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Statins: Can we advocate them for primary prevention of heart disease?

Surg Cdr Sougat Ray [a,*], *Col A.K. Jindal, YSM* [b], *Lt Col S. Sengupta* [c], *Lt Col S. Sinha* [d]

[a] *Associate Professor, Dept of Community Medicine, Armed Forces Medical College, Pune 411040, India*
[b] *Professor, Dept of Community Medicine, Armed Forces Medical College, Pune 411040, India*
[c] *Classified Specialist (Medicine and Cardiology), Military Hospital, Jalandhar, India*
[d] *Associate Professor, Dept of Pharmacology, Armed Forces Medical College, Pune 411040, India*

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ABSTRACT

The discovery of cholesterol-lowering agents, namely HMG-CoA reductase inhibitors or statins, ushered in a series of large cholesterol reduction trials. The first of these studies was the Scandinavian Simvastatin Survival Study (4S) in which hypercholesterolemic men with CHD who were treated with simvastatin had a reduction in major coronary events of 44% and a reduction in total mortality of 30%. Many more secondary prevention trials followed to establish unequivocally the benefit of cholesterol reduction. Strategies that aim to improve primary prevention are important for managing the overall burden of disease. Recently therefore, the role of statin in primary prevention is being debated. The JUPITER trial and more recently the Cholesterol Treatment Trialists collaborators, proved that incidences of first major cardiovascular events in apparently healthy individuals were reduced by statins. Statins have also been discussed to be having certain pleiotropic effects on other diseases like diabetes, cancer and osteoporosis. However, issues of cost effectiveness and adverse effects like myositis, and transaminitis still loom large. The medical community needs to debate and evolve a possible consensus on the path breaking subject.

Introduction

Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality worldwide. High blood cholesterol is associated with CVD and is an important risk factor. Reducing high blood cholesterol or LDL-Cholesterol (LDL-C) by statins, thus remains the medical goal of reducing the chances of suffering a CVD. As is known, for managing the overall burden of a disease, strategies to improve primary prevention should be aimed at. In case it is established that statins can prevent or delay CVS disorders in healthy individuals, it would not only reduce human misery but also will reduce costs of healthcare as treating heart disease is expensive, and in a developing country like ours often out of reach of the majority of the population. Several studies have been carried out to evaluate the cost effectiveness of low-cost generic statins available in

* *Corresponding author*. Tel.: +91 8390367279.
E-mail address: sougatray@hotmail.com (S. Ray).
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the market for primary prevention. Lawrence et al found that primary prevention with statins was cost-saving in different LDL cholesterol thresholds (@160, @130, and @100 mg/dL) and at different levels of cardiovascular risks. They observed that with wide availability of low-cost generics, primary prevention with statins might become less expensive and cost-effective for most persons with even moderate dyslipidemia or with any other lifestyle risk factors.[1] In this mini review, we have attempted to analyse the cost effectiveness of using statins as a primary prevention pharmacological agent vis-a-vis its use in secondary prevention, as cited by few of the systematic reviews of recent time.

Statins in secondary prevention

The first important secondary prevention statin trial was the Scandinavian Simvastatin Survival Study (4S Trial). This was essentially a double-blinded randomized control trial. In this study, 4444 patients of angina pectoris or with old MI and cholesterol in the range of 5.5–8.0 mmol/L, on a fat reducing diet, were treated either with simvastatin or placebo and followed up for a period of 5.4 years. The effects of Simvastatin on total cholesterol, LDL-C, and HDL-C were −25%, −35%, and +8% respectively, with few side effects.[2] Statins have since been found to be associated with significant reduction of cardiovascular morbidity and mortality as demonstrated in several secondary prevention trials like 4S, CARE, LIPID, AFCAPS, GREACE and HPS with different lipid lowering agents like atorvastatin, pravastatin, lovastatin and rosuvastatin. In recent times however, rosuvastatin has been found to be more effective and promising for reducing LDL-C levels and attaining the NCEP ATP III LDL-C goals than other statins.[3]

The secondary prevention theory of statins has also been proved by several meta-analyses hitherto. Law et al analysed three meta-analyses, first one, a 164 randomized placebo controlled trials of six statins and LDL cholesterol reduction; second one, 58 randomized trials of cholesterol lowering by any means and IHD events; and thirdly, 9 cohort studies and the same 58 trials on stroke. They observed that as LDL cholesterol concentration was reduced by an average of 1.8 mmol/L, the risk of heart diseases decreased by about 60% and stroke by 17%.[4] In another meta-analyses in 2012 with eleven trials representing 43,193 patients, overall statin therapy was associated with a reduced risk of cardiovascular events in women with (RR 0.81 [95% CI, 0.74–0.89]) and men with (RR 0.82 [95% CI, 0.78–0.85]). However, no reduction in all-cause mortality in women vs men (RR, 0.92 [95% CI, 0.76–1.13] vs RR, 0.79 [95% CI, 0.72–0.87]) or stroke (RR, 0.92 [95% CI, 0.76–1.10] vs RR, 0.81 [95% CI, 0.72–0.92]) was found.[5] These studies have thus proven to a certain extent that potent statin therapy can reduce disease progression, particularly in those with greater baseline coronary atherosclerosis.

Statins in primary prevention

Though statins are still approved for use in subjects with established coronary artery disease or at high-risk for coronary events, several studies have expanded the indications of treatment to include persons at progressively lower risk. The breakthrough was in 2008, when the results of the JUPITER (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) trial[6] showed that patients with high C reactive proteins might benefit from preventive statin administration, regardless of their LDL-C level. Treatment with Rosuvastatin 20 mg/d reduced the occurrence of any major cardiovascular events like myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes in apparently healthy individuals with low-density lipoprotein cholesterol (LDL-C) levels below 130 mg/dL, but with hs-CRP levels of 2 mg/L or more by 44% as compared with placebo. The study was closed after a median follow-up of 1.9 years (initially 5 years) because of these positive results.[6] In a meta-analysis in 2011 for efficacy of statins in primary prevention, comprising of 29 eligible trials involving a total of 80,711 participants, Tonelli et al[7] found that the all-cause mortality was significantly lower among patients receiving a statin than among controls (RR = 0.90, 95% CI 0.84–0.97) in trials with a 10-year risk of cardiovascular disease < 20% (primary analysis) and RR = 0.83, 95% CI 0.73–0.94, for trials with 10-year risk < 10% (sensitivity analysis). It was also observed that patients in the intervention group were also significantly less likely to have nonfatal myocardial infarction (RR 0.64, 95% CI 0.49–0.84) and nonfatal stroke (RR 0.81, 95% CI 0.68–0.96) than controls.

A Cochrane review[8] during the same time (2011) on the use of cholesterol-lowering statin drugs sparked some controversy. The authors found that out of fourteen randomized control trials (16 trial arms; 34,272 participants), eleven trials included patients with conditions like dyslipidemia, diabetes, hypertension and microalbuminuria. Mortality was reduced by statins (RR 0.84, 95% CI 0.73–0.96) than combined fatal and nonfatal CVD endpoints (RR 0.70, 95% CI 0.61–0.79). It is significant to mention here that there was no clear evidence of any side effects caused by statins. In another interesting study, Ray et al[9] undertook a meta-analysis of published clinical trials to assess whether statins reduce all-cause mortality in the setting of high-risk primary prevention populations and provided combined information from 11 randomized controlled trials (like JUPITER, ALLHAT, WOSCOPS, etc) involving a total of 65,229 participants. The authors observed that in high-risk primary prevention setting, use of statins was not associated with a statistically significant reduction (RR = 0.91; 95% CI, 0.83–1.01) in the risk of all-cause mortality.

The controversy – primary versus secondary prevention

Heneghan[10] in a Cochrane editorial commented that in majority of these trials, the power calculations were based on composite outcomes; in over one third of trials, outcomes were reported selectively and in eight trials, they did not report any adverse events at all. He also brought out that to date only one trial has been publicly funded, while the authors of nine trials reportedly have been sponsored either fully or partially by pharmaceutical companies. Thus the allegations that it is the pharmaceutical industry that is pushing for this drug to be used for primary prevention, to improve