Mortality and morbidity of lowering low-density lipoprotein cholesterol with simvastatin


SUMMARY

Statins have been proven undisputedly to reduce cardiovascular morbidity and mortality.¹ The information on the safety of long-term use of statins is limited. The current study presents the results of 11 years of follow-up to Heart Protection Study (HPS) participants in the UK. In the HPS, 20,536 men and women between 40 and 80 years of age who were at high risk of developing cardiac events were randomized to receive either 40 mg of simvastatin or placebo for a mean period of 5 years between 1994 and 2002. The eligibility criteria included elevated risk of coronary heart disease death because of past history of myocardial infarction or other coronary heart disease, occlusive disease of non-coronary arteries, diabetes mellitus or treated hypertension; had baseline blood total cholesterol of 3.5 mmol/dl. These participants were further followed up for another 6 years post-trial, totalling to 11 years of follow-up. The primary outcome of the study was first major cardiac event or cardiac mortality. The other outcomes included cancer mortality and incidence of non-fatal cancer. End-points were assessed by mailing a questionnaire to the participants every year. For those participants who failed to respond, this information was sought from their primary physicians. The occurrence of cancer and cause of death was accessed from UK national registries for cancer and mortality, respectively.

About three-quarters of the participants were assessed for primary outcomes at the end of 11 years, providing a total of 96,784 person-years of follow-up. Almost all participants were assessed for occurrence of cancer and mortality (except 74 participants). The non-trial statin use group was comparable between the previously allocated simvastatin group (74%) and placebo group (74%) at the fifth year of post-trial follow-up. The HPS found a significant 23% reduction of major cardiac events among the simvastatin group compared to placebo at the end of the trial period; this difference continued to persist at the first year of post-trial follow-up (about 14% reduction in the simvastatin group). However, from the second post-trial follow-up onwards, there was no difference in major cardiac events between groups previously allocated to either simvastatin or placebo. Cardiac mortality was 18% lower in the simvastatin group during the trial and non-cardiac mortality of various causes did not differ between the groups. Post-trial, there was no difference of mortality cardiac or otherwise between the two groups previously allocated to simvastatin or placebo in an intention-to-treat analysis. There was no difference between the trial groups in first incidence of any cancer or specific cancer both during the trial and after the trial follow-up [1749 (17%) allocated simvastatin v. 1744 (17%) allocated placebo; RR 0.98 (0.92–1.05); p=0.60]. In the subgroup analysis of the elderly (>70 years) and participants with below average pre-treatment cholesterol (<5.0 mmol/L), the study did not find a higher occurrence of cancer among group previously allocated to simvastatin.

The authors of the study conclude that absolute benefits of prolonged statin treatment are likely to be much greater than indicated by analyses restricted merely to in-trial periods of statin trials. And prolonged follow-up in HPS provide considerable reassurance—both to prescribers and to patients—about the long-term safety of lowering low-density lipoprotein (LDL) cholesterol substantially for about 5 years. These findings provide further support for the prompt initiation and long-term continuation of statin treatment in people at increased risk of vascular events.

COMMENT

There is an increasing trend for the use of statin among high cardiac risk individuals in the developed world. Use of statin for high-risk cardiac patients is recommended by most organizations such as the American Diabetic Association (ADA),² European Society of Cardiology (ESC),³ and Adult Treatment Panel (ATP).⁴ There is also evidence of benefits of statin use in reducing C-reactive protein among individuals with low levels of LDL cholesterol.⁵ In contrast, there is still speculation of long-term safety about the use of statins in the light of findings from observational studies with long-term follow-up.⁶ Therefore, this article is relevant for both researchers and practitioners.

This was a well-conducted trial with a methodologically sound design and high retention rate for such a long duration of follow-up. The population selection for the trial was appropriate, as this population (age >40 years with high cardiac risk) is most likely to be prescribed statin therapy. Exposure and end-point measurements are appropriate and clearly mentioned in the article. After 11 years of follow-up, this study did not find any association between 5 years of simvastatin use and cancer. However, there was a high level of use of non-study statins, on an average of 74% in both simvastatin and placebo groups. The use of non-study statins could have diluted the effect of low LDL cholesterol on cancer incidence, if there was any. Despite this minor shortcoming, this study reassures that benefits of use of statin outweigh its adverse effects, if any.

Implication for healthcare in India

Cardiovascular disease is a major burden in India; 20%-25% of all hospital admissions and 25% of all mortality is due to coronary artery disease.⁷ Use of statins among individuals with high cardiac risk is an effective strategy to reduce cardiac morbidity and mortality. The WHO guidelines for National Programme for Prevention and Control of Diabetes, Cardiovascular disease, and Stroke (NPPDCS), India suggests the use of statins for all individuals with >30% cardiac risk for the next 10 years.⁸ However, in practice, use of lipid-lowering drugs is low and not uniform in Indian healthcare. An audit of the prescription pattern in Rajasthan revealed very low prescription of statins for secondary prevention at primary and secondary care levels.⁹ The CREATE registry
Does early initiation of antiretroviral therapy prevent HIV transmission in serodiscordant couples?


Gaitonde Centre for AIDS Research and Education, Chennai, India; National AIDS Research Institute, Pune, India; University of Zimbabwe, Harare; Instituto de Pesquisa Clinica Evandro Chagas, Fiocruz, and Hospital Geral de Nova Iguaçu and Laboratorio de AIDS e Imunologia Molecular-IOC/Fiocruz, Rio de Janeiro; Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand; Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; Fenway Health and Harvard School of Public Health, Boston; Johns Hopkins University School of Medicine and Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; Botswana Harvard AIDS Institute, Gaborone; Centers for Disease Control and Prevention [CDC] Division of HIV/AIDS Prevention, Atlanta, USA; Kenya Medical Research Institute–CDC Research and Public Health Collaboration HIV Research Branch, Kisumu; Perinatal HIV Research Unit Department of Medicine, University of the Witwatersrand, Johannesburg, South Africa; University of California at San Francisco, San Francisco; University of Nebraska Medical Center, Omaha; Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda; David Geffen UCLA School of Medicine, Los Angeles,