Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

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Statins: Review and interpretation of the evidence for efficacy and safety

A recently published review may help us make better informed decisions about statin therapy for the prevention of heart attacks and strokes. It explains how the large body of evidence from randomised controlled trials (RCTs) provides reliable information about efficacy and safety of statins, while evidence from observational studies may overestimate the adverse effects attributed to statin therapy. Further, while muscle-related adverse effects such as myopathy can be reversed by stopping treatment, the effects of heart attacks or strokes 'can be devastating'. These factors should be considered when having an informed discussion with people who are considering taking a statin in line with NICE guidance.

Reference: Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. Published online September 8, 2016.

What do we know already?

- The NICE Clinical Guideline on lipid-modification (CG181) highlights the importance of lifestyle modification and a cardioprotective diet in all people at risk of cardiovascular disease (CVD).
- CG181 also highlights the importance of working with patients to make decisions and the role of Patient Decision Aids.
- First choice statin treatment in people with CVD is atorvastatin 80 mg daily but lower doses should be used if any of the following apply: potential drug interactions; high risk of adverse effects; or patient preference.
- In the general population and in people with type 2 diabetes NICE CG181 advises that atorvastatin 20 mg daily should be offered to people who have a 10% or greater 10-year risk of developing CVD, estimated using QRISK2, as the initial treatment (for primary prevention).
- Despite the recommendations on primary prevention having informed patient choice at the centre of the decision, these proved controversial. Several doctors claimed that this would result in 'over-medicalisation' of a large proportion of the population, and that it could result in many people being harmed, particularly through statins causing muscle-related adverse effects.
- The Medicines and Healthcare products Regulatory Agency (MHRA) reviewed the safety of statins in 2014. They advised that muscle-related problems are the most frequently reported side effect of statins; the following incidences were estimated based on randomised trial data, cohort studies, published case reports and spontaneous reports: mild muscle pain, 190 cases per 100,000 patient years; myopathy, 5 cases per 100,000 patient years; rhabdomyolysis, 1.6 cases per 100,000 patient years.

What does this evidence add?

- This review considers the relative strengths and limitations of using RCTs and observational studies for assessing the effects of treatment, and then considers the specific evidence that is available on the efficacy and safety of statin therapy. It is a useful critique of these research methods.
- The review concludes that overestimates of adverse event rates for statins and the exaggerated media coverage of them may have led to some doctors having reservations about offering statins to patients who may benefit from them. This may have also led the general population to have raised awareness and expectation about perceived side effects and reluctance to choose to take and then adhere to statin therapy.
- The review cites evidence that uptake of statins might be less than expected, and this is worrying in those who already have cardiovascular disease, where harm from under treatment becomes a major concern.
- Drug discontinuation rates are also relatively high, particularly among people who have not suffered from recent cardiovascular events.
- The review thus highlights that misleading claims made about the balance of safety and efficacy of statins may pose a serious threat to the public's health.

Study details

Participants:

- The methods describing how the literature was identified are not provided, and for these reasons this cannot be described as a systematic review. The evidence from RCTs was drawn from the Cholesterol Treatment Trialists' (CTT) Collaboration which includes data from 174,000 participants in 27 randomised trials.

Intervention and comparison:

- The review explored research where people had been treated with statins compared to the use of placebo in RCTs, and to 'no use' in observational studies. It highlighted the strengths and limitations of each study design.

Outcomes and results:

Benefits

- The evidence from RCTs shows that effective low-cost statin treatment, such as 40mg atorvastatin, can reduce low-density lipoprotein (LDL)-cholesterol levels by more than 50%.
- In the CTT meta-analysis, after one year of therapy:
  - 17 trials of statin therapy versus no statin therapy showed a reduction of < 1.1mmol/L (average 0.9mmol/L)
  - 5 trials of statin therapy versus no statin therapy showed a reduction of >1.1mmol/L (average 1.4mmol/L).
  - 5 trials of more versus less intensive statin therapy showed a mean further reduction of 0.5mmol/L in LDL-cholesterol levels.
- Reduction in LDL-cholesterol levels was associated with a proportional reduction in major vascular event rates, such as heart attacks and related deaths, strokes and coronary revascularisations.
  - Evidence showed each 1mmol/L reduction in LDL-cholesterol was responsible for about a 25% reduction in the rate of major vascular events, and reducing cholesterol by 2mmol/L could reduce risk by about 45%.
- The absolute benefits of statin therapy depend on an individual's absolute risk of occlusive vascular events and the absolute reduction in LDL cholesterol that is achieved:
  - Reducing LDL-cholesterol by 2mmol/L over five years in 10,000 people would prevent about 1,000 vascular events in people who were taking a statin after a previous heart attack or stroke (secondary prevention). This means the drugs would prevent further events in 10% of high-risk patients **(the 5-year Number Needed to Treat [NNT] is 10).**
  - For people taking statins because they had cardiovascular disease risk factors but had not yet had an event (primary prevention), the drugs would prevent events in 500 out of 10,000 people – benefiting 5% **(the 5-year NNT is 20).**

Harms

- Statin therapy has been linked with a rare risk of muscle weakness (myopathy), haemorrhagic stroke and increased risk of new-onset diabetes:
  - Typically for 10,000 patients who take a standard-dose statin for five years, 5 individuals would suffer from myopathy (one of which might progress to rhabdomyolysis) and 5 to 10 people would suffer from a haemorrhagic stroke. This means these event rates are extremely low **(the 5-year Numbers Needed to Harm [NNH] are greater than 1,000).**
  - For new cases of diabetes, the risk was slightly higher – 50 to 100 new cases per 10,000 over five years **(the 5-year NNH is around 100 to 200).**
  - Any adverse impact of these side-effects on major vascular events has already been taken into account in the estimates of the absolute benefits, i.e. although diabetes may occur the risks of cardiovascular disease events are reduced.
- Statin therapy may cause symptomatic adverse events (e.g. muscle pain or weakness) in up to about 50–100 patients (**the 5-year NNH is around 100 to 200).** These resolve when the statin is stopped or changed.

Level of evidence:

Level 1 (good quality patient-oriented evidence) according to the **SORT criteria.**

Study funding:

The review was carried out by researchers from a variety of international institutes, including the University of Oxford and the London School of Hygiene and Tropical Medicine in the UK, Johns Hopkins University in the USA, and the University of Sydney in Australia. Although the review was not directly funded by pharmaceutical companies, the majority of the authors receive funding from such companies.