

Paris Hepatology Conference

NASH: Optimal Management

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Disclosures

- Advisory boards for Gilead, Intercept, Pfizer, Promethera, GMP Orphan
- Speaker fees from Dr Falk, Gilead, Intercept

Do you have a dedicated NAFLD clinic?

- Yes
- No

Do you have MDT input in the clinic?

- Yes
- No

Clinical case

- Mr PC, 45 year old Accountant
- First seen Sep 2015
- PMH: Hypertension, hyperlipidaemia, type 2 DM
- Coronary angiogram 2010, 40-50% LAD stenosis
- Recent diabetic retinopathy

Clinical case

- Family history: Brother fatal MI at 41, father CKD
- No alcohol, never smoker
- Prescribed losartan, metformin, aspirin, simvastatin
- Not taking any of his medications but trying lifestyle interventions instead!

Investigations

Variable	Value
Weight, Kg	131
BMI, Kg/m ²	41.3
Blood Pressure, mm Hg	156/72
ALT, U/L	43
AST, U/L	27
Platelet count	273
HBA1C, mmol/mol	59.2
Total cholesterol, mmol/L	4.7
LDL cholesterol, mmol/L	2.7

Profile

Heart Age

Healthy Years

Outlook

more

Profile

Date of Birth: Day: 1 Month: 1 Year: 1975

Gender: ☒ male ☐ female

Ethnic group: Chinese

Height (m): 1.80 5' 11" (71.0") Weight (kg): 130.7 29st 8 (288 lb) BM: 40.3

Townsend quintile (3 if unknown): 3: Average



I have never suffered from Cardiovascular Disease ☒

I have read the terms and conditions ☒

Do you smoke? No

Total Cholesterol: 6.2 mmol/L

HDL Cholesterol: 1.2

NonHDL Cholesterol: 5.0

Systolic Blood Pressure: 156 mm Hg

Have you received blood pressure treatment? ☒

Do you suffer from diabetes? ☒

Does a close relative under 60 suffer from CVD? ☒

Do you have a chronic kidney disease? ☐

Have you suffered atrial fibrillation? ☐

Do you have rheumatoid arthritis? ☐

Save

Load

Next

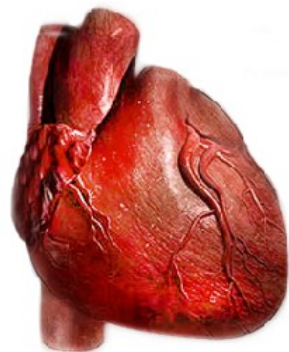
Profile

Heart Age

Healthy Years

Outlook

more



Your heart age is about
67

compared to a person of the same age, gender
and ethnicity with optimal risk factors

Interventions

Future smoking category

No

Systolic Blood Pressure

156

→

156

Total Cholesterol

6.2

→

6.2

HDL Cholesterol

1.2

→

1.2

NonHDL Cholesterol: 5.0

BMI: 40.3

Reset

Profile

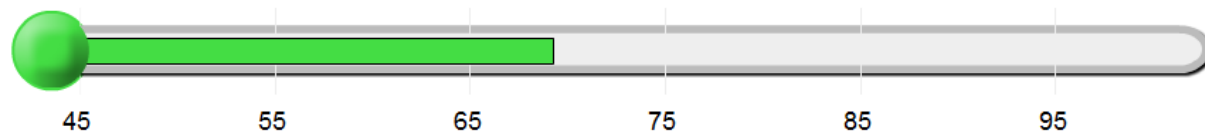
Heart Age

Healthy Years

Outlook

more

On average, expect
to survive to age 69
without a heart attack or stroke



expected life without a heart attack or stroke

Your risk of a heart attack or stroke
in the next 10 years is
13%

assuming you don't die of anything else

Interventions

Future smoking category

No

Systolic Blood Pressure

156

156

Total Cholesterol

6.2

6.2

HDL Cholesterol

1.2

1.2

NonHDL Cholesterol: 5.0

BMI: 40.3

Reset

Profile

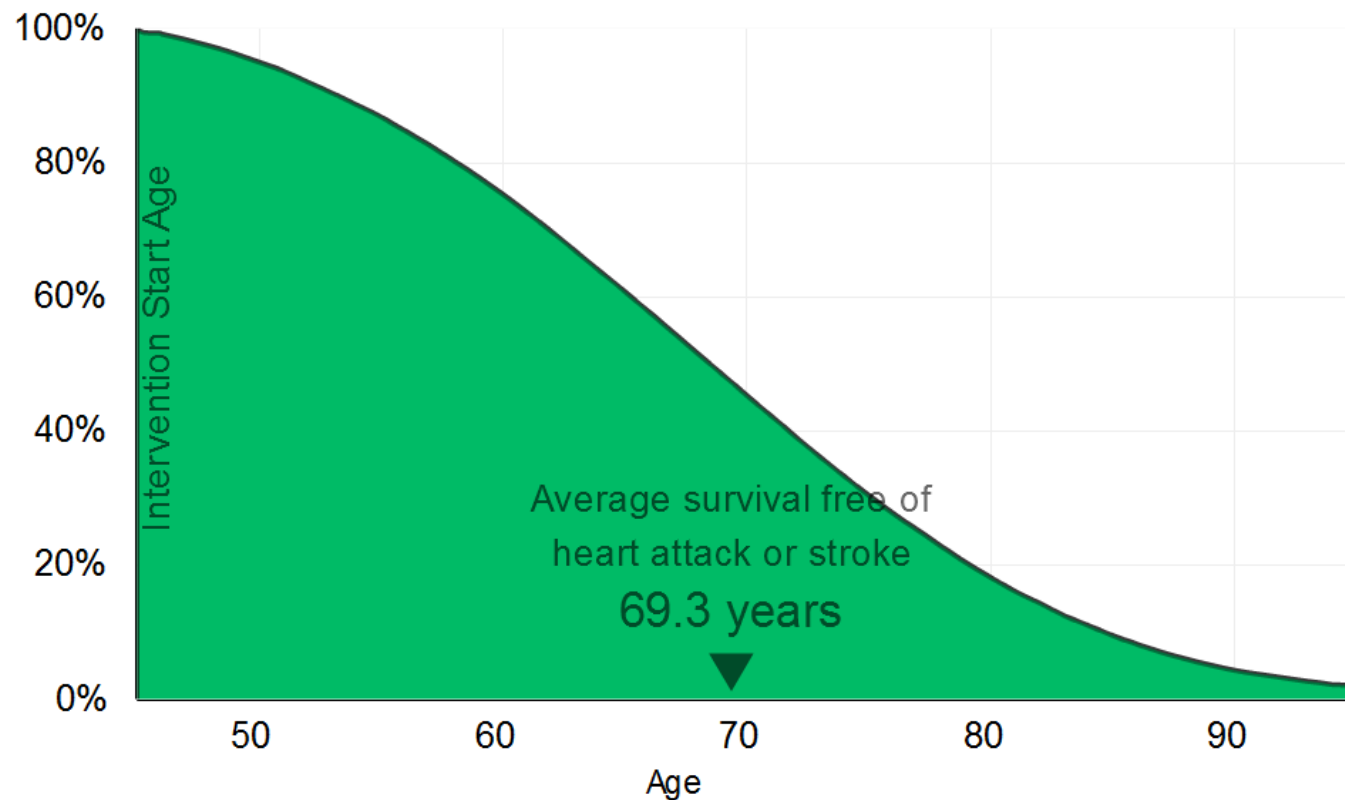
Heart Age

Healthy Years

Outlook

more

% Chance of survival free of Heart Attack or Stroke



Interventions

Future smoking category

No

Systolic Blood Pressure

156 → 156

Total Cholesterol

6.2 → 6.2

HDL Cholesterol

1.2 → 1.2

NonHDL Cholesterol: 5.0

BMI: 40.3

Intervention start age 45

Reset

Non-invasive fibrosis assessment

- FIB-4 score 0.88
- Fibroscan 8.1 KPa
- Shear wave elastography 7.8 KPa

Would you perform a biopsy?

- Yes
- No

Diagnostic accuracy of Fibroscan

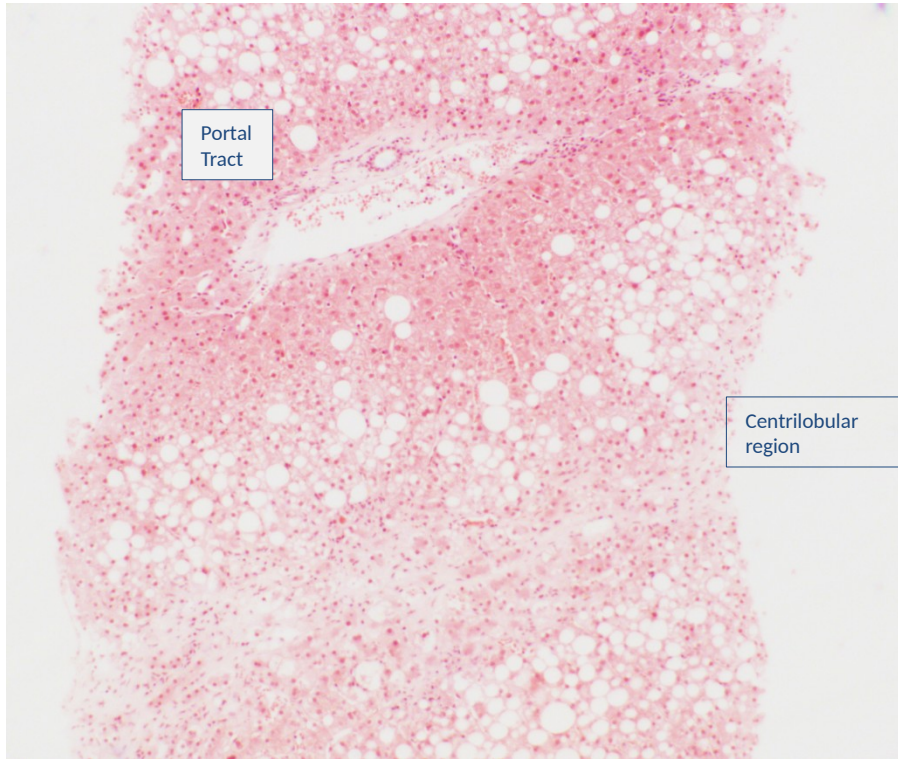
Prospective UK study, 450 patients

Fibrosis stage	Cut-off	Sensitivity	Specificity	Cut-off 90% Se	Cut-off 90% Sp
≥F2	8.2	0.71	0.70	6.1	12.1
≥F3	9.7	0.71	0.75	7.1	14.1
F4	13.6	0.85	0.79	10.9	20.9

Clinical course

- Patient had US guided liver biopsy
- Stopped aspirin 7 days prior to procedure
- Developed 10 minutes CCP post procedure, no ECG changes, Troponin negative
- Angiogram – eccentric moderate to severe LAD stenosis
- LAD stents placed

Biopsy 2016

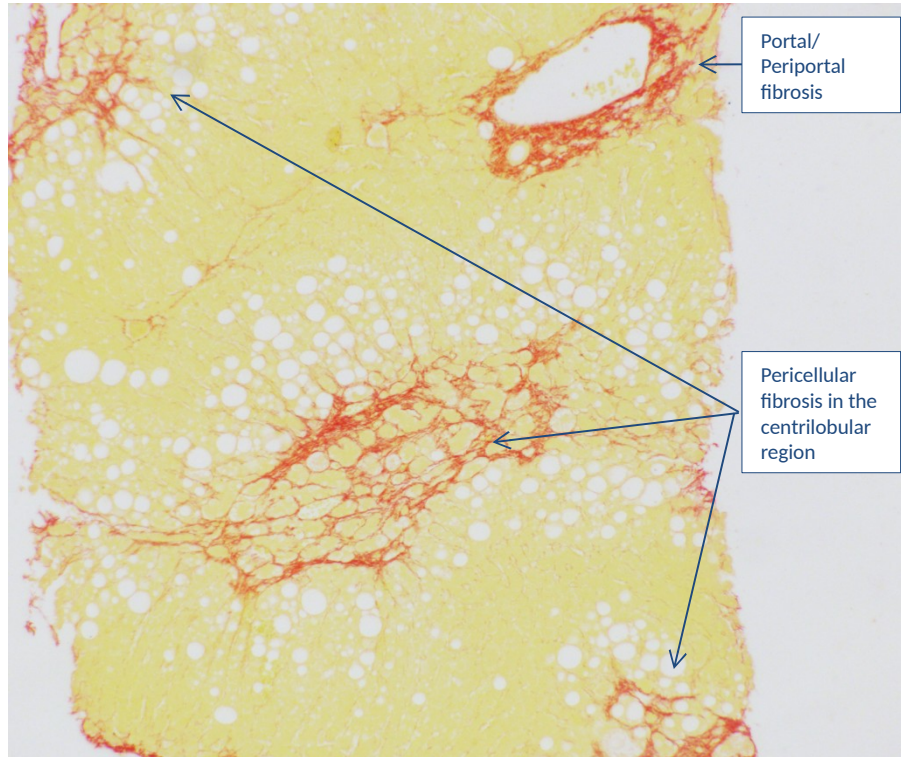


H&E

Steatosis, hepatocellular ballooning and a minimal inflammatory cell infiltrate. Steatosis is predominantly centro-mid lobular with a tendency to spare the periportal region

*Courtesy of Mr Andrew Hall and Prof Alberto Quaglia
Department of Cellular Pathology
Royal Free London*

Biopsy 2016

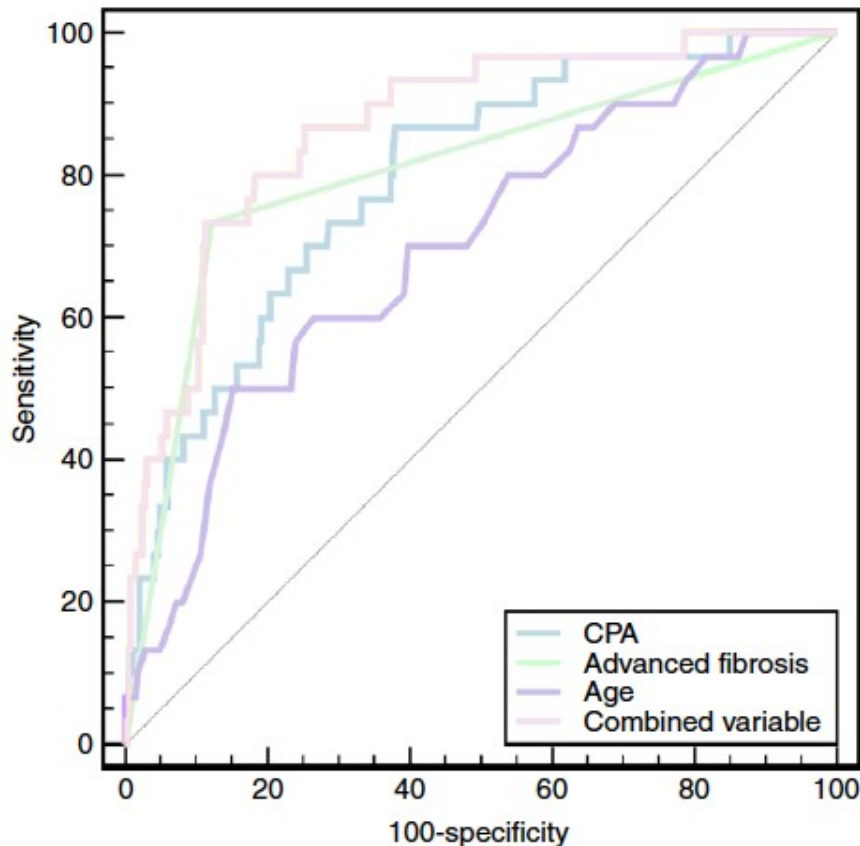


Picrosirius red

Fibrosis is portal/periportal and centrilobular/pericellular. Collagen proportionate area 5%.

*Courtesy of Mr Andrew Hall and Prof Alberto Quaglia
Department of Cellular Pathology
Royal Free London*

CPA and long term outcomes



437 patients with LBx
9 years follow up
32 (7.3%) decompensating events
56 (12.8%) deaths
16 (3.6%) liver-related deaths
Age, CPA, fibrosis predicted events

Next steps?

Structured dietetic program?

Bariatric surgery?

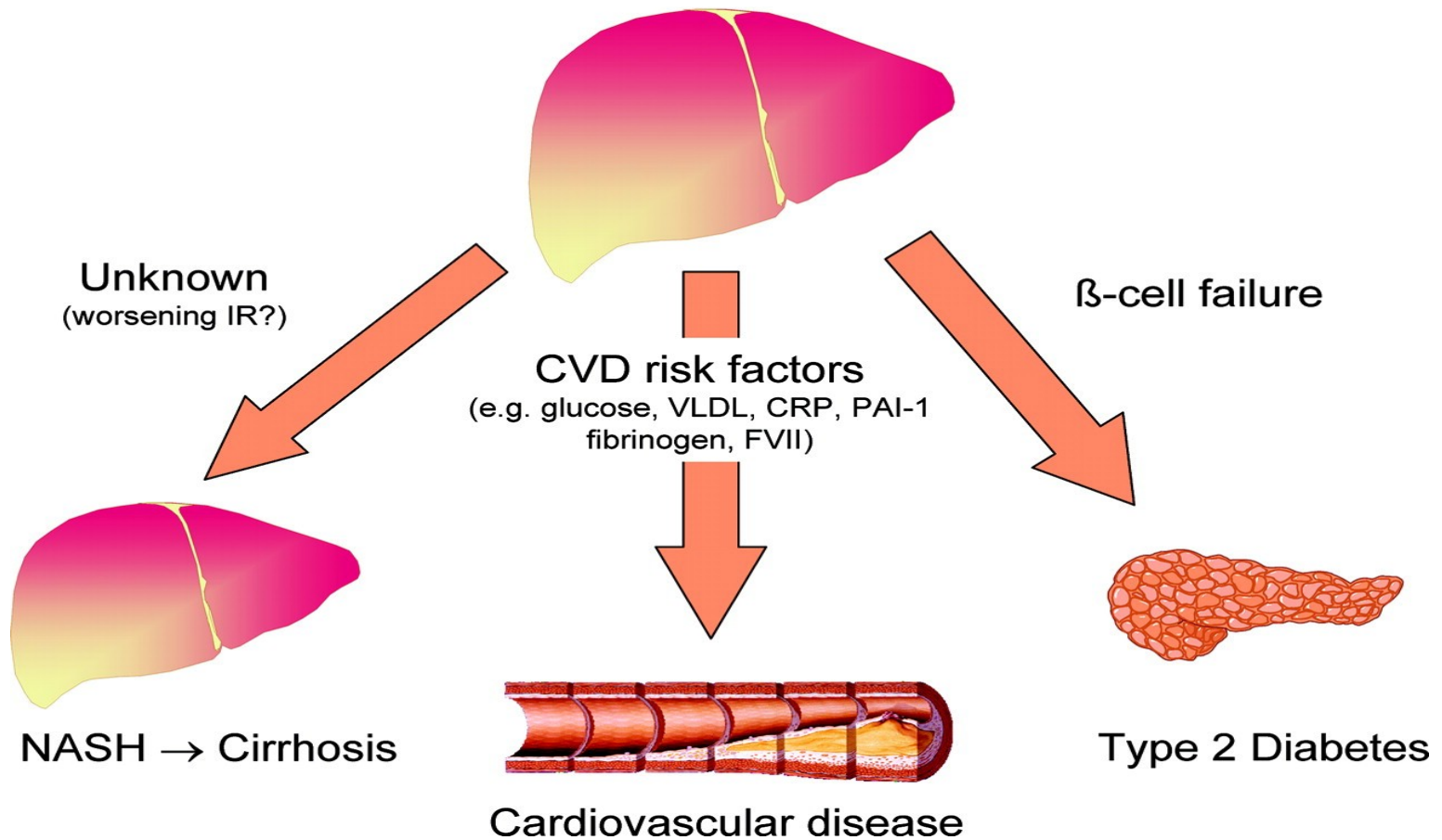
Vitamin E?

Liraglutide?

Pioglitazone?

NASH clinical trial?

NAFLD: consequences



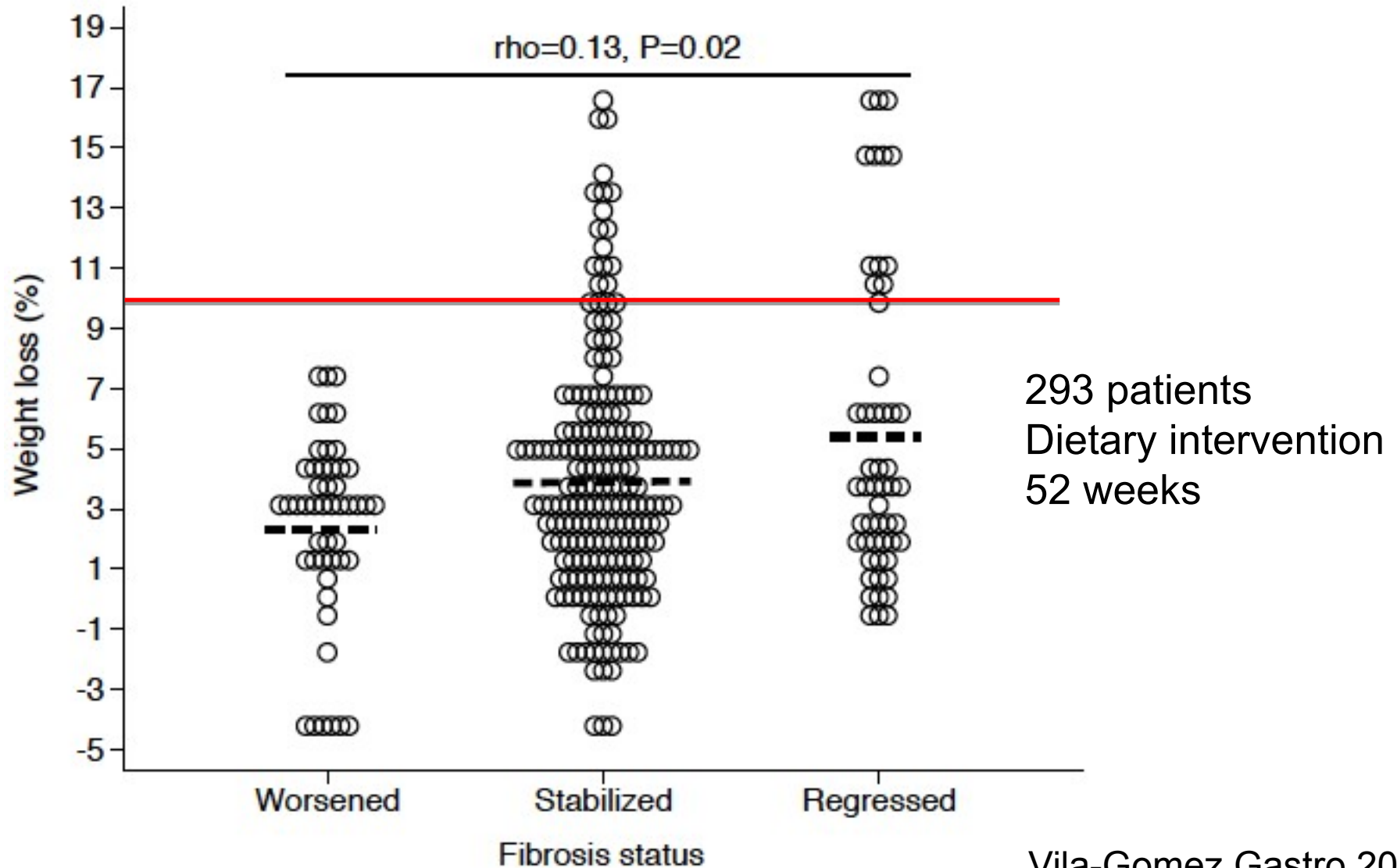
NASH and mortality

- CVS main cause of death
- Liver disease only 3d cause of mortality

Treatment goals in NAFLD

- >10% weight loss
- Lifestyle advice (diet and physical exercise)
- Treat components of metabolic syndrome
(hypertension, diabetes, hyperlipidaemia)
- Smoking cessation

Weight loss improves NASH and fibrosis



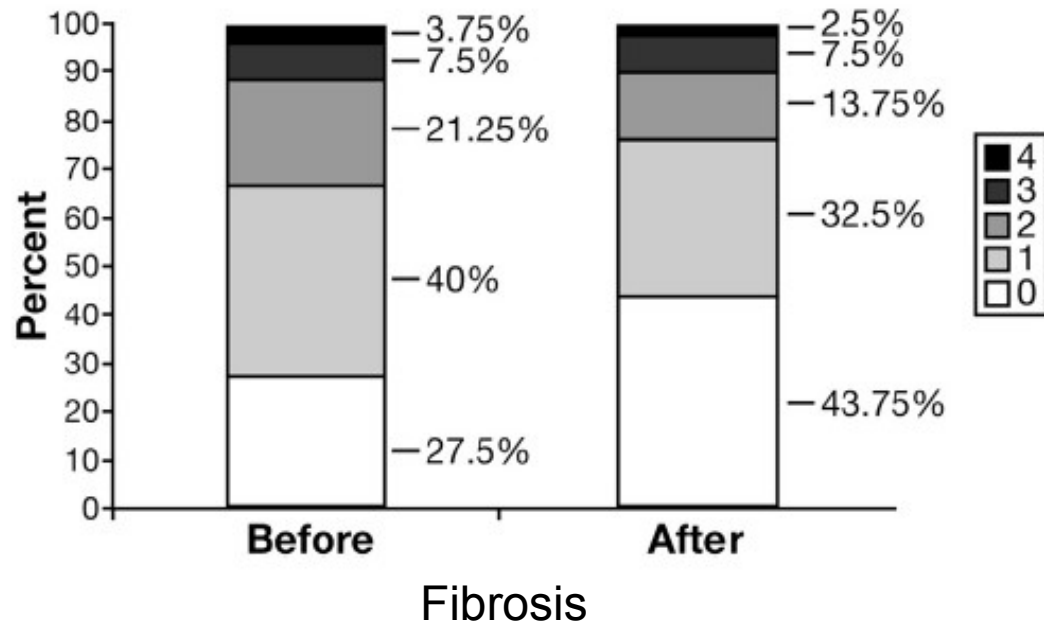
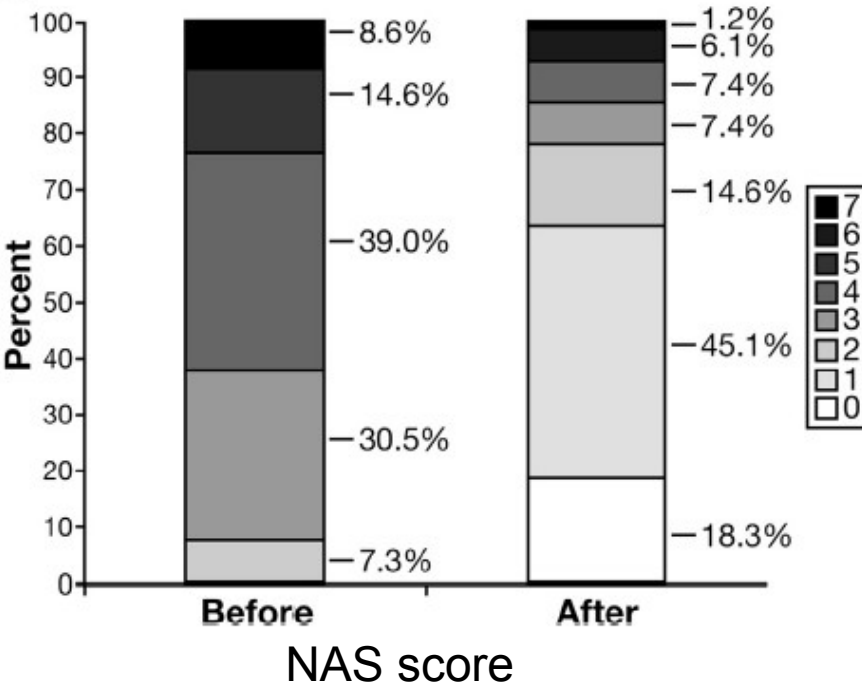
NASH and bariatric surgery

109 morbid obese patients

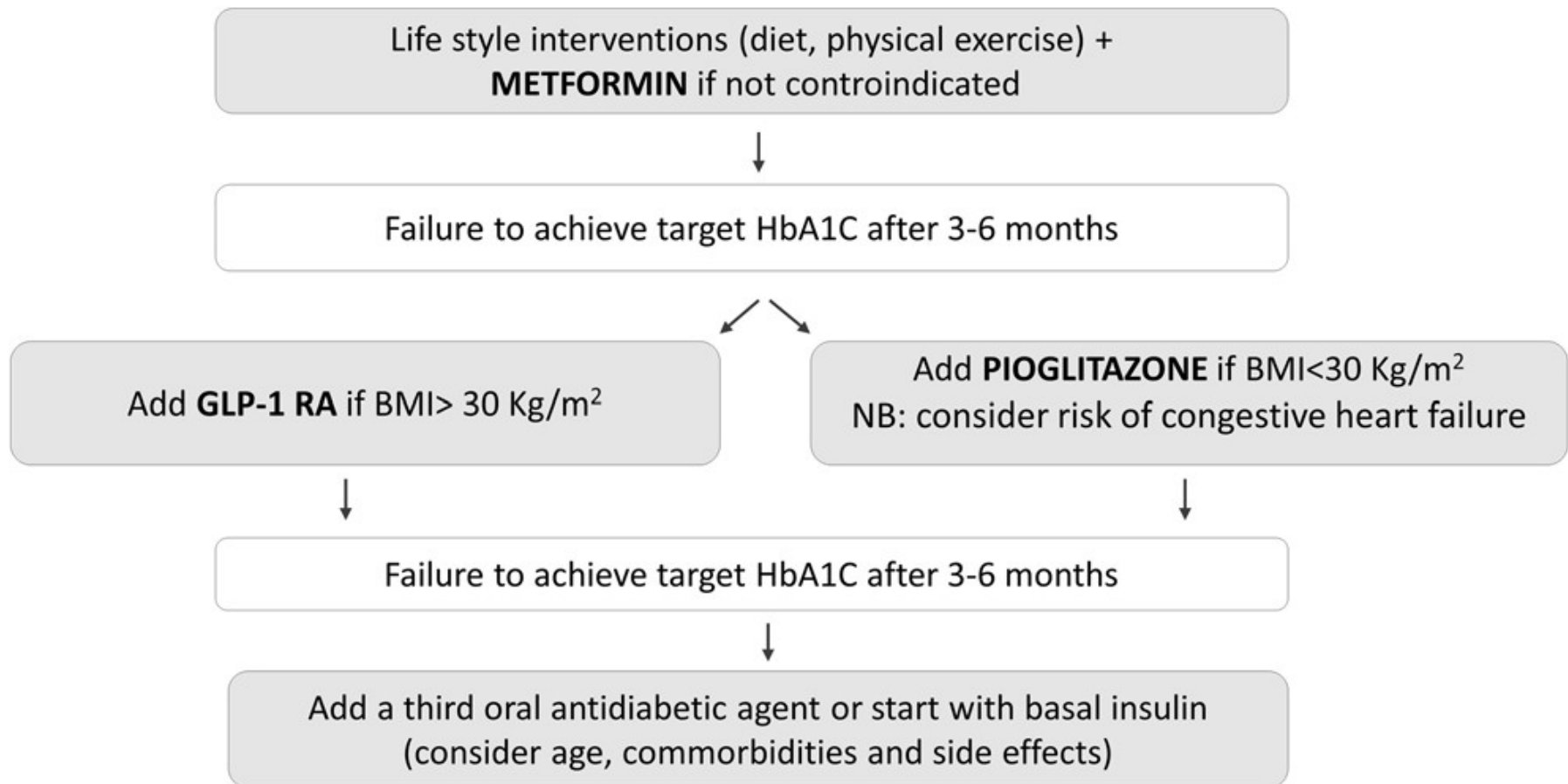
LBX at baseline and one year

Mean BMI reduction by 12 kg/m²

B



Stepwise management of diabetes

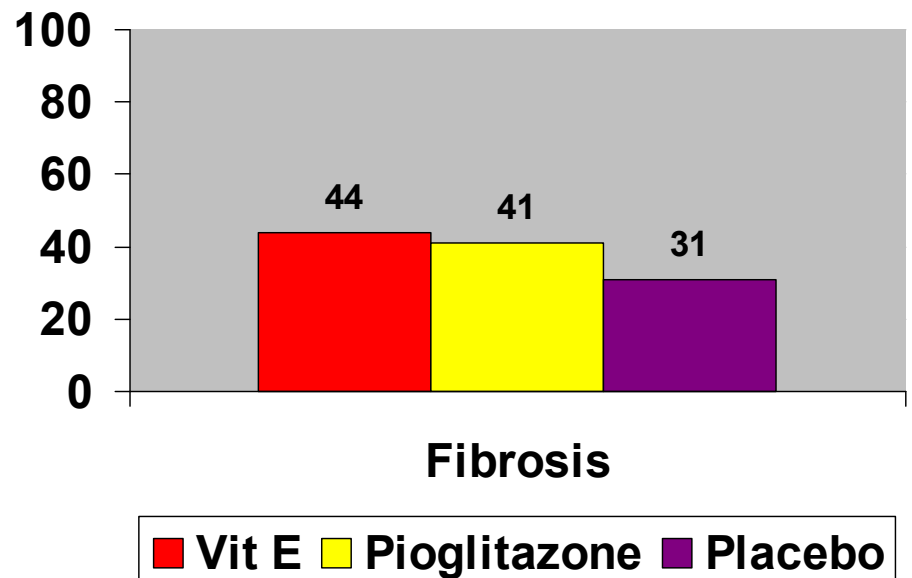
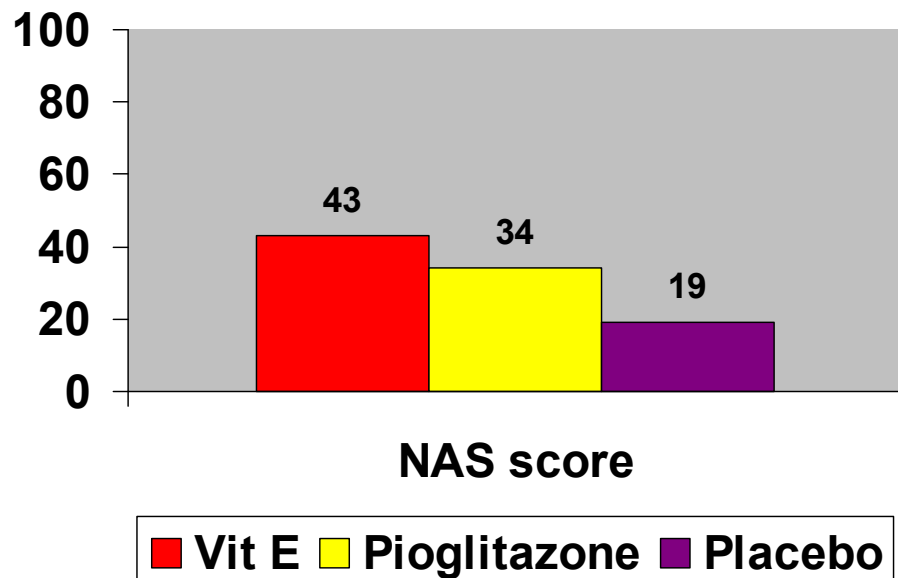


LEAN – liraglutide vs. placebo

Χαρακτηριστικό	Liraglutide (n=23)	Placebo (n=22)	P
NASH resolution	9 (39%)	2 (9%)	<0.05
NAS score	-1.3	-0.8	NS
Fibrosis improvement	6 (26%)	3 (14%)	NS
Fibrosis worsening	2 (9%)	8 (36%)	<0.05
Ballooning improvement	14 (61%)	7 (32%)	NS
Steatosis improvement	19 (83%)	10 (45%)	<0.05
Improvement of lobular inflammation	11 (48%)	12 (55%)	NS

PIVENS trial: Pioglitazone vs Vitamin E vs Placebo

287 non-diabetic patients
2 years treatment



Vitamin E: Existing evidence

- Effective in two RCTs (PIVENS, TONIC)
- BUT:
 - Increased mortality in doses >400 IU/day
Miller 2005, Bjelakovic 2007
 - Increased incidence of haemorrhagic stroke (but decreases ischaemic strokes)
Schwartz, 2010
 - Increased risk for prostate cancer
Lippman 2009, Klein 2011

Clinical course

- Follow-up in MDT clinic
- Dietitian
- Cardiovascular specialist
- Clinical nurse specialist
- Refused psychologist

Clinical course

- Restarted his anti-hypertensives, statin and Metformin
- Seen by Dietitian
- Refused Bariatric surgery
- Next visit Feb 2016
 - \leftrightarrow BMI 41.3, \downarrow BP 156/72,
 - \uparrow HbA1c 59.2mmol/mol,
 - \downarrow Chol 4.7 and LDL 2.7mmol/L
- Increased Metformin dose

Clinical course

- Third visit April 2016
 - Lost 6kg weight, BP 142/88, HbA1c 55.3mmol/mol, Chol 3.0 LDL 1.6 mmol/L
- Missed/cancelled appointments
- Fourth visit Jan 2017
 - Gained 4kg weight, HbA1c 78mmol/mol
 - BP and lipid profile still to target
- Refused additional medication for diabetes

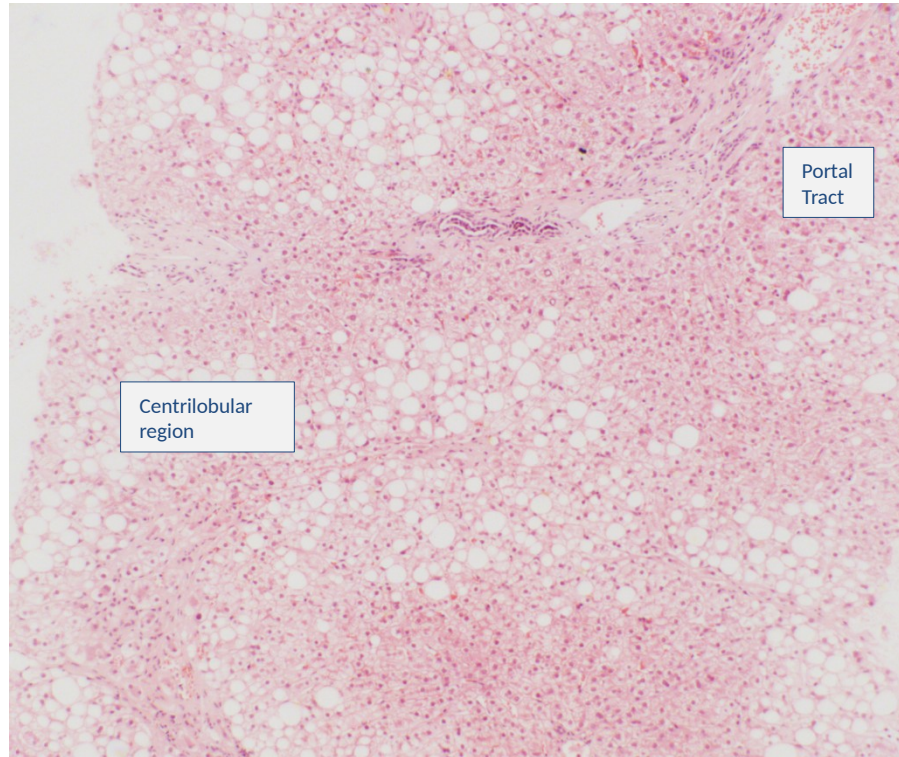
Repeat non-invasive assessment (Oct 2018)

- Shear wave Elastography 14.5 Kpa
- Fibroscan 20 Kpa
- ALT 61, AST 35, PLT 270, FIB-4<1

Would you repeat LBx?

- Yes
- No

Biopsy 2018

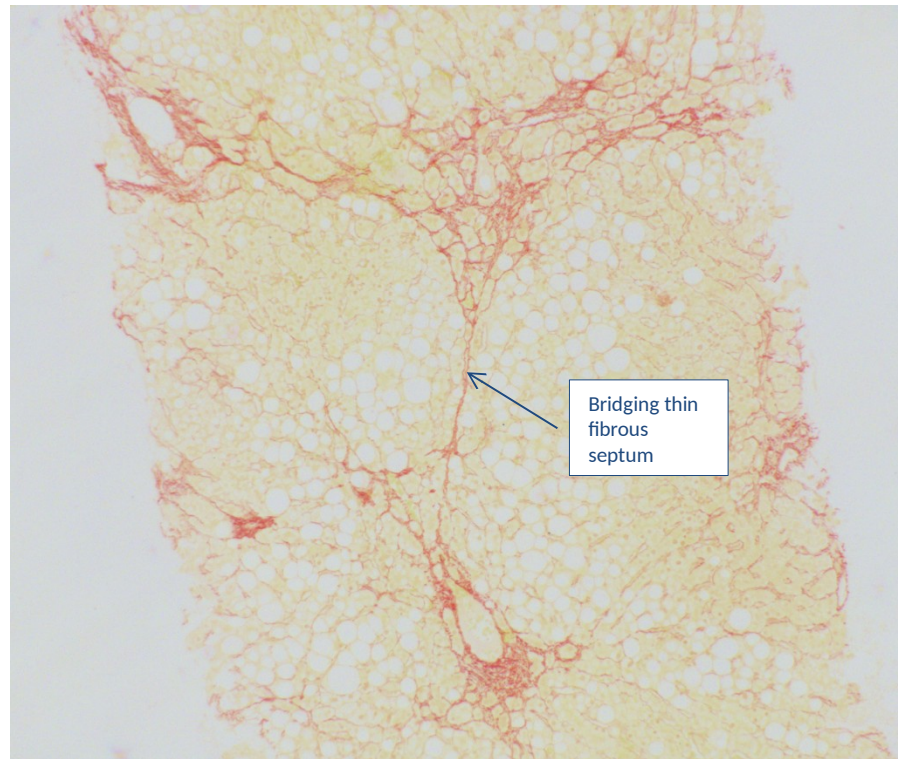


H&E

The sample shows steatosis, hepatocellular ballooning and a minimal inflammatory cell infiltrate. Steatosis is predominantly centro-mid lobular with a tendency to spare the periportal region

*Courtesy of Mr Andrew Hall and Prof Alberto Quaglia
Department of Cellular Pathology
Royal Free London*

Biopsy 2018



Bridging thin fibrous septa are present,
Collagen proportionate area 11%.

NASH and histological progression

Knowledge gaps

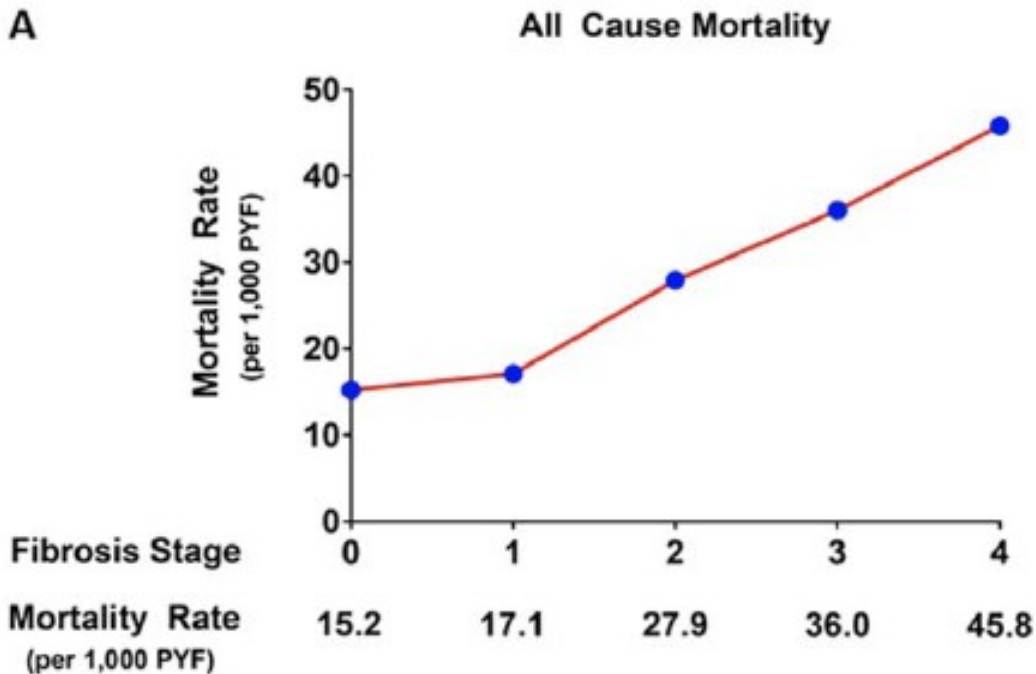
- No long term studies with protocol biopsies
- Second biopsy as a response to clinical events
- Selection bias – over-interpretation of findings

Fibrosis progression

- Individual patient meta-analysis
- 11 studies, 411 patients with two biopsies
- 150 NAFL, 261 NASH
- 33.6% progression, 43,1% stable, 22.3% improved
- 1-stage progression: 14 years for NAFLD, 7 years for NASH
- Hypertension associated with fibrosis progression

Histological progression

A



5 studies
1,495 patients
17,452 patient years of fup

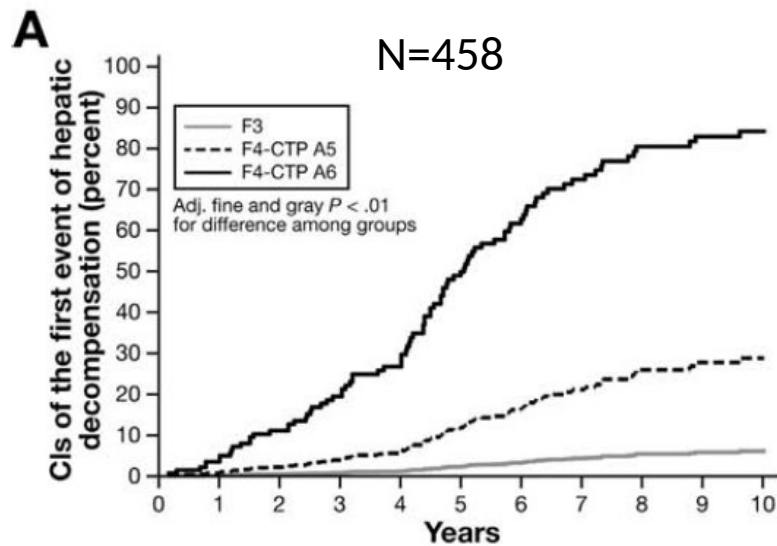
Risk of liver related death significantly higher only after progression to F2

NASH and advanced fibrosis

- 475 patients with F3 or F4 (simtuzumab RCT)
- 96 weeks of follow-up
- 22% of F3 progressed to cirrhosis
- 19% of F4 developed liver-related events
- HVP, collagen content and ELF associated with progression

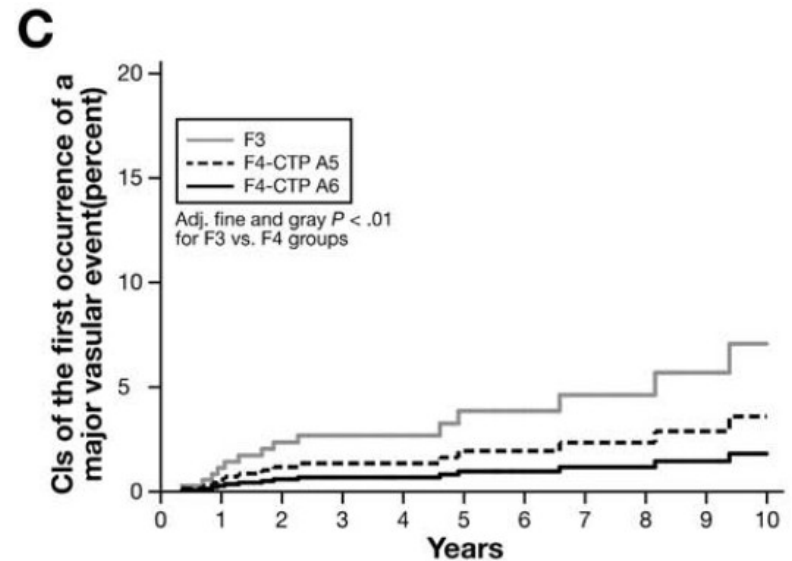
Fibrosis and cause-specific mortality

First decompensation



No. at risk	159	157	143	114	101	80	70	52	39	29	19
F3	159	157	143	114	101	80	70	52	39	29	19
F4-CTP A5	222	209	185	153	126	98	81	65	49	43	30
F4-CTP A6	77	72	55	43	35	23	12	7	4	4	2

Major vascular events



No. at risk	159	154	142	113	100	77	69	51	39	31	19
F3	159	154	142	113	100	77	69	51	39	31	19
F4-CTP A5	222	211	189	155	127	112	96	77	63	55	42
F4-CTP A6	77	74	58	55	53	44	30	23	17	10	5

Clinical course

- Started seeing a psychologist
- Started on liraglutide
- Accepted referral to bariatric services
- Last visit (10/10/2019)
 - Weight 128.6 , BP 135/85, HbA1c 63mmol/mol, Chol 3.4 LDL 1.7 mmol/L

Profile

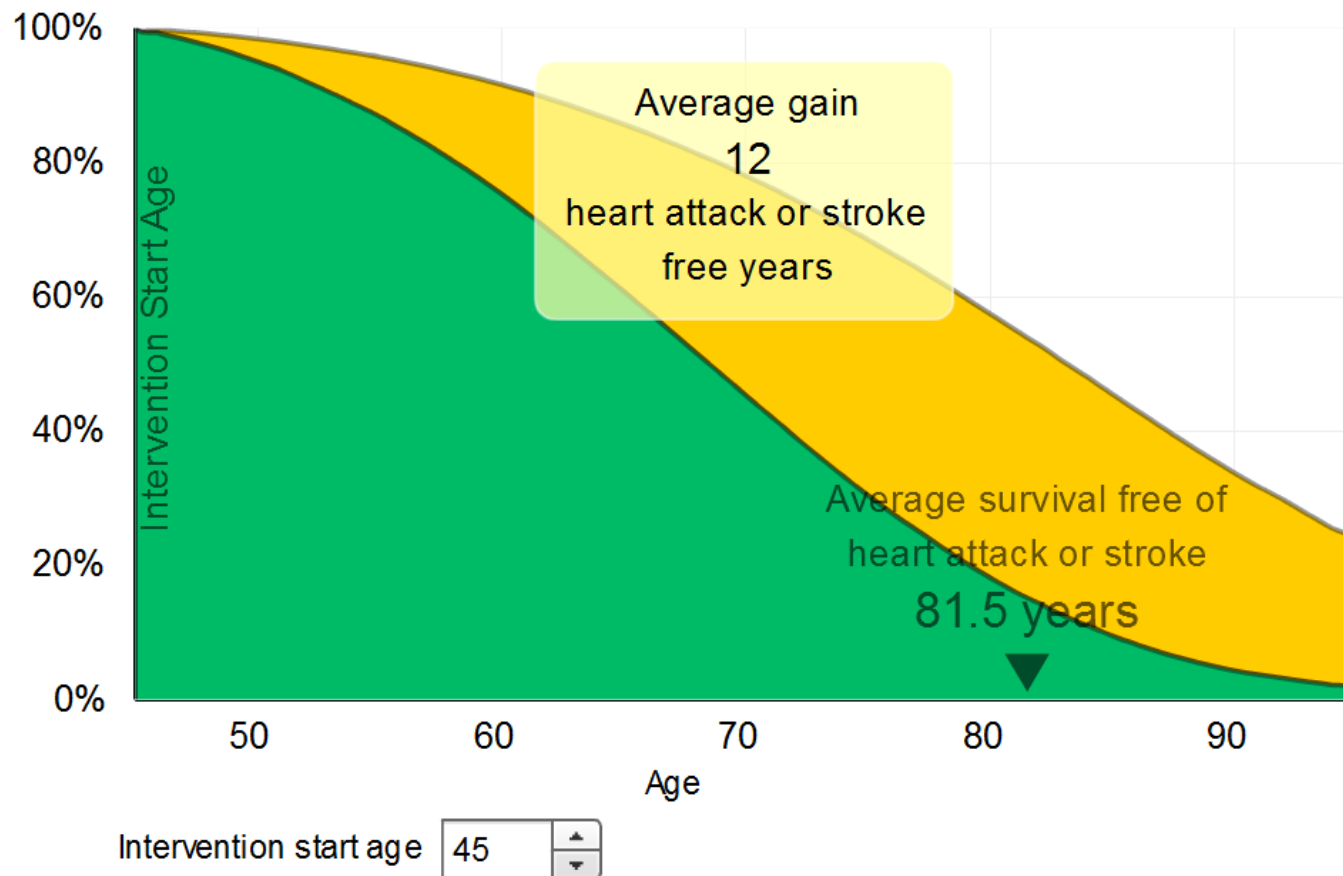
Heart Age

Healthy Years

Outlook

more

% Chance of survival free of Heart Attack or Stroke



Interventions

Future smoking category

No

Systolic Blood Pressure

156 → 135

Total Cholesterol

6.2 → 3.4

HDL Cholesterol

1.2 → 1.1

NonHDL Cholesterol: 2.3

BMI: 40.3

Reset

Profile

Heart Age

Healthy Years

Outlook

Compare

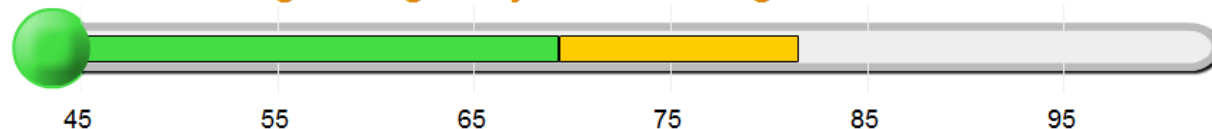
Risk by age

Outcomes

Balance

less

On average, expect
to survive to age 81
without a heart attack or stroke
gaining 12 years through interventions



expected life without a heart attack or stroke

Your risk of a heart attack or stroke
in the next 10 years is
3.8%

assuming you don't die of anything else

Interventions

Future smoking category

No

Systolic Blood Pressure

156 → 135

Total Cholesterol

6.2 → 3.4

HDL Cholesterol

1.2 → 1.1

NonHDL Cholesterol: 2.3

BMI: 40.3

Reset

Profile

Heart Age

Healthy Years

Outlook

Compare

Risk by age

Outcomes

Balance

less

% chance of a Heart Attack or Stroke
within 10 years (before age 55)

Interventions

Future smoking category

No

Systolic Blood Pressure

156 → 135

Total Cholesterol

6.2 → 3.4

HDL Cholesterol

1.2 → 1.1

NonHDL Cholesterol: 2.3

BMI: 40.3

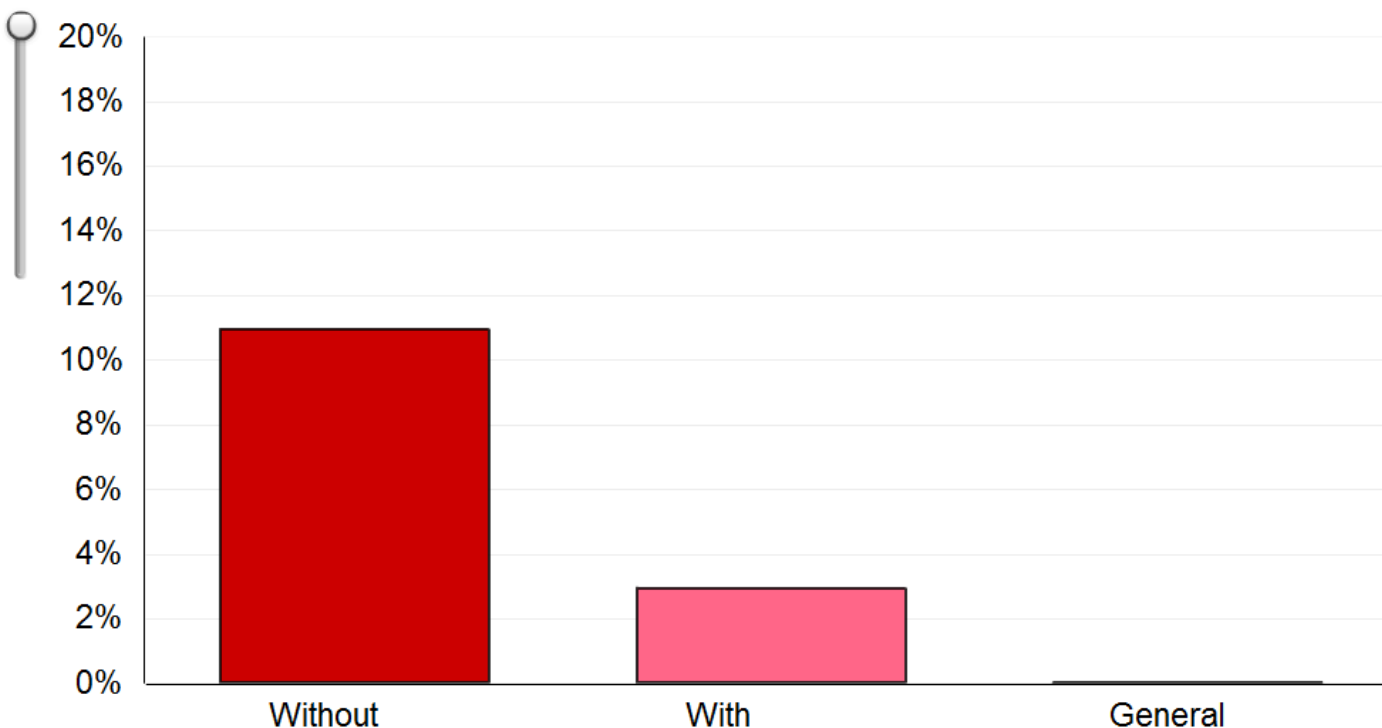
Reset

Intervention start age

45

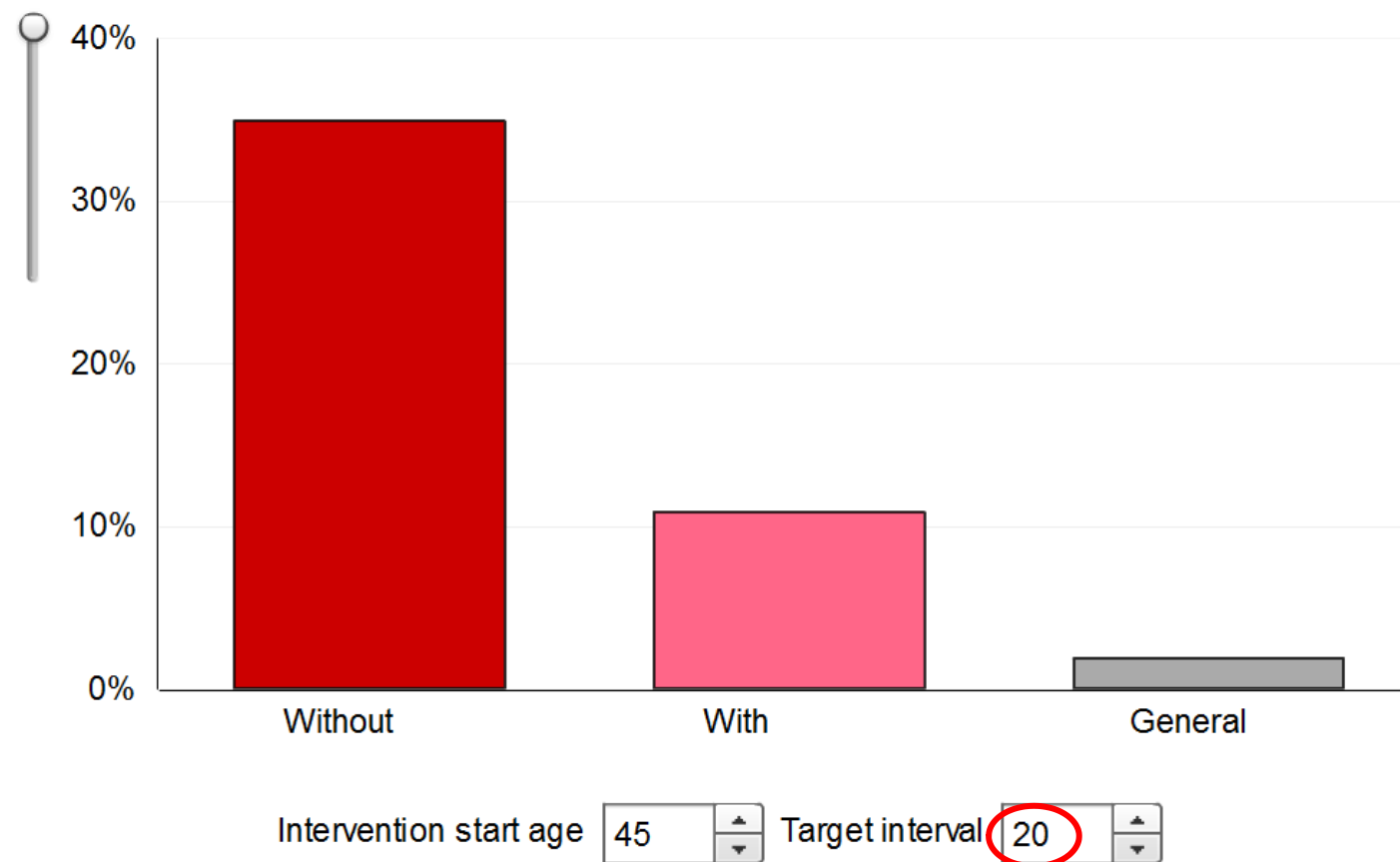
Target interval

10





% chance of a Heart Attack or Stroke within 20 years (before age 65)



Interventions

Future smoking category: No

Systolic Blood Pressure: 156 → 135

Total Cholesterol: 6.2 → 3.4

HDL Cholesterol: 1.2 → 1.1

NonHDL Cholesterol: 2.3

BMI: 40.3

Reset

The importance of an MDT approach

NAFLD Clinic –CVD Risk numbers

- 509 Consultations
 - 201 – Single Consultation
 - 91 – Two consultations
 - 26 – Three consultations
 - 12 – Four or more consultations
- Total of 273 individual patients with NAFLD undergone cardiovascular risk assessment

Frequency of pre-existing co-morbidities

Co-morbidity	Frequency
Hyperlipidaemia	93.1%
Hypertension	67.4%
Diabetes Mellitus	40.3%
Known CVD	13.2%
Current Smokers	12.1%

NAFLD Clinic – Interventions

Hyperlipidaemia

- **50.8%** of patients had sub-optimal lipid profile at baseline primary prevention.
- **47.2%** of patients had sub-therapeutic lipids for secondary prevention at baseline

NAFLD Clinic – Interventions

Hyperlipidaemia

- **41.3%** Patients had Lipid treatment altered or commenced
- Primary prevention **72.5%** achieved the LDL reduction of $<3\text{mmol/L}$
- Secondary prevention, **69.4%** reached the LDL target of $<2\text{mmol/L}$

NAFLD Clinic – Interventions

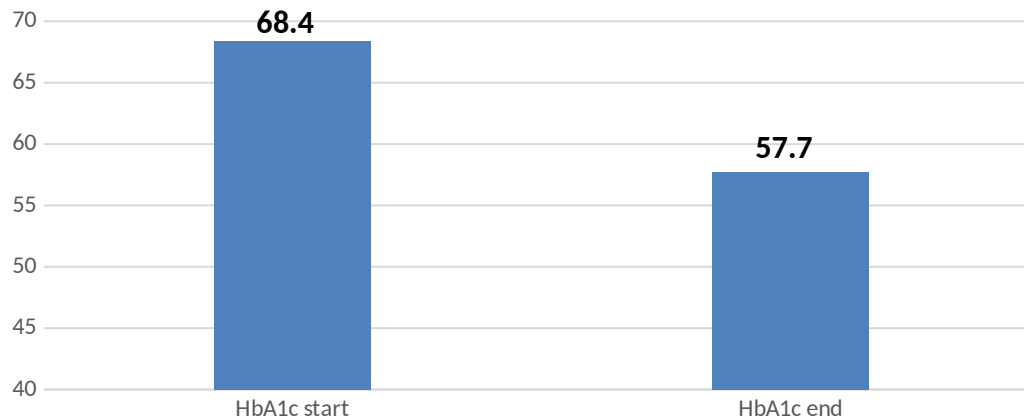
Diabetes Mellitus

- n = 110 (40.3%)
- We picked up 14 patients (**11.3%**) with **undiagnosed** diabetes mellitus
- 53 patients (**42.7%**) with sub-optimally controlled Type 2 Diabetes had treatment alterations.
 - Mean HbA1c – **68.4 mmol/mol**
 - Mean HbA1c – **57.7 mmol/mol**

NAFLD Clinic – Type 2 Diabetes

- Type 2 Diabetes Mellitus Treatment
- Mean HbA1c – **68.4** mmol/mol \Rightarrow **57.7** mmol/mol

Mean change in HbA1c concentrations (mmol/mol)



$p < 0.05$

- Mean HbA1c improvement **10.7** mmol/mol (**15.6%**)

NAFLD Clinic – Interventions

Hypertension

- n = 184 (67.4%)
- 56 patients (**30.4%**) with sub-optimally controlled hypertension had treatment alterations recommended/commenced.
 - Mean BP – **159 / 92**
 - Mean BP – **139 / 84**

QRISK-3 Score

- Mean QRISK-3 score at Baseline **15.8%**
- Mean QRISK-3 score at Endpoint **12.4%**
- Mean QRISK-3 score reduction **3.4%**
- Mean Gain of 6.1 'heart attack and stroke' free years

Conclusions

NAFLD a multi-morbid condition

Mortality mainly cardiovascular

Fibrosis most important predictor of liver outcomes

MDT approach to improve outcomes

