Who should receive a statin drug to lower cardiovascular risk? Does the drug and the dose of the drug matter?

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Abstract: As the numbers of completed outcomes based clinical trials evaluating the use of statin drugs for the management of cardiovascular risk continue to increase, it is clear that the numbers of patients that may benefit from these drugs continues to grow. The recently published studies are reviewed in this summary. The distinction is made between patients requiring either primary or secondary cardiovascular preventive management. The review identifies the increasing numbers of patients who may benefit from the use of statins as primary preventive management, and the changing concepts of the utilization of statin drugs for secondary preventive management, including the more aggressive titration of the drugs to provide incremental improvement in patient outcomes. Available data on the use of statins in the elderly patient are reviewed, and observations are made regarding the intrinsic properties and adverse effects of the drugs.

Keywords: cardiovascular risk, statins, elderly patient.

The management of cholesterol levels in individuals with or without documented coronary artery disease continues to be modified as more outcomes based research directed at such individuals is published (Nixon 2004). These trials and studies expand the profile of the individual or the patient that may potentially benefit from the use of a statin drug as primary and secondary preventive care in the reduction of their cardiovascular risk and the consequent improvement in their prognosis.

General principles of cardiovascular risk management

The management of cholesterol must be placed in the context of the importance of managing and modifying all cardiovascular risk factors, including obesity and diet, lack of exercise, and cigarette smoking, risk factors exclusively under the control of the individual patient. Life style modification, diet, and exercise are essential components of the management of cardiovascular disease, irrespective of age or gender, and thus must be emphasized during discussions of patient management. Well-balanced and prolonged dietary programs, regularly maintained exercise programs and cessation of cigarette smoking are all critical components of the patient's ongoing care. These principles have been reinforced in the recently published extension to the National Cholesterol Education Program guidelines on detection, evaluation and treatment of high blood cholesterol in adults (NCEP Expert Panel 2001; Grundy et al 2004).

Preventive management utilizing statin therapy

Reduction of cardiovascular risk of death and/or cardiovascular events in any given patient may be divided into primary and secondary prevention (Knopp 1999). Primary prevention incorporates people or patients without a diagnosis of coronary artery disease and/or who have not suffered an acute cardiovascular event. Secondary prevention involves patients who have a diagnosis of coronary disease (confirmed by the documentation of a prior acute cardiac event, coronary disease identified during cardiac

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catheterization, or a positive stress or stress imaging study) or who have recently suffered an acute cardiac event or acute coronary syndrome. The recently published outcomes based research trials using statins as treatment for the reduction of cardiovascular risk and/or cardiovascular events will be reviewed under these respective definitions.

Primary prevention

Studies have documented the value of statin drugs for primary preventive care to lower cardiovascular risk. The West of Scotland Coronary Prevention Study (WOSCOPS), considered the pioneer study, was a randomized double blind primary prevention study that showed that the administration of pravastatin in 6595 men aged 45 to 64 years with cholesterol levels greater than 6.23 mmol/L significantly reduced cardiovascular mortality and morbidity in the treatment group during a follow up period of almost 5 years (Shepherd et al 1995a). A similar study, the Air Force/Texas Coronary Atherosclerosis Prevention trial (AFCAPS/TexCAPS), included both men and women with elevated cholesterol levels and utilized another statin drug, lovastatin (Downs et al 1998). This study found similar results, a significant reduction in cardiovascular mortality and morbidity in the treatment group.

Recently an attempt has been made to address the management of an individual with multiple cardiovascular risk factors and a cholesterol level below what is currently considered to be an indication for statin therapy. The lipid arm of the Anglo-Scandinavian Cardiac Outcomes Trial— Lipid Lowering Arm (ASCOT-LLA) trial has followed 10 305 individuals with hypertension and three other cardiovascular risk factors, but not a prior acute cardiac event, and total cholesterol levels of less than 6.49 mmol/L, randomized to atorvastatin 10 mg or a placebo (Sever et al 2003). In a prematurely terminated follow up period of 3.3 years, individuals randomized to the treatment group had a significantly lower incidence of acute cardiac events.

These data on individuals at a high cardiovascular risk with borderline cholesterol levels have been reinforced by the Atorvastatin Cardiac Outcomes Trial (CARDS) (Colhoun et al 2004). In this outcomes-based trial, 2838 type II diabetic patients, none of who had suffered an acute cardiac event, and all of who had LDL levels less than 4.16 mmol/L, were randomized to atorvastatin 10 mg or a placebo. Again, in a prematurely terminated follow up period of almost four years, those randomized to the treatment group had a significantly lower incidence of cardiovascular events. The subsequent publication of the extension to the NCEP-ATPIII guidelines which now confirms diabetes mellitus patients as individuals at high cardiovascular risk and thus falling into a secondary cardiovascular prevention category probably renders the findings of CARDS as superfluous (Grundy et al 2004). However, because it preceded the release of the extension to the guidelines, it assists in their validation.

It is reasonable to conclude, as a result of these studies, that individuals should be routinely surveyed for an elevated cholesterol level, particularly if other cardiovascular risk factors are present, and if found such patients should be commenced on a statin drug. Furthermore, individuals with several cardiovascular risk factors and a normal or minimally elevated cholesterol level should also be commenced on statin therapy, a concept reinforced by recently published trials data. The numbers of individuals or patients now being considered for statin therapy for primary cardiovascular prevention are gradually increasing with an increasing understanding of the individuals' cardiovascular risk and how this risk may be reduced.

Secondary Prevention

There are numerous outcomes based clinical studies that have confirmed the value of secondary prevention using statins in patients with documented coronary artery disease or who have suffered an acute cardiovascular event (Four S Group 1994; Sacks et al 1996; HPS Group 2002; Pitt et al 1999; Reigger et al 1999; Farnier et al 2000; Schwartz et al 2001; Athyros et al 2002). The Scandinavian Simvastatin Survival Study (4S) randomized 4444 patients with elevated cholesterol levels to the statin drug simvastatin, average dose 26 mg (qd), or a placebo, and documented the prognostic benefits of the statin drug in the treatment group (Four S Group 1994). The Cholesterol and Recurrent Events Trial (CARE) showed similar results in 4159 patients with normal cholesterol levels at the time of entry to the study, utilizing pravastatin 40 mg (qd) in the treatment arm of the study (Sacks et al 1996). Confirmation of the concept of treating a patient with coronary disease and normal cholesterol with a preventative statin drug has been provided by the recently published Heart Protection Study (HPS), which randomized 20 536 patients with normal cholesterol levels, the majority of which fell into the secondary prevention category, and utilized simvastatin 40 mg (qd) in the treatment arm of the study, with identical results (HPS Group 2002).

Several other trials, utilizing maximal available or appropriate doses of atorvastatin and fluvastatin, have provided

similar conclusions regarding the reduction in cardiovascular risk, confirming the concept that the capability of these statin drugs to reduce cardiovascular mortality and the incidence of cardiac events appeared to be a class effect of these medications (Pitt et al 1999; Reigger et al 1999; Farnier et al 2000; Schwartz et al 2001; Athyros et al 2002). Furthermore, the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study (MIRACL) showed clearly that these medications may be commenced promptly following the patient's acute cardiac event (Schwartz et al 2001). In the MIRACL study, 3086 patients admitted with an acute cardiac event were randomized within 24 to 96 hours of their event, to atorvastatin 80 mg (qd) or a placebo for 16 weeks. The composite endpoint of mortality, nonfatal myocardial infarction and unstable angina was significantly lower in the treatment group.

All the trials addressing the issue of secondary prevention of cardiovascular mortality and morbidity using statin therapy indicate that standard management of cardiovascular risk in a patient with coronary artery disease or one who has suffered an acute cardiac event incorporates the use of a statin drug as an integral part of their continuing care, irrespective of the cholesterol level of the individual patient (Grundy 1998; Gould et al 1998). Most recently the issues of dose and even selection of statin drug have been raised by the outcomes based studies addressing differing statin drugs at varying doses or equivalent doses that have been recently published. These issues are addressed subsequently in this review.

Guidelines for management, choices of statins, and doses of statins

Guidelines have been provided by expert peers for the lipid management of the cardiovascular patient. The report of the National Cholesterol Education Program Expert Panel provided these guidelines (NCEP Expert Panel 2001). Furthermore, these guidelines have recently been extended and clarified to include the diabetic patient and the elderly patient, as well as lowering the targets for low-density lipoprotein (LDL) for high risk and very high risk patients (Grundy et al 2004). The revisions of the guidelines have encouraged the use of methods of general cardiovascular risk factor scoring, in particular to identify the individual with multiple cardiovascular risk factors who still falls into the category of primary prevention. Such an evaluation includes screening for obesity, lack of exercise, cigarette smoking, hypertension, and diabetes mellitus.

It is also clear that all the currently available statin drugs are not capable of achieving the LDL targets provided in the NCEP guidelines. Several studies have addressed this issue. The CURVES trial has addressed the issue of the capability of five of the currently available statins to lower LDL levels, showing that atorvastatin has the greatest capability followed by simvastatin (Jones et al 1998). The STELLAR trial showed similar capabilities when comparing LDL lowering with rosuvastatin, atorvastatin, simvastatin, and pravastatin (Jones et al 2003).

Until recently, secondary preventive management utilizing a statin required merely the selection of the drug and ensuring that the patient would take the drug for the rest of their life. In patients at very high risk, it is now recommended that the dose of the selected statin be titrated to an LDL level of less than 70 mg/dL (Grundy et al 2004). The retrospective analysis of the HPS patients with LDL levels of less than 2.6 mmol/L showed that patients randomized to the treatment group had improved outcomes compared to those randomized to the placebo group (HPS Group 2002). Aggressively titrating patients appeared to improve outcomes. This concept of higher doses of more efficacious statins providing incrementally increased benefit is illustrated by the Pravastatin or Atorvastatin Evaluation and Infection Therapy––Thrombolysis in Myocardial Infarction 22 (PROVE IT- TIMI 22) (Cannon et al 2004). The trial involved 4162 patients hospitalized for an acute coronary syndrome randomized to pravastatin 40 mg or atorvastatin 80 mg and followed for cardiovascular outcomes for a mean of 24 months. The study showed that the more efficacious dose of atorvastatin was associated with a greater reduction in cardiovascular events than the less effective dose of pravastatin. The subsequent extension to the guidelines for the secondary prevention of cardiovascular risk consolidated the recommendation that the aggressive lowering of LDL levels by higher doses of the more efficacious statin drugs provides incrementally increased prognostic benefit to the patient. This has been further fortified by the publication of the REVERSAL study, where patients placed on the more efficacious dose of atorvastatin 80 mg arrested the progression of ultrasonically documented coronary artery disease compared with those placed on the less effective dose of pravastatin 40 mg, where the disease was shown to continue to progress (Nissen et al 2004a). These findings have been recently reaffirmed in the ASTEROID trial with similar ultrasonic parameters utilizing rosuvastatin (Nissen 2006).

The concept of class effect of statins regarding the secondary preventive management of cardiovascular risk has existed for several years and has been supported by multiple outcomes based secondary prevention trials providing similar

results utilizing all the available statin drugs except rosuvastatin (Nixon 2004). These patients clearly appear to benefit from early commencement of therapy as well as the incremental titration of the dose of the statin drug to the highest necessary or the highest tolerated dose determined by the level of LDL. Recent outcomes based trials have suggested that some statins may provide even greater benefit by the utilization of their pleotropic effects. This issue has come under consideration with the recent publication of phase Z of the A to Z trial (de Lemos et al 2004). This study of 4497 acute coronary syndrome patients randomized to simvastatin, first 40 mg and then 80 mg, or to a control group initially given a placebo and subsequently simvastatin 20 mg, had patients followed for cardiovascular outcomes for up to 24 months. The study showed trends but no significant differences in outcomes between the two groups, a different finding compared with the PROVE IT study (Cannon et al 2004). It has been suggested that the substantial differences in C reactive protein levels between the two treatment groups in these studies may be an explanation for the variant findings (Nissen 2004b). The respective C reactive protein differentials were 38% in the PROVE IT trial and 17% in the A to Z trial (Cannon et al 2004; de Lemos et al 2004). While these differences may suggest that the varying pleotropic effects of different stains may, in addition to their LDL lowering capability, influence the individual statin drug's capacity for lowering cardiovascular risk in patients requiring secondary preventive management, this issue at present remains unresolved until further studies elucidating these differences are completed.

Preventive management in the elderly

For several years questions have been asked as to whether there should be an upper age limit for preventative management of cardiovascular disease, in particular regarding the use of statin therapy in an older age population (Grundy et al 1999). Mortality and morbidity of cardiovascular disease is more prevalent over 65 years in a numerically growing population, accounting for 35% of all deaths in this age group, at substantial financial cost. These questions are fortified by the fact that many outcomes based clinical trials have upper age cut-offs of 65–70 years. Among the primary prevention data using statin drugs, WOSCOPS had an upper age cut-off of 65 years (Shepherd et al 1995a). In the AFCAPS/TexCAPS study, approximately one quarter of the randomized subjects were over 65 years (Whitney et al 1998). No significant differences in endpoints were found when these subjects were analyzed separately.

Several observational studies have addressed the association between age, cholesterol levels and mortality in an older population. The Framingham Study, the Epidemiological Study of the Elderly and the Honolulu Heart program have shown that, in the average population over the age of 70 years, there appears to be no statistical relationship between age, cholesterol, and mortality (Kronmal et al 1993; Krumholz et al 1994; Schatz et al 2001). Furthermore, a recent review of individuals 85 years and older showed increased cholesterol levels were associated with longevity, and adjustments for age, gender, and cardiovascular risk factors failed to influence these findings (Weverling-Rijnsburger 1997).

Secondary prevention of cardiovascular mortality and morbidity using statin drugs in this age population, however, has been addressed in several of the outcomes based trials. In the 4S, CARE and the Heart Protection Study, the significant differences in the trial between the treatment and the placebo groups persisted in the older populations in the studies (Miettinen et al 1997; Lewis et al 1998; HPS Group 2002). The Prospective Study of Pravastatin in the Elderly at Risk trial (PROSPER), an outcomes based prospective study of 5804 individuals aged 70–82 years randomized to pravastatin or a placebo, showed a significant reduction in the secondary endpoints of coronary heart disease death or nonfatal myocardial infarction but not fatal and non-fatal stroke in the treatment group compared with the placebo group after an average follow up of 3.2 years (Shepherd et al 2002).

It is reasonable to conclude that over the age of 70 years, statin drug utilization for the reduction of cardiovascular mortality and morbidity risk should be confined to the patient population who have a diagnosis of coronary disease or who have had an acute cardiac event, which is as secondary preventative therapy. Primary preventative therapy with statins does not appear to be indicated in this age group. These recommendations are now part of the extension to the guidelines that were published recently (Grundy et al 2004).

Statins: properties and adverse effects

Statin drugs are efficacious and safe, as has been confirmed by the very low incidence of adverse effects in the many large clinical trials already completed. Older individuals are more likely to have side-effects of all therapies, including statins (Gaist et al 2001). Adverse effects do not appear to be dose related in all statins. They do, however, appear more frequently in association with combination therapy, including with niacin and fibrates (Shepherd et al 1995b). Because most

statins utilize the cytochrome P450 3A4 metabolic pathway, drugs inhibiting this pathway may potentially increase the incidence of the adverse effects of the statins (Gruer et al 1999). This may apply particularly to other cardiovascular drugs the patient may be taking. The most common complaints are non-specific muscular aches and pains, without associated muscle or hepatic enzyme changes, occurring in 3%–8% of patients. Elevated hepatic enzymes occur in 0.5% to 1.0% of patients. Rhabdomyolysis is rare (less than 1 death per million patients). Attention has been drawn to the increased risk of adverse effects with higher doses of simvastatin particularly when used in combination therapy with niacin or fibrates, and when given with verapamil and/or amiodarone (Gruer et al 1999).

It is clear that the statins have multiple properties, so called pleiotropic properties, some of which are intriguing and will require further elucidation. It is well established that these medications alter the lipid profile in specific ways. Furthermore, there is evidence that the drugs improve endothelial dysfunction and lower inflammatory markers, including C-reactive protein (Rader 2000). There are observational data to suggest that these medications may prevent the onset of type II diabetes mellitus, osteoporosis, atherosclerotic aortic valve disease, ventricular arrhythmias, colon cancer, and senile dementia (Freeman et al 2001; Raja and Dreyfus 2004). Clearly, further outcomes based prospective studies are required to confirm these observations.

Summary

The concept of the control of cholesterol levels in clinical practice is now well established. Guidelines, recently extended, are now provided to assist in management. The use of statin drugs as an integral part of multifactorial management as primary and secondary preventative therapy utilized to lower cardiovascular mortality and morbidity risk is clearly indicated. The patient population requiring primary preventive care using statins continues to be extended. Patients requiring secondary preventive care using statins are now clearly identified, as is the recommendation of secondary preventive care for the remainder of a patient's life. Aggressive titration of statin drugs to lower LDL levels for secondary prevention is also now recommended. Recent data suggesting preferential statins will require further elucidation.

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