MÁSTER EN HEPATOLOGÍA

Universidad Autónoma de Madrid

Universidad de Alcalá

Asignatura de Enfermedad hepática autoinmune

Colangitis biliar primaria

Criterios diagnósticos y pronósticos
Tratamientos de segunda línea

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Universidad de Alcalá, CIBERehd, Madrid

Índice

- Changes in natural history
- Diagnosis: risk stratification, monitoring
- The ”responder” to UDCA
- 2nd line therapies

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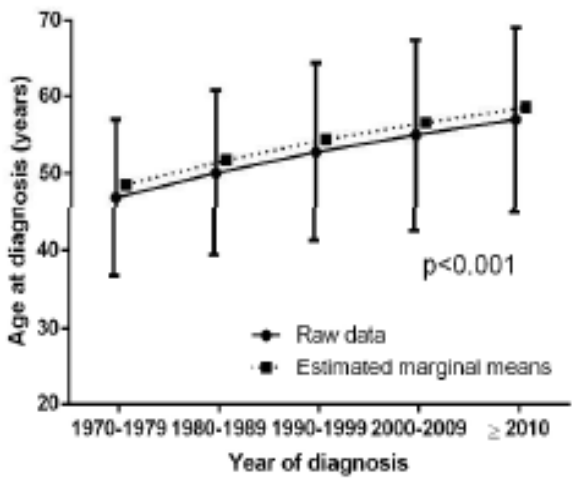
Milder disease in patients with PBC over a 44-year period

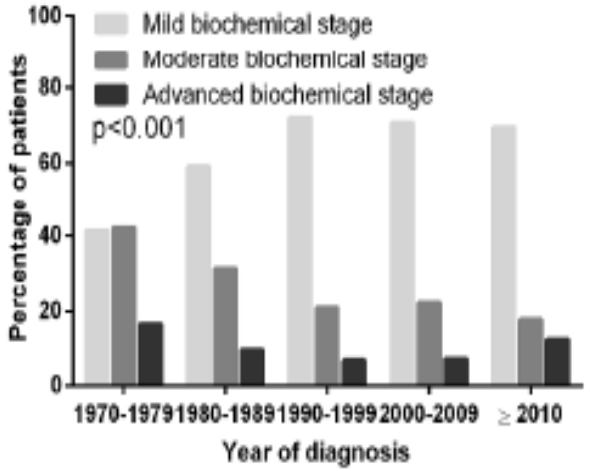
4805 patients, 1970-2014, GLOBAL PBC study
17 centers of Europe and North America

Age at diagnosis

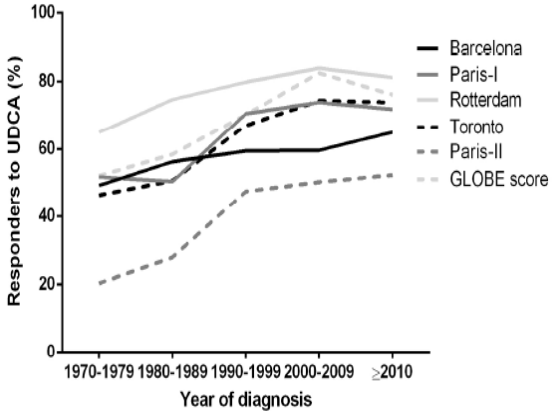


75% >50 yr

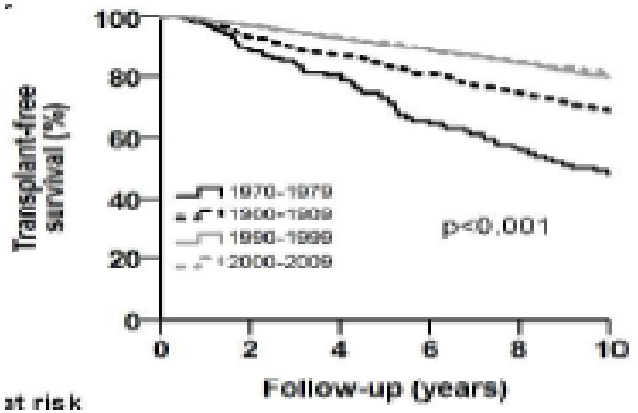
Stage at diagnosis



Response to UDCA



Survival



2000-09

1970-79

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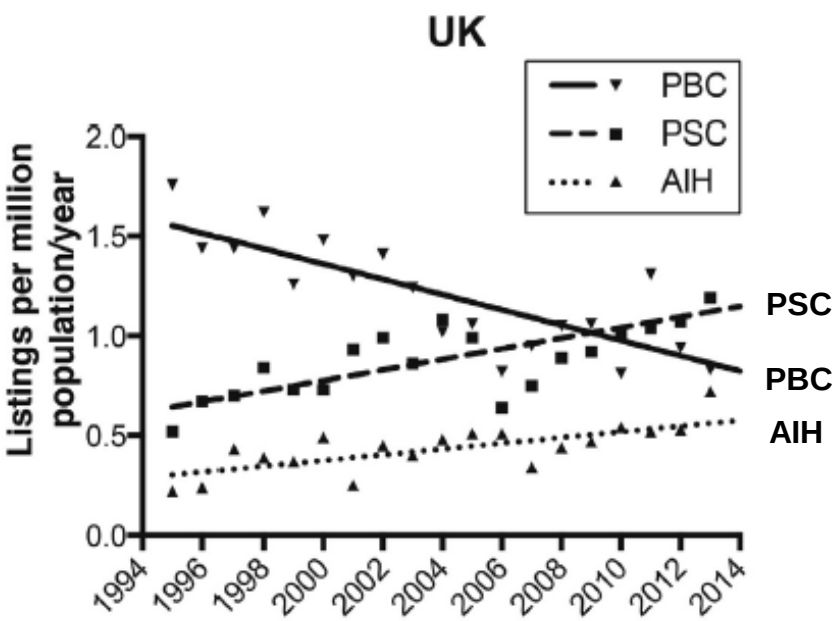
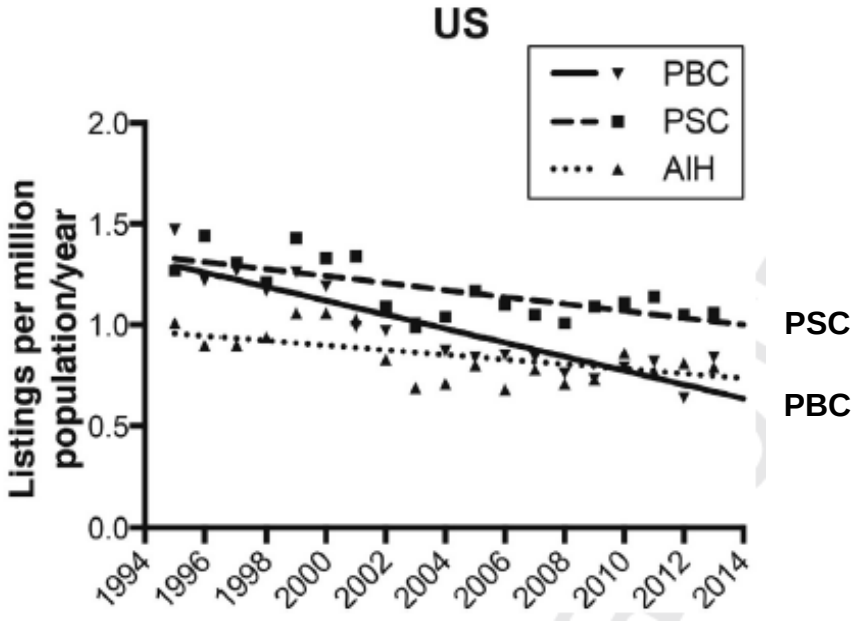
F Murillo-Perez et al. Hepatology 2018

20-year analysis of autoimmune liver diseases on transplant waitlists

Comparative analysis 1995-2014





- **PSC** leading indication of LT for autoimmune LD
- **PBC** ↓ 50%: number of patients
  women/men ratio

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GJ Webb et al. CGH 2017

Índice

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- **Diagnosis: risk stratification, monitoring**
- The ”responder” to UDCA
- 2nd line therapies

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Diagnosis

Suspect PBC
Persistent cholestasis
↑ ALP and/or **GGT**

Supportive clinic
Symptoms & signs

Autoimmune disease
(dryness, Raynaud, arthritis, thyroid)
Family history of autoimmune disease

Rule out other causes cholestasis
Drugs associated with cholestasis
Abdominal US (extrahepatic biliary pathol)

Diagnostic criteria of PBC
2/3

1. ↑ Alkaline phosphatase (ALP)
2. Positive AMA
   (or specific PBC-ANA gp210/sp100)
3. Liver biopsy with consistent findings

Diagnostic scenarios

Scenario **1**
1. Chronic ↑ ALP
2. Positive AMA >1:40

Absence of other liver disease

Scenario **2**
1. Chronic ↑ ALP
2. Negative AMA, *but*
   Positive specific PBC-ANA
   anti-gp210/sp100

Scenario **3**
1. Chronic ↑ ALP
2. Negative AMA >1:40 (and gp210)
3. Biopsy: destructive cholangitis,
   interlobular BD destruction

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EASL CPG: PBC, JHEP 2017
ZM Younossi et al, AJG 2019

PBC-associated antinuclear antibodies in AMA-positive and negative PBC

Antibody	Frequency		Clinical Significance
	AMA (+)	AMA (-)	
Anti-gp210, rim-like pattern	16-18%	15-45%	60-100% specific, commercially available Poorer transplant-free survival
Anti-sp100, multiple nuclear dots pattern	24-31%	13-54%	60-100% specific, commercially available
Anti-hexokinase 1	39-56%	12-40%	95% specific, not commercially available Poorer transplant-free survival
Anti-kelch	19-26%	10-29%	95% specific, not commercially available

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KK Leung et al, Clin Liv Dis 2022

Diagnostic pitfalls

Request MRI?

Not in classical AMA+ PBC
Confuse the patient

AMA-negative PBC with ANA positive?

Not an AIH variant
PBC AMA negative:
85% ANA positive
20% PBC specfic ANA +ve

Is interface hepatitis overlap?

Prominent feature in young
Higher ALT
High-risk phenotype, 2nd line therapy
Not a trigger for immunosuppresion

AMA positive with normal ALP?

Not enough for PBC diagnosis
Follow-up

When liver biopsy?

- Variant presentations:
  AMA/gp210-, MRI normal
- Suspiction of added liver injury:
  NASH, AIH

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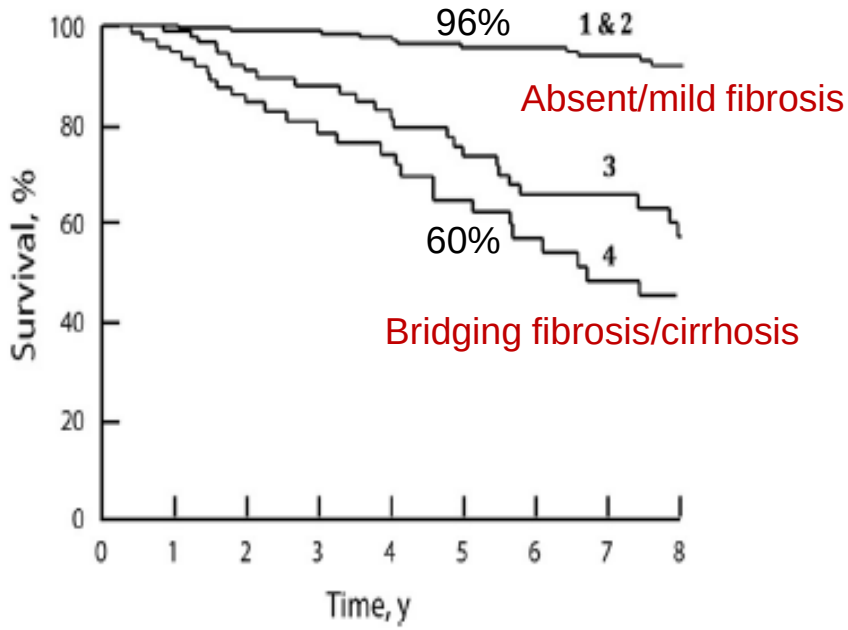
EASL CPG: PBC, JHEP 2017
ZM Younossi et al, AJG 2019

Impact of fibrosis stage on survival in PBC

Relationship between fibrosis stage and survival in PBC

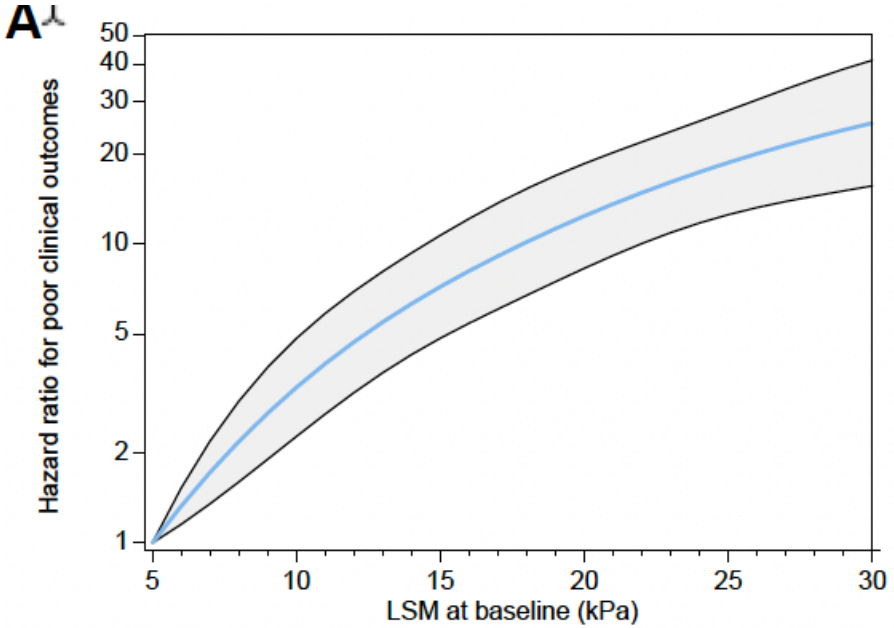
292 patients on UDCA



C Corpechot et al. Clin Liver Dis 2016

Performance of LSM in predicting poor clinical outcomes at baseline

3985 patients, retrospective
23 centers of Europe and North America



C Corpechot et al. JHEP 2022

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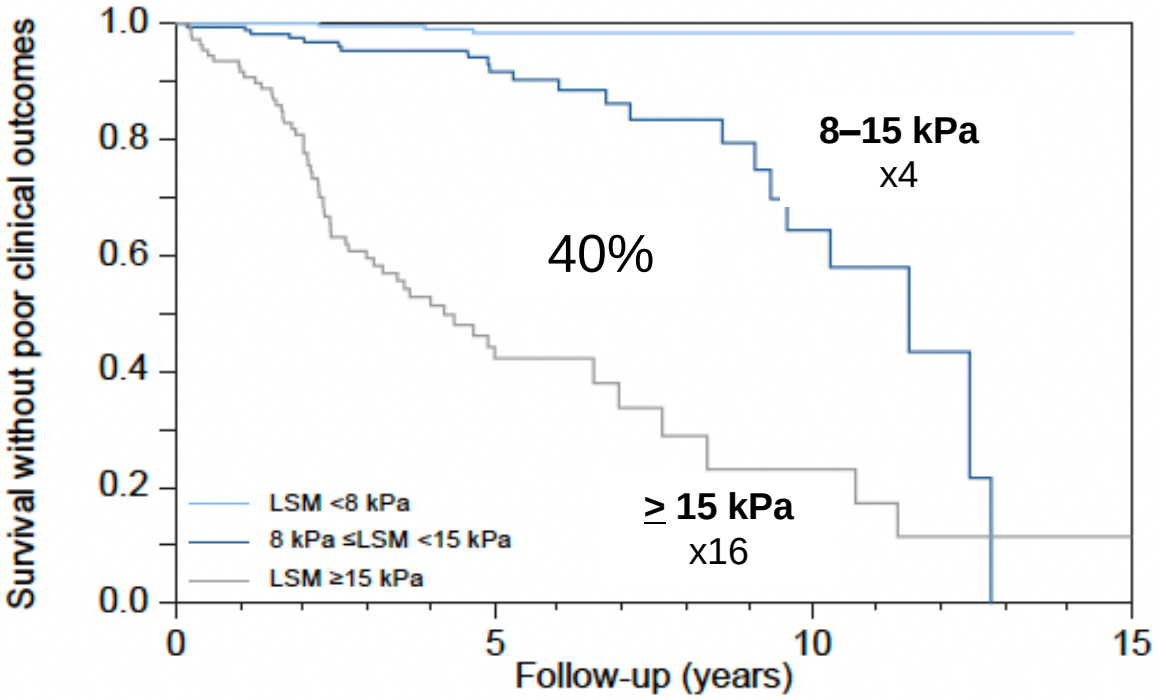
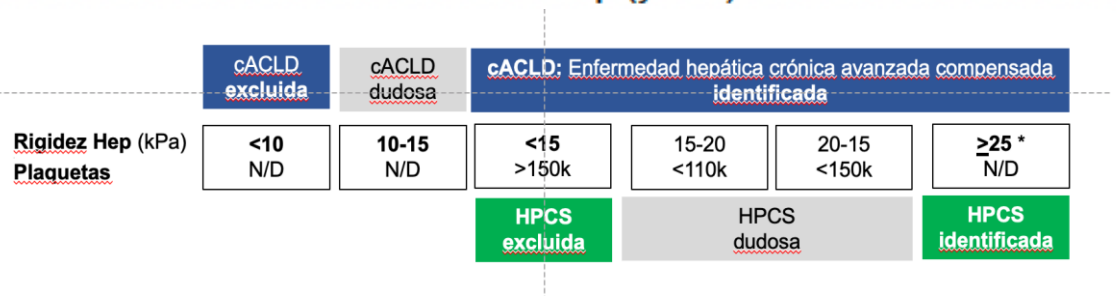
Liver stiffness by elastography (Fibroscan®) in UDCA-treated PBC

Survival w/o poor clinical outcome





- 3985 patients, retrospective
  23 centers of Europe and North America
- LSM improved prediction of survival beyond biochemical response criteria and prognostic scores
- Thresholds: **8 kPa** and **15 kPa** discriminated into low, medium, and high-risk groups.

C Corpechot et al. JHEP 2022

Risk stratification and monitoring in clinical practice

- **At baseline**
  - Disease stage → ***early vs. advanced***
    - Elastography → *LSM <8 or >8 kPa*
    - Bilirubin and albumin → *both normal vs. one abnormal*
    - Histology (if available) → *absent/mild fibrosis vs. bridging/cirrhosis*
  - Symptom profile → *severe pruritus*
  - Serological profile

- **Biochemical response to UDCA at 1 year**
  - Response to UDCA → ***responder vs. inadequate responder***

- **Monitoring**
  - bilirubin, ALP, AST, albumin, platelet count
  - **Elastography** (interval between exams, low evidence) →
    every 2 yr in responders with <8 kPa,
    yearly in other cases?
  - US every 6 mo. if cirrhosis

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Índice

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- **The ”responder” to UDCA**
- 2nd line therapies

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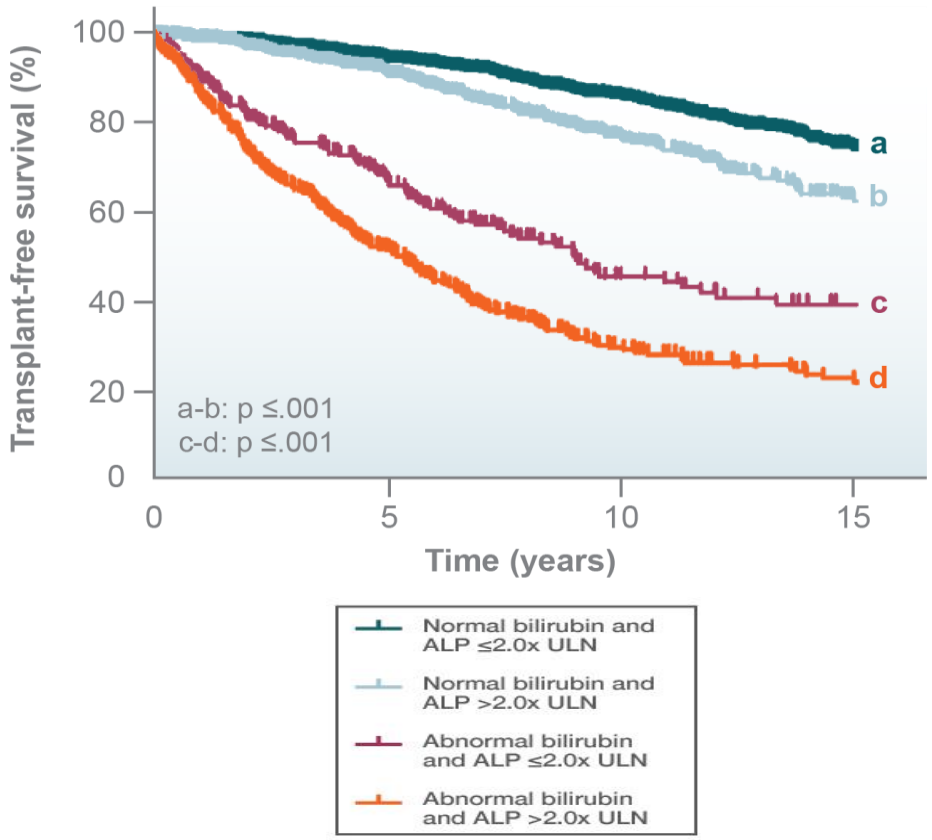
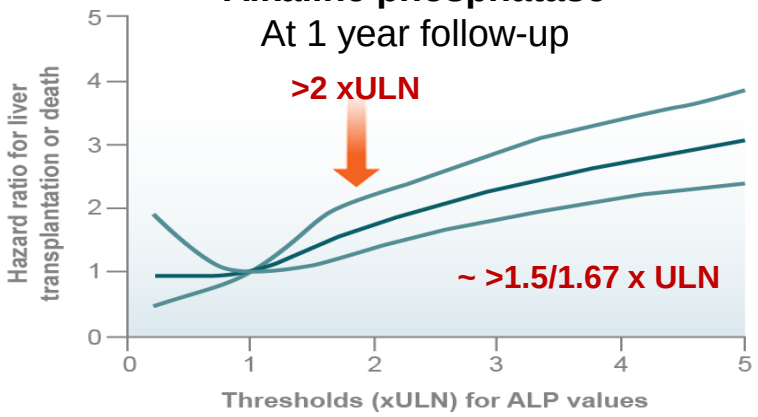
Lower ALP and bilirubin levels associated with longer transplant-free survival (at 10 yr)

Bilirubin and ALP at 10-year follow-up



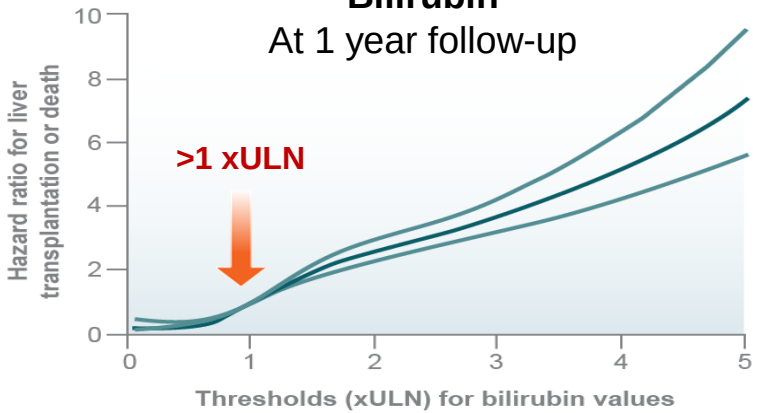
HR for liver Tx or death

Alkaline phosphatase
At 1 year follow-up



*3710/4635 patients were included for this analysis

Bilirubin
At 1 year follow-up

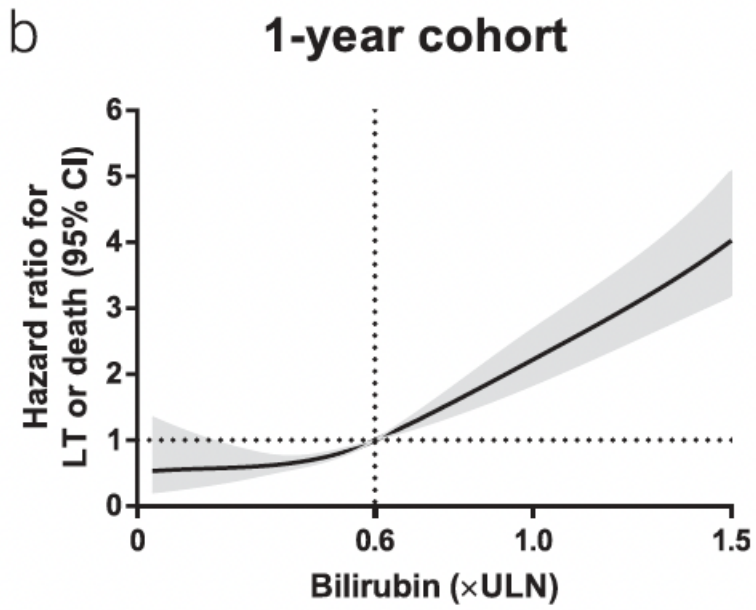


*3710/4635 patients were included for this analysis

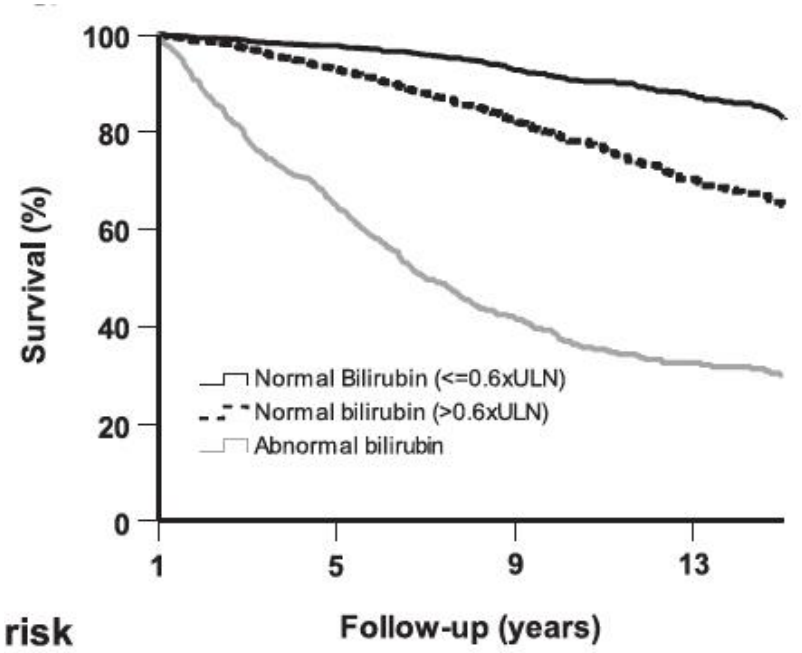
WJ Lammers et al. Gastroenterology 2014

Treatment target: bilirubin within normal range and normalization of alkaline phosphatase

Association between bilirubin (xULN) **and risk for LT or death**



Survival in patients with normal and abnormal (>0.6xULN) **bilirubin <u>at 1-year</u>**



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C Murillo-Perez et al. AJG 2020

Therapies to slow disease progression

1st line therapies

- **Ursodeoxycholic acid**
  (licensed indication)

2nd line therapies

- **Obeticholic acid**
  (unlicensed indication)

- **Fibrates** (beza-/feno-fibrate)
  (unlicensed indication)

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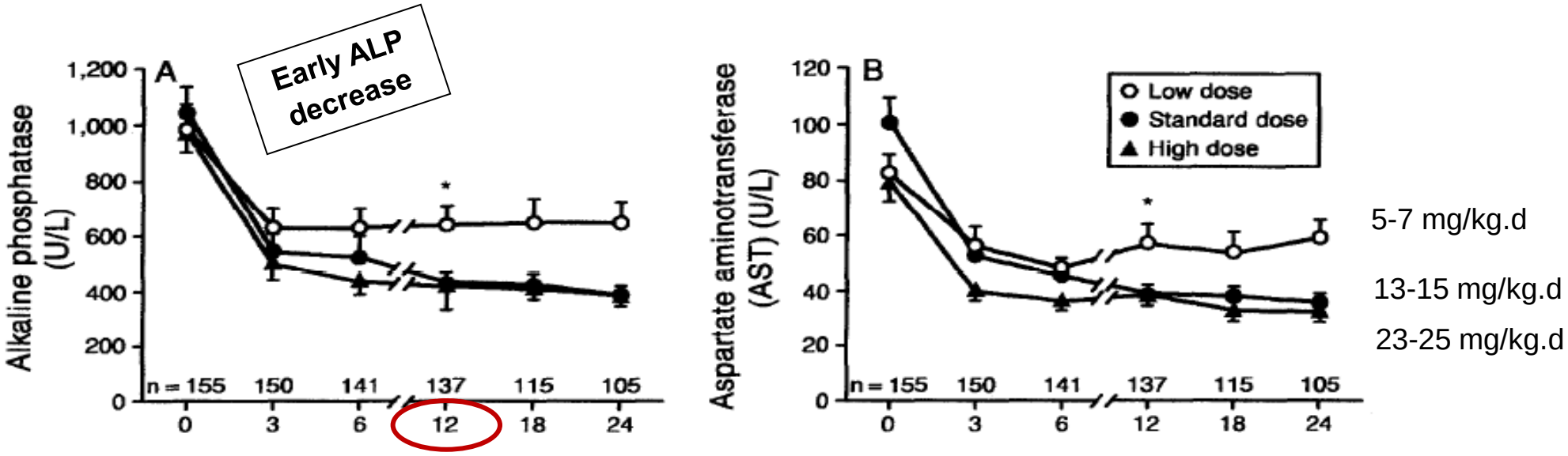
EASL CPG: PBC, JHEP 2017
ZM Younossi et al, AJG 2019

UDCA dosing in PBC

UDCA, a weight-based therapy
13-15 mg/kg daily
Higher doses *not* needed
Maintain effective dose



5-7 mg/kg.d

13-15 mg/kg.d

23-25 mg/kg.d

P Angulo et al. JHEP 1999

WJ Lammers et al, Neth J Med 2016

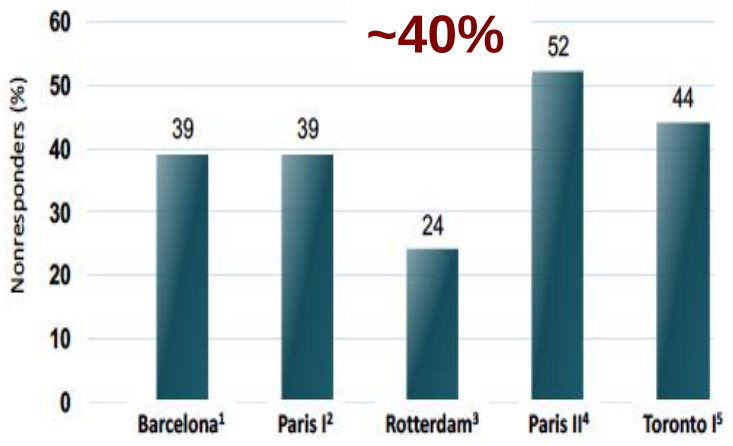
- 851 Dutch PBC patients, 1998-2012
- ↑ UDCA dose in non-responders → ↑**35% responders**

- Evaluating **at 6 mo.** of UDCA equally discriminant

Zang LM et al. Hepatology 2013

Response to UDCA

Patients with inadequate response to UDCA



Biochemical criteria of response

Qualitative binary definitions	Time (months)	Treatment failure
Rochester [101]	6	ALP ⩾2× ULN or Mayo score ⩾4.5
Barcelona [62]	12	Decrease in ALP ⩽40% and ALP ⩾1× ULN
Paris-I [63]	12	ALP ⩾3× ULN or AST⩾ 2× ULN or bilirubin >1 mg/dl
Rotterdam [102]	12	Bilirubin ⩾1× ULN and/or albumin <1× ULN
Toronto [98]	24	ALP >1.67× ULN
Paris-II [104]	12	ALP ⩾1.5× ULN or AST ⩾1.5× ULN or bilirubin >1 mg/dl
Ehime [103]	6	Decrease in GGT ⩽70% and GGT ⩾1× ULN

EASL CPG 2017 → Lower threshold of ALP>1.5, close to normal
Bilirubin <1mg/dl (→ <0.6 mg/dl?)

In responders, UDCA:

- Improves liver biochemistries
- Delays histological disease progression
- Improves liver transplant-free and overall survival

NNT To prevent one LT or death within 5 yr is **11**
Harms MH et al. Gut 2019;69:1502-9

1. Parés A, et al. *Gastroenterology*. 2006;130(3):715-720.
2. Corpechot C, et al. *Hepatology*. 2008;48(3):871-877.
3. Kuiper EMM, et al. *Gastroenterology*. 2009;136(4):1281-1287.
4. Corpechot C, et al. *J Hepatol*. 2011;55(6):1361-1367.
5. Kumagi T, et al. *Am J Gastroenterol*. 2010;105(10):2186-2194.

UDCA response and phenotypes

Variables associated with lower probability of UDCA response

- **Higher ALP!! (>3x ULN)**
- Higher total bilirubin (>2 mg/dl))
- **Younger age (<50 yr)**
- Advanced fibrosis stage
- Treatment time lag
- Worsening ALP from diagnosis
- PBC specific-ANA

M Carbone et al. Lancet 2018
A Pares Gastro 2006
C Huang Dis Markers 2019

PBC phenotypes

The low-risk patient

- Response to UDCA
- ALP: <x1.5, bili: <1 mg/dl
- Elder >50 yr
- Female
- No advanced fibrosis
  (LSM <8 kPa)
- Absence of AIH features

The high-risk patient

- Inadequate response UDCA
- ALP: >x1.5, bili: >1 mg/dl
- Younger <50 yr
- Male
- Cirrhosis/advanced fibrosis
  (LSM >15 kPa)
- AIH features

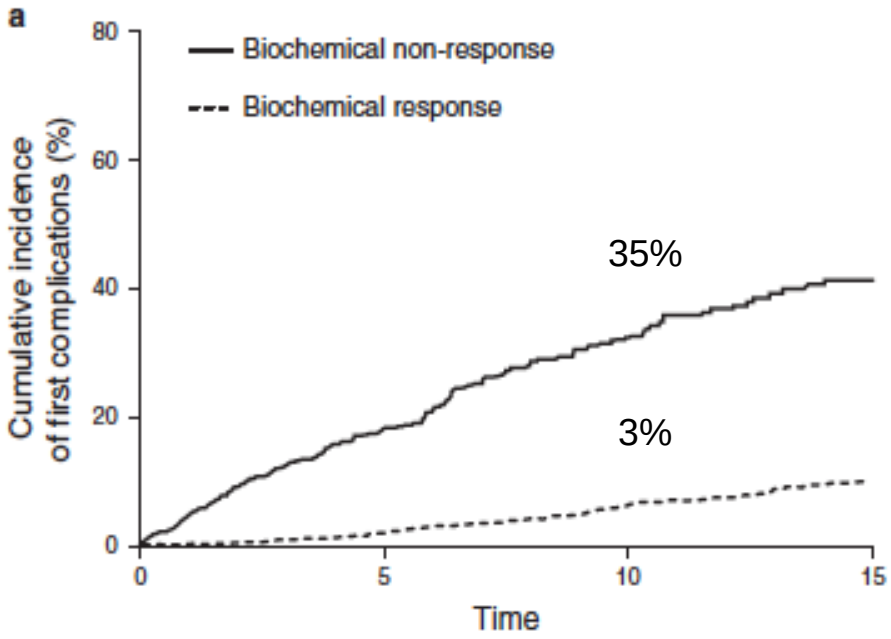
M Carbone et al. Lancet 2018
M Carbone et al. Gastroenterology 2013
C Quarneti et al. Liver Int 2015
O Chazouillieres et al. Hepatology 1998

Major hepatic complications in UDCA-treated PBC

3224 patients, 1970-2014, GLOBAL PBC study
15 centers of Europe and North America
UDCA response/APRI at 12 mo

Hepatic complications: 9% at 10 yr, 15% at 15 yr

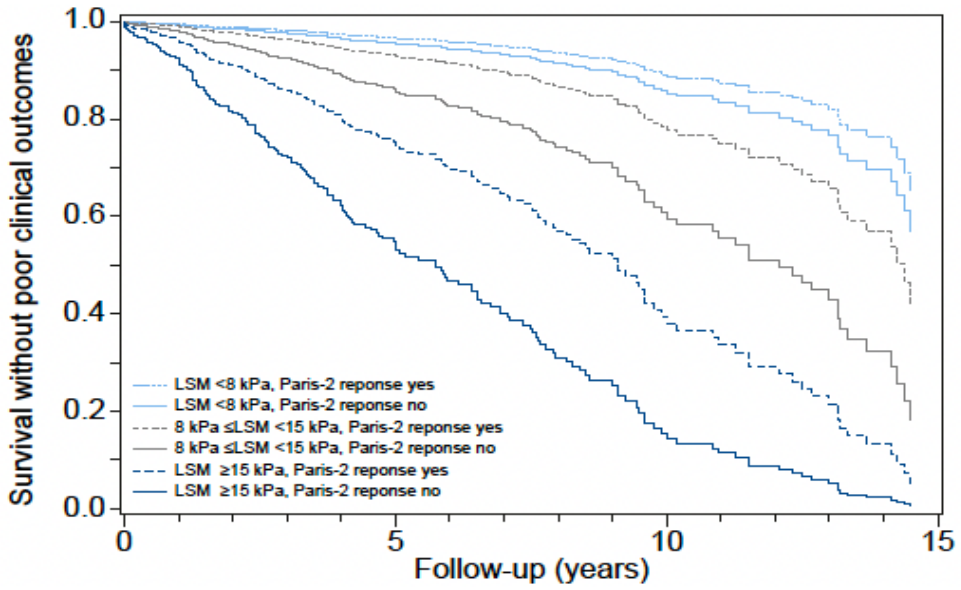
Incidence of 1st complications according to the biochemical response



MH Harms et al. AJG 2017

3985 patients, retrospective
23 centers of Europe and North America

Survival w/o poor clinical outcomes LSM and Paris-2 criteria



C Corpechot et al. JHEP 2022

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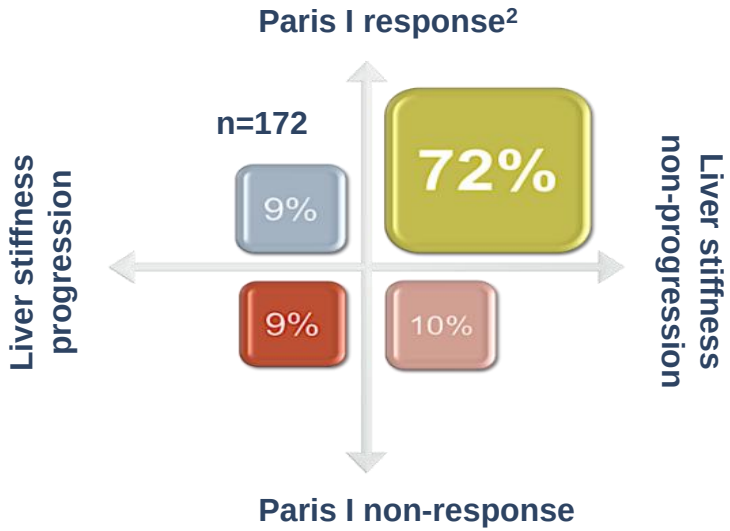
Progression of liver stiffness by elastography (Fibroscan®) in UDCA-treated PBC



Response to UDCA and **liver stiffness progression**:

Responders: **10%**

Non-responders: **50%** (“only”) at 3 yr follow-up

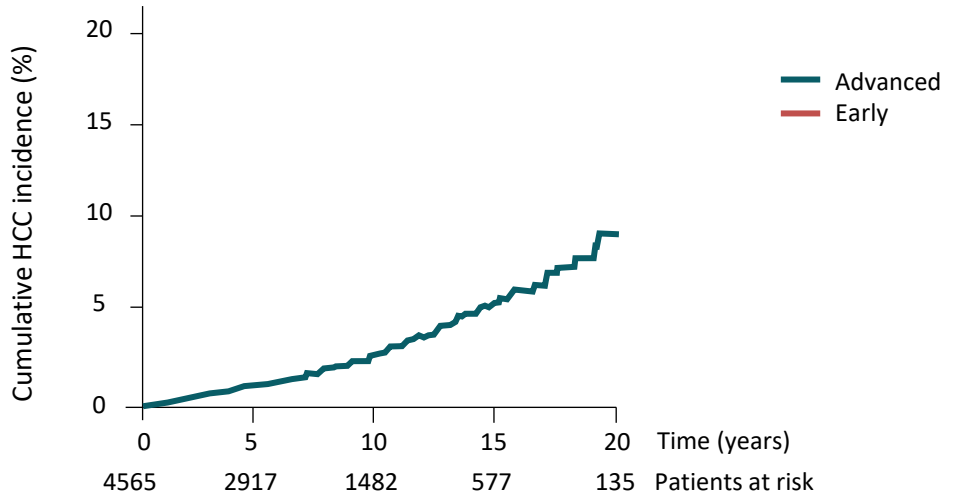
C Corpechot et al. AASLD 2016

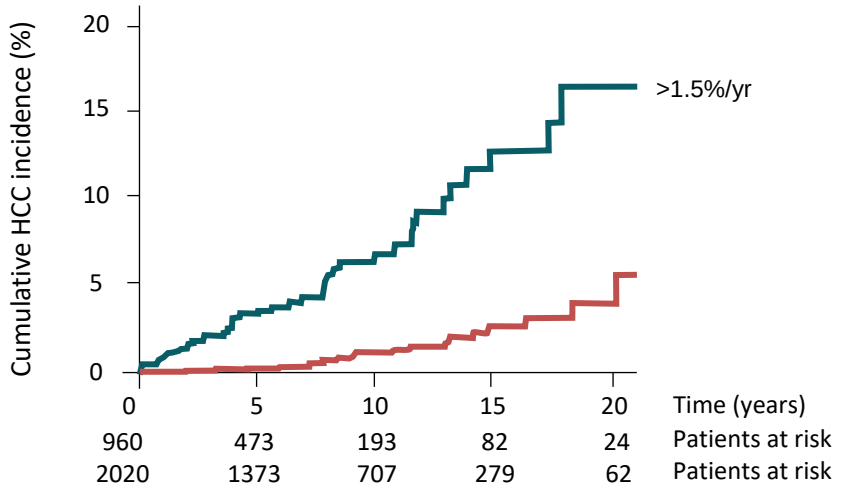
Risk of hepatocellular carcinoma in PBC

4845 US and European patients from Global PBC Group

.

Incidence: 3.4 cases/1000 patient-years,





Risk factors for HCC development

- Male (7.2 vs 2.6/1000 patient-yr)
- Moderate/late disease at baseline (7.6 vs 1.3/1000 patient-yr)
- Fibrosis: stage I/II vs III/IV at baseline
- Biochemical response to UDCA

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P Trivedi et al. Gut 2016

Risk stratification and monitoring in clinical practice

- **At baseline**
  - Disease stage → ***early vs. advanced***
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  - Serological profile

- **Biochemical response to UDCA at 1 year**
  - Response to UDCA → ***responder vs. inadequate responder***

- **Monitoring**
  - bilirubin, ALP, AST, albumin, platelet count
  - **Elastography** (interval between exams, low evidence) →
    every 2 yr in responders with <8 kPa,
    yearly in other cases?
  - **US every 6 mo**. if cirrhosis

Índice

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- The ”responder” to UDCA
- **2nd line therapies**

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Response-guided therapy in PBC

Baseline and at 12-m on UDCA
Staging: biochemistry, elastography
Risk stratification
Prognosis
Celiac disease? Thyroid disease?

UDCA
(13-15 mg/kg)

Biochemical response

yes → Continue UDCA

~40% no

Liver histology ?

Indications of 2nd line therapy
- Bilir >1 mg/dl after 12-m of UDCA
- ALP >1.5 UI/dl after 12-m of UDCA
- ↑ALP after 12-m of UDCA
- Fibrosis progression while on UDCA?

Add second line therapy

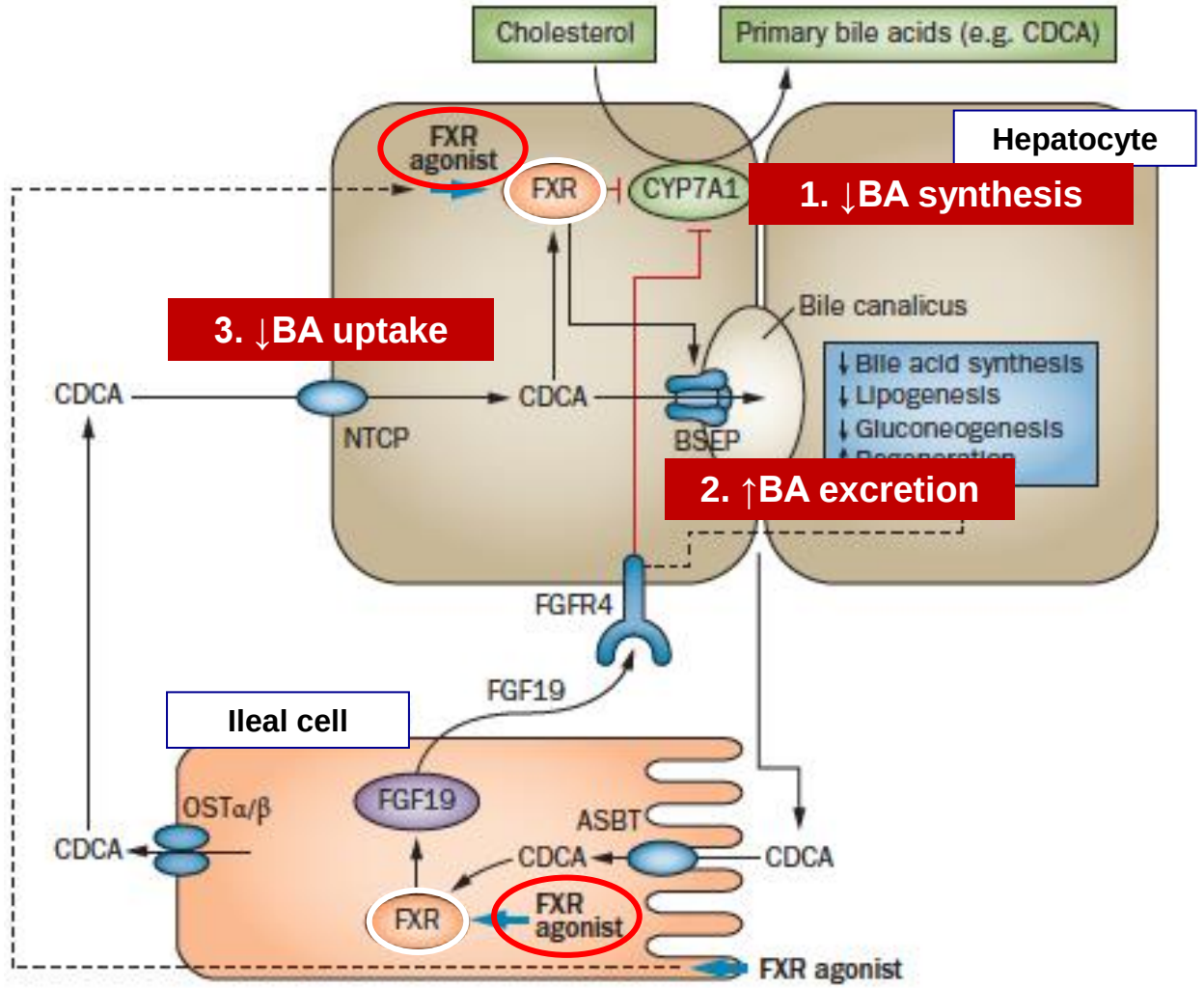
FXR-ligands
- Steroidal: **Obeticholic acid**
- Non-steroidal

PPAR-ligands
- α: Fenofibrate, **Bezafibrate**
- β: Elafibranor
- δ: Seladerpar

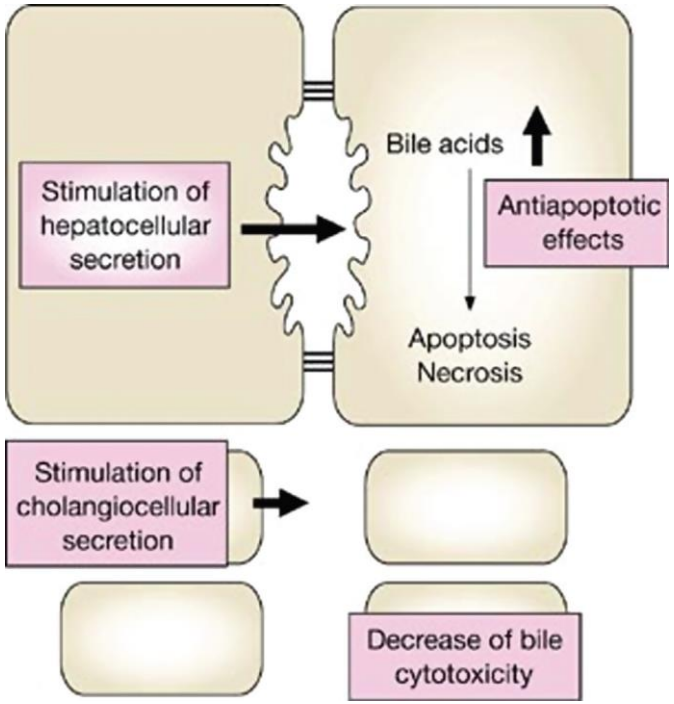
Licensed drugs for PBC
Non-licensed/investigational drugs

EASL CPG: PBC, JHEP 2017
ZM Younossi et al, AJG 2019

Enterohepatic actions of FXR agonists



Mechanism of action of UDCA

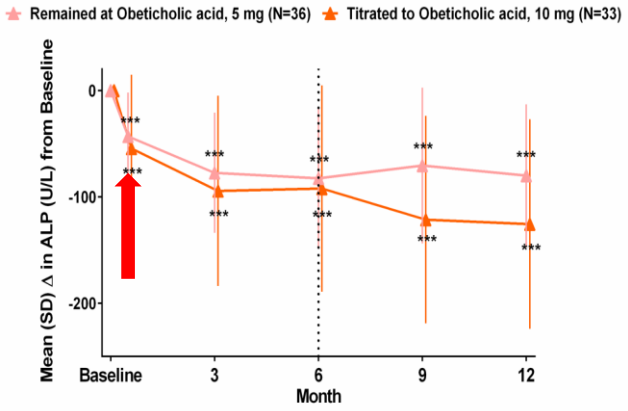


FG Schaap et al. NRGH 2014

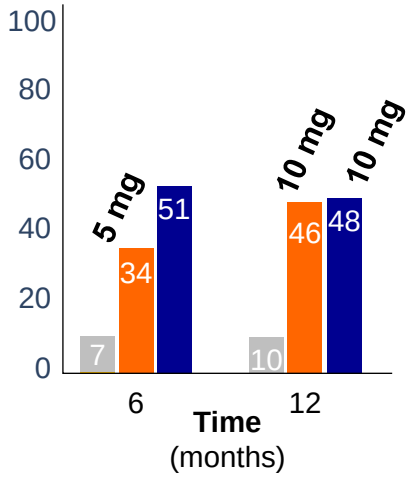
Sustained improvements in ALP with UDCA + obeticholic acid (OCA) in UDCA non-responders

217 PBC with **non-response** (93%)
or intolerant (7%) to UDCA (**ALP >1.67** x ULN)

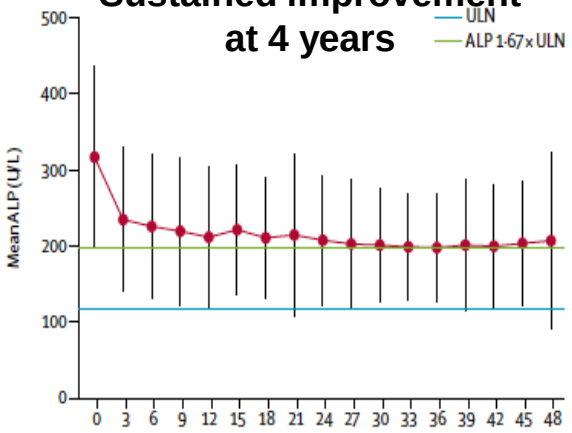
ALP change from baseline in the OCA 5-10 mg group



Patients with response (%)



Sustained improvement at 4 years



— **Response** in ~50%

— **Indication** in non- or compensated (Child A) cirrhosis with

- non-response to UDCA
- intolerance to UDCA

— **Dosing:**

initiate at 5 mg once daily

titrate to 10 mg if non-response at 6 months

— **Side effects**

pruritus in ~20%, dose dependent, most within 1st mo., resolved with continuous dosing, titration and resins

— ***Caution*** in decompensated cirrhosis, indicated?

dosing starting at 5 mg *once weekly*

OCALIVA, FDA, 2016

F Nevens et al. NEJM 2016
Kowdley KV et al. Hepatology 2018
Trauner M et al. Lancet 2019

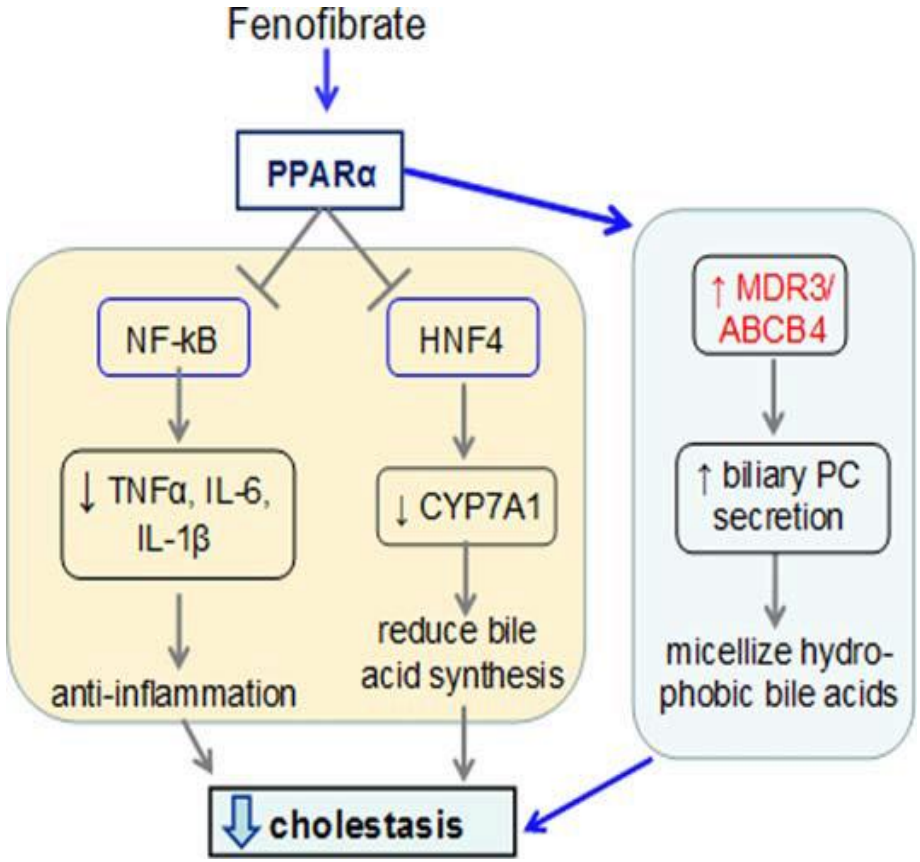
Peroxisome proliferator-activated receptors (PPARs) in cholestasis

- 3 isoforms: α, β, δ

- PPARs also impact biliary homeostasis
  - Regulates biliary synthesis/detoxification
  - Modulates phospholipid secretion

- Fibrates target PPAR
  Fenofibrate → α
  Bezafibrate → slighthly broader
  Beneficial effects in PBC (& PSC)

- Novel drugs targeting PPAR
  Elafibranor – α/δ
  Seladelpar (MBX8025) - δ



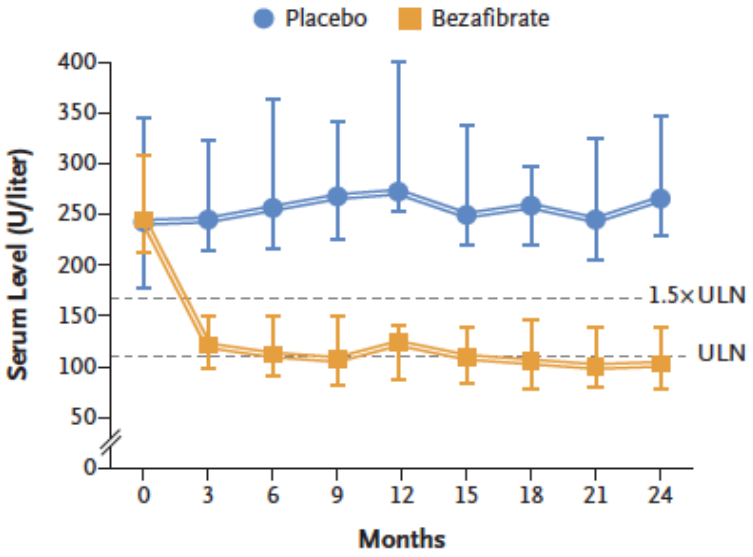
MÁSTER EN HEPATOLOGÍA

T Ghonem et al. Hepatology 2015

Sustained improvements in ALP with UDCA + bezafibrate in UDCA non-responders

100 PBC patients with **inadequate-response** to UDCA by Paris-2 criteria
Placebo/**Bezafibrate** 400 mg/d, 24 mo.

Alkaline phosphatase

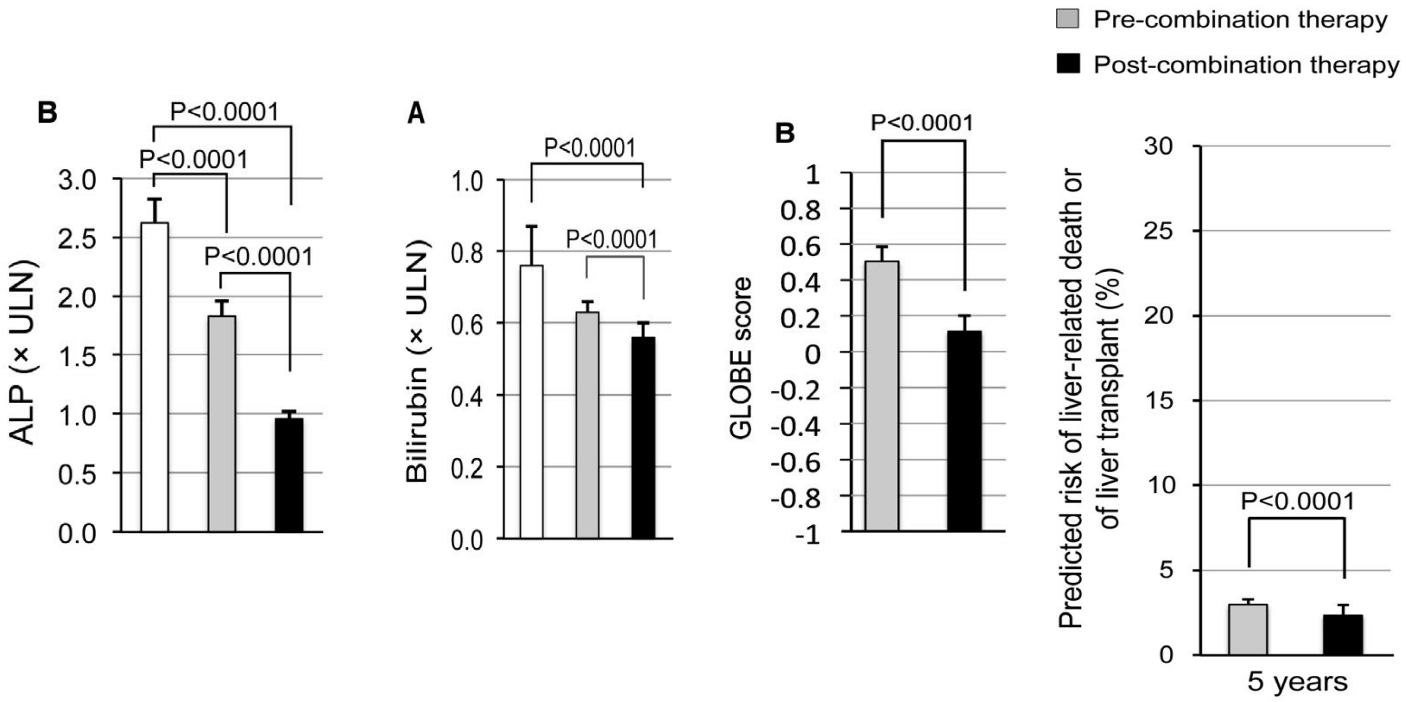


Primary outcome:
Complete biochemical response in 30%
(Normal: bili, ALP, ALT, AST, album, PT)

Biochem response/**normal ALP in ~70%**

C Corpechot et al. NEJM 2018

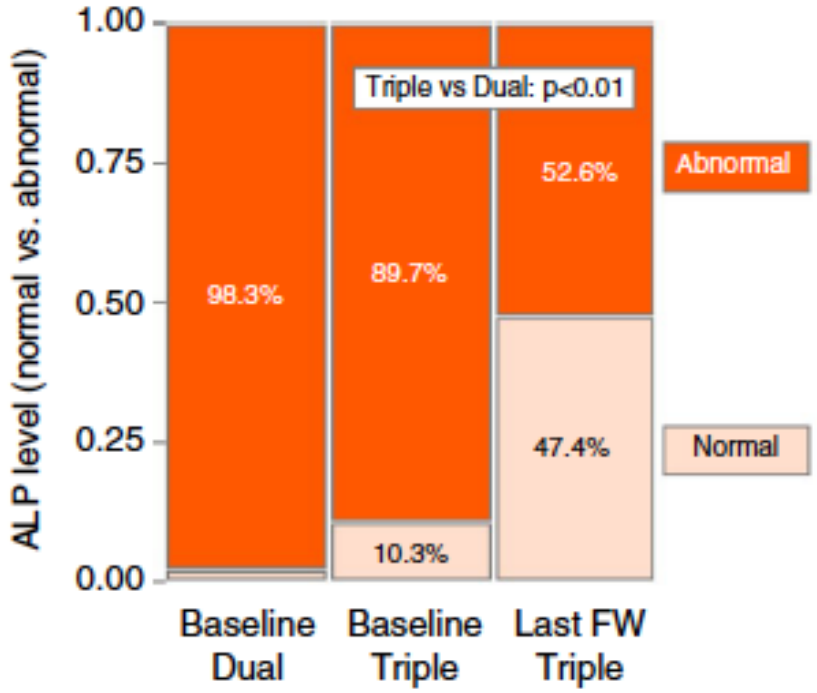
118 PBC with **non-response** to UDCA treated with **Bezafibrate** for at least 1 year



A Honda et al. Hepatology 2019

Improvements in ALP with UDCA + fibrate + OCA in non-responders to DUAL therapy (UDCA+Fibrate/or OCA)

58 PBC with **non-response to DUAL**: UDCA+OCA or fibrates
(dual) Treated with **TRIPLE**: UDCA + **OCA + fibrate**
F-up 11 mo.



PA Soret et al. APT 2021

Drug, NCT	Mechanism of Action	Number of patients in phase 2 trial, study duration	Summary of Findings to Date
Seladelpar NCT04620733	PPAR-delta agonist	N=112, 1 year; Long term extension in progress	69 % met POISE with 10 mg/day at 1 year, 79% at 2 years 33 % normalized ALP at 1 year Improvement in pruritus Improvement in sleep
Elafibranor NCT04526665	PPAR-alpha/delta agonist	N=45, 12 weeks	79 % met POISE with 120mg/day 21 % normalized ALP Improvement in pruritus
Saroglitazar NCT05133336	PPAR-alpha/gamma agonist	N=37, 16 weeks	71 % met POISE
Setanaxib NCT05014672	NOX 1/4 inhibitor	N= 111, 24 weeks	24% reduction in ALP among patients with liver stiffness > 9.6 kPa treated with 400 mg bid; post hoc analyses with improvement in fatigue scores
Linerixibat NCT04950127	ASBT inhibitor	N=147, 12 weeks; Long term extension in progress	Improvement in itching Improvement in sleep

Side effects of drugs used in PBC

UDCA

- Pruritus, 2%
- Diarrhea, 2%
- Hair thinning
- Weight gain (~3 kg in 12 mo)

Obeticholic acid

- Pruritus, 20%
- Liver damage in Child B-C cirrhosis
- ↓HDL, ↑LDL

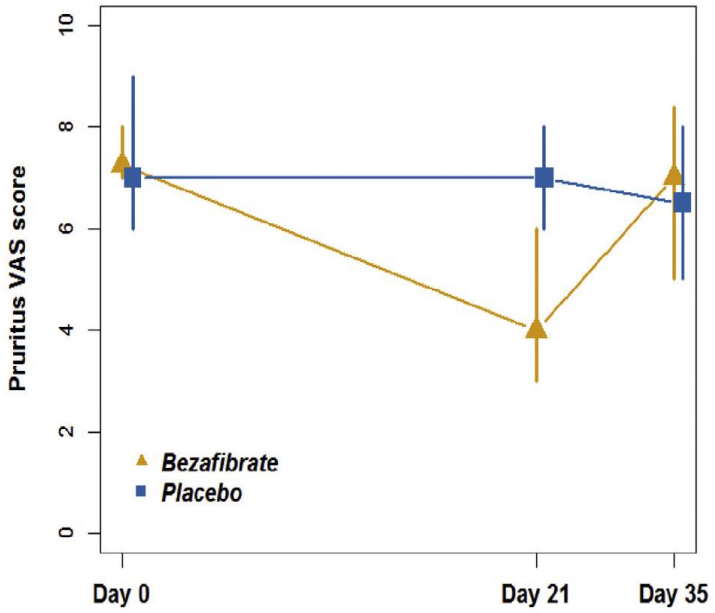
Bezafibrate/Fenofibrate

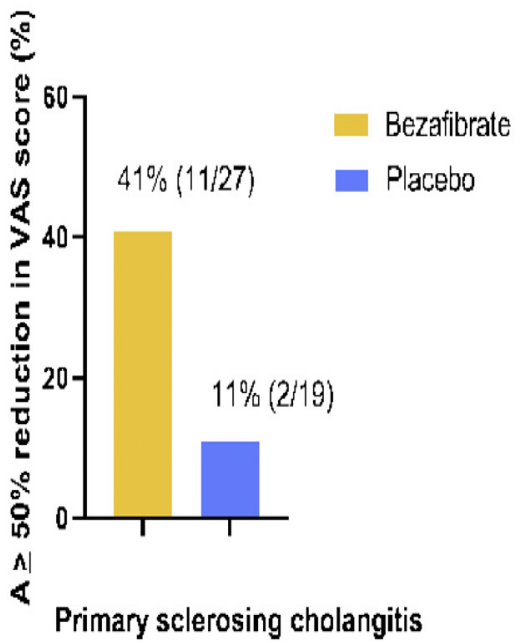
- Miopathy, 5-10%, especially if ↑creatinine
- ↑creatinine

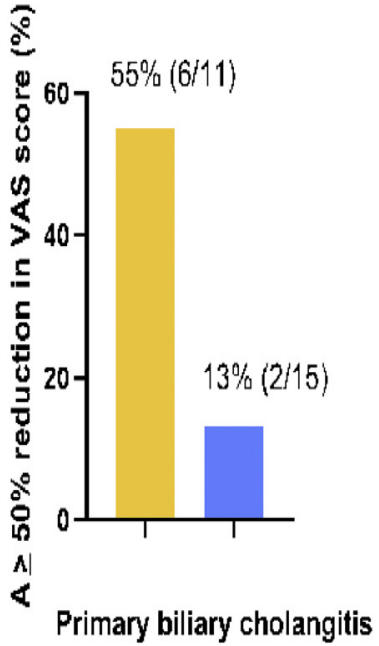
EASL CPG: PBC, JHEP 2017
ZM Younossi et al, AJG 2019

Bezafibrate improves pruritus in chronic cholestatic liver disease: the FITCH trial

74 patients with CLD: 44 PSC, 24 PBC, 2SSC
Bezafibrate 400 mg/d, for 21 d or Placebo





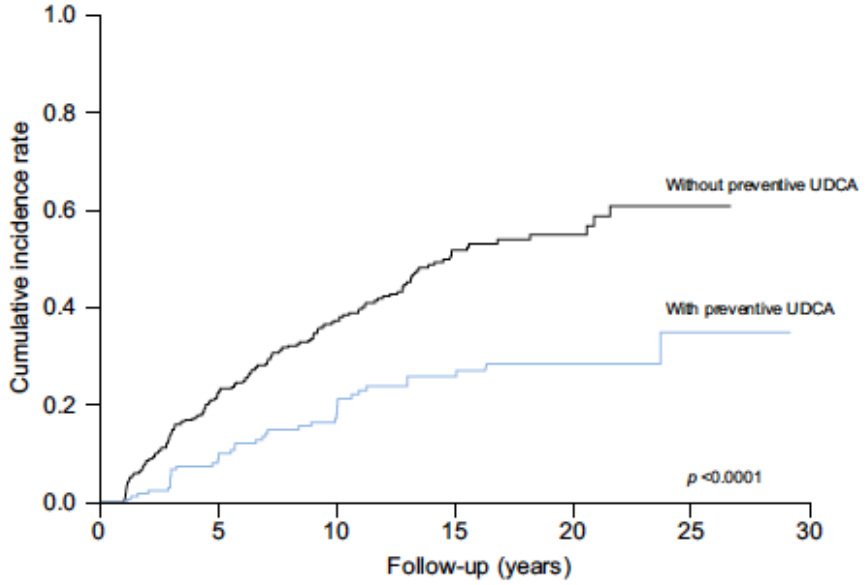


Vries de ES et al. Gastroenterology 2021

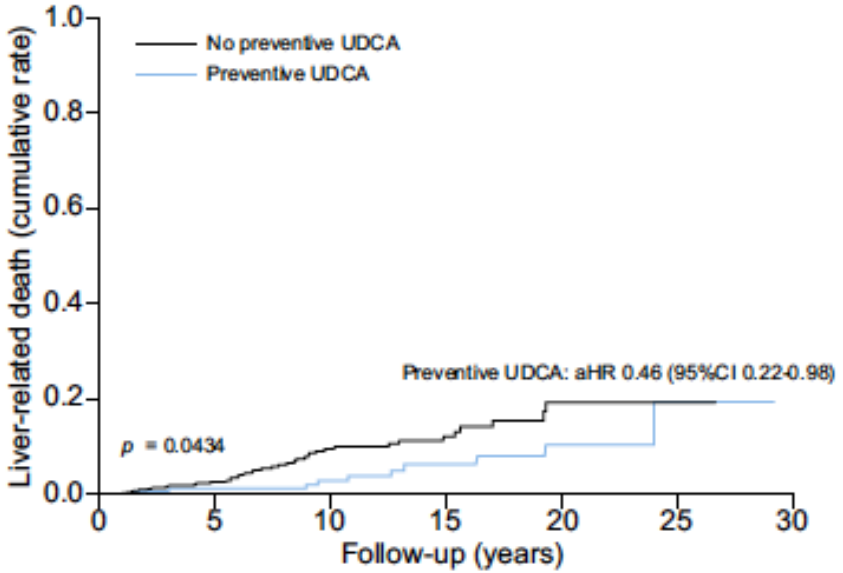
Recurrence of PBC after liver transplantation

780 transplants for PBC
1983-2017, 16 centers, 9 countries, f-up 11 yr

Recurrent PBC after LT



Liver-related death



C Corpechot et al. JHEP 2021

Conclusiones

— Aumento del diagnóstico en pacientes de más edad con enfermedad más leve

— Biopsia hepática **no** es necesaria en la mayoría para el diagnóstico.

Reservada para identificar la contribución al daño de una enfermedad hepática concomitante, especialmente MAFLD, diagnosticar casos con AMA y ANA-específicos negativos e identificar HAI concomitante o secuencial

— Medir rigidez hepática basalmente y de forma periódica (frecuencia no establecida)

— **Respuesta a AUDC al año** como principal parámetro de estratificación del riesgo

— Objetivo terapéutico es alcanzar una concentración de fosfatasa alcalina normal o mínimamente elevada y una bilirrubina normal (<1 mg/dl)

— **Respuesta inadecuada a AUDC en 40%** de los pacientes, y en ellos indicados los tratamientos de segunda línea, ácido obeticólico y fibratos (bezafibrato, fenofibrato), cuyo efecto es sinérgico al del AUDC

— Prurito es el principal efecto adverso del ácido obeticólico, mientras que los fibratos son una buena opción para su tratamiento