Cohort study

Statin use associated with increased risk of cataract, myopathy, liver dysfunction and acute renal failure with varying numbers needed to harm

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Context

Cardiovascular disease is the leading cause of premature death and a major cause of disability in most industrialised nations. Multiple studies and international guidelines support the use of statins to reduce the risk of cardiovascular disease. As such, statins are among the most widely prescribed medications. However, the intended as well as unintended consequences of their widespread use are unknown in large representative populations. Therefore, investigators performed a large population-based study to examine a range of clinical outcomes that have been found to be positively or negatively associated with statin use, including myopathy and rhabdomyolysis, Parkinson's disease, dementia, liver dysfunction, venous thromboembolism, rheumatoid arthritis, cataract, common cancers, osteoporotic fracture as well as acute renal failure.

Methods

This is a large prospective cohort study of primary care patients in England and Wales aged 30–84 years from January 2002 through June 2008. To correspond to an intention to treat analysis, statin use was classified by type of statin first prescribed (atorvastatin, simvastatin, fluvastatin, pravastatin or rosuvastatin). In total, 2 004 692 patients aged 30–84 years of whom 225 922 (10.7%) were new users of statins: 159 790 (70.7%) were prescribed simvastatin, 50 328 (22.3%) atorvastatin, 8103 (3.6%) pravastatin, 4497 (1.9%) rosuvastatin and 3204 (1.4%) fluvastatin.

Several outcomes were assessed using Read codes recorded in the patients' electronic records: acute renal failure; venous thromboembolism; Parkinson's disease, dementia; rheumatoid arthritis; cataract; osteoporotic fracture (spine, hip or wrist); common cancers (gastric, colon, oesophageal, lung, renal, breast, prostate, melanoma); moderate or severe liver dysfunction, defined as an alanine transaminase concentration >120 IU/l (ie, more than three times the upper limit of normal) among patients without diagnosed chronic liver disease, as this is the severity at which guidelines recommend treatment is discontinued; and moderate or serious myopathic events, which for the purposes of the study was defined as a diagnosis of myopathy or rhabdomyolysis or a raised creatine kinase concentration of four or more times the upper limit of normal.

To estimate the HRs for each outcome for type of statin first prescribed for men and women separately, Cox proportional hazards models were utilised to compare new users with non-users adjusting for potential confounding variables. When associations for individual statins were significant, a time varying Cox regression analysis was used to examine the effects of duration of use and time since stopping any statin. The investigators examined statins overall and by type. To determine the risk of each outcome within a year, 1–3 years, 3–5 years and 5 or more years of taking statins, non-users were compared with new users.

Finally the number needed to treat (NNT) or number needed to harm (NNH) over 5 years was calculated for patients at high risk of cardiovascular disease.

Findings

Individual statins were not significantly associated with risk of Parkinson's disease, rheumatoid arthritis, venous thromboembolism, dementia, osteoporotic fracture, gastric cancer, colon cancer, lung cancer, melanoma, renal cancer, breast cancer or prostate cancer. Statin use was associated with decreased risks of oesophageal cancer but an increase in risks of moderate or serious liver dysfunction, acute renal failure, moderate or serious myopathy and cataract. Adverse effects were similar across statin types for each outcome except liver dysfunction where risks were highest for fluvastatin. A dose-response effect was apparent for acute renal failure and liver dysfunction. All increased risks persisted during treatment and were highest in the first year. After stopping treatment, the risk of cataract returned to normal within a year in men and women. Risk of oesophageal cancer returned to normal within a year in women and within 1–3 years in men. Risk of acute renal failure returned to normal within 1–3 years in men and women and liver dysfunction within 1–3 years in women and from 3 years in men. Based on the 20% threshold for cardiovascular risk for women, the NNT with any statin to prevent one case of cardiovascular disease over 5 years was 37 (95% CI 27 to 64) and for oesophageal cancer was 1266 (850 to 3460) and for men, the respective values were 33 (24 to 57) and 1082 (711 to 2807). In women, the NNH for an additional case of acute renal failure over 5 years was 434 (284 to 783), of moderate or severe myopathy was 259 (186 to 375), of moderate or severe liver dysfunction was 136 (109 to 175) and of cataract was 33 (28 to 38). Overall, the NNHs and NNTs for men were similar to those for women except for myopathy where the NNH was 91 (74 to 112).

Commentary

This study examined and quantified the unintended risks and benefits of statins in a large representative primary care population over a 6-year period. According to this study, the claimed unintended benefits of statins, except for oesophageal cancer, remain unsubstantiated. The study confirms other studies that reported no clear association between statins and risk of cancers with the possible exception of oesophageal cancer where a decreased risk was noted, and colon cancer where there was decreased risk in men prescribed pravastatin and an increased risk in men prescribed rosuvastatin. While these findings could represent a genuine association, they could also be due to chance. Further studies using independent datasets should be undertaken to confirm or refute these findings particularly as the use of statins is likely to increase.

As far as adverse effects associated with statins, including myopathy, liver dysfunction, acute renal failure and cataract, these appear to be a class effect. A dose-response effect existed for acute renal failure and liver dysfunction consistent with other reports. All risks persisted during treatment and were highest in the first year of treatment. After stopping treatment, the risk of cataract returned to normal within a year in men and in women while the risk of oesophageal cancer returned to normal within a year in women and within 1–3 years in men. The risk of acute renal failure returned to normal within 1–3 years in men and women and liver dysfunction within 1–3 years in women and from 3 years in men.

While this is one of the largest studies to date to explore non-cardiovascular potential benefits and harm of statins, observational studies may suffer from bias and unmeasured confounding. Despite this, the detailed epidemiological analysis of the unintended effects of statins in a large representative primary care population for a range of outcomes by type of statin, dose and duration of use provides important information for practicing clinicians. It is the largest study to assess 'real-world' use and impact of statins. Based on this study, it appears that individual statins were not significantly associated with risk of Parkinson's disease, rheumatoid arthritis, venous thromboembolism, dementia, osteoporotic fracture and several common cancers, and that the risk of oesophageal cancer was reduced. Of note, and consistent with other studies, rates of liver dysfunction, acute renal failure, myopathy and cataract were increased. These adverse effects were similar across the statin types for each outcome except liver dysfunction where fluvastatin was associated with the highest risks.

Competing interests JF works as a consultant for Pfizer, Merck and Sanofi-Aventis.