Historical outcome parameters used in PBC and the search for potential alternatives

EMA stakeholder interaction on the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH)

3 December 2018

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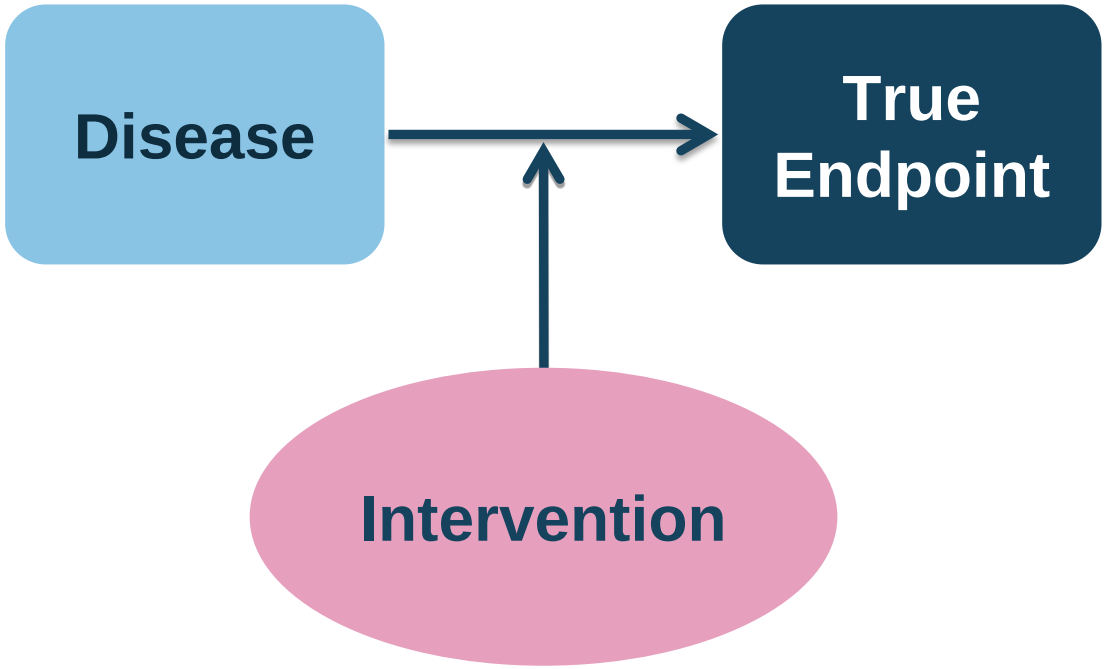
TORONTO CENTRE FOR LIVER DISEASE

Definition of True Endpoint

- Meet criteria recognized by academia/ guidelines
- Meet requirements from regulatory agencies:
  - a clinical event relevant to the patient
  - measures directly how a patient feels, functions or survives



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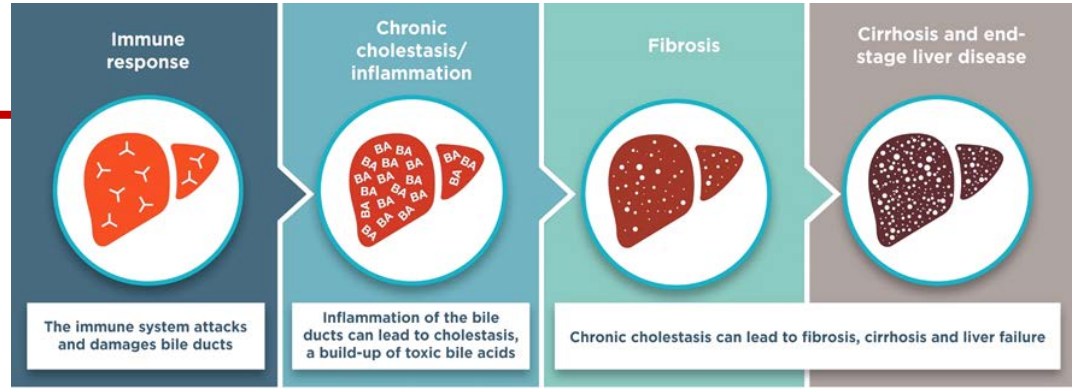
Long term outcome for PBC



True endpoint

- Death (all-cause)
- Liver transplantation
- Decompensation of cirrhosis (variceal bleed, encephalopathy, spontaneous bacterial peritonitis, uncontrolled ascites)
- MELD score ≥ 15 (above specific threshold)

Reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH); 2018

- *Hepatocellular carcinoma ?*
- *Rotterdam Severe Disease Stage ?*
  (abnormal bilirubin AND abnormal albumin)

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Long term outcome for PBC

PROS

- Measures direct benefit/harm
- No potential bias

CONS

- Requires large population and often long follow-up
- **trial duration 8-15 years**
- Event may be confounded by competing risks
- Event may be effected by cross over of therapies or subsequent therapies
- Does not capture symptom benefit
- Ethical unacceptable

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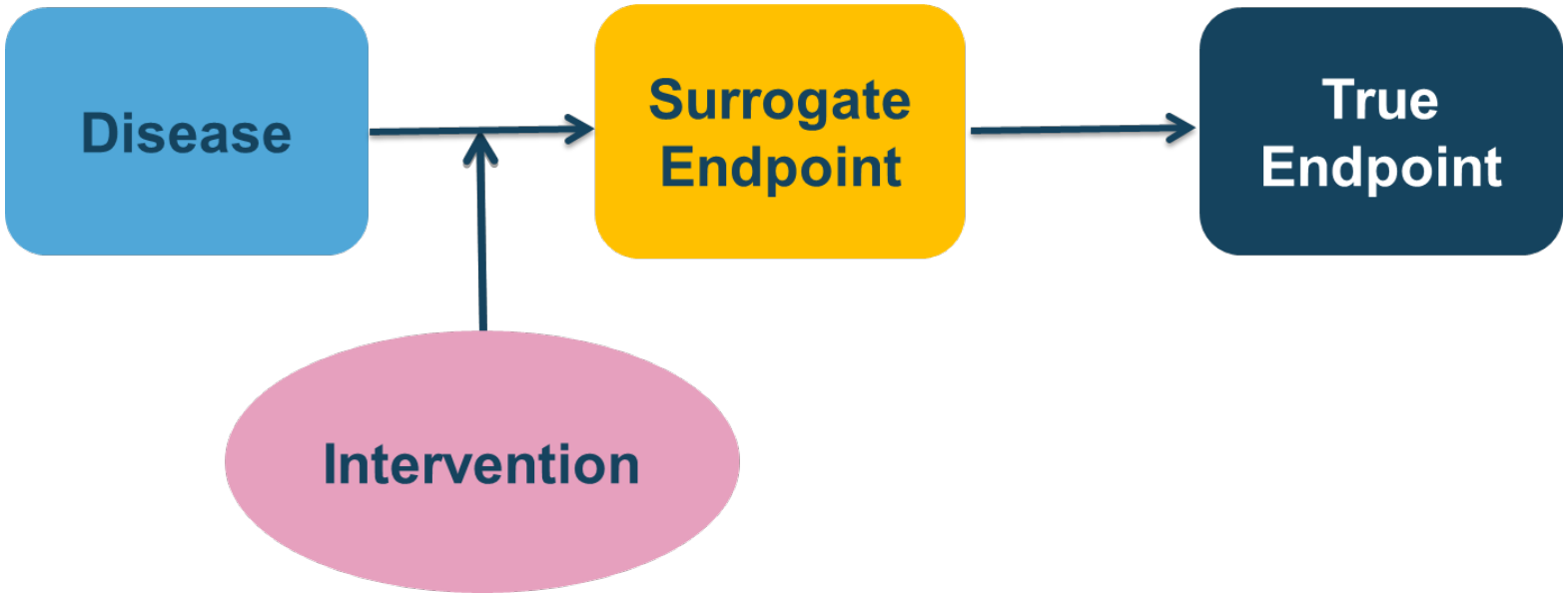
Intermediate endpoint = surrogate endpoint

An acceptable regulatory strategy in case of unmet need is to consider intermediate endpoints:

- A validated substitute for the true endpoint: changes observed in the surrogate endpoint is expected to reflect changes in the true endpoint
- Requires confirmation of efficacy (and safety) of the compound after approval



Reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH); 2018; Prentice, Stat in Med; 1989

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Surrogate Endpoint

PROS

- Time and Care
  - a new intervention is quicker available for the patient in need
  - the benefit/harm of an intervention is observed quicker
- Benefit for design of a new trial
  - Influence on sample-size calculation
  - Shorter duration of study
  - Influence of recruitment and participation enthusiasm
  - Endpoint not effected by cross over of therapies or subsequent therapies

CONS

- Measurements may be subject to bias
- Validation needed
- Various definitions: cut points, combined endpoints
- Depends on mode of action of intervention

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Phase 3 current intermediate endpoints

Duration: 1 year

POISE[1] – trial

Inclusion: ALP>1.67 OR abnormal bilirubin, but bilirubin < 3xULN

Response: ALP<=1.67 AND min. 15 % reduction compared to baseline AND normal bilirubin

BEZURSO[2] - trial

Inclusion: Non-responder according to Paris I

Response: normal bilirubin, normal ALP, AST, ALT, albumin and PT

[1]*Nevens et al ; NEJM 2016;* [2]*Corpechot at al; NEJM 2018*

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Intermediate endpoint = surrogate endpoint

EMA advocates a more stringent definition of response and duration of study:

- Duration of study 1-2 years add on to SOC (UDCA)
- Intermediate endpoint:
  - ALP < 1.5xULN AND
  - 40% reduction compared to baseline AND
  - normal bilirubin

→Impacts sample size calculation

→$ALP_{baseline}$ = 1.5 → ALP_{1yr} < 0.9

→$ALP_{baseline}$ = 2 → ALP_{1yr} < 1.2

Reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH); 2018; Prentice, Stat in Med; 1989

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Historical Biochemical Response Criteria

Group	Year of publication	Number of patients	Response Criteria assessed at 1 or 2 years
Barcelona[1]	2006	192	**ALP** >40% decrease from baseline or normalization
Paris 1[2]	2008	292	**ALP** ≤ 3 x ULN and AST ≤ 2 x ULN and bilirubin ≤ 1 mg/dl
Rotterdam[3]	2009	375	Normalization of albumin and/or bilirubin
Toronto[4]	2010	69	**ALP** ≤ 1.67 ULN
Paris 2[5]	2011	165	**ALP** ≤ 1.5 x ULN and AST ≤ 1.5 x ULN and bilirubin ≤ 1 mg/dl
Japan[6]	2011	138	GGT normalization or > 70% reduction

[1]Parés, Gastroenterology, 2006. [2]Corpechot, Hepatology, 2008. [3]Kuiper, Gastroenterology, 2009. [4]Kumagi, the American Journal of Gastroenterology, 2010. [5]Corpechot, Journal of Hepatology, 2011 [6]Azamoto, Hepatology Research, 2011

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Databanks

Global PBC Study Group

- individual patient data
- N >6000 PBC patients, 30.000 patient visits, >20 years follow-up
- 21 sites in Europe, North America, Asia

UK PBC

- individual patient data
- from all UK centers
- N >6000 PBC patients
- genetic data, prospective lifestyle data

from

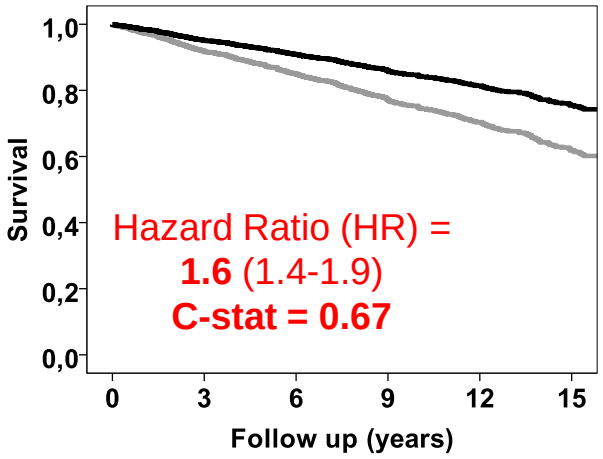
a rare disease

to

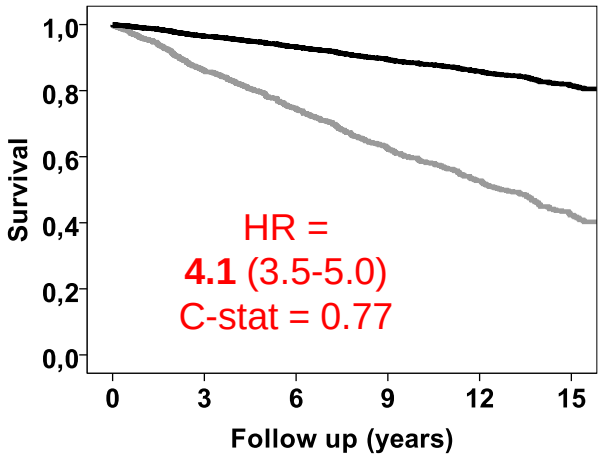
gigantic databases

Biochemical response criteria associated with improved liver transplantation free survival

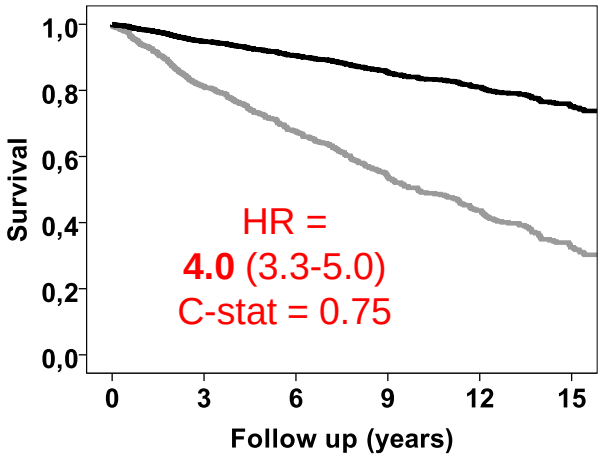
Barcelona



Paris1



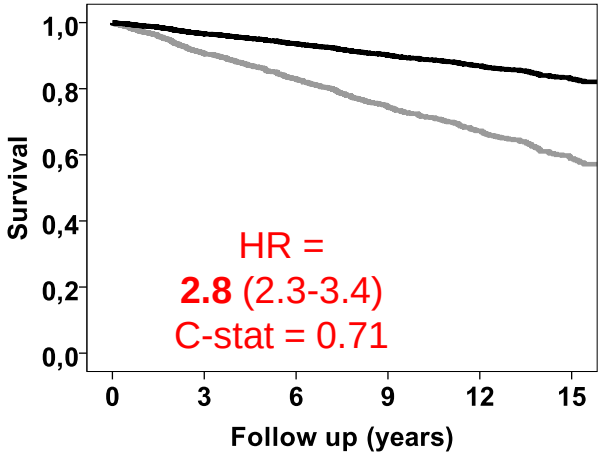
Rotterdam



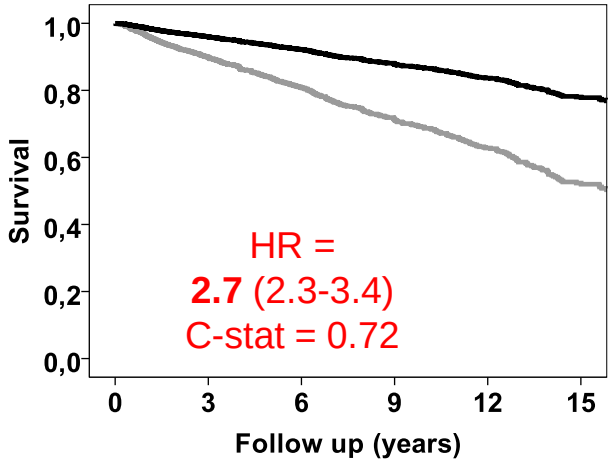
Responders

Non- responders

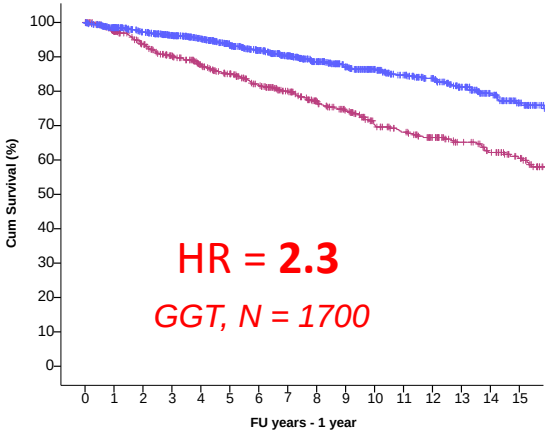
Paris2



Toronto



GGT 70% reduction



Hansen, Data Global PBC Study Group

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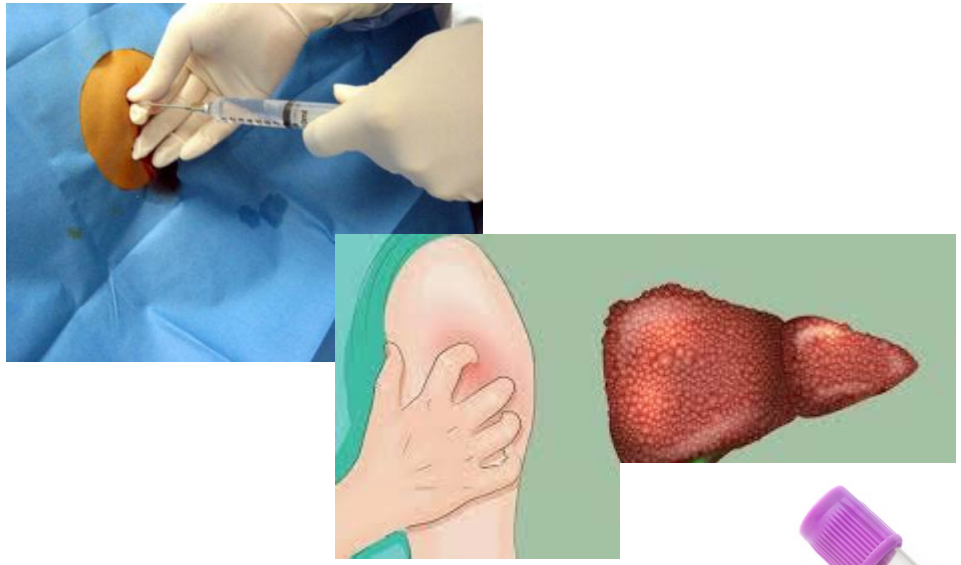
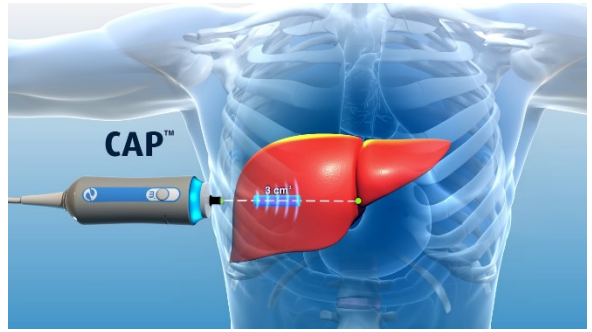
What Makes a Good Surrogate Endpoint?

- Frequently observed
- Assessed within a short timeframe
- Easy to measure
- Preferably non-invasive and at low costs
- Epidemiology/clincal studies demonstrates that surrogate endpoints is linked to clinical outcomes
- Clinical trials demonstrate that treatment effects on the surrogate endpoint correspond to effects on the clinical outcome





Boissel JP et al. Eur J Clin Pharm 1992;43:235-44
Espeland MA et al. Current controlled trials in Cardiovascular Med 2005;6:3-6

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Biomarker endpoints

Bilirubin

Key diagnostic variable for liver detoriation

Numerous studies showing prognostic significance of bilirubin

Component of established prognostic models:

- Mayo model
- MELD score
- Child-Pugh score

Alkaline phosphatase

Key diagnostic variable

Mutiple studies indicating prognostic significance

Component of Paris I & II, Barcelona, Toronto established criteria

Useful as surrogate endpoint?

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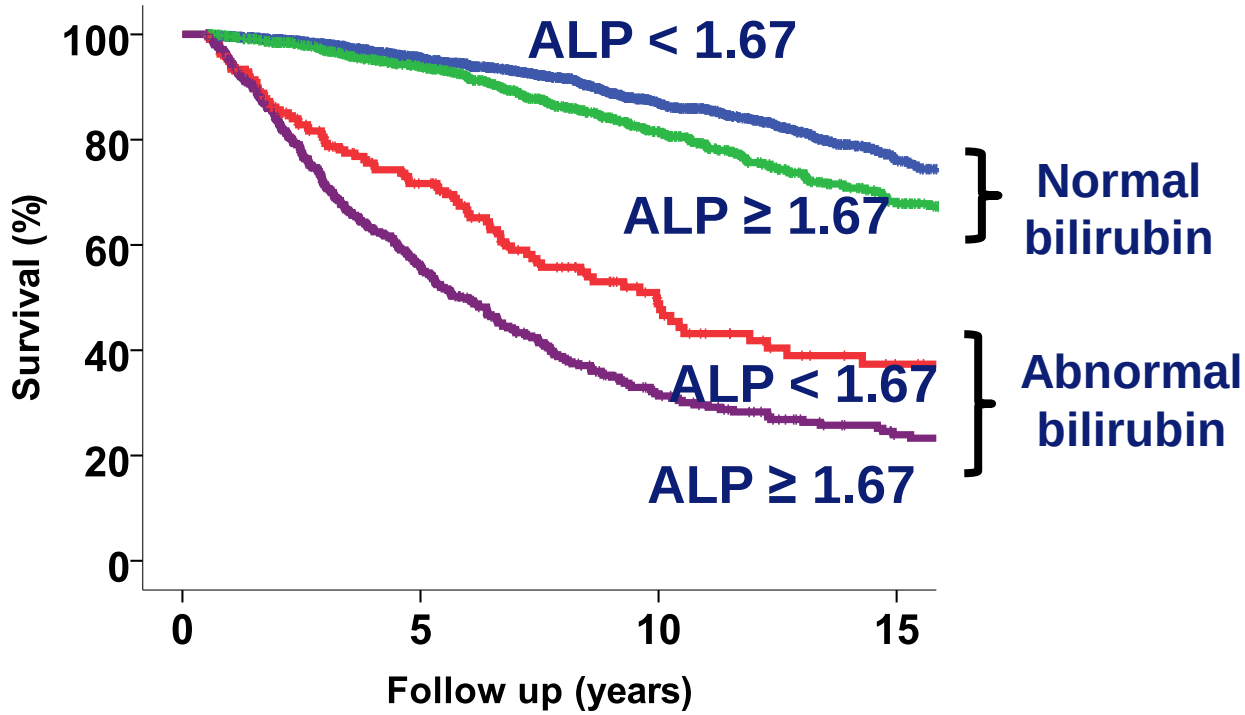
Challenges in assessing drug efficacy by utilizing biomarker endpoints in clinical studies

- Biomarker often *continuous*:
  - threshold ?
  - magnitude of efficacy ?
  - % difference ?
- Biomarker response measured at *one fixed time point*
  - which time point ?
  - durability/sustainable response ?



Lammers et al, Gastroenterology 2014

- What is the impact on the true endpoint
  - in the natural history of disease ?
  - association and mechanism of action?
- Is 'biomarker response' = level 3 'surrogate' endpoint ?
  - influence independent of therapies (depends on mode of action)
  - biomarker endpoint influenced through other pathways

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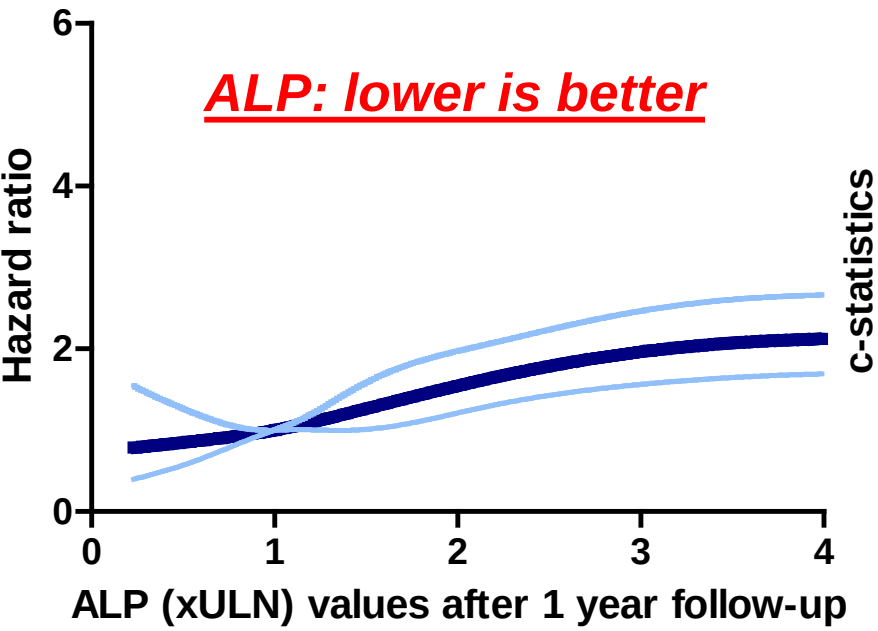
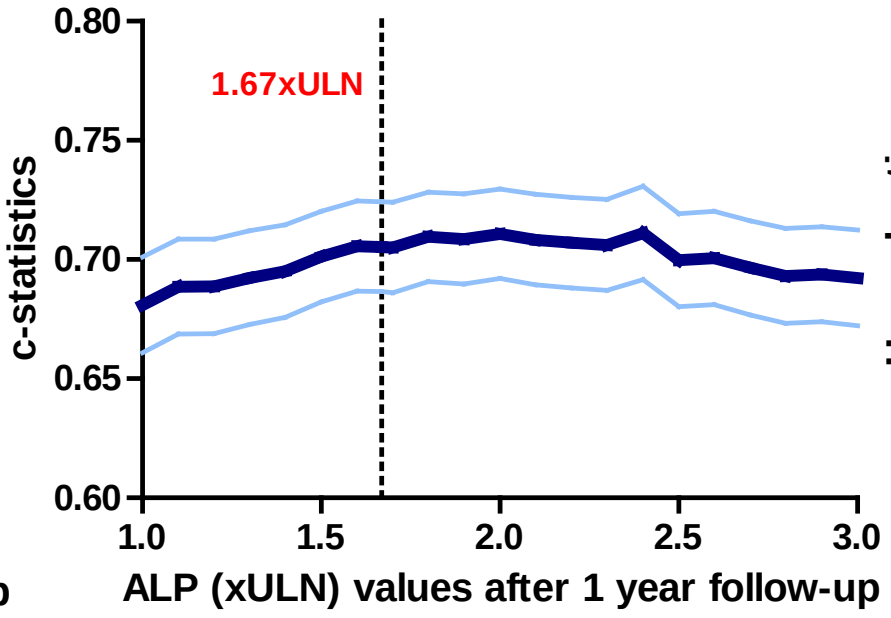
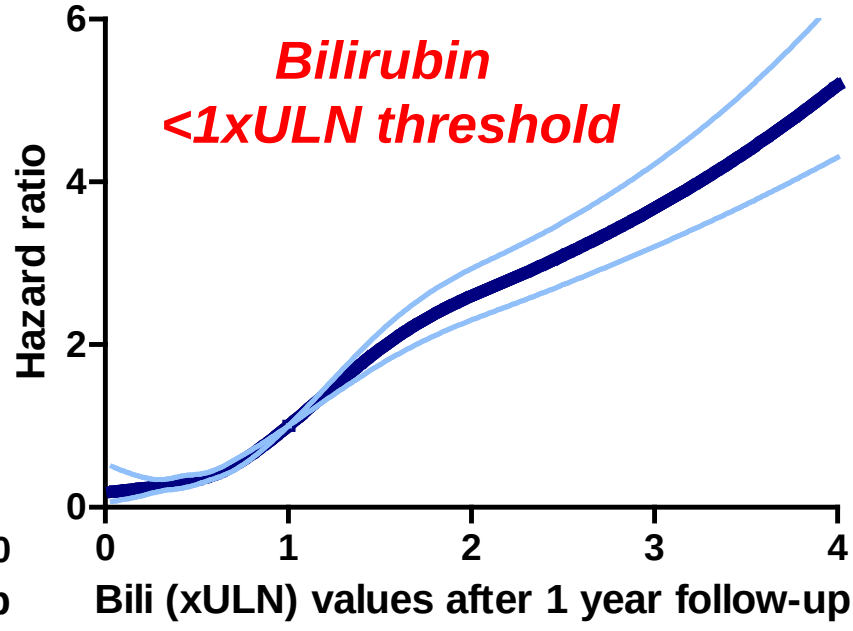
Higher ALP and bilirubin values are associated with higher hazard of liver transplantation/death

Alkaline phosphatase (ALP)





Bilirubin



Lammers et al., Gastroenterology 2014

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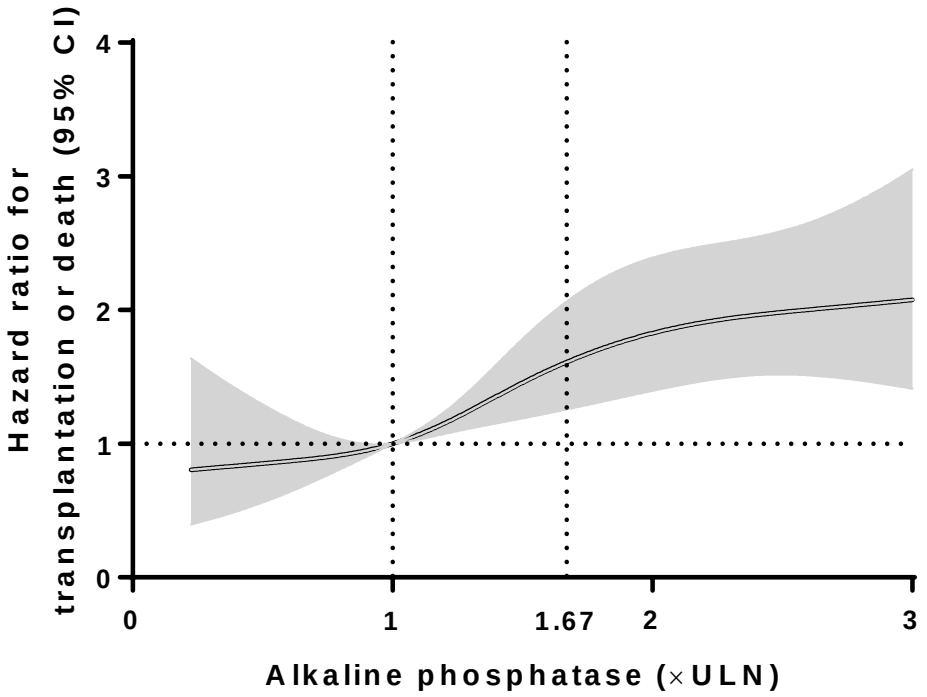
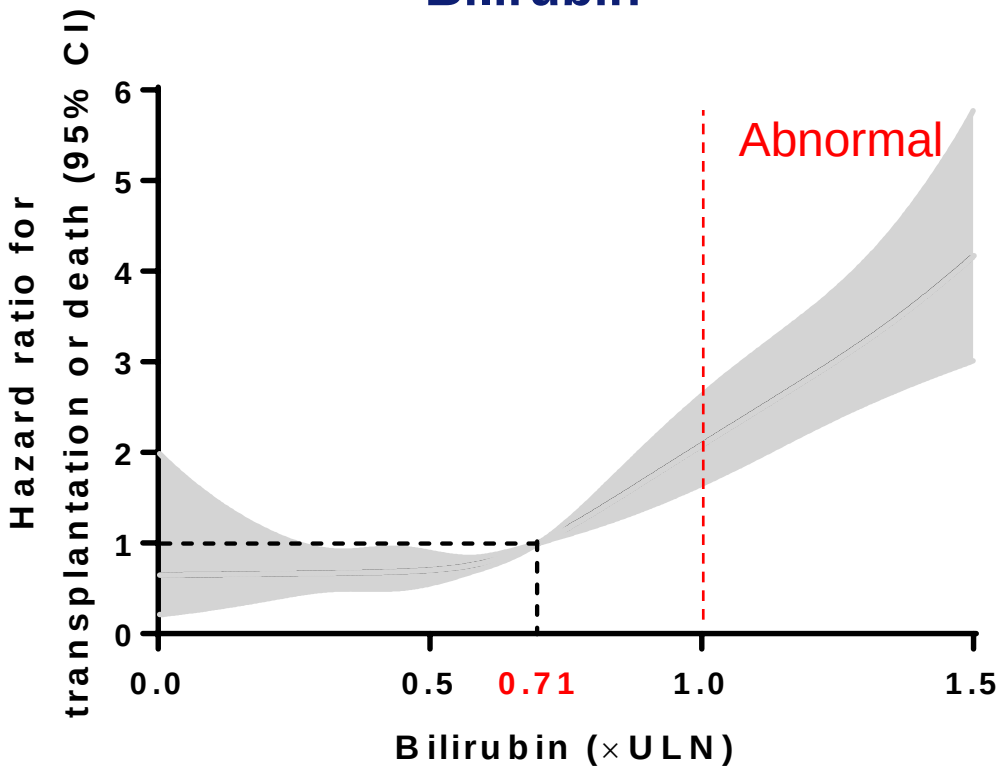
Zooming in on ALP below 2 and normal bilirubin

Alkaline phosphatase (ALP)



ALP: lower is better

Bilirubin



Bilirubin: > 0.6 - 0.7 at higher risk

Murillo et al., AASLD 2017; Murillo et al., AASLD 2018

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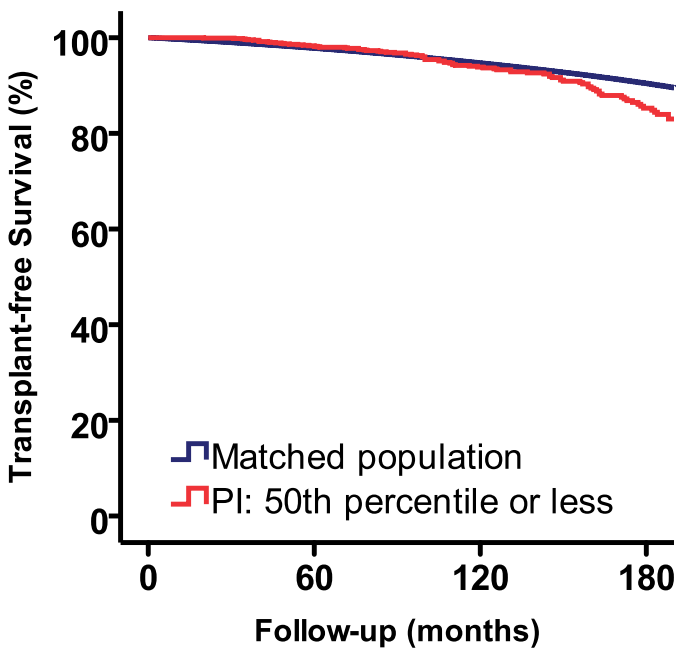
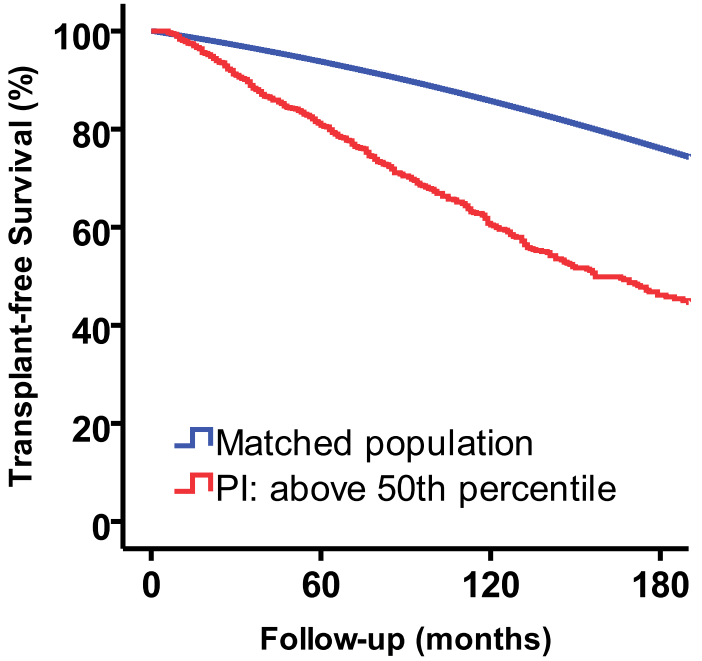
Design of Risk Scores: combination of biomarkers

Biochemical + APRI[1] (2014)	*Biochemical response (Barcelona, Paris-I/II, or Toronto) and APRI ≤0.54 after 1 year UDCA*
UK-PBC Risk Score[2] (2015)	*Prognostic index comprising baseline albumin and platelet count, plus bilirubin, ALT or AST, and ALP after 1 year UDCA*
GLOBE Score[3] (2015)	*Prognostic index comprising baseline age, and bilirubin, ALP, albumin, and platelet count after 1 year UDCA*

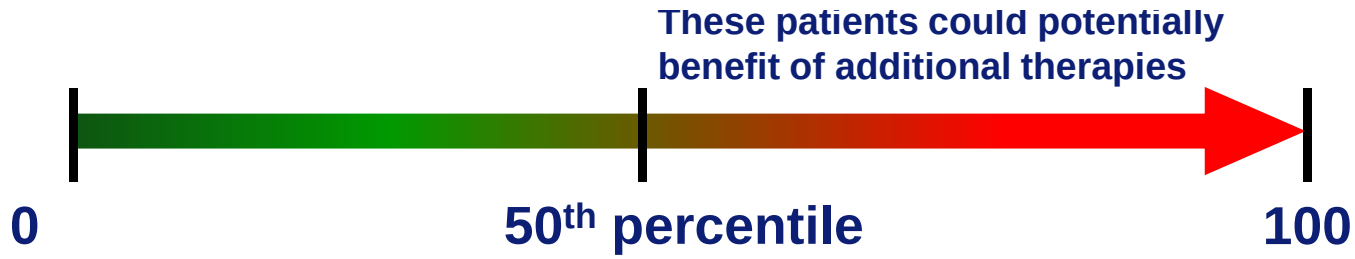
1. *Trivedi PJ, et al. J Hepatol. 2014;60:1249-1258.*
2. *Carbone M, et al. Hepatology. 2015 Jul 29.*
3. *Lammers WJ, et al. Gastroenterology. 2015 Aug 7.*

Design of Risk Scores: Globe score





HR globe score > threshold = 4.5
C-stat = 0.82



Lammers et al., Gastroenterology 2015

http://globalpbc.com/globe

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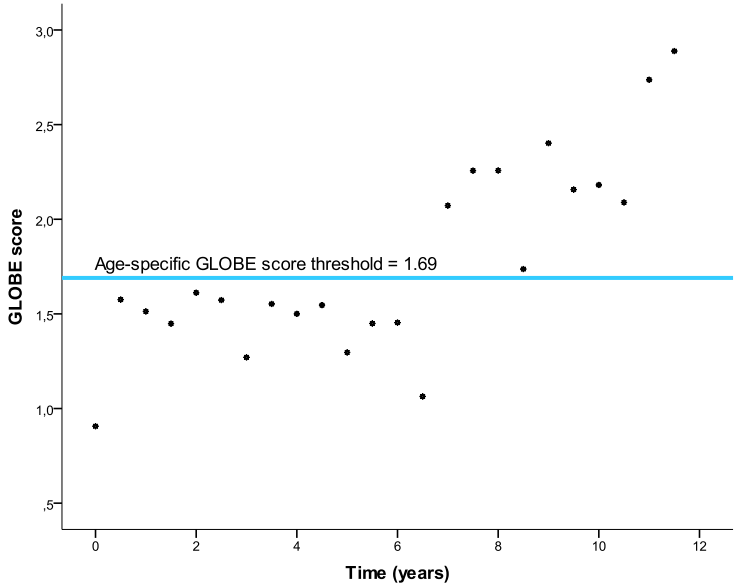
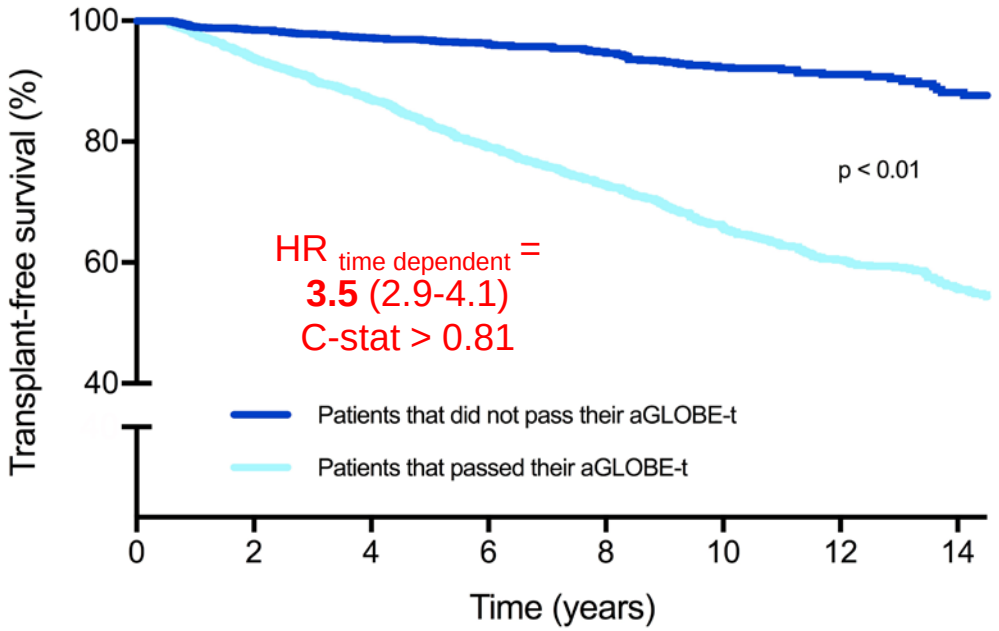
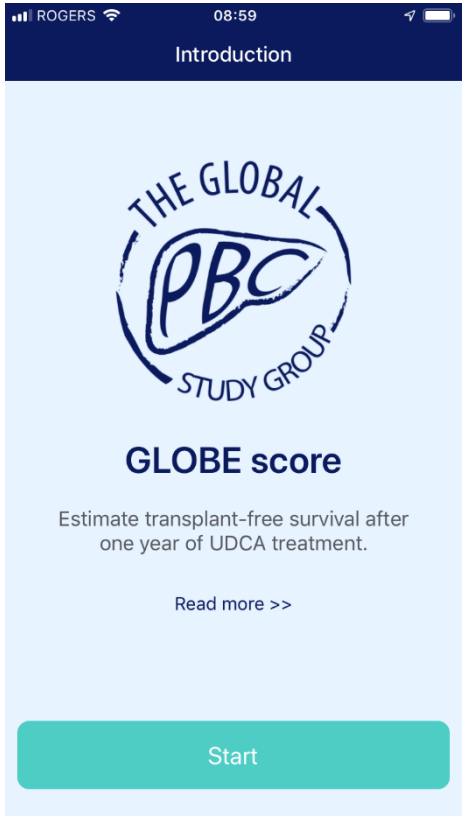
Globe-score for PBC – use as dynamic risk score



Patient example

- 67 years at start of UDCA
- Bilirubin&albumin normal at 0 and 12 months
- GLOBE score threshold passed at 7 years
- † (liver-related) after 11.5 years follow-up





Mobile App

Goet et al. JHep 2017

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Established Response Criteria in UDCA treated PBC

	Bilirubin	ALP	AST (ALT)	Albumin	GGT	Platelets
Barcelona [1]		✓				
Paris I[2]	✓	✓	✓			
Paris II[3]		✓	✓			
Rotterdam[4]	✓			✓		
Toronto[5]		✓				
Mayo[6]	✓	✓				
Ehemi[7]					✓	
APRI[8]			✓			✓
UK[9]	✓	✓	✓	✓		✓
GLOBE[10]	✓	✓		✓		✓

1. Parés, Gastroenterology 2006; 2. Corpechot, Hepatology 2008; 3. Corpechot;,J Hep 2011; 4. Kuiper, Gastroenterology 2009; 5. Kumagi, Am J Gastroenterol 2010; 6. Momah, Liver Int 2011; 7. Azemoto 2011 Hepatology Research; 8 Trivedi, J Hep 2014; Zhang. Hepatology, 2013. 9. Carbone, Hepatology 2014; 10. Lammers, Gastroenterology 2014

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Phase 3 current intermediate endpoints

Duration: 1 year

POISE[1] – trial

Inclusion: ALP>1.67 OR abnormal bilirubin

Response: ALP<=1.67, min. 15 % reduction compared to baseline AND normal bilirubin

BEZURSO[2] - trial

Inclusion: Non-responder according to Paris I

Response: normal bilirubin, normal ALP, AST, ALT, albumin and PT

[1]*Nevens et al ; NEJM 2016;* [2]*Corpechot at al; NEJM 2018*

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Phase 3 intermediate endpoints: emerging alternatives

Do we need new response definitions ?

Minimum requirement: level 3 endpoint; a non-validated surrogate, yet one established to be "reasonably likely to predict clinical benefit"

- Use the created path: ALP≤1.67 AND min 15 % reduction AND normal bilirubin
- Further use of ALP and bilirubin: lower than 1 for bilirubin; ALP lower than 1.67
- Other bicemical tests: GGT, AST, platelets, Albumin *depends on the mode of action of the intervention*
- Risk scores: Mayo / MELD score, APRI, FIB4, UK, GLOBE
- Fibroscan / Fibrotest / imaging/ histology
- Combinations of above

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Summary

- We are on the right track
- Use of other associated biomarkers as surrogate endpoints need additional attention
- Validation of potential new surrogate endpoints, also in cohorts treated with other drugs than UDCA
- Use of biomarkers in a dynamic model to update patient profile
- Use of biomarkers/fibroscan/fibrotest to replace histology and define disease stage and progression

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Discussion

- What should be the standard for alkaline phosphatase normalization?
  - 1xULN, 1.5, 1.67 ?
  - 15% reduction - 40% reduction ?

- What are the most important secondary endpoints?
  - Fibroscan, …

Stop treatment

- When should new drugs be stopped ?
  - Assessment of a stopping-rule
  - Stop if no benefit on life expectancy ?

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