Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

Published: September 2013

Primary prevention of cardiovascular disease: do the right people get treatment with statins?

Document as included in MAW

Two UK observational studies found that the population at high risk of cardiovascular disease may be under treated with statins, and those at low risk may be over treated. Health professionals should continue to follow current NICE guidance on lipid modification and take additional measures to ensure that the people who receive treatment with statins are those recommended in the guidance.

Overview and current advice

NICE guidance on Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (NICE clinical guideline 67, currently being updated; expected publication date July 2014) recommends statin therapy as part of the management strategy for the primary prevention of cardiovascular disease (CVD) for adults who have a 20% or greater 10-year risk of developing CVD (estimated using an appropriate risk calculator, or by clinical assessment for people for whom an appropriate risk calculator is not available or appropriate). NICE also recommends statins for secondary prevention of cardiovascular disease.

The clinical and cost effectiveness of statins has been assessed by NICE in technology appraisal guidance 94: Statins for the prevention of cardiovascular events. This appraisal will be updated and replaced as part of a review of NICE clinical guideline 67: lipid modification.

NICE also recommends statins in certain circumstances for people with type 1 and type 2 diabetes (both of these guidelines are being updated; publication date to be confirmed). In addition NICE recommends statins as the initial treatment for all adults with familial hypercholesterolaemia.
New evidence

A UK observational study by Wu et al, 2013\(^1\) has assessed the extent to which GPs follow primary prevention of lipid modification guidelines when prescribing lipid-lowering drugs, and what clinical factors influence prescribing decisions. A cohort of 365,718 people aged between 30 and 74 years without evidence of CVD, who had not been prescribed lipid-lowering drugs at baseline, and with complete data on specified cardiovascular risk factors, was formed from The Health Improvement Network (THIN) database of electronic primary care records from 421 participating UK general practices. Ten-year cardiovascular risk for each person was calculated using a modified Framingham equation. Patients were assessed as being eligible for treatment if they met 1 or more of the following criteria (an amalgamation of recommendations taken from NICE guidance on type 2 diabetes, lipid modification and familial hypercholesterolaemia; SIGN guidance and the Joint British Societies’ guidance): 10-year cardiovascular risk of 20% or more (calculated using the modified Framingham equation), diabetes and aged 40 years or more, those with specified threshold levels for total cholesterol and HDL that may indicate familial hypercholesterolaemia, and those with a total cholesterol to HDL ratio 6 or more. Analysis of variables such as age, total and HDL cholesterol levels, blood pressure, and frequency of blood pressure measurements was completed to investigate their association with the prescription of lipid-lowering drugs.

After 2 years of follow up 13.8% (50,558/365,718) of people in the cohort had been prescribed a lipid-lowering drug. Of the 74,137 people in the cohort who were eligible for treatment according to the criteria above, only 28.5% (21,101) were prescribed it. However, 10.1% (29,457) of the 291,581 other people who were not eligible for treatment were prescribed a lipid-lowering drug. Thus, less than half of those prescribed lipid-lowering drugs (41.7%; 21,101/50,558) were actually eligible for treatment according to the criteria used in the study.

Prescription of lipid-lowering drugs was most strongly associated with increasing age (odds ratio [OR] for age 65 years or more 4.21, 95% confidence interval [CI] 4.05 to 4.39); diabetes (OR 4.49, 95% CI 4.35 to 4.64); total cholesterol level (OR for total cholesterol level of 7 mmol/L or more 2.20, 95% CI 2.12 to 2.29) and frequency of blood pressure monitoring in the last year (OR for 4 or more measurements 4.24, 95% CI 4.06 to 4.42).

A sensitivity analysis including patients for whom data on cholesterol levels and blood pressure were missing (n=1,364,383) found similar results.

A second UK-based observational study by van Staa et al, 2013\(^2\) aimed to evaluate the current UK strategy to target statin treatment based on cardiovascular risk score. Two cohorts were formed from the November 2011 version of the UK Clinical Practice Research Datalink (CPRD, formerly the General Practice Research Database). The general population (3.8 million people) consisted of people aged 35 to 74 years registered in CPRD databases, including statin users and non-users. In this cohort, the index date was a randomly selected date between 1993 and 2011. The statin cohort (300,914 people) consisted of people who initiated statin treatment in 1993 or later. The cohorts were followed up for an average of 4 years. People with a history of CVD prior to the index date (and, in the case of the statin cohort, in the first 6 weeks after starting statin treatment) or diabetes mellitus were excluded from both cohorts.

In the general population, 10-year CVD risks were predicted using Framingham, ASSIGN and QRISK2 using risk factors measured at the index date (or at the start date of statin treatment if statins had been initiated before the index date). The extent of statin prescribing in this cohort was measured for different categories of CVD risk as predicted by the different risk scores and was also stratified for calendar year. In the statin cohort 10-year CVD risk scores were estimated at the start of statin treatment. In addition 5-year CVD risks during statin treatment were also estimated using Kaplan-Meier life table analyses. High risk patients were defined as those with a 10-year CVD risk 20% or more according to at least 1 of the risk estimators, and low risk patients were defined as those with a 10-year CVD risk less than 15% according to at least 1 of the risk estimators.

The number of high-risk people in the general population that were receiving a statin at the index date increased substantially over time. For example 7.0% of high-risk people (measured using QRISK score) received statins before 2007 (when the NICE clinical guideline was published), increasing to 30.4% from 2007 onwards. However an increase was also seen in prescribing for low-risk people,
from 1.9% to 5.0%. The absolute numbers of low-risk people receiving statins in 2007 onwards exceeded the number of high-risk people. Only about half of people initiating treatment with statins were high-risk according to CVD risk scores.

There was a large variation in statin prescribing between practices, ranging in 2007 onwards from 8.2% to 61.5% for high-risk people and from 2.1% to 29.1% for low-risk people. Practices that prescribed higher levels of statins to high-risk people tended to prescribe higher levels to low-risk people too.

Over 100,000 people used statins and had follow-up for over 5 years. The observed 5-year CVD risk during statin treatment (estimated using Kaplan Meier life tables) was on average 8.9% (95% CI 8.7% to 9.0%). The observed 5-year cardiovascular risks during statin treatment decreased over time and were 17% (95% CI 16.3% to 17.7%) for those starting statins in 1993 to 1999, 12.4% (95% CI 12.1% to 12.8%) in 2000 to 2002, 8.6% (95% CI 8.4% to 8.8%) in 2003 to 2005, and 7.1% (95% CI 6.9% to 7.3%) in 2006 to 2008.

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Numerous guidelines, including NICE, provide suggestions for treatment thresholds for statins in primary prevention. Typically these guidelines include the suggestion that "high" risk (greater than 20% 10-year CVD risk or diabetes) should receive a statin. Given these recommended thresholds, policy makers and health care organisations are often interested as to how well clinicians and patients adhere to these recommendations in real life.

The observational studies by Wu et al and van Staa et al, despite some limitations (missing data, inability to account for over the counter statin use), do a solid job of showing that despite these recommendations, in very large cohorts of the general population only approximately 30% of those people considered high-risk received a statin. They also showed that 5-10% of patients that fell below the high-risk category, were also receiving statins and that there is considerable variation between practices. While van Staa et al infer that statin use might be responsible for an actual reduction in observed CVD these results should be taken in context of the general reduction in cardiovascular deaths that seems to have occurred since the seventies.

Higher risk patients in theory should get a greater absolute benefit from a statin than those who have a lower risk and that is the premise behind most statin guideline recommendations.

Assuming statins reduce CVD risk by 25% (relative), a high risk (20% 10-year CVD risk) patient would have their risk reduced from 20% down to 15%, or an absolute benefit of 5% and a number needed to treat (NNT) of 20. For a patient whose risk is 10% (considered low-risk) the corresponding numbers would be an absolute benefit of 2.5% and an NNT of 40.

Patients armed with this information along with the knowledge of the potential statin adverse effects could, should they wish, make an informed decision about the use of a statin.

However, a recent look at five Canadian chronic disease state guidelines showed that only 99 of 91,000 words in those guidelines mentioned anything about incorporating patient values and preferences into the decision making process. Given this, it is likely that patients’ values and preferences may not be front and centre when it comes to making a decision about a statin.

Is there really inappropriate overuse or underuse of statins? If these papers are describing underuse in cases where if given the evidence of potential benefit and harm patients would have chosen to use a statin then this is unfortunate. Conversely, if these papers are describing overuse where a patient would not consider taking a statin if they knew the best available evidence then this is also disappointing.
However, the answer to this is probably unknown because this crucial question is rarely examined.

**Study sponsorship**

The Wu J et al study was partly funded by the National Institute for Health and Research (NIHR).

The van Staa TP et al study was funded by the Wellcome Trust.

**References**


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