Prise en charge optimale d' un patient ayant une NASH

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GHPSO-Creil

Titre

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Cas clinique

- Homme de 46 ans vue en novembre 2015 pour augmentation des transaminases évoluant depuis 8 mois
- Pas de consommation d'alcool régulière
- Traitement: metformine 1 g /24h pour diabète de type 2
- Fenofibrate 160 mg/24H pris irrégulièrement
- Asthénie, troubles du sommeil, poids à 88 kg pour 1m75 (IMC à 29 2 kg/m^2).
- Périmètre abdominal 102cm

Cas clinique-2

- ASAT 52 UI/L, ALAT 172 UI/L
- GGT 363 UI/L, P alcalines 92 UI/L
- Glycémie 1,36 g/L, HbA1c 6,83%,
- Cholestérol total 4,56 g/L, HDL 0,41 g/L, Triglycérides 3,91 g/L
- Hb 14 g/dL, leucocytes 8,4 Giga/L, plaquettes 334 giga/L
- Albuminémie 38 g/L
- Sérologies virales B et C négatives
- Ferritinémie 500ug/L , CS 30%
- Echographie abdominale:stéatose

Parmi les examens suivants, lequel est le meilleur pour prédire la stéatose?

A. l'échographie abdominale

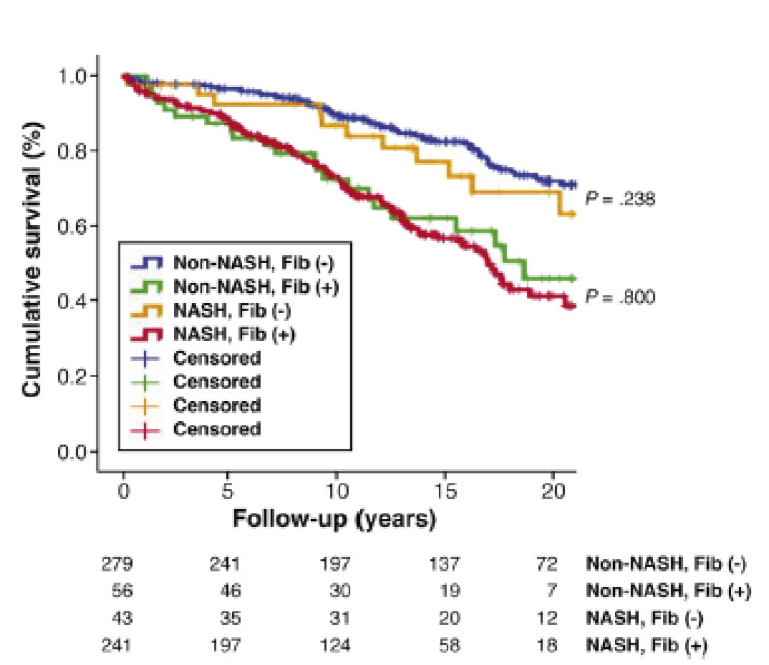
B. l'IRM : *chez ce patient stéatose 45%*

C. le *fatty liver index (FLI)*

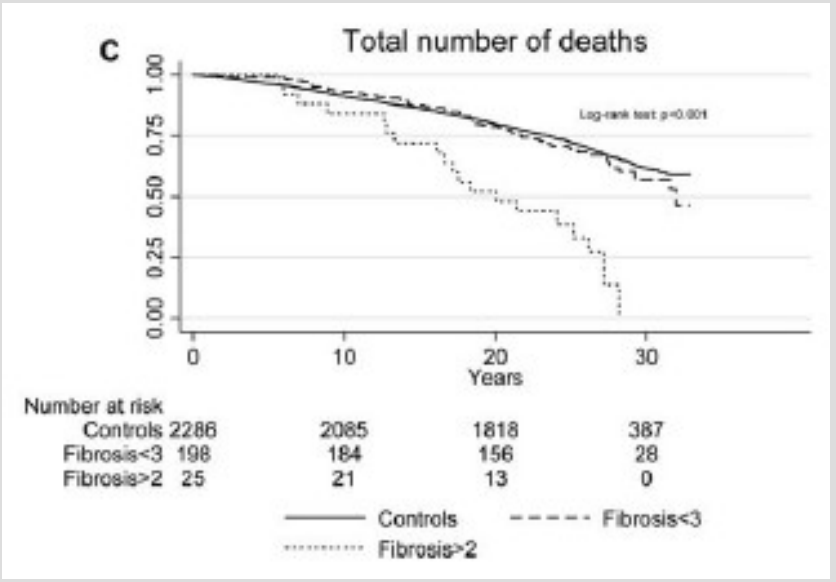
D. le *NAFLD liver fat score*

E. le Steatotest®

Quel est le facteur pronostique le plus important au cours de la NASH?



Angulo P et al. Gastroenterology 2015

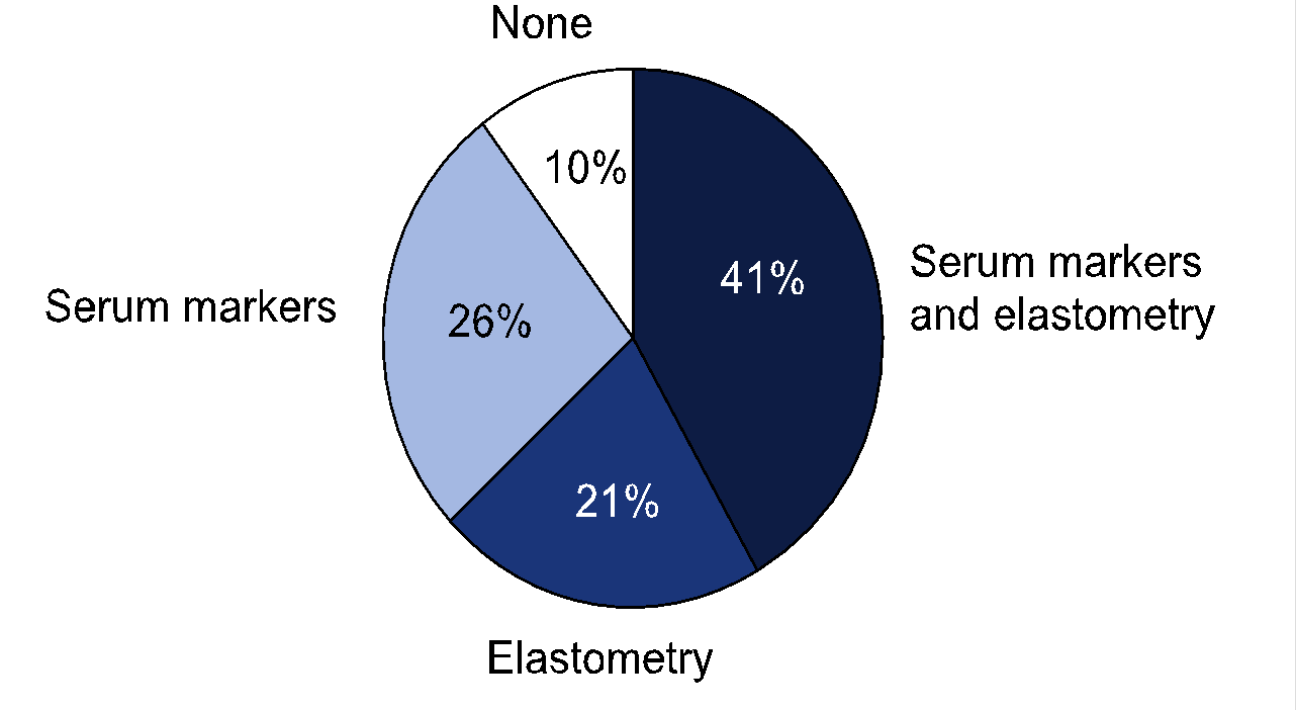


Ekstedt M et al. Hepatology 2015

Quel(s) examen(s) réalisez-vous dans votre pratique pour évaluer la fibrose? (sondage)

A. NAFLD fibrosis score
B. FIB-4
C. Test commercialisé (Fibromètre® , Fibrotest®)
D. Fibroscan®
E. Biopsie hépatique

Practice survey among French gastroenterologists
Non invasive diagnostic procedures



Ratziu R , Cadranel JF, Serfaty L et al. J Hepatol 2012; 57: 376-83

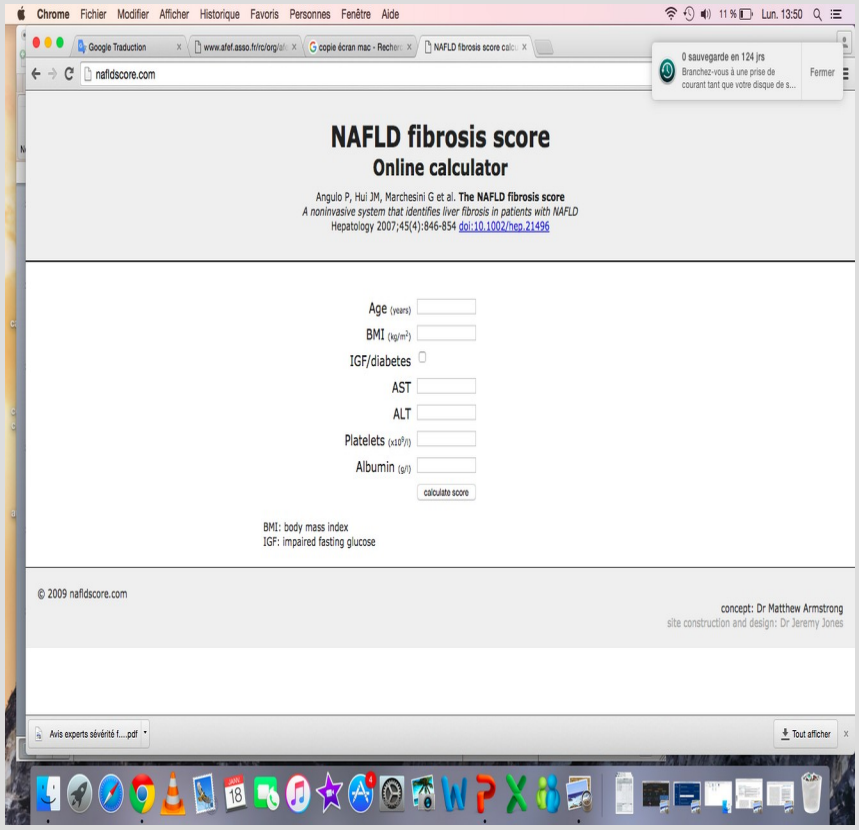
Autres Marqueurs non invasif de fibrose

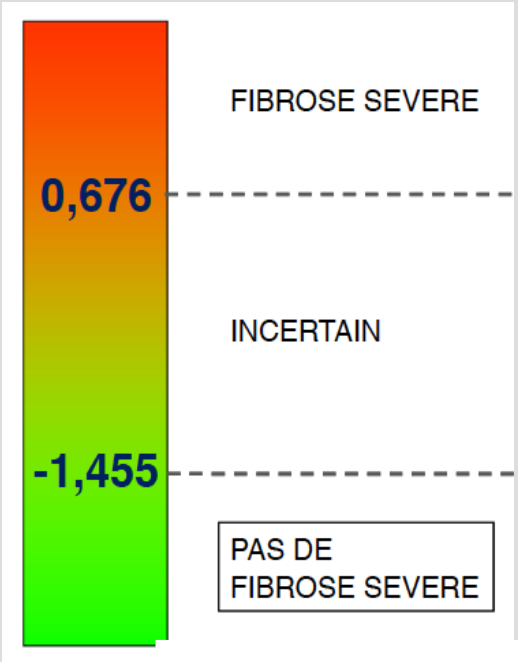
Fibrotest (0,30 F1-F2)
FIB 4 : 0,57

Tests sanguins

Test	Eléments	Seuil	AUROC	Sensibilité %	Spécificité %	VPP %	VPN %
Fibrotest®	Age, alpha 2 macroglobuline, bilirubine, GGT, apolipoprotéine A1	> 0,30	0,81	92	71	33	92
NAFLD score	Âge, glycémie, IMC, plaquettes, albumine, ASAT/ALAT	≥0,676	0,84	43	96	82	80
BARD	IMC, ASAT/ALAT, diabète	2-4	0,81	Na	NA	43	96
FIB-4	Âge, ASAT, ALAT, plaquettes	≥2,67	0,8	33	98	80	83
Fibromètre®	Glycémie, plaquettes, ASAT, ALAT, ferritine, poids, âge	≥0,715	0,94	79	96	88	92

NAFLD Fibrosis Score





VPP 85%
Se 67%/Sp 97%

VPN 90%
Se 90%/Sp 60%

Score de ce patient: - 2,50

http://nafldscore.com/
Angulo P et al. Hepatology 2007

Cas clinique (suite)

Le Fibroscan montre une élasticité médiane à :
7,9 kPa (IQR 1,2; TDR 100%)

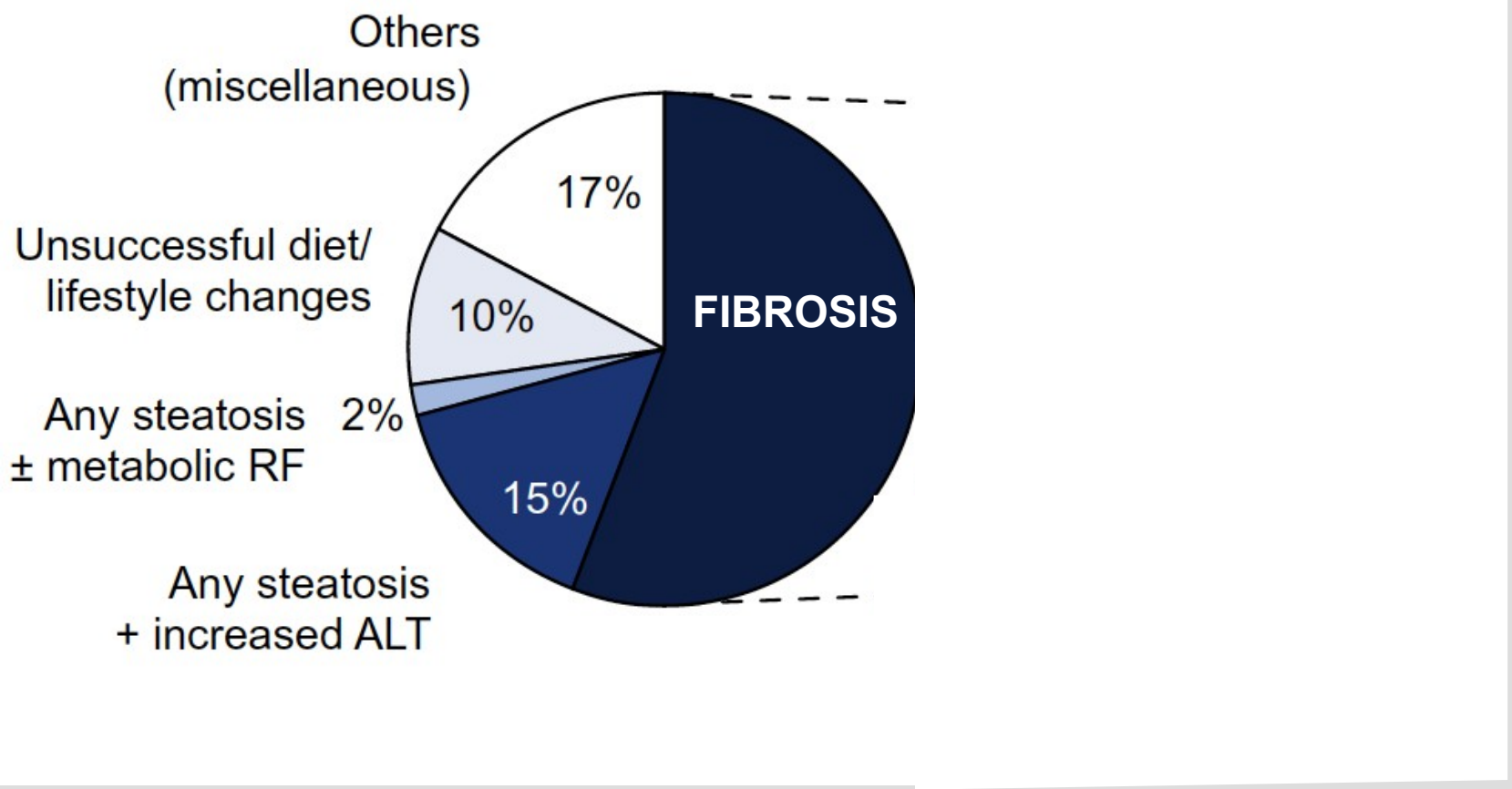
FibroScan® au cours de la stéatopathie métabolique

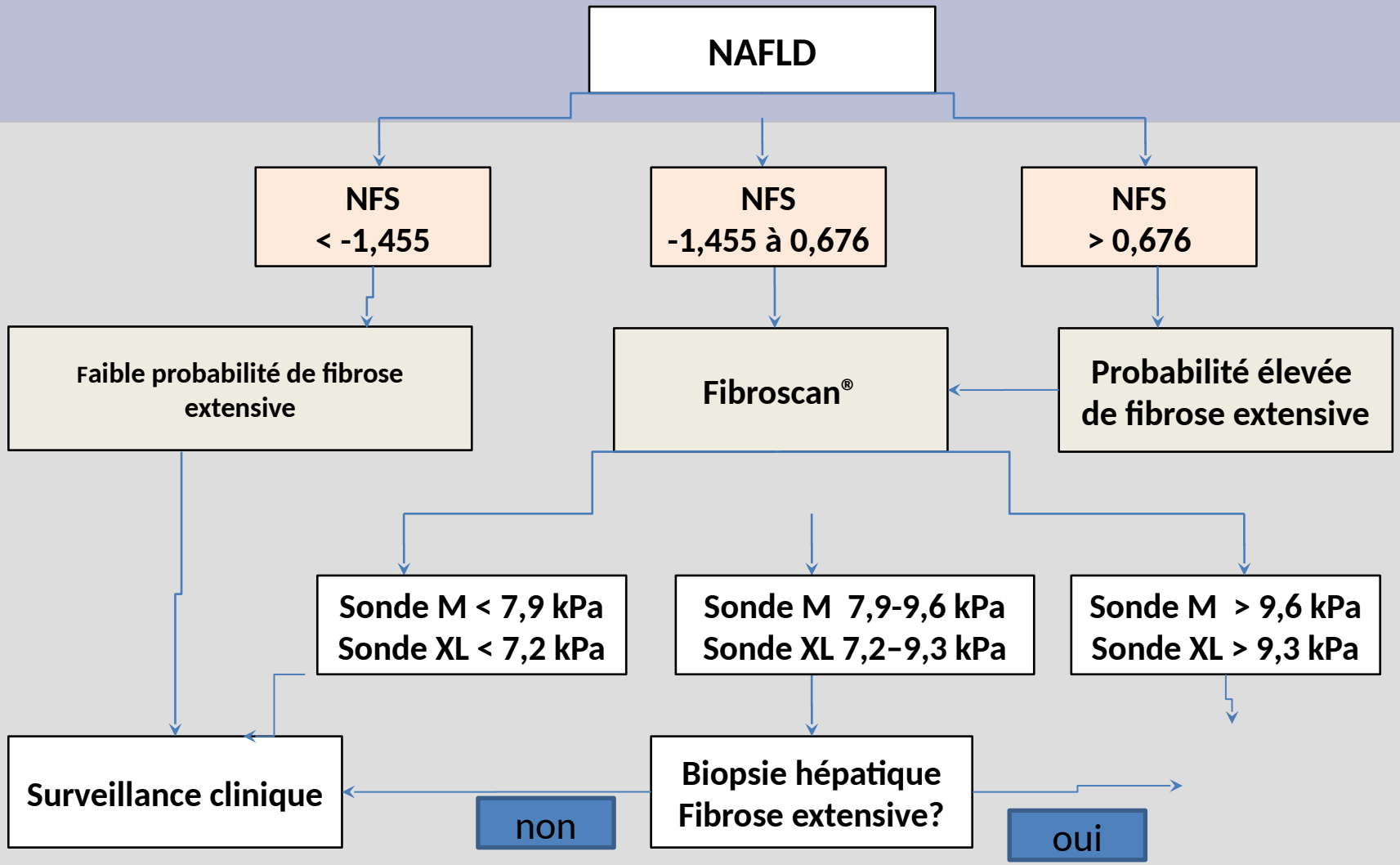
	Fibrose ≥ F2		F4	
	Seuil (kPa)	AUROC	Seuil (kPa)	AUROC
Yoneda et al, Dig Liver Dis 2008	**6,6**	0,86	17	0,99
Nobili et al, Hepatology 2008	**7,4**	0,99		
Wong et al, Hepatology 2010	**7**	0,84	10,3	0,95
Gaia et al, J Hepatol 2011	**7**	0,80	10,5	0,94
Myers et al, Hepatology 2012	**7,8**	0,86	22,3	0,88
Wong et al, Am J Gastroenterol 2012	**7**	0,83	10,3	0,89

Elasticité < 7,9 kPa : faible risque de fibrose sévère/cirrhose

Practice survey among French hepato-gastroenterologists
Indications for liver biopsy

67% of respondents performed liver biopsy





NFS: NAFLD Fibrosis Score

castera L et al. Nat Rev Gastroenterol Hepatol 2013

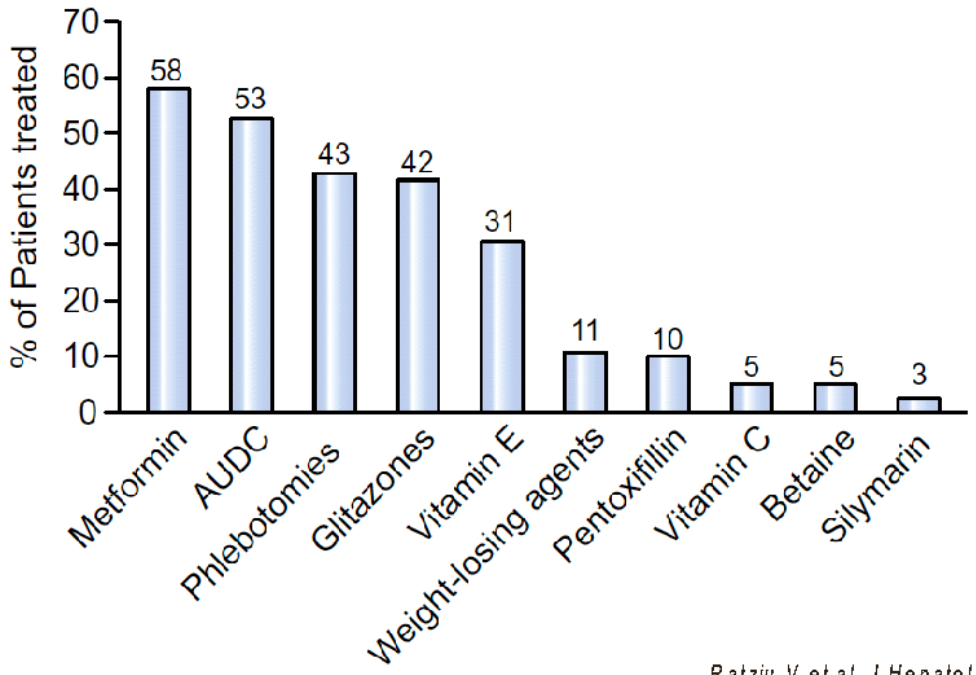
QUELS OPTIONS THERAPEUTIQUES EN 2015

- Le patient a été confié a un médecin nutritionniste
- Toco 500 un cp par jour
- Cholurso 500 mg 3fois par jour

Practice survey among French gastroenterologists
Therapeutic management

Only diet and life style changes: 72%

Pharmacological agents: 28%

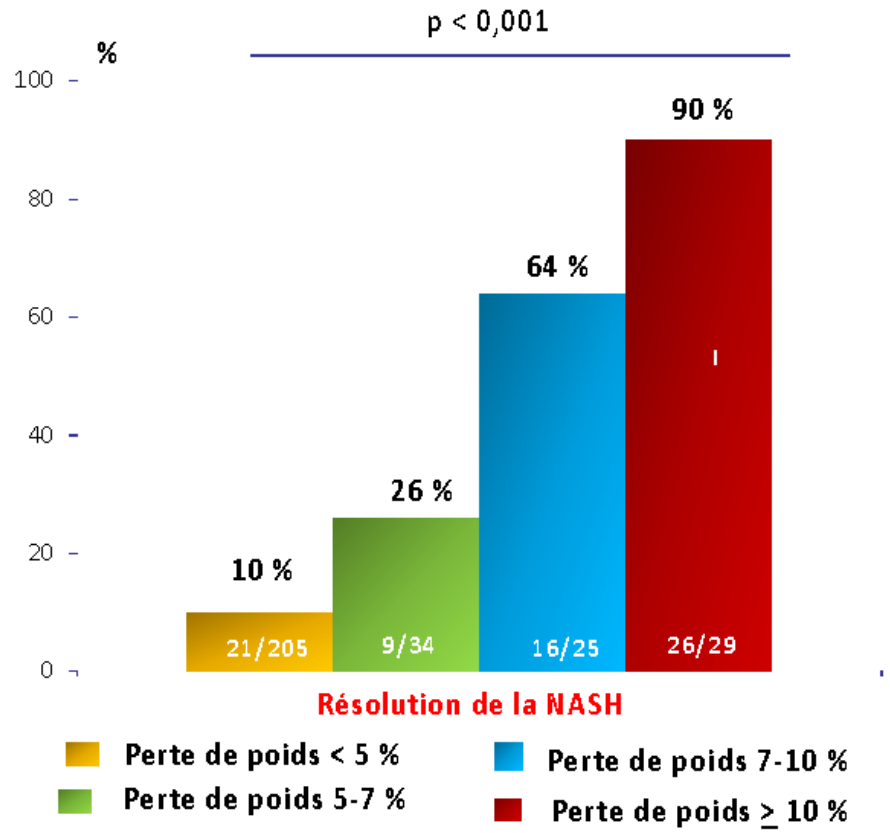


UPMC PARISUNIVERSITAS

Ratziu V et al. J Hepatol 2012; 57: 376-83

Perte de poids + activité physique

Taux de résolution de la NASH en fonction de la perte de poids



- **293 malades non cirrhotiques**
- âge moyen : 48,5 ans
- 56 % d'obèses
- IMC moyen = 31,3

- Régime hypocalorique, pauvre en graisses
- Marche 200 mn/semaine

- Biopsie initiale et à S52.

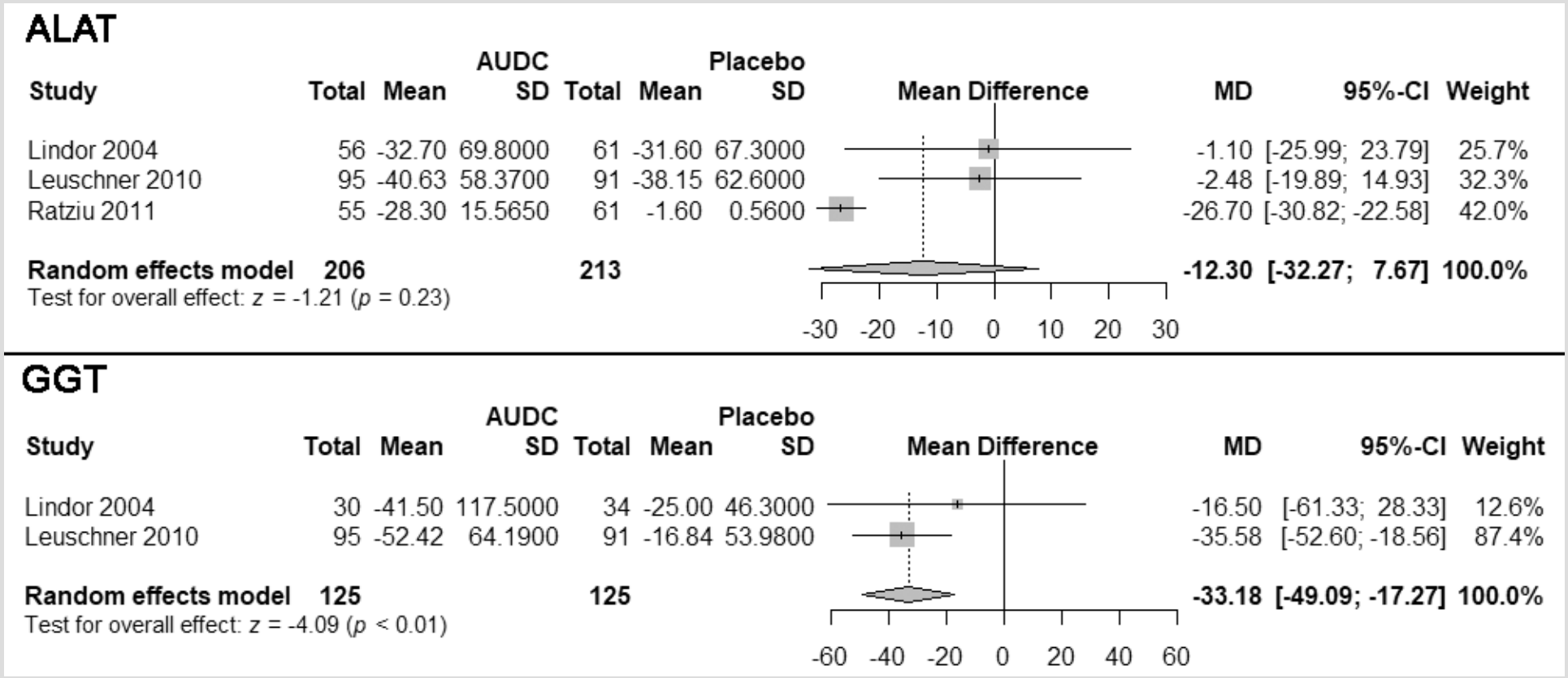
Vilar-Gomez et al. Gastroenterology 2015

Available drugs with reported NASH efficacy

	RATIONALE	EFFICACY (level of evidence)	SIDE EFFECTS	DEFINITIVE DEMONSTRATION
PIOGLITAZONE	+++ adipose IR	high	Weight gain Fractures, Heart failure	**NO**
VITAMIN E	+ antiox	medium	Prostate CV, stroke	**NO**
UDCA	+, antiox Cytoprot	low	none	**NO**
LIRAGLUTIDE	++ Weight loss	low	GI	**NO**
PENTOXYFILLIN	+/-	Very low	GI	**NO**
ORLISTAT	+ Weight loss	low	GI	**NO**

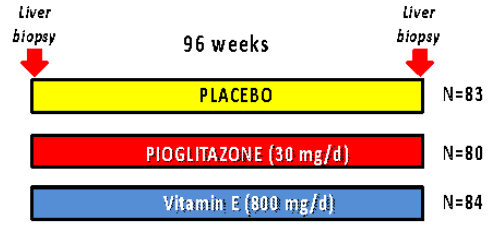
Slide courtesy of V Ratziu

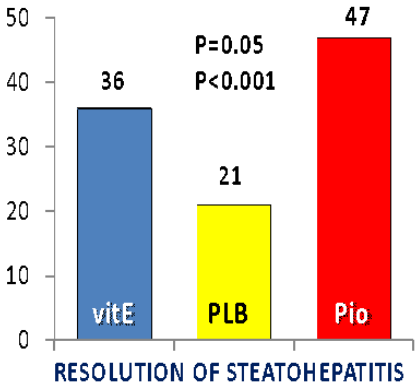
Meta -analyse de l AUDC dans la NASH



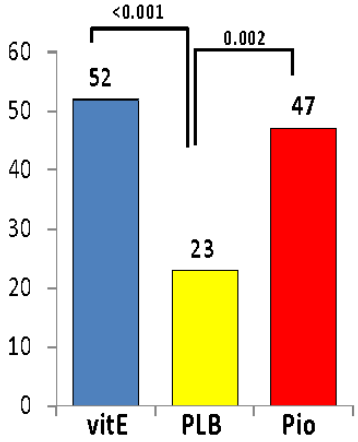
R Heng , JF Cadranel , JB Nousbaum et al. JFHOD 2020

Results of the PIVENS trial in non-diabetic NASH





RESOLUTION OF STEATOHEPATITIS



IMPROVEMENT PRIMARY ENDPOINT

(in Pts with well defined NASH)

Pioglitazone improved :

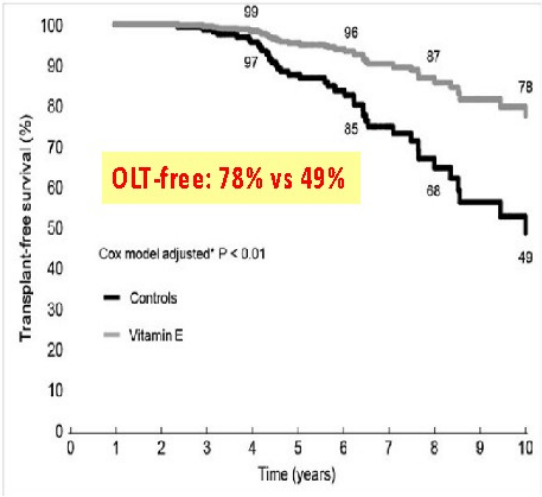
- Steatosis
- Inflammation
- Ballooning
- NAS score

Sanyal, NASH CRN, NEJM 2010

Slide courtesy of V Ratziu

Vitamin E prevents hepatic events in patients with advanced NASH

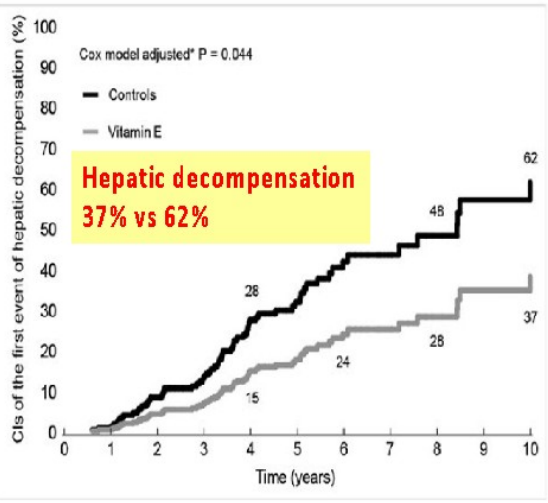
A



OLT-free: 78% vs 49%

OLT-free: HR 0.3 (0,12-0,74, p<0,01)

B



Hepatic decompensation
37% vs 62%

Hepatic decompensation: HR 0.52 (0,28-0,96, p<0,04)

No change in HCC risk

90 patients with NASH F3-F4 on Vit E > 2 years,
90 matched controls
5,6 years follow-up

Vilar-Gomez, Hepatology 2019

Slide courtesy of V Ratziu

JANVIER 2017

Poids 84kg
Perimètre absominal 95 cm
AST 50 ui/l
ALAT 80 ui/l
GGT 100 Ui/l
IRM stéatose :18 %

OCTOBRE 2019

Poids 79kg
Perimètre absominal 95 cm
AST 35 ui/l
ALAT 40 ui/l
GGT 75Ui/l
IRM stéatose :12 %

OCTOBRE 2019

Fibroscan: 5.9 (IQR:1)

FIB4:0,40

Fibrotest : F1

Share Wave Elastography:8 (2)

H Zougmore , JF Cadranel ; M Medmoun et al.

PERSPECTIVES

Emerging Treatments in NASH: Phase III

Drug(s)	Mechanism of Action	Study Population	Trial	Primary Endpoint(s)
Elafibranor	PPAR α/δ agonist[1]	NASH with fibrosis	RESOLVE-IT	Resolution of NASH w/o fibrosis worsening
Obeticholic acid	FXR agonist bile acid[2]	NASH with fibrosis	REGENERATE	Improvement in fibrosis and NASH;
Cenicriviroc	Inhibitor of CCR2/CCR5[3]	NASH with liver fibrosis	AURORA	Improvement in fibrosis w/o NASH worsening
Selonsertib	ASK1 inhibitor[4]	NASH with F2-F3 liver fibrosis	STELLAR	Improvement in fibrosis and NASH

1. Ratziu V, et al. Gastroenterology. 2016;150:1147-1159.
2. ClinicalTrials.gov. 2015;385:956-965.
3. ClinicalTrials.gov NCT03028740
4. .ClinicalTrials.gov. NCT03053063.

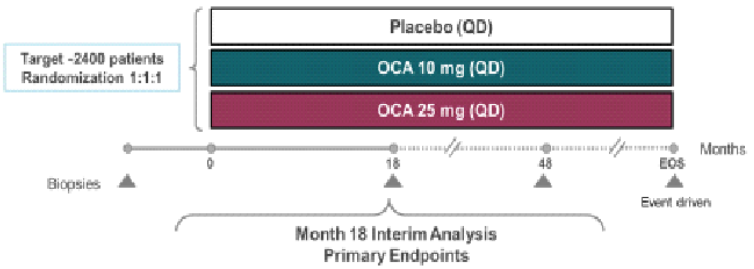
BACK UP

Positive results from REGENERATE: A phase 3 international, randomized, placebo-controlled study of obeticholic acid treatment for NASH

BACKGROUND & AIMS

- OCA is a potent FXR agonist shown in preclinical models to have a direct antifibrotic effect in the liver[1]
- In the phase 2b FLINT study, OCA 25 mg for 72 weeks improved fibrosis and other histological features of NASH[2]
- OCA is the only investigational drug to have received Breakthrough Therapy designation by the US FDA for the treatment of NASH patients with liver fibrosis
- This Month 18 interim analysis of REGENERATE evaluated OCA on liver histology in NASH patients with F2/F3 fibrosis

METHODS



Study success was defined as achievement of one of these two primary endpoints

1. Albanis A, et al. AASLD 2005 (Hepatology 2005;42:1040A);
2. Neuschwander-Tetri BA, *et al.* Lancet 2015;385:956–65.
Younossi Z, *et al.* ILC 2019; GS-06

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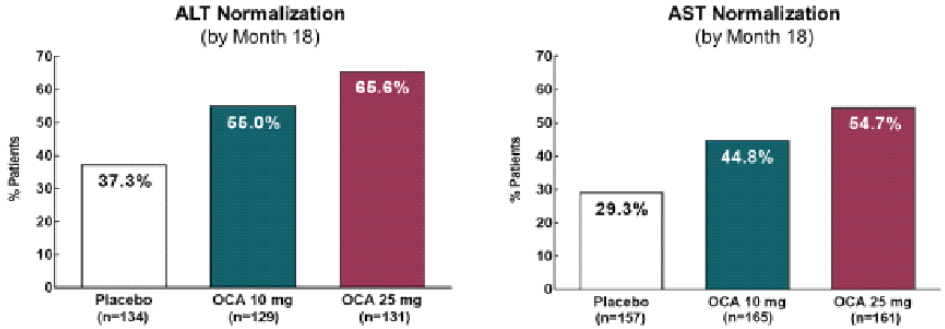
Positive results from REGENERATE: A phase 3 international, randomized, placebo-controlled study of obeticholic acid treatment for NASH

RESULTS (Cont.)

- OCA rapidly decreased ALT, AST and GGT levels, which are routinely monitored by clinicians
- AEs were mostly mild to moderate in severity and the most common were consistent with the known profile of OCA

Normalization of aminotransferases in patients with elevated baseline levels



CONCLUSION REGENERATE is the first successful phase 3 study in NASH. These results are highly relevant because fibrosis is a strong predictor of liver-related morbidity and mortality in NASH.[1] The REGENERATE study is ongoing to confirm benefit on clinical outcomes

1. Dulai PS, et al. Hepatology 2017;65:1557–65.
Younossi Z, et al. ILC 2019; GS-06

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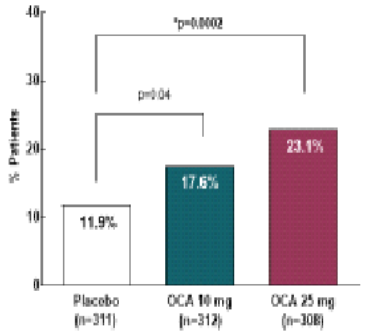
Positive results from REGENERATE: A phase 3 international, randomized, placebo-controlled study of obeticholic acid treatment for NASH

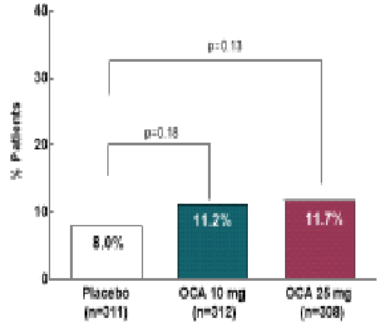
RESULTS

- OCA 25 mg QD met the primary endpoint of improvement in liver fibrosis with no worsening of NASH (p=0.0002* vs. placebo)
  - The antifibrotic effect of OCA was dose dependent and consistent across endpoints and key subgroups
- Although the additional primary endpoint of NASH resolution with no worsening of fibrosis was not met, OCA improved NASH disease activity based on key histological parameters including NAFLD activity score, hepatocyte ballooning and lobular inflammation

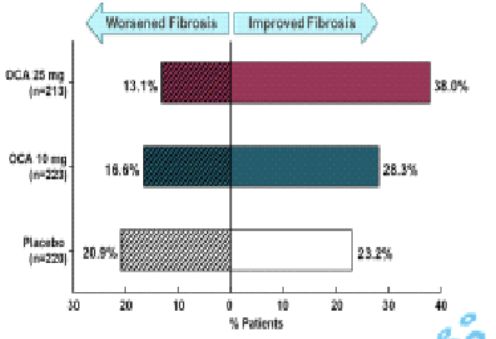
Primary endpoint (ITT): fibrosis improvement by ≥1 stage with no worsening of NASH



Primary endpoint (ITT): NASH resolution with no worsening of fibrosis



Fibrosis improvement or worsening by ≥1 stage (per protocol with post-baseline biopsy)



*Statistically significant in accordance with the statistical analysis plan agreed with the FDA. All other p values are nominal.

Younossi Z, et al. ILC 2019; GS-06

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->Traiter les comorbidités

->Evaluer la fibrose

->Prise en charge nutritionnelle

->Molécules en cours développement

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