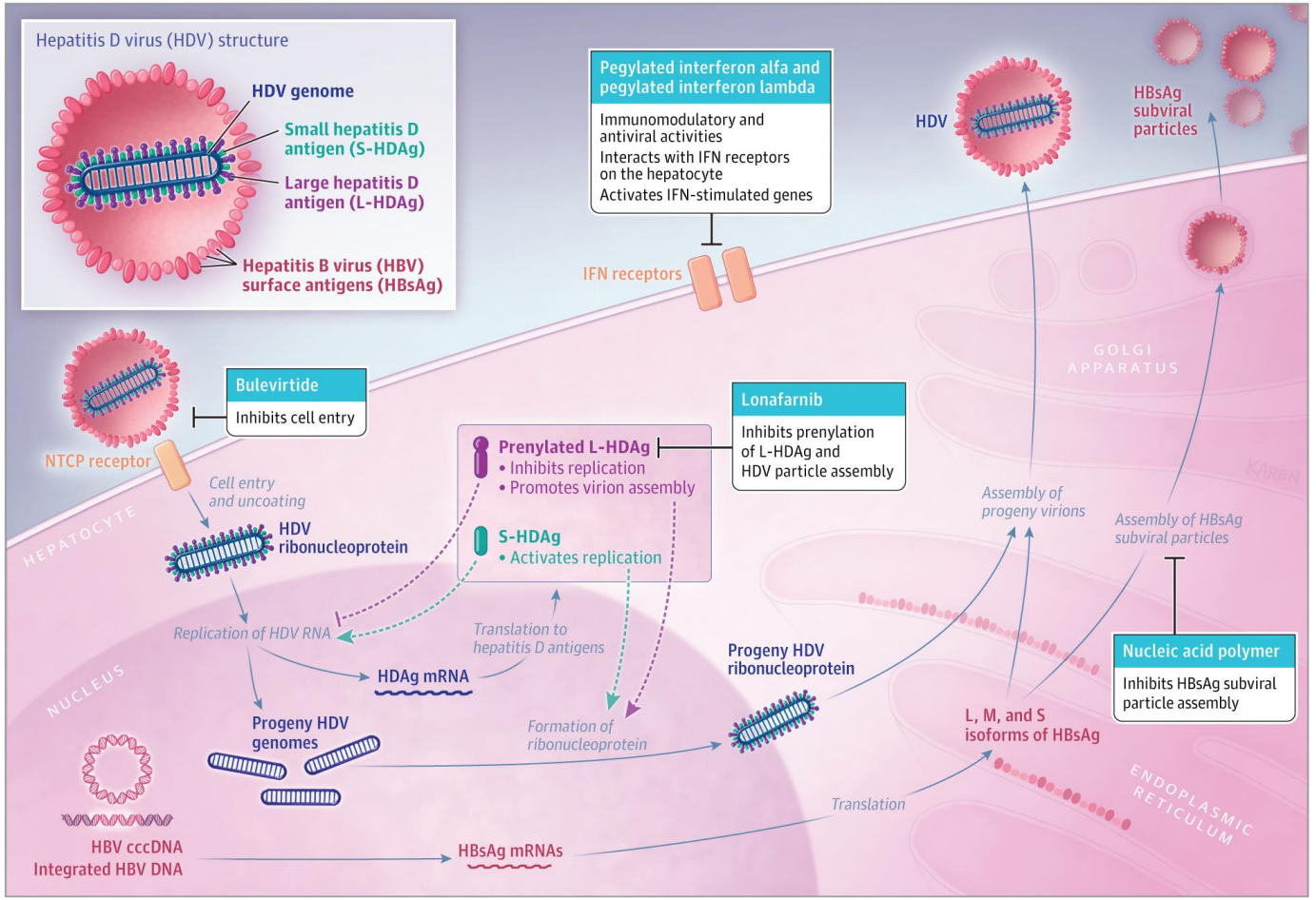
HDV is the most severe form of viral hepatitis

Progression to compensated cirrhosis	RR 1.74 (95% CI: 1.24 - 2.45)
Progression to decompensated cirrhosis	HR 3.82 (95% CI: 1.60 - 9.10)
HCC	HR 2.97 (95% CI: 1.87 - 4.70)
Liver transplantation	HR 7.07 (95% CI: 1.61 - 30.99)
Liver-related mortality	HR 3.78 (95% CI: 2.18 - 6.56)

Metanalysis on 12 studies, n=4876; HDV RNA+ vs HDV RNA-

Gish et al, Hepatology 2024

Bulevirtide



Lok & Negro, JAMA 2023

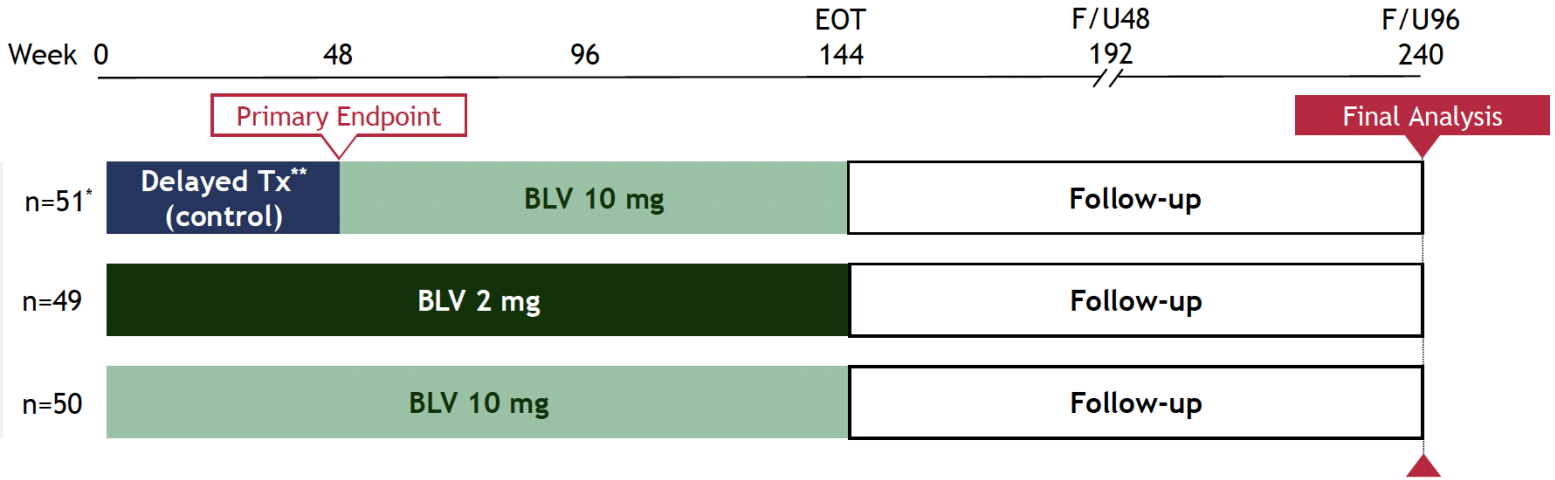
MYR301 Study Design

Multicenter, open-label, randomized, Phase 3 study

Key Inclusion Criteria:

- Adults with chronic hepatitis delta with or without compensated cirrhosis
- CTP score ≤7
- ALT >1× to <10× ULN
- Platelets ≥60,000 cells/mm^3
- Controlled HIV coinfection allowed

MYR301:
N=150
Randomized
1:1:1



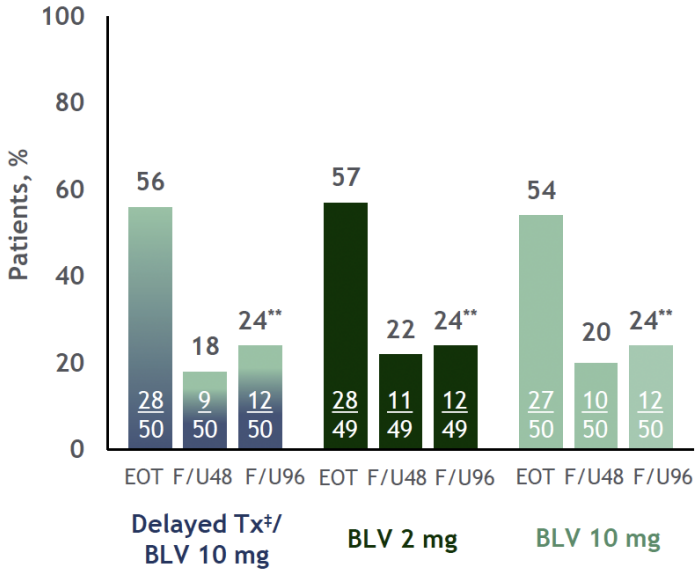
Endpoints reported at F/U96	
Virologic response	HDV RNA undetectable or decreased by ≥2 $\log_{10}$ IU/mL from baseline
ALT normalization	• ≤31 U/L for female patients and ≤41 U/L for male patients (Russian sites) • ≤34 U/L for female patients and ≤49 U/L for male patients (all other sites)
Undetectable HDV RNA	HDV RNA levels by RT-PCR using RoboGene® 2.0 (limit of detection 6 IU/mL)
Combined response	Virologic response + ALT normalization

Wedemeyer et al, EASL 2025

MYR301: BLV Efficacy at EOT and at FUwk96

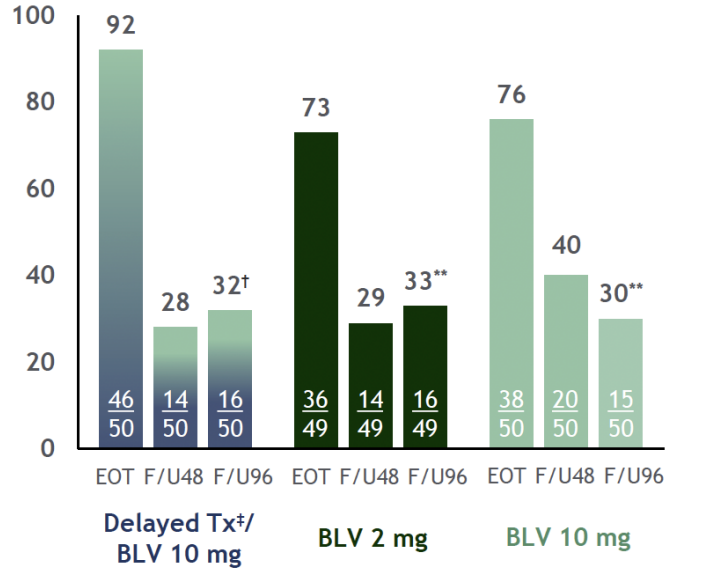
Combined Response

Undetectable HDV RNA or ≥2 $\log_{10}$ IU/mL decrease from BL and ALT normalization*



Virologic Response

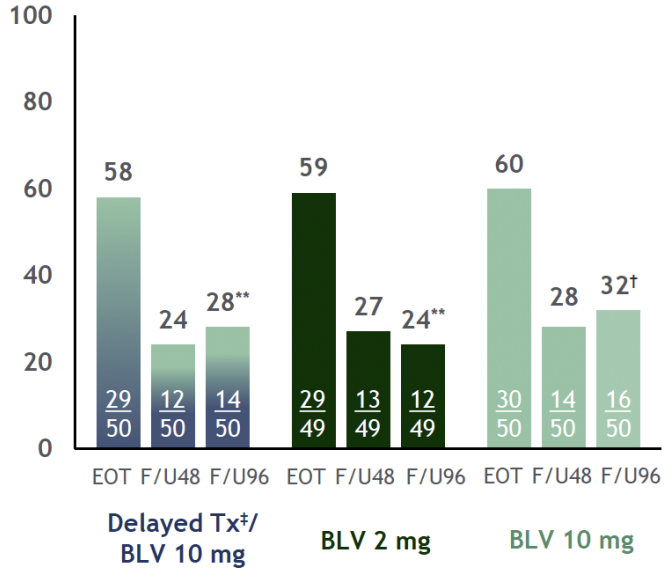
Undetectable HDV RNA or ≥2 $\log_{10}$ IU/mL decrease from BL



Undetectable HDV RNA,* %

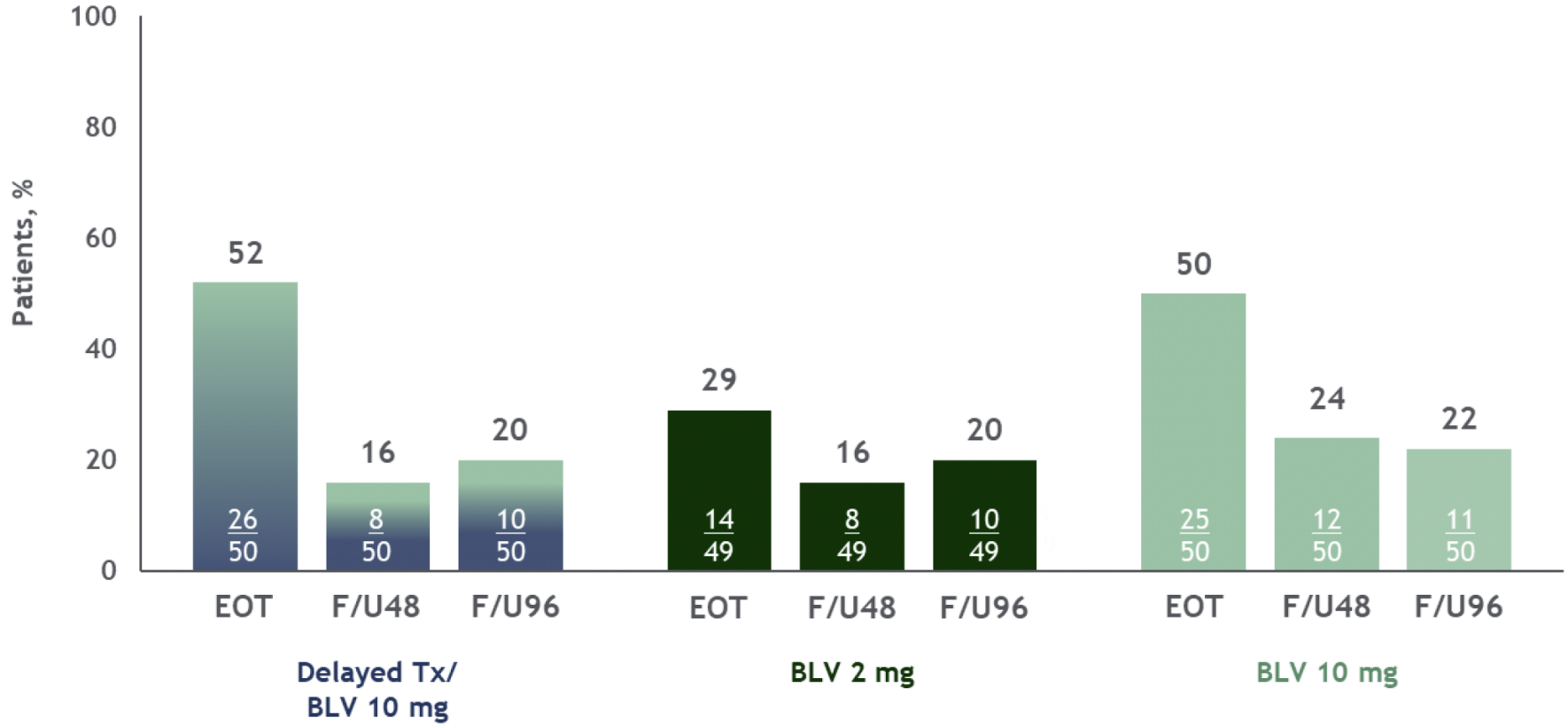
Delayed Tx‡/ BLV 10 mg			BLV 2 mg			BLV 10 mg		
52	16	20	29	16	20	50	24	22

ALT Normalization



Wedemeyer et al, EASL 2025

MYR301: Undetectable HDV RNA at EOT and During FU



92% of patients reached EOT, 72% completed FU48, and 57% completed FU96
Relapses occurred in 38 (93%) by FU24, and none after FU48

Wedemeyer et al, EASL 2025

MYR301: Safety Analysis

Liver-Related Events and ALT Flares

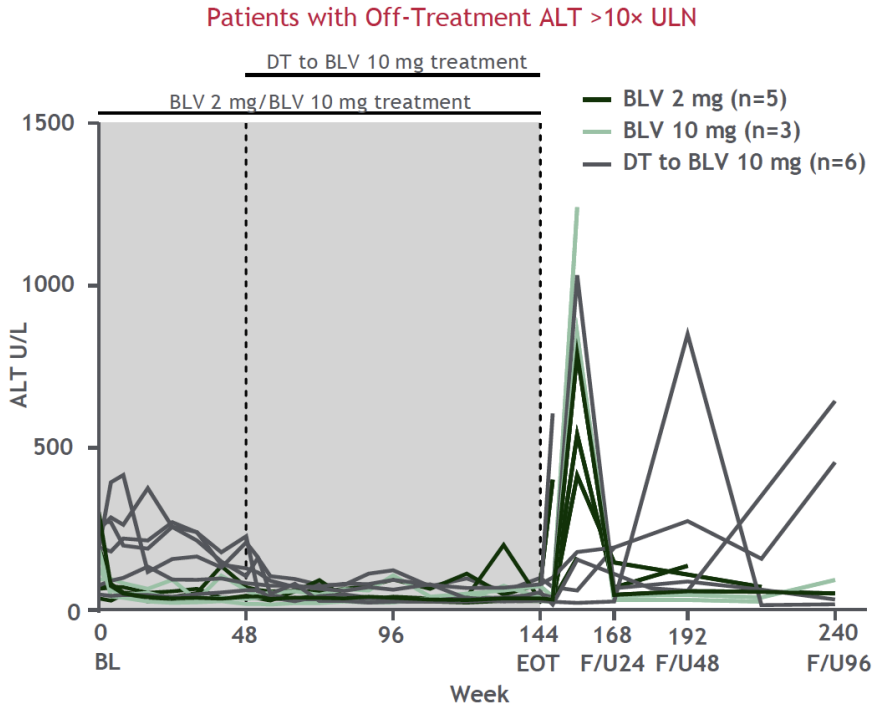
Patients, n/N	Delayed Tx/BLV 10 mg		BLV 2 mg		BLV 10 mg	
	W48 to EOT* (n=50)	EOT to F/U96 (n=49)	BL to EOT (n=49)	EOT to F/U96 (n=46)	BL to EOT (n=50)	EOT to F/U96 (n=47)
Liver-related outcomes**	1/50	1/49†	0/49	2/46†	0/50	1/47†

On Treatment

- 1 case of nonserious ascites in the Delayed Tx/BLV 10 mg group

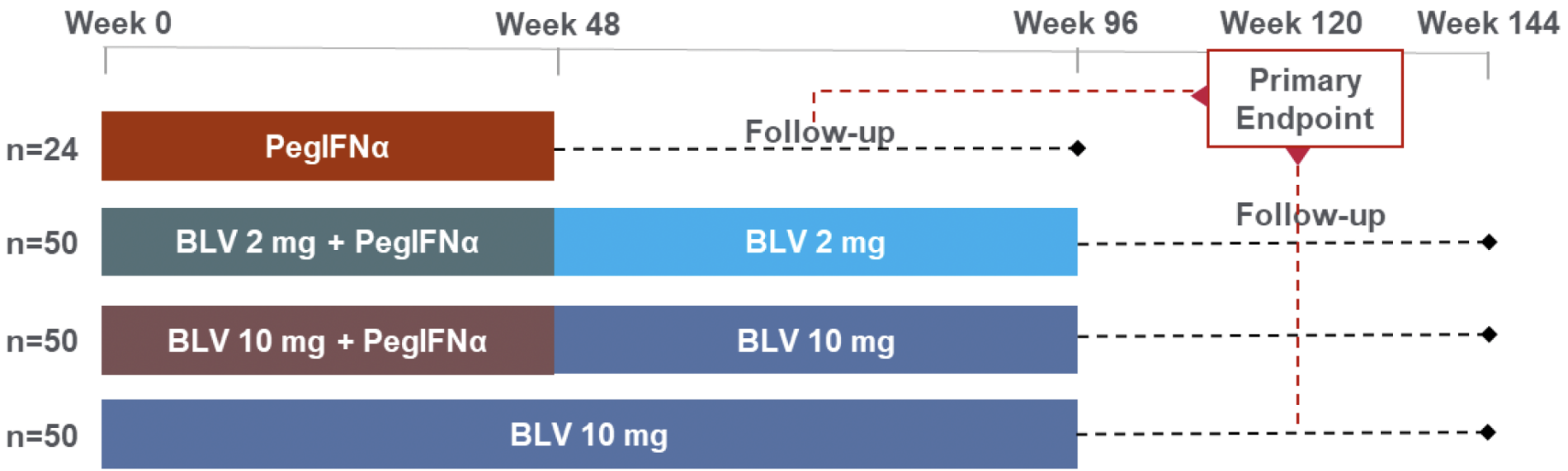
Off-Treatment

- 1 case of bleeding from varices and 1 instance of HCC in the BLV 2 mg group
- 1 case of hepatic encephalopathy in the BLV 10 mg group
- 1 case of ascites in the Delayed Tx/BLV 10 mg group



Wedemeyer et al, EASL 2025

Open-label, randomized, multicenter, Phase 2b MYR 204 study



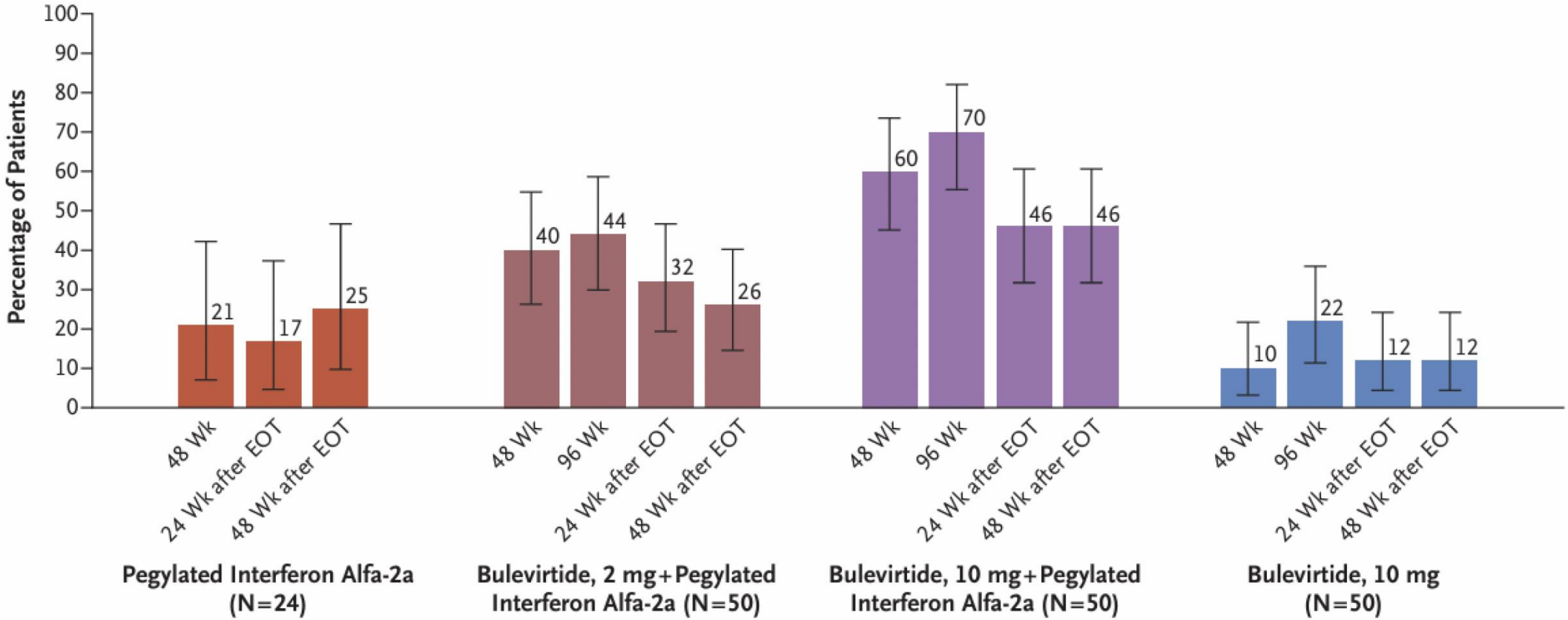
34% with cirrhosis (all CTP score ≤6, platelets >90,000 cells/mm^3)

No IFN-α within 6 months before enrollment

Asselah et al, NEJM 2024

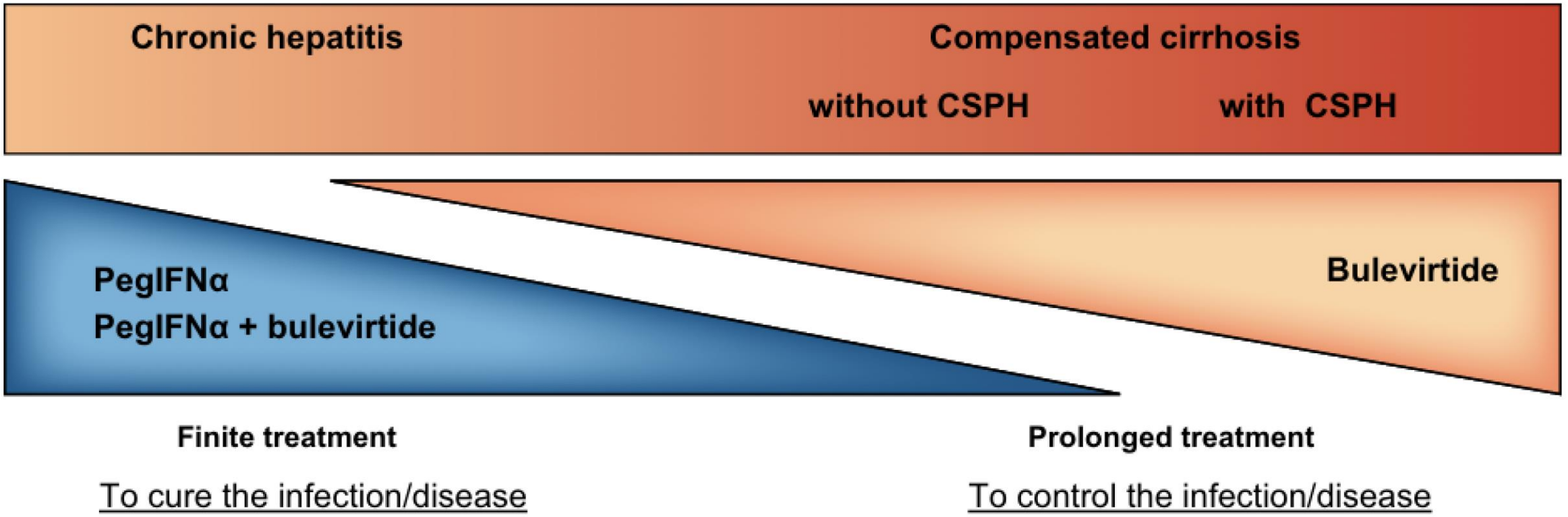
Undetectable HDV RNA 24 weeks after the end of therapy

MYR 204 phase 2 study, n=174, 59 with cirrhosis [34%]



Asselah et al, NEJM 2024

Pegylated IFN-α … or … bulevirtide?



EASL CPG 2023

Take home messages

1. Diagnosi non invasiva di
   compensated Advanced Chronic Liver Disease: Fibroscan® vs biopsia

2. MASLD:
nuova nomenclatura, scores per screening fibrosi nello studio medico
   nuovi farmaci: resmetiron, semaglutide

3. Epatite delta:
   non così rara, aggressiva, nuova terapia