

Statin use in primary prevention of coronary heart disease: Issues and perspectives

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ABSTRACT

Results from clinical trials have conclusively shown that statins lower the risk of morbidity and mortality associated with cardiovascular disease. It has been argued that access to low-dose non-prescription statin therapy may complement life-style changes in modifying risk profile of individuals to coronary heart disease (CHD). A major statin trial confirmed that primary prevention was clinically feasible in a lower intermediate-risk population, benefit being consistent across the range of baseline LDL cholesterol quartiles. However, there are constraints limiting the advocacy for use of OTC statins in primary prevention of CHD. It is generally acknowledged that although statins may be great prescription drugs, they are certainly not very suitable as OTC for primary prevention of CHD. The conditions for which statins are indicated are usually not self-diagnosable. OTC drugs are generally indicated for relief of symptoms and not for prevention. Notwithstanding, the prospects of statins in attaining non-prescription OTC status still remain promising. The need for enlightenment and education of the general public, particularly the population at risk, on the adverse effects and benefits of statin use can never be over-emphasized.

Key words: Coronary Heart Disease (CHD), Over-the-Counter(OTC),
Primary Prevention, Statins.

INTRODUCTION

Clinical trials have demonstrated a marked reduction in cardiovascular mortality in patients treated with statins. Extensive research has suggested that instead of an improvement in endothelial function¹; the clinical benefit of statins could be related to a reduction in blood thrombogenicity and anti-inflammatory properties².

The introduction of low dose simvastatin in the United Kingdom as OTC statin in 2004, radically shifted the landscape of what kind of drugs may be considered candidates for OTC statins³. The United States Food and Drug Administration (FDA) later convened a panel to review evidence for possible consideration of a non-prescription preparation of lovastatin for approval as OTC statin; but the panel recommended against its approval⁴.

A recent study suggested that understanding the differences in the pharmacokinetics and interaction potentials of various statins could help in the selection and consideration for possible OTC status⁵. Non-prescription OTC statins, nevertheless, have assumed significance as subject of debate for the future of cardiovascular risk prevention⁶.

Proposition for statin USE

A study has recommended routine lipid lowering drug therapy in the free living population for individuals at increased risk of CHD⁷. It further revealed that a descriptive data on the ratio LDL-C to HDL-C in the free living population would be invaluable asset to clinicians and researchers in predicting the risk of atherosclerosis. Another study suggested routine screening of lipid profile in the general population to identify individuals with abnormal lipid profile at increased risk of CHD, who

may benefit from lipid lowering drug therapy⁸. The same study revealed a rise in lipid profile in the ratio TC/HDL-C in both sexes varying with age.

Primary prevention trials have affirmed that low to moderate risk patients have coronary benefit with statin treatment, and the safety profile of available agents suggests a low risk for adverse side effects⁹. Access to low-dose over-the-counter (OTC) statins may help complement life style to modify the risk profile, in the group of patients at intermediate coronary risk. High risk patients or those who may be more susceptible to toxicity should not be considered candidates for OTC therapy.

Therapeutic lifestyle changes alone frequently do not help patients at risk achieve target cholesterol values. Patients ideally suited for statin therapy in primary prevention under the Third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program, were those with multiple (≥ 2) risk factors, a 10-year CHD risk of 20% or lower, no contraindications to use of statins and a favorable likelihood of having benefit versus risk. Individuals with an intermediate risk for near-term CHD have a goal of LDL cholesterol lower than 3.36mmol/L (130mg/dL)¹⁰.

The Airforce/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAP) was the first major statin trial to confirm that primary prevention was clinically feasible in a lower intermediate-risk population, and benefit was consistent across the range of baseline LDL cholesterol quartiles. The 5.6% of 10 year CHD event rate in the placebo-treated group from AFCAPS/TexCAPS was significantly lower than any treatment threshold currently recommended for lipid-lowering drugs in the context of primary prevention¹¹. AFCAPS/TexCAPS, unlike other primary prevention studies, permitted drug titration. Lovastatin was begun at 20mg/d and was then titrated at week 18 to 40mg/d if an LDL cholesterol target goal of 110mg/dl was not attained. Eight-one percent (81%) of the group randomized to lovastatin reached the ATP III target goal of 130mg/dl (3.36mmol/L) as compared with 12% of the patients receiving placebo. Therapy with lovastatin resulted in a statistically significant 37% reduction in the rate of first acute coronary events, after a median of 5.2 years defined as a

composite endpoint including fatal or non-fatal myocardial infarction, unstable angina and sudden cardiac death incidence.

There was no increase in non-cardiac mortality rate with statin therapy and the discontinuation rate was similar in the placebo and statin-treated groups. The investigators reported no significant liver toxicity¹². A retrospective analysis detected no greater risk over a 6 month period for statin-related hepatotoxicity among treated individuals with elevated baseline liver enzyme levels compared with untreated individuals¹³. The risk for myopathy or hepatotoxicity with the currently approved statins does not exceed the potential benefit of preventing coronary and other cardiovascular events, although the real incidence of statin side effects may be higher in clinical situations in which patients are not selected or monitored closely as they are in clinical trials¹⁴.

The consumer use study of over-the-counter lovastatin (CUSTOM) was an open-label, uncontrolled, multicenter study that examined the behaviour of potential over-the-counter purchasers intended to stimulate a real-world pharmacy setting¹⁵. The materials developed for the study's self-management system (SMS) focused on describing a primary prevention of coronary heart disease in the intermediate-risk population and encouraged participants to discuss their concerns about cholesterol; including OTC statin treatment with their physicians. An overall 20% decrease in LDL cholesterol was achieved. Participants reported that they would have found more information on drug interactions useful and approximately 25% of participants did not undergo lipid testing before OTC statin use.

It is important to note that CHD risk falls along a continuum and no cholesterol threshold has been identified below which there is no further benefit of treatment. Consequently, the coronary risk of an individual whose LDL cholesterol level marginally differs from another, may not be appreciably different, all other risk factors assumed to be same. It is therefore, reasonable to expect some degree of flexibility in these marginal cases when determining the appropriateness of OTC statins.

Constraints in the use of OTC statins

Notwithstanding the promising prospects of statins for primary prevention of CHD, considering their substantial efficacy and relatively low toxicity there are still enormous challenges to contend with. It is generally posited that drugs that qualify for the switch to OTC are intended for symptom control rather than disease prevention¹⁶. It has been suggested, that although statins are great prescription drugs they would make poor OTC drugs for primary prevention of CHD. Concerns have been expressed that unlike the indications for virtually all other OTC drugs, the condition being treated is not self-diagnosable; efficacy is dose-related and requires monitoring for titration, which is optional for OTC use; the lower dose proposed for OTC availability, primarily to increase the margin of safety could prevent more appropriate dosing; the efficacy of statins for a self-diagnosed condition has never been clearly demonstrated; complications and contraindications of statins are not self-diagnosable; and adherence which is notoriously poor in long-term prescription drug therapy is likely to be even worse for an OTC drug.

It must be stressed that primary prevention carries with it a particular responsibility, that is, the need to be extra careful in minimizing potential harm. The ethical issue involved is analogous to that of screening for purpose of primary prevention. Individuals who undergo such screening are asymptomatic, and most will not have the disease for which they are being screened. The efficacy of statins in preventing cardiovascular events; in terms of absolute risk reduction or number needed to treat (NNT) would almost certainly be considerably less under OTC use, primarily because baseline risk is likely to be lower in an OTC population. The efficacy of primary prevention with statins estimated from AFCAPS/TexCAPS to be an NNT of about 35 patients treated for 6 years to prevent one cardiovascular event, melts way under conditions of OTC use. Consequently, it has been argued that approving statins for OTC primary prevention would amount to a high uncontrolled experiment in which neither the benefit nor the risk side of the equation is known. Moreover, it has been shown, that the ability to collect good clinical data to fill in the gaps in our knowledge would be even worse under conditions of OTC use than it is under prescription

¹⁷. It must be emphasized that the benefits of statins may be delayed; and OTC statin users would therefore, need to understand that although the benefits may be significant and quantifiable across an entire population, the benefit to any single user may be uncertain or in fact, merely statistical¹⁸. Again, there is need to understand that a variety of factors can affect the degree of benefits and that when and if they occur, are manifest only after about 2 years of continuous use. The cost of primary prevention of CHD with statin use, which may not be considered by regulatory agencies due to their paternalistic role need to be critically examined. The issue here is not pure cost; but the cost of primary prevention with OTC statins in relation to its clinical value and the cost effectiveness of that intervention in relation to that of other medical interventions. A study revealed that under the conditions of prescription use at the time, the cost-effectiveness ratio for primary prevention with statin ranged from \$ 54,000 to \$ 400,000 per quality-adjusted life year¹⁹.

It has been argued that single-dose OTC product may delay the introduction of drug titration or combination therapy to patients who warrant it. Thus, patients might be tempted to misuse the product either because they are at high risk and wish to bypass a doctor's care or because they are at low risk but have decided to incur the expense of long-term treatment that has an unfavorable cost/benefit ratio¹⁷. The approval of non-prescription statin may prompt prescription drug benefit managers and managed care organizations to take steps to limit usage of prescription statins to control drug benefit costs. It has been suggested that there would continue to be a commitment, in principle, to support access to prescription strength statins if an OTC version was approved; but this would certainly warrant a review of co-payment levels and formularies to optimize the entire class²⁰. Presently, proponents of non-prescription statins would require a major breakthrough to overcome the stalemate over consideration and approval of OTC statin use. A study has suggested that a change in the law that facilitates behind-the-counter pharmacy services, a more convincing use study that addresses the concerns raised by CUSTOM or data that demonstrate the public health benefit of OTC statin access could provide the much needed impetus²¹.

CONCLUSION

The prospects of statins in being widely accepted and attaining non-prescription OTC status appear quite promising. This is in view of its undisputed role as a cardio-protective drug in

reducing morbidity and mortality associated with CHD. However, there is need for extensive public enlightenment and advocacy on the risks and benefits associated with statin use as OTC, particularly in making informed choice and patient selection.

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