

# Management of NAFLD - Clinical case

*9th PHC*

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**Vlad Ratziu, Université Pierre et Marie Curie, Hôpital Pitié  
Salpêtrière, Paris, France**



## ***Woman, age 39, increased LFT and steatosis***

- Family history: overweight, hyper CT (father); CAD (mother); diabetes (aunt).
- History teacher (high school)
- ***Starting age 39 (1985):***
  - Increased LFTs (ALT 70 IU/L; GGT 107 IU/L)
  - Steatosis on ultrasound
  - Type IIb hyperlipidemia
- ***Age 44 (1990) liver biopsy:***
  - Diffuse mixed steatosis predominant in zone 3
  - Rare Mallory bodies; PMN infiltrates
  - No fibrosis
  - Does not drink alcohol
  - Diagnosis : steatohepatitis due to dyslipidemia

# CLINICAL—LIVER

## Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis



Eduardo Vilar-Gomez,<sup>1,2</sup> Yadina Martinez-Perez,<sup>1</sup> Luis Calzadilla-Bertot,<sup>1</sup> Ana Torres-Gonzalez,<sup>1</sup> Bienvenido Gra-Oramas,<sup>3</sup> Licet Gonzalez-Fabian,<sup>3</sup> Scott L. Friedman,<sup>4</sup> Moises Diago,<sup>5</sup> and Manuel Romero-Gomez<sup>2</sup>

**Table 2.** Improvement of Histologic Outcomes Across Different Categories of Weight Loss at the End of Treatment

Variables	Overall (n = 293)	WL <5 (n = 205)	WL = 5–6.99 (n = 34)	WL = 7–9.99 (n = 25)	WL ≥10 (n = 29)	P value
Weight loss, %	3.8 ± 2.7	1.78 ± 0.16	5.86 ± 0.09	8.16 ± 0.22	13.04 ± 6.6	—
Resolution of steatohepatitis <sup>a</sup>	72 (25)	21 (10)	9 (26)	16 (64)	26 (90)	<.01

« ...among patients with weight loss btw 7-10%, the presence of female sex, fasting glucose levels >5.5 mmol/l, many ballooned cells at baseline and a BMI >35 kg/m<sup>2</sup> clearly reduced the probability of steatohepatitis resolution. »

## *Past history – c'ted*

- **Age 51 (1997):**

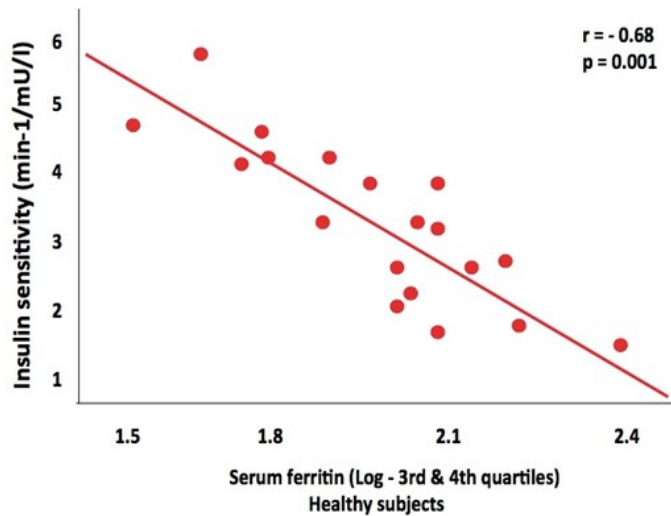
- BMI 27.5 kg/m<sup>2</sup>; android fat deposition; waist 98 cm
- Type 2 diabetes, HbA1c 6.1% glycemia 7.5 mmol/l
- Liver US : hepatomegaly, steatosis
- Liver biopsy in 1998:
  - Steatosis 70%; portal lymphocytic infiltrate; mild lobular inflammation
  - Mild portal fibrosis; no perisinusoidal fibrosis
- Lost weight on orlistat (5 kg) normalized AST, ALT<2 ULN

## *Past history – c'ted*

- Stopped Orlistat after 1 year; regained weight
- **2000 :**
  - Ferritin 568 ng/ml;
  - transferrin saturation 55%
  - Iron quantification by MRI: 70  $\mu\text{mol/g}$

*Q: How do you deal with the hyperferritinemia ?*

# Hyperferritinemia is correlated with insulin resistance...



Fernandez-Rial JM, Diab Care 1998; 21: 62-67

## ... and predicts diabetes onset

### 1299 persons with normal glucose – 3-year follow-up

n	Serum glucose at 3 years	Serum ferritin at baseline
1068	< 6.1 mmol/L	93 (42-175)
200	6.1 – 6.9 mmol/L	167 (102-169)
31	≥ 7 mmol/L	166 (68-353)

Fuméron F. Diab Care 2006;29:2090-4

Orban E, Diabetes Metabol Res Rev 2014;30:372-394

## Metabolic abnormalities

### HYPERFERRITINEMIA

**DIOS**

**50%**

Cell necrosis, inflammation  $\pm$  alcohol

**10-25%**

**NAFLD**

**↑ IRON STORES ↔ ↑ RISKS**

**DIABETES  
CANCER  
CARDIOVASCULAR COMPLICATIONS  
HEPATIC FIBROSIS**





# Effect of blood letting on insulin-resistance

- Randomized controlled study

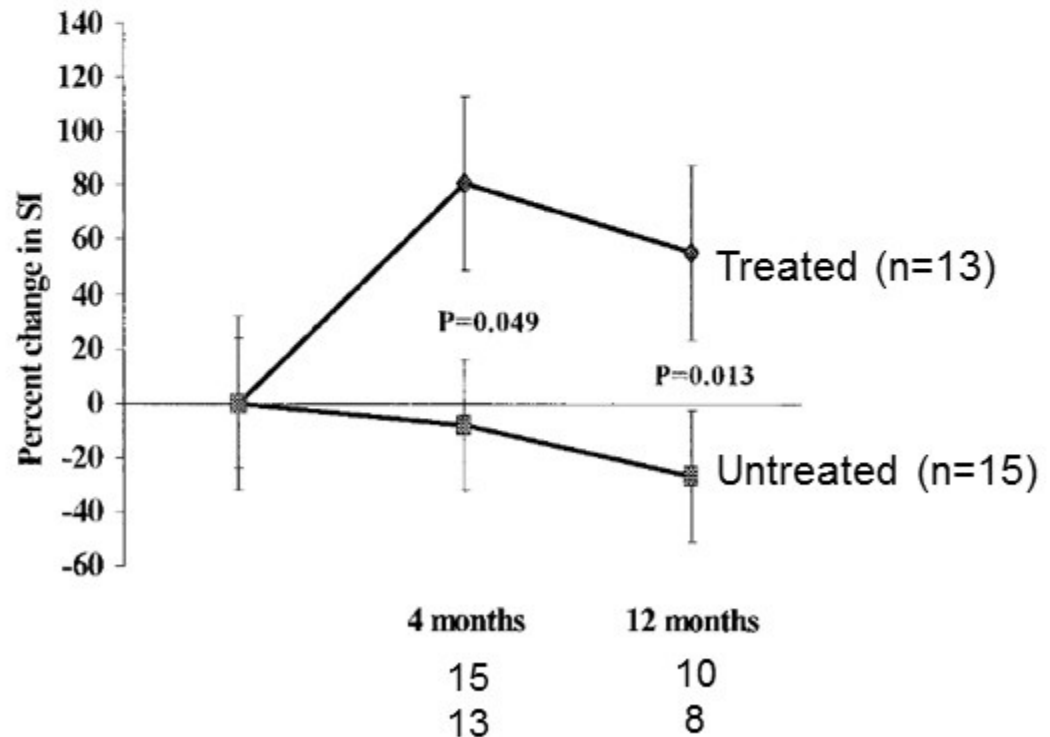
*Fernandez-Real JM, Diabetes 2002;51:1000-4*

Type 2 diabetes with serum ferritin > 200

Blood removal 500 ml w0, w2, w4

Insulin secretion & sensitivity m0, m4 & m12

Randomization  
(age, BMI, HbA1C)





# Effect of blood letting on IR-related conditions

- Randomized controlled study: **cancer incidence**

Zacharski LR et al, JNCI 2008;100:996-1002

1277 patients with peripheral arterial disease

Blood removal to maintain ferritin 25 - 60

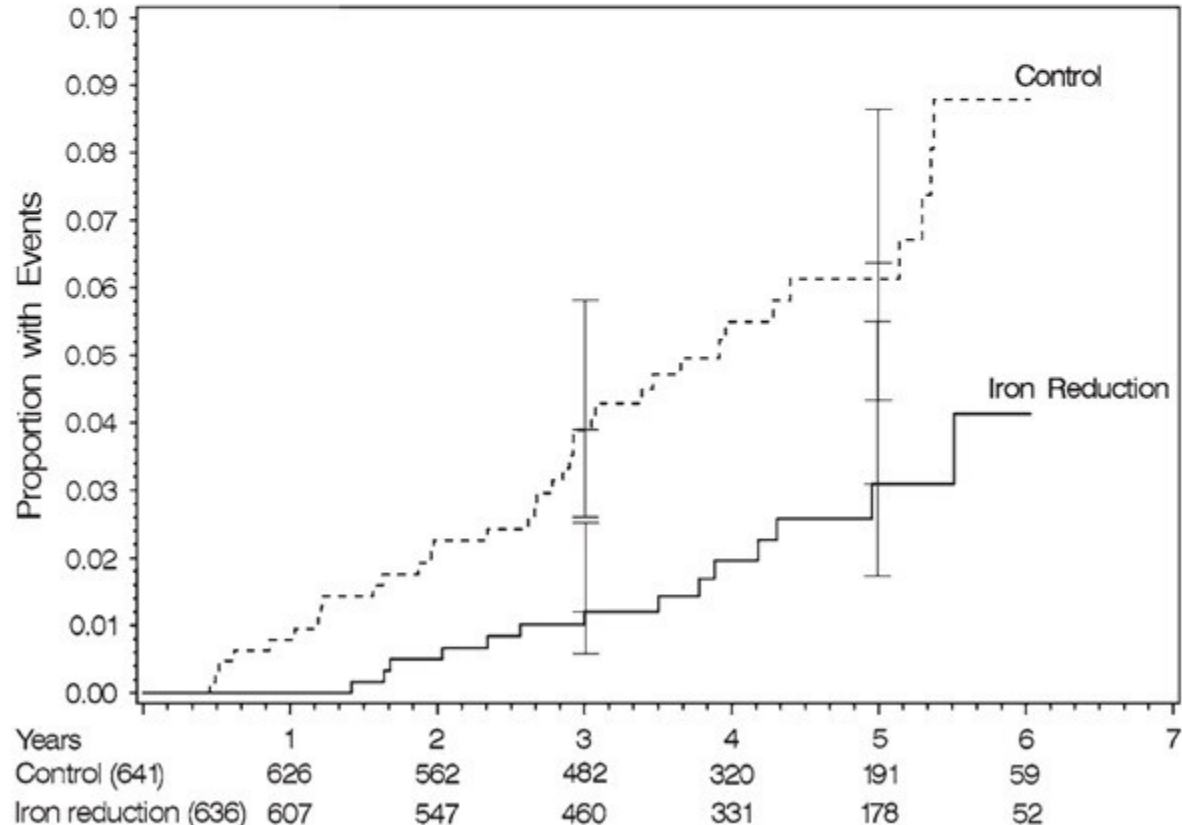
Incidence of cancer (secondary objective). 4.5-y follow-up

Hazard ratio 0.39

95% CI : 0.21 – 0.72

$p = 0.003$  (two-sided log-rank test)

Cox proportional hazards  $X^2 = 8.96$



Slide courtesy Prof. Deugnier

Time to Event in Years and Number of Patients at Risk for each Group



# Effect of blood letting on IR-related conditions

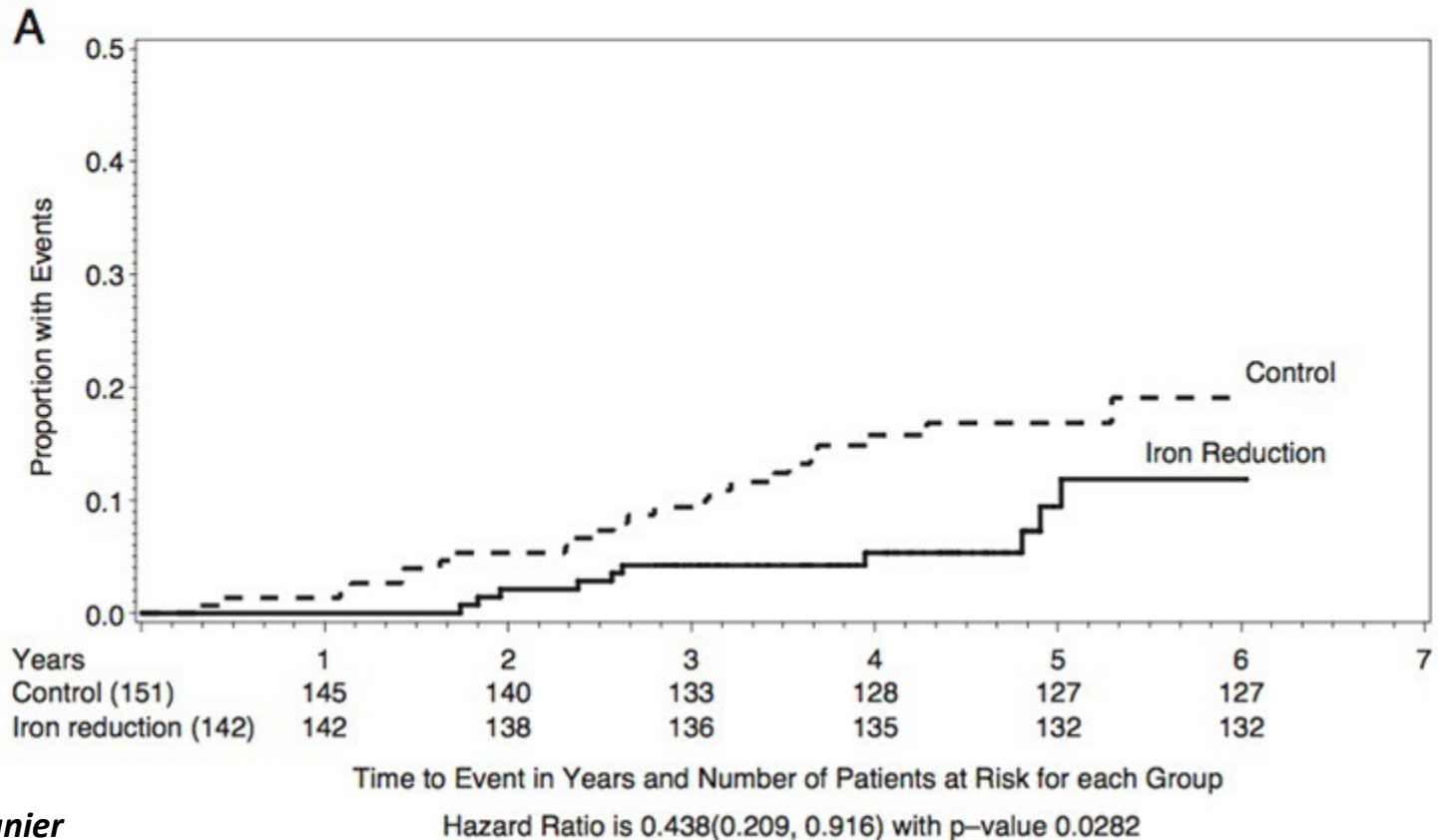
- Randomized controlled study : **CV events**

Zacharski LR, *Am Heart J* 2011

1277 patients with peripheral arterial disease

Blood removal to maintain ferritin 25 - 60

Incidence of CV events (secondary objective). 6-y follow-up



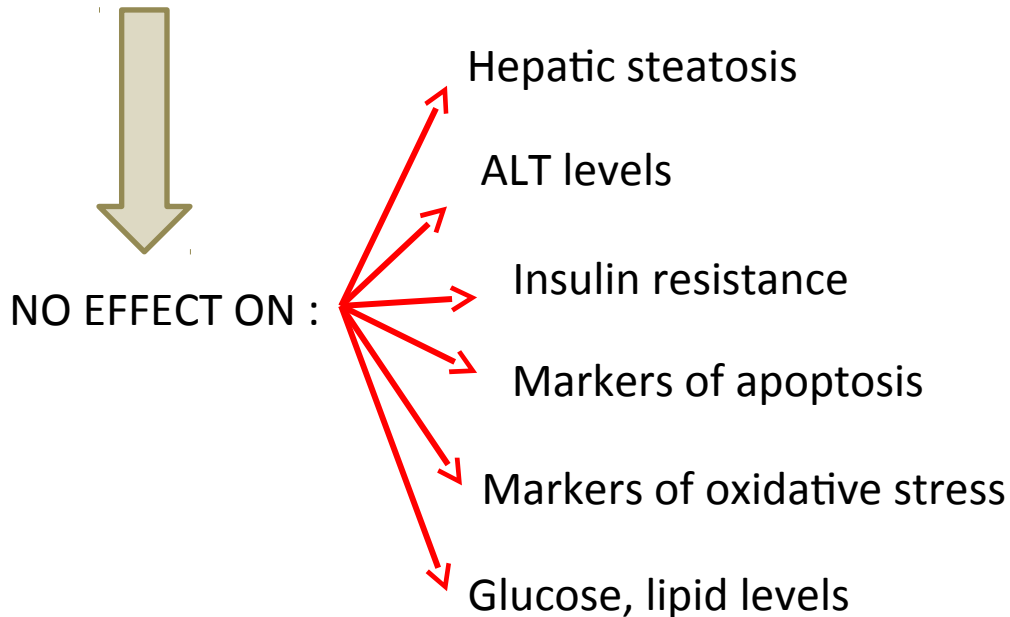
# The Impact of Phlebotomy in Nonalcoholic Fatty Liver Disease: A Prospective, Randomized, Controlled Trial

Leon A. Adams,<sup>1,2</sup> Darrell H. Crawford,<sup>3,4</sup> Katherine Stuart,<sup>4</sup> Michael J. House,<sup>5</sup> Timothy G. St. Pierre,<sup>5</sup> Malcolm Webb,<sup>6</sup> Helena L.I. Ching,<sup>2</sup> Jenny Kava,<sup>7</sup> Michael Bynevelt,<sup>8</sup> Gerry C. MacQuillan,<sup>1,2</sup> George Garas,<sup>1,2</sup> Oyekoya T. Ayonrinde,<sup>7,9,10</sup> Trevor A. Mori,<sup>1</sup> Kevin D. Croft,<sup>1</sup> Xianwa Niu,<sup>1</sup> Gary P. Jeffrey,<sup>1,2</sup> and John K. Olynyk<sup>7,9,10</sup>

(*HEPATOLOGY* 2015;61:1555-1564)

29 Pts with venesection and lifestyle advice vs. 32 Pts with lifestyle advice

6 months venesection





**Heterogeneity of studies (patients, design, end point of phlebotomies), but beneficial effect of blood letting on**

- **insulin resistance : likely**
- **IR associated conditions**
  - **cancer & CV events : likely**
  - **liver: to be proven**



**Current practice (in the absence of clinical trial)**

**If serum ferritin > 500  $\mu\text{g/l}$  after treatment of MetS**

- **MRI**
- **or liver biopsy if indicated (NAFLD)**

**If hepatic iron concentration > 50  $\mu\text{mol/g}$  (N < 36)**

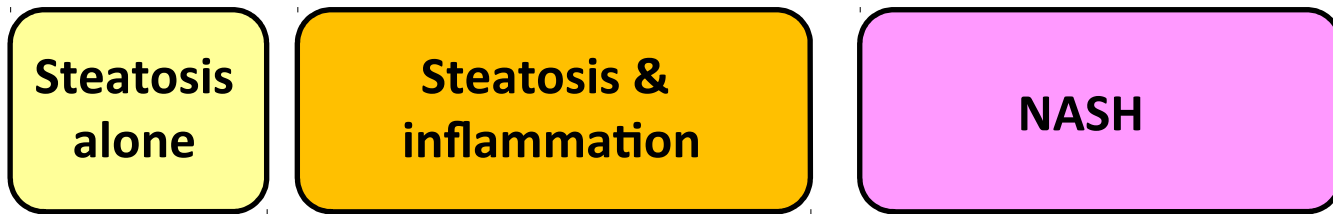
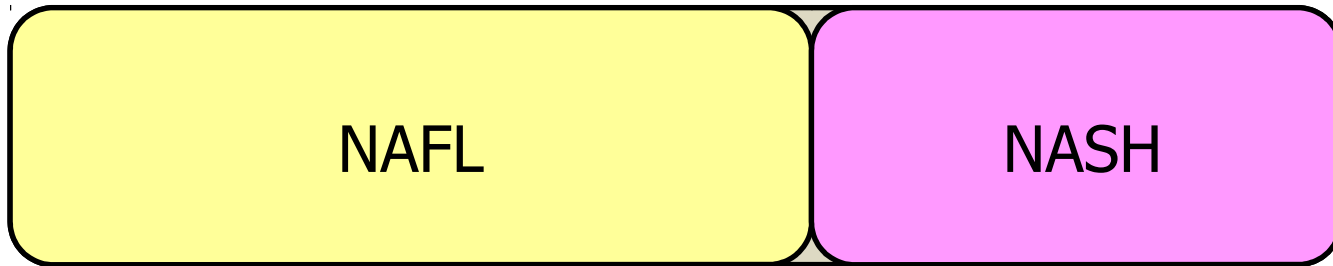
- **Blood removal 5-7 ml/kg / 2 weeks  $\rightarrow$  serum ferritin < 50-100**
- **No maintenance therapy.**

# Hyperferritinemia in NAFLD Pts

- A 1/3 of NAFLD patients have increased serum ferritin, with normal transferrin saturation and no iron overload
- High serum ferritin correlates with several components of the metabolic syndrome, with fasting insulin and insulin resistance
- In patients with NAFLD and the metabolic syndrome ferritin 400-1200  $\mu\text{g/L}$ , especially when transferrin saturation is normal denotes insulin resistance and not iron overload
- If high transferrin saturation and high ferritin, HFE mutations should be determined and hepatic iron overload should be measured by hepatic MRI
- Phlebotomies improve insulin sensitivity but their effect on liver injury is unknown/uncertain

## *Past history – c'ted*

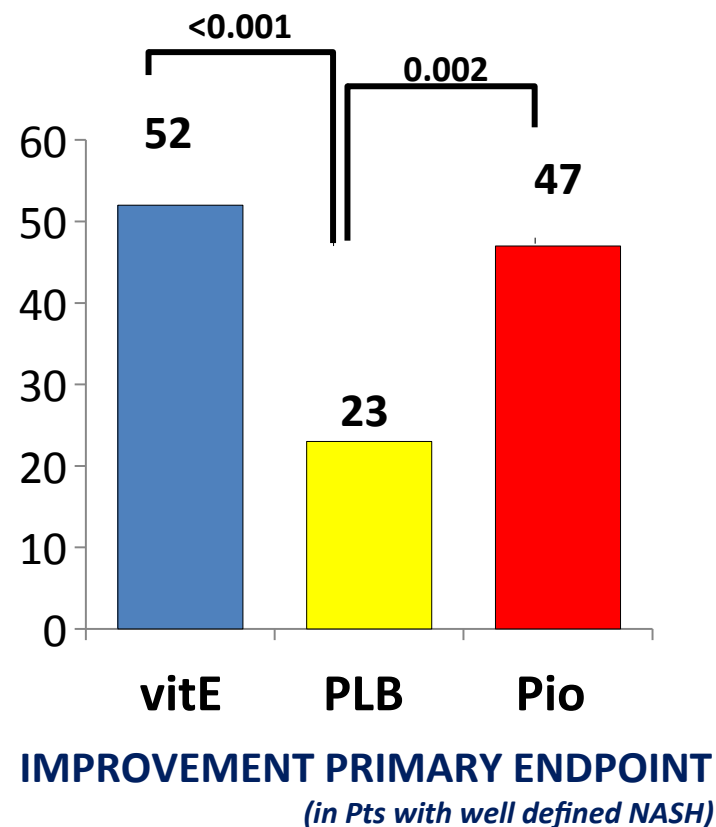
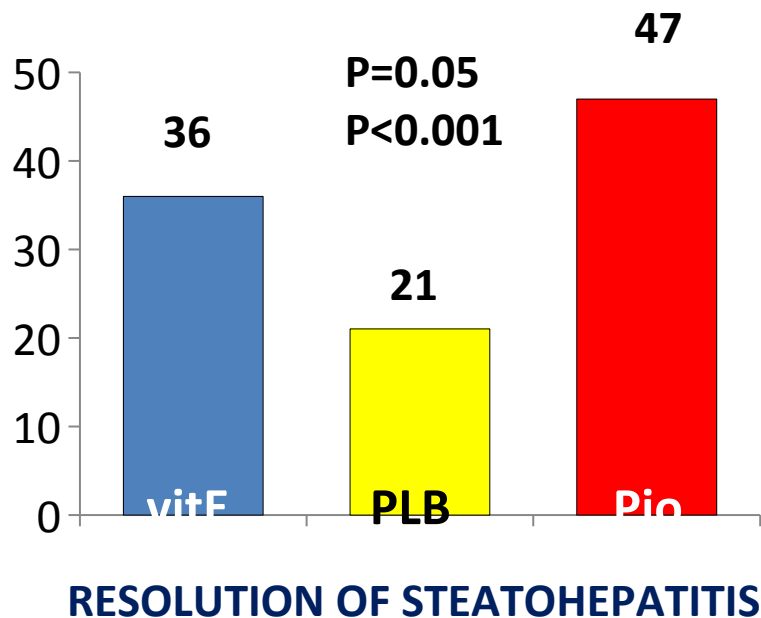
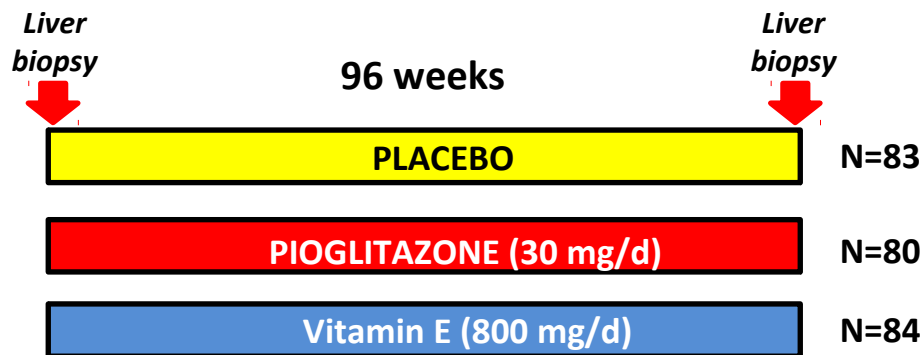
- C282Y +/-; H63 D -/-
- Repeat MRI (2001) : 30 $\mu$ mol/g
- Liver staining for iron (1998): very mild iron stain
- Decision not to perform phlebotomy
- 2003: third liver biopsy (inclusion clinical trial rosiglitazone)
  - 40 mm, 31 portal spaces. Steatosis = 30%, severe lobular inflammation and ballooning; Portal fibrosis with few septa, perisinusoidal fibrosis. **NAS Score = 5, Stage 3; NASH with advanced fibrosis**



Potential for progression



# Results of the PIVENS trial in non-diabetic NASH



## Pioglitazone improved :

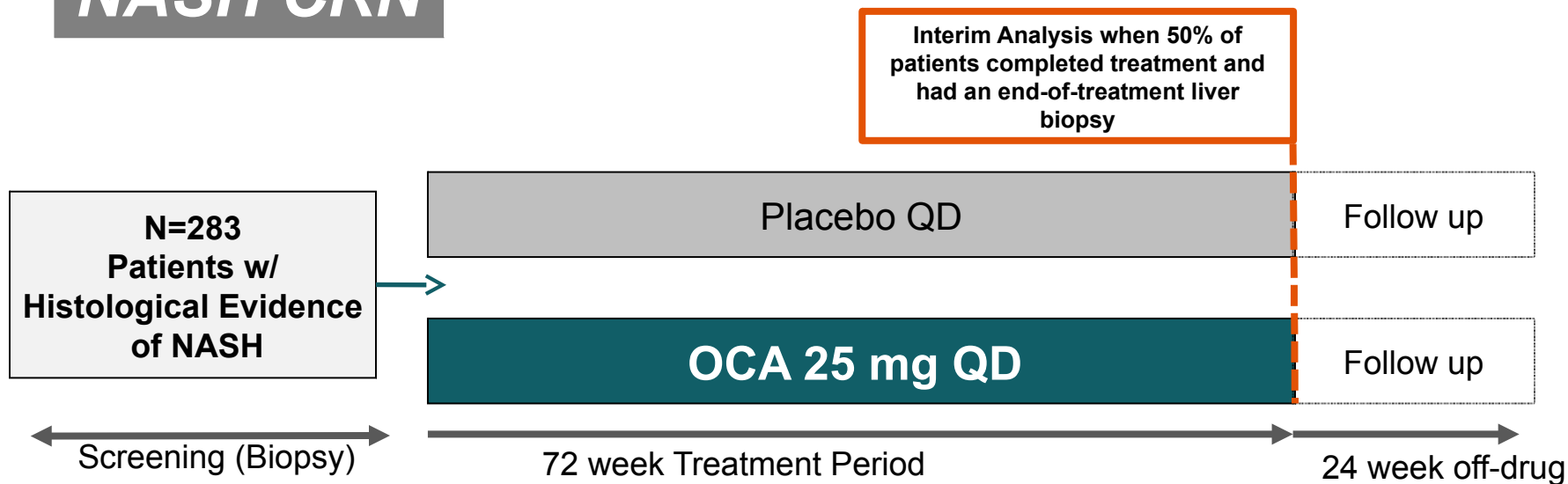
- Steatosis
- Inflammation
- Ballooning
- NAS score

# FLINT Phase 2 Trial Design

The Farnesoid X Receptor Ligand Obeticholic Acid (OCA) in NASH Treatment



**NASH CRN**



**Primary endpoint:** Histological improvement defined as:

- No worsening in fibrosis; and
- Decrease in NAS of  $\geq 2$  points

# Primary Outcome: Improved Liver Histology after 72 Weeks of Treatment

\*\*\* $p < 0.001$ ; Relative risk (95% CI): 1.9 (1.3 to 2.8); p-value and relative benefit were obtained using Cochran-Mantel-Haenszel Chi-square test stratified by center and diabetes status; Missing week 72 biopsy results were imputed as no improvement among patients at risk of week 72 biopsy; Neuschwander-Tetri BA, et al. *Lancet*. 2014;S0140-6736(14)61933-4.

# Secondary Outcomes: Improvement in Histological Parameters



\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ ; p-value was based on the Cochran-Mantel-Haenszel chi-square test stratified by center and diabetes status; Neuschwander-Tetri BA, et al. *Lancet*. 2014:S0140-6736(14)61933-4.

# LEAN ‘Liraglutide’s Efficacy & Action in NASH’

50 patients

Randomised, Double-blinded  
(stratified: site, diabetes)

Control Group

n = 25

Placebo 0.6mg OD

(Days 1-7)

Placebo 1.2mg OD

(Days 8-14)

Placebo 1.8mg OD

(Days 15-336)

Experimental Group

n=25

Liraglutide 0.6mg OD

(Days 1 – 7)

Liraglutide 1.2mg OD

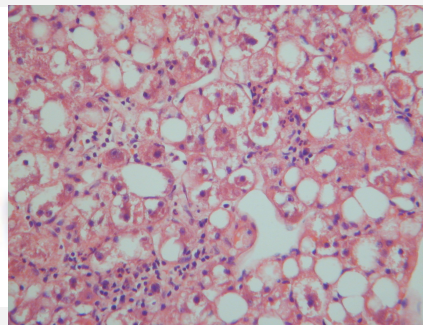
(Days 8 – 14)

Liraglutide 1.8mg OD

(Days 15 – 336)

**Inclusion criteria:**  
NASH Biopsy < 6mths  
Age 18-70  
T2DM or non-T2DM  
(HbA1c <9.0%; no insulin)

**Week 48 (visit 7)**



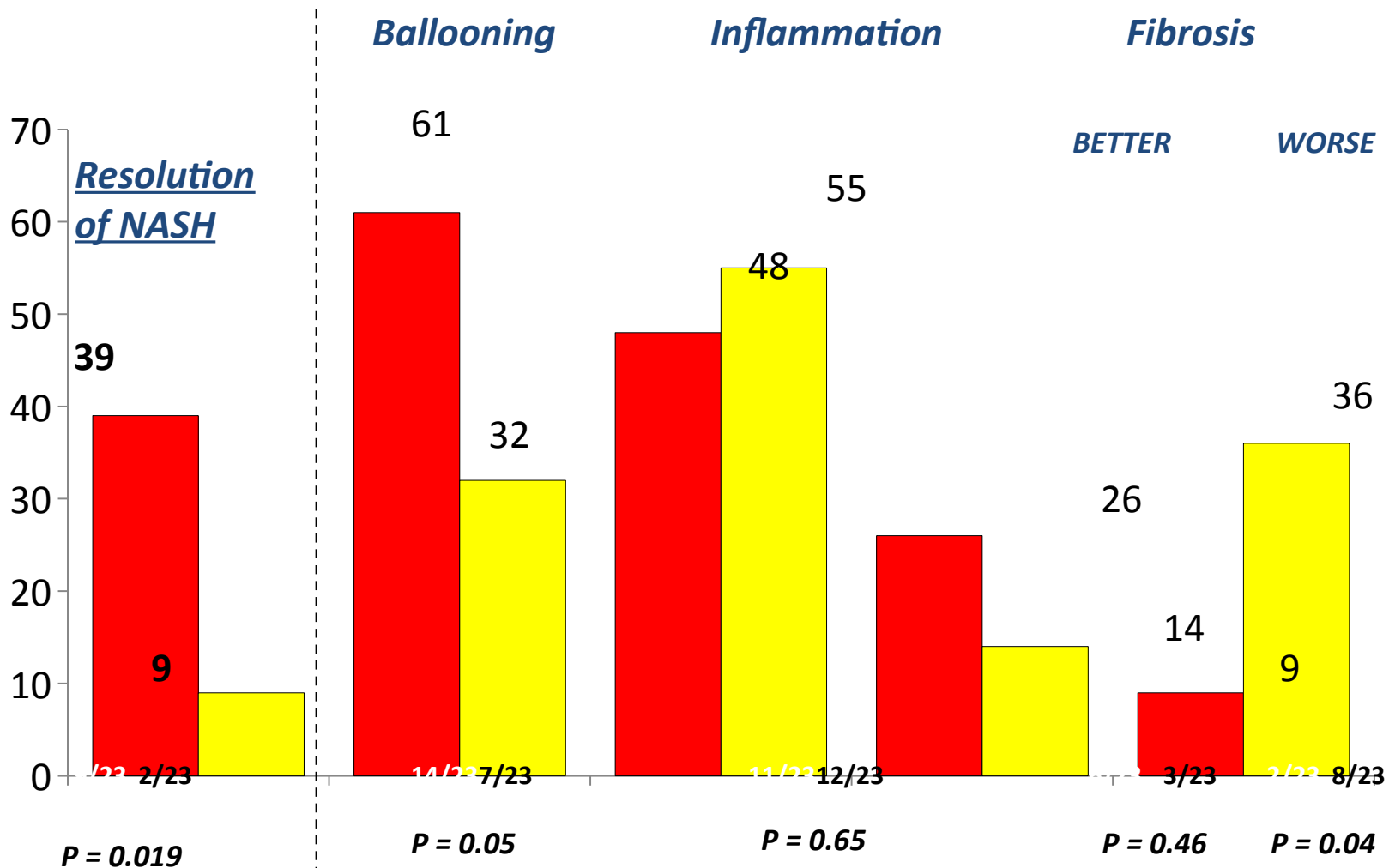
**Liver Biopsy**

**Primary End-point:**  
Disappearance of ballooning

**Secondary End-points:**  
Safety; liver biomarkers;  
metabolic

*Armstrong & Newsome*

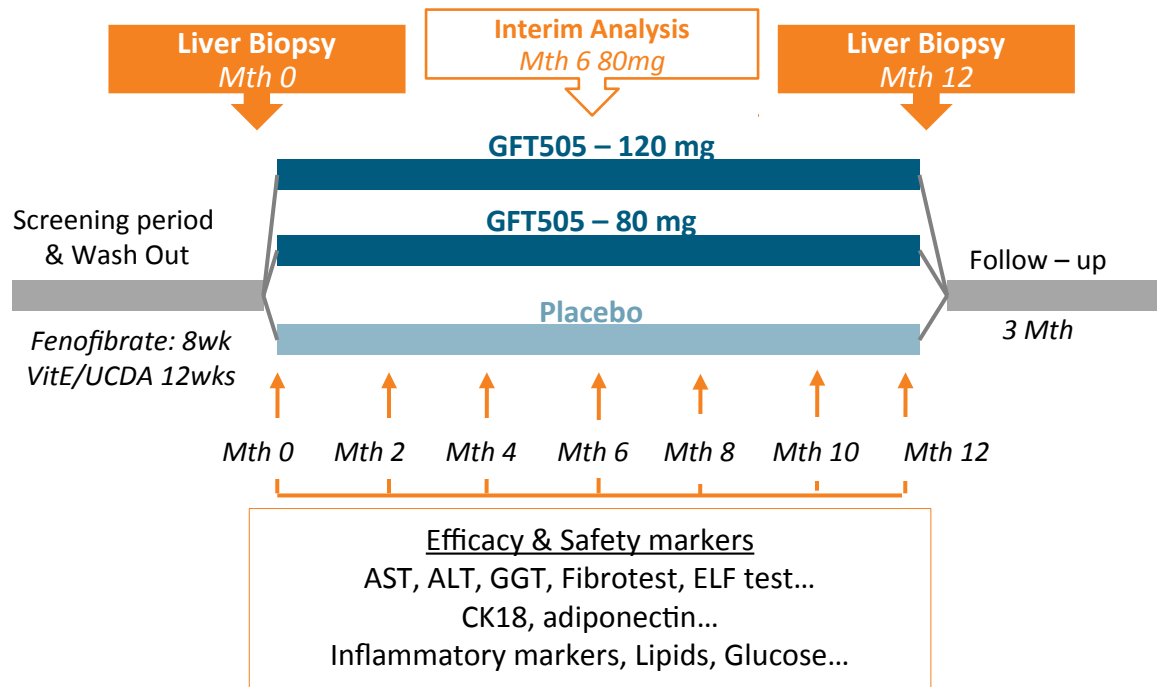
# Histological improvement in the LEAN trial



# GFT505-212-7 GOLDEN Study

## Phase IIb trial design

- **3 parallel groups:** placebo, GFT505 80mg & GFT505 120mg (secondarily after interim safety analysis of 80 mg) once daily for **52 weeks**
- **270 patients** with histological diagnosis of NASH
- **74-90 clinical centres** distributed in **Europe + US**
- Data Monitoring Committee for safety & efficacy



## Results 1. Resolution of NASH w/o worsening of fibrosis, ITT (N=274)

Placebo (N92)	Elafibranor 80 mg (N93)	Elafibranor 120 mg (N89)	OR* 95% CI	P (120 mg vs. Plb)
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*UPDATED DEFINITION, (% responders)*

12 %	13 %	19 %	2.31 (1.02-5.24)	0.045
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## Results 2. Exploratory analyses (bNAS<sub>≥</sub>4, N=234)

Placebo (N76)	Elafibranor 80 mg (N83)	Elafibranor 120 mg (N75)	OR* 95% CI	P (120 mg vs. Plb)
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*UPDATED DEFINITION, (% responders)*

9 %	13 %	19 %	3.52 (1.32-9.40)	0.013
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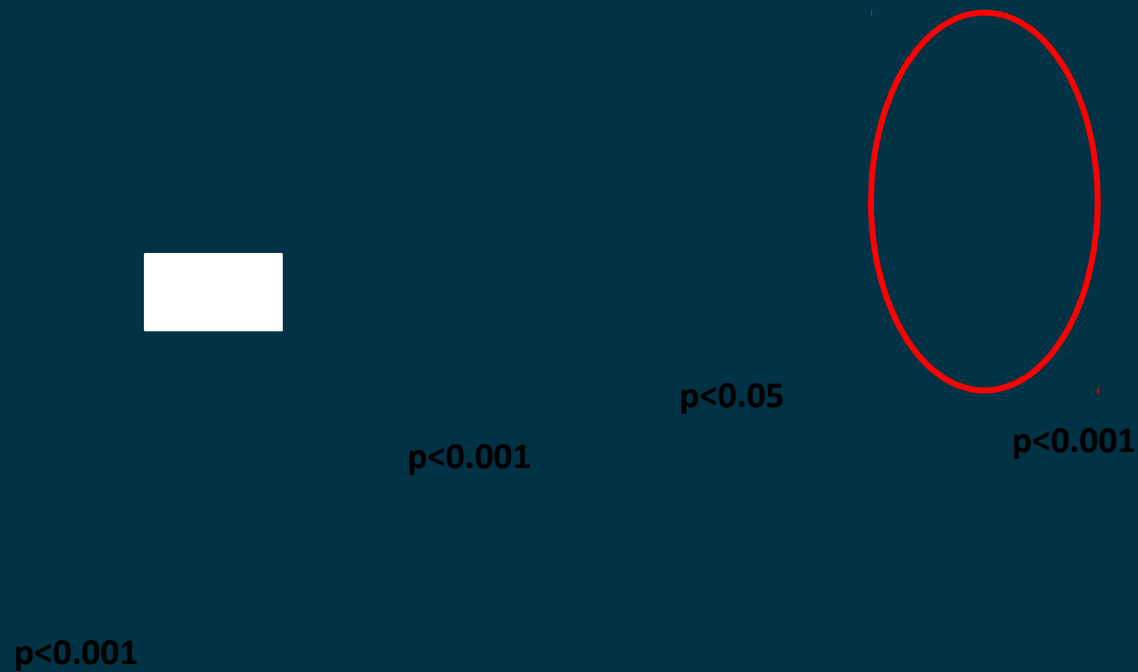
\* 120 mg vs. placebo



# Results 4. Secondary analyses

## Resolution of NASH is associated with Fibrosis reduction

Responders vs Non-Responders for the primary endpoint in completers on 120 mg (N=78)



## ***Past history – c'ted***

- **2006:**

- steatosis 40%,
- lobular inflammation moderate;
- ballooning : severe
- NAS 6; *cirrhosis*

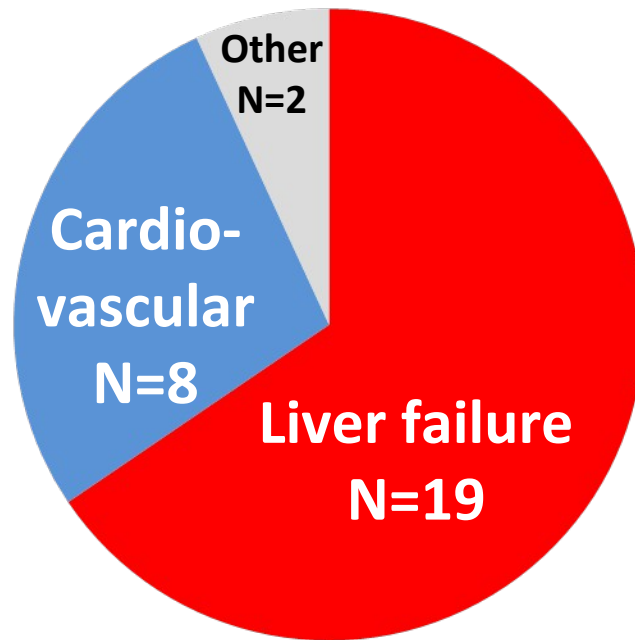
- FibroTest: 0.61 (in 2003 0.23)
- Fibroscan : 42 kPa
- Upper endoscopy : normal
- PT 89%; Platelet count 161k; Alb 46 g/l; Bilirubin 14  $\mu$ mol/l
- AST 53; ALT 50; GGT 202

# Causes of death in NASH cirrhosis

- Same as in any other cause of cirrhosis
- Same prognostic value of MELD, Child-Pugh, ...

**N=152 NASH-cirrhosis**  
**8 yrs f/u**  
**29 Deaths**

**COMPETITIVE  
RISK**

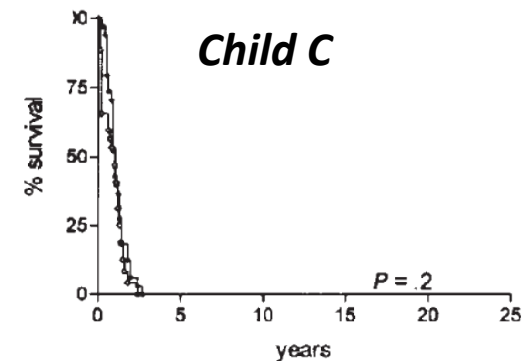
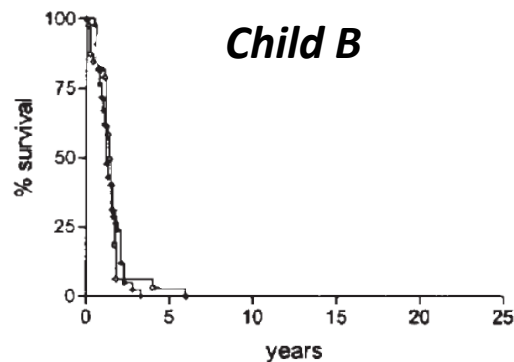
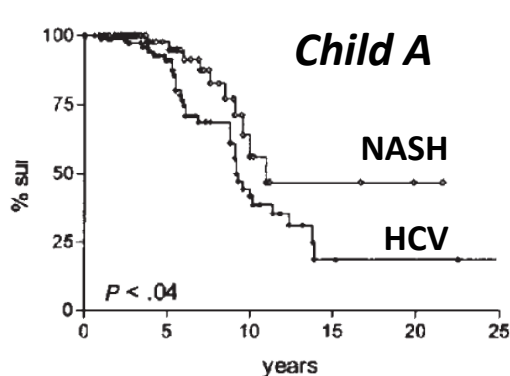


- Sepsis +++
- Variceal hemorrhage ++
- HCC +

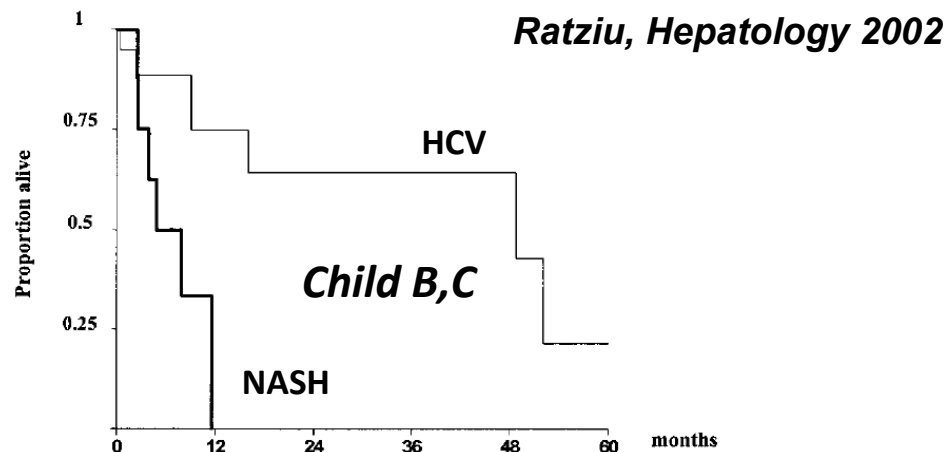
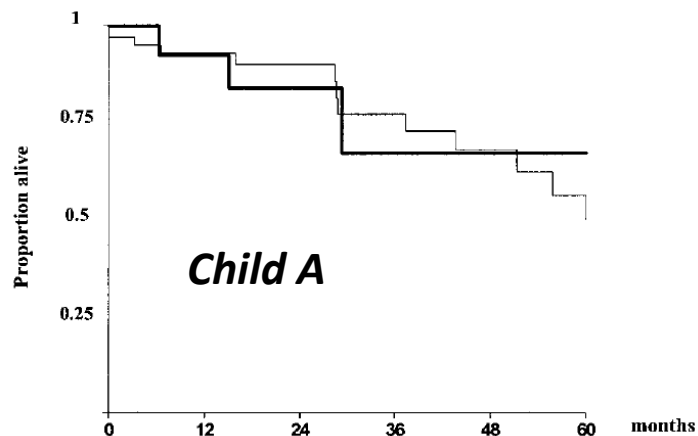
# Progression to liver-related death

- N=152 NASH-cirrhosis & 150 HCV-cirrhosis

*Sanyal, Hepatology 2006*



- N=27 CC/NASH-cirrhosis & 85 matched HCV-cirrhosis



## *Past history – c'ted*

- **2009:**

- PT : 78%; Albumin 42 g/l; Bilirubin 9  $\mu$ mol/l
- HbA1c 6.2%
- AFP : 4.6 ng/ml

- **2013:**

- PT :73%; Albumin 38 g/l; Bilirubin 10  $\mu$ mol/l
- Platelet count 123000
- AST : 52 IU/L; ALT 47 IU/L; GGT 174 IU/L
- Ultrasound Normal spleen size 14 cm

- **2014 :**

- Upper endoscopy normal
- Platelet count 83000; ultrasound : spleen 16 cm
- PT: 62%; AST 54 IU/L; ALT : 57 IU/L; GGT 164 IU/L
- HbA1c 6%, weight 84 kg BMI 31 kg/m<sup>2</sup>

# Current status

- **May 2015:**

- Diagnosis of breast cancer
- Tumorectomy (PT 55% post-operatively)
- Radiotherapy
- Hormone therapy

- **Oct 2015:**

- Ascites (large) paracentesis
- Upper endoscopy : large oesophageal varices, band ligation

- **Dec 2015:**

- ascites, lower limb oedema, fatigue
- Diuretic therapy
- PT : 66%; Alb, Bili 26  $\mu\text{mol/l}$ : Plt 91k