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Statins for primary prevention in people with a 10% 10-year cardiovascular risk:

too much medicine too soon?

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INTRODUCTION

The National Institute for Health and Care Excellence (NICE) guidelines on lipid modification advise offering statins for primary prevention to patients with over 10% 10-year modelled risk of a cardiovascular event, a change from 20%. This has generated controversy among clinicians, researchers, and journal editors. Patients already taking statins were more likely to stop taking them after the intense media coverage between March and October 2014, though there was no associated change in initiation.[1]

Clinicians' worries were crystallised in a letter of concern from leading UK medical figures to NICE concerning the frequency of adverse events and the magnitude of the effectiveness of statins.[2] Two sources of evidence were cited regarding risk levels, the meta-analyses by the Cholesterol Collaboration Trialists (CTT) Collaboration and Cochrane.[3,4]

EVIDENCE OF BENEFIT

The CTT Collaboration meta-analysis used individual patient data from 22 randomised controlled trials (RCTs) of statin versus control (n = 134 537);[3] authors were able to stratify individuals into risk categories. The CTT Collaboration is the only group to have been granted access to individual patient data by pharmaceutical companies funding RCTs, but they were not allowed to share data with third parties and were not granted access to individual patient adverse event data.[5] For primary prevention, among those at high risk (10–20% risk over 5 years), statins led to a significant relative risk reduction in major vascular events and a non-significant relative risk reduction in vascular mortality.

Among intermediate-risk patients (5–10% risk over 5 years), statins were associated with a significant relative risk reduction in major vascular events and major coronary events, but to non-significant reductions in coronary heart disease (CHD) mortality and all-cause mortality. Among those receiving statins for 5 years and attaining a 1 mmol/L reduction in LDL cholesterol, this equates to absolute risk reductions in those with intermediate risk of 4 vascular deaths saved per 1000 and 15 vascular events per 1000.

It may be difficult for a GP to interpret these data in the UK clinical context. The UK risk scores used a 10-year risk of having an event, whereas the CTT meta-analysis describes risk groups in terms of 5-year risk. Is 5–10% risk over 5 years equivalent to the NICE 10–20% 10-year risk? Kaplan–Meier estimates of the 10-year cumulative total cardiovascular morbidity and mortality in a large UK population-based cohort suggest they may not be equivalent.[6] Some have questioned why this meta-analysis reported outcomes per 1 mmol/L reduction in LDL cholesterol. It is not the standard way of displaying benefit from statins and can be confusing. Do all patients who take statins experience a 1 mmol/L drop in LDL cholesterol? A meta-analysis by Law *et al*[7] of 164 trials examining the effects of statins on LDL reduction found that statins lower LDL cholesterol concentration by an average of 1.8 mmol/L. Overall this analysis demonstrates a statistically non-significant mortality benefit, a significant relative risk morbidity benefit, and a modest absolute risk morbidity benefit.

The Cochrane meta-analysis in 2013 examined 18 RCTs (19 trial arms; n = 56 934) comparing treatment with statins for at least 12 months with placebo.[4] It described the benefit of statins for primary prevention across all risk levels, but not stratified by baseline risk. Thus, it does not provide evidence for a change in risk level to 10%, but supports use of statins in primary prevention generally. The authors reported that all-cause mortality was reduced by statins versus placebo, as were combined fatal and non-fatal CHD events. This equates to a number-needed-to-treat (NNT) of 138 people treated with statins for 5 years to prevent one death, 49 people to prevent one cardiovascular disease (CVD) event, and 155 people to prevent one stroke.

EVIDENCE OF HARM

Millions of patients are currently taking statins without problems, but clinical experience suggests that statins cause more problems than reported in trials, and the incidence of side effects in electronic medical records is higher than those reported in clinical trials. RCTs might report lower relative frequencies of side effects by excluding patients with comorbidities, pre-randomisation run-in periods with exclusion of those not tolerating statins, moderate dropout rates, not assessing certain adverse events, and under-ascertainment of others.

Strong defences against these assertions have been made and it remains unclear how much they influence interpretation of the available RCT evidence. Tobert *et al* argue that despite exclusions these trials include significant numbers of women, older patients, and patients with comorbid disease.[8] In patients with comorbid disease, rates of withdrawal due to adverse events are consistently similar in the statin and placebo arms. The HPS trial had a pre-randomisation phase, with similar rates of adverse events causing withdrawal in both statin and placebo run-ins.[9]

Proponents of wider use of statins suggest that potential adverse events were well assessed in trials, and in national health registry data, but potential adverse events not routinely assessed in RCTs have come to light in clinical practice. For example, it has been suggested that fatigue and myalgia may adversely affect tertiary outcomes such as physical activity, and that exercise-induced myalgia may limit adherence to and cardiovascular benefits of statins.[10]

Meta-analyses contribute evidence on adverse events.[4,11,12] The Cochrane review relied on two earlier reviews that included published-only data to examine rates of adverse events.[4] They found no excess adverse events (cancer, myopathy, rhabdomyolysis, haemorrhagic stroke, or liver enzyme elevation) in participants who took statins versus placebo, although not all trials reported these data. This echoes Finegold's meta-analysis of 14 primary prevention RCTs ($n = 46\,262$) of statin versus placebo, which found no increased statin-attributable adverse outcomes,[11] but did find that statins increased the absolute risk of diabetes by 0.5%.[11] Sattar *et al*, in a meta-analysis of 13 RCTs examining incident diabetes risk in statin versus control groups ($n = 91\,140$), found statins were associated with a 9% increased risk of incident diabetes.[12] In the Cochrane review, an increased risk of incident diabetes was found in the two trials reporting this outcome. It reported that 99 people need to be treated with statins for 5 years to cause one case of diabetes (number-needed-to-harm [NNH]),[4] although it is important to bear in mind that the reduction in overall cardiovascular risk associated with statins is likely to outweigh the additional cardiovascular risk associated with small increases in blood glucose levels. These outstanding uncertainties have led to calls for greater transparency of reporting of adverse event data from existing trials.

CONCLUSION

Whatever the risk level clinicians set, the decision about taking a statin is up to the individual. When communicating risk, patients and clinicians understand absolute risks better than relative risks,[13] and the most striking omission from the NICE guidelines was clear evidence regarding absolute risks at the different risk levels. If a clinician is ill-prepared to communicate the benefits of a preventive intervention such as statins, negotiations with patients are likely to be suboptimal.

Perhaps we should worry less about side effects if statins allow us to live longer, as side effects are rarely fatal. However, if statins do not extend life in those at lower CVD risk then the balance of risks and benefits becomes more important. There is clear evidence of benefit of statins for primary prevention, even in those at lower risk of CVD and this is likely to translate to avoidance of reductions in quality of life associated with some cardiovascular events. Tough decisions have to be made by policymakers on the balance of evidence, but without the full backing of the medical community the NICE recommendation may have lost some of its potency. Coverage is important for a population-wide approach to have an impact. Guidelines are of course only a guide, although the integration of this recommendation into NHS Health Checks and potentially the Quality and Outcomes Framework goes some way to compelling its implementation.

Some time has passed since the release of the guidelines and little progress appears to have been made in allaying some of the worries that have been voiced. There is still a need to clarify the risk and benefits of statins for the ultimate success of this policy. This guideline highlights the difficult role evidence sometimes has to play in modern medicine and suggests that clinicians themselves might consider reflecting on the research underpinning everyday practice.

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