CIRROSI EPATICA:
Una malattia curabile?

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… la cirrosi è reversibile?

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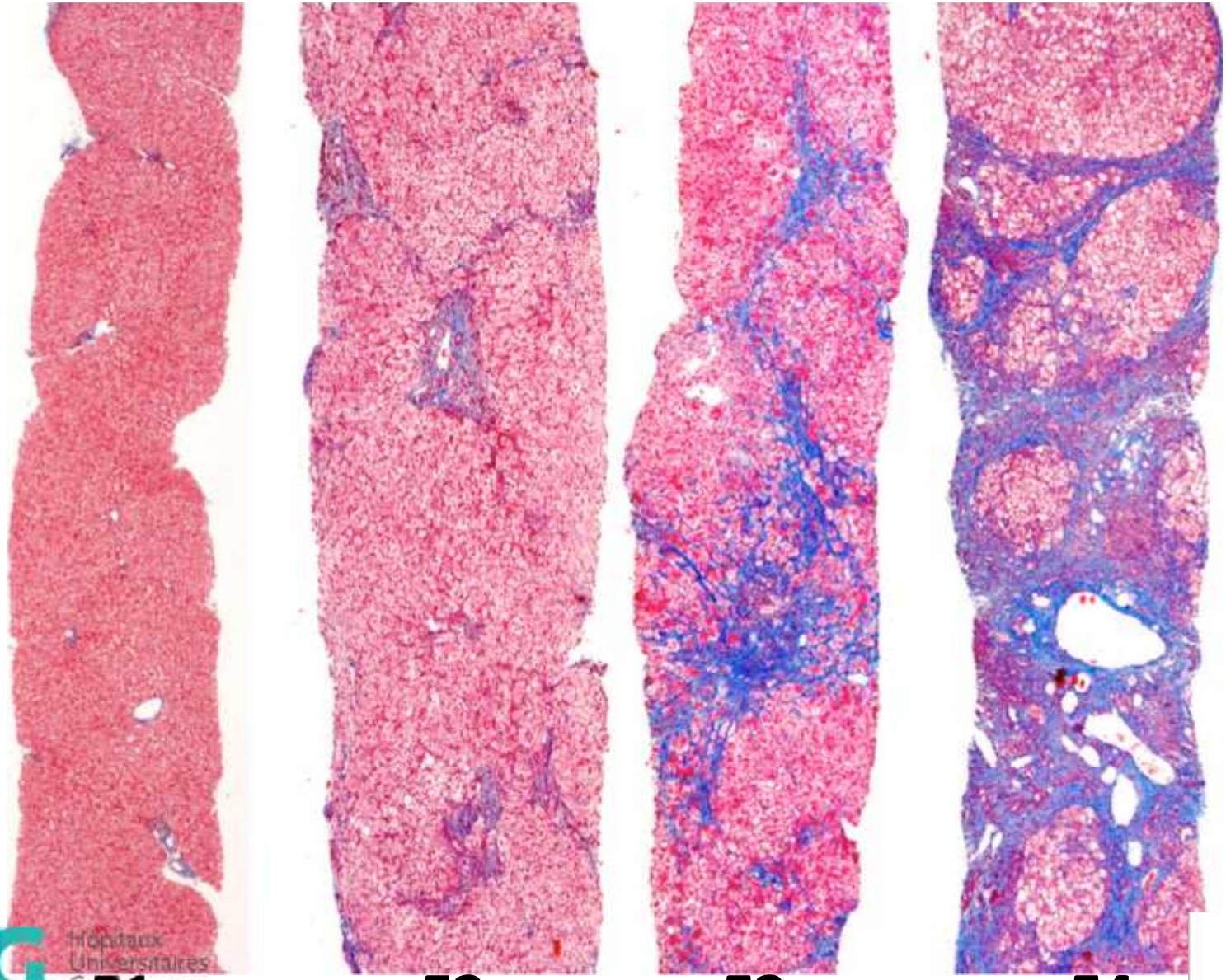
Definizione FIBROSI

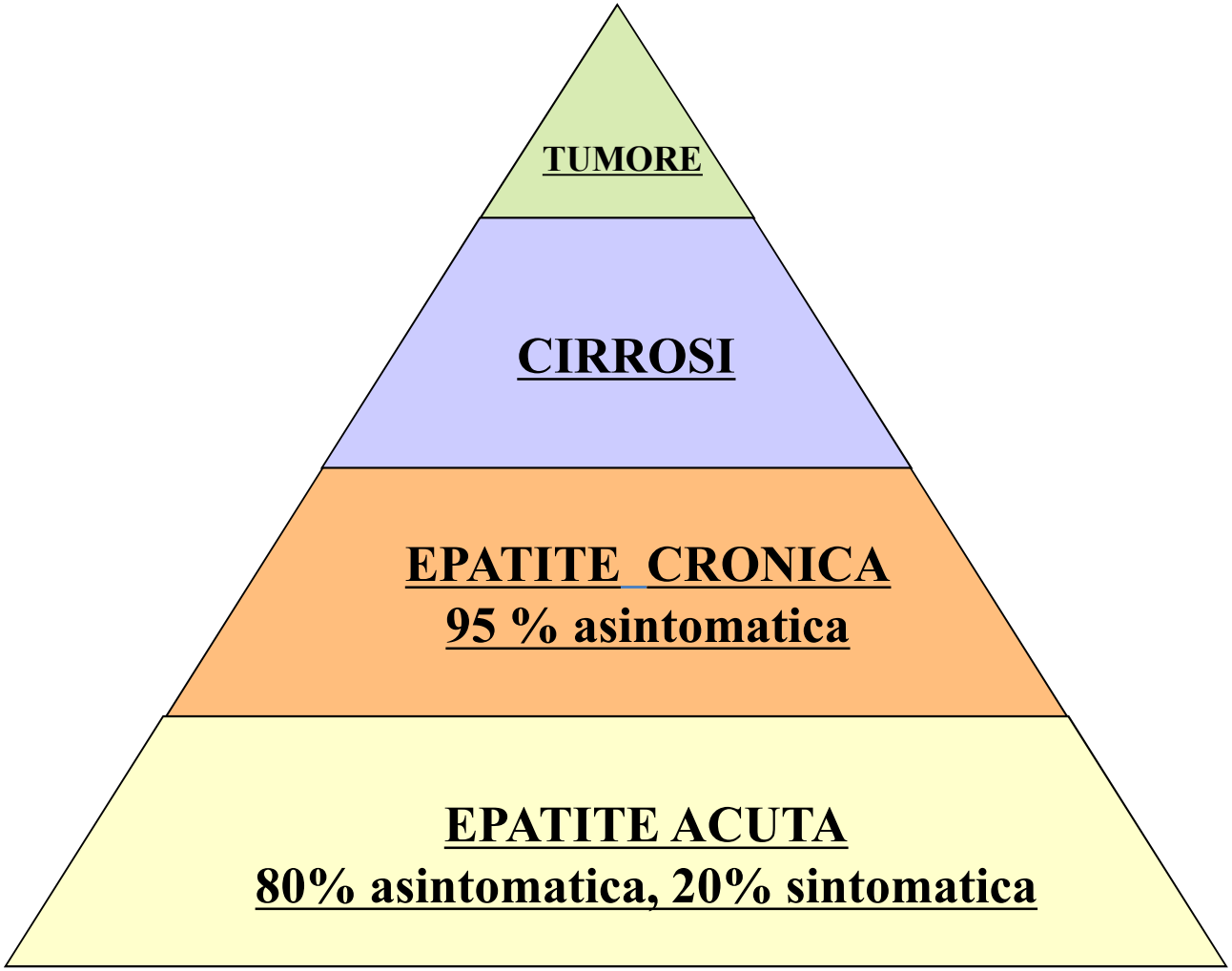
Un processo dinamico, multicellulare, lento e (parzialmente) reversibile di cicatrizzazione (wound healing).

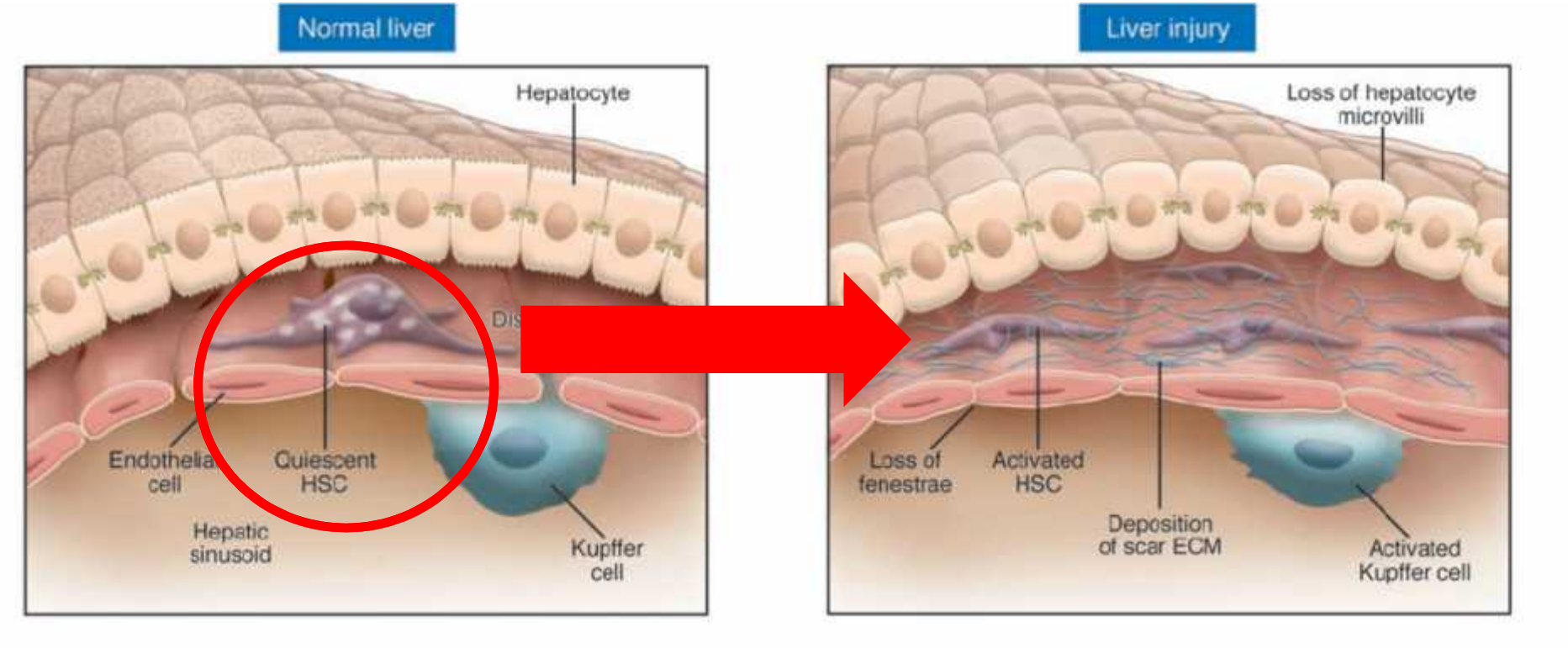
Evoluzione di fibrosi



F1 F2 F3 F4

Evoluzione di una malattia epatica

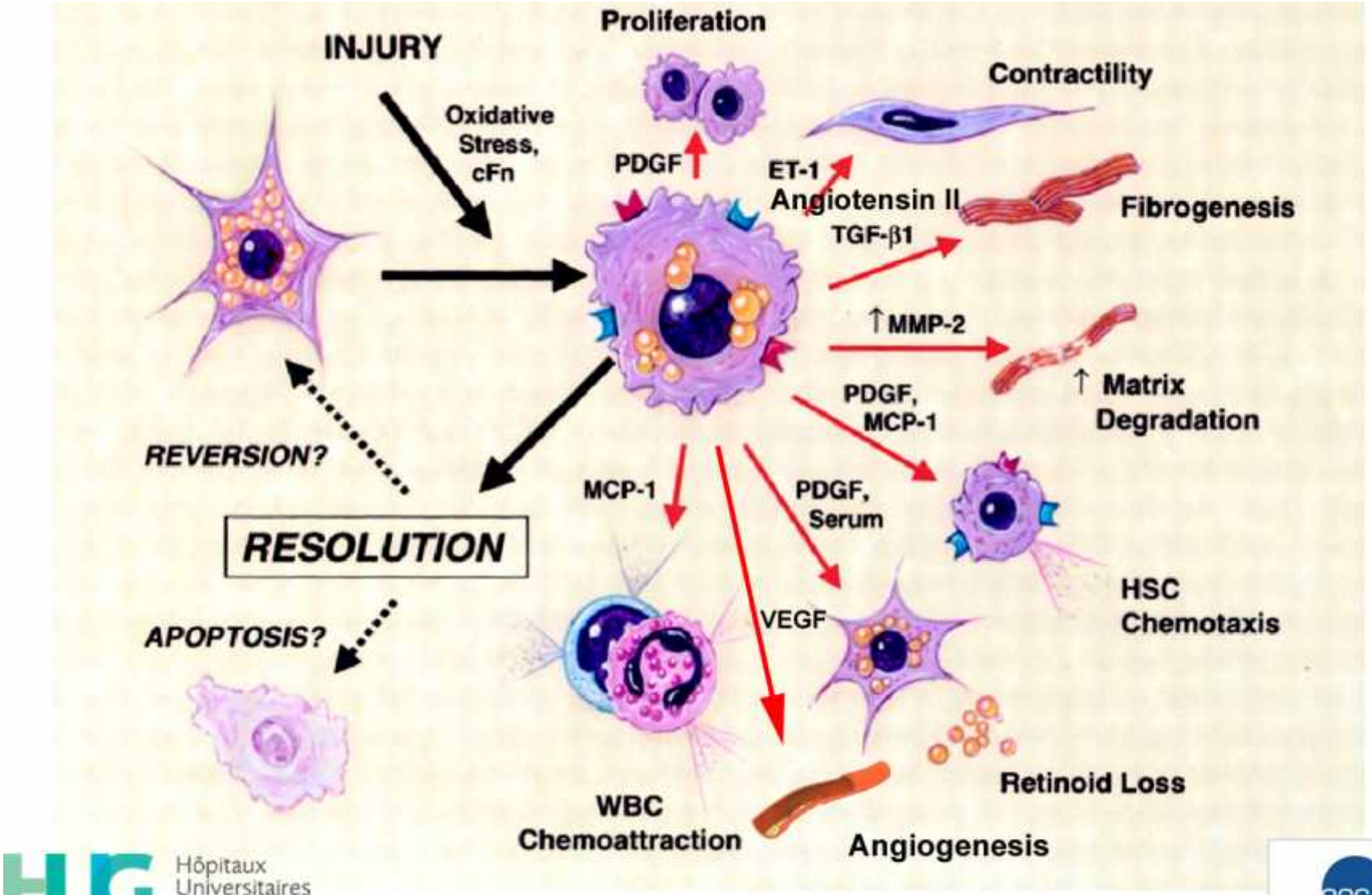




L'attivazione delle cellule stellate porta a proliferazione dei fibroblasti e deposito di collagene, attivazione di Kupffer cells, perdita di microvilli degli epatociti

Iredale, J Clin Invest 2007;

Hepatic stellate cells: the effectors of liver wound healing



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Friedman SL, J Biol Chem 20

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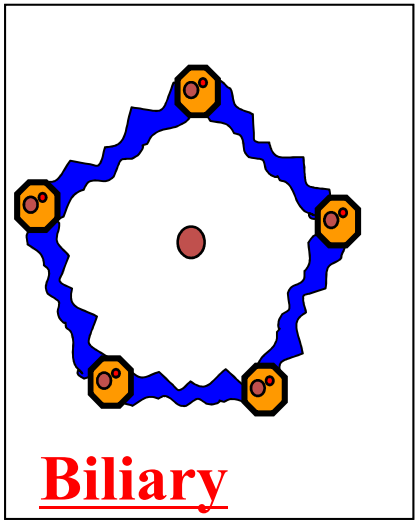
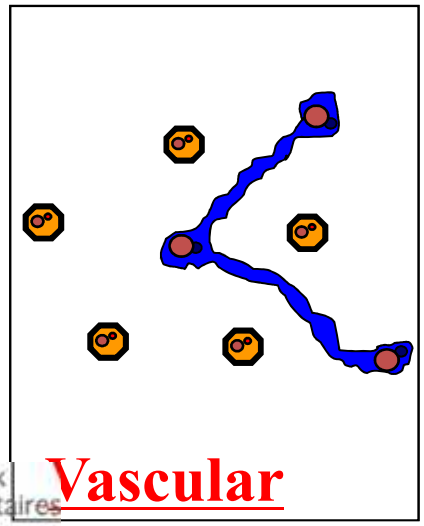
Patterns of fibrosis development

Viral



Biliary



Vascular

ASH/NASH

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Concetti chiave

- La fibrosi epatica si sviluppa con pattern morfologici e spaziali diversi
- Differenti meccanismi molecolari e fisici sono alla base dello sviluppo di fibrosi (ess: sinusoidal pressure hypothesis)
- Il processo coinvolge cellule residenti e distanti

Cause della fibrogenesi I

- **Virus epatitici (HCV, HBV) stomolano vari meccanismi di fibrogenesi**
  - Stimulating the extracellular matrix (collagens, TGF-beta, CTGF, etc)
  - Up-regulation of MMP-2 (index of HSC activation)
  - Down-regulation of fibrolytic matrix-metalloproteinases (e.g. MMP-1)
  - Induction of ROS generation
  - Up-regulation of pro-inflammatory cytokines and cell-adhesion molecules)

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Bataller et al. Gastroenterology 2004;126:529. Mazzocca A et al., J Biol Chem 2005; 280:11329. Schulze-Krebs A Gastroenterology 2005;129:246

Cause della fibrogenesi II

Adipokine stimolano la fibrogenesi

↑ LEPTIN

↑ RESISTIN

↑ VISFATIN

↓ ADIPONECTIN

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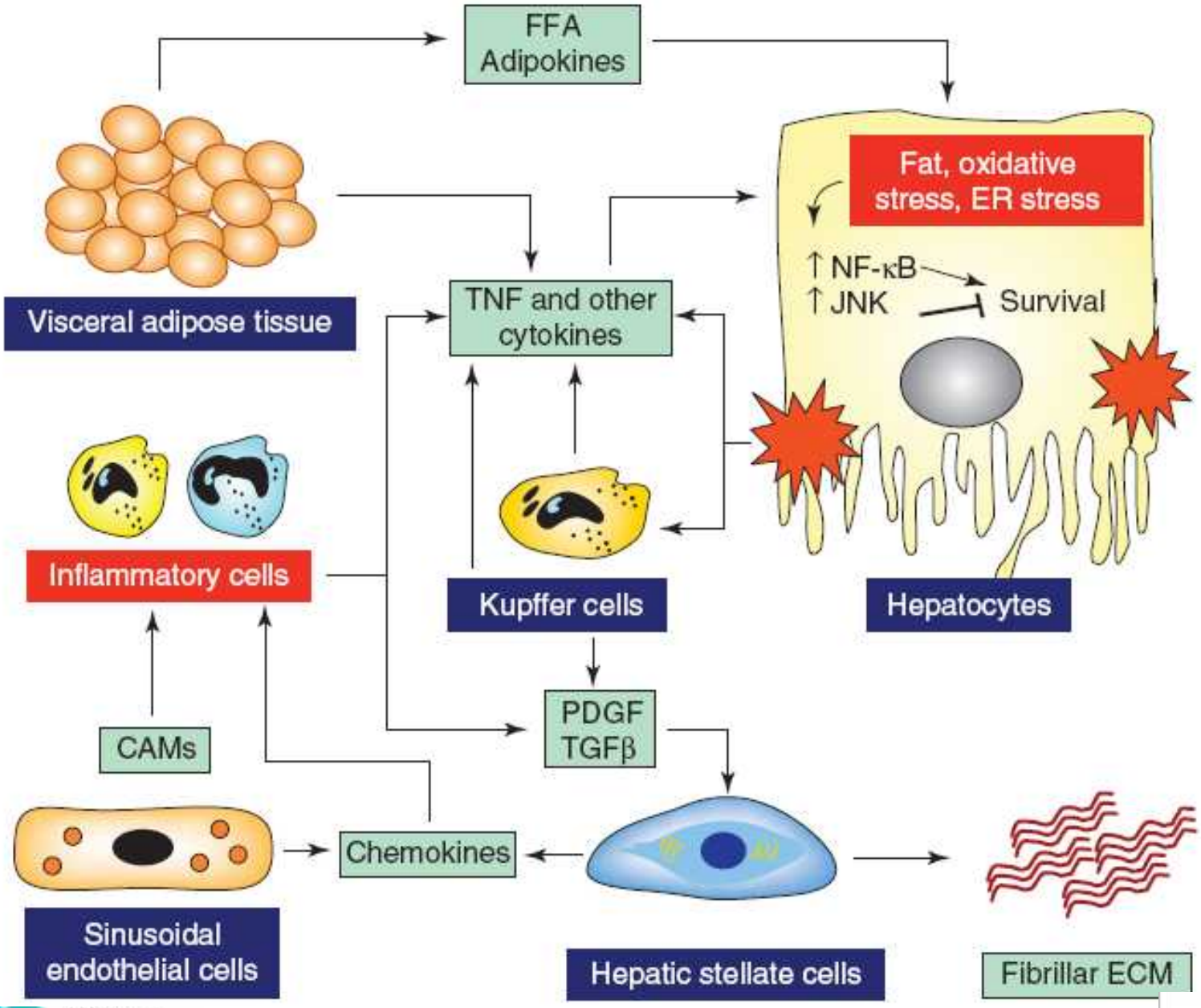

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Marra et al, Trends Mol Med 20

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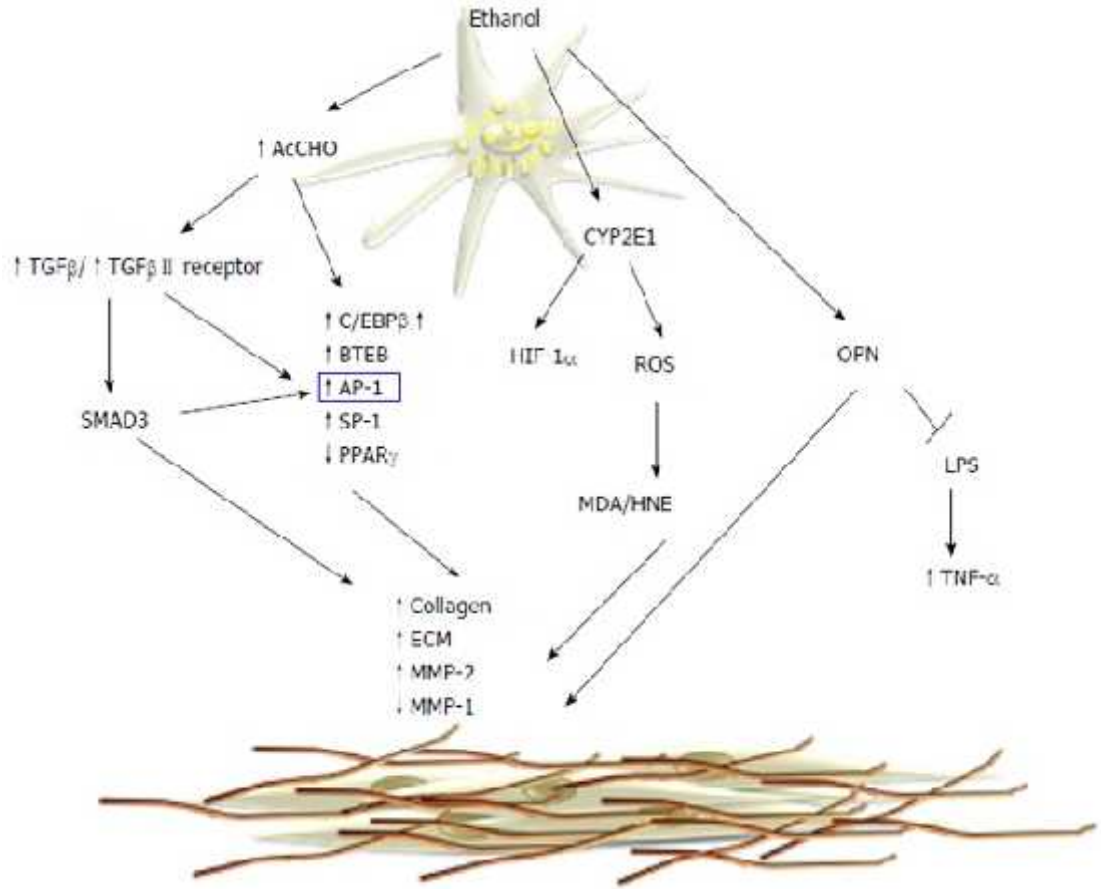
Alcohol-mediated fibrogenesis



Cenni E, et al. World J Gastroenterol 2014 Dec;

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Ipotesi della pressione intrasinusoidale **come causa della fibrogenesi**

- Finora, un cambio della pressione sinusoidale è stato visto come consequenza di una cirrosi

- L'aumento della pressione porta ad uno "streching delle perisinusoidal cells" che stimola cellule stellate e quindi collagene

- Progressione della fibrosi dipende dall'entità e durata della pressione sinusoidale (≥ 12mmHg > 4 settimane)

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Müller S, World J Gastroenterol, 2016 Dec; 22(48): 10482

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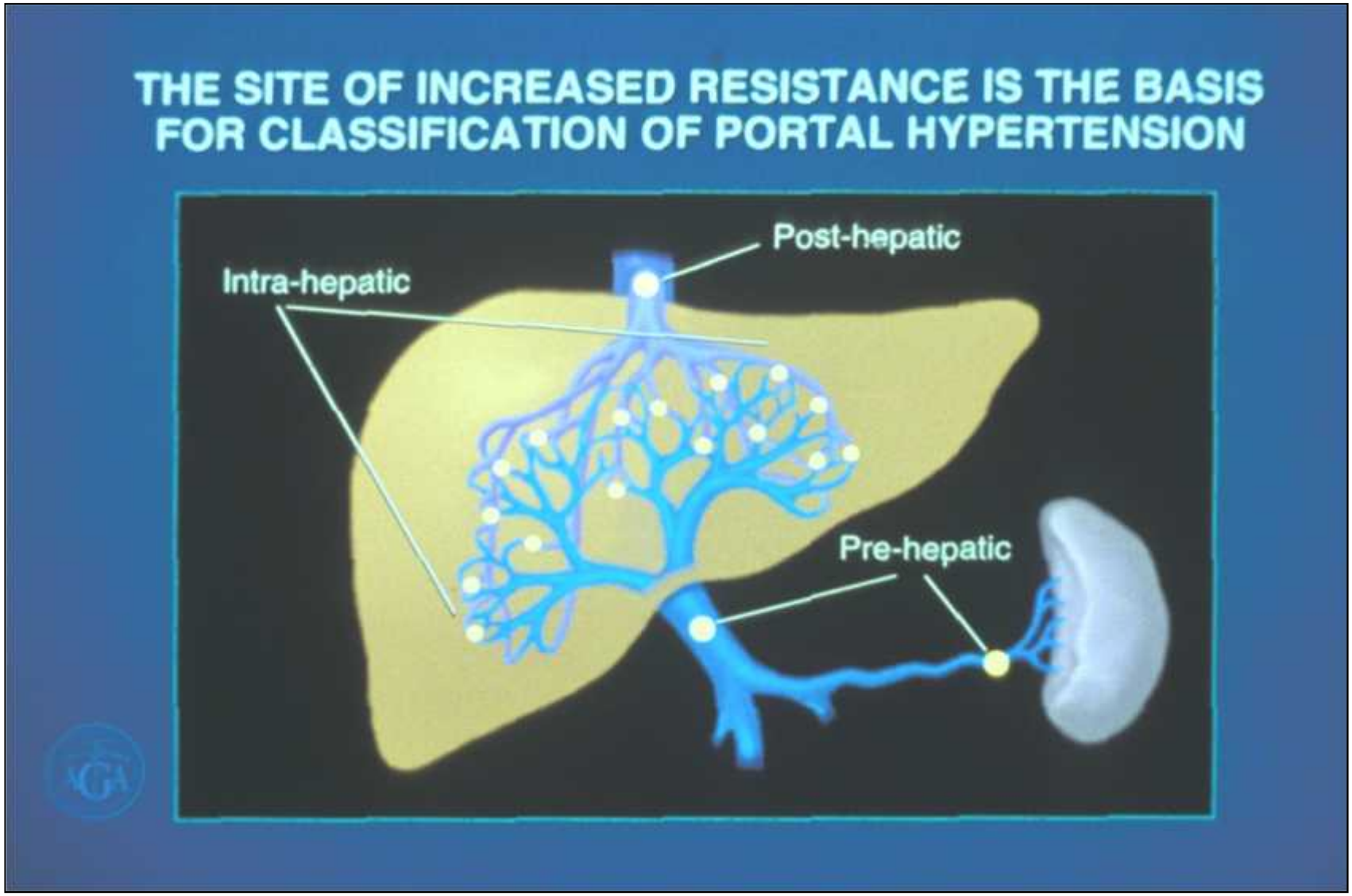
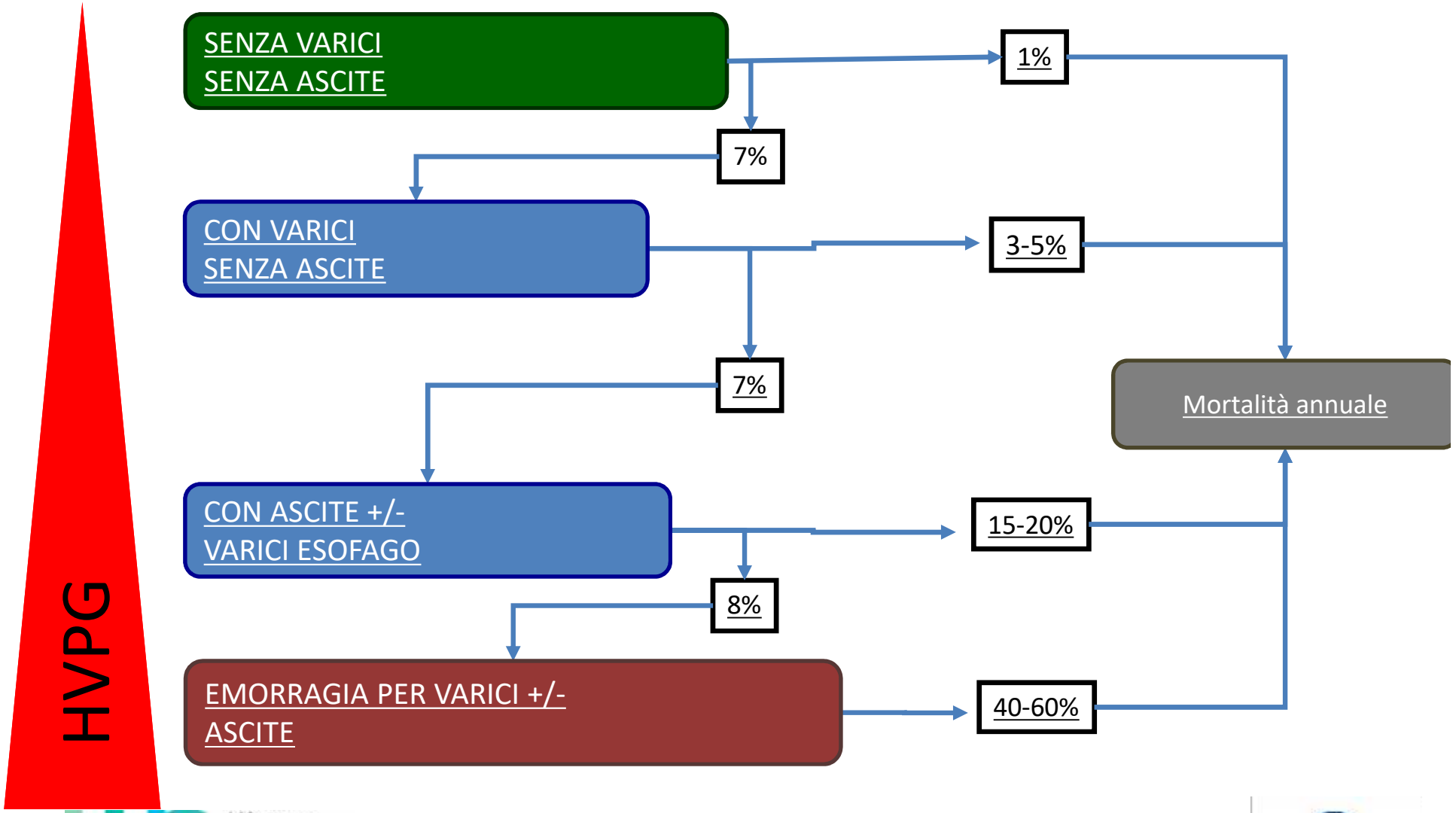


Hepatic venous pressure gradient (mmHg)	< 6	6-10	> 10	> 12	> 20-22
	normale	HTP non significativa	varici e rischio OP	emorragia varici	mo

Marcatori di prognosi



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

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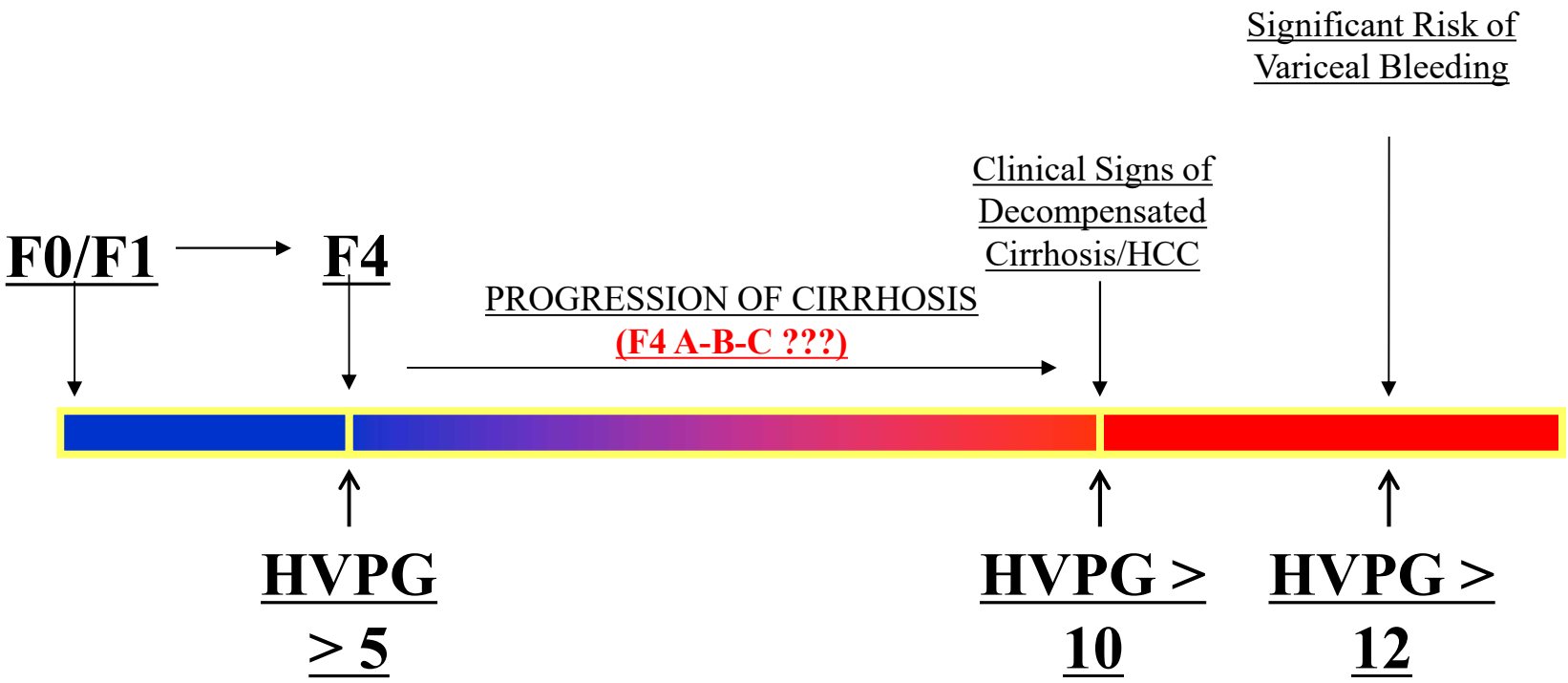
Beyond F4…?



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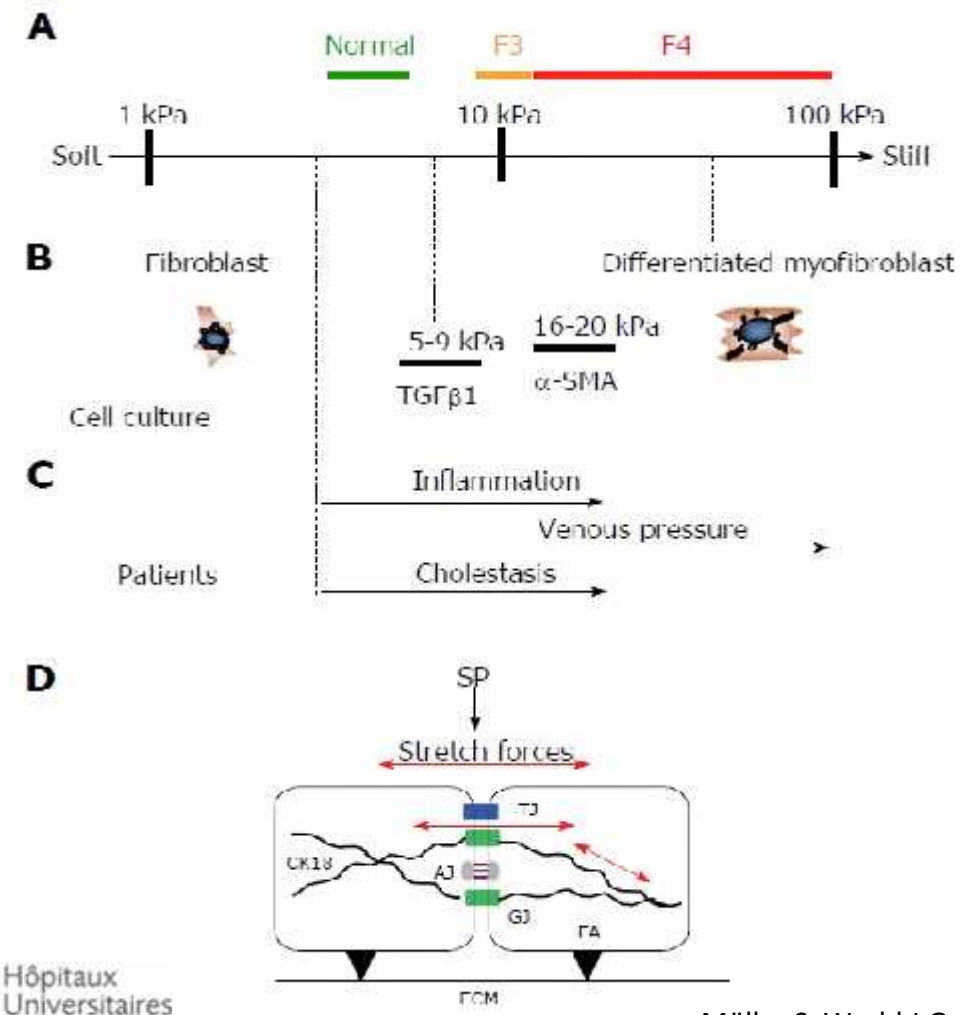
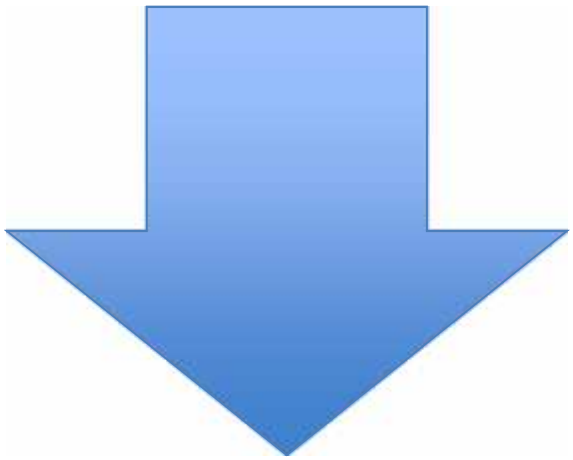
“Ipotesi della pressione intrasinusoidale”
come causa della fibrogenesi



Müller S, World J Gastroenterol, 2016 Dec; 22(48):

Quindi la **progressione della fibrosi dipende dalla malattia di base?**



La **regressione** dell'ipertensione sinusoidale migliora la prognosi

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Si può trattare la fibrosi ?

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Siti d'azione di trattamenti anti-fibrotici

- Cura della malattia di base (virus, noxae, etc)
- Riduzione infiammazione
- Riduzione dell'attivazione delle cellule stellate
- Diminuzione della pressione sinusoidale
- Promuovere degradazione della matrice di collagene

The “suppressive” interferon trials

EPIC³ trial

- Long-term, low-dose interferon in pazienti non responders

HALT-C trial

- Ipotesi: Soppressione virale limita la fibrogenesi o lo riduce

COPILOT trial

- Effetto antifibrotico dell’interferone alfa

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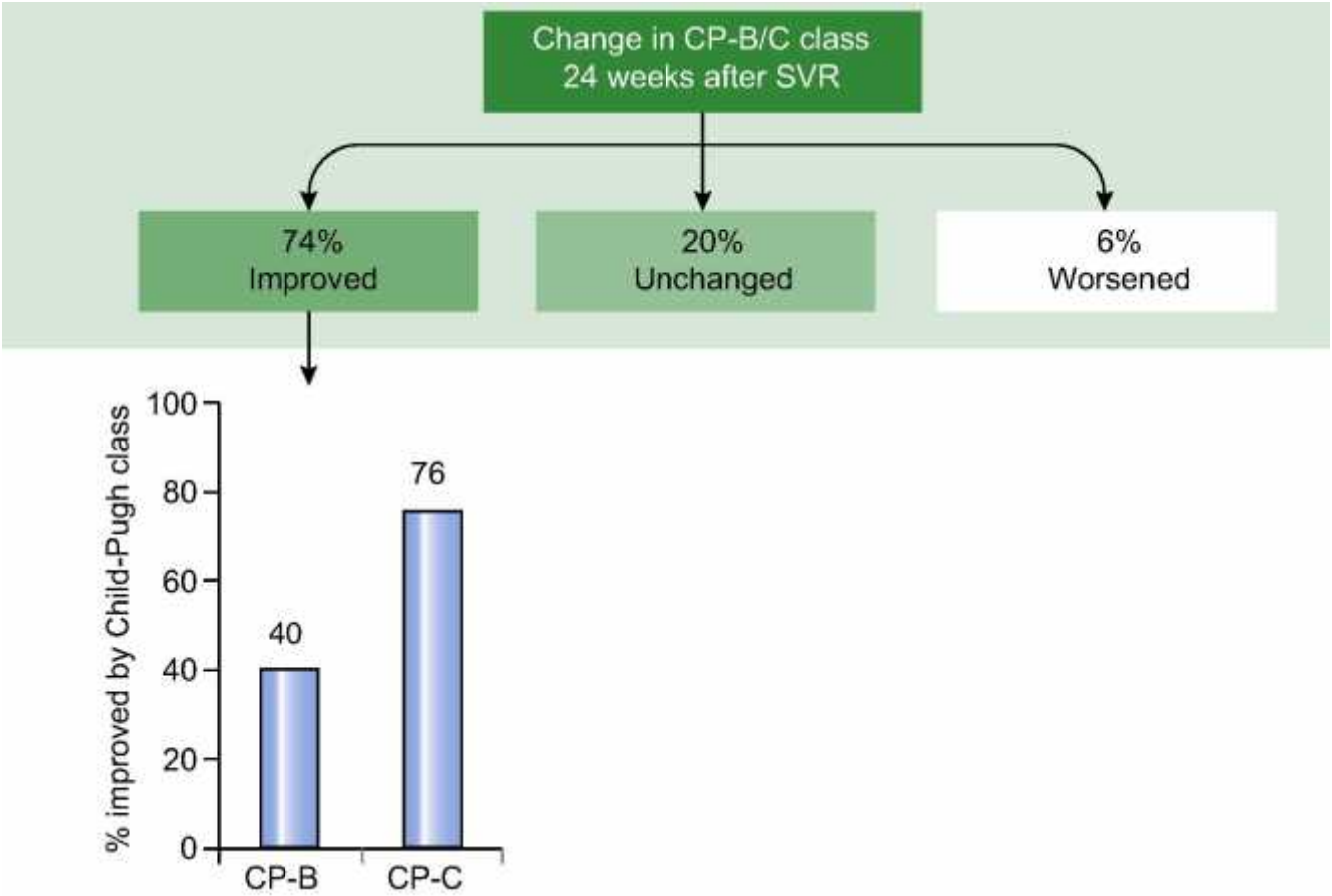
Farmaci anti-HCV migliorano il CHILD score



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Charlton M et al. (SOLAR-1) Gastroenterol 2015 Sep;14

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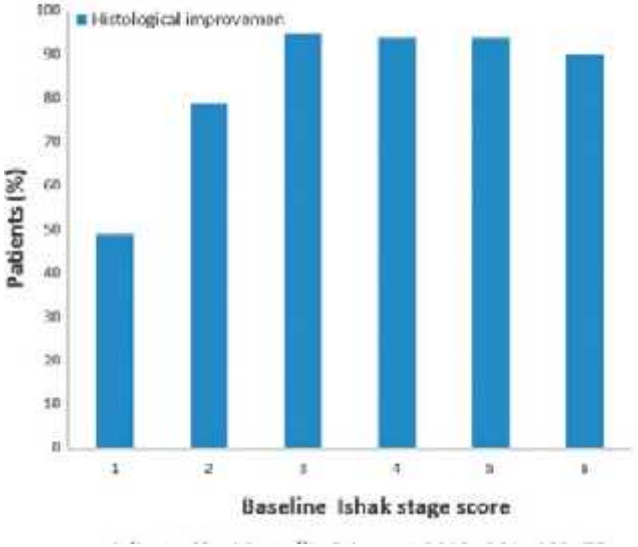
Farmaci antivirali HBV diminuiscono la fibrosi

Table 1. Rate of the regression of fibrosis in patients with chronic hepatitis B and cirrhosis treated with nucleos(t)ide analogues.

	Patient N.	HBsAg status	Regression of fibrosis				Reference
			1	2	3	5 (yr)	
Lamivudine	30	+			67%		4
Adefovir	16	–				75%	6
	15	+				60%	9
	90/125	±				49%/12%	49
Entecavir	10	±				100%	11
	57	±				96%	12
	(10*)		40%			100%	
Tenofovir	133	±	27%			68%	14
	(96*)	±				74%	49
	176/250					71%/67%	
Telbivudine	921/446	±		65%/67%			51

*Patients with cirrhosis

CalvarusoV, Craxì A, Liver International, 2013; 34(s1): 23.



Marcellin P, et al. Lancet 2013 Feb; 381 (9865): 468.

5 anni trattamento antivirale anti-HBV porta a regressione istologica di cirrosi

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Statine come antifibrotici

HEPATOLOGY

AASLD

HEPATOL

EDITORIAL

STAT order: Should patient prescribed statins to prever hepatocellular carcinoma?

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HEPATOLOGY

AASLD

HEPATOLOGY, VOL. 64, NO. 1, 2016

Atorvastatin and Fluvastatin Are Associated With Dose-Dependent Reductions in Cirrhosis and Hepatocellular Carcinoma, Among Patients With Hepatitis C Virus: Results From ERCHIVES

Tracey G. Simon,[1,2*] Hector Bonilla,[3*] Peng Yan,[4,5] Raymond T. Chung,[1,2] and Adeel A. Butt[6-8]

Statins are associated with delayed fibrosis progression and a reduced risk of hepatocellular carcinoma (HCC) in chronic hepatitis C virus (HCV). Limited data exist regarding the most effective type and dose of statin in this population. We sought to determine the impact of statin type and dose upon fibrosis progression and HCC in patients with HCV. Using the Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES) database, we identified all subjects initiated on HCV antibody (anti-HCV) therapy from 2001 to 2014, and all incident cases of cirrhosis and HCC. Statin use was measured using cumulative defined daily dose (cDDD). Multivariable Cox's proportional hazard regression models were used to examine the relationship between statin use and development of cirrhosis and HCC. Among 9,135 eligible subjects, 1,649 developed cirrhosis and 239 developed incident HCC. Statin use was associated with a 44% reduction in development of cirrhosis (adjusted hazard ratio [HR]: 0.6; 95% confidence interval [CI]: 0.53, 0.68). The adjusted HRs (95% CI) of fibrosis progression with statin cDDD 28-89, 89-180, and >180 were 0.74 (0.59, 0.93), 0.71 (0.59, 0.88), and 0.6 (0.53, 0.68), respectively. Mean change in FIB-4 score with atorvastatin (n = 944) and fluvastatin (n = 34) was -0.17 and -0.13, respectively ($P = 0.04$), after adjustment for baseline FIB-4 score and established predictors of cirrhosis. Statin use was also associated with a 49% reduction in incident HCC (adjusted HR: 0.51; 95% CI: 0.36, 0.72). A similar dose-response relationship was observed. *Conclusion:* In patients with chronic HCV, statin use was associated with a dose-dependent reduction in incident cirrhosis and HCC. Atorvastatin and fluvastatin were associated with the most significant antifibrotic effects, compared with other statins. (HEPATOLOGY 2016;64:47-57)

SEE EDITORIAL ON PAGE 13

Hepatitis C virus (HCV) is one of the most common causes of chronic liver disease (CLD) and the leading indication for liver transplantation worldwide.[1,2] Estimates suggest that over a period of 20-30 years, cirrhosis will develop in 10%-25% of patients with chronic hepatitis C (CHC) and hepatocellular carcinoma (HCC) in 1%-5%.[2] Despite the great success of oral direct-acting antiviral

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Statine come antifibrotici

- Statine *prevengono/diminuiscono fibrosi* via attivazione dei PPAR-γ (evidenza per cuore, polmone, fegato)
- Statine sembrano *diminuire il rischio di svilluppo epatocarcinoma*
- Statine sembrano *diminuire l'ipertensione portale*

Uso clinico:

- Statine **possono essere usati** in pazienti cirrotici
- Pazienti con indicazione di una statina **dovrebbero essere trattati**

Come seguire pazienti con cirrosi?

Quale follow-up per pazienti con cirrosi?

Follow-up di routine	
F0	Nessun follow up specialistico necessario
F1-F2	Controlli annuali specialistici (labor, ecografia, fibroscan)
F3 e F4 compensati	Controlli ogni 6 mesi (labor, ecografia, fibroscan annuale)
F4 scompensati	Controlli ogni 3 mesi (labor, ecografia e fibroscan semestrale)

Sorveglianza complicazioni	
Varici esofagee	Gastroscopia ogni 1-2 anni (dipende dallo stato iniziale delle varici)
Screening Epatocarcinoma	Ecografia ogni 6 mesi/IRM annuale +/- alfa-fetoproteina
Evoluzione fibrosi	Fibroscan ogni 12-24 mesi

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Norah A. Terrault, et al., JHep, October 2016; 65 (1), S12

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Conclusione

- La regressione di una fibrosi è possibile!
- La diminuzione della pressione sinusoidale migliora la prognosi di una cirrosi!
- Questioni da risolvere:
  - Come diagnosticare precocemente una fibrosi epatica (ess NASH, ASH)
  - Sviluppo di farmaci anti-fibrotici epato-specifici

… la cirrosi è reversibile…!

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