Newer lipid-lowering therapies in type 2 diabetes

Cardiovascular risk and lipid-lowering therapies are not new concepts in type 2 diabetes management. However, over recent years, lipid therapies have evolved and clinicians are now faced with more options than just statins. This *At a glance factsheet* is a brief guide to the newer lipid-lowering therapies available, their different modes of action and their place in treatment. A previous factsheet has discussed cardiovascular risk and how this should be assessed to guide whether lipid-lowering therapy is indicated.

Primary prevention: Assessing cardiovascular risk

QRISK3 (available at: https://qrisk.org/index.php) is generally the tool of choice for cardiovascular disease (CVD) risk assessment in the UK. However, it is important to note that this should not be used in the following groups:[1]

Do not use QRISK3
People aged <25 years or ≥85 years
People with type 1 diabetes
eGFR <60 mL/min/1.73 m^2
ACR ≥3 mg/mmol
Familial hypercholesterolaemia or other inherited disorders of lipid metabolism

For people with type 2 diabetes, regardless of other risk factors, males aged ≥52 years and females aged ≥60 years will generate a QRISK score of over 10%, thus qualifying them for primary prevention of cardiovascular disease and treatment according to NICE CG181.[1] Therefore, a large proportion of people living with type 2 diabetes are potentially eligible for lipid-lowering therapy.

Note that QRISK3 is only valid for patients who **do not** already have a diagnosis of coronary heart disease (including angina or heart attack) or stroke/transient ischaemic attack. CVD risk tools may also **underestimate risk** in certain groups of people (e.g. HIV, taking medications to treat CVD risk factors, recently stopped smoking, taking medicines that can cause dyslipidaemia such as immunosuppressant drugs, severe mental illness, autoimmune disorders, other systemic inflammatory disorders).[1]

Statins

Statins remain the preferred first-line treatment for primary prevention of CVD. For people with a QRISK3 score of ≥10%, atorvastatin 20 mg should be offered (making use of the NICE patient decision aid, if helpful), which can then be titrated as needed.

Where a person at high cardiovascular risk reports potential intolerance to recommended high-intensity statin treatment, the NHS Accelerated Access Collaborative's Statin Intolerance Pathway can be referred to.

If lipid targets are not achieved on the maximally tolerated statin dose, combination lipid-lowering therapy should be considered. A useful summary of NHS and NICE guidance on lipid management is available here.

Ezetimibe

Ezetimibe (Ezetrol®) provides an option for those who do not achieve treatment targets (a >40% reduction in non-HDL cholesterol)[1] in the following scenarios:[2]

- After 3 months of maximal statin therapy.
- If statin treatment is contraindicated or not tolerated.

Dose/frequency	Mechanism of action	Cautions/ contraindications	Prescribing setting	Combination with other agents
10 mg daily Can be taken with or without food No dose adjustment required in renal impairment	Inhibits NPC1L1 protein. Sometimes called a "cholesterol absorption inhibitor" as it decreases intestinal cholesterol absorption This differing mechanism to statin therapy can be beneficial to explain in a consultation if the person has previously not tolerated statins and is cautious about alternative medication options. Informing them that ezetimibe works differently is key to ensuring they can make an informed decision about their lipid management	**Pregnancy:** Only use if benefit outweighs risk **Breastfeeding:** Avoid **Hepatic impairment:** Avoid in moderate to severe impairment	Can be prescribed in primary and secondary care	Can be used in combination with statin therapy. When added to a statin, can reduce LDL by approximately 20% Ezetimibe when combined with any statin is likely to give greater reductions in non-HDL and LDL cholesterol than doubling the dose of the statin Can be used in combination with bempedoic acid (see later sections)

Bempedoic acid

Bempedoic acid (Nilemdo®) is a relatively new therapy that works similarly to statins; thus, it can be considered a good option for true statin-intolerant individuals. It is licensed for use in combination with a statin ± other lipid-lowering therapies, or with other lipid-lowering therapies or alone if a statin is contraindicated or not tolerated, for people who have not responded adequately to other appropriate measures. The agent has recently been shown to reduce the risk of major adverse cardiovascular events (MACE) by 13% in people with established or high risk of CVD.[3]

Dose/frequency	Mechanism of action	Cautions/contraindications	Prescribing setting	Combination with other agents
180 mg daily	ATP citrate lyase inhibitor which inhibits cholesterol synthesis in the liver, thus lowering LDL cholesterol	**Pregnancy:** Avoid (toxicity in animal studies) **Breastfeeding:** Avoid (no information available)	Can be prescribed in primary and secondary care	Can be used in combination with a statin* Can be used in combination with ezetimibe (see next section)

*When coadministered with simvastatin, the simvastatin dose should be limited to 20 mg daily (or 40 mg daily for patients with severe hypercholesterolaemia and high risk of cardiovascular complications, who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks).

Bempedoic acid/Ezetimibe combination

As per NICE TA694 guidance,[4] bempedoic acid with ezetimibe is an option when statins are contraindicated or not tolerated and when ezetimbe alone does not control LDL cholesterol sufficiently. Bempedoic acid when combined with ezetimibe produces an additional LDL cholesterol reduction of approximately 28% (range 22–33%), but no clinical outcome evidence for this specific combination is currently available.

Treatment can be with separate tablets (Nilemdo®) or a fixed-dose combination (Nustendi®), which reduces tablet burden for patients. Nustendi® contains 180 mg bempedoic acid and 10 mg ezetimibe, enabling once-daily dosing.

Icosapent ethyl

Granted NICE approval in July 2022, icosapent ethyl (Vazkepa®) is the newest lipid-lowering therapy available in the UK market. NICE TA805 recommends icosapent ethyl as an option for secondary prevention of cardiovascular events in adults.[5] It is recommended if the person has a high risk of cardiovascular events and raised fasting triglycerides (≥1.7 mmol/L) and is taking statins, but only if they have:

- Established CVD (defined as a history of acute coronary syndrome, coronary or other arterial revascularisation procedures, coronary heart disease, ischaemic stroke or peripheral arterial disease),

and

- LDL cholesterol levels above 1.04 mmol/L and ≤2.60 mmol/L.

Dose/frequency	Mechanism of action	Cautions/contraindications	Prescribing setting	Combination with other agents
1996 mg twice daily (two capsules twice daily) Should be taken with or following a meal. Capsules to be swallowed whole and not broken, crushed, dissolved or chewed	Ethyl ester of the omega-3 fatty acid eicosapentaenoic acid The mechanism of action is not fully understood. Likely multi-factorial, including improved lipoprotein profile with reduction of triglyceride-rich lipoproteins, anti-inflammatory and antioxidant effects, reduction of macrophage accumulation, improved endothelial function, increased fibrous cap thickness/stability, and antiplatelet effects	Caution in people with known hypersensitivity to fish and/or shellfish (obtained from fish oil) Avoid in patients with hypersensitivity to soya or peanuts (contains soya lecithin) **Pregnancy:** Avoid unless benefit outweighs risk (limited information available) **Breastfeeding:** Avoid (present in milk in animal studies) Caution with antithrombotic treatment (bleeding time increased), history of atrial fibrillation or flutter	Can be prescribed in primary and secondary care	Licensed as an adjunct to statin therapy

These recommendations were made as there are currently no treatment options to reduce the risk of cardiovascular events in people taking statins who have controlled levels of LDL cholesterol but raised levels of triglycerides. Thus, this agent is suitable for a very specific cohort of patients. It was previously shown to reduce four-point MACE risk by 26% in such a cohort.[6]

PCSK9 inhibitors

The PCSK9 inhibitors alirocumab (Praluent®) and evolocumab (Repatha®) have tight criteria for use and are restricted to secondary care prescribing only. They are potent medicines which can result in large reductions in lipid levels.

They are both subcutaneous injectable agents which can be self-administered by the patient at home.

NICE criteria for use of PCSK9 inhibitors are summarised in the table below:[7,8]

	Without CVD	With CVD	
		High risk of CVD*	Very high risk of CVD†
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/L	Recommended only if LDL-C concentration is persistently above 3.5 mmol/L
Primary heterozygous-familial hypercholesterolaemia	Recommended only if LDL-C concentration is persistently above 5.0 mmol/L	Recommended only if LDL-C concentration is persistently above 3.5 mmol/L	

*High risk of CVD is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; coronary heart disease; ischaemic stroke; or peripheral arterial disease.

†Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than one vascular bed (that is, polyvascular disease).

Abbreviations: CVD=cardiovascular disease; LDL-C=low-density lipoprotein cholesterol.

Alirocumab (Praluent®)

Dose/frequency	Mechanism of action	Cautions/contraindications	Prescribing setting	Combination with other agents
Initially 75 mg every 2 weeks, increased if necessary to 150 mg every 2 weeks. Alternatively, 300 mg every 4 weeks. Patients requiring an LDL reduction of >60% may be initiated on 150 mg every 2 weeks or 300 mg every 4 weeks Dose adjustments should be made at 4- to 8-weekly intervals	The monoclonal antibody binds to the PCSK9 pro-protein, inhibiting the breakdown of LDL receptors in the liver cells; receptor numbers are thus increased, raising capacity for cholesterol uptake and recycling	**Pregnancy:** Avoid unless clinical condition requires treatment (maternal toxicity in animal studies) **Breastfeeding:** Avoid (no information available) **Hepatic impairment:** Use with caution in severe impairment (no information available) **Renal impairment:** Use with caution in severe impairment (limited information available)	Secondary care only	Can be used in combination with other lipid-lowering therapies or alone depending on indication

Evolocumab (Repatha®)

Dose/frequency	Mechanism of action	Cautions/contraindications	Prescribing setting	Combination with other agents
Depends on indication: Either 140 mg every 2 weeks, 420 mg every month or 420 mg every 2 weeks	Described above	**Pregnancy:** Avoid unless essential (limited information available) **Breastfeeding:** Avoid (no information available) **Hepatic impairment:** Caution in moderate to severe impairment (risk of reduced efficacy; no information available in severe impairment)	Secondary care only	Can be used in combination with other lipid-lowering therapies or alone depending on indication

Factsheet continues overleaf

Inclisiran

Inclisiran (Leqvio®) is another new drug for lipid management that acts via the PCSK9 protein, in this case by inhibiting its production. As a newer agent, there is limited data on outcomes for inclisiran at present. Inclisiran can be prescribed in primary or secondary care, although roll-out in primary care has been met with concern from the RCGP and BMA.[9]

Inclisiran is an injectable agent, and this is something to be discussed with patients when considering initiation; some may benefit and prefer the reduced frequency of the injectable route, while others may prefer oral options listed previously.

NICE TA733 recommends inclisiran as an option for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet in adults. It is recommended only if:[10]

- There is a history of acute coronary syndrome (e.g. myocardial infarction or unstable angina needing hospitalisation), coronary or other arterial revascularisation procedures, coronary heart disease, ischaemic stroke or peripheral arterial disease,

and

- LDL cholesterol concentrations are persistently ≥2.6 mmol/L despite maximum tolerated lipid-lowering therapy (i.e. maximum tolerated statins with or without other lipid-lowering therapies, or other lipid-lowering therapies when statins are not tolerated or are contraindicated).

Dose/frequency	Mechanism of action	Cautions/contraindications	Prescribing setting	Combination with other agents
284 mg for 1 dose, followed by 284 mg after 3 months for 1 dose and then 284 mg every 6 months thereafter If a dose is more than 3 months late, treatment should be re-initiated	The small interfering RNA molecule limits production of PCSK9, increasing uptake of LDL cholesterol and thereby lowering levels in blood	**Pregnancy:** Avoid (no information available) **Breastfeeding:** Avoid (no information available) **Hepatic impairment:** Caution in severe impairment (no information available) **Renal impairment:** Caution in severe impairment (no information available)	Can be prescribed in primary or secondary care	Can be used in combination with a statin ± other lipid-lowering therapies, or with other lipid-lowering therapies or alone if a statin is contraindicated or not tolerated

Summary

Lipid management remains an intrinsic part of management for people living with type 2 diabetes to reduce their cardiovascular risk. The range of therapies available has expanded in recent years; however, each has different criteria for use and so should be checked on each occasion prior to prescribing to ensure the person meets the appropriate indications for use.

Reassessment of cardiovascular risk and review of whether lipid-lowering therapy is needed should be done opportunistically in the diabetes review, remembering that checking cholesterol is one of the eight annual care processes for people living with diabetes.

Individualised discussion with the person living with diabetes is imperative to ensure that an informed decision is made on treatment and the treatment choice.

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