National Medicines Information Centre

VOLUME 29
NUMBER 4
2023

St James's Hospital, Dublin 8
Tel 01 4730589 or 0818727727; twitter @NationalNmic; nmic@stjames.ie

LIPID LOWERING THERAPY (2): PHARMACOLOGICAL MANAGEMENT

- **A large body of evidence supports the use of lipid lowering therapy (LLT) such as statins for primary and secondary prevention of cardiovascular disease**
- **Patients should be informed about the benefits and risks of LLT**
- **An important cause of statin non-adherence is "statin intolerance", which is thought to be over-estimated**
- **Patients who do not meet their lipid lowering therapeutic targets need consideration for intensification of LLT**

INTRODUCTION

A healthy lifestyle is the backbone of lipid lowering therapy (LLT) but may not be adequate, especially in patients at high risk of cardiovascular disease (CVD).[1] Several classes of LLT are used to reduce lipid levels, of which statins are the most commonly prescribed.[2,3] Other LLT that act on different parts of the cholesterol pathway, are options for those who need additional lipid lowering or who cannot tolerate a statin or for whom a statin is contra-indicated.[2,3]

STATINS

Statins are the medicines of choice for treating hypercholesterolaemia, moderate hypertriglyceridaemia and for the primary and secondary prevention of CVD.[2-4] Different statins have varying effects on lipid profiles; statins result in reduced low-density lipoprotein cholesterol (LDL-C) levels (see table 1),[2] reduced triglycerides (TGs) by 10 to 20%[5] and increased high-density lipoprotein cholesterol (HDL-C) by 1 to 10%.[6]

Table 1: Reduction in low-density lipoprotein cholesterol with statins[2]

Therapy intensity	Medication daily dose (reduction in low-density lipoprotein cholesterol)
High-intensity	Atorvastatin: 20 mg (43%); 40 mg (49%); 80 mg (55%)
	Rosuvastatin: 10 mg (43%); 20 mg (48%); 40 mg (53%)
Medium-intensity	Atorvastatin: 10 mg (37%)
	Fluvastatin: 80 mg (33%)
	Rosuvastatin: 5 mg (38%)
	Simvastatin: 20 mg (32%); 40 mg (37%)
Low-intensity	Pravastatin: 10 mg (20%); 20 mg (24%); 40 mg (29%)
	Simvastatin: 10 mg (27%)

A large body of evidence supports the use of statins for primary and secondary prevention of CVD.[7-19] The clinical benefit of statins is largely a class effect, that is driven by the absolute reduction in LDL-C;[7] **use of statins reduces major CV events by 20% to 25% for each 1 mmol/L reduction in LDL-C.**[7] However, **the absolute risk reduction of CVD with statins is proportional to the baseline risk of CVD;**[7,15,20] for example, lowering LDL-C by 2 mmol/L with an effective statin regimen (e.g. atorvastatin 40 mg daily) for 5 years in 10,000 patients would typically prevent major CVD events from occurring in about 1,000 patients (i.e. 10% absolute benefit) as secondary prevention, and in 500 patients (i.e. 5% absolute benefit) as primary prevention.[21] Therefore, the decision to use statin therapy must consider the patient's baseline CVD risk (see previous bulletin).

Most guidelines recommend high-intensity statins (e.g. atorvastatin 40 to 80mg) for familial hypercholesterolaemia (FH) and secondary prevention of CVD.[5,22-26] Guidelines recommend statins (e.g. atorvastatin 20mg) for primary prevention of CVD according to the level of risk in people aged ≤75 years,[5,22-25,27,28] and to consider statins for those aged >75 years if at high risk of CVD.[5,22,23] Moderate-intensity statins may be considered in those patients at risk of adverse effects or potential drug-drug interactions (DDIs).[2,23] The statin dose should be titrated to achieve the LDL-C goal (see previous bulletin).[2] Note that the HSE Medicines Management Programme recommends atorvastatin as the preferred statin for the treatment of hypercholesterolaemia and prevention of CV events.[29]

Adverse effects: While statins generally have an acceptable safety profile, questions have been raised about possible unintended effects on glucose homeostasis, cognitive, renal, and hepatic function, as well as the risk for haemorrhagic stroke or cataract.[30] A European atherosclerosis consensus panel (2018) addressed these uncertainties, concluding that statin treatment is remarkably safe.[31] While there is a modest risk (about one new case per 1000 patients per year of exposure) of new onset DM with long-term statin treatment, this comes with the benefit of five new CVD events avoided.[31] Statin use is not associated with adverse effects on cognitive function or clinically significant deterioration of renal function and does not increase the risk of cataract or haemorrhagic stroke in individuals without prior stroke,[31] although some previous data suggest that statins may increase the risk of haemorrhagic stroke in those with prior haemorrhagic stroke.[32] Clinical liver injury with statin therapy is rare.[31]

Statins are usually well tolerated,[5,24] however statin-associated muscle symptoms (SAMS) are the predominant adverse effect seen in clinical practice.[5,24] SAMS is thought to be frequently overestimated and care should be given to attributing muscle symptoms to statin treatment without further investigation (see below).[33-37] The risk of myopathy does however increase with co-administration of certain medicines (e.g. atorvastatin and clarithromycin).[38] Severe myopathy presenting as rhabdomyolysis is rare and associated with raised creatine kinase (CK) levels ≥10 times upper limit of normal (ULN) and liver function tests (LFTs) ≥40 times ULN.[5] Raised LFTs (e.g. alanine aminotransferase [ALT]) may also occur with statins, more commonly with potent statins or high doses and this is frequently transient.[5] Statins are not recommended in pre-menopausal women who are considering pregnancy or not using adequate

contraception, and should be suspended prior to conception and until breastfeeding is completed.[5]

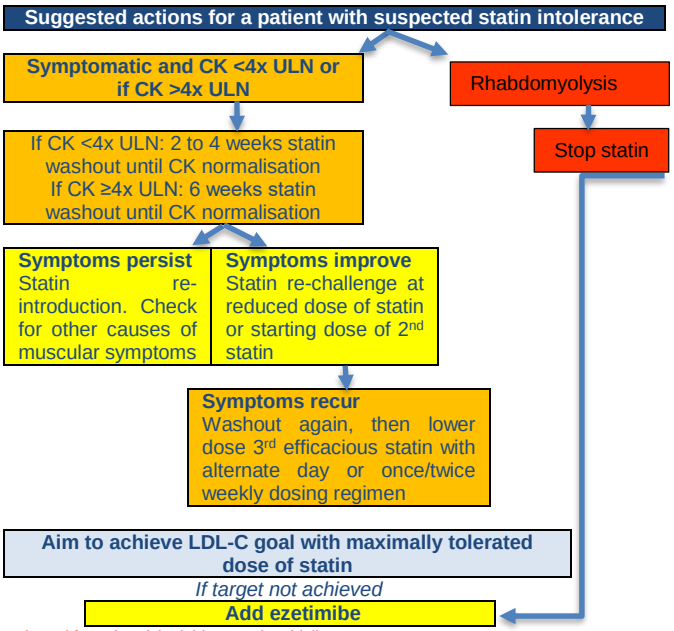
Drug-drug interactions (DDIs) are important to consider when prescribing statins. Most statins (apart from pravastatin and rosuvastatin) are metabolised by cytochrome P450 (CYP) isoenzymes,[5] of which CYP3A4 is the most common.[5] Rosuvastatin is a substrate for certain transporter proteins, and co-administration with medicines that are inhibitors of these transporter proteins (e.g. ciclosporin, gemfibrozil) may result in increased circulating rosuvastatin levels and peripheral tissue exposure and ultimately an increased risk of myopathy and rhabdomyolysis.[38] The temporary cessation of a statin may be required when an interacting medicine is prescribed (e.g. atorvastatin and systemic fusidic acid).[39] **The Summary of Product Characteristics (SmPC) for each medicine should be consulted for full prescribing information including DDIs.**

Adherence to statins overall is reported to be suboptimal. Non-adherence to statins is reported to be up to 60% after 2 years;[40,41] an Australian observational study (2019) of older adults (aged ≥65 years) reported that 50% were non-adherent and >40% discontinued statins within the first year.[42] A Scottish study (2023) found that statin use is sub-optimal for secondary CVD prevention (only 81% initiated statins following hospitalisation for CVD, of whom 24% later discontinued the statin), especially in women and older adults.[43] Some evidence suggests that high-intensity statins are associated with improved adherence compared with medium-intensity especially in those with previous CVD.[44] **Non-adherence to LLT (e.g. statins) with non-achievement of lipid targets is associated with increased risks of all-cause and CVD mortality,[40,41,45]** therefore, it is important to identify and encourage adherence in non-adherent patients.[46]

Statin intolerance: An important cause of statin non-adherence is "statin intolerance", which can be defined as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce statin adherence.[46] Statin intolerance, which usually presents as muscular symptoms, is thought to be over-estimated.[33-37] There is a concern that patients may be prematurely mislabelled as being "statin intolerant",[47] which may be made worse by negative media coverage.[33,48] Randomised controlled trials (RCTs) that compared statins to placebo suggest that muscular symptoms are also experienced by an almost equal number (>90%) of those on placebo,[34,49] the so-called nocebo effect.[46] A nocebo effect is caused by negative expectations about the effects of treatment, arising from information provided by clinicians and/or the media about possible adverse effects, which lead to higher reporting rates for adverse effects of the treatment than expected.[46] A recent meta-analysis (2022) suggests that the majority (>90%) of muscle pain reported in the studies was not due to the statin,[35] and that **the small risks of muscle symptoms associated with statins are much lower than their known CV benefits.[35,37,50]**

Due to the high discontinuation rate associated with statins, the management of a patient with suspected statin intolerance requires a detailed history and laboratory assessment (e.g. creatine kinase), to determine the appropriate course of action – see figure 1.[26,39,41,47,51] **Muscular aches, pain and weakness are more likely to be statin related if they are symmetrical and bilateral, involve proximal muscles, occur within weeks to months after statin initiation, after an increase in statin dose or initiation of an interacting medicine, resolve following cessation of the statin and recur following rechallenge; CK levels are not normally markedly increased.[26]** Specialist advice should be considered regarding treatment options in patients at high risk of CVD who are intolerant of **three different statins.[3,23]** Useful resources on statin intolerance include guidance from the Irish Lipid Network and the NHS England Statin Intolerance Pathway.

Figure 1: Suggested actions for a patient with suspected statin intolerance*[26]



*Adapted from the Irish Lipid Network guidelines
CK-creatine kinase; LDL-C-low-density lipoprotein cholesterol; ULN-upper limit of normal

EZETIMIBE

Ezetimibe is the most commonly used non-statin LLT and is considered second-line LLT for patients with FH and prevention of CV events.[5,24,52] Ezetimibe monotherapy reduces LDL-C by 18.5%, TG by 8% and increases HDL-C by 3%.[53] Co-administration of ezetimibe with statins results in further lowering effects on LDL-C,[5,54] and additional reductions in CV events (including non-fatal MI and stroke).[5,54-56] It is more beneficial in those at very high or high CV risk, rather than those with moderate or low CV risk.[56] Ezetimibe is used in combination with statins or as an alternative to statins when statins are contra-indicated or not tolerated in order to achieve the patient's therapeutic goals.[2,3,5,22,24,52,57] Patients using ezetimibe may experience increased LFTs or myalgia, usually associated with co-administration of statins.[52]

FIBRATES

Fibrates (e.g. fenofibrate and gemfibrozil) are estimated to reduce LDL-C levels by ≤20%, TG levels by 50% and increase HDL-C by ≤20%.[58] The evidence to support the use of fibrates to prevent CVD is more limited and weaker than that of statins;[59] some evidence suggests that fibrates reduce the risk of CV events (mainly non-fatal MI),[60,61] however there is no corresponding reduction in CV or all-cause mortality.[60,62-65] **Current UK guidelines do not recommend the routine use of fibrates for CVD prevention,[23,27] and in agreement with other sources advise that fibrates should only be initiated on specialist advice.[2,23,59]** Fibrates are more effective than statins in reducing TG concentration,[2] and have a role in hypertriglyceridaemia, principally to reduce the risk of pancreatitis.[5,59,66] Fibrates are associated with many potential DDIs; the SmPC should be consulted for full prescribing information. **Co-administration of a statin**

with gemfibrozil is associated with an increased risk of rhabdomyolysis and is contra-indicated.[2,67,68]

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 (PCSK9) INHIBITORS

Alirocumab and evolocumab are monoclonal antibodies that are administered subcutaneously every 2 to 4 weeks.[69] PCSK9 inhibitors reduce LDL-C levels by an average of 60%, TG levels by 26% and increase HDL-C by 9%.[5] Evidence suggests that PCSK9 inhibitors reduce the risk of CVD, MI and stroke.[54,70-72] The results of a recent systematic review suggested that for people taking maximally tolerated statin therapy, the addition of ezetimibe or a PCSK9 inhibitor may reduce non-fatal MI and stroke in those at very high or high CV risk but not in those with moderate or low CV risk.[55] PCSK9 inhibitors are indicated for hypercholesterolaemia and secondary CV prevention in patients on statins or other LLT not achieving targets;[73,74] evolocumab is also indicated for FH.[74] Guidelines recommend PCSK9 inhibitors for patients with a high or very high risk of CVD, who are already using statins and ezetimibe or are intolerant of statins.[75] Further data on long-term safety is required.[5,69] In Ireland PCSK9 inhibitors are available to prescribe under the High Tech Arrangement by designated physicians and a Managed Access Protocol is in place;[76] criteria for reimbursement include patients with established ASCVD with LDL-C levels persistently ≥3.5 mmol/L and patients with heterozygous FH with LDL-C levels persistently ≥4 mmol/L.[76]

OMEGA-3 FATTY ACIDS

Omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) have been reported to reduce TG levels by up to 45% in some studies.[5] There is little evidence to suggest that omega-3 fatty acids can prevent CV events or mortality;[77-80] they are not recommended in many guidelines for the primary or secondary prevention of CVD.[5,22,23,25,27] They may be beneficial in patients with severe hypertriglyceridaemia (>11 mmol/L) in order to reduce the risk of pancreatitis.[24] Icosapent ethyl (not available in Ireland), which is a derivative of eicosapentaenoic acid,[81] was reported in a study (n=8,000) to reduce CV events in statin treated patients with raised triglycerides and at high risk of CV events.[81]

Table 2 summarises the LLT marketed in Ireland.

Table 2: Lipid lowering therapy marketed in Ireland[5,29,38,39,67,68,73,82-85]

CLASS/ Name	Mode of action	Special precautions	Potential DDIs with medicines including*
STATINS Atorvastatin** Simvastatin Rosuvastatin Fluvastatin Pravastatin	Inhibit cholesterol synthesis by blocking HMG-CoA reductase	GI upset; myalgia, rhabdomyolysis, ↑ LFTs; ↑ risk of developing T2DM. Not to be used in pregnancy	Macrolides, amiodarone, protease inhibitors, gemfibrozil***, azole antifungals, ciclosporin, grapefruit juice, (many additional DDIs)
INTESTINAL INHIBITOR Ezetimibe	↓ absorption of cholesterol	GI upset; ↑ LFTs; myalgia. Not to be used during pregnancy	Fibrates, ciclosporin and warfarin
FIBRATES Fenofibrate Gemfibrozil***	↓VLDL synthesis and lipoprotein lipase	GI upset; ↑ LFTs; myopathy; pancreatitis; ↓dose in renal impairment.	Warfarin, statins (contra-indicated with gemfibrozil), ciclosporin, glitazones (many additional DDIs)
OMEGA-3 FATTY ACIDS Eicosapentaenoic acid and docosahexaenoic acid	Lowers triglycerides	GI upset; ↑ bleeding time; risk of ↑ LFTs	Anticoagulants
PCSK9 INHIBITORS Alirocumab Evolocumab *Administered S/C every 2 to 4 weeks*	↑ LDL receptor expression resulting in ↑ liver clearance of LDL	upper respiratory tract infections, arthralgia and injection site reactions	No pharmacokinetic drug interactions anticipated

DDI-drug-drug interactions; GI-gastrointestinal; LDL-low-density lipoprotein; LFTs-liver function tests; PCSK9-proprotein convertase subtilisin/kexin type 9; S/C-subcutaneously; T2DM-type 2 diabetes mellitus; VLDL-very low-density lipoprotein

**The Summary of Product Characteristics for each medicine should be consulted for full prescribing information; **preferred statin as per the HSE Medicines Management Programme; ***use in combination with a statin is contraindicated due to risk of serious myopathy, including rhabdomyolysis*

There is no consensus from guidelines on the use of bile acid sequestrants (e.g. colestyramine).[5,22-26] They are not associated with reduced CVD outcomes, have significant gastrointestinal adverse effects (e.g. flatulence, constipation and nausea) which limit their practical use, and have the potential for a significant amount of DDIs;[5,86] specialist advice is recommended.[2]

Other lipid lowering therapies

There are other LLT **not currently available in Ireland** that are used with specialist advice.

Bempedoic acid is an adenosine triphosphate citrate lyase (ACL) inhibitor (administered orally) which inhibits cholesterol synthesis in the liver resulting in upregulation of liver LDL receptors and increased clearance of LDL-C with, between 18% to 28% reduction in circulating LDL-C.[87-93] Recent studies (2023) report that bempedoic acid used for primary and secondary prevention in statin-intolerant patients has the potential to reduce major CV events.[94,95] Bempedoic acid is licensed as an adjunct to diet in adults with primary hypercholesterolaemia or mixed dyslipidaemia in combination with a statin (or statin with other LLT) in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or alone, or in combination with other LLT if a statin is not tolerated or is contra-indicated.[96,97] Common adverse effects associated with bempedoic acid include anaemia, gout, hyperuricaemia and pain in the extremity.[87,88,97,98] Bempedoic acid may increase plasma levels of some medicines including statins.[87,96,97] **Patients who are co-administered bempedoic acid with a statin should be monitored for statin-related adverse effects** (e.g. myopathy), as statin levels may increase.[87,96,97]

Inclisiran is a small interfering RNA molecule (administered subcutaneously every 6 months) that reduces production of PCSK9 resulting in a lower level of LDL-C (by approximately 50%).[99-104] There is no published evidence of the effects of inclisiran on CV outcomes, however a RCT evaluating CV outcomes is currently underway.[105] Inclisiran is licensed as an adjunct to diet in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in combination with a statin (or statin with other LLT) in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or alone or in combination with other LLT if a statin is not tolerated or is contra-indicated.[103,105] Inclisiran is not expected to have clinically significant DDIs.[99] Adverse effects include injection site reactions.[99,104]

PRACTICAL ISSUES

LLT should be considered after an informed discussion with the patient about the benefits of LLT for their individual CVD risk, the therapeutic goals (see previous bulletin) and the risks of therapy. Factors such as lifestyle

modifications (e.g. smoking cessation, alcohol consumption, diet and exercise), secondary causes of dyslipidaemia, co-morbidities, polypharmacy and DDIs should also be considered.[3,23]

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.[107,108] This population may have many co-morbidities and associated polypharmacy, and an increased risk of adverse events, particularly from DDIs.[107] Older people with significant renal impairment and/or the potential for DDIs should be commenced at a low dose of statin and gradually titrated upwards.[5] A patient with a limited life expectancy (<1 year) may not be a candidate for LLT; deprescribing a statin in someone with limited life expectancy is safe and associated with improved quality of life.[107] However, a healthy older individual should not be denied LLT on the basis of age alone.[107,108]

Some patients may have mildly abnormal LFTs due to non-alcoholic fatty liver disease and statin initiation does not result in worsening of liver disease in these patients.[20,26,109,110] Specialist advice is however recommended for statin initiation in patients with active hepatitis or chronic liver disease.[26] Prior to starting statins, risk factors for statin-related muscle toxicity and statin intolerance (table 3) should be considered, with avoidance of high-dose statins when appropriate.[47]

Table 3: Risk factors for statin-related muscle toxicity and statin intolerance[47]

Endogenous factors	Exogenous factors
Female gender Age >75 years History of muscle disorder or high creatine kinase, impaired renal or hepatic function Hypothyroidism Personal or family history of statin intolerance	Excessive alcohol intake High intensity exercise Drug interactions with statins Vitamin D deficiency

Choice of therapy: Statins are usually first-line LLT for reducing LDL-C; **guidelines recommend that a statin is prescribed up to the highest tolerated dose to reach the LDL-C goal for the designated risk.[5,22-27]** Some patients may require lower doses of statins (e.g. renal impairment, risk factors for adverse effects and potential DDIs).[23,27] If the patient's LDL-C goal is not achieved, adherence to statins should be assessed and lifestyle modifications optimised,[3] followed by intensification of statin therapy.[3,5,27] LDL-C goals may be achieved by many patients with a maximally tolerated statin, however a significant proportion of patients at high or very high risk require additional LLT such as ezetimibe and/or PCSK9 inhibitors (under the High Tech Arrangement – see previous section).[5,22,24,25,27,75,111] The use of ezetimibe as monotherapy may also be considered in those with statin intolerance.[5,23,27] Recently published UK guidelines also recommend bempedoic acid in patients intolerant of statins not achieving their therapeutic goal on ezetimibe.[27] There is no consensus on the use of bile acid sequestrants, which are recommended in some guidelines[5,22,23,25,26] but not in others.[23,27]

Statins are recommended for reducing CVD risk in high-risk individuals with hypertriglyceridaemia (TG levels >2.3 mmol/L), where TG cannot be lowered by lifestyle measures.[5,23,24] The European Society of Cardiology advises that fenofibrate may be considered for patients taking statins who are at their LDL-C goal, with TG levels >2.3 mmol/L.[5,22] Some guidelines recommend that icosapent ethyl (not available in Ireland) be considered in high-risk patients with increased TG levels despite statin treatment.[5,22,27]

Patient education: Patients should be informed of the benefits and risks of LLT, and to seek medical advice if muscle symptoms develop.[23] They should be advised that evidence suggests that adverse events associated with statins are mild and rare, and that the increased risk of these adverse events does not outweigh the reduction in major CVD events.[37,52] Patients should be informed that some medicines and foods (e.g. grapefruit juice) may interfere with statins (and other LLT) and that the patient information leaflet and/or HCP should be consulted when starting other medicines or foodstuffs.[23] They should be reminded to recommence a statin if it was temporarily stopped due to a concern about a potential DDI or due to intercurrent illness.[23]

Baseline assessment and monitoring: In addition to baseline investigations, ongoing monitoring of patients on LLT is required – see table 4. An annual medication review is recommended for patients who have achieved their therapeutic goal to discuss medication adherence, lifestyle modification and CVD risk factors.[3]

Table 4: Summary of recommendations for monitoring lipids and enzymes in patients, before and while on lipid lowering therapy[5]

Testing lipids	
• 2 lipid measurements at an interval of up to 12 weeks before starting LLT • 8 weeks after starting LLT and after adjusting LLT until therapeutic goal achieved • Annually once the therapeutic goal has been achieved unless concerns (e.g. adherence)	
Testing liver enzymes	
• Before starting LLT • 8 to 12 weeks after commencing LLT or after dose increase • Routine ALT not recommended with statin therapy (unless liver symptoms develop), however ALT measurement required with fibrate therapy	
What to do if patient develops raised liver enzymes on LLT	
If ALT <3x ULN • Continue therapy • Recheck liver enzymes in 4 to 6 weeks	If ALT increases to ≥3x ULN • Stop LLT or ↓dose and recheck liver enzymes in 4 to 6 weeks • Cautious reintroduction of LLT if liver enzymes return to normal • ALT remains ↑ consider other factors
Testing creatine kinase	
Pre-treatment • Before staring LLT • If baseline CK >4x ULN, do not start LLT; recheck	Monitoring • Routine monitoring not required • Check CK if myalgia occurs
What to do if patient develops raised creatine kinase on LLT Re-evaluate the indication for statin therapy	
If CK <4x ULN • Asymptomatic: continue LLT, patient to return if becomes symptomatic and check CK • Symptomatic: monitor symptoms and CK regularly • Symptoms persist: stop LLT and reassess symptoms and need for LLT after 6 weeks • Consider rechallenge with same or another statin • Consider low-dose statin, alternate day or once/twice weekly dosing regimen or combination therapy	If CK ≥4x ULN • CK >10x ULN: stop LLT, check renal function and monitor CK every 2 weeks • CK <10x ULN: asymptomatic, continue LLT and monitor CK 2 to 6 weeks • CK <10x ULN: symptomatic, stop LLT, monitor CK until normal, then consider reintroduction of statin at lower dose • Consider the possibility of ↑CK due to other reasons (e.g. exertion) • Consider myopathy if ↑CK persistent • Consider combination or alternative drug
Testing HbA1c or blood glucose	
• Consider monitoring in patients at high risk of developing diabetes and on high-dose statin	

LLT-lipid lowering therapy; ALT-alanine aminotransferase; ULN-upper limit of normal; CK-creatine kinase

List of references available on ePublication on www.nmic.ie.
Date of publication: August 2023

References - lipid lowering therapy: bulletin 2 (29/08/2023)

1. Tokgozoglu L, Orringer C, Ginsberg HN et al, The year in cardiovascular medicines 2021: dyslipidaemia, European Heart Journal 2022;43:807-817
2. BNF - Treatment summary: Dyslipidaemias (last update 23rd March 2018) accessed from medicinescomplete.com on the 24th April 2023
3. BNF – Treatment summary: Cardiovascular disease risk assessment and prevention, (last update 31st October 2022) accessed from medicinescomplete.com on the 24th April 2023
4. Chapter V - Drugs acting on the renal and cardiovascular systems: 25 Antihyperlipidemic drugs pages, Pharmacology: an essential textbook second edition (Mark A. Simmons), New York Thieme publishers 2020
5. Mach F, Baigent C, Catapano A et al, 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk, Developed by the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS), European Heart Journal 2020;41:111-188
6. Barter PJ, Brandrup-Wognsen G, Palmer MK, Nicholls SJ. Effect of statins on HDL-C: a complex process unrelated to changes in LDL-C: analysis of the VOYAGER Database. J Lipid Res 2010;51:1546-1553
7. Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380:581–90
8. Chou R, Cantor A, Dana T et al, Statin use for the primary prevention of cardiovascular disease in adults – updated evidence report and systematic review for the US preventive services task force, JAMA 2022;328(8):754-771
9. Hodkinson A, Tsimpida D, Kontopantelis E et al, Comparative effectiveness of statins on high-density lipoprotein cholesterol in people with diabetes and at risk of cardiovascular disease: systematic review and network meta-analysis, British Medical Journal 2022;376:e067731
10. Cholesterol Treatment Trialists Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a metaanalysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670-1681.
11. Cholesterol Treatment Trialists Collaboration, Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, Simes J, Collins R, Kirby A, Colhoun H, Braunwald E, La Rosa J, Pedersen TR, Tonkin A, Davis B, Sleight P, Franzosi MG, Baigent C, Keech A. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet 2015;385:1397-1405
12. Mills EJ, Rachlis B, Wu P, Devereaux PJ, Arora P, Perri D. Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. J Am Coll Cardiol 2008;52:1769-1781.
13. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-1278
14. Cholesterol Treatment Trialists Collaboration, Herrington WG, Emberson J, Mihaylova B, Blackwell L, Reith C, Solbu MD, Mark PB, Fellstrom B, Jardine AG, Wanner C, Holdaas H, Fulcher J, Haynes R, Landray MJ, Keech A, Simes J, Collins R, Baigent C. Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. Lancet Diabetes Endocrinol 2016;4:829-839
15. Naci H, Brugts JJ, Fleurence R, Tsoi B, Toor H, Ades AE. Comparative benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials. Eur J Prev Cardiol 2013;20:641-657
16. Cholesterol Treatment Trialists Collaboration, Herrington WG, Emberson J, Mihaylova B, Blackwell L, Reith C, Solbu MD, Mark PB, Fellstrom B, Jardine AG, Wanner C, Holdaas H, Fulcher J, Haynes R, Landray MJ, Keech A, Simes J, Collins R, Baigent C. Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. Lancet Diabetes Endocrinol 2016;4:829-839
17. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellstrom B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Gronhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R; SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney

disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011;377:2181-2192.
18. Cholesterol Treatment Trialists Collaboration, Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, Armitage J, Baigent C. Efficacy of cholesterol lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008;371:117-125
19. Giugliano RP, Cannon CP, Blazing MA, Nicolau JC, Corbalan R, Spinar J, Park JG, White JA, Bohula EA, Braunwald E; IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) Investigators. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). Circulation 2018;137:1571-1582
20. Byrne P, Demasi M, Jones M, et al. Evaluating the association between low-density lipoprotein cholesterol reduction and relative and absolute effects of statin treatment: a systematic review and meta-analysis. JAMA Intern Med 2022;182:474–81
21. Collins R, Reith C, Emberson J et al, Interpretation of the evidence for the efficacy and safety of statin therapy, Lancet 2016;388;2532-61
22. Visseren FLJ, Mach F, Smulders YM et al, 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice (**Version 2021**). Developed by the task force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies, European Heart Journal 2021;42:3227-3337
23. NICE – Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181) last updated 24th May 2023, accessed at www.nic.org.uk on the 5th June 2023
24. Grundy SM, Stone NJ, Bailey AL et al, Cholesterol Clinical practice guidelines – 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA /AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol, Circulation 2019;139:e1082-e1143
25. Pearson, G.J.; Thanassoulis, G.; Anderson, T.J.; Barry, A.R.; Couture, P.; Dayan, N.; Francis, G.A.; Genest, J.; Grégoire, J.; Grover, S.A.; et al. Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. Can. J. Cardiol. 2021, 37, 1129–1150
26. Maher V, Gallagher J, Agar R et al, Abbreviated lipid guidelines for clinical practice, Irish Journal of Medical Science 2023
27. NHS England. Summary of national guidance for lipid management, updated December 2022, accessed at https://www.england.nhs.uk/aac/publication/summary-of-national-guidance-for-lipid-management/ on the 7th April 2023
28. ICGP Quality & Safety in Practice Committee, Quick Reference Guide – Cardiovascular disease: prevention in general practice, available at www.icgp.ie (subscription required) accessed 6th April 2023
29. HSE Medicines Management Programme Preferred Drugs - Statin monotherapy for the treatment of hypercholesterolemia and prevention of cardiovascular events in adults, July 2020 accessed from https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/preferred-drugs/ on the 27th April 2023
30. Piepoli MF, Hoes AW, Agewall S, et al, Authors/Task Force Members, 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR).Eur Heart J 2016;37:2315–2381
31. Mach F, Ray KK, Wiklund O et al, Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract, Eur Heart J 2018;39(27):2526-2539
32. Goldstein LB, Amarenco P, Szarek M, Callahan A, 3rd, Hennerici M, Sillesen H, Zivin JA, Welch KM; SPARCL Investigators Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study. Neurology 2008;70:2364–2370
33. Saul H, Gursul D, Cassidy S et al, NIHR alerts – statins do not commonly cause muscle pain and stiffness, British Medical Journal 2021;375:n3060
34. Howard JP, Wood FA, Finegold JA, etal. Side effect patterns in a crossover trial of statin, placebo, and no treatment. J Am Coll Cardiol 2021;78:-22. doi: 10.1016/j.jacc.2021.07.022 pmid: 34531021
35. Cholesterol Treatment Trialists Collaboration, Effect of statin therapy on muscle symptoms: an individual participant data meta-analysis of large-scale, randomised, double-blind trials, Lancet 2022;400:832-45
36. Herrett E, Williamson E, Brack K et al, The effect of statins on muscle symptoms in primary care: the StatinWISE series of 200 N-of-1 RCTs, Health Technol Assess.2021 Mar; 25(16): 1–62
37. Cai T, Abei L, Longford O et al, Associations between statins and adverse events in primary prevention of cardiovascular disease: systematic review with pairwise,

network and dose response meta-analyses, British Medical Journal 2021;374:n1537
38. SmPC Crestor® (rosuvastatin) accessed from www.medicines.ie on the 2nd May 2023
39. SmPC Lipitor® (atorvastatin) accessed from www.medicines.ie on the 2nd May 2023
40. Banach M, Cannon CP, Paneni F et al, Individualised therapy in statin intolerance: the key to success, European Heart Journal 2023;44(7):544-546
41. Alonso R, Cuevas A, Cafferata A, Diagnosis and management of statin intolerance, Journal of Atherosclerosis and Thrombosis 2019;26:207-215
42. Ofori-Asenso R, Ilomaki J, Tacey M et al, Predictors of first-year nonadherence and discontinuation of statins among older adults: a retrospective cohort study, Br J Clin Pharmacol 2019;85:227-235
43. Thalmann I, Preiss D, Schlackow I et al, Population-wide cohort study of statin use for the secondary cardiovascular disease prevention in Scotland in 2009-2017, Heart 2023;109(5):388-3952
44. Rezende Macedo do Nascimento RC, Mueller T, Godman B et al, Real-world evaluation of the impact of statin intensity on adherence and persistence to therapy: A Scottish population-based study, Br J Clin Pharmacol 2020;86:2349-2361
45. Brown R, Lewsey J, Wild S et al, Associations of statin adherence and lipid targets with adverse outcomes in myocardial infarction survivors: a retrospective cohort study, BMJ Open 2021;11:e054893
46. Wood F, Howard J, Finegold J et al, N-of-1 Trial of a Statin, Placebo, or No Treatment to Assess Side Effects, New England Journal of Medicine, 2020;383:2182-4
47. NHS England – Statin Intolerance Pathway (Review date June 2021) accessed at www.heart.org.uk on the 4th July 2023
48. Matthews A, Herrett E, Gasparrini A, et al, Impact of statin related media coverage on use of statins: interrupted time series analysis with UK primary care data, British Medical Journal 2016;353:i3283
49. Herrett E, Williamson E, Brack K et al, Statin treatment and muscle symptoms: a series of randomised, placebo controlled trials, British Medical Journal 2021;371:n135
50. Insani WN, Whittlesea C, Chengsheng J et al, Statin-related adverse drug reactions in UK primary care consultations: a retrospective cohort stud to evaluate the risk of cardiovascular events and all-cause mortality, Br J Clin Pharmaco 2022;88:4902-4914
51. Bytyci I, Penson PE, Mikhailidis DP et al, Prevalence of statin intolerance: a meta-analysis, European Heart Journal 2022;43(34):3213-3223
52. SmPC Ezetrol® (ezetimibe) accessed from www.hpra.ie on the 24th April 2023
53. Pandor A, Ara RM, Tumur I, Wilkinson AJ, Paisley S, Duenas A, Durrington PN, Chilcott J. Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials. J Intern Med 2009;265:568-580
54. Cannon CP, Blazing MA, Giugliano RP, et al, IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387-97. doi:10.1056/NEJMoa1410489
55. Khan SU, Yedlapati SH, Lone AN, et al, PCSK9 inhibitors and ezetimibe with or without statin therapy for cardiovascular risk reduction: a systematic review and network meta-analysis, British Medical Journal 2022;377:e069116
56. Zhan S, Tang M, Liu F, Xia P, Shu M, Wu X. Ezetimibe for the prevention of cardiovascular disease and all-cause mortality events. Cochrane Database of Systematic Reviews 2018, Issue 11. Art. No.: CD012502. DOI: 10.1002/14651858.CD012502.pub2
57. NICE Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (TA385), accessed from www.nice.org.uk on the 24th April 2023
58. Chapman MJ, Redfern JS, McGovern ME, Giral P. Niacin and fibrates in atherogenic dyslipidemia: pharmacotherapy to reduce cardiovascular risk, Pharmacol Ther 2010;126:314-345
59. Floyd CN, Review: Time to review fibrate prescribing, Drug and Therapeutics bulletin 2019;57(10):154-157
60. Jakob T, Nordmann AJ, Schandelmaier S, Ferreira-González I, Briel M. Fibrates for primary prevention of cardiovascular disease events. Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD009753. DOI: 10.1002/14651858.CD009753.pub2
61. Wang D, Liu B, Tao W, Hao Z, Liu M. Fibrates for secondary prevention of cardiovascular disease and stroke. Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No.: CD009580. DOI: 10.1002/14651858.CD009580.pub2
62. Jun M, Foote C, Lv J, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. The Lancet 2010;375:1875–84
63. Keene D, Price C, Shun-Shin MJ, et al. Effect on cardiovascular risk of high density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomised controlled trials including 117,411 patients. BMJ 2014;349:g4379
64. Ip CK, Jin DM, Gao JJ, et al. Effects of add-on lipid-modifying therapy on top of background statin treatment on major cardiovascular events: a meta-analysis of randomized controlled trials. Int J Cardiol 2015;191:138–48
65. Pradhan AD, Glynn RJ, Fruchart JC et al, Triglyceride lowering with pemafibrate to reduce cardiovascular risk, New England Journal of Medicine 2022;387:1923-34
66. Virani SS, Editorial – the fibrates story – a tepid end to a PROMINENT drug, New England Journal of Medicine 2022;387:1991-1992

67. SmPC Lipantil® (fenofibrate) accessed from www.medicines.ie on the 4th May 2023
68. SmPC Lopid® (gemfibrozil) accessed from www.medicines.ie on the 4th May 2023
69. Anon, Two new lipid-regulating drugs, Drug and Therapeutics Bulletin, February 2016;54(2):18-21
70. Schmidt AF, Carter J-PL, Pearce LS, Wilkins JT, Overington JP, Hingorani AD, Casas J. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2020, Issue 10. Art. No.: CD011748. DOI: 10.1002/14651858.CD011748.pub3
71. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713-1722
72. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD, Zeiher AM; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097-2107
73. SmPC Praluent® (alirocumab) accessed from www.medicines.ie on the 5th May 2023
74. SmPC Repatha SureClick® (evolocumab) accessed from www.medicines.ie on the 5th May 2023
75. Hao Q, Aergeerts B, Guyatt G et al, PCSK9 inhibitors and ezetimibe for the reduction of clinica events: a clinical practice guidelines with risk-stratified recommendations, BMJ 2022;377:e069066
76. HSE Medicines Management Programme, Managed Access Protocol, PCSK9 inhibitors, accessed from https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/managed-access-protocols/pcsk9-inhibitors/ on the 6th July 2023
77. Abdelhamid AA, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database of Syst Revs 2018;7:10.1002/14651858. CD003177.pub3
78. Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, Gibson H, Albert CM, Gordon D, Copeland T, D'Agostino D, Friedenberg G, Ridge C, Bubes V, Giovannucci EL, Willett WC, Buring JE; VITAL Research Group. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. N Engl J Med 2019;380:23-32
79. ASCEND Study Collaborative Group, Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, Murphy K, Aung T, Haynes R, Cox J, Murawska A, Young A, Lay M, Chen F, Sammons E, Waters E, Adler A, Bodansky J, Farmer A, McPherson R, Neil A, Simpson D, Peto R, Baigent C, Collins R, Parish S, Armitage J. Effects of n-3 fatty acid supplements in diabetes mellitus. N Engl J Med 2018;379:1540-1550
80. Abdelhamid AS, Brown TJ, Brainard JS, Biswas P, Thorpe GC, Moore HJ, Deane KHO, Summerbell CD, Worthington HV, Song F, Hooper L. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2020, Issue 3. Art. No.: CD003177. DOI: 10.1002/14651858.CD003177.pub5
81. European Public Assessment Report - Vazkepa® (icosapent ethyl) accessed from www.ema.europa.eu on the 24th April 2023
82. SmPC Zocor® (simvastatin) accessed from www.medicines.ie on the 2nd May 2023
83. SmPC Pravastatin Mylan accessed from www.medicines.ie on the 2nd May 2023
84. SmPC Fluvastatin accessed from www.medicines.ie on the 2nd May 2023
85. SmPC Omacor® (Omega-3-acid ethyl esters) accessed from www.hpra.ie on the 4th May 2023
86. SmPC Questran® (colestyramine) accessed from www.hpra.ie on the 4th May 2023
87. Anon, Bempedoic acid ▼: another cholesterol-lowering drug, Drug and Therapeutics Bulletin, August 2022;60(8):120-124
88. BNF – Bempedoic acid (last updated 10th August 2021) accessed from medicinescomplete.com on the 24th April 2023
89. Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of Bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: the clear wisdom randomized clinical trial. JAMA 2019;322:1780–8
90. Laufs U, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance. J Am Heart Assoc 2019;8:e011662
91. Ray KK, Bays HE, Catapano AL, et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. N Engl J Med 2019;380:1022–32
92. Ballantyne CM, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: a randomized, placebo-controlled study. Atherosclerosis 2018;277:195–203
93. Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. Eur J Prev Cardiol 2020;27:593–603
94. Nissen SE, Lincoff AM, Brennan D et al, Bempedoic acid and cardiovascular outcomes in statin-intolerant patients, New

England Journal of Medicine 2023;DOI:10.1056/NEJMoa2215024
95. Nissen SE, Lincoff AM, Brennan D et al, Bempedoic acid for primary prevention of cardiovascular events in statin-intolerant patients, Journal of the American Medical Association June 2023;DOI:10.1001/jama.2023.9696
96. SmPC Nilemdo® (bempedoic acid) accessed at www.ema.europa.eu on the 7th April 2023
97. European Medicine Agency, Assessment report Nilemdo® (published 2020), accessed at www.ema.europa.eu on the 7th April 2023
98. Ballantyne CM, Bays H, Catapano AL, et al. Role of bempedoic acid in clinical practice. Cardiovasc Drugs Ther 2021;35:853–64
99. Anon, Inclisiran▼: more hope less hype, Drug and Therapeutics Bulletin, July 2022;60(7):102-107
100. BNF – Inclisiran (last update 12th April 2022) accessed from medicinescomplete.com on the 24th April 2023
101. Raal FJ, Kallend D, Ray KK, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. N Engl J Med 2020;382:1520–30.
102. Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med 2020;382:1507–19
103. European Medicines Agency. Assessment report Leqvio, 2020, accessed at https://www.ema.europa.eu/en/documents/assessmentreport/leqvio-epar-public-assessment-report_en.pdf on the 7th April 2023
104. Ray KK, Troquay RPT, Visseren FLJ, Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial, Lancet Diabetes Endocrinology 2023;DOI.org/10.1016/S2213-8587(22)00353-9
105. National Institutes of Health. A randomized trial assessing the effects of inclisiran on clinical outcomes among people with cardiovascular disease (ORION-4) Accessed at https://clinicaltrials.gov/study/NCT03705234 on the 6th July 2023
106. SmPC Leqvio® (inclisiran) accessed at www.ema.europa.eu on the 7th April 2023
107. Kutner J, Blatchford P, Taylor D et al, Safety and Benefit of Discontinuing Statin Therapy in the Setting of Advanced, Life-Limiting Illness, JAMA Internal Medicine 175(5):691-700
108. Marcellaud E, Jost J, Tchalla A et al, Statins in primary prevention in people over 80 years, American Journal of Cardiology 2023;187:62-73
109. Pastori D, Pani A, Di Rocco A et al, Statin liver safety in non-alcoholic fatty liver disease: a systematic review and meta-analysis, British Journal of Clinical Pharmacology 2022;88:441-451
110. Newman C, Preiss D, Tobert J et al, Statin Safety and Associated Adverse Events: A Scientific Statement from the American Heart Association, Arteriosclerosis, Thrombosis and Vascular Biology, 2019;39(2):e38-e81
111. Lee M, Cheng CY, Wu YL et al, Association between intensity of low-density lipoprotein cholesterol reduction with statin-based therapies and secondary stroke prevention – a meta-analysis of randomised controlled trials, JAMA Neurology 2022;79(4):349-358