Non-alcoholic fatty liver disease: current concepts and treatment strategies

CP Day

University of Newcastle

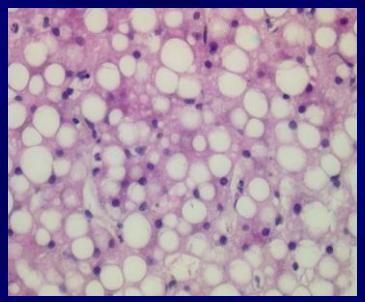
NAFLD

- What is it?
- How common is it?
- Why do diabetologists need to know about it
- How does it present?
- How should it be investigated?
- What is the course and prognosis?
- What are the mechanisms?
- How should it be managed?

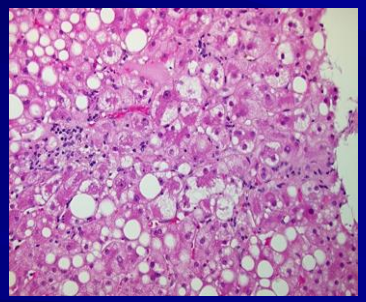
Stages of non-alcoholic fatty liver disease

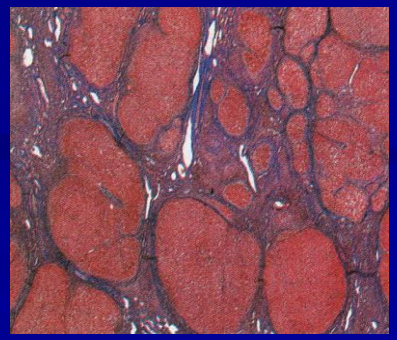
Normal

Steatosis (NAFL)



Steatohepatitis (NASH)





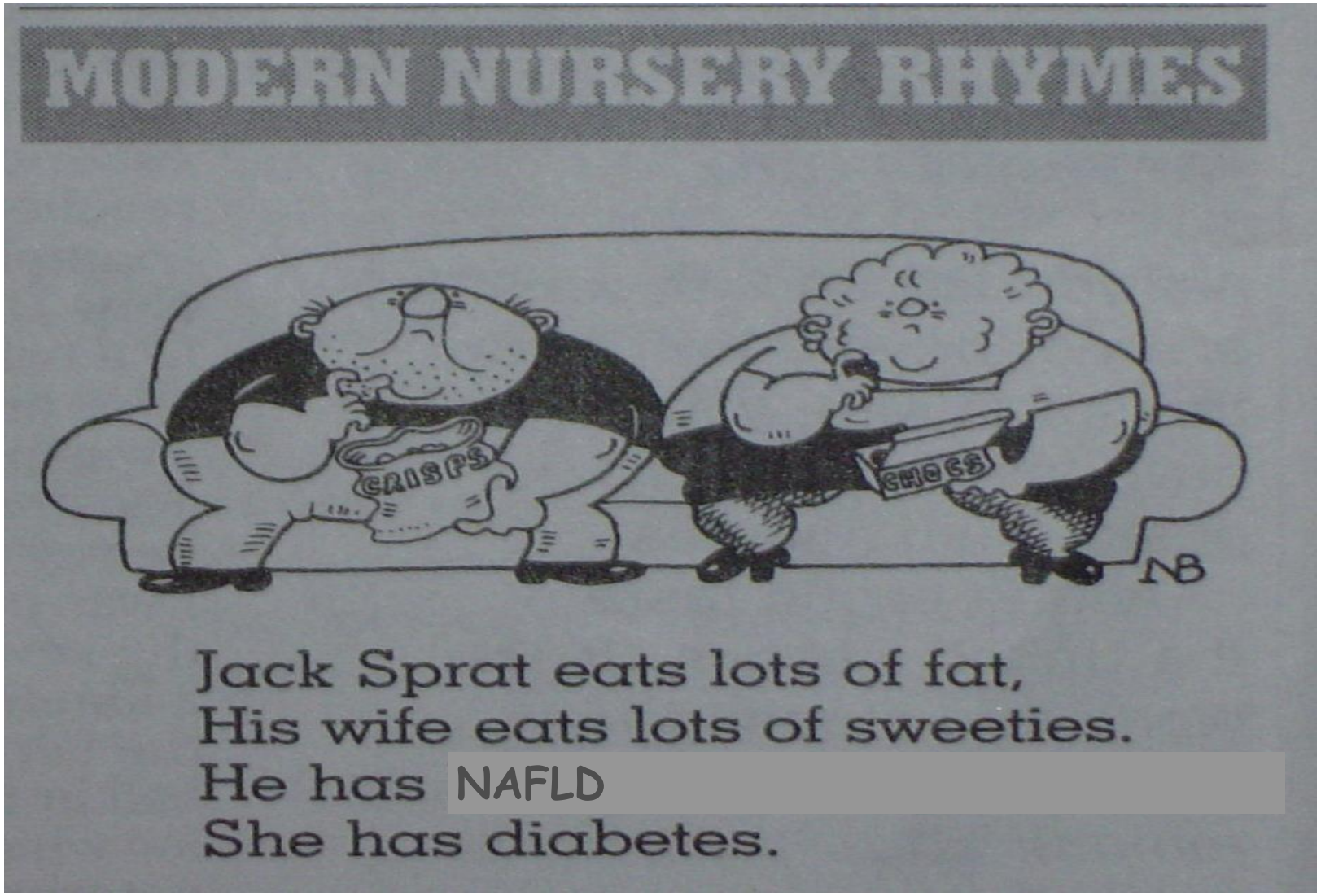
Fibrosis/ cirrhosis

NAFLD is common

- "*Effects 10-24% of general population in various countries*" *Angulo NEJM 2002*
- Based on "cryptogenic" ↑ALT/AST: effects 3-6% of the US population

  Ruhl 2003, Clark 2003
- Diagnosis in 72% of 249 pts with "cryptogenic" ↑ ALT/γGT/ALP (< x2): 44% with NASH and/or fibrosis *Ryder BASL 2003*

Who gets NAFLD?



Who gets NAFLD?

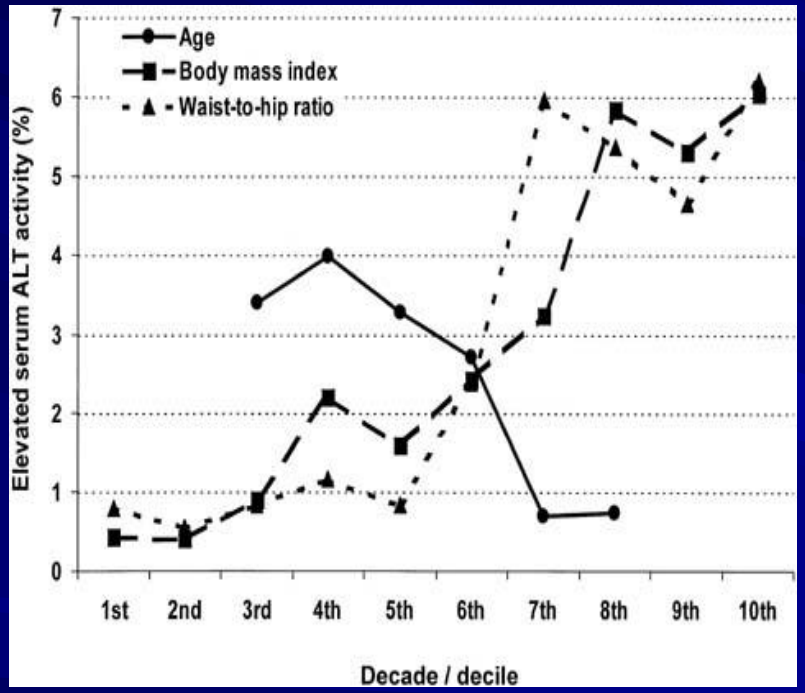
- Obesity (50-100%): central/visceral
- Men > women
- T2DM (30-40%)/Insulin resistance (~100%)
- Hypertriglyceridemia (20-60%)
- Hypertension

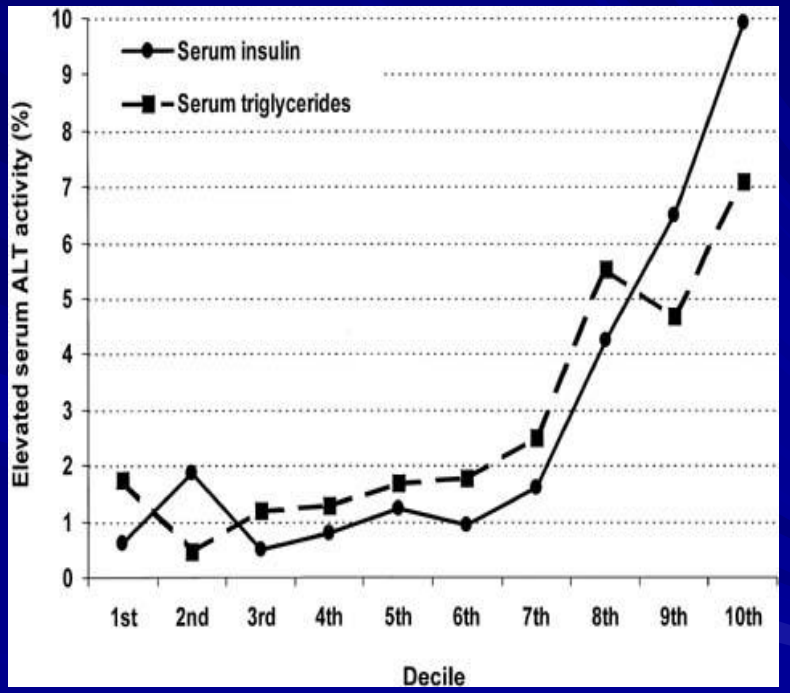
Donati et al 2004

= Liver manifestation of the Metabolic Syndrome

Ferrannini 2000, Marchesini 2001

Correlations of ↑ALT in NHANESIII





Ruhl & Everhard Gastro 2003

NAFLD and insulin resistance

Marchesini et al Diabetes 2001

- Insulin sensitivity with euglycaemic clamp in:
- 30 pts with biopsy proven NAFLD (21 NASH) with normal GTT and BMI<30 versus:
- 10 healthy controls/10 well controlled T2DM
- NAFLD = type 2 DM: versus controls
  - ↓glucose disposal during clamp (50%)
  - ↑ Basal FFAs/↓suppression of lipolysis
  - ↓ insulin-mediated suppression of HGP

Liver problems in T2DM

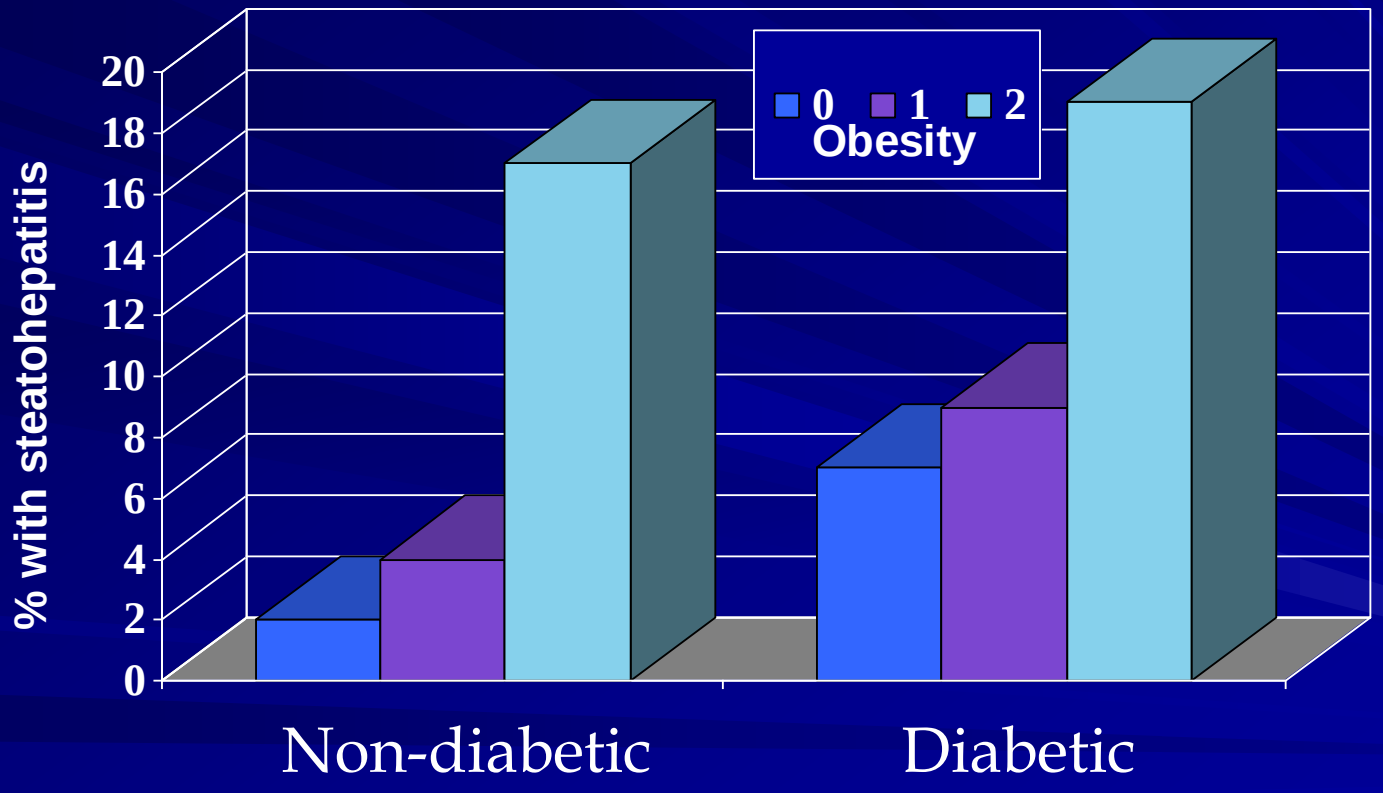
- 102/1550 (8-10%) T2DM have ↑ALT

  Erbey et al Am J Med 2000

  Dutta et al BDA 2004
- 20% obese T2DM have NASH *Wanless 1990*
- HRR for chronic liver disease: 1.98 [1.88-2.09]
- HRR for liver cancer: 2.16[1.86-2.38]

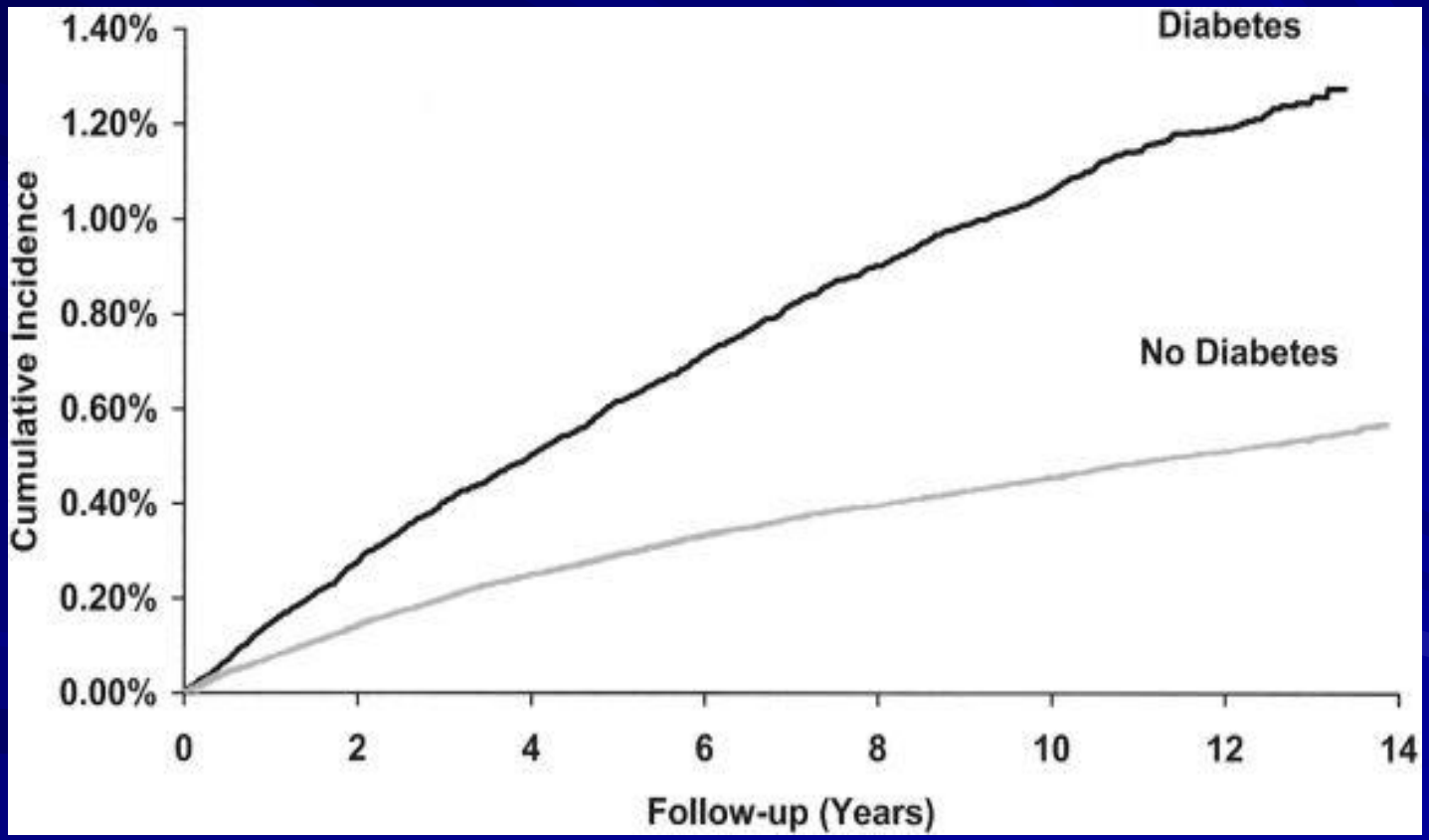
  El-Serag 2004, Vecchia 1997
- SMR for cirrhosis 2.52 (> CVD) *De Marco 1999*

Type 2 DM is associated with NASH in Obesity



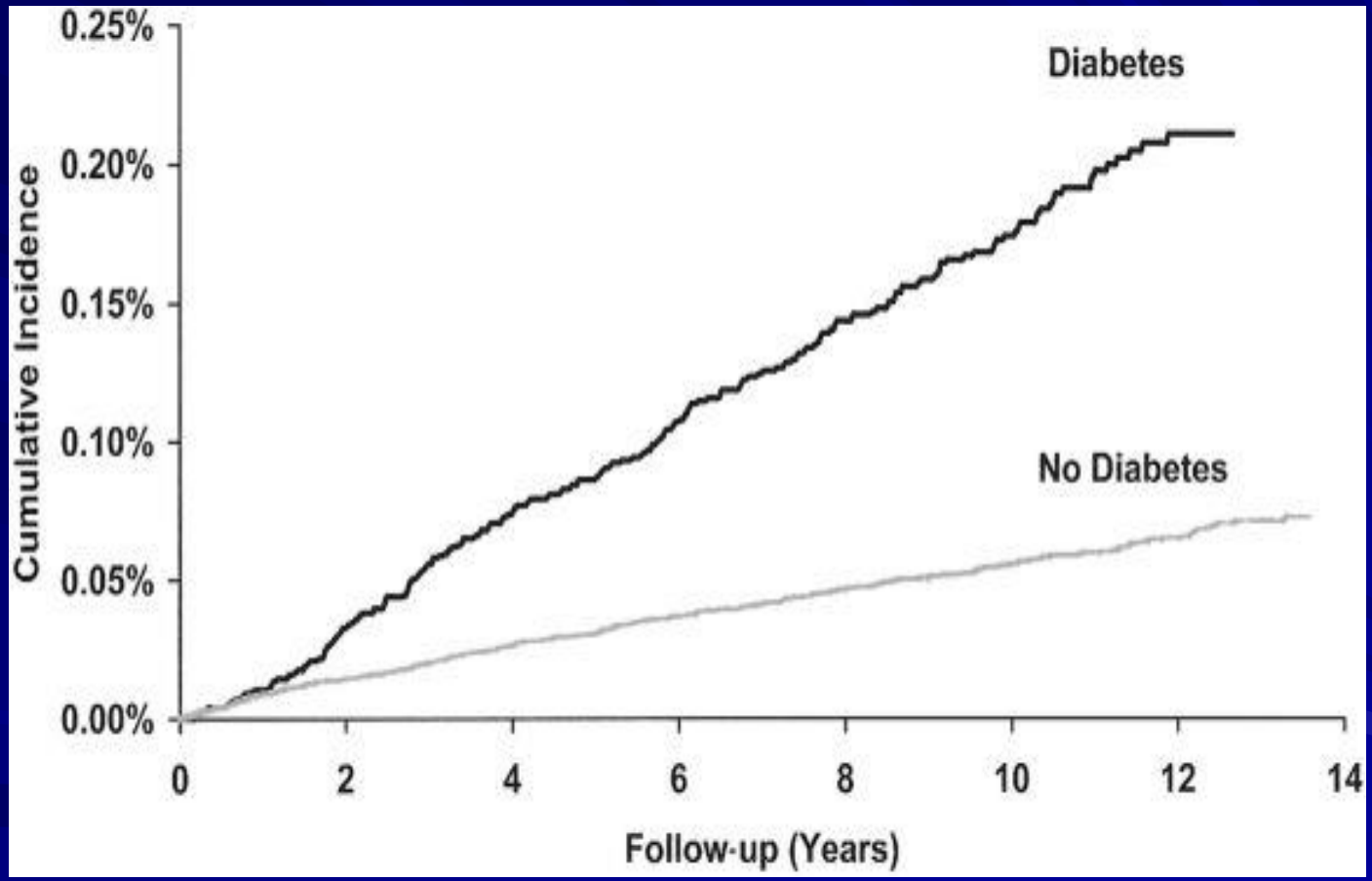
Wanless et al Hepatology 1990

Cumulative risk of chronic NAFLD in 820,000 male veterans in hospital ’85-90



El-Serag 2004

Cumulative risk of HCC in 820,000 male veterans in hospital ’85-90



El-Serag 2004

NAFLD as a *cause of/contributor to* insulin resistance/T2DM?

- In T2DM insulin requirements correlate with the severity of steatosis

  Ryysy 2000

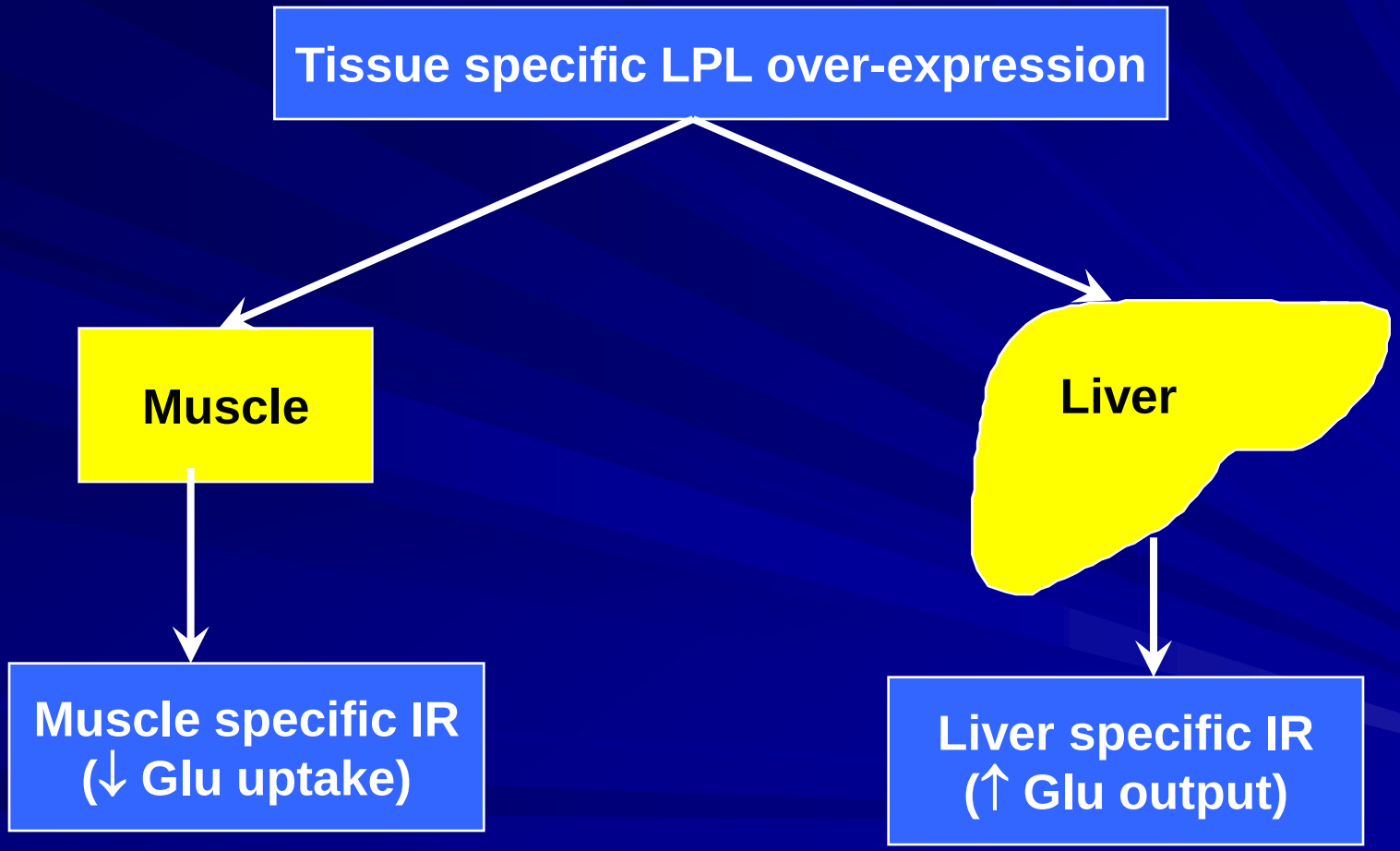
- Hepatic insulin resistance (by clamp/isotope) is universal in patients with NAFL

  Sanyal 2001

- Ins R ↓ post-OLTx in type 2 diabetics transplanted for NASH cirrhosis

  Cauble 2001

Non-adipose tissue steatosis



Kim et al PNAS 2001

How does it present?

- 48 year old man
- Presenting with malaise
- Past medical history
  - Always obese
  - Type 2 diabetes,
  - Hypertension
- Drinks < 8 units per week
- On metformin and ACE inhibitor
- BMI 41.5
- WHR 148/139 = 1.06

Special investigations

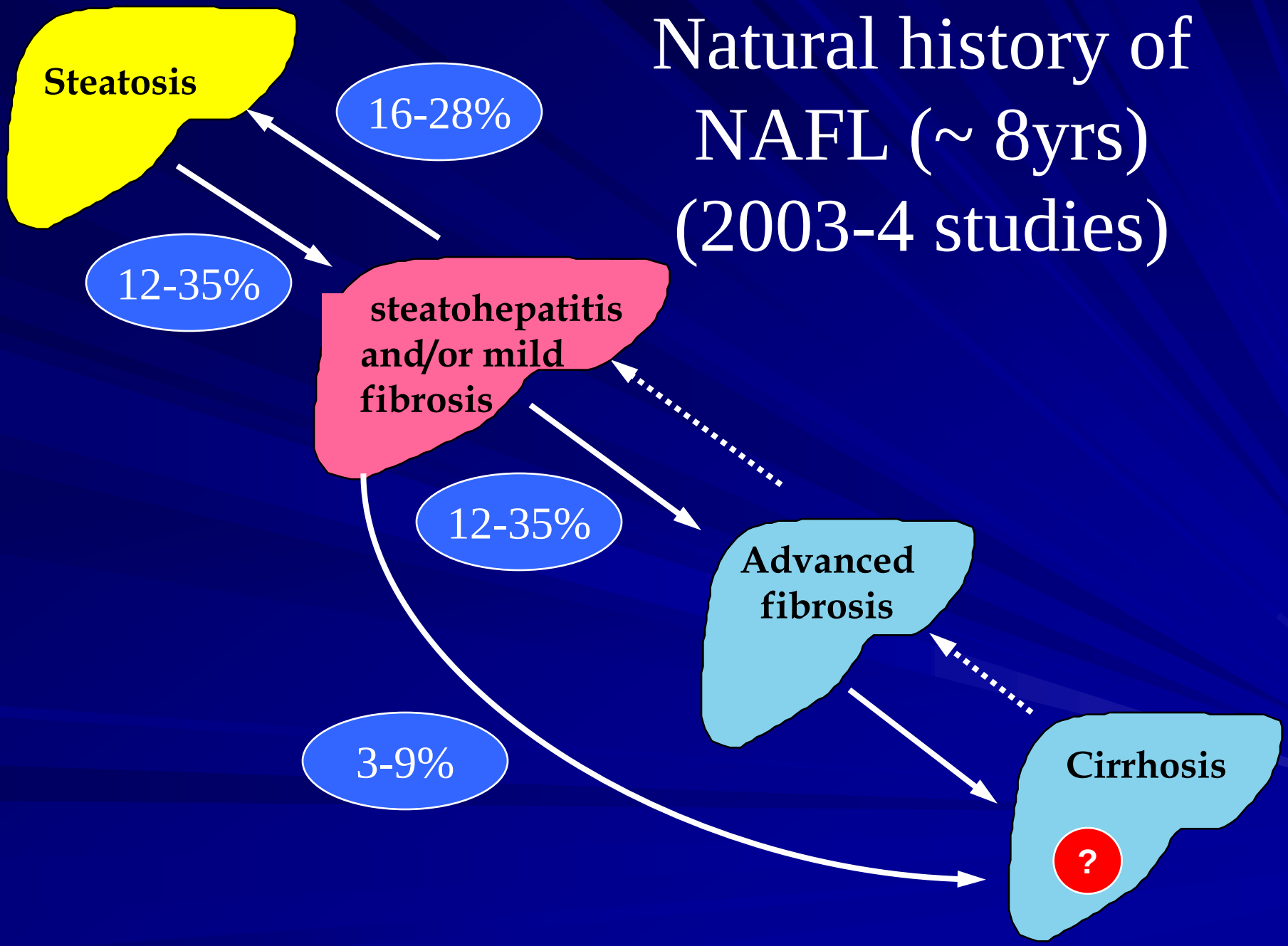
- ALT 65 U/l, AST 86 U/l, GGT 118 U/l
- Albumin 36g/l, Bili 17μmol/l
- IgG 15.8g/l, IgA 7.98g/l
- Triglycerides 3.7mmol/l, HDL cholesterol 0.7
- Viral serology negative
- Ferritin 456μg/l
- Autoantibodies negative
- Ultrasound: enlarged “fatty” liver

Does this man need a liver biopsy?

1. To make the diagnosis of NAFLD?
   - Probably not *Clark Am J Gastro 2003*
2. To provide prognostic information?
   - Almost certainly
   - Different stages have different prognoses
   - Imaging (USS/MRI/CT) cannot distinguish between different stages

Saadeh Gastro 2002

Natural history of NAFL (~ 8yrs) (2003-4 studies)

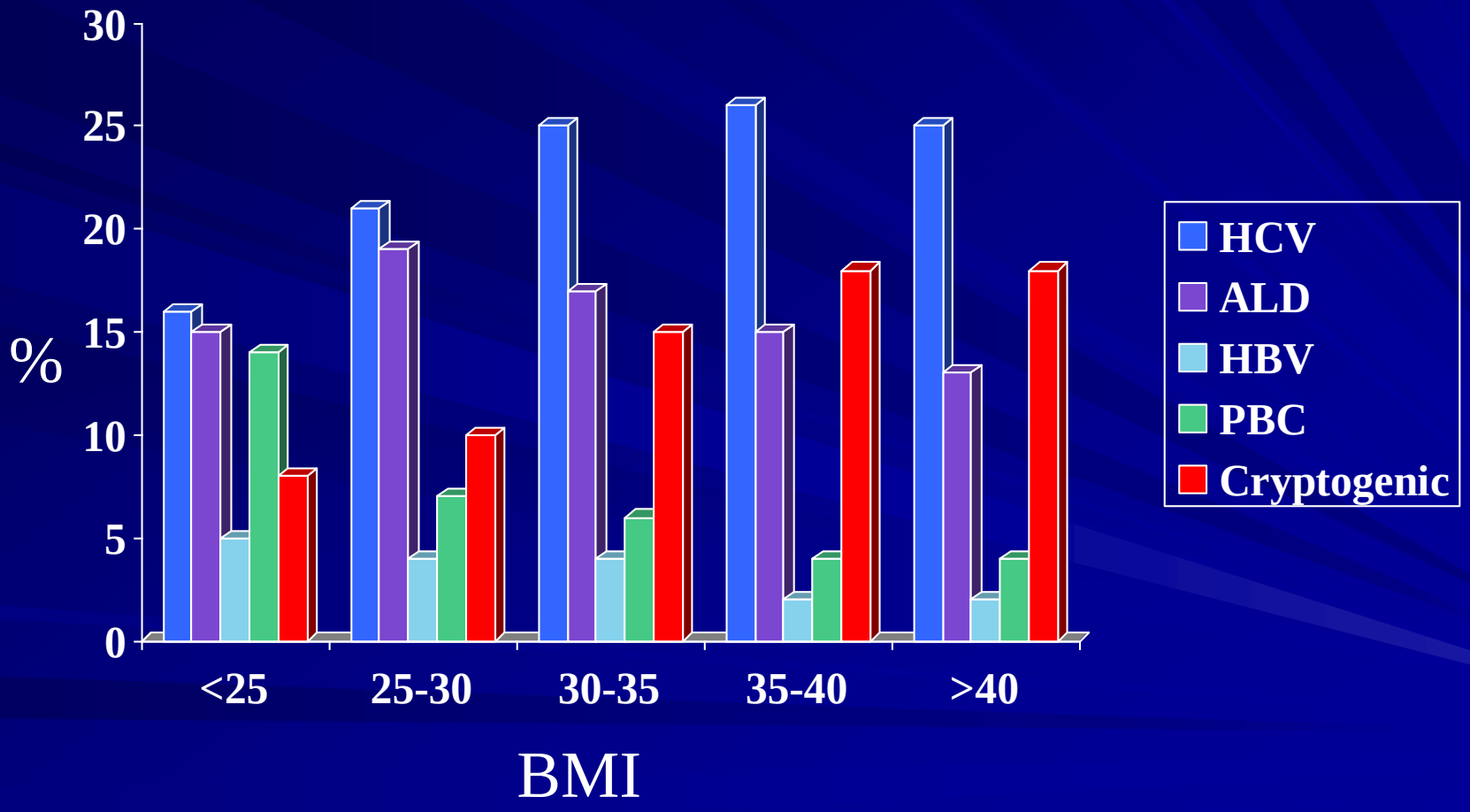


Where's all the NASH cirrhosis? Is it "cryptogenic" *Caldwell et al 1999*

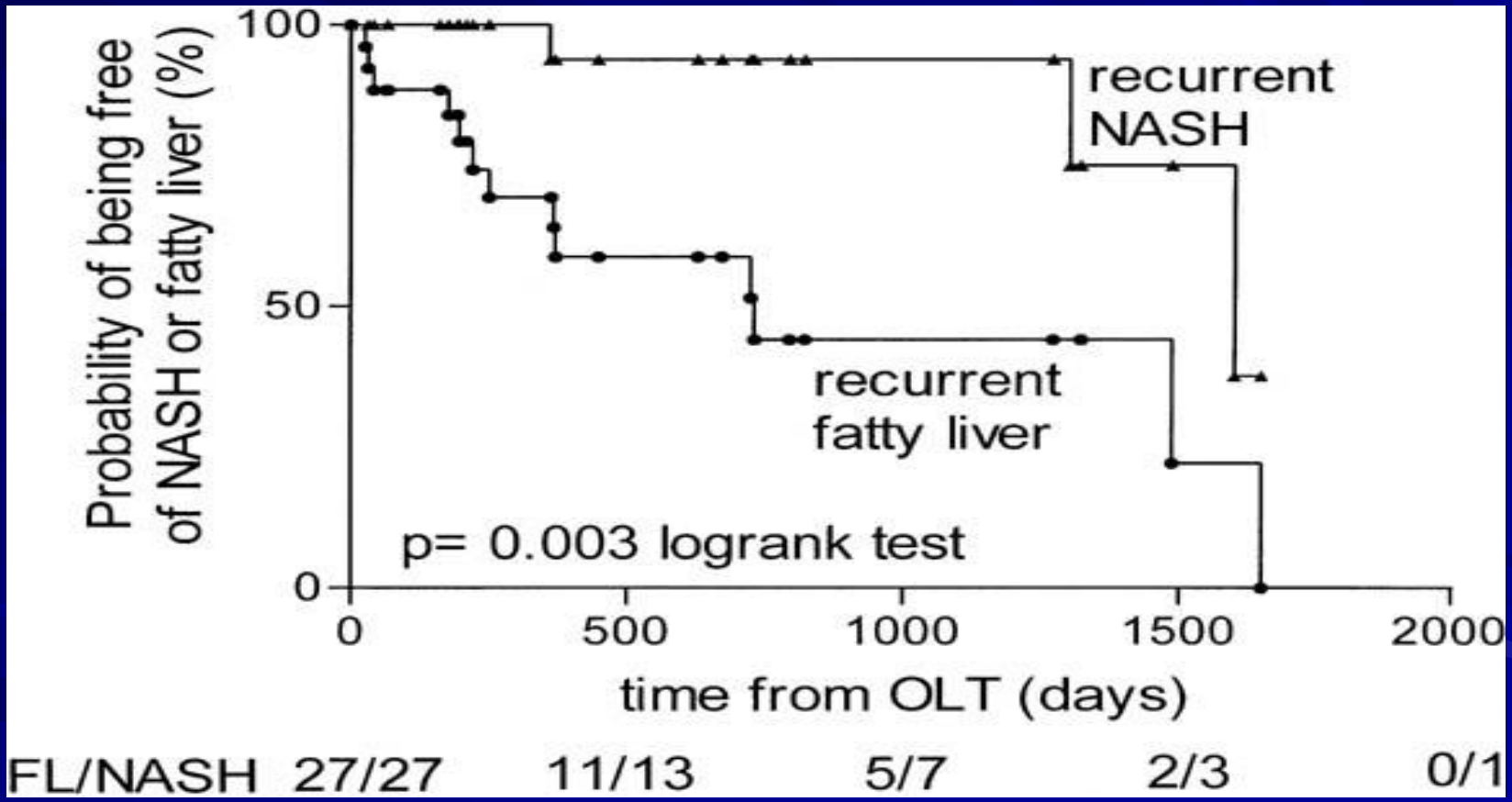
- Compared incidence of obesity and /or NIDDM in:
  - 70 cryptogenic cirrhotics: 73%
    mean age 63yrs
  - 50 NASH patients: 70%
    mean age 50yrs
  - 46 HCV/ 67PBC: 28/33%
- Confirmed by Poonawala *et al* 2000

BMI & Indication for OLTx: UNOS

Nair et al 2002



Recurrence of NASH post OLTx for cryptogenic cirrhosis: *Contos 2001*



Natural history of obesity-related cryptogenic cirrhosis: *Ratziu 2002*

- 27 obese cryptogenic cirrhotics vs
- 85 HCV cirrhotics matched for age and sex at time of diagnosis
- 33% died a “liver” death vs 24% (22 mo f/up)
- HCC risk identical (~25%)
  - Consistent with other reports *Shimada J Hep 2002, Bugianesi Gastro 2002, Nair Hepatology 2002*
  - BMI correlates with risk of HCC *Calle NEJM* 2003

Does this man need a liver biopsy?

3. Influences management decisions

- NAFL
  - Treat associated conditions
  - ? Discharge or “long” hospital follow-up
- NASH
  - Treat associated conditions
  - Close hospital follow-up (varices, HCC screening..)
  - Consider “2nd line” therapy (???)

Can we restrict biopsy to those most likely to have NASH±fibrosis?

Predictors of advanced NAFLD

- LFTs: ↑GGT, ALT > x2N, AST>ALT
- Serum hyaluronic acid *Laine 2004*
- Age (>45)
- Features of the metabolic syndrome (MS)
  - 88% NASH vs 53% steatosis 1+ features
- Severity of insulin resistance

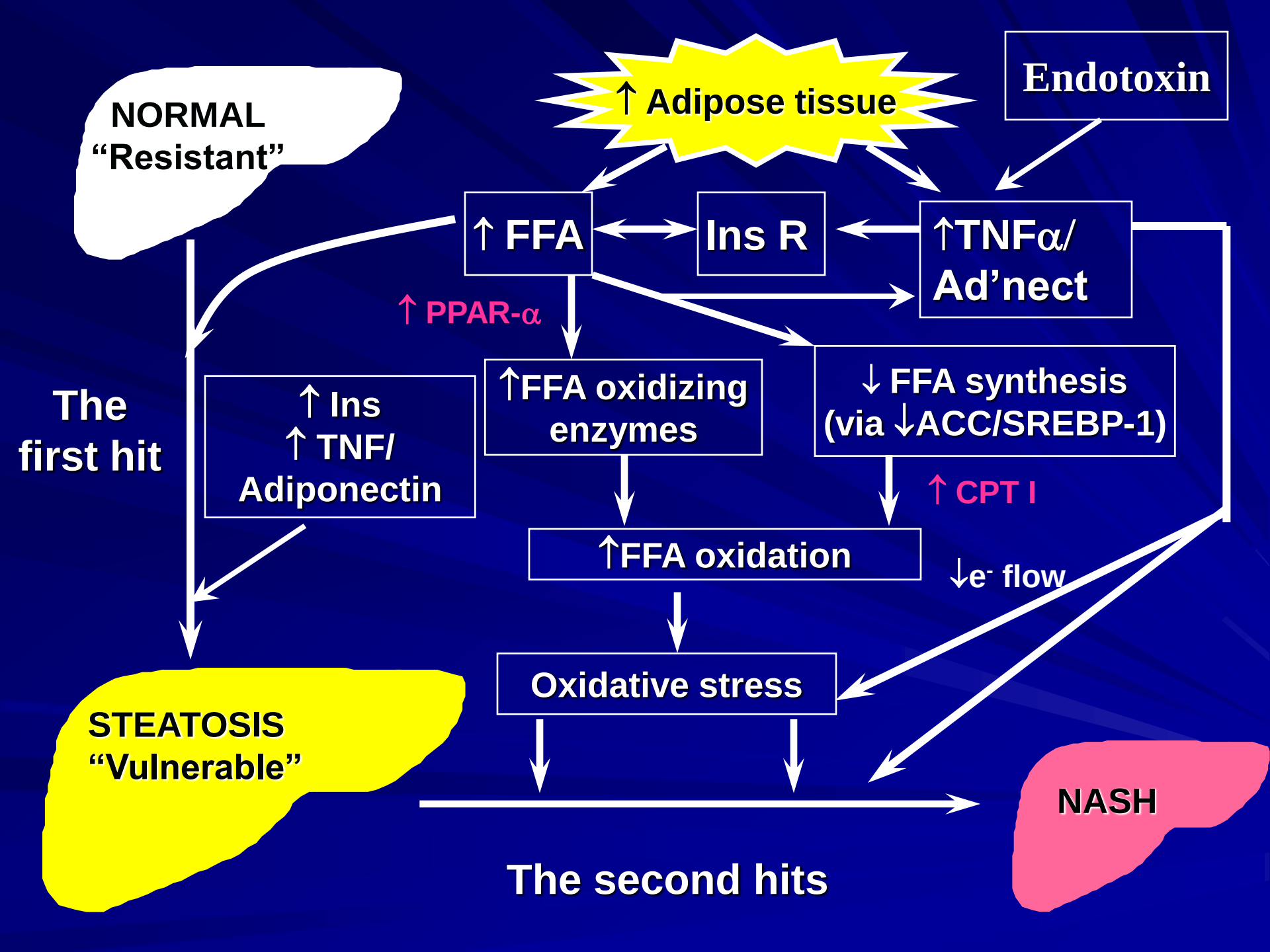
Luyckx 1998, Marceau 1999, Angulo 1999, Ratzui 2000, Marchesini 2001 & 2003, Dixon 2001, Sanyal 2001, Chitturi 2002

Mayo, Newcastle, Italy, Australian study

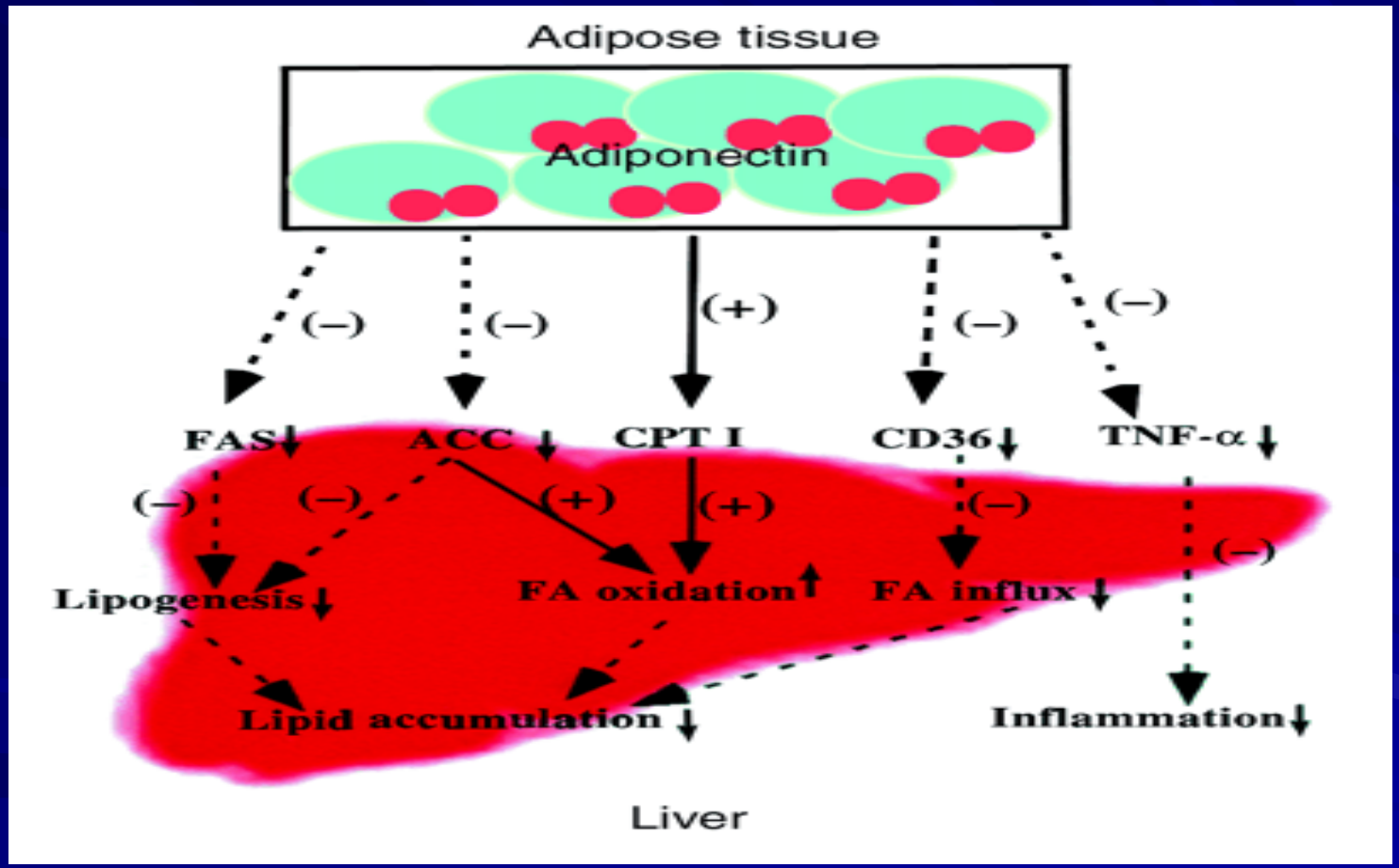
- 736 patients, 493 estimation group, 243 validation group
- Independent predictors of advanced (bridging or cirrhosis) fibrosis on MVA:
  - Age >45
  - AST/ALT > 1
  - TG > 1.8
  - Diabetes
  - Platelet <150,000
  - AST/platelet ratio > 1
  - BMI > 30

Mayo, Newcastle, Italy, Australian study

- Model with 6/7 variables (not obesity)
  - AUROC = 0.862 (±0.021) and 0.832
- Risk score based on 6 dichotomous variables:
  - Low cut-off: NPV for fibrosis = 90% & 80%
  - High cut-off: PPV for fibrosis = 91% & 89%
  - Only 22% of cohort were indeterminate
- ? Liver biopsy avoided in 78% with 90% accuracy

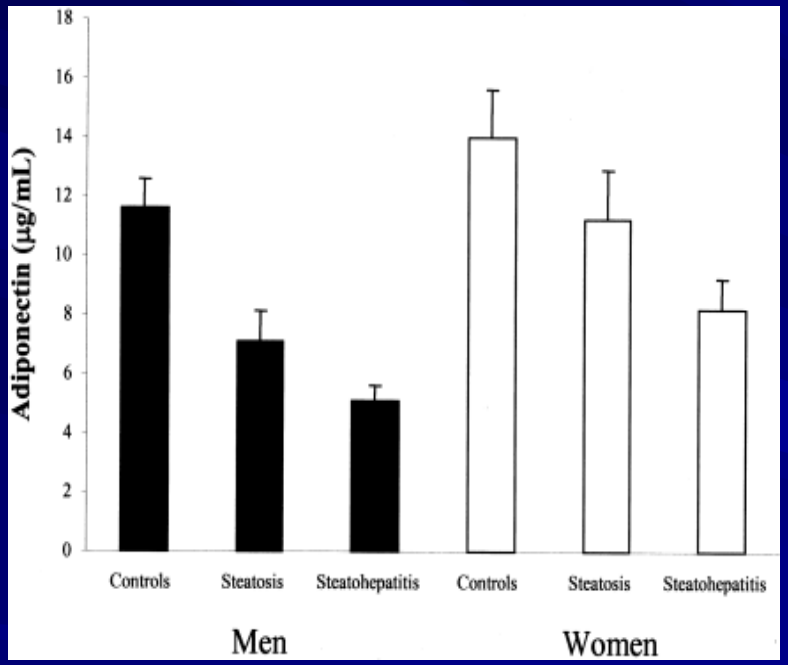

NORMAL
"Resistant"
↑ Adipose tissue
Endotoxin
↑ FFA
Ins R
↑TNFα/
Ad'nect
↑ PPAR-α
The
first hit
↑ Ins
↑ TNF/
Adiponectin
↑FFA oxidizing
enzymes
↓ FFA synthesis
(via ↓ACC/SREBP-1)
↑ CPT I
↑FFA oxidation
↓e- flow
Oxidative stress
STEATOSIS
"Vulnerable"
NASH
The second hits

Adiponectin: a key anti-inflammatory, anti-steatotic adipokine



From Xu et al JCI 2003

Adiponectin levels are low in NASH



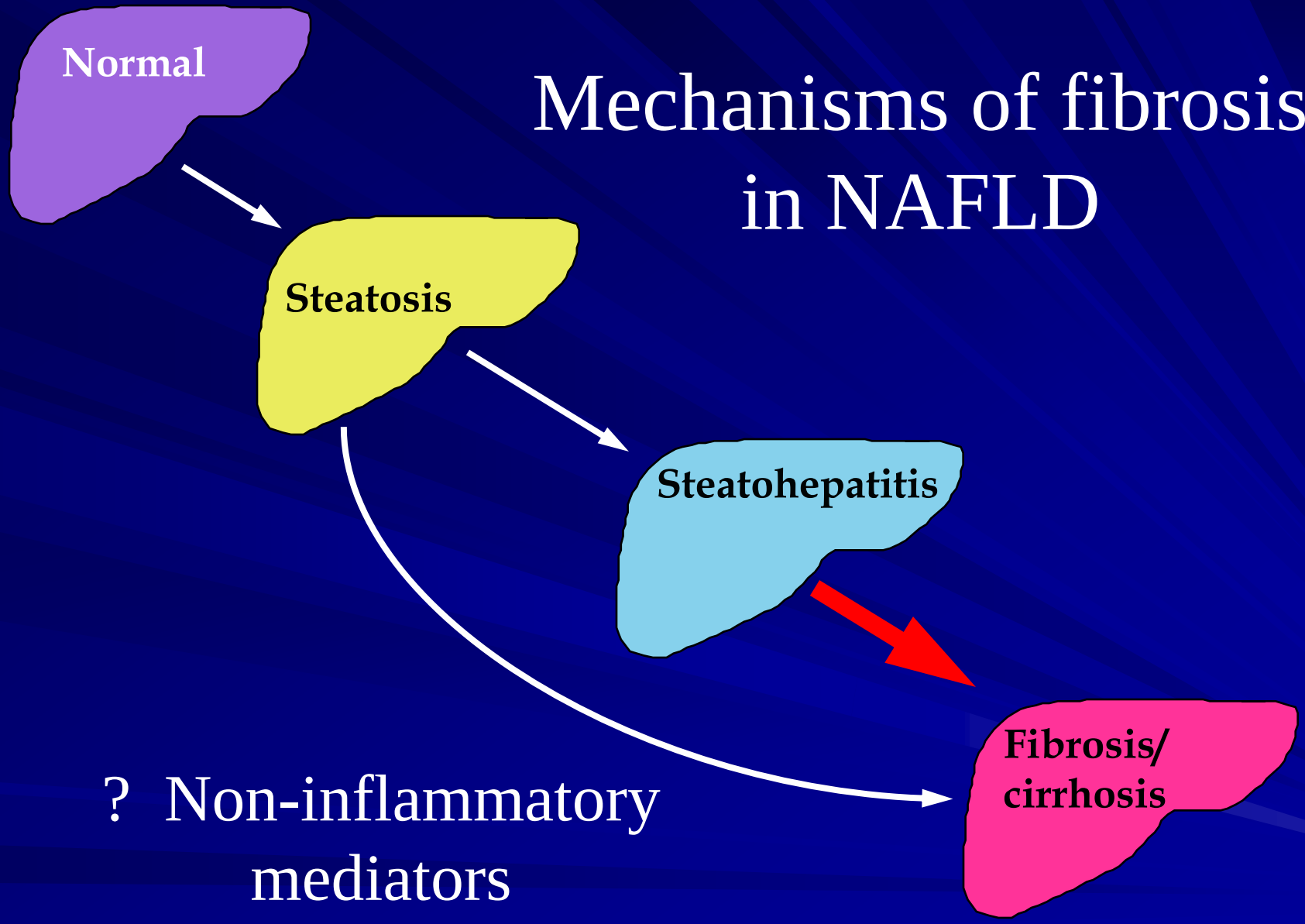
- Adiponectin levels lower in NASH vs steatosis
- Independent of Ins R
- TNFα and sTNFR2 not different

Hui et al 2004

- Hepatic receptor (R2) also ↓ in NASH

Tilg et al in press

Mechanisms of fibrosis in NAFLD



Non-inflammatory mediators of fibrosis in NAFLD

- Insulin & glucose via ↑ CTGF by HSC

  Paradis et al 2001

- "Adipokines"
  - Angiotensinogen — *Yoshiji 2001, Bataller 2003*
  - Norepinephrine — *Oben 2003,2004*
  - Leptin — *Leclerq 2002, Saxena 2002, Honda 2002*

Treatment of associated conditions: the metabolic syndrome

- "Lifestyle intervention"
  - Weight loss
  - Increase physical activity
  - 58% ↓ in Ins R → T2DM *DPP NEJM 2002*
- Treat CV risk factors if they persist
  - Diabetes
  - Dyslipidaemia
  - Statins for all T2DM *Heart Protection Study 2003*
  - Hypertension
- All shown to ↓ mortality

Weight loss & exercise

- Sound theoretical basis (↓IR, Ins, FFA, leptin)
- But: only 2 controlled trials of Diet + Ex
  - ↓ALT in **13 pts** losing >10% BW *Park 1995*
  - ↓ALT *and steatosis* in **15 pts** *Ueno 1997*
- Too rapid weight loss is deleterious
  - NIDDK recommend 1-2lb/week
- Encouraging pilots with Orlistat
  Koliouskas 2002, Harrison 2004
- Surgery
  - JIB abandoned due to liver disease risk
  - Gastric banding surgery beneficial *Dixon 2004*
  - NOT liposuction! *Klein et al 2004*

Treatment of diabetes & NAFLD

- Insulin sensitisers rational choice
- Mechanism is via ↓ liver/muscle steatosis
- Metformin drug-of-choice for obese type 2 DM (↓mortality) *PDS Lancet 1998*
- Avoid sulphonylureas and insulin
  - Weight gain
  - ? ↑fatty liver
  - ? ↑fibrosis (via CTGF)

Insulin sensitisers (1) metformin

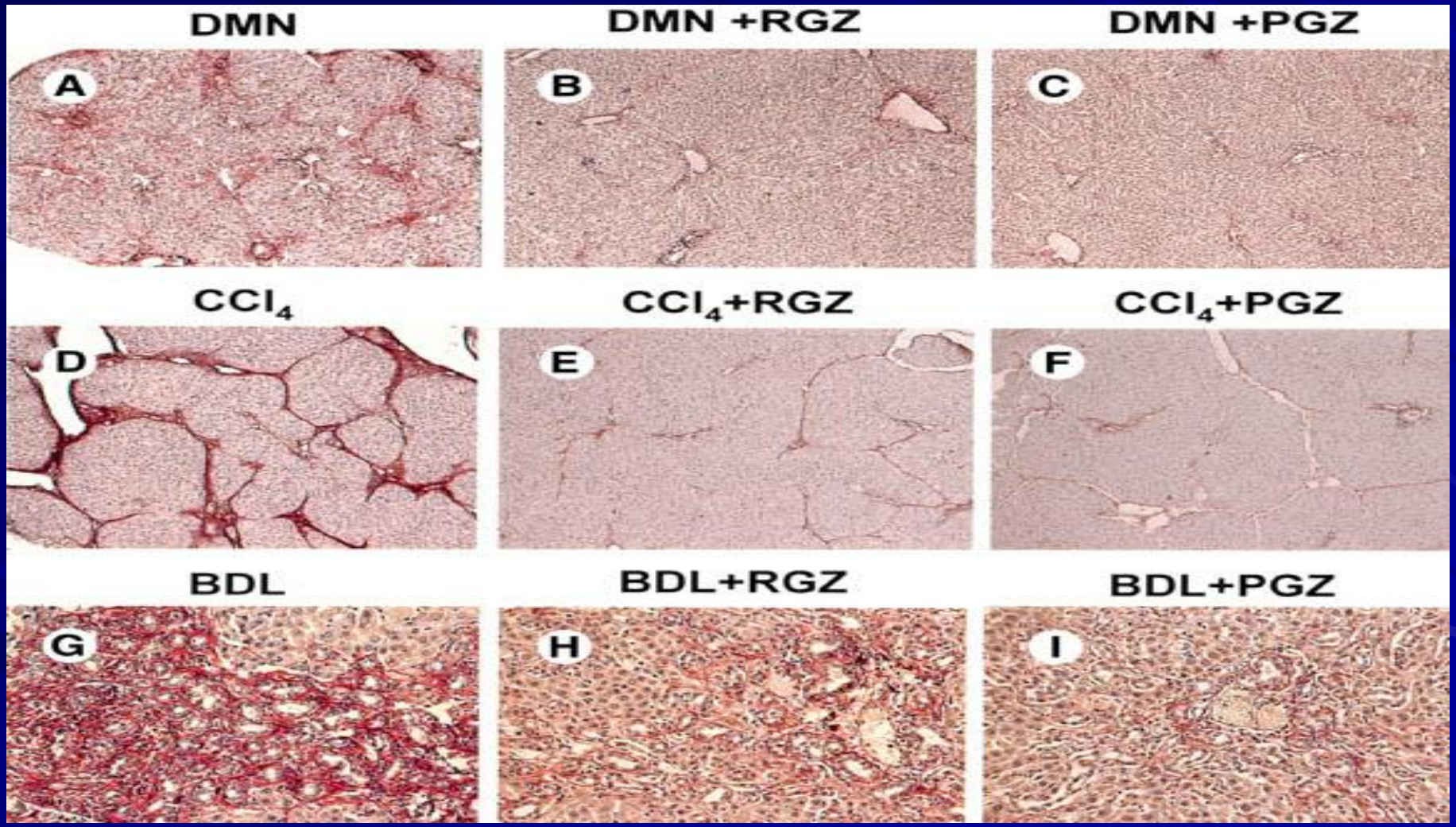
- Sound theoretical basis
  - ↓FFA & VLDL synthesis, ↑FFA oxidation in hepatocytes *Zhou JCI 2001*
  - ↓ steatosis, TNFα & ALT in ob/ob mouse *Lin Nat Med 2000*
- Contradictory pilot data in human NAFL *Marchesini 2001, Tiikkainen 2004, Nair 2004*
- RCTs underway

Insulin sensitisers (2) glitazones

- Sound theoretical basis - PPARγ agonists
  - Insulin-sensitising
  - Anti-steatotic (? via ↑adiponectin) *Maeda 2001, Mayerson 2002*
  - Anti-inflammatory *Jiang 1998, Xu 2003*
  - Anti-fibrotic *Galli 2002*
  - PPARγ mutations → NASH *Savage 2003*
- "Encouraging" pilot studies: *Neuschwander-Tetri 2003, Tiikkainen 2004, Promrat 2004*
- Case report of fatal liver failure *Farley-Hills 2004*
- NIH sponsoring pioglitazone vs vit E RCT

Anti-fibrotic effect of glitazones

Galli et al 2002



Lipid lowering agents

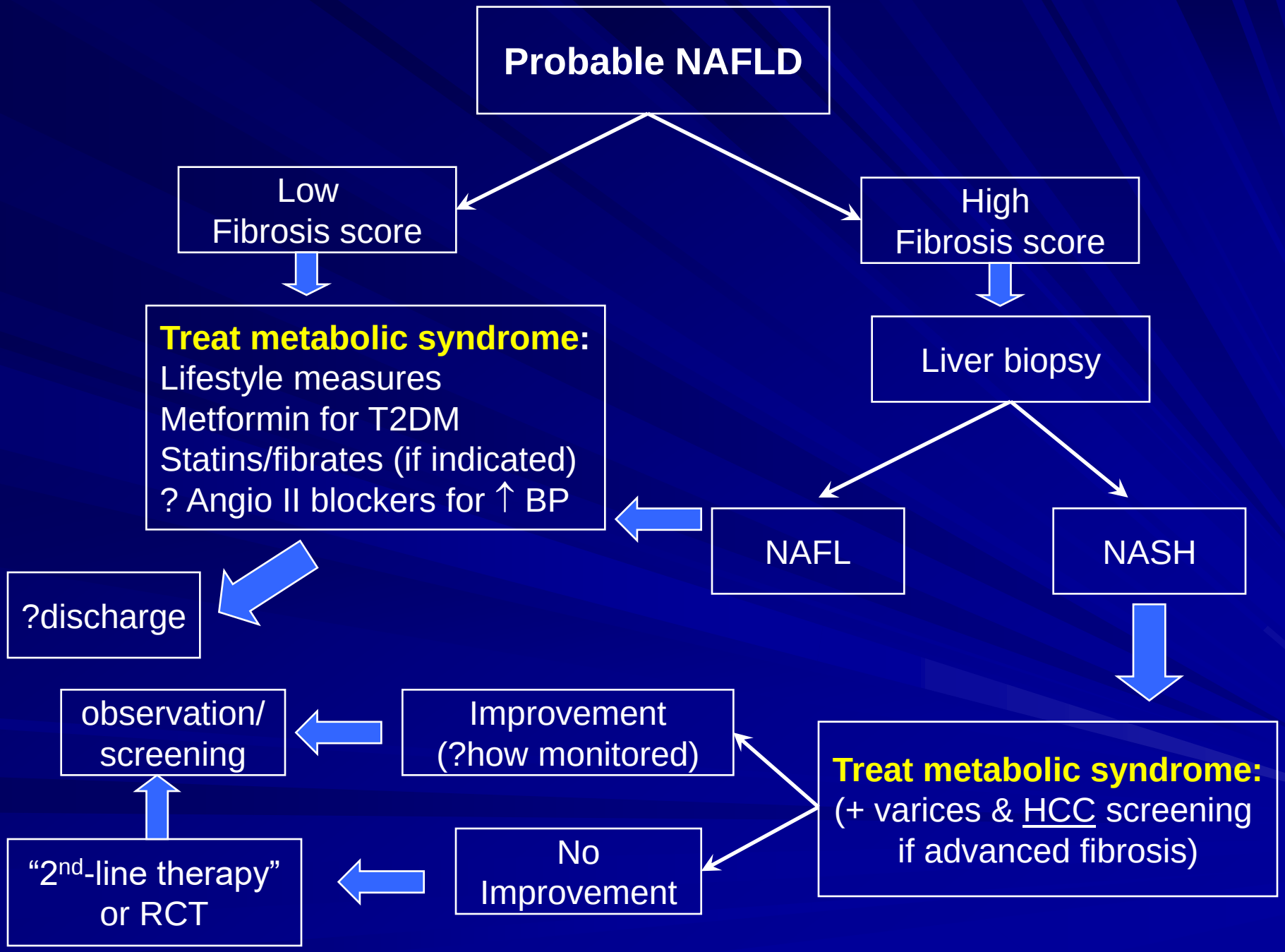
- Fibrates (PPARα agonists)
  - Good rationale from animal studies:
  - PPARα agonist ↓NASH and PPARα (-/-) ↑NASH in MCD mouse model *Ip 2003 & 2004*
  - 1 RCT of gemfibrozil (4/52) - ↓ LFTs
  - 1 open trial of clofibrate (52/52) – no effect on biochemistry or histology

    Basaranoglu 1998 Laurin 1996
- Statins
  - No rationale but appear to be safe

    Chalasani Gastro 2004

“Liver-specific” strategies

- Advice on alcohol - how much? *Dixon 2001*
- Remember steatohepatitis-inducing drugs
- Antioxidants:
  - Vitamin E: No benefit in RCT *Harrison 2003*
  - Betaine: ↓ALT and histology *Abdelmalek 2001*
- Urso: No benefit in large RCT *Lindor 2004*
- ?anti-TNFα/endotoxin *Satapathy 2004*
- OLTx – successful but recurs *Contos et al 2001*


Probable NAFLD
Low
Fibrosis score
High
Fibrosis score
Treat metabolic syndrome:
Lifestyle measures
Metformin for T2DM
Statins/fibrates (if indicated)
? Angio II blockers for ↑ BP
Liver biopsy
NAFL
NASH
?discharge
observation/
screening
Improvement
(?how monitored)
Treat metabolic syndrome:
(+ varices & HCC screening
if advanced fibrosis)
"2nd-line therapy"
or RCT
No
Improvement