Cardiovascular prevention: Frontiers in lipid guidelines

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Cardiovascular disease (CVD) remains one of the principal causes of morbidity and mortality in the world. International guidelines are being updated to take into account new evidence and improved health economics as drug patents expire. Recent studies have investigated the best lipid fractions to predict CVD, suggested additional CVD risk factors and a potential role for novel biomarkers while big data approaches have allowed improvements to be made to CVD risk calculators. The increasing availability of next generation sequencing is allowing systematic efforts to be made to detect monogenic familial hypercholesterolaemia.

Previous trials have validated the low-density lipoprotein cholesterol (LDL-C) hypothesis of atherosclerosis. Statins now form part of universal treatment advice for CVD and trial data on ezetimibe also suggests it has a place in the treatment pathway. New data has been published on novel lipid-lowering therapies such as proprotein convertase subtilisin kexin 9 inhibitors but the role of these expensive drugs has yet to be fully settled and a diversity of approaches exists between guidelines.

The role of lipid fractions outside LDL-C is unclear. There will be challenges in incorporating new non-linear data on omega-3 fatty acids that not only affect triglycerides but more directly CVD.

Introduction

A new cycle of guideline updates is underway for hyperlipidaemia prompted by advances in the last 5 years including:

> a greater emphasis on early detection and diagnosis of disease, and the introduction of genetic tests

> new biomarkers or updated information on older biomarkers

> advances in technology and availability of imaging

> the expiration of patent protection for most statins and now ezetimibe leading to a substantial reduction in acquisition costs

> novel therapeutics including proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors

> novel trial data in secondary prevention populations.

Recently updated major specialist society guidelines include the US American College of Cardiology (ACC) / American Heart Association (AHA), and European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS) guidelines (Table 1). In the UK, specialist society guidelines have been superseded by the National Institute for Health and Care Excellence (NICE) programmes (Table 1). One of the major differences between guidelines is their authorship and how this relates to health policy. Specialist societies do not need to take into account cost or time constraints while NICE uses health economics to determine the optimum use of resources and has indirect responsibility for implementation.

Detection of disease

Lipid guidelines used to use single parameter initiation thresholds for low-density lipoprotein cholesterol (LDL-C; e.g. 5 mmol/L ≈ 190 mg/dL) in primary prevention. However, a unifactorial approach to cardiovascular disease (CVD) is simplistic and the ACC/AHA and NICE have moved to a global CVD risk approach. The original risk threshold was set at the equivalent rate for CVD events in patients with stable coronary artery disease; 2% per year (20% per decade) with CVD risk.

Currently, all major guidelines recommend that all individuals undergoing evaluation for cardiovascular disease risk should have measurements of non-high-density lipoprotein cholesterol. Measurement of non-high-density lipoprotein cholesterol does not require fasting and is superior to low-density lipoprotein cholesterol for predicting cardiovascular risk.

For secondary prevention – the maximum tolerated dose of statin (e.g. atorvastatin 80 mg) should be used whereas moderate doses (atorvastatin 20 mg) are adequate for primary prevention.

Key points

All current guidelines favour evaluating global cardiovascular disease risk when taking treatment decisions.

Familial hypercholesterolaemia affects ~1 in 350 individuals and when suspected, diagnosis should be confirmed by sequencing the four familial hypercholesterolaemia associated genes.

Measurement of non-high-density lipoprotein cholesterol does not require fasting and is superior to low-density lipoprotein cholesterol for predicting cardiovascular risk.

For secondary prevention – the maximum tolerated dose of statin (e.g. atorvastatin 80 mg) should be used whereas moderate doses (atorvastatin 20 mg) are adequate for primary prevention.

There is a 21% reduction of cardiovascular disease events per 1 mmol/L reduction in low-density lipoprotein.

KEYWORDS: Cardiovascular disease, cholesterol, LDL, cardiovascular risk, statins
| ACC/AHA | ESC/EAS | NICE |
|---------|---------|------|
| **Initiation threshold for intervention** | **Initiation threshold for intervention** | **Initiation threshold for intervention** |
| LDL-C > 4.9 mmol/L | Total CVD risk, score % | Primary prevention |
| ASCVD risk > 7.5 % | LDL-C, mmol/L | > 10% CVD risk or FH |
| DM and age 40–75 years | Primary prevention | Very high-risk |

| **Risk measures calculator system, age range and components** | **Risk measures calculator system, age range and components** | **Risk measures calculator system, age range and components** |
|----------------------------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------------|
| Pooled cohort equations (PCE) 40–75 years | European SCORE calculator (fatal CVD only) 40–70 years | QRISK2 (QRISK3) in England and Wales, ASSIGN in Scotland 35–75 (25–85) years |
| Age | Low-risk vs high-risk regions of Europe | Age |
| Gender | | Gender |
| Smoking | | Smoking |
| Systolic blood pressure | | Systolic blood pressure |
| Total cholesterol | | Total cholesterol |
| HDL-cholesterol | | HDL-cholesterol |

(Continues)
### Table 1. Comparison of principal components of guidelines for management of cardiovascular disease risk in the USA, Europe and UK (Continued)

| ACC/AHA | ESC/EAS | NICE |
|---------|---------|------|
| **Additional CVD risk factors** | **Family history CVD <55 years** | **Family history CVD <55 years** |
| Family history CVD (male <55 years; female <65 years) | Social deprivation | Social deprivation |
| Coronary Artery Calcium Score >100 | Major psychiatric disease | Major psychiatric disorder |
| Lp(a) >50 mg/dL (125 nmol/L) | Chronic autoimmune disease | T1DM |
| ApoB >130 mg/dL | Obesity (central or morbid) | Systemic lupus erythematosus |
| CRP >2 mg/L | Obstructive sleep apnoea | Major psychiatric disease: use of atypical antipsychotics |
| Chronic kidney disease | Atrial fibrillation | Use of steroid therapy |
| Chronic inflammation | Left ventricular hypertrophy | |
| Premature menopause | Non-alcoholic fatty liver disease | |
| High-risk race/ethnicity | Physical inactivity/psychosocial stress | |
| Persistent LDL-C >4.1 mmol/L or triglycerides >2.0 mmol/L | Carotid or femoral plaques | |
| Ankle-brachial index <0.9 | Coronary artery calcium score >100 | |
| Lp(a) elevation >180 mg/dL (430 nmol/L) | Ankle-brachial index <0.9 or >1.40 | |
| ApoB (see targets) | Carotid-femoral pulse wave velocity >10 m/s | |
| Triglycerides >2.3 mmol/L | CRP >2 mg/dL | |
| Albuminuria | | |

(Continues)
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|                         | ACC/AHA         | ESC/EAS | NICE                                      |
|-------------------------|-----------------|---------|-------------------------------------------|
| **Targets for primary prevention by risk category** |                 |         |                                           |
| **LDL-C** mmol/L        | Highest intensity statin | >10 (or very high risk) | <1.4 | Non-HDL-C, mmol/L and ApoB, mg/dL | No target, start moderate intensity statin eg atorvastatin 20 mg or equivalent increment for additional risk, adherence check if non-HDL-C change <40% |
| >4.9                    | Regardless of ASCVD risk | >5 to <10 | <1.8 | <2.2 and <65 |
| 1.8–4.9                 | High risk, >20   |         |                                           |
| Intermediate, 7.5–20     | Statin to reduce LDL-C, >50% | 1–5           | <2.6 | <3.4 and <100 |
| Borderline, 5–7.5        | Discuss moderate dose statin | <1           | <3.0 |                                           |
| **Targets for secondary prevention** | LDL-C <1.8 mmol/L | LDL <1.4 mmol/L | Non-HDL-C <2.2 mmol/L and ApoB <65 mg/dL | No target, high dose high intensity statin eg atorvastatin 80 mg and ezetimibe (some cases), adherence check if non-HDL-C change <40% |
| Very-high risk group LDL-C <1.4 mmol/L | 2nd ASCVD event LDL-C <1.0 mmol/L |                                           |
| **Definition of very high-risk patients** | LDL-C >4.9 mmol/L | ASCVD, either clinical or diagnosed on imaging |                                           |
| ASCVD risk >20%          | DM with target organ damage or >3 major risk factors or T1DM (>20 years duration) | SCORE >10% |                                           |
| Previous CVD             | Severe CKD (CKD4) |                                           |
|                         | SCORE >10%       |                                           |
|                         | FH with ASCVD or another risk factor |                                           |
| **Criteria for use of PCSK9-inhibitor** | FH or recurrent ACS (very high risk) | FH or recurrent ACS (very high risk) | Primary prevention: FH with LDL-C >5 mmol/L |                                           |
| LDL-C >2.5 mmol/L        | Failure to reach LDL-C goal (based on risk) on maximal statin and ezetimibe | Failure to reach LDL-C goal (based on risk) on maximal statin and ezetimibe | Secondary prevention: CVD with LDL-C >4 mmol/L, with monovascular disease, CVD with LDL-C >3.5 mmol/L with multivascular/recurrent disease |

ACC = American College of Cardiology; AHA = American Heart Association; ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; ACS = acute coronary syndrome; AHA = American Heart Association; ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; CKD = chronic kidney disease; CRP = C-reactive protein; DM = diabetes mellitus; EAS = European Atherosclerosis Society; ESC = European Society of Cardiology; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); non-HDL-C = non-high-density lipoprotein cholesterol; PCSK9-inhibitor = proprotein convertase subtilisin/kexin 9 inhibitor; RA = rheumatoid arthritis; SCORE = Systematic Coronary Risk Estimation chart for European populations; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
Risk Evaluation (SCORE) calculator (only able to predict fatal CVD events) and the multichannel atherosclerotic cardiovascular disease (ASCVD) calculator which better reflects the ethnic diversity of the USA were devised to replace the original Framingham study score. In the UK, general practitioner databases allowed the development of specific scores for England–Wales (QRISK) and Scotland (ASSIGN) adding CVD risk factors such as ethnicity, deprivation, mental health disease and autoimmune disease. QRISK2 is being updated to QRISK3. Validation studies have shown ASCVD 7.5% and QRISK 10% are approximately equivalent with differences driven by definitions of CVD endpoints. Neither correlates with SCORE effectively due to its restrictive definition. The intervention thresholds have been reduced from 20% to 7.5% (USA) or 10% (UK) based on consensus (USA) or health economic modelling (UK). This increased the number screened threefold to 30% of the UK population but doubled the potential amount of future CVD detected to 65%. 

Other risk factors

The ESC and US guidelines introduced risk factors beyond lipids. Chronic kidney disease stage 3 and diabetes are recognised by all guidelines. Others, such as autoimmunity, HIV or mental health disorders, are recognised by some (Table 1). 

Monogenic lipid disorders

Genetic diagnostics is being introduced into medicine. In hyperlipidaemia, as opposed to hypertension or type 2 diabetes, genetic disorders are common. Revisions in the prevalence of monogenic autosomal dominant familial hypercholesterolaemia (FH) suggest it occurs in one in 350 as opposed to one in 500 individuals. However, a substantial overlap exists in LDL-C between FH and non-FH populations. Updated diagnostic criteria (Dutch Lipid Clinic scores) combine elevated LDL-C with a family history of premature CVD (<60 years) to increase rates of detection of FH though a 50% chance of monogenic disease is present if total cholesterol (TC) >9 mmol/L or LDL-C >7 mmol/L. 

Next generation sequencing of four FH-associated genes is recommended for diagnosis of FH in all guidelines. It is already done in Wales and Scotland and will be available England in 2020. 

Biomarkers

Blood tests are inconvenient, over-ordered and disliked by patients. Meta-analysis of CVD risk with different lipid fractions shows that non-HDL-C is superior for CVD risk prediction to LDL-C or TC as it captures risk due to triglyceride-rich particles. Fasting blood samples are not required for non-HDL-C and its calculation is robust unlike the Friedewald equation for LDL-C. NICE recommends the use of non-HDL-C in lipid assessment as it is simple and its components (TC and HDL-C) are required for CVD risk calculation. A full lipid profile is still required by all guidelines if hyperlipidaemia is suspected. The US and European guidelines still prefer the traditional LDL-C measure as some studies show little effect of fasting on calculated LDL-C. 

Both ESC and US guidelines recognise lipoprotein (a) as an additional CVD risk factor and a predominantly genetically inherited CVD risk factor which is now better standardised. However, it may not be useful in the general population as opposed to populations with a family history of early CVD. Elevated C-reactive protein (>2 mg/dL) is also mentioned in US and ESC guidelines. Neither NICE nor the UK National Screening Committee have considered adding these to CVD risk profiles yet. No guideline has yet reviewed the potential role of high sensitivity troponin as a risk stratifier.

Imaging

Risk calculation systems only identify 70% of individuals who later have events. Big data approaches may raise this to 75% by incorporating additional factors such as variances in CVD risk factors. Numerous biomarker panels have been proposed but none have made it into guidelines. Both the European and US guidelines incorporate coronary artery calcium (CAC) scores from cardiovascular computer tomography (CT) >100 Agatston units in their risk algorithms as this imaging technology reclassifies 30% of intermediate-risk individuals correctly (high CAC and no CVD risk factors (RFs) = high risk; zero CAC and multiple CVD RFs = low risk). Carotid plaque and intima–media thickness generally reclassify 10% and confirm the mean CVD risk estimate. NICE has not reviewed the use of CAC or other imaging technologies in primary prevention though CAC does form part of the pathway for investigation of chronic CVD.

Therapeutics

Statins and ezetimibe

In recent years statins (except pitavastatin) have gone off-patent, substantially reducing their cost and improving the health economic efficiency. All guidelines now recommend the maximum tolerated dose of statin for secondary prevention (ideally 80 mg atorvastatin or equivalent) and moderate doses (eg 20 mg atorvastatin) in primary prevention. Type 2 diabetes is viewed as a secondary prevention risk equivalent (US and ESC guidelines) but, following large epidemiological studies, as intermediate risk by NICE with a specific risk calculator. The use of ezetimibe after statin therapy is included following results in acute coronary syndromes (ACS) in established CVD if not reaching target (USA and Europe) or if patients have FH or are statin-intolerant (all guidelines). Statin intolerance is defined as having tried three different drugs by all guidelines. The position of NICE on ezetimibe added to statins outside FH or intolerance is unclear as the guidance has not been revised recently.

PCSK9 inhibitors

All guidelines agree on using ezetimibe prior to initiating a PCSK9-inhibitor. PCSK9-inhibitors lower LDL-C by 50–55% and CVD events in line with predictions (21% reduction in CVD events per 1 mmol/L LDL-C) in outcome studies of populations with recent CVD events, additional CVD risk factors (eg age, smoking or diabetes) and LDL-C >2.5 mmol/L. Although little ezetimibe use, PCSK9-inhibitors are expensive and show poor cost-effectiveness making them difficult to incorporate into guidelines. The ACC/AHA and ESC introduced the concept of ultrahigh-risk groups based on the secondary prevention populations recruited to trials to solve this. Patients with FH or recurrent ACS, LDL-C >2.5 mmol/L and additional risk factors qualify for treatment. The ESC has gone further by extending the concept to ultrahigh-risk primary prevention. NICE is conservative in preserving the concept.
of one category of established CVD and suggesting prescription in FH with LDL-C >5 mmol/L, or patients with CVD and LDL-C >4 mmol/L for monovascular or >3.5 mmol/L in multivascular bed or recurrent disease in patients despite maximally tolerated statin and ezetimibe. Subgroup data from the PCSK9-inhibitor trials has confirmed the higher CVD risk and benefits of treating multivascular bed disease. Chronic kidney disease (CKD) stage 3 is mentioned as a CVD risk factor for PCSK9 initiation in US and European guidelines but no trials of PCSK9-inhibitors have been performed in this population. However, no guidelines have incorporated the benefits of cheaper hypoglycaemic drugs such sodium-glucose transport protein 2 inhibitors on CVD death and events or glucagon-like peptide 1 agonists on CVD events in patients with diabetes yet.

Omega-3 fatty acids

All guidelines recognise the importance of diets containing omega-3 fatty acids based on older trials as well as the Prevención con Dieta Mediterránea (PREDIMED) study. All concur with the recent meta-analysis and the European Medicines Agency’s review of low dose omega-3 studies in not recommending low doses (1 g) of these drugs for primary or secondary prevention. Only the recent ESC guidelines incorporate the data from the high dose eicosapentaenoic acid trial (REDUCE-IT) which showed a lipid-independent 25% benefit on CVD events in patients with CVD, mild-moderate hypertriglyceridaemia (1.5–4.5 mmol/L) and well controlled LDL-C.

Monitoring lipids

The US (2016) and NICE guidelines removed the need to monitor lipid levels (apart from for adherence) as clinical trials were based on fixed dose approaches. The new US (2019) and European guidelines reintroduce LDL-C targets. In the US and European guidelines <1.8 mmol/L (70 mg/dL) remains the desired target for established CVD but they also recommend lower LDL-C (1.4 mmol/L, 55 mg/dL) in ultra-high-risk situations. NICE has not made a specific distinction within established CVD though the technology appraisals for PCSK9-inhibitors do mention their prescription in progressing CVD. In primary prevention the US and European guidelines suggest intervention at LDL-C >3 mmol/L (low risk; 120 mg/dL) and >2.5 mmol/L (moderate risk; 100 mg/dL) with the aim of achieving a target of <1.8–2 mmol/L (70 mg/dL). NICE recommends intervention in FH or in patients with CVD risk >10%/decade. NICE reduced monitoring to allow further new cases to be identified and recommends no target after initiation of a fixed dose of statin. Studies suggest this is adequate in 85% of UK individuals. Regulatory agencies have reviewed the need for liver function test (LFTs) and creatine kinase (CK) measurement. Baseline and post-dose change LFTs are preserved in guidelines but CK measurement is no longer necessary unless there is likely prior muscle pain, disease or post-statin myopathy.

Future directions

In CVD guideline terms, Brexit occurred many years ago; some would say the UK never joined the EU. The UK has never followed US or European practice. The key distinction of late has been the strict use of evidence appraisal and health economic modelling by NICE. This constraint has not operated in Europe until recently or appeared in the USA until the arrival of PCSK9-inhibitors. The guideline cycles are also out of step, with NICE being last in the queue. Substantial concordance exists between the guidelines. Treating all patients with established CVD using high-dose statin and ezetimibe to achieve LDL-C <1.4 mmol/L (55 mg/dL) is likely to be achieved in 50% on combination therapy. The intervention is cheap and monitoring (beyond adherence) may be not be necessary. PCSK9 therapy will be required for a small number of patients with FH or CVD with high initial LDL-C and problems tolerating medications. The guidelines for PCSK9-inhibitors will not change in the UK unless their price changes. It is possible to speculate by analogy with antithrombotics that health economic studies might favour short-term use of PCSK9-inhibitors for 1–2 years until baseline recurrent event risk after ACS is reduced.

Other new oral LDL-C lowering drugs in development such as bempedoic acid may be more cost effective in primary prevention and/or statin intolerance. The place of omega-3 fatty acids remains controversial. Fibrates remain a second line option for elevated triglycerides or statin intolerance and a combination fibrate-statin therapy in diabetes with complex dyslipidaemia is underway.

Conflicts of interest

Professor Wierzbicki chaired the NICE guidelines on lipids (2014) and hypertension (2019) and was a clinical topic expert for technology appraisals of ezetimibe (2007) and PCSK9-inhibitors (2017). The views in this article are his own and do not represent the views of NICE.

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