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Side effects reported in those taking statins are not actually attributable to the drugs

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At a time when the wider prescription of statins is under renewed public scrutiny, a substantial analysis of placebo-controlled randomised trials of statins has found that only a small minority of side effects reported by those taking the cholesterol-lowering drugs are actually attributable to them. Almost all the side effects reported in these trials "occurred anyway when patients were administered placebo", say the investigators.

The study, a meta-analysis involving more than 80,000 patients and reported today in the *European Journal of Preventive Cardiology*, was performed without funding from any agency in the public, commercial or not-for-profit sectors.(1)

Explaining the need for such a study, the authors note that evaluation of the efficacy of statins is always based on the evidence of randomised controlled trials (RCTs) against placebo, while the evaluation of side effects is not. Adverse events listed for statins come from many sources, they note, including observational studies, in which most are unable to differentiate between events caused by the drug or caused by chance.

"Patients and doctors need clear reliable information about benefits and risks to make informed decisions," they write, adding that those reporting symptomatic side effects during statin therapy need reliable confirmation that a symptom is truly caused by the drug.

This study analysed the prevalence of side effects in 29 eligible RCTs performed for the primary (46,262 participants) and secondary (37,618)

prevention of cardiovascular disease. Data on all adverse effects, cardiovascular events and death were recorded in both the treatment and control (placebo) arms of the studies. Using a statistical model, the investigators calculated the increase in risk for each side effect in the statin and placebo arms.

Among a long list of side effects assessed - which included nausea, renal disorder, myopathy and rhabdomyolysis (muscle breakdown), muscle ache, insomnia, fatigue, and gastrointestinal disturbance - only the risk of new onset diabetes mellitus was increased by statin therapy.

In the 14 primary prevention trials, randomisation to statins rather than placebo significantly increased the prevalence of diabetes by 0.5% (and similarly reduced mortality rate by 0.5%). And across both primary and secondary prevention trials, the rate of developing diabetes with statins was 3%, against 2.4% with placebo, thus indicating that around one in five of new cases of diabetes was actually caused by statins.

Otherwise, the authors report, the many side effects commonly attributed to statins (notably myopathy, fatigue, muscle aches, and rhabdomyolysis) were no more common in the statin arms of these RCTs than in the placebo arms.

Overall, the study found serious adverse effects in 14.6% of patients receiving statins and 14.9% given placebo in the primary prevention trials, and in 9.9% of those on statins and 11.2% on placebo in the secondary prevention trials. Similarly, comparable numbers of patients withdrew from the trials because of symptomatic adverse events (around 12-15%).

In their bid to provide doctors with a clear estimate of the risk of side effects genuinely attributable to statins, the investigators have calculated a "clear, understandable metric for everyday clinical use" - the

proportion of side effects not attributable to their pharmacological action, or PSN.

Thus, in the diabetes risk noted above, 20% (0.6/3.0) of all new diabetes diagnoses on statins were directly attributable to the drugs, giving a PSN of 80.

Despite the findings, the authors acknowledge that many real-world patients do report symptoms with statins - which of course contrasts markedly with their results. In explaining this, the study's first author, Dr Judith Finegold from the National Heart and Lung Institute in London, says: "We clearly found that many patients in these trials - whose patients are usually well motivated volunteers who didn't know if they were getting a real or placebo tablet - that many did report side effects while taking placebo. In the general population, where patients are being prescribed a statin for an asymptomatic condition, why would it be surprising that even higher rates of side effects are reported?

"Most people in the general population, if you repeatedly ask them a detailed questionnaire, will not feel perfectly well in every way on every day. Why should they suddenly feel well when taking a tablet after being warned of possible adverse effects?"

Asked if the study results add weight to the case for the wider prescription of statins, Dr Finegold said: " No, we think that our results will help improve the patient-doctor consultation. We believe that patients should be empowered to make their own decisions, but we must first make sure they have top quality unbiased information. This is why we call on drug regulators to highlight in the long lists of side effects those few whose rate is incrementally greater than that experienced with a dummy tablet."

More information: 1. Finegold JA, Manisty CH, Goldacre B, et al.

What proportion of symptomatic side effects in patients taking statins are genuinely caused by the drug? Systematic review of randomized placebo-controlled trials to aid individual patient choice. *Eur J Prevent Cardiol* 2014; DOI: 10.1177/2047487314525531

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