Editorial

Lipid management: Insights from NICE clinical guidelines 2023

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Abstract
The available lipid-lowering therapy guidelines are reviewed in a succinct manner in this article. In addition, NICE Guidelines on Lipids are recapitulated and compared with EAS/ESC guidelines.
Key words: lipids, management, guidelines

(Heart Vessels Transplant 2024; 8: doi: 10.24969/hvt.2024.476)

Atherosclerotic Cardiovascular Disease (ASCVD) is the leading cause of mortality and morbidity worldwide. Different studies and trials have shown that lipid-lowering therapies improve cardiovascular outcomes. The main lipid-lowering therapies are outlined here.

NICE Clinical Guidelines CG 181

In 2014, NICE published its clinical guideline, 'Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181)', which were subsequently updated in 2016 and 2023 (1).

The mainstay of NICE guidelines is based on estimation of 10-year cardiovascular disease (CVD) risk to guide decision-making regarding the use of statin therapy for primary prevention, as calculated by the prediction algorithm QRISK3. QRISK3 is a tool used to calculate the estimated CVD risk within the next 10 years for people aged between 25 and 84 without CVD and for type 2 diabetes patients aged between 25 and 84. It is not to be used in patients over the age of 84 or patients with type 1 diabetes, estimated glomerular filtration rate (eGFR) less than 60mL/min/1.73 m^2 or albuminuria, familial hypercholesterolemia or other inherited disorders of lipid metabolism. It is also acknowledged that risk is underestimated in patients with some underlying medical conditions (including but not limited to HIV, systemic inflammatory disorders, hypertriglyceridemia) or who take certain medications (eg, antipsychotic drugs). QRISK also incorporates age, gender, postcode, history of smoking, diabetes and hypertension, family history of CVD, height and weight due to the fact that ASCVD risk is not related solely to the plasma concentration of low density lipoprotein-cholesterol (LDL-c).

Measures

The vast majority of clinical trials employed change in plasma concentration of LDL-c as their main biochemical endpoint, debate still continues to exist on measure of choice for assessment and follow up of patients in the long run and for prediction of ASCVD. While some experts justify using LDL-c as the marker of choice, others agree to use non-HDL cholesterol or apolipoprotein B (ApoB) as preferred markers, each with pros and cons. Considering the fact of not requiring a fasting state for measurement and superiority to LDL-c in estimation of ASCVD risk, NICE decided to incorporate non high density liptorotein cholesterol (HDL-c), rather than LDL-c, as the lipid parameter of choice in estimation of ASCVD risk.

However, this approach has not been consistent because the industry submissions of evidence for the technology appraisals were based on LDL-c, and in more recent NICE technology appraisals, LDL-c thresholds have been employed to assess eligibility for medicines such as evolocumab, alirocumab and inclisiran. In addition, the diagnosis of familial hypercholesterolaemia is made predominantly on LDL-c concentration, the disease being characterized as a disorder of LDL metabolism. Thus, both non-HDL-c and LDL-c measurements are currently required to assess the dyslipidemic patient appropriately.

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Received: 31.01.2024 **Accepted:** 01.02.2024

Goals

While a specific lipid target is not recommended by NICE CG181, the advice is to repeat measurement of non-HDL-c at 3 months and that, for patients who do not achieve a non-HDL-c reduction of greater than 40%, a discussion around adherence should be undertaken with consideration of dose escalation. Therefore, patients should be treated with drug and dose combinations expected to achieve LDL-C reduction of greater than 40%, which equates to high-intensity statin therapy. It was agreed that response should be assessed by non-fasting non-HDL-C and if 40% reduction was not achieved, concordance should be checked and/or lower doses titrated up.

In summary, lipid targets for people taking statins for primary prevention of CVD is to aim for a greater than 40% reduction in non-HDL cholesterol.

For secondary prevention of CVD, the clinicians should aim for LDL cholesterol levels of 2.0 mmol per litre or less (≤77.3mg/dL), or non-HDL cholesterol levels of 2.6 mmol per litre or less (≤100.5mg/dL).

Lipid Lowering Therapies

Statins

Statins remain the cornerstone of lipid-lowering therapy to reduce ASCVD risk. Subjectively perceived statin intolerance remains a major problem with the use of statins. To help clinicians address this, NHS England have devised a Statin Intolerance Algorithm to provide a structured approach for managing patients with statin intolerance. Strategies may include stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin, reducing the dose within the same intensity group or changing the statin to a lower intensity group.

Advise people who are being offered a statin that the risk of muscle pain, tenderness or weakness associated with statin use is small and the rate of severe muscle adverse effects (rhabdomyolysis) because of statins is extremely low.

Also advise that other drugs, some foods (for example, grapefruit juice) and some supplements may interfere with statins. Remember to not routinely exclude from statin treatment people who have liver transaminase levels that are raised but are less than 3 times the upper limit of normal.

Before offering a statin, ask the person if they have had persistent generalized unexplained muscle symptoms (pain, tenderness or weakness), whether associated or not with previous lipid-lowering treatment. If they have, measure creatine kinase (CK) levels. If CK levels are more than 5 times the upper limit of normal, re-measure creatine kinase after 7 days; if creatine kinase levels are still 5 times the upper limit of normal, do not start statin treatment. If CK levels are raised but less than 5 times the upper limit of normal, start statin treatment at a lower dose.

Be aware that statins are contraindicated in pregnancy and should be stopped if pregnancy is a possibility. Statins should be stopped 3 months before attempting to conceive and should not be restarted until breastfeeding is finished. It is worth mentioning that before starting statins, comorbidities and secondary causes of dyslipidemia should be addressed.

Based on percentage reduction in LDL cholesterol, statins are divided into 3 main categories of high-intensity, medium-intensity and low-intensity, which differ, and are defined, based on the dosage and type of statins used.

Atorvastatin 20-80 mg or rosuvastatin 10- 40 mg are categorized as high-intensity statin while medium-intensity statin therapy is referred to atorvastatin 10 mg, fluvastatin 80 mg, rosuvastatin 5 mg, and simvastatin 20-40 mg. The low-intensity category includes fluvastatin 20-40 mg, pravastatin 5-40 mg and simvastatin 10 mg

Initial treatment

NICE CG181 recommends that those with a 10-year risk of an ASCVD event greater than 10% should be offered atorvastatin 20mg per day to lower their CVD risk. By contrast, patients with established ASCVD, whose risk of (recurrent) events is higher, should commence 80mg of atorvastatin per day, regardless of their cholesterol level. In case of possibility of reaction with other drugs, high risk of adverse effects and the patient preference to take a lower dose, a lower dose of atorvastatin can be offered. Statin therapy should not be delayed for secondary prevention of CVD and lifestyle changes should be discussed at the same time if appropriate. If a person has acute coronary syndrome, do not delay statin treatment. Measure full lipid profile on admission and at 2 to 3 months after starting treatment.

Assessing response to treatment

When to repeat laboratory tests? Measure liver transaminase and full lipid profile at 2 to 3 months after starting or changing lipid-lowering treatment. Measure liver transaminase at 12 months, but not again unless clinically indicated.

When to measure creatine kinase? Advise people who are being treated with a statin to seek medical advice if they develop unexplained muscle symptoms (pain, tenderness or weakness). If this occurs, measure CK. If people report muscle pain, tenderness or weakness while taking a statin and have a CK level less than 5 times the upper limit of normal, reassure them that their symptoms are unlikely to be due to the statin and explore other possible causes. Measurement of CK levels in asymptomatic people who are being treated with a statin is not required.

Statins for primary and secondary prevention of cardiovascular disease in people with chronic kidney disease (CKD)

People on renal replacement therapy are outside the scope of this guideline.

Offer atorvastatin 20 mg for the primary or secondary prevention of CVD to people with CKD. If the lipid target for primary or secondary prevention of CVD is not met and eGFR is ≥30 ml per minute per 1.73 m2, increase the dose of atorvastatin. Consult the use of higher doses with a renal specialist if eGFR is less than 30 ml per minute per 1.73 m2.

Optimizing treatment for people on statins

If the lipid target for primary or secondary prevention of CVD is not met, discuss adherence and timing of statin dose with the person, encourage them to continue improvements to their diet and lifestyle, and to make further changes if appropriate, and consider increasing the statin intensity/dose if the person is not currently taking a high-intensity statin at the maximum tolerated dose.

If the person reports adverse effects when taking a high-intensity statin, discuss strategies with like stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin, changing to a different statin in the same intensity group (rosuvastatin if already receiving atorvastatin), reducing the dose and/or changing to a lower-intensity statin.

If a person is not able to tolerate a high-intensity statin, aim to treat with the maximum tolerated intensity and dose of statin. Inform the patient that any statin at any dose reduces CVD risk.

Contrary to what is practiced by some physicians, coenzyme Q10 or vitamin D should not be offered to increase adherence to statin therapy by patients.

Ezetimibe

This drug reduces absorption of cholesterol from the intestine and interrupts enterohepatic recirculation of bile.

Bempedoic acid

Bempedoic acid is an inhibitor of ATP–citrate lyase, a key enzyme in the cholesterol synthesis pathway. Bempedoic acid is a prodrug and requires activation by an enzyme, which is present in the liver but absent in most peripheral tissues. Therefore, an important feature differentiating bempedoic acid from statins is its liver-specific action.

The drug is available in a fixed dose combined formulation with ezetimibe which NICE recommends if statins are contraindicated or not tolerated and ezetimibe alone does not control LDL-c. There is currently no CVD outcome data available for bempedoic acid, with or without ezetimibe.

Monoclonal antibodies targeting PCSK9

PCSK9 is a protein that binds the LDL receptor and directs it to destruction in the lysosome. Both evolocumab and alirocumab, monoclonal antibodies to PCSK9, reduce LDL-c by approximately 60% and have demonstrated reduction in major adverse cardiovascular events. Based on their clinical benefits and cost, both agents have strict LDL-c thresholds and clinical criteria for eligibility for which NICE recommend their initiation by specialists.

Small interfering ribonucleic acid (siRNA) targeting PCSK9

The first licensed siRNA-based therapy for cardiovascular disease, inclisiran is a double-stranded siRNA that suppresses PCSK9 translation in the liver, leading to sustained reductions in LDL-c by approximately 50% with twice-yearly dosing. It is prescribable as a subcutaneous injection by a healthcare professional.

Icosapent ethyl

Icosapent ethyl was recently assessed in the REDUCE-IT trial (2) and found to lower CVD outcomes in patients with previous CVD or at high risk of developing CVD, with elevated triglyceride levels despite the use of statins.

Other therapies

Some other lipid-lowering therapies are outlined as follows:

Fibrates: Although they promote lipolysis and improve hypertriglyceridemia, raise HDL-c, and lower LDL-c to a modest degree, trials have reported inconsistent findings for the effect of fibrates on cardiovascular risk and therefore NICE CG181 does not recommend the routine use of fibrates for CVD prevention.

Bile acid sequestrants (anion exchange resins): Though largely superseded by other more favorable treatment options, NICE recommends that they should be initiated by specialists and limited to cases of familial hypercholesterolemia (FH). However, colesevelam is designated by the FDA as category B (no risk to pregnancy in animal studies) and may be used in place of other drugs for women in pregnancy or while breastfeeding. These agents are not offered for prevention of CVD.

Nicotinic acid

It is not considered as an option for prevention of CVD.

Omega 3 fatty acid compounds

Inform the patients that there is no evidence that omega 3 fatty acid compounds help to prevent CVD, except use of icosapent ethyl as described in NICE's technology appraisal guidance on icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides.

Lipoprotein apheresis

Extracorporeal removal of ApoB-containing lipoproteins is the mainstay of treatment for homozygous familial hypercholesterolemia (FH), both in children and adults. In heterozygous FH, NICE CG71 recommends that, in exceptional instances such as when there is progressive, symptomatic coronary heart disease, despite maximal tolerated lipid-modifying drug therapy, healthcare professionals should consider offering lipoprotein apheresis.

Using the NHS England lipid management pathway to guide lipid lowering

NHS England decided to create simple diagrammatic lipid management pathways to provide clinicians with guidance on how to approach lipid management for the individual (available at: https://heart.bmj.com/content/heartjnl/109/9/661.full.pdf).

The primary prevention pathway takes a risk-based approach, recommending 20mg of atorvastatin as first-line pharmacotherapy. The patient is then assessed 3 months later. If 40% reduction in non-HDL-c is not achieved, discussion onadherence and lifestyle is advised, with the possibility of increasing the statin dose. Another option is the addition of ezetimibe.

In secondary prevention, the prescribing of atorvastatin 80mg once daily should not be delayed unless there is a specific clinical reason. If non-HDL-c is not reduced by 40% at 3 months, ezetimibe or injectable therapies can be added. For evolocumab, alirocumab and inclisiran, specific NICE eligibility criteria apply.

How do nice guidelines compare with ESC/EAS AND ACC/AHA guidance?

NICE guidelines are not purely based on the current science and expert opinion, but also take into account the cost-effectiveness of treatments and health economics, this is what makes NICE guidelines different from Joint British Societies and ESC/EAS guidelines on lipid management (1). In addition, NICE guidance tends to be very focused on evidence from randomized clinical trials within specific cohorts of patients and there is little scope to extend this for more generalizability to other patient cohorts who may also benefit.

The American Heart Association/American College of Cardiology (AHA/ACC) guidelines (3) do take into account the cost of therapies and are therefore more conservative than the European guidelines, but more liberal than NICE. This has led to some very clear differences in policy between NICE and the specialist society statements.

One stark difference is the use of non-HDL-c as the lipid biomarker of choice by NICE whereas the Europeans and Americans have stayed with LDL-c. The European LDL-c targets are much more stringent than the American ones. NICE does not recommend imaging of subclinical atherosclerosis whereas the ESC/ EAS and AHA/ACC do. ESC/EAS (4) have much broader eligibility criteria for some of the more costly agents. For example, under NICE, patients without FH, being treated for primary prevention, would not qualify for PCSK9 monoclonal antibodies; however, they would under the ESC guidelines if considered ‘very-high risk’. The 2018 AHA/ACC guidelines and the 2019 ESC/EAS guidelines for lipid management were published within 9 months of each other.

These guidelines therefore have not advised on the use of some of the newer therapies such as inclisiran, bempedoic acid and icosapent ethyl. One of the advantages of the NICE approach is that each new agent is assessed as part of the technology appraisal process with the intent for them to become 'live guidelines'.

Future perspectives

For the primary prevention of ASCVD, 10-year CVD risk is used to guide clinical decision-making. Moving forward, lifetime risk should be considered and this is especially pertinent to young patients with strong family history of ASCVD whose 10-year risk may be very low, but lifetime risk is very high.

Lipoprotein(a) is already recognized in the European and American guidelines, and both consider those patients with elevated lipoprotein(a) to be at higher risk of ASCVD.

Finally, clinicians, particularly in primary care, find percentage reduction in non-HDL-c challenging to implement and audit. Patients often find this a tricky concept to grasp. In practice, many lipidologists and cardiologists employ absolute targets to guide clinical care. The practicality of guidelines should be taken into account in future iterations.

Peer-review: Internal
Conflict of interest: None to declare
Authorship: K.A.A.
Acknowledgement and funding: None to declare

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