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LIPID LOWERING THERAPY (1): CARDIOVASCULAR DISEASE PREVENTION

- **Cardiovascular disease (CVD) is a major cause of morbidity and mortality**
- **Dyslipidaemia is one of the main causal and modifiable risk factors for CVD**
- **Familial hypercholesterolaemia is frequently underdiagnosed and undertreated**
- **Lifestyle interventions are the cornerstone of management for all patients in the prevention and management of CVD**

INTRODUCTION

Cardiovascular disease (CVD), of which atherosclerotic CVD (ASCVD) is the main component, is a major cause of morbidity and mortality worldwide.[1,2] Even though the incidence of CVD has declined in many European countries in recent years,[1] CVD remains the most common cause of death in Europe.[3] In Ireland, CVD is estimated to result in approximately 9,000 deaths annually.[4] It is estimated that 80% of premature myocardial infarctions (MIs) and strokes are preventable.[2] The most important way to prevent ASCVD is the promotion of a healthy lifestyle (e.g. a Mediterranean diet, regular exercise and avoidance of smoking).[1] ASCVD risk factors are often poorly treated, even in patients considered to be at high risk of CVD.[1] Dyslipidaemia (lipid abnormalities) is one of the main causal and modifiable risk factors for ASCVD.[1] Other modifiable risk factors for CVD include high blood pressure (BP), cigarette smoking, obesity and diabetes mellitus (DM).[1] **Substantial evidence exists that the development or progression of CVD can be prevented by lowering lipid levels, in particular LDL cholesterol (LDL-C)** (often referred to as "bad cholesterol").[5-17] However, evidence suggests that the lowering of lipid levels at a population level is suboptimal, including in Ireland.[18] The management of dyslipidaemia is an important aspect of CVD prevention and management guidelines.[1,19-21]

This first bulletin on lipid lowering therapy (LLT) reviews the current guidance on lipid modification in the management of CVD in clinical practice, while a second bulletin describes the various available LLT pharmacological agents.

LIPIDS AND LIPOPROTEINS

The two most clinically relevant lipids are cholesterol and triglycerides (TG), which originate from hepatic synthesis and dietary sources; they are transported within lipoprotein particles along with phospholipids and apolipoproteins (Apo).[20,22,23] Cholesterol rich lipoproteins include low-density (LDL), high-density (HDL) and lipoprotein(a) (Lp(a)). Triglyceride rich lipoproteins include chylomicrons, very low-density (VLDL) and intermediate-density (IDL) lipoproteins.[20]

Importance of the various lipid components: Lowering lipid levels has been shown to lower the risk of vascular events in people with and without CVD.[5-17,24]

- LDL and other apolipoprotein B (ApoB)-containing lipoproteins (e.g. VLDL and IDL) play a central role in the pathogenesis of ASCVD.[5,8,24,25] **A recent updated review of the evidence confirmed that the key initiating event in the formation of an atherosclerotic plaque is the retention of ApoB-containing lipoproteins in the arterial wall (under most conditions >90% of circulating ApoB-containing lipoproteins are LDL particles), which leads to lipid deposition and the initiation of an atheroma.[25]** The size of the atheromatous plaque and subsequent development of ASCVD is dependent on the total concentration of circulating LDL (and other ApoB-containing lipoproteins) and duration of exposure.[26] LDL-C is a measure of the cholesterol mass carried by LDL particles, which provides an estimate of the LDL concentration.[20] **Each 1 mmol/L reduction in LDL-C has been shown to reduce major CV events by 20% to 25%.[5]**
- Non-HDL cholesterol (non-HDL-C) is a measure of the total cholesterol (TC) carried by all ApoB-containing lipoproteins.[20] The relationship between non-HDL-C and CV risk is at least as strong as the relationship with LDL-C.[1,20,27]
- Lp(a) is a form of LDL; raised levels are a genetically determined risk factor for ASCVD, stroke and aortic stenosis.[28]
- Increased plasma TG levels are associated with an increased risk of ASCVD.[20] Hypertriglyceridaemia may be described as mild to moderate (i.e. TG levels from 2 to 9.9 mmol/L) where the clinical consequence is excess ASCVD risk, or severe HTG (i.e. TG >10 mmol/L), which is associated with pancreatitis.[23]

DYSLIPIDAEMIAS

Dyslipidaemia is a general term used to describe a broad spectrum of lipid abnormalities including high levels of LDL-C, or TGs or low levels of HDL-C.[3,22,23,29] Dyslipidaemia includes primary (such as the monogenic disorder heterozygous familial hypercholesterolaemia [FH]) and secondary dyslipidaemias.[3,29]

Familial hypercholesterolaemia is an important cause of premature mortality;[30,31] the global prevalence of premature coronary artery disease (CAD) in individuals with FH is approximately 20 times higher than in the general population.[32] FH includes heterozygous FH and homozygous FH.[20] Heterozygous FH is the most common autosomal dominant genetic condition, which affects approximately 1 in 310 people globally and causes markedly elevated LDL-C from birth;[30,32]

homozygous FH is rare.[33] **It is estimated that <10% of patients with FH are diagnosed or treated,[1] and it is often overlooked in patients who have other risk factors for CVD.[31]** If left untreated, 50% of men with heterozygous FH may develop CAD before the age of 50 years and 30% of women before the age of 60 years.[34] **FH is an autosomal dominant condition, therefore if a person has FH, there is a 50% chance that their children will inherit the condition.[35]** It is recommended that FH is considered in certain patient populations[1] (see table 1). A diagnosis of FH is usually based on clinical presentation and family history of young ASCVD, with the Dutch Lipid Clinic Network Score (DLCN) the most commonly used criteria.[20,21,31]

Table 1: Populations in which to consider familial hypercholesterolaemia[20,31]

Consider FH in the following:
• People diagnosed with premature CHD (men aged <55 years; women aged <60 years)
• People with relatives with premature fatal or non-fatal CVD
• People with or whose relatives have clinical signs of FH (e.g. tendon xanthomas, corneal arcus and xanthelasma)*
• People with severely elevated LDL-C (in adults >5 mmol/L and children >4mmol/L)
• People who are first degree relatives of FH patients

CHD-coronary heart disease; CVD-cardiovascular disease; FH- familial hypercholesterolaemia; LDL-C-low-density lipoprotein cholesterol
*note that an absence of these signs does not exclude familial hypercholesterolaemia

Secondary causes of dyslipidaemia include unhealthy lifestyle, hypothyroidism, excess alcohol, liver disease, nephrotic syndrome, type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD).[3,19,29,36] T2DM is a major risk factor for CVD and is characterised by a range of lipoprotein abnormalities including raised TGs and ApoB-containing lipoproteins and decreased HDL.[20] CKD is also associated with an increased risk of CVD.[20] Table 2 outlines some medicines that may cause dyslipidaemia (list not exhaustive).

Table 2: Medicines that may cause dyslipidaemia[21,36]

Medicines that may cause dyslipidaemia include:
• Corticosteroids
• Androgenic steroids
• Progestogens
• Oestrogens
• Thiazide diuretics
• Beta blockers
• Retinoic acid derivatives (e.g. used in the management of acne)
• Protease inhibitors
• Antipsychotics

ASSESSMENT OF DYSLIPIDAEMIA

Lipid assessment is recommended in certain populations (see table 3).

Table 3: Populations in whom to consider lipid assessment[21]

• Patients with proven ASCVD, CKD, DM
• Family history of premature CVD (≤55 years male, ≤60 years female [first degree relative])
• Family history of significant dyslipidaemias
• Children and family of those with known FH
• Known ASCVD risk factors e.g. smoking, hypertension, obesity
• History of pancreatitis (due to hypertriglyceridaemia)
• Men ≥40 years, women ≥50 years or postmenopausal women

ASCVD-atherosclerotic cardiovascular disease; CKD-chronic kidney disease; CVD-cardiovascular disease; DM-diabetes mellitus; FH-familial hypercholesterolaemia

A fasting sample is not required for most people when measuring a patient's lipid profile,[1,19] however a fasting lipid profile is required for patients with a raised TG level (>4.5 mmol/L).[23] A standard lipid profile measures the concentration of TC, HDL and TG, from which the LDL-C can be calculated using a formula.[20] An alternative to this formula is to measure the non-HDL-C (calculated as TC minus HDL-C).[20] Non-HDL-C is recommended for risk assessment especially in those with high TGs, DM, obesity or very low LDL-C.[1,20] A recent European consensus statement (2022) recommends that Lp(a) should be measured once (in specialist settings) in all individuals especially in patients with premature ASCVD (men ≤55 years, women ≤60 years), family history of premature ASCVD and/or elevated Lp(a), FH, or recurrent ASCVD despite optimal LLT.[28]

Other investigations such as renal, hepatic and thyroid function, $HbA1_C$, blood pressure (BP) and body mass index should also be considered as baseline investigations to identify and treat co-morbidities and secondary causes of dyslipidaemia.[19] Genetic testing may also be required in specialist settings in those with suspected FH.[20,23] The Coronary Artery Calcium (CAC) score may also be used to improve risk classification around treatment decision thresholds.[1,20]

MANAGEMENT OF DYSLIPIDAEMIA

The management of dyslipidaemia should include an assessment (see the section to follow) of the patient's risk of CVD, as the lipid lowering intervention goals may differ depending on the individual risk.[1] In addition, **patients with a history of CVD, FH, DM and CKD should be identified, as these patients have a higher risk of CVD than healthy people and may require lower LLT treatment goals.[1]** The patient should be involved in the decision making process and other modifiable CVD risk factors such as high BP, cigarette smoking and obesity should be considered.[1]

Secondary causes of dyslipidaemias should be identified and treated where possible, before starting pharmacological interventions, and similarly for new or acute elevations of lipid parameters, as **treatment of the secondary cause (e.g. alcohol excess) may resolve the dyslipidaemia.[36]** If a medicine is suspected as the cause of the lipid abnormality, the benefits of the medicine versus the risks should be considered before discontinuing the medicine.[36] Referral for specialist advice is recommended for those with possible or definite FH (e.g. DLCN score >5) for assessment and potential genetic testing.[31] Table 4 summarises an approach to the management of a patient with dyslipidaemia.

Table 4: Approach to an individual with possible dyslipidaemia

Initial evaluation:
• Clinical features
○ Signs and symptoms of CVD, DM, CKD
○ Signs of FH (e.g. tendon xanthomata, corneal arcus, xanthelasma)
○ Identify patients with possible FH (e.g. using the Dutch Lipid Clinic Network Score)
• Laboratory assessment
○ Lipid profile
○ Other investigations including renal, hepatic and thyroid function, $HbA1_C$, blood pressure, body mass index
○ Consider genetic testing if FH is suspected
Identify and manage secondary causes of dyslipidaemia
Undertake CVD risk assessment and identify treatment goals
Management:
• Lifestyle interventions for all (including diet and exercise)
• Modify ASCVD risk factors
• Commence lipid lowering therapy when indicated by the treatment goals
Monitor effects of treatment:
• Assess adherence
• Modify therapy as required

ASCVD-atherosclerotic cardiovascular disease; CKD-chronic kidney disease; CVD-cardiovascular disease; DM-diabetes mellitus; FH-familial hypercholesterolaemia

CARDIOVASCULAR DISEASE RISK ASSESSMENT

CVD risk can be defined as the likelihood of a person developing an atherosclerotic CV event over a defined period of time.[20] Risk factor screening for CVD

may be considered in men aged >40 years and in women aged >50 years (or postmenopausal) with no known ASCVD risk factors; it should be repeated at intervals (e.g. every 5 years).[1] **In general, the higher the absolute CVD risk, the higher the absolute benefit of risk factor treatment.[1] Age is a major driver of CVD risk;** men <40 years and women <50 years of age in general have a low 10-year CVD risk (those with unfavourable modifiable risk factors may have increased longer term CVD risk), while men aged >65 years and women aged >75 years have a high CVD risk.[1]

Risk calculators for healthy people: CVD risk scoring plays a pivotal role in clinical practice by quantifying an individual's susceptibility to heart disease and guiding personalised preventive strategies. It is however important to note that certain conditions have inherent high risk for CVD such as FH, DM and CKD, and these high risk conditions should be excluded from conventional scoring models as they already require intensive intervention.[1,19,20,37] For example, young patients with FH have a significant lifetime risk of CVD due to cumulative exposure to high levels of LDL-C,[38,39] and traditional 10-year risk calculators will significantly underestimate their risk.[1,20] There are several CV risk calculators available to predict the approximate likelihood (expressed as a percentage) of a CV event occurring over a given period of time.[1,20]

In Europe, the updated Systematic Coronary Risk Estimation (SCORE2), primarily focuses on CV mortality risk by estimating the 10-year risk of fatal and non-fatal CVD events in apparently healthy people aged 40 to 69 years.[40] It covers risk factors for CVD including age, sex, lipid levels, BP and smoking,[40] and is stratified into four distinct European risk regions according to country-specific mortality (Ireland is categorised as a moderate risk country). The SCORE2-OP (older persons) algorithm estimates 5-year and 10-year risks of fatal and non-fatal CVD events for healthy people aged ≥70 years.[40] The SCORE2 charts, are freely available at ***www.heartscore.org*** or to download as apps.

Other CVD risk calculators that are also used in Ireland[41] include the QRISK®3-2018 available at QRISK3, which estimates an individual's risk of developing a myocardial infarct or stroke over 10 years in those aged 25 to 84 years.[42]

In general, risk factor treatment recommendations and goals for healthy people are based on the categories of CVD risk, estimated by a risk calculator. While CVD risk assessment tools provide an approximate value for CVD risk, clinical judgement is always important for interpretation of the CVD risk scores.[19]

Table 5 summarises the CVD risk categories based on SCORE2 and SCORE2-OP.[1]

Table 5: Cardiovascular disease risk categories based on SCORE2 and SCORE2-OP in apparently healthy people according to age[1]

CVD risk factor category: Recommendation	SCORE2		SCORE2-OP
	<50 years	50 to 69 years	≥70 years
Low-to-moderate CVD risk: Risk factor treatment generally not recommended	<2.5%	<5%	<7.5%
High CVD risk: Risk factor treatment should be considered	2.5 to <7.5%	5 to <10%	7.5 to <15%
Very high CVD risk: Risk factor treatment generally recommended	≥7.5%	≥10%	≥15%

These risk calculators do not apply to individuals with high-risk conditions such as ASCVD, FH, DM and CKD; Table 6 summarises the 2021 European Society of Cardiology (ESC) CVD prevention guidelines categorisation of CVD risk for these conditions.[1]

Table 6: Patient categories and associated cardiovascular disease risk[1]

Patient category	Risk category
Patients with chronic kidney disease	
• Moderate CKD ○ eGFR 30-44 mL/min/1.73m² and ACR <30 mg/g OR ○ eGFR 45-59 mL/min/1.73m² and ACR 30-300 mg/g OR ○ eGFR ≥60 mL/min/1.73m² and ACR >300 mg/g	High CVD risk
• Severe CKD ○ eGFR <30 mL/min/1.73m² OR ○ eGFR 30-44 mL/min/1.73m² and ACR >30 mg/g	Very high CVD risk
Familial hypercholesterolaemia	High CVD risk
Patients with type 2 diabetes	
• Patients with well controlled short-standing DM (e.g. <10 years), no evidence of TOD and no additional ASCVD risk factors	Moderate CVD risk
• Patients with DM without ASCVD and/or severe TOD, and not fulfilling the moderate risk criteria	High CVD risk
• Patients with DM with established ASCVD and/or severe TOD ○ eGFR <45 mL/min/1.73m² irrespective of albuminuria ○ eGFR 45-59 mL/min/1.73m² and microalbuminuria (ACR 30-300 mg/g) ○ Proteinuria (ACR >300 mg/g) ○ Presence of microvascular disease in at least 3 different sites (e.g. microalbuminuria plus retinopathy plus neuropathy)	Very high CVD risk
Patients with established atherosclerotic cardiovascular disease	Very high CVD risk

ASCVD-atherosclerotic cardiovascular disease; ACR-albumin-to-creatinine ratio; CKD-chronic kidney disease; DM-diabetes mellitus; TOD-target organ damage (e.g. nephropathy, neuropathy, retinopathy)

TREATMENT TARGETS AND GOALS

The individual should be made aware of his/her estimated 10-year CVD risk and encouraged to work with the relevant healthcare professional to manage/reduce this risk on a long-term basis.[1,20] **The absolute benefit of lowering LDL-C depends on the absolute risk of ASCVD and the absolute reduction in LDL-C**, therefore even a small reduction in LDL-C may result in a significant absolute risk reduction in a high or very high risk patient.[1] International guidelines base the intensity of their lipid lowering recommendations on the degree of CVD risk,[1,19,20,28,37,38] however they use different risk calculators and may have different thresholds. The ESC guidelines on dyslipidaemia (2019) and CVD prevention (2021) recommend that LDL-C is reduced to as low a level as possible, especially in patients at very high risk, following a stepwise approach with prevention goals for the individual patient – see table 7.[1,20]

Table 7: ESC recommendations for treatment goals for low-density lipoprotein cholesterol[1,20]

Cardiovascular disease risk category	Recommended treatment goal
Individuals at very high risk	LDL-C reduction of ≥50% from baseline AND LDL-C goal of <1.4 mmol/L (non-HDL-C goal <2.2 mmol/L)*
Individuals at high risk	LDL-C reduction of ≥50% from baseline AND LDL-C goal of <1.8 mmol/L (non-HDL-C goal <2.6 mmol/L)*
Individuals at moderate risk	LDL-C goal of <2.6 mmol/L (non-HDL-C goal <3.4 mmol/L)*

HDL-C-high-density lipoprotein cholesterol; LDL-C-low-density lipoprotein cholesterol
*non-HDL-C is a good marker of triglyceride rich lipoproteins and is a secondary objective of therapy

ESC and North American guidelines recommend treatment of an individual with an LDL-C level >5

mmol/L regardless of the risk score.[20,28,37] The ESC guidelines recommend that a treatment goal of LDL-C <3 mmol/L is considered for those assessed with a low risk of CVD.[1,20]

Hypertriglyceridaemia: No specific goals for TG levels have been determined, however there is an increased risk of CVD when fasting TGs are >1.7 mmol/L.[1,20]

Patients with newly diagnosed hypertriglyceridaemia frequently have contributing secondary causes (e.g. excess alcohol, poor glycaemic control, renal disease, drug-induced),[19,23] **which when addressed may result in lowering the TG level.**[23] Referral for specialist advice is recommended for patients with a fasting TG between 10 and 20 mmol/L and urgent specialist review is recommended if a patient has a TG concentration of >20 mmol/L.[19]

LIPID LOWERING INTERVENTIONS

Lipid lowering interventions include both pharmacological LLT (this will be covered in detail in the next bulletin) and lifestyle interventions.

Lifestyle interventions

Lifestyle interventions are the cornerstone of management for every patient and should be recommended for all, irrespective of their level of CVD risk.[1,19,20,43] Interventions that impact on LDL-C levels including diet, body weight, physical exercise, alcohol consumption and smoking status, should be discussed with the patient at every visit.[20]

Saturated fatty acids are the dietary factors with the greatest impact on LDL-C levels, however dietary trans fatty acids have a similar effect on LDL-C.[20] Refined carbohydrate-rich foods are associated with increased TG levels.[20] **Consistent evidence suggests that diets with a higher consumption of fruit, non-starchy vegetables, nuts, legumes, fish, olive oils, yoghurt and wholegrains, along with a lower intake of red and processed meats, refined carbohydrate-rich foods and salt are associated with a lower incidence of CVD;**[20] such diets should be recommended and adjusted according to the individual.[19,37] Diets including the Dietary Approaches to Stop Hypertension (DASH) and the Mediterranean diet have proved to be effective in reducing CV risk factors.[20]

Body weight reduction and physical exercise (e.g. moderate intensity exercise of ≥150 min/week) also reduce lipid levels, and are beneficial for other CVD risk factors (e.g. hypertension and diabetes).[3,19,20] Alcohol intake has a major impact on TG levels (moderate alcohol consumption is acceptable if TG levels are not increased) and smoking cessation has benefits on LDL-C.[19,20]

PRACTICAL ASPECTS OF MANAGEMENT

The decision to initiate pharmacological LLT is dependent on the individual, and should consider lifetime CVD risk, the benefits of treatment, co-morbidities, frailty and other modifiable risk factors;[1] individuals can move to a lower risk category by modifying other risk factors such as stopping smoking.[1] **Interventions such as lifestyle interventions are recommended for all individuals irrespective of the level of CVD risk.**[1,19,20] The need for pharmacological LLT depends on the estimated level of CVD risk for those with no overt CVD (i.e. primary prevention) and whether the person has established ASCVD, FH, CKD or DM.[43]

Primary prevention: The benefit of LLT in primary prevention depends on the initial level of CVD risk: the higher the risk, the greater the benefit.[1] Individuals assessed as low risk should be offered advice to maintain their low risk status.[1] As outlined above, ESC and North American guidelines also recommend treatment of an individual with an LDL-C level >5 mmol/L regardless of the risk score.[20,28,37] In addition to lifestyle interventions, treatment with statins is recommended according to the level of risk in healthy people aged ≤70 years,[1,13,19,20] and in those patients aged >70 years, who are considered at high or very high risk.[1] The decision on whether to treat an elevated LDL-C in an older individual should be individualised based on both chronological and biologic age, and the level of CVD risk especially in primary prevention (see next bulletin).[44]

Established ASCVD: Patients with established ASCVD are assessed as very high risk therefore, in addition to lifestyle interventions, LLT (high-intensity statins as first choice) should be offered to all patients with established CVD to enable patients to achieve their therapeutic goal – see table 7.[20] For patients with ASCVD who experience a second vascular event within 2 years, while taking a maximally tolerated statin therapy, a lower LDL-C goal (<1.0 mmol/L) may be considered.[1,20] If LDL goals are not achieved with a maximum tolerated dose of a statin, combination with ezetimibe is recommended.[1]

Familial hypercholesterolaemia: LLT is essential for patients with FH, who by definition are at high risk of ASCVD.[31,43] In addition to lifestyle interventions, LLT including high-intensity statins, ezetimibe, bempedoic acid (when available) and proprotein convertase subtilisin/kexin type 9 (PCSK9 inhibitors) (only accessible via High Tech Arrangement for patients who meet criteria – see next bulletin) may be required to enable the individual to reach their therapeutic goal.[1,20,31]

Diabetes mellitus: LLT may also be considered for those with DM depending on whether the patient has evidence of target organ damage and / or CVD risk factors – see table 6.[20] LLT (e.g. statins) in patients with DM is associated with improved CVD outcomes.[16,17]

Chronic kidney disease: Patients with CKD are at high or very high risk of ASCVD – see table 6.[2,20] LLT (particularly statins) reduces the risk of CVD in non-dialysis dependent patients with stage 3 to 5 CKD.[14,15] Doses may need adjustment depending on the estimated glomerular filtration rate.[20]

Useful Resources

- 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice available at www.escardio.org
- 2019 ESC/EAS Guidelines for the management of dyslipidaemia available at www.escardio.org
- ESC Systematic Coronary Risk Estimation (SCORE2) and SCORE2-OP risk charts available at www.escardio.org
- Irish Lipid Network: abbreviated lipid guidelines for clinical practice (Irish Journal of Medical Science published online February 2023)
- The HSE Medicines Management Programme – includes guidance on preferred statin and high tech arrangement for proproetin convertase subtilisin/kexin type 9 (PCSK9) inhibitors available at www.hse.ie/yourmedicines
- Irish College of General Practitioners (ICGP) Quick Reference Guide – CVD: prevention in clinical practice (published May 2021) available at www.icgp.ie (ICGP members only)
- NICE – Cardiovascular disease: risk assessment and reduction, including lipid modification – CG181 (Updated May 2023) available at www.nice.org.uk
- National Institute for Health and Care Excellence patient education leaflet on "Should I take a statin?"

List of references available on ePublication on www.nmic.ie.
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