KISS: Inclisiran

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What is Inclisiran and how does it work?

- Inclisiran is a novel drug that lowers LDL-C by interfering with the production of the PCSK9 protein.
- The PCSK9 protein inhibits LDL receptor recycling predominantly in the liver; thus by interfering with the production of PCSK9 more LDL receptors are available to increase LDL clearance from the blood.
- The PCSK9 inhibitors (e.g. alirocumab and evolocumab) are monoclonal antibodies that bind to the PCSK9 protein to inactivate it, allowing up-regulation of LDL receptors.
- Inclisiran works in a different way - it is a **'small interring RNA' drug (siRNA) that interferes with the PCSK9 RNA causing PCSK9 breakdown**, leading to up-regulation of LDL receptors which increases LDL clearance from the blood and lowers LDL-C levels.

Who is it for (NICE guidance - see below for Scotland) and how is it administered?

- Inclisiran is recommended as an option for primary hypercholesterolaemia or mixed dyslipidaemia (as an adjunct to diet) if:
  - **History of any of the following CVD events** - ACS, coronary or other arterial revascularisation, CHD, ischaemic stroke, PAD, **AND**
  - **LDL-C persistently ≥2.6 mmol/mol despite maximal lipid-lowering therapy**:
    - That is max tolerated statin with or without other lipid-lowering therapies, or
    - Other lipid-lowering therapies when statins are not tolerated or contraindicated.
- It is NOT recommended for primary prevention (including those with familial hypercholesterolaemia), unless part of a research trial.
- It is administered via **subcut injection**.
- **First 2 doses 3 months apart then twice yearly**, leading some to liken it to a cholesterol 'vaccine'.

Side Effects, interactions and precautions:

- Thus far no significant difference in any side effects vs placebo has been noted, apart from **local injection site reactions** (8.2% Inclisiran vs 1.8% placebo) with only 0.2% withdrawing.
- Renal/hepatic impairment - no dose adjustment; BNF advises avoiding in severe renal/hepatic impairment.
- Elderly? No dose adjustments; overall in studies 54% were ≥65 and 13% were ≥75.
- Inclisiran is not expected to have clinically significant interactions with other drugs (inc. statins).

Supporting evidence:

- The 2 key studies are ORION-10 (atherosclerotic CVD and LDL-C ≥1.8mmol/mol) and ORION-11 (mixed secondary prevention as per ORION-10 plus some primary prevention with risk factors and LDL-C ≥2.6).
- Most patients were on statins (89% in ORION-10 and 95% in ORION-11) with the **majority on high intensity statins** (69% in ORION-10 and 78% in ORION-11), although only small numbers were on ezetimibe (11% and 9% respectively).
- Both placebo controlled RCTs showed a **reduction of LDL-C of ~50% maintained by 18 months**.
- It's important to note **2 important caveats to the data so far**:
  - We have NO hard CVD outcome data yet on this drug - all studies so far have used LDL-C as a surrogate marker; a UK based study (ORION-4) is planned to report in 2026 with CVD outcomes.
  - We have NO comparative data comparing this drug to any current lipid-lowering therapy.

Why has NICE made this recommendation?

- NICE clearly feel there is a 'gap' in treatment for those at high risk of CVD (i.e. secondary prevention) who still have elevated LDL-C ≥2.6 despite statins (or due to intolerance of statins), and who are not eligible for the PCSK9 inhibitors (need LDL-C ≥ 3.5 or 4.0 depending on high risk/very high risk).
- They also note **significant barriers to PCSK9 inhibitors** even if eligible - v expensive and have to be prescribed by specialists, lack of such services/capacity issues and need for injections every 2-4 weeks.
- Crucially there is a **cost reduction agreement with Novartis** allowing this to be deemed cost-effective, and NICE specify that this drug can only be used if *'the company provides inclisiran according to the commercial arrangement'.* This agreement is inevitably commercially sensitive and has not been put into the public domain.

Potential implications for primary care:

- NICE are clear ***'Inclisiran is likely to be used in a primary care setting'.***
- We will need to do LDL-C levels in those with CVD (rather than current guidance using non-HDL-C).
- NHS data suggests 300,000 patients will be eligible for this - potential significant workload implications for us in primary care.
- How this rollout will actually happen in practice is still very uncertain, with many questions still to be answered, including:
  - Where the final cost of the drug will lie - primary care, secondary care or both?
  - Will it just be primary caregiving this drug or will secondary care also have access to it?
  - What about monitoring of side effects, given this is a novel drug?

What about Scottish recommendations?

Inclisiran has also been accepted by NHS Scotland for use, however, there are **much tighter restrictions on use**, including higher LDL levels, and importantly is **restricted to specialist use only** (unlike NICE recommendation for England/Wales which looks set for implementation in primary care), although they are recommending use in some patients with familial hypercholesterolaemia for primary prevention (unlike NICE).

- SMC restriction: for **specialist use only in patients at high cardiovascular risk** as follows:
  - Patients with heterozygous familial hypercholesterolaemia (HeFH) and LDL-C ≥5.0mmol/L, for primary prevention of cardiovascular events or,
  - Patients with HeFH and LDL-C≥3.5mmol/L, for secondary prevention of cardiovascular events or,
  - Patients with high risk due to previous cardiovascular events and LDL-C≥4.0mmol/L or,
  - Patients with recurrent/polyvascular disease and LDL-C≥3.5mmol/L.