NIHR | Southampton Biomedical Research Centre

UNIVERSITY OF Southampton

NAFLD as a multisystem disease:

Type 2 diabetes and the updated NICE diabetes guideline ng 28

www.nice.org.uk/guidance/NG28

Chris Byrne

Professor Endocrinology & Metabolism,

University of Southampton
& Southampton NIHR BRC, University Hospital Southampton

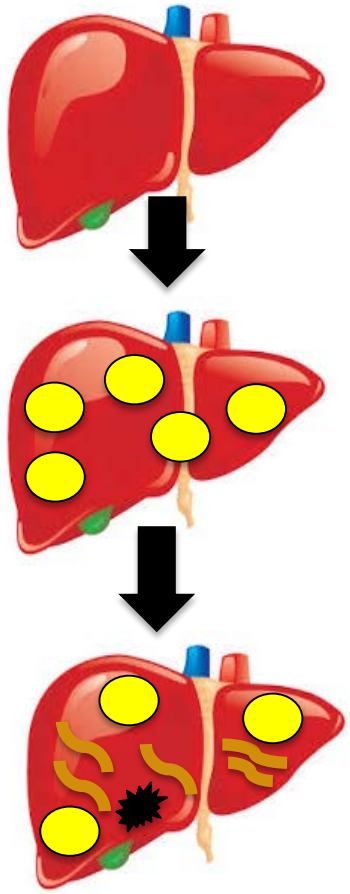
NAFLD: a multisystem disease

J Hepatology. 2015 & Lancet Gastroenterol Hepatol. 2021

Normal liver

Steatosis

NASH ± fibrosis



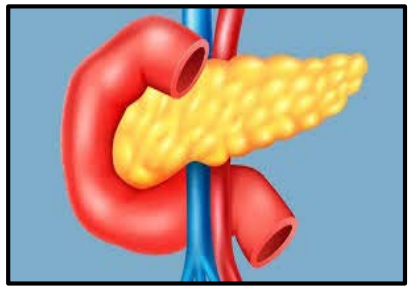
Insulin resistance/hyperinsulinaemia and related disorders
(e.g. atherogenic dyslipidaemia, hypertension, dysglycaemia, high non-esterified fatty acids)

Vasoactive and thrombogenic molecules
(e.g. fibrinogen, transforming growth factor-beta, plasminogen activator inhibitor-1, reactive oxygen species)

Proinflammatory factors
(e.g. interleukin-1 beta, interleukin-6, tumour necrosis factor-alpha, C-reactive protein)

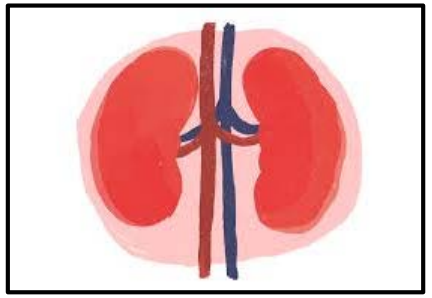
CVD & Arrhythmias

Lancet Gastroenterol Hepatol.
2021 Nov;6(11):903-913



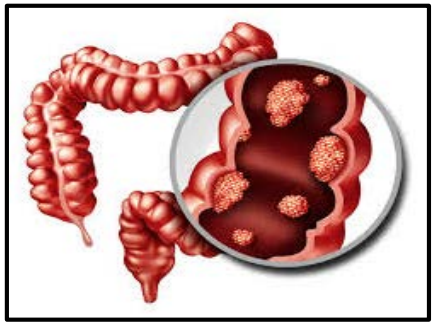
Type 2 diabetes

Gut. 2021 May;70(5):962-969



Chronic kidney disease

Gut. 2022 71:156-162.



Extra-hepatic cancers

Gut. 2022;71:778-788

Arteriosclerosis, Thrombosis, and Vascular Biology

AHA SCIENTIFIC STATEMENT

Nonalcoholic Fatty Liver Disease and Cardiovascular Risk: A Scientific Statement From the American Heart Association

P. Barton Duell, MD, Chair; Francine K. Welty, MD, Vice Chair; Michael Miller, MD; Alan Chait, MD; Gmerice Hammond, MD, MPH; Zahid Ahmad, MD; David E. Cohen, MD, PhD; Jay D. Horton, MD; Gregg S. Pressman, MD; Peter P. Toth, MD, PhD; on behalf of the American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Hypertension; Council on the Kidney in Cardiovascular Disease; Council on Lifestyle and Cardiometabolic Health; and Council on Peripheral Vascular Disease

ATVB April 2022

NAFLD and CVD

hepatocellular carcinoma. In addition to these serious complications, NAFLD is a risk factor for atherosclerotic cardiovascular disease, which is the principal cause of death in patients with NAFLD. Accordingly, the purpose of this scientific statement is to review the underlying risk factors and pathophysiology of NAFLD, the associations with atherosclerotic cardiovascular disease, diagnostic and screening strategies, and potential interventions.

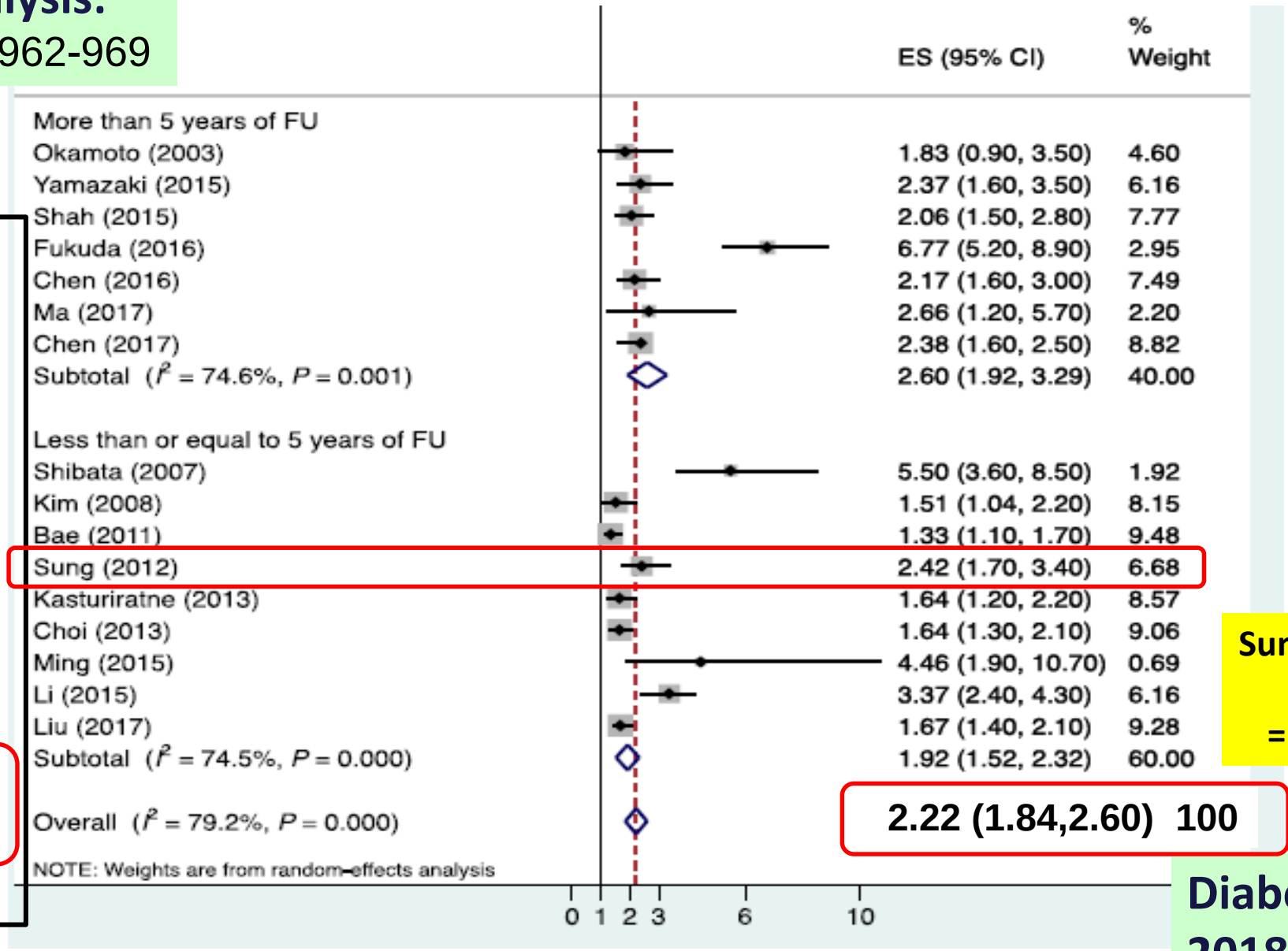
Key Words: AHA Scientific Statements ■ cardiovascular diseases ■ diabetes mellitus ■ hepatocytes ■ hypertriglyceridemia ■ insulin resistance ■ metabolic syndrome ■ nonalcoholic fatty liver disease ■ triglycerides

NAFLD increases risk of incident diabetes

Updated meta-analysis:
Gut. 2021 May;70(5):962-969

- **33 studies (501 022 individuals) (30.8% with NAFLD)**
- **27 953 cases of incident diabetes over a median of 5 years (IQR: 4.0-19 years).**
- **Patients with NAFLD had a higher risk of incident diabetes than those without NAFLD**

random-effects HR 2.19, 95% CI 1.93 to 2.48; I^2 =91.2%)



Summary HR (95%CIs)

= 2.22 (1.84, 2.60)

Diabetes Care 2018; 41: 372-382

NAFLD improves risk prediction for type 2 diabetes and effect modification by sex and age

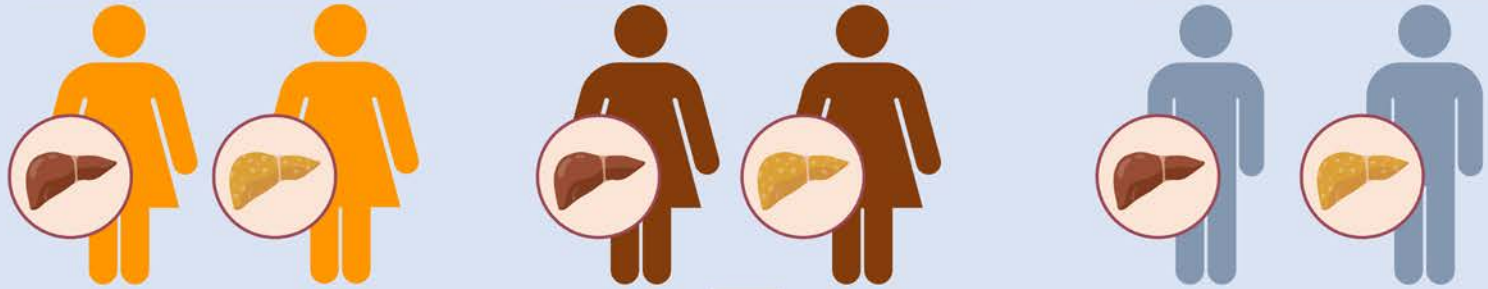
Kim Y, Chang Y, Ryu S, Wild SH, Byrne CD. HEPATOLOGY 2022 accepted

A total of 245,054 adults without diabetes were included.

Premenopausal women (n=109,810)

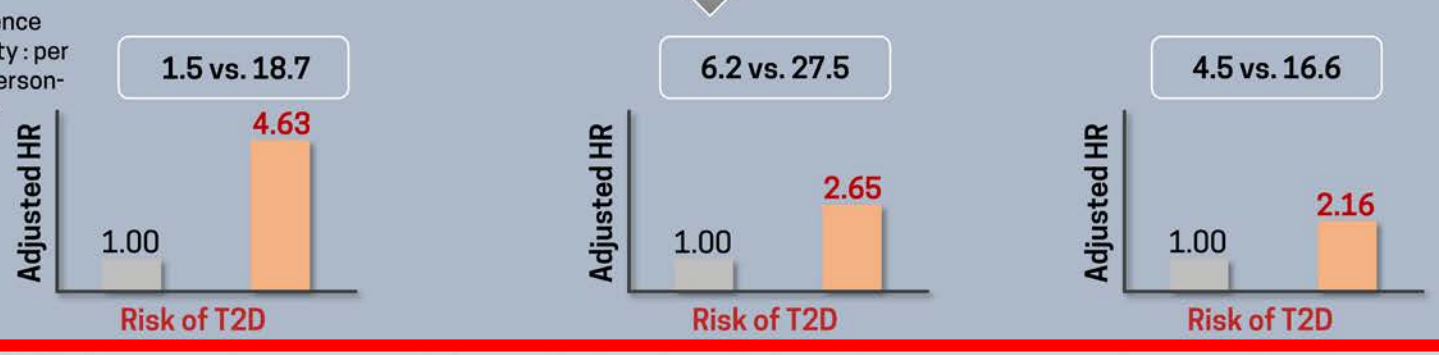
Postmenopausal women (n=4,958)

Men (n=130,286)



Median follow-up: 5.3 years

Incidence density : per 10^3 person-years



NAFLD is a much stronger risk factor for incident diabetes in premenopausal women than in post-menopausal women or men.

Conventional risk factors

NAFLD

Age, Family history of diabetes, Hypertension, BMI, waist circumference

Combined risk prediction model for T2D (AUROC)

	Base	+NAFLD
Premenopausal	0.823	0.838 ↑
Postmenopausal	0.708	0.743 ↑
Men	0.744	0.758 ↑

The addition of NAFLD to conventional risk factors improved risk prediction for incident T2D in both sexes, with a highest discriminatory power in pre-menopausal women than men or post-menopausal women.

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

J. Hepatology 2016; 65: 589-600 → Updated systematic review and meta-analysis → Lancet Gastroenterol Hepatol. 2021 Nov;6(11):903-913

SUMMARY:

36 longitudinal studies aggregate data on 5.8 million middle-aged adults

Mean (SD) age 53 (7) years

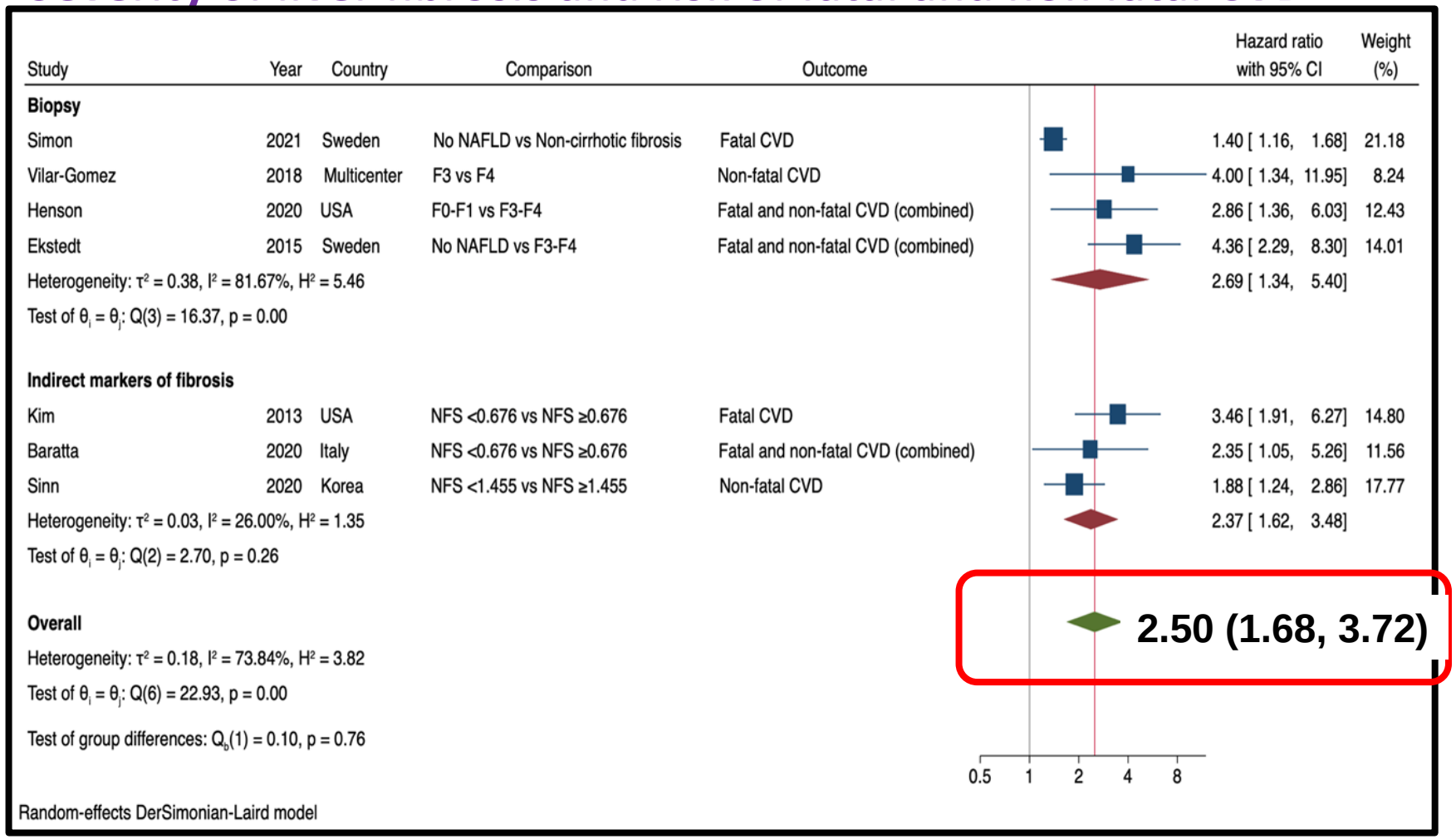
99668 incident fatal and non-fatal CVD events

Median (IQR) follow up 6.5 (5.0-10.2) years

NAFLD associated with increased risk of incident CVD events pooled random-effects **HR 1.45 (95%CI 1.31, 1.61)**

(independent of age, sex, diabetes, adiposity measures, common CVD risk factors.

Severity of liver fibrosis and risk of fatal and non fatal CVD



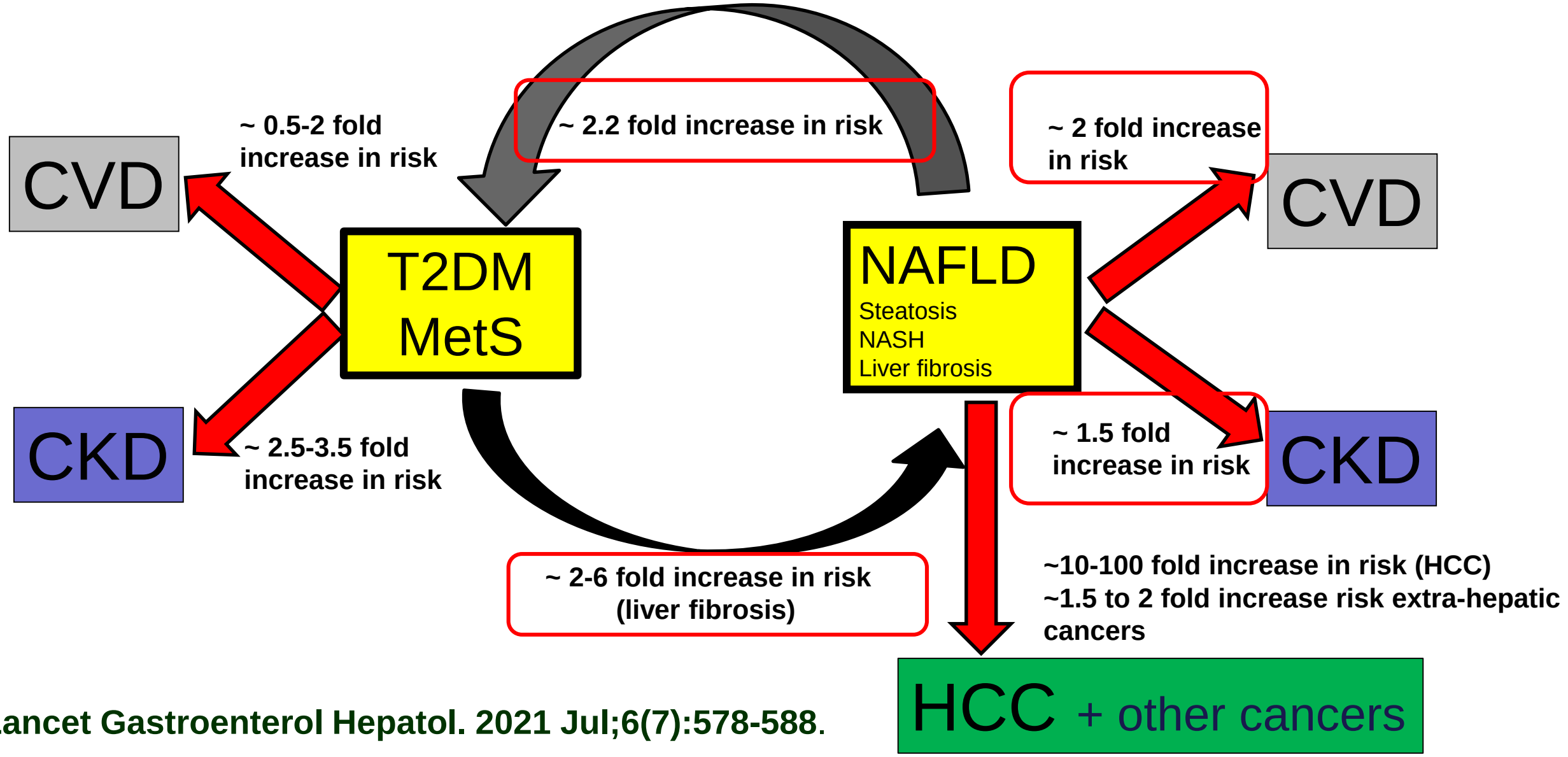
NAFLD and risk of CVD: modified by T2DM, genotype and maybe LDL-C

- Meta-regression analyses to examine the effect of potential moderator variables, showed a significant positive association between the proportion of patients with pre-existing type 2 diabetes (p=0·001) and LDL-C (p=0.04) **Lancet Gastroenterol Hepatol. 2021 Nov;6(11):903-913**
- NAFLD increases risk of CVD in patients with T2DM

  Wild et al. Diabetes Care 2018

- Risk of CVD increases with liver fibrosis **Lancet Gastroenterol Hepatol. 2021 Nov;6(11):903-913**
- Risk of CVD attenuated with PNPLA3 I148M & TM6SF2 E167K

Type 2 diabetes and NAFLD: a vicious spiral of adverse outcomes



Lancet Gastroenterol Hepatol. 2021 Jul;6(7):578-588.

As health care professionals why do we need to diagnose NAFLD in our patients with diabetes?

In patients with type 2 diabetes, NAFLD (versus no NAFLD) is a risk factor for incident /recurrent CVD, all cause mortality and hepatocellular carcinoma (HCC)

N.B Incident/recurrent HCC risk is markedly increased

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)

HCC HR (95%CIs) = 19.3 (11.8, 31.4)

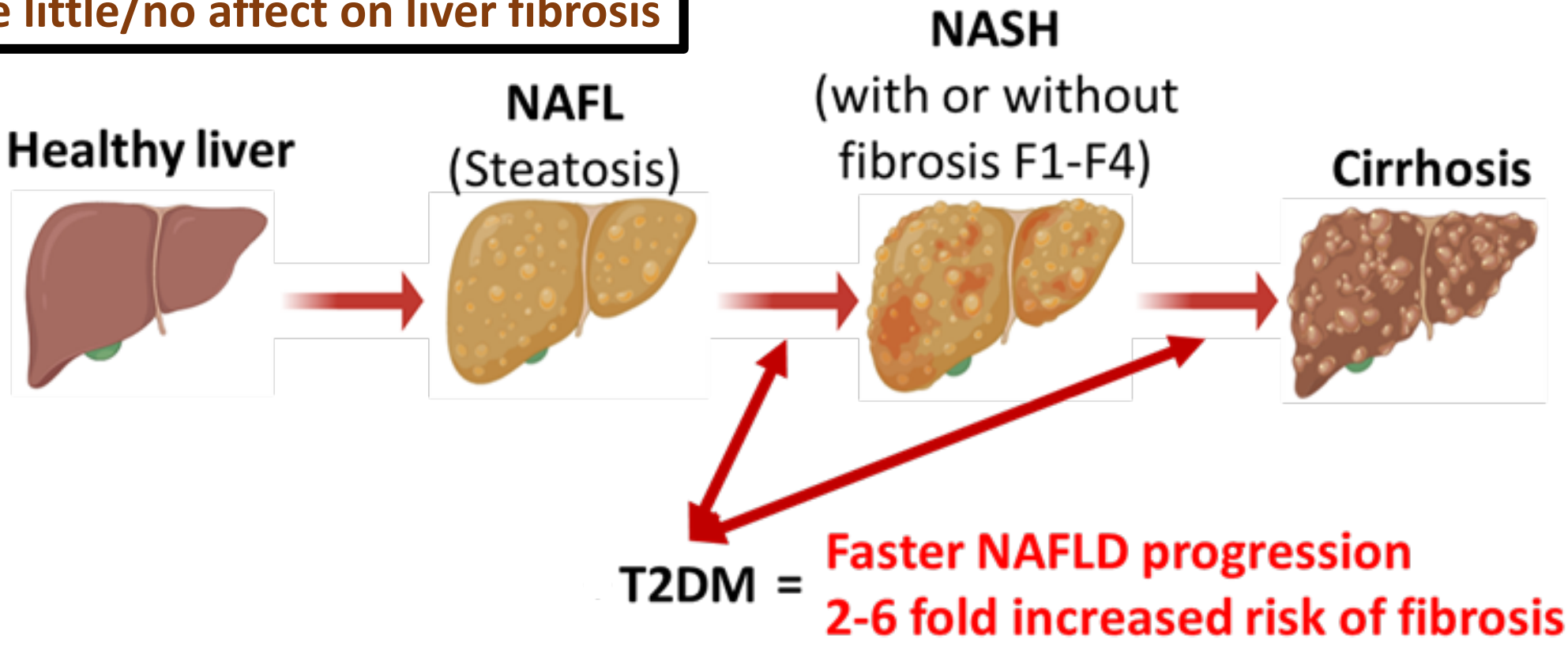
Sarah Wild

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

Type 2 diabetes increases risk of liver fibrosis, cirrhosis and HCC: why?

N.B. Lifestyle change interventions have little/no affect on liver fibrosis



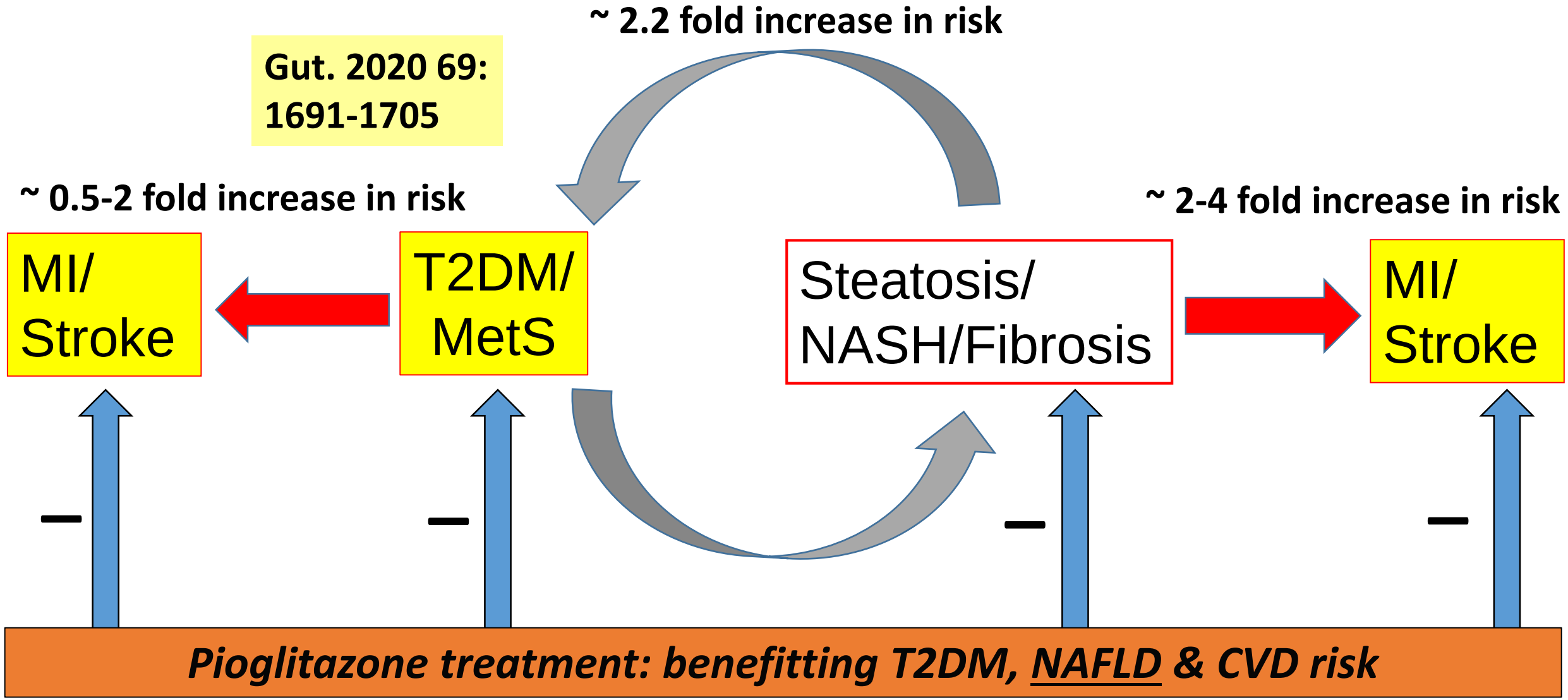
Lancet Gastroenterol Hepatol. 2021 Jul;6(7):578-588.

Drugs used to decrease glucose in type 2 diabetes that may be useful in the treatment of NAFLD: a systematic review

- **Efficacy of drugs to treat NAFL and NASH:**
  - **peroxisome proliferator-activated receptor gamma agonists - yes**
  - **glucagon-like peptide-1 receptor agonists - yes**
  - **sodium-glucose cotransporter-2 inhibitors - possibly**

Lancet Gastroenterol Hepatol 2022 Jan 11;S2468-1253(21)00261-2

‘Pioglitazone the forgotten, cost effective, cardio-protective drug for the treatment of type 2 diabetes’ – De Fronzo 2019



www.nice.org.uk/guidance/NG28.

Published date: 02 December 2015.
Last updated: 15 February 2022 (amended March 2022).

NICE Type 2 Diabetes

Continuous glucose monitoring

1.6.17 Offer intermittently scanned continuous glucose monitoring (isCGM, commonly referred to as 'flash') to adults with type 2 diabetes on multiple daily insulin injections if any of the following apply:

- they have recurrent hypoglycaemia or severe hypoglycaemia
- they have impaired hypoglycaemia awareness
- they have a condition or disability (including a learning disability or cognitive impairment) that means they cannot self-monitor their blood glucose by capillary blood glucose monitoring but could use an isCGM device (or have it scanned for them)
- they would otherwise be advised to self-measure at least 8 times a day.

For guidance on continuous glucose monitoring (CGM) for pregnant women, see the NICE guideline on diabetes in pregnancy. **[2022]**

1.6.18 Offer isCGM to adults with insulin-treated type 2 diabetes who would otherwise need help from a care worker or healthcare professional to monitor their blood glucose. **[2022]**

1.6.19 Consider real-time continuous glucose monitoring (rtCGM) as an alternative to isCGM for adults with insulin-treated type 2 diabetes if it is available for the same or lower cost. **[2022]**

1.6.20 CGM should be provided by a team with expertise in its use, as part of supporting people to self-manage their diabetes. **[2022]**

1.6.21 Advise adults with type 2 diabetes who are using CGM that they will still need to take capillary blood glucose measurements (although they can do this less often). Explain that is because:

- they will need to use capillary blood glucose measurements to check the accuracy of their CGM device
- they will need capillary blood glucose monitoring as a back-up (for example when their blood glucose levels are changing quickly or if the device stops working).

Provide them with enough test strips to take capillary blood glucose measurements as needed. **[2022]**

1.6.22 If a person is offered rtCGM or isCGM but cannot or does not want to use any of these devices, offer capillary blood glucose monitoring. **[2022]**

1.6.23 Ensure CGM is part of the education provided to adults with type 2 diabetes who are using it (see the section on education). **[2022]**

1.6.24 Monitor and review the person's use of CGM as part of reviewing their diabetes care plan (see the section on individualised care). **[2022]**

1.6.25 If there are concerns about the way a person is using the CGM device:

- ask if they are having problems using their device
- look at ways to address any problems and concerns to improve their use of the device, including further ed Continuous glucose monitoring psychological support. **[2022]**

1) National Institute for Health and Care Excellence. Type 2 diabetes in adults: management (NG28) (2022). https://www.nice.org.uk/guidance/ng28

Diet and weight loss

• Encourage adults with type 2 diabetes to follow the same healthy eating advice as the general population, which includes:

• eating high-fibre, low-glycaemic-index sources of carbohydrates, such as fruit, vegetables, wholegrains and pulses

• choosing low-fat dairy products

• eating oily fish

• controlling their intake of saturated and trans fatty acids

•For adults with type 2 diabetes who are overweight, discuss and agree an initial body weight loss target of 5% to 10%. Remember that a small amount of weight loss may still be beneficial, and a larger amount will have advantageous metabolic impact in the long term

HbA_{1c} measurement

Measurement

•Measure HBA_{1c} levels in adults with type 2 diabetes every:

- 3 to 6 months (tailored to individual needs) until HbA_{1c} is stable on unchanging therapy
- 6 months once the HbA_{1c} level and blood glucose lowering therapy are stable.

•Measure HbA_{1c} using methods calibrated according to International Federation of Clinical Chemistry (IFCC) standardisation.

•If HbA_{1c} monitoring is invalid because of disturbed erythrocyte turnover or abnormal haemoglobin type, estimate trends in blood glucose control using one of the following:

- quality-controlled plasma glucose profiles
- total glycated haemoglobin estimation (if abnormal haemoglobins)

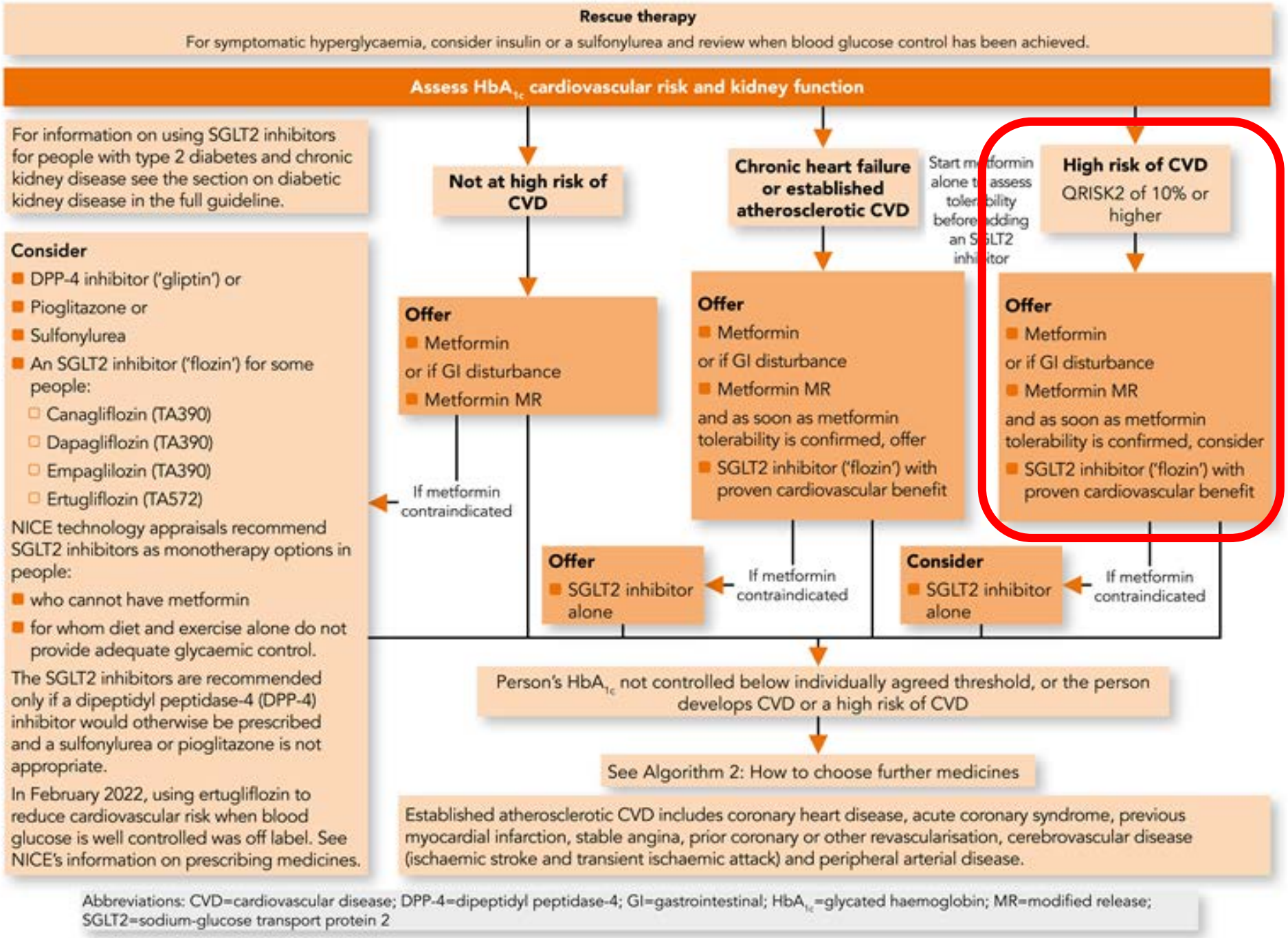
HbA_{1c} targets

Targets

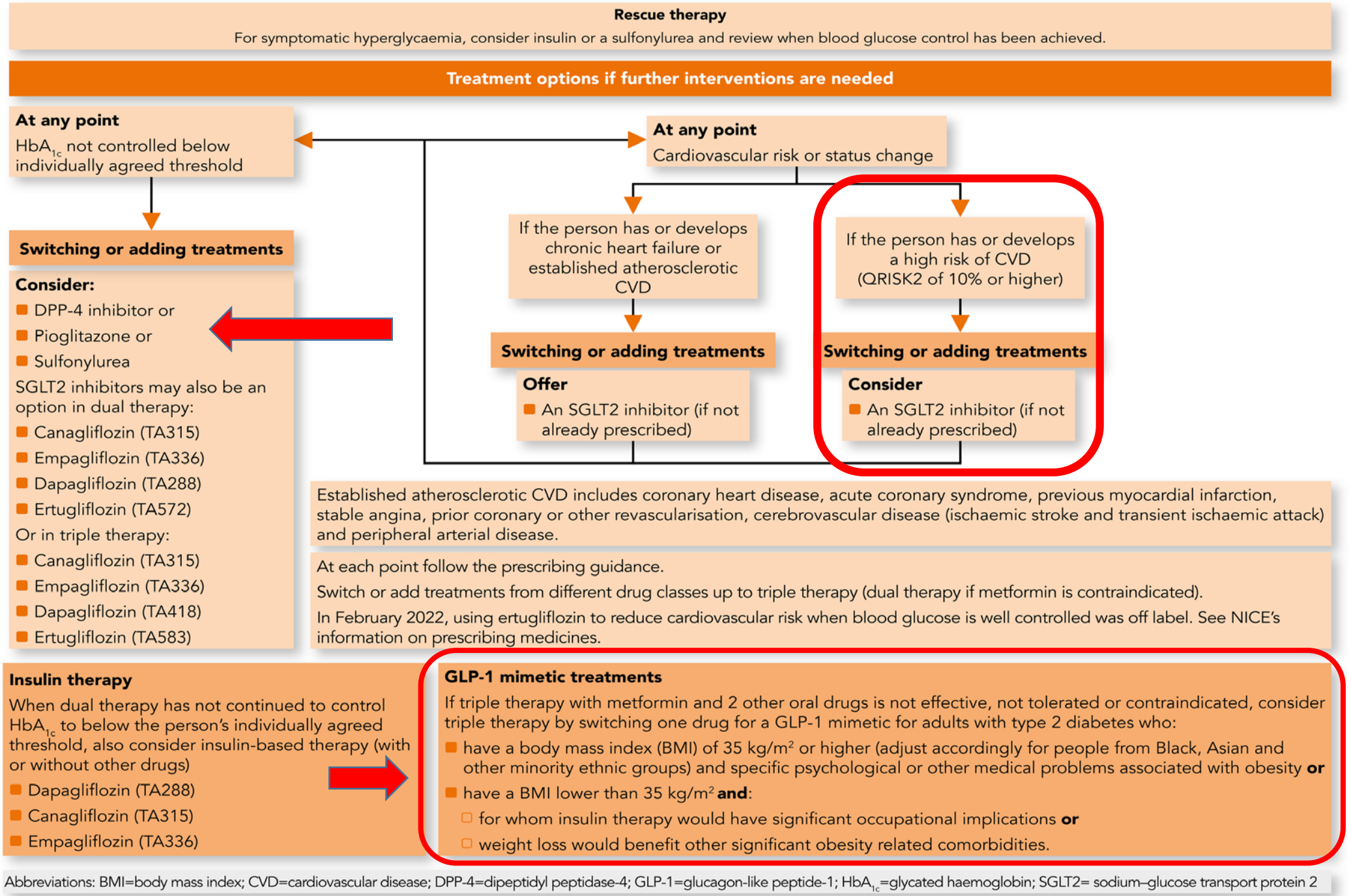
- For adults whose type 2 diabetes is managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycaemia, support them to aim for an HbA_{1c} level of 48 mmol/mol (6.5%).
- For adults on a drug associated with hypoglycaemia, support them to aim for an HbA_{1c} level of 53 mmol/mol (7.0%).
- In adults with type 2 diabetes, if HbA_{1c} levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher:
    - reinforce advice about diet, lifestyle and adherence to drug treatment **and**
    - support the person to aim for an HbA_{1c} level of 53 mmol/mol (7.0%) **and**
    - intensify drug treatment

Algorithm 1: How to choose first-line medicines

N.B. the absence of GLP-1R agonists!

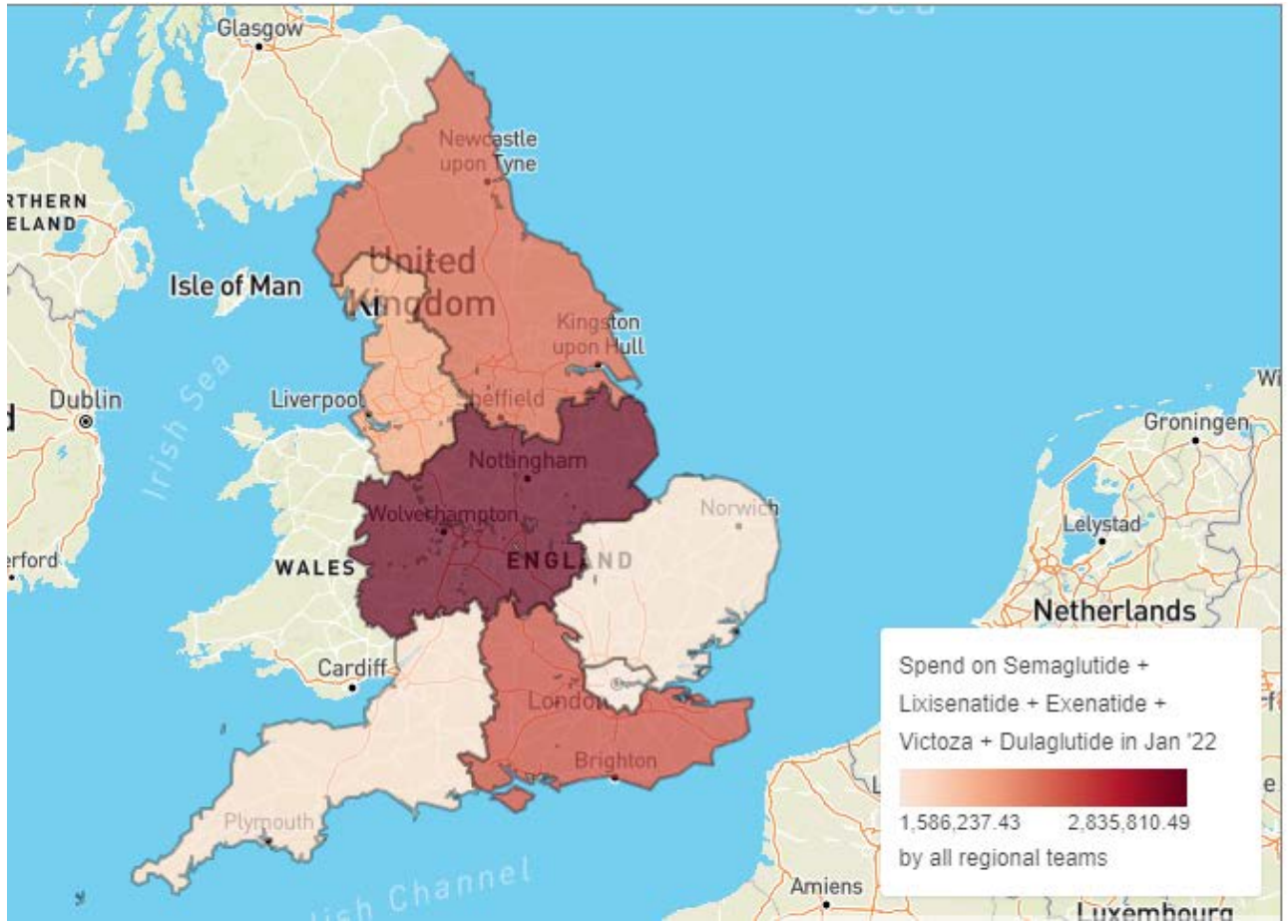


Algorithm 2: How to choose further medicines

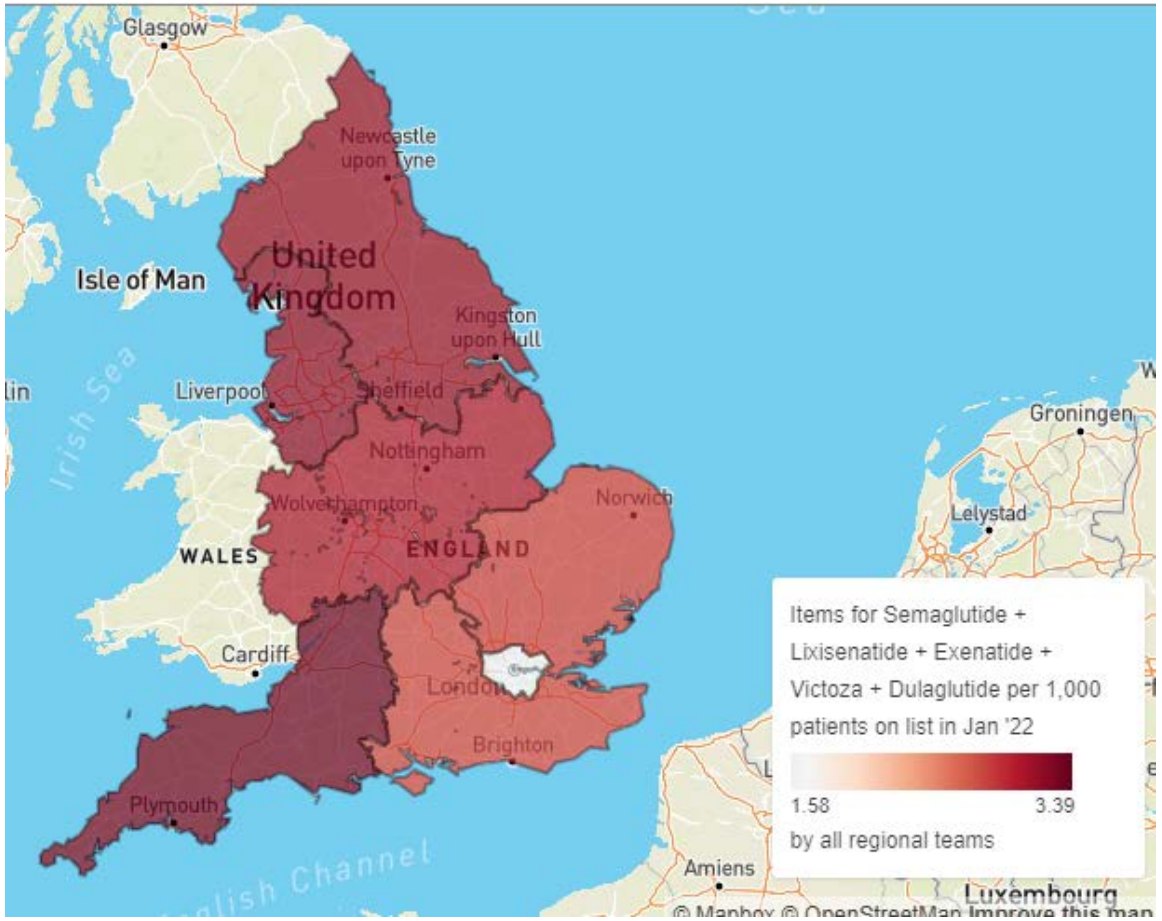


GLP-1 R agonists: the “costly” medicines

Spend annually



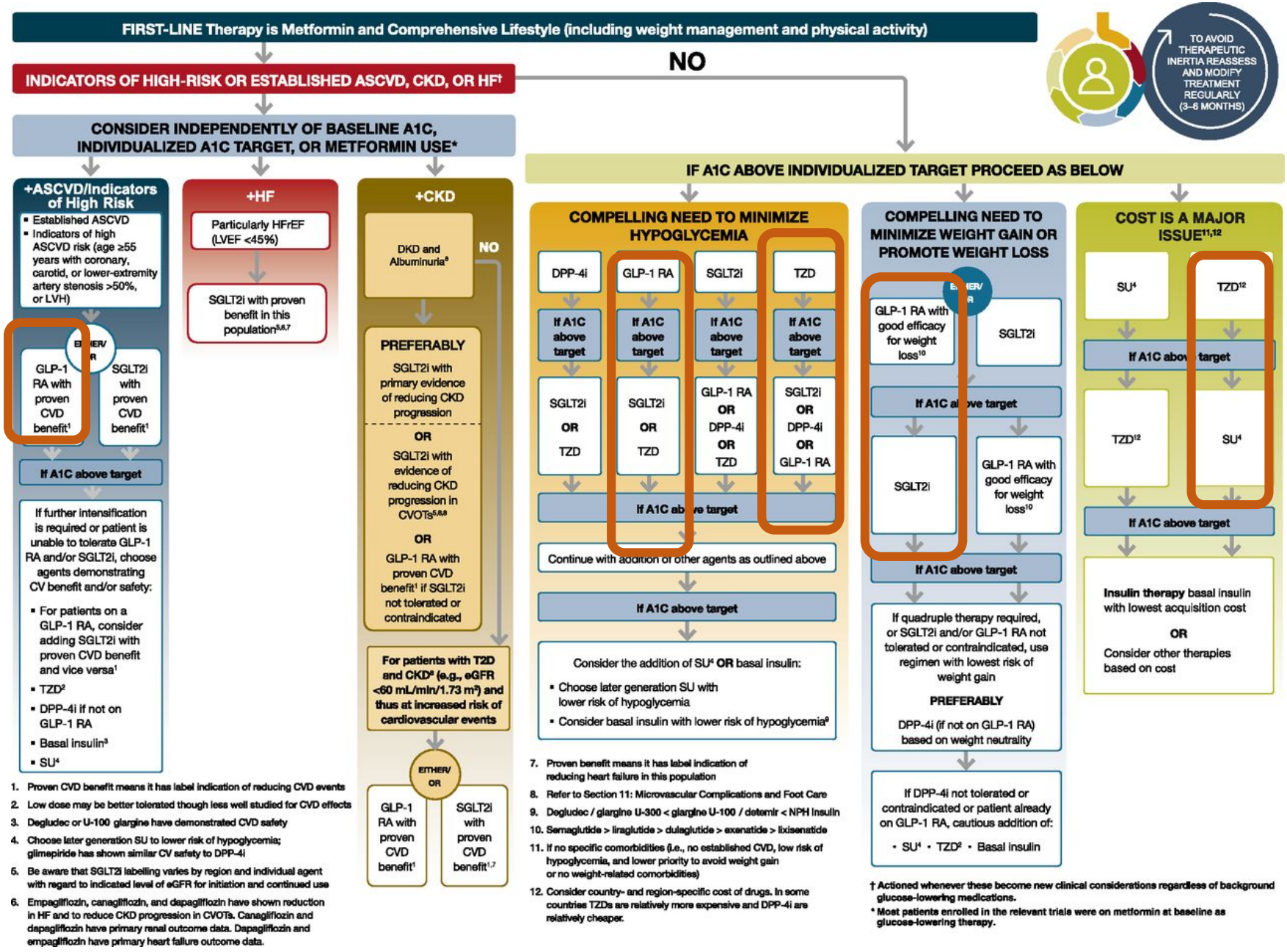
Spend annually/ 1000 population



High CVD risk

US Guidelines much greater focus on the use of GLP-1R agonists

Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2021*



Diabetes Care 2021;44(Supplement_1):S111–S124 https://doi.org/10.2337/dc21-S009

Conclusions: NAFLD as a multisystem disease

- The relationship between NAFLD and cardiovascular disease is complex and is influenced by T2DM:
- Diabetes is a strong risk factor for liver fibrosis and HCC and GDF-15 level may be involved in fibrosis development and is strongly associated with HbA1c concentration
- (Excess) nutrients (e.g. sucrose and fructose) are important.
- Treatments such as GLP-1 agonists (weight loss) and PPAR gamma agonists (lipid remodelling and decreased inflammation) should be considered
- In adults with type 2 diabetes, if HbA_{1c} levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher:
  - reinforce advice about diet, lifestyle and adherence to drug treatment **and**
  - support the person to aim for an HbA_{1c} level of 53 mmol/mol (7.0%) **and**
  - intensify drug treatment