Q&A from Session 1

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What side effect profile do we have with the new cholesterol meds? Do we need any special monitoring?

- The most commonly reported side effects of both inclisiran and PCSK9 inhibitors are mild injection site reactions (e.g. pain, erythema, swelling).

- A small proportion of patients receiving PCSK9i may experience flu-like symptoms – these symptoms occur most commonly after the first injection and are less frequently reported with subsequent doses. Some also report pain and arthralgia.

- Excepting for baseline bloods, there is no need for routine monitoring for inclisiran but we re-check LDL-c before the 2nd dose and then annually. For PCSK9 inhibitors we would re-check lipid profile (~3 months) to assess response and then annually.

Is intolerance of statins/ezetimibe an indication for the usage of the novel agents especially in primary prevention?

Inclisiran is currently only approved for use in **secondary prevention** in patients whose LDL-c remains ≥2.6 mmol/L despite maximally tolerated statin therapy with or without ezetimibe.

PCSK9 inhibitors are approved for use in:

- **Secondary prevention** in patients who do not achieve LDL-C targets despite maximally tolerated lipid-lowering therapy, and
- In **primary prevention** for patients with familial hypercholesterolaemia whose LDL-C remains above the specified treatment threshold (5.0 mmol/L) despite maximal tolerated lipid-lowering therapy.

Maximal tolerated lipid-lowering therapy means either the maximum dose has been reached or further titration is limited by intolerance.

When can we expect meaningful data for end outcomes for inclisiran and PCSK9i? Do we have any evidence of cardiovascular risk reduction or atheroma reduction with inclisiran?

We have robust CV outcome data in PCSK9 inhibitors. These drugs lead to ~15% risk reductions in major CV events, especially MI and stroke, across trials. They are effective in both secondary prevention (FOURIER in Evolocumab[1] and ODYSSEY[2] in Alirocumab) and selected primary prevention populations (VESALIUS-CV Adults with ASCVD or diabetes without prior MI or stroke).

The benefits are likely greater in higher-risk subgroups, including diabetes and those with polyvascular disease. Mortality reduction remains unproven (although some data that alirocumab added to intensive statin therapy has the potential to reduce death after acute coronary syndrome[3]), but atherothrombotic event reduction is robust.

There is good evidence that Inclisiran leads to an average ~50% LDL-c reduction (ORION trials), but definitive cardiovascular outcome evidence is still forthcoming. The major outcome trial for inclisiran is **ORION-4**, a large phase III, randomised, placebo-controlled study in ~16,000 patients with established ASCVD (data currently expected towards the end of 2026).

1. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *New England Journal of Medicine* 2017; **376**(18): 1713-22.
2. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *New England Journal of Medicine* 2018; **379**(22): 2097-107.
3. Steg PG, Szarek M, Bhatt DL, et al. Effect of Alirocumab on Mortality After Acute Coronary Syndromes. *Circulation* 2019; **140**(2): 103-12.