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STATINS FOR ALL -TRUTH OR HYPE

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ABSTRACT

Rapid advances have been witnessed in the understanding and management of dyslipidemia which has led to widespread use of statins. Statins have been proved to be beneficial in primary prevention of cardiovascular diseases and in secondary prevention of cardiovascular diseases and stroke. Preliminary studies have also documented benefit of statins in lipid independent conditions. The rate of occurrence of adverse events determines the risk benefit ratio of statins in low risk individuals. Hence, the irrational overuse of statins is a matter of concern. Statins for all will be a reality only if backed by clinical reasoning and quality evidence.

KEYWORDS

Statins; Primary prevention; Cardiovascular diseases.

INTRODUCTION

In the last decade, rapid advances in understanding and management of dyslipidemiahas led to irrational use of statins, which is a matter of concern. "Statins for all - truthor hype", is a topic for debate. Clinicians should identify cardiovascular risk factors, calculate the risk of a cardiovascular event, enforce life style changes and then initiate or intensify statins rather than starting statins for all.

History and growth of statin

The search for cholesterol lowering drug dates back to 1971 when efforts of Akira Endo, a Japanese biochemist led to the identification of a molecule mevastatin (ML-236 B) from the fungus Penicilliumcitrinum which had HMG CoA reductase inhibition property. The same compound had been isolated in 1976 from Penicilliumbrevicompactum, named compactin. It was identified as antifungal but its HMG CoA reductase inhibitor property was not realised. Due to adverse effects and mortality in experimental animals, Mevastatin could not clear clinical trials and was never marketed. P Roy Vageloscontinued the search and finally succeeded in isolating lovastatin (mevinolin, MK 803) in 1978 from Aspergillusterreus and it was the first statin to be marked in 1987 as mevacor.

With establishing of lipid hypothesis which clearly defined the relation between cholesterol and cardiovascular disease(CVD), growing public awareness regarding good and bad cholesterol and the building confidence among doctors that statins were effective in preventing cardiovascular disease led to many pharmaceutical companies manufacturing, marketing and promoting their own statins like simvastatin, atorvastatin, cerivastatin , pravastatin, rosuvastatin, fluvastatin and pitavastatin. Cerivastatin was very potentbut was withdrawn form market in August 2001 due to risk of serious rhabdomyolysis. Some naturally occurring statins are found in oyster mushroom and red yeast rice[1] but their efficacy needs to be scientifically proved.

Mechanism of action

Statins are lipid lowering drugs which act by inhibiting the hepatic conversion of HMG – CoA to L - mevalonate by inhibiting the enzyme HMG CoA reductase thereby preventing subsequent cholesterol,

ubiquinone and dolichol dependents effects. It also reduces low density lipoprotein (LDL), plasma triglycerides and apolipoprotein B. There is some evidence that it increases high density lipoprotein. [2].

Statins have action apart from lipid lowering activity in the prevention of atherosclerosis. There is evidence to show that statins prevent cardiovascular disease by improving endothelial function, modulating inflammatory response, maintaining plaque stability and preventing thrombus formation. Statins anti-inflammatory properties is exemplified by reduced plasma concentrations of the inflammatory cytokines like Tumour Necrosis Factor á and Interleukin 6.There is considerable evidence that statins may activate endothelial nitric oxide synthase (eNOS) but there is limited evidence of its effect on inducible nitric oxide synthase (iNOS). Further studies are required to establish the interplay between statins and free radical formation and their potential role in sepsis.

Statins and primary prevention of cardiovascular disease (CVD)

A literature based meta-analysis of randomised controlled trials including 65,229 participants observed that statin therapy for an average period of 3.7 years had no benefit on all-cause mortality in a high – risk primary prevention population.[3] However, methodological deficiencies were a limitation as it was a retrospective research. Heterogeneity in demographic and clinical characteristics of subjects enrolled,the type, dose and duration of statin used and bias in reporting adverse events was also a factor to influence the conclusion.

Effectiveness of statins in primary prevention of CVD has been evidenced and most guidelines recommend statin use for high risk subjects in reducing fatal and non-fatal vascular events. Baseline estimated cardiovascular score and LDL thresholds are taken as indicators for initiating statin therapy for primary prevention by various societies including European Society of Cardiology and European Atherosclerosis society. Adults with LDL cholesterol greater than 190mg/dl are recommended for primary prevention by American College of Cardiology and American Heart Association . Adults with an estimated 10 years risk of developing CVD of 10% or more should be initiated on statin therapy, as recommended in the draft guidance of National Institute for Health and Clinical Excellence (NICE) 2014.[4]

Society of General Internal Medicine in its meeting in April 2014 discussed a study which made the observation that patients on statins for dyslipidemia did not adhere to life style modifications. They consumed more fat and calories and did less physical activity as compared to non-statin users. Clinical practice guidelines also recommend lifestyle modification before initiating statin therapy as it would also offset the risk of developing diabetes mellitus. The drug lifestyle interaction maybe the explanation as to why the striking reductions upto 30% to 50% in LDL cholesterol does not translate to proportionate health benefits.

Statins and secondary prevention

The effect of statins in lowering LDL – cholesterol (LDL-c) and associated cardiovascular risk has been proved beyond doubt in both sexes and across all age groups. Use of statin has been associated with reduction in myocardial infarction (fatal and non-fatal), unstable angina and ischemic stroke in patients with CVD , Acute coronary syndrome, diabetes mellitus(DM), hypertension, metabolic syndrome or previous history of ischemic strokes.

Statins can reduce LDL-c by 70mg/dl (1.8 mmol/L) which can lead to an estimated 17% reduced risk of stroke and 60% reduction in cardiac events[5] along with decreased revascularisation procedures. National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) recommends a target of LDL <100mg/dl for those with 10 years CVD risk>20%, DM or clinical CVD. NCEP-ATP 2004 report set the LDL goal to<70mg/dl for those with established CVD and additional risk factors (risk factors for Metabolic Syndrome, CVD and DM). Guidelines from most of the cardiological societies recommend statin use for secondary prevention and are backed by evidence from randomised controlled trials.

Statins in NAFLD and NASH

Non-alcoholic fatty liver disease (NAFLD) can progress to non-alcoholic steato hepatitis (NASH). Statin use in NASH has been associated with reduction in aminotransferases in small studies but failed to show benefit in improving liver histology and reducing morbidity. Statins can be used to control hyperlipidemia which is frequently associated with NASH but its role as a therapy for NAFLD and /or NASH by itself is doubtful and warrants further research.

Statins in perioperative care

Beneficial effect of statins in preventing cardiac complications in non-cardiac surgery during perioperative period[6] and reducing risk of stroke in 'at risk' patients[7] has been reasonably proved but evidence from prospective randomised studies is required before advocating routine use of statins for perioperative cardiovascular risk reduction. Which statin, in what dose and for how long should be used also needs to be answered. However there is convincing evidence that patients already on statins should continue in perioperative period as it has better outcome. Sudden cessation of use is associated with increased morbidity and mortality[8].

Other uses of statins

Apart from its lipid lowering effect, statins also exhibit anti-inflammatory and pleiotropic effects and this has been explored in various diseases. There is evidence to show beneficial effects of statins on lipid independent conditions such as decreasing mortality rates in sepsis, rate of renal damage in diabetes mellitus, incidence & progression of dementia and Alzheimer's disease, rejection rates in organ transplantation, incidence of esophageal, gastric, colorectal and hepatocellular carcinoma, the risk of macular degeneration, inflammatory bowel disease and osteoporosis and reducing activity in rheumatoid arthritis. But as of now, statin use is not recommended for these indications and further prospective trials are required.

Side effects

Undoubtedly statins have obvious beneficial effects but they also have a number of side effects which cannot be ignored. The most severe side effects include extreme muscle pain, myopathy, rhabdomyolysis, increase in liver transaminases.The addition of a fibrate or niacin to statins further increases the risk of rhabdomyolysis. Increase in the risk of a haemorrhagic stroke [9] and diabetes mellitus has also been reported.[10] Other rare side effects include neuropathy, cognitive decline, pancreatic & sexual dysfunction.The rate of occurrence of adverse events determines the risk benefit ratio of statins in low risk population and is the reason forextensive debate on the incidence of side effects.

Beneficial effects of cholesterol

Cholesterol has always been addressed to as the culprit for all that is related to atherosclerosis & heart disease. But this is not the whole truth. Cholesterol has beneficial effect in regulating cell membrane permeability & fluidity. It is a precursor molecule for synthesis of vitamin D, steroid hormones and sex hormones. Thus statin also effect the synthesis of other molecules that have a beneficial effect in atherosclerosis & CVD. A question which needs to be answered is that whether cholesterol lowering is a double edged sword. Whereby on one hand CVD risk is being reduced but on the other hand inhibition of other by products from HMG CoA reductase pathway may increase CVD risk.

Future of statins

Nitric oxide releasing statins like nitro pravastatin[11] and nitro atorvastatin[12] are being researched. Improved vascular function and enhanced ability to decrease iNOS expression in LPS treated macrophages was observed. This effect could be beneficial in preventing endothelial damage in sepsis and is worthy of long term research.

CONCLUSION

Use of statins in low risk individuals would unnecessarily increase adverse effects without overall health benefit. Hence, statins for all is a truth only when backed by clinical reasoning and good

quality evidence.

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