Lipid-lowering for primary prevention of CVD in young adults with type 2 diabetes: the rationale

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Lucy

32 yr old female

Went to GP – lethargy, dry mouth and weight loss 3kg last 4 months

Family history of type 2 diabetes Non-smoker

BMI 35 BP 148/83

HbA1c 70 mmol/mol

Tot cholesterol 5.6 mmol/l triglyceride 3.8 mmol/l HDL 0.91 mmol/l

Diagnosed with type 2 diabetes

Clinical question:

Is statin needed for this patient?

This patient has 4 risk factors for CVD – T2D, obesity, hypertension, dyslipidaemia

Topics to be covered:

- Definition of young type 2 diabetes and size of the problem

- Evidence for elevated CVD risk:
  - Adverse biological phenotype vs older-onset
  - Comparison to young type 1 diabetes

- CVD risk assessment in young T2D - NICE NG28 (2022)

- Proposed SY ICB lipid-lowering guideline for primary prevention of CVD

Definition of young-onset type 2 diabetes:

Age of diagnosis <40 years

Two groups:

Childhood/youth-onset – diagnosed below age 18

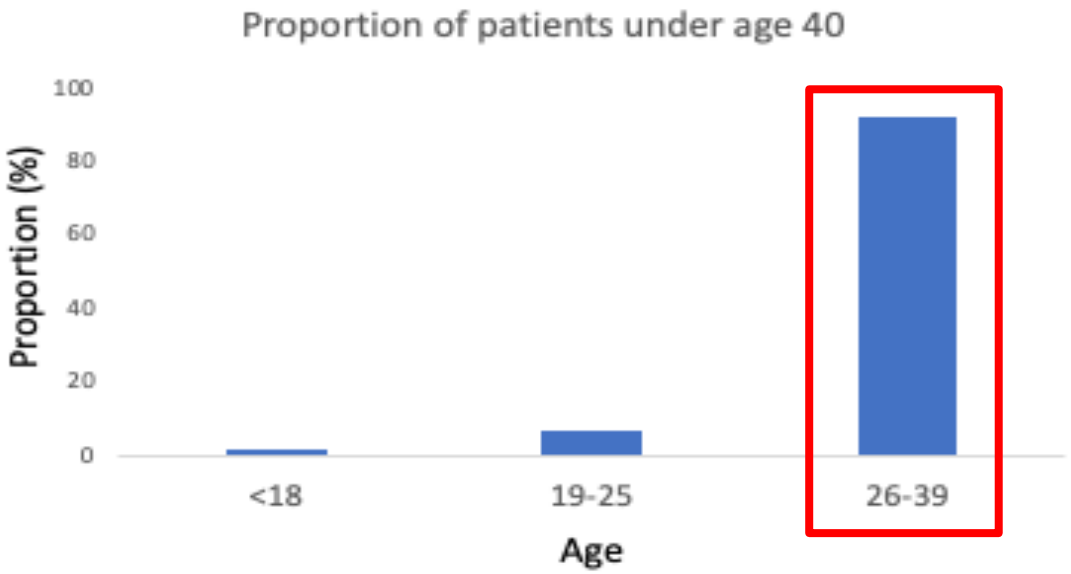
Young adult-onset – diagnosed age 18-39

Size of the problem:

NDA data 2021-2022 in England and Wales

139,255 patients with T2D under age 40

5% of overall T2D population



Most are aged 26-39 and under primary care

20 patients per GP practice

Among young adults with diabetes age 18-39 - majority has T2D (60%)

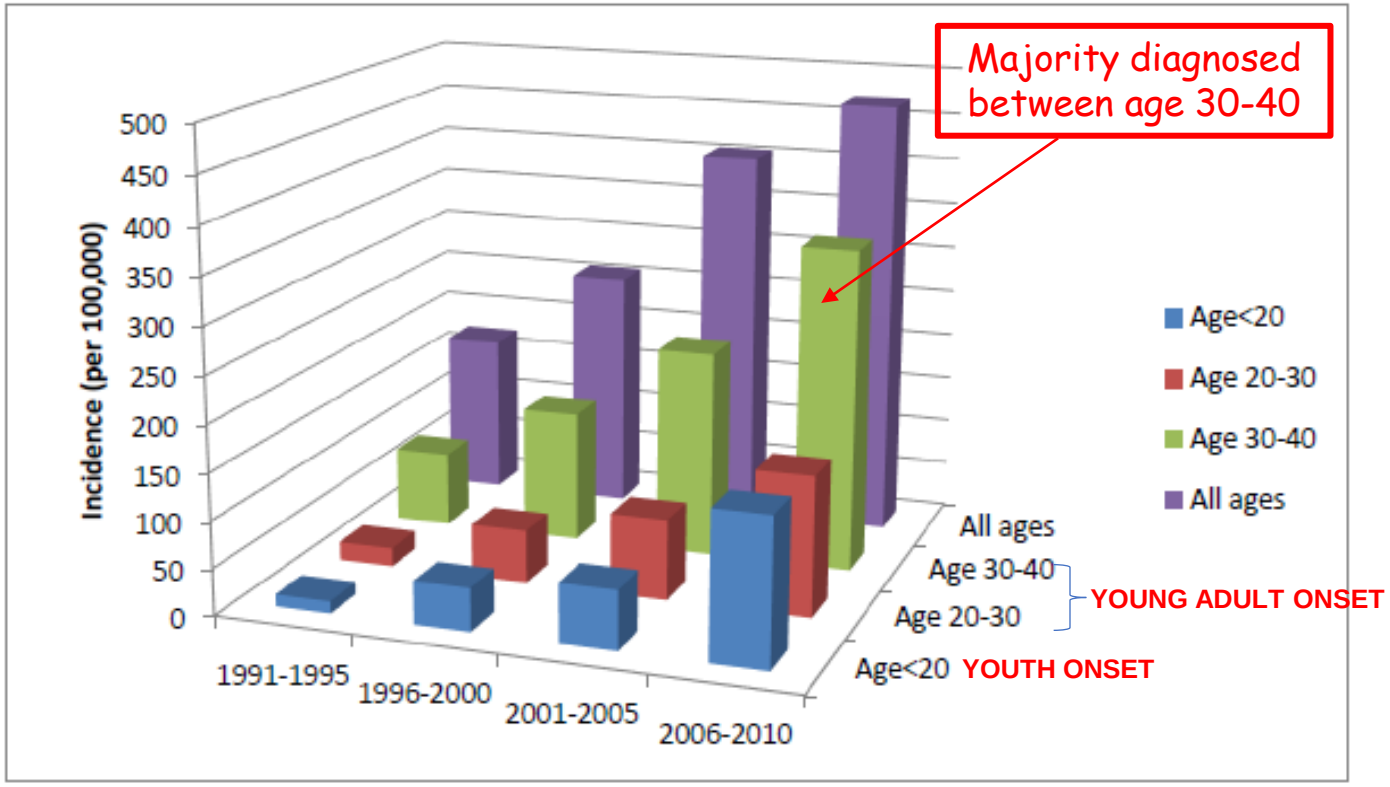
Type 2 diabetes is no longer a condition of the middle-aged

Young-onset type 2 diabetes is increasing in the UK

Increasing since 1990s

Affects all ages under 40

Figure 1. Incidence of T2DMY per 100,000 population by age and year (modified with permission)[11]



Holden et al Diabetes Obesity Metab 2013;15:844-52

Trend has continued….

Age group	Number of people*		
	2019/20	2020/21	2021/22
Under 12 years	110	120	150
12-15 years	570	610	690
16-18 years	1,005	1,015	1,160
19-25 years	8,785	9,065	9,765
26-39 years	118,725	121,190	127,495

Table 1: Number of young people with Type 2 diabetes in England, by age group[3].

NDA data

Type 2 diabetes is typically seen as a middle-aged disease
ALAMY

HEALTH

Record number of under-40s diagnosed with type 2 diabetes

Eleanor Hayward, Health Correspondent
Tuesday November 01 2022, 5.50pm, The Times

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Cases of diabetes in young adults have soared by 23 per cent in the past five years due to the obesity epidemic, new figures show.

There are now a record 148,000 people in the UK under the age of 40 who have been diagnosed with type 2 diabetes.

'Alarming' rise in type 2 diabetes among UK under-40s

Figures underline growing prevalence of conditions related to obesity in younger demographic, says head of Diabetes UK

The number of people under 40 diagnosed with type 2 diabetes has jumped 23% from about 120,000 in 2016-17 to 148,000 in 2020-21, according to Diabetes UK. Photograph: x-reflexnaja/Getty Images/iStockphoto

The number of people under 40 in the UK being diagnosed with type 2 diabetes is rising at a faster pace than the over-40s, according to "shocking" and "incredibly troubling" data that experts say exposes the impact of soaring obesity levels.

New diabetes cases

Increasing at faster pace in those aged <40

38% vs 25% for age >40 (between 2017-2023)

Diabetes UK report May 2024

Clinical characteristics:

Compared to older people (age >40) with type 2 diabetes, young type 2 diabetes:

More likely to be female up to age 25

Ethnic minority over-represented

Asian ethnicity - 24.4% vs 14.8% for age >40

Significant proportion resided in deprived areas

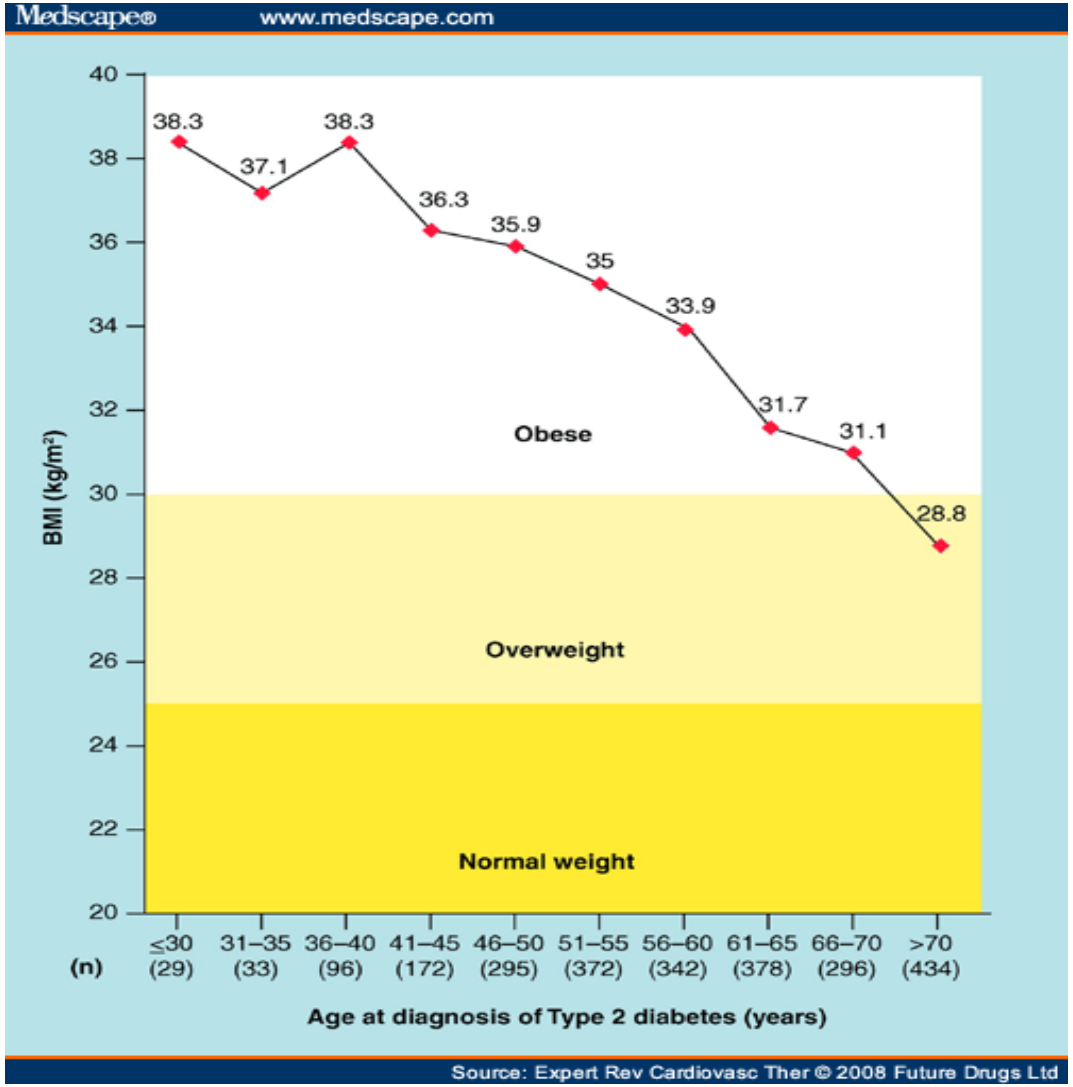
34.6% vs 25% for age >40

More obese

NDA data

Adverse phenotype – young vs older-onset

(1) Greater degree of obesity – at diagnosis



Hillier et al. Diabetes Care 2001;24:1522-1527

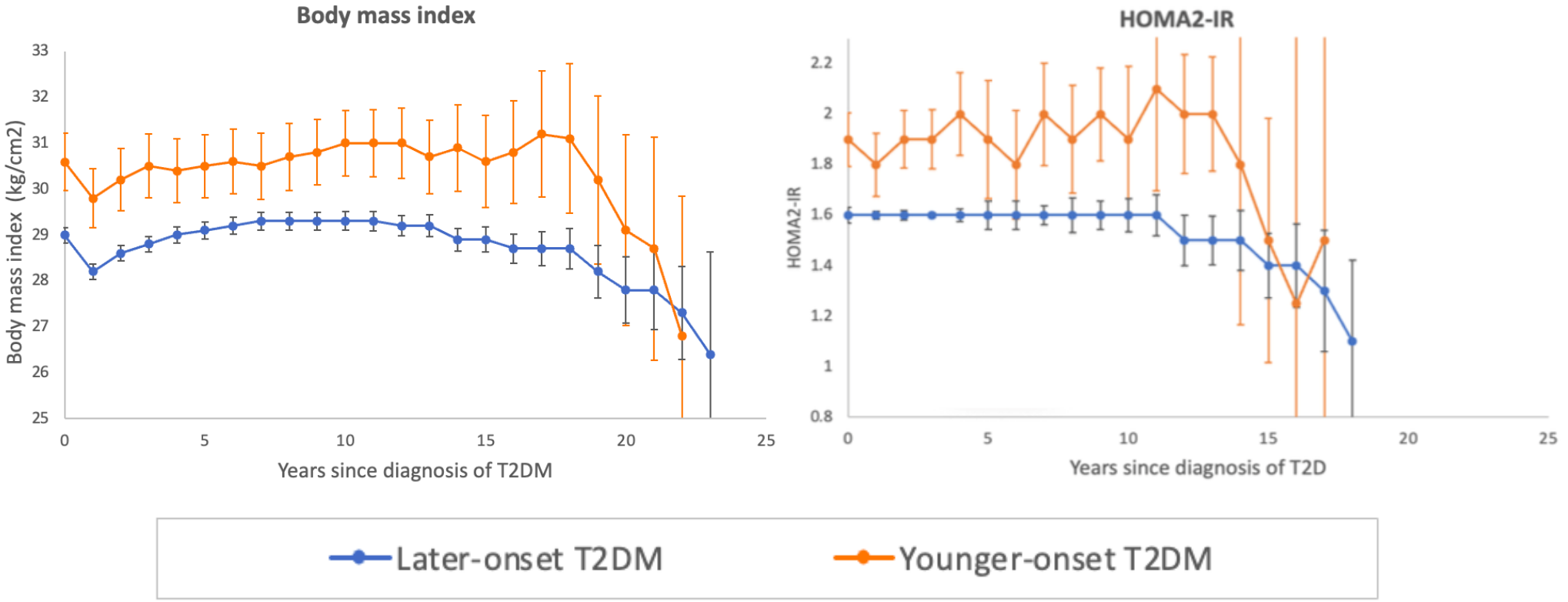
Age of T2D diagnosis and BMI

Greater obesity with younger age of diagnosis

Obesity:
Major risk factor for young-onset T2D

Adverse phenotype – young vs older-onset

(2) Greater obesity persists throughout lifespan - associated with higher insulin resistance



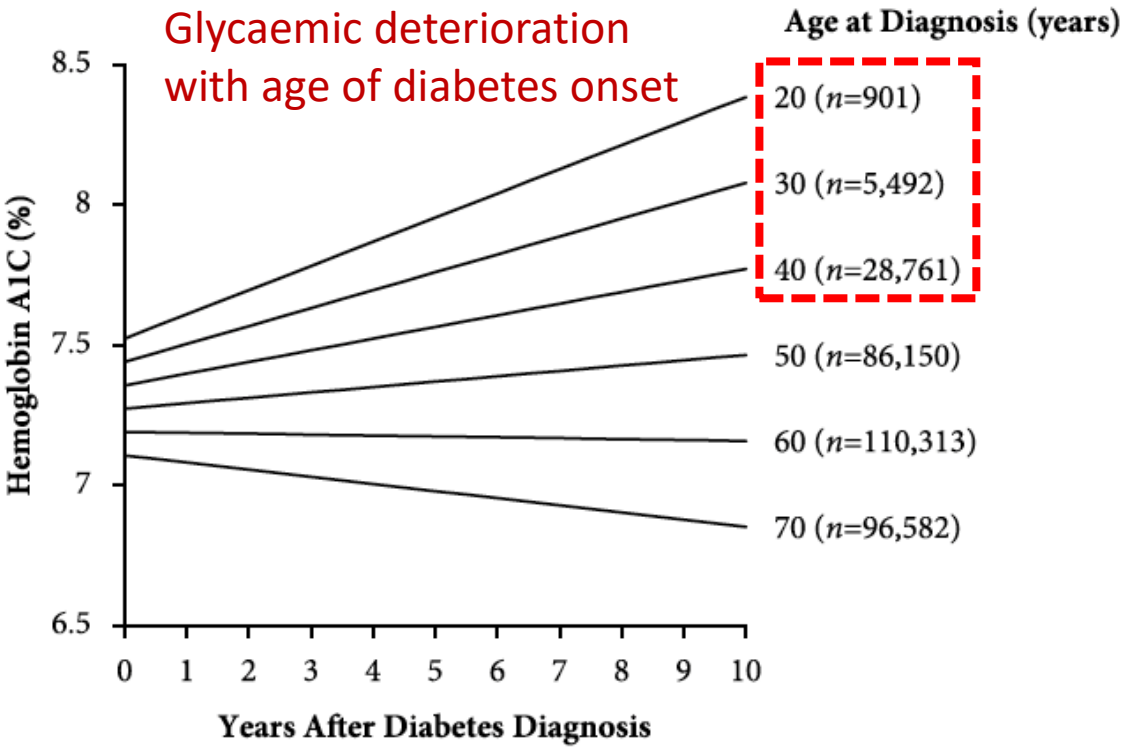
UKPDS study

Greater obesity and insulin resistance persist in the lifespan of young vs older-onset T2D

Lin et al. Lancet Diabetes Endocrinol 2024;12:904-14

Adverse phenotype – young vs older-onset

(3) More rapid beta cell failure



Decline in beta cell function more rapid below age 40 [1]

Up to 3x faster
(20-35% vs 7-11% decline per year [2])

Clinical implications:

Less responsive to non-insulin diabetes medications

Likely to need insulin therapy at an earlier stage

[1] Ke et al. *PLoS Med*. 2020;17(9):e1003316
[2] TODAY Study Group. Diabetes Care. 2013;36:1749-1757

Adverse phenotype – young vs older-onset

(4) Elevated CVD risk – risk factor burden

Table 1. Characteristics of early (<40 years) and later (>40 years) onset type 2 diabetes patients without history of cardiovascular disease

	<40 years	>40 years	p-value
Age (yr)*	34.1 (4.9)	63.4 (10.4)	<0.0001
Male (%)*	46.3	50.8	NS
Diabetes duration (yr)*	4.8 (4.1)	10.7 (7.9)	<0.0001
HbA_{1c} (%)*	8.6 (2.1)	8.1 (1.7)	<0.0001
Obesity			
Weight (kg)*	96.4 (25.7)	92.6 (20.9)	NS
BMI (kg/m^2)*	34.0 (9.0)	33.5 (7.0)	NS
BMI 25–29.9 (%)	28.3	25.6	NS
BMI 30–39.9 (%)	32.8	49.3	<0.05
BMI >40 (%)	23.9	16.9	<0.05
Blood pressure			
Systolic BP (mmHg)*	131.3 (21.0)	144.6 (19.9)	<0.0001
Diastolic BP (mmHg)*	80.2 (13.0)	76.9 (11.4)	<0.05
Hypertensive (%)**	80.6	77.2	NS
Hypertensive not on treatment (%)	64.8	35.5	<0.0001
Lipid			
Total cholesterol (mmol/L)*	4.8 (1.1)	4.4 (1.0)	<0.005
HDL (mmol/L)*	1.04 (0.22)	1.17 (0.35)	<0.005
Triglyceride (mmol/L)*	2.5 (1.9)	2.1 (1.6)	<0.05
Dyslipidaemia (%)†	82.1	69.8	<0.05
Treatment			
Statin (%)	23.9	67.0	<0.0001
Anti-hypertensive (%)	39.6	75.8	<0.0001

* Mean (SD). ** Hypertension defined as BP >130/80mmHg and/or anti-hypertensive treatment. † Dyslipidaemia defined as low HDL (<1.03mmol/L in male or <1.29mmol/L in female) and/or raised triglyceride >1.7mmol/L.

Table 2. Prevalence of cardiovascular disease risk factor clustering (BMI >25, hypertension, dyslipidaemia)

No of risk factors	<40 years	>40 years	p-value
1	9.0%	9.7%	NS
2	31.3%	39.3%	NS
3	58.2%	50.2%	NS

Song et al *Pract Diabetes Int* 2007;24:20-24

Sheffield experience (in 2007)

Mean age 34 vs 63 yrs

Poorer glycaemic control

High prevalence of obesity, hypertension and dyslipidaemia

Risk factor clustering

Less treatment with statin and anti-hypertensive agents

This observation confirmed in large population studies (China[1], HK[2], Australia[3], Sweden[4])

[1] Huo et al. Lancet Diabetes Endocrinol 2016;4:115-124
[2] Yeung et al. Lancet Diabetes Endocrinol 2014;2:935-943
[3] Nanayakkara et al. J Diabetes Complications 2018;32:279-290
[4] Steinarsson et al. Diabetologia.2018;61:599-606.

Adverse phenotype – young vs older-onset

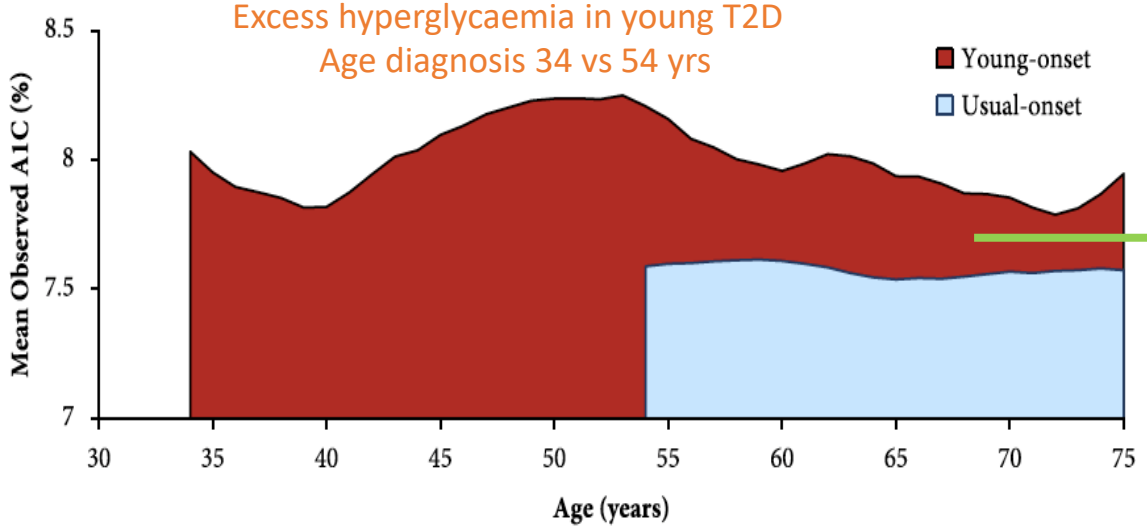
(5) Elevated complication risk – greater lifetime exposure to adverse metabolic milieu

Poorer diabetes control, more obese and worse dyslipidaemia at diagnosis

Prolonged exposure to adverse metabolic (hyperglycaemia, obesity and dyslipidaemia) environment for years

High lifetime risk to develop complications

Excess hyperglycaemia in young T2D
Age diagnosis 34 vs 54 yrs



Lifetime exposure to hyperglycaemia

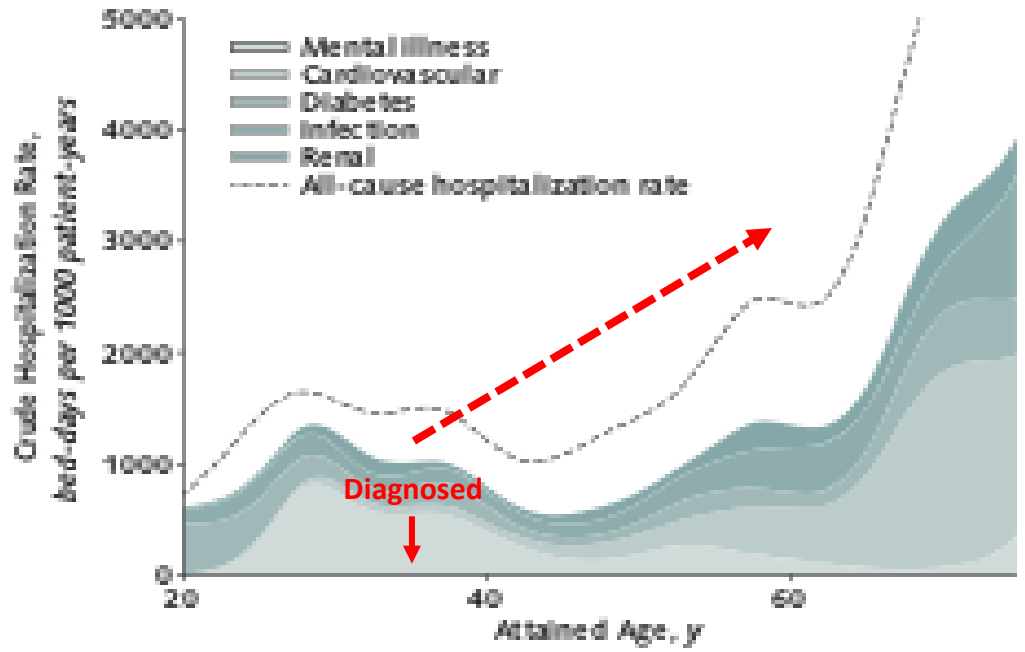
Greater exposure (3X) to hyperglycaemia in young T2D

Ke et al. PLOS Medicine 2020; 17(9):e1003316

Adverse phenotype – young vs older-onset

(6) Premature CVD complications at a young productive age

Figure 2. Crude hospitalization rates (bed-days per 1000 patient-years) for selected principal diagnoses, by attained age, among persons with young-onset type 2 diabetes in the registry cohort.



Young adult-onset T2D diagnosed age 30-35

By age 60
High rate of hospitalization for CVD, renal, diabetes, infection and mental health complications

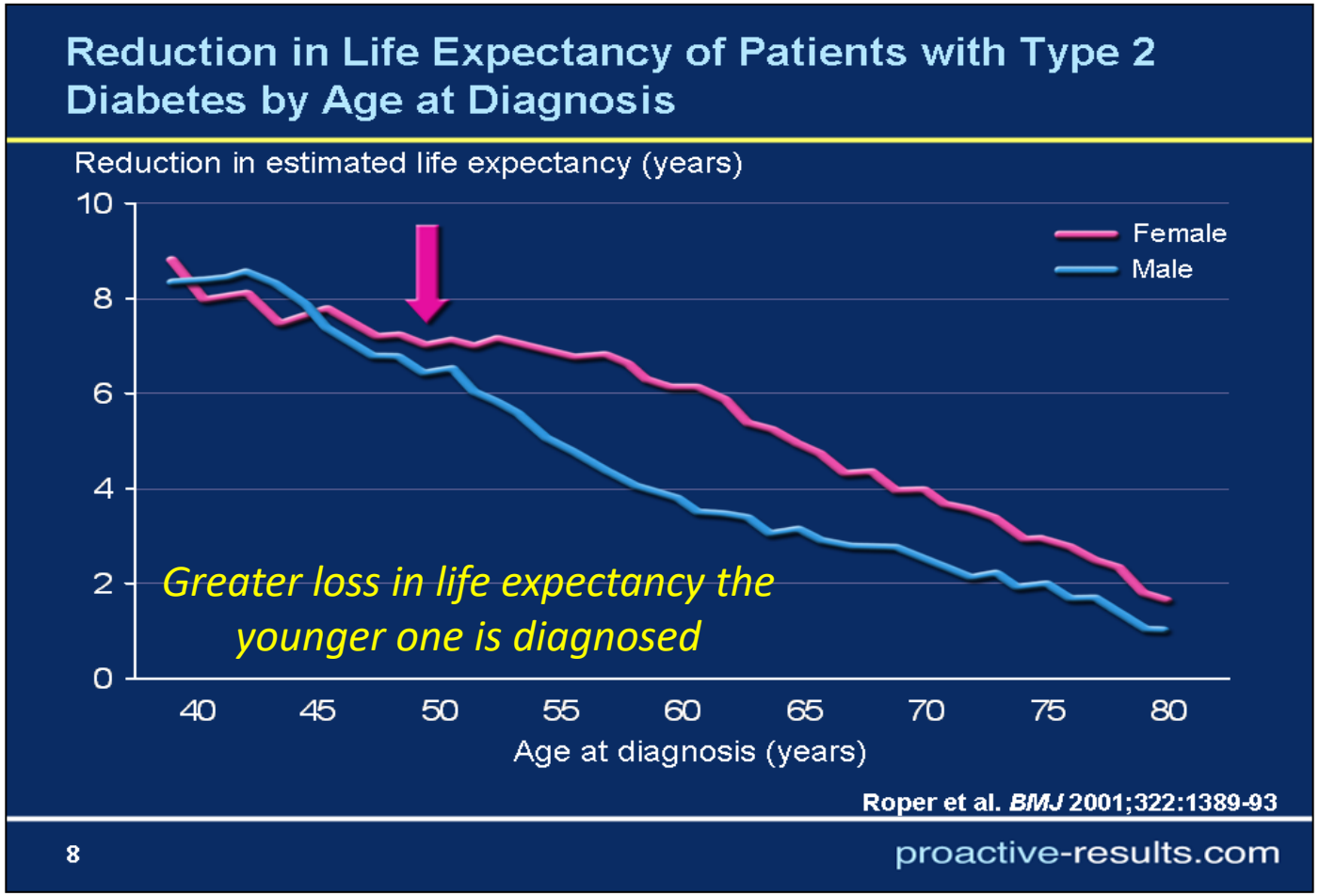
Ke et al Ann Internal Med 2019;170:145-154

Adverse phenotype – young vs older-onset

(7) Greater loss in life expectancy

T2D diagnosed at age 20:

Lose 12-13 years in life expectancy [1]



[1] Sattar et al. Circulation 2019;139:2228-2237

Young-onset T2D vs T1D – clinical characteristics and complications

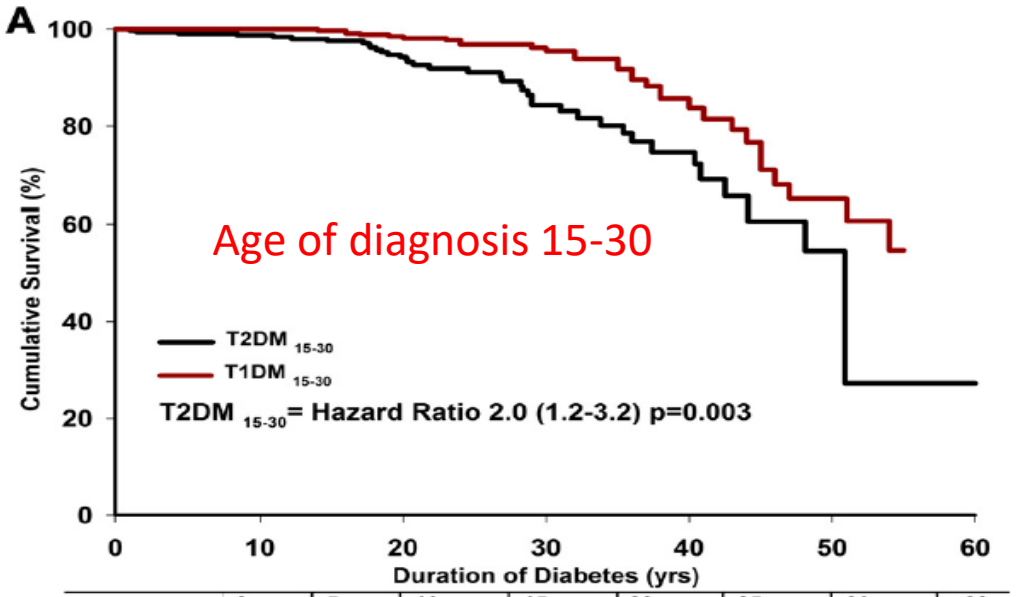
T2D are more likely:

(1) obese, hypertensive and dyslipidaemic [1,2]

(2) higher burden of neuropathy, nephropathy and CVD [1,2,3]

(3) may be more susceptible to significant retinopathy [4,5]

(4) higher mortality from CVD than T1D [6]



	0	5	10	15	20	25	30	>30
T2DM 15-30	354	334	297	247	188	134	83	56
T1DM 15-30	470	454	422	366	293	210	142	95

2-fold higher mortality in young T2D vs T1D mainly from CVD

[1] Song SH. BMJ Open Diabetes Research and Care 2015
[2] Luk et al. Diabetes Care 2014;37:149-157
[3] Dart et al Diabetes Care 2012;35:1265-71
[4] Song SH. Int J Clin Pract. 2016;70:853-60
[5] Middleton et al. Diabet Med 2020;37:991-9
[6] Constantino et al Diabetes Care 2013;36:3863-9

Guideline: NICE guideline NG28 (2022) - young adult with type 2 diabetes

For the first time, young type 2 diabetes (age 18-39) was included in a UK guideline

- method of CVD risk assessment

High risk of cardiovascular disease

Adults with type 2 diabetes who have:

- QRISK2 more than 10% in adults aged 40 and over or
- an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factors in someone under 40).

Cardiovascular disease risk factors: hypertension, dyslipidaemia, smoking, obesity, and family history (in a first-degree relative) of premature cardiovascular disease.

Advocates LIFETIME risk assessment for age <40 (NOT QRISK-3 10-yr risk)

QRISK-3 under-estimates CVD risk because of the young age

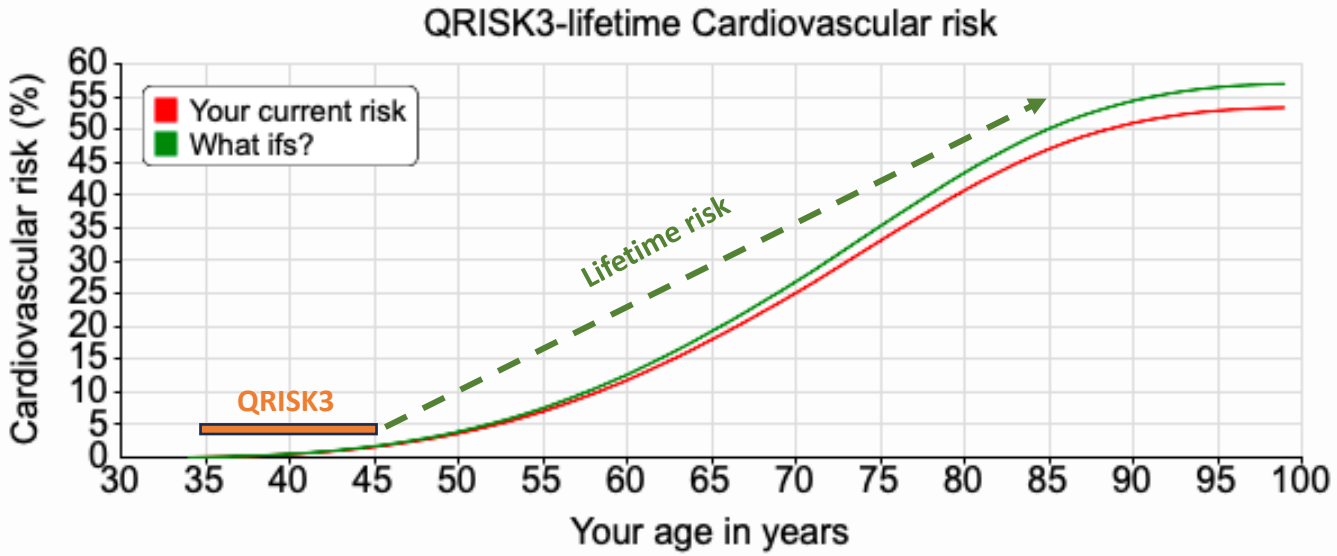
High lifetime CVD risk definition – young T2D and at least 1 risk factor

QRISK®3-lifetime cardiovascular risk calculator: https://qrisk.org/lifetime

Significant difference between lifetime vs 10-year risk assessment

Your QRISK3-lifetime score

	Current	What if?
Your lifetime risk (i.e. by the time you are 99)	53.3%	57%
Your risk up to age 85	47%	50.1%



In other words, in a crowd of 100 people like you,

- 47 will develop heart disease or have a stroke/TIA by the time they are 85, and
- 53 will do so by the time they reach 99.

34 year old male

BMI 33

BP 139/83

Total chol 4.5 mmol/L

HDL 1.19 mmol/L

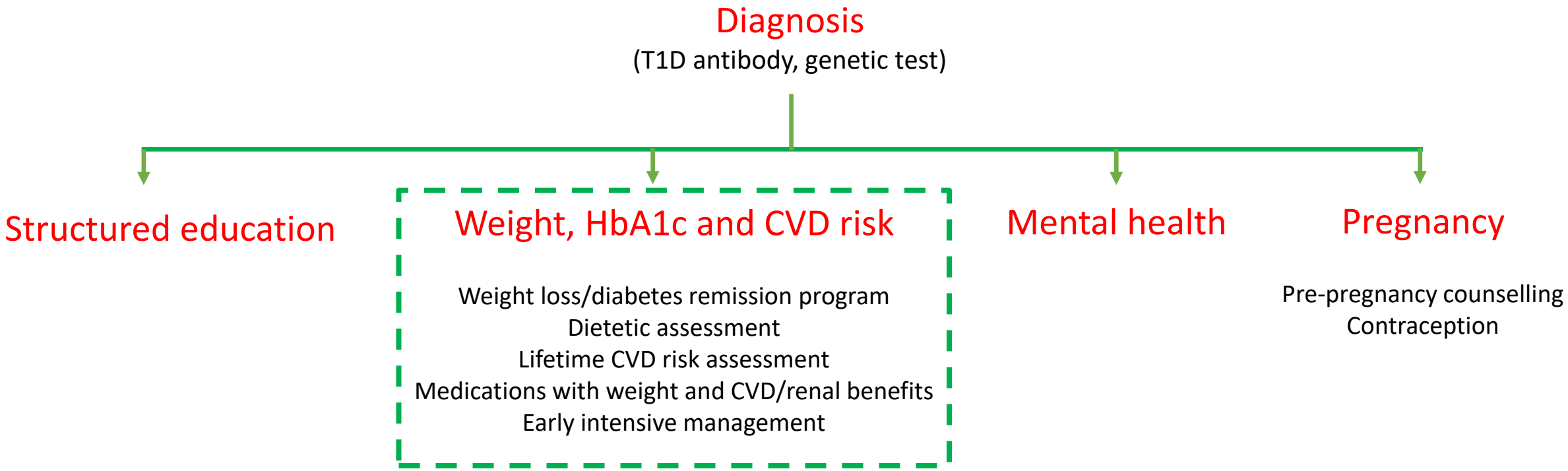
Triglyceride 1.5 mmol/L

QRISK3 over 10 yrs 3%

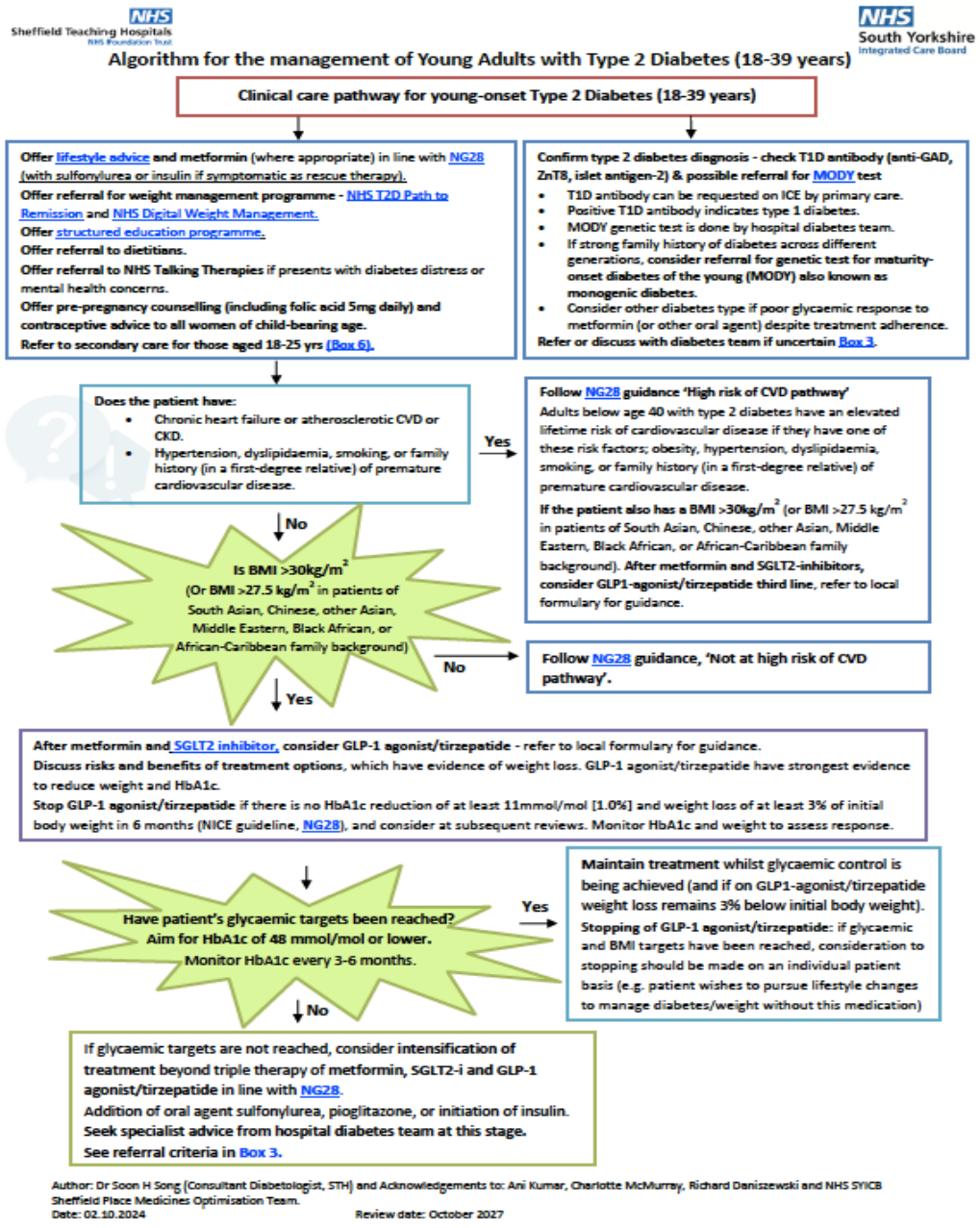
Lifetime risk of CVD 50%

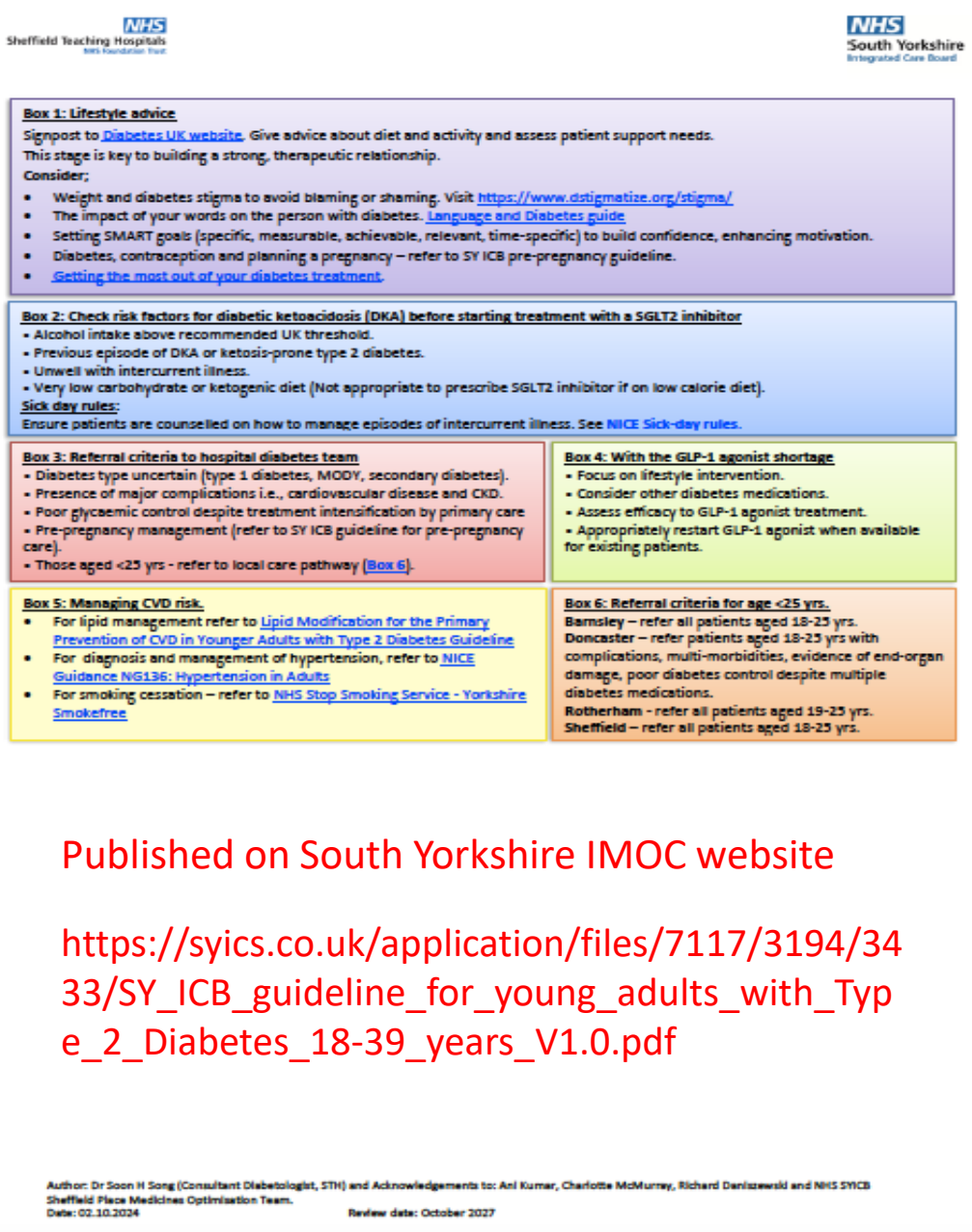
Care pathway for young adults with type 2 diabetes

Elements of care (5 key areas)



South Yorkshire ICB pathway for young type 2 diabetes





Published on South Yorkshire IMOC website

https://syics.co.uk/application/files/7117/3194/3433/SY_ICB_guideline_for_young_adults_with_Type_2_Diabetes_18-39_years_V1.0.pdf

Box 1: Lifestyle advice

Signpost to Diabetes UK website. Give advice about diet and activity and assess patient support needs.

This stage is key to building a strong, therapeutic relationship.

Consider;

- Weight and diabetes stigma to avoid blaming or shaming. Visit https://www.dstigmatize.org/stigma/
- The impact of your words on the person with diabetes. Language and Diabetes guide
- Setting SMART goals (specific, measurable, achievable, relevant, time-specific) to build confidence, enhancing motivation.
- Diabetes, contraception and planning a pregnancy – refer to SY ICB pre-pregnancy guideline.
- Getting the most out of your diabetes treatment.

Box 2: Check risk factors for diabetic ketoacidosis (DKA) before starting treatment with a SGLT2 inhibitor

- Alcohol intake above recommended UK threshold.
- Previous episode of DKA or ketosis-prone type 2 diabetes.
- Unwell with intercurrent illness.
- Very low carbohydrate or ketogenic diet (Not appropriate to prescribe SGLT2 inhibitor if on low calorie diet).

Sick day rules:

Ensure patients are counselled on how to manage episodes of intercurrent illness. See **NICE Sick-day rules.**

Box 3: Referral criteria to hospital diabetes team

- Diabetes type uncertain (type 1 diabetes, MODY, secondary diabetes).
- Presence of major complications i.e., cardiovascular disease and CKD.
- Poor glycaemic control despite treatment intensification by primary care
- Pre-pregnancy management (refer to SY ICB guideline for pre-pregnancy care).
- Those aged <25 yrs - refer to local care pathway (Box 6).

Box 4: With the GLP-1 agonist shortage

- Focus on lifestyle intervention.
- Consider other diabetes medications.
- Assess efficacy to GLP-1 agonist treatment.
- Appropriately restart GLP-1 agonist when available for existing patients.

CVD risk management

Resources for hypertension, lipid and smoking cessation

Box 5: Managing CVD risk.

- For lipid management refer to Lipid Modification for the Primary Prevention of CVD in Younger Adults with Type 2 Diabetes Guideline
- For diagnosis and management of hypertension, refer to NICE Guidance NG136: Hypertension in Adults
- For smoking cessation – refer to NHS Stop Smoking Service - Yorkshire Smokefree

Box 6: Referral criteria for age <25 yrs.

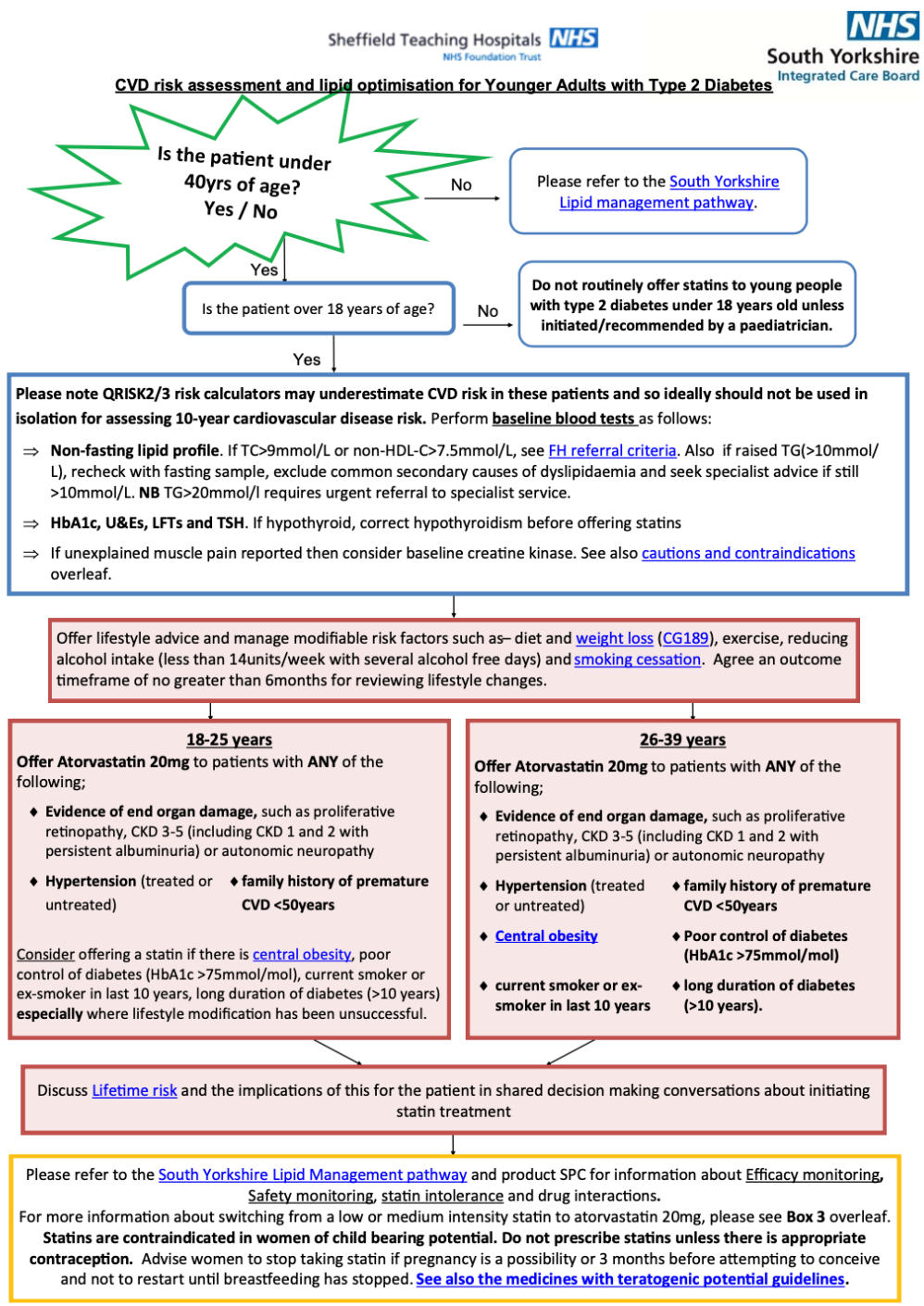
Barnsley – refer all patients aged 18-25 yrs.

Doncaster – refer patients aged 18-25 yrs with complications, multi-morbidities, evidence of end-organ damage, poor diabetes control despite multiple diabetes medications.

Rotherham - refer all patients aged 19-25 yrs.

Sheffield – refer all patients aged 18-25 yrs.

Proposed SY ICB lipid-lowering for primary prevention of CVD for young adults with type 2 diabetes (age 18-39 yrs)



Sheffield Teaching Hospitals NHS
NHS Foundation Trust

NHS
South Yorkshire
Integrated Care Board

CVD risk assessment and lipid optimisation for Younger Adults with Type 2 Diabetes

Is the patient under 40yrs of age? Yes / No

No → Please refer to the South Yorkshire Lipid management pathway.

Yes ↓

Is the patient over 18 years of age?

No → **Do not routinely offer statins to young people with type 2 diabetes under 18 years old unless initiated/recommended by a paediatrician.**

Yes ↓

Please note QRISK2/3 risk calculators may underestimate CVD risk in these patients and so ideally should not be used in isolation for assessing 10-year cardiovascular disease risk. Perform **baseline blood tests** as follows:

⇒ **Non-fasting lipid profile**. If TC>9mmol/L or non-HDL-C>7.5mmol/L, see FH referral criteria. Also if raised TG(>10mmol/L), recheck with fasting sample, exclude common secondary causes of dyslipidaemia and seek specialist advice if still >10mmol/L. **NB** TG>20mmol/l requires urgent referral to specialist service.

⇒ **HbA1c, U&Es, LFTs and TSH**. If hypothyroid, correct hypothyroidism before offering statins

⇒ If unexplained muscle pain reported then consider baseline creatine kinase. See also cautions and contraindications overleaf.

18-25 years

Offer Atorvastatin 20mg to patients with **ANY** of the following;

- **Evidence of end organ damage,** such as proliferative retinopathy, CKD 3-5 (including CKD 1 and 2 with persistent albuminuria) or autonomic neuropathy
- **Hypertension** (treated or untreated)
- **family history of premature CVD <50years**

Consider offering a statin if there is central obesity, poor control of diabetes (HbA1c >75mmol/mol), current smoker or ex-smoker in last 10 years, long duration of diabetes (>10 years) **especially** where lifestyle modification has been unsuccessful.

26-39 years

Offer Atorvastatin 20mg to patients with **ANY** of the following;

- **Evidence of end organ damage,** such as proliferative retinopathy, CKD 3-5 (including CKD 1 and 2 with persistent albuminuria) or autonomic neuropathy
- **Hypertension** (treated or untreated)
- **family history of premature CVD <50years**
- Central obesity
- **Poor control of diabetes (HbA1c >75mmol/mol)**
- **current smoker or ex-smoker in last 10 years**
- **long duration of diabetes (>10 years).**

Discuss Lifetime risk and the implications of this for the patient in shared decision making conversations about initiating statin treatment

Please refer to the South Yorkshire Lipid Management pathway and product SPC for information about Efficacy monitoring, Safety monitoring, statin intolerance and drug interactions.

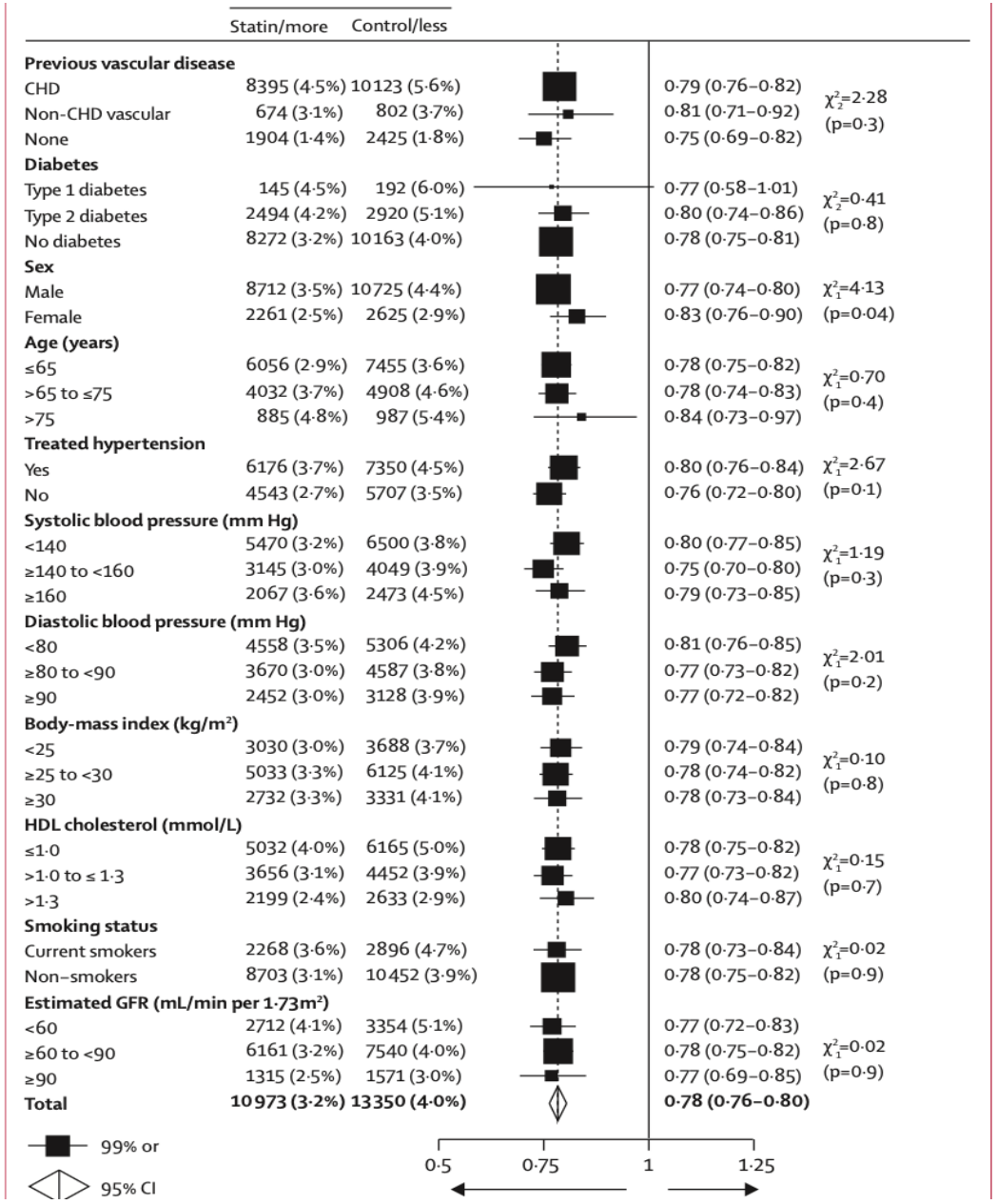
For more information about switching from a low or medium intensity statin to atorvastatin 20mg, please see **Box 3** overleaf.

Statins are contraindicated in women of child bearing potential. Do not prescribe statins unless there is appropriate contraception. Advise women to stop taking statin if pregnancy is a possibility or 3 months before attempting to conceive and not to restart until breastfeeding has stopped. **See also the medicines with teratogenic potential guidelines.**

Rationale for lipid-lowering in young T2D:

- High lifetime risk for premature CVD
- Statin is cardio-protective regardless of age and baseline cholesterol

Pre-pregnancy counselling will be needed in women of child-bearing age



Cholesterol Treatment Trialists' (CTT) Collaboration *Lancet.* 2010; **376**:1670-1681

Conclusions:

Young adult-onset type 2 diabetes heralds a poor prognosis

Younger-onset type 2 diabetes is rapidly increasing in prevalence, with the majority presenting in adulthood aged 18–39 years.[1] This change in diabetes topography presents a challenge to health-care professionals that is hindered by a paucity of research to inform clinical practice. In the UK, the fastest rate of increase in new type 2 diabetes cases (40% between 2016 and 2023) is in people younger than 40 years,[2] which reflects the scale of this looming crisis. Comprehension of the natural history, phenotypic characteristics, and complication risk, assessed longitudinally over time, can help to inform which areas of care require clinical attention and direct future research.

The heightened risk of diabetes complications, despite a similar length of follow-up to the older-onset group, shows the elevated lifetime risk in young adult-onset type 2 diabetes, which is more prominent for retinal and renal complications, revealing an aggressive phenotype. It is debatable whether the elevated

Lancet Diabetes Endocrinol 2024
Published Online
October 23, 2024
https://doi.org/10.1016/S2213-8587(24)00282-1
See Online/Articles
https://doi.org/10.1016/S2213-8587(24)00242-0

Song SH, Frier BM. Lancet Diabetes Endocrinol 2024;12:869-70

Young type 2 diabetes has a high lifetime risk for premature CVD complications

Early optimal management is important to improve long-term prognosis

National recognition of its importance - NDA (2021), NICE NG28 (2022), T2Day (2023), NDA QIP (2025) impetus for systemic change to improve care and outcomes