Lipids, cardiovascular risk and treatment targets

Calculating cardiovascular risk

Cardiovascular risk calculators generate a score which estimates the probability of an individual developing cardiovascular disease (CVD) over a specified time frame. The QRISK®2 and QRISK®3 algorithms both calculate a person's 10-year risk of developing CVD based on a number of known risks.

QRISK2 is recommended in the NICE CG181 guideline *Cardiovascular disease: risk assessment and reduction, including lipid modification*[1] and considers the factors shown in *Box 1.*

There are certain groups of people at increased cardiovascular risk for whom a CV risk calculator should **not** be used. These include:

- Those on treatment for HIV infection.
- Those with serious mental health problems.
- Those taking medicines that can cause dyslipidaemia (e.g. antipsychotic medications, corticosteroids, immunosuppressant drugs).
- Those with autoimmune disorders such as systemic lupus erythematosus, and other systemic inflammatory disorders.
- Those already taking antihypertensive or lipid modification therapy, or have only recently stopped smoking.

The current and updated version of the tool, QRISK3, considers some of these additional risk factors and others, including chronic kidney disease stages 3–5, migraine, corticosteroid use, systemic lupus erythematosus, use of atypical antipsychotics, severe mental illness, erectile dysfunction and variability of systolic blood pressure.

Importantly, neither the QRISK2 nor QRISK3 tool should be used in the following groups, as they are already at increased cardiovascular risk:

- People with established CVD or those who are at high risk of developing CVD because of familial hypercholesterolaemia or other inherited disorders of lipid metabolism.
- People with type 1 diabetes, or eGFR <60 mL/min/1.73 m^2 and/or albuminuria.
- People aged ≥85 at increased risk of CVD because of age alone.
- Particularly people who smoke or have raised blood pressure.

The recently published *Summary of national guidance for lipid management* also warns about underestimation of cardiovascular risk in these groups, but also in those with severe obesity (BMI >40 kg/m^2), significant hypertriglyceridaemia (fasting triglyceride 4.5–9.9 mmol/L) and recent risk factor changes (e.g. quit smoking, blood pressure or lipid treatment). Socioeconomic status should also be considered as an additional factor contributing to CVD risk.[2]

The Joint British Societies for the Prevention of Cardiovascular Disease JBS3 calculator extends its estimation to include the lifetime risk of CVD and should be used in those under the age of 40 years (in whom the 10-year CVD risk is likely to be low).

The QRISK®-lifetime cardiovascular risk calculator may also be used to identify younger patients who, because of their age, have a low absolute 10-year risk but who have a high relative risk compared to their peers.

Box 1. Cardiovascular risk factors considered in the QRISK2 algorithm

- Age (25–84 years)
- Sex
- Ethnicity
- Postcode (for Townsend deprivation score)
- Smoking status
- Diabetes status
- Angina or heart attack in a first-degree relative <60 years
- Chronic kidney disease (stage 4 or 5)
- Atrial fibrillation
- On blood pressure treatment
- Rheumatoid arthritis
- Total:HDL cholesterol ratio
- Systolic blood pressure
- BMI

References can be found in the online article page.

Citation: Diggle J (2022) At a glance factsheet: Lipids, cardiovascular risk and treatment targets. *Diabetes & Primary Care* **24**: [Early view publication]

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Measuring lipids

Most organisations recommend obtaining a full lipid profile to diagnose dyslipidaemia, the key components of which are:
● Total cholesterol ● Triglycerides ● High-density-lipoprotein (HDL) cholesterol ● Low-density-lipoprotein (LDL) cholesterol ● Non-HDL cholesterol ● Total:HDL cholesterol ratio.

Total cholesterol is a measurement of both atherogenic (LDL) and anti-atherogenic (HDL) cholesterol fractions. While high levels of LDL cholesterol are associated with an increased risk of heart disease, elevated levels of HDL cholesterol are associated with lower risk. HDL lipoprotein particles appear to be involved in clearing and removing cholesterol from arteries and atherosclerotic plaques, while LDL particles seem to participate directly in atherosclerosis formation.

Measuring total cholesterol provides limited information about risk because it includes both HDL and LDL cholesterol; therefore, LDL and non-HDL cholesterol are the preferred measurements.

Virtually all drug trials are based on total and LDL cholesterol levels. In most studies and laboratories, LDL cholesterol is calculated (in mmol/L) using the Friedewald equation:

$$LDL = \text{Total cholesterol} - HDL - (0.45 \times \text{triglycerides})$$

However, this calculation is only valid when the concentration of triglycerides is <4.5 mmol/L, and it requires a fasting sample.[4] In contrast, non-HDL cholesterol (= Total cholesterol – HDL) does not require triglyceride levels to be <4.5 mmol/L for calculation, is accurate in a non-fasting sample and may more accurately correlate with CVD risk in people with diabetes.

There is also emerging evidence that non-HDL cholesterol may be a better predictor of risk of major adverse cardiovascular events because it captures information of all atherogenic lipid fractions.[4]

	NICE National Institute for Health and Care Excellence **NICE *Cardiovascular disease: risk assessment and reduction, including lipid modification* [CG181][1]**	NHS **NHS England *Summary of national guidance for lipid management*[2]**
Measuring lipids	Before starting lipid modification therapy for the primary prevention of CVD, take at least one lipid sample to measure full lipid profile (including total cholesterol, HDL cholesterol, non-HDL cholesterol and triglyceride concentrations). A fasting sample is not needed **Follow-up:** Measure total, HDL and non-HDL cholesterol in all people who have been started on high-intensity statin treatment at 3 months of treatment	**Baseline measurements:** ● Non-fasting full lipid profile, plus renal, thyroid and liver profiles (including albumin) and HbA_{1c} to exclude secondary causes and co-morbidities ● Measure baseline liver transaminase (ALT or AST) before starting a statin ● Measure CK if unexplained muscle pain before starting a statin. CK should **not** be measured routinely, especially if a patient is asymptomatic (see Statin intolerance pathway) **Follow-up:** ● Repeat full lipid profile (non-fasting) and liver transaminase test 3 months after starting statin (and within 3 months of every additional uptitration) and then again at 12 months ● If ALT or AST is greater than 3-times the upper limit of normal (ULN), do not initiate a statin, or discontinue statin therapy if already prescribed, and repeat the tests in a month ● If ALT or AST is elevated but less than 3-times the ULN: ➤ Continue the statin and repeat in a month ➤ If they remain elevated but less than 3-times the ULN, continue statin and repeat again in 6 months
Calculating CV risk and initiating a statin*	● Offer atorvastatin 20 mg for primary prevention of CVD to people with type 2 diabetes with a 10-year QRISK2 score of ≥10% ● For people aged ≥85 years, consider atorvastatin 20 mg (to reduce risk of myocardial infarction) ● Consider statin treatment for primary prevention in all adults with type 1 diabetes, but offer to adults with type 1 diabetes who: ➤ Are aged >40 years, **or** ➤ Have had diabetes for >10 years, **or** ➤ Have established nephropathy, **or** ➤ Have other CVD risk factors	Consider statin therapy for adults without established CVD who have: ● Type 2 diabetes and 10-year QRISK2 score of ≥10% ● eGFR <60 mL/min/1.73 m^2 and/or albuminuria ● Type 1 diabetes, if they have one or more of the following: ➤ Age >40 years ➤ Diabetes for >10 years ➤ Established nephropathy ➤ Other CVD risk factors ● In those aged ≥85 years, if appropriate (consider comorbidities, frailty and life expectancy)
Treatment targets	Aim for a >40% reduction in non-HDL cholesterol	Aim for a >40% reduction in non-HDL cholesterol. If non-HDL reduction remains <40% of baseline despite maximal tolerated lipid-lowering therapy (including people with intolerances and contraindications), consider referral to a specialist lipid management clinic according to local arrangements

*Be aware of underestimation of CVD risk in the situations listed on the previous page.

	ESC (2021) CVD prevention guideline[3]	ABCD and Renal Association (2021) Clinical practice guidelines[4]
Measuring lipids	Non-fasting sampling of lipid parameters is recommended for general risk screening, since it has the same prognostic value as fasting samples. Calculated LDL cholesterol from non-fasting samples should be interpreted with care in those with diabetes	Evaluation of a non-fasting full lipid profile (total, non-HDL, HDL and LDL cholesterol, and triglycerides) should be performed at least annually in those with diabetic kidney disease (repeat with fasted sample where triglycerides >4.5 mmol/L)
Calculating CV risk and initiating a statin	Uses the Systemic Coronary Risk Estimation (SCORE2) for those aged 40–69 years and the adjusted SCORE2-OP for those aged >70 years to calculate CVD risk Different lipid targets apply according to CVD risk category. Type 1, type 2 and pre-diabetes are regarded as independent risk factors for ASCVD, and thus people with diabetes are never regarded as low-risk **Very high risk:** ● People with diabetes and CVD ● or other target organ damage ● or 3 or more major risk factors ● or early-onset type 1 diabetes of >20 years' duration **High risk:** ● Patients with diabetes ≥10 years without target organ damage plus any other additional risk factor **Moderate risk:** ● Young patients (age <35 years for type 1 or <50 years for type 2) with diabetes duration <10 years, without other risk factors	Do not use CV risk calculators in people with established CVD or who are at high risk of developing CVD (e.g. those with familial hypercholesterolaemia) In addition, risk assessment tools are not necessary in people with an eGFR <60 mL/min/1.73 m^2 and/or albuminuria (due to the already elevated risk of CVD) Lipid-lowering therapy should be offered to: ● People aged >30 years with persistent microalbuminuria ● People aged 18–30 years with persistent microalbuminuria and one or more additional CVD risk factor ● People with stage G3–5 diabetic kidney disease (eGFR <60 mL/min/1.73 m^2) regardless of albuminuric status
Treatment targets	Stepwise approach recommended, with goals based on 10-year and lifetime CVD risk and treatment benefits, comorbidities, frailty and patient preference Secondary goals for non-HDL cholesterol are defined by inference (although not extensively studied) and should be 0.8 mmol/L higher than the corresponding LDL goal **Very high risk or established CVD or severe target organ damage:** ● Step 1: LDL ≥50% reduction and <1.8 mmol/L (non-HDL <2.6 mmol/L) ● Step 2: LDL <1.4 mmol/L (non-HDL <2.2 mmol/L) **High risk:** ● Step 1: LDL <2.6 mmol/L (non-HDL <3.4 mmol/L) ● Step 2: LDL <1.8 mmol/L (non-HDL <2.6 mmol/L) **Moderate risk:** ● Additional prevention goals generally not recommended	Statin use should aim to reduce total cholesterol to ≤4.0 mmol/L, non-HDL cholesterol to ≤2.5 mmol/L and LDL cholesterol to ≤2.0 mmol/L

QOF indicators[5]	JBS3 Risk calculator[6]
The 2019–20 QOF total cholesterol target ≤5 mmol/L has been removed and replaced with the following indicators: **DM022:** The percentage of patients with diabetes aged ≥40 years, with no history of CVD and without moderate or severe frailty, who are currently treated with a statin (excluding patients with type 2 diabetes and CVD risk score of <10% recorded in the preceding 3 years) **DM023:** The percentage of patients with diabetes and a history of CVD (excluding haemorrhagic stroke) who are currently treated with a statin	The Joint British Societies for the Prevention of Cardiovascular Disease JBS3 calculator (available at: http://www.jbs3risk.com/pages/risk_calculator.htm) extends its estimation of CV risk to include the lifetime risk of CVD JBS3 criteria set a non-HDL cholesterol target of <2.5 mmol/L