



脂肪肝的西醫藥治療

Western medicine treatment on fatty liver

Vincent Wong

黃煒燊

Institute of Digestive Disease

消化疾病研究所

香港中文大學醫學院

Faculty of Medicine

The Chinese University of Hong Kong

Disclosures

- Advisory board member: AbbVie, Gilead, Janssen, Otsuka, Roche
- Consultancy: Merck, Novomedica
- Speaker: Abbott, AbbVie, Echosens, Gilead, Novartis

Fatty liver



Less common causes:

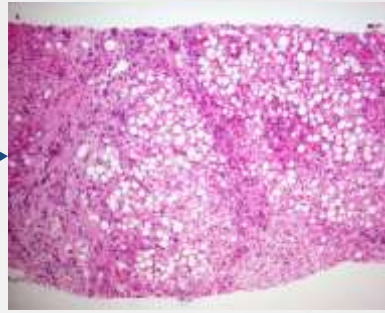
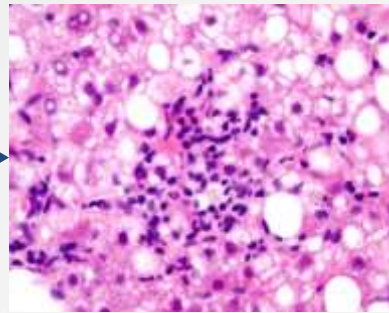
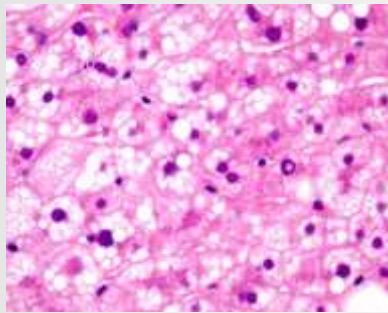
Drugs (e.g. methotrexate, steroids)

Rapid weight loss

Acute fatty liver of pregnancy

Non-alcoholic fatty liver disease (NAFLD)

The spectrum of disease

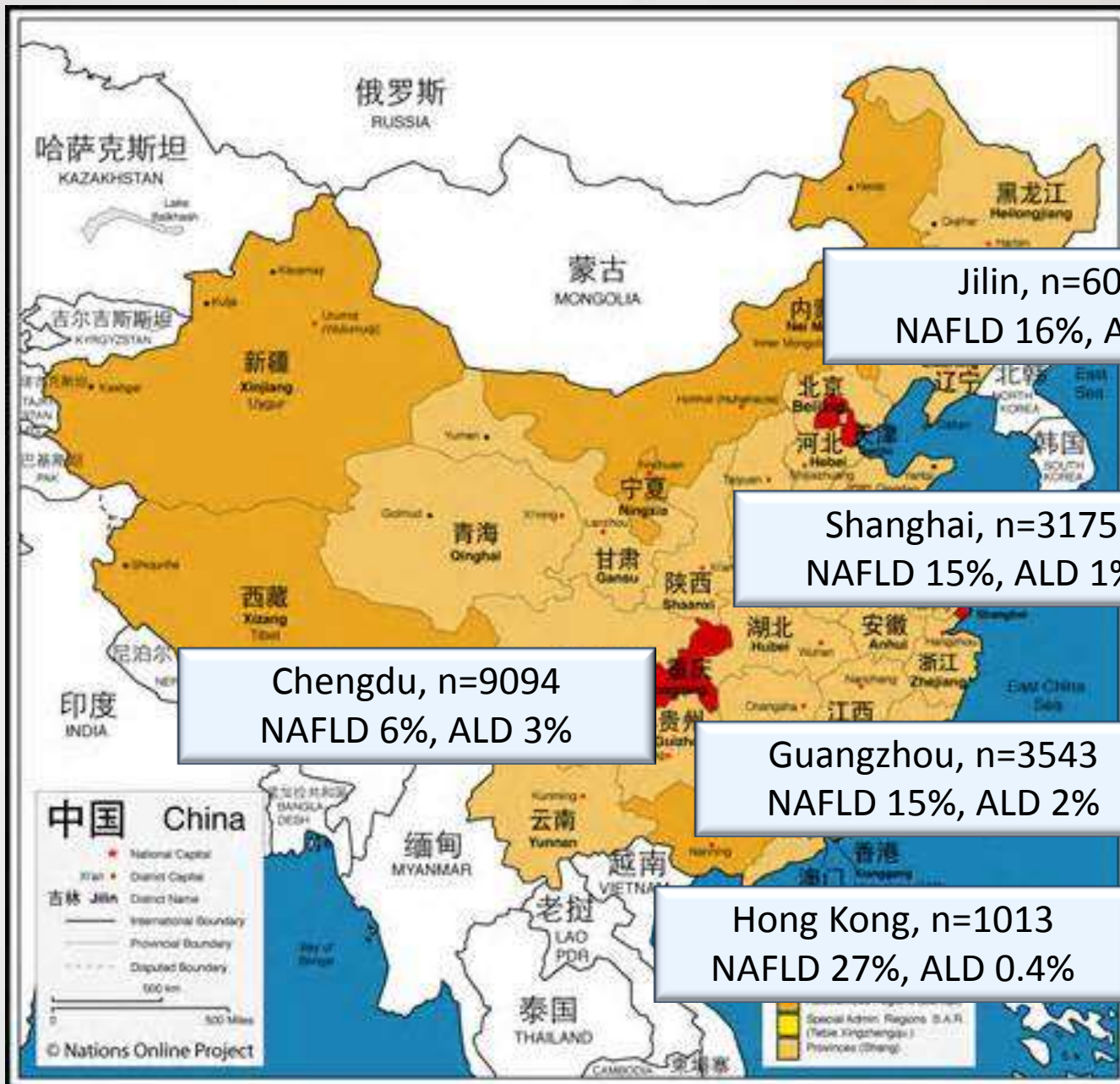


Non-alcoholic
fatty liver
(NAFL)

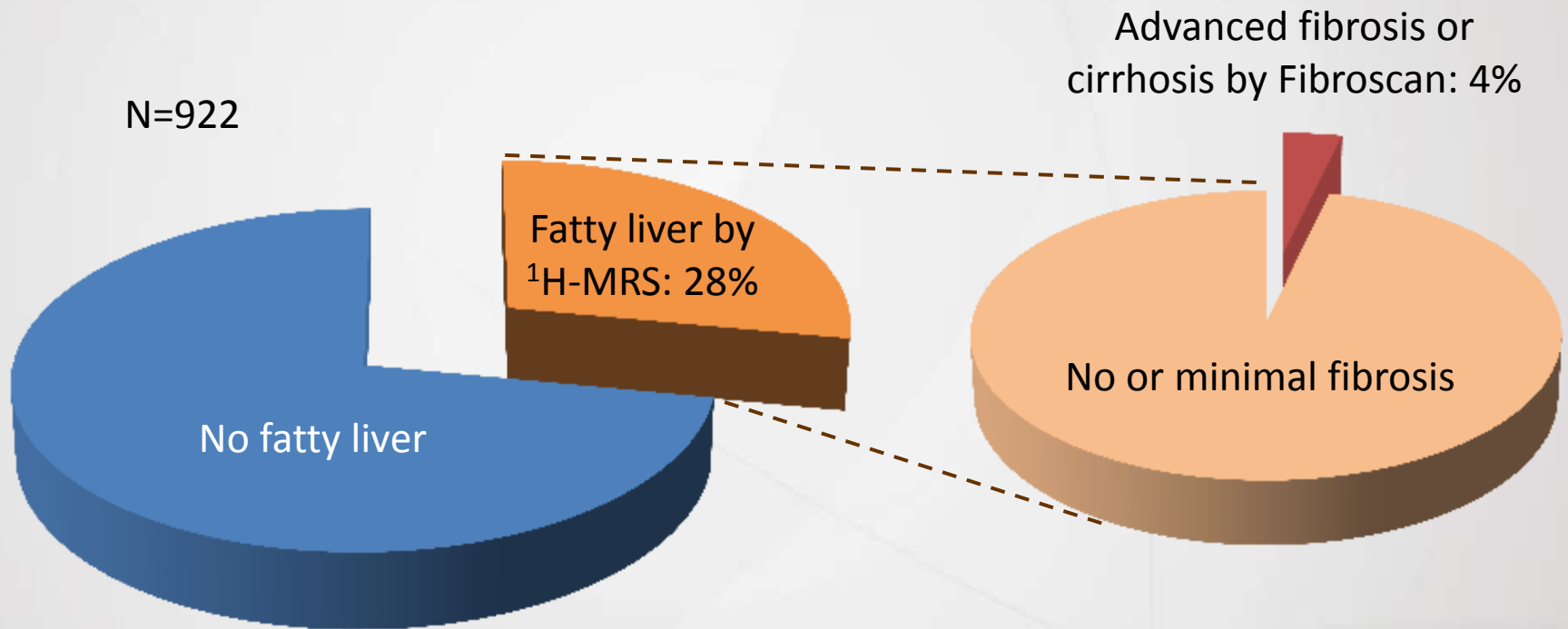
Non-alcoholic
steatohepatitis
(NASH)

Progressive
liver fibrosis

Cirrhosis

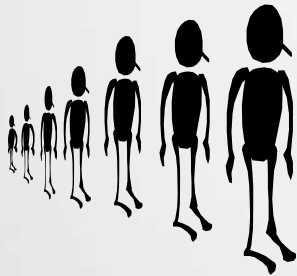
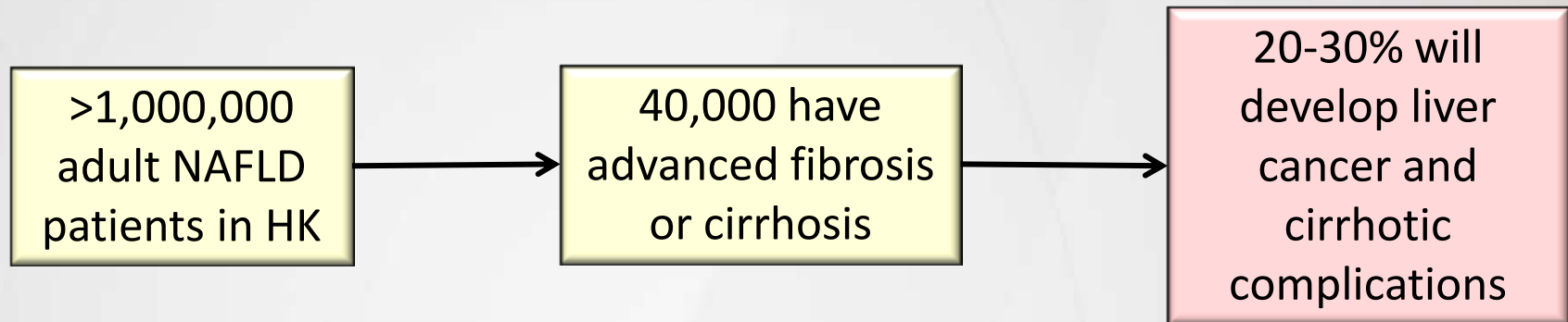


The HK-MRS Study



Wong VW et al. Gut 2012;61:409

Public health implications

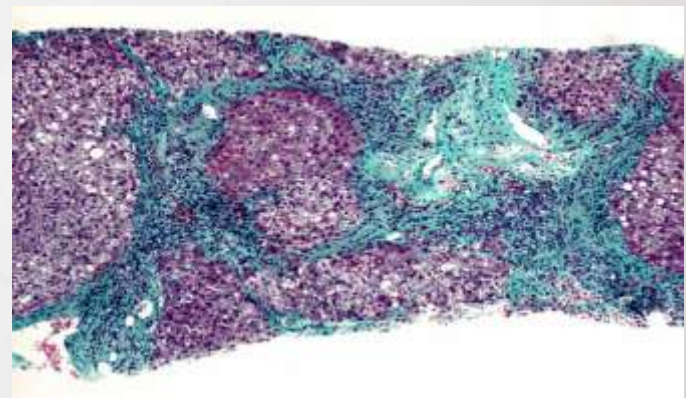
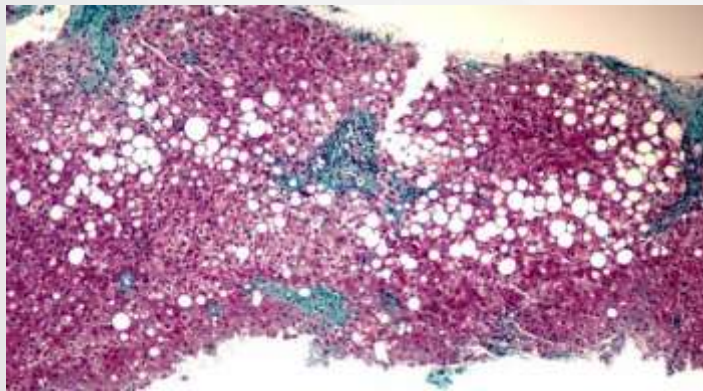
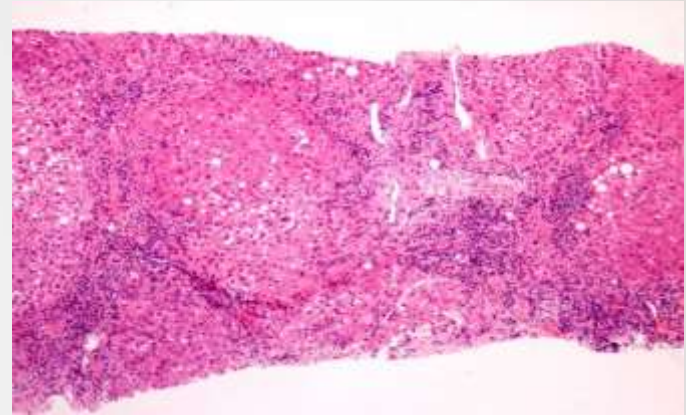
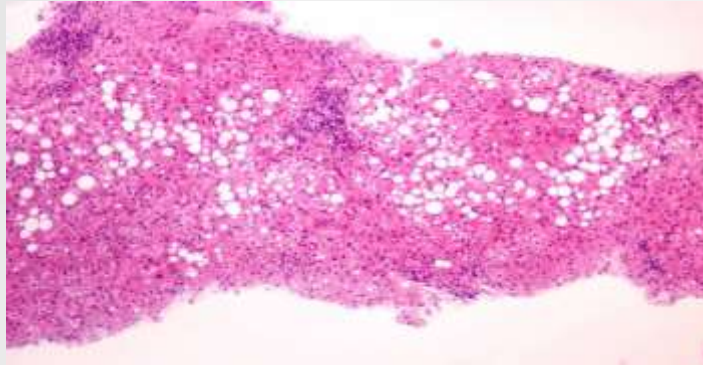


Fibrosis progression in NAFLD

Year 3	F0	F1	F2	F3	F4	Total
Baseline						
F0	17	7	0	1	1	26
F1	7	7	1	2	0	17
F2				1	1	7
F3				0	0	1
F4				0	1	1
Total	28	15	2	4	3	52

1/4 patients had increased liver fibrosis

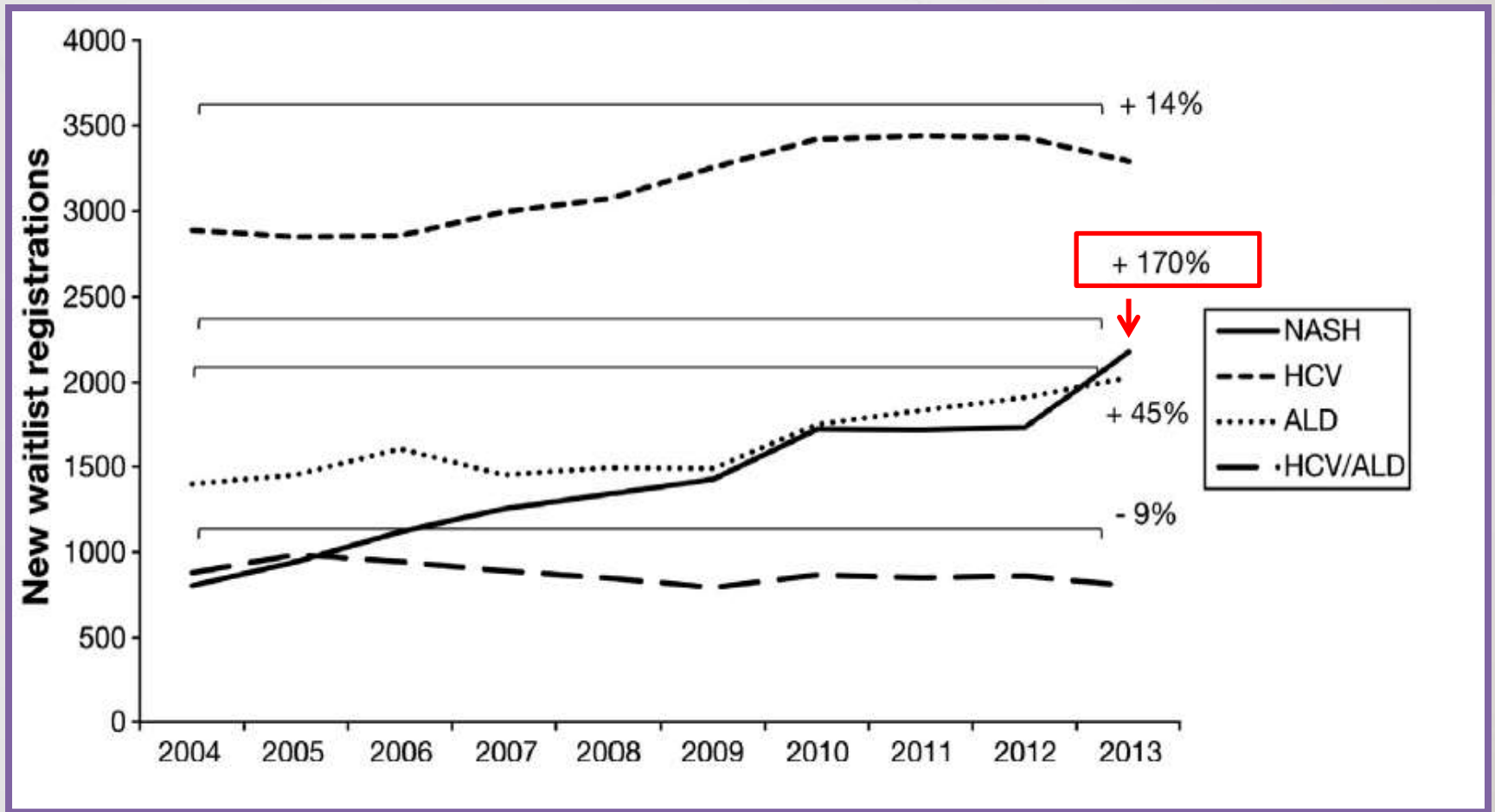
Histological progression of NAFLD



First Liver Biopsy

Second Liver Biopsy

Fatty liver has become the 2nd leading indication for liver transplantation in USA

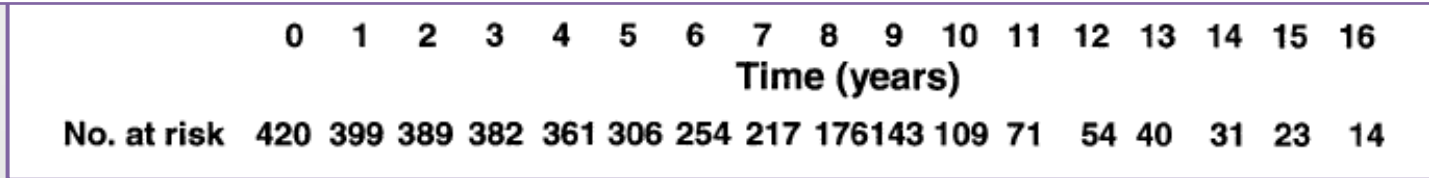


Mortality of NAFLD patients

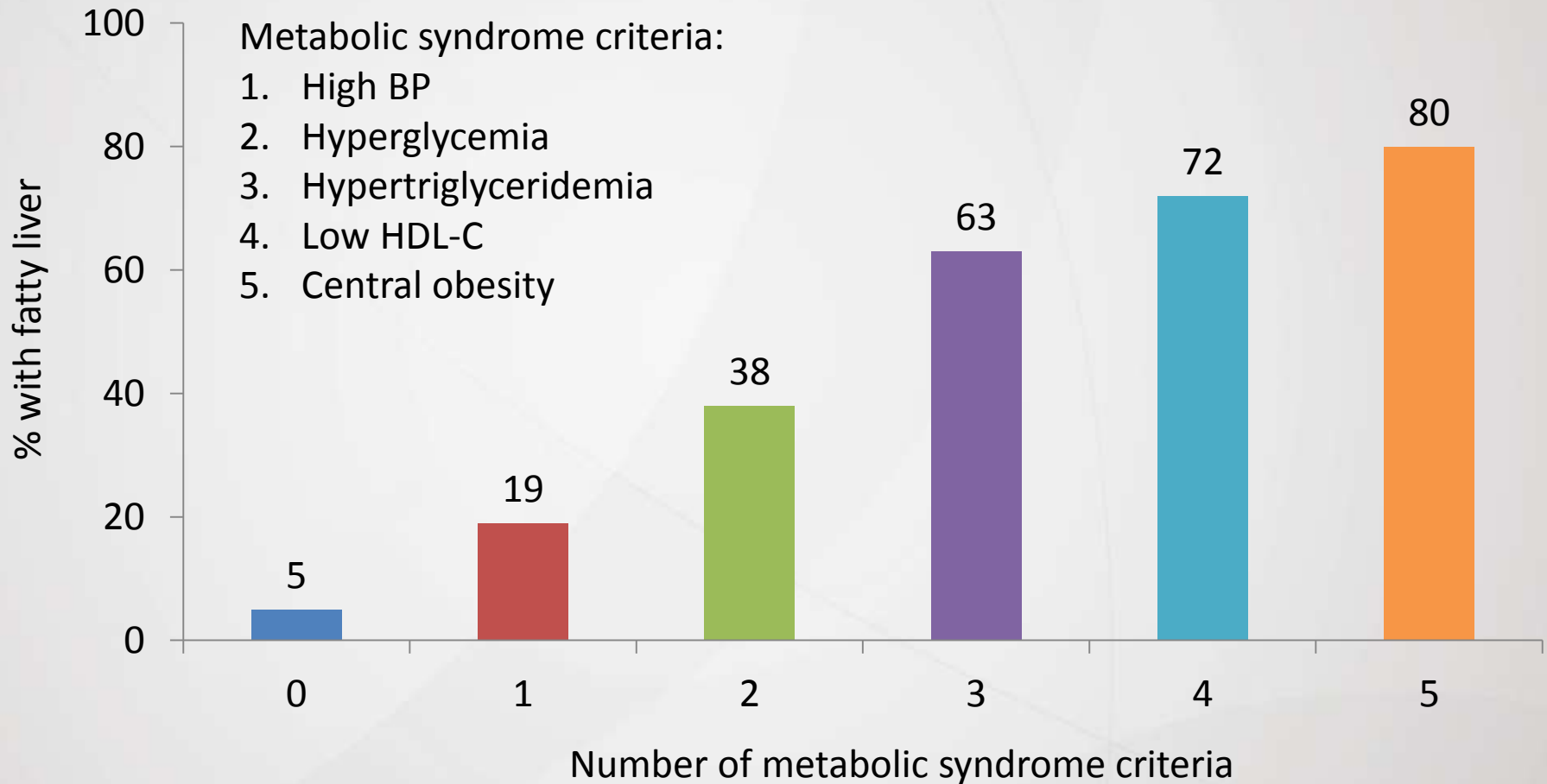


Causes of death (rank)

	Normal population	NAFLD patients
Malignancy	1	1
CVS disease	2	2
Liver disease	13	3



Metabolic syndrome and fatty liver



Investigations for suspected NAFLD

- Confirm the diagnosis
- Assess disease severity
- Associated cardiometabolic diseases

Diagnosis

- Bright liver under ultrasound
- Liver enzymes can be normal in >half of cases
- Exclude other liver diseases (e.g. viral hepatitis)

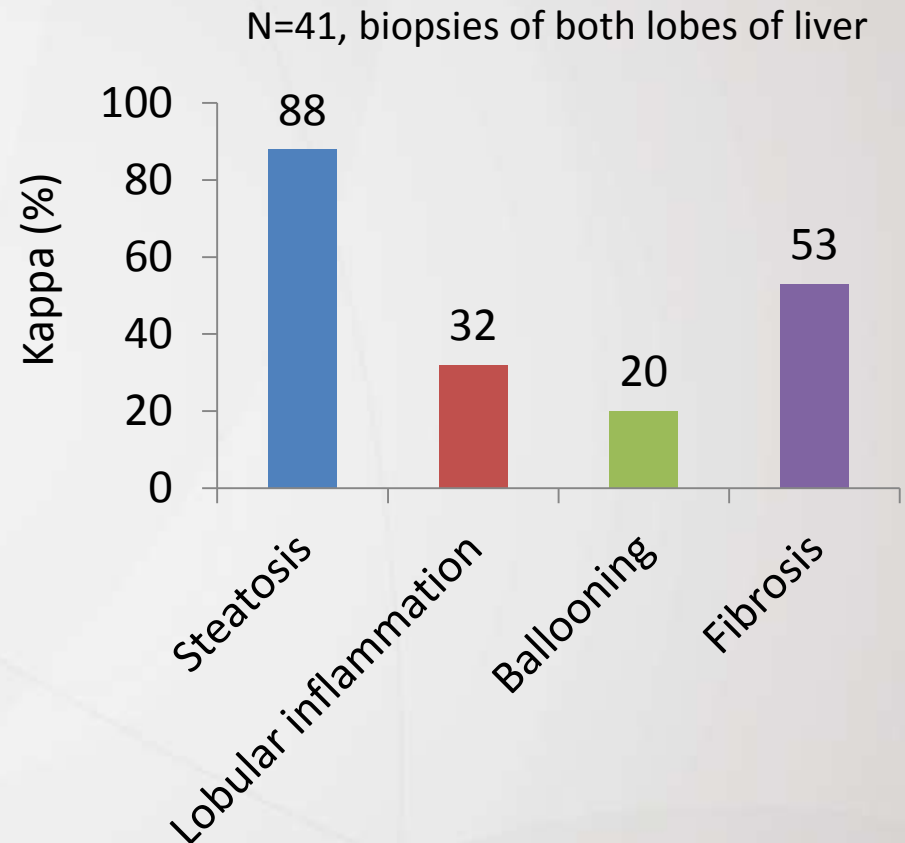


Diagnostic workup

- Minimal workup: HBsAg, anti-HCV
- Alcohol and drug history
- Less common liver diseases according to clinical presentation and local epidemiology

Problems of liver biopsy for the evaluation of NAFLD

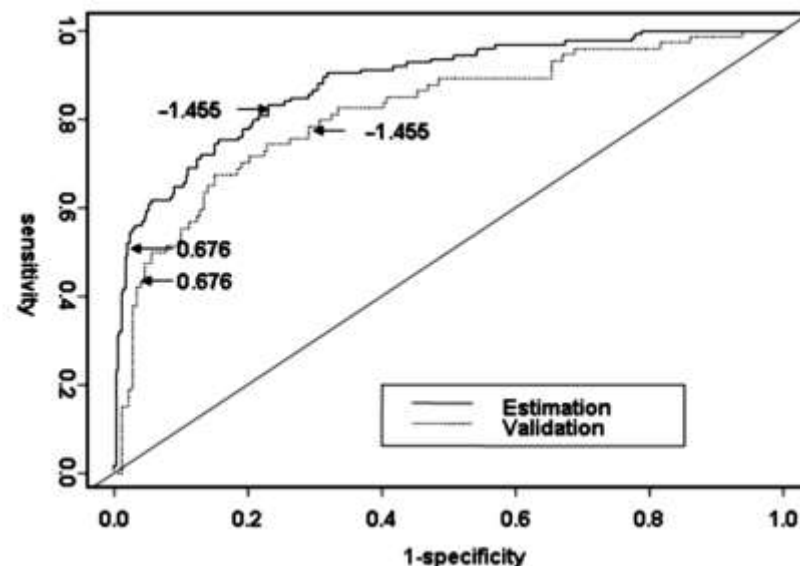
- Contraindications
 - Bleeding tendency
 - Ascites
- Complications
 - Pain
 - Bleeding
- Sampling error



NAFLD fibrosis score

- Derivation and validation in 733 NAFLD patients
- 6 parameters: age, hyperglycemia, BMI, platelet, albumin, AST/ALT ratio

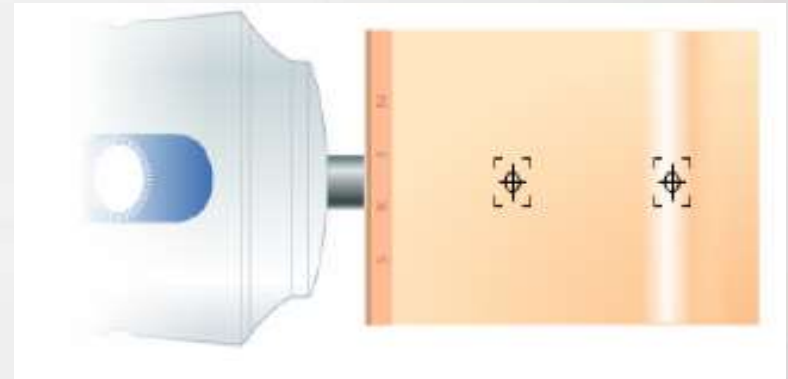
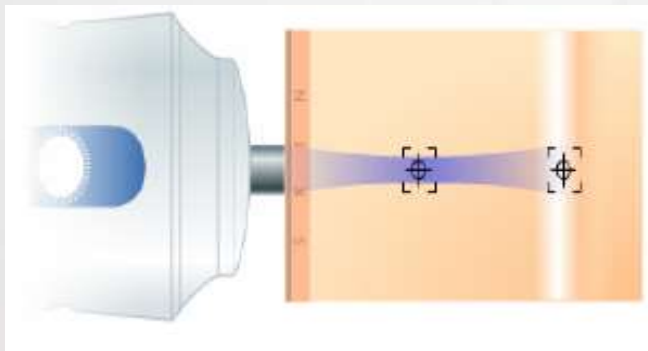
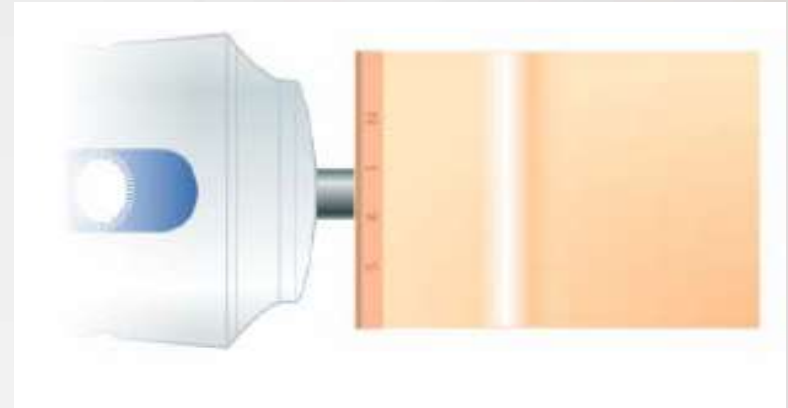
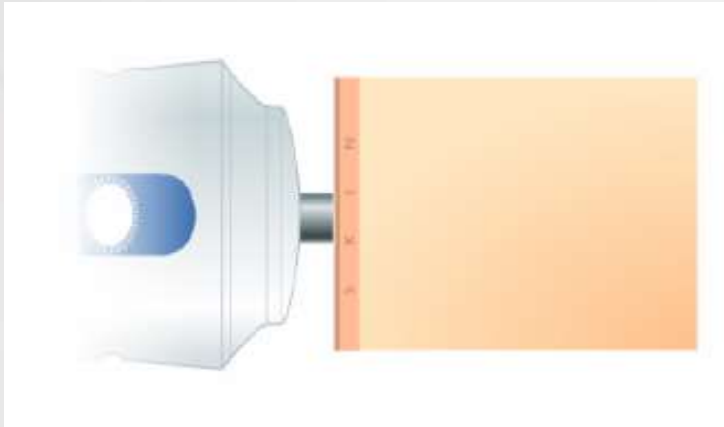
AUROC for F3 disease:
0.88 in estimation group
0.82 in validation group



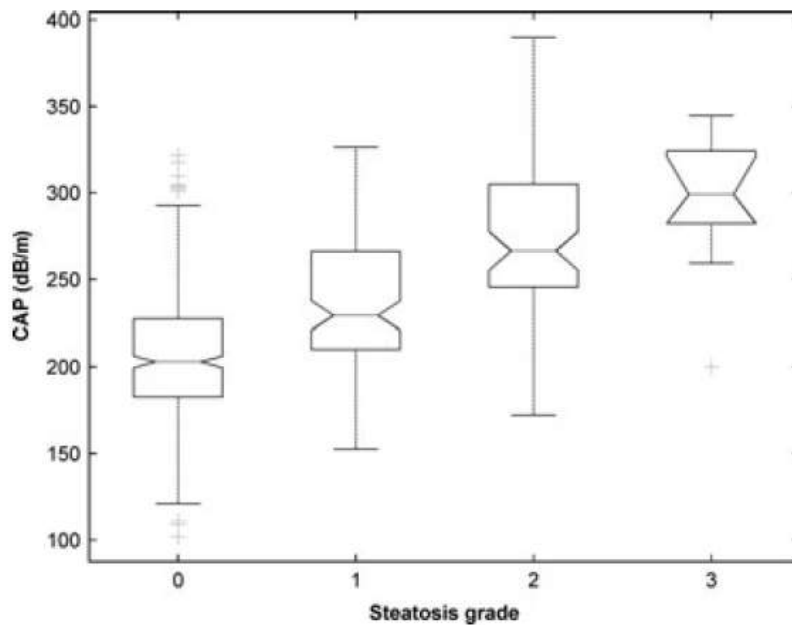
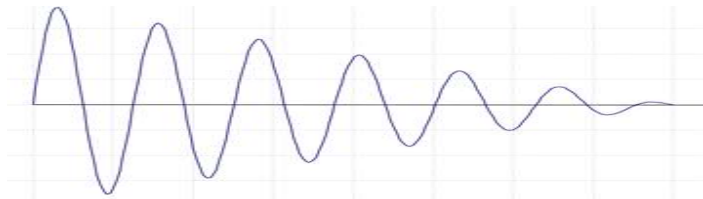
Transient elastography (FibroScan®)



Liver stiffness measurement (LSM)



Controlled attenuation parameter (CAP) and liver fat

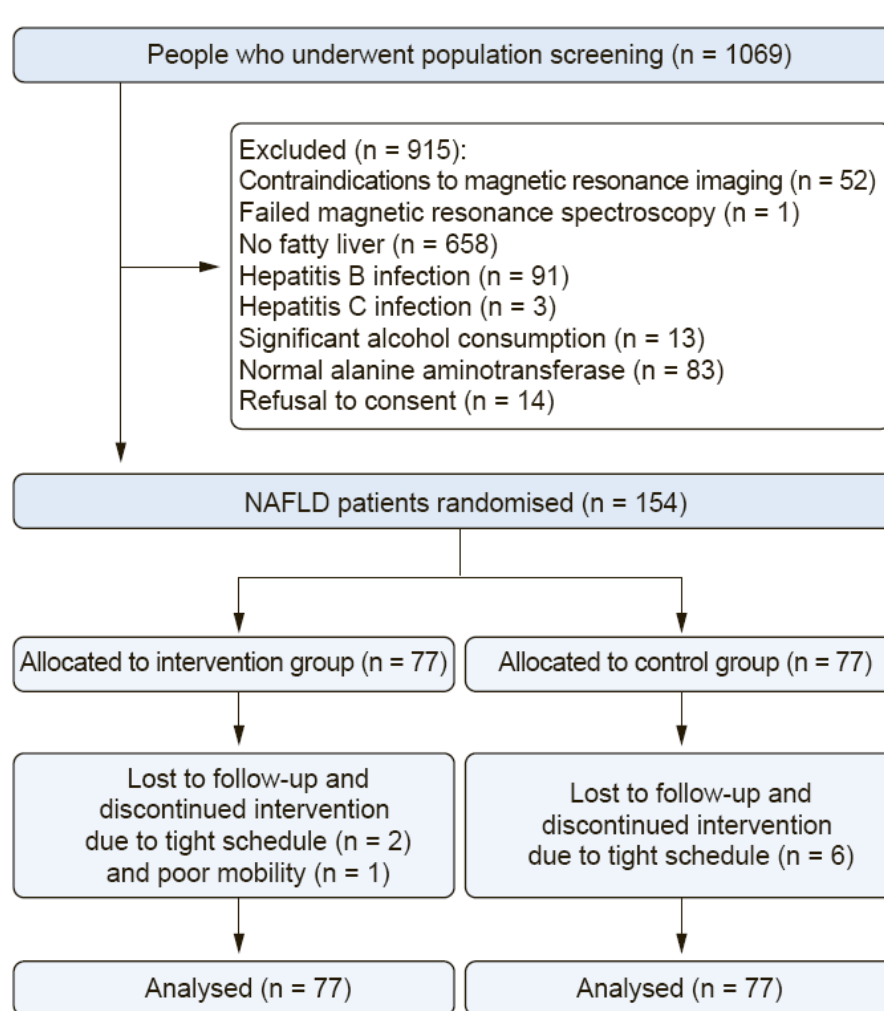


Steatosis	≥10%	≥33%	≥66%
AUROC	0.80	0.86	0.88
Cutoff	222	233	290
Sensitivity	76%	87%	78%
Specificity	71%	74%	93%

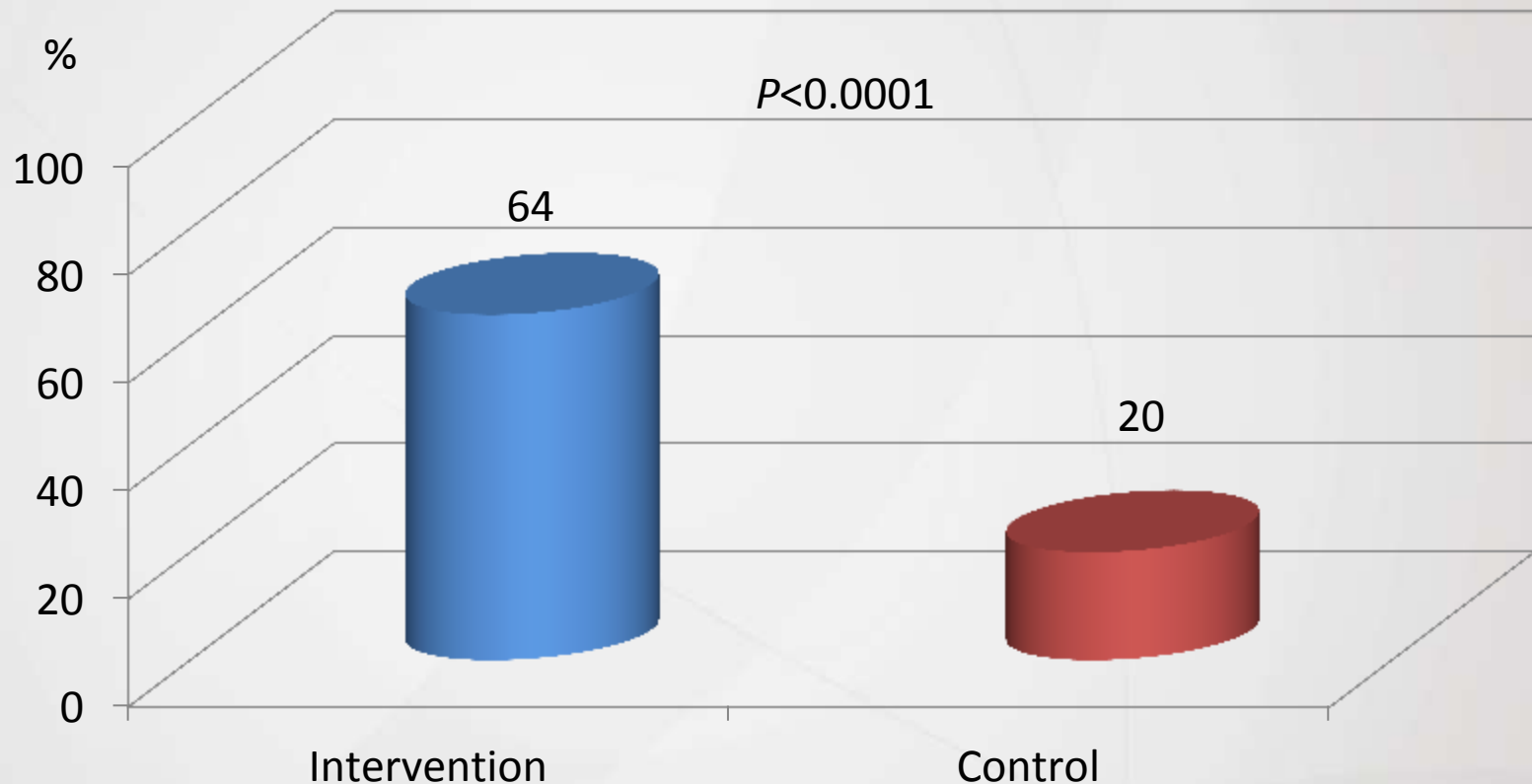
Treatment of NAFLD

- Lifestyle modification, weight reduction
- Treat associated metabolic disorders (statin is safe)
- Pharmacological treatment for NASH
- Bariatric surgery if morbidly obese

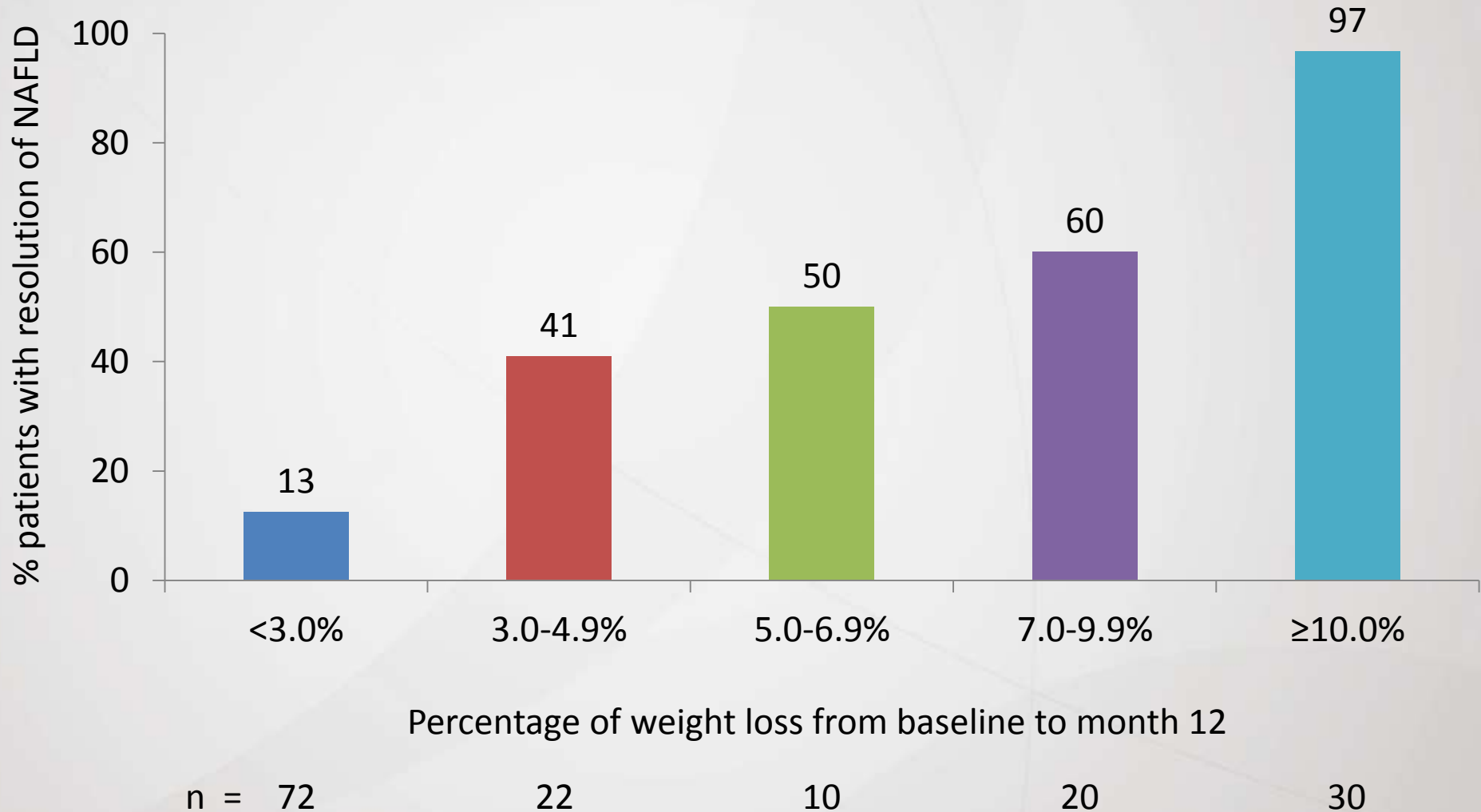
NAFLD-Diet Study



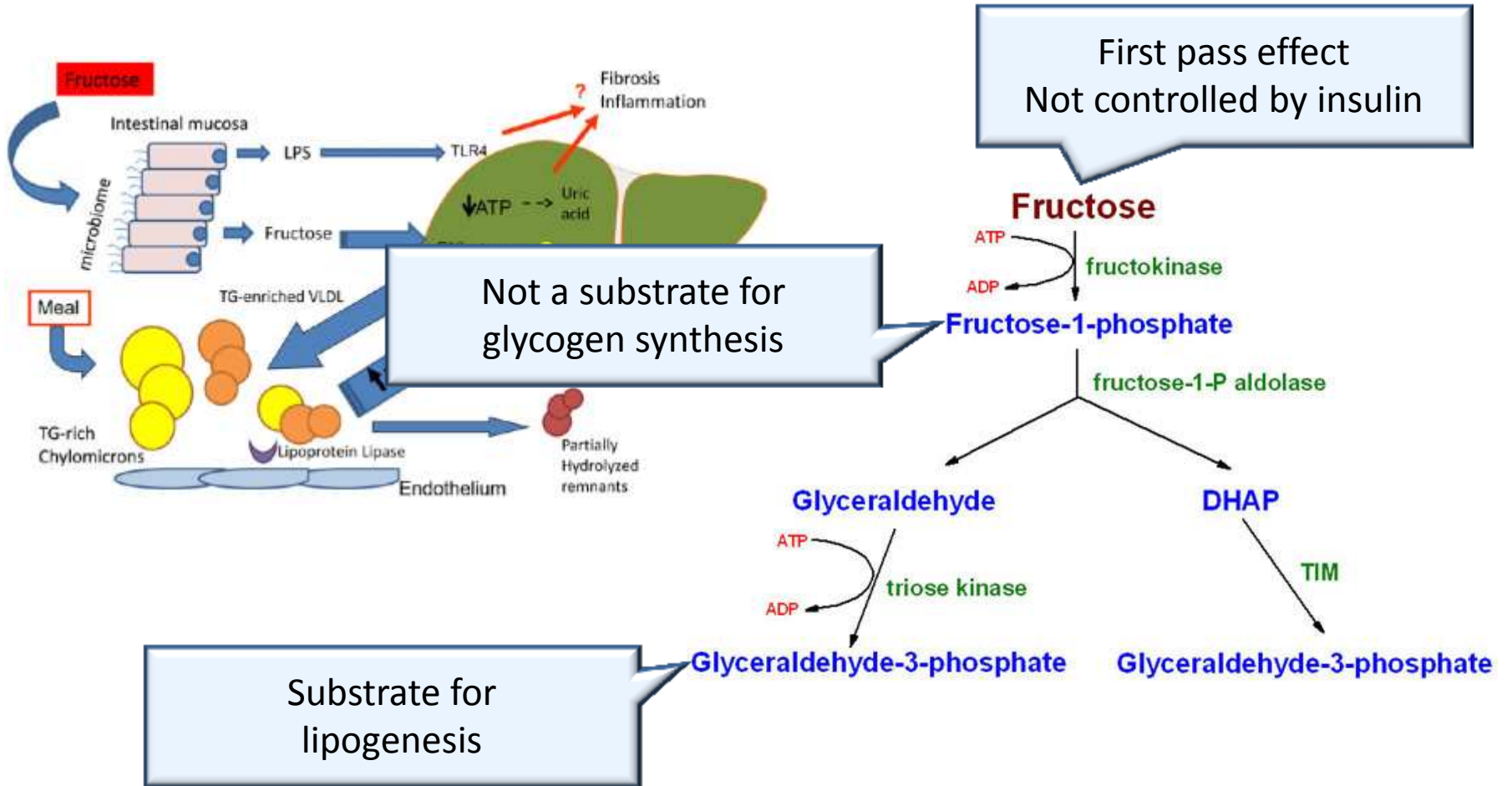
Proportion of patients with resolved NAFLD



Degree of weight loss and remission of NAFLD



Fructose and NAFLD



Pharmacological treatment of NASH

Vitamin E

- Anti-oxidant
- Reduces liver fat and inflammation
- Neutral effects on insulin resistance
- Uncertain effects on the cardiovascular system and malignancy

Pioglitazone

- Insulin sensitizer
- Reduces liver fat and inflammation
- Causes weight gain \pm fluid retention
- May increase the risk of bladder cancer

ORIGINAL ARTICLE

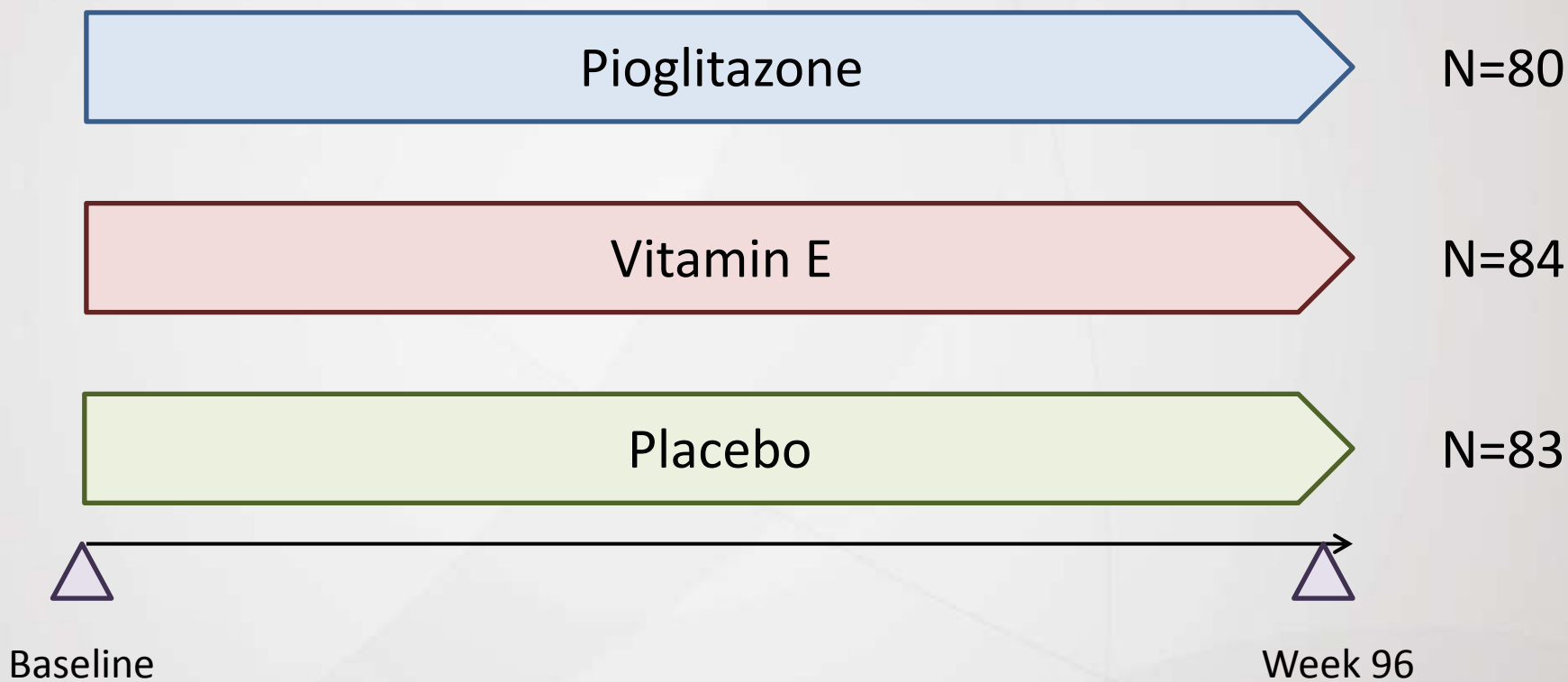
Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

Arun J. Sanyal, M.D., Naga Chalasani, M.B., B.S., Kris V. Kowdley, M.D.,
Arthur McCullough, M.D., Anna Mae Diehl, M.D., Nathan M. Bass, M.D., Ph.D.,
Brent A. Neuschwander-Tetri, M.D., Joel E. Lavine, M.D., Ph.D.,
James Tonascia, Ph.D., Aynur Unalp, M.D., Ph.D., Mark Van Natta, M.H.S.,
Jeanne Clark, M.D., M.P.H., Elizabeth M. Brunt, M.D.,
David E. Kleiner, M.D., Ph.D., Jay H. Hoofnagle, M.D.,
and Patricia R. Robuck, Ph.D., M.P.H., for the NASH CRN*

NEJM 2010;362:1675

PIVENS Study

247 patients with biopsy-proven NASH

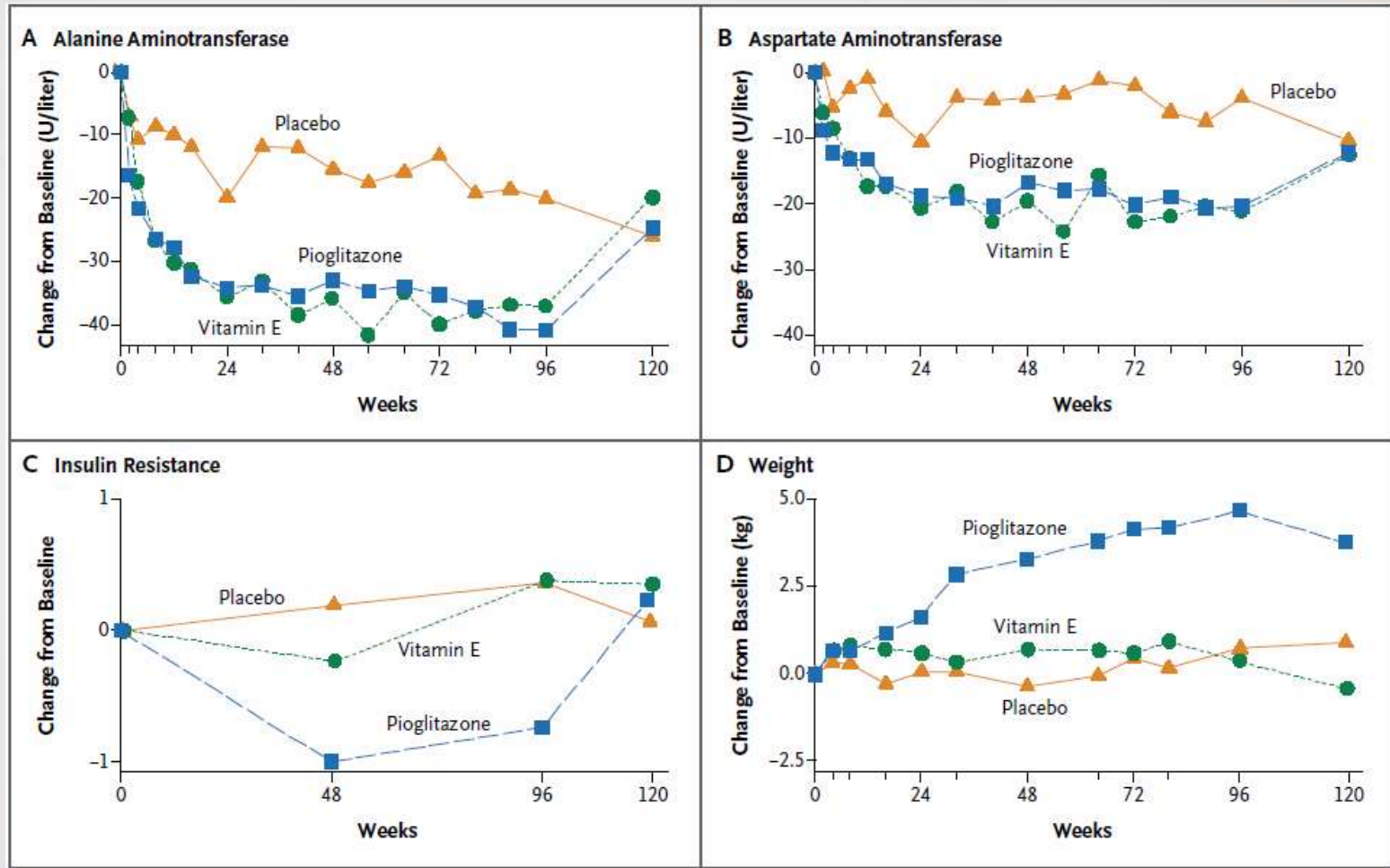


Histological changes at 96 weeks

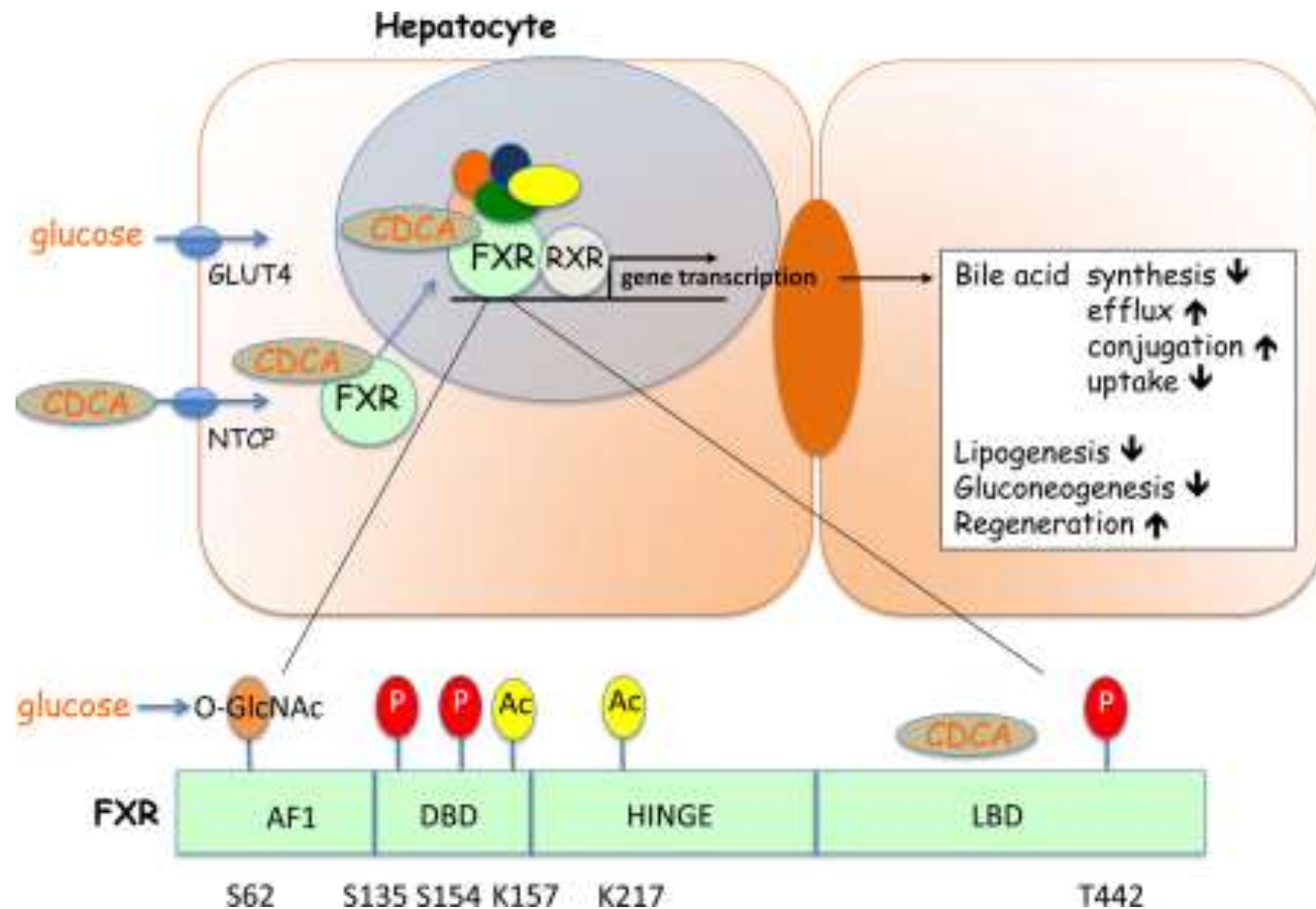
Variable	Placebo	Vitamin E	Pioglitazone	P (Vitamin E vs placebo)	P (Pioglitazone vs placebo)
Primary outcome*	19%	43%	34%	0.001	0.04
Improvement in steatosis	31%	54%	69%	0.005	<0.001
Improvement in lobular inflammation	35%	54%	60%	0.02	0.004
Improvement in ballooning	29%	50%	44%	0.01	0.08
Improvement in fibrosis	31%	41%	44%	0.24	0.12
Resolution of NASH	21%	36%	47%	0.05	0.001

* Improvement of ballooning by ≥ 1 point; no increase in fibrosis; NAFLD activity score declines by ≥ 2 points or to ≤ 3 points

Biochemical and weight changes



Farnesoid X receptor (FXR)

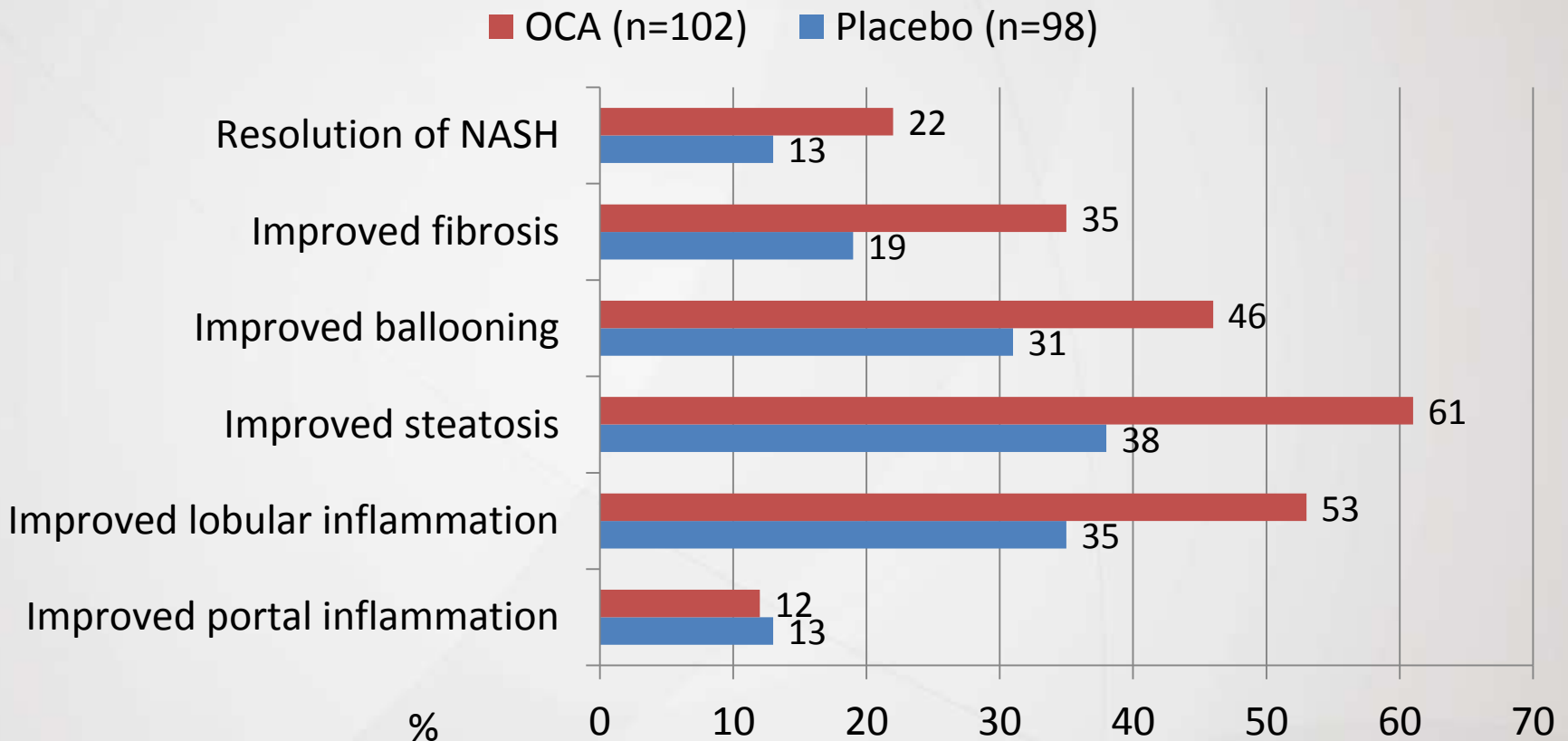


FXR agonist in NAFLD and T2DM

	Placebo (n=23)		25 mg OCA (n=20)			50 mg OCA (n=21)		
	Baseline	D43	Baseline	D43	P	Baseline	D43	P
ALT (U/L)	37	48	41	31	0.003	36	46	0.84
TC (mg/dL)	166	174	163	181	0.08	170	183	0.15
LDL-C (mg/dL)	98	107	98	120	0.01	104	129	0.008
HDL-C (mg/dL)	40	40	37	35	0.42	43	37	0.01
TG (mg/dL)	178	178	193	170	0.09	156	120	0.02
ELF	8.2	8.5	8.4	8.2	0.004	8.0	8.1	0.21

Mudaliar et al. Gastroenterology 2013;145:574

FLINT Study: Obeticholic acid for NASH



Take home messages

- NAFLD is the most common chronic liver disease worldwide and is emerging to be an important cause of cirrhosis and liver cancer.
- NAFLD is strongly associated with metabolic syndrome, cardiovascular disease and malignancy.
- Apart from diagnosis and risk stratification, it is important to detect and manage the associated metabolic disorders.
- Vitamin E and pioglitazone may be considered in selected NASH patients.

Thank you!



Vincent Wong
Institute of Digestive Disease
The Chinese University of Hong Kong
E-mail: wongv@cuhk.edu.hk