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Contemporary Issue

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

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ARTICLE INFO

Article history:

Received 12 August 2012

Accepted 27 May 2013

Available online 30 August 2013

Keywords:

Statins

Primary prevention

Heart disease

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.

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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

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<http://dx.doi.org/10.1016/j.mjafi.2013.05.008>

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) trial⁶ 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 al⁷ 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 review⁸ 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 al⁹ 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

Heneghan¹⁰ 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

their fiscal health rather than public health, may be having some basis. The fear is definitely not unfounded considering the high cost of statins. So is use of statins a saviour or a spam?

The debate continues. To counter the above, a recent public funded meta-analysis (Lancet, May 2012) by Cholesterol Treatment Trialists (CTT) collaborators included data from 22 trials of statin vs control ($n = 134537$; mean LDL-C difference 1.08 mmol/L; median follow-up 4.8 years) and five trials of more vs less statin ($n = 39612$; difference 0.51 mmol/L; 5.1 years). The study observed that reduction of LDL cholesterol with a statin, reduced the risk of major cardiovascular events (RR 0.79, 95% CI 0.77–0.81, per 1.0 mmol/L LDL-C reduction), independent of age, sex, baseline LDL cholesterol or previous vascular disease. The CTT analysis predicts that six and 15 major vascular events would be avoided per 1000 people treated for 5 years in both the baseline risk categories, respectively, giving numbers needed to treat of 167 and 67. This benefit was significant and may be considered to be similar to treatment of mild hypertension.¹¹

The Cost Effectiveness of using statins for primary prevention

The controversy as to whether statins are cost-effective for patients at low cardiovascular disease risk and whether the LDL-C reduction of 1 mmol/L be sustained in routine primary care still remain to be solved. Another systematic review in 2013,¹² to assess the effects of statins in primary prevention of CVD, found that out of 1000 people treated with a statin for 5 years, 18 avoided a major CVD and the findings were comparable with other modalities of treatment and with other primary prevention trials. They also observed that statins did not increase the risk of serious side effects and recommended that statins may be cost-effective in primary prevention.

A relatively newer concept is that of Coronary Artery Calcification (CAC) quantification, which is being used as a surrogate for coronary events, and it is believed that CAC

progression, rather than baseline CAC correlates with worsening atherosclerosis. However most of the clinical studies have shown that there was a non-significant increase in percentage CAC progression with the use of statins, despite a significant reduction in low-density lipoprotein cholesterol (LDL-C) and CRP levels.¹³

Beneficence vs harm

The pleiotropic effects of statins, observed in several studies during treatment of cardiovascular disease, should also deserve a mention. Statins, as we know, act through both cholesterol-dependent and cholesterol-independent pathways. Some of these effects involve improving endothelial function, enhancing the stability of atherosclerotic plaques, decreasing oxidative stress and inflammation, and inhibiting the thrombogenic response^{14–16} as depicted in Table 1. Pleiotropic effects have also been observed in Alzheimer's disease and osteoporosis^{17–19} and recently in 2013, a study found significant preventive association with Prostate Cancer-specific mortality (PCSM) in a prospective, population-based cohort study.²⁰

Though the safety and tolerability of statins support their use as first-line treatment for hypercholesterolemia, myopathy and its serious complication, rhabdomyolysis, are known potential side effects of therapy with the available statins.²¹ Again, the dose dependent association of different statins and new onset diabetes in a recent²² meta-analysis is a cause for concern and needs to be treated with caution and further investigated.

Conclusion

A wealth of data thus demonstrates that reduction of cholesterol levels is associated with reduction of coronary artery disease risk and the magnitude of the benefit, acting primarily by reducing LDL-C, is greater than that observed with any other lipid-modifying intervention. The recent Cochrane review of statin use for primary prevention supports the conclusion that statins are safe and effective in reducing vascular events and overall mortality even in primary prevention. The benefits were found to be statistically small, which is expected for a preventive measure in a low risk population. It is thus still unclear where to draw the line in terms of which kind of patients should receive statins, but these data will help practitioners and patients make individualized decisions about cholesterol management and vascular prophylaxis.

Statin therapy for primary prevention thus will depend on the balance between the benefits of treatment and its long-term safety and cost. With increasing number of Indians in the younger age group and not necessarily from the higher income group being diagnosed with heart disease, it is time that the medical community evolves a consensus on the subject. The present guidelines on LDL lowering statin therapy might be required to be reconsidered in view of the recent developments. However, till then, lifestyle counselling should remain the focus of primary prevention efforts.

Table 1 – Pleiotropic effects of statins.

Action of statin	Effect
Improve endothelial dysfunction	Prevents Atherosclerosis
Increase myocardial perfusion	Vasodilatation
Prevent downregulation of endothelial nitric oxide synthase (eNOS)	Increased bioavailability of nitric oxide, as antioxidant
Reduction of serum CRP	Antiinflammatory effects
Reduce adhesion and chemotactic molecules, plaque stabilization	Antiinflammatory effects
Decrease interferon-induced major histocompatibility complex-II	Immunomodulatory effects
Induce apoptosis in cancer cell lines in vitro	Prevents Colorectal cancer

Conflicts of interest

All authors have none to declare.

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