



# NAFLD as a multisystem disease: Type 2 diabetes and the updated NICE diabetes guideline ng 28

www.nice.org.uk/guidance/NG28



**Chris Byrne** 

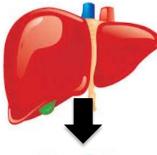
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# NAFLD: a multisystem disease

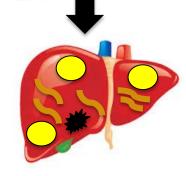
J Hepatology. 2015 & Lancet Gastroenterol Hepatol. 2021





**Steatosis** 





# Insulin resistance/hyperinsulinaemia and related disorders

(e.g. atherogenic dyslipidaemia, hypertension, dysglycaemia, high non-esterified fatty acids)

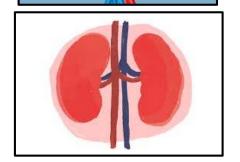
## Vasoactive and thrombogenic molecules

(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

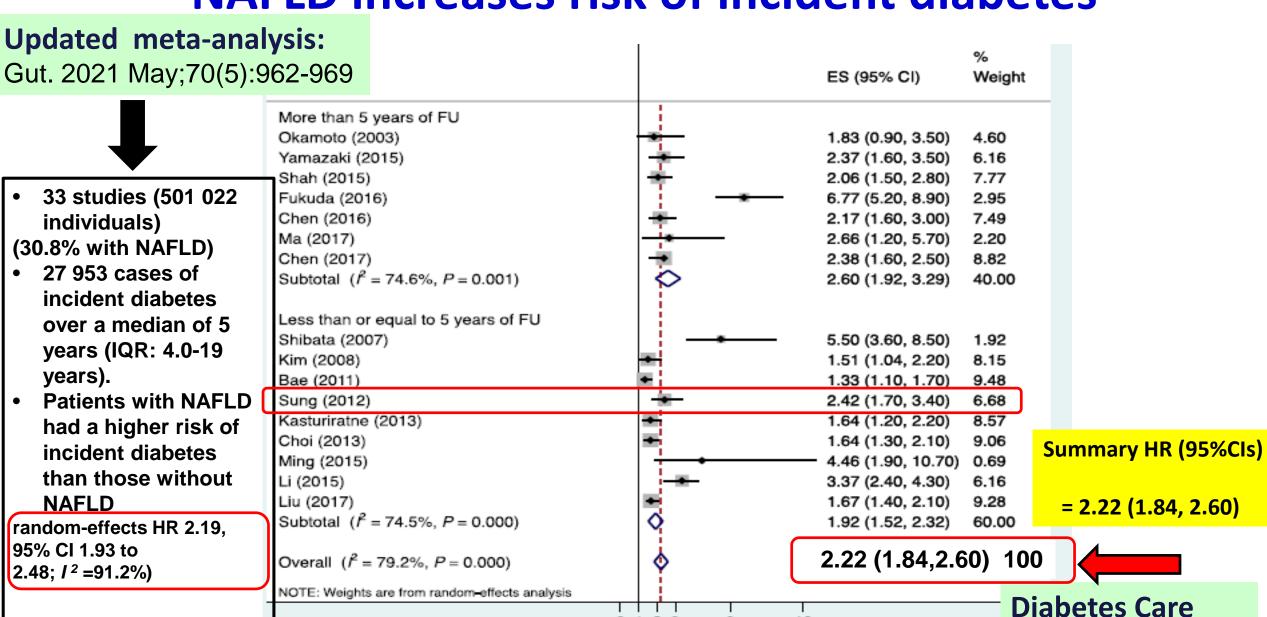
# **ATVB April 2022**

# **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.

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Key Words: AHA Scientific Statements ■ cardiovascular diseases ■ diabetes mellitus ■ hepatocytes ■ hypertriglyceridemia ■ insulin resistance ■ metabolic syndrome ■ nonalcoholic fatty liver disease ■ triglycerides
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# **NAFLD** increases risk of incident diabetes



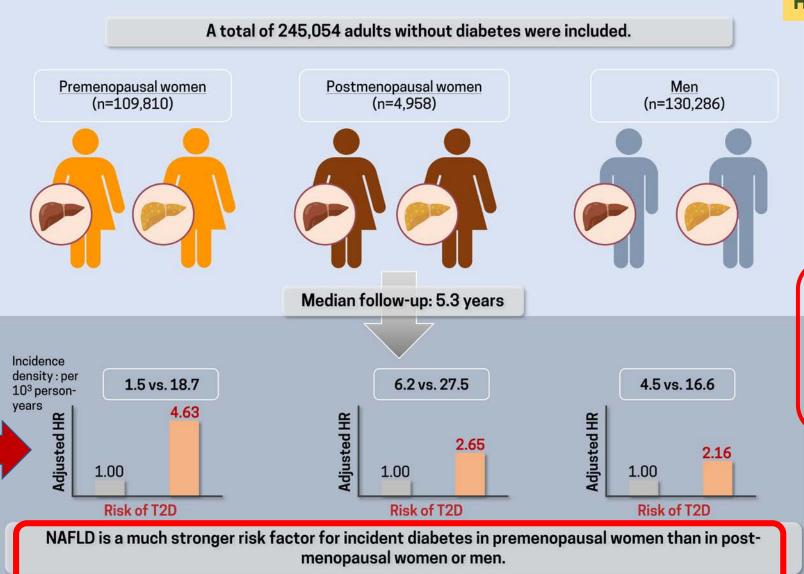
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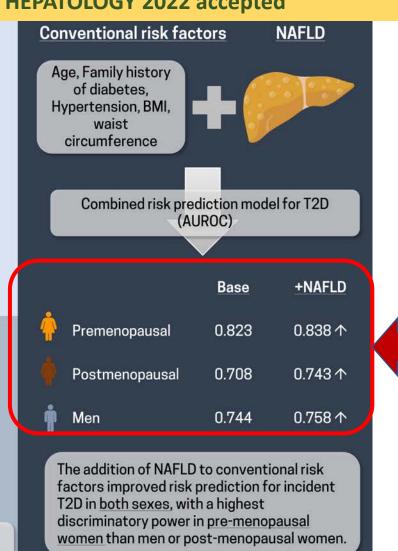
2018; 41: 372-382

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



# 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

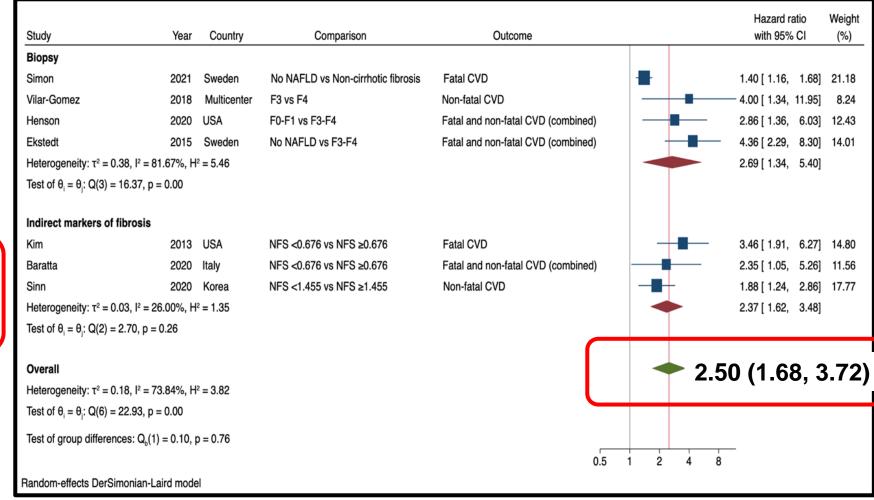
Mean (SD) age 53 (7) years 99668 incident fatal and non-fatal CVD events

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.

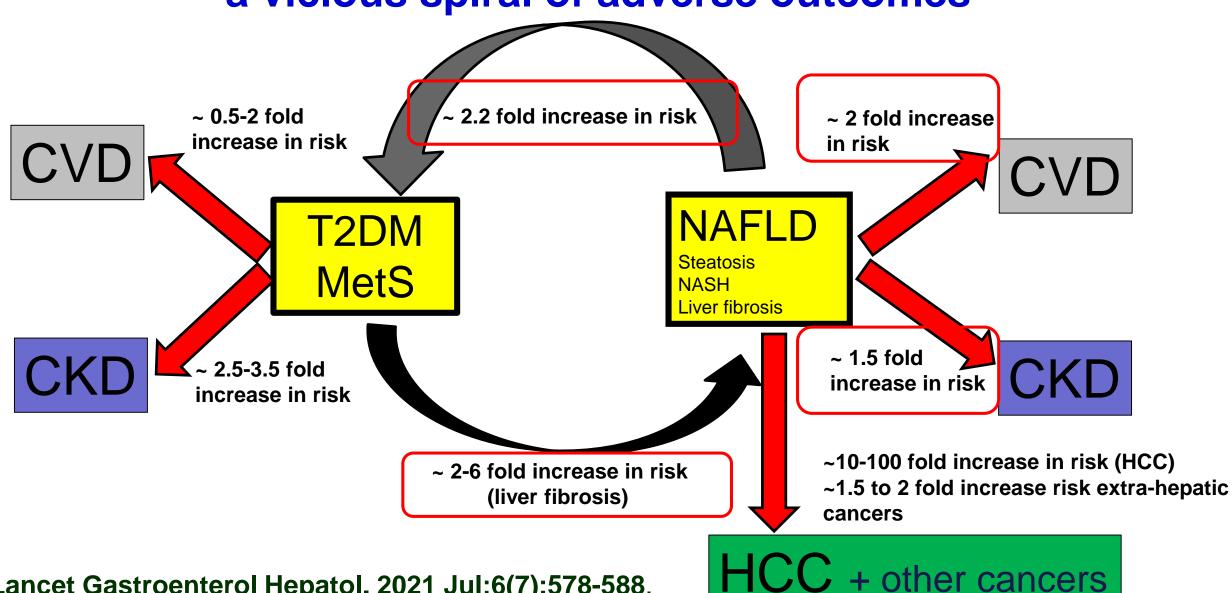
Severity of liver fibrosis and risk of fatal and non fatal CVD



# 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

		HR (95% CI)	
	Outcome ICD coded diagnoses	ALD (n = 1,707)	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%Cls) = 1.70 (1.52, 1.90)

> HCC HR (95%Cls) = 19.3 (11.8, 31.4)

> > Sarah Wild

National cohort = 134,368 people with T2DM - mean follow up of 4.3 years

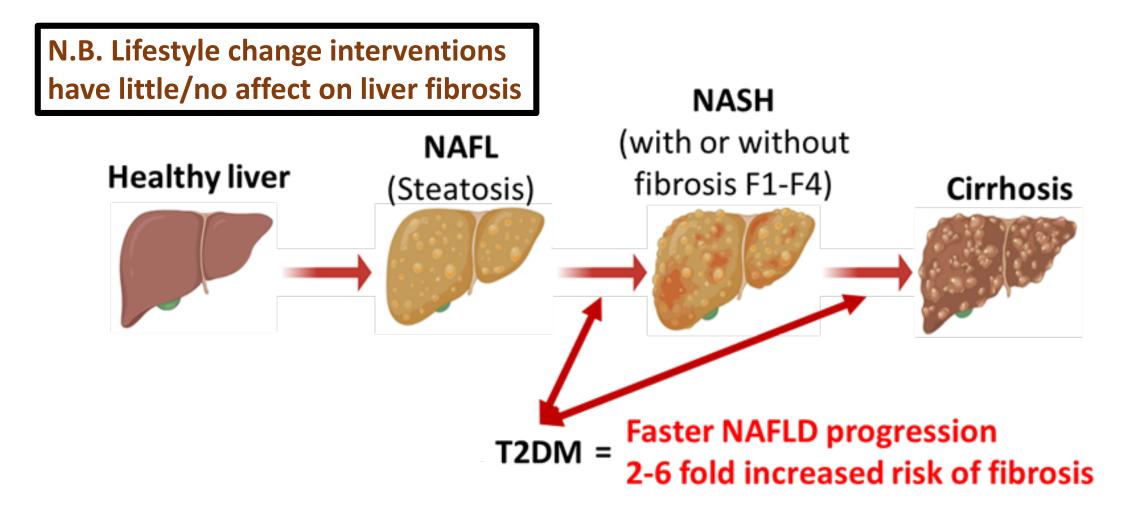
No liver disease = 21,873 CVD events

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?



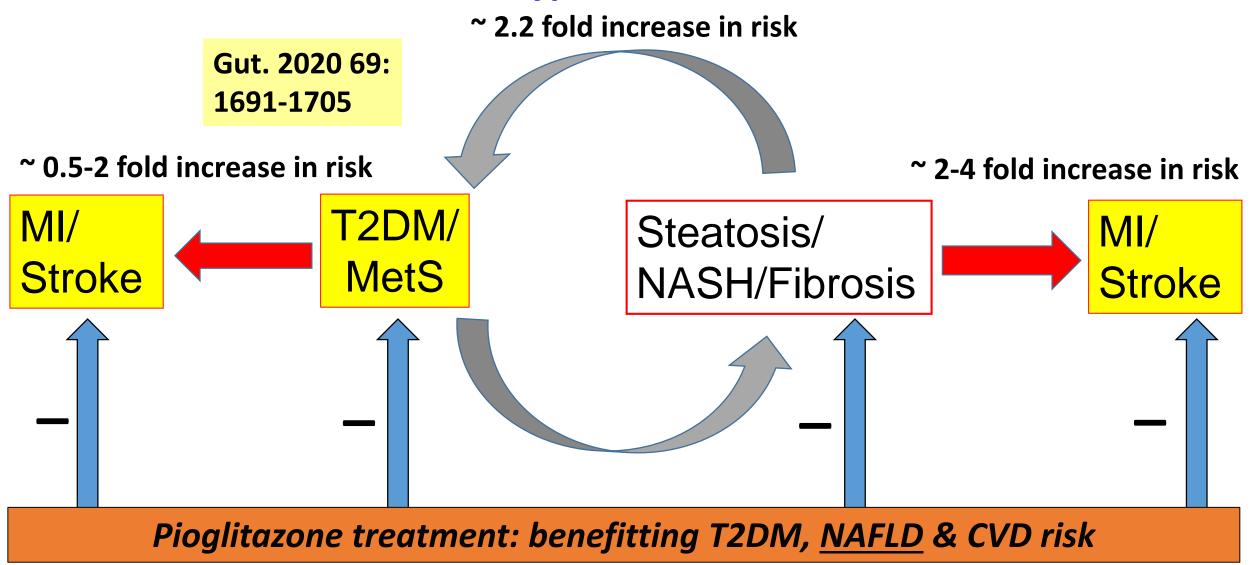
Lancet Gastroenterol Hepatol. 2021 Jul;6(7):578-588.

# 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 <u>continuous glucose monitoring</u> (isCGM, commonly referred to as 'flash') to adults with type 2 diabetes on <u>multiple daily insulin injections</u> 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 <u>continuous glucose monitoring</u> (CGM) for pregnant women, see the <u>NICE guideline on diabetes in pregnancy</u>. [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 <u>section on education</u>). [2022]
- 1.6.24 Monitor and review the person's use of CGM as part of reviewing their diabetes care plan (see the <u>section on individualised care</u>). [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]

# 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<sub>1c</sub>** measurement

#### Measurement

•Measure HBA<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> level of 53 mmol/mol (7.0%) and
  - intensify drug treatment

# Algorithm 1: How to choose firstline medicines

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

#### For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved. Assess HbA, cardiovascular risk and kidney function For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic Chronic heart failure Start me formin High risk of CVD kidney disease see the section on diabetic Not at high risk of alone t assess or established QRISK2 of 10% or kidney disease in the full guideline. bility CVD toler atherosclerotic CVD higher before adding Consider DPP-4 inhibitor ('gliptin') or Offer Offer Pioglitazone or Offer Metformin Metformin Sulfonylurea Metformin or if GI disturbance or if GI disturbance An SGLT2 inhibitor ('flozin') for some or if GI disturbance people: Metformin MR Metformin MR Metformin MR Canagliflozin (TA390) and as soon as metformin and as soon as metformin tolerability is confirmed, offer tolerability is confirmed, consider Dapagliflozin (TA390) SGLT2 inhibitor ("flozin") with SGLT2 inhibitor ('flozin') with Empaglilozin (TA390) proven cardiovascular benefit proven cardiovascular benefit If metformin Ertugliflozin (TA572) contraindicated NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in Offer Consider people: If metformin If metformin SGLT2 inhibitor SGLT2 inhibitor contraindicated who cannot have metformin contraindicated alone alone for whom diet and exercise alone do not provide adequate glycaemic control. The SGLT2 inhibitors are recommended Person's HbA, not controlled below individually agreed threshold, or the person only if a dipeptidyl peptidase-4 (DPP-4) develops CVD or a high risk of CVD inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate. See Algorithm 2: How to choose further medicines In February 2022, using ertugliflozin to Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous reduce cardiovascular risk when blood myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease glucose is well controlled was off label. See NICE's information on prescribing medicines. (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

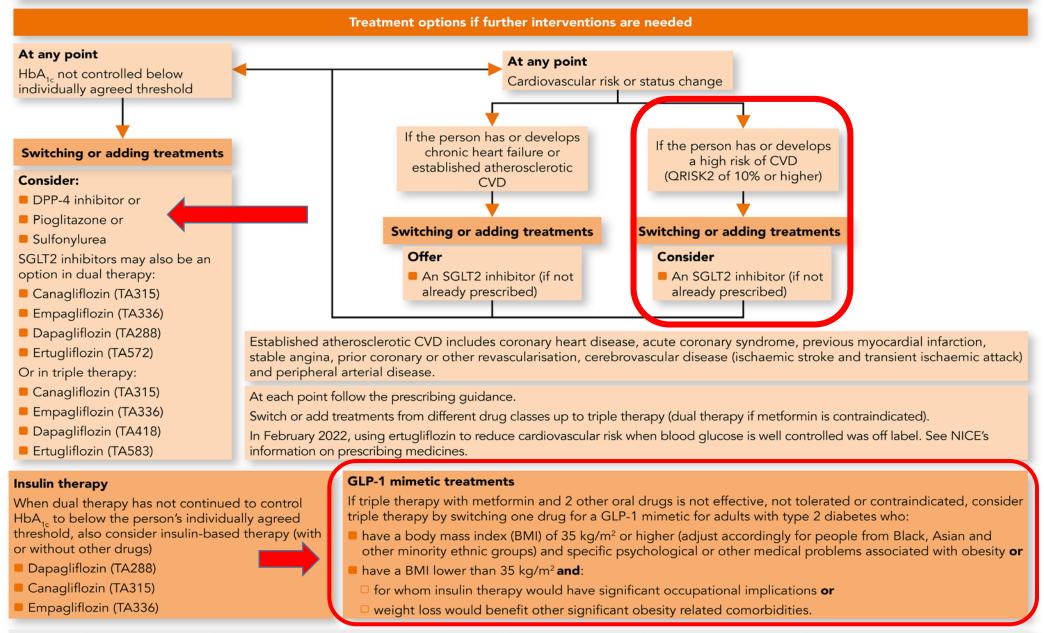
Rescue therapy

Abbreviations: CVD=cardiovascular disease; DPP-4=dipeptidyl peptidase-4; GI=gastrointestinal; HbA<sub>1c</sub>=glycated haemoglobin; MR=modified release; SGLT2=sodium-glucose transport protein 2

# Algorithm 2: How to choose further medicines



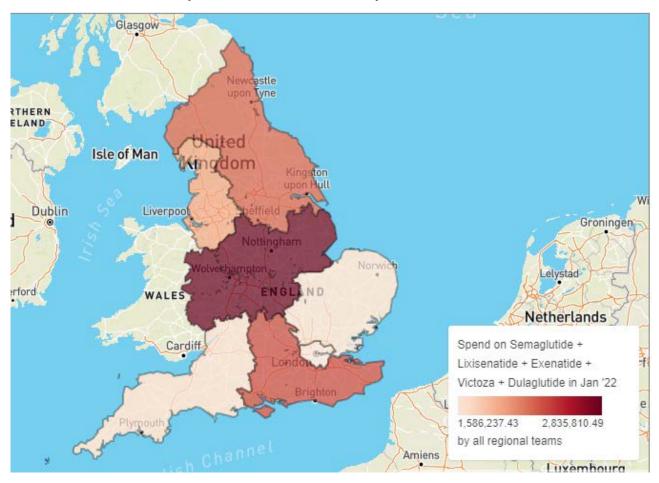
For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.



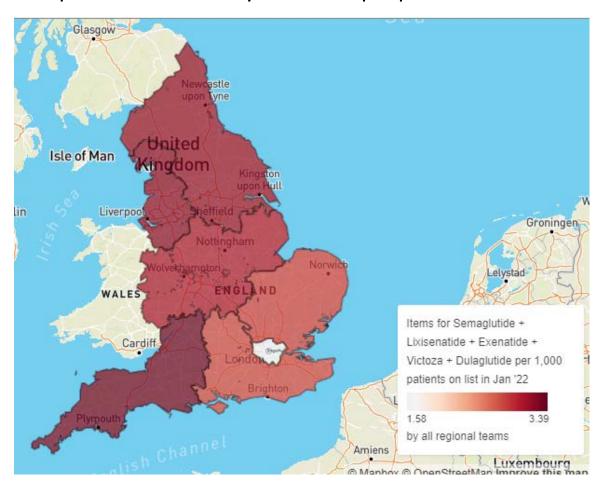
Abbreviations: BMI=body mass index; CVD=cardiovascular disease; DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; HbA $_{1c}$ =glycated haemoglobin; SGLT2= sodium-glucose transport protein 2

# 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

#### INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HFT

#### CONSIDER INDEPENDENTLY OF BASELINE A1C. INDIVIDUALIZED A1C TARGET, OR METFORMIN USE\*

#### +ASCVD/Indicators of High Risk

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary. carotid, or lower-extremity artery stenosis >50%, or LVH)



#### If A1C above target

If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety:

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit and vice versa1
- TZD²
- DPP-4i if not on GLP-1 RA
- Basal insulin<sup>3</sup>
- · SU4
- 1. Proven CVD benefit means it has label indication of reducing CVD events
- 2. Low dose may be better tolerated though less well studied for CVD effects
- 3. Degludec or U-100 glargine have demonstrated CVD safety
- 4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
- 5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
- 6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empaglificzin have primary heart fallure outcome data.

#### Particularly HFrEF (LVEF <45%) SGLT2i with proven benefit in this population5.6.7

#### +CKD DKD and Albuminuria<sup>8</sup> **PREFERABLY** SGLT2i with primary evidence of reducing CKD progression

OR SGLT2i with evidence of reducing CKD progression in CVOTs5,8,8

GLP-1 RA with proven CVD benefit1 if SGLT2i not tolerated or

contraindicated

For patients with T2D and CKDs (e.g., eGFR <60 mL/mln/1.73 m²) and thus at increased risk of cardiovascular events

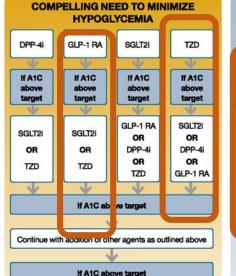
ETHER/ GLP-1 SGLT2i RA with proven proven CVD CVD benefit1,7 benefit1

#### NO



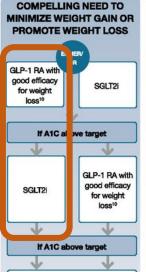
**COST IS A MAJOR** 

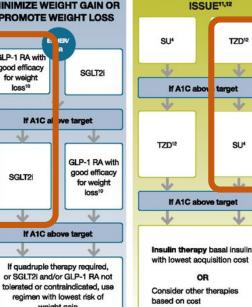
#### IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW



Consider the addition of SU\* OR basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia<sup>6</sup>
- 7. Proven benefit means it has label indication of reducing heart failure in this population
- 8. Refer to Section 11: Microvascular Complications and Foot Care 9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
- Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
- 11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
- 12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.





If DPP-4i not tolerated or contraindicated or patient already

on GLP-1 RA, cautious addition of: · SU4 · TZD2 · Basal insulin

weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

# 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<sub>1c</sub> level of 53 mmol/mol (7.0%) and
  - intensify drug treatment