The new NICE lipid modification guidelines and their implications for diabetes care

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Article points

1. The QRISK®2 risk assessment tool is used to assess cardiovascular disease (CVD) risk for primary prevention.
2. A risk assessment tool is not required to assess CVD risk for primary prevention in people with chronic kidney disease or type 1 diabetes.
3. The threshold for the consideration of statin therapy for primary prevention has been lowered to a 10-year risk of developing CVD of at least 10%, supporting earlier intervention
4. High-intensity statin therapy is recommended for both primary and secondary prevention of CVD.
5. Non-fasting non-HDL-cholesterol replaces fasting LDL-cholesterol for monitoring and assessment of adequacy of response to therapy.

Key words

- Cardiovascular risk
- Lipid modification
- NICE guidelines

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Cardiovascular disease (CVD) remains the leading cause of mortality in the UK, and people with diabetes are at an increased risk of cardiovascular complications, including acute coronary syndrome, arrhythmias, stroke and heart failure. Dyslipidaemia is strongly related to CVD risk. It is usually present at the time of diagnosis, it often persists despite treatment of hyperglycaemia, and it is modifiable with therapeutic intervention using statin drugs. The new NICE guidelines on lipid modification were published in July this year. People should now be prioritised for full formal risk assessment if their estimated 10-year risk of CVD is 10% or more. The QRISK®2 assessment tool is recommended to assess CVD risk, in the context of primary prevention, for people aged up to 84 years, including those with type 2 diabetes. People should be encouraged to participate in reducing their own CVD risk. Diet and lifestyle modification is particularly important for people with diabetes. Non-fasting non-HDL-cholesterol replaces fasting LDL-cholesterol for monitoring and assessment of adequacy of response to lipid modification therapy. Atorvastatin is the drug of choice.

Cardiovascular disease (CVD) remains the leading cause of mortality in the UK, being responsible for over one-quarter of all deaths. The total cost of premature death, lost productivity, prescriptions and hospital treatment relating to CVD is estimated to be around £19 billion (British Heart Foundation, 2014).

Patients with diabetes are at an increased risk of cardiovascular complications, including acute coronary syndrome, arrhythmias, stroke and heart failure (Haffner et al, 1998; Malmberg et al, 2000; Donohoe et al, 2007). Research has shown that people with diabetes and no history of heart disease have the same risk for future cardiovascular death as people without diabetes and a history of previous myocardial infarction (Haffner et al, 1998). In the INTERHEART study, diabetes was associated with an increase in the risk of myocardial infarction of more than two-fold (Yusuf et al, 2004). Coronary artery disease (CAD) is the main cause of death in European adults with diabetes, and their risk is 2–3 times higher than that of people without diabetes (Laakso, 1999).

Sadly, people with diabetes do not appear to have experienced the same reductions in mortality rates that have been observed in people without diabetes since the 1970s (Gu et al, 1999). Recently published research found that adults treated pharmacologically for diabetes had a 45% increased risk of mortality at 5 years, mainly owing to cardiovascular complications. CVD was listed on 60% of death certificates of people with diabetes in France, 68–70% of those in the US and 62% of those in Sweden. This highlights the need for further prevention (Romon et al, 2014).

The increased risk of CVD in people with diabetes is primarily related to early and extensive atherosclerosis (which often involves the smaller vessels), increased plaque burden and increased plaque vulnerability

(Burke et al, 2004). In type 2 diabetes, the pathogenesis of atherosclerosis-related disease is multifactorial (Betteridge, 2011). Glycaemic control has been consistently shown to prevent microvascular complications. However, large, randomised trials have failed to demonstrate the same consistent beneficial effects of intensive glycaemic control on improving cardiovascular outcomes. Thus, optimal glucose control in isolation is not sufficient to reduce cardiovascular risk (Stranges and Khanderis, 2012).

Dyslipidaemia is strongly related to CVD risk. In people with diabetes, it is usually present at the time of diagnosis, it often persists despite treatment of hyperglycaemia and it is modifiable with therapeutic intervention (Betteridge, 2011; Rydén et al, 2007). The effective management of dyslipidaemia is an essential component of the overall management of vascular risk in people with diabetes. The main goal of therapy is a reduction in the levels of LDL-cholesterol and other apolipoprotein-B-containing lipoproteins, and this is primarily achieved with the statin class of drugs (Betteridge, 2011).

Large-scale randomised controlled trials have demonstrated unequivocal benefits of statins in reducing the incidence of CVD events in people with diabetes with or without established CVD (Betteridge, 2011). Although most of the available trial evidence relates to patients with type 2 diabetes, the increased lifetime risk of CVD in people with type 1 diabetes should not be overlooked (Soedamah-Muthu, 2006; Betteridge 2011), and this is emphasised in the latest NICE guidelines (NICE, 2014).

The new NICE guidelines on lipid modification were published in July this year (NICE, 2014). They update and replace the previous guidance on lipid modification and statin use (clinical guideline 67 [published in May 2008] and technology appraisal guidance 94 [published in January 2006]).

The latest guidelines are reviewed below, concentrating particularly on the relevance for people with diabetes.

Identifying and assessing CVD risk

For primary prevention in primary care, NICE advises that we continue to use a systemic strategy to identify individuals likely to be at high risk. However, people should now be prioritised for full formal risk assessment if their estimated 10-year risk of CVD is at least 10%. The QRISK®2 assessment tool is recommended to assess CVD risk, in the context of primary prevention, in people aged up to 84 years, including those with type 2 diabetes (NICE, 2014).

Risk assessment tools should not be used to assess CVD risk in people with type 1 diabetes or those known to be at high risk owing to other reasons, such as pre-existing CVD, inherited disorders of lipid metabolism, or an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2, albuminuria or both. Severe obesity (BMI >40 kg/m^2) increases the risk of CVD and this should be taken into account when using risk scores to inform treatment decisions (NICE, 2014).

Lifestyle modification for primary and secondary prevention

People should be encouraged to participate in reducing their own CVD risk. Diet and lifestyle modification is particularly important for people with diabetes. NICE recommends that individuals at high risk of, or with, CVD are advised to eat a healthy diet in which total fat intake is no more than 30%, and saturated fat is at most 7%, of the total energy intake. Dietary cholesterol should be less than 300 mg/day and saturated fats should be replaced with mono- and polyunsaturated fats where possible. Refined sugars should be reduced and whole-grain varieties of starchy foods chosen where possible. People should be advised to eat at least five portions of fruit and vegetables a day, and at least two portions of fish (one oily) and four to five portions of unsalted nuts, seeds and legumes a week (NICE, 2014).

Plant sterols or stanols are now not advised for the prevention of CVD in people with type 1 or type 2 diabetes (NICE, 2014).

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1. Large-scale randomised controlled trials have demonstrated unequivocal benefits of statins in reducing the incidence of CVD events in people with diabetes with or without established CVD.
2. For primary prevention in primary care, NICE now advises that we continue to use a systemic strategy to identify individuals likely to be at high risk. However, people should now be prioritised for full formal risk assessment if their estimated 10-year risk of CVD is at least 10%.
3. People should be encouraged to participate in reducing their own CVD risk. Diet and lifestyle modification is particularly important for people with diabetes.

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1. Before initiating lipid modification therapy for primary prevention, NICE recommends a full lipid profile, including the measurement of total cholesterol, HDL-cholesterol, non-HDL-cholesterol and triglycerides.
2. Non-HDL-cholesterol is now preferred instead of LDL-cholesterol.
3. When deciding which statin to use, NICE advises using one of high intensity and low acquisition cost, and atorvastatin is now recommended for both primary and secondary prevention.

Regarding alcohol, men should be advised to consume a maximum of 3–4 units a day and women a maximum of 2–3 units a day. Binge drinking should be avoided (NICE, 2014).

Dietary advice should be tailored to individuals, taking account of their relevant drug therapy, comorbidities (especially diabetes) and other lifestyle modifications, such as exercise levels (NICE, 2014).

Diet and eating patterns should be adjusted to avoid hypoglycaemia, especially when excessive exercise is taken.

NICE recommends that individuals at high risk of, or with CVD, are advised to do the following physical activity every week (NICE, 2014):

- At least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic activity, or a mix of both.
- Muscle-strengthening exercises that work all major muscle groups on at least 2 days.

People should be advised to exercise at their maximum safe capacity, taking into account their personal needs, preferences and circumstances (NICE, 2014).

People with type 2 diabetes are often overweight. Individuals at high risk of, or with, CVD who are obese or overweight should be offered appropriate advice and support to achieve and maintain a healthy weight (NICE, 2014).

People with type 1 diabetes need quite specific dietary and physical activity advice. More information on this can be found on the diabetes pathway available on the NICE website (see http://pathways.nice.org.uk/pathways/diabetes [accessed 03.09.13]).

All smokers should be advised to stop and offered referral to an intensive support service. If they are unable or unwilling to accept referral, they should be offered appropriate pharmacotherapy (NICE, 2014).

Lipid modification

Before initiating lipid modification therapy for primary prevention, NICE recommends a full lipid profile, including the measurement of total cholesterol, HDL-cholesterol, non-HDL-cholesterol and triglycerides. Non-HDL-cholesterol is now preferred instead of LDL-cholesterol. Calculated as total cholesterol minus HDL-cholesterol, non-HDL-cholesterol is more convenient because it is not affected by other parameters such as triglycerides and it does not require a fasting sample (NICE, 2014).

Other new recommendations include: the exclusion of possible common secondary causes of dyslipidaemia, such as uncontrolled diabetes, before referring an individual for specialist review; and referring people for urgent review if they have a triglyceride concentration above 20 mmol/L that is not due to poor glycaemic control or excess alcohol (NICE, 2014).

Statins for the prevention of CVD

NICE recommends that statin therapy is started after an informed discussion with the individual about the risks and benefits of treatment, accounting for related factors such as lifestyle modifications, comorbidities and polypharmacy, as well as the person's preference, frailty and life expectancy (NICE, 2014).

Before initiating statin therapy, the individual should receive clinical assessment and baseline blood tests, including: smoking status; alcohol intake; blood pressure; BMI or equivalent; a full lipid profile; HbA_{1c}; renal function and eGFR; transaminase level; and thyroid-stimulating hormone. Any comorbidities and secondary causes of dyslipidaemia should be treated appropriately (NICE, 2014).

When deciding which statin to use, NICE advises using one of high intensity and low acquisition cost, and atorvastatin is now recommended for both primary and secondary prevention.

Primary prevention of CVD

Before statins are offered for primary prevention, NICE recommends discussing the benefits of lifestyle modification and optimising the management of all other modifiable risk factors. People should be offered the opportunity to have their risk

re-assessed after initiating any lifestyle changes. If lifestyle modification is inappropriate or ineffective, statin treatment should be offered following risk assessment (NICE, 2014).

NICE has halved the threshold for primary prevention and atorvastatin 20 mg is recommended in people with a 10-year risk of CVD of at least 10%, including those with type 2 diabetes (NICE, 2014).

NICE now recommends that statin treatment is considered for primary prevention in all adults with type 1 diabetes and treatment with atorvastatin 20 mg should be offered to those who:

- Are above 40 years of age.
- Have had the condition for over 10 years.
- Have established nephropathy.
- Or have other risk factors for CVD.

Secondary prevention of CVD

For secondary prevention, statin treatment should not be delayed to first attempt to manage modifiable risk factors. For people with pre-existing CVD, treatment should be initiated with atorvastatin 80 mg (although this drug's UK licence does not currently include a secondary prevention indication [see http://www.medicines.org.uk/emc/]). A lower dose should be used if there is a high risk of adverse effects, there is the potential for drug interactions, or the patient's preference dictates it (NICE, 2014).

Chronic kidney disease (CKD) is more common in people with diabetes. Atorvastatin 20 mg should also be offered for primary or secondary prevention to people with CKD. The dose should be increased if a reduction in non-HDL-cholesterol of more than 40% is not achieved and eGFR is at least 30 mL/min/1.73 m^2. If the eGFR is less than 30 mL/min/1.73 m^2, use of the higher doses should be agreed with a renal specialist (NICE, 2014).

Follow-up of people taking statin treatment

Individuals started on high-intensity statin therapy should be reviewed after 3 months, with the measurement of total cholesterol, HDL-cholesterol and non-HDL-cholesterol. If a reduction in non-HDL-cholesterol of more than 40% is not achieved, NICE advises discussing adherence and time of dosing, trying to optimise adherence to diet and lifestyle interventions, and considering an increase in dose if the person was started below 80 mg and is judged to be at higher risk. Annual medicine reviews should follow, which can be informed by a non-fasting blood test for non-HDL-cholesterol (NICE, 2014).

The new Joint British Societies recommendations on the prevention of Cardiovascular Disease (JBS3) still advocate a treat-to-target approach, and they advise aiming for a non-HDL-cholesterol of below 2.5 mmol/L, which approximately equates to an LDL-cholesterol of 1.8 mmol/L (JBS3 Board, 2014).

Advice and monitoring for adverse effects

People taking statins should be advised that other drugs, some supplements, and food and drink (e.g. grapefruit juice) can affect the way they work and to always consult the patient information leaflet, a pharmacist or a prescriber for advice on possible interactions (NICE, 2014).

Before being offered statin treatment, the individual should be asked about persistent, generalised unexplained muscle pain, associated (or not) with previous lipid-lowering therapy. If they have experienced this, their creatine kinase levels should be measured. If these are more than 5 times the upper limit of normal, they should be re-measured after 7 days. If they are still this high, statin treatment should not be started. If creatine kinase levels are raised but less than 5 times the upper limit of normal, statin treatment should be started at a lower dose (NICE, 2014).

People taking statins should be advised to seek medical advice if they develop muscle symptoms (weakness, pain or tenderness), and if this occurs, they should have their creatine kinase levels measured. If statin therapy has been tolerated for more than

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2. If a reduction in non-HDL-cholesterol of more than 40% is not achieved, NICE advises discussing adherence and time of dosing, trying to optimise adherence to diet and lifestyle interventions, and considering an increase in dose if the person was started below 80 mg and is judged to be at higher risk.
3. Before being offered statin treatment, the individual should be asked about persistent, generalised unexplained muscle pain, associated (or not) with previous lipid-lowering therapy.

"The new NICE guidelines include some major changes. The focus for primary care is on prevention to help make a long-term difference. This has seen the threshold for primary prevention halved to 10%, despite concerns that this will significantly increase GPs' workloads and lead to over-treatment. Nevertheless the cost-effectiveness argument is well made and evidence-based."

3 months previously, other causes of the muscle symptoms and raised creatine kinase levels should be explored (NICE, 2014).

Statin treatment should not be stopped because of an increase in blood glucose levels or HbA_{1c} (NICE, 2014).

Other treatments

In line with their previous guidelines, NICE recommends that ezetimibe is considered for people with primary hypercholesterolaemia (NICE, 2014), and this drug is useful where there is statin intolerance.

Fibrates, nicotinic acid, bile acid sequestrants and omega-3 fatty acid compounds are not recommended for the prevention of CVD in people who are being treated for this, including those with type 1 or type 2 diabetes (NICE, 2014).

Conclusion

The new NICE guidelines include some major changes. The focus for primary care is on prevention to help make a long-term difference. This has seen the threshold for primary prevention halved to 10%, despite concerns that this will significantly increase GPs' workloads and lead to over-treatment. Nevertheless the cost-effectiveness argument is well made and evidence-based. Non-adherence to statin therapy is commonplace, particularly in primary prevention, and positive effects from this lower threshold may ultimately be compromised if we fail to encourage people to take their medication reliably in the long term. The QRISK®2 assessment tool is now recommended to assess CVD risk, and the measurement of LDL-cholesterol has been replaced by non-HDL-cholesterol. NICE has also moved away from the "treat-to-target" approach, which has been the subject of much debate over the years, mainly on the basis that the major clinical trials used fixed doses rather than treatment targets. The recommendation of atorvastatin 20 mg for primary prevention and atorvastatin 80 mg for secondary prevention should help simplify things for GPs and practice nurses by removing the need for titration against specific cholesterol levels, although there is the need to check that a reduction in non-HDL-cholesterol of more than 40% is achieved. ■

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