NAFLD: a diabetologist's view

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Diabetes is the most important risk factor for cirrhosis and HCC
18 million patients four European cohorts

- Four databases, the median duration of follow-up was 3.3 years (IQR 1.8–5.3) totalling 531,452 person-years for patients with coded NAFLD/NASH and 43,385,495 person-years for controls (no NAFLD/NASH).

- Coded NAFLD/NASH: more likely to have diabetes/hypertension/obesity
- Apart from a diagnosis of NAFLD/NASH, diabetes was the strongest independent risk factor for acquiring a diagnosis of cirrhosis or HCC.
- HR for cirrhosis in patients compared to controls was 4.73 (95% CI 2.43–9.19) and for HCC, 3.51 (95% CI 1.72–7.16).

- N.B. In the matched control population, the HR for diabetes was even higher than the coded NAFLD/NASH cohort, which may reflect a significant number of individuals with undiagnosed NAFLD/NASH among the controls

Alexander et al. BMC Medicine (2019) 17:95

Association between covariates and risk of liver outcomes: cirrhosis or HCC with NAFLD/NASH or no NAFLD/NASH (controls)

	NAFLD/NASH HR (95% CI)	Matched control HR (95% CI)
Smoking status (current/not current)	1.19 (0.94; 1.51)	1.50 (1.41; 1.60)
Age (years)	1.04 (1.03; 1.05)	1.04 (1.03; 1.04)
History of diabetes (yes/no)	**2.30 (1.90, 2.78**	**2.92 (2.76; 3.08)**
History of hypertension (yes/no)	0.92 (0.76; 1.12)	1.07 (1.01; 1.13)
BMI (kg/m^2)	1.01 (1.00; 1.03)	1.04 (1.03; 1.04)

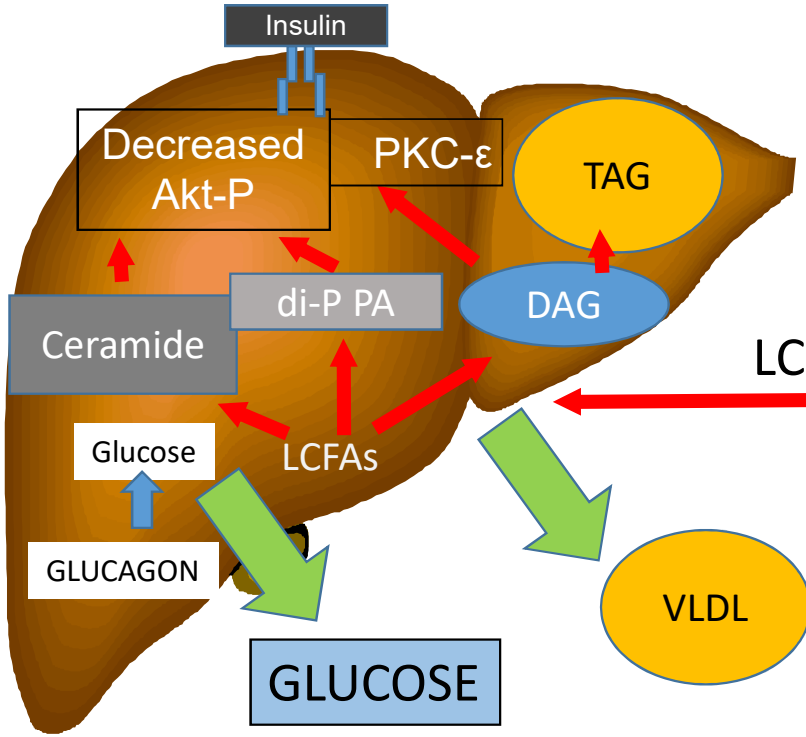
Alexander et al. BMC Medicine (2019) 17:95

Management of diabetes in patients with NASH:

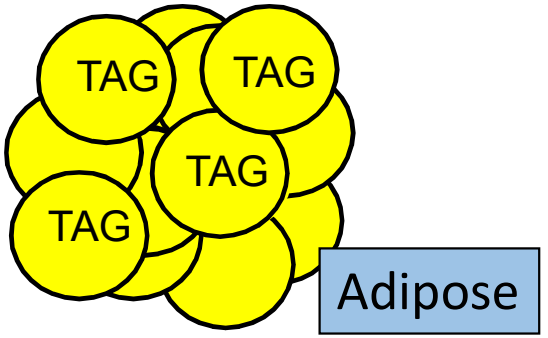
Questions:

How to diagnose NAFLD, which treatments and which targets for treatment?

Type 2 diabetes and NAFLD: decreased insulin action/insulin resistance and unopposed glucagon action



‘Inflammed’ adipose tissue activated macrophages



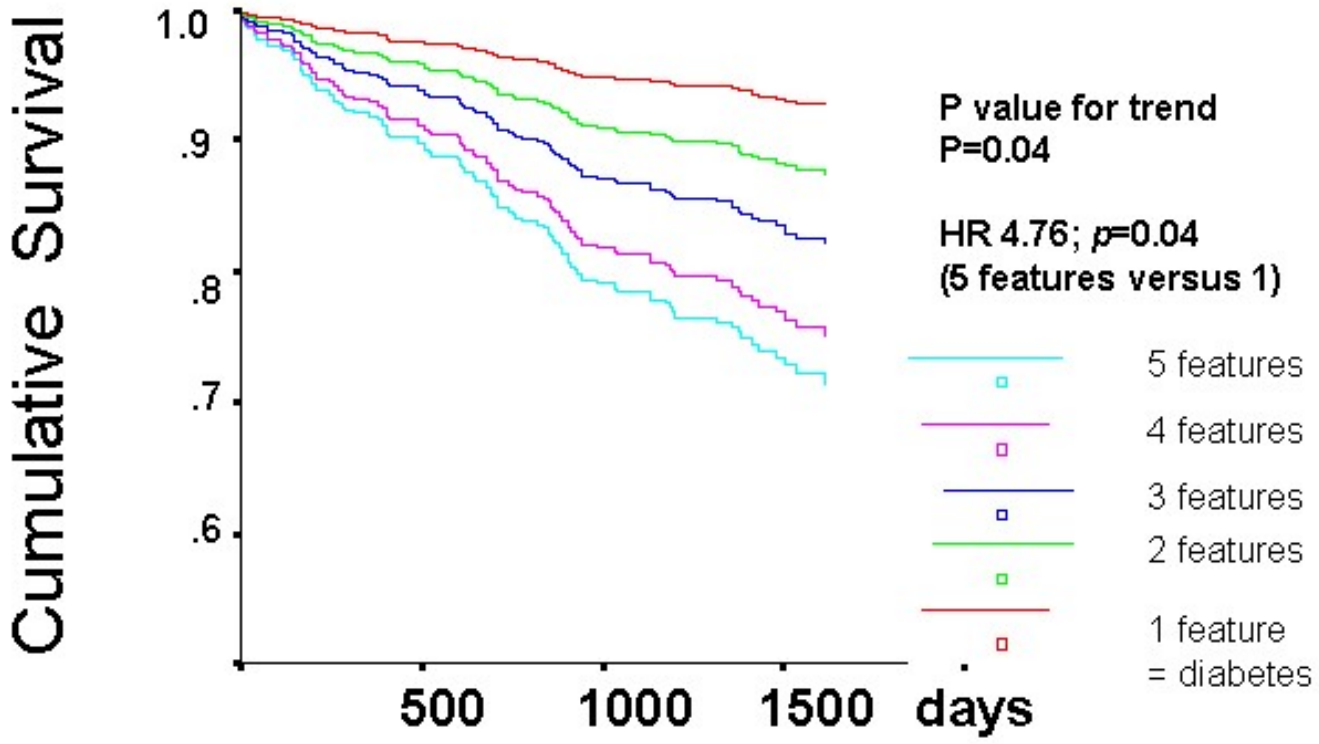
LCFAs

Metabolic Syndrome Features 2009

Waist	> 94/80 cm
BP	≥ 130 / 85
TG	≥ 1.7mmol/l
Glucose	≥ 6 mmol/l
HDL	< 1.0/1.3 mmol/l

Type 2 diabetes:

Survival is worsened with increasing number of features of Metabolic syndrome



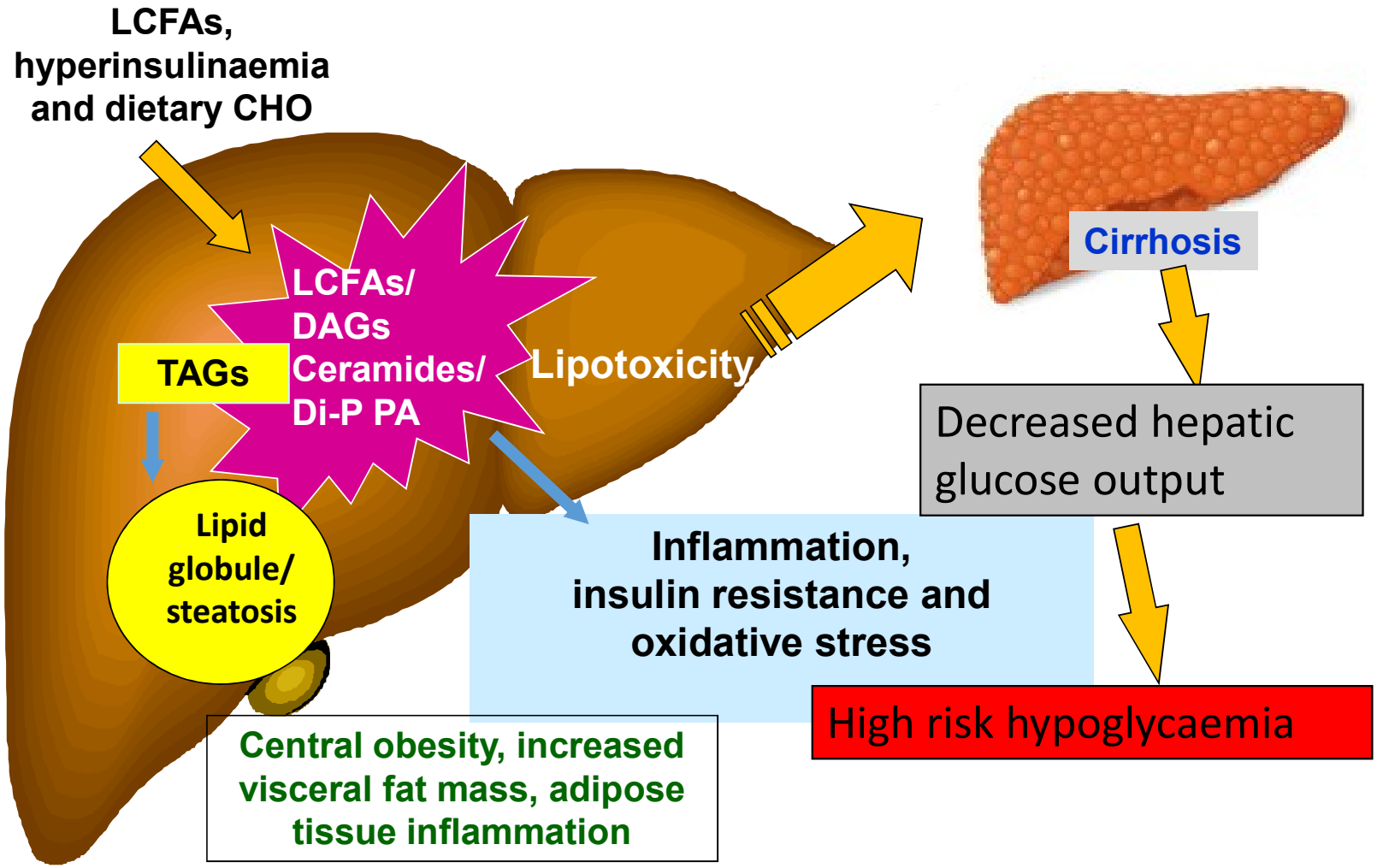
Gudzer, Gatling, Mullee, Byrne Diabetologia 2006 Jan;49(1):49-55

NAFLD occurs frequently with MetS features

Metabolic Syndrome Features

Waist	**> 94/80 cm**
BP	**≥ 130 / 85**
TG	**≥ 1.7mmol/l**
Glucose	**≥ 6 mmol/l**
HDL	**< 1.0/1.3 mmol/l**

NASH and decompensating cirrhosis: decreased hepatic gluconeogenesis

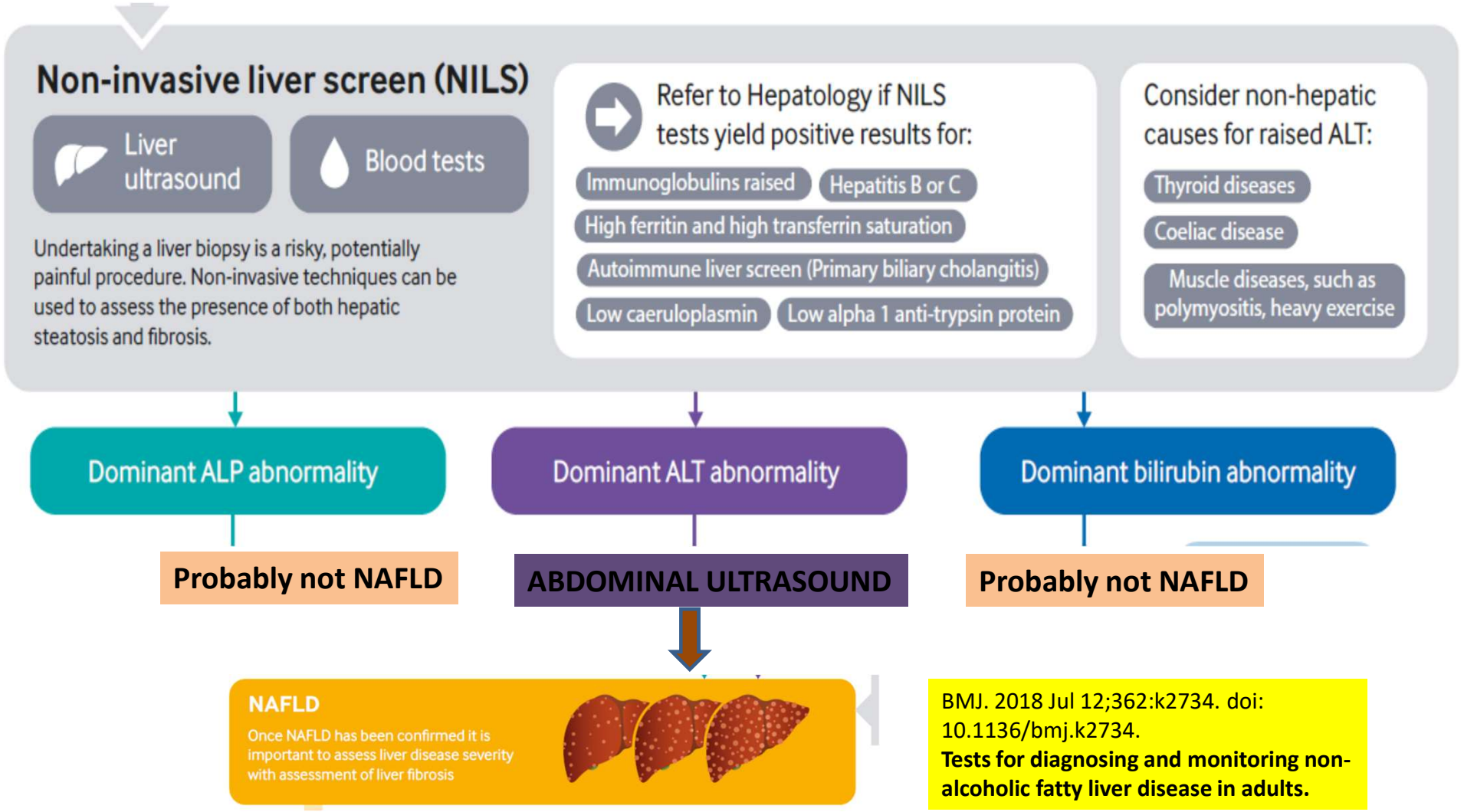


Rational Testing

Tests for diagnosing and monitoring non-alcoholic fatty liver disease in adults

Christopher D Byrne, Janisha Patel, Eleonora Scorletti, Giovanni Targher.

BMJ. 2018 Jul 12;362:k2734.

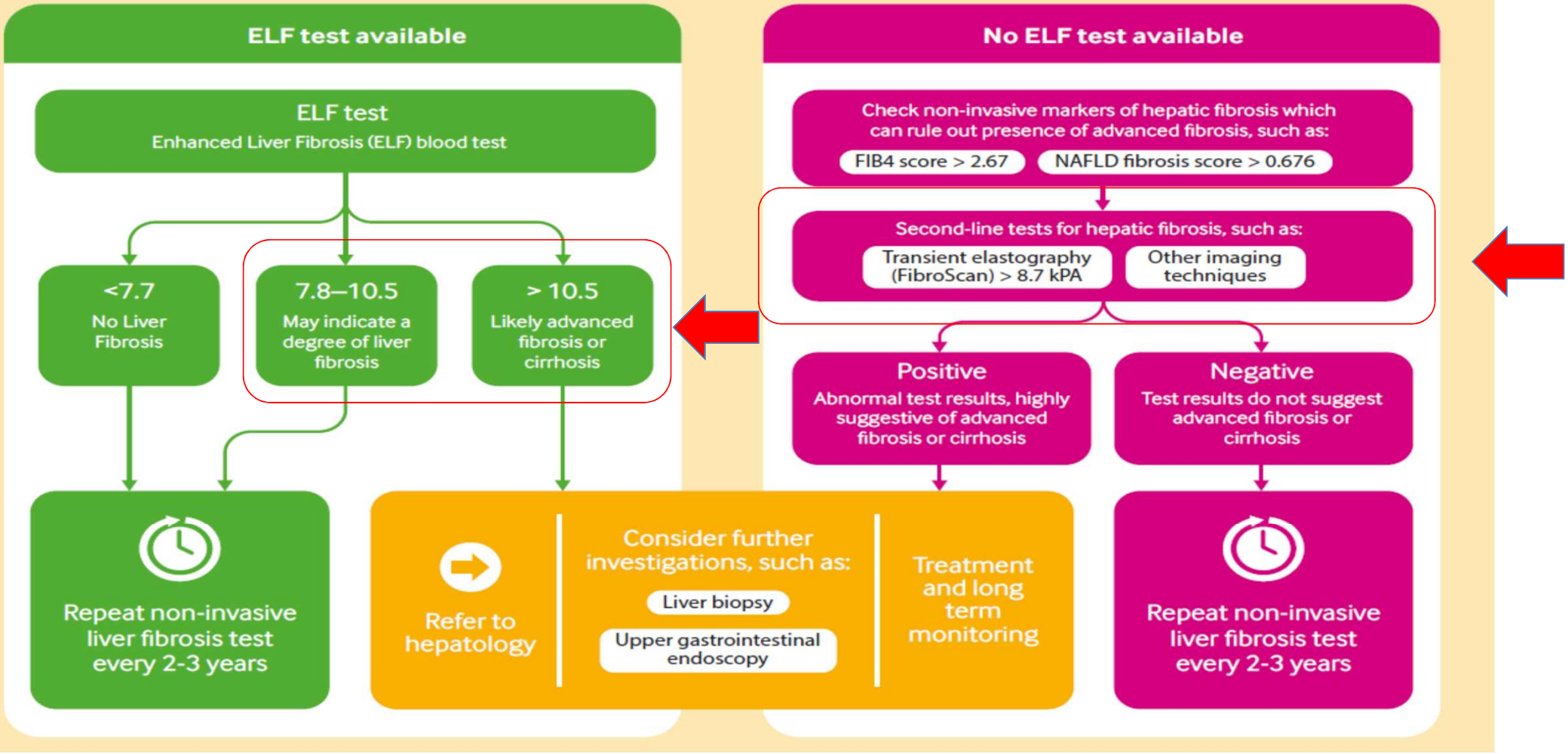


BMJ. 2018 Jul 12;362:k2734. doi: 10.1136/bmj.k2734.
Tests for diagnosing and monitoring non-alcoholic fatty liver disease in adults.

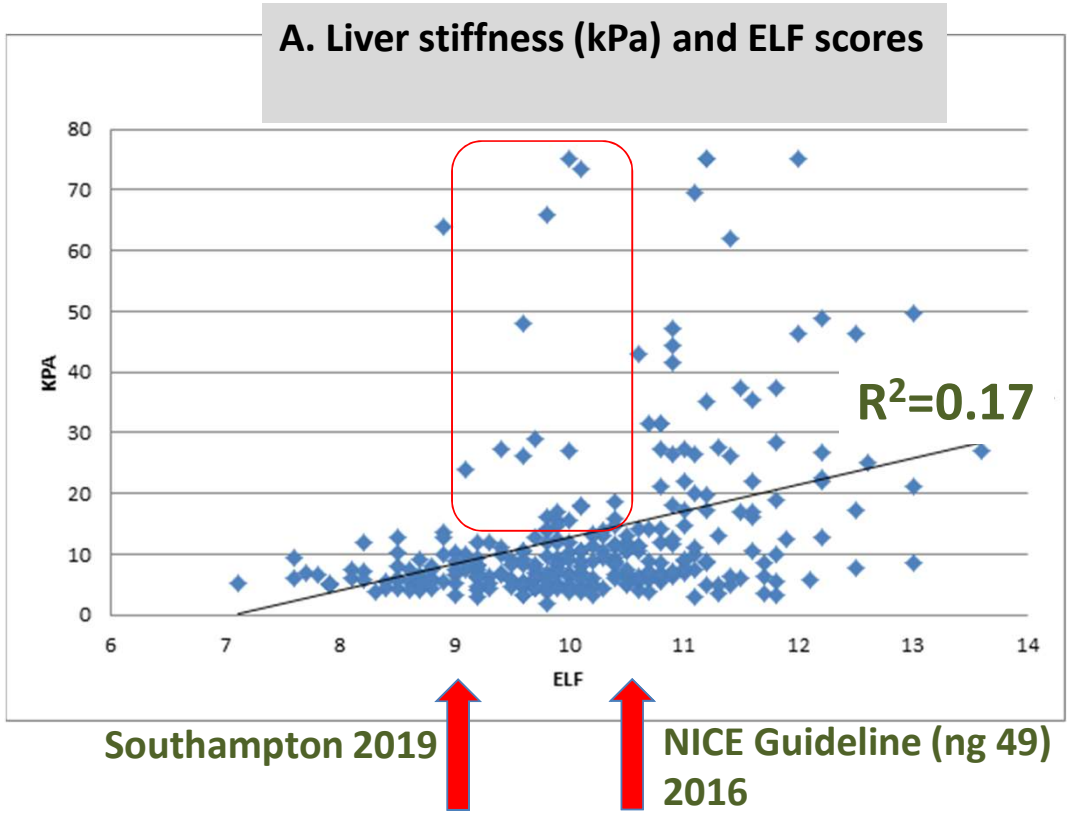
BMJ. 2018 Jul 12;362:k2734. doi: 10.1136/bmj.k2734.
Tests for diagnosing and monitoring non-alcoholic fatty liver disease in adults.

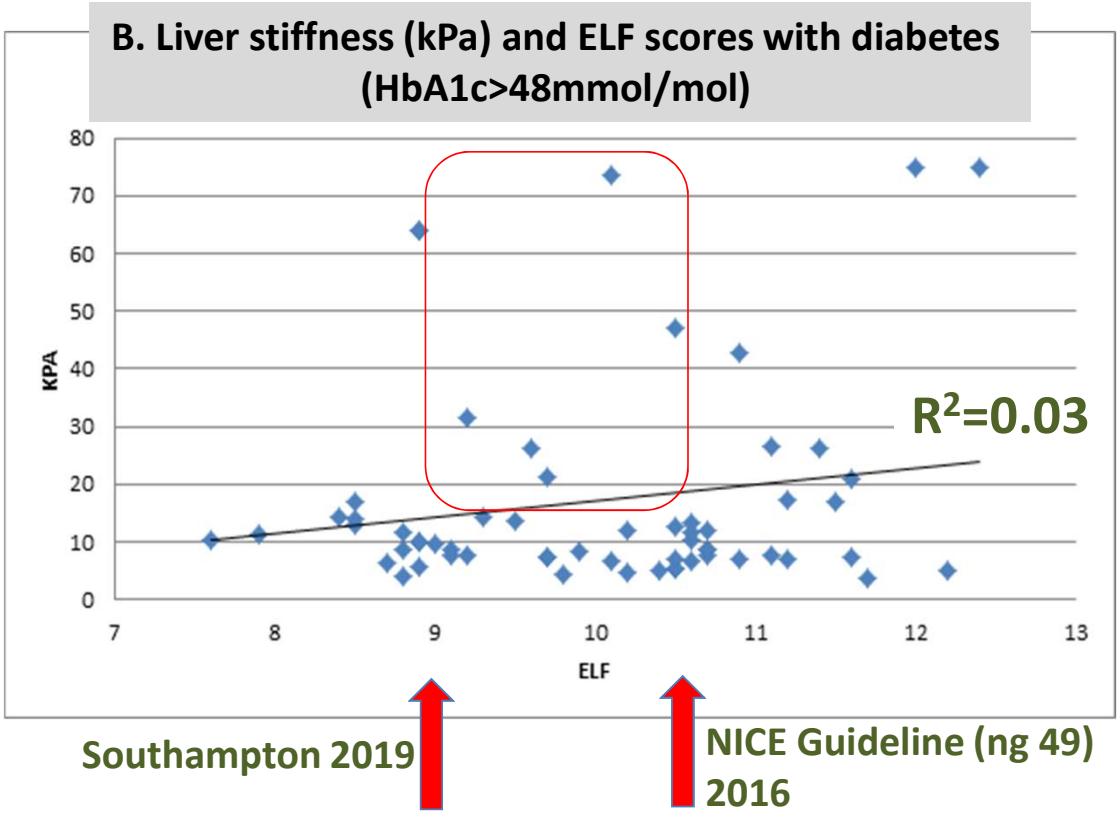
Investigate the severity of liver fibrosis

Although biopsy is the most accurate way of staging fibrosis, it is usually reserved for patients who are most likely to have substantial fibrosis or where there is diagnostic uncertainty. If available, the enhanced Liver Fibrosis test (ELF) is preferred by NICE guidelines in the UK. If it is not available, use another non invasive test as recommended by European and American guidelines.



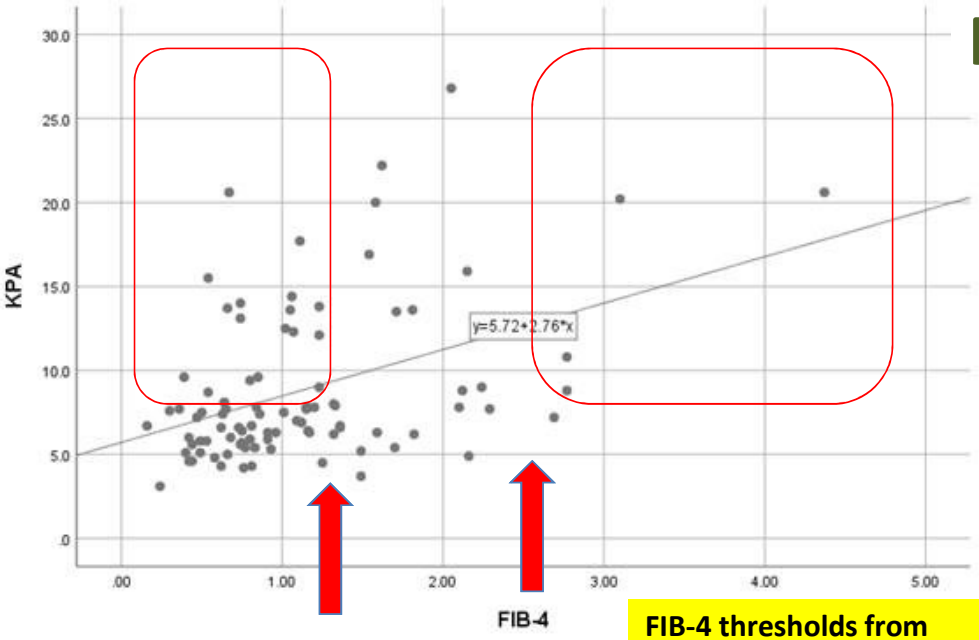
Scatter plots showing associations in NAFLD between liver stiffness and ELF scores (A) and liver stiffness and ELF scores in patients with diabetes (B)





Scatter plots showing associations in NAFLD between liver stiffness and FIB-4 scores (A)

A. Liver stiffness (kPa) and FIB-4 scores



R^2=0.17

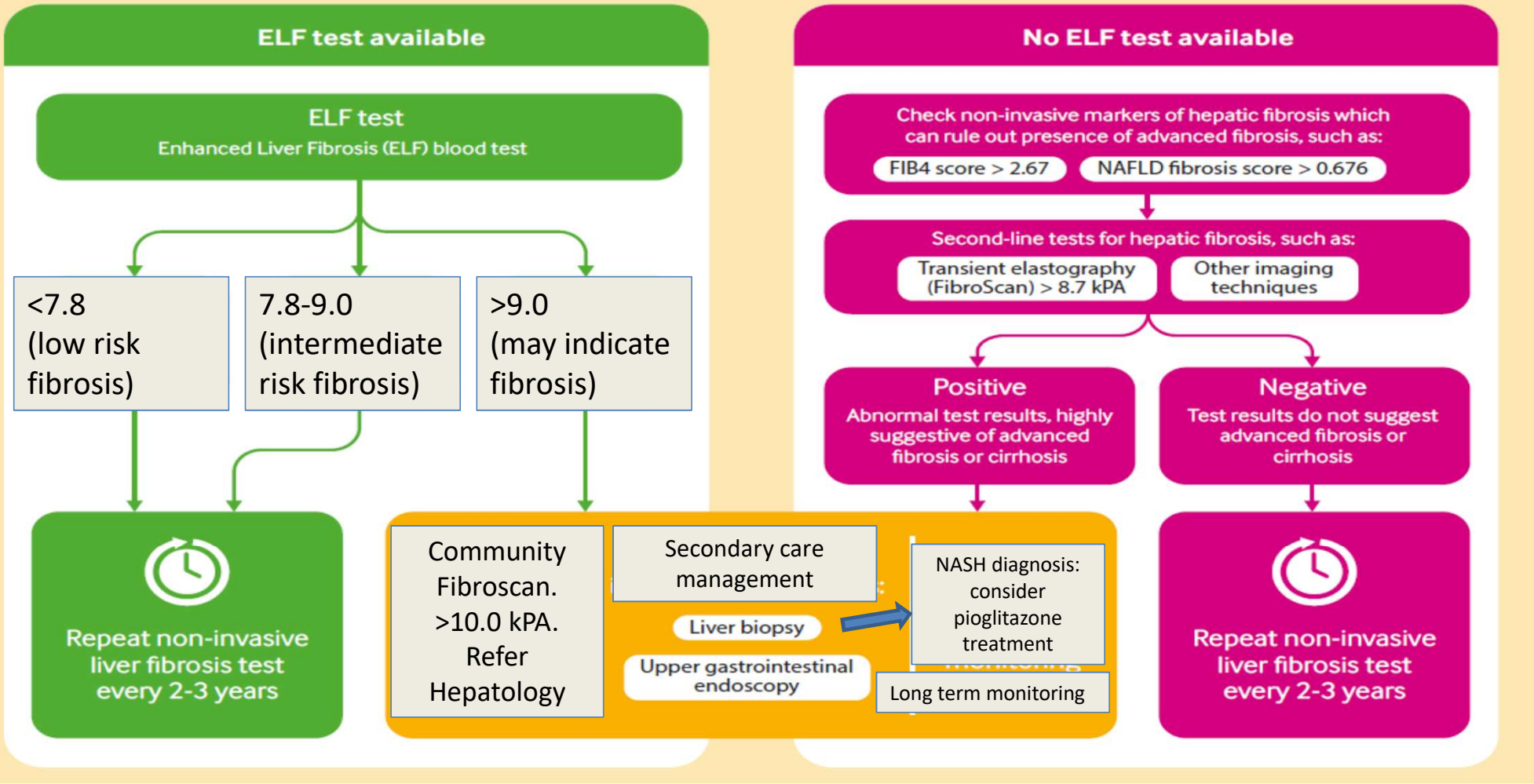
FIB-4 thresholds from BMJ. 2018 Jul 12;362:k2734. doi: 10.1136/bmj.k2734.

Investigate severity of liver fibrosis

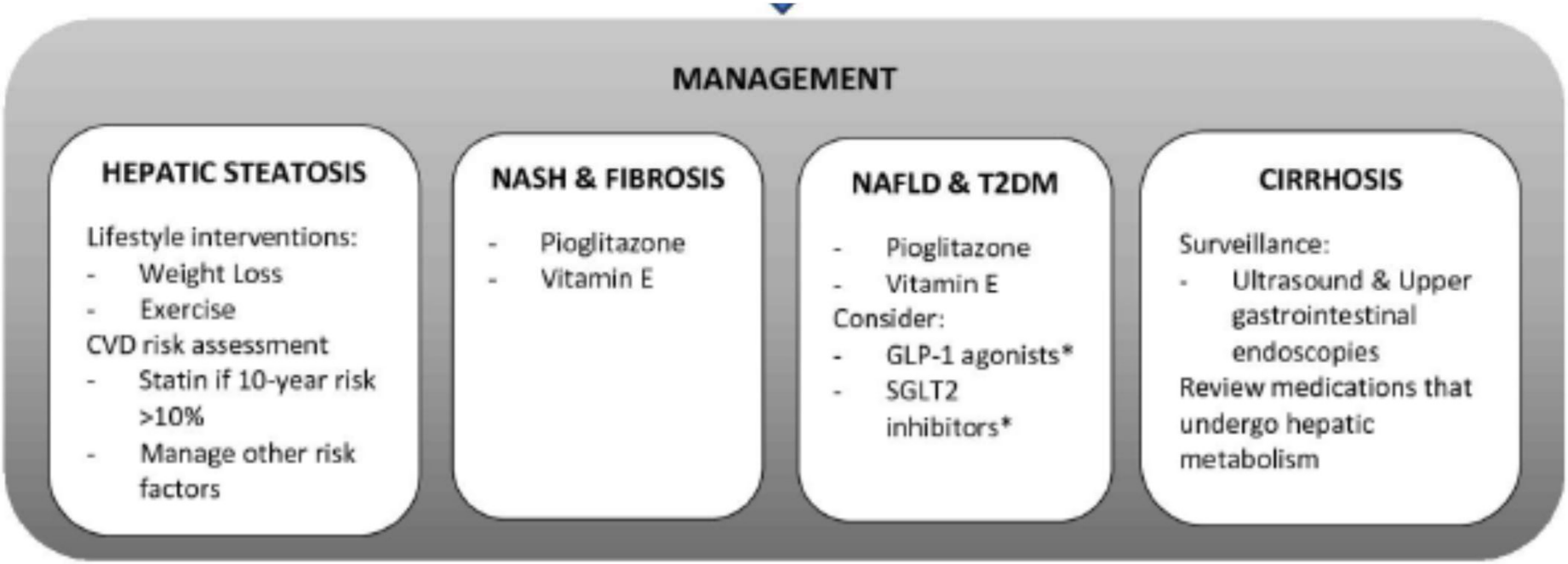
Although biopsy is the most accurate way of staging fibrosis, it is usually reserved for patients who are most likely to have substantial fibrosis or where there is diagnostic uncertainty. If available, the enhanced Liver Fibrosis test (ELF) is preferred by NICE guidelines in the UK. If it is not available, use another non invasive test as recommended by European and American guidelines.

Modified from BMJ. 2018 Jul 12;362:k2734. doi: 10.1136/bmj.k2734.

2019: ELF score pathway modified and Community Fibroscanning added

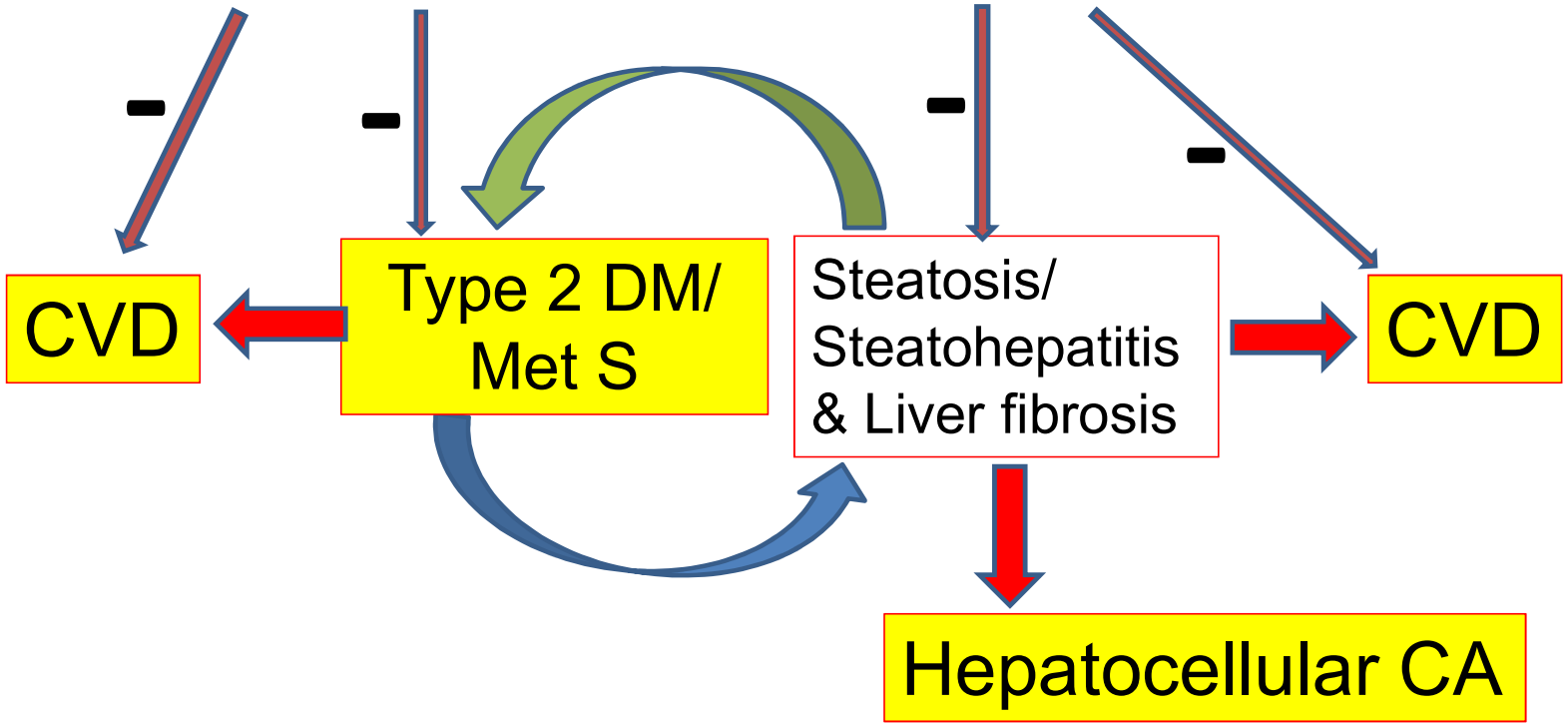


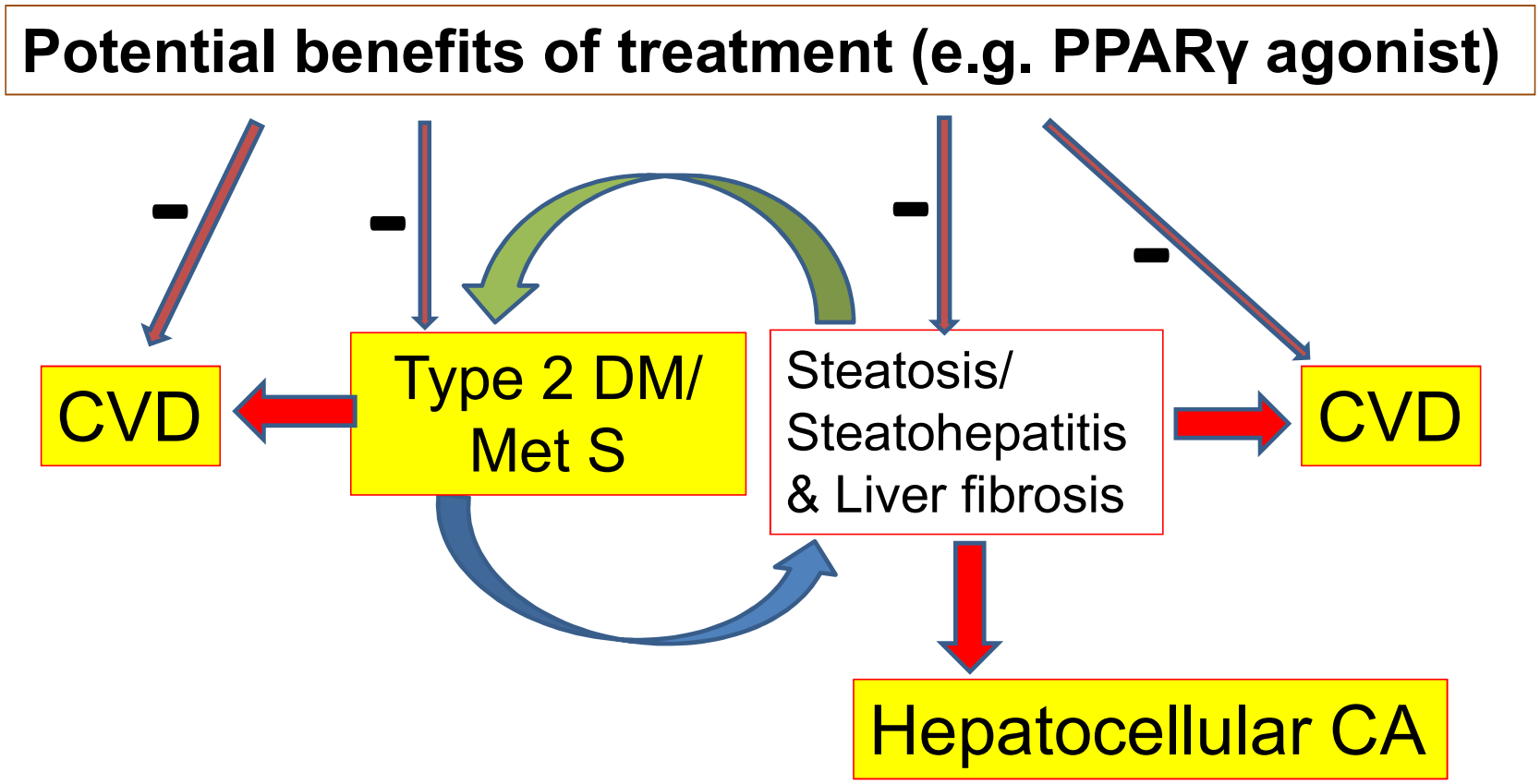
MANAGEMENT OF NAFLD ACCORDING TO NAFLD SEVERITY AND DIABETES STATUS



Postgrad Med J. 2019 May 13. pii: postgradmedj-2018-136316

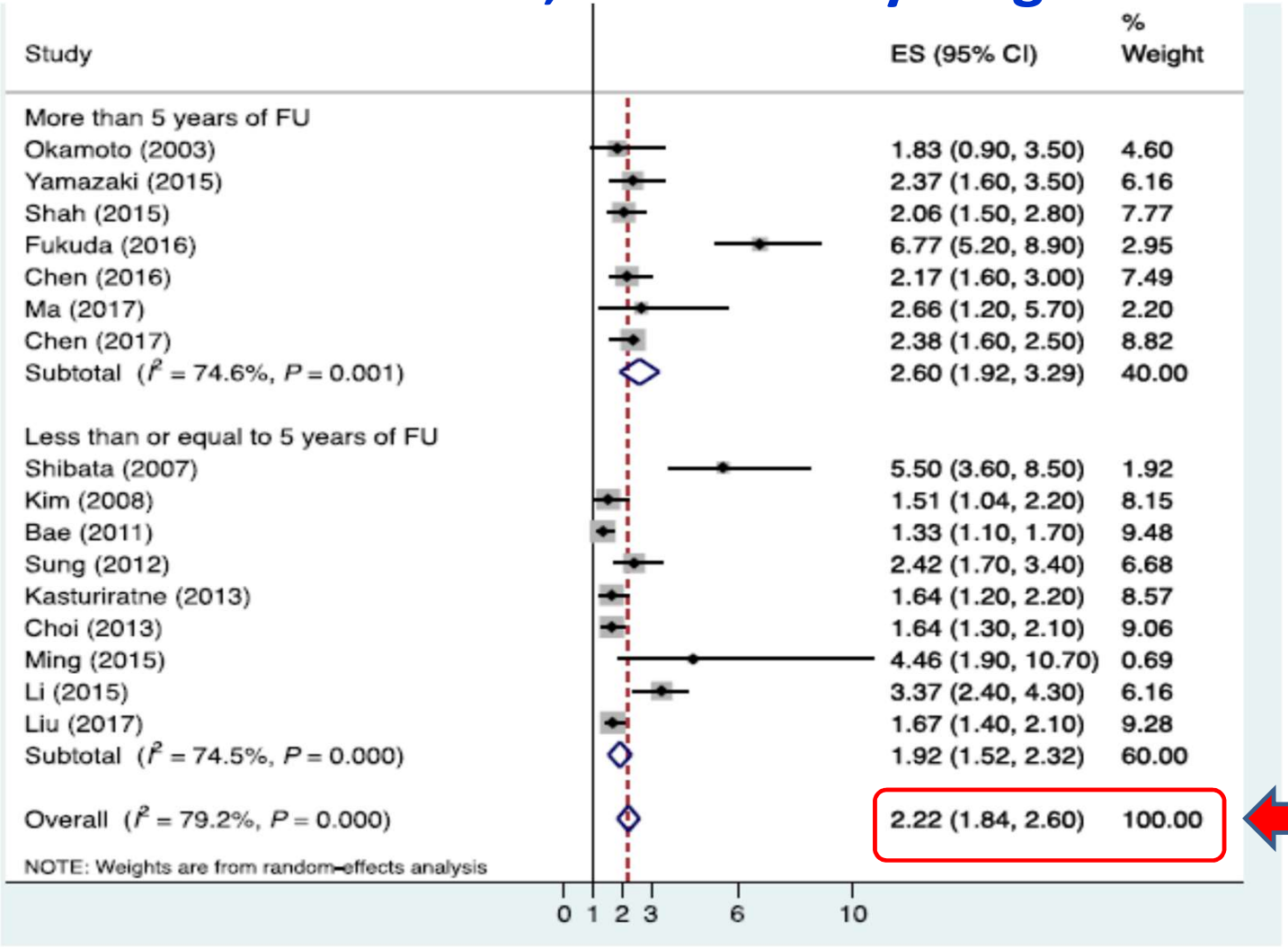
What is the aim of drug treatment in NASH?





Potential side effects of pioglitazone :Weight gain
(fluid retention/increase in gluteofemoral adipose). Small increase in risk of fracture

Forest plot and pooled estimates of the effect of NAFLD on risk of incident diabetes, stratified by length of follow up



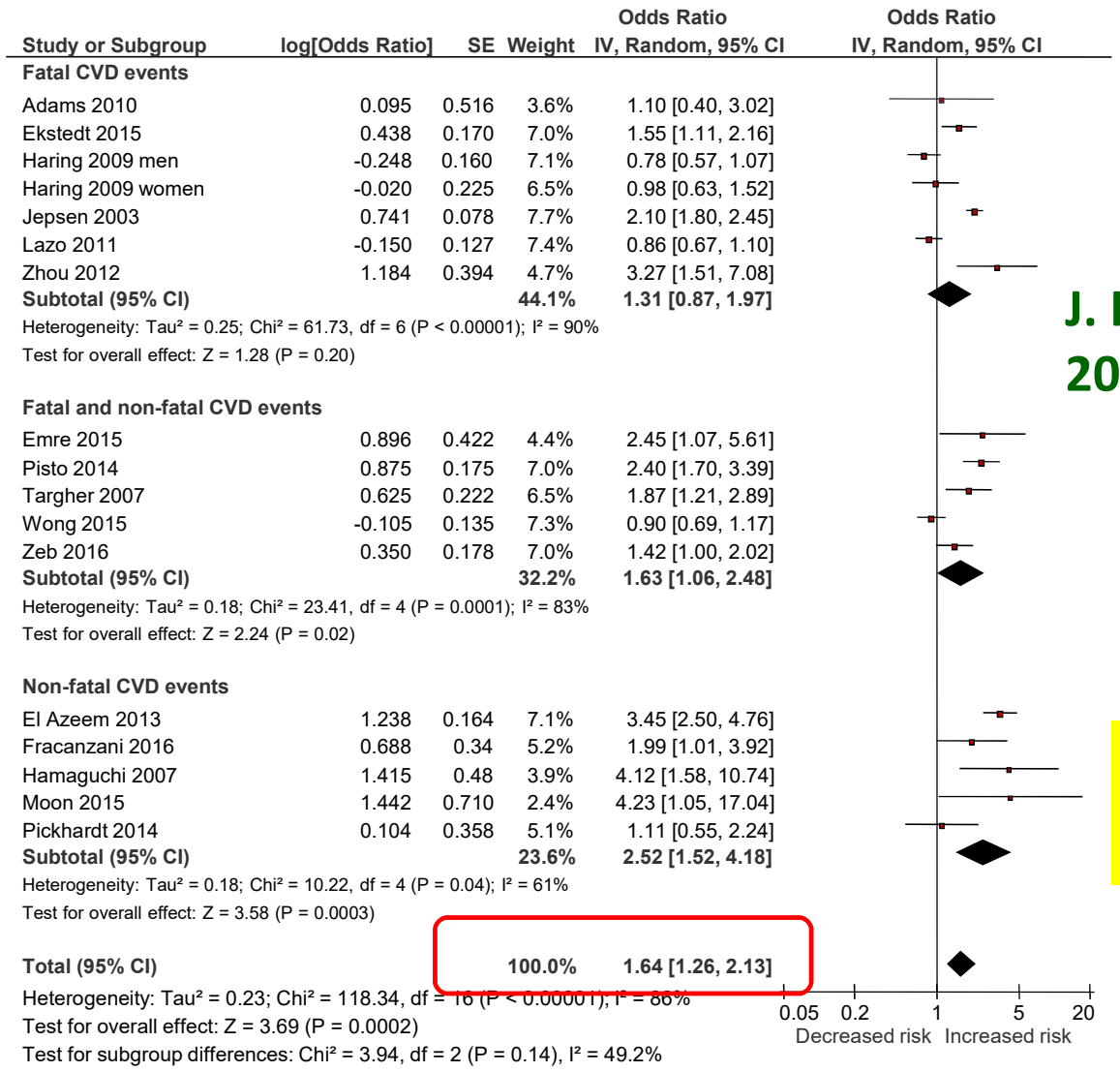
Summary HR (95%CIs)

= 2.22 (1.84, 2.60)

Diabetes Care 2018; 41: 372-382

NAFLD increases risk of incident CVD events (fatal, non-fatal or both)

Meta-analysis of the risk of incident CVD events associated with NAFLD.



J. Hepatology 2016; 65: 589-600

Summary HR (95%CIs)

=1.64 (1.26, 2.13)

Cardiovascular disease, cancer and mortality among people with type 2 diabetes with NAFLD (or ALD) requiring hospital admission

Outcome (ICD coded diagnoses)	HR (95% CI) ALD (*n* = 1,707)	HR (95% CI) NAFLD (*n* = 1,452)
Incident/recurrent CVD event*	1.59 (1.43, 1.76)	1.70 (1.52, 1.90)
Incident/recurrent HCC†	41.7 (30.0, 57.8)	19.3 (11.8, 31.4)
Incident/recurrent cancer, excluding HCC‡	1.28 (1.12, 1.47)	1.10 (0.94, 1.29)
All-cause mortality§	4.85 (4.49, 5.23)	1.60 (1.40, 1.83)
CVD mortality*	2.05 (1.63, 2.58)	1.15 (0.85, 1.57)
HCC mortality†	20.5 (13.9, 30.1)	6.16 (3.02, 12.6)
Cancer mortality, excluding HCC‡	1.24 (0.98, 1.57)	0.76 (0.55, 1.04)
Other causes of death	3.50 (3.00, 4.07)	1.60 (1.28, 1.99)

CVD events HR (95%CIs)

= 1.70 (1.52, 1.90)

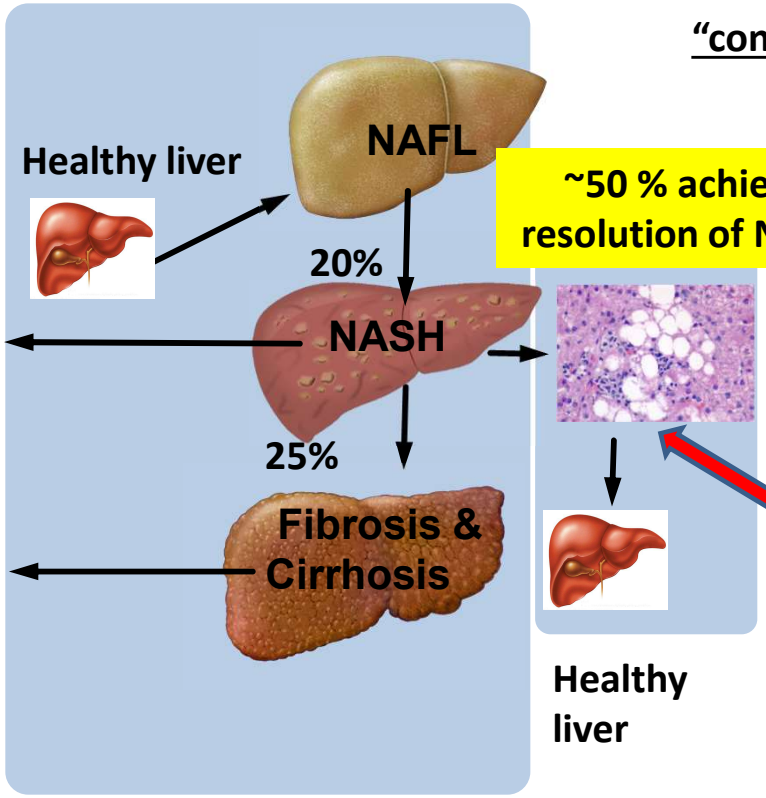
National cohort = 134,368 people with T2DM - mean follow up of 4.3 years
No liver disease = 21,873 CVD events
NAFLD =320 CVD events
ALD = 378 CVD events

Diabetes Care 2018; 41: 1-7

Potential drug treatment for NASH: pioglitazone

No licensed treatment for NAFLD :

Spectrum of disease in NAFLD:



Diabetes
CVD
CKD
Colonic tumours

Liver failure
Liver cancer
Liver transplant

~50 % achieve resolution of NASH

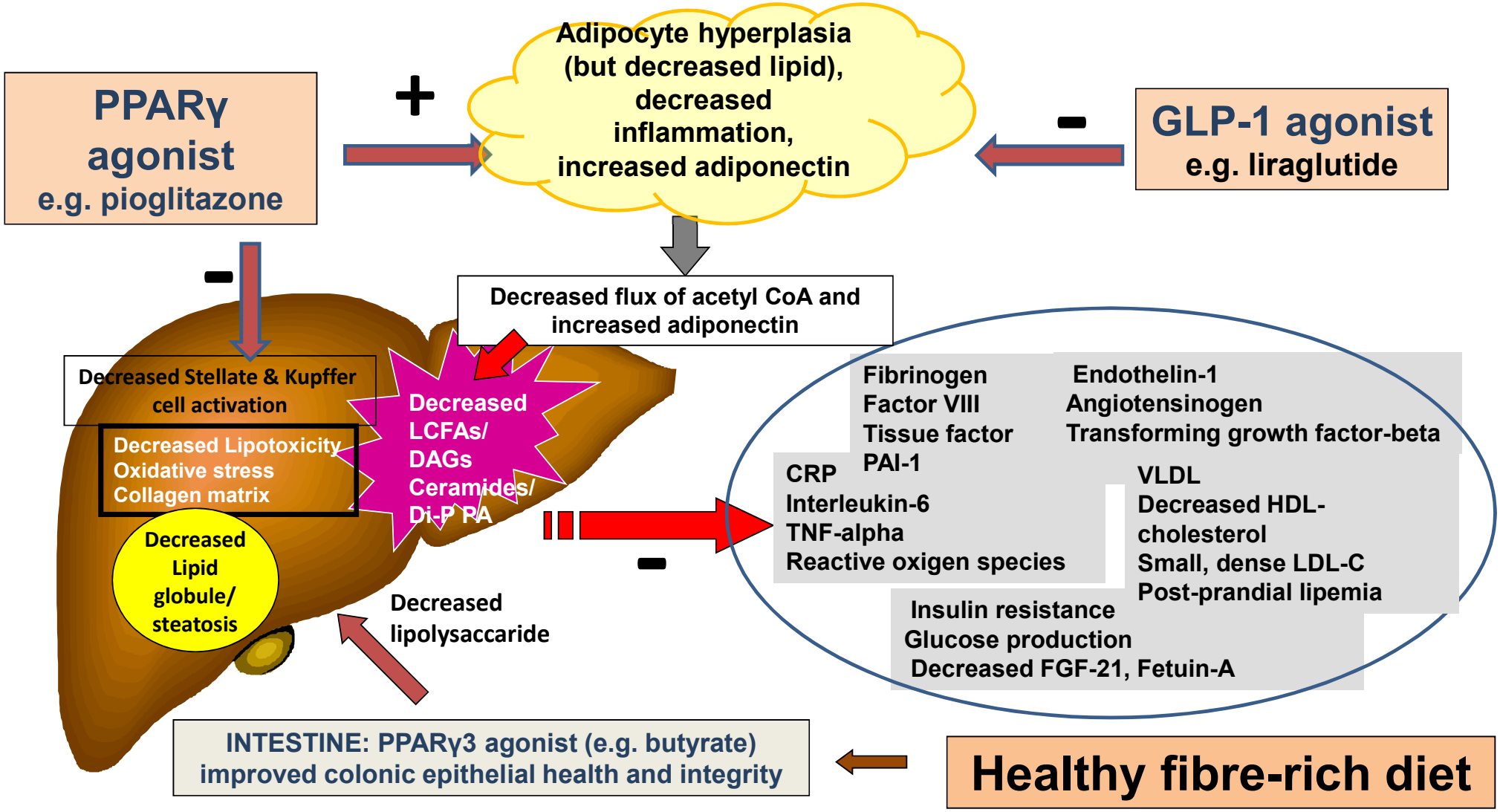
"consider pioglitazone treatment for NASH"

- *NICE NAFLD Guidelines ng49 2016*
- *EASD/EASL/EASO NAFLD Guidelines 2016*
- *American Society Gastroenterology 2012 & 2018*

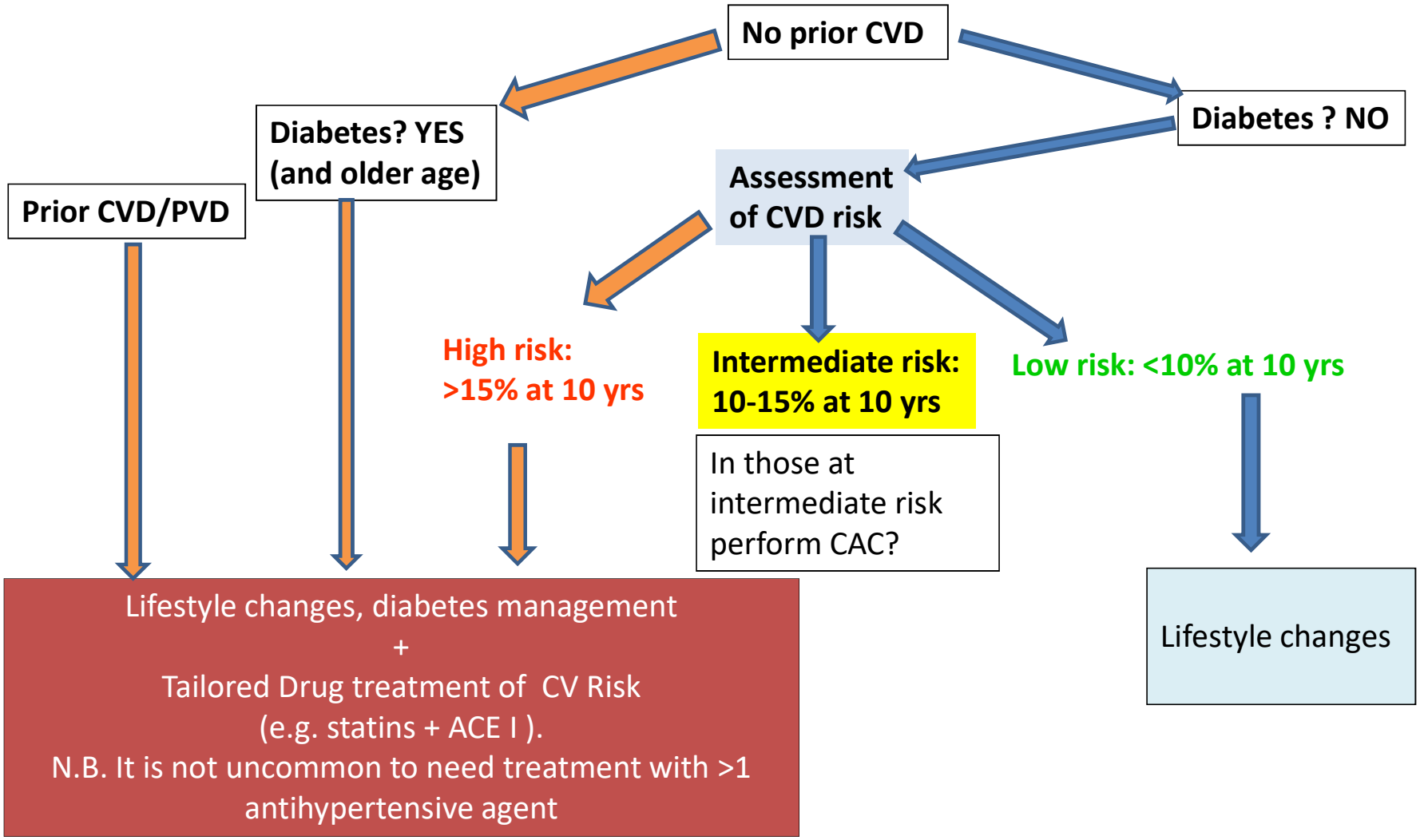
PPAR-γ agonist pioglitazone treatment of NASH

Effectiveness proven in 3 major placebo-controlled clinical trials and meta-analysis:

Potential benefits of combining pioglitazone and GLP-1 agonist?


PPARγ agonist
e.g. pioglitazone
+
Adipocyte hyperplasia (but decreased lipid), decreased inflammation, increased adiponectin
-
GLP-1 agonist
e.g. liraglutide
-
Decreased flux of acetyl CoA and increased adiponectin
Decreased Stellate & Kupffer cell activation
Decreased Lipotoxicity
Oxidative stress
Collagen matrix
Decreased Lipid globule/ steatosis
Decreased LCFAs/ DAGs Ceramides/ Di-P PA
Decreased lipolysaccaride
-
Fibrinogen
Factor VIII
Tissue factor
PAI-1
Endothelin-1
Angiotensinogen
Transforming growth factor-beta
CRP
Interleukin-6
TNF-alpha
Reactive oxigen species
VLDL
Decreased HDL-cholesterol
Small, dense LDL-C
Post-prandial lipemia
Insulin resistance
Glucose production
Decreased FGF-21, Fetuin-A
INTESTINE: PPARγ3 agonist (e.g. butyrate) improved colonic epithelial health and integrity
Healthy fibre-rich diet

At what level of CVD risk should patients with NAFLD be treated?



Type 2 diabetes and cirrhosis/fibrosis/sclerosis/portal hypertension with NAFLD: Markedly increased risk of adverse outcomes compared with T2DM alone

Reference group Type 2DM & No NAFLD	Hazard ratios (95% CI)		
Outcome	Whole NAFLD group [a] (n = 1998)	Fatty liver/NASH sub-group [a,b] (n = 1283)	Cirrhosis / fibrosis/ Sclerosis/ PH sub-group [a,c] (n = 715)
Incident or recurrent CVD event after diagnosis of diabetes	1.62 (1.47, 1.77)	1.66 (1.47, 1.87)	1.57 (1.36, 1.80)
All-cause mortality	2.11 (1.92, 2.32)	1.29 (1.10, 1.51)	3.20 (2.84, 3.60)
CVD mortality	1.39 (1.10, 1.74)	1.10 (0.78, 1.54)	1.78 (1.31, 2.42)
HCC mortality	41.89 (27.1, 64.8)	2.42 (0.33, 17.5)	90.81 (58.0, 142.1)
Cancer mortality (excluding HCC)	1.15 (0.92, 1.42)	0.81 (0.58, 1.13)	1.60 (1.21, 2.10)
Other causes of death	3.16 (2.77, 3.59)	1.89 (1.52, 2.35)	4.82 (4.11, 5.64)

134,368 people with type 2 diabetes with one or more hospital admission records and no record of other chronic liver diseases aged 40-89 years in Scotland from 2004-2013.

Diabetic Medicine, 2019; 36 (Suppl. 1), 5–33 A36

Assessment of liver disease severity and liver dysfunction in patients with diabetes. The Child-Pugh classification to assess liver disease function.

HbA1c = 9.6% (DCCT) Or 81 mmol/mol (IFCC)

= poor glycaemic control

eGFR = 51 mls/min

Child-Pugh B 8 points

Enterococcus & Hepatic encephalopathy

	1 point	2 points	3 points
Child-Pugh score parameters			
Serum bilirubin micromoles/L (mg/dl)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin (mg/dl)	>35	28-35	<28
International Normalized Ratio	<1.70	1.71-2.20	>2.20
Ascites	None	None with medication	Persistent
Hepatic encephalopathy	None	Grade I-II (or none with treatment)	Grade III-IV (or persistent)

Child-Pugh score A = 5-6 points; B = 7-9 points; C = ≥10 points

Potential treatments for diabetes in patients with cirrhosis.

HbA1c = 9.6% (DCCT)
Or 81 mmol/mol (IFCC)

= poor glycaemic control

eGFR = 51 mls/min

Child-Pugh B 8 points

Enterococcus & Hepatic encephalopathy

Treatments*	Usefulness for diabetes and cirrhosis	Side effects
Lifestyle	Maybe useful	May worsen malnutrition common
Metformin	Useful	Caution with eGFR <45 ml/min. Avoid with eGFR <30 ml/min
PPAR-gamma agonists	Maybe useful but caution with liver failure	Avoid with Child-Pugh A, B, or C
Secretagogues Sulphonylureas	Avoid	Major risk of hypoglycaemia with worsening liver function
Incretin modifiers	Useful	Nausea
Glucosidase inhibitors	Maybe useful with encephalopathy	Diarrhoea/flatulence
Insulin	Useful	Hypoglycaemia with worsening liver function

***All treatments can be used in patients with type 2 diabetes. Only insulin should be used in patients with type 1 diabetes and possibly metformin if the patient is obese. eGFR, estimated glomerular filtration rate.**

Statin usage in severe chronic liver disease

HbA1c = 9.6% (DCCT)
Or 81 mmol/mol (IFCC)

= poor glycaemic control

eGFR = 51 mls/min

Child-Pugh B 8 points

Enterococcus & Hepatic encephalopathy

- Benefits of statin treatment in most patients outweigh their potential hepatotoxic risk. Especially in patients with severe chronic liver injury and high risk of CVD
- Statin treatment may help to prevent the progression of liver fibrosis to cirrhosis and HCC.
- Therefore, the reasons for statin use in chronic liver diseases are more convincing than the reasons against
- Statins definitely safe in Child Pugh A
- Statins metabolised by microsomal cytochrome P450s
- Atorva- and simvastatin metabolised by P450 3A4 (drug interactions)
- But Pravastatin NOT metabolised in liver (probably safest statin)
- Pravastatin 40mg/day = Simvastatin 20 mg/day (approx.)

- N.B Statin usage too risky in decompensated cirrhosis

Conclusions (i)

- Diagnose the severity of NAFLD

- Advocate weight loss and Mediterranean-style diet
  - Lifestyle advice targetting no smoking, increase physical activity if possible.
  - Good glycaemic control
- Consider pioglitazone
- Consider liraglutide

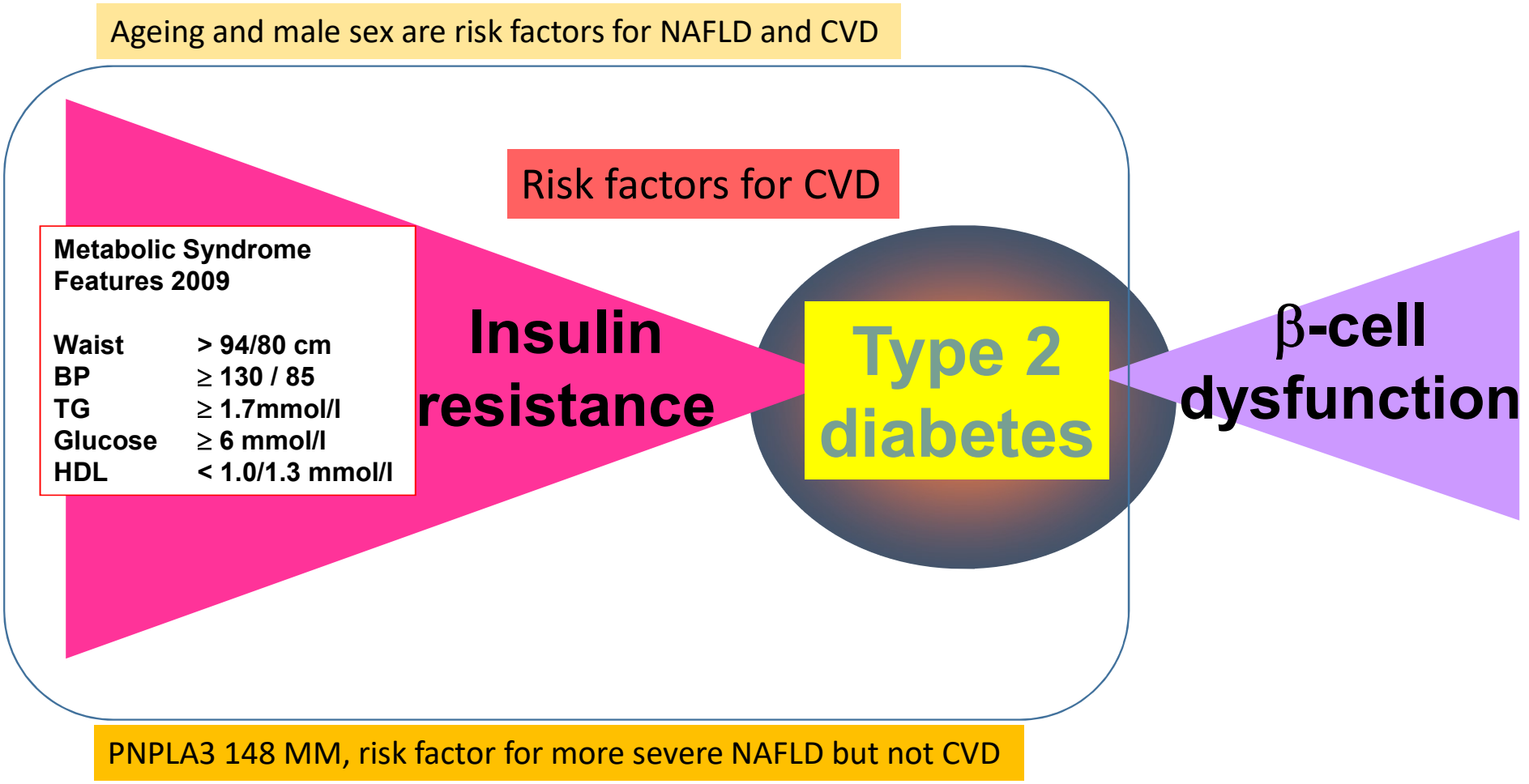
Conclusions (ii)

- Red flags for CVD= MetS features and type 2 diabetes
- CVD risk increased ~64-250% (regardless of diabetes status)
- Assess CVD risk in NAFLD using risk calculators but beware of underestimation of CVD risk – CAC estimation may be useful
- Treat early and aggressively to decrease CVD risk
  - E.g. statins to decrease CVD risk (atorvastatin 10 mg o.d)
  - Treat BP (e.g. >140/80 mmHg, Ramipril, then bendroflumethiazide, then calcium antagonist, consider low dose aspirin)

Conclusions (iii)

- Patients with cirrhosis and type 2 diabetes (T2DM) are at increased risk of cardiovascular disease and non-liver cancer mortality, compared to subjects with T2DM who did not have liver disease.
- Patients with diabetes are at an increased risk of a range of different bacterial infections and patients with poor glycaemic control are particularly at risk of bacterial peritonitis and the development of septicaemia
- Bacteraemia or septicaemia increases insulin resistance and causes hyperglycaemia
- Recovery from infection improves insulin sensitivity necessitating a review of glucose lowering mediations and dosages
- When considering which drug to choose to manage hyperglycaemia in patients with diabetes and cirrhosis it is important to formally assess the level of liver dysfunction (and use of the Child-Pugh criteria are useful).
- Use of insulin is often the easiest and safest treatment for managing fluctuating glucose concentrations in patients with diabetes and cirrhosis requiring hospitalisation

MetS and type 2 diabetes are important CVD risk factors



Diagnosing liver fat

Technique for diagnosing liver fat	Result compatible with NAFLD	Pros and cons of technique
Ultrasonography	Liver echogenicity exceeds that of renal cortex and spleen and there is attenuation of the ultrasound wave, loss of definition of the diaphragm, and poor delineation of the intrahepatic architecture	The sensitivity of ultrasound is poor below levels of fat infiltration <20%-25%, however, the technique is highly sensitive and specific at higher levels of fat infiltration. Combining standard ultrasound with computer software technology (MATLAB) (eg, combined ultrasound hepatic/renal ratio and hepatic echo-intensity attenuation rate evaluation), improves the sensitivity of ultrasound even further
Fatty liver index (FLI) (Algorithm derived score using body mass index, waist circumference, fasting serum triglycerides, and gamma-glutamyltransferase concentrations)	FLI ≥60 suggestive of hepatic steatosis and validated against ultrasound, or magnetic resonance spectroscopy (MRS)	Inexpensive, but requires waist circumference measurements. Not validated against liver histology
NAFLD liver fat score (Algorithm derived score using the presence of metabolic syndrome and type 2 diabetes, fasting serum insulin, AST, and the AST/alanine aminotransferase ratio)	Optimal cut-off point = -0.640 for diagnosing hepatic steatosis on MRS	Inexpensive, but requires serum insulin and AST measurements. Not validated against liver histology

Combining standard ultrasonography with computer software technology (MATLAB), eg combined ultrasound hepatic/renal ratio and hepatic echo-intensity attenuation rate evaluation, improves the sensitivity of ultrasonography. and compared with proton-magnetic resonance spectroscopy (ie, the gold standard for detecting low levels of liver fat content), at levels of <15% liver fat content, the sensitivity and specificity of the aforementioned ultrasound quantitative model was 81.4% and 100%.

Diagnosing liver fat – imaging

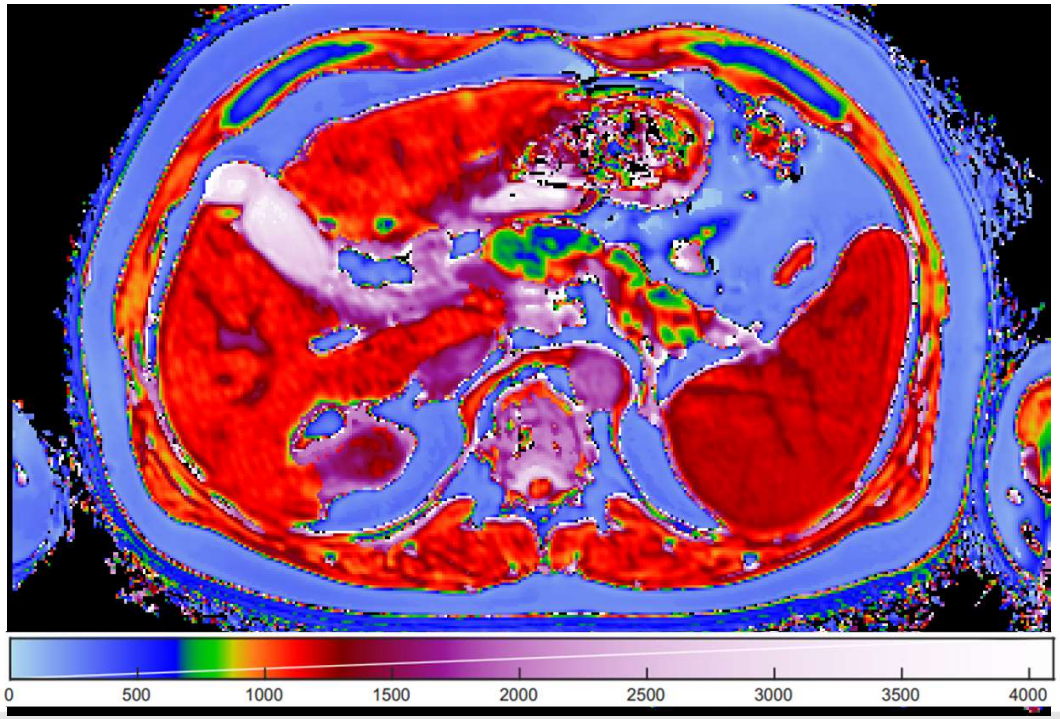
Technique	Result compatible with NAFLD	Pros and cons of technique
Transient elastography (FibroScan)	Optimal controlled attenuation parameter (CAP) thresholds ≥248, ≥268 dB/m for those above stage 1 steatosis grade, respectively[27]	Transient elastography is a promising technique, but further evidence and validation of its utility for diagnosing hepatic steatosis (by CAP measurement) is required. The signal can be affected in severely obese patients
Computed tomography	Attenuation of the liver is at least 10 Hounsfield Units (HU) less than that of the spleen, or attenuation of the liver less than 40 HU[28]	Good for investigating other potential abdominal pathologies. Computed tomography has limited sensitivity to detect low levels (<30% liver fat) and exposes the patient to substantial levels of radiation
Magnetic resonance imaging (MRI) or MRS	MRI: Chemical shift gradient-echo imaging with in-phase and opposed-phase acquisitions identifying ≥5.5% liver fat accumulation MRS: Proton MR spectroscopy identifying ≥5.5% liver fat accumulation[29]	MRI and MRS are very sensitive non-invasive techniques for diagnosing liver fat, but are currently expensive techniques for this indication

Invasive and non-invasive techniques for diagnosing advanced fibrosis in NAFLD

Technique	Result compatible with NAFLD
Biopsy	Advanced fibrosis thresholds=F3 or F4 stages Fibrosis may vary from no fibrosis (F0), portal fibrosis without septa (F1), portal fibrosis with few septa (F2), bridging fibrosis between portal and central veins (F3), and cirrhosis (F4)
Liver fibrosis tests (biochemical variables+/−anthropometry)	Advanced fibrosis thresholds Fibrosis-4 score (FIB4) >2.67[26] NAFLD fibrosis score (NFS) >0.676[27] ELF blood test score ≥10.51[28]
Transient elastography eg, FibroScan with M or XL probes (measurement of liver stiffness)	Advanced fibrosis threshold Vibration controlled transient elastography >8.7 kPA[29 30]
Acoustic radiation force impulse elastography (ARFI)	Advanced fibrosis threshold ARFI >1.4 m/s[31]
Magnetic resonance imaging techniques eg, magnetic resonance elastography (MRE)	Advanced fibrosis threshold MRE >3.64[32]

1. The FIB4 score is calculated as (age×AST)÷(platelet count×√ALT)
2. The NFS is calculated as follows:−1.675+0.037×age+0.094×BMI+1.13×IFG or diabetes (yes=1, no=0)+0.99×AST/ALT ratio−0.013×platelet count−0.66×serum albumin
3. The ELF score is a commercial blood test that combines quantitative measurements of three serum direct fibrosis biomarkers (ie, tissue inhibitor of metalloproteinase 1, procollagen III N-terminal peptide, and hyaluronic acid) to a single value. In a recent meta-analysis, the summary sensitivities and specificities of ELF score for detecting significant fibrosis were 83% and 73%, respectively; those for detecting advanced fibrosis were 78% and 76%, whereas those for detecting cirrhosis were 80% and 71%, respectively.[33]
4. In a recent meta-analysis, the summary sensitivities and specificities of FibroScan with the M probe (threshold of 8.7-9.0 kPA) for detecting advanced fibrosis were 87% and 79%, respectively.[30] A Fibroscan with the XL probe has also been validated for severely obese patients, and has a diagnostic accuracy substantially comparable with that of the standard M probe
5. Magnetic resonance elastography has the highest diagnostic accuracy for staging fibrosis in NAFLD.

Diagnosing NASH with Magnetic resonance imaging
-Multiparametric MRI to assess fat, inflammation and fibrosis



Statistics Summary

Fat: **10.9 %**	Normal range: <5.6% [1]	**LIF 3.4**
Iron: **1.2 mg/g liver**	Normal range: <1.8mg/g [2]	
cT1: **1092.4 ms**	Normal range: 645ms - 822ms [3]	

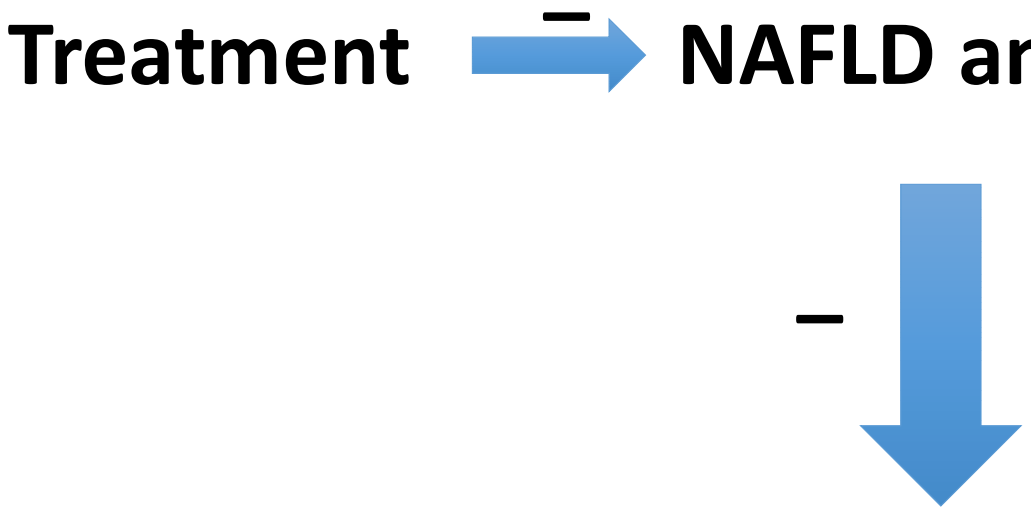
Comments

Severe disease, likely florid steatohepatitis, or autoimmune hepatitis

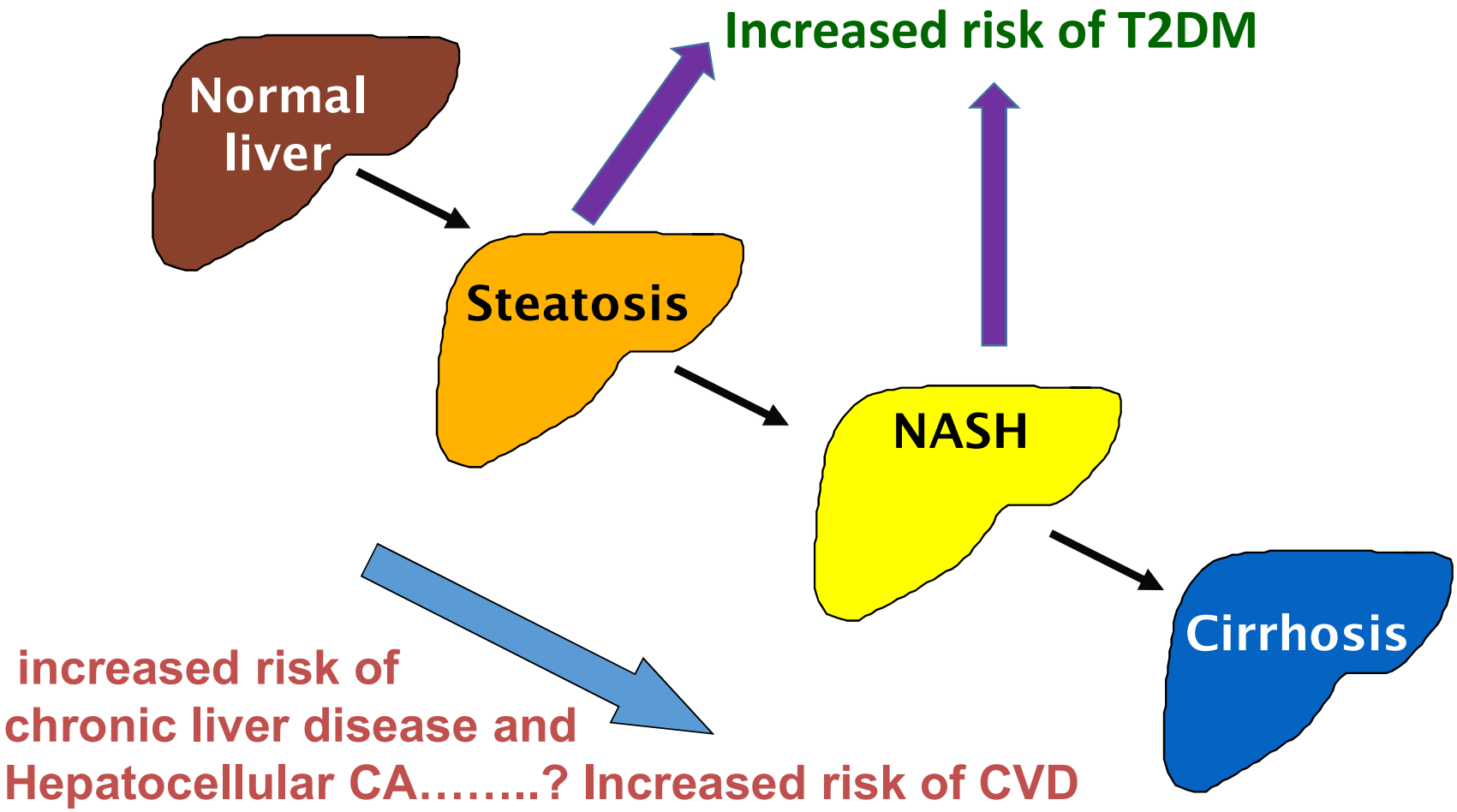
Banerjee R
J Hepatology 2014

Courtesy of Dr R Banerjee

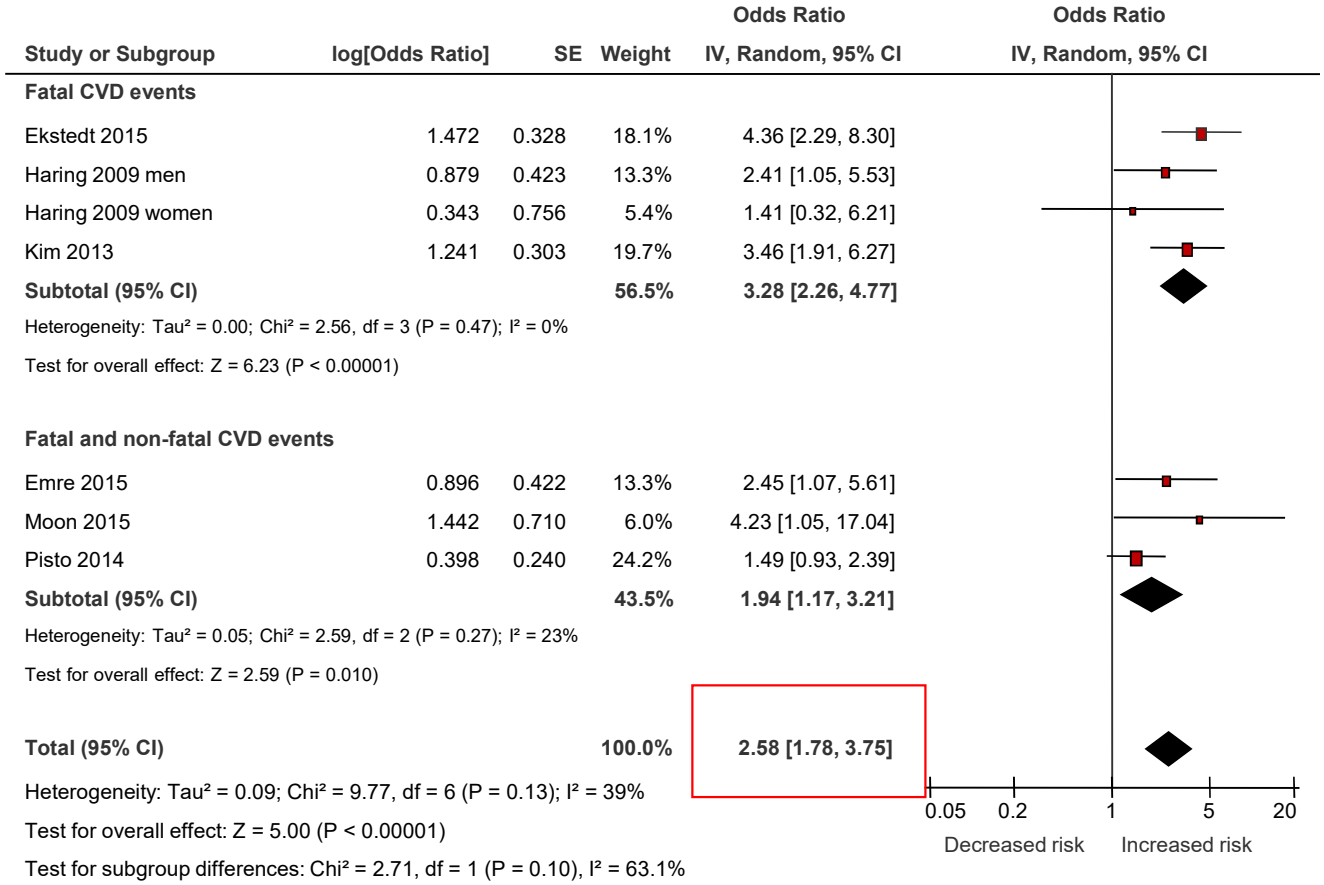
NAFLD and multimorbidity: treatment needs to consider multimorbidity



Does progression of NAFLD further increase risk of CVD?



Random-effects meta-analysis of the risk of fatal and non-fatal CVD events associated with more severe NAFLD

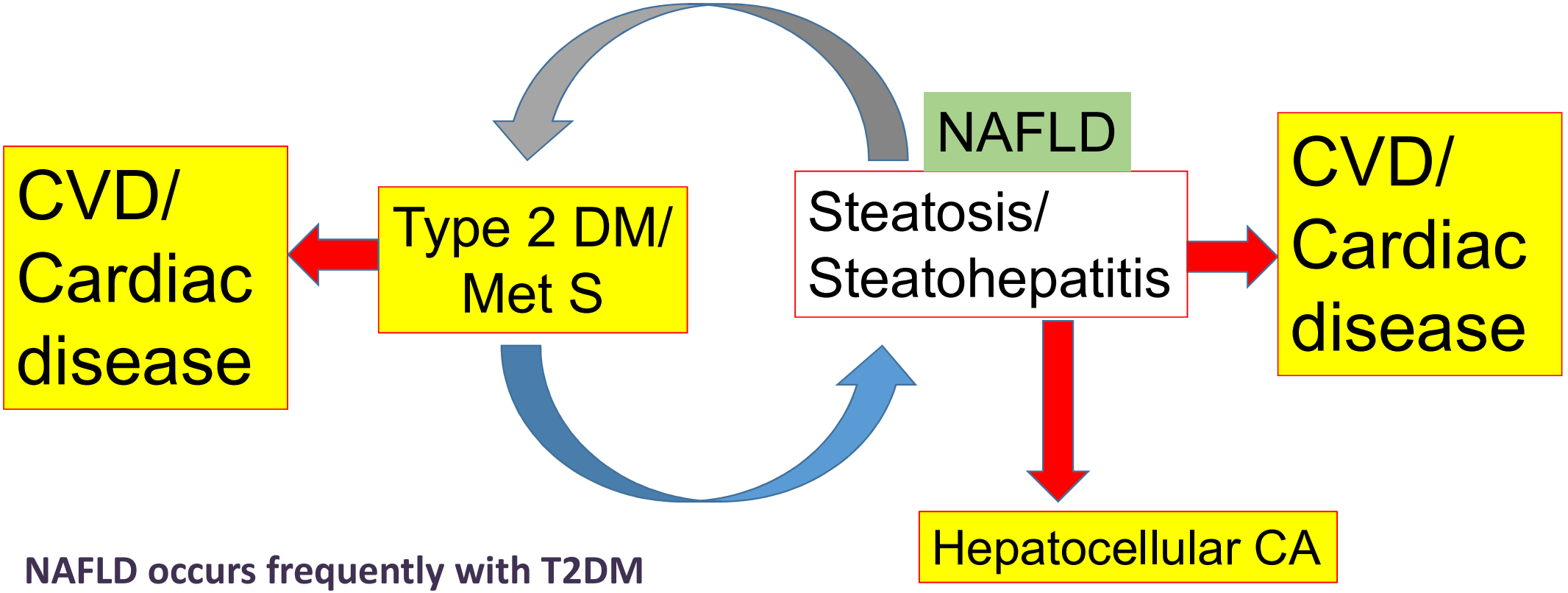


J. Hepatology 2016; 65: 589-600

Summary HR (95%CIs) = 2.58 (1.78, 3.75)

More severe NAFLD defined either by presence of fatty liver on imaging *plus* either elevated serum gamma-glutamyltransferase concentrations or high NAFLD fibrosis score or high FDG uptake on positron emission tomography, or by increasing fibrosis stage on liver biopsy).

Type 2 diabetes and NAFLD: a vicious cycle for cardiovascular and cardiac disease



- NAFLD occurs frequently with T2DM
- T2DM is an important risk factor for CVD
- Does NAFLD increase risk of CVD in people with T2DM?

J Nutr Sci. 2017 May 8;6:e15.

NAFLD, type 2 diabetes and CVD

In patients with established type 2 diabetes

Question:

-Does NAFLD increase risk of CVD?

Visceral ectopic fat, adipose tissue inflammation, MetS type 2 diabetes

Poor nutrition (e.g. high fat, high carbohydrate, high fructose)
Genetic factors
(e.g. PNPLA3 genotype)

LCFAs, hyperinsulinaemia, adipocytokines

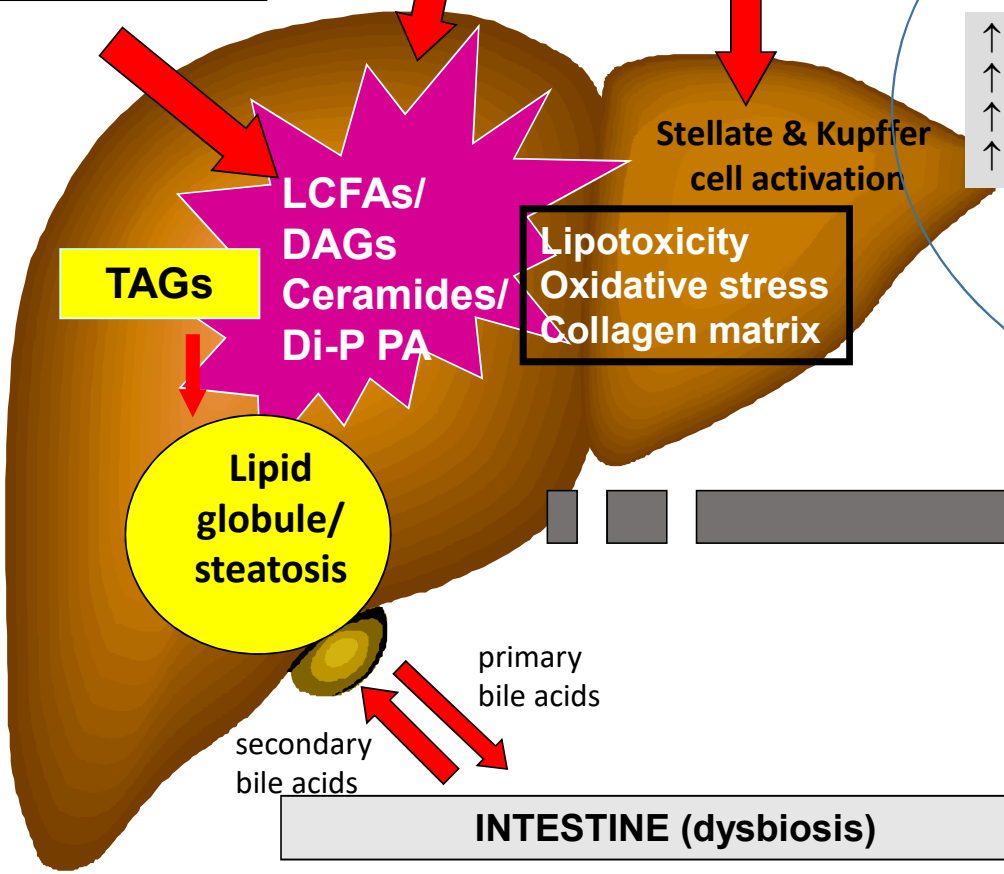
↑ Fibrinogen
↑ Factor VIII
↑ Tissue factor
↑ PAI-1

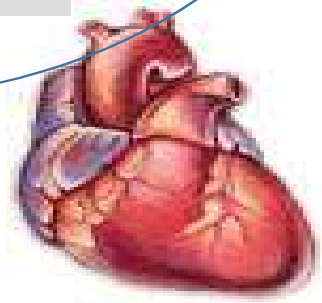
↑ Angiotensinogen
↑ Endothelin-1
↑ Tranforming growth factor-beta

↑ CRP
↑ Interleukin-6
↑ TNF-alpha
↑ Reactive oxigen species

↑ VLDL
↓ HDL-cholesterol
↑ Small, dense LDL-C
↑ Post-prandial lipemia

↑ Insulin resistance
↑ Glucose production
↑ FGF-21
↑ Fetuin-A





INTESTINE (dysbiosis)

Poor nutrition (e.g. high fat, high carbohydrate, high fructose)
Genetic factors