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Regression of fibrosis. Is HBV cirrhosis reversible?

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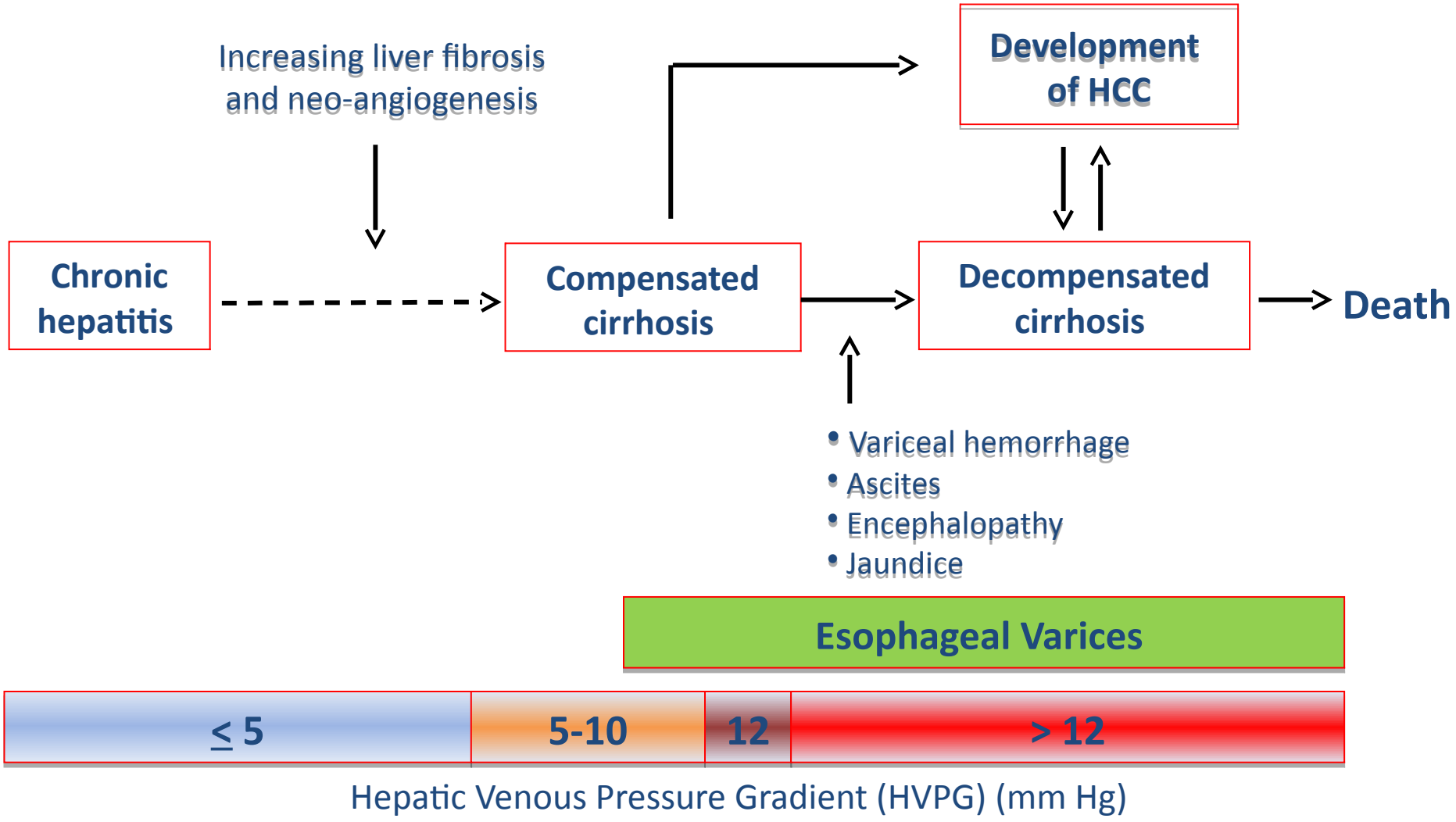
The natural history of chronic liver disease



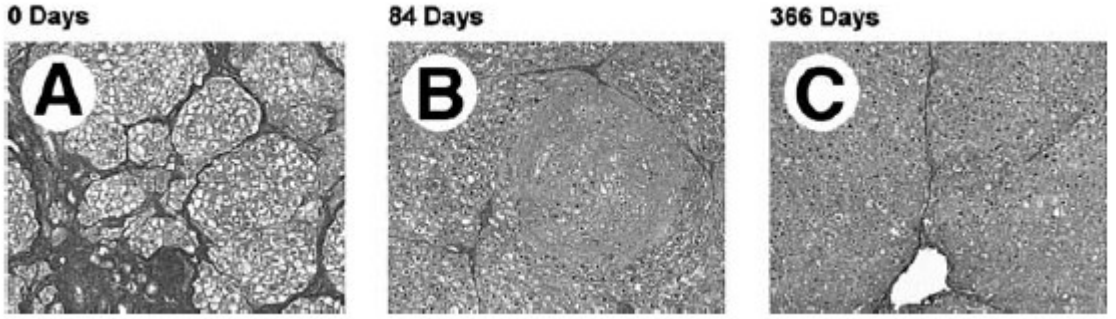
Cirrhosis is a progression of stages of increasing severity and non-reversibility

	Metavir F4 Ishak S 5-6	**Metavir F4 Ishak S 6**	**Metavir F4 Ishak S 6**	**Metavir F4 Ishak S 6**	**Metavir F4 Ishak S 6**
Biology:	**Fibrogenesis & angiogenesis**	**Scar X-linking**	**Acellular scar Nodule size**	**Insoluble scar & small nodules**	**Scars & large nodules**
HVPG:		**> 5**	**≥ 10**	**≥ 12**	**≥ 12**
			increasing vasodilatation		
Clinical:	**none**	**none**	**Varices formation**	**Ascites (without VH)**	**VH (± ascites)**
Stage:	**Early stage cirrhosis**	**Compensated (stage 1)**	**Compensated (stage 2)**	**Decompensated (stage 3)**	**Decomp (stage 4)**

Stages according to D'Amico et al, J Hepatol 2006;44: 217-31

Spontaneous Recovery From Micronodular Cirrhosis: Evidence for Incomplete Resolution Associated With Matrix Cross-Linking

- Micronodular cirrhosis induced in rats after 12 weeks of CCl4 intoxication
- Over 366 days of recovery, micronodular cirrhosis underwent significant remodeling to a macronodular cirrhosis



GASTROENTEROLOGY 2004;126:1795–1808

Regression of Human Cirrhosis

Morphologic Features and the Genesis of Incomplete Septal Cirrhosis

Ian R. Wanless, MD; Eisuke Nakashima, MD; Morris Sherman, MBBCh, PhD

ARCH PATHOL LAB MED 2000;124:1599–607

Clinical endpoints for anti-HBV NUC therapy

Histological regression of fibrosis

Regression of cirrhosis:

a - histological

b - indirect (reduction of portal hypertension)

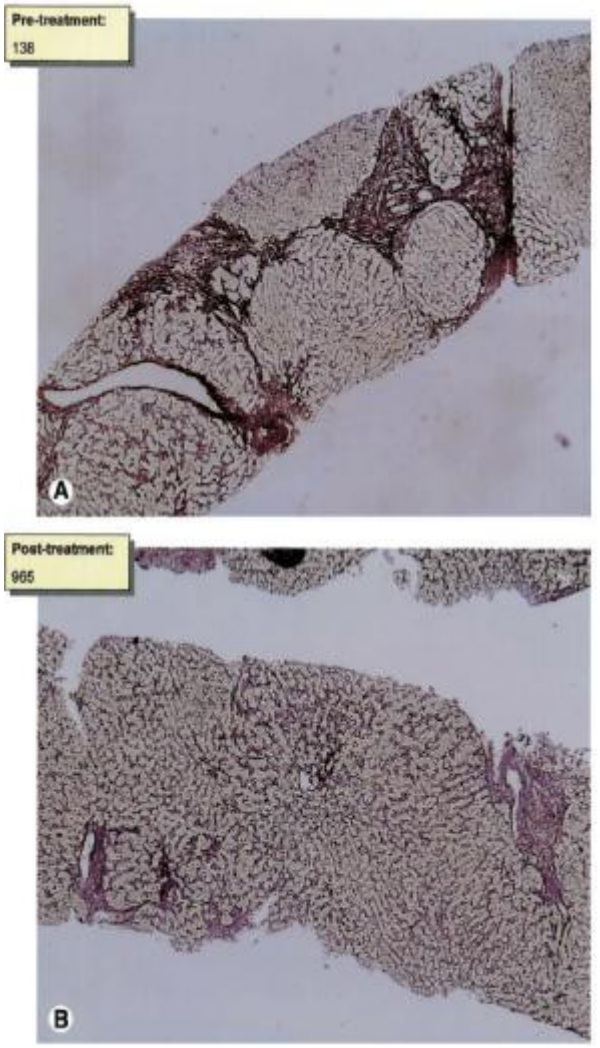
Reversal of liver decompensation

Prevention of HCC

Prevention of HBV flares

Histological outcome during long-term lamivudine treatment

- Sets of 3 liver biopsies from **63 patients** before and after 1 year of randomised lamivudine treatment, and after 2 years of further open-label treatment
- Bridging fibrosis improved by ≥1 level in 12/19 (63%), and **cirrhosis improved (score of 4 to ≤3) in 8/11 (73%)**
- Only 1/52 (2%) showed progression to cirrhosis and 3/34 (9%) showed progression to bridging fibrosis (all with YMDD variants)



Dienstag JL, *et al. Gastroenterology* 2003; 124:105–117.

Fibrosis regression during long-term anti-HBV therapy with NUCs

Nucleos(t)ide	n	HBeAg	Duration (yrs)	Fibrosis regression
Lamivudine	63	+	3 yrs	33%
Entecavir	21	+/-	3 yrs	57%
Adefovir	15/24	+/-	5 yrs	60%/71%
Entecavir[a]	57	+/-	6 yrs	88%
Tenofovir[b]	348 (96[b])	+/-	5 yrs	51% (74%[b])

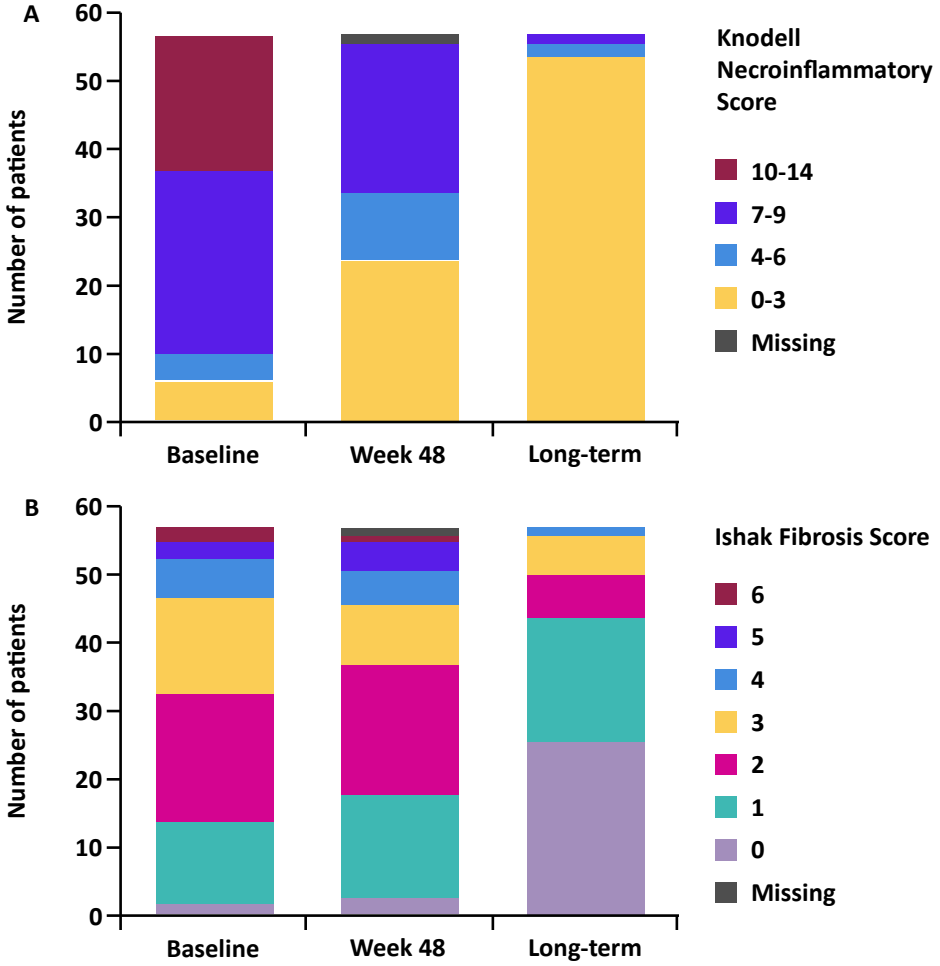
a. ETV improved Ishak fibrosis (-1.53) 2 in 58% and in all 4 cirrhotics (Chang et al Hepatology 2010)

b. Cirrhosis at baseline, 2/3 ↓ in 73/58% (Marcellin et al Lancet 2013)

Liaw YF Liver Int 2013

Reversal of fibrosis and cirrhosis following ETV therapy: phase III and rollover studies

- 57 patients with < 300 copies/ml HBV-DNA had long-term liver biopsy (3-7 years)
- 10 had Ishak S > 5. 4 patients had Ishak S reduced by 1 to 4 points

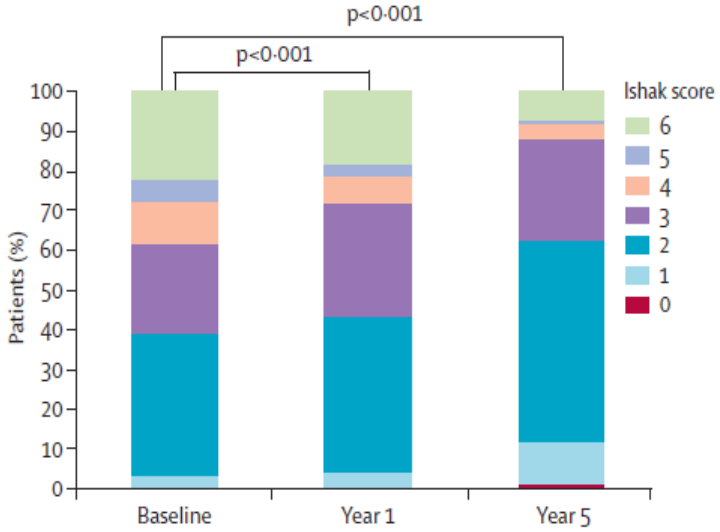


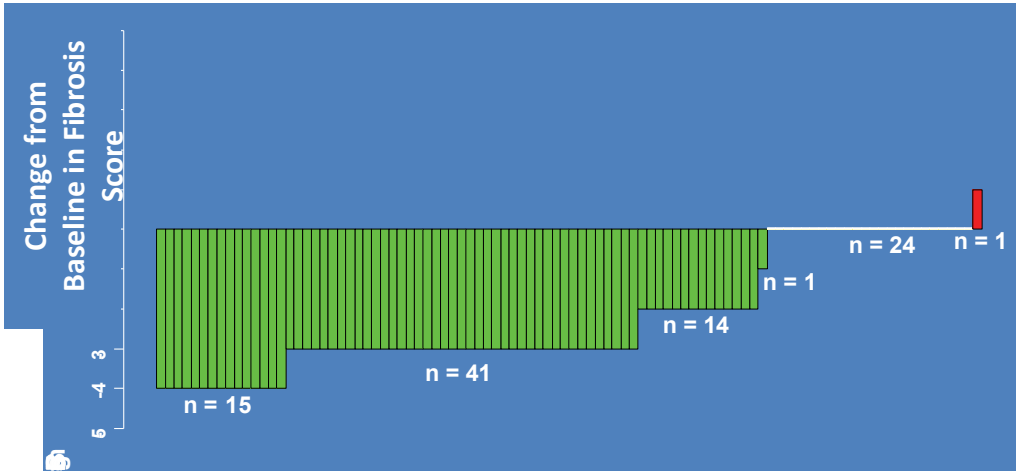
A ≥1-point improvement in the Ishak fibrosis score occurred in 88% of patients, including **all 10 patients with advanced fibrosis or cirrhosis at baseline**

Chang et al, Hepatology 2010;52:886-893

Five-year TDF Treatment in Patients with CHB
Changes of Fibrosis in Cirrhotics

- 344 patients with liver biopsy at baseline, year 1 and year 5 (study 102/103)
- 133/344 (38.7%) ≥ Ishak 4
- 96/344 (28%) ≥ Ishak 5 (i.e. cirrhosis)





96 patients with cirrhosis (Ishak fibrosis score ≥5) had paired BL and Year 5 biopsies

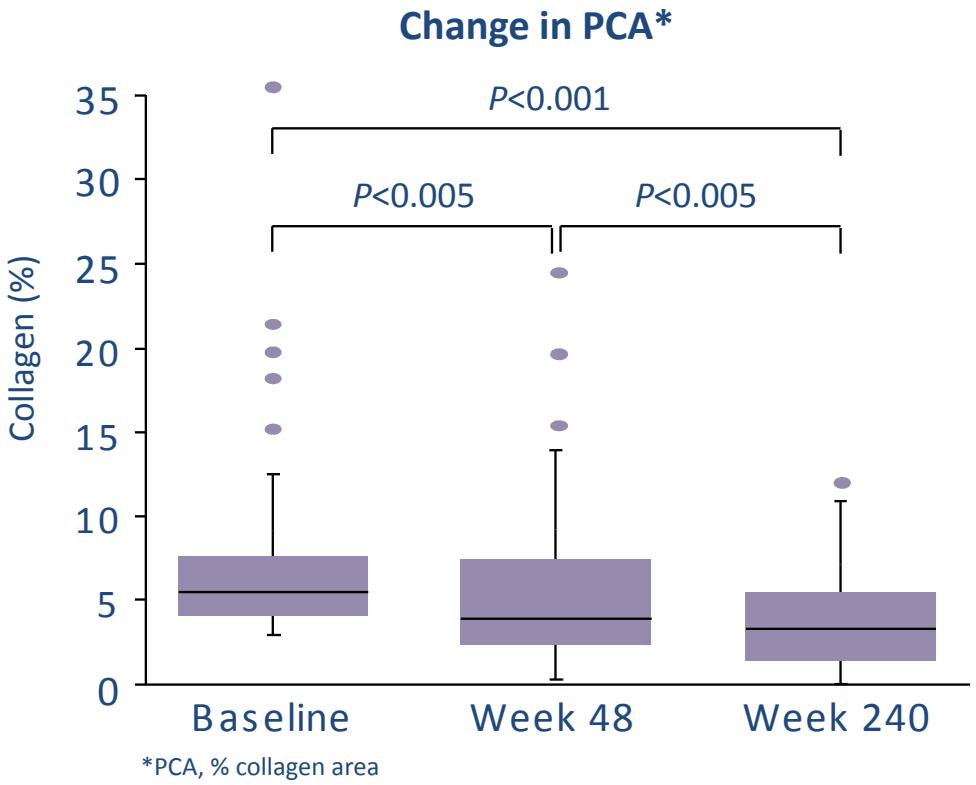
- BMI ≥ 25 negative predictor of fibrosis regression
- 29/32 (90%) patients with normal BMI no longer cirrhotic

Marcellin et al, Lancet. 2013;381:468-75

Studies 102/103
Morphometric Assessment of Liver Biopsies

Percent collagen area (PCA) measurement in liver biopsies at Baseline, Week 48 and Week 240 in subjects treated with TDF1

- Biopsy slides were stained with Sirius red:
  - Digital image analysis used to calculate relative collagen content of each biopsy
- Slides with < 5 mm2 tissue and slides with < 3% collagen at baseline were excluded
- Mean PCA decreased over time:
  - 7.1% at Baseline
  - 5.3% at Week 48
  - 3.9% at Week 240



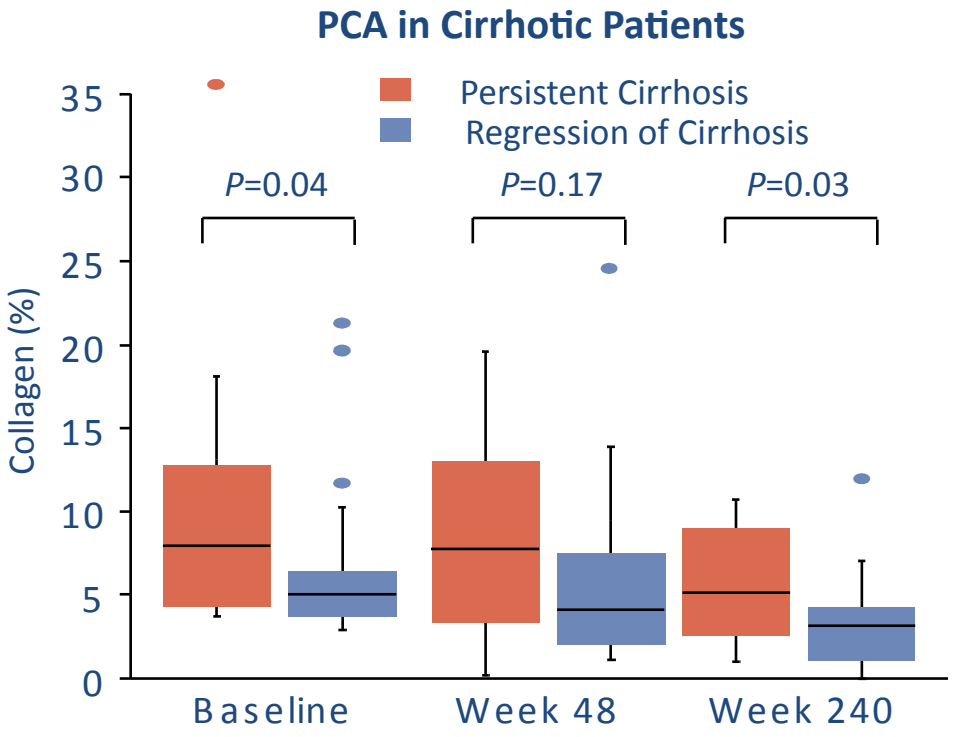
1Histology described previously: Marcellin P, et al. *The Lancet* 2013;381(9865):468–475

Goodman Z, et al. AASLD 2013. Washington, DC. #820

Studies 102/103
Morphometric Assessment of Liver Biopsies

Among 344 subjects with biopsies, 71/96 had histologic regression of cirrhosis by Week 2401 under TDF treatment

- For cirrhotics, mean PCA decreased from 7.8% at Baseline to 4.1% at Week 240 (*P*<0.001)
  - Those with persistent cirrhosis by Ishak stage had significantly higher mean collagen in their baseline biopsies
    - Patients with regression of histologic cirrhosis had a 42% mean reduction in collagen while those with persistent cirrhosis had a mean reduction of 17%



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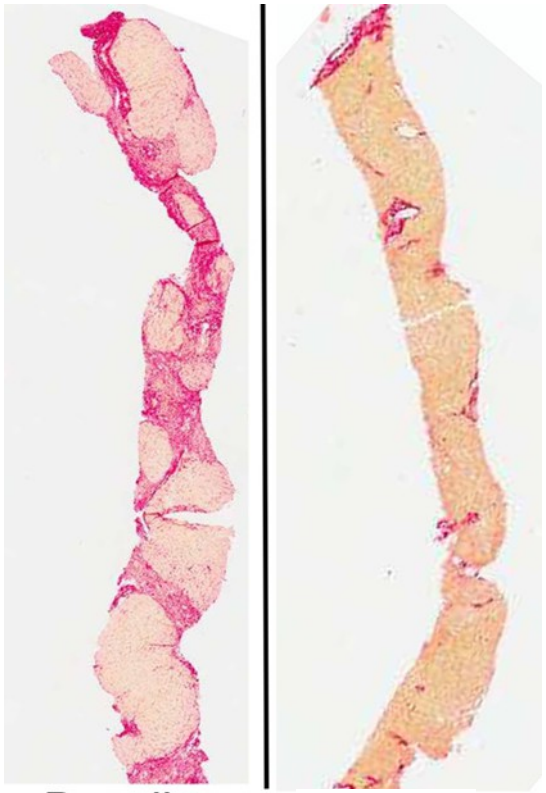
Studies 102/103
Morphometric Assessment of Liver Biopsies

An example of liver biopsies in a TDF-treated subject with histological regression of cirrhosis at Week 240 shows a marked decrease in PCA over time

- Percent collagen area decreased by 79% from Baseline to Week 240



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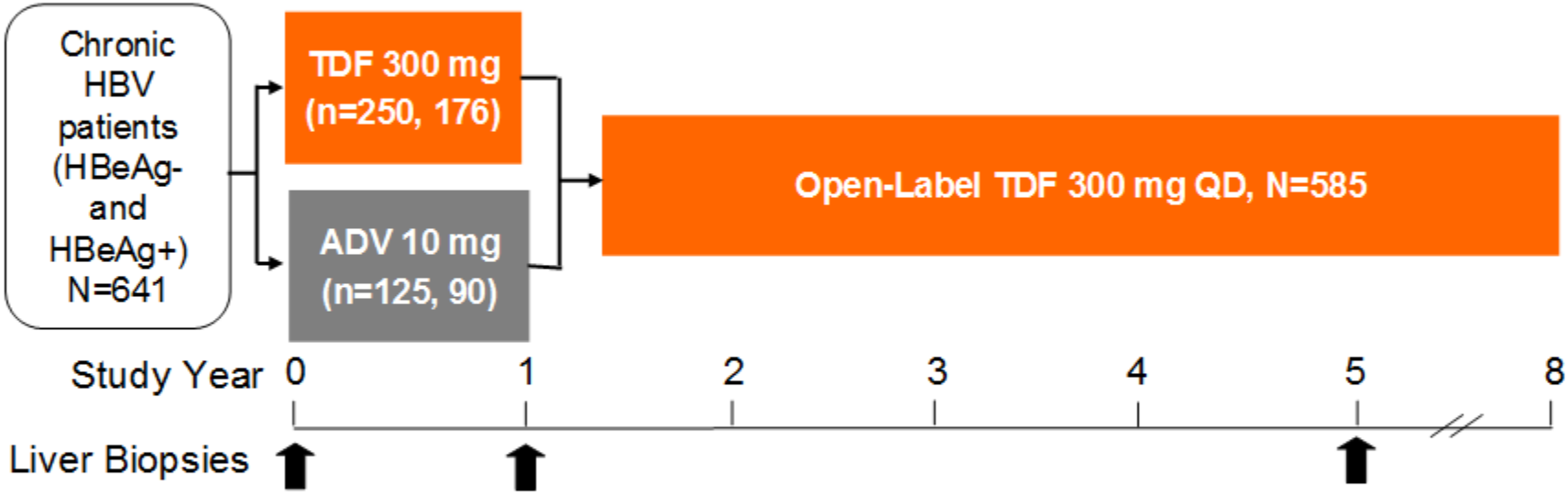
Studies 102/103

LOXL2 Enzyme Levels in CHB Patients Treated with TDF

344 participants in two ongoing TDF Phase 3 trials had assessments of serum lysyl oxidase-like 2 (LOXL2) enzyme levels



- Part A: Retrospective study measured serum LOXL2 levels at baseline, and Weeks 12, 44, and 240 in a subset of patients (n=88); preferentially focusing on those with cirrhosis at baseline
- Part B: A second set of samples was taken from patients in study of HBV patients with decompensated liver disease, as a validation group (n=81)

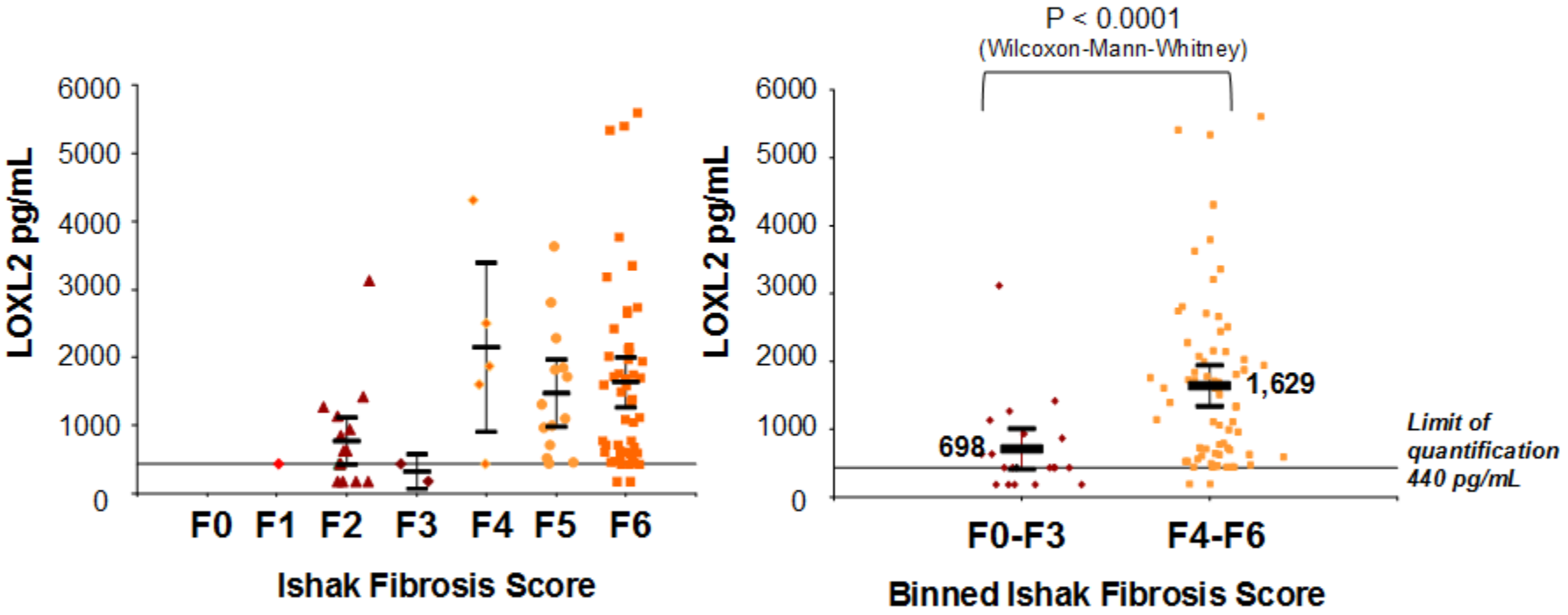
Talal A, et al. AASLD 2012; Boston. #141.

Marcellin P, et al. AASLD 2012; Boston. #374.

Patients had the option to add FTC at the discretion of the investigator if confirmed HBV DNA ≥400 copies/mL at Week 72 or beyond. Neither Truvada (TVD = TDF + FTC) or emtricitabine (FTC) are licensed for use to treat CHB.

Studies 102/103

Baseline LOXL2 and Ishak Stage

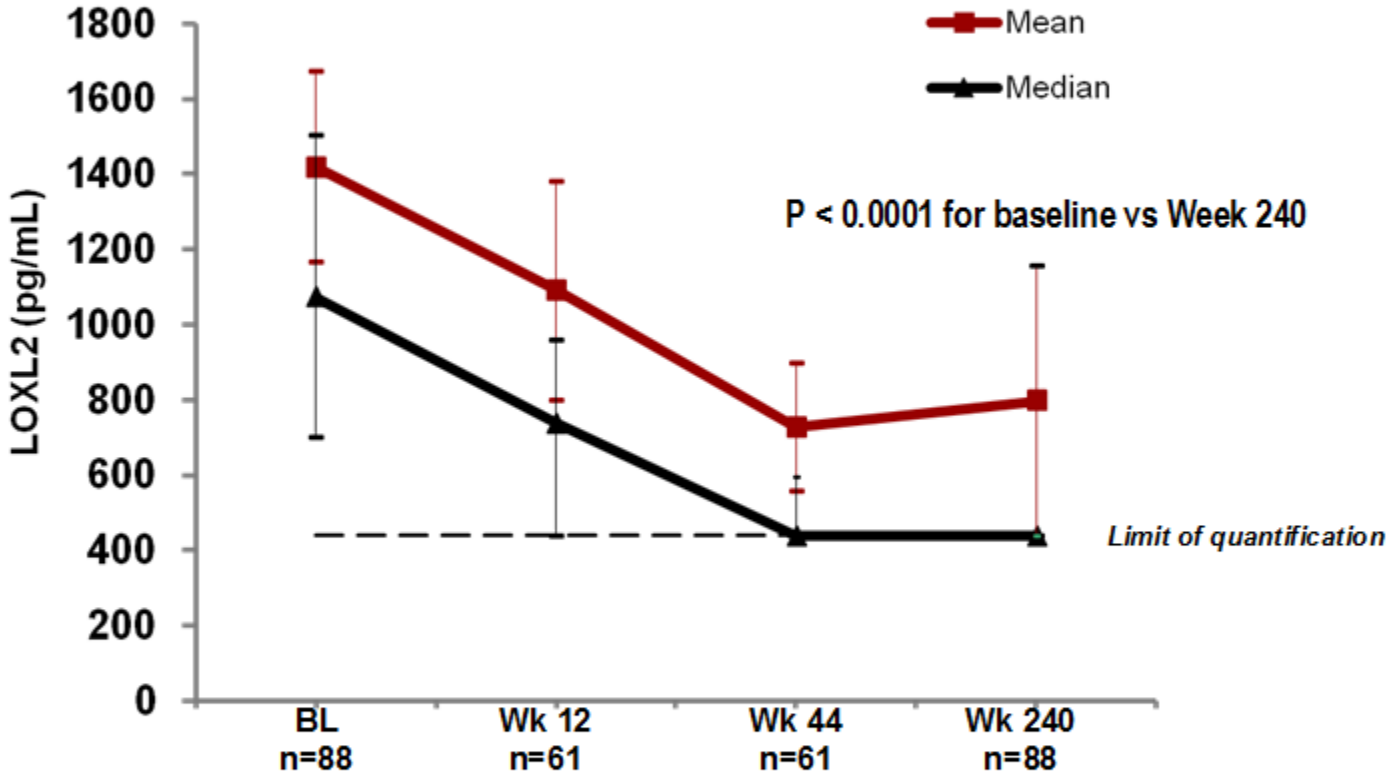


- Baseline serum LOXL2 levels were higher in patients with more advanced fibrosis

Talal A, et al. AASLD 2012; Boston. #141.

Studies 102/103

LOXL2 Decline Over 240 Weeks



- Serum LOXL2 was detectable at baseline in 93% of subjects overall and 97% of cirrhotic subjects
- Successful viral suppression resulted in a decrease in serum LOXL2 levels

Talal A, et al. AASLD 2012; Boston. #141.

How to assess regression of cirrhosis ?

Histology:

✓ Fibrosis scoring systems: sampling error

Non-invasive methods (transient elastography):

✓ Controversial results

✓ Limitations:

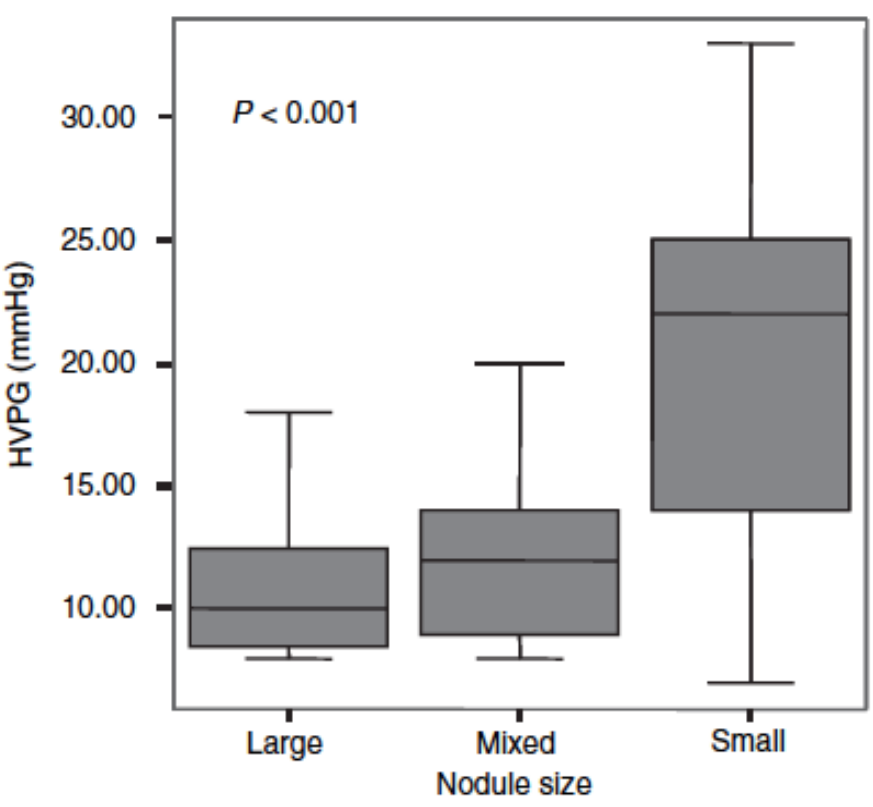
- Values influenced by ALT levels
- Accuracy between stages

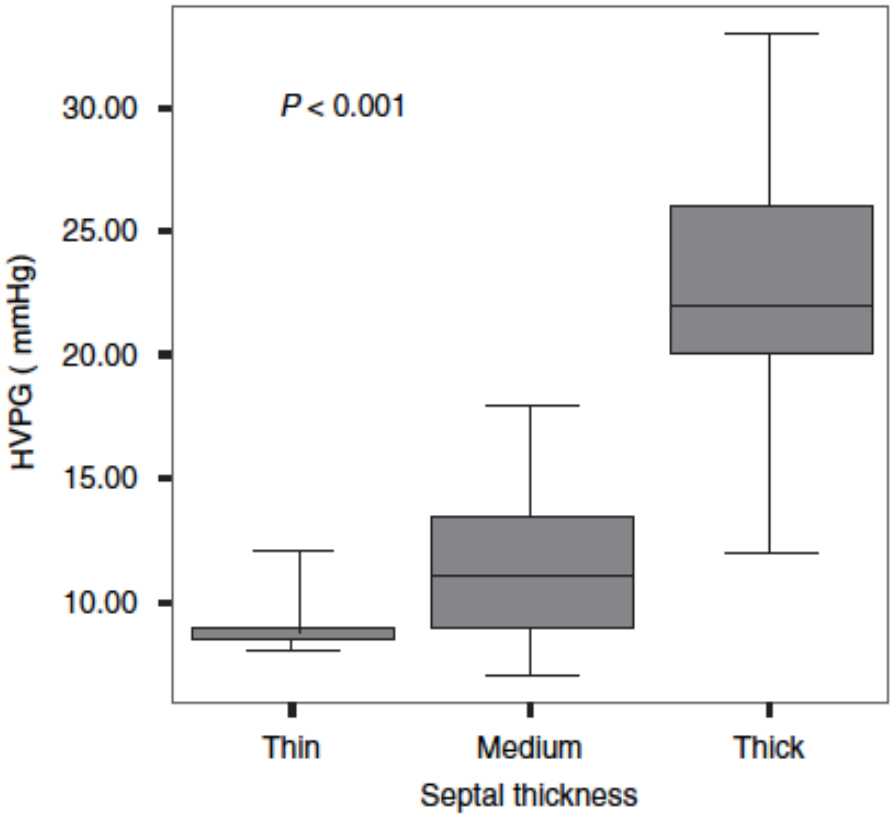
Portal hypertension measurement:

Direct (HVPG)

Indirect (endoscopy for varices)

Distribution of HVPG according to nodule size and septal thickness (55% HBV cirrhosis)

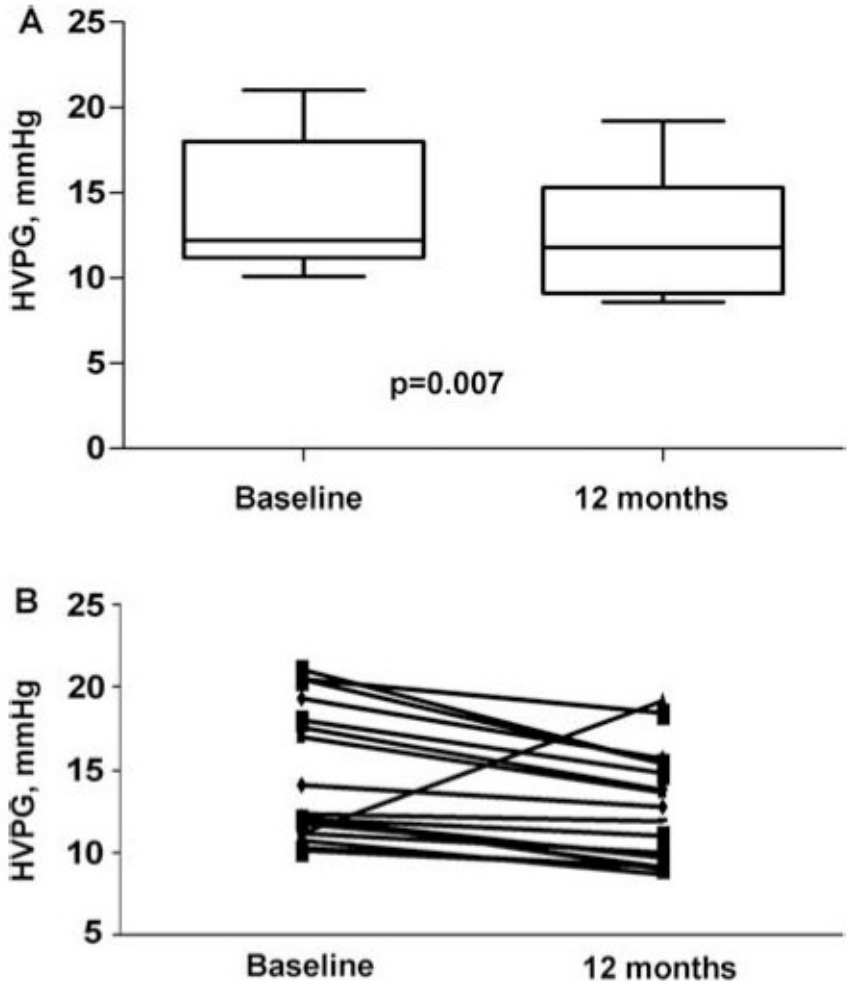




Median HVPG, 25–75th percentile box and complete range of measurements.

Kumar M et Al, Aliment Pharmacol Ther 2008

Effect of lamivudine on hepatic venous pressure gradient (HVPG)



HVPG values
baseline
14.4 ± 3.9 (10.1–21)
mm Hg

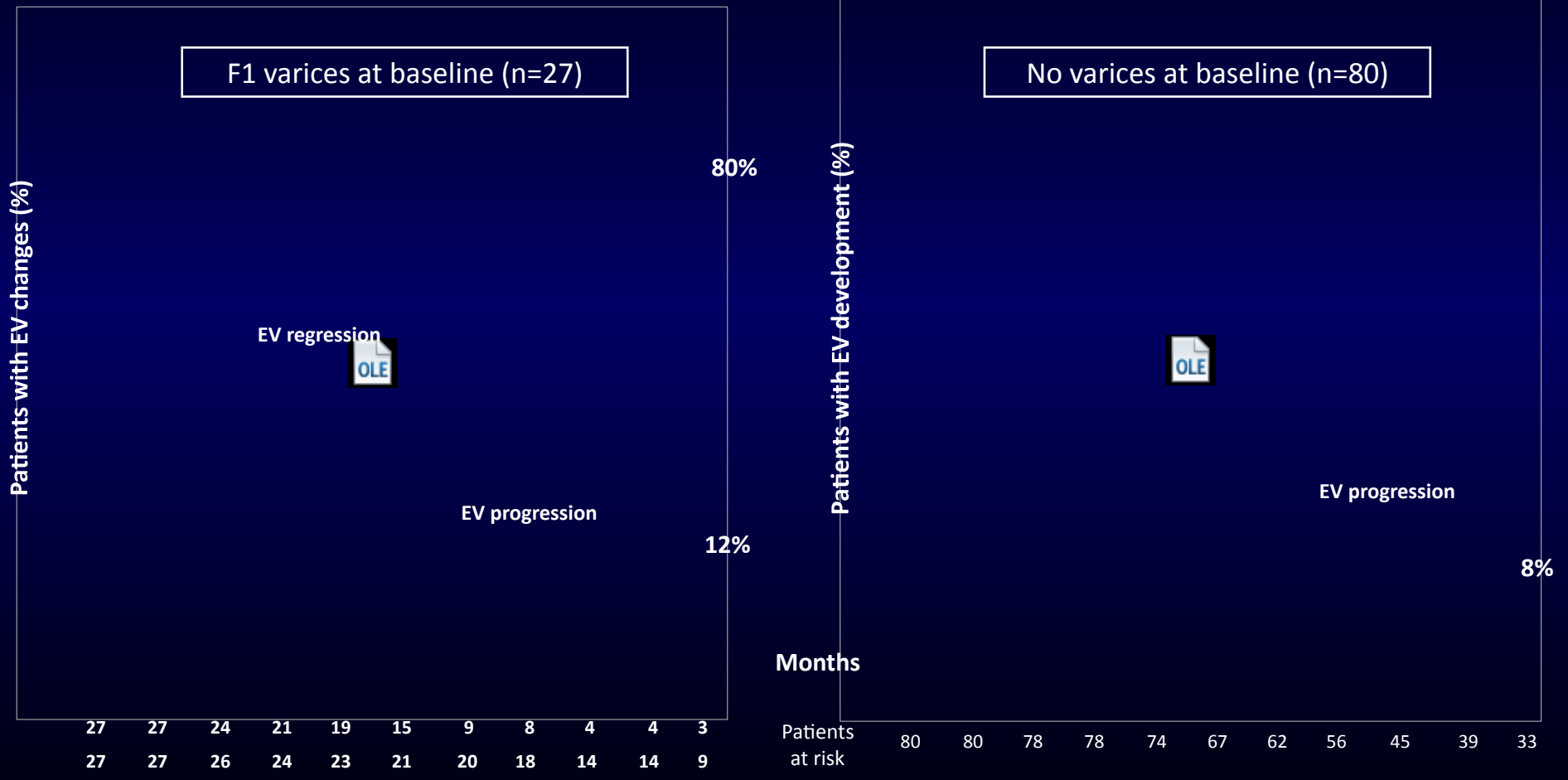
12 months:
12.4 ± 3.3 (8.6–19.2)
mm Hg

(p = 0.007)]

Manolakopoulos S et al. J Hepatol 2009

Changes of esophageal varices (EV) in compensated cirrhotics treated with LAM±TDF for 10 years

Overall, EV worsening rate per year: 0.9%*



* 6 of 7 progressors (86%) had either LMV-R and/or HCC

Courtesy of Pietro Lampertico, 2013

Is portal hypertension reversible in HBV cirrhosis?

75 Caucasian patients with compensated cirrhosis

- Mean age 57.3 years, 84% males
- 89% HBeAg negative; 94% genotype D; mean serum HBV-DNA 5.7 log
- Therapy: 18 ETV; 43 TDF; 4 LDT; 10 COMBO
- Mean time on NUCs: 96 months (range 24- 192)
- Follow-up: US every 6 months; endoscopy every 24-36 months

Esophageal varices at baseline	Varices at last endoscopy	Patients (%)	Time first - last endoscopy (months, mean)	Disease events	
				Ascites	HCC
F0 (32 patients, 42%)	F0	20 (63%)	79.7	0	2 (10%)
	F1	12 (37%)	75.5	1 (8%)	1 (8%)
F1 (26 patients, 35%)	F0	7 (27%)	64.3	0	1 (14%)
	F1	14 (54%)	57.7	2 (14%)	3 (21%)
	F2/F3	5 (19%)	47.4	4 (80%)	1 (20%)
F2/F3 (17 patients, 23%)	All F2/F3 or treated		43.4	10 (59%)	4 (14%)

Di Marco V et al. unpublished data

Regression of fibrosis. Is HBV cirrhosis reversible? Take-home messages for 2014

- Long-term HBV suppression by NUCs causes quantitative and qualitative regression of fibrosis in most patients with non-cirrhotic (F1 to F3) disease
- F4 fibrosis can also regress, but less consistently
- Reduction of portal hypertension is observed in a minority of patients with HBV cirrhosis on long-term suppressive therapy
- Severe portal hypertension could be the hallmark for non-reversible cirrhosis